JASN®

Journal of the American Society of Nephrology

KIDNEY WEEK EDITION

KIDNEY WEEK 2024

Abstract Supplement

Abstract Supplement

Abstract Publication
More than 4,000 abstracts are published in this supplement. Abstracts are arranged by the abstract type**, then by presentation date* for orals and posters, and then by chronological publication number. Abstracts with a "PUB" number will not be presented at the ASN Annual Meeting.

* TH = Thursday, FR = Friday, SA = Saturday
** OR = Oral, PO = Poster, PUB = Publication Only

The presenting author's name is underlined.

Abstract Author Index
The Author Index lists all abstract authors in alphabetical order. To locate an abstract, first reference the abstract type (OR, PO, or PUB), then the presentation day (TH, FR, or SA), and then the chronological publication number.

Abstract Keyword Index
The Keyword Index lists major keywords from each abstract in alphabetical order. To locate an abstract, first reference the abstract type (OR, PO, or PUB), then the presentation day (TH, FR, or SA), and then the chronological publication number.

Abstract Reference Format
To cite abstracts in this publication, please use the following format: Author Names: Abstract Title [Abstract]. J Am Soc Nephrol 35, 2024: Page(s).

Abstract Disclaimer and Copyright
This abstract issue of JASN® contains proprietary information belonging to the American Society of Nephrology. It is published as a service for the personal, noncommercial, and informational use only of the kidney community. Any commercial use is strictly prohibited. ASN's program materials and publications facilitate scientific discourse for educational purposes. ASN accepts no responsibility for any products, presentations, opinions, statements, or positions expressed, and inclusion of such materials within Kidney Week and other ASN publications or online postings does not constitute endorsement by ASN.

Abstract Experts
Abstract submissions were rigorously reviewed and graded by multiple experts. ASN thanks the abstract category chairs and reviewers for assistance with the abstract process. The ASN website lists all abstract experts.

ASN General Information
Kidney Week Program and Presentations
The Kidney Week program, which can be found on the ASN website, includes:

- Plenary Sessions
- Basic/Clinical Science Sessions
- Clinical Practice Sessions
- Translational Sessions
- Special Sessions
- Educational Symposia
- Oral Abstract Sessions
- Poster Sessions

Disclosure Statement
ASN requires all individuals in a position to control content for Kidney Week to complete a disclosure form. Responses are listed on the ASN website.

Trademark

Contact ASN
American Society of Nephrology
1401 H Street, NW, Suite 900
Washington, DC 20005
Phone 202-640-4660
kidneyweek@asn-online.org
www.asn-online.org

TH-OR01

Nonoptimal ESKD Starts before and after Medicaid Expansion

Nicholas S. Roetker,[1] Jiannong Liu,[1] Haifeng Guo,[1] David T. Gilbertson,[1,2] James B. Wetmore,[1,2] Kirsten L. Johansen.[1,2] *[1]Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN; [2]University of Minnesota Twin Cities, Minneapolis, MN.*

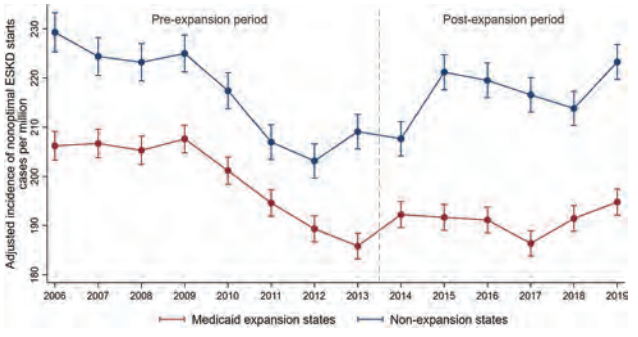
Background: Initiating in-center hemodialysis with a central venous catheter represents a nonoptimal start of end-stage kidney disease (ESKD). We studied whether nonoptimal start rates were higher in residents of 11 states that did not expand Medicaid access in 2014 relative to residents of 27 states that did.

Methods: We included yearly data from 2006-2019 for persons aged 18-64 years. We identified age, sex, and race/ethnicity state-level population estimates using US Census Bureau data and counts of nonoptimal ESKD starts from the US Renal Data System. We compared incidence rates between expansion and non-expansion states in the pre- and post-expansion periods using age, sex, and race/ethnicity adjusted Poisson regression.

Results: Before Medicaid expansion, the yearly rate of nonoptimal ESKD starts was 216.8 cases per million persons (PMP) in non-expansion states and 199.3 PMP in expansion states, with rates decreasing in both groups across this period (**Figure**). After Medicaid expansion, nonoptimal start rates were relatively stable in the expansion states (191.2 cases PMP) but increased in the non-expansion states (216.9 cases PMP). Thus, compared with the expansion states, the average yearly incidence was 17.4 (95% CI 15.8–19.1) PMP higher in non-expansion states in the pre-expansion period and 25.7 (95% CI 23.9–27.5) PMP higher in the post-expansion period (post vs pre difference in difference: 8.2; 95% CI 5.8–10.7 PMP). Notably, the difference in difference estimates were highest among the age 45-64 years (17.3; 95% CI 12.0–22.7 PMP) and non-Hispanic White (16.2; 95% CI 13.6–18.8 PMP) subgroups.

Conclusions: In the 6 years after enactment of the Affordable Care Act, rates of nonoptimal ESKD start were stable in states that expanded access to Medicaid but increased in states that did not. Further studies should examine whether increases in nonoptimal starts in non-expansion states may be attributable to less access to healthcare among uninsured persons with kidney disease.

Funding: NIDDK Support



TH-OR02

Age-Dependent Racial Differences in Kidney Function Decline between Black and White Veterans after CKD Onset

Guofen Yan,[1] Julia J. Scialla,[1] Nan Hu,[2] Wei Yu,[1] Tom Greene,[3] Robert Nee,[4] Fei Heng,[5] Alfred K. Cheung,[3] Keith C. Norris.[6] *[1]University of Virginia, Charlottesville, VA; [2]Florida International University, Miami, FL; [3]University of Utah Health, Salt Lake City, UT; [4]Walter Reed National Military Medical Center, Bethesda, MD; [5]University of North Florida, Jacksonville, FL; [6]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.*

Background: Recent research reveals that, when CKD onset was determined using the new race-free eGFR equation, Black adults still had a higher risk of subsequent progression to kidney failure than their White peers. We examined the extent to which rates of eGFR decline over time differ in Black and White veterans after CKD onset, and whether age modified the racial difference.

Methods: The study included 54,728 non-Hispanic Black and 256,479 non-Hispanic White veterans, aged 18-85 years, with new onset of CKD between 2005 and 2012 in the US Veterans Health Administration, and quarterly eGFR measurements for up to 6 years. eGFRs were calculated from outpatient serum creatinine measurements based on the 2021 CKD-EPI creatinine equation. We employed a linear spline mixed-effects model with random intercepts and random slopes to estimate age-specific rates of stable eGFR decline over 6 years from quarter 4 after CKD onset for each race, controlling for sex and calendar year of CKD onset.

Results: Upon CKD onset, the two race groups had similar mean eGFR levels (51 mL/min/1.73m^2). The rate of eGFR decline accelerated as the age of CKD onset decreased in Black veterans; the reverse was observed in White veterans (Table). As a result, racial differences in eGFR slopes were modified by the age of CKD onset, with larger differences at younger onset of CKD. For example, at age of CKD onset of 45 years old, the rate of eGFR decline was 0.79 mL/min/1.73m^2 per year faster in Black than White veterans. In distinct contrast, similar decline rates were observed in the two race groups at onset age of 85 years.

Conclusions: Racial differences in kidney function decline were larger among patients who developed CKD at a younger age, likely driven by more rapid decline in a subset of young Black patients. Delineating biological and social factors underlying the younger onset of CKD and subsequent fast progression for Black patients is warranted.

Funding: NIDDK Support

Age-specific rates of eGFR changes after CKD onset by race

Age at CKD onset (years)	Black eGFR slope (mL/min/1.73m2 per year)	White eGFR slope (mL/min/1.73m2 per year)	Difference between Black and White (mL/min/1.73m2 per year)	P value
45	-1.35	-0.56	-0.79	<0.001
55	-1.22	-0.64	-0.58	<0.001
65	-1.09	-0.72	-0.37	<0.001
75	-0.97	-0.81	-0.16	<0.001
85	-0.85	-0.89	0.04	0.25

A negative value means eGFR decline.

TH-OR03

Impact of Predialysis Nephrology Care on Incident Vascular Access Outcome among Hispanic Individuals: A Causal Mediation Analysis

Grant D. Scheiffele,[1] Serena Jingchuan Guo,[2] Wenxi Huang Huang,[2] Yi Guo,[2] Ashutosh M. Shukla.[1,2] *[1]US Department of Veterans Affairs, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: Predialysis care is a dominant predictor of incident vascular access outcomes. Prior studies have shown significant disparities in predialysis nephrology care among Hispanic patients with ESKD, compared to non-Hispanic Whites; however, its relative contributions to disparities in vascular access outcomes is unknown.

Methods: Analyzing patients initiating hemodialysis between 2009 and 2019 in URSDS, we examined the impact of disparities in predialysis nephrology care on incident vascular access use among Hispanic individuals, compared to non-Hispanic White individuals. Adjusting for critical patient-level variables, we conducted series of logistic regression and causal mediation analyses to dissect the attributable influence of disparities in predialysis nephrology care on vascular access use.

Results: Among the 427,340 adult Medicare recipients initiating their first-ever hemodialysis between 2010-2019; 269,697 Non-Hispanic White and 46,146 Hispanic individuals, 276,652 initiated with pure central venous catheter (CVC) without any maturing Arteriovenous Fistula (AVF) or Arteriovenous Graft (AVG) and 75,238 initiated with AVF or AVG. After adjusting for patient-level variables, compared to Non-Hispanic Whites, odds of predialysis nephrology care were 64% (95%CI: 63–66%) and odds of incident AVF/AVG use were 71% (95%CI:69-74%) amongst patients with Hispanic ethnicity. Causal mediation analysis showed that 33% (95%CI:29-37%) of the incident vascular access underuse was attributable to the disparities in predialysis renal care. Sensitivity analyses examining stronger mediators in form of more than 6-month nephrology care and predialysis kidney disease education showed even stronger mediating influence on vascular access outcomes (Table 1).

Conclusions: Disparities in predialysis nephrology care mediate nearly a third of disparities in vascular access outcomes among Hispanic ESKD population. Efforts are needed to universalize predialysis nephrology care and kidney disease education services for all Hispanic individuals at high risk of kidney failure.

Funding: Veterans Affairs Support

	Total Effect		Natural Direct Effect (95%CI)		Natural Indirect effect (95% CI)		Adjusted Percentage Mediated	p value*
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)		
Nephrology Care	0.75 (0.73, 0.76)	0.73 (0.70, 0.75)	0.84 (0.81, 0.86)	0.82 (0.79, 0.84)	0.89 (0.88, 0.89)	0.89 (0.88, 0.90)	32.78%	<0.0001
Nephrology Care Range	0.73 (0.70, 0.75)	0.70 (0.67, 0.73)	0.84 (0.81, 0.87)	0.82 (0.79, 0.85)	0.87 (0.86, 0.88)	0.85 (0.84, 0.86)	40.01%	<0.0001
KDE	0.53 (0.47, 0.60)	0.52 (0.45, 0.58)	0.73 (0.62, 0.83)	0.70 (0.60, 0.80)	0.74 (0.70, 0.79)	0.74 (0.69, 0.78)	37.63%	<0.0001

TH-OR04

Racial Disparities in Access to Preemptive Living Donor Kidney Transplantation in the United States from 2001-2023

Fawaz Al Ammary,[1] Abimereki Muzaale,[2] Simeon Adeyemo.[1] Living Donor Transplant Outcome Collaborative (LDTOC). *[1]University of California Irvine, Irvine, CA; [2]Johns Hopkins University, Baltimore, MD.*

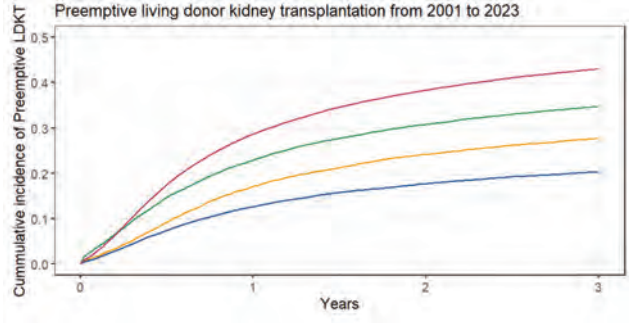
Background: Preemptive kidney transplantation for ESRD patients, before dialysis is needed, improves patient survival. However, access depends on early referral for transplant evaluation, as patient eligibility starts when eGFR less or equal 20 ml/min/1.73m2. We studied the impact of race/ethnicity on transplant waitlisting and access to preemptive living donor kidney transplantation over time.

Methods: We used the Scientific Registry of Transplant Recipients of 111,126 adult first-time kidney transplant candidates listed preemptively between 2001 and 2020. Outcome was wait time to preemptive living donor kidney transplantation, with race/ethnicity as the exposure. We used competing risk survival to estimate the cumulative incidence of preemptive transplantation, competing with death. Multivariable Cox regression adjusted for confounders. Analyses were stratified by era (2001–2005, 2006–2010, 2011–2015, and 2016–2020). Patients were followed for 3 years, with last follow-up in Dec. 2023.

Results: Overall, the cumulative incidence of preemptive living donor transplantation for patients on waitlist varied by race [Figure]. Compared to White patients, in the eras 2001–2005, 2006–2010, 2011–2015, and 2016–2020, Black patients were less likely to be transplanted by 52%, 58%, 60%, and 65%; Hispanic patients by 19%, 20%, 25%, and 34%; and Asian patients by 54%, 47%, 42%, and 47%, respectively [Table].

Conclusions: This study highlights persistent racial disparities in access to preemptive living donor kidney transplantation over the last two decades. These findings emphasize the need for interventions to address systemic barriers and ensure equitable access to early transplant evaluation for racial minorities.

Funding: NIDDK Support



At Risk				
Asian	6936	4920	3700	2729
Black	19244	14027	10835	8051
Hispanic	12060	7478	5512	3971
White	72886	41535	27854	18400
Events				
Asian	0	1111	1513	1680
Black	0	2238	3026	3362
Hispanic	0	2532	3272	3581
White	0	19046	24377	26397

Preemptive Living Donor Kidney Transplantation by Era, Adjusted HR (95% CI)

Waitlisted Patients	2001-2005	2006-2010	2011-2015	2016-2020
White	Ref	Ref	Ref	Ref
Black	0.48 (0.44-0.52)	0.42 (0.39-0.45)	0.40 (0.37-0.42)	0.35 (0.33-0.38)
Hispanic	0.81 (0.73-0.88)	0.80 (0.75-0.86)	0.75 (0.70-0.80)	0.66 (0.62-0.70)
Asian	0.46 (0.40-0.53)	0.53 (0.48-0.58)	0.58 (0.53-0.63)	0.53 (0.48-0.57)

All models were adjusted for age at listing, sex, race, ABO blood type, BMI, and DM as the cause of ESRD

TH-OR05

Trends in Dialysis Facility Access in the United States from 2018-2023 and Association with Area Socioeconomic Disadvantage

Meri Varkila, Maria E. Montez-Rath, Xue Yu, Nivetha Subramanian, Glenn M. Chertow, Julie Parsonnet, Shuchi Anand. *Stanford University School of Medicine, Stanford, CA.*

Background: After several years of stable growth, recent data indicate that the dialysis market in the US may be contracting. We sought to examine trends in US dialysis facility growth and closures, and evaluate whether closures were disproportionately affecting socio-economically disadvantaged populations.

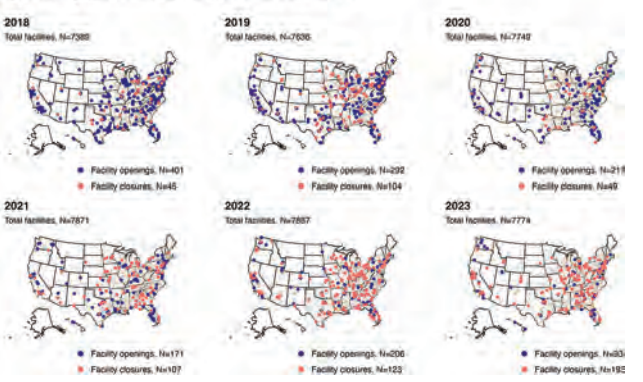
Methods: We conducted a serial cross-sectional study of dialysis facilities from 2018 until 2023 using the Provider of Services data from Centers for Medicare & Medicaid Services. We performed geospatial analysis of facility openings and closures across the U.S. and examined differential trends in dialysis facility access over time. We evaluated differences in CDC/ATSDR social vulnerability index (SVI), census region, rural or urban area designation, and racial and ethnic composition between census tracts (CT) in which the total number of dialysis facilities decreased, increased or remained unchanged between 2018 and 2023.

Results: We identified 8220 unique dialysis facilities across 7120 CTs between 2018 and 2023. During this time– as the number of individuals with prevalent end-stage renal disease rose from 782,844 in 2018 to 815,142 by the end of 2023– the annual number of facility closures increased consistently, whereas the number of newly opened facilities decreased (**Fig 1**). Facility closures and openings tended to occur in distinct CTs. Overall, access to dialysis services decreased in 563 (7.9%) neighborhoods. CTs in rural areas and in the Midwest were more likely to experience dialysis facility closures compared with urban CTs (10.5% of rural CTs vs. 8.4% of urban CTs with closures, p=0.01, and 10.3% of Midwest CTs vs. 6.2% of West CTs with closures, p <0.01). Neighborhoods with higher SVI did not experience more closures (p=0.61).

Conclusions: Trends in dialysis facility closure raise concerns about loss of access to dialysis services nationwide, with rural communities most urgently affected.

Funding: Other NIH Support - 1R21MD01939401

Figure 1. Geographic distribution of dialysis facilities in 2018-2023



TH-OR06

Quality Improvement Project Addressing Involuntary Discharged Hemodialysis Patients in an Urban, Predominantly Black US Population

Siddartha Bhandary, Zikora U. Nnadike, Anjuli Shah, Carol A. Gray, Jared A. Darrow, Jose E. Navarrete, Jason Cobb. *Emory University, Atlanta, GA.*

Background: Insurable, involuntarily discharged hemodialysis (HD) patients receiving maintenance HD in the hospital are a growing, vulnerable population. We present a quality improvement (QI) project examining second chance placement of involuntary discharged HD patients receiving maintenance HD through inpatient care in our urban predominantly Black population

Methods: QI project at Emory Hospitals and Grady Memorial Hospital. We included all patients involuntarily discharged from a HD center, and those who started HD as inpatient and were seen for inpatient dialysis >60 days, from 1/2020 – 9/2023. Clinical information followed until 3/2024

Results: We included 30 ESKD patients. 21 (70%) male Mean age 49.8 years.100% (n=30) identified as Black, and 77% (n=23) with Medicaid insurance. Most common reasons for discharge: noncompliance (n=17) & disruptive behavior (n=9). 11 (37%) patients had documented substance abuse, and 12 (40%) documented psychiatric disorders. 6 patients with HIV and 6 were homeless. 16 patients received second chance HD placement prior to QI project and 9 patients received second chance HD placement as our QI intervention (5/2023 – 9/2023). 6 of the 9 second-chance placement patients had reduced admissions. 1 patient was an outlier with 43% of HD admissions. The remaining patients had 52 admissions for HD prior, and only 5 admissions after with a 90% reduction. Average outpatient HD billing is approximately $280 to 335 per treatment and inpatient cost for HD only admissions is approximately $1300

Conclusions: This QI project brings attention to a vulnerable nephrology patient population. The subjective analyses used to adjudicate the 'lack of adherence' and 'disruptive behaviors' may be vulnerable to cultural bias and lead to discrimination against these patients. This QI project demonstrated 9 patients were successfully placed with a dramatic decrease in HD associated admissions. Considering that outpatient dialysis billing averages about 25% of the cost of inpatient dialysis admissions, this in turn adds to the significant financial costs. Further investigations of insurable HD patients receiving maintenance HD in the hospital settings are warranted to determine the prevalence, financial burden and possible interventions to improve outcomes

TH-OR07

Racial and Gender Disparities among Nephrology Fellowship Trainees: Trends over a Decade and the Impact of COVID-19

Ohm S. Tripathi. *University of Connecticut, Storrs, CT.*

Background: This study examines trends in racial and gender diversity among nephrology fellowship trainees from 2014 to 2023, evaluating representation and assessing the influence of the COVID-19 pandemic on the demographic composition of trainees.

Methods: Data from the Accreditation Council for Graduate Medical Education (ACGME) were analyzed to identify nephrology fellows during the study period, categorized by self-reported race and gender. The pre-COVID era was defined as 2017-2020, and the post-COVID era as 2020-2023. Chi-square tests assessed differences between groups and longitudinal trends.

Results: Female fellows (36.7%) were significantly underrepresented compared to males (62.9%) ($p<0.05$). Female representation remained relatively stagnant, ranging from 39.0% in 2014-2015 to 38.5% in 2022-2023, with a slight increase post-COVID (38.0%) versus pre-COVID (35.5%) ($p=0.050$). Black individuals (24.7%) were underrepresented compared to Whites and Asians ($p<0.05$). The percentage of Black fellows declined from 23.5% in 2014-2015 to 11.0% in 2022-2023, while Hispanics increased from 6.4% to 10.3%. Black fellow representation decreased significantly post-COVID (10.2%) compared to pre-COVID (23.7%) ($p<0.05$).

Conclusions: Significant gender and racial disparities persist in ACGME-accredited nephrology fellowships. While a modest increase in female fellows post-COVID is encouraging, representation remains stagnant overall. Concerningly, Black fellow representation has declined substantially, despite the disproportionate burden of kidney disease in this population. Urgent action is needed to enhance diversity and address systemic barriers for racial minorities and women in nephrology training.

TH-OR08

Improving CKD Clinical Trial Representation with Educational Videos and Generative Artificial Intelligence

Kevin Timms. *Tea Leaf Health, San Francisco, CA.*

Background: The prevalence of Chronic Kidney Disease (CKD) among underserved communities means representative study cohorts are a requirement for scientifically robust and equitable CKD clinical trials. However, despite the importance of representative cohorts and increased attention on the problem, CKD trials remain largely unrepresentative. This is largely due to the many barriers to trial enrollment faced largely by Hispanic and African-American CKD communities – things like logistics (eg, dialysis centers being more accessible than trial sites to many urban minorities), distrust of the healthcare system, and research unawareness. Efforts like peer-based recruitment & research literacy education have been promising in an effort to address those barriers and increase representative trials.

Methods: Here, we present a proof-of-concept showing how Generative AI (GenAI) can be used to address barriers to enrollment faced by diverse communities. Specifically, we show how a set of GenAI models produces 120-second videos with CKD clinical trials information, where the videos are tailored to be accessible, inclusive, and ultimately more meaningful to different local demographic CKD patients. In this research, we show a case study in which our GenAI algorithms were trained and tuned to specifically create educational videos for a ESRD study whose protocol and Informed Consent Form were downloaded from clinicaltrials.gov. Model training and tuning was based on open source GenAI models, academic research literature, public & nonpublic structured data, and subject matter expertise from Clinical Research Coordinators, IRB reviewers, and sensitivity readers.

Results: As a case study, we generated three semi-personalized videos educating about a study of Empagliflozin in ESRD patients; in each video, the GenAI adapts tone, language, visual style, and content emphasis for a unique ESRD patient profile – a 65 year old African-American female in rural Alabama, a 35 year old African-American male in Chicago, and a 25 year old Hispanic male in suburban Tampa, Florida.

Conclusions: We highlight how the GenAI's recommendations – like defining what clinical research is and why it is important for the elderly patient profile vs. describing onsite childcare options for the younger Hispanic profile – helps address underserved communities' barriers to trial enrollment more effectively.

Funding: Commercial Support - Tea Leaf Health, Inc

TH-OR09

Diversity, Equity, and Inclusion in Nephrology: Assessing Artificial Intelligence's Impact on Decision-Making and Advocating for Ethical Regulation

Suryanarayanan Balakrishnan,[1] Charat Thongprayoon,[2] Jing Miao,[2] Michael A. Mao,[3] Iasmina Craici,[1] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic Health System, Mankato, MN; [3]Mayo Clinic in Florida, Jacksonville, FL.*

Background: "Kidney Care for All" advocates for the crucial role of diversity, equity, and inclusion (EDI) in nephrology. As Artificial Intelligence, especially Large Language Models (LLMs), becomes more prevalent in healthcare, concerns about the regulatory oversight of AI applications have emerged. Without proper regulation, AI outputs could inappropriately sway nephrologists' decisions in patient care and affect inclusivity in nephrology staff recruitment. This study assesses how well the AI models, ChatGPT 3.5 and ChatGPT 4.0, handle the intricate ethical EDI considerations in nephrology-related scenarios.

Methods: In March 2024, we created 80 nephrology-focused simulation cases to evaluate AI decision-making across broad areas, such as treatment of kidney disease, organ donation ethics, transplant evaluations, and staff recruitment. Each case was developed by two nephrologists and reviewed for its medical accuracy and relevance in assessing ethical sensitivity and decision-making capabilities of ChatGPT 3.5 and 4.0.

Results: ChatGPT 3.5 consistently selected treatment choices predicted to yield the best outcomes across all questions, demonstrating a utilitarian approach that incorporates various EDI factors. However, ChatGPT 3.5 did not refuse to make decisions under any circumstances. This approach was misaligned with the fundamental EDI requirement not to base decisions on discriminatory criteria. In contrast, ChatGPT 4.0 did decline to make decisions based on potentially discriminatory criteria in 16.25% of scenarios, stating EDI factors should not affect decisions about treating patients or hiring nephrology staff.

Conclusions: ChatGPT 4.0's refusal to engage in discriminatory decision-making represents an important evolution in AI ethics. However, its occurrence in only 16.25% of scenarios highlights the need for robust AI regulation to ensure appropriate EDI principles application. We also need policies that make sure AI is used responsibly and follows principles of EDI before its application in nephrology, both in clinical settings and in the hiring of staff.

TH-OR10

Complementary Role of Transcriptomic Endotyping and Protein-Based Biomarkers for Risk Stratification in Sepsis-Associated AKI

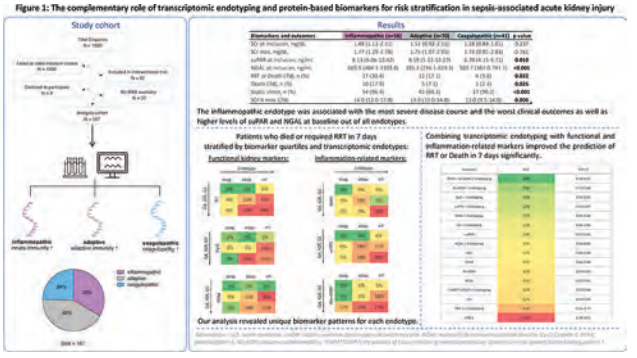
Christian Nusshag,[1] Bengi S. Tavris,[1] Christian Morath,[1] Florian Uhle,[2,4] Timothy Sweeney,[4] Oliver S. Liesenfeld,[4] Mascha O. Fiedler-Kalenka,[2] Thorsten Brenner,[3] Martin G. Zeier,[1] Markus A. Weigand.[2] Nusshag Lab. *[1]Heidelberg University Hospital, Department of Nephrology, Heidelberg, Germany; [2]University Hospital Heidelberg, Department of Anesthesiology, Heidelberg, Germany; [3]University Hospital Essen, Department of Anesthesiology, Essen, Germany; [4]Inflammatix Inc, Burlingame, CA.*

Background: Sepsis-associated acute kidney injury (SA-AKI) is the most common form of AKI in critically ill patients. Heterogeneous immune responses in sepsis contribute to the failure of uniform treatment strategies. Transcriptomic endotyping (TE) may identify septic patients with common pathophysiological drivers, enhancing risk stratification and outcome prediction. This study evaluated TE's clinical value in predicting kidney-related outcomes and its complementary role with protein-based biomarkers.

Methods: ICU patients meeting Sepsis-3 criteria were assigned to inflammopathic (IE), adaptive (AE), or coagulopathic endotype (CE) using a gene expression-based classifier. Baseline measurements included SCr, CysC, PENK, NGAL, KIM-1, suPAR, and BioADM in blood, and TIMP2*IGFBP7 in urine. Clinical outcomes were tracked for 30 days.

Results: From 167 sepsis patients, 33% were classified as IE, 42% as AE, and 24% as CE. IE was associated with the worst outcomes, including higher seven-day mortality, need for renal replacement therapy (RRT), sepsis scores, and septic shock incidence (Figure 1). Baseline NGAL and suPAR, both related to immune activation and inflammation, were highest in IE. SCr and CysC for AE; NGAL, suPAR, and TIMP2*IGFBP7 for IE; and BioADM for CE best stratified RRT or death within seven days of sepsis diagnosis. Combining TE with functional and inflammation-related markers significantly improved outcome prediction. The combination of PENK, BioADM, and TE best predicted RRT or death within seven days with an AUC of 0.84.

Conclusions: TE enhances risk stratification and predictive enrichment in sepsis patients, improving the clinical validity of protein-based biomarkers for specific endotypes. This supports a more individualized approach to managing SA-AKI, with distinct biomarker patterns reflecting different pathophysiological mechanisms.



TH-OR11

Molecular Phenotyping of Patients with Sepsis and Kidney Injury and Differential Response to Fluid Therapy: Secondary Analysis of a Clinical Trial

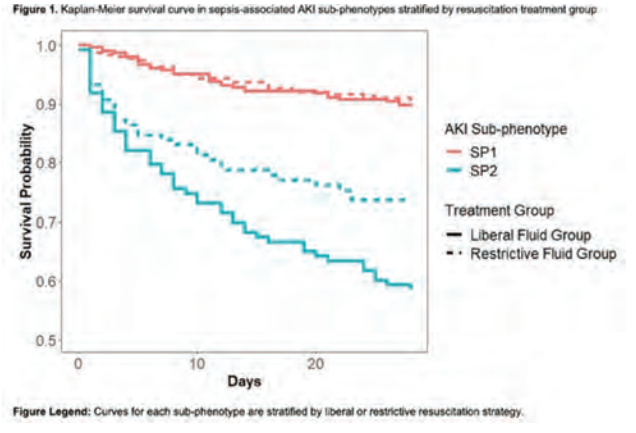
Elizabeth Kiernan, Leila R. Zelnick, Bryan R. Kestenbaum, Jonathan Himmelfarb, Pavan K. Bhatraju. On behalf of CLOVERS Investigators. *University of Washington, Seattle, WA.*

Background: We previously identified AKI sub-phenotypes (SP1 and SP2) characterized by differences in inflammation and endothelial dysfunction. Here we identify these sub-phenotypes in the emergency department and test for differences in treatment response to a restrictive versus liberal fluid strategy in patients with sepsis-induced hypotension in the Crystalloid Liberal or Vasopressors Early in Sepsis (CLOVERS) trial. The original CLOVERS study demonstrated no differences in clinical outcomes between treatment arms or in sub-groups with AKI or ESKD on enrollment.

Methods: We applied latent class analysis methodology to 23 study enrollment variables and applied a previously developed 3-variable model using plasma angiopietin-1 and 2, and soluble tumor necrosis factor receptor-1 to classify sub-phenotypes in patients with kidney dysfunction (AKI or end-stage kidney disease [ESKD]).

Results: Among 1289 CLOVERS patients with available plasma, 771 had AKI and 75 had ESKD on enrollment. Latent class analysis identified a two sub-phenotype model as the optimal fit for the data with high correlation to two sub-phenotypes identified with the 3-biomarker model (Cohen's Kappa 0.8). The model identified 605 as SP1 and 241 as SP2. The risk of 28 and 90-day mortality was greater in SP2 relative to SP1 independent of AKI stage and sequential organ failure assessment scores. Patients with SP2, characterized by more severe endothelial injury and inflammation, had a reduction in 28-day mortality with a restrictive fluid strategy versus a liberal fluid strategy (26% vs 41%), while patients with SP1 had no difference in 28-day mortality (10% vs 11%) (*p-value-for-interaction* = 0.03).

Conclusions: Clinically distinct sub-phenotypes can be identified in biospecimens collected in the emergency department and respond differently to fluid strategy in sepsis. This could inform a precision-guided therapeutic approach for patients with sepsis-induced hypotension and kidney injury.



TH-OR12

AKI in the Kidney Precision Medicine Project: Acute Tubular Injury vs. Acute Interstitial Nephritis

Jennifer A. Schaub,[1] Angela M. Victoria Castro,[4] Steven Menez,[2] Yumeng Wen,[2] Rajasree Menon,[1] Pavan K. Bhatraju,[3] Francis P. Wilson,[4] Steven G. Coca,[5] Michael T. Eadon,[6] Andrew S. Bomback,[7] Dennis G. Moledina,[4] Lloyd G. Cantley,[4] Paul M. Palevsky,[8] Vivette D. D'Agati,[7] Parmjeet S. Randhawa,[8] Raghavan Murugan,[8] Charles E. Alpers,[3] Matthias Kretzler,[1] Jonathan Himmelfarb,[3,5] Chirag R. Parikh.[2] Kidney Precision Medicine Project (KPMP). *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]Johns Hopkins Medicine, Baltimore, MD; [3]University of Washington, Seattle, WA; [4]Yale University, New Haven, CT; [5]Icahn School of Medicine at Mount Sinai, New York, NY; [6]Indiana University, Bloomington, IN; [7]Columbia University, New York, NY; [8]University of Pittsburgh, Pittsburgh, PA.*

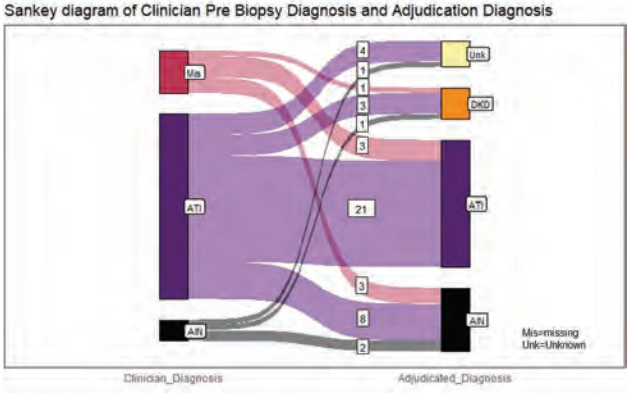
Background: Kidney biopsies are rarely obtained in patients with acute kidney injury (AKI) when the suspected diagnosis is acute tubular injury (ATI).

Methods: The Kidney Precision Medicine Project obtained non-clinically indicated kidney biopsies and independently adjudicated diagnosis based on the clinical history and pathology features. We evaluated the patient's clinical and pathologic features to correlate with adjudicated diagnosis.

Results: Of the 47 participants, the average age was 49 (+/-15) years; 72% were male and 40% were black. Clinical characteristics included hypertension (40%), diabetes (31%), and baseline eGFR was 58 (+/- 5) ml/min/1.73m2. On adjudication, 24 patients (51%) had a primary diagnosis of ATI, 12 (26%) patients had a diagnosis of acute interstitial nephritis (AIN), 6 had diabetic kidney disease and consensus could not be obtained for 5 patients for the primary diagnosis. A total of 30 biopsies were scored for histological descriptor features, and there was a significant increase in the number of interstitial WBCs (p=0.01), tubulitis (p=0.01), and lymphocytic tubulitis (p<0.01) in AIN compared to ATI, but the remaining 27 features were not different. We subsequently evaluated the clinician's pre-biopsy suspected diagnosis with the adjudicated diagnosis. Of the 24 ATI cases, ATI was suspected in 21 of them (88%); of the 12 AIN cases, ATI was suspected pre-biopsy in 8 (67%) (**Figure**).

Conclusions: In conclusion, kidney biopsy in the AKI setting is helpful as AIN is clinically under recognized.

Funding: NIDDK Support



TH-OR13

AKI in Care Transitions (ACT): A Randomized Controlled Feasibility Trial

Caroline B. Ledet,[1] Heather P. May,[1] Kristin C. Cole,[1] Joan M. Griffin,[1] Joseph Herges,[1] Kianoush Kashani,[1] Andrea G. Kattah,[1] Rozalina G. Mccoy,[2] Angeliki G. Tinaglia,[1] Andrew D. Rule,[1] Erin F. Barreto.[1] ACT Study. *[1]Mayo Clinic Minnesota, Rochester, MN; [2]University System of Maryland, Baltimore, MD.*

Background: Acute kidney injury (AKI) survivors are at risk for not receiving needed follow-up medical care after discharge. This study assessed the feasibility and preliminary efficacy of a multidisciplinary AKI survivor care delivery model (AKI in Care Transitions - ACT).

Methods: This was a single-center randomized controlled trial of individuals with stage 3 AKI during a hospitalization discharged to home and not on dialysis. Patients were randomized 1:1 to the ACT intervention or usual care. The ACT intervention group received education from nurses and coordination of laboratory and clinical follow-up with a primary care provider and a pharmacist ideally within 14-days after hospital discharge. The primary objective was to determine feasibility of the ACT trial from the proportion of patients screened, who consented, randomized, and actually participated in the trial. Secondarily, efficacy outcomes were explored.

Results: Over 18 months, 118 individuals were eligible and 50 (42% of those approached) consented and were randomized. Participants were similar to nonparticipants. The ACT intervention group received education and care coordination as intended in 22 (88%) cases. More ACT intervention patients had complete clinical and laboratory follow-up in 30-days (ACT 60% vs Usual Care 24%; P = 0.01), and fewer experienced a >30% decline in estimated glomerular filtration rate at 90-days (ACT 14% vs Usual Care 38%; P = 0.088), although this difference was not statistically significant.

Conclusions: The results demonstrated the feasibility of the ACT trial and justify an adequately powered trial of the efficacy of ACT in non-dialysis dependent AKI survivors.

Funding: Other NIH Support - AHRQ, NIAID

TH-OR14

Clinical Predictors of Fluid-Responsive AKI

Cindy Khanh Nguyen, Abinet M. Aklilu, Yu Yamamoto, Claudia Coronel-Moreno, Bashar A. Kadhim, Francis P. Wilson. Clinical and Translational Research Accelerator. *Yale University School of Medicine, New Haven, CT.*

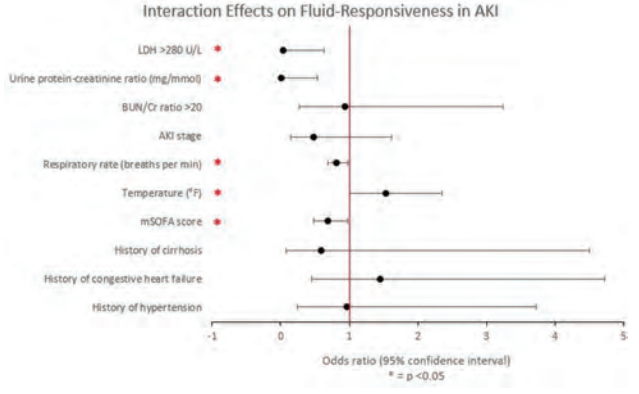
Background: It is challenging to predict in clinical practice whether an episode of AKI may be reversible with volume expansion. No simple tool exists to aid in this decision-making process.

Methods: We prospectively enrolled patients at Yale-New Haven Hospital with AKI, as defined by the Kidney Disease: Improving Global Outcomes creatinine criteria. We collected fluid administration data and standardized all volumes based on sodium concentration. The exposure was receiving at least 2L of normal saline (NS) equivalent in the 24h post-AKI. The outcome of interest was fluid-responsiveness–a plateau or decrease in serum creatinine within the 48h period beginning 24h post-AKI. We excluded patients meeting criteria for acute heart failure exacerbation and those who received ≥1L of NS equivalent in the 24h pre-AKI. We used inverse-probability weighting to estimate the interaction effects of receiving volume with 60 variables of interest collected in the 24h pre- or at the time of AKI on the outcome.

Results: Of 3206 patients with AKI, 2313 met inclusion criteria, and 143 received the exposure. The interaction effects of select clinical variables are shown in Figure 1. Significant positive predictors of fluid-responsiveness in AKI patients receiving volume included higher temperature, higher urine chloride, and serum calcium >10.5 mg/dL. Significant negative predictors included higher respiratory rate, higher urine protein-creatinine ratio, higher modified Sequential Organ Failure Assessment (mSOFA) score, lactate dehydrogenase >280 U/L, and having serum uric acid checked. AKI in which a nephrologist suspected pre-renal etiology (excluding cardiorenal and hepatorenal syndromes) trended toward higher odds of fluid-responsiveness.

Conclusions: Common clinical variables may be helpful in identifying who will benefit from volume challenge when the fluid-responsiveness of AKI is unclear.

Funding: Other U.S. Government Support



TH-OR15

Ultrasound-Guided Diuretic Therapy in Type 1 Cardiorenal Syndrome: A Randomized, Double-Blind Controlled Trial

Victor H. Gomez Johnson, Erika E. Jaime Borja, Alfredo Fuentes Mercado, Eder J. Amaro Palomo, Romeo Arias Escarpulli, Rodrigo Gopar-Nieto, Salvador L. Gil. NEEDED-Trial. *Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico*.

Background: Traditional diuretic titration in cardiorenal syndrome (CRS) relies on physical exams. New tools like VExUS show potential, but evidence is limited. This study compares VExUS-guided decongestion to physical exams in improving outcomes.

Methods: In this double-blind, randomized, controlled trial, 34 CRS patients undergoing decongestive therapy were enrolled. Clinical Congestion Score (CCS) group with a single observer assessed orthopnea, jugular venous distension, and edema on a scale of 0-3. VExUS group had a different observer evaluating inferior vena cava diameter, hepatic vein, portal vein, and intra-renal venous doppler. Both assessments continued until decongestion (CCS<3;VExUS 0-1) or 7 days.

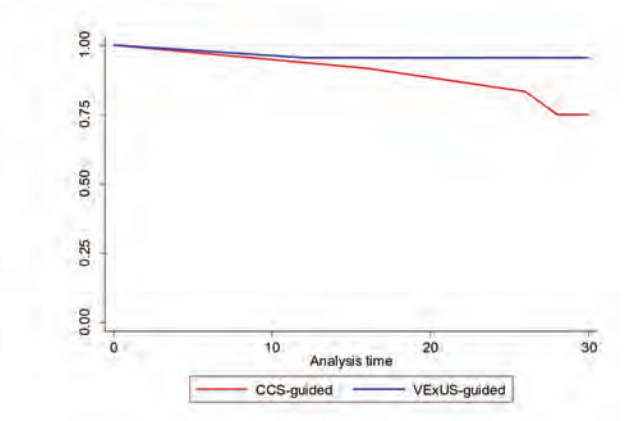
Results: Baseline characteristics were similar, including sick patients (SCr 2.1mg/dL, LVEF 27%, NT-proBNP 19336pg/mL). VExUS-guided treatment showed better trends: higher UNa, lower discharge NT-proBNP, fewer readmissions, and lower in-hospital mortality (see table 1). 30-day mortality was lower in the VExUS-guided group (p=0.05).

Conclusions: VExUS-guided treatment was associated to lower 30-day mortality (p=0.05), increased UNa, decreased NT-proBNP at discharge, fewer readmissions, and reduced in-hospital mortality. As the trial continues, a larger population is anticipated to provide more definitive results. Further studies should assess the relevance and impact on these patients.

Table 1. Outcomes

Variables	Total n=34	Control group n=12	VExUS group n=22	p
Heart failure readmission n(%)	7(21.9)	4(33.3)	3(15)	0.37
NT-proBNP at discharge (pg/mL) Median (IQR)	9333(4064-29058)	15658(3492-34813)	7997(4500-26380)	0.19
In-hospital mortality n(%)	4(12.1)	3(25)	1(4.8)	0.12
Urinary sodium (mmol/L) Median (IQR)	86.2(65-112.6)	85.4(63.5-100.4)	91.5(69-117)	0.36
30-day mortality n(%)	2(6.2)	2(16.7)	0	0.05

Figure 1. Kaplan Meier survival at 30 days



TH-OR16

Trajectories of Fluid Management after Initiation of Kidney Replacement Therapy in Critically Ill Patients: Insights from the STARRT-AKI Trial

William Beaubien-Souligny,[1] Ehsan Ghamarian,[3] Sean M. Bagshaw,[2] Kevin Thorpe,[3] Ron Wald.[4] *[1]Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]University of Alberta, Edmonton, AB, Canada; [3]Applied Health Research Centre, Toronto, ON, Canada; [4]St. Michael's hospital, Toronto, ON, Canada*.

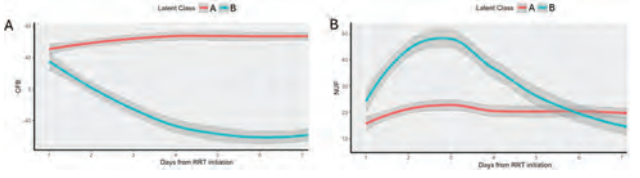
Background: Fluid management is an essential component of renal replacement therapy (RRT) in critically ill patients. Both a positive cumulative fluid balance (CFB) and high net ultrafiltration (NUF) have been associated with adverse outcomes but fluid management trajectories remain incompletely described by previous efforts. We aimed to analyze the CFB/NUF as a trajectory over the first week after the initiation of RRT.

Methods: This is a secondary analysis using fluid balance data from individuals enrolled in the standard-strategy arm of the STARRT-AKI trial who initiated RRT. Cumulative fluid balance (CFB) since RRT initiation and daily net ultrafiltration (NUF)

adjusted for body weight during the first 7 days after initiation of RRT were the main variables studied. We employed multivariable joint longitudinal models to determine the association with 90-day mortality. We then modeled the trajectory of fluid parameters using spline functions and used latent class analysis methods to identify predominant trajectories to compare patients' characteristics and outcomes.

Results: We included 855 patients in the analysis. After adjustments, an association between CFB and 90-day mortality was found (HR: 1.075 (1.04; 1.11) p<0.001) but no association with net daily NUF (HR: 0.95 (CI: 0.64; 1.39) p=0.78). Using latent class analysis, we identified two distinct CFB/NUF trajectories. Class A was characterized by a slight increase in CFB and low/stable NUF after RRT initiation while class B was characterized by an increasingly negative CFB with initially higher daily NUF during the first 4 days followed by a stabilization after day 4. In adjusted analysis, individuals classified in class A were at higher risk for 90-day mortality (aOR: 2.22 CI: 1.52; 3.28) p<0.001) compared to class B.

Conclusions: Beyond cumulative fluid balance and daily NUF rate, the overarching CFB/NUF trajectory should be considered when attempting to elucidate the safety of fluid balance management strategies.



Predominant trajectories of A) cumulative fluid balance (CFB) in mL/kg and B) daily ultrafiltration rate (UF) in mL/kg/d.

TH-OR17

Multidisciplinary Inter-rater Reliability of Muscle Ultrasonography in Patients with AKI Requiring Continuous Kidney Replacement Therapy

J. Pedro Teixeira,[1] Felipe Gonzalez-Seguel,[2,3] Vinh Tran,[1] Chaitanya A. Pal,[1,4] Zan Shareef,[1] Hayley Israel,[1] Arimitsu Horikawa-Strakovsky,[3,5] Yuan Wen,[5,6] Benjamin R. Griffin,[7] Javier A. Neyra,[8] Kirby Mayer.[2,3] *[1]University of New Mexico School of Medicine, Albuquerque, NM; [2]University of Kentucky College of Health Sciences, Lexington, KY; [3]University of Kentucky Center for Muscle Biology, Lexington, KY; [4]Memorial Sloan Kettering Cancer Center Department of Anesthesiology and Critical Care Medicine, New York, NY; [5]University of Kentucky Institute for Biomedical Informatics, Lexington, KY; [6]University of Kentucky College of Medicine, Lexington, KY; [7]University of Iowa Hospitals and Clinics, Iowa City, IA; [8]The University of Alabama at Birmingham Department of Medicine, Birmingham, AL.*

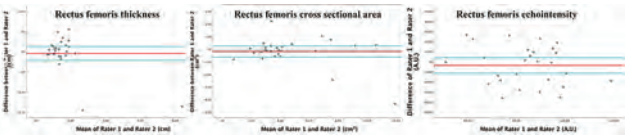
Background: Early diagnosis of muscle wasting in critically ill patients with acute kidney injury requiring continuous kidney replacement therapy (AKI-CKRT) may improve outcomes via timely rehabilitation and nutrition. Musculoskeletal ultrasound (MSK-US) has gained traction for assessing muscle atrophy in the intensive care unit (ICU) but requires training to achieve reproducibility. We evaluated the inter-rater reliability (IRR) of MSK-US in patients with AKI-CKRT carried out by a multidisciplinary group of providers including nephrologists.

Methods: Two blinded and independent raters used portable US devices to acquire images of rectus femoris (RF) at baseline (within 48h of CKRT initiation), day 3, day 7, ICU discharge, hospital discharge, and 1–3 months after discharge. All raters were clinicians or trainees routinely caring for patients with AKI-CKRT in the ICU and were initially novices in MSK-US. They underwent three 2-h teleconference training sessions in MSK-US led by an experienced physiotherapist. IRR was evaluated with intraclass correlation coefficient (ICC) [95% confidence interval] using a 2-way random-effects model.

Results: Raters acquired 54 (27 per rater) US images from 9 subjects at baseline (n=16), day 3 (n=6), day 7 (n=8), ICU discharge (n=10), hospital discharge (n=10), and 1–3 months after discharge (n=4). The mean (± standard deviation) values of RF thickness, cross-sectional area (CSA), and echointensity (EI) were 1.7 ±1.4 cm, 4.6 ±2.7 cm^2, and 84.0 ± 17.7 AU, respectively. IRR was excellent for muscle thickness (ICC = 0.96 [0.91–0.98], p<0.001) and CSA (ICC = 0.92 [0.83–0.96], p<0.001) and moderate for EI (ICC = 0.41 [0.04–0.68], p<0.05). The absolute agreement between raters is shown by Bland-Altman plots (**Fig 1**).

Conclusions: Our results demonstrate reliable assessment of muscle quality and especially size in ICU patients with AKI-CKRT using US performed by multidisciplinary clinicians and trainees including nephrologists. This study suggests MSK-US may be a useful tool to diagose critical illness myopathy in the AKI-CKRT population.

Funding: Other NIH Support - Clinical and Translational Award (CTSA) Inter–Institutional Pilot Project Award U24TR002260 (NCATS)



TH-OR18

Prognostication of 90-Day Kidney Function Recovery in Patients with AKI Receiving Outpatient Dialysis

Seda Babroudi,[1] Carolien C. Maas,[3] Daniel E. Weiner,[1] Javier A. Neyra,[2] David M. Kent,[5,1] Ronald Sanders,[4] Harold Manley,[4] Eduardo K. Lacson,[4,1] David A. Drew.[1] *[1]Tufts Medical Center, Boston, MA; [2]UAB Hospital, Birmingham, AL; [3]Erasmus MC, Rotterdam, Netherlands; [4]Dialysis Clinic Inc, Nashville, TN; [5]Tufts Medical Center Predictive Analytics and Comparative Effectiveness (PACE) Center, Boston, MA.*

Background: Prognostic uncertainty regarding kidney function recovery for patients with AKI-D may result in suboptimal dialysis care. We developed and internally validated a prognostic model for 90-day kidney function recovery to dialysis independence in patients with AKI-D.

Methods: Candidate predictors included demographic, clinical, laboratory, and dialysis characteristics readily available as part of usual care, ascertained in the first week of outpatient dialysis from a national dialysis provider. We derived a parsimonious model by applying backward selection guided by the Bayesian Information Criterion to a multivariable Cox proportional hazards model. Model calibration and discrimination were assessed. Internal-external cross-validation was performed using three geographic regions.

Results: Of 2,544 individuals with AKI-D, 771 patients recovered kidney function within 90-days of outpatient dialysis initiation (cumulative incidence 33.8%, 95% CI 31.8-35.7). Thirteen predictor variables were retained in the final model. Internal-external cross-validation suggested good external calibration and discrimination (Uno's C-index 0.70 (95% CI 0.67-0.73) Figure 1).

Conclusions: We developed a prediction model to prognosticate 90-day kidney function recovery among patients with AKI-D within the first week of outpatient dialysis initiation. The model demonstrated good performance, supporting its use to inform shared decision-making between dialysis clinicians and patients.

Funding: Other NIH Support - National Center for Advancing Translational Sciences, National Institutes of Health, Award Number TL1TR002546

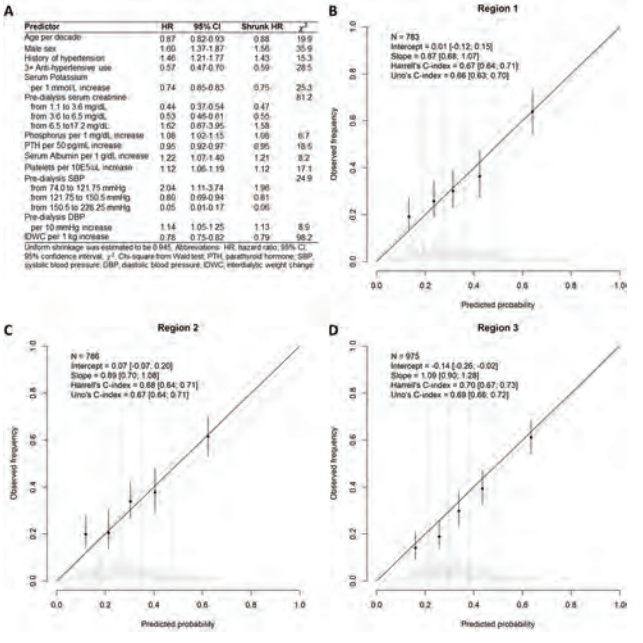


Figure 1. (A) Predictors and Calibration Plots of Final Model after Uniform Shrinkage using (B) Region 1; (C) Region 2; or (D) Region 3 as an external validation set

TH-OR19

Multicenter Development and Validation of a Multimodal Deep Learning Model to Predict Severe AKI

Jay L. Koyner,[1] Jennifer Martin,[2] Kyle Carey,[1] John Caskey,[2] Dmtriy Dligach,[2] Majid Afshar,[2] Matthew M. Churpek.[2] *[1]University of Chicago Division of the Biological Sciences, Chicago, IL; [2]University of Wisconsin-Madison, Madison, WI.*

Background: Electronic health record(EHR) -based risk algorithms for acute kidney injury(AKI) have been reported but these have focused on structured data(e.g. vital signs & laboratory values). We aimed to develop & validate a deep learning time series model to predict AKI by combining structured data & unstructured data from clinical notes

Methods: Patients(≥18 years) admitted to the University of Wisconsin (2009-20) & the University of Chicago Medicine (2016-22) were included. Patients were excluded if they had no documented serum creatinine (SCr), an admission SCr≥3.0mg/dL, developed Stage 2 AKI before reaching the wards or intensive care unit (ICU), or if they required dialysis(RRT) within the first 48 hrs. AKI was defined by the KDIGO SCr definition. Fifty-eight structured features were used in the model, and the raw text from unstructured clinical notes were mapped to standardized Concept Unique Identifiers (CUIs) to create unstructured data features. An intermediate fusion deep learning recurrent neural network architecture was used to predict Stage ≥2 AKI within the next 48 hrs. The model was developed in the first 80% of the data by date & temporally validated in the next 20%.

Results: There were 339,998 subjects in the derivation cohort & 84,581 in the validation cohort with 12,748(3%) across both cohorts, developing Stage 2 AKI. Those with Stage 2 AKI were more likely to be older, male, have higher baseline SCr, and more likely to be in the ICU. CUIs related to intubation, ventilation, and airway management were more common in those with AKI. AUCs overall and across important subgroups were above 0.85 for most outcomes.

Conclusions: We developed and validated a novel deep-learning risk assessment tool using structured & unstructured data from the EHR in real time to predict the development of Stage 2 AKI across the entire hospital. A real-time version of this model has now been implemented at both health systems.

Funding: NIDDK Support

AUC for AKI Outcomes in the Next 48 hours

All Values AUC(95%CI)	At Least Stage 2 AKI	Receipt of RRT
All Encounters	0.87 (0.87-0.87)	0.90 (0.90-0.90)
Ward Patients	0.86 (0.86-0.86)	0.88 (0.87-0.88)
ICU Patients	0.83 (0.83-0.83)	0.84 (0.84-0.84
Baseline Creatinine < 1.0 mg/dL	0.86 (0.86-0.87)	0.89 (0.89-0.90)
Baseline Creatinine 1.0-1.99 mg/dL	0.88 (0.88-0.88)	0.90 (0.90-0.90)
Baseline Creatinine >2.0 mg/dL	0.88 (0.88-0.88)	0.87 (0.87-0.87)

TH-OR20

Network Analysis of Paired Plasma-Urine Metabolomes Reveals Genetic Determinants of Metabolite Clusters

Pascal Schlosser,[1,2] Maren Hackenberg,[1] Sara Monteiro-Martins,[1] Stefan Haug,[1] Anna Kottgen.[1,2] *[1]Universitatsklinikum Freiburg, Freiburg, Germany; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

Background: Metabolites are often part of biochemical pathways, regularly in complex relations that may be influenced by genetic variants in the involved enzymes. Many of the metabolic reactions driving the biological network are non-linear (e.g. cyclic). Motivated by the success of deep learning-based approaches to detect complex patterns, we investigated whether such models can provide representations of metabolomics that capture their complex, non-linear relations and provide a link to the underlying genetics.

Methods: We present an integrated analysis of data from both plasma (1,096 metabolites) and urine (1,139 metabolites) via an unsupervised method for clustering and local dimension reduction in 4,850 individuals from the GCKD study, a prospective cohort of adults diagnosed with CKD. First, we group the metabolites into modules using a sparse hierarchical clustering approach. On each module, we fit a principal component (PC) analysis and train a variational autoencoder (VAE), a type of neural network, to infer low-dimensional representations of the central factors of variation underlying the data. We then search for genetic associations of these module representations by performing genome-wide association study (GWAS).

Results: We identified 165 modules of correlated metabolites. GWAS identified significant associations (p-values<5e-8/165) with81 VAE- and 150 PC-informed representations of these clusters. An association at *NAT8* showed 575 magnitudes lower p-values when investigating metabolite modules (p-value=2.1e-2217) compared to analyses of its individual metabolites. The strongest association was observed for *PYROXD2* (module p-value=1.4e-3275). This module integrated the plasma and urine levels of six methyllysine-related metabolites, and displayed independent associations with genetic variants in *PYROXD2*, *NAT8*, their interaction, eGFR and UACR in multivariate models. This suggests interactions between these two enzymes and a core role of plasma N6-methyllysine in these associations.

Conclusions: Our results show that VAE- and PC-based representations of metabolic pathways can facilitate the detection of genetic associations beyond those identified by single-metabolite GWAS, indicating existing linear and non-linear genetic regulation on a pathway level.

Funding: Commercial Support - Bayer Pharma AG, Government Support - Non-U.S.

TH-OR21

Hb Co-Pilot: Machine Learning Algorithm for Real-Time Hemoglobin Estimation during Hemodialysis and a Multicenter International Validation Trial

Chin-Chi Kuo,[1,2] Sheng-Hsuan Chen,[1] Hsiu-Yin Chiang,[1] Chuan-Hu Sun,[1] Mei-Chuan Hsieh,[1] Che-yi Chou,[3,2] Stephen G. Holt.[4] *[1]Big Data Center, China Medical University Hospital, Taichung, Taiwan; [2]China Medical University Hospital Department of Internal Medicine, Taichung, Taiwan; [3]Asia University Hospital, Taichung, Taiwan; [4]SEHA Kidney Care, Abu Dhabi, United Arab Emirates.*

Background: Anemia is linked to premature death among patients receiving hemodialysis (HD). We developed and validated a timely, non-invasive, and simple smartphone APP (Hb Co-Pilot) that captures images of HD dialysis tube and predicts hemoglobin (Hb) level using a machine-learning model.

Methods: **Training & Testing Set** We enrolled adult HD patients with arteriovenous fistula (AVF) or graft at China Medical University Healthcare System (CMUHS). HD tubing photos on Fresenius 4008(s) machine were taken with a color correction matrix (CCM) on the day of blood testing. A total of 5,453 images were taken by 13 smartphones from 5 HD centers. **Feature Extraction & Modeling** Images were pre-processed to ensure similar lighting conditions. We cropped the areas of HD tube and CCM and extracted the 192-dimension vector of image features from both areas by encoding the color information in histograms using a bin size of 64 on each RGB channel. An XGBoost model was used to predict Hb >10 g/dL using image features, age, gender, and last Hb level, with a testing accuracy of 0.93. **Validation Trial** CMUHS, Asia University Hospital (AUH) in Taiwan, and SEHA Kidney Care (SKC) in Abu Dhabi participated in our validation trial, with a total of 504 images collected. The targeted area under the receiver operating curve (AUROC) was set to 0.80.

Results: In the validation study, the median age was 62 years, 67% were male, 40% from SKC, 85% had AVF, 26% had Hb ≤10 g/dL, and 40% were taken from Fresenius 5008. The mean of difference between predicted and true Hb was 0.83 g/dL. The AUROC and accuracy was both 0.81, and the sensitivity and positive predictive value both reached 0.87. The F1 and Kappa was 0.87 and 0.50, respectively.

Conclusions: Hb Co-Pilot had robust external validity in Taiwanese and Emirati across different dialysis machines. Model improvement will focus on capturing extreme Hb levels and evaluating its clinical effectiveness.

Funding: Government Support - Non-U.S.

Table 1. Model performance of the Hb Co-Pilot for predicting Hb > 10 g/dL.

	CMUH	AUH	SKC	All 3 sites
N	202	100	202	**504**
AUROC	0.87	0.75	0.83	**0.81**
Accuracy	0.83	0.76	0.82	**0.81**
Sensitivity	0.88	0.85	0.87	**0.87**
Specificity	0.66	0.61	0.64	**0.64**
PPV	0.89	0.78	0.90	**0.87**
NPV	0.62	0.72	0.57	**0.63**
F1 score	0.89	0.82	0.88	**0.87**
Kappa	0.5253	0.4746	0.4836	**0.5024**

Abbreviations: AUH, Asia University Hospital; AUROC, area under the receiver operating curve; CMUHS, China Medical University Healthcare System; NPV, negative predictive value; PPV, positive predictive value; SKC, SEHA Kidney Care.

TH-OR22

Artificial Intelligence-Enabled Electrocardiography for Predicting Dyskalemia Using Home-Based Electrocardiography Devices

Shih-Hua P. Lin, Chih-Chien Sung, Ang Lu, Chien-Chou Chen, Chin Lin. *Tri-Service General Hospital, Taipei, Taiwan.*

Background: Dyskalemia is the common electrolytes abnormality associated with an increased morbidity and mortality. We have developed a bloodless artificial Intelligence-enabled electrocardiogram (AI-ECG) system capable of predicting hyperkalemia and hypokalemia using Philips ECG devices and providing quantitative serum potassium (K^+) detection and monitoring. This study aims to validate the application of a newly-developed home-based ECG device for dyskalemia detection.

Methods: Home-based ECG device is a portable 12-lead ECG machine developed by QT Medical (PCA500). We conducted a preliminary study with 107 hospitalized patients for various causes including acute kidney injury and advanced CKD on hemodialysis at a single academic medical center, resulting in 1033 ECG recordings. Among them, eighty-eight

ECGs had the corresponding serum K^+ concentration measured within the previous three hours. The dataset included 12 patients with hyperkalemia (Lab-K^+ ≥ 5.5 mmol/L) and 11 hypokalemia (Lab-K^+ ≤ 3.5 mmol/L).

Results: The AI-ECG system demonstrated an AUC of >0.95 for predicting hyperkalemia and an AUC of 0.809 for hypokalemia. The correlation coefficient between ECG-derived K^+ levels (ECG-K^+) and laboratory-measured K^+ levels (Lab-K^+) was 0.796, with a mean absolute error (MAE) of 0.456

Conclusions: Using this home-based ECG device, these results show that AI-ECG predict hyperkalemia better than hypokalemia and may be applied to future remote detection or monitoring of hyperkalemia in high-risk patients. A further validation with larger sample sizes is still required to confirm these findings.

TH-OR23

Automated Extraction of Kidney Failure Concepts from Clinical Notes Using Artificial Intelligence

Luke Harris,[1] Samuele Buosi,[2] Sarah Monahan,[1] Finn Krewer,[1,4] Mohan Timilsina,[2] Niamh Corcoran,[1] Nina Deacon,[1] Michael Wrynn,[1] Richard Farnan,[1] Donal N. Reddan,[1] George S. Mellotte,[3] Peter J. Conlon,[5] Conor S. Judge.[1,4]
[1]Galway University Hospitals, Galway, Ireland; [2]Insight Data Analytics, University of Galway, Galway, Ireland; [3]HSE National Renal Office, Dublin, Ireland; [4]HRB Clinical Research Facility, Galway, Ireland; [5]Beaumont Hospital, Dublin, Ireland.

Background: The Kidney Disease Clinical Patient Management System (KDCPMS) contains structured (e.g. date of birth) and unstructured or free-text data fields (clinic notes). Unstructured data is challenging to use for audit, QI and research.

Methods: Bidirectional Encoder Representations from Transformers (BERT) are a transformer-based machine learning architecture useful for Natural Language Processing (NLP). Galway University Hospital data were extracted from KDCPMS, anonymised, pre-processed, annotated as Diabetes-Y/N and IgA Nephropathy-Y/N by physicians using Prodigy annotation software, and NLP model trained using a modified BERT algorithm running in HSE Integrated Information Services. We compared the NLP classification with an algorithmic classification using ICD-10/EDTA codes, medication and HbA1c and a retrospective chart review by physicians (gold standard).

Results: 43314 patient notes were extracted. 10000 notes were annotated by 5 physicians. Classification was performed on 33314 notes. 955 patients were classified as Diabetes-Y, 4190 as Diabetes-N, 269 as IgA Neph-Y and 2609 as IgA Neph-N. 1744 patients were then classified algorithmically as Diabetes-Y and 214 patients were classified algorithmically as IgA Neph-Y. For Diabetes, the NLP method achieved an accuracy of 79.0% (95% CI [77.4%,80.6%]), a sensitivity of 73.3% and specificity of 81.3%. Precision was 61.1%, F1 score 66.7% and macro F1 score 0.757. The algorithmic method outperformed the NLP method with an accuracy of 98.1% (95% CI [97.5%,98.6%]), sensitivity 96.7% and specificity 98.7%. Precision was 96.7%, F1 score 96.7% and macro F1 score 0.977. For IgA Nephropathy, the NLP method demonstrated high accuracy of 96.2% (95% CI [95.1%,97.2%]), with sensitivity 83.3% and specificity 97.8%. Precision was 83.3%, F1 score 83.3% and macro F1 score 0.906. The algorithmic method achieved perfect scores across all metrics, with accuracy, sensitivity, specificity, precision, F1 score, and macro F1 score all at 100.0% (95% CI [99.9%,100%]).

Conclusions: These results highlight the superior performance of the algorithmic method over the NLP method, particularly in terms of accuracy and sensitivity. However the NLP method demonstrated substantial potential, especially for IgA Nephropathy.

Funding: Government Support - Non-U.S.

TH-OR24

Improving Dietary Choices Using a Digital Health Intervention in People with CKD

Courtney J. Lightfoot, Gurneet K. Sohansoha, Ella C. Ford, Noemi Vadaszy, Thomas J. Wilkinson, Alice C. Smith, Matthew Graham-Brown. *University of Leicester, Leicester, United Kingdom.*

Background: We co-developed a digital health intervention (DHI) 'My Kidneys & Me' (MK&M) to support people with non-dialysis CKD to better self-manage health and lifestyle. MK&M includes theory-based educational and action (behaviour change) sessions about a healthy balanced diet, plus trackers for dietary goals. Here we report findings on dietary behaviours from a multicentre randomised control trial of MK&M.

Methods: 420 participants aged ≥18 years with CKD stages 3-4 were recruited from 26 hospitals and randomised 2:1 to intervention (MK&M) (n=280) or control (n=140) groups. The UK Diabetes Diet Questionnaire (UKDDQ) was collected at baseline and 20-weeks via an online survey. The UKDDQ asks respondents how often they consumed certain foods and drinks over the last month. Items are scored on the frequency of consumption and classified into "healthy", "less healthy" and "unhealthy" choices. Access to and usage data of MK&M were collected. Linear regression models, adjusted for baseline values, were conducted.

Results: Of the 280 participants assigned to the intervention group, 225 (80%) used MK&M at least once. Over 20-weeks, the diet educational session was accessed by 107 (48%) participants and viewed 10.5 (±5.4) times for 11.0 (±15.0) minutes; the diet action session was accessed by 77 (35%) participants and viewed 12.1 (±5.7) times for 7.5 (±6.7) minutes. The healthy eating tracker was used by 32 (14%) participants. 30 (13%) participants set healthy eating goals (mean:1.6±1.2). At baseline, 44% MK&M (n=122) and 40% control (n=55) participants had a UKDDQ score in the healthy range (≥4) (mean:3.3±0.4). At 20-weeks, the proportion with a UKDDQ in the healthy range increased by 45% in MK&M group (44-64%, P<0.001) and 28% in control (40-51%, P<0.001). Significant between-group differences were observed for changes in the number of healthy (±0.8, P=0.024) and less healthy dietary choices (±0.5, P=0.027), with MK&M group increasing the number of healthy food choices (+0.7, P=0.005) and decreasing the number of less healthy food choices (-0.6, P=0.009).

Conclusions: The use of MK&M DHI improved dietary food choices. People with CKD are interested in and actively engaged with DHIs to support healthy dietary habits. MK&M can be used to support people with CKD to improve their dietary behaviours.

TH-OR25

Enhancing Nephrology with Artificial Intelligence (AI)-Assisted ICD-10 Coding: Improving Health Care Reimbursement, Patient Care, Research, and Previsit Test Workflow Efficiency through Case Scenarios

Yasir Abdelgadir, Charat Thongprayoon, Jing Miao, Justin Pham, Supawadee Suppadungsuk, Iasmina Craici, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Accurate ICD-10 coding is crucial for healthcare reimbursement, patient care, and research. Inaccuracies in coding, can lead to issues with reimbursement, compromised patient care and skewed research findings. These challenges stem from the complexity and time-consuming nature of coding tasks, burdening physicians. AI, such as ChatGPT, has the potential to improve accuracy and reduce workload. A recent study showed that large language models (LLMs) performed poorly on medical code querying tasks. However, the assessment of AI-assisted ICD-10 coding in nephrology through case scenarios for pre-visit testing remains unexplored.

Methods: This study involved 100 simulated cases covering various nephrology conditions. Two nephrologists created these cases to mirror typical nephrology diagnoses in inpatient and outpatient settings, incorporating case scenarios and pre-visit testing data. The performance of ChatGPT versions 3.5 and 4.0 was assessed by comparing AI-generated ICD-10 codes against expected correct codes for each case. Assessments were conducted in two trials, two weeks apart, in April 2024.

Results: ChatGPT 3.5 reached an average accuracy of 89% over two trials, with a slight variation between them (91% in the first trial and 87% in the second). ChatGPT 4.0 showed a consistent and higher accuracy of 99% in both trials. This indicates that 94% of the AI-coded diagnoses correctly matched the expected ICD-10 codes. However, specific challenges were noted with ChatGPT 3.5, particularly with repeated inaccuracies in diagnosing conditions like Obstructive uropathy due to BPH and Acute Emphysematous Pyelonephritis. ChatGPT 4.0 demonstrated a more stable performance, with only one repeated misdiagnosis (Bartter Syndrome) across the trials.

Conclusions: The findings suggest that AI, particularly ChatGPT 4.0, can significantly improve the accuracy of ICD-10 coding in nephrology when provided with case scenarios and pre-visit testing data. This approach can enhance healthcare reimbursement, patient care, research, and pre-visit test nephrology workflow efficiency. However, the small percentage of errors highlights the need for ongoing review and improvement of AI diagnostic systems.

TH-OR26

Using a Smartphone Camera at the Bedside to Detect and Quantify Residual Blood Clots in Single-Use Dialyzers with Paired-Image Classification

Hugo Y. Lin,[1,2] Yi-Ren Yeh.[3] *[1]Kaohsiung Medical University Chung Ho Memorial Hospital, Kaohsiung, Taiwan; [2]Kaohsiung Municipal Ta-Tun Hospital, Kaohsiung, Taiwan; [3]National Kaohsiung Normal University, Kaohsiung, Taiwan.*

Background: Blood clot formation and subsequent blockage of the capillary fibers of dialyzers is challenging for patients with end-stage kidney disease (ESKD) on hemodialysis. This study aimed to develop a machine learning detection model that utilizes the information obtained from dialyzer images to detect blood clots of dialyzers early.

Methods: We gather dialyzer images captured at the bedside using mobile devices daily. Initially, we segment the image to extract the dialyzer part and filter out background noise unrelated to the residual blood clot analysis. Subsequently, we apply data augmentation to enhance robustness. Capturing snapshots at both ends of the dialyzer provides two distinct perspectives merged into a single composite image. Our classification task involves two classes: instances with less than 10% residual blood clots (666 samples) and those with 30% residual blood clots (538 samples). Due to the limited image dataset, we utilize a pre-trained image classification model, EfficientNet, and fine-tune it using our collected data.

Results: In our experiment, we strategically split the dataset into training (60%), validation (20%), and testing (20%) sets. Conducting ten random trials provided insights into the model's stability and consistency. The proposed model achieved an average recognition rate of 76.33%, surpassing human evaluators who scored 62.71% and 60.05% on the testing set. It demonstrates the model's superior performance and potential to enhance recognition capabilities in relevant domains. The results prove the viability of employing image-based approaches for detecting blood clots in dialyzers.

Conclusions: Our proposed framework, including data preprocessing and model training, exhibits potential for applications in various clinical scenarios where recognition relies on information derived from images. This approach involves using image data to amalgamate information from both ends of the dialyzer. By employing the EfficientNet model to detect blood clots, this integrated approach significantly improves blood clot detection in dialyzers compared to human evaluators.

Funding: Government Support - Non-U.S.

TH-OR27

Performance and Global Integration in Clinical Practice of a Fistula Failure Risk-Estimate Tool Based on Artificial Intelligence (AI)

Jasmine Ion Titapiccolo,[1] Milind Nikam,[2] Stefano Stuard,[3] Jeffrey L. Hymes,[4] John W. Larkin,[4] Suman K. Lama,[4] Sheetal Chaudhuri,[4] Francesco Bellocchio,[1] Julianna Yeung,[2] Len A. Usvyat,[4] Luca Neri.[1] *[1]Fresenius Medical Care AG, Vaiano Cremasco, Italy; [2]Fresenius Medical Care AG, Singapore, Singapore; [3]Fresenius Medical Care AG, Bad Homburg, Germany; [4]Fresenius Medical Care AG, Boston, MA.*

Background: Accurate prediction of fistula failure risk (FFR) in hemodialysis patients is critical for timely intervention and improved clinical outcomes. This study evaluates the performance of an AI-based FFR estimate tool in clinical practice. The data, collected over 12 months (February 2023-January 2024), encompass multiple countries, highlighting variations in clinical outcomes.

Methods: Data were collected from hemodialysis centers in seven countries (Australia, Czech Republic, Italy, Portugal, Singapore, Slovakia, Spain), totaling 83,126 records. The AI risk estimation tool is integrated in the clinical system EuCliD® (Fresenius Medical Care) and provides nephrologists with a monthly estimate of FFR over the next 90 days. Predictive accuracy in comparison with actual failure incidence was assess using AUC of ROC curve. Fistula failures include angioplasty (with/without stent), thrombectomy, switch to a new dialysis access, temporarily unusable fistula, and hospitalization due to fistula complication.

Results: The AI tool exhibited a varied performance across countries, with the global AUC being 78.1%. The global failure incidence percentage was 6.2%. Failure percentages for each of the four considered categories are reported in Table 1. Differences in the habit of reporting data in the clinical system can be highlighted from the table. Risk metrics also varied across countries.

Conclusions: The AI-based FFR estimate tool demonstrated robust predictive performance across diverse clinical settings. The depicted variability shows the importance of localized adaptation of AI tools.

Funding: Commercial Support - Fresenius Medical Care, Private Foundation Support

					Vascular Access (VA) failure categories			
Country	#	AUC	Failure Incidence (Count)	Fistula Failure Risk	Angioplasty/ Thrombectomy : Incidence (Count)	Switch to new VA: Incidence (Count)	Temporarily unusable fistula: Incidence (Count)	Hospitalization due to VA: Incidence (Count)
Australia	7512	70.3%	5.1% (386)	5.4±6.0%	78.2% (302)	25.4% (98)	8.8% (34)	3.4% (13)
Czech Republic	9997	79.2%	8.5% (854)	8.4±10.6%	83.5% (713)	26.6% (227)	5.7% (49)	0% (0)
Italy	13184	79.9%	2.6% (342)	3.4±5.4%	56.4% (193)	68.7% (235)	37.7% (129)	7.6% (26)
Portugal	15714	77.5%	9.3% (1464)	7.8±9.5%	92.8% (1358)	21.1% (309)	9.7% (142)	0.2% (3)
Singapore	9795	71.5%	8.3% (808)	5.6±6.2%	87.5% (707)	16.1% (130)	8.9% (72)	6.7% (54)
Slovakia	10214	74.8%	3.6% (368)	5.7±8.6%	45.4% (167)	75.8% (279)	17.7% (65)	1.6% (6)
Spain	16710	79.1%	5.3% (891)	4.8±7.0%	73.3% (653)	50.1% (446)	22.5% (200)	0.1% (1)

Table 1. Overview of the Fistula Failure Risk (FFR) tool performance across countries. FFR is reported in terms of mean±std. Total sum of failure causes can be higher than 100% because the four causes of failure are not mutually exclusive.

TH-OR28

Heparin Variants Differ in Their Effect on Fibroblast Growth Factor 23 and Fibroblast Growth Factor Receptor 4 Binding

Madison Thomas, Christopher Yanucil, Qing Li, Kylie Heitman, Abul Fajol, Svetlana Komarova, Christian Faul. *The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.*

Background: Fibroblast growth factor (FGF) 23 is a bone-derived hormone that targets the kidney via FGF receptor (FGFR) isoform 1c and klotho and increases phosphate excretion. In Chronic Kidney Disease (CKD) patients, renal FGF23-responsiveness is impaired, leading to high serum FGF23 levels that clinical studies have shown to be associated with cardiac hypertrophy and cardiovascular mortality. In previous studies we found that elevated FGF23 can directly target cardiac myocytes and activate FGFR4 in a klotho-independent manner, resulting in hypertrophic cell growth. Surprisingly, we also found that unfractionated heparin (UFH) increases the FGF23:FGFR4 binding affinity and when injected into mice with elevated FGF23 levels aggravates cardiac hypertrophy. Heparin exists in different variants with a large range of structures and charges. In this study, we investigate whether heparin variants differ in their ability to modulate FGF23:FGFR4 binding.

Methods: FGF23:FGFR4 binding affinity was analyzed using our plate-based binding assay. 96-well plates were coated with recombinant FGF23 protein and sequentially incubated with heparin variants, Fc-tagged FGFR4, horse radish peroxidase (HRP)-coupled anti-Fc antibody, and HRP substrate. Reactions were analyzed using a plate reader at 450 nm wavelength. All samples were run in triplicates.

Results: FGF23:FGFR4 binding affinity was increased by large UFHs, including dialysis UFH, and by low-molecular heparins. In contrast, smaller heparin variants, like the pentasaccharide fondaparinux sodium, did not increase FGF23:FGFR4 binding. Desulfated heparins only had a minor impact on FGF23:FGFR4 binding.

Conclusions: Our study indicates that the ability of heparin to mediate FGF23:FGFR4 binding depends on its length and negative charges. Small and uncharged heparin variants do not increase FGF23:FGFR4 binding affinity. Next, we will test the effects of heparin variants on FGF23-induced cardiac hypertrophy in cell culture and animal models. Most patients with end-stage kidney disease undergo hemodialysis, during which UFH is commonly administered as an anticoagulant. Since hemodialysis does not lower serum FGF23 levels, we postulate that frequent UFH infusions contribute to cardiac injury and high mortality rates and that replacing UFH with small-chain heparin variants might extend the lifespan of hemodialysis patients.

Funding: NIDDK Support, Private Foundation Support

TH-OR29

Association of the Ratio of Intact-to-C-terminal Fibroblast Growth Factor 23 with Heart Failure with Preserved Ejection Fraction

Cassianne Robinson-Cohen,[1] Farzana Perwad,[2] Joachim H. Ix,[4] Valentin David,[3] Elvis A. Akwo.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of California San Francisco, San Francisco, CA; [3]Northwestern University Feinberg School of Medicine, Chicago, IL; [4]University of California San Diego, La Jolla, CA.*

Background: Previous studies report an association between high levels of circulating fibroblast growth factor 23 (FGF23) and the risk of heart failure with preserved ejection fraction (HFpEF) particularly in chronic kideney disease (CKD). One such mechanism for FGF23 elevation is decreased proteolytic cleavage marked by increased circulating intact-to-C-terminal FGF23 ratio (iFGF23:cFGF23). The aim of this study was to investigate the association between the iFGF23:cFGF23 ratio and the risk of HFpEF using a two-sample Mendelian Randomization (MR) approach.

Methods: Genetic instruments were independent significant single nucleotide polymorphisms (SNPs) from a genome-wide association study (GWAS) of iFGF23:cFGF23 ratio in 745 participants in the Cardiovascular Health Study. Summary-level data for HFpEF were from a GWAS conducted among 17,030 participants in Vanderbilt's DNA Biobank (BioVU). The main analysis was conducted using the random-effects inverse variance weighted (IVW) estimator. Sensitivity analyses used the weighted median and MR-Egger methods. Analyses were performed separately in individuals of European and African ancestry and then meta-analyzed.

Results: In the transethnic meta-analysis, genetically predicted higher values of the iFGF23:cFGF23 ratio were associated with greater odds of HFpEF (OR=1.07, 95% CI: 1.02-1.12, p=0.007). The MR estimate was consistent in models adjusted for eGFR (OR=1.06, 95%CI: 1.02-1.12, p=0.02) and across statistical approaches (weighted median and MR-Egger). The p-value for the MR-Egger intercept test was consistently greater than 0.05 across analytic subgroups suggesting no evidence of directional pleiotropy.

Conclusions: This MR suggests that higher values of iFGF23:cFGF23 – a marker of decreased FGF23 cleavage – is associated with greater risk of HFpEF. Additional work into the mechanisms of FGF23 elevation in CKD and its relationship with heart failure is needed.

Funding: NIDDK Support

TH-OR30

Involvement of COMMD5 in Vascular Calcification in CKD

Zewen Zhao, Shuangxin Liu. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: Chronic kidney disease (CKD) is a prevalent and recurring health condition affecting a significant number of individuals. Among CKD patients, approximately 2-3% progress to end-stage renal disease (ESRD). Vascular calcification emerges as a prevalent complication in ESRD cases and has a strong correlation with the incidence of cardiovascular events. The disruption of calcium and phosphorus metabolism stands out as a primary factor contributing to vascular calcification. Recently, the hypertension-associated calcium regulatory gene (HCaRG) unveiled a connection with COMM domain-containing 5 (COMMD5). Identified as a gene influenced by extracellular calcium levels, COMMD5 encodes a compact intracellular protein composed of 225 amino acids. Past research suggests that parathyroidectomy (PTX) can reduce vascular calcification, and increased levels of COMMD5 are associated with decreased blood pressure. Nevertheless, the literature lacks substantial reports on the relationship between COMMD5 and vascular calcification. Our hypothesis ventures that COMMD5 could indeed be intricately linked to chronic vascular calcification.

Methods: The blood vessels of the arteriovenous fistula are tested for calcification and COMMD5 expression. Human aortic smooth muscle cells (HASMC) and rat aortas were cultured in vitro and incubated with high phosphorus.

Results: (1)COMMD5 expression is reduced in arteriovenous fistula vascular calcified tissues.(2)In comparison to the control group, the expression of COMMD5 in HASMC exhibited lower levels under high phosphorus stimulation.(3)HASMCs were subjected to stimulation using small interfering RNA (siRNA). This led to an upregulation of Runt-related transcription factor 2 (RUNX2) expression and downregulation of Anti-Smooth Muscle Antibody (α-SMA) expression in the cells.(4)Rat aortas were cultured in vitro and incubated with high phosphorus to stimulate isolated arteries. Upon conducting alizarin red staining, the group incubated with COMMD5 under high phosphorus stimulation displayed reduced levels of calcification in comparison to the high phosphorus group.

Conclusions: COMMD5 plays a crucial role in inhibiting calcification in human aortic smooth muscle cells, consequently contributing to the reduction of vascular calcification.

Funding: Government Support - Non-U.S.

TH-OR31

Spatial Detection and Consequences of Nonkidney Calcitriol Production as Assessed by Targeted Mass Spectrometry Imaging

Mark B. Meyer,[1] Seong Min Lee,[1] Shannon R. Cichanski,[1] Diego F. Cobice,[3] J. W. Pike.[2] *[1]University of Wisconsin-Madison Department of Nutritional Sciences, Madison, WI; [2]University of Wisconsin-Madison Department of Biochemistry, Madison, WI; [3]Ulster University, Coleraine, United Kingdom.*

Background: The benefits of vitamin D supplementation beyond calcium and phosphate maintenance in humans are highly clinically debated. Kidney expression of CYP27B1 is the source of endocrine $1,25(OH)_2D_3$ (active form of vitamin D) that maintains serum calcium and phosphate. $1,25(OH)_2D_3$ may also be made by the CYP27B1 enzyme in non-renal cells, like immune cells, in a process driven by cellular availability of precursor $25(OH)D_3$ and inflammation. Due to the endocrine nature of renally produced $1,25(OH)_2D_3$ in circulation, it is difficult to discern between these two sources.

Methods: We have recently created a regulatory deletion model of *Cyp27b1* (M1/M21-DIKO) where the mice have normal inflammatory-regulated *Cyp27b1* expression in non-renal tissues (unlike global *Cyp27b1*-KO), but no expression within the kidney. Using these unique M1/M21-DIKO mice, we hypothesized that vitamin D supplementation will increase $25(OH)D_3$ circulation and tissue availability, and therefore increase the production of $1,25(OH)_2D_3$ in non-renal tissues. Utilizing on-tissue chemical derivatization (OTCD) and targeted Matrix Assisted Laser Desorption Ionization-Mass Spectrometry Imaging (MALDI-MSI), we investigated the tissue distribution of $1,25(OH)_2D_3$ and $25(OH)D_3$ in the M1/M21-DIKO mice compared to *Cyp27b1*-KO mice and wildtype littermates after PBS perfusion in the kidney, liver, spleen, and thymus.

Results: MALDI-MSI demonstrated that the levels of $25(OH)D_3$ were greatly affected by vitamin D supplementation and increased in all tissues examined. We confirmed that the M1/M21-DIKO mouse, like the *Cyp27b1*-KO mouse, had no kidney production of $1,25(OH)_2D_3$ even in the animals with high levels of supplementation. However, we saw increased production of $1,25(OH)_2D_3$ in tissues outside of the kidney such as the spleen in the M1/M21-DIKO mouse. Gene expression found increased *Il4* and decreased *Tnfa* in the spleen indicating an initiation of an anti-inflammatory program as observed with vitamin D in immune cells *ex vivo*.

Conclusions: Taken together, these data verify, visualize, and quantify, for the first time, non-renal production of $1,25(OH)_2D_3$ *in vivo*, provide a consequence of non-renal $1,25(OH)_2D_3$ production in cytokine changes, and offer a benefit to elevated vitamin D supplementation in potential positive outcomes for inflammatory disease.

Funding: NIDDK Support, Other NIH Support - NHLBI - HL159645

TH-OR32

Bone Sialoprotein Regulates Phosphate Metabolism and Reduces Hyperparathyroidism in Mice with CKD

Marie-Helene Lafage-Proust,[1,2] Lauriane Hivert,[1] Christophe O. Soulage,[3,4] Laurent Beck,[5,6] Luc Malaval.[1] Sainbiose Lab. *[1]Université J Monnet, Inserm U1059, Saint-Etienne, France; [2]Chu Saint-Etienne, Saint-Etienne, France; [3]Université Lyon 1, Lyon, France; [4]INSA, Lyon, France; [5]UMR_S 1087 / UMR_C 6291 l'Unité de Recherche de l'Institut du Thorax, Nantes, France; [6]Nantes Universite, Nantes, France.*

Background: Bone Sialoprotein (BSP), Osteopontin (OPN), DMP1 and MEPE, regulate bone mineralization and are closely co-regulated. While DMP1 and MEPE are known to impact phosphate (Pi) metabolism, we hypothesized that BSP might also influence body Pi handling.

Methods: Nine-week-old (WT) and BSP knockout (KO) mice fed a normal Pi diet (0.55% Pi, ND). We collected 24h urine, feces, blood, femur, kidneys and gut samples for biochemical and molecular analyses.

Results: WT and KO had normal Pi and FGF23 serum levels **(s)** but KO were hypophosphaturic (-75% vs WT). KO expressed lower NaPi2c renal transporter mRNA levels ($p<0.006$ vs WT) while NPT2b and Pit1/2 gut expression were similar to WT. We suspected impaired paracellular Pi gut absorption, a key pathway under ND. Indeed, KO exhibited significant higher water (200%), K^+ (50%), Na^+ and Pi levels in feces ($p<0.01$ vs WT). Multiplex gene expression analysis of gut revealed differential regulation of genes related to matrix remodeling, including higher DMP1, confirmed by RT-PCR (x10 in KO vs WT), BSP and MEPE mRNAs being undetectable. As Chronic kidney disease (CKD) raises systemic Pi load, increasing cardiovascular mortality, we hypothesized that lack of BSP could mitigate CKD-Mineral and Bone Disorders (CKD-MBD) by reducing Pi intestinal absorption. We performed 5/6 nephrectomy (Nx) or sham surgery on 20-wk-old WT and KO mice. After 3 months of CKD, both genotypes showed higher ureamia compared to their sham controls. However, FGF23 **(s)** rose less in Nx-KO compared to Nx-WT ($p<0.05$) while serum Pi remained normal. Fractional urine Pi excretion increased in both genotypes but remained twice lower in Nx-KO than in Nx-WT ($p<0.05$). After 3 months of high Pi diet (1.65% Pi, HP), Nx-KO were neither hypophosphaturic nor had lower FGF23 **(s)** compared to Nx-WT. In addition, KO displayed higher PTH serum levels (x1.5) and cortical porosity (μCT) compared to Nx-WT.

Conclusions: Deletion of BSP, a bone-specific protein, decreased gut paracellular Pi absorption, possibly involving DMP1, known to regulate Blood Brain Barrier permeability. In CKD and under ND, the blunting of FGF23 increase in KO suggests an adverse role of BSP in Pi homeostasis, while, under HP, BSP might protect against CKD-MBD by reducing secondary hyperparathyroidism and its harmful effects on cortical bone.

Funding: Commercial Support - KIOWA-KRIRIN

TH-OR33

Exercise Mimetic Restores Muscle and Bone Outcomes in a Rat Model of CKD

Ashley D. Troutman,[1] Neal X. Chen,[2] Shruthi Srinivasan,[2] Corinne E. Metzger,[2] Kalisha O'Neill,[2] Landon Tak,[2] Michael Schulte,[2] Sharon M. Moe,[2] Keith G. Avin.[2,1] *[1]Indiana University, Department of Physical Therapy, Indianapolis, IN; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: Chronic kidney disease (CKD) progressively deteriorates skeletal muscle and bone leading to sarcopenia and CKD-bone mineral disease (CKD-MBD). Exercise studies have demonstrated variable success, which supports the need for pharmacological interventions. We used an investigational drug, Locamidazole (LAMZ), with documented muscle and bone anabolic effects that mimic exercise. We hypothesized that LAMZ would improve physical function and bone outcomes in a rat model of CKD.

Methods: We used a naturally occurring and progressive rat model of CKD (Cy/+; n=10-12/gr): 1) normal littermates (NL), 2) Cy/+ (CKD), and 3) CKD-LAMZ (LAMZ). LAMZ s.q. injections, 2x/day at 0.625mg/kg for 5 weeks, beginning at 27 weeks (CKD stage 3). At 33 weeks (end-stage renal disease), rats were terminated for specimen collection. Outcomes: serum biochemistry, electrically stimulated muscle strength and fatigue (series of 50 muscle contractions), maximal running distance, bone microarchitecture, and vascular calcification. Data analysis included one-way ANOVA with Tukey's multiple comparisons test.

Results: *Disease Effects (CKD vs NL)*- CKD was confirmed via elevated blood urea nitrogen (BUN; $p<0.0001$) and creatinine ($p<0.0001$), muscle weakness ($p<0.05$), muscle fatigue ($p<0.01$), lower running distance ($p<0.05$), increased cortical bone porosity ($p<0.001$), and reduced cortical bone area ($p<0.01$), and cortical thickness ($p<0.001$). *LAMZ Effects (CKD-LAMZ vs CKD)*- LAMZ did not impact disease progression. LAMZ improved muscle function with significantly improved maximally stimulated muscle strength ($p<0.05$) and trending improvements for electrically stimulated muscle fatigue ($p=0.08$). LAMZ improved bone health with reduced cortical porosity ($p<0.01$) and increased cortical thickness ($p<0.01$). Maximal running distance demonstrated an intermediate level of adaptation (i.e., not statistically different from NL or CKD); additional samples pending for biochemistry and vascular calcification.

Conclusions: LAMZ administered for 5 weeks significantly improved both muscle strength and bone microarchitecture. The potential for an exercise mimetic is exciting for nephrologists and patients with CKD alike, as an alternative method to improve musculoskeletal health and quality of life.

Funding: Other NIH Support - Indiana University Indianapolis

TH-OR34

Noninvasive Method to Diagnose Renal Osteodystrophy: A Study on 19 Circulating MicroRNAs

Clement Vachey,[1,2] Roth-Visal Ung,[1] Sylvain Picard,[1] Marie-Eve Dupuis,[3] Thomas Nickolas,[4] Fabrice Mac-Way.[1,2] *[1]Centre de recherche du CHU de Québec-Université Laval Site Hôtel Dieu, Quebec, QC, Canada; [2]Universite Laval Faculte de Medecine, Quebec, QC, Canada; [3]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [4]Columbia University Irving Medical Center, New York, NY.*

Background: Current approach to manage bone fragility in chronic kidney disease (CKD) is in part based on assessment of bone turnover (BT) and mineralization. Prior work suggests that circulating microRNAs (miRNAs) identify low *vs* non-low cortical BT in CKD. We aimed to assess whether 19 miRNAs discriminate BT and biopsy proven contraindications (CI) to antiresorptive therapies (ART) in CKD patients.

Methods: Single-site cross-sectional study. Patients with stage 4-5 CKD having a high fracture risk underwent iliac crest bone biopsy for assessment of BT and mineralization levels according to ASBMR guidelines. Absolute CI to ART were defined by the presence of adynamic bone disease or osteomalacia. Relative CI were defined by the presence of mineralization defects without osteomalacia and low BT without adynamic bone. At the time of the biopsy, blood test were drawn for assessment of mineral biochemistry as per local standard and for measurement of 19 circulating miRNAs using the osteomiR kit (TAmiRNA, Austria). Each miRNA was compared between low *vs* high/normal BT, low/normal *vs* high BT, patients with absolute CI *vs* relative or no-CI to ART. Diagnostic accuracy was tested using the median and lowest tertile of each miRNA.

Results: Fourty four patients were included (women 56.8%, mean age 69.6±9.2, 45.4% dialysis). 19 had low BT, 16 normal, and 9 high BT; 7 patients had absolute CI to ART (2 osteomalacia, 5 adynamic bone). miRNA levels did not differ between low and normal/high BT groups. However, miRNA-31-5p was higher in patients with high BT (p=0,02), a value above the lowest tertile being associated with high BT status (sensitivity 100%, specificity 57,1% (95%CI: 40,8-73,5%), negative predicted value (NPV) 100%). We found 7 miRNAs (let7b5p, miRNA-141-3p, 143-3p, 17-5p, 19b-3p, 29b-3p, 550a-3p) with a very good capability to rule out CI to ART. A value above the median being associated with absolute CI to ART (sensitivity 85,7% (95%CI: 59, 8-100%), specificity<60%, NPV 95.5% (95%CI: 86.8-100%)). A value above the lowest tertile was even more discriminant (NPV 100% for 5/7).

Conclusions: Circulating miRNAs can help clinical decision in the approach of bone fragility in CKD. Large studies in heterogeneous cohorts are needed to validate these results.

TH-OR35

Reliability of Time-Lapse High-Resolution Peripheral Quantitative CT (HR-pQCT) in Determining Bone Remodeling in Patients with ESKD

Minhao Zhou,[1] Saghi Sadoughi,[1] Lauren Go,[1] Isabel Yu,[2] Po-hung Wu,[1] Isra Saeed,[1] Bo Fan,[1] Isidro B. Salusky,[3] Thomas Nickolas,[4] Joachim H. Ix,[5] Galateia J. Kazakia.[1] *[1]University of California San Francisco, San Francisco, CA; [2]University of California Berkeley, Berkeley, CA; [3]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [4]Columbia University Irving Medical Center, New York, NY; [5]University of California San Diego Department of Medicine, La Jolla, CA.*

Background: Patients with end-stage kidney disease (ESKD) have elevated fracture risk in part due to abnormally high or low bone turnover, requiring treatment from patient-specific turnover assessments. However, a reliable, accessible, and non-invasive tool to determine turnover in individual patients does not exist. High-resolution peripheral quantitative computed tomography (HR-pQCT) captures high-resolution in vivo bone microstructure. Time-lapse (TL) analysis uses longitudinal spatially-aligned HR-pQCT scans to evaluate temporospatial bone remodeling (**FigA**). This work evaluates the feasibility of TL HR-pQCT to assess turnover in patients with ESKD. We hypothesized that a 2-month TL period could capture remodeling in ESKD.

Methods: Distal tibia and radius scans were acquired on XtremeCT II. Bone formation and resorption fraction (BFF and BRF) were evaluated with respect to baseline integral, cortical, and trabecular bone volumes. Total and net bone turnover (TBT and NBT) were calculated as BFF+BRF and BFF-BRF, respectively (**FigB**). All rates were annualized (%/year). Annualized least significant change (LSC) in remodeling was established from a cohort of 15 healthy participants scanned twice ~1 year apart.

Results: Eight patients with ESKD on dialysis underwent 2 scans ~2 months apart (mean months on dialysis: 46; **FigC**). TL analysis showed that BFF and BRF in the ESKD cohort were >2- and >6-fold higher than the respective LSC (**FigD-E**). Radius cortical bone loss of 10.6%/year was found in ESKD (**FigE**).

Conclusions: This study showed that individual bone remodeling in ESKD can be captured by TL HR-pQCT in a 2-month TL period, shorter than that needed for gold standard tetracycline double-labeled bone biopsy. The assessed trabecular BFF in ESKD (9.6-21.3%/year) agrees with reported histomorphometric formation (3.5-22.4%/year), and the observed cortical bone loss aligns with known ESKD pathology, both verifying the reliability of TL HR-pQCT in ESKD bone turnover assessments. Future work will further validate TL HR-pQCT.

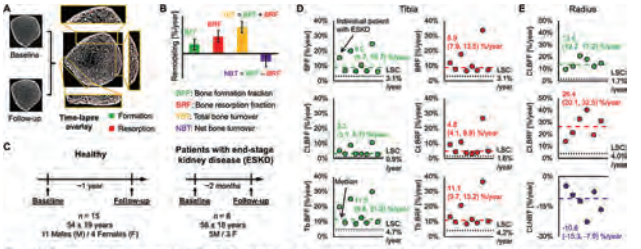


Fig (A) Representative sequential HR-pQCT scans with the time-lapse (TL) overlay visualizing bone remodeling in a patient with ESKD. **(B)** TL HR-pQCT turnover metrics. **(C)** Study design. **(D)** TL HR-pQCT turnover metrics at the distal tibia, presented as annualized median (interquartile range) by dashed lines for the integral bone, cortical (Ct.), and trabecular (Tb.) bone in ESKD (circles) vs. respective LSC (dotted lines). **(E)** TL HR-pQCT turnover metrics at the distal radius in the cortical bone, highlighting the cortical bone loss with ESKD.

TH-OR36

Acute Effect of High Fat Intake on Urinary Acidification Parameters in Uric Acid Stone Formers and Non-stone Forming Controls

Alireza Zomorodian, Xilong Li, Naim M. Maalouf, Orson W. Moe, Khashayar Sakhaee. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: The prevalence of uric acid nephrolithiasis (UAN) has increased contemporaneously with obesity and metabolic syndrome in recent decades. The key pathogenic factor in UAN is acidic urine pH (< 5.5), which results from reduced buffering of H^+ by ammonia ($NH_3 + H^+ \rightarrow NH_4^+$). Ammoniagenesis by the renal proximal tubule (PT) consumes amino acids and generates ATP. In this study, we tested whether provision of free fatty acid (FFA) as an alternative energy (ATP) precursor impairs renal ammoniagenesis in uric acid stone formers (UASF) and controls (Ctrl) by substrate competition.

Methods: Seven UASF and eight BMI-matched Ctrl were equilibrated on a fixed metabolic diet for 4 days. After sampling fasting urine and blood, subjects received an oral fat load (heavy cream 0.50 ml/kg body weight) hourly for 10 hours. Blood and urine samples were collected every 2 hours during this period. Outcomes: urine acid-base parameters and blood FFA and ketone bodies (KB).

Results: Both groups showed significant and similar increases in serum FFA and KB following the fat load. Urine pH (UpH) progressively decreased from 6.6 to 5.6 in the Ctrl group over the 10-hour period ($p < 0.001$), while UpH started lower (5.3) in the UASF group and remained unchanged over 10 hrs (p=0.59). While the fraction of net acid excretion (NAE) in the form of ammonium (NH_4^+) (NH_4^+/NAE) was notably lower in fasting urine in the UASF group compared to Ctrl ($p = 0.002$), this ratio significantly decreased in both groups during the 10-hour fat load (Ctrl: $p < 0.001$; UASF: $p = 0.01$).

Conclusions: Acute elevation in serum FFA by an oral fat load leads to a reduction in urine pH and NH_4^+/NAE in Ctrl, to levels comparable to UASF. These findings are compatible with a substrate switch, whereby high FFA provision in UASF reduces amino acid metabolism and nitrogen provision for ammoniagenesis, resulting in aciduria and predisposition to UAN.

Funding: NIDDK Support, Private Foundation Support

TH-OR37

Predictors of the Plasma and Fecal Metabolomes in CKD: The CRIC Gut Study

Amanda H. Anderson,[1] Robin L. Baudier,[2] Shuo Bai,[3] Hongzhe Li,[4] Gary Wu.[4] The CRIC Study. *[1]The University of Alabama at Birmingham School of Public Health, Birmingham, AL; [2]Oregon Health & Science University, Portland, OR; [3]Tulane University, New Orleans, LA; [4]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

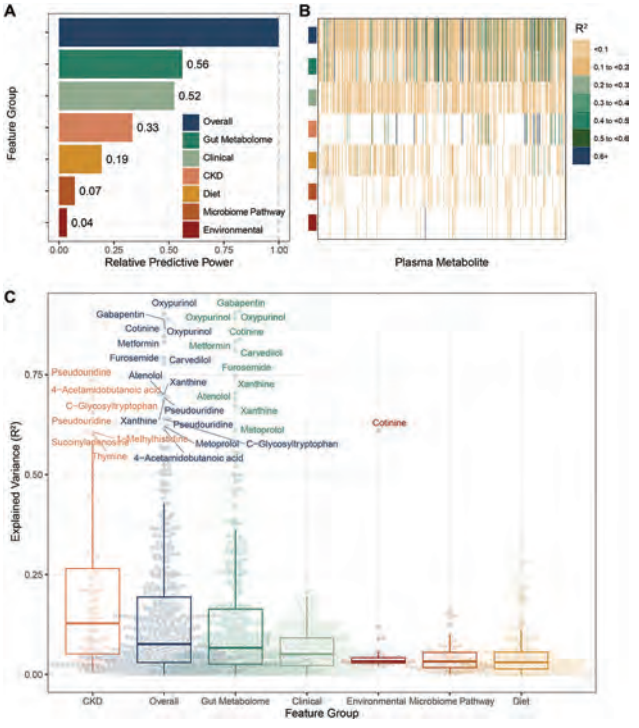
Background: The importance of kidney function and gut microbiota relative to other clinical and behavioral factors in predicting the plasma and fecal metabolomes is unclear in CKD.

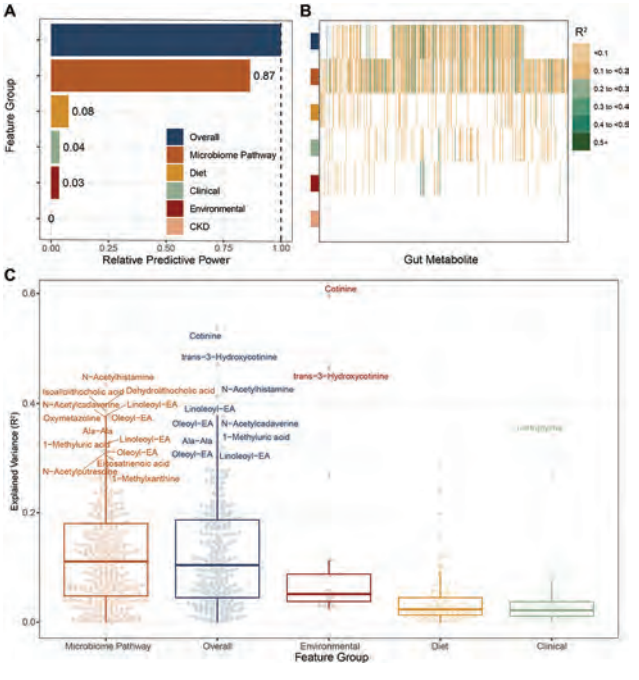
Methods: Among N=291 adults in the Chronic Renal Insufficiency Cohort (CRIC) Gut Study, we used random forest models to determine relative predictive power of clinical factors, kidney measures, diet, environmental factors, gut microbiota, and the fecal metabolome in explaining the plasma and fecal metabolomes and individual metabolite levels in CKD.

Results: The fecal metabolome and clinical factors best predicted variance in the entire plasma metabolome, while kidney measures (eGFR and proteinuria) had the highest median explained variance for individual plasma metabolites, in particular, several nucleobases and amino acids (Fig 1). By contrast, gut microbiome pathways outperformed any feature to explain variance in the fecal metabolome (Fig 2).

Conclusions: The gut microbiome strongly predicts the fecal metabolome which, in addition to kidney measures, explains the majority of variability in the plasma metabolome in CKD potentially through dysbiosis, disruption of gut barrier function, and/or reduced renal clearance of gut-derived metabolites.

Funding: NIDDK Support





TH-OR38

PURE Healthy Diet Score, Genetic Susceptibility, and New-Onset CKD

Sisi Yang, Fan Fan Hou, Xianhui Qin. *Southern Medical University Nanfang Hospital, Guangzhou, China.*

Background: The Prospective Urban Rural Epidemiology (PURE) score, a novel dietary pattern that focuses exclusively on protective foods, is more practical than highly restrictive diets. However, its association with new-onset chronic kidney disease (CKD) and its performance in comparison to some conventional dietary patterns, including Dietary Approaches to Stop Hypertension (DASH), Alternate Mediterranean diet (aMed), Alternate Healthy Eating Index-2010 (AHEI-2010), and healthful Plant-Based Diet Index (hPDI) remain unclear.

Methods: 179,569 participants without CKD and with complete dietary data at baseline from the UK Biobank were included. The PURE score was calculated based on six foods (fruits, vegetables, legumes, nuts, fish, and dairy), ranging from 6 to 30. The study outcome was new-onset CKD.

Results: During a median follow-up of 12.1 years, 4,822 participants developed CKD. The PURE score was inversely associated with new-onset CKD (per 1 quintile increment: HR, 0.92; 95%CI,0.90-0.94). Compared to participants with PURE score <14 (unhealthy PURE score) and high genetic risk, those with PURE score ≥14 (healthy PURE score) and low genetic risk had the lowest risk of CKD (HR, 0.46; 95%CI, 0.42-0.51). The inverse association between PURE score and new-onset CKD remained, regardless of the levels of DASH, aMed, AHEI-2010, hPDI, and genetic risk of CKD (all *P* for interactions >0.05). None of the conventional dietary patterns (per 1 quintile increment: HRs ranging from 0.91 to 0.96) was significantly superior to PURE score in reducing the risk of CKD.

Conclusions: Adherence to a high PURE score was associated with a lower risk of CKD, suggesting the importance of protective foods in CKD prevention.

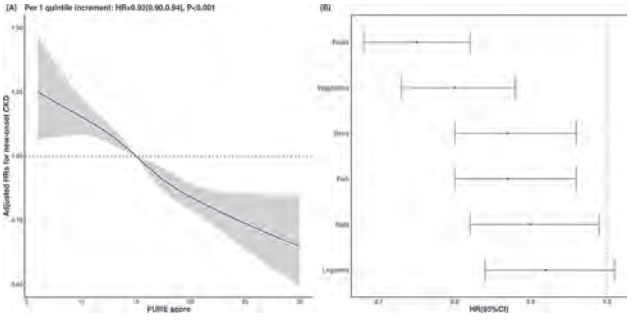


Figure 1. Associations of PURE score (A) and its components (B) with the risk of new-onset CKD.

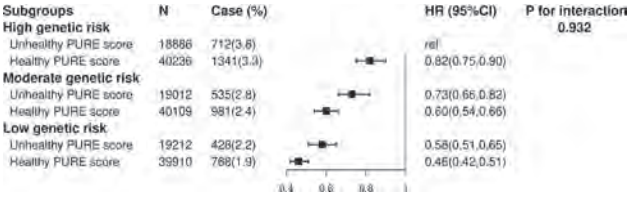


Figure 2. Joint association of PURE score and genetic susceptibility with the risk of new-onset CKD.

TH-OR39

Mitochondrial DNA Copy Number Is Associated with Incident AKI, CKD, and Inflammatory Biomarkers

Pukhraj S. Gaheer,[1,2] Giuliano Caltagirone,[1,2] Adeera Levin,[3] Wei Q. Deng,[1,2] Michael R. Chong,[1,2] Matthew B. Lanktree.[1,2] *[1]McMaster University Faculty of Health Sciences, Hamilton, ON, Canada; [2]Population Health Research Institute, Hamilton, ON, Canada; [3]The University of British Columbia, Vancouver, BC, Canada.*

Background: Mitochondrial DNA copy number (mtDNA-CN) is an estimate of the number of mitochondria per leukocyte and a surrogate measure of net mitochondrial function. Reduced mtDNA-CN has been reported associated with diabetes, cardiovascular disease, and CKD. We sought to evaluate the association of blood mtDNA-CN with incident acute kidney injury (AKI), CKD, and inflammatory biomarkers.

Methods: mtDNA-CN was estimated from whole-genome sequencing data in the UK Biobank cohort, consisting of 38,440 samples from the general population. We estimated mtDNA-CN using a quantitative polymerase chain reaction (qPCR) in the Canadian study of prediction of death, dialysis, and interim cardiovascular events (CanPREDDICT) cohort, consisting of 1,435 patients with advanced CKD. Linear and Cox proportional hazard regressions were adjusted for blood cell counts, age, sex, and comorbidities. We

also used two-sample Mendelian randomization to test if genetically predicted mtDNA-CN was associated with eGFR. Reverse Mendelian randomization tested the opposite direction: if genetically predicted kidney function was associated with mtDNA-CN.

Results: In the UK Biobank, we observed a 12% higher risk of incident AKI (hazard ratio (HR)=0.88, 95% CI = 0.86–0.91, P=2.4x10^{-6}) and 8% increased odds of incident CKD (odds ratio=0.92, 95% CI = 0.89-0.94, P=0.0008) per 1 standard deviation (SD) decrease in mtDNA-CN while adjusting for baseline eGFR. Meta-analyzing across CanPREDDICT and UK Biobank revealed a 16% higher risk of incident kidney failure (HR=0.84, 95% CI = 0.76-0.93; P=0.0006) and a 3% increase in uACR (95% CI = 1%-5%, P=0.002) per 1 SD decrease in mtDNA-CN. In CanPREDDICT, mtDNA-CN was also associated with transforming growth factor-ß1 (TGFß1, ß=-9.5% per 1 SD decrease, P=0.0005) and C reactive protein (CRP, ß=8.9% per 1 SD decrease, P=0.005). Bidirectional Mendelian randomization analysis did not support either mtDNA-CN or eGFR as causally impacting the other (P>0.05).

Conclusions: mtDNA-CN was associated with incident AKI, CKD, and kidney failure, as well as pro-inflammatory markers TGFß1 and CRP. However, Mendelian randomization analysis did not support a causal relationship between kidney function and mtDNA-CN, suggesting a separate causal pathway mediates the association.

Funding: Government Support - Non-U.S.

TH-OR40

Kidney Volume and Risk of Incident CKD

Jianhan Wu,[1] Yifan Wang,[4] Caitlyn Vlasschaert,[2] Ricky Lali,[1] James Feiner,[1] Pukhraj S. Gaheer,[1] Serena Yang,[1] Nicolas Perrot,[5] Michael R. Chong,[5] Guillaume Pare,[1] Matthew B. Lanktree.[3] *[1]McMaster University Faculty of Health Sciences, Hamilton, ON, Canada; [2]Queen's University, Kingston, ON, Canada; [3]St. Joseph Health Care Hamilton, Hamilton, ON, Canada; [4]University of Ottawa Faculty of Medicine, Ottawa, ON, Canada; [5]Population Health Research Institute, Hamilton, ON, Canada.*

Background: Low total kidney volume (TKV) is a risk factor for CKD. However, evaluations of causal inference and prognostic utility beyond traditional biomarkers are lacking.

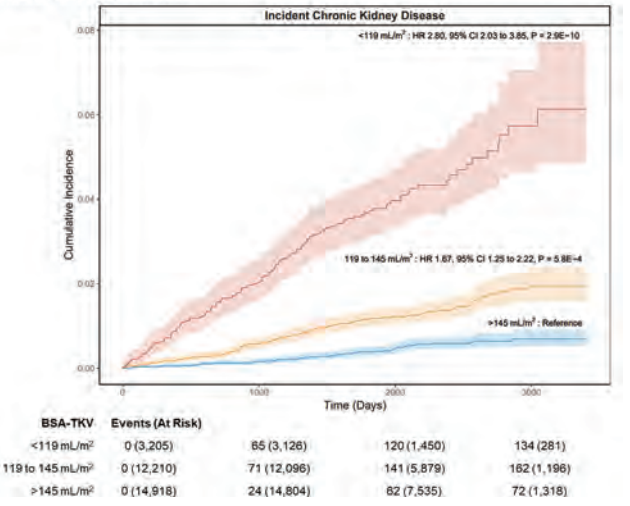
Methods: TKV of 34,595 White British ancestry participants were derived from the UK Biobank. Association with incident CKD were assessed with Cox proportional hazard models. Prognostic thresholds for CKD risk stratification were identified using a modified Mazumdar method with bootstrap resampling. Overall improvement in model performance was assessed using likelihood ratio test. Risk reclassification was evaluated with 5-fold cross-validation. Bidirectional associations of genetically predicted TKV with kidney traits were assessed using two-sample Mendelian randomization (MR).

Results: Adjusted for eGFR and albuminuria, a lower TKV of 10 mL was associated with a 6% higher risk of incident CKD (HR 1.06, 95% CI 1.03 to 1.08, P = 5.8 x 10^{-6}). Individuals below the prognostic threshold of body surface area adjusted TKV (BSA-TKV) at 119 mL/m^2 (10th percentile) exhibited 2.8-fold (95% CI 2.03 to 3.85, P = 2.9 x 10^{-10}) higher risk of incident CKD after accounting for eGFR, albuminuria, and traditional risk factors. Addition of BSA-TKV improved model performance of the CKD Prognosis Consortium Incident CKD Risk Score (likelihood ratio P = 4.8 x 10^{-14}) and improved reclassification of high-risk prognostication at a rate of 1 per 3.3 cases (95% CI 3.1 to 3.6). In MR, a lower genetically predicted TKV by 10 mL was associated with 10% higher CKD risk (OR 1.10, 95% CI 1.06 to 1.14, P = 1.3 x 10^{-7}). Reciprocally, an elevated risk of genetically predicted CKD by 2-fold was associated with a lower TKV by 7.88 mL (95% CI -9.81 to -5.95, P = 1.2 x 10^{-15}).

Conclusions: Kidney volume was associated with incident CKD independent of traditional risk factors including baseline eGFR and albuminuria. Mendelian randomi–zation demonstrated a bidirectional relationship between kidney volume and CKD.

Funding: Government Support - Non-U.S.

Figure 2: Cumulative incidence and hazard ratios of incident chronic kidney disease, adjusted for eGFR, uACR and other traditional risk factors, according to body surface area adjusted total kidney volume (BSA-TKV) thresholds.



BSA-TKV	Events (At Risk)			
<119 mL/m²	0 (3,205)	65 (3,126)	120 (1,450)	134 (281)
119 to 145 mL/m²	0 (12,210)	71 (12,096)	141 (5,879)	162 (1,196)
>145 mL/m²	0 (14,918)	24 (14,804)	62 (7,535)	72 (1,318)

TH-OR41

Metabolomics Study of APOL1-Associated CKD Progression

Ruiyuan Zhang,[1] Tanika Kelly,[2] Morgan Grams,[3] Jing Chen,[1] Jiang He,[1] Changwei Li.[1] *[1]Tulane University, New Orleans, LA; [2]University of Illinois Chicago College of Medicine, Chicago, IL; [3]New York University Grossman School of Medicine, New York, NY.*

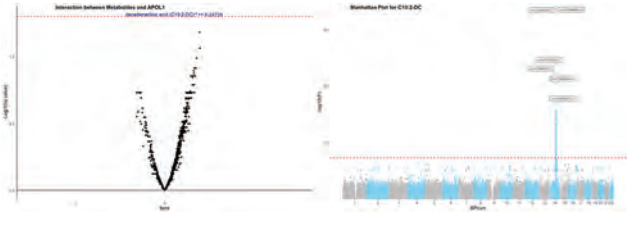
Background: The apolipoprotein L1 (APOL1) gene risk variants are a major cause for chronic kidney disease (CKD) and its progression in African Americans (AA). Identifying factors that can modify the genetic risk holds great promise for personalized prevention of CKD progression. However, such factors have not been well studied. We aimed to identify urinary metabolites modifying the risk of APOL1 associated CKD progression in AA patients of the Chronic Renal Insufficiency Cohort (CRIC).

Methods: By using an untargeted approach, we measured 1,350 metabolites from 24-hour urine samples collected at baseline for all 1,513 AA participants of the CRIC. CKD progression was defined as the onset of end-stage renal disease or a 50% reduction in estimated glomerular filtration rate (eGFR) during 20 years' follow-up. We tested interactions of each metabolite with APOL1 risk variants on CKD progression using Cox proportional hazard models adjusting for age, sex, study site, smoking, drinking, body mass index, systolic blood pressure, diabetes, cardiovascular disease, urine protein creatinine ratio, and eGFR. Metabolites with a false discovery rate corrected q <0.05 were deemed significant. Genome-wide analyses were performed for significant metabolites to identify genes associated with them.

Results: Two metabolites, *decadienedioic acid (C10:2-DC)* and *X_24728*, significantly modified the effect of APOL1 risk variants on CKD progression (**Figure**). The APOL1 variants only increased risk for CKD progression among those with higher than median of *C10:2-DC* (hazard ratio [HR]= 1.63, 95% confidence interval [CI]: 1.24-2.16) but not among those with less than the median (HR=0.85; 95% CI: 0.62-1,16). Similarly, the HRs for APOL1 risk variants were 0.88 (95% CI: 0.66-1,18) and 1.87 (95% CI: 1.39-2.52) for participants with lower than and higher than median of *X_24728*, respectively. In genome-wide analyses, *ACOT2* upstream variant rs11626972 was associated with urinary *C10:2-DC* (beta for the minor G allele=-0.50, P=5.04×10^{-35}, **Figure**).

Conclusions: Two urinary metabolites modified the risk of APOL1 associated CKD progression.

Funding: Other NIH Support - P20GM109036-07



TH-OR42

CKD Symptoms in Patients Receiving Kidney Supportive Care (KSC)

Jennifer S. Scherer, Chen Lyu, Michal L. Melamed, Daniel Cukor, David M. Charytan. *NYU Langone Health, New York, NY.*

Background: Reducing symptoms is essential to improving quality of life in CKD. KSC can achieve this, and can be used for all treatment modalities, including conservative kidney management (CKM). However, KSC is not widely available in the US, and its impact is not well described.

Methods: Patients completed the IPOS-Renal, a CKD symptom survey for which higher scores represent greater burden, at each visit to our KSC clinic between May 2016 and December 2023.

Results: 189 patients were followed for a mean of 5 months (range 0-58), with a mean of 3 surveys/patient. 69 (37%) were on dialysis, 42 (23%) had chosen CKM, the remainder were deciding (26%), planning for dialysis (5%), or without advanced CKD (9%). Compared to dialysis patients, CKM patients were older (84 vs. 64 years), more likely to be White (69% vs. 39%), non-Hispanic (74% vs. 58%), and have a higher Charlson comorbidity score (10 vs. 6). Mean GFR of CKM patients was 12 mL/min/1.73m^2. CKM patients had a lower initial symptom burden than dialysis patients (21 vs. 29), and this was maintained over time (Figure 1). Both groups had an initial decrease in their symptoms, however, KSC was more effective at sustaining this response in CKM. Linear mixed models assessing longitudinal change over 58 months showed that IPOS renal scores were 7.7 points higher in dialysis patients than in those on CKM (p=0.03), after adjusting for comorbidities.

Conclusions: To our knowledge, this is the first US data showing that KSC appears to be an effective at reducing CKD symptoms. The benefits appear to be more sustained in patients who had chosen CKM. Additional investigation of the impact of KSC and the trajectory of CKM symptoms is warranted.

Funding: NIDDK Support

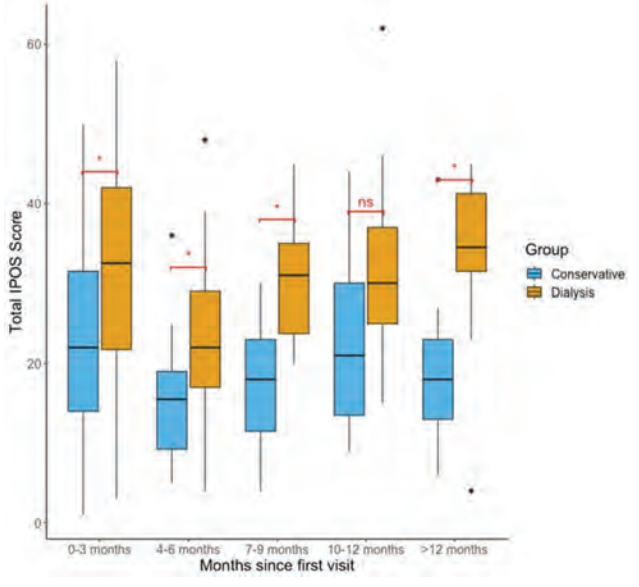


Figure 1: Total IPOS-Renal score over time in people receiving kidney supportive care, Dialysis vs. Conservative Kidney Management, *significance = p<0.05

TH-OR43

Comprehensive Conservative Kidney Management among an Older Population Using a Large Administrative Claims Database

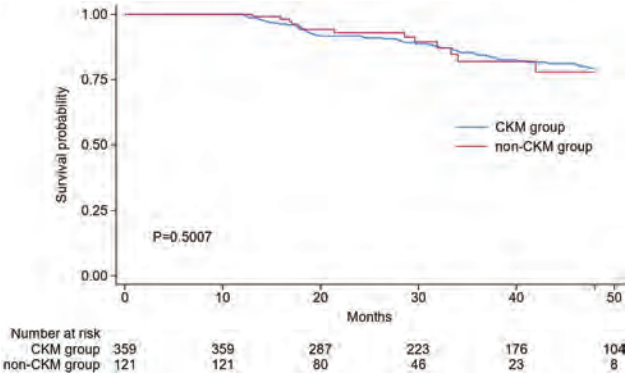
Arisa Kobayashi,[1,2] Keita Hirano,[1] Tatsuyoshi Ikenoue,[1] Takashi Yokoo,[2] Shingo Fukuma.[1] *[1]Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu, Kyoto, Japan; [2]Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan.*

Background: Choosing renal replacement therapy for the older is complex due to complications and quality of life concerns. Conservative kidney management (CKM) is increasingly accepted for older CKD patients. This study aims to examine CKM status and related factors in aging Japanese society.

Methods: This cohort study used health screening and medical claims data from April 2014 to May 2023. We included people aged 75 or older with advanced kidney disease (eGFR<8), observed for at least one year and not receiving maintenance dialysis at inclusion. The population was divided into two groups: planned initiation of dialysis (non-CKM group) and selected for CKM (CKM group). A Cox proportional hazards model with age, sex, body mass index (BMI) and frailty categorized by Electronic Frailty Index assessed factors impacting CKM selection. All-cause mortality and total hospitalizations were also examined in both groups.

Results: A total of 480 were included in this analysis (median [IQR] age, 81.1 [77.9-84.8] years; 247 women [51.5%]). Of these, 359 (74.8%) did not undergo necessary practice for dialysis and were defined as choosing CKM. Cox regression showed no significant differences in age, sex, or BMI between the groups. By contrast, the non-frail group was significantly less likely to initiate dialysis compared to the severe-frail group (HR 0.11 [95% CI, 0.02-0.82]). Cox regression analysis of all-cause mortality showed no significant difference between the groups (HR 1.25 [95% CI, 0.70-2.24]). Kaplan-Meier curves for death are shown in the Figure. Poisson regression indicated the hospitalization rate was significantly higher in the non-CKM group (IRR 1.98 [95% CI, 1.67-2.34]). In the non-CKM group, hospitalizations were significantly more frequent in the severe-frail group (OR 8.75 [95% CI, 1.36-56.3]).

Conclusions: In the older population, non-frail individuals often chose CKM. These findings suggest the importance of considering clinical backgrounds when determining CKM indications.



TH-OR44

ANU-ADRI, BDSI, CAIDE, and LIBRA as Predictors of Mild Cognitive Impairment Dementia in CKD

Amara Sarwal,[1,2] Robert E. Boucher,[1,2] Sydney E. Hartsell,[1,2] Guo Wei,[1,2] Ravinder Singh,[1,2] Niharika Katkam,[1,2] Augustine Takyi,[1,2] Akhil Ramanujam Chakravartula,[1,2] Farahnaz A. Moghaddam,[1] Srinivasan Beddhu.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

Background: The four commonly used risk prediction scores for dementia in the general population include Australian National University Alzheimer's Disease Risk Index (ANU-ADRI), Brief Dementia Screening Indicator (BDSI), Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE), and LIfestyle for BRAin Health (LIBRA). There is a paucity of data on the applicability of these scores for predicting cognitive function decline in CKD.

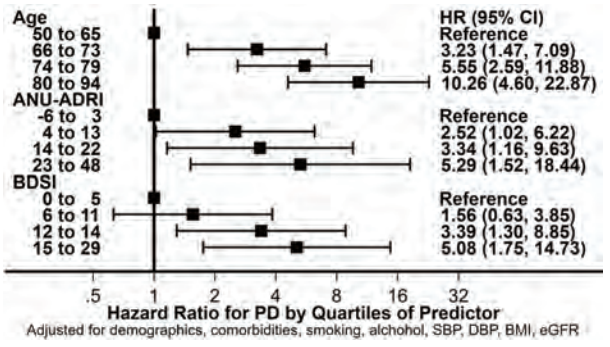
Methods: In Systolic Blood Pressure Intervention Trial (SPRINT)- MIND Study participants with CKD at baseline (N=2105), we compared the predictive ability of age alone, ANU-ADRI, BDSI, CAIDE and LIBRA scores for adjudicated incident mild cognitive impairment (MCI) or probable dementia (PD) in separate multivariate Cox regression models adjusted for BP group in SPRINT, age, sex, race/ethnicity, education, comorbidities such as CVD, PVD, depression and tobacco use as well as BP, BMI and eGFR.

Results: The mean age was 72 ± 9 years, 40% female and 37% African American. Mean eGFR was 47 ± 10. There was a total of 418 MCI events/9156 person years, and 137 PD events/9649 person years. As shown in Table, age had the strongest association with MCI but with modest c-statistic (0.66). Age, ANU-ADRI and BDSI were strong predictors of PD (Table and Figure) with c-statistic of 0.71, 0.74 and 0.73, respectively. CAIDE and LIBRA fared poorly for both MCI and PD.

Conclusions: ANU-ADRI and BDSI offer modestly higher concordance for predicting PD than age alone in CKD. Both age and the existing scores are poor predictors of MCI in CKD. Better tools to predict MCI in CKD are warranted.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support

	MCI		PD	
	HR per 1 SD	C-statistic	HR per 1 SD	C-statistic
Age	1.75 (1.51, 2.03)	0.66	2.55 (1.96, 3.32)	0.71
ANU-ADRI	1.10 (0.83, 1.46)	0.65	2.45 (1.48, 4.07)	0.74
BDSI	1.23 (1.00, 1.51)	0.66	1.80 (1.23, 2.62)	0.73
CAIDE	1.10 (0.96, 1.27)	0.51	1.19 (0.94, 1.50)	0.54
LIBRA	1.01 (0.84, 1.21)	0.52	1.48 (1.08, 2.04)	0.51



TH-OR45

Inpatient Outcomes of Gastrointestinal Bleeding in Advanced CKD: A National Analysis, 2016-2019

Mingyue He,[1] Shaan H. Desai,[1] Yichen Wang,[2] Avrum Gillespie.[1] *[1]Temple University Hospital, Philadelphia, PA; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: Patients with Advanced Chronic Kidney Disease (ACKD) and End-Stage Kidney Disease (ESKD) have an elevated risk of Gastrointestinal Bleeding (GIB). This study aims to investigate the incidence, causes, interventions, and outcomes of GIB among these groups compared to patients without CKD (NCKD).

Methods: Using the Nationwide Inpatient Sample, we analyzed non-elective admissions for GIB from 2016 to 2019, encompassing upper, lower, and unspecified GIB cases across ACKD (CKD stages 4 or 5), ESKD, and NCKD groups. We compared various outcomes and conducted subgroup analyses based on the timing of endoscopy within the ACKD and ESKD cohorts.

Results: The study included 2,163,929 patients. The incidence of GIB hospitalizations was higher in the ACKD (3.2%) and ESKD (3.4%) groups compared to NCKD (2.2%). ACKD and ESKD patients exhibited increased mortality (adjusted Odds Ratio 1.33 and 1.94, respectively; p<0.001) compared to NCKD. Patients with ESKD demonstrated increased rates of mechanical ventilation, pressor support, and blood transfusion, along with prolonged and costly hospitalizations ($p < 0.001$ for all). There was decreased early endoscopic evaluation (<24 h) and increased late evaluations (> 48h) in the ACKD and ESKD groups ($p < 0.001$ for all) compared to NCKD. Multivariate analysis revealed that early endoscopy was significantly associated with decreased mortality while delayed endoscopy was significantly associated with increased mortality in ACKD and ESKD patients (p<=0.001 for all). The primary causes of GIB in both the ACKD and ESKD groups were gastric/duodenal bleeding and angiodysplasia bleeding. ACKD and ESKD were independent risk factors for angiodysplasia bleeding.

Conclusions: ACKD and ESKD are independent risk factors for GIB and in-hospital mortality. ESKD patients with GIB demonstrated significantly elevated rates of adverse outcomes compared to those without CKD. Both groups had a lower rate of early endoscopy and a higher rate of delayed endoscopy, which emerged as independent risk factors for mortality. Further investigation to understand the reasons for delayed endoscopic evaluations in ESKD patients is crucial for improving patient outcomes.

TH-OR46

Finerenone in Patients with Type 2 Diabetes and CKD by SGLT2 Inhibitor and Glucagon-Like Peptide 1 Receptor Agonists Receptor Agonist Use: A FIDELITY Analysis

Ajay K. Singh,[1] Stefan D. Anker,[2] Bertram Pitt,[3] Peter Rossing,[4,5] Luis M. Ruilope,[6,7] Christiane Ahlers,[8] Youssef M. Farag,[9,10] Marc Lambelet,[11] Meike Daniela Brinker,[12] Katja Rohwedder,[13] Gerasimos Filippatos,[14] George L. Bakris.[15] *[1]Harvard Medical School, Renal Division, Brigham and Women's Hospital/Dana Farber Cancer Institute, Boston, MA; [2]Department of Cardiology (CVK) of German Heart Center Charité; German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany; [3]Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI; [4]Steno Diabetes Center Copenhagen, Herlev, Denmark; [5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [6]Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain; [7]CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain; [8]Statistics and Data Insights, Bayer AG, Berlin, Germany; [9]Postgraduate Medical Education, Harvard Medical School, Boston, MA; [10]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [11]Chrestos Concept GmbH & Co. KG, Essen, Germany; [12]Cardiology and Nephrology Clinical Development, Bayer AG, Berlin, Germany; [13]Cardio-Renal Medical Affairs Department, Bayer AG, Berlin, Germany; [14]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece; [15]Department of Medicine, University of Chicago Medicine, Chicago, IL.*

Background: Finerenone significantly reduced the risk of cardiovascular and kidney outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in FIDELITY, a prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials. Here, we explored the treatment effect of finerenone in concomitant use with sodium-glucose co-transporter-2 inhibitor (SGLT-2i) + glucagon-like peptide-1 receptor agonist (GLP-1RA).

Methods: Patients in FIDELITY were on optimized renin–angiotensin system inhibition and randomized 1:1 to finerenone or placebo. Key outcomes in this analysis were change in urine albumin-to-creatinine ratio (UACR) over time and treatment-emergent adverse events (including serum potassium [K^+]).

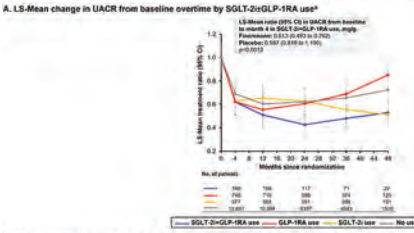
Results: Of 12,990 patients analyzed, 167 received concomitant use of finerenone with SGLT-2i+GLP-1RA at baseline. Baseline characteristics were similar despite concomitant use of finerenone with SGLT2i±GLP-1RA. Finerenone led to a greater reduction in UACR from baseline to month 4 vs placebo; at month 12, reduction was 49%, 45%, 35% and 40% with concomitant use of finerenone with SGLT-2i+GLP-1RA, GLP-1RA, SGLT-2i, and finerenone alone, respectively (Fig 1A). Safety profile of finerenone was not modified by concomitant SGLT2i±GLP-1RA use. Overall, the risk of hyperkalemia leading to treatment discontinuation or hospitalization with finerenone were low. There were fewer patients with serum [K+] of >5.5/>6 mmol/l in the treatment group with concomitant use of finerenone with SGLT-2i+GLP-1RA vs finerenone alone (Fig 1B).

Conclusions: In FIDELITY, concomitant use of finerenone with SGLT-2i+GLP-1RA at baseline may have additive kidney benefits vs placebo in patients with T2D and CKD.

Funding: Commercial Support - Bayer AG

Figure 1: LS-Mean change in UACR over time (A), and any treatment-emergent AE, hyperkalemia and serum [K⁺] (B) by SGLT-2i±GLP-1RA use at baseline

A. LS-Mean change in UACR from baseline overtime by SGLT-2i±GLP-1RA use*



B. Any treatment-emergent AE, hyperkalemia and serum [K⁺] by SGLT-2i±GLP-1RA use at baseline*

n (%)	SGLT-2i+GLP-1RA use at baseline		GLP-1RA only at baseline		SGLT-2i only at baseline		Non-use	
	Finerenone (n=68)	Placebo (n=81)	Finerenone (n=410)	Placebo (n=241)	Finerenone (n=350)	Placebo (n=266)	Finerenone (n=5843)	Placebo (n=5876)
Any treatment-emergent AE	77 (89.5)	76 (93.8)	363 (80.4)	334 (82.5)	320 (91.4)	306 (85.0)	4802 (85.1)	4878 (85.9)
Any treatment-emergent hyperkalemia	12 (14.0)	5 (6.2)	67 (15.1)	31 (8.6)	39 (9.4)	7 (2.0)	901 (14.2)	466 (7.1)
Leading to permanent discontinuation of study drug	0	1 (1.2)	9 (2.2)	3 (0.8)	5 (1.4)	2 (0.6)	98 (1.7)	32 (0.5)
Serious treatment-emergent hyperkalemia leading to hospitalization	0	1 (1.2)	2 (0.5)	1 (0.3)	1 (0.3)	0	58 (1.0)	8 (0.1)
	SGLT-2i+GLP-1RA use at baseline		GLP-1RA only at baseline		SGLT-2i only at baseline		Non-use	
Serum [K⁺] value, n/N (%)	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo
>5.5 mmol/l	7/58 (9.1)	3/80 (3.8)	55/405 (13.6)	18/304 (5.1)	27/343 (7.9)	10/262 (2.8)	983/5047 (17.7)	439/5059 (7.3)
>6.0 mmol/l	1/66 (1.2)	0/80 (0)	5/400 (1.2)	3/306 (0.8)	3/345 (0.9)	3/265 (0.8)	202/5081 (3.6)	74/5057 (1.5)

*For each subgroup category a mixed model was applied with factors of treatment group, region, eGFR category at screening, type of albuminuria at screening, CVD history, time, treatment*time, study, study*treatment, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariates. Values after the onset of ESKD are excluded from this analysis. Treatment may displace finerenone vs placebo.
†Safety analysis set included 6489 and 6474 patients in the finerenone and placebo treatment groups, respectively, who received any combined SGLT-2i+GLP-1RA use at baseline. For laboratory evaluations % represents all patients at risk or a treatment-emergent laboratory abnormality. Patients must have both a baseline and post-baseline treatment-emergent value and the baseline value must not exceed the displayed threshold. n represents the number of patients at risk with at least one treatment-emergent laboratory assessment meeting the criterion for treatment-emergent assessments from start of treatment until 2 days after any temporary or permanent interruption of study drug were considered.
AE, adverse event; CI, confidence interval; ESKD, end-stage kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; [K⁺], potassium concentration; LS, least-squares; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

TH-OR47

Urinary Clusterin as a Pharmacodynamic Response Biomarker for the Endothelin Receptor Antagonist Atrasentan

Wenjun Ju,[1] Viji Nair,[1] Priya Vart,[2] Johannes D. Smeijer,[2] Maria Larkina,[1] Kerby Shedden,[5] Edmond Lee,[1] John R. Hartman,[1] Markus Bitzer,[1] Kevin L. Duffin,[7] Maria F. Gomez,[6] Charles E. Alpers,[4] Matthias Kretzler,[1] Hiddo J. Heerspink.[2,3] SONAR. *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [3]The George Institute for Global Health, Sydney, NSW, Australia; [4]University of Washington School of Medicine, Seattle, WA; [5]University of Michigan Department of Statistics, Ann Arbor, MI; [6]Lunds universitet Institutionen for kliniska vetenskaper Malmo, Malmo, Sweden; [7]Eli Lilly and Company, Indianapolis, IN.*

Background: Endothelin-1 pathway activation in the kidney is associated with progressive kidney injury and GFR decline. The endothelin-1 receptor antagonist atrasentan reduces the risk of kidney failure in patients with diabetic kidney disease (DKD) in the phase 3 SONAR clinical trial. However, the individual patient's response varies. This study aimed to identify biomarkers predictive of atrasentan response and its underlying molecular mechanisms.

Methods: SOMAscan was used to discover urinary biomarkers associated with atrasentan response in 180 patients from the SONAR trial. Logistic regression was used to identify markers whose change from baseline to 6 weeks of treatment are predictive to response. Top candidate markers were validated using ELISA. Biomarker concentration was normalized by urine creatinine. Transcriptomic data from patients with DKD and atrasentan-treated DKD mouse model were analyzed for mechanistic insight. The top candidate biomarker was validated in the remaining SONAR cohort using a Cox proportional hazard regression model.

Results: Putative biomarkers predictive of atrasentan response were identified. Of these, urinary clusterin (uCLU) emerged as the top candidate and was further evaluated. Kidney transcriptomic data revealed that *CLU* is upregulated in DKD in mice and humans, and correlated with an endothelin activation score, generated from atrasentan-treated BTBR ob/ob mice using DKD-associated endothelin 1 pathway genes that are reversely regulated by atrasentan. Higher uCLU at baseline is significantly associated with an increased risk of a composite endpoint of kidney failure or 57% eGFR decline [HR1.09 (95% CI 1.03, 1.16; p=0.005)] in the SONAR clinical trial (N=3060). Atrasentan reduced uCLU during six weeks treatment by 42.6% and this early change in uCLU was independently associated with a lower risk of the composite kidney endpoint after adjustment for all covariates [HR 0.90 (95% CI 0.84, 0.97); p=0.009].

Conclusions: Our study identified and validated uCLU as a promising pharmacodynamic biomarker for assessing treatment response to atrasentan. This calls for further clinical evaluation and implementation, and fosters indivdualized treatment through molecular stratification.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR48

Ephrin Signaling and the Development of Early Progressive Kidney Function Decline

Zaipul Md Dom,[1,2] Eiichiro Satake,[1,2] Sok Cin Tye,[1,2] Andrzej S. Krolewski.[1,2] *[1]Joslin Diabetes Center, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: We were the first to report a novel role of Ephrin family members in the progression of kidney failure in diabetes (Satake *et al.* JASN 2021). However, whether higher Ephrin protein levels are associated with or causally related to the development of early progressive kidney function decline (PKFD) is unknown.

Methods: We assessed EPHA2 and EFNA4 protein levels using Joslin Olink proteomics platform among participants in the Joslin Kidney Study (JKS, n=1,269) and the Chronic Renal Insufficiency Cohort study (CRIC, n=1,170). We compared baseline levels of EPHA2 and EFNA4 across albuminuria categories with T1D and T2D and evaluated their associations with kidney outcomes (kidney failure, eGFR slope and eGFR-based outcomes).

Results: EPHA2 and EFNA4 levels increased progressively from non-diabetics to normoalbuminuria (NA), microalbuminuria (MA), and proteinuria (PT) in both cohorts (Figure 1A). Significant variations were observed between T1D and T2D, and across all albuminuria categories with the highest levels observed in PT. T2D individuals consistently had higher EPHA2 and EFNA4 levels compared to T1D. Both proteins showed significant negative correlations with eGFR, particularly pronounced in MA and PT. In the CRIC cohort, EPHA2 and EFNA4 had significant positive correlations with UACR across all albuminuria categories. Baseline EPHA2 levels were significantly associated with kidney failure in models adjusted for HbA1c, eGFR and UACR (Figure 1B, JKS PT: HR [95%CI] =1.52 [1.21-1.91], p=0.00035, c-index=0.797); CRIC NA: HR [95%CI] =2.61 [1.05-6.19], p=0.029, c-index=0.789, adjusted for competing mortality).

Conclusions: Our findings suggest that elevated levels of circulating EPHA2 and EFNA4 play a role in the initiation of early PKFD and can be used as predictors for the development of early PKFD.

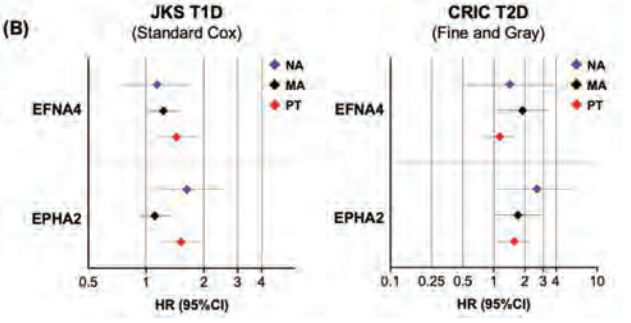
Funding: NIDDK Support

(A)

	EPHA2		EFNA4	
	JKS T1D	CRIC T2D	JKS T1D	CRIC T2D
Non-diabetics	7.7	-	61.9	-
Normoalbuminuria (NA)	8.2	21.1	62.8	107.1
Microalbuminuria (MA)	11.6	26.0	76.7	118.4
Proteinuria (PT)	26.6	33.4	113.1	131.6

Protein concentrations are presented as median (pg/ml)

(B)



TH-OR49

Advancing KidneyIntelX Precision Medicine Platform in CKD

Steven G. Coca,[1] Sharon Stapleton,[2] Katherine L. Edwards,[2] Emily Cho Kiu Au,[2] Fergus Fleming,[2] Girish N. Nadkarni.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Renalytix plc, London, United Kingdom.*

Background: NBL1 and WFDC2 have been identified in experimental animals and omics-based platforms as markers of fibrosis in diabetic kidney disease and are associated with progression to kidney failure. The kidneyintelX.dkd test is an FDA De Novo marketing authorized test that currently incorporates measurement of three biomarkers via electrochemiluminescence Meso Scale platform with clinical variables and categorizes patients at low, moderate, or high risk for progression of DKD. We aimed to advance the translation of NBL1 and WFDC2 for inclusion in future versions of the KidneyIntelX platform through clinical assay development and independent validation of prognostic performance.

Methods: We established analytical characteristics using CLSI guidelines for two biomarkers of kidney disease progression (NBL1, WFDC2). We measured plasma concentrations at baseline in a replication cohort of 601 patients with DKD from the Penn Medicine Biobank (eGFR of 30-59 ml/min/1.73 m^2 or eGFR ≥60 ml/min/1.73 m^2 with UACR ≥30 mg/g). The associations of baseline levels with a composite outcome of ≥40% sustained decline in eGFR, or kidney failure (over 5 years) were evaluated using Cox proportional hazard models.

Results: Robust analytical parameters including repeatability were demonstrated (CV ≤5.5% for NBL1 and CV ≤5.2% for WFDC2) over clinically relevant ranges. Reference intervals at 95% confidence demonstrated discrimination between healthy populations (476 to 3366 pg/mL for NBL1 and 1342 to 5880 pg/mL for WFDC2) and those with diabetic kidney disease (807 to 20102 pg/mL for NBL1 and 2566 to 26538 pg/mL for WFDC2). The replication cohort had baseline median eGFR of 56 ml/min/1.73 m^2 and median UACR of 57 mg/g with 92 (15.3%) composite events. The adjusted hazard ratio per SD increment of log2 baseline concentration for NBL1 was 1.6 (p<0.001) and was 2.5 (p<0.001) for WFDC2 after adjustment for UACR, eGFR and HbA1c.

Conclusions: NBL1 and WFDC2 assays demonstrated robust analytical performance on transfer to the KidneyIntelX clinical laboratory platform. Both biomarkers were strongly associated with the kidney outcome and therefore merit further investigation for potential incorporation into the KidneyIntelX precision medicine platform.

Funding: Commercial Support - Renalytix AI Inc.

TH-OR50

Identification of Circulating Microbial DNA and Its Correlation in Patients with Diabetic Kidney Disease

Hoang T. Linh, Norihiko Sakai, Miho Shimizu, Shinji Kitajima, Takashi Wada, Yasunori Iwata. *Kanazawa Daigaku, Kanazawa, Japan.*

Background: In recent years, substantial studies have been accumulated to indicate the important role of gut microbiota in diabetic kidney disease (DKD). The abnormal changes of bacterial-derived products could imply specific injuries or play beneficial or harmful roles in DKD progression. Our previous study reported a "leaky gut" was induced in mice with DKD, leading to intestine-derived *Klebsiella oxytoca* translocation to circulation and kidneys then promoting DKD progression. However, the presence of *K. oxytoca* was not investigated in DKD patients. Therefore, the present study examines the *K. oxytoca* levels in circulation and their association with clinical characteristics in patients with DKD.

Methods: We enrolled a total of 16 healthy participants, 17 patients with DKD, 5 patients with DKD needing hemodialysis (HD), and 7 patients with CKD without diabetes, who were admitted to Kanazawa University Hospital in 2021. Bacterial-derived DNA (*16S rDNA* and a specific *K. oxytoca* gene) in the blood was detected using droplet digital PCR, then investigated the relationship with clinical characteristics.

Results: The *K. oxytoca* gene was detected in all patient groups with rates of 64.7% in patients with DKD without HD, 60% in DKD with HD group, and 42.9% in the non-DKD CKD group, but only 1/11 (6.25%) in healthy participants. Patients with DKD (with or without HD) exhibited trends of higher levels of *K. oxytoca* copies and *K. oxytoca / 16S rDNA ratio* compared to patients with non-DKD CKD. Interestingly, blood *K. oxytoca* copies and *K.oxytoca/ 16S rDNA* ratio have been identified to have a positive correlation with blood creatinine (r=0.7007 and 0.6492) or BUN levels (r=0.582 and 0.5619) in DKD patients. Considering eGFR, negative correlations were observed with both *K. oxytoca* copies and the *K.oxytoca/16S rDNA* ratio, with correlation coefficients of -0.4509 and -0.4664, respectively. Moreover, there was a correlation between *K. oxytoca* gene copies and higher neutrophil percentages (r=0.4816), along with a lower lymphocyte frequency (r=-0.5558), and elevated neutrophil-to-lymphocyte ratio (r=0.4998).

Conclusions: The presence of the *K. oxytoca* gene in the circulation could serve as a biomarker reflecting reduced renal function and chronic inflammation in DKD patients.

Funding: Government Support - Non-U.S.

TH-OR51

Autophagy-Related Gene Expression in Diabetes and CKD

Christine P. Limonte,[1] Sean Eddy,[2] Sina Gharib,[1] Charles E. Alpers,[1] Laura Barisoni,[3] Rajasree Menon,[2] Viji Nair,[2] Sylvia E. Rosas,[4] Emilio D. Poggio,[5] Ian De Boer.[1] Kidney Precision Medicine Project (KPMP). *[1]University of Washington, Seattle, WA; [2]University of Michigan, Ann Arbor, MI; [3]Duke University, Durham, NC; [4]Joslin Diabetes and Endocrinology Research Center, Boston, MA; [5]Cleveland Clinic, Cleveland, OH.*

Background: Autophagy impairment is implicated in diabetic nephropathy pathophysiology. We examined autophagy-related gene (ARG) expression in human kidney biopsies from the Kidney Precision Medicine Project (KPMP).

Methods: KPMP is performing research kidney biopsies in adults with CKD. Single cell RNA sequencing has been performed in a subset of kidney biopsy samples using the 10xChromium v3 assay. We assessed differential expression of proximal tubular epithelial cell (PTEC) ARGs (n=604 genes identified from literature) in subjects with diabetes and CKD (n=32) versus controls (n=25). We used k-means consensus clustering to group subjects with diabetes and CKD by PTEC ARG expression patterns.

Results: 326 ARGs were differentially expressed between subjects with diabetes and CKD and controls. Subjects with diabetes and CKD were clustered into 3 groups based on PTEC ARG expression (Table). Adjudicated diagnoses differed across clusters, with Clusters 1, 2, and 3 including 35%, 56%, and 0% people with a primary diagnosis of diabetic nephropathy, respectively. While eGFRs were similar across clusters, Cluster 2 members had more albuminuria and higher HbA1cs. Cluster 2 members had more severe structural tubulointerstitial pathology and the greatest proportion of injured PTECs.

Conclusions: PTEC ARG expression patterns may be able to distinguish between clinically relevant phenotypes of diabetes and CKD with distinct profiles of glycemic exposure, tubulointerstitial pathology, and cellular injury.

Funding: NIDDK Support

	Cluster 1 (n=17)	Cluster 2 (n=9)	Cluster 3 (n=6)
Adjudicated diagnosis, N (%)			
Diabetic nephropathy	6 (35%)	5 (56%)	0 (0%)
Hypertensive nephrosclerosis	4 (24%)	1 (11%)	2 (33%)
Cannot be determined	4 (24%)	1 (11%)	2 (33%)
Other	1 (6%)	1 (11%)	2 (33%)
HbA1c category, N (%)			
<6.5%	5 (29%)	1 (11%)	1 (17%)
6.5 to <7.5%	5 (29%)	1 (11%)	4 (67%)
7.5 to <8.5%	3 (18%)	2 (22%)	0 (0%)
>8.5%	2 (12%)	4 (44%)	0 (0%)
eGFR Cr-Cys, ml/min/1.73m2, mean (SD)	45 (19)	47 (17)	54 (34)
UACR, mg/g Cr, median [Q1, Q3]	230 [2, 1374]	710 [87, 4995]	676 [19, 1560]
Interstitial fibrosis, %, mean (SD)	24 (17)	33 (17)	20 (16)
Tubular atrophy %, mean (SD)	20 (15)	31 (17)	18 (18)
Interstitial mononuclear white blood cells, %, mean (SD)	16 (13)	27 (16)	10 (6)
Adaptive/maladaptive/repairing PTEC, N (% total cells)	5128 (45%)	7166 (83%)	2560 (59%)

TH-OR52

Association of Urinary Epidermal Growth Factor with Kidney Outcomes and Effects of SGLT2 Inhibition: Results from the CANVAS and CREDENCE Trials

Erik Moedt,[1] Akihiko Koshino,[1,2] Niels Jongs,[1] Wenjun Ju,[3] Michael K. Hansen,[4] Clare G. Arnott,[5,6] Bruce Neal,[5] Stephan J. Bakker,[1] Hiddo J. Heerspink.[1,5] *[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]Kanazawa Daigaku Daigakuin Iyaku Hokengaku Sogo Kenkyuka Iyaku Hoken Gakuiki Igakurui, Kanazawa, Japan; [3]University of Michigan Department of Internal Medicine, Ann Arbor, MI; [4]Janssen Research and Development LLC, Spring House, PA; [5]The George Institute for Global Health, Sydney, NSW, Australia; [6]Royal Prince Alfred Hospital, Camperdown, NSW, Australia.*

Background: Epidermal growth factor (EGF) is involved in the regenerative processes of kidney tubular cells. Higher urinary EGF (uEGF) levels are associated with a reduced risk of kidney failure in observational studies. The SGLT2 inhibitor canagliflozin reduces the risk of kidney failure in patients with type 2 diabetes (T2D). We investigated the association of uEGF with kidney outcomes and assessed the effect of canagliflozin on uEGF.

Methods: We performed a post-hoc analysis of the combined CANVAS and CREDENCE trials, which assessed efficacy and safety of canagliflozin versus placebo in those with T2D +/- albuminuric chronic kidney disease. The primary outcome was defined as a 40% decline in eGFR, kidney failure, or death due to kidney failure. Hazard ratios were estimated using multivariate Cox regression. We examined the effect of canagliflozin 100 mg/d on change from baseline in uEGF at years 1 and 3 in 2038 CREDENCE patients (year 3 CANVAS samples were not available) using a repeated measures model.

Results: We analyzed data for 3521 (81.3% of the total cohort) CANVAS patients (mean age 62.8 years, eGFR 77.0 mL/min/1.73m^2, median UACR 11.6 mg/g) and 2457 (55.8% of the total cohort) CREDENCE patients (mean age 63.2 years, eGFR 57.0 mL/min/1.73m^2, median UACR 918 mg/g), with available urine samples. Every doubling in baseline uEGF/Cr was associated with a reduced risk of the kidney outcome (HR 0.86 [95% CI 0.79, 0.93]; p<0.001). This association was consistent across baseline eGFR and UACR subgroups. The uEGF/Cr change from baseline to year 1 was -12.5% ([95% CI -15.6, -9.1]; p<0.001) in the placebo group and -5.4% ([95% CI -8.7, -1.9]; p=0.002) in the canagliflozin group, corresponding to a between-group difference of 8.1% ([95% CI 1.1, 15.6]; p=0.016). The effect of canagliflozin on uEGF was more pronounced at week 156 with a between-group difference of 16.5% ([95% CI 2.1, 32.8]; p=0.016).

Conclusions: Higher baseline uEGF/Cr was significantly associated with lower risk of kidney disease progression in patients with T2D with and without CKD. Canagliflozin consistently attenuated the uEGF/Cr decrease compared to placebo.

Funding: Commercial Support - Janssen

TH-OR53

Modeling Cardiorenal Protection with SGLT2 Inhibition in Type 1 Diabetes: An Analysis of EASE-2 and -3

Luxcia Kugathasan,[1] Pritha Dutta,[2] Massimo Nardone,[1] Vikas Sridhar,[1] David Campbell,[3] Anita T. Layton,[2] Bruce A. Perkins,[4] Sean Barbour,[5] Tony K. Lam,[1] Adeera Levin,[5] Leif Erik Lovblom,[1] Istvan Mucsi,[1] Remi Rabasa-Lhoret,[6] Valeria E. Rac,[1] Peter A. Senior,[7] Ronald J. Sigal,[3] Aleksandra Stanimirovic,[1] Alessandro Doria,[8] David Cherney.[1] *[1]Toronto General Research Institute, Toronto, ON, Canada; [2]University of Waterloo, Waterloo, ON, Canada; [3]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [4]Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada; [5]The University of British Columbia, Vancouver, BC, Canada; [6]Universite de Montreal, Montreal, QC, Canada; [7]University of Alberta, Edmonton, AB, Canada; [8]Harvard Medical School, Boston, MA.*

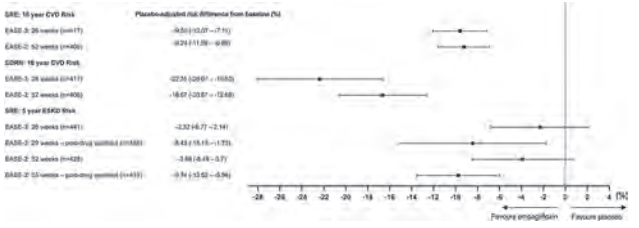
Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors significantly reduce cardiorenal risk in people with type 2 diabetes. It is unknown if these protective effects extend to individuals with type 1 diabetes (T1D). To better understand the potential benefits of SGLT2 inhibition in T1D, we applied the Steno T1 risk engine (SRE) and Scottish Diabetes Research Network (SDRN) risk prediction models to estimate risk of cardiovascular disease (CVD) and end-stage kidney disease (ESKD) in two large T1D cohorts.

Methods: Medical history, demographic and biomarker data were extracted from 730 and 960 participants with T1D from the EASE-2 and 3 trials, respectively. The SRE and SDRN risk prediction models were employed at baseline, week 26 (EASE-3) or 52 (EASE-2), and 3 weeks post drug washout to estimate the 10-year CVD and 5-year ESKD risk. Risk reduction was calculated as the percent change in estimated CVD and ESKD risk from baseline between empagliflozin (pooled 10 and 25mg) vs. placebo groups, and compared using a two-way repeated measures ANOVA.

Results: Empagliflozin significantly reduced the estimated 10-year CVD risk following 26 weeks (SRE: -9.6% [-12.1, -7.1] & SDRN: -22.4% [-28.1, -16.6]; p<0.01)

and 52 weeks (SRE: -9.2% [-11.6, -6.9] & SDRN: -16.7% [-20.7, -12.7]; p<0.01) of treatment compared with placebo. No significant reduction in 5-year ESKD risk was observed while on treatment. The ESKD risk was significantly lower after a 3-week drug washout (SRE: -8.4% [-15.1, -1.7] (EASE-3) & -9.7% [-13.5, -6.0] (EASE-2); p<0.01), in keeping with the expected rise in eGFR.

Conclusions: Empagliflozin improves predicted CVD and ESKD risk in T1D participants, thus demonstrating the need for dedicated outcome trials in patients with T1D and established kidney or cardiovascular disease. ESKD risk estimation using GFR-based models may be best implemented after drug washout as to avoid the reversible hemodynamic eGFR "dip" with SGLT2 inhibition.



TH-OR54

Glycemic Patterns of Peritoneal Dialysis Patients Assessed by Continuous Glucose Monitoring

Nathaniel Ashford,[1,2] Laura Mayeda,[2,3] Leila R. Zelnick,[1,2] Lisa D. Anderson,[1,2] Evelin N. Jones,[1,4] Subbulaxmi Trikudanathan,[4,2] Christopher Marnell,[3] Irl B. Hirsch,[4,2] Yoshio N. Hall,[1,2] Ian De Boer.[1,2] Kidney Research Institute. *[1]Kidney Research Institute, Seattle, WA; [2]University of Washington School of Medicine, Seattle, WA; [3]Northwest Kidney Centers, Seattle, WA; [4]UW Diabetes Institute, Seattle, WA.*

Background: Peritoneal dialysis (PD) utilizes hypertonic dextrose solution, resulting in known complications with the peritoneal membrane, and absorption into the systemic system. Glucose absorbed from the peritoneal cavity likely leads to insulin resistance and hyperglycemia, but we have limited knowledge about the glycemic patterns of PD patients.

Methods: The BLOSSOM study observed dysglycemia in dialysis patients. Participants wore a Dexcom G6 Pro continuous glucose monitor (CGM) for up to 10 days and completed PD prescription diaries. This interim analysis describes glycemic patterns during day (8:00-20:00) and night (20:00-8:00) in this population.

Results: We enrolled 40 participants treated with PD[AN1], 23 with diabetes mellitus (DM) with and 17 without. Hemoglobin A1C (SD) for participants with DM was 7.3% (1.7%). Mean BG was high, and time in range (TIR) was low (TIR above 70% is recommended) for PD participants with and without DM (Table). At night, high blood glucose levels were seen, and this persisted throughout the day. Dialysate 2.5% dextrose groups had the highest nighttime blood glucose levels (Figure).

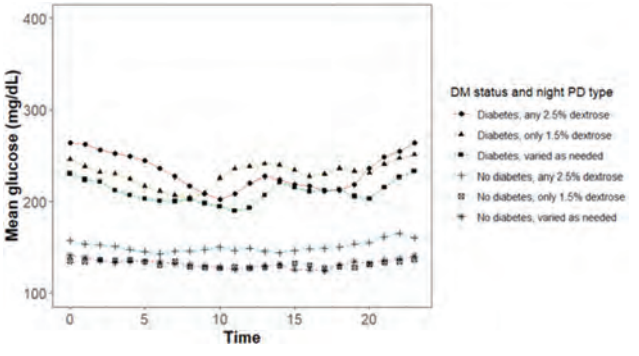
Conclusions: Persistent hyperglycemia was seen in PD patients night and day. TIR was far below target for participants with DM, who spent about a third of time >250 mg/dL. PD patients without DM were in target range only about half the time. Our data suggest a need to closely monitor PD patients for dysglycemia regardless of diabetes status.

Funding: NIDDK Support

CGM Statistics

	No diabetes (N = 17)			Diabetes (N = 23)		
	All	Night[1]	Day	All	Night	Day
Mean blood glucose (mg/dL) (SD)	142 (19)	145 (19)	138 (20)	223 (62)	232 (71)	215 (58)
Glucose management indicator[2] (%) (SD)	6.7 (0.5)			8.7 (1.5)		
Time in range[3] %(SD)	54 (27)	49 (30)	60 (25)	38 (27)	34 (28)	41 (27)
Time above 250 mg/dL %(SD)	0 (1)	1 (2)	0 (1)	32 (29)	35 (34)	28 (27)

[1]20:00-8:00; [2]Mean glucose derived from CGM, complementing HbA1c for glycemic assessment.; [3]TIR 70 –140 mg/dL for participants without DM. TIR 70-180 mg/dL for participants with DM



TH-OR55

Kir5.1 Is Essential to Formation of Kir4.2/Kir5.1 Heterotetramer in the Basolateral Membrane of Mouse Proximal Tubules

Wen-Hui Wang. *New York Medical College School of Medicine, Valhalla, NY.*

Background: Kir5.1 is encoded by *Kcnj16* in the mouse kidney and it is expressed in the basolateral membrane of the proximal tubule (PT), distal-convoluted-tubule (DCT) and cortical- collecting-duct. In DCT, Kir5.1 interacts with Kir4.1 to form a 40-pS K^+ channel, a main type of K^+ channel in the basolateral membrane. Moreover, Kir4.1 can also form a homotetramer in the absence of Kir5.1 and provides the basolateral K^+ conductance of DCT. In PT, Kir5.1 interacts with Kir4.2 to form Kir4.2/Kir5.1 heterotetramer, a main type basolateral K^+ channel. However, it is not clear whether Kir4.2 along is sufficient for forming a Kir4.2 homotetramer without Kir5.1 in the basolateral membrane and maintains PT membrane conductancel.

Methods: We now conduct immunofluorescence-staining and patch-clamp-experiments in Kir5.1-knockout (KO) mice and corresponding wild-type (WT) mice to examine the expression of Kir4.2 and to determine the basolateral K^+ channel activity and PT membrane potential.

Results: The single-channel-recording identified a 50-pS K^+-channel in the basolateral membrane of PT of WT mice. This 50-pS K^+-channel is a main type basolateral K^+ channel and is most likely Kir4.2/Kir5.1 heterotetramer. However, this 50-pS inwardly-rectifying-K^+-channel was completely absent in the PT of Kir5.1-KO mice. Moreover, patch-clamp-experiments failed to detect additional basolateral K^+ channels in the PT of Kir5.1-KO mice. Immunofluorescence-staining shows that Kir4.2 is exclusively expressed in the PT. While the basolateral membrane staining of Kir4.2 was clearly visible in WT mice, it was largely absent in Kir5.1-KO mice. This is in sharp contrast to Kir4.1, which has a clear basolateral membrane staining in both WT and Kir5.1-KO mice. Also, the membrane potential of PT was more positive in Kir5.1-KO mice than WT mice, suggesting that deletion of Kir5.1 impairs Kir4.2 membrane expression. Immunoblotting also showed that the expression of Kir4.2 and Na/H exchanger-3 was lower in Kir5.1-KO mice than WT mice.

Conclusions: We conclude that Kir5.1 is essential for forming the basolateral 50-pS K^+-channel in the PT and plays a role in determining Kir4.2 basolateral membrane abundance. Also, Kir4.2 could not form a homeotetrammer in the absence of Kir5.1 and the membrane potential of PT is depolarized in the Kir5.1-KO mice.

Funding: NIDDK Support

TH-OR56

Spalt-Like Transcription Factor 3 (Sall3) Is Essential for Maintaining Distal Convoluted Tubule Differentiation

Hyun Jun Jung,[1] Boyoung Kim,[1] Mohammed Z. Ferdaus,[2] Lama Al-Qusairi,[1] Rick Grimm,[1] Eric J. Delpire,[2] Paul A. Welling.[1] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Vanderbilt University Medical Center, Nashville, TN.*

Background: Activation of the sodium chloride cotransporter (NCC) in the distal convoluted tubule (DCT) by the WNK-SPAK signaling pathway is paralleled by an adaptive remodeling process, characterized by DCT cell proliferation and hypertrophy. Regulatory networks responsible for remodeling and maintaining DCT fate have not been identified. Here we identify a DCT-specific transcription factor (TF), Sall3, that is rapidly induced by SPAK-dependent signaling, and characterize the consequences of conditionally and specifically deleting Sall3 from the DCT.

Methods: Genome-wide single-nucleus and bulk RNA sequencing (RNA-Seq) was performed in the kidney tissues of wild-type (WT) mice and mice genetically engineered to constitutively activate the SPAK kinase (CA-SPAK) in the DCT, causing constitutive NCC activation. Multimodal-bioinformatic analyses were used to identify the DCT-specific TFs that are induced downstream of SPAK-NCC. An inducible DCT-specific knockout (KO) mouse model was generated for one of the SPAK-induced TFs, Sall3, and the phenotype of the mice was characterized.

Results: RNA-Seq and bioinformatic analysis of WT and CA-SPAK mouse kidneys identified Sall3 as a key DCT TF that was significantly induced by chronic SPAK-NCC activation in the DCT. Immunolabeling confirmed that Sall3 is primarily expressed in DCT cell nuclei, and supported snRNA-Seq that Sall3 is also expressed in a minority population of AQP2-negative CNT cells. In the CA-SPAK mice, SALL3 protein abundance only significantly increased in the DCT nuclei. A similar response was observed in WT mice when WNK-SPAK was physiologically activated with low K diet. Induction of DCT-specific Sall3 KO significantly reduced the expression of DCT-specific genes, indicative of loss of DCT patterning.

Conclusions: In summary, Sall3 is a key component of the core transcriptional regulatory circuit that maintains DCT cell identity in the basal state and as the tubule expands.

Funding: NIDDK Support, Private Foundation Support

TH-OR57

COP9 Signalosome CSN4 and CSN5 Subunits Protect NKCC2 against Endoplasmic Reticulum Stress and Cellular Hypoxia

Kamel Laghmani,[1,2] Stephanie Kharma,[1,2] Sylvie Demaretz,[1,2] Dalal Bakhos Al Douaihy.[1,2] *[1]Centre de Recherche des Cordeliers, Paris, France; [2]Sorbonne Université, INSERM U1138, CNRS ERL 8228, Paris, France.*

Background: MAGE-D2 mutations cause a severe but transient form of antenatal Bartter syndrome (tBS) associated with impaired expression of the sodium–chloride cotransporters NKCC2 and NCC. Cellular hypoxia is particularly interesting to elucidate the molecular basis of the disease because it is one of the major differences between the antenatal symptomatic period of MAGE-D2-related tBS and the post-natal asymptomatic stage. In support of this, MAGE-D2 was found to be required for appropriate induction of HIF-1α and the protection of NKCC2 against ER stress during hypoxia. The present study aimed to explore further the molecular mechanisms involved in the protection of NKCC2 by MAGE-D2 against ER stress and hypoxia.

Methods: A yeast two-hybrid system (Y2H) was used to identify novel NKCC2 binding partners. Protein-protein interactions were analyzed using co-immunoprecipitation (CO-IP) and co-immunolocalization assays. Cellular hypoxia was induced chemically by incubating HEK cells for 16 hours with cobalt chloride (CoCl2). NKCC2 protein expression was monitored by immunoblotting in HEK cells transfected with the co-transporter. NKCC2 stability was assessed by cycloheximide chase assay.

Results: Y2H identified the COP9 signalosome CSN4 and CSN5 subunits as novel binding partners of NKCC2. This is of particular interest because CSN5 is a MAGE-D2 interactor and also a regulator of HIF-1α stability. Co-IP and co-immunolocalization experiments confirmed CSN4 and CSN5 interactions with NKCC2. Similar to MAGE-D2, CSN4 or CSN5 overexpression increased total and surface NKCC2 abundance. Conversely, CSN4 or CSN5 knockdown enhanced the ER-associated degradation (ERAD) of the cotransporter. Subjecting HEK cells transiently with NKCC2 to cellular hypoxia, significantly decreased NKCC2 stability and maturation. Most importantly, like MAGE-D2, the effect of hypoxia on NKCC2 stability and maturation was more severe following CSN4 or CSN5 knockdown.

Conclusions: Our data reveal that CSN4 and CSN5 are novel key players in the ERAD of NKCC2 under ER stress conditions. Most importantly, our findings strongly suggest that MAGE-D2 cooperates with these COP9 signalosome subunits to protect NKCC2 against ERAD induced by cellular hypoxia, which could contribute to the transient nature of antenatal Bartter's syndrome in carriers of MAGED2 mutations.

Funding: Government Support - Non-U.S.

TH-OR58

Mucin 1 Stimulates TRPM6 Single-Channel Activity and Cell Surface Abundance by Impairing Dynamin-Dependent TRPM6 Endocytosis

Matthias T. Wolf,[1,2] Jing Zhang,[2] Julia Kozlitina,[2] Joost Hoenderop,[3] Sung Wan An.[1,2] *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]The University of Texas Southwestern Medical Center, Dallas, TX; [3]Radboud Universitair Medisch Centrum, Nijmegen, Netherlands.*

Background: Genome-wide association (GWAS) studies revealed an association of *Mucin 1* (*MUC1*) variants with hypomagnesemia. The role of MUC1 in Mg^{2+} homeostasis remains unclear. Therefore, we evaluated if MUC1 enhances the activity of the Mg^{2+} channel TRPM6.

Methods: We analyzed the association of *MUC1* variants and hypomagnesemia in the Dallas Heart Study (DHS), a cohort containing over 3,500 individuals. In a more focused study, 24 h urine samples of 12 control and 12 calcium-nephrolithiasis patients were analyzed for urinary electrolytes and MUC1 protein content. MUC1 and TRPM6 plasmids were co-expressed in HEK293 cells to investigate the effect of MUC1 on TRPM6 single channel and whole-cell current density by patch-clamp recording. Results were confirmed applying cell surface biotinylation and protein co-immunoprecipitation.

Results: We found that the *MUC1* variant rs4072037 associated with hypomagnesemia. Urine samples from control and calcium-nephrolithiasis patients showed significantly lower urinary MUC1 levels and hypermagnesuria in nephrolithiasis patients pointing to a stimulatory role of MUC1 towards Mg^{2+} absorption. *In vitro*, co-expression of MUC1 with TRPM6 stimulated TRPM6 single channel current and whole-cell current density. In biotinylation experiments, MUC1 enhanced TRPM6 cell surface abundance. Co-immunoprecipitation confirmed physical interaction between MUC1 and TRPM6. We found that MUC1 interferes with TRPM6 endocytosis by examining the effect of dominant-negative dynamin and dynasore with co-transfected MUC1 and TRPM6. We tested TRPM6 endocytosis more specifically by knocking down clathrin heavy chain or caveolin-1 applying siRNA. Knockdown of both proteins abolished the stimulation of TRPM6 by MUC1. Furthermore, the *N*-glycan mutant TRPM6 (N787A) was not activated by MUC1. Finally, knockdown of the endogenous urinary lectins Galectin-1 and Galectin-3 also impaired MUC1 activation of TRPM6.

Conclusions: The *MUC1* variant rs4072037 associates with hypomagnesemia. *In vitro*, MUC1 stimulates TRPM6 single channel activity, TRPM6 whole-cell current density and TRPM6 cell surface abundance by impairing dynamin-dependent TRPM6 endocytosis. TRPM6 and MUC1 physically interact and form lattice with the TRPM6 *N*-glycan N787. Urinary Galectin-1 and Galectin-3 stabilize this complex.

Funding: Other U.S. Government Support

TH-OR59

Role of mTORC2 in Aldosterone-Independent Potassium Regulation: Resolution of the Aldosterone Paradox

Bidisha Saha, John E. Demko, Enzo Takagi, Robert Weber, David Pearce. *University of California San Francisco, San Francisco, CA.*

Background: ENaC activity and potassium (K^+) secretion in the DCT2 and early CNT (eCNT) are not regulated by aldosterone due to constitutive activation of MR by cortisol. Under low aldosterone conditions, ENaC and ROMK activity are higher in the DCT2 and eCNT than in the late CNT and CD. Acute high K^+ (HK) loads stimulate ENaC and K^+ secretion via mTORC2 independently of aldosterone. Prolonged HK conditions involve aldosterone-dependent activation of ENaC and ROMK for maximal K^+ secretion. This study examined mTORC2's role in K+ secretion across distal nephron segments, focusing on the aldosterone-independent DCT2/eCNT and its role in the aldosterone paradox.

Methods: Rictor, a key mTORC2 component, was selectively knocked out (KO) in DCT2, CNT and CD using Calbindin as Cre-driver (CRKO) or in late CNT and CD using AQP2 as the Cre-driver (ARKO). Both wild-type (WT) and KO mice were subjected to a HK diet for 48 hours. Parameters assessed included urinary and blood electrolyte levels, plasma membrane expression and intracellular localization of renal transporters, and phosphorylation of mTORC2 targets

Results: On a normal K^+ diet, both CRKO and ARKO mice maintained Na^+ and K^+ balance with normal plasma [K^+] levels, but CRKO mice had elevated plasma aldosterone. On a HK diet, CRKO mice showed lower K^+ excretion, hyperkalemia, and elevated aldosterone. Apical αENaC was reduced in DCT2 and eCNT, while late CNT and CCD were mostly unaffected. Phosphorylation of mTORC2 targets like SGK1 and its target, Nedd4-2 was reduced in CRKO mice. In contrast, ARKO mice maintained normal Na^+ and K^+ levels, elevated aldosterone, and preserved ENaC apical localization in the late CNT and CCD.

Conclusions: The data suggest that the DCT2 and eCNT are crucial for ENaC regulation supporting K^+ secretion under HK conditions with mTORC2 playing a key role. This regulation is aldosterone-independent; so we propose the term "Aldosterone Independent Distal Nephron" (AIDN). High aldosterone action in the late CNT and CCD can partly compensate for mTORC2 deficiency to maintain ENaC activity but, ENaC activity in the more distal segments cannot fully compensate, disrupting K^+ balance. Thus, local control of K^+ secretion along the distal nephron ensures potassium homeostasis across various aldosterone levels and highlights the importance of AIDN in resolving the aldosterone paradox.

Funding: NIDDK Support, Private Foundation Support

TH-OR60

Chlorthalidone-Induced Salt Appetite Is Prevented by Afferent Renal Denervation

Babatunde S. Anidu,[1] Amanda Costa Veiga,[1,2] Jaryd Ross,[1] Rawan N. Almutlaq,[1] Alexander R. Dayton,[1] Louise C. Evans.[1] *[1]University of Minnesota Twin Cities, Minneapolis, MN; [2]Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Excessive sodium intake is a significant public health concern, with the average American consuming approximately 3,400 mg daily, ~1g more than the American Heart Associations' recommended daily maximum. Reducing sodium intake is one of the most cost-effective ways to reduce death from non-communicable diseases and improve health outcomes. Our lab has shown that afferent renal denervation (ARDN) reduces sodium intake in male hypertensive DOCA-salt rats. We hypothesize that when the body needs to conserve sodium, afferent renal nerves are activated in response to increased sodium reabsorption in the collecting duct and this stimulates salt intake. To test this, we used chlorthalidone (CTD) to inhibit the sodium-chloride cotransporter (NCC) in the distal convoluted tubule. This increases sodium delivery to the collecting duct. We examined whether CTD causes increased sodium intake and whether this is prevented by ARDN.

Methods: Male Sprague-Dawley rats aged 10-14 weeks were divided into three groups: vehicle (peanut butter, p.o, n=9), CTD (5mg/kg, p.o, n=8), and CTD-ARDN (n=6). The CTD-ARDN group underwent bilateral ARDN (periaxonal capsaicin, 33mM). The other two groups underwent sham surgery. Telemeter catheters were inserted in the femoral artery of all rats for the assessment of mean arterial pressure (MAP). After surgical recovery, all rats had ad libitum access to a low-salt diet (0.01% NaCl) and deionized water and 1.8% saline for 14 days.

Results: Chronic CTD caused a significant increase in saline intake relative to the vehicle treated rats ($p<0.001$). This effect was specific for saline, and water intake was not higher in CTD than vehicle rats ($p=0.4$). ARDN caused a significant reduction in saline

(p=0.02) but not water (p=0.5) intake. Neither CTD nor ARDN had a significant effect on MAP. Ongoing studies are evaluating whether CTD increases salt-appetite in female rats, and if this is dependent on afferent renal nerves.

Conclusions: These studies show, for the first time, that inhibition of NCC causes a specific increase in salt appetite which is driven by the activation of the afferent renal nerves. In future studies, we will use the administration of amiloride to evaluate whether this response is dependent on the activation of ENaC.

Funding: Other NIH Support - LCE is funded by NHLBI R01HL152166

TH-OR61

WNK1 as an Osmolality Sensor: Mechanism and Structure-Function Studies

Xin Jin, Jian Xie, Mohammad Amir, Chou-Long Huang. *University of Iowa Health Care, Iowa City, IA.*

Background: The circumventricular organs (CVO's) of the brain lack a blood-brain barrier. CVO neurons detect serum hyperosmolality to stimulate the production and release of arginine vasopressin (AVP). We recently reported that WNK1 in CVO neurons senses hyperosmolality and activates Kv3.1 channel to increase action potential to increase AVP release. Boyd-Shiwarski et al reported that WNK1 forms condensates during cellular dehydration and activates NKCC1 to restore cell volume. The C-terminal intrinsically disordered region (IDR) is important for formation of the condensates. Here, we studied the role of OSR1/SPAK for WNK1 to activate Kv3.1 and the role of IDR in this activation.

Methods: Mice with CVO deletion of SPAK and OSR1 were produced by stereotaxic injection of Cre-recombinase-carrying AAV virus into CVO of Spak-null and Osr1-floxed mice ($Spak^{-/-}$;$Osr1^{flox/flox}$). Water homeostasis was examined in metabolic cage studies. AVP levels were measured. The Kv3.1 current was studied in HEK cells expressing recombinant WNK1 (or mutants), SPAK, and Kv3.1. Biochemical kinase activity of WNK1 was examined by western blot.

Results: Hyperosmolality increased p-OSR1/SPAK in mouse CVOs. Mice with OSR1/SPAK deletion in CVOs exhibited polyuria with decreased urine osmolality that persisted in water restriction, indicating diabetes insipidus. Circulating levels of AVP and copeptin were lower in water restricted OSR/SPAK deletion mice vs controls. In whole-cell recording with 20 mM Cl^- in the pipette (intracellular), exposure to physiological extracellular hyperosmolality (5 mM NaCl, "HTS") increased Kv3.1 currents in HEK cells expressing full-length WNK1, SPAK, and Kv3.1. Increasing pipette Cl^- to 100 mM blunted the activation of Kv3.1 by HTS. Importantly, cells expressing just the kinase domain of WNK1 (aa 1-491), SPAK, and Kv3.1 responded to HTS. Moreover, HTS induced autophosphorylation of WNK1 (1-491).

Conclusions: The WNK1-mediated osmosensation in CVO neurons involves activation of Kv3.1 through SPAK/OSR1. WNK1 kinase domain can detect extracellular hyperosmolality independently of the C-terminal IDR region. The results support the structural data that water and chloride in the cavity of WNK kinase domain negatively regulate the kinase activity. How IDR coordinates with the kinase domain to regulate downstream effectors awaits future studies.

Funding: NIDDK Support

TH-OR62

Facilitation of Mg2+ Extrusion by the Murine Distal Convoluted Tubule-Specific Isoform of SLC41A3

Gijs A. Franken,[1] Willem Bosman,[1] Hyun Jun Jung,[3] Caro Bos,[1] Femke Latta,[1] René J. Bindels,[1] Mark A. Knepper,[2] Joost Hoenderop,[1] Jeroen H. De Baaij.[1] *[1]Radboud Universitair Medisch Centrum, Nijmegen, Netherlands; [2]National Institutes of Health, Bethesda, MD; [3]Johns Hopkins Medicine, Baltimore, MD.*

Background: The distal convoluted tubule (DCT) plays an indispensable role in magnesium (Mg^{2+}) reabsorption in the kidney. Here, transcellular Mg^{2+} transport takes place, yet the extrusion mechanism is currently unknown. The solute carrier 41 A3 (SLC41A3) has been suggested to be involved in Mg^{2+} extrusion. Yet *in vitro* and *in vivo* studies could not demonstrate the molecular function of SLC41A3. In this study, we describe two distinct SLC41A3 isoforms with unique expression patterns and functions.

Methods: Using available RNA-sequencing data and RT-qPCR, expression of the two alternative *Slc41a3* transcripts, encoding isoform (iso) 1 or -2, were assessed in kidney and isolated DCT tubules. HEK293 or HAP1 cells were transfected with plasmids expressing either of the isoforms, followed by $^{25}Mg^{2+}$ uptake and extrusion studies. Identification of DCT-specific cis-regulatory elements (CRE) was achieved by combining data from available ATAC sequencing data and luciferase assays in HeLa cells.

Results: Expression studies revealed the presence of a distinct transcript of *Slc41a3* in the DCT with an alternative promoter, leading to a shorter protein with a distinct N-terminus (iso2). HEK293 cells overexpressing SLC41A3-iso2 exhibited 2.7-fold higher $^{25}Mg^{2+}$ uptake compared to mock. In contrast, SLC41A3-iso1-transfected cells increased $^{25}Mg^{2+}$ uptake by 1.7-fold, while on average protein expression of SLC41A3-iso2 was ~35 fold lower dan SLC41A3-iso1. SLC41A3-iso2 overexpressing cells showed 1.5-fold higher $^{25}Mg^{2+}$ extrusion compared to mock-transfected cells, whereas iso1-transfected cells did not show this increase. Using TRPM7 KO HAP1 and CNNM3 and -4 KO HEK293 cell models, $^{25}Mg^{2+}$ extrusion by SLC41A3-iso2 was demonstrated to be independent of these Mg^{2+} transporting proteins. Via available ATAC sequencing data, a CRE accessible in the DCT was identified, ±3.3kb upstream of the TSS of *Slc41a3-iso2*. Luciferase assays demonstrated that the presence of the CRE increased the *Slc41a3-iso2* promoter activity ±4-fold, indicating the CRE contains an enhancer function.

Conclusions: In conclusion, we identified two alternative transcripts of *Slc41a3* in mouse. *Slc41a3*-iso2 is enriched expressed within the DCT with specific gene regulatory elements. We speculate that specifically in the DCT, SLC41A3-iso2 orchestrates Mg^{2+} extrusion.

TH-OR63

Foxp1/Dmrt2/Hmx2 Transcriptional Network Regulates Intercalated Cell Differentiation in Kidney Collecting Ducts

Xiangjian Zheng, Yu Feng, Yanmiao Qi. *Tianjin Medical University, Tianjin, China.*

Background: Kidney collecting ducts are comprised of principal cells (PCs) and intercalated cells (ICs), with ICs playing a crucial role in kidney acid-base regulation through H^+ and HCO_3^- secretion. Despite its significance, the molecular mechanisms controlling IC development remain incompletely understood. Single cell sequencing analysis found Foxp1 is selective expressed in ICs relative to PCs, DMRT2 and HMX2 are selective expressed in type-A ICs and type-B ICs respectively.

Methods: To investigate the specific role of Foxp1 and its downstream trascriptional factors in kidney tubular system, we specifically deleted *Foxp1* expression in kidney distal nephrons and collecting ducts. We examined the effects of *Foxp1* on IC differentiation and urine acidification. RNA sequencing and Chip-seq were used to identify Foxp1 target genes. To dissect genetic network regulates IC differentiation, *Dmrt2 and Hmx2*-deficient mice were generated to determine the role of Dmrt2 and Hmx2 in IC differentiation. *Foxp1* deficient mice were cross with *Notch2* deficient mice to dissect the relation between Foxp1 and Notch signaling.

Results: Immunostainings confirmed Foxp1 is selectively expressed in ICs in collecting ducts. Absence of Foxp1 in kidney tubules led to the abolishment of IC differentiation in the collecting ducts, resulting in distal renal tubular acidosis. ChIP-seq and Ribo-Seq analysis found that Foxp1 binds to the promoters of Hmx2 and Dmrt2, two genes encoding transcription factors specifically expressed in type-A and -B ICs, respectively, and promotes their expression. Genetic disruption of Dmrt2 and Hmx2 expression blocks type-A and type-B IC differentiation, respectively. Deletion of Foxp1 blocks the excessive IC differentiation driven by loss-of-function of Notch2, but conditional knockin of Foxp1 do not alter the balance of PC/IC ratio in collecting ducts.

Conclusions: Foxp1 is required at the downstream of Notch signaling for the renal ICs differentiation and participated in acid-base regulation. Foxp1 regulated downstream transcriptional factors, Dmrt2 and Hmx2, which involved in the specification of distinct subsets of ICs.

TH-OR64

Aryl Hydrocarbon Receptor Pathway Enhances Peritoneal Fibrosis in a Murine CKD Model Exposed to Peritoneal Dialysate

Pranav Yadati,[1] Saran Lotfollahzadeh,[1] Wenqing Yin,[1] Jean M. Francis,[1] Vipul C. Chitalia.[1,2] *[1]Boston University, Boston, MA; [2]VA Boston Healthcare System Jamaica Plain Campus, Boston, MA.*

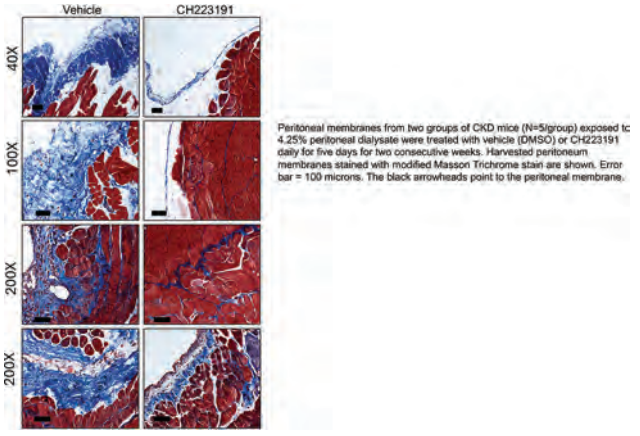
Background: Peritoneal dialysis (PD) results in profound alterations in the peritoneal membrane. Chronic kidney disease (CKD) is a profibrotic condition characterized by the retention of uremic toxins. The mechanisms contributing to the alterations in the peritoneal membrane, specifically due to uremic solutes and peritoneal dialysate remain poorly understood.

Methods: A mouse model of CKD with peritoneal dialysis was employed along with the molecular and imaging technique for mechanistic probing.

Results: We show in humans that CKD induces peritoneal membrane thickening, fibrosis, and collagen deposition and activates the Aryl Hydrocarbon Receptor pathway (AHR) in the subperitoneal vasculature. Leveraging a novel model of peritoneal dialysis in CKD mice, we confirm these CKD-induced changes in the peritoneal membrane, which are exacerbated upon exposure to the peritoneal dialysate. Peritoneal dialysate further augmented AHR activity in the endothelial cells of peritoneal microvasculature beyond CKD. Treatment of CKD mice with an AHR inhibitor in peritoneal dialysate resulted in a 5-fold decrease in subperitoneal space, a 9-fold decrease in fibrosis (see attached figure) and collagen deposition compared to vehicle-treated CKD mice. AHR inhibition reduced inflammation, subperitoneal neovascular areas, and its downstream target, tissue factor. An AHR inhibitor normalized pro-inflammatory and profibrotic cytokines, such as IL-6, MCP1, and MIP1 levels, in the peritoneal dialysate of CKD mice.

Conclusions: This study, for the first time, demonstrates the AHR activation in the endothelial cells of subperitoneal vessels in human CKD and mice, which is likely to prime the peritoneal membrane to dialysate-induced alterations. This study supports further exploration of AHR as a potential therapeutic target to preserve the structural and functional integrity of the peritoneal membrane in peritoneal dialysis.

Funding: Private Foundation Support



Peritoneal membranes from two groups of CKD mice (N=5/group) exposed to 4.25% peritoneal dialysate were treated with vehicle (DMSO) or CH223191 daily for five days for two consecutive weeks. Harvested peritoneum membranes stained with modified Masson Trichrome stain are shown. Error bar = 100 microns. The black arrowheads point to the peritoneal membrane.

TH-OR65

Unveiling the Role of Mucosal-Associated Invariant T Cells in Peritoneal Fibrosis and Its Therapeutic Targeting

Yuxiang Sun, Qiang Huang, Hui Peng. *The Third Affiliated Hospital of Sun Yet-sun University Department of Nephrology, Guangzhou, China.*

Background: One of the most common causes of discontinued peritoneal dialysis (PD) is progressive peritoneal fibrosis. Persistent low-grade inflammation induced by PD treatment is a driving force of peritoneal fibrogenesis. Mucosal-associated invariant T (MAIT) cells, known for their role in immune responses against microbial infections, have also been implicated in various inflammatory and fibrotic diseases. Despite their known importance, the specific mechanisms through which MAIT cells contribute to peritoneal fibrosis remain poorly understood.

Methods: Utilizing single-cell RNA sequencing (scRNA-seq) and flow cytometry, we characterized the activation and function of peritoneal MAIT cells from patients receiving long-term peritoneal dialysis (PD). We explored the molecular pathways activated by these cells, focusing on the MR1-mediated interaction with mesothelial cells and the subsequent activation of the mTORC1 signaling pathway. The effects of MAIT cell inhibition on fibrogenesis were examined using both in vitro models and Mr1 knockout mice.

Results: Our findings indicate that long-term PD enhances the activation of MAIT cells, specifically increasing the population of pro-inflammatory MAIT17 subtype cells. These cells contribute to peritoneal fibrosis by binding to the MR1 receptor on mesothelial cells, inducing hyperglycolysis via the mTORC1 pathway, which leads to peritoneal fibrogenesis. Furthermore, we demonstrate that blocking the MR1-MAIT interaction, either through genetic knockout or pharmacological inhibition with Ac-6-FP, mitigates fibrosis, suggesting a novel therapeutic strategy.

Conclusions: This study underscores the crucial role of MAIT cells in the pathogenesis of peritoneal fibrosis and identifies them as potential targets for therapeutic intervention. The findings suggest that while some aspects of MAIT cell involvement in fibrosis are beginning to be understood, comprehensive insights into their roles in various pathological conditions remain limited, warranting further investigation.

TH-OR66

Iron Deficiency Increases Mortality Risk among Incident Peritoneal Dialysis Patients

Vladimir Rigodon,[1,2] Brianna Hartley,[1,3] Peter G. Pecoits,[4] John W. Larkin,[2] Yue Jiao,[2] Luca Neri,[5] Len A. Usvyat,[2] Dinesh K. Chatoth,[2] Jeffrey L. Hymes,[2] Franklin W. Maddux,[6] Jeroen Kooman,[7] Thyago P. Moraes,[1] Pasqual Barretti,[10] Peter Kotanko,[8,9] Roberto Pecoits-Filho,[1] Murilo H. Guedes.[1] *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Fresenius Medical Care, Waltham, MA; [3]Nova Southeastern University, Clearwater, FL; [4]Indiana University, Bloomington, IN; [5]Fresenius Medical Care, Crema, Italy; [6]Fresenius Medical Care AG, Bad Homburg, Germany; [7]Maastricht University Medical Center, Maastricht, Netherlands; [8]Renal Research Institute, New York, NY; [9]Icahn School of Medicine at Mount Sinai, New York, NY; [10]Universidade Estadual Paulista, São Paulo, Brazil.*

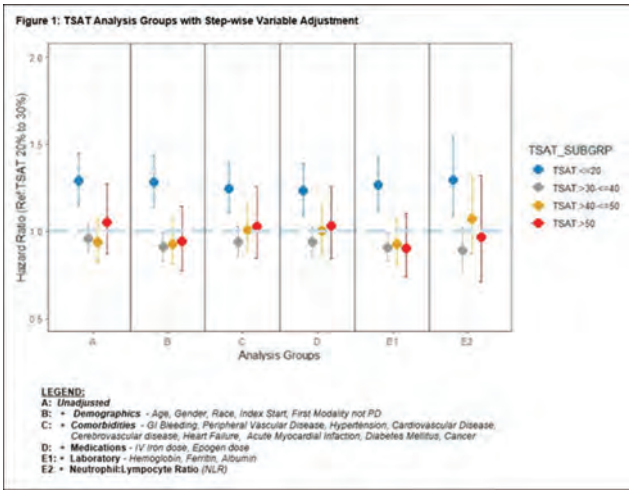
Background: Iron deficiency (ID) can be more common in peritoneal dialysis (PD) vs hemodialysis. Administration of IV iron can be more challenging in PD and may influence iron repletion. Outcomes related to ID in PD are undefined. We investigate mortality risk associated with transferrin saturation (TSAT) and ferritin levels among patients starting PD in a national dialysis network.

Methods: We evaluated data on adults (age ≥18 years) who started PD at a US dialysis network (Fresenius Medical Care, Waltham, MA) between December 2004 and January 2011. Patients were required to be on PD for ≥180 days, and have ≥1 value for TSAT, ferritin and hemoglobin (Hgb). We considered categories for TSAT (≤20%, >20-≤30% reference, >30-≤40%, >40-≤50% and >50%). Cox proportional hazards model assessed mortality risk with stepwise adjustment across 6 models.

Results: Of 11,261 patients, majority were male (54.4%), Caucasian (70.4%) and mean age of 55.2 years. Mean Hgb, TSAT and ferritin values at baseline (≤180 days after PD start) were 12.1 g/dL, 31% and 443.6 ng/ml, respectively. ID (TSAT ≤20%) was present in 10.4% of patients. TSAT ≤20% was found to associate with higher mortality risk across all models (fully adjusted model hazard ratio (HR)=1.30, 95% confidence interval (CI)=1.09, 1.55) (**Figure 1**). TSAT levels >20% were not associated with mortality risk.

Conclusions: We observed about 10% of patients starting PD have ID as seen by TSAT ≤20% during the first 6 months of therapy. ID in incident PD was found to associate with a 30% increased mortality risk. These findings expand upon the emerging science on ID risks in non-dialysis dependent kidney disease (Guedes M et al., JASN 2021), and highlight the importance of evaluating ID in PD, regardless of Hgb status.

Funding: Commercial Support - Fresenius Medical Care, Pontifícia Universidade Católica do Paraná, Baxter Healthcare



TH-OR67

Initial Evaluation of Sodium-Free Intraperitoneal 30% Icodextrin/ 10% Dextrose Solution to Test Short-Term Safety, Tolerability, and Preliminary Efficacy

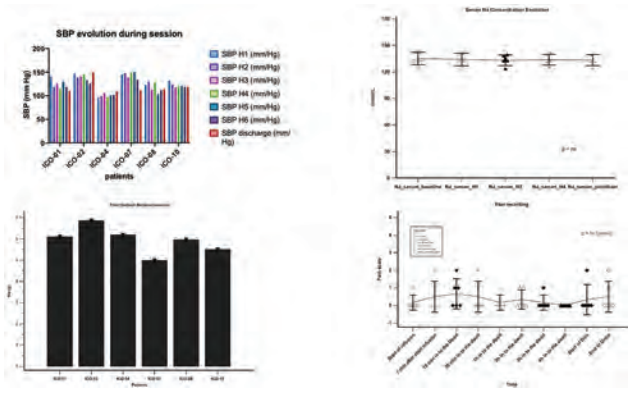
Christopher W. McIntyre,[1] Patrik Deleaval,[1,2] Jarrin D. Penny,[1] Amy Freeman.[1] *[1]London Health Sciences Centre London Kidney Clinical Research Unit, London, ON, Canada; [2]Nephrocare Tassin Charcot, Sainte-Foy-les-Lyon, France.*

Background: Currently used peritoneal dialysis (PD) solutions contain salt limiting their diffusive ability to remove sodium (Na). Na removal is largely dependent on convection, and this becomes increasingly challenging with impending ultrafiltration failure, leading to accumulation of tissue based Na and contributing to increased morbidity/mortality. The aim of this study was to demonstrate the short-term safety, tolerability, and efficacy of a Na-free, PD solution (based 30% Icodextrin) to achieve high-efficiency peritoneal Na and volume removal.

Methods: We studied 10 patients in a single-arm, open label, interventional trial. Stable PD patients aged > 18 years without uncontrolled diabetes mellitus or active infections were enrolled. Study participants received one 4-6-hour dwell of a Na-free PD solution (500 ml instillation volume). They were monitored for pain, hemodynamics, serum sodium and peritoneal removal of sodium and water.

Results: Participants who completed the study reported mild to moderate abdominal pain (1-2/5 pain scale). BP, HR, cardiac output, and stroke volume did not change throughout procedure. Total Na removed per session was 5.69 ± 0.88 g (effluent), ultrafiltrate volume removed was 1975 ± 319 mL, total weight reduction 1.02 ± 0.24kg (p= 0.03). Serum Na remained stable throughout treatment (134.4 ± 5.7mmol/L - 133.3 ± 6.8mmol/L). Na concentration in effluent progressively increased each hour from 90.80 ± 12.36 to 125.4 ± 7.61 mmol/L (p = 0.002). Serum osmolality remained unchanged

Conclusions: We have demonstrated the safety, efficacy, and tolerability of a new Na-free hypertonic PD solution, able to remove >5 g of Na and approximately 2 L of fluid in a single session, without hemodynamic challenge or short term hyponatremia.



TH-OR68

Return to Peritoneal Dialysis after a Hemodialysis Transfer: A Multistate Analysis of the Canadian Organ Replacement Register

Louis-Charles Desbiens,[1] Remi Goupil,[2] Karthik K. Tennankore,[3] Jeffrey Perl,[4] Emilie Trinh,[5] Christopher T. Chan,[6] Annie-Claire Nadeau-Fredette.[7] *[1]Universite de Montreal, Montreal, QC, Canada; [2]Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada; [3]Dalhousie University, Halifax, NS, Canada; [4]St Michael's Hospital, Toronto, ON, Canada; [5]McGill University Health Centre, Montreal, QC, Canada; [6]University Health Network, Toronto, ON, Canada; [7]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada.*

Background: Transfers to hemodialysis (HD) are challenging for patients on peritoneal dialysis (PD). Clinical outcomes after these transfers are poorly known.

Methods: We analyzed patients from the Canadian Organ Replacement Registry (CORR) who received at least 30 days of PD between 2005 and 2019. All transfers from PD to facility HD were identified, regardless of their duration. Patients were followed until December 2019 for outcomes (death, kidney transplant, transfer to home HD, return to PD) and were censored if a second PD-to-HD transfer occurred. We used a multi-state modelization approach, treating different outcomes as states between which patients can sequentially transition.

Results: From 18,956 patients entering PD, 9,746 (51%) patients experienced a total of 18,683 PD-to-HD transfers (mean 1.92 transfers/patient, range 1 to 27) after a median vintage of 1.8 years. Populational trajectories after these transfers are displayed in **Figure 1a**. A majority of patients (66%) resumed PD in the following year; this odd was highest during the first months and sharply fell afterwards (**Figure 1b**). Mortality rates were also high following a PD-to-HD transfer, but resuming PD remained more likely than death up to nine months after the transfer (**Figure 1c**). Five years after a transfer, 50% of patients had died, 6% of patients had transferred to home HD and 34% had received a transplant.

Conclusions: Transfers to HD are common among patients receiving PD in Canada, and, despite a heighten post-transfer mortality risk, a majority of patients can resume PD. These findings identify the post-transfer window as a key period to enhanced clinical care (e.g. using a nurse navigator) in order to improve patients' outcomes.

Funding: Government Support - Non-U.S.

Figure 1a. Event probabilities after a PD to HD transfer

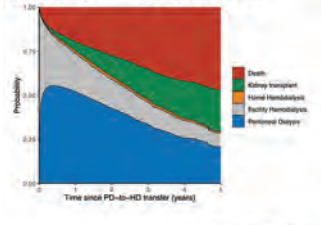


Figure 1b. Odds of returning in PD after a PD to HD transfer

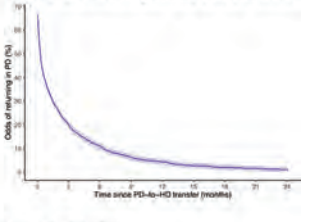
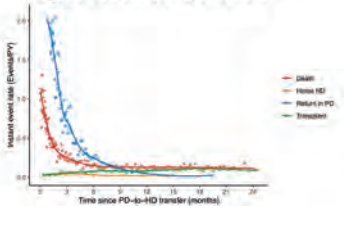


Figure 1c. Event rates after a PD to HD transfer



TH-OR69

Prepivotal Study Exploring Safety, Efficacy, and Usability of the Automated Wearable Artificial Kidney (AWAK) PD Device

Marjorie W. Foo,[1] Edwina A. Brown,[3] Arsh Jain,[4] Martin J. Schreiber,[2] Sheena Gow,[2] Jason T. Lim,[2] Sanjay Singh,[2] Mandar Gori,[2] Suresha B. Venkataraya,[2] Htay Htay.[1] *[1]Singapore General Hospital, Singapore, Singapore; [2]AWAK Technologies Pte Ltd, Singapore, Singapore; [3]Imperial College London, London, United Kingdom; [4]London Health Sciences Centre, London, ON, Canada.*

Background: The AWAK PD is an innovative, wearable sorbent-based device providing tidal PD. The device, weighing about 3kg, automates fills and drains, with adjustable glucose for customized ultrafiltration (UF) requirements.

Methods: 14 subjects underwent screening (30 days), titration period (up to 21 days), washout (2 days), and a treatment period of at-home use (7 days) with an optional extension (23 days), at a single Singapore hospital. A nomogram and PD prescribing titration guide were developed to determine cartridge type, therapy duration, initial fill tonicity and glucose (absorbed/added) to achieve target UF. The primary aim was to complete at least 70% of sorbent dialysis in each therapy. Other aims included maintaining body weight within 5% of target weight, having stable plasma biochemistry and electrolytes, and assessing patients' experience using symptom and device usability questionnaires. Illness Intrusiveness Rating Scale (IIRS) was assessed in the 3 subjects using AWAK for 30 days.

Results: 11 subjects (10 male, mean±SD age 60±7 years and dialysis vintage 21±9 months) entered the 7-day treatment period, with 1 withdrawal. 3 of these subjects completed 30 days. No device-related serious adverse events occurred. 95% of therapies conducted (76/80) were completed. Optimal UF was achieved by adjusting the dextrose concentrations. All subjects remained within 5% of their target weight. Table 1 depicts plasma biochemistry and UF results. Usability scores were high; 10/11 patients agreed they were confident using the device and 8 felt the device was useful, 3 were neutral. IIRS scores improved in the 3 patients on AWAK for 30 days (average score: 38 at baseline; 20 after AWAK).

Conclusions: AWAK PD is safe to use and a reduction in the IIRS is noted after 30 days of use; reasons could range from ease of use of the device to increased flexibility to suit their lifestyle. Minor device modifications can be done to optimize solute clearance.

Funding: Commercial Support - AWAK Technologies Pte Ltd

Table 1: Summary of analytes and UF - median (IQR). Interim data - database lock in Aug

Measure	UF (mL)	Weight (kg)	Urea (mmol/L)	Creatinine (µmol/L)	β2-microglobulin (µg/L)	Sodium (mmol/L)	Potassium (mmol/L)	Bicarbonate (mmol/L)
Baseline	340 (158-660)	73.7 (64.9 - 88.0)	20.8 (19.9 - 22.9)	866 (761 - 1008)	23787 (20397 - 29819)	138 (136 - 141)	4.2 (3.8 - 4.5)	26.0 (25.0 - 28.1)
AWAK	599 (288-829)	73.8 (63.9 - 87.0)	24.3 (21.2 - 28.0)*	987 (835 - 1066)*	23707 (20816 - 33471)	138 (136 - 139)	4.3 (4.1 - 4.5)	24.6 (23.8 - 26.2)

*p-value <0.05

TH-OR70

Comparing Care Models in Assisted Peritoneal Dialysis: Insights from the Alberta Experience

Veronica Hammer,[1] Warda Munawar,[1] Chel Lee,[4] Danielle E. Fox,[1] Robert R. Quinn,[1,2] David Ward,[1] Jennifer M. MacRae.[1,3] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]University of Calgary Department of Community Health Sciences, Calgary, AB, Canada; [3]University of Calgary Department of Cardiac Sciences, Calgary, AB, Canada; [4]University of Calgary, Calgary, AB, Canada.*

Background: Assisted peritoneal dialysis (aPD) provides home-based support by trained healthcare professionals for individuals otherwise ineligible for independent peritoneal dialysis (PD). Alberta Kidney Care South (AKC-S) initiated an aPD program in 2011, initially led by licensed nursing practitioners (LPNs) until transitioning to healthcare aides (HCAs) in July 2018. Our objective was to assess outcomes of participants in the aPD program based on the care delivery model (LPN vs. HCA).

Methods: This quantitative study utilized an interrupted time-series model to analyze participants in the AKC-S aPD program from its inception in 2011 until December 31, 2021. Deidentified data was extracted from the Nephrology electronic database. Participants were categorized into two phases based on the implementation of the care delivery model change from LPN to HCA on July 1, 2018. Phase one comprised participants who initiated aPD before this date, while phase two included those who began aPD after. The primary outcome was monthly median exit time from PD between the two care groups. Endpoints were defined as death, transplant, transfer to in-center HD, transfer to independent PD, or exit from the program. Secondary outcomes included reason for program exit and rates of peritonitis compared between the two phases.

Results: A total of 135 patients received aPD (mean age= 70.7 ± 11.2 years; 44.4% female). We had 57 individuals in phase one, and 55 in phase two (23 still active participants were excluded), with no difference in sex between groups (p = 0.055). We found no difference in the time spent on PD between the LPN phase (1.89 [1.02, 3.85] years) and

the HCA phase (1.41 [0.59, 3.25]), p= 0.41. There was no significant difference in the reason for exit after the change in care model (p= 0.64). The incidence rate of peritonitis in phase one was 0.403 (25 participants) and 0.466 (29 participants) in phase two, which was not statistically significant, p = 0.60.

Conclusions: Our study revealed no significant difference in the duration of peritoneal dialysis (PD), reasons for program exit, or incidence of peritonitis between the LPN and HCA care models. The HCA model offers a cost-effective alternative to in-center modalities while offering personalized, in-person services that may greatly enhance the quality of care for those undergoing peritoneal dialysis.

TH-OR71

Impact of a Home Dialysis Virtual Longitudinal Education Series

Wen Qing Wendy Ye,[1] Anjali B. Saxena,[5,6] Kerry Leigh,[4] Yuvaram N. Reddy.[2,3] *[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [3]Corporal Michael J Crescenz VA Medical Center, Philadelphia, PA; [4]American Society of Nephrology, Washington, DC; [5]Stanford University School of Medicine, Stanford, CA; [6]Santa Clara Valley Medical Center, San Jose, CA.*

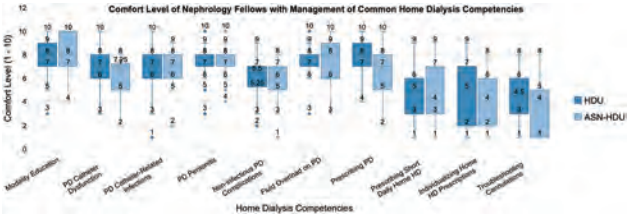
Background: Home dialysis has clinical benefits over in-center hemodialysis (HD), yet as of 2020, home dialysis use is low at 13.3% in the United States. One barrier to expanding home dialysis is a lack of experience amongst fellows due to inadequate training opportunities. In 2023, the American Society of Nephrology (ASN) launched the Home Dialysis Virtual Longitudinal Education Program with Home Dialysis University (HDU) to increase exposure for fellows through virtual case-based discussions. We aimed to understand the impact of this program.

Methods: We evaluated the ASN-HDU program using mixed-methods. We sampled participants from (1) fellows who attended HDU and the ASN virtual program (ASN-HDU), and (2) fellows who only attended HDU from Aug-Sep 2023. We sent a survey in Sep 2023 to assess baseline comfort in home dialysis. Results of the survey were used to design the interview guide for qualitative thematic analysis. We used a constant comparative method to identify themes that described the participant's experiences with home dialysis and the impact of the ASN-HDU program.

Results: Survey response rates were 65.5% (19/29) and 50% (33/66) in the ASN-HDU arm and HDU arm, respectively. Participants felt comfortable with management of peritoneal dialysis but not home HD (Fig 1). We completed 10 semi-structured interviews between Dec 2023 – Mar 2024, with 5 participants from the ASN-HDU arm and 5 from the HDU arm. Three themes emerged: (1) HDU complements fellowship training by filling in gaps in home dialysis knowledge, (2) the ASN virtual program provides an opportunity for longitudinal exposure to topics learned during HDU, which helps retain knowledge and incorporate learning into practice, and (3) all participants voiced desire for more exposure to home dialysis including in-person training, and expansion of the ASN-HDU program.

Conclusions: Baseline survey results suggest a lack of comfort in home HD. ASN-HDU trainees felt the program addresses training gaps in home dialysis and provides an opportunity to retain knowledge. Results from a follow-up survey, sent May 2024, will be available at Kidney Week to evaluate changes in comfort levels among ASN-HDU fellows.

Funding: Other U.S. Government Support



TH-OR72

Home Hemodialysis Skills Assessment Predicts Treatment Survival in Patients on Home Hemodialysis

Koji Tomori, Tsutomu Inoue, Daichi Fukaya, Hiroaki Amano, Yusuke Watanabe, Hirokazu Okada. *Saitama Ika Daigaku, Iruma-gun, Japan.*

Background: During home hemodialysis (HHD), patients require adequate skills and self-care abilities. At HHD initiation, patients are instructed in standard procedures and emergency protocols. However, adherence to these instructions may decrease as dialysis duration increases. Additionally, the required skills and self-care abilities may decline with age and changes in physical abilities, which may interfere with the proper execution of instructions. Our hospital administered the Home Hemodialysis Skills Assessment (HHSA) to patients on HHD to assess their adherence to standard procedures and emergency protocols. This study aimed to examine whether HHSA results can predict the subsequent HHD continuation rates.

Methods: This was a retrospective cohort study of patients who underwent HHSA at our hospital between January 1, 2015, and December 31, 2016. The HHSA consists of six items (45 total points): 1. Dialysis machine setup, 2. needle cannulation and initiation, 3. procedures during treatment, 4. alarm response, 5. termination procedures, and 6. Post-treatment clean-up. Patients were divided into two groups based on the median total score and followed up until failure of the HHD technique, death, or the end of the study (December 2021). The primary outcome was the treatment survival rate, while the secondary outcomes were the death-censored technique and overall survival rates.

Results: Fifty-four patients with a mean age of 56.8 years and a median HHD treatment duration of 67 months were included. The median HHSA total score was 35. There were no significant differences between the high-score group (score >35) and the low-score group (score ≤35) in terms of age, comorbidities, HHD treatment history, or training duration at HHD initiation. However, over the total follow-up period of 300 patient-years, the low-score group had higher rates of HHD discontinuation (15.3% vs. 46.4%, p = 0.023) and technique failure (35.7% vs. 11.5%, p = 0.046) than the high-score group. Multivariate analysis identified age, heart disease, and HHSA total score as predictors of survival after HHD treatment.

Conclusions: HHSA is a predictor of treatment continuation rate in patients undergoing HHD. It may predict individual capability to continue HHD and determine the appropriate timing for transitioning from HHD to in-center dialysis.

TH-OR73

Increased Blood Pressure in Mice with Impaired Function of Afferent Renal Nerves Due to Lack of Sodium Nav1.8 Channels

Kristina Rodionova,[1] Eva Hutter,[1] Tilmann Ditting,[1,2] Nada Cordasic,[1] Karl F. Hilgers,[1] Peter Linz,[1] Mario Schiffer,[1] Roland E. Schmieder,[1] Kerstin U. Amann,[1] Roland Veelken.[1,2] *[1]Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany; [2]Paracelsus Medizinische Privatuniversitat - Nurnberg, Nurnberg, Germany.*

Background: Recently we demonstrated that reduced activity of the afferent renal neural pathway is associated with absent voltage-gated sodium Nav1.8 channels. Now we tested the hypothesis that Nav1.8 KO mice show elevated blood pressure and end organ damage with signs of increased sympathetic activity.

Methods: In Nav1.8 KO mice and C57BL6 (28th week of age), we measured blood pressure (BP), heart rate (HR), activity of renal afferent neurons (portion of highly active tonic neurons with renal afferents harvested from dorsal root ganglion neurons DRG Th11-L2), afferent renal nerve activity (ARNA), renal sympathetic nerve activity (RSNA) as well as infiltration and fibrosis in heart and kidney tissue (deposition of collagen 1 and 4, Counts of CD 68 and CD 3 positive cells).

Results: Blood pressure of Nav1.8 KO mice (C57BL6J-Scn10atm1Jwo) was significantly elevated compared to wild type controls (11±4.8mmHg vers 98±5.2 mmHg; Nav1.8 KO mouse vs control * $p<0.05$.) Nav1.8 KO mice showed increased Collagen Type 1 and 4, CD 68 and CD 3 cells in the kidney and heart (t-test, * $p<0.05$). In Nav1.8 KO mice, only a single cell out of 70 showed a high firing frequency in neurons with dendrites from the kidney versus C57BL6 controls 28 out of 115 (Nav1.8 KO mouse vs control, z-test, *$p<0.05$). Eventually, all data suggested reduced ARNA with disinhibition of RSNA.

Conclusions: We demonstrate for the first time that the absence of a single specific sodium channel impairing afferent renal neural pathways leads to disinhibition of sympathetic nerve traffic with increased blood pressure and end-organ damage

TH-OR74

High Phosphate-Induced Hypertension Is Mediated by Peripheral Fibroblast Growth Factor 23 Translocation into the Central Nervous System, Fibroblast Growth Factor Receptor Activation, and Sympathetic Nervous System Stimulation

Isabelle Carroll, Johanne V. Pastor, Han Kyul Kim, Wanpen Vongpatanasin, Orson W. Moe. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Recent research links high phosphate (P) intake to hypertension via activation of the sympathetic nervous system, but the intermediate mechanisms are unknown. P-rich diets prompt the release of fibroblast growth factor 23 (FGF23) from bone cells to promote negative P balance. In the kidney, FGF23 inhibits P reabsorption and vitamin D activation. Although FGF23 protein and its receptors are known to be present in the central nervous system (CNS), their function and specifically their role in blood pressure regulation during high P intake remain elusive.

Methods: Morphometric features and renal sympathetic nerve activity (RSNA) body weight and organ-body weight ratios were assessed in normal-P (NP) and high P-treated (HP) rats under anesthesia and after decerebration. FGF23 protein in the CNS was measured by immunoblots (IB) and immunochemistry (IHC). FGF23 translocation into the brain was measured by infrared (IR) labelled FGF23 injected intravenously. FGF23 activity blockade was achieved by intracerebroventricular injection of FGFR inhibitors.

Results: Resting mean arterial pressure was higher in HP rats compared to NP rats (P<0.01). FGF23 protein was higher in peripheral blood, cerebrospinal fluid (CSF) and brain tissue in HP rats. IHC revealed FGF23 in choroid plexus and areas of the brainstem, and IB showed higher FGF23 in the hippocampus and brainstem but not cerebral cortex. Injection of IR-FGF23 showed robust signals in choroid plexus, and parts of the brain stem. The HP-induced hypertensive effects were blocked by pharmacologic inhibition of FGFR by broad spectrum and FGFR4 inhibitors injected intracerebroventricularly; and not by the FGF23 C-terminal peptide. FGFR4 inhibition in the CNS reduced HP-induced sympathetic nervous system activation.

Conclusions: We conclude that the hypertensive effects of HP during simulated exercise are mediated by the translocation of circulating FGF23 across the blood/CSF barrier (BCSFB) and occurs independently of the canonical FGF23 pathway leading to exaggerated sympathetic outflow and elevated blood pressure during muscle contraction.

TH-OR75

Key Role of Neuroendothelial Cells in Renal Blood Flow Regulation

Georgina Gyarmati, Alejandra Becerra Calderon, Audrey Izuhara, Sachin K. Deepak, Greta H. Trogen, Janos Peti-Peterdi. *University of Southern California, Los Angeles, CA.*

Background: Transcriptomic studies identified many vascular endothelial cell (EC) subtypes in multiple organs including the kidney. However, their functions are incompletely understood. Our recent studies discovered and characterized the novel minority EC subtype named neuro-endothelial cells (NECs) with endothelial and neuronal characteristics. NECs were found exclusively in small resistance arterioles of the three most metabolically active organs that show the best blood flow regulation, with the highest density in the brain and retina> kidney >heart. Here we hypothesized that NECs are key players in organ blood flow regulation.

Methods: A comprehensive NEC research toolbox including high-resolution transcriptome analysis of mouse brain and kidney ECs, transgenic mouse models, and intravital multiphoton microscopy (MPM) were used.

Results: Single-cell transcriptome analysis demonstrated that in contrast to other ECs, NECs highly express several traditional (e.g., Nos1, Adra2c, Vegfc, Angpt1, Egfl8) and novel (e.g., Cytl1, Mgp, Gkn3) vasoactive and angiogenic factors. Gene Set Enrichment Analysis of the top NEC genes suggested the role of NECs in blood vessel diameter maintenance and vasculature development. MPM of intact kidney arterioles revealed robust NEC-specific calcium responses to acute norepinephrine challenge suggesting the role of NEC adrenoceptors in stress-induced redistribution of regional blood flow. MPM imaging of NEC-Ai27 mouse model revealed that acute optogenetic stimulation of NECs led to rapid vasodilation (D/D0=152+/-7%, p<0.0001). This effect was blunted in mice pretreated with the Nos1 specific inhibitor 7NI suggesting the main role of NEC neuronal nitric oxide synthase in the maintenance of organ blood flow. In contrast, the acute optogenetic inhibition of single NECs in NEC-Ai39 mouse model resulted in imminent vasoconstriction (D/D0=75+/-4%, p<0.01). Further, treatment with Cytl1, a novel angiogenic factor highly enriched in NECs, resulted in EC calcium responses and vasodilation acutely, and in increased capillary density and clonal EC remodeling chronically in Cdh5-GCaMP and Confetti mice, respectively.

Conclusions: In conclusion, the newly discovered NEC molecular mechanisms may play a major role in organ blood flow regulation and may be targeted in future therapeutic development for kidney diseases.

Funding: NIDDK Support, Private Foundation Support

TH-OR76

Activation of the Skin Renin-Angiotensin System Exacerbates Angiotensin II-Induced Hypertension via Skin Vasoconstriction

Shinya Taguchi,[1] Kengo Azushima,[1] Kento Kitada,[2] Norihiko Morisawa,[3] Hiromichi Wakui,[1] Ryutaro Morita,[1] Kentaro Kawasoe,[1] Akira Nishiyama,[2] Kouichi Tamura.[1] *[1]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [2]Department of Pharmacology, Faculty of Medicine, Kagawa University, Kida-gun, Japan; [3]Cardiovascular and Metabolic Disorders Program, Duke-NUS Medical School, Singapore, Singapore.*

Background: Recent studies suggest skin vasoconstriction and sodium (Na^+) accumulation are linked with hypertension. The skin has a localized renin-angiotensin system (RAS), a key regulator of blood pressure (BP), but its functional role remains unclear. This study aims to investigate the role of skin RAS in hypertension.

Methods: Skin tissue from 58 individuals, including hypertensive patients, was used to evaluate the association between skin RAS component expression and office BP. Mice lacking ATRAP (type-1 angiotensin II (Ang II) receptor (AT1R)-associated protein), which selectively inhibits pathological AT1R signaling, in skin keratinocytes (KO: $K14^{Cre}$;$ATRAP^{flox}$) were generated. Hypertension was induced by Ang II (500 ng/kg/min) administration.

Results: In the human study, skin expression of ATRAP was inversely correlated with systolic BP ($r = -0.41$, $P < 0.01$). Telemetry analysis showed that BP elevation and related cardiac hypertrophy were exacerbated in KO mice compared to controls (mean BP, 123.3 ± 4.7 vs. 132.6 ± 3.1 mmHg, $P < 0.05$; heart/body weight, 4.7 ± 0.4 vs. 5.2 ± 0.7, $P < 0.05$). Ang II-infused KO mice had higher skin angiotensinogen levels ($P < 0.05$), while levels in the kidney and heart were similar in both groups. Ang II levels in the skin were also significantly higher in Ang II-infused KO mice than in controls, whereas plasma Ang II levels were comparable in both groups, suggesting skin-specific enhancement of local RAS activity. AT1R blocker treatment eliminated exaggerated Ang II-induced hypertension and enhancement of skin RAS activity in KO mice. Sympathetic nerve activity, plasma volume, and skin Na^+ content did not differ between the groups. In Ang II-infused KO mice, urine volume per water intake increased ($P < 0.001$), despite similar body weight changes in both groups, suggesting decreased extra-renal water loss. Consistent with these findings, skin blood flow and transepidermal water loss were decreased in Ang II-infused KO mice ($P < 0.001$ and $P < 0.01$, respectively). These differences, including exaggerated BP elevation, were eliminated by skin vasodilation via body temperature elevation.

Conclusions: Enhanced skin RAS activity contributes to BP elevation via skin vasoconstriction. Skin RAS may be a novel target for treating hypertension.

TH-OR77

T Cells Drive Kidney Memory for Hypertension

Katherine S. Deck, Yunmeng Liu, Christoph J. Mora, Tonya M. Rafferty, Shengyu Mu. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: For decades, it has been known that the kidney contains a pathogenic memory for salt-sensitive hypertension. For example, kidney transplantation may transfer salt sensitivity and high blood pressure from hypertensive donors to normotensive recipients. However, the culprit cells and mechanisms behind this memory of salt sensitivity remain elusive. Our recent findings suggest that during hypertension, CD8+ T cells (CD8Ts) persist long-term within the kidney, potentially acting as a memory population that perpetuates salt retention. Here, we hypothesize that the establishment of kidney resident memory CD8Ts (CD8Trms) generates the memory of salt sensitivity, resulting in chronic progression and recurrence of hypertension.

Methods: In this study, we utilized two mouse models of hypertension: a classic DOCA-salt model and a novel Angiotensin-II (Ang II) + high salt rechallenge-induced salt memory model. To investigate the role of Trms in the pathogenesis of salt-sensitive hypertension, we employed T-cell specific TGFβRII KO (mTSP-TGFβR KO) mice, which are deficient in Trm formation, alongside wild-type (WT) controls. Blood pressure in all mice was recorded using biotelemetry, and T cells were analyzed using flow cytometry.

Results: In DOCA-salt-treated WT mice, a significant expansion of CD8Trms occurred accompanied by elevated blood pressure. In contrast, mTsp-TGFβR KO mice, which could not develop Trm, exhibited attenuated blood pressure. Testing the recurrence of hypertension, both WT and mTSP-TGFβR KO achieved a similar degree of hypertension during the initial Ang II-salt administration. Intriguingly, only WT mice, with a significant Trm population, showed rapid recurrence of hypertension upon high salt rechallenge. In contrast, mTSP-TGFβR KO mice, lacking Trm development, appeared protected against recurrent hypertension induced by the high salt re-challenge. Flow cytometry confirmed the presence of a substantial CD8Trm population in WT mice, which was absent in mTSP-TGFβR KO mice.

Conclusions: In summary, our study elucidates the mechanisms by which immunological memory, through the formation of kidney-resident memory CD8Ts, underpins the kidney's "memory of salt sensitivity," leading to lifelong and recurring hypertension.

Funding: Other NIH Support - NIH R01-HL146713 (Mu), T32 T-SPaT GM150536 (Deck), Private Foundation Support

TH-OR78

Endoplasmic Reticulum Stress Immediate Early Response 3 Gene Mediates Myeloid-Specific Salt-Sensitive Hypertension in Humans

Jeremiah M. Afolabi,[1] Annet Kirabo.[1,2] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt Institute for Global Health, Nashville, TN.*

Background: Salt sensitivity of blood pressure is a significant risk factor for cardiovascular morbidity and mortality, and currently lacks a diagnostic marker or established treatment protocol. Our previous research indicated that immune cells play a role in salt-sensitive hypertension, but the specific mechanisms are not fully understood. Expression of the early response gene, Immediate early response 3 (IER3) is induced by varying forms of cellular stress and proinflammatory cytokines, but its role in salt-sensitive hypertension is unknown. We hypothesize that high dietary salt intake activates IER3 expression via proinflammatory signaling thereby contributing to salt-sensitive hypertension.

Methods: To test this hypothesis, we conducted bulk RNA sequencing analysis on isolated human monocytes with and without high salt. We also performed in vivo studies on humans living with hypertension using the rigorous Weinberger protocol, followed by single-cell transcriptome profiling using RNA-Seq analysis in peripheral blood mononuclear cells (PBMCs).

Results: We found that in vitro high salt treatment increased human monocyte expression of the ER stress marker, ATF4 (5216.09 ± 343.86 vs 7566 ± 549.17, p=0.0014), in addition to TNF-α (117.09 ± 23.71 vs 357.82 ± 59.62, p=0.0013), FAS (201.45 ± 25.42 vs 422.64 ± 52.15, p=0.0024), NFKB2 (4182.18 ± 401.24 vs 6061.82 ± 692.49, p=0.0192), and IER3 (10146.64 ± 2868.74 vs 19009.09 ± 5343.53, p=0.0759) when compared to normal salt (n=11). In vivo single cell transcriptomic analysis in PBMCs revealed that in response to high salt treatment, IER3 expression changes dynamically with blood pressure (Diastolic Blood Pressure (DBP): r= -0.641, p=0.0074; Mean arterial pressure (MAP): r= -0.6321, p=0.0086; Pulse Pressure (PP): r=0.5033, p=0.0468) in salt-sensitive but not salt-resistant patients (n=8). Furthermore, changes in blood pressure were positively correlated with increased NFKB2 (SBP: r=0.5276, p=0.0357; DBP: r=0.5366, p=0.0321; MAP: r=0.5872, p=0.0168), and TNF-α (PP: r=0.4505, p=0.0799) but not FAS gene expressions in salt-sensitive, but not salt-resistant patients (n=8).

Conclusions: These findings suggest that IER3 plays a role in salt-sensitive hypertension, possibly through the NFKB signaling pathway. The IER3 gene could serve as a valuable diagnostic marker for salt-sensitive hypertension or a novel treatment approach.

TH-OR79

Renal Medullary Bilirubin and Biliverdin Reductase Attenuate Angiotensin II-Induced Hypertension

Gertrude Arthur, David E. Stec. Stec Lab. *University of Mississippi Medical Center Holmes County, Jackson, MS.*

Background: Hypertension is a risk factor for CKD and despite the major advances in drug development to target this disease, uncontrolled blood pressure is a significant problem among hypertensive patients. An increase in circulating bilirubin has been shown to attenuate angiotensin (Ang) II-induced hypertension and improve renal hemodynamics. However, the intrarenal mechanisms that mediate the anti-hypertensive effects of bilirubin are not yet known. The goal of the present study was to test the hypothesis that generation of bilirubin in the renal medulla plays an important role in the regulation of blood pressure (BP) in response to Ang II.

Methods: Twenty-week-old male C57Bl/6J mice were implanted with intrarenal medullary interstitial (IRMI) catheters following unilateral nephrectomy. After this time, biliverdin IXα was specifically infused into the kidney (3.6 mg/day) for 3 days prior to implantation with an osmotic minipump delivering Ang II (1000 ng/kg/min). BP was recorded for 3 days, 1 week after minipump infusion, in conscious mice. To further explore the antihypertensive role of renal medullary bilirubin generation, mice with specific deletion of biliverdin reductase-A (BVRA) in the thick ascending loop of Henle (TALH) were generated by crossing $BVRA^{flox/flox}$ mice with Tamm-Horsfall Cre (THP-Cre) mice. At 20 weeks, THP-Cre/$BVRA^{flox/flox}$ and control mice were infused with Ang II for 2 weeks.

Results: IRMI infusion of biliverdin significantly decreased BP as compared to mice infused with vehicle (118 ± 4 vs. 158 ± 2 mmHg, p<0.05, n=6/group). THP-Cre/$BVRA^{flox/flox}$ mice did not exhibit any differences in baseline BP as compared to $BVRA^{flox/flox}$ mice (108 ± 2 vs. 108 ± 2 mmHg, n=5/group). However, Ang-II infusion resulted in significantly higher BP measured in conscious mice 7 days after implantation in THP-Cre/$BVRA^{flox/flox}$ as compared to $BVRA^{flox/flox}$ mice (152 ± 2 vs. 140 ± 3 mmHg, p<0.05, n=5/group). Also, protein expression of renal outer medullary potassium (ROMK) channel was increased in THP-Cre/$BVRA^{flox/flox}$ mice infused with Ang II (1.05 ± 0.09 vs. 0.7 ± 0.20 AU, p<0.05, n=4/group)

Conclusions: Together, these findings show that medullary bilirubin and biliverdin reductase can improve hypertension and that mechanisms that increase bilirubin and biliverdin reductase in the renal medulla could be an effective approach to treat hypertension.

Funding: NIDDK Support

TH-OR80

Mild Hyperuricemia Is Beneficial for Males with Salt-Sensitive Hypertension and Associated Kidney Damage

Lashodya V. Dissanayake,[1] Adrian Zietara,[1] Vladislav Levchenko,[1] Christine A. Klemens,[1,2] Oleg Palygin,[3] Alexander Staruschenko.[1,4] *[1]University of South Florida Morsani College of Medicine, Tampa, FL; [2]Hypertension and Kidney Research Center, Tampa, FL; [3]Medical University of South Carolina, Charleston, SC; [4]James A. Haley Veterans' Hospital, Tampa, FL.*

Background: Hyperuricemia is associated with worse outcomes for chronic kidney disease (CKD). In large-cohort clinical trials, attempts to control uric acid (UA) did not produce clinically meaningful benefits. Humans don't have the enzyme uricase due to an evolutionary mutation that is hypothesized to have been an adaptation to increase blood pressure under low-salt conditions. We hypothesized that mild asymptomatic hyperuricemia is beneficial in controlling the progression of salt-sensitive (SS) hypertension (HTN), a prevalent trait that occurs in half of HTN patients.

Methods: Both male and female Dahl SS rats were fed a diet with a uricase inhibitor, oxonic acid (2%) (Oxo), and high salt (HS) (4% NaCl). Radiotelemetry, immunohistochemistry, and RNA-Seq were used for analyses.

Results: After 3 wks, in response to Oxo supplementation, both sexes showed a significant increase of UA in plasma compared to their respective HS-only controls (males: 0.63±0.07 vs. 2.17±0.34; females: 0.78±0.15 vs. 2.04±0.35 mg/dl, HS vs. HS/Oxo). Interestingly, only male HS/Oxo rats showed a significant increase in uricosuria (males: 0.23±0.03 vs. 0.45±0.06; females: 0.26±0.06 vs. 0.26±0.01 UA/Cre, HS vs. HS/Oxo). Moreover, mild hyperuricemia was associated with a significant attenuation of the progression and magnitude of the mean arterial pressure in male but not female rats (males: 157±3 vs. 136±3; females: 155±6 vs. 154±5 mmHg, HS vs. HS/Oxo). The male HS/Oxo group had a lower kidney weight/body weight ratio and lower protein cast accumulation, indicating lower kidney damage. Oxo treatment led to less oxidative damage in the tubules compared to HS-only, as evidenced by the lower fluorescence intensity of 8-oxodG. RNA-Seq of male kidneys revealed that HS/Oxo treatment (vs. HS only) increased expression in *Mas1* (MAS receptor), *Klk-1* (Kallikrein-1), and *Pcsk6* (PCSK6 enzyme), which can all lead to the activation of different vasodilatory pathways.

Conclusions: Our study showed that in male but not female Dahl SS rats, asymptomatic mild hyperuricemia accompanied by hyperuricosuria ameliorates the progression of SS HTN and protects kidneys from further damage. Thus, our findings challenge the notion of hyperuricemia being inherently detrimental to health.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

TH-OR81

Glucagon-Like Peptide 1 Receptor Agonist Attenuates Cardiovascular Injury Caused by Renal Fibrosis

Ping-Chi Tsai,[1] Daniel H. See,[1] Yue-Jhu Huang,[1,2] Shin Yun Liu,[2] Jenq-wen Huang,[1,3] Chi-Ting Su.[2,3] *[1]National Taiwan University Hospital, Taipei, Taiwan; [2]National Taiwan University Cancer Center, Taipei, Taiwan; [3]National Taiwan University College of Medicine, Taipei, Taiwan.*

Background: The term "cardiorenal syndrome" has been coined to describe the condition in which a disorder of either the heart or kidneys affects the other organ. Liraglutide, a glucagon-like peptide-1 (GLP-1) analog that acts as a GLP-1 receptor agonist (GLP-1RA), exerts cardioprotective effects. We hypothesized that liraglutide treatment could alleviate secondary damage to the heart stemming from chronic kidney disease (CKD).

Methods: We fed adenine to C57BL/6 mice at the age of 9 weeks (CKD mice) to induce renal fibrosis. Renal function was evaluated using a Transdermal GFR Measurement System (MediBeacon) before, during, and after adenine feeding, with or without liraglutide, at a dose of 1 mg/kg/day. A Prospect High-Frequency Ultrasound Imaging System was used to evaluate left ventricular function. Mitochondrial function, fibrotic markers and caspase activity were studied to understand the molecular pathology in cardiac tissue. We used NHCF-V human cardiac fibroblasts (HCFs) to investigate cellular respiration by use of a Seahorse XF Analyser. Conditional media (CM) collected from hypoxic human proximal tubule (HK-2) cells were used to treat HCFs to determine reactive oxidative species (ROS) levels, inflammatory signaling and apoptosis.

Results: The echocardiography results revealed poorer ejection fraction (EF) in adenine-fed mice than in wild-type mice, which could be abrogated by liraglutide treatment (EF: 43% vs. 55%; $p<0.001$). Cardiac tissue showed higher levels of inflammatory markers (TNF-α, IL-10, VCAM-1; $p<0.001$) in CKD mice, with liraglutide treatment reducing the levels of these markers ($p<0.001$). Moreover, HCFs expressed high levels of ROS and apoptotic markers when treated with CM of hypoxic HK-2, based on results of flow cytometry assays. Liraglutide treatment reduced said oxidative stress and apoptosis. ATP production and glycolysis tended to be lower in the HCFs stressed with CM of hypoxic HK-2, and this reduction was partially reversed with liraglutide.

Conclusions: Our findings showed that renal fibrosis negatively impacts the heart. We demonstrated that GLP-1RA attenuated the damage to the heart caused by CKD to some degree. This cardioprotective effect highlights the potential therapeutic benefits of GLP-1RA in reducing secondary heart damage caused by CKD in the context of cardiorenal syndromes.

TH-OR82

Enhanced Diagnostic Precision in APOL1-Mediated Kidney Disease with the p.N264K M1 Protective Variant

Elena Martinelli,[1,2] Juntao Ke,[1] Atlas Khan,[1] David R. Vanderwall,[7] Janewit Wongboonsin,[3,4] Tze Yin Lim,[1] Moin A. Saleem,[5] Rasheed A. Gbadegesin,[6] Friedhelm Hildebrandt,[7] Ali G. Gharavi,[1] Krzysztof Kiryluk,[1] Matt G. Sampson,[7] Martin Pollak,[8] Simone Sanna-Cherchi.[1] *[1]Columbia University, Division of Nephrology, New York, NY; [2]Universita degli Studi di Parma, Parma, Italy; [3]Renal division, Brigham and Women's Hospital, Boston, MA; [4]Renal division, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [5]Division of Pediatric Nephrology, University of Bristol, Bristol, United Kingdom; [6]Division of Pediatric Nephrology, Duke University, Durham, NC; [7]Division of Nephrology, Boston Children Hospital, Boston, MA; [8]Division of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: The *APOL1* M1 (p.N264K) variant protects against G2-associated APOL1 kidney disease. Utilization of this knowledge can potentially inform precise diagnosis in individuals with *APOL1* high-risk (HR) genotypes (G1/G2, G2/G2). Here we tested two hypotheses: (I) in APOL1-HR individuals, M1 genotyping can help in guiding accurate diagnosis of APOL1 kidney disease or non APOL1 CKD; (II) in APOL1 low-risk (LR), M1 might confer an independent protective effect against FSGS and kidney disease.

Methods: We analyzed exome/genome sequencing data from 118,749 individuals with: FSGS or steroid resistant nephrotic syndrome (SRNS) (N= 3,464), kidney disease non FSGS/SRNS (N= 28,475), and non-kidney disease controls (N=86,810). We extracted G1 and G2 genotypes to infer *APOL1* HR and LR genotypes, and rs73885316 (p.N264K) to infer M1 prevalence in these groups. Pairwise M1 carrier prevalence comparisons were conducted across categories by Fisher's exact test.

Results: In the *APOL1*-HR (N=1,590), M1 was, as expected, significantly depleted in FSGS/SRNS cases (0.63%) compared to non-kidney disease controls (4.14%; $P=1.3 \times 10^{-4}$; OR=0.15, 95%CI 0.02-0.58), driven by APOL1 G2-containing genotypes. CKD non FSGS/SRNS cases were 4-fold more likely to harbor M1 as compared to FSGS/SRNS cases. Chart review identified an alternative, non APOL1, cause for CKD (autoimmune, structural, metabolic, cystic, or al) in all APOL1-HR-M1 cases. Conversely, in APOL1-LR individuals, we detected no protective effect of M1 for FSGS/SRNS.

Conclusions: We did not detect an independent protective effect of M1 in the absence of *APOL1*-HR genotypes, consistent with its role as a genetic modifier. In *APOL1*-HR individuals, M1 enhanced diagnostic precision and can help identify cases with an alternative and potentially treatable cause of CKD not driven by *APOL1*. Given the prevalence of M1 carriers in CKD, we estimate that at least 1 in 23 individuals who carry a G2-containing *APOL1*-HR genotype do not have APOL1 kidney disease or FSGS.

Funding: NIDDK Support, Other NIH Support - DOD grant

TH-OR83

Genome-Wide Glomerular Allele-Specific Expression in Human Proteinuric Kidney Tissue

Ana C. Onuchic-Whitford,[1,2] Junmo Sung,[1,2] Erotokritos Sakkas,[2] Michelle Mcnulty,[2] Anya Greenberg,[2] Jihoon Yoon,[3,4] Sowmya Badina,[1,2] Matt G. Sampson,[2,5] Dongwon Lee.[2,5] NEPTUNE (Nephrotic Syndrome Study Network). *[1]Brigham and Women's Hospital, Boston, MA; [2]Boston Children's Hospital, Boston, MA; [3]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [4]Gangnam Severance Hospital, Seoul, Republic of Korea; [5]Harvard Medical School, Boston, MA.*

Background: Regulation of gene expression plays a key role in disease pathophysiology and contributes to penetrance of pathogenic variants. Allele-specific expression (ASE), where each copy of a gene contributes differentially to total gene expression, is a robust measure of cis-regulatory effects. While this phenomenon is well described in other organs, ASE analysis in kidneys is limited, mainly to normal tissue. Here, we successfully generated a genome-wide, high-quality ASE dataset in glomerular tissue from individuals with proteinuric kidney disease in NEPTUNE, using a rigorous computational pipeline.

Methods: We leveraged whole-genome sequencing (WGS) paired with kidney biopsy-derived glomerular RNA-seq from 240 NEPTUNE participants to robustly quantify ASE events across the genome. WGS was population-phased using WhatsHap and SHAPEIT4 with a large reference panel of phased haplotypes (~500K individuals) from UK Biobank. RNA alignment was done with STAR/WASP to address read mapping bias; duplicate reads were removed. phASER was used to integrate phased WGS and RNA-seq to generate SNP- and gene-level allelic expression data for all individuals. We applied the same pipeline to 88 individuals from GTEx with kidney cortex samples and paired WGS/RNA data.

Results: Using an RNA read count >=20 cutoff, we calculated allelic expression for a mean of 7,173 genes per individual. Applying the binomial test with correction for multiple comparisons, we identified genes with significant ASE (FDR<0.05). 19,175 genes had ASE observed in ≥1 person and 14,148 of these genes were protein-coding. Individuals had a mean of 1,433 ASE genes and 55 genes with monoallelic expression. *PLA2R1* ranked 8th (genome-wide) as most common ASE gene among NEPTUNE participants, with *PLCG2* ranking 12th and *NPHS2* ranking 13th. While these key glomerular genes were also significantly expressed in GTEx kidney samples, they had less ASE among individuals, ranking as 954th (*PLA2R1*), 1719th (*PLCG2*) and 206th (*NPHS2*) most common ASE genes.

Conclusions: We generated a genome-wide dataset of ASE in proteinuric glomerular tissue through a rigorous multi-step process integrating several computational tools. Our initial analysis reveals overrepresentation of ASE in known proteinuric kidney disease-related genes among NEPTUNE participants.

Funding: NIDDK Support, Other NIH Support - NHGRI Support, Private Foundation Support

TH-OR84

Contribution of Germline TET2 Variants to the Pathogenesis of Kidney Diseases through Impaired DNA Damage Repair and Activation of Cytosolic Nucleotide Sensors

Xiujie Liang, Hongbo Liu, Hailong Hu, Jianfu Zhou, Amin Abedini, Andrea Sanchez Navarro, Konstantin A. Kloetzer, Katalin Susztak. Susztak Lab. *University of Pennsylvania, Philadelphia, PA.*

Background: Genome-wide association studies (GWAS) have identified over 800 loci associated with kidney function, yet the specific genes, variants, and pathways involved remain elusive.

Methods: To pinpoint the genes linked to kidney disease, we combined kidney function GWAS, human kidney expression quantitative trait analysis (eQTL), and methylation quantitative trait analysis (meQTL). To discover the variants that modify gene expression in kidney cells, we utilized single-cell chromatin accessibility (snATACseq) and (Crispr-based) genome editing. We created kidney-specific Tet2 knockout mice and manipulated gene expression in human kidney cells using CRISPR to study its role in kidney disease progression. We performed single-nucleus RNA sequencing studies in knock-out mice and RNA sequencing studies in TET2 knockdown tubule cells to delve into the role of Tet2.

Results: By integrating kidney function GWAS, human kidney eQTL and meQTL analyses, we identified TET2 as a novel kidney disease risk gene. Utilizing single-cell chromatin accessibility and CRISPR-based genome editing, we highlight GWAS variants that influence *TET2* expression in kidney proximal tubule cells. Experiments using kidney/tubule-specific *Tet2* knockout mice indicated its protective role in cisplatin-induced acute kidney injury, as well as chronic kidney disease and fibrosis, induced by unilateral ureteral obstruction or adenine diet. Single-cell gene profiling of kidneys from *Tet2* knockout mice and *TET2*-knock-down tubule cells revealed the altered expression of DNA damage repair and chromosome segregation genes, notably including *INO80*, another kidney function GWAS target gene itself. Remarkably both *TET2*-null and *INO80*-null cells exhibited an increased accumulation of micronuclei after injury, leading to the activation of cytosolic nucleotide sensor cGAS-STING. Genetic deletion of cGAS or STING in kidney tubules or pharmacological inhibition of STING protected TET2 null mice from disease development.

Conclusions: Our findings highlight TET2 and INO80 as key genes in the pathogenesis of kidney diseases, indicating the importance of DNA damage repair mechanisms.

Funding: NIDDK Support

TH-OR85

Implication of Heterozygous Variants in PROX1 in Congenital Anomalies of the Kidneys and Urinary Tract

Caroline M. Kolvenbach,[1] Lea M. Merz,[1] Faiza Aslam,[5] Simone Sanna-Cherchi,[3] Hila Milo Rasouly,[3] Ali G. Gharavi,[3] Sergio D. Pena,[6] Velibor Tasic,[4] Zhongwei Li,[2] Shirlee Shril,[1] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]University of Southern California Keck School of Medicine, Los Angeles, CA; [3]Columbia University Vagelos College of Physicians and Surgeons, New York, NY; [4]Saints Cyril and Methodius University in Skopje Medical Faculty, Skopje, Macedonia (the former Yugoslav Republic of); [5]Yale University School of Medicine, New Haven, CT; [6]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.*

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) constitute one of the most frequent birth defects and represent the most common cause of chronic kidney disease in the first three decades of life. Despite the discovery of numerous monogenic disease genes, the identification of an underlying molecular diagnosis often remains challenging.

Methods: We applied exome sequencing (ES) to our cohort of 229 CAKUT trios. Subsequent functional analysis of the identified candidate gene *PROX1* was performed *in vitro* and *in vivo*, employing subcellular localization analyses, luciferase reporter assays, nephron organoid studies and morpholino *knockdown* experiments in *Xenopus* larvae.

Results: Through ES and collaboration, we identified 6 individuals with CAKUT and heterozygous variants in *PROX1*, 2 of them occurring *de novo*. Of note, one individual additionally presented with lymphedema. This phenotype has been previously associated

with heterozygous variants in *PROX1* and thus connects the CAKUT phenotype together with the lymphedema manifestations to *PROX1*. In subcellular localization studies, 1/6 mutants exhibited an aberrant nuclear signal compared to the wild type, which potentially interferes with DNA-interaction of the transcription factor. Luciferase reporter assays demonstrated impaired Wnt (4/6 mutants) and retinoic acid (RA; 5/6 mutants) pathway signaling. In addition, PROX1 partially colocalized with NRIP1, a known CAKUT disease gene. NRIP1 is a key regulator of RA signaling, which we could show was influenced by coexpressing PROX1. RNA-sequencing data of nephron progenitor cells showed expression of *PROX1* at this early stage during nephron development, which persisted through the differentiation process to kidney organoids. Moreover, human disease features are replicated in *knockdown Xenopus* larvae, exhibiting abnormal tubular structure.

Conclusions: Our data indicate that *PROX1* variants cause CAKUT by interference with Wnt and RA transcriptional signaling, two major pathways of nephrogenesis.

TH-OR86

A Drosophila Model for Dent Disease

Matias Simons,[1] Olivier Devuyst,[3] Indira Dibra,[2] Salómon Christer.[2]
[1]University Hospital Heidelberg, Institute of Human Genetics, Heidelberg, Germany; [2]University Hospital Heidelberg, Institute of Human Genetics, Heidelberg, Germany; [3]Universitat Zurich, Zurich, Switzerland.

Background: Dent's disease is an inherited disease characterized by the loss of protein uptake receptors cubilin and megalin and subsequent impairment of the endocytic pathway in the proximal tubule of the kidney. The predominant cause for Dent's disease is mutations in the human *CLCN5* gene, encoding the kidney-specific chloride-proton exchanger ClC-5. Utilizing a *Drosophila* model for Dent's disease, we sought to uncover the pathogenic mechanisms behind the protein uptake receptor loss.

Methods: The functional orthologue of ClC-5, ClC-c, was knocked down in *Drosophila* Nephrocytes through UAS-GAL4 based-expression of specific RNAi constructs. The effects of knockdown of ClC-c and other genes were measured using immunofluorescence (IF) analysis or by co-expression with fluorescent reporters. Endocytic function was measured through uptake of FITC-albumin. IF analysis was additionally performed on kidney sections from age matched control and *Clcn5* knockout mice.

Results: Utillizing ClC-c-deficient *Drosophila* nephrocytes we were able to recapitulate the loss of surface cubilin and decreased endocytic activity phenotypes that are characteristic of Dent's disease. Cubilin was found to localize to the endoplasmic reticulum (ER) and, faintly, to degradative compartments. A similar ER retention of cubilin could be produced upon loss of Rab11. Dent's disease nephrocytes also displayed large autolysosomal compartments with strong cholesterol storage. Knockdown of dynamin and cubilin mimicked these phenotypes, suggesting they occur downstream of impaired endocytosis. Additionally, cortical actin accumulation and mislocalization of slit diaphragms could be observed at the cortex of ClC-c knockdown nephrocytes, in line with previously published glomerular defects in Dent's disease patients. Finally, ER retention, lysosomal cholesterol storage and actin accumulation could be reproduced in a mouse model for Dent's disease.

Conclusions: We have found that cubilin is retained in the ER which seems to occur through perturbed function of the endosomal recycling pathway. The impaired endocytosis in turn leads to reduced protein uptake, which is possibly linked to the enhanced autophagy. Our study has uncovered a broad range of evolutionarily conserved phenotypes associated with Dent's disease which may pave the way for new therapeutic strategies in Dent's disease.

Funding: Government Support - Non-U.S.

TH-OR87

Mapping the Genetic Architecture of Kidney Stones in the Million Veteran Program

Ryan Hsi,[1] Otis D. Wilson,[1,2] Hua-Chang Chen,[1,2] Jefferson L. Triozzi,[1,2] Cassianne Robinson-Cohen,[1,2] Zhihong Yu,[1,2] Guanchao Wang,[1,2] Talat Alp Ikizler,[1,2] Edward D. Siew,[1,2] Ran Tao,[1,2] Adriana Hung.[1,2] Million Veteran Program. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]VA Tennessee Valley Healthcare System, Nashville, TN.*

Background: Kidney stones are common, with a 10-20% lifetime prevalence. The prevalence is higher in men and are commonly recurrent. Treatment for recurrent stones has been linked to a decline in renal function. The heritability of kidney stones is 45-50%.

Methods: We identified 29,815 veterans of European ancestry with a diagnosis of kidney stones. Patients with bladder stones, with endocrine causes, or diagnoses of gastrointestinal malabsorption, were excluded. There were 408,294 controls. GWAS was performed using logistic regression, additive model (MAF>1%), imputed to TOPMed, adjusted for age, sex, and first 10 principal components of ancestry.

Results: Mean age 62 (SD12), 4% were women and 36% had diabetes. We identified 80 SNPs in 35 loci at the significance threshold of p=5E-08. Known loci included: The strongest signal was for *UMOD/PDILT (*p-value 1.86E-37), uric acid transporter *ABCG2* (p-value 9.31E-15), alkaline phosphatase gene ALPL (p-value 9.55E-13), calcium-sensing receptor gene CASR (p value 1.23E-11), *PLCL1* associated with Alkaline phosphatase levels, *STAP2* associated with Vit D levels, *LINC02003* associated with levels of PTH. Others: *DGKD, DGKH, HIBADH, MRPL33, ZFPM1, BCAS3.* Novel loci included: NSD1(p-value 1.72E-40) associated with urate levels and BMI, polycystin 2 *PKD2* (p-value 3.22E-17), Corticotropin Releasing Hormone Receptor 1 *CRHR1* (p-value 1.58E-22) and Growth Hormone Releasing Hormone Receptor *GHRHR* (p-value 2.44E-09), Calcineurin Like EF-Hand Protein 1, CHP1(p-value 1.61E-09) all involved in calcium metabolism. Other novel loci, many of which are associated with kidney function or bone density included: *MAPT, MED1, PLEKHM1, PDE3A, TTC33, CHAF1B, PPHLN1, RAB36, WDFY1, MICA, HLA-C, EXD1, FBXL20, FGFR4, GCAT, CKD12, ARHGAP27.*

Conclusions: Our study identified several loci (13 known and 22 novel) involved in renal tubular handling of lithogenic substrates and of inhibitors of crystallization. Some of these loci may represent therapeutic targets. Future work should include functional analyses.

Funding: Veterans Affairs Support

TH-OR88

Development of ABO-101, a Novel Gene Editing Therapy for Primary Hyperoxaluria Type 1

Winston Yan, Tia Ditommaso, Michael Kuefner, Sneha Halwasia, Anthony J. Garrity, Sejuti Sengupta, Lijun Liu, Dan Ory, John E. Murphy. *Arbor Biotechnologies Inc, Cambridge, MA.*

Background: Primary Hyperoxaluria, or PH, is a group of rare genetic metabolic disorders characterized by the overproduction of oxalate by the liver. Oxalate builds up and accumulates in the kidneys and other organ systems, causing kidney damage and progression towards renal failure. PH1, the most common and clinically severe subtype of PH, results from a mutation of the AGXT gene which is expressed primarily in the liver. Here we present pre-clinical in vivo evidence supporting ABO-101 as a novel CRISPR-Cas-mediated gene editing therapy for the treatment of PH1. The current standard of care siRNA therapy for PH1 requires lifelong treatment and targets HAO1, which encodes the glycolate oxidase enzyme (GO) and is upstream of the mutant AGXT. Inhibition of HAO1 lowers the availability of oxalate precursors and thus results in a therapeutically meaningful reduction of oxalate levels and a corresponding increase in serum glycolate, a metabolic byproduct of HAO1 inhibition.

Methods: ABO-101 was designed to specifically inactivate the HAO1 gene in liver hepatocytes and provide a durable reduction of oxalate levels through a single course of treatment. ABO-101 is comprised of a lipid nanoparticle (LNP) which encapsulates our proprietary engineered variant of Cas12i2 (ABR-001) and a guide RNA (gRNA), selected to share 100% sequence complementarity to the cynomolgus macaque NHP HAO1 gene.

Results: In NHPs treated with ABO-101, we achieved HAO1 editing of approximately 60% in whole liver tissue, which correlates to a greater than 2x increase in serum glycolate, all with a well-tolerated safety profile. We also observed a dose-dependent increase in editing levels with a concomitant increase in serum glycolate levels and reduction of GO enzyme activity levels. In addition to both rodent and primate pharmacology data, we also describe our approach optimizing our lead gRNA, ratios of components inside the LNP, and the mRNA encoding the gene editing machinery; these optimizations resulted in our lead therapeutic candidate ABO-101.

Conclusions: Taken together, these results provide in vivo proof of pharmacology for a gene editing approach and support further advancement of ABO-101 towards the clinic as a potential treatment for PH1.

TH-OR89

PHYOX3: Long-Term Safety and Efficacy of Nedosiran in Patients with Primary Hyperoxaluria Type 1

John C. Lieske,[1] María Gema Ariceta Iraola,[2] Jaap Groothoff,[7] Graham Lipkin,[10] Shabbir H. Moochhala,[3] Anne-Laure A. Sellier-Leclerc,[4] Gesa Schalk,[8] Verity Rawson,[5] Sara Estupiñan Torres,[9] Jing Zhou,[5] Bernd Hoppe.[6] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [3]Royal Free Hospital, London, United Kingdom; [4]Hospices Civils de Lyon, Lyon, France; [5]Novo Nordisk A/S, Bagsvaerd, Denmark; [6]German Hyperoxaluria Center, Bonn, Germany; [7]Emma Kinderziekenhuis Amsterdam UMC, Amsterdam, Netherlands; [8]Kindernierenzentrum Bonn, Bonn, Germany; [9]Hospital Universitario de Canarias, La Laguna, Spain; [10]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.*

Background: Primary hyperoxaluria (PH) is a disease characterized by oxalate overproduction leading to calcium oxalate stones, nephropathy and kidney failure. Nedosiran, an RNA interference therapy, has been approved in the US for the treatment of PH type 1 (PH1), including mild to moderate renal impairment.

Methods: PHYOX3 (NCT04042402) is an open-label extension trial aiming to evaluate long-term safety and efficacy of once-monthly nedosiran in patients with PH. This interim analysis includes 40 participants with PH1 from PHYOX1 (NCT03392896; N=13) and PHYOX2 (NCT03847909; N=27) trials. No patients had previous kidney or

liver transplantation, dialysis, or evidence of systemic oxalosis. Efficacy was assessed via estimated glomerular filtration rate (eGFR), urinary oxalate (Uox) excretion, and relevant clinical outcomes. Safety and efficacy were assessed up to 42 months.

Results: Baseline, mean (SD) age was 24.9 (9.72) years (55% female; 42.5% White), eGFR mean (SD) was 80.0mL/min/1.73m^2 (28.65), and median number of kidney stone events was 3. Mean eGFR remained stable (range 71.0-81.5mL/min/1.73m^2), and reduction in mean 24-hour Uox excretion was maintained through month 42 (**Fig. 1**). Annualized stone event rate decreased from 0.40 at baseline to 0.20 (22 events/108.8 person years). Eight out of 40 participants experienced ≥1 serious adverse event (SAE), none of which were associated with nedosiran treatment. Most common non-serious treatment-related AEs were injection site reactions occurring in 6 patients (15%). Four subjects discontinued treatment (1 pregnancy and 3 withdrawals), and no deaths were reported during the study.

Conclusions: Nedosiran treatment in patients with PH1 was well-tolerated, reduced average Uox levels to normal or near-normal, reduced kidney stone occurrence, and maintained stable renal function for more than 3 years.

Funding: Commercial Support - Dicerna Pharmaceuticals, a Novo Nordisk Company

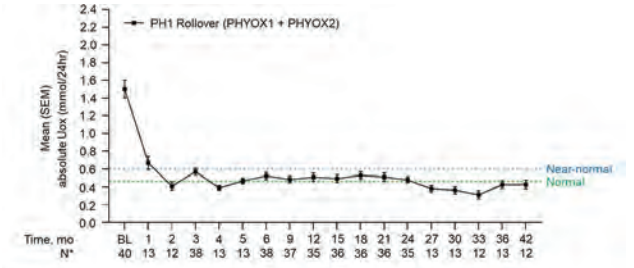


Figure 1. Mean absolute Uox over time. Dotted lines indicate normal (<0.46 mmol/24h, ULN) and near-normal (≥0.46 to <0.60 mmol/24, ≥ULN to <1.3x ULN) limits.
*Values 12-13 in the graph represent data exclusively from patients who rolled over from the PHYOX1 study.
Abbreviations: SEM, standard error of the mean; Uox, urinary oxalate; mo, month; ULN, upper limit of normal.

TH-OR90

Development of a Nonviral Gene Therapy for X-linked Alport Syndrome by Targeted Transcutaneous Ultrasound-Mediated Gene Delivery

Katie Benthall, Bert J. Frederich, Jonathan Chan, Margarita Krivega, David Kim, Nana Ingram, Dhruv Bole, Elizabeth Del Greco, Julia Poniatowski, Surabhi Rao, Victor Foster, Charles S. Levine, Adel Alonso, Glenda Arauz, Celia Ortiz, Belinda Cabriga, Oliver Chen, David Satyadi, Tanaya Ghosh, Ivan Krivega, Steven Feinstein, Kenneth Greenberg. *SonoThera, Inc., South San Francisco, CA.*

Background: X-linked Alport syndrome (XLAS) is a genetic condition characterized by kidney disease, as well as hearing loss and eye abnormalities. Kidney disease in XLAS is caused by a dysfunction of the glomerular basement membrane (GBM), due to a mutation in the *COL4A5* gene encoding the type IV collagen a5 chain. Ultrasound mediated gene delivery (UMGD) is an effective approach for noninvasive targeted transgene delivery into kidney cells and so offers the opportunity to develop a *COL4A5* gene replacement therapy for XLAS.

Methods: Multiple codon-optimized *COL4A5* open-reading frame sequences under control of podocyte-specific promoters were engineered and screened *in vitro* in primary human kidney cells with the goal of developing a podocyte-specific *COL4A5* DNA construct. The top *COL4A5* candidate was tested *in vivo* using SonoThera's proprietary noninvasive UMGD-based gene delivery platform targeting the kidney of an XLAS mouse model. Safety of gene delivery was also evaluated using established methods.

Results: Genetic engineering and *in vitro* screening allowed for the development of an optimized podocyte-specific *COL4A5* construct, which was successfully delivered using UMGD to the kidney of the XLAS mouse model. Molecular analysis of XLAS mouse model kidney tissue samples demonstrated gene expression localized to podocytes. Established safety and tolerability endpoints were evaluated which provided an excellent safety profile without off-target delivery to liver or other non-targeted organs, supporting continued therapeutic development.

Conclusions: COL4A5 expression in podocytes of the XLAS mouse model kidney along with the favorable safety profile of noninvasive targeted UMGD delivery supports translation of this approach towards clinical development for the treatment of the XLAS.

TH-OR91

B Cell Depleting Agents and Outcomes in Membranous Nephropathy

Salem Almaani,[1] Dhruti P. Chen,[2] Margaret Helmuth,[3] Abigail R. Smith,[4] Vimal K. Derebail.[2] CureGN Membranous Nephropathy Writing Group. *[1]The Ohio State University, Columbus, OH; [2]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of Michigan, Ann Arbor, MI; [4]Northwestern University, Evanston, IL.*

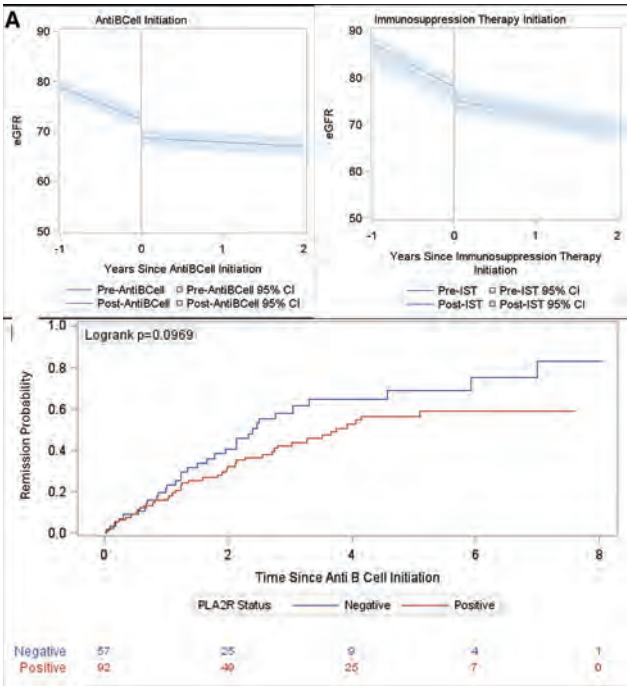
Background: B cell depleting therapy (BCDT) is increasingly used in membranous nephropathy (MN). We hypothesized that BCDT improves outcomes in MN and leads to faster remission in those with anti-PLA2R antibodies.

Methods: Use of BCDT among MN patients in Cure Glomerulonephropathy (CureGN) was reviewed. Interrupted time series analysis (IST) was done for eGFR slope prior and post treatment, including only participants with ≥2 eGFR values before and within 2 years post-therapy initiation. Time to remission was compared in those with negative vs. positive anti-PLA2R antibodies (any time), excluding those without definitive testing.

Results: In the MN cohort (n = 623), 456 (72%) patients were treated with non-B cell directed therapy and 215 (47%) of those had no BCDT use throughout their disease follow-up. 277 (44%) of MN patients had BCDT during their disease follow up, a majority (93%) were treated with rituximab. We compared eGFR trajectory pre and post therapy (n= 183 for those who received BCDT and n=88 who received other immunosuppressives but no BCDT). Among those receiving BCDT, eGFR slope (standard deviation) after treatment was -0.86 (0.93) mL/min/1.73m^2 compared to -3.04 (1.45) mL/min/1.73m^2 in patients receiving other immunosuppression (who never received BCDT), **Figure 1A**. Among those without anti-PLA2R antibodies (n=71) or with anti-PLA2R antibodies (n=113) treated with BCDT at time of active disease, there was no statistically significant difference in time to remission (median time to remission 2.4 vs. 3.8 years, respectively, logrank p = 0.097, **Figure 1B**).

Conclusions: BCDT is associated with decreased rate of eGFR decline in MN patients when compared to other therapies. Time to remission after BCDT is not influenced by anti-PLA2R status though there is a trend to faster remission among PLA2R negative patients.

Funding: NIDDK Support



TH-OR92

MAJESTY: A Phase 3, Randomized, Open-Label, Active Comparator-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Obinutuzumab in Patients with Primary Membranous Nephropathy

Fernando C. Fervenza,[1] Loreto Gesualdo,[2] Gianna Mastroianni-Kirsztajn,[3] Fan Fan Hou,[4] Gerald B. Appel,[5] Sylvie Prot,[6] Eriola Berisha,[7] Leena Khatri,[8] Tom Parsons,[7] Ed Spinks,[8] Heather Boston,[8] William Riboulet,[6] Xiaoyan Han,[9] Debbie Chen,[10] Andrew S. Bomback.[5] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Universita degli Studi di Bari Aldo Moro, Bari, Italy; [3]Universidade Federal de Sao Paulo, Sao Paulo, Brazil; [4]Nanfang Hospital, Southern Medical University, National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Guangdong Provincial Institute of Nephrology, Guangdong Provincial Key Laboratory of Renal Failure Research, Guangzhou, China; [5]Columbia University Irving Medical Center, New York, NY; [6]F Hoffmann-La Roche AG, Basel, Switzerland; [7]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [8]Roche UK Ltd, Welwyn Garden City, United Kingdom; [9]Roche (China) Holding Ltd, Shanghai, China; [10]Genentech Inc, South San Francisco, CA.*

Background: The MENTOR study demonstrated that rituximab was superior to cyclosporine in maintaining long-term remission in primary membranous nephropathy (pMN). Obinutuzumab, a type II anti-CD20 monoclonal antibody, depletes B cells more effectively than rituximab. The MAJESTY study (NCT04629248) assesses the efficacy and safety of obinutuzumab versus tacrolimus among patients with pMN.

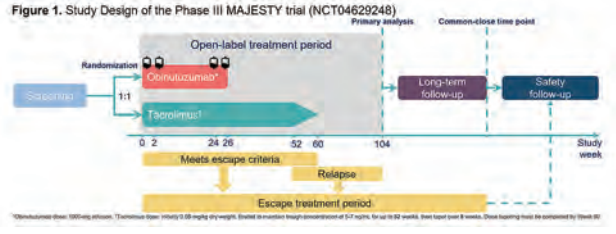
Methods: Participants were randomized 1:1 to receive obinutuzumab or tacrolimus (**Figure 1**). Obinutuzumab (1000 mg) is dosed on Day 1 and Weeks (Wks) 2, 24, and 26; tacrolimus (0.5 mg/kg) is given twice daily. Participants enter escape treatment with obinutuzumab if any of the following criteria are met: 1) Wk 24 urine protein-to-creatinine ratio (UPCR) >3.5 g/g and <25% decrease from baseline; 2) Wk 52 UPCR>3.5 g/g and <50% decrease from baseline; 3) Wk 52-104 UPCR >3.5 g/g after previously achieving proteinuric complete or partial remission (CR/PR); 4) tacrolimus discontinuation criteria. The primary endpoint is the proportion of patients with CR, defined as UPCR ≤0.3 g/g with a stable estimated glomerular filtration rate (eGFR) at Wk 104. Secondary endpoints include the proportion of participants who achieve CR or PR (UPCR >0.3 and ≤3.5 g/g and ≥50% decrease from baseline) at Wk 104 and the proportion who achieve CR at Wk 76.

Results: MAJESTY is fully enrolled with 142 participants across 86 sites and 11 countries. The study population comprises 31% women, and 25% Asian, 3% Black and 70% White participants; 29% received prior immunosuppressive therapy. At baseline, mean (SD) age was 51.2 (11.1) years and albumin was 2.9 (0.6) g/dL; median (IQR) eGFR was 87.0 (62.5-104.5) mL/min/1.73 m^2 and 24 hours UPCR was 6.8 (5.2-9.0) g/g. Among 110 (78%) participants with anti-PLA2R antibody >14 RU/mL, median (IQR) titer was 147 (52-287) RU/mL.

Conclusions: Full results of the MAJESTY study will be available upon completion.

Funding: Commercial Support - F. Hoffmann-La Roche Ltd.

Figure 1. Study Design of the Phase III MAJESTY trial (NCT04629248)



TH-OR93

Long-Term Outcomes of Rituximab-Treated Adults with Primary Podocytopathies

Philipp Gauckler,[1] Anna Matyjek,[1,2] Gert J. Mayer,[1] Andreas Kronbichler.[1] RITERM Study Group. *[1]Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria; [2]Medical University of Lodz, Lodz, Poland.*

Background: Long-term outcomes of rituximab-treated adult patients with primary podocytopathies (either minimal change disease or focal segmental glomerulosclerosis) are largely unknown.

Methods: A retrospective study at 30 nephrology departments from 15 countries worldwide included rituximab-treated adults with primary podocytopathies and a minimum follow-up of 36 months. The primary outcome was relapse-free survival at 36-months.

Results: Of 183 rituximab-treated adults with difficult-to-treat nephrotic syndrome (68% steroid-dependent/frequently relapsing, 22% steroid-resistant, 84% previously treated with two or more lines of immunosuppressive therapy), complete or partial remission at 6 months after rituximab treatment was achieved in 83%. Eighty-three of 151 (55%) initial responders achieved long-term relapse-free survival over three years. Maintenance therapy with rituximab was associated with a better relapse-free survival (HR 2.05, 95% CI: 1.07-3.91). Relapses per year were reduced from an annual rate of 1.0 relapses/year before to 0.17 relapses/year after rituximab initiation ($p < 0.001$). During follow-up, a stable course of estimated glomerular filtration rate was observed in patients with initial treatment response, whereas non-responders experienced a reduction in eGFR reaching -11 (-33 to -6) mL/min/1.73m2 ($p < 0.001$). Concomitant immunosuppressive treatment with glucocorticoids and calcineurin inhibitors could be reduced over 36 months, especially in patients with initial response.

Conclusions: Rituximab facilitates achievement of initial and long-term response in most adult patients with difficult-to-treat primary podocytopathies. Maintenance treatment with rituximab further increases long-term relapse-free survival over three years. Non-response to initial rituximab treatment is associated with poor renal prognosis.

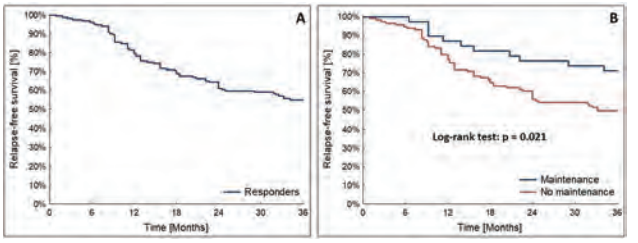


Figure 1. Three-year relapse-free survival in rituximab-responders
Kaplan-Meier plots comparing the three-year relapse-free survival in rituximab-responders in the total cohort (panel A) and subgroup comparison with maintenance (red line) versus without maintenance (blue line) treatment with rituximab (panel B).

TH-OR94

Circulating Anti-nephrin Antibodies in Idiopathic Nephrotic Syndrome: A Large Cohort Study Testing Association with Disease Activity

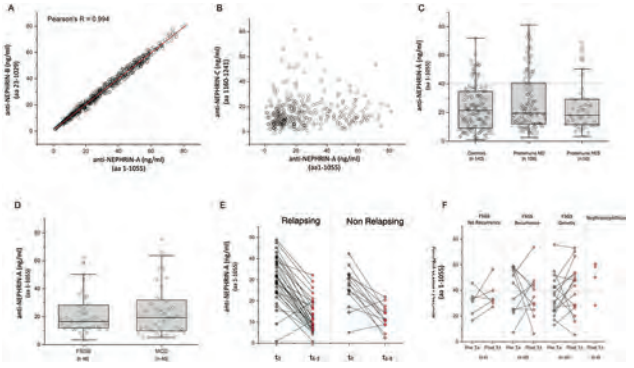
Andrea Angeletti,[1] Sonia Spinelli,[1] Xhuliana Kajana,[1] Gianluca Caridi,[1] Paolo Cravedi,[2] Francesca Lugani,[1] Carolina Bigatti,[1] Gian Marco Ghiggeri,[1] Maurizio Bruschi.[1] *[1]Istituto Giannina Gaslini, Genova, Italy; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Circulating anti-NEPHRIN antibodies (Abs) have been proposed as responsible for the disarrangement of the slit diaphragm in patients with idiopathic nephrotic syndrome (INS). However, available publications included limited cases and controls, focused on adults, and used multiple ELISAs for Abs detection, preventing comparisons across studies.

Methods: We included 156 INS patients with serum samples (396 samples), 32 kidney transplants with or not FSGS recurrence, and 143 controls. We also analyzed samples from an independent cohort of 47 INS enrolled in RCT (NCT02394119). We compared the performance of the three ELISA assays used in previous studies, two targeting the extracellular domain (NEPHRIRIN-A and B), and the intracytoplasmic domain (C).

Results: Levels of Abs against extracellular domains (anti-NEPHRIN-A, aa 1-1055 and anti-NEPHRIN-B, aa 23-1029) correlate. In contrast, not with the cytoplasmic domain (**Fig 1A-B**). Therefore, we show only the results relative to anti-NEPHRIN-A Abs. Contrary to our prediction, we did not detect a significant difference in anti-NEPHRIN Abs between controls and INS patients, regardless of proteinuria (**Fig 1C**). We identified 40ng/ml as the positivity threshold for our ELISA assay (Youden's index). Circulating anti-NEPHRIN Abs did not correlate with histology (**Fig 1D**), nor FSGS recurrence after kidney transplant (**Fig 1E**). In 47 patients enrolled in RCT, anti-NEPHRIN-A Abs significantly decreased after treatment. However, when stratified based on relapse or not at 12 months of follow-up, serum levels at $t_{6\text{-}9\ months}$ were similar in relapsing and non-relapsing subjects (**Fig 1F**).

Conclusions: Circulating anti-NEPHRIN Abs are present in a subset of INS patients and in kidney transplant recipients with FSGS recurrence, but they are not associated with disease activity. Our data are consistent with a potential pathogenic role of these antibodies, but they question their clinical utility in monitoring patients with INS.



TH-OR95

Co-localization of IgG with Nephrin in Immune-Mediated Idiopathic Nephrotic Syndrome

Yuta Inoki,[1] Yuta Ichikawa,[1] Nana Sakakibara,[1] Yuka Kimura,[1] Yu Tanaka,[1] Chika Ueda,[1] Hideaki Kitakado,[1] China Nagano,[1] Shingo Ishimori,[1] Tomoko Horinouchi,[1] Tomohiko Yamamura,[1] Kazumoto Iijima,[2,3] Kandai Nozu.[1]
[1]Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan; [2]Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan; [3]Department of Advanced Pediatric Medicine, Kobe University Graduate School of Medicine, Kobe, Japan.

Background: In minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), increased serum anti-nephrin antibody titers and co-localization of nephrin and IgG in kidney tissues have been reported, indicating the involvement of anti-nephrin antibodies in nephrotic syndrome (NS). However, comprehensive studies on the association of kidney tissue-specific anti-nephrin antibodies in nephritis, including NS, are lacking.

Methods: To investigate the co-localization of IgG and nephrin, we included 52 kidney tissue samples, comprising NS in the acute phase (n = 25; MCD n=13, FSGS n=7, diffuse mesangial proliferation(DMP) n=5), NS in remission (n = 6), NS with monogenic variants (n = 3), and other kidney diseases (n = 18). The age of patients ranged from 0 to 88 years. We performed double-immunofluorescence staining of nephrin/IgG on unfixed frozen sections and subsequently evaluated the nephrin/IgG co-localization using optical sectioning in a fluorescence microscope.

Results: In acute phase NS, nephrin/IgG co-localization was observed in 80% (20/25) of cases. The proportions of observed nephrin/IgG co-localization were 88% (14 of 16) in pediatric cases (age at onset: 0-16 years) and 67% (6 of 9) in adult cases (age at onset: 47-88 years). Specifically, co-localization was observed in 85% (11 of 13) of MCD cases, 71% (5 of 7) of FSGS cases, and 80% (4 of 5) of DMP cases. Except for 1 case with NS in remission and 1 case with asymptomatic proteinuria (which later developed into NS and responded to steroids), co-localization was not observed in cases with NS in remission, NS with monogenic variants, or other kidney diseases.

Conclusions: In acute phase NS, nephrin/IgG co-localization was observed with high probability, strongly suggesting an association of anti-nephrin antibodies with the onset of idiopathic NS (INS). Staining of kidney tissue is fast, simple, and effective for investigating the pathogenesis of INS and for differential diagnosis of immune-mediated NS from other diseases, including genetic NS.

TH-OR96

Endothelial-Released CD93 Predicts Poor Clinical Outcomes in Idiopathic Nephrotic Syndrome: A Study from the NEPTUNE Consortium

Gabriel M. Cara-Fuentes,[1] Colin D. Bauer,[2] Federica Piani,[6] Jonathan P. Troost,[4] Petter Bjornstad,[2] Laura H. Mariani,[4] Matthias Kretzler,[4] Christine B. Sethna,[5] Tarak Srivastava,[3] Richard J. Johnson.[2]
[1]Nationwide Children's Hospital, Columbus, OH; [2]University of Colorado Anschutz Medical Campus, Aurora, CO; [3]Mercy Health Children's Hospital, Kansas City, MO; [4]University of Michigan, Ann Arbor, MI; [5]Northwell Health, New Hyde Park, NY; [6]Universita degli Studi di Bologna, Bologna, Italy.

Background: Idiopathic nephrotic syndrome (INS) is a complex podocytopathy with highly diverse clinical trajectories. This study investigates the role of CD93, a protein primarily expressed by endothelial cells, as a predictive biomarker in INS.

Methods: We included 298 patients with INS (unbiopsied, minimal change disease -MCD-, focal segmental glomerulosclerosis-FSGS) from the NEPTUNE study. Soluble CD93 was measured in serum (n=108) and/or urine (n=228) samples, using commercial ELISA, collected at month-4 of enrollment. Mean follow-up was 38.2 months. We evaluated the relationship between soluble CD93 and 1) kidney disease progression including time to end-stage kidney disease or 40% decline in kidney function (eGFR), 2) time to complete remission, and 3) time to develop proteinuria. Kaplan-Meier curves including CD93 quartiles were used for data visualization; and Cox-Proportional hazards models (adjusting for histological diagnosis [FSGS vs. MCD] proteinuria [log transformed UPCR], and histology [interstitial fibrosis]) were used for analyses of time to event. Experimental studies were performed to identify cellular source of soluble CD93 in INS.

Results: Soluble CD93 levels were high in urine (Figure 1a) and sera from ~90% patients during relapse, irrespective of the histological pattern. Remarkably, levels remained high in ~50% patients during remission. High urinary CD93 levels associated with faster decline in kidney function (p<0.0001, Figure 1b), slower response to immunosuppression (p<0.0001), and higher risk to develop proteinuria (p=0.06). Serum CD93 levels showed no association with the studied outcomes. In cell culture studies, sera from patients in relapse, compared to controls, stimulated human glomerular endothelial cells to release CD93.

Conclusions: High urinary CD93 is a predictor of poor clinical outcomes in INS.

Funding: Private Foundation Support

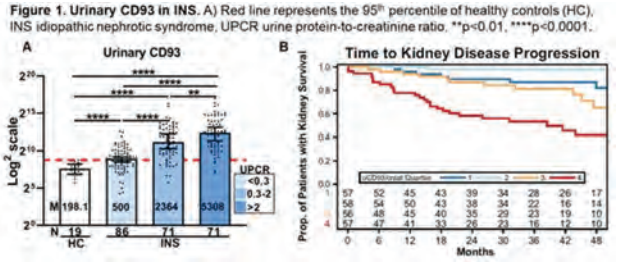


Figure 1. Urinary CD93 in INS. A) Red line represents the 95th percentile of healthy controls (HC), INS idiopathic nephrotic syndrome, UPCR urine protein-to-creatinine ratio. **p<0.01, ****p<0.0001.

TH-OR97

Predicting Calcineurin Inhibitor Response in Glomerular Diseases

Sean Eddy,[1] Margaret Helmuth,[1] Phillip J. McCown,[1] Viji Nair,[1] Charlotte M. Boys,[3] John R. Hartman,[1] Maria Larkina,[1] Wenjun Ju,[1] Julio Saez-Rodriguez,[2,3] Laura H. Mariani,[1] Matthias Kretzler.[1]
[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]European Bioinformatics Institute, Cambridge, United Kingdom; [3]UniversitatsKlinikum Heidelberg, Heidelberg, Germany.

Background: Glucocorticoids and calcineurin inhibitors (CNI) are part of KDIGO guidelines for treatment of steroid resistant glomerular diseases. Despite widespread use, predicting whether a patient will respond to therapy remains elusive. Given toxicities associated with prolonged CNI use, identifying patients who are both likely and unlikely to respond to CNI presents an opportunity to improve patient care. We hypothesized that patients' intrarenal molecular profile would be predictive of future CNI response, and that this profile could be linked to non-invasive markers that predict remission.

Methods: Kidney biopsy cores were obtained from participants in the Nephrotic Syndrome Study Network (n=362) and RNAseq profiles generated as previously described. Clinical phenotypes including, steroid and CNI exposure were recorded prior to biopsy and throughout study follow up. Gene co-expression network analysis was performed to identify co-expressed gene modules associated with future complete remission (CR) during CNI exposure. Functional enrichment of module genes was performed using cell type enrichment from a dataset of 1,407,781 single cell and single nuc (sn-)RNAseq profiles. MOFAcell was used to determine cell states in patients. Modules and cell states were correlated (Pearson) with 7,000 SomaScan profiles to identify candidate blood and urine markers of CNI response, which were validated by ELISA. AUC was used to determine the ability of markers to predict future CNI response.

Results: In glomeruli and tubulointerstitium (TI), we identified 42 and 24 modules, respectively. In steroid naïve patients at time of Bx, four TI modules were associated with CR during future CNI exposure (p<0.05). Functional enrichment analysis of modules indicated immune biology and angiogenesis networks associated with lack of response, consistent with cell level expression of module genes from sn-RNAseq. Plasma (KIM-1, MMP7) and urine (TNFR-2) markers were correlated with module expression. Biomarker profiles closed to CNI exposure improved CR prediction (AUC=0.85) over a base model (eGFR, UPCR, age, sex, and race) alone (AUC=0.77).

Conclusions: Co-expression modules helped identify blood and urine markers predictive of CR during future CNI exposure. Validation of these markers in independent cohorts is ongoing.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR98

Urinary TNFR2 and Association with Kidney Injury in Patients with Nephrotic Syndrome

Viji Nair, Edmond Lee, Sean Eddy, Margaret Helmuth, Damian Fermin, Silpa Chinnakotla, Jeffrey B. Hodgin, Laura H. Mariani, Matthias Kretzler, Wenjun Ju. NEPTUNE (Nephrotic Syndrome Study Network).
University of Michigan Michigan Medicine, Ann Arbor, MI.

Background: Tumor necrosis factor receptor 2 (TNFR2) in plasma (pTNFR2) has been identified as a prognostic biomarker strongly associated with DKD progression. The association of urinary TNFR2 (uTNFR2) levels with kidney injury, clinical outcome, and intra-kidney TNFR2 expression remains poorly understood.

Methods: uTNFR2 (normalized by urine creatinine) and pTNFR2 levels were obtained using SOMAscan proteomics analysis for a subgroup of patients with nephrotic syndrome (NS) with matching urine, plasma, and kidney biopsy transcriptomic data (n=96) in the NEPTUNE cohort. uTNFR2 level was validated using ELISA. Glomeruli (glom) and tubulointerstitium (TI) expression values for *TNFRSF1B*, the gene encoding TNFR2, and the TNF pathway score (TNFPAS) were extracted from published RNA-seq profiles. Mono-nuclear white blood cells (MWBCs) were used to evaluate tubulointerstitial inflammation. Correlations were performed using Pearson's correlation. Single cell RNA-seq was used to determine the expression in kidney cells. Cox regression model was used to evaluate the association with outcome.

Results: SOMAscan uTNFR2 is tightly correlated with ELISA results (r=0.95, p=1e-043). uTNFR2 was higher in patients than healthy controls (p<0.0001). Higher uTNFR2 is correlated with lower GFR, higher proteinuria, inflammation by MWBCs, and TNFPAS. uTNFR2 is significantly correlated with TI but not glom *TNFRSF1B* mRNA. uTNFR2 was correlated with pTNFR2. Notably, pTNFR2 showed weaker correlation with above parameters than uTNFR2. Enriched expression of *TNFRSF1B* is observed in kidney endothelial and immune cells. Furthermore, uTNFR2 showed significant association with progression to composite endpoint of kidney failure or 40% reduction of baseline GFR after adjusting for age, sex, race, GFR, and UPCR (HR 2.11, 95% CI (1.03,4.31), p = 0.04).

Conclusions: uTNFR2 is significantly associated with cross-sectional and longitudinal outcome in patients with NS. The enriched expression of *TNFRSF1B* mRNA in kidney cells, and the stronger correlation of uTNFR2 over pTNFR2 with TI *TNFRSF1B* and MWBCs suggest that kidney cells could contribute to uTNFR2 level. The significant correlation of uTNFR2 with TNFPAS suggests that uTNFR2 may serve as a non-invasive biomarker for kidney TNF pathway activation.

Funding: NIDDK Support

TH-OR99

Associations between APOL1 Genotypes and Major Adverse Cardiovascular Events (MACE) in Proteinuric Glomerulopathies: A CureGN and NEPTUNE Study

Matthew Schuchman,[1,13] Roy O. Mathew,[2] Abigail R. Smith,[3] Agustin Gonzalez-Vicente,[4] Crystal A. Gadegbeku,[5] Sharon G. Adler,[11] Dorey A. Glenn,[7] Meryl Waldman,[6] Markus Bitzer,[8] Fadhl Alakwaa,[8] Bryce A. Kerlin,[9] Patrick H. Nachman,[10] Bruce M. Robinson,[8] Myda Khalid,[12] Vimal K. Derebail,[7] Tarak Srivastava,[14] Gentzon Hall,[15] Katherine R. Tuttle,[16] Michelle M. O'Shaughnessy,[17] Gabriel M. Cara-Fuentes,[20] Bethany A. Roehm,[19] Jarcy Zee,[18] Christine B. Sethna.[1,13] On behalf of the NEPTUNE Cardiovascular Working Group. *[1]Cohen Children's Medical Center, Queens, NY; [2]VA Loma Linda Healthcare System, Loma Linda, CA; [3]Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Case Western Reserve University, Cleveland, OH; [5]Cleveland Clinic, Cleveland, OH; [6]National Institutes of Health, Bethesda, MD; [7]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [8]University of Michigan Michigan Medicine, Ann Arbor, MI; [9]Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [10]University of Minnesota Twin Cities, Minneapolis, MN; [11]Harbor-UCLA Medical Center, Torrance, CA; [12]Riley Hospital for Children at Indiana University Health, Indianapolis, IN; [13]Northwell Health, New Hyde Park, NY; [14]Children's Mercy Kansas City, Kansas City, MO; [15]Duke Health, Durham, NC; [16]Providence St Joseph Health, Renton, WA; [17]University College Cork, Cork, Ireland; [18]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [19]The University of Texas Southwestern Medical Center, Dallas, TX; [20]Nationwide Children's Hospital, Columbus, OH.*

Background: Patients with proteinuric glomerulopathies are at increased risk for cardiovascular disease, but the relationship between *APOL1* genotype and MACE remains poorly understood.

Methods: Participants enrolled in the Nephrotic Syndrome Study Network (NEPTUNE) or Cure Glomerulonephropathy (CureGN) with completed *APOL1* genotyping and biopsy-proven minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy or IgA nephropathy were included. Cox regression with an outcome of MACE, defined as time from enrollment to first stroke, heart failure or coronary artery disease (CAD), was conducted by *APOL1* genotype (high risk defined as having two copies of G1 and/or G2 risk variants). Models were adjusted for age, sex, obesity, glomerular diagnosis, urine protein:creatinine and glomerular filtration rate (eGFR) at enrollment, prior MACE and time from biopsy to enrollment.

Results: Among 3224 participants, 296 (9.2%) individuals (age 31.3 ± 20 yrs, 80% self-identified Black, 34.7% children, median 61.3 months follow-up) had the high-risk *APOL1* genotype. In the full cohort, 134 individuals (4%) experienced MACE, with a total of 158 events (39 stroke, 47 heart failure, 72 CAD). After adjustments, high-risk *APOL1* genotype was significantly associated with MACE (HR 2.84, 95% CI 1.56-5.15, p<0.001) (Figure).

Conclusions: Among participants in two large observational studies of proteinuric glomerular disease, high risk *APOL1 g*enotype had greater than a two-fold effect on MACE, independent of kidney disease risk factors. Future analyses are required to confirm this relationship at the time of diagnosis.

Funding: NIDDK Support

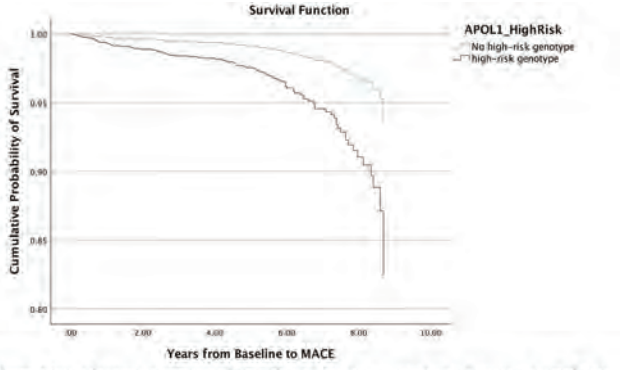


Figure. Adjusted Cox survival curve to MACE by APOL1, adjusted to age, sex, obesity, diagnosis, prior MACE, urine protein-creatinine ratio and estimated Glomerular Filtration Rate at enrollment and time from biopsy to enrollment.

TH-OR100

Defining Molecular Mechanisms in Antibody-Mediated Rejection Using Unbiased Proteomics in Donor-Specific Antibody-Positive and -Negative Recipients

Maya A. Allen,[1] Kieran Manion,[2] Rohan John,[3] Ana Konvalinka.[3]
[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]Toronto General Research Institute, Toronto, ON, Canada; [3]University Health Network, Toronto, ON, Canada.

Background: Kidney transplantation is the optimal treatment for patients with end-stage kidney disease. Unfortunately, many kidney allografts fail prematurely due to antibody-mediated rejection (AMR). AMR is caused by donor-specific antibodies (DSAs) against human leukocyte antigens (HLA) on the graft endothelium. DSAs may cause injury through endothelial activation, complement activation, or interactions with Fcγ receptors (FcγRs) on immune cells. Intriguingly, 30-60% of DSA-positive kidney allograft recipients never develop rejection, and 30-50% of patients that exhibit AMR do not have any detectable DSAs, suggesting the presence of unidentified contributors to the pathogenicity of AMR. Our goal is to define the molecular mechanisms of AMR and uncover these underlying contributors to injury.

Methods: Indication biopsies from 115 patients with DSA+AMR, DSA-AMR, no rejection despite having DSAs (DSA+NR), and T cell mediated rejection (TCMR) were subjected to unbiased proteomics analysis using LC-MS/MS on Q-Exactive mass spectrometer. Significance between groups was established using ANOVA, with p<0.05 considered significant.

Results: We analyzed the glomerular and tubulointerstitial compartments of each biopsy separately. Of the 1203 proteins quantified in the tubulointerstitium, 30 were significantly differentially expressed, and of the 628 quantified in the glomeruli 15 were significantly differentially expressed (ANOVA, p<0.05). Importantly, the expression of complement factors was increased in DSA-AMR tubulointerstitium when compared to DSA+AMR and DSA+NR. However, in the glomeruli complement proteins were dominant in DSA+AMR. Furthermore, proteins downstream of FcγR activation and phagocytosis were increased in the glomeruli of DSA-AMR and DSA+AMR biopsies when compared to DSA+NR. In the tubulointerstitium, proteins implicated in phagocytosis were highest in DSA-AMR.

Conclusions: The differential expression of complement proteins and proteins implicated in FcγR-mediated phagocytosis suggests distinct patterns of injury in the two kidney compartments and an unanticipated role of complement and phagocytosis in DSA-AMR.

TH-OR101

Unbiased Proteomics Distinguishes Chronic and Acute Antibody-Mediated Rejection in Donor-Specific Antibody-Positive Kidney Transplant Recipients

Kieran Manion,[1] Maya A. Allen,[1,2] Sergi Clotet Freixas,[3] Rohan John,[4,2] Ana Konvalinka.[1,2] *[1]Toronto General Research Institute, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]McMaster University, Hamilton, ON, Canada; [4]University Health Network, Toronto, ON, Canada.*

Background: Nearly a million North Americans have end-stage renal disease, for which transplantation of a new kidney is the best treatment; however, >50% of grafts fail by 10 years due mainly to antibody-mediated rejection (ABMR), where recipient donor-specific antibodies (DSA) can drive tissue injury. Unfortunately, presence of DSA alone cannot predict ABMR, as 30-60% of DSA$^+$ patients do not develop rejection. We aim to identify factors regulating kidney protein expression in DSA$^+$ kidney transplant recipients with and without ABMR.

Methods: Kidney biopsies were obtained from DSA$^+$ kidney transplant recipients with no rejection (NR; n=45) or ABMR (acute, n=25; chronic, n=25; mixed ABMR/cellular rejection, n=25). Glomeruli (glom) and tubulointerstitium (TI) extracted from kidney biopsies using laser capture microdissection were digested to peptides and analyzed by liquid chromatography mass spectrometry. MaxQuant and Perseus software were used for protein identification and differential expression. Differentially expressed proteins (ANOVA, $p<0.05$) were mapped to signaling pathways using pathDIP (FDR: BH, $q<0.05$).

Results: 180 glomerular and 325 tubulointerstitial proteins were significantly differentially expressed between DSA$^+$ patients with NR or with a subtype of ABMR (Fig 1). Proteins upregulated in acute or mixed ABMR mapped significantly to pathways for MHC and interferon (IFN) signaling in TI (MHC pathway, q=5.5e-12; IFN signaling, q=3.3e-8). In contrast, proteins upregulated in chronic ABMR mapped to the complement cascade (glom, q=2.9e-3; TI, q=6.8e-11) and extracellular matrix organization (glom, q=2.1e-7; TI, q=2.5e-4) in both compartments. DSA$^+$ patients with any ABMR subtype showed significant downregulation of proteins linked to pyruvate metabolism in both compartments compared to NR (glom, q=2.7e-4; TI, q=6.9e-14).

Conclusions: Our results suggest that while both acute and chronic ABMR in DSA$^+$ kidney transplant patients involve altered metabolism, distinct immune-mediated mechanisms may drive tissue damage in the individual subtypes.

Funding: Government Support - Non-U.S.

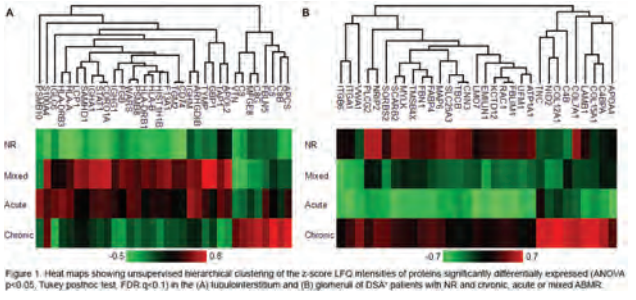


Figure 1. Heat maps showing unsupervised hierarchical clustering of the z-score LFQ intensities of proteins significantly differentially expressed (ANOVA p<0.05, Tukey posthoc test, FDR q<0.1) in the (A) tubulointerstitium and (B) glomeruli of DSA$^+$ patients with NR and chronic, acute or mixed ABMR.

TH-OR102

Innate Immune Cells, Memory T Cells, and Interferon Gamma Responses Characterize Transplant Glomerulopathy of Chronic Antibody-Mediated Rejection

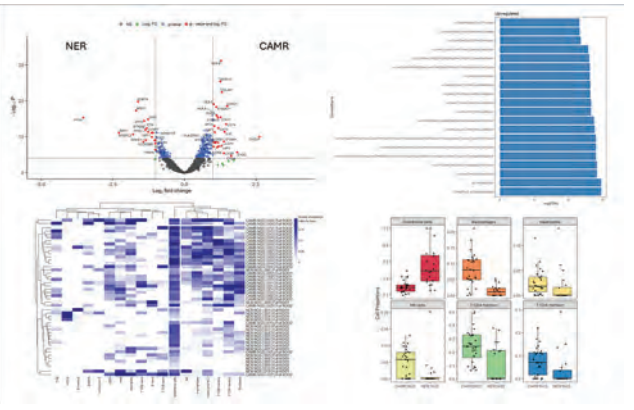
Alessia Giarraputo,[1,2] Ira Doressa Anne L. How,[1,2] Amaya Pankaj,[1,2] Michael Raabe,[1,2] Nicole L. Brousaides,[1,2] Robert B. Colvin,[1,2] Ivy A. Rosales.[1,2] Immunopathology Research Lab. *[1]Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: Transplant glomerulopathy (TG) in chronic antibody mediated rejection (CAMR) portends poor graft survival and outcome. Despite many studies on CAMR using bulk mRNA analysis, the pathogenesis of TG remains unexplored. Here we used spatial transcript analysis on allograft biopsies to reveal potential pathogenetic mechanisms of glomerular injury in CAMR.

Methods: Five-micron sections from archived FFPE allograft biopsies with CAMR (n=10) and no evidence of rejection (NER, n=6) were mounted on slides and hybridized to the Whole Transcriptome Atlas Panel (Nanostring). Using the GeoMx Digital Spatial Profiler-NGS system (Nanostring, Illumina), slides were scanned and whole glomeruli regions of interest (ROI) were created. Oligo tags from ROIs were quantified and analyzed performing differential expression, pathway analysis, cell typing (Immune Cell Atlas) and cell deconvolution.

Results: Differential expression between 50 CAMR and 35 NER glomeruli showed enrichment of macrophage associated transcripts (*C1QA, C1QB, C1QC),* interferon-associated transcripts *(IFITM1, STAT1, CXCL9)* and increased Class II-associated transcripts (*CD74, HLA-DRA, HLA-DRB1, HLA-DPA1*) (*FDR adjusted p-value <0.05)* in CAMR, while the top significant pathways were related to MHC antigen presentation, complement system, cytokine mediated pathways and interferon-gamma response. Cell typing and deconvolution revealed increased proportions of macrophage, NK cells, CD8 and CD4 memory T cells together with neutrophils localized in CAMR glomeruli (Figure). These findings were associated with endothelial dedifferentiation (decreased *EHD3, SOST;* increased *COL4A1*) and decreased podocyte number.

Conclusions: Spatially resolved transcripts of TG in CAMR reveal immune cell-related pathways of glomerular endothelial injury, suggesting a novel interplay of endothelial dedifferentiation in the pathogenesis of TG.



TH-OR103

Advancing a Humanized Mouse Model to Study the Regulation of Germinal Center Response in Alloimmunity

John Y. Choi,[1,2] Samuel Mon-Wei Yu,[3] Joseph V. Bonventre,[1,2] Michael Brehm,[4] Jamil R. Azzi.[1,2] *[1]Mass General Brigham Inc, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]University of Massachusetts Chan Medical School, Worcester, MA.*

Background: In a fully mismatched mouse kidney transplant model, we showed that regulatory CD8 T cells (CD8 Tregs) are essential in controlling germinal center response, thus inhibiting antibody-mediated rejection. Thus far, humanized mice models have failed to develop mature immune subsets due to a lack of proper thymic education and human cytokines, significantly hindering the clinical translatability of our pre-clinical findings. To overcome such limits, we established a novel humanized model that allows us to study the mechanism of germinal center regulation.

Methods: NSG, NSG-hu-IL6, NSG-hu-IL15, and NSG-hu-IL6/IL15 mice that produce physiological levels of respective human cytokines were engrafted with fetal bone marrow, liver, and thymus tissue (BLT). Upon human immune cell engraftment, 8 to 10 3D-kidney organoids derived from H9 or BJFF embryonic stem cells were engrafted under the host kidney capsule. Mice were sacrificed on day 20 or 30 for the analysis. Spleens were harvested for immunophenotyping. T cells isolated from the spleen were co-cultured with 2D-kidney organoids to induce memory response. Serum was obtained to measure specific human cytokine levels and the development of alloantibodies. Kidney organoid allografts were harvested for light microscopy, immunofluorescence, and immunophenotyping of graft-infiltrating immune cells.

Results: NSG-BLT mice developed mature T cells that rejected kidney organoid allografts. T cells isolated from NSG-BLT demonstrated memory response, judged by cytokine excretion (TNFa, IFNg) and proliferation upon re-exposure to the alloantigens (2D-organoids). Ex vivo human IL15 salvaged NK and CD8 Treg functionality isolated from NSG-BLT, while NSG-hu-IL15-BLT hosts naturally developed mature NK and CD8 Tregs. While NSG-BLT shows limited B Cell frequency and maturation, NSG-hu-IL6-BLT showed significantly increased Tfh, class-switched B cells as we all as memory B cells, signifying the enhanced germinal center response. Finally, reduced germinal center response was observed in NSG-hu-IL6/IL15-BLT compared to NSG-hu-IL6-BLT hosts, suggesting the immunoregulatory role of CD8 Treg.

Conclusions: Exploiting our advanced humanized mice kidney organoid transplant model, we show that human CD8 Treg plays an essential role in germinal center response in alloimmunity.

Funding: NIDDK Support, Other NIH Support - NIAID, Dialysis Clinic Inc, ASN, AST, Private Foundation Support

TH-OR104

T Follicular Regulatory Cells Restrain Alloimmunity through Limiting Proinflammatory Cytokines in B Cells

Hengcheng Zhang,[1,2] Manuel A. Podestà,[1,2] Cecilia Bataglioli Cavazzoni,[1,2] Jeong-Mi Lee,[1,2] Paulo L. Raeder,[1,2] Pragya Chandrakar,[1,2] Maya G. Gempler,[1,2] Deepjyoti Ghosh,[3] Ismail Sayin,[3] Anita S. Chong,[3] Peter Sage.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]The University of Chicago, Chicago, IL.*

Background: Pathogenic antibodies produced by alloreactive B cells mediate antibody-mediated rejection (ABMR) after kidney transplantation. Follicular regulatory T (Tfr) cells modulate Tfh cell-mediated B cell responses but their roles in controlling ABMR are unknown.

Methods: Mouse models of kidney transplantation were performed. The transcriptional program and TCR clonality of Tfr cells were assessed by single-cell sequencing. Selective elimination of Tfr in mice was used to dissect the function. Donor-specific antibody (DSA) test and histology were used to monitor ABMR. I-E tetramer and a single B cell culture detected the germinal center (GC) responses. Bulk RNA-seq analyzed GC B cells to investigate transcriptional programming regulated by Tfr cells and its mechanism.

Results: Tfr cells differentiate after allogeneic transplantation and undergo development through three distinct stages. Clinical immunosuppression alters the development and disproportionately skews the subsets by decreasing GC-like Tfr cells and increasing follicular-like Tfr cells. Functionally, Tfr cell deletion early, but not late, after transplantation results in accelerated rejection and increases in alloreactive B cell clones, DSA, and ABMR leading to reduced recipient survival. At the GC level, deletion of Tfr cells results in B cells with enhanced pathogenic potential which are marked by increased production of proinflammatory cytokines IL-15. Neutralization of IL-15 rescued the accelerated rejection with Tfr deletion and prolonged survival.

Conclusions: Tfr cells are key regulators of kidney transplant ABMR with unique development signals and regulate alloimmunity by suppressing donor-specific GC B cells from the early stages of kidney transplantation.

Funding: Other NIH Support - R01AI153124, R01AI158413, P01AI056299, P01 HL158505

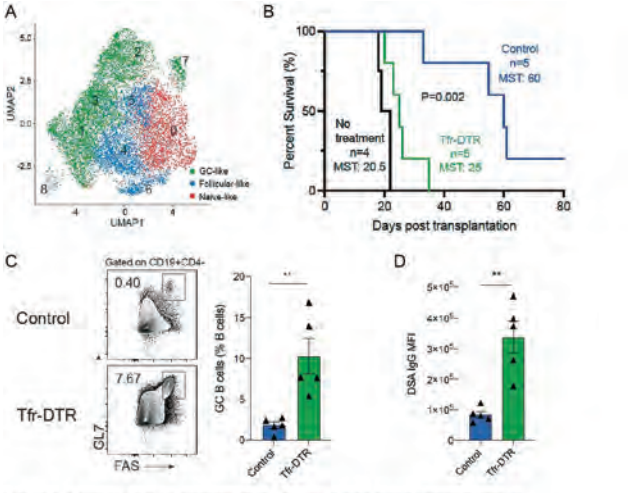


Figure A. Clusters feature annotation of Tfr cells during kidney transplantation.
Figure B. Deletion of Tfr cells resutls in reduced recipient survival. Tfr-DTR: Tfr deletion mice.
Figure C. Deletion of Tfr cells promoted CD19+GL7+FAS+ GC B cells proportion.
Figure D. Tfr cells regulate the serological DSA production in kidney transplantation.

TH-OR105

Time Course Analysis of Serial Biopsies Post-Kidney Transplant Reveals a Time Zero Cell State Negatively Associated with Delayed Graft Function

Andrew F. Malone,[1,2] Aidan Leckie-Harre,[4] Amish Asthana,[3] Rohan S. Paul,[4] Giuseppe Orlando,[3] Benjamin D. Humphreys.[4] *[1]St Vincent's University Hospital, Dublin, Ireland; [2]University College Dublin, Dublin, Ireland; [3]Wake Forest University School of Medicine, Winston-Salem, NC; [4]Washington University in St Louis School of Medicine, St Louis, MO.*

Background: One fifth of the kidneys procured for transplantation in the US are discarded. Identification of kidneys with sufficient functional reserve at the time of procurement may increase the number of kidneys transplanted. We hypothesized that single-cell RNA-seq analysis of allograft biopsies obtained at time 0, 1 and 12 months will identify a signature of functional reserve predictive of successful graft function in marginal organs and thus minimize discard rates.

Methods: As part of the Double R study (IRB00027118) we analysed time 0, 1 and 12 month biopsies of DCD kidney allografts from 6 patients with either DGF (n=3) or no DGF (n=3). We performed single nucleus RNA-seq on snap frozen biopsies using the 10X FLEX kit. We used Seurat and Monocle2 to generate data objects and perform analyses. We also estimated the proportion of male cells with chromosome Y loss (LOY) per cell type over time.

Results: We integrated 17318 post-QC cells from 6 patients with and without DGF across three time points (0, 1, 12 months) post DCD kidney transplant. These included 5658 proximal tubule cells. Using Monocle we identified a cell state present in time 0 biopsies that did not develop DGF (figure1A+B). This cell state was absent in biopsies that progressed to DGF but recovered by 1 month. This cell state was defined by upregulation of fructose metabolism genes and had a high median LOY proportion (0.2459) (figure1C).

Conclusions: We identified a time zero cell state that is negatively associated with DGF in the setting of DCD kidney transplantation. These renal proximal tubule cells differentially express fructose metabolism genes and have a high proportion of LOY.

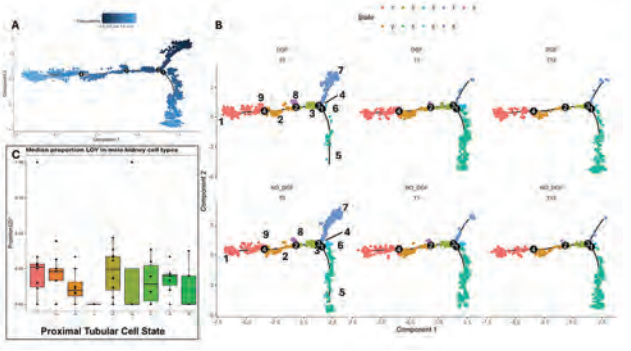


Figure1. Monocle pseudotime analysis of proximal tubule cells defines 9 cell states (A+B). Cell state 5 is absent at time 0 in biopsies that progress to DGF (B). This cell state has a high proportion of chromosome Y loss (C).

TH-OR106

Derivation of Human Leukocyte Antigen Molecular Mismatch Risk Thresholds in a Diverse Cohort of Kidney Transplant Recipients

Clarkson Crane, Elizabeth G. Ingulli, Gerald P. Morris. *University of California San Diego, La Jolla, CA.*

Background: Development of donor specific antibodies (DSA) is a known risk factor for rejection and poor allograft outcomes. HLA molecular mismatch (molMM) algorithms are increasingly being studied to risk stratify kidney transplant recipients (KTR). Studies associating incremental molMM and adverse outcomes generally consider molMM as a continuous variable. In clinical practice, use of a binary threshold is a more practical approach to assess those at high risk for de novo DSA or rejection. We derived such a cutoff and applied to our KTR cohort to compare common molMM algorithms, hypothesizing equivocal prognostic value to agMM using this approach.

Methods: KTR with high resolution recipient and donor HLA typing were identified. We fit Cox proportional hazards models using predictors of agMM, HLA-Matchmaker (ver 3), HLA-EMMA, and PIRCHE-II (ver 4) as continuous and binary (90% sensitivity of those with +DSA) variables.

Results: Of 431 KTR, 70 developed de novo DSA (16%). Correlation of molMM with agMM is seen in Fig 1. As continuous variables, all were significantly associated with dnDSA. This was consistent when using the binary cutoff, where total agMM had similar hazard to molMM for dnDSA. However, loci-specific moIMM had higher hazard for DSA than agMM (Table 1).

Conclusions: In theory, molMM provides a more granular assessment of alloimmune risk. However, this has not been consistently shown in large, diverse cohorts using a clinically relevant threshold. Our results indicate application of moIMM at a sensitive cutoff has similar prognostic value to agMM for development of dnDSA when considering total mismatch, but molMM may be superior at HLA class II loci. This merits further investigation and prior to routine clinical use, we advocate evaluation of these algorithms on a biologic level.

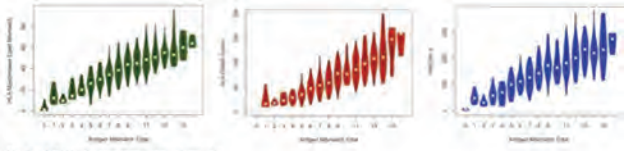


Fig 1: MolMM by total antigen mismatch.

HLA Locus	Mismatches	Hazard Ratio (CI95)	p-value
Total	Antigen	**2.4 (1.3-4.6)**	**0.007**
	HLA-Matchmaker	**2.9 (1.4-6.1)**	**0.004**
	HLA-EMMA	**3.2 (1.6-6.8)**	**0.002**
	PIRCHE-II	**2.4 (1.2-5.1)**	**0.018**
HLA-Class I	Antigen	**2.2 (1.0-4.8)**	**0.044**
	HLA-Matchmaker	**2.5 (1.3-4.9)**	**0.006**
	HLA-EMMA	**2.9 (1.1-7.6)**	**0.028**
	PIRCHE-II	2.6 (0.9-7.3)	0.079
HLA-Class II	Antigen	**1.9 (1.0-3.9)**	**0.036**
	HLA-Matchmaker	1.7 (0.8-3.8)	0.17
	HLA-EMMA	1.9 (0.9-4.2)	0.07
	PIRCHE-II	**2.4 (1.1-5.3)**	**0.029**
HLA-DRB1/3/4/5	Antigen	1.9 (0.8-4.9)	0.138
	HLA-Matchmaker	1.8 (0.5-5.9)	0.369
	HLA-EMMA	2.9 (0.9-8.9)	0.051
	PIRCHE-II	**5.7 (1.7-19.5)**	**0.005**
HLA-DQA/B	Antigen	1.9 (0.9-3.6)	0.58
	HLA-Matchmaker	**3.2 (1.5-6.8)**	**0.003**
	HLA-EMMA	**2.2 (1.1-4.7)**	**0.033**
	PIRCHE-II	**2.5 (1.0-6.5)**	**0.047**

Table 1: Single predictor cox models comparing agMM to molMM for development of nDSA. Total n = 431.

TH-OR107

Abstract Withdrawn

TH-OR108

Kidney Allograft Microvascular Inflammation Reveals Distinct Phenotypes and Outcomes: A Multinational Cohort Study

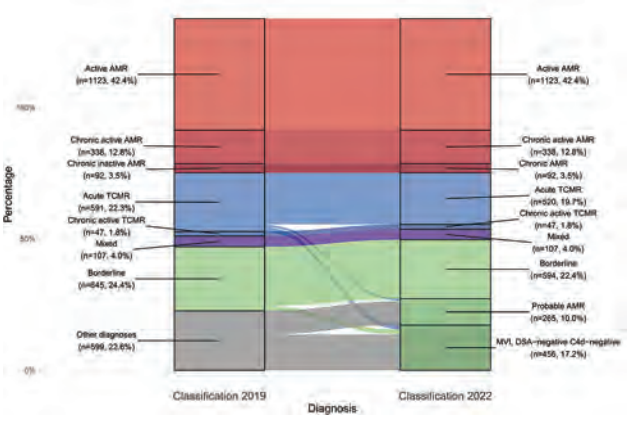
Aurelie Sannier, Marta Sablik, Gillian Divard, Olivier Aubert, Valentin Goutaudier, Carmen Lefaucheur, Alexandre Loupy. *Paris Institute for Transplantation and Organ Regeneration, Paris, France.*

Background: Microvascular inflammation (MVI) is a key predictor of adverse kidney allograft outcomes, prompting the Banff 2022 Classification to introduce two MVI categories: MVI, DSA-negative and C4d-negative (MVI+DSA-C4d-) and probable antibody-mediated rejection (probable AMR). To date, the clinical significance of these phenotypes remains unclear.

Methods: We included 6,099 kidney transplant recipients from 20 transplant centers, who underwent an allograft biopsy between 2004 and 2023. Multimodal data was integrated to classify biopsies according to the Banff 2019 and 2022 Classification. We assessed diagnostic reclassifications and their association with graft outcome, transplant glomerulopathy, and AMR episodes.

Results: Among the 14,081 transplant biopsies, MVI+DSA-C4d- and probable AMR were diagnosed in 456 (3.2%) and 265 (1.9%) biopsies, respectively. A total of 721 biopsies were reclassified, with mainly non-rejection biopsies (n=599) being reclassified as MVI+DSA-C4d- (n=361) and probable AMR (n=238). Patients reclassified as MVI+DSA-C4d- showed worse graft survival compared to non-rejection cases (HR=2.3, 95% CI: 1.6-3.3; P<0.001), but better than patients with active AMR (HR=3.0, 95% CI: 2.5-3.7; P<0.001). Those reclassified as probable AMR had a graft survival similar to non-rejection cases (HR=1.5, 95% CI: 0.9-2.5; P=0.122). We observed a similar increased risk for developing transplant glomerulopathy and an AMR episode for both MVI+DSA-C4d- and probable AMR, compared to non-rejection (P<0.001).

Conclusions: We demonstrated that MVI+DSA-C4d- and probable AMR are distinct clinical phenotypes, and reclassification of these cases refined patient risk stratification for allograft outcome. Our findings support the introduction of these phenotypes, as their clinical recognition will aid in standardizing therapeutic approaches, improving allograft outcomes.



FR-OR01

Patterns of Care among Patients with Documented CKD in the United States

Csaba P. Kovesdy,[1] Satabdi Chatterjee,[2] Adrian R. Levy,[3] Sydnie Stackland,[4] Bonnie M. Donato,[2] Ling Zhang.[2] *[1]University of Tennesse, Memphis, TN; [2]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; [3]Dalhousie University, Halifax, NS, Canada; [4]Panalgo LLC, Boston, MA.*

Background: Guidelines for pharmacotherapy in chronic kidney disease (CKD) recommend a multifactorial strategy to slow kidney disease progression by inhibiting the renin-angiotensin-aldosterone system (RAASi; using angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]) and lowering cardiovascular risk by using statins. In light of newer therapies available for CKD and the underdiagnosis of this condition, little is known regarding patterns of care in patients prior to documenting diagnosis. This study aimed to compare the patterns of care for RAASis and statins at the onset of CKD using laboratory data; vs documentation of CKD using ICD codes.

Methods: A retrospective study using electronic health record-linked claims data from 2009-2020 Optum® Market Clarity was conducted. The cohort included adults with two estimated glomerular filtration rate (eGFR) measures <60mL/ min/1.73 m^2, 3-12 months apart, followed by documented clinical diagnosis of CKD (using ICD 9/10 codes). The proportion of patients who were prescribed, administered, or ordered RAASis and/ or statins within ±90 days of: the second eGFR<60 mL/min/1.73 m^2 (index date), and the date of first documented diagnosis in claims were computed.

Results: A total of 1.39 million adults with laboratory evidence of CKD (mean [±SD] age 71 [±10]; 63% women; 87% Caucasian) were identified; of them, 740,088 (53.1%) received a documented diagnosis of CKD during follow-up, and formed the study cohort. Among those with documented CKD, 39% received RAASis and 36% received statins at index date; utilization increased to 46% and 45% respectively, at diagnosis. On average, use of RAASis increased from 38% between 2010-2012 to 48% between 2018-2020, while use of statins increased from 37% to 48% during the same time period.

Conclusions: Despite the utilization of RAASis and statins increasing between onset of CKD and documented diagnosis, the overall low uptake of these guideline-recommended therapies (<50%) reinforces the need to improve pharmacologic management in CKD. As new treatments become available, optimizing care using evidence-based guideline-recommended therapies offers the opportunity of reducing risk of cardiorenal syndrome, and improving outcomes in CKD.

Funding: Commercial Support - Boehringer Ingelheim

FR-OR02

Predictors of CKD Care in African American and American Indian or Alaska Native Patients in Two Large Health Systems

Kiara Mayhand,[1] Radica Z. Alicic,[2] Lindsey M. Kornowske,[2] Cami R. Jones,[2] Kenn B. Daratha,[2] Christina Reynolds,[2] Susanne B. Nicholas,[3] Roland J. Thorpe,[1] Alex Bui,[3] Keith C. Norris,[3] Katherine R. Tuttle.[2] *[1]Johns Hopkins University, Baltimore, MD; [2]Providence St Joseph Health, Renton, WA; [3]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.*

Background: Racially minoritized populations in the United States, including African American (AA) and American Indian/Alaska Native (AI/AN), experience disproportionately higher rates of CKD and CKD risk factors compared to other populations. The study aim was to assess predictors of CKD care provided to AA and AI/AN populations.

Methods: The Center for Kidney Disease Research, Education, and Hope Registry identified AA (n=25,589), AI/AN (n=4,391), and reference (White, n=351,031) populations with CKD in 2015-2020. CKD was defined by ICD-9/10 codes, CKD-EPI 2021 estimated glomerular filtration rate <60 mL/min/1.73 m^2, urine albumin/creatinine ratio (UACR) ≥30 mg/g, or urine protein/creatinine ratio (UPCR) ≥0.15 g/g ≥90 days

apart. Patients were assessed during 1 year for: CKD guideline-directed medical therapy (GDMT) and testing for UACR/UPCR. Adjusted logistic regression identified care predictors.

Results: AA (62±17 years) and AI/AN (57±18 years) patients with CKD were younger than the reference population (68 ±17 years). Prevalence of GDMT (AA: 46%, AI/AN: 38%, reference: 40%) and UACR/UPCR testing (AA: 22%, AI/AN: 13%, reference: 14%) was suboptimal across populations. The AA population had higher odds of GDMT compared to reference. AI/AN had higher odds of GDMT, but lower odds of UACR/UPCR testing **(Figure)**. Women had lower odds of receiving GDMT or UACR/UPCR testing compared to men.

Conclusions: The disproportionate burden of CKD in AA and AI/AN populations is not solely attributable to disparities in CKD care. Women consistently experienced these disparities across race groups.

Funding: Other NIH Support - AIM-AHEAD Consortium - OT2OD032581

Predictors of CKD care outcomes in AA and AI/AN (reference: WNH) patients with CKD: 2015-2020

Study Population	AA N=374,008		AI/AN N=352,888	
	OR (95% CI)	p	OR (95% CI)	p
Outcome: GDMT[1]				
Race identity (reference: WNH)	1.20 (1.17-1.23)	<0.001	1.07 (1.00-1.15)	0.046
Age (per 10 years)	1.07 (1.06-1.08)	<0.001	1.07 (1.06-1.08)	<0.001
Women (reference: men)	0.79 (0.78-0.80)	<0.001	0.78 (0.77-0.79)	<0.001
Medicare (reference: non-Medicare	1.37 (1.34-1.39)	<0.001	1.37 (1.33-1.40)	<0.001
Urban (reference: rural)	0.95 (0.93-0.97)	<0.001	0.94 (0.92-0.96)	<0.001
Providence (reference: UCLA)	0.92 (0.90-0.94)	<0.001	0.92 (0.90-0.94)	<0.001
eGFR (per -10 mL/min/1.73 m²)	1.06 (1.05-1.06)	<0.001	1.06 (1.05-1.06)	<0.001
Diabetes (yes/no)	2.46 (2.42-2.50)	<0.001	2.46 (2.42-2.49)	<0.001
Hypertension (yes/no)	3.98 (3.90-4.07)	<0.001	3.97 (3.89-4.06)	<0.001
ASCVD (yes/no)	1.47 (1.44-1.49)	<0.001	1.47 (1.44-1.50)	<0.001
Outpatient visits	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	<0.001
Hospitalization (yes/no)	0.91 (0.90-0.93)	<0.001	0.91 (0.89-0.92)	<0.001
Outcome: UACR/UPCR Testing				
Race identity (reference: WNH)	1.34 (1.29-1.38)	<0.001	0.73 (0.67-0.81)	<0.001
Age (per 10 years)	0.86 (0.85-0.86)	<0.001	0.85 (0.84-0.86)	<0.001
Women (reference: men)	0.84 (0.82-0.86)	<0.001	0.84 (0.82-0.86)	<0.001
Commercial Insurance (reference: noncommercial)	1.28 (1.25-1.31)	<0.001	1.25 (1.22-1.28)	<0.001
Urban (reference: rural)	1.27 (1.23-1.31)	<0.001	1.27 (1.23-1.31)	<0.001
Providence (reference: UCLA)	1.16 (1.13-1.20)	<0.001	1.09 (1.06-1.13)	<0.001
Diabetes (yes/no)	8.35 (8.22-8.49)	<0.001	8.50 (8.35-8.65)	<0.001
Hypertension (yes/no)	1.23 (1.20-1.27)	<0.001	1.21 (1.18-1.25)	<0.001
ACE inhibitor/ARB (yes/no)	1.40 (1.37-1.43)	<0.001	1.40 (1.36-1.43)	<0.001
Outpatient visits	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001

Abbreviations: AA-African American; AI/AN-American Indian or Alaska Native; WNH-White non-Hispanic; CI=odds ratio; CI-confidence interval; GDMT-guideline-directed medical therapy; eGFR-estimated glomerular filtration rate; ASCVD-atherosclerotic cardiovascular disease; ACE-angiotensin converting enzyme; ARB-angiotensin II receptor blocker; [1]GDMT outcome defined as 90 days supply prescription for ACE inhibitor or ARB

FR-OR03

Defining Kidney Health Dimensions and Their Associations with Adverse Outcomes in Persons with Diabetes and CKD

Vanessa-Giselle Peschard,[1,2] Rebecca Scherzer,[1,2] Ronit Katz,[4] Mark J. Sarnak,[5] Simon Ascher,[6] James P. Lash,[12] Sarah J. Schrauben,[7] Chirag R. Parikh,[9] Titilayo O. Ilori,[8] Paul L. Kimmel,[13] Steven G. Coca,[14] Orlando M. Gutierrez,[15] Vasan S. Ramachandran,[11] James H. Sondheimer,[10] Katharine L. Cheung,[16] Joseph V. Bonventre,[17] Emily B. Levitan,[15] Jeffrey R. Schelling,[18] Jonathan J. Taliercio,[22] Panduranga S. Rao,[19] Jason H. Greenberg,[20] Jing Chen,[21] Michelle M. Estrella,[1,2] Joachim H. Ix,[3] Michael Shlipak.[1,2] CKD Biomarkers Consortium. *[1]University of California San Francisco, San Francisco, CA; [2]San Francisco VA Health Care System, San Francisco, CA; [3]University of California San Diego, La Jolla, CA; [4]University of Washington, Seattle, WA; [5]Tufts Medical Center, Boston, MA; [6]University of California Davis, Davis, CA; [7]University of Pennsylvania, Philadelphia, PA; [8]Boston University, Boston, MA; [9]Johns Hopkins University, Baltimore, MD; [10]Wayne State University, Detroit, MI; [11]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [12]University of Illinois Chicago, Chicago, IL; [13]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [14]Icahn School of Medicine at Mount Sinai, New York, NY; [15]The University of Alabama at Birmingham, Birmingham, AL; [16]University of Vermont, Burlington, VT; [17]Brigham and Women's Hospital, Boston, MA; [18]Case Western Reserve University, Cleveland, OH; [19]University of Michigan Michigan Medicine, Ann Arbor, MI; [20]Yale University, New Haven, CT; [21]Tulane University, New Orleans, LA; [22]Cleveland Clinic, Cleveland, OH.*

Background: Individual kidney tubule biomarkers are known to be associated with risks for CKD progression and mortality in persons with diabetes. Integrating multiple kidney biomarkers using an exploratory factor analysis could define distinct dimensions of kidney health, and their associations with adverse outcomes.

Methods: We conducted a factor analysis of 17 candidate urine and plasma biomarkers in 1,256 participants with diabetes and eGFR <60 ml/min/1.73 m² from the Chronic Renal Insufficiency Cohort (CRIC; n=701) and the Reasons for Geographic and Racial Differences in Stroke (REGARDS; n=555) studies. We used Cox proportional hazards models to evaluate the associations of identified factors with CKD progression and mortality, adjusting for baseline clinical risk factors, eGFR and albuminuria.

Results: Three factors comprising 10 biomarkers were identified: *systemic inflammation and filtration* (plasma TNFR-1, TNFR-2, suPAR, SDMA), *tubular function* (urine EGF, ADMA, SDMA), and *tubular damage* (urine α1m, KIM-1, MCP-1). In CRIC, lower *tubular function* and higher *tubular damage* were jointly and independently associated with CKD progression risk. Associations in REGARDS were weaker but directionally consistent for both *tubular function* and *tubular damage*. Lower *tubular function* and higher *tubular damage* were associated with higher mortality risk in CRIC, but not REGARDS. Higher *systemic inflammation and filtration* was associated with higher mortality risk in both cohorts.

Conclusions: Three distinct kidney health dimensions were identified, and each associated with CKD progression or mortality in persons with diabetes and CKD.

Funding: NIDDK Support, Other NIH Support - the CKD Biomarker Consortium via NIDDK grant U01DK106962. CRIC Study under grants U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, U01DK060902, and U24DK060990. REGARDS via the U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service

CKD Progression		
	CRIC subcohort and cases (n=701)	REGARDS subcohort (n=555)
Factor Score	HR (95% CI)	Sub-HR (95% CI)
Systemic inflammation and filtration	1.23 (0.99, 1.53)	0.92 (0.67, 1.28)
Tubular Function	0.74 (0.62, 0.88)*	0.77 (0.46, 1.30)
Tubular Damage	1.53 (1.24, 1.88)*	1.12 (0.77, 1.65)
All-Cause Mortality		
	CRIC subcohort (n=589)	REGARD subcohort (n=555)
Factor Score	HR (95% CI)	HR (95% CI)
Systemic inflammation and filtration	1.31 (1.04, 1.65)*	1.40 (1.18, 1.67)*
Tubular Function	0.81 (0.66, 0.98)*	0.99 (0.81, 1.20)
Tubular Damage	1.30 (1.06, 1.61)*	1.15 (0.97, 1.36)

Systemic inflammation and filtration factor score = weighted average of plasma tumor necrosis factor receptor-1 (TNFR-1), plasma tumor necrosis factor receptor-2 (TNFR-2), plasma soluble urokinase plasminogen activator receptor (suPAR) and plasma symmetric dimethylarginine (SDMA); tubular function factor score= weighted average of urine epidermal growth factor (EGF), urine asymmetric dimethylarginine (ADMA) and urine symmetric dimethylarginine (SDMA); tubular damage factor score = weighted average of urine α-1 microglobulin (α1m), urine kidney injury molecule-1 (KIM-1), urine monocyte chemoattractant protein-1 (MCP-1)

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval

All models are adjusted for baseline core covariates, demographic and clinical characteristics, eGFR and albuminuria

*Per 1 SD higher factor score

FR-OR04

No Rest for the Wicked: The Complexity of Nephrology Inpatients Is Increasing over Time

Anukul Ghimire,[1] Natasha Wiebe,[2] Braden J. Manns,[1] Brenda Hemmelgarn,[2] Marcello Tonelli.[1] *[1]University of Calgary, Calgary, AB, Canada; [2]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada.*

Background: Patients seen by nephrologists are known to be more complex than those seen by other medical specialties. Anecdote suggests that the complexity of nephrology inpatients has increased over time, but this has not been studied. We assessed temporal trends in the complexity of inpatients seen by nephrologists.

Methods: We did a retrospective cohort study of all adults in Alberta, Canada who were seen by one or more nephrologists during a hospitalization between 2011-2020. We used validated algorithms applied to population-based administrative data to assess patient characteristics. We evaluated 10 markers of complexity; 8 were measured in the year prior to admission to minimize the competing risk of mortality (presence of ≥10 comorbidities, >15 prescribed drugs, presence of a mental health condition, presence of frailty, number of physician specialties involved in care, number of individual physicians involved in care, ≥2 prior hospitalizations, and >5 emergency visits). We assessed all-cause death and placement in long-term care (LTC) during the year following admission. Differences over time were assessed using generalized linear models.

Results: Among 45,156 inpatients, median age remained stable at 65y over 2011-2020. The table shows the secular changes in the 10 complexity markers. The proportion with a mental health condition and the likelihood of placement in LTC remained stable, whereas the risk of mortality decreased. Complexity as assessed by the remaining 7 markers increased over time, often to a substantial extent. For example, the proportion of patients with ≥10 comorbidities increased by 23%, whereas the proportion with frailty increased by 51%. Trends were similar after adjustment for age (data not shown).

Conclusions: The complexity of nephrology inpatients is increasing over time and is not explained by population aging. The secular decrease in mortality is encouraging and warrants further investigation. These findings have implications for workforce planning, nephrology training programs and physician reimbursement policies.

Complexity markers by fiscal year among inpatients seen by a nephrologist

	Fiscal year										
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	P for trend
Assessed during 12 months prior to admission											
≥10 comorbidities	6.9	7.0	7.4	7.6	7.5	7.6	7.8	7.8	8.2	8.5	<0.001
Mental health condition	32.5	32.7	33.5	34.2	33.5	33.6	33.0	32.4	33.2	32.7	0.49
Frailty	7.2	8.1	9.0	9.0	9.7	7.7	9.0	9.5	9.8	10.9	<0.001
>15 prescriptions	27.9	28.3	29.8	31.1	29.6	30.1	31.9	29.0	31.2	32.4	<0.001
Number of specialties	5.5	5.5	5.5	5.6	5.7	5.6	5.9	5.8	5.9	6.0	<0.001
Number of physicians	12.3	12.2	12.7	13.0	13.1	13.0	14.0	13.6	14.2	14.4	<0.001
≥2 hospitalizations	23.3	24.0	23.6	25.2	24.1	22.6	24.5	22.7	24.3	25.9	<0.001
>5 emergency visits	9.0	8.3	9.1	10.3	10.4	9.8	10.5	10.0	10.5	10.8	<0.001
Assessed during 12 months following admission											
Placement in long-term care	9.3	10.1	9.9	10.2	8.3	7.4	8.7	9.8	9.5	8.5	0.59
Death	25.9	25.8	24.5	24.2	25.2	22.7	24.1	23.1	22.7	22.9	0.02

FR-OR05

Kidney-Adipose Tissue Cross-Talk during Weight Loss in Adults with Obesity and CKD

Helen L. MacLaughlin,[1,2] Ying Chun Yuen,[1] Marguerite M. Conley,[1,3] Lisa K. Philp.[1] *[1]Queensland University of Technology, Brisbane, QLD, Australia; [2]Royal Brisbane and Women's Hospital, Herston, QLD, Australia; [3]Princess Alexandra Hospital, Woolloongabba, QLD, Australia.*

Background: Mechanisms linking obesity and chronic kidney disease (CKD) include energy, adipokine and metabolic homeostasis imbalances. Adiponectin, leptin and fetuin-A play critical roles in these pathophysiological processes, contributing to insulin resistance, inflammation and kidney damage. This study investigated the effect of intentional weight loss on adipokines, fetuin-A, and urinary NGAL levels in people living with obesity and CKD.

Methods: Blood and urine samples were obtained at baseline, 3 and 6 months from 49 adults with BMI >30kg/m^2, CKD stages 1-3b and urinary protein/creatinine ratio >3mg/mmol, who were randomised to either a low energy diet and exercise intervention (LED) or usual care (UC) in the SLOW CKD feasibility study. Serum adiponectin, leptin, fetuin-A, cystatin-C and urinary NGAL levels were measured using commercially available quantitative sandwich enzyme-linked immunosorbent assays (ELISA). Median differences using Mann-Whitney tests and associations between changes in variables using linear or rank regression were examined.

Results: Median BMI, estimated glomerular filtration rate (eGFR) and urinary protein to creatinine ratio were 38.6 kg/m^2, 57 mL/min/1.73m^2 and 84 mg/mmol respectively at baseline. Median weight change was -9 kg (IQR -12 to -7) in LED and 0.5 kg (IQR -4 to 2) in UC at 6M. Biomarker data were available for 35 participants (14 LED, 21 UC). Leptin was high (41.2 ± 27.7 ng/mL), and adiponectin was low (12.6 ± 16.1 μg/mL) at baseline across groups. Adiponectin/leptin ratio improved in LED and remained unchanged in UC (p=0.45), and was inversely associated with weight loss (r=-0.49, p=0.008) and trended towards positive association with fetuin-A (r=0.42 p=0.08) at 6M. Change in leptin was associated with weight (r=0.71, p⟨0.001) and waist circumference (r=0.57, p=0.001) changes at 6M. Change in fetuin-A was inversely associated with change in cystatin-C at 6M (r=-0.59, p=0.008). Urinary NGAL was unexpectedly inversely associated with weight loss at 6M (r=-0.43, p=0.02).

Conclusions: Adults with obesity and CKD had altered leptin and adiponectin levels, and intentional weight loss resulted in favourable changes in adiponectin/leptin ratio and fetuin-A, which was associated with reduced cystatin-C. Findings demonstrate potential kidney-adipose tissue cross-talk mechanisms linking obesity and CKD.

Funding: Private Foundation Support

FR-OR06

Exercise Training and Progression of CKD (GFR-Ex): A Randomized Controlled Feasibility Study

Mark Davies,[1] Aamer Sandoo,[3] Abdulfattah Alejmi,[4] Sharlene A. Greenwood,[2] Jamie H. Macdonald.[3] *[1]NHS Wales Cardiff and Vale University Health Board, Cardiff, United Kingdom; [2]Department of Renal Medicine, King's College Hospital NHS Trust, London, United Kingdom; [3]Institute for Applied Human Physiology, Bangor University, Bangor, United Kingdom; [4]NHS Wales Betsi Cadwaladr University Health Board, Bangor, United Kingdom.*

Background: Whether exercise intervention can delay kidney function decline is not known. The GFR-Ex study assessed the feasibility of a 12-month exercise training program to attenuate the rate of decline in isotope-measured (mGFR) and estimated (eGFR) Glomerular Filtration Rate.

Methods: In a multicenter feasibility study, people with stage 3-4 kidney disease (CKD) with declining function were randomized to either 12 months exercise training (home-based aerobic and resistance program) or usual care. The primary outcome was feasibility, assessed by recruitment and retention rates, intervention adherence (target >80%), and harms. Scientific feasibility outcomes included difference in mGFR ($^{99}Tc^m$-DTPA injection) between groups at 12 months; eGFR decline (cystatin C and creatinine method); and comparison between mGFR and eGFR.

Results: Between December 2018 and July 2022, 2260 patients were screened. Seventy-four participants were randomized (mean age (SD): 56 (14) years; eGFR: 34 (13) ml/min/1.73m^2; 62% male; 61% white) and 34 completed the study (11 exercise,; 23 control). The screening eligibility rate was 11%, consent rate was 48%, and 12-month retention rate was 43% (COVID-19 was implicated in 23% of participants who withdrew). The median (IQR) exercise sessions completed was 69 (63.0, 72.0) %. No adverse events related to the exercise program were recorded. The mGFR and eGFR data are shown in Table. The mean difference (eGFR minus mGFR) was -1.6 ml/min/1.73 m^2 (95% CI: -2.6 to -0.6); the 95% limits of agreement were 8.8 and -11.7 ml/min/1.73 m^2.

Conclusions: In people with progressive, moderate CKD, a 12-month exercise training program was safe and feasible. High dropout and low exercise adherence were in part due to the COVID pandemic. Scientific feasibility was suggested by an encouraging trend for exercise to attenuate GFR decline, and eGFR being a practical and sufficiently accurate alternative to mGFR. This study supports that progression to a definitive trial is warranted, provided modifications (e.g. use of a telehealth exercise intervention) are made to enhance participant recruitment, retention and exercise adherence.

Funding: Private Foundation Support

Outcome Measure	Exercise group	Usual care group
Measured GFR at 12 months (ml/min/1.73 m^2)	36.1 (12.1)	33.8 (14.7)
eGFR decline between 0 & 12 months (ml/min/1.73 m^2/year)	-3.9 (3.4)	-5.1 (6.5)

Values are mean (SD)

FR-OR07

A Home-Based, Video-Supervised 12-Week Exercise Program Improves Physical Performance in CKD: Results from a Pilot Randomized Controlled Trial

Gwenaelle Begue,[1] Alec Foster,[1] Amanda Marie F. Lopez,[2] Lynea B. Kaethler,[2] Chenoa R. Vargas,[2] Tae Youn Kim,[2] Thomas Jue,[2] Hiba Hamdan,[2] Jorge Gamboa,[3] Baback Roshanravan.[2] *[1]California State University Sacramento, Sacramento, CA; [2]University of California Davis, Davis, CA; [3]Vanderbilt University, Nashville, TN.*

Background: Sarcopenia is prevalent in CKD and is a central component of the frailty phenotype associated with adverse clinical outcomes. Regular exercise improves muscle function and physical capacity in CKD. There is a need to test the efficacy of practical and personalized exercise program on improving physical functioning in CKD.

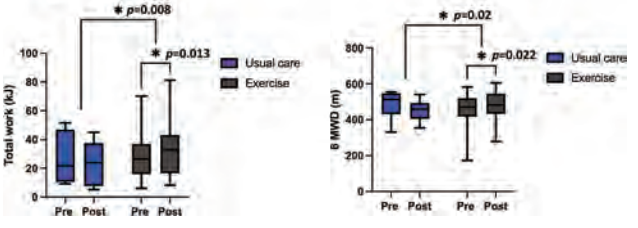
Methods: We performed a 12-week pilot randomized (3:1) clinical trial (NCT02923063) of home-based, personalized, and video-supervised exercise intervention (EX), compared to usual care (UC) in stage 3-5 non-dialysis CKD. Pre- and post-intervention cardiorespiratory fitness (VO2peak) and total work were measured using a graded cycle ergometer test and physical performance was assessed by the 6-minutes walking distance (6MWT) test. Linear mixed effects models were used to test changes in cardiorespiratory fitness, total work, and physical performance comparing 12-week and baseline measurements.

Results: Participants randomized to EX (n=21, 47% male, 47% diabetic) had a mean eGFR of 35±12 mL/min/1.73m2 and mean age of 63±10.3 years, compared to 32.3±12 mL/min/1.73m2 and 67.1±8.3 years for those randomized to UC (n=9, 22% male, 44% diabetic). EX led to improved endurance with significant (p<0.05) 5.25kJ increase in total work (95% CI:0.70-6.43, p=0.008) at the graded cycle test and a clinically meaningful improvement of 39m at 6MWT (95% CI:3-52, p=0.02) compared to UC (Fig. 1). Cardiorespiratory fitness (VO2 peak) did not differ between groups (p=0.3). The increase in total work was independent of change in VO2 peak, suggesting improved muscular health in EX.

Conclusions: A 12-weeks home-based video-supervised exercise program is efficacious in improving physical endurance in CKD. It provides a tool for studying metabolic and molecular health and may shed new light on the pathophysiology of sarcopenia in CKD. **Funding:** R01DK129793, R01DK125794, DCI-4112

Funding: NIDDK Support, Private Foundation Support

Fig. 1



FR-OR08

Cardiovascular, Kidney, and Safety Outcomes with Canagliflozin in Older Adults: A Pooled Secondary Analysis of the CANVAS Program and CREDENCE Trial

Amanda Siriwardana,[1,2] Meg Jardine,[3,4] Vlado Perkovic,[2,5] Min Jun,[2] Sradha S. Kotwal,[2,6] Clare G. Arnott,[2,8] Brendon L. Neuen.[2,7] *[1]The University of Sydney School of Medicine, Sydney, NSW, Australia; [2]The George Institute for Global Health, Sydney, NSW, Australia; [3]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [4]Concord Repatriation General Hospital, Concord, NSW, Australia; [5]University of New South Wales Medicine & Health, Sydney, NSW, Australia; [6]Prince of Wales Hospital and Community Health Services, Randwick, NSW, Australia; [7]Royal North Shore Hospital, St Leonards, NSW, Australia; [8]Royal Prince Alfred Hospital, Camperdown, NSW, Australia.*

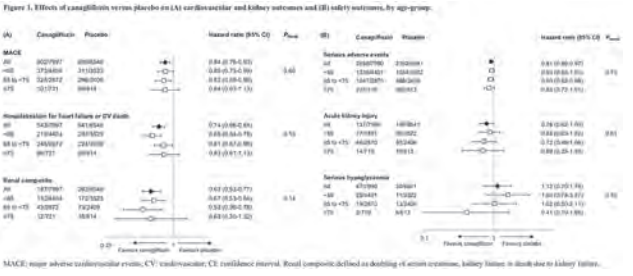
Background: Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular and kidney outcomes in patients with type 2 diabetes (T2DM). With the growing prevalence of T2DM among older adults, it is important to understand whether the efficacy and safety of SGLT2 inhibitors differs in older individuals.

Methods: In this post hoc analysis, individual participant data from the CANVAS Program (n=10,142) and CREDENCE trial (n=4401) were pooled and analysed according

to baseline age (<65 years, 65 to <75 years, and ≥75 years). Outcomes of interest were: major adverse cardiovascular events (MACE, defined as nonfatal myocardial infarction, nonfatal stroke or cardiovascular death), hospitalisation for heart failure or cardiovascular death, CKD progression (defined as doubling of serum creatinine, kidney failure or death due to kidney failure), and safety outcomes. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards models, stratified by age group.

Results: Among the 14,543 participants, 7,927 (54.5%) were <65 years, 5,281 (36.3%) were 65 to <75 years, and 1,335 (9.2%) were ≥75 years. Older participants had higher rates of hypertension and heart failure, longer diabetes duration, lower mean eGFR and lower median urine albumin:creatinine ratio. Across age groups, consistent relative risk reductions were observed with canagliflozin for MACE, hospitalisation for heart failure or cardiovascular death, and for CKD progression (all P trend > 0.10, **Figure 1 Panel A**). Similarly, the effects of canagliflozin on serious adverse events, acute kidney injury, and serious hypoglycaemia, were consistent across age categories (all P trend >0.10; **Figure 1 Panel B**).

Conclusions: In this pooled CANVAS and CREDENCE analysis of T2DM patients with varying degrees of kidney impairment, canagliflozin demonstrated consistent benefits across the spectrum of age for cardiovascular and kidney outcomes, with no additional safety concerns identified.



FR-OR09

Dietary Acid Reduction with Fruits and Vegetables or Sodium Bicarbonate to Avoid or Delay Need for Kidney Replacement Therapy (KRT) in Patients Initially with Stage 3 CKD: A 10-Year Randomized Trial

Nimrit Goraya,[1] Jan Simoni,[2] Maninder Kahlon,[3] Nazan Aksan,[3] Donald E. Wesson.[3] *[1]Baylor Scott and White Central Texas, Temple, TX; [2]Texas Tech University System, Lubbock, TX; [3]The University of Texas at Austin Dell Medical School, Austin, TX.*

Background: Previous studies show that dietary acid reduction with addition of either base-producing fruits and vegetables (F&V) or oral sodium bicarbonate (NaHCO3) slowed eGFR decline in study participants with CKD stage 3 (G3) hypertension-associated CKD. We examined the comparative benefits of F&V vs. NaHCO3 to avoid or delay need for KRT, a goal of kidney protective therapy

Methods: One hundred eight macroalbuminuric, non-diabetic G3 participants with mean baseline eGFR ~39 ml/min/1.73 m2 and baseline high acid-producing diets (mean potential renal acid load [PRAL] ~61 mmol/day) were randomized to F+V (n=36) to reduce dietary PRAL by half, oral NaHCO3 (HCO3, n=36) 0.4 mmol/kg bw/day to approximate the base-producing potential of F&V, or to Usual Care (UC, n=36). The primary outcome was the proportion in each group not lost to follow up who reached the need for KRT, whether or not they were alive after the 10-year follow up. We annually measured systolic blood pressure (Sys BP), eGFR, and urine albumin-to-creatinine ratio (UACR), the latter two parameters measured until the time participants began KRT.

Results: Baseline Sys BP, eGFR, and UACR were not different among groups. At 10 years, Sys BP was lower in F&V ([mean (SD)], 129.7 (5.2) mm Hg) than both, HCO3 [141.4 (5.4) mm Hg] and UC [134.2 (5.4), p< 0.01]). In addition, the F&V trajectory for UACR during follow up was lower (p< 0.01) than that for both HCO3 and UC. The likelihood of KRT when combining the two intervention groups, F&V and HCO3 (18/58 = 31.0%) relative to UC (16/31 = 51.6%), was not different (p > 0.05). When the intervention groups were NOT combined, those in the F&V arm (4/29=13.8%) had fewer participants reach KRT than those in UC or HCO3 (14/29 or 48.3%) at p<0.004

Conclusions: Dietary acid reduction with F&V but not oral NaHCO3 yielded fewer study participants reaching the need for KRT than UC, supporting greater kidney protection with ten years follow up in these participants with CKD and macroalbuminuria at study entry. Given previous data showing that F&Vs were associated with better improvement of cardiovascular disease risk indices than NaHCO3 (Am J Nephrol 49:438–448, 2019), these data support F&V over NaHCO3 as kidney protection for patients with CKD 3.

FR-OR10

Integrin α1β1 Regulates Myofibroblast Expansion in Polycystic Kidney Disease

Richard W. Naylor,[1] Celine Grenier,[1] Dorien J. Peters,[3] Ambra Pozzi,[2] Rachel Lennon.[1] Naylor Lab. *[1]The University of Manchester, Manchester, United Kingdom; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Universiteit Leiden, Leiden, Netherlands.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common, potentially lethal disease, affecting 1 in 1000 individuals. A major issue preventing effective treatment is the lack of anti-fibrotic therapies to preclude the interstitial fibrosis that ultimately causes kidney failure in patients with ADPKD and other chronic kidney diseases.

Methods: Mass spectrometry (MS)-based proteomics were used to determine how extracellular matrix (ECM) protein composition changes in whole kidneys taken from a hypomorphic mouse model of ADPKD (*Pkd1*$^{nl/nl}$) and littermate controls. Postnatal day 1 (P1) and P28 were used to determine temporal changes in the proteome. scRNA-seq and immunofluorescence on mouse and human tissue was used to further investigate integrin α1.

Results: Proteomic and histological analysis at P1 showed no fibrosis, but by P28 extensive ECM deposition was observed along with other markers of fibrosis (*Acta2, Lcn2, Serpine1, Postn*). We found integrin α1 to be up-regulated, along with other cell-matrix receptors. Integrin α1 has previously been shown to regulate cell proliferation in dermal fibroblasts and regulate collagen deposition in the glomerulus. However, a role for integrin α1 in PKD has not previously been investigated. In human healthy and ADPKD kidney biopsies, integrin α1 expression was observed in the interstitial mesenchyme. scRNA-seq data confirmed integrin α1 is expressed in fibroblasts and myofibroblasts. To determine a functional role for integrin α1 in PKD, we created *Pkd1*$^{nl/nl}$*Itga1*$^{-/-}$ mice. These mice had reduced kidney weight, kidney dysfunction (BUN/uACR), and cyst size when compared to *Pkd1*$^{nl/nl}$ mice, suggesting depletion of integrin α1 is protective. Strikingly, interstitial fibrosis was significantly reduced in *Pkd1*$^{nl/nl}$*Itga1*$^{-/-}$ kidneys. Analysis of αSMA in these mice showed that, whilst myofibroblast transdifferentiation occurred, there were far fewer myofibroblasts present in *Pkd1*$^{nl/nl}$*Itga1*$^{-/-}$ kidneys. Cell proliferation assays *in vivo* and in primary fibroblast cultures determined myofibroblast expansion was reduced when integrin α1 is depleted.

Conclusions: Integrin α1 is a regulator of cell proliferation in kidney fibroblasts. Given its depletion is non-lethal, integrin α1 is likely to be and is a promising future target for anti-fibrotic therapies for kidney diseases involving interstitial fibrosis.

FR-OR11

Renal Myofibroblasts Undergo Autophagy to Support Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

Abeda Jamadar, Viji Remadevi, Reena Rao. *The University of Kansas Medical Center, Kansas City, KS.*

Background: Myofibroblasts often surround renal epithelial cysts in autosomal dominant polycystic kidney disease (ADPKD). Our previous studies showed that myofibroblast depletion ameliorates disease progression in the RC/RC mouse model of ADPKD. Based on our observation that myofibroblasts in ADPKD kidneys undergo autophagy, we examined if autophagy in myofibroblasts contributes to renal cyst growth in ADPKD.

Methods: Cell proliferation of human ADPKD renal cyst epithelial cells exposed to cell culture conditioned media from human ADPKD myofibroblasts treated with vehicle or autophagy inhibitor- chloroquine was measured. Autophagy protein 5 (ATG5) is crucial for autophagy. We made myofibroblast-specific *Atg5* gene knockout- RC/RC;*Atg5* $^{f/f}$;*PDGFRb*^{cre}*ER*^{T2} mouse by breeding RC/+;*PDGFRb*^{cre}-*ER*^{T2} mouse with *Atg5*$^{f/f}$ mice. Wild type (WT), *Atg5*KO; RC/RC, RC/RC:*Atg5*KO mouse littermates were treated with vehicle or tamoxifen and sacrificed at 28 weeks of age and their kidneys were analyzed.

Results: Immunofluorescence staining in human ADPKD kidneys and RC/RC mouse kidneys showed that myofibroblasts surrounding renal cysts undergo autophagy. Human ADPKD renal cyst epithelial cells exposed to human ADPKD renal myofibroblast-conditioned media proliferated more compared to cells exposed to control media. Inhibition of autophagy in ADPKD human-renal myofibroblasts reduced the ability of their conditioned media to induce cyst epithelial cell *proliferation in vitro*. RC/RC:*Atg5*KO group had significantly lower kidney/body weight ratio, cyst number and cystic index when compared to RC/RC group. RC/RC:*Atg5*KO group had significantly reduced fibrosis and extracellular matrix related gene expression when compared to RC/RC group. No morphological changes were observed in Atg5KO mice when compared to WT.

Conclusions: Our results suggest that myofibroblasts in ADPKD kidneys undergo autophagy to support cyst growth, and inhibition of autophagy in renal myofibroblasts leads to reduced renal cyst growth and fibrosis.

Funding: NIDDK Support

FR-OR12

Endoplasmic Reticulum (ER)-Mitochondrion Connection Is Important in the Pathogenesis of Autosomal Dominant Polycystic Kidney Disease

Biswajit Padhy, Jian Xie, Danish Idrees, Chou-Long Huang. Huang Lab. *University of Iowa Carver College of Medicine, Iowa City, IA.*

Background: Mutations on *PKD1* and *PKD2* coding for PC1 and PC2 cause ADPKD. Metabolic reprogramming/mitochondrial dysfunction is an important modifier of ADPKD cystogenesis. The cause of mitochondrial dysfunction in ADPKD remains elusive. PC2 is a cation channel that conducts monovalent cation K^+ and Na^+ more than Ca^{2+}. We have recently shown that ER-localized PC2 functions as a K^+-permeable channel to mediate K^+-Ca^{2+} exchange to facilitate ER Ca^{2+} release. TricB is an ER-restricted K^+ channel. We showed that TricB reverses ER Ca^{2+} release defect in PC2-deficient cell line and cystogenesis in Pkd2-cKO mice. ER and mitochondrion each occupies a large share of cell volume and form close inter-organelle contact known as mitochondria-associated ER membranes (MAMs). We examined the role of ER-mitochondria connection in ADPKD pathogenesis.

Methods: Mitochondria morphology in pre-cystic (4 weeks) and cystic (16 weeks) kidneys in Pax8-LC1 driven Pkd2-cKO mice were examined by transmission (TEM) and scanning electron microscopy (SEM). Mitochondrial respiration in isolated proximal tubules were studied by Seahorse oxygen consumption rate (OCR) assays. Mitochondrial DNA mass and regulator gene expression were examined by real-time PCR.

Results: TEM showed that Pkd2-cKO kidneys vs control have altered mitochondria morphology including decreased area and cristae density, and increased roundness. The distance between ER-mitochondria contact was increased and the length of contact was decreased in Pkd2-cKO. These changes occurred in pre-cystic kidneys, and no further progression from precystic to cystic kidneys. SEM with 3D rendering showed decreased individual mitochondria size. Proximal tubules isolated from cKO kidneys showed decreased OCR. Mitochondria master regulators PGC1α and PPARα, DNA mass, and mitofusin-2 (a mitochondria profusion factor and MAM regulator) were decreased in cKO kidneys. All above changes in cKO, in precystic as well cystic stages, were reversed by TricB.

Conclusions: Mitochondria defects occur in early precystic stages. ER and mitochondria are in close contact with 60% mitochondria surface in contact with ER. TricB transgene reverses cystogenesis and mitochondria defects in Pkd2-cKO mice. The results support that ER Ca^{2+} homeostasis defect is important in mitochondrial dysfunction and the pathogenesis of ADPKD.

Funding: NIDDK Support

FR-OR13

Electrophysiological Analysis of a Gain-of-Function Polycystin-1/Polycystin-2 Ion Channel

Tobias Staudner,[1] Juthamas Khamseekaew,[1] M. Gregor Madej,[2] Linda Geiges,[1] Bardha Azemi,[1] Christine M. Ziegler,[2] Christoph Korbmacher,[1] Alexandr V. Ilyaskin.[1] *[1]Friedrich-Alexander-Universitat Erlangen-Nurnberg Institut fur Zellulare und Molekulare Physiologie, Erlangen, Germany; [2]Universitat Regensburg Fakultat fur Biologie und Vorklinische Medizin, Regensburg, Germany.*

Background: Autosomal-dominant polycystic kidney disease (ADPKD) is caused by mutations in the polycystin-1 (PC1) or polycystin-2 (PC2) coding gene. Structural data imply that PC1 and PC2 form a heterotetrameric channel with a 1:3 stoichiometry. This study investigates the assembly and ion channel properties of PC1/PC2 complexes using a novel gain-of-function (GOF) PC1 construct.

Methods: Amino acid residues identified as critical for ion permeation in the cryo-electron microscopy (cryo-EM) model of the PC1/PC2 complex [PDB ID: 6A70] were mutated to alanine in PC2 and the C-terminal fragment of PC1 (aa: 3049-4303) to obtain the known $PC2^{GOF}$ (L677A/N681A)) and a putative $PC1^{GOF}$ (R4100A/R4107A/H4111A) construct. Wildtype (WT) and mutant PC1 and PC2 were expressed in *Xenopus laevis* oocytes and analysed using the two-electrode voltage clamp technique. Cell surface expression of PC1 and PC2 was detected using a biotinylation approach. The formation of PC1/PC2 complexes was confirmed by co-immunoprecipitation experiments.

Results: Co-expression of $PC1^{WT}$ and $PC2^{GOF}$ decreased Na^+ inward currents compared to $PC2^{GOF}$ alone. Importantly, Na^+ inward currents were ~5-fold larger in oocytes co-expressing $PC1^{GOF}$/$PC2^{GOF}$ than in those co-expressing $PC2^{GOF}$/$PC1^{WT}$. A mutagenesis approach identified the residues R4107 in PC1 and L677 in PC2 as critical for the GOF effect. Homomeric $PC2^{GOF}$ channels exhibit a preference for K^+ over Na^+ and Li^+ and are inhibited by DMA^+ and DEA^+. In contrast, $PC1^{GOF}$/$PC2^{GOF}$ heteromers conduct Na^+, K^+, Li^+, and DMA^+ equally well. Intriguingly, $PC2^{GOF}$ channels exhibit a permeability for Ca^{2+}, whereas $PC1^{GOF}$/$PC2^{GOF}$ complexes do not. By varying the expression ratio of $PC1^{GOF}$ and $PC2^{GOF}$, we demonstrate that PC2 preferentially forms heteromeric complexes with PC1. A re-interpretation of the published cryo-EM map of PC1 implies that its pore-forming domain exhibits a TRP-like conformation. This interpretation is supported by cysteine-modification experiments.

Conclusions: Taken together, these results support the concept that PC2 homomers and PC1/PC2-heteromers are ion channels with distinct physiological functions. The novel $PC1^{GOF}$ construct described here may serve as a tool to investigate the effect of pathogenic ADPKD mutations on PC1/PC2 ion channel function.

Funding: Government Support - Non-U.S.

FR-OR14

A Cross-Model Single-Cell and Spatial Transcriptomic Atlas of Polycystic Kidney Disease

Kurt Zimmerman,[1] Sarah J. Miller,[1] Yi Jiang,[3] Jason R. Stubbs,[2] Qin Ma,[3] Anjun Ma.[3] *[1]The University of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]The University of Kansas Medical Center, Kansas City, KS; [3]The Ohio State University, Columbus, OH.*

Background: Polycystic kidney disease (PKD) affects over 12 million people worldwide and is caused by mutations in cilia related genes. In humans, mutations in the PKD1 or PKD2 gene account for about 93% of Autosomal Dominant Polycystic kidney disease (ADPKD) cases, although recent reports highlight that other genes, such as GANAB5, DNAJB116, IFT1407, and ALG98, can also cause an ADPKD phenotype. Further adding to the complexity, different types of genetic mutations are present within the PKD1 and PKD2 family and result in varying disease severity. To model PKD in mice, researchers use both orthologous (i.e. mutations in Pkd1 or Pkd2 gene) and non-orthologous (i.e. Cys1cpk, Ift88, etc) models, which can be either congenic or inducible. Because of this, there is likely significant variation in the cellular and molecular features associated with each mouse model of disease.

Methods: To unbiasedly analyze the cellular and molecular features associated with mouse models of PKD, we generated a single cell RNA sequencing (scRNAseq) atlas comprised of 5 different mouse models of PKD as well as respective non-cystic controls. We also performed spatial transcriptomics on two of the cystic mouse models.

Results: Analyses of scRNAseq data reveal model specific differences in cell type abundance and gene expression. For example, our data indicate that rapidly progressing mouse models of PKD have little S3 nephron segment expansion whereas slowly progressing models have massive S3 nephron expansion, independent of the type of genetic mutation. Further analyses of the data indicate that almost all of the cystic epithelium in all models is derived from the distal nephron. Using the scRNAseq atlas as a reference, we mapped cell-type specific signatures to spatial transcriptomics data and inferred spatially-resolved signaling niches within cystic mice. These analyses identified several ligand-receptor interactions that were significantly enriched within cystic niches including Spp1-Cd44. Loss of Spp1 in one PKD mouse model resulted in worsened cystic disease verify the in vivo relevance of our computational approach.

Conclusions: Our single cell and spatial transcriptomic atlas in mice can be used to identify novel biological targets for treating PKD.

Funding: NIDDK Support, Private Foundation Support

FR-OR15

Characterization of Stepwise Transformation from Cysts to Carcinoma in Tsc1 Mutant Kidneys

Sara Clerici,[1] Daniel Spies,[1,2] Alessandra Boletta.[1] *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Universita Vita Salute San Raffaele, Milano, Italy.*

Background: A novel mouse model of Renal Cell Carcinoma (RCC) was generated by deletion of *Tsc1* using the Cadherin16 Cre (KspCre). This results in cysts undergoing epithelial transformation to cancerous lesions with time. The peculiarity of *Tsc1;kKO* model is the time-driven progression from cysts to papillae, to cystadenomas, and carcinomas with full penetrance. As the malignant phenotype progresses canonical epithelial markers are lost. To overcome this problem, we generated a *mTmG;Tsc1;kKO* mouse in which KO cells express membrane GFP (mG) upon Cre expression.

Methods: RCC kidneys were characterized by IHC, IF analysis, and FACS. scRNA-seq was performed on early- (P30) and late-stage (P80) ctrl and RCC kidneys using 10X genomics. Multiplexed error-robust FISH (MERFISH) analysis on 500 genes panel is currently being conducted to spatially resolve the clusters identified.

Results: *mTmG;Tsc1;kKO* kidneys developed cysts and malignant structures at the same rate and time as the *Tsc1;kKO*. All the structures were mG^+, with a considerable expansion of mG^+ cells in P80 kidneys analyzed by FACS, in line with the increased proliferation of *Tsc1* mutants. scRNA-seq on freshly dissociated kidneys at two time points (P30 and P80) identified clusters from all the major nephron segments in both ctrl and mutant kidneys. *Egfp* transcript was uniquely identified in several new epithelium-derived clusters, enriched at P80 in the mutant. We defined two distinct branches of progressive transformation originating from either principal or intercalated cells of the collecting duct. Interestingly, the two trajectories converge on a cluster with a papillary RCC signature. Initial pathway enrichment analysis of transcripts identified multiple metabolic pathways that are increasingly deranged during transformation. Novel, non-canonical markers were identified and used to design a MERFISH panel to spatially resolve stages of transformation in the murine kidneys and will be used to design a mini-panel to be validated on human specimens.

Conclusions: Our new RCC murine model allows to discriminate early cystogenic processes from subsequent transformation. The combination of scRNA-seq and spatial validation allows to identify new RCC populations, likely the cell of origin of the transforming clusters, and finally to define the mechanism causing the gradual transformation. Complete analysis will be presented.

FR-OR16

Genetic Landscape in Population-Based ADPKD Cohort: Beyond PKD Type 1 and PKD Type 2

Nikola Zagorec,[1,2] Marie-Pierre Audrezet,[1,3] Jean-Michel Halimi,[4] Frank Bridoux,[5] Jean Francois Augusto,[6] Jacques Dantal,[7] Yannick Le Meur,[1,3] Emilie Cornec-Le Gall.[1,3] European Renal Association. *[1]Centre Hospitalier Regional et Universitaire de Brest, Brest, France; [2]Sveuciliste u Zagrebu Farmaceutsko-biokemijski fakultet, Zagreb, Croatia; [3]Universite de Bretagne Occidentale, Brest, France; [4]Groupement Hospitalier de Territoire Touraine-Val de Loire, Tours, France; [5]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [6]Centre Hospitalier Universitaire d'Angers, Angers, France; [7]Centre Hospitalier Universitaire de Nantes, Nantes, France.*

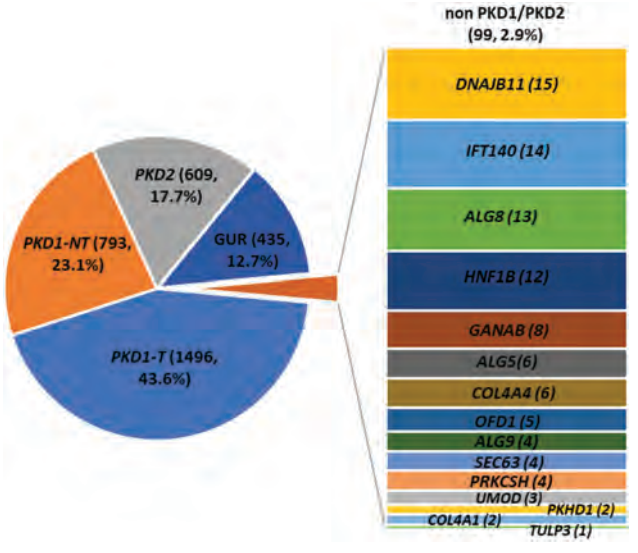
Background: A substantial proportion of individuals with ADPKD-like phenotype carry pathogenic variants in other cystic genes or genes phenocopying ADPKD or are genetically unresolved (GUR). Deciphering this variability is a reseach priorities highlighted in the KDIGO guidelines.

Methods: Genkyst is a population based ADPKD cohort including all patients with (a) typical ADPKD in 28 centers. A panel of 27 known or candidate genes was employed, whole exome sequencing (WES) was performed in a subset of the GUR cases.

Results: Genetic analysis was performed in 3432 individuals (48.4% males), included at the median age of 54.5y [16-95]. Likely pathogenic or pathogenic variants (LP/P) were identified in 87.1%. While *PKD1* and *PKD2* LP/P variants were identified in 66.7 and 17.7% of participants, 2.9% had atypical forms of ADPKD caused by variants in 15 different genes, the most common being *DNAJB11* (n=15), *IFT140* (n=14), *ALG8* (n=13), *HNF1B* (n=12) and *GANAB* (n=8)(Figure). WES was performed in 151 GUR cases, revealing some important ADPKD-differentials like heterozygous *COL4A4*, *OFD1* or biallelic *TULP3*, with significant clinical implications. Of interest, monoallelic loss-of-function variants were detected within 13 different ciliopathy genes (15 patients); causality is being investigated. A total of 435 individuals (416 families) remain GUR, with WES ongoing in 258. Compared to *PKD1-PKD2* patients, GUR individuals were more often males (65vs46%), significantly older (65.1vs53 y), more often diagnosed incidentally (40vs24%) with less common PKD familial history (24vs74%), and less kidney failure (16vs42%)(all P<0.01).

Conclusions: ADPKD is genetically heterogeneous, with in our cohort 8 ADPKD-associated genes and 9 phenocopies. Further genetic heterogenity is likely, with candidate genes identified by WES being currently characterized.

Funding: Government Support - Non-U.S.



FR-OR17

Small Interfering RNA (siRNA) Therapy Using Kidney Targeting Nanoparticles for Treating Polycystic Kidney Disease

Joshua Giblin, Eun ji Chung. *University of Southern California, Los Angeles, CA.*

Background: ADPKD is the most prevalent genetic kidney disease in the world, affecting over 12 million people worldwide. It is characterized by the expansion of fluid-filled cysts that result in the development of enlarged kidneys and eventually kidney failure. Despite its prevalence, the sole FDA-approved therapy, Tolvaptan, offers only modest therapeutic relief. To address the need for precise therapeutic interventions in ADPKD, our study focuses on the development of kidney targeting nanoparticles that enable siRNA-mediated knockdown of ANO1 and MCP1, genes implicated in driving cystic fluid secretion and facilitating renal macrophage infiltration, for suppressing cyst growth.

Methods: A collecting duct (CD) targeting peptide was conjugated to PEGylated lipids and collecting duct targeting peptide amphiphile micelles (CD-PAMs) were formed using thin-film hydration. The kidney targeting ability of CD-PAMs was analyzed using an ADPKD mouse model by flow cytometry and *ex vivo* organ imaging. Furthermore, CD-PAMs were loaded with siRNAs (CD-siRNA PAMs) and gene knockdown efficiency was tested on IMCD PKD1 KO cells using RT-qPCR and the impact of siRNA delivery on cyst growth was tested on a 3D cyst model. In addition, an ADPKD mouse model was used to evaluate the impact of CD-siRNA PAMs on kidney size and cystic index.

Results: CD-PAMs exhibited higher kidney accumulation after 24 hours compared to the non-targeting PAMs (NT-PAMs) (45.9% vs 35.6% NP+ kidney cells, p=0.005). Moreover, flow cytometry analysis revealed the targeting nanoparticles exhibited a pronounced affinity for collecting duct cells relative to non-targeting nanoparticles (49.9% vs. 38.5% DBA+NP+ cells, p<0.001). In addition, CD-PAMs were effectively loaded with ANO1 and MCP1 siRNA (CD-siRNA PAMs), resulting in substantial gene knockdown rates of 76% and 66% in IMCD PKD1 KO cells, respectively. Notably, these interventions successfully suppressed cyst growth in a 3D cyst model, underscoring their therapeutic potential.

Conclusions: We have successfully developed nanoparticles that can be functionalized with targeting peptides for increasing kidney accumulation. Furthermore, these nanoparticles can be loaded with small RNAs for manipulating gene expression and suppressing cyst growth in ADPKD. We are currently working to evaluate the therapeutic efficacy of our siRNA-loaded NPs in an ADPKD mouse model.

Funding: Other U.S. Government Support

FR-OR18

In Vivo Base Editing Rescues ADPKD in Mice

Shasha Cheng, Xiaoyan Li, Peter C. Harris, Xia Zhou, Xiaogang Li. *Mayo Clinic Minnesota, Rochester, MN.*

Background: ADPKD is the most prevalent genetic kidney disease, caused by mutations of the PKD1 and PKD2 genes, which drive renal cyst growth and extrarenal complications, including cardiac hypertrophy. Adeno-associated virus (AAV) delivered CRISPR-Cas9 base editing is a revolutionary approach for treating inherited diseases. However, thus far, the effect of AAV-BEs on DNA editing in ADPKD have not been reported.

Methods: To determine whether correction of the *Pkd1* gene mutation in $Pkd1^{RC/RC}$ mice, carrying an arginine (R) to cystine (C) mutation as in ADPKD patients, delays cyst growth and decreases heart hypertrophy, we treated $Pkd1^{RC/RC}$ mice with one dose of two newly developed ABE9-AAV9 base editors through intravenous (IV) injection. To evaluate the effect of the ABE9-AVV9 base editing on lifespan, we treated $Pkd1^{RC/null}$ mice with both base editor systems.

Results: We developed 1) a broadly expressed AAV9-ABE9 base editor system to correct *Pkd1* gene mutation in whole body, and 2) a kidney specific AAV9-ABE9 base editor system to increase the efficiency and specificity of ABE9 base editor on correction of *Pkd1* gene mutation in kidney only. We showed that one dose of broadly expressed AAV9-ABE9 base editor can effectively delay renal cyst growth and decrease cardiac hypertrophy in $Pkd1^{RC/RC}$ mice, and that one dose of kidney-specific AVV9-ABE9 base editor is selectively expressed in kidneys, but not in hearts, resulting in efficiently delaying cyst growth in $Pkd1^{RC/RC}$ kidneys. The precise editing efficiency with one dose of these two AAV9-ABE9 base editor systems remained stable in kidneys six months after treatment, increasing the expression of *Pkd1* mRNA and a decrease of cyst index, KW/BW ratios, BUN levels in $Pkd1^{RC/RC}$ mice. Treatment with AAV9-ABE9 base editors also decreased cystic cell proliferation and the accumulation of macrophages at interstitial and pericystic regions, and increased cyst lining epithelial cell apoptosis in $Pkd1^{RC/RC}$ kidneys. Treatment with one dose of either the broadly expressed or kidney specific ABE9 base editor increased the survival rate of $Pkd1^{RC/null}$ mice.

Conclusions: This is the first proof-of-principle study that use CRISPR/Cas9 base editing to correct a pathogenic single-nucleotide variant in an ADPKD mouse model, which demonstrates considerable potential for single-dose genetic therapies to correct pathogenic variants and prevent the development of ADPKD in the clinic.

Funding: NIDDK Support, Other NIH Support - AHA, Other U.S. Government Support

FR-OR19

Real-World Evidence on Hemodialysis Modality and Hospitalization Outcomes

Yan Zhang,[1] Anke Winter,[1] Belen Alejos,[1] Paola Carioni,[2] Otto Arkossy,[1] Len A. Usvyat,[3] Franklin W. Maddux.[4] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care Italia SpA, Palazzo Pignano, Italy; [3]Fresenius Medical Care Holdings Inc, Waltham, MA; [4]Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany*.

Background: Recent clinical trials have highlighted the benefits of hemodiafiltration (HDF) for clinical outcomes, such as mortality. We assessed the association of dialysis modality (HDF vs hemodialysis [HD]) with hospital admission and length of stay (LOS) in a large, unselected patient population treated in real-world setting prior to and during COVID-19 pandemic.

Methods: We included 78,608 hemodialysis patients treated in 2019-2022 at NephroCare Clinics of 23 EMEA countries from European Clinical Database (EuCliD®). Rate of all-cause hospital admission and cumulative LOS was calculated separately for patients receiving at least 75% of treatments with HDF or HD during follow-up. Incident rate ratio (IRR) was estimated by negative binomial regression, accounting for patients with multiple events, and adjusted for multiple confounders. Convection volume (standardized by body surface area) specific analyses were conducted by classifying HDF patients into 3 groups: (LV-HDF, <19 L; MV-HDF,19-23 L; HV-HDF>23L).

Results: The mean age of the study population was 63.2 years and 60% were male. During a median follow-up of 22.6 months, HDF patients showed lower rate of both hospital admission and LOS (adjusted IRR [95% CI] of 0.83 [0.81–0.85] and 0.91 [0.87–0.94], respectively), compared to HD patients. Incident patients (vintage <90 days) had higher rate of hospital admission and LOS than prevalent patients (vintage ≥ 90 days) for both HDF and HD group. However, IRRs of both hospital admission and LOS for HDF group compared to HD group were lower in the incident patients than in the prevalent patients. HV-HDF and MV-HDF showed lowest and intermediate IRR of hospital admission (IRR [95% CI], 0.77 [0.75–0.79] and 0.82 [0.75–0.79], respectively) and LOS (IRR [95% CI], 0.82 [0.75–0.79] and 0.86 [0.75–0.79], respectively).

Conclusions: This study suggests that HDF was associated with reduced rate of hospitalization as well as time that patients spent in the hospital. Our findings add to the growing body of evidence that HDF provides a spectrum of clinical benefits for dialysis patients.

Table 1. The association of dialysis modality with hospital admission and length of stay (LOS)

Group	No. Patients	No. hospital admission	Hospital admission rate (/Person-Year)	Hospital LOS Rate (/Person-Year)	IRR (95% CI)* Hospital admission	IRR (95% CI)* Hospital LOS
Overall						
HD	36,012	66,773	1.02	8.30	Ref.	Ref.
HDF	42,596	78,302	0.82	7.70	0.83 (0.81 - 0.85)	0.91 (0.87 - 0.94)
Incident patients						
HD	16,198	26,548	1.27	10.20	Ref.	Ref.
HDF	13,471	23,249	1.06	9.60	0.80 (0.77 - 0.83)	0.82 (0.78 - 0.87)
Prevalent patients						
HD	19,814	40,225	0.91	7.41	Ref.	Ref.
HDF	29,125	55,053	0.75	7.14	0.84 (0.82 - 0.86)	0.95 (0.91 - 0.99)

*IRR estimated by negative binomial regression, adjusted for COVID-19 infection, age, gender, ethnicity, tobacco use, renal etiology, comorbidities at baseline (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, malignant disease), dialysis vintage at baseline, vascular access (frequency of 75% over the past 6 months prior to baseline used to define type of vascular access, if not available at baseline), average of systolic blood pressure and blood flow rate over the past 6 months prior to baseline, if not available at baseline.

FR-OR20

Mortality Risk on Hemodiafiltration Compared with High-Flux Hemodialysis: Real-World Evidence from a Large Brazilian Cohort

Maria Eugenia F. Canziani,[1] Jorge P. Strogoff-de-Matos,[2] Ana Beatriz L. Barra.[3] *[1]Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil; [2]Universidade Federal Fluminense, Niteroi, Brazil; [3]Fresenius Medical Care AG, Rio de Janeiro, Brazil.*

Background: Patients undergoing online hemodiafiltration (HDF) have been associated with better survival compared to those on high-flux hemodialysis (HD). Recently, the use of HDF has grown markedly in Brazil, but there is no robust real-world Brazilian study on the impact of this dialysis modality on patient's outcomes.

Objective: To compare the mortality risk in patients treated with HDF and high-flux HD in a large cohort population in Brazil.

Methods: This is an observational cohort study of all adult patients on maintenance dialysis (HD and HDF) at 29 facilities in Brazil from January 1, 2022, to December 31, 2023.

Results: A total of 8,391 unselected patients were included in the study: 6,787 on high-flux HD, 1,604 on HDF only, and 1,222 who migrated from high-flux HD to HDF during the follow-up period, making a total of 2,826 patients on HDF. Patients on HDF, compared to those on HD, were older (66 vs. 62 years; $p < 0.001$) and with a higher prevalence of diabetes (36.8% vs. 32.6%; $p < 0.001$). Most patients reached the target dialysis dose along the follow-up period, with a median of 25.3 (interquartile range [IQR] 20.9 – 28.4) liters of convection volume per session for HDF patients, and a single-pool Kt/V of 1.58 (IQR 1.36 – 1.81) per session for those undergoing HD. The median follow-up was 14,3 ± 8,8 months for the patients in the two treatment groups. Death from any cause occurred in 1.243 patients, 311 in the HDF, and 932 in the HD group. The two-year survival rates in these groups were 81.2% and 77.9%, respectively ($p < 0.001$). In the analysis of the subdistribution proportional hazard ratio (sHR) by the Fine-Gray model, including the adjustment for competing outcomes and time-varying covariates, a significant reduction in the death risk was found for patients on HDF (sHR 0.75; 95% confidence interval [CI] 0.65 to 0.86]). In the analysis of subgroups, the reduction of death risk associated with HDF was more pronounced for patients aged < 65 (sHR, 0.49; 95% CI, 0.38 to 0.65) than for those aged 65 or more (sHR, 0.82; 95% CI, 0.71 to 0.95).

Conclusions: Online HDF was associated with a lower risk of death than conventional high-flux HD in a large cohort of patients in Brazil.

FR-OR21

At the Foot of the Hemodialysis Room: Online Hemodiafiltration and High-Flux Hemodialysis, a Multicenter Study

Shaira Martinez Vaquera, Antoni B. Gil, Gustavo A. Useche Bonilla, Christian I. Alfaro Sanchez, Jose Luis Pizarro Leon. *Diaverum Espana, Madrid, Spain*.

Background: Several studies highlight the relevance of convective transport versus diffusive transport in the elimination of substances of higher molecular weight with great advantages in the prevention of chronic complications. Convective techniques improve them substantially. Among them, on-line hemodiafiltration (HDF-OL) is the one that eliminates more medium and high molecular weight toxins, although high-flux hemodialysis with high permeability dialyzers comes close to the advantages offered by HDF-OL. The aim of the present study is to estimate whether there are differences in the different parameters between high-flux hemodialysis (HD-FH) and OL-HDF.

Methods: Multicenter, retrospective, descriptive study, analyzing the evolution in one year in both techniques. Variables of interest: demographics, Charlson comorbidity index, Karnofsky index, analytical parameters (urea kinetics, nutrition, inflammation, bone-mineral metabolism, anemia, dyslipidemia), interdialysis weight gain, diabetes, arterial hypertension and hospitalization among others.

Results: A total of 1674 in OL-HDF and 889 in HD-HF. No differences in: sex, diabetes, etiology of nephropathy, physical activity, smoking, months on dialysis, dry weight, interdialysis gain. There were statistically significant differences in favor of OL-HDF in: KtV, ß2-microglobulin, hemoglobin levels and PTH. In favor of HDF-HF-HDF: albumin and aluminum. The proportion of hospitalized patients was higher in the OL-HDF group (41%) compared to the high-flow HD group (37%) (p 0.044).

Conclusions: These results highlight the complexity of choosing the optimal dialysis technique, which must be customized according to the patient's specific needs and clinical situation. Although OL-HDF offers advantages in the removal of larger toxins, which is crucial to prevent chronic complications, the observed hospitalization rate suggests the need for vigilance.

Funding: Other NIH Support - Diaverum Renal Services, SL, Other U.S. Government Support

FR-OR22

Effect of Expanded Hemodialysis with Theranova Dialyzer on Preservation of Residual Kidney Function in Incident Hemodialysis Patients: THREAD Randomized Controlled Trial

Jeong-Hoon Lim, Youn sik Oh, Mingyu Kim, You Hyun Jeon, Hee-Yeon Jung, Sun-Hee Park, Chan-Duck Kim, Yong-Lim Kim, Jang-Hee Cho. *Kyungpook National University, Daegu, Republic of Korea*.

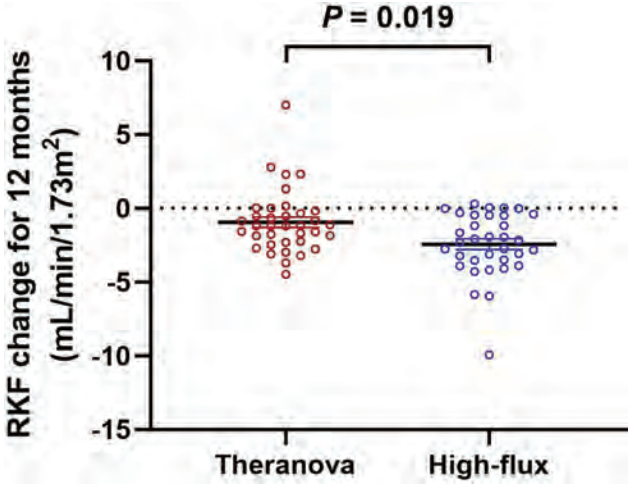
Background: Expanded hemodialysis (HDx) using a medium cut-off dialyzer can improve the clearance of middle-molecular uremic toxins compared to conventional hemodialysis (HD). However, its effect on residual kidney function (RKF) remains unclear. This study evaluated the effect of HDx on preserving RKF in incident HD patients.

Methods: Patients who initiated HD were randomized to receive dialysis with either an HDx with Theranova 400 or a high-flux (HF) dialyzer with a similar surface area over 12 months. The primary outcome was a change of glomerular filtration rate (GFR) over 12 months, as determined by the average of urea and creatinine clearance. The secondary outcome was a change in 24-hour urine volume, middle molecules, and kidney injury markers.

Results: A total of 80 HD patients (mean age: 62.7±11.9 years; male: 52 [65.0%]) underwent randomization. During 12 months, the Theranova group demonstrated a significantly smaller decrease in GFR than the HF group (−1.20 [IQR, −2.29, −0.22] mL/min/1.73m^2 vs. −2.24 [IQR, −3.62, −0.46] mL/min/1.73m^2, P=0.019) (Fig 1). No significant difference in 24-hour urine volume was observed at 12-month, whereas Theranova maintained greater 24-hour urine volume until 9-month compared to the HF dialyzer. After 12 months, the Theranova group showed a significantly lower increase in β2-microglobulin. The increase in kidney injury markers such as IGFBP-7 and KIM-1 was significantly reduced in the Theranova group compared to the HF group. The reduction ratio for κ/λ free light chains, TNF-α. and GDF-15 was higher in the Theranova group than the HF group. There were no differences in hospitalization rate or mortality between the two groups.

Conclusions: HDx using the Theranova dialyzer has preserved the decline in RKF compared to the HF dialyzer of similar size in newly initiated HD patients.

Funding: Commercial Support - Baxter



FR-OR23

First-in-Human Trial of the NeoKidney Portable Hemodialysis Device Sorbent System

Titus W. Lau,[1,2] Christian Bluechel,[3] Paiboon Khaopaibul,[3] Han Jie Tan,[3] Yu En Toh,[3] Sabrina Haroon.[1,2] *[1]National University Hospital, Singapore, Singapore; [2]National University of Singapore, Singapore, Singapore; [3]Nextkidney, Singapore, Singapore.*

Background: The Neokidney™ is a sorbent-based regenerative hemodialysis device intended for Short Daily Hemodialysis (SDHD). Unlike conventional hemodialysis (CHD), Neokidney™ requires only 4.5L of dialysate by continuous regeneration of spent dialysate in a sorbent cartridge. The device has undergone pre-clinical testing with good treatment efficacy in animal studies.

Methods: The primary objective of this trial was to assess the clinical safety of a Neokidney™ prototype (PAK HD). The secondary objective was to assess the therapeutic efficacy of Neokidney™ sorbent therapy in comparison to CHD. We conducted a cross-over clinical trial. Each patient received one CHD therapy and one Neokidney™ sorbent therapy in the mid-week session in two consecutive weeks. The dialysis treatment prescription was similar for both therapies with 2 hours duration, use of high-flux dialyzer, a dialysate flow rate 300mL/min and a blood flow rate 300mL/min. Following two hours of therapy, all patients completed a further 2 hours of conventional dialysis therapy to receive a total of 4 hours of therapy to match their usual treatment time.

Results: A total of 3 patients were recruited. All patients tolerated and completed treatment with Neokidney™ with no adverse events. The sorbent cartridges removed approximately all urea, creatinine, and phosphate from spent dialysate during the dialysate regeneration process. The average plasma reduction ratios (RR) at 2 hours with Neokidney™ for urea, creatinine and phosphate were 54%, 52% and 58%, respectively. In comparison, the RR at 2 hours CHD were 50%, 49% and 46%, respectively. The average sodium concentration was at 139.0 mmol/L and 140.1mmol/L for regenerated and spent dialysate, respectively, thus maintained within ±0.5% of the concentration in spent dialysate, providing isonatremic dialysis. The dialysate bicarbonate concentration was maintained within ±4.7% of the concentration in spent dialysate. There were no significant differences in leukocyte count or complement concentration at the conclusion of both therapies.

Conclusions: The clinical trial demonstrated safety and efficacy of the Neokidney™ sorbent system. The toxin removal with sorbent therapy was comparable to CHD and the regenerated dialysate composition accuracy met the design specifications to provide isonatremic dialysis with stable acid-base balance.

Funding: Commercial Support - Nextkidney

FR-OR24

Measurement of Cerebral Blood Flow Using Transcranial Doppler Ultrasonography: Comparison of Two Populations of Patients on Chronic Hemodialysis

Néstor H. Cruz Mendoza,[1] Noemi Del Toro-Cisneros,[1] Jose A. Geraldo Murillo,[1] Juan M. Ardavin Ituarte,[2] Ismael A. Gómez Ruiz,[1] Ricardo Correa-Rotter,[1] Olynka Vega.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Médica Santa Carmen, Ciudad de Mexico, Mexico.*

Background: Patients on hemodialysis (HD) experience systemic and cerebral hemodynamic changes that are associated with cognitive impairment. The objective of this study was to quantify and compare hemodynamic changes at the cerebral level during an HD session in patients with AVF vs. those with a high-flow catheter (HFC).

Methods: Cross-sectional study, controls were sought for AVF patients matched for age, sex, and time on HD. Three measurements of mean cerebral blood flow velocity (CBFV) were performed using transcranial Doppler ultrasound (during the first 15 minutes, 120 and 240 minutes after HD). Other interventions were carried out before and after HD, including measurement of cardiac output (CO), cognitive evaluation using the Montreal Cognitive Assessment (MoCA), and measurement of AVF flow velocity.

Results: Fifty patients were included, 20 women, average age 56 years, time on HD 3.2 years, 25 patients with AVF (50%). The groups were not different in their baseline characteristics. All patients presented a drop in CBFV, on average -26.5%, with the drop being greater in AVF vs. HFC (-28.2% vs -21.2%, p=0.27). The change in CO pre and post HD was also greater in those with AVF vs. HFC (-12.5% vs -7.6%, p=0.73). Regarding mean arterial pressure (MAP), the change was -11.3% in patients with AVF and -9.4% in HFC (p=0.90). (**Fig. 1**). There was no difference in MoCA score between the groups.

Conclusions: All patients studied presented a significant decrease in cerebral blood flow, CO and MAP during the HD session. Interestingly, these changes are more pronounced in patients with AVF, but no statistically significant difference was observed between the study groups.

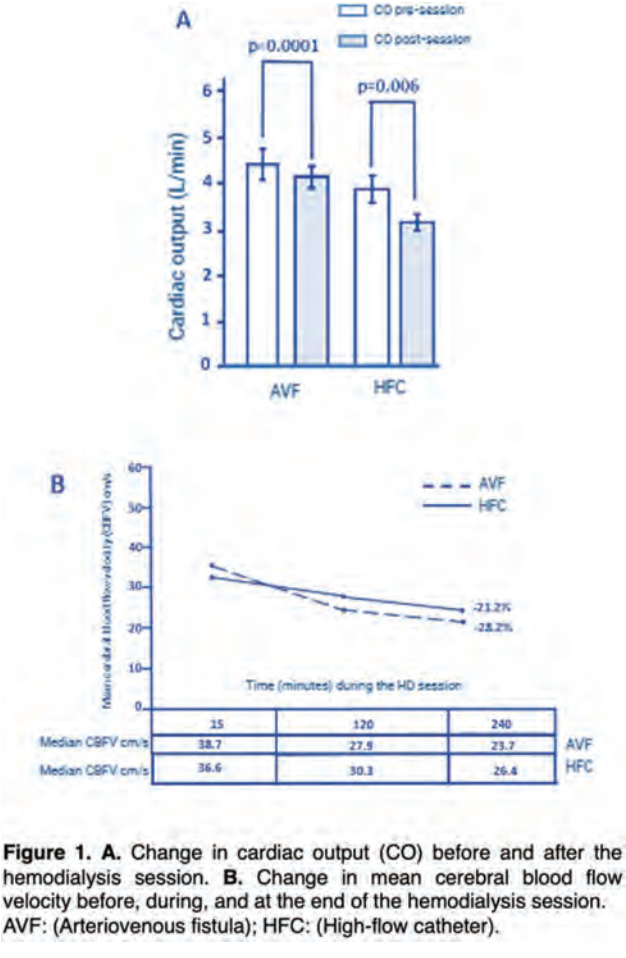


Figure 1. A. Change in cardiac output (CO) before and after the hemodialysis session. **B.** Change in mean cerebral blood flow velocity before, during, and at the end of the hemodialysis session. AVF: (Arteriovenous fistula); HFC: (High-flow catheter).

FR-OR25

Efficacy and Safety of Tool-Guided Dry Weight Adjustment among Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials

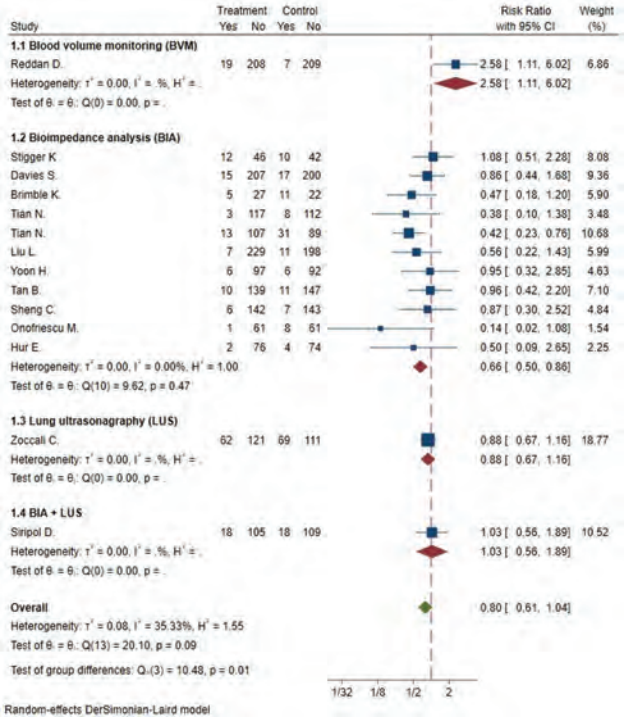
Wannasit Wathanavasin,[1,2] Charat Thongprayoon,[2] Paul W. Davis,[2] Wisit Cheungpasitporn.[2] *[1]Charoenkrung Pracharuk Hospital, Bangkok, Thailand; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Recently, various instrumental techniques adjunct to standard clinical evaluation have been used to improve fluid balance and guide dry weight adjustments in dialysis population. We aimed to explore the efficacy and safety of using tool-guided dry weight adjustment among dialysis patients.

Methods: A systematic review was conducted in PubMed, Scopus, and Cochrane Central Register of Controlled trials for relevant RCTs published until April 28, 2024. Studies were selected if they reported at least 1 outcome of interest (e.g. mortality, cardiovascular (CV) events, hospitalization, intradialytic hypotension, hypovolemic events, cardiac arrhythmia or vascular access problems).

Results: A total of 22 RCTs involving 4,310 dialysis patients were analyzed. The meta-analysis revealed that the incorporating tool-guided dry weight adjustment was associated with a significant 21% reduction in CV events (relative risk (RR), 0.79; 95% confidence interval (CI) 0.71 to 0.88), but also resulted in a significant 28% increase in vascular access problems (RR, 1.28; 95% CI, 1.08 to 1.53). In a subgroup analysis, using BIA was associated with a significant reduction in mortality (RR, 0.66; 95% CI 0.50 to 0.86). Additionally, the intervention led to a significant reduction in systolic blood pressure and left ventricular mass index pressure (mean difference, -3.36; 95% CI -5.93 to -0.79 and -0.24; 95% CI -0.48 to 0.00, respectively).

Conclusions: The use of instrumental techniques adjunct to standard clinical evaluation for dry weight adjustment has a positive effect on cardiovascular parameters, including SBP and LVMI, and lowers the risk of CV events in dialysis patients. However, these benefits are accompanied by an increased risk of vascular access problems.



FR-OR26

Effectiveness and Safety of Apixaban Initiation following Newly Diagnosed Atrial Fibrillation in Patients with Kidney Failure on Hemodialysis

Wolfgang C. Winkelmayer,[1] Tara I. Chang,[2] Kevin F. Erickson,[1] Jingbo Niu.[1] *[1]Baylor College of Medicine Margaret M and Albert B Alkek Department of Medicine, Houston, TX; [2]Stanford University School of Medicine, Stanford, CA.*

Background: Atrial fibrillation (AF) is common in the kidney failure population. While recent guidelines deem it "reasonable to prescribe […] apixaban for oral anticoagulation to reduce the risk of stroke" in patients on dialysis, the data supporting this recommendation are limited.

Methods: We used the USRDS to retrospectively identify adult, Medicare-insured patients on hemodialysis who were newly-diagnosed with AF between 2014 and 2019 and who had not received any oral anticoagulant (OAC) prior to AF. Using propensity score methods integrating baseline demographics, comorbidities, cardiovascular medication use, and CROWNWEB clinical data we compared patients who, within 30 days after the index AF diagnosis, were newly initiated on apixaban to otherwise similar patients who were not initiated on any OAC. We compared the groups in their time to ischemic stroke, systemic thromboembolism, hemorrhagic stroke, clinically meaningful bleeding, and death. We conducted as-treated and per-protocol analyses and estimated cause-specific hazard ratios (HR) for death or sub-distribution HR for all other outcomes.

Results: Of 75,269 patients newly-diagnosed with AF, who were previously OAC-naïve, 4283 initiated apixaban, whereas 63,806 did not initiate any OAC within 30 days. Propensity matching 3985 apixaban users with 3985 OAC non-users balanced all measured baseline characteristics. Apixaban was initiated a median 5 (IQR: 2-12) days after AF. Users were mean age 68 yrs, 46% female, 63% of white and 30% of Black race, and 16% Hispanic. Median CHA_2DS_2-VASc score was 4 (IQR: 3-5). Median duration of apixaban use was 69 (IQR: 42-171) days. The rate of ischemic stroke was 46% lower (HR=0.54; 95%CI, 0.40–0.72) and that of systemic thromboembolism was 34% lower (HR=0.66; 95%CI, 0.53-0.83) in apixaban users. While there was no difference in hemorrhagic stroke (HR=0.94; 95%CI, 0.58-1.53), apixaban users had higher rates of clinically important bleeding (HR=1.20; 95%CI, 1.08-1.33) than OAC non-users. The HR for mortality was 0.39 (95%CI, 0.33-0.44) in as-treated and 0.61 (95%CI, 0.56-0.67) in per-protocol analyses.

Conclusions: Initiation of apixaban soon after newly-diagnnosed AF was associated with lower risk of ischemic stroke and systemic thromboembolism, but at the expense of higher rates of clinically meaningful bleeding.

Funding: NIDDK Support

FR-OR27

Reduction of Calciphylaxis-Related Infections with Hexasodium Fytate Treatment in a Randomized, Double-Blind, Phase 3, Placebo-Controlled Trial

Smeeta Sinha,[1,2] Sagar U. Nigwekar,[3,4] Lisa Gould,[5] Thomas E. Serena,[6] Sharon M. Moe,[7] George R. Aronoff,[8] Dinesh K. Chatoth,[9] Jeffrey L. Hymes,[9] Gabriela Alperovich Lehrer,[10] Laurence H. Keller,[11] Alex Gold,[12,13] Peter Szecsödy,[10] Jana Radewonuk,[14] Joan Perelló,[10,15] Glenn M. Chertow.[13] CALCIPHYX Study Investigators. *[1]Northern Care Alliance NHS Foundation Trust, Salford, United Kingdom; [2]The University of Manchester, Manchester, United Kingdom; [3]Massachusetts General Hospital, Boston, MA; [4]Harvard Medical School, Boston, MA; [5]South Shore Hospital, Weymouth, MA; [6]SerenaGroup Research Foundation, Cambridge, MA; [7]Indiana University School of Medicine, Indianapolis, IN; [8]DaVita Inc, Denver, CO; [9]Fresenius Medical Care Holdings Inc, Waltham, MA; [10]Vifor Pharma Management AG, Glattbrugg, Switzerland; [11]Clinical Development Consultant, Ann Arbor, MI; [12]Clinical Development Consultant, Incline Village, NV; [13]Stanford University School of Medicine, Stanford, CA; [14]CSL Behring LLC, King of Prussia, PA; [15]Universitat de les Illes Balears, Palma de Mallorca, Spain.*

Background: CALCIPHYX was an international, phase 3, randomized, double-blind, placebo-controlled clinical trial that investigated hexasodium fytate (SNF472), an inhibitor of vascular calcification, for the treatment of calciphylaxis. Infection of calciphylaxis skin lesions is a serious complication and effective strategies to reduce the rate of calciphylaxis-related infection are lacking. In this post-hoc analysis, we compare rates of calciphylaxis-related infections between groups as randomized through Week 12.

Methods: Adults with an ulcerated calciphylaxis lesion and pain visual analog scale score ≥50/100 received double-blind hexasodium fytate 7 mg/kg or placebo intravenously during maintenance hemodialysis to Week 12 and open label hexasodium fytate to Week 24 with an end of study (EOS) visit at Week 28. Exploratory post-hoc analyses of calciphylaxis-related infection (adverse events in the Infections and Infestations system organ class) included time to first event (Kaplan-Meier, Greenwood variance with hazard ratio and confidence interval [CI] by bootstrapping Cox proportional regression and Exact Wilcoxon p-value) and rate ratios (negative binomial regression). P-values were nominal.

Results: Any calciphylaxis-related infection was reported for 1/37 patients (1 event total) in the hexasodium fytate group and 7/34 patients (10 events total) in the placebo group (Figure). The hazard ratio for hexasodium fytate vs placebo at Weeks 12 and 24 was 0.11 (95% CI: 0.00-0.64; p=0.026). Exposure-adjusted rate ratios for hexasodium fytate vs placebo were: Week 12, 0.086 (95% CI: 0.021-0.346; p<0.001); Week 24, 0.061 (95% CI: 0.015-0.250; p<0.001); and EOS, 0.057 (95% CI: 0.014-0.238; p<0.001).

Conclusions: In this exploratory analysis, hexasodium fytate treatment during hemodialysis reduced the incidence of first and multiple calciphylaxis-related infections.

Funding: Commercial Support - Sanifit, a CSL Vifor company

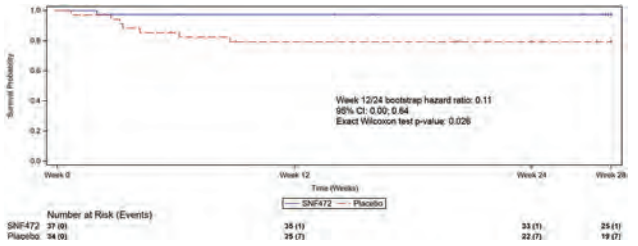


Figure. Time to first calciphylaxis-related infection

FR-OR28

Association between Cerebral Blood Flow Changes during Hemodialysis Treatment and Cognitive Function Decline in Elderly Patients Undergoing Hemodialysis

Yang Luo, Yidan Guo. *Beijing Shijitan Hospital Capital Medical University, Beijing, China.*

Background: The etiology of cognitive impairment in hemodialysis patients is multifactorial and still not clear, among those, the relationship between cerebral blood flow and cognitive function is poorly understood. Our study was to investigate the association between changes in cerebral blood flow (CBF) during hemodialysis treatment and the decline of cognitive function in elderly patients undergoing hemodialysis.

Methods: In this prospective observational cohort study of 121 elderly patients undergoing hemodialysis, we used transcranial Doppler ultrasound (TCD) to measure cerebral arterial mean flow velocity (MFV) as the index of CBF; assessed cognitive function at baseline and 12-month follow-up, and then explored associations between MFV and changes of cognitive scores.

Results: TCD recordings demonstrated a significant decline in MFV throughout dialysis, which significantly associated with combined diabetes (β=3.889, 95% CI 1.373-6.405, P=0.003), lower serum albumin (β=- 0.456, 95% CI -0.877-0.036, P=0.034), higher ultrafiltration rate (β=11.099, 95% CI 6.402-15.797, P<0.001) and the decline in systolic blood pressure throughout dialysis (β=0.062, 95% CI 0.008-0.116, P=0.026). After 12 months of follow-up, test scores of cognitive functions decreased in 5 cognitive domains (P<0.05). The decreased MFV was significantly associated with worsening scores in global cognitive function (MOCA) (β=0.066, 95% CI 0.018-0.113, P=0.007); the test of memory function (Auditory Verbal Learning Test) (β=0.050, 95% CI 0.004-0.097, P=0.035) and executive function tests including Trail Making Tests B (TMT-B) (β=1.955, 95% CI 0.457-3.453, P=0.011), and a modified version of the Stroop Color-Word Test (SCWT) (β=1.955, 95% CI 0.457-3.453, P=0.011; β=0.298, 95% CI 0.112-0.484, P=0.002) were also associated with the reduced MFV.

Conclusions: Conventional Hemodialysis may significantly reduce cerebral blood flow in elderly patients. Repetitive intradialytic decreases in CBF may be one of the underlying mechanisms for the deterioration of cognitive function in elderly hemodialysis patients.

FR-OR29

RNA Sequencing Analysis of Skeletal Muscle in Moderate to Advanced CKD

Mert Demirci,[1] Dungeng Peng,[1] Jennifer E. Norman,[2] Gwenaelle Begue,[3] Baback Roshanravan,[2] Talat Alp Ikizler,[1] Jorge Gamboa.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of California Davis, Davis, CA; [3]California State University Sacramento, Sacramento, CA.*

Background: Patients with moderate to advanced kidney disease suffer a higher prevalence of sarcopenia and frailty. MicroRNAs (miRNAs) play an important role in muscle cell proliferation and differentiation, as well as muscle hypertrophy and atrophy. We hypothesized that the miRNA expression profiling in skeletal muscle from patients with CKD is altered, and it would provide mechanistic insight into sarcopenia and frailty.

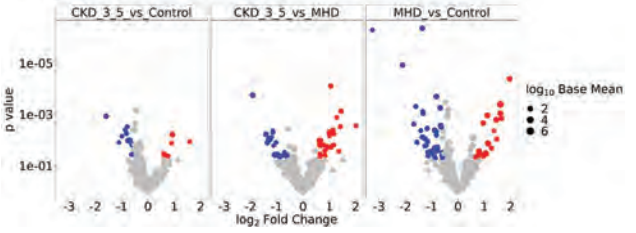
Methods: In a cross-sectional study, we performed small RNA sequencing analysis in skeletal muscle biopsies from three groups (matched for gender, body mass index, and history of diabetes): controls (n=13), patients with CKD 3-5 not yet on hemodialysis (n=13), and patients on maintenance hemodialysis (MHD, n=10). Total RNA was extracted and used to construct libraries for small RNA sequencing using Illumina NovaSeq 6000 system. Differentially expressed genes (DEGs) were identified with a false discovery rate (FDR) <0.05 and fold change > 2.

Results: We identified 57 DEGs between controls and MHD groups, 43 DEGs between CKD 3-5 and MHD groups, and 16 DEGs between controls and patients with CKD 3-5 (**Figure 1**). The DEGs were found to be involved in cachexia (mir-450), muscle atrophy (miR-23), and muscle wasting/protein synthesis (miR-424). In patients with CKD, we observed an upregulation of miR-542, which has been associated with promoting mitochondrial dysfunction and enhancing SMAD 2/3 phosphorylation, a downstream effect of myostatin.

Conclusions: Our results suggest that miRNA expression profiling is altered in moderate to advanced CKD. The differential expressed miRNAs may explain the loss of muscle mass in CKD. Thus, miRNAs may enhance atrophy and inhibit muscle growth pathways. Further studies should identify the specific miRNA targets to prevent sarcopenia and frailty in CKD.

Funding: NIDDK Support

Figure 1. Volcano plots for the different comparisons



FR-OR30

Continued Activation of Hypoxia Inducible Factor 1α by Roxadustat and Inhibition of Differentiation in Skeletal Muscles

Yuya Miki, Akinobu Ochi, Hideki Uedono, Yoshinori Kakutani, Yuki Nagata, Katsuhito Mori, Yasuo Imanishi, Tetsuo Shoji, Tomoaki Morioka, Masanori Emoto. *Osaka Koritsu Daigaku, Osaka, Japan.*

Background: Patients with chronic kidney disease are prone to develop renal anemia. Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors, such as roxadustat, have recently been recognized as a viable treatment option for this condition by stabilizing hypoxia-inducible factor-1α (HIF-1α). Nonetheless, the consequences of continued HIF-1α activation on skeletal muscle differentiation are not fully understood. This study explores the effects of continued HIF-1α activation on the differentiation of skeletal muscles.

Methods: We cultured mouse C2C12 myoblasts to differentiate into myotubes using horse serum, with or without 100 μM roxadustat. We evaluated the extent of muscle differentiation and measured the expression of muscle differentiation-related proteins and genes (MyoD and myogenin) and muscle constituent proteins (myosin heavy chain, MHC). Additionally, two groups of nine-week-old male C57BL/6 mice were treated with either roxadustat or a vehicle control via intraperitoneal injections three times a week for four weeks. We analyzed the expression of HIF-1α, muscle differentiation and constituent proteins in the gastrocnemius muscle.

Results: Addition of roxadustat to C2C12 myoblast cultures results in an increased expression of HIF-1α protein. Treatment with roxadustat for 72 hours suppressed myotube formation in C2C12 cells, reducing both the differentiation and fusion indices compared to untreated controls. Gene and protein expression levels of MyoD, myogenin, and protein expression level of MHC were also lower in the roxadustat-treated C2C12 myotubes than untreated C2C12 myotubes. The decrease in MHC protein expression induced by roxadustat was attenuated by siRNA targeting HIF-1α. In the in vivo experiments, roxadustat treatment led to an increase in HIF-1α protein levels and a decrease in the protein expression of MyoD, myogenin, and MHC in the gastrocnemius muscle of the treated mice compared to controls.

Conclusions: The results indicate that continued activation of HIF-1α by roxadustat inhibits skeletal muscle differentiation.

FR-OR31

Home-Based Exercise Improves Muscle Mitochondrial Function in CKD: Results from a Pilot Randomized, Controlled Clinical Trial

Christopher Hayden,[1] Gwenaelle Begue,[2] Usman Rehman,[1] Armin Ahmadi,[1] Chenoa R. Vargas,[1] Thomas Jue,[1] Jorge Gamboa,[3] Baback Roshanravan.[4] *[1]University of California Davis, Davis, CA; [2]California State University Sacramento, Sacramento, CA; [3]Vanderbilt University School of Medicine, Nashville, TN; [4]University of California Davis School of Medicine, Sacramento, CA.*

Background: Chronic kidney disease (CKD) leads to impaired muscle mitochondrial function contributing to mobility impairment and frailty. Exercise training improves muscle function and physical capacity, but proper equipment and instruction can be difficult to access. We tested the impact of home-based exercise on in vivo muscle mitochondrial function.

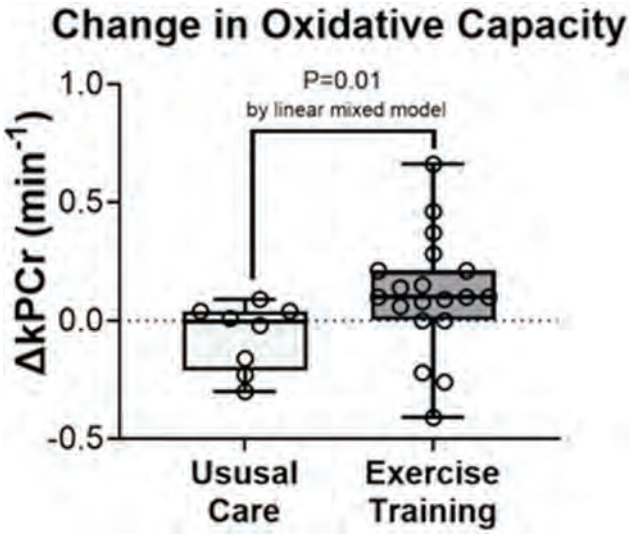
Methods: We conducted a pilot randomized controlled trial (NCT02923063) of a 12 wk home-based, virtually supervised exercise (EX) in CKD sedentary patients compared to usual care (UC). Exercise consisted of one high-intensity interval training, one resistance training, and one power walking session per week. Primary endpoint was leg muscle oxidative capacity measured using ^{31}Phosphorus Magnetic Resonance Spectroscopy. Participants performed one knee extension per second against an elastic

resistance band for 42s depleting phosphocreatine (PCr) by 25-50%. PCr recovery was measured and fit with a monoexponential equation. The rate constant of this equation (kPCr, min^{-1}) is an indicator of mitochondrial oxidative capacity. Linear mixed models were used to test the effect of exercise on kPCr.

Results: Muscle oxidative capacity was 1.23±0.33min^{-1} in UC (n=9, mean±SD age=67 ± 8yr, eGFR=32±12, 22% male, 44% diabetic) and 1.24±0.26 in EX (n=21, mean age=63.0±10yr, eGFR=35±12, 47% male, 47% diabetic) at baseline. Home-based exercise improved muscle oxidative capacity by 0.197min^{-1} (95% CI: 0.05-0.35, P=0.01) compared to usual care (Fig 1).

Conclusions: Twelve weeks of virtually supervised at-home training can improve muscle oxidative capacity in CKD patients. These results support the use of exercise to combat mitochondrial dysfunction in CKD and demonstrate the efficacy of a low barrier to access intervention.

Funding: NIDDK Support



FR-OR32

Skeletal Muscle Extracellular Matrix in Patients on Hemodialysis

Jorge Gamboa,[1] Anthony C. Dematteo,[1] Dungeng Peng,[1] Mert Demirci,[2] Jennifer E. Norman,[2] Gwenaelle Begue,[3] Tae Youn Kim,[2] Lucas R. Smith,[2] Baback Roshanravan,[2] Talat Alp Ikizler.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of California Davis, Davis, CA; [3]California State University Sacramento, Sacramento, CA.*

Background: Frailty and sarcopenia are common in patients with chronic kidney disease (CKD). The extracellular matrix (ECM) plays an important role in muscle proliferation as the scaffold for muscle growth. We have previously shown that ECM gene expression is altered in patients on hemodialysis (HD). We now test the hypothesis that the content of collage, the major structural protein in skeletal muscle, is decreased in patients on HD.

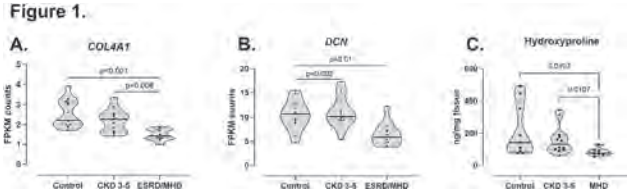
Methods: In a cross-sectional study, we obtained vastus lateralis muscle biopsies from three groups (matched for gender, body mass index, and history of diabetes): controls (n=13), patients with CKD 3-5 not yet on hemodialysis (n=13), and patients on maintenance hemodialysis (MHD, n=10). Using data from RNA sequencing, we evaluated the gene expression of specific ECM genes. We also evaluated the collagen content using the hydroxyproline assay.

Results: We found the downregulation of 16 ECM genes between controls and MHD groups, and 24 ECM genes between CKD 3-5 and MHD groups. There was no difference in ECM gene expression between controls and patients with CKD 3-5. *COL4A1*, which encodes for alpha 1 chain of type IV collagen, and *DCN*, which encodes for decorin, were among these genes (Figure 1 A and B). Total collagen content was also decreased in patients on MHD compared to the other two groups (Figure 1C).

Conclusions: Our results suggest a reduced content of ECM components in skeletal muscle in patients on MHD. Alterations in ECM remodeling may play a role in sarcopenia in CKD. ECM not only provides structural support but also inhibits atrophic factors, such as myostatin inhibition by decorin. Further studies should identify potential targets of the ECM pathways to prevent sarcopenia and frailty in CKD.

Funding: NIDDK Support

Figure 1.



FR-OR33

Altered Muscle Bioenergetic in CKD: Focus on Inorganic Phosphate and Acidosis

Dungeng Peng,[1] Zuofei Wang,[1] Anthony C. Dematteo,[1] Mert Demirci,[1] Gwenaelle Begue,[2] Thomas Jue,[3] Baback Roshanravan,[3] Talat Alp Ikizler,[1] Jorge Gamboa.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]California State University Sacramento, Sacramento, CA; [3]University of California Davis, Davis, CA.*

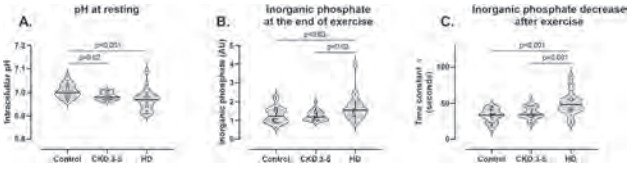
Background: Patients with chronic kidney disease (CKD) commonly experience fatigue. Muscle acidosis and inorganic phosphate accumulation have been widely associated with fatigue in the non-CKD population. We hypothesized that altered muscle bioenergetics (inorganic phosphate and pH) are present in patients with CKD and associated with physical performance measurements.

Methods: In a cross-sectional study, we evaluated 63 participants: 20 with CKD stage 3-5 not on hemodialysis (HD), 20 on hemodialysis, and 23 matched controls with no history of CKD). Muscle bioenergetics was evaluated using ^{31}phosphorus magnetic resonance spectroscopy at resting and after sub-maximal exercise. The relative concentration inorganic phosphate was obtained using AMARES and jMRUI. Intracellular pH was calculated from the chemical shift of the inorganic phosphate signal relative to phosphocreatine. Inorganic phosphate levels after exercise were fitted to a mono-exponential function to determine the time constant tau (τ).

Results: Groups were matched by gender, body mass index, and history of diabetes and hypertension. Plasma phosphate levels were higher in patients on HD. We found that resting intracellular pH was slightly but significantly lower in patients on HD and with CKD 3-5 compared to controls (**Figure 1A**). The concentration of inorganic phosphate at the end of exercise was significantly higher in patients on HD (**Figure 1B**). The constant tau of inorganic phosphate decrease after exercise was prolonged in patients on HD compared to the other two groups (**Figure 1C**), and it was associated with the six-minute walk distance (rho= -0.45, p<0.001). These changes were not associated with phosphate or bicarbonate levels in plasma.

Conclusions: Our results suggest that intracellular energy metabolism is impaired in patients with CKD. The changes in inorganic phosphate mirror our previous findings of impaired mitochondrial function in CKD and may play a role in physical activity in this population. Further studies should evaluate the contribution of intracellular acidosis or increased inorganic phosphate on fatigue in patients with CKD.

Funding: NIDDK Support



FR-OR34

Cardiorespiratory Fitness in Kidney Transplant Recipients and the Effects of Home-Based Rehabilitation

Roseanne E. Billany,[1] Ella C. Ford,[2] Gurneet K. Sohansoha,[1] Stephanie E. Burns,[3] Noemi Vadaszy,[1] Zahra Mubaarak,[1] Nicolette C. Bishop,[4] Alice C. Smith,[1] Matthew Graham-Brown.[1] *[1]University of Leicester, Leicester, United Kingdom; [2]Leeds Beckett University, Leeds, United Kingdom; [3]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [4]Loughborough University, Loughborough, United Kingdom.*

Background: Kidney transplant recipients (KTR) have an increased burden of cardiovascular disease (CVD) and poor cardiorespiratory fitness (CRF) is associated with poorer clinical outcomes; particularly cardiovascular related. The aims of this study were: (1) to compare CRF parameters in KTR and age-sex matched healthy volunteers (HV), (2) explore the CRF related effects of 12-weeks of home-based exercise rehabilitation in KTR.

Methods: 30 KTR (14 male; age 61±8 years) and 30 HV (14 male; age 61±7 years) completed a continuous ramp cardiopulmonary exercise test (CPET) to volitional exhaustion. 50 KTR (>1-year post-transplant; 50±14 years; 23 male) were randomised 1:1 to: intervention (INT: a 12-week home-based combined aerobic and resistance exercise programme) or control (CT: guideline-directed care).

Results: KTR had reduced exercise capacity and increased ventilatory response to exercise compared to HV (Fig 1). Relative VO_{2peak} was 5.29 ±1.35 ml/kg/min lower in KTRs v HV. Post-intervention VO_{2peak}, after baseline adjustment, was greater in INT v CT (+1.50 ml/kg/min (95%CI: 0.1-2.9; p=.03)) as was max power (+8 W, p<.03) and heart rate (+10 bpm, p<.04). Total number of aerobic exercise session performed was associated with greater change in VO_{2peak} (R_2=.252, p=.04).

Conclusions: CRF is impaired in KTR compared to age-sex matched HV. This may relate to low levels of physical activity, but could imply underlying cardiovascular dysfunction. Home-based rehabilitation significantly improved CRF. These results indicate the need to prioritise the development and implementation of structured exercise and educational programmes for KTR as part of routine care.

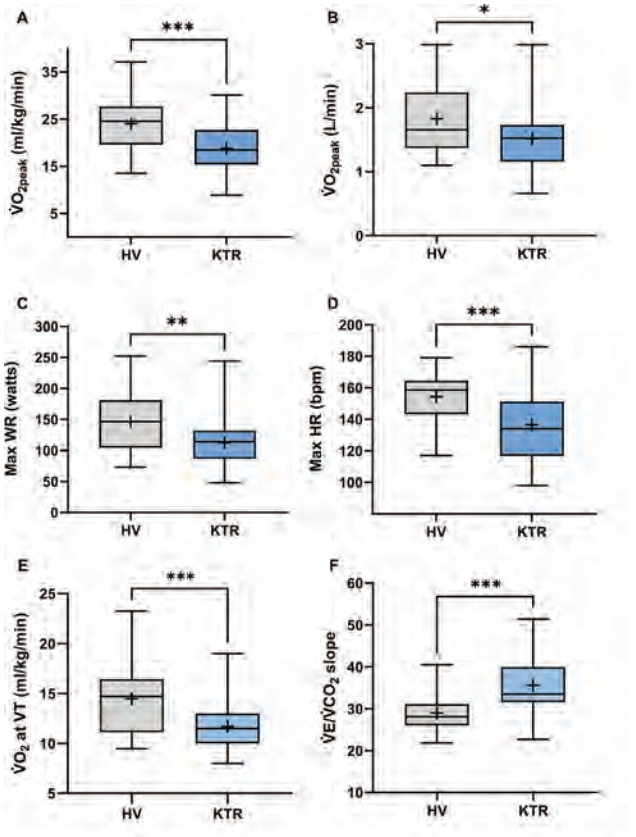


Figure 1. Distribution of values for basic peak cardiorespiratory fitness parameters in HVs and KTRs. (A, $\dot{V}O_{2peak}$ [ml/kg/min]; B, $\dot{V}O_{2peak}$ [L/min]; C, maximum work rate [watts]; D, maximum heart rate [bpm]; E, $\dot{V}O_2$ at ventilatory threshold [ml/kg/min]; F, $\dot{V}E/\dot{V}CO_2$ slope).
Abbreviations: HR, heart rate; HV, healthy volunteers; KTR, kidney transplant recipients; $\dot{V}E$, volume of air inspired or expired per minute; VT, ventilatory threshold; WR, work rate.
*p ≤.05, ** p ≤.01, ***p ≤.001. "+" indicates mean value.

FR-OR35

Efficacy of a Remote Exercise Program on Fatigue in Persons with CKD

Tae Youn Kim,[1] Hiba Hamdan,[1] Jennifer E. Norman,[1] Jesse Gipe,[1] Thomas Jue,[1] Gwenaelle Begue,[2] Jorge Gamboa,[3] Baback Roshanravan.[1] *[1]University of California Davis, Sacramento, CA; [2]California State University Sacramento, Sacramento, CA; [3]Vanderbilt University, Nashville, TN.*

Background: Physical frailty and fatigue are prevalent in persons with chronic kidney disease (CKD), contributing to poor quality of life and increased morbidity and mortality risk. While previous studies show positive impact of exercise programs on reducing inflammation and fatigue, little is known about the efficacy of a structured exercise program on immune cell mitochondrial bioenergetics and fatigue in persons with CKD.

Methods: We conducted a pilot randomized (3:1) clinical trial of a 12-week video-supervised individualized exercise program (NCT02923063). Outcomes include 1) aerobic exercise capacity (measured with a total distance of a 6-minute walk test (6MWT)), 2) peripheral blood mononuclear cells (PBMC) mitochondrial bioenergetics (measured using the high resolution respirometry), and 3) fatigue measured using a 13-item validated scale (FACIT-Fatigue). We classified exercise responders by performance on 6MWT (>=17meters). Linear mixed effects models were used to examine the association of exercise with PBMC bioenergetics and fatigue adjusting for depressive mood measured with the 8-item PROMIS Depression scale.

Results: Of 30 participants with CKD, nine were randomized in the usual care group (UC) and 21 in the exercise group (EX). No difference was found at baseline between the groups in sex (60% male), diabetes (47%), age (64±10 years), eGFR (34±12ml/min per 1.73m^2), depression (47±8.4), fatigue (38±10), and 6MWT (463±88 meters). We also found no difference in the mean values of PBMC ATP-linked respiration between the UC (1.1±0.5 pmol O2/min/10K cells) and EX (1.2±0.8) at baseline. With a mean change of 17 meters or greater for 6MWT, 12 of the 21 EX improved exercise capacity and reduced fatigue (a mean difference: 5.13, 95% CI[0.44, 9.81], p=0.03) at follow-up. Further adjustment for depression showed that each 1 standard deviation decline in PBMC ATP-linked respiration was associated with a 14-point decrease in fatigue (95%CI[-24.52, -3.48], p=0.009).

Conclusions: Among responders to our exercise program with improved 6MWT, exercise program reduced fatigue which was inversely correlated with PBMC ATP-linked respiration. Further investigation is needed to examine long-term effects of exercise on ameliorating mitochondrial dysfunction and its links to inflammation responses and fatigue in a larger cohort of CKD.

Funding: NIDDK Support, Clinical Revenue Support

FR-OR36

Exercise Increases Resident Macrophage Abundance and Lipoxin A4 in Kidneys

Sophia M. Sears, Ernesto H. Pena Calderin, Haley Asplund, Richa A. Singhal, Jason Hellmann, Brian Sansbury, Steven P. Jones. *University of Louisville School of Medicine, Louisville, KY.*

Background: Exercise contributes to human health via benefits to several physiological systems; however, the mechanisms by which exercise impacts renal health remain poorly understood. Although exercise can be acutely stressful on the kidneys due to transient reductions in renal blood flow, studies show that moderate intensity exercise slows the age-related decline in kidney function. Additionally, exercise protects against AKI in both ischemic and nephrotoxic rodent models. We hypothesize that exercise triggers adaptative responses in kidney resident macrophages (KRMs) including production of specialized pro-resolving lipid mediators (SPMs), which preserves hemodynamic balance in the kidneys under stress.

Methods: We performed a time course analysis of exercise-induced adaptations in the kidneys of 10 wk old C57BL/6J male mice. Mice were subjected to daily forced treadmill running at 70% capacity for 40 minutes for 1 or 2 wk. We also evaluated mice 24 h after a single bout of exhaustive exercise to discern acute responses from chronic adaptations. Sedentary mice were used as controls. We performed flow cytometry, targeted lipidomics, histopathology, and bulk mRNA sequencing to evaluate exercise-induced adaptations.

Results: We found a significant increase in KRMs (CD45$^+$CD11b$^+$F4/80^{hi}) after 2 wk of exercise compared to sedentary controls (p=0.0005). This increase was not present at either 24 h or 1 wk (**Fig 1**). We believe this was driven by expansion of KRMs rather than infiltration of monocyte derived macrophages as the population was primarily CX3CR1$^+$CCR2$^-$. Moreover, we found that 2 wk of exercise significantly increased renal lipoxin A4 (p=0.04), a vasoactive SPM that can be produced by macrophages and has been demonstrated to have renoprotective effects.

Conclusions: Taken together, these data suggest that exercise alters the immune landscape of the kidney in a way that may preserve renal blood flow and reduce renal vascular congestion during kidney injury and recovery from insults. This study provides support for the utilization of exercise programs in the management of kidney disease.

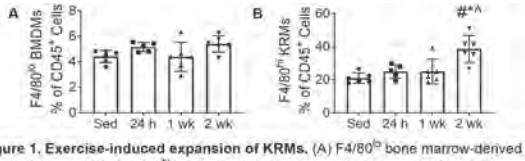


Figure 1. Exercise-induced expansion of KRMs. (A) F4/80^{lo} bone marrow-derived macrophages and (B) F4/80^{hi} KRMs in sedentary and exercised mice. Populations are identified from hierarchical gated CD45$^+$ CD3$^-$ CD19$^-$ CD11b$^+$ cells. Data are expressed as the mean±SEM of the percentage of identified cells from the CD45$^+$ pool. Results were analyzed with a one-way ANOVA and Tukey's multiple comparison test. #p<0.05 vs sedentary, *p<0.05 vs 24 h, and ^p<0.05 vs 1 wk. n=5-6 biological replicates per group.

FR-OR37

T Cell Egress from the Kidney to the Renal Lymph Node Is Regulated by Their Activation State and Controls Tissue Inflammation

Jonas Engesser, Jan-Hendrik Riedel, Nariaki Asada, Hans-Joachim Paust, Robin Khatri, Zeba Sultana, Catherine Meyer-Schwesinger, Thorsten Wiech, Victor G. Puelles, Stefan Bonn, Christian F. Krebs, Ulf Panzer. *Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: A hallmark of autoimmune diseases such as crescentic glomerulonephritis (cGN) is the infiltration of pathogenic leukocytes into the kidney. Here, especially CD4$^+$ T cells play a key role in orchestrating the immune response and driving tissue damage. While T cell infiltration is described well, little is known about T cell emigration out of the kidney via lymph vessels and its role in controlling tissue inflammation. In this study, we aim to decipher T cell emigration signals and their role on tissue injury.

Methods: Human kidney biopsies from ANCA glomerulonephritis (ANCA-GN) patients were analyzed using 3D-immunofluorescence of lymphatics, and combined scRNA-seq and spatial transcriptome analysis. To investigate the trafficking of T cells from the kidney to the draining lymph node, we developed a new experimental system using the photoconvertible *Kaede* mouse. Using this system, we labelled renal T cells by photoconversion and analyzed their *in vivo* migration under homeostatic and nephritic conditions (experimental cGN).

Results: In ANCA-GN, lymphangiogenesis was primarily observed in the inflamed areas, accompanied by a predominance of $CD4^+$ T cells and macrophages. However, during inflammation, only T cells emigrated out of the kidney via afferent lymphatics. To elucidate the mechanisms regulating T cell egress, we used our *Kaede*-mouse model to identify differential expression of the chemokine receptors CXCR6 and S1PR1 in emigrated vs. resident cells. T cell activation was linked to CXCR6 upregulation and tissue retention, while loss of activation led to CXCR6 downregulation, S1PR1 upregulation, and tissue egress. Blocking S1PR1 signaling exacerbated tissue damage by increasing T cell retention. Finally, flow cytometry and scRNA-seq analysis of human kidney, blood, and lymph fluid confirmed our observations from the murine model, including the downregulation of activation markers in tissue-emigrated T cells.

Conclusions: T cell emigration from the kidney to the renal lymph node is regulated by T cell activation signals and controls tissue inflammation and resolution. These data indicate that strategies to promote T cell egress offer potential options for treating immune mediated kidney diseases.

Funding: Government Support - Non-U.S.

FR-OR38

Setting a Pig Model of Crescentic Glomerulonephritis and Testing a Heparin-Binding Epidermal Growth Factor-Like Growth Factor (HB-EGF) Antagonist as a New Treatment

Pierre-Louis Tharaux,[1,2] Nassim Mahtal,[1] Julien Dang,[1] Sylvain Pichard,[3] Léa Resmini,[1] Daniel Gillet.[3,4] *[1]Paris Centre de Recherche Cardiovasculaire, Paris, France; [2]Universite Paris Cite UFR de Medecine, Paris, France; [3]Commissariat a l'energie atomique et aux energies alternatives Direction de la recherche fondamentale, Gif-sur-Yvette, France; [4]Universite Paris-Saclay, Gif-sur-Yvette, France.*

Background: Current crescentic glomerulonephritis (CGN) treatments are based only on drugs targeting the immune compartment responsible for glomerular injury. Despite state-of-the-art immunosuppression, many patients develop CKD and, ultimately, ESRD. Glomerular destruction following immune aggression is due to dedifferentiation and proliferation of parietal epithelial cells (PECs) and podocytes. These events are mediated by *de novo* expression of HB-EGF, a growth factor activating EGF receptor (EGFR) signaling (Bollée et al., Nat Med 2011). We developed an HB-EGF antagonizing strategy to prevent glomerular destruction during CGN. We described previously DTR8, an antagonist of HB-EGF derived by molecular evolution from the receptor-binding domain of the diphtheria toxin, a natural and highly selective binder of HB-EGF (Gillet et al., Patent WO/2013/140335). We engineered DTR8 to reach a pM affinity and reduce immunogenicity and antigenicity.

Methods: A model of CGN was induced in pigs by injection of decomplemented nephrotoxic serum (NTS) from sheep immunized against pig glomerular basement membrane. Ten pigs received intramuscular injections of 0.3 $mg.kg^{-1}$ of DTR8 twice daily for 20 days, and 12 pigs received vehicle only. Five normal control animals received pre-immune sheep serum. On day 21, the kidneys were harvested for histopathological observations.

Results: Pigs receiving NTS developed nephritic syndrome with high proteinuria, hypoalbuminemia, edema, and crescentic lesions typical of CGN. Their glomerular cells displayed immunoreactive HB-EGF, loss of podocyte differentiation markers, and exhibited phosphorylation of the EGFR. Periglomerular lymphocyte infiltration and interstitial fibrosis were observed. All these features were absent in control pigs receiving pre-immune sheep serum. Group-blinded comparison of DTR8-treated pigs showed a significant reduction of crescentic lesions ($p=0.037$), nephrin loss ($p=0.003$), EGFR phosphorylation ($p=0.016$), and interstitial fibrosis ($p=0.031$) compared to vehicle-treated animals.

Conclusions: We developed a valid model of CGN in pigs. Treatment with the HB-EGF antagonist DTR8 significantly reduced the histopathological damage. Reduction of EGFR phosphorylation highly suggests that DTR8 acts by inhibiting the HB-EGF/EGFR cascade.

FR-OR39

Deciphering the Contribution of Macrophages to the Development of Focal Segmental Glomerulosclerosis

Claudio Sierra Gonzalez,[1,2] Jasper F. Nies,[1,2] Bastian Trinsch,[1,2] Paul Diefenhardt,[1,2] Paul T. Brinkkoetter,[1] Bernhard Schermer,[2] Thomas Benzing,[1,2] Sebastian Braehler.[1,2] *[1]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany; [2]University of Cologne Center for Molecular Medicine Cologne, Cologne, Germany.*

Background: FSGS is a severe kidney disease characterized by glomerular scarring, following podocyte injury. In its worst face, it leads to a significant kidney damage, resulting in nephrotic syndrome and end-stage kidney disease in both children and adults. A dysregulation of the immune system finds great acceptance as a driver of the disease. To further analyze this, we make use of a murine model of a slowly progressing FSGS.

Methods: In a longitudinal fashion, we performed flow cytometry in order to phenotype the immune cell composition during disease progression. Among clinical parameters, like ACR and BUN, we assessed the histological damage via PAS and localized immune cells via IHC and IF. To further profile these immune cells, we performed single-nucleus RNA sequencing of isolated glomeruli.

Results: Based on our snRNAseq data, we detect an inflammatory and pro-fibrotic milieu with high activation of CX3CL1 as strong immune cell-recruiting factor. In accordance with this, flow cytometry data confirms an increase in mononuclear phagocyte infiltration and moreover, suggesting a functional shift in renal macrophages from a pro-inflammatory M1–like phenotype to a pro–fibrotic M2–like phenotype in diseased mice. Immunohistochemistry and immunofluorescence analyses underline this higher abundance of M2–like macrophages along disease progression. The lack of CX3CL1 in this model leads to an aggravated disease phenotype with a slightly shortened life span, increased BUN levels and an exacerbated M1-like to M2-like phenotypical alteration.

Conclusions: We identified mononuclear phagocytes to be the most prominent immune cells to infiltrate the kidney during FSGS progression, especially macrophage subpopulations displaying a pro-fibrotic transcriptomic signature. Furthermore, our findings suggest a strong association between the CX3CL1/CX3CR1 axis and the recruitment and polarization of renal macrophages. Notably, its absence has been shown to exacerbate the M1–like to M2–like phenotype shift, highlighting its potential regulatory role in macrophage polarization. Further research is necessary to elucidate the precise mechanism of how the CX3CL1/CX3CR1 axis might contribute to renal fibrosis and understanding this could pave the way for the development of targeted therapies.

FR-OR40

The "TNFa-suPAR" Axis Links Bone Marrow Alterations to Kidney Dysfunction

Alexis P. Jimenez Uribe,[1] Ryan Spear,[1] Yanxia Cao,[1] Steve Mangos,[1] Jochen Reiser,[2] Eunsil Hahm.[1] *[1]Rush University, Chicago, IL; [2]The University of Texas Medical Branch at Galveston Development Office, Galveston, TX.*

Background: Previous study identified bone marrow (BM)-derived immature myeloid cells as the source of soluble urokinase plasminogen activator receptor (suPAR), a key inflammatory mediator causing glomerular damage and proteinuria in mice. However, the factor driving the expansion of these pathogenic myeloid cells and suPAR increase remains unknown. Preliminary data show elevated TNFα and suPAR levels in the BM of CKD patients with altered hematopoiesis. This study tests the hypothesis that TNFa induces BM alterations and subsequent suPAR increase, thereby contributing to the renal dysfunction

Methods: TNFa levels were measured from three proteinuric animal models; TGFb-Tg mice (progressive glomerulosclerosis), nephrotoxic serum (NTS)-injected mice (glomerulonephritis), and LPS-injected mice (acute kidney injury). Functional in vivo tests included TNFa blockade, suPAR-deficient mice, and TNFa injection alone or with IFNg. In vitro myelopoiesis assays were performed using human hematopoietic stem cells or HL-60 promyelocytic cell line, with or without TNFa. Immunophenotyping, secretome analysis, and metabolic evaluation were conducted using multiparametric flow cytometry, multiplex, ELISA, and Seahorse assays

Results: Our results revealed elevated TNFa levels in three proteinuric animal models characterized by high suPAR and expanded immature myeloid cells in the BM. Blocking TNFa reduced both proteinuria and suPAR levels. TNFa alone was not enough to cause renal injury without suPAR or active myelopoiesis. However, when co-injected with IFNg (a key cytokine for myelopoiesis), TNFa triggered significant myeloid cell expansion, increased suPAR levels, and proteinuria in mice. In vitro myelopoiesis assays demonstrated that TNFa attenuates granulocytic lineage development, favoring monocytic lineage differentiation. Additionally, TNFa enriched a glycolytic and oxidative metabolic phenotype in monocytic cells, enhancing suPAR and proinflammatory cytokines secretion.

Conclusions: Our study suggests that renal function is regulated by bone marrow alterations through the 'TNFa-suPAR' axis, resembling findings from CKD patients and mouse models of proteinuria. This implies that the 'TNFa-suPAR' axis serves as a common key pathway linking bone marrow alterations to renal dysfunction.

Funding: NIDDK Support

FR-OR41

Loss of CELF4 in Kidney Dorsal Root Ganglion Neurons Leads to Acute Onset of Glomerular Diseases

Lindsey A. Fitzsimons,[1,2] Madison G. Mueth,[3] Michael C. Akom,[4,5] Grant Oakley,[4,5] Benjamin J. Harrison.[2,1] *[1]University of New England, College of Osteopathic Medicine, Biddeford, ME; [2]University of New England, Center for Excellence in Neurosciences, Biddeford, ME; [3]University of Maine, Graduate School of Biomedical Science & Engineering, Orono, ME; [4]Maine Medical Center, Portland, ME; [5]Maine Medical Partners Nephrology, Portland, ME.*

Background: Sustained upregulation of renal sympathetic and sensory nerve reflexes, known as *renorenal hyperreflexia* (RRH), promote the onset/ progression of chronic kidney disease (CKD). RRH consequences are exacerbated with the onset of inflammation and secretion of trophic factors (e.g. nerve growth factor; NGF), previously shown to promote structural and functional damage to the glomerulus. Our preliminary data demonstrate that pathogenic activation of peripheral sensory nerve fibers is controlled by an RNA binding protein, known as CUGBP Elav-Like Family Member 4 (CELF4). The goal of this study was to investigate the role of CELF4 as a tonic regulator of renal DRG neuron (RDN) excitability, RRH and overall kidney function.

Methods: An inducible, *CGRP^{cre}* mouse was used to direct *Celf4*-knockout (KO) from adult sensory neurons, followed by behavior assessments of peripheral neuropathy, RDN electrophysiology, semiquantitative blood and urinalysis and histopathological analyses of kidney and glomerular cytostructure.

Results: *Celf4* KO mice displayed robust hind-paw hypersensitivity to mechanical and thermal stimuli that was further exacerbated with NGF injection. Patch-clamp recordings confirmed acutely-dissociated, capsaicin-sensitive RDN become hyperexcitable following *Celf4* KO. Immunofluorescence confirmed coexpression of CGRP, TRPV1 and CELF4 in RDN. *Celf4* KO kidneys displayed hydronephrosis and increased pre-fixation weight and semi-quantitative urinalysis revealed *Celf4* KO mice develop 2-3+ proteinuria and microscopic hematuria. Histological analyses with H&E, PAS and PAS-silver stained kidney sections revealed a novel and unexpected renal phenotype in *Celf4* KO, characterized by pronounced mesangial expansion, extracellular matrix deposition, hypercellularity and incidence of glomerular sclerosis. When combined, these findings suggest a *Celf4* KO renal phenotype that is consistent with membranoproliferative glomerulonephritis (MPGN).

Conclusions: We demonstrate that CELF4 is co-expressed with TRPV1 in CGRP+ RDN, and that loss of CELF4 increases neural excitability and sensitivity of RDN, leading to development of MPGN. These data represent preliminary data from ongoing studies in our lab investigating CELF4 as a possible protective regulator against RRH mechanisms responsible for impairing renal/glomerular function in hypertension and CKD.

Funding: Other NIH Support - 1R01NS121533-01A1, PI: Benjamin J. Harrison; COBRE grant P20GM103642 supporting the UNE Behavior Core, P.I. Ian Meng, Private Foundation Support

FR-OR42

Phenome-Wide Mendelian Randomization Analysis of the Plasma Proteins, Immune Cell Types, and Immune Cell Traits in IgAN

Ruilian You, Zhiying Liu, Mengshi Li, Yang Li, Xu-jie Zhou, Hong Zhang. *Peking University First Hospital, Beijing, China.*

Background: IgA nephropathy (IgAN) remains the most frequent primary glomerular disease worldwide with poor outcomes leading to end-stage renal disease. Although there were significant advances in the understanding of the pathogenesis of IgAN in the past decade, an unmet need exists for further knowledge on the contribution and cause-effect of each cell type and protein in its pathogenesis.

Methods: We conducted a Mendelian randomization phenome-wide association study (MR-pheWAS) to identify potential causal factors of IgAN (Kiryluk Lab, N=26734) among 791 plasm proteins, 17 circulating immune cells and 731 immune cell traits (118 absolute cell counts, 389 MFIs of surface antigens and 32 morphological parameters, 192 relative ratios between cell counts). FinnGen database (N=412181) of IgAN was applied for genetic replication. Reverse MR and Bayesian co-localization were performed to consolidate the results. Further, GO and KEGG pathway enrichment and protein-protein interaction of the putative proteins fowling hub module and hue genes were conducted to search for the underlying mechanism.

Results: As for the MR-pheWAS of the pQTLs, CFH was identified as a significant protective factor for IgAN (OR 0.54, 95%CI [0.45,0.65], P=1.47E-10), while CFHR1 (OR 1.21, [1.12,1.31], P=8.49E-07) and ERAP2 (OR 1.14, [1.07,1.21], P=7.33E-06) showed as the risk factors. Additional 5 common putative proteins are suggestive in both datasets. As for the circulating immune cell types, it indicated a causal association between neutrophil (OR 1.64, [1.30,2.08], P=3.95E-05), white blood cell (OR 1.47, [1.20,1.81], P=2.32E-04) and an increased risk of IgAN. Activated & secreting Treg %CD4+, CD25hi %CD4+, T cell absolute count (AC), CD4+ AC, and Central memory (CM) CD4+ AC were indicated as the top 5 risk immune cell traits of IgAN. Enrichment analysis showed the complement activation cascade is a key pathway.

Conclusions: Our results showed causal-effect clues of some key proteins, cell types, and cell traits in IgAN, highlighting complement and certain CD4+ T cells may warrant further mechanism investigation and therapy development.

FR-OR43

Single-Cell Metabolic Profiling of Kidney T Cells Reveals Key Importance of Glycolysis in Crescentic Glomerulonephritis

Jasper F. Nies,[1,2] Bastian Trinsch,[1,2] Claudio Sierra Gonzalez,[1,2] Paul Diefenhardt,[1,2] Tobias Eckey,[1,2] David L. Puetz,[1,2] Bernhard Schermer,[1,4] Thomas Benzing,[1,2] Mauro Corrado,[3,2] Paul T. Brinkkoetter,[1,2] Sebastian Braehler.[1,2] Braehler Group. *[1]Universitatsklinikum Koln, Koln, Germany; [2]University of Cologne Center for Molecular Medicine Cologne, Cologne, Germany; [3]University of Cologne, Faculty of Mathematics and Natural Sciences, Institute for Genetics, Cologne, Germany, Cologne, Germany; [4]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany.*

Background: Crescentic glomerulonephritis (cGN) is a devastating, T cell mediated autoimmune disease. The supply with various metabolites and their utilization is crucial for T cell function and activation. How employment of oxidative phosphorylation and glycolysis govern T cell fate and function during cGN is unclear but of central importance to expand our understanding of the disease's pathogenesis. These insights could open up new avenues for therapeutic intervention.

Methods: We use the model of nephrotoxic nephritis (NTN) to investigate T cell metabolism in homeostasis and disease. Due to the scarcity of T cells in mouse kidneys, we use single-cell-based methods including innovative immunometabolic assays in flow cytometry (SCENITH) and mass spectrometry (scMEP) as well as the analysis of scRNAseq datasets. To investigate the functional relevance of mitochondria and aerobic glycolysis in T cells, we use T cell-specific knockout mice for *Ptpmt1* (an enzyme essential for mitochondrial integrity) and *Ldha* (the key enzyme for aerobic glycolysis), respectively.

Results: Our data indicate a mitochondrial activation in T cells during NTN as measured by an increase in mitochondrial mass and mitochondrial membrane potential. Despite a strong dysregulation in T cell subsets in flow cytometry, mice with a mitochondrial dysfunction in T cells (CD4 Cre *Ptpmt1* flox) show no differences in clinical parameters during NTN compared to wildtype mice. Analysis of metabolic dependencies with SCENITH points towards a strong dependence of kidney T cells on glycolysis in the diseased state, which was not observed in spleens or kidney draining lymph nodes. This finding is further investigated in mice with a T cell-specific *Ldha* knockout.

Conclusions: Kidney T cells rewire their metabolism in the NTN model by increasing both mitochondrial and glycolytic activity. Given the strong dependence on glycolysis seen in our SCENITH analyses and the lack of a difference in the clinical outcome in mice with a mitochondrial dysfunction in T cells, we hypothesize that the glycolytic activation is functionally more relevant for the pathological activity of T cells, which would be of great interest for therapeutic intervention.

Funding: Government Support - Non-U.S.

FR-OR44

Genome Sequencing and Genetic Association Analyses of Primary Glomerular Disorders in CureGN, NEPTUNE, and Columbia CKD Biobank

Chen Wang,[1] Simone Sanna-Cherchi,[1] Matt G. Sampson,[2] Rasheed A. Gbadegesin,[3] Ali G. Gharavi,[1] Matthias Kretzler,[4] Krzysztof Kiryluk.[1] CureGN Genomics Workgroup. *[1]Columbia University, New York, NY; [2]Boston Children's Hospital, Boston, MA; [3]Duke University, Durham, NC; [4]University of Michigan, Ann Arbor, MI.*

Background: Glomerular disorders (GD) represent a heterogenous group of kidney diseases with known inherited risk contributions from genetic variants. Whole genome sequencing (WGS) provides the most comprehensive method for profiling common and rare variants. In this study, we generated the largest WGS dataset for patients with primary GD. The aim was to identify common variants (CVs) associated with GD and to comprehensively test for associations of rare variants (RVs) collapsed over genes and/or their regulatory regions.

Methods: WGS (30x) was conducted for 4,307 GD cases and 3,845 controls from the CureGN and NEPTUNE studies and the Columbia CKD Biobank. Variant calling was performed with DRAGEN for individual samples and GATK for cross-sample joint calls. Principal component (PC) analysis was used to estimate genetic ancestry and divide the cohort into 3 ancestral groups (EUR, AFR, EAS). Genome-wide association studies (GWAS) for CVs with adjustment for sex and PCs were performed within each ancestry using PLINK and meta-analyzed across ancestries with METAL. RV collapsing analyses with REGENIE included rare loss-of-function and deleterious missense variants within coding genes; and functional variants within cis-regulatory elements based on the ABC model and ENCODE annotations.

Results: The combined cohort included 1,513 participants with IgA nephropathy (IgAN), 377 with IgA vasculitis (IgAV), 1,023 with membranous nephropathy (MN),

745 with minimal change disease (MCD), 649 with focal segmental glomerulosclerosis (FSGS) and 3,845 controls. GWAS of each GD type identified genome-wide significant associations in the *MHC* region (IgAN, IgAV, MN, MCD), *PLA2R1* (MN), and *APOL1* (FSGS). Among the 45 known risk loci previously identified by GWASes, 41 had the same effect direction and 22 replicated with at least nominal significance. Due to limited power, RV collapsing analyses demonstrated no exome-wide significant signals but nominated new candidate genes and regions for follow up studies.

Conclusions: Jointly called WGS data enhanced the resolution of genetic discovery for GD. We replicated most of the known disease associations, indicating substantial potential for a planned meta-analysis incorporating the published studies. The WGS data is accessible via dbGAP (phs002480).

FR-OR45

Combined Genome and Transcriptome Sequencing of the CureGN Study Generates Comprehensive Maps of Glomerulonephritis-Specific Blood Expression Quantitative Trait Loci (eQTL) Effects

Lili Liu,[1] Chen Wang,[1] Felix H. Eichinger,[2] Damian Fermin,[2] Simone Sanna-Cherchi,[1] Matt G. Sampson,[4] Rasheed A. Gbadegesin,[3] Ali G. Gharavi,[1] Matthias Kretzler,[2] Krzysztof Kiryluk.[1] *[1]Columbia University, New York, NY; [2]University of Michigan, Ann Arbor, MI; [3]Duke University, Durham, NC; [4]Harvard Medical School, Boston, MA.*

Background: IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and minimal change disease (MCD) account for the majority of idiopathic glomerulopathies (GN). GWASes started to delineate their genetic mechanisms, but there are no adequately powered transcriptomic datasets coupled to genetic data to investigate functional consequences of identified risk alleles in different GN forms.

Methods: We performed 30x whole genome sequencing (WGS) coupled with blood RNA-seq on the CureGN cohort. In total, 1826 participants had high quality WGS and RNA-seq data for analysis. The bulk gene expression profiles were deconvolved into 6 major immune cell types using CIBERSORTx. We then generated transcriptome-wide maps of eQTL effects for FSGS (N=450), IgAN (N=403), IgA vasculitis (N=123), MCD (N=408) and MN (N=442). Cis- and trans-eQTL signals for each condition were defined using linear regression in tensorQTL, adjusting for age, sex, genetic PCs, PEER factors. The analyses were performed with and without additional adjustment for immune cell fractions. We then performed interaction eQTL mapping for each cell type as well as GN type.

Results: We identified 13,115 unique cis-eGenes (N_{FSGS}=10,004, N_{IgAN}=9,589, N_{IgAV}=3,757, N_{MCD}=9,686, and N_{MN}=9,899). About 5% of eGenes were unique to one phenotype, and 95% were shared between at least two conditions. For trans-eQTLs, 645 trans-eGenes were detected (N_{FSGS}=298, N_{IgAN}=136, N_{IgAV}=47, N_{MCD}=229, and N_{MN}=215). Interestingly, a larger proportion of trans-eGenes was disease-specific compared to cis-signals. After additionally adjusting for cell fractions, we gained extra 279 cis-eGenes and 70 trans-eGenes, but lost 362 cis-eGenes and 114 trans-eGenes. By interaction eQTL mapping, we further refined a set of cis-signals specific to each cell type and each GN form. These data were then used to prioritize candidate causal genes at the GN risk loci identified in the latest GWASes.

Conclusions: Using the CureGN dataset, we identified immune cell type-specific and GN-context-specific genomic regulators for gene expression by blood eQTL mapping. Our comprehensive eQTL maps provide a powerful resource for integrative gene discovery studies for primary GN.

FR-OR46

Acylcarnitines and Cardiovascular Outcomes in the CKD in Children (CKiD) and Chronic Renal Insufficiency Cohort (CRIC) Studies

Arthur Lee,[1] Xuan Cai,[3] Mark Mitsnefes,[12] Susan L. Furth,[1] Bradley A. Warady,[2] Tamara Isakova,[3] James P. Lash,[4] Farsad Afshinnia,[5] Jiang He,[9] Bernard G. Jaar,[6] Jordana B. Cohen,[10] Mirela A. Dobre,[11] Mahboob Rahman,[11] Morgan Grams,[7] Josef Coresh,[7] Eugene P. Rhee,[8] Michelle Denburg,[1] Rupal Mehta.[3] *[1]The Children's Hospital of Philadelphia, Philadelphia, PA; [2]Children's Mercy Kansas City, Kansas City, MO; [3]Northwestern University Feinberg School of Medicine, Chicago, IL; [4]University of Illinois Chicago College of Medicine, Chicago, IL; [5]University of Michigan Medical School, Ann Arbor, MI; [6]Johns Hopkins Medicine, Baltimore, MD; [7]New York University Grossman School of Medicine, New York, NY; [8]Massachusetts General Hospital, Boston, MA; [9]Tulane University School of Medicine, New Orleans, LA; [10]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [11]University Hospitals, Cleveland, OH; [12]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: CKD is associated with poor cardiovascular (CV) outcomes in children and adults despite differences in etiology and cardiometabolic risk factors. We hypothesize that acylcarnitines (ACs), mitochondrial dysfunction biomarkers, are associated with poor CV outcomes in children and adults with CKD.

Methods: The CKiD and CRIC studies are multicenter prospective cohorts of children and adults with CKD respectively, with echocardiographic and metabolomic data. CKiD had follow-up echocardiograms and metabolomics. CRIC had follow-up echocardiograms. Multivariable regression models assessed the associations of ACs and left ventricular mass index (LVMI), elevated filling pressure (E/e'>8) (CKID), and heart failure (HF) events (CRIC).

Results: 556 CKiD participants were included (median [interquartile range] age 11[8,15] years, eGFR 50[37,64] ml/min/1.73m^2, LVMI z-score 0.2[-0.7,1.0], 15% with E/e'>8) with 44 ACs assayed. 1747 CRIC participants were included (mean [standard deviation] age 59[11] years, eGFR 43[17] ml/min/1.73m^2, LVMI 64[24] g/m^2, 354 HF events over 10.1 years median follow-up) with 24 ACs assayed. Table 1 shows regression results of ACs and LVMI. Figure 1 shows regression results of ACs and elevated filling pressure and HF events.

Conclusions: ACs are associated with CV outcomes in both children and adults in CKD, despite their differences in CKD etiology and prevalence of diabetes and preexisting CV disease. This suggests a role for CKD-associated mitochondrial dysfunction in the development of CV disease.

Funding: NIDDK Support, Other NIH Support - K38HL169660

CKiD baseline	Linear regression			+ adjustment for eGFR		
Adjusted for age, sex, BMI z-score, hypertension, ACEi/ARB usage, CKD duration, glomerular CKD etiology, anemia, urine protein:creatinine. Estimates are reports as change in LVMI z-score per 2-fold increase in acylcarnitine level.						
Baseline acylcarnitine, vs 2-year LVMI z-score	**Estimate (95% CI)**	**p-value**	**FDR**	**Estimate (95% CI)**	**p-value**	**FDR**
3-methylglutarylcarnitine (C5)	0.12 (0.03, 0.22)	<0.01	0.27	0.01 (-0.27, 0.09)	0.83	0.91
3-hydroxyhexanoylcarnitine (C6)	0.19 (0.03, 0.35)	<0.05	0.27	0.12 (-0.04, 0.28)	0.14	0.84
Pimeloylcarnitine/3-methyladipoylcarnitine (C7)	0.15 (0.03, 0.24)	<0.05	0.27	0.01 (-0.12, 0.14)	0.85	0.91
Suberoylcarnitine (C8)	0.10 (0.01, 0.19)	<0.05	0.34	0.01 (-0.09, 0.11)	0.80	0.91
CKiD follow-up	Linear mixed effects model			+ adjustment for eGFR		
2,4-year acylcarnitine, vs 4,6-year LVMI z-score	**Estimate (95% CI)**	**p-value**	**FDR**	**Estimate (95% CI)**	**p-value**	**FDR**
2-methylbutyrylcarnitine (C5)	0.19 (0.02, 0.36)	<0.05	0.31	0.15 (-0.05, 0.34)	0.14	0.94
Glutarylcarnitine (C5)	0.20 (0.02, 0.39)	<0.05	0.31	0.15 (-0.09, 0.30)	0.21	0.94
Pimeloylcarnitine/3-methyladipoylcarnitine (C7)	0.22 (0.09, 0.34)	<0.001	<0.05	0.22 (0.07, 0.38)	<0.01	0.25
Suberoylcarnitine (C8)	0.14 (0.04, 0.24)	<0.01	0.16	0.12 (0.01, 0.24)	<0.05	0.57
Ximenoylcarnitine (C26)	0.27 (0.03, 0.52)	<0.05	0.30	0.29 (0.05, 0.54)	<0.05	0.38
CRIC baseline	Linear regression			+ adjustment for eGFR and 24h urine protein		
Adjusted for age, sex, race, ethnicity, study site, BMI, diabetes, smoking status, SBP, total cholesterol, CRP, number of antihypertensive medications, ACEi/ARB usage, diabetes medications, statins, and cardiovascular disease history. Estimates are reported as change in LVMI per 2-fold increase in acylcarnitine level.						
1-year acylcarnitine, vs 1-year LVMI	**Estimate (95% CI)**	**p-value**	**FDR**	**Estimate (95% CI)**	**p-value**	**FDR**
C3-DC-CH3 carnitine	2.04 (0.68, 3.39)	<0.05	<0.05	1.33 (-0.28, 2.95)	0.11	0.67
C4 carnitine	1.58 (0.11, 3.04)	<0.05	0.18	0.85 (-0.79, 2.49)	0.31	0.77
C7 carnitine	2.01 (0.66, 3.36)	<0.01	<0.05	1.49 (-0.04, 3.02)	0.06	0.61
C9 carnitine	1.57 (0.40, 2.73)	<0.01	0.06	1.14 (-0.11, 2.39)	0.07	0.61
C10:2 carnitine	1.99 (0.83, 3.15)	<0.01	<0.05	1.66 (0.33, 2.98)	<0.05	0.35
CRIC follow-up	Linear mixed effects model			+ adjustment for eGFR and 24h urine protein		
1-year acylcarnitine, vs 2,3,4-year LVMI	**Estimate (95% CI)**	**p-value**	**FDR**	**Estimate (95% CI)**	**p-value**	**FDR**
C3-DC-CH3 carnitine	2.50 (1.35, 3.66)	<0.001	<0.01	1.78 (0.40, 3.16)	<0.05	0.28
C5-DC carnitine	1.77 (0.65, 2.87)	<0.01	<0.05	0.77 (-0.68, 2.22)	0.30	0.73
C7 carnitine	2.16 (1.00, 3.31)	<0.001	<0.01	1.42 (0.11, 2.73)	<0.05	0.28
C9 carnitine	1.40 (0.41, 2.40)	<0.01	<0.05	0.43 (-0.60, 1.46)	0.41	0.73
C10:2 carnitine	1.88 (0.89, 2.86)	<0.001	<0.01	1.31 (0.18, 2.45)	<0.05	0.28

Table 1

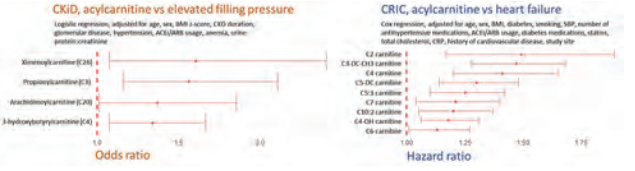


Figure 1

FR-OR47

Urine Ammonium Concentrations and Cardiovascular and Kidney Outcomes in SPRINT

Alexander L. Bullen,[1] Dena E. Rifkin,[1] Joachim H. Ix,[1] Ronit Katz.[2] *[1]University of California San Diego, La Jolla, CA; [2]University of Washington, Seattle, WA.*

Background: Impaired urine ammonium excretion is common in chronic kidney disease (CKD) and may identify risk of metabolic acidosis earlier than reductions in serum bicarbonate or pH, and thus may have associations with cardiovascular disease (CVD) outcomes. We evaluated the association of urine ammonium with CVD and kidney outcomes among persons with hypertension and non-diabetic CKD enrolled in a trial of blood pressure reduction.

Methods: We measured urine ammonium concentration in spot urine specimens collected at baseline among 2092 participants. We used multivariable-adjusted Cox models to evaluate associations of urine ammonium concentration with the SPRINT primary CVD composite outcome (myocardial infarction, acute coronary syndrome, stroke, heart failure, or CVD death), all-cause mortality, the SPRINT kidney composite outcome (50% kidney function decline, end stage kidney disease, or transplant), and acute kidney injury (AKI).

Results: The mean (SD) age was 73 (9) years; 40% were female; and 25% were Black participants. The mean (SD) serum bicarbonate was 25.6 (2.8) mmol/L, median (interquartile range, IQR) urine ammonium concentration was 14.4 (9.5, 23.1) mmol/L, and median (IQR) eGFR was 49 (39,55) ml/min/1.73 m^2. There were 255 CVD composite events, 143 deaths, 63 kidney composite events, and 146 AKI events during a median follow-up of 3.8 years. In multivariable models, each 2-fold higher urinary ammonium

concentration was associated with a 26% (95% CI 1.05, 1.52) higher risk of the CVD composite, whereas there was no association with all-cause mortality, the SPRINT kidney composite outcome, or AKI.

Conclusions: Among non-diabetic individuals with hypertension and CKD, higher urine ammonium concentration is associated with higher risk of CVD.

Funding: Veterans Affairs Support

FR-OR48

Aprocitentan in Patients with CKD: Subgroup Analysis of the PRECISION Trial

Markus P. Schlaich,[1] George L. Bakris,[2] Peter Cornelisse,[4] Roland F. Dreier,[4] Bruno Flamion,[4] Johannes F. Mann,[3,6] Patrick Rossignol.[5] *[1]The University of Western Australia Medical School, Perth, WA, Australia; [2]The University of Chicago Medicine, Chicago, IL; [3]Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany; [4]Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland; [5]Centre Hospitalier Princesse Grace, Monaco, Monaco; [6]McMaster University, Hamilton, ON, Canada.*

Background: Resistant hypertension is common and often difficult to control in patients with CKD. Hyperkalemia and decrease in eGFR are two main limitations of available antihypertensive therapies. The phase-3 PRECISION trial demonstrated that aprocitentan, a dual endothelin receptor antagonist, lowers blood pressure in patients with resistant hypertension and is safe. We now investigated the subgroup with CKD of the PRECISION trial.

Methods: Of the 730 patients with resistant hypertension on a standardized fixed-dose combination of amlodipine, valsartan and hydrochlorothiazide, 147 were classified as high-risk or very high-risk based on the KDIGO criteria. They were randomized to 2 doses of aprocitentan or placebo in PRECISION. Changes in office systolic blood pressure (SBP), the primary endpoint in PRECISION, urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) were assessed at multiple time points: a) the end of the double-blind treatment phase at Week 4; b) the single-blind aprocitentan 25mg treatment phase at Week 36; c) the double-blind withdrawal phase at Week 40.

Results: Changes in office SBP and UACR are summarized in Table 1. At Week 4, aprocitentan reduced office SBP by 13.5 mm Hg and 16.6 mm Hg in the 12.5 mg and 25 mg groups, respectively, compared with a 4.4 mm Hg reduction in the placebo group. At Week 36, the reduction in office SBP was maintained (16.4 mm Hg vs baseline). UACR was also reduced by 62% at Week 36 in the 25 mg group. Baseline eGFR of the subgroup was 50 ml/min/1.73 m^2. Changes in eGFR (mL/min/1.73m^2) from baseline to Week 4 were 0.5 and -2.5 in the 12.5 mg and 25 mg groups, respectively, and -0.4 in placebo. An eGFR slope of -0.9 mL/min/1.73m^2/year was observed ("chronic slope") from Week 6 to Week 36 (all patients on 25 mg aprocitentan). At Week 4, edema or fluid retention occurred in 14% and 17% of patients receiving aprocitentan 12.5mg and 25mg, respectively, vs 1% in the placebo group.

Conclusions: In patients with CKD and resistant hypertension, aprocitentan substantially reduced BP and UACR vs placebo.

Funding: Commercial Support - Idorsia Pharmaceuticals Ltd.

	Aprocitentan 12.5mg	Aprocitentan 25mg	Placebo
Baseline Office SBP (mmHg)	154.2	155.3	155.8
Week 4 Office SBP (mmHg)	140.6	138.8	151.2
Week 36 Office SBP (mmHg)	Not applicable	137.5	Not applicable
Week 40 Office SBP (mmHg)	Not applicable	138.3	146.8
Week 4 UACR (ratio from DB baseline)	0.53	0.40	0.96
Week 36 UACR (ratio from DB baseline)	Not applicable	0.38	Not applicable
Week 40 UACR (ratio from DBWD baseline)	Not applicable	0.87	2.08

Table 1: Office SBP and UACR reduction in PRECISION: high-risk and very high-risk patients

FR-OR49

Renal Denervation Is Effective in Reducing Blood Pressure in Patients with CKD: Results of a Multicenter, Prospective, Randomized, Sham-Controlled, Blinded, Investigator-Initiated Trial

Dennis Kannenkeril,[1] Roland E. Schmieder,[1] Michael Böhm,[3] Felix Mahfoud,[3] Lars C. Rump,[4] Johannes Stegbauer,[4] Markus van der Giet,[5] Mario Schiffer,[1] Roland Veelken,[1,2] Michael Uder,[6] Axel Schmid.[6] *[1]University Hospital Erlangen, Friedrich- Alexander University Erlangen-Nuremberg (FAU), Erlangen, Germany; [2]Paracelsus Private Medical School Nuremberg, Nuremberg, Germany; [3]Universitätskliniken des Saarlandes, Saarland University, Homburg, Germany; [4]University Hospital, Heinrich-Heine-University, Düsseldorf, Germany; [5]Charité – Universitätsmedizin Berlin, Berlin, Germany; [6]Institute of Radiology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany.*

Background: Arterial hypertension is the predominant driving force of the progression of chronic kidney disease (CKD). The activity of the sympathetic nervous system (SNS) is increased in patients with CKD and endovascular ultrasound renal denervation (uRDN) offers the opportunity to modulate SNS activity and thereby blood pressure and renal outcome.

Methods: In a multicenter prospective randomized sham-controlled clinical trial (clingov:NCT04264403), patients with CKD stage 3 and uncontrolled hypertension despite 1-5 antihypertensive medications were enrolled. Patients were randomly allocated to either uRDN or a sham procedure. The primary endpoint was the change in mean ambulatory systolic BP (ASBP) at 6 months while on stable medication and blinding maintained. Secondary endpoints were changes of other 24h ambulatory BP values, office BP and safety. Due to slow recruitment, the trial was prematurely stopped.

Results: Of 25 randomized patients (mean age 67yrs), 20 subjects had a 6 month visit per protocol. There was no difference in clinical characteristics, pretreatment 24 hour/day/night ambulatory and office BP between the uRDN (N=10) and the sham group (N=10). After 6 months the decrease in 24h (and day) ambulatory diastolic BP (ADBP) was significantly greater in the uRDN compared with sham (p=0.035 (and 0.030)). There was a numerically greater reduction in 24h ASBP in the uRDN group compared to sham, but it did not reach statistical significance. eGFR did not change within 6 months in either group, albuminuria decreased after 3 months in the uRDN group (p=0.023), with significantly greater decrease compared to sham (p=0.029), but this was not found after 6 months. No safety concerns related to uRDN emerged.

Conclusions: In this randomized sham-controlled blinded study, in face of its premature stop leading to a small cohort, we observed a decrease of diastolic BP after uRDN and no safety signals in these hypertensive patients with CKD.

Funding: Commercial Support - Recor Medical, Inc., Palo Alto, CA, USA

(all BP in mmHg)	24h amb. systolic BP pretreatment	24h amb systolic BP at 6 month	Change from pretreatment	p-value vs pre-treatment	24h amb. diastolic BP pretreatment	24h amb diastolic BP at 6 month	Change from pretreatment	p-value vs pre-treatment
uRDN	143 ± 11	138 ± 15	-4.70 ± 8.12	0.100	82.0 ± 7.8	78.5 ± 10.9	-3.75 ± 5.53	0.061
Sham	142 ± 10	141 ± 10	-0.90 ± 9.35	0.768	85.5 ± 9.0	88.9 ± 7.2	2.15 ± 6.06	0.291
p-value uRDN vs sham	0.748	0.641	0.170	-	0.342	0.022	0.035	-

FR-OR50

Endothelial Glycocalyx Changes in Pregnancy: Relationship with Kidney Injury in Preeclampsia

Oscar A. Garcia Valencia,[1] Sonja Suvakov,[1] Natasa Milic,[1,2] Darah Dilmaghani,[1] Vladimir Dokic,[1] Paul Gavrilovici,[1] Jennet Hatamova,[1] Jing Miao,[1] Vesna D. Garovic.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Univerzitet u Beogradu, Beograd, Serbia.*

Background: Degradation of glycocalyx (GCX), a proteoglycan/glycoprotein layer lining and protecting endothelial cells, has been associated with preeclampsia (PE). Limited data exists for its changes during normotensive pregnancies (NP). We aimed to assess the longitudinal changes of GCX in NP; to correlate GCX with urinary podocyte markers, podocin-nephrin (P/N) positive extracellular vesicles; and to compare P/N ratio, a marker of podocyte/kidney injury, between NP and PE.

Methods: Plasma, urine samples and GCX measurements via non-invasive imaging, were collected at each trimester from 31 pregnant women. Twenty-six women had NP while 5 developed PE. Plasma GCX components, syndecan 1 (SDC1), heparan sulfate proteoglycan (HSPG), and hyaluronic acid (HA) were measured by ELISA; urine P/N positive extracellular vesicles were measured by flow-cytometry and expressed as a ratio.

Results: In NP, GCX degradation, assessed by the width of the perfused boundary region, significantly increased from the 1st to 2nd trimester (p=0.008) and returned to 1st trimester values in the 3rd trimester (p=0.008). Microvascular perfusion decreased from the 1st to 2nd trimester (p=0.006), and increased back to 1st trimester values (p=0.039) by the 3rd trimester. Plasma SDC1 levels increased steadily from the 1st to 2nd trimester (p<0.001), with further increase in the 3rd trimester (p<0.001); HA increased from the 1st to the 2nd trimester (p=0.016) and stabilized. GCX degradation, predominant in the 2nd trimester, was linked to higher P/N ratio from the 1st to the 2nd trimester of NP, which remained stable through the 3rd trimester. The association between GCX degradation and presence of podocyte markers was further documented by a strong correlation between P/N ratio and SDC1 and HA levels in the 3rd trimester. These physiological changes in NP were further compared to PE: comparison of P/N ratios between NP and PE showed significantly higher values in PE across all trimesters (p=0.028).

Conclusions: GCX changes during NP are associated with an increase in urinary podocyte markers. An increase of the P/N ratio in PE compared to NP across gestation provides additional evidence that podocyte injury is an extension of physiological changes in pregnancy, and that it predates the clinical presentation of PE.

FR-OR51

Outcomes of Real-World Adults with CKD Who Are Not Represented in Blood Pressure Target Trials

June Li,[1,2] Jaejin An,[3,5] Matt M. Zhou,[5] Maria E. Montez-Rath,[1] Mengjiao Huang,[2] Fang Niu,[6] John J. Sim,[4,5] Michelle Odden,[1,2] Vivek Charu,[1] Manjula Kurella Tamura.[2,1] *[1]Stanford University School of Medicine, Stanford, CA; [2]VA Palo Alto Geriatric Research Education and Clinical Center, Palo Alto, CA; [3]Kaiser Permanente Bernard J Tyson School of Medicine, Pasadena, CA; [4]Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA; [5]Kaiser Permanente Southern California Department of Research & Evaluation, Pasadena, CA; [6]Kaiser Permanente Southern California, Pasadena, CA.*

Background: Blood pressure (BP) target trials often include adults with chronic kidney disease (CKD) who are healthier and have less chronic conditions compared to their real-world counterparts. We assessed whether clinical outcomes differed between trial eligible and ineligible adults with CKD.

Methods: We identified adults with CKD and hypertension in the Veterans Health Administration (VA) and Kaiser Permanente Southern California (KPSC) in 2019 who met eligibility for one of three BP target trials, SPRINT, ACCORD, and AASK. We compared the relative and absolute risks of death, major cardiovascular events (MACE), serious adverse events (SAEs), and end stage kidney disease (ESKD) between trial eligible and ineligible adults. Patients were followed until an outcome or up to September 30, 2022.

Results: We identified 503,480 adults in the VA (76.1% ineligible) and 73,412 adults in KPSC (79.2% ineligible) with CKD and hypertension. Compared to trial eligible adults, trial ineligible adults had a moderately elevated risk of death, MACE, and SAEs (Hazard ratio (HR) ranges, VA: 1.43-4.17; KPSC: 1.11-3.60), and a markedly elevated risk of ESKD (HR ranges, VA: 4.08-6.22; KPSC: 5.93-8.38). The corresponding absolute risk differences (RD, per 1000 person-years) were largest for death, MACE, and kidney related SAEs (RD ranges, VA: 3.6-17.4; KPSC: 4.5-16.1), and smallest for ESKD (RD ranges, VA: 0.4-4.3; KPSC: 0.8-13.2). Adults ineligible due to diabetes or end-organ damage had the highest relative and absolute risks in outcomes.

Conclusions: Trial ineligible adults with CKD and hypertension have higher risks for death, MACE, ESKD and SAEs compared to trial eligible adults, but the pattern of risk differed by outcome. The benefit-risk profile of hypertension treatment in the real-world population may differ from that of adults with CKD included in trials.

Funding: NIDDK Support

Figure 1. Hazard ratios and risk differences for all outcomes in trial ineligible versus eligible adults with CKD and hypertension in the VA and KPSC.

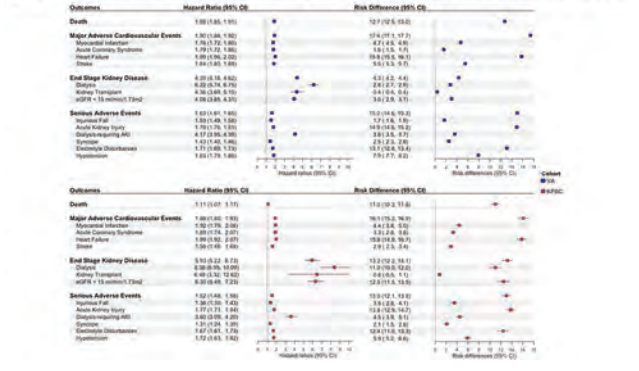


Figure. HR and RD for outcomes in trial eligible vs. ineligible adults in the VA and KPSC.

FR-OR52

Long-Term Kidney Outcomes in Children and Adolescents with Hypertension

Cal Robinson,[1] Junayd Hussain,[2] Tammy M. Brady,[3] Janis M. Dionne,[4] Sabine Karam,[5] Ashlene M. McKay,[1] Rukshana Shroff,[6] Rahul Chanchlani.[7] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]McMaster University Michael G DeGroote School of Medicine, Hamilton, ON, Canada; [3]Johns Hopkins Children's Center, Baltimore, MD; [4]BC Children's Hospital, Vancouver, BC, Canada; [5]University of Minnesota Medical School, Minneapolis, MN; [6]University College London Faculty of Medical Sciences, London, United Kingdom; [7]McMaster Children's Hospital, Hamilton, ON, Canada.*

Background: Hypertension affects 6% of all children and its prevalence is increasing. Pediatric hypertension has been associated with elevated risks of all-cause mortality and cardiovascular events among children and adults. In children with chronic kidney disease, hypertension is associated with progression to kidney failure. However, in those with no prior kidney diseasedirect evidence linking pediatric hypertension, with long-term kidney outcomes is limited. We aim to determine the long-term risks of developing chronic kidney disease and kidney failure among children with hypertension.

Methods: Population-based retrospective cohort study of all children (ages 3-18 years) diagnosed with hypertension from 1996 to 2021 in Ontario, Canada, using validated case definitions in health administrative databases. Each case was propensity score-matched with five normotensive controls by age, sex, birthweight, maternal gestational hypertension, prior diabetes mellitus, cardiovascular surgery, and a propensity score for hypertension diagnosis. Primary outcomes were incident stage 3 chronic kidney disease and end-stage kidney disease (initiation of chronic dialysis, or receipt of kidney transplant).

Results: A total of 25,605 children and adolescents with hypertension were matched to 128,025 controls without hypertension. Children were followed until death(0.7%), emigration from Ontario(11.2%), or study end(88.1%). Median age was 15 years[IQR 11-17], 49% were female, and prior comorbidities were uncommon(1% had congenital heart disease, 1.7% malignancy, 0.4% diabetes). During a median of 12.9 years[IQR 6.8-19.9) of follow up, the incidence rate(IR) of chronic kidney disease was 4.84/1000 person-years(py) in children with hypertension vs 0.42/1000py in controls (adjusted hazard ratio(aHR) 5.9, 95% CI 5.5-6.4). Children with hypertension were also at increased risk of end-stage kidney disease (IR 1.11 vs 0.03/1000py; aHR 9.6, 95% CI 7.8-11.9) compared to controls.

Conclusions: Children and adolescents diagnosed with hypertension are at higher long-term risks of chronic kidney disease and kidney failure, compared to non-hypertensive controls. Improved pediatric hypertension recognition and control may prevent progressive kidney function decline. These findings should be confirmed by large-scale, well controlled prospective studies.

FR-OR53

Subclinical Cardiopulmonary Changes of Heart Failure with Preserved Ejection Fraction (HFpEF) in CKD

Alexis Stevenson,[1] Marija Zimkute,[1] Xuan Cai,[1] Moeed Ahmed,[1] Patrick T. Schiller,[1] Lonnie Thach,[1] Alexander J. Kula,[2] Sanjiv Shah,[1] Ravi B. Patel,[1] Rupal Mehta.[1] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Ann and Robert H Lurie Children's Hospital of Chicago Pritzker Research Library, Chicago, IL.*

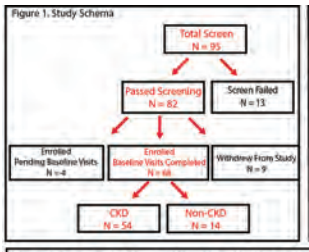
Background: Phenotypic data which include dynamic measurements of cardiac mechanics and cardiopulmonary function that characterize HFpEF in patients with CKD are limited.

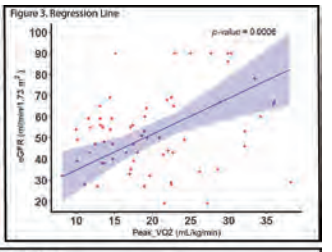
Methods: We performed pre-, peak- and post-exercise speckle tracking echocardiography (2D-STE) and cardiopulmonary exercise testing (CPET) in individuals with and without CKD, and without diabetes or HF as part of a primary recruitment, detailed physiologic, patient-oriented study (Figure 1), We used regression models adjusted for age, sex, race, systolic blood pressure and body mass index to test the independent association between estimated glomerular filtration rate (eGFR) and 2D-STE and CPET indices.

Results: Table 1 displays baseline characteristics of 68 individuals according to CKD status. Only 3 patients with CKD met American Heart Association 2D-echocardiographic criteria for diastolic dysfunction. However, 13/54 and 26/54 with CKD and 1/14 and 2/14 without CKD had reduced left atrial reservoir strain (LARS) and left ventricular longitudinal strain (LVLS), markers of subclinical HFpEF, on resting 2D-STE. At 50 Watts exercise, 20/53 with CKD and 5/13 without CKD had lack of LARS or LVLS augmentation (Figure 2, LVLS Strain). During exercise, 32/53 with CKD and 4/13 without CKD had depressed peak V02, a manifestation of HFpEF. eGFR was independently associated with peak V02 (β-estimate 0.11 per 1 unit increase in eGFR, p value 0.0006, Figure 3).

Conclusions: Exercise 2D-STE and CPET can elucidate relevant physiologic changes suggestive of HFpEF that may be missed on resting 2D-echocardiography. Dynamic exercise testing in patients with CKD can lead to early and more accurate HFpEF diagnoses in a population at high risk for developing HFpEF.

Funding: Other NIH Support - NHLBI K23





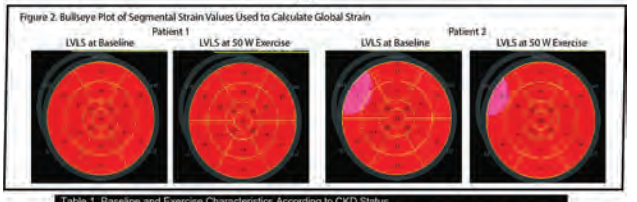


Table 1. Baseline and Exercise Characteristics According to CKD Status

	CKD N = 54	Non-CKD N = 14
Demographics and Clinical Characteristics		
Age, years	58.2 (13.1)	54.1 (10.0)
Female, %	23 (42.6%)	8 (57.1 %)
Black, %	39 (72.2%)	12 (85.7%)
Hypertension, %	38 (70.4%)	5 (35.7 %)
Systolic blood pressure, mmHg (baseline visit)	124 (13.3)	124 (9.53)
Body Mass Index, kg/m^2	28.5 (5.8)	25.7 (2.8)
Laboratory Parameters		
eGFR, ml/min/1.73m^2 (baseline visit)	45.7 (12.8)	79.2 (13.1)
UACR, mg/gram (baseline visit)	24.7 (67.2)	2.37 (5.5)
AHA Echocardiographic Criteria for Diastolic Dysfunction (Meets 3/5)		
Septal e' < 7 cm/sec, N yes	6 (11.1%)	1 (7.1%)
Lateral e' < 10 cm/sec, N yes	8 (14.8%)	0 (0%)
Average E/e' ratio > 14, N yes	1 (1.9%)	0 (0%)
LA volume index >34 mL/m2, N yes	5 (9.3%)	4 (28.6%)
Peak TR velocity > 2.8 m/sec, N yes	2 (3.7%)	0 (0%)
Pre-Exercise 2D-STE Myocardial Strain Parameters		
Left Ventricular Longitudinal Strain (LVLS)	18.5 (2.8)	19 (1.8)
Left Atrial Reservoir Strain (LARS)	31.2 (8.9)	31.5 (6.9)
CPET Parameters		
Peak oxygen consumption, ml/kg/min	19.1 (7.0)	24.2 (7.6)
Peak Respiratory Exchange Ratio (RER)	1.03 (0.7)	1.05 (0.04)
2D-STE and CPET findings suggestive of subclinical HFpEF		
Pre-exercise LV Longitudinal Strain (LVGLS) < 18%, N yes	26 (48.1%)	2 (14.3%)
Pre-exercise LA Reservoir Strain < 25%, N yes	13 (24.1%)	1 (7.1%)
Peak VO2 Females: ≤ 18 mL/kg/min or Peak VO2 Males During Exercise: ≤ 20 mL/kg/min, N yes	32 (59.3%)	4 (28.6%)
Lack of LVLS Augmentation During Exercise, N yes	5 (9.4%)	2 (15.4%)
Lack of LARS Augmentation During Exercise, N yes	17 (32.7%)	3 (23%)

FR-OR54

Performance of Creatinine and Cystatin Equations in People with Heart Failure

Silvia Titan, Sandra Herrmann, John C. Lieske, Andrew D. Rule.
Mayo Clinic Minnesota, Rochester, MN.

Background: Performance of eGFRs among patients with heart failure (HF) may be worse than in the average population, with implications for clinical care.

Methods: We retrieved cases with mGFR (urinary iothalamate) performed at Mayo Clinic between 2011-23 that had an echocardiogram performed within 1 year and serum creatinine (Cr Cohort) or Cr and cystatin (CrCysC Cohort) available within 7 days of the mGFR. Patients were then classified based on ICD codes for HF present 1 year prior to the mGFR and ejection fraction (< or >=50%). CKD-EPI and EKFC eGFRcr, eGFRcys, and eGFRcrcys were computed. Bias was defined as mGFR minus eGFR, and P30 as the proportion of people with eGFR >=30% difference to mGFR.

Results: Results are shown in Table 1. eGFRcr was the most biased equation, prone to overestimation of mGFR in HF groups compared to NoHF. eGFRcr also had the worst precision in the HF groups, with larger errors in HFrEF. eGFRcrcys was the most accurate in NoHF and HFpEF, while eGFRcysC was the most accurate in HFrEF. The CKD-EPI and EKFC performed similarly.

Conclusions: In people with HF, eGFRcr tends to overestimate mGFR and has worse precision compared to people without HF. eGFRcrcys was the most accurate in NoHF and HFpEF, while eGFRcys was the most accurate in the HFrEF group.

	Cr Cohort			CrCys Cohort		
	NoHF (n=13131)	HFpEF (n=1517)	HFrEF (n=1011)	NoHF (n=1886)	HFpEF (n=184)	HFrEF (n=115)
Median Bias (CI)						
CKDEPIcr	0.5 (0.2, 0.8)	-3.7 (-4.7, -2.8)	-4 (-5.1, -3)	0 (-0.6, 0.9)	-6 (-8.1, -4.5)	-8.1 (-11.4, -4.4)
CKDEPIcys	-	-	-	4.2 (3.3, 5.3)	4.7 (3.7, 6.4)	2.6 (-0.4, 4.7)
CKDEPIcrcys	-	-	-	1.1 (0.5, 1.8)	0.5 (-0.8, 2.1)	-1.5 (-3.4, 1.1)
EKFCcr	6 (5.6, 6.3)	0.7 (0, 1.7)	-0.5 (-1.6, 0.4)	5.1 (4.2, 6)	-2.2 (-3.9, -0.4)	-4 (-6.7, -0.5)
EKFCcys	-	-	-	3.3 (2.2, 4.4)	0.9 (-1.3, 2.7)	-0.9 (-3.4, 0.7)
EKFCcreys	-	-	-	4.1 (3.3, 4.7)	-1.2 (-3.1, -0.3)	-4.1 (-7.9, -0.7)
I - P30 (CI)						
CKDEPIcr	22.4 (21.7, 23.1)	30.5 (28.1, 32.8)	37.6 (34.4, 40.4)	22.5 (20.6, 24.4)	35.9 (28.8, 42.4)	60 (51.3, 68.7)
CKDEPIcys	-	-	-	24.7 (22.7, 26.6)	32.1 (25.3, 38.6)	27.8 (20.5, 36.1)
CKDEPIcrcys	-	-	-	15.5 (14.0, 17.2)	25.0 (19.0, 31.0)	33.9 (26.1, 42.6)
EKFCcr	23.3 (22.5, 24)	27.9 (25.4, 30.2)	35 (32.2, 37.8)	22.9 (21.0, 24.6)	34.2 (27.2, 42.1)	58.3 (49.6, 67.8)
EKFCcys	-	-	-	20.8 (18.7, 22.6)	31 (23.9, 38)	33 (23.5, 40.9)
EKFCcreys	-	-	-	15.4 (13.7, 17.1)	27.2 (19.6, 33.4)	39.1 (28.7, 47)
RMSE						
CKDEPIcr	19.5	17.4	19.4	18.2	18.7	22.0
CKDEPIcys	-	-	-	19.2	16.1	13.4
CKDEPIcrcys	-	-	-	16.0	13.3	13.5
EKFCcr	20.7	16.3	18.0	19.3	16.6	19.6
EKFCcys	-	-	-	18.2	14.9	12.8
EKFCcreys	-	-	-	17.0	13.2	13.8

Bias was computed as mGFR - eGFR. Bias and RMSE are expressed as mL/min/1.73m2.

FR-OR55

Optimizing IgAN Treatment: Comparing Prednisone and Budesonide Efficacy and Safety

Abhi Lohana,[1] Usman Akbar,[1] Syed Adil Mir Shah,[2] Nouman Shafique,[3] Fnu Muhibullah,[1] Neeharika Muddana.[1] *[1]Camden Clark Medical Center, Parkersburg, WV; [2]Dow Medical College, Karachi, Pakistan; [3]Nishtar Medical College and Hospital, Multan, Pakistan.*

Background: IgA nephropathy (IgAN) is characterized by mesangial deposition of dominant, polymeric, galactose-deficient IgA1 antibodies originating from the intestinal mucosal lymphoid tissue. It is one of the most common causes of chronic kidney disease worldwide, with 20-40% of patients progressing to end-stage renal disease (ESRD). According to the KDIGO guidelines, steroids, including prednisone, are recommended for patients with persistent proteinuria despite optimal conservative care. Recently, budesonide, a targeted steroid, was introduced, focusing on the gut-associated lymphoid tissue to reduce the production of IgA1. This study compares the efficacy of budesonide in the treatment of IgAN to prednisone.

Methods: We utilized the US collaborative Network database to identify patients aged 18 and above diagnosed with IgAN who received either budesonide or prednisone. Patients were characterized and matched based on propensity scores using current ICD terminology codes. Each cohort comprised 1330 patients.

Results: In comparative analysis, mortality was lower in the prednisone cohort (4.3% vs. 6.2%, risk difference -1.9%, p=0.030). However, the incidence of ESRD was significantly higher in the prednisone group (13.4% vs. 5.0%, risk difference 8.3%, p<0.001). Hematuria was more common in the prednisone cohort (12.7% vs. 9.6%, risk difference 3.1%, p=0.038), whereas microalbuminuria showed no significant difference (0.8% in both cohorts, p=0.996). Osteoporosis rates (2.8% vs. 2.4%, p=0.541), and fungal infection rates (2.4% in both cohorts, p=0.990) were similar. Proteinuria was higher in the prednisone group (35.0% vs. 25.3%, risk difference 9.7%, p=0.003). These results indicate significant differences in mortality, ESRD, hematuria, and proteinuria between the groups.

Conclusions: This study reveals that while both prednisone and budesonide are effective in managing IgAN, budesonide offers a more favourable safety profile with significantly lower rates of ESRD and proteinuria. These findings support the use of budesonide as a viable and superior alternative to prednisone for the long-term management of IgA nephropathy.

Table 1: IgA Nephropathy Outcomes Comparison

Outcome	Patients with Outcome (Prednisone)	Patients with Outcome (Budesonide)	Total Patients (Prednisone)	Total Patients (Budesonide)	Risk Difference	p-value
Mortality	57	82	1330	1332	-0.019	0.03
ESRD	115	51	861	1012	0.083	0
Hematuria	123	83	967	861	0.031	0.038
Microalbuminuria	10	10	1322	1319	0	0.996
Osteoporosis	36	30	1286	1244	0.004	0.541
Fungal Infection	31	29	1284	1205	0	0.99
Proteinuria	142	94	406	372	0.097	0.003

FR-OR56

NeflgArd Open-Label Extension: Efficacy and Safety of Nefecon in Patients with IgAN Who Completed the 2-Year Phase 3 Trial

Richard A. Lafayette,[1] Jens Kristensen,[2] Russell Jones,[3] Jürgen Floege,[4] Vladimir Tesar,[5] Hernan Trimarchi,[6] Heather N. Reich,[7] Hong Zhang,[8] Brad H. Rovin,[9] Jonathan Barratt.[10] *[1]Division of Nephrology, Department of Medicine, Stanford University, Stanford, CA; [2]JDK Pharmaconsulting, Espergarde, Denmark; [3]Calliditas Therapeutics AB, Stockholm, Sweden; [4]Department of Nephrology and Clinical Immunology, Rheinisch Westfälische Technische Hochschule Aachen University Hospital, Aachen, Germany; [5]Department of Nephrology, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czechia; [6]Nephrology Service, Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [7]Division of Nephrology, University Health Network, Department of Medicine, University of Toronto, Toronto, ON, Canada; [8]Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, Beijing, China; [9]Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, OH; [10]College of Medicine Biological Sciences and Psychology, University of Leicester, Leicester, United Kingdom.*

Background: Nefecon was approved for the reduction of kidney function loss in adults with primary immunoglobulin A nephropathy (IgAN) at risk of disease progression, based on the 2-year NeflgArd trial findings (Lafayette. *Lancet* 2023;402:859). Nefecon 16 mg/d for 9 months (mo.) led to a statistically significant benefit in time-weighted average estimated glomerular filtration rate (eGFR) and a durable proteinuria reduction vs placebo. We report data from an open-label extension (OLE) study (NCT04541043) of the effect of Nefecon treatment (tx) in patients (pts) who completed the NeflgArd trial.

Methods: This Phase 3b, multicenter, OLE enrolled pts with IgAN who completed the NeflgArd trial, with persistent proteinuria ≥1 g/d or urine protein–creatinine ratio (UPCR) ≥0.8 g/g and eGFR ≥30 mL/min/1.73 m^2 despite optimized renin–angiotensin system blockade. Pts who completed a full 9-mo. course of Nefecon 16 mg/d without dose reductions were included. OLE pts received Nefecon 16 mg/d for 9 mo. (+2 wks' tapering at 8 mg/d). Blinding to previous NefIgArd tx was maintained. Primary efficacy endpoints were the ratios of eGFR and UPCR at 9 mo. vs OLE baseline. Adverse events occurring during the OLE were captured as new or ongoing from the NefIgArd trial.

Results: Of the 326 pts completing the NefIgArd trial, 119 entered the OLE (45 [38%] Nefecon-experienced; 74 [62%] Nefecon-naïve). 94 (79%) pts were men and 100 (84%) identified as white. At the OLE baseline, median eGFR in Nefecon-experienced vs Nefecon-naïve pts was 50.4 and 49.2 mL/min/1.73 m^2, respectively; median UPCR was 1.28 and 1.37 g/g, respectively. For all 119 pts, UPCR reduction from baseline at 9 mo. was 32%, with an absolute eGFR decline of 1.43 mL/min/1.73 m^2 also reported. In the OLE, similar UPCR reductions and eGFR changes after 9 mo. of Nefecon were seen in Nefecon-experienced and -naïve pts. Tx in the OLE was well tolerated without any new safety signals.

Conclusions: These study findings provide valuable insights into the efficacy and safety of additional tx with Nefecon and demonstrate that, in pts previously treated with Nefecon, a second 9-mo tx course had an effect on proteinuria and kidney function decline similar to a first tx course, without additional safety concerns.

Funding: Commercial Support - Calliditas Therapeutics AB

FR-OR57

PROTECT Subgroup Analysis: Clinical Benefits of Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with IgAN Who Have Proteinuria above and below 1 g/g

Laura Kooienga,[1] Hernan Trimarchi,[2] Jürgen Floege,[3] Priscila Preciado,[5] Edward Murphy,[5] Jai Radhakrishnan.[4] On behalf of the DUPRO Steering Committee and PROTECT Investigators. *[1]Colorado Kidney Care, Denver, CO; [2]Nephrology Service, British Hospital of Buenos Aires, Buenos Aires, Argentina; [3]Division of Nephrology, RWTH Aachen University Hospital, Aachen, Germany; [4]Division of Nephrology, Colombia University Irving Medical Center, New York, NY; [5]Travere Therapeutics, Inc., San Diego, CA.*

Background: SPAR is a nonimmunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA) approved in the US and EU for adults with IgAN. In the pivotal PROTECT trial, SPAR showed sustained proteinuria reduction and better kidney function preservation vs the maximum labeled dose of IRB. Elevated proteinuria (>0.5 g/day) is associated with more rapid disease progression, and proteinuria reduction may lead to improved kidney survival. A post hoc analysis of pts in PROTECT with urine protein-to-creatinine ratio (UPCR) of <1.0 vs ≥1.0 g/g at baseline is presented.

Methods: PROTECT was a 110-week, double-blind, randomized (1:1) trial of SPAR (400 mg) vs active control IRB (300 mg) in adults with biopsy-proven IgAN, urine protein excretion of ≥1.0 g/day despite maximized renin-angiotensin system inhibition for ≥12 weeks, and estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2. We report treatment effects in pt subgroups with UPCR of <1.0 vs ≥1.0 g/g at baseline.

Results: This analysis included 404 pts (UPCR: <1.0 g/g, n=145; ≥1.0 g/g, n=259). Baseline characteristics were well balanced between treatment arms (**Table**). Consistent with primary results, SPAR-treated pts showed a clear treatment benefit vs IRB, with a greater proteinuria reduction and smaller change in eGFR from baseline to week 110, regardless of baseline UPCR. SPAR was generally well tolerated.

Conclusions: SPAR showed clinically meaningful benefits vs IRB across baseline UPCR, supporting its use as a foundational, long-term nephroprotective treatment in pts with IgAN not traditionally considered high risk for disease progression.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table. Baseline Characteristics, Key Efficacy Outcomes, and Treatment Effects of SPAR vs IRB in Pts With Baseline UPCR of <1.0 and ≥1.0 g/g Over 110 Weeks

	Baseline UPCR <1.0 g/g		Baseline UPCR ≥1.0 g/g	
Baseline characteristics	**SPAR (n=77)**	**IRB (n=68)**	**SPAR (n=125)**	**IRB (n=134)**
Age at informed consent, mean (SD), years	46.2 (12.31)	47.2 (12.21)	46.8 (13.07)	44.5 (12.02)
Female, n (%)	14 (18)	10 (15)	49 (39)	49 (37)
eGFR, mean (SD), mL/min/1.73 m^2	57.6 (24.79)	61.3 (25.59)	56.3 (24.13)	54.9 (22.27)
UPCR, median (IQR), g/g	0.72 (0.54-0.92)	0.76 (0.62-0.88)	1.69 (1.29-2.34)	1.52 (1.24-1.95)
UPE, median (IQR), g/day	1.15 (0.95-1.40)	1.31 (1.04-1.57)	2.51 (1.77-3.30)	2.32 (1.77-3.02)
Key efficacy outcomes	**SPAR (n=77)**	**IRB (n=68)**	**SPAR (n=125)**	**IRB (n=134)**
Change in UPCR from baseline to week 110, LS mean (95% CI), %	−34.41 (−46.29 to −19.91)	13.88 (−8.31 to 41.45)	−48.19 (−55.98 to −39.03)	−12.53 (−26.02 to 3.43)
Change in eGFR from baseline to week 110, LS mean (95% CI), mL/min/1.73 m^2	−4.1 (−6.72 to −1.57)	−6.0 (−8.63 to −3.36)	−7.1 (−9.19 to −5.13)	−11.3 (−13.36 to −9.32)
Annualized eGFR chronic slope (weeks 6 to 110), LS mean (95% CI), mL/min/1.73 m^2/year	−1.9 (−3.09 to −0.81)	−2.9 (−4.17 to −1.72)	−3.4 (−4.28 to −2.59)	−4.5 (−5.35 to −3.61)
Annualized eGFR total slope (day 1 to week 110), LS mean (95% CI), mL/min/1.73 m^2/year	−2.1 (−3.21 to −1.04)	−3.6 (−4.17 to −1.83)	−3.6 (−4.45 to −2.72)	−4.5 (−5.37 to −3.62)
UPE <0.3 g/day (complete remission) achieved at any time, n (%)	37 (48.1)	13 (19.1)	25 (20.0)	10 (7.5)
UPE <0.5 g/day achieved at any time, n (%)	48 (62.3)	26 (38.2)	55 (44.0)	22 (16.4)
Treatment effects	**SPAR vs IRB (n=145)**		**SPAR vs IRB (n=259)**	
Change in UPCR from baseline to week 110, ratio (95% CI)	0.58 (0.43-0.77)		0.59 (0.47-0.75)	
Change in eGFR from baseline to week 110, difference (95% CI), mL/min/1.73 m^2	1.9 (−1.96 to 5.80)		4.2 (1.39-7.06)	
Annualized eGFR chronic slope (weeks 6 to 110), difference (95% CI), mL/min/1.73 m^2/year	1.0 (−0.67 to 2.67)		1.1 (−0.15 to 2.29)	
Annualized eGFR total slope (day 1 to week 110), difference (95% CI), mL/min/1.73 m^2/year	0.9 (−0.72 to 2.47)		0.9 (−0.32 to 2.14)	
UPE <0.3 g/day (complete remission), relative risk (95% CI)	2.47 (1.30-4.70)		2.73 (1.31-5.69)	
UPE <0.5 g/day, relative risk (95% CI)	1.63 (1.00-2.65)		2.76 (1.58-4.82)	

eGFR, estimated glomerular filtration rate; IRB, irbesartan; LS, least squares; pt, patient; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.

FR-OR58

Immunodeposits and Urinary Complement Activation Fragments Are Linked to IgAN Activity and Progression: Findings from the CureGN Study

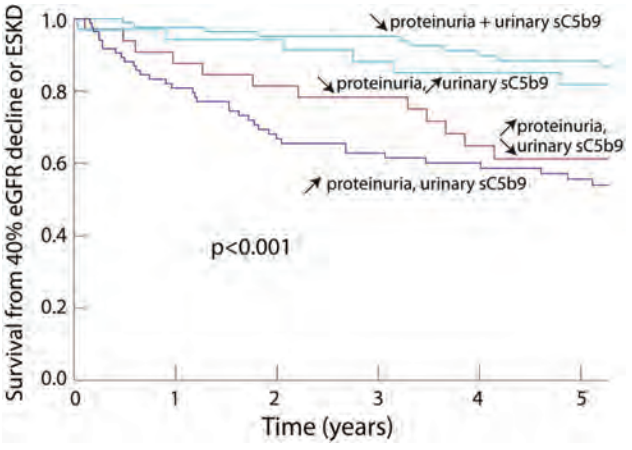
Virginie Royal,[1] Yasar Caliskan,[2] Krista L. Lentine,[2] Arnaud Bonnefoy,[3] Clémence Merlen,[3] Mark Schnitzler,[2] Louis-Philippe Laurin,[1] Stephan Troyanov.[4] *[1]Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, QC, Canada; [2]SSM Health Saint Louis University Hospital, Saint-Louis, MO; [3]Centre Hospitalier Universitaire Sainte-Justine, University of Montreal, Montréal, QC, Canada; [4]Hôpital du Sacré-Cœur-de-Montréal, University of Montreal, Montreal, QC, Canada.*

Background: Small cohorts have reported variable associations between immunodeposits and complement activation with clinical outcomes in IgA nephropathy (IgAN). In parallel, therapeutic trials show encouraging results using complement inhibition. We sought to confirm the value of immunofluorescence findings and urinary complement fragments in defining disease activity and progression.

Methods: Using IgAN patients with available pathology assessment from the CureGN cohort, we tested associations between immunoglobulins and C3 distribution and intensity by immunofluorescence with the Oxford MEST-C score, urinary membrane attack complex (sC5b9), proteinuria, and survival from a combined outcome; kidney failure or 40% decline in eGFR.

Results: We analyzed 247 IgAN patients, including 115 incident subjects enrolled within 6 months of kidney biopsy. IgA and C3 staining intensity were associated with mesangial hypercellularity. Localization of IgM, C3, and IgA deposits along capillaries was associated with endocapillary hypercellularity, cellular crescents, and foot process effacement. In incident subjects, urinary sC5b9 showed associations with global endocapillary hypercellularity, crescent formation, and IgM and C3 deposition along capillaries. While immunodeposits were not associated with a combined outcome, urinary sC5b9 was. When adjusting for the level of proteinuria, significant interaction existed (p=0.009), indicating elevated urinary sC5b9 correlated with a reduced outcome in those with elevated proteinuria (illustrated by Kaplan Meier curves using dichotomizing urinary measurements).

Conclusions: In IgAN, intensity and localization of immunodeposits correlate with mesangial, endocapillary, and extracapillary hypercellularity and the level of urinary sC5b9. In turn, the urinary sC5b9 is independently associated with eGFR loss.



FR-OR59

The Anti-APRIL Antibody Sibeprenlimab Reduces Circulating Immune Complexes in Patients with IgAN: The Phase 2 ENVISION Randomized Controlled Trial

Jonathan Barratt,[1] Mohit Mathur,[2] Adrian Liew,[3] Muh Geot Wong,[4] Laura Kooienga,[5] Richard A. Lafayette,[6] Manisha Sahay,[7] Bobby Chacko,[8] Lee G. Andrews,[2] Lauren E. Olinski,[2] Elizabeth Kong,[2] Zhen Zhang,[9] Yusuke Suzuki.[10]
[1]University of Leicester, Leicester, United Kingdom; [2]Visterra Inc., Waltham, MA; [3]Mount Elizabeth Novena Hospital, Singapore, Singapore; [4]Concord Repatriation General Hospital, New South Wales, NSW, Australia; [5]Colorado Kidney Care, Denver, CO; [6]Department of Medicine, Stanford University, Stanford, CA; [7]Department of Nephrology, Osmania General Hospital and Osmania Medical College, Hyderabad, India; [8]John Hunter Hospital and University of Newcastle, New South Wales, NSW, Australia; [9]Otsuka, Princeton, NJ; [10]Juntendo University, Nephrology, Tokyo, Japan.

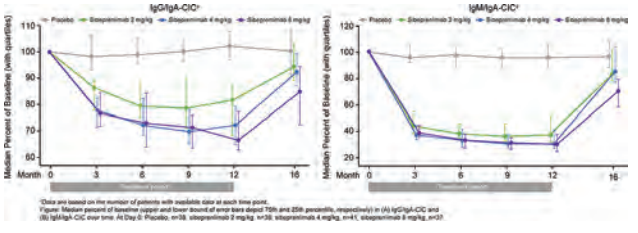
Background: Deposition of IgA-containing circulating immune complexes (CICs) in the kidney is a hallmark of IgA nephropathy (IgAN); A PRoliferation-Inducing Ligand (APRIL) is a driver in this pathogenesis. Sibeprenlimab, an APRIL-neutralizing, humanized IgG2 monoclonal antibody, demonstrated acceptable safety with robust reductions in circulating IgA and uPCR, with eGFR stability at 12 months in the Phase 2 ENVISION trial of patients with IgAN.[1] We now report the effect of sibeprenlimab on change in IgA-containing CICs in IgAN patients.

Methods: ENVISION (NCT04287985) was a 12-month, global, randomized, controlled trial evaluating monthly sibeprenlimab (2, 4, or 8 mg/kg IV) in adults with IgAN. Change in IgG/IgA- and IgM/IgA-CICs over time was examined as an exploratory endpoint. Serum CICs were measured using a semi-quantitative plate-based sequential electrochemiluminescence immunoassay (ECLIA). IgG/IgA- and IgM/IgA-CICs were captured with an anti-IgA antibody and detected with ruthenylated anti-IgG or anti-IgM antibody, respectively.

Results: Sibeprenlimab recipients exhibited sustained, dose-dependent, reversible reductions in IgG/IgA- and IgM/IgA-CICs vs placebo (**Figure**). Median percent of baseline at Month 12 for sibeprenlimab 2, 4, and 8 mg/kg was 81.65, 72.34, and 66.67 for IgG/IgA-CIC, respectively (placebo, 102.26), and 37.05, 30.37, and 30.11 for IgM/IgA-CIC, respectively (placebo, 95.54).

Conclusions: Sibeprenlimab demonstrated robust reduction of IgG/IgA- and IgM/IgA-CICs at all study doses. In the ENVISION trial, reduction of CICs along with galactose-deficient IgA1 and uPCR over time provide further mechanistic evidence for the effects of APRIL inhibition, resulting in stabilization of kidney function as demonstrated by reduction in proteinuria and improvement in eGFR profiles. Together, these results support the disease-modifying activity of sibeprenlimab in the treatment of IgAN. [1]Mathur M et al., *N Engl Med*. 2024;390(1):20–31.

Funding: Commercial Support - Funded by Otsuka



FR-OR60

Efficacy and Safety of Ravulizumab in IgAN: Week 50 Results from a Phase 2 Randomized Controlled Trial

James A. Tumlin,[1] Richard A. Lafayette,[2] Jonathan Barratt,[8] Mai-Szu Wu,[3] Sung Gyun Kim,[4] Jessica K. Kaufeld,[5] Shih-Han S. Huang,[6] Eric Alamartine,[9] Miguel Angel Pérez Valdivia,[7] Kara Rice,[10] Andreas Kateifides,[10] Katherine Garlo,[10] Dario Roccatello.[11]
[1]Emory University, Atlanta, GA; [2]Stanford University, Stanford, CA; [3]Taipei Medical University, Taipei, Taiwan; [4]Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea; [5]Medizinische Hochschule Hannover, Hannover, Germany; [6]London Health Sciences Centre, London, ON, Canada; [7]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [8]University of Leicester, Leicester, United Kingdom; [9]Hopital Nord Service de Nephrologie, Saint Priest en Jarez, France; [10]Alexion Pharmaceuticals Inc, Boston, MA; [11]Universita degli Studi di Torino, Torino, Italy.

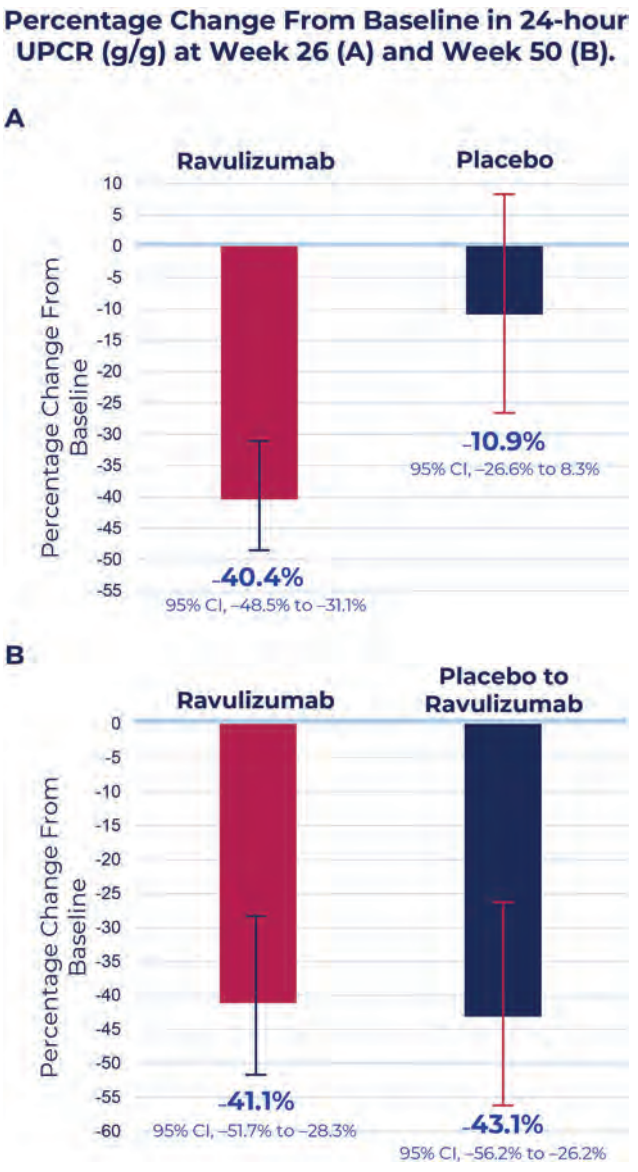
Background: In IgA nephropathy (IgAN), terminal complement pathway activation contributes to inflammation and glomerular damage. Early and meaningful reductions in proteinuria were demonstrated with complement C5 inhibitor ravulizumab (RAV) in the phase 2 SANCTUARY trial (NCT04564339) through 26wks; efficacy and safety data through 50wks are presented.

Methods: Adults with primary IgAN, proteinuria ≥1 g/d, eGFR ≥30 mL/min/1.73 m^2, and on stable/optimal RASi were randomized 2:1 to RAV or placebo (PBO) (IV; q8w) for 26wks. At wk26, PBO group switched to open label RAV (PBO-RAV). Primary endpoint: change in proteinuria at 26wks; secondary endpoints: change in proteinuria and eGFR at 50wks. Safety and PK/PD were assessed.

Results: Of 66 randomized patients (pts; RAV n=43; PBO n=23), 64 completed wk50. In RAV and PBO arms, respective baseline (BL) UPCR was 1.7 and 1.8 g/g; BL eGFR was 76.0 and 70.4 mL/min/1.73 m^2. At 26wks, a –33.2% treatment effect on UPCR was demonstrated with RAV vs PBO (p=0.0011). At 50wks, RAV pts had a 41.1% reduction from BL in UPCR. PBO-RAV pts had a 43.1% decrease in UPCR from BL (wk0) to wk50 (Figure). Annualized eGFR slope in RAV pts was –1.4 at 26wks and –2.3 at 50wks and in PBO-RAV pts was –6.7 and –4.1 at 26 and 50wks, respectively. The majority of AEs were mild; no serious treatment-related AEs, discontinuations from AEs, or deaths occurred.

Conclusions: Treatment with RAV was well-tolerated and demonstrated early and sustained proteinuria reduction through ~1 year, and after wk26 switch from PBO to RAV.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease



FR-OR61

Effect of Iptacopan on Proteinuria and Complement Biomarkers in IgAN: Interim Analysis of the Phase 3 APPLAUSE-IgAN Study

Dana V. Rizk,[1] Dmitrij Kollins,[2] Olympia Papachristofi,[2] Thomas Hach,[2] Marie-Anne Valentin,[2] Tobias Merkel,[2] Ronny W. Renfurm,[2] Vlado Perkovic.[3]
[1]University of Alabama at Birmingham, Birmingham, AL; [2]Novartis Pharma AG, Basel, Switzerland; [3]University of New South Wales, Sydney, NSW, Australia.

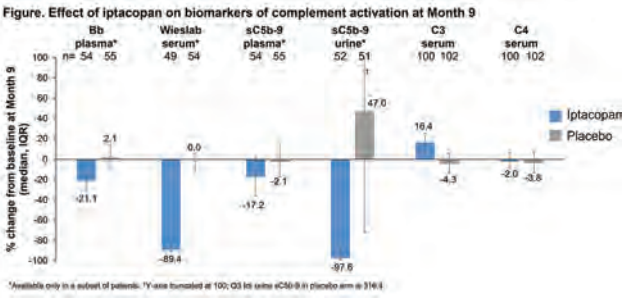
Background: The alternative complement pathway (AP) plays a key role in IgAN pathogenesis and there is an unmet need for targeted disease-modifying treatments. In IgAN, the AP is often activated in urine but not in plasma, indicating renal complement activity. Iptacopan binds to Factor B and specifically inhibits the AP. In a Phase 2 study, iptacopan decreased plasma Bb and Wieslab activity, and urinary sC5b-9 decreased to almost healthy volunteer range. The APPLAUSE-IgAN trial is evaluating iptacopan vs placebo on top of optimized stable supportive therapy. In the pre-specified interim analysis (IA), iptacopan was superior to placebo in reducing proteinuria at Month 9 relative to baseline (24h urine protein-creatinine ratio reduction 38.3%; $P<0.0001$). Here, we present complement biomarker exploratory results from the IA.

Methods: APPLAUSE-IgAN (NCT04578834), a Phase 3, randomized, double-blind, placebo-controlled trial, enrolled adults with biopsy-confirmed IgAN with proteinuria ≥1 g/g despite stable supportive therapy. Patients were randomized 1:1 to iptacopan 200 mg or placebo twice daily for 24 months while remaining on supportive therapy. IA was performed when 250 patients reached Month 9 or discontinued the study. Change from baseline in biomarkers of complement activity was assessed: C3 and C4 in all patients; Bb, sC5b-9, and Wieslab were only assessed in a subset of patients.

Results: Iptacopan selectively inhibited the AP, with reductions in serum Wieslab activity, plasma Bb and sC5b-9, and increases in serum C3, while serum C4 was unchanged (**Figure**). Median decrease in urinary sC5b-9 was 97.6% (IQR 86.1-99.2) in the iptacopan arm; the Month 9 value was within the range observed in healthy individuals.

Conclusions: Iptacopan inhibited systemic and intrarenal activation of the AP in patients with IgAN at Month 9, supported by reductions in serum Wieslab, plasma Bb and sC5b-9, and urinary sC5b-9.

Funding: Commercial Support - Novartis Pharma AG



FR-OR62

ALIGN Subgroup Analyses: Clinically Meaningful Urinary Protein-to-Creatinine Ratio Reductions across Subgroups

Hiddo J. Heerspink,[1] Meg Jardine,[2] Donald E. Kohan,[11] Richard A. Lafayette,[3] Adeera Levin,[4] Adrian Liew,[5] Hong Zhang,[6] Todd E. Gray,[7] Khushboo Sheth,[7] Ronny W. Renfurm,[8] Hetal S. Kocinsky,[9] Jonathan Barratt.[10]
[1]University Medical Center Groningen, Groningen, Netherlands; [2]University of Sydney, Sydney, NSW, Australia; [3]Stanford University, Stanford, CA; [4]The University of British Columbia, Vancouver, BC, Canada; [5]Mount Elizabeth Novena Hospital, Singapore, Singapore; [6]Peking University First Hospital, Beijing, China; [7]Chinook Therapeutics, a Novartis Company, Seattle, WA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Chinook Therapeutics, a Novartis Company, Seattle, WA; [10]University of Leicester, Leicester, United Kingdom; [11]University of Utah Health, Salt Lake City, UT.

Background: Approximately 30% of IgAN patients (pts) with proteinuria 1–2 g/day develop kidney failure within 10 years; even pts with low levels of persistent proteinuria (<1 g/d) are at risk. Endothelin (ET)-1 upregulation and ET_A receptor activation drive proteinuria, kidney inflammation and fibrosis in IgAN. Atrasentan is a potent and selective ETA receptor antagonist. ALIGN is a Phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of atrasentan vs placebo in adult IgAN pts on optimized supportive care (SC).

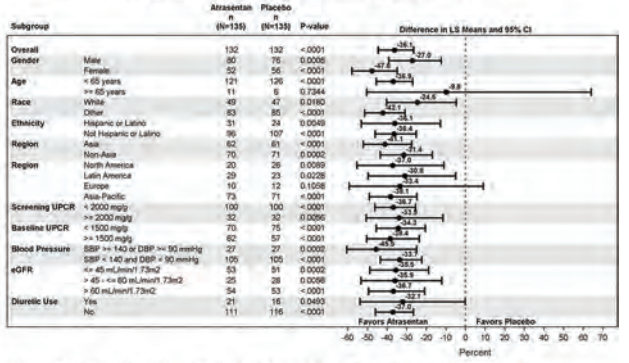
Methods: Pts with biopsy-proven IgAN and proteinuria of ≥ 1g/day were randomized to receive atrasentan 0.75 mg or placebo orally once daily for 132 weeks while continuing SC. The primary endpoint, the change from baseline (CFB) in proteinuria at Week 36, based on UPCR from 24-hour urine collection was evaluated in a prespecified interim analysis of the first 270/340 patients randomized to the main stratum. Subgroups evaluated included key demographic (gender, age, race, ethnicity and region), and baseline disease characteristics (baseline UPCR, BP, eGFR and diuretic use).

Results: The prespecified interim analysis of the primary endpoint showed a 36.1% (26.4%, 44.6%; p<0.0001) relative reduction in LS mean % UPCR CFB at Week 36. Proteinuria reduction was of similar magnitude regardless of age, sex, race, ethnicity or region, and baseline levels of proteinuria, eGFR, BP or diuretic usage (Fig). Atrasentan was well-tolerated with a favorable safety profile. Results for an exploratory SGLT2i stratum were consistent with the main stratum.

Conclusions: Clinically meaningful proteinuria reductions were observed with atrasentan in all subgroups regardless of baseline demographic or disease characteristics.

Funding: Commercial Support - Chinook Therapeutics, a Novartis company

Figure: UPCR Week 36 percentage change from baseline in LS means by subgroup: MMRM analysis primary efficacy set



Note: UPCR values are censored (excluded) for subjects with intercurrent events (i.e. restricted) medication use, chronic dialysis, kidney transplant) beginning at the start date of the earliest event. n=number of subjects included in subgroup. MMRM: mixed model repeated measures.

FR-OR63

Sparsentan (SPAR) as First-Line Treatment of Incident Patients with IgA Nephropathy: Interim Analysis of the SPARTAN Trial

Chee Kay Cheung,[1] Stephanie Moody,[2] Neeraj Dhaun,[3] Sian V. Griffin,[4] Alexandra L. Howson,[1] Radko Komers,[2] Alex Mercer,[5] Matthew Sayer,[3] Smeeta Sinha,[6] Lisa C. Willcocks,[7] Jonathan Barratt.[1] *[1]University of Leicester & Leicester General Hospital, Leicester, United Kingdom; [2]Travere Therapeutics, Inc., San Diego, CA; [3]Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; [4]Department of Nephrology and Transplantation, University Hospital of Wales, Cardiff, United Kingdom; [5]JAMCO Pharma Consulting, Stockholm, Sweden; [6]Department of Renal Medicine Salford Royal Hospital Northern Care Alliance NHS Foundation Trust, Salford, United Kingdom; [7]Department of Renal Medicine, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, United Kingdom.*

Background: SPAR is a nonimmunosuppressive, dual endothelin and angiotensin receptor antagonist (DEARA) approved in the US and EU for the treatment of adults with IgAN. SPARTAN (NCT04663204) is an open-label, single-arm, multicenter, exploratory trial investigating the safety, efficacy, and mechanistic action of SPAR as first-line therapy in patients newly diagnosed with IgAN. We report interim findings.

Methods: Twelve patients ≥18 y old with biopsy-proven IgAN, proteinuria of ≥0.5 g/d, eGFR of ≥30 mL/min/1.73 m^2, and no prior treatment with ACEis/ARBs (≤12 mo) were enrolled. SPAR is given for 110 wk with 4-wk safety follow-up. In a prespecified 24-wk interim analysis, proteinuria, GFR, BP, body weight, total body water (bioimpedance), and safety were assessed.

Results: Mean age at enrollment was 35.8 (SD 12.2) y (5 female), with median (IQR) proteinuria of 1.7 (0.6-3.3) g/d and mean eGFR of 70.2 (SD 25.0) mL/min/1.73 m^2 at baseline (BL). Proteinuria reductions were rapid (−61.9% [±SE −66.9 to −56.1] from BL to wk 4) and sustained over 24 wk (**Figure**); 58% of patients achieved complete proteinuria remission (<0.3 g/d) at any time during the first 24 wk of treatment. After an initial decrease from BL (125/78 mm Hg), BP remained stable during follow-up; eGFR, total body water, and body weight were generally stable (**Table**). The most frequent AE was dizziness (50% of patients); 1 patient discontinued due to hypotension.

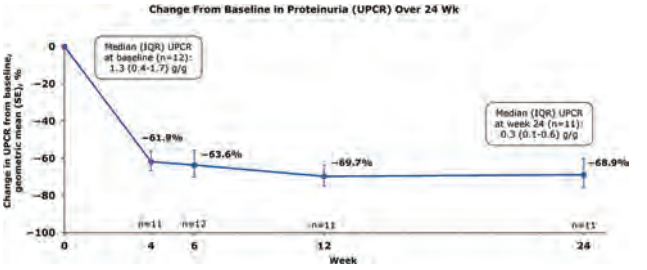
Conclusions: In patients newly diagnosed with IgAN, interim findings show that SPAR as first-line treatment was generally well tolerated and reduced proteinuria ≈70% over 24 wk.

Funding: Commercial Support - Travere Therapeutics, Inc.

Summary Interim Data Over 24 Wk

Mean change from baseline (SD)	Week 2 (n=12)	Week 4 (n=11)	Week 6 (n=11)	Week 12 (n=11)	Week 24 (n=11)
Weight, kg	−0.3 (0.7)	−0.2 (1.4)	0.2 (1.4)	0.1 (2.7)	−1.0 (3.3)
Total body water, L	–	–	−2.2 (7.5)	−2.0 (7.5)	−2.4 (7.4)
Office BP, mm Hg Systolic Diastolic	−7 (7) −7 (11)	−13 (9) −7 (8)	−12 (9) −7 (9)	−13 (7) −7 (7)	−15 (6) −8 (9)
Ambulatory BP, mm Hg Systolic Diastolic	– –	– –	−12 (12)* −9 (9)*	– –	– –
eGFR, mL/min/1.73 m^2	1.1 (7.6)	−3.4 (6.5)	−1.3 (5.1)	1.3 (6.5)	−5.6 (6.2)

*n=7.



FR-OR64

Derivation of a Simple Risk Model for Cardiac Surgery-Associated AKI

Lavanya Durai,[1] Julie-Alexia Dias,[3] Samuel Short,[1] Ashraf Sabe,[1] Simone Redaelli,[2] Maximilian S. Schaefer,[2] Daniela Garcia,[2] Kamal Khabbaz,[2] Shahzad Shaefi,[2] David E. Leaf.[1] *[1]Brigham and Women's Hospital, Boston, MA; [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]Harvard T H Chan School of Public Health, Boston, MA.*

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequent postoperative complication. Existing models to predict CSA-AKI have key limitations, including reliance on diagnostic codes, use of noncontemporary data, a focus on AKI requiring dialysis, and inclusion of intra/postoperative variables. Further, most studies are single-centered.

Methods: We collected detailed data from 36,658 adults who underwent cardiac surgery at 3 academic medical centers in Boston, MA, between 2008-2022. Data were derived from the Society for Thoracic Surgeons Database, which includes >1,000 perioperative variables, along with electronic medical records. Candidate predictors included demographics, comorbidities, medications, labs, illness severity, and surgical characteristics, each assessed preoperatively. The primary outcome was CSA-AKI, defined as a ≥100% increase in serum creatinine or dialysis initiation within 5 days following surgery. We used multivariable logistic regression with backward elimination.

Results: A total of 1687 patients (4.6%) developed CSA-AKI. The final model included 15 variables (**Fig. 1A**). A higher CSA-AKI score monotonically predicted a higher risk of CSA-AKI (**Fig. 1B**). Patients in the highest risk group had a 33.10-fold higher risk of CSA-AKI than those in the lowest risk group (**Fig. 1C**). The model had significantly better discrimination for CSA-AKI (AUC 0.75) than previously published models tested in the current cohort, the AUCs for which ranged from 0.64 to 0.69 (P<0.001) (**Fig. 1D**).

Conclusions: A simple 15-variable risk score predicts CSA-AKI more accurately than previously published models.

A

Risk Factor	Odds Ratio (95% CI)	Score
Mitral regurgitation	1.23 (1.09–1.37)	4
Thiazide diuretics	1.47 (1.28–1.69)	5
Peripheral artery disease	1.34 (1.17–1.54)	5
Liver disease	1.49 (1.28–1.74)	5
Other cardiac procedure	1.31 (1.17–1.46)	5
Preoperative IABP	1.92 (1.54–2.41)	7
Emergent surgery	3.00 (2.46–3.66)	10
Prior cardiac surgery		
None	1.00 (REF)	0
Isolated CABG or valve	1.57 (1.38–1.79)	5
CABG + valve	1.90 (1.35–2.68)	7
Surgery category		
CABG only	1.00 (REF)	0
1 valve only	1.24 (1.05–1.45)	4
≥2 valves only	1.61 (1.29–2.00)	6
CABG + 1 valve	1.91 (1.62–2.25)	7
Aortic or CABG + ≥2 valves	2.61 (2.23–3.07)	9
Age (years)		
<67	1.00 (REF)	0
67-79	1.18 (1.05–1.33)	4
80-84	1.44 (1.21–1.71)	5
≥85	1.83 (1.45–2.30)	6
BMI (kg/m²)		
≤34	1.00 (REF)	0
35-44	1.35 (1.15–1.57)	5
≥45	2.04 (1.48–2.80)	7
RDW (%)		
<13	1.00 (REF)	0
13-14.4	1.21 (1.04–1.40)	4
≥14.5	1.79 (1.52–2.10)	6
Serum albumin (g/dl)		
>4.5	1.00 (REF)	0
4.1-4.5	1.47 (1.22–1.78)	5
3.7-4.0	1.80 (1.48–2.19)	6
3.3-3.6	2.38 (1.92–2.94)	8
2.8-3.2	2.61 (2.03–3.34)	9
<2.8	3.73 (2.71–5.14)	13
Serum potassium (mEq/L)		
>3.6	1.00 (REF)	0
≤3.6	1.23 (1.05–1.45)	4
Baseline SCr (mg/dl)		
0.80-1.09	1.00 (REF)	0
0.60-0.79 or 1.10-1.49	1.16 (1.04–1.30)	4
<0.60 or 1.50-1.99	1.59 (1.35–1.87)	5
2.00-2.29	2.05 (1.45–2.89)	7
≥2.30	2.50 (1.85–3.37)	9

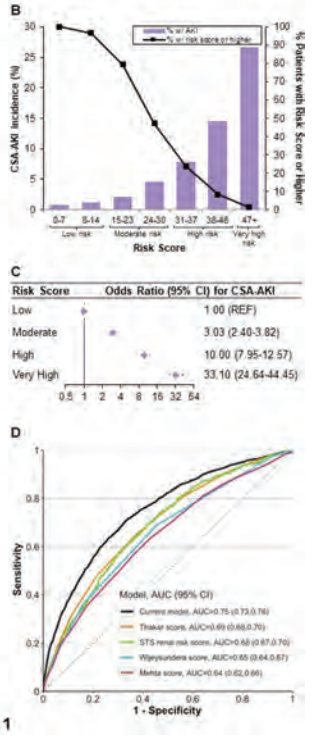


Fig. 1

FR-OR65

Association of Urinary CCL14 with Host-Response and Outcomes in Critically Ill Sepsis Patients with Persistent AKI

Thei S. Steenvoorden, Liffert Vogt, Frederike J. Bemelman, Marcus Schultz, Tom van der Poll, Hessel Peters-Sengers. *Amsterdam UMC Locatie AMC, Amsterdam, Netherlands.*

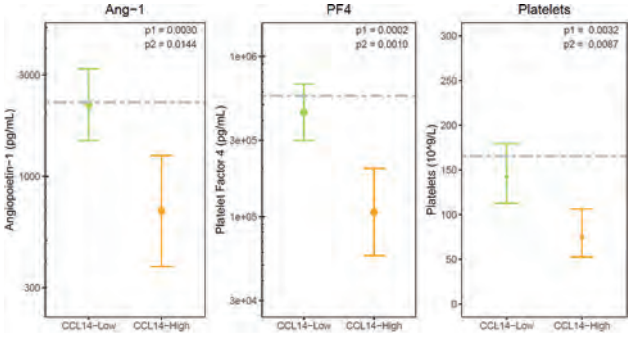
Background: Urinary concentrations of CC chemokine ligand 14 (CCL14) have recently been identified as a strong predictor of acute kidney injury (AKI) persistence. Whether CCL14 plays a role in the pathogenesis of AKI is still unknown. We postulated that looking at the host-response could help determine a correlation of CCL14 with specific AKI pathophysiologic pathways.

Methods: Critically ill patients with sepsis associated (SA) AKI were included from the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) prospective cohort (N=92). They were grouped by high (>1.3ng/ml) and low CCL14. Plasma levels of 15 biomarkers reflective of: systemic inflammation and cytokine responses, endothelial cell activation, and coagulation activation were quantified. In a subset of 24 SA-AKI patients, whole-blood leukocyte genome-wide transcriptomes were determined.

Results: High CCL14 (n=26, 28.3%) was associated with more severe and persistent renal injury, skin and urinary tract infections compared with low CCL14 (n= 66, 71.7%). Adjusted for disesease severity, age and source of infection High CCL14 was associated with endothelial barrier dysfunction and platelet use (Figure), but also with a heightened transcription of neutrophil degranulation pathways, a dampened response in interferon signaling pathways, upregulated cellular stress response pathways, and a net upregulation of leukocyte activation pathways.

Conclusions: These findings suggest that urinary CCL14 can be used to distinguish a specific subtype of severe AKI with more prominent endothelial activation and barrier disruption, and might be a useful guide for future therapeutic strategies.

Funding: Private Foundation Support



Differences in plasma markers of endothelial activation and coagulation in plasma of AKI patients with high (orange) and low (green) urinary CCL14.

FR-OR66

Nuclear Magnetic Resonance-Based Glomerular Filtration Rate Estimation Is More Closely Associated with Serum Vancomycin Target Trough Achievement vs. Serum Creatinine-Based Equations

Jason N. Barreto,[1] Amauri Schwäble Santamaría,[2] Marcello Grassi,[2] Andrew Robertson,[2] John C. Lieske,[1] Jeff W. Meeusen,[2] Eric Schiffer,[2] Erin F. Barreto.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Numares, Regensburg, Germany.*

Background: The clinical utility of glomerular filtrate rate (GFR) estimation based on a panel of analytes (creatinine, cystatin C, myoinositol and valine) measured by nuclear magnetic resonance spectroscopy (GFR_{NMR}) as compared to standard eGFR equations based on serum creatinine for patients receiving vancomycin is unclear.

Methods: This prospective, single-center study included consecutive adults prescribed intravenous vancomycin at Mayo Clinic in Rochester, MN, from 2022 to 2024. Vancomycin indication, dose, frequency, and goal concentration range were determined by the clinical care team. Pearson's product-moment correlation analysis and ordinary least squares regression techniques were used to compare GFR estimating equations as predictors of serum vancomycin trough concentration, accounting for relevant covariates.

Results: 66 patients were enrolled. The median (IQR) age was 61 (50, 70) years, 45 (68%) were male, and 59 (89%) were non-Hispanic White individuals. Vancomycin was most often prescribed for skin, soft tissue, or musculoskeletal infections (n=24, 32%). Thirty-five (53%) patients had a steady state trough concentration within the goal range of 10-20 mg/L. Seven (11%) patients had troughs > 20 mg/L and six (9%) patients developed AKI within seven days of vancomycin initiation. Both GFR_{NMR} and CKD-EPI 2021_{Cr} were negatively correlated with vancomycin concentrations (GFR_{NMR}: t_{64} = -6.81, p-value < 0.001, r = -0.65 [-0.77, -0.48]; CKD-EPI 2021_{Cr}: t_{62} = -4.22, p-value < 0.001, r = -0.47 [-0.64, -0.26]). In multivariable analyses, the GFR_{NMR} inclusive model for prediction of vancomycin trough concentrations had a higher adjusted R^2 (mean [95%CI]) 0.51 [0.45, 0.6] than the CKD-EPI 2021_{Cr} inclusive model at 0.34 [0.29, 0.4] (p-value = 0.008).

Conclusions: Vancomycin trough prediction models with GFR_{NMR} were more predictive than models with CKD-EPI 2021_{Cr} in hospitalized patients. Future research should evaluate the potential for GFR_{NMR} to guide individualized vancomycin dosing.

Funding: Commercial Support - Numares

FR-OR67

Pharmacokinetic/Toxicodynamic Approach to Evaluate Platinum Nephrotoxicity Using the Kidney Injury Molecule-1 Biomarker

Sarah C. Asby,[1] Lauren E. Thompson,[1] Avisek Ghimire,[1] Xia Wen,[3] Christine Kim,[3] Cathleen Doherty,[3] Brian Buckley,[3] Edgar A. Jaimes,[2] Lauren Aleksunes,[3] Melanie S. Joy.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Rutgers The State University of New Jersey, New Brunswick, NJ.*

Background: Cisplatin is a platinum-based chemotherapeutic drug that causes acute kidney injury (AKI), as assessed by serum creatinine (SCr) in over 30% of patients. Urinary kidney injury molecule-1 (KIM-1) is an excellent biomarker to detect subclinical and clinical kidney injury secondary to cisplatin. The aim of this study was to develop a predictive population pharmacokinetic/toxicodynamic (PKTD) model of cisplatin-induced kidney injury that incorporates total platinum concentrations in plasma and structural kidney injury changes, as measured by KIM-1.

Methods: As part of study NCT03817970, cancer patients undergoing their first or second round of cisplatin chemotherapy (n=39) were prospectively randomized to one of three $5\text{-}HT_3$A antiemetics (ondansetron, granisetron, or palonosetron) and had blood and urine collected for 10 days following cisplatin administration. Plasma total platinum concentrations were quantified using ICP/MS (LOQ 0.48-2.40 ng/mL). Urinary KIM-1 concentrations were measured using a commercial ELISA kit (R&D Systems) and normalized to urinary creatinine (UCr). Plasma concentrations of total platinum and urinary concentrations of KIM-1 were used in the development of a nonlinear mixed effect population PKTD model using Phoenix® NLME (v8.3, Certara Inc.). Covariates were screened by stepwise search to determine influence on PKTD parameters.

Results: A two-compartment pharmacokinetic model for total platinum concentrations in plasma was expanded to an effect compartment Emax PKTD model using urinary KIM-1 concentrations as the toxicodynamic marker. Significant covariate effects for the PKTD model included 1) prior exposure to cisplatin on volume of distribution 1 (V1), 2) $5\text{-}HT_3$A antiemetic treatment on V2, and 3) baseline urinary KIM-1 levels on Emax. Additional analyses demonstrated that treatment with the $5\text{-}HT_3$A ondansetron resulted in a 163% increase in exposure to plasma total platinum, a 94% increase in urinary KIM-1 maximum concentrations, and a 235% increase in total urinary KIM-1 excretion compared to palonosetron treatment.

Conclusions: Inclusion of urinary biomarkers such as KIM-1 in PKTD modeling can reveal novel predictors of total plasma platinum PK and subclinical and clinical kidney injury as the TD response.

Funding: NIDDK Support, Other NIH Support - NIGMS, NCATS, NIEHS

FR-OR68

Semaglutide Improves Kidney Function and Inflammatory Status in a Mouse Model of Glomerulonephritis

Günaj Rakipovski,[1] Maria K. Ougaard,[2,1] Nicolas Belmar,[1] Mette V. Østergaard,[1] Nicole Endlich,[3] Bidda Rolin.[1] *[1]Novo Nordisk A/S, Bagsvaerd, Denmark; [2]Gubra A/S, Horsholm, Denmark; [3]NIPOKA, Greifswald, Germany.*

Background: Semaglutide, a GLP-1 receptor agonist, used for weight management and treatment of type 2 diabetes has recently shown a reduction in kidney disease progression and mortality in the FLOW trial. In this study, we used a mouse model of glomerulonephritis known as nephrotoxic serum nephritis (NTN) to evaluate the effects of semaglutide on kidney function, inflammation and morphology

Methods: Glomerulonephritis was induced in female CD1 mice (8-10 weeks old) by intravenous injection of 100 µl nephrotoxic serum (NTS) and allocated to 4 groups: semaglutide (n=12), enalapril (n=10), NTN control (n=12) and healthy control (n=10). Active compound or vehicle was administrated once daily for 14 days. Urine samples were collected in metabolic cages and urinary albumin, creatinine and neutrophil gelatinase-associated lipocalin (NGAL) excretion were measured. The glomerular filtration rate (GFR) was measured on day 12 by transcutaneous method. At termination, the kidneys were collected and processed for histopathological analyses. Renal inflammation was evaluated by staining for CD45 by immunohistochemistry and mesangial expansion was measured as a mean score of PAS stained kidney sections. The podocyte foot process morphology was assessed by measuring the filtration slit density (FSD) by staining for nephrin.

Results: Treatment with semaglutide significantly increased GFR on day 12, and significantly reduced uACR and NGAL on days 7-8 compared to the vehicle treatment. The CD45 staining was significantly reduced in kidneys from mice receiving semaglutide, indicating a reduction in inflammation. Evaluation of mesangial expansion showed that treatment with semaglutide significantly reduced renal lesions compared to the vehicle

group. Finally, semaglutide significantly improved FSD. Enalapril showed the expected efficacy by improving urinary markers of kidney function and histopathology.

Conclusions: Semaglutide improved the kidney function in the NTN mice by significantly increasing GFR and lowering uACR and NGAL. Furthermore, semaglutide significantly reduced renal inflammation and measangial expansion and improved renal filtration barrier function in the NTN mice. These data support the notion that semaglutide has anti-inflammatory properties beyond the well known diabetes and weight management properties.

Funding: Commercial Support - Novo Nordisk A/S

FR-OR69

Felzartamab Durably Reduces Disease-Relevant Biomarkers through Targeting of CD38+ Plasma Cells and Plasmablasts, the Upstream Drivers of IgAN

Jonathan Barratt,[1] Millie Shah,[2] Lisa Kivman,[2] Tabea Kräft,[3] Julia Rauser,[3] Rainer Boxhammer,[3] Stefan Haertle,[3] Brian M. Schwartz,[2] Paul Manser,[2] Leslie Chinn,[2] Uptal D. Patel,[2] Donna Flesher,[2] Krzysztof Kiryluk.[4]
[1]University of Leicester, Leicester, United Kingdom; [2]Human Immunology Biosciences Inc, South San Francisco, CA; [3]MorphoSys AG, Planegg, Germany; [4]Columbia University, New York, NY.

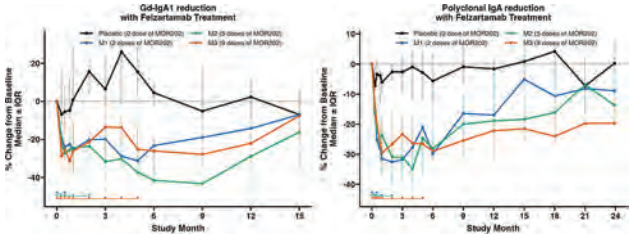
Background: IgAN is driven by antibody secreting cell (ASC) production of galactose-deficient IgA1 (Gd-IgA1) and anti-Gd-IgA1 autoantibodies resulting in immune complex deposition-induced kidney damage. Felzartamab (felza) is a fully human anti-CD38 mAb that directly depletes CD38+ ASCs, the upstream cellular mediators of disease. In a placebo-controlled IgAN Ph2 trial (NCT05065970, IGNAZ), felza resulted in clinically meaningful prolonged UPCR reductions and eGFR stabilization. Here, we evaluate disease relevant biomarkers to understand molecular mechanisms of felza efficacy and durability in IgAN.

Methods: Whole-blood and serum from IGNAZ subjects were collected at baseline, on treatment, and during follow-up of a 2-year study. Samples were assessed for immune cells (flow cytometry), polyclonal immunoglobulins (turbidometry), and Gd-IgA1 (ECLIA).

Results: Felza induced rapid and durable depletion of Gd-IgA1 and total IgA. Patients who received 9 doses over a 5-month period maintained Gd-IgA1 reduction for at least 15 months after the first dose. Similar reductions in IgA were observed for 24 months after treatment start. IgG reduction was modest (< 20%) and rebounded to baseline by 12M. Circulating plasmablasts decreased on-treatment in felza arms versus placebo. Treatment did not impact early or memory B cell subsets or survival factors. Immunomodulation of other CD38+ cell types was observed.

Conclusions: Felza targets and depletes the upstream cellular drivers of IgAN resulting in rapid reduction of major disease related biomarkers. Effects are maintained off-treatment while also preserving humoral immunity. These observations are consistent with other indications, supporting the disease modifying potential of felza in immune mediated diseases.

Funding: Commercial Support - Human Immunology Biosciences, Inc



FR-OR70

Metabolomic Insights into Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors' Kidney Protection in Contrast-Induced Nephropathy

Takashi Tani, Hitomi Tani, Akiko Mii, Rei Nakazato, Natsumi Kamijo, Akira Shimizu, Yukinao Sakai. *Nihon Ika Daigaku, Bunkyo-ku, Japan.*

Background: Contrast-induced nephropathy (CIN) is an acute kidney injury (AKI) associated with the use of contrast medium. We have recently reported that administration of HIF prolyl hydroxylase (HIF-PH) inhibitor, enarodustat play a protective role in rat model of CIN, suggested by improved renal dysfunction, 24-hour creatinine clearance levels and histopathological findings compared to a vehicle-treated group. HIF-PH inhibitors are thought to restore tissue homeostasis under anaerobic conditions by activating HIF1α, 2α, contributing to organ-protective effects. This study aimed to elucidate the mechanism through metabolomics analysis.

Methods: Sprague-Dawley rats were assigned to sham (Nx-S), vehicle-treated CIN (Nx-V), or drug-treated CIN (Nx-E) groups. At 15 weeks, Nx-V and Nx-E underwent right nephrectomy. Enarodustat or vehicle was given at 10 mg/kg for 3 days pre-CIN induction. At 17 weeks, CIN was induced, and rats were sacrificed 2 days later for kidney metabolomic analysis.

Results: CE-TOFMS and CE-QqQMS metabolomic analysis differentiated Nx-S from CIN groups (Nx-V and Nx-E). Nx-S maintained normal purine metabolism, implied by abundance of sedoheptulose 7-phosphate, hypoxanthine, and uric acid. In contrast, Nx-V and Nx-E showed elevated urea and amino acid metabolites, such as *N*-carbamoylaspartic acid, indicating nitrogen waste management due to kidney injury. Oxidative stress response was suggested by increased glutathione (GSH and GSSG) levels in CIN groups. PLS analysis revealed Nx-E had higher levels of metabolites involved in energy metabolism, purine metabolism, and cellular repair, like serine, aspartic acid, and hydroxyproline, suggesting enarodustat's renoprotective effects. Additionally, reduced levels of creatinine and phosphocreatine in Nx-E implied decreased renal stress byproducts. Changes in citric acid cycle intermediates, such as citric acid and isocitric acid, in Nx-E suggested improved mitochondrial function and energy production.

Conclusions: This study has clarified the biochemical changes from contrast medium and enarodustat's modulation. Enarodustat appeared to promote a metabolic shift aiding renal recovery post-CIN. Elevated metabolites related to energy and repair in Nx-E suggested enhanced AKI protection. Reduced stress-linked metabolites supported HIF-PH inhibitors' therapeutic potential in CIN.

Funding: Government Support - Non-U.S.

FR-OR71

Snake Toxin for Treatment of Kidney Diseases: From Bench to, Hopefully, Bedside

Nicolas Gilles,[1,2] Goran Stanajic Petrovic,[2,1] Mathilde Keck,[1,2] Stefano Palea,[3] Denis Servent,[1,2] Charles Truillet.[2,1] Medicines and Healthcare Technologies Dept. *[1]Commissariat a L'energie Atomique et Aux Energies Alternatives Siege Administratif, Gif-sur-Yvette, France; [2]Universite Paris-Saclay, Gif-sur-Yvette, France; [3]Humana, Toulouse, France.*

Background: V2R blockade is a validated therapeutic strategy for hyponatremia and the autosomal polycystic kidney disease. With the aim of discovering a safe V2R antagonists, we screened animal venoms and identified the MQ1 which shown sufficiently interesting properties to be the starting point for the development of a potential drug candidate.

Methods: Toxins were synthesized. Human T-cell assays was used to mitigate MQ1 immunogenicity risk, resulting in the MQ232. The MQ232 dynamic biodistribution in mice was done by positron emission tomography using an MQ232-derived imaging agent. PK, PD and toxicity tests were performed on healthy rats. A rat experimental model of dDAVP-induced hyponatremia, an *ex vivo* mice model of renal cysts and a mice orthologous model of ADPKD were used to validate MQ232 in these pathologies.

Results: 4 mutations were introduced in MQ1 to generate the MQ232. The MQ232 safety was demonstrated by a first toxic dose as high as 3,000 nmol/kg and an absolute kidney organ selectivity by TEP imaging. In addition, TEP imaging shown almost no interaction between MQ232 and the liver. The MQ232 efficacy was demonstrated, first with an effective dose of 3 nmol/kg on hyponatremic model, second on models of kidney polycystic on which MQ232 significantly reduced cyst growth.

Conclusions: We showcased, employing diverse translational techniques MQ232's outstanding safety and efficacy. MQ232 selectively targets the kidney and showed an effective to toxic dose ratio of 1,000-fold. Its molecular identity, bio-distribution and creatinine-like clearance suggest a renal metabolism rather than a hepatic one. MQ232, as the head of a new biological class of vaptan-unrelated aquaretic agents, is a favorable candidate as a therapeutic option for untreated patients.

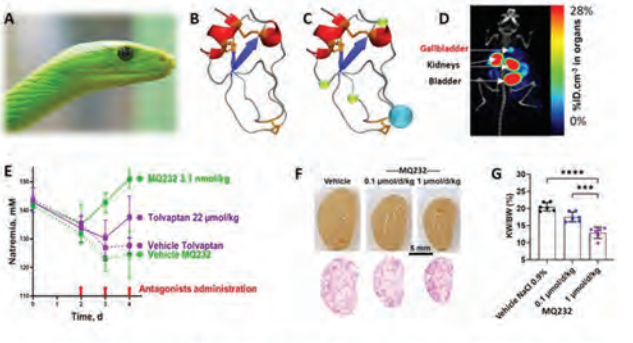


Figure 1. (A) The African snake *Dendroaspis angusticeps*. (B) The natural MQ1, K_i=4.56 nM for the hV2R. (C) The optimized drug candidate MQ232, K_i=0.37 nM for the hV2R. (D) Dual PET/CT imaging at 4 h post injection of 4.28 ± 0.18 MBq of [^{89}Zr]Zr-DFO-MQ232 i.v. injected in the tail of healthy mice. A strong signal is observed in the kidneys, whereas the liver and gallbladder exhibit minimal residual signal. The presented image showcases a composite of CT (gray scale) and PET (color scale) for enhanced subject visualization. (E) Male rat model of hyponatremia. Rats were infused through an osmotic pump with 10 ng/h of dDAVP inducing a clear hyponatremia in 2 days. Blood samples were taken just before tolvaptan per os or MQ232 i.p. administration indicated by red arrows. (F) The genotype Pkd1$^{flox/flox}$; Ksp-Cre was selected at postnatal day 2 and mice administrated s.c. with MQ232 (0.1 or 1 µmol/kg BW per day) or saline vehicle (NaCl 0.9%). Representative images at day 12 of hematoxylin/eosin staining kidney sections (lower) and kidney photography (upper) from *Pkd1$^{flox/flox}$; Ksp-Cre* mice. (G) Kidney weight (KW) indexes (KW/BW) of *Pkd1$^{flox/flox}$; Ksp-Cre* mice at day 12. *** P < 0.001, **** P < 0.0001.

FR-OR72

Prospective and External Evaluation of an Artificial Intelligence Model for Continuous and Early Prediction of Moderate and Severe AKI in Critically Ill Patients

Kianoush Kashani,[1] Francesca Alfieri,[2] Andrea Ancona,[2] Simone Zappalà,[2] Carmine D. Votta,[3] Laura Maderna,[3] Josep S. Gomez,[4] Federico Esteban,[4] Mari C. Gilavert,[4] Maria Bodí,[4] Stefano Finazzi,[5] Alessandro Bacci,[2] Valentina Cauda.[2] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]U-Care Medical s.r.l, Torino, Italy; [3]Ospedale Maggiore di Lodi - ASST Lodi, Lodi, Italy; [4]Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain; [5]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy.*

Background: Acute Kidney Injury (AKI) is associated with clinical and economic burdens on patients and healthcare systems. We previously proposed an AI-based model for the early and continuous prediction of moderate and severe ICU-acquired AKI episodes (ICU-A-AKI-2/3). In this study, the AI model was able to handle missing data and it was validated it in retrospective and prospective cohorts.

Methods: The predictive performance of the AI model was first internally and externally validated in retrospective cohorts in three countries (US, Netherlands, Italy; N=70107) from 176 different ICUs. Subsequently, the model was integrated and prospectively validated into the production in 2 European hospitals (Italy, Spain; N=225) from May 2023 to October 2023. The model analyses spot and temporal profiles of clinical variables from ICU patients, and its output is hourly risk-probability of developing AKI Stages 2 and 3, according to the KDIGO definition. The model only requires routinely-available clinical variables.

Results: In the multicenter external retrospective cohorts, the predictive model obtained the area under the receiver operating characteristic curve (auROC) of >0.89 for the early detection of ICU-A-AKI-2/3. In the prospective validation, the model achieved auROCs ranging from 0.82 (CI 95% 0.73, 0.92) up to 0.87 (CI 95% 0.802, 0.943) in the different hospitals, with a lead time for AKI-2/3 onset varying from 14 to 18 hours after the first day of ICU hospitalization.

Conclusions: In this study, the AI model for early prediction of ICU-A-AKI-2/3 episodes was successfully validated in both rettrospetive and prospective cohorts, achieving high predictive performances. This successful validation marks a significant milestone in integrating it into clinical workflows and represents an essential advancement in bringing the AI model to ICU settings.

Funding: Commercial Support - U-Care Medical s.r.l.

FR-OR73

VHL-Deficient Human Kidney Organoids to Model Clear Cell Renal Cell Carcinoma

Yixuan Wang, Yun Xia. *Lee Kong Chian School of Medicine, Singapore, Singapore.*

Background: Renal cancer ranks among the top ten most prevalent cancers worldwide, with clear cell renal cell carcinoma (ccRCC) emerging as the predominant subtype, accounting for 70-80% of cases and displaying a relatively aggressive phenotype. The inactivation of Von Hippel-Lindau (VHL) tumor suppressor gene, found in approximately 90% of cases, was identified as the primary driver event of ccRCC development. Existing genetic engineered mouse models cannot fully capture the distinctive features of ccRCC, limiting our understanding of the role of VHL mutation in ccRCC initiation. Human pluripotent stem cell derived 3D human kidney organoid comprises of segmentally patterned nephron structures and vascular network, manifesting higher physiological relevance with the human kidney. In this study, we aim to develop VHL knockout human kidney organoids to better understand the role of VHL in tumor initiation.

Methods: CRISPR/Cas9 was utilized to generate VHL biallelic loss-of-function mutant human embryonic stem cells (ESCs). WT and VHL-/- human ESCs were differentiated into kidney organoids which were characterized via histology, immunofluorescence, PAS staining, Oil Red O staining, and qRT-PCR, etc.

Results: Immunostaining confirmed that patterned nephron segments, including glomeruli, proximal tubules, and distal tubules were successfully generated from VHL-/- human ESCs. Histological analysis revealed the emergence of a 'clear cell-like' phenotype in kidney tubular epithelium upon VHL loss. PAS and Oil Red O staining detected accumulation of glycogen and lipids in VHL-/- tubular epithelial cells. qRT-PCR analysis demonstrated metabolic alterations akin to those observed in human ccRCC patients, characterized by the upregulation of genes associated with glycolysis and lipid synthesis, alongside downregulation of genes involved in beta-oxidation. Additionally, VHL-/- kidney organoids acquired higher proliferation competency upon long-term culture.

Conclusions: Human ESC-derived VHL-/- kidney organoids effectively replicate critical morphological and metabolic features reminiscent of human ccRCC patients, thereby offering a novel in vitro platform for studying ccRCC tumorigenesis.

FR-OR74

Macrophages as Potential Mediators of Lung Cancer-Kidney Cross-Talk

Dana Hammouri, Dianet Sanchez Vega, Sophia M. Sears, Levi J. Beverly, Leah J. Siskind. *University of Louisville School of Medicine, Louisville, KY.*

Background: Cisplatin (CDDP) is a widely used chemotherapeutic agent for solid organ cancers. However, its efficacy is hindered by dose-limiting nephrotoxicity. Thirty percent of cancer patients treated with CDDP develop acute kidney injury (AKI). AKI not only complicates cancer management but also increases the risk of chronic kidney disease (CKD). Despite promising preclinical studies, there is no FDA-approved treatment for CDDP-induced kidney injury (CDDP-KI). This is partly attributed to the reliance of preclinical studies on non-cancer models of CDDP-KI, which fail to capture the complex pathophysiology of cancer patients, thus compromising clinical relevance. Our group has recently demonstrated that lung cancer adversely affects kidney function and physiology and exacerbates CDDP-KI, indicating cancer-kidney crosstalk. However, the underlying mechanism driving this interaction remains unclear. Our preliminary data indicate an accumulation of renal macrophages concomitant with the pathological alterations in the kidney of lung cancer mice, implying their role in cancer-kidney crosstalk. We hypothesize that depleting macrophages attenuates cancer-induced nephrotoxicity.

Methods: Eight-week-old B6;129 mice, with or without lung cancer, received three weekly doses of intravenous clodronate-encapsulated liposome (clodrosome) or saline-encapsulated liposome (encapsome) for 28 days. The kidney immune profile, injury, and fibrosis were then assessed.

Results: Clodrosome efficiently depleted renal macrophages and prevented kidney injury, evidenced by decreased KIM-1 expression and preservation of the proximal tubular brush border membrane. Moreover, it reduced the production of extracellular matrix components and attenuated fibrosis.

Conclusions: Our findings indicate that macrophages mediate cancer-induced nephrotoxicity and support further investigation into macrophage-based immunotherapy as a novel treatment for CDDP-KI within the context of cancer-kidney crosstalk.

Funding: NIDDK Support

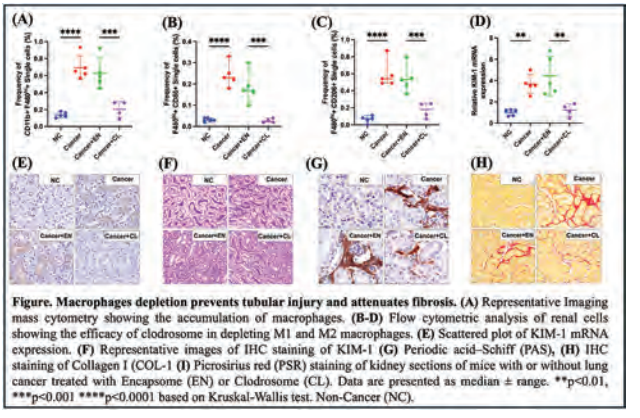


Figure. Macrophages depletion prevents tubular injury and attenuates fibrosis. (A) Representative Imaging mass cytometry showing the accumulation of macrophages. **(B-D)** Flow cytometric analysis of renal cells showing the efficacy of clodrosome in depleting M1 and M2 macrophages. **(E)** Scattered plot of KIM-1 mRNA expression. **(F)** Representative images of IHC staining of KIM-1 **(G)** Periodic acid–Schiff (PAS), **(H)** IHC staining of Collagen I (COL-1 **(I)** Picrosirius red (PSR) staining of kidney sections of mice with or without lung cancer treated with Encapsome (EN) or Clodrosome (CL). Data are presented as median ± range. **p<0.01, ***p<0.001 ****p<0.0001 based on Kruskal-Wallis test. Non-Cancer (NC).

FR-OR75

Single-Cell RNA Sequencing Reveals Conserved T Cell Populations Detected across Inflamed Kidney Tissue and Urine of Patients with Immune Checkpoint Inhibitor-Associated Nephritis

Kavita Mistry,[1,2] Isabela Kernin,[2] Neal P. Smith,[2] Joie Sun,[2] Kerry Reynolds,[2] Shruti Gupta,[3] Meghan E. Sise,[2] Alexandra-Chloe Villani.[2] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Massachusetts General Hospital, Boston, MA; [3]Brigham and Women's Hospital, Boston, MA.*

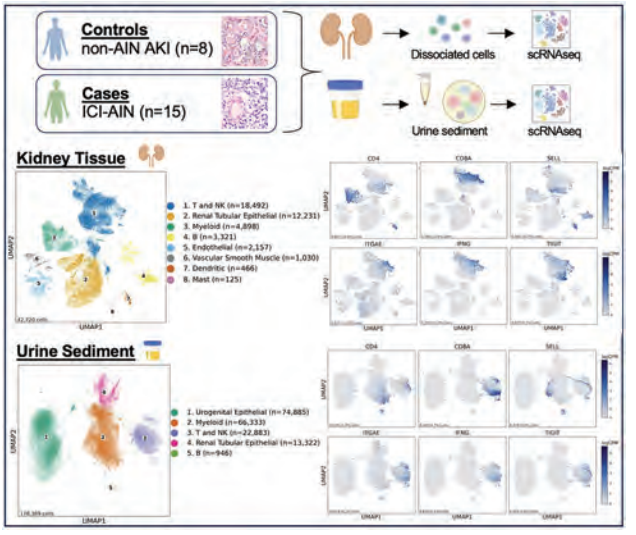
Background: Immune checkpoint inhibitors inhibit the negative regulation of T cells, leading to both anti-tumor activity and immune-related adverse events such as acute interstitial nephritis (ICI-AIN). The immunologic drivers of ICI-AIN are unknown. We hypothesized that both resident and circulating CD8+ T cell subsets are present in ICI-AIN and that they are conserved across kidney tissue and the urine sediment.

Methods: To characterize the cellular populations that are enriched in ICI-AIN, we used scRNAseq to analyze epithelial and immune cells in kidney tissue and urine from a cohort of 15 patients with biopsy-proven ICI-AIN and 8 ICI-treated controls with non-AIN acute kidney injury. A total of ~200,000 cells were analyzed and revealed 23 transcriptionally distinct cell subsets, including CD8+ and CD4+ T cells, NK cells, B cells, myeloid cells, renal tubular epithelial cells, and urogenital epithelial cells.

Results: A range of T cell subsets was identified, existing on a phenotypic spectrum spanning circulation (*KLF2, SELL*) to residency (*ITGAE*), and cytotoxicity (*IFNG, GZMK*) to exhaustion (*TIGIT*). These cell subsets were conserved across both kidney tissue and urine. Gene expression analysis in ICI-AIN samples revealed populations of CD8+ T cells expressing CXCR3 and myeloid cells expressing the interferon-γ-stimulated ligands CXCL9/10, suggesting potential cell-cell interactions.

Conclusions: Taken together, our data contribute to improved understanding of the cellular perturbations in ICI-AIN and reinforce a role for the IFN-γ pathway in driving ICI-AIN. The conservation of T cell types observed across kidney tissue and urine suggests the potential for development of a non-invasive urine-based diagnostic test for ICI-AIN.

Funding: NIDDK Support, Private Foundation Support



FR-OR76

Association of Novel Urine Biomarkers with Immune Checkpoint Inhibitor Nephrotoxicity

Jamie S. Lin, James P. Long, Shailbala Singh, Yanlan Dong, Cassian Yee.
The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Immune checkpoint inhibitor (ICI)-based cancer therapy saves lives, but ~20% of patients undergoing therapy develop acute kidney injury (AKI), and 2-5% face acute interstitial nephritis (AIN) with actionable consequences. Urine protein markers can correlate with specific kidney pathologies, yet exploring the urine proteome is challenging due to low concentrations of potential immunodiagnostic proteins. NUcleic acid Linked Immuno-Sandwich Assay (NULISA™) represents cutting-edge technology reported to be more sensitive than proximity extension assays like OLINK. We hypothesized that leveraging this ultrahigh sensitivity and parallel multiplexing proteomic technology could reveal novel urine or plasma biomarkers for non-invasive ICI-AIN detection.

Methods: We used NULISA™ to assess 203 proteins in urine and plasma from AKI patients on ICI therapy. Cohorts were categorized as either ICI-AIN (n = 22) or non-AIN (n = 27) based on renal biopsy pathology and/or clinical diagnosis. Sample profiling was evaluated using log2 normalized count data, with P-values computed using Wilcoxon tests, and False Discovery Rate (FDR) adjustment.

Results: Of the 203 targets, 149 (73.4%) were detectable in urine samples, and 193 (95.1%) in plasma samples. Clustering and principal component analysis (PCA) revealed distinct proteomic profiles and KEGG pathway analysis identified JAK-STAT and TNF signaling in urine compared to TLR and IL-17 signaling in plasma. Larger differences in protein levels between ICI-AIN and non-AIN were observed in urine. Top urine proteins with AUC > 0.8 (indicating a strong ability to discriminate ICI-AIN from non-AIN) and fold change > 8.0 (FDR 0.01) were associated with hypersensitivity, autoimmunity, immune checkpoint proteins, and immune cell activation. Statistical models, including L1 regularized logistic regression and CART, identified a novel 2-protein signature, as the most effective combination for identifying ICI-AIN. A logistic regression model of this ICI-AIN signature achieved an AUC of 0.94 in distinguishing ICI-AIN from non-AIN, outperforming any other marker(s) including CXCL9 (AUC 0.83).

Conclusions: Our use of state-of-the-art NULISA technology demonstrates that urine and plasma proteomic profiles exhibit distinct characteristics. Statistical modeling identified a novel ICI-AIN signature for non-invasive immune nephritis detection.

Funding: NIDDK Support

FR-OR77

Fludeoxyglucose F 18 Positron Emission Tomography/Computed Tomography: A Novel Diagnostic Tool for Immune Checkpoint Inhibitor-Associated AKI

Shruti Gupta, Olivia Green-Lingren, Sudhir Bhimaniya, David E. Leaf. ICI-AKI Consortium. *Brigham and Women's Hospital, Boston, MA.*

Background: No clinical features reliably differentiate immune checkpoint inhibitor-associated AKI (ICI-AKI) from other AKI etiologies. We examined the role of F^{18}-FDG PET-CT in diagnosing ICI-AKI.

Methods: We used data from a multicenter international cohort study of 429 patients with ICI-AKI, along with data from 2 control groups: patients with acute tubular injury from non-ICI nephrotoxic chemotherapies or from the cancer itself, and patients treated with ICI therapy who did not have AKI. Patients were required to have PET-CT scans at baseline and within 14 days of AKI onset (or, for the second control group, a follow-up PET scan between 90-365 days following ICI initiation). Nuclear radiologists reviewed the PET-CTs at baseline and follow-up and recorded the mean radiotracer standardized uptake value (SUV_{mean}) in the renal cortices. We then calculated the average percent change in SUV_{mean} from baseline to follow-up for each patient. A receiver operating characteristic curve was generated to evaluate the accuracy of percent change in SUV_{mean} for diagnosing ICI-AKI.

Results: 53 patients were included (9 with ICI-AKI, 24 with AKI from other causes, and 20 on ICIs but without AKI). Representative images from baseline and follow-up PET-CTs are shown in **Figure 1A**. The median percent change in SUV_{mean} increased by 57.4% (IQR, 40.3-119.8) from baseline to follow-up among patients with ICI-AKI, but changed minimally among patients in the two control groups (P<0.001; **Figure 1B**). The AUC for the differentiation of ICI-AKI from the two control groups based on percent change in SUV_{mean} was 0.97 (95% CI, 0.93-1.00) **(Figure 1C)**.

Conclusions: F^{18}-FDG PET-CT may be a useful test for diagnosing ICI-AKI, particularly for patients who cannot be safely biopsied due to a contraindication.

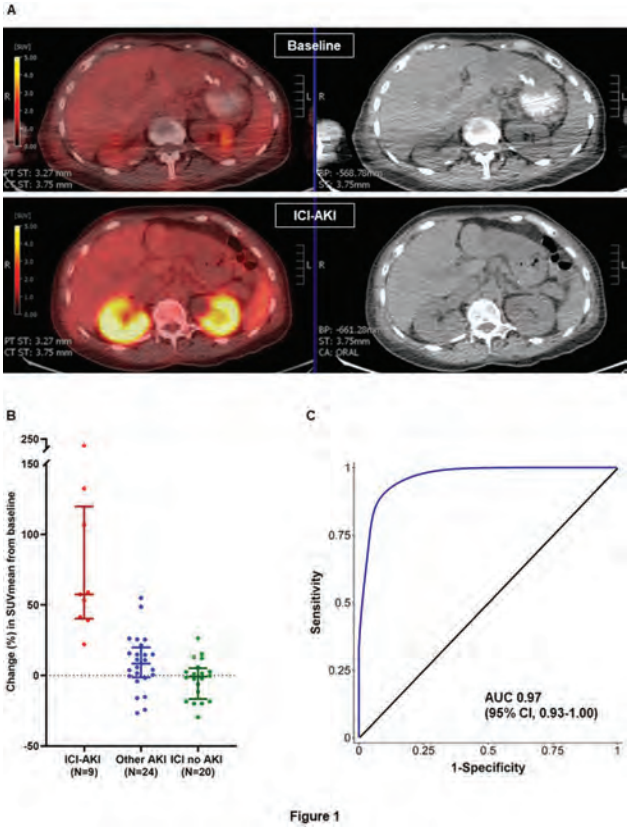


Figure 1

FR-OR78

Effect of Intravenous Magnesium on Cisplatin-Associated AKI

Shruti Gupta,[1] Ilya Glezerman,[2] Jamie S. Hirsch,[3] Sophia L. Wells,[1] Jessica L. Ortega,[1] Anip Bansal,[4] Melanie S. Joy,[4] Ala Abudayyeh,[5] David E. Leaf.[1]
[1]Brigham and Women's Hospital, Boston, MA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Northwell Health, New Hyde Park, NY; [4]University of Colorado Anschutz Medical Campus, Aurora, CO; [5]The University of Texas MD Anderson Cancer Center, Houston, TX.

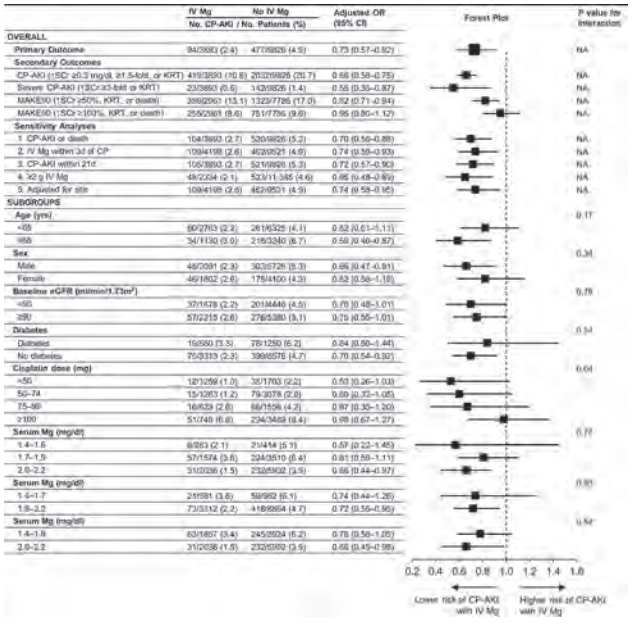
Background: In animal models, prophylactic administration of IV magnesium (Mg) attenuates cisplatin-associated acute kidney injury (CP-AKI), whereas Mg deficiency increases susceptibility to CP-AKI. These findings may be due to the direct effect of Mg on the expression of cisplatin transporters in the proximal tubules. We examined the association between IV Mg administration and risk of CP-AKI in a large cohort.

Methods: We emulated a hypothetical randomized clinical trial (RCT) in which patients receiving cisplatin did or did not receive IV Mg on the day of cisplatin administration. We used data from a multicenter cohort study of adults treated with their first dose of IV cisplatin between 2006-2022 at five major cancer centers across the US. The primary outcome was moderate-to-severe CP-AKI, defined as a ≥2-fold rise in rise in serum creatinine or receipt of dialysis within 14 days following IV cisplatin. We used multivariable logistic regression to adjust for confounders, including age, race, sex, comorbidities, baseline laboratory values, exposure to other nephrotoxic chemotherapy, and cisplatin dose.

Results: Of the 13,719 patients included in the study, 92 of 3893 patients (2.4%) who received IV Mg and 477 of the 9826 (4.9%) who did not receive IV Mg, developed CP-AKI. The adjusted odds ratio for development of CP-AKI among those who did vs. did not receive IV Mg was 0.73 (95% CI, 0.57-0.92). Findings were consistent across a number of sensitivity and subgroup analyses (**Figure**). The protective effect of IV Mg on CP-AKI was consistent across different cisplatin doses, though there was a trend toward greater benefit in patients receiving lower doses of cisplatin.

Conclusions: Administration of IV Mg may be associated with a lower risk of CP-AKI. These findings should be confirmed in a RCT.

Funding: NIDDK Support



FR-OR79

Post-transplantation Cyclophosphamide-Based Regimen for Graft-vs.-Host Disease Prophylaxis Reduces Risk of CKD in Allogenic Stem-Cell Transplant Recipients

Nathaniel Klair,[1] Shernan Holtan,[1] Nattawat Klomjit.[2] *[1]University of Minnesota Twin Cities Division of Nephrology and Hypertension, Minneapolis, MN; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY.*

Background: Allogenic stem cell transplant (Allo-SCT) is associated with higher risk of acute kidney injury (AKI) and chronic kidney disease (CKD). Post-transplantation cyclophosphamide (PTCy)-based regimen for graft-versus-host disease (GVHD) prophylaxis has emerged as a new paradigm in reducing GVHD risk by up to 40%. However, little is known about the impact of kidney outcomes in a PTCy-based regimen.

Methods: We included all adult patients (age ≥ 18 years) who underwent Allo-SCT at the University of Minnesota Medical Center between 1/1/2015 and 5/31/2022. Patients were categorized based on their GVHD prophylaxis: PTCy-based regimen (PTCy/Tacrolimus/Mycophenolate), calcineurin inhibitor (CNI) -based regimen and others. Outcomes include AKI at day 100 (D100), dialysis at D100, eGFR at 1 year and CKD at last follow-up.

Results: We included 488 patients in our cohort, of which 166 (34.0%) received PTCy, 276 (56.6%) received CNI and 46 (9.4%) received other GVHD prophylaxis. Mean age was 54.3 ±15.0 years and the majority were male (59.8%). Baseline eGFR was 107.2±16.6 ml/min/1.73m^2 and only 9 (1.8%) patients had CKD at baseline. PTCy [157 (94.6%)] and CNI-based regimens [255 (92.4%)] had a significantly higher rate of AKI at D100 than the other group [21 (45.7%)]. However, there were no difference in the rate of AKI stage 3 and dialysis among groups (p>0.05). However, eGFR at 1 year was not different. CNI toxicity was the most common cause of AKI in PTCy and CNI groups whereas pre-renal cause was the most common cause of AKI in the other group. At last follow-up, PTCy [31 (18.7%)] had the lowest rate of CKD compared to CNI-based [86 (31.2%)] and the other group [14 (30.4%)]. Multivariate analysis showed that the PTCy group had significantly lower risk of CKD compared to the CNI-based group with OR 0.23 (95% CI 0.09-0.57). Furthermore, PTCy had lower rates of thrombotic microangiopathy, veno-occlusive disease, acute GVHD and chronic GVHD compared to the CNI-based regimen

Conclusions: Although AKI is common in the PTCy regimen, most patients recover and sustain comparable eGFR to CNI and the other regimens at 1 year. PTCy also demonstrates the lowest rate of CKD and is possibly due to lower transplant-related complications such as acute and chronic GVHD.

FR-OR80

Exposure to Glucagon-Like Peptide 1 Receptor Agonists Does Not Increase the Risk of AKI Associated with Anticancer Therapy

Swetha Rani Kanduri, Rosemary Kovacic, Gavin R. Skipper, Juan Carlos Q. Velez. *Ochsner Health, New Orleans, LA.*

Background: Glucagon-like peptide-1-receptor agonists (GLP-1RA) are increasingly prescribed for patients with type 2 diabetes mellitus (T2D) and congestive heart failure (CHF). Notably, reports of GLP-1RA associated acute kidney injury (AKI) have emerged. However, the risk of GLP-1RA-associated AKI among patients on anti-cancer therapies remains unknown. Considering the vulnerability of patients with cancer to acquire AKI during administration of chemotherapy, we hypothesized that exposure to GLP-1RA may further increase the risk of AKI.

Methods: We conducted a retrospective review of medical records extracting cases of patients treated with anti-cancer therapies (cytotoxic, eg, alkylating agents, anti-metabolites; targeted therapy, eg, anti-VEGF, TKI; immunotherapy, eg, ICPI) over a 1-year period and were additionally exposed to a GLP-1RA during the same time period. AKI was defined per KDIGO criteria. Diagnosis of AKI was captured during the first 90 days of GLP-1RA exposure by using ICD codes. To assess the association of GLP-1RA and AKI risk, we conducted a logistic regression model including age, gender, CHF, T2D, chronic kidney disease (CKD) and anti-cancer therapy class.

Results: A total of 14,783 patients were included in the study. Mean age was 67 years, 64% women, 24% had T2D, 8% CHF and 13% had CKD. Nine percent were treated with a GLP-1RA. AKI occurred in 7.2% (92/1278) of those exposed to GLP-1RA versus 6.4% (862/13505) of those with no GLP-1RA exposure (p=0.25). By univariate logistic regression analysis, exposure to GLP-1RA was associated with an OR 1.14 (95% CI 0.91-1.42; p=0.25) for AKI, whereas CKD had an OR 7.26 (95% CI 6.29, 8.29, p<0.0001), CHF an OR 4.92 (95% CI 4.19, 5.76; p<0.0001), T2D an OR 2.36 (95% CI 2.06, 2.70, p<0.0001), targeted therapy an OR 2.84 (95% CI 2.49-3.24, p<0.0001), immunotherapy an OR 2.21 (95% CI 1.55, 3.14, p<0.0001) and cytotoxic chemotherapy an OR 1.89 (95% C1 1.65, 2.17, p<0.0001).

Conclusions: Contrary to our hypothesis, our data suggest that exposure to GLP-1RA is not associated with an increased risk of AKI in patients receiving anti-cancer therapies. Given the cardiovascular and anti-diabetic benefits of GLP-IRA, we suggest that these agents can be safely continued during administration of anti-cancer therapy.

FR-OR81

Cancer Incidence and Outcomes in the Dialysis Population: Nationwide Registry Analysis of Time Trends and Outcomes

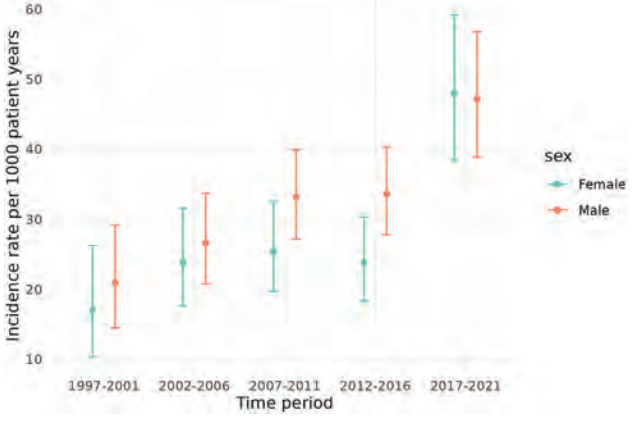
Benjamin M. Elyan,[1,2] Ailish Nimmo,[5] Patrick B. Mark,[1,2] Jennifer S. Lees,[1,2] Samira Bell.[3,4] *[1]University of Glasgow College of Medical Veterinary and Life Sciences, Glasgow, United Kingdom; [2]Queen Elizabeth University Hospital, Glasgow, United Kingdom; [3]University of Dundee School of Medicine, Dundee, United Kingdom; [4]Ninewells Hospital and Medical School, Dundee, United Kingdom; [5]NHS Lothian, Edinburgh, United Kingdom.*

Background: Individuals with end-stage kidney disease have an increased risk of developing and dying from cancer compared to the general population. It is unclear how cancer incidence has changed over time. We aimed to assess cancer incidence over time in the Scottish dialysis population.

Methods: The cohort comprised of adults receiving chronic dialysis (haemodialysis or peritoneal dialysis) in Scotland between 1997-2021. Data were linked between the Scottish Renal Registry, Scottish Cancer Registry and mortality records. Cancers were defined using the International Classification of Diseases for Oncology, 3rd Edition with codes C00-C80, excluding non-melanomatous skin cancer (C44). Cancer incidence rates per 1000 population-years (IRs) were calculated per 5-year time periods and cox regression analyses were performed to examine factors associated with the development of de-novo cancer.

Results: Of 9003 people on long-term dialysis, 727 developed de novo cancer. Median follow-up was longer for people with de-novo cancer (3.6 years vs 2.6 years, p <0.001). The most common cancers were lung (22.8%), colorectal (13.1%), haematological (7.8%), breast (6.7%) and bladder (6.7%). Incidence rate of cancer from 1997-2001 was 19.2 per 1000 patient-years. IRs for later time periods were higher (Figure). The IRR for 2017-2021 was 2.58 compared to the reference period (1997-2001). Increased hazards of de novo cancer were observed with older age at dialysis initiation (aHR 1.01 per year, 95% CI: 1.00-1.02, p=0.001) and with a diagnosis of glomerular diseases compared with other primary renal diagnoses (aHR 1.28, 95% CI 1.01-1.62, p=0.046).

Conclusions: Incidence rates of cancer in the Scottish dialysis population are increasing. These findings emphasise the importance of understanding the role of cancer screening, diagnosis and treatment pathways in dialysis patient care.



Cancer incidence rates in the dialysis population over 5-year period.

FR-OR82

Nephro-Neurovascular Interactions in the Human Kidney Using Light Sheet Fluorescence Microscopy

Liam J. McLaughlin, Bo Zhang, Amanda Knoten, Sanjay Jain.
Washington University in St Louis School of Medicine, St Louis, MO.

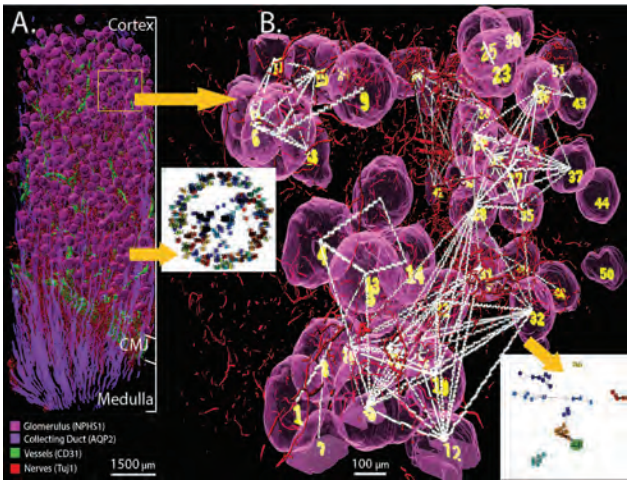
Background: Light sheet fluorescence microscopy (LSFM) is a powerful way to create large 3D tissue images and glean insights into kidney physiology. Here we developed imaging and analytical methods using LSFM on human kidneys to study the neurovascular connectivity of its functional tissue units (FTUs).

Methods: We developed a pipeline from processing slices of human kidney lobes to clearing, image acquisition, image processing, and analysis with available and in-house coded software. Analytical pipelines included segmentation of FTUs and neurovasculature to study patterning of kidney nerves via the creation of neural networks (Fig 1) at macro, meso, and microscopic scales.

Results: In addition to volumetric properties of organization, we report novel observations related to the patterns renal nerves establish between glomeruli and tubules. We define seven motifs of neuro-glomerular networks emanating from the renal vascular pole that organize glomeruli into communities. This includes the same nerve innervating multiple glomeruli together with nearby tubules, and/or the medullary ray, suggesting a neural feedback mechanism between communities of nephrons. Throughout the renal cortex, glomerular neural communities are interconnected through “mother glomeruli”. This organization likely permits FTUs to synchronize responses to perturbations in fluid homeostasis, utilizing mother glomeruli as network control centers. Mathematical modelling of this arrangement suggests that if a part of the network is damaged, the remaining FTUs can compensate till a threshold beyond which normal function deteriorates.

Conclusions: We provide several novel contributions ranging from 3D analytical tools to discoveries that are paradigm shifting and transformational in relation to how 3D structural relationships and organization between kidney FTU and nerves may enable the kidney to adapt to hemodynamic alterations and maintain homeostasis.

Funding: Other NIH Support - NIH Grant ID: U54DK134301



FR-OR83

Spatial Transcriptomics Differentiates Donor-Specific Antibody-Positive and -Negative Microvascular Inflammation

Kelly D. Smith, Yuan Huang, Christopher D. Blosser, Nicolae Leca, Shreeram Akilesh. *University of Washington, Seattle, WA.*

Background: In kidney allografts, microvascular inflammation (MVI) is a hallmark of antibody-mediated rejection and can be seen in patients with and without donor-specific antibodies (DSA). The pathophysiology of MVI in DSA-negative patients is speculated to be mediated by non-HLA antibodies or cellular immune responses.

Methods: Kidney allograft biopsies from 2018-2022 that had donor-derived cell-free DNA (dd-cfDNA) and DSA testing were reviewed for allograft pathology. Clinical and pathologic data were collected. Biopsy material from representative DSA+ (n= 12) and DSA- (n= 16) cases with and without MVI were analyzed using digital spatial profiling (GeoMx, Nanostring) and compared to control biopsies. Biopsies were hybridized with the Whole Transcriptome Atlas and bound probes were collected, sequenced and quantified from glomerular and tubulointerstitial regions of interest (ROI).

Results: We analyzed 237 ROIs from glomeruli (113) and tubulointerstitium (124) from the allograft biopsies. There was strong concordance in differentially expressed genes (DEG) between MVI+ and cfDNA+ biopsies (~80% overlap). In contrast, DSA+ and DSA- biopsies with MVI showed distinct but overlapping patterns of DEG compared to controls (~30% overlap)(Fig. 1). Pathway analysis of the differentially expressed glomerular genes revealed DSA- biopsies with MVI were enriched in interferon-gamma and T cell receptor signaling compared to DSA+ biopsies with MVI.

Conclusions: DSP reveals molecular differences between DSA+ and DSA- biopsies with MVI, supporting distinct pathophysiological mechanisms for MVI-induced renal allograft pathology in the presence and absence of DSA. These results provide additional insight into the molecular pathophysiology of DSA- MVI that may help provide insight into the superior outcome and prognosis reported for these patients.

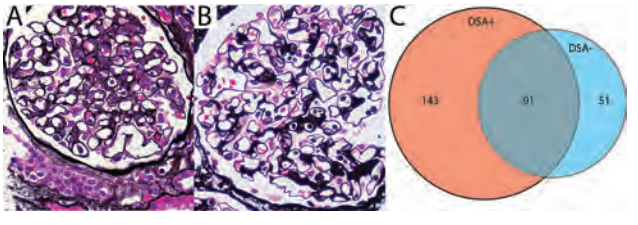


Figure 1. DSP ditinguishes DSA+ and DSA- MVI. A) Glomerulus with DSA+ MVI, and B) histologically indistinguishable glomerulus with DSA- MVI. C) Venn diagram of DEG from DSA+ and DSA- glomeruli with MVI relative to controls.

FR-OR84

A Novel Bioinformatics Strategy to Explore Key Biomarkers in IgA Nephropathy Using Network Biomarkers and Machine Learning

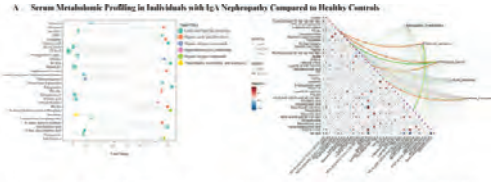
Jiantong Sun, Jiaxing Tan, Wei Qin. *West China Hospital of Sichuan University, Chengdu, China.*

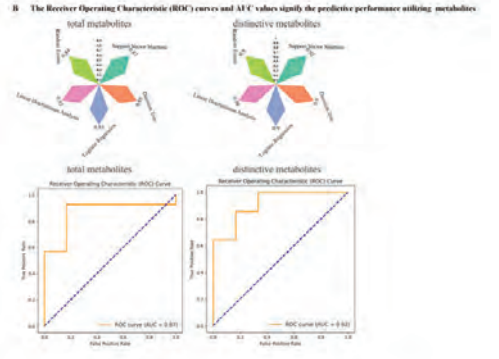
Background: Serum metabolites have been established as pivotal biomarkers for a multitude of diseases. This study explored serum metabolic differences between IgAN patients and healthy controls, aiming to identify potential biomarkers for IgAN.

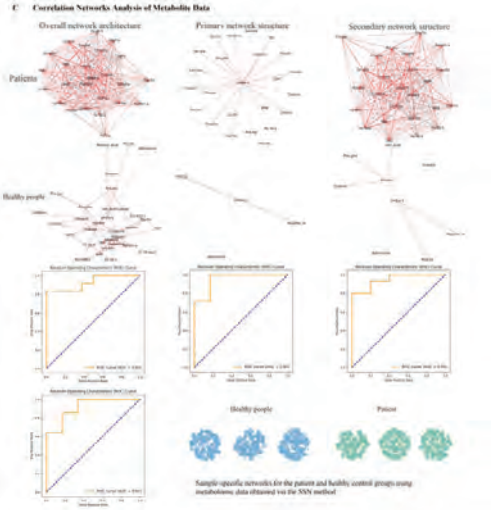
Methods: Serum from 31 healthy individuals and 65 IgAN patients was analyzed using ultra-performance liquid chromatography-mass spectrometry. Machine learning algorithms combined with traditional molecular/ network biomarkers differentiated IgAN from controls, identifying key metabolites and interaction networks. All subjects were followed for >3 years to assess their prognostic value, with mechanisms explored by Mendelian Randomization(MR), network pharmacology, and molecular docking.

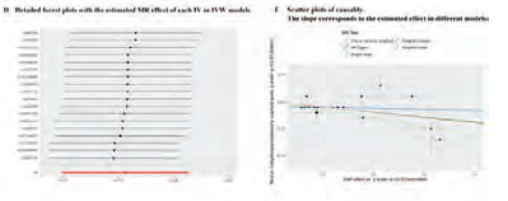
Results: Volcano plot and PLS-DA analyses showed distinct serum metabolite profiles in IgAN patients compared to healthy controls, correlating with kidney damage. A machine learning model utilizing network biomarkers also surpassed traditional biomarkers in performance. SHAP analysis recognized Dehydroepiandrosterone sulfate (DHEA-S) as a crucial differentiator, and networks differed significantly between IgAN cases and controls, supporting its strong linkage to IgAN. MR analysis established a causal link between reduced DHEA-S levels and IgAN onset. Long-term follow-up revealed higher DHEA-S levels correlated with better renal outcomes. Network pharmacology identified 42 potential targets and a protein-protein interaction network pinpointed 6 central targets; molecular docking showed stable binding of DHEA-S with 4 proteins, suggesting its involvement in signaling pathways and mechanisms in IgAN.

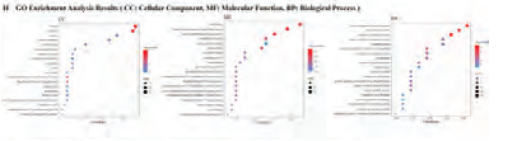
Conclusions: The network structure of serum metabolites in IgAN was significantly different from that of healthy controls, with changes of DHEA-S closely related to the progression of IgAN.

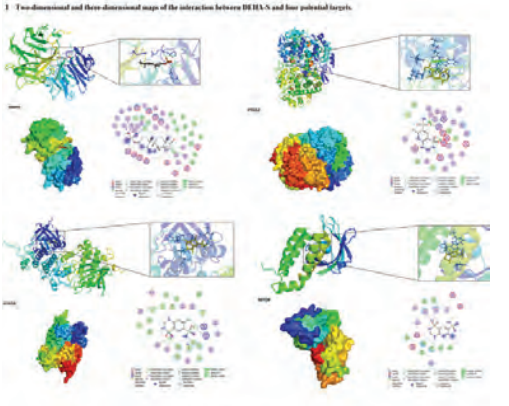












Protein	Lowest Binding Energy	Mean Binding Energy
MMP9	-7.18 kcal/mol	-7.18 kcal/mol
PTGS2	-7.15 kcal/mol	-7.08 kcal/mol
GSK3B	-6.77 kcal/mol	-6.77 kcal/mol
MTOR	-6.33 kcal/mol	-6.32 kcal/mol
HSP90AA1	-5.39 kcal/mol	-5.39 kcal/mol
CASP3	-5.77 kcal/mol	-5.71 kcal/mol

FR-OR85

Development and Validation of a Deep-Learning Algorithm to Estimate Human Podometrics

Kotaro Haruhara,[1] Hiroki Kawai,[2] Eisuke Kubo,[1] Takaya Sasaki,[1] Yusuke Okabayashi,[1] Nobuo Tsuboi,[1] Takashi Yokoo.[1] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [2]LPIXEL Inc., Tokyo, Japan.*

Background: Podocyte depletion is a common pathway in most progressive kidney diseases. We have recently established a method for estimating podometrics, namely podocyte number and size indices, using model-based stereology by measuring the number and diameter of podocyte nuclei on a double immunofluorescence for podocyte-specific markers. However, this method is time-consuming and lacks objectivity.

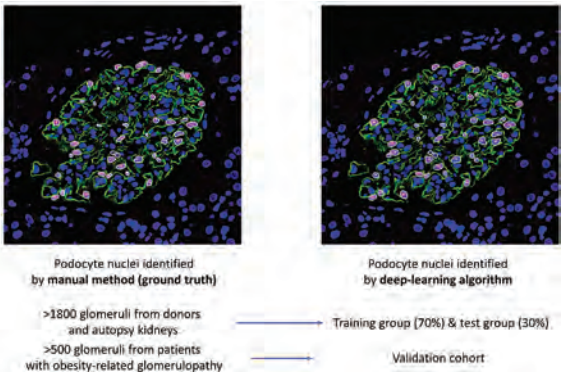
Methods: In the present study, we have developed a deep learning-based algorithm using modified UNet++ for segmenting podocyte nuclei and glomerulus areas in immunofluorescence images, which includes seed prediction for watershed analysis to enhance the identification of nuclei. Data for >43,000 podocyte nuclei on >1800 glomeruli from donors and autopsy kidneys that were manually counted were used as a ground truth. Approximately 70% of these data were randomly allocated for training deep learning algorithms, and the remaining approximately 30% of data were used as a test group. As a validation cohort, independent >500 images of podocyte immunofluorescence from patients with obesity-related glomerulopathy were used (**Figure**).

Results: In the test group consisting of donors and autopsy kidneys, our algorithm showed good accuracy with a precision of 0.92 and recall of 0.95 for podocyte identification. The correlation coefficient for the diameter of podocyte nuclei was 0.80. In the validation cohort, similar results were obtained. While the manual method to identify podocyte nuclei required approximately 30 minutes per glomerulus, our algorithm could detect much faster at a few seconds per glomerulus.

Conclusions: We developed and validated a deep-learning program to estimate podometrics with good accuracy and high throughput. This technology enables us to perform further podometric studies with a large sample size of subjects and glomeruli.

Funding: Government Support - Non-U.S.

Figure



FR-OR86

Computational Characterization of Lymphocyte Topology in FSGS/ Minimal Change Disease

Xiang Li,[1] Manav P. Shah,[4] Gina Sotolongo,[1] Qian Liu,[5] Jin Zhou,[1] Jeffrey B. Hodgin,[2] Laura H. Mariani,[2] Lawrence B. Holzman,[6] Andrew Janowczyk,[3,7] Jarcy Zee,[6,5] Laura Barisoni,[1] Kyle J. Lafata.[1] *[1]Duke University, Durham, NC; [2]University of Michigan, Ann Arbor, MI; [3]Emory University, Atlanta, GA; [4]Georgia Institute of Technology, Atlanta, GA; [5]The Children's Hospital of Philadelphia, Philadelphia, PA; [6]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [7]Hopitaux Universitaires Geneve, Geneve, Switzerland.*

Background: The semi-quantitative visual scoring of inflammation does not capture the distribution of inflammatory cells in the kidney tissue. This study computationally quantified the topology of inflammation and evaluates their clinical relevance.

Methods: H&E-stained whole slide images (WSIs) of renal biopsies from N=190 NEPTUNE (104 FSGS and 86 MCD) and N=141 CureGN (75 FSGS and 66 MCD) participants were used. Deep learning models were developed to segment renal cortex and lymphocytes. Graph modeling was applied, where nodes were defined as lymphocytes and edges as the spatial connections between lymphocytes. We developed a novel graph-based clustering algorithm to capture dense vs. sparse lymphocytic regions. 30 pathomic features were extracted to capture cell density, connectivity, clustering, and centrality. The prognostic value of the features was evaluated by modeling their association with disease progression (time from biopsy to a 40% decline in eGFR or kidney replacement therapy) in the NEPTUNE dataset. To identify the most informative features, lasso regularization was applied to a Cox model. Next, L2-regularized Cox models including clinical features with and without the selected features were constructed. The selected features were then re-fitted in the CureGN dataset for validation.

Results: The selected pathomic features include topology features from both sparsely (n=8) and densely (n=11) inflamed regions. The addition of pathomic features to clinical feature increased the Concordance index from 0.71 to 0.78 in NEPTUNE and from 0.76 to 0.79 in CureGN.

Conclusions: We developed a computational approach to quantify topological characteristics of lymphocytic inflammation on WSIs. These digital signatures have potential as biomarkers of disease progression in FSGS/MCD and increase our ability to predict clinical outcome above and beyond current approaches.

Funding: NIDDK Support, Private Foundation Support

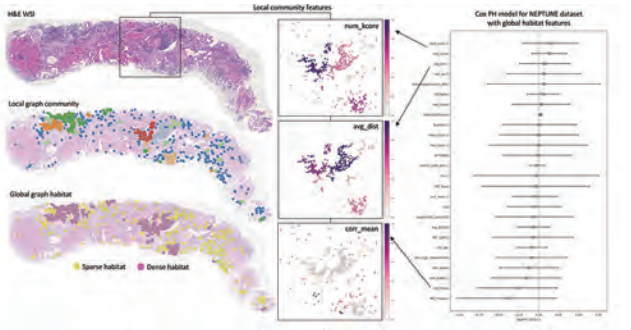


Figure 1. Visualization of lymphocyte graph and region modeling, topology features, and Cox regression hazard ratio plots of all input variables.

Sparse habitat features	Sparse habitat features	Dense habitat features	Dense habitat features
max_kcore: Maximum of k-core values	num_high_between: Ratio of betweenness above and below mean value	max_kcore: Maximum of k-core values	corr_var: Variance of assortativity score of all nodes
num_kcore: Number of different k-core values	eigen_central: Eigenvector centrality	mean_kcore: Mean of k-core values	central_node_dom: Central node dominance
clus: Global clustering score	num_nodes: Number of nodes	num_kcore: Number of different k-core values	num_nodes: Number of nodes
corr_mean: Average of assortativity score of all nodes	avg_degree: Average degree of all nodes	clus: Global clustering score	diameter: Maximum distance between two nodes
corr_var: Variance of assortativity score of all nodes		corr_mean: Average of assortativity score of all nodes	avg_dist: Average of distance between two nodes

FR-OR87

Host-Cell Line Origin of Recombinant Human Nephrin Impacts Anti-nephrin Antibody Enzyme-Linked Immunosorbent Assay (ELISA): Insights into Glycan-Mediated Discrepancy

Maryam Ghasemi, Astrid Weins, Andrew J. Watts. *Brigham and Women's Hospital, Boston, MA.*

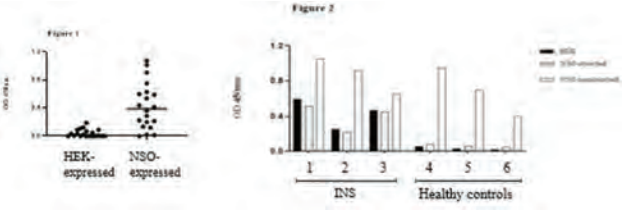
Background: We identified circulating autoantibodies targeting the extracellular domain (ECD) of human nephrin in a subset of patients with minimal change disease. We observed a discrepancy in ELISA results when utilizing human nephrin ECD expressed in a human versus a murine cell line. Nephrin is glycosylated and notably this murine cell line expresses two immunogenic glycans, galactose-α-1,3-galactose (α-Gal) and N-glycolylneuramic acid (Neu5Gc), which are not expressed in human cells. Most human sera contain immunoglobulin G (IgG) against α-Gal and Neu5Gc, which we hypothesized may account for the observed difference in the IgG binding.

Methods: Indirect ELISA for anti-nephrin antibodies in sera was conducted as previously described using affinity-purified recombinant human nephrin ECD (>90% purity) expressed in either human embryonic kidney (HEK) or non-secreting murine myeloma (NSO) cell lines, purchased from Sino Biological (Cat. 17757-H08H) and R&D systems (Cat. 9399-NN) respectively. The amino acid sequence was similar. α-Gal and Neu5Gc expression on the nephrin ECD were evaluated by ELISA. Serum was pre-incubated with porcine RBCs, which express α-Gal and Neu5Gc, and IgG binding to nephrin was evaluated pre- and post-incubation.

Results: Using healthy control sera, we observed more IgG binding to the human nephrin expressed in the NSO compared with the HEK cell line (Fig. 1). We confirmed α-Gal and Neu5Gc presence only on the NSO-expressed human nephrin. Pre-incubation of the sera with porcine RBCs abrogated this higher IgG binding with NSO-expressed nephrin to a level observed with HEK-expressed nephrin (Fig. 2)

Conclusions: We observed more IgG binding from healthy control sera to human nephrin ECD expressed in a murine NSO cell line compared with a human HEK cell line, and this was abrogated by pre-incubating the sera with porcine RBCs. This suggests that IgG binding to α-Gal and Neu5Gc may explain this difference. We therefore recommend using recombinant human nephrin specifically expressed in human cell lines when evaluating patient sera for nephrin autoantibodies by ELISA to minimize false positives.

Funding: NIDDK Support



FR-OR88

Longitudinal In Vivo Monitoring of Kidney Fibrosis Using Collagen I Luciferase Transgenic Mice

Hualin Ma,[1,2] Jianyong Zhong,[2] Jun Zou,[3,2] Haichun Yang,[2] Agnes B. Fogo.[2]
[1]Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, The First Affiliated Hospital, Southern University of Science and Technology, Shenzhen, China; [2]Vanderbilt University Medical Center, Nashville, TN; [3]XinHua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Background: Interstitial fibrosis is closely associated with progression of chronic kidney disease. However, direct assessment of tissue-level fibrosis is limited by the invasiveness of biopsies. We investigated the potential of using collagen I-luciferase (Col(I)-Luc) transgenic mice to track dynamic changes in kidney fibrosis over time in vivo.

Methods: In Col(I)-Luc transgenic mice, the luciferase gene is driven by the collagen I promoter. We induced tubular injury in Col(I)-Luc mice by folic acid (FA) injection and treated a subgroup with dimethyloxaloylglycine (DMOG), an inhibitor of HIF-alpha prolyl hydroxylase. We also crossbred Col(I)-Luc mice with Nep25 mice, which express human CD25 under the nephrin promoter on podocytes. Podocyte injury can be induced by injection of LMB2 toxin that binds the receptor. We induced podocyte injury in Col(I)-Luc/Nep25 mice and treated a subgroup with angiotensin receptor blockers (ARB). In vivo bioluminescence imaging was performed at intervals.

Results: In vivo bioluminescence imaging captured luciferase activity in the kidneys, which correlated with kidney collagen I mRNA. The luciferase activity increased from baseline until week 6 in FA-injured mice, while the normal control had stable luciferase activity. Collagen I mRNA and protein were higher in FA vs control at week 6. DMOG reduced collagen I protein but not mRNA and luciferase activity. In the Nep25 model, low dose LMB2 induced increased proteinuria and luciferase activity at week 2, returning to normal at week 6. However, medium and high dose LMB2 markedly increased proteinuria and luciferase activity from week by week 6. ARB treatment in the high dose LMB2 mice numerically reduced luciferase activity reflecting decreased Col I mRNA but did not change the collagen I protein.

Conclusions: The Col(I)-Luc transgenic mouse model is an effective tool to longitudinally follow changes in collagen I mRNA in kidney disease. This model could be used to validate drug effects in preclinical studies. Utility will be greatest to monitor interventions that change Col I(mRNA), as the model design does not detect posttranslational changes in protein level.

Funding: NIDDK Support

FR-OR89

Detection and Characterization of NELL1 Autoantibodies in NELL1-Positive Membranous Nephropathy

Tiffany Caza,[1] Brock A. Arivett,[2] Samar Hassen,[1] Christopher P. Larsen,[1] Dorin-Bogdan Borza.[2] *[1]Arkana Laboratories, Little Rock, AR; [2]Meharry Medical College, Nashville, TN.*

Background: Discovery of novel autoantigens in membranous nephropathy (MN) holds promise for development of serologic tests to monitor disease activity and guide treatment. Neural epidermal growth factor-like 1 (NELL1) is the second most common antigen in MN. Anti-NELL1 antibodies are currently detected within patient sera by western blotting against NELL1 recombinant protein, but no reproducible, high-throughput clinical assay is yet available.

Methods: Serum samples from 29 patients with NELL1 MN, 33 with PLA2R MN, and 25 healthy controls were collected. Samples were not obtained at the time of biopsy and serologic remission cannot be entirely excluded. We developed a quantitative enzyme-linked immunosorbent assay (ELISA) for NELL1 antibodies using a NELL1 recombinant protein as an antigen source and an indirect immunofluorescence assay for detection of anti-NELL1 antibodies using HEK-293 cells stably transfected with a NELL1-FLAG plasmid vector. IgG subclasses were examined within sera and tissue using subclass specific antibodies.

Results: We detected antibodies within patient sera against NELL1 in 16/33 NELL1 samples and 3/61 controls by ELISA with a sensitivity of 55.2% and specificity of 95.1%. Circulating anti-NELL1 antibodies were predominantly IgG1 and IgG4, with IgG1 antibodies present within all positive samples. Sensitivity of the indirect immunofluorescence assay was 71.4% and specificity 98.6%. Western blots were performed in a subset of cases with good concordance of results between all three methods.

Conclusions: Our data provide methods for serologic testing that can be utilized for serologic evaluation of NELL1-associated MN. High specificity was achieved (95.1-98.6%), however sensitivity was low, which could be due to patients being in serologic remission at the time of serum collection. Further work will establish if antibody titers correlate with disease activity and response to immunosuppressive therapy.

Funding: NIDDK Support

FR-OR90

Purine and Pyrimidine Metabolism Decrease in the First Hour of Warm Ischemia in Kidney Tissue: Spatiotemporal Detection by Mass Spectrometry Imaging

Carine Peutz-Kootstra,[1,2] Benjamin Balluff,[3] Tim C. Van smaalen,[2] Maarten G. Snoeijs,[2] Ron M.A. Heeren,[3] Patrick A. de Hoogt.[2] *[1]Gelre Ziekenhuizen, Apeldoorn, Netherlands; [2]Maastricht Universitair Medisch Centrum+, Maastricht, Netherlands; [3]Maastricht Multimodal Molecular Imaging Institute - M4i, Maastricht, Netherlands.*

Background: Warm ischemia is an important cause of acute kidney injury. Mass Spectrometry Imaging (MSI) can visualize metabolic alterations in renal tissue biopsies.

Methods: In order to identify alternating metabolites during the first hour of warm ischemia, kidney samples from five pigs were measured by high-mass resolution matrix-assisted laser desorption/ionization (MALDI) MSI after 0, 20, 40, and 60 minutes of warm ischemia.

Results: Contrasting the metabolites' distributions with the kidney's microanatomy revealed a cortical decrease in abundance of 56 metabolite signals between 0 and 40 minutes, and of 89 signals between 0 and 60 minutes. Tandem MS identified eleven metabolites of which ten belong to the purine and pyrimidine pathways. There was an attenuated loss of adenosine tri- and diphosphate (ATP and ADP) in medullary rays. Phosphatidylserine 18:0_18:1 was decreased in the cortex, but only in the first 40 minutes of ischemia.

Conclusions: In conclusion, MSI discerns metabolites with differential spatial and temporal expression during warm ischemic injury in renal tissue. Rapid cortical, but slow medullary loss of ATP and ADP metabolism discriminates energy homeostasis pathways affected by acute kidney injury.

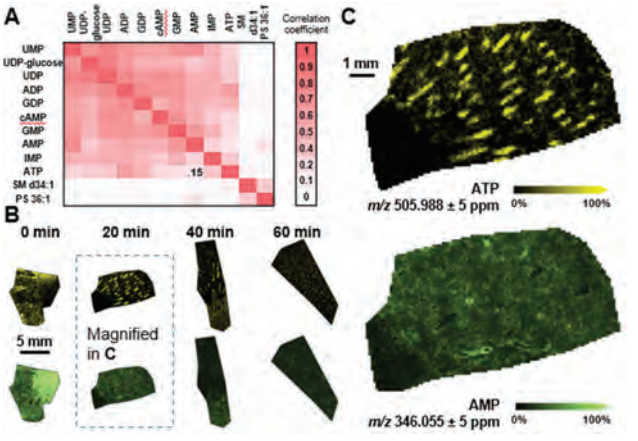


Figure 1. Different spatiotemporal expression patterns of metabolites identified by MSI and MS/MS. Heat map analysis (panel A) of the eleven identified compounds shows differences in spatial expression pattern over time. Panell B shows a different spatial expression for ATP (yellow) and AMP (green) at 0 minutes in cortex and medulla, with a decrease after 20, 40 and 60 minutes of warm ischemia. Higher magnification (panel C) shows that expression of ATP remains in the medullary rays, while AMP expression is still diffusely present in the cortex after 20 minutes of warm ischemia.

FR-OR91

Global, National, and Regional Trends in the Burden of CKD among Women from 1990-2021: A Comprehensive Global Analysis

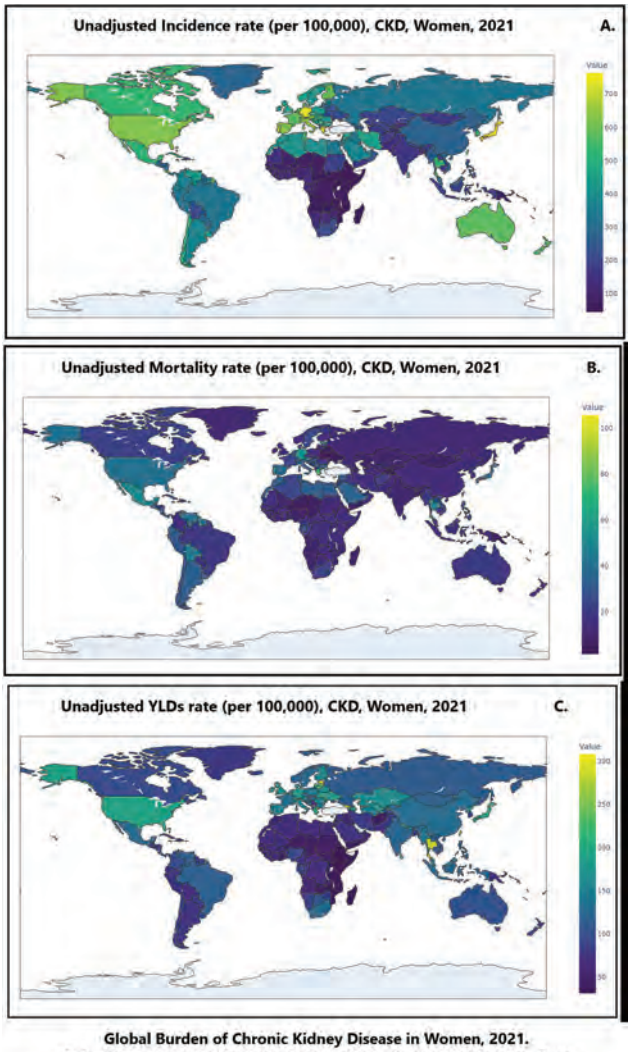
Sree Abhilekha Purohit,[1] Harsha Choudary Pudhota,[2] Ashwinikumar Shandilya,[4] Ram Prasanjith Reddy,[3] Mohit Lakkimsetti,[5] Vishrant Amin,[6] Juhi Patel,[6] Rohan Raj,[8] Hardik Desai.[7] *[1]Shadan Institute of Medical Sciences College of Nursing, Hyderabad, India; [2]Guntur Medical College, Guntur, India; [3]MediCiti Institute of Medical Sciences, Medchal, India; [4]Pravara Institute of Medical Sciences (Deemed to be University), Ahmednagar, India; [5]Mamata Medical College, Khammam, India; [6]Gujarat Medical Education and Research Society Medical College & Hospital Valsad, Valsad, India; [7]Gujarat Adani Institute of Medical Science, Bhuj, India; [8]Nalanda Medical College and Hospital, Patna, Patna, India.*

Background: Chronic Kidney Disease (CKD) ranked as the 7th leading cause of death among women in 2021. This pioneering study presents the 1st comprehensive evaluation of the global burden of CKD in women over the past 3 decades, including an analysis of the initial 2 years of the COVID-19 pandemic-a period that significantly challenged the management of non-COVID-19 diseases.

Methods: Utilizing the 2021 GBD Study framework, we estimated the prevalence, incidence, mortality, Disability Adjusted Life Years(DALYs), and Years Lived with Disability(YLDs) by age, year, and location across 204 countries and territories.

Results: The average annual percentage change(AAPC) in prevalence increased by 2.10%, mortality by 3.39%, and DALYs by 2.48%. Regionally, we observed the highest incidence rates of CKD due to Type 1 diabetes occurred in Eastern Europe (2.07 cases per 100,000 persons), while CKD due to Type 2 diabetes led in the Middle East and North Africa(MENA) with 43 cases per 100,000 persons. Additionally, CKD attributed to hypertension(HTN) (25.18 cases per 100,000 persons) and glomerulonephritis (5.69 cases per 100,000 persons) were notably prevalent in MENA and Central Latin America, respectively. The most substantial incidence counts were observed in the 70-74 age group with 1,663,821 cases, while the highest death rates occurred among those aged 85-89, totaling 92,279 in 2021.

Conclusions: Type 2 DM was the leading cause of CKD related deaths among women in 2021, followed by CKD due to HTN. There is a critical need for increased awareness, education, and comprehensive campaigns aimed at women's health involving public stakeholders and clinicians to address and mitigate these impacts.



Global Burden of Chronic Kidney Disease in Women, 2021.
A: Incidence Rate, B: Mortality Rate, C: Years lived with Disability Rate

FR-OR92

Risk of Congenital Malformation in Newborns of Mothers with Kidney Diseases: A Retrospective Cohort Study Using National Health Insurance Service Data

Seung hyun Han,[1] Jeongin Song,[3] Sehoon Park,[2] Hajeong Lee.[2] *[1]Seoul National University Borame Medical Center, Seoul, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [3]Dongguk University Ilsan Hospital, Ilsan, Republic of Korea.*

Background: The risk of congenital malformations in pregnancies of mothers with kidney disease, including chronic kidney disease (CKD), end-stage kidney disease (ESKD) and kidney transplant (KT) remains unclear.

Methods: A retrospective cohort study using National Health Insurance Service (NHIS) data from 2008 to 2017 was conducted in Korea, including women who delivered during this period and their newborns. The risk of congenital malformations in women with CKD, ESKD, and KT was compared with healthy controls without diabetes or hypertension. Multivariate logistic regression models were used to assess the risk of congenital malformations.

Results: A total of 2,605,422 pregnant women and their 3,637,903 children were included in the present study. Among them, 47,166 women had kidney diseases, including CKD (n = 46,930), ESKD (n = 49), and KT (n = 187). After adjusting for age, parity, hypertension, diabetes, fetal sex, smoking, BMI, preterm birth, and preeclampsia, the KT and CKD group showed a significantly increased risk of any congenital malformations (hazard ratio [HR], 1.81; 95% confidential interval [CI], 1.31-2.45; HR, 1.20; 95% CI, 1.17-1.22, respectively). The ESKD group also tended to show an increased risk of congenital malformation (HR, 1.71; p = 0.080).

Conclusions: This large-scale, population-based study indicated that neonates born to mothers with kidney diseases, especially KT and CKD, have an increased risk of congenital malformations compared to those born to healthy mothers. This highlights the need for specialized prenatal care and monitoring to improve potential fetal malformations.

FR-OR93

Pregnancy Protects against Kidney Injury in Aged Female Mice Lacking G Protein-Coupled Estrogen Receptor

Ravneet Singh,[1] Rawan N. Almutlaq,[2] Sho Sugahara,[1] Craig R. Brooks,[1] Lisa M. Curtis,[2] Eman Y. Gohar.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of Alabama at Birmingham, Birmingham, AL.*

Background: Chronic kidney disease affects more than 1 in 7 US adults, with prevalence increasing with age. In particular, kidney disease is one of the top ten leading causes of death for women. In female rodents, estrogen elicits protective responses against various kidney injuries through G protein-coupled estrogen receptor 1 (GPER1). GPER1-induced vasodilation in rats is increased with pregnancies. The impact of GPER1 signaling and pregnancy on long-term renal health is not clear yet. We hypothesized that GPER1 and previous pregnancies (PP) protect against kidney injury in aged female mice.

Methods: In our study, we used 16-20 month-old GPER1 wild-type (WT) and global knock-out (KO) female mice with or without a history of PP (n=6-8/group). We collected 24-hour urine samples, plasma, and kidneys. Urinary levels of kidney injury biomarkers including protein, albumin, nephrin (glomerular injury marker), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL, tubular injury marker) were measured. Plasma creatinine levels were measured. Kidney sections were stained for KIM-1 and assessed for apoptosis by the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay.

Results: Urinary protein, albumin and plasma creatinine were elevated and PP eliminated this difference. In aged virgin GPER1 KO mice urinary excretion of nephrin [0.63±0.12 vs. 0.36±0.07 ng/day; p=0.0488], KIM-1 [3.11±0.59 vs. 0.79±0.29 ng/day; p=0.0004], and NGAL [208.48±28.17 vs.70.55±11.32; ng/day; p<0.0001] was increased. However, aged previously pregnant KO mice elicited lower levels of excretion of nephrin [0.295±0.04 ng/day; p= 0.0159], KIM-1 [1.38±0.28 ng/day; p=0.0058], and NGAL [67.06±15.69 ng/day; p<0.0001] compared to virgin KO mice. More KIM-1 positive tubules were identified in the aged virgin KO mice compared to the aged virgin WT mice. Further, GPER1 deletion increased TUNEL-positive nuclei in the renal cortex of the virgin mice [662±42 vs. 407±30; p=0.0002]. This genotypic difference was blunted with PP [282±12; p<0.0001].

Conclusions: Our data indicates that GPER1 and former pregnancies protect from kidney injury in aged female mice. This data could provide insight into the development of renoprotective therapeutic agents for postmenopausal women.

Funding: NIDDK Support

FR-OR94

Preclinical Murine Model of Gender-Affirming Hormone Therapy

Han Eckenrode, Caroline Carwie, Rohan S. Balkawade, Chunlan Fan, Lisa M. Curtis. *The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.*

Background: Gender-affirming hormone therapy (GAHT) is a common part of transgender medical care, involving the alteration of sex hormone levels. Although sex hormones are known to be implicated in kidney health and disease, few studies have explicitly examined the effects of GAHT on kidney health.

Methods: Male and female C57Bl6/J mice were used. At 8 weeks of age, males were implanted with 17β-estradiol (E2) and spironolactone pellets (MH), or dose matched placebo pellets (MP). Female mice were implanted with a testosterone (T) pellet (FH), or a dose-matched placebo pellet (FP). Untreated male (MQ) and female (FQ) mice were used as comparators. During the hormonal acclimation, 24 hour urine was collected, and body composition, glomerular filtration rate (GFR), and plasma creatinine (PCr) were measured. After 11 weeks of acclimation, mice were euthanized, and tissues were collected. Plasma was collected at euthanasia.

Results: MH had higher E2 level compared to MQ, although T levels were not different. FH did not have different E or T levels compared to FP or FQ. Percent lean and fat mass did not differ between groups. IL2 in MH were decreased compared to MP, but no differences were noted in the female groups. IL5 in FH were slightly lower than FP and FQ, although significance was not reached. In MH, bone mineral density sharply increased; no significant changes were noted in other groups. No differences in PCr were noted between groups, although all groups experience a sharp increase during the acclimation, which resolved. GFR remained stable across time. Kidney expression of KIM-1 and NGAL was not detected in any groups. At 10 weeks of hormonal acclimation, an increase in urine creatinine was noted in both MH and FH.

Conclusions: Administration of exogenous sex hormones in a murine model does not independently cause kidney damage. Although a spike in PCr was noted, GFR remained stable, which may indicate an extra-renal cause. Slight modulations in cytokine levels may indicate changes in an inflammatory milieu that would be further reflected with kidney injury. Although FH did not have significantly different T levels than FP and FQ, differences in other parameters, including cytokine expression and urine creatinine, may indicate that T administration may have an effect on parameters affecting kidney function.

Funding: NIDDK Support

FR-OR95

Assessing Kidney Function in Pregnancy

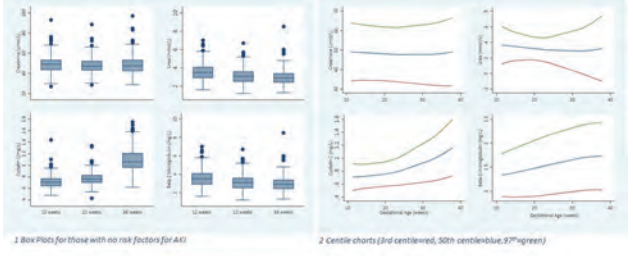
Katherine R. Clark,[1] Kathryn Dalrymple,[1] Olivia Snowball,[2] Hannah R. Judah,[2,3] Argyro Syngelaki,[1,3] Kypros Nicolaides,[2,3] Kate Bramham.[1,2] *[1]King's College London, London, United Kingdom; [2]King's College Hospital, London, United Kingdom; [3]Fetal Medicine Foundation, London, United Kingdom*.

Background: Deterioration in maternal kidney function is associated with morbidity and mortality for mother and baby. This study aims to define normal centile ranges in pregnancy for serum creatinine, urea, cystatin c and beta-2-microglobulin.

Methods: Prospective cohort study of women at two UK hospitals(2018-2021). Inclusion criteria:6+ weeks gestation, singleton pregnancy. Exclusion criteria:renal disease; previous AKI; chronic hypertension; diabetes; connective tissues disease; thrombophilia; cardiovascular disease. Venous serum samples taken at routine ultrasound scans. Participants who developed a risk factor for AKI were excluded from the centiles. Xrigls command was used in Stata 18.0 to allow reference interval estimation using generalized least squares.

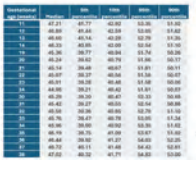
Results: 739 participants. 644(87.1) had an uncomplicated pregnancy and delivery, 95(12.9%) developed a risk for AKI(T.1). Cystatin C had greater variability with increasing gestation even in those with no risk factors(F.1). Figure 2 shows centile charts for all biomarkers for those with no AKI risk factors with detail provided for serum creatinine(F.3).

Conclusions: In this ethnically diverse study creatinine values were lower than reported with >63umol/l at any gestation above the 97thcentile. Cystatin C and beta-2-microglobulin vary increasingly towards term, even in women with no AKI risk factors thus are unlikely to be useful biomarkers.



1 Box Plots for those with no risk factors for AKI

2 Centile charts (3rd centile=red, 50th centile=blue, 97th=green)



3 Median and centile values for creatinine

Table 1 Demographics

Characteristics	No Risk Factors N=644	New AKI Risk Factor N=95
Maternal age (years)	33.0(4.8)	32.4(5.4)
Body Mass Index	24.7(5.2)	25.9(5.4)
Ethnicity		
Black	122(18.9)	24 (25.2)
White	446(69.3)	61 (64.2)
South Asian	20(3.1)	4 (4.2)
East Asian	19(3.0)	5 (6.3)
Mixed	37(5.2)	0(0.0)
Parity		
Nulliparous	378(8.7)	66(69.5)
Multiparous	266(41.3)	29(30.5)
Smoking	10(2.3)	3(3.2)
Index Pregnancy		
Assisted Conception	18(2.8)	4(4.2)
First Trimester Blood Pressure (mmHg)		
SBP	116.7(9.4)	118.0 (11.0)
DBP	70.6(6.8)	72.4(8.7)
Hypertension		
Pregnancy Induced Hypertension	0(0.0)	16(17.8)
Pre-eclampsia	0(0.0)	15(16.7)
Gestational diabetes	0(0.0)	31(34.4)
Pregnancy Outcome		
Livebirth	644(100.0)	88(92.6)
Stillbirth	0(0.0)	1(1.1)
Neonatal death	0(0.0)	1(1.1)
Outcome not available	0(0.0)	5(5.3)
Gestational Age (weeks)	40.1(1.1)	37.8(2.8)
Neonatal unit admission	14(3.2)	16(17.8)
Birth weight (g)	3447.3(416.9)	2875.7(814.9)
Apgar score below 7		
5min	3(0.7)	4(4.2)
10min	1(0.2)	2(2.1)

FR-OR96

More than 16,000 Transplant Recipients and Previous Living Donors at Risk for Poor Access to Reproductive Health Care

Elizabeth M. Hendren, Gal Av-Gay, Matthew J. Kadatz, John S. Gill. *The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada*.

Background: It is imperative that kidney transplant recipients (KTR) and living kidney donors (LKD) have access to reproductive health care. Since the overturning of Roe v Wade in 2022, 14 states have banned abortion in all or almost all circumstances and 7 states have significantly restricted access (between 6-18 weeks). It is unknown how many KTR and LKD are affected by these policies.

Methods: We characterized the demographics of female KTR and LKD 18-45 years old in the United States as of May 1, 2024 from the OPTN dataset. Because policies are frequently changing, patients were stratified into 3 categories based on their home state policy for abortion as of May 1, 2024. P-values are calculated from Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables.

Results: Overall 9,001/21,673 KTR (41%) and 7,476/18,988 LKD (39%) live in states with either a total or partial restriction on abortion. KTR who live in areas with less access to reproductive care were also more likely to have additional risk factors for pregnancy complication including Black race, high BMI, and diabetes as a cause of kidney failure and were less likely to have received a living donor transplant (Table 1).

Conclusions: A significant proportion of KTR and LKD live in areas with decreased access to reproductive health care. Medical comorbidities and demographic risk factors can exacerbate the pre-existing pregnancy risk. These findings quantify the magnitude of the health challenge created by recent changes in state policies and may be useful in planning for alternative strategies and advocacy efforts to ensure KTR and past LKD receive access to essential reproductive health care.

Demographics of Female KTR by abortion access in home state

	Abortion Banned (1) n=5,333 (24.6%)	Limited Abortion Access (2) n=3,688 (17%)	Legal Access to Abortion n=12,652 (58.4%)	p-value
Recipient Current Age Mean (SD)	36.4 (30.5 - 41.3)	36.8 (30.7 - 41.4)	36.6 (30.9 - 41.3)	0.31
Recipient Race n (%)	Black 1,683 (31.6%) White 1,980 (37.1%) Other 1,670 (31.3%)	Black 1,362 (36.9%) White 1,280 (34.7%) Other 1,046 (28.4%)	Black 2,656 (21.0%) White 4,985 (39.4%) Other 5,011 (39.6%)	< 0.0001
Recipient BMI Mean (SD)	26.4 (±7.1)	25.9 (±6.5)	25.3 (±6.6)	< 0.0001
Insurance N (%)	Private 1,843 (34.6%) Public 3,456 (64.8%)	Private 1,262 (34.2%) Public 2,411 (65.4%)	Private 3,131 (40.6%) Public 7,462 (59.0%)	< 0.0001
Diabetes as cause of ESRD N (%)	531 (10.0%)	290 (7.9%)	949 (7.5%)	<0.0001
Transplant Vintage (years) Mean (SD)	8.1 (±5.3)	7.8 (±5.4)	8.5 (±5.5)	< 0.0001
Transplant from Living Kidney Donor N (%)	1,885 (35.3%)	1,240 (33.6%)	5,625 (44.5%)	< 0.0001

1. States where abortion is illegal in all or most circumstances AL, AR, ID, IN, KY, LA, MS, MO, ND, OK, SD, TN, TX, WV
2. States with restrictions on abortion (6-18 weeks) AZ, FL, GA, NE, NC, SC, UT

FR-OR97

The Contraceptive Care Gap: Women with CKD Report Lower Rates of Contraception Use

Sarah Rokaw, Kathryn Kompa, Cancan Zhang, Kenneth J. Mukamal.
Beth Israel Deaconess Medical Center, Boston, MA.

Background: Pregnancy in patients with chronic kidney disease (CKD) is associated with complications, including low birth weight, gestational diabetes, pre-eclampsia, and pre-term birth. Clinical practice guidelines recommend contraception counseling for women with CKD of childbearing age. Furthermore, given the potential risk of complications, reproductive care should be prioritized when caring for young women with CKD. Currently, large-scale population data quantifying rates of contraception usage among women with CKD are lacking.

Methods: We utilized the Behavioral Risk Factor Surveillance System in 14 states and territories in 2017, 2019, and 2022. For women aged 21-49, we extracted data on self-reported diagnosis of CKD, contraception use, and method of contraception use. We adjusted for age, sex, race/ethnicity, US census region, reported access to a primary physician, and educational level using a log-binomial regression model. We subsequently examined factors associated with contraception use among women with CKD and explored the methods used.

Results: Women aged 21-49 with CKD were less likely to report contraception usage than women without CKD, even when adjusting for confounders (RR 0.88, 95% CI [0.80,0.97], p=0.01). This difference did not meaningfully vary over the 5-year period of our analysis (p=0.35). Among analyzed co-variates, the only factor associated with contraception use among women with CKD was age, with younger women more likely to use contraception (p<0.001). The most used methods of contraception among women with CKD were barrier methods or topical spermicide (29.1%), female or male surgical sterilization (20.7%), and hormonal methods including contraceptive pills, transdermal patches, hormonal rings, and the Depo-Provera injection (20.0%).

Conclusions: Despite substantially higher rates of pregnancy-related complications, rates of reported contraception usage were significantly lower among women of childbearing age with CKD as compared to women without CKD. Likelihood of contraception usage declined with age, even in this age group. Assuring access to and counseling about contraception among women with CKD should be a priority for physicians treating these patients.

FR-OR98

Cellular Senescence as an Underlying Mechanism of Kidney Injury in a Mouse Model of Preeclampsia

Sonja Suvakov, Xiaoyan Li, Jennet Hatamova, Vladimir Dokic, Paul Gavrilovici, Xiaogang Li, Vesna D. Garovic. *Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN.*

Background: Preeclampsia (PE) is a hypertensive complication of pregnancy often associated with kidney injury which is characterized by proteinuria and podocyturia. The mechanism leading to kidney injury in PE, however, is poorly understood. Our recently published data indicate the presence of cellular senescence in women with PE. We hypothesized that cellular senescence is present in the kidneys of mice (IL-10KO mouse model of PE), and that senescence-associated genes are upregulated in podocytes and endothelial cells of kidneys in these animals.

Methods: We utilized the mouse model where PE is induced by i.p. injection of human PE sera into 10–12-week-old animals. PE is observed around the 18th gestational day when the animals are euthanized. Regular pregnant mice with no PE serum injected (PG) served as a control group. We measured blood pressure, proteinuria, urinary alpha Klotho (α-Klotho), and the expressions of senescence-associated genes in the kidneys (n=4-5 per group). To identify which senescence-associated genes are affected in podocytes and endothelial cells, which are injured in preeclampsia, we performed kidney single-cell RNA sequencing (scRNAseq) in the PG (n=2) and PE groups (n=3).

Results: Significant increase in blood pressure and proteinuria was observed in PE mice. Urinary α-Klotho, an anti-aging marker, was significantly decreased in PE mice compared to the PG group. Significant decrease in α-Klotho was observed in PE mice upon injection of PE serum compared to the values before injection. Kidneys of PE mice had increased expressions of senescence-associated genes p16, il6, and pai1. Using scRNAseq we clustered 15 transcriptionally different kidney cell types based on cell type-specific marker genes. Among those cells we identified five subclusters of endothelial cells and four of podocytes. We compared and identified 7 differentially expressed genes associated with senescence in endothelial cells (Ccl5, Csf2rb, Cxcl1, Cxcl10, Cxcl2, Igfbp5, and Il15) and 10 in podocytes (Angpt1, Areg, C3, Ccl7, Cxcl2, Gem, Il15, Nrg1, Pappa, Tnf).

Conclusions: These results indicate that cellular senescence could represent a potential mechanism of kidney injury in preeclampsia.

FR-OR99

Sex Differences in Kidney Prognosis in Patients with ADPKD: Attribute-Based Medicine (ABM) Insights

Hiroshi Kataoka, Toshio Mochizuki, Shun Manabe, Yusuke Ushio, Momoko Seki, Ken Tsuchiya, Kosaku Nitta, Junichi Hoshino. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Background: Recently, the importance of attribute-based medicine has been emphasized. We aimed to examine the influence of sex differences to kidney disease progression of autosomal dominant polycystic kidney disease (ADPKD).

Methods: We enrolled 553 ADPKD patients who were not undergoing renal replacement therapy, with a median age of 43 years, an estimated glomerular filtration rate of 55.9 mL/min/1.73 m^2, and a total kidney volume of 1335.4 mL. The renal outcome, defined as a 50% reduction in estimated glomerular filtration rate or initiation of renal replacement therapy, was assessed using Cox regression analysis. Factors influencing kidney prognosis in ADPKD patients were compared based on sex categories (men or women).

Results: Over a median 9.1-year follow-up, renal outcomes were assessed in 189 patients. Multivariate Cox analysis identified several significant risk factors for kidney disease progression: female gender (HR=1.56), age (HR for 10-year increase=0.63), eGFR (HR for 10 mL/min/1.73 m^2 increase=0.48), urinary protein excretion (grades 0–3) (HR=2.05), total kidney volume (HR for 100 ml increase=1.02), and hypertension (HR=1.48). Significantly, interactions were observed between gender and urinary protein excretion (grades 0–3) (P=0.0158), hypertension (P=0.0065), and higher pulse pressure (≥50mmHg) (P=0.0117) concerning kidney disease progression. Subgroup analysis by gender clarified age and eGFR's association with kidney prognosis across both sub-cohorts. Conversely, hypertension (HR=2.47), pulse pressure ≥50 mmHg (HR=2.28), and urinary protein (grades 0–3) (HR=3.11) emerged as factors associated with kidney prognosis in females, whereas hypertension (HR=0.82), pulse pressure ≥50 mmHg (HR=0.90), and urinary protein (grades 0–3) (HR=1.62) were less associated with renal outcomes in males.

Conclusions: Female sex was a factor for poor renal prognosis in patients with ADPKD. Hypertension, high pulse pressure, and increased proteinuria were significantly worse factors for renal prognosis in women than in men. In recent years, treatments and research that are tailored to patient attributes have been proposed, but in the case of ADPKD patients, it is necessary to change treatment policies depending on sex attributes.

Funding: Government Support - Non-U.S.

SA-OR01

Understanding Pathophysiology of Acute Interstitial Nephritis through Spatial Characterization of Cell-Cell Interactions Using Imaging Mass Cytometry in a Human Biopsy Cohort

Megan L. Baker,[1,2] Vijayakumar R. Kakade,[1] Tifanny Budiman,[1] Marlene Weiss,[1,4] Ashish Shelar,[3] Dennis G. Moledina,[1] Lloyd G. Cantley.[1]
[1]Yale University School of Medicine, New Haven, CT; [2]Yale University Graduate School of Arts and Sciences, New Haven, CT; [3]Yale University, New Haven, CT; [4]Charite Universitatsmedizin Berlin, Berlin, Germany.

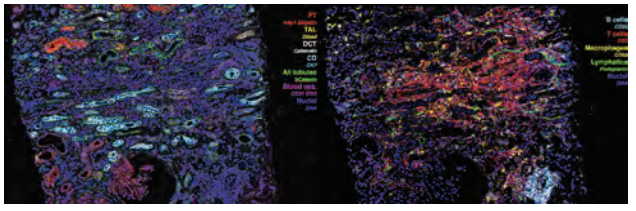
Background: Kidney damage in AIN is believed to result from immune-mediated tubular injury, with ongoing inflammation leading to fibrosis and progression to CKD. Delineation of the immune cell signature and corresponding tubular and vascular cell responses in AIN should lead to more targeted therapies.

Methods: Adjudicated human kidney biopsy tissues with AIN(13), ATI(13), DKD(7), and healthy reference tissue(13) underwent imaging mass cytometry using 34 customized metal conjugated antibodies (Fig1). Cell identities and activation states were defined in spatial context. A customized deep-learning-based algorithm (Mesmer) was used for segmentation. Downstream data analyses used open-source analytic pipelines *steinbock* and *imcRtools*.

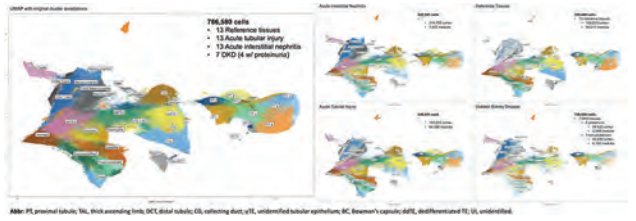
Results: Across samples 786,580 cells were analyzed. Preliminary findings show 37 cell clusters with 17 primary cell types (Fig2). Immune populations are increased in AIN and ATI compared to reference. AIN showed the largest increase in CD4+ T cells (8.6%, 2.5% ATI, 1.6% ref, p<0.0001). Lymphatics were expanded in AIN and ATI (both 1.1%) above reference tissues(0.5%) and colocalized with lymphocyte enrichment. Mast cells also show enrichment with injury (2.4% AIN, 1.3% ATI, 0.2% ref, p<0.0001).

Conclusions: Our initial analysis is supportive of the role of CD4+ T cells, and perhaps mast cells and lymphatics, in the pathophysiology of AIN. Subsequent analyses, including subclustering for improved phenotyping, cell quantification by tissue area, neighborhood and interaction analyses, and integration with clinical data, are underway and expected to result in the identification of specific cell-cell interactions which will advance our understanding of AIN.

Funding: NIDDK Support



Raw IMC output from 1 AIN section pseudocolored by resident cell markers(L) and immune cell markers(R).



Initial UMAP and initial cell phenotypes across tissue types.

SA-OR02

Stat5b SNP Reduces Sexual Dimorphism of Renal Gene Expression and Protects against Acute Injury

Jakub Jankowski, Hye kyung Lee, Lothar Hennighausen. *National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.*

Background: The extent of the single nucleotide polymorphisms' (SNP) impact on disease vulnerability is not well understood. Two *Stat5b* Y665 SNPs, Y665F and Y665H, have been found by genome sequencing of leukemia patients. They are thought to respectively increase or attenuate STAT5b activity but have not been confirmed as a disease driver.

Methods: Using base editing, we developed mice mimicking the two SNPs and investigated their phenotype. We saw an increased infiltration of CD3+ cells in the kidney tissue of the Y665F strain using immunohistochemistry, suggesting increased vulnerability to development of inflammation. To investigate, we used 30′ bilateral kidney ischemia-reperfusion injury (IRI) model and measured serum creatinine after 24 hours. To elucidate involvement of JAK/STAT pathway, we performed kidney RNA-seq analysis in WT, Y665F and Y665H strains, including male and female mice, before and after IRI.

Results: Y665F males had lower creatinine levels than controls (mean 0.66 vs 1.23, p<0.001, n=8), suggesting protection against IRI. In contrast Y665F females displayed no statistically significant difference in plasma creatinine compared to control (0.79 vs 1.04 respectively, n=5). Similar effect was absent in Y665H mice, indicating protective effect of STAT5b activation in an IRI setting. RNA-seq revealed 582 deregulated genes (DEGs) between male WT and Y665F mice at the baseline, but no statistically significant DEGs were found in females. After IRI, 1801 DEGs were found in male mice, but only six in females. Similar number of sexually dimorphic genes is present in WT and Y665F strains at the baseline (1269 vs 1290 respectively), but not after injury (1790 vs 733). Y665F DEGs include genes involved in JAK/STAT signaling and linked to kidney health and development such as *Il15*, *Xdh*, *Sepp1* or *Prickle1*, hinting at potential mechanisms of protection. We did not observe differences in *Stat5b* mRNA nor STAT5b and CD3 immunohistochemical staining after injury in WT or Y665F mice, suggesting long-term changes in renal gene transcription programming rather than acutely altered injury response.

Conclusions: Those results strongly indicate that *Stat5b* Y665 SNP has a sexually dimorphic, renoprotective effect. This work highlights the far-reaching effects of a singular SNPs and lays foundation of personalized medicine approaches incorporating patient's genome.

Funding: NIDDK Support

SA-OR03

WWP2 Deletion Aggravates AKI by Targeting the CDC20/Autophagy Axis

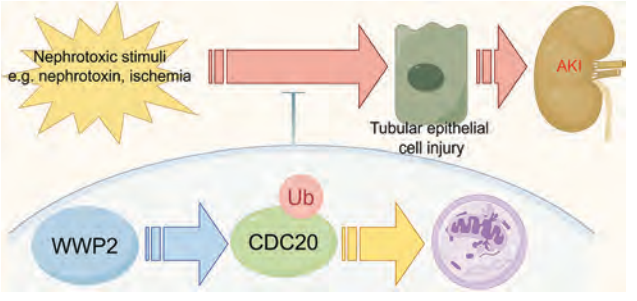
Ran You,[1,2] Yanwei Li,[1,3] Yuteng Jiang,[1,3] Zhanjun Jia,[1,2] Aihua Zhang.[1,2] *[1]Children's Hospital of Nanjing Medical University, Nanjing, China; [2]Nanjing Medical University, Nanjing, China; [3]Southeast University, Nanjing, China.*

Background: Acute kidney injury (AKI) is associated with high morbidity and mortality rates. The molecular mechanisms underlying AKI are currently being extensively investigated. WWP2 is an E3 ligase that regulates cell proliferation and differentiation. Whether WWP2 plays a regulatory role in AKI remains to be elucidated. We aimed to investigate the implication of WWP2 in AKI and its underlying mechanism in the present study.

Methods: We utilized renal tissues from patients with AKI and established AKI models in global or tubule-specific knockout (cKO) mice strains to study WWP2's implication in AKI. We also systemically analyzed ubiquitylation omics and proteomics to decipher the underlying mechanism.

Results: We found that WWP2 expression significantly increased in the tubules of kidneys with AKI. Global or tubule-specific knockout of WWP2 significantly aggravated renal dysfunction and tubular injury in AKI kidneys, whereas WWP2 overexpression significantly protected tubular epithelial cells against cisplatin. WWP2 deficiency profoundly affected autophagy in AKI kidneys. Further analysis with ubiquitylation omics, quantitative proteomics and experimental validation suggested that WWP2 mediated poly-ubiquitylation of CDC20, a negative regulator of autophagy. CDC20 was significantly decreased in AKI kidneys, and selective inhibiting CDC20 with apcin profoundly alleviated renal dysfunction and tubular injury in the cisplatin model with or without WWP2 cKO, indicating that CDC20 may serve as a downstream target of WWP2 in AKI. Inhibiting autophagy with 3-methyladenine blocked apcin's protection against cisplatin-induced renal tubular cell injury. Activating autophagy by rapamycin significantly protected against cisplatin-induced AKI in WWP2 cKO mice, whereas inhibiting autophagy by 3-methyladenine further aggravated apoptosis in cisplatin-exposed WWP2 KO cells.

Conclusions: Taken together, our data indicated that the WWP2/CDC20/autophagy may be an essential intrinsic protective mechanism against AKI. Further activating WWP2 or inhibiting CDC20 may be novel therapeutic strategies for AKI.



SA-OR04

RNA Polymerase II Subunit POLR2A/RPB1 Upregulation Is Detrimental in Kidney Injury

Sian E. Piret, Samaneh DiMartino, Maanasa S. Hanubal, Jiakang Wang, Tej Bahadur, Nehaben A. Gujarati, Sandeep K. Mallipattu. *Stony Brook University Renaissance School of Medicine, Stony Brook, NY.*

Background: Proximal tubule (PT) injury is a major factor in the severity of acute kidney injury (AKI) and transition to fibrosis. Our single nuclear RNA-sequencing (snRNA-seq) in a PT-specific nephrotoxin [aristolochic acid I (AAI)]-induced AKI in mice revealed an injured PT cluster with high enrichment of *Polr2a*, encoding RPB1, the largest subunit of RNA polymerase II (RNAPII). Our aim was to study the role of PT-specific RPB1 in AKI.

Methods: Immunofluorescence (IF) for RPB1 was undertaken in mice after multiple 2mg/kg AAI injections, 7mg/kg repeated low dose cisplatin (RLDC) for 4 weeks, or unilateral ureteral obstruction (UUO) for 3 or 7 days, or in human AA-exposed chronic kidney disease (CKD) patient samples, with PT brush border counterstaining. HK-2 cells were treated with DMSO or 25μM AAI and scrambled or *POLR2A* siRNA, with quantification of cell number (CyQuant assay); *IL6*, *CTGF*, and *CDKN1A* mRNA expression; and IF for vimentin (dedifferentiation) or gH2A.X (DNA damage) at 48 hours. Single cell ATAC-seq was undertaken in mice after one dose of AAI.

Results: Over a series of 4 AAI injections, despite PT loss, RPB1-positive (RPB1+) tubular nuclei accumulated, and were associated with dedifferentiated PT. This was replicated in mice after RLDC and UUO. Knockdown of *POLR2A* in HK-2 cells treated with AAI resulted in increased cell death, but the remaining cells expressed less *IL6* and *CTGF*, were less dedifferentiated, had less DNA damage, and more normal cell cycle,

with reduced *CDKN1A* expression. ATAC-seq indicated a new region of open chromatin in *Polr2a* intron 1 in the injured PT cluster, containing AP-1 and Krüppel-like factor 6 (KLF6) transcription factor binding sites. Trajectory and RNA velocity analysis showed that *Klf6* upregulation preceded *Polr2a* induction, suggesting regulation of *Polr2a* by KLF6. RPB1 remained high in the fibrotic phase after AAI, and mice overexpressing human KLF6 had more RPB1+ nuclei than control mice. Dedifferentiated PT in human AA-exposed CKD patients also had RPB1+ nuclei.

Conclusions: To date, this is first study to show that sustained high RPB1 expression after AKI may trap PT cells in a dedifferentiated state, and clearance of cells by *POLR2A* knockdown may be beneficial to attenuate the progression of AKI to CKD.

Funding: NIDDK Support

SA-OR05

Endothelial Prolyl Hydroxylase 3 (PHD3) Regulates Post-Ischemic Kidney Injury Repair and Inflammation

Rajni Sharma, Ratnakar Tiwari, Gabriella Borkowski, James O'Sullivan, Pinelopi P. Kapitsinou. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Endothelial cells (EC) are prime targets for ischemia reperfusion injury (IRI) but the role of endothelial oxygen sensing in IRI remains poorly defined. Recently, we showed that post-ischemic concurrent inactivation of endothelial Phd1, Phd2 and Phd3 but not Phd2 alone promotes maladaptive kidney repair. Analysis of human and mouse scRNA-seq data suggested a potential role for the Phd1 and/or Phd3 isoforms in renal endothelial oxygen sensing. Here, we investigated the role of endothelial Phd1 and Phd3 in kidney repair following IRI.

Methods: Post-ischemic inactivation of Phd1, Phd3 and Arnt (HIFβ) in ECs was achieved by the Cdh5(PAC)CreER. Analysis was performed on day 14 post-unilateral IRI. To inactivate PHD3 and ARNT genes in-vitro in ECs we used siRNA approach, while overexpression of PHD3 was achieved by lentivirus-based transduction. IFNγ was used to induce a pro-inflammatory response in-vitro.

Results: Post-ischemic inactivation of endothelial Phd1 failed to alter post-IRI kidney repair, however, inactivation of endothelial Phd3 following IRI exacerbated kidney damage and fibrosis as indicated by significantly increased *Kim1*, *Tgf*β, and *Acta2* transcripts as well as enhanced collagen deposition and macrophage infiltration (n=5-6; $p<0.05$), compared to *Cre*$^-$ controls. A cytokine array detected increase in multiple cytokines in the injured mutant kidney. Notably, post-ischemic concurrent deletion of endothelial Phd3 and Arnt restored kidney damage as shown by mRNA expression of pro-fibrotic genes and collagen deposition (n=6-7, $p<0.05$). In vitro, PHD3 knockdown enhanced IFNγ induced pro-inflammatory responses in EC based on mRNA expression of *ICAM1*, *VCAM1*, and other IFNγ responsive genes (n=3, $p<0.05$). Concurrent silencing of endothelial PHD3 and ARNT rescued the pro-inflammatory activation of ECs by IFNγ stimulation. Importantly, lentiviral PHD3 overexpression suppressed EC activation by IFNγ.

Conclusions: Endothelial inactivation of PHD3 promotes post-ischemic AKI to CKD transition in a HIF dependent manner. Our studies a) identify PHD3 as a crucial regulator of post-ischemic kidney repair through mechanisms that involve regulation of IFNγ derived EC inflammation and b) have critical implications for the potential application of non-selective PHD inhibitors in ischemic AKI.

Funding: NIDDK Support

SA-OR06

MARCKS Upregulation in Macrophage Reprogramming as a Therapeutic Target in Kidney Injury and Fibrosis

Ssu-Wei Hsu,[1] So-Yi Chang,[1] Purva Bhatia,[1] Vincent Kao,[2] Wen-Hsien Chang,[1] Andrew I. Chin,[1] Ching-Hsien Chen.[1] *[1]University of California Davis, Davis, CA; [2]Davis Senior High School, Davis, CA.*

Background: Acute kidney injury (AKI) is characterized by sudden, reversible kidney dysfunction, with incomplete recovery potentially leading to chronic kidney injury. Macrophage infiltration and polarization are crucial in AKI recovery, yet their roles in injury development and progression remain unclear. This study aimed to identify novel therapeutic targets within pathogenic macrophages during kidney injury and resolution.

Methods: We analyzed macrophage transcriptomes to pinpoint regulators of AKI, confirming upregulation of MARCKS in macrophages within injured kidneys. To investigate the contributions of MARCKS to macrophage-mediated inflammation and fibrosis, we conducted in vitro, ex vivo, and in vivo studies using primary macrophages, precision-cut kidney slices (PCKS), and cisplatin-exposed mice with macrophage-specific MARCKS deletion.

Results: Mice with macrophage-specific Marcks deletion exhibited improved kidney function and increased survival in a severe AKI model. Furthermore, macrophage Marcks deletion conferred protection against renal fibrosis in mice with cisplatin-induced chronic kidney disease (CKD). Notably, we observed reduced macrophage infiltration and activation within the injured kidneys in both mouse models. Bone marrow–derived monocytes (BMDMs) from Marcks-knockout mice showed downregulated MARCKS phosphorylation, podosome formation, and cell motility. Co-culturing these BMDMs with injured kidney slices led to diminished chemotactic responses to macrophage chemoattractants, decreased activation of PI3K/AKT pathways, and increased apoptosis markers. PCKS derived from macrophage-specific MARCKS-knockout mice displayed fewer fibrotic lesions, less collagen deposition, and reduced pro-fibrotic macrophage presence following exposure to fibrosis inducers. Pharmacological inhibition of MARCKS activity in macrophages not only downregulated pathogenic macrophages but also reduced serum creatinine and blood urea nitrogen levels in both cisplatin-induced AKI and AKI-to-CKD models.

Conclusions: Our findings highlight the critical role of MARCKS and its phosphorylation in driving kidney fibrosis by reprogramming macrophages and modulating their pathogenic activities. This suggests that targeting MARCKS could be an effective therapeutic strategy for managing cisplatin-induced kidney diseases.

Funding: Other NIH Support - R01HL146802

SA-OR07

Cell-Intrinsic C3 and Complement Factor B from Proximal Tubular Epithelial Cells Drive Post-Injury Kidney Fibrosis

Tilo Freiwald,[1,2] Md Tajmul,[3] Jorge L. Trujillo-Ochoa,[3] Daniel Chauss,[3] Nardos T. Cheru,[10] Dhaneshwar Kumar,[3] Baktiar O. Karim,[4] Julius F. Jäger,[1,2] Yubing Guo,[1,2] Maja Gunkel,[1,2] Claudia Kemper,[5] Tobias B. Huber,[1,2] Thorsten Wiech,[6] Martin Kolev,[7] Majid Kazemian,[8] Didier Portilla,[9] Behdad Afzali.[3] Immunoregulation Section. *[1]University Medical Center Hamburg-Eppendorf, III. Department of Medicine, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Hamburg Center for Kidney Health (HCKH), Hamburg, Germany; [3]Immunoregulation Section, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, Bethesda, MD; [4]Molecular Histopathology Laboratory, Frederick National Laboratory, Leidos Biomedical Research, Frederick, MD; [5]Complement and Inflammation Research Section (CIRS), National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda, MD; [6]Section of Nephropathology, Institute of Pathology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [7]Apellis Pharmaceuticals Inc, Waltham, MA; [8]Departments of Biochemistry and Computer Science, Purdue University, West Lafayette, IN; [9]Division of Nephrology and Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia, Charlottesville, VA; [10]Yale University School of Medicine, New Haven, CT.*

Background: Local complement (C') deposition is strongly associated with kidney diseases. Current therapeutic efforts target plasma-circulating C', but C' components are also locally produced within tissues, where they regulate essential (patho) physiological functions, as we have previously shown in COVID-19. The role of C' made by kidney cells remains under-explored. We hypothesized that tubular epithelial cell-derived intrinsic C' regulates the local inflammatory milieu and influences outcomes.

Methods: We analyzed existing and *de novo* bulk and single-cell high-throughput data from multiple acute kidney injury (AKI) models and investigated transcription factor binding genome-wide. Mechanistic studies utilized genome editing, cell-permeable CFB inhibitors, mass spectrometry, reporter and tissue-specific gene knockout mice, metabolic profiling, histological and confocal analyses.

Results: Multiple AKI models, particularly folic acid nephropathy (FAN), showed enriched C' gene transcription. Single-nucleus RNA sequencing of FAN identified co-expression of *C3* and Factor B (*Cfb*) in Vcam1$^+$ kidney tubules, which emerged post-injury and interacted with immune cells via C3a-C3AR1 and integrins. IL-1β was the critical inducer of *C3* and *Cfb*. *Il1r1* deletion reduced *C3* and *Cfb* expression in response to injury. AP-1 and NF-κB downstream of IL-1β, were confirmed as transactivators through SCENIC-derived regulon activity, CUT&RUN, and CRISPR studies, showing binding at *C3* and *Cfb*. Confocal imaging revealed C3 trafficking to the ER, Golgi, endosomes, lysosomes, and mitochondria, co-localizing with CFB. Conditional deletion of *C3* in proximal tubular epithelial cells and chemical intracellular CFB inhibition reduced glycolysis and oxidative phosphorylation, consistent with mitochondrial localization of C3. C3 deletion also reduced fibrosis scores in FAN mice. In patients, *C3* and *CFB* correlated with each other across glomerular diseases and negatively with eGFR.

Conclusions: These data elucidate the transcriptional and post-translational regulation and subcellular trafficking of C3 within PTECs, offering therapeutic implications for targeting the intracellular complement system in inflammatory kidney diseases.

Funding: NIDDK Support, Other NIH Support - NHLBI, NCI, Commercial Support - Apellis Pharmaceuticals, Government Support - Non-U.S.

SA-OR08

Circulating Osteopontin (OPN) Released by Kidney Injury Causes Acute and Chronic Hippocampal Neuroinflammation and Behavioral Dysfunction

Andreas Herrlich, Poornima Dilhani Ekanayake Weerasinghe Mudiyanselage, Liang Ning, Rupal Ojha, Yohei Komaru, Anusha Suresh, Stuart Friess, Marta Celorrio Navarro. *Washington University in St Louis School of Medicine, St Louis, MO.*

Background: Acute kidney injury (AKI) is very common in hospitalized patients. 50% of AKI patients show persistent neurocognitive dysfunction long after AKI is resolved and 7% of patients develop dementia within 2 years after AKI. While the pathophysiological mechanism(s) of this kidney-brain crosstalk is largely unknown, limited studies have implicated neuroinflammation as a possible cause.

Methods: AKI was induced in WT and OPN-KI mice using bilateral ischemia reperfusion injury. At different survival points after AKI mice were tested for neurocognitive function by using a battery of behavioral tests. Hippocampal inflammatory changes were assessed using flow cytometry and histological analysis.

Results: Here we show that monocytes infiltrate the hippocampus acutely and accumulate chronically long after AKI resolution in parallel with neurocognitive dysfunction. Acutely after AKI in wt mice we observed reduced exploration in the elevated plus maze test, and chronically at 1 + 6 months after AKI we observed lower recall memory to cue/context and reduced spatial learning, linking hippocampal neuroinflammation to neurocognitive dysfunction. AKI induced acute and chronic elevations of kidney and serum levels of the innate immune system activating molecule osteopontin (OPN). Although we were able to detect a small trend to increased OPN protein levels in the hippocampus after AKI, hippocampal OPN mRNA expression was not significantly elevated, suggesting either deposition from the circulation or production by infiltrating monocytes. OPN acts via its thrombin cleavage products. OPN-KI mice with an OPN mutation rendering it uncleavable by thrombin were protected acutely and chronically against monocytic neuroinflammation and neurocognitive dysfunction after AKI. OPN injection into OPN-KO mice with AKI induced hippocampal monocyte accumulation and neurocognitive dysfunction, linking circulating osteopontin released from the injured kidney to neurocognitive dysfunction after AKI.

Conclusions: Together with our previous findings that linked kidney-released OPN to kidney-lung crosstalk, our kidney-brain data highlight the involvement of this kidney-released soluble mediator in driving secondary brain complications after AKI.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR09

Anti-inflammatory Effects of Vagus Nerve Stimulation Are Mediated by the Notch Signaling Pathway during Sepsis-Associated AKI

Shuhei Kuwabara, Hiro Inoue, William Nash, Junlan Yao, Shuqiu Zheng, Mark D. Okusa. *University of Virginia, Charlottesville, VA.*

Background: Activating the cholinergic anti-inflammatory pathway (CAP), a neuroimmune circuit, is a novel strategy for the treatment of acute kidney injury (AKI). The CAP is initiated by vagus nerve stimulation (VNS) and subsequent activation of α7-nicotinic acetylcholine receptor (α7nAChR) on macrophages (MΦ), leading to suppression of pro-inflammatory cytokine production. Our RNA-Seq analysis revealed that an increase in hairy and enhancer of split 1 (Hes1) in MΦ contributes to the kidney protective effects of CAP. Hes1 is a transcriptional factor and is involved in the Notch signaling pathway. However, a direct relationship between the CAP and Notch signaling has been unclear. In this study, we focused on Notch signaling in MΦ to unravel the detailed molecular mechanism of CAP and to determine the utility of Notch signaling in ameliorating AKI.

Methods: We used a mouse lipopolysaccharide (LPS)-induced AKI model. MΦ-specific *Notch2* KO (*Cx3cr1Cre; Notch2$^{fl/fl}$*) or WT mice were subjected to VNS 24 hours before LPS administration. The expression of cytokines and Notch components in the spleen and kidney injury was assessed. Mouse peritoneal MΦ were also used for *in vitro* experiments to examine the relationship between α7nAChR and Notch signaling.

Results: VNS suppressed an LPS-induced increase in spleen size and the levels of pro-inflammatory cytokines and chemokines such as Ccl2, M-CSF, and G-CSF (regulators of MΦ and neutrophil populations) in splenic MΦ. In the kidneys, LPS-induced inflammation including MΦ and neutrophil infiltration, and histological damage were also attenuated by VNS. These events were accompanied by an increase in Notch2 and *Hes1* expression in splenic MΦ. On the other hand, in MΦ-specific *Notch2* KO mice, the anti-inflammatory effects of VNS were attenuated in both the spleen and kidneys. We further found that during LPS treatment, chemical stimulation of α7nAChR by GTS-21 reduced Ccl2 release and upregulated *Hes1* expression in peritoneal MΦ, indicating that Notch signaling might be activated downstream of α7nAChR to dampen inflammatory responses.

Conclusions: Our findings suggest VNS protects the kidneys against sepsis-associated AKI via activation of the Notch2 signaling in MΦ.

Funding: Government Support - Non-U.S.

SA-OR10

Single-Cell Spatial Map of the Developing Human Kidney Highlights Insulin-Like Growth Factor 2-Mediated Signaling in Renewal

Jonathan Levinsohn,[1,2] Bernhard Dumoulin,[2] Amin Abedini,[2] Andi M. Bergeson,[2] Konstantin A. Kloetzer,[2] Eunji Ha,[2] Laura S. Finn,[1] Oren Pleniceanu,[3] Katalin Susztak.[2] *[1]The Children's Hospital of Philadelphia, Philadelphia, PA; [2]University of Pennsylvania, Philadelphia, PA; [3]Sheba Medical Center, Tel Hashomer, Israel.*

Background: The developing human kidney is a complex multi-lineage structure. It has long been understood that interplay between these lineages is crucial to form functional nephrons, however large gaps remain in our understanding of this process. Specifically, the mechanisms by which the nephron stem cell population is maintained are unclear.

Methods: To address this, we generated a comprehensive single cell dataset of 5 developing human kidneys and CosMx sinlge cell spatial transcriptomic map of 3 developing human kidneys. By integrating our spatial and single cell data, using a novel approach, allowing us to impute whole transcriptome expression for our spatial data.

Results: We generate an integrated atlas of spatial and single cell expression allowing is to map trajectories in space. We find that nephron progenitor renewal genes decrease in expression over gestational age, preceding nephrogenic zone exhaustion. We also use H&E histology to define neighborhoods for our spatial dataset allowing us to identify genes enriched within the blastema, early tubular structures and early glomeruli. Using this approach We identify IGF2 ligand as being specific to the blastema, where we also note increased expression of insulin signaling pathways, suggesting a specific role for *in vivo* human NPC renewal.

Conclusions: We identify potential mediators of NPC renewal in humans which localize to the blastema. Among these genes is *IGF2*. We propose that this may help explain the epidemiologic data showing that uncontrolled gestational diabetes is associated with smaller fetal kidneys and poor fetal outcomes. This analysis shows the power of an integrated approach to spatial transcriptomics.

Funding: NIDDK Support, Private Foundation Support

SA-OR11

Modeling Development and Disease from Human Pluripotent Stem Cell-Derived Mature and Functional Cortical Collecting Duct Organoid

Chennan Zhang, Zipeng Zeng, Biao Huang, Megan Schreiber, Nuria M. Pastor-Soler, Andrew P. McMahon, Zhongwei Li. *University of Southern California, Los Angeles, CA.*

Background: Directed differentiation of kidney cell types from human pluripotent stem cells (hPSCs) empowers the study of kidney development and diseases and is essential for kidney regenerative medicine. During embryogenesis, *Wnt11^{+}* ureteric progenitor cells (UPCs) self-renew and differentiate to form a tree-like collecting duct (CD) system that refines and drains the urine. Previously, we have established long-term culture platforms to expand primary mouse and human UPCs, and UPCs induced from hPSCs, in the format of 3D expandable ureteric bud (UB) organoids. Starting from expandable mouse UPCs, we generated spatially organized CD organoid consisting of principal cells (PCs) and intercalated cells (ICs). However, robust human CD organoid models with the presence of both PCs and ICs are still lacking.

Methods: Starting from expandable hPSC-derived UPCs, we developed a stepwise chemically defined culture system to generate elongated cortical human CD organoids with spatially organized PCs and ICs. Electrophysiological analysis of these generated CD organoids was demonstrated through patch clamp and ussing chamber to measure ion channel activities. CRISPR/Cas9 genome editing was used to generate an efficient and scalable organoid model for polycystic kidney disease (PKD).

Results: The elongated human CD organoids well recapitulate both maturity and functionality of human cortical CD. Differentiation from UPCs to CD recapitulates normal human CD development, with the transcriptome transitioning sequentially from UB tip, UB trunk, to the mature CD profiles. Importantly, these cortical CD organoids demonstrate electrophysiologic functions, such as active sodium, potassium, and chloride ion channel activities as recorded by patch clamp. Moreover, a robust CD organoid model of PKD was developed upon *PKD2* gene knockout, reflecting cystic phenotypes and a variety of pathogenic features of the disease. Transcriptome analyses further identified molecular features unique to cystogenesis in the kidney's CD. A scalable PKD organoid model was developed, enabling high-throughput drug screening.

Conclusions: Taken together, this mature and functional human cortical CD organoid platform opens new avenues for studying human CD development and modeling kidney diseases of the ureteric lineage.

Funding: NIDDK Support, Other NIH Support - NIH Office of the Director, Private Foundation Support

SA-OR12

Engineering Scalable Vascularized Kidney Organoids with the Integration of Human Endothelial Cells for In Vivo Glomerular Filtration

Murat Tekguc,[1,2] Ryuji Morizane.[1,2] Morizane Lab. *[1]Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: Kidney organoids derived from human pluripotent stem cells have emerged as promising models for studying kidney disease pathogenesis and the development of novel therapeutics. However, previous conventional production methods rely on traditional static cell cultures, thereby limiting the scalability of organoids in the absence of vascularized glomeruli, a pivotal structure responsible for the kidney's blood filtration function. Here, we present a practical dynamic-flow culture protocol using a stirred tank bioreactor (STR) with a delta-wing-shaped impeller, which can overcome the limitations of current methods by boosting large-scale manufacture of kidney organoids exhibiting glomerular vascularization.

Methods: 1-Differentiation of human iPSCs (BJFF.6) and ESCs (H9) in both static and STR cultures 2-Treatment of STR organoids with the α2β1 integrin inhibitor 3-Generation and implantation of nephron sheets into immunocompromised NOD/SCID/IL-2 receptor common gamma chain-deficient (NSG) mice 4-Immunostaining, confocal microscopy, and 3D image analysis 5-Multiphoton Intravital Microscopy 6-Transmission Electron Microscopy (TEM) 7-qRT-PCR, RNA-seq Library preparation, sequencing, and RNA-seq Data Analysis

Results: The incorporation of a dynamic culture environment in delta-wing stirred bioreactors has significantly enhanced the glomerular vascularization and maturation of kidney organoids via mechanosensory integrin α2β1. This robust, scalable, labor- and cost-efficient platform provided large quantities of vascularized kidney organoids, enabling the fabrication of a nephron sheet with nephron numbers equivalent to those found in two rat kidneys. Intravital imaging of a nephron sheet implanted in a dorsal skinfold chamber of mice revealed in vivo filtration function with size selectability in the organoid glomeruli vascularized with human endothelia. In summary, we have developed a cost-effective mass-production method to manufacture functional vascularized kidney organoids, which has improved production efficiency by more than 50 times compared to conventional culture systems.

Conclusions: This work may represent a significant step towards bridging the gap between basic research and therapeutic applications for patients, paving the way towards facilitating the biofabrication of 3D large kidney tissues for kidney replacement therapy.

Funding: Other NIH Support - NIH DP2 award (EB029388/ DK13382), NIH R56 grant (DK122380), NIH U01 477 grant (EB028899/ DK127587), NIH UC2 grant (DK126023)

SA-OR13

Integrating Collecting Systems via Nephron-Ureteric Bud Fusion in Kidney Organoids

Min Shi, Kyle McCracken. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Kidney organoids are generated from human pluripotent stem cells (hPSCs) through directed differentiation of nephrogenic mesenchyme (NM) that subsequently epithelializes to form nephron-like structures. The nephrons lack collecting ducts (CDs) and instead terminate as blind-ended tubules, a limitation that has hampered their maturation into potentially functional tissue. Here we report an innovative, developmentally inspired system that addresses this deficiency through the incorporation and integration of hPSC-derived ureteric bud (UB) progenitor tissues, the embryologic building blocks of the kidney's CDs and urinary collecting system.

Methods: We established and optimized methods to grow kidney organoids comprising both NM and UB progenitor cells derived from hPSCs, and we used fluorescently labelled cells to trace the respective lineages. Both the early development and later differentiation were extensively characterized through wholemount staining, confocal imaging, and scRNA-seq.

Results: Following recombination, NM rapidly and efficiently epithelialized into renal vesicle structures while the UB progenitors grew into extensive tubular networks. The resulting organoids contained both CDs and segmented nephrons, many of which were directly connected to the CDs via a connecting tubule-like anastomosis. The fusion process occurred during an early period of nephrogenesis, and it mimicked conserved steps by which the connection occurs *in vivo*. The ability to fuse with the UB was specific to only the distal-most nephron segments despite the greater abundance of proximal tubules, preserving normal polarity, and we identified pathways to manipulate nephron patterning and the frequency of fusion. Finally, the epithelial fusion also occurred *in vivo* following transplantation.

Conclusions: By recapitulating developmental interactions, we established a novel organoid model with organized nephron-CD architecture and the first described system that recapitulates *bona fide* anastomoses between distal nephron and CD epithelia. This innovative system provides an unparalleled platform to interrogate the mechanisms of this important fusion event, and this approach is an important advance in kidney tissue engineering since generating a continuous drainage pathway from nephrons is an obligatory step toward production of functional renal tissue.

SA-OR14

Microfluidic Tissue Chip Technologies to Study Normal and Disease Podocyte Behaviors

Balaji Karthick Subramanian, Martin Pollak. *Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Unraveling the complex behavior of healthy and diseased podocytes by analyzing the changes in their unique arrangement of foot processes, slit diaphragm, and three-dimensional (3D) morphology is a long-standing goal in kidney-glomerular research. The complexities surrounding podocyte accessibility in animal models and growing evidence of differences between human and animal systems have compelled researchers to look for alternate approaches to study podocyte behaviors. With the advent of bioengineered models, an increasingly powerful and diverse set of tools is available to develop novel podocyte culture systems.

Methods: Using multi-layer photolithography, we created a microfluidic chip to co-culture podocytes with endothelium. We used normal, INF2, and APOL1 FSGS patient-sourced induced pluripotent stem cells (IPSCs) to prepare podocytes and endothelial cells. We derived podocytes from kidney organoids while we directed the IPSCs differentiation to prepare endothelial cells. Unidirectional fluid flow for various time frames and shear stress were introduced through the system, and changes in the podocyte structure and function were examined. Changes in podocyte morphology, marker protein expression and localization, and transport properties were assessed and compared between normal and FSGS disease tissue chips.

Results: Endothelial cells formed a vessel in our chip system with proper marker protein (VE-cadherin) localization and barrier function. When podocytes were introduced to the chip system, they migrated toward endothelial cells and interacted with the outer curvature of endothelial vessels, thus recapitulating the invivo-like arrangement. Tissue characterization analysis of the tissue–-system confirmed fenestration-like structures in endothelium and foot processes-like extension in the podocyte. More importantly, podocytes recapitulated defective cell spreading, actin arrangement, and transport phenotype in the mutant-INF2 and APOL1 risk variant-based tissue chips.

Conclusions: We have developed and validated a model system to study podocyte behaviors ex vivo. Our platform will allow mechanistic studies and drug testing in an invivo-like environment. Establishing the tissue system using human iPSC-derived endothelial cells and podocytes enables researchers to study disease and test therapeutics in a personalized manner.

Funding: NIDDK Support, Other U.S. Government Support

SA-OR15

Developmental Programming of CKD

Hongbing Liu, Vanessa W. Menard, Joseph Harkrider, Samir S. El-Dahr, Madiha Mumtaz, Chaohui Chen. *Tulane University, New Orleans, LA.*

Background: Chronic kidney disease (CKD) is growing in prevalence throughout the world. However, the developmental origins of CKD mechanisms remain largely unknown. Gestational effect is believed to be mediated by gene expression reprogramming, including epigenetic changes.

Methods: To determine the significance of epigenetic regulation by histone deacetylases (HDACs) in the programming of CKD, we established an intrauterine growth restriction (IUGR) mouse model by feeding the pregnant mice 6% protein diet (low protein diet, LPD) throughout gestation, while the control group was fed with isocaloric 20% protein diet (normal protein diet, NPD).

Results: Gross and histological examination of IUGR mice at P0 showed smaller kidney size, smaller nephrogenic zone, fewer nephrons, increased interstitial collagen, cellular infiltration, and tubular atrophy, compared to the control group. Immunostaining results also demonstrated a diminished nephrogenic zone with a smaller Six2+ progenitor pool and nascent nephron deficit in P0 IUGR kidney ($p<0.001$, $n=4$). The glomeruli number of P21 pups was found to be about 20% reduction in LPD pups compared to NPD group. Additionally, our results indicate concurrent overactive Hdac1/2 and reduced expression of Bmp7 (both at mRNA and protein levels) in the developing kidneys of IUGR mice. To investigate transcriptional regulation of *Bmp7* by HDAC1/2 in mammalian nephron progenitor cells, we performed Chromatin Immunoprecipitation Sequencing for Hdac1 and Hdac2 in isolated E16.5 NPCs and demonstrated the binding of Hdac1/2 to *Bmp7* enhancer in vivo. Consistently, loss of *Hdac1/2* leads to an obvious augmentation of *Bmp7* expression in developing kidney of conditional knock-out mice. *Sirius red* and Masson's Trichrome Staining indicated an *increased fibrosis extracellular* in the kidneys of IUGR mice at age of 15 months. *We also detected a significantly higher level of α-SMA and fibronectin in IUGR Kidneys.*

Conclusions: Together, our findings demonstrate that IUGR predisposes to CKD by reprograming renal development via aberrant activation of Hdac1/2, which in turn represses Bmp7 expression. A mechanistic determination of how Hdac1/2-Bmp7 mediates CKD will provide a novel link between overactive HDAC1/2 to the developmental origin of CKD and effective clinical approaches to prevention and treatment of kidney disease and fibrosis.

Funding: Private Foundation Support

SA-OR16

Sall1-NuRD Cooperate in Nephron Progenitor Cells to Determine Cell Fate

Jeannine M. Basta,[1] Lynn Robbins,[2] Lisa Stout,[1] Michelle Brennan,[3] Michael I. Rauchman.[1,2] *[1]Washington University in St Louis, St Louis, MO; [2]VA Medical Center, St. Louis, MO; [3]Saint Louis University, St Louis, MO.*

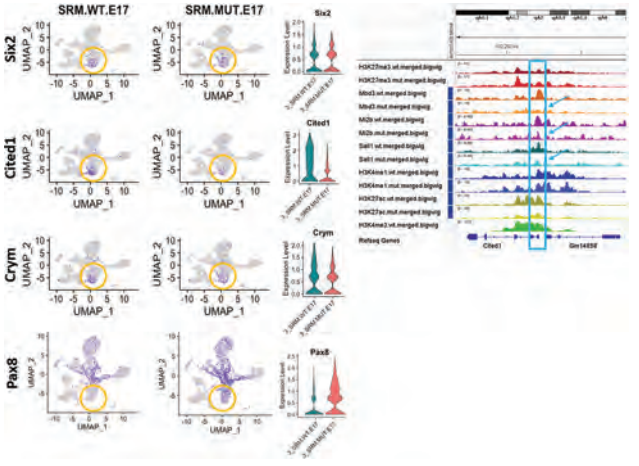
Background: We created a knock-in mutant mouse (Δ*SRM*) that disrupts the interaction between the transcription factor Sall1 and the NuRD chromatin remodeling complex, resulting in accelerated nephron progenitor cell (NPC) differentiation, renal hypoplasia, and altered progenitor cell fate [Basta et al, Development (2017) 144 (17): 3080–3094].

Methods: To investigate the molecular mechanisms responsible for the altered cell fate of Δ*SRM* NPCs, we performed CUT&RUN in wild type and mutant NPCs, and 10X single-cell multiome experiments (RNA-seq and ATAC-seq in the same cell) in wild type and mutant kidney.

Results: In wild type NPCs NuRD components Mi2b and Mbd3 bound 76% of promoters also bound by Sall1. In Δ*SRM* NPCs Sall1-NuRD common binding at promoters is reduced 50% compared to wild type NPCs. Reduced binding of Sall1-NuRD components was observed at both progenitor genes (*Cited1, Meox2, Crym*) and genes induced with nephron differentiation (*Notch1, Pax8*). E17 multiome data revealed decreased expression of progenitor genes and upregulation of genes associated with nephron differentiation (*Notch1, Pax8*) in the mutant NPC cluster.

Conclusions: Loss of Sall1-NuRD binding in mutants suggests that Sall1-NuRD maintains the balance between self-renewal and differentiation by directly maintaining expression of progenitor genes and restricting activation of genes induced by differentiation signals. Our multiome data revealed that Six2+ cells in the mutant NPC cluster exhibited a mixed lineage phenotype in which some progenitor genes are reduced in expression while differentiation marker genes (*Pax8*, *Notch1*) are ectopically activated.

Funding: NIDDK Support, Private Foundation Support



10X multiome gene expression (left), orange circle highlighting NPC cluster, showing retained *Six2*, decreased *Cited1*, *Crym*, and ectopic *Pax8* expression in mutant NPCs. CUT&RUN in control and mutant NPCs (right), blue box highlighting promoter region of *Cited1*, showing reduced binding of Mi2b, Mbd3, and Sall1 (arrows) in mutant NPCs.

SA-OR17

Transcription Factor ZEB2 Determines the Cell Fate of Kidney Stroma Progenitors and Loss of ZEB2 Protects Mice from Proteinuria

Sudhir Kumar, Simon L. Lu, Harshita Pattam, Kun Yan, Yu-Chen Liu, Chao Zhang, Weining Lu. *Boston University, Boston, MA.*

Background: ZEB2 is a transcription factor mutated in Mowat-Wilson syndrome, a congenital disorder with renal and urinary tract anomalies. ZEB2 is highly expressed in developing kidney stromal progenitors, and loss of ZEB2 in FOXD1+ developing stromal progenitors leads to abnormal kidney stroma differentiation and kidney fibrosis. Interestingly, no proteinuria can be detected in ZEB2 kidney-specific knockout mice. However, the molecular mechanism is unclear.

Methods: We analyzed the single-cell RNA sequencing (scRNA-seq) data generated from the kidney tissues isolated from *Zeb2* stroma-specific conditional knockout mice $Zeb2^{flox/flox}$;$Foxd1Cre^{+}$ (*Zeb2* cKO) and their wild-type (WT) littermate controls. We performed 10x Genomics Chromium single-cell transcriptional profiling of 3-week-old *Zeb2* cKO and WT mouse kidney tissues and analyzed the data using our in-house computational pipeline. Immunostaining and RNAscope in situ hybridization (ISH) were performed to confirm the scRNA-seq findings.

Results: After removing experimental batch effects and individual variance, our clustering analysis identified nine major cell types. We observed a significant increase in the proportion of podocytes and a decrease in macrophages in the Zeb2 cKO samples. Differential expression analysis revealed upregulation of myofibroblast markers Vimentin and Nestin in the Zeb2 cKO kidney compared to the wild-type control kidney. We also found that interstitial cells expressed podocyte and parietal cell markers such as WT1, TLE4, and claudin 1, suggesting that stroma cell takes podocyte/parietal cell fate. Trajectory and functional enrichment analysis provided further insights into the potential pathways and changes in cell differentiation influenced by Zeb2 deletion in kidney stromal progenitors. Immunostaining and RNAscope ISH results validated the scRNA-seq findings.

Conclusions: ZEB2 regulates the cell fate of FOXD1+ kidney stroma progenitors. ZEB2-deficient FOXD1+ stromal progenitors adopt podocyte and parietal-like cell fates that might strengthen the glomerular function barrier and protect mice from proteinuria.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

SA-OR18

Role of Tcf21 in Mediating Renal Stromal Cell Fate Determination: Insights from Single-Cell Transcriptomics

Gal Finer,[1,2] Yalu Zhou,[2] Mohammad Daud Khan,[3] Gaurav Gadhvi,[3] George S. Yacu,[1] Joo-Seop Park,[2] Roberto Ariel Gomez,[4] Maria Luisa S. Sequeira Lopez,[4] Susan E. Quaggin,[2,5] Deborah R. Winter.[3] *[1]Division of Pediatric Nephrology, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [2]Feinberg Cardiovascular and Renal Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL; [3]Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Department of Pediatrics, Child Health Research Center, University of Virginia, Charlottesville, VA; [5]Division of Nephrology and Hypertension, Northwestern Memorial Hospital, Chicago, IL.*

Background: Normal kidney development requires coordinated interactions between multiple progenitor cell lineages. The Foxd1+ stromal progenitors are critical for normal nephrogenesis and their heterogeneity is increasingly appreciated. However, the molecular mechanisms and trajectories that drive the differentiation of Foxd1+ cells into renal stroma, capsule, mesangial cells, renin cells, pericytes, and vascular smooth muscle cells are poorly understood. Our previous work demonstrated that deletion of the mesoderm-specific bHLH transcription factor Tcf21 from Foxd1+ cells leads to a significant reduction in medullary stroma size and perivascular cell number. Here we investigate the role of Tcf21 in kidney stromal cell fate determination.

Methods: We isolated single cells from kidneys of $Foxd1^{Cre/+}$;$Rosa26^{mTmG/+}$;$Tcf21^{f/f}$ cKO and $Foxd1^{Cre/+}$;$Rosa26^{mTmG/+}$;$Tcf21^{+/+}$ control mice at E14.5. Following enrichment for GFP+ cells by flow cytometry sorting, cDNA library was prepared using the 10x Genomics Chromium Platform and sequenced at a depth of 50,000 reads per cell.

Results: Clustering of the entire dataset (n=32,461) identified a large stromal population and a smaller representation of non-stromal lineages. Sub-clustering of stromal cells (n=22,355) identified seven molecularly distinct populations: medullary/perivascular, proliferating, ECM-expressing, differentiating nephron, nephrogenic, collecting duct, and ureteric-associated stroma. Loss of Tcf21 resulted in a dramatic reduction in medullary/perivascular, proliferating, nephrogenic, and collecting duct associated stroma. Lineage tracing of Foxd1 indicated a severe reduction in the medullary stromal space from E14.5 through E18.5. A novel population, expressing elevated levels of extracellular matrix components, was exclusively present in *Tcf21* cKO kidneys. DEG analysis demonstrated that members of the Tgfβ/SMAD signaling were among the upregulated genes in *Tcf21* cKO.

Conclusions: Taken together, these data underscore a role for Tcf21 in the emergence of the milieu of Foxd1+ derivatives; loss of Tcf21 leads to a shift in stromal cell fates that results in abnormal kidney development.

Funding: NIDDK Support

SA-OR19

Neonatal Fc Receptor: More than a Transcytosis Receptor

Eileen Dahlke, Yaman Anan, Jan-Hendrik Mittag, Lea Klie, Ariane Hartkopf, Franziska Theilig. *CAU Kiel Institute of Anatomy, Kiel, Germany.*

Background: Chronic kidney disease (CKD) increases worldwide and is a high social economic burden. Diabetic kidney disease is the leading cause for the development of CKD. GWAS studies presented a strong association between the neonatal Fc receptor (FcRn) and high fructosamin levels in diabetes mellitus. Previously, we found a strong FcRn mRNA reduction in STZ-treated type 1 diabetic mice. The role of FcRn decline in the progression towards CKD remain unknown.

Methods: 3-, 6- and 15-month-old mice lacking FcRn (FcRn-/-) in comparison to wildtype mice (WT) were analyzed. Renal functional parameters and morphology were analyzed, immunohistological stainings, RNA sequencing and western blot analyses were performed. CRISPR/Cas9 FcRn knockout in BN16 yolk sac cells were used for western blotting, immunocytological and seahorse cellular respiration analyses, in addition to fructosamin treatment.

Results: A reduction in FcRn expression could be induced *in vitro* by treating BN16 cells (expressing FcRn endogeneously) with fructosamin. *In vivo*, deletion of FcRn leads to a significant reduction in the glomerular filtration rate in 3-month-old mice. After 6 month a significant reduction of renal cortices in FcRn-/- was observed and progressed over time due to shortening of proximal tubules, which was accompanied by reduced endocytosis capacity. The number of Ki-67 positive proximal tubule (PT) and endothelial cells was significantly reduced in FcRn-/- compared to WT mice. In addition, the area of the lysosomal compartment and connective tissue increased. RNAseq analysis revealed altered genes important for autophagy and ciliogenesis. An elongation of cilia in PT of FcRn-/- was confirmed immunohistologically. FcRn-/- CRISPR/Cas9 knockout cells confirm reduced proliferation and elevated autophagic flux and a higher oxygen consumption. Additionally, FcRn deletion leads to activation of mTORC1, lysomal protein expression (Lamp2), amino acid and ion transporter (B0AT1, Lat2, Lat4, NBC1).

Conclusions: In conclusion, loss of FcRn results in a switch of cellular metabolism with enhanced autophagy and respiration combined with proximal tubule reduction and functional impairment. Therefore, loss of FcRn results in a decline in kidney function mirroring some features of CKD and could contribute to the progression of DN towards CKD in diabetes mellitus.

SA-OR20

Targeting CD153+PD-1+CD4+ Senescence-Associated T Cells Ameliorates Kidney Damage by Attenuating Tertiary Lymphoid Structure Formation

Keisuke Taniguchi,[1] Takahisa Yoshikawa,[1] Yuki Sato,[1] Kenji Kohno,[2] Satoru Takahashi,[4] Satoshi Nagata,[3] Haruhiko Kamada,[3] Motoko Yanagita.[1]
[1]Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu, Kyoto, Japan; [2]Hyogo Kenritsu Daigaku, Kobe, Japan; [3]Epitope Science Co., Ltd., Ibaraki, Japan; [4]Tsukuba Daigaku, Tsukuba, Japan.

Background: We previously reported that tertiary lymphoid structures (TLSs) develop in the aged injured kidneys, with tissue maladaptive repair. In addition, we showed that the interactions between senescence-associated T cells (SA-T cells) and age-associated B cells (ABCs) via CD153-CD30 signaling are essential for TLS expansion. However, it remained unclear whether the intervention targeting SA-T cells can improve kidney prognosis.

Methods: CD153 knocked-in (CD153KI) mice, expressing enhanced green fluorescent protein (EGFP) and human diphtheria toxin receptor (hDTR) downstream of the CD153 promoter, were generated and subjected to ischemia-reperfusion injury (IRI), followed by DT administration. In addition, we made a mouse chimeric recombinant antibody (mcRM153) by using an antibody variable domain derived from the commercially available rat-derived anti-mouse CD153 antibody (RM153) and administered it to aged C57BL/6J mice after renal IRI. In both models, injured kidneys and spleens were analyzed by flow cytometry, immunostaining, *in situ* hybridization, and quantitative PCR.

Results: In the aged CD153KI mice, EGFP and hDTR-coexpressing T cells were identified in the spleens and within renal TLSs. Flow cytometry revealed that the majority of SA-T cells and smaller populations of CD4+ memory T cells expressed EGFP in the spleen and kidney, but other types of immune cells did not. One day after the first DT administration, the number of SA-T cells was reduced in the spleen and renal TLSs. Following the decrease in SA-T cells, the expression of chemokines, such as CCL19 and CXCL9, by proinflammatory fibroblasts within TLSs decreased by day 3, and TLSs were almost completely diminished by day 7. We also found that mcRM153 markedly reduced SA-T cells in the kidneys and spleen, significantly suppressed TLS formation, and reduced the VCAM1+ failed-repair proximal tubules and fibrosis in aged injured kidneys. In both models, the intervention reduced the proportion of germinal center B cells, but not ABCs.

Conclusions: Interventions targeting CD153 inhibit the formation of TLSs, ameliorate kidney damage, and may be therapeutic for CKD.

Funding: Commercial Support - Boehringer Ingelheim, Government Support - Non-U.S.

SA-OR21

DNA Damage Sensor BRCA1 Potentiates Fibrosis by Inducing Proximal Tubule G2/M Arrest and Senescence

Amrendra K. Ajay,[1,2] Akinwande A. Akinfolarin,[3,1] Joseph V. Bonventre.[1,2]
Bonventre Laboratory. *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Dallas Nephrology Associates, Dallas, TX.*

Background: DNA damage is a major contributing factor in the progression of fibrotic renal disease. Proximal tubular epithelial cells (PTECs) are the primary site of injury caused by toxins, ischemia, and obstructive injury in the kidney, leading to DNA breaks and triggering the DNA damage response (DDR). In response to DNA damage, the ATM-mediated phosphorylation of BRCA1^{Ser1524} initiates the DDR. We hypothesized that the effect of BRCA1 on arresting the cell cycle would exacerbate maladaptive repair through the initiation of G2/M cell cycle arrest and senescence.

Methods: We utilized human CKD kidney tissues, *Slc34a1-Cre* mice crossed with *Brca1*$^{flox/flox}$ mice, yielding PTEC *Brca1 exon 11* gene deletion. We performed bilateral ischemia/reperfusion (BIRI) or aristolochic acid (AA)-induced injury models in mice. Markers of DNA damage, cell cycle arrest, senescence, and fibrosis were evaluated by immunofluorescence staining and western blot analysis of tissue sections. We utilized in vitro models of patient-derived PTCs and HKC8 cells treated with AA or cisplatin. In addition, siRNA and shRNA-mediated knockdown, followed by cisplatin or AA treatment, was employed to study the role of BRCA1 in growth arrest and senescence.

Results: Human CKD kidneys showed a significant increased expression of BRCA1 protein expression compared to kidneys without CKD. Following BIRI or AA treatment in mice, the expression of *Brca1 exon 11* was increased. Deletion of *Brca1* from PTECs protected mice from the development of fibrosis, as shown by Sirius red staining, fibronectin, collagen 1, and a-smooth muscle actin following BIRI or AA. Following BIRI or AA treatment, PTECs-Brca1 depleted mice had reduced pH3^{+} cells, a G2/M cell cycle phase marker, and reduced S-β-Gal, a senescence marker. Primary PTCs displayed increased p-BRCA1^{Ser1524} after 48h AA or cisplatin treatment, with increased activation of growth arrest genes p53 and p21. siRNA and shRNA-induced reduction of BRCA1 in HKC8 and HK2 cells decreased cell viability and increased the gene expression of pro-fibrotic factors (*Acta2*, *Fibronectin*, and *Collagen1*).

Conclusions: BRCA1 in PTECs induces G2/M cell cycle arrest and cellular senescence *in vivo* and *in vitro* following injury. Transient inhibition of BRCA1 represents a novel treatment strategy to prevent the development of fibrosis after acute injury.

Funding: NIDDK Support

SA-OR22

KLF4 Drives Fibroblast Activation to Promote Kidney Fibrosis via YAP Signaling

Juanjuan Jiang, Kang Liu, Lishan Liu, Jiafa Ren. *The First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Fibroblasts are the primary cellular sources of scar-forming myofibroblasts, which synthesize excessive quantities of extracellular matrix (ECM) and contribute to kidney fibrosis. KLF4, one of the Yamanaka transcription factors, controls various essential cellular functions, including proliferation, differentiation, and embryonic development, and has been implicated in kidney diseases. However, the role and mechanism of KLF4 in regulating fibroblast phenotype transition and kidney fibrogenesis remain undefined.

Methods: In our study, we examined the expression of Klf4 in renal biopsy tissue samples from patients with chronic kidney disease (CKD), as well as in two murine models of kidney fibrosis: unilateral ureteral obstruction (UUO) and ischemia-reperfusion (IR)-induced kidney fibrosis. We generated conditional knockout mice in which KLF4 gene was selectively and inducibly ablated in fibroblasts, and subjected these mice to UUO or IR. Additionally, we treated mice with a KLF4 inhibitor after UUO or IR.

Results: In this study, we initially observed the induction of KLF4 in interstitial myofibroblasts from mouse and human fibrotic kidneys. In in vitro experiments, KLF4 expression in NRK-49F cells was induced after exposure to TGFβ1. Blocking KLF4 signaling by siRNA or KLF4 inhibitor Kenpaullone attenuated TGFβ1-induced fibroblast activation. Conversely, the KLF4 agonist Apto253 enhanced fibroblast activation induced by TGFβ1. Further in vitro studies indicated that activation of KLF4 signaling induced upregulation of Yes-associated protein (YAP) signaling in response to TGFβ1, which was reversed by KLF4 silencing. Mice with fibroblast-specific deletion of KLF4 showed reduced ECM deposition and downregulation of YAP-related signaling components compared to WT mice in both fibrotic models. Treatment with KLF4 inhibitor Kenpaullone ameliorated kidney ECM deposition in fibrotic nephropathy induced by UUO or IRI. Additionally, treatment with the YAP inhibitor VTP further reduced ECM deposition and ameliorated fibrotic nephropathy in knockout mice after UUO.

Conclusions: These findings suggest that KLF4 significantly promotes fibroblast activation and kidney fibrogenesis potentially through activating the YAP singling pathway. Targeting this singling pathway may shine light on ways to protect against kidney fibrosis in patients with chronic kidney diseases.

Funding: Government Support - Non-U.S.

SA-OR23

The Role of D-dopachrome Tautomerase (Macrophage Migration Inhibitory Factor 2) in Kidney Fibrosis

Lea Herkens,[1] Patrick Droste,[1,2] Konstantinos Karyniotakis,[1] Peter Boor,[1,2] Sonja Djudjaj.[1] Laboratory of Nephropathology. *[1]Institute of Pathology, RWTH Aachen University, Aachen, Germany; [2]Division of Nephrology and Clinical Immunology, Aachen, Germany.*

Background: The progression of most kidney diseases leads to kidney fibrosis. Numerous factors were shown to be involved in driving fibrosis, less is known about endogenous factors limiting fibrosis. One such protective factor is macrophage migration inhibitory factor (MIF), which was found to limit kidney fibrosis by abrogating the cell cycle arrest of tubular cells. Macrophage migration inhibitory factor-2 (MIF-2), also known as D-dopachrome tautomerase (D-DT), is a structural and functional homolog of MIF. Very little is known about the location, expression, and functional role of D-DT in kidney fibrosis.

Methods: The expression of D-DT in kidney fibrosis was analyzed in different animal models, i.e., unilateral ureteral obstruction (UUO), ischemia-reperfusion (IR), and patients' biopsies using immunohistochemistry, immunofluorescence, rt-PCR, RNA *in situ* hybridization, Western blot and enzyme-linked immunosorbent assay (ELISA). Publicly available datasets and arrays were also re-analyzed and complemented by *in vitro* studies using human embryonic kidney (HEK) 293T cells. The functional role of D-DT *in vivo* was analyzed in D-DT knockout (KO) mice compared to wildtype littermates (WT) and by administration of recombinant D-DT in WT mice with UUO.

Results: D-DT mRNA and protein expression were mainly located in proximal tubules in both healthy murine and human kidneys. Its expression was significantly reduced in fibrosis in patients and animals with UUO and IR. Re-analysis of *Ddt*/*DDT* expression in murine and human publicly available array data further confirmed these findings. *In vitro*, HEK293T cells showed significantly decreased D-DT expression when challenged with the profibrotic transforming growth factor-β1 (TGF-β1). *In vivo*, compared to WT, D-DT KO mice developed significantly aggravated fibrosis in the UUO model while treatment with recombinant D-DT significantly improved fibrosis.

Conclusions: The data suggested that D-DT is mainly expressed in the proximal tubules in both mice and men and similarly decreased in fibrosis in both species. *In vivo* experiments suggested a protective role of D-DT in kidney fibrosis, similar to MIF; adding a new endogenous fibrosis-limiting factor. Future work will focus on potential mechanisms of the renoprotective effects of D-DT.

Funding: Government Support - Non-U.S.

SA-OR24

RARRES1 of Renal Tubular Epithelial Cells Aggravates Renal Fibrosis through Interaction with KHDRBS1/Src to Enhance Phosphorylation of STAT3

Anqun Chen, Lin Ye. *The Second Xiangya Hospital of Central South University, Changsha, China.*

Background: The underlying mechanisms of Renal fibrosis are uncertain. RARRES1, a retinoic acid receptor protein, is normally found in podocytes but upregulates in renal tubules during disease. This study aims to investigate the role and mechanism of RARRES1 in renal fibrosis.

Methods: 1. NEPTUNE and C-PROBE cohorts studied the link between RARRES1 expression in the renal tubular interstitium and CKD outcomes. 2. RNAscope confirmed the RARRES1 gene expression in renal tubular cells in CKD patients. Using Nephroseq data, we correlated RARRES1 expression with CKD fibrosis, with validation by Immunofluorescence staining. 3. Tubular cell-specific RARRES1 knockout mice were subjected to UUO-D10 and FA-D14 models to assess renal function and evaluate fibrosis. 4. Mass Spectrometry, CO-IP, and molecular cloning identified RARRES1 interactions and specific binding domains. 5. Protein interaction analysis and genetic manipulation were used to investigate the downstream mechanism.

Results: 1. RARRES1 was upregulated in the renal tubular interstitium of CKD patients. Higher RARRES1 expression in renal tubules correlated with lower GFR and worse outcomes in CKD patients. 2. RARRES1 gene expression positively correlated with fibrosis, as validated by immunofluorescence staining of α-SMA. 3. RARRES1 knockout in tubular cells alleviated renal injury and fibrosis in UUO-D10 and FAN-D14 mouse models. 4. KHDRBS1 was identified as an interacting protein of RARRES1 by CO-IP, with amino acids 263-269 of RARRES1 being crucial for this interaction. 5. Overexpression of RARRES1 and knockdown of KHDRBS1 in HK-2 cells led to a significant decrease in fibrosis markers within renal tubular epithelial cells. 6. KHDRBS1 interacts with STAT3 and Src, and overexpression of RARRES1 in HK-2 cells lead to a notable increase in phosphorylated STAT3 (p-STAT3). Additionally, RARRES1 knockdown in primary human renal tubular epithelial cells significantly reduced fibronectin expression upon TGF-β stimulation and the nuclear translocation of p-STAT3.

Conclusions: Elevated RARRES1 in CKD renal tubular cells exacerbates fibrosis via interaction with KHDRBS1, Src and STAT3, which promotes STAT3 phosphorylation and nuclear translocation. Targeting this RARRES1-KHDRBS1-Src axis may offer a therapeutic approach for renal fibrosis.

SA-OR25

Shroom3-Rock Interaction and Profibrotic Function: Resolving the Mechanism of a CKD Genome-Wide Association Study Risk Allele

Anand Reghuvaran,[1] Ashwani Kumar,[1] Gabriel Caldato Barsotti,[1] John F. Pell,[1] E M Tanvir,[1] John C. He,[2] Madhav C. Menon.[1] *[1]Yale University School of Medicine, New Haven, CT; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

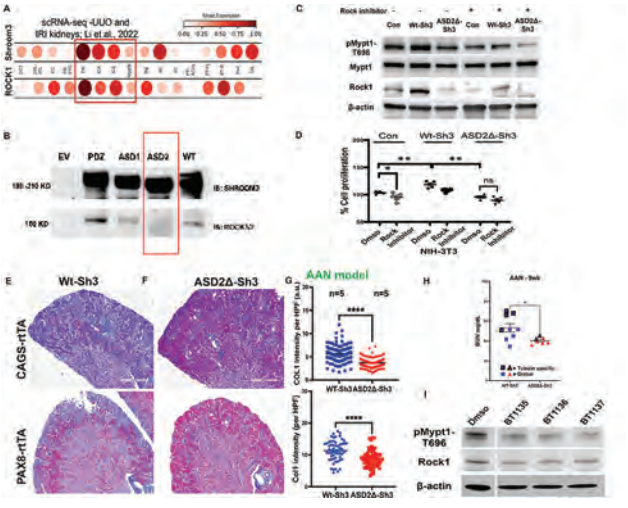
Background: We previously showed that a common intronic SNP (A-allele at rs17319721) is an enhancer for Shroom3 expression in donor kidneys promoting fibrosis. Given known therapeutic roles for Rho-kinase (ROCK) inhibitors in CKD, and the established interaction between Shroom3 and Rock via its ASD2 domain, we proposed that Shroom3-mediated ROCK activation played a crucial role in its profibrotic function in high expressors.

Methods: To test this, we developed transgenic mice and cell lines that inducibly overexpress wild-type- (WTS3) or ASD2-domain deletion- Shroom3 (ASD2ΔS3) and evaluated in fibrosis models.

Results: Prior scRNAseq data showed Shroom3 and Rock co-expression in injured PCT, distal nephron and fibroblasts during fibrosis [Fig A]. We used tubular cell lines (mIMCD3, HEK293T) to confirm absent ROCK binding (Co-IP)[B], reduced Rock activation (phospho-MYPT1) and reduced fibroblast proliferation (3T3) in ASD2ΔS3 cells vs WTS3 tubular cells [C-D].. In vivo, we studied ureteric obstruction (UUO) and Aristolochic nephropathy (AAN) as fibrosis models ASD2ΔS3. In vivo, in AAN models, both global (CAGS) and Pan-tubular(PAX8) specific WTSh3 mice showed increased fibrosis (Trichrome [E-F] and Collagen I staining [G]), and ASD2Δ mice showed reduced Azotemia (N=5 mice each [H]). Fibroblast specific mice are pending. For therapeutics, using homology modelling we developed 7 boron-based agents to inhibit Shroom3-Rock interaction (BT1131-BT1137). BT1135-BT1137 showed significant inhibition pMYPT1 [I] and 3T3 proliferation. Subsequent dose-response efficacy and toxicity studies identify BT1137 as optimal candidate for in vivo work.

Conclusions: We show the critical role of Shroom3-Rock interaction in renal fibrosis and show druggability of this interaction with applicability to individuals with the high expressor Shroom3 risk-allele.

Funding: NIDDK Support



SA-OR26

Promotion of Mitochondrial Recovery Prevents Proximal Tubular Cell Maladaptive Repair and AKI-to-CKD Transition

Sho Sugahara,[1,2] Tomofumi Moriyama,[1,3] Kensei Taguchi,[3] Bertha C. Elias,[1] Craig R. Brooks.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Shiga Ika Daigaku, Otsu, Japan; [3]Kurume Daigaku Igakubu Daigakuin Igaku Kenkyuka, Kurume, Japan.*

Background: Acute kidney injury (AKI) is a major clinical complication which results in a four-fold increase in mortality and predisposes patients to developing chronic kidney disease (CKD) through the AKI-to-CKD transition. Following AKI, the transition to CKD is largely driven by injured proximal tubule cells that fail to recover from injury and remain in a state of maladaptive dedifferentiation termed maladaptive repair. Here, we study whether improving the mitochondrial health of maladaptively repaired PTCs can prevent CKD progression.

Methods: In vitro, maladaptive repair was induced by treatment of LLC-PK1 cells with aristolochic acid (AA). In vivo, AKI-to-CKD transition was induced by administration of AA to 8-12 weeks old male BL57Bl/6 (WT) mice. Mitochondrial morphology was improved by pharmacological administration of the mitochondrial fusion promoter M1

or genetic deletion of Drp1 under the control of the inducible Pax8 promotor (Drp1$^{\Delta PT}$). Fibrosis and dedifferentiation markers were measured by immunofluorescence, protein expression and mRNA levels. Mitochondrial function was analyzed using Seahorse analyzer. Mitochondrial morphology was measured by super-resolution microscopy.

Results: In vivo and in vitro analysis of mitochondrial morphology revealed that maladaptively repaired cells have shorter and smaller mitochondria, indicating pathological mitochondrial fragmentation. In vitro, reversing mitochondrial fragmentation with M1 improves mitochondrial function and increases expression of mitochondrial fatty acid oxidation (FAO) genes. The increased mitochondrial function not only prevents maladaptive repair, but it also promotes redifferentiation of cells already in the maladaptively repaired state. In vivo, pharmacological treatment with M1 or deletion of Drp1 reverses the mitochondrial fragmentation, which is associated increased expression of mitochondrial FAO genes. Remarkably, improving mitochondrial morphology/function also induces redifferentiation of maladaptively repaired cells and halts progression of CKD and kidney fibrosis.

Conclusions: These data indicate that promoting mitochondrial recovery improves mitochondrial health, reverses PTC maladaptive repair, and ultimately prevents CKD progression. Future therapeutics targeting mitochondrial fragmentation have the potential to prevent AKI-to-CKD transition.

Funding: Private Foundation Support

SA-OR27

Multimodal Single-Cell and Spatial Atlas of Interstitial and Vascular Niches in Reference and Diseased Kidneys

Blue Lake,[1] Rajasree Menon,[2] Ricardo Melo Ferreira,[3] Xi Chen,[4] Jens Hansen,[7] Rachel S. Sealfon,[4] Jennifer A. Schaub,[2] Sylvia E. Rosas,[5] Joseph Gaut,[8] Laura Barisoni,[6] Matthias Kretzler,[2] Kun Zhang,[1] Jeffrey B. Hodgin,[2] Michael T. Eadon,[3] Sanjay Jain.[8] HuBMAP, KPMP. *[1]Altos Labs Inc, San Diego, CA; [2]University of Michigan, Ann Arbor, MI; [3]Indiana University School of Medicine, Indianapolis, IN; [4]Flatiron Institute, New York, NY; [5]Joslin Diabetes Center, Boston, MA; [6]Duke University School of Medicine, Durham, NC; [7]Icahn School of Medicine at Mount Sinai, New York, NY; [8]Washington University in St Louis, St Louis, MO.*

Background: Multiomic studies at a single cell and spatial resolution are powerful approaches to define molecular and cellular landscape of the human kidney and understand etiology of failed or successful repair in acute or chronic injury. We expand KPMP AtlasV1 with clinicopathological correlations and maps of immune-fibroblast-vascular niches with insights into AKI-CKD transition.

Methods: We generated data from >250 kidney KPMP and HuBMAP tissue samples (reference, AKI, CKD) using snRNA-seq, paired snRNA-ATAC-seq and scRNA-seq technologies and performed integrated analyses. 10X Visium, Slide-Seq2, CosMx and Xenium spatial transcriptomics (ST) assays were used to validate and discover putative niches, pathways associated with altered states and their associations with clinicopathological features.

Results: Analysis of 1.5M+ datasets revealed 160 cellular identities including more than ~40 immune, 20 stromal, 20 endothelial and > 70 nephron cell clusters along the cortico-medullary depth. There were ~60 unique niches identified by ST including cellular neighborhoods of profibrogenic and reparative fibroblasts associated with distinct myeloid and altered tubular cells. Several of the cell states were associated with tubular inflammation, interstitial fibrosis or reduced eGFR. This led to the identification of cellular identities that were associated with AKI or CKD. For example, two spatially distinct groups of fibroblasts localized either to perivascular or interstitial sites. Perivascular fibroblasts showed a distinct trajectory from reference fibroblasts to myofibroblasts reminiscent of failed repair and fibrosis. Cell-level functions enriched in altered states include translation, cytoskeleton dynamics, immune response activities and ECM turnover. Paired RNA-ATAC analysis revealed key transcriptional factors, regulatory circuits and accessible chromatin regions that were linked to CKD-associated GWAS variants, identifying genes potentially associated with disease pathogenesis.

Conclusions: We provide a comprehensive blueprint of spatially resolved altered cellular identities, regulatory circuits and molecular codes that inform on mechanisms of unsuccessful repair and acute and chronic kidney dysfunction.

Funding: NIDDK Support

SA-OR28

Multiomics Reveal c-Jun and SLC4A4 as Key Drivers of Kidney Fibrosis in Diabetic Nephropathy

Qiwen Deng, Yu Liu, Vivek Charu, Gerlinde Wernig. *Stanford University School of Medicine, Stanford, CA.*

Background: Diabetic nephropathy (DN) is a major cause of chronic kidney disease globally. However, the lack of targeted treatments for renal fibrosis in DN is due to an incomplete understanding of disease progression. We generated a detailed map of human diabetic nephropathy by employing multiplexed single-cell imaging and spatial transcriptomic profiling of DN patients and controls.

Methods: We utilized an integrative multi-omic approach, combining single-cell RNA sequencing, chromatin accessibility assays, spatial transcriptomics, and CODEX multiplexed imaging. This comprehensive analysis provided unprecedented spatial and molecular resolution of kidney tissues from DN patients and controls.

Results: Our multi-omic analysis revealed novel, cell-type-specific regulatory changes and provided unique mechanistic insights into DN progression. We identified the transcription factor cJun as a novel and pivotal driver of epithelial-to-mesenchymal transition (EMT) in proximal tubule and renal fibrosis. Additionally, we discovered that the sodium bicarbonate cotransporter SLC4A4 is a crucial modulator of proximal tubular injury, causally regulated by cJun. Overexpression of SLC4A4 in human proximal epithelial cells led to reduced expression of epithelial markers (E-cadherin, cingulin), indicative of EMT. Functional assays demonstrated that intracellular pH regulation, highly dependent on SLC4A4, is critical for maintaining epithelial cell function. Disruption of this regulation promoted EMT and exacerbated tubular injury, contributing to DN progression. Using an inducible cJun mouse model, we confirmed that cJun overexpression in tubule drives renal fibrosis in chronic kidney disease. Spatially resolved transcriptomics and CODEX imaging provided detailed insights into the spatial organization of these molecular changes, emphasizing the critical role of multi-omics in uncovering these novel drivers of DN.

Conclusions: Our study underscores the power of multi-omics in identifying novel molecular drivers of diabetic nephropathy. The discovery of cJun and SLC4A4 as key regulators highlights their potential as unique therapeutic targets to mitigate renal fibrosis in DN. These findings offer a robust foundation for future research aimed at developing targeted treatments to improve outcomes for patients with DN.

Funding: Private Foundation Support

SA-OR29

A Therapeutic Lead Compound for Diabetic Kidney Disease with a Unique Lipophagy Activation Mechanism

Rachel Njeim,[1] Haley Gye,[1] Colin B. Kelly,[1] Cole M. Foster,[1] Judith T. Molina David,[1] Sandra M. Merscher,[1] Marc Giulianotti,[2] Alessia Fornoni,[1] Hassan Ali.[1] *[1]University of Miami Miller School of Medicine, Miami, FL; [2]University of Minnesota, Minneapolis, MN.*

Background: In 2021, 537 million people worldwide had diabetes, and this number is expected to increase to 783 million by 2045. Approximately 30% of individuals with diabetes develop Diabetic kidney disease (DKD), which ultimately leads to end stage renal failure. We previously demonstrated that lipid droplets (LDs) accumulation in podocytes leads to increased lipotoxicity and cell death in DKD. Furthermore, we reported that reducing LD accumulation in podocytes preserves cell function and attenuates albuminuria in experimental DKD. Drugs that reduce lipids systemically do not prevent DKD progression. We hypothesize that specifically reducing LD accumulation in podocytes prevents DKD progression.

Methods: We developed a phenotypic assay using immortalized human podocytes and deployed it to screen a combinatorial library. We identified a novel series of hit compounds, from which we generated a lead candidate with improved drug-like properties. We performed RNAseq, molecular biology and phenotypic profiling (Cell Painting) analyses to elucidate the mechanism of action (MoA) of these compounds. Finally, we tested the lead compound in a murine model of DKD.

Results: Our screen identified a series of novel compounds that effectively reduced LD accumulation in stressed podocytes. Mechanistic studies revealed that the lead candidate, compound 2726.007, activates autophagy/lipophagy, thereby reducing LD accumulation in stressed podocytes and rescuing them from cell death. When compared to other autophagy inducers with diverse MoAs, including metformin, rapamycin, and L690,330, only compound 2726.007 decreased LD accumulation in stressed podocytes and prevented cell death. Unbiased phenotypic-based profiling of these compounds further demonstrated that compound 2726.007 has a unique MoA that is not reproduced by the other autophagy inducers. Importantly, compound 2726.007 significantly reduced albuminuria and renal damage in *db/db* mice.

Conclusions: Taken together, we have developed a therapeutic lead compound that reduces LD accumulation in podocytes by activating lipophagy through a mechanism distinct from other autophagy inducers, thereby preventing DKD progression. Next steps include lead optimization and preclinical development to ultimately advance the candidate towards clinical trials.

Funding: NIDDK Support, Private Foundation Support

SA-OR30

C/EBPβ-XOR Axis Confers Genetic Predisposition to Diabetic Kidney Disease

Ubong S. Ekperikpe, Liping Yu, Ilse S. Daehn. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Diabetes-induced chronic kidney disease (CKD) is the leading cause of renal failure globally and in the United States of America. Interestingly, only about 30% of patients with diabetes develop diabetic kidney disease (DKD), underscoring the

role of genetics in the pathophysiology of DKD. Despite this observation, the underlying molecular mechanisms that confer genetic predisposition to DKD remain unclear. Glomerular injury, characterized by podocyte depletion and glomerular hypertrophy are a major feature of progressive DKD. Previously, we reported that mitochondrial dysfunction-induced oxidative damage in glomerular endothelial cells (GECs) drives podocyte loss via GEC-podocyte crosstalk in DKD-susceptible DBA/2J (D2) versus DKD-resistant C57BL/6J (B6) mice.

Methods: We mapped potential quantitative trait loci (QTL) that are associated with podocyte depletion in DKD-susceptible DBA/2J (D2) and DKD-resistant C57BL/6J (B6) mice, and in a panel of recombinant BXD mouse strains. Through this, we identified a significant *cis*-acting variant in the promoter region of xanthine oxidoreductase (*Xor*). XOR catalyzes the metabolism of purines to uric acid, generating reactive oxygen species (ROS) in the process. Via CRISPR/Cas9, we knocked-in the identified *Xor* risk variant into DKD-resistant B6 mice to generate mutant B6-*Xor*^{em1} mice that displayed markedly higher XOR activity versus wild-type B6 mice. We also determined the effect of this *Xor* risk variant on susceptibility to DKD in B6-*Xor*^{em1} mice.

Results: The identified *Xor* promoter risk variant is a transcription factor binding site for C/EBPβ. We detected higher expression of C/EBPβ in GECs from diabetic B6-*Xor*^{em1} mice. Diabetic B6-*Xor*^{em1} mice exhibited increased mitochondrial ROS in GECs, and this was associated with podocyte depletion, glomerular basement membrane thickening, glomerulosclerosis, and albuminuria. More importantly, these pathophysiologic changes were prevented by the XOR inhibitor, febuxostat. B6-*Xor*^{em1} mice also displayed age-related glomerulosclerosis and insulin resistance. Furthermore, *In vitro* studies in GECs support a possible *Xor*-mitochondrial ROS interplay in endothelial cells that resulted in GEC dysfunction.

Conclusions: High-risk variants in the promoter region of *Xor* confer genetic susceptibility to DKD and may predispose to other complications of diabetes, and aging-related renal disease.

Funding: NIDDK Support, Other U.S. Government Support

SA-OR31

Targeting RNF145 in Renal Proximal Tubular Cells Protects against Lipotoxicity in Diabetes

Matias Simons, Lena Hipp, Angel Loza Valdes. *UniversitatsKlinikum Heidelberg, Heidelberg, Germany*.

Background: In diabetic patients, dyslipidemia is associated with both excessive deposition of triacylglycerol (TAG) in lipid droplets (LDs) and lipotoxicity. Yet, it is unclear how these two effects correlate with each other in the kidney and how they are influenced by dietary patterns. By using a diabetes mouse model, we previously found that a high fat diet enriched in the monounsaturated oleic acid (OA) caused more lipid storage in LDs in renal proximal tubular cells (PTCs), but less tubular damage than a corresponding butter diet with the saturated palmitic acid (PA). Mechanistically, endoplasmic reticulum (ER) stress was caused by elevated levels of saturated TAG precursors, reduced LD formation, and, consequently, higher membrane order in the ER (Perez-Marti et al, eLife 2022).

Methods: Rnf145 knockout induced renal epithelial cells (iRECs) were generated using adenoviral CRISPR/Cas9. Cells were treated for 16 - 18 hrs with PA and subsequently analyzed for protein and mRNA expression, cell viability (crystal violet) and apoptosis (IncuCyte). Proteomic and lipidomic analyses were performed, and mitochondrial respiration and glycolysis were measured with Seahorse.

Results: To identify pathways mediating PA-induced lipotoxicity, we applied transcriptomics to PA- and OA-treated induced renal epithelial cells (iRECs) and uncovered a set of genes differentially regulated by PA and OA, including the ER resident E3-ubiquitin ligase RNF145. Interestingly, RNF145 knockout protected iRECs against PA-mediated cytotoxicity and reduced ER stress, while its overexpression had opposite effects. Moreover, inhibition of desaturases in conditions of high lipid saturation rendered the Rnf145 depleted cells more sensitive than control cells, indicating that desaturases, such as SCD1, play a crucial role in Rnf145 deficient cells. Since proteomic analysis revealed changes in mitochondrial proteins and proteins involved in glycolysis and lipid metabolism, we confirmed that Rnf145-knockout cells undergo a shift from glycolysis towards mitochondrial respiration which might potentially contribute to the higher PA resistance.

Conclusions: Altogether, our findings suggest RNF145 as a major regulator of lipid homeostasis and cellular metabolism, providing an interesting target for counteracting lipotoxicity in renal PTCs.

Funding: Government Support - Non-U.S.

SA-OR32

Characterization of a Novel ASAH2 Variant Associated with Diabetes and Kidney Failure in Tongan and Samoan Patients

Rebekah Nicholson, Jacob Taloa, John A. Maschek, Marcus G. Pezzolesi, Scott Summers. *University of Utah Health, Salt Lake City, UT*.

Background: Ceramides are bioactive lipids which modulate metabolic pathways to drive insulin resistance, apoptosis, and fibrosis. In search of novel genetic divers of high ceramides and their resulting contribution to heritable metabolic pathologies, we have identified a novel coding mutation in neutral ceramidase (*ASAH2*). The mutation is exclusive to patients of Tongan and/or Samoan ancestry, a population which faces the highest rates of obesity, diabetes, and end-stage renal disease (ESRD) of any racial or ethnic group in the United States.

Methods: We profiled circulating ceramides in 5 founder *ASAH2* point mutant (chr10:50236064C→G(hg38), c.G511C, p.V171L) carriers and characterized the effect of the mutation on neutral ceramidase activity and ASAH2 mRNA splicing *in vitro* with CRISPR Cas9 knock-in and/or mutant expression constructs in HEK293 cells. Lastly, we tested for renal and metabolic consequences of loss-of-ceramidase function in *Asah2* knockout mice challenged with high-fat diet or streptozotocin-induced diabetic kidney disease (DKD).

Results: Heterozygous carriers of the *ASAH2* mutation have 29% higher circulating ceramides compared to Polynesian non-carriers with diabetes and ESRD (p=0.009). Sequencing of RNA from ASAH2$^{c.G511C}$ knock-in cells revealed that the point mutation located at the first base pair of exon 5 causes excision of exon 5, which encodes crucial amino acids within the ASAH2 catalytic domain. Functional studies in cells overexpressing *ASAH2* lacking exon 5 confirm ablation of ceramidase activity. *In vivo*, both male and female *Asah2*$^{-/-}$ mice displayed worsened insulin sensitivity by insulin tolerance test compared to *Asah2*$^{+/+}$ littermate controls with diet-induced obesity. Additionally, female *Asah2*$^{-/-}$ mice had exacerbated albuminuria (473.3±83.6 (-/-) vs. 159.3±37.7 (+/+) ug/mg creatinine, p<0.0001), kidney hypertrophy (7.7 (-/-) vs. 5.9 (+/+) mg/g body weight, p<0.0001), and cortex expression of markers related to fibrosis (*Tgfb1, Col1a1, Col3a1, Col4a1, Fn1*) and kidney damage (*Havcr1, Lcn2*) compared to *Asah2*$^{+/+}$ littermate controls in the setting of DKD.

Conclusions: These data reveal a novel risk allele for diabetes and kidney disease that is present in 1 in 10 individuals of Tongan or Samoan descent, which could be treated with precision therapies designed to lower ceramides.

Funding: NIDDK Support

SA-OR33

Diabetes-Specific Kidney Function Loci Identified in Genome-Wide Association Study of eGFR in 52,000 Individuals with Diabetes

Joanne B. Cole,[1] Damian Fermin,[2] Hongbo Liu,[3] Petter Bjornstad,[1] Andrew Paterson,[4] Andrzej S. Krolewski,[5] Niina Sandholm,[6] Jose C. Florez.[7]
[1]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [2]University of Michigan Michigan Medicine, Ann Arbor, MI; [3]University of Pennsylvania, Philadelphia, PA; [4]Sick Kids Foundation, Toronto, ON, Canada; [5]Joslin Diabetes Center, Boston, MA; [6]Helsingin yliopisto Laaketieteellinen tiedekunta, Helsinki, Finland; [7]Mass General Brigham Inc, Boston, MA.

Background: Diabetic kidney disease (DKD) is a distinct life-altering pathological condition that is caused by both environmental and genetic factors. Previous genome-wide association studies (GWAS) have identified several loci associated with kidney disease and function both in the general population and in diabetes. While type 2 diabetes (T2D) is more common than type 1 diabetes (T1D), individuals with T2D have higher rates of kidney-damaging co-morbidities, and thus many develop non-specific kidney disease. Therefore, a comprehensive approach which incorporates T1D and T2D to maximize sample size and also integrates diabetes subtype, duration, and co-morbidities is key to improving the success of large-scale genomic discovery for DKD.

Methods: As part of the GENIE consortium, we leveraged widely available eGFR as a powerful quantitative trait to conduct the largest GWAS of eGFR in diabetes, including 17 T1D cohorts, UK Biobank, and SUMMIT Consortium T2D data with a total of 17K individuals with T1D and 36K individuals with T2D. To identify genetic loci most likely impacting kidney function via hyperglycemic pathways, we analyzed eGFR in a variety of settings that considered DKD disease status, diabetes subtype and duration, BMI, HbA1c, and the relationship between eGFR and albuminuria. We integrated multi-omics data to nominate candidate genes and elucidate mechanism.

Results: GWAS identified 13 loci associated with eGFR (P<5x10^{-8}); five were not associated or were in opposite directions with eGFR in the general population. rs11032245 near *HIPK3* had opposite effects on eGFR in DKD cases versus diabetes controls, and single-cell RNA sequencing revealed a large difference in *HIPK3* expression in podocytes between youth-onset T2D and healthy controls. rs76300256 near *LPP* had opposite effects in diabetes versus no diabetes and is a methylation QTL in kidney tissue for 3 CpGs in a kidney enhancer.

Conclusions: Together, our multi-faceted approach enabled us to identify candidate genes with diabetes-specific impact on kidney function, a critical step towards elucidating DKD pathophysiology and the development of novel more personalized therapies.

Funding: NIDDK Support

SA-OR34

Peptide-Based PROTAC Degrader of CDA1 Suppresses Diabetic Kidney Disease

Jiao Wu, Shasha Cheng, Yingying Zhang, Xiaoyan Li, Xia Zhou, Xiaogang Li. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Diabetic kidney disease (DKD) is a leading cause of mortality and morbidity in diabetes, representing a predominant cause of renal failure worldwide. The expression of cell division autoantigen 1 (CDA1) is elevated in the kidneys of diabetic animal models, which can promote renal fibrosis through the TGF-β signaling pathway. PROTAC is a protein depletion approach that utilizes small molecules or peptides to artificially bridge a protein of interest with E3 ligase for subsequent proteasomal degradation. We hypothesize that targeting CDA1 with peptide based PROTAC may be a promising approach for attenuation of renal fibrosis and DKD.

Methods: To test the effect of a pharmacological approach of peptide-based PROTAC on the degradation of CDA1 and DKD progression, streptozotocin (STZ)-induced and db/db DKD mouse models were treated with different doses of the peptide-based PROTAC molecule CPV. The treated kidneys were collected and analyzed with H&E staining, immunofluorescence, immunohistochemistry staining and TUNEL assay. The expression of key factors in DKD were analyzed by WB and qRT-PCR analysis in DKD cells and kidneys.

Results: We generated a new peptide-based PROTAC degrader, CPV, and demonstrated that treatment with the CPV induced ubiquitin-mediated degradation of CDA1 protein in DKD cells and kidneys, indicating by that the degradation of CDA1 could be reversed by co-treatment with proteasome inhibitor MG132. Among three doses tested, treatment with a dose of 5 ug/kg of CPV already could delay disease progression in two DKD mouse models as seen by a decrease of blood urea nitrogen (BUN) levels and urinary proteins, and an increase of serum albumin. In addition, treatment with CPV mitigated interstitial fibrosis and renal inflammation as seen by a decrease of the expression of profibrotic markers, including TGF-β, a-SMA and collagen 1, and proinflammatory factors, including TNF-a, MCP-1 and IL-1. It also reduced renal extracellular matrix (ECM) accumulation and glomerular injury index. Notably, no deleterious effects were observed in other organs.

Conclusions: This study indicates that the peptide-based PROTAC degrader, CPV, can induce ubiquitin-mediated degradation of CDA1 protein in cells and kidneys from DKD mouse models, and suggest that peptide-based PROTAC therapy a safe and novel therapeutic strategy for the treatment of diabetic kidney disease.

Funding: NIDDK Support, Other U.S. Government Support

SA-OR35

Mapping the Microenvironment: A Single-Cell Spatial Atlas of Diabetic Nephropathy

Bernhard Dumoulin, Jonathan Levinsohn, Konstantin A. Kloetzer, Eunji Ha, Andi M. Bergeson, Katalin Susztak. Susztak Lab. *University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: The kidney is an architectural masterpiece, comprising nearly 100 distinct cell types. Despite this complexity, the cellular architectural principles of the kidney in both health and disease remain poorly understood. Our study aims to elucidate these principles by profiling healthy and diabetic kidney samples at true cellular resolution. We seek to uncover the molecular and spatial signatures that characterize the disease condition.

Methods: We utilize the spatial transcriptomics platform CosMx, which enables the spatial profiling of 1,000 transcripts at true single-cell resolution. We applied deep learning-based algorithms to integrate our spatial transcriptomics dataset with human kidney single-nuclear gene expression information. This integration allows us to map annotations and cell states onto our spatial dataset, providing a comprehensive view of the kidney's cellular landscape in both health and disease.

Results: We profiled gene expression and spatial information for 1,7 million cells across healthy, diabetic, and diabetic kidney disease samples. We identified 19 distinct major cell populations within these samples. Leveraging the spatial information of these cell populations, we identified 13 distinct kidney niches. In diabetic kidney disease, we found an enrichment of injured tubular epithelial niches, as well as fibroblast and immune niches. Further subclustering of these injured epithelial populations based on their spatial location revealed microenvironments almost exclusively associated with disease. Within these microenvironments, injured epithelial cells exhibited a distinct transcriptional signature, and colocalized with immune cells. To further analyze these immune cells, we integrated seven datasets comprising approximately 150 patients and 165,000 immune cells into a single kidney immune cell atlas. Using the cell states inferred from our integrations, we mapped cell-cell interactions within these disease-specific microenvironments.

Conclusions: This study underscores the potential of spatial transcriptomics in dissecting the heterogeneity of kidney disease. By providing a detailed map of cellular and molecular landscapes, our findings pave the way for a better understanding of disease mechanisms and potential therapeutic targets.

Funding: NIDDK Support, Government Support - Non-U.S.

SA-OR36

Mitochondrial Complex I Assembly Factor NDUFAF1 Regulates Tubulointerstitial Fibrosis in Diabetic Kidney Disease via a Tricarboxylic Acid Cycle Metabolite

Koki Mise,[1,2] Jianyin Long,[2] Jun Wada,[1] Benny B. Chang,[2] Farhad R. Danesh.[2] *[1]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [2]Nephrology Section, The University of Texas MD Anderson Cancer Center, Houston, TX.*

Background: The mitochondrial electron transport chain (ETC) is a highly adaptive process that is crucial for meeting the metabolic demands of the cell. Dysregulation of the ETC has been associated with various clinical pathologies. We have recently highlighted the central role of NDUFS4, a subunit of Complex I, as a regulator of cristae remodeling and mitochondrial function in kidney podocytes (Mise K. et al. *Nat Commun* 2024 4;15:1965). However, the mechanism of ETC remodeling in the tubules of diabetic kidney disease (DKD) remains elusive.

Methods: We examined ETC remodeling in kidney tubules of two established mouse models of DKD, and generated DKD mice with proximal tubule-specific overexpression of Ndufaf1 (NADH: Ubiquinone Oxidoreductase Complex Assembly Factor 1, *Ins2*$^{Akita/+}$;*Ndufaf1*^{PTCTg}), an assembly factor of mitochondrial complex I, as a model to investigate the role of ETC integrity in diabetic tubules.

Results: We found that the rotenon-sensitive complex I enzymatic activity and the density of mitochondrial cristae were significantly reduced in proximal tubules of diabetic kidneys. Mitochondrial proteomic analysis revealed that several complex I assembly factors, including NDUFAF1, were significantly decreased in the tubular mitochondria of DKD mice. Importantly, the generation of diabetic mice with conditional overexpression of Ndufaf1 in proximal tubules (*Ins2*$^{Akita/+}$;*Ndufaf1*^{PTCTg}) exhibited reduced urinary KIM-1 and decreased collagen I and fibronectin along with improved cristae morphology. Primary proximal tubules from these mice exhibited increased ATP production and complex I enzymatic activity along with reduced mitochondrial ROS as compared to diabetic *Ins2*$^{Akita/+}$ mice. Mechanistically, we found that α-KG, a causal factor of renal fibrosis and enhanced TFG-β secretion, was significantly increased in the mitochondria from established models of DKD, whereas the levels of α-KG were normalized in *Ins2*$^{Akita/+}$;*Ndufaf1*^{PTCTg} mice.

Conclusions: This study discovered an unexpected role of Ndufaf1 as a powerful regulator of ETC in kidney fibrosis. These findings provide important insights into the mitochondrial mechanisms underlying the development of DKD and highlight the potential therapeutic targeting of the ETC assembly factor, NDUFAF1, for the management of this devastating condition.

Funding: NIDDK Support

SA-OR37

PRINTcision Medicine: A Reusable, Three-Dimensional-Printed, Patient-Specific, In Vitro Model of Arteriovenous Fistulas for Endothelial Cell Studies

Nasir A. Shah,[1,2] Zoltan Endre,[1,2] Tracie Barber,[4] Blake Cochran,[3] Jonathan H. Erlich.[1,2] *[1]University of New South Wales School of Clinical Medicine, Sydney, NSW, Australia; [2]Prince of Wales Hospital and Community Health Services, Randwick, NSW, Australia; [3]University of New South Wales School of Biomedical Sciences, Sydney, NSW, Australia; [4]University of New South Wales School of Mechanical and Manufacturing Engineering, Sydney, NSW, Australia.*

Background: Approximately 850 million people worldwide have CKD. For those with end stage kidney disease on haemodialysis, vascular access is best achieved using a native AVF. Though the molecular mechanisms underpinning AVF maturation are not well-established, endothelial cells appear to play a critical role in AVF maturation. Standard cell culture provides valuable insight into endothelial cell function, but the flat surface neglects the complex physiology of disturbed blood flow through intricate vessel geometries. We have developed and refined a macrofluidic model of AVFs using true patient geometries.

Methods: Patient AVFs were imaged using a modified ultrasound machine, digitally segmented to generate AVF geometries, and 3D-printed using a water-soluble filament. Prints were cast in silicone and dissolved leaving an AVF-shaped cavity. Human dermal microvascular endothelial cells (HMEC-1) were cultured on the internal surface of these models. Custom components were fabricated to create a flow circuit using autoclave-sterilisable materials. Patient-specific AVF doppler recordings were used to program a peristaltic pump.

Results: Immunofluorescence with DAPI and Phalloidin confirmed the presence of a HMEC-1 monolayer on the luminal surface of the patent-specific AVF models. Using autoclave sterilised components, the flow circuit ran for 10 days without bacterial contamination. Pulsatile flow was successfully achieved using the programmable peristaltic pump.

Conclusions: Our macrofluidic device overcomes many of the limitations of current cell culture techniques and animal models. By using patient-specific geometries, physiologic pulsatile flow, and running flow experiments over biologically relevant timelines, this novel *in vitro* model will facilitate investigation of endothelial cell biology under patient-relevant conditions.

SA-OR38

Light Sheet Fluorescence Microscopy: A Novel Tool for Three-Dimensional Optical Reconstructions of Mouse Arteriovenous Fistulae in Control and Uremic Animals

Unimunkh Uriyanghai,[1] Edward M. Bahnson,[2] Christine Wai,[1] Lianxia Li,[2] Eric W. Livingston,[2] Vinay A. Sudarsanam,[1] Samuel Haddad,[1] Huanjuan Su,[1] Eyla C. Arteaga,[1] Boyce E. Griffith,[2] Prabir Roy-Chaudhury,[1] Gang Xi.[1]
[1]The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC; [2]The University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: The arteriovenous fistula (AVF) is currently the gold standard for dialysis vascular access. Unfortunately over 50% of AVFs fail to mature, most often as a result of a venous segment stenosis. We and others have hypothesized that this is likely due to two interactive upstream pathogenetic pathways (hemodynamic stress and uremic vascular biology) which then results in two interacting downstream pathological pathways (neointimal hyperplasia and inadequate outward remodeling) that result in venous segment stenosis. To better elucidate the mechanisms involved in these processes, we have developed a novel approach termed Light Sheet Fluorescence Microscopy (LSFM), which can generate 3D optical reconstructions of AVF vessel architecture, with regard to volume, geometry, and the presence or absence of neointimal hyperplasia. The goal of this study was to describe the use of LSFM in normal and uremic animals.

Methods: Carotid-jugular AVFs were created in 16-week-old wild-type and uremic mice on a C57BL/6 background. Uremia was induced by a 5/6 nephrectomy on day 14 and Day 7 using a two-step surgical approach. Animals were sacrificed at 21d and the AVF was harvested for LSFM and conventional histomorphometry.

Results: Uremic mice had a decrease in the average (6 sections at 100 micron intervals across the venous segment) percentage luminal patency as compared to control animals on histomorphometric analysis (12±1.4% vs 36.1±11.5%, $p<0.05$) at 21 days post-surgery. Consistent with this data, the LSFM analysis documented that lesion volume within the venous segment was increased in the uremic mouse model (0.79 cubic mm versus 0.25 cubic mm) and the length of lesion was also doubled in the uremic mouse model (1mm vs 2mm) (see Fig 1).

Conclusions: Our results suggest that LSFM could be a particularly useful tool for obtaining a holistic assessment of both 3D anatomy and stenosis across the entire venous segment as opposed to looking at discreet sections every 100-200 microns. While the latter is the current technical standard, it is unfortunately prone to miss short regions of maximal stenosis.

Funding: NIDDK Support

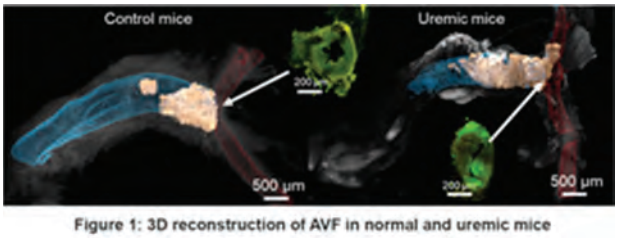


Figure 1: 3D reconstruction of AVF in normal and uremic mice

SA-OR39

Periadventitial Delivery of Nanoparticle-Encapsulated AZD8797 Reduces Venous Stenosis in a Murine Arteriovenous Fistula Model

Prabh G. Singh, Sreenivasulu Kilari, Alaura Lemieux, Jamie Kane, Sanjay Misra. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Venous neointimal hyperplasia (VNH) and venous stenosis (VS) decrease the patency of arteriovenous fistulas (AVFs) for hemodialysis. Immune cell infiltration drives VNH/VS, with the CX3C motif chemokine receptor 1 (CX3CR1) playing a key role in leukocyte adhesion and migration. This study evaluates if the peri-adventitial delivery of nanoparticle encapsulated AZD8797, a CX3CR1 inhibitor, immediately after AVF creation prevents VNH/VS in a murine AVF model with established chronic kidney disease (CKD).

Methods: Thirty-six male C57BL/6J mice (7-8 weeks old, weighing 26.42 ± 0.29 g) underwent partial nephrectomy to induce CKD. AVFs were created 28 days later, and the mice received peri-adventitial delivery of PLGA nanoparticles in 20% Pluronic F127 hydrogel only (NP C) or the same formulation with AZD8797 (AZD8797 NP) on the outflow vein (GV). Three days post-AVF, 20 mice were sacrificed for the drug dose study, while 16 mice underwent weekly Doppler scans and were sacrificed 28 days post-AVF for histomorphometry and immunohistochemical evaluations.

Results: Drug response study showed that 50 μM AZD8797 NP significantly reduced CX3CR1 gene expression in GV. AZD8797 NP group exhibited significantly higher peak systolic velocity, wall shear stress, and blood flow, with histomorphometric analysis showing an increase in average lumen vessel area. (32,282.67 ± 4,770.40 μm^2 vs. 7,983.80 ± 1,695.85 μm^2, p=0.0027) and reduced neointimal cell density (0.0047 ± 0.0006 cells/μm^2 vs. 0.0092 ± 0.0012 cells/μm^2, p=0.0107). AZD8797 NP group showed decreased immune markers CX3CR1 (5.15 ± 1.11 vs. 15.45 ± 1.02, p=0.0001), CX3CL1 (2.78 ± 0.45 vs. 9.63 ± 1.23, p=0.0028), CD68 (4.78 ± 0.88 vs. 12.71 ± 1.19, p=0.0008) and NF-κB (1.88 ± 0.56 vs. 5.43 ± 0.37, p=0.0011) expression. Smooth muscle and fibroblast staining were significantly decreased in the AZD8797 NP group (α-SMA: 5.44 ± 0.57 vs. 19.15 ± 0.53, p=0.0015; FSP-1: 11.22 ± 0.78 vs. 16.79 ± 1.36, p=0.0117). Ki67 staining was significantly decreased (5.16 ± 0.83 vs. 8.40 ± 0.72, p=0.0229) with increased TUNEL assay in the AZD8797 NP group (2.04 ± 0.23 vs. 0.88 ± 0.19, p=0.0149).

Conclusions: Peri-adventitial delivery of AZD8797 NPs significantly reduces VNH/VS with improved vascular remodeling. This approach shows promise as a therapeutic strategy to enhance AVF patency.

Funding: NIDDK Support, Other NIH Support - HL098967 and DK135407

SA-OR40

National Estimates of Direct Health Care Costs Associated with Catheter-Related Bloodstream Infection among Hospitalized Hemodialysis Patients in Australia

Jayson Catiwa,[1,2] Martin P. Gallagher,[3,1] Stephen Jan,[1,7] Kevan Polkinghorne,[4] Nicholas A. Gray,[5] Kathryn Higgins,[1] Sradha S. Kotwal.[1,6] *[1]The George Institute for Global Health, Sydney, NSW, Australia; [2]University of New South Wales, Sydney, NSW, Australia; [3]University of New South Wales SWS Clinical Skills and Simulation, Liverpool, NSW, Australia; [4]Monash University Department of Epidemiology and Preventive Medicine, Melbourne, VIC, Australia; [5]Sunshine Coast University Hospital, Sunshine Coast, QLD, Australia; [6]Prince of Wales Hospital and Community Health Services, Randwick, NSW, Australia; [7]Imperial College London, London, United Kingdom.*

Background: The risk of hospitalization and complications among hemodialysis (HD) patients increases with catheter-related bloodstream infection (CRBSI). The treatment of HD CRBSI often requires substantial healthcare resource; however, the direct hospitalization cost of CRBSI in adult chronic HD patients in Australia remains unknown.

Methods: We used hospitalization records from each Australian State and Territory (excluding Western Australia) and the Australian and New Zealand Dialysis and Transplant Registry to identify national cohort of patients on chronic HD with a catheter and linked the prospectively collected REDUcing the burden of dialysis Catheter ComplicaTIOns: a National approach (REDUCCTION) trial data to identify HD CRBSI episodes. We used inpatient Australian-modified ICD 10 codes and Australian Refined Diagnosis Related Groups to define HD CRBSI-related admissions between December 2016 to March 2020. The cost per inpatient HD CRBSI episode was determined by multiplying the Australian National Weighted Average Unit (NWAU) to the annual National Efficiency Price, with estimates adjusted to USD in 2024 prices. An NWAU is a measure of health service activity weighted for its clinical complexity. The value of 1.00 NWAU in 2024 is $4,375.93.

Results: Study cohort included 10,341 linked hospitalizations among 3,775 HD patients with incident catheter enrolled into REDUCCTION within the 40-month period. Of these, there were 159 (1.5%) hospitalizations attributed to HD CRBSI across 34 participating HD services, with 83% (n = 133) involving tunneled catheters. Overall, mean age of patients was 59 years, 67% male, and 69% Caucasian. The mean NWAU for inpatient HD CRBSI was 3.88 (SD 3.85) with an attributable adjusted cost of $16,767.01 (SD $16,618.74).

Conclusions: The economic burden of inpatient HD CRBSI among chronic HD patients is substantial in Australia, which forms part of the larger actual costs of all bloodstream infections. This first economic analysis of HD CRBSI in Australia using large, linked datasets, offers invaluable insights into the considerable financial strain on health systems. The estimate of out-of-hospital and other indirect costs (social, carer, etc.) associated with HD CRBSI needs to be evaluated in future studies.

Funding: Government Support - Non-U.S.

SA-OR41

Extra Aseptic Measures in Permanent Catheter Connection: Twister System, 6-Year Experience

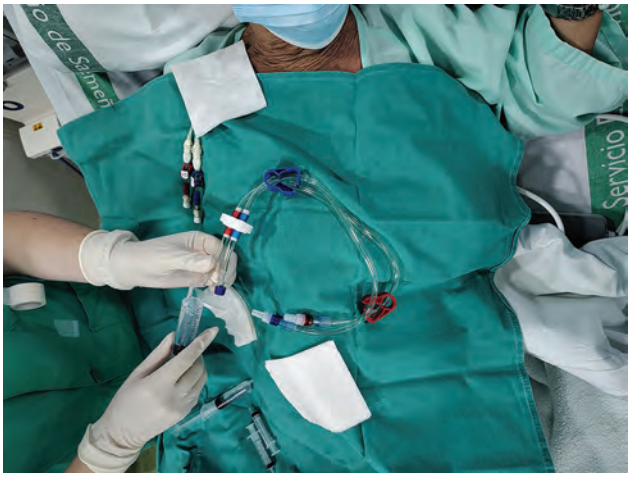
Miguel Suarez,[1,2] Vanesa Garcia Bernalt,[1] Pedro Dorado.[2] *[1]Servicio Extremeno de Salud, Merida, Spain; [2]Universidad de Extremadura, Badajoz, Spain.*

Background: Hemodialysis requires venous access por its performed. Arteriovenous fistula is preferable due to less associated comorbidity compared to catheter. However, in some units, catheters are a highly prevalent access. Aseptic measures are required to prevent their intraluminal contamination, The guidlines recommen rates of less than 2 events/1,000 catheter-days. The TWISTER® reverse flow device (TWR) is a closed system device that allows the flow of a catheter to be reversed without the need to manually disconnect the blood lines, which reduces exposure to blood or connection systems to air or contact with non-sterile areas, therefore reducing the risk of pathogens reaching the blood.

Methods: Retrospective study of 205 incident patients that compares the application of an extended aseptic protocol in the management of the catheter with the use of the Twisterr versus a standard protocol, as an extra measure to avoid bacteremia

Results: The number of bacteremias was 34; 2(3.6%) in the TWR group vs 32(24.4%) in the standard protocol; Confirmed bacteremia ratio by guideline criteria; 0.11 vs 0.81 /1000 catheter days. This represents a mean length of stay of 0.23+/-1.21 Vs 3.40+/-6.86 (p 0.001) in favor of the extended protocol and therefore reduces the total cost per 1000 catheter days; 4,884.6 Vs 5,992.08 euros in favor of TWR. In the binary logistic regression, the only factor (analyzed DM, Cardiopathy, catheter days, Starting Age, Sex and Chalson Index) with statistical significance is the center where the catheter is treated. P0,014

Conclusions: The use of the TWR system seems to be a useful tool in its fight. Among the weaknesses of the study are the non-randomization or extension to other areas. We believe that the design of studies for this purpose is necessary.



SA-OR42

Long-Term Outcomes of Subcutaneous vs. Transvenous Implantable Cardioverter Defibrillator Use among Dialysis Patients

Patrick H. Pun,[1,2] Li Qin,[3] Karl Minges,[3,4] Sana Al-Khatib,[1,2] Daniel J. Friedman.[1,2] *[1]Duke Clinical Research Institute, Durham, NC; [2]Duke University School of Medicine, Durham, NC; [3]Yale New Haven Health System, New Haven, CT; [4]Yale University School of Medicine, New Haven, CT.*

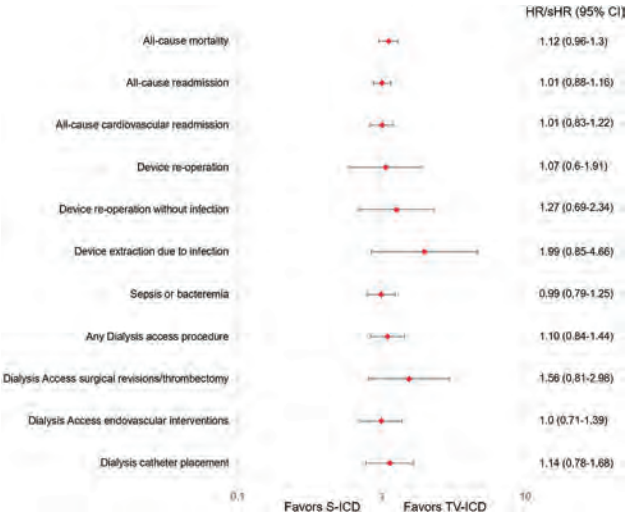
Background: Despite high risks of sudden cardiac death among dialysis patients, implantable cardioverter defibrillators(ICDs) have not been shown to improve mortality and are associated with high complication risks. Compared to transvenous(TV-) ICDs, subcutaneous(S-)ICDs may reduce the risk of infection, device- and vascular complications due to absence of intravascular leads. However, the long-term risks and benefits of S-ICD vs. TV-ICD in this population are unknown.

Methods: Retrospective analysis of ICD implants in Fee-For-Service Medicare beneficiary dialysis patients from 2012-2019 in the National Cardiovascular Data Registry ICD Registry. Outcomes were ascertained from Medicare claims data. We compared ICD and dialysis access complications, hospital admissions, and survival outcomes between eligible S-ICD and single chamber TV-ICD recipients using stabilized inverse probability of treatment weighting.

Results: 535 dialysis patients with S-ICDs and 842 with TV-ICDs met inclusion criteria. Median follow-up was 1.9 years. S-ICD recipients were younger, more likely to be Black, and had higher burdens of cardiac disease and prior dialysis access procedures. After propensity weighting, there was no difference in the risk of death (HR 1.12, 95%CI 0.96-1.30), device reoperation (HR 1.07, 95%CI 0.60-1.91), sepsis/bacteremia (HR 0.99, 95%CI 0.79-1.25) and hospital admission (HR 1.01, 95% CI 0.88-1.16) between ICD groups. Dialysis access interventions were more frequent among S-ICD recipients (8.4 vs 6.7% annually, p<0.01), but there was no risk difference after accounting for competing risks of death (HR 1.10, 95%CI 0.84-1.44).

Conclusions: In the largest longitudinal cohort of dialysis patients with S-ICD reported to date, compared to TV-ICD recipients, S-ICD was not associated with improved survival, device- and dialysis access-complication rates.

Funding: Private Foundation Support



SA-OR43

Use of a Digital Stethoscope to Evaluate Arteriovenous Fistulae before and after Intervention

Saad Mohammed Shariff,[1] Samuel Haddad,[1] Sora Lee,[1] Spencer Kieu,[2] George Mathew,[2] Gang Xi,[1] Prabir Roy-Chaudhury.[1,3] *[1]The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC; [2]Eko Health, Emeryville, CA; [3]VA Salisbury Healthcare System, Salisbury, NC.*

Background: Arteriovenous fistula (AVF) maturation failure, defined as the inability of the AVF to support dialysis via two-needle cannulation, remains a common, costly, and deleterious problem among dialysis patients, with stenosis within the venous segment a common cause. Evaluation of AVF patency and flow currently relies on imaging techniques like doppler ultrasound and fistulagrams to assess AVF dysfunction, procedures that both generally occur outside of the dialysis unit. In an attempt to develop screening tools for vascular access dysfunction that could be used in the hemodialysis unit itself, we herein present before and after phonocardiogram recordings obtained from patients undergoing AVF angioplasty for AVF maturation failure.

Methods: By physical examination, we identified the site of the arteriovenous anastomosis. We used the Eko Littman® CORE Digital Stethoscope and Eko smartphone app to obtain phonocardiogram recordings from three sites associated with the AVF: distal venous (8cm distal to the anastomosis), proximal arterial (2cm proximal to the anastomosis), and distal arterial (2cm distal to the anastomosis). De-identified recordings were labeled by location and exported prior to analysis.

Results: We observed differences in both the amplitude and profile (Fig. 1) of phonocardiogram recordings taken at the same site before and after intervention (angioplasty).

Conclusions: 1. We have demonstrated the technical feasibility of using a portable, user-friendly, digital stethoscope and smartphone app in the setting of AVF maturation failure. 2. Clear differences in both the amplitude and profile of AVF phonocardiograms suggest that the Eko device could be used to risk stratify patients at high risk of a failed angioplasty for AVF maturation. 3. The Eko phonocardiograms could be an effective, low-cost screening tool for angioplasty success or failure in the setting of AVF maturation failure in the hemodialysis unit itself.

Funding: Commercial Support - Eko Health

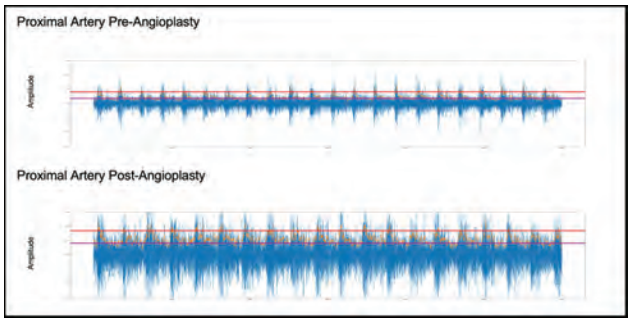


Figure 1. Change in amplitude and profile observed following angioplasty.

SA-OR44

Midterm Outcomes of a Novel First-in-Human Percutaneous Arteriovenous Fistula

Dirk M. Hentschel,[1] Robert Shahverdyan,[2] Erik van der Burg,[3] Shant M. Vartanian.[4,3] *[1]Brigham and Women's Hospital, Boston, MA; [2]Asklepios Kliniken Hamburg GmbH, Hamburg, Germany; [3]Venova Medical, Los Gatos, CA; [4]University of California San Francisco, San Francisco, CA.*

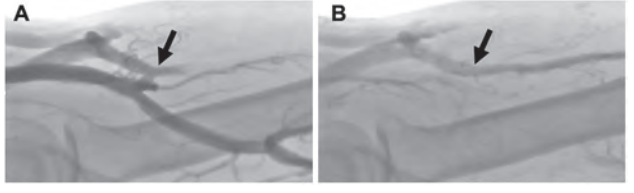
Background: Percutaneous arteriovenous fistulas (pAVF) can address barriers to starting hemodialysis with an AVF. Commercial devices often lose flow into the deep venous system, requiring reinterventions for effective cannulation. A novel implant-based pAVF was developed to create a single outflow AVF between the proximal radial artery and the cubital perforating vein, mimicking surgical AVF anatomy. The objectives of this study were to establish technical feasibility and safety.

Methods: The VENOS-1 trial (NCT 05757726) is a prospective, single-arm, early feasibility study. The primary endpoint is procedural success, and the primary safety endpoints are serious adverse device events and major reinterventions at 6 weeks. Secondary endpoints included physiologic maturation (flow > 500 ml/min and vein d. > 5 mm), reintervention rate, and functional maturation.

Results: Ten ESRD patients were enrolled with follow-up to 6 months. The average age was 45.1 yrs (range 27-61) and the BMI 24.3 kg/m^2 (SD ± 9.2). Procedural success was 100% with no safety events at 6 weeks. Mean brachial artery flow was 972 ml/min (SD ± 229 ml/min), and upper arm vein diameter increased to 6.3 mm (SD ± 1.0 mm). Physiologic maturation was achieved in all patients, on average by day 18 (range 13-40). No reinterventions were needed prior to maturation. Four of 10 patients achieved unassisted cannulation by 6 weeks, and two-needle cannulation of the cephalic vein was achieved in 70% of subjects by 6 months.

Conclusions: Mid-term results show this novel pAVF is highly effective at creating, maturing, and supporting early clinical use of a proximal forearm AVF. The method promotes rapid maturation without needing subsequent flow-diverting procedures and avoids thermal injury. These results suggest this novel pAVF could lead to more optimal starts in the HD population and warrants study in a larger patient population.

Funding: Commercial Support - Venova Medical



Angiogram showing an AVF from the radial artery to the cubital perforating vein, without flow into the deep veins. The arrow denotes implant location. A. Early antegrade filling of the pAVF. B. Late retrograde flow from the radial artery into the CPV.

SA-OR45

Photo-Activated Verteporfin-Loaded Polymeric Nanocarrier-Thermogel Hybrid System for Preventing Venous Neointimal Hyperplasia and Stenosis in Murine Arteriovenous Fistulas

Yongdong Wu, Ming Liang. *Guangzhou First People's Hospital, Guangzhou, China.*

Background: The patency of the Arteriovenous Fistula (AVF) is a prerequisite for the smooth operation of hemodialysis patients, while the dysfunction of vascular access due to endothelial hyperplasia and stenosis is an important factor in the increase of mortality in patients, and the transformation of VSMCs and their migration is an important factor in the endothelialization of AVFs. The Hippo-YAP signaling pathway regulates the proliferation and migration of VSMCs, which are involved in the process of vascular injury and remodeling. Verteporfin (VER) has great potential as a YAP inhibitor to ameliorate AVF intimal hyperplasia, but how to deliver VER to the stenosis site effectively and release VER in a controlled manner is a challenge.

Methods: 1. Expression of YAP in the neointima of arteriovenous fistula and its role in the proliferation of vascular smooth muscle cells; 2. Construction and characterization of nanoparticle/hydrogel system loaded with verteporfin; 3. The effect of blocking YAP signal by ^{TK}hbPPE/VER@PPP system on VSMCs proliferation; 4. Exploration of ^{TK}hbPPE/VER@PPP system in AVF of CKD mice.

Results: 1. The high expression of YAP in the neointima of arteriovenous fistula was associated with the migration and proliferation of vascular smooth muscle cells. 2. ^{TK}hbPPE/VER@PPP nanoparticle/hydrogel system loaded with verteporfin was successfully constructed. 3. The effect of blocking YAP signal by ^{TK}hbPPE/VER@PPP system on VSMCs proliferation. 4. Application of drug-loaded nanoparticle/hydrogel ^{TK}hbPPE/VER@PPP system in mouse blood vessels.

Conclusions: 1. There was high expression of YAP protein in the neointima of the arteriovenous fistula of mice, and YAP was involved in the proliferation and migration of vascular smooth muscle cells. 2. The drug-loading nanoparticles ^{TK}hbPPE/VER were successfully prepared and characterized, and the drug-loading nanoparticle/hydrogel system ^{TK}hbPPE/VER@PPP was constructed. 3. The system can promote the self-degradation of drug-loaded nanoparticles through red light irradiation, release VER, inhibit cell proliferation and migration by acting on VSMCs, and downregulate the expression of YAP protein in cells. 4. The g^{TK}hbPPE/VER is capable of perivascular retention and photoregulated release of VER to ameliorate AVF endothelial stenosis.

Funding: Government Support - Non-U.S.

SA-OR46

Impact of Simulated Microgravity on Human Kidney Function: Identification of Early Biomarkers and Orthostatic Intolerance during Bedrest

Giovanna Valenti, Annarita Di Mise, Marianna Ranieri, Mariangela Centrone, Maria Venneri, Angela Ferrulli, Grazia Tamma. *Universita degli Studi di Bari Aldo Moro, Bari, Italy.*

Background: Astronauts have been reported to have an unusually high rate of kidney stone formation during spaceflight, which represents a risk for the heath and for the space mission success. Studies in humans adapted to actual or simulated microgravity (bedrest) demonstrate that exposure to microgravity results in alterations of renal function, fluid redistribution, and bone loss, which is coupled to a rise of urinary calcium excretion thus increasing the risk of renal stone formation. However, high calcium delivery to the collecting duct reduces local Aquaporin 2 (AQP2)-mediated water reabsorption under vasopressin action, thus limiting the maximal urinary concentration to reduce calcium saturation. To investigate early renal adaptation into simulated microgravity, we investigated the effects of 10 days of strict bedrest in 10 healthy volunteers.

Methods: Ten young healthy, were enrolled in the study. Each subject was evaluated before and after 10 days of strict horizontal bedrest and during bedrest no deviations from the lying position was allowed. Orthostatic blood pressure was measured during supine to stand test immediately after waking up after 10 days of bedrest. For each subject, blood and spot urine samples were taken every day and urinary excretion of AQP2 was quantified by ELISA. Other biomarkers were measured in the urine or in blood.

Results: 10 days of immobilization was associated with a transient, significant decrease (day 5) in vasopressin (copeptin) paralleled by a decrease in AQP2 excretion, consistent with an increased central volume to the heart, resulting in reduced water reabsorption. Moreover, bedrest caused a significant increase in calciuria secondary to bone demineralization paralleled by a decrease in PTH. Urinary osteopontin, a glycoprotein exerting a protective effect on stone formation, was significantly reduced during bedrest. A significant increase in adrenomedullin, a peptide with vasodepressor properties, was observed at day 5, which may contribute to the known reduced orthostatic capacity postbedrest.

Conclusions: We conclude that renal function is altered in simulated microgravity and is associated with an early increase in the risk of stone formation and reduced orthostatic capacity post-bedrest within a few days of inactivity.

Funding: Government Support - Non-U.S.

SA-OR47

Plasma Sodium Correction Rates in Patients with Severe Hyponatremia Treated with Hypertonic Saline with and without Desmopressin

Zain AlShanableh,[1] Anna Ralchenko,[1] Jonathan G. Yabes,[2] Richard H. Sterns,[4] Steven D. Weisbord,[2,3] Helbert Rondon Berrios.[2,1] *[1]UPMC, Pittsburgh, PA; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA; [3]VA Pittsburgh Healthcare System, Pittsburgh, PA; [4]University of Rochester School of Medicine and Dentistry, Rochester, NY.*

Background: Co-administration of desmopressin and hypertonic saline 3% (HTS) from the outset of treatment (the "DDAVP clamp") has been suggested to prevent inadvertent overcorrection of hyponatremia, but the effectiveness and safety of this strategy remain uncertain.

Methods: We identified adult patients hospitalized between 7/1/18 and 6/30/23 at four UPMC hospitals with a plasma sodium (PNa) ≤120 mEq/L at admission or during hospitalization who were treated with HTS, excluding patients on renal replacement, eGFR <15 ml/min/1.73m2, plasma glucose >300 mg/dl, prior desmopressin treatment, or absence of PNa data within 12 h of starting HTS. Between-group comparisons were performed using t-test and Chi-square or Fisher exact test.

Results: A total of 184 patient admissions (57.6% female, mean age 60.6 years) met inclusion and exclusion criteria. Hyponatremia was chronic in 92.9%; leading causes were SIAD (51.6%), hypovolemia (25.5%), and low solute intake (15.8%); and 20.1% had seizures. Cases treated with HTS and desmopressin (n=46) were compared to cases treated with HTS without desmopressin (n=138). Despite a lower baseline PNa (110.5±6.4 vs. 115.1±7.2 mmol/L, p<0.001), correction by >8 mEq/L (6.5% vs. 27.5%, p=0.006) or >10 mEq/L (0% vs. 15.2%, p=0.011) within the first 24 hours was significantly less frequent in the desmopressin group than in the non-desmopressin group. Furthermore, presumably to prevent or reverse overcorrection, desmopressin was given to 40% of patients in the non-desmopressin group within 48 h of HTS initiation. Hospital mortality (6.5% vs. 6.5%, p>0.99), length of hospital (12.2 d vs. 11.8 d, p=0.810) and ICU stays (5.8 d vs. 5.5 d, p=0.678), fluid overload (8.7% vs.9.6%, p>0.99), and worsening of hyponatremia (2.2% vs. 1.5%, p>0.99) were similar in the two groups (HTS and desmopressin vs. HTS alone) but PNa was checked significantly more often in the desmopressin group (20.7 vs. 17.4, p<0.001). No cases of osmotic demyelination syndrome were identified.

Conclusions: Treating severe hyponatremia with HTS and desmopressin was associated with lower rates of rapid correction without significant adverse events compared to HTS alone.

SA-OR48

Mortality and Neurologic Complications Associated with Rapid vs. Slow Correction of Severe Hyponatremia

Juan Carlos Ayus,[1] Pablo N. Cherne,[2,3] Nora Fuentes,[2,3] Ezequiel P. Libovich,[2,3] Sofia Vartorelli,[2,3] Camila Naudi,[2,3] Gino Bonetto,[2,3] Jessica Moreira,[2,3] Martina Flamini Marczuk,[2,3] Michael L. Moritz,[4,5] Anaclara Murujosa.[2,3] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [3]Hospital Privado de Comunidad, Mar de Plata, Argentina; [4]University of Pittsburgh School of Medicine, Pittsburgh, PA; [5]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA.*

Background: Hyponatremia guidelines recommend limiting the rate of correction within the first 24 hours for patients with serum sodium (SNa) ≤ 120 mEq/L to prevent osmotic demyelination syndrome (ODS). Recent studies suggest rapid correction of ≥ 8 mEq/L in the first 24 hours may reduce mortality without increasing ODS risk.

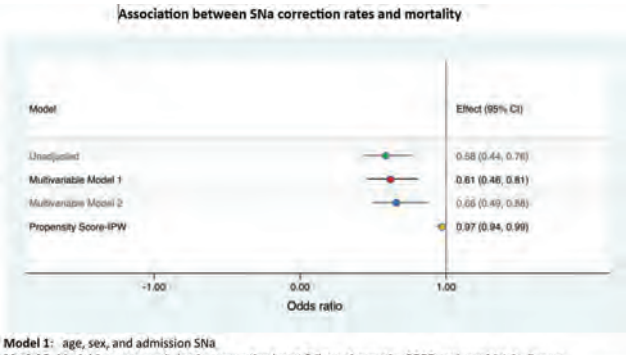
Methods: A single-center retrospective observational study conducted in Buenos Aires, Argentina, evaluating the impact of rapid (≥ 8 mEq/L) versus slow correction (< 8 mEq/L) of severe hyponatremia on mortality and ODS. Hospitalized adults with severe hyponatremia (SNa ≤ 120 mEq/L) upon admission between 2010 and 2023 were enrolled. Analysis involved logistic regression and propensity score-inverse probability weighting, adjusting for confounders

Results: The cohort included 2037 patients. Rapid correction occurred in 53%, with mean 24-h rates of 12.4 ± 3.9 mEq/L and 4.1 ± 2.6 mEq/L for rapid and slow groups, respectively. Rapid correction was associated with lower in-hospital and 30-day mortality. The adjusted odds ratio (OR) for in-hospital mortality was 0.59 (0.44 - 0.76), adjusted OR was 0.66 (0.49 - 0.89). ODS incidence was rare (0.14%) and not linked to rapid correction.

Conclusions: Rapid correction of severe hyponatremia by ≥ 8 mEq/L within 24-h is associated with decreased adjusted mortality without an increased risk of ODS.

Rapid vs slow correction within 24-h of admission

Characteristic	< 8 mEq/l/24hours	≥ 8 mEq/l/24hours	p
No. of patients	939	1098	–
Age – years	77.8 ± 13.8	76.8 ± 14	0.149
Male sex	319 (34)	302 (27.5)	0.002
Charlson Comorbidity Index ≥ 6	298 (31.7)	356 (32.4)	0.777
SNa at admission (mEq/L)	116.6 ± 3.6	115.4 ± 4.3	< 0.001
Δ SNa at 24-hour post- admission (mEq/L)	4.1 ± 2.6	12.4 ± 3.9	< 0.001
In – hospital mortality	138 (14.7)	100 (9.1)	< 0.001
30-Day mortality	173 (18.4)	136 (12.4)	< 0.001
ODS	2	1	< 0.001



Model 1: age, sex, and admission SNa
Model 2: Model 1 + cancer, cirrhosis, congestive heart failure, dementia, COPD and psychiatric disease
Propensity score–IPW: age, admission SNa and SK, hypertonic saline use, congestive heart failure, cirrhosis and cancer

SA-OR49

Critical Appraisal of Volume Status, Urine Sodium Concentration, and Urine Osmolality in the Differential Diagnosis of Hypotonic Hyponatremia

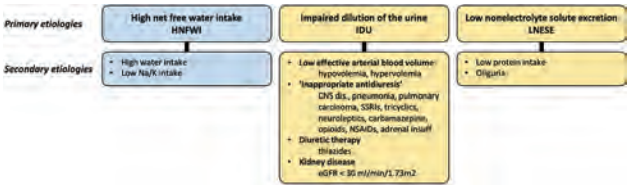
Florian Buchkremer,[1] Bettina Winzeler,[2] Stephan Segerer,[1] Mirjam Christ-Crain.[2] *[1]Kantonsspital Aarau AG, Aarau, Switzerland; [2]Universitatsspital Basel, Basel, Switzerland.*

Background: Traditional algorithms of hypotonic hyponatremia use specific thresholds of volume status, urine sodium concentration (una), and urine osmolality (uosm) to identify its most relevant pathomechanism. In contrast, we hypothesized, that different etiologic factors occur together and that these thresholds do not reliably discriminate between them.

Methods: We used patient data (n=298) from a previous, prospective, observational study. We analyzed multiple etiologies of hypotonic hyponatremia (Figure) in subgroups defined by volume status (hypo-/eu-/hypervolemia), una (<= or > 30mmol/l), and uosm (<= or > 100mosm/kg). We quantified three primary etiologies (Figure), (1) high net free water intake (HNFWI), (2) impaired dilution of the urine (IDU), and (3) low nonelectrolyte solute excretion (LNESE), by projected, equivalent treatment effects, the 'standard delta sodium' values (Buchkremer F et al., Kidney Int Rep. 2023).

Results: Prevalence and extent of all primary etiologies (Figure) showed only minor variations between hypo-, eu-, and hypervolemic patients. With una >30mmol/l, the impact of IDU was significantly higher than with una <=30mmol/l, while HNFWI and LNESE were similar in both groups. Uosm <=100mosm/kg did identify patients with very high levels of HNFWI. However, this group consisted of only 4 individuals, a mere 1.3% of the whole cohort, and less than 5% of those patients, where HNFWI had the highest quantitative impact of all primary etiologies. As a remarkable result among the secondary etiologies, we found that factors associated with 'inappropriate antidiuresis' (Figure) were present in 63.8% of all patients and that their prevalence was independent of volume status and una. Notably, two thirds of these patients showed additional secondary etiologies of IDU, that would preclude a traditional diagnosis of SIAD.

Conclusions: Current thresholds of volume status, urine sodium concentration, and urine osmolality provide only limited etiologic differentiation of hypotonic hyponatremia and do not reflect its mostly multifactorial etiology.



SA-OR50

Detection of Low Osmolar Excretion Rate for the Etiology of Hyponatremia

William Da Silva,[1,2] Alexander M. Smith,[1,2] Karthik Kovvuru,[1,2] Juan Carlos Q. Velez.[1,2] *[1]Ochsner Medical Center, New Orleans, LA; [2]The University of Queensland, Brisbane, QLD, Australia*.

Background: Low solute intake and resulting low osmolar excretion rate (OER), colloquially known as "tea/toast" diet, is a known precipitant of hyponatremia (hypoNa). However, diagnostic evaluation of hypoNa does not routinely include assessment of OER. We hypothesized that identification of low OER by a 24-hr urine collection may help unmasking low solute intake as a cause or aggravating factor of hypoNa.

Methods: A retrospective review of medical records was conducted searching for cases of hypoNa seen in our nephrology clinic who completed a 24-hr urine collection to measure volume (V), urea nitrogen (UN), sodium (Na) and potassium (K) over a 6-year period. HypoNa was defined as a serum Na < 135 mmol/L. We defined low OER as < 6 mOsm/kg/day and was calculated as: [2 (Na + K) + UN/2.8]*V. Low protein intake (< 8 g UN/day), low Na intake (< 100 mmol/day) and low K intake (< 60 mmol/day) were also estimated. In a subset of patients with low OER, we assessed the impact of increasing solute intake on correction of hypoNa (serum Na rise ≥ 4 mmol/L). SIADH was diagnosed by spot urine Na, spot urine osmolality and standard criteria.

Results: We identified 24 patients who met the criteria. Median age was 71 years, median BMI was 25 kg/m^2, median weight was 74 kg, 58% women, 96% white. Median serum Na was 130 mmol/L (range 121 – 132). By 24-hr urine, UN was assessed in all 24 patients, Na in 22 (92%) and K in 19 (79%). Full OER was completed in 17 patients: 11 (65%) had low OER. Moreover, low Na intake, low K intake, and low protein intake were found in 64%, 52% and 73%, respectively. SIADH was the cause of hyponatremia in 13/19 patients with available spot urine osmolality (68%), and among them, 9/11 (82%) had low OER. Following implementation of higher dietary solute intake, OER increased by ≥ 25% (by 69% on average) in 4/5 (80%) and hypoNa improved by ≥ 4 mEq/L (by 6 mEq on average) in all of those who increased solute intake.

Conclusions: Our findings revealed evidence of low solute intake in an ambulatory cohort of patients with chronic hypoNa. Thus, assessment of OER via 24 hour urine collection may be a useful test to identify individuals in whom low solute intake may drive or contribute to the etiology of chronic hypoNa, particularly in cases of SIADH, and to track responses to dietary therapeutic interventions.

SA-OR51

Copeptin and Body Fluid Responses to the Combined Use of an SGLT2 Inhibitor and Conventional Diuretics in Patients with CKD: The DAPA-BODY Trial

Takahiro Masuda, Maki Kinoshita, Kentaro Oka, Tetsu Akimoto, Daisuke Nagata. *Jichi Medical Univeristy, Shimotsuke, Japan*.

Background: We previously reported that SGLT2 inhibitors exert sustained fluid homeostatic actions through compensatory increases in osmotic diuresis-induced vasopressin secretion and fluid intake (Physiol Rep 2020, AJP Renal 2022). However, SGLT2 inhibitors alone do not produce durable amelioration of fluid retention.

Methods: We examined the comparative effects of the SGLT2 inhibitor dapagliflozin (SGLT2i group, n=53) and the combined use of dapagliflozin and conventional diuretics including loop diuretics and/or thiazides (SGLT2i+diuretic group, n=23) on serum copeptin, a surrogate marker of vasopressin release, and body fluid status measured by bioimpedance device (InBody S10).

Results: After six months of treatment, the change in copeptin was significantly lower in the SGLT2i+diuretic group than in the SGLT2i group (SGLT2i 31.5±56.3% vs. SGLT2i+diuretic -1.4±31.5%, p=0.0153). The change in the estimated plasma volume calculated using the Strauss formula (-1.7±5.2% vs. -2.6±5.3%, p=0.2563) and brain natriuretic peptide (26.3±84.5% vs. 4.0±60.8%, p=0.1716) were not significantly different between the two groups. Contrastingly, changes in interstitial fluid (-1.7±5.4% vs. -8.8±12.5%, p=0.0013), extracellular water (-1.7±5.4% vs. -8.8±12.5%, p=0.0013), intracellular water (-2.1±5.1% vs. -5.8±9.3%, p=0.0183), and total body water (-2.1±4.8% vs. -6.2±9.0%, p=0.0089) were significantly lower in the SGLT2i+diuretic group than in the SGLT2i group. Changes in renin (16.3±102.8% vs. 26.6±91.0%, p=0.3765) and aldosterone (9.8±48.0% vs. 20.3±52.0% p=0.2560), and absolute epinephrine levels (21.3±13.8 pg/mL vs. 21.0±10.4 pg/mL, p=0.4854) were not significantly different between the two groups.

Conclusions: The combined use of the SGLT2 inhibitor dapagliflozin and conventional diuretics inhibited the increase in copeptin levels and remarkably ameliorated fluid retention without excessively reducing plasma volume and activating the renin-angiotensin-aldosterone and sympathetic nervous systems.

Funding: Private Foundation Support

SA-OR52

Anchoring Sepsis Management: A Retrospective Cohort Study on Fluid Resuscitation in Advanced and ESRD

Hunter Reed, Abraheim AL-Nasseri, Adam M. Robarge, Usman Kazi, Ahmed Eddib. *HCA Florida Citrus Hospital, Inverness, FL*.

Background: Physicians are hesitant to give fluid boluses to renal failure patients, which is significant given the frequency end stage renal disease (ESRD) patients develop sepsis and septic shock. The aim of this study was to assess the relationship between the volume of fluid given for sepsis and mortality in patients with advanced chronic kidney disease (CKD) and ESRD.

Methods: A multicenter retrospective cohort study of CKD and ESRD patients who were admitted for sepsis was conducted across 16 West Florida hospitals. Inclusion criteria was non-pregnant adult patients admitted between January 1, 2021 and December 31, 2022 with CKD4, CKD5 or ESRD for sepsis and having received a fluid bolus within 6 hours of admission. Patients (n=4,265) were grouped by Standard (greater than 30mL/kg), Conservative (15-30ml/kg), or Ultra-conservative (less than 15mL/kg) fluid bolus. Sub-analysis was then performed among those patients who were either oliguric (less than 0.5mL/kg/hr) or anuric (n=2,344). Inhospital mortality was the primary outcome assessed, with secondary outcomes of ICU admission, vasopressor use, mechanical ventilation, and inpatient initiation of dialysis (IID).

Results: In the Ultra-conservative group there was a reduction in odds ratio (OR) of vasopressor use (OR 0.723) and ICU admission (OR 0.484), with an increase in IID (OR 1.45) compared to Standard. No difference was seen in mortality or mechanical ventilation. In the Conservative group there was a reduction in vasopressor use (OR 0.717) and ICU admission (OR 0.67). No difference was seen in mortality, mechanical ventilation or IID. Within the oliguric and anuric subgroup, the Ultra-conservative group only had a significant reduction in Mechanical ventilation (OR 0.703) and ICU admissions (OR 0.536). Within the oliguric and anuric subgroup, the Conservative group had no difference in outcomes compared to Standard.

Conclusions: There was no significant difference in mortality in either decreased volume group compared to Standard, although differences in ICU, vasopressor and dialysis use were noted. This study supports physician discretion for fluid bolus to patients who have poor renal function.

Outcomes in CKD and ESRD	<15ml/kg vs >30ml/kg Ultra-conservative				15-30mL/kg vs >30mL/kg Conservative				Outcomes in CKD and ESRD with Oliguria or Anuria	<15ml/kg vs >30mL/kg Ultra-conservative				15-30mL/kg vs >30mL/kg Conservative			
	P-value	OR	95% CI		P-value	OR	95% CI			P-value	OR	95% CI		P-value	OR	95% CI	
Mortality	0.3172	0.831	0.58	1.20	0.6911	0.924	0.63	1.37	Mortality	0.8774	0.967	0.64	1.43	0.8398	0.953	0.60	1.52
Vasopressors	**0.0375**	**0.723**	**0.53**	**0.98**	**0.0485**	**0.717**	**0.52**	**1.00**	Vasopressors	0.1259	0.752	0.52	1.08	0.2282	0.784	0.53	1.17
Mechanical ventilation	0.0683	0.752	0.55	1.02	0.1412	0.780	0.56	1.09	Mechanical ventilation	0.0527	0.703	0.49	1.00	0.0919	0.716	0.49	1.06
IID	**0.0142**	**1.45**	**1.08**	**1.96**	0.8336	0.966	0.70	1.33	IID	0.1171	1.35	0.93	1.95	0.6441	1.10	0.74	1.64
ICU admission	**<0.001**	**0.484**	**0.37**	**0.64**	**0.0073**	**0.67**	**0.50**	**0.90**	ICU admission	**0.0030**	**0.539**	**0.36**	**0.81**	0.2578	0.776	0.50	1.20

SA-OR53

Identifying Opportunities to Reduce Fluid Overload: A Multicenter Quality Improvement Partnership

Adam Dziorny,[1] Ulka Kothari,[2] Stephen C. Drury,[1] Heda R. Dapul,[2] Ami Shah,[2] Julie C. Fitzgerald,[3] Chloe G. Braun,[4] Andrew J. Barbera,[4] James D. Odum,[4] Susan D. Martin,[1] Denise C. Hasson.[2] *[1]University of Rochester Medical Center, Rochester, NY; [2]New York University Grossman School of Medicine, New York, NY; [3]The Children's Hospital of Philadelphia, Philadelphia, PA; [4]The University of Alabama at Birmingham, Birmingham, AL*.

Background: Fluid overload (FO), characterized by a pathological percentage cumulative fluid balance (%CFB), is prevalent among critically ill children and is linked to extended length of stay (LOS), morbidity, and mortality. The objective of this project is to reduce FO and associated %CFB in Pediatric Intensive Care Units (PICUs). We automated data collection across this multisite quality improvement collaborative through a federated data collection framework, local analysis, and central result aggregation. By applying this paradigm alongside sampled observations and nursing surveys, we aimed to identify strategies to reduce %CFB and ultimately enhance patient outcomes.

Methods: We identified key drivers of ICU positive %CFB, developed SMART Aims, and chose key metrics including demographics, %CFB, urine occurrence counts, relationship to Holliday-Segar (H-S) maintenance fluid rates, and associations with mechanical ventilation (MV) and ICU LOS. Individual sites extracted data, ran analysis scripts, then collected rounds' discussions of FO and nursing surveys.

Results: Over a 6-month period we included 2336 ICU encounters encompassing 1984 children. Mean number (%) of patients with day 2 CFB >5% significantly differed by site (A: 153 (54.4%), B: 157 (37.6%), C: 489 (46.4%); p<0.001). Mean number of patients with urine occurrences and number of patients receiving >100% of H-S fluids on day 1 differed by site (p<0.001 for each). MV orders were significantly associated with receiving >100% of H-S fluids on day 2 at each site (A: 25.0% vs 15.4%; B: 34.0% vs 23.4%; C: 43.0% vs 15.8%). Days 1 and 2 CFB >5% was significantly associated with increased ICU LOS at each site (p<0.001). Rounds discussions (N=76 days, 791 patients) demonstrated 64.3% discussed fluid balance and 22.9% set fluid balance goal. Nurse survey results (N=117 nurses) were remarkably similar across sites, identifying barriers to accurate fluid balance capture, achievable opportunities for improvement, and desired educational opportunities.

Conclusions: Positive %CFB is a common but variable issue across multiple ICUs. Our findings pinpoint specific areas for improvement at each site, guiding the development of Plan-Do-Study-Act cycles for better fluid management.

Funding: NIDDK Support

SA-OR54

Respiratory Alkalosis Accounts for Nearly Half of Cases of Low Serum Bicarbonate in Patients with Cirrhosis with AKI

Kirsten Johnson,[1] Dustin R. Chalmers,[4] Sumukh Shetty,[1] Montana D. Ellis,[1] Ghaith Hashem,[1] Vipin Varghese,[2] Juan Carlos Q. Velez.[3] Ochsner Group. *[1]UQ-Ochsner Clinical School, New Orleans, LA; [2]University of Michigan Division of Nephrology, Ann Arbor, MI; [3]Department of Nephrology, Ochsner Health, New Orleans, LA; [4]LSU Internal Medicine, Baton Rouge, LA.*

Background: Metabolic (Met) acidosis (Acid) is the most common acid-base disorder in the context of acute kidney injury (AKI). As a result, a low serum carbon dioxide (sCO_2) level from a chemistry panel in a patient with AKI is usually presumed to be caused by Met Acid. Respiratory (Resp) alkalosis (Alk) is the most common acid base disorder in cirrhosis. However, whether the predominance of Resp Alk prevails in cirrhosis even during AKI has not been investigated. We hypothesized that Resp Alk is a frequent cause of low sCO_2 in cirrhosis with AKI.

Methods: We prospectively collected data of patients seen in nephrology consultation for AKI who had a urine specimen subjected to microscopic examination of the urinary sediment (uSEDI) as part of the clinical evaluation. Within this cohort, we identified patients with cirrhosis with a low sCO_2 (< 22 mEq/L) in which acid-base status was assessed by either arterial blood gas (ABG) or venous blood gas (VBG) analysis. VBG results were corrected to an ABG equivalent (venous pH + 0.03 = arterial pH; venous $pCO_2 - 6$ = arterial pCO_2).

Results: Among 801 patients assessed by uSEDI over a 5-year period, 267 (33%) had cirrhosis. A low sCO_2 was recorded in 225/267 (84%). Among those with low sCO2, 109 (48%) had acid-base status assessed (77 ABG, 32 VBG). Mean age was 53 years, 44% women, 74% White, 16% Black, 4% Hispanic. Main causes of cirrhosis were alcoholic (58%) and NASH (20%). Main causes of AKI were ischemic/toxic acute tubular injury (49%) and hepatorenal syndrome (40%). Median serum creatinine at diagnosis was 3.6 mg/dL. The most common single acid-base disorders were Resp Alk in 25 (23%) and Met Acid in 24 (22%). Combined 2 disorders included Resp Alk + Met Acid in 34 (31%) and Met Acid + Resp Acid in 12 (11%) and Resp Alk and Met Alk in 6 (6%). A triple disorder was found in 16 (15%). Altogether, Resp Alk was found in 65 (60%). Furthermore, 27 (42%) of patients with isolated Resp Alk or combined Resp Alk + Met Acid (with pH > 7.35) were treated with oral or intravenous bicarbonate.

Conclusions: In patients with cirrhosis and AKI, sCO2 is often caused by Resp Alk. Default administration of bicarbonate supplementation without assessment of acid-base status should be avoided.

SA-OR55

Extracellular Vesicles of Podocytes Impact Intraglomerular Signaling and Parietal Epithelial Cell Activation

Pamella Marie Sendon,[1] Alexander Pausch,[1] Annika Gathmann,[1] Kilian Teicher,[1] Inka C. Homeyer,[1] Moritz Lassé,[1] Anja Obser,[1] Hetty N. Wong,[2] Maja Lindenmeyer,[1] Lawrence B. Holzman,[2] Markus M. Rinschen,[1] Franz L. Ricklefs,[1] Uta Erdbruegger,[3] Victor G. Puelles,[1] Tobias B. Huber,[1] Fabian Braun.[1] Braun Lab. *[1]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]University of Pennsylvania, Philadelphia, PA; [3]University of Virginia, Charlottesville, VA.*

Background: Extracellular vesicles (EVs) have the ability to impact basic pathological processes such as malignant, metabolic and autoimmune diseases through intercellular signaling. However, we lack a concise knowledge about their role in kidney health and disease. Our study aims to characterize the intraglomerular signalling propagated by medium-sized (mEVs) and small EVs (sEVs) shed by podocytes.

Methods: Using differential (ultra-) centrifugation we separated mEVs and sEVs from cell culture supernatants, kidney tissue and urine samples. Using Western Blot, immunofluorescence microscopy employing antibody stainings and pKH membrane dyes as well as image flow cytometry and cryo-electron microscopy (cryo-EM) we investigated the release dynamics of podocyte-specific EVs in different models of murine podocyte damage *in vitro* and *in vivo*. Potential signaling factors contained in EVs were analysed through proteomics. Live microscopy and cross-culture experiments were used to determine the effect of podocyte specific EVs on parietal epithelial cells (PECs).

Results: Upon podocyte damage, we detected a unified response in the form of an increase in EV release with a size-shift towards larger vesicles revealed in Cryo-EM. Depending on EV size and the initial insult, podocyte-specific EVs exerted different effects on the migratory behavior and proliferation of PECs while proteomics revealed limited differences in the EV proteome in different stress conditions. We shortlisted the first candidate proteins potentially propagating the effect on PECs. *In vivo*, decreased EV release by podocytes resulted in reduced PEC activation and limited recruitment of macrophages in a model of crescentic glomerulonephritis.

Conclusions: We present essential insights on podocyte-specific release of different sizes of EVs, their protein contents and functional implications in health and upon podocyte damage. Ongoing experiments focus on further elucidating the impact of podocyte-specific release *in vivo* and the impact of knocking-out identified EV candidate proteins.

Funding: Government Support - Non-U.S.

SA-OR56

Rapid Podocyte Loss Triggers Formation of Intercellular Bridges

Nina Cintron Pregosin,[1] Emily T. Dang,[1] Yiqing Guo,[1] Robert Bronstein,[1] Chelsea C. Estrada,[1,2] Nehaben A. Gujarati,[1] Vivette D. D'Agati,[3] Lewis Kaufman,[4] Sandeep K. Mallipattu.[1,2] *[1]Stony Brook University Renaissance School of Medicine, Stony Brook, NY; [2]Northport VA Medical Center, Northport, NY; [3]Columbia University Irving Medical Center, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Podocytes are highly specialized terminally differentiated cells that are critical for maintenance of the glomerular filtration barrier. Podocyte loss triggers the activation and proliferation of PECs, leading to crescent formation and glomerular injury. We recently identified intercellular bridges between podocytes and PECs in murine models of proliferative glomerulopathy. However, the role of these bridges between podocytes and PECs is unclear. The goal of this study is to investigate the functional role of podocyte-PEC intercellular bridges in kidney diseases.

Methods: The following models of podocyte injury were used: podocyte-specific loss of *Klf4* (*Klf4*$^{\Delta Pod}$), nephrotoxic serum (NTS) treatment, diabetic kidney disease (*db/db*), HIV-1 transgenic mice (*Tg26*), lipopolysaccharide-induced podocyte injury (LPS), and human FSGS. Single-nucleus (sn)RNA-seq, immunohistochemistry, confocal, transmission and scanning electron microscopy (TEM, SEM) were performed. Bridges were studied *in vitro* using a coculture of immortalized mouse podocytes and PECs.

Results: Intercellular bridges formed in response to rapid podocyte loss (*Klf4*$^{\Delta Pod}$, *Tg26*, NTS, FSGS). In NTS-treated mice bridges formed after proteinuria occurred – suggesting bridges play a physiological, rather than pathological role. In contrast, limited bridges formed in models with slow podocyte loss (*db/db*) or no podocyte loss (LPS). SEM and TEM revealed multiple double-membraned cytoplasmic extensions on the podocyte cell body that resembled slender filopodia, with projections making bridges with neighboring cell bodies. Numerous projections extended from podocytes to the surface of cells lining the bowman's capsule. To identify a mechanism for bridge formation, snRNA-seq showed enrichment of several genes encoding trafficking proteins (BIRC3, RAB8A, RAB11A, DYNC1H1). Immunofluorescence staining of a coculture of mouse podocytes and PECs validated the presence of these proteins and mitochondria within intercellular bridges. Live imaging of DiD-labeled cells showed the transport of cellular vesicles via intercellular bridges.

Conclusions: Intercellular bridges form in response to rapid podocyte injury and may serve as a direct, physical mechanism for cellular trafficking between injured podocytes and PECs.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR57

Intranephron Cross-Talk through Exosomes

Janina Kern,[1] Sindhu Thiagarajan,[1] Stefan Uderhardt,[2] Nina Sopel,[1] Mario Schiffer,[1] Janina Müller-Deile.[1] *[1]Universitatsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; [2]Universitatsklinikum Erlangen Medizinische Klinik 3 Rheumatologie und Immunologie, Erlangen, Germany.*

Background: Insufficient cell-cell communication of glomerular endothelial cells (GECs) and podocytes leads to a dysfunctional glomerular filtration barrier and not much is known about the intra-glomerular as well as the glomerular to tubular signaling. Exosomes are 30 nm to 160 nm small extracellular vesicles released by multivesicular bodies from various cell types. These transport vehicles encapsulate signaling molecules such as mRNAs, microRNAs or proteins. Exosomes secreted from cells acing the urinary space might be taken up by tubular cells. However, it is unclear if exosomes can serve as mediators of GEC to podocyte crosstalk *in vivo* as it is unknown if they are able to pass the glomerular basement membrane (GBM).

Methods: RNA seq analysis and proteomics were used to characterize exosome cargo of glomerular cells. A CD63 (surface protein of exosomes) plasmid tagged with mScarlet and pHluorin (labeling intracellular exosomes in red and secreted exosomes in green) was used to investigate exosome secretion in glomerular cell culture models. By injecting zebrafish eggs in one cell stadium with a pHluorin CD63 reporter plasmid including one with a podocin promotor for podocyte specific exosome labeling, exosomes could be visualized in zebrafish larvae with a multiphoton microscope in high resolution. Moreover, *in vitro* labeled exosomes were injected in the zebrafish circulation and visualized with immunofluorescence and electron microscopy, to examine their ability to pass the GBM.

Results: *In vitro* podocytes and GECs secreted exosomes that could be live-tracked with the help of a spinning disc microscope. Live tracking analyses in 2D and 3D glomerular co-culture detected exosome-transfer from one cell type to another. Incubation of GECs derived exosomes changed expression in podocytes and likewise podocyte derived exosomes had effects on tubular cell expression. Injecting fluorescently labeled exosomes into the zebrafish circulation allowed to study the permeability of exosomes for the GBM. Using CD63 plasmids encoding podocyte-specific labeled exosomes helped to investigate cell-cell communication via exosomes originated from podocytes.

Conclusions: Live tracking experiments of glomerular cell type derived exosomes will help to get more insights into inter-glomerular and glomerular to tubular cell-cell communication.

Funding: Government Support - Non-U.S.

SA-OR58

Podocyte-Derived Soluble RARRES1: A Primary Instigator of CKD Progression via Direct Injury to Podocytes and Proximal Tubules

Ye Feng,[1] Zeguo Sun,[1] Jia Fu,[1] Fang Zhong,[1] Weijia Zhang,[1] Bi-Cheng Liu,[2] John C. He,[1] Kyung Lee.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Southeast University School of Medicine, Nanjing, China.*

Background: RARRES1 is a podocyte-enriched membrane protein, whose expression correlates with human glomerular disease progression. We previously showed that RARRES1 induces podocyte apoptosis to promote glomerulosclerosis. Interestingly, the cytopathic actions of RARRES1 are entirely dependent on its proteolytic cleavage into a soluble form (sRARRES1), as cleavage mutant RARRES1 exerted no effects. As RARRES1 expression is upregulated in glomerular diseases, here we investigated the functional consequence of podocyte-specific overexpression of RARRES1 in glomerular diseases.

Methods: Mice with podocyte-specific overexpression of human wildtype-RARRES1 (Pod-RARRES1^{WT}) were generated and subjected to adriamycin-induced FSGS and streptozotocin-induced DKD. We also examined the effects of long-term RARRES1 overexpression on slowly developing aging-induced kidney injury. Wildtype and transgenic mice with cleavage-mutant RARRES1 (Pod-RARRES1^{MT}) overexpression served as controls.

Results: Pod-RARRES1^{WT}mice had significantly worsened glomerular injuries and kidney function in all three models, while the phenotype of Pod-RARRES1^{MT} mice was indistinguishable from those of wildtype control mice. Remarkably, a direct uptake of sRARRES1 was observed in proximal tubules of injured Pod-RARRES1^{WT} mice and associated with exacerbated tubular injuries, vacuolation, and lipid accumulation in disease settings. Remarkably, the tubular uptake of sRARRES1 and injury was independent of albuminuria or glomerular injury, as RARRES1 podocyte expression alone was sufficient to induce tubular injury directly. scRNAseq analysis of mouse kidneys demonstrated RARRES1 led to a marked deregulation of lipid metabolism in proximal tubule subsets. We further identified matrix metalloproteinase 23 (MMP23) to be a podocyte-specific metalloproteinase responsible for RARRES1 cleavage in disease settings, as adeno-associated virus 9-mediated knockdown of MMP23 abrogated sRARRES1 uptake in tubular cells in vivo.

Conclusions: Our study delineates a previously unrecognized mechanism by which a podocyte-derived protein directly facilitates podocyte and tubular injury in glomerular diseases and suggests that podocyte-specific functions of RARRES1 and MMP23 may be targeted to ameliorate glomerular disease progression in vivo.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR59

Organelle Communication and Maintenance of Podocyte Mitochondrial and Endosomal Homeostasis in Obesity-Related Kidney Diseases

Sho Hasegawa, Masaomi Nangaku, Madina Saipidin, Reiko Inagi. *Tokyo Daigaku, Bunkyo-ku, Japan.*

Background: Organelle stress exacerbates podocyte injury, contributing to perturbed lipid metabolism. Although organelles closely interact with one another at membrane contact sites, limited studies have explored their involvement in kidney homeostasis. The endoplasmic reticulum (ER) protein, PDZ domain-containing 8 (Pdzd8), is implicated in multiple organelle tethering processes and cellular lipid homeostasis. In this study, we aimed to elucidate the role of organelle communication in podocyte injury using podocyte-specific Pdzd8-knockout mice.

Methods: Podocyte-specific Pdzd8-knockout mice (podocin-Cre: Pdzd8 flox/flox) and littermate wild-type controls (Pdzd8 flox/flox) were generated. The mice were fed either a normal diet or a high-fat diet for 12 weeks. To elucidate the role of Pdzd8 in organelle stress, glomeruli were isolated for a comprehensive proteomic analysis. To corroborate *in vivo* proteomic phenotypes, cell culture experiments including lipidome analysis were performed using mouse podocyte cells.

Results: *In vivo*, Pdzd8 deletion exacerbated podocyte injury in an accelerated obesity-related kidney disease model. Proteomic analysis of isolated glomeruli revealed that Pdzd8 deletion exacerbated mitochondrial and endosomal dysfunction during podocyte lipotoxicity. Additionally, electron microscopy revealed the accumulation of "fatty abnormal endosomes" in Pdzd8-deficient podocytes during obesity-related kidney diseases. *In vitro*, Pdzd8 knockdown inhibited mitochondrial and fatty acid oxidation activity in podocytes, in association with a reduction of mitochondria-ER contact sites. In addition, enlarged endosomes were observed in palmitic acids-treated Pdzd8 knockdown podocytes, resembling *in vivo* "fatty abnormal endosomes." Lipidomic analysis indicated that glucosylceramide accumulated in Pdzd8-deficient podocytes, owing to accelerated production and decelerated degradation.

Conclusions: The organelle-tethering factor, Pdzd8, plays a crucial role in maintaining mitochondrial and endosomal homeostasis during podocyte lipotoxicity. Collectively, our findings highlight the importance of organelle communication at the three-way junction among the ER, mitochondria, and endosomes in preserving podocyte homeostasis.

Funding: Government Support - Non-U.S.

SA-OR60

Comprehensive Characterization of Podocyte Lipotoxicity to Elucidate New Mechanisms for Podocyte-Protective Strategies

Sebastian Sewerin,[1] Dylan Boone,[1] Lindsey Ross,[1] Choah Kim,[1] Juan Lorenzo B. Pablo,[1] Anna Greka.[1,2] *[1]Broad Institute, Cambridge, MA; [2]Harvard Medical School, Boston, MA.*

Background: Dyslipidemia constitutes a defining characteristic of nephrotic syndrome. Yet, its contribution to podocyte injury and how it affects their recovery potential is not well understood. Excess circulating lipids can induce a dysfunctional cell state, a phenomenon referred to as lipotoxicity. While podocyte lipotoxicity has been implicated in many diseases including diabetic kidney disease, it has only been studied in the context of a limited number of lipids. Free fatty acids (FFAs) are building blocks of many complex lipids found in human plasma and affect a wide range of cellular functions. Here, we systematically investigate the effects of a comprehensive library of >60 FFAs on podocytes using our FALCON (Fatty Acid Library for Comprehensive ONtologies) platform.

Methods: Through image-based FALCON screens, we assayed immortalized mouse podocytes for readouts such as cell morphology and viability. This allowed us to generate a functional lipotoxicity profile for podocytes which we compared to a similarly acquired profile from an immortalized human tubular epithelial cell (TEC) line. In isolated mouse glomeruli, we validated the most podocytotoxic FFA's deleterious effects using super-resolution microscopy and investigated the associated glomerular injury pattern. To assess the mechanistic underpinnings of FFA toxicity, we screened a library of 6800 small molecules for their potential to ameliorate FFA-induced podocyte injury.

Results: Screening a wide spectrum of structurally diverse FFAs, we generated a multi-dimensional lipotoxicity profile for podocytes, revealing distinct morphological states of FFA-treated cells and functionally diverse FFA clusters. This functional profile proved distinct from that of TECs. Toxic FFA-treated isolated mouse glomeruli exhibited podocyte foot process disintegration with a focal segmental glomerular injury pattern akin to focal segmental glomerulosclerosis. Targeted experiments showed that membrane rigidification and ER stress are involved in podocyte lipotoxicity. Finally, the compound library screen provided further insights into the mechanisms of lipotoxic injury.

Conclusions: Our FALCON platform and follow-on mechanistic studies provided a comprehensive characterization of lipotoxic injury in podocytes, with potential therapeutic implications for podocytopathies.

Funding: NIDDK Support, Private Foundation Support

SA-OR61

Inhibition of Sphingosine-1-Phosphate Receptor 4 Improves Renal Outcomes in a Mouse Model of Alport Syndrome

Matthew Tolerico, Arianna Carrazco, Judith T. Molina David, Armando Mendez, Alessia Fornoni, Sandra M. Merscher. Peggy and Harold Katz Family Drug Discovery Center. *University of Miami Miller School of Medicine, Miami, FL.*

Background: Col4a3 knockout (KO) mice, a model of Alport Syndrome, develop glomerular disease associated with renal neutral lipid accumulation and progressive renal failure that can be partially prevented and treated by lipid-lowering agents. Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid which was found to accumulate in patients with nephrotic syndrome carrying mutations in the gene coding for S1P lyase. S1P exerts its effects by interacting with one of its five G-protein coupled receptors (S1PR1-5). The role of S1P signaling in podocytes and its therapeutic potential in glomerular disease is not well understood.

Methods: S1P levels were measured in kidney cortices of 8-week-old mice by LC-MS and normalized to protein concentration. S1PR4 expression levels in kidney cortices and cell lysates were determined by Western blot and qRT-PCR analysis. *In vitro*, podocytes were treated with an S1PR4 antagonist (CYM50358) for 24 hours. Neutral lipid levels were quantified using an enzymatic assay. Lipid droplets were stained by Nile Red staining and imaged on Opera Phenix HCS system. Apoptosis was determined by ApoTox-Glo™ Assay (Promega). CYM50358 (10mg/kg) was administered to *Col4a3*

KO by intraperitoneal injection starting at 4 weeks of age and until sacrifice at 8 weeks of age. Plasma and urine samples were collected at baseline and time of sacrifice and used to determine albumin to creatinine ratio (ACR), blood urea nitrogen (BUN), and plasma creatinine. Mesangial expansion was evaluated through Periodic Acid Schiff (PAS) staining. Renal fibrosis was evaluated by Picro-Sirius Red staining.

Results: Kidney cortices from *Col4a3* KO mice had increased levels of S1P, and S1PR4 expression. Immortalized podocytes isolated from *Col4a3* KO mice showed increased S1PR4 expression, apoptosis, and neutral lipid accumulation in form of lipid droplets. Antagonism of S1PR4 resulted in a reduction of apoptosis and neutral lipids. Treatment of *Col4a3* KO mice with a S1PR4 antagonist was sufficient to reduce ACRs, BUN, and plasma creatinine. Treated mice displayed reduced mesangial expansion and renal fibrosis.

Conclusions: Our results suggest that inhibition of S1PR4 may be beneficial in preventing glomerular disease progression in a mouse model of Alport Syndrome, possibly by reducing neutral lipid accumulation.

Funding: NIDDK Support, Other U.S. Government Support

SA-OR62

Early Intervention with Intravenous AAV9 Gene Therapy Significantly Improves Biomarkers and Phenotypes in a Floxed Mouse Model of X-linked Alport Syndrome

Hiroyuki Nakai,[1] Ranjan Das,[1] Taisuke Furusho,[1] Anusha Sairavi,[1] Hideyuki Hakui,[1] Shuhua Luo,[1] Lena Li,[1] Jeffrey H. Miner.[2] *[1]Oregon Health & Science University, Portland, OR; [2]Washington University in St Louis School of Medicine, St Louis, MO.*

Background: Previously, we established a novel floxed X-linked Alport syndrome (XLAS) mouse model. A delayed intervention with a higher dose of AAV-Cre (at 17 weeks of age) improved lifespan and reduced glomerulosclerosis and tubular injuries. Here, we report the results of an early intervention (before the onset of CKD) with a lower dose of AAV-Cre to these XLAS mice.

Methods: LSL-Col4a5 hemizygous male mice (n=3) were injected intravenously (IV) with 3.0 x 10^{11} vg of the AAV9-CAG-Cre vector at 4 weeks of age. They were monitored for body weight, urinary albumin-to-creatinine ratio (ACR), and blood biomarkers of chronic kidney disease (CKD). Type IV collagen expression recovery was evaluated using immunofluorescence microscopy and kidney histology was examined in H&E-stained sections.

Results: AAV-injected mice, unlike the untreated counterparts, exhibited no discernible loss of body weight until 31 weeks of age, indicating therapeutic effects. Rescue of collagens was confirmed in one of the mice at 21 weeks post-injection. The vector-treated XLAS mice showed significant rescue of Col4a4 and Col4a5 proteins in the glomerular basement membrane using anti-Col4A4 and anti-Col4A5 antibodies. A non-injected LSL-Col4a5 hemizygous mouse was used as a negative control. There was a significant reduction in urinary ACR in the vector-treated group at 10 and 13 weeks post-injection compared to the untreated control. Notable decreases in blood creatinine (treated vs. untreated: 0.3 vs. 0.7 mg/dL, n=2) and BUN (treated vs. untreated: 47 vs. 129 mg/dL, n=2) were observed in the treated group. Kidney histology revealed a noticeable reduction in glomerulosclerosis, tubular atrophy and interstitial fibrosis. These results illustrated the successful transduction of podocytes by IV-injected AAV9 vectors in juvenile mice, preceding CKD onset.

Conclusions: This study highlights a crucial advantage of early intervention with a lower AAV dose in XLAS mice in reducing blood biomarkers of nephrotic syndrome, which was not observed in a delayed intervention strategy of AAV gene therapy. Thus, this study offers pioneering evidence of the efficacy of intravenous AAV vector-mediated gene therapy for Alport syndrome, especially notable for its effectiveness at pre-CKD establishment.

SA-OR63

Podocyte Gene Therapy Enables Glomerular Complement Modulation for IgAN Treatment

Ambra Cappelletto,[1] Rowan I. Asfahani,[1] James Matthews,[1] Alice Gennari,[1] Hannah L. Wood,[1] Sam Illingworth,[1] Gavin I. Welsh,[1,2] Alice C. Brown,[1] Moin A. Saleem.[1,2] *[1]Purespring Therapeutics, London, United Kingdom; [2]University of Bristol, Bristol, United Kingdom.*

Background: Adeno associated vector (AAV) gene therapy targeting the podocyte could pave the way to treat many glomerular diseases. We have recently shown successful podocyte targeting to rescue a genetic mutation. Here we present a novel AAV gene therapy candidate, PS-002, which targets podocytes enabling them to become 'bio-factories' secreting a complement regulator to specifically modulate complement activation in the glomerulus.

Methods: Efficacy of PS-002 was demonstrated using the grouped ddY mouse, a highly translationally relevant IgAN disease model. Safety and biodistribution of PS-002 were evaluated in Gottingen minipigs, a clinically translatable model for assessing dosing parameters via local infusion.

Results: The PS-002 candidate inhibited complement activation in grouped ddY mice as shown by reduced mesangial C3 deposits, and amelioration of disease phenotype by preservation of podocytes, reduction in mesangial expansion, inflammation and casts, and decreased proteinuria. In minipigs, we demonstrated successful gene expression across all kidney glomeruli at 28 days (100% glomeruli, n=3 pigs) and 56 days (99% glomeruli, n=3 pigs) post dosing, with a dose-response observed by RNAscope, qPCR and RT-qPCR. Low levels of AAV delivered protein were detected in the serum. These data demonstrate homogenous and sustained transduction of all kidney glomeruli using PS-002. Toxicological assessments of renal and other organ function and post-study histopathological assessments revealed no treatment-related safety concerns and only low levels of transcript were detected in the liver, with no expression in the spleen or pancreas.

Conclusions: These data demonstrate (i) the feasibility of podocyte targeted gene therapy for glomerular specific modulation of complement, (ii) substantial non-clinical data to enable translation of PS-002 to clinical development for the treatment of IgAN, and (iii) the potential to use podocyte targeting AAV candidates to regulate complement activation in diseases beyond IgAN.

SA-OR64

Ravulizumab in Atypical Hemolytic Uremic Syndrome: Final Analysis of Efficacy and Safety Outcomes in Two Phase 3 Trials

Bradley P. Dixon,[1] David Kavanagh,[9] Brigitte Adams,[10] Hee Gyung Kang,[2] Edward Wang,[3] Katherine Garlo,[3] Masayo Ogawa,[3] Spero R. Cataland,[4] Yoshitaka Miyakawa,[5] Yosu Luque,[6] Veronica Taylor,[7] Larry A. Greenbaum.[8] *[1]Renal Section, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO; [2]Division of Pediatric Nephrology, Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Alexion, AstraZeneca Rare Disease, Boston, MA; [4]Division of Hematology, The Ohio State University Medical Center, Columbus, OH; [5]Department of Hematology, Saitama Medical University, Saitama, Japan; [6]Renal Intensive Care Unit, Nephrology Department, Tenon Hospital, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France; [7]Division of Pediatric Nephrology, University of Nebraska Medical Center, Children's Nebraska, Omaha, NE; [8]Division of Pediatric Nephrology, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA; [9]National Renal Complement Therapeutics Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Translational and Clinical Research Institute, Newcastle University, Newcastle, United Kingdom; [10]University Hospital UZ Leuven, Leuven, Belgium.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare thrombotic microangiopathy (TMA) caused by complement dysregulation. Ravulizumab (RAV) is a complement C5 inhibitor (C5i) approved for the treatment of aHUS.

Methods: This analysis reports final efficacy and safety data from two phase 3, single-arm clinical trials of C5i-naive adults (NCT02949128) and pediatric patients (pts) (NCT03131219) who were C5i-naive or switched to RAV from eculizumab (pediatric switch pts). Intravenous RAV was administered every 4–8 weeks, depending on body weight, in pts with aHUS. The primary endpoint was complete TMA response (platelet count normalization, lactate dehydrogenase normalization, and ≥25% improvement in serum creatinine from baseline, at two consecutive assessments ≥4 weeks apart). The primary endpoint evaluation was at Week 26; the extension period was up to 4.5 years or product approval/registration (whichever occurred first).

Results: 54 pts completed the study (C5i-naive adults: n=28; C5i-naive pediatric pts: n=16; pediatric switch pts: n=10). The median (interquartile range) treatment duration was 130 (49–178) weeks for C5i-naive adults, 131 (15–160) weeks for C5i-naive pediatric pts, and 114 (114–123) weeks for pediatric switch pts. Among pts with available genetic data, 12/45 (27%) C5i-naive adults, 10/17 (59%) C5i-naive pediatric pts, and 6/10 (60%) pediatric switch pts had complement abnormalities and entered the extension. In C5i-naive adults (n=56), complete TMA response rates were 54% at Week 26 and 64% at end of study. In C5i-naive pediatric pts (n=20), complete TMA response rates were 75% at Week 26 and 90% at end of study. Among C5i-naive adults and pediatric pts, mean eGFR gradually improved up to Week 26 and remained stable until the end of the study. Most adverse events and serious adverse events were Grade 1 or 2 and occurred up to Week 26. No meningococcal infections were reported.

Conclusions: This final analysis over a median of 114–131 weeks demonstrated that continuation of RAV treatment is associated with sustained control of aHUS and clinical benefit through improvement and long-term preservation of renal function, with no unexpected safety concerns.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease.

SA-OR65

Serial Measures of Urine Soluble CD163 Predict Kidney Failure in ANCA-Associated Glomerulonephritis

Sinead Stoneman,[1,2] Cliona Cowhig,[1] Conor Coughlan,[1] Niall P. Conlon,[3] Jean Dunne,[3] Jennifer Scott,[4] Julie Power,[4] Mark A. Little,[4] Michael Clarkson,[1,2] Sarah M. Moran.[1,2] On behalf of RITA-Ireland. *[1]Cork University Hospital, Cork, Ireland; [2]University College Cork, Cork, Ireland; [3]St James's Hospital, Dublin, Ireland; [4]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland.*

Background: ANCA vasculitis-glomerulonephritis [AAV-GN] affects 70 – 85% of ANCA vasculitis [AAV] patients. 26% of patients progress to end-stage kidney disease [ESKD] and 43% progress without a recognised disease flare. Identifying those at highest risk of progression to kidney failure is an unmet need. Urine soluble CD163 [usCD163] has excellent biomarker characteristics and has been validated as a clinical biomarker in detecting active AAV-GN at diagnosis and flare. The use of usCD163 to predict ESKD in those considered to be in clinical remission is undefined.

Methods: We utilised longitudinal clinical data and biobank urine samples from a national multicentre rare kidney disease registry to evaluate the utility of serial usCD163 measurements to predict of kidney failure in AAV-GN. Inclusion criteria were 4 or more urine sCD163 measurements and diagnosis of AAV. The primary endpoint was kidney failure defined as death, ESKD or GFR <15mls/min/1.73m^2. Statistical analysis was performed using GraphPad Prism and R.

Results: We identified 113 participants with 4 or more usCD163 measurements over at least a 12-month period. 26 (23%) participants developed kidney failure (death (13), ESKD (17), GFR <15 (16)). Excluding the initial urine sample (generally from a period of disease activity) the median usCD163 level normalized to urine creatinine was higher in those meeting the endpoint (median 385ng/mmol vs 89ng/mmol, p<0.0001). In those with kidney failure 62.6% (128) of values were above the diagnostic threshold for active renal vasculitis. Analysis of this cohort identified the optimal diagnostic threshold for usCD163 for the future development of kidney failure as 160ng/mmol, with a sensitivity of 77.7%, a specificity of 69%, negative predictive value [NPV] of 92.3, and positive predictive value [PPV] 39.4.

Conclusions: A urine sCD163 result less than 160 ng/mmol has a strong NPV for predicting future kidney failure. This suggests that in addition to detecting active GN, urine sCD163 may provide reassurance that subclinical glomerular injury is not missed in AAV. The suppression of usCD163 associates with a significantly lower risk of progression to kidney failure, supporting a key role for undetected disease activity as the major driver of progression to kidney failure.

Funding: Private Foundation Support

SA-OR66

Efficacy and Safety of Iptacopan in Patients with C3 Glomerulopathy: 12-Month Results from the Phase 3 APPEAR-C3G Study

Carla M. Nester,[1] Richard J. Smith,[2] David Kavanagh,[3,4] Marina Vivarelli,[5] Giuseppe Remuzzi,[6] Ming-Hui Zhao,[7] Edwin K. Wong,[3,4] Yaqin Wang,[8] Angelo J. Trapani,[8] Induja Krishnan,[8] Nicholas J. Webb,[9] Matthias Meier,[9] Andrew S. Bomback.[10] *[1]The University of Iowa Stead Family Children's Hospital, Iowa City, IA; [2]The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, IA; [3]Newcastle University, Newcastle upon Tyne, United Kingdom; [4]National Renal Complement Therapeutics Centre. Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; [5]Ospedale Pediatrico Bambino Gesu, Roma, Italy; [6]IRCCS Istituto di Ricerche Farmacologiche Mario Negri Centro Anna Maria Astori, Bergamo, Italy; [7]Peking Union Medical College Hospital, Beijing, China; [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [9]Novartis Pharma AG, Basel, Switzerland; [10]Columbia University Vagelos College of Physicians and Surgeons, New York, NY.*

Background: The Phase 3 APPEAR-C3G study evaluated the efficacy, safety, and tolerability of iptacopan vs placebo in C3G patients (pts).

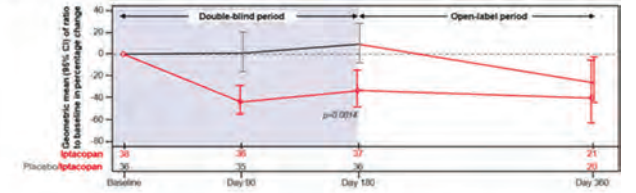
Methods: APPEAR-C3G (NCT04817618) was a multicenter, randomized, double-blind, placebo-controlled, pivotal Phase 3 study that included adult pts with biopsy confirmed C3G. The study comprised a 6 month (m) randomized double-blinded treatment with iptacopan 200mg bid. vs. placebo followed by 6m open-label iptacopan treatment, as previously described.[1]

Results: 74 pts were randomized 1:1 to either iptacopan (n=38) or placebo (n=36). Baseline pt demographics were generally balanced; the iptacopan arm exhibited a more severe disease phenotype. 43 (58.1%) pts in the iptacopan (n=22) and placebo (n=21) arms completed 12m treatment at data cut-off (when all pts completed 6m of treatment). The study met its primary endpoint, demonstrating a statistically significant reduction in 24h UPCR with iptacopan treatment at 6m (35.1%, 1-sided p=0.0014, 95% CI:13.8%, 51.1%) vs. placebo, sustained up to 12m (**Figure**). Iptacopan showed a sustained improvement in pts meeting the composite renal endpoint (≥50% reduction UPCR + ≤15% reduction in eGFR at 12m), 43.5% (iptacopan vs. placebo) and 25.0% (switched to iptacopan). Iptacopan led to improvements in the trajectory of eGFR compared to pts' historical eGFR decline. Iptacopan demonstrated a favorable safety profile with no new safety signals identified. Other 12m primary and key secondary endpoints will be presented.

Conclusions: Iptacopan demonstrated a significant and clinically meaningful proteinuria reduction on top of supportive care at 6m in the APPEAR-C3G study; sustained up to 12m. Iptacopan was well tolerated with a favorable safety profile in C3G pts. **Reference:** 1. Bomback AS, et al. *Kidney Int Rep*. 2022;7:2150–9

Funding: Commercial Support - Novartis Pharma AG

Figure. Proteinuria reduction (UPCR 24h) sustained to 12m



Full analysis set. Note that there was one intercurrent event of increasing corticosteroid dose on Day 106 in the iptacopan group
Robustness of primary endpoint results demonstrated by consistency of results across sensitivity analyses.

SA-OR67

Avacopan beyond the 52-Week Treatment Course

Abdallah Sassine Geara,[1] Julia Ford,[2] Duvuru Geetha.[3] *[1]University of Pennsylvania, Philadelphia, PA; [2]University of Michigan, Ann Arbor, MI; [3]Johns Hopkins University, Baltimore, MD.*

Background: The landmark ADVOCATE trial treated patients with AVP for 52 weeks. In real-world use, some patients are prescribed AVP for a longer duration. In this study, we describe a multi-center experience of prolonged courses of AVP including the outcomes at 52w and adverse effects of AVP treatment beyond 52w.

Methods: We performed a multi-center retrospective cohort study of 15 pts with new and relapsing AAV treated with AVP for a duration of 52w or longer.

Results: Mean age 54 (20) years, 53% female, 10/15 MPO-AAV, 5/15 PR3-AAV 4/15 renal involvement and 5/15 relapsing AAV. RTX induction (12/15) and maintenance (14/15) All pts discontinued prednisone within the first 26w, mean eGFR rose by 15 and 18 mL/min/1.73m^2 at 26w and 52w respectively. Remission was 13/15 at 26w and 15/15 at 52w Reasons for treating with AVP beyond 52w: physician and/or patient preference in 12/15 pts, inability to give rituximab in 3/15 pts 8/15 stopped AVP after a median duration of 63 (7) w, 7/15 are still taking AVP for a median (IQR) duration of 99 (29) w Beyond 52w, 3/15 could not be maintained on rituximab During a mean follow-up period of 96 (21) w, 1/15 patients experienced AAV flare, and none progressed to ESKD. On last follow-up, the mean eGFR rise from baseline was 16 ml/min/1.73m^2. Infections were the most commonly reported adverse effects including 5 infections requiring hospitalization. No patient had to discontinue AVP due to abnormal LFTs during the follow up period.

Conclusions: This real-world experience shows that AVP is being used in real-world practice beyond week 52, with patient/physician preference being the main reason. Rituximab was used alongside AVP for remission maintenance in majority of patients. Infection complications were the most observed adverse effects. Further data on the longer-term use of AVP is needed.

Age Female	54 (20) 8
MPO PR3 Relapse	10 5 5
baseline BVAS baseline eGFR	19 (9) 36 (24)
Time of disease onset to start of AVP	87 (100) days
Time from start AVP to stop of prednisone	36 (30) days
induction RTX Induction CYC Induction RTX + CYC	12 1 2
Maintenance RTX Maintenance MTX None	14 1 1
Physician/patient preference Unable to give rituximab for maintenance	12 3
Duration of follow-up total duration of AVP for pts who stopped total duration of AVP for pts who are still on AVP	96 (21) weeks 64.2 (7) weeks 92.8 (17.4) weeks
CR at 26w CR at 52w	13 (87%) 15 (100%)
eGFR rise at 26w eGFR rise at 52w eGFR rise at last follow up ESRD Relapse	15 (23) 18 (19) 16 (21) 1 0
infections requiring hospitalization Increase LFTS	5 0

SA-OR68

Noninvasive Assessment of the Presence or Absence of Histologic Activity in Kidney Biopsies from Patients with Lupus Nephritis

Jorge E. Rojas-Rivera,[1] Juan M. Mejia-Vilet,[2] Valeria Navarro Sanchez,[2] Brad H. Rovin.[1] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: Withdrawal of immunosuppressive therapy for lupus nephritis (LN) may be considered if histologic activity completely resolves. Soluble urine CD163 (uCD163) is released from intra-renal macrophages and strongly correlates with the LN activity index (AI). We examined whether uCD163 could differentiate histologically active from quiescent LN, avoiding the need for a repeat kidney biopsy before withdrawing therapy.

Methods: Urine collected at the time of diagnostic kidney biopsy from Ohio (OSU, discovery, n=119) and Mexican (MEX, validation, n=113) LN cohorts was assessed for uCD163 by ELISA. The relationship between uCD163 and AI was tested by Spearman's correlation. The ability of uCD163 to distinguish between the presence and absence of histologic activity was examined by receiver operating characteristic (ROC) analysis, and the strength of prediction by the area under the ROC curve (AUC).

Results: Table 1 shows the correlation between uCD163 and other commonly measured clinical parameters and components of the AI. uCD163 significantly associated with each AI component but correlated best with endocapillary hypercellularity. uCD163 distinguished the absence (AI=0) or presence (AI≥1) of biopsy histologic activity with AUCs of 0.778 (OSU) and 0.791 (MEX), and correctly classified 84% (OSU) and 93% (MEX) of patients. The AUCs to discriminate presence or absence of endocapillary hypercellularity were 0.805 (OSU) and 0.787 (MEX). The uCD193 cutoffs(Younden's Index) to differentiate AI=0 from AI ≥1 were 8.82 (OSU) and 8.83 (MEX) ng/mg creatinine.

Conclusions: Urine soluble CD163 is a robust noninvasive biomarker that accurately differentiates LN patients with ongoing disease activity from those with histologic resolution of LN. We suggest uCD163 may be used in lieu of a repeat biopsy to manage immunosuppression withdrawal in LN.

Funding: Other NIH Support - NIAMS

Table 1. Association of urine CD163 and routine clinical biomarkers with histological activity parameters in lupus nephritis

Biomarker	Cohort	Stats	Endocapillary hypercellularity	Karyorrhexis & neutrophils	Fibrinoid necrosis	Wire loops	Cellular crescents	Interstitial inflammation	Total AI score
uCD163	OSU	r, p-value	0.631 <0.0001	0.523 <0.0001	0.454 <0.0001	0.439 <0.0001	0.499 <0.0001	0.388 <0.0001	0.664 <0.0001
	Mexico	r, p-value	0.627 <0.0001	0.467 <0.0001	0.386 0.0008	0.445 <0.0001	0.506 <0.0001	0.374 0.003	0.730 <0.0001
uPCR	OSU	r, p-value	0.408 <0.0001	0.388 <0.0001	0.288 0.004	0.314 0.0006	0.298 0.0012	0.366 0.0001	0.450 <0.0001
	Mexico	r, p-value	0.225 0.017	0.071 0.453	0.069 0.462	0.417 <0.0001	0.226 0.016	0.216 0.022	0.369 0.0001
SCr	OSU	r, p-value	0.252 0.007	0.233 0.017	0.193 0.039	0.166 0.078	0.235 0.012	0.444 <0.0001	0.360 0.0001
	Mexico	r, p-value	0.183 0.168	-0.012 0.903	0.135 0.155	0.164 0.040	0.208 0.029	0.437 <0.0001	0.306 0.001
C3	OSU	r, p-value	-0.327 0.0024	-0.266 0.011	-0.226 0.032	-0.253 0.016	-0.201 0.057	-0.130 0.220	-0.317 0.0025
	Mexico	r, p-value	-0.328 0.0004	-0.208 0.028	-0.243 0.0098	-0.348 0.0002	-0.341 0.0002	-0.334 0.198	-0.457 <0.0001

SA-OR69

PRRC2A rs114580964 Variant as an Independent Predictor of Poor Kidney Prognosis in Chinese Patients with Lupus Nephritis

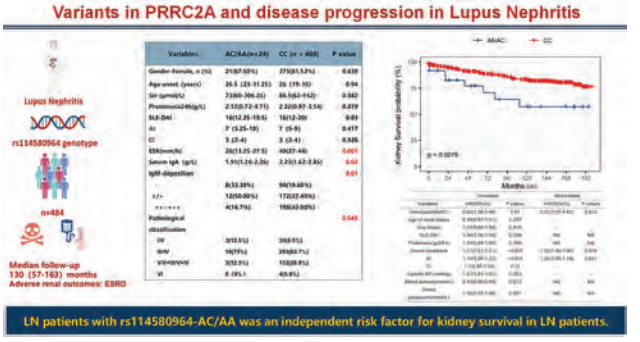
Wang Xiang, Xiuzhi Jia, Xi Xia, Rui H. Tang, Wei Chen. Chen Lab LN. *The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Lupus nephritis (LN) is a significant manifestation of systemic lupus erythematosus (SLE) with profound immune complex deposition in the glomerulus. The prognosis of LN varies across ethnic groups, with Asian populations often exhibiting higher rates of renal involvement and poorer outcomes. In our prior genome-wide association study, the PRRC2A variant rs114580964 was identified as a novel genetic determinant for susceptibility to LN. However, the correlation between the rs114580964 variant and clinical outcomes as well as prognosis of LN remains unclear.

Methods: This cohort study included 484 Chinese patients with LN in First Affiliated Hospital of Sun Yat-sen University. Clinical characteristics and outcomes were analyzed, with 469 patients included in the prognostic analysis after 15 patients were lost to follow-up. The primary outcome was the incidence of end-stage renal disease (ESRD).

Results: Among 484 patients, 24 (5%) had the rs114580964-AA/AC genotype, while 460 (95%) had the rs114580964-CC genotype. Patients with the rs114580964-AA/AC genotype exhibited weaker mesangial IgM deposition, lower erythrocyte sedimentation rate (ESR), and lower IgA levels compared to those with the rs114580964-CC genotype. Kidney survival analysis indicated that the rs114580964-AA/AC genotype was associated with poorer long-term kidney outcomes in LN. Cox regression analysis identified the rs114580964-AA/AC genotype as an independent risk factor for kidney survival in LN patients.

Conclusions: The PRRC2A rs114580964-AA/AC variant independently predicts poor kidney prognosis in Chinese patients with lupus nephritis.



SA-OR70

Dispelling the Myth of Sex Differences in Lupus Nephritis (LN): A Pooled Analysis of 779 Patients

Kristina K. Nasr,[1] Ryan B. Coopergard,[1] Sisi Ma,[1] Brad H. Rovin,[2] Patrick H. Nachman.[1] *[1]University of Minnesota Medical School, Minneapolis, MN; [2]The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: LN is reported to be more severe and have worse outcomes in men than women based on cohort studies with small numbers of men. We compared LN in men and women utilizing data pooled from 3 randomized controlled trials (RCT) and 7 cohort studies. We aimed to determine if differences exist for: 1- disease severity at diagnosis or flare; 2- first treatment choice; and 3- key outcomes at 1yr.

Methods: Baseline was defined as the date of LN flare. The entire data set was used to compare baseline characteristics between sexes and the outcomes at 1yr (complete renal response; composite of doubling of creatinine, dialysis, or death). Data were imputed using the median for variables with <30% missing data. Analysis of treatment choice (4 groups: cytotoxic, antimetabolite, calcineurin inhibitor, other) used only cohort data. Descriptive statistics used two-sample t-tests or Chi-square. Mixed model regression with studies as the random effects, controlled for age and race, were used to determine the effect size and p-values of sex on key clinical variables. For outcomes, we used logistic regressions controlling for treatments and baseline characteristics significantly correlated to outcomes.

Results: The pooled cohort included 94 men and 675 women (25% Asian, 11% Black, 53% White, 11% other). There were no statistically significant differences between sexes in age, race, duration of SLE or LN, C3, anti-dsDNA, LN class distribution or SLE Disease Activity Index 2K. No deaths were recorded. Key findings are in the table.

Conclusions: Compared to women, men have a lower eGFR and more proteinuria at baseline, but have similar LN class distribution and fewer have low C4. The lower eGFR may be related to markers of kidney histopathology (e.g. activity or chronicity indices) or comorbidities that were not captured. We found no significant outcome differences between sexes at 1yr adjusting for relevant variables in this large international pooled analysis.

Variable	Effect Size of Sex (M)	Raw p-value	BH corrected p-value
eGFR (ml/min/1.73m2)	-9.802	0.005	0.032
24 hr Urine Protein (g/day)	1.013	0.005	0.032
Complement C4 (% abnormal)	0.494	0.007	0.032
First Treatment Choice	N/A	0.472	N/A
Doubling S.Cr or Dialysis	0.975	0.320	0.568
Complete Renal Response	0.948	0.366	0.568

SA-OR71

Increased Risk of Cancer in Glomerular Diseases: A Population-Level Analysis

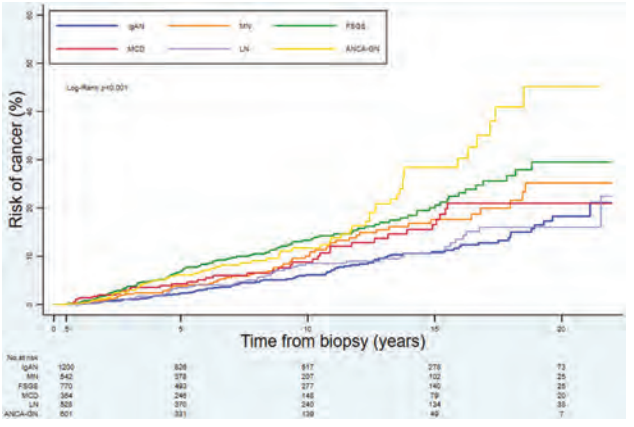
Jialin Han,[1] Yinshan Zhao,[1] Mark Canney,[2] Mohammad Atiquzzaman,[1] Adeera Levin,[1,3] Sean Barbour.[1,3] *[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]University of Ottawa, Ottawa, ON, Canada; [3]BC Provincial Renal Agency, Vancouver, BC, Canada.*

Background: Patients with glomerular disease (GN) may be at an increased risk of cancer due to immunosuppression, chronic inflammation and infection with oncogenic viruses. However, there is limited epidemiologic data such that the absolute risk of cancer and cancer-related risk factors in GN remain unknown.

Methods: We conducted a population-level analysis of all adults with biopsy-proven GN in British Columbia, Canada from 2000 to 2020, using a centralized pathology database linked to a provincial cancer database. Age- and sex- standardized incidence ratios (SIR) of cancer events were calculated. Kaplan-Meier curves were used to describe time to the first cancer event.

Results: The cohort comprised 4,006 patients, including IgAN (N=1200), membranous nephropathy (MN, N=542), FSGS (N=770), MCD (N=364), lupus nephritis (LN, N=528) and ANCA-GN (N=602). During a median of 7.9 years follow up, cancer events occurred in 386 patients (9.6%) including colon (N=56), lung (N=50), prostate (N=45), breast (N=24), kidney (N=23), lymphoma (N=22) and cervical (N=19) cancer. Those with cancer had more severe disease activity, with lower eGFR (45.3 vs 57.2 ml/min/1.73m^2) and higher proteinuria (2.5 vs 2.0 g/day), and more comorbidity burden at baseline. The risk of cancer was increased compared to the general population (SIR 1.5), including age groups 20-40, 40-60, 60-80, and >80 years (SIR 6.6, 1.7, 1.4 and 1.2 respectively). The risk of cancer was increased in ANCA-GN, FSGS, MN and MCD compared to IgAN or LN (Figure 1).

Conclusions: Patients with GN have an increased risk of cancer compared to the general population, particularly amongst younger patients who have a longer life expectancy and may benefit most from improved cancer screening. The risk of cancer varied by disease activity and type of GN, both of which may be correlated with immunosuppression use. Future steps will be to investigate risk factors for cancer in GN, including the type and extent of immunosuppression exposure.



SA-OR72

Major Adverse Cardiovascular Events (MACE) in Proteinuric Glomerulopathies: A CureGN and NEPTUNE Study

Matthew Schuchman,[1,2] Christine B. Sethna,[1,2] Abigail R. Smith,[9] Crystal A. Gadegbeku,[3] Dorey A. Glenn,[4] Meryl Waldman,[5] Patrick H. Nachman,[6] Bryce A. Kerlin,[10] Bruce M. Robinson,[7] Fadhl Alakwaa,[7] Sharon G. Adler,[11] Agustin Gonzalez-Vicente,[8] Markus Bitzer,[7] Tarak Srivastava,[20] Myda Khalid,[17] Vimal K. Derebail,[18] Gentzon Hall,[21] Katherine R. Tuttle,[19] Michelle M. O'Shaughnessy,[22] Gabriel M. Cara-Fuentes,[16] Bethany A. Roehm,[15] Jarcy Zee,[14] Alexis C. Gomez,[12] Howard Trachtman,[7] Roy O. Mathew.[13] On behalf of the NEPTUNE Cardiovascular Working Group. *[1]Northwell Health, New Hyde Park, NY; [2]Cohen Children's Medical Center, Queens, NY; [3]Cleveland Clinic, Cleveland, OH; [4]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]National Institutes of Health, Bethesda, MD; [6]University of Minnesota Twin Cities, Minneapolis, MN; [7]University of Michigan Michigan Medicine, Ann Arbor, MI; [8]Case Western Reserve University, Cleveland, OH; [9]Northwestern University Feinberg School of Medicine, Chicago, IL; [10]Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [11]Harbor-UCLA Medical Center, Torrance, CA; [12]Boston Children's Hospital, Boston, MA; [13]VA Loma Linda Healthcare System, Loma Linda, CA; [14]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [15]The University of Texas Southwestern Medical Center, Dallas, TX; [16]Nationwide Children's Hospital, Columbus, OH; [17]Indiana University, Bloomington, IN; [18]University of North Carolina Chapel Hill, Chapel Hill, NC; [19]Providence St Joseph Health, Renton, WA; [20]Children's Mercy Kansas City, Kansas City, MO; [21]Duke Health, Durham, NC; [22]University College Cork, Cork, Ireland.*

Background: Relationships between clinical characteristics and MACE have not been well characterized in patients with proteinuric glomerulopathies.

Methods: Participants in NEPTUNE and CureGN (N=3224) with biopsy-proven minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy or IgA nephropathy/vasculitis were included. The primary outcome was time from enrollment to MACE (first heart failure, stroke, or coronary artery disease event). Crude Cox regressions (Table) identified clinical characteristics with p<0.2 for inclusion in multivariable Cox regression using backwards selection to find best fit for final model. Age, sex, obesity and days from biopsy were forced into the model *a priori* .

Results: Mean age was 33.3±21.5 yrs, 35% <18 yrs, median follow-up 55 months. 158 total events in 134 (4.2%) participants were recorded: 39 stroke, 47 heart failure, and 72 coronary artery disease. In multivariable modeling, older age (HR 1.04, CI 1.03-1.06 p<0.001), obesity (HR 1.56, CI 1.07-2.3 p=0.02), prior history of MACE (HR 11.46, CI 7.33-17.92, p<0.001) and chronic kidney disease (CKD) stage 5 (HR 4.41, 1.45-13.44, p<0.01) at enrollment were associated with MACE.

Conclusions: Surprisingly, proteinuria and glomerulopathies were not associated with MACE, but risk factors identified in other CKD cohorts retain importance. Further analyses will characterize additional non-traditional predictors of cardovascular disease.

Funding: NIDDK Support

Table: Crude Cox Regressions for baseline characteristics associated with MACE

	Hazards Ratio (HR)	95% CI	p-value
Age	1.07	1.06-1.08	<0.001
Male sex	1.07	0.76-1.51	0.70
Diagnosis (Ref: Minimal Change)	—	—	—
Focal Segmental Glomerulosclerosis	1.93	1.12-3.32	0.02
Membranous Nephropathy	2.45	1.47-4.09	<0.001
IgA Nephropathy	0.79	0.43-1.43	0.44
Days from biopsy to baseline	1.000	1.000-1.001	0.12
Obesity	1.66	1.17-2.37	0.005
Dyslipidemia	1.79	0.89-3.60	0.10
HTN	2.99	1.91-4.65	<0.001
On ACEi	1.56	1.08-2.24	0.02
eGFR	0.975	0.969-0.980	<0.001
Urine protein creatinine ratio	1.023	1.000-1.047	0.047
CKD Stage 5 (Ref: CKD stage 1)	8.84	3.00-36.65	<0.001
Prior MACE	28.44	20.22-39.99	<0.001

SA-OR73

Comparative Effectiveness of Immunosuppressive Medications in Nephrotic Syndrome: A Cure Glomerulonephropathy (CureGN) Study Report

Cal Robinson,[1,6] Pietro A. Canetta,[2] Gabriel M. Cara-Fuentes,[3] Larry A. Greenbaum,[4] Margaret Helmuth,[5] Michelle A. Hladunewich,[6] Jason M. Kidd,[7] Maria Larkina,[5] Kimberly J. Reidy,[8] Rulan S. Parekh.[9] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Columbia University Irving Medical Center, New York, NY; [3]Nationwide Children's Hospital, Columbus, OH; [4]Emory University, Atlanta, GA; [5]University of Michigan, Ann Arbor, MI; [6]University of Toronto, Toronto, ON, Canada; [7]Virginia Commonwealth University, Richmond, VA; [8]Children's Hospital at Montefiore, New York, NY; [9]Women's College Hospital, Toronto, ON, Canada.*

Background: Rituximab is increasingly used to treat frequently-relapsing nephrotic syndrome in children and young adults. Yet, the real-world comparative effectiveness of immunosuppressive medications is unclear.

Methods: Using target trial methods, we emulated a multi-center, open-label, pragmatic randomized controlled trial with CureGN data. We included children and young adults (<40 years) diagnosed with minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) that had prior complete remission and initiated rituximab, mycophenolate mofetil (MMF), or calcineurin inhibitors (CNI). Randomization was emulated by propensity score overlap weighting. The primary outcome was time-to-relapse using weighted Cox proportional hazards models.

Results: Of 221 eligible CureGN participants, 111 initiated rituximab, 46 MMF, and 64 CNI. Baseline characteristics were balanced after propensity score weighting. Mean age was 13.3 years and 80% had prior steroid-sparing drug use. During median 4.3-year (IQR 1.9-6.1) follow-up, relapse occurred in 56%, 46%, and 58% after rituximab, MMF, and CNI use, respectively. There was no difference in relapses after rituximab vs. MMF or CNI (weighted HR 1.16, 95%CI 0.74-1.81). There were also no differences in relapse rates, kidney function decline, or adverse events.

Conclusions: There was no difference in relapse risk after rituximab vs. MMF or CNI among children and young adults with difficult-to-treat nephrotic syndrome. Therapeutic selection should be a shared decision, considering medication-specific side-effects, costs, access, duration, and patient adherence.

Funding: Government Support - Non-U.S.

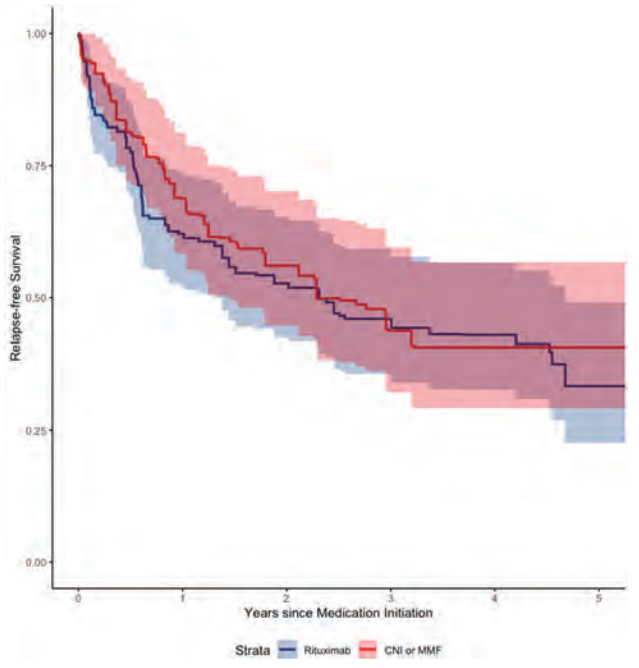


Figure. Weighted relapse-free survival after rituximab vs. MMF or CNI use

SA-OR74

Initial Treatment of Idiopathic Nephrotic Syndrome in Children with Mycophenolate Mofetil vs. Prednisone: A Prospective, Randomized, Controlled, Multicenter, Open, Phase 3, Noninferiority Study

Marcus R. Benz,[1,2] Rasmus Ehren,[1] Britta Höcker,[3] Alexander Fichtner,[3] Uwe Querfeld,[4] Peter F. Hoyer,[5] Markus J. Kemper,[6] Dieter Haffner,[7] Jörg Dotsch,[1] Martin Konrad,[8] Anja C. Sander,[9] Jan Meis,[9] Burkhard Toenshoff,[3] Lutz T. Weber.[1] German Society of Pediatric Nephrology (GPN). *[1]University Hospital of Cologne, Cologne, Germany; [2]Pediatric Nephrology Dachau, Dachau, Germany; [3]University Children's Hospital Heidelberg, Heidelberg, Germany; [4]Charite Universitatsmedizin Berlin, Berlin, Germany; [5]Universitat Duisburg-Essen, Duisburg, Germany; [6]Asklepios Kliniken GmbH & Co KGaA, Hamburg, Germany; [7]Medizinische Hochschule Hannover Zentrum fur Kinderheilkunde und Jugendmedizin, Hannover, Germany; [8]Universitat Munster, Munster, Germany; [9]Universitat Heidelberg, Heidelberg, Germany.*

Background: Initial treatment of idiopathic nephrotic syndrome (iNS) in children requires sufficient immunosuppressive therapy to induce and sustain remission and consists of a prolonged course with glucocorticoids (GC). Even though being effective, this treatment is associated with pronounced GC associated toxicity. Mycophenolate mofetil (MMF) is effective in sustaining remission in patients with frequently relapsing or GC-dependent nephrotic syndrome. The hypothesis of the INTENT-Study (initial treatment of idiopathic nephrotic syndrome in children with mycophenolate mofetil vs. prednisone) was that MMF is not inferior to standard therapy with GC in the iNS in children with regard to maintenance of remission and subsequent recurrence rate.

Methods: 272 children (mean age at onset 4.1±2.3 years; 64.3% males) with a first episode of SSNS were randomized to either standard treatment (12 weeks of GC) or experimental treatment (MMF only after induction of remission with GC for a total treatment period of 12 weeks). Primary end-point was occurrence of treated relapse within follow-up of 24 months after completion of initial treatment. Secondary end-points included i.a. course of the disease and drug toxicities.

Results: MMF was not inferior to GC treatment in terms of the primary end-point (imputed mITT set: relapse rate 79.1% (MMF group) vs. 74.8% (GC group), difference 4.3% [-4.2%;12.7%], p=0.019; imputed per protocol set: relapse rate 79.2% (MMF group) vs. 77.7% (GC group), difference 1.5% [-7.7%;10.8%], p=0.008). In the MMF arm, there were fewer GC-related side effects, such as lower blood pressure and body mass index as well as less frequent psychological abnormalities and cushingoid appearance. Cytopenias were more frequent in the MMF group but overall rare and mild. The rate of frequently relapsing nephrotic syndrome in the follow-up was comparable between the groups (MMF: 47.2%, GC: 45.2%).

Conclusions: The presented results of the INTENT-Study show non-inferiority of the MMF arm to the standard GC arm with no safety concerns and fewer GC-related side effects. They have the potential to alter the standard of care in SSNS.

Funding: Government Support - Non-U.S.

SA-OR75

Immunomodulatory Effects of Levamisole in Children with Idiopathic Nephrotic Syndrome

Antonia Bouts,[1] Floor Veltkamp,[1] Gerarda H. Khan.[2] LEARNS Consortium. *[1]Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; [2]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands.*

Background: This study aimed to systematically investigate the effects of Levamisole (LMS) on the human immune system, including its impact on isolated human immune cells in vitro. The objectives were to elucidate the immunological mechanisms underlying idiopathic nephrotic syndrome (INS) in children, assess the immunomodulatory effects of LMS, and investigate its potential therapeutic implications in INS management

Methods: Blood samples were collected from INS pediatric patients and age-matched healthy controls (HC) for flow cytometry and immunoplexing analysis. Additionally, whole blood samples from INS patients treated with LMS or placebo were stimulated with lipopolysaccharide (LPS) or anti-CD3/anti-CD28, and cytokine production was measured.

Results: Compared to HC, INS patients exhibited elevated levels of circulating T-cells, particularly CD8+ T-cells, and an increased presence of plasmablasts. Moreover, INS patients demonstrated heightened IgM production and reduced IgG levels at diagnosis, suggesting early activation of the humoral immune response. LMS-treated patients showed decreased B-cell counts and altered cytokine profiles, with enhanced production of TNF-α, IFN-γ, and IL-2 upon stimulation, and reduced levels of IL-13 compared to placebo-treated patients. Earlier work from our group has shown that LMS suppresses the proliferation and activation of both CD4+ and CD8+ T-cells by modulating gene expression associated with cell cycle progression and p53 activation [1]. Additionally, LMS treatment decreases B-cell proliferation, Ig production, and metabolism, while inducing upregulation of genes involved in plasmablast differentiation.

Conclusions: These findings highlight the immunomodulatory effects of LMS on the human immune response, shedding light on its potential therapeutic role in INS management in children. LMS appears to suppress immune cell proliferation, alter gene expression profiles, and induce DNA damage, suggesting its capacity as an immunosuppressive agent. Further research is needed to fully elucidate the therapeutic implications of LMS in immune-mediated disorders and its underlying mechanisms of action. [1]. Khan *et al.* European Journal of Immunology 2023 Nov;53(11):e2350562.

Funding: Private Foundation Support

SA-OR76

Urine Output (UO) and AKI Diagnosis in Neonates and Infants: A Prospective Study in Cardiac Surgery Patients with Indwelling Urinary Catheters

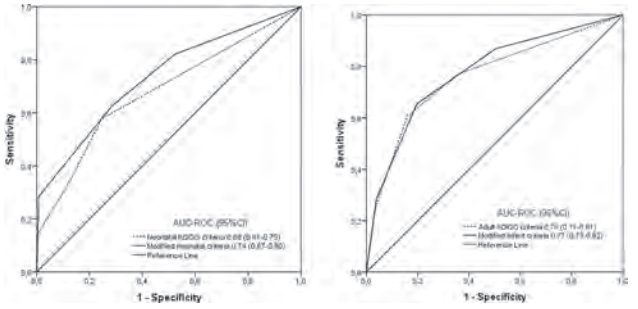
Alexandre B. Liborio, Adriana T. Girão, Candice T. Cavalcante. *Universidade de Fortaleza, Fortaleza, Brazil.*

Background: AKI in neonates and younger infants is associated with significant mortality, yet a precise definition, especially concerning UO thresholds, remains elusive. This study aimed to evaluate UO thresholds for AKI in neonates and infants (1 month to 2 years old) with indwelling urinary catheters.

Methods: Six-year prospective cohort study involving children aged 2 years or younger who were undergoing cardiac surgery. All patients had indwelling urinary catheters for accurate urine output measurements up to the second postoperative day and at least two sCr measurements—one before surgery. The main objective of this study was to determine the optimal UO thresholds for AKI definition and staging in neonates and infants compared with the currently used criteria—neonatal and KDIGO definitions. The outcome was a composite of severe AKI, KRT or hospital mortality.

Results: The study included 1,024 patients: 253 in the neonatal group and 772 in the infant group. In both groups, the lowest UO at 24 h had good discriminatory capacity for the composite outcome. In neonates, the best thresholds (evaluated by ROC curves) were 3.0, 2.0 and 1.0 mL/kg/h, and in infants, the thresholds were 1.8, 1.0 and 0.5 mL/kg/h. These values were used for modified AKI staging for each age group. In neonates, this modified criterion was associated with the best discriminatory capacity (see figure left) and net reclassification improvement (NRI) - 17.3% in comparison with the neonatal KDIGO criteria. In infants, the modified criteria was comparable to the adult KDIGO criteria, and the NRI was near zero. sensitivity analysis according to diuretic use was performed with similar results.

Conclusions: For the first time, using indwelling catheters for UO measurements, our study reinforced that the current KDIGO criteria may require adjustments to better serve the neonate population. Additionally, using the UO criteria, we validated the adult KDIGO criteria in infants.



SA-OR77

Circulating Extracellular Vesicles as Mediators of Impaired Angiogenesis in Pediatric CKD

Felix Behrens, Johannes Holle, Chia-Yu Chen, Harithaa Anandakumar, Ulrike Löber, Nicola Wilck, Hendrik Bartolomaeus, Wolfgang M. Kuebler, Szandor Simmons. *Charite - Universitatsmedizin Berlin, Berlin, Germany.*

Background: Patients with chronic kidney disease (CKD) suffer from high morbidity and mortality due to cardiovascular disease (CVD). Nonetheless, underlying mechanisms of CVD in CKD remain elusive. Extracellular vesicles (EVs) have lately been identified as facilitators of inter-organ communication and EVs of endothelial origin (EC-EVs) have been linked to CVD development. We hypothesized that altered EV release and cargo mediate CVD development in CKD.

Methods: 94 children with different CKD stages (before or on dialysis, after kidney transplantation and age-matched healthy donors), were enrolled in this study, yielding analyses on plasma EV phenotype in the absence of age-related comorbidities. The impact of CKD EVs on CVD processes was analyzed *in vitro* on transcriptomic and functional level.

Results: Concentrations of EC-EVs were increased in hemodialysis patients and decreased after kidney transplantation. According to small RNA sequencing, CKD EVs had lower abundance of 30 specific microRNAs, which were predicted to affect angiogenesis and smooth muscle cell proliferation. *In vitro*, CKD EVs altered the transcriptome of aortic endothelial cells, with most differentially enriched genes implicated in angiogenesis pathways. CKD EVs functionally impaired angiogenic properties of umbilical vein endothelial cells, as illustrated by reduced vascular tube formation with reduced vascular density, impaired migration and lowered proliferation. The combination of high shear stress, as present in arterio-venous fistulas, and the uremic toxin indoxyl sulfate was identified as trigger of increased EV formation from venous endothelial cells, which also recapitulated EV microRNA changes observed in CKD *in vivo*.

Conclusions: CKD leads to quantitative and compositional dysregulation in EV release. Altered EV microRNA cargo associates with detrimental effects of CKD EVs on angiogenesis, going in line with the cardiovascular phenotype of CKD patients. EVs and in particular their microRNA cargo could form promising targets for novel therapeutic strategies to fight CVD in CKD.

SA-OR78

Low Serum Bicarbonate and Cardiovascular Disease Risk in Children with CKD

Denver D. Brown,[1] Jennifer Roem,[2] Kimberly J. Reidy,[6] Susan L. Furth,[4] Bradley A. Warady,[3] Michal L. Melamed,[5] Tammy M. Brady.[2]
[1]Children's National Hospital, Washington, DC; [2]Johns Hopkins Medicine, Baltimore, MD; [3]Children's Mercy Kansas City, Kansas City, MO; [4]The Children's Hospital of Philadelphia, Philadelphia, PA; [5]NYU Langone Health, New York, NY; [6]Children's Hospital at Montefiore, New York, NY.

Background: In adults, metabolic acidosis (MA) has been linked to worse cardiovascular disease (CVD) outcomes but this association has not been studied in children with chronic kidney disease (CKD). We investigated if low serum bicarbonate (a MA surrogate) is associated with adverse CVD risk measurements in children with CKD.

Methods: This observational study included children ≥1 year of age enrolled in the Chronic Kidney Disease in Children (CKiD) study who had a baseline estimated glomerular filtration rate (eGFR) between 30-90 ml/min/1.73m^2, ambulatory blood pressure measurement (ABPM) and left ventricular mass (LVM) data. Linear and logistic regression models were used to characterize associations between serum bicarbonate, ABPM, and LVM. As normative values for ABPM and LVM change in childhood, index measurements were calculated for ABPM and LVM (LVMI) based on participants' age, sex, and height. Serum bicarbonate was analyzed continuously and categorized as <22mEq/L (low) and ≥22mEq/L (normal). Analyses were adjusted for age, sex, race, body mass index, CKD etiology group (nonglomerular and glomerular causes of CKD), and eGFR.

Results: The study population comprised 933 children- 696 with nonglomerular and 237 with glomerular CKD. The median age was 11 years old, 63% were males, and >50% were Caucasian. A total of 677 children were included in analyses that examined MA and ABPM and 819 children were included in analyses of MA and LVMI. In adjusted analyses, significant but opposite associations were noted between serum bicarbonate, ABPM index, and LVMI. Specifically, wake and sleep systolic and diastolic ABPM indices decreased with each 1meq/L decrease in serum bicarbonate level. However, LVMI increased with decreasing bicarbonate level: specifically, LVMI z-score increased 0.02 [0.01, 0.04] per 1mEq/L decrease in serum bicarbonate. The association with ABPM indices did not change when serum bicarbonate was categorized; however, low serum bicarbonate (<22mEq/L) was no longer significantly associated with LVMI once analyses were adjusted for eGFR.

Conclusions: Low serum bicarbonate was associated with decreasing systolic and diastolic ABPM indices, but increasing LVMI. Future studies will investigate if treatment of MA with sodium-based alkali therapies mitigates the associations between serum bicarbonate, ABPM, and LVMI.

Funding: NIDDK Support

SA-OR79

Health Care Utilization in Infants with ESKD

Ashna Pudupakkam, Shweta S. Shah, Catherine Joseph, Sarah J. Swartz, Poyyapakkam Srivaths, Michael C. Braun. *Baylor College of Medicine, Houston, TX.*

Background: In 2021 Medicare expenditures for patients with ESRD exceeded $51 billion, with inflation adjusted per-person per year (PPPY) Medicare fee for service expenditures of nearly $68,000. With recent advances in prenatal interventions and infant specific renal replacement therapy, survival of neonates with ESRD has improved over the last decade. Dialysis in neonates with ESRD is often associated with multiple comorbidities and the need for more intensified dialysis regimens. Little is known however about the impact on the health care system of improved survival in this population. Our primary aim was to investigate healthcare utilization in infants with ESRD.

Methods: We conducted a retrospective review of patients with ESRD at Texas Children's Hospital (TCH) from 2011 to 2022. We included patients ≤ 1 year of age who initiated dialysis in the Neonatal Intensive Care Unit (NICU) at TCH. We excluded patients who started dialysis prior to transfer to TCH. Data abstracted included patient demographics, initial and subsequent length of stay, comorbidities, and pediatric sub-specialist care. Data was also collected on gross charges related to the initial hospitalization, dialytic care, and gross charges following discharge up to 2 years of age.

Results: 19 patients met inclusion criteria of which 68% were male, 79% had a gestational age ≥ 37 weeks, and 90% had a birth weight ≥2500 g. The most common etiology of ESRD was lower urinary tract obstruction (LUTO) followed by genetic causes. The average length of stay for the initial hospitalization was 200 days with an average of 8 sub-specialists consulted inpatient and 4.9 admissions following discharge. The average gross charge for the initial hospitalization was $2,868,980 of which 14% was associated with dialytic care. The aggregate average hospital gross charges was $946,205 from discharge up to age 2. 84% of patients were discharged on peritoneal dialysis;16% were discharged on hemodialysis. 89% of patients survived and 5% received a kidney transplant by age 2 years.

Conclusions: Infant ESRD is associated with significant healthcare utilization including hospitalizations, sub-specialty care, and financial expenditures that far exceed adults with ESRD. Further investigation of healthcare utilization in this patient population can help determine the need for appropriate allocation of resources to support care delivery.

SA-OR80

Risk HLA-DQ Heterodimer Mismatch Is Associated with De Novo Donor-Specific Antibodies in Pediatric Kidney Transplant Recipients

Vaka Sigurjonsdottir,[1] Kim H. Piburn,[3] Lin Wang,[5] Daniel Turudic,[4] Paul C. Grimm,[5] Anat R. Tambur,[2] Bing M. Zhang.[5] *[1]University of Miami Miller School of Medicine, Miami, FL; [2]Northwestern University Feinberg School of Medicine, Chicago, IL; [3]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [4]University Hospital Centre Zagreb, Zagreb, Croatia; [5]Stanford University, Stanford, CA.*

Background: Recently, the role of HLA-DQα/β heterodimer mismatches in transplantation was recognized, suggesting that heterodimers including the DQα05 chain as part of the mismatched donor allele, carry a higher risk of developing de-novo donor-specific antibodies (dnDSA).

Methods: Children who underwent kidney transplantation from 1/1/2010-3/1/2018 at Stanford Children's Health, with ≥12-month follow-up, were included and followed through 9/1/2022. DQα/β heterodimers were paired based on linkage disequilibrium with HLA-DRB1 and mismatches were determined at the level of the heterodimers. A risk mismatch was defined as the presence of DQα05 heterodimer in the donor, not the recipient. Outcome of interest was development of dnDSA to HLA-DQ, defined when

detected mean fluorescence intensity (MFI) was ≥ 1000. All patients were tested for dnDSA at 0, 1, 2-, 3-, 6-, and 12 months following transplant, at least annually after that, and as clinically indicated. Survival analysis was performed by the Kaplan-Meier method and odds ratios were used to compare the relative odds.

Results: A total of 227 patients were included. The median age was 13 (IQR 9), 24% had living donor transplant and 49% were female. The median follow-up time was 68 months (IQR 40). 87 (38%) formed dnDSA against HLA-DQ. 77/227 (34%) had a DQα05-heterodimer mismatch, of those 43/77 (56%) formed dnDSA, vs. 44/150 (29%) **Figure.** The **table** shows frequency of heterodimers and dnDSA formation.

Conclusions: DQα05 heterodimer mismatch was highly associated with the formation of HLA- dnDSA in our cohort. Identification of immunogenic DQ mismatches may help optimize allocation systems, guide the selection of organs for sensitized patients, and immunologic risk stratification post-transplant to improve graft outcomes.

Table: Frequency of mismatched heterodimers in cohort. Frequency is reported if present in ≥15.

Heterodimer	Patients with mismatched heterodimer (n)	DSA (n)	No DSA (n)	Percentage that formed DSA (%)	OR	95% CI	P value
DQA1*01/DQB1*05	54	17	37	31	0.7	0.4, 1.3	0.2
DQA1*01/DQB1*06	52	10	42	19	0.3	0.1, 0.6	0.001
DQA1*03/DQB1*03	116	44	72	38	0.9	0.6, 1.7	0.9
DQA1*04/DQB1*04	15	8	7	53	1.9	0.7, 5.7	0.2
DQA1*05/DQB1*02	32	19	13	59	2.7	1.1, 5.2	0.01
DQA1*05/DQB1*03	69	38	31	55	2.7	1.5, 4.9	0.0001

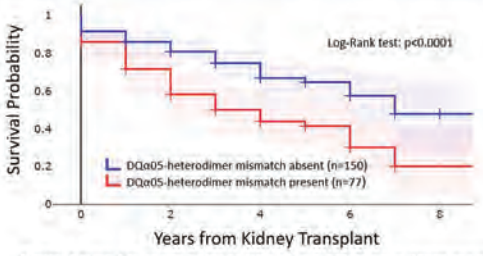


Figure: Kaplan-Meier estimates of time to HLA-DQ de-novo donor-specific antibodies

SA-OR81

pOKRA Study: Biomarker-Based Diagnosis and Histological Correlation of Allograft Rejection in Pediatric Kidney Transplantation

Vikas R. Dharnidharka,[1,2] Raja Dandamudi,[1,2] Mansi Agarwal,[1] Charles Goss,[1] Megan Kelton,[3] Jodi M. Smith.[3] *[1]Washington University in St Louis, St Louis, MO; [2]Saint Louis Children's Hospital, St. Louis, MO; [3]Seattle Children's Hospital, Seattle, WA.*

Background: To improve acute rejection(AR) detection in pediatric renal transplants, we propose KidneyCare, combining AlloSure(donor-derived cell-free DNA) and AlloMap(gene expression profiling). AlloMap assesses 5 genes expression, generating a score of 0-20. AlloSure quantifies allograft tissue injury as a percentage of total circulating cell-free DNA. We suggest this combined approach may boost diagnostic accuracy and correlate with Banff lesion intensity

Methods: In the study, 72 AlloSure and 69 AlloMap samples were collected prospectively pre-biopsy from 61 patients across 3 centers in the first year post-transplant Assays were conducted at CareDx labs. Samples were categorized as AR or Quiescence. Area under the ROC assessed their ability to distinguish AR from quiescence. Principal component analysis condensed variables for logistic regression. Histology scores followed Banff 2018 update

Results: In our study, comprising 18 AR biopsy specimens and 59 without AR, median AlloSure levels were significantly higher in the AR group (1.7%;IQR, 0.42%–3.9%) compared to the quiescent group (0.28%;IQR,0.18%–0.46%). AlloMap scores were also significantly elevated in the AR group (median 13;IQR,12–14) compared to the quiescent group (median 9.9;IQR,8.2–11). The AUC for AlloSure alone to identify AR was 0.83, for AlloMap alone was 0.82, and the combined AUC improved to 0.94. The combination of tests correctly predicted and potentially avoided 40 out of 41 biopsies. AlloSure levels increased with Banff lesions:from 0.77 ± 0.13% to 3.8 ± 0.52% for glomerulitis (G grades 1-2),0.44 ± 0.01% to 2.9 ± 2.1% for peritubular capillaritis (PTC grades 0-3),0.40 ± 0.05% to 3.0 ± 0.52% for interstitial inflammation (IF grades 0-3), 0.51 ± 0.07% to 3.0 ± 0.8% for tubulitis grades 0-3,0.5 ± 0.1% to 2.6 ± 0.27% for interstitial fibrosis (IF grades 0-3), and 0.42 ± 0.8% to 3.9 ± 1.3% for tubular atrophy (TA grades 0-3). Similarly, AlloMap levels increased with Banff lesion severity: from 10 ± 2.8 to12 ± 1.6 for G1-2,9.8 ± 2.6 to14 ± 2.5 for PTC 0-3, 9.7 ± 2.1 to 14 ± 2.6 for IF0-3, 9.4 ± 2.1 to 13.0 ± 1.9 for tubulitis 0-3, 9.8 ± 2.9 to 14 ± 1 for IF 0-3, and 9.8 ± 2.8 to 13 ± 1.6 for TA 0-3.

Conclusions: Combining AlloSure and AlloMap yields highly accurate AR assessment, correlating positively with allograft tissue injury severity

Funding: Commercial Support - American Society of Transplantation/CareDx, Private Foundation Support

SA-OR82

Favorable Treatment Responses of Recurrent Focal Segmental Glomerulosclerosis in Children after Kidney Transplantation: A Contemporary Multicenter Electronic Health Record Data Analysis

Vikas R. Dharnidharka,[1] Rebecca R. Scobell,[2] Mahmoud Kallash,[3] Nicole Marchesani,[2] Michelle Denburg.[2] PedsNet GLEAN Investigators. *[1]Washington University in St Louis, St Louis, MO; [2]The Children's Hospital of Philadelphia, Philadelphia, PA; [3]Nationwide Children's Hospital, Columbus, OH.*

Background: Recurrence of focal segmental glomerulosclerosis (FSGS) after kidney transplant leads to significant morbidity and potentially earlier allograft loss. To date however, reported rates, risk factors and treatment outcomes have varied widely.

Methods: We applied computational phenotypes to a multicenter aggregation of electronic health records data from 7 large pediatric health systems in the USA, to identify recurrence rates, risk factors and treatment outcomes. We refined the data collection by chart review.

Results: From >7 million patients, we compared children with primary FSGS who received a kidney transplant between 2009-2020 and who either developed recurrence (n =67/165; 40.6%) or did not (n = 98/165). 64/67 had recurrence in the first week (Figure 1, panel A). Serum albumin level at time of transplant was significantly lower and recipient HLA DR7 presence was significantly higher in the recurrence group. By 36 months post-transplant, complete remission occurred in 58.2% and partial remission in 17.9% (panel B). Through 6 years post-transplant, no remission after recurrence associated with an increased risk of allograft loss over time (p<0.0001), but any remission showed similar allograft survival (panel C) and function decline (panel D) to those with no recurrence. Since treatments were used in non-random fashion, using spline curves and multivariable non-linear analyses, complete + partial remission chance was significantly higher with greater plasmapheresis sessions, CTLA4-Ig doses or LDL-apheresis sessions. Only treatment with anti-CD20, CTLA4-Ig agents or LDL-apheresis sessions were associated with complete remission (panel E). Excluding 25 patients with mutations raised the recurrence rate to a range between 45-47.14% but did not significantly change other results.

Conclusions: Our contemporary high-risk cohort had higher favorable response rates than most prior reports, from combinations of agents.

Funding: Other U.S. Government Support

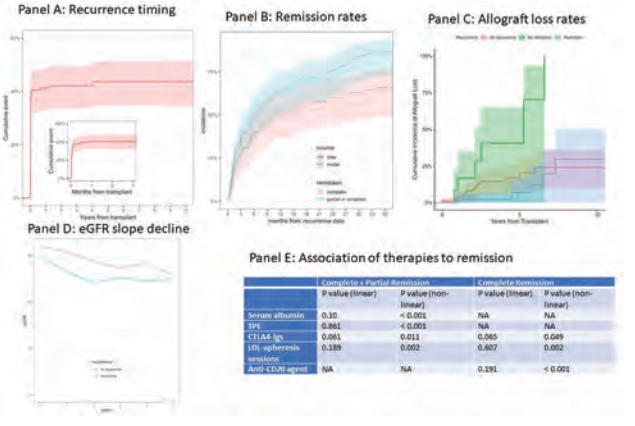


Figure 1

SA-OR83

Superiority of Imlifidase over Plasma Exchange in Rapid and Efficient Elimination of All IgGs, Including Donor Specific Antibodies (DSAs) Assessed in an Antibody-Mediated Rejection (AMR) Trial

Stanley C. Jordan,[1] Georg Bohmig,[2] Lionel Couzi,[3] Carmen Lefaucheur,[4] Robert A. Montgomery,[5] Lionel Rostaing,[6] Christophe M. Legendre,[7] Peter D. Hughes,[8] Anil K. Chandraker,[9] Gunilla Einecke,[10] Kate Wyburn,[11] Anna Runström,[12] Jan G. Tollemar,[12] Paola A. Lefèvre,[12] Fabian Halleck.[13]
[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]Medizinische Universitat Wien Universitatsklinik fur Innere Medizin III, Wien, Austria; [3]Centre Hospitalier Universitaire de Bordeaux Service d'endocrinologie diabetologie et nutrition, Bordeaux, France; [4]Hopital Saint-Louis, Paris, France; [5]NYU Langone Health, New York, NY; [6]Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; [7]Hopital Necker-Enfants Malades Service de Genetique Clinique, Paris, France; [8]The Royal Melbourne Hospital, Melbourne, VIC, Australia; [9]Brigham and Women's Hospital, Boston, MA; [10]Medizinische Hochschule Hannover, Hannover, Germany; [11]Royal Prince Alfred Hospital, Sydney, NSW, Australia; [12]Hansa Biopharma AB, Lund, Sweden; [13]Charite Universitatsmedizin Berlin, Berlin, Germany.

Background: Antibody depletion using (PLEX) is regarded as SOC in the treatment of AMR. However, PLEX has inconsistencies in removal of pathogenic IgG (i.e., DSAs) due to multiple factors including re-equilibration from IgG distributed in extravascular spaces. Imlifidase, a protease that specifically inactivates all human subclasses of soluble and membrane bound IgG. Imlifidase is currently utilized for desensitization prior to kidney transplantation with inactivation of DSAs both in the intra- and extravascular space. In this AMR trial (NCT03897205), the primary endpoint was to compare removal of IgG DSAs with imlifidase to 5-10 PLEX sessions.

Methods: The comparison occurred in a phase 2 randomized, open-label, multi-center, multi-national trial with a 6-month follow-up conducted at 14 transplant centers. The trial included 30 patients with active or chronic active AMR after kidney transplantation. The primary endpoint analyzed the maximum reduction of all DSA levels for 5 d following the start of either treatment. The purpose of this presentation is the efficacy of removing IgG between the two treatment modalities.

Results: The median reduction of DSA was 97% for imlifidase compared to 42% for PLEX on day 5. The time to median maximum DSA depletion was 15h after imlifidase compared to day 9 for a median of 6 PLEX sessions. No complement-binding DSA was detectable 24h after treatment in any imlifidase patients, whereas no reduction was seen in PLEX treated patients. After the initial elimination of DSA, a rebound occurred to approximately 70% of baseline values for both groups. On average 3% of the pre-treatment IgG level remained after imlifidase, compared to 50% after PLEX at any timepoint. No meaningful safety issues were observed in the trial.

Conclusions: In a head-to-head comparison in kidney transplant recipients with AMR, one dose of imlifidase given over a 15-min infusion was more efficacious in reducing all IgG, both in speed and magnitude, compared to several PLEX sessions. Thus, imlifidase offers a rapid and effective option of hindering any IgG-mediated attack momentarily with a beneficial safety profile.

Funding: Commercial Support - Hansa Biopharma AB

SA-OR84

Clazakizumab in Chronic Active Antibody-Mediated Kidney Transplant Rejection: Results of the IMAGINE Phase 3 Study

Arjang Djamali,[1] Georg Bohmig,[2] Steven J. Chadban,[3] Deepali Kumar,[4] Roslyn B. Mannon,[5] Teun van Gelder,[6] Gabriele Schultz-Hauser,[7] Gabriela Alperovich Lehrer,[8] Ralph Preiss,[9] Aparna Raychaudhuri,[10] Laurie Lee,[10] Peter W. Nickerson.[11]
[1]Maine Medical Center, Portland, ME; [2]Medical University of Vienna, Vienna, Austria; [3]Royal Prince Alfred Hospital, Sydney, NSW, Australia; [4]University of Toronto, Toronto, ON, Canada; [5]University of Nebraska Medical Center, Omaha, NE; [6]Leiden University Medical Center, Leiden, Netherlands; [7]CSL Behring, Marburg, Germany; [8]CSL Vifor, Madrid, Spain; [9]CSL Behring, Berne, Switzerland; [10]CSL Behring LLC, King of Prussia, PA; [11]University of Manitoba, Winnipeg, MB, Canada.

Background: Chronic active antibody-mediated rejection (caAMR) is a common cause of graft loss after kidney transplant with no approved therapies. Clazakizumab, a high-affinity, humanized monoclonal antibody that binds IL-6, decreased donor-specific antibody (DSA) production and microvascular inflammation and stabilized eGFR in a phase 2 study in kidney transplant recipients (KTRs) with caAMR.

Methods: IMAGINE (NCT03744910; start date: Oct 2019), a global (66 sites) double-blind phase 3 study, aimed to recruit ~350 KTRs with caAMR determined by kidney biopsy based on Banff 2015 criteria. KTRs were randomized 1:1 to clazakizumab (12.5 mg SC q4w) or placebo. Primary endpoint was time to all-cause graft loss (return to dialysis, graft nephrectomy, re-transplantation, eGFR <15 mL/min/1.73m^2, death from any cause or sustained 40% reduction in eGFR). 1-yr eGFR was accepted as a reasonably likely surrogate endpoint (RLSE) for accelerated approval by the FDA. Temporary dose reduction was allowed at investigator discretion. This interim analysis (IA) was conducted when ~100 KTRs completed 1 yr of study participation.

Results: At the time of the IA, 194 KTRs had been enrolled, and 115 were followed for 52 weeks for eGFR change from baseline. The analysis indicated that the study was unlikely to meet the primary efficacy outcome (time to composite all-cause allograft loss or irreversible loss of allograft function), and the data and safety monitoring board recommended to stop the study. No gastrointestinal perforations or other safety concerns were noted.

Conclusions: Despite encouraging phase 2 results, the data from the IMAGINE IA did not support continuation. Nonetheless, this was the largest placebo-controlled study in KTRs with caAMR and was first transplant study for which the FDA accepted a 1-yr eGFR slope as a RLSE. No safety concerns were noted. Detailed primary analyses will be presented after the database has been unblinded prior to ASN Kidney Week.

Funding: Commercial Support - CSL Behring

SA-OR85

Impact of Induction Agents on Torque Teno Viral Load and Year-1 Post-transplant Complications in Kidney Transplant Recipients

Louise Benning,[1] Marvin Reineke,[1] Claudius Speer,[1] Julian Klein,[2] Christian Bundschuh,[2] Martin G. Zeier,[1] Paul Schnitzler,[2] Christian Morath.[1]
[1]Department of Nephrology, University Hospital Heidelberg, Heidelberg, Germany; [2]Medical Faculty Heidelberg, Department of Infectious Diseases, Virology, University Hospital Heidelberg, Heidelberg, Germany.

Background: Torque teno viral load (TTVL) is gaining importance as a surrogate parameter to assess immunocompetence in kidney transplant recipients and as a potential biomarker for predicting complications post-transplant. Although TTVL kinetics have been examined in several studies, it is unknown to what extent different induction therapies affect TTVL.

Methods: In this retrospective study, TTVL was quantified in 553 plasma or serum samples from 138 patients who underwent kidney transplantation between 2018 and 2021. TTVL was quantified at the time of transplantation and 30, 90, 180, and 360 days thereafter. To evaluate the influence of induction therapy on TTVL, 69 patients receiving anti-thymocyte globulin (ATG) induction were matched with 69 patients receiving an interleukin-2 receptor antagonist (IL2-RA) in terms of age, gender, and donor modality.

Results: Regardless of the type of induction therapy, there was a steep increase in TTVL post-transplant in all patients with peak viral loads at 90 days post-transplant (median TTVL [IQR] 6.62×10^6, [4.00×10^5 – 1.04×10^8]) followed by subsequently declining viral loads. Compared to patients receiving IL2-RA as induction therapy, patients receiving ATG had significantly higher peak viral loads (P=0.0006), as well as significantly higher viral loads one year post-transplant (P=0.012). Among the 69 patients who received ATG induction therapy, 17 patients underwent simultaneous pancreas-kidney transplantation, yet their TTVL did not differ significantly from others receiving ATG as induction therapy. Despite higher TTVL, patients with ATG as induction therapy did not have an increased risk of hospitalization due to infection when compared to patients receiving IL2-RA (HR=0.9363; P=0.6949). Patients whose TTVL 90 days post-transplant exceeded the currently proposed cutoff to prevent infections within the first year post-transplant [6.2 log10] had a higher risk of being hospitalized with an infection in the following 9 months, albeit without being statistically significant (HR=1.569, P=0.0899).

Conclusions: The type of induction agent used markedly affects TTVL post-transplant and should therefore urgently be considered for interpreting and applying TTVL to immunomonitor kidney transplant recipients post-transplant.

SA-OR86

Kidney Rejection Prediction Model Combining Blood Gene Expression, Donor-Derived Cell-Free DNA, Urine Chemokines, and Torque Teno Virus

Kenny W. Chen,[1] Lihui Zhao,[1] Sujay D. Paudel,[1] Sookhyeon Park,[1] Amishi Desai,[1] Ronnie Lacombe,[2] Rohita Sinha,[2] Steven Kleiboeker,[2] John J. Friedewald.[1]
[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Eurofins Viracor BioPharma Services, Lenexa, KS.

Background: Blood gene expression (GEP), dd-cfDNA, and urine chemokines have all been shown to be useful non-invasive biomarkers in predicting kidney rejection. Torque teno virus (TTV) is an emerging biomarker of net IS. We aim to integrate these 5 biomarkers into a prediction model for kidney rejection.

Methods: We analyzed 638 biopsy-paired blood and urine samples from the CTOT-08 trial (NCT01289717). We fit a logistic regression model using log dd-cfDNA, GEP, urine CXCL9 and CXCL10 normalized to Ucreat, and log TTV viral load to predict kidney rejection. Sensitivity, specificity, PPV, NPV and AUC was used to evaluate diagnostic performance.

Results: In the 5-biomarker model, dd-cfDNA, GEP, and TTV VL were statistically significant (p-value < 0.05) adjusting for other covariates (TABLE). Model AUC was 0.816 (Figure). When maximizing Youden's index, we obtained a sensitivity of 0.71, specificity of 0.78, accuracy of 0.76, NPV of 0.87, and a PPV of 0.56. Out of all rejection

types, the model correctly predicted 51/66 AMR cases, 33/41 mixed AMR/ACR, 42/71 ACR, and 360/460 no rejection cases.

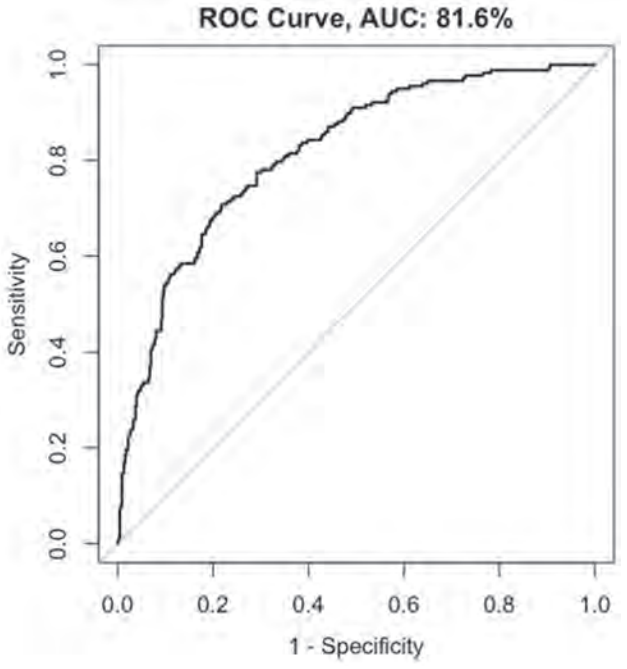
Conclusions: Combining non-invasive biomarkers into prediction models to monitor kidney allograft rejection could assist in reducing the need for biopsies and better inform safe immunosuppression titration. We found that dd-cfDNA, blood GEP and TTV VL all significantly improved the prediction model, whereas the addition of urine CXCL9/10 did not significantly impact model performance in predicting kidney rejection.

Funding: Other NIH Support - NIAID, Commercial Support - Eurofins - Viracor, Eurofins - Transplant Genomics

Model Covariates

Covariate	log(OR)	95% CI	p-value
Log(ddcf-DNA)	0.77	0.57, 0.99	<0.001
GEP	0.05	0.03, 0.06	<0.001
CXCL9	0.01	-0.01, 0.04	0.4
CXCL10	0.05	-0.08, 0.19	0.4
Log(TTV)	-0.15	-0.28, -0.02	0.030

OR = Odds Ratio, CI = Confidence Interval



SA-OR87

Hypothermic Perfusion in Kidney Allografts with Extended Cold Ischemia Time

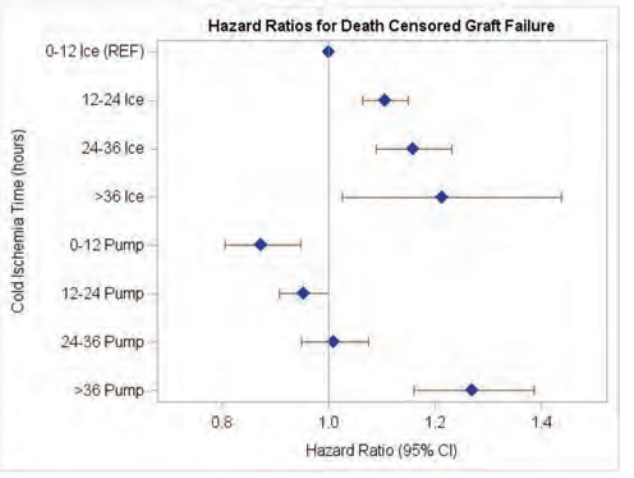
Angelica Perez-Gutierrez, Rita L. McGill. *University of Chicago Division of the Biological Sciences, Chicago, IL.*

Background: Hypothermic perfusion reduces reperfusion injury of kidney allografts. We investigated whether use of hypothermic perfusion offsets effects of extended cold ischemia time (CIT). This is important, as changes in the allocation system have increased CIT for recipient candidates located more than 250 nautical miles from the donor hospital.

Methods: UNOS Star Files were used to analyze first-time, single kidney-only allografts from deceased donors from 2005-2022, in order to compare organs preserved only with ice to organs with hypothermic perfusion; those with transient perfusion were excluded. A multivariable Cox model for death-censored graft failure (dcGF) was adjusted for recipient, donor, and transplant characteristics. CIT was categorized as ≤12 hours, 12-24 hours, 24-36 hours, and >36 hours. Kidneys on ice with ≤12 hours CIT served as a reference group, as these are normally considered acceptable for transplantation.

Results: Among 120,438 allografts, 62.7% were on ice and 37.3% were pumped. DcGF increased in a dose-dependent fashion as CIT increased, regardless of preservation method. Perfused kidneys with ≤36 hours CIT did not differ from the reference group (Figure). After 36 hours, dcGF was about 25% higher than the reference category, whether perfused kidneys or kidneys on ice. However, in the ≤12 hour, 12-24 hour, and 24-36 hour time categories, pump perfusion was associated with a 13% decrease in the hazard of dcGF (P<0.001 for all).

Conclusions: When CIT ≤36 hours, hypothermic perfusion of allografts was associated with signifcantly less dcGF compared to kidneys preserved on ice with similar CIT, with results comparable to kidneys on ice for ≤12 hours. The additional organ longevity may improve organ utilization and promote recipient safety by permitting complex recipients to have their transplant surgeries performed during daylight hours when optimal resources are available.



SA-OR88

First-in-Human Phase 2a (ATMIRe) Trial of Ex Vivo Allograft Treatment with iCM012 to Mitigate Ischemia-Reperfusion Injury in Kidney Transplantation

Ali R. Biglarnia,[1,3] Bo Nilsson,[2] Carl J. Raihle,[3] Oleg Slivca,[3] Clara H. Paul.[3] *[1]Lunds Universitet, Malmö, Sweden; [2]Uppsala universitet Rudbecklaboratoriet, Uppsala, Sweden; [3]Skanes universitetssjukhus Malmo, Malmo, Sweden.*

Background: iCM012 is an amphiphilic polymer that forms a dense protective coat on cell surfaces. In porcine transplant studies, ex vivo administration of iCM012 to kidney allografts produced a robust but transient non-toxic cell coating that consistently mitigated ischemia-reperfusion injury (IRI)-induced early thromboinflammation, reduced late systemic cytokine release, and improved allograft function. A first-in-human trial evaluated the safety and tolerability of iCM012 in clinical kidney transplantation.

Methods: A phase IIa, randomized, double-blind, placebo-controlled trial (NCT05246618) was conducted at a single center in Sweden, enrolling 18 de novo kidney transplant patients. Participants were randomized 2:1 to receive either iCM012 (n=12) or placebo (n=6). iCM012 was administered ex vivo to the retrieved kidney allografts as a single arterial infusion by gravity at the end of organ preservation. Primary endpoints were safety and tolerability over 12 months. Secondary endpoints included delayed graft function (DGF) and estimated glomerular filtration rate (eGFR) at 12 months. Urine and plasma samples were collected for exploratory analysis.

Results: Patient characteristics were balanced between the groups; however, the median Kidney Donor Profile Index was higher in the iCM012 group compared to placebo (76 [32-97] vs. 41 [30-94], P=0.062). There were no differences in cold ischemic time or use of continuous machine perfusion between groups. No DGF occurred and all transplanted kidneys showed excellent primary function, even one iCM012-treated kidney with a CIT of 25.7 hours that experienced technical complications, resulting in prolonged warm ischemia and re-anastomosis. In the iCM012 group, innate immune activation (sC5b-9) and tubular injury markers (IL-18, KIM-1, NGAL, Cystatin-C, and L-FABP) were at lower levels in 24-hour urine samples on day 1. At 12 months, there was no difference in median relative eGFR between the iCM012 and placebo groups (42 [32-58] vs. 45.5 [32-72]).

Conclusions: iCM012 demonstrated a favorable safety profile and showed promising efficacy in mitigating IRI and preserving allograft function within a 12-month follow-up. These findings strongly support further investigation in larger, multicenter trials to confirm its therapeutic potential in kidney transplantation.

Funding: Commercial Support - iCoat Medical

SA-OR89

Effects of Empagliflozin on Proteinuria in Kidney Transplant Recipients: Preliminary Data of a Randomized Control Trial

Chanyanuch Rakpithayanon,[1] Thunyatorn Wuttiputhanun,[1,2] Suwasin Udomkarnjananun,[1,2] Kearkiat Praditpornsilpa,[1,3] Yingyos Avihingsanon,[1,2] Natavudh Townamchai.[1,2] *[1]King Chulalongkorn Memorial Hospital Department of Internal Medicine, Bangkok, Thailand; [2]Excellence Center for Solid Organ Transplantation, Bangkok, Thailand; [3]Hemodialysis center, Benchakittipark Hospital, Bangkok, Thailand.*

Background: Post-kidney transplant proteinuria poses a substantial risk of cardiovascular events, graft loss, and mortality. Although evidence suggests the potential efficacy of empagliflozin in proteinuria reduction, a definitive comprehension of its therapeutic and safety profile in kidney transplant recipients (KTRs) remains elusive.

Methods: This preliminary double-blinded, randomized controlled trial systematically investigated the impact of empagliflozin on proteinuria in KTRs in comparison to a placebo. The inclusion criteria were stable graft function and the absence of rejection or alterations in immunosuppressive regimens within the preceding 3 months. Participants in the intervention arm were administered empagliflozin at a daily dosage of 10 mg for 3 months. The primary outcome measures included the mean differences in proteinuria, while secondary outcomes encompassed estimated glomerular filtration rate (eGFR), metabolic parameters such as blood sugar, blood pressure, and body weight.

Results: A total of 41 KTRs underwent enrollment and randomization, with both intervention and control groups exhibiting comparable baseline characteristics, including age, gender, underlying renal disease, history of rejection, and chronic calcineurin inhibitor toxicity. The intervention group demonstrated a significant proteinuria reduction with mean UPCI difference of -726.01 mg/gCr (95% CI -1426.62 to -25.41, P=0.043). The eGFR displayed no statistically significant difference (mean difference -1.82 ml/min/1.73m2, 95% CI -5.81 to 2.17, P=0.361). Evaluation of potential adverse effects, including urogenital infections, or metabolic acidosis, revealed no significant distinctions between groups.

Conclusions: Despite being underpowered by sample size, this study still demonstrates a statistically significant reduction in proteinuria with empagliflozin among kidney transplant recipients. The observed trend suggests a potential therapeutic benefit. Furthermore, the absence of notable side effects underscores the favorable safety profile of empagliflozin in this patient population.

SA-OR90

Triglyceride-Glucose Index and Risk of Cardiovascular Events, Kidney Allograft Loss, and New-Onset Diabetes after Transplantation in Kidney Transplant Recipients

Yu ho Lee,[1] Jin Sug Kim,[2] Kyunghwan Jeong,[2] Soo-Young Yoon,[2] Hyeyun Jeong,[1] Jihyun Baek,[1] So-young Lee,[1] Hyeon Seok Hwang.[2] *[1]CHA University Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea; [2]Kyung Hee University Medical Center, Dongdaemun-gu, Seoul, Republic of Korea.*

Background: Insulin resistance is prevalent disorder, but its clinical significance remains undermined. We explored the clinical implication of triglyceride-glucose (TyG) index in renal transplant recipients, recognizing it as a valuable marker for insulin resistance.

Methods: A total of 6,354 renal transplant recipients were enrolled from a nationwide, prospective cohort between May 2014 and December 2022. The TyG index was assessed between 6- and 12-months post-transplantation. We evaluated the association between TyG index and the risk of composite of cardiovascular events and death, renal allograft loss, and new onset diabetes after transplantation (NODAT).

Results: During the mean follow-up period of 39.2 ± 26.1 months, a total of 106 composite events of cardiovascular events and death, 174 events of renal allograft loss, and 438 events of NODAT were observed. The cumulative rate for composite events, graft loss, and NODAT was greater in patients with higher TyG quartile (all $P < 0.001$). In multivariate analysis, patients in quartile 4 TyG index was associated with an increased risk of composite events (HR 1.81, 95% CI 1.14 – 2.86), renal allograft loss (HR 2.13, 95% CI 1.28 – 3.55), and NODAT (HR 2.52, 95% CI 1.90 – 3.34). Higher quartile of TyG was associated with future graft dysfunction (adjusted mean eGFR differences of -4.72, 95% CI -7.39 – -2.04). There was a linear escalation in the risk of composite events and graft loss with the incremental rise in the TyG index, concomitant with an exponential augmentation in the risk of NODAT.

Conclusions: Renal transplant recipients with higher TyG index are associated with higher risk of composite of cardiovascular event and death, renal allograft loss, and NODAT.

TH-PO001

Retina and Deep Learning-Based CVD Biomarker in Patients with Varying eGFR Levels: Data from the UK Biobank

Yunnie Cho,[1,2] Young Su Joo,[3] Tyler H. Rim,[1,4] Jung Tak Park.[3] *[1]Mediwhale Inc., Seoul, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [3]Yonsei University, Seoul, Republic of Korea; [4]Singapore Eye Research Institute, Singapore, Singapore.*

Background: Retinal imaging is a non-invasive method for assessing systemic disease risk. Reti-CVD, a deep learning-based retinal biomarker, predicts atherosclerotic cardiovascular disease (ASCVD) events with performance comparable to coronary artery calcium. Cardiovascular risk assessment is critical for patients with chronic kidney disease, given their higher CVD event risk. This study evaluates the prognostic value of Reti-CVD in patients with varying renal function, as measured by estimated glomerular filtration rate (eGFR).

Methods: A retrospective cohort study was conducted using the UK Biobank, including patients in three eGFR groups: G1 (eGFR ≥ 90; N=6600), G2 (eGFR 60-89; N=5130), and G3-G5 (eGFR < 60; N=183). Survival analysis focused on ASCVD events, with a mean follow-up duration of 9.9 years. Reti-CVD's predictive performance for each eGFR group was assessed using Cox proportional hazards models and concordance statistics. Hazard ratios (HR) of Reti-CVD were adjusted for eGFR groups, age, gender, hyperlipidemia, diabetes, and smoking status.

Results: In G1, Reti-CVD had a C-statistic of 0.715 [95% CI: 0.677 - 0.754], indicating strong predictive capability. The combined model of Reti-CVD, age, and gender improved the C-statistic to 0.727 [0.691 - 0.763]. In G2, Reti-CVD showed a C-statistic of 0.711 [0.679 - 0.744], with the combined model achieving 0.716 [0.684 - 0.748]. In G3-G5, the predictive performance of Reti-CVD was lower (0.605 [0.468 - 0.742]), but improved with age and gender (0.670 [0.521 - 0.819]). Multivariable HR analysis revealed the medium Reti-CVD category had more than double the risk compared to the low category (adjusted HR = 2.08 [1.52 - 2.94]), and the high Reti-CVD category had nearly four times the risk (3.78 [2.48 - 5.76]).

Conclusions: Reti-CVD, performing similarly to CAC in predicting cardiovascular risk, was effective in patients with kidney disease in the UK Biobank. This suggests potential for improved cardiovascular risk monitoring in chronic kidney disease patients.

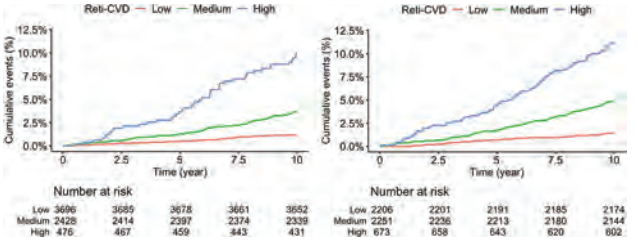


Figure1. Kaplan-Meier curves in G1 and G2 eGFR group according to Reti-CVD risk categories

TH-PO002

Advancing Precision Medicine with scSpectra: Single-Cell Functional Profiling of Individual Patients with Kidney Diseases

Konstantin A. Kloetzer,[1,2] Amin Abedini,[1] Michael S. Balzer,[1,3] Xiujie Liang,[1] Jonathan Levinsohn,[1] Eunji Ha,[1] Max Schuller,[2] Bernhard Dumoulin,[1] Jonathan Hogan,[1,4] Kathrin Eller,[2] Roy D. Bloom,[1] Nancy Zhang,[5] Katalin Susztak.[1] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]Medizinische Universitat Graz, Graz, Austria; [3]Charite Universitatsmedizin Berlin, Berlin, Germany; [4]Cabaletta Bio Inc, Philadelphia, PA; [5]University of Pennsylvania Wharton School, Philadelphia, PA.*

Background: Single-cell RNA sequencing atlases, comprising millions of cells from hundreds of individuals, could guide molecular precision diagnostics in nephrology. However, the clinical application of single-cell transcriptomics to identify cell-type-specific molecular changes in individual patients remains unestablished.

Methods: We developed scSpectra, a novel computational tool that quantifies changes in gene expression coordination across cellular functions in individual samples. To demonstrate scSpectra's capabilities, we created the largest known human single-nuclei atlas. We expanded our cross-species integrated single-cell kidney atlas to include 150 kidney samples and biopsies from various diseases, such as diabetic kidney disease, chronic kidney disease with hypertension, acute kidney injury, and ADPKD. Comprising over 700,000 cells, our atlas, combined with scSpectra, powers our Single-Cell Functional Profiling Report, identifying the most significantly dyscoordinated pathways in each cell type of individual patients.

Results: By analyzing 100 patients, we demonstrate scSpectra's ability to distinguish diseases based on cell type involvement. For instance, a patient with IgA nephropathy showed the most significant changes in inflammation-related functions within podocytes, which was rarely observed in other diseases. Comparing the dyscoordination prevalence of thousands of cellular functions across diseases, we identified functions frequently dyscoordinated in CKD patients with hypertension but not in those without hypertension. We also found disease-specific changes for ADPKD samples, sex differences, and heterogeneity in potentially druggable pathways such as Interleukin-1-related signaling.

Conclusions: With scSpectra, we introduce one of the first computational frameworks for functional contextualization and precision diagnostics from scRNA-seq data. Based on a novel statistical approach, scSpectra revolutionizes single-cell analysis and enables a detailed examination of individual samples. Implemented in clinical investigations, scSpectra could identify patients most likely to benefit from specific treatments, advancing precision medicine in the management of complex diseases.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO003

Development and Validation of Machine-Learning Model to Predict the Risk of Major Cardiovascular Events and Death for Patients with Kidney Failure Having Noncardiac Surgery

Gurpreet S. Pabla,[1] Navdeep Tangri,[2,4] Tyrone Harrison,[3] Thomas W. Ferguson,[4] Emir Sevinc,[3] Reid Whitlock.[4] *[1]University of Manitoba Faculty of Health Sciences, Winnipeg, MB, Canada; [2]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [3]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [4]Seven Oaks General Hospital, Winnipeg, MB, Canada.*

Background: Patients with kidney failure undergoing non-cardiac surgery face significantly higher risk of adverse cardiovascular events and mortality compared to those with normal kidney function. Existing risk prediction tools are limited in estimating these risks for kidney failure patients. We developed and validated a machine-learning model for major cardiovascular events and mortality in kidney failure patients within 30 days of undergoing outpatient or inpatient non-cardiac surgery in Alberta and Manitoba, Canada.

Methods: Derivation data was sourced from Manitoba Health, including adults (≥ 18 years) with kidney failure (eGFR < 15 mL/min/1.73m^2 or on maintenance dialysis) undergoing non-cardiac surgery between April 1, 2007, and December 31, 2019. We focused on a composite outcome of acute myocardial infarction, cardiac arrest, ventricular arrhythmia, and all-cause mortality. Data was split into 70% for training, 15% for validation, and 15% for testing. The training set was used to tune the hyperparameters and train the models; the validation dataset was used for feature selection and evaluate model performance, while the testing set evaluated the model's final performance. The model's performance was evaluated using C-statistics, Area Under the Precision-Recall Curve (AUC-PR), calibration plots, and Brier Score. We used XGBoost and Random Forest, selecting a model with reasonable and balanced C-statistics and AUC-PR. The final model was externally tested using Alberta data.

Results: We identified 12,082 surgeries and 569 outcomes. The final model (XGBoost) included surgery type, surgery setting (emergency inpatient, outpatient), history of myocardial infarction, albumin, and hemoglobin levels. It had an estimated C-statistic of 0.86, an AUC-PR of 0.30, and a Brier score of 0.04 in the testing cohort. External testing in Alberta showed similar performance. Calibration plots demonstrated excellent calibration, except for underestimation at the highest predicted risks.

Conclusions: Our XGBoost model for adverse peri-operative outcomes in patients with kidney failure demonstrated good performance, with improved parsimony compared to existing tools. Future work should compare these tools and test the impact of risk-guided approaches to perioperative care.

Funding: Government Support - Non-U.S.

TH-PO004

Health System Economic Burden in Patients with CKD: Insights from the Klinrisk Model

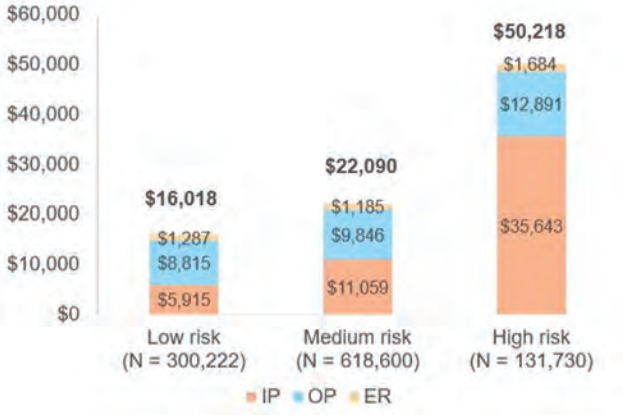
Navdeep Tangri,[1,2] Rakesh Singh,[3] Keith A. Betts,[4] Yuxian Du,[3] Sophie Gao,[4] Arvind Katta,[3] Youssef M. Farag,[3] Samuel T. Fatoba,[3] Hongjiao Liu,[4] Jingyi Chen,[4] Thomas W. Ferguson,[1] Reid Whitlock,[1] Silvia J. Leon Mantilla,[1] Ajay K. Singh.[5] *[1]University of Manitoba, Winnipeg, MB, Canada; [2]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [3]Bayer U.S. LLC, Whippany, NJ; [4]Analysis Group Inc, Los Angeles, CA; [5]Harvard Medical School, Boston, MA.*

Background: CKD is associated with substantial economic burden. Early identification of at-risk CKD can facilitate appropriate and timely intervention and reduce CKD-related medical costs. This study assessed the association between CKD progression risk and healthcare burden.

Methods: A retrospective observational study was conducted in 1,050,552 adult patients with CKD from Optum's electronic health records database (1/1/2007 - 9/30/2022). A previously published and validated machine learning model, Klinrisk (Tangri N, et al Clin Kidney J. 2024 Mar 6;17(4)) was applied to classify patients into 3 groups based on their risk of CKD progression (low, medium, and high). All-cause inpatient (IP) admissions, emergency room (ER) visits, outpatient (OP) visits were evaluated in each risk group during the 1 year after CKD. Average medical costs (2023 USD) were calculated as the average length of stay for IP admissions, average number of ER and OP visits multiplied by the corresponding unit costs as estimated from a prior study.

Results: Patients with higher predicted CKD progression risk had higher healthcare utilization (HRU). High-risk patients averaged 1.49 IP admissions, 0.83 ER visits, and 35.75 OP visits per year compared with 0.31 IP admissions, 0.63 ER visits, and 24.45 OP visits among low-risk patients. The total annual medical costs for low-, medium-, and high-risk patients were $16,018, $22,090, and $50,218, respectively (Figure). IP costs were the major cost driver for high-risk patients.

Conclusions: Patients at high risk of CKD progression as predicted by Klinrisk were associated with high HRU and medical costs and may benefit from early intervention with guideline-directed therapies, to reduce economic burden.



Annualized all-cause medical costs stratified by CKD progression risk

TH-PO005

Predicting CKD Progression Using Machine Learning

Adam E. Gaweda, Salgram Jaisinghani, Vibha S. Nayak, Rosemary Ouseph. *University of Louisville, Louisville, KY.*

Background: Chronic Kidney Disease (CKD) increases morbidity and mortality. With multiple new interventions available, there will be a need for optimal combination therapies to slow or reverse the progression of CKD. We present a first step in building a computational framework for achieving this goal. We develop an Artificial Neural Network (ANN) model to predict CKD trajectory based on current patient status and selected therapeutic interventions.

Methods: Using data from Chronic Renal Insufficiency Cohort (CRIC) we predicted GFR (CKD-EPI) trajectory, based on age, BMI, smoking status, hypertension, proteinuria, diabetes, and the prescription of antidiabetic medication, beta blockers, ACE inhibitors, and ARB's. We used a transformer ANN combining Multi-Head Self-Attention with Multi-Layer Perceptron. Training was performed using 10-fold Cross-Validation. Predictive performance was assessed using Root Mean Square Error (RMSE) and R^2.

Results: The mean Cross-Validation RMSE achieved was 6.98 +- 0.37 and the R^2 was 0.83 +- 0.02 (Table 1). Figure 1 shows an example of GFR trajectory prediction for an individual subject (left) and the regression plot for one of the Cross-Validation folds.

Conclusions: Modern Machine Learning techniques facilitate sequential prediction tasks, such as modeling CKD progression. A transformer ANN model predicts individual CKD trajectories with high accuracy. The model will be used to discover optimal treatment combinations. As more data become available about the use of new classes of therapeutic agents for CKD, those data can be incorporated into the model to enhance its utility. **Acknowledgment:** CRIC data were provided by NIDDK Central Repository, a program of the National Institute of Diabetes and Digestive and Kidney Diseases

Prediction quality metrics

CV Fold	1	2	3	4	5	6	7	8	9	10
RMSE	6.8	7.1	6.5	7.4	6.9	7.5	7.1	7.2	6.4	6.7
R^2	0.83	0.82	0.86	0.80	0.83	0.86	0.84	0.80	0.84	0.82

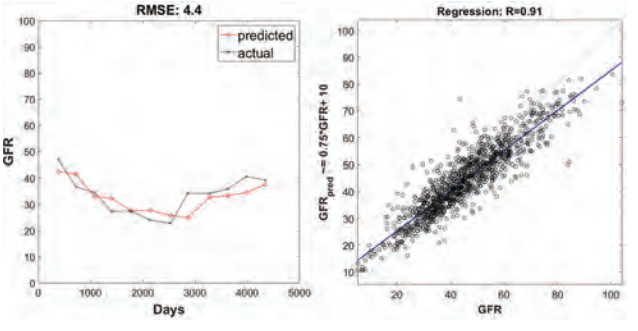


Figure 1: GFR trajectory prediction for an individual subject (left) and the regression plot on data from a single validation fold (right).

TH-PO006

Validation of Artificial Intelligence (AI)-Based Kidney Disease Progression Prediction (KDPP) Models in the US Population

Chin-Chi Kuo,[1] Yichun Chen,[4] Yi-Ching Chang,[1] Yu-Ting Lin,[1] Priyanka Arya,[3] Ricardo Aguilar,[3] Arsh Jain.[2] *[1]China Medical University Hospital, Taichung, Taiwan; [2]London Health Sciences Center, London, ON, Canada; [3]AWAK Technologies, Singapore, Singapore; [4]Ever Fortune.AI, Taichung, Taiwan.*

Background: AI and big data are revolutionizing personalized CKD management. KDPP models use deep learning to risk stratify patients for optimal treatment planning. Initially validated in Taiwan and granted **FDA breakthrough device designation**, this study tests KDPP's generalizability in U.S. using NIDDK's CRIC database.

Methods: KDPP includes 2 deep-learning models built using 9,529 CKD stage 3-5 patients from CMUH Taiwan: KDPP-RP for predicting rapid disease progression and KDPP-IR for forecasting renal replacement therapy (RRT). KDPP-IR was validated with CRIC (4,465 participants); KDPP-RP validation was limited by data scarcity. The models categorize patients into risk tiers (low, moderate, high) and are evaluated using AUC, sensitivity, specificity, and PPV/NPV.

Results: The CMUH cohort is older, has lower median eGFR (27 vs. 41.9 mL/min/1.73m^2) than CRIC. KDPP-IR accurately predicted RRT with AUCs of 0.96 for CMUH and 0.89-0.92 for CRIC, performing well across races (**Table 1**). KDPP-IR's sensitivity and precision slightly decreased, but specificity improved. It reliably identified low-risk CRIC patients with NPVs of 0.99-1.00, though PPVs for high-risk varied (0.31-0.79). Kaplan-Meier curves showed distinct risk stratification, and calibration plots showed better agreement between observed and predicted risks than KFRE. (**Figure 1**).

Conclusions: The validation demonstrated robust AUCs and generalizability for risk prediction. Future enhancements will optimize both models for diverse ethnic groups to broaden their applicability.

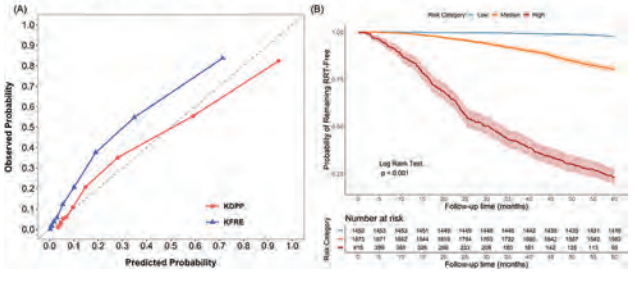
Funding: Commercial Support - AWAK Technologies

Table 1. Performance measures of the KDPP-IR in internal and external validation dataset.

Population	Timeframe	AUC	Sensitivity	Specificity	Precision
CMUH					
Asian	2-year	0.96	0.93	0.85	0.61
	5-year	0.96	0.91	0.86	0.80
CRIC					
Overall	2-year	0.92	0.75	0.90	0.33
	5-year	0.89	0.70	0.89	0.60
White	2-year	0.94	0.72	0.92	0.30
	5-year	0.90	0.69	0.91	0.55
African American	2-year	0.90	0.72	0.90	0.31
	5-year	0.87	0.67	0.88	0.62

Abbreviations: AUC, area under receiver operating characteristic curve; CMUH, China Medical University Hospital; CRIC, Chronic Renal Insufficiency Cohort.

Figure 1. KDPP-IR 5-year Timeframe Prediction of (A) Calibration plots for KDPP-IR vs 4-Variable Kidney Failure Risk Equation (B) Kaplan-Meier Analysis.



TH-PO007

Construction of a Predictive Equation for CKD Exacerbation by Multifactorial Analysis Using Machine Learning and Analysis on Differences in CKD Exacerbation Factors in Each CKD Stage

Koki Ogawa,[1] Hiroaki Hara,[1] Yasushi Takahashi,[2] Seiko Oana,[2] Yumiko Nakamura,[1] Akito Maeshima,[1] Hajime Hasegawa.[1] *[1]Saitama Ika Daigaku Sogo Iryo Center, Kawagoe, Japan; [2]NEC Solution Innovator Kabushiki Kaisha, Koto-ku, Japan.*

Background: Multiple factors such as comcomitant disorders, prescribed medications and physical characteristics are involved in CKD exacerbation. In recent years, machine-learning has enabled us to analyze the CKD exacerbation in relation to the multiple factors. We aimed to construct a predictive equation for the CKD exacerbation by analyzing changes in the multiple factors by machine-learning. Additionally, the differences in exacerbation factors per CKD stage were also examined.

Methods: The analysis included 3098 of CKD patients at our institution between Apr. 2006 and Mar. 2021 for which data analysis was possible more than once a year apart. For each case, 209 items such as blood test results, blood pressure, body weight, age and medications were learned and analyzed using machine learning. We defined the CKD exacerbation as "change in CKD heat map" (eg. green to yellow) because final renal outcome involves both decreased eGFR and worsening proteinuria during follow-up period. For the case in which CKD heat map exacerbated, the item of which the exacerbation contribution was large was extracted, and the difference of exacerbation factors (EF) by CKD stage was examined.

Results: The prediction equation was constructed using 85% of population, and its accuracy was verified by adapting the constructed equation to the remaining 15% of the population. The accuracy rate was 76.8% in Green group, 75.6% in Yellow group, and 70.8% in Orange group, respectively. The largest EF was the proteinuria throughout all CKD stage, and it was baseline eGFR next. Except for these two factors, EF differed according to CKD stage, and EF next to the above two factors were concomitant hypertension in Green group, elevation of serum uric acid in Yellow group, and the presence or progression of anaemia in Orange group.

Conclusions: The prediction equation constructed in this study showed sufficient accuracy for clinical use. And, that principal CKD exacerbation factors greatly differed for each stage except for proteinuria and baseline eGFR seemed to be the key knowledge for the management of CKD patients.

TH-PO008

Predicting the Risk of Albuminuria in Patients with Diabetes: A Systematic Review and Development Study

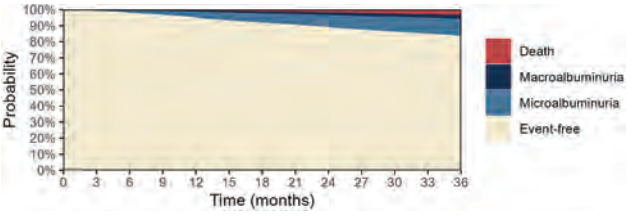
Roemer J. Janse,[1,2] Marretje W. Oomen,[1] Chava L. Ramspek,[1] Friedo W. Dekker,[1] Juan J. Carrero,[2] Merel van Diepen.[1] *[1]Leids Universitair Medisch Centrum, Leiden, Netherlands; [2]Karolinska Institutet, Stockholm, Sweden.*

Background: Patients with type 2 diabetes mellitus (T2DM) are at high risk of kidney disease, which may be ameliorated by early detection of albuminuria. Clinical prediction models (CPMs) can tailor guideline screening to the individual patient. To allow this, we aimed to 1) identify available CPMs and their shortcomings and 2) predict albuminuria risk, albuminuria-free time, and progression through albuminuria stages.

Methods: We systematically identified albuminuria CPMs and appraised their risk of bias (ROB). New models were developed in the Stockholm Creatinine Measurements cohort. We divided Stockholm residents with an albumin/creatinine test between 2006-2021 with T2DM and no albuminuria into a development and temporal validation cohort. Predictors were selected based on clinical expertise, literature, and previous CPMs. We predicted micro- and macroalbuminuria within 3 years. We predicted 1) the risk using a Fine-Gray CPM accounting for the competing risk of death, 2) the expected albuminuria-free days using an accelerated failure time (AFT) CPM, and 3) the risk of different albuminuria stages using a multi-state CPM. CPM discrimination and calibration were assessed in the development and validation cohorts.

Results: We identified 9 studies reporting on 11 CPMs. Most models were at high ROB. We developed new models on 38649 individuals with 6904 events and validated these in 45009 individuals with 6499 events. The Fine-Gray CPM had adequate discrimination internally (C-statistic, 95%CI; 0.64, 0.64-0.65) and temporally (0.66, 0.66-0.67). Calibration was good. The AFT CPM had adequate discrimination (internally: 0.63, 0.62-0.63; temporally: 0.65, 0.64-0.65), but poor calibration. An individual prediction from the multi-state CPM can be seen in **Figure 1**.

Conclusions: Predicting albuminuria in T2DM patients allows tailoring albuminuria screening to the individual. We developed multiple CPMs that provide different information on the risk of albuminuria within 3 years. These models can serve to improve albuminuria screening and ameliorate the risk of kidney damage in patients with T2DM.



TH-PO009

Artificial Intelligence (AI)-Driven Screening for Undiscovered CKD

Thomas L. Salazer,[1] Naitik Sheth,[1] Avais Masud,[1] David Serur,[1] Guillermo Hidalgo,[1] Iram Aqeel,[1] Linara Adilova,[2] Michael Kamp,[2] Tim Fitzpatrick,[2] Sriram Krishnan,[2] Kanishka Rao,[2] Bharat Rao.[2] *[1]Hackensack Meridian Health, Edison, NJ; [2]Carenostics, Philadelphia, PA.*

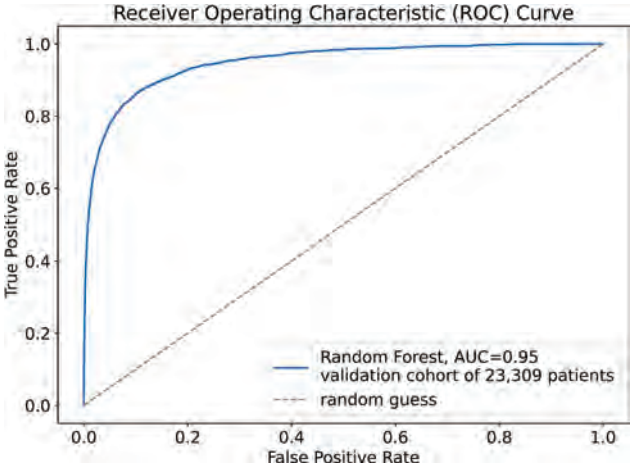
Background: We developed and validated a predictive model to identify patients at risk of undiagnosed CKD. Given the progressive nature of CKD, our model incorporates a crucial temporal dimension, allowing it to assess whether undiagnosed patients have

Stage 3 CKD based on prior EHR data. We developed the model to enable proactive evaluation and intervention on patients.

Methods: Patients aged 18 to 85 with no previous diagnosis of CKD as of January 1, 2018, were considered to identify which patients are at risk of undiagnosed CKD. The data set included patients with no prior eGFR, or at most one abnormal eGFR. We extracted 237 variables from the EHR, including demographics, labs, medications, and prior diagnoses. Multiple machine learning models were trained on a training set, and performance was measured on the test set using ROC curves, sensitivity, specificity and accuracy, as well as temporal stability.

Results: A Random Forest model trained on 46,775 patients achieved an AUC of .95 to predict whether next eGFR measured would be abnormal (eGFR < 60) on an independent test set of 23,039 patients whose eGFR was measured in the subsequent year. A selected set point achieved a sensitivity of 0.51 and PPV of 0.84. (ML models trained to predict the first abnormal eGFR in subsequent 2/3/4 years, achieved AUCs of 0.94/0.93/0.92 demonstrating the temporal stability of our approach.)

Conclusions: The model developed using a random forest machine learning algorithm was able to identify undiagnosed patients at risk of Stage 3 CKD with high accuracy and discriminatory power. This predictive model demonstrates the potential of an AI-driven approach to identify patients earlier in the disease process. In the next phase of this work, we intend to apply this model to identify high risk patients, and proactively recommend them for evaluation and targeted interventions.



Random Forest model ROC Curve

TH-PO010

Using Machine-Learning Algorithms to Predict the Risk of AKI and CKD during the COVID-19 Pandemic Based on National Electronic Health Records

Yue Zhang, Nasrollah Ghahramani, Vernon M. Chinchilli, Djibril Ba.
Penn State College of Medicine, Hershey, PA.

Background: The application of machine learning algorithms in predicting the risk of acute kidney injury (AKI) and chronic kidney disease (CKD) has shown promise within local healthcare organizations. However, their performance using national electronic health records (EHR) remains unclear. Moreover, the impact of including COVID-19 infection histories in predictive models is not clear.

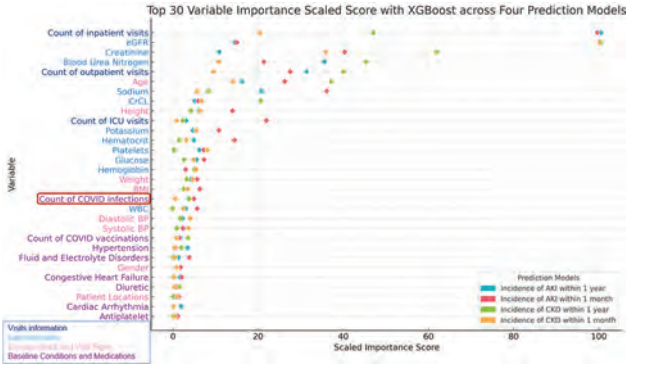
Methods: Data were sourced from the TriNetX Research Network, with study cohort period from 2022/07/01 to 2024/03/31. The incidence of AKI or CKD was extracted based on ICD-10 codes after the index date. Covariates were assessed within 1 year before the index dates, including 4 demographics, 33 comorbidities, 18 lab test results, 13 medications, 5 vital signs, 3 visit histories, and COVID-19 infections. Missing values were imputed, and upsampling methods were used to address data imbalances. Extreme gradient boosting was used to build machine learning algorithms for predicting AKI and CKD separately, for each of the two prediction windows.

Results: We included 104,565 participants. The area under the receiver operating characteristic (AUROC) curve was stable across the prediction windows, with the highest score for CKD within 1 month (0.87) and the lowest for AKI within 1 year (0.79) (Table). Counts of inpatient visits and eGFR were the most important variables for predicting AKI and CKD, respectively. The count of COVID-19 infections was the most important variable among baseline conditions (Figure).

Conclusions: Machine learning with national EHR data shows promising performance for AKI and CKD predictions. COVID-19 status should be included in the prediction model.

Performance of Predictive Models

Prediction Models	AUROC	Precision	Sensitivity	Specificity	Accuracy	F1 score
Incidence of CKD within 1 year	0.8624	0.9958	0.7944	0.7926	0.7944	0.8838
Incidence of AKI within 1 year	0.7880	0.9937	0.8081	0.6403	0.8057	0.8913
Incidence of CKD within 30 days	0.8659	0.9991	0.8410	0.7778	0.8408	0.9133
Incidence of AKI within 30 days	0.8025	0.9987	0.7681	0.7248	0.7680	0.8664



TH-PO011

Machine-Learning Model for Predicting Early Mortality in Critically Ill Patients Requiring Continuous Kidney Replacement Therapy

Kullaya Takkavatakarn,[1] Joshua Lambert,[2] Justin Kauffman,[1] Tomonori Takeuchi,[4] Augusto Cama-Olivares,[4] Stuart Goldstein,[3] Jin Chen,[4] Lili Chan,[1] Girish N. Nadkarni,[1] Javier A. Neyra.[4] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]University of Cincinnati, Cincinnati, OH; [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [4]The University of Alabama at Birmingham, Birmingham, AL.*

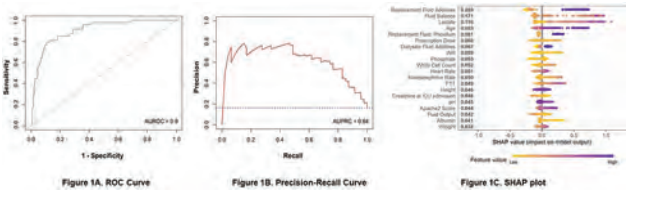
Background: Critically ill patients with acute kidney injury requiring continuous renal replacement therapy (CRRT) have high mortality and require significant resource utilization. Accurately predicting early mortality would facilitate clinical decision-making by identifying high morbid patients who may benefit from personalized care intensity with CRRT. We aimed to develop a model to predict mortality within the first 72 hours after initiating CRRT.

Methods: We obtained data from CRRTnet, a prospective multicenter data registry of adult patients undergoing CRRT for at least 24 hours. The cohort was divided into training and test datasets (80/20). We trained and validated XGBoost model with 10-fold cross-validation to predict mortality within 72 hours of CRRT initiation using patient demographics, laboratory results, vasopressors, fluid balance, and CRRT-related variables. We chose the parameters for the XGBoost model using Bayesian optimization. Bayesian optimization models the anticipated value of an objective function with a gaussian process over the space of all hyper parameters and uses Bayesian updating to choose parameter sets that maximize this function. Area under the receiver operating characteristic (AUROC) and precision-recall curve (AUPRC) were used to evaluate model performances. Shapley additive explanation (SHAP) value was applied to explain the model.

Results: We included 1,446 patients (59% men). Median age was 60 years (IQR 50-69), serum creatinine at CRRT initiation was 5.4 mg/dL (IQR 2.9-6.7), and APACHE II score was 29 (IQR 26-31). Among these patients, 236 (16.3%) died within 72 hours of CRRT initiation. The AUROC was 0.90 (95% CI 0.86 to 0.95), and the AUPRC was 0.64 (0.50 to 0.79) **(Fig1A,1B).** SHAP plot shows the importance of the top 20 features **(Fig1C).**

Conclusions: The proposed XGBoost model, the first to incorporate clinical and CRRT-related variables, shows promise in predicting early mortality in critically ill patients undergoing CRRT. Implementing the model could serve as an additional clinical tool for personalizing early CRRT use.

Funding: Commercial Support - Baxter Healthcare via an Investigator Initiated Research grant award



TH-PO012

A Data-Driven Digital Health Approach to Improve CRRT Delivery in the Intensive Care Unit (ICU)

Ruben Raposo,[1,2] Javier A. Neyra,[2] Ashita J. Tolwani.[2] *[1]Dialytix Technologies Inc., Birmingham, AL; [2]The University of Alabama at Birmingham, Birmingham, AL.*

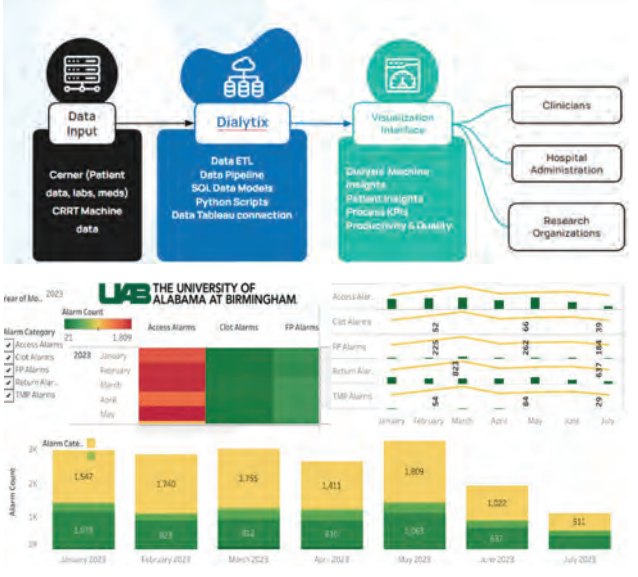
Background: Acute kidney injury (AKI) is a frequent complication in the intensive care unit (ICU). About 15% of critically ill patients with AKI require renal replacement therapy, commonly in the form of continuous renal replacement therapy (CRRT). The aims is to develop a data pipeline to feed scalable dashboards of patient- and CRRT-relevant data to monitor key performance indicators and patient outcomes.

Methods: We utilize EHR and CRRT device data from the University of Alabama at Birmingham from January 2022 to February 2024. The data from each of the 42 CRRT machines (2022 to 2024) operating UAB. We extracted the CRRT device data every month via a manual process and were then uploaded to a secure storage location for data processing. We created an ETL (extract, process, and loading) data process using Python code to clean and normalize data. We then connected the Python data pipeline to feed the visualization layer via the Tableau cloud server. We designed interactive dashboards with Tableau that show the key performance indicators for various stakeholders that want to monitor and track on a weekly or monthly basis.

Results: We developed clinical dashboards in Tableau that incorporate data visualization with KPIs, filters, and AI-powered data analytics techniques to support providers in viewing and exploring EHR data for clinicians to inform decisions and improve patient care, thereby identifying previously unnoticed patterns in EHR data to support clinical decision-making.

Conclusions: With the collection of CRRT machine data and the creation of a data processing pipeline including EHR data, we can provide our clinical, administrators, and medical researchers further data insights on the performance of the CRRT treatment and enhance the monitoring capabilities so that we can continue to understand where possible gaps are and find ways to improve on them.

Funding: NIDDK Support, Commercial Support - Dialytix Technologies Inc.



TH-PO013

NefroAssist: A Machine-Learning Prediction Model for Early Nephrology Intervention in Hospitalized Patients at Christus Muguerza Group

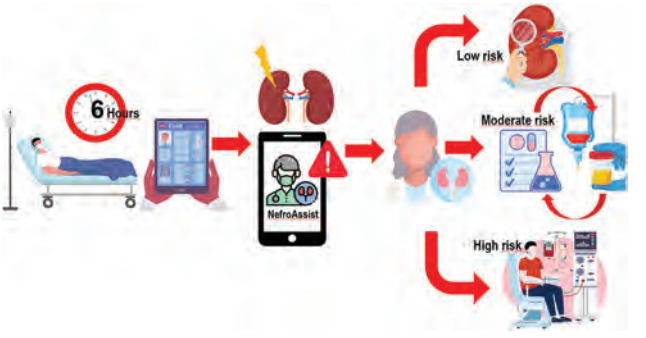
Mariana N. Zavala, Ricardo A. Garza Treviño, Santiago Chavez, Andres O. Nevarez, Juan O Galindo, Lilia M. Rizo Topete. *Christus Muguerza Sistemas Hospitalarios SA de CV, Monterrey, Mexico*.

Background: Delay in nephrology consultation is associated to severe AKI stages and critical illness, resulting in urgent RRT, increased mortality, reduced renal recovery, greater dialysis dependence, and higher costs. To prevent AKI, based on the article "Acute Kidney Injury Risk Assessment and the Nephrology Rapid Response Team", which describes a model based in the "Fantastic 4", to identify patients at high risk for AKI; we developed NefroAssist. This machine learning algorithm has the objective to predict the likelihood of requiring nephrology consultation for patients within the first 6 hours of admission. It employs information from the electronic medical record and allows collaboration with a nephrologist to improve outcomes.

Methods: A predictive model was developed with database from the electronic medical record system available from 2023 of 4 hospitals. The methodology for handling the data was a ETL process (extract, transformation, and load). The initial load data were 23,104 individual records. Through the elimination of irrelevant data, data imputation, and the creation of new data, a split of 80-10-10 was performed. Where 80% was allocated for training, 10% for data validation, and 10% for testing the models. In the evaluation, the logistic regression model with has been able to fit correctly the data.

Results: Using logistic regression we train a model which demonstrated optimal performance in classifying patients who will require a nephrology consultation. With a specificity of 89% and sensitivity of 73%. The factors identified from the F4 were F1: polytrauma, antibiotics, coronary angiography, major surgery, and sepsis; F2 diabetic and hypertensive patients; and F4 creatinine, proteinuria.

Conclusions: Nefroassist successfully predicted which patients will require nephrology intervention, with a sensitivity of 73% and a specificity of 88%. We have validated it retrospectively, the next step is to apply and validate it prospectively.



TH-PO014

Artificial Intelligence/Machine Learning Externally Validated Models for AKI Risk-Classification: A Systematic Review and Meta-Analysis

Augusto Cama-Olivares,[1] Chloe G. Braun,[2] Tomonori Takeuchi,[1,3] Kathryn A. Kaiser,[4] Lama Ghazi,[5] Jin Chen,[1] Lui G. Forni,[6,7] Sandra L. Kane-Gill,[8] Marlies Ostermann,[9] Benjamin Shickel,[10] Jacob Ninan,[11] Javier A. Neyra.[1] *[1]The University of Alabama at Birmingham Division of Nephrology, Birmingham, AL; [2]The University of Alabama at Birmingham Department of Pediatrics, Birmingham, AL; [3]Tokyo Ika Shika Daigaku Daigakin Ishigaku Sogo Kenkyuka, Bunkyo-ku, Japan; [4]The University of Alabama at Birmingham Department of Health Behavior, Birmingham, AL; [5]The University of Alabama at Birmingham Department of Epidemiology, Birmingham, AL; [6]University of Surrey Department of Clinical and Experimental Medicine, Guildford, United Kingdom; [7]Royal Surrey NHS Foundation Trust, Guildford, United Kingdom; [8]University of Pittsburgh Department of Pharmacy and Therapeutics, Pittsburgh, PA; [9]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [10]University of Florida Division of Nephrology Hypertension & Renal Transplantation, Gainesville, FL; [11]Mayo Clinic Minnesota, Rochester, MN.*

Background: Artificial Intelligence (AI) through machine learning (ML) models can provide accurate and precise acute kidney injury (AKI) risk classification, but their extent and performance in real-world settings have not been established.

Methods: PubMed, EMBASE, Web of Science, and Scopus were searched until 08/2023. Articles reporting on externally validated models for prediction of AKI onset, AKI severity, and post-AKI complications in hospitalized adult and pediatric patients were searched using text words related to AKI, AI, and ML. Two independent reviewers screened article titles, abstracts, and full texts. Areas under the receiver operating characteristic curves (AUCs) were used to compare model discrimination and pooled using random-effects model.

Results: Of 4,280 articles initially identified and screened, 85 were included with 2.8 million admissions (study sample dates ranged from 1996 to 2022). The KDIGO criteria were the most frequently used to define AKI (72.9%). We identified 291 models, with the most commonly reported being logistic regression (35.1%), random forest (9.6%), and XGBoost (9.6%). The most frequently reported predictors of AKI onset were age, sex, diabetes, serum creatinine, and hemoglobin. The pooled AUC for AKI onset was 0.82 (95% CI, 0.80-0.84) and 0.78 (95% CI, 0.76-0.80) for internal and external validation, respectively. Pooled AUC across multiple clinical settings, AKI severities, and post-AKI complications ranged from 0.78 to 0.87 for internal validation and 0.75 to 0.84 for external validation. Although data were limited, results in the pediatric population aligned with those observed in adults. Between-study heterogeneity was high for all outcomes (I^2 >90%), and most studies presented high-risk of bias (72.9%) according to the Prediction model Risk Of Bias ASsessment Tool (PROBAST).

Conclusions: Most externally validated models performed well in predicting AKI onset, AKI severity, and post-AKI complications in hospitalized adult and pediatric populations. However, heterogeneity in clinical settings, study populations, and predictors limits their generalizability and implementation.

TH-PO015

Advancements in Predicting Pediatric AKI Using Artificial Intelligence: A Systematic Review

Arwa Nada.[1,2] *[1]Loma Linda University, Loma Linda, CA; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN.*

Background: The prediction and management of Acute Kidney Injury (AKI) in pediatric patients remain challenging due to its rapid onset and diverse etiologies. Recent advancements in artificial intelligence (AI) offer promising tools for early detection and improved clinical outcomes.

Methods: Search Strategy: Utilized PubMed with keywords and MeSH terms related to pediatric AKI and artificial intelligence. Inclusion Criteria: Studies published from 2019-2023, involving AI models for pediatric AKI prediction or management. Data Extraction: Study characteristics, AI methods, population, key findings, and references were extracted and tabulated.

Results: Table I shows summary of the studies (image of table uploaded) The studies colectively showed: high Accuracy: GBM, ensemble learning, and RF models demonstrated high predictive accuracy. Early Detection: AI models enabled early AKI detection, facilitating timely interventions. Risk Stratification: Effective in identifying high-risk patients for personalized treatment. Data Integration: AI successfully integrated diverse data sources for comprehensive analysis.

Conclusions: AI integration in clinical practice holds the potential for revolutionizing pediatric AKI management and improving patient outcomes through proactive and personalized care. Further research should focus on standardizing AI applications and ensuring equitable healthcare delivery.

Study Title	Year	AI Method	Population	Aim	Key Findings	Reference
Machine Learning Model for Early Prediction of AKI	2021	Ensemble Learning	Pediatric critical care	To predict AKI risk using age and biochemical markers	AUROC 0.87–0.89; age and biochemical markers	Dong et al., Critical Care, 2021
Predicting AKI in Pediatric Cardiac Intensive Care	2023	Random Forest	Pediatric cardiac ICU	To predict severe AKI 48 hours in advance	Predicted severe AKI 48 hours in advance	Smith et al., Journal of Anesthesia, Analgesia and Critical Care, 2023
AI Applications for Perioperative AKI Prediction	2022	GBM, RF, ANN	Pediatric perioperative patients	To evaluate AI model performance in predicting perioperative AKI	Varying performance by surgery type	Brown et al., BMC Nephrology, 2022
Gradient Boosting Machine for Neonatal AKI	2021	Gradient Boosting Machine	Neonatal patients	To predict early AKI in neonates	Promising early AKI prediction	Jones et al., Pediatrics, 2021
Ensemble Learning for Pediatric ICU AKI Prediction	2020	Ensemble Learning	Pediatric ICU	To improve AKI prediction accuracy using ensemble models	Improved prediction accuracy	Lee et al., Journal of Anesthesia, Analgesia and Critical Care, 2020. Link
Artificial Neural Network for AKI Prediction in Nephrology	2022	Artificial Neural Network	Pediatric nephrology	To predict AKI using clinical and biochemical markers	High accuracy with clinical and biochemical markers	Martinez et al., Nature, 2022.
Support Vector Machine for Early AKI Detection	2021	Support Vector Machine	Pediatric ICU	To detect AKI early in pediatric ICU patients	Improved prediction over traditional methods	Wang et al., Pediatric Research, 2021.
Logistic Regression for Identifying AKI Risk Factors	2020	Logistic Regression	Hospitalized pediatric patients	To identify key risk factors for AKI	Key risk factors identification	Patel et al., Springer, 2020
Deep Learning Model for Real-Time AKI Risk Assessment	2019	Deep Learning	Pediatric ICU	To provide real-time AKI risk assessment	Real-time AKI risk assessment	Gupta et al., BMC Nephrology, 2019 Link
KIM-1, IL-18, and NGAL in ML Prediction of Kidney Injury in HSCT	2023	Machine Learning	Pediatric HSCT patients	To predict AKI using biomarkers	Identified key biomarkers for early AKI prediction	Mostaf et al., Int J Mol Sci, 2023.
ML for Predicting Cardiac Surgery-Associated AKI	2024	Supervised ML	Pediatric cardiac surgery patients	To predict AKI post-cardiac surgery	Effective prediction using demographic and clinical data	Nagy et al., Pediatr Nephrol, 2024.
XGBoost for Outcome Prediction in AKI	2023	XGBoost	Hospitalized pediatric patients	To predict outcomes in pediatric AKI	The model demonstrated high accuracy in early prediction of AKI, improving patient outcomes through timely interventions.	Dang et al., Sci Rep, 2022.
Pre-anastomosis Model for AKI Prediction	2020	ML Algorithm	Hospitalized pediatric patients	To develop a concise model for AKI prediction	Accurate AKI predictions with minimal data	Sandoki et al., J Am Soc Nephrol, 2020.
ML for Predicting AKI in Aortic Arch Reconstruction	2023	Multiple ML Models	Pediatric cardiac surgery patients	To develop a model for AKI prediction post-surgery	Identified risk factors and effective prediction	Kong et al., Eur J Med Res, 2023.
ML Tools for Assessing AKI Risk in HSCT	2024	ML Tools	Pediatric HSCT patients	To identify AKI risk factors using ML	Effective in predicting AKI and guiding interventions	Mostaf et al., J Clin Med, 2024.
ML Model for Community-Acquired AKI Hospitalization	2020	ML	General pediatric population	To predict hospitalization risk for community-acquired AKI	Accurate prediction of hospitalization risk	Hsu et al., J Med Internet Res, 2020.
ML Predicts AKI in Sickle Cell Disease	2024	XGBoost	Pediatric SCD patients	To predict AKI in SCD using physiological data	Early and accurate AKI predictions	Taha et al., Am J Nephrol, 2024.
Chemoinformatics and ML for Drug Properties in Kidney and Liver Diseases	2021	ML and Chemoinformatics	Pediatric and adult patients	To analyze drug properties affecting kidney and liver	Identified molecular properties influencing disease	Nigam et al., Pharmaceutics, 2021.
Predicting AKI with an AI-driven model in a pediatric cardiac ICU	2023	ML	Pediatrics admitted to cardiac intensive care unit	To build a ML train-model with Random Forest (RF) algorithm, based on electronic health record (EHR) data, able to	AI models significantly enhanced AKI prediction accuracy in pediatric cardiac ICU settings.	Francesco F et al. J Anesth Analg Crit Care.

				Forecast AKI continuously after 48 h in post-cardiac surgery children, and to test its performance.		
Machine Learning Based Prediction of AKI Following Pediatric Cardiac Surgery	2023.	Multiple ML models including XGBoost	One month to 18 years who underwent cardiac surgery with cardiopulmonary bypass	To develop and validate machine learning models to predict the development of CSA-AKI in the pediatric population.	The study highlighted machine learning's potential in predicting post-surgery AKI with high precision.	Luo SQ et al. J Med Internet Res.
Oxygen delivery in pediatric cardiac surgery and its association with AKI using machine learning	2023	ML, Random Forest	pediatric cardiac surgery with cardiopulmonary bypass	To determine the oxygen delivery indexed to body surface area (DO2I) threshold associated with postoperative AKI in pediatric patients during CPB, and whether it remains clinically important in the context of other known independent risk factors.	Machine learning identified key oxygen delivery factors linked to AKI, aiding in risk stratification and management	Hayward A et al. J Thorac Cardiovasc Surg
A time-aware attention model for prediction of acute kidney injury after pediatric cardiac surgery	2022	A time-aware deep learning mode	Children admitted to hospital	Prediction of AKI	The time-aware deep learning model showed high accuracy (ROC AUC 0.960) in predicting postoperative AKI, outperforming existing models and aiding in timely preventive measures.	Tang X et al. J Am Med Inform Assoc
Identification and validation of an explainable prediction model of acute kidney injury with prognostic implications in critically ill children: a prospective multicenter cohort study	2023		Children admitted to ICU	Prediction of AKI	The model demonstrated high accuracy in predicting AKI and its outcomes, providing critical insights for clinical interventions.	Zhang H et al. Crit Care Med
Machine Learning Based Prediction of Acute Kidney Injury Following Pediatric Cardiac Surgery: Model Development and Validation Study	2023.	XGBoost	Pediatric cardiac surgery	Prediction of AKI	The XGBoost model achieved high predictive performance for CSA-AKI, with an AUROC of 0.912 for the derivation cohort and 0.889 for the validation cohort, highlighting key predictors such as serum creatinine, perfusion time, and intraoperative blood loss.	Luo SQ et al. J Med Internet Res

TH-PO016

Forecasting Intradialytic Hypotension: A Comparative Analysis of Machine-Learning and Deep-Learning Approaches

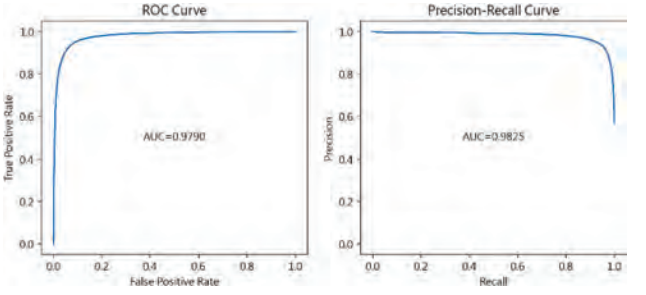
Chun-Te Huang.[1,2] *[1]Taichung Veterans General Hospital, Taichung, Taiwan; [2]National Yang Ming Chiao Tung University - Yangming Campus, Taipei, Taiwan.*

Background: Intradialytic hypotension (IDH) poses significant risks to patients undergoing dialysis, necessitating reliable predictive tools for early intervention. This study evaluates the efficacy of machine learning and deep learning models in predicting IDH.

Methods: We developed predictive models on a Taichung Veterans General Hospital dataset using XGBoost (eXtreme Gradient Boosting) and RNN (Recurrent Neural Network) algorithms. The dataset encompasses the period from 2015 to 2020, consisting of 211,535 timestamps from 20,946 hemodialysis sessions across 2,118 patients. We defined intradialytic hypotension as a decrease in systolic blood pressure ≥20 mm Hg and/or a mean arterial pressure decrease ≥10 mm Hg. The dataset was split into 80% for training, employing 5-fold cross-validation, and 20% for testing. Features selected for training included age, sex, comorbidity, vital signs, laboratory data, medication, and specific hemodialysis characteristics.

Results: The XGBoost model exhibited superior performance in predicting intradialytic hypotension, achieving an Area Under the Receiver Operating Characteristic curve (AUROC) of 0.9790 and an Area Under the Precision-Recall Curve (AUPRC) of 0.9825. While still effective, the RNN model showed slightly lower performance with an AUROC of 0.976 and an AUPRC of 0.978. These results emphasize the slight edge of XGBoost in predictive accuracy compared to the RNN model, demonstrating its enhanced capability in clinical forecasting without specifically relying on demographic variables like age and weight.

Conclusions: The findings from this study highlight the slightly superior performance of the XGBoost model over the RNN in predicting intradialytic hypotension. XGBoost demonstrated higher predictive accuracy and offers potential advantages in clinical implementation due to its less intensive computational demands. This makes it an especially viable option for real-time clinical applications with limited computational resources.



The model performance of XGBoost

TH-PO017

Development of Artificial Intelligence for Clinical Decision Support to Optimizes Erythropoietin-Stimulating Agents in Patients with CKD

Sathit Kurathong, Pattanan Buranasaksathien, Wanjak Pongsitisak, Thananda Trakarnvanich, Tanun Ngamvichchukorn, Solos Jaturapisanukul, Punnawit Laungchuaychok, Nitcha Suphatheerawatr, Kavee Limbutara, Padoemwut Teerawongsakul. Vajira Big Data and Machine Learning for Applied in Healthcare Research Group. *Faculty of Medicine Vajira Hospital, Bangkok, Thailand.*

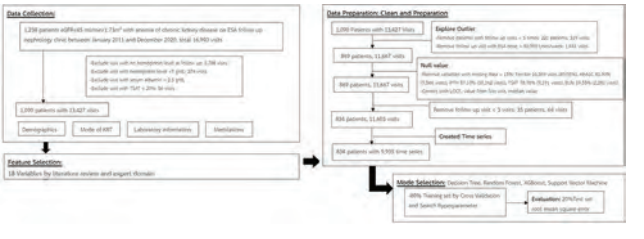
Background: The application of AI in predicting Hb levels and determining appropriate ESA doses for managing anemia of CKD is a promising development. Previous studies using AI for anemia of CKD treatment have demonstrated positive outcomes, such as increased percentages of patients achieving target Hb levels and reduced ESA dosages. The replication of these findings in the Thai population could have significant implications for managing anemia of CKD in Thailand.

Methods: The development of the AI model included 4 steps: data collection, feature selection, data preparation, and model selection. CKD patients with eGFR <45 ml/min/1.73m^2 who used ESA were included. The data was cleaned and prepared by removing outlier data and correcting missing values. Variables were used to create time series. Time series were divided into training and test set to create the best models (Decision Tree, Random Forest, XGBoost, and SVM). Finally, the models were evaluated by Pearson r correlation and RMSE. (Fig 1)

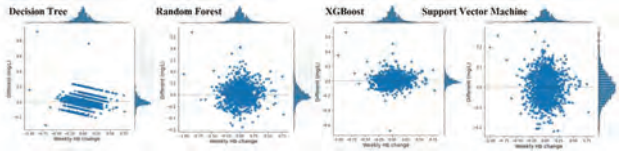
Results: A total of 9,935 time series were collected. The median follow-up time was 9 months. The models did not perform well in predicting weekly change of Hb level on the entire dataset (RMSE for Decision Tree was 0.141, for Random Forest was 0.135, for XGBoost was 0.137, and for SVM was 0.135), and the difference in weekly change of Hb ranged from -0.2 to 0.2 g/dL, approximately 0-40%. The best models are Random Forest, XGBoost and SVM with similar results. (Fig 2)

Conclusions: This study showed that AI model can predict weekly change in Hb level. Although the performance may not be able to accurately predict weekly changes in Hb levels. Future studies should aim to include a larger number of participants to improve the performance of the models.

Funding: Government Support - Non-U.S.



Trial Flow Chart



The Difference of weekly Hb change of the model

TH-PO018

Machine-Learning Algorithm of Two Continuous Assessment Methods of Dialysis Quality Indicators-Based Prediction Scheme for Assessing Mortality Risk in Patients on Maintenance Hemodialysis

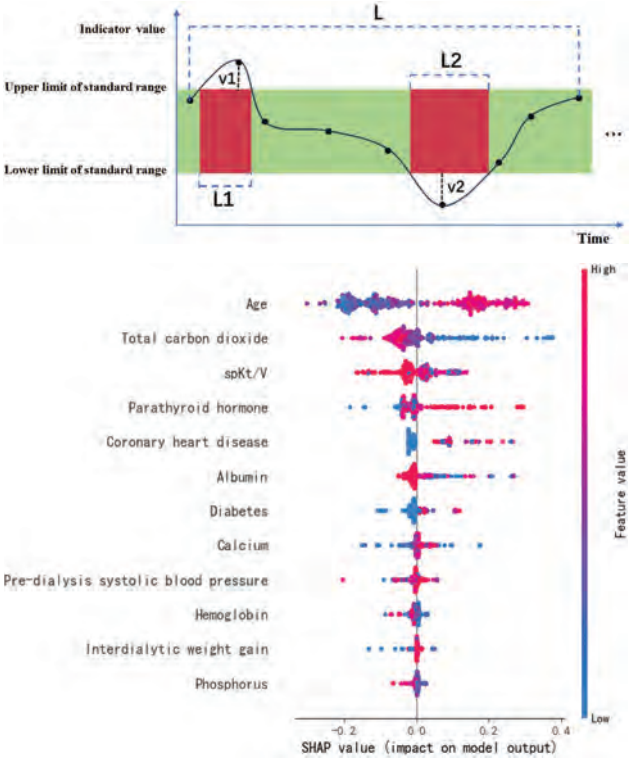
Jianhua Dong, Yongchun Ge. National Clinical Research Center of Kidney Diseases. *Nanjing General Hospital of Nanjing Military Command Research Institute of Nephrology, Nanjing, China.*

Background: Use machine learning method to analyze the impact of two continuous assessment methods of dialysis quality indicators on the prognosis of maintenance hemodialysis (HD) patients

Methods: A total of 240 patients who received HD treatment were screened, and dialysis quality was assessed more than three times a year. The indicator time-to-standard ratio and indicator fluctuation value were used as the evaluation methods for the continuous achievement of nine dialysis quality indicators. A prediction model for survival or death of HD patients after 1 year was constructed based on a machine learning algorithm. Shapley additive explanation (SHAP) values were used to measure the marginal contribution of each feature to the models.

Results: Six machine learning methods are used to build prediction models based on the indicator time-to-standard ratio and the indicator fluctuation value. The ExtraTrees model based on the indicator time-to-standard ratio has the best prediction effect, with its accuracy, precision, recall, F1 score and area under the receiver operating curve reaching 0.92, 0.86, 0.96, 0.91 and 0.93 respectively, while confirming 0.65 as the optimal probability threshold for the model. Visualization of the TreeSHAP interpretation results of the prediction model helps physicians understand the global prediction mechanism of the model and explain the importance of a patient's characteristic parameters in influencing the outcome of the patient.

Conclusions: The machine learning model based on the indicator time-to-standard ratio has a good prediction effect on the prognosis of HD patients.



TH-PO019

Development of Machine Learning-Based Models for Detection of Cognitive Impairment in Patients Receiving Maintenance Hemodialysis

Tsai-chieh Ling,[1] Chiung-Chih Chang,[3] Jia-Ling Wu,[2,1] Wei-Ren Lin,[1] Chien Yao Sun,[1] Chieh-Hsin Huang,[1] Yu T. Chang.[1,2] *[1]National Cheng Kung University Hospital, Tainan, Taiwan; [2]National Cheng Kung University, Tainan, Taiwan; [3]Chang Gung Memorial Hospital Linkou, Kaohsiung, Taiwan.*

Background: Cognitive impairment is common but frequently undiagnosed in the dialysis population. There is no recommended screening tool specifically designed for them. We aimed to develop and validate a quick and accurate screening tool composed of only a few items in the Mini-Mental State Examination (MMSE) and Cognitive Abilities Screening Instrument (CASI) using machine-learning based approaches in hemodialysis patients.

Methods: We conducted a cross-sectional observational study in which the MMSE and CASI were administered in 508 hemodialysis patients and randomly divided into a derivation set (70%) and a validation set (30%). Cognitive impairment was defined as a CASI score below the 20th percentile of age- and education-matched norms. Using three to five key items from MMSE and CASI as predictors, we developed six machine learning models, including Lasso, classification and regression tree (CART), random forest (RF), extreme gradient boosting (XGboost), support vector machine (SVM), and artificial neural networks (ANN) in derivation set. We then evaluated the predictive performance of these models in the validation set.

Results: The derivation samples (n = 357) had a mean (SD) age of 64.13 (11.92) years and a mean education level of 8.76 (4.91) years. Around 40% participants were identified as cognitive impairment according to their total CASI score. Among all the developed machine-learning models, the RF model achieved the highest performance of prediction, with an accuracy of 0.94, an area under the curve (AUC) of 0.95, and an F1 score of 0.92 in the validation set. The other models, except for CART, performed equally well in terms of AUC. The RF and SVM models demonstrated the greatest net benefit over clinical thresholds according to decision curve analysis.

Conclusions: Our study demonstrates that using machine-learning models can efficiently identify patients with CASI score < 20 percentile of age- and education-matched norms with only several questions in CASI and MMSE within 5 minutes. Since cognitive impairment implicates decision making and is associated with poor outcomes, early detection might improves patient care and enables timely referral.

Funding: Clinical Revenue Support

TH-PO020

Automatic Noninvasive Peritonitis Detection and Monitoring in Patients on Peritoneal Dialysis Using High-Resolution Ultrasonography and Artificial Intelligence

Maria Quero,[1] Beatrice M. Jobst,[2] Sara Guillén Fernández-Micheltorena,[2] Francesc Carandell Verdaguer,[2] Roberto F. Santos Abreu,[2] Javier Jimenez,[2] Rita Quesada,[2] Alex Andujar Asensio,[1] Ana M. Rau,[1] Yolanda Molina,[3] Fátima Moreno Guzmán,[3] Jose Jesus Broseta Monzo,[4] Ana Sanchez Escuredo,[5] Maria F. Slon Roblero,[6] Inés Rama.[1] *[1]Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; [2]Kriba, Barcelona, Spain; [3]Consorci Sanitari de Terrassa, Terrassa, Spain; [4]Hospital Clinic de Barcelona, Barcelona, Spain; [5]Hospital de Sant Joan Despi, Sant Joan Despi, Spain; [6]Complejo Hospitalario Navarra, Pamplona, Spain.*

Background: Peritonitis is a significant complication in peritoneal dialysis (PD) due to its high incidence and associated consequences, such as technique failure and mortality. Early diagnosis and treatment are crucial to reduce complications. We developed an automatic, quick, non-invasive leukocyte counting and differential method based on high-resolution ultrasound (HRUS) and artificial intelligence (AI). This method could be useful for early peritonitis detection and home monitoring in PD patients to extend technique's survival and reduce mortality.

Methods: We acquired HRUS in vitro data from polystyrene particles suspended in distilled water in drainage bags (Baxter's and Fresenius') at concentrations 0-4000 cells/μl. Four AI models were trained on these data: one to classify concentrations below and above 200 cells/μl; two models to predict leukocyte numbers in the respective range, and a fourth to classify between polymorphonuclear cells and lymphocytes. Patient effluent samples with >4000 cells/μl were automatically filtered by intensity. Each model was tested with 3 measurements on each of the 62 samples from 6 patients with confirmed peritonitis. Results were compared to laboratory measurements (LM).

Results: The counting models yielded an R^2 score of 0.94 (0-4000 cells/μl). For LM<200, containing the diagnostic threshold of 100 cells/μl, the mean error over patient samples was 18.1±22.0 cells/μl. 18/20 measurements >4000 cells/μl were correctly filtered. The remaining 2 were predicted with >2700 cells/μl. For classification below and above 100 cells/μl, we obtained a sensitivity/specificity (SE/SP) of 95.1/94.7%, respectively. Additionally, the cell-type classification model achieved an accuracy of 90.2% (SE/SP: 86.5/92.5%).

Conclusions: These results demonstrate the potential of this non-invasive AI and HRUS based leukocyte counting and differential system for early detection and objective home monitoring of peritonitis in PD patients.

Funding: Commercial Support - Kriba, Government Support - Non-U.S.

TH-PO021

A Systematic Approach to Map Downstream Effects of Proteins on the Paired Plasma and Urine Metabolome

Inga Steinbrenner,[1] Anna Kottgen,[1,2] Pascal Schlosser.[1,2] *[1]Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.*

Background: Proteins mediate and catalyze many metabolic functions, including enzymatic reactions or transport processes. The kidneys operate at the interface of plasma and urine by clearing molecular waste from the body while retaining valuable solutes, underscoring the importance of understanding the connection between transporters and enzymes and their substrates across biofluids. Using quantitative readouts of the proteome and metabolome, we employed hypothesis-generating genetic causal inference methods to study their molecular relations.

Methods: We conducted proteome-wide association studies (PWAS, 1,303 proteins) for the levels of 1,296 plasma and 1,399 urine metabolites as a causal inference approach, based on summary statistics from genome-wide association studies of metabolite levels (N= 7,213 and 5,023, respectively). Downstream analyses included statistical colocalization to control for the risk of genetic confounding due to linkage disequilibrium and a phenome-wide PWAS to highlight (patho-) physiological effects for the proteins with a significant metabolite association with over 4,000 phenotypes in the UK Biobank.

Results: We identified 284 putative causal effects of proteins on metabolite levels, arising from 61 unique proteins and 176 unique metabolite-biofluid combinations and balanced between plasma and urine (141 vs. 143). Colocalization analyses prioritized 169/284 findings (posterior probability of a shared causal variant > 80%). For 31 of the 61 proteins, 326 putative causal effects on health outcomes were identified (p<1.8e-7). For example, the kidney membrane enzyme DPEP1 displayed the strongest association with urine prolylglycine (p-value=1.1e-292) and was associated with 13 metabolite levels and 25 health outcomes including higher hemoglobin concentration and less frequently diagnosed high blood pressure. Another example were UGT1A1 and UGT1A6, enzymes that transform small lipophilic molecules into water-soluble, excretable metabolites. Accordingly, they were among the proteins with the highest number of associated metabolites and linked to risk of gallstone disease.

Conclusions: This hypothesis-generating *in vivo* causal inference screen of the proteome and metabolome highlights dozens of enzymes and their corresponding metabolites and clinical correlates.

TH-PO022

Multimodal Spatial Transcriptomic Characterization of Mouse Kidney Injury and Repair

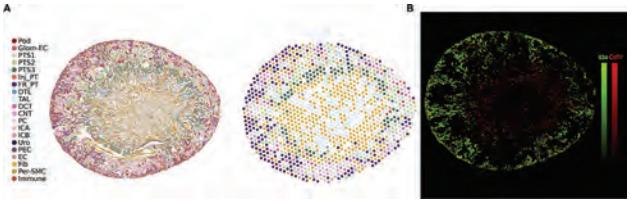
Qiao Xuanyuan, Haojia Wu, Yuhei Kirita, Yoshiharu Muto, Pierre Isnard, Benjamin D. Humphreys. *Washington University in St Louis, St Louis, MO.*

Background: Repair after acute kidney injury (AKI) involves complex interactions among epithelial, stromal, and immune cells, with incomplete recovery potentially leading to fibrosis and chronic kidney disease (CKD). Traditional single-cell sequencing technologies fail to capture the spatial context of these interactions. This study leverages high-resolution in situ sequencing (Xenium) with whole-transcriptome spatial transcriptomics (Visium) to elucidate cellular networks across the full murine kidney injury and repair timecourse.

Methods: We collected mouse kidneys at multiple stages post bilateral ischemia-reperfusion injury (sham, 4 h, 12 h, 2 d, 14 d, and 42 d). We performed analyses using Xenium (300 gene panel) and Visium on two serial sections of formalin-fixed, paraffin-embedded tissue from each time point. Data integration from both platforms mapped the spatial and temporal gene expression across the timeline.

Results: Aligning Xenium and Visium datasets revealed a strong correlation for transcript detection. Xenium analysis identified a total of 1,374,915 cells with an average detection of 123 ± 97 transcripts per cell. Unsupervised clustering resolved twenty distinct cell types and disease states. This single-cell resolution spatial data allowed us to spatially map disease cell states to different regions in the kidney throughout injury and repair. Importantly, we identified the formation of a fibrotic neighborhood dominated by failed repair proximal tubule (FR-PT) cells, immune cells, and fibroblasts during the repair phase through cell neighborhood analysis. Additionally, ligand-receptor interactions enabled the identification of FR-PT expression of *Il34* (ligand) recruiting *Csfr1+* (receptor) immune cells. Finally, integration with Visium data validated the co-expression of ligand-receptor pairs and elucidated potential mechanisms underlying the transition from AKI to CKD.

Conclusions: This study demonstrates the utility of combining high-resolution in situ sequencing with spatial transcriptomics to explore the cellular landscape during renal injury and repair.



A) Spatial cell type map in Xenium and Visium. B) *Il34* (ligand) and *Csf1r* (receptor) expression.

TH-PO023

Validation of a Cloud-Based Convolutional Neural Network Classifying Arteriovenous Access Aneurysms in a Multicenter Study

Zijun Dong,[1] Hanjie Zhang,[1] Lin-Chun Wang,[1] Sarah Ren,[1] Maggie Han,[1] Lela Tisdale,[1] Valeria Gusmao Bittencourt,[1] Laura Rosales M.,[1] Piotr Starakiewicz,[2] Denzil Douglas,[2] Norbert Shtaynberg,[2] Andrzej Kozyra,[2] Nicholas Fuca,[2] Sindhuri Prakash-Polet,[2] Stephan Thijssen,[1] Dean C. Preddie,[2] Peter Kotanko.[1,3] *[1]Renal Research Institute, New York, NY; [2]Azura Vascular Care, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Arteriovenous (AV) access aneurysms may become life-threatening, e.g., in the event of ruptures. We developed an artificial intelligence classification application (ACA) that categorizes aneurysms using AV access images. This study prospectively evaluates ACA's classification of AV aneurysms against physicians specializing in access care.

Methods: The study took place at two vascular access centers in New York, NY, USA. Subjects were assessed by physicians and classified as having "Advanced" or "Not Advanced" AV aneurysms. Six images, two from above the access and two on each side, were taken (Figure. 1c), uploaded to the cloud, and classified by a convolutional neural network within seconds (Figure. 1b). ACA classifications were compared to those made by physicians, and the area under the receiver operating characteristics (AUROC) curves were computed (Figure. 1a). Physicians were blinded to ACA results. Their assessment served as the ground truth.

Results: We included 720 images from 120 subjects (Figure. 1d). Physicians identified a 22% prevalence of advanced aneurysms. ACA classifications resulted in a mean AUROC of 0.907 (95% CI: 0.840-0.952), a median AUROC of 0.893 (95% CI: 0.823-0.942), a minimum AUROC of 0.866 (95% CI: 0.792-0.921), and a maximum AUROC of 0.910 (95% CI: 0.844-0.955) (Figure. 1e).

Conclusions: ACA demonstrated actionable accuracy in classifying AV aneurysms, even with angled images. Our results align with Zhang (CKJ, 2021), where ACA achieved an AUROC of 0.96 (n=402). Importantly, in the 2021 study physicians evaluated only images, whereas in the current study detailed physical exams were performed. ACA has potential to support aneurysm monitoring, expediting detection and interventions.

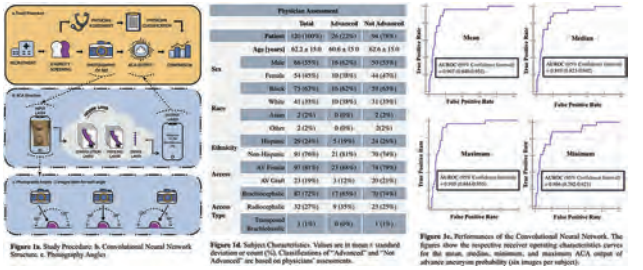


Figure 1a. Study Procedure. b. Convolutional Neural Network Structure. c. Photography Angles

Figure 1d. Subject Characteristics. Values are in mean ± standard deviation or count (%). Classifications of "Advanced" and "Not Advanced" are based on physicians' assessments.

Figure 1e. Performances of the Convolutional Neural Network. The figures show the respective receiver operating characteristics curves for the mean, median, minimum, and maximum ACA output of advance aneurysm probability (six images per subject).

TH-PO024

Automated Segmentation for Measuring Kidney Volume and Length in CT Images: A Cross-National Evaluation Study

Zhongyi Zhang,[1] Yiyi Hui,[2] Gang Liu,[1] Lina Sun,[3] Xiangchun Liu.[1] *[1]The Second Hospital of Shandong University, Jinan, China; [2]Shandong Provincial Qianfoshan Hospital, Jinan, China; [3]Linyi People's Hospital, Linyi, China.*

Background: Kidney structure is an essential biomarker for evaluating kidney diseases. The main kidney structure biomarkers include the total kidney volume (TKV), parenchymal kidney volume (PKV), and kidney lengths. Although the most common form of diagnostic kidney imaging is ultrasound in a 2D manner, in more complex clinical settings or emergencies, patients usually only have CT scans for other diseases, such as acute abdominal pain, or abdominal surgery; so renal physicians need to estimate the kidney structure directly from CT imaging for patients who have kidney injury to differential diagnosis between CKD and acute kidney diseases. Measuring these biomarkers is labor-intensive for radiologists to require manual declinations of

kidney boundaries slice by slice. However, an automated method of kidney structure measurements in both non-contrast and contrast CT images is still not established.

Methods: Our retrospective study included a total of 1,153 CT images with and without contrast materials from nine countries. Reference standards of kidney volumes and lengths were manually measured and validated by one experienced radiologist. We developed a deep-learning (DL) method for measuring the TKV, PKV, and kidney lengths in CT images. The DL model was trained and tuned on the development data (n=526), and then the model was tested on a held-out internal test set (n=166) and external test sets (n=461). Kidney volumes and lengths were then automatically measured using 3D kidney segmentations.

Results: DL-based total kidney segmentation achieved an internal Dice similarity coefficient (DSC) of 0.986 ± 0.013 and an external DSC of 0.967 ± 0.016. In addition, parenchymal segmentation achieved an internal DSC of 0.977 ± 0.019 and an external DSC of 0.948 ± 0.020. DL-based measurements of TKV, RPV, and kidney lengths demonstrated statistical equivalence with the reference standards across all test images ($p > 0.05$).

Conclusions: We developed a fully automated segmentation method to measure TKV, PKV, and kidney lengths in CT images. The fully automated approach achieved a radiologist-equivalent accuracy on both contrast-enhanced and unenhanced CT modalities. With public access to algorithms and segmentations, our method could identify more potential kidney disease patients and reduce the clinical workload of renal physicians and imaging experts.

TH-PO025

Magnetic Resonance Imaging Radiomics Analysis of Noncystic Kidney Parenchyma to Differentiate among Mayo Imaging Classification Classes

Linnea E. Kremer,[1] Arlene B. Chapman,[2] Sam Armato.[1] *[1]The University of Chicago, Chicago, IL; [2]The University of Chicago Medicine, Chicago, IL.*

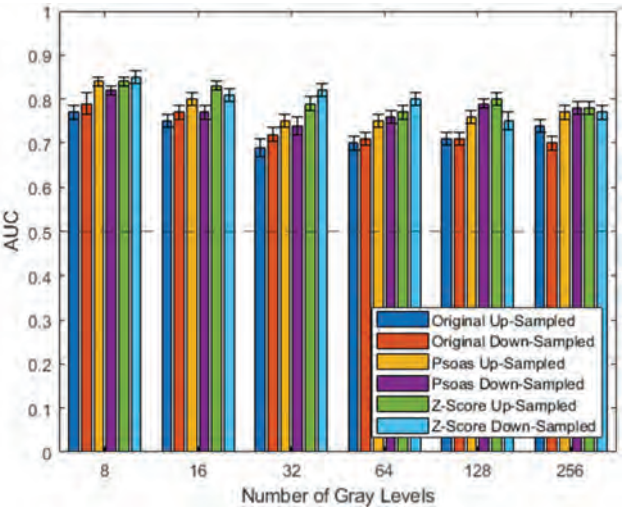
Background: Mayo Imaging Classification (MIC) serves as a prognostic biomarker for the prediction of kidney function decline of patients with autosomal dominant polycystic kidney disease (ADPKD). Radiomics analysis—the extraction of quantitative image features—may provide additional power in identifying patients that are fast progressors to kidney function decline. Specifically, characterizing the non-cystic kidney tissue using radiomic features extracted from magnetic resonance images (MRI) may differentiate among MIC classes. This work (1) determined whether radiomic features can differentiate between low/intermediate- and high-risk MIC classes in the non-cystic components of the kidney and (2) investigated the effect of image pre-processing on subsequent classification.

Methods: Radiomic features were extracted from T2-weighted fat saturation MRI scans of 138 MIC 1A/1B patients and 324 MIC 1C/1D/1E patients for classification. A pre-processing pipeline was developed for (1) normalization of MRI signal intensity (z-score or psoas muscle as a reference tissue), (2) pixel resampling (upsampling or downsampling) schemes, and (3) gray-level discretization (fixed bin size method with 8-256 gray levels for discretization). Area under the receiver operating characteristic curve (AUC) was used as a performance-assessment metric.

Results: The range of AUC values across pre-processing parameters was 0.69-0.85. Radiomic features for classification include gray-level co-occurrence matrix inverse difference and first-order kurtosis.

Conclusions: The results indicate the potential of radiomics to distinguish between patients based on low/intermediate- and high-risk MIC classification.

Funding: NIDDK Support, Other NIH Support - U2CDK129917 and TL1DK132769



Area under the receiver operating characteristic curve (AUC) values in classifying Mayo Imaging Classification using radiomic features extracted from the non-cystic kidney parenchyma using fixed bin size discretization. The dotted line at an AUC of 0.5 is random guessing.

TH-PO026

Development of a Multimodal "Kidney Age" Prediction Based on Automatic Segmentation of Magnetic Resonance Imaging in Individuals with Normal Kidney Function: A Preliminary Report

Zuoxian Hou, Yixin Ma, Lubin Xu, Gu-Mu-Yang Zhang, Peng Xia, Limeng Chen. *Peking Union Medical College Hospital, Beijing, China.*

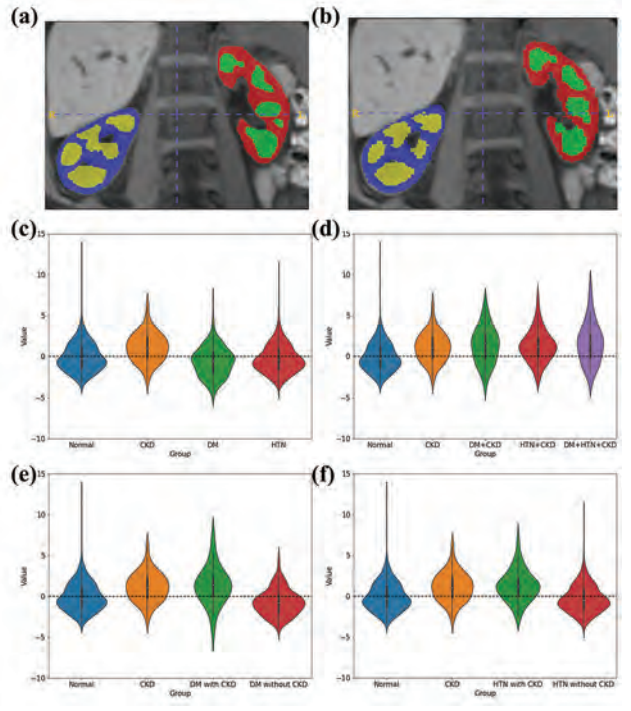
Background: Traditional kidney health assessments rely on clinical indicators and demographics. We introduced KAGE-NET, an artificial intelligence model, to predict kidney age (K-AGE) by combining auto-segmentation and radiomics features from renal MR images to understand kidney health better.

Methods: MR images (T1-weighted and T1-mapping) from UK Biobank, comprising 5693 participants, were utilized in four groups (healthy control (Normal), hypertension (HTN), diabetes (DM) and chronic kidney disease (CKD)). All data underwent auto-segmentation and image-derived phenotype extraction. Control group data was divided into an 8:2 ratio for KAGE-NET training and testing. In the disease groups, the kidney age gap (KAG) metric (K-AGE minus biological age) described the acceleration of kidney aging. KAG greater than 0 indicates accelerated kidney aging; vice versa for KAG less than 0.

Results: A total of 3007 female and 2682 male subjects were included, with a mean age of 53.7±7.8 years old and sCr of 72.28±13.92 μmol/L. Ground truth (Fig.1a) and auto-segmentation (Fig.1b) show high correlation. KAG is around 0 in control group but significantly different with disease groups (CKD: 1.16; DM: -0.58; HTN: -0.25; $p<0.01$; Fig.1c). As health conditions worsen, KAG widens significantly, especially in more complex situations (Fig.1d). Essentially, when DM co-exists without/with CKD, a heightened KAG comparison is noticeably evident (-0.75 vs. 1.52, Fig.1e). A similar outcome is detectable in the KAG comparison between HTN without/with CKD (-0.35 vs. 1.41, Fig.1f).

Conclusions: We introduced KAGE-NET based on MRI multimodal data, presenting a promising comprehensive kidney health assessment tool.

Funding: Government Support - Non-U.S.



(a-b) An auto-segmentation example. (c-f) KAG between groups.

TH-PO027

A Deep-Learning Approach to Grading Kidney Interstitial Fibrosis: Evaluation of a VGG-16 Model on Trichrome-Stained Biopsy Images

Odianosen J. Eigbire-Molen,[1] Swathi Muni Reddy,[2] Shree G. Sharma.[1]
[1]Arkana Laboratories, Little Rock, AR; [2]University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Renal interstitial fibrosis is an important morphologic predictor of outcome in kidney disease. Grading of interstitial fibrosis is routinely performed by renal pathologists during renal biopsy evaluation. The most common technique for grading interstitial fibrosis is visual estimation on stained sections, typically a trichrome stain. However, this technique is prone to interobserver variability. Deep learning models have shown good performance in image classification tasks with robust reproducibility. We present a deep learning classification model trained to grade renal interstitial fibrosis using static low magnification images of trichrome stained sections.

Methods: 505 low magnification overview images of trichrome stained renal biopsy sections were obtained from the archive of cases signed out in 2023 at Arkana Laboratories. A VGG-16 deep learning model was trained to classify the images into four categories - no fibrosis (0-5%), mild fibrosis (6-25%), moderate fibrosis (26-50%), and severe fibrosis (51-100%). The gold standard was the signout pathologist grading. The dataset was split into a train (80%), validation (10%) and test set (10%). The model consisted of a base VGG-16 model with a dense layer and softmax classifier for categorical classification (Figure 1).

Results: The deep learning model attained an overall accuracy of 95% on the training dataset and 92% on the validation dataset. In comparison to the pathologist gold standard, the deep learning model had an overall accuracy of 82% and differentiated between varying degrees of fibrosis (Figure 2).

Conclusions: This study demonstrates the application of a deep learning model to reproduce grading of renal interstitial fibrosis. The model was able to differentiate various grades of interstitial fibrosis, demonstrating a potential prognostic value.

Figure 1: Model

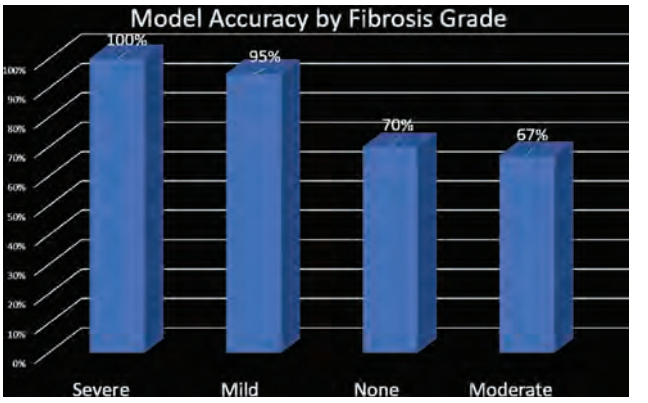


Figure 2: Model Accuracy by Fibrosis

TH-PO028

Automated, Scalable, and Comprehensive Three-Dimensional Analysis of Glomeruli and Whole Nephrons in Kidney Tissues

Chetan Poudel,[1] David Brenes,[1] Ruben M. Sandoval,[2] Michelle M. Martinez-Irizarry,[2] Ken Dunn,[2] Pierre C. Dagher,[2] Jonathan T. Liu,[1] Joshua C. Vaughan.[1] *[1]University of Washington, Seattle, WA; [2]Indiana University School of Medicine, Indianapolis, IN.*

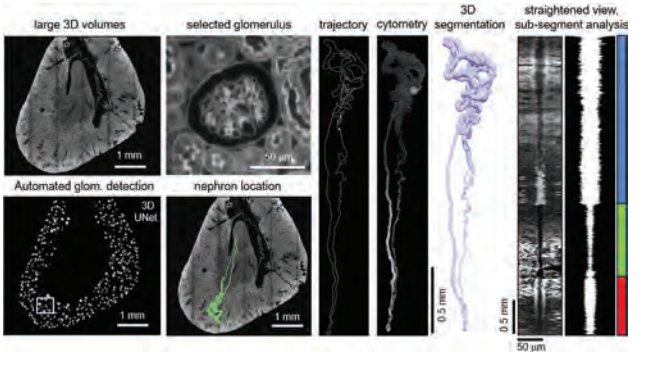
Background: Studying intact functional units or nephrons in 3D has so far been challenging as it requires organ-scale imaging at cellular resolution. The entire field has relied mostly on 2D assays with sparse sampling and thin tissue sections. 2D imaging, however, obscures the relationships between different parts of the same nephron, between nearby nephrons, and between nephrons and other units (e.g. vasculature, lymphatics). There is a great need for advanced imaging and analytical tools to study whole functional units in 3D.

Methods: We developed an end-to-end pipeline to stain, optically clear, image, and analyze thick kidney tissues (both mouse and human) in 3D. We used fluorescent FLARE stains and an open-top lightsheet microscope. For analysis, we trained machine learning models to segment all glomeruli in the tissue. We developed new algorithms with deep learning to dynamically travel through nephrons and accurately extract their entire paths. We can also untwist nephrons to visualize sub-segments and compare between nephrons. This enables 3D morphology analysis (location, trajectory, curvature, lengths, diameters) and in situ cytometry.

Results: We demonstrate orders of magnitude (>100X) faster analysis over manual 3D segmentation methods. The speed and scalability allow us to study a hundred nephrons in a single tissue, and extract 3D models and highly quantitative information. We applied this method to study glomeruli and nephrons in young, mid-aged, and aged mouse kidneys and correlate morphology to functional attributes. We note several interesting changes to glomeruli, glom-tubule connections, and tubule morphology in aged mice.

Conclusions: We established an automated pipeline using artificial intelligence to comprehensively assess 3D morphology of mouse and human kidney tissues. This analysis could assist organ atlas efforts by providing 3D data complementary to existing 2D assays. It could pave the way for 3D renal pathology of human biopsies.

Funding: NIDDK Support, Private Foundation Support



TH-PO029

Developing a Novel Deep Learning-Based Method for Kidney Transmission Electron Microscopy Image Analysis

Anqi Zou,[1] Jiayi Ji,[1] Xueping Fan,[1,2] Winston Tan,[1] Laura Dodd,[1] Emily Oei,[1] Hui Chen,[1,2] Yu-Chen Liu,[1] Simon L. Lu,[1] Joel M. Henderson,[1,2] Chao Zhang,[1] Weining Lu.[1,2] *[1]Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [2]Boston Medical Center, Boston, MA.*

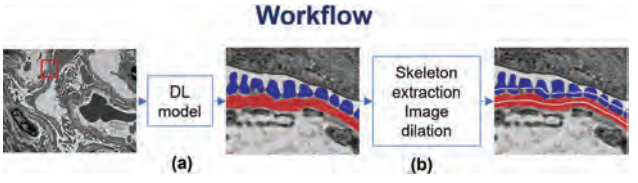
Background: Abnormal glomerular basement membrane (GBM) and podocyte foot process (PFP) widths are critical diagnostic criteria for proteinuric kidney disease. The standard method for quantifying GBM and PFP widths is unbiased stereology, which is labor-intensive and not routinely used in research or clinical diagnosis. To address this gap, we developed a novel deep learning (DL) based algorithm to quantify GBM and PFP widths from glomerular transmission electron microscopy (TEM) images.

Methods: Our algorithm has a two-stage workflow (see Figure): (a) We first used DL for image segmentation, employing a PSPNet-based model with self-training techniques to iteratively collect annotated data, reducing the manual labeling time and improving accuracy. (b) We then used image processing techniques to measure GBM and PFP widths, developing a graph-based method to refine GBM skeleton extraction and compute GBM and PFP widths. We used glomerular TEM datasets from two animal models of proteinuric kidney disease to train and validate our algorithm: the ILK podocyte-specific knockout (ILK cKO) mice and the Passive Heymann's Nephritis (PHN) rats.

Results: The segmentation performance on the validation dataset showed a mean IoU of 0.77, Dice of 0.87, and accuracy of 0.88. In a PHN rat validation dataset, the relative mean error compared to manual measurements is 0.7% for GBM width and 3% for PFP width, indicating overall interchangeability between these two methods. Comparisons of DL-based measurements between wild-type (WT) and ILK cKO groups showed significant differences in GBM width ($p = 1.5e-07$) and PFP width ($p = 3.1e-06$), suggesting that the method effectively distinguished healthy from pathological specimens.

Conclusions: We have established and validated a new DL-based algorithm for automatic GBM and PFP width measurements on rodent glomerular TEM images. This tool is compatible with human kidney biopsy TEM images, which can be translated into clinical applications.

Funding: NIDDK Support, Other U.S. Government Support



Two-stage workflow to quantify kidney GBM and PFP widths: (a) DL for image segmentation. (b) Image processing techniques to measure GBM and PFP widths.

TH-PO030

Artificial Intelligence (AI) Reveals Dynamic Morphological Shifts in Parietal Epithelial Cells after Acute Tubular Injury

Mengmeng Yin,[1] Oliver S. Zhao,[1] Yu Wang,[1] Shilin Zhao,[1] Ruining Deng,[2] Yuankai Huo,[1] Jianyong Zhong,[1] Haichun Yang,[1] Agnes B. Fogo.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University, Nashville, TN.*

Background: We previously found that pre-existing acute tubular injury (ATI) sensitizes glomeruli to subsequent injury. Through spatial transcriptomics, we identified key ligand-receptor pairs that could contribute to this sensitivity, with ligands from the proximal tubules (PTs) and their corresponding receptors on adjacent parietal epithelial cells (PECs). In this study, we utilized artificial intelligence (AI) to evaluate the morphological changes in PECs and their spatial transcriptomics profiles following ATI.

Methods: Wild type (WT) and transgenic mice (n=7/group) expressing diphtheria toxin (DT) receptor in PTs were injected with DT at week 0 and week 1 to induce ATI and sacrificed at week 7. Periodic acid-Schiff stained kidney sections from normal mice were utilized to train an AI model. Spatial transcriptomics were conducted using the NanoString GeoMx DSP platform.

Results: We utilized fluorescent staining of claudin-1 as a PEC biomarker to train an AI model for classification and segmentation of PECs. This allowed for the quantification of 246 morphological profiles for each PEC nucleus. In mice with ATI, PECs nuclei from DT transgenic mice showed increased eccentricity and a greater proportion of staining intensity at the nucleus periphery, as well as reduced form factor of roundness and texture entropy compared to WT mice, suggesting a flatter nuclear morphology with reduced complexity in DT PECs nuclei. Furthermore, 153 differentially expressed genes were detected in PEC nuclei of DT vs WT mice, with enrichments in several pathways, including actin cytoskeleton regulation and PI3K-Akt-mTOR signaling. RPS6 gene expression, a gene involved in cell size regulation, was significantly increased in PECs nuclei of DT compared to WT. In contrast, PECs immunostaining of p-RSK1, a key enzyme involved in RPS6 phosphorylation, was decreased in DT compared to WT mice, suggesting decreased activity.

Conclusions: AI reveals dynamic morphological shifts in PECs following ATI, with flatter, less round nuclei and more chromatin staining at the nuclear periphery. These altered nuclear properties could represent activation states, potentially mediated by decreased activation of the RSK1-RPS pathway. These findings have significant implications for PEC-podocyte interactions and glomerular injury responses after ATI.

Funding: NIDDK Support

TH-PO031

StarFunc: Accurate Protein Function Prediction Reveals Novel Human Proteins Involved in Ubiquitination

Chengxin Zhang, Lydia Freddolino. *University of Michigan, Ann Arbor, MI.*

Background: Even in the very well-studied human proteome, many proteins remain poorly annotated, yet may still make important contributions to health and disease. Deep learning has significantly advanced the development of novel methods for protein function prediction. Yet, even for state-of-the-art deep learning approaches, template information remains an indispensable component. While many prediction methods use templates identified through sequence homology or protein-protein interactions, very few methods detect templates through structural similarity, even though protein structures are the basis of their functions.

Methods: In this work, we developed StarFunc, a composite approach that integrates state-of-the-art deep learning models seamlessly with template information from structural similarity, sequence homology, protein-protein interaction partners, and protein domain families (**Fig. 1**).

Results: We compared the accuracy of StarFunc against 6 existing deep learning methods and 3 template-based methods on 2475 proteins. The weighted F-measure of StarFunc is 12% higher than the second-best approach. StarFunc participated in the Critical Assessment of Function Annotation 5 (CAFA5) challenge and was ranked 5th among 1625 teams from 96 countries. We applied StarFunc on all 20389 proteins from the human reference proteome curated by the neXtProt and identified significant enrichments of several important functions among the set of currently cryptic human proteins. For example, we discovered 15 uncharacterized proteins that are likely components of protein-ubiquitin transferase complexes and 1 putative deubiquitinase.

Conclusions: Large-scale benchmark demonstrates StarFunc's advantage when compared to both deep learning methods and conventional template-based predictors. Application of StarFunc on human proteome reveals novel functions of previously uncharacterized proteins, especially those involved in (de) ubiquitination, providing an entry point for studying fundamental new biology involving those proteins.

Funding: Other NIH Support - This work was supported by the National Institute of Allergy and Infectious Diseases [AI134678 to P.L.F.]., Private Foundation Support

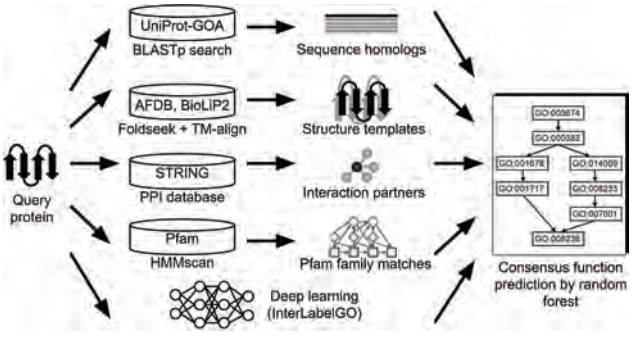


Fig. 1. Flowchart of StarFunc.

TH-PO032

Deep Learning Tubulometrics to Stratify Tubular Injury in Whole-Slide Kidney Specimens

Martin Klaus, Philipp M. Gaßmann, Rosch Abdullah, Louisa Ehreiser, Hao Long, Julia Lichtnekert, Stefanie Steiger, Maciej Lech, Hans J. Anders. *Division of Nephrology, Department of Medicine IV, University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany.*

Background: Acute kidney injury is highly prevalent and most often involves tubular injury. However, studies on detailed assessment of tubular epithelial cell morphometry within tubuli are missing. To this end, we provide a deep learning-enhanced method to segment and analyze tubular epithelial cells and tubuli ("tubulometrics") in whole slide kidney specimens of wild-type mice and mice models of acute and chronic tubular injury.

Methods: Kidneys were embedded in paraffin and stained with PAS and immunohistochemistry before digital scanning. More than 1200 tubuli and 6800 tubular epithelial cells of control mice, mice suffering ischemia-reperfusion injury or chronic

tubular injury were manually annotated. Subsequently, a deep learning algorithm was trained to segment tubuli and tubular epithelial cells and morphometric readouts were obtained. Furthermore, tubulometrics were compared to traditional tubular injury scores.

Results: Tubular area, tubular cell number and density per tubulus section were identified as morphometric readouts. These tubulometrics were able to complement a traditional tubular injury score (PAS score) and interstitial fibrosis tubular atrophy score (IFTA). In wild-type mice PAS score was 0, IFTA 0, mean tubular area 2339 [μm^2], mean tubular cell count per tubulus 7.27, and mean tubular cell density 3.09 [$10^{-3}/\mu m^2$]. In mice with ischemia-reperfusion injury PAS score was 3.44, IFTA 10%, mean tubular area 1818 [μm^2], mean tubular cell count per tubulus 2.02, mean tubular cell density 1.11 [$10^{-3}/\mu m^2$]. In mice with crystal-induced chronic tubular injury PAS score was 3.06, IFTA 40%, mean tubular area 2746 [μm^2], mean tubular cell count per tubulus 7.71, and mean tubular cell density 2.81 [$10^{-3}/\mu m^2$]. The deep learning segmentation algorithm ensured time-efficiency and scalability by taking 5 minutes per slide.

Conclusions: We propose the analysis of tubular epithelial cell morphometry in kidney specimens to better identify and stratify tubular injury. Whereas tubular epithelial cell loss was found in acute injury, tubular hypertrophy together with cell regeneration were observed in the chronic model. Integrated with existing histopathological scores a more detailed assessment of kidney biopsies might become possible. Further studies are needed to validate the findings in larger cohorts.

Funding: Government Support - Non-U.S.

TH-PO033

Artificial Intelligence Discovers a Novel Antifibrotic Drug for Preventing Chronic Kidney Failure by Targeting Macrophage-Myofibroblast Transition

Patrick Ming-Kuen Tang,[1] Yat Fai Chung,[1] Chiu Tsun Philip Tang,[1] Max Kam Kwan Chan,[1] Francis C. Wong,[4] Chi Fai Ng,[1] David J. Nikolic-Paterson,[3] Hui Y. Lan,[1] Sydney Tang.[2] *[1]The Chinese University of Hong Kong, Hong Kong, Hong Kong; [2]The University of Hong Kong, Hong Kong, Hong Kong; [3]Monash University, Melbourne, VIC, Australia; [4]Prince of Wales Hospital, Hong Kong, Hong Kong.*

Background: Kidney failure (end-stage renal disease) is one of the leading causes of death not only in patients with kidney disease but also other non-communicable diseases e.g. diabetes, cardiovascular disease, cancer. Nevertheless, effective treatments to halt the progression of kidney failure remain an unmet clinical need worldwide.

Methods: We recently discovered a novel phenomenon "Macrophage-Myofibroblast Transition" (MMT) as a key pro-fibrotic mechanism and ideal therapeutic target to prevent chronic renal failure. By single-cell RNA sequencing and unbiased bioinformatics analysis, we have identified a neural transcription factor as a key regulator of MMT [Tang et al., PNAS 2020]. Here, by using artificial intelligence (AI) drug discovery platform, we successfully identified a novel anti-fibrotic drug "ISO" for targeting the MMT-driven renal failure.

Results: We found that ISO specifically blocks DNA binding of the neural transcription factor at the molecular level, therefore preventing MMT formation on TGF-β1-stimulated macrophages *in vitro*. More importantly, by conducting macrophage-specific fate mapping with our unique LyzM-tdTomato transgenic mice, we demonstrated that ISO markedly prevents MMT-driven renal fibrosis induced by unilateral ureteral obstruction (UUO) and renal ischemia/reperfusion injury (IRI) without side effects *in vivo*.

Conclusions: Thus, our AI-guided novel anti-fibrotic drug ISO may represent a safe and effective MMT-targeted therapy for preventing chronic renal failure in clinics.

Acknowledgements Health and Medical Research Fund (10210726, 11220576), Passion for Perfection Scheme (PFP202210-004) and CUHK Faculty Innovation Award (4620528).

Funding: Government Support - Non-U.S.

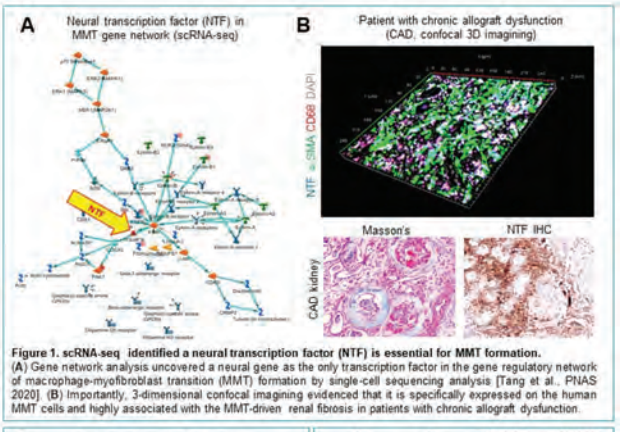


Figure 1. scRNA-seq identified a neural transcription factor (NTF) is essential for MMT formation. (A) Gene network analysis uncovered a neural gene as the only transcription factor in the gene regulatory network of macrophage-myofibroblast transition (MMT) formation by single-cell sequencing analysis [Tang et al., PNAS 2020]. (B) Importantly, 3-dimensional confocal imagining evidenced that it is specifically expressed on the human MMT cells and highly associated with the MMT-driven renal fibrosis in patients with chronic allograft dysfunction.

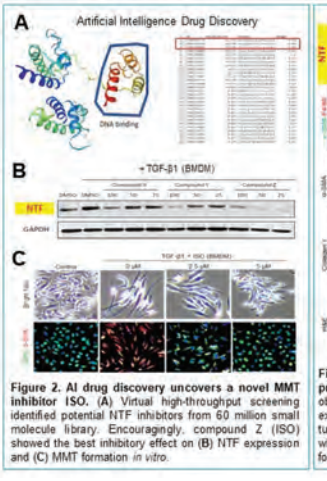


Figure 2. AI drug discovery uncovers a novel MMT inhibitor ISO. (A) Virtual high-throughput screening identified potential NTF inhibitors from 60 million small molecule library. Encouragingly, compound Z (ISO) showed the best inhibitory effect on (B) NTF expression and (C) MMT formation *in vitro*.

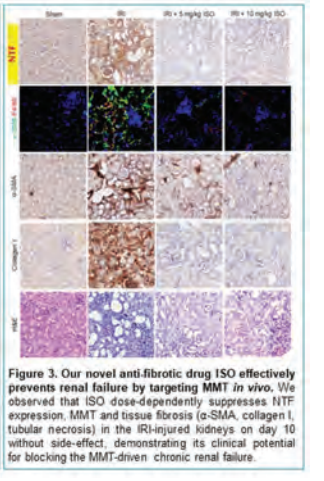


Figure 3. Our novel anti-fibrotic drug ISO effectively prevents renal failure by targeting MMT *in vivo*. We observed that ISO dose-dependently suppresses NTF expression, MMT and tissue fibrosis (α-SMA, collagen I, tubular necrosis) in the IRI-injured kidneys on day 10 without side-effect, demonstrating its clinical potential for blocking the MMT-driven chronic renal failure.

TH-PO034

Inflammation Education-Empowered Extracellular Vesicles Targeting Inflammation-Oxidative Stress Interplay for AKI Therapy

Chuyue Zhang. Dept of Nephrology and Institute of Kidney Diseases, West China Hospital, Sichuan University. *Sichuan University, Chengdu, China.*

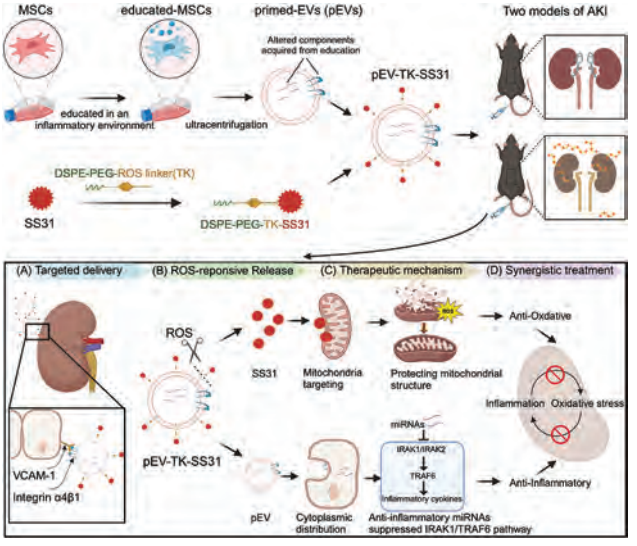
Background: Acute kidney injury (AKI) lacks effective pharmacological interventions, and the mutually exacerbating inflammation and oxidative stress are major pathophysiological mechanisms.

Methods: Inspired by mesenchymal stem cells' (MSCs) capability to respond to inflammatory environment, we educated them to generate primed extracellular vesicles (pEVs) endowed with anti-inflammatory properties. Further we engineered these pEVs by conjugating them with a mitochondria-targeted antioxidant SS31 using a reactive oxidative species (ROS)-responsive linker, resulting in the creation of pEV-TK-SS31.

Results: This pEV-TK-SS31 achieved kidney-targeting through the upregulation of integrin α4β1 acquired from the education process, which facilitated binding to inflammatory ligand VCAM-1 at injured sites. By analyzing renal function, pathological damage, oxidative stress and inflammation, pEV-TK-SS31 demonstrated superior therapeutic efficacy in both ischemia/reperfusion and sepsis-induced AKI models. Mechanistically, pEVs, carrying increased anti-inflammatory miRNAs due to education process, mitigated inflammation via suppressing IRAK1/TRAF6 signaling, and alleviated oxidative stress by site-specifically releasing SS31 upon ROS-induced cleavage.

Conclusions: This smart system, which could be employed for other combination therapies of customized anti-inflammatory cargo and therapeutic agents, holds promise for AKI treatment and inflammation/oxidative stress-related disorders.

Funding: Government Support - Non-U.S.



TH-PO035

Cilastatin in the Prevention and Treatment of Lipopolysaccharide-Induced AKI

Maria Angeles Gonzalez-Nicolas Gonzalez,[1,2] Alberto Lazaro Fernandez.[1,2] Renal Physiopathology Laboratory. *[1]Universidad Complutense de Madrid Facultad de Medicina, Madrid, Spain; [2]Hospital General Universitario Gregorio Maranon, Madrid, Spain.*

Background: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and a significant cause of death in critically ill patients. In hospital mortality rate for patients with sepsis is about 15%–25%. Acute kidney injury (AKI) is the most complication of sepsis and is recognized as an independent factor for elevated lethality. More than 50% of patients with sepsis develop AKI, and sepsis associated AKI increases the risk of developing chronic comorbidities. Cilastatin, a renal dehydropeptidase-I inhibitor, has demonstrated its usefulness in the protection of AKI induced by nephrotoxic drugs. Here, we evaluate the utility of cilastatin as a protector against renal damage induced by lipopolysaccharide (LPS).

Methods: Sepsis was induced in Male Wistar rats by administering LPS 10 mg/kg bw i.p. (or its vehicle). Cilastatin 150 mg/kg bw i.p. (or its vehicle), was administered concomitantly and the animals were sacrificed at 24h. Kidney function was assessed by measuring serum creatinine, blood urea nitrogen (BUN), glomerular filtration rate (GFR), proteinuria, renal tissue morphology, kidney injury molecule 1 (KIM-1), as well as apoptotic, oxidative and inflammatory parameters.

Results: LPS-administrated rats showed significant elevations in BUN, creatinine and proteinuria, and decreased the GFR when compared with control rats. These renal effects of sepsis were confirmed by the increased in the KIM-1 and exhibited severe morphological changes such as vacuolization, swelling of tubular cells, brush border loss and hyaline cast in the tubular lumen. Also, apoptotic, inflammatory and oxidative biomarkers were increased. Cilastatin, prevented these changes in renal function in LPS treated animals, decreasing significantly all other parameters (as shown by reductions of BUN, creatinine and proteinuria and increased GFR), restoring KIM-1 levels to normal control and reducing many of the histological symptoms of renal damage.

Conclusions: Our findings support the potential use of cilastatin as a useful drug in the prevention and treatment of AKI-induced by LPS. Therefore, cilastatin could be a very beneficial therapeutic strategy for septic patients susceptible to renal damage in clinical practice.

Funding: Government Support - Non-U.S.

TH-PO036

Urine-Derived Stem Cells Display Homing, Incorporation, and Repair in Human Organoid and Mouse Models of AKI

Julie Bejoy,[1] Richard C. Welch,[1] Eddie Qian,[1] Felisha M. Williams,[1] Matthew H. Wilson,[1,2] Neal Paragas,[3] Lauren E. Woodard.[1,2] Woodard Lab. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Department of Veterans Affairs, Nashville, TN; [3]University of Washington, Seattle, WA.*

Background: Kidney lacks the regenerative capacity to replace nephrons lost during injury and disease resulting in end-stage kidney disease (ESKD). Due to their therapeutic properties, stem cells have become a promising candidate for the creation of new disease treatments including kidney injury. Urine-derived stem cells (USCs) are multipotent stem cells that originate in the kidney with high expandability, self-renewal capacity.

Methods: USCs are isolated from human urine samples and plated on gelatin coated plates for culturing *in vitro*. We employed mouse models of glycerol-induced rhabdomyolysis (Rhabdo) or unilateral nephrectomy with clamping ischemia reperfusion injury (UNI/R) to induce AKI. The homing and incorporation of luciferase transfected USCs in the mice was measured using the InVivoPLOT™ (InVivo Analytics) and were reconstructed with InVivoAx™ software at various timepoints (3h, 24h and 48h). To evaluate the therapeutic effects of USCs on injured human kidney cell types, we cultured kidney organoids from human induced pluripotent stem cells (hiPSCs). We established a nephrotoxic injury model of AKI by adding cisplatin (5 μM) to kidney organoid and followed up with a treatment of 5 x 10^4 USCs for 48h.

Results: InVivoAnalytics software confirmed the presence of luc-USCs in both Rhabdo and UNI/R models within 3h of injection and localizations persisted upto 48h. Immunostaining confirmed USC localization in renal tubules and glomeruli of injured mice. Improved morphology as well as reduced kidney injury molecule-1 (KIM-1) ($p<0.05$) were observed in treated group compared to untreated group. When treated with USCs, cisplatin-injured organoids showed reduced expression of KIM-1 as well as cytotoxicity ($p < 0.001$). USCs incorporated within injured organoids differentiated into tubule (LTL+) and glomeruli (NEPHRIN+) cells.

Conclusions: The current study explored the USC's ability to home to sites of injury in multiple models of AKI including rhabdomyolysis, IR injury, and drug-induced nephrotoxicity. USCs demonstrated a differentiation potential for renal cell types within injured kidney organoids. Taken together, these results indicate that USCs can home to a site of injury and may reduce the damage done to tubule cells during AKI suggesting requirement of further development.

Funding: Veterans Affairs Support

TH-PO037

TRIM27 Alleviates AKI by Reducing GLIS1 DNA Methylation and Promoting GLIS1 Expression through Inhibiting PRC2 Activity

Chongxiang Xiong. *The First Dongguan Affiliated Hospital of Guangdong Medical University, Dongguan, China.*

Background: Proliferation of dedifferentiated renal tubular epithelial cells (RTECs) is a major cellular event that contributes to renal repair after renal ischemia and reperfusion injury (RIRI)-induced acute kidney injury (AKI). Nevertheless, the underlying mechanism that initiates RTEC dedifferentiation remains unknown. Herein, the role of tri-domain proteins 27 (TRIM27) in the progression of RIRI-induced AKI was investigated.

Methods: The animal model of RIRI-induced AKI was established by IRI, and mRTECs were treated with H2O2 to establish a cell injury model in vitro. The pathological changes in kidney tissues were assessed using HE and PAS staining. Cell viability and migration were assessed by CCK-8 assay and wound healing assay, respectively. Flow cytometry was employed to determine cell apoptosis. Co-IP assay was employed to analyze the interaction between TRIM27 and EZH2. The interaction between DNMT1 and GLIS1 was analyzed by ChIP assay.

Results: TRIM27 expression was reduced in kidney tissues of IRI mice and H2O2-treated mRECs. TRIM27 overexpression enhanced mRTEC dedifferentiation, proliferation, and migration while inhibiting apoptosis after H2O2 treatment. Mechanistically, TRIM27 reduced PRC2 activity in mRTECs by mediating EZH2 ubiquitination degradation. PRC2 reduced GLIS1 expression in mRTECs through mediating H3K27me3 and DNA methylation. TRIM27 overexpression ameliorated IRI-induced AKI in mice by enhancing mRTEC dedifferentiation.

Conclusions: TRIM27 upregulation alleviated RIRI-induced AKI by reducing GLIS1 DNA methylation and promoting GLIS1 expression through inhibiting PRC2 activity.

TH-PO038

Exercise Training Has Striking Effects on the Kidney Proteome and Protects Kidney from Ischemic Injury: The MoTrPAC Study

Takaaki Higashihara, Tiziana Caputo, Anders H. Baum, Krithika Ramachandran, Michael F. Hirshman, Laurie J. Goodyear. Molecular Transducers of Physical Activity Consortium (MoTrPAC). *Joslin Diabetes Center, Boston, MA.*

Background: Chronic kidney disease (CKD) poses a significant global health threat due to increasing rates of CKD-related morbidity and mortality, emphasizing the need for interventions to mitigate its impact. While regular exercise training is broadly recognized to promote human metabolic health, the mechanisms by which exercise may provide protection from kidney disease are poorly understood.

Methods: To elucidate the effects of exercise training on kidney, we first analyzed the data from MoTrPAC, the NIH-funded Molecular Transducers of Physical Activity Consortium, that investigates the multi-tissue molecular responses to exercise training in rats. Female rats underwent 4-8 weeks of treadmill exercise training, kidney collected and proteomics analysis performed. Next, we used a murine ischemic-reperfusion injury model (IRI) to determine the direct effects of exercise training on kidney. Female C57BL6J mice were housed in cages with or without running wheels for 11 days. Mice were then either sham or unilateral IRI-treated with no further access to running wheels. At 7 and 28 days post-IRI or sham, we conducted qPCR, western blotting, and kidney histological analysis.

Results: Kidney proteomic analysis of MoTrPAC data showed that exercise training increased fatty acid β-oxidation (FAO) related proteins (e.g. Cpt1b, Acox1). Given the importance of FAO in proximal tubule function, these results led us to investigate the hypothesis that chronic exercise can protect kidneys from tubular injury. At 7 days post IRI, prior exercise training significantly reduced IRI-induced tubular damage areas and expression of tubular damage marker genes (KIM1, NGAL). At 28 days post IRI, prior exercise training significantly ameliorated IRI-induced fibrotic area and expression of fibrotic marker protein (αSMA). Among the FAO related proteins that were up-regulated by exercise in the MoTrPAC data, we found that prior-exercise training significantly ameliorated the IRI-induced reduction of peroxisomal FAO related proteins (e.g. Acox1, Ehhadh).

Conclusions: Exercise training decreases IRI-induced kidney tubular damage, an affect associated with upregulation of FAO related proteins. Regular physical activity may provide a means to help prevent the severity of CKD.

Funding: NIDDK Support, Other NIH Support - NIA, U01AG055135, Private Foundation Support

TH-PO039

Kidney-Protective Effect of Remote Ischemic Conditioning: Involvement of the Spleen

Man J. Livingston,[1,2] Zheng Dong.[1,2] *[1]Augusta University Medical College of Georgia, Augusta, GA; [2]Charlie Norwood Department of Veterans Affairs Medical Center, Augusta, GA.*

Background: Remote ischemic conditioning (RIC), performed at a remote site, protects multiple organs including the heart and brain, but its role in the kidney is controversial and much less understood. The signal transmission of RIC protection is also unknown. This study examined the effects of RIC on acute kidney injury (AKI) and post-AKI kidney repair using different experimental models.

Methods: Anesthetized mice were placed on a homeothermic station with the hind limbs wrapped in cuffs. RIC was conducted by 4 cycles of alternating 5-minute inflation at 200 mmHg and 5-minute deflation.

Results: RIC suppressed renal dysfunction and tubular injury during ischemic AKI. RIC also alleviated cisplatin-induced AKI and prevented body weight loss but appeared nonprotective against LPS-induced septic AKI. Daily RIC for 2 weeks after ischemic AKI promoted kidney repair, as indicated by the amelioration of kidney fibrosis and the preservation of renal function and tubular integrity. However, RIC was much less effective in promoting kidney repair after repeated low dose cisplatin treatment, showing minimal effects on renal dysfunction and kidney fibrosis. To understand how RIC signals from the limb to the kidney, we examined the spleen, an organ involved in neuroimmune modulation. Splenectomy diminished the beneficial effects of RIC on ischemic AKI and subsequent kidney repair whereas barely affected the effects of RIC in cisplatin-treated mice.

Conclusions: These results suggest that the renal protective effect of RIC and its regulation may vary depending on the etiology of AKI. Mechanistically, the spleen and associated neuroimmune modulation play a critical role in the renal effect of RIC.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO040

Early Detection of AKI Using Intraoperative Urine pO2, pCO2, and Lactate during Cardiopulmonary Bypass

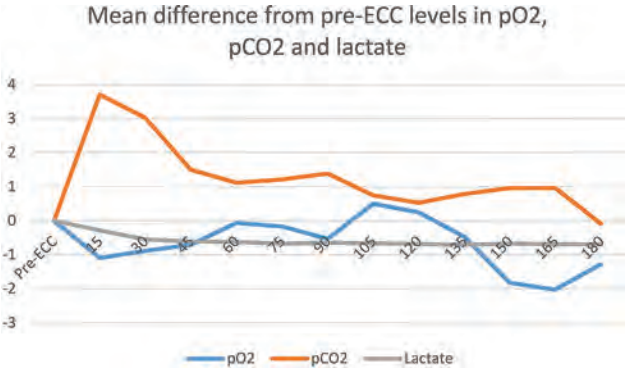
Anders S. Svensson,[1] John-Peder E. Kvitting,[2] Jonas Holm,[1] Zoltan Szabo,[1] Csaba P. Kovesdy.[3] *[1]Linkopings universitet, Linkoping, Sweden; [2]Universitetet i Oslo, Oslo, Norway; [3]The University of Tennessee Health Science Center, Memphis, TN.*

Background: Intraoperative acute kidney injury (AKI) is a common complication after cardiopulmonary bypass (CPB), and it is associated with poor outcomes. Methods to detect AKI in CPB are limited by delayed diagnosis or limited availability. Urinary biomarkers can be measured continuously in the operating room, but their role in detecting AKI is unclear.

Methods: A pilot study in 18 patients undergoing CPB at a single institution. Urine was collected immediatley prior to CPB and every 15 minutes intraoperatively until the end of CPB. Urine biomarkers (pO_2, pCO_2 and lactate) were measured in the operating room using a standard blood gas analyser. Intraoperative AKI was defined as a 0.3 mg/dl increase in serum creatinine within 48 hours post-CPB. We analysed urine biomarkers overall and in patients stratified by AKI status. We used repeated measures ANOVA and Tukey's HSD, and characterized intraindividual changes using mixed effect models adjusted for baseline demographics, EuroScore-II, precence of CKD, CRP level and intraoperative hemodilution.

Results: Five of 18 patients (28%) developed AKI. Overall, intraindividual levels of urine pO_2 (p=0,03), pCO_2 (p=<0,001) and lactate (p=<0,001) levels were significantly different in ANOVA analyses (figure). In patients with vs. without AKI, pO_2 showed more substanial decline (slope in mixed effect models:-0,06 vs. -0,005 mmHg/min); pCO_2 showed less decline (-0,006 vs. -0,11 mmHg/min); and lactate showed more increase (0,007 vs. 0,004 mmol/L/min) during CPB in adjusted mixed effect models.

Conclusions: Urine pO_2, pCO_2 and lactate show significant changes during CPB. These changes are different in patients with vs. without AKI. Intraoperative monitoring of urine biomarkers may offer a rapid and readily available means of diagnosing AKI in clinical practice. Larger studies are needed to confirm these findings.



TH-PO041

Therapeutic Efficacy of FEx-022 in Protecting the Kidneys during Ischemia-Reperfusion Injury

Sung ki Kim,[1] Jayoung Kim,[3] Wesley R. Stiles,[1] Hee Young Lee,[2] Kyung Ho Park,[2] Larry C. Park,[2] Min-Woong Kang,[3] Hak Soo Choi.[1] *[1]Massachusetts General Hospital, Boston, MA; [2]Naason Science Inc, Osong-eup, Republic of Korea; [3]Chungnam National University, Daejeon, Republic of Korea.*

Background: Acute kidney injury (AKI) is a common yet critical clinical problem, significantly increasing the morbidity and mortality of patients, particularly in critical care settings. AKI is characterized by a sudden decline in kidney function, leading to the accumulation of waste products in the blood, an imbalance in body fluids, and potential progression to chronic kidney disease. Despite the prevalence and severity of AKI, there is currently no approved or effective treatment available in the clinic. In a previous study with rhabdomyolysis-induced AKI model, a novel polymer-drug conjugate, FEx-022, demonstrated kidney protection and ameliorated glomerular filtration rate (GFR) by two-fold compared to the negative control. In this study, we further evaluated the effectiveness of FEx-022, using an ischemia-reperfusion injury (IRI) AKI model.

Methods: FEx-022 was prepared in large scale for in vitro and in vivo assays. In the following study, mice were divided into four groups: sham control, IRI with vehicle, IRI with reference drug, and IRI with FEx-022. Plasma and urine samples were collected to analyze plasma creatinine, blood urea nitrogen (BUN), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and GFR. Survival rates, kidney histology, and inflammatory cytokines are also evaluated.

Results: In this study, FEx-022 demonstrated kidney protection, measured in various parameters such as survival rate and GFR. Other analysis will provide deeper insights on the compound's ability to suppress reactive oxygen species (ROS) damage and cell death biomarkers, primarily through the inhibition of ferroptosis.

Conclusions: FEx-022 exhibits therapeutic effects in the IRI-AKI model, which demonstrates that FEx-022 can protect kidneys in AKI. Our findings suggest that FEx-022 could be a potential candidate as a novel therapeutic targeting AKI, offering a promising avenue to address a critical unmet need in nephrology.

Funding: Commercial Support - Ferrex Therapeutics, Inc., Government Support - Non-U.S.

TH-PO042

Characterization of Regulatory B Cells and IL-10 in Response to Ischemic Reperfusion and Potential for Infusion Therapy

Yuya Yamashita, Kensei Taguchi, Yunosuke Yokota, Tomofumi Moriyama, Kei Fukami. *Kurume Daigaku, Kurume, Japan.*

Background: Acute kidney injury (AKI) occurs in approximately 15% of hospitalized patients and it predisposes the patients to chronic kidney disease (CKD). Interleukin-10 (IL-10) is a pleiotropic cytokine, and exogenous IL-10 replacement therapy is renoprotective effect against AKI. However, the required concentration of IL-10 seems not feasible to achieve when applied to human. Subpopulation of B cells presenting with CD1dhiCD5+ (regulatory B cells; Breg) are known to be responsible for producing and secreting IL-10. Thus, in the present study, we investigated the role of Breg and the main sources in AKI. Further, we investigated whether exogenous Breg would adhere in the kidneys of the recipients and prevent the AKI-to-CKD transition.

Methods: IL10^{+}/eGFP mice were employed to trace IL-10-producing Breg in the context of AKI. Ischemia-reperfusion (IR)-AKI was induced in IL10^{+}/eGFP mice and

the number of GFP-labelled Breg were evaluated in several organs, such as kidneys and spleens. Subpopulation of B-1 cells isolated from peritoneal cavity of IL10^{+}/eGFP mice were infused into wild-type mice with IR-AKI to examine whether exogenous regulatory B cells adhere to the injured kidneys. Third, spleens, the main source of Breg, were removed before IR-AKI to explore whether deletion of Breg exacerbates AKI in IL10^{+}/eGFP mice.

Results: The number of GFP+ Breg was increased in the spleens 24 hrs after onset of IR-AKI. The number of GFP+ Breg was increased in the kidneys with the upregulation of IL-10 gene expression on day7 and 14 after IR-AKI. Furthermore, when GFP+ B-1 cells were exogenously infused, we identified GFP+ cells in kidneys of wild-type mice with IR-AKI, the number of which was increased in injured kidneys. Splenectomy in the context of AKI reduced the number of GFP+ cells in kidneys of IR-AKI with the reduction in gene expression of IL-10. Renal dysfunction and tubular damage in IR-AKI were worsened by splenectomy and immune cells infiltration, such as CD68+ microphages and CD3+ T cells, were enhanced.

Conclusions: We identified that IL-10-producing Breg were mainly released from the spleens in response to IR-AKI, which may be involved in repair process after IR-AKI via producing IL-10. In addition, the infusion with autologous Breg might be potent to promote proper repair and prevent AKI-to-CKD.

TH-PO043

Injured Tubules-Derived CCN1 Exacerbates Renal Congestion-Mediated AKI and Fibrosis

Atsushi Minamida, Tetsuro Kusaba, Tomohiro Nakata, Yuhei Kirita, Keiichi Tamagaki. *Kyoto Prefectural University of Medicine, Kyoto, Japan.*

Background: In recent studies on cardio-renal syndrome (CRS), researchers have focused on the relationship between increased renal venous pressure and renal dysfunction. We generated a novel mouse model where the inferior vena cava between the left and right renal vein was constricted, causing renal congestion only in the left kidney (Kidney Int. 2022). However, the responsible molecular mechanisms for congestion-mediated acceleration of kidney fibrosis after injury are still unclear. We found thatCellular Communication Network Factor 1 (CCN1) which is upregulated at the acute phase after kidney injury contributed to the fibroblast mobilization to the injury site. On this basis, we investigated the impact of CCN1 on the exacerbation of AKI caused by renal congestion with using proximal tubule-specific CCN1-KO mice (SLC34a1GCE/CCN1-floxed).

Methods: We performed bilateral ischemia-reperfusion injury (IRI) and unilateral renal congestion in wild-type (WT) mice and proximal tubule-specific CCN1-KO mice. Furthermore, we analyzed the role of CCN1 on the fibroblasts, tubular epithelial cells, and macrophages in vitro.

Results: One day after the injury, qPCR analysis of WT mice revealed a significant increase in CCN1 levels in the congestion-IRI group compared to the IRI group, but no difference in renal injury markers between those. Positive staining of phosphorylated focal adhesion kinase (pFAK), a downstream signaling of CCN1, was observed in the fibroblasts at injury sites in the congestion-IRI kidneys. Seven days after the injury, qPCR and histological analyses showed a significant increase in fibrosis markers in the congestion-IRI group. In vitro, CCN1 activated the phosphorylation of FAK and ERK, resulting in the acceleration of migration in the fibroblasts (NRK49F) and macrophages, but not in tubular epithelia. Lastly, we examined the effect of CCN1 deletion in tubular epithelia on congestion-mediated kidney injury in vivo. pFAK expression in injury sites was reduced in CCN1-KO mice, and tissue fibrosis was significantly ameliorated.

Conclusions: We clarified the important role of injured tubular-derived CCN1 on pFAK-mediated fibroblast migration in congestive kidneys. Inhibition of CCN1 can be an attractive therapeutic candidate for preventing renal congestion-mediated kidney injury to fibrosis transition.

TH-PO044

Urinary Acidification and Pharmacological Inhibition of OCT/OAT Reduce the Severity of Experimental Vancomycin-Induced AKI

Yosu Luque,[1,2] Thibault Le Moulec,[1] David Rozenblat,[2] Liliane Louedec,[1] Juliette Hadchouel,[3] Gaëtan Girault,[3] Marine Marquié,[3] Laurent Mesnard,[1,2] Placier Sandrine.[3] *[1]Sorbonne Universite, Paris, France; [2]Assistance Publique - Hopitaux de Paris, Paris, France; [3]INSERM, Paris, France.*

Background: Vancomycin, a glycopeptide antibiotic, is used clinically but causes nephrotoxicity in 5-43% of cases via direct tubular damage and vancomycin-uromodulin casts. While vancomycin's solubility increases in acidic media, uromodulin's decreases, complicating the prediction of urinary pH modulation effects. Vancomycin is excreted through glomerular filtration and proximal tubular secretion via organic cation (OCT) and anion (OAT) transport systems. This study investigates the effects of urinary pH modulation and OCT/OAT blockade with cimetidine and probenecid on vancomycin-induced renal lesions in a murine model.

Methods: Eight-week-old male C57BL/6J mice received an intraperitoneal injection of vancomycin at a dose of 0.5 mg/g once daily for two consecutive days, followed by euthanasia and tissue collection on the third day. Urinary alkalinization was induced by providing 0.2 M sodium bicarbonate in drinking water, while acidification was achieved by incorporating 2% ammonium chloride (NH4Cl) into their food. Cimetidine (100 mg/kg) and probenecid (150 mg/kg) were administered intraperitoneally 30 minutes before each vancomycin injection.

Results: Urinary acidification reduced vancomycin-induced renal failure, as evidenced by lower creatinine levels (31.88 ± 16.89 vs. 46.39 ± 15.47 μmol/L, p = 0.0212) and plasma urea levels (29.48 ± 15.48 vs. 46.19 ± 13.31 mmol/L, p = 0.0013). Urinary alkalinization had no effect in kidney injury. Probenecid also reduced vancomycin-induced kidney injury, as indicated by serum creatinine (16.20 ± 3.088 vs. 46.39 ± 15.47 μmol/L, p < 0.0001) and plasma urea levels (22.65 ± 12.96 vs. 47.99 ± 16.85 mmol/L, p < 0.001). Additionally, there was a significant decrease in tubular lesions and the number of casts. Cimetidine showed significant improvement in creatinine levels only (28.67 ± 10.40 vs. 46.39 ± 15.47 μmol/L, p = 0.0116).

Conclusions: Urinary acidification, but not alkalinization, prevents vancomycin-induced renal failure and kidney damage. These results suggest that uromodulin is not necessary for vancomycin cast formation. Additionally, administering probenecid before vancomycin injections also prevents renal failure and kidney damage, suggesting potential therapy options for these patients.

Funding: Government Support - Non-U.S.

TH-PO045

Dietary Supplementation with Bacillus Superoxide Dismutase Protects against Contrast-Induced AKI in Mice

Young Eun Choi,[1] Yookyung Jang,[1] Ko Yoon Sook,[1] Lee Hee Young,[1] Tai yeon Koo,[1] Sewon Oh,[1] Myung-Gyu Kim,[1] Sang-Kyung Jo,[1] Jihyun Yang.[2] *[1]Korea University Anam Hospital, Seoul, Republic of Korea; [2]Kangbuk Samsung Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: Superoxide dismutase (SOD) is a metalloenzyme that play an important role in antioxidant defense against oxidative stress. Oxidative stress was known as one of the main pathophysiology in contrast-induce acute kidney injury (CI-AKI). Based on recent data showing the important role of gut dysbiosis, using probiotics could have a potential to modify systemic oxidative stress. We investigated the renoprotective potential of orally administered enteric-coated SOD protein purified from *Bacillus amyloliquefaciens* (SOD-BA) in contrast-induced acute kidney injury (CI-AKI) in mice.

Methods: CI-AKI model was induced with unilateral nephrectomy using 5 week-old C57BL/6 male mice. Giving oral gavage SOD-BA once a day, 48 hours before intravenous contrast injection (10mg/kg) 4 weeks after unilateral nephrectomy. Serum blood urea nitrogen (BUN), creatinine, and kidney tissue NGAL were determined.

Results: SOD-BA did not have kidney toxicity in the vehicle group. The unilateral CI-AKI model showed minimal kidney function deterioration based on creatinine level. However, the serum BUN and NGAL were strikingly increased. SOD-BA oral administration group showed decreased BUN and kidney NGAL level.

Conclusions: Prophylactic treatment of oral SOD-BA could serve as a potent antioxidant in the prevention and treatment of CI-AKI.

Funding: Commercial Support - Department of, Biomlogic/Genofocus

TH-PO046

Identifying a Potential New Weapon against AKI in Cisplatin-Treated Patients

Lara Valiño Rivas,[1] Maria Angeles Gonzalez-Nicolas Gonzalez,[1,2] Estefanía Moreno-Gordaliza,[3] Elena V. Ogando,[1] Milagros Gómez-Gómez,[3] Alberto Lazaro Fernandez.[1,2] *[1]Renal Physiopathology Laboratory, Department of Nephrology, Instituto de Investigación Sanitaria Gregorio Marañón, Hospital General Universitario Gregorio Marañón., Madrid, Spain; [2]Department of Physiology, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain; [3]Department of Analytical Chemistry, Faculty of Chemistry, Universidad Complutense de Madrid., Madrid, Spain.*

Background: Cisplatin is a highly effective chemotherapeutic agent, widely used in clinical practices against a large number of tumors, whose common side effect limiting its dose-duration of treatment is Acute Kidney Injury (AKI). Cisplatin-AKI is associated with a high morbidity and mortality rate and currently, there is no effective treatment for it. ALME23 (under intellectual property rights protection) is an organic anion transporters (OATs) inhibitor used at the clinical level for which some old scientific studies suggested a link with nephroprotection in AKI. In this study, we investigated *in vitro* a potential new drug against cisplatin-induced AKI.

Methods: Human proximal tubular cells (HK2) were treated with cisplatin in the presence or absence of ALME23. Apoptosis was assessed by MTT, direct microscopic observation and flow-cytometry. Apoptotic mediator's levels of the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways were measured by confocal microscopy, Western Blot and JC-1 assay. Cell regeneration was also assessed by crystal violet. Some tumor cisplatin-target lines were also used to evaluate cisplatin tumorigenic activity in presence of ALME23. Intracellular accumulation of cisplatin was

measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Inflammation was also measured at early stages of AKI by RT-qPCR.

Results: Our results suggested that ALME23 seems to protect HK2 cells against cisplatin-induced apoptosis and both the intrinsic and extrinsic pathway, promoting cell regeneration. Furthermore, ALME23 resulted harmless to the cells without affecting their growth and viability, nor does it affect the chemotherapeutic activity of cisplatin in tumor lines, protecting them in an organ-specific manner. Cotreatment of cisplatin with ALME23 also reduced inflammatory damage in early stages of cisplatin-AKI. Regarding the mechanism of action, some of these protective effects may be due to the fact that it partially prevents cisplatin from entering the cell.

Conclusions: This study provides evidence that ALME23 could be a new therapeutic alternative to nephrotoxicity in cisplatin-treated patients without compromising its chemotherapeutic efficacy. However, studies in animal models and later in humans, will be required.

Funding: Government Support - Non-U.S.

TH-PO047

Changes in eGFR after Acute Mechanical Circulatory Support in Patients with Acute Heart Failure

Nusrath Jahan,[1] Hocine Tighiouart,[2,3] Michael S. Kiernan,[2] Hannah L. Sarnak,[2] Ki Jung Lee,[2] Marcelle Tuttle,[2,3] Tatsufumi Oka,[2] Amanda I. Moises,[1] Mark J. Sarnak,[2] Wendy I. McCallum.[2] *[1]Tufts University School of Medicine, Boston, MA; [2]Tufts Medical Center, Boston, MA; [3]Tufts Clinical and Translational Science Institute, Boston, MA.*

Background: It has been suggested that estimated glomerular filtration rate (eGFR) may improve among patients admitted for acute heart failure (AHF) following hemodynamic support with acute mechanical circulatory support (MCS), but descriptions of changes in eGFR are limited.

Methods: Among adult patients admitted to an academic medical center from 2015-21 for a primary diagnosis of AHF requiring a pulmonary artery (PA) catheter, we examined the subgroup requiring acute MCS. Using the CKD-EPI 2021 equation, we examined absolute change in eGFR from one day prior to acute MCS placement to 7-days after placement. Patients on inotropes or MCS prior to admission were excluded.

Results: Of 755 patients, 53 (7%) required the use of acute MCS. Mean (SD) age was 58 (13) years, 11 (21%) were women; median [IQR] baseline eGFR was 50 [30, 69] ml/min/1.73 m^2. Initial acute MCS device was an intra-aortic balloon pump in 44 (83%), Impella in 7 (13%), and extracorporeal membrane oxygenation in 2 (4%) patients. At 1-day post-MCS, 26 patients (49%) had an eGFR increase, 26 patients (49%) had an eGFR decrease, and one patient started renal replacement therapy. By 7-days post-MCS, 7 (13%) patients had died or transitioned to hospice. Of those who survived to 7-days, overall the eGFR increased by 2.8 (IQR -2.1, 14.9) ml/min/1.73 m^2, with 32 patients (70%) had an eGFR increase (median [IQR] increase by 9.0 [2.4, 21.6] mL/min/1.73 m^2) while 14 patients (30%) had an eGFR decrease (median decrease of -10.6 [-27.7, -4.0] mL/min/1.73 m^2). There was no difference in eGFR change by device type (Table). Age, sex, baseline comorbidities including hypertension and diabetes were no different between those with eGFR increase versus decrease.

Conclusions: Among patients admitted for AHF requiring PA catheter to guide management, of the subgroup needing acute MCS support, about two-thirds had a mild improvement in eGFR with MCS support. However, one-third had a decline in eGFR despite cardiac support, without any identifiable differences in baseline characteristics to distinguish those with increase or decrease in eGFR.

Funding: NIDDK Support

Table. Descriptions of eGFR changes among Patients on Acute MCS Stratified by Device Type

	N	Age, years	Acute MCS duration, days	eGFR Change at 3-days*	eGFR Change at 7-days**	Outcomes During Follow-up		
						Received Durable LVAD	Heart Transplant	Death
Overall	53	58 (13)	7 (8)	1.6 [-3.6, 10.0]	2.8 [-2.1, 14.9]	28 (53%)	19 (36%)	21 (40%)
IABP	44	57 (13)	8 (8)	1.6 [-3.5, 7.9]	2.8 [-0.5, 16.2]	24 (55%)	16 (36%)	16 (36%)
Impella	7	66 (13)	4 (5)	-3.2 [-12.6, 15.6]	5.8 [-2.4, 14.7]	3 (43%)	3 (43%)	3 (43%)
ECMO	2	63 (5)	3 (3)	28.9 [23.4, 34.3]	-9.9 [-9.9, -9.9]	1 (50%)	0 (0%)	2 (100%)

Values presented as mean (standard deviation), n (%), or median [IQR]
Abbreviations: MCS = mechanical circulatory support, ECMO = extracorporeal membrane oxygenation, IABP = intra-aortic balloon pump, eGFR = estimated glomerular filtration rate, LVAD = left ventricular assist device
*number of patients with eGFR available at day 3: n=46
**number of patients with eGFR available at day 7: n=46

TH-PO048

Prognostic Significance of Total Body Surface Area in Rhabdomyolysis Assessed by Bone Scan

Sehyun Jung,[1] Seunghye Lee,[1] Hani Jang,[1] Hyun-Jung Kim,[1] Eunjin Bae,[2] Tae won Lee,[2] Dong Jun Park,[2] Se-Ho Chang.[1] *[1]Gyeongsang National University Hospital, Jinju, Republic of Korea; [2]Gyeongsang National University Changwon Hospital, Changwon, Gyeongsangnam-do, Republic of Korea.*

Background: Rhabdomyolysis involves skeletal muscle damage. Its severity ranges from asymptomatic enzyme elevation to life-threatening conditions. Bone scans can reveal muscle damage extent and location, aiding diagnosis even with normal biochemical tests. It is important to estimate the total body surface area (TBSA) of the burned area in burn injuries, using the rule of nine and Lund and Browder chart. This study aimed to determine rhabdomyolysis prognosis by applying these tools to muscle damage on bone scans.

Methods: We conducted a retrospective observational study from 2010 to 2022, enrolling 94 rhabdomyolysis patients who underwent bone scans. Cox regression analysis assessed the association between TBSA and all-cause mortality, adjusting for potential confounders.

Results: Applying the rule of nine and Lund and Browder chart to bone scan-assessed muscle damage, TBSA correlated positively with serum BUN, AST, ALT, LDH, and hospitalization length, and negatively with eGFR. Patients with rhabdomyolysis had a higher hazard ratio for all-cause death (HR 1.17; 95% CI 1.04-1.31).

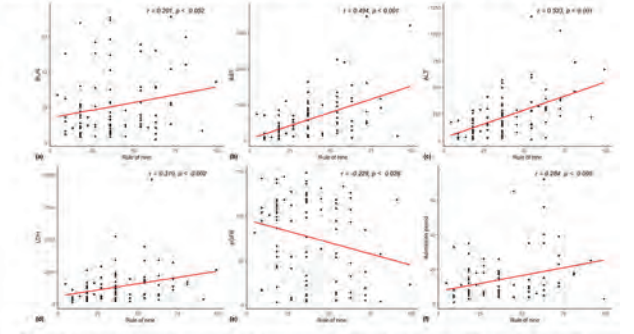
Conclusions: The application of the rule of nine and Lund and Browder chart to bone scans in rhabdomyolysis patients provides a valuable prognostic tool. TBSA correlates with key biochemical markers and clinical outcomes, including mortality. Accurate muscle damage estimation is crucial in managing rhabdomyolysis and improving patient outcomes.

Risk of all-cause death

All Cause Death	levels	all	Univariable model		Multivariable model	
			HR (95% CI)	P value	HR (95% CI)	P value
Rule of nine	Mean (SD)	38.3 (20.8)	1.10 (1.03-1.17)	0.004	1.17 (1.04-1.31)	0.008
Sex (male)		60 (63.8%)	0.25 (0.04-1.37)	0.110	14.56 (0.55-385.57)	0.109
Age	Mean (SD)	51.7 (21.2)	1.02 (0.99-1.06)	0.257	1.03 (0.97-1.10)	0.313
BMI	Mean (SD)	24.1 (3.8)	0.88 (0.68-1.13)	0.314	0.65 (0.37-1.13)	0.128

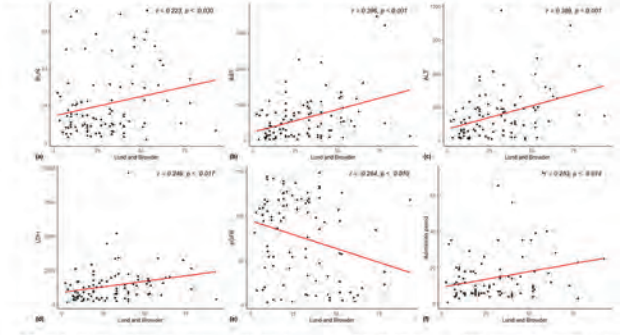
BMI, body mass index

Figure 1. Correlation between the biochemical result, admission period and the Rule of nine.



BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactic dehydrogenase; eGFR, estimated glomerular filtration rate

Figure 2. Correlation between the biochemical result, admission period and the Lund and Browder chart.



BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactic dehydrogenase; eGFR, estimated glomerular filtration rate

TH-PO049

Evaluation of Procalcitonin-to-Albumin Ratio (PCT/ALB) in Predicting the Prognosis of Patients with AKI Caused by Sepsis Secondary to Bloodstream Infection

Yue Gu, Han Li, Jing Zhou, Lei Yan, Fengmin Shao. *Henan Provincial People's Hospital, Zhengzhou, China.*

Background: To evaluate the procalcitonin/albumin (PCT/ALB) in predicting the prognosis of patients with acute kidney injury caused by sepsis secondary to bloodstream infection.

Methods: The S-AKI patients aged ≥18 years who were admitted to the Intensive Care Unit (ICU) from September 2018 and September 2020 were enrolled. S-AKI was defined as primary bloodstream infection, infective endocarditis, or catheter-related bloodstream infection. The enrolled patients were divided into survival group and death group based on the diagnosis of S-AKI within 28 days. Within 48 hours after ICU admission, various biochemical, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sepsis-Related Organ Failure Assessment (SOFA) score, Glasgow Coma Scale(GCS), oxygenation index, and machine ventilation time were also recorded.

Multivariate logistic regression analysis and receiver operating characteristic curve(ROC) analysis were performed to determine risk factors for 28-day prognosis in S-AKI patients and to evaluate the PCT/ALB in predicting the prognosis.

Results: The APACHE II score, SOFA score, PCT/ALB ratio, PCT levels, C-reactive protein (CRP) levels, and international normalized ratio (INR) were higher in the death group compared to the survival group ($P<0.05$). Platelet count, total protein (TP), albumin (ALB), alanine aminotransferase (ALT), and partial pressure of carbon dioxide were lower in the death group compared to the survival group ($P<0.05$). Multivariate regression analysis revealed that PCT/ALB ratio, TP levels, and APACHE II score were independent factors influencing mortality in S-AKI patients($P<0.05$). The area under the ROC curve for predicting 28-day mortality was 0.943 for PCT/ALB ratio with a cutoff value of 0.810; sensitivity of 0.904; and specificity of 0.906. For TP levels, it was 0.661 with a cutoff value of 0.316; sensitivity of 0.731; and specificity of 0.585. The area under the ROC curve (AUC) for predicting 28-day mortality was 0.809, with a cutoff value of 0.564, sensitivity of 0.904, and specificity of 0.660.

Conclusions: PCT/ALB is an important indicator for predicting the source of primary bloodstream infection in S-AKI patients. It has certain reference value in clinical assessment.

TH-PO050

Impact of AKI on Prognosis of Hospitalized Patients with Malignancy-Related Ascites

Mohammad A. Sohail,[1,2] Juan C. Calle.[1] *[1]Cleveland Clinic, Cleveland, OH; [2]Cleveland Clinic Glickman Urological and Kidney Institute, Cleveland, OH.*

Background: Malignant diseases can cause ascites by a variety of mechanisms, including peritoneal carcinomatosis and hepatic metastases leading to portal hypertension. Acute kidney injury (AKI) is frequently observed in hospitalized patients with malignancy-related ascites (MRA) and is associated with increased length of stay and hospital costs. Although there is robust data to support that AKI in cirrhotic patients with ascites is associated with increased mortality, to our knowledge, the prognosis of patients with MRA and AKI has not yet been described in the literature. Our study evaluates the impact of AKI severity and progression on in-hospital mortality in patients with MRA.

Methods: We conducted a retrospective cohort study of all hospitalized patients at the Cleveland Clinic from January 2012 to December 2022 with MRA who fulfilled AKI criteria at the time of admission. Baseline kidney function was defined by the serum creatinine and eGFR obtained prior to admission up to three months before hospitalization. Utilizing the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, we assessed the association between AKI severity and progression with in-hospital mortality. AKI progression was defined as the increase from lower KGIDO stages of AKI to higher stages during the first seven days of hospitalization.

Results: Of the 116 patients who were reviewed in this study, 35 (30.2%) died during their hospitalization. The mean patient age was 62.9 ± 11.1 years. 64 (55.2%) and 87 (75.0%) were male and White respectively. Etiologies of MRA included peritoneal carcinomatosis (n=78; 67.2%) and portal hypertension caused by hepatic metastases (n=38; 32.8%). 45 (38.8%) patients had a baseline eGFR <60 ml/min/m^2 and 44 (37.9%) patients progressed to a higher KDIGO AKI stage after initially fulfilling AKI criteria on admission. Patients achieved a peak severity of AKI stage 1, 35.3%, stage 2, 24.2%, and stage 3, 40.5%. AKI progression and need for kidney replacement therapy were significantly more common and peak AKI stage was higher in non-survivors than in survivors ($P<0.001$).

Conclusions: AKI in hospitalized patients with MRA is frequently severe and progressive and is associated with mortality in a stage-dependent manner. Methods for earlier identification of AKI and its progression may result in improved outcomes by facilitating the targeted and prompt management of AKI.

TH-PO051

Trend Analysis of Acute Kidney Failure-Related Mortality, 1999-2020

Mohammad Gul Yousaf Khan,[2] Hadia Ahmad,[1] Mohammad Ammar ur Rahman,[1] Luqman Munir,[1] Amna Khalid,[1] Ahsan Zil-E-Ali,[2] Umar Farooq.[2] NEURALKEy. *[1]King Edward Medical University, Lahore, Pakistan; [2]Penn State College of Medicine, Hershey, PA.*

Background: Acute renal failure (ARF), is a sudden decline in kidney function, leading to the accumulation of waste products and electrolyte imbalances. It has various causes and poses risks to patients, including increased morbidity and mortality. There is a growing incidence of fatalities attributed to ARF across the US. By employing age-adjusted mortality rates (AAMR), we examined variations across significant demographic variables and scrutinized shifts in mortality rates from 1999 to 2020.

Methods: We examined mortality data related to ARF acquired from the CDC WONDER (Wide-Ranging Online Data for Epidemiological Research) Database, from 1999-2020. Utilizing 95% confidence intervals, the Joinpoint Regression Program calculated annual percent changes (APC) and age-adjusted mortality rates (AAMR) per 1,000,000 individuals. For $p<0.05$, the parallelism test was deemed significant for non-parallel results.

Results: A total of 1,180,886 deaths have been reported in the US from 1999-2020 due to ARF. From 1999 to 2010, AAMR showed an upward trend, it declined from 2010 to 2018 and peaked again from 2018 to 2020, with an APC of 4.40 from 1999-2010, -2.28 from 2010 to 2018 and 11.28 from 2018 to 2020. Males, Blacks or African Americans, and people aged 85 years or above were the highest mortality populations. Heightened mortality rates were primarily concentrated in the southern, mid-western and non-metropolitan populations. Disparate trends were found in the tests for parallelism among male and female (0.0002), American Indian and Black (0.003), Asian and Indian American (0.002), Asian and Black (0.0013), Asian and Hispanic (0.042), Black and White (0.0004), Black and Hispanic (0.0002), White and Hispanic (0.0004) demographics. Test for parallelism shows disparity between large and small metropolitan (0.0002), large metropolitan and non-metropolitan(0.0002) areas, Northeast and Midwest (0.0002), Northeast and South (0.0002), Northeast and West (0.0002), Midwest and South (0.001).

Conclusions: Following a surge, the mortality rate attributed to ARF, having initially decreased to a certain extent, is now seeing a resurgence in the US, prompting concern. Certain demographics persistently exhibit higher mortality rates emphasizing the need for further research.

TH-PO052

External and Temporal Validation of Acute Tubulointerstitial Nephritis (AIN) Diagnostic Index: An Electronic Health Record-Based Multivariable Diagnostic Model for Assessing Probability of Acute Interstitial Nephritis on Kidney Biopsy

Kyra A. Shelton,[1,2] Steven Menez,[3] Melissa M. Shaw,[2] Candice Kent,[1,2] Jack Bitzel,[3] Heather Thiessen Philbrook,[4] Francis P. Wilson,[1,2] David Hu,[3] Yumeng Wen,[3] Chirag R. Parikh,[3] Dennis G. Moledina.[1,2] *[1]Section of Nephrology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; [2]Clinical and Translational Research Accelerator, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; [3]Division of Nephrology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD; [4]Division of Nephrology, Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD.*

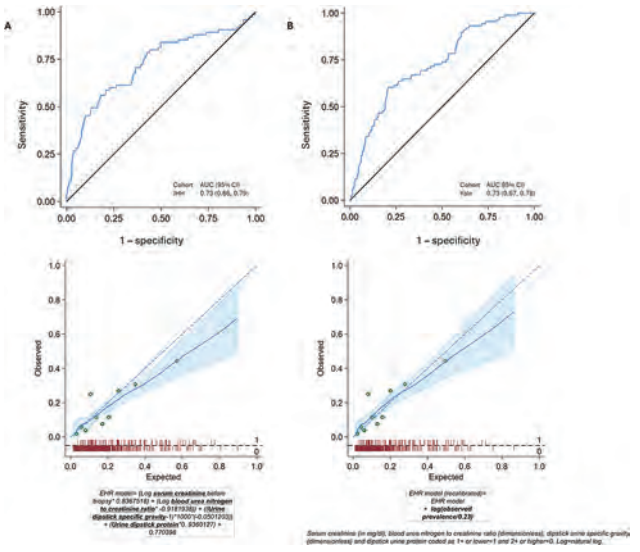
Background: Kidney biopsy is essential in cases of suspected acute tubulointerstitial nephritis (AIN), as there are limited diagnostic tests and clinical features associated with the disorder. Previously, we developed a multivariable model for biopsy-confirmed AIN containing serum creatinine, blood urea nitrogen to creatinine ratio, urine dipstick specific gravity and protein with an AUC of 0.73, which outperformed the clinicians' prebiopsy AUC of 0.60. Here we perform validation of this diagnostic index.

Methods: In two geographically and temporally distinct cohorts of patients who received a kidney biopsy at either Johns Hopkins Hospital (JHH) or Yale between 2019-2023, we tested discrimination (area under receiver operating characteristics curve, AUC) and calibration of the diagnostic index. We used model weights from the previous model and followed TRIPOD guideline for validation of multivariable models.

Results: We included 1,973 participants, with 1,444 from JHH and 529 from Yale. The prevalence of AIN at Yale (21%) was similar to what we previously observed (23%) whereas that of JHH was lower (5%). We noted similar AUC at JHH (panel A) and Yale (panel B) as the development set. However, the JHH cohort showed poor calibration (panel C) that improved after application of an intercept correction factor, accounting for the lower prevalence of AIN in this cohort (panel D).

Conclusions: The diagnostic model retained discrimination in these two distinct cohorts but required recalibration based on the prevalence of biopsy proven AIN. This indicates that the model may be a useful tool in identifying specific clinical features associated with AIN and assisting providers in discerning whether an AIN diagnosis is warranted based on laboratory and dipstick values. Calculator: https://ainriskprediction.shinyapps.io/ain_calc/.

Funding: NIDDK Support



TH-PO053

Heparin Prevents AKI to CKD Transition via HDAC1-Mediated Deacetylation of p65 Exerting Anti-inflammatory Effect Independent from Its Anticoagulant Properties

Anqun Chen, Lijun Yin. *The Second Xiangya Hospital of Central South University, Changsha, China.*

Background: The long-term outcome of acute kidney injury (AKI) is not good, since the survivors of AKI are prone to developing chronic kidney disease (CKD). Chronic inflammation is recognized as a pivotal determinant in the transition from AKI to CKD. Heparin, an anticoagulant, exhibits anti-inflammation/anti-complement activities, whose role in AKI to CKD transition remain elusive.

Methods: C57/B6 mice were subjected to unilateral renal ischemia-reperfusion (uIR) and folic acid (FA) intervention to construct AKI to CKD mouse models with or without low doses heparin(5 units/mouse) and its chemically modified variant lacking anticoagulant properties (N-Acetyl heparin sodium salt, NAH : 200μg/mouse) treatment. Potential mechanism of heparin was investigated by bulk RNA-seq analysis. Downstream target of heparin was screened in Swiss Target Prediction database, and detected by drug affinity responsive target stability (DARTS) analysis and cellular thermal shift assay (CETSA). BUMPT cells were used to further validate the effect and target of heparin and NAH in vitro.

Results: Treatment of low doses of heparin and its non-anticoagulant derivatives (NAH) significantly alleviated the uIR- and FA-induced renal tubular injury, and tubulointerstitial fibrosis, and improved renal function. Bulk RNA-seq analysis claimed that heparin might downregulate inflammatory pathways, including cytokine-cytokine receptor interaction, and MAPK signaling pathway, which were confirmed by decreasing immune cell infiltration and inflammatory cytokine expression in heparin-treated mice. Mechanistically, heparin and NAH bound to histone deacetylase 1 (HDAC1) independent on anticoagulant active sites in renal tubular epithelial cells and reduced the level of acetylated p65, leading to decreased expression of inflammatory factors.

Conclusions: Heparin and its non-anticoagulant derivatives inhibited inflammation by targeting HDAC1 to reduce the acetylation of p65. They inhibited the AKI to CKD transition, which could be potentially developed as a novel therapy for preventing AKI to CKD progression.

Funding: Government Support - Non-U.S.

TH-PO054

SGLT2 Inhibitors Reduce the Progression from AKI to CKD by Inhibiting Ferroptosis

Yutaro Hirashima. Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University. *Kyushu Daigaku, Fukuoka, Japan.*

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are known for their renoprotective effects in diabetes but their role in acute kidney injury (AKI) remains less explored. This study evaluates the impact of the SGLT2 inhibitor luseogliflozin on the transition from AKI to chronic kidney disease (CKD) in a mouse model, focusing on its anti-ferroptotic effects.

Methods: Using C57BL/6 mice, ischemic reperfusion (I/R injury was induced via bilateral renal pedicle clamping. Luseogliflozin or vehicle was administered for 2 weeks prior to and until sacrifice after the I/R injury. Renal function was assessed by serum creatinine and urea levels, and tissue damage by histological scoring. Renal fibrosis was assessed by Sirius Red Staining and Masson trichrome Staining. Metabolic shifts, oxidative stress and ferroptosis were evaluated through biochemical assays, histology, western blotting, and metabolomic analysis.

Results: Luseogliflozin significantly reduced markers of renal dysfunction and histological damage in the early post-ischemic phase. It also attenuated renal fibrosis and inflammation markers at one-week post-injury. Metabolic analysis revealed an inhibition of the glycolytic pathway and an enhancement of fatty acid oxidation and mitochondrial function. Key signaling molecules such as AMPK and Nrf2 were activated, correlating with reduced oxidative stress and suppressed ferroptosis.

Conclusions: Luseogliflozin mitigates the progression from AKI to CKD by modulating metabolic pathways and reducing oxidative stress and ferroptosis. This study suggests a potential therapeutic role for SGLT2 inhibitors in the management of AKI, advocating for further clinical investigation.

Funding: Commercial Support - Taisho Pharmaceutical Co

TH-PO055

Impacts of Skeletal Muscle Mass and Quality on Kidney Recovery after AKI Receiving Continuous Kidney Replacement Therapy

Jin hyuk Paek,[1] Jiyun Jung,[3] Jeong-Hoon Lim,[4] Yong Chul Kim,[5] Tae Hyun Ban,[10] Soyoung Lee,[6] Kipyo Kim,[7] Hyosang Kim,[9] Jeongin Song,[2] Jangwook Lee,[2] Sung Joon Shin,[2] Etienne Macedo,[8] Woo Yeong Park,[1] Jae Yoon Park.[2] *[1]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [2]Dongguk University College of Medicine, Gyeongju, Gyeongsangbuk-do, Republic of Korea; [3]Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; [4]Kyungpook National University School of Medicine, Daegu, Republic of Korea; [5]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [6]Daejeon Eulji University Hospital, Daejeon, Republic of Korea; [7]Inha University School of Medicine, Incheon, Republic of Korea; [8]University of California San Diego Department of Medicine, La Jolla, CA; [9]Asan Medical Center, Songpa-gu, Seoul, Republic of Korea; [10]The Catholic University of Korea Eunpyeong St Mary's Hospital, Eunpyeong-gu, Seoul, Republic of Korea.*

Background: Recent study revealed that muscle mass was significant determinant of mortality in patients with patients with severe acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT). However, there is little evidence on how muscle mass affects kidney recovery in these patients.

Methods: We collected 1,771 AKI patients who underwent CKRT from eight medical centers between 2006 and 2021. The skeletal muscle area (SMA) was measured from the automated software from CT images at 3rd lumbar vertebra within 15 days of CKRT initiation, and classified as normal attenuation muscle area (NAMA) and low attenuation muscle area (LAMA) according to muscle density. We used Cox proportional hazard model to investigate the effects of muscle index adjusted by height^2 on kidney recovery. In addition, Fine-Gray sub-distribution hazard models were used to consider the competing risks on mortality.

Results: The average duration of dialysis was 10.7 days, and 729 patients (41.2%) were discharged from the hospital independent of dialysis. The average of SMA/height^2, NAMA/height^2, and LAMA/height^2 were 41.2cm^2, 19.0cm^2, and 22.2cm^2, respectively. SMA/height^2 (HR 1.01, 95% CI 1.00-1.02, p=0.03), NAMA/height^2 (HR 1.02, 95%CI 1.01-1.03, p < 0.01), and NAMA/LAMA ratio (HR 1.09, 95% CI 1.01-1.17, p = 0.03) were associated with an increased probability of dialysis independence (DI) at discharge. In addition, while SMA/height^2 was identified as a factor that increased the probability of DI, it was not associated with mortality in Fine-Gray sub-distribution hazard models.

Conclusions: The amount of skeletal muscle mass was related to kidney recovery after AKI requiring CKRT. And muscles of normal density particularly supported these results. Furthermore, after considering mortality as a competing risk, an increase in skeletal muscle mass was associated with a higher probability of DI.

Table. The effects of several muscle mass index on independence of Renal Replacement Therapy

Group	Exposure		RRT independence	Persons-years	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
SMA/height^2								
	Quartile	Q1 [≤35.0)	150	4420	1 (ref)		1 (ref)	
		Q2 [35.0~40.3)	174	4198	1.25 (1.01,1.56)	0.04	1.31 (1.04,1.65)	0.02
		Q3 [40.3~47.0)	264	5219	1.29 (1.05,1.60)	0.02	1.37 (1.08,1.74)	0.01
		Q4 [≥47.0]	301	5189	1.24 (1.00,1.53)	0.05	1.36 (1.08,1.73)	0.01
	Linear		729	19004	1.01 (1.00,1.01)	0.16	1.01 (1.00,1.02)	0.03
NAMA/height^2								
	Quartile	Q1 [≤12.5]	166	4311	1 (ref)		1 (ref)	
		Q2 [12.5~17.9)	171	5537	0.93 (0.77,1.13)	0.45	0.90 (0.72,1.13)	0.36
		Q3 [17.9~24.3)	190	4208	1.24 (1.01,1.52)	0.04	1.28 (1.01,1.62)	0.04
		Q4 [≥24.3]	193	4446	1.19 (0.97,1.47)	0.09	1.29 (1.01,1.67)	0.05
	Linear		729	19004	1.01 (1.00,1.02)	0.01	1.02 (1.01,1.03)	<0.01
LAMA/height^2								
	Quartile	Q1 [≤13.7]	186	4010	1 (ref)		1 (ref)	
		Q2 [13.7~21.7]	170	3726	0.93 (0.78,1.17)	0.81	1.01 (0.81,1.23)	0.96
		Q3 [21.7~26.4]	172	4883	0.80 (0.65,0.98)	0.04	0.87 (0.69,1.09)	0.24
		Q4 [≥26.4]	192	6385	0.82 (0.67,1.00)	0.05	0.87 (0.70,1.09)	0.23
	Linear		729	19004	0.99 (0.98,1.00)	0.11	0.99 (0.98,1.01)	0.38
NAMA/LAMA								
	Quartile	Q1 [≤0.50]	167	4010	1 (ref)		1 (ref)	
		Q2 [0.50~0.80)	183	4643	1.17 (0.95,1.44)	0.14	1.15 (0.92,1.44)	0.22
		Q3 [0.80~1.52)	192	4348	1.35 (1.10,1.67)	<0.01	1.37 (1.09,1.73)	0.01
		Q4 [≥1.52]	187	4703	1.31 (1.06,1.61)	0.01	1.36 (1.08,1.75)	0.02
	Linear		729	19004	1.08 (1.00,1.12)	0.04	1.09 (1.01,1.17)	0.03

Adjusted by sex, age, Charlson comorbidity index, hypertension, sepsis, ventilator, sequential organ failure assessment, creatinine, white blood cell, hemoglobin, albumin, and PT INR.

TH-PO056

Mitotherapy-Dependent PGC1α Activation Mitigates Mitochondrial Electron Chain Complexes Dysfunction in Cisplatin-Induced AKI

Mohammad A. Afjal,[1] Amanda S. Stayton,[1] Prisha Patel,[1] Murat Dogan,[1] Christine Watkins,[1] Canan Kuscu,[1] Cem Kuscu,[1] Navjot Pabla,[2] Amandeep Bajwa.[1] *[1]The University of Tennessee Health Science Center, Memphis, TN; [2]The Ohio State University, Columbus, OH.*

Background: Cisplatin (CP)-induced Acute kidney injury (AKI) is a significant clinical problem. While the etiology of AKI is multifactorial, evidence suggests that mitochondrial dynamics plays a critical role in its pathogenesis. Mitochondria are central to cellular energy production, and mitochondrial dysfunction decreases ATP and induces oxidative stress, apoptosis, and mitochondrial damage, all of which contribute to renal dysfunction. This study investigated the potential of mitotherapy to mitigate mitochondrial complex dysfunction in CP-induced AKI, focusing on the role of PGC1α (Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha) activation.

Methods: CP was used to induce AKI in male mice. Functional assessment: BUN and plasma creatinine. Histopathological: H&E). Mitochondria source: Mouse Liver (See timeline Fig1 A)

Results: Mitotherapy improve kidney function and reduced structural damage in CP-treated mice (Fig 1 B-E). Mitotherapy enhanced activation of PGC1-α and restored OXPHOS activity (Fig 1 G&F). Mitotherapy restored the balance of mitochondrial dynamics by promoting fusion (Mfn1 and Mfn2) and attenuating fission by decreased expression of Drp1 (Fig 1 H-J). These findings suggest that mitotherapy-dependent activation of PGC1-α plays a crucial role in mitigating mitochondrial complex dysfunction and protecting against cisplatin-induced AKI.

Conclusions: This study highlights the therapeutic potential of mitotherapy in enhancing mitochondrial health and offers a promising strategy for alleviating CP-induced AKI.

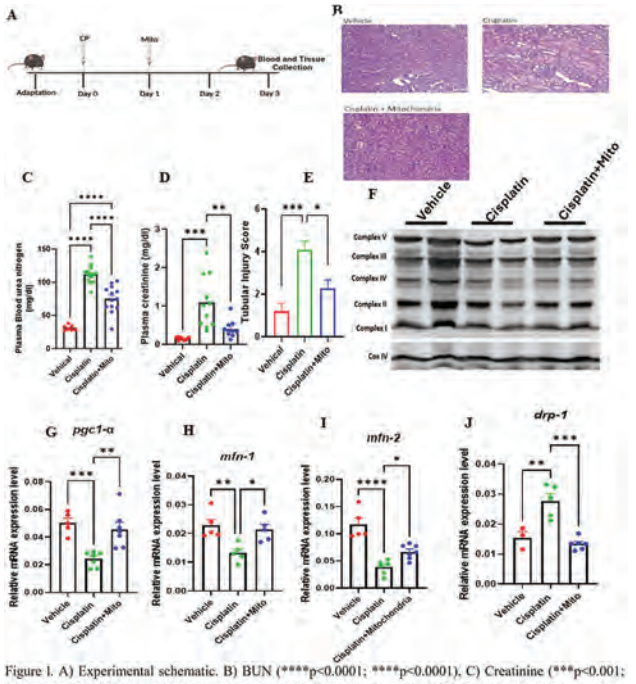


Figure l. A) Experimental schematic. B) BUN (****p<0.0001; ****p<0.0001), C) Creatinine (***p<0.001; **p<0.01), D) ATN Score (***p<0.001; *p<0.05), E) Histopathology, F) OXPHOS (Complex V-I), G pgc1-α (***p<0.001; **p<0.01), H) mfn-1 (**p<0.01; *p<0.05), I) mfn-2 (****p<0.0001; *p<0.05), J), drp-1 (**p<0.01; ***p<0.001: (Comparison is between Veh vs Cisplatin and Cisplatin vs Mito)

Fig 1

TH-PO057

JP4-039 Mitigates Cisplatin-Induced Nephrotoxicity and Prevents AKI

Merlin Airik, Rannar Airik. *University of Pittsburgh, Pittsburgh, PA.*

Background: Cisplatin is a commonly used highly effective therapeutic in cancer treatment. However, its use is limited by its nephrotoxicity which occurs in about 30 percent of patients receiving cisplatin chemotherapy. Since cisplatin induced AKI remains a major unmet medical need without any pharmacological interventions, we decided to explore the nephroprotective effects of a novel mitochondria-targeted reactive oxygen species (ROS) and electron scavenger JP4-039.

Methods: Male mice (129Sv-Elite, Charles River) were +/- treated with JP4-039 (10 mg/kg) 24 hours before or after cisplatin (10 mg/kg) injection, and kidneys analyzed 72 hours later for functional and molecular changes. Histological analysis was performed using PAS staining. Markers of tubular injury, DNA damage, lipid peroxidation, ROS and apoptosis were assessed by immunofluorescence and immunohistochemistry. Blood urea nitrogen was used to assess kidney function and qPCR was used to assess changes in gene expression.

Results: A single dose of cisplatin induced significant BUN elevation and kidney injury (KIM1, NGAL expression) in 129Sv-Elite mice after 72 hours, indicative of AKI. These pathologic changes were absent in mice who had received pre- or post-cisplatin JP4-039 injections, demonstrating a prevention of AKI. In addition, treatment with JP4-039 mitigated kidney morphology and histology in cisplatin-treated mice. Specifically, JP4-039 reduced the levels of tissue oxidative lesions, including oxidative DNA damage (8-OHdG) and lipid peroxidation (4-HNE), and mitigated tubular apoptosis. Mechanistically, we propose that JP4-039 exerts its renoprotective action by suppressing the NRF2 pathway, as the expression of NRF2 and its target genes (Nqo1, Txnrd1) was downregulated in JP4-039 kidneys. Further, JP4-039 attenuated the expression of various inflammatory cytokines associated with AKI in cisplatin injured kidneys.

Conclusions: Our data demonstrate that the novel antioxidant compound JP4-039 protects the kidneys from cisplatin induced AKI by suppressing tubular oxidative stress and inhibiting proinflammatory and proapoptotic pathways. Moreover, our studies show that JP4-039 can be administered both as a preventative or interventional therapy to suppress AKI induction.

Funding: NIDDK Support

TH-PO058

Bardoxolone Methyl Demonstrates Mitigation of Cisplatin-Induced Kidney Injury in a Mouse Model with Cancer

Sarah C. Asby,[1] Lauren E. Thompson,[1] M. Scott Lucia,[1] Lauren Aleksunes,[2] Charles L. Edelstein,[1] Melanie S. Joy.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Rutgers The State University of New Jersey, New Brunswick, NJ.*

Background: Acute kidney injury (AKI) occurs in approximately one-third of patients treated with the chemotherapeutic drug cisplatin. Multiple low-to-moderate doses of cisplatin in tumor-bearing mice recapitulates cisplatin-induced AKI in cancer patients and can be used to test potential mitigation strategies. Bardoxolone methyl (BARD) is an attractive mitigation therapeutic due to its ability to enhance anti-oxidative responses through activation of the Nrf2 transcription factor and potential anti-tumorigenic effects.

Methods: C57BL/6J mice (8-10 wk) were injected with CMT167 murine lung carcinoma cells (50,000) in the right flank and allowed to engraft for 7 days. Then, cisplatin (10-15 mg/kg) or vehicle (saline) were administered IP once weekly for 4 wks. Likewise, BARD (10 mg/kg) or vehicle (34.5% PEG-300, 30% DMSO, 30% saline, 5% propylene glycol, and 0.5% Tween-80) were injected IP 5x/wk per week. Body weight, tumor size, and survival were assessed weekly for 4 wks and urine and blood were also collected. Kidney injury was quantified by urinary kidney injury molecule-1 (KIM-1), serum creatinine (SCr) and assessment of renal histopathology.

Results: Co-treatment with BARD significantly enhanced survival of cisplatin-treated mice with cancer (p=0.01). Cisplatin treatment, with or without BARD, significantly reduced tumor growth compared to vehicle-treated mice (p<0.05). BARD did not demonstrate any significant anti-tumorigenic properties as a single agent. BARD protected the mice from cisplatin-induced kidney injury, as measured by urinary KIM-1 levels (p<0.01). BARD also mitigated the loss of kidney function caused by cisplatin, as measured by SCr (p<0.01). All Veh/CIS treated mice demonstrated tubular injury after just two doses of cisplatin and had significantly higher tubular injury scores (scores 1 or 2) than Veh/Veh and BARD/Veh mice (scores 0; p<0.05). Approximately 30% of BARD/CIS mice had no apparent tubular injury after receiving the 4 cisplatin doses, although not statistically different from Veh/CIS-treated mice.

Conclusions: Overall, the results of this study demonstrate the potential utility of using acute BARD administration during cisplatin treatment to reduce drug-induced AKI.

Funding: Other NIH Support - NIGMS

TH-PO059

Trends and Racial and Geographic Disparities in AKI-Related Mortality Rate in the United States, 1999-2019

Ewuradjoa Ayirebi-Acquah,[1] Zaneta Frimpong,[4] Abena A. F. Gyamfi,[5] Nii A. Addo-Quaye,[3] Sandra Oppong-Twum,[3] Stella Nyamikeh,[2] Isaac Prempeh.[6]
[1]Lekma Hospital, Accra, Ghana; [2]37 Military Hospital, Accra, Ghana; [3]Korle Bu Teaching Hospital, Accra, Ghana; [4]University of Ghana Medical Centre, Accra, Ghana; [5]Ridge Medical Center, Accra, Ghana; [6]New Hope Specialist Hospital, Aflao, Ghana.

Background: Acute kidney injury (AKI) is associated with increased risk of death. However, previous studies before 2010 showed conflicting trends in AKI-related mortality rate (AKI-MR) in the United States (US). Also, little is known about racial disparities in AKI-MR. We examined the trends and racial disparities in AKI-MR in adults in the US from 1999 to 2019.

Methods: This was a retrospective cross-sectional analysis of national death certificate data from the CDC's Wide-ranging Online Database for Epidemiological Research from 1999-2019. We used ICD-10 codes N17 and O90.4 to identify adults >18 years old whose death certificates mentioned AKI as a cause of death. The exposure variables were calendar year, race, and geographic region. The outcome variable was the crude AKI-MR which was calculated per 100,000 population. The Mann-Whitney U test and ANOVA were used to compare groups and P<0.05 defined statistical significance. We evaluated temporal trends with Joinpoint regression, which was expressed as average annual percentage change (AAPC) with 95% confidence intervals (CI).

Results: There were 1,093,865 AKI-related deaths out of a population of 4,784,988,012 [overall crude AKI-MR 22.9 per 100,000 (95% Cl, 22.8-22.9). The AKI-MR was higher in males (24 vs 21.7 in females; P=0.03), non-Hispanic White (NHW) [26.1 vs 23.8 in non-Hispanic Black (NHB), P=0.04], rural areas (30.3 vs 21.5 in urban areas; P<0.001), and the Midwest (24.8). From 1999-2019, the overall crude AKI-MR increased from 15.3 to 24.6 (AAPC 2.4%; CI: 2.3-2.6). The AKI-MR increased for males (AAPC 2.6%; CI: 2.5-2.8), females (AAPC 2.3%, CI: 2.2-2.5), NHB (AAPC 1.6, CI: 1.4-1.8), NHW (AAPC 2.8%, CI: 2.7-2.9), urban areas (AAPC 2.4%, CI: 2.2-2.5), rural areas (AAPC 3.3%, CI: 3.1-3.6), and across all census regions. When limited to AKI as the underlying cause of death, the crude AKI-MR increased overall, and for all genders, racial groups, urban and rural areas, and all census regions.

Conclusions: The AKI-MR increased significantly in the US from 1999-2019 and it varied by race, sex, and geographic region. These underscore the public health importance of AKI as a significant contributor to mortality in adults and it is an opportunity for further studies into the optimization of the care of patients with AKI.

TH-PO060

Increased Bone Fracture Risk after Recovery from AKI

Thomas R. McCune,[1,2] Marie V. Ozanne,[3,1] Xian Qiao,[1,4] Angela J. Toepp,[1,4] Melissa A. Kacena.[5] EVMS/IU Metabolic Bone Disease Consortium.
[1]Eastern Virginia Medical School, Norfolk, VA; [2]Nephrology Associates of Tidewater LTD, Norfolk, VA; [3]Mount Holyoke College, South Hadley, MA; [4]Sentara Healthcare Inc, Norfolk, VA; [5]Indiana University Purdue University Indianapolis, Indianapolis, IN.

Background: Acute kidney injury(AKI) that requires dialysis can be a complication during hospitalization. A population study from Taiwan found that patients recovered from AKI observed an increased risk fractures in weight bearing bones the first year (HR = 6.02, 95% CI 1.43–17.22; p = 0.02). We evaluated the risk of weight bearing fractures after recovery (>6 months) in a similar population data base.

Methods: This is a retrospective cohort study using data (accesed 1/23/24) from TriNetX COVID-19 Research Network, including deidentified EHR of 115+ million individuals in 85 healthcare organizations. Inclusion criteria: inpatient encounter (1/20/20-12/2022). Exclusion criteria: ESRD (N18.6), renal transplant (Z94.0/Z48.22), COVID infection, or neoplasm (C00-D49). Age 18 to 89 years. Propensity score matching (1:1) balanced three covariates between groups. Univariate logistic regression was conducted predicting AKI and weight bearing fractures (>6 months).

Results: Table 1: Study population fracture rates Figure 1: Risk of fractures by location (ICD-10)

Conclusions: 1. AKI increases the risk of weight bearing bone fractures(>6 months) (HR=1.527, 95% CI 1.455-1.603; p=0.01). 2. All weight bearing bone groups are impacted after AKI. 3. Managemant of AKI should address alterations in bone mineral metabolism.

Funding: Private Foundation Support

Cohort Statistics

	Cohort	Patients in Cohort	Patients with Outcome	Median Survival (Days)	Survival Probability at End of Time Window
1	All(6m): controls + AKI (inpat...	124,511	3,652	-	87.174%
2	All(6m): controls + no AKI (in...	133,071	2,978	-	90.246%

Log-Rank Test

χ^2	df	p
297.374	1	< 0.0001

30,002 patients in Cohort 1 and 21,442 patients in Cohort 2 were excluded from results because they had the outcome prior to the time window.

Table 1: Population analysis of fracture free survival AKI vs. NO AKI

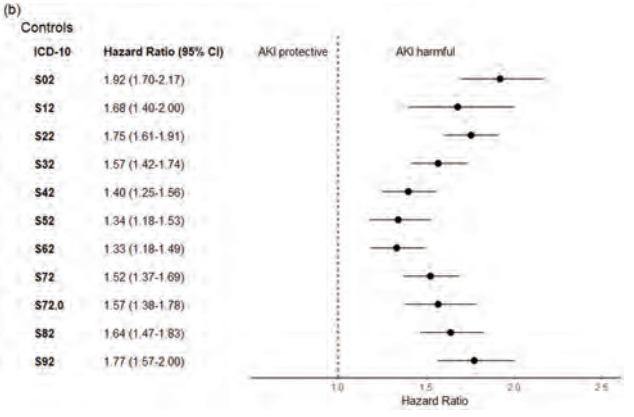


Figure 1: Risk of fracture after recovery of AKI (6 months+). ICD-10 codes for fracture locations

TH-PO061

Incidence of AKI and Kidney Replacement Therapy (RRT) after Outpatient Chimeric Antigen Receptor T (CAR-T) Cell Therapy in Patients with Hematological Malignancies

Bibi Maryam, Adolfo Diaz-Barba, Noha Soror, Taha Al-Juhaishi. *The University of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: AKI is characterized by an abrupt loss of kidney function resulting in decreased GFR, reduced urine output, and increased serum creatinine. CAR-T therapy is a newer cancer immunotherapeutic treatment that utilizes genetically altered cytotoxic T cells in destroying cancer cells. There have been very few studies studying the repercussions of inpatient CAR-T therapy on kidneys, but so far no studies have covered the renal safety profile of outpatient CAR-T therapy. We performed a retrospective analysis on incidence of AKI, resolution vs progression of disease requiring RRT and devolpment of CKD, in patients who underwent outpatient CAR-T therapy at our institute.

Methods: We obtained IRB approval and identified 79 adult patients who underwent outpatient CAR-T therapy between 9/2019 to 11/2023 for hematological malignancies at our National Cancer Institutes (NCI)-designated cancer center. Then we performed a retrospective chart review and determined the rates of hospital admissions and development of AKI within 7 days of CAR-T infusion, and followed the hospital course to assess the need for RRT, resolution of AKI, and progression to CKD. We also looked at the past medical history to assess if patients had preexisting diabetes, hypertension, and CKD.

Results: Out of the 79 patients who underwent outpatient CAR-T therapy infusion, 74.6 % ended up being admitted in the hospital. Within 7 days of infusion, 3 patients developed AKI, requiring hospitalization. Among these, one patient had preexisting CKD, and developed AKI on CKD. All three had hypertension on baseline, and interestingly none had diabetes. Incidence of AKI in all patients was at 3.7 %, whereas incidence of AKI in hospitalized patients was at 5.08%. 1 patient developed severe AKI requiring

RRT, bringing incidence rate of RRT at 1.26 % among all patients and 33% among the AKI group. Kidney function returned to baseline within 30 days in two of our patients, while one patient passed away during the hospitalization. None of our patients progressed to CKD.

Conclusions: We found a lower rate of AKI compared to rates reported in previous studies for patient who underwent inpatient CAR-T therapy, favoring the theory that outpatient CAR-T has a less severe side effect profile than inpatient CAR-T.

TH-PO062

Incidence of Postsurgical AKI for Emergent Surgery and Associated Clinical Outcomes

Stuart M. Carter, Ashita J. Tolwani. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: The purpose of this study is to identify the incidence of AKI in the two weeks immediately following an emergent surgical procedure in patients that did not received dialysis prior to their surgery. Our goal is to determine how often AKI is developed after an emergent procedure with the end goal of better identifying ways to prevent post-surgical AKI.

Methods: The target population is patients with an Emergent surgical procedure during their encounter (ASA Class 1-5E) admitted between October 1st, 2023 and May of 2024 at the University of Alabama at Birmingham Medical Center. Patients with Inpatient dialysis before the surgery were excluded. AKI was determined by retrospectively analyzing serum creatinine data, using the lowest pre-surgical creatinine level during the encounter as the baseline. The KDIGO criteria were applied, excluding urine output values. Patient outcomes were compared between those who developed AKI and those who did not.

Results: After excluding patients with end-stage renal disease (ESRD) and those treated for AKI prior to surgery, 827 patients were analyzed. Of these, 137 (16.6%) developed AKI, while 680 (83.4%) did not. Significant differences were found in median length of stay (15.5 days for the AKI group vs. 6.5 days for the non-AKI group). The mortality rate was also significantly higher in the AKI group (13%). Demographics and comorbidities are provided within the table below for the two sample groups.

Conclusions: The preliminary findings indicate that a significant population develops AKI following emergent surgery, suggesting that further research is needed to identify factors contributing to post-surgical AKI and potential preventive measures.

	AKI Group		Non-AKI Group	
	Count	Percentage	Count	Percentage
n	137		690	
ICU	90	65.69	255	37.5
Mean Age (Years)	53	N/A	44	N/A
Male	73	53.28	251	36.91
Female	55	40.15	324	47.65
Other Sex	9	6.57	105	15.44
White	63	45.99	282	41.47
Black or African American	37	27.01	212	31.18
Decline/Unknown	17	12.41	144	21.18
Hispanic or Latino	8	5.84	24	3.53
Asian	0	0	13	1.91
Other	8	0	5	0.74
CKD	18	13.14	22	3.24
Diabetes	48	35.04	124	18.24
Hypertension	85	62.04	271	39.85
Median LOS (Days)	16	N/A	6	N/A
Expired	19	13.87	24	3.53
Discharged	108	78.83	621	91.32
Still Hospitalized	10	7.3	35	5.15
Dialysis Dependent at Discharge	2	1.46	0	0

TH-PO063

Mortality and Kidney Function Recovery in Patients with Sepsis-Associated AKI vs. Nonseptic AKI Treated with Continuous Kidney Replacement Therapy

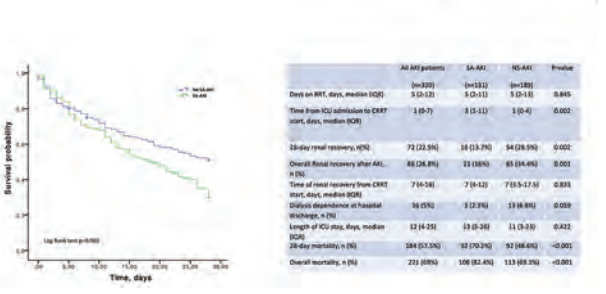
Marco Fiorentino, Francesco La Fergola, Sabrina Carparelli, Loreto Gesualdo. *Universita degli Studi di Bari Aldo Moro, Bari, Italy.*

Background: It was recently suggested that sepsis-associated AKI (SA-AKI) is characterized by different pathogenesis and outcomes compared to non-Septic AKI (NS-AKI). We aim to examine risk factors and outcomes of SA-AKI vs NS-AKI among critically ill patients who developed AKI requiring renal replacement therapy (RRT).

Methods: We performed a single-center retrospective analysis, including patients admitted to ICU who developed AKI requiring RRT at Policlinico of Bari (Jan. 2021 to July 2023). We classified patients in NS-AKI and SA-AKI groups based on the leading cause of AKI. The primary outcome was to assess mortality and kidney functional recovery (KFR) rate between SA-AKI and NS-AKI groups. 28-day survival probability was analyzed using the Kaplan–Meier method. Risk factors associated with in-hospital mortality were evaluated using Cox regression models.

Results: 320 patients were included in the study; 131 patients developed SA-AKI (40.9%), while the remaining 189 were classified as NS-AKI (59.1%). 268 patients (83.8%) developed AKI Stage 3 and 40 patients AKI stage 2 (12.5%). There was no significant difference in CRRT duration and median lenght of ICU stay. The timing of CRRT initiation from ICU admission was late in the SA-AKI group (3 vs 1 days, p=0.002). 184 patients (57.5%) died at 28 days, with a higher percentage in the SA-AKI (70.2 vs 48.6%, p<0.001)(**Figure 1**). In-hospital mortality was reported in 221 patients (69%), with impressive percentages in the SA-AKI group (82.45 vs 69.3%, p<0.001). KFR was significantly higher in the NS-AKI (28.5% vs 13.7%, p=0.002). Median time of KFR was similar between groups (p=0.833). Multivariate Cox Regression analysis showed that only SA-AKI (HR 1.442, 95%CI 1.052-1.978, p=0.023) was independently associated with mortality risk.

Conclusions: SA-AKI was associated with high mortality rate and lower likelihood of renal recovery compared to NS-AKI in critically ill patients requiring RRT.



	All AKI patients (n=320)	SA-AKI (n=131)	NS-AKI (n=189)	P-value
Days on RRT, days, median (IQR)	5 (3-12)	5 (3-11)	5 (3-13)	0.845
Time from ICU admission to CRRT start, days, median (IQR)	1 (0-7)	3 (1-11)	1 (0-4)	0.002
28-day renal recovery, n(%)	72 (22.5%)	18 (13.7%)	54 (28.5%)	0.002
Overall Renal recovery after AKI, n (%)	86 (26.8%)	23 (18%)	65 (34.4%)	0.001
Time of renal recovery from CRRT start, days, median (IQR)	7 (4-14)	7 (4-12)	7 (3.5-17.5)	0.833
Dialysis dependence at hospital discharge, n (%)	16 (5%)	3 (2.3%)	13 (6.8%)	0.059
Length of ICU stay, days, median (IQR)	12 (4-25)	13 (3-26)	11 (3-23)	0.422
28-day mortality, n (%)	184 (57.5%)	92 (70.2%)	92 (48.6%)	<0.001
Overall mortality, n (%)	221 (69%)	108 (82.45)	113 (69.3%)	<0.001

Clinical outcomes between SA-AKI and NS-AKI groups

TH-PO064

Brain-Kidney Interplay during Sepsis-Associated AKI: Results from the RACERS Study

Marco Fiorentino,[1] Maria Teresa Cimmarusti,[1] Alessandra Stasi,[1] Rossana Franzin,[1] Sabrina Carparelli,[1] Monica Campioni,[1] Rosa Losapio,[1] Gianvito Caggiano,[1] Paola Pontrelli,[1] Constance Keyserling-Peyrottes,[2] Cyrille Tupin,[2] Loreto Gesualdo.[1] [1]*Universita degli Studi di Bari Aldo Moro, Bari, Italy;* [2]*Abionyx Pharma, Toulouse, France.*

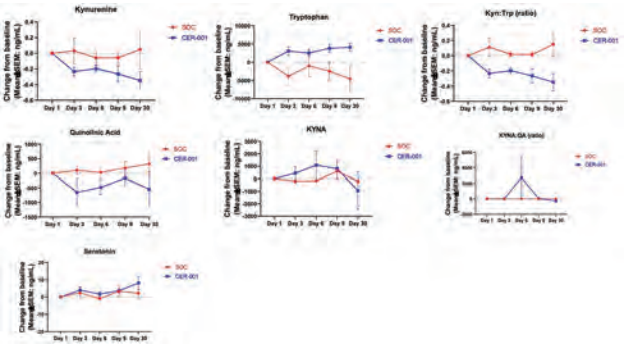
Background: Recent preclinical studies have revealed a strong association between low levels of HDL and dysregulation of the kynurenine pathway (KP) in sepsis-associated AKI and cognitive dysfunction. In our preclinical model, treatment with a new engineered HDL (CER-001) downregulated the Indolamine-2,3-dioxygenase 1 (IDO1) enzyme, a crucial mediator of KP, by reducing kynurenine/tryptophan (KYN/Trp) ratio and quinolinic acid (QA) levels. We aim to analyze the effects of treatment in mitigating brain dysfunction in a Phase 2a clinical trial.

Methods: We performed a randomized Phase 2a study (RACERS study) including 20 patients with Gram negative sepsis, randomized to receive CER-001 (twice a day on Days 1, 2, 3 and 6) or standard of care (SOC) only. We analyzed the activity of KP between patients treated with CER-001 and SOC groups, by reporting changes from baseline of specific neuroactive metabolites such as KYN, KYN/Trp ratio, kynurenic acid (KYNA), QA and serotonin values.

Results: CER-001 treatment significantly reduced bloodstream concentrations of LPS, pro-inflammatory cytokines and circulating s-VCAM-1 and s-ICAM-1. Patients presenting with AKI at enrollment presented a tendence to higher values of KYN/Trp ratio (0.22, IQR 0.12-0.46) compared to patients without any stage of AKI at enrollment (0.12, IQR 0.07-0.28). CER-001 treatment reduced QA, KYN values and KYN/Trp ratio, suggesting the downregulation of IDO1, thus reducing the production of potential neurotoxic metabolites (**Figure 1**). We showed increased levels of tryptophan and the neuroprotective KYNA during treatment course, as well as a slight increase in serotonin, supporting the different regulation of tryptophan metabolism leading to neuroprotection.

Conclusions: CER-001 treatment downregulated IDO1 and reduce neuroactive metabolites and waste accumulation.

Funding: Commercial Support - Abionyx Pharma



Effects of CER-001 on the kynurenine pathway in the RACERS study

TH-PO065

Nephrotoxicity Associated with Vancomycin and Piperacillin/Tazobactam: Insights from Kidney Biopsy

Sofia Yamada,[1,2] Xavier F. Parada,[3,4] Sphoorthy Pasala,[1,2] Rajesh Anumolu,[1,2] Saif A. Alenizi,[1,2] Astrid Weins,[1,2] David B. Mount.[1,2] *[1]Brigham and Women's Hospital Department of Medicine, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]UMass Memorial Health, Worcester, MA; [4]University of Massachusetts Chan Medical School, Worcester, MA.*

Background: The antibiotics vancomycin and piperacillin-tazobactam are co-prescribed together in hospital settings; there are concerns regarding the potential nephrotoxicity. Both antibiotics have been independently implicated in AKI and there is no consensus about any mechanism of injury when administered together. This case series explores kidney biopsy findings in patients receiving these antibiotics, to elucidate potential mechanisms of injury, risk factors and compare them with the literature. Notably, there is minimal biopsy data for patients with AKI after this antibiotic combination

Methods: This is a single center, observational cohort study. Clinical and biopsy data were retrospectively collected from hospitalized AKI patients with recent exposure to vancomycin and piperacillin-tazobactam who underwent native kidney biopsy between Feb/2010 to Nov/2023 at Brigham and Women's Hospital. All seven included AKI patients were de-identified; since there was no interaction or intervention with human subjects, there is no need for IRB review

Results: Kidney biopsies revealed a range of pathological findings, including acute tubular necrosis (ATN), acute interstitial nephritis (AIN), and tubular injury potentially related to drug induced nephrotoxicity. Notably, among the 7 patients examined, 2 developed acute kidney injury (AKI) within 48 hours of antibiotic prophylaxis, while 1 during day 2, 3 exhibited symptoms on day 3, and 1 on day 5 following the initiation of antibiotic treatment

Conclusions: AKI after co-administration of vancomycin/ piperacillin-tazobactam is an increasingly important clinical problem, with some evidence for "pseudo-AKI" from elevated creatinine levels without acute kidney injury. Here we report that this antibiotic combination is associated with a mixture of ATN and AIN after co-administration, providing new biopsy confirmation of an association with *bona fide* AKI. Further research is necessary to elucidate underlying mechanisms and develop strategies for early detection and management of antibiotic associated renal toxicity

TH-PO066

Precipitous AKI in Association with Vancomycin Exposure: A Cohort Study

Montana D. Ellis,[1] Dustin R. Chalmers,[3] Ghaith Hashem,[1] Kirsten Johnson,[1] Danielle N. Aliano,[2] Vipin Varghese,[4] Swetha Rani Kanduri,[2,1] Juan Carlos Q. Velez.[2,1] Ochsner Group. *[1]UQ-Ochsner Clinical School, New Orleans, LA; [2]Ochsner Health, New Orleans, LA; [3]Louisiana State University, Baton Rouge, LA; [4]University of Michigan Division of Nephrology, Ann Arbor, MI.*

Background: Precipitous acute kidney injury (p-AKI) is a distinct form of AKI characterized by a steep rise in serum creatinine (sCr). An association between exposure to vancomycin and p-AKI has been previously reported via large electronic database mining, case reports, and case series. Herein, we aimed to expand our understanding of this entity by examining the relationship between exposure to vancomycin and the incidence of p-AKI in a prospectively generated AKI Cohort.

Methods: We prospectively collected data of patients seen in inpatient nephrology consultation who had a urine specimen subjected to microscopic examination of the urinary sediment (uSEDI) as part of the clinical evaluation for AKI over a 6-year period. AKI was defined by KDIGO criteria. p-AKI was defined as a rise in sCr ≥ 1.6 mg/dL within 24 +/- 2 hrs at any point during the course of the AKI episode. Within this uSEDI cohort, we identified patients who had been exposed to intravenous vancomycin during the preceding 5 days prior to the day of AKI consultation and determine its association with p-AKI occurrence.

Results: 801 patients entered the study. Median age was 60, 42% women, 59% White, 31% Black. Preexisting CKD was reported in 42%. Main etiologies of AKI were ischemic acute tubular injury (ATI) (44%), hepatorenal syndrome (13%) and toxic ATI (12%). Exposure to vancomycin was registered in 265 (33%) patients. Median sCr at the time of AKI was 3.2 (IQR 2.4-4.6) mg/dL. p-AKI occurred in 95 (12%) patients, the steepest 24-hr sCr rise recorded was 4.2 mg/dL. Exposure to vancomycin was associated with an increased risk of p-AKI [18% vs. 9%, for exposed to vancomycin vs non-exposed, respectively; odds ratio 2.24 (95% CI 1.45-3.46, z statistic=3.643, p=0.0003)].

Conclusions: Exposure to vancomycin doubles the risk of p-AKI. This study adds to a body of evidence that defines a unique AKI phenotype associated with vancomycin that should be recognized in clinical grounds. The mechanism behind the precipitous sCr rise due to vancomycin may relate to a combination of true ATI and reduced tubular sCr secretion due to injury to proximal tubular organic transporters, but more investigation is still required.

TH-PO067

A Clinicopathological Description of Kidney Features in VEXAS Syndrome

Martin Mathurin,[1] Pierre Hirsch,[1] David Buob,[1,2] Khalil El Karoui.[1,2] FRENVEX Group. *[1]Assistance Publique - Hopitaux de Paris, Paris, France; [2]INSERM, Paris, France.*

Background: VEXAS (Vacuoles, enzyme E3, X linked, Autoinflammatory, Somatic) is a recently reported autoinflammatory syndrome characterized by myeloid lineage-restricted acquired variants in the ubiquitin-activating E1 (UBA1) gene. Renal lesions of VEXAS patients are poorly characterized.

Methods: We searched for patients with kidney biopsy (KB) among 303 VEXAS cases from the french nationalVEXAS cohort. We extracted data from medical records, and performed a centralized review of renal biopsies. We investigated the presence of UBA1 mutated clones within the kidney by sequencing DNA extracted from whole kidney tissue.

Results: We identified 11 patients with KB. All were male, mean age was 70 years old. Renal presentation included progressive chronic kidney disease in 5 patients and acute kidney injury (AKI) in 6 (including two needing renal replacement therapy). AKI episodes were chronologically linked with VEXAS flares in 3 patients. Mean sCreatinine was 363 µmol/l. All patients presented with extra renal manifestations. Renal function evolution was usually favorable after treatment with corticosteroids and various immunosuppressors. Histopathological findings were heterogenous, including acute interstitial nephritis (n=4), ANCA negative pauci-immune vasculitis (n=1), IgA nephropathy superimposed with minimal change disease (n=1), IgA nephropathy (n=1), diabetic nephropathy with extensive fibrosis (n=1), acute tubular necrosis (n=2), and AA amyloidosis (n=1). Interstitial inflammatory infiltration was noticed in 8/11 cases, whatever the primary diagnosis. Immunohistochemical characterization of interstitial inflammatory cells demonstrated the presence of lymphocytes and plasma cells, admixed with macrophages and neutrophil cells. MPO and CD68 immunostaining was positive in all cases, with a variable degree of expression. We performed molecular analysis of DNA extracted from 8 available frozen samples by next generation sequencing. UBA1 variation was detected in 7/8 samples, with VAF ranging from 2% to 17% of total kidney DNA.

Conclusions: This series highlights the heterogeneous clinical and histological presentation of VEXAS-associated kidney disease. The molecular analysis of kidney tissue along with the frequent histological finding of interstitial infiltration may suggest the existence of a specific involvement of clonal cells directly targeting the kidney during VEXAS.

TH-PO068

Gut Microbiome Metagenomic Sequencing Reveals Distinct Profiles in Participants with AKI and CKD from the KPMP

Sanjeev Noel,[1] James R. White,[2] Shishir K. Patel,[1] Steven Menez,[1] Dominic S. Raj,[3] Chirag R. Parikh,[1] Hamid Rabb.[1] Kidney Precision Medicine Project (KPMP). *[1]Johns Hopkins University, Baltimore, MD; [2]Resphera Biosciences LLC, Balitmore, MD; [3]The George Washington University, Washington, DC.*

Background: Previous experimental studies using 16S RNA sequencing demonstrated distinct gut microbial changes following acute kidney injury (AKI) in mice and dysbiosis in chronic kidney disease (CKD) patients. Metagenomic whole genome sequencing (mWGS) has several advantages over 16S, including the ability to identify bacteria, fungi and viruses plus provide functional information. We applied mWGS to KPMP stool samples from AKI and CKD participants for species level identification and functional pathway analysis.

Methods: mWGS on AKI (n=7) and CKD (n=70) stool was performed to achieve >25 million reads/sample. Metagenomic data of healthy controls (n=94) from 4 published studies was downloaded from the NCBI Sequence Read Archive. Kraken2 and Metaphlan3 were used for taxonomic assignment and HUMAnN3 for functional annotation. Unsupervised clustering was performed using pheatmap, and comparisons between groups were computed with the non-parametric Mann-Whitney U test.

Results: Kraken2 analysis showed a decline in the percent mean abundance of *Ruminococcus bicirculans* in AKI (1.82) compared to CKD (6.47; p=0.07) and healthy individuals (2.42; p=0.01). Furthermore, genus *Chryseobacterium* declined in AKI (0.05) compared to CKD (0.07; p=0.05) and healthy individuals (0.20). Conversely, *Gordonibacter pamelaeae* increased in AKI (0.07) compared to healthy individuals (0.03) but was less abundant compared to CKD (0.30; p=0.05). Metaphlan3 identified a significant increase in *Clostridium asparagiforme* in AKI (11.68) compared to CKD (0.03; p=0.06) and healthy (0.01; p=0.001) individuals. *Gemmiger formicilis* was significantly reduced in AKI (0.01) compared to CKD (0.51; p=0.06) and healthy (0.26; p=0.001) individuals. HUMAnN3 analysis showed significant correlation between amino acid metabolism and *Clostridium asparagiforme* in AKI compare to CKD and healthy individuals.

Conclusions: These preliminary results demonstrate distinct microbiota profile during an episode of AKI compared to CKD and healthy individuals. Future studies with larger sample sizes are needed to confirm these findings and highlight the pathophysiologic significance of these changes.

Funding: NIDDK Support, Other NIH Support - Kidney Precision Medicine Project

TH-PO069

Immunomodulatory Effect of Selective Cytopheretic Device (SCD) on Neutrophil-to-Lymphocyte Ratio (NLR) and Hematologic Parameters from Multiple AKI Trials

Sai Prasad N. Iyer,[1] Nicholas J. Ollberding,[4] Jay L. Koyner,[2] Lenar T. Yessayan,[3] Kevin K. Chung,[1] H. David Humes.[3] *[1]SeaStar Medical, Denver, CO; [2]University of Chicago Division of the Biological Sciences, Chicago, IL; [3]University of Michigan Michigan Medicine, Ann Arbor, MI; [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: SCD is an immunomodulatory cell-directed extracorporeal therapy (CDET) that targets activated neutrophils and monocytes in hyperinflammatory conditions such as AKI and sepsis. Inflammatory imbalance can be measured by examining relationships of leukocytes to other immune cells, such as NLR. High NLRs have been associated with poor outcomes across a wide range of diseases, including AKI and sepsis. We examined the effect of SCD treatment from prior AKI clinical studies on NLR and other hematological measures to gain insights into the mechanism of SCD.

Methods: Complete blood count, NLR, monocyte: lymphocyte ratio (MLR), and platelets were included from 5 prior adult and pediatric studies (pooled n=133) in patients with AKI requiring continuous kidney replacement therapy (CKRT). Patients were treated for up to 10 days with SCD + CKRT in all studies. Control CKRT only group included patients from a pivotal study (SCD-003), and from a contemporaneous matched cohort (CRRTnet) (n=32). All parameters were analyzed from the treatment period across these studies between control vs. SCD treated patients using linear mixed effects regression.

Results: Treatment with SCD reduced NLR across all studies during the treatment period. The control group in the SCD-003 study displayed an upward trend in NLR after an initial drop but was not statistically significant vs. the SCD treated group (p = 0.38). When analyzed as a pooled group, SCD treated patients demonstrated a significant reduction in NLR vs. control patients (p=0.007). This difference was maintained following sensitivity analysis excluding pediatric patients (p=0.013). No statistically significant differences were observed between groups for MLR levels or platelets in the treatment period.

Conclusions: SCD treatment demonstrated reductions in NLR across multiple AKI clinical studies. This analysis provides further mechanistic evidence of leukocyte immunomodulation in targeting inflammatory neutrophils and effector immune cell dysregulation in hyperinflammatory conditions such as AKI.

Funding: Commercial Support - SeaStar Medical

TH-PO070

Cost Impact of an Immunomodulatory Selective Cytopheretic Device in Pediatrics (SCD-PED) in AKI Due to Sepsis (AKI-S)

Jennifer A. Kammerer,[1] Nathan L. Kleinman,[2] Alec Kleinman,[2] Kevin K. Chung,[1] Sai Prasad N. Iyer,[1] Charuhas V. Thakar.[3] *[1]SeaStar Medical, Inc, Denver, CO; [2]Kleinman Analytic Solutions LLC, Frisco, TX; [3]Queen's University Belfast, Belfast, United Kingdom.*

Background: Acute kidney injury (AKI) occurs in 3.9/1000 US pediatric hospitalizations—often with septicemia (OR 1.37 (1.32 to 1.43))—and requiring ICU care and continuous kidney replacement therapy (CKRT). Poor outcomes include prolonged stays, mechanical ventilation (MV), and up to 50% mortality. SCD-PED is an authorized humanitarian device for patients ≥10kg, age ≤22 years with AKI-S on CKRT. Using Kids' Inpatient Database (KID) and SCD-PED study data, hospitalization costs are estimated.

Methods: KID extract (2019) included patients ages 1-20 years on CKRT. Modeled from hospital perspective were inputs for length of stay (LOS), age, gender, death at discharge, vasopressor use, MV, sepsis or AKI, total parenteral nutrition (TPN), mortality risk, SCD-PED cost/number used. Mean mortality was 45% in external controls and 27% on SCD-PED. Costs are adjusted to 2024 USD. Cost savings are derived from mortality benefit or simulated for 1-day reduction in LOS. Generalized linear regression was used to model costs. All variables were significant except gender and AKI.

Results: Mean hospitalization cost was $461,736 in KID controls, reflecting heterogenous, complex cases and costly burden. With continuous 6-day SCD-PED, savings from lower mortality is predicted for device price up to $4381. With theoretically lower LOS, further savings may be realized.

Conclusions: The SCD-PED is likely cost beneficial to implement with presumed survival benefit in critically ill pediatric AKI-S. Other benefits may include clinical value of lower mortality and costs from a) reduced total or ICU LOS, b) outcomes beyond hospitalization (avoided dialysis, renal recovery), and c) sepsis or readmission quality measurements.

Funding: Commercial Support - SeaStar Medical, Inc.

Inputs (Events During Hospitalization)	KID CKRT Controls	SCD Study Type	SCD Users, Theoretical LOS
Length of Stay	36.2	36.2	35.2
Age	9.5	9.5	9.5
Female	45%	45%	45%
Died	45%	27%	27%
Vasopressors	68%	68%	68%
MV	95%	95%	95%
Sepsis	68%	68%	68%
AKI	100%	100%	100%
TPN	24%	24%	24%
Mortality Risk (MR) = 1	0	0	0
MR = 2	0	0	0
MR = 3	0	0	0
MR = 4	1	1	1
% w/MR = 1 and Sepsis	0	0	0
% w/MR = 2 and Sepsis	0	0	0
% w/MR = 3 and Sepsis	0	0	0
% w/MR = 4 and Sepsis	1	1	1
Cost per SCD	$0	$4381	$4381
Number of SCD Used	0	6	6
Estimated Cost Per Patient	**$461,736**	**$461,732**	**$453,350**
KID CKRT averages			
SCD study user values			
SCD external ppCRRT control values			
Theoretical simulation			

SCD-PED Cost Model

TH-PO071

Intraoperative Microvascular Perfusion in Cardiac Surgery-Associated AKI: A Prospective Longitudinal Cohort

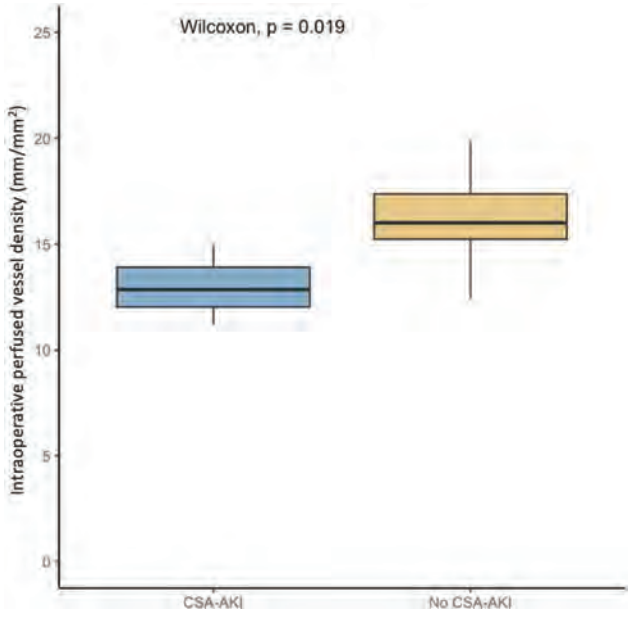
Jennifer R. Joslin,[1,2] Simon C. Satchell,[3] Claire C. Sharpe,[2] Kate Bramham.[1,2] *[1]King's College London, London, United Kingdom; [2]King's College Hospital, London, United Kingdom; [3]University of Bristol, Bristol, United Kingdom.*

Background: We have previously presented the association between intraoperative endothelial glycocalyx (EGx) degradation (quantified by plasma syndecan-1 (SDC1)) and cardiac surgery-associated acute kidney injury (CSA-AKI). This novel study aimed to explore the relationship between intraoperative microvascular perfusion and CSA-AKI.

Methods: Twenty patients selected from a prospective observational cohort study of 61 patients undergoing coronary artery bypass graft (CABG) surgery were included. Sublingual microvascular perfused vessel density (PVD) was assessed by incident dark field videomicroscopy at three time-points: preoperatively, intraoperatively after haemostasis, and immediately postoperatively. CSA-AKI within 48 hours was assessed (KDIGO criteria). Demographic, clinical and surgical variables were evaluated.

Results: 3/20 (15%) participants developed CSA-AKI. Intraoperative PVD was significantly lower in those who did develop CSA-AKI than in those who did not (Figure 1). There were no significant differences in preoperative or postoperative results between groups. There was a moderate negative correlation between intraoperative PVD and SDC1 levels measured at the same time point: R = -0.54, p = 0.015. Intraoperative PVD was the best predictor of CSA-AKI with an area under the curve of 0.92 (95% confidence interval 0.79 – 1.00).

Conclusions: This is the first demonstration of impaired intraoperative microvascular perfusion in CABG patients who later developed CSA-AKI, and highlights the association between EGx health and microvascular perfusion. These findings offer potential targets for early therapeutic intervention and / or earlier identification of patients at greatest risk of CSA-AKI.



Intraoperative PVD in patients with and without CSA-AKI

TH-PO072

Is AKI an Independent Risk Factor for Subsequently Decreased Kidney Function after Accounting for Pre-AKI Proteinuria and Pre-AKI eGFR Slope?

Victor E. Prado,[1] Ian E. McCoy,[1] Yue Zhang,[7] Kathleen D. Liu,[1] Anthony N. Muiru,[1] Vernon M. Chinchilli,[7] Steven G. Coca,[2] Alan S. Go,[6] Jonathan Himmelfarb,[3] James S. Kaufman,[8] Paul L. Kimmel,[9] Talat Alp Ikizler,[5] Chirag R. Parikh,[4] Edward D. Siew,[5] Mark M. Wurfel,[3] Chi-yuan Hsu.[1]
[1]University of California San Francisco School of Medicine, San Francisco, CA; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]University of Washington, Seattle, WA; [4]Johns Hopkins University, Baltimore, MD; [5]Vanderbilt University, Nashville, TN; [6]Kaiser Permanente, Oakland, CA; [7]The Pennsylvania State University, University Park, PA; [8]New York University, New York, NY; [9]National Institutes of Health, Bethesda, MD.

Background: A recent Chronic Renal Insufficiency Cohort (CRIC) analysis showed that after accounting for pre-AKI eGFR slope, pre-AKI proteinuria and other confounders, an episode of mild to moderate AKI was not an independent risk factor for changes in subsequent eGFR or eGFR slope (Ann Intern Med. 2023;176:961-8). We sought to confirm or refute these findings leveraging comparable data from the ASsessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study in which participants also underwent yearly study protocol driven measurements of eGFRcr (CKD-EPI 2021), eGFRcys (CKD-EPI 2012), urine protein-Cr ratio (uPCR) and had capture of interim AKI episodes by inpatient SCr values.

Methods: Hospitalized AKI was defined as ≥50% difference in nadir to peak inpatient SCr. Linear mixed-effects regression models were used to examine whether AKI was associated with abrupt loss of eGFR (i.e. incomplete recovery) or steeper eGFR slope after AKI.

Results: We analyzed all 1603 enrolled ASSESS-AKI study participants (37.6% female, 12.5% non-Hispanic Black). At baseline, mean age was 65 (SD±13) years, eGFRcr 72 (±26) mL/min/1.73 m², eGFRcys 56 (±27) mL/min/1.73 m² and median uPCR 0.13 g/g [IQR0.08 to 0.25]. 41% had diabetes mellitus, and 21% had a history of heart failure. During median follow-up of 4.6 years, 698 AKI episodes (83.1% stage 1 in severity) were observed among 407 participants. In the fully adjusted model, AKI was independently associated with a -2.22 mL/min/1.73m² abrupt loss of eGFRcr but not with steeper subsequent eGFRcr slope. Similar results were seen with eGFRcys (Table).

Conclusions: Contrary to what was observed in CRIC, among ASSESS-AKI study participants, an AKI event was associated with a loss of kidney function (i.e. incomplete recovery), even after accounting for pre-AKI proteinuria and pre-AKI eGFR slope. However, the slope of eGFR decline did not worsen after AKI.

Funding: NIDDK Support

Table

	Change in eGFRcr Value After Each AKI (95% CI), mL/min/1.73 m2	Change in eGFRcr Slope After Each AKI (95% CI), mL/min/1.73 m2 per year	Change in eGFRcys Value After Each AKI (95% CI), mL/min/1.73 m2	Change in eGFRcys Slope After Each AKI (95% CI), mL/min/1.73 m2 per year
Unadjusted	-2.91 (-4.43, -1.37)	0.21 (-0.18, 0.60)	-4.20 (-5.72, -2.68)	0.63 (0.26, 1.01)
Fully adjusted*	-2.22 (-3.46, -0.98)	0.16 (-0.16, 0.48)	-3.55 (-4.76, -2.34)	0.63 (0.32, 0.94)

*Adjusted for demographics, baseline eGFR, time-updated comorbidities, uPCR, SBP, ACEI/ARB use

TH-PO073

Preoperative Ionized Calcium Levels and Risk of AKI after Cardiac Surgery

Sung Jin Moon,[1] Lee Ji-Ho,[1] Jin Hyeog Lee,[1] Jae Hyun Chang,[2] Jung Tak Park,[3] Hee Byung Koh.[1] International St. Mary's Hospital, Catholic Kwandong University, Incheon, Republic of Korea. *[1]Catholic Kwandong University International Saint Mary's Hospital, Incheon, Republic of Korea; [2]Gachon University Gil Medical Center, Incheon, Republic of Korea; [3]Yonsei University Institute of Kidney Disease, Seodaemun-gu, Seoul, Republic of Korea.*

Background: Despite its close correlation with cardiovascular diseases, the association between serum calcium levels and postoperative AKI is not fully elucidated.

Methods: Patients aged ≥18 years who underwent cardiac surgery at two tertiary hospitals between 2006 and 2020 were retrospectively evaluated. Their preoperative serum ionized calcium levels were categorized into quartiles. The primary outcome was postoperative AKI within 48 hours, classified in accordance with the KDIGO criteria. AKI was further categorized into mild AKI (stage 1) and moderate-to-severe AKI (stage 2-3).

Results: Of the 9,779 patients (mean age, 64.0 years; male, 60.1%), postoperative mild AKI and moderate-to-severe AKI were noted in 3,848 (39.3%) and 719 (7.4%) patients, respectively. AKI were more prevalent in patients with lower ionized calcium levels (mild AKI: 46.9%, 38.7%, 35.1%, and 36.8%; moderate-to-severe AKI: 11.6%, 7.1%, 5.4%, and 5.3% from Q1-4, respectively, both P-trend <0.001). In logistic regression analysis, compared with Q4, the adjusted odds ratios (aORs) [95% CI] for mild AKI were 1.57 [1.38-1.79], 1.16 [1.02-1.32], and 0.99 [0.87-1,13] for Q1-3, respectively (P-trend <0.001). Similar results were observed in analysis for the moderate-to-severe AKI (aOR of Q1-3; 2.11 [1.66-2.68], 1.35 [1.05-1.73], and 1.04 [0.80-1.36] compared with Q4; P-trend <0.001). In mediation analysis, cardiopulmonary bypass time and intra-operative inotropic use explained 12.1-16.9% and 12.9-19.5% of the association between calcium levels and AKI, respectively (all of P <0.001).

Conclusions: Lower serum ionized calcium levels were associated with a higher incidence of AKI in patients undergoing cardiac surgery. Hemodynamic factors may have influenced this association, and further studies are needed to investigate the underlying mechanism.

	Univariate		Multivariate [a]	
	OR (95% CI)	P	OR (95% CI)	P
Mild AKI [b]				
Q1	1.52 (1.35 - 1.70)	0.000	1.56 (1.37 - 1.78)	0.000
Q2	1.09 (0.97 - 1.22)	0.164	1.15 (1.01 - 1.31)	0.032
Q3	0.93 (0.83 - 1.05)	0.234	0.99 (0.87 - 1.13)	0.907
Q4	(Reference)		(Reference)	
P for Trend [c]		< 0.001		< 0.001
Moderate to Severe AKI [b]				
Q1	2.36 (1.90 - 2.92)	0.000	2.10 (1.66 - 2.67)	0.000
Q2	1.36 (1.07 - 1.72)	0.011	1.34 (1.04 - 1.72)	0.023
Q3	1.03 0.80 - 1.32)	0.812	1.04 (0.80 - 1.35)	0.770
Q4	(Reference)		(Reference)	
P for Trend [c]		< 0.001		< 0.001
In-hospital Mortality				
Q1	2.63 (1.81 - 3.83)	0.000	2.55 (1.69 - 3.84)	0.000
Q2	1.24 (0.81 - 1.90)	0.326	1.37 (0.88 - 2.15)	0.166
Q3	(Reference)		(Reference)	
Q4	1.46 (0.97 - 2.21)	0.069	1.34 (0.86 - 2.11)	0.197
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	P
Length of ICU Stay, day				
Q1	8.17 (4.73 - 14.13)	0.000	6.91 (3.93 - 12.15)	0.000
Q2	1.54 (0.89 - 2.66)	0.124	1.57 (0.90 - 2.73)	0.110
Q3	(Reference)		(Reference)	
Q4	1.84 (1.06 - 3.17)	0.029	1.38 (0.78 - 2.42)	0.264

Association between preoperative ionized calcium levels quartiles and clinical outcomes

TH-PO074

Characterising the Natural History of Kidney Recovery after AKI in a Prospective Cohort: Does Timing Matter?

Rebecca A. Noble,[1,2] Nicholas M. Selby.[1,2] Centre for Kidney Research and Innovation. *[1]University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom; [2]University of Nottingham, Nottingham, United Kingdom.*

Background: Acute kidney injury (AKI) is associated with an increased risk of chronic kidney disease (CKD). It is known that failure of recovery of serum creatinine by 90 days after AKI strongly associates with subsequent CKD, but detailed prospective descriptions of the 'renal recovery phase' between AKI and day 90 are lacking. Here we describe outcomes at serial timepoints for a prospective cohort of hospitalised inpatients with AKI in Derby, England.

Methods: Single centre, prospective cohort study of participants will all stages of AKI. Participants characterised in detail, including AKI aetiology, co-morbidities and frailty. Baseline blood and urine samples were obtained at the time of consent, day 30, 60 and 90 with clinical measurements, blood and urine sample collection. Outcomes of interest: (1) of serum creatinine to within 1.15x baseline, (2) Major Adverse kidney Events (MAKE) a composite of death, renal replacement therapy and persistent renal dysfunction, defined as a 25% or greater drop GFR.

Results: 122 participants were recruited. Most patients had more severe AKI (58% stage 3, 23% stage 2, 19% stage 1). M:F (70:52), median age 67.5yrs. Leading cause of AKI was dehydration (n=52, 42.6%). 18.9% (n=23) of participants required renal replacement therapy. Rates of non-recovery were high. Recovery of renal function (creatinine <1.15xbaseline) was seen in 45% at day 30 (n=49), 50% at day 60 (n=51) and 44% at day 90 (44%). Similar outcomes were observed using MAKE, MAKE30 n =40 (39.6%), MAKE60 n=41 (43.2%), MAKE90 n=41 (46%). There was no statistically significant difference between the baseline characteristics in the group who did and not recover, including diabetes, 38% vs 50% p=0.47 and duration of AKI, (13 days vs 5 days, p=0.21).

Conclusions: In this cohort of patients with predominantly severe AKI, rates of non-recovery of renal function were high. The lack of difference between the baseline characteristics of the recovered and non-recovered group highlights the difficulty in predicting which patients are going to recover and who will not. Whilst there is some dynamic change over time, most changes are observed by day 30, suggesting the key time for renal repair may be the first 30 days. This is important when considering the timing of future interventional strategies, suggesting that interventions need to be implemented prior to 30 days.

TH-PO075

Association of Z-codes and Mortality in Patients with AKI and Heart Failure

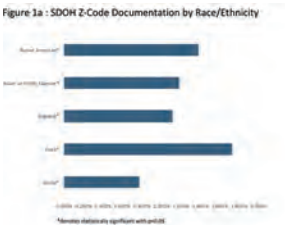
Samuel Tan, Wenchy Tan, Lili Chan. *Icahn School of Medicine at Mount Sinai, New York, NY.*

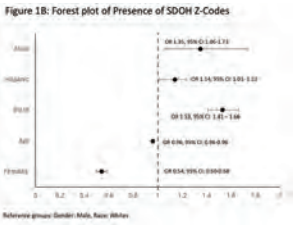
Background: Acute kidney injury (AKI) is a serious complication in patients admitted for acute decompensated heart failure (ADHF). Z-codes are part of the ICD-10-CM coding system codes for social determinants health (SDOH). There is a lack of data regarding the association of coding for SDOH on outcomes in patients admitted for ADHF.

Methods: This was a retrospective study using the National Inpatient Sample to identify patients admitted for ADHF and diagnosed with AKI from 2016 to 2020. Patients who had ESKD were excluded. The primary outcome was in-hospital all-cause mortality. Patients with Z-codes were compared to propensity matched patients without Z-codes. To determine if having Z-codes modifies the odds of requiring dialysis by race, we included an interaction term of Race x having any Z-code.

Results: There were 481,298 patients admitted for ADHF and diagnosed with AKI during their hospital stay. 4,650 patients with Z-codes were propensity matched with 4,650 patients without Z- codes. Compared to the control group, those who had Z-codes are associated with signficantly lower odds of mortality (OR: 0.96 CI:0.96 -0.97). Females (OR 0.54; CI: 0.50- 0.578) and older (OR 0.96; CI: 0.96 - 0.96) individuals were significantly less likely to have any Z-codes. Compared to Whites, Black (OR 1.53; CI: 1.41 - 1.66), Hispanic (OR 1.14; CI:1.01 - 1.23) and Asian (OR 1.35 ; CI: 1.06-1.73) patients were significantly more likely to have Z-codes. Z-Code is associated with a significantly decrease odds of dialysis (OR: 0.52; CI: 0.36 – 0.76). Compared to Whites those who are Hispanic (OR:1.21; CI: 1.11- 1.31) and Asians (OR 1.32; CI:1.15 - 1.51) are significantly more likely to end up on dialysis during their hospital stay. However, there is no significant association for odds of requiring dialysis when comparing Whites with Z-Codes and Blacks (p=0.72) and Hispanics (p=0.61) with Z-Codes.

Conclusions: We found that in matched cohorts, the presence of a Z-code lead to lower odds of mortality. Black, Hispanic, and Asian individuals were significantly more likely to have Z-codes than White individuals. These results maybe due to provider recognition and documentation of unmet SDOH, noting the importance of unmet SDOH.





TH-PO076

Urine Proteomic Signatures of Kidney Function Decline after Hospitalization

Yumeng Wen,[1,2] Steven Menez,[2] Heather Thiessen Philbrook,[2] Dennis G. Moledina,[3] Pavan K. Bhatraju,[4] Steven G. Coca,[5] Vernon M. Chinchilli,[6] Alan S. Go,[7] Edward D. Siew,[8] Paul L. Kimmel,[10] Talat Alp Ikizler,[8] Chi-yuan Hsu,[9] Jonathan Himmelfarb,[4] Lloyd G. Cantley,[3] Chirag R. Parikh.[2] Kidney Precision Medicine Project (KPMP). *[1]Genentech Inc, South San Francisco, CA; [2]Johns Hopkins Medicine, Baltimore, MD; [3]Yale University School of Medicine, New Haven, CT; [4]University of Washington School of Medicine, Seattle, WA; [5]Icahn School of Medicine at Mount Sinai, New York, NY; [6]Penn State College of Medicine, Hershey, PA; [7]Kaiser Permanente, Oakland, CA; [8]Vanderbilt University School of Medicine, Nashville, TN; [9]University of California San Francisco School of Medicine, San Francisco, CA; [10]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.*

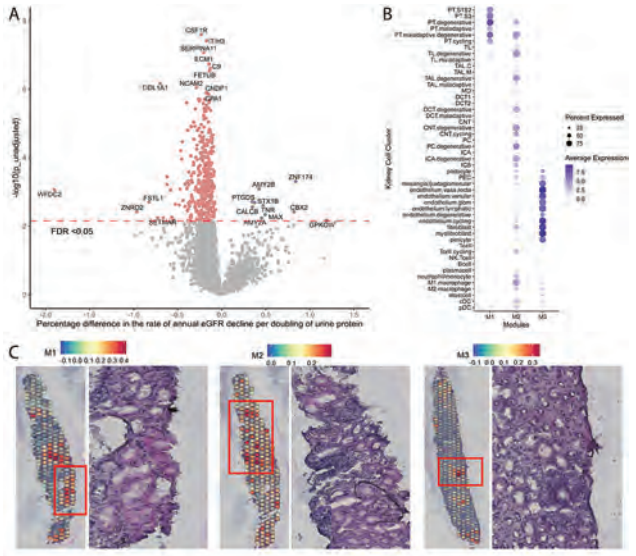
Background: Urine proteomics may identify proteins specifically excreted by the kidney that provide mechanistic insights into future adverse kidney outcomes.

Methods: In 174 patients (48% with acute kidney injury [AKI]) from the Assessment, Serial Evaluation, and Subsequent Sequelae in AKI (ASSESS-AKI) cohort, we used Olink to profile 2783 urine proteins in samples from 3 months after index hospitalization. We used linear mixed-effects models to identify proteins associated with estimated glomerular filtration rate (eGFR) decline after 4.8 years (median) follow-up. We used weighted correlation network analysis to determine proteins' cellular enrichment in the kidney transcriptome (single-cell/nucleus RNA sequencing, spatial transcriptomics) in 20 patients with diverse causes of AKI who received research kidney biopsy from the Kidney Precision Medicine Project.

Results: The ASSESS-AKI patients had median (IQR) age of 67 (59-75) years and median (IQR) eGFR of 65 (41-85) ml/min/1.73m^2 at 3 months post-discharge. We identified 387 and 10 proteins associated with faster and slower eGFR decline, respectively (**Fig. 1A**), including 283 expressed by kidney cells and 114 not expressed. The expression formed 3 clusters enriched in the proximal tubule (Module 1 [M1], **Fig.1B**), degenerative tubule and myeloid cells (M2), and stromal cells (M3), and correlated with histopathological features of AKI, such as tubular injury, interstitial inflammation, and fibrosis (**Fig.1C**).

Conclusions: By integrating the urine proteome and kidney transcriptome, we identified degenerative tubular injury, inflammation, and fibrosis as pathways associated with eGFR decline in recently hospitalized patients.

Funding: NIDDK Support



A. Proteins associated with annual eGFR decline in participants with and without AKI in the ASSESS-AKI cohort; **B.** Proteins associated with eGFR decline in ASSESS-AKI participants have genes forming 3 expression clusters in the kidney transcriptome (single-cell and single-nucleus RNA sequencing) in 20 participants with AKI receiving research biopsies in the KPMP cohort; **C.** Expression clusters of proteins associated with eGFR decline further correlated with histopathological features of AKI, including proximal tubule injury (left), inflammation (middle), and fibrosis (right) in spatial transcriptomics from participants with AKI receiving research biopsies in KPMP.

TH-PO077

Impaired De Novo NAD+ Biosynthesis Is a Feature of Pediatric AKI

Kyle Q. Vu,[1] Amanda J. Clark,[1,2] Marie Christelle Saade,[1] Anders H. Berg,[3] Samir M. Parikh.[1] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]Children's Medical Center Dallas, Dallas, TX; [3]Cedars-Sinai Medical Center, Los Angeles, CA.*

Background: Impaired cellular energy metabolism is a known feature of acute kidney injury (AKI). NAD+ is a critical cofactor required for ATP synthesis. Suppression of NAD+ biosynthesis, most notably the de novo pathway commencing from tryptophan, is a well-described feature of AKI and critical illness in animal models and humans. Reduction in flux through de novo NAD+ biosynthesis can be tracked non-invasively with urinary accumulation of the bottleneck metabolite quinolinate relative to tryptophan. Significantly, impaired NAD+ biosynthesis represents a therapeutic target in AKI as replacement of NAD+ via nutritional precursors of alternate NAD+ biosynthesis pathways can mitigate AKI severity in animals and early clinical trials in humans. To date, all studies evaluating de novo NAD+ biosynthesis impairment in clinical AKI have been performed in adult patients.

Methods: Discarded pediatric urine samples were collected from the laboratory of a tertiary care children's hospital and sorted into groups: AKI, ICU, control (Con), based on patient status at the time of collection obtained from the medical record. Control urines were obtained from otherwise healthy children undergoing screening evaluations. NAD+ related metabolites were measured using liquid chromatography mass spectrometry.

Results: Urines from 26 children with AKI, 44 patients in the ICU, and 40 control patients were collected. Patients with AKI and/or critical illness exhibited accumulation of de novo NAD+ biosynthesis metabolites in the urine, including elevated quinolinate:tryptophan ratio (Con 0.971, AKI 15.1, ICU 5.69, p <0.001). In critically ill children, urine quinolinate:tryptophan ratio was elevated in patients with and without AKI (6.45 and 5.30 respectively, p <0.001 and 0.037 compared to Con).

Conclusions: To our knowledge, these data provide the first demonstration that impaired de novo NAD+ biosynthesis may be a feature of pediatric AKI and pediatric critical illness, as described in adults. Therefore, children may benefit from clinical trials targeting NAD+ replacement to mitigate AKI and severity of critical illness

Funding: NIDDK Support

TH-PO078

Urinary Apoptosis Inhibitor of Macrophage Reflects the Severity of Tubular Damage in Patients with ANCA-Associated Vasculitis

Shunsuke Takahashi,[1] Yoshinori Takei,[3] Kaori Takayanagi,[1] Keiju Hiromura,[2] Hajime Hasegawa,[1] Akito Maeshima.[1] *[1]Department of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; [2]Department of Nephrology and Rheumatology, Gunma University Graduate School of Medicine, Maebashi, Japan; [3]Department of Nephrology, Fukaya Red Cross Hospital, Fukaya, Japan.*

Background: Apoptosis inhibitor of macrophage (AIM) produced by tissue macrophages has been implicated in a variety of pathological conditions, including acute kidney injury (AKI). AIM protects renal cells from apoptosis, modulating inflammation, and promotes tissue repair. AIM helps in maintaining kidney function by preventing excessive cell death and supporting the regeneration of damaged renal tissue in AKI. However, the role of AIM in ANCA-associated vasculitis (AAV) remains unknown. In the present study, we investigated whether AIM can be detected in the urine and kidneys of patients with AAV to evaluate the potential of urinary AIM as a marker for AAV.

Methods: AAV patients (n=34) who were treated in our departments (December 2011 to December 2022) and healthy adults (n=16) were enrolled in this study. Serum and urinary AIM were measured by ELISA. The correlation of urinary AIM with renal function, urinary protein level, clinical parameters and various AKI biomarkers were analyzed. Localization of AIM in the kidney of AAV patients was examined by immunostaining using the renal biopsy specimens. This study was approved by the Ethics Committee on Human Research of our institutions (Approval number 855, 2487). Written informed consent was obtained from all patients.

Results: Compared to healthy subjects, urinary AIM was significantly increased in AAV (0.00 ± 0.0 vs. 19.2 ± 3.6 μg/gCr, p<0.01). Urinary AIM levels significantly decreased following immunosuppressive therapy. We found a significant correlation between urinary AIM and serum creatinine, urinary protein, urinary NAG, urinary β2-microglobulin, MPO-ANCA, and C-reactive protein. However, no significant correlation was observed between urinary AIM and either urinary kidney injury molecule-1 or serum AIM. AIM was absent in normal kidney but was detected in renal tubules of the kidney of AAV patients. AIM-producing cells were positive for aquaporin-1, but was negative for uromodulin, and aquaporin-2.

Conclusions: Urinary AIM, which was produced by proximal tubules, might be useful as a marker reflecting the severity of tubular damages in patients with AAV.

TH-PO079

Infectious Complications in Critically Ill Children and Young Adults Receiving Continuous Kidney Replacement Therapy

Shina Menon,[1] Sai Prasad N. Iyer,[2] H. David Humes,[3] Stuart Goldstein,[4] Mihaela Damian,[1] Andrea Cappoli,[8] Catherine Joseph,[9] Danielle E. Soranno,[5] Michelle C. Starr,[5] Ashita J. Tolwani,[6] Kevin K. Chung,[2] Theresa A. Mottes,[7] Huaiyu Zang,[4] Nicholas J. Ollberding,[4] Katja M. Gist.[4] Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease. *[1]Stanford University School of Medicine, Stanford, CA; [2]Seastar Med, Denver, CO; [3]University of Michigan Health System, Ann Arbor, MI; [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [5]Indiana University School of Medicine, Indianapolis, IN; [6]University of Alabama at Birmingham School of Medicine, Birmingham, AL; [7]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [8]Ospedale Pediatrico Bambino Gesu, Roma, Italy; [9]Texas Children's Hospital, Houston, TX.*

Background: AKI is known to be associated with subsequent infection. The Regional Citrate *vs* Systemic Heparin for continuous renal replacement therapy (CRRT) (RICH) study reported higher infection rate in adults treated with regional citrate anticoagulation (RCA) *vs* heparin (HA). We aimed to determine if RCA was associated with development of infectious complications (positive blood, urine or respiratory culture) in children & young adults after CRRT start.

Methods: We performed 2 secondary analyses using data from Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease. We excluded patients who died ≤ 72 hours of CRRT start, had minor trauma or were post-surgical (n=169) for the first. Additional second analysis exclusions (n=709) were sepsis before CRRT, chronic immunosuppression (organ transplant/immune deficiency). Primary outcome was culture positive infection (blood, urine, respiratory) after CRRT start. Primary predictor was anticoagulation (RCA vs. other).

Results: In the first analysis (n=874) patients, post-CRRT start infection rates were higher for RCA (29%) compared to HA (23%) and others (15%) (p=0.008). Multivariable analysis showed no association between RCA and infection rates (Figure 1A). Second analysis (n=283) patients confirmed no association between RCA and infections in univariable (HA: 94 [33%], RCA: 155 [55%], other: 34 [12%]) or multivariable analyses (Figure 1B).

Conclusions: In this multinational cohort, anticoagulant type was not associated with an increased risk for infection after CRRT start. This is in contrast to the RICH study. Future work will determine if infection after CRRT start worsens outcomes.

Funding: Commercial Support - Seastar Medical

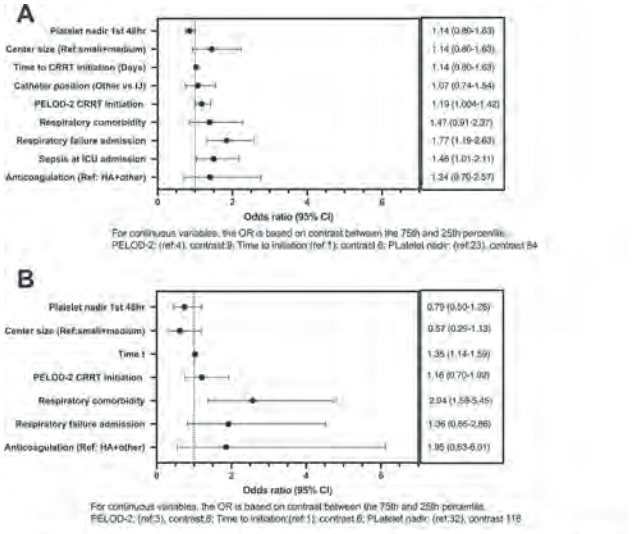


Figure 1. Forest plot demonstrating the associations with infection after CRRT initiation among the entire cohort (A) and restricted to those without immune suppression or sepsis/infection before CRRT initiation (B).

TH-PO080

Association between Hemoglobin Levels and Kidney Recovery after AKI Requiring Continuous Kidney Replacement Therapy

Jae Yoon Park,[1] Hyun Lee Ko,[2] Jiyun Jung,[1] Sung Woo Lee,[2] Yong Chul Kim,[3] Jeong-Hoon Lim,[4] Jin hyuk Paek,[5] Woo Yeong Park,[5] Kipyo Kim,[7] Jeongin Song,[1] Jangwook Lee,[1] Sung Joon Shin,[1] Etienne Macedo.[6] *[1]Dongguk University Medical Center, Goyang, Gyeonggi, Republic of Korea; [2]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [3]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [4]Kyungpook National University Chilgok Hospital, Buk, Daegu, Republic of Korea; [5]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [6]University of California San Diego, La Jolla, CA; [7]Inha University, Incheon, Republic of Korea.*

Background: Anemia is a prevalent complication in patients with acute kidney injury (AKI) who require continuous kidney replacement therapy (CKRT), and it significantly contributes to the increased mortality and morbidity rates seen in these patients. Despite its significant clinical implications, there is limited evidence on the specific serum hemoglobin (Hb) thresholds that may impede, delay, or alter the course of kidney recovery in these patients.

Methods: We conducted a retrospective analysis of 2,856 patients with AKI who underwent CKRT across four university hospitals from 2006 and 2021. Hb levels were systematically recorded during CKRT, and the mean Hb level during treatment was designated as the primary exposure variable. To assess the impact of average Hb levels on the likelihood of dialysis dependence (DD) at discharge, we calculated the odds ratio (OR) while adjusting for several variables: sex, age, Charlson Comorbidity Index, hypertension history, cause of AKI (sepsis-related or other), systolic and diastolic blood pressure, white blood cell count, serum albumin, serum creatinine, APACHE II score, SOFA score, duration of CKRT, volume of transfusions received, and use of mechanical ventilation.

Results: In our cohort, 61.6% of the patients were male, with an average age of 65.4 years. The average duration of CKRT was 7.7 days, and 65.2% of patients were dialysis-dependent at hospital discharge. A U-shaped correlation between average Hb levels and DD was evident from spline curve analysis. The range between 9.1 and 10.1 g/dL was significant for the lowest risk for DD with ORs below 1.0 and a 95% confidence interval supporting this finding. Furthermore, logistic regression using continuous average Hb levels revealed that each 1 g/dL increase in average Hb was associated with a 6% reduction in the risk of DD. Also, each additional day of Hb within this range decreased the risk of DD by 6%.

Conclusions: This study indicates that average Hb levels between 9.1 and 10.1 g/dL during CKRT were associated with the lowest ORs for DD. These findings underscore the need for further research into the optimal Hb thresholds for transfusion in patients undergoing CKRT, as this may significantly influence kidney recovery outcomes.

TH-PO081

Stress Hyperglycemia and Long-term Outcomes in Patients with AKI Requiring Continuous Kidney Replacement Therapy

Minhyung Kim, Junseok Jeon, Danbee Kang, Seungmin Song, Kyungho Lee, Jung eun Lee, Wooseong Huh, Hye Ryoun Jang. *Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.*

Background: Stress hyperglycemia is hyperglycemia that occurs during various stressful situations in patients without diabetes and is associated with poor outcomes in critically ill patients. We investigated the impact of stress hyperglycemia on outcomes during hospitalization in patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: This retrospective cohort study using the Korean Health Insurance Review and Assessment database included 11,013 adult patients with AKI who received CRRT for ≥ 3 days between 2010 and 2019 and survived until discharge. Patients with pre-existing diabetes were excluded to evaluate stress hyperglycemia. Patients were divided into the two groups: hyperglycemia group and control group. Hyperglycemia was defined as the prescription of oral hypoglycemic agents or insulin treatment ≥ 7 days during hospitalization. Cox proportional model was used to estimate the risk of cardiovascular events, all-cause mortality, new-onset diabetes.

Results: Among the patients who survived and discharged, 2,409 (21.9%) patients have hyperglycemia during hospitalization. While overall incidence of major cardiovascular events was comparable between the groups, the hyperglycemia group had a higher risk of incident acute myocardial infarction (HR = 1.53, 95% CI = 1.11–2.12) and revascularization (HR = 1.41, 95% CI = 1.02–1.94) compared to the control group. There was no difference in mortality between the two groups (HR = 0.92, 95% CI = 0.86–0.99). Among the patients who were alive for ≥ 1 year after discharge (N = 5,944), the hyperglycemia group had a higher risk of new-onset diabetes (HR = 10.10, 95% CI = 6.92–14.73).

Conclusions: In critically ill patients with AKI requiring CRRT, stress hyperglycemia during hospitalization is associated with an increased risk of coronary events and new-onset diabetes after discharge, suggesting aggressive screening and treatment in these patients.

TH-PO082

Association of Age, Frailty, and Strategy for Initiation of Kidney Replacement Therapy: A Post Hoc Analysis of the STARRT-AKI Trial

Amanda Y Wang,[1,2] Ary Serpa Neto,[3] Martin P. Gallagher,[1,4] Ron Wald,[5] Sean M. Bagshaw,[6] Rinaldo Bellomo.[3] The STARRT-AKI Investigators. *[1]The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia; [2]The Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia; [3]Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), School of Public Health and Preventive Medicine, Melbourne, VIC, Australia; [4]Liverpool Clinical School, UNSW, Liverpool, NSW, Australia; [5]Division of Nephrology, St. Michael's Hospital, University of Toronto, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON, Canada; [6]Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta and Alberta Health Services, Edmonton, AB, Canada.*

Background: Acute kidney injury (AKI) is a significant public health issue, and its incidence continues to rise. Older age is associated with a high risk of AKI and mortality, which often poses a clinical dilemma particularly with the implementation of invasive management such as renal-replacement therapy (RRT). The aim of this study is to assess the association of age and frailty with clinical outcomes in patients with severe AKI, according to accelerated and standard RRT initiation strategies in the STARRT-AKI trial.

Methods: This was a secondary analysis of an international randomized trial. Older age was defined as ≥65 years. Frailty was assessed using the clinical frailty scale (CFS) score and defined as a score ≥5. The primary outcome was all-cause mortality at 90 days. Secondary outcomes included RRT dependence and RRT-free days at 90 days. We used logistic and linear regression and interaction testing to explore the impact of age and frailty on clinical outcomes.

Results: Of 2927 patients randomized in the STARRT-AKI trial, 1616 (55.2%) were aged ≥ 65 years (median [IQR] 73.9 [69.4 - 78.9]). Older patients had greater comorbid cardiovascular and chronic kidney disease, were more likely to be surgical admissions and to receive vasopressors at baseline. Older patients had higher 90-day mortality (50.4% vs. 35.6%, adjusted-OR, 1.81 [1.53 to 2.13], p<0.001). There was no significant difference in RRT dependence at 90 days between older and younger patients (8.7% vs. 7.8%, adjusted-OR, 1.21 [0.82 to 1.79], p=0.325). Patients with frailty had higher mortality; but no difference in RRT dependence at 90-days. There was no significant interaction between age and CFS score in relation to mortality, RRT dependence at 90 days, and other secondary outcomes. There was no significant difference in the proportion of patients who received RRT in the standard-strategy stratified by age groups (adjusted-OR, 0.85 [0.67 to 1.08], p=0.180).

Conclusions: In this secondary analysis of the STARRT-AKI trial, older and frail patients had higher mortality at 90 days; however, there was no difference in RRT dependence. Mortality and RRT dependence were not modified by RRT initiation strategy in older or frail patients.

TH-PO083

Incidence of Hypophosphatemia and Clinical Outcomes in Patients Exposed to Kidney Replacement Therapy: A Post Hoc Analysis of the STARRT-AKI Trial

Javier A. Neyra,[1] Ehsan Ghamarian,[3] Sean M. Bagshaw,[2] Ron Wald.[3]
[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Alberta, Edmonton, AB, Canada; [3]University of Toronto, Toronto, ON, Canada.

Background: Patients receiving renal replacement therapy (RRT) are at increased risk of hypophosphatemia, which can predispose to functional muscle weakness and prolonged respiratory failure. The impact of hypophosphatemia on clinical outcomes in patients receiving RRT has been described in small retrospective studies, yet has not been evaluated in a contemporary, large prospective study. We conducted a secondary analysis of the STARRT-AKI trial to identify clinical parameters associated with incident hypophosphatemia during RRT and to examine the association of hypophosphatemia with clinical outcomes.

Methods: This was a *post hoc* study of the STARRT-AKI trial, a multinational RCT comparing 2 RRT initiation strategies in critically ill adult patients with AKI. Eligibility for this analysis included 1) receipt of RRT, 2) CRRT >24 hours or IHD/SLED >1 session, 3) normal serum phosphate on the day of RRT initiation, and 4) >1 serum phosphate measurement during RRT. A truncated hurdle model was built to determine which baseline characteristics were associated with any hypophosphatemia (<0.7 mmol/L) and severe hypophosphatemia (<0.5 mmol/L). The primary outcome of ventilator-free days (VFD) at 28 days was assessed with an inverse probability weighted zero-inflated negative binomial model and a win-ratio analysis (mortality as first hierarchy). Secondary outcomes of RRT dependence and mortality at 90 days were assessed with logistic regression.

Results: Of 1,940 patients included, hypophosphatemia occurred in 33%. Male sex, higher weight, standard-strategy arm, and higher baseline phosphate were associated with the occurrence of hypophosphatemia during RRT. Duration of hypophosphatemia was associated with lower first-day serum phosphate and the use of CRRT. Patients without severe hypophosphatemia during RRT had more VFD at 28 days (β 1.16 [95% CI 1.06- 1.27], p<0.001. A similar trend of VFD was found among those without any hypophosphatemia during RRT (β 1.06 [95% CI 1.0 - 1.1], p=0.05. These associations were consistent in the win-ratio analysis. There was no association between incident hypophosphatemia and RRT dependence or mortality at 90 days.

Conclusions: Among patients in the STARRT-AKI trial who received RRT, incident hypophosphatemia following RRT initiation was associated with fewer ventilator-free days.

TH-PO084

Kidney and Hepatic Support in Severe Septic Shock from Leptospirosis: A "Case Series" and the Adoption of a New Dialysis Protocol

Paolo Lentini, Giorgio Laudadio, Antonino Previti, Claudia Benedetti.
Nephrology, St Bassiano Hospital, Bassano del Grappa, Italy.

Background: Leptospirosis is a zoonosis caused by a gram-negative bacterium of the Spirochetales family(leptospiraceae) associated with high mortality if not treated in time. The infection is contracted through direct exposure with the urine of carrier animals. Clinical manifestations can range from pauci-symptomatic flu-like pictures, to manifestations with renal tubular damage (25-40%), to extremely severe conditions with potentially fatal multi-organ involvement (10-15%) known as Weil's disease. The aim of this work is to analyze the benefit in applying our treatment protocol in patients with septic shock with AKI and ALF in the ICU, in terms of dose reduction of vasopressors and improvement of blood chemistry parameters

Methods: The patients were all subjected to mechanical ventilation and the circulation supported by inotropes. All had severe AKI (Stage 3) and ALF (MELD Score> 16 or Bilirubin> 20 mg/dL). Patients underwent a combined treatment of CVVH (Amplya Medtronic ©) together with the use of CytoSorb ©. The CVVH was performed with Qb 150 ml/min, with a dialysis dose of at least 40 ml/kg/h (70% in pre-dilution). In four patients citrate was used as anticoagulant in the third patient the treatment was performed with a high pre-dilution (80%). The cartridge was replaced every 24 hours for three consecutive cycles. Antibiotic therapy was adequate considering an estimated removal of 40-50% of the recommended effective dose. Blood samples were taken to determine the rate of reduction of bilirubin, creatinine, WBC and PCR for each session

Results: 11 patients, all male, mean age 57 years, were enrolled following the diagnosis of leptospira-related septic shock. The starting conditions appeared homogeneous (Saps II 78 ± 6, SOFA 15 ± 5, Apache II 34 ± 6) with high total bilirubin values (> 20 mg/dl) and high inflammation indices (WBC, PCR, ESR). In all patients there was a progressive improvement in vital parameters with a reduction in the dose of vasopressors, ventilatory performance and in blood chemistry parameters (Total Bilirubin, RRS = 37.4%). All 11 patients survived after a prolonged stay in the ICU (LOS 31 +/- 3 dd).

Conclusions: Supportive treatment of hepatic and renal function in AKI and ALF performed with CVVH and Cytosorb was be safe and effective.

TH-PO085

A Young Man with an Unusual Pulmonary-Renal Syndrome

Joyita Bharati, Ashish Upadhyay. *Boston Medical Center, Boston, MA.*

Introduction: Pulmonary-renal syndrome commonly denotes an autoimmune disease characterized by pulmonary capillaritis and crescentic glomerulonephritis. Rarely, pulmonary-renal syndrome is from non-immune causes such as infections and heart failure. We report a rare cause of pulmonary-renal syndrome in a young man from Boston.

Case Description: A 27-year-old man from Boston presented with 1 week of fever, headaches, non-productive cough, and 1 day of dyspnea. He vaped nicotine and kratom and swam regularly in freshwater ponds for recreation. There were occasional rats noted at home. Physical examination was only remarkable for respiratory distress with hypoxia without hypotension or hypertension. Chest X-ray showed bilateral reticulonodular opacities. Sulfamethoxazole-trimethoprim and oral prednisone (40 mg twice daily) were started on day 1, considering pneumocystis jiroveci pneumonia. Doxycycline was started as the patient was exposed to pond water and rodents. Serum creatinine was 1.74 mg/dL on presentation and increased to 5.46 mg/dL over 72 hours with preserved urine output. Urine microscopy revealed numerous red and white blood cells without casts. On day 2, he developed one episode of hemoptysis and worsening hypoxia, requiring mechanical ventilation. Bronchoscopy was suggestive of diffuse alveolar hemorrhage (DAH). Intravenous methylprednisolone pulse 1 g daily and daily plasma exchange were then started, considering vasculitis (pulmonary-renal syndrome). ANCA and anti-GBM antibodies returned negative on day 5, and plasma exchange was stopped. Urine for leptospira PCR, sampled on admission, was reported positive on day 10. Microbiological tests were negative. The patient received doxycycline for seven days and cefepime for five days. Fever resolved in the first week of hospitalization. Kidney function, liver function, and platelets normalized within one week. Steroids were tapered and stopped after day 6. The patient was extubated on day 10. The final diagnosis was a leptospirosis-induced pulmonary-renal syndrome with hepatic and hematologic involvement.

Discussion: Leptospirosis is increasingly reported in the United States, especially in urban areas at risk of rodent exposure. It can present with severe kidney involvement and pulmonary hemorrhage with or without icterus. A high index of suspicion is crucial to reach the diagnosis in non-endemic regions.

TH-PO086

An Unfortunate Outing

Douglas R. Farrell, Martin Sedlacek. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Tickborn illnesses are increasing in prevalence in part because of more ticks surviving milder winters. Here we present a case of AKI secondary to babesiosis induced hemolysis in a self described lifelong city dweller who spent all her life in Manhattan without travelling, except one excursion to the lower Hudson valley for a wedding where she noted an insect bite after a group hike.

Case Description: A 66 year old woman with a history of MGUS and breast cancer treated with lumpectomy, radiotherapy and on hormone therapy presented with fever, nightsweats, weight loss, dyspnea and weakness for three weeks. A month before falling ill she had noted an insect bite after a group hike on a wedding. She was cachectic on exam. The patient had pancytopenia WBC 2.8 Hb 6.5g/dl Plat 124, elevated LDH 1057U/L, acute kidney insufficiency with creatinine 1.44mg/dl and mildly elevated bilirubin 1.3g/dl, ALT 50U/L, AST 72U/L. Albumin was low 2.4g/dL, CK was normal, HIV was negative, a Coombs test was negative, her blood group was A positive, ADAMST13 activity was mildly decreased 63%, C3 low 64mg/dl and haptoglobin was undetectable. No schistocytes or inclusion bodies were seen on a blood smear. The urinalysis showed moderate blood with no RBC, typical for free heme as in hemolysis or rhabdomyolysis. The patient's AKI and mild hyponatemia resolved with IV saline. A diagnosis of babesiosis was made by PCR. There was no coinfection by oher tick borne pathogens. The patient was successfully treated with Atovaquone and azithromycin and all symptoms resolved..

Discussion: The patient had pigment induced AKI from hemolytic anemia secondary to babesiosis. Babesia is a parasitie that utlizes RBC similar to malaria but without a liver phase, a smaller genome and not responding to artemisins. Babesiosis can cause severe illness in the elderly and the immunocompromised as this patient, who is a cancer survivor. As with malaria, certain blood groups reportedly have a protective effect but did not protect our patient (Non-B and Rhesus positive). A diagnosis of babesiosis is unexpected in a self described life long Manhattan resident who does not travel but went on a single outing to the countryside for a wedding. Babesiosis is an emerging global health problem and this patient illustrates how the numer of cases of babesiosis are likely to increase, even in unexpected places.

TH-PO087

Anaplasmosis: A Rare Case of Rhabdomyolysis and Interstitial Nephritis

Jordana Yahr, Sheldon Bastacky, Jyotsana Thakkar. *UPMC, Pittsburgh, PA.*

Introduction: Human Granulocytic Anaplasmosis (HGA) is a tick-borne illness caused by the bacterium *Anaplasma phagocytophilum*. Clinical manifestations of HGA include fever, malaise, but in severe cases can lead to neurologic dysfunction, liver dysfunction, and rarely, renal dysfunction. We present a case of anaplasmosis leading to acute kidney injury (AKI) requiring kidney replacement therapy. Kidney biopsy was suggestive of rhabdomyolysis with acute tubular injury and interstitial nephritis.

Case Description: A 59-year-old man presented to the emergency department with altered mental status. One week prior, he had experienced fevers and malaise. Laboratory data was significant for a platelet count of 23 x10^9/L, mild transaminitis, and rhabdomyolysis (CPK 29,818 IU/L). Serum creatinine was 2.8 mg/dL, baseline unknown, and peaked at 9.8 mg/dL. Urinalysis showed large blood, large protein, 10 red blood cells per high power field, and muddy brown casts on sediment. Spot urine protein/creatinine ratio was 2.37 g/g. Serum polymerase chain reaction was positive for *A. phagocytophilum*. He was treated with doxycycline and his mental status improved. His renal function worsened and hemodialysis was initiated. A kidney biopsy showed interstitial inflammatory infiltrates and focal acute tubular injury with myoglobin positive casts (Figure 1). His renal function improved and hemodialysis was discontinued. He did not require corticosteroid therapy.

Discussion: HGA is a tickborne illness whose incidence is increasing in certain locations. We present a rare case of HGA causing severe AKI requiring dialysis. This case is unique in that the kidney biopsy revealed both rhabdomyolysis with acute tubular injury and interstitial nephritis. AKI from HGA requires prompt diagnosis as antimicrobial therapy can lead to significant improvement in renal function. Nephrologists should consider HGA as a cause of AKI in tick endemic areas.

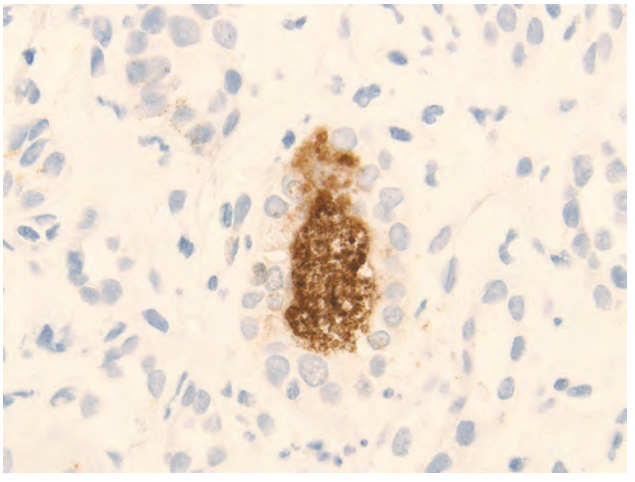


Figure 1: 600x. Myoglobin cast, myoglobin immunoperoxidase stain

TH-PO088

Perinephric Hematoma in Dengue Fever

Phoenix Xu, Melissa Notis, Daniel Stalbow, Priya Deshpande. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Dengue is a mosquito-borne infection that presents with a wide spectrum of symptoms, including fever, multi-organ failure, dengue hemorrhagic fever, and shock. Acute kidney injury (AKI) is commonly reported with dengue. We are presenting a unique presentation of dengue hemorrhagic fever and AKI.

Case Description: A 24-year-old man with a history of epilepsy, autism, and diabetes, presented with persistent fever with Tmax 104.4 F eleven days after returning from the Dominican Republic. On day 5 of admission, he developed stage III AKI (Cr increased from 0.7mg/dL baseline to 6.5mg/dL). At this time, our differential included acute tubular injury (ATI), glomerulonephritis, and DRESS syndrome. Other labs were significant for thrombocytopenia, elevated AST/ALT, CK 1017U/L, and haptoglobin 340mg/dL. Serologies showed elevated C3/C4 and negative ANA, dsDNA, and ANCA. Urine microscopy showed granular casts. On day 6, he acutely developed significant abdominal pain and CT abdomen/pelvis revealed a 7.6x6.9x8.3 cm left perinephric hematoma (hemoglobin declined from 11.6mg/dL on admission to 9.5mg/dL). Page kidney was suspected when he developed hypertension, and he was started on captopril. However, his kidney function continued to worsen and he ultimately required dialysis for refractory hyperkalemia. Infectious workup showed dengue IgM 10.15 and IgG 6.95. His course was complicated by secondary HLH (ferritin > 16,000; positive soluble IL-2R and CXCL9) and he was given a course of methylprednisolone. On day 13, the patient defervesced and started to show kidney recovery. Dialysis treatments were discontinued and steroids were tapered. Serum Cr was 1.3mg/dL on discharge and 1mg/dL two weeks later.

Discussion: Dengue can trigger AKI through several proposed mechanisms including rhabdomyolysis, immune complex mediated glomerular damage, hemolytic uremic syndrome, cytokine storm, and bleeding diathesis (mucosal, intramuscular, retroperitoneal bleeding have been reported). While the cause of AKI in this patient is likely multifactorial, the perinephric hematoma ("page kidney") is a novel manifestation of dengue hemorrhagic fever. Page kidney results from the external compression of the kidney by subcapsular hematoma and can result in renin-angiotensin system activation, leading to hypertension.

TH-PO089

Legionella-Induced Rhabdomyolysis Unmasks Underlying Metabolic Myopathy

Najiyah Salwa, Tripti Singh. *University of Wisconsin System, Madison, WI.*

Introduction: We present a case of rhabdomyolysis that illustrates the importance of having a broad differential while evaluating the etiology of rhabdomyolysis.

Case Description: 29-year-old male without any past medical history presented to the Emergency Department with headache, diarrhea, muscle weakness and pain for past 4 days. He was taking acetaminophen 1gm daily for myalgias for the past 3 days. Family history revealed sister with sickle cell trait. On examination, Temperature 103°F, HR 140 bpm, BP 140/90 mm Hg, respiratory rate 16/min, O2 saturation 100% on room air. His physical examination was unremarkable, except for significant tenderness on palpation of lower extremities. His laboratory data showed Na 131 mmol/L, K 2.9 mmol/L, AST/ALT: 162/889 U/L, creatine of 1.3mg/dl. Urinalysis showed 3+ blood, RBC 5-10/HPF and Granular cast 30-40/HPF. CK level was elevated to 96000U/L. His chest X-Ray showed right upper lobe consolidation. The nasal swab for COVID and flu were negative, and the urine test was positive for Legionella antigen. He was started on levofloxacin for treatment of legionella pneumonia. His CK levels continued to rise to 600,000U/L. Despite intravenous fluids, he became oliguric and required hemodialysis (HD) on day 4 of hospitalization. His extensive autoimmune and Myositis panel work-up for rhabdomyolysis was negative except for total and free carnitine levels which were elevated to 140 umol/L and 83 umol/L respectively, raising suspicion for Carnitine-palmitoyl transferase 1A deficiency which could present as myopathy triggered by fasting, fever or infection. He was discharged home on day 23 of hospitalization on HD and required HD for additional 5 weeks when he had renal recovery and was taken off dialysis. His kidney function continues to improve with the most recent serum creatine 1.2 mg/dL. He has been referred to a genetic clinic for further evaluation.

Discussion: Myopathies can be dormant, until there is a second hit that can unmask them making individuals susceptible to severe rhabdomyolysis with a common condition such as legionella pneumonia. Hence, broad differential and thorough work up should be sought in the cases where clinical scenario does not explain the findings.

TH-PO090

A 20-Year-Old Woman Presenting with Hemoptysis Most Likely Caused by H1N1 Influenza-Induced Thrombotic Microangiopathy

Aman Pal, Emmanuel A. Aydin-Ghormoz, Swati Mehta, Mj Hajianpour, Krishnakumar D. Hongalgi. *Albany Medical Center, Albany, NY.*

Introduction: Thrombotic Microangiopathy (TMA) is a pathological description which clinically presents with thrombocytopenia, microangiopathic hemolytic anemia, and organ dysfunction. The etiology of TMA is broadly classified into four categories: primary hereditary, primary acquired, secondary and infection associated. H1N1 influenza is a rare etiology of complement mediated TMA (CM-TMA) with there being under 30 cases reported to date, and its presentation with hemoptysis makes it a challenging diagnosis.

Case Description: A Caucasian female in her 20s presented to the hospital with a viral prodrome in setting of a new AKI (creatinine 8.2mg/dL), thrombocytopenia (platelet count 14,000/mm^3), and H1N1 influenza positive. She developed hemoptysis the next day, with no respiratory distress. Serology for antineutrophilic cytoplasmic antibodies, anti-glomerular basement membrane, and antiphospholipid antibodies were negative. CT chest was also negative for pulmonary hemorrhage. Plasma exchange was commenced until ADAMTS13 activity returned normal. The patient was further commenced on eculizumab after an aHUS/TMA/C3G gene panel was sent. She was found to have splice site variant of MCP/CD46, which was reiterated on a renal biopsy. The genetic results were relayed, including predisposition to future events and the importance of long-term eculizumab treatment.

Discussion: CM-TMA is a consequence of alternative pathway dysregulation with genetic mutations being far more prevalent than acquired antibodies. This dysregulation is generally not causative, rather predisposes affected individuals to CM-TMA. A proposed mechanism that can unmask these latent deficits include infections, such as Influenza virus. Its pathophysiology is thought to be related to the production of neuraminidase (NA), which results in platelet aggregation and endothelial injury. Our case highlights the importance of keeping a broad differential beyond classic pulmonary-renal syndromes in patients presenting with hemoptysis and TMA, while understanding the pathophysiology of infections unmasking genetic mutations in CM-TMA.

TH-PO091

Navigating Challenges: A Case of IgA-Dominant Postinfectious Glomerulonephritis

Aashvi R. Dalal, Michael Liben, Ronald D. Villareal. *NewYork-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY.*

Introduction: IgA-dominant postinfectious glomerulonephritis (IgA-PIGN) a variant of Acute Post Infectious Glomerulonephritis is caused by immune complexes that deposit in the glomeruli with dominance or codominance of IgA with C3. Commonly associated with gram-positive infections, especially in elderly and diabetic population, it manifests as renal dysfunction, hematuria, and proteinuria. Here, we present a case highlighting diagnostic and treatment challenges in IgA-PIGN.

Case Description: A 63-year-old male with congestive heart failure, hypertension, type 2 DM, and CKD stage 4 presented to the hospital for evaluation of fever and purulent left foot ulcer. Recent previous hospitalisation involved left food osteomyelitis complicated by MSSA bacteremia. Lab results revealed leukocytosis (12.85 x 103 /ul), hyperkalemia (6.1mmol/L) and elevated creatinine (7.29 mg/dl with baseline 2-3 mg/dl). Urinalysis showed >100 rbc/hpf, and >300 mg/dl protein with UPCR of 4.4 gm. C3, C4, ANA, ANCA, and hepatitis panel were unremarkable. Renal biopsy confirmed IgA dominant mesangial immune complex disease, post infectious, cellular crescents with severe acute interstitial nephritis (AIN). Granular pattern seen for 1+ IgA and 2+ C3 on immunofluorescence. On Electron Microscopy, increase in mesangial matrix and electron dense deposit was noted. Hemodialysis was initiated due to worsening kidney function. Since infection was the culprit, antibiotics were continued and steroids were initially withheld. However, prednisone was later started due to AIN findings, with reassuring evidence of negative blood cultures and no evidence of endocarditis on echocardiogram. Partial recovery led to discharge on hemodialysis with tapering steroids.

Discussion: Distinguishing IgA-PIGN from IgA nephropathy is crucial as treatments and prognosis differ. While IgA nephropathy warrants immunosuppression, IgA-PIGN relies on antibiotics for underlying infection management. As seen with this patient, challenges arose in initiating steroids due to concurrent AIN. This case highlights the need to consider IgA-dominant PIGN in sepsis patients with worsening renal function, often misdiagnosed as acute tubular necrosis or ischemic injury. Importance of high clinical suspicion in the prompt diagnosis in infection-related AKI is crucial for accurate diagnosis and intervention of IgA-dominant APIGN.

TH-PO092

Disseminated Coinfections of Cytomegalovirus and Herpes Simplex Virus in Lupus Nephritis

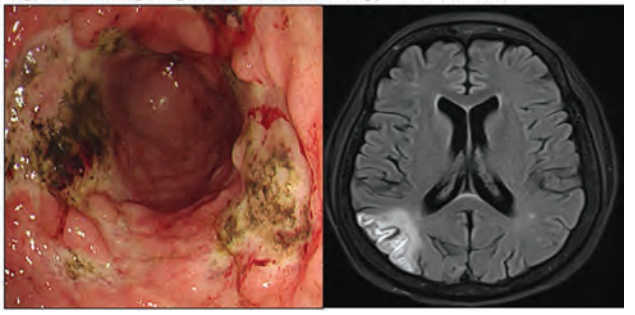
Bo Sun Park, Seokjin Hwang, Kewon Baik, Soyoung Lee, Sua Lee. *Eulji University School of Medicine, Daejeon, Republic of Korea.*

Introduction: Cytomegalovirus (CMV) and herpes simplex virus (HSV) are ubiquitous virus in general population, but these viruses are critical pathogen in immunocompromised patients, particularly with HIV. We report a case of disseminated coinfections of CMV and HSV in patient without HIV.

Case Description: A 57-year-old woman visited hospital due to renal dysfunction. She had preeclampsia during first pregnancy about 30 years ago and underwent steroid therapy due to nephrotic syndrome. After that time, renal function has been stable. Laboratory findings revealed MDRD-eGFR 19.0 ml/min/1.73m2, anti-dsDNA titer 88 IU/mL and decreased complement level. In the renal biopsy findings, lupus nephritis Class IV-G was confirmed, and then methylprednisolone and cyclophosphamide were administered. After second cyclophosphamide administration, she had fever and dyspepsia. In gastrointestinal endoscopy findings, multiple patches-like lesions and ulceration with a geographic shape were observed in the antrum with immunohistochemically staining showing CMV. Esophageal ulceration with feature such as molding of nuclear contours, margination of chromatin to the periphery of nuclei was consistent with HSV esophagitis. She suddenly developed a confused mentality, and brain MRI revealed regional patchy high signal on diffusion-weighted images and fluid-attenuated inversion recovery images at the right temporal-occipital white matter. In the CSF analysis, CMV PCR positivity was confirmed. Finally, serum CMV real time-PCR revealed $1.71*10^6$ copies/mL, and HSV type 1 PCR positive finding was observed. Ganciclovir and foscarnet were administered for the disseminated coinfections of CMV and HSV type 1. After administering for 8 weeks, she was successfully recovered. After discharge, SLE activity maintained stable, and she underwent hemodialysis for end-stage kidney disease.

Discussion: It is essential to consider the possibility of multiple opportunistic coinfections in patients suspected of being immunocompromised, even if patients are HIV negative.

Figure 1. Findings of gastrointestinal endoscopy and Brain MRI



TH-PO093

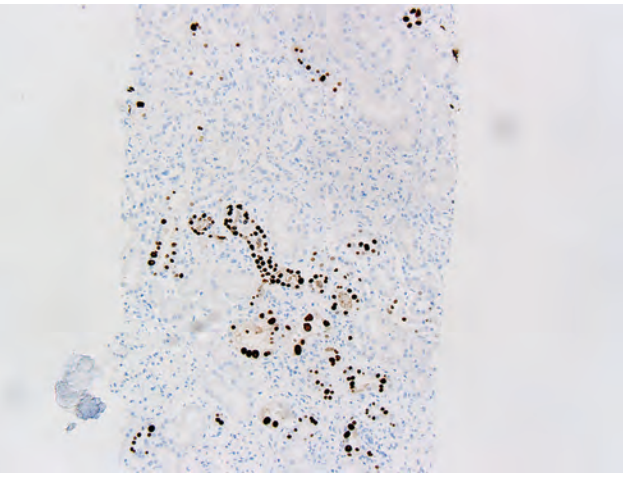
Native BK Virus Nephropathy in a Patient with Multiple Myeloma

Lynley Farmer, Manish K. Saha, Gerald A. Hladik. *The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC.*

Introduction: BK virus nephropathy (BKVN) is a common opportunistic infection in kidney transplant recipients and associated with increased risk of allograft dysfunction and loss; however, it is much less common for BK virus to cause harm in native kidneys.

Case Description: A 73M with PMH of IgG kappa multiple myeloma s/p autologous stem cell transplant (2010) on pomalidomide monotherapy in remission (2014) and bladder cancer s/p TURBT (2022) was admitted for worsening creatinine and hypercalcemia. Eight months prior to admission, the patient's previously normal serum creatinine (0.9 mg/dL) began to slowly rise and was stable around 1.4 mg/dL for the last several months. He established with nephrology outpatient and no etiology was determined for his CKD. On admission, labs showed elevated serum creatinine (2.59 mg/dL) and calcium (11.9 mg/dL). Symptoms only notable for fatigue. Urine sediment microscopy showed ATN. Labs also showed suppressed PTH (8.9 pg/mL) and elevated vitamin D 1,25-dihydroxy (74 pg/mL). The patient's myeloma panel was stable. A kidney biopsy was performed and showed polyoma (BK) virus nephropathy and foci of chronic (active) tubulointerstitial nephritis with eosinophils. Serum BK virus levels showed quantitative blood level of 912,000. After multidisciplinary discussion, IVIG was initiated for BKVN and viremia. The patient's pomalidomide was stopped.

Discussion: There is a growing literature of native kidney BKVN in patients with non-renal transplants, hematopoietic cell transplants, HIV infections, autoimmune disease, and hematologic malignancy. Kidney biopsy is the gold standard in diagnosis. In a recent systematic review, there are only 65 biopsy proven cases reported. BKVN needs to be on the differential diagnosis for immunosuppressed or immunocompromised patients with native kidney dysfunction and there should be a low threshold to perform a kidney biopsy in these patients.



SV40 IHC staining showing infected tubular epithelial cells

TH-PO094

AKI as the Initial Presentation of Polycythemia Vera with von Willebrand Disease in a Young Adult

Mayara L. Bechuate,[1] Renan G. Diniz,[1] Luciana G. Lutf,[1] Milena V. Cunha,[1] Felipe L. Ledesma,[2] Gabriel T. Sales,[1] Lucia Andrade.[1] *[1]Nephrology, University of Sao Paulo School of Medicine, São Paulo, Brazil; [2]Pathology, University of Sao Paulo School of Medicine, São Paulo, Brazil.*

Introduction: Polycythemia vera (PV) is a rare myeloid neoplasm that commonly affects individuals over 60 years of age, and 97% of cases are accompanied by a JAK2 mutation. Thrombosis and leukemia are common in PV. Renal manifestations (typically podocyte injury, IgA nephropathy or CKD) are rare, as is thrombotic microangiopathy (TMA). Here, we report a case of acute kidney injury (AKI) secondary to malignant hypertension and TMA, with subsequent diagnoses of PV and acquired von Willebrand disease (VWD).

Case Description: A 22-year-old male presented with altered mental status, nausea, vomiting and severely elevated blood pressure (BP, 220/130 mmHg). Labs showed hemoglobin of 18.4 mg/dL, hematocrit of 55%, 600,000 platelets, serum creatinine (SCr) of 3.74 mg/dL, proteinuria (2.2 g/g), no hematuria and no serum markers of hemolysis. Tests for secondary hypertension were negative. The hypertension resolved after treatment with a titrated intravenous vasodilator and oral antihypertensives. Hematologic investigation revealed a JAK2 V617F mutation, and bone marrow biopsy findings were consistent with PV. The von Willebrand factor (VWF) level was normal, although the VWF activity was very low. A diagnosis of PV with acquired VWD was made. After treatment with hydroxyurea, VWF activity increased and percutaneous renal biopsy showed diffuse mesangiolysis with focal segmental scarring in the glomeruli, moderate interstitial fibrosis and vascular intimal proliferation with narrowing of the lumina and arterial hyalinosis, consistent with reparative changes in TMA. Treatment with hydroxyurea was continued, and the patient remained under outpatient care, with a sustained SCr of 2.6 mg/dL (eGFR 35 ml/min/1.73 m^2) and BP of 123/64 mmHg.

Discussion: To our knowledge, this is the first report of a young patient with PV and VWD in whom the initial presentation was AKI due to malignant hypertension and TMA.

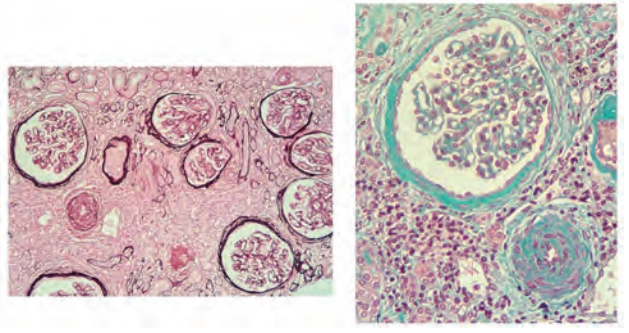


Figure 1: Findings consistent with reparative changes in TMA

TH-PO095

The Lysozyme Kidney

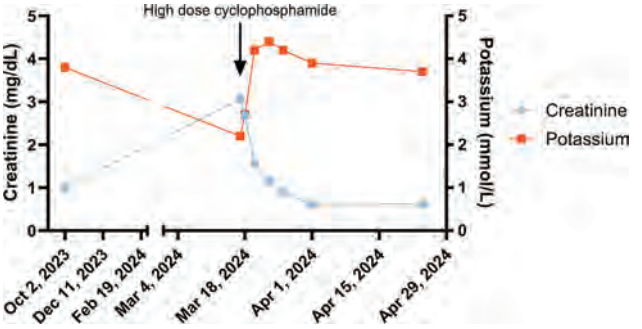
Nazish Khan, Evan Zeitler. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Introduction: Acute kidney injury (AKI) is a common complication of acute leukemias. Common causes include tumor lysis syndrome (TLS), leukemic kidney infiltration and injury due to nephrotoxic chemotherapy. Less recognized is lysozyme-induced nephropathy (LyN). Differentiating between common and less common causes of AKI in acute leukemia is critical for directing therapy.

Case Description: A 37-year-old man with history of schizophrenia, and type 2 diabetes presented with chest pain and dyspnea. Vital signs were significant for tachycardia and hypoxemia and labs demonstrated WBC count of 204, hemoglobin 8.5 and platelets 61. He had severe AKI (creatinine of 3.06 mg/dl from baseline of 1 mg/dl five months prior), hypokalemia, hypophosphatemia and hyperuricemia. He was diagnosed with acute leukemia and nephrology was consulted with concern for TLS. Urine sediment exam revealed granular debris. Kidney ultrasound was negative for kidney enlargement or hydronephrosis. He was admitted to the medical ICU for cytoreductive therapy with cyclophosphamide and hydroxyurea followed by induction chemotherapy with midostaurin. Once his leukocytosis improved, his kidney function steadily improved as well and creatinine was 0.6 mg/dl at discharge. Given his presentation with acute leukemia, hypokalemia, hypophosphatemia without evidence of other kidney injury, a diagnosis of LyN was made.

Discussion: Lysozyme is a small bactericidal enzyme that is freely filtered by the glomerulus. However, in acute leukemia due to the increased production, the reabsorbed enzyme becomes toxic to the proximal tubule, resulting in tubular injury characterized by hypokalemia, hypophosphatemia and often hyperuricemia. While rare, LyN should be considered in patients presenting with acute leukemia and AKI, especially when hypokalemia is present. If identified in time, treatment of primary malignancy results in resolution of kidney injury and may obviate the need for other therapies, including KRT.

	Cairo Bishop Criteria for TLS 3 days prior to or within 7 days of cytoreductive therapy	Patient's labs on presentation
Uric Acid	> 8 mg/dL	15.8 mg/dL
Potassium	>6 meq/L	2.7 mg/dL
Phosphorus	>4.5 mg/dL	1.6 mg/dL
Calcium	<7 mg/dL	8.8 mg/dL



Creatinine trend

TH-PO096

Maximal Change Disease

Andrew Murphy, Matthew Sangoi, Evani Patel, Kwon Soo Kim. *Pennsylvania Hospital, Philadelphia, PA.*

Introduction: Minimal change disease (MCD) accounts for the majority of cases of nephrotic syndrome in children and a minority of cases in adults. We report a case of MCD in a middle-aged patient with severe acute kidney injury (AKI) requiring dialysis who did not respond to steroids but eventually improved with rituximab.

Case Description: A 64 year old male with a history of mantle cell lymphoma (in remission) presented with reduced urinary output. Physical examination was notable for anasarca. Labs showed acute kidney injury (creatinine 4.31 mg/dL, baseline 1), hypoalbuminemia (albumin 2.7 g/dL), and nephrotic range proteinuria (urine protein creatinine ratio 22 mg/mg). His AKI worsened over several days as evidenced by rising creatinine to a peak of 9.1 mg/dL, volume expansion and anuria for which hemodialysis was initiated. A renal biopsy was performed, demonstrating podocytopathy with global foot process effacement, consistent with minimal change disease. A workup for recurrent lymphoma was unrevealing. He was treated with a course of prednisone 60 mg daily followed by a taper. After no improvement in renal function was seen with prednisone, he was considered steroid-refractory, and treatment with rituximab was started. He received two infusions. He remained dialysis dependent at discharge following a two month hospital admission but was subsequently weaned off dialysis with recovery of renal function two months later.

Discussion: AKI in MCD has been reported in approximately 20-30% of adult cases, some of whom may require dialysis. The pathophysiology of AKI in MCD is usually related to acute tubular necrosis. Interestingly, there was no tubular necrosis seen on biopsy for this patient. It was unclear as to whether the history of lymphoma was a contributing factor to this patient's presentation considering there was no evidence of lymphoma recurrence. However, a retrospective review examining MCD in non-Hodgkin lymphoma found that while they most often occur simultaneously, MCD may be diagnosed before or after non-Hodgkin lymphoma. Rituximab is considered to be an effective therapy for adult patients with frequently relapsing MCD, especially for those at risk of developing adverse effects of steroids. The mechanism by which rituximab improves outcomes in MCD is not fully understood, but the depletion of CD20 expressing cells using rituximab in MCD has led to the hypothesis that B cells have a pathogenic role in the condition.

TH-PO097

A Rare Cause of AKI in an Even Rarer Syndrome

Natasha Freeman, Joshua Herbert, Anthony M. Valeri, Dominick Santoriello. *New York-Presbyterian/Columbia University Irving Medical Center, New York, NY.*

Introduction: TEMPI syndrome is a rare condition characterized by Telangiectasias, Erythrocytosis, Monoclonal gammopathy, Perinephric fluid collections, and Intrapulmonary shunting. This case presents an unexpected - but unsurprising - cause of AKI in the setting of newly-diagnosed TEMPI syndrome.

Case Description: A 58-year-old man with a history of hypertension and type 2 diabetes mellitus presented with 4 days of fatigue, weakness, and myalgias. On exam, he was noted to have widespread telangiectasias on his face, mucosal membranes, and abdomen. Labs were notable for a hemoglobin of 18, creatinine of 2.7 (baseline of 1.0), paraprotein gap of 4.8, and microscopic hematuria. Kidney ultrasound noted bilateral echogenic kidneys, as well as trace perinephric fluid adjacent to the right kidney. 24-hour urine protein electrophoresis was significant for monoclonal IgG Lambda and Lambda Bence-Jones proteins. Taken together, these findings were consistent with TEMPI syndrome. A kidney biopsy was performed, which revealed acute tubular injury, interstitial edema with scattered extravasated RBCs, marked congestion of peritubular capillaries, and a probable small venous thrombus. He was therefore started on plasma cell targeted therapy as well as serial sessions of therapeutic phlebotomy, and discharged in stable condition with planned follow-up. Unfortunately, the patient returned 2 weeks later with severe sepsis secondary to pneumonia, and subsequently died.

Discussion: This case describes an AKI in a patient with newly-diagnosed TEMPI syndrome, which is broadly characterized as a plasma cell neoplasm with associated paraneoplastic syndrome. Beyond the simple educational value of exposure to such a rare disorder, an additional lesson can be gleaned from the kidney biopsy findings. Given the profile of TEMPI syndrome, and the UPEP findings of monoclonal and Bence-Jones proteins, the patient's AKI was presumed to be yet another manifestation of his plasma cell disorder, perhaps in the form of a monoclonal gammopathy of renal significance. The biopsy, however, implicated the erythrocytosis and consequent venous congestion and thrombosis as the likely primary cause of AKI. This case serves as an ever-important reminder to overcome one's anchoring bias, as well as to consider not just the apparent manifestations of a disease, but the sequalae and downstream effects of the underlying disease process.

TH-PO098

Steroid-Responsive AKI in a Patient with Hemophagocytic Lymph Histiocytosis (HLH)

Arfa Amjad,[1] Thin Thin Soe,[1] Muhammad Azhar.[2] *[1]SUNY Downstate Health Sciences University, New York City, NY; [2]New York City Health and Hospitals Corporation, New York, NY.*

Introduction: Acute kidney injury (AKI) in patients with hemophagocytic lymphohistiocytosis (HLH) is a frequent presentation that accounts for 30% to 50% of HLH cases. Most of these patients are managed with renal replacement therapy (RRT). We present a case that showed complete recovery of renal function to its baseline with steroid therapy in HLH patients without requiring RRT.

Case Description: 64 y/o, African American Male with a history of hypertension, chronic kidney disease stage 3a who presented with 2 days of dizziness and malaise. He was febrile to 102.9 Fahrenheit and was found to be in multiorgan failure with Acute Kidney Injury, Acute liver injury & cytopenia. Labs revealed serum creatinine of 12.62 mg/dL from a baseline of ~1.28 mg/dL, thrombocytopenia, anemia, hyperferritinemia, elevated ESR & CRP with Soluble CD25: 2321.7, Urinalysis positive for cast cells of > 20. Renal ultrasound was unremarkable. His calculated HScore showed > 95% probability of HLH (hypertriglyceridemia, hyperferritinemia, cytopenia, elevated AST with liver of 14.6 cm). His AKI was likely due to acute tubular necrosis related to HLH. He was started on dexamethasone for the treatment of HLH and was noticed to have a gradual recovery of renal function to its baseline without requiring renal replacement therapy.

Discussion: Hemophagocytic lymphohistiocytosis (HLH) is a rare heterogenous clinical syndrome involving massive activation and proliferation of natural killer cells and cytotoxic T lymphocytes, resulting in cytokine storm and hemophagocytosis. Acute kidney injury in HLH results from ischemic or inflammatory lesions of the renal tubules. The most frequent presentation of renal involvement is acute tubular necrosis; an autopsy series found such lesions in up to 45 % of patients with HLH. AKI typically exhibits poor prognosis in affected HLH patients; a retrospective analysis of 600 patients showed 53.3% mortality in patients with AKI vs 17.5% without AKI. Treatment of HLH usually requires specific treatment of underlying infection or malignancy, chemoimmunotherapy to suppress inflammation, and in some cases hematopoietic stem cell transplantation. Most of these patients with AKI are managed with renal replacement therapy. Our case was interesting since the renal function normalizes with a shorter duration of steroids than what is usually prescribed in these cases.

TH-PO099

An Interesting Case of Atypical Hemolytic Uremia

Jacob Lane. Medical University of South Carolina. *Medical University of South Carolina, Charleston, SC.*

Introduction: Atypical Hemolytic Uremia Syndrome is a rare condition characterized by anemia, thrombocytopenia with evidence of hemolysis and lack of evidence of shiga toxin preset. This disease has serious health considerations such as development of hypertension, renal failure and carries a high mortality. More recently identifiable genetic mutations and newer treatments with monoclonal antibodies working to block the complement mediated pathway have revolutionized the way this disease can be treated.

Case Description: 29 year old white female patient with a past medical history of TTP, obesity, and PCOS presented to an outside hospital (OSH) with abdominal pain, fever/chills and symptoms of upper respiratory infection. She was found to have AKI and concerns for atypical hemolytic uremic syndrome recurrence. She was treated for aHUS several months prior which was thought to have been triggered by influenza infection. She was found to have anasarca, hypertension and developed new onset seizures. MRI following seizure was concerning for PRES (posterior reversible encephalopathy syndrome), she also had spinal tap performed which demonstrated elevated pressures. She was started on CVVHDF given the concerns for increased intracranial pressures. Her blood pressure was controlled and kidney biopsy was performed with findings consistent with thrombotic microangiopathy (TMA). She was started on eculizumab prior to her transfer, this was continued. Here platelets and markers of hemolysis showed signs of improvement. She had genetic studies demonstrating heterozygous CD46/MCP mutation.

Discussion: This patient was found to have a genetic mutation likely responsible for repeated occurance of atypical hemolytic uremia syndrome. She responded well to the infusion of C5 inhibitor, eculizumab. This case was marked by multiple complications including seizures, hypertension, PRES all which complicated patient care. Patient currently continues to be dialysis dependent. She is also being continued on eculizumab as an outpatient.

TH-PO100

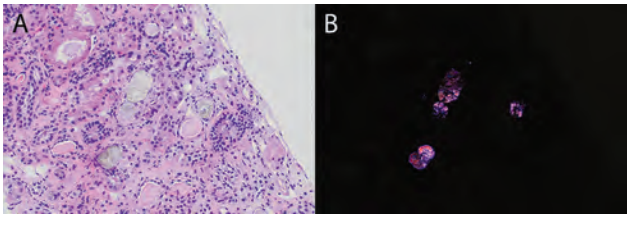
An Unusual Presentation of Oxalate Nephropathy in a Kidney Transplant Patient

Omar A. Ayah, Sarwat Gilani, Susan Wright. *The University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Introduction: Hyperoxaluria results from either inherited disorders of glyoxylate metabolism leading to hepatic oxalate overproduction (primary hyperoxaluria) or increased intestinal oxalate absorption (secondary hyperoxaluria).

Case Description: A 62-year-old male with a history of deceased donor kidney transplant 7 years prior, diabetes mellitus type 2, left foot ulcer presented for acute kidney injury (AKI) evaluation. He had undergone partial ray amputation of his left 4th and 5th digits for osteomyelitis and was started on 500mg erythromycin 4 times daily and doxycycline 100 mg twice daily to complete a 6-week course. He developed diarrhea shortly after erythromycin initiation, having up to 15 bowel movements daily for 30 days. He developed an AKI with peak serum creatinine (Scr) of 3.56mg/dL (baseline 1.1 -1.4), and serum bicarb of 16mmol/L. AKI was attributed to interaction of erythromycin and tacrolimus. Scr failed to improve after discontinuation of erythromycin. Scr was 2.35mg/dL on presentation to our hospital. Renal biopsy revealed AKI and several calcium oxalate crystals, with mild interstitial fibrosis. Urine microscopy was negative for calcium oxalate crystals. He was prescribed calcium carbonate tablets to increase oxalate excretion. Chart review showed oxalate crystals had been reported on urinalysis 2 years after his kidney transplant on routine follow up without further workup. His Scr was 1mg/dL and remained as such until his recent presentation.

Discussion: We suspect our patient has baseline predisposition to hyperoxaluria which was exacerbated by antibiotic use as well as a prolonged course of diarrhea, leading to alteration/ destruction of gut microbiota, including Oxalobacter formigenes, (a bacterium which metabolizes oxalate), leading to hyperoxaluria. Plasma oxalate is excreted by the kidney via glomerular filtration and tubular secretion. Increased production, dehydration and acidosis lead to accumulation and deposition in the tubules, causing AKI and oxalate nephropathy. Oxalate nephropathy should be considered in the differential for AKI



Histologic sections show polarizable intratubular calcium oxalate crystals in renal medulla (A&B. H&E section, 200x).

TH-PO101

Uveitis in Nephrology: A Presentation of a Case of Tubulointerstitial Nephritis with Uveitis (TINU)

Hasan T. Ozpolat, Dory E. Arevalo Salazar, Erika R. Bracamonte, Iyad S. Mansour. *Banner - University Medical Center Tucson, Tucson, AZ.*

Introduction: Tubulointerstitial nephritis with uveitis is a rare oculorenal disease. Patients with TINU usually present with kidney involvement, followed by ocular involvement. Here we presented a case of TINU initially presented with uveitis.

Case Description: A 24-year-old female patient with a red eye, pain, and blurry vision was diagnosed with uveitis/episcleritis a few months ago and was treated with

prednisone and cyclopentolate eye drops with mild improvement in her symptoms. She visited her primary care physician recently for the evaluation of intermittent vomiting that started a few weeks ago with decreased oral intake. Laboratory tests revealed elevated acute phase reactant (ESR> 120 mm/h, CRP; 120 mg/dL), anemia (10.5 g/dl), significant renal failure (BUN: 43 mg/dl, creatinine 6.0 mg/dl), urinalysis was positive for WBCs, urine microscopy showed many hyaline casts, a few granular casts, and a WBC. The urine protein-to-creatinine ratio was 457 mg/day. The antinuclear antibody (ANA), and antineutrophil cytoplasmic antibody (ANCA) results were negative, and the angiotensin-converting enzyme level was within normal levels. Chest CT and echocardiography findings were unremarkable. Renal biopsy findings were consistent with acute interstitial nephritis (AIN), non-caseating granuloma, and significant eosinophilia (Figure 1). In the setting of recent uveitis with AIN, the patient was diagnosed with TINU. Pulse steroid (methyl-prednisone, 250 mg IV) was initiated, followed by a steroid tapering regimen (1 mg/kg PO). The patient was followed up in our outpatient clinic with normal kidney function.

Discussion: TINU should be considered in the differential diagnosis with other oculorenal diseases including Sjogren's syndrome, sarcoidosis, tuberculosis, and Behcet's disease.

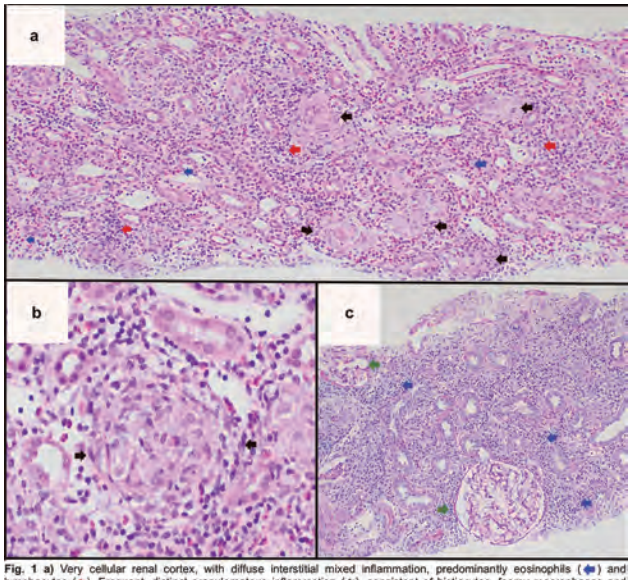


Fig. 1 a) Very cellular renal cortex, with diffuse interstitial mixed inflammation, predominantly eosinophils (⬅) and lymphocytes (⬅). Frequent, distinct granulomatous inflammation (⬅), consistent of histiocytes, foamy macrophages and loose rim of lymphocytes. [H&E x40] b) Close-up of the granulomatous inflammation (⬅), consistent of histiocytes, foamy macrophages and loose rim of lymphocytes. [H&E x400] c) Unremarkable, spare glomeruli (⬅) with a background of diffuse mixed interstitial inflammation, mostly consistent of eosinophils and lymphocytes (⬅). [PAS x40]

TH-PO102

A Unique Presentation of Thrombotic Microangiopathy with Cardiac Tamponade

Eduardo Pino Domenech,[1,2] Andrew A. Moses,[1,2] Jordan L. Rosenstock,[1,2] Maria V. DeVita,[1,2] Tasnin M. Khan,[1,2] Tina Kana.[1,2] *[1]Lenox Hill Hospital, New York, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, NY.*

Introduction: We are presenting a unique case of TMA that was complicated by cardiac tamponade.

Case Description: 55-year-old female with hypertension, chronic tooth infection, multiple ED visits over the past month for facial and bilateral leg swelling. Workup revealed creatinine of 2.1mg/dl rising to 3.1mg/dl with 2.9g of proteinuria and hematuria. She denied diarrhea, dysuria, abdominal pain, cough, fever, headache or confusion during the last month. Lab data revealed platelets 156K and hemoglobin 8.6g/dl, with a normal coagulation panel. POCUS performed showing kidney with mildly increased echogenicity and normal size; also pericardial effusion noted. Formal Echo revealed a moderate pericardial effusion with systolic invagination of the right atrium, an evidence of Cardiac Tamponade(CT). Urgent pericardiocentesis was performed, showing hemorrhagic pericardial effusion and hemosiderin laden macrophages suggestive of subacute hemorrhage and delayed cardiac tamponade. Glomerulonephritis and infectious panel were normal, including C3/C4. sCr increased to 4.48mg/dl, platelets and hemoglobin decreased to103K and 7.6g/dl respectively; LDH level was 789 and Haptoglobin<10, with abundant schistocytes in peripheral smear. Kidney biopsy showed thrombotic microangiopathy(TMA). Atypical Hemolytic Uremic Syndrome complement functional panel resulted non-diagnostic, AdamsTS13 activity was normal, and genetic testing is pending. Patient received Eculizumab and started on dialysis. Platelets and Haptoglobin, normalized in one week after Eculizumab therapy, LDH decreased to 582, and continue down trending in further labs.

Discussion: Pericardial effusion is not a common complication of TMA, and only a few cases are reported, mostly in the pediatric literature. Many of these cases are typical Hemolytic Uremic Syndrome with confirmed E. coli O157:H7 infection, or after hematopoietic stem cell transplantation, with only one case reported complicated by CT. This case proves the wide variety of clinical signs/symptoms, laboratory, and radiologic findings that TMA can have. Prompt diagnosis with kidney biopsy is key to confirm the diagnosis. Early initiation of specific therapy correlates with higher chances of better outcomes.

TH-PO103

Renal-Limited Antiphospholipid Syndrome: No-Less-than-Catastrophic

Remy Fadel, Trevor C. Stevens, Edward Gould. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Antiphospholipid syndrome (APS) is clinically defined by recurrent vascular thrombosis or pregnancy morbidity and the presence of at least one antiphospholipid antibody (aPL). On rare occasions renal limited disease can lead to acute kidney injury. We herein describe a case of a 26-year-old female with acute renal failure secondary to APS-mediated complete cortical necrosis, whose diagnostic journey began with an elevated partial thromboplastic time (PTT).

Case Description: A 26-year-old female with no medical history presented with vomiting and diarrhea caused by adenovirus. She had a prior pregnancy with near-full-term delivery. On admission, her creatinine was elevated at 10 mg/dL, and her urine protein/creatinine ratio was 14 g/day. Her PTT was prolonged at 75s and she tested positive for aPL. Other work up, including ANA, was negative. Peripheral blood smear did not reveal schistocytes, and her complement levels and atypical hemolytic uremic syndrome panel were normal. Renal biopsy (Figure 1) showed diffuse cortical necrosis and marked TMA with extensive fibrin thrombi involving all arterioles, arteries, and glomeruli. She required long-term hemodialysis and was initiated on Warfarin with follow up with hematology. Repeat antibody testing at 6 months was negative.

Discussion: This case illustrates that intrarenal TMA can be the initial presentation of primary APS. Morphological abnormalities of TMA alone are not sufficient for a diagnosis and necessitate further investigations. In this patient's case, the biopsy findings, prolonged PTT, and positive aPL favor a diagnosis of APS nephropathy. There have been some case reports of adenovirus associated with transient aPL and thrombosis. However, the clinical significance of this remains unknown. No consensus exists on treating renal limited APS beyond standard anticoagulant therapy for APS. A deeper understanding of the pathogenic mechanisms in APS nephropathy may lead to targeted therapies.

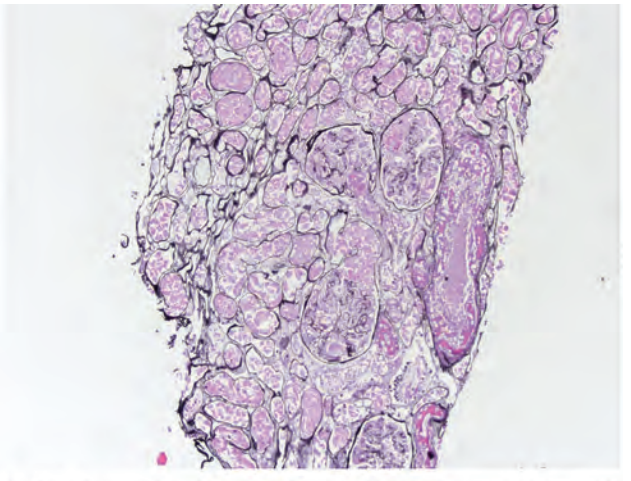


Figure 1: Light microscopy shows diffuse cortical necrosis and tubular injury. Thrombi can be observed in the arterioles and glomeruli.

TH-PO104

Recurrent Bilateral Renal Artery Thromboembolism as a Late Complication of Bentall Procedure with Mechanical Aortic Valve

Juan Salvatierra,[1] Rohini Rao,[2] Rafael O. Duchesne.[1] *[1]Hamilton Medical Center, Dalton, GA; [2]Riverview Regional Medical Center, Gadsden, AL.*

Introduction: Thromboembolic events are uncommon in patients who have undergone ascending aorta replacement with an aortic graft and composite (mechanical or bioprosthetic) valve, also known as Bentall procedure. We present a rare case of recurrent bilateral renal infarction from a cardioembolic source, i.e. Bentall procedure with mechanical aortic valve.

Case Description: A 51-year-old man with history of right renal infarct and non-insulin-dependent diabetes presented to the emergency department complaining of left flank pain of 1 hour duration. He was compliant with warfarin. He had undergone

Bentall procedure with mechanical valve for bicuspid aortic valve fifteen years before. Examination revealed blood pressure 143/101 mmHg, a systolic murmur with opening and closing click and left flank tenderness. Laboratory analyses showed leukocytosis, creatinine 2.5 mg/dL (baseline 1.4), INR 1.64, 2+ proteinuria and 1+ hematuria. CT angiography of the abdomen revealed a clot within an anterior branch of the left renal artery and a large infarct. He was started on unfractionated heparin and hydromorphone via PCA pump. Vascular surgery deemed him not a revascularization candidate for being outside an 1-hour window. He was managed expectantly and maintained good urine output with stable creatinine. He was discharged home on a higher warfarin dose with enoxaparin bridging. On three-week follow-up, he felt well and creatinine had improved to 2 mg/dL, INR 2.45 was below goal of 2.5-3.5.

Discussion: Renal infarct should be a differential diagnosis of flank pain in patients with prosthetic heart valves. Our patient's multiple thromboembolic events were secondary to subtherapeutic INR in the setting of Bentall procedure. Revascularization with percutaneous endovascular rather than surgical approach is preferred if feasible. In patients with a mechanical valve, anticoagulation with unfractionated or low molecular weight heparin is recommended.

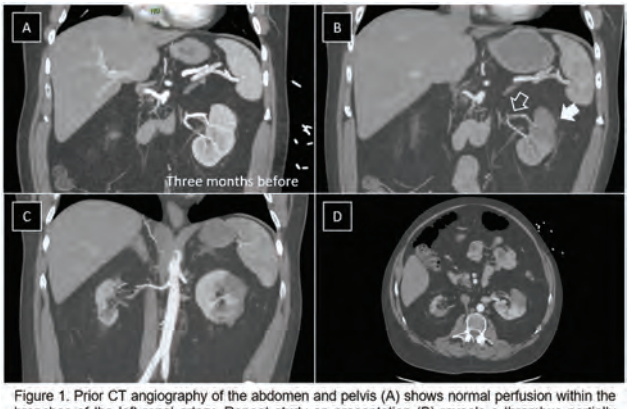


Figure 1. Prior CT angiography of the abdomen and pelvis (A) shows normal perfusion within the branches of the left renal artery. Repeat study on presentation (B) reveals a thrombus partially occluding one of these branches (hollow arrow) and a large infarct within the left kidney (solid arrow). Bilateral chronic renal infarcts with right kidney atrophy are also identified (C and D).

TH-PO105

Renal Cortical Necrosis in Pregnancy: A Rare Yet Critical Condition with Varied Pathogenic Mechanisms

Hillary Gan, Nerihan Hadji, Prashant N. Bhenswala, Mahmoud Abdelaziz, Richard L. Barnett, Mala Sachdeva, Purva D. Sharma. *Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY.*

Introduction: Renal cortical necrosis (RCN) is a form of severe AKI characterized by ischemic necrosis of the renal cortex, resulting from severely diminished renal arterial perfusion involving vascular spasm and intravascular thrombosis. RCN is an uncommon entity, with a higher incidence in developing countries. We report two cases of RCN in the postpartum setting, each diagnosed differently, with two different pathogenetic mechanisms

Case Description: Case 1: 40-year-old female who had an uneventful dilation and evacuation (D&E) for fetal anomaly presented with weakness and decreased urination for 1 week. Labs revealed a creatinine (Cr) of 20 mg/dl, BUN of 115 mg/dl, UA revealed 30 mg/dL of protein, 1 RBC/hpf. CT abdomen/pelvis (CTAP) did not reveal obstruction. Patient underwent repeat D&E for retained products. After no improvement in kidney function, she was initiated on hemodialysis (HD). Serologic workup was negative. Renal biopsy revealed severe thrombotic microangiopathy (TMA) involving glomeruli, arterioles and arteries extensively, together with diffuse acute tubular necrosis, suggestive of cortical infarction. Given concern for a complement-mediated process in the setting of profound TMA, she received Eculizumab empirically and was evaluated for atypical hemolytic-uremic syndrome. Functional and genetic complement testing was negative. After 6 weeks, patient remains HD dependent, however with improved urine output. Case 2: 39-year-old female presented for induction of labor and subsequently had a cesarean section complicated by severe postpartum hemorrhage and shock requiring 5 Units PRBCs, 3 Units of FFP due to DIC and coagulopathy. She developed anuric AKI with a Cr of 4.8 mg/dl. CTAP revealed reverse cortical rim sign consistent with RCN. HD was initiated given worsening volume status and electrolyte abnormalities. Patient remains HD dependent.

Discussion: RCN is a rare but devastating cause of obstetrical AKI, often resulting in poor outcomes. The mechanisms can include severe hypoperfusion and vascular endothelial injury. These cases illustrate the different pathogenetic mechanisms of RCN in obstetric AKI and its possible diagnosis by imaging and kidney biopsy. Work up for an underlying cause including complement testing may be indicated in some cases and may affect management.

TH-PO106

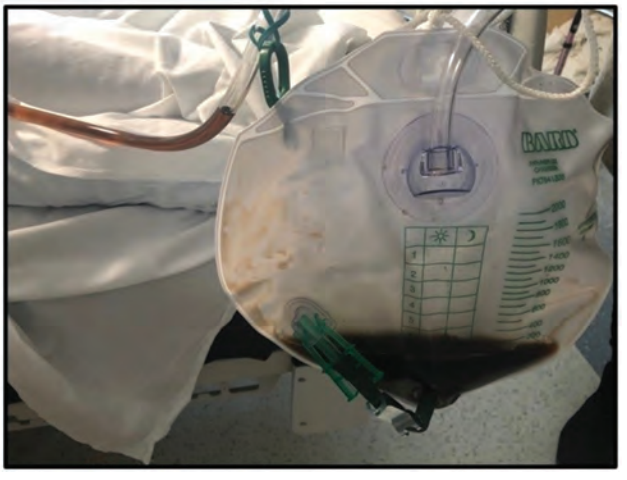
Exertional Rhabdomyolysis Requiring Kidney Replacement Therapy in a Man with Sickle Cell Trait

Steven T. Heidt, Roger A. Rodby. *Rush University Medical Center, Chicago, IL.*

Introduction: Sickle cell trait (SCT) is generally asymptomatic. Rarely, patients with SCT develop exertional rhabdomyolysis (ER) after strenuous exercise. ER can lead to compartment syndrome, DIC, and myoglobinuric AKI. We present a case of acute oliguric renal failure requiring renal replacement therapy (RRT) secondary to ER in a patient with previously unknown SCT.

Case Description: After completion of police academy training, a 39 y/o black man developed bilateral leg weakness and muscle spasms. Exercise consisted of push-ups, sit-ups, and a one-mile run. He had no significant PMH, no FH of SS disease or trait, and took no medications. Exam was notable for weakness and diffuse muscle tenderness. Initial laboratory findings included serum creatinine 2.0 mg/dL, lactic acid 8.8 mmol/L, and creatine kinase (CK) 1,516 U/L. Urine was brown (Figure) and urinalysis had 4+ blood with 1 RBC/hpf. Urine drug screen was negative. His CK level peaked at 565,070 U/L and he was started on CVVHD for worsening acidosis. Work-up had normal TFTs and negative autoimmune and glycogen storage disease panels. Hemoglobin electrophoresis showed 35.1% hemoglobin S, consistent with SCT. He remained on RRT for 18 days. He ultimately had full recovery of renal function.

Discussion: SCT may be present in up to 300 million patients worldwide and is typically asymptomatic; ER is a very rare but established condition associated with SCT. We present a patient who completed relatively low-intensity exercise, yet still developed ER requiring RRT. Our patient developed ER because of a mandated training required for policy academy admission. Screening protocols for SCT in those whose careers involve heavy exercise, such as police work or the armed forces, can be seen as discriminatory. We conclude that further study is required in patients with SCT who develop ER to determine if secondary factors impact the risk of ER.



Tea colored urine on day one of hospital admission.

TH-PO107

Black Urine after Surgery: Rare Cause of Rhabdomyolysis and Malignant Hyperthermia Syndrome (MHS)

Harshil Fichadiya, Marie C. Hogan. *Mayo Clinic Minnesota, Rochester, MN.*

Introduction: Mutations in RyR1, DHP, SH3 and STAC3 predispose to MHS by increasing cytosolic calcium levels. Most mutations are AD with incomplete penetrance explaining phenotypic differences. RyR1 is a Ca channel located on skeletal muscle sarcoplasmic reticulum, mediates calcium influx for muscle contraction. Activating RyR1mutations cause sustained calcium influx, muscle contraction and hypermetabolism, acidosis, hyperthermia and rhabdomyolysis, following exposure to volatile anesthetics +/- succinylcholine. In addition to MHS, RyR1 mutation has been associated with Central Core Disease, Multi-minicore disease, Centronuclear myopathy, congential fiber-type disproportion and predispose to statin-induced myopathy and exertion induced rhabdomyolysis

Case Description: 49 y/o Caucasian male s/p bony hearing aid placement for congenital mixed hearing loss developed black urine, myalgia and masseter spasm in the immediate postop period after iv succinylcholine 120 mg and propofol anesthesia. He described dark urine post OR in 2015, proximal muscle weakness after exertion, lifelong muscle cramps, + FHx of cramps, previous uncomplicated anasthesia for appendectomy at 18yr. Dipstick urinalysis revealed large hematuria, proteinuria & 3-10 RBC on microscopy, with large myoglobin. Post OR CPK was 14143U/L, peaked at 74320U/L POD1 and improved to 2682U/l on POD 5 with aggressive IVF. Electrolytes and creatinine

remained normal, improving hepatic transaminitis. Whole genome sequencing revealed heterozygous, pathogenic variant in the RYR1, specifically c.1840C>T(p. Arg614Cys)

Discussion: Pathogenic variant in RYR1 are the commonest genetic causes of MHS, wide spectrum neuromuscular disorders and congenital myopathies. MHS is characterized by a severe reaction to specific anesthetic drugs, a result of uncontrolled skeletal muscle hypermetabolism. Symptoms are preceded by specific anesthetics, with or without depolarizing muscle relaxant, like succinylcholine. Affected individuals can have severe muscle rigidity or spasms, cardiac arrhtymias, hyperthemia, rhabdomyolysis. Rarely, at risk patients demonstrate symptoms after intense physical activity. Contracture test with caffeine-halothane with high sensitivity may be used for screening. Genetic testing may not identify all involved genes, avoidance of triggers may be preferred. Treatment includes dantrolene, electrolytes management and aggressive IVF

TH-PO108

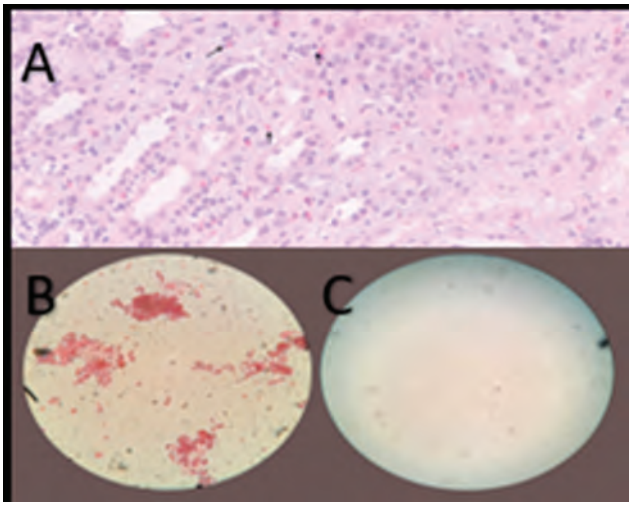
A Unique Case of Benralizumab Treatment for Drug-Induced Acute Interstitial Nephritis

Alexander Saadia, Assaf Potruch, Aviv Talmon. *Hadassah University Medical Center, Jerusalem, Israel.*

Introduction: Acute interstitial nephritis (AIN) is a common cause of acute kidney injury (AKI), which may be induced by infections, systemic and localized autoimmune processes, or most commonly drug-induced. AIN may result in fibrosis and permanent kidney damage. Treatment options for drug induced AIN mainly steroids, although evidence of efficacy is lacking.

Case Description: A 55-year-old male, presented with abdominal pain, vomiting and anuria following excessive alcohol intake. Medical history included hypertension treated with ramipril and amlodipine, and recently, etoricoxib for back pain. Patient developed severe AKI despite fluid resuscitation and cessation of Etrocoxib, and required hemodialysis. Kidney biopsy showed AIN with numerous eosinophil infiltrates (figure 1A). Prominent eosinophiluria was observed in the urianalisis persistently throughout treatment (figure 1B). High-dose steroids intravenously did not improve urine output. Following informed consent Benralizumab (30 mcg SC) was given off label. Kidney function recovered immediately, with polyuria ensuing within hours (<12 hr) of treatment, and coincided with a complete disappearance of eosinophils and leukocytes in the urine at 48 hours after treatment (figure 1C). Patient was weaned off dialysis within a few days while renal function normalized.

Discussion: Benralizumab, a humanized monoclonal antibody targeting interleukin 5 (IL5) α receptor, is used for severe eosinophilic asthma. Benralizumab has been used in different diseases in which pathophysiology mechanism implicates eosinophil-mediated response such as eosinophilic cystitis and eosinophilic esophagitis. This case highlights a future potential use of anti IL5 receptor treatment for AIN which involves rich eosinophilic inflammation of the kidneys. To our knowledge this is the first reported case of Benralizumab treatment for drug induced AIN.



TH-PO109

Fluid Conundrum: Unraveling a Case of Urinothorax

Anvitha Rangan, Mariana Vanoye Tamez, Paulo Henrique Rodrigues Assis, Vignesh Ponnusamy. *Landmark Medical Center, Woonsocket, RI.*

Introduction: Pleural effusion of extra-vascular origin (PEEVO) is an effusion that does not originate from the pleural vasculature. Urinothorax, an infrequent form of PEEVO, is the leakage of urine into the pleural cavity due to obstructive uropathy, iatrogenic, or blunt trauma to the genitourinary (GU) system. We report a case of urinothorax occurring after nephrostomy.

Case Description: A 74-year-old male with prior bilateral (B/L) obstructing renal calculi and ureteral stents presented with oliguria and acute renal failure. A nephrostogram showed severe right hydronephrosis and occluded ureteral stent. The stent was removed, and a nephrostomy tube was placed. Persistent hematuria led to tube exchange and stone removal, which revealed a large blood clot in the renal pelvis. The procedure was complicated by bleeding and limited visualization. Post-operatively, the patient developed transient hemorrhagic shock, managed with blood transfusions. A CT scan revealed right hydronephrosis, blood in the collecting system, and a new large right pleural effusion. A CT-guided chest tube drained 2L of serosanguinous fluid. Analysis showed the fluid was transudative, ruling out a hemothorax. The fluid had elevated creatinine (5) and low pH (7.0). The ratio of pleural fluid to serum creatinine (PF/SCr) >1. A renal angiogram revealed active bleeding from the right interlobar artery, which was later embolised.

Discussion: Urinothorax develops rapidly, presenting with dyspnea and chest pain. Raised intraperitoneal or retroperitoneal pressure leads to the direct flow of urine through diaphragmatic pores or indirectly via the retroperitoneal and pleural lymphatics. Identifying anatomic defects like reno-pleural fistulas and urinomas is crucial to prevent recurrence. Biochemically, urinothorax is a transudative effusion with characteristically low pH (<7.40). The glucose and protein content are low. A PF/SCr >1 is the hallmark of urinothorax, with >90% sensitivity. Renal scintigraphy can detect urine migration into the pleural space if imaging is inconclusive. This patient likely sustained an iatrogenic injury to the renal system and interlobar artery, which led to leakage of urine and blood into the retroperitoneal space, resulting in a urinothorax. This rare but underdiagnosed entity must be an important consideration for new onset pleural effusion following GU procedures or obstructive uropathy.

TH-PO110

In Vivo Pharmacokinetic Evaluation of Molnupiravir in Patients with Severe CKD

Qiuling Fan. *Shanghai General Hospital, Shanghai, China.*

Background: This study aims to explore the plasma concentration of Molnupiravir in patients with severe renal insufficiency, providing a basis for rational clinical use of drugs.

Methods: Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to detect the plasma concentrations of MPV and NHC. Plasma working calibration standards for MPV and NHC were prepared by diluting 1.0, 5.0, 10.0, 50.0, 100, 500, 1000, and 2500 ng/mL in blank, drug-free plasma. Add 10 μl of internal standard solution to 100 μl of plasma sample. Quality control (QC) samples include high QC (HQC: 2000 ng/mL MPV and NHC), medium QC (MQC: 200 ng/mL MPV and NHC), low QC (LQC: 2.0 ng/mL MPV and NHC), and quantitative Limit (LLOQ: 1.0 ng/mL MPV and NHC). All analytes were extracted by protein precipitation using acetonitrile at a ratio equivalent to 3:1, and QMPV and QNHC were evaluated by calculating the ratio of plasma concentrations.

Results: A total of four patients with stage 4/5 chronic kidney disease were included in the study. The blood samples collected 12 hours after taking the drug showed that the patients' MPV blood drug concentration was at a low level, while NHC and healthy subjects (C12h: Compared with patients with mild to moderate renal insufficiency (16.7 ng/mL) and patients with mild to moderate renal insufficiency (C12h: 31.1 ng/mL), patients with severe renal insufficiency have higher C12h than patients with mild to moderate renal insufficiency (43~1600 ng/mL). Among them, the NHC plasma concentration in patients with stage 5 chronic kidney disease is 1600 ng/mL, which is maintained at a relatively high level.

Conclusions: After patients with severe renal insufficiency were administered 800 mg/12 hours according to the instructions, MPV was rapidly hydrolyzed to NHC in the body and maintained at a low level. The NHC is significantly higher than that of patients with mild to moderate symptoms, especially those with stage 5 chronic kidney disease. The blood drug concentration is equivalent to Cmax, which suggests that when used clinically in patients with uremia, the dosing interval should be adjusted to avoid drug accumulation and occurrence of AEs.

TH-PO111

A GFR-Independent Method for Measuring Kidney Tubular Function

Isaac Z. Karel,[1] Amandeep Bajwa,[2] Navjot Pabla.[1] *[1]The Ohio State University, Columbus, OH; [2]The University of Tennessee Health Science Center, Memphis, TN.*

Background: Glomerular filtration rate (GFR) is the main functional index of kidney health and disease. Currently, no methods are available to directly measure tubular mass and function. Here we report a serendipitous finding that the in vitro cell viability dye resazurin, can be used in mice as an exogenous sensor of tubular function.

Methods: Mouse models of renal ischemia reperfusion, cisplatin nephrotoxicity, and rhabdomyolysis were used to assess the utility of resazurin as a sensor of tubular function and injury. Resazurin and its metabolites were measured in the blood and urine by fluorescence and mass spectrometry measurements.

Results: Intravenously injected resazurin exhibited significant plasma protein binding and was found to mainly undergo tubular secretion. Mechanistic studies showed that the blue-colored weakly fluorescent resazurin is taken up by tubular cells through the organic anion transporters, followed by conversion to highly fluorescent pink-colored resorufin by mitochondrial and cytosolic reductases, glucuronidation of resorufin to an orange-colored resorufin β-d-glucuronide, and subsequent efflux into the urine. We report a simple method where the intravenous injection of resazurin is followed by measurement of fluorescent metabolites in the urine provides a sensitive read-out of tubular function. In bilateral ischemia reperfusion, cisplatin nephrotoxicity, and rhabdomyolysis-associated AKI models, the resazurin-based method was able to sensitively detect loss of tubular function much earlier than the increase in serum creatinine levels. Strikingly, in mice with unilateral ischemia reperfusion injury, and genetic mutation-linked kidney hypoplasia, the resazurin-based method was able to detect loss of tubular mass and function despite normal GFR levels.

Conclusions: These findings establish the preclinical utility of resazurin as a rapid and sensitive exogenous marker of tubular function and support future examination in larger animals for potential clinical translation.

Funding: NIDDK Support

TH-PO112

An Artificial Intelligence-Based Program Significantly Reduces ESA (Erythropoiesis-Stimulating Agent) Use and Maintains Hemoglobin

Michael E. Brier,[1,2] Adam E. Gaweda.[1] *[1]University of Louisville, Louisville, KY; [2]VA Robley Rex Medical Center, Louisville, KY.*

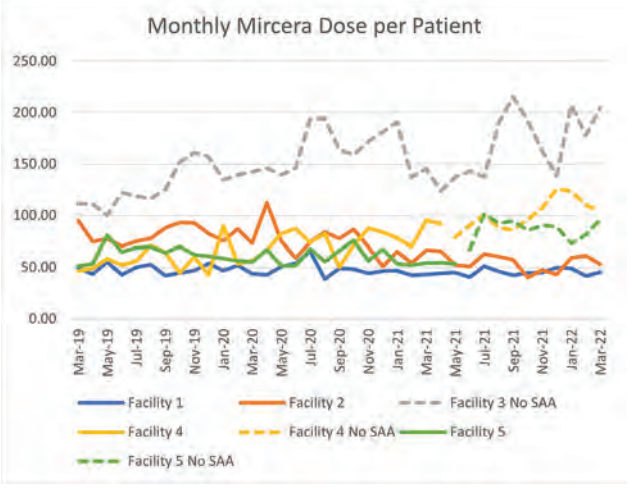
Background: ESAs have experienced dramatic dose fluctuations prompted by reimbursement challenges, shifting targets, and poorly designed anemia management protocols (AMP). The package insert recommends using the lowest dose to avoid transfusion. Our hypothesis is that SAA is superior to the commonly used expert system approach (AMP).

Methods: SAA is an AI-powered planning and decision support system based on two components: 1) pattern matching to identify individual dose-response profile, and 2) Model Predictive Control to perform look-ahead treatment planning. PEG epoetin beta data were obtained from the USRDS 2023 annual report and from the Dosis database and the University of Louisville dialysis facilities. Collection was approved by the University of Louisville institutional review board. PEG dose in the USRDS was reported as the mean monthly dose for the year. Individual monthly doses were obtained for the treatment groups.

Results: Table shows yearly means for all PEG treatments. 95% CI show that SAA resulted in a dose reduction of between 20 and 41%. A separate analysis of PEG use in the University of Louisville dialysis facilities shows that use of SAA results in immediate changes in dose decreasing when SAA is started and increasing when withdrawn Fac3 never used SAA and had poorest performance. Fac1 and Fac2 used SAA continuously and had best performance Fac4 and Fac5 stopped use and immediately increased consumption by 50 and 43%. Simultaneously Hb fell 6 to 11% following -SAA.

Conclusions: SAA is superior to physician-based AMP. The results of the RCT are confirmed in this analysis. There is a definitive cost benefit without sacrificing quality.

	2016	2017	2018	2019	2020	2021	2022
USRDS PEG	149	151	151	149	143	139	137
SAA PEG			82-88(4953)	106-110 (n=12081)	86-96(n=1911)	95-111(n=847)	



TH-PO113

Effect of Continuous Venovenous Hemodialysis (CVVHD) on the Time to Reach Therapeutic Vancomycin Levels

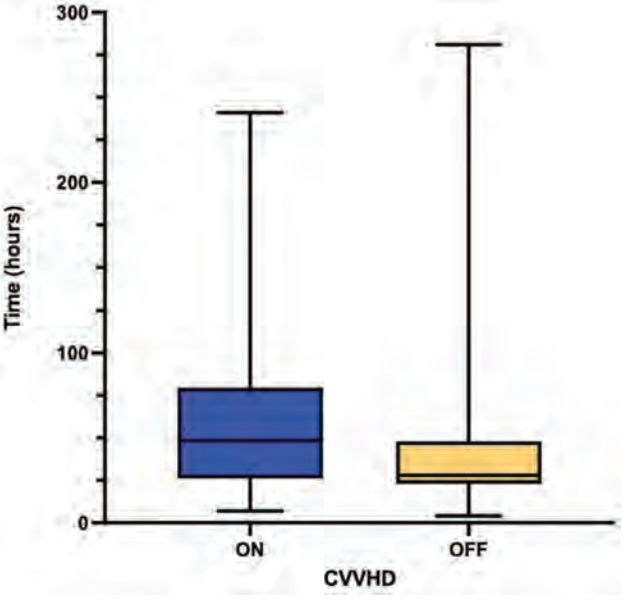
Danica Quickfall, Jay L. Koyner. *University of Chicago Division of the Biological Sciences, Chicago, IL.*

Background: Vancomycin is a commonly used antibiotic in the intensive care unit (ICU). Early attainment of therapeutic vancomycin levels is associated with lower rates of antimicrobial resistance and improved outcomes. Several studies have tried to identify the optimal dosing of vancomycin during the receipt of continuous veno-venous hemodialysis (CVVHD), but few have identified its impact on time to achieving therapeutic vancomycin levels. We sought to determine the impact of CVVHD on time to achievement of a therapeutic vancomycin level.

Methods: A retrospective chart review identified 843 patients admitted to University of Chicago Medicine between May 2016 and April 2020 who received both vancomycin and CVVHD during an ICU admission. Patients were classified based on initiation of vancomycin while on or off CVVHD. The time from initial vancomycin administration to first vancomycin level ≥ 10 mg/L was calculated. Patients were excluded if they received vancomycin within 10 days prior to starting treatment.

Results: Two hundred (23.7%) patients started vancomycin on CVVHD, while 470(55.8%) started outside the CVVHD window. Vancomycin levels were not measured in 173(20.5%) patients. Thirty patients failed to achieve a therapeutic level 17(8.5%) vs 13(2.8%) in the on- and off-CVVHD groups respectively. The median time to reach a therapeutic level was 48.9 h (IQR 26.7-78.9 h) vs 28.5h (IQR 23.4-48.3 h) for individuals on and off CVVHD respectively, see Figure 1 ($p < 0.0001$). Additionally, the incidence of vancomycin levels ≥40 mg/L is higher in patients who are not receiving CRRT (7.5% vs 17.2%, $p = 0.009$).

Conclusions: The time to reach a therapeutic vancomycin level in patients on CVVHD is significantly longer than those who are not receiving CVVHD. Supratherapeutic levels occur more often in patients who are not receiving CVVHD.



TH-PO114

Pharmacokinetics (PK) of Subcutaneous (SC) Furosemide (Furoscix) in CKD: A New Option for Outpatient Diuresis

Christian W. Mende,[1] Katie H. Luepke,[2] Phanisyam Kamineni,[2] Matthew M. Goodwin,[2] John Mohr,[2] Barbara Cornelius.[2] *[1]scPharmaceuticals, Burlington, MA; [2]University of California San Diego, La Jolla, CA.*

Background: Furoscix is approved as a 5-hour SC infusion via an on-body delivery device for treatment of congestion due to fluid overload in chronic HF. In a PK/PD study of HF patients, bioavailability was 99.6% with similar diuresis and natriuresis as IV furosemide. Purpose of analysis was to evaluate furosemide PK/PD in patients with reduced eGFR.

Methods: Furoscix 80 mg was administered SC over 5 hours in biphasic regimen (30 mg in 1st hr, 12.5 mg/hr remaining 4 hrs). IV furosemide was given as two 40 mg bolus doses 2 hours apart. Plasma was collected for furosemide concentrations and urine output (UO) was quantified over 24-hour period. Renal function was estimated using the Modification of Diet in Renal Diseases (MDRD) equation; results were stratified by eGFR. Patients with eGFR <45 mL/min/1.73m^2 were excluded from study.

Results: 15 patients were available for analysis. Despite exclusion criteria, 2 patients were enrolled with eGFR <45 mL/min/1.73 m^2. Median (min-max) eGFR was 60 (41-98) mL/min/1.73 m^2. 7/15 (47%) patients had eGFR 60-89 mL/min/1.73 m^2, 7/15 (47%) had eGFR 30-59 mL/min/1.73 m^2, 1/15 (6%) had eGFR> 90 mL/min/1.73 m^2. As eGFR declined, furosemide levels increased but mean C_{max} values from SC were lower than IV. Regardless of eGFR, neither C_{max} from SC nor IV was associated with ototoxicity (>100,000 ng/mL). Mean (SD) 8-hour UO in patients with eGFR ≥ 60 and <60 mL/min/1.73 m^2 from SC was 2818 (1034) and 2486 (1057) mL, respectively. 8-hour UO was consistent between SC and IV regardless of eGFR.

Conclusions: As eGFR declined, furosemide exposure from SC increased but remained below threshold for ototoxicity. UO between SC and IV remained consistent regardless of eGFR. Furoscix is new option for patients with CKD and fluid overload; future research needed for patients with eGFR <45 mL/min/1.73m^2.

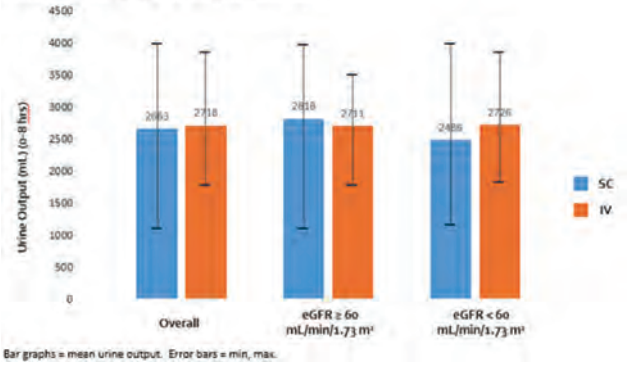
Funding: Commercial Support - scPharmaceuticals

Furosemide Noncompartmental PK parameters after SC and IV Administration

Route	SC			IV
eGFR, mL/min/1.73 m^2	≥ 60 n=8	< 60 n=7	Overall population n=15	Overall population n=15
C_{max} (ng/mL)	1835 (418)	2269 (383)	2040 (449)	8,580 (2,540)
AUC$_\infty$ (h*ng/mL)	11,444 (3494)	15,411 (3810)	13,100 (4010)	13,200 (4170)
$t_{1/2}$ (h)	2.92 (0.88)	3.45 (0.91)	3.16 (0.91)	2.55 (0.34)
CL (L/h)	7.59 (2.27)	5.51 (1.52)	6.71 (2.21)	6.71 (2.31)

Data reported as mean (SD).
C_{max}: peak plasma concentration; $t_{1/2}$: half-life; AUC$^{\infty}$: plasma concentration to infinity; CL: clearance.

8-hour Urine Output after SC and IV Administration



Bar graphs = mean urine output. Error bars = min, max.

TH-PO115

Baclofen Toxicity in Patients with Impaired Kidney Function: A Review of Cases in the Literature

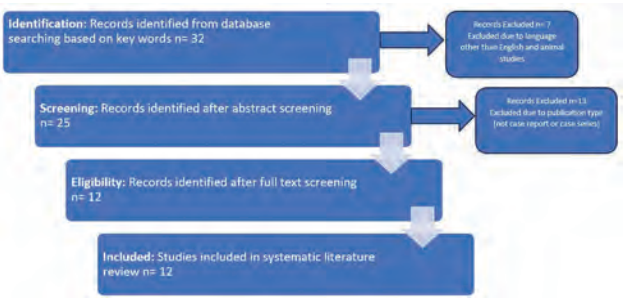
Amna Rehman, Xavier F. Parada. *Berkshire Medical Center, Pittsfield, MA.*

Background: Baclofen is a gamma-aminobutyric acid derivative that inhibits presynaptic motor neurons, resulting in central anti spasticity. It is commonly used to treat muscle spasticity caused by central nervous system disorders. Baclofen neurotoxicity cases are usually iatrogenic but are poorly recognized resulting in significant health problems, mortality, and hospital resource utilization. Therefore, we present here a review of cases published in literature in regard to baclofen induced toxicity in patients with impaired renal function.

Methods: We searched pubmed database for key words: baclofen (adverse effects, poisoning, toxicity), chronic kidney failure, chronic renal insufficiency, end stage renal disease (Figure 1).

Results: We reviewed 12 published articles, with 16 patients of avg. CKD stage IV or V who received variable baclofen dose and developed neurotoxicity (Figure 2).

Conclusions: Our review emphasizes the association of baclofen use with adverse side effects in patients with chronic kidney disease including encephalopathy, dyskinesia, lethargy and tremors. The review highlights that as providers we need to recognize contraindications of baclofen use in patients with impaired renal function and consider other treatment options. Another important aspect is that there are currently no clear guidelines for dosing of baclofen in patients with decreased kidney function. Finally, the management of baclofen toxicity remains variable with no standard recommendations especially for patients with chronic kidney disease.



AUTHOR (Location, Year)	Presenting complaints	Age	Gender	Chronic Kidney Disease (CKD)	Indication for Baclofen	Baclofen dose	Management	Outcome
Mohsin et al. (USA, 2015)	Altered mental status	57	M	CKD V (on dialysis)	Muscular spasms	10 mg BID	Daily hemodialysis (for 3 days)	After third dialysis session complete return to baseline mental status.
Diana et al. (USA, 2015)	Ataxia and dysarthria	61	F	CKD III		10mg PO TID	Baclofen discontinued	Return of mental status to baseline.
Matthew et al. (USA, 2016)	Dyskinesia	60	M	CKD III	Back strain	10 mg BID	Baclofen discontinued	Symptoms resolved within 48 hours
Lauren et al. (USA, 2016)	Ataxia and dystonia	69	F	CKD V	Chronic back pain	10 mg BID (was increase to total 40mg a day prior)	Emergent hemodialysis	Returned to baseline neurologic function on Day 3 (72 hours)
Erol et al. (USA, 2018)	Altered mental status	58	M	CKD V (on dialysis)	Back spasms	10 mg every 8 hours	Baclofen discontinued and emergent hemodialysis	Significant improvement in mental status after 1 session.
Emad et al. (Palestine, 2018)	Decreased level of consciousness and sleepiness.	47	F	CKD V (on dialysis)	Lower back and bilateral knee pain	25 mg once	Daily hemodialysis (for 3 days)	Improvement after second hemodialysis session.
Lakshmi et al. (USA, 2019)	Altered mental status, drowsiness and morbilliform rash in both hands.	59	F	CKD V (on dialysis)	Intractable facial pain	2.5 mg BID prescribed but took 10 mg tablet (by mistake)	Baclofen discontinued and emergent hemodialysis	Patient's mental status returned to normal and her skin rash resolved.
Prem et al (India, 2022)	CASE 1: Altered mental status	83	M	CKD IV	Intractable hiccup	5 mg BID prescribed, but took 20 mg (by mistake)	Hemodialysis twice (12 hours apart)	Complete recovery of consciousness
	CASE 2: Altered mental status	84	M	CKD V (on dialysis)	Intractable hiccup and nausea	2.5 mg BID prescribed, but took 10 mg BID	Daily hemodialysis (for 2 days)	Responsive after 2 days
	CASE 3: Altered mental status	46	M	CKD V (on dialysis)	Nausea, vomiting and bothersome hiccups	2.5mg BID	Daily hemodialysis (for 3 days)	Patient's sensorium started improving after a day of hemodialysis
Samar et al. (Saudi Arabia, 2021)	Altered mental status	48	F	S/P kidney transplantation and chronic dysfunction on dialysis.	Severe back pain	25 mg BID for 3 days	Emergent hemodialysis	Complete recovery of consciousness after 6 consecutive days of dialysis
Edward et al. (UK, 2023)	Lethargy and vomiting	62	F	CKD V (not on dialysis)	low back pain	10 mg BID x 2 days	Baclofen discontinued and emergent hemodialysis	All neurological function resolved after 1 hemodialysis session.
Asma et al. (Muscat, 2023)	Altered mental status	78	F	CKD V (on dialysis)	Chronic back pain	10 mg (consumed 20 mg over the span of 24 hours)	Emergent hemodialysis (no improvement), then intermittent venovenous hemodialysis.	Complete restoration of her sensorium within two days
Manudi et al. (Sri Lanka, 2023)	CASE 1:Myoclonic movements involving both upper and lower limbs followed by AMS	72	M	CKD IV	Pelvic pain s/p surgical drainage for abscess	30 mg TID	Baclofen discontinued and emergent hemodialysis	Around 12 hours after the completion of the dialysis the myoclonus gradually subsided.
	CASE 2: Bilateral Myoclonic movements of upper and lower limbs	50	M	CKD V (on dialysis)	mechanical neck pain	10 mg TID	Baclofen discontinued and emergent hemodialysis	His symptoms improved within 24 hours of hemodialysis.

TH-PO116

Evaluating Sex-Biased Adverse Event-Associated Drugs to Improve Kidney Disease Drug Prioritization

Brittany N. Lasseigne, Timothy C. Howton, Elizabeth Wilk. Lasseigne Lab. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Sex differences impact disease pathology, including kidney diseases (e.g., polycystic kidney disease, PKD; acute kidney injury, AKI). Also, women are more likely to have drug-related adverse events (unintended medication effects), and men are more likely to experience events resulting in hospitalization or death. These sex-biased adverse events (SBAEs) are due to many factors, but it is critical to evaluate the impact of sex when prioritizing drug targets and repurposing candidates.

Methods: Previously, we evaluated sex-specific gene expression (GE) of known drug targets and metabolism enzymes for SBAE-associated drugs. We also assessed sex-biased GE and gene-regulatory network properties for 45 tissues to determine if known SBAE-associated drug targets and metabolism enzymes had sex-specific gene properties. We applied these findings to drugs approved for or in clinical trials to treat PKD, AKI, and other kidney diseases.

Results: We found ~85% of SBAE-associated targets had sex-biased GE or were core genes of sex- and tissue-specific network communities and demonstrated these data can prioritize drugs for preclinical/clinical kidney disease trials.

Conclusions: Our approach may be useful for studies seeking to explain or predict SBAEs, critical for realizing precision medicine for kidney-associated diseases.

Funding: Other NIH Support - NIH Office of the Director

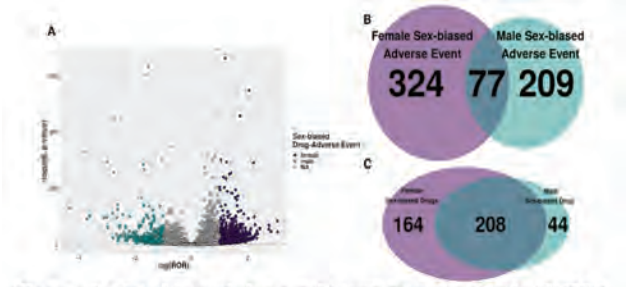
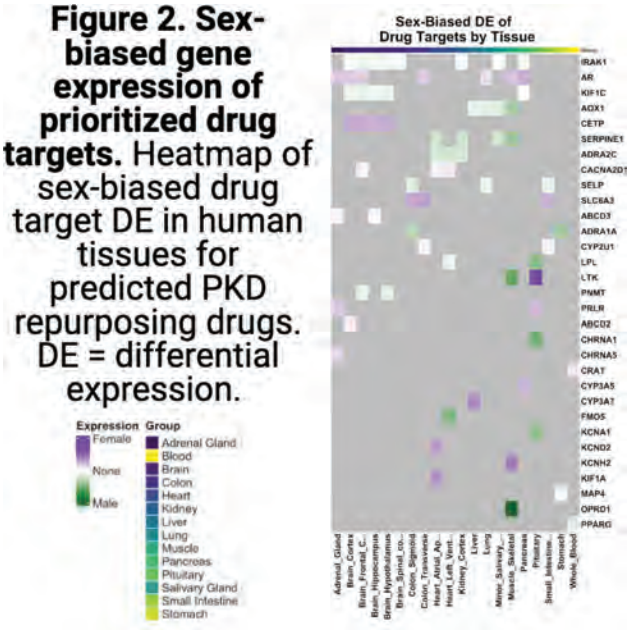


Figure 1. Sex-biased drug-adverse event pairs in FAERS. A) Log-transformed reporting odds ratio (ROR) and the negative log-transformed B-H p-values from Fisher's exact test of drug & SBAE overlap. **B)** Drugs from male- & female-biased drug-adverse event pairs. **C)** Adverse events from male- and female-biased drug-adverse event pairs.

1. Sex-biased drug-adverse event pairs.

Figure 2. Sex-biased gene expression of prioritized drug targets. Heatmap of sex-biased drug target DE in human tissues for predicted PKD repurposing drugs. DE = differential expression.



2. Sex-biased GE of PKD drug targets.

TH-PO117

Safety and Efficacy of D-mannose as Prophylaxis of Urinary Tract Infection: A Systematic Review and Meta-Analysis

Antonio M. Mutarelli,[1] Carlos E. Franca Vargas,[1] Luís Gustavo Menegardo Siqueira de Oliveira,[2] Acza K. Silva,[3] Patrícia R. Vieira,[4] Jiandra Da Luz,[5] Luis Claudio Santos Pinto.[6] *[1]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [2]Escola Superior de Ciencias da Santa Casa de Misericordia de Vitoria, Vitoria, Brazil; [3]Universidade Federal de Alagoas, Maceio, Brazil; [4]Universidade Estadual de Campinas, Campinas, Brazil; [5]Universidad Nacional de la Plata, La Plata, Argentina; [6]Centro Universitario da Amazonas, Manaus, Brazil.*

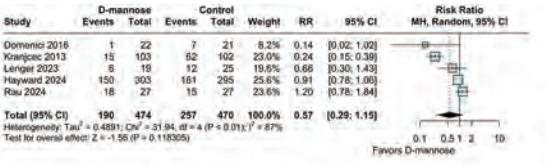
Background: Urinary tract infection (UTI) is the most common bacterial infection, with over 404.6 million cases and more than 230,000 deaths in 2019. Recurrent UTIs significantly impact quality of life due to symptoms, avoidance of sexual activity, persistent pain, and recurrent antibiotic use. A previous meta-analysis suggested the efficacy of D-mannose for UTI prophylaxis, but as new evidence emerges further analysis can be conducted. This systematic review and meta-analysis aimed to evaluate the efficacy of D-mannose for preventing recurrent UTIs.

Methods: Inclusion criteria were prospective randomized studies comparing D-mannose with control or antibiotics in high-risk populations for recurrent UTIs. We excluded abstracts, multi-interventional treatments including D-mannose, and studies using D-mannose for current UTI treatment rather than prophylaxis. The primary outcome was recurrent UTI, analyzed using relative risk (RR) and 95% confidence intervals (CI).

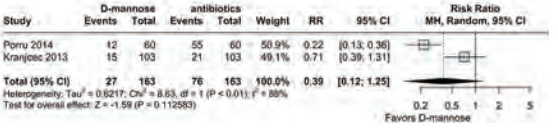
Results: We searched EMBASE, MEDLINE, and the Cochrane Library, identifying 958 articles and abstracts, with 853 remaining after deduplication. We selected 34 for full-text review and included 6 studies. These studies involved 534 patients treated with D-mannose, of whom 521 (97.6%) were women. D-mannose was not associated with a reduction in recurrent UTI compared to control (RR: 0.57, 95% CI 0.29-1.15; p<0.01) or antibiotics (RR: 0.39, 95% CI 0.12-1.25; p<0.01). Further analyses showed that D-mannose did not reduce time to recurrence of UTI and did not improve outcomes in postmenopausal women.

Conclusions: D-mannose does not reduce recurrent UTIs compared to control or antibiotics and it should not be recommended as prophylaxis. Further studies should target different populations to enhance the sample size, including postmenopausal women.

A)



B)



TH-PO118

Comparative Sudden Cardiac Death Risk of Haloperidol vs. Chlorpromazine among People Receiving Hemodialysis

Sherin Ismail Atta,[1] Rebekah P. Nash,[2] Bradley N. Gaynes,[2] Jennifer E. Flythe.[2,3] *[1]The University of North Carolina at Chapel Hill Gillings School of Global Public Health, Chapel Hill, NC; [2]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; [3]Cecil G.Sheps Center for Health Services Research, Chapel Hill, NC.*

Background: Sudden cardiac death (SCD) is the leading cause of death in the hemodialysis population. Haloperidol and chlorpromazine are the most prescribed typical antipsychotic agents in this population, and both agents have known QT-interval prolonging potential. Data from the non-dialysis population suggest that chlorpromazine may confer higher SCD risk than haloperidol. However, the comparative cardiac safety of these agents in the hemodialysis population is unknown.

Methods: We conducted a new-user, active-comparator, cohort study using US Renal Data System data (2007-2019) to assess the comparative 1-year risk of SCD between initiators of haloperidol vs. chlorpromazine. We used inverse probability of treatment weighting and Fine and Gray proportional subdistribution hazard models to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). We used an intention-to-treat approach and treated non-SCD as a competing event. In secondary analyses, we considered broader cardiac outcomes.

Results: Among 10,225 individuals receiving maintenance hemodialysis, 6,266 (61%) initiated haloperidol and 3,959 (39%) initiated chlorpromazine. The median (interquartile range, IQR) age was 65 (55, 74) years, median (IQR) dialysis vintage was 3.1 (1.4, 5.6) years, and 34.9% were female. Haloperidol vs. chlorpromazine initiation was associated with higher relative and absolute 1-year risks of SCD, aHR (95% CI) = 1.39 (1.21, 1.59); weighted risk difference (95% CI) = 2.62% (-0.27, 5.51). The number needed to harm was 38 for haloperidol initiations. Analyses of other cardiac outcomes yielded similar findings.

Conclusions: Initiation of haloperidol vs. chlorpromazine associates with higher absolute and relative 1-year risks of SCD among hemodialysis patients. Our findings may inform prescribing decisions.

Funding: Other NIH Support - NHLBI

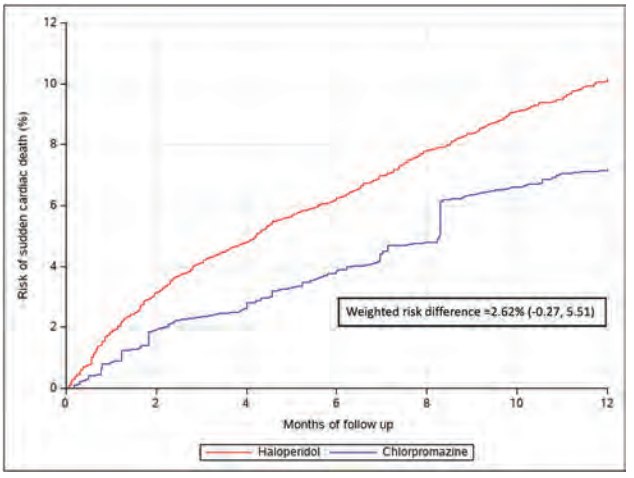


Figure 1. The 1-year risk of sudden cardiac death (%) among hemodialysis patients initiating haloperidol vs. chlorpromazine.

TH-PO119

Unsafe Opioid Prescribing among Patients with ESKD in 2020

Joshua Mannix, Melissa L. Mccarthy. *The George Washington University Milken Institute School of Public Health, Washington, DC.*

Background: A large proportion of End Stage Renal Disease (ESRD) patients report moderate to severe pain. Opioid analgesics are commonly prescribed to address pain in this population. Opioid analgesic overuse and potential for abuse pose a cause for concern. This study measures the prevalence of unsafe opioid prescribing as defined by the CMS project "Practitioner Level Opioid Safety Measure Development."

Methods: We used 2020 annual data from the United States Renal Data System to estimate unsafe opioid use in Hemodialysis (HD) and Peritoneal Dialysis (PD) patients who had Medicare Part A,B and D coverage. Outcomes include chronic use of opioids (more than 90 days of opioid use in a year), concomitant use of opioids and benzodiazepines, daily morphine milligrams equivalents (MME) ≥ 50, and an aggregate of the three outcomes. We conducted a multivariate logistic regression model to identify factors associated with unsafe opioid prescribing.

Results: Figure 1 shows the proportion of 176,626 beneficiaries who had unsafe opioid prescribing. Our multivariate model revealed that HD and PD patients were at an increased odds of unsafe opioid prescribing if they were non-Hispanic white, female, were un-employed prior to ESRD, were dual eligible, had an ESRD vintage of 5+ years, had a diagnosis of anxiety or depression, and a higher Charlson comorbidity index.

Conclusions: The results demonstrate that unsafe opioid prescribing impacted 1 in 6 HD patients and about 1 in 7 PD patients. Given the high need for symptom management for patients with kidney failure, the results underscore the need to improve access to alternative pain management strategies and to monitor unsafe opioid prescribing for this population.

Figure 1

Outcome	HD (n 158,279) %	PD (n 18,347) %
At least one day of daily MME ≥ 50	4.2%	3.6%
At least one day of Opioid and Benzodiazepines Concomitance	6.5%	5.8%
Chronic use (Opioid use > 90 days)	13.2%	9.1%
One of more of the above	17.4%	13.9%

TH-PO120

Evaluation of Ravulizumab Trough Levels in Pediatric Atypical Hemolytic Uremic Syndrome at Remission

Samantha Brokenshire, Samara M. Mendez Nunez, Poyyapakkam Srivaths, Shweta S. Shah, Joseph R. Angelo, Mini Michael. *Texas Children's Hospital, Houston, TX.*

Background: Ravulizumab is a complement C5 inhibitor used for atypical hemolytic uremic syndrome (aHUS). Phase III trials in adults and children suggest the standard dosing regimen provides troughs about 3-fold higher than needed to suppress the complement cascade. Ravulizumab trough monitoring as a tool for individualized dosing regimens has not been described in aHUS or in children. We describe maintenance ravulizumab use in a cohort of pediatric patients with aHUS, exploring potential for targeted dosing strategies using trough and AH50.

Methods: This single-center, retrospective cohort study included pediatric patients with aHUS at remission receiving outpatient ravulizumab infusions between 6/30/23 and 3/31/24 with at least one ravulizumab trough. Patients received maintenance ravulizumab infusions according to the standard (SR) or a modified (MR) regimen at the discretion of the nephrologist. The primary objective was to describe troughs and corresponding AH50 for patients on at least two equal doses. Secondary, exploratory outcomes included comparison of troughs for patients receiving SR and MR, and for patients with multiple troughs. Frequency of potential adverse drug events (pADE) and estimated drug costs are reported.

Results: Nine patients with 28 drug levels were included. The median weight was 17.2 kg (IQR 12.0-39.3) at ravulizumab initiation and 19.1 kg (IQR 14.6-50.8) at first trough. Four patients (44%) received a MR, where dose was not increased for weight gain (n=4) and frequency was extended due to scheduling conflicts (n=1). Rationale for MR included elevated troughs (n=4), clinical stability (n=4), and concern for pADE (n=1). The mean ravulizumab trough for the cohort was 399.9 mcg/mL (SD 104.6). All troughs exceeded goal of 175 mcg/mL and achieved AH50 <10%. There was no difference in troughs between patients receiving SR and MR (diff 30 mcg/mL, 95%CI -131 to 192). For patients with multiple troughs, intra-patient variability was low (CV <25%). Rates of pADE were similar between regimens and drug cost of MRs were lower.

Conclusions: Individualized ravulizumab regimens based on trough and complement monitoring seems to be safe and effective while reducing drug costs. Further study is needed to better understand impact on lab and clinical parameters to determine optimal ravulizumab regimen.

TH-PO121

Imperatorin Ameliorates Ferroptosis-Associated Cell Death, Inflammation, and Kidney Fibrosis in a Unilateral Ureteral Obstruction Mouse Model

Cheng-Tien Wu,[1] Ssu-chia Lin,[1] Yu-Syuan Chen,[1] Pei-Yu Weng,[1] Huey-liang Kuo,[1] Chih-Kang Chiang,[2] Shing-Hwa Liu.[2] Dept of Nutrition CMU. *[1]China Medical University Hospital, Taichung, Taiwan; [2]National Taiwan University, Taipei, Taiwan.*

Background: Chronic kidney disease (CKD) poses a global health problem with high prevalence, morbidity and mortality rates, and various complications. Imperatorin is a naturally occurring furocoumarin derivative and is found in traditional Chinese medicine *Angelica Dahurica* with anticancer, antihypertensive, and antidiabetic properties.

Methods: In this study, we aim to investigate the protective effects of imperatorin treatment and the specific underlying mechanisms on progressive CKD in a unilateral ureteral obstruction (UUO) mouse model.

Results: We found that imperatorin treatment alleviated kidney histology alternations, collagen depositions, and the protein expression of the fibrotic and EMT-related markers (**F**ibronectin, α-smooth muscle actin, E–cadherin, and **Tumor growth factor**-β). Additionally, we found the inhibition of the inflammatory cells infiltration, and moderation of the overload oxidative stress protein markers **(Catalase, superoxide dismutase 2/SOD-2, NADPH oxidase 4/NOX-4, and thioredoxin reductase 1/Trxr-1)**. More important, administration imperatorin mitigates the induced ferroptosis (Cystine transporter SLC7A11/xCT, TFR-1, and Glutathione peroxidase 4/GPX4) as well as renal cell apoptotic death.

Conclusions: Our results suggested that imperatorin treatment improves the fibrotic features of CKD, inflammatory cell infiltration, oxidative stress overload, and ferroptosis-related apoptosis in UUO mice, highlighting its potential as a therapeutic target for CKD treatment in the future.

TH-PO122

Gut Microbial-Derived Short-Chain Fatty Acids Enhance Kidney Proximal Tubule Cell Secretory Function

Rosalinde Masereeuw, Laura Giordano, Sabbir Ahmed, Thomas K. van der Made, Silvia M. Mihaila. *Universiteit Utrecht, Utrecht, Netherlands.*

Background: The organic anion transporter-1 (OAT1) in kidney proximal tubule cells is actively involved in metabolic waste excretion, including uremic toxins; yet its activity becomes impaired upon kidney disease development. Chronic kidney disease also leads to gut dysbiosis, resulting in an increased production of uremic toxins and a reduced production of nephroprotective short chain fatty acid (SCFAs), mainly acetate, propionate and butyrate, thereby contributing to disease progression. Here, we studied whether SCFAs can modulate OAT1 in human kidney proximal tubule cells and stimulate uremic toxin excretion.

Methods: The conditionally immortalized human proximal tubule epithelial cell line overexpressing OAT1 (ciPTEC-OAT1) were exposed to SCFAs for 24h at 1 mM alone or in combination (mix). OAT1 activity was measured using fluorescein as substrate and confirmed with a kidney-on-chip (KoC) system perfused basolateral with the uremic toxin and natural substrate, indoxyl sulfate (IS). Gene and protein expression of OAT1 were analyzed along with histone deacetylase (HDAC) inhibition. Bulk RNA sequencing was used to evaluate gene expression signatures.

Results: Propionate and butyrate significantly boosted OAT1 activity ($p<0.001$) by upregulating *SLC22A6* gene ($p<0.001$) encoding for OAT1 protein expression ($p<0.05$), with butyrate enhancing the secretion of IS to the luminal compartment in our KoC system ($p<0.05$). Interestingly, SCFAs were shown to act independently of GPCR activation, while instead inhibiting gene expression of class II HDAC enzymes (acetate, $p<0.05$; propionate and butyrate, $p<0.01$; SFCA mix, $p<0.001$). Transcriptome analysis suggests HDAC inhibition affects the cAMP signaling pathway, activating CREB1 and PI3K gene expressions. These regulate cell metabolism and stress responses, promote proliferation and survival, enhance SLC22A6/OAT1 function, supporting overall cellular health, function, and resilience, thus enhancing cellular fitness.

Conclusions: Propionate and butyrate exert a significant enhancement of OAT1 activity through *SLC22A6* gene upregulation. Further investigations into the direct effects of SCFAs could potentially introduce them as a novel and effective approach for restoring impaired OAT1 function and maintaining kidney health. This project was funded by EU Horizon 2020 MC STRATEGY-CKD (860329).

Funding: Government Support - Non-U.S.

TH-PO123

Gut Microbiome Signature Associated with Mycophenolate Mofetil Enterohepatic Recirculation

Guillaume C. Onyeaghala,[1,2] Duy Vo,[2] Bryan P. Brito Sanchez,[2] Abdelrahman Saqr,[1] Moataz Mohamed,[1] Christopher Staley,[1] Levi Teigen,[1] Casey R. Dorr,[2,1] Weihua Guan,[1] Rasha El-Rifai,[1] Arthur J. Matas,[1] Rory P. Remmel,[1] William S. Oetting,[1] Pamala A. Jacobson,[1] Ajay K. Israni.[2,1] *[1]University of Minnesota Twin Cities, Minneapolis, MN; [2]Hennepin Healthcare Research Institute, Minneapolis, MN.*

Background: Bacterial b-glucuronidase (BGUS) converts mycophenolic acid glucuronide back to mycophenolic acid (MPA) through enterohepatic recirculation (EHR), likely enhancing immunosuppression and toxicity in kidney transplant recipients (KTRs). We hypothesized that BGUS producing gut taxa are associated with EHR in KTRs.

Methods: Adult KTRs (n=84, 37 prospective and 47 cross-sectional) underwent simultaneous pharmacokinetic(PK) study and stool collection (71 KTRs completed a pre-PK 48hr food recall). We defined MPA %EHR as MPA $AUC_{5\text{-}12\ hr}$ / $AUC_{0\text{-}12\ hr}$ x100. Microbiome shotgun data were processed with HUMAnN3 and differentially abundant taxa associated with EHR adjusted for cohort were identified with MaAsLin2. We further adjusted for age, sex, diet and standardized creatinine clearance using zero inflated Poisson regression. In an exploratory analysis stratified by cohort, we compared the relative abundances of 12 known BGUS producers across EHR levels using the Wilcoxon sum rank test.

Results: Higher relative abundances of *Blautia obeum* and *Faecalibacillus intestinalis* were associated with high EHR ($p=0.007$ and <0.001 respectively), whereas high *Gordonibacter pamelaeae* abundance was associated with low EHR ($p= 0.001$) (FIG 1). In our exploratory analysis, high *Collinsella aerofaciens* abundance was associated with high EHR in the prospective cohort($p=0.04$). Alpha or beta-diversity at the time of PK were not associated with EHR.

Conclusions: Our findings suggest a microbiome signature including *Blautia*, a known BGUS producing taxa, associated with MPA EHR after adjusting for age, sex, diet, and standardized creatinine clearance at the time of PK. Future BGUS assesments may provide opportunities to facilitate MMF dosing based on the stool microbiome.

Funding: NIDDK Support

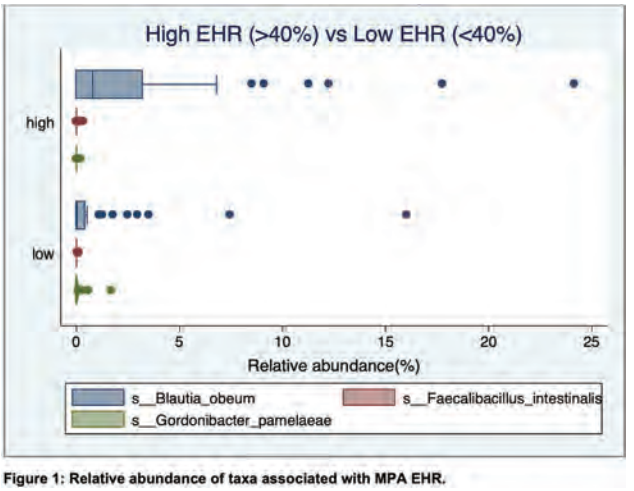


Figure 1: Relative abundance of taxa associated with MPA EHR.

TH-PO124

Phantom Lactic Acidosis Secondary to a Drug-Drug Interaction between Ribociclib and Metformin in the Setting of CKD

Bibi Maryam, Adolfo Diaz-Barba. *The University of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Introduction: Ribociclib is a CDK4 and CDK6 inhibitor widely used for treating hormone receptor-positive and human epidermal growth factor receptor 2 (HER-2)-negative metastatic breast cancers. Metformin is a biguanide, one of the most essential and primitive medications for type 2 diabetes. We present a unique drug-drug interaction between ribociclib and metformin, causing severe lactic acidosis in a 54-year-old postmenopausal woman with Invasive Ductal Carcinoma of breast, CKD stage 3, and Diabetes

Case Description: A 54-year-old woman incidentally felt a mass in the left breast and was subsequently diagnosed with Invasive Ductal Carcinoma (IDC) (ER 100%, PR 10%, Her2 -ve, Ki-67 33%), histologic grade 3 with lymphovascular invasion (T1 NO M0) by core needle biopsy. She underwent lumpectomy with sentinel lymph node biopsy. She underwent re-excision and was started on radiation therapy. Iliac bone biopsy showed metastatic poorly differentiated adenocarcinoma. She was given radiation therapy to the iliac bone, resulting in theresolution of her hip pain. She was given zoledronic acid for the bony lesions, and started on Fulvestrant and Ribociclib. 5 months later, she presented with generalized weakness and nausea, workup revealed Bicarbonate at 17, AKI on CKD with creatinine elevation from baseline of 1.7 to 2.2, potassium of 5.3, with a pH of 7.34, PCO2 of 28, and lactic acid levels at 5.1. Metformin was immediately stopped. She was started on oral and IV sodium bicarbonate and fluids. Her creatinine improved to 1.7, potassium improved to 4.4, and lactic acid dropped to 2.4. She was subsequently discharged with a follow-up lactic acid and kidney function test in clinic, which remained satisfactorily close to the baseline, and the patient remained asymptomatic.

Discussion: Ribociclib-induced AKI is usually reversible but may require treatment interruption or hemodialysis in severe cases. Metformin uptake from the circulation into renal epithelial cells occurs via OCT2, and from the renal cell into the lumen is mediated by MATE1 and MATE2-K. Ribociclib has the potential to inhibit OCT2 and MATE1, causing decreased renal clearance of metformin if administered together, leading to severe lactic acidosis. The use of metformin and ribociclib in consortium results in high metformin levels and subsequently, type B lactic acidosis, specifically in patients with preexisting CKD.

TH-PO125

Unexpected Consequences: Rosuvastatin-Induced Proteinuria and Hematuria

Badar U Din Shah, Kartik Kalra. *Geisinger Health, Danville, PA.*

Introduction: Statins have been used for treatment of hyperlipidemia with established efficacy in cardiovascular diseases. Prior clinical trials examining the safety and efficacy of high dose rosuvastatin demonstrated an increased incidence of proteinuria, hematuria, rhabdomyolysis, and other acute kidney injury of unknown cause at high doses (20 mg and above). We present 5 patients with proteinuria and microscopic hematuria with spontaneous remission after switching to alternative statin.

Case Description: Case 1: 67 y/o male with history of Chronic Kidney Disease (CKD) 4 on rosuvastatin 20 mg presents with proteinuria, 4 weeks after starting statin therapy. Spot Urine Protein/ Creatinine (PCR) ratio was 1.6 gm/gm. Case 2: 55 y/o male with a history of coronary artery disease (CAD) on rosuvastatin 40 mg presented for evaluation of proteinuria, 24-hour protein was quantified to be 1.8 gm. Case 3: 38 y/o male with family history of premature CAD on rosuvastatin 20 presents for microscopic hematuria and proteinuria evaluation. PCR 1.4 gm/gm. Case 4: 46 y/o female with hyperlipidemia on rosuvastatin 20 mg referred for microscopic hematuria evaluation. Case 5: 63 y/o male with a history of CAD (rosuvastatin 40 mg), CKD 3b complaining of foamy urine. PCR 2.1 gm/gm. All 5 cases underwent thorough immunologic workup which was negative. Rosuvastatin was held and was switched to alternative statin. Within 1-2 weeks, repeat spot urine protein quantification and UA suggested resolution of proteinuria and hematuria..

Discussion: The association of rosuvastatin with proteinuria and hematuria can be related to its renal clearance (10%–25%) when compared with other statins that are hepatically metabolized. Proposed mechanisms for proteinuria with statin use included a dose-dependent impaired albumin tubular absorption via receptor-mediated endocytosis in proximal tubules due to β-hydroxy β-methylglutaryl-coenzyme A reductase inhibition. Another study noted oxidative stress leading to mitochondrial dysfunction due to reduced ubiquinone synthesis. Proteinuria and hematuria in a patient triggers workup which may include a kidney biopsy. We recommend interval monitoring of renal function, urine protein and RBCs at baseline when starting patient on high dose rosuvastatin. The initial rosuvastatin dose should be reduced to 5 mg daily to a maximum dose of 10 mg daily in patients with severe CKD (eGFR <30 mL/min per 1.73 m2).

TH-PO126

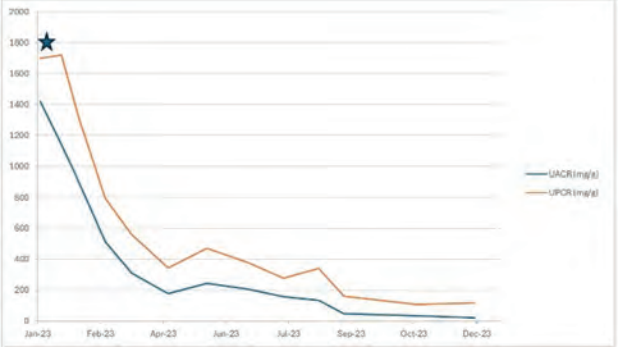
Essential Medication Reconciliation: A Hidden Cause of Proteinuria

Christine Palazzolo, Toni Sabbouh. *Pennsylvania Hospital, Philadelphia, PA.*

Introduction: Alpha-lipoic acid (ALA) is an organic compound which is becoming a popular dietary supplement in many chronic conditions. We review the case of an older male whose new proteinuria rapidly improved after discontinuation of ALA.

Case Description: A 66-year-old male with medical history significant for prostate cancer post resection and prediabetes was referred to the nephrology clinic for worsened proteinuria. He had been on multiple supplements initiated by his primary care physician including nattokinase, chromium picolinate, and ALA. He had a normal physical exam and normal creatinine between 0.9-1 mg/dL. Further workup was negative for hepatitis, HIV, syphilis, autoimmune disease, primary membranous nephropathy, and monoclonal gammopathies. The patient was initiated on an angiotensin receptor blocker and advised to stop taking ALA. Within 1 month, his proteinuria reduced by approximately 55%, and within 8 months, he had complete resolution of proteinuria. Kidney biopsy was not pursued given absence of nephrotic syndrome and stable kidney function.

Discussion: ALA is a supplement growing in popularity for its use in diabetes, multiple sclerosis, Alzheimer's, and schizophrenia to reduce neuropathic symptoms and improve weight loss, memory, and balance. ALA was thought to be the cause for this gentleman's presentation since chromium has only been associated with acute tubular necrosis and chronic kidney disease, and nattokinase has not been reported to cause proteinuria. Despite therapeutic promise, emerging evidence implicates ALA supplementation with unwarranted proteinuria. NELL1+ membranous nephropathy has been observed within 2 to 12 months of starting ALA supplementation and remission is largely achieved within 1 year of supplementation cessation, suggesting the nephropathy's reversibility. This case highlights the importance of a thorough medication reconciliation especially when approaching new proteinuria for which no other obvious risk factors are present.



Discontinuation of ALA (star) improved urine albumin creatinine ratio (UACR) and urine protein creatinine ratio (UPCR).

TH-PO127

Correlation and Dissociation Factors between Ionized, Total, and Corrected Calcium in Patients on Hemodialysis

Chiharu Aizawa, Akio Nakashima, Kazuhiko Kato, Arisa Kobayashi, Ichiro Ohkido, Takashi Yokoo. *Tokyo Jikeikai Ika Daigaku Igakubu Igakuka Jinzo Koketsuatsu Naikagaku, Minato-ku, Japan.*

Background: It is important to optimize serum calcium concentrations in dialysis patients because abnormal calcium levels are associated with the risk of all-cause mortality and cardiovascular events. Ionized calcium (iCa) has physiological activity in the body; however, the direct measurement of iCa is limited technically. Although total serum calcium (tCa) and corrected calcium (cCa) using the Payne correction formula have been utilized to assess calcium levels, their limitations have been pointed out. The degree to which the correlation between ionized, total, and corrected calcium is dissociated in dialysis patients has rarely been examined, and the factors influencing this correlation are poorly understood. This study aimed to clarify the degree of correlation and dissociation among iCa, tCa, and cCa levels in patients undergoing hemodialysis.

Methods: A cross-sectional study assessed the correlation between iCa, tCa, and cCa levels in patients undergoing hemodialysis. Factors involved in the correlation between the iCa and tCa levels were evaluated using multiple regression analysis. Based on these results, we proposed a novel iCa prediction equation.

Results: Two hundred thirteen patients were enrolled. Patients were 65 ± 10.2 years, and 67.1% of patients were male. The correlation coefficients were 0.8665 for iCa and tCa and 0.8537 for iCa and cCa. Correlations were also observed when the albumin concentration and pH were divided by known correlation factors. In multiple regression analysis of the relationship between tCa and iCa, albumin, pH, phosphorus, and Mg levels were significant factors. Based on these results, a new corrected calcium equation (mg/dL) = 0.828×total calcium - 0.314×albumin (g/dL) + 0.007×age + 2.922 was derived using age and albumin.

Conclusions: There was a correlation between iCa, tCa, and cCa in hemodialysis patients, with a stronger correlation with tCa in iCa assessments. Correcting for tCa levels may not be necessary when predicting iCa levels. We propose a novel prediction equation for estimating iCa by age and albumin without blood gas analysis.

TH-PO128

Intravenous Calcium Supplementation in Patients with Secondary Hyperparathyroidism after Total Parathyroidectomy: Serum Phosphorus as an Indicator

Wei Liang. *Wuhan University Renmin Hospital, Wuhan, China.*

Background: Intravenous calcium supplementation (ICS) regimen after parathyroidectomy (PTX) mostly relies on immediate serum calcium level(SC-ICS) to adjust the dose and maintenance time of calcium supplementation, and there is a lack of standardized treatment regimen, with a wide range of individual variations, and the short-term/long-term efficacy and safety are still unclear. In this study, we propose a serum phosphorus level-guided ICS(SP-ICS) regimen to improve the efficiency and recurrence rate of hypocalcemia treatment after PTX.

Methods: This study retrospectively analyzed the clinical data of 36 cases of SHPT patients with total parathyroidectomy (tPTX). According to ICS is divided into serum calcium-guided ICS regimen (SC-ICS) and serum phosphorus-guided ICS regimen (SP-ICS). Both groups of patients were allowed to have a free diet after the operation, and oral calcium and osteotriol supplementation were given. The occurrence of (Hungry Bone Syndrome) HBS and hypocalcemia after surgery was recorded in all patients.

Results: A total of 36 cases were recruited in the respective cohort (18 cases in SC-ICS and 18 ones in SP-ICS). There was no significant difference in the baseline data between the two groups. Postoperative serum PTH and serum calcium levels were significantly decreased in both groups and hypocalcemia occurred in all patients. Compared with the SC-ICS group, the SP-ICS group had a longer postoperative hospitalization [9.5 (7.25,12.75) vs 5.0 (5.0,9.5), p=0.015] and a greater cumulative dose of 10% GN supplementation (540 ml±100 ml vs 190 ml±50 ml, p=0.039). At 6 month postoperative follow-up, one case died of hypocalcemia in the SC-ICS group, and the incidence of hypocalcemia was lower in the SP-ICS group than in the SC-ICS group (8.3% vs. 27.3%, p=0.022), and at one-year postoperative follow-up, the incidence of hypocalcemia was lower in the SP-ICS group than in the SC-ICS group (8.3% vs. 50%, p=0.024).

Conclusions: Both SC-ICS and SP-ICS can effectively correct hypocalcemia after tPTX, and the dose and duration of calcium supplementation of SP-ICS regimen is higher than that of SC-ICS regimen, and SP-ICS regimen significantly reduces the incidence of long-term hypocalcemia and the risk of lethal hypocalcemia, and improves the quality of patient survival.

TH-PO129

Hungry Bone Syndrome after Parathyroidectomy Is Associated with Better Outcomes in ESKD

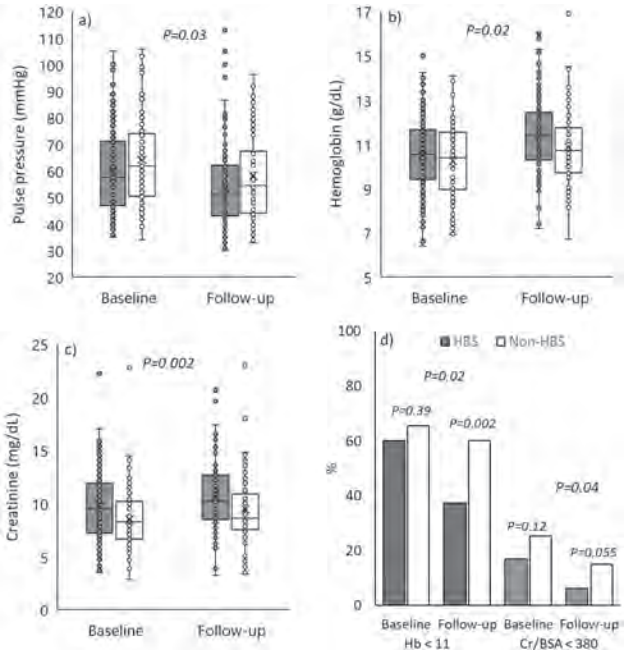
Sinee Disthabanchong. *Mahidol University Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand.*

Background: Hyperparathyroidism (HPT) is common in patients with end-stage kidney disease (ESKD). Parathyroidectomy (PTX) is still necessary for patients who do not respond adequately to medications. Hungry bone syndrome (HBS) frequently occurs after PTX. Beyond lower recurrence rates of HPT, the long-term outcomes associated with HBS are largely unexplored.

Methods: In this retrospective single-center study conducted between 2012 and 2022, 322 PTX were identified in 314 patients with ESKD. HBS was defined as serum albumin-corrected Ca levels <8.5 mg/dL occuring between 5-30 days post-PTX. The study evaluated baseline biochemical factors associated with HBS and examined adverse events, as well as changes in blood pressure, hematologic, and nutritional parameters 3-12 months after PTX, stratified by HBS status.

Results: HBS was observed in 207 cases (64%). Male sex, lower serum Ca and higher PTH levels, and lack of active vitamin D treatment at baseline were independent predictors of HBS. Adverse events were similar between the HBS and no-HBS groups. Between group comparisons revealed HBS group experienced a more significant reduction in pulse pressure after surgery. There was a greater increase in Hb and serum Cr in the HBS group. The number of cases with Hb <11 g/dL and Cr/BSA <380 mg/m^2 post-PTX was lower in the HBS group. Serum albumin levels increased significantly in both groups, with no significant difference between them. HBS was associated with a more substantial reduction in serum Ca and PO_4 but not PTH levels, from baseline. At the end of the follow-up period, serum Ca levels remained lower in the HBS group, while serum PO4 and PTH levels were comparable between the two groups.

Conclusions: In conclusion, HBS was associated with a more substantial improvment in blood pressure, anemia and muscle mass in ESKD patients.



TH-PO130

Paricalcitol Capsule (HR081702) for Secondary Hyperparathyroidism (SHPT) in Stages 3 and 4 CKD: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Jianghua Chen,[1,2] Jun Cheng,[1,2] Xiaoying Du,[1,2] Changhua Liu,[3] Ping Luo,[4] Wenxiu Chang,[5] Yanning Zhang,[6] Hong L. Lin,[7] Lihua Wang,[8] Hua Zhou,[9] Wenbin Li,[10] Xiaoyong Yu,[11] Wanhong Lu,[12] Chaosheng Chen,[13] Linghui Zhou,[14] Xiaoyi Sun,[15] Lingling Xu.[15] *[1]Kidney Disease Center, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; [2]Zhejiang Clinical Research Center of Kidney and Urinary System Disease, Hangzhou, China; [3]Northern Jiangsu People's Hospital, Yangzhou, China; [4]The Second Hospital of Jilin University, Changchun, China; [5]Tianjin First Central Hospital, Tianjin, China; [6]General Hospital of the Northern Theatre, Shenyang, China; [7]First Affiliated Hospital of Dalian Medical University, Dalian, China; [8]Second Hospital of Shanxi Medical University, Taiyuan, China; [9]Shengjing Hospital of China Medical University, Shenyang, China; [10]The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, China; [11]Shaanxi Traditional Chinese Medicine Hospital, Xi'an, China; [12]the First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an, China; [13]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [14]The First Affiliated Hospital of Xiamen University, Xiamen, China; [15]Jiangsu Hengrui Pharmaceuticals Co., Ltd, Shanghai, China.*

Background: Paricalcitol capsule is a good choice to treat SHPT as a vitamin D analogue with a convenient dosage form for patients. This study aimed to investigate the efficacy and safety of paricalcitol capsule (HR081702) in stages 3/4 CKD patients with SHPT.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study in Chinese adult patients in stages 3/4 CKD with SHPT (ClinicalTrials.gov, NCT04994080). Patients were enrolled if, in the screening period and run-in period, the mean serum intact parathyroid hormone (iPTH) was ≥150 pg/mL (≥120 pg/mL in both periods), serum calcium level was between 8.0 and 10.0 mg/dL (1.99 and 2.50 mmol/L), and serum phosphorus level was ≤5.2 mg/dL (1.68 mmol/L). Eligible patients were randomized (2:1) to receive HR081702 or placebo orally once a day for 24 weeks, with the initial dose determined by iPTH level and adjusted depending on subsequent serum iPTH, calcium, and phosphorus levels. The primary endpoint was the proportion of patients with at least two consecutive iPTH reductions of ≥30% from baseline within 24 weeks of treatment.

Results: A total of 90 patients were randomized (60 in HR081702 group and 30 in placebo group) with similar baseline characteristics between the two groups. During the 24 weeks treatment period, 91.7% of patients in the HR081702 group achieved two consecutive reductions of ≥30% from baseline in iPTH levels, compared with 16.7% of patients in the placebo group (difference, 75.0% [95% CI 59.9-90.1]; P<0.0001). Furthermore, 68.3% of HR081702-treated patients achieved four consecutive decreases of ≥30% in iPTH levels from baseline, compared with 6.7% of placebo-treated patients. There were no obvious differences in the excretion of calcium and phosphorus or in the decline of kidney function between the two groups. Treatment-related adverse events were reported by 50% in HR081702 group and 26.7% in placebo group (all were mild or moderate). The most common ones were hyperphosphatemia and urinary tract infection.

Conclusions: Paricalcitol capsule (HR081702) was an effective and safe treatment for stages 3/4 CKD patients with SHPT.

Funding: Commercial Support - Jiangsu Hengrui Pharmaceuticals Co., Ltd

TH-PO131

Central vs. Peripheral Access Samplings in Patients on Hemodialysis Induce Variations in Parathyroid Hormone Levels

Simon Schreiber, Simon Desmeules, Mohsen Agharazii, Pierre Douville, Fabrice Mac-Way. *Universite Laval Faculte de Medecine, Quebec, QC, Canada.*

Background: Parathyroid hormone (PTH) levels are routinely measured in dialysis patients, but international guidelines do not specify the optimal site from which PTH should be drawn. Previous findings suggest that centrally drawn PTH may significantly vary from peripherally sampled PTH[1]. This study aimed to compare PTH levels drawn from central venous catheters (C-PTH), peripheral veins (P-PTH) and arteriovenous fistula (AVF-PTH) in hemodialysis patients.

Methods: C-PTH, P-PTH and/or AVF-PTH were simultaneously measured in hemodialysis patients at the CHU de Québec (cohort A) and CISSS Chaudières-Appalaches (cohort B) in Canada from January 1st to February 28th, 2024. Architect Intact PTH™ (Abbott, normal range 25 to 115 ng/L) was used in cohort A and IMMULITE Intact PTH™ (Siemens, normal range 20 to 100 ng/L) in cohort B. Demographic data were collected and mineral biochemistry were measured according to local standard. PTH levels were classified as "on target" according to sampling site if they were between two and nine times the upper limit of normal.

Results: Cohort A included 69 hemodialysis patients (mean age 69 ± 13 years, dialysis vintage 69 ± 13 months, 86% with a central venous catheter). Mean C-PTH, P-PTH and AVF-PTH were respectively 546 ± 309 ng/L, 409 ± 227 ng/L and 533 ± 325 ng/L. Classification of PTH levels being "on target" were different between C-PTH and P-PTH in 29% of patients. Cohort B included 50 hemodialysis patients (mean age 67 ± 13 years, dialysis vintage 50 ± 60 months, 54% with a central venous catheter). Mean C-PTH, P-PTH and AVF-PTH were respectively 357 ± 264 ng/L, 352 ± 236 ng/L and 475 ± 255 ng/L. Similarly to cohort A, "on target" PTH levels were different between C-PTH and P-PTH in 18.3% of patients.

Conclusions: Our results suggest that sites of sampling may influence PTH levels and could impact the treatment of hyperparathyroidism in hemodialysis patient. Standardization of sampling site should therefore be recommended. 1-Vulpio C, et al. Influence of blood sampling site on intact parathyroid hormone concentrations in hemodialysis patients. Clin Chem. 2010;56(3):489-90.

Funding: Government Support - Non-U.S.

TH-PO132

Parathyroid Axis Irregularities in Patients with Hyperaldosteronism

Loai Dweik,[1] Dania Salih Bacha,[2] Vaidehi A. Mendpara,[2] Huijun Xiao,[2] George Thomas,[2] Pratibha P. Rao,[2] Georges Nakhoul,[2] Jonathan J. Taliercio,[2] Elias Bassil,[2] Ali Mehdi.[2] *[1]Cleveland Clinic, Cleveland, OH; [2]Cleveland Clinic Akron General, Akron, OH.*

Background: Patients with hyperparathyroidism (HPT) have increased cardiovascular risks. A bi-directional relationship between the renin-aldosterone axis and the parathyroid-calcium (PTH-Ca) axis has been proposed whereby PTH and aldosterone can activate one another and exacerbate vascular damage. This study aims to investigate the prevalence of PTH-Ca axis abnormalities in patients with primary aldosteronism (PA).

Methods: In this retrospective review, patients 18 years or older with PA who had PTH levels measured between 2018 and 2023 were included. Patients with secondary HPT were excluded. The prevalence of HPT, hypercalcemia (HyperCa), and hypophosphatemia (HypoP) was calculated.

Results: 164 patients were identified. Median age was 70 years and 44% were female. Primary HPT was prevalent in 13% of the cohort. HyperCa (Ca > 10.2 mg/dL on 2 occasions) and HypoP (P<2.5 mg/dL on 2 occasions) were observed in 32% and 33% of patients respectively. After excluding patients on Calcium, vitamin D supplements, or thiazides, 24% of the remaining 66 patients had HyperCa. Among patients with HyperCa and/or HypoP (N=83), median interquartile range (IQR) PTH was 59.5 pg/mL (41.0 – 88.8), median (IQR) 24-hour urinary Ca:166.5 mg/day (77.9 – 257.6), and 22% had nephrolithiasis. We then excluded patients with a diagnosis of primary HPT from this sub-cohort and were left with 65 patients. The median (IQR) PTH was unsuppressed at 47.0 pg/mL (38.0 – 79.5), median (IQR) 24-hour urinary Ca: 144.0 mg/day (101.4 – 221.7), and 24% had nephrolithiasis.

Conclusions: In a cohort of PA patients, the prevalence of PTH-Ca abnormalities is quite high. Primary HPT was seen in 13% of patients as compared to <1% in the general population. HyperCa was also seen in a third of patients, many folds higher than the general population (1-2%). This remained true even after excluding those on medications

that can raise serum Ca. Looking at patients with HyperCa and/or HypoP and excluding those with primary HPT, the biochemical profile (unsuppressed PTH and 24 urine Ca) suggested undiagnosed primary HPT. True primary HPT is likely more prevalent in this population. Further studies are needed to better understand this interaction and therapeutic implications.

TH-PO133

Parathyroid Hormone and Cardiovascular Risk in Patients with CKD

Caroline S. Pichat,[1] Ellen Linnea F. Ballegaard,[3] Iain O. Bressendorff,[1] Hanne S. Joergensen,[2,4] Nicholas Carlson,[3] Ditte Hansen.[1,5] *[1]Herlev Hospital, Herlev, Denmark; [2]Aarhus Universitetshospital Risskov, Risskov, Denmark; [3]Rigshospitalet, Kobenhavn, Denmark; [4]Aalborg Universitet, Aalborg, Denmark; [5]Kobenhavns Universitet, Kobenhavn, Denmark.*

Background: Cardiovascular disease is highly prevalent in patients with chronic kidney disease (CKD). The aim of this study was to describe the association between parathyroid hormone (PTH) level and risk of cardiovascular disease in CKDG3-5.

Methods: The cohort was based on nationwide Danish health care registries. All Danish residents ≥18 years with eGFR <60 ml/min/1.73 m2 and measured PTH were identified between 2010 and 2022. Individuals with prior kidney transplantation, multiple myeloma, suppressed PTH, hypercalcemia ≥1.4mmoL, and current dialysis therapy were excluded. PTH was standardized based on the assay-specified upper normal limit (normal, 1.1-2.0xUNL, 2.1-4.0xUNL, and ≥4.0xUNL) with comparison of cumulative incidences of major cardiovascular outcomes (cardiomyopathy, heart failure, myocardial infarction, stroke, thromboembolism, and/or peripheral artery disease) based on the Aalen-Johansen estimator and multiple cause-specific Cox regression models adjusted for age, sex, and CKD stage with death as competing risk. Results were further tested in sensitivity analyses adjusted for phosphate.

Results: A total of 80,937 individuals were included. Median age was 74 yrs (IQR 65;82), 58% were female, 87% with CKDG3, and 62% with normal PTH. Male, sex and lower eGFR were associated with higher PTH levels. A total of 17,701 events were identified during a mean follow-up of 4.4 yrs. Cumulative incidence was highest with PTH >4xUNL (Figure 1). Higher PTH associated with increased rates of cardiovascular events (Figure 2). Principal results remained unchanged following adjustment for phosphate.

Conclusions: Increasing PTH may contribute to cardiovascular disease in patients with CKDG3-5. Further studies are needed to determine the PTH targets in pre-dialysis CKD.

Figure 1

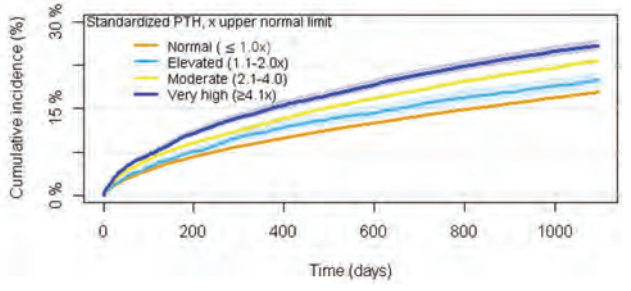
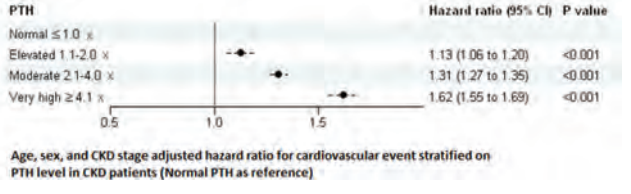


Figure 2



Age, sex, and CKD stage adjusted hazard ratio for cardiovascular event stratified on PTH level in CKD patients (Normal PTH as reference)

TH-PO134

SHR6508, a Calcium-Sensing Receptor Agonist, in Patients on Hemodialysis Who Have Secondary Hyperparathyroidism: A Phase 2 Trial

Xueqing Yu,[1] Zhiming Ye,[1] Li Fan,[1] Yuqing Chen,[2] Pei Wang,[3] Rui Yan,[9] Bin Liu,[4] Yong Wei,[8] Hong Ye,[5] Bi hu Gao,[6] Xin Zhang,[7] Xinyu Yang,[7] Xue Yang.[7] *[1]Guangdong Provincial People's Hospital, Guangzhou, China; [2]Peking University First Hospital, Beijing, China; [3]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [4]Wuxi People's Hospital, Wuxi, China; [5]The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; [6]Affiliated Zhongshan Hospital of Dalian University, Dalian, China; [7]Jiangsu Hengrui Pharmaceuticals Co Ltd, Shanghai, China; [8]The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, China; [9]The Affiliated Hospital of Guizhou Medical University, Guiyang, China.*

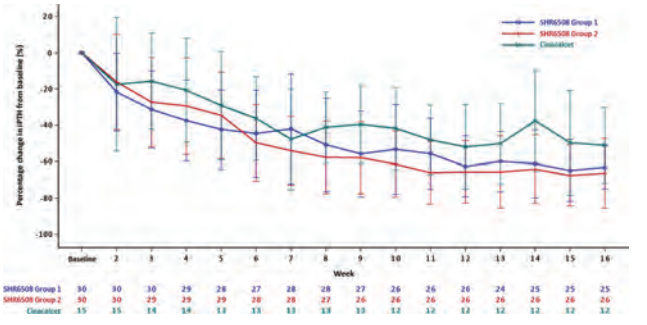
Background: Secondary hyperparathyroidism (SHPT) is a common clinical manifestation among patients receiving hemodialysis (HD). SHR6508 is a calcimimetic developed to reduce parathyroid hormone (PTH) secretion in HD patients with SHPT. We aimed to evaluate the efficacy and safety of SHR6508 compared with cinacalcet in HD patients with SHPT.

Methods: This was a multicenter, randomized, open-label, active-controlled, dose titration phase 2 trial conducted in 34 sites in China. Adult patients who had received HD for at least 12 weeks and with intact PTH (iPTH) ≥400 pg/ml and serum corrected calcium (cCa) ≥2.25 mmol/L were recruited. Eligible patients were randomized in a 2:2:1 ratio to SHR6508 Group 1 (slow titration), SHR6508 Group 2 (rapid titration), and cinacalcet group, stratified by the baseline iPTH level (<700 or ≥700 pg/mL). Patients in SHR6508 Group 1 and 2 received SHR6508 2.5-20 mg by intravenous injection after HD section for 16 weeks, and those in cinacalcet group received oral cinacalcet 25-100 mg once daily for 16 weeks, with the dosage adjusted based on iPTH and cCa levels. The primary outcome was percentage change in iPTH from baseline to week 16.

Results: A total of 75 HD patients were randomized (n=30 for SHR6508 Group 1 and 2, respectively; n=15 for cinacalcet). iPTH significantly declined in patients treated with SHR6508 than those treated with cinacalcet during treatment period (**Figure 1**). The percentage changes in mean iPTH from baseline to week 16 were -62.7%, -61.7% and -38.9% in SHR6508 Group 1, Group 2 and cinacalcet group, respectively ($P<0.05$). The treatment-related adverse events (TRAEs) were comparable among three groups (83.3% vs 83.3% vs 86.7%) and all SHR6508-related TRAEs were mild or moderate. Nausea (3.3% vs 3.3% vs 6.7%) and vomiting (0 vs 0 vs 13.3%) were less common in patients treated with SHR6508.

Conclusions: SHR6508 showed greater efficacy in iPTH reduction and similar safety profiles compared to cinacalcet in HD patients with SHPT.

Funding: Commercial Support - Jiangsu Hengrui Pharmaceuticals Co., Ltd



TH-PO135

Impact of Upacicalcet on Bone Metabolism in Patients on Hemodialysis Who Have Secondary Hyperparathyroidism: Post Hoc Analysis Based on Baseline Alkaline Phosphatase

Suguru Yamamoto,[1] Shinji Yoneda,[2] Junichiro J. Kazama,[3] Ichiei Narita.[1] *[1]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Medical Affairs Department, Sanwa Kagaku Kenkyusho Co., Ltd., Nagoya, Japan; [3]Division of Nephrology and Hypertension, Fukushima Medical University, Fukushima, Japan.*

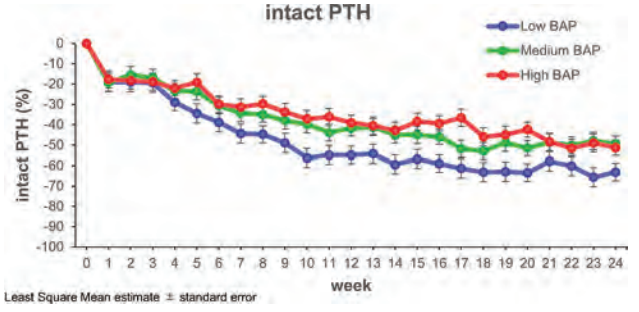
Background: Secondary hyperparathyroidism (SHPT) is a major complication in hemodialysis (HD) patients. Calcimimetics have been shown to improve bone turnover by suppressing parathyroid hormone (PTH) production. However, it remains unclear whether the degree of bone turnover influences the efficacy of calcimimetics. This study aimed to evaluate the efficacy of Upacicalcet on PTH suppression and changes in bone turnover, based on baseline alkaline phosphatase levels.

Methods: A post-hoc analysis was conducted on data from a phase 3, placebo-controlled, double-blind study of Upacicalcet in HD patients with SHPT. Patients were categorized into three groups based on tertiles of baseline serum bone-specific alkaline phosphatase (BAP) concentrations. Serum concentrations of intact PTH, BAP, tartrate-resistant acid phosphatase-5b (TRACP-5b), and BAP/TRACP-5b ratio were measured. Percent change from baseline in these parameters was assessed using a mixed-effects models for repeated measures. Differences in bone turnover markers among the three BAP groups at 24 weeks were evaluated using Tukey-Kramer multiple comparison adjustment.

Results: The analysis included 103 HD patients with SHPT treated with Upacicalcet. Patients were categorized into low BAP (<12.8 μg/L), medium BAP (12.8–18.8 μg/L), and high BAP (>18.8 μg/L) groups based on baseline serum BAP concentrations. After 24 weeks intervention with Upacicalcet, intact PTH concentration decreased in all baseline BAP groups. There was a tendency for a greater decrease in PTH in the low BAP group compared to the medium (13.7±5.4%, p=0.0287) and high BAP groups (11.9±5.7%, p=0.0906). Serum concentrations of BAP and TRACP-5b decreased, while the serum BAP/TRACP-5b ratio increased in all groups.

Conclusions: Upacicalcet decreased serum intact PTH concentration regardless of the degree of bone turnover. The effect was more pronounced in patients with low BAP levels, however, Upacicalcet may improve bone turnover in HD patients with any bone metabolism state.

Funding: Commercial Support - Sanwa Kagaku Kenkyusho co.,ltd.



TH-PO136

Comparison between the Different Doses of Preoperative Calcitriol to Prevent Hungry Bone Syndrome after Parathyroidectomy in ESKD: A Randomized Controlled Clinical Trial

Ompan Thookhamme, Pitchamon Inkong. *Phramongkutklao College of Medicine, Bangkok, Thailand.*

Background: The most common complication of parathyroidectomy in end-stage kidney disease (ESKD) is hungry bone syndrome (HBS), resulting in prolonged hospitalization. Administering calcitriol before surgery is one strategy for preventing these complications; however, limited studies on the recommended calcitriol dose. The study aims to compare the efficacy and safety of different doses of calcitriol in preventing hypocalcemia in end-stage kidney disease (ESKD).

Methods: ESKD patients on regular hemodialysis with renal hyperparathyroidism undergoing parathyroidectomy were randomly assigned to receive 4 mcg/day of calcitriol or 2 mcg/day for 3 days before surgery. The primary outcome was hungry bone syndrome, defined as severe hypocalcemia or hypocalcemia on day 7, and secondary outcomes included electrolyte disturbances and hospitalization length.

Results: 28 ESKD patients who underwent parathyroidectomy were enrolled, 14 received 4 mcg and the other 14 received 2 mcg of calcitriol. The mean age was 47.11±11.47 years, the mean serum calcium was 10.56±0.78 mg/dL, and the mean serum parathyroid hormone was 1866±677.62 pg/mL. The incidence of HBS was 62.5%, occurring in 5 (38.5%) and 10 (90.1%) participants in the high and low calcitriol groups, respectively (p = 0.008). The incidence of severe hypocalcemia within 72 hours were 5 (35.7%) in high-dose and 7 (50%) in low-dose groups, respectively (p = 0.704). Other factors including hypophosphatemia and length of hospitalization were similar in both groups. No serious adverse events were reported.

Conclusions: 4 mcg of calcitriol showed significant benefits in preventing hungry bone syndrome after parathyroidectomy compared to 2 mcg of calcitriol, without serious adverse effects.

Table 2. Primary, Secondary, and Safety outcomes

Outcomes	Calcitriol 4 mcg/d	Calcitriol 2 mcg/d	p-value
Primary outcome			
Hungry bone syndrome	5/13 (38.5%)	10/11 (90.1%)	0.008
• Severe hypocalcemia requiring IV calcium within 72 hours	5/14 (35.7%)	7/14 (50%)	0.704
• Hypocalcemia on day 7	2/12 (16.7%)	8/10 (80%)	0.008
Secondary outcomes			
Early hypocalcemia	10/14 (71.4%)	9/14 (64.3%)	1.000
Severe hypocalcemia and hypophosphatemia within 72 hours	4/14 (28.6%)	4/14 (28.6%)	1.000
Hypophosphatemia within 72 hours	9/14 (64.3%)	8/14 (57.1%)	1.000
Hypomagnesemia	0/14 (0%)	0/14 (0%)	N/A
Hyperkalemia	3/14 (21.4%)	3/14 (21.4%)	1.000
Cumulative oral calcium supplement (g)	8.31 ± 3.03	10.51 ± 7.23	0.307
Hospitalization stays*	92.43 ± 14.88	90.14 ± 36.88	0.831
Adverse events			
Hypercalcemia	0/14 (0%)	0/14 (0%)	N/A
Phlebitis	1/14 (7.1%)	0/14 (0%)	1.000
Others	1/14 (7.1%)	0/14 (0%)	1.000

*Data presents as mean ± SD

TH-PO137

Vitamin D Metabolite Ratio as a Marker of Bone Turnover and Change in Volumetric Bone Mineral Density in Older Men

Emma A. Mulligan, O. Alison Potok, Joachim H. Ix, Charles Ginsberg. *University of California San Diego, La Jolla, CA.*

Background: The vitamin D metabolite ratio(VMR), calculated by the ratio of 24,25-dihydroxyvitamin D3 to 25-hydroxyvitamin D(25[OH]D3), is a marker of vitamin D stores that may be a better predictor of bone health outcomes than 25(OH)D. Previously, we found that a higher VMR was cross-sectionally associated with higher volumetric bone mineral density (vBMD) in older men. In this analysis we examined the relationship between the VMR and 25(OH)D with biomarkers of bone turnover (BTM's) and changes in vBMD in older men in the Osteoporotic Fractures in Men (MrOS) study.

Methods: We used multiple linear regression models to evaluate the relationship between the VMR and 25(OH)D with BTM's, including parathyroid hormone(PTH), C-terminal telopeptide of type I collagen(CTX-I) and N-terminal propeptide of type I procollagen(PINP). vBMD was assessed at the distal radius and tibia by high resolution peripheral quantitative computed tomography (HRpQCT). We similarly evaluated the relationship of the same vitamin D measures with annualized percent change in vBMD.

Results: 254 men with repeat measures of vBMD were included in this analysis. Mean time (SD) between scans was 6(0.6) years. Mean age of participants was 83(3.3) years, with a mean eGFR of 71(14)mL/min/1.73m^2, and 22% had chronic kidney disease (eGFR<60). Mean VMR and 25(OH)D were 6.5(2.2)[(ng/mL)/(ng/mL)] and 39(14)ng/mL, respectively. Mean PTH, CTX-I and P1NP were 50(30) pg/mL, 0.29 (0.18) ng/mL and 50(23) ng/mL, respectively. In fully adjusted models both VMR and 25(OH)D were inversely associated with parathyroid hormone concentrations (**Table**), but only the VMR was inversely associated with CTX-I. Neither VMR nor 25(OH)D was associated with a marker of bone formation or annualized change in vBMD.

Conclusions: In community living older men, only the VMR was inversely associated with a marker of bone resorption, CTX-I. Neither VMR nor 25(OH)D was associated with a marker of bone formation or annualized change in vBMD. Further studies are needed to evaluate how the VMR may affect bone longitudinally.

Funding: NIDDK Support, Other NIH Support - NIA, NIAMS, NCATS, NIH Roadmap for Medical Research

Table: The association of the VMR and 25(OH)D with biomarkers of bone turnover*

	PTH	P	CTX	P	P1NP	P
	Per SD Lower (95% CI)		Per SD Lower (95% CI)		Per SD Lower (95% CI)	
VMR	9.3 (6.2, 12.5)	<0.001	0.024 (0.004, 0.046)	0.016	1.49 (-0.97, 4.09)	0.240
25(OH)D	4.7 (2.0, 7.6)	<0.001	0.004 (-0.014, 0.022)	0.690	0.80 (-1.48, 3.21)	0.500

*Models adjusted for age, race, BMI, smoking history, study site, season, blood pressure, physical activity, self-report of diabetes mellitus and estimated glomerular filtration rate (eGFR)

TH-PO138

Alfacalcidol vs. Calcitriol in the Management of Secondary Hyperparathyroidism in CKD

Muriel Ghosn, Wasim El Nekidy, Jihad Mallat, Fadi A. Hijazi, Rakesh Madhyastha, Emna Abidi, Iyad Ghazal, Amir R. Malik. *Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates.*

Background: This study aims to assess the efficacy of alfacalcidol compared to calcitriol in reducing iPTH levels in patients with chronic kidney disease

Methods: This retrospective cohort study was conducted at our quaternary care hospital between January 1st, 2022, and December 31st, 2022. Adult Patients diagnosed with CKD stage 3 to 5 (not on dialysis) who received alfacalcidol for at least 3 months followed by calcitriol for another 3 months were included. Laboratory values were assessed at baseline, at 3 months while on alfacalcidol then at 3 months while on calcitriol. The primary outcome was the suppression of the iPTH, while the secondary outcome was the effect on total serum calcium. The study was approved by the hospital's research ethics committee

Results: Seventy adult patients were included in the analysis. Statistical analysis was conducted using Wilcoxon signed rank test and McNemer test. CKD stage 3 comprised 47.1% of the sample while stage 4 comprised 37.1%. The median dose of alfacalcidol was 0.5 (0.25-0.8) mcg, compared to 0.5 (0.25-0.5) mcg for calcitriol (p= 0.001). The median time between baseline and outcome laboratory measurements was 94 (83-106) days for alfacalcidol and 94 (78.5-110.5) for calcitriol (p= 0.676). No significant differences were observed in the use of phosphate binders or non-active vitamin D between the time periods. Alfacalcidol did not significantly suppress the iPTH levels with median values of 13.31 (8.23 - 24.4) pg/mL at baseline and 12.5 (8.86 - 24.7) pg/mL after 3 months (p= 0.937). In contrast, calcitriol significantly reduced the iPTH levels from 12.5 (8.86 - 24.7) pg/mL to 10.7 (5.7 -19) pg/mL (p= 0.017). Additionally, alfacalcidol did not significantly increase calcium levels, with values of 2.29 (2.2 - 2.3) mmol/L at baseline and 2.3 (2.23 - 2.36) mmol/L after 3 months (p=0.237), whereas calcitriol significantly increased calcium levels from 2.3 (2.23 - 2.36) mmol/L to 2.34 (2.27 - 2.43) mmol/L (p=0.001). Albumin values remained unchanged throughout the study period

Conclusions: Calcitriol, at significantly lower doses, was more effective than alfacalcidol in reducing iPTH levels and increasing calcium levels over 3 months. Larger prospective controlled studies are needed to confirm these findings

TH-PO139

Association of Serum Magnesium Levels and Calcimimetic Use for Cardiovascular Events (CVE) in Patients on Hemodialysis

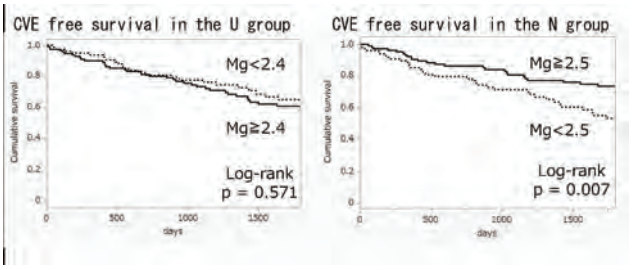
Tomohiro Saito,[1] Masahide Mizobuchi,[2] Kiryu Yoshida,[3] Tadashi Kato,[1] Noriyuki Kato,[4] Hiroaki Ogata,[3,5] Fumihiko Koiwa,[2] Hirokazu Honda.[1] *[1]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [2]Division of Nephrology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [3]Division of Nephrology, Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan; [4]Saiyu Clinic, Saitama, Japan; [5]Department of Medical Education, Showa University School of Medicine, Tokyo, Japan.*

Background: Lower serum Mg levels have been shown to be associated with all-cause death and CVE in hemodialysis patients. Calcimimetics use is likely to reduce CVE risk. Serum Mg concentrations are suggested to affect responsiveness of calcimimetics. However, the interaction of caicmimimetics and Mg on CVE remains unclear.

Methods: We conducted a retrospective analysis on 403 HD patients (female, 36.7%; age (median), 62; HD vintage (median), 76 months) in a single facility in Japan. The patients were divided into the user (U; n=196) and the non-user groups (N; n=207), based on status of calcimimetics use at baseline. CVE included cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, transient ischemic attack, or hospitalization for heart failure or ventricular arrhythmia. Multivariable Cox regression analysis and Kaplan-Meier analysis were applied for analytical approach.

Results: Median observation period was 64 months. CVE significantly occurred in patients in the below-median Mg levels than in those in the above-median Mg levels (Hazard ratio (HR), 0.34 [95% confidence interval, 0.13-0.80]; P = 0.018) among the N group, but the incidence of CVE was comparable among the U group (HR, 1.48 [0.60-3.68]; P = 0.397). A similar trend was observed in all-cause mortality.

Conclusions: These results suggest that low Mg levels may be a predictor of CVE in hemodialysis patients without calcimimectis and the CVE benefits of Mg may be attenuated under the use of calcimimetics.



TH-PO140

Serum Magnesium and Progression of Coronary Artery Calcification: A Report from the Chronic Renal Insufficiency Cohort (CRIC) Study

Mehreen Mehmood,[1] Radhika Kanthety,[1] Zhengyi Chen,[2] Mahboob Rahman,[1] Mirela A. Dobre,[1] Lavinia A. Negrea.[1] *[1]University Hospitals, Cleveland, OH; [2]Case Western Reserve University, Cleveland, OH.*

Background: Magnesium may play a protective role against the progression of vascular calcification in chronic kidney disease (CKD), however the evidence remains scarce. Higher serum magnesium levels are consistently associated with a reduced volume of vascular calcification in CKD populations. This study aims to evaluate the association between serum magnesium level and progression of coronary artery calcification (CAC) in a cohort of individuals with CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study. We hypothesize that low serum magnesium level, is a risk factor for CAC progression.

Methods: Serum magnesium and CAC were measured in 862 CRIC participants at baseline and after 3 years. CAC was measured using electron beam or multidetector computed tomography and calculated using Agatston score. CAC progression was defined as follows: CAC> 0 at follow-up if CAC=0 at baseline; annualized change ≥10 Agatston units at follow-up if 0<CAC≤100 at baseline; and annualized percent change (annualized change in CAC score divided by the baseline CAC score) ≥ 10% at follow-up, if CAC > 100 at baseline. Logistic regression models were built to study the association of interest.

Results: The mean eGFR was 44±15ml/min per 1.73m^2, mean serum magnesium was 1.96± 0.28 mg/dL, and 42.7% participants had diabetes. A total of 412 (48%) participants experienced CAC progression. No significant correlation was observed between baseline magnesium level and total Agaston score (r=0.032, p=0.58). Compared to participants with high baseline magnesium level, those with low magnesium (<2 mg/dL) were more likely to have CAC >400 at baseline (59.3% vs 40.7%) but the difference was not statistically significant (p=0.62). Each mg/dL increase in magnesium level was associated with 17% lower but not statistically significant lower risk of CAC progression, in models adjusted for demographics, baseline co-morbidities, medications, calcium level, eGFR and proteinuria (OR 0.73; 95%CI: 0.32–1.64). Subgroup analyses by sex, race and CKD stages reveal similar findings.

Conclusions: In a cohort of patients with CKD stages 2-4, serum magnesium level was not associated with CAC progression. Further studies will be needed to test the magnesium's potential role to inhibit vascular calcification.

TH-PO141

Magnesium-Sensitive Changes in Serum Calciprotein Crystallization Test (T50): A Post Hoc Analysis from a Randomized Controlled Trial

Iain O. Bressendorff,[1,2] Daniel Cejka,[3] Andreas Pasch,[4,5] Morten Schou,[1] Lisbet Brandi,[2] Ditte Hansen.[1] *[1]Herlev Hospital, Herlev, Denmark; [2]Nordsjaellands Hospital, Hillerød, Denmark; [3]Ordensklinikum Linz GmbH Elisabethinen, Linz, Austria; [4]Calciscon AG, Biel, Switzerland; [5]Johannes Kepler Universitat Linz, Linz, Austria.*

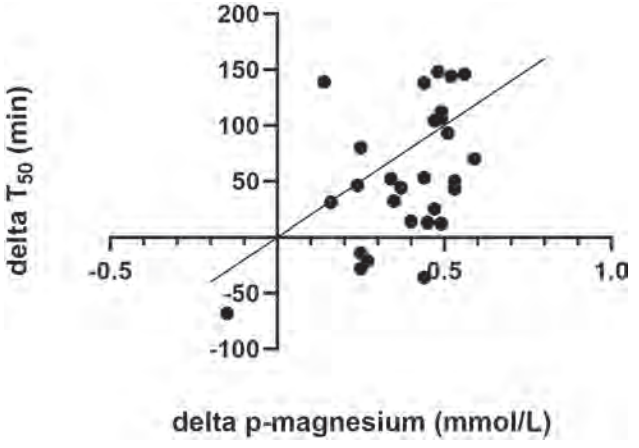
Background: Serum calciprotein crystallization test (T50) associates with risk of cardiovascular and all-cause mortality in end-stage kidney disease. We have previously demonstrated that increasing dialysate Mg also prolongs T50. We hypothesized that there is an inter-patient variability in responses in T50 to increases in plasma Mg with putatively "Mg sensitive" and "Mg resistant" patients.

Methods: Post-hoc analysis of a previous randomized controlled trial of increasing dialysate Mg from 0.5 mmol/L to 1.0 mmol/L. Based on *in vitro* data, we expected an increase in T50 of 20 min for every 0.1 mmol/L increase in plasma Mg. We plotted changes in T50 and plasma Mg for subjects randomized to dialysate Mg of 1.0 mmol/L to identify subjects with changes as expected (Mg-sensitive) or changes less than expected (Mg-resistant). We also plotted individual measurements of T50 and plasma Mg to visually inspect associations between the two.

Results: Among the 28 subjects analyzed, 13 (46%) were characterized as Mg-sensitive and 15 (54%) were characterized as Mg-resistant. Visual inspection of T50 plotted against plasma Mg showed linear associations for Mg-sensitive individuals versus scattered associations for Mg-resistant individuals. Mg-sensitive individuals had

significantly lower baseline T50 and fetuin-A, but no differences in plasma magnesium, phosphate, ionized calcium, bicarbonate, or albumin. Mg-sensitive individuals had significantly greater increases in T50 during high dialysate Mg of 1.0 mmol/L compared to Mg-resistant individuals despite similar increases in plasma Mg.

Conclusions: Patients with end-stage kidney disease have differential responses to T50 despite similar levels of plasma Mg, suggesting that some patients may benefit more than others from a targeted increase in plasma Mg. This suggests an opportunity for personalization of treatments targeting T50.



TH-PO142

Effect of Dialysate Bicarbonate on Calciprotein Crystallization Time (T50) in Hemodialysis Patients: The D-Bic Study

Daniel Cejka,[1] Peter S. Neufeld,[1] Andreas Pasch,[2,3] Edward R. Smith,[4,6] Martina M. Gaggl,[5] Maria C. Haller,[1] Jennifer D. Machacek.[1]
[1]Ordensklinikum Linz GmbH Elisabethinen, Linz, Austria; [2]Calciscon AG, Biel, Switzerland; [3]Johannes Kepler University, Faculty of Medicine, Departement of Physiology and Pathophysiology, Linz, Austria; [4]Royal Melbourne Hospital, Parkville, Department of Nephrology Victoria, Australia, Melbourne, VIC, Australia; [5]Center for Public Health, Public Health Nutrition, Medical University Vienna, Vienna, Austria; [6]Department of Medicine, University of Melbourne, Parkville, VIC, Australia.

Background: Short calciprotein crystallization time (low T50) is directly associated with increased risk of cardiovascular events and mortality. Higher serum bicarbonate levels consistently correlate with higher T50 time in observational studies. However, oral supplementation of sodium bicarbonate failed to increase T50 times in interventional studies in CKD patients. Here, we investigated whether increases in dialysate bicarbonate concentrations increase T50 times.

Methods: In a prospective, single center, single arm, interventional trial, dialysate bicarbonate was decreased from baseline settings to 27 mmol/l (D-Bic 27) in a step-wise fashion (2 mmol/l change per dialysis session), followed by a step-wise increase in dialysate bicarbonate settings to 37 mmol/l (D-Bic 37), over a course of 6 weeks. The primary endpoint was the change in T50 time between the D-Bic 27 and D-Bic 37 phase.

Results: Of 29 recruited patients, 24 completed the study per protocol. T50 time increased significantly from 246 ± 77 to 282 ± 81 minutes from the D-Bic 27 to the D-Bic 37 phase ($p<0.0001$). The hydrodynamic radius (size) of secondary calciprotein particles generated in the T50 test ($CPP\text{-}2_{Rh}$) did not differ significantly between the D-Bic 27 and D-Bic 37 phase (251± 75 vs. 240 ± 78 nm, p=0.27). Serum bicarbonate, serum pH, and intact parathyroid hormone (PTH) increased significantly, while ionized serum calcium decreased significantly from the D-Bic 27 to the D-Bic 37 phase. Serum potassium, phosphate and magnesium did not change significantly throughout the study.

Conclusions: Increases in dialysate bicarbonate led to significant increases in T50 time.

TH-PO143

ESKD, Calciphylaxis Subtypes, and Patient Demographics

Christopher El Mouhayyar, Aaron M. Seto, Houda Bouchouari, Tianqi Ouyang, Sagar U. Nigwekar. *Massachusetts General Hospital, Boston, MA.*

Background: Calciphylaxis is a rare life-threatening vascular calcification disease associated with morbidity and mortality. Calciphylaxis presents heterogeneous outcomes and poses challenges in management due to limited treatment options and poor prognosis. This study aims to assess the associations between End Stage Kidney Disease (ESKD), different calciphylaxis subtypes and demographics.

Methods: This is a prospective cohort study of calciphylaxis patients within the Partners Calciphylaxis Biorepository and Patient Registry between 2017 and 2023. We examined the associations between ESKD status, lesion location, clinical and histopathological characteristics.

Results: Among 166 adult patients with calciphylaxis, 112 had ESKD while 54 did not. Compared to non-ESKD calciphylaxis patients, ESKD patients were more likely to be Black (OR:5.20, 95% CI: 1.58,21.40, P =0.011), hypertensive (49% vs 28%, P=0.015), coronary artery disease (46 vs 28%, P=0.043), peripheral vascular disease (48%vs 24%, P=0.005). Upon diagnosis, 104 patients exhibited at least one lesion proximal to the elbows and knees and were classified as having central calciphylaxis distribution while 62 patients had lesions solely distal to the elbows and knees and were classified as having peripheral calciphylaxis distribution. Patients with peripheral lesions were more likely to be older (67 years [55, 73] vs (59 [49, 68], P=0.008), males (44% vs 27%, P=0.042), with indurations (77% vs 47% P<0.001), plaques (63% vs 40% P=0.009), and nodules (42% vs 13% P<0.001) and less likely to have a history of congestive heart failure (31% vs 51% P=0.017) compared to those with central lesions.

Conclusions: Our study identified associations between ESKD status and calciphylaxis lesion location with patient demographics and cutaneous lesion characteristics.

Funding: NIDDK Support

Table 1. Uremic status, lesion location and patient demographics

	Uremic vs Non-Uremic Lesions						Central vs Peripheral Lesions					
	Univariable Analysis			Multivariable Analysis			Univariable Analysis			Multivariable Analysis		
Characteristics	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.00	0.98,1.05	0.718	1.00	0.99,1.05	0.307	1.03	1.01,1.06	**0.010**	1.05	1.02,1.09	**<0.001**
Male Gender	1.89	0.93,4.04	0.085	2.01	0.87,4.87	0.111	2.09	1.08,4.08	**0.029**	2.31	1.00,5.48	**0.053**
Race												
Asian	1.14	0.11,24.8	0.919	1.00	0.00,24.2	0.998	3.84	0.34,79.7	0.298	3.51	0.30,1.1E	0.192
Black	5.56	0.89,9.25	0.107	5.20	1.58,21.40	**0.011**	0.85	0.31,2.18	0.743	1.79	0.57,5.64	0.306
Latino/Other	2.08	0.61,9.55	0.279	2.45	0.63,12.4	0.225	2.43	0.89,7.80	0.120	4.27	1.26,15.50	**0.021**
Localization: peripheral	0.57	0.29,1.11	0.108	0.41	0.18,0.92	**0.033**						
Diabetes	2.16	1.08,4.35	**0.028**	2.30	1.08,5.36	**0.032**	1.52	0.76,3.16	0.247	1.59	0.54,5.04	0.669
Hx of Warfarin	1.63	0.88,3.19	0.148	3.65	0.76,3.64	0.205	0.89	0.47,1.67	0.716	0.88	0.27,3.25	0.151
Serum Calcium	0.75	0.56,1.08	0.164	0.71	0.47,1.04	0.094	1.00	0.74,1.54	0.981	1.02	0.72,1.48	0.932
Serum Phosphorus	1.33	1.07,1.69	**0.014**	1.44	1.12,1.89	**0.006**	1.02	0.85,1.24	0.866	1.13	0.90,1.44	0.296
Uremic vs non ESKD							0.57	0.29,1.11	0.100	0.23	0.01,2.81	0.204
							0.62	0.32,1.23	0.171	1.87	0.15,46.3	0.638

ESKD: end stage kidney disease, Hx: History

TH-PO144

SEAPORT 1: An Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of INZ-701 in Participants with ESKD Undergoing Hemodialysis: Interim Analysis

Asghar A. Chaudhry,[1] Steven Zeig,[4] Bruce J. Fisch,[2] Yves Sabbagh,[2] Kurt C. Gunter,[2] Sagar U. Nigwekar.[3] *[1]South Florida Nephrology Research, Coral Springs, FL; [2]Inozyme Pharma, Boston, MA; [3]Massachusetts General Hospital, Boston, MA; [4]Elixa, Hollywood, FL.*

Background: Calciphylaxis is a dire complication of end-stage kidney disease (ESKD) with high mortality and no approved therapies. It is characterized by calcification and occlusion of arterioles in the skin leading to painful lesions, ulceration, and infection. Plasma pyrophosphate (PPi), a critical inhibitor of ectopic vascular calcification, is low in chronic kidney disease (CKD) patients and even lower in ESKD patients, who are at highest risk of developing calciphylaxis. Moreover, lower PPi is associated with worse survival in calciphylaxis patients. The ectonucleotide pyrophosphatase/phosphodiesterase type 1 (ENPP1) enzyme is responsible for generating most of the body's PPi via catalysis of extracellular ATP. INZ-701 is a novel fusion protein comprised of functional ENPP1 enzyme fused to the Fc portion of human immunoglobulin 1. Treatment of a CKD rat model with INZ-701 prevented or reduced vascular calcification. Objective: To evaluate the safety, pharmacokinetics and pharmacodynamics of INZ-701 in patients with ESKD receiving hemodialysis. The primary endpoint is change from baseline in plasma PPi.

Methods: Open-label phase 1 trial of INZ-701 in individuals aged 18 – 69 years with ESKD receiving hemodialysis thrice weekly and who had low PPi (< 700 nM) at screening. Participants were administered 1.8 mg/kg of INZ-701 subcutaneously once weekly for four weeks.

Results: Thirteen participants were screened and 8 have been entered into the study to date. Median baseline age for entered participants was 67 years (range 28-69) and 5 participants (63%) were male. Six participants (75%) had type 2 diabetes. The majority of participants were Black or African American (n=5, 63%). Median (IQR) plasma PPi at baseline in the 8 entered participants was 281 nM (322). Median PPi for all screened patients was 502 nM (422).

Conclusions: Median PPi at screening in 13 patients with ESKD on hemodialysis was substantially lower than what is reported in healthy volunteers (1002-2169 nM; n=10), which supports previous findings implicating PPi in the pathophysiology of ESKD. INZ-701 safety, tolerability, pharmacokinetics, and pharmacodynamics results will be presented.

Funding: Commercial Support - Inozyme Pharma

TH-PO145

Association of Damaged Cardiovascular-Bone-Skeletal Muscle Axis with All-Cause Mortality and CKD Progression in Patients with Predialysis CKD: The Fukuoka Kidney Disease Registry (FKR) Study

Shunsuke Yamada,[1] Hokuto Arase,[3] Shigeru Tanaka,[1] Kazuhiko Tsuruya,[2] Takanari Kitazono,[1] Toshiaki Nakano.[1] *[1]Kyushu University, Department of Medicine and Clinical Science, Fukuoka, Japan; [2]Nara Medical University, Department of Nephrology, Nara, Japan; [3]NHO Fukuokahigashi Medical Center, Department of Nephrology, Fukuoka, Japan.*

Background: The cardiovascular system, bones, and skeletal muscles are interrelated and often concurrently damaged in patients with chronic kidney disease (CKD). While organ-related associations such as the bone-vascular axis and osteosarcopenia have been proposed, the impact of combined disorders in these three systems on all-cause mortality and CKD progression in pre-dialysis CKD patients remains unclear.

Methods: We defined organ damage in bones, skeletal muscles, and the cardiovascular system as a history of fractures, low skeletal muscle mass, and cardiovascular disease, respectively. Skeletal muscle mass was estimated using Yamada's formula, with the first quartile classified as low skeletal muscle mass. A total of 3,792 pre-dialysis CKD patients were categorized into four groups based on the number of damaged organs: G1 (no damaged organ), G2 (one damaged organ), G3 (two damaged organs), and G4 (three damaged organs). We then evaluated the association between the number of damaged organs and all-cause mortality as well as composite renal events (defined as a 1.5-fold increase in serum creatinine, kidney transplantation, or initiation of dialysis).

Results: Over a 5-year observation period, 382 patients died, and 1,305 experienced composite renal events. The numbers of patients in the G1, G2, G3, and G4 were 2,168, 1,217, 364, and 43, respectively. Survival analysis showed that the adjusted hazard ratios (HRs) for all-cause mortality, using the G1 group as a reference, were: G2: 1.54 (95% CI: 1.16-2.06), G3: 2.07 (95% CI: 1.47-2.92), and G4: 3.54 (95% CI: 2.07-6.07). Similarly, the adjusted HRs for composite renal events were: G2: 1.25 (95% CI: 1.10-1.42), G3: 1.30 (95% CI: 1.07-1.59), and G4: 2.01 (95% CI: 1.24-3.26). When all-cause death was set as a competing risk, a Fine-Gray competing risk model showed a similar association between the number of damaged organs and the composite renal events.

Conclusions: The risk of all-cause mortality and CKD progression increases with the number of damaged organs in the cardiovascular, bone, and skeletal muscle axis in patients with pre-dialysis CKD. Protection of the cardiovascular-bone-skeletal muscle axis may be a therapeutic option for preventing death and ESKD in this population.

TH-PO146

Phosphate Loading per Nephron Predicts CKD Progression and All-Cause Death in Patients with Nondialysis-Dependent CKD: The Fukuoka Kidney Disease Registry (FKR) Study

Shunsuke Yamada,[1] Shigeru Tanaka,[2] Kazuhiko Tsuruya,[3] Takanari Kitazono,[1] Toshiaki Nakano.[1] *[1]Kyushu University, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Fukuoka, Japan; [2]Fukuoka Dental College, Department of Medicine, Fukuouka, Japan; [3]Nara Medical University, Department of Nephrology, Nara, Japan.*

Background: CKD-MBD develops in the early stages of CKD and contributes to the increased risk of end-stage kidney disease and death. Thus, it is critical to identify new indicators that reflect early events of CKD-MBD and initiate appropriate interventions in the non-dialysis CKD population.

Methods: We examined 3,320 patients enrolled in the FKR study, a prospective observational study of patients with non-dialysis CKD stages G1–G5. We focused on the urinary phosphate excretion per nephron as an indicator of early CKD-MBD pathogenesis. Urinary phosphate excretion per nephron was determined by using the estimated urinary phosphate excretion divided by eGFR as a proxy for nephron number. Estimated phosphate excretion was calculated using estimated 24-hour creatinine (Cr) excretion and urinary Cr and phosphate concentrations. After patients were divided into quartiles(Q1-Q4) according to the baseline urinary phosphate loading per nephron, we determined the association of phosphate loading per nephron with the risk of all-cause death and composite kidney event using longitudinal data. The composite kidney event was defined as the development of end-stage kidney failure and/or a 1.5-fold increase in serum creatinine concentrations.

Results: Over 5 years, 1,132 patients developed a composite kidney event, and 295 died. Urinary phosphate loading per nephron elevated as early as an eGFR of 70 mL/min/1.73m^2 and preceded the changes in serum PTH, calcium, and phosphorus concentrations. Multivariate-adjusted Cox proportional hazard regression analyses revealed a significant association between an increased phosphate loading per nephron and a heightened risk of developing a composite renal event and all-cause death. The hazard ratios (95%CI) for all-cause death and composite kidney events in Q4 were significantly higher than those in Q1: 1.70 (1.01-2.85) and 1.57 (1.16-2.10), respectively. These associations were independent of the serum PTH, calcium, and phosphorus concentrations.

Conclusions: Phosphate loading per nephron may reflect the early stage of CKD-MBD pathophysiology and predict CKD progression and all-cause death in patients with non-dialysis CKD. Early intervention for phosphate overload may retard the progression of CKD and decrease the death risk in this population.

TH-PO147

Getting Insights from Oral Metabolomics into Vascular Calcification among Patients with ESKD

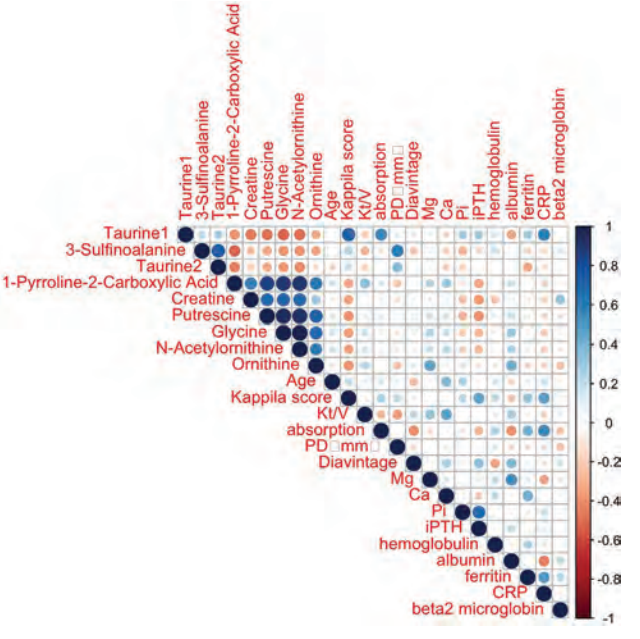
Wen Wen, Yuehong Li. *Beijing Tsinghua Changgung Hospital, Beijing, China.*

Background: Oral inflammatory diseases, chronic kidney disease (CKD), and vascular calcification (VC) are closely related. Here, we investigated the changes in oral metabolites caused by vascular calcification among patients with end-stage kidney disease.

Methods: Patients were divided into VC group (Kauppila score ≥ 8) and HC group (Kauppila < 8). The patients in the two groups were matched according to their age, gender, and diabetes status. Gingival crevicular fluid was extracted and non-target metabolomics was performed. Two normalization methods were used, one was the total amount normalization, and the other was the creatinine value normalization. Metabolites were compared between the two groups. Differential metabolites were included in the enrichment analysis to find the key metabolites and pathways. Pearson correlation analysis was performed between differential metabolites of key pathways involved in the enrichment analysis and clinical indicators.

Results: The gingival crevicular fluid samples of 30 patients (VC group 15 cases vs. HC group 15 cases) were examined. In enrichment analysis, 35 and 105 differential metabolites were observed. Four key metabolic pathways, including taurine and the secondary metabolism of taurine, arginine and proline metabolism, arginine biosynthesis, and glutathione metabolism, were discovered. It is shown that the key metabolites including taurine, 3-sulfinoalanine, 1-dihydropyrrolo-2-carboxylic acid, creatine, putamyldiamine, glycine, ornithine, and acetylornithine were found to be correlated with CKD-MBD parameters, inflammatory factors, and periodontal disease parameters.

Conclusions: Oral metabolites were diverse in ESRD patients with and without severe VC and linked closely to the CKD-MBD parameters, indicating the pivotal role of oral disease in the development of CKD-MBD.



Correlation analysis between metabolites involved in key pathways and clinical indicators

TH-PO148

Detection of Medial Vascular Calcification in Patients with CKD Using Cost-Effective Classifiers

Bengt Lindholm,[1] Urszula Bialonczyk,[2] Malgorzata Debowska,[2] Abdul Rashid T. Qureshi,[1] Leon Bobrowski,[2] Magnus Soderberg,[3] Peter Stenvinkel,[1] Tomasz Lukaszuk,[4] Jan T. Poleszczuk.[2] *[1]Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; [2]Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw, Poland; [3]Pathology, Clinical Pharmacology and Safety Sciences, AstraZeneca R&D, Gothenburg, Sweden; [4]Faculty of Computer Science, Bialystok University of Technology, Bialystok, Poland.*

Background: Despite medial vascular calcification (mVC) being linked to high cardiovascular morbidity and mortality in chronic kidney disease (CKD) patients, identifying mVC remains challenging. This study evaluates the cost-effectiveness of various machine learning (ML) frameworks for mVC assessment using circulating biomarkers and traditional risk factors.

Methods: A dataset of 152 CKD patients without (n=93) or with (n=59) mVC was used as an input to classifiers combined with feature selection algorithms: 1) logistic regression (LR), 2) support vector machine (SVM), 3) random forest (RF), 4) elastic net (EN) and 5) relaxed linear separability (RLS). These methods selected features that inform about the mVC probability. Incremental cost-effectiveness ratio (ICER) was calculated for each framework, considering both performance and procedure costs. Prevalence rate and possible years gained were treated as unknown parameters.

Results: On the analyzed dataset, the number of features selected by the methods varied between 5 (LR) and 21 (SVM), but all classifiers offered similar predictive performance, Tab. 1. LR emerged as the most cost-effective option, Fig. 1.

Conclusions: The results provide novel insights into biomarkers related to mVC and support the use of ML algorithms as a complementary tool to imaging techniques. The study emphasizes considering cost-effectiveness when selecting classifiers, as minor performance improvements may not justify the additional costs of required inputs.

Tab. 1. The results.

	Logistic regression	Support vector machines	Random forest	Elastic net	Relaxed linear separability
Accuracy	0.74	0.71	0.74	0.76	0.77
Selected features	age, copeptin, diabetes mellitus, sex, fat body mass index	age, copeptin, diabetes mellitus, choline, osteoprotegerin, sex, body mass index, fat body mass index, sclerostin, carboxy-terminal collagen crosslinks, desphospho-uncarboxylated MGP, homocysteine, IgM antibodies against phosphorylcholine, advanced glycation end products (skin autofluorescence), angiopoietin 2, undercarboxylated osteocalcin, high sensitivity C-reactive protein, insulin-like growth factor 1, IgM antibodies against malondialdehyde, lean body mass index, troponin T	age, copeptin, choline, osteoprotegerin, body mass index, sclerostin	age, copeptin, diabetes mellitus, choline, osteoprotegerin, sex, body mass index, sclerostin, desphospho-uncarboxylated MGP, homocysteine, IgM antibodies against phosphorylcholine	age, copeptin, diabetes mellitus, choline, osteoprotegerin, sex, fat body mass index, carboxy-terminal collagen crosslinks, apolipoprotein B1, free triiodothyronine, triglycerides, carboxylated osteocalcin, pentraxin-related protein, trimethylamine N-oxide, thyroid-stimulating hormone, uric acid

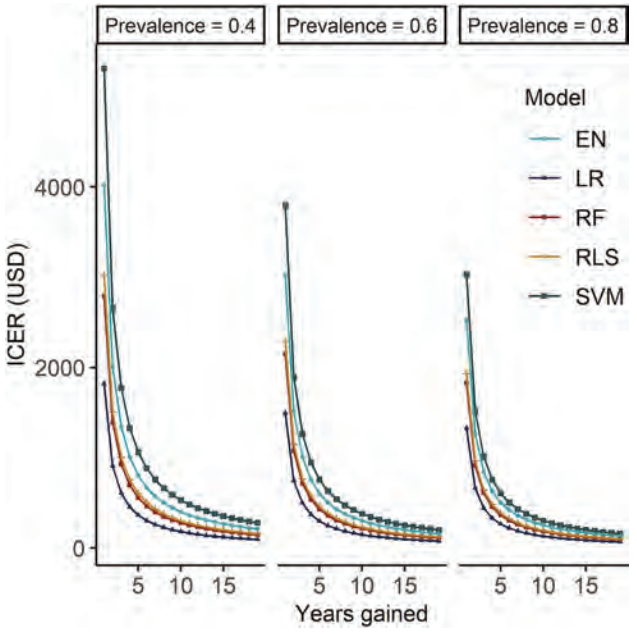


Fig. 1. ICER with the respect to mVC prevalence.

TH-PO149

Mineral Bone Disease (MBD) and Glycocalyx Injury in CKD in the Dallas Heart Study (DHS)

Shota Watanabe,[1] Peter N. Van Buren.[1,2] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]VA North Texas Health Care System, Dallas, TX.*

Background: MBD in CKD causes vascular calcification as a cardiovascular (CV) disease mediator. High phosphate (Ph) and parathyroid hormone (PTH) promote calcification, while osteopontin (OPN) is a calcification inhibitor. In dialysis patients, high Ph also associates with endothelial cell dysfunction (ECD), which may further increase CV risk. We aimed to determine how OPN, Ph, and PTH associated with syndecan-1 (SDC1), an endothelial glycocalyx injury marker, in CKD patients enrolled in a large multiethnic cohort study.

Methods: We retrospectively analyzed baseline data of CKD patients (estimated glomerular filtration rate [eGFR] <60 mL/min or urine albumin/creatinine [UACR] >30 mg/g) enrolled in DHS. We used Pearson correlation for associations between serum SDC1, OPN, PTH, Ph, eGFR, UACR, and age. We used all variables in a linear regression model with SDC1 as the outcome also controlling for race, sex, and diabetes.

Results: In 171 participants (Table1), mean age was 47.9 (9) years, mean eGFR 86.0 (34) mL/min, and median UACR 59.5 (35, 198) mg/g. Log SDC1 correlated with log OPN (r=0.8, p<.0001; Fig1), log PTH (r=0.2, p=.03), and eGFR (r=-0.2, p=.004). OPN independently predicted SDC1 (β=0.6, p<0.001), but Ph and log PTH (p=.1, p=.2) did not.

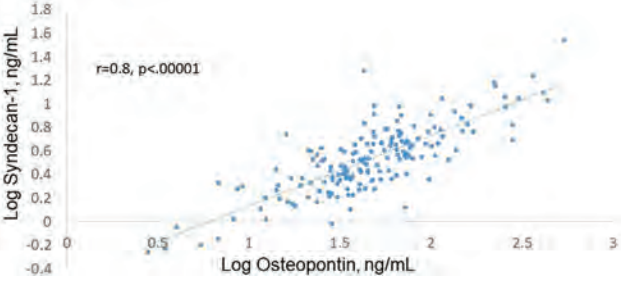
Conclusions: In CKD patients (mostly early CKD), OPN independently and strongly predicted SDC1, an endothelial glycocalyx injury marker. While OPN inhibits calcification in the context of MBD, it may exacerbate ECD even in early CKD.

Funding: NIDDK Support, Veterans Affairs Support

Patient Characteristics (n=171)

Age (years)	47.9 (9.0)
Number (%) male	82 (48%)
Number (%) Black race	114 (67%)
Number (%) with diabetes	56 (33%)
Body Mass Index (kg/m^2)	30.8 (26, 36)
Serum Syndecan-1 (ng/mL; median, IQR)	3.42 (2.3, 5.0)
Serum Osteopontin (ng/mL; median, IQR)	44.8 (29, 73)
Estimated MDRD glomerular filtration rate (mL/min; mean, SD)	86.0 (34)
Urine albumin/creatinine (mg/g; median, IQR)	59.5 (35, 200)
Serum Intact parathyroid hormone (pg/mL; median, IQR)	43.1 (28, 61)
Serum phosphate (mg/dL; median, IQR)	3.3 (2.9, 3.8)

Figure 1. Correlation Plot of Log-Syndecan-1 vs. Log-Osteopontin



TH-PO150

Fibroblast Growth Factor 23 (FGF-23) and Endothelial Cell Dysfunction (ECD) in the Dallas Heart Study Cohort

Peter N. Van Buren,[1,2] Jyothsna Gattineni.[1] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]VA North Texas Health Care System, Dallas, TX.*

Background: Mineral bone disease (MBD) and ECD are mortality risk factors that associate with each other in advanced chronic kidney disease (CKD). Phosphate (Ph) and parathyroid hormone (PTH) are late CKD MBD markers, but FGF23 is an early marker. Using data from Dallas Heart Study (DHS), a multi-ethnic cohort with largely preserved renal function, we assessed if FGF23 predicted ECD markers.

Methods: We measured FGF23 in stored DHS plasma. We compared demographic and lab measurements across FGF23 quartiles and used linear regression to identify associations with FGF23 and the following markers: asymmetric dimethylarginine (ADMA), vascular cell adhesion molecule (VCAM1), intracellular adhesion molecule (ICAM1), CD40 ligand, monocyte chemotactant protein 1 (MCP1), syndecan-1, and endoglin.

Results: In 1186 participants (37% male, 40% Black, 16% CKD), mean FGF23 was 44.0 (86) pg/mL. Across increasing FGF23 quartiles, coronary artery calcification, PTH, ADMA, MCP1, cholesterol, and CD40 ligand significantly increased while endoglin decreased (Table 1). ICAM1, VCAM1 and syndecan did not differ. Controlling for age, sex, race, diabetes, GFR, Ph, and PTH, log FGF23 independently predicted ADMA (β=0.03, p=.003), log syndecan-1 (β=0.1, p=.03), and log MCP1 (β=0.1, p=.04).

Conclusions: Multiple ECD markers associate with high FGF23. FGF23 independently predicts ADMA, syndecan-1, and MCP1 warranting prospective studies to determine if early MBD exacerbates ECD when renal function is normal or mildly reduced.

Funding: NIDDK Support, Veterans Affairs Support

Characteristics Across FGF23 Quartiles

	Quartile 1 (6.2-28.3 pg/mL)	Quartile 2 (28.3-36.4 pg/mL)	Quartile 3 (36.4-45.2 pg/mL)	Quartile 4 (45.3-2034 pg/mL)	p-value for trend
Age (years)	43 (35, 52)	42 (36, 50)	44 (37, 52)	45 (37, 52)	.1
Diabetes (%)	17 (6%)	27 (9%)	19 (6%)	35 (12%)	.03
BMI (kg/m^2)	27.3 (24-32)	27.8 (24-32)	28.8 (25-34)	29.1 (25-34)	.003
Estimated MDRD Glomerular Filtration Rate (mL/min)	101 (90-116)	99.5 (87-114)	94.1 (81-111)	91.1 (78-104)	<.0001
Serum Phosphate (mg/dL)	3.1 (2.8-3.5)	3.2 (2.8-3.5)	3.1 (2.8-3.5)	3.3 (2.9-3.7)	.001
Serum Calcium (mg/dL)	9.2 (9-9.5)	9.2 (9-9.5)	9.3 (9.1-9.5)	9.3 (9-9.6)	.02
Intact Parathyroid Hormone (pg/mL)	35.6 (27-51)	37 (27-50)	35.3 (28-46)	40.3 (29-57)	.03
Total cholesterol (mg/dL)	167 (147-196)	175 (151-201)	179 (154-203)	191 (160-208)	.0001
Electron Beam Computed Tomography Coronary Artery Calcification (Agatston)	0 (0-2.6)	0.5 (0-3.8)	0.5 (0-8.8)	1 (0-11.5)	.001
Asymmetric Dimethylarginine (µmol/L)	0.47 (0.41-0.53)	0.47 (0.42-0.54)	0.48 (0.41-0.56)	0.51 (0.44-0.57)	.0001
CD40 Ligand (ng/mL)	1.35 (0.8-2.2)	1.36 (0.8-2.3)	1.42 (0.8-2.3)	1.85 (1.1-3.2)	<.0001
Monocyte Chemotactant Protein-1 (pg/mL)	160 (113-211)	163 (111-214)	170 (127-242)	187 (137-248)	<.0001
Soluble endoglin (ng/mL)	1.71 (1.3-2.1)	1.64 (1.3-2.0)	1.58 (1.3-2.0)	1.56 (1.2-2.0)	.008
Syndecan-1 (ng/mL)	3.05 (2.3-4.3)	3.16 (2.3-4.3)	3.11 (2.3-4.2)	3.01 (2.4-4.4)	.6
Intracellular Adhesion Molecule-1 (ng/mL)	594 (462-819)	605 (435-801)	584 (417-787)	641 (468-886)	.3
Vascular Cell Adhesion Molecule 1 (ng/mL)	968 (706-1372)	982 (659-1342)	975 (700-1313)	994 (752-1404)	.4

TH-PO151

Association between Serum Glycerol-3-Phosphate and Fibroblast Growth Factor 23 in Nondiabetic Incident Hemodialysis Patients

Shari J. Zaslow,[1,2] Scott M. Wilson,[2] Stephen M. Sozio,[3,4] Bernard G. Jaar,[3,4] Michelle M. Estrella,[5,6] Aline Martin,[7] Rulan S. Parekh,[8,9] Wei Chen.[2,10]; *[1]University of Vermont The Robert Larner MD College of Medicine, Burlington, VT; [2]Albert Einstein College of Medicine, Bronx, NY; [3]Johns Hopkins University, Baltimore, MD; [4]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [5]University of California San Francisco, San Francisco, CA; [6]San Francisco VA Health Care System, San Francisco, CA; [7]Northwestern University Feinberg School of Medicine, Chicago, IL; [8]Women's College Hospital, Toronto, ON, Canada; [9]The Hospital for Sick Children, Toronto, ON, Canada; [10]Montefiore Medical Center, New York, NY.*

Background: Glycerol-3-phosphate (G3P), a byproduct of glycolysis that can be derived from injured kidneys, has been identified as a stimulator of fibroblast growth factor-23 (FGF-23) production. Furthermore, G3P is strongly correlated with circulating FGF-23 in people without kidney disease and in the setting of AKI. Since FGF-23 increases risk of mortality in patients with ESKD, understanding the relationship between G3P and FGF-23 may inform our diagnostic and treatment practices.

Methods: In a cross-sectional study of 99 nondiabetic patients with ESKD on incident hemodialysis from the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) cohort, we measured baseline G3P by mass spectrometry and C-terminal FGF-23 by ELISA. Participant characteristics were compared among G3P terciles using the Fisher's exact or Kruskal-Wallis's tests. Linear regression was used to examine the association between G3P terciles with log transformed FGF-23 while adjusting for sociodemographics, prevalent coronary artery disease, phosphorus, and parathyroid hormone.

Results: The median age of participants was 54 years (IQR 44-63), 38% were women, 71% were Black, 27% had coronary artery disease. Median FGF-23 level was 777 (IQR 222-1310) RU/mL. Participants with higher G3P were younger and had higher levels of serum phosphate and intact parathyroid hormone. Higher G3P was associated with higher FGF-23 in both unadjusted and adjusted models (p<0.001 and 0.004, respectively). Those with G3P in the highest tercile had 92% higher level of FGF-23 (95% CI: 5%, 252%; p=0.004) compared to participants within the lowest G3P tertile.

Conclusions: Higher G3P is positively associated with higher FGF-23 in those with ESKD. Our findings suggest that there may be a kidney-independent role of G3P in FGF-23 regulation. Future studies will need to address the relationship between G3P and FGF-23 with earlier stages of CKD.

Funding: NIDDK Support

TH-PO152

Soluble Klotho and Baseline Clinical Characteristics in the Systolic Blood Pressure Intervention Trial

David A. Drew,[1] Johanne V. Pastor,[3] Xilong Li,[3] Joachim H. Ix,[2] Mark J. Sarnak,[1] Orson W. Moe,[3] Javier A. Neyra.[4] *[1]Tufts Medical Center, Boston, MA; [2]UC San Diego Health, San Diego, CA; [3]The University of Texas Southwestern Medical Center, Dallas, TX; [4]The University of Alabama at Birmingham, Birmingham, AL.*

Background: αKlotho is produced within the kidney and is released into circulation as soluble klotho. Animal data demonstrate that klotho is directly correlated with GFR. Due to promising preclinical data, there is significant interest in klotho as a potential biomarker in chronic kidney disease.

Methods: Soluble klotho was measured by two distinct assays using baseline samples from the Systolic Blood Pressure Intervention Trial. All individuals had chronic kidney disease (eGFRcr-cys < 60 ml/min/1.73m²) and never-thawed serum samples available for klotho measurement. The first assay was an immuno-precipitation immunoblot assay (IP-IB) utilizing two separate anti-klotho antibodies, while the second assay was a commercially available ELISA (IBL). Demographics, clinical characteristics, and laboratory data were examined for linear trends across quartiles of klotho concentrations.

Results: There were 2291 subjects with klotho IPIB measures and 1216 subjects with klotho ELISA measures. The intra-assay CVs of the klotho assays were 6.9% and 6.1% (IPIB & ELISA respectively). The median [25th, 75th] klotho concentration was 11.0 pM [7.7,16.0] for the IP-IB and 4.6 pM [3.4,6.6] for the ELISA. For both assays, higher quartiles of klotho were significantly associated with higher eGFR. For the IPIB, higher klotho was associated with a lower proportion of current smokers and loop diuretic use, and fewer number of anti-hypertensives. Higher IP-IB klotho was associated with higher serum magnesium, calcium, and bicarbonate, higher urine calcium, and lower serum FGF-23. For the ELISA assay, there was a similar but weaker association with mineral metabolism markers.

Conclusions: Both klotho assays had acceptable performance and results were consistent with known klotho pathobiology. The IP-IB klotho concentrations were more consistently associated with other measures of mineral metabolism.

Funding: NIDDK Support

Klotho IPIB with Baseline Clinical Characteristics from CKD sub-cohort of the Systolic Blood Pressure Intervention Trial

Variable	#	Entire Cohort	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Klotho (pM)	2291	11.0 [7.7 , 16.0]	6.0 [5.0 , 6.9]	9.5 [8.6 , 10.2]	13.1 [12.1 , 14.4]	20.2 [17.8 , 24.2]	<0.0001
eGFR (Cystatin)	2291	45.5 [36.4 , 52.5]	43.8 [34.1 , 51.2]	45.9 [34.0 , 53.9]	45.7 [36.7 , 53.7]	46.8 [37.0 , 53.4]	<0.0001
eGFR (Creatinine & Cystatin)	2291	50.2 [39.8 , 57.4]	48.1 [37.4 , 56.0]	50.0 [38.1 , 57.4]	51.1 [41.3 , 57.6]	51.8 [42.9 , 58.2]	<0.0001
eGFR (Creatinine)	2291	50.8 [41.9 , 58.7]	49.2 [39.7 , 57.0]	49.1 [40.3 , 57.4]	52.1 [43.1 , 59.2]	52.8 [43.5 , 60.6]	<0.0001
Urine Albumin/Creatinine	2218	15 [7 , 49]	16 [7 , 52]	16 [7 , 47]	15 [7 , 54]	14 [7 , 48]	0.3
Age	2291	75 [68 , 80]	74 [65 , 79]	75 [69 , 80]	76 [69 , 82]	75 [68 , 80]	0.002
Female	948	948 (41%)	246 (43%)	230 (40%)	242 (42%)	230 (40%)	0.8
Race/Ethnicity							
Hispanic	199	199 (9%)	29 (5%)	35 (7%)	48 (9%)	44 (8%)	0.06
Black	591	591 (26%)	146 (26%)	138 (24%)	150 (26%)	157 (27%)	
White	1505	1505 (66%)	391 (69%)	391 (69%)	367 (64%)	356 (62%)	
Other	36	36 (2%)	6 (1%)	6 (1%)	8 (1%)	16 (3%)	
10 year CVD risk	2287	20 [13 , 29]	20 [13 , 29]	19 [12 , 29]	20 [12 , 29]	20 [13 , 30]	0.4
Body Mass Index	2274	28.6 [25.0 , 32.7]	29.2 [25.1 , 32.8]	29.2 [25.1 , 32.1]	28.3 [25.3 , 32.6]	28.6 [25.2 , 33.2]	0.9
Systolic BP	2291	139 [129 , 149]	139 [129 , 150]	139 [130 , 149]	139 [130 , 150]	139 [129 , 149]	0.9
Diastolic BP	2291	74 [66 , 83]	74 [66 , 83]	74 [66 , 82]	74 [65 , 82]	74 [67 , 82]	0.5
Clinical or Subclinical CVD	577	577 (25%)	152 (27%)	144 (25%)	146 (26%)	135 (24%)	0.3
Intensive BP Arm	1179	1179 (51%)	295 (52%)	287 (50%)	309 (54%)	288 (51%)	0.2
Smoking status							
Never	1051	1051 (46%)	247 (43%)	238 (42%)	282 (49%)	284 (50%)	0.01
Former	1047	1047 (46%)	265 (46%)	281 (49%)	248 (43%)	253 (44%)	
Current	193	193 (8%)	61 (11%)	54 (9%)	43 (8%)	35 (6%)	
Any of ARB	1631	1631 (71%)	402 (70 %)	420 (73%)	408 (71%)	401 (70%)	0.7
Loop Diuretic	339	334 (15%)	107 (19%)	83 (15%)	82 (14%)	62 (11%)	0.0003
Any Diuretic	1288	1288 (56%)	308 (53%)	310 (54%)	322 (56%)	298 (52%)	0.001
Beta Blocker	1078	1078 (47%)	291 (51%)	260 (45%)	254 (44%)	273 (48%)	0.0
Calcium Channel Blocker	1087	1087 (47%)	258 (45%)	292 (51%)	247 (43%)	270 (47%)	0.8
Statin	1175	1175 (52%)	315 (54%)	291 (50%)	299 (53%)	285 (50%)	0.3
Number of BP agents	2291	2 [1 , 3]	2 [2 , 3]	2 [1 , 3]	2 [1 , 3]	2 [1 , 3]	0.002
Cholesterol, Total	2291	179 [151 , 205]	175 [134 , 205]	184 [156 , 203]	184 [158 , 210]	173 [151 , 200]	0.6
HDL Cholesterol	2291	50 [42 , 60]	48.5 [41 , 58]	51 [43 , 61]	51 [43 , 63]	49 [42 , 60]	0.14
Random Glucose	2291	97 [90 , 104]	98 [91 , 106]	97 [90 , 103]	96 [90 , 104]	97 [91 , 104]	0.6
Triglycerides	2291	111 [80 , 152]	119 [82 , 162]	106 [80 , 145]	110 [81 , 147]	107 [77 , 147]	0.007
Urine Calcium	2282	3.7 [1.7 , 8.9]	2.8 [1.3 , 5.1]	3.6 [1.9 , 8.0]	3.8 [1.8 , 7.9]	4.4 [2.0 , 7.8]	<0.0001
Urine Phosphate	2282	47.6 [29.9 , 66.8]	49.4 [29.7 , 69.5]	47.1 [30.4 , 65.9]	47.7 [29.3 , 65.8]	46.3 [30.1 , 67.3]	0.3
Serum Magnesium	738	2 [1.9 , 2.2]	2 [1.9 , 2.1]	2.1 [1.9 , 2.2]	2 [1.9 , 2.2]	2.1 [1.9 , 2.2]	0.006
Serum FGF-23	2273	66.4 [52.1 , 87.0]	68.6 [54.1 , 93.1]	66.3 [51.7 , 86.9]	66.8 [50.1 , 84.2]	64.9 [51.2 , 85.0]	0.003
Serum Phosphate	2285	3.5 [3.2 , 3.9]	3.6 [3.3 , 3.9]	3.5 [3.3 , 3.8]	3.5 [3.2 , 3.8]	3.5 [3.2 , 3.8]	0.08
Serum PTH	2272	47 [35 , 67]	47 [36 , 69]	46 [35 , 65]	47 [35 , 66]	47 [34.5 , 67]	0.7
Serum Calcium	2285	9.6 [9.3 , 9.8]	9.5 [9.3 , 9.8]	9.6 [9.3 , 9.8]	9.6 [9.3 , 9.8]	9.6 [9.3 , 9.8]	0.02
Serum Bicarbonate	2291	26 [24 , 27]	25 [24 , 27]	26 [24 , 27]	26 [24 , 28]	26 [24 , 28]	<0.0001

Quartiles of Klotho IPIB in SPRINT

TH-PO153

Expansion of Visceral Adipose Tissue over 12 Months Is Associated with Changes in Leptin and Fibroblast Growth Factor 23 (FGF-23) and Alterations in Vitamin D Metabolism in Patients with ESKD

Rachel M. Holden,[1] Patrick A. Norman,[2] Martin Kaufmann,[1] Mandy E. Turner,[5] Louise M. Moist,[3] Deborah Lynn Zimmerman,[4] Emilie C. Ward,[1] Martin P. Petkovich,[1] Michael A. Adams,[1] Marina Mourtzakis.[6] *[1]Queen's University, Kingston, ON, Canada; [2]Kingston Health Sciences Centre, Kingston, ON, Canada; [3]Western University, London, ON, Canada; [4]University of Ottawa, Ottawa, ON, Canada; [5]Harvard University, Cambridge, MA; [6]University of Waterloo, Waterloo, ON, Canada.*

Background: Visceral adipose tissue (VAT) is hormonally active. Leptin, produced by adipocytes, is a cytokine-like hormone that is increased with obesity. Leptin stimulates FGF-23 expression in bone and decreases kidney expression of CYP27B1 in leptin-deficient mice. The objective was to examine the relationship between visceral and subcutaneous adipose tissue and changes over 12 months with leptin, FGF-23, and vitamin D metabolism through assessment of vitamin D metabolite (VMR) ratios of $25(OH)_2D_3$ and $1,25(OH)_2D_3$ in patients with ESKD.

Methods: Visceral (VAT) and subcutaneous (SAT) adipose tissue cross sectional area (CSA) was assessed by computed tomography at the third lumbar vertebra at baseline and 12 months in hemodialysis patients. Serum vitamin D metabolites were measured by LC-MS/MS and leptin and iFGF-23 were measured by ELISA at baseline and 12 months.

Results: There were 28 participants, 61% with diabetes. At baseline, VAT CSA was associated with higher $1,24,25(OH)_3D_3$:$1,25(OH)_2D_3$ VMR with (r=0.43, p=0.04) and without (r=0.46, p=0.02) adjustment for iFGF-23. Increase in VAT was significantly associated with increase in leptin (r=0.6, p<0.001) and iFGF-23 (r=0.42, p<0.05), as well as increases in the $25(OH)D_3$:$1,25(OH)_2D_3$ VMR (r=0.5, p<0.05) and $1,24,25(OH)_3D_3$:$1,25(OH)_2D_3$ VMR (r=0.5, p<0.05). Participants with an increase in VAT over 12 months (n=17) had significantly greater percent increase in leptin (22.4 [-33.0, 113.3]) and FGF-23 (94.8[26.4,208.9]) compared to those where VAT decreased (n=10) (-54.8 [-58.2, 11.1], p=0.03 for leptin) and -3.0[-31.7, 68.9], p=0.02 for FGF-23. In a linear regression model using log-transformed variables, a 10% increase in the change leptin was associated with a 1.9% increase in the change in FGF-23 (p=0.035) after adjustment for baseline FGF-23 and PTH. In contrast to VAT, SAT CSA was not associated with any VMR at baseline and there was no difference in leptin, FGF-23 or in any VMR between participants who gained SAT versus those where SAT decreased.

Conclusions: VAT may contribute to calcitriol deficiency in patients with ESKD. Expanding VAT appears to enhance FGF-23 regulation of vitamin D metabolism possibly mediated by leptin.

Funding: Government Support - Non-U.S.

TH-PO154

Fluorine F 18 Sodium-Fluoride Positron Emission Tomography to Study Renal Osteodystrophy and Aortic Microcalcification in Patients with CKD: A Pilot Study

Aspan M. Shokrekhuda,[1] Rylen Stratford,[1] Wenzhu Mowrey,[2] Na Song,[1] Kexin Zhang,[2] Sara Saini,[2] Mario T. Didea,[1] Gabriel K. Duah,[1] Nicholas Sibinga,[2,1] Jeffrey M. Levsky,[1] Mark Travin,[1] Wei Chen.[2,1] *[1]Albert Einstein College of Medicine, Bronx, NY; [2]Montefiore Medical Center, New York, NY.*

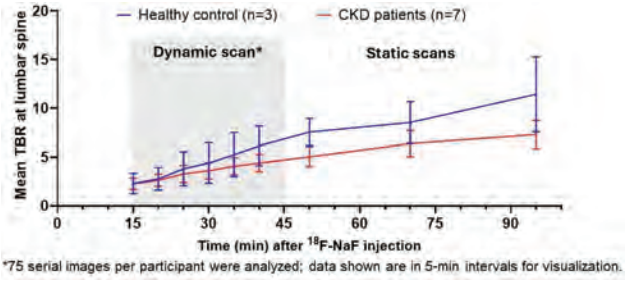
Background: Recent advances in positron emission tomography (PET) may accelerate the adoption of ^{18}Fluorine-sodium fluoride (^{18}F-NaF) PET as a clinical diagnostic tool for renal osteodystrophy and arterial micro- or early calcification in CKD. Herein, we aimed to define the optimal timing of ^{18}F-NaF PET imaging and show its feasibility in patients with moderate CKD.

Methods: In 7 patients with CKD 3b-4 and 3 healthy controls, we acquired a 30-min dynamic scan followed by 3 static scans 15 min after the injection of ^{18}F-NaF. ECG-gated CT was done to detect macro- or advanced calcification in coronary arteries (CAC). ^{18}F-NaF uptake was quantified for regions over bilateral kidneys, lumbar spine, and lumbar aorta using tissue-to-background ratios (TBRs), which were calculated by dividing standardized uptake values (SUVs) of the regions by the SUV of reference blood pool. The Mann-Whitney U tests were used for group comparisons.

Results: Median (IQR) $eGFR_{Cys\text{-}Cr}$ for CKD patients (age: 54-80) and controls (age: 57-69) was 40 (32-43) and 95 (64-103) ml/min/1.73m^2, respectively. CKD patients had a significantly slower renal clearance of ^{18}F-NaF than controls (median biological half-life: 20 vs. 8 min, p=0.02). Time to reach optimal TBRs at lumbar spine was similar (43 vs. 44 min, p>0.99). Among CKD patients (n=7), there was a trend toward significance in correlation between mean TBR in lumbar spine at 60-min and intact PTH levels (spearman r=0.75, p=0.07). Median (IQR) Agaston CAC score was 473 (30-559), and among those with CAC (n=8), peak TBR in lumbar aorta at 60-min was positively correlated with CAC score (spearman r=0.79, p=0.048).

Conclusions: We report for the first time the renal clearance kinetics of ^{18}F-NaF and define the optimal time for its PET imaging in people with moderate CKD. We also demonstrated the feasibility of using ^{18}F-NaF PET as a promising diagnostic tool for evaluating both renal osteodystrophy and aortic micro-calcification.

Funding: NIDDK Support, Other NIH Support - NHLBI



*75 serial images per participant were analyzed; data shown are in 5-min intervals for visualization.

TH-PO155

Bone Histomorphometry in Patients with CKD Stage 2-5ND with or without Bone Loss Defined by Bone Densitometry

Karla M. Alves,[1] Fellype Barreto,[2] Cássia G. Santos,[2] Maria Eugenia F. Canziani,[1] Aluizio B. Carvalho.[1] *[1]Universidade Federal de Sao Paulo, São Paulo, Brazil; [2]Universidade Federal do Parana, Curitiba, Brazil.*

Background: Bone biopsy followed by histomorphometry is the gold standard for diagnosing renal osteodystrophy. New evidence has shown that bone mass loss, diagnosed by bone densitometry (DXA), could estimate the fracture risk in patients with CKD stages 3a-5D. However, there is no consensus on the relationship between DXA and bone histomorphometry in this population. This study compared bone histomorphometry in patients with CKD 2-5ND who had or did not have DXA-identified bone mass loss.

Methods: This cross-sectional study includes 50 asymptomatic patients with CKD stage 2-5ND, aged 18-70 ys. The exclusion criteria were infectious, inflammatory or neoplastic diseases, use of phosphate binders, vitamin D, corticosteroids, or bisphosphonates. Clinical evaluation included laboratory tests, DXA, and bone biopsy followed by histomorphometric analysis, proposed by ASBMR. Undecalcified bone samples were submitted to histomorphometry using the semiautomatic system Osteomeasure®. Bone mineral density (BMD) by DXA (g/cm^2), was measured at the lumbar spine (L1L4) and femoral neck (FN) on the densitometer LUNAR®. Bone loss was defined as a BMD T-score less than -1.0 SD for young subjects.

Results: A total of 50 patients, 52±10 ys, 68% men, 30% diabetics, with eGFR=34±16mL/min/1.73m^2 was included. BMD was 1.18±0.19 and 0.93±0.15g/cm2 (L1L4 and FN, respectively). BMD reduction was observed in 40% of patients in L1L4 and FN. Patients with reduced BMD, compared with those without, showed in L1L4 an increased osteoblastic (2.70±2.69 vs 1.24±1.58%;p=0.04), osteoclastic (10.5±6.5 vs 6.0±5.7%;p=0.01), and eroded (1.12±0.78 vs 0.47±0.69%;p<0.01) surfaces, respectively. Moreover, increased fibrosis (0.08±0.1 vs 0.02±0.04%;p=0.02) and bone formation rate (0.035±0.030 vs 0.014±0.015μ^3/μ^2/d;p<0.01) were observed in patients with reduced BMD. Patients with reduced BMD in FN, compared with those without, showed decreased trabecular bone volume (14.2±4.7 vs 19.1±5.5%;p<0.01) and trabecular number (1.19±0.34 vs 1.51±0.36N/mm;p<0.01), and increased trabecular separation (781.6±251.8 vs 576.1±189.6mm;p<0.01), respectively.

Conclusions: Bone loss in the lumbar spine is associated with mild hyperparathyroid bone disease, while in the femoral neck, it is associated with decreased bone volume and altered bone microarchitecture.

Funding: Government Support - Non-U.S.

TH-PO156

Bone Mineralization Deficit in Patients on Dialysis: Who Has It and Who Doesn't? What Are the Differences?

Bruna R. Rodrigues,[1] Ana Paula Gueiros,[1] Vanda Jorgetti,[2] Jose E. Gueiros.[1] *[1]Hospital das Clinicas, Recife, Brazil; [2]Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil.*

Background: Bone mineralization is essential for bone health. Defective bone mineralization can be present both in diseases with high bone turnover, such as mixed disease (MD), and in low bone turnover, in osteomalacia (OM). The objective of this study was to assess the factors associated with defective bone mineralization found in the bone biopsy (BB) of patients on dialysis.

Methods: This was a retrospective, cross-sectional study. The medical records were reviewed of patients on dialysis, who underwent BB, from January 2004 to January 2024. The clinical parameters were: age, sex, time on dialysis, etiology of chronic kidney disease, previous use of aluminum-based chelators, diagnosed with osteoporosis, occurrence of fractures, presence vascular calcification and parathyroidectomy. Laboratory parameters were: total calcium, phosphorus (mg/dL), alkaline phosphatase (ALP) (U/L), intact parathyroid hormone and 25OH vitamin D. The number of times that ALP was above the upper limit of normality (xALP) was used. A transiliac bone biopsy was performed, after double labeling with tetracycline. A comparative analysis was conducted between patients with defective mineralization (Group 1) and patients without (Group 2). Group 1 was made up of patients with MD and OM. Group 2 corresponded to patients with osteitis fibrosa and adynamic bone disease. Univariate and multivariate analyzes were performed to verify factors associated with defective mineralization.

Results: A total of 263 patients were studied, with a median age of 47 years, 87 (33%) of whom belonged to Group 1. Patients in Group 1 differed from those in Group 2 because they had been on dialysis for a longer period of time (years) (10 x 9; p=0.023); they presented lower serum phosphorus (5.1 x 5.9; p<0.001), a higher ALP level (xALP 2.28 x 1.31; p<0.001) and less aluminum toxicity (34.5% x 52.3%; p=0.006). In the multivariate analysis, phosphorus (OR 0.78, 95% CI 0.64 - 0.93; p=0.008) and ALP (xALP OR 1.21.95% CI 1,08 - 1.38; p=0.002) remained independently associated with defective mineralization.

Conclusions: Our results have demonstrated the importance of phosphorus for bone mineralization and have confirmed the role of ALP as a marker for defective mineralization. In this study, aluminum toxicity was not associated with defective mineralization

TH-PO157

Serum Alkaline Phosphatase Is Associated with Mortality and the Incidence of Hip Fracture in Patients on Dialysis: A Nationwide Cohort Study in Japan

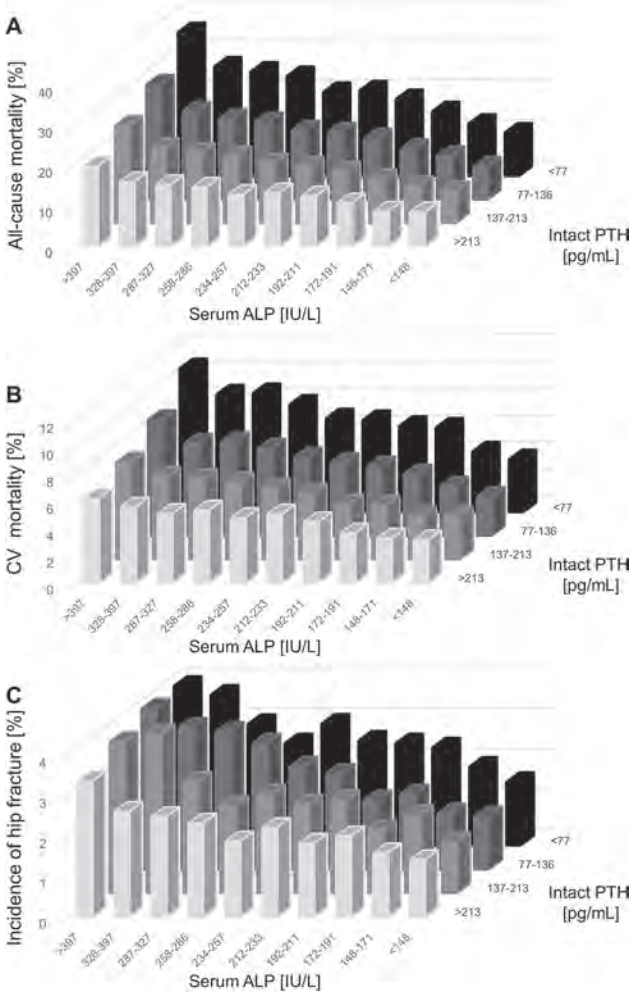
Yukio Maruyama,[1] Akio Nakashima,[1] Masanori Abe,[2] Norio Hanafusa,[3] Shigeru Nakai,[4] Takashi Yokoo.[1] *[1]Division of Nephrology and Hypertension, The Jikei University School of Medicine, Tokyo, Japan; [2]Division of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, Tokyo, Japan; [3]Department of Blood Purification, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan; [4]Department of Clinical Engineering, Fujita Health University, Aichi, Japan.*

Background: The monitoring of serum alkaline phosphatase (ALP) is recommended in the management of chronic kidney disease-mineral bone disorder (CKD-MBD) because of its association to poor outcome among dialysis patients. However, this association is thought to be changed due to several advances in the management for CKD-MBD in the decade.

Methods: Baseline data of 241,670 dialysis patients (age, 69 ± 12 years; male, 65.9%; median dialysis duration, 68 months) were extracted from a nationwide dialysis registry in Japan at the end of 2019. Outcomes, including all-cause mortality (ACM), cardiovascular mortality (CVM) and the hip fracture, were then evaluated using the registry at the end of 2020 and 2021. ACM was assessed using Cox regression analysis, whereas CVM and incidence of hip fracture were assessed using competing-risks regression analysis.

Results: Within two year, a total of 40,449 (16.7%) died, including 13,562 (5.6%) of CV deaths. Additionally, 4,136 (2.4%) suffered hip fracture. Higher serum ALP was independently associated with higher ACM, CVM and higher incidence of hip fracture, however the effect on CVM was marginal (hazard ratio [HR] 1.18, 95% confidence interval [CI] 1.15 to 1.21, sub-HR [SHR] 1.04, 95%CI 1.002 to 1.09 and SHR 1.27, 95%CI 1.18 to 1.37, respectively). The association between serum ALP and ACM and CVM differed according to intact parathyroid hormone (PTH) levels.

Conclusions: Higher serum ALP was independently and linearly associated with higher ACM, CVM and higher incidence of hip fracture in Japanese dialysis patients. Additionally, these associations differed by intact PTH. These findings did not change, in spite of the development of the management for CKD-MBD in the decade.



TH-PO158

Presence and Progression of Changes in Bone Mass, Bone Quality, and Vascular Calcifications in Patients with Moderate to Advanced Reduction in Kidney Function

Hartmut H. Malluche,[1,3] Qi Qiao,[4,5] Jin Chen,[4,5] Mohamed Issa,[2] Florence Lima.[1,3] *[1]University of Kentucky College of Medicine, Lexington, KY; [2]University of Kentucky Department of Radiology, Lexington, KY; [3]University of Kentucky Division of Nephrology Bone and Mineral Metabolism, Lexington, KY; [4]University of Kentucky Department of Internal Medicine, Lexington, KY; [5]University of Kentucky Division of Biomedical Informatics, Lexington, KY.*

Background: CKD patients have serum, bone and vascular abnormalities presenting as CKD-Mineral and Bone Disorder (MBD). This study sought to identify the parameters with the greatest relative impact on progression of CKD-MBD.

Methods: This prospective study measured the impact of 262 parameters including serum markers, clinical variables and bone parameters on vascular calcifications and bone quality and quantity at baseline and after 2-3 years. These impacts were assessed using machine learning, a subset of artificial intelligence analyses.

Results: Baseline kidney function values ranged from an estimated glomerular filtration rate (eGFR) 18–70 ml/min, it declined in 52% of subjects by at least 3.3% annually during the study. Machine learning analyses was able to detect relationships between annual changes in eGFR as low as 1% annually with decreases in hip bone mineral quantity, bone mineral crystallinity and a serum resorption marker (TRAP-5b). Arterial calcifications were associated with collagen crosslinking heterogeneity, serum phosphorus level, diuretic use and atorvastatin treatment. Baseline collagen crosslinking heterogeneity was an important factor impacting progression of coronary, but not aortic calcification. Baseline serum phosphorus was a factor associated with progression of arterial calcification (Fig. 1). Median serum phosphorus levels starting as low as 4.0 mg/dl impacted progression of arterial calcification.

Conclusions: Identification of these parameters enhances our understanding of the breadth of abnormalities before dialysis requirements. Attention to these abnormalities in mild to moderate loss of kidney function should improve the management and quality of life for patients with CKD.

Funding: NIDDK Support, Private Foundation Support

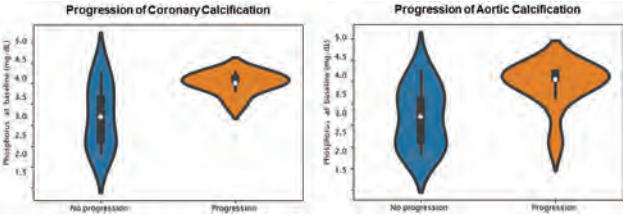


Figure 1. Baseline serum phosphorous concentrations for coronary (left panel) and aortic arteries (right panel) evaluated in subjects with and without progression of calcification.

TH-PO159

SGLT2 Inhibitors and Fracture Risk in Individuals with Advanced CKD

Rochell Issa,[1] Yasameen Fardi,[2] Andrei Brateanu,[1] Lavinia A. Negrea,[2] Mirela A. Dobre.[2] *[1]University Hospitals, Cleveland, OH; [2]Cleveland Clinic, Cleveland, OH.*

Background: The risk of fracture in elderly individuals with advanced chronic kidney disease (CKD) treated with sodium-glucose cotransporter-2 inhibitors (SGLT2i) is debated.

Methods: In this retrospective cohort study of electronic health records (EHRs) of approximately 105.3 million patients from 61 healthcare organizations from the US Collaborative Network TriNetX, a prevalent new-user design was applied. Two cohorts of adults age 65 or older, with CKD stages 4, 5, and 5D were assembled between January 2014 and December 2019, with follow-up until April 2024. The cohort of patients initiated on SGLT2i was matched in a 1:1 ratio, to a cohort of patients not on SGLT2i, but otherwise prescribed the same background drugs, duration of background drugs, co-morbidities, and time conditional propensity score. Cox proportional hazards models were fitted to estimate the hazard ratio (HR) and 95% confidence interval (CI) of major central or peripheral fractures separately at 6 months, 1 and 5 years.

Results: We identified a total of 18,391 (with CKD stage 4 and 5) and 11,084 (with CKD-5D) new users of an SGLT2i. The 6 month, 1 and 5 year risks of a central or peripheral fragility fracture did not significantly differ between new users of SGLT2i versus non-users (Table). Individuals with CKD 5D demonstrated the same trend. Similar results but with wider confidence intervals were obtained in analyses restricted to Canagliflozin use across all CKD stages and fracture types.

Conclusions: In this large US cohort, the use of SGLT-2i was not associated with an increased risk of either central of peripheral fractures in individuals with advanced CKD stages 4, 5, or 5D.

Funding: Other NIH Support - NHLBI

Fracture Risk	Fracture at 6 months	Hazard Ratio (95% CI)	Fracture at 1 year	Hazard Ratio (95% CI)	Fracture at 5 years	Hazard Ratio (95% CI)
CKD 4 and 5						
Spinal						
SGLT2i +, n= 17,346	127	0.89 (0.70-1.14)	204	0.86 (0.71-1.04)	350	0.89 (0. 77 – 1.04)
SGLT2i -, n = 17,253	135		221		358	
Pelvic						
SGLT2i +, n = 18,057	29	0.64 (0.40-1.03)	47	0.59 (0.41-0.85)	86	0.64 (0.49 – 0.85)
SGLT2i -, n = 18, 030	43		74		122	
Femur						
SGLT2i +, n= 17,782	87	0.83 (0.62 – 1.11)	137	0.81 (0.64-1.02)	221	0.80 (0.67 – 0.96)
SGLT2i -, n = 17,703	99		157		252	
Shoulder/upper arm						
SGLT2i +, n=17,701	60	1.01 (0.70-1.46)	94	0.99 (0.74-1.33)	168	0.99 (0.80 – 1.24)
SGLT2i -, n = 17,652	56		88		154	
Forearm/Wrist/Hand						
SGLT2i +, n= 17,580	53	0.93 (0.64-1.36)	91	1.05 (0.77 – 1.41)	166	1.05 (0.84 – 1.31)
SGLT2i -, n = 17,594	54		81		144	
CKD – 5D						
Spinal						
SGLT2i +, n= 10,233	96	0.86 (0.66-1.13)	152	0.94 (0.75 -1.17)	317	0.92 0.78 – 1.07)
SGLT2i -, n = 10,344	108		150		304	
Pelvic						
SGLT2i +, n = 10,764	27	0.95 (0.56 – 1.61)	47	1.20 (0.78 – 1.85)	74	0.82 (0.60 – 1.12)
SGLT2i -, n = 10,830	27		36		80	
Femur						
SGLT2i +, n= 10,702	44	0.79 (0.53 – 1.18)	82	0.89 (0.66 – 1.21)	179	0.94 (0.76 – 1.16)
SGLT2i -, n = 10,657	52		83		167	
Shoulder/upper arm						
SGLT2i +, n=10,465	34	0.68 (0.44 – 1.06)	60	0.77 (0.55 – 1.09)	125	0.77 (0.60 – 0.98)
SGLT2i -, n = 10,584	47		71		142	
Forearm/Wrist/Hand						
SGLT2i +, n= 10,533	36	0.72 (0.47 – 1.11)	49	0.74 (0.51 – 1.08)	125	0.86 (0.67 -1.10)
SGLT2i -, n = 10,602	47		61		126	

Fracture risk by CKD stage and fracture type at 6 months, 1 and 5 years in SGLT2i users (+) vs non-users (-)

TH-PO160

DKK1 Expression in Osteocytes in Patients with Type 2 Diabetes and CKD-MBD

Aline A. Deus, Cleonice Silva, Ivone B. Oliveira, Luciene dos Reis, Wagner Dominguez, Rosa M. Moyses, Vanda Jorgetti. *Laboratorio de Fisiopatologia Renal, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Chronic kidney disease mineral bone disorder (CKD-MBD) is influenced by factors such as age, race, CKD etiology, hormones, dialysis modality. Proteins expressed in osteocytes emerged as important players in bone tissue of CKD-MBD patients as FGF23, sclerostin, DKK1, RANKL, and OPG. However, little is known about the effects of these proteins on bone tissue in patients with type 2 diabetes (DM2) and CKD-MBD.

Methods: 30 DM2 hemodialysis patients were matched with CKD patients due to other etiologies by age, sex, and time on dialysis. All underwent bone biopsies with histomorphometric analysis. Osteocyte protein expression for DMP1, MEPE, Sclerostin, FGF23, RANKL, and DKK1 was studied through immunohistochemistry.

Results: Table 1 shows that DM2 patients have lower PTH and higher BMI. Bone histomorphometry showed that bone formation parameters and Oc.S/BS were lower in DM patients. We found a significant increase in DKK1 expression in DM2 patients.

Conclusions: DKK1, known as an inhibitor of Wnt/Bcatenin pathway, was increased in bone tissue of DM patients. Although BV/TV wasn't different between the groups, formation parameters were decreased in DM patients, suggesting that DKK1 may be involved in low bone turnover observed in DM patients.

Funding: Other NIH Support - Fapesp - Fundação de Amparo à Pesquisa do Estado de São Paulo

	Diabetic Mellitus (n=30)	Non-diabetic (n=30)	p
Age,year	59.8±9.1	58.4±9.1	0.57
Sex,men	19 (63%)	19 (63%)	1.00
Hemodialysis time,month	21.5 (29;60)	25.5 (41.5;55.5)	0.28
BMI,kg/m2	24.8 (26.4;29.5) n=22	20.9 (24.1;25.6) n=12	0.007
Calcium,mg/dl	8.3 (9.0;9.7)	8.5 (9.4;9.9)	0.33
Phosphorus,mg/dl	5.7±1.5	5.3±1.3	0.21
Alk phosphatase,UI/l	84.5 (116;220.5)	100 (163;271)	0.28
Parathyroid hormone,pg/ml	225 (325;831)	367 (955;1513)	0.012
DKK1,%	0.56 (0;3.03)	0.08 (0;0.40)	0.03
Sclerostin,%	7.70 (1.3;23.3)	3.45 (1.44;6.92)	0.079
Osteocytes,n	530 (204;806)	673 (325;1062)	0.128
BV/TV,%	16.9 (12.9;22.5)	17.7 (12.7;29.6)	0.31
OV/BV,%	1.79 (0.9;6.6)	6.8 (3.9;12.4)	0.004
O.Th,µm	6.2 (4.9;8.9)	10.8 (8.0;15.1)	0.0001
OS/BS,%	21.6 (9.5;45.0)	40.6 (29.4;49.7)	0.03
Ob.S/BS,%	4.5 (1.1;12.3)	9.8 (6.0;16.0)	0.03
Oc.S/BS,%	0.57 (0.1;1.3)	1.75 (0.2;3.2)	0.047
BFR/BS, µm3/µm2/day	0.03 (0.01;0.08)	0.05 (0.02;0.09)	0.43
Mlt,day	65.3 (28.5;205.3)	85.6 (39.7;161.3)	0.65

TH-PO161

Multidisciplinary Team Evaluation of Bone Health, Fracture Risk, and Incidence of Frailty in Patients on Haemodialysis

Varisha Shahzad, Lucy E. Collins, Lynn Redahan. *Mater Misericordiae University Hospital, Dublin, Ireland.*

Background: Bone disease is prevalent in patients with chronic kidney disease on dialysis (CKD-5D). It can lead to fragility fractures. The KDIGO guidelines suggest that patients with CKD G3a–G5D with evidence of mineral bone disease (MBD) and/or risk factors for osteoporosis, undergo a fracture risk assessment, if results will impact treatment decisions. Frailty is also a known risk factor for fragility fractures. The clinical frailty scale (CFS) is a nine-point validated outcome measure that is used to measure cognition, function, co-morbidities, and mobility in patients over 65 years. The aim of our service evaluation was to assess the fracture risk using the FRAX® tool for our HD patient cohort and to identify incidence of frailty using the CFS in those aged over 65 years.

Methods: In total, 76 chronic haemodialysis (HD) patients were included for the assessment of fracture risk. Acute dialysis patients were excluded. The FRAX score, the use of bone protection, and results of DEXA scanning (where available) were recorded for all patients. The CFS was calculated for 37 HD patients over the age of 65 using available clinical information. eMed and local databases were used to collect data.

Results: Average risk of major osteoporotic fracture was 10.1% and average risk of hip fracture was 4.03%. Out of 76 patients, 15 patients had a DEXA scan performed. Only three patients were in receipt of treatment with denosumab. A high incidence of frailty was recorded in the 37 HD patients aged >65 years, with 73% of patients recording a CFS of 5 (mild frailty) or greater which is significantly higher than the prevalence of frailty (7.0%) among community-dwelling individuals aged 60 years or older.

Conclusions: This data reveals a high fracture risk amongst incident HD patients. The low proportion of patients prescribed specific treatment, such as denosumab, probably reflects the challenges of diagnosing and treating low bone mineral density (BMD) in this cohort. The prevalence of frailty was high in the subgroup of elderly HD patients. Features of frailty overlap with risk factors for fragility fractures; this highlights the importance of providing patients with an integrated, multidisciplinary management plan to reduce the risk of fragility fracture, targeting CKD-MBD, low BMD and frailty.

TH-PO162

Clinical Implications of Radiopharmaceutical Uptake in the Skull as a New Marker of CKD-MBD: Findings of Bone Scintigraphy

Keunyoung Kim,[1,2] Sang Heon Song.[1,2] *[1]Pusan National University School of Medicine, Busan, Republic of Korea; [2]Pusan National University Hospital, Busan, Republic of Korea.*

Background: The aim of this study is to evaluate the potential role of radiopharmaceutical uptake in skull using bone scintigraphy as a new objective maker for CKD-MBD.

Methods: We retrospectively reviewed 122 CKD patients (M:F, 70:52) who were evaluated with bone scintigraphy. The control of 195 subjects (M:F, 66:129) who have no evidence of disease state of the breast cancer for female and the prostate cancer for male were also recruited. The quantitative indices were defined as the radiopharmaceutical uptake in skull and the ratio of the skull to the ilium (SIR). The bone mineral density (BMD) values and trabecular bone score (TBS) were acquired from dual energy X-ray absoroptiometry (DXA).

Results: In all enrolled CKD patients, median TBS showed deteriorated state compared with control group. The SIR had negatively correlation with DXA values; lumbar spine (r =-0.309, P<0.001); femoral neck (r=-0.262, P<0.001), total femur (r =-0.264, P<0.001) and TBS (r=-0.251, P<0.001). SIR and TBS were remained as the independent variables showed significant correlation with levels of parathyroid hormone, calcium and creatinine in CKD patients using multiple regression.

Conclusions: The SIR was significant for the assessment of metabolic status of CKD-MBD and may therefore potentially be used as an objective tool for the assessment of bone health in CKD patients.

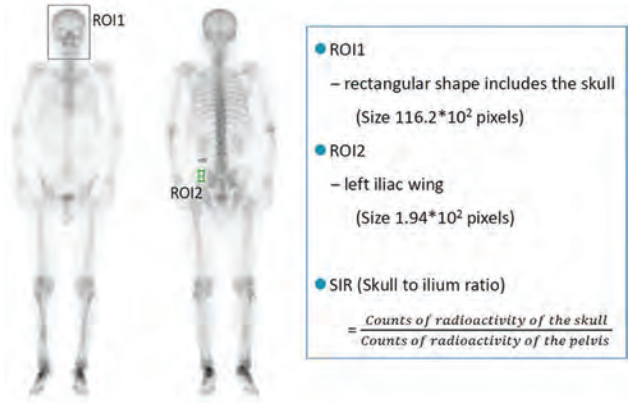


Figure 1. Quantitative Analysis of Bone scan

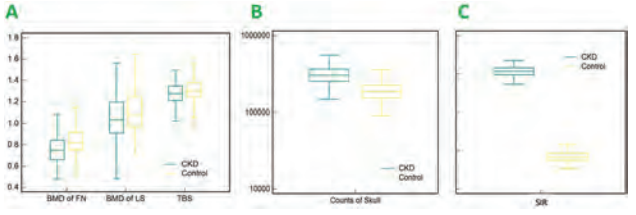


Figure 2. Representative results from the analysis

A. All values from DXA were significantly lower in the CKD patients compared with the control group.

B. The radioactivity counts in the skull was significantly higher in the CKD patients.

C. The normalized value of SIR showed exaggerated the difference between CKD and control.

TH-PO163

Low Muscle Mass Is Associated with Low Bone Mineral Density in Patients with CKD Stages G4-5

Anahita Rashid,[1] Sabina C. Hauge,[1] Anders Nordholm,[1,2] Anne Sofie Fredberg Jørgensen,[4] Subagini Nagarajah,[4] Bo Zerahn,[5] Charlotte Suetta,[6] Morten Frost,[3,7] Ditte Hansen.[1,8] *[1]Department of Nephrology, Herlev and Gentofte, Herlev, Denmark; [2]Department of Nephrology, Rigshospitalet, Copenhagen, Denmark; [3]Department of Endocrinology, Odense University Hospital, Odense, Denmark; [4]Department of Nephrology, Odense University Hospital, Odense, Denmark; [5]Department of Nuclear Medicine, Herlev & Gentofte Hospital, Herlev, Denmark; [6]Geriatric Research Unit, Department of Medicine, Herlev & Gentofte Hospital, Herlev, Denmark; [7]Osteoporosis Clinic & Clinic for Molecular Endocrinology, Denmark; [8]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.*

Background: Patients with chronic kidney disease (CKD) experience a decrease in bone mineral density (BMD), which raises their risk of fractures. Preclinical studies have shown a cross-talk between bone and muscle, emphasizing the importance of investigating the relationship between muscle mass and BMD in patients with CKD. Sarcopenia a condition characterized by low muscle mass and strength is common in CKD. CKD-related sarcopenia is believed to develop more rapidly and occur earlier in adult life, further increasing the risk of fractures in patients. Therefore, this study aimed to explore the association between muscle mass and BMD in patients with CKD.

Methods: This cross-sectional study included patients with CKD G4-5. All patients were examined by whole-body dual-energy x-ray absorptiometry (DXA). BMD of the spine and hips were determined. The muscle mass was measured as the appendicular skeletal muscle mass (ASMM). Linear regression analysis was performed to explore the association between BMD and ASMM, and multivariate linear regression analysis was performed, adjusting for age, gender, body mass index (BMI), and level of 25-OH-Vitamin D.

Results: We included 140 patients; 66 (47%) were female with a mean age of 68 (SD 13) years and a mean eGFR of 18 (SD 7) ml/min/1.73m^2. Thirty-five patients (25%) had a BMD of <-2.5 standard deviations below peak bone mass in at least one site (T-score). The mean ASMM was 21 kg (SD 6). Thirty-six (26%) patients had an ASMM lower than the European Working Group on Sarcopenia in Older People cut-off point. Unadjusted regression analysis revealed a significant positive association between both the right femural neck and ASMM (β=0.0175; $p < 0.001$) and the lumbar spine (L1-4) and ASMM $\beta = 0.04$; $p = 0.04$), which remained statistically significant after adjusting for factors that influence BMD, such as gender, BMI, and 25-OH-Vitamin D (right femural neck BMD β=0.01; p=0.002, BMD of the lumbar spine β= 0.04; p=0.02).

Conclusions: In patients with CKD G4-5, low appendicular skeletal muscle mass was associated with low bone mineral density in the hip and spine. The increased fracture risk in patients with CKD may be due to the co-occurrence of osteoporosis and sarcopenia, i.e., osteosarcopenia, although this requires further investigation.

Funding: Private Foundation Support

TH-PO164

Sustained Phosphate Reduction Assessed by Phosphate Area under the Curve with Tenapanor Is Associated with Reduced Fibroblast Growth Factor 23 in Patients with CKD and Hyperphosphatemia on Dialysis

Kevin J. Martin,[1] Simon Higgins,[2] Yang Yang,[2] David P. Rosenbaum,[2] David M. Spiegel.[2] *[1]Saint Louis University School of Medicine, St Louis, MO; [2]Ardelyx Inc, Waltham, MA.*

Background: The 2017 KDIGO CKD-MBD guidelines recommend that strategies for managing hyperphosphatemia (HP) be based on the use of serial measurements. Average phosphate (P) area under the curve (AUC) has been identified as a stronger predictor of outcomes than other P estimates. Intact fibroblast growth factor 23 (iFGF23) is elevated in end-stage kidney disease and is associated with increased cardiovascular mortality, but is often not well correlated to single-point estimates of P. Tenapanor (TEN) is approved to reduce serum P in adults with CKD as add-on therapy in patients (pts) who have an inadequate response to P binders (PBs) or who are intolerant of any dose of PBs. We used P AUC to assess whether better long-term P control with TEN is associated with lower iFGF23.

Methods: In a secondary analysis of the Ardelyx-supported PHREEDOM study, a 52-week, phase 3 trial of TEN as a monotherapy for HP in adults on maintenance dialysis, pts with P ≥6.0 and ≤10.0 mg/dL and a P increase ≥1.5 mg/dL after PB washout were treated for 26 weeks with TEN 30 mg bid during an open-label randomized treatment period (RTP). Correlation analyses between average daily P AUC above 4.5 mg/dL over the RTP and iFGF23 at the end of the RTP were performed along with summaries of changes in iFGF23 by P AUC categories.

Results: In the full analysis set (n=407), TEN reduced P by 1.3 (SD: 1.8) mg/dL on average at the end of the RTP. Median iFGF23 was reduced from 6417.5 pg/mL at baseline to 5051.6 pg/mL at the end of the RTP (median percent change: −23.2%). There was a positive correlation between average daily P AUC and iFGF23 (ρ=0.499, P<0.001). A trend of higher median iFGF23 was seen across categories of P AUC. Greater percent reductions from baseline in iFGF23 were seen in P AUC categories representative of better P control than categories representative of worse control (Table).

Conclusions: Improved P control with TEN, as measured by P AUC, was associated with lower iFGF23.

Funding: Commercial Support - Ardelyx, Inc.

iFGF23 at Week 26 and Change From Baseline (CFB) by P AUC Category Above 4.5 mg/dL

	P AUC category: >0–0.5 mg/dL	P AUC category: >0.5–1 mg/dL	P AUC category: >1–2 mg/dL	P AUC category: >2 mg/dL
iFGF23 at Week 26, median	623 pg/mL	2450 pg/mL	4127 pg/mL	10866 pg/mL
iFGF23 CFB, %	−36%	−48%	−19%	−12%

TH-PO165

Association of Urinary Phosphate Excretion and Osteoporosis in Patients with CKD: Result from KNOW-CKD

Yewon Jo, Sung Joon Park, Hyuk Huh, Taehee Kim, Yeong Hoon Kim, Yunmi Kim. KNOW-CKD (The KoreaN Cohort Study on the Outcome of Chronic Kidney Disease Patients). *Inje University Busan Paik Hospital, Busan, Republic of Korea.*

Background: The mechanism of osteoporosis is more complex in patients with chronic kidney disease (CKD) than general population because of accompanying chronic kidney disease-mineral bone disorder. We aimed to investigate the association of ability to handling urinary phosphate excretion and osteoporosis.

Methods: We analyzed 1,647 patients who were enrolled in the KNOW-CKD and have baseline 24-hour urinary phosphate value and dual-energy x-ray absorptiometry results. The subjects were divided into three groups according to tertile of urinary phosphate excretion. Osteoporosis was defined as T-score of -2.5 or less for one of L1 spine, total hip, or femur neck. The association of osteoporosis and urinary phosphate excretion was evaluated.

Results: The patients with higher urinary phosphate excretion tended to be younger, have higher body mass index and higher estimated glomerular filtration rate (eGFR), lower serum phosphate level. The osteoporosis was observed in 88 patients (16.0%), 31 patients (5.7%), and 14 patients (2.5%) for 1st (< 494mg), 2nd (494-660 mg), and 3rd (>660mg) tertile, respectively. In multivariate logistic regression analysis adjusted for age, sex, body mass index, hemoglobin, serum albumin, phosphate, calcium, and eGFR, patients belonged to 2nd tertile (odds ratio 0.543, 95% confidence interval 0.338-0.857, p = 0.010), and 3rd tertile (odds ratio 0.438, 95% confidence interval 0.223-0.812,

p = 0.012) showed lower risk of osteoporosis compared to the patients in 1st tertile. In the subgroup analysis, the risk of osteoporosis was not significantly different among patients with CKD 1-2, however the decreasing risk of osteoporosis according to the tertile of urinary phosphate excretion was more prominent among patients with CKD 3-4.

Conclusions: Higher urinary phosphate excretion was associated with lower risk of osteoporosis in patients with CKD.

Funding: Government Support - Non-U.S.

TH-PO166

Pill Burden and Clinical Outcomes in Patients with Hyperphosphatemia Undergoing Hemodialysis

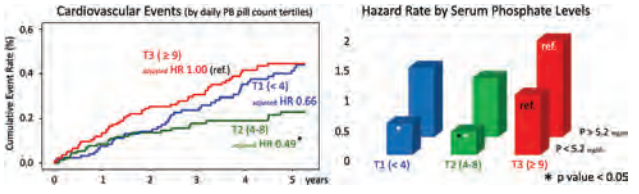
Kiryu Yoshida,[1] Tomohiro Saito,[2] Tadashi Kato,[2] Noriyuki Kato,[3] Masahide Mizobuchi,[4] Hiroaki Ogata,[1,5] Fumihiko Koiwa,[4] Hirokazu Honda.[2]
[1]Division of Nephrology, Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan; [2]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [3]Saiyu Clinic, Saitama, Japan; [4]Division of Nephrology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [5]Department of Medical Education, Showa University School of Medicine, Tokyo, Japan.

Background: Phosphate binders (PB) improve clinical outcomes in HD patients; however, high pill burden might impair PB adherence. This study assesses association between the number of prescribed PB and clinical outcomes in patients on HD.

Methods: A retrospective study using data from 395 HD patients in a single facility in Japan, from August 2018 to November 2023. Outcomes include cardiovascular events (CVE), all-cause mortality, and fractures. Cox proportional hazards models were used to assess the relationship between PB pill count and outcomes. Baseline analysis and time-averaged analysis were performed.

Results: Patients were divided into tertiles based on baseline daily PB pill count: <4 (T1), 4-8 (T2), and ≥9 pills/day (T3), respectively. For CVE, the baseline analysis showed that, compared to T3, the hazard ratio (HR) for T1 was 0.66 (95% CI: 0.43-1.02, p=0.062) and for T2 was 0.49 (95% CI: 0.29-0.80, p=0.005). The time-averaged analysis revealed that the HR for T1 was 0.44 (95% CI: 0.27-0.71, p=0.001) and for the T2 was 0.45 (95% CI: 0.29-0.69, p<0.001). In patients with serum phosphate levels <5.2 mg/dL, the baseline analysis indicated that the HR for T1 was 0.53 (95% CI: 0.26-1.06, p=0.074) and for T2 was 0.39 (95% CI: 0.19-0.81, p=0.011). There were no significant differences in HR for all-cause mortality and fractures among the three groups.

Conclusions: A higher pill burden of PB might be associated with an increased risk of CVE, even in patients with well-controlled phosphate levels.



TH-PO167

Managing Hyperphosphatemia in Patients on Hemodialysis: A Comparison of Sucroferric Oxyhydroxide (SO) Monotherapy and Tenapanor with Other Non-SO Phosphate Binders

Meijiao Zhou, Linda Ficociello, Hao Han, Michael S. Anger. *Fresenius Medical Care Global Medical Office, Waltham, MA.*

Background: The pharmacological treatment options for managing hyperphosphatemia among dialysis patients (pts) have expanded. To examine the real-world experience with phosphate binders (PB) and phosphate absorption inhibitors, we examined serum phosphorus (sP) levels and pill burden amongst pts who switched to sucroferric oxyhydroxide (SO) monotherapy or added tenapanor (TN) to non-SO PB.

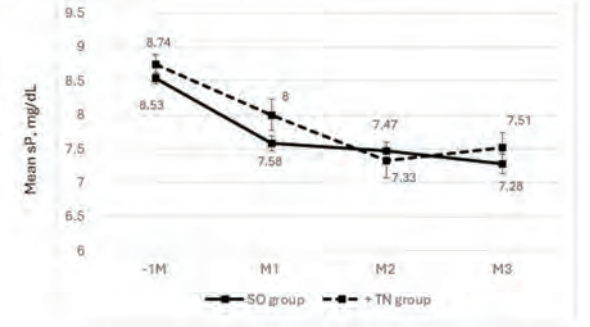
Methods: Adult Fresenius Kidney Care hemodialysis (HD) pts who switched from non-SO monotherapy at baseline to either (1) SO monotherapy (SO group) or (2) add-on TN to the baseline PB (+TN group) during 11/2023 -12/2023 were included. Eligible pts had sP the month before (-1M) and 3 months after switch (Q1; M1 to M3). To ensure comparability of baseline sP, we restricted analysis to pts with sP at -1M >7 mg/dL. PB pill burden and sP during the study period were described. General linear models were used to examine differences in sP between the two groups at M3.

Results: On average, pts in the SO group (n=262) were 56 years old with HD vintage of 49 months, while pts in the +TN group (n=63) were 51 years with vintage of 80 months. SO pts were more likely to dialyze with a catheter (23%) compared to +TN pts (11%). The reductions in sP from -1M to M3 were comparable in both groups (diff=1.25 mg/dL in the SO group and diff=1.23 mg/dL in the +TN group), however, SO group had lower pill burden (4.3 pills in SO vs 9.8 pills in the +TN group at M3). Results from univariate and adjusted linear models (controlling for age, vintage and catheter use) showed that there were no statistically significant differences in sP at M3 between the two groups.

Conclusions: For HD pts who had sP > 7 mg/dL despite treatment with non-SO monotherapy, switching to SO monotherapy or adding TN resulted in comparable reductions in sP. However, pts with SO monotherapy had less than half the PB pill burden, compared to those adding TN.

Funding: Commercial Support - Fresenius Medical Care

Figure 1. Mean sP with standard error bars during the study period in the SO and +TN groups



		-1M	M1	M2	M3
PB pills	SO group	7.0	4.1	4.1	4.2
	+TN group	8.1	9.9	10.0	9.8

TH-PO168

Hyperphosphatemia Is Associated with Kidney Prognosis in Patients with Autosomal Dominant Polycystic Kidney Disease

Kosaku Nitta. *Tokyo Women' Medical University, Tokyo, Japan.*

Background: The relationship between serum phosphate (P) levels and progression of kidney disease in patients with autosomal dominant polycystic kidney disease (ADPKD) remains unclear. Compared with other kidney disorders, patients with ADPKD typically have lower levels of serum P, potentially masking its clinical importance. This study sought to assess whether serum P levels can serve as a predictor of renal outcomes in ADPKD patients.

Methods: We included 235 patients with ADPKD who were not taking drugs to treat hyperphosphatemia. Survival analysis was performed for the renal outcome of a 50% reduction in estimated glomerular filtration rate (eGFR) or initiation of renal replacement therapy.

Results: The patients had mean age of 46 yeras, eGFR of 41.8 mL/min/1.73 m^2, and total kidney volume (TKV) of 1254.0 mL. The median follow-up period was 10.4 years, and the renal outcome was observed in 116 patients. Multivariable Cox regression analyses revealed that serum P (1 mg/dL increase, HR=2.03, P<0.0001) was a significant risk factor associated with kidney disease progression. Similarly, hyperphosphatemia (P>4.0 mg/dL, HR=1.90, P=0.0157; P>4.5 mg/dL, HR=2.78, P=0.0047; P>5.0 mg/dL, HR=27.22, P<0.0001) was significantly associated with renal prognosis. Kaplan-Meier analysis showed that kidney survival rates were significantly lower in patients with P>3.5 mg/dL than in those without hyperphosphatemia (log-rank test, P<0.0001). The 2-year kidney survival rate of ADPKD patients with P>4.0 mg/dL was 46.8% in the entire cohort and 28.2% in patients with stage 4-5 CKD, indicating an extremely poor renal prognosis.

Conclusions: Hyperphosphatemia was associated with renal prognosis in patients with ADPKD. In these patients, attention should be paid to even mild serum P elevation of P>3.5 or P>4.0 mg/dL.

TH-PO169

Tenapanor Reduces Serum Phosphate with Similar Efficacy and Tolerability Profiles When Added to Various Phosphate Binders

Stuart M. Sprague,[1] David P. Tietjen,[3] Jesslyn Roesch,[4] Yang Yang,[2] Suling Zhao,[2] Susan A. Edelstein,[2] David P. Rosenbaum,[2] David M. Spiegel.[2]
[1]NorthShore University HealthSystem University of Chicago, Chicago, IL; [2]Ardelyx Inc, Waltham, MA; [3]Nephrology Consultants, Huntsville, AL; [4]Apogee Clinical Research, Huntsville, AL.

Background: Tenapanor (TEN) is approved to reduce serum phosphorus (P) in adults with chronic kidney disease on dialysis as add-on therapy in patients (pts) who have an inadequate response to phosphate binders (PBs) or who are intolerant of any dose of PBs. While PBs are generally required in hyperphosphatemia management, they often cause gastrointestinal side effects of varying severity and have a high pill burden. This post hoc analysis examines the efficacy and tolerability of TEN when added to different PBs.

Methods: In the Ardelyx-supported AMPLIFY (NCT03824587) and OPTIMIZE (NCT04549597) trials, pts on maintenance dialysis with uncontrolled serum P (P ≥5.5 and

>5.5 mg/dL, respectively), despite stable PB doses, received TEN. In AMPLIFY, TEN was added to baseline (BL) PB therapy, which remained stable during the 4-week efficacy period. In OPTIMIZE (cohort 2), TEN was added to BL PB which was then reduced by ≥50%. After week 2, PB could be dose adjusted to achieve P ≤5.5 mg/dL during the 10-week efficacy and 16-week open-label extension periods.

Results: In AMPLIFY, P decreased when TEN was added to sevelamer (SEV)-based and non–SEV based PB regimens, with no appreciable difference in least-squares mean P reductions at week 4 between SEV- (0.9 mg/dL, n=60) and non-SEV based (1.1 mg/dL, n=56) regimens. In OPTIMIZE, a mean P reduction of 1.0 mg/dL was achieved at the end of the 10-week treatment period, regardless of whether TEN was added to PB regimens including SEV (n=52) or not including SEV (n=80). Diarrhea was the only adverse reaction that occurred in >5% of pts; pooled rates were similar when TEN was added to SEV alone (38.9%; 42/108), calcium-based PB alone (46.8%; 22/47), iron-based PB alone (33.3%; 18/54), lanthanum carbonate alone (28.6%; 2/7), and multiple PB types (56.6%; 30/53). Study discontinuation rates in pooled analyses were similar when TEN was added to SEV alone (13.0%; 14/108), calcium-based PB alone (8.5%; 4/47), iron-based PB alone (16.7%; 9/54), lanthanum carbonate alone (14.3%; 1/7), and multiple PB types (9.4%; 5/53).

Conclusions: TEN provides a clinically meaningful serum P reduction with similar efficacy and tolerability when added to PBs, regardless of the type of PB.

Funding: Commercial Support - Ardelyx, Inc.

TH-PO170

Assessing Potential Heightened Sensitivity to Tenapanor in Japanese Patients on Hemodialysis (HD)

Mayu Iwata, Satoshi Funakoshi, Jyunichiro Hashiguchi, Shinichi Abe, Kenji Sawase. *Nagasaki Kidney Center, Nagasaki, Japan.*

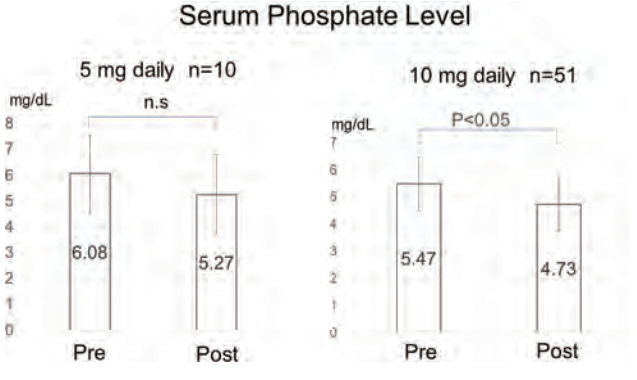
Background: Hyperphosphatemia is associated with arterial calcification, bone fractures, and cardiovascular mortality, making its treatment a cornerstone of dialysis care. However, strategies for managing hyperphosphatemia in patients undergoing maintenance dialysis, such as dietary restrictions and phosphate binders, yield only moderate efficacy. Tenapanor, the world's first phosphate absorption inhibitor, holds promise for addressing this challenge.

Methods: We enrolled 88 patients with hyperphosphatemia despite the use of phosphate binders in our maintenance dialysis facility. Given that soft stools and diarrhea were the most frequently reported adverse events in previous trials, we initiated tenapanor administration at a minimal dose of 5mg once daily, gradually increasing it while monitoring gastrointestinal symptoms and phosphate reduction effects, and concurrently tapering phosphate binders.

Results: The study population comprised 88 patients: 39 males, 19 females, with a mean age of 67 ± 12.1 years, mean dialysis vintage of 9.6 ± 6.5 years, and mean weight of 54.8 ±18.3 Kg. Within the first month of starting tenapanor, 27 patients discontinued treatment due to drug-related diarrhea, resulting in a dropout rate of 30.7%. Among the evaluable 61 patients, serum phosphate levels in those receiving 5mg of tenapanor once daily (n=10) decreased nonsignificantly from 6.08 ± 1.19 mg/dL to 5.27 ± 1.11 mg/dL, whereas in those escalated to 10mg once daily (n=51), there was a significant decrease from 5.47 ± 1.0 mg/dL to 4.73 ± 0.9 mg/dL, as depicted in the figure.

Conclusions: The maintenance dosage of tenapanor has been established as 10-20mg orally twice daily in previous studies. While we observed a notably higher dropout rate due to diarrhea with tenapanor compared to previous reports, there remains potential for managing serum phosphate levels with relatively low doses of tenapanor in Japanese HD patients. The variability in tenapanor's effects, influenced not only by patient weight but also dietary habits and race, was suggested.

Funding: Private Foundation Support



TH-PO171

A Postmarketing Study Assessing Safety and Efficacy of Velphoro in Korean Adult Dialysis Patients

Weiwei Qi,[1] Won Min Hwang,[2] Shin-Young Ahn,[3] Young-Ki Lee,[4] Byung Chul Shin,[5] Jong hoon Lee,[6] Seon Gun Kim,[7] Hye-Jung Kim,[7] Manuela Stauss-Grabo,[8] Carmen So,[9] Astrid Feuersenger.[8] *[1]Fresenius Medical Care Shanghai Co Ltd, Shanghai, China; [2]Konyang University Hospital, Daejeon, Republic of Korea; [3]Korea University Guro Hospital, Guro-gu, Seoul, Republic of Korea; [4]Hallym University Kangnam Sacred Heart Hospital, Yeongdeungpo-gu, Seoul, Republic of Korea; [5]Chosun University Hospital, Gwangju, Republic of Korea; [6]Gimpo Woori hospital, Seoul, Republic of Korea; [7]Fresenius Medical Care Korea Ltd, Seoul, Republic of Korea; [8]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [9]Fresenius Medical Care Asia Pacific Ltd, Hong Kong, Hong Kong.*

Background: Hyperphosphatemia is a frequent sequalae of chronic kidney disease and often requires phosphate binders to control. Velphoro® (calcium-free polynuclear iron (III)-oxyhydroxide phosphate binder, Vifor Fresenius Medical Care Renal Pharma Ltd., Switzerland) is a chewable tablet and had been approved in adult dialysis patients in Europe and the US since 2013 and in Korea since 2018. As clinical trials may not reflect real-world use of medications, we performed a post-marketing study (PMS) to monitor the safety profile of Velphoro® in Korea.

Methods: We conducted a non-interventional, prospective PMS in 647 dialysis patients from 18 sites with a 6-week short term and 24-week long term observation. Subjects enrolled in this study should newly receive Velphoro® for up to 1 week. Both safety and efficacy information were observed.

Results: A total of 596 subjects finished short-term observation and were included in safety analysis. Of these, 82 subjects finished the long-term observation. For short-term cohort, 284 adverse events (AE) and 91 adverse drug reactions (ADR) were reported. Gastrointestinal (GI) disorders were the most common ADR reported at 10.91% mainly diarrhea (5.37%). 27 serious AEs were reported but none of them was serious ADR. Besides, unexpected ADRs were reported for 15 cases mainly GI disorders, and none was severe. The 82 subjects who comprised the long-term cohort reported 46 AEs and 3 of them were ADR. None of the ADR was serious but 2 were reported as unexpected which were chest pain and abdominal discomfort. For iron test, a small increase in ferritin was observed at week 6 (351.51±286.99ng/ml) and week 24 (420.82±325.74ng/ml) while only an increase trend at week 6 (35.65±17.38%) but no further increase was observed at week 24 (38.05±15.11%) in TSAT level. For serum phosphorus control, the average serum phosphorus reduction at week 6 was -0.97±1.6 mg/dl while at week 24 from baseline was -0.82±1.48mg/dl.

Conclusions: In this PMS, GI disorders were the main ADR. No obvious iron accumulation was observed. In conclusion, Velphoro® has a favourable safety and tolerability profile in Korean patients that is consistent with that observed in Phase 3 trial (PA-CL-05A).

Funding: Commercial Support - Fresenius Medical Care

TH-PO172

Leontiasis Ossea in Hyperparathyroidism Secondary to Inadequate ESKD Management

Ruby Garcia,[1] Greilys Lazcano,[2,3] Jorge A. Lamarche,[2,3] Marina Antar-Shultz,[2,3] Mohamed M. Taha,[2,3] Endri Ceka,[2] Panagiotis Zervogiannis.[2,3] *[1]University of Nevada Reno, Reno, NV; [2]University of South Florida, Tampa, FL; [3]VA James A Haley Hospital, Tampa, FL.*

Introduction: Management of PO4, Ca, and parathyroid hormone (PTH) levels is essential for proper bone health in End Stage Renal Disease (ESRD). Leontiasis ossea (LO) is a severe form of osteodystrophy characterized by skeletal growth abnormalities that occurs in ESRD with long-standing, uncontrolled overproduction of PTH. Presentation includes facial swelling and/or jaw pain. Severe cases present with facial disfigurement due to bony expansion of maxillary bones extending into the orbit, mouth, nose or sinuses. This leads to complications such as dysphagia, exophthalmos, or visual loss if compression of the optic nerve occurs.

Case Description: 28 y/o undocumented M with ESRD on hemodialysis (HD) for 19 years presented with facial swelling, dysphagia, and dysarthria (Figure 1). The patient was unable to have adequate ESRD management due to financial constrains. Laboratory tests revealed a high PTH level at 5470 pg/ml. Ca++ and PO4 levels were normal. CT scan revealed bone changes consistant with LO.

Discussion: Excess PTH production, caused by ESRD, leads to increased osteoclast and osteoblast activity. There is unprecedented unmineralized bone formation and expansion in LO. LO is rare and only presents in inadequate ESRD management. There are no standardized methods to diagnose and treat LO. Preventative treatment include strict medical management of metabolic derangements with adherence to dialysis, calcimimetics, and PO4 binders. Parathyroidectomy is an alternative when medical therapy fails and has been shown to halt bone remodeling. There is no evidence to surgically remove excess bone unless is considered to improve quality of life and to treat life-threatening complications.

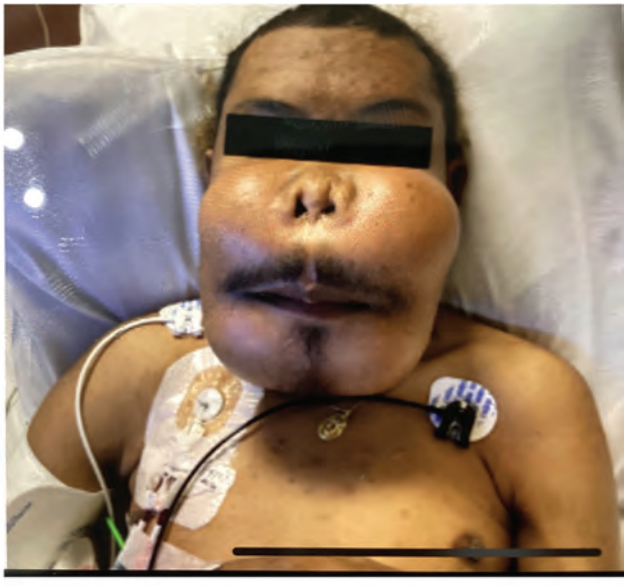


Figure 1. Facial photographs of the patient presenting with facial deformation and swelling of the maxilla and mandible caused by leontiasis ossea.

TH-PO173

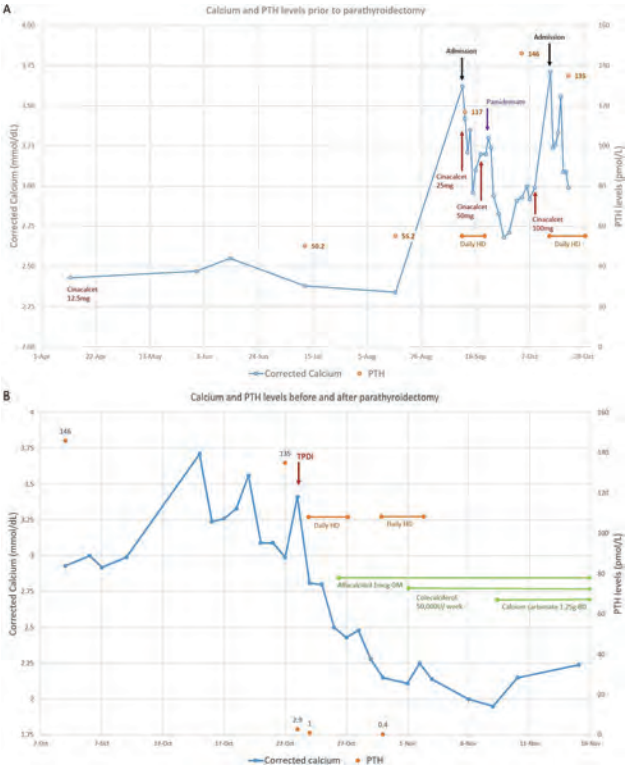
Systemic Amyloid Presenting with Rapidly Worsening Hyperparathyroidism in Patients with ESKD

Yi-Ting Ong, Julia G. Andres, Jiunn Wong. *Singapore General Hospital, Singapore, Singapore.*

Introduction: Hypercalcemia in ESKD patients is commonly associated with tertiary hyperparathyroidism and can be challenging to manage. We report a case of unusually severe PTH-mediated symptomatic hypercalcemia in a hemodialysis patient though to be secondary to rapidly deteriorating hyperparathyroidism. She failed medical therapy and underwent parathyroidectomy. Subsequent histology shows presence of amyloid deposit in the parathyroid specimen. Our case is unusual for rapidly worsening hypercalcemia and hyperparathyroidism and histology finding of amyloid deposit in the parathyroid specimen. We postulated the worsening of hyperparathyroidism and hypercalcemia was related to the amyloid infiltrate in the parathyroid gland

Case Description: A 67-year-old woman with background history of ESKD on hemodialysis who has stable hyperparathyroidism from CKD-MBD on medical therapy. She presented with two-week history of gradual functional decline and symptomatic hypercalcemia. Corrected serum calcium was markedly elevated at 3.62mmol/L, with raised iPTH at 117pmol/L. This is significantly higher than her results just 1 month prior to presentation. Ultrasound showed a well-defined 29 x 22 x 12mm hyperechoic nodule posterior to the right thyroid lower pole, consistent with a parathyroid adenoma which was congruent with a region of increased sestamibi tracer uptake with delayed tracer washout on parathyroid scintigraphy. Despite treatment with repeated sessions of hemodialysis, maximal doses of cinacalcet, calcitonin and anti-resorptives, her calcium levels remained high. She underwent parathyroidectomy with expected response in iPTH levels and improvement of hypercalcemia. Histology subsequently reviewed congo red deposit within intertrabecullar, perifollicular and paracortical stroma of parathyroid, thyroid and lymph node tissue.

Discussion: Unexplained rapidly worsening hypercalcemia in secondary hyperparathhyroidsm should prompt clinician to investigate for alternative cause of hypercalcemia and systemic amyloid may present with severe hypercalcemia and hyperparathyroidism



TH-PO174

Case Report of CyberKnife Radiosurgery Treatment for Secondary Hyperparathyroidism in a Patient Undergoing Dialysis

Bengang Huo, Rong He, Chuan Chen, Shihui Hou, Kehong Chen. *Army Medical Center of PLA, Chongqing, China.*

Introduction: We present a compelling case where CyberKnife effectively treated a patient suffering from bone pain and poor response to medication following a prior surgery for medullary thyroid carcinoma.

Case Description: A 41-year-old patient who has been undergoing peritoneal dialysis combined with hemodialysis for 7 years, underwent a total thyroidectomy for medullary thyroid cancer 4 years ago. His iPTH levels rose to 1062.66 pg/ml, leading to bone pain in shoulders, wrists, and knees 2 years ago. Cinacalcet 50mg/day was prescribed, but iPTH levels remained uncontrolled, and bone pain persisted. MIBI imaging revealed a parathyroid nodule approximately 1.5*1.1cm in size on the right neck. Cyberknife treatment of 27Gy/3F was carried out. After 11 weeks of treatment, MIBI imaging showed reduced parathyroid volume and decreased uptake (Figure 1). The iPTH changes are detailed in table 1. No adverse events were reported during follow-up.

Discussion: This is the first report of using Cyberknife to treat secondary hyperparathyroidism. After treatment, the patient's bone pain improved. MIBI imaging also indicated a decrease in parathyroid gland size and weakened uptake, suggesting treatment effectiveness. Further investigation is needed due to the limited experience in using cyberknife for SHPT. Prolonged observation is essential to assess efficacy and potential adverse effects.

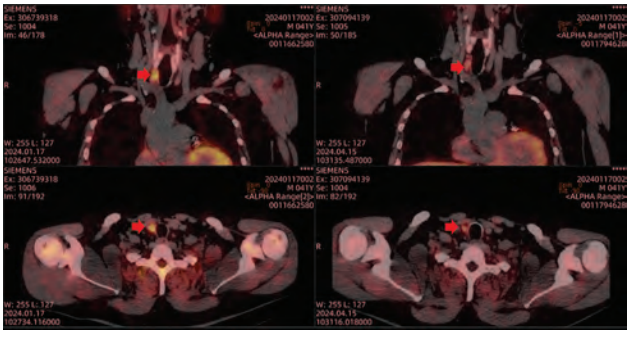


Figure 1. MIBI imaging before and after cyberknife treatment.

Table 1. Changes of iPTH, calcium and phosphorus before and after cyberknife treatment

Date	iPT (pg/ml)	Calcium (mmol/L)	Phosphate (mmol/L)	Treatment
2024-5-10	339.27	2.11	1.44	Cinacalcet 25mg/day,
2024-4-14	274.70	1.96	1.92	lanthanum carbonate
2024-3-31	161.62	2.04	2.28	
2024-3-2	971.68	2.15	2.37	
2024-2-25	218.45	2.57	2.10	Suspend cinacalcet, lanthanum carbonate
2024-2-11	470.23	2.16	1.89	Cinacalcet 25mg/day,
2024-2-4	507.33	2.28	2.06	lanthanum carbonate
2024-1-27	1152.70	2.55	2.31	Cyberknife, cinacalcet 50mg/day, lanthanum carbonate
2024-1-4	1467.32	2.43	2.33	Cinacalcet 50mg/day, lanthanum carbonate

Table 1. Changes of iPTH, calcium and phosphorus before and after cyberknife treatment.

TH-PO175

Heart of Stone: Cardiogenic Shock from Myocardial and Mitral Valve Calcification with Systolic Anterior Motion (SAM) Defect after Valve Replacement in a Patient on Chronic Hemodialysis (CHD)

Ashish Verma, Gregory L. Braden, Barbara A. Greco, Spencer Hodgins.
Baystate Medical Center, Springfield, MA.

Introduction: Myocardial & valve calcification has been descibed in CHD autopsy studies but has rarely been reported to be a clinical cause for CHF in CHD pts. We describe a pt who after 16 years of dialysis developed severe dyspnea & mitral stenosis from annular calcification(C) She had HFpEF & later developed cardiogenic shock & SAM after mitral replacement with severe LV outflow track obstruction. Autopsy showed severe myocardial C & 50 % myocaridal fibrosis, a new cause of clinical HFpEF in CHD pts.

Case Description: A CHD pt with years of PTH > 2000 pg/ml, hypercalcemia and CaPhosphorous(P) product 54-123 developed dyspena with mitral stenois with a 16 mmHg gradient. She was on CHD from 1988-90 & then 1992 -2006. After PTH removal in 1997 she had severe hypocalcmia, PTH < 1.0 pg/ml, & she got over 2000 mcg of iv calcitriol & 11,100 grams of CaP binders from 1992 to 2006. Cardiac studies showed a small heart with a cardiothoracic ratio of .36, LVEF 70 %, severe mitral gradient of 14-16 mmHg, LVH, & pulmonary artery presssure of 79 mmHg & mild tricuspid regurg. The coronary arteries had minimal changes. At surgery severe mitral annular calcification allowed only a pediatric St.Jude's valve. On day 3 she devleoped shock requiring fluids & 3 pressors. TEE showed marked SAM with severe obstruction of the LV ouflow track, severe pulmonay hypertension & severe tricuspid regurg & RV failure. LVEF was 65%. At death autopsy showed a small heart size despite a weight of 600 gms.with diffuse myocardial C on H&E & 50 % of the myocadium had fibrosis on trichrome stains. Calcium deposits were minimal in the coronary arteries.

Discussion: We conclude: 1) Diffuse myocardial C & fibrosis can occur in CHD pts from parathyroid & CaP dysrgulation & over use of calcium based P binders and IV Calcitriol. 2) Myocardial calcium causing severe fibrosis is a rare but important cause of dyspnea & HFpEF with a small heart in CHD pts. 3) SAM of the mitral valve has never been reported in CHD pts & can occur after mitral valve replacement 4) Prexisting tricuspid regurg & pulmonary hypertension are risk factors for severe RV failure after mitral valve replacement. 5) Simultaneous tricuspid valve replacement or repair may be needed in such pts receivng a mitral valve prosthesis.

TH-PO176

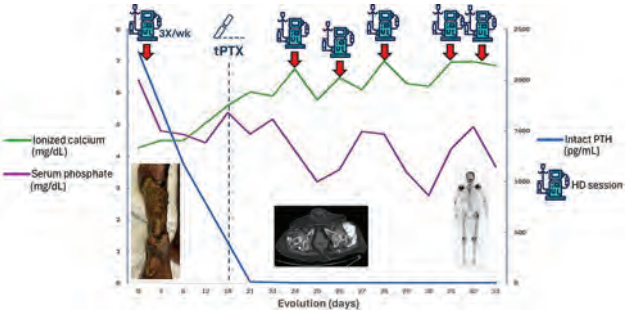
Unexpected Early Hypercalcemia after Parathyroidectomy in a Patient with Tumoral Calcinosis and Severe Calciphylaxis

Ana C. Gonzalez Medina, Vianca A. Canaviri, Ana L. Ruelas Villavicencio, Paul A. Parra, Ivan Perez Diaz, Jose A. Paz Cortes, Juan Carlos Ramirez-Sandoval.
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.

Introduction: Hypocalcemia due to hungry bone syndrome commonly occurs after total parathyroidectomy (tPTX) in kidney failure patients. This is a paradoxical hypercalcemia case after tPTX in a patient with severe calcific uremic arteriolopathy (CUA) and extensive extraosseous calcium deposits (tumoral calcinosis, TC).

Case Description: A 54-year-old woman with kidney failure on hemodialysis for 4 years (2X/week), admitted to the emergency room with fever and severe neuropathic pain in extremities. Physical examination showed huge ischemic ulcers on lower limbs (see figure). Additionally, asymptomatic palpable masses were found in her shoulders, knees and hips. A skin biopsy confirmed the diagnosis of CUA, while a PET-CT scan revealed extensive vascular calcifications and calcium phosphate deposits (CPD) in soft tissues and periarticular areas (TC). Lab tests revealed severe hyperparathyroidism (HPT) with iPTH 2049pg/mL, alkaline phosphatase (ALP) 245U/L, normocalcemia (free calcium 4.5 mg/dL), hyperphosphatemia (6.5 mg/dL) and low vitamin D. She received IV antibiotics, surgical debridement, hemodialysis (HD), calcimimetics and opioids. A tPTX was performed (post-surgery iPTH <50pg/mL). However, she experienced sustained elevations in calcium levels (free calcium >7mg/dL), which required frequent HD for lowering. After tPTX, pain intensity decreased as did ALP, iPTH remained low and ALP levels, yet hypercalcemia persisted. Other causes of hypercalcemia were discarded.

Discussion: We present a novel case of early hypercalcemia development post-tPTX in a patient with CUA and extensive CPD. Mobilization of calcium from extraosseus stores and a poor bone resorption (early adynamic bone disease) seem the main cause of early hypercalcemia in this case. While tPTX has proven effective in managing TC and CUA associated with severe HPT, paradoxical hypercalcemia after tPTX may occur early in cases with extensive extraosseouss CPD.



Clinical presentation and evolution

TH-PO177

Successful Treatment Using Oral Vitamin K in a Patient on Peritoneal Dialysis with an Extensive Right Hip Lesion Due to Calcific Uremic Arteriolopathy (CUA, Calciphylaxis): A Rare but Highly Fatal Condition

Niladri Mal, Arshad Ali, Shoaib A. Chowdhury. Munson Healthcare.
Munson Healthcare Cadillac Hospital, Cadillac, MI.

Introduction: Calciphylaxis is a rare but serious disorder commonly seen in patients with end-stage renal disease, however, rarely occurs in patients with normal renal function, acute renal failure or earlier stages of chronic kidney disease (non-uremic CAU). CAU typically present as painful skin lesion as results from calcification of the medial layer of arterioles and small arteries leads to tissue ischemia and infraction, a fatal condition with one-year mortality upto 30-80%, mostly due to sepsis.

Case Description: 73 y old Female on peritoneal dialysis who presented with severe progressive calciphylaxis on her right thigh. Patient was intolerant to sodium thiosulfate therapy. The patient was given high dose (100 x of daily requirements) Vit K therapy 10 mg on Mon-Wed-Fri for 6 months, which was the principal therapy, resulted in skin healing and complete resolution of the CUA (Fig 1). Hence, CAU is a rare, fatal condition that requires prompt diagnosis and treatment and should be suspected in a dialysis patient with painful skin lesion. Although previous study shows poor effectiveness of Vitamin K therapy, our study for the first time strongly validates effectiveness of high dose Vit K therapy in treating calciphylaxis in peritoneal dialysis patients.

Discussion: Matrix G1a protein which is dependent on Vit K dependent carboxylation for its activity, may prevent vascular calcification [(1) Dobry AS]. Therefore, Warfarin use has been implicated as a risk factor for calciphylaxis and Vit K therapy has potential in treatment of calciphylaxis. In our patient, we successfully able to diagnose her early and treat her with Vit K supplement, resulted in her rapid pain relief, wound healing, and prevention of death.

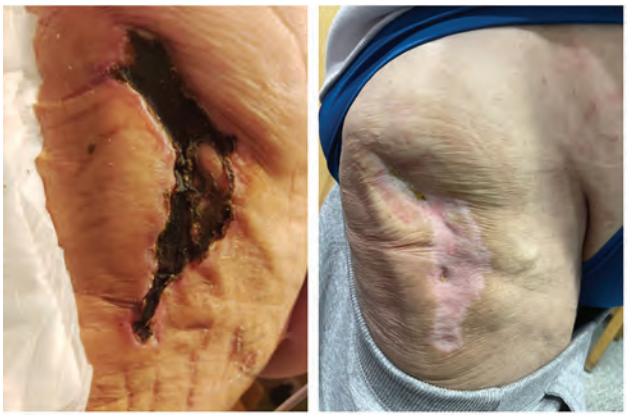


Fig 1. Shows an extensive necrotic ulcer in right thigh due to calciphylaxis (left image) and complete wound healing after completion of Vit K therapy for six months (right image).

TH-PO178

Familial Hypercalcemia and Hypercalciuria with a Novel Calcium-Sensing Receptor Mutation

Kenneth Brand,[1,2] Barbara A. Greco.[1,2] *[1]Baystate Medical Center, Springfield, MA; [2]University of Massachusetts Chan Medical School, Worcester, MA.*

Introduction: The most common cause of hereditary hypercalcemia is Familial Hypocalciuric Hypercalcemia (FHH). Over 200 loss-of-function CaSR mutations have been associated with FHH. We report a family with hypercalcemia due to a novel mutation in the CaSR with associated hypercalciuria.

Case Description: An 80-year-old white man initially presented at age 67 with longstanding hypercalcemia, no history of renal stones or osteoporosis, and on no supplemental calcium. Over the years, his serum calcium ranged from 10 to 11.6 mg/dl, phosphorus 1.9-2.9 with PTH levels between 29-50 pg/ml. Vit D and magnesium levels were normal. Several 24-hour urine collections confirmed hypercalciuria and hyperphosphaturia. Two 24-hour renal calcium to creatinine clearance ratios (CCCR) were 0.013 and 0.017. NM sestamibi scan showed no parathyroid adenoma. Genetic testing (Invitae) identified a cytosine to thymine substitution at position 1880 of the CaSR gene with threonine replacing isoleucine at position 627 in the intramembranous portion, a variant of unknown significance (VUS). Cinacalcet 30 mg daily had no effect whereas 60 mg daily normalized serum calcium. His daughter was found to be hypercalcemic and hypercalciuric (210 mg) at age 40 and her 16-year-old son had hypercalcemia, 10.6 mg/dl.

Discussion: The finding of a CaSR VUS in a family with hypercalcemia supports the diagnosis of FHH. This patient's CCCRs were nondiagnostic for differentiating primary hyperparathyroidism from FHH. Our patient had hypercalciuria and hyperphosphaturia. The mechanism is unclear but raises the question as to whether this mutation affects the function of the CaSR in the parathyroid gland and renal tubules differently- reducing the activity of the CaSR in the parathyroid and proximal tubule to a greater extent than in the thick ascending limb. Response to moderate but not low dose cinacalcet is consistent with an inactivating CaSR mutation.

Laboratory Investigations

Year	Calcium* mg/dl	Phosphorus mg/dl	PTH pg/ml	Urine Calcium mg/day	Urine phosphorus mg/day	Intervention
2010	10.2-10.7	2.2-2.9	42.9-50.6	260	1400	None
2016	11.4-11.6	2.1-2.7	27.5-35.7	410-480	1300-2300	None
2016	11.4	2.3		270	1500	Cinacalcet 30 mg/day
2018-2020	10-11.3					None
2023	11.2	2.8				None
2023	9.7-10	2.5-2.9		Not done as ordered	Not done as ordered	Cinacalcet 60 mg/day
2023	11.2	4.7	25	Not done as ordered	Not done as ordered	None
2023	9.8	3.7		Not done but ca/creat 0.022	Not done as ordered	Cinacalcet 60 mg/day

TH-PO179

Muscle-Limited Sarcoidosis Presenting as Recurrent Hypercalcemia of Unknown Origin

Atlee Baker, Ignacio A. Portales Castillo. *Washington University in St Louis, St Louis, MO.*

Introduction: Hypercalcemia is a commonly encountered clinical entity, affecting approximately 1-2% of the general population. Elevation of the parathyroid hormone (PTH), parathyroid hormone related peptide (PTHrP) or vitamin D is frequently observed in these cases. Most often, hypercalcemia is caused by elevated parathyroid hormone (PTH) levels; however, there is a broad differential for hypercalcemia. Occasionally, the cause of hypercalcemia is not apparent despite extensive work-up. We present a case of a young woman with severe and recurrent hypercalcemia of unknown origin.

Case Description: An18-year-old Amish female with history of hypothyroidism secondary to childhood thyroid toxicosis, Raynaud's disease, fibromyalgia, and spina bifida presented for evaluation of recurrent hypercalcemia. She initially presented to her community naturopathic healer after developing myalgias, fevers, night sweats, and constipation. Six months later, her symptoms worsened, and she presented to our institution. Evaluation revealed AKI with sCr 1.69mg/dL, hypercalcemia with Ca 16 mg/dL, low-normal phosphorus of 2.7mg/dl, suppressed PTH at 5pg/ml, undetectable PTHrP, low 25-vitamin D of 10ng/dL, and normal 1, 25-vitamin D of 66pg/mL. 24-hour urinary calcium was elevated at 310 mg. Additional work up including evaluation for paraprotein disease, vitamin A levels, bone marrow biopsy, and skeletal survey were all negative. After medical management with intravenous fluids and bisphosphonate she was discharged. The patient had recurrent hospital admissions with severe hypercalcemia. It was noted that she had again had normal 1-25 vitamin D levels and an elevated 24:24,25-vitamin D ratio of 33, despite very elevated intact FGF-23 of 352pg/mL, suggesting a non-regulated production of 1-25 vitamin D. Genetic investigations were negative for CYP24A1, SLC34A1 and ALPL mutations. In a search for the occult source of 1-25 vitamin D, the levels of angiotensin converting enzyme and aldolase were found to be elevated, with positive uptake noted at her shoulder in a PET scan suggestive of muscle limited sarcoidosis. She was started on plaquenil with resolution of hypercalcemia.

Discussion: We present a case of occult hypercalcemia, ultimately ascribed to muscle limited sarcoidosis which responded to Plaquenil. The case illustrates the interpretation of hormonal parameters in a challenging case of hypercalcemia.

TH-PO180

Hypercalcemia: It's Only Skin Deep

Branavan V. Ragunanthan, Clay A. Block, Charles W. Hopley. *Dartmouth Health, Lebanon, NH.*

Introduction: Hypercalcemia is a common electrolyte abnormality with multi-systemic consequences that has been associated with several etiologies including genetic conditions, various pathologies, and certain medications. Dialysis patients usually experience hypercalcemia because of hyperparathyroidism and its treatment. Here, we present a dialysis patient with parathyroid hormone (PTH)-independent hypercalcemia resulting from psoriasis treatment.

Case Description: A 43-year-old man with end-stage renal disease (ESRD) treated by home hemodialysis, and severe psoriasis presented to his home dialysis clinic with labs demonstrating up-trending monthly calcium levels between 10.7 mg/dL to 11.6 mg/dL (normal range: 8.5 – 10.5mg/dL). Corresponding PTH levels were down-trending from 699 pg/mL to 77 pg/mL (normal range: 16 – 80 pg/mL). Home medications as documented in multiple electronic medical record systems (EMR) were notable for calcitriol 0.25mg three time weekly and cholecalciferol 2000units daily - both of which were discontinued. The patient reported no significant intake of calcium supplements. Paraprotein studies were unremarkable. 25-OH and 1,25 dihydroxy vitamin D were 34.2 ng/mL (normal range: 30.0 - 100.0 ng/mL) and 118 pg/mL (normal range: 19.9 - 79.3 pg/mL) respectively. Imaging was negative for adenopathy, masses or infiltrates. Angiotensin converting enzyme was normal at 82 units/L (16 - 85 units/L). Upon further review, the patient reported seeing his dermatologist several months prior to the onset of hypercalcemia for psoriasis and received a prescription for calcipotriene cream, which he was applying liberally. Calcipotriene cream was discontinued and hypercalcemia resolved while PTH increased to 560 pg/mL.

Discussion: There are only several reports illustrating the association of hypercalcemia with calcipotriene. Calcipotriene is a topical vitamin D analog that is a cornerstone therapy for psoriasis. Cutaneous absorption can result in excessive 1,25 dihydroxy vitamin D, thereby creating a PTH-independent mechanism for hypercalcemia. This case exemplifies a pitfall of EMR medication lists if medications are not uploaded or reviewed during visits. Topical agents, drops, over the counter medications, and herbal supplements may be particularly prone to this problem. In this case, there was considerable diagnostic delay and prolonged exposure to hypercalcemia related to incomplete EMR medication list.

TH-PO181

Hypercalcemia Due to Elevated 1,25-Dihydroxyvitamin D in Severe Tophaceous Gout

Madhia B. Ahmad, Harshad Chaudhari, Smita Mahendrakar, Michael Yudd. *Rutgers Health, Newark, NJ.*

Introduction: Granulomatous disorders, like sarcoidosis and tuberculosis, can cause hypercalcemia by increasing production of calcitriol through the activation of extrarenal 1-alpha-hydroxylase by macrophages in granuloma. Patients often are asymptomatic and have low parathyroid hormone (PTH) level and elevated 1,25 dihydroxyvitamin D levels. Severe tophaceous gout can cause granulomatous inflammation and is a rare cause of hypercalcemia.

Case Description: A 68-year-old male with severe tophaceous gout and possible seronegative rheumatoid arthritis resulting in extensive deformities presented with asymptomatic hypercalcemia 13.1 mg/dL and worsening kidney function. His laboratory testing notable for creatinine 2.6 mg/dL with baseline chronic kidney disease creatinine 2.0 mg/dL, low PTH, elevated serum 1,25-dihydroxyvitamin D and angiotensin converting enzyme (ACE) levels. Extensive workup ruled out sarcoidosis, malignancy, fungal infections, and tuberculosis. He had resection of his elbow tophi which showed many granulomas. Renal Biopsy consistent with ateriosclerosis disease. Aggressive treatment of his gout with steroids and urate lowering therapy febuxostat improved his hypercalcemia.

Discussion: Our patient presented with relatively long-standing hypercalcemia with minor symptoms. This occurred in the setting of severe tophaceous gout and probable seronegative rheumatoid arthritis. In normal states, 25-hydroxyvitamin D is hydroxylated to the active 1,25-dihydroxyvitamin D in renal proximal tubular cells through the enzyme 1α-hydroxylase. In hypercalcemia this conversion is inhibited. Elevated 1,25-dihydroxyvitamin D in the setting of hypercalcemia as seen in this patient points to abnormal unregulated extrarenal conversion, typically found in granulomatous states and lymphomas.

Table 2 Review of the 6 cases found in the literature of hypercalcemia associated with tophaceous gout

References	Age (Years)	Serum Calcium/Uric Acid (mg/dL)	Extensive Tophi	Granulomas in Tophi	Serum 1,25-Vitamin D	Serum ACE	ULT/ steroids	Reported cause of hypercalcemia
Rodriquez et al [6]	42	14.5/14.0	Yes	Yes	N	ND	Yes/Yes	Transient increase PTH-RP
Sachdeva et al [7]	41	13.5/ND	Yes	Yes	Elevated	ND	Yes/Yes	Increased 1,25-Vitamin D
Gallego-Bayas et al [10]	75	14.0/10.4	Yes	Yes	N	Yes	Yes/Yes	Increased 1,25-Vitamin D
Hasbani et al [11]	62	11.7/11.3	Yes	ND	ND	Yes	Yes/Yes	PTH independent
Lee et al [12]	49	15.3/11.7	Yes	ND	N	Normal	Yes/ No	Immobilization
Gudlawar, S American Society of Nephrology [13]	40	13.4/11	Yes	ND	Elevated	ND	Yes/Yes	Increased 1,25-Vitamin D

ND = No Data; N = Normal; ACE = serum Angiotensin Converting Enzyme; ULT = Urate Lowering Therapy
* when measured during hypercalcemia

TH-PO182

Calcium Chaos: When Siliconoma Steals the Show

Anna V. De la Pena,[1,2] Celine Garcia,[1,2] Priya A. Savani,[1,2] Maryam Tajamal,[1,2] Akshay Kumar,[1,2] Danny Haddad.[2] *[1]Rutgers Health, Newark, NJ; [2]Jersey City Medical Center, Jersey City, NJ.*

Introduction: Kidney damage resulting from silicone implants is a rarely reported phenomenon. Rare complications from wound dehiscence can trigger an autoimmune response eliciting cascade of reactions causing hypercalcemia and nephrocalcinosis. We report a case of hypercalcemia-induced CKD following silicone buttock augmentation.

Case Description: A 52-year-old transgender woman with a past medical history of asthma, hypertension, and silicone injection in the glutes presented to the ED with polyuria, polydipsia, and constipation. Bloodwork showed calcium of 16 mg/dL, BUN 38 mg/dL, and creatinine 2.03 mg/dL. Further work-up revealed low PTH 6.3 pg/mL, low PTHrP 16 pg/mL, low 25-hydroxyvitamin D 15 ng/mL, and elevated 1,25-dihydroxyvitamin D 66 pg/mL. The patient was treated with IV fluids, zoledronic acid, and calcitonin for 5 days and discharged on alendronate 70 mg weekly. Four months later, she was hospitalized with symptomatic hypercalcemia and was managed similarly. Further work-up revealing a negative SPEP and immunofixation, and elevated LDH 234 U/L, elevated ACE levels 162.9 U/L, suggesting granulomatous disease. A CT of the abdomen/pelvis showed infiltration throughout the bilateral gluteal subcutaneous fat with scattered calcified granulomas. A bone scan showed diffuse radionuclide accumulation in the buttocks corresponding with soft tissue attenuation and scattered calcifications. Over the next two years of receiving denosumab 120 mg monthly, hypercalcemia persisted, leading to recurrent nephrolitiasis and hydronephrosis, which further compromised kidney function. Calcium levels began to stabilize by the third year of treatment. Unfortunately, this improvement coincided with the patient progressing to CKD stage 4.

Discussion: This case underscores the importance of considering rare causes like siliconoma in cases of recurrent hypercalcemia. Siliconoma, though difficult to treat and often leading to complications like CKD, can result from an immune reaction to silicone, causing hypercalcemia by increasing calcium absorption through the production of 1,25 Vitamin D3.(1) Normalization of calcium could be related to the development of secondary hyperparathyroidism due to advanced CKD compared to treatment response as observed in this case. Due to the challenge in removing extensive granulomas, the development of alternative management strategies is crucial.

TH-PO183

Hypercalcemia, from the Doctor's Office to the Hospital: The Path to Diagnosis in a Patient with Pott Disease

Francisco Velasco Garcia Lascurain, Mario Alamilla-Sanchez, Carolina Gonzalez-Fuentes, Juan D. Diaz Garcia, Jose L. Torres Cuevas. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico*.

Introduction: Mycobacterium tuberculosis is the second leading cause of death secondary to an infectious agent worldwide. The primary infection can originate from a pulmonary infection. In some cases, it can spread to the spine, known as Pott's disease. The wide variability of clinical manifestations makes timely diagnosis a challenge. This case describes a patient with CKD who came for consultation to initiate a renal transplant protocol. However, asymptomatic hypercalcemia was detected, resulting in her admission to our service for diagnostic assessment.

Case Description: A 32-year-old female with CKD diagnosed 1 year ago, underwent a transplant protocol referral while already on PD. She presented with a history of unintentional weight loss. Lab tests indicated hypercalcemia, hypoalbuminemia, normocytic normochromic anemia, and low PTH levels. Hospitalization was required for peritoneal dialysis adjustments as well as the commencement of the transplant protocol. Thoracoabdominal tomography unveiled hypodense lesions in the spine, prompting further investigation. Bronchoscopy confirmed Mycobacterium bovis, leading to treatment initiation and discharge. A month later, she was readmitted due to catheter dysfunction, and peritoneal fluid cultures tested positive for Mycobacterium. Finally the patient's condition deteriorated, ultimately resulting in her demise.

Discussion: Mycobacterium bovis is a significant cause of tuberculosis in both cattle and other mammals, particularly impacting healthcare systems in developing nations. Extrapulmonary tuberculosis affects about 2% of cases, with spinal cord involvement possible through hematological dissemination. Pott's disease presents with constitutional symptoms and progressive back pain. Limited access to diagnostic facilities and the disease's insidious nature complicate timely identification. Patients with CKD undergoing renal replacement therapy face heightened tuberculosis risk, with extrapulmonary presentations more prevalent. Renal involvement, peritonitis in peritoneal dialysis patients, and spinal column infections are notable. Hypercalcemia, driven by granuloma formation due to increased macrophage alpha-1 hydroxylase expression, aids diagnosis, as seen in our patient with Pott's disease.

TH-PO184

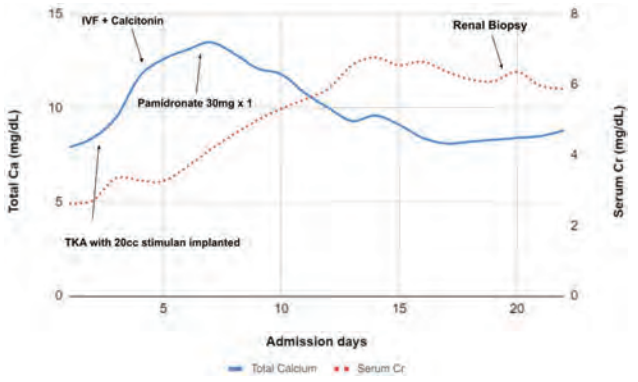
Hypercalcemia and Kidney Complications from Joint Implants

Anthony T. Nguyen, Dinna Cruz. *University of California San Diego, La Jolla, CA.*

Introduction: Acute kidney injury after revision knee and hip arthroplasty is common with rates of 20% reported. An uncommon complication for the nephrologist to be aware of is hypercalcemia, which can occur with use of calcium sulfate-based volume expanders i.e. Stimulan. These absorbable drug-eluting beads deliver local antibiotics to manage prosthetic joint infections (PJI). Complications of transient hypercalcemia are reported in 5%, with treatment required in 0.2% of cases. We present a case of symptomatic severe hypercalcemia suspected from Stimulan use.

Case Description: A 67 year old male with history of DM, HTN, CKD stage 4, and knee arthroplasty with recurrent PJI who presented for joint revision. His post-op course was complicated by non-oliguric AKI related to perioperative hemodynamic changes with low renal reserve. On POD#3, he had symptoms of constipation, nausea/vomiting; hypercalcemia was noted (Fig 1). Serological workup for hypercalcemia was unrevealing with PTH appropriately low; serum electrophoresis, PTHrp, 25-OH and 1,25-OH Vit D levels were low-normal. OR notes indicated implantation of 20mL stimulan beads during surgery. Interestingly an additional 20mL of stimulan was also implanted 6 months earlier during prior revision. Due to worsening hypercalcemia and renal function despite adequate IV hydration, pamidronate was given at reduced dosing, with subsequent normalization of Ca levels. However, he continued to have rising serum Cr suspected from bisphosphonate use. A renal biopsy showed ATN with 53% global glomerulosclerosis from HTN and 50% IFTA.

Discussion: Hypercalcemia has been reported with calcium sulfate-based volume expanders, typically associated with higher bead volumes, e.g. 30-40mL. Many cases are mild and self-resolving up to a reported 2-6 weeks. In 0.2% of cases, severe or persistent hypercalemia requires treatment similar to other causes of severe hypercalcemia including use of bisphosphonates or RANK-L receptor antibodies. Washout of beads may not be beneficial and can exacerbate hypercalcemia from bead agitation.



TH-PO185

Atypical Location of Tumor-Induced Osteomalacia (TIO) and Its Clinical Implications

Carla A. Nicolau, Miguel Bigotte Vieira. *Unidade Local de Saude Sao Jose, Lisboa, Portugal.*

Introduction: Tumor Induced Osteomalacia (TIO) is a rare but potentially treatable paraneoplastic syndrome. Thus, increasing awareness, may lead to prompt recognition and effective management of TIO, which is crucial in reducing long-term disability and morbidity.

Case Description: A 63-year-old woman was referred to our hospital with 2 years of muscle weakness and bone pain. She had progressive incapacity to walk and pathologic fractures. DEXA scan revealed osteoporosis. Initial laboratory measurements showed severe hypophosphatemia 1,6mg/dL, normal calcium, magnesium and creatinine values. Further work-up revealed low vitamin D1,25 <1,6 pg/mL, high serum alkaline phosphatase 459 U/L and high normal PTH 78 pg/mL. Urine testing showed high fractional excretion of phosphate 29%. Urinalysis didn't show proteinuria or glicosuria. FGF-23 was abnormally high (348 UA/mL) and genetic testing was normal. A bone biopsy confirmed the diagnosis of osteomalacia. A 68 Ga-DOTANOC PET/CT scan showed a cervical infiltrative lesion. Following the surgical excision of the tumor, serum phosphate and FGF-23 levels returned to normal in three weeks, and the patient regained the ability to walk. One year later, the patient reported a recurrence of musculoskeletal symptoms. Laboratory results indicated hyphosphatemia and an elevated fractional excretion of phosphate, suggesting tumoral recurrence. The patient is currently being evaluated for burosumab treatment and surgical candidacy.

Discussion: The initial presentation of TIO can be non-specific and misleading, posing a diagnostic challenge. Delayed diagnosis results in significant morbidity and, if left untreated, can be fatal. Complete surgical resection remains the optimal treatment. However, up to 14% of surgically treated cases may experience recurrence due to incomplete resection, leading to devastating implications. Historically, this condition has been treated with calcitriol and phosphate supplementation. However, this requires multiple daily doses, increasing the burden of disease and presenting risk of nephrocalcinosis and non-compliance. Additionally, in patients with CKD, dose titration is limited by renal disease and secondary hyperparathyroidism. Therefore, Burosumab, a monoclonal antibody against FGF-23, is a crucial second-line therapy for enhancing clinical outcomes and quality of life in patients with non-surgical or non-localized TIO.

TH-PO186

Transfer Learning Predicts Network Biology for Fibroblast Growth Factor 23 (FGF-23) and Cardiac Disease

Farzana Perwad,[1] Elvis A. Akwo,[2] Cassianne Robinson-Cohen.[2]
[1]University of California San Francisco, San Francisco, CA; [2]Vanderbilt University Medical Center, Nashville, TN.

Background: Multi-trait analysis of Genome-wide association (MTAG) is a novel method to explore overlapping genetic architecture between traits. We investigated genetic traits common to mineral metabolism to identify novel genetic associations for fibroblast growth factor 23 in the context of cardiac disease. We utilized transfer learning, a novel machine learning tool to enable context-specific predictions in a setting with limited data in network biology.

Methods: We applied MTAG to genetic variants common to 5 genetically correlated mineral metabolism markers (phosphorus, FGF23, calcium, vitamin D and PTH) in European-ancestry subjects from UKBioBank (n=366,484), and CHARGE consortium (n=45,779). We applied a context-aware, attention-based deep learning model, Geneformer, pre-trained on a large-scale corpus of ~ 30 million single-cell transcriptomes to enable context-specific predictions. We also queried for genes functionally related to uremia using gene reference into function database.

Results: MTAG identified independent genome-wide significant SNPs for all traits, including novel and known loci for FGF23. We identified statistical overlap of GWAS variants with Geneformer-derived genetic targets obtained from modeling single nuclear cell RNA seq from human heart transplant recipients and from deceased organ donors with healthy hearts (Figure 1). In silico gene perturbations revealed genes that, when activated or deleted, were protective against hypertrophic or dilated cardiomyopathy (Table 1). Further, we identified uremic solutes, glyoxal, erythritol and calcitonin gene-related peptide associated with both MTAG variants and pathophysiology of cardiac disease.

Conclusions: Novel genetic traits for FGF23 were identified with MTAG and associated with cardiac disease. Geneformer revealed networks that inform unique biological processes and cellular functions that could be targeted to develop therapeutics for human heart failure.

Funding: NIDDK Support

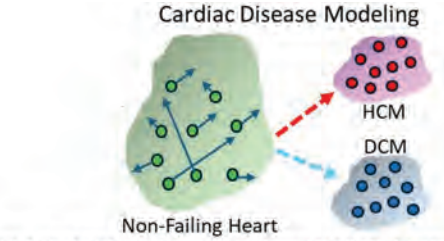


Fig. 1. Fine-tuning in Geneformer was performed to distinguish cardiomyocytes from non-failing hearts from hypertrophic (HCM) or dilated cardiomyopathy (DCM). Disease modeling is performed by in silico deletion or activation of random genes within non-failing cardiomyocytes to define the random distribution and to identify genes whose in silico deletion or activation shifts the embedding significantly towards either hypertrophic or dilated cardiomyopathy state.

Table 1. Disease modeling for hypertrophic and dilated cardiomyopathy in Geneformer

Pairing for Fisher's test	P_Value	Odds_Ratio (95% CI)	Gene Ratio
MTAG genes vs Hypertrophic cardiomyopathy_in silico gene activation	0.005	2.5 (1.3, 4.3)	14/2177
MTAG genes vs Dilated Cardiomyopathy_in silico gene activation	0.015	2.6 (1.1, 5.3)	8/1144
MTAG genes vs Hypertrophic cardiomyopathy_in silico gene deletion	0.067	3.3 (0.7, 9.9)	3/333
MTAG genes vs Dilated Cardiomyopathy_in silico_gene deletion	0.047	3.8 (0.8, 11.5)	3/288

Genes were filtered for non-failing (NF) heart, false discovery rate (FDR) < 0.01, and Shift to NF > 0. Gene ratio represents number of genes in MTAG over total number of genes that represent hypertrophic or dilated cardiomyopathy state.

TH-PO187

Prostaglandin E2 Receptor 4 Contributes to Regulating Epithelial Sodium Channel (ENaC) Activity in the Kidney Collecting Duct

Ting Yang,[1] Oleh Pochynyuk.[2] *[1]Duke University, Durham, NC; [2]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.*

Background: PGE_2 and its EP4 receptor (EP4R) play important role in blood pressure control. Our previous work showed conditional deletion of EP4R from whole kidney epithelia caused exacerbated blood pressure elevation, sodium retention, and increased responsiveness to ENaC inhibitor during Ang II-HTN. Thus, we hypothesize that EP4R resists the development of hypertension through actions in the CD to reduce sodium reabsorption via ENaC.

Methods: We used the patch clamp electrophyhsiology techniques in isolated CD from C57BL/6 mice to characterize the contribution of EP4 to ENaC activity. Additionally, we used an immortalized mouse collecting duct cell line (mpkCCDc14) to investigate the potential contribution of EP4 downstream signaling in regualting ENaC function.

Results: PGE_2 significantly inhibited the P_o of ENaC. This effect was abolished by EP4R antagonist (L161,982, Fig. 1). Using the mpkCCDc14 cells, we found that EP4 silencing using siRNA significantly inhibited the PGE_2 (10mM, 10min) induced phosphorylation of p-44/42 MAPK/ERK (Fig. 2).

Conclusions: Our results indicate that PGE_2 directly inhibits the kidney collecting duct ENaC channel open probability via EP4 receptor. The phosphorylation of MAPK/ERK pathway may contribute to teh ENaC regulation mediated by PGE2-EP4 signaling.

Funding: NIDDK Support

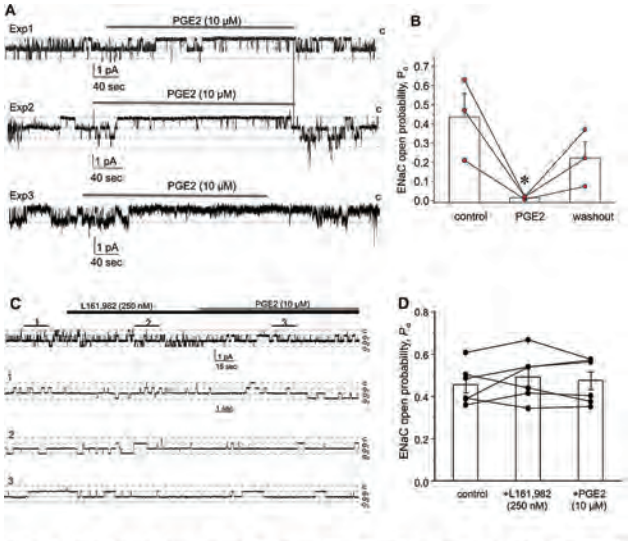


Figure 1. PGE2 inhibits ENaC activity in isolated cortical CDs via actions on EP4 receptors. (A) Current traces from patches monitoring ENaC activity in split-opened CDs under control and 10 mM of PGE2. (B) PGE2 significantly inhibits the ENaC open probability (Po). (C, D) EP4 receptor antagonist (L161,982, 250nM) abolished the PGE2 mediated inhibition of ENaC Po. * p<0.05 vs control and washout.

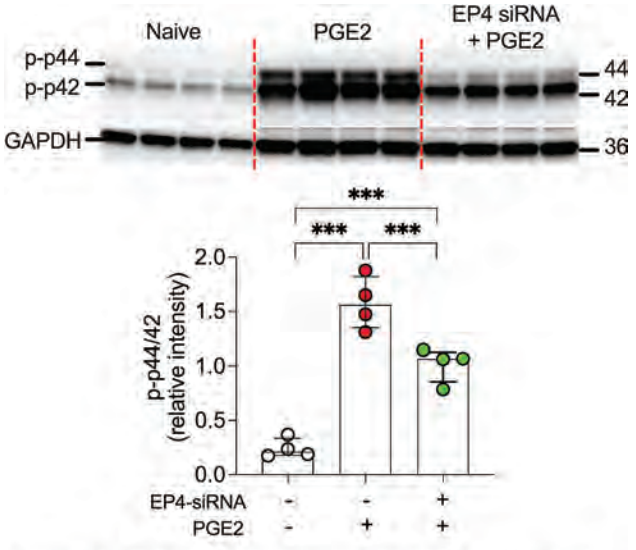


Figure 2. MAPK/ERK phosphorylation. EP4 silencing by targeted siRNA significantly reduced the PGE2 (10mM, 10 min) dependent p44/p42 MAPK phosphorylation (normalized by GAPDH). ***p<0.01.

TH-PO188

Activation and Targetability of TYMP-IL-6-TF Axis in the Skin Microenvironment in Patients with Uremic Calciphylaxis

Adam Lazowski,[1] Austin P. Morrissey,[1] Scott Krinsky,[3] Abbas Brahim Malloum,[1] Thierry Edwards,[1] Asha Jose,[1] Houda Bouchouari,[3] Wenqing Yin,[1] Rosalynn Nazarian,[3] Sagar U. Nigwekar,[3] Vipul C. Chitalia.[1,2] *[1]Boston University, Boston, MA; [2]Veterans Health Administration, Washington, DC; [3]Mass General Brigham Inc, Boston, MA.*

Background: Calciphylaxis is a rare disease characterized by calcification and thrombosis of subdermal microvessels, resulting in painful necrosis. It is seen predominantly in patients with end-stage kidney disease (ESKD) and has high mortality, elusive pathogenesis, and no approved therapies.

Methods: Sera and skin biopsies of ESKD patients with calciphylaxis were analyzed using O-linked proteomics and spatial transcriptomics, respectively. The validation and mechanistic probing were conducted using an array of techniques, including multiple ELISA, Immunofluorescence, and neutralizing assays.

Results: We demonstrate that the calciphylaxis sera upregulate IL-6, soluble IL-6 receptor (sIL-6R) levels and induce JAK2-STAT3 phosphorylation in the primary human subdermal microvascular endothelial cells (ECs) in a feedforward manner. Spatial transcriptomics and space-constrained probability analyses revealed a gain of proximal and distal IL-6 ligand-receptor interactions in calciphylaxis skin with heterogeneity between vessels, adipocytes, and eccrine glands. Microvessels served as the predominant senders and recipients of IL-6 signaling. Increased ADAM17, sIL-6R, and normal IL-6R levels in the skin microenvironment supported trans-IL-6 signaling in calciphylaxis. Additionally, calciphylaxis vessels showed an upregulation of *thymidine phosphorylase* (*TYMP*). Further mechanistic probing in ECs revealed that calciphylaxis serum-induced TYMP expression augmented IL-6 levels, which activated tissue factor (TF), the primary trigger of the extrinsic coagulation cascade. This TYMP-IL-6-TF axis was supported by strong correlations among TYMP, IL-6, and TF in calciphylaxis vessels. Calciphylaxis sera induced higher TF activity in ECs in a manner dependent on serum IL-6 levels and was suppressed by an anti-hIL-6R antibody.

Conclusions: This work, for the first time, identifies TYMP as an IL-6 regulator and characterizes calciphylaxis as a systemic state of high levels of IL-6 and a local state of activation of the TYMP-trans-IL-6-TF loop in the subdermal microenvironment perpetuating the thrombotic phenotype. Our work uncovers IL-6 as a potential biomarker and a therapeutic target for uremic calciphylaxis.

Funding: NIDDK Support, Other NIH Support - R01HL166608, R01 HL159620, R21DK132784, R21DK119740, Private Foundation Support

TH-PO189

Inhibition of NaPi2a Improves Pressure-Overload Heart Failure and Doxorubicin-Induced Cardiac Damage

Hiroko Yamauchi, Tomoharu Ida, Tetsuro Kusaba, Keiichi Tamagaki. *Department of Nephrology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan.*

Background: Recently, the number of heart failure (HF) patients is increasing worldwide. Based on the success of SGLT2 inhibitor in HF treatment, targeting proximal tubular sodium channel is an attractive therapeutic strategy for HF. We hypothesized that inhibition of Sodium-phosphate co-transporter 2a (NaPi2a), predominantly expressed in the renal proximal tubule, can attenuate the progression of HF via 1) reduction in serum FGF23 levels through phosphate excretion and 2) decrease in fluid volume via sodium excretion.

Methods: Using NaPi2a-KO mice, we examined the cardioprotective effect of loss of function of NaPi2a in following HF mouse model; 1) pressure-overload heart failure induced by transverse aortic constriction (TAC), 2) Doxorubicin (Dox) cardiomyopathy and 3) uremic cardiomyopathy by 5/6 nephrectomy

Results: In the TAC model, decreased serum phosphate and FGF23, and increased urinary sodium excretion were observed in NaPi2a-KO mice. Left ventricular ejection fraction (LVEF) in echocardiography was preserved in NaPi2a-KO mice. qPCR analysis revealed that upregulation of myocardial injury and fibrosis markers by TAC surgery was ameliorated in NaPi2a-KO mice. In the Dox cardiomyopathy model, LVEF was preserved in NaPi2a-KO mice. qPCR analysis showed that the Dox-induced upregulations of myocardial fibrosis markers were ameliorated in NaPi2a-KO mice. In the uremic cardiomyopathy model, serum phosphate and FGF23 were notable increased, but there were no differences between WT and NaPi2a-KO mice. No significant differences were noted in cardiac function, or expressions of myocardial injury and fibrosis markers by qPCR between the two groups, either. FGF23 levels were not correlated with cardiac contractility in all HF models.

Conclusions: NaPi2a inhibition ameliorated the progression of cardiac injury in pressure-overload heart failure and Dox cardiomyopathy but not in uremic cardiomyopathy. Urinary sodium excretion, rather than the decrease in serum FGF23 levels, may involve the effect of NaPi2a inhibition. In the uremic cardiomyopathy model, loss of kidney parenchyma and subsequent high serum phosphorus reduced NaPi2a expression may attributed to the less cardioprotective effect by NaPi2a inhibition. NaPi2a inhibition can be a novel therapeutic candidate for HF especially in the patients with preserved renal function.

TH-PO190

Aminopeptidase A: A Potential Novel Therapy for Angiotensin-Dependent Hypertension?

Peter Forster, Jan Wysocki, Daniel Batlle. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: We have shown that mice with a genetic deficiency in Aminopeptidase A (APA) have elevated blood pressure. APA is an enzyme that removes a single aspartate residue from the amino-terminus of several peptides in the renin-angiotensin systems (RAS), including angiotensin (Ang) II. In this study, we investigated the impact of a recombinant APA on the formation of various RAS peptides and its effect on blood pressure.

Methods: An in vitro assay was used to identify Ang peptides as substrates for APA. Ang peptides identified as APA substrates using this assay were then injected to anesthetized *WT and APA-deficient* mice to assess their pressor effect by measuring systolic blood pressure (SBP). Subsequently, murine recombinant (r)APA was used to evaluate its action on the acute SBP elevation elicited by Ang peptides that were identified to trigger pressor response.

Results: In the *in vitro* assay, Ang II (22427±3353, n=12), Ang I (21883±1692, n=3), Ang1-7 (15833±3395, n=3), Ang1-9 (15773±3395, n=3) and Ang1-12 (13170±220, n=3), were identified as a substrate for rAPA as indicated by a strong aspartate-driven fluorescence formation. When these five Ang peptides were administered to WT mice, only Ang I, Ang II and Ang 1-12 caused a significant increase in SBP. This effect was exaggerated in APA deficient mice. The SBP increase elicited by Ang I and Ang II in WT mice was markedly reduced by the pre-administration of rAPA (Fig. 1).

Conclusions: Aminopeptidase A can cleave the N-terminal aspartate from Ang II as well as from other RAS peptides that elicit (Ang 1-12, Ang I) do not elicit (Ang 1-9, Ang 1-7) pressor response in mice. APA deficiency is associated with an exaggerated SBP response to Ang I, Ang II and Ang 1-12 while the recombinant enzyme mitigates the acute hypertensive effect. rAPA markedly reduced the increase in SBP caused by Ang I and Ang II infusion suggesting that it may be used to treat hypertension resulting from RAS overactivity.

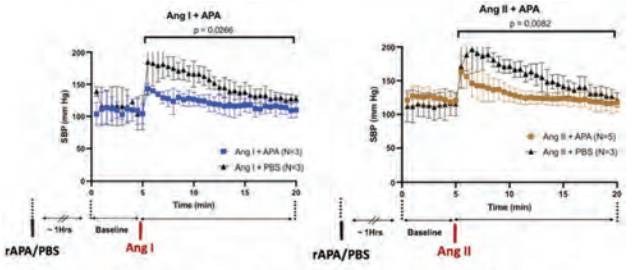


Figure 1. SBP after injection of Ang I and Ang II in WT mice that were pre-treated with either rAPA or vehicle (PBS).

TH-PO191

Transmembrane Protein 184A (TMEM184a) Expression in Rat Medullary Thick Ascending Limbs

Darshan Jadhav,[1] Beau Forester,[1] Najeong Kim,[1] Jeffrey L. Garvin,[1] Agustin Gonzalez-Vicente.[1,2] Kidney Precision Medicine Project (KPMP). *[1]Case Western Reserve University School of Medicine, Cleveland, OH; [2]Cleveland Clinic Glickman Urological and Kidney Institute, Cleveland, OH.*

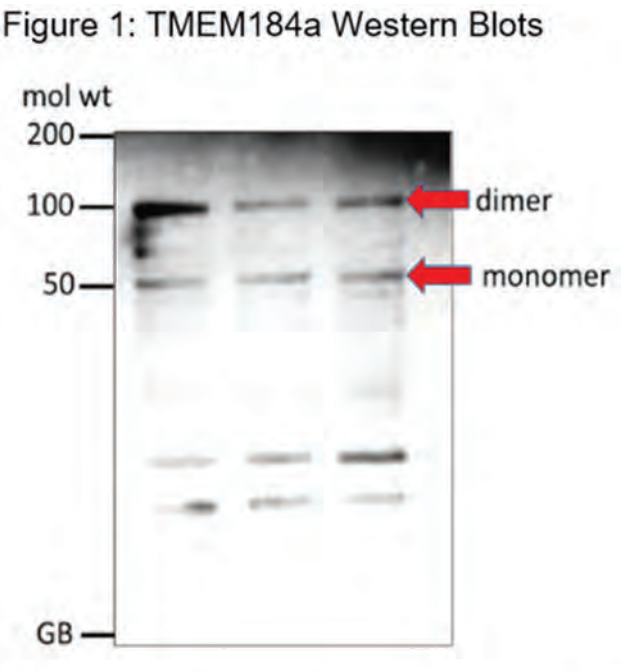
Background: Nitric oxide production by NOS3 in thick ascending limbs (TAL) is essential for proper kidney function. TMEM184A is a heparin receptor found in endothelial cells that mediates NOS3 phosphorylation. The kidneys express TMEM184A, but its localization in nephron segments expressing NOS3 remains unclear. The Kidney Precision Medicine Project (KPMP) single cell (sc) and single nuclei RNA sequencing (RNAseq) transcriptomes show TMEM184A expression in proximal tubules and inner medullary collecting ducts, but not in TALs. On the contrary, KPMP's regional transcriptomes show that TMEM184A is significantly overexpressed in the TAL (Δfc0.7; p≤0.05) as compared to other regions. The expression of Tmem184a in published rodent transcriptomes is similarly in dispute. The same laboratory reported that mouse medullary TAL had stronger TMEM184A mRNA expression than any nephron segment, while expression in rat medullary TAL was undetectable.

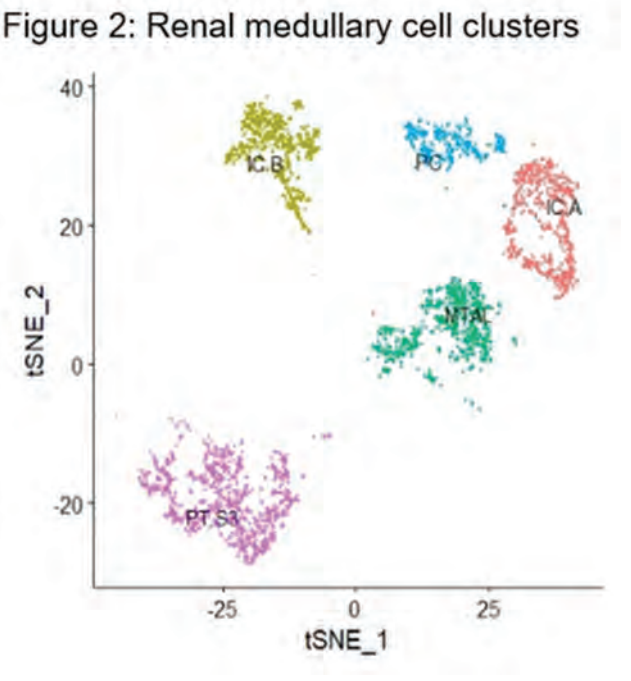
Methods: Consequently, we measured TMEM184A protein and mRNA expression by Western blot and scRNAseq in the outer medulla from Sprague Dawley rats.

Results: We found that the rat outer medulla expressed both, monomers and dimers of TMEM184A (Figure 1). Additionally, TMEM184A mRNA was significantly overexpressed in medullary TALs (Δfc1.7 p-Adj≤$4x10^{-18}$) when compared to other outer medullary epithelial cells types, i.e. proximal tubule S3 cells and the collecting duct principal and intercalated cells (Figure 2).

Conclusions: These data show that the rat medullary TAL express TMEM184A where it may play a role in NO production by NOS3 as it does in endothelial cells.

Funding: NIDDK Support





TH-PO192

Modulation of Blood Pressure through Microbiome Exchange between Milan Normotensive and Hypertensive Rat Strains

Giovambattista Capasso,[1,2] Yoko Suzumoto,[1,3] Cristoforo Silvestri,[4] Abbas Shams,[1,2] Luciano D'Apolito,[1,2] Antonio Villanova,[1,2] Francesco Trepiccione,[2,1] Vincenzo Di Marzo.[4] *[1]Biogem, Biology and Molecular Genetics Institute, Ariano Irpino, Italy; [2]University of Campania 'L. Vanvitelli', Naples, Italy; [3]Institute of Biochemistry and Cell Biology, National Research Council of Italy (CNR), Naples, Italy; [4]CRIUCPQ, INAF and Centre NUTRISS, Université Laval, Québec, QC, Canada.*

Background: Hypertension constitutes a major health problem leading to cardiovascular diseases. A number of studies showed gut microbiome changes in hypertension, suggesting kidney-gut axis in hypertension. A congenic strain of Milan hypertensive (NA) rats with a mutation in α-adducin gene develops hypertension at 3 months age. Our preliminary study revealed diverse expression of renal sodium transporters in NA rats compared with normotensive strain (MN) rats, indicating

abnormal renal salt handling in NA rats. Present study aimed at investigating a possible connection between gut microbiome and blood pressure phenotype in these two strains. We evaluated whether exchange of faeces between two strains may transfer phenotypes via gut microbiome, and mechanisms underlying altered phenotypes were investigated.

Methods: NA and MN rats were subjected to 'homogenization (HOM)' of the microbiome, consisted of exchanges of bedding with faeces, followed by co-housing in the same cage (MN-HOM and NA-HOM groups). For the baseline (BSL) condition, rats were homogenized within the same strain (MN-BSL and NA-BSL). Systolic blood pressure (SBP) was measured every month. Faeces were collected for microbiota metataxonomic analysis using next generation sequencing of 16S ribosome encoding DNA.

Results: At 5 month, SBP in MN-BSL was averaged at 143.6 mmHg, while SBP of NA-BSL was 163.3 mmHg, confirming the hypertensive phenotype in NA rats at baseline. MN-HOM showed a significantly enhanced SBP compared to MN-BSL, reaching 153.5 mmHg. The average SBP of NA-HOM was163.7 mmHg, indicating that homogenization did not have impact on SBP in NA rats. The SBP of MN-HOM was still significantly lower than both the NA-BSL and NA-HOM groups. Different gut microbiota compositions were observed in the two strains of rats at baseline, and HOM altered both.

Conclusions: We have demonstrated that the hypertensive phenotype in NA rats was transferred to MN rats through homogenization, indicating that the intestinal microbiota or metabolites derived therefrom could eventually modulate SBP. Further studies are required to unveil the molecular mechanisms by which the gut microbiome modulates blood pressure.

TH-PO193

Sex Differences in Renal Blood Flow Autoregulation Do Not Explain the Sex Disparity in CKD Progression

Aaron J. Polichnowski,[1] Jacqueline M. Chivers,[1] Purva R. Chopde,[2] Geoffrey A. Williamson,[2] Karen A. Griffin.[3,4] *[1]East Tennessee State University James H Quillen College of Medicine, Johnson City, TN; [2]Illinois Institute of Technology, Chicago, IL; [3]Loyola University Chicago Stritch School of Medicine, Chicago, IL; [4]Edward Hines Junior VA Hospital, Hines, IL.*

Background: We recently demonstrated an increased susceptibility to hypertensive renal injury in male vs. female rats. Sex differences in renal blood flow (RBF) autoregulation (AR) may contribute, in part, to the sex disparity in susceptibility to hypertensive renal injury and progression of chronic kidney disease (CKD); however, there are limited data available. Here, we investigated whether sex differences exist in RBF AR in uninephrectomized (UNX) rats before and during the administration of deoxycorticosterone acetate (DOCA) + salt.

Methods: Male (n=7) and female (n=8) Sprague-Dawley (SD) rats (10-13-week-old) underwent UNX. Two weeks later, rats were instrumented with a blood pressure (BP) radiotelemeter and a RBF probe. One week later, BP and RBF were assessed in the conscious state for 2-3 hours/day over 3 consecutive days prior to (i.e., baseline) and during days 3-7 of DOCA (3.3 mg/day) + salt (1% NaCl via drinking water) administration. We assessed dynamics of RBF AR using the short-segment AR index (SSARI, PMID 31792155) applied to adjacent time segments with >2.5 mmHg BP differences, as well as transfer function analysis. A 2-way repeated measures ANOVA with Sidak post hoc test was used for analysis. Data are mean±SE and P<0.05 was considered statistically significant.

Results: As shown in Table 1, RBF was higher (P<0.05) and renal vascular resistance (RVR) lower (P<0.05) in males at baseline and during DOCA + salt administration; however, no sex differences were observed in mean arterial pressure (MAP). DOCA + salt increased RBF and decreased RVR in both sexes (P<0.05), but only increased MAP (P<0.05) in males. No significant sex differences were observed in any measure of RBF AR. DOCA + salt decreased SSARI (i.e., strengthened RBF AR) for 2.5 second segments in females (P<0.05) but not males (P=0.10), and increased (P<0.05) the operating frequency of the myogenic mechanism in both sexes. In contrast, DOCA + salt decreased (P<0.05) the fractional gain at the myogenic frequency in both sexes.

Conclusions: Sex differences in RBF AR do not appear to be playing a significant role in the sex disparity in susceptibility to hypertensive renal injury and CKD progression.

Funding: Other NIH Support - NHLBI

Table 1

Group	Hemodynamics			SSARI		Transfer Function			
	MAP (mmHg)	RBF (ml/min)	RVR (mmHg / ml/min)	SSARI Index at 2.5 sec	SSARI Index at 20 sec	Myogenic Operating Frequency (Hz)	Fractional Gain at Myogenic Frequency	TGF Operating Frequency (Hz)	Fractional Gain at TGF Frequency
Baseline									
Female (n=8)	113 ± 1	9.4 ± 1	13.1 ± 1	0.77 ± 0.06	0.05 ± 0.07	0.21 ± 0.01	2.28 ± 0.12	0.048 ± 0.001	0.79 ± 0.05
Male (n=7)	112 ± 2	13.0 ± 1[a]	9.2 ± 1[a]	0.70 ± 0.09	-0.18 ± 0.05	0.20 ± 0.01	2.35 ± 0.10	0.044 ± 0.002	0.80 ± 0.14
DOCA + salt									
Female (n=8)	115 ± 4	11.3 ± 1[a]	11.1 ± 1[a]	0.63 ± 0.05[a]	0.10 ± 0.08	0.34 ± 0.02[a]	1.66 ± 0.10[a]	0.043 ± 0.002	0.71 ± 0.08
Male (n=7)	121 ± 4[a]	17.0 ± 1[a,b]	7.2 ± 1[a,b]	0.59 ± 0.07	-0.07 ± 0.07	0.24 ± 0.02[a]	1.47 ± 0.10[a]	0.039 ± 0.003	0.66 ± 0.13

Data are mean ± standard error. [a] P<0.05 vs. baseline; [b] P<0.05 vs. female. MAP = mean arterial pressure; RBF = renal blood flow; RVR = renal vascular resistance; SSARI = short-segment autoregulatory index; TGF = tubuloglomerular feedback.

TH-PO194

Conditional Genetic Disruption of Podocyte Cell-Specific Npr1 Provokes Kidney Dysfunction in Male and Female Mutant Mice in a Sex-Dependent Manner

Chandramohan Ramasamy, Kailash N. Pandey. *Tulane University School of Medicine, New Orleans, LA.*

Background: Atrial and brain natriuretic peptides (ANP and BNP) are cardiac hormones that induce diuresis, natriuresis, and vasorelaxation and reduce blood pressure (BP) and blood volume homeostasis via activation of transmembrane guanylyl cyclase/natriuretic peptide receptor-A (GC-A/NPR-A) with increased accumulation of intracellular cGMP. The role of ANP/NPRA/cGMP signaling in podocytes, which are highly specialized epithelial cells covering the outer surfaces of renal glomerular capillaries, is not well understood.

Methods: In this study, we determined the impact of conditional gene-knockout (KO) of podocyte (PD)-specific *Npr1* (encoding NPRA) in male and female mice. Tamoxifen-treated wild-type control (PD *Npr1* f/f; WT), heterozygous (PD-Cre-*Npr1* f/+; HT), and gene-knockout (PD-Cre-*Npr1* f/-; KO) mice were fed a normal-, low-, or high-salt diet for 28 days. Podocytes isolated from KO male and female mice exhibited a complete absence of *Npr1* mRNA and NPRA protein levels compared with WT mice.

Results: On a normal-salt diet, mean arterial pressure (MAP) and heart rate (HR) were significantly higher ($p<0.05$; $p<0.01$; $p<0.001$) in both male and female PD-*Npr1* KO mice compared with WT mice at 2, 4, 6, 8, and 12 weeks as measured by radiotelemetry. On a high-salt diet, the systolic blood pressure (SBP) was significantly ($p<0.01$; $p<0.001$) higher in the PD-*Npr1* HT mice (male:109.50 ± 1.20; female: 102.30 ± 0.60) and KO mice (male:116.20 ± 1.1; female: 104.40 ± 1.20) compared with WT mice (male: 96.30 ± 0.70; female: 92.60 ± 0.60) after 28 days as measured by computerized tail-cuff method. On normal-, low-, and high-salt diets, plasma sodium, and albumin/creatinine ratio were significantly ($p<0.05$; $p<0.01$; $p<0.001$) increased, while creatinine clearance and urinary sodium levels were significantly ($p<0.05$; $p<0.01$; $p<0.001$) reduced in the HT and KO male and female mice compared to WT mice. These changes were significantly greater in males than females. Immunofluorescence of podocin and synaptopodin were also significantly ($p<0.01$; $p<0.001$) reduced in HT and KO mice compared to WT mice.

Conclusions: These observations suggest that in podocytes, ANP/NPRA/cGMP signaling may be crucial in the maintenance and regulation of BP and GFR suggesting as a biomarker of renal function in a sex-dependent manner.

Funding: NIDDK Support

TH-PO195

Renal Solute Handling in ABCA1-Deficient Kidneys

Karin Carneiro de Oliveira,[1,2] Yuan Wei,[1,2] Rajeev Rohatgi.[1,2] *[1]James J. Peters VAMC, Bronx, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Na sensitive blood pressure (BP) and restricted cholesterol (chol) efflux are risk factors for cardiovascular mortality. Renal tubular ablation of ABCA1, a chol efflux protein, raises systolic BP (SBP) compared to wildtype (WT) mice. Enriched chol diets additionally raise SBP in mice of ABCA1 deficient kidneys while Na restriction quenches SBP difference between mice. In contrast enriched Na diets do not further raise SBP in ABCA1 deficient mice. Chol-fed ABCA1 deficient mice show increased renal NKCC2 and ENaC protein expression vs. WT chol-fed mice. The goal of this investigation is to determine whether renal solute transport is dysregulated in ABCA1 deficient mice fed a standard chol diet and whether these changes contribute to the development of high BP.

Methods: Transgenic mice, which express a doxycycline(dox)-inducible CRE in tubules, were bred with mice expressing floxed ABCA1 to produce tubule-specific deficiency of ABCA1 (FF). Mice (WT and FF) were fed dox in water, and then fed a standardNa (0.39%) and chol (0.0196%) for at least 1 week. The mice were then placed in metabolic cages to collect urine at 2 hr intervals for 6 hrs. Urine osmolality and [Na] were measured. RNAseq analysis was performed on the renal cortex.

Results: The weights of WT (n=10; 26.0±0.7 g) and FF (n=10; 25.7±0.4 g) mice did not differ. Surprisingly, FF mice excreted a larger urine volume at 2 hr (15.6±1.4 μL/g body weight[BW]) and over the entire collection period (33.7±2.2 μL/g BW) compared to WT mice (10.5±0.8 uL/g and 25.8± 2.2 uL/g BW, $p<0.05$; respectively). Urine osmolality did not differ, but osmole excretion was greater over the collection period in the FF (30.2±2.6 μosm/g BW; $p<0.05$) compared to WT (22.5±2.2 μosm/g BW). The urinary Na concentration rose over 6 hrs in WT and FF, but at 6hr the urine [Na] was greater in FF (97.4±6.9 mM; $p<0.05$) than WT (57.6±7.6 mM). Net Na excretion was greater in FF (1.49±0.15 μeq/g BW; $p<0.05$) than WT (0.92±0.17 μeq/g BW). RNAseq showed increased renal cortical Ren1 mRNA and western blot confirmed the increase of renin protein in FF (n=4) compared to WT (n=4).

Conclusions: Renal tubular ABCA1 deficiency, in mice fed a standard Na and chol diet, enhances urine volume, osmolar and Na excretion with greater renal renin expression. We speculate that loss of ABCA1 functionality mediates higher SBP via greater intra-renal renin which raises systemic BP to excrete more Na.

Funding: Veterans Affairs Support

TH-PO196

Novel Role of BK-Channel Activation in Ameliorating Cardiac Fibrosis in the Ischemia-Reperfusion (IR)-Induced Heart Failure Mouse Model

Xiaomao Luo,[1,2] Zimeng Liu,[1] Shuyang Bian,[1] Faten Hassounah,[1] Qiang Yue,[1] Xiaonan H. Wang,[1] Hui Cai.[1,2] *[1]Emory University, Atlanta, GA; [2]Joseph Maxwell Cleland Atlanta VA Medical Center, Decatur, GA.*

Background: Ischemic heart disease poses a significant global health challenge, impacting over 244 million adults worldwide. Our previous study has shown that the Big Potassium (BK) ion channel prevents renal fibrosis. However, it remains unclear whether BK channel has anti-fibrotic role in the heart.

Methods: Heart failure model was induced by Ischemic-Reperfusion (I/R) surgery in C57/BL6 mice. To upregulation of BKα, BMS-191011 (10 mg/kg BW) was given by IP injection daily for 8 weeks. Single channel recordings were used to analyze the activation of BKα channel. Cultured H9C2 cardiac myoblasts were used to assess the impact of BK opener (NS1916 10mM) on fibrosis markers and oxidative stress. Hydrogen peroxide (H2O2), superoxide and superoxide dismutase (SOD) were deternubed by Amplex Red Hydrogen Peroxide Kit, Dihydroethidium (DHE) Assay and colorimetric activity kit, respectively. The mRNA expression of BKα and inflammatory cytokines were assayed by qPCR.

Results: The expression of BKα mRNA and protein was decreased while cardiac fibrosis increased in the hearts of I/R mice. Fibronectin, vimentin, and αSMA were significantly elevated in I/R hearts; conversely, BMS treatment attenuated the levels of these proteins. Echocardiogram revealed an increase in left ventricular end-diastolic dimension in I/R mice, which returned to normal following BK opener treatment. Ejection fraction also improved with this treatment. In addition, the activation of BKα channel prevented I/R-induced upregulation of inflammatory cytokines, such as TNFα, IL-1β, TGFβ and phospho-smad 2/3 in the heart of I/R mice. Single channel recordings found that TGFβ inhibited BKα activity. In H9C2 cells TGFβ increased fibronectin and collagen I production, while BKα openers (NS1619) limited the TGFβ -induced increase in both proteins. TGFβ also significantly increased H_2O_2 and superoxide production in H9C2 cells. Activation of BKα channel abolished this effect along with reversing TGFβ-induced down-regulation of SOD production.

Conclusions: Our findings suggest that BK channel activation has a protective role in I/R-induced chronic heart failure by reducing cardiac fibrosis and improving cardiac function, which provide the potential therapeutic target of BK in treating fibrosis and improving heart function following cardiac I/R.

Funding: Veterans Affairs Support

TH-PO197

Impaired Long-Term and Short-Term Control of Sympathetic Nerve Activity in Nonhypertensive Dahl S Salt-Sensitive Rats

Eva Hutter,[1] Tilmann Ditting,[1,2] Clara Meißner,[1] Nada Cordasic,[1] Peter Linz,[1] Karl F. Hilgers,[1] Mario Schiffer,[1] Kerstin U. Amann,[1] Roland Veelken,[1,2] Kristina Rodionova.[1] *[1]Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany; [2]Paracelsus Medizinische Privatuniversitat - Nurnberg, Nurnberg, Germany.*

Background: Our recent research on neurons with afferent dendrites from the kidneys as well as direct renal nerve recordings suggested that the afferent renal innervation tonically inhibits sympathetic activity under normal conditions. Now, we wanted to test the hypothesis that the afferent renal innervation is already impaired in prehypertensive salt-sensitive Dahl S rats receiving a normal salt diet.

Methods: Prehypertensive Dahl salt sensitive rats (DSS) and Sprague-Dawley (SD) controls were kept on normal salt diet. Dorsal root ganglion neurons (Th11-L2) with dendrites from the kidney of both groups of rats were investigated in voltage clamp mode to assess inward currents and current clamp mode to assess action potential (AP) generation. Neurons were classified as tonic (high AP generation upon stimulation) or phasic (AP < 5 upon stimulation). Measurement of arterial blood pressure, heart rate, and direct recordings of renal sympathetic nerve activity (RSNA) were performed in both groups of rats (n=6). To assess neural control of volume homeostasis, rats underwent volume expansion (VE) (0.9% NaCl; 5% of body weight in 30 min) to decrease RSNA.

Results: In vitro, the portion of tonic highly active neurons was significantly smaller in DSS than in SD rats suggesting decreased afferent renal nerve activity (24 % tonic neurons in DSS vs. 51% in SD, *p<0.05, z-test). In vivo, the initial decrease of RSNA during volume expansion was similar for both groups, but RSNA in DSS rats returned to control levels within 15 minutes after cessation of VE but remained significantly decreased in SD rats.

Conclusions: In salt sensitive Dahl S rats on a normal salt rat chow, renal sympathetic nerve activity was likely insufficiently controlled by long term (tonic sympathoinhibitory renal afferent nerves) as well as short term (cardiopulmonary reflex) regulatory mechanisms. These findings suggest a severely impaired function of the autonomous nervous system even in the prehypertensive phase of salt sensitve Dahl S rats.

TH-PO198

Differential C-X-C Motif Chemokine Receptor 4 (CXCR4) Expression in Aldosterone-Producing vs. Nonfunctional Adenomas

Chunyi Wu.[1,2] Molecular and Integrative Physiology and Internal Medicine, University of Michigan. *[1]University of Michigan, Ann Arbor, MI; [2]Taichung Veterans General Hospital, Taichung, Taiwan.*

Background: Primary aldosteronism (PA) is the leading cause of secondary hypertension and may have detrimental renal consequences. Unilateral PA can be cured with adrenalectomy. However, subtyping into unilateral or bilateral disease can be costly, invasive, and clinically challenging. Aldosterone-producing adenoma (APA)-targeted positron emission tomography/computed tomography (PET/CT) has emerged as a potential non-invasive imaging technique for subtype determination that could circumvent the need for gold standard adrenal venous sampling (AVS). Radiolabeled probes have been developed that bind the enzyme aldosterone synthase (CYP11B2) and chemokine receptor 4 (CXCR4). However, the expression of CXCR4 in APA and non-functional adenomas (NFA) has not been extensively studied. **Objective:** To evaluate the differential expression of CXCR4 in APA versus NFA, thereby assessing its viability as a reliable biomarker in PET/CT imaging for PA subtyping.

Methods: A cohort of twenty PA patients who underwent unilateral adrenalectomy that were found to have an APA and an adjacent NFA from the university of Michigan were included in this study. Formalin-fixed, paraffin-embedded (FFPE) sections of resected adrenal tissue were used for the analysis. Aldosterone synthase (CYP11B2) immunohistochemistry (IHC) was performed to identify APA (CYP11B2 positive) and NFA (CYP11B2 negative). APA and NFA RNA was isolated followed by quantitative RT-PCR (qPCR) for *ACTB* (β-actin), *CYP11B2*, and *CXCR4*.

Results: In APA the average fold increase of *CYP11B2* mRNA relative to the adjacent NFA was 2726(± 323) (P<0.001). For *CXCR4* the average fold increase of APA relative to the adjacent NFA was 2.23(±0.83) (P=0.03). Although APA *CXCR4* mRNA expression did reach statistical significance compared to NFA, 3 of 20 patients had higher *CXCR4* transcript levels in the adjacent NFA.

Conclusions: Our finding confirm *CYP11B2* expression as a robust APA marker with significantly lower levels observed in NFA. The transcript analysis of *CXCR4*, however, raises concerns of its utility as a marker for APA over NFA. Additional studies are needed to examine CXCR4 protein levels in APA versus NFA to ensure specificity of CXCR4 as an APA marker in PET/CT imaging modalities.

TH-PO199

Aberrant Trafficking of Intestinal Immune Cells in Salt-Sensitive Hypertension

Ariana Rauch, Hendrik Bartolomaeus, Alex Yarritu, Wibke Anders, Harithaa Anandakumar, Nicola Wilck. Wilck lab. *Charite Universitatsmedizin Berlin, Berlin, Germany.*

Background: Essential hypertension is the leading risk factor for cardiovascular disease. In addition to elevated blood pressure, hypertension is characterized by an inflammatory immune response that precedes the clinical detection of organ-damage. Yet, the activation and origin of target-organ-infiltrating immune cells are not fully understood. This study takes a systems view on inflammation in hypertension and aims to investigate the extent to which the gut-associated immune cells contribute to the immune response in salt-sensitive hypertension.

Methods: Immune cell trafficking from the intestine to hypertensive target-organs was analyzed using *in vivo* labelling of intestinal immune cells via targeted UV photoconversion in *Kaede*-transgenic mice. Salt-sensitive hypertension was induced in male mice by oral L-NAME pretreatment and two 3-week periods of high-salt feeding (HSD), separated by a 2-week normal-salt (NSD) wash-out phase. Hypertensive organ damage and trafficking of photolabelled cells was analyzed 5 days after photoconversion. Subsets of mice received additionally FTY720 or an oral antibiotic cocktail or *Lactobacillus murinus* during the second HSD-period.

Results: HSD-fed mice displayed target organ damage assessed by mRNA-expression (qPCR and mRNAseq) of markers of kidney damage, inflammation and fibrosis. Intestinal immune cell trafficking was observed both in homeostasis (NSD) and disease (HSD). Infiltration of photolabelled intestinal immune cells was detected in various organs such as the spleen and kidney (flow cytometry and scRNAseq). B cells and T cells were among the major migrating populations. FTY720 strongly reduced photolabelled cells in target organs, indicating S1P-dependent immune cell trafficking. Salt-sensitive hypertension was characterized by a dysregulation of the intestinal-renal immune cell axis. Modulation of the microbiome via antibiotics or *Lactobacillus murinus* lead to a modulated immune cell trafficking.

Conclusions: Immune cells originating from the intestine migrate and populate various organs via the S1P-axis, both in homeostasis and in an aberrant manner in salt-sensitive hypertension. Our findings provide insight into mechanisms underlying hypertension-induced organ damage and could argue for interventions targeting intestinal immune cells.

Funding: Government Support - Non-U.S.

TH-PO200

Macrophage-Epithelial Sodium Channel (ENaC) Interactions Regulate Kidney Sodium Handling and Salt-Sensitive Hypertension

Alicja Czopek, Josselin Nespoux, Matthew A. Bailey, Neeraj Dhaun. Edinburgh Kidney. *The University of Edinburgh College of Medicine and Veterinary Medicine, Edinburgh, United Kingdom*.

Background: A third of people are salt-sensitive, showing an exaggerated blood pressure (BP) response to high salt intake. Salt-sensitivity is an independent cardiovascular risk factor, but its underlying causes are unresolved. Immune cells, including monocytes and macrophages (MΦ), are emerging as important regulators of both salt homeostasis and blood pressure physiology. Here, we investigated the impact of macrophage depletion on salt-sensitive hypertension in the mouse.

Methods: Male transgenic mice, with myeloid cell-specific expression of the human diphtheria toxin receptor (CD11b-DTR mice) were fed a high salt diet (8% NaCl) (HSD) for 4 weeks to develop hypertension. During the final (4th week) mice received diphtheria toxin (DT) to deplete tissue MΦ. In another group, liposomal clodronate (LC) was used as a second depletion strategy. We measured renal function, BP (by radiotelemetry) and collected kidneys for sodium transporters gene expression analysis. Renal MΦ number was assessed by immunohistochemistry.

Results: HSD increased systolic and diastolic BP by ~8mmHg and ~6mmHg from baseline. DT significantly reduced the MΦ count in renal cortex and induced complete depletion in the renal medulla. Although LC reduced the number of cortical MΦ, there was an increase in medullary MΦ count. There was also a differential effect on BP and renal Na^+ handling. DT amplified salt-sensitive hypertension by a further ~15mmHg ($p<0.0001$ *vs.* no depletion); LC had no additional effect. DT mice showed reduced urinary Na^+ excretion and hypernatremia; LC treated animals had no abnormalities in Na^+ status. High salt intake supressed aldosterone in all groups but DT depletion caused an inappropriate activation of *ENaC* at the mRNA and functional levels. ENaC blockade with benzamil significantly increased Na^+ excretion and reduced salt-sensitive hypertension in DT-treated animals.

Conclusions: We show that tissue MΦ distribution influences ENaC regulation and renal Na^+ handling independent of aldosterone, which can contribute to the development of salt-sensitive hypertension.

TH-PO201

Role of Anaphylatoxin Receptors C5aR1 and C5aR2 in Hypertension and Hypertensive End-Organ Damage

Leonie Dreher,[1,2] Sarah Walachowski,[3] Georg R. Herrnstadt,[1,2] Nicolas Ehnert,[1] Catherine Meyer-Schwesinger,[4,2] Joerg Koehl,[5] Tobias B. Huber,[1,2] Markus Bosmann,[3] Ulrich O. Wenzel.[1,2] AG Wenzel. *[1]III. Department of Medicine, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [2]Hamburg Center for Kidney Health (HCKH), Hamburg, Germany; [3]Pulmonary Center, Department of Medicine, Boston University School of Medicine, Boston, MA; [4]Department of Cellular and Integrative Physiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [5]Institute for Systemic Inflammation Research, University Hospital Schleswig-Holstein, Lübeck, Germany*.

Background: Elevated blood pressure induces activation of the complement system. The anaphylatoxin C5a, a major inflammatory effector of the complement system, binds to the C5a receptor 1 and 2 (C5aR1, C5aR2). We have recently shown that C5aR1 knockout (KO) mice have reduced hypertensive renal injury. However, the role of the second C5a receptor and the extent of functional overlap between C5aR1 and C5aR2 remains enigmatic. We set out to examine the role of the C5aR2 and potential additional beneficial or antagonistic effects of combined deficiency of C5aR1 and C5aR2.

Methods: With single cell RNA sequencing we addressed the expression of C5aR2 in patients with hypertensive nephropathy. Murine expression of the C5aR2 was examined using a tandem dye Tomato-C5aR2 reporter mouse. For further investigation we used an aggravated model of hypertension with unilateral nephrectomy, infusion of angiotensin (Ang) II and high salt diet in both C5aR2 KO and mice with double deficiency of C5aR1 and C5aR2 (C57BL/6J-Del(7C5ar2-C5ar1)1Bosm; generated by CRISPR/Cas9 guided editing).

Results: Main expression of C5aR2 was found in myeloid cells in human kidneys with increased expression in hypertensive patients. Flow cytometric analysis of leucocytes isolated from kidneys of the tandem dye Tomato-C5aR2 reporter mice also showed main expression in myeloid cells. The expression pattern was comparable to that of C5aR1. No differences in blood pressure and renal injury (albuminuria, GFR, glomerular and tubulointerstitial injury) between hypertensive wildtype (WT) and C5aR2 KO (n=14) or C5aR1xC5aR2 KO (n=24) mice were found. To examine whether the effects are specific for Ang II induced hypertension, we also induced deoxycorticosterone acetate (DOCA) salt hypertension for 6 weeks in WT and C5aR1/2-deficient mice (n=12). Consistent with the findings in Ang II induced hypertension no significant differences regarding blood pressure or renal injury were found also in DOCA salt hypertension.

Conclusions: Both, C5aR1 and C5aR2 are mainly expressed on myeloid cells in humans and mice. While C5aR1 deficiency is potentially beneficial in hypertensive renal injury, deficiency of C5aR2 alone or in combination with C5aR1 has no effect on blood pressure and hypertensive end organ damage.

Funding: Government Support - Non-U.S.

TH-PO202

SGLT2 Knockout Suppressed High Salt-Induced Organ Damage in Dahl Salt-Sensitive Rats

Hiroki Ito, Takuo Hirose, Shigemitsu Sato, Chika Takahashi, Risa Ishikawa, Akari Endo, Ikuko Yabana, Takefumi Mori. *Tohoku Ika Yakka Daigaku, Sendai, Japan*.

Background: SGLT2 (sodium-glucose cotransporter 2) inhibitors have renoprotective properties through multiple mechanisms. DahlS (Dahl salt-sensitive) rats develop renal congestion and damage as a consequence of salt-sensitive hypertension. We aimed to investigate the effects of SGLT2 deficiency on the development of hypertension and renal injury in the DahlS rats fed a high-salt diet.

Methods: The Sglt2 gene was knocked out in DahlS rats (DahlS/mcwi) using the CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats-CRISPR-associated 9) system. DahlS-Sglt2$^{+/+}$ and DahlS-Sglt2$^{-/-}$ male rats (8 weeks old) were fed normal salt (0.6% NaCl) or high salt (4% NaCl) diets for 2 weeks. The kidneys and hearts were harvested and analyzed by molecular and histological techniques.

Results: Elevated blood pressure by the tail-cuff method was observed in both DahlS-Sglt2$^{+/+}$ and DahlS-Sglt2$^{-/-}$ rats following high-salt intake, with no significant difference between the two groups. Kidney and heart weights were significantly increased by the high-salt diet in DahlS-Sglt2$^{+/+}$ rats, while no changes were observed in DahlS-Sglt2$^{-/-}$ rats. The expression of tubulointerstitial damage markers; Havcr1 (Kim1) and Spp1 (Opn) and interstitial fibrosis markers; Fn1, Vim, and Acta2 (α-Sma) was elevated in DahlS-Sglt2$^{+/+}$ rats fed a high-salt diet when compared with DahlS-Sglt2$^{+/+}$ rats fed a normal-salt diet. In contrast, no significant change was observed in the expression of these markers between the normal-salt and high-salt diets in DahlS-Sglt2$^{-/-}$ rats. The levels of these markers in Dahl-Sglt2$^{-/-}$ rats were significantly lower than those of Dahl-Sglt2$^{+/+}$ fed a high salt diet. The histological analysis also confirmed the results of the molecular analysis in both DahlS-Sglt2$^{+/+}$ and DahlS-Sglt2$^{-/-}$ rats.

Conclusions: Our findings implicate that SGLT2 may play a protective role in the development of renal injury and fibrosis, independent of the increase in aortic blood pressure caused by salt-sensitive hypertension.

TH-PO203

Establishing a Mouse Model of Heart Failure with Preserved Ejection Fraction Secondary to CKD

Lauren Elizabeth Lee,[1,2] Nicholas A. Forelli,[1,4] Dhanunjay Mukhi,[1,3] Zoltan P. Arany.[1,2] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of Pennsylvania Cardiovascular Institute, Philadelphia, PA; [3]Penn Division of Renal Electrolyte and Hypertension, Philadelphia, PA; [4]University of Pennsylvania Department of Medicine, Philadelphia, PA*.

Background: Chronic kidney disease (CKD) affects 37 million US adults and significantly elevates cardiovascular disease and heart failure (HF) risk, causing ≥50% of CKD mortalities. Proximal tubule cells in CKD and cardiomyocytes in HF exhibit parallel metabolic switches: increased glycolysis reliance and decreased fatty acid oxidation and oxidative phosphorylation reliance. Notably, non-diabetic CKD patients show a correlation of decreased estimated glomerular filtration rate (eGFR) with increased myocardium glucose uptake. It is unknown if CKD contributes to HF by causing cardiac metabolism to be glucose reliant. This has yet to be confirmed *in vivo* due to no reliable HF-secondary-to-CKD mouse model.

Methods: We placed wild-type 8 wk/old male mice on a 0.2% adenine diet, assessing kidney function (GFR, urine/serum markers, histology) and heart function (echocardiography, serum markers, histology) at 4 and 8 weeks. At 8 weeks, we performed an *in vivo* steady state ^{13}C-labled metabolite isotope infusion with our novel ^{13}C labeled metabolite cocktail (3-hydroxybutyrate, glutamine, valine, lactate, glucose) and ^{13}C labeled palmitate to quantify nutrient contribution to kidney and heart TCA cycle intermediates.

Results: At 4 weeks, mice develop CKD (hyperfiltration, elevated serum creatinine and urine albumin/creatinine ratio, moderate renal fibrosis) but with unchanged heart function or histology. At 8 weeks, mice progress to severe CKD (significantly decreased GFR, significantly increased serum creatinine and urine albumin/creatinine ratio, severe renal fibrosis) and have heart failure with preserved ejection fraction (increased serum markers, diastolic and strain parameters, cardiomyocyte hypertrophy). Preliminary data from our ^{13}C-labled metabolite isotope infusions indicate nutrient contribution patterns to TCA cycle intermediates in CKD are similar in kidney and heart tissue.

Conclusions: We conclusively established a mouse model of HF secondary to CKD, in which mice first develop CKD at 4 weeks, then develop heart failure with preserved ejection fraction (HFpEF) by 8 weeks, phenocopying the human literature where CKD is an independent risk factor to HFpEF. Tracing studies indicate the heart and kidney have similar nutrient use in CKD, offering insights into targeted metabolic interventions for improved CKD and HF patient outcomes.

Funding: Other U.S. Government Support

TH-PO204

Oxidative Stress-Induced Suppression of Metabolism Pathways in Dahl Salt-Sensitive Rats

Satoshi Shimada, Chun Yang, Ranjan K. Dash, Allen W. Cowley.
Medical College of Wisconsin, Milwaukee, WI.

Background: We have reported that a high-salt (HS) diet enhances glycolysis as determined in normal Sprague Dawley (SD) rats by measuring the flux of kidney metabolites in rats chronically instrumented with a renal blood flow probe and renal arteriovenous catheters, which provided sequential samples for global metabolic analysis combined with tissue transcriptomic analyses (PMID: 37575482). In the present study, the kidney cortical (Cx) and outer medullary (OM) transcriptomic responses to a HS diet are reported in Dahl salt-sensitive (SS) rats compared to SS$^{Nox4-/-}$ rats with a global knockout of NADPH oxidase 4 (NOX4) to reduce oxidative stress, and compared to salt-resistant SD rats.

Methods: Male SS, SS$^{Nox4-/-}$ and SD rats were fed either a 0.4% diet, a 4% diet for 7 days, or for 21 days (HS21). Cx and OM were removed for mRNAseq analysis (Novogene, Inc). Comparisons with previously published SD data was performed by publicly available software (RNAseqChef and DAVID).

Results: 1724 mRNAs in Cx and 2775 in OM had FDR < 0.05 and fold change > 2, comparing SS and SD at HS21. Among these mRNAs, we selected those with patterns of response to salt that are unique in SS relative to SD and SS$^{Nox4-/-}$ by divisive clustering analysis. There were 446 mRNAs in Cx and 1550 in OM that followed this pattern. Only the "Protein digestion and absorption" pathway was significant in the pathway analysis of these mRNAs in Cx. This pathway includes Slc3a1 (amino acid transporter), and Atp1A4 (Na/K ATPase) which was consistently greater in SS. Collagen mRNAs were increased only in SS with HS. The OM, in contrast, revealed 11 pathways including "carbon metabolism", "biosynthesis of amino acid" and others. Aco1 (aconitase), Pc (pyruvate carboxylase), Pklr (pyruvate kinase) and Ass1 (argininosuccinate synthase) in these pathways were consistently low in SS.

Conclusions: Transcriptomic response to HS clearly differed when comparing kidneys of SS to SS$^{Nox4-/-}$ and SD rats. Carbon metabolism and amino acid synthesis related genes were suppressed in OM in SS which could functionally lead to lactate accumulation and eventually renal damage as energy demand increased with HS. These changes appear to be driven by increased oxidative stress given the absence of such changes in the SS$^{Nox4-/-}$ and SD rats. Metabolite responses and their relationship with transcriptomic changes are currently being analyzed.

Funding: Other NIH Support - NHLBI, Private Foundation Support

TH-PO205

Circadian Clock Provides Beneficial Effects against Atherogenesis by Regulating Heme Oxygenase-1 Expression and Heme Synthesis

Hideyuki Negoro.[1,2] [1]*Harvard Medical School, Boston, MA;* [2]*Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu Seirigaku, Bunkyo-ku, Japan.*

Background: The circadian clock is a molecular mechanism that confers 24 hours variations in gene expression and function to regulate many physiological functions. Chronic circadian clock disruption is associated with vascular stiffness and dysfunction in endothelial signaling and responses. Heme is a ligand of REV-ERBα and REV-ERBβ which modulate circadian rhythms by binding to the ROR region of CLOCK or BMAL1 to suppress the expression of these genes. 5-Aminolevulinic acid (ALA) is the common precursor of porphyrin and heme. The iron ion is inserted into protoporphyrin IX to form heme in the mitochondria and incorporated into hemoproteins. Heme oxygenase-1 (HO-1) is an intracellular enzyme which catalyzes the oxidation of heme to generate ferrous iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin. These products have anti-inflammatory, anti-apoptotic and anti-thrombotic properties. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence HO-1 which play an important part in the protection of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type, CLOCK-KO, and Bmal1-KO littermate mice were generated from heterozygote breeding to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of HO-1 expression in the knocked down cells. To synchronize circadian rhythms, serum stimulations were performed. Cells were also pre-incubated with or without 1 mM ALA and 0.5 mM sodium ferrous citrate (SFC).

Results: In aorta from Bmal1 KO mice, there was a reduction in HO-1 expression with a dysfunctional circadian rhythm. Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to the regulation of key risk factors for cardiovascular disease. These include HO-1 which is significantly reduced in Bmal1 KO mice. ALA/SFC co-incubation affected the oscillation and phase of core clock genes and led to increase of HO-1. HO-1 levels followed a circadian pattern, and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against atherogenesis by regulating HO-1 expression and heme synthesis. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO206

Matrix Metalloprotease Activity in Vascular Lesions of Malignant Hypertensive Rats

Andrea Hartner, Nada Cordasic, Mario Schiffer, Roland Veelken, Kerstin U. Amann, Christoph Daniel, Karl F. Hilgers. *Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany.*

Background: In malignant hypertension (MH), far more severe kidney injury occurs than in the "benign" form (NMH) of the disease. In a previously reported RNA-Seq analysis of renal cortical tissue from a rat model of MH, we observed an altered expression of several matrix metalloproteases (MMP). We now investigated gelatinase activity localized to the characteristic vascular lesions of MH.

Methods: Renovascular hypertension in rats was induced by placing a 0.2 mm clip on the left renal artery (2K1C), controls were sham operated. To distinguish MH from NMH, we considered weight loss and typical vascular lesions (onion-skin and fibrinoid necroses). The expression of MMPs was measured by RT-PCR; immunohistochemistry was performed for MMP-2 and 9. In-situ zymography was performed to localize gelatinase activity.

Results: Mean blood pressure measured intra-arterially was elevated to a similar degree in MH (220±7 mmHg) and NMH (192±6 mmHg), compared to controls (119±2 mmHg, $p<0.05$). MMP-2, -7, -8, -10, -12, -16 and -19 expression were all elevated in NMH and significantly higher increased in MH. The only exception was MMP-9 mRNA which barely changed in NMH but decreased by 0.2-fold in MH ($p<0.05$). In situ zymography revealed gelatinase activity predominantly in preglomerular vascular lesions of MH (52.8 ± 7.2 versus 20.5 ± 6.1 per medium power field in NMH, $p<0.05$) in right kidneys exposed to high blood pressure. The number of these gelatinase activity lesions correlated with the glomerulosclerosis score ($r=0.75$, $p<0.0001$). There was no gelatinase activity in sham operated animals, or in left (post-stenotic) kidneys of MH or NMH. MMP-2 staining was detected in, or closely surrounding, vascular lesions (3.46 ± 0.9 MMP-2 positive lesions per 10 high power fields in MH versus 0.22 ± 0.09 in NMH and 0 in sham, $p<0.05$). MMP-9 staining was observed in proximal tubules, individual interstitial cells, and intact or hypertrophic preglomerular vessels but absent from malignant vascular lesions.

Conclusions: In malignant hypertension of 2K1C rats, most MMPs are upregulated, broadly consistent with enhanced tissue injury. However, the gelatinases MMP-2 and MMP-9 exhibited a strikingly divergent regulation, with MMP-2 clearly localized to malignant vascular lesions with gelatinase activity.

Funding: Government Support - Non-U.S.

TH-PO207

Endothelial Cell-Specific Inducible G2APOL1 Risk Variant Induces Hypertension and Hypertensive Kidney Damage

Fang Li,[1,2] Junnan Wu,[1,2] Konstantin A. Kloetzer,[1,2] Katalin Susztak.[1,2]
[1]*Department of Medicine, Renal Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA;* [2]*University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: GWAS showed a strong association between the apolipoprotein1 (*APOL1*) gene and hypertension in AA adults. Nearly 45% of AAs carry a coding variant of the *APOL1* gene (G1 *APOL1* or G2 *APOL1*). The disease phenotypes associated with *APOL1* risk variants (RV) depend on the cell type-specific expression and toxicity of APOL1. Our recent studies (single-cell, single nuclei, and in-situ hybridization) have shown APOL1 is highly expressed in the endothelial cells of human kidneys. Individuals who carry the G1 or G2 *APOL1* RV have a high risk of developing hypertensive kidney disease. However, the direct role of APOL1 in the development of hypertension and hypertensive kidney disease remains unclear.

Methods: Endothelial-specific inducible expression of APOL1 (EC/G0-APOL1, EC/G2-APOL1) mice were generated by using Tet-off system. Upon removal of doxycycline diet, APOL1 expression was obtained in various vascular beds. For the high salt diet model, UNX surgery was performed on WT control, EC/G0-APOL1, and EC/G2-APOL1 mice, followed by a high-salt diet (4%) for 12 weeks post-surgery. We processed snRNA-seq, bulk RNA-seq, and spatial transcriptomics, and combined these with genetic and pharmacologic approaches to investigate the role of G2*APOL1* RV in the development of hypertension.

Results: Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were statically increased in Cdh5tTA/TRE-G2APOL1 mice compared to control WT/G0 mice after 14 weeks of continuous *G2APOL1* RV expression

in endothelial cells. A high-salt diet following UNX surgery further augments elevated blood pressure and induces renal dysfunction in EC/G2APOL1 mice. Comprehensive in vivo and in vitro investigations revealed that RV *APOL1* expressed in endothelial cells triggers the activation of the STING pathway, fostering the production of endothelin-1 (ET-1). STING-specific knockout in endothelial cells of Cdh5tTA/TRE-G2APOL1 mice led to reduced ET-1 production, as well as reductions in SBP, DBP, and MAP post-UNX surgery and high-salt diet.

Conclusions: Endothelial-specific expression of G2*APOL1* RV activates the STING pathway, promoting ET-1 production and contributing to hypertension development, subsequently results in renal damage.

Funding: NIDDK Support

TH-PO208

Kidney Hypoplasia Increases Kidney Injury following Reversal of Unilateral Ureteral Obstruction

Samaneh Goorani, John D. Imig. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Studies have found that short-term kidney injury by unilateral ureteral obstruction (UUO) results in long-term consequences of hypertension and CKD. Not known is whether renal hypoplasticity and low nephron number increases the long-term consequences.

Methods: Male and female renal hypoplastic ROP *Os*/+ and wild type ROP +/+ mice underwent UUO, or sham surgery followed ureter clip removal on day 7 (RUUO). BP was measured by telemetry to determine SBP, MAP, and HR weekly. Renal artery resistive index (RI) was evaluated by ultrasound. Urine was collected at the end to assess CysC and NGAL. A terminal kidney tissue collection was conducted for gene expression, and histology.

Results: At baseline, ROP +/+ and ROP *Os*/+ MAP, SBP, and HR were not different in either sex of mice. SBP and MAP increased, and HR decreased in RUUO ROP *Os*/+ and RUUO ROP +/+ mice compared to sham mice groups. Interestingly, RUUO ROP *Os*/+ mice demonstrated 35-40 mmHg higher SBP and 100-150 beats lower HR than RUUO ROP +/+ mice 35 days following clip removal. RI was higher in RUUO ROP *Os*/+ and RUUO ROP +/+ mice compared to sham mice. Moreover, RUUO ROP *Os*/+ had a higher RI than RUUO ROP +/+ mice indicating a greater reduction in renal blood flow in RUUO ROP *Os*/+ mice. CysC and NGAL were 2-fold higher in RUUO ROP *Os*/+ than RUUO ROP +/+ mice. Fibrotic PCR pathway array demonstrated higher fibrotic markers in RUUO ROP *Os*/+ than RUUO ROP+/+ mice. RT-PCR confirmed markedly higher expressions of Fn1, collagen1, vimentin in RUUO ROP *Os*/+ than RUUO ROP +/+ mice. Renal tubular cast formation in RUUO ROP *Os*/+ and RUUO ROP +/+ mice was higher compared to sham mice. The increase in renal tubular cast formation was higher in RUUO ROP *Os*/+ than RUUO ROP+/+. Similarly, α-SMA deposition was higher (3 vs 2-fold) in RUUO ROP *Os*/+ compared to RUUO ROP +/+ mice. $Mac2^{+}$ inflammatory cells were increased in RUUO ROP *Os*/+ to a greater extent than RUUO ROP +/+ mice. There were no differences between male and female mice for all groups and parameters measured.

Conclusions: These data demonstrate renal hypoplasia and low nephron number ROP *Os*/+ mice had increased blood pressure, renal inflammation, and kidney injury compared to ROP +/+ mice 35 days following ureter clip removal.

Funding: NIDDK Support

TH-PO209

SNX19 and p27 kip1 Regulate D1R Endocytosis in Renal Proximal Tubule Cells

Bibhas Amatya,[1] Laureano D. Asico,[1] Jun Feranil,[1] Raisha L. Campisi Cadme,[1] Jacob Q. Polzin,[1] Ines Armando,[1] Robin A. Felder,[2] Pedro A. Jose,[1] Hewang Lee.[1] *[1]The George Washington University School of Medicine and Health Sciences, Washington, DC; [2]University of Virginia, Charlottesville, VA.*

Background: SNX19, a member of the SNX-PXA-RGS-PXC subfamily of sorting nexin proteins, is localized in lipid raft microdomains and regulates dopamine D1 receptor (D_1R) endocytosis, renal sodium transport, and subsequently blood pressure. The interaction between SNX19 and $p27^{Kip1}$, a scaffold protein in lipid rafts, in the regulation of D_1R endocytosis is unknown.

Methods: Colocalization was observed by confocal immunofluorescence microscopy; protein-protein interaction was determined by co-immunoprecipitation. Blood pressure was measured in conscious C57BL/6 mice treated with a 7-day renal subcapsular infusion of Snx19 siRNA; mock siRNA served as the control.

Results: In human renal proximal tubule cells (RPTCs), SNX19 colocalized with caveolin-1 and flotillin-1. SNX19 and caveolin-1 or flotillin-1 also co-immunoprecipitated in human RPTCs. Fenoldopam (FEN, 25 nM, 30 mins, n=3), a D_1R/D_5R agonist, increased their co-immunoprecipitation. Interestingly, $p27^{Kip1}$, a canonical cyclin-dependent kinase inhibitor, colocalized with calveolin-1 and flotillin-1 in mouse and human RPTCs, confirming electron and confocal microscopic studies that $p27^{Kip1}$ is a lipid raft protein. Confocal immunofluorescence microscopy showed that in mouse RPTCs, FEN (25nM, 30 min) increased the colocalization of $p27^{Kip1}$ with α-tubulin which is essential in SNX19-mediated D_1R endocytosis. The D_1R/D_5R antagonist, Sch 39916 (SCH, 1 μM, 30min), prevented the FEN-mediated increase in the colocalization of $p27^{Kip1}$ with α-tubulin. Moreover, nocodazole (10 μM, 1hr), a microtubule depolymerization inhibitor, interfered with the FEN-mediated increase in the colocalization of SNX19 with D_1R, confirming the importance of the microtubule in the SNX19-mediated D_1R endocytosis. The D_1R is downstream of SNX19 because silencing *DRD1* in human RPTCs decreased D_1R but not SNX19 expression. SNX19 and D1R play a role in blood pressure regulation. In C57BL/6 mice on a normal salt diet (0.9% NaCl), renal subcapsular infusion of Snx19 siRNA (3 mg/day; 7 days) increased systolic BP (mock siRNA: 99.3 ± 1.52 mmHg, n=3; Snx19 siRNA: 114.1 ± 5.44 mmHg, n=3) and decreased renal D_1R expression.

Conclusions: SNX19 in the RPT interacts with $p27^{Kip1}$ in the lipid rafts to regulate SNX19-mediated D_1R endocytosis and subsequently, blood pressure.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO210

Zyxin Attenuates Hypertension-Induced Kidney Fibrosis by Modulating the CDK8-YAP Axis

Wei Huang, Chun Zhang. *Union Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, China.*

Background: Hypertensive nephropathy (HN) is characterized by progressive renal tubulointerstitial fibrosis. However, the mechanisms of tubulointerstitial fibrosis in HN remains obscure. Zyxin, a focal adhesion protein, has been implicated in hypertensive myocardial fibrosis, but its role in HN remains unclear.

Methods: A hypertensive nephropathy model was established in C57BL/6 mice using subcutaneous DOCA particles and AngII pumps. Human renal tubular epithelial cells (HK-2) were stimulated with AngII in vitro. Zyxin was knocked down or overexpressed in HK-2 cells after exposure to AngII. The expression levels of zyxin, CDK8, YAP, and TRPC3 were assessed using Western blot, PCR, immunohistochemistry, and immunofluorescence.

Results: In hypertensive kidney tissues and AngII-stimulated HK-2 cells, zyxin expression was significantly downregulated, while CDK8, YAP, and TRPC3 expressions were upregulated. Overexpression of zyxin in kidney significantly ameliorated hypertensive renal fibrosis. In HK-2 cells, zyxin overexpression inhibited AngII-induced fibrosis markers, whereas zyxin knockdown promoted them. Overexpression of zyxin attenuated the increase in CDK8 and YAP, while zyxin knockdown exacerbated it. Inhibition of TRPC3 blocked the changes in zyxin, CDK8, and YAP expressions.

Conclusions: In hypertensive conditions, activated TRPC3 in the kidney inhibits zyxin expression, thereby activating the CDK8-YAP axis and promoting renal fibrosis. These findings suggest that zyxin might be a promising therapeutic target for hypertensive nephropathy.

TH-PO211

Effect of Dual Blockade of Neprilysin and Renin-Angiotensin System in Angiotensin II-Dependent Salt-Sensitive Hypertension

Masahiro Eriguchi, Takayuki Uemura, Masatoshi Nishimoto, Kazuhiko Tsuruya. *Nara Kenritsu Ika Daigaku, Kashihara, Japan.*

Background: Neprilysin (NEP) is a Zn-metalloprotease whose substrate is brain natriuretic peptide (BNP), but also angiotensin II (Ang II). Interestingly, angiotensin converting enzyme (ACE) is also a Zn-metalloprotease, and both are strongly expressed in the brush border of the proximal tubule. These two proteases are thought to be involved in the regulation of sodium balance by regulating the Intrarenal Ang II by the degradation (NEP) and production (ACE) of Ang II.

Methods: An Ang II-dependent salt-sensitive model was induced by a 4% high-salt diet (HS) after continuous low-dose Ang II infusion for 1 week (300 ng/Kg/min). Blood pressure (BP) and salt sensitivity were examined using Wild-type, NEP KO, renal-ACE KO, and NEP/renal-ACE double-KO mice.

Results: BP of NEP KO mice significantly increased after Ang II infusion (Ang II BP), but the increase in BP 3 days after starting a high-salt diet (Ang II+HS BP) was blunted. (baseline BP: 102 mmHg, Ang II BP: 119 mmHg, Ang II+HS BP: 119 mmHg) On the other hand, in renal-ACE KO mice, no increase in BP was observed in response to Ang II infusion, but BP increased significantly after starting a high-salt diet. (baseline BP: 104 mmHg, Ang II BP: 101 mmHg, Ang II+HS BP: 119 mmHg) At the final observation (Ang II+HS for 10 days), the BP of NEP/renal-ACE double-KO mice was significantly lower than that of NEP KO, renal-ACE KO, and Wild-type mice. (NEP/renal-ACE double-KO: 122 mmHg, NEP KO: 139 mmHg, renal-ACE KO: 137 mmHg, Wild-type: 148 mmHg) Under 1-week Ang II infusion, 3-h urinary Na excretion in response to intraperitoneal saline challenge was significantly increased in NEP/renal ACE double-KO mice compared with wild-type mice. (NEP/renal-ACE double-KO: 0.193 mEq, NEP KO: 0.171 mEq, renal-ACE KO: 0.164 mEq, Wild-type: 0.113 mEq) Also, intrarenal Ang II concentration was elevated in NEP KO mice, whereas the increase in intrarenal Ang II was suppressed in renal-ACE KO and NEP/renal-ACE double-KO mice. (NEP/renal-ACE double-KO: 199 fmol/g kidney weight, NEP KO: 448 fmol/g, renal-ACE KO: 210 fmol/g, Wild-type: 294 fmol/g)

Conclusions: Dual blockade of NEP and renin-angiotensin system was shown to have a complementary anti-hypertensive effect by BNP-induced natriuresis and suppressing salt sensitivity due to an increase in intrarenal Ang II concentration.

TH-PO212

Trimethylamine N-oxide Can Trigger Cardiovascular Disease by Affecting Endothelial Cell-to-Cell Junctions through ZO-1 Expression Decreasing

Carolina A. Azevedo, Regiane S. Cunha, Guilherme Miniskiskosky, Paulo C. Gregório, Andréa M. Stinghen. *Universidade Federal do Parana, Curitiba, Brazil.*

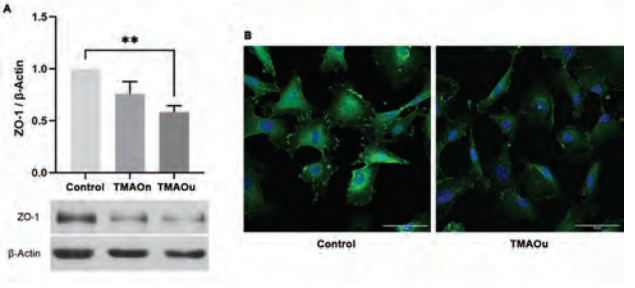
Background: Trimethylamine N-oxide (TMAO) is a uremic toxin that is associated with the development of cardiovascular disease in patients with chronic kidney disease (CKD). At uremic concentrations, TMAO-induced vascular damage is characterized by increased expression of inflammatory markers and vascular calcification. However, there is limited understanding regarding whether this uremic toxin adversely affects endothelial cell-cell junctions and permeability. This study aims to evaluate the effects of TMAO on the expression of Zonula occludens-1 (ZO-1), a protein component of tight junctions that plays a crucial role in regulating endothelial permeability.

Methods: Human endothelial cells (EA.hy926, ATCC CRL-2922) were exposed to TMAO at normal (2.83 mg/L) and uremic concentrations (7.49 mg/L) for 24 hours. ZO-1 gene expression was assessed by RT-qPCR, while its protein levels were evaluated by western blotting and immunofluorescence.

Results: ZO-1 gene expression showed no significant difference between treatments. However, we observed a significant reduction in ZO-1 protein levels in endothelial cells exposed to TMAO at uremic concentrations compared to control cells (untreated) (Figure 1A). Immunofluorescence analysis also showed a reduction in ZO-1 immunostaining in subconfluent endothelial cells after exposure to TMAO (Figure 1B). Figure's subtitle: **Figure 1 - ZO-1 protein levels in endothelial cells exposed to TMAO at normal (TMAOn) and uremic (TMAOu) concentrations for 24 hours.** (A) Western blotting, Kruskal-Wallis test: ***P*<0.01. (B) Immunofluorescence for ZO-1 (green) and nuclear staining (DAPI, blue). The scale bar indicates 50 μm, magnification 600x.

Conclusions: Our data demonstrated a reduction in ZO-1 levels in endothelial cells, which may be related to increased endothelial permeability. Alterations in the endothelial barrier might contribute to the onset of cardiovascular diseases, notably atherosclerosis, which is highly prevalent among patients with CKD.

Funding: Government Support - Non-U.S.



TH-PO213

Activation of Aryl Hydrocarbon Receptor by an Indolic Uremic Toxin Increases the Risk of Deep Venous Thrombosis

Blanca Pina Beltran,[1] Sandrine Roffino,[1] Nathalie Mc kay,[1] Stéphane Poitevin,[1] Stephane Burtey.[1,2] *[1]Aix-Marseille Universite, Marseille, France; [2]Hôpital de la Conception, Service de Néphrologie, Marseille, France.*

Background: During chronic kidney disease (CKD), the accumulation of indolic uremic toxins, such as indoxyl sulfate (IS), occurs. Activation of the aryl hydrocarbon receptor (AHR), their receptor, leads to increased tissue factor expression, resulting in a prothrombotic state. Our goal is to explore if the activation of AHR could explain the risk of deep venous thrombosis (DVT) during CKD.

Methods: We induced DVT in mice by partially ligating the inferior vena cava (IVC) (Figure 1A). To investigate the role of AHR and uremic toxins, we administered IS or its control (KCl) to 9-week-old normorenal wild-type or $Ahr^{-/-}$ mice for 4 days prior to the IVC ligation procedure, immediately after, and 8h post-procedure. Mice were sacrificed 24h after ligation. The primary evaluation criterion was the presence of a thrombus. TAT and IS were dosed and gene expression of IS/AHR related genes at the liver level determined.

Results: Injection of IS led to increased thrombus presence (58% in IS-injected mice vs. 24% in control) without a sex-related impact. The absence of AHR significantly reduced thrombotic risk (11% in IS-injected $Ahr^{-/-}$ mice vs. 25% in control) (Figure 1B). IS appeared to increase thrombus size and weight compared to control (Figure 1C). The effect of IS is believed to be local (at the ligature site, where the blood flow is diminished), since mice showed no differences in their hypercoagulable state (similar TAT levels). Preliminary results revealed a fibrin sponge-like structure in regions with abundant red blood cells, while platelet-rich areas exhibited a more compact structure, with a higher concentration of white blood cells (Figure 2). There may also be differences in thrombus composition among the different groups.

Conclusions: Accumulation of IS and activation of AHR are associated with an increased number of thrombotic events in our murine DVT model. This likely explains the heightened risk of venous thromboembolism observed in CKD, as well as during exposure to AHR agonists such as certain pesticides or tobacco smoking.

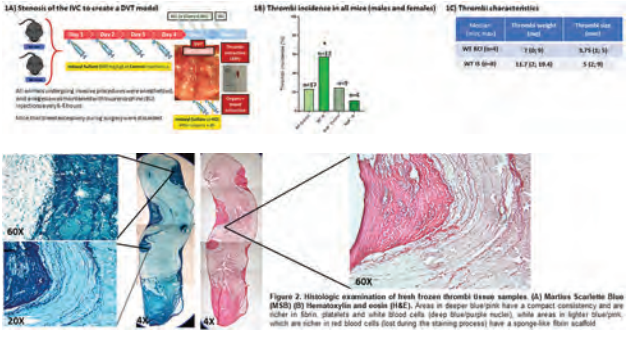


Figure 2. Histologic examination of fresh frozen thrombi tissue samples. (A) Martius Scarlette Blue (MSB) (B) Hematoxylin and eosin (H&E). Areas in deeper blue/pink have a compact consistency and are richer in fibrin, platelets and white blood cells (deep blue/purple nuclei), while areas in lighter blue/pink, which are richer in red blood cells (lost during the staining process) have a sponge-like fibrin scaffold

TH-PO214

Defining Stromal Cell Heterogeneity in the Kidney with Single-Nucleus RNA Sequencing

Arjun Lakshmanan, Susan B. Gurley, Jonathan W. Nelson. *University of Southern California Keck School of Medicine, Los Angeles, CA.*

Background: The kidney stroma are critical perivascular cells that support multiple kidney functions such as regulation of regional blood flow and maintenance of the glomerular filtration barrier. While they are commonly identified by abundant expression of Pdgfrb, recent studies have hinted at more heterogeneity. We examined their heterogeneity by performing single-nucleus RNA sequencing (snRNAseq) on nuclei that were enriched for kidney stromal cells with the goal of defining robust gene markers for unique stromal cell subpopulations.

Methods: Pdgfrb-creERT2 mice were bred to the INTACT mouse to create Pdgfrb-INTACT mice which express GFP attached to a nuclear envelope protein within stromal cells. We isolated nuclei from Pdgfrb-INTACT mice and enriched for GFP expressing nuclei with Fluorescent Activated Nuclei Sorting and then transcriptionally profiled them on the 10X Genomics platform. The resulting transcriptome data was analyzed with Seurat to perform dimensional reduction which delineated unique populations of stromal cells. We then identified differentially expressed genes (DEGs) that defined each subpopulation. The specificity of these DEGs was confirmed by RNAscope. We then analyzed a separate kidney snRNAseq dataset that was not enriched for Pdgfrb nuclei to determine whether these unique stromal cell populations were present.

Results: We transcriptionally profiled 59,349 nuclei from Pdgfrb-INTACT mice which divided into 11 subpopulations, including 4 populations of fibroblasts, 4 populations of contractile cells, 2 populations of mesangial cells, and a proliferating population. Kcnd3, 6530403H02Rik, Itgbl1, Ahrr delineated the fibroblast populations; Hpse2, Tenm2, Lhfpl3, and Mannr delineated the contractile populations; and Grip1 and Limch1 delineated the mesangial subpopulations. We localized these distinct stromal cell subpopulations in mouse kidney using population-specific DEGs with RNAscope. Analysis of a separate kidney snRNAseq dataset revealed subpopulations with similar gene expression profiles to the subpopulations we identified in the Pdgfrb-INTACT mice.

Conclusions: Stromal cells are functionally and genetically diverse and can be characterized through distinct genetic markers. Enriching for stromal cells with the Pdgfrb-INTACT mouse enabled us to identify robust genetic markers of the kidney stroma that have been previously unrecognized.

Funding: NIDDK Support, Private Foundation Support

TH-PO215

Effects of Suppressed Indoxyl Sulfate Production on Kidney Injury-Associated Cardiac Pathogenesis in Sult1a1-Deficient Mice

Aina Sugiura,[1] Kaito Makise,[1] Yuki Narita,[5] Yutaka Kakizoe,[3] Yuichiro Izumi,[3] Takashige Kuwabara,[3] Yuichiro Arima,[2] Kenichi Tsujita,[4] Hirofumi Jono,[5] Hideyuki Saito.[5] *[1]Kumamoto Daigaku Yakugakubu Daigakuin Yakugaku Kyoikubu, Kumamoto, Japan; [2]Kumamoto University Laboratory of Developmental Cardiology, Kumamoto, Japan; [3]Kumamoto University Hospital Department of Nephrology, Kumamoto, Japan; [4]Kumamoto University Hospital Department of Cardiovascular Medicine, Kumamoto, Japan; [5]Kumamoto Daigaku Byoin Yakuzaibu, Kumamoto, Japan.*

Background: Chronic kidney disease (CKD) is a risk factor for cardiovascular disease (CVD) and CVD mortality increases as renal function declines. However, no effective medication has been established to prevent the CVD progression in CKD. Therefore,

we focused on indoxyl sulfate (IS), a typical sulfo-conjugated uremic toxin, which is exclusively generated in the liver via the metabolic processes by hepatic metabolizing enzymes, CYP2E1/2E6 and Sulfotransferase (Sult)1a1. IS accumulates systemically in CKD patients, thereby being reported as one of the risk factors for developing cardio-renal disease, whereas the mechanism is unclear. Then, Sult1a1-deficient (*Sult1a1*$^{-/-}$) mice were used to examine the pathogenetic role of IS in a model of cardio-renal disease exhibiting both kidney and heart damages. In this study, cardiac pathological alterations in the model mice were investigated whether the restricted production of IS could prevent those.

Methods: C57BL/6J (WT) and *Sult1a1*$^{-/-}$ were used to create an ANS model with angiotensin II administration, nephrectomy, and saline drinking. Mice were sacrificed 4 weeks after the treatment, and blood and tissue samples were collected.

Results: In the ANS model, both WT and *Sult1a1*$^{-/-}$ showed increased BUN and expression of IL-6 and col1a1 in renal tissue. On the other hand, WT+ANS increased serum IS concentrations, while *Sult1a1*$^{-/-}$+ANS significantly suppressed IS levels (WT vs *Sult1a1*$^{-/-}$: 5.96±2.96μM vs 2.35±1.09μM). WT+ANS showed cardiac hypertrophy, upregulation of BNP, fibrotic markers TGF-βand col1a1, and oxidative stress marker NOX4 in cardiac tissue, whereas *Sult1a1*$^{-/-}$+ANS suppressed them. Furthermore, cardiac tissue fibrosis formation assessed by Sirius Red staining indicated the reduced fibrotic area in *Sult1a1*$^{-/-}$+ANS compared to WT+ANS (WT vs *Sult1a1*$^{-/-}$: 3±2% vs 1.67±2.08%), suggesting that IS could be involved in the cardiac fibrosis as an intervening toxin.

Conclusions: In *Sult1a1*$^{-/-}$, cardiac hypertrophy and fibrosis development in the ANS model were suppressed with a decreased serum IS accumulation. Therefore, suppression of IS accumulation could prevent and attenuate cardiac pathogenetic events in renal failure.

TH-PO216

Validation of an Organoid Model for CKD-Related Vasculature Changes and Vascular Calcifications Development

Julie Bernardor,[1,2] Justine Simonin,[1] Elise Larché,[1] Claudine Blin,[1] Zakariya Caillot,[1] Maria Bartosova,[3] Claus Peter Schmitt,[3] Matthieu Rouleau.[1] Ostéoimmunologie, Niches et Inflammation. *[1]Laboratoire de Physiomédecine Moléculaire (LP2M), UMR 7370 CNRS, Nice, France; [2]University Hospital of Nice, Nice, France; [3]University Hospital Heidelberg, Heidelberg, Germany.*

Background: Chronic kidney disease (CKD) is associated with high cardiovascular risk, mainly due to vascular calcifications (VC). Mortality rate is high, due to a significant increase of the risk of cardiovascular diseases, related to vascular calcifications. Current understanding indicates that vascular calcifications in CKD involve complex mechanisms, including gene expression changes and endothelial dysfunction. To elucidate complex pathomechanisms leading to VC development, there is a critical need for an in vitro model reflecting CKD induced vascular disease.

Methods: We developed a vascular organoid model using human-induced pluripotent stem cells (hiPSCs). Organoids were formed through differentiation into mesodermal and then vascular cells, followed by embedding in a 3D-collagen matrix. Organoids were maintained in culture for over 30 days. We then induced CKD with pro-calcifying (inorganic phosphate), inflammatory (IL-1β, IL-6, TNF-α), and uremic toxin (indoxyl sulfate) treatments. Analyses included immunofluorescence for vascular markers (CD31, CD140b, αSMA, Collagen IV); RT-qPCR for gene expression; and Alizarin Red staining/ Osteosense assays for calcium deposits.

Results: The vascular organoids developed endothelial cells surrounded by pericytes and smooth muscle cells within a collagen IV-rich matrix. Cytokine treatments resulted in reduced density of endothelial and smooth muscle cells, particularly with IL-6 and TNF-α. Indoxyl sulfate also decreased vascular density. Treatment with inorganic phosphate led to decreased vascular density, increased vessel diameter, and calcium deposits, alongside with modified osteoblastic gene expression (*RUNX2; Sp7, APLP, Spp1*).

Conclusions: We successfully established a vascular organoid model that replicates key features of human vasculature networks and CKD induced changes. It now provides a valuable tool for studying CKD-related pathomechanisms and testing putative therapeutic interventions. Future research using this model should employ single-nucleus RNA sequencing (snRNA-seq), spatial transcriptomics, and CRISPR-Cas9 analyses to further investigate the CKD-related cardiovascular disease.

TH-PO217

Role of Peroxisomes in CKD-Associated Vascular Calcification

Fan He, Cailin Zhang, Qing Li. *Department of Nephrology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.*

Background: Vascular calcification is highly prevalent and strongly correlated to all-cause and cardiovascular mortality in CKD patients. Peroxisomes are important organelles that regulate various metabolic processes, such as fatty acid oxidation and phospholipid synthesis, thus play an important role in the maintenance of cellular homeostasis. However, the regulatory role of peroxisomes in vascular calcification has not been elucidated. This study aimed to explore the role of peroxisomes in CKD associated vascular calcification.

Methods: The vascular calcification model of CKD mice was used to collect thoracic aortas for transcriptomics, fee-targeted metabolomics and lipidomics analysis. Knockdown or overexpression of peroxisome biogenesis-related genes or ether-lipid synthesis-related genes in vascular smooth muscle cells were performed to detect changes in the degree of vascular calcification. Western blotting, calcium deposition assay, ARS staining, and Von Kossa staining were used to detect vascular calcification.

Results: Combined with the results of transcriptomic analysis, we found that that the peroxisome pathway and ferroptosis pathway were elevated in response to vascular calcification. Moreover, taking advantage of RNA-seq and in vitro experiments, we found that modulating peroxisome content can modulate vascular calcification via regulating ferroptosis. In addition, lipidomic analysis revealed abnormal lipid metabolism in calcified vessels. By knocking down AGPS, the ether-lipid synthesis gene, vascular calcification can be attenuated by inhibiting ferroptosis.

Conclusions: The present results indicate that peroxisomes may regulate ferroptosis levels and ultimately vascular calcification by regulating ether-lipid synthesis.

Funding: Government Support - Non-U.S.

TH-PO218

Serum-Derived Exosomes from Patients on Dialysis Promote Endothelial-Mesenchymal Transition and Vascular Calcification

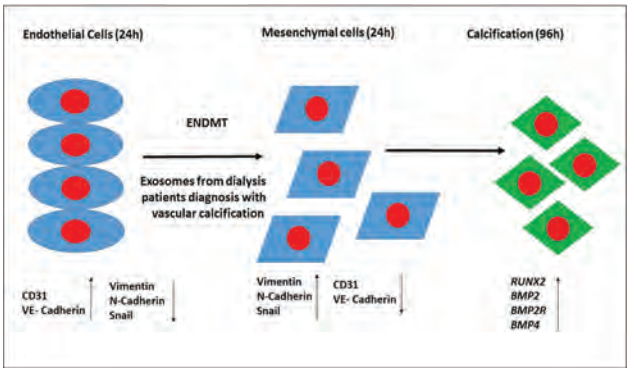
Keren Cohen-Hagai,[1,2] Eran Kuchuk,[1,2] Shelly Tartakover Matalon,[1,2] Sydney Benchetrit,[1,2] Tali Zitman Gal.[1,2] *[1]Meir Medical Center, Kfar Saba, Israel; [2]Tel Aviv University Faculty of Medicine, Tel Aviv, Israel.*

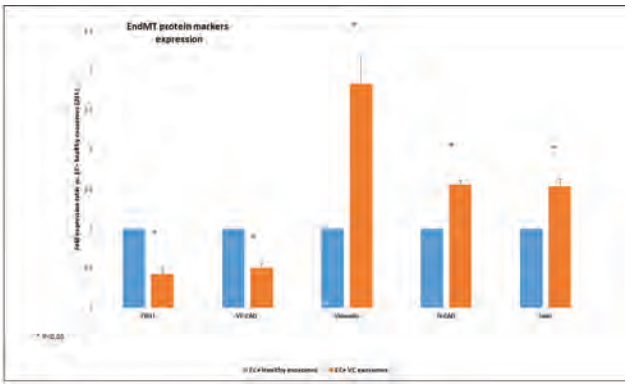
Background: Vascular calcifications (VC) is prevalent among dialysis patients and associate with Cardiovasculare events (CVE). Exosomes, small extracellular vesicles secreted by cells, are mediators of cell-cell interactions and are also involved in biological processes such as apoptosis and inflammation. Endothelial-Mesenchymal Transition (EndMT) has been observed in pathological conditions involving vascular damage and inflammation. Bone morphogenetic protein (BMP) associates with CVE and vascular inflammation. BMPs and the RUNX2 transcription factor are able to stimulate osteoblast differentiation and bone formation. We aimed to assess the effect of serum derived exosomes on EndMT and VC markers

Methods: Serum samples from Twenty dialysis patients with confirmed VC and 10 healthy volunteers were taken at dialysis initiation for exosome isolation. H*uman umbilical vein endothelial cells* (HUVECs) were treated with 100 μg/mL exosomes for 24-96 hours. At the end of incubation, cells were collected for *mRNA and protein* analysis.

Results: VC exosomes induced EndMT in HUVECs; after 24h, a decrease in endothelial markers CD31 and VE-cadherin vs. healthy exosomes (↓ 31% and ↓51%, respectively; P<0.001) N-cadherin and Vimentin vs. healthy exosomes (↑156% and ↑ 283%, respectively; P<0.001). These two cytokines upregulated the expression of Snail (↑153% ;P=0.03). After 96h of incubation, expression of genes essential for osteoblast differentiation that include bone morphogenetic genes (*BMP2, BMPR2, BMP4* and *BMP9*), as well as the transcription factor *RUNX2* were significantly elevated.

Conclusions: Exosomes derived from dialysis patients' serum induced EndMT and contributed to calcification





TH-PO219

Apolipoprotein-L1 G1 Variant Contributes to Hydrocephalus but Not to Atherosclerosis

Teruhiko Yoshida,[1,2] Zhi-Hong Yang,[3] Shinji Ashida,[4] Zu-Xi Yu,[3] Shashi Shrivastav,[1] Danielle A. Springer,[3] Matthew Starost,[5] Avi Z. Rosenberg,[6] Alan T. Remaley,[3] Jeffrey B. Kopp.[1] *[1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [2]Tokyo Daigaku Igakubu Fuzoku Byoin, Bunkyo-ku, Japan; [3]National Heart Lung and Blood Institute, Bethesda, MD; [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD; [5]National Institutes of Health Office of the Director, Bethesda, MD; [6]Johns Hopkins University, Baltimore, MD.*

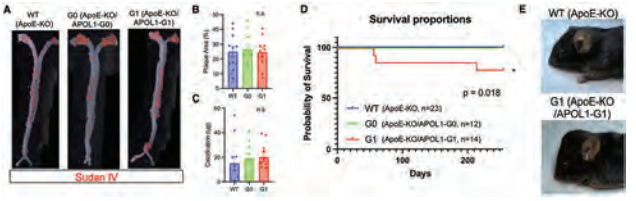
Background: In the USA, six million individuals with sub-Saharan ancestry carry two apolipoprotein L1 (*APOL1)* high-risk genetic variants, which increase risk for kidney diseases. Whether APOL1 high-risk variants are independent risk factors for cardiovascular diseases requires further investigation.

Methods: Transgenic mice carrying APOL1 (G0 low-risk variant and G1 high-risk variant) on bacterial artificial chromosomes (BAC/APOL1 mice) were crossed with the apolipoprotein E knock-out (ApoE-KO) atherosclerosis mouse model. The dual transgenic mice were evaluated for the impact of APOL1 variants on systemic phenotypes. The associations between *APOL1* variants and hydrocephalus were analyzed in the NIH All of Us cohort.

Results: ApoE-KO mice carrying APOL1-G0 and APOL1-G1 transgenes did not show differences in the extent of atherosclerotic lesions or aortic calcification, as evaluated by Sudan IV staining and radiographic examination (**Figure A-C**). All these mice lacked albuminuria. However, ~21% of APOL1-G1 mice developed hydrocephalus and died early (**Figure D, E**). The hydrocephalus was likely due to excess CSF production by the choroid plexus, where epithelial cells expressed APOL1. Single-nucleus RNA-seq of choroid plexus identified multiple solute transporter upregulation and mTORC2 pathway activation in APOL1-G1-expressing epithelial cells. Further, in the NIH All of Us cohort, there was higher hydrocephalus prevalence among African-Americans with the *APOL1-G1* variant, in both recessive (odds ratio 4.35 [1.93-8.88]) and dominant models (3.86 [2.09-7.50]), supporting the mouse findings.

Conclusions: While APOL1-G1 expression in ApoE-KO mice did not worsen cardiovascular or kidney disease, we identified hydrocephalus as a novel APOL1-G1 variant-mediated phenotype. These findings extend the spectrum of APOL1-associated pathologies.

Funding: NIDDK Support



(**A**) Sudan IV-stained images of whole dissected aorta, (**B**) quantitative results of aortic plaque area, (**C**) quantitative results of aortic calcification, (**D**) Kaplan-Meier survival curve, and (**E**) domed-head appearance of hydrocephalus in ApoE-KO/APOL1-G1 mice.

TH-PO220

Oxalate Cardiotoxicity in CKD

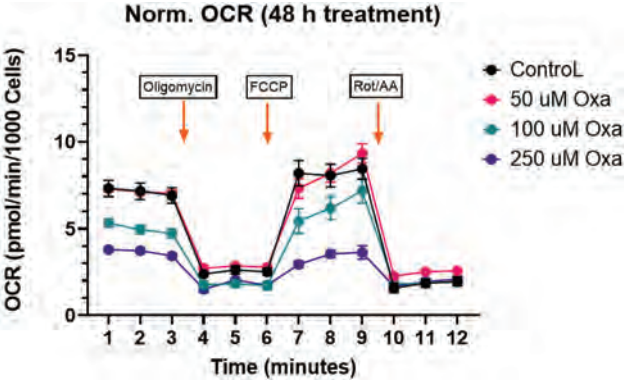
Karim Jaber,[1] Xiaozhong Xiong,[1] Kyle Merritts,[1] Yaw A. Akosah,[2] Evgeny Pavlov,[2] Lama Nazzal.[1] *[1]NYU Langone Health, New York, NY; [2]New York University College of Dentistry, New York, NY.*

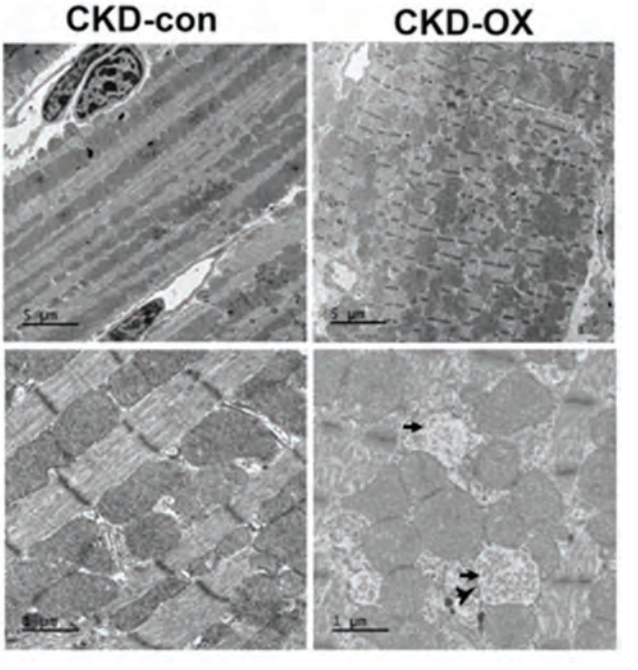
Background: Cardiovascular (CV) events are the leading cause of death among patients with chronic kidney disease (CKD), yet the underlying mechanisms remain poorly understood. Oxalate retention could significantly contribute to CVD in this population. Mitochondrial damage stands out as a potential mechanism of oxalate-induced toxicity, given its association with CKD-induced cardiac damage and oxalate nephrotoxicity. We hypothesize that oxalate-enriched diet increases plasma oxalate levels, induces CV toxicity and mitochondria dysfunction.

Methods: H9C2 cardiomyocytes were cultured and treated with 0, 50, 100 and 250 uM of sodium oxalate (NaOx) for 48 hrs. Mitochondrial function was evaluated via the Seahorse assay, and mitochondrial morphology and membrane potential were assessed through staining. 12 5/6 nephrectomy (CKD) mice were administered either a 1% sodium oxalate supplemented normal chow (NC) or NC for three months. Plasma samples were collected for oxalate and creatinine measurements. Histology and mitochondrial imaging were performed on the heart tissue at sacrifice.

Results: In vitro studies demonstrated that sodium oxalate induces mitochondrial dysfunction in a dose-dependent matter. Mice from both dietary groups showed a comparable degree of CKD at sacrifice but abnormal mitochondrial morphology was observed in the hearts of these oxalate fed mice, when compared to their controls.

Conclusions: Oxalate induces cardiotoxicity, possibly through mitochondrial damage.





TH-PO221

Role of Urokinase in Chronic Hypertension with Albuminuria in DOCA-Salt Murine Model

Marie L. Bach, Camilla Enggaard, Sai Sindhu Thangaraj, Boye Jensen. BLJ Group. *Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Odense, Denmark.*

Background: In proteinuria, aberrant filtration of urokinase-type plasminogen activator (uPA) and plasminogen (plg) leads to intratubular activation of plasmin with potential proteolytic activation of the epithelial sodium channel (ENaC). The ENaC and uPA inhibitor amiloride, reduces blood pressure in patients with treatment resistant hypertension and albuminuria. However, the non-redundant role for uPA is unresolved. Objective: The study aimed to test the hypothesis that uPA is necessary for the development of chronic hypertension in DOCA-salt murine model with albuminuria.

Methods: FVB/uPA wildtype (WT) and gene-targeted (KO) mice were anesthetized (xylazine 10 mg/kg, ketamine 100 mg/kg i.p.) and subjected to unilateral nephrectomy or sham operation. 14-days post-surgery, 4%NaCl diet was introduced and DOCA/sham-pellets were inserted subcutaneously. Blood pressure was measured by indwelling chronic femoral catheters for 15 days. A subset of mice was housed in metabolic cages for 24 hr urine collection. Kidney tissue was collected and used for immunoblotting for γENaC abundance. In a second series, angiotensin II (ANGII) (60ng/min kg) was used to compare blood pressure to low ANGII DOCA-salt mice. Normally distributed data was analyzed by two-way ANOVA followed by post-hoc Bonferroni t-test.

Results: Urine from DOCA-salt treated mice showed glomerular proteinuria with significantly increased albumin excretion (0,4 mg/24 hr/g bodyweight(BW)) compared to control (0,0007 mg/24hr/gBW) with no difference between genotypes. DOCA-salt WT urine showed plg and plasmin abundance, while KO mice only showed plg abundance. Kidney tissue showed increased cleaved γENaC/full-length γENaC abundance in DOCA-salt treated mice with no difference between uPA KO and WT. DOCA-salt increased mean arterial pressure (133 ±4 mmHg), systolic (152±4 mmHg) and diastolic (111±3mmHg) blood pressure significantly from day 1 to 15 compared to control (99±4 mmHg, 108±7 mmHg, 79±4 mmHg) with no difference between genotypes. Heart rate was unchanged (586 bpm), and no difference between day and night pressure. ANGII infusion for 7d led to similar blood pressure elevation in WT and uPA KO mice.

Conclusions: In chronic hypertension with albuminuria, uPA is necessary for activation of plasminogen to plasmin in urine, but does not contribute to hypertension, albuminuria, or kidney γENaC cleavage.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO222

Postfilter Hematocrit Is a Predictor of Continuous Kidney Replacement Therapy Filter Life

Gwyndolyn M. Radford,[1] Javier A. Neyra,[2] Melissa L. Swee,[1] Kianoush Kashani,[3] Masaaki Yamada,[1] Mary V. Sarrazin,[1] Diana I. Jalal,[1] Benjamin R. Griffin.[1] *[1]University of Iowa Hospitals and Clinics, Iowa City, IA; [2]The University of Alabama at Birmingham, Birmingham, AL; [3]Mayo Clinic Minnesota, Rochester, MN.*

Background: Premature filter clotting occurs in up to a quarter of continuous renal replacement therapy (CRRT) filters resulting in blood loss, reduced treatment efficacy, and increased cost. Modifiable factors associated with clotting include access type and location, CRRT modality, and anticoagulation. One additional factor is post-filter hematocrit (Hct), which is a function of pre-filter Hct and filtration fraction (FF). Experts recommend monitoring and minimizing post-filter Hct to reduce clotting risk. However, post-filter Hct is not routinely measured in clinic practice due in part to a paucity of data to support these recommendations. In this study, we hypothesized that there would be an inverse relationship between post-filter Hct and CRRT filter life.

Methods: In this secondary analysis of a previously published study (PMID: 36630406), post-filter Hct was calculated using published formulas utilizing systemic Hct and FF. FF was derived from ultrafiltration rates, rates of pre- and post-filter replacement fluid, and blood flow rate. The primary outcome was filter life (hours). Circuits were excluded if they lasted <2 hours, or if any of the variables used to calculate post-filter Hct were absent. A Generalized Linear Model (GLM) was used to account for multiple filters per patient, and was adjusted for age, race, sex, illness severity, and type of anticoagulation.

Results: A total of 412 filters from 111 patients were included in the analysis. In the final GLM analysis, post-filter Hct was inversely associated with filter life (adjusted estimate = -0.53, 95% CI -0.11 to -0.96, p=0.01). For categorical classification, a post-filter Hct of 29%, the 33rd percentile, was most clinically meaningful. Filters with a post-filter Hct <29% had a median filter life of 34.7 (IQR 18.0-65.6) hours, compared to 24.0 (IQR 13.2-50.9) with post-filter Hct ≥29% (p = 0.04).

Conclusions: In patients receiving CRRT, post-filter Hct was independently associated with decreased filter life and may represent a feasible parameter to monitor during CRRT to maximize filter life. Future prospective studies should determine whether prescription adjustments based on measured post-filter Hct can prolong filter life.

TH-PO223

Hypotension at Initiation of Continuous Kidney Replacement Therapy: A Harbinger of Poor Outcomes

Sameer Thadani,[1,2] Christin N. Silos,[1,2] Kristin J. Dolan,[1,2] Poyyapakkam Srivaths,[1,2] Ayse Akcan Arikan.[1,2] *[1]Baylor College of Medicine, Houston, TX; [2]Texas Children's Hospital, Houston, TX.*

Background: Hypotension occurs in 27-50% of connections to continuous renal replacement therapy (CRRT) yet its impact on outcomes in children has not been thoroughly investigated. Using machine learning techniques and clinical expertise, we aim to build upon prior research by examining the impact of hypotension at CRRT initiation on dialysis liberation.

Methods: Single center retrospective study of critically ill children who received CRRT between 9/2016-10/2018 at Texas Children's Hospital. We utilized high resolution hemodynamics (1-minute intervals) to diagnose hypotension which was defined by a 20% decrease from baseline mean arterial pressure (MAP). Baseline MAP was the average MAP one hour prior to CRRT initiation. Illness severity was assessed using the PELOD-2 score. Liberation was defined as discontinuation of all dialytic modalities 30 days after CRRT initiation. We applied the LASSO method and clinical expertise to construct our final adjusted model.

Results: Our cohort included 59 patients with a median age and weight of 59 months (12-152) and 18 kgs (9-41) respectively. The median PELOD-2 score was 8 (6-10) and a total of 25 (42%) of patients required vasoactive medications at CRRT initiation. A total of 16 (27%) of patients had hypotension at CRRT initiation and 9 (15%) did not liberate. LASSO regression identified cardiac and gastrointestinal indications for ICU admission, history of organ transplantation, locations of hemodialysis catheter, and hypotension after initiation as significant variables. With addition of clinically relevant variables (PELOD-2, vasoactive inotropic score, age, and weight) and utilizing backwards selection, hypotension at CRRT initiation (aOR 0.21 (CI 0.04-0.98) remained negatively associated with liberation

Conclusions: Our model, which integrated machine learning and medical expertise, revealed that hypotension during CRRT initiation was associated with decreased odds of dialysis liberation. Our findings require further external validation but have identified a potentially modifiable factor associated with morbidity. Additional studies should investigate the variation in hypotension during CRRT and how its timing and duration impact patient outcomes.

TH-PO224

Troponin Clearance via Continuous Kidney Replacement Therapies in the Intensive Care Unit (ICU)

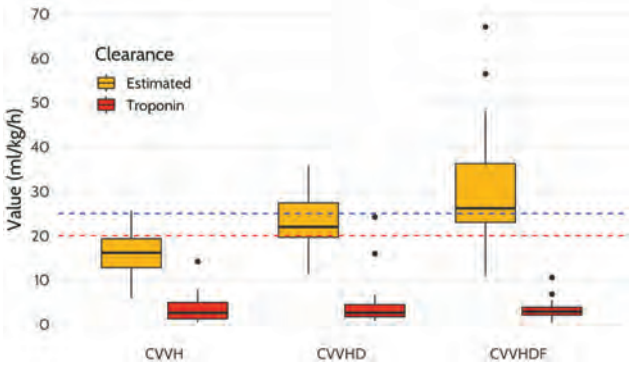
Sabina Mason,[1] Evelyn Deasy,[1] Maria Donnelly,[1] Deirdre M. D'Arcy,[3] Julio L. Chevarria,[1] Yvelynne P. Kelly.[1,2] *[1]Tallaght University Hospital, Dublin, Ireland; [2]Trinity College Dublin School of Medicine, Dublin, Ireland; [3]The University of Dublin Trinity College, Dublin, Ireland.*

Background: Our aim was to compare the clearance of cardiac troponin T via continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD) and continuous venovenous haemodiafiltration (CVVHDF) as a function of circulating serum troponin levels in critically ill patients.

Methods: This was a single-centre, prospective observational study conducted at Tallaght University Hospital in Dublin. Adult patients admitted to ICU and commenced on continuous renal replacement therapy (CRRT) were included. All included patients required a serum troponin T level of greater than 50 ng/L. All patients were required to have commenced CRRT at least four hours before the first sample was taken. We took three serum samples per patient every 24 hours, i.e. over a total of 72 hours, with simultaneous sampling of the waste effluent of the RRT to measure effluent troponin. Our primary outcome measure was estimated troponin clearance according to CRRT modality.

Results: We found no significant difference in estimated troponin clearance according to CRRT modality; with an overall median troponin clearance of 2.6 ml/kg/hour. The percentage of troponin clearance was statistically significantly higher for CVVH compared to CVVHD and CVVHDF (17 vs 14 vs 12% respectively; p = 0.008), though this was not felt to be clinically significant.

Conclusions: In this single-centre, prospective observational study, we measured simultaneous blood and effluent troponin T levels in patients on either CVVHDF, CVVHD or CVVH to compare estimated troponin clearance between the three CRRT modalities. We found no significant difference in estimated troponin clearance according to CRRT modality. Our results show that clearance of troponin T on CRRT is generally small across all modalities and that therefore ongoing treatment with CRRT should not significantly impact our interpretation and tracking of troponin T results in patients with concern for acute coronary syndrome.



Estimated clearance and troponin clearance per CRRT modality

TH-PO225

Effect of Continuous Kidney Replacement Therapy (CRKT) on Thyroid Function

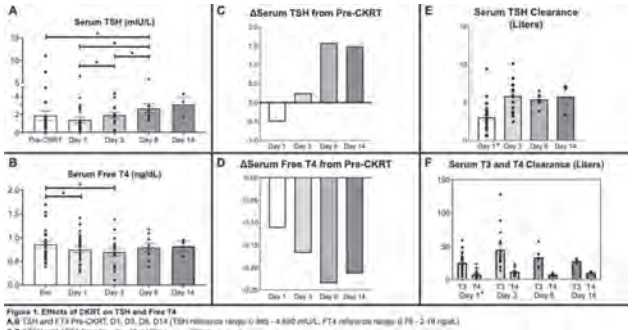
Matt R. Kennis, David Madison, North Foulon, Kayo Okamura, Sarah Haeger, Isadore Budnick, Zhibin He, Warren H. Capell, Sarah Faubel. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Thyroxine (T4) and triiodothyronine (T3) are low molecular weight proteins (0.78 and 0.65kDa, respectively) amenable to removal by CKRT. Herein, we quantified T3/T4 clearance during CKRT and tested the hypothesis that CKRT would affect the hypothalamic-pituitary-thyroid (HPT) axis and cause a rise in serum thyroid stimulating hormone (TSH).

Methods: In 24 patients undergoing continuous veno-venous hemodialysis, we measured CKRT effluent and serum levels of TSH, free T4 (FT4), free T3 (FT3), and reverse T3 (rT3) on Days 1, 3, 8 and 14 of CKRT. Baseline TSH and FT4 was measured <12 hours prior to CKRT initiation. In all cases, fresh samples were measured in the clinical lab. On each day of CKRT, sieving coefficient (SCx=[x]effluent/[x]serum), clearance (liters cleared=SCx*total effluent volume in prior 24 hours), and Sequential Organ Failure Assessment (SOFA) scores were calculated. Thyroid function tests were interpreted by an endocrinologist using prespecified definitions of euthyroid sick syndrome (ESS) and hypothyroidism.

Results: Mean SC of TSH, FT4, and FT3 was 0.15 (n=48), 0.27 (n=46), and 1.04 (n=49), respectively and did not change between days on CKRT. SOFA scores were similar on each day. Serum TSH was higher on D8 vs. D3, D8 vs. D1, D8 vs. Pre-CKRT and D3 vs. D1 (Figure 1A). Serum T4 decreased on D3 and D1 of CKRT, relative to pre-CRKT (Figure 1B). TSH, FT4, and FT3 clearance is shown in Figure 1E-F. One patient met criteria for hypothyroidism, with the remaining patients in various stages of ESS.

Conclusions: T3 and T4 removal occurs during CKRT. To our knowledge this is the first report to quantify T3 and T4 removal during CKRT and the first to describe the development of hypothyroidism after CKRT initiation (n=1). Even in patients with ESS (n=23), a physiologic effect of T3 and T4 removal on the HPT axis is suggested by the significant rise in TSH. These data suggest that hypothyroidism is a novel complication of CKRT.



TH-PO226

Hyperparathyroidism as a Cause of Low Calcium Requirement during Regional Citrate Anticoagulation: Two Case Reports

Afsheen Afzal,[1] Frank Liu.[2,1] *[1]Weill Cornell Medicine, New York, NY; [2]Rogosin Institute, New York, NY.*

Introduction: CRRT with regional citrate anticoagulation (c-CRRT) relies on a predictable calcium (Ca) balance between effluent removal and Ca replacement to maintain a stable physiologic peripheral ionized Ca (iCa). Our c-CRRT protocol utilizes Ca gluconate for replacement targeting peripheral iCa of 1.05-1.25 mmol/L. In our experience, the majority of patients require 1-2 g/hr of Ca gluconate with variation due primarily to effluent volume. Patients who have unusually low Ca requirements are in negative Ca balance, which can lead to significant demineralization of bone. Existing literature has centered on immobility hypercalcemia as the cause of unusually low Ca requirements during c-CRRT. We present 2 cases of unusually low Ca requirements due to hyperparathyroidism (HPT), which normalized after initiating cinacalcet.

Case Description: Case 1: A 44-year-old male with history of ESKD on hemodialysis (HD) and atrial fibrillation was admitted with cardiogenic/septic shock requiring c-CRRT. His pre-CRRT peripheral iCa was 1.26 mmol/L. He was noted to have unusually low Ca gluconate requirements (400 mg/hour). Subsequent workup revealed an elevated parathyroid hormone (PTH) level of 867 pg/ml. He was started on cinacalcet 30 mg daily; effluent volume was not changed. By 24h after the first dose, his Ca requirement had increased, with stabilization at 1.3 g/hr by 36h. Case 2: A 71-year-old male with history of ESKD on HD, coronary artery disease, and congestive heart failure was admitted with septic shock. His pre-CRRT peripheral iCa was 1.42 mmol/L; hypercalcemia workup was not done at that time. He was noted to have a low Ca gluconate requirement (as low as 400 mg/hr) on c-CRRT. PTH was elevated at 499 pg/ml in spite of systemic hypercalcemia (iCa 1.3 mmol/L). Cinacalcet 30 mg twice daily was initiated; effluent volume was not changed significantly. After 2 doses of cinacalcet, his Ca requirement increased, with eventual stabilization at 1.3-1.4 g/hr by 48h after cinacalcet start.

Discussion: These cases suggest that in addition to immobilization-induced hypercalcemia, HPT should be considered as a cause of hypercalcemia and unexpectedly low Ca requirements in critically ill ESKD patients on c-CRRT. In such patients, treatment of the underlying HPT with cinacalcet can minimize negative Ca balance and subsequent detrimental bone effects while on c-CRRT.

TH-PO227

Regional Citrate Anticoagulation (RCA) Compared with No Heparin in Continuous Kidney Replacement Therapy (CKRT) among Liver Patients: A Single-Center, Retrospective, Interim Analysis

Chandani Bhagat, Hari S. Meshram. *Institute of Liver and Biliary Sciences, New Delhi, India.*

Background: We divided the study population into chronic liver disease (CLD), and acute liver failure (ALF) or acute on chronic liver failure (ACLF) and compared the outcomes of RCA with no heparin.

Methods: This was an ethically approved, retrospective, single-center study conducted between 10 July 2022 to 26 Sept 2023. The study population (n = 309) was divided into CLD (n =173), ALF (n = 62) and ACLF (n = 74). CVVHDF modality was used where citrate dosing of 3 mmol/L maintaining a range of 2 mmol/L to 2.4 mmol/L was used. The primary outcome measured was difference in filter life span. Secondary outcomes were ammonia, lactate and pH improvement.

Results: 309 patients were studied.173 CLD patients, 44 received RCA and 129 received no anticoagulation. The median age of CLD was 50(40-57) years. A total of136 comprised of ALF and ACLF patients. ALF and ACLF cases were contributed by hepatitis A (43.5%) and acute alcoholic hepatitis, CLD (56.7%) respectively. In this group, 36 received RCA and 100 had no anticoagulation. The median age of this group was 38(28.75-47) years. The baseline clinical and laboratory parameters in the all the groups were statistically insignificant. The median duration of CKRT duration overall was 42 hours. In the KM analysis, RCA group had longer filter clotting time compared to no anticoagulation (log rank p-test = 0.001172). The length of stay from hospital admission to last follow-up or death was 11 days. Overall there was no difference in mortality between the groups with respect to choice of anticoagulation. There was no statistical difference in terms of pre and post CKRT serum ammonia, lactate, and blood pH in any of the sub groups.

Conclusions: CKRT at low dose RCA is feasible in liver patients including ALF and ACLF. There were no additional metabolic complications or mortality risks associated with RCA. Also, there was significant improvement in filter life span which prompts its consideration in this high risk group of patients. Further, prospective studies are encouraged to confirm our preliminary findings.

TH-PO228

Extracorporeal Carbon Dioxide Removal Instead of Mechanical Ventilation in a Patient with Respiratory Distress and Acute Kidney Failure, with Active Bleeding Using Regional Anticoagulation

Milton Kalil, Renato E. Eick, David Saitovich, Anna C. Stein, Lucas G. Da Luz, Illan G. Balestrin, Marcelo B. Gazzana, Mauricio L. André. *Hospital Moinhos de Vento, Porto Alegre, Brazil*.

Introduction: There are only a few reports so far describing the use of citrate (regional) anticoagulation for CO2 removal (ECCO2R) probably due to the metabolic complications and electrolyte disturbances that occur with the high blood flow rate (for efficient CO2 removal) and higher than usual citrate flow rate, necessary for the procedure.

Case Description: Citrate anticoagulation in continuous venovenous hemodiafiltration (CVVHDF) associated with extracorporeal carbon dioxide removal (ECCO2R) was performed in a 71 years old patient with active bleeding and severe respiratory acidosis for 5 days. This procedure was carried out with a Fresenius (multiECCO2R), a single gas exchanger combined with continuous kidney replacement therapy (CKRT). Dialysis prescription was blood flow rate of 300ml/min, sodium citrate 4% infusion rate of 300ml/h, calcium chloride 3.38% replacement solution rate of 30ml/h, and oxygen flow rate of 4.5L/min. Dialysis and replacement solutions bicarbonate and sodium concentration were respectively 10mEq/L and 129mEq/L. The patient remained without endotracheal intubation during the procedure period. A reduction of approximately 30% pCO2 was attained, respiratory acidosis was controlled and the hydroelectrolytic balance was maintained(Table1).

Discussion: In cases of CO2 removal in the context of regional anticoagulation with citrate, it is important to adjust calcium replacement according to effluent volume and also to adjust bicarbonate and sodium concentrations in dialysis solutions. We conclude that it is possible and safe to remove CO2 in a CVVHDF + multi ECCO2R single system, using sodium citrate for regional anticoagulation.

	Before procedure	After 15 minutes	Day 1	Day 2	Day 3	Day 4	Day 5
pH a	7.19	7,28	7.41	7,43	7,40	7,39	7,39
PaCO2	79	57	58	55	53	56	55
HCO3	30	27	37	37	33	34	33
PaO2	99	90	80	118	127	93	78
pH v pre	-	7.30	7.35	7,37	7,33	7,35	7,36
pH v post	-	7.8	7.76	7,77	7,68	7,59	7,79
PCO2 pre filter CO2 removing	-	54	59	57	65	56	52
PCO2 post filter CO2 removing	-	7	17	16	18	25	13
Na mEq/L	-	147	149	148	149	150	148
Ca i (mmol/L)	-	1.43	1.48	1,57	1,24	1,16	1,42
Ca i post (mmol/L)	-	0.39	0.67	0,79	0,62	0,60	0,68

TH-PO229

Development of a Novel Protocol for Successful Discontinuation of Continuous Kidney Replacement Therapy: A Pilot Study

Daun Song,[1] Ji won Lee,[1] Se-Hee Yoon,[1] Won Min Hwang,[1] Sung-Ro Yun,[1] Sua Lee,[2] Soyoung Lee,[2] Yohan Park.[1] Div of Nephrology, Dept of Internal Medicine, Konyang University Hospital; Div of Nephrology, Dept of Internal Medicine, Daejeon Eulji Medical Center. *[1]Konyang University Hospital, Daejeon, Republic of Korea; [2]Daejeon Eulji University Hospital, Daejeon, Republic of Korea*.

Background: The discontinuation of continuous kidney replacement therapy (CKRT) lacks a well-established protocol. Creatinine and cystatin C (CysC) are well-known markers of kidney function, with molecular weights of 113 Da and 13.3 kDa, respectively. This study aimed to develop a novel CKRT discontinuation protocol by predicting kidney function using changes in serum cystatin C (CysC) levels after switching the CKRT mode to continuous veno-venous hemodialysis (CVVHD), which has a lower clearance rate for middle molecular weight solutes.

Methods: This pilot study included 17 patients undergoing CKRT. Patients who maintained stable vital signs without vasopressor support were switched from continuous veno-venous hemodiafiltration (CVVHDF) to CVVHD. Serum creatinine and CysC levels were measured at 6, 12, and 24 hours after switching to CVVHD mode, along with daily urine output. Kidney replacement therapy (KRT) reinitiation was defined as the resumption of KRT within 7 days after discontinuing CKRT.

Results: Out of 17 patients, 7 experienced KRT reinitiation. Following the switch to CVVHD mode, serum creatinine levels remained stable or decreased in all patients, whereas an increase in serum CysC was observed in the KRT reinitiated group. Receiver operating characteristic (ROC) curve analysis was conducted to predict KRT reinitiation. The 12hr CysC to baseline CysC ratio had the highest area under the ROC curve (AUROC) value of 0.857, with a cutoff value of 0.97. The AUROC value for daily urine output was 0.871, with a cutoff value of 214 mL. A multivariate model incorporating both the 12hr CysC to baseline CysC ratio and daily urine output demonstrated an AUROC value of 0.986, showing exceptional predictive performance for KRT reinitiation.

Conclusions: The multivariate model using the 12hr CysC change and daily urine output after switching to CVVHD mode proved to be an excellent predictor of KRT reinitiation. Based on this pilot study, a CKRT discontinuation protocol could be developed, and if validated in larger studies, may lead to a paradigm shift in CKRT discontinuation practices.

TH-PO230

Predicting Liberation from Continuous Kidney Replacement Therapy in Critically Ill Patients Using a Machine Learning Model

Kianoush Kashani,[1] Francesca Alfieri,[2] Andrea Ancona,[2] Simone Zappalà.[2] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]U-Care Medical s.r.l, Torino, Italy*.

Background: Continuous renal replacement therapy (CRRT) is utilized in nearly 14% of critically ill patients. Currently, there are no standardized practice guidelines to wean CRRT, apart from clinicians' discretion, as per the KDIGO guidelines. This study aims to develop and validate a model to predict successful CRRT liberation.

Methods: For this single-center, retrospective cohort study, we used data from 661 adult patients connected to 668 disinct ICU stays from MIMIC-IV dataset who received CRRT between 2008 to 2019. CRRT liberation was defined as renal replacement therapy (RRT)-free survival within seven days after the liberation. We randomly divided the cohort into derivation (70%) and validation sets [KK1] (30%). The outcomes were successful CRRT liberation vs. unsuccessful CRRT liberation and/or death. A multiclass decision tree model was developed and internally validated.

Results: The final cohort included 668 ICU stays requiring CRRT, among them 266 (39.8%) were successfully liberated from CRRT, 265(39.7%) had unsuccessful CRRT liberation, and 137(20.5%) died while on CRRT. The auROC of the model reflects its ability to discriminate between successful and unsuccessful liberation, varying from 0.797(CI 95% 0.743, 0.864) to 0.739(CI 95% 0.700, 0.810) when the model is activated at the time of CRRT liberation up to 12 hours later. Moreover, the model outputs a probability of mortality within seven days from the CRRT discontinuation, achieving auROCs from 0.746 (CI 95% 0.682, 0.861) to 0.861(CI 95% 0.795, 0.944) moving forward over time.

Conclusions: The model is designed to be used by clinicians at the time of CRRT liberation and can be consulted up to 12 hours after the discontinuation. This validated model could be integrated into the clinical practice with the aim of assisting the decision-making related to the CRRT liberation in critically ill patients with AKI hospitalized in intensive care units, facilitating a timely reinstitution of CRRT where needed and ensuring better patient outcomes.

Funding: Commercial Support - U-Care Medical s.r.l.

TH-PO231

Oxiris Membrane Performance in Patients with Septic Shock and Continuous Kidney Replacement Therapy Requirement: A Randomized Controlled Trial

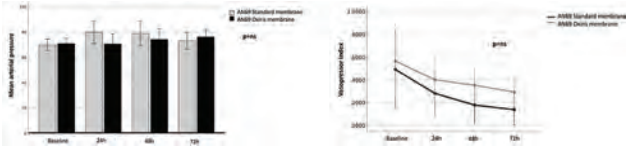
Omar Fueyo,[1] Adrián Esteban Caballero-Islas,[1] Mauricio Arvizu Hernández,[1] Ricardo Correa-Rotter,[1] Pablo E. Galindo,[2] Néstor H. Cruz Mendoza,[1] Olynka Vega.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico*.

Background: Highly selective semipermeable Oxiris membranes have shown to provide endotoxin adsorption and removal of different cytokines which could improve hemodynamic stability in patients with septic shock and continuous kidney replacement therapy (CKRT) requirement. The aim of this study was to compare the clinical efficacy of Oxiris membrane vs a conventional AN69 standard membrane to maintain the mean arterial pressure (MAP) after 72 hours in critically ill patients with CKRT requirement

Methods: Multicenter randomized controlled trial in critically ill patients and CKRT requirement. Patients were randomized to receive continuous veno-venous hemodiafiltration using either an AN69 standard membrane or an AN69 Oxiris membrane. Regional citrate anticoagulation was used, all patients had a prescribed dose of 30mL/kg/h for 72 hours, the filters were changed every 24h. Clinical variables were registered, vasopressor dependency index was calculated to express relationship between vasopressor dose and MAP

Results: Originally 36 patients were intended to be included. At the time of this cut point 30 patients have been included, 15 (50%) in the Oxiris group, 14 (46%%) in the control group and 1 (3%) had to be excluded because of death in the first 24 hours. Most common infection was pneumonia, 28% due to COVID-19, mean initial SOFA was 11 points. There were no differences in MAP between groups (Oxiris vs. Control) at 0, 24, 48 and 72 h; 66 vs 68, 71 vs 74, 73 vs 77 and 73 vs 79 respectively. **Figure 1**. The rate of vasopressors was not different as shown in **Figure 2**. Fluid removal tended to be greater in the control group with a median rate of 1.2 vs 0.5 (p = 0.03) at 24 h, 0.9 vs 1.0 at 48 h (p=0.72), and at 72 h with a rate of 1.5 vs 0.7 (p=0.03). There were no differences in daily fluid balance

Conclusions: In this study there were no differences in the requirement of vasopressors to maintain hemodynamic stability in patients with septic shock and CKRT using Oxiris membrane compared to standard membrane.



MAP and Vasopressor Index at baseline, 24, 48 and 72 h

TH-PO232

Role of Hemodiafiltration in Calcium Channel Blocker (CCB) Overdose

Steven Pham. *Unity Health, Searcy, AR.*

Introduction: Overdose of CCBs, a common medication used to treat hypertension, is associated with high mortality rates. Amlodipine, a dihydropyridine class of CCB, is a highly protein-bound medication. Current management of CCB overdose includes intravenous fluid, vasopressor, lipid emulsion, and methylene blue. However, overdose often leads to metabolic acidosis and multiorgan failures, prompting other therapies such as continuous veno-venous hemodiafiltration (CVVH) or extracorporeal membrane oxygenation support (ECMO). We report a case of amlodipine overdose resulting in refractory shock and acidosis, in which CVVH and ECMO were successful.

Case Description: A 34-year-old male was admitted due to unresponsiveness. His wife reported an empty bottle of amlodipine next to him. Upon arrival, his oxygen saturation was 70%. Blood pressure (BP) was 70/30 mmHg. Due to severe hypotension, he was started on norepinephrine and vasopressin, with phenylephrine and epinephrine soon being added. Poison control recommended starting methylene blue to reverse amlodipine's vasodilator effect. Lipid emulsion was initiated to sequester amlodipine, with the mean arterial pressure (MAP) improving from 45 to 62. He also developed acute kidney injury (AKI) with creatinine of 3.57 mg/dL and blood urea nitrogen (BUN) of 30 mg/dL. Arterial blood gas (ABG) showed pH 7.10 and pCO2 59.3 mmHg. Anion gap was 21 mmol/L and lactic acid was 9.9 mmol/L. CVVH was started, maintaining his MAP in the 70s and systolic BP in the 110s. His urine output was around 100-150 cc/hour. However, his acidosis remained refractory (last ABG showed pH of 7.22 and pCO2 of 61.9 mmHg), so he was transferred to another facility for ECMO. At the time of this writing, the patient has fully recovered.

Discussion: Hemodialysis is ineffective for eliminating protein-bound medication like amlodipine. Previous literature has suggested the use of albumin as a dialyzer to enhance clearance, although in our case, traditional CVVH was preferred due to other indications such as severe metabolic acidosis, oliguria, and AKI. Our patient's condition improved significantly following CVVH and ECMO, possibly due to restored kidney function and pH correction, thereby facilitating amlodipine clearance and enhancing responses to other treatments. Further research is warranted to explore the effectiveness of albumin over traditional CVVH in clearing overdose of protein-bound medications.

TH-PO233

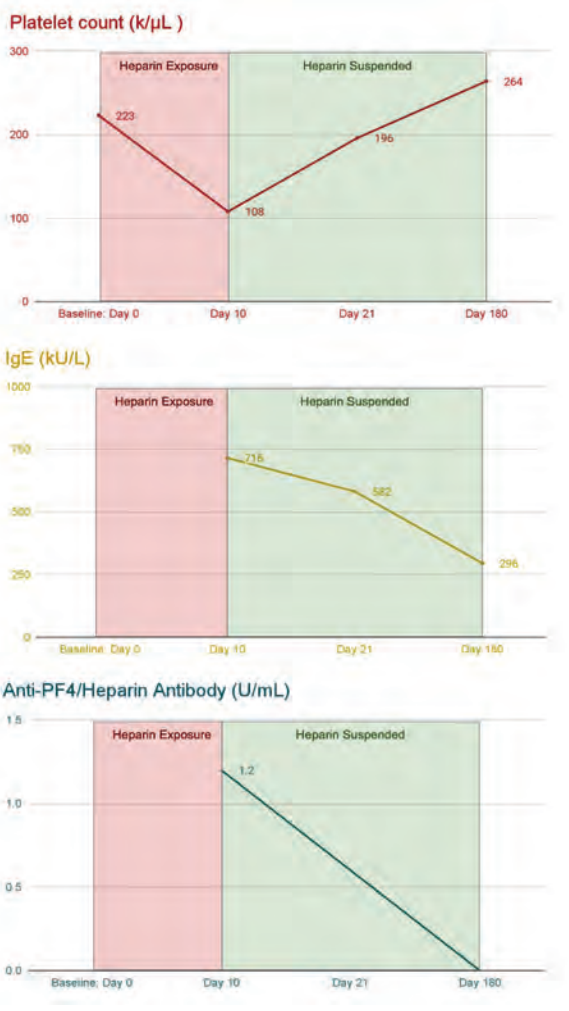
Unusual Presentation of Type II Heparin-Induced Thrombocytopenia Successfully Managed with Predilution Online Hemodiafiltration

Felipe Pascoal, Adolfo Simon, Istenio Pascoal, Juliane Lauar, Kelia Xavier, Vilber Bello. *Centro Brasiliense de Nefrologia Ltda, Brasilia, Brazil.*

Introduction: Type II heparin-induced thrombocytopenia (HIT) is portrayed by antibody production against PF4/Heparin complex. While it typically presents with thrombocytopenia and thrombosis, allergic features have also been reported. Predilution Online hemodiafiltration (OL-HDF) can dismiss heparin and is safely used when this anticoagulant is contraindicated. Herein, we present a rare case of type II HIT with wheezing, elevated IgE levels and thrombocytopenia in a dialysis patient effectively handled with predilution OL-HDF.

Case Description: An 83-year-old male with unresolved obstructive uropathy was referred to our clinic for dialysis initiation. After four uneventful sessions, he experienced wheezing, 88% oxygen saturation and high filter transmembrane pressures half an hour into the next therapies, despite switch of filter and line brands. Bloodwork revealed 108 k/µL platelets (from 223k/µL), 4Ts score was 6 (high probability) and Anti-PF4/Heparin assay yielded 1.2 U/mL (RR: < 0,6 U/mL), confirming the diagnosis of type II HIT. IgE levels were also elevated at 716 kU/L. Since equipment clotting persisted despite intermitent saline flushes and Apixaban prescription, dialysis therapy was shifted to short daily heparin free predilution OL-HDF. Sessions resumed uneventfully ever since and, six months later, IgE decreased to 296 kU/L, platelets increased to 264k/µL and Anti-PF4/Heparin levels were undetectable, as shown in the graphs attached.

Discussion: Type II HIT may display with thrombocytopenia, hypercoagulability and unusual allergic features in a manifold fashion. As management for this condition relies on heparin cessation and clot-preventing strategies, predilution OL-HDF presents a safe and effective dialysis modality in this group of patients.



TH-PO234

Comparison of Autonomic Response to Orthostatic Challenge before Hemodiafiltration in Patients with Different Intradialytic Blood Pressure Profiles

Erika E. Jaime Borja, Salvador L. Gil, Claudia Lerma, Alfredo Fuentes Mercado. *Instituto Nacional de Cardiologia Ignacio Chavez, Ciudad de Mexico, Mexico*.

Background: The heart rate variability (HRV) response to active standing (AS) has shown preserved autonomic modulation in maintenance hemodiafiltration (HDF) patients. The aim was to compare the HRV response to AS before HDF between patients with different profiles of intradialytic systolic blood pressure (SBP).

Methods: We included 55 HDF sessions from 26 patients (age 40 ± 13 years, 62% were women, and five had diabetes). Using linear regression analysis, the SBP intradialytic profile was classified into three groups: decreased SBP, increased SBP, or unchanged SBP. HRV indices were obtained during the supine position and AS. The mean values were compared by ANOVA for repeated measures, p value < 0.05 was considered significant.

Results: Age, comorbidity, total ultrafiltration volume, initial SBP, and final SBP were similar between groups. In both positions, the HRV indices were similar between groups (Table 1). Although all groups had a response to AS of faster mean heart rate and lower variability (pNN50), only the group with decreased SBP responded to AS by increasing the low-frequency (LF) power and decreasing the high-frequency (HF) power.

Conclusions: The autonomic response to an active orthostatic challenge before HDF shows a preserved sympathetic increase and parasympathetic decrease only in those patients who had an intradialytic SBP decrease in the subsequent HDF session.

Table 1. HRV indices grouped by intradialytic SBP response.

HRV indices	Decreased SBP (n = 28)	Increased SBP (n = 15)	Unchanged SBP (n = 12)
Supine position			
Heart rate (bpm)	71.4 ± 7.8 *	70.4 ± 8.7 *	67.0 ± 8.7 *
SDNN (ms)	298 ± 172	449 ± 283 *	475 ± 245 *
pNN50 (%)	24.4 ± 22.1 *	33.6 ± 27.6 *	36.9 ± 25.1 *
LF (n.u.)	64.2 ± 23.1 *	72.1 ± 20.4	73.8 ± 22.7
HF (n.u.)	36.1 ± 23.0 *	29.8 ± 16.7	28.2 ± 21.6
Log (LF/HF)	0.34 ± 0.56	0.46 ± 0.46	0.50 ± 0.55
Active standing			
Heart rate (bpm)	77.0 ± 11.3	76.3 ± 7.1	72.5 ± 7.9
SDNN (ms)	275 ± 127	299 ± 118	312 ± 108
pNN50 (%)	14.2 ± 15.5	20.7 ± 20.6	19.6 ± 16.8
LF (n.u.)	75.7 ± 15.2	70.7 ± 20.1	63.0 ± 19.5
HF (n.u.)	25.3 ± 15.5	29.3 ± 20.1	37.0 ± 19.5
Log (LF/HF)	0.56 ± 0.40	0.47 ± 0.47	0.27 ± 0.42

* $p < 0.05$ compared to active standing

TH-PO235

Adequate Convective Volume Can Be Achieved in Majority of Multiethnic Asian Patients Receiving Hemodiafiltration in Singapore

Cindy Chan,[1] Yan Zhang,[2] Yan Yi Cheung,[3] Nandakumar Mooppil,[3] Tripti Singh,[3] Anke Winter,[2] Franklin W. Maddux,[4] Jeffrey L. Hymes,[4] Milind Nikam.[3] *[1]Fresenius Medical Care Asia Pacific Ltd, Hong Kong, Hong Kong; [2]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [3]Fresenius Medical Care Asia Pacific Ltd, Singapore, Singapore; [4]Fresenius Medical Care Holdings Inc, Waltham, MA.*

Background: High volume hemodiafiltration (HDF) has been shown to improve patient outcomes. However, there is a very common concern amongst healthcare practitioners about the feasibility of achieving optimal convective volume (CV) in Asian patients.

Methods: A 5-year retrospective cohort analysis was conducted on patients dialyzing at Fresenius Kidney Care clinics in Singapore from 2019 to 2023, aiming to evaluate HDF practice patterns and outcomes. We adjusted the CV to body surface area (BSA) as has been suggested by some publications.

Results: A total of 1404 patients received 291,822 HDF sessions during the study period. At baseline, the cohort's mean age was 64 (±13) years and it was followed up for 34 (±17) months on average, with 60% males. The majority were Chinese (51%), followed by Malay (11%) and Indian (4%) patients. The most common modality was post-dilutional HDF (70%) followed by pre-dilutional in 25% cases. In 5% cases the modality was not recorded. The CVs achieved in various sub-groups in this cohort are listed in Table 1.

Conclusions: Contrary to the common belief, adequate CVs can be achieved in majority of Asian patients. With growing interest and experience of HDF, this is likely to improve further. Of note, Malay patients had lower CV compared to those of Chinese and Indian ethnicity – a further study of patient and practice related factors in Asian geographies on CV achievement is warranted.

Funding: Commercial Support - Fresenius Medical Care

Table 1. Mean and S.D. of Convection volume by dilution mode and other factors

Clinical variables	Mean ± SD			
	Achieved convection volume (L) (Post-dilution)	BSA standardized convection volume (L) (Post-dilution)	Achieved convection volume (L) (Pre-dilution)	BSA standardized convection volume (L) (Pre-dilution)
Age				
18-<50 years	22.3 ± 6.5	21.4 ± 7.1	42.5 ± 11.9	40.2 ± 12.6
50-65 years	21.9 ± 6.3	21.6 ± 6.7	40.8 ± 10.8	41.2 ± 13.0
>65 years	21.5 ± 6.3	22.4 ± 7.1	40.4 ± 11.9	42.9 ± 12.8
Gender				
Female	21.2 ± 6.3	23.1 ± 7.5	39.8 ± 11.2	44.2 ± 13.7
Male	22.2 ± 6.4	21.2 ± 6.5	41.6 ± 11.7	40.3 ± 12.1
Ethnicity				
Chinese	22.1 ± 6.3	22.5 ± 7.0	41.5 ± 11.8	43.5 ± 13.7
Indian	21.5 ± 6.2	22.2 ± 6.9	40.4 ± 11.9	40.2 ± 12.1
Malay	21.1 ± 5.4	20.2 ± 5.6	41.1 ± 11.2	39.5 ± 11.5
Other	22.0 ± 7.6	21.4 ± 8.5	39.7 ± 12.1	39.9 ± 15.1
Unknown	21.6 ± 6.8	21.6 ± 7.1	39.6 ± 10.9	40.1 ± 10.9
Vintage				
< 2 years	21.8 ± 6.7	21.6 ± 7.4	40.4 ± 12.2	41.4 ± 13.5
2-5 years	21.8 ± 6.3	21.9 ± 6.7	40.8 ± 11.1	41.0 ± 11.3
> 5 years	21.8 ± 5.9	22.4 ± 6.7	41.8 ± 10.6	43.5 ± 13.0

TH-PO236

Hemodiafiltration Is Associated with Lower Hospitalization Rates Compared with Hemodialysis in a Singapore Cohort

Cindy Chan,[1] Yan Zhang,[2] Yan Yi Cheung,[3] Nandakumar Mooppil,[3] Tripti Singh,[3] Anke Winter,[2] Franklin W. Maddux,[2] Jeffrey L. Hymes,[4] Milind Nikam.[3] *[1]Fresenius Medical Care AG, Hong Kong, Hong Kong; [2]Fresenius Medical Care AG, Bad Homburg, Germany; [3]Fresenius Medical Care AG, Singapore, Singapore; [4]Fresenius Medical Care AG, West Nashville, TN.*

Background: Hemodialysis (HD) patients suffer from high rates of hospitalization leading to significant morbidity, mortality, and costs. Hemodiafiltration (HDF) has been shown to improve patient outcomes.

Methods: A retrospective cohort analysis was conducted on patients receiving HD at Fresenius Kidney Care clinics in Singapore between 2019 and 2023. Clinical data were extracted from the electronic information system – EuCliD® to assess the association of dialysis modality with hospitalization outcomes. Patients were classified into 3 groups, i.e., HD and HDF groups, comprising of patients receiving ≥75% of treatments with HD or HDF, respectively, and others as the mixed group. Negative binomial regression was applied to estimate the incident rate ratio (IRR) of hospitalization and length of stay (LOS), adjusted for confounders.

Results: A total of 3298 patients were included, with 59% males. The mean age was 64(±13) years, and dialysis vintage as 26(±48) months. The modality group distribution was: HD: 75%, HDF: 16% and mixed: 9%. The HDF group had a lower hospitalization rate per person-year compared to the mixed and HD groups (HDF: 1.18, Mixed: 1.40, HD: 1.76), with a significantly lower IRR of 0.80 [95% CI: 0.72, 0.88] compared to the HD group (Table 1). Also, the HDF group had a lower number of hospitalization days per person-year than the other groups (HDF: 8.99, Mixed: 11.38, HD: 15.13; IRR, 0.73 [95% CI: 0.63, 0.84]).

Conclusions: In this cohort, HDF showed significantly lower hospitalization rates and shorter LOS compared to conventional HD and the mixed modality groups.

Funding: Commercial Support - Fresenius Medical Care

Table 1. Incident Rate Ratios of hospitalization outcomes

Dialysis modality (HD as reference group)	Hospitalization events (per patient-year) IRR (95% CI)*	Hospital days (per patient-year) IRR (95% CI)*
HDF	0.80 (0.72 – 0.88)	0.73 (0.63 – 0.84)
Mixed	0.92 (0.80 – 1.05)	0.87 (0.73 – 1.03)

*Adjusted for COVID-19 status, age, sex, race, dialysis vintage, pre-existing diabetes, cardiovascular disease, hypertension, Charlson comorbidity index, BMI, dialysis frequency, effective treatment time, OCM Kt/V, blood flow rate, systolic and diastolic blood pressure at baseline, and most frequent vascular access during follow-up.

TH-PO237

Exploring the Impact of Hemodialysis Modalities on NETosis in Diabetic and Nondiabetic Patients

Etty Kruzel-Davila,[1,2] Olga O. Vdovich,[1,2] Lital Remez.[1,2] *[1]Galilee Medical Center, Nahariya, Israel; [2]Bar-Ilan University The Azrieli Faculty of Medicine, Ramat Gan, Israel.*

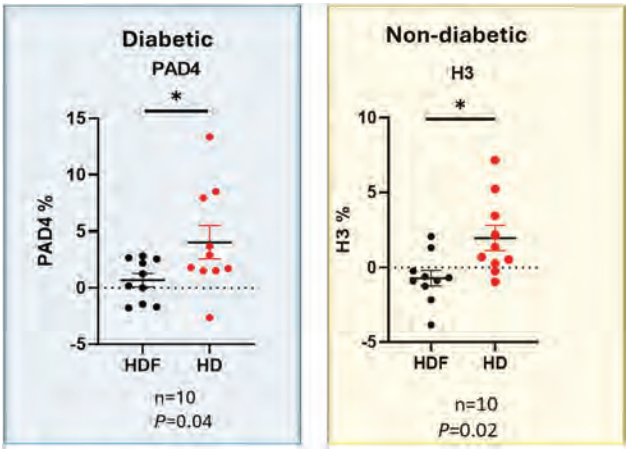
Background: Patients suffering from chronic kidney disease (CKD) and diabetes mellitus (DM) face an increased risk of developing cardiovascular complications and infections. Neutrophils are recruited to sites of infection and form Neutrophil extracellular traps, a conserved mechanism known as NETosis, function to eradicate pathogens by releasing decondensed chromatin decorated with proteins from neutrophil intracytoplasmic granules. However, when NETosis becomes dysregulated, it can potentially exacerbate the detrimental inflammatory pathways linked to complications of CKD and diabetes. Considering the higher survival rates observed among patients treated with hemodiafiltration (HDF) as opposed to hemodialysis (HD), along with the dysregulated NETosis observed in individuals with HD and DM, our objective is to investigate the impact of hemodialysis modality on NETosis in patients undergoing hemodialysis, with and without diabetes.

Methods: Twenty hemodialysis patients participated in the study, comprising 10 diabetic patients, 10 non-diabetic patients, and 10 healthy controls. Blood samples were obtained from patients undergoing hemodiafiltration (HDF) and subsequently transitioning to high flux hemodialysis (HFHD). Neutrophils were isolated from these samples and stimulated with 100 nM PMA for one hour. Subsequently, they were stained for markers of NETosis such as PAD4, PE, MPO, Histone H3, and 7AAD Viability Dye. Data acquisition was performed using a flow cytometry.

Results: Our findings reveal significantly reduced levels of NETosis activation and NETosis markers following HDF treatment compared to HD, irrespective of diabetes status ($p<0.05$). Furthermore, diabetic patients exhibited lower NETosis activation compared to non-diabetic patients ($p=0.03$, 0.01, for HD and HDF respectively).

Conclusions: The study suggests that the reduction in dysregulated NETosis may contribute to the favorable outcomes of HDF, ultimately leading to decreased mortality among hemodialysis patients.

Funding: Private Foundation Support



TH-PO238

Serum (1-3)-β-D-glucan Levels after Oral β-D-glucan Load in Controls and People with ESKD on High-Flux Hemodialysis (HD) and Hemodialysis Filtration (HDF)

Oscar Swift,[1,2] Malcolm A. Finkelman,[3] Yonglong Zhang,[3] Sivakumar Sridharan,[1,2] Enric Vilar,[1,2] Ken Farrington.[1,2] *[1]East and North Hertfordshire NHS Trust, Stevenage, United Kingdom; [2]University of Hertfordshire, Hatfield, United Kingdom; [3]Associates Of Cape Cod Inc, East Falmouth, MA.*

Background: (1-3)-β-D glucan (BDG) is elevated in ESKD in the absence of active infection. Elevated levels may reflect increased gut permeability. This study aimed to: 1. Establish differences in serum levels of BDG in controls and individuals with ESKD following an oral BDG load. 2. Evaluate relationships between fasting pre- and post-HD BDG levels and high-flux HD and HDF in a larger cohort.

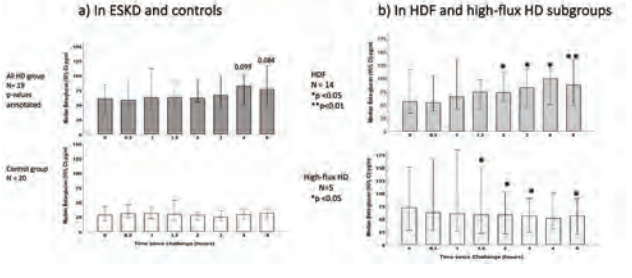
Methods: 1. 20 adults with ESKD receiving high-flux HD (n=5) or HDF (n=15) with chronic inflammation (baseline hs-CRP ≥5mg/L) and 20 controls were recruited. Following a BDG oral load, serial serum BDG levels were taken. One participant (HDF subgroup) was excluded post-hoc due to acute diverticulitis soon after study participation. 2. Fasting serum BDG samples from 443 outpatients receiving high flux-HD (n=156) or HDF (n=287) were obtained pre- and post-HD.

Results: 1. Serum BDG was higher at all timepoints in the ESKD group compared to controls. There were no differences in change from baseline BDG in either group post-BDG load (Figure 1a), but levels in the HDF subgroup were higher (Figure 1b). 2. Pre-HD fasting BDG levels were similar in high flux-HD and HDF groups (57(42) vs 64(45)pg/ml; p = 0.057). Weight, hs-CRP, and presence of diabetes and liver disease were independent predictors of pre-HD BDG. BDG levels (high flux-HD group) were similar pre- and post-HD (57(42) vs 53(53); p=0.132). In contrast, BDG levels (HDF group) were higher post-HD (64(45) vs 76.6(51)pg/ml; p<0.001).

Conclusions: BDG levels were higher at baseline in ESKD compared to controls. Following an oral BDG load, there was a significant increase in BDG levels from baseline in the HDF subgroup but not high-flux HD. Higher BDG levels were also observed post-HD in patients receiving HDF in the absence of an oral BDG load. This finding is unexpected and warrants further investigation as HDF is theoretically associated with greater haemodynamic stability and should protect against gut permeability and systemic translocation of BDG-rich material.

Funding: Other NIH Support - National Institute for Health and Care Research (NIHR) Research Capability Funding and funding from East and North Hertfordshire Hospitals Charity, Commercial Support - Associates of Cape Cod provided assays for BDG measurements gratis

Figure 1 Changes in serum beta-D-glucan levels from baseline following an oral challenge



TH-PO239

Comparison of Protein-Bound and Large Molecular-Weight Uremic Toxin Removals with Novel Super High-Flux Dialyzer between Hemodialysis (HD) and High-Volume Online Hemodiafiltration Modalities: A Cross-Over Randomized Controlled Study

Rossanun Shoosanglertwijit, Khajohn Tiranathanagul. *King Chulalongkorn Memorial Hospital Department of Internal Medicine, Bangkok, Thailand.*

Background: Protein-bound uremic toxins (PUBT) and large molecular weight uremic toxins (LMWT) are poorly removed by the standard hemodialysis (HD) using high-flux dialyzer (HF) and associated with long-term morbidity and mortality in end-stage kidney disease (ESKD) patients undergoing chronic HD. Two removal enhancing approaches including modality upgrade from HD to higher cost high-volume online hemodiafiltration (HDF) with HF or dialyzer upgrade from HF to novel super high-flux dialyzers (SHF) (such as ELISIO-21HX) with standard HD have been innovated and provide comparably improving both PUBT and LMWT removals. Whether the combined approaches, HDF using SHF, could yield additional benefit when compared with single approach, HD using SHF, were explored in the present crossover randomized controlled study.

Methods: Fourteen ESKD patients treated with HDF using HF were included. After a run-in period, the patients were randomly allocated to receive either 8-week of HDF using SHF, ELISIO-21HX, or HD using SHF as the control treatment. After a wash-out period of HDF using HF, they were crossovered to receive the other treatment for 8 weeks. The removal capacities in-term of plasma reduction ratio (RR) of PBUT (free and total indoxyl sulfate, IS) and LMWT (β2-microglobulin, kappa and lambda free light chains) as well as the adverse albumin loss in dialysate were assessed. The 8-week longitudinal changes of these plasma parameters were also compared.

Results: There was no significant reduction ratio between free and total indoxyl sulfate between SHF-HD and SHF-HDF at 8 weeks period. The reduction ratio of kappa and lambda free light chain were higher in SHF-HDF and kappa was more eliminated. There were no significant reduction ratio between β2-microglobulin and urea. There was no significant dialysate albumin loss (0.7 vs 1.2 g/session, P-value 0.14) between both groups and did not affect the serum albumin at 8th weeks.

Conclusions: SHF-HD and SHF-HDF provided comparable PBUTs removal but higher large middle molecule uremic toxin reduction. SHF-HD might be the alternative treatment for PBUTs and LMWTs removals. SHF-HDF may be an option for further LMWT (i.e. kappa and lambda FLC) removal. Longer intervention and follow up period should be further conducted.

Funding: Government Support - Non-U.S.

TH-PO240

A Randomized Trial of Middle Molecule Clearance in Patients on Chronic Hemodialysis: Results from the ROCKeT Study

Li Zuo,[1] Liangying Gan,[1] Leyi Gu,[3] Yongchun Ge,[4] Hong L. Lin,[12] Yiwen Li,[9] Fengling Chen,[7] Wenge Li,[6] Bi hu Gao,[5] Feng Ding,[8] Xinzhou Zhang,[10] Zhenwei Shi,[11] Jiayao Ji,[2] Qiang Yao,[2] Brad Keller,[2] Surupa Sarkar.[2] *[1]Peking University People's Hospital, Beijing, China; [2]Baxter Healthcare Corporation, Round Lake, IL; [3]Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, China; [4]General Hospital of Eastern Theatre Command, Nanjing, China; [5]Affiliated Zhongshan Hospital of Dalian University, Dalian, China; [6]China-Japan Friendship Hospital, Beijing, China; [7]First Affiliated Hospital of Soochow University, Suzhou, China; [8]Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Shanghai, China; [9]Zhejiang Provincial People's Hospital, Hangzhou, China; [10]Shenzhen People's Hospital, Shenzhen, China; [11]Beijng Huaxin Hospital First Hospital of Tsinghua University, Beijing, China; [12]First Affiliated Hospital of Dalian Medical University, Dalian, China.*

Background: This study aimed to establish noninferiority of λ FLC and β2M molecular clearance with HDx therapy using Theranova 400 compared to post-dilution online HDF therapy using FX800 (control arm) in Chinese patients with kidney failure.

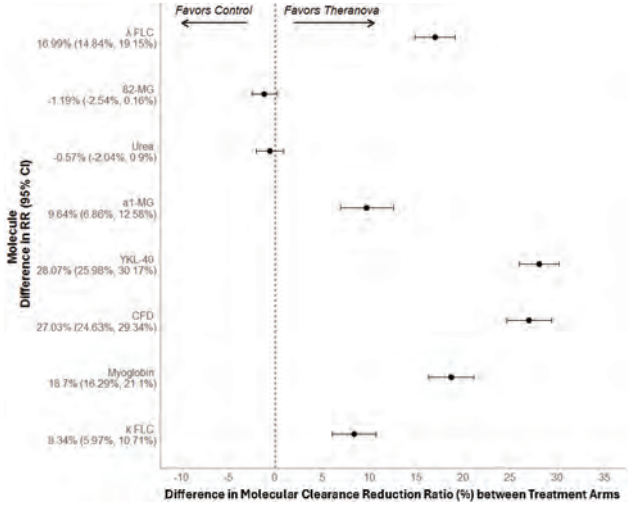
Methods: The clearance of λ FLC, β2M, urea, α1-MG, YKL-40, CFD, myoglobin, and κ FLC was measured using the reduction ratio (RR) of the molecule after treatment at the mid-week dialysis session. Kt/V_{urea} was assessed to establish dialysis adequacy. Two-sample t-tests were performed to compare the 95% CI of the difference in RRs for λ FLC and β2M in the HDx arm against predefined noninferiority margins of -3.783 and -7.848, respectively (10% of assumed mean RR). Any noninferior RRs were then tested for superiority using hierarchical testing. The safety profile of the Theranova dialyzer was also assessed.

Results: 274 adult patients receiving thrice-weekly dialysis were randomized (N=138 on HDx; N=136 on HDF). No differences were observed between the arms in terms of demographics, baseline characteristics and treatment parameters. The average utilized replacement volume in the HDF arm was 17±2.4L. The RR of λ FLC in the HDx arm was both noninferior and superior to the HDF arm; ΔRR=17.0% (14.8%,19.2%). The RR of β2M in the HDx arm was noninferior to the HDF arm; ΔRR=-1.2% (-2.5%,0.2%).

Overall, Kt/V_{urea} and urea RRs were similar between the arms (p=0.37 and p=0.45, respectively). The HDx arm had significantly higher clearance of α1-MG, YKL-40, CFD, myoglobin, and κ FLC than the HDF arm. No difference was observed in the incidence rate of complications between the arms (p=0.15).

Conclusions: Our study demonstrates the effectiveness of HDx theraphy in clearing multiple middle molecules when compared to HDF therapy, with no observed differences in the overall safety or efficacy of dialysis.

Funding: Commercial Support - Baxter Healthcare Corporation



TH-PO241

Transitioning from Frequent High-Flux Hemodialysis to Frequent Online Hemodiafiltration: Successive Paradigm Shifts towards Optimal Dialysis Therapy

Istenio Pascoal, Adolfo Simon, Vilber Bello, Kelia Xavier, Andre Fernandes, Juliane Lauar. *Centro Brasiliense de Nefrologia e Dialise, Brasilia, Brazil.*

Background: Frequent highflux hemodialysis (fHD) has improved outcomes compared to conventional thrice-weekly schedule (cHD). Likewise, thrice-weekly high-volume online hemodiafiltration has shown benefits compared to cHD. We previously established the feasibility, safety, and potential advantages of fHDF over fHD and transitioned our long-term in-center dialysis program from short daily highflux hemodialysis (SDHD) to short daily high-volume online hemodiafiltration (SDHDF). This study aims to delineate the transition process of implementing fHDF as the standard therapy in our in-center dialysis program.

Methods: We documented patient demographics including number, age, dialysis vintage, presence of diabetes, vascular access type and kidney transplantation (KTx) waitlist. The fHDF parameters encompassed 6 x 2-hour sessions/week, 350 ml/min blood flow and 500 ml/min dialysate flow. Equipment included the Aquaboss Osmosis System, BBraun Diálog+HDF and IQ-HDF Machines with Xevonta Hi23 single-use dialyzer. Anticoagulation adjustments, HDF modalities and substitution volume goals were assessed. We also analyzed this transtion's cost implications for providers and payors.

Results: In November 2023, seventy patients were switched from SDHD to SDHDF, 40Males/30Females, age 63.2±15.2 years (29-91), dialysis vintage 53.5±55.1 months (3-227), 38% diabetes, 53% AVF, 38% PermCath, 9% Graft, 44% waitlisted for KTx, 90% post-dilution HDF and 10% pre-dilution HDF due to limited blood flow rate, substitution volume aimed for post-dilution HDF: 12.5 L/2h-session (75 L/week) or pre-dilution HDF: 25 L/2h-session (150 L/week). There was a 23% mean increase in heparin doses. Cost of consumables increased about 21%, while mean reimbursement by payors increased 35.3%. In Brazil, each new HDF machine costs 4,000.00-7,500.00 US dollars more than a new HD machine.

Conclusions: The transition from in-center fHD to fHDF represents a second paradigm shift in our dialysis program (cHD to fHD was the first, in 2006). Whilst requiring comprehensive evaluation of patient demographics, treatment parameters, equipment considerations and cost implications, this successfully managed modality switch yields potential clinical benefits towards optimizing modern dialysis care.

TH-PO242

Increased Dialyzer Membrane Hydrophilicity Improves Hemocompatibility and Performance: A Randomized Investigation

Petra Ronova,[1] Maria Krizsan,[2] Bettina Griesshaber,[5] Ansgar Erlenkoetter,[7] Adam M. Zawada,[7] Robert Nitschel,[7] Bertram Ottillinger,[6] Bingbin Zhao,[3] Natalia Korolev,[5] Jennifer Braun,[5] John W. Larkin,[4] Manuela Stauss-Grabo.[5] *[1]Fresenius Nephrocare Praha 9, Praha, Czechia; [2]Péterfy II. Dialízis Központ, Budapest, Hungary; [3]Fresenius Medical Care, Beijing, China; [4]Fresenius Medical Care, Waltham, MA; [5]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [6]Ottillinger Life Sciences, Brunnthal (Munich), Germany; [7]Fresenius Medical Care Deutschland GmbH, Sankt Wendel, Germany.*

Background: Dialyzer performance and hemocompatibility can get compromised during treatment due to adsorption of plasma proteins to the membrane. Increased membrane hydrophilicity reduces membrane fouling and was implemented in the novel FX CorAL dialyzer. In a randomized trial we investigated the performance and hemocompatibility profiles of the FX CorAL dialyzer vs. two comparators during post-dilution online hemodiafiltration (HDF).

Methods: This prospective, multicentric, crossover study with 4-week randomized treatment sequences compared the FX CorAL 600 vs. FX CorDiax 600 (both Fresenius Medical Care Germany) and xevonta Hi 15 (B. Braun). Primary outcome was β2-microglobulin removal rate (β2-m RR). Secondary endpoints were RR and clearance of small and middle molecules, and intra-/interdialytic profiles of hemocompatibility markers. Further endpoints were patient reported outcomes (PROs) and clinical safety.

Results: 82 subjects (76 Intention-to-treat group) were enrolled. FX CorAL showed the highest β2-m RR (76.28%), followed by FX CorDiax (75.69%) and xevonta (74.48%), which was non-inferior to both comparators ($p<0.0001$ each) and superior to xevonta ($p<0.0001$). Secondary endpoints related to middle molecules affirmed these results; small molecule performance was comparable between dialyzers. For intradialytic hemocompatibility, the typical drop in leucocytes, monocyte, and neutrophil during dialysis as well as the rise of complement, cell and platelet activation markers were lower during treatment with FX CorAL vs comparators (Figure 1). There were no differences in interdialytic hemocompatibility, PROs, or clinical safety.

Conclusions: During HDF, the novel FX CorAL with increased membrane hydrophilicity showed high performance and a favorable hemocompatibility profile as compared to other commonly used dialyzers. Further long-term investigations are warranted to examine if the benefits of FX CorAL translate into improved cardiovascular and mortality endpoints.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH

Figure 1: Differences of hemocompatibility markers within HDF session

Activation pathway	Variable (molecular weight) [unit]	FX CorAL 600	FX CorDiax 600	xevonta Hi15	FX CorAL vs FX CorDiax	FX CorAL vs xevonta
		LS mean	LS mean	LS mean	p value	p value
Complement Activation	C3a (9 kDa)[µg/L] at 15 min-pre	15.99	42.18	37.33	0.0034	0.0287
	sC5b-9 (1000 kDa) [µg/L] at 60 min-pre	45.59	52.19	78.16	0.3371	<0.0001
Cell activation / Inflammation	Leukocytes [10^3/µL] at 15 min-pre	-0.56	-0.81	-0.67	0.0150	0.2456
	Monocytes [10^3/µL] at 15 min-pre	-0.20	-0.22	-0.25	0.5326	0.0116
	Neutrophiles [10^3/µL] at 15 min-pre	-0.15	-0.36	-0.25	0.0193	0.2576
	PMN elastase (30 kDa) [µg/L] at 60 min-pre	11.23	20.92	22.93	0.0033	0.0003
	LTB-4 (336 Da) [pg/mL] at 15 min-pre	160.6	219.4	178.4	0.0470	0.5391
PLT activation	β-TG (36 kDa) [IU/mL] at 60 min-pre	-23.6	7.6	26.3	<0.0001	<0.0001

Values indicate LS mean differences to the baseline (pre) values before the start of HDF. LS mean: Least Squares mean

TH-PO243

Middle-Molecular Weight Toxin Removal: Asymmetric Cellulose Triacetate vs. Helicoidal Polysulfone during Online Hemodiafiltration (CHORALS Study)

Marco Ferrarini,[1] Niccolò Morisi,[1] Silvia Giovanella,[1] Giulia Ligabue,[1] Gaetano Alfano,[1] Dario Troise,[2] Giovanni Stallone,[2] Gabriele Donati.[1] *[1]Universita degli Studi di Modena e Reggio Emilia, Modena, Italy; [2]Universita degli Studi di Foggia, Foggia, Italy.*

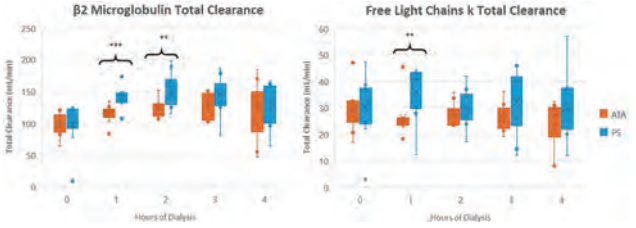
Background: Middle-molecular weight toxins (MMT) are involved in cardiovascular and neurological morbidity and in a high risk of mortality of HD patients. In this study we evaluate the efficiency of Asymmetric Cellulose Triacetate (ATA) vs Helicoidal Polysulfone (PS) in MMT removal during online hemodiafiltration (OLHDF).

Methods: Twenty anuric HD patients who needed OLHDF were selected. Ten patients underwent PS OLHDF as gold standard treatment, 10 patients underwent ATA OLHDF when a history of hypersensitivity was ascertained. B2 Microglobulin (B2M) and K light chain (Lk) were assayed hourly on blood and on spent dialysate. Total clearance (Ktot) and Sieving coefficient (S) were firstly evaluated separately through time for each filter with ANOVA. To compare Ktot and S between filters, we performed t-test on data from each hour separately and 2-way ANOVA on the whole series.

Results: No significant efficiency variation over time was observed in the ATA filter. The PS filter showed significant variation of B2M Ktot and S due to rising efficiency at the first hour (Ktot p=0.001, S p=0.001) but not in Lk. Considering the whole series, Ktot and S of B2M were significantly higher for PS ($p<0.0001$). Comparing filters, PS showed significantly higher Ktot and S after 1 hour of treatment for both B2M (Ktot p=0.001, S p=0.001) and Lk (Ktot p=0.022, S p=0.02) and after 2 hours of treatment for B2M only

(Ktot p=0.015, S p=0.008). No significant Ktot and S variation was observed between filters at other time points (Figure 1).

Conclusions: Globally, removal performance of MMT is similar for both filters tested. Given the features of ATA membrane, which is predicted to be more biocompatible for hypersensitivity prone patients, slightly lower performances are observed in the first half of treatment. As a consequence, the choice of ATA membrane should be considered suitable for MMT removal in patients with hypersensitivity.



p<0.05 (**); p<0.01 (***)

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani
UNIMORE

TH-PO244

Use of the Seraph 100 Dialysis Filter in a Patient with Toxic Shock Syndrome from Streptococcus pyogenes Bacteremia

Hernan Rincon-Choles, Sunny R. Parmar, Sydney Moseley. *Cleveland Clinic, Cleveland, OH.*

Introduction: The Seraph 100 Microbind Affinity Blood Filter (Seraph 100) is a hemoperfusion dialysis filter which employs pathogen adsorption therapy using heparin-coated polyethylene beads. Data exists supporting its effectiveness among COVID-19 patients where the filter was allowed under emergency use authorization by the FDA. It has been shown to bind various pathogens (with affinity for streptococcus pyogenes (GAS)), endotoxins and cytokines, allowing their removal from the bloodstream.

Case Description: A 26 year-old female who gave birth four days prior was admitted to the intensive care unit with high fevers and septic shock requiring 3 vasopressors causing severe lactic acidosis (to 11.6 mmol/L). For GAS bacteremia causing toxic shock syndrome (TSS) she received meropenem, clindamycin, and vancomycin. She suffered necrosis of her nose, fingers and toes as well as disseminated intravascular coagulation (DIC). She also suffered anuric renal failure requiring continuous renal replacement therapy (CRRT). Five days into hospitalization, despite emergent hysterectomy for source control, intravenous hydroxycobalamin, and methylene blue, she still required 3 vasopressors for persistent shock. The Seraph 100 filter was obtained and was installed in series with an M100 filter in a PrismaFlex dialysis machine. The day after installation, her shock completely resolved, then enabling fluid removal with CRRT and initiation of feeding. With shock resolved, her necrotic lesions showed some improvement and did not auto-amputate. Additionally, her DIC improved which enabled her to be treated with heparin for thrombi in distal extremities. Each night, clotting of the Seraph 100 filter would require its replacement the following day; in total 8 filters were used.

Discussion: This case demonstrates use of the Seraph 100 filter in a patient suffering from persistent GAS-related TSS after source control. By improving rapidly she avoided further complications of shock, including worsening of necrosis which may be attributed to vasopressor induced acute limb ischemia, as well as improved ultrafiltration enabling weaning off mechanical ventilation. No clear adverse events were attributed to use of this filter. Given the high mortality rate associated with TSS, future studies should evaluate for this filter's efficacy in improving outcomes for such patients.

TH-PO245

Changes in Coronary Artery Calcification Score in ESKD: Comparison of Hemodialysis and Online Hemodiafiltration

Toshiki Doi,[1,2] Kenichi Morii,[1,2] Aiko Okubo,[1] Sonoo Mizuiri,[1] Yoshiko Nishizawa,[1] Takao Masaki.[2] *[1]Iryo Hojin Ichiyokai Harada Byoin, Hiroshima, Japan; [2]Hiroshima Daigaku Byoin, Hiroshima, Japan.*

Background: It has been shown that high-dose hemodiafiltration (OHDF) reduces the risk of all-cause mortality compared to conventional high-flux hemodialysis (HD) (N Engl J Med. 389: 700, 2023). The primary reason for this reduction was a decrease in infections. Still, there are also many reports that OHDF reduces the risk of cardiovascular death, a significant cause of mortality in dialysis patients, compared to HD (Nephrol Dial Transplant. 31: 978, 2016) (Cochrane Database Syst Rev. 2015: CD006258, 2015). The coronary artery calcification score (CACS), measured by multi-slice CT, has significant evidence linking it to cardiovascular events, and its usefulness has been reported in dialysis patients (Clin Exp Nephrol. 8: 54, 2004). In this study, we compared changes in CACS between standard HD treatment and OHDF treatment in maintenance dialysis patients.

Methods: A retrospective cohort study was conducted on hemodialysis patients who underwent CACS evaluation using CT at our institution from January 2018 to February 2021. Patients who did not undergo re-evaluation after one year and those with a logarithmically transformed initial Agatston CACS of less than 100 were excluded. The patients were classified into the HD treatment group and the OHDF treatment group. Propensity score matching was performed based on age, sex, dialysis vintage, presence of diabetes, Ca, P, Mg, TSAT levels, and initial Agatston CACS. The aim was to examine whether there was a difference in the change rate of the Agatston CACS after one year between the HD and OHDF groups. The data were presented as medians and interquartile ranges, and JMP16 was used for analysis. Pearson's chi-square and Mann-Whitney U tests were used for statistical testing.

Results: Of the 560 patients who underwent CACS evaluation during the study period, 263 were included in the study. Through propensity score matching, 49 patients were selected for each group. No significant differences were observed in the baseline characteristics between the groups. The median increase rate of the Agatston CACS after one year was 15.8% (interquartile range 3.2 - 37.2) in the HD group and 6.6% (0.6 - 17.2) in the OHDF group (p = 0.02).

Conclusions: OHDF may suppress coronary artery calcification compared to HD in patients with end-stage renal disease.

TH-PO246

Hemoperfusion Is Associated with Reduced Mortality in Outpatient Maintenance Hemodialysis Patients with COVID-19

Wenjun Lin. *Department of Nephrology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.*

Background: High mortality rates have been observed in patients with COVID-19 undergoing maintenance hemodialysis, potentially attributable to exacerbated inflammatory responses. Hemoperfusion, a therapeutic technique based on adsorption for removing inflammatory mediators, presents a promising therapeutic approach. However, its efficacy in improving outcomes for this patient population remains to be established.

Methods: This was a single-center retrospective cohort study conducted from December 7, 2022, to May 24, 2023, following the cancellation of the 'Dynamic Zero-COVID' policy during the Omicron variant surge. Patients with COVID-19 were stratified based on their hemoperfusion treatment status. We investigated all-cause mortality as the primary outcome, using adjusted Cox regression analysis. The risk of hospitalization, our secondary outcome, was examined through logistic regression models.

Results: Among the 224 patients who met the eligibility criteria, 118 (52.7%) underwent hemoperfusion treatment. The cohort's mean age was 62.8 ± 13.1 years, predominantly male (71.0%), with 89.3% lacking prior immunity to SARS-CoV-2. Over a 120-day follow-up, 25 patients succumbed, with mortality rates of 18.9% (20 patients) in the control group compared to 4.2% (5 patients) in the hemoperfusion group (p=0.001). Hemoperfusion was significantly associated with a reduced risk of all-cause mortality (HR, 0.234; 95% CI, 0.079 to 0.696; p=0.012) and hospitalization (OR, 0.423; 95% CI, 0.196 to 0.917; p=0.029), compared to controls. Additionally, the hemoperfusion group exhibited significantly lower mean changes in CRP, D-dimer, and serum ferritin levels than the control group within one month after COVID-19.

Conclusions: Hemoperfusion treatment in patients with COVID-19 on maintenance hemodialysis was linked to a decreased risk of all-cause mortality and a reduced in early inflammatory markers. These findings suggest that hemoperfusion may be a beneficial therapeutic strategy for COVID-19 management in the hemodialysis population, meriting further exploration.

TH-PO247

Evaluation of the Performance of the HA130 Hemoperfusion Cartridge in Patients Treated with Postdilution Hemodiafiltration (HDF): A Comparative Study with HDF Online Alone

Matteo Floris,[1] Alice Atzeni,[1] Claudia Puddu,[1] Giulia Spanu,[1] Cristina Pani,[1] Francesco Trevisani,[2] Andrea Angioi,[1] Nicola Lepori,[1] Gianfranca Cabiddu,[1] Antonello Pani.[1] *[1]Azienda Ospedaliera Brotzu, Cagliari, Italy; [2]IRCCS Ospedale San Raffaele, Milano, Italy.*

Background: Adsorption is a new frontier in extracorporeal purification for continuous and intermittent RRT. Evidence mainly comes from its use with bicarbonate dialysis. As OL-HDF is the new standard, we explored its benefits in HDF. This pilot study assesses the efficacy, safety, and tolerability of the HA130 cartridge with HDF-POST, compared to HDF alone.

Methods: Ten ESRD patients with AVF were treated with hemoperfusion using the HA-130 cartridge in series with POST-HDF with a TCA membrane (Solacea™ 1.7 and 1.9), reaching a 23 L x 1.73 m^2 exchange volume. A control group of ten similar patients received POST-HDF with the Solacea filter alone. Removal rates (RR) for various markers were evaluated and corrected for hemoconcentration. Session tolerability was assessed by monitoring intradialytic symptoms and circuit coagulation.

Results: For the HA130 + Solacea group, the exchanged infusion volumes were 22.9 ± 1L. The treatment was generally well tolerated without significant intradialytic symptoms or circuit coagulation. For the Solacea alone group, the exchanged infusion volumes were 23 ± 1L. The treatment was also well tolerated without significant intradialytic symptoms or circuit coagulation. The RR data for both groups are reported in Table 2 and Figure 1.

Conclusions: The combined HDF-POST + hemoperfusion treatment demonstrated superior depurative efficacy with high RRs for medium and high molecular weight molecules compared to the Solacea filter alone. The high tolerability and absence of significant complications during HDF-POST sessions highlight the potential of this technological combination in high-efficiency RRT settings.

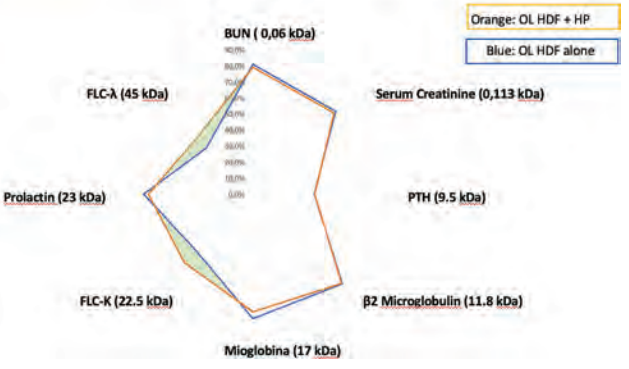
Table 1. Treatment characteristics

Parameter	HA130 + Solacea	Solacea Alone	p-value
Qb [ml/min]	345	350	ns
Qd [ml/min]	415	420	ns
Duration [min]	240	240	ns
Weight loss [kg]	2.4	2	ns
Baseline Urea [mg/dL]	72.1	69.5	ns
Baseline Creatinine [mg/dL] (0.013 KD)	9.41	8.47	ns
Baseline PTH [pg/ml] (9.5 KD)	365.15	332.67	ns
Baseline β2-microglobulin [mg/L]	28.91	27.85	ns
Baseline Myoglobin [µg/L]	174.5	127.5	ns
Baseline FLC-κ [mg/L] (22.5 KD)	162.1	177.5	ns
Baseline Prolactin [ng/ml] (23 KD)	14.95	28.16	ns
Baseline FLC-λ [mg/L] (45 KD)	103.82	127.93	ns
Baseline Albumin [g/dL] (60 KD)	3.81	3.53	ns

Table 2: RR Parameters

RR Parameter	HA130 + Solacea (%)	Solacea Alone (%)	p-value
Urea [mg/dL] (0.06 KD)	79	81	0.136
Creatinine [mg/dL] (0.013 KD)	72	73	0.405
PTH [pg/ml] (9.5 KD)	39	38	0.286
β2-microglobulin [mg/L] (11.8 KD)	79	79	1.000
Myoglobin [µg/L] (17 KD)	64	78	0.001*
FLC-κ [mg/L] (22.5 KD)	60	50	0.016
Prolactin [ng/ml] (23 KD)	65	68	0.204
FLC-λ [mg/L] (45 KD)	50	41	0.008*
Albumin [g/dL] (60 KD)	1	0	0.317

Figure 1: RR of Uremic Toxins



TH-PO248

Hemodialysis Coupled with Hemadsorption: Benefits on Uremic Toxins Retention and Oxidative Stress

Matteo Marcello,[1] Grazia Maria Virzì,[1] Vincenzo Cantaluppi,[2] Alessandra Brendolan,[1] Claudio Ronco.[1] *[1]Ospedale San Bortolo di Vicenza, Vicenza, Italy; [2]Universita degli Studi del Piemonte Orientale Amedeo Avogadro Scuola di Medicina, Novara, Italy.*

Background: Retention of middle-molecules and Protein Bound Uraemic Toxins (PBUT) in dialysis patients increases morbidity and mortality. Current dialysis techniques do not adequately clear these toxins. Furthermore, in dialysis patients, there's an increased inflammation and oxidative stress only partially attenuated by biocompatibility of newly developed membranes. This pathologic inflammatory response is associated to a particular form of programmed cellular death involving red blood cells, called Eryptosis. This study aimed to assess the safety of dialysis coupled with hemadsorption (HA+HD) in terms of biocompatibility and efficacy in terms of removal of middle-molecules and PBUTs.

Methods: This analysis of a multicentre observational study evaluated 4 dialysis sessions focusing on 7 chronic dialysis patients of our dialysis center. Patients were treated with HA+HD with HA130 cartridge (Jafron) in the early-week dialysis session and then returned to their usual prescription. Blood samples were taken before and after the dialysis session to measure Eryptosis as a marker of biocompatibility and a few uremic toxins to assess the efficacy of the treatment by using Removal Ratio.

Results: This study was carried out on 7 patients (4 women) with a mean age of 65.7 ± 11.5 years and a median dialysis vintage of 33 months (IQR 28-51). All patients had AVF with Qb of 330 ml/min. Dialysis lenght was 210 minutes. We didn't find any differences between Eryptosis values measured before and after dialysis (Table 1), and between different timepoints. We found significant reduction of PTH (pre: 391.5 ng/L, IQR 206.5-602.8 vs post: 162.0 ng/L, IQR 95.0-363.3; p=0.005) and β2-microglobulin (pre: 23.10 mg/L, IQR 22.1-24.1 vs post: 6.72 mg/L, IQR 6.2-8.3;p>0.005) throughout the HA+HD session.

Conclusions: We found that the addition of Hemadsorption allows a great removal of middle molecular-weight uremic toxins without compromising biocompatibility and thus represents a better treatment option in patients with high retention of these toxins.

Eryptosis values pre and post dialysis session

	pre	post	p
session 1	0.40, IQR 0.3-0.55	0.25, IQR 0.2-0.38	0.31
session 2	0.20, IQR 0.2-0.35	0.30, IQR 0.2-0.4	0.37
session 3	0.20, IQR 0.2-0.45	0.40, IQR 0.25-0.55	
session 4	0.30, IQR 0.15-2.9	0.20, IQR 0.15-0.35	

TH-PO249

Molecular Adsorbent Recirculating System (MARS) in Pediatric Patients

Kenneth M. Delgado, Kelli A. Krallman, Stuart Goldstein, Francisco X. Flores. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

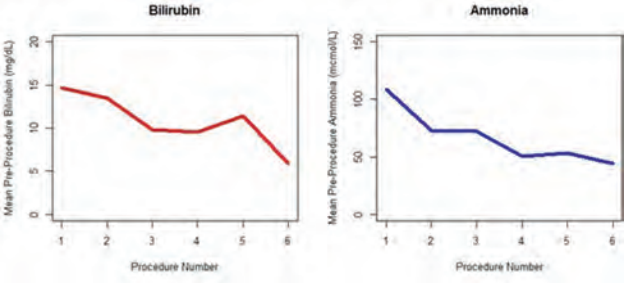
Background: The Molecular Adsorbent Recirculating System (MARS®) uses an albumin enriched dialysis solution to remove protein-bound molecules that are not removed by conventional renal replacement therapy. Its use was approved in the United States for management of drug overdose and intoxication. Other proposed indications include acute liver failure and Data regarding the efficacy of MARS® in pediatric patients remain scarce.

Methods: Retrospective analysis of patients who received MARS® therapy at Cincinnati Children's Hospital Medical Center between January 1st, 2018 and November 30th, 2020. Collected data included age, sex, laboratory data, medical history, vascular catheter size, specifics of therapy, complications, and outcomes. Data existing in the electronic medical record were transcribed by investigators into a secure database.

Results: 17/25 patients demonstrated at least one sign of clinical improvement. 13/22 patients experienced improvement in encephalopathy. 6/20 patients demonstrated hepatic recovery. 6/18 patients experienced renal recovery. 4/21 patients underwent liver transplant. 16/25 patients survived until ICU discharge. Youngest patient to receive MARS® was 29 days old. Lowest weight was 2.1 kilograms.

Conclusions: We provide data on pediatric patients receiving MARS® at a high-volume tertiary care center. To our knowledge, this is the largest study on pediatric MARS® to date. We plan to expand this analysis to include data from 2014 – 2018 and 2020 – 2024.

Demographics	Media(IQR) or N
Unique Patients	23
Courses of Treatment	25
# of Procedures	83
Age	13.2 years (3.8, 17.9)
Weight	41.7 kg (18.6, 60.3)
Sex	Males: 12 Females: 13
Invasive Mechanical Ventilation at Initiation	Yes: 14 No: 10
Multiorgan Dysfunction at Initiation	Yes: 21 No: 4
CRRT at Initiation	Yes: 17 No: 8
Anticoagulation	Citrate: 57 Heparin: 18 None: 8



TH-PO250

Innovative Microfluidic Dialyzer: Redefining Care for Patients on Dialysis

Daniel R. Greene, Saeed Moghaddam. *University of Florida, Gainesville, FL.*

Background: Development of a miniature dialyzer can benefit patients with kidney failure, especially infants and patients that perform in-home low-flow-rate dialysis. Despite a few decades of research, an alternative to the existing bulky dialyzers has remained elusive. Here, a breakthrough microfluidic dialyzer with an order of magnitude smaller size and blood compartment volume compared to the existing dialyzers is presented.

Methods: A miniature microfluidic dialyzer (MD) has been developed and its hydrodynamics and sieving characteristics have been analyzed through comprehensive numerical and experimental studies. An iterative design process has been pursued to minimize the dialyzer pressure drop well below that of the existing dialyzers such that it could also be operated with the arterial blood pressure. Measurements at different flow rates and urea removal under static and variable hemodynamic conditions have been performed, aimed at characterizing the device performance and control measures for reliable dialysis.

Results: The new dialyzer has a blood compartment volume of 16.3 mL substantially smaller than ~100 mL blood volume of the current dialyzers. It operates on a reduced blood flow rate of 100 mL/min compared to the typical 300-500 mL/min practiced in conventional dialyzers as planned for eventually targeted patient groups. A dialyzer with a pressure drop of 6.2 ± 1.4 mmHg has been developed for a blood flow rate of 100 ml/min. This pressure drop is an order of magnitude less than that of a conventional dialyzer with a pressure drop of 31.1 ± 3.4 mmHg, tested under identical conditions. The urea sieving coefficient of the developed microfluidic dialyzer is 0.74, only marginally lower than that of a conventional dialyzer of 0.83 measured under identical conditions. The accompanying numerical models for pressure drop and urea removal predicted the outcomes of the tests.

Conclusions: The innovative microfluidic dialyzer represents a significant advancement in dialysis technology, offering a smaller size, lower pressure drop, and comparable urea removal efficiency compared to conventional dialyzers. This breakthrough has the potential to greatly benefit patients with kidney failure, particularly infants and those requiring in-home low-flow-rate dialysis.

Funding: NIDDK Support

TH-PO251

Intradialytic Microvascular Tissue Perfusion Is Affected by Dialyzer Membrane Characteristics

Barry Janssen,[1,2] Yanmin Zhang,[2,1] Lisa Hur,[1,2] Alireza Akbari,[1,2] Christopher W. McIntyre.[1,2] *[1]Lawson Health Research Institute, London, ON, Canada; [2]Western University, London, ON, Canada.*

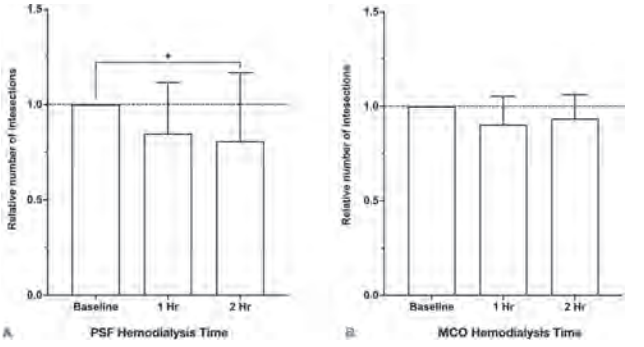
Background: During hemodialysis (HD), microvascular perfusion in tissues and organs is often compromised. The role of dialyzer clearance characteristics and general biocompatibility in this process is unknown. This study compared the effects of HD using either conventional high flux polysulfone (PSF) or newer mid-cut-off (MCO) dialyzers (characterized by an extended clearance spectrum into the middle molecule range) on microvascular perfusion in an established rat model of HD. We hypothesize that using different dialyzer membranes will result in different microvascular responses, affecting the quality of tissue blood flow.

Methods: HD using in-house-designed mini-dialyzers was performed on male Wistar Kyoto rats, and microvascular perfusion in skeletal muscle was observed using intravital video microscopy. A carotid catheter was used for hemodynamic monitoring, while indwelling catheters in the left femoral artery and left femoral vein were connected to the mini-dialyzer. Blood samples were taken for biochemical analysis, a C5b-9 ELISA assay and hematocrit determination to ensure the procedure was euvolemic.

Results: HD using PSF dialyzers significantly reduced microvascular muscle perfusion, unlike the MCO dialyzers (Fig 1). Blood pressure reduction was similar between the two groups, with a better conservation of the cardiac response in the MCO group. There were no differences in small solute clearance or circulating electrolyte levels. Analysis of [C5b-9] plasma levels shows significantly higher levels after a two-hour HD procedure with PSF dialyzers.

Conclusions: Our analysis indicates that the separate effects of the different dialyzers on microvascular perfusion may be related to differences in complement activation. The exact mechanisms underlying these differences warrant further study. This small animal model allows us to preclinically evaluate membrane materials and dialyzer designs, facilitating the design of subsequent human studies.

Funding: Other NIH Support - Lawson Health Research Fund I.R.F. #: 20-18; New Frontiers in Research Fund NFRF-E-2019-01285; MITACS IT24035., Commercial Support - Baxter International



TH-PO252

A Novel Anticoagulation-Free Hemodialysis Paradigm: A Second-Generation Hemodialysis Filter Rotator Prototype Using the NxStage Machine Is Ready for Clinical Trials

Macaulay A. Onuigbo. *The University of Vermont Medical Center, Burlington, VT.*

Background: There is a critically unmet need for a new method of anticoagulation-free hemodialysis (AFHD). Current alternatives are often ineffective, expensive, technically challenging and/or with potential serious adverse effects. In the 2021 Mayo Clinic Proceedings Innovations Quality Outcomes journal, we described the 'Locke-Onuigbo maneuver', a new original hemodialysis filter rotational approach to achieve AFHD using the NxStage HD machine. We completed the design and development of an advanced second-generation HD filter rotator (HDFR) prototype in 2023.

Methods: This was a Capstone Project from "bedside to manufacture" translational research utilizing the 'Locke-Onuigbo maneuver'.

Results: In 2023, we completed the design and development of an advanced second-generation HDFR prototype that is now ready for clinical testing (Figures). These Youtube links show some of the demonstrations: https://www.youtube.com/watch?v=nCDraOlZZF8 and https://youtube.com/shorts/ncR3VieJkEY?feature=share.

Conclusions: There is a long overdue imperative for a robust, safe, and sustainable modality for AFHD. Our second-generation HDFR prototype with its enhanced new features of increased resilience, longer running times, enhanced angle and speed consistency, improved ergonomics, solid state sensors for temperature and angle fidelity verifications, and an accompanying user-friendly versatile smartphone App with Bluetooth Connectivity to facilitate ease and convenience of monitoring and control of the HDFR, is the solution for this long overdue imperative for anticoagulation-free hemodialysis. It is ready for clinical testing.

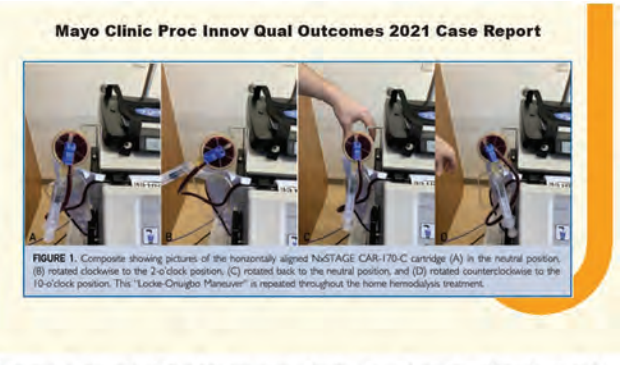


Figure 1: The "Locke-Onuigbo Maneuver", Mayo Clinic Proc Innov Qual Outc, 2021

Excerpt - 2021 Mayo Clin Proc Innov Qual Outcomes article

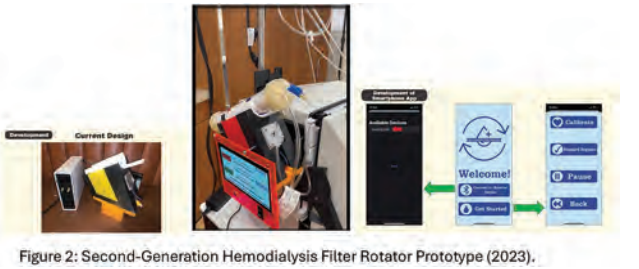


Figure 2: Second-Generation Hemodialysis Filter Rotator Prototype (2023).

The second HDFR prototype from 2023

TH-PO253

New Kirpa Kit: A Manual Dialysis Device for Low- and Middle-Income Countries in Catastrophic Environments

Lilia M. Rizo Topete, Paola Borbolla-Flores, Mara C. Olivo Gutierrez, Juan P. Gomez Villarreal, Ricardo A. Garza Treviño, Sofia Lopez-Guzman. *Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico*.

Background: Alarming data about the increased incidence of acute kidney injury (AKI) in low- and middle-income countries around the globe is a trigger to research. While much is being done to prevent AKI, we must also investigate easy and economic options for renal replacement therapy (RRT) in resource-limited environments. After *in vitro* experiments showed promising results, we decided to join forces with Dialysis Without Borders to find a way to help these vulnerable populations.

Methods: Last year we witnessed in our hospital increased incidence of AKI from heatwave. We commonly treat patients who present late to care because they live in low-resource, rural settings or even un urban Mexico. To improve treatment options, we look forward to using a manual dialysis equipment for acute ultrafiltration, and if necessary, hemodialysis to treat life threatening conditions, as a temporary treatment or bridge to the treatment needed.

Results: We introduce the KIRPA Kit, a manual dialysis device without the need for electricity, at very low cost. We can draw out blood (60 ml) from the patient via the bypass line into Syringe 1. Then the blood will be pushed out of the syringe through the filter and be returned to the patient. While the blood passes through the filter, the dialysate (for purposes of HD) will come from the syringe 3 through the filter. While for the ultrafiltration, this will get to the effluent bag through the syringe 2. There is a syringe that acts as a deaeration chamber located proximal to the patient that may serve to pull off any air bubbles visualized in the circuit (syringe 4).

Conclusions: It is quite important the learning and training before the use of KIRPA in humans. Although it is simple and quickly. The manual dialysis may serve as a future tool for patients without timely access to necessary RRT. It is a new and innovative therapy for clinical scenarios where deficiencies, sometimes even of light, wreak havoc on patients with fluid overload or require RRT.

TH-PO254

Pseudo-Blood Leak Alarm and Pseudo-Lactic Acidosis: A Hydroxocobalamin-Ethylene Glycol Combination

Nathaniel Leonardi, Jonathan Hall, David A. Mcmillan, Ryan Mullane. *University of Nebraska Medical Center, Omaha, NE*.

Introduction: Blood leak alarms exist on intermittent hemodialysis machines to prevent contaminated blood from returning to the patient when errors occur. While the risk of this occurring is low, hydroxocobalamin has been linked with causing pseudo-blood leak alarms. Ethylene glycol intoxication, while deadly, has been associated with pseudo-lactic acidosis on whole blood analysis. We present a case of a pseudo-blood leak and pseudo-lactic acidosis from hydroxocobalamin and ethylene glycol.

Case Description: A 23-year-old female presented to the hospital for encephalopathy. Initial labs revealed: potassium of 6.5 mmol/L, chloride of 112 mmol/L, bicarbonate of 5 mmol/L, Blood Urea Nitrogen of 11 mg/dL, and serum creatinine of 1.11 mg/dL. Venous blood gas revealed a pH of 6.8 and pCO2 of 21. The whole blood analysis lactate was 26 mmol/L; however, serum lactate was 2.4 mmol/L. Due to concern for acute cyanide ingestion, the patient was given hydroxocobalamin. Serum osmolality was 326 mOSM/KG, with an osmolar gap of 29. Ethylene Glycol level was 31 mg/dL. Urine microscopy revealed calcium oxalate monohydrate crystals. Given acute intoxication with ethylene glycol, fomepizole was administered, and intermittent hemodialysis was initiated with a Fresenius 2008T hemodialysis machine. A blood leak alarm then occurred. A second Fresenius 2008T was used, however a recurrent blood leak alarm triggered. The patient was transitioned to continuous kidney replacement therapy with NxStage, which functioned appropriately. The patient survived and was weaned from kidney replacement therapy.

Discussion: This case presents a phenomenon of hydroxocobalamin-induced blood leak alarms in certain intermittent hemodialysis machines. Given the increase in use of hydroxocobalamin, as it is deemed a safe treatment for cyanide poisoning, treatment of other toxic ingestions with dialysis may be impacted. This may lead to a delay in appropriate treatment for toxic ingestions as it may disrupt the ability to start clearance of toxins by dialysis. Pseudo-lactic acidosis can occur during ethylene glycol breakdown and excretion, as glycolic acid is created. Glycolic acid is reported as lactic acid on whole blood analysis, causing a pseudo-lactic acidosis, which is not present when measured in serum lactic acid levels.

TH-PO255

Innovation in Dialysis: Air Trap Level Management

Stephanie Wall, Vitas B, Emiline Victoria Hernandez, Nicholas Hyun, Clayton Poppe, Osman Khawar. *Diality, Inc., Irvine, CA.*

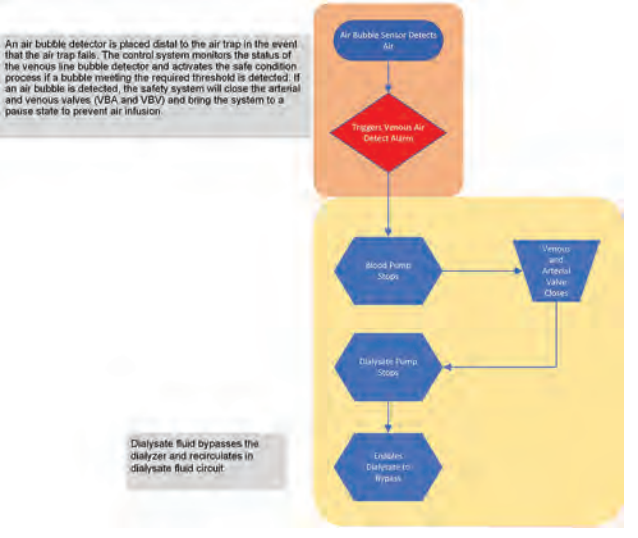
Background: Millions with end-stage kidney disease rely on hemodialysis, making the safety of dialysis devices crucial. Air traps in these devices prevent air embolism by removing air bubbles. However, traditional air traps often fail to remove all air, detect microbubbles, or operate autonomously thus increasing the risk for care disruptions and complications.

Methods: The Moda-flx Hemodialysis System™ uses a dual mechanism to manage air infusion. The primary system includes an air trap/drip chamber with a level control system. Additionally, a venous air sensor detects air downstream of the air trap. This design ensures introduced air is vented or detected before reaching the patient. Testing scenarios use Dialin to simulate air bubbles in various operational modes. System performance and fault conditions are evaluated at low, moderate, and high rates of continuous air infusion. See Figure 1.

Results: At low air infusion rates, the system vents excess air, preventing air from entering the venous line. At moderate rates, if the blood level in the air trap doesn't recover quickly, the system triggers an alarm, stops the blood pump, and clamps the venous line. At high rates, rapid blood level drops prevent quick venting, allowing air into the venous line. The system triggers an alarm, stops the blood pump, clamps the venous line, and activates dialysate bypass. Comprehensive testing confirms Moda-flx effectively manages air infusion at all rates.

Conclusions: The Moda-flx Hemodialysis System™ introduces an innovative approach to air trap management, significantly enhancing patient safety in dialysis treatments. The primary air trap level control system maintains optimal blood levels within the air trap and is complemented by a secondary venous air bubble detection system, ensuring comprehensive risk mitigation. This dual mechanism represents advancements in dialysis device design, ensuring reliable protection in all conditions.

Funding: Commercial Support - Diality



TH-PO256

Enhanced Dialysis Efficiency through Reverse Filtration in a Novel Single-Needle Dialysis System: A Pilot Study

Hideki Kawanishi.[1,2] *[1]Tsuchiya Sogo Byoin, Hiroshima, Japan; [2]Akane-medical Corporation Tsuchiya General Hospital, Hiroshima, Japan.*

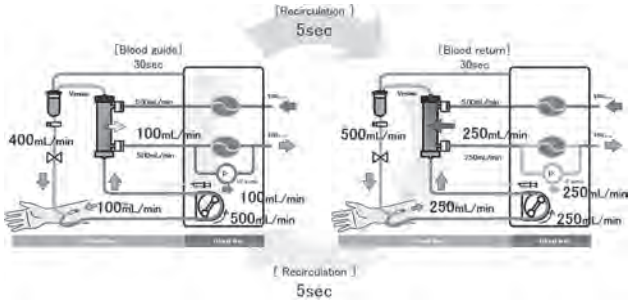
Background: As the population of elderly dialysis patients increases, addressing vascular access issues becomes paramount. The single needle dialysis system (SN) has emerged as a potential solution, yet its efficacy is hampered by inadequate blood flow and recirculation. This study introduces a novel approach utilizing reverse filtration to enhance solute removal efficiency in single needle dialysis (NSN).

Methods: Building upon automated dialysis principles (on-line HDF system, GG-X01, JMS, Co. Japan), the system alternates between ultrafiltration and reverse filtration to optimize treatment outcomes The process of NSN repeats itself: guiding circulating, returning and circulating of blood. Blood is constantly circulated, and during the guiding process, the ultrafiltration pump is rotated to filter the blood until a set amount of guiding is

achieved. Subsequent circulation agitates the blood in the circuit and diffuses substances. In the return phase, the ultrafiltration pump is reversed and returned to the circuit (Figure). A two-armed crossover pilot study of NSN vs SN involving five patients evaluated the system's efficacy compared to conventional methods. Dialysis efficiency was evaluated by measuring the solute of urea, and β2microglobulin (BMG) removal rate (RR), the amount removal volume (RV) into the spend dialysate and Kt/Urea.

Results: Blood flow rate 250mL/min, Dialysate flow rate 500mL/min, 4 hour and dialyzer NVF26H (Tore Co, Japan) were sated. Mean Kt/Vurea 1.26, RR (urea 66.3, BMG 70.2%) and RV(urea 8.4g, BMG 23.5mg) at NSN, an increase over SN was obtained.

Conclusions: Newly development of single needle system used reverse filtration creased dialysis efficiency, especially for middle molecule. However, further study is needed to improve the efficiency of the system.



TH-PO257

Dynamic Patient-Reported Outcome Measures Evaluate Durability of Expanded Hemodialysis on Health-Related Quality of Life (HR-QoL) and Symptom Variability

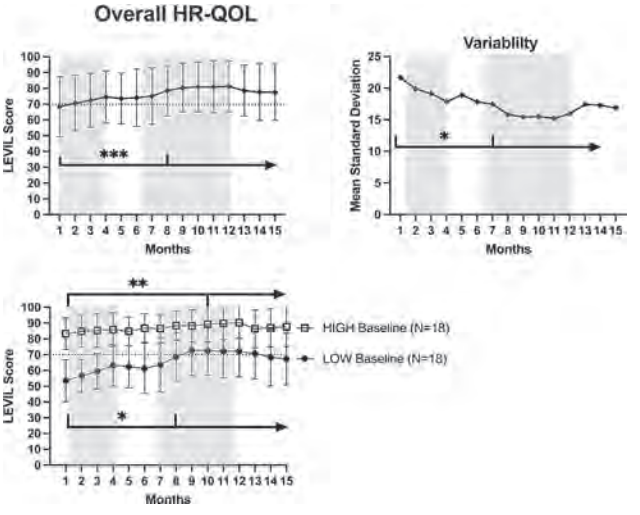
Jarrin D. Penny,[1,2] Christopher W. McIntyre.[1,2] *[1]London Health Sciences Centre, London, ON, Canada; [2]Lawson Health Research Institute, London, ON, Canada.*

Background: Current hemodialysis (HD) utilizing high-flux dialyzers, is handicapped by clearance limitations contributing to poor health-related quality-of-life (HR-QoL) and symptom-burden. Recent international guideline-setting efforts have prioritized identification and management of symptoms and subjective experience. This study aimed to utilize dynamic patient-reported-outcome-measurement tool (PROM), London Evaluation of Illness (LEVIL), to iteratively interrogate patient-experience and benefits of the use of expanded hemodialysis (HDx) on HR-QoL and symptom burden, including durability-of-effects, variability of symptoms and impact of HDx withdrawal.

Methods: Multi-centre interventional study in 47 patients established on conventional thrice weekly centre-based HD in Ontario, Canada. Study was 15-months with five phases 1) one-month observation (high-flux-HD), 2) three-months HDx 3) two-month wash-out (high-flux-HD), 4) six-months HDx, 5) three-month wash-out (high-flux-HD). HR-QoL and symptom-burden were evaluated using LEVIL throughout study.

Results: HDx-therapy improved HR-QoL p 0.0006 (19%) and a variety of symptoms including general wellbeing p 0.005 (23%), energy p 0.004 (33%), sleep-quality p 0.001 (33%), pruritus 0.003 (30%), pain p 0.01 (19%), restless leg syndrome p 0.0006 (15%), mood p 0.02 (12%), appetite p 0.03 (9%), breathlessness p 0.001 (9%), and HD-recovery p 0.004 (26%). Response was more pronounced in those with poorer HR-QoL and higher symptom-burden. Improvements were durable over time with less symptom-variability. Improvements diminished with return to high-flux-HD. Drivers of poor HR-QoL were general-wellbeing, energy, sleep-quality, pruritus, and bodily pain.

Conclusions: Dynamic PROM effectively evaluates HR-QoL and impact of therapy. HDx improved subjective outcomes that are durable and associated with less variation in important symptomx than patients experience with conventional high-flux-HD.



TH-PO258

Clinical Evidence of Frequent Home Hemodialysis Therapy in the Gulf Cooperation Council (GCC) Countries: A Preliminary Study of a Unique Experience

Satarupa Gogoi. *HHD Home Healthcare LLC, Dubai, United Arab Emirates.*

Background: Frequent home hemodialysis is more prevelant and in trend as one of the practical dialysis treatment option. Nurse Assisted Home Hemodialysis (NAHHD) treating active, autonomous, and relatively, healthy dialysis patients and mostly debilitated and frail patients with comorbidities at home and long-term care facilities. Presenting clinical outcomes of Home Hemodialysis treatment, at HHD, service provider in the GCC.

Methods: This is a prospective observational study including 447 patients undergoing frequent home hemodialysis treatment, for more than 3 months with a portable HD machine at home. Patients received adequate frequent dialysis with average 4 sessions/ week (min-3.5; max-5). Estimated the HD adequacy and key performance indicators (KPI) with a target standardised KT/V ≥2.1.

Results: A study group of 477 patients (>3months on HHD). Female- 53% and Male- 47%. The mean average age of the patients, 68.11 ± 15.96 (17 ≤ X ≤ 108 yrs.). The average comorbidities: 6.3 ± 3.45 (Min-2, Max-14). The vascular access: AVF/ AVG- 39.6%, PC- 60.4%. One year average of the biological KPI with HD adequacy are shown in Table 1.

Conclusions: Patients treated with frequent home hemodialysis showed better clinical health outcomes and better quality of life with more energy, better sleep, flexibility in active schedule and feeling more in control. Considering the outcomes of the presented data, frequent home hemodialysis can deliver much beneficial experience.

TABLE 1: HD ADEQUACY & BIOLOGICAL OUTCOMES

HD ADEQUACY	YEARLY AVERAGE
Session Length (minutes)	223.70
Number of Sessions/Week	4.00
Filtration/Flow Fraction (FF%)	55.89
Dialysate Volume (L)	32.46
Blood Flow Rate mL/min	309.92
Post weight (Kg)	65.52
UF Volume (L)	2.32
HB (g/L)	108.50
Albumin (g/L)	37.43
Serum Calcium (mmol/L)	2.51
PO4 (mmol/L)	1.66
K (mmol/L)	4.95
PTH (pg/mL)	421.33
Std Kt/V	2.27

TH-PO259

Longitudinal Assessment of Clinical Outcomes for Transitional Care Units

Derek M. Blankenship, Michael A. Kraus. *Fresenius Medical Care Holdings Inc, Waltham, MA.*

Background: Transitional Care Units (TCUs) are designed to enhance patient support at time of dialysis initiation and provide comprehensive education on renal replacement therapies. We previously published a Propensity Score Matched (PSM) study and reported dialysis patients attending a TCU had higher rates of transplant referral (TR) and preferred modality compared to controls and no difference in mortality and hospitalizations (Blankenship 2022). The purpose of this project was to further understand the potential impact of TCUs throughout the follow-up of the original study. Specifically, TR, modality, mortality, and hospitalizations were assessed for their consistency and timing of results over the 2-year study period.

Methods: The study identified Fresenius Kidney Care (FKC) patients new to dialysis and starting incenter hemodialysis (ICHD) within a TCU between Oct. 1st, 2019 and Sept. 30th, 2020 with a follow-up through Oct. 1st, 2021. This 2-year study period was divided into 8 quarters consisting of the patients and outcome information available at each look. PSM and statistical methods were performed as in the published analysis at each time point.

Results: Modality and TR were consistently significant after 6 months and throughout the remainder of the study. At 6 months, 19% of TCU patients chose a home modality as compared to 4% of controls, and 52% of TCU patients were at least referred for transplantation as compared to 36% of controls. Hospitalization was not statistically significant after correcting for multiple tests. Interestingly, mortality trended positive and was statistically significant after 1 year. At a time corresponding with an initial wave of COVID-19, mortality was no longer statistically significant at 15 months, but trended positive thereafter.

Conclusions: This study found the positive association of TCUs with chosen modality and TR was relatively early at 6 months and consistent thereafter. Although mortality was not statistically significant in the original analysis, the longitudinal analysis determined TCU patients had favorable mortality outcomes after 1 year (HR=0.16) which were negated during the first year of COVID-19 pandemic. This finding warrants further investigation and follow-up. **Funding:** Commercial Support-Fresenius Medical Care

Funding: Commercial Support - Fresenius Medical Care

TH-PO260

Personalized Hemodialysis vs. Standard Therapy: Is a Change Needed?

Miguel Suarez,[1,2] Vanesa Garcia Bernalt,[1] Pedro Dorado.[2] *[1]Servicio Extremeno de Salud, Merida, Spain; [2]Universidad de Extremadura, Badajoz, Spain.*

Background: In our unit, hemodialysis therapy is personalized based on patient characteristics and available techniques: conventional versus incremental, high-flow, extended, supra-HD, in-line, or mid-dilution. Since 1970 we have reduced the objective to an adequate KT/V, forgetting about other uremic toxins until the arrival of the online modality. In the study area there are two concerted centers with standard therapy (90% High-Flow and 10% Postdilutional On-line) and public centers with personalized therapy.

Methods: Retrospective study of 205 (n 84 vs 121) incident patients comparing the application of a personalized hemodialysis protocol vs. standard therapy. Study period 2015-2021 with a minimum observation period of 24 months or until event. Costs obtained from the prices of public tenders and contracted personnel for HD performance. Determine whether personalization is justified compared to standard therapy, compared to the associated clinical variables (pharmaceutical expenditure, hospital admission and mortality).

Results: Number of admissions 84 (72.4%) vs 32 (27.6%) in favor of the personalized therapy group; this represents an average of 10.78 vs 4.97 ($p < 0.005$) days of admission per 365 days of treatment. Risk Estimate 0.082 (0.335-0.666) vs 0.295 (1.374-2.516). According to public tenders, the price per session for Personalized vs Standard is €173.4 vs €129. The indirect cost per year for Personalized vs Standard is: in Pharmacy €2,988 vs €6,308 in Admission €4,478.46 vs €9,713.85 and in Incremental HD - €1,484.06 vs - €0. Costs that fall on the hospital center. Total cost is the sum of direct plus indirect cost: €27,050.4 + €2,988 + €4,478.46 - €1,484.06 vs €20,124 + €6,308 + €9,713.85 - €0 therefore €33,032.26 in personalized therapy vs €36,145.85 standard therapy. In the binary logistic regression, the factors related to the risk of admission (analyzed DM, Cardiopathy, catheter days, Age of Start, Sex and Chalson Index) with statistical significance are personalized therapy, initial vascular access and sex.

Conclusions: Despite the limitations of the study, retrospective and observational, personalizing therapy seems to reduce the morbidity and mortality associated with the technique, achieving greater efficiency of it. It is necessary to design a study to this effect to determine the need to personalize therapies in the SES authorized centers.

TH-PO261

Clinical Features of a Multiethnic Cohort of Patients on Twice-Weekly Incremental Hemodialysis

Lewis Simon,[1,2] Diana Tran,[2,3] Rina Takahashi,[2] Adnan M. Ismail,[2,3] Peter Sohn,[4] Ji Hoon Yoon,[2] Lisa Le,[2] Andrea C. Daza Aguilar,[2] Alejandra Novoa Vargas,[2] Yongen Chang,[3] Lili Tong,[3] Connie Rhee,[2] Kamyar Kalantar-Zadeh.[2,3] *[1]University of California Irvine, Irvine, CA; [2]The Lundquist Institute, Torrance, CA; [3]VA Long Beach Healthcare System, Long Beach, CA; [4]SoCal Kidney Consultants, Garden Grove, CA.*

Background: While current KDOQI guidelines support starting incident ESRD patients with substantial KRU on incremental hemodialysis (HD), many of these patients are started on thrice-weekly HD regardless of KRU. Few studies have examined characteristics of diverse ESRD patients on incremental twice-weekly incident HD patients in the United States. We aimed to characterize a diverse cohort of ESRD patients started on incident HD and explore factors associated with their transition to conventional HD.

Methods: We conducted a case-series of 59 incident incremental HD patients at a local dialysis center, with patients observed from September 2021 to May 2022. Data such as KRU, incremental HD duration, HD schedule and demographics were extracted from EMR. Differences were examined across sex and ethnicity and across two subgroups- those who transitioned from incremental to conventional HD and those who did not.

Results: The cohort was 64% Hispanic and 41% female. Mean age at HD start and transition were 51.9 and 49.6 years, respectively. Thirty-eight (64.4%) patients transitioned to thrice-weekly HD, most often due to volume overload (34%). The most prevalent incremental HD schedules were Monday/Friday (42%) and Tuesday/Saturday (44%). Mean twice-weekly HD duration for transitioners was 47 weeks. Mean baseline and transition KRU were 3.8 and 1.7 mL/min./1.73m^2, respectively. Non-Hispanic Whites had higher transition rates compared to Asians and Hispanics but these differences were not significant ($p=0.12$). Among transitioners, males had longer incremental HD duration ($p=0.03$), and females had higher transition rates by the 52-week mark ($p=0.04$). Median weeks-to-transition was 24.3 (95% CI: 20.5-30.0) for males and 16.0 (95% CI: 14.7-16.6) for females.

Conclusions: We characterized a diverse cohort of twice-weekly incremental HD patients. Differences in incremental HD duration and incremental-to-conventional HD transition rates across sex and ethnicity were identified. These findings can inform researchers and clinicians regarding disparities in incremental HD effects across diverse ESRD populations. More research is needed to further assess the long-term effects of incremental HD, particularly in underrepresented and underserved ESRD patient populations.

TH-PO262

Incremental Hemodialysis (IHD) Is a Cost-Effective and Patient-Centered Kidney Replacement Therapy

Toshimasa Takahashi.[1,2] *[1]Bosei Shinjyuku-Minamiguchi Clinic, Tokyo, Japan; [2]Organization for Kidney and Metabolic Disease Treatment, Tokyo, Japan.*

Background: Hemodialysis (HD) in Japan is the highest quality of Renal Replacement Therapy (RRT) in the world, but its cost is increasing continuously. The conventional thrice-weekly regimen is a common way to introduce HD but not Incremental hemodialysis (IHD) in Japan. When HD patients' conditions are sufficiently managed by once-/twice-weekly HD with good adherence to their diet, its cost-reduction effect can be expected.

Methods: We selected 62 CKDG5 outpatients with good adherence to diet, we initiated IHD considered residual renal function individually and careful follow-ups from 2013 to 2023. The average age was 62 (21 to 90), and 74% was men. Their causes of ESRD include chronic glomerulonephritis (35%), diabetic kidney disease (34%), nephrosclerosis (21%), and others (10%; polycystic kidney disease, chronic interstitial nephritis, Hypoplastic kidney).

Results: 4.3, Ccr was 5.9mL/min, and mean urine volume (UV) was 1586 mL/day. 24 patients were treated with twice-weekly HD; their mean eGFR was 4.4, Ccr was 4.8mL/min, and mean UV was 1273 mL/day. We determined the number of dialysis cycles, taking into account the patient's background, underlying disease, and compliance before the initiation of dialysis, and individually studied the dialysis conditions based on laboratory data and weight gain. A significant difference was observed in UV between once-weekly and twice-weekly HD (The data were analyzed for statistical student's t-test. Difference was assessed with a two-sided test with a level of 0.05.) and no significant difference in eGFR and Ccr. The overall 1-year survival rate of IHD was 98.4%, and the 5-year survival rate was 81.2%. In these 62 patients, the total number of once-weekly HD was 357M (8.7M/person), the total number of twice-weekly HD was 1234M (23.7M/person), and the cost reduction during this period was 41.8% compared with that all patients did thrice-weekly HD. Limitation: The cost of dialysis was based on the Japanese medical insurance system in 2023. Selection bias cannot be avoided.

Conclusions: IHD is a patient centered RRT that provides cost-effective and sustainable treatment for ESRD patients.

TH-PO263

Vascular Access Survival with Thrice-Weekly, In-Center, Nocturnal Haemodialysis

Katherine L. Hull,[1,2] Ann Bugeja,[3,4] Matthew Graham-Brown,[1,2] Lindsay Reid,[4] Aiden J. Smith,[5] Brigit C. van Jaarsveld,[6] James Burton.[1,2] *[1]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [2]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [3]Ottawa Hospital, Ottawa, ON, Canada; [4]University of Ottawa, Ottawa, ON, Canada; [5]University of Leicester Department of Population Health Sciences, Leicester, United Kingdom; [6]Amsterdam Universitair Medische Centra, Amsterdam, Netherlands.*

Background: This study explores vascular access complications in patients established on in-centre nocturnal haemodialysis (INHD) compared to conventional haemodialysis.

Methods: Retrospective cohort study with patients acting as their own control. Data were collected from: Leicester Renal Network, UK (project number 12494) and The Ottawa Hospital, Canada (project number 20230336-01H). Adults established on INHD (intervention period) preceded by usual daytime in-centre haemodialysis (control period) with an established vascular access were eligible. Data were collected between 01/01/2009-31/12/2021. The primary outcome measure was a composite of outcomes due to vascular access complication: hospitalisation, intervention, change in vascular access modality, change in dialysis modality and death. The primary outcome was evaluated by time-to-event rate in days using Kaplan-Meier plots. Statistical significance was accepted at $P<0.05$.

Results: 123 individuals were included (UK, n=66; Canada, n=57). The mean age was 51.2 years (±17.0), 69.1% (n=85) were male, 56.1% (n=69) were white. There was no difference in the primary outcome for the intervention period (n=33, 26.8%) and the control period (n=31, 25.2%): $P=0.868$. The 12-month vascular access survival probability was 69.8% (95%CI 61.0–78.6%) for the intervention period and 70.5% (95%CI 61.5-79.5%) for the control period (Figure 1). During the intervention period, arteriovenous grafts were associated with lower vascular access survival ($P<0.001$), and during the control period, regular vitamin K antagonist use was associated with lower vascular access survival ($P=0.002$).

Conclusions: Vascular access type and use of regular anticoagulation were associated with a reduced vascular access survival probability. There does not appear to be an increased risk to vascular access survival and safety for INHD compared to conventional haemodialysis.

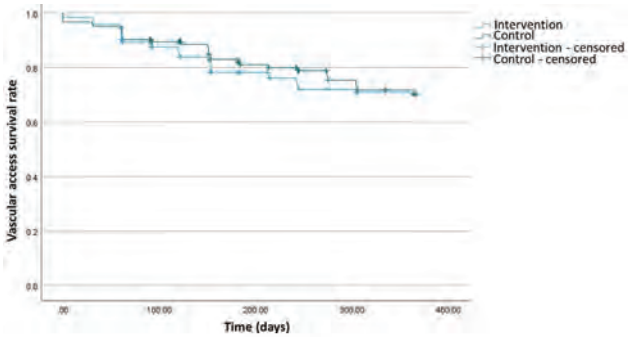


Figure 1 – Kaplan-Meier plot demonstrating vascular access time-to-event rate

TH-PO264

Exploring the Adoption of Thrice-Weekly, Extended-Hours, In-Center, Nocturnal Hemodialysis in Routine Clinical Practice through the NightLife Study: A Qualitative Content Analysis

Katherine L. Hull,[1,2] Victoria Cluley,[3] Matthew Graham-Brown,[1,2] James Burton.[1,2] *[1]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [2]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [3]University of Nottingham School of Sociology and Social Policy, Nottingham, United Kingdom.*

Background: In-centre nocturnal haemodialysis (INHD) is a complex intervention and little is known about the factors influencing implementation. NightLife (ISRCTN87042063) is a randomised controlled trial comparing the clinical and cost-effectiveness of INHD to usual care. This study aims to understand the facilitators and barriers to INHD adoption within the NightLife trial, focusing on the infrastructure, research environment and healthcare professional perspective.

Methods: This study was completed as a qualitative content analysis, using an inductive approach following Braun and Clarke's framework for reflexive thematic analysis. Content for analysis was derived over a three-year period from three business cases, 80 e-mail discussions (each discussion containing one to 10 e-mails), one internal pilot report, 60 meeting minutes, and seven semi-structured interviews with members of the multidisciplinary team.

Results: Four key themes were identified: 1. Inequity: differential access to healthcare resources specific to dialysis treatment. 2. Role of knowledge and evidence: the impact of known benefits of INHD and the need for more research. 3. Staff perception and experience: motivation to start and continue with INHD site set-up. 4. Resources, support and complexity: multiple logistical challenges to negotiate and the impact of support from clinical and research teams. These four themes contributed to both the adoption and non-adoption of INHD within the NightLife study.

Conclusions: Site set-up and INHD service delivery have been the greatest challenges to NightLife study progression. Although each site appears to have unique challenges, this qualitative content analysis demonstrates commonality in the facilitators and barriers to dialysis service innovation. Utilising these findings will support site set-up of INHD within the NightLife study and are transferable to the development and evaluation of future complex interventions for the dialysis community.

TH-PO265

Survival Sex Differences among Pediatric and Young Adult Hemodialysis Patients in the Global MONDO Registry

Xiaoling Ye,[1] Ana Catalina Alvarez-Elias,[1] Rasha H. Hussein,[1] Guido Filler,[3] Maria E. Ferris,[2] Peter Kotanko.[1] MONDO Initiative. *[1]Renal Research Institute, New York, NY; [2]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Western University, London, ON, Canada.*

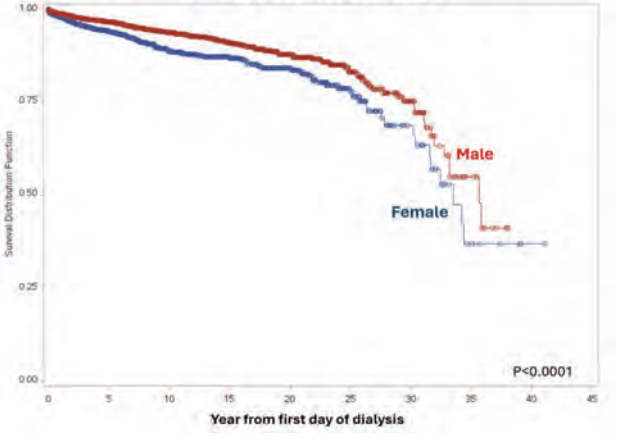
Background: For all age groups, women with ESKD on HD have higher rates of cardiovascular (CV) events compared to men, but their all-cause mortality is reduced. Survival in pediatric and young adult HD patients (pts) from across the globe is understudied.

Methods: In this retrospective cohort study, we included all the ptsaged from 0-40 and treated with HD from the global MONDO database (2000 - 2012). Primary cause of ESKD were identified at dialysis initiation. Kaplan-Meier estimate was used to study the survival of male versus female in all age group and each of the age group (0- ≤12, >12-≤18, >18-≤26, >26-≤33, and >33-40) separately.

Results: Of the 21,450 pts, 8,765 (40.9%) were females. Totally, 398,1.9% were 0-≤12; 13,92 (6.5%) were >12-≤18; 4,657 (21.7%) were >18-≤26; 6,398 (29.8%) were >26-≤33; and 8,623 (40.2%) were >33-40. Etiology by condition included 23.9% glomerular disease, 6.5% congenital and acquired urinary diseases, 32.1% other diagnoses, and 37.5% unknown causes of ESKD. There were no difference of pts with CV comorbidity in male vs. females (13%vs.11%). Pts distribution by region included 26.5% from Asia, 41.3% from Europe, 27.7% from Latin America and 4.5% from the US. The median survival time in both sexes was 32 years. Overall, males had a slightly better survival (p=0.0022). Age-stratified survival analysis revealed that males had a better survival than females (P=0.1099) significantly better survival in the >18≤26 age cohort (P<0.0001); all other stratified age groups showed no difference.

Conclusions: In the global MONDO Registry, of 0–40-year-old HD pts, only young adult males (>18≤26 years) had slightly better survival. Otherwise, there is no sex difference. In contrast to the existing literature for all age groups, we did not observe an inequity of survival in male HD pts<40 years old.

Figure 1. Sex differences in survival among HD patients (Age >18- <=26) in the global registry PICCOLO MONDO



TH-PO266

Colon Collectibles: Unearthing Coin-Shaped Treasures in Kidney Disease

Remy Fadel, Saud A. Alsaleh, Megha Salani. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Differentiating ingested foreign bodies and radio-opaque medications is critical due to their similar radiographic appearances. We present a case of a patient with end-stage kidney disease (ESKD) who was found to have sucroferric oxyhydroxide tablets in his colon, initially misinterpreted as metallic foreign bodies.

Case Description: A 69-year-old man with ESKD on hemodialysis presented with symptoms of nausea and vomiting. A CT scan of the abdomen revealed rounded, hyperattenuating intraluminal foci throughout the colon, possibly coins or buttons (Figure 1). General surgery was consulted and opted for a watchful management approach as there was no perforation. Further investigation revealed that the patient had been swallowing his phosphate binders, sucroferric oxyhydroxide, whole rather than chewing them. Radiology confirmed that the coin-shaped anomalies detected on imaging matched the size and shape of these tablets. Subsequently, the tablets were recovered intact from the patient's stool.

Discussion: Ingestion of foreign bodies can pose serious risks, necessitating prompt identification and management to prevent potentially life-threatening complications. It is imperative to differentiate such cases from instances of ingesting radio-opaque medications. The CHIPS mnemonic (chloral hydrate, heavy metals, iron, phenothiazines, and slow-release preparations) was developed to aid in identifying culprit medications. Sucroferric oxyhydroxide, a chewable iron-based phosphate binder, has negligible systemic absorption. Due to its insoluble iron content, unchewed sucroferric oxyhydroxide tablets appear as highly radio-opaque round objects on imaging. Understanding the properties and absorption mechanisms of such medications, coupled with thorough patient history-taking, can mitigate the need for invasive interventions and guide appropriate management strategies.

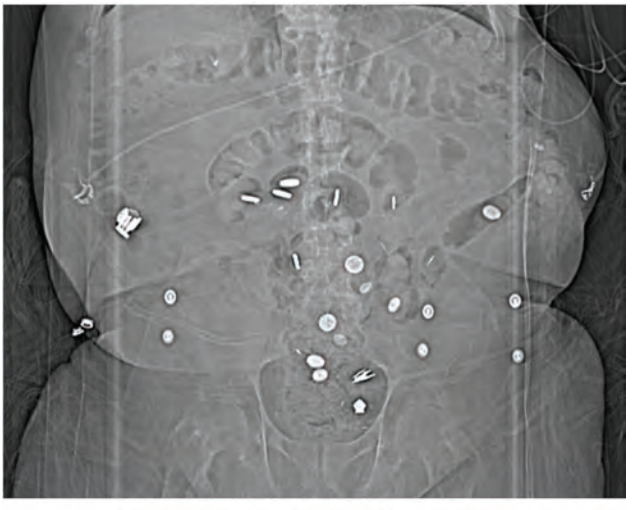


Figure 1 - CT Scan image showing rounded, hyperattenuating intraluminal foci throughout the colon

TH-PO267

Contrast-Induced Encephalopathy: A Rare Complication of Angiography in a Patient on Dialysis

David G. Sanders, Chloe West, Koyal Jain. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Introduction: Contrast-induced encephalopathy (CIE) is a rare complication of contrast use in angiographic procedures. The kidneys filter iodinated contrast agents, making patients with end-stage kidney disease (ESKD) higher risk for CIE. We present a case of CIE to highlight the gravity of early diagnosis in patients with reduced kidney function.

Case Description: A 66-year-old woman with hypertension and ESKD on home hemodialysis (HD)(4 times/week; no missed sessions) underwent diagnostic cerebral angiography for aneurysms noted incidentally on MRA during renal transplant evaluation. 300mg of iohexol was given intra-arterially. Patient was initially alert but 30 minutes later was disoriented, aphasic and not following commands. CT head showed no infarction or hemorrhage but noted extensive intracranial arterial atherosclerotic calcifications. Vitals and labs were normal, making other diagnoses unlikely. CIE was considered given the timeline. Mental status improved with urgent dialysis and was baseline after 2 sessions. To our knowledge, this is the first report of CIE in a patient receiving home HD.

Discussion: CIE is a severe complication in <0.1% of patients receiving contrast. Incidence increases in CKD(6.8%) and ESKD(37.5%). Pre-existing diabetes, hypotension, dehydration, and large contrast volume also increase risk. Intracranial arterial atherosclerotic calcifications likely affected the disease process in this case. CIE is thought to occur from disruption of the blood-brain barrier and direct neurotoxicity of iodinated contrast. It presents with confusion, headache and agitation to seizures, blindness and stroke-like symptoms onset minutes-days after contrast. Transient cortical blindness is often reported. Treatment is discontinuing contrast, IV hydration, and early and frequent HD in HD patients. Failure to treat in severe cases can cause permanent neurologic damage and death. How the type/timing of dialysis impacts CIE risk is not well understood due to rarity of cases. Our patient recovered following 2 HD sessions, suggesting early and frequent HD is an effective treatment in patients already on HD. This rare case highlights the importance of early CIE recognition to avoid prolonged complications. It is important to also recognize that contrast use has other risks even in patients on dialysis and should be used cautiously.

TH-PO268

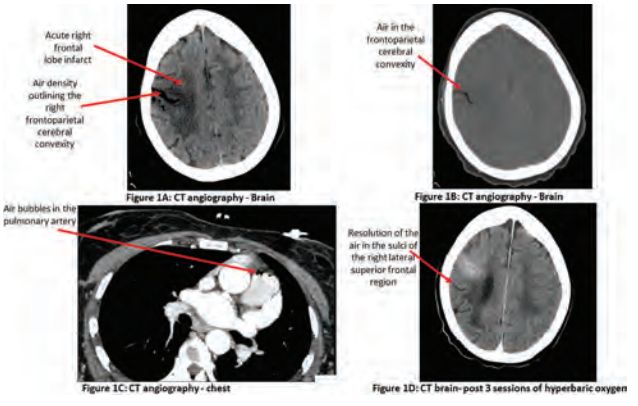
Unveiling a Rare Complication: Arterial Air Embolism during Hemodialysis without Intracardiac Shunt

Matthew W. Gross, C. E. Cervantes, Mohamad A. Hanouneh. *Johns Hopkins University, Baltimore, MD.*

Introduction: Air embolism is a rare complication during hemodialysis, due to safety measures like venous air traps and alarms. It's typically linked to the use of central venous catheters or the administration of anticoagulation or saline during dialysis. We report a case of arterial air embolization during dialysis in a patient without intracardiac shunt.

Case Description: A 56-year-old woman with ESRD on intermittent hemodialysis via a central venous catheter experienced facial droop and left-sided weakness during hemodialysis soon after receiving a heparin bolus with saline flushes. Her vitals remained stable. The venous line clamped, treatment was terminated, and the patient was positioned in trendelenburg. A CT scan showed an acute right frontal lobe infarct due to an air embolism (Figure 1A and 1B) and bubbles in the pulmonary artery (Figure 1C). Patient underwent three sessions of hyperbaric oxygen therapy. Her neurologic exam returned to baseline, and imaging confirmed resolution of air in the sulci of the right lateral superior frontal region (Fig 1D). Transthoracic echocardiography with agitated saline was done twice and did not demonstrate any intracardiac shunt.

Discussion: The usual manifestation of air embolism during hemodialysis is related to the air entering the cardiopulmonary circulation and includes chest pain, dyspnea and hypotension. Arterial air embolization, while less prevalent, presents a heightened risk, potentially leading to seizures or strokes. Such occurrences may arise in the presence of a right-to-left shunt or, as in our case, if pulmonary capillaries fail to adequately purge a significant volume of air, thereby overburdening the filtration capacity of the pulmonary vasculature. Quick identification is crucial, and treatment involves administering 100% oxygen, placing the patient in the trendelenburg position to contain the air in the right ventricle apex, clamping the venous line, stopping the blood pump, addressing any catheter disruptions, and providing intubation and cardiopulmonary support if needed.



TH-PO269

Complete Kidney Recovery after Prolonged Hemodialysis Dependency in Multiple Myeloma-Associated Kidney Failure: A Case Report

Hyun Joon Cho,[1] Bassam H. Rao,[2] Minahil Mukhtar,[2] Jee H. Kim,[1] Stela Teferici,[1] Mohamad Bakro,[1] Dawn Maldonado,[1] Hameeda T. Khan,[1] Nitzy N. Munoz Casablanca.[1] *[1]Mount Sinai Health System, New York, NY; [2]Shifa College of Medicine, Islamabad, Pakistan.*

Introduction: Renal impairment is an important complication of Multiple Myeloma (MM), with 20-40% of patients demonstrating some renal injury at diagnosis, related primarily to light chain cast nephropathy. Bortezomib and steroid based therapy are the

backbone for MM management, compounded with hemodialysis in patients with renal failure. Here, we present a case of MM associated renal failure requiring hemodialysis for 11 months, with subsequent spontaneous renal recovery.

Case Description: A 49 year-old male, without any significant past medical/surgical history who had 1 month of intermittent urinary symptoms, weakness, nausea and loss of appetite and was prompted to come to the ED when outpatient workup revealed anemia with Hb 8.4 g/dL and serum creatinine (Cr) levels of 11 mg, without known previous baseline. Initial workup showed markedly elevated serum lambda light chains at 1435 mg/dL. Urinalysis with trace protein, but a urine protein creatinine ratio of 3.5g. The patient underwent kidney biopsy which came back positive for light chain (myeloma) cast nephropathy, lambda type, minimal interstitial fibrosis, tubular atrophy and unremarkable vessels. Bone marrow biopsy was also consistent with multiple myeloma. He was initiated on renal replacement therapy and continued for 11 months. Patient was treated with cyclophosphamide, bortezomib and dexamethasone and then subsequently with Bortezonib, Lenalidomide and Dexamethasone. After being on hemodialysis for 11 months, his eGFR gradually improved, and a decision was made to withhold hemodialysis. Since then, the patient's renal function has been stable, with Cr around 2 mg/dL and eGFR >30.

Discussion: The burden of renal disease in MM can be ascertained from its place as the second leading cause of mortality, with lack of renal recovery bearing a poor prognosis. In recent times, high cut-off hemodialysis has emerged as an adjunct to steroids and bortezomib based chemotherapy in this class of patients for improving renal outcomes. The data on this however, remains sparse. Although the patient was managed as per standard guidelines, our unique case signifies the potential space of renal recovery even after prolonged hemodialysis dependance in MM patients.

TH-PO270

Morphological Changes in a Nephrectomized End-Stage Kidney 10 Years after Hemodialysis (HD) Initiation for Atypical Hemolytic Uremic Syndrome (aHUS)

Kruti Shah,[1] Tiane Dai,[1] Cynthia C. Nast,[2] Sharon G. Adler.[1] *[1]Harbor-UCLA Medical Center, Torrance, CA; [2]Cedars-Sinai Medical Center, Los Angeles, CA.*

Introduction: A nephrectomy (Nx) for renal cell carcinoma (RCC) in a patient on long-term dialysis receiving C5 inhibitor treatment (C5i) for aHUS afforded the opportunity to morphologically evaluate changes in the end-stage kidney due to end-stage kidney disease (ESKD) milieu, hyperparathyroidism, and treated aHUS.

Case Description: A 23-year-old man presented in 2014 with uremic symptoms and hypertensive emergency (BP 200/120 mmHg). His serum creatinine was 12 mg/dL. He had low complement C3, normal C4, no thrombocytopenia or microangiopathic hemolytic anemia. Renal biopsy showed a large artery with thrombotic microangiopathy (TMA) and immune complex-mediated membranoproliferative Type I pattern of injury. Additional studies showed low Complement Factors B, H (CFH), and I (CFI). Genotyping revealed a novel nonsense mutation in CFI predicted to prematurely truncate the CFI protein and 3 heterozygous polymorphisms in CFH, common in healthy people but enriched in aHUS. Eculizumab was not started because of hematologically silent aHUS and functionally end-stage kidneys. In time, he required parathyroidectomy for tertiary hyperparathyroidism. Subsequently, he presented with right-sided numbness and a cerebrovascular lesion coinciding with the sensory symptom distribution. At this time C5 inhibitor was started for presumptive cerebral TMA, with resolution of aHUS symptoms. After 10 years of dialysis, he developed erythrocytosis, kidney cysts, and renal cell carcinoma (RCC) necessitating nephrectomy (Nx). Nx showed acquired cystic disease, RCC, diffusely calcified glomeruli likely due to tertiary hyperparathyroidism, and chronic TMA with minimal activity, likely reflecting the beneficial effect of long-term complement C5 inhibitor treatment.

Discussion: Nx was done for RCC after 10 years of dialysis and ESKD from aHUS secondary to CFI mutation. This afforded the opportunity to observe the rare finding of diffuse glomerular calcification likely due to tertiary hyperparathyroidism. Additionally, there was chronic and minimally active TMA, likely reflecting long-term complement C5 inhibition.

TH-PO271

Community Hemodialysis for a Patient with a Left Ventricular Assist Device: A Case Report

April Toh, Zheng Xi Kog, Hui-Lin Choong, Jiunn Wong. *Singapore General Hospital, Singapore, Singapore.*

Introduction: Heart transplant remain the treatment of choice for patient with advance heart failure. However, due to lack of donor organ, left ventricular assist devices (LVADs) are used as a bridge until donor organs becomes available. We are seeing more patients with advanced heart failure where LVADs are being used for long term. These patients are surviving longer and hence it is not uncommon for them develop ESKD requiring dialysis. We presents a case of a patients who was on LVAD for 2 years prior to developing ESKD and how we transit her from hospital to community for her dialysis.

Case Description: Ms K is a 33 year old lady who suffered from doxorubicin induced cardiomyopathy following treatment of childhood Acute Myeloid Leukemia. She presented with intra-partum decompensated heart failure requiring inotropic and ECMO support in 2021. She eventually underwent LVAD implantation. Her peri-operative and postoperative period was complicated with multiple infective issues and complications. During tthat admission she developed AKI following cardiac surgery requiring dialysis for 3 months before weaning off dialysis. Unfortunately, she had recurrent admissions over the next 2 years and developed recurrent episodes of AKI, ultimately leading to her becoming dialysis dependent. She recieve intermittent dialysis in hospital setting and was subsequently successfully transited to outpatient community dialysis after 2 month stay in hospital.

Discussion: There are numerous challenges a LVAD patient on dialysis faces compared to the routine patient on maintenance dialysis. For patient on LVAD, the blood flow is none pulsatile and traditional method of measuring BP would not be able to accurately record BP. US Doppler BP measurement for mean arterial pressure is the only way to measure BP in these patients. Besides difference in monitoring, resuscitation plan also differs from routine dialysis patients. CPR peformed on these patients may disloge the LVAD and cause more harm than good. This is the first case of a patient on LVAD undergoing successful transition from the inpatient setting to community dialysis in Singapore. With more LVAD procedures being performed and patient surviving longer on LVAD, dialysis center would need to adapt to care for these patients. Dialysis nurses need to have knowlege and training in order to care for patients on LVAD.

TH-PO272

Abstract Withdrawn

TH-PO273

Correlation between Intradialytic Blood Pressure Variability and Cognitive Impairment in Patients on Maintenance Hemodialysis

Jingfang Wan, Jun Liu, Yani He, Kehong Chen. *Army Medical Center of PLA, Chongqing, China.*

Background: Cognitive impairment (CI) is a risk factor for death and poor prognosis in maintenance hemodialysis (MHD) patients. MHD patients are more likely to have fluctuating BP during dialysis, which may have a greater impact on CI. Our present study aimed to illustrate the correlation between intradialysis BPV and CI in MHD patients.

Methods: Overall cognitive function was assessed by the Beijing version of the Montreal Cognitive Assessment (MoCA-B) scale. The patient's SBP was converted to the following 4 candidate BPV indices: standard deviation (SD), coefficient of variation (CV), average real variability (ARV), RANGE. $P < 0.05$ was considered statistically significant.

Results: 170 patients were enrolled, with a total of 6,662 dialysis recordings and 26,580 SBP measurement recordings. The mean age of the patients was 57.99 years. The proportion of males was 58.24%, and CI prevalence was 78.24%. SBP ARV is an independent risk factor for CI (Table 1). We observed a non-linear relationship between SBP ARV and CI (Figure 1). We compared two fitting models to explore the curved associations, the p-value of the log-likelihood ratio test is 0.008. The inflection point of SBP ARV was 7.52. When SBP ARV ≥ 7.52, the risk of CI increased as the SBP ARV increased (OR: 4.10, 95 % CI1.61-10.46, P = 0.003). When SBP ARV < 7.52, there was no significant correlation between SBP ARV and CI (OR = 0.43, 95 % CI 0.15-1.26, p = 0.125).

Conclusions: Intradialytic BPV was associated with CI in MHD patients. Intradialytic SBP ARV may be a better candidate for predicting CI in MHD patients, with nonlinear dose-response relationship.

Funding: Government Support - Non-U.S.

Table1. The results of mutivariate analysis between SBP ARV and CI

Parameters	Non-adjusted			Model I			Model II		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
SBP ARV (mmHg)	1.24	1.01-1.51	0.041	1.17	0.97-1.42	0.1	1.16	0.95-1.42	0.146
SBP ARV (mmHg) dichotomous									
Low	Reference			Reference			Reference		
Middle	3.50	1.39-8.80	0.008	3.29	1.28-8.45	0.014	3.47	1.33-9.08	0.011
High	3.57	1.42-8.97	0.007	2.86	1.10-7.41	0.031	2.71	1.02-7.25	0.047

Outcome variable: CI. Non-adjusted model adjust for: None. Model I adjust for: Age, gender. Model II adjust for: Age,gender, spKt/v, history of diabetes, history of stroke, total holesterol, triglyceride SBP: systolic blood pressure, ARV: Average real variability, CI: cognitive impairment.

Table1. The results of mutivariate analysis between SBP ARV and CI

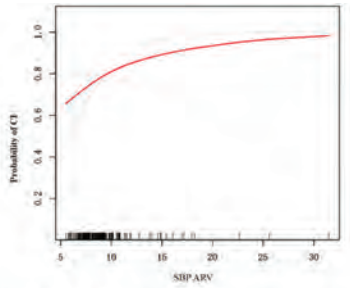


Figure 1. Curve fitting between SBP ARV and CI. Adjusted for Age; gender, tpKt/v, history of diabetes, history of stroke, total holesterol, triglyceride.
SBP: systolic blood pressure, ARV:Average real variability, CI: cognitive impairment.

Figure 1. Curve fitting between SBP ARV and CI.

TH-PO274

Neurofilament Light Chain and Cognitive Function in Patients Undergoing Hemodialysis: A Cross-Sectional Study

Kazuhiko Kato, Akio Nakashima, Arisa Kobayashi, Ichiro Ohkido, Takashi Yokoo. *Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan.*

Background: Dementia poses a global challenge for geriatric care and social welfare, including for aging dialysis patients. In recent years, non-invasive blood biomarkers have garnered increasing attention in predicting the development of Alzheimer's disease. Within the general populace, neurofilament light chain (NFL) prognosticates forthcoming cognitive function alongside amyloid-beta (Aβ). Nevertheless, investigation into this matter has yet to be extended to chronic kidney disease patients, including those undergoing hemodialysis.

Methods: A cross-sectional study of hemodialysis patients investigated the association between serum Aβ (1-42) and NFL levels with cognitive function as assessed by the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE).

Results: This study involved 362 patients whose median age was 74 (interquartile range 70-80) years and who had been receiving hemodialysis for a median of 87 (36-168) months. Aβ (1-42) exhibited a median of 2.84 (1.84-4.27) pmol/L, and NFL exhibited a median of 196.2 (146.5-262.2) pg/mL with a non-parametric distribution. The median MoCA and MMSE scores were 25 (22-26) and 28 (26-29). NFL levels transformed by the natural logarithm significantly negatively correlated with cognitive function in a multivariate linear regression analysis, including confounding factors (β coefficient [95% confidence interval], -0.98 [-1.76, -0.2]; P=0.014 for MoCA, and -0.67 [-1.3, -0.05]; P=0.034 for MMSE). No significant associations existed between cognitive function and Aβ (1-42) levels.

Conclusions: Low levels of NFL were associated with preserved cognitive function in patients undergoing hemodialysis.

Funding: Private Foundation Support

TH-PO275

How Pervasive Is Pervasive Sensing in Hemodialysis? Results from a Clinical Research Survey of Urban Dialysis Clinics

Maggie Han,[1] Lemuel Rivera Fuentes,[1] Lin-Chun Wang,[1] Ohnmar Thwin,[1] Lela Tisdale,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Currently, there is a wealth of commercially available activity and fitness trackers that have become available, allowing insights into physical activity, sleep, heart rate, and a plethora of other parameters that could lead to timely intervention prior to a manifest clinical decline. We aimed to determine the percentage of in-center hemodialysis (HD) patients using commercially available wearable devices.

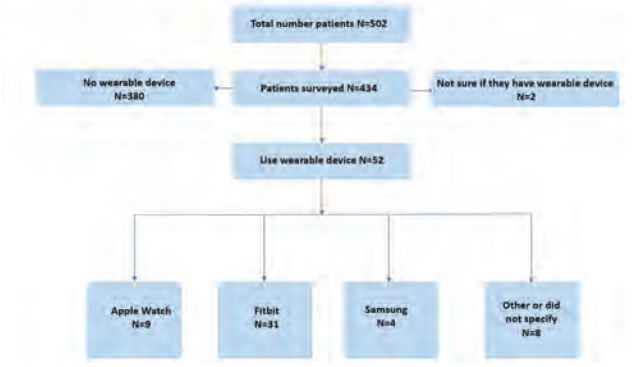
Methods: Patients from four HD clinics located in New York City, NY, were surveyed. The study was exempt from the requirement of collecting informed consent by the Western Institutional Research Board (ES-21-004). In March 2021, patients were asked if they owned a wearable activity tracker, and if so, what type of device they owned (Fitbit, Garmin, Apple Watch, Samsung, etc.).

Results: Census data of these four HD clinics from September 2020 indicated that the population is 51 % black, 31 % Hispanic, and 59 % male. In total, 502 patients were approached, and 434 (86.5 %) agreed to respond. Of the responders to the survey, 52 (12 %) owned a wearable activity tracker, 380 (87.6 %) did not, and 2 (0.5 %) were unsure if they did. Of those 52 patients who owned a wearable activity tracker, 9 (17%) patients owned an Apple Watch, 31 (60%) a Fitbit, 4 (8%) a Samsung, and 8 (15%) owned another device or did not specify brand (**Figure 1**).

Conclusions: In our study of urban in-center HD patients, only a small proportion (around 10%) own wearable activity trackers. Possible barriers to the adoption of these devices are lack of access to the internet and smartphones, and technology literacy.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

Figure 1. Results of a survey regarding wearables in urban in-center hemodialysis patients



TH-PO276

Trends in Physical Activity before Hospitalization: A Prospective Observational Study in Patients on Hemodialysis Using Wearable Activity Trackers

Maggie Han,[1] Yuedong Wang,[2] Xia Tao,[1] Priscila Preciado,[1] Lela Tisdale,[1] Ohnmar Thwin,[1] Peter Kotanko.[1,3] *[1]Renal Research Institute, New York, NY; [2]University of California Santa Barbara, Santa Barbara, CA; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

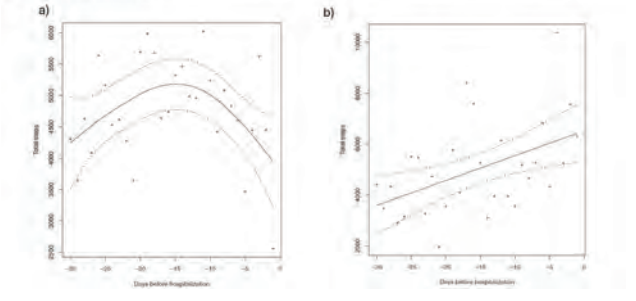
Background: Data collected by wearable devices may lead to timely intervention prior to a marked clinical decline. We aimed to determine if physical activity levels, measured with a wearable activity tracker, changed prior to hospitalization in hemodialysis (HD) patients.

Methods: HD patients from 4 New York City clinics were enrolled starting in June 2018 and followed for up to 1 year. Ambulatory patients ≥18 years, on maintenance HD, and owning a mobile device were included. Each patient was provided with and taught how to use a wearable activity tracker (Fitbit Charge 2®), and they were instructed to wear the device continuously. Hospitalization events were recorded and separated into two categories: unexpected hospitalizations and expected hospitalizations (vascular access procedure, scheduled surgeries). Rehospitalizations were not included in the analysis. We fit cubic spline models to daily averages of total steps 30 days prior to expected and unexpected hospitalizations, respectively, and compute p-values for testing the hypothesis of a constant function prior to hospitalizations using the bootstrap method.

Results: 42 patients (54±13 years, 57% Black, 71% male, 33% diabetic) were included in this analysis. 59 hospitalizations were recorded, with 51 unexpected and 8 expected hospitalizations. Prior to unexpected hospitalizations, the number of steps per day declined significantly (p=0.030) **(Figure 1a)**. In contrast, steps per day increased significantly in expected hospitalizations (p=0.039) **(Figure 1b)**.

Conclusions: Physical activity levels decline prior to unexpected hospitalizations. A marked decrease in steps per day may be an early indication of subsequent clinical decline. Additional research is warranted to further investigate the relationship between wearables data, clinical events, and intervention strategies.

Figure 1. Steps per day prior to hospitalization
a) total steps decreased prior to unexpected hospitalization (p=0.030). A notable decline starts about two weeks prior hospitalization.
b) total steps increased prior to expected hospitalization (p=0.039). We hypothesize that the increase may be related to errands prior expected hospitalization.



TH-PO277

Virtual Reality (VR)-Based Exercise and Exergaming for Patients on Hemodialysis: Rapid Systematic Review and Meta-Analysis

Davey Li,[1] Yunan Han,[1] Tanika Kelly,[2] Takeshi Hasegawa,[4] Erika Ota,[3] Hisashi Noma,[5] Taihei Suzuki,[4] Yoshitaka Watanabe,[9] Naonori Tashiro,[6] Hiroki Nishiwaki.[7,8] *[1]University of Illinois Chicago College of Medicine, Chicago, IL; [2]University of Illinois Chicago, Chicago, IL; [3]St.Luke's International University, Chuo, Japan; [4]Showa University, Shinagawa, Japan; [5]Institute of Statistical Mathematics, Tachikawa, Japan; [6]Showa University Fujigaoka Rehabilitation Hospital, Yokohama, Japan; [7]University of Illinois Chicago, Chicago, IL; [8]Showa University Fujigaoka Hospital, Yokohama, Japan; [9]Showa University Northern Yokohama Hospital, Yokohama, Japan.*

Background: Hemodialysis (HD) patients are at high risk for CVD; approaches to reducing the risk of CVD include pharmacologic therapies and nonpharmacologic interventions, with exercise representing an important nonpharmacologic intervention. Recently, conventional exercise interventions have been supplemented with technological advancements like virtual reality (VR) and exergaming, providing engaging, multisensory rehabilitation options.

Methods: In this systematic review and meta-analysis, we searched MEDLINE, and CENTRAL through April 2024 for interventional studies involving VR-based exercise and exergaming interventions among patients on HD. Study quality was assessed using the Cochrane Collaboration risk-of-bias 2.0 tools. Across eligible studies, random-effects meta-analyses were used to combine effects of VR-based exercise and exergaming on four study endpoints, exercise tolerance, gait speed, and depression in HD patients.

Results: Out of the 45 references, 14 studies consisting were applicable, 5 of which reported eligible outcomes (3 for exercise tolerance, 4 for gait speed, and 2 for depression). VR-based exercise and exergaming were associated with significantly increased exercise tolerance, with an average increase 78.3 m [95% CI 31.6 to 125.0, I^2=31%] in distance on the 6-minute walk compared to the control group (**Fig1**). Likewise, walking speed was increased an average of 0.16 m/sec [95%CI 0.09-0.24, I^2=0%] among those in the intervention group (**Fig2**), and depression was decreased, with standardized mean difference (hedge's g) of -0.49 [95% -0.84 to -0.19, I^2=0%] (**Fig3**).

Conclusions: VR-based exercise and exergaming increased exercise tolerance and gait speed, and decreased depression in the current meta-analysis.

Fig1. Exercise tolerance

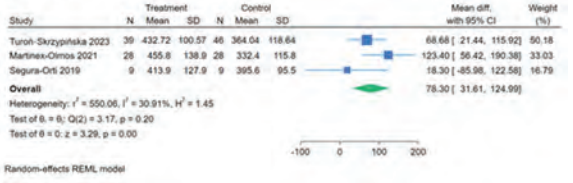


Fig2. Gait speed

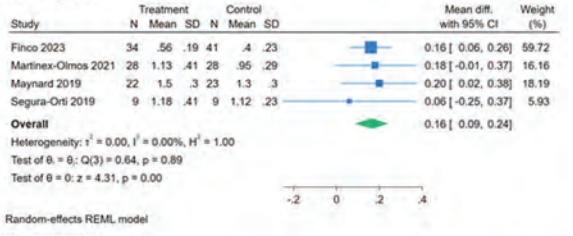
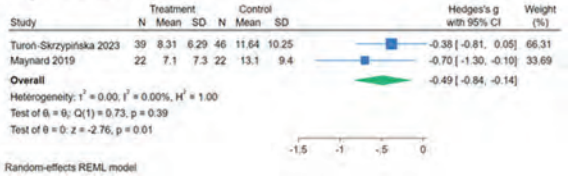


Fig3. Depression



TH-PO278

Use of β2-Microglobulin Adsorption Columns for More than 10 Years Contributes to the Maintenance of Physical Activity in Patients on Long-Term Dialysis Who Have Hemodialysis-Related Amyloidosis

Junichiro J. Kazama,[1] Suguru Yamamoto.[2] *[1]Fukushima Kenritsu Ika Daigaku, Fukushima, Japan; [2]Niigata Daigaku Ishigaku Sogo Byoin, Niigata, Japan.*

Background: The β2-microglobulin adsorption column (BMC) was developed in the 1990s to prevent the progression of dialysis-related amyloidosis (DRA) by removing β2-microglobulin from blood in conjunction with hemodialysis. However, the long-term effects of its use are still not well understood. We investigated the condition of dialysis patients who have been using BMC for over 10 years.

Methods: We selected maintenance hemodialysis patients in Japan who have been continuously treated with BMC for over 10 years and conducted interviews with patients who provided consent. The study protocol was approved by the Ethics Review Committee of Fukushima Medical University (FMU23-066).

Results: We obtained responses from 59 patients (70.0±7.2 years old, 22 males and 37 females, dialysis history of 38.2±6.0 years, BMC usage period of 15.0±3.9 years) across 35 facilities. Histological evidence of the deposition of Aβ2M amyloid fibrils was confirmed in all of these patients. Among the 59 patients, 38 had symptoms such as pain in the hands or fingers, hand numbness, hand stiffness, shoulder pain, and lower limb numbness before using BMC. Of these 38 patients, 35 (92.1%) reported a reduction in these symptoms. Eighteen patients experienced a recurrence of these symptoms when BMC treatment was interrupted. Eight patients testified that BMC improved symptoms compared to hemodiafiltration (HDF), while no testimonies indicated that HDF improved symptoms compared to BMC. The daily living abilities evaluated by the Eastern Cooperative Oncology Group Performance Status (ECOG) were PS0: 8.6%, PS1: 34.5%, PS2: 46.6%, PS3: 6.9%, and PS4: 3.4%. The proportions of PS0, PS3, and PS4 were lower, and the proportion of PS2 was higher compared to the data of general maintenance dialysis patients with over 30 years of dialysis history in previous reports.

Conclusions: The pain relief effect of BMC in this study was almost at the same level as previously reported. The pain-relieving effect of BMC observed in this study may have contributed to maintaining the motor function of these patients, preventing their progression to PS3 and PS4 over time. Thus, the long-term use of BMC may contribute to the maintenance of physical activity in dialysis patients with DRA.

TH-PO279

Do Baseline Parathyroid Hormone Levels Influence the Effect of Intradialytic Exercise on Bone Turnover Markers in Patients on Haemodialysis?

Diogo V. Leal,[1,2] Daniela F. Cardoso,[1,2] Francini P. Andrade,[1,2] Pedro M. Martins,[1,5] Manuel A. Ferreira,[5,6] Luke A. Baker,[3,4] Alice C. Smith,[3,4] Joao L. Viana.[1,2] *[1]Centro de Investigacao em Desporto Saude e Desenvolvimento Humano, Maia, Portugal; [2]Universidade da Maia, Maia, Portugal; [3]Leicester Kidney Lifestyle Team, Leicester, United Kingdom; [4]University of Leicester College of Life Sciences, Leicester, United Kingdom; [5]Nephrocare Portugal SA, Lisboa, Portugal; [6]Universidade Nova de Lisboa Medical School, Lisboa, Portugal.*

Background: Mineral and bone disorders are common in patients on haemodialysis (HD). We previously observed that regardless of type, exercise appears to have had a modulatory effect on bone remodelling by attenuating bone resorption and maintaining its formation. Parathyroid hormone (PTH) exerts impactful effects on skeletal homeostasis through many mechanisms, with continuous hyperparathyroidism exacerbating both bone formation and resorption. Here we aimed to investigate whether PTH influences the sensitivity of bone biomarkers' responses to exercise training.

Methods: This is a secondary analysis from an RCT completed on 88 HD patients who undertook a 6-week run-in period followed by 12 weeks of intradialytic aerobic (n= 36, male: 66%, age: 67±14 years), or resistance exercise (n= 29, male: 74%, age: 65±14 years), where we combined the exercise groups and stratified patients in low <150 pg/mL (L-PTH), normal 150-600 pg/mL (N-PTH), or high PTH >600 pg/mL (H-PTH). Circulating TRAP-5b, sclerostin, RANKL, osteoprotegerin, and osteocalcin (OCN) were measured by ELISA.

Results: At baseline, there were 15 patients in L-PTH, 55 in N_PTH, and 7 in H-PTH. Most biomarkers were unchanged after the control period, except for a reduction in OCN observed in L-PTH only (p= 0.026). Following exercise, an elevation in TRAP-5b was observed in both L-PTH and N-PTH (p<0.001). No changes in bone biomarkers were observed in patients with H-PTH at any timepoint (p>0.05 in all).

Conclusions: Exercise led to increased bone resorption in patients with low and normal PTH levels and maintained bone formation in patients with low PTH levels, but no such effects were observed in those with high PTH levels. This differential response suggests a protective effect of exercise in patients with low PTH by activating the cycle of bone formation through and increase in resorption and conservation of bone formation, which might be clinically relevant considering their reduced bone turnover. Funding: The Research Center in Sports Sciences, Health Sciences and Human Development is funded by the Portuguese Foundation of Science and Technology (UID/04045/2020). DC is supported by an FCT doctoral grant (SFRH/BD/138940/2018).

Funding: Government Support - Non-U.S.

TH-PO280

Decreased Skeletal Muscle Mass as a Risk Factor for the Progression of Peripheral Artery Disease (PAD) in Patients Receiving Maintenance Hemodialysis: 10-Year Outcomes of the Q-Cohort Study

Masumi Shojima,[1] Shunsuke Yamada,[1] Tatsuya Suenaga,[1] Kazuhiro Okamura,[1] Hiromasa Kitamura,[2] Hiroto Hiyamuta,[5] Masatomo Taniguchi,[4] Kazuhiko Tsuruya,[3] Takanari Kitazono,[1] Toshiaki Nakano.[1] *[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Department of Nephrology, Nara Medical University, Kashihara, Japan; [4]Fukuoka Renal Clinic, Fukuoka, Japan; [5]Department of Nephrology, Steel Memorial Yawata Hospital, Fukuoka, Japan.*

Background: Peripheral arterial disease (PAD) is a life-threatening complication in patients undergoing hemodialysis. It is unclear whether sarcopenia, as evidenced by a lower value of skeletal muscle mass surrogates, is a risk factor for PAD.

Methods: A total of 3,506 patients receiving hemodialysis registered in the multicenter, prospective, observational study were followed up for 10 years. The primary outcome was an intervention for PAD composed of endovascular therapy, revascularization, and amputation. The main exposure was the modified creatinine index, a surrogate of skeletal muscle mass calculated by age, sex, pre-dialysis serum creatinine, and Kt/V for urea. The patients were divided into sex-specific quartiles (Q1-Q4) according to the modified creatinine index level at baseline. Cox proportional hazard risk models were employed to estimate the intervention risks for PAD.

Results: In total, 257 patients required intervention for PAD during a median follow-up period of 8.2 years. The multivariable-adjusted Cox proportional hazards risk model showed that the risks of intervention for PAD in the lower quartiles (Q1 and Q2) were significantly (P<0.05) higher than the highest quartile (Q4): hazard ratio (95% confidence interval) for Q1 and Q2 were 1.75 (1.01–3.04) and 1.63 (1.04–2.58), respectively. Each 1 mg/kg/day decrease in the modified creatinine index was significantly (P=0.017) associated with the elevated risk of the intervention for PAD: hazard ratio (95% confidence interval) was 1.11 (1.01–1.22).

Conclusions: Sarcopenia, as expressed by a lower modified creatinine index level, was an independent risk factor for intervention for PAD in patients undergoing hemodialysis.

TH-PO281

Association of Serum Urotensin II with Sarcopenia and Mortality in Patients on Hemodialysis

Chi-Ta Hsieh, Lim Paik Seong. *Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan.*

Background: Sarcopenia significantly impacts dialysis patients. Our prior research evaluated 6 muscle biomarkers for early sarcopenia detection and found that Urotensin II (UT II) had a strong correlation with sarcopenia. This study further investigates UT II's effectiveness in predicting cardiovascular (CV) mortality.

Methods: A cross-sectional study was conducted on 175 stable HD patients at Tungs' Taichung Metroharbour Hospital. The associations of these biomarkers with CV mortality and sarcopenia were analyzed using multivariate Cox regression models, categorizing biomarkers into quartiles for statistical analysis. The predictive value of UT II against sarcopenia diagnosed by DEXA was also compared. Statistical analyses were performed using SAS software version 9.4.

Results: In this cohort, Cox regression analysis revealed that elevated UT II levels were significantly associated with increased CV mortality (aHR = 5.209, p = 0.0146, Fig. 1). Further analysis, integrating UT II with DEXA measurements, confirmed the significant predictive value of UT II (aHR = 6.040, p = 0.0216, Fig. 1) for CV mortality, while sarcopenia and presarcopenia diagnosed via DEXA were non-significant (Fig. 2).

Conclusions: UT II emerges as a better biomarker for predicting CV mortality in HD patients. This study emphasizes that serum UT II reflects not only muscle wasting but protein-energy wasting (PEW), which are related to CV diseases.

Table 1 Cox multivariate regression of Muscle Biomarkers for CV mortality

Variables	Cardiovascular mortality Adjusted hazard ratio (95%CI)	P
Urotensin II		
quartile categories level	5.209 (1.386-19.58)	0.0146
Myostatin		
quartile categories level	1.322 (0.484-3.611)	0.5867
Myonectin		
quartile categories level	0.579 (0.173-1.934)	0.3744
Antichymotrypsin		
quartile categories level	2.396 (0.663-8.657)	0.1823
Insulin-like growth factor-1		
quartile categories level	0.748 (0.283-1.98)	0.5593
Irisin		
quartile categories level	0.639 (0.228-1.786)	0.3930
Gender		
Male	0.002 (0.001-0.170)	0.0060
Age	1.095 (0.948-1.264)	0.2162
Percent Fat	1.094 (0.872-1.371)	0.4389
Hypertension (ref: no)	8.535 (0.113-644.1)	0.3311
Diabetes (ref: no)	9.779 (0.809-118.2)	0.0729
Metabolic syndrome	0.035 (0.001-2.622)	0.1276
Vintage In June 2015	0.989 (0.968-1.010)	0.2833
Albumin	0.026 (0.001-3.117)	0.1354
nPCR	28.87 (0.060-999.9)	0.2860
High-sensitivity CRP (mg/L)	0.574 (0.301-1.095)	0.0919
Ferritin	1.002 (1.000-1.004)	0.1278
High-Density Lipoprotein	0.851 (0.742-0.977)	0.0220
KT/V Daugirdas	0.001 (0.001-999.9)	0.3127
Urea reduction ratio	999.1 (0.001-999.9)	0.0972

Adjustment for gender, age, percent fat, hypertension, diabetes, metabolic syndrome, vintage, albur
nPCR, high-sensitivity crp (mg/l), ferritin, high-density lipoprotein, kt/v daugirdas, urea reduction ratio
nPCR, normalized Protein Catabolic Rate; CI, confidence interval

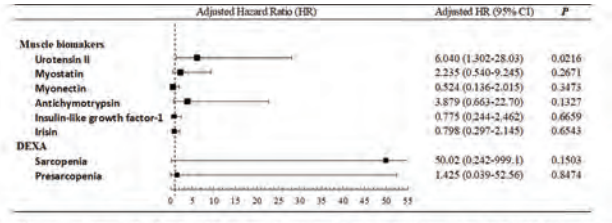


Figure 2 Cox multivariate regression After adjusting for gender, age, percent fat, hypertension, diabetes, metabolic syndrome, vintage, albumin, nPCR, high-sensitivity CRP (mg/L), ferritin, high-density lipoprotein, KT/V Daugirdas, and urea reduction ratio, the associations between muscle biomarkers and DEXA results were analyzed.

TH-PO282

Paricalcitol Treatment Upregulates Exosome-Derived Muscle Tissue-Specific MicroRNAs in Sarcopenic Male Patients on Hemodialysis

Hyeong cheon Park,[1] Hoon Young Choi,[1] Hyung Jong Kim,[2] Hyo Jeong Kim.[1] *[1]Division of Nephrology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea.*

Background: Muscle tissue specific microRNAs (myomiRNAs) are special group of miRNAs that play important roles by targeting genes involved in muscle development, differentiation, and regeneration. Vitamin D administration has been reported to have beneficial effects on skeletal muscle. Aim was to compare myomiRNAs between sarcopenic and non-sarcopenic patients on hemodialysis treatment and assess the effects of paricalcitol treatment on their expression.

Methods: Fifty male patients undergoing hemodialysis were included in the study and were given paricalcitol (Alvogen Korea) according to KDIGO clinical practice guidelines for treatment of secondary hyperparathyroidism for 12 weeks. Skeletal muscle index (SMI) value was derived by bioimpedance measurement and study subjects were classified into sarcopenia (n=13) or non-sarcopenia (=37) according to the criteria of the Asian Working Group for Sarcopenia 2019. The patients' blood derived exosomes were isolated and evaluated for expression of skeletal myomiRNAs (miR; miR-1, miR-133a, miR-206, miR-499),), associated with enhanced skeletal muscle differentiation and myoblast proliferation, using real-time quantitative PCR.

Results: The mean age was 67.3 ± 10.8 years and mean hemodialysis vintage was 9.4±6.2 years. Mean SMI value was 6.0±0.4 and 7.4±0.4, respectively in sarcopenia and non-sarcopenia group. Sarcopenia group showed significantly decreased expression of exosomal myomiRNAs (miR-1, miR-133a, miR-206, miR-499) compared to non-sarcopenia group [RQ: relative quantification; mean, (standard deviation)]: 0.40 (0.13), 0.49 (0.10), 0.37 (0.08), and 0.43 (0.09) (p<0.01) Paricalcitol treatment for 12 weeks significantly increased expression of all exosomal myomiRNAs in sarcopenia group whereas non-sarcopenia group showed increase in miR-1, miR-133a, and miR-206. Interestingly, the response to paricalcitol treatment was independent of serum vitamin D levels.

Conclusions: Sarcopenic hemodialysis patients showed decreased myomiRNA expression for skeletal muscle differentiation and myoblast profliferation that was upregulated by short term vitamin D treatment. Therefore, vitamin D treatment may have beneficial roles in treatment of sarcopenia.

TH-PO283

Sarcopenia Is Associated with Increased Major Adverse Cardiovascular Event Incidence in Patients on Maintenance Hemodialysis: A Prospective Cohort Study and Mediation Analysis

Lu Jiang, Huijuan Mao. *Nanjing Medical University, Nanjing, China*.

Background: Few studies have investigated the relationship between sarcopenia and the incidence of major adverse cardiovascular events (MACE) in maintenance hemodialysis (MHD) patients. This study thus explored the association between sarcopenia and MACE in a prospective cohort with mediation analysis.

Methods: The exposure was sarcopenia. The primary endpoint was the occurrence of MACE, defined as the composite of all-cause mortality or hospital admission with a primary diagnosis of acute myocardial infarction, stroke, or heart failure during a 3-year follow-up period. Multivariate Cox regression analyses were used to test the association between sarcopenia and subsequent MACE incidence. Mediation analyses were used to investigate whether potential mediators influenced the association between sarcopenia and MACE.

Results: Of the 230 patients enrolled, 57% were male, and a median dialysis vintage of 67 months (IQR: 32 to 119). The prevalence of sarcopenia was 45.2%. The presence of sarcopenia was significantly correlated with age (Spearman's r = 0.47, $P < 0.001$), C-reactive protein (Spearman's r = 0.13, $P = 0.044$), serum albumin (Spearman's r = –0.22, $P < 0.001$), 25(OH) vitamin D (Spearman's r = –0.26, $P < 0.001$), and coronary artery calcification score (Spearman's r = 0.20, $P = 0.002$). Over the 3-year follow-up period, MACE were observed in 59/104 (56.7%) patients with sarcopenia and 38/126 (30.2%) patients without sarcopenia (log-rank $P < 0.001$). After accounting for potential confounders, patients with sarcopenia presented a 66% (4–168%, $P = 0.035$) increase in their risk of MACE incidence as compared to non-sarcopenic individuals. However, adjusted mediation analyses did not detect any indication of a causal mediation pathway linking the effects of sarcopenic status on coronary artery calcification score, C-reactive protein, serum albumin, or 25(OH) vitamin D levels to MACE outcomes. Conversely, sarcopenia exhibited a direct effect (average direct effect range: –0.50 to –0.69, all $P < 0.05$) on MACE incidence.

Conclusions: The presence of sarcopenia was associated with a higher incidence of MACE in MHD patients. The putative effects of sarcopenia on this cardiovascular endpoint appear to be direct and not mediated by any causal pathways that include vascular calcification, inflammation, hypoalbuminemia, or vitamin D.

Funding: Government Support - Non-U.S.

TH-PO284

Relationship between Muscle Mass, Strength, and Physical Performance in Patients on Maintenance Hemodialysis

Daeun Park, Seok hui Kang. *Yeungnam University School of Medicine and College of Medicine, Daegu, Republic of Korea*.

Background: A relationship between muscle mass, muscle strengh, and physical performance in hemodialysis (HD) patients could be not established by a unidirectional pathway. This study aimed to assess the causal association of the aforementioned three variables using a mediation analysis.

Methods: We included 84 HD patients. The collected data included appendicular lean mass index (ALM/Ht^2), handgrip strength (HGS), gait speed (GS), five-times sit-to-stand test, 30-s-sit-to-stand test (STS30), 6-min walk test (6MWT), timed up and go test, and short physical performance battery. Mediation analysis was done using Baron and Kenny's regression approach to investigate the mediating effect.

Results: The mean ALM/Ht^2 and HGS were 6.6 ± 1.0 kg/m^2 and 26.1 ± 7.4 kg, respectively. ALM/Ht^2 or HGS showed a positive association with GS, STS30, or 6MWT, and the association between ALM/Ht^2 and HGS was significant. After adjusting for HGS, the association between ALM/Ht^2 and three physical performances did not remain significant; however, after adjusting for ALM/Ht^2, the association between HGS and three physical performances remained significant.

Conclusions: The present study demonstrated that physical performance tests were associated with both ALM/Ht^2 and HGS, but the association between ALM/Ht^2 and physical performance tests is completely mediated by HGS.

TH-PO285

Gait Speed as a Crucial Independent Predictor of Mortality and Cardiovascular Risk in Patients on Maintenance Hemodialysis

Yuan Luo, Bing Zhuang, Guiling Wei, Hong Ye, Chunsun Dai. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China*.

Background: Low gait speed is an important criterion for diagnosing sarcopenia, which is prevalent in maintenance hemodialysis (MHD) patients. This prospective cohort study evaluated the impact of sarcopenia on myocardial structure and function, survival, hospitalization, and cardiovascular events (CVE) in MHD patients.

Methods: Participants were derived from a single dialysis center. Skeletal muscle mass, handgrip strength, gait speed (GS), and echocardiography were assessed. GS is measured by a 6-minute walk test. Lower gait speed was defined at <0.8m/s. The primary endpoints were CVE, hospitalization, and all-cause mortality.

Results: We studied 307 participants, 46 (15.0%) with lower gait speed. Participants with lower gait speed were characterized by older age (68.1±9.8 years vs. 57.2±12.3 years, P<0.001) and a higher prevalence of diabetes (12.8% vs. 33.1%, P<0.001). Participants with lower gait speed had higher left ventricular posterior wall (12.33±0.93 vs 12.09±0.98 mm, P=0.040), higher interventricular septum thickness (13.36±1.07 vs 13.10±1.06 mm, P=0.037), higher right ventricular wall (10.28±1.12 vs 9.79±1.12 mm, P<0.001), and faster tricuspid valve regurgitation velocity (1.51±0.79 vs 1.19±0.50 cm/s, P=0.001). Lower gait speed participants also had higher left ventricular mass index (129.2±27.6 vs 120.7±23.9, P=0.005), a higher proportion of right ventricular diastolic dysfunction (60.0% vs 35.8%, P=0.016), and a higher proportion of valve calcification (57.9% vs 34.9%, P=0.006). Lower gait speed was strongly negatively correlated with left ventricular mass (LVM) (r =-0.273, P< 0.001). Within 24 months of followup, gait speed was independently predicted CVE (adjusted hazard ratio (HR)=0.402; 95% CI [0.190–0.850]; P=0.017), hospitalization (HR=0.316; 95% CI [0.193–0.518]; P<0.001), and all-cause mortality (HR=0.082; 95% CI [0.028–0.244]; P<0.001).

Conclusions: Gait speed is associated with left ventricular mass and right ventricular dysfunction in MHD patients. Gait speed is an independent predictor of all-cause mortality, hospitalization, and cardiovascular risk in Maintenance Hemodialysis Patients.

Funding: Government Support - Non-U.S.

TH-PO286

Risk Factors and Characterization of Falls in Patients on Hemodialysis: A Multicenter Study

Yan-ru Chen, Huifen Han, Xiaoxia Gu, Qiuyan Li, Zengchun Ye, Hui Peng. *The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*.

Background: Hemodialysis (HD) patients have an increased risk of falls, which raises healthcare expenses in addition to morbidity and mortality. The purpose of this study was to assess the risk factors and characterize the features of falls in hemodialysis patients to provide direction for developing prevention strategies.

Methods: 820 HD patients from four hemodialysis facilities participated in this multi-center cross-sectional study. Online self-made questionnaires was used to gather general information about HD patients as well as fall characteristics. We analyzed the characteristics of fall patients and employed the multivariate logistic regression model to assess the risk factors of falls.

Results: A total of 820 hemodialysis patients were actually included in the statistics, consisting of 60.1% males (493 patients) and 39.9% females (327 patients), with an average age of 58.5±14.3 years old and a median dialysis vintage of 42 months. A total of 187 patients (22.8%) experienced falls, with an average age of 60.5 ± 14.6 years old. The incidence of falls was 19.7% (97 fallers) in males and 27.5% (90 fallers) in females. 358 falls occurred overall, of which 50.8% happened during daytime activity. 78.8% of falls led to varying degrees of injury, with the most common injury being soft tissue contusion. Falls most often occur in the living room or bedroom of the home. The leading symptoms in hemodialysis patients before falling was dizziness (26.3%) or lower limb weakness (34.4%). The results of multivariate logistic regression analysis indicated that age 65 and over (OR=1.699, 95%CI: 1.183-2.439, P=0.004), females (OR=1.505, 95%CI:1.070-2.118, P=0.019), and longer dialysis vintage (OR=1.475, 95%CI:1.224-1.779, P=0.000) were independent risk factors for falls among hemodialysis patients.

Conclusions: In summary, our results showed that the incidence of falls was higher in hemodialysis patients (22.8%), with females having a higher incidence than males. Female gender, age older than 65 years, and longer dialysis vintage are critical risk factors for falls among hemodialysis patients. Future research should explore specific interventions to reduce the risk of falls and improve the overall safety and quality of life for hemodialysis patients.

TH-PO287

Comparison of Daily Physical Activity between Dialysis Periods in Patients Undergoing Sessions Three Times per Week

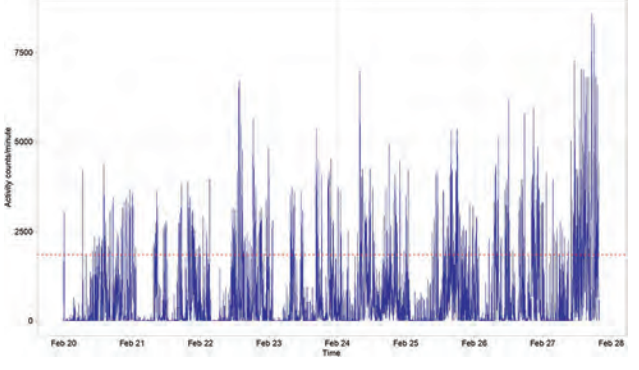
Alfredo Fuentes Mercado,[1] Salvador L. Gil,[1] Erika E. Jaime Borja,[1] Rodrigo Gopar-Nieto,[1] Pablo Martinez Amezcua.[2] *[1]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico; [2]Johns Hopkins University, Baltimore, MD.*

Background: Patients undergoing hemodialysis are significantly less active than healthy sedentary controls. Particularly on hemodialysis days, they have fewer steps than on interdialytic days. Accelerometers are non-invasive wearable devices that measure the acceleration of the body part they are attached to. We aimed to describe daily physical activity in patients undergoing hemodialysis sessions thrice a week and quantify differences in daily activity across inter-dialytic days and dialytic days.

Methods: This was a cross-sectional study. Patients 18 and older undergoing HD without contraindications for physical activity or major mobility limitations were included. Physical activity was measured with a wrist-worn triaxial accelerometer (ActiGraph GT9X, Pensacola, FL). Participants wore the device continuously on the non-dominant wrist for 4-8 days. Valid days had≥90% of wear time. We derived total activity counts (TAC), daily active time, and the active-to-sedentary transition probability (ASTP–a measure of activity fragmentation). We estimated differences in activity measures across interdialytic periods with mixed-effects linear models to account for the clustering of observations.

Results: Among 27 participants (mean age=39.6, [SD=12.5]; 40.7% female), the mean TAC was 2.34 million (SD=0.77 million), mean active time was 446.8 (SD=137.12) minutes, and mean ASTP was 0.25 (SD=0.07). Physical activity was lower (mean active time= -103 minutes [1 hr and 43 mins], 95% CI: -148.5 to –58.6; TAC –0.7 million, 95% CI –0.9 to -0.4), and more fragmented (AST= 0.05, 95% CI 0.03 to 0.07) on dialysis days compared to interdialytic days.

Conclusions: Our findings indicate that physical activity levels are lower and more fragmented during dialysis than interdialytic days. Future efforts should focus on promoting physical activity on dialytic days.



Activity count for a week of one of the participants in our study, an example of the data we analize for the results.

TH-PO288

Fragmented Physical Activity and Mortality in Patients on Hemodialysis: Insights from the Fitbit Study

Rakesh Malhotra,[1] Britta Larsen,[1] Subhasis Dasgupta,[1] Tushar Chopra,[6] Sarah J. Schrauben,[5] David A. Drew,[3] Talat Alp Ikizler,[4] Peter Kotanko,[2] Joachim H. Ix.[1] *[1]University of California San Diego, La Jolla, CA; [2]Renal Research Institute, New York, NY; [3]Tufts Medical Center, Boston, MA; [4]Vanderbilt University, Nashville, TN; [5]University of Pennsylvania, Philadelphia, PA; [6]University of Virginia, Charlottesville, VA.*

Background: Limited data suggest that lower physical activity (PA) overall is associated with poor health outcomes in hemodialysis (HD). Above and beyond total PA, little is known about fragmentation of PA (activity time before breaks). This study evaluates the association between PA fragmentation, and mortality risk among HD patients.

Methods: HD patients wore wearable activity trackers (Fitbit) between March 2018 and April 2020, with mortality data collected until December 2023. Minute-by-minute activity data over a 7-day period were used to categorize each minute as active (≥10 steps/minute) or sedentary (<10 steps/minute). Activity was further categorized by activity patterns: activity fragmentation (active to sedentary transition probability, calculated as the reciprocal of the average active bout duration), and segment length of consecutive active minutes (<5, 5-10, and ≥10 minutes). Cox proportional hazards models were used to assess the associations between activity patterns and mortality risk, adjusting for demographic, device wear time and comorbidities.

Results: We collected data on 85 HD patients (mean [SD] age, 62 [13] years; 45% women), 37 died (44%) during follow-up (mean [SD] of 3.1 [1.6] years. Participants who died tended to have a 10% higher activity fragmentation (mean [SD], 47% [6%] vs 37% [8%]; P<0.001), and a higher percentage of short activity segments (<5 minutes) (mean [SD], 51% [12%] vs 35% [10%]; P<0.001), than those who were alive at follow-up. In fully adjusted analyses, greater activity fragmentation was linked to an increased mortality risk (HR 1.54, 95% CI, 1.08-2.04). Short activity segments of < 5 minutes were associated with higher mortality risk (HR 1.32, 95% CI, 1.08-1.66) but activity segments of 5-10 and ≥ to minutes were not associated with mortality risk (Figure 1).

Conclusions: Our findings suggest that fragmented daily physical activity, especially short activity bouts < 5 minutes, is associated with mortality risk in HD patients.

Figure 1. Hazard Ratios for Activity Fragmentation, and Time Spent in Various Bout Lengths

Variables	Hazard ratio Unadjusted	Model 1	Model 2
Activity fragmentation*	1.80 (1.18-2.21)	1.78 (1.20-2.14)	1.54 (1.08-2.04)
Activity spent in bouts, %**			
<5 min	1.49 (1.12-1.72)	1.40 (1.14-1.75)	1.32 (1.08-1.66)
5-10 min	1.05 (0.80-1.51)	1.04 (0.81-1.54)	1.12 (0.95-1.42)
≥10 min	0.88 (0.72-0.99)	0.87 (0.70-1.16)	0.94 (0.72-1.13)

Model 1: Adjusted for baseline age, sex, and race/ethnicity.
Model 2: Model 1 + device wear time + diabetes, hypertension, heart disease, pulmonary disease
*Scaled per 10% higher degree of activity fragmentation, or a 10% higher probability of transitioning from an active to a sedentary state.
** Scaled per 10% higher activity fragmentation,

TH-PO289

Move More: Development, Testing, and Feasibility of a Patient-Centered Physical Activity Program with a Maintenance Phase for Patients on Hemodialysis

Alexis King,[1,2] Ashley Morgan.[1] *[1]University of Illinois Urbana-Champaign, Urbana, IL; [2]University of the Pacific College of the Pacific, Stockton, CA.*

Background: Individuals with end-stage kidney disease (ESKD) receiving maintenance hemodialysis (HD) often experience low physical activity (PA) levels and poor physical function (PF), contributing to reduced quality of life (QOL) and increased mortality risk. Exercise programs frequently fail to significantly improve these outcomes. This study compares the efficacy of an individualized patient-centered PA program, Move More (MM), to a standard intradialytic cycling (IDC) program in improving PF and QOL among HD patients.

Methods: Twenty-three HD participants were randomly assigned to MM (N=13) or IDC (N=10) for 14 weeks. Primary outcomes measured PA participation via a logbook and point system. Secondary outcomes assessed PF (STS-60, max handgrip strength, and normal 4-meter gait speed walk), patient reported outcomes (depression, fatigue, and perceived wellness), and program feasibility. Participants assigned to MM were encouraged to continue the program during a 12-week maintenance phase, with seven opting to proceed. The study evaluated participants' behavior towards PA participation by using the Behavior Stages of Change Questionnaire.

Results: Mean age was 63.1 (± 10) years; 73.9% male; and 65.2% Black with an average BMI of 36 (± 10.3). At 14 weeks, MM participants showed significant improvements in total PA minutes compared to IDC at 14 weeks (p=0.001) and marked improvements in 4-meter gait speed walk (p=0.006) and handgrip strength (p=0.014). No significant changes were found between groups in PF changes, though trends towards increased handgrip strength were observed (p=0.077). Additionally, MM participants PA levels and PF were maintained during the maintenance phase.

Conclusions: The MM program increased PA levels more than the standard IDC program. However, further research with larger cohorts is necessary to ascertain if MM can lead to substantial improvements in PF. The study highlights the value of a personalized PA program to diverse physical abilities and preferences, suggesting MM's potential for sustainable effectiveness in fostering a long-term PA engagement in HD patients.

TH-PO290

Chronic Pain Characteristics and Associated Symptoms in Patients on Maintenance Hemodialysis: Findings from the HOPE Consortium Trial

Michael J. Fischer,[1] Jesse Y. Hsu,[1] Joanna Walsh,[1] David M. Charytan,[1] Susan T. Crowley,[1] Daniel Cukor,[1] Laura M. Dember,[1] Ardith Z. Doorenbos,[1] Denise Esserman,[1] Manisha Jhamb,[1] Kirsten L. Johansen,[1] Francis J. Keefe,[1] Paul L. Kimmel,[2] Mark Lockwood,[1] Rajnish Mehrotra,[1] Benjamin J. Morasco,[1] Sagar U. Nigwekar,[1] Patrick H. Pun,[1] Raghd Qamhiyeh,[1] Jennifer S. Scherer,[1] Rebecca J. Schmidt,[1] Jennifer L. Steel,[1] Mark L. Unruh,[1] Jonathan G. Yabes,[1] Sahir Kalim.[1] *[1]HOPE Trial Consortium, Philadelphia, PA; [2]National Institutes of Health, Bethesda, MD.*

Background: Pain is one of the symptoms reported most frequently by maintenance hemodialysis (HD) patients. However, there is limited information on its etiologies, characteristics, and associations with other symptoms.

Methods: The HOPE Consortium Trial to Reduce Pain and Opioid Use in Hemodialysis is a multicenter randomized trial to address chronic pain in adults receiving maintenance HD. We enrolled patients with moderate or severe chronic pain on maintenance HD at 103 dialysis facilities across the US from January 2021 to April 2023. Pain interference and severity were assessed by the Brief Pain Inventory (BPI) [range 0-10]. We used multivariable regression with LASSO to examine associations between pain interference/severity and participant characteristics, and Pearson's correlation to examine relationships between pain interference/severity and other symptoms at enrollment.

Results: Among 643 participants, the median (IQR) BPI interference score was 6.6 (5.1-7.8) and severity score was 6.0 (4.5-7.5). 84% of participants experienced pain >1 year and 75% had daily pain. 89% of participants cited musculoskeletal pain and 66% cited neuropathic pain. The median (IQR) number of painful body regions was 8 (4-14), and the most common were lower back (~70%), knees (~50%), feet (~45%), neck (~40%), and hands (~40%). In multivariable regression analyses, female sex, unemployment, diabetes, cardiovascular disease, anxiety, and depression were associated with significantly greater pain interference whereas White race, non-Hispanic ethnicity, higher education, and greater years on dialysis were associated with significantly lower pain interference. PCS SF-6 (pain catastrophizing), PROMIS fatigue, PHQ-9 (depression), and GAD-7 (anxiety) scores were moderately correlated with BPI interference (r>0.4).

Conclusions: Among HD patients with chronic pain, pain characteristics were heterogeneous. Sociodemographic and psychological were more strongly associated with pain interference and severity than comorbidity and dialysis factors.

Funding: NIDDK Support, Other NIH Support - HEAL support

TH-PO291

Cannabis Use in Patients on Maintenance Hemodialysis (HD) with Chronic Pain: A Secondary Analysis of the HOPE Trial

Jennifer S. Scherer,[1] Wenbo Wu,[1] James B. Wetmore,[1] Jane Liebschutz,[1] Elenore P. Bhatraju,[1] Kerri L. Cavanaugh,[1] Benjamin J. Morasco,[1] Jesse Y. Hsu,[1] Laura M. Dember,[1] Paul L. Kimmel,[2] Sahir Kalim,[1] Martin Cheatle,[1] Christopher C. Holden,[1] Joanna Walsh,[1] Caroline M. Wilkie,[1] William Becker,[1] David M. Charytan.[1] *[1]HOPE Trial Consortium, Philadelphia, PA; [2]National Institutes of Health, Bethesda, MD.*

Background: Legalization may increase cannabis use by maintenance hemodialysis (HD) patients. Data on frequency or factors associated with use by HD patients are limited.

Methods: The HOPE Consortium Trial to Reduce Pain and Opioid Use in HD is a multicenter randomized trial that enrolled patients with at least moderate chronic pain receiving HD at 103 US dialysis facilities from 01/2024 to 04/2023. Demographics, social and medical history, cannabis use, pain intensity and interference, depression, and anxiety, were collected at baseline. Multi-variable logistic regression was used to examine associations of cannabis use with baseline data.

Results: Among 643 participants, 102 (16%) reported current cannabis use, 133 (21%) former use, and 408 (63%) never used. Of current users, 39% resided in states with full cannabis legality, 40% in states that legalized use during the study, 15% in states with medical use legality, and 5% in states where medical use was legalized during enrollment. Compared to non-users/past users, current cannabis users were younger (54 vs. 63 years), more likely to be disabled (79% vs. 66%), to have received dialysis for >5 years (40% vs. 30%), to have a diagnosis of depression (41% vs. 31%), anxiety (28% vs. 20%), or any psychological disorder (51% vs. 38%), and less likely to be married (16% vs. 34%). In adjusted models, there was a lower likelihood of cannabis use in older individuals (OR=0.23 [95%CI 0.12-0.44], 0.25 [0.14-0.50], in age groups 55-65, and 65-75 respectively, compared to ages 18-55, p<0.01) and in married individuals (OR=0.49 [0.26-0.93], p =0.03). Use was more likely in current (OR=2.95 [1.51-5.76]) or former (OR=2.16 [1.20-3.91]) smokers, and alcohol users (OR=2.67 [1.32-5.41]). We did not find significant associations of cannibas use with pain or psychological measurements.

Conclusions: Cannabis use is common in HD patients with chronic pain. Younger, unmarried individuals, who use other substances may be the most likely to use cannabis.

Funding: NIDDK Support

TH-PO292

Music Therapy for People with CKD Undergoing Haemodialysis: Rapid Systematic Review and Meta-Analysis

Yunan Han,[1] Davey Li,[1] Tanika Kelly,[2] Takeshi Hasegawa,[4] Hisashi Noma,[5] Erika Ota,[3] Taihei Suzuki,[4] Yoshitaka Watanabe,[6] Hiroi Tomioka,[6] Hiroki Nishiwaki.[2,7] *[1]University of Illinois Chicago College of Medicine, Chicago, IL; [2]University of Illinois Chicago, Chicago, IL; [3]St.Luke's International University, Chuo, Japan; [4]Showa University, Shinagawa, Japan; [5]Institute of Statistical Mathematics, Tachikawa, Japan; [6]Showa University Nortern Yokohama Hospital, Yokohama, Japan; [7]Showa University Fujigaoka Hospital, Yokohama, Japan.*

Background: Patients receiving hemodialysis (HD) experience various types of symptom burden. Anxiety, depression, and pain are common comorbidities for patients with CKD receiving HD. Randomized controlled trials have shown music to have positive health benefits among patients receiving HD.

Methods: In this systematic review and meta-analysis, we searched MEDLINE, and CENTRAL through April 2024 for interventional studies involving music-based interventions among patients on HD. Study quality was assessed using the Cochrane Collaboration risk-of-bias 2.0 tools. Across eligible studies, random-effects meta-analyses were used to combine effects of music intervention on three study endpoints; anxiety, depression, and pain in hemodialysis patients.

Results: Among the 83 citations identified by our search strategy, 19 studies met our eligibility criteria for inclusion, and 11 (total n =765) reported effect sizes and measures of variance for quantitative synthesis (7 for anxiety, 3 for depression, and 4 for pain). Music was associated with significantly decreased anxiety, with standardized mean difference (hedge's g) of -0.65 [95% CI -1.10 to -0.20, I^2=76%] compared to the control group (**Figure 1**). Depression, on the other hand, showed no statistically significant difference with a standardized mean difference of -0.56 [95% CI -1.27 to 0.15, I^2=61%] for the intervention group compared to the control group (**Figure 2**). Pain was decreased in the intervention group compared to the control group, with standardized mean difference of -1.91 [95% -2.74 to -1.35, I^2=11%] in visual analog scale (**Figure 3**).

Conclusions: Music decreased anxiety and pain among the patients with HD in the current meta-analysis.

Fig1. Anxiety

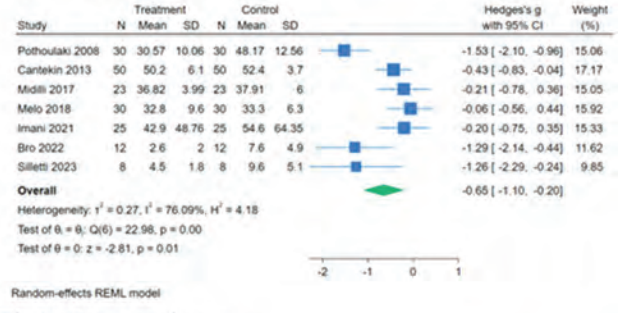


Fig2. Depression

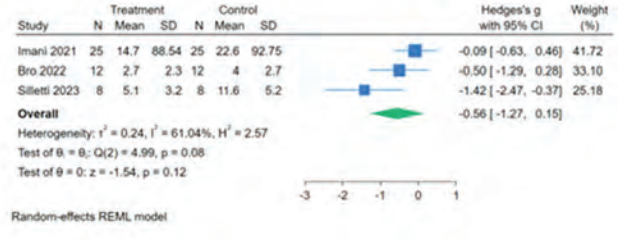
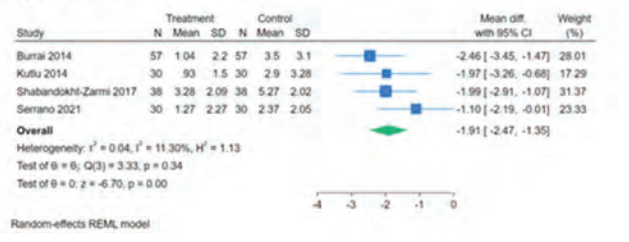


Fig3. Pain



TH-PO293

Point-of-Care Ultrasound-Guided Cannulation of Arteriovenous Fistula Comparison with Standard Cannulation Technique: A Systematic Review and Meta-Analysis

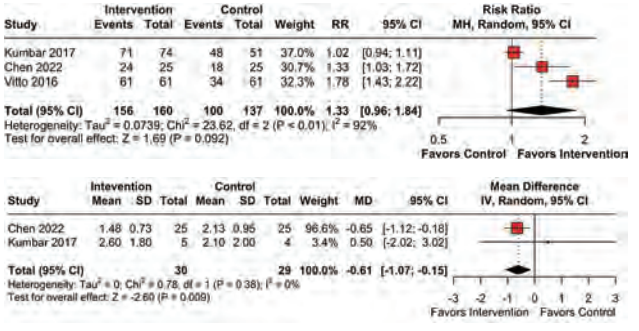
Luis Claudio Santos Pinto,[1] Jiandra Da Luz,[2] Lucas Barbosa,[3] Ofonime Chantal Udoma-Udofa,[4] João L. de Magalhães Leal Moreira,[5] Lucianna B. Luborrigueiro.[6]
[1]Metropolitan University Center of Amazon, Belem, Brazil; [2]Universidad Nacional de la Plata, La Plata, Argentina; [3]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [4]Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil; [5]Universidade Estadual de Feira de Santana, Feira de Santana, Brazil; [6]European Atlantic University, Santander, Spain.

Background: Ultrasound-guided (US-guided) cannulation in arteriovenous fistulas (AVF) is a well-established practice for patients with kidney disease undergoing hemodialysis. Although there is no absolute consensus, studies demonstrated that US guidance increases cannulation success rates compared with conventional techniques. This meta-analysis aims to evaluate the effectiveness of US-guided compared with the standard cannulation technique.

Methods: We systematically searched PubMed, Embase, and Cochrane databases to identify randomized controlled trials (RCTs) comparing US-guided versus standard cannulation in hemodialysis patients. The primary outcome of interest was the cannulation success rate. The pain score was evaluated using the VAS score. We pooled risk ratios (RR) for binary outcomes, and mean difference (MD) for continuous endpoints with 95% confidence intervals (CI), employing a random-effects model. We used R version 4.3.2 for all statistical analysis.

Results: Our study included 5 RCTs comprising 224 patients who underwent either US-guided (40.6%) or standard cannulation(40.2%). US-guided and standard cannulation had a similar success rate (RR 1.33; 95%CI 0.96 to 1.84; p=0.09; I2=). US-guided cannulation was associated with a reduction in pain score (MD -0.61; 95%CI -1.07 to -0.15; p<0.05; I2=). There was no significant difference between groups in procedure length (MD -20.87 min; 95%CI -82.94 to 41.20; p=0.51; I2=) and complication rate (RR 0.89; 95%CI 0.55 to 1.44; p=0.64; I2=).

Conclusions: In patients undergoing hemodialysis, US-guided cannulation had a similar success rate compared with the standard technique. However, it showed a difference, albeit small, associated with reduced pain perception, providing greater comfort to the patient.



TH-PO294

Efficacy and Safety of Difelikefalin Compared with Placebo in Patients Receiving Concomitant Opioid Medication

James Burton,[1] Thilo Schaufler,[2] Satkiran Grewal,[3] Despina Ruessmann,[2] Murray Lowe,[2] Warren Wen,[4] Steven Fishbane.[5] *[1]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [2]CSL Vifor, Glattbrugg, Switzerland; [3]CleanSlate Centers Inc, Philadelphia, PA; [4]Cara Therapeutics Inc, Stamford, CT; [5]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY.*

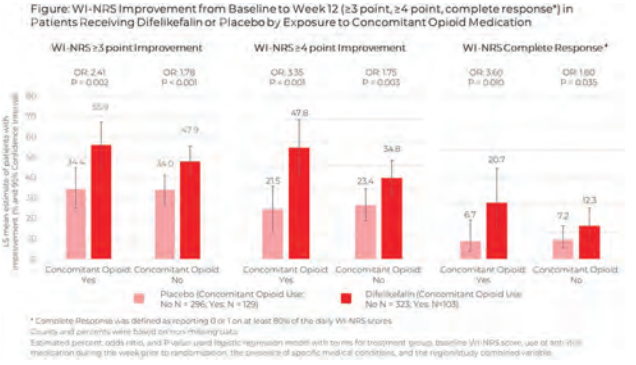
Background: Difelikefalin (DFK) is a selective kappa opioid receptor agonist approved to treat moderate to severe CKD-associated pruritus (CKD-aP) in patients on hemodialysis (HD). Pruritus is a known side effect of mu opioid receptor agonistic drugs, but it is unknown if their concomitant use influences the antipruritic effects or safety of DFK.

Methods: Phase-3 studies KALM-1 and -2 established the efficacy and safety of DFK over placebo (PBO) in HD patients with CKD-aP. Itch intensity was assessed with the weekly mean of the Worst Itching Intensity Numerical Rating Scale (WI-NRS) measured at baseline and after 12 weeks of treatment. Patients were asked daily for the worst itch intensity in the past 24 hours from 0 (no itch) to 10 (worst itch imaginable). This exploratory post-hoc analysis of pooled KALM trial data assesses the efficacy and safety of DFK compared to PBO, dependent upon exposure to concomitant opioid medication.

Results: Of participants randomized to receiving DFK/PBO, 24.2%/30.4% were taking concomitant opioid medications. More patients treated with DFK vs. PBO achieved WI-NRS improvements of ≥3point, ≥4point and complete response (defined as ≥80% of daily scores 0 or 1) at week 12, regardless of their concomitant use of opioids (Figure). More patients on concomitant opioids reported any non-fatal treatment emergent adverse event (TEAE) independent of treatment exposure (concomitant vs. no concomitant opioid exposure: DFK: 44.7% vs. 19.0%; PBO: 38.0% vs. 15.9%). Similarly, severe TEAEs were more common in patients on concomitant opioids (concomitant vs. no concomitant opioid exposure: DFK: 22.3% vs. 10.9%; PBO: 23.3% vs. 8.1%).

Conclusions: This exploratory analysis confirms that DFK can effectively relieve CKD-aP in HD patients despite the use of concomitant opioid medications. The higher rate of TEAEs in patients receiving either DFK or PBO in combination with opioids makes careful assessment of continued use of opioid medications advisable.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma, Cara Therapeutics



TH-PO295

Influence of Concomitant Opioid Medications on Antipruritic Effect and Safety of Difelikefalin in Patients on Hemodialysis

James Burton,[1] Thilo Schaufler,[2] Satkiran Grewal,[3] Despina Ruessmann,[2] Murray Lowe,[2] Warren Wen,[4] Steven Fishbane.[5] *[1]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [2]CSL Vifor, Glattbrugg, Switzerland; [3]CleanSlate Centers Inc, Philadelphia, PA; [4]Cara Therapeutics Inc, Stamford, CT; [5]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY.*

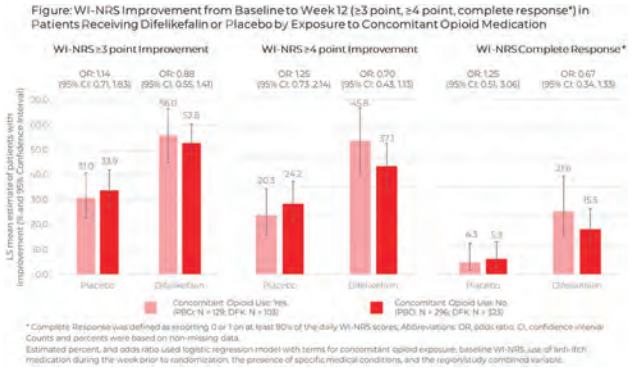
Background: Pruritus is a known side-effect seen with mu-opioid receptor agonists, and hemodialysis (HD) patients receive such treatments. Difelikefalin (DFK) is a selective kappa-opioid receptor agonist indicated to treat moderate to severe CKD-associated pruritus (CKD-aP) in patients on HD. This exploratory post-hoc analysis assesses if using concomitant opioid medications affects efficacy or safety of DFK.

Methods: Phase-3 clinical studies KALM-1 & -2 randomized patients to receive either DFK or placebo (PBO) for 12 weeks after each HD session. Itch severity was measured daily with the Worst Itching Intensity Numerical Rating Scale (WI-NRS); patients indicated their worst itch intensity in the past 24 hours from 0 (no itch) to 10 (worst itch imaginable). We analyzed pooled KALM study data based on concomitant exposure to opioid medications.

Results: Of patients randomized to DFK/PBO, 24.2%/30.4% received other opioids. In both groups the likelihood of achieving improvements at 12 weeks in weekly mean WI-NRS scores of ≥3point, ≥4point or complete response (defined as ≥80% of daily scores 0 or 1) was not influenced by exposure to opioids (Figure). Concomitant opioid medication use was associated with a higher incidence of treatment-emergent adverse events (TEAEs) in both the DFK and PBO groups. Patients receiving opioids experienced TEAEs at a rate of 44.7% (DFK) & 38.0% (PBO) compared to 19.0% (DFK) & 15.9% (PBO) in those not on opioids. The incidence of severe TEAEs was 22.3% (DFK) & 23.3% (PBO) in patients using opioids compared to those who were not (10.9% for DFK & 8.1% for PBO).

Conclusions: Concomitant use of opioid medications did not influence the efficacy of DFK to relieve CKD-aP in HD patients. The increase in TEAEs in patients prescribed concomitant opioids in either the DFK or PBO arms indicates the importance of carefully evaluating polypharmacy, especially continuation of opioid treatments in HD patients treated with DFK for CKD-aP.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma, Cara Therapeutics



TH-PO296

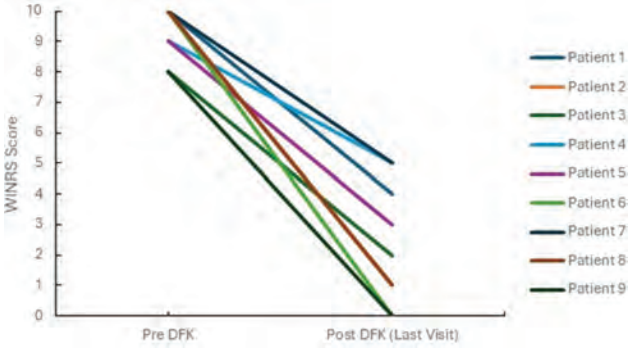
Single-Center Experience from Quebec with Intravenous Difelikefalin to Treat CKD-Associated Pruritus

Isabelle I. Letourneau, Karine Cousineau. *Centre Integre de Sante et de Services Sociaux de Lanaudiere du Quebec, Joliette, QC, Canada.*

Introduction: Chronic kidney disease-associated pruritus (CKD-aP) is a debilitating condition associated with several adverse outcomes in end-stage kidney disease patients including reduced quality of life, sleep quality, and increased mortality. There is a lack of formalized practice guidelines integrating approved new treatments for CKD-aP. Difelikefalin (DFK), a highly selective peripherally acting κ-opioid receptor agonist was approved by Health Canada in 2022 for the treatment of moderate-to-severe CKD-aP.

Case Description: Here, we report implementation of a practice changing initiative in our hemodialysis center as well as a treatment algorithm for CKD-aP. First, we screened patients for pruritus by asking them about itch. We then used the Worst Itch Numerical Rating Scale (WI-NRS) and Self-Assessed Disease Severity (SADS) scales to measure the intensity of pruritus and evaluate its impact on the patient's quality of life respectively. If WI-NRS score was ≥7 (severe) and SADS was B (moderate) or C (severe), DFK was prescribed as first-line therapy. In total, 303 patients were screened. Twelve patients had severe pruritus and were prescribed DFK. Of these patients, 9 responded with a reduction by at least 3 points on their WI-NRS and 4 patients had a complete response (Figure). In some patients, these changes correlated with an improvement in the quality of life as measured by SADS. Safety profile was acceptable. Two patients discontinued treatment due to adverse events of gait disturbance and fatigue in one and somnolence/mental status change in the other. A third patient discontinued treatment due to diagnosis of bullous pemphigus.

Discussion: Our protocol has helped us identify patients with CKD-aP in our hemodialysis center and has allowed to improve patient quality of life. Our experience represents well the feasibility to incorporate framework for screening and diagnosis as well as a treatment algorithm of CKD-aP published in a recent Canadian narrative review.



TH-PO297

Validity of a Single Worst Itch Numeric Rating Scale (WI-NRS) Measurement to Identify Patients with Moderate or Severe CKD-Associated Pruritus

Kieran Mccafferty,[1] Thilo Schaufler,[2] Isabelle Morin,[2] Warren Wen,[3] Lili Chan.[4] *[1]Barts Health NHS Trust, London, United Kingdom; [2]CSL Vifor, Glattbrugg, Switzerland; [3]Cara Therapeutics Inc, Stamford, CT; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Clinical studies use the mean of repeat measurements with the Worst Itching Intensity Numerical Rating Scale (WI-NRS) to assess itch intensity in patients. This is often difficult to implement in daily dialysis practice, raising the question whether a single measurement with the WI-NRS is sufficiently reliable to guide treatment decisions.

Methods: The WI-NRS asks patients to indicate the worst itch intensity in the past 24 hours (range 0 [no itch] to 10 [worst itch imaginable]). Phase 3 clinical studies KALM-1 and -2 demonstrated the favorable benefit–risk profile of difelikefalin over placebo in patients on hemodialysis with moderate to severe chronic kidney disease-associated pruritus (CKD-aP) and calculated the weekly mean of daily WI-NRS measurements to assess baseline itch intensity and change from baseline over up to 12 weeks of treatment. This post-hoc analysis uses the data collected to assess the Pearson correlation between the WI-NRS measurements collected on study days 29, 57, 71 and 85 and the weekly mean of the daily measurements in the respective previous study week (weeks 4, 8, 10 and 12).

Results: The Pearson correlation across all time points for the overall study population was consistent and very high (≥0.93, p<0.0001), indicating a strong correlation between the mean of multiple measurements versus a single WI-NRS measurement. A similar picture was seen when assessing the difelikefalin and placebo arm separately (Table).

Conclusions: A one-off measurement of the WI-NRS can reliably assess itch intensity and identify patients suffering from bothersome itch. Patients reporting a value of ≥4 on a single WI-NRS can be considered to suffer from moderate or severe CKD-aP, and those with a reduction of ≥3 points between two WI-NRS measurements to have a clinically meaningful improvement of their itch. These findings confirm that the WI-NRS is an easy-to-use and consistent tool that can be implemented in daily dialysis care without relevant disruptions to routine tasks.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma, Cara Therapeutics

Table: Pearson correlation between single WI-NRS and mean of the previous week's WI-NRS measurements (all p<0.0001)

	One-off, single WI-NRS (Overall / Placebo / Difelikefalin)			
Weekly mean WI-NRS	Day 29	Day 57	Day 71	Day 85
Week 4	0.930 (N=768) / 0.930 (N=388) / 0.927 (N=380)			
Week 8		0.935 (N=760) / 0.948 (N=388) / 0.920 (N=372)		
Week 10			0.940 (N=742) / 0.948 (N=382) / 0.927 (N=360)	
Week 12				0.956 (N=672) / 0.960 (N=343) / 0.950 (N=329)

TH-PO298

Gabapentin Use and Adverse Effects among Hemodialysis Patients Diagnosed with Pruritus or Neuropathic Pain in US Claims Data

Claudio Rigatto,[1] Ting Lu,[2] Thilo Schaufler,[3] Despina Ruessmann,[3] Ronald L. Pisoni,[2] Brian Bieber,[2] Angelo Karaboyas,[2] Michael Strupp.[4] *[1]Seven Oaks General Hospital, Winnipeg, MB, Canada; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Vifor Pharma Management AG, Glattbrugg, Switzerland; [4]Ludwig-Maximilians-Universitat Munchen, Munchen, Germany.*

Background: Chronic kidney disease-associated pruritus (CKD-aP) is linked with numerous clinical and patient-reported outcomes. Gabapentin (Gaba) is indicated for neuropathic pain (NP), and also used off-label to reduce pruritus symptoms. There are, however, concerns about adverse events (AEs), namely altered mental status and risk of falls. We explored real-world Gaba utilization patterns and relevant AEs in US hemodialysis (HD) patients, and how they may differ by diagnosis of CKD-aP vs. NP.

Methods: We used claims data from 533,232 adult HD patients in the USRDS database between 2016-2020 with Fee-For-Service Medicare Part D coverage. Gaba use, dose, and time to discontinuation were stratified by time-updated diagnosis of CKD-aP or NP. The associations between time-varying Gaba dose – defined as current prescription updated continuously – and six AEs were analysed by recurrent event Andersen-Gill model and adjusted for potential confounders, separately by time-updated diagnosis of CKD-aP or NP.

Results: Point-prevalence of Gaba prescription was 13.9% overall, and was higher among patients with NP (21.1%) than with CKD-aP (11.0%). Median [IQR] time to discontinuation was 5.2 [2.0, 13.0] months in the NP group and 4.2 [1.5, 11.6] months in the CKD-aP group. Mean Gaba dose was higher (503 vs. 433 mg/day) in the NP vs. CKD-aP group, and increased during the first year of use from 410 to 494 mg/day. AE rates ranged from 9.3 (fracture) to 37.8 (altered mental status) per 100 patient-years. We observed a strong dose-response association between Gaba dose and AEs, particularly among patients with CKD-aP (**Table**).

Conclusions: Use of Gaba in HD patients was associated with a higher risk of AEs (including altered mental status, dizziness, falls, and fracture), even at doses as low as 100 mg/day. The increase was greater when Gaba was used off-label in CKD-aP patients. Prescribers should consider the clinically relevant side effects of Gaba when providing treatment options to their patients with CKD-aP.

Funding: Commercial Support - Commercial support by Vifor Fresenius Medical Care Renal Pharma

Table. Adjusted hazard ratios (95% CI) for associations between gabapentin dose and adverse events, by diagnosis group

	Altered mental	Dizziness	Diarrhea	Somnolence	Any fracture	Falls
Rate per 100 PY	37.8	19.3	21.8	15.2	9.3	20.4
Among patients with CKD-aP diagnosis						
Dose = 0	1(ref)	1(ref)	1(ref)	1(ref)	1(ref)	1(ref)
Dose 100	1.21(1.12-1.32)	1.24(1.11-1.39)	1.12(1.01-1.24)	1.05(0.90-1.23)	1.34(1.16-1.56)	1.29(1.16-1.43)
Dose 200	1.44(1.32-1.57)	1.28(1.13-1.44)	1.17(1.05-1.31)	1.34(1.18-1.52)	1.39(1.16-1.66)	1.43(1.27-1.61)
Dose 300	1.50(1.41-1.59)	1.26(1.16-1.37)	1.16(1.05-1.27)	1.46(1.33-1.61)	1.30(1.14-1.48)	1.42(1.31-1.55)
Dose 400-800	1.45(1.33-1.58)	1.33(1.18-1.49)	1.13(1.00-1.28)	1.40(1.24-1.59)	1.22(0.99-1.50)	1.54(1.37-1.73)
Dose 900+	1.56(1.43-1.71)	1.49(1.33-1.68)	1.09(0.96-1.23)	1.48(1.29-1.69)	1.57(1.31-1.86)	1.66(1.48-1.86)
Among patients with neuropathic pain diagnosis						
Dose = 0	1(ref)	1(ref)	1(ref)	1(ref)	1(ref)	1(ref)
Dose 100	1.10(1.07-1.14)	1.12(1.08-1.17)	1.10(1.05-1.14)	1.05(1.00-1.10)	1.13(1.06-1.20)	1.22(1.17-1.27)
Dose 200	1.20(1.16-1.24)	1.15(1.09-1.21)	1.11(1.06-1.15)	1.19(1.14-1.25)	1.16(1.09-1.23)	1.26(1.21-1.31)
Dose 300	1.25(1.22-1.28)	1.16(1.13-1.20)	1.16(1.13-1.19)	1.20(1.16-1.25)	1.09(1.04-1.15)	1.28(1.24-1.32)
Dose 400-800	1.31(1.27-1.34)	1.17(1.13-1.21)	1.14(1.10-1.18)	1.25(1.20-1.30)	1.19(1.13-1.25)	1.39(1.34-1.44)
Dose 900+	1.40(1.37-1.44)	1.21(1.16-1.25)	1.18(1.14-1.22)	1.34(1.29-1.40)	1.22(1.16-1.29)	1.49(1.44-1.54)

Andersen-Gill model for recurrent events, adjusted for age, time on dialysis, prior events, race, sex, Hispanic, primary cause of ESKD
Among Gaba users, dose distribution was 17% with 100, 15% with 200, 29% with 300, 19% with 400-800, and 20% with 900+ mg/day

TH-PO299

Dedicated Patient Optimization Program Improves Lives of Vulnerable Patients

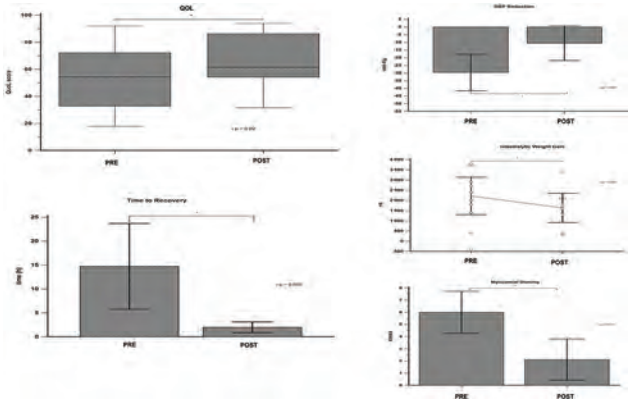
Jarrin D. Penny,[1,3] Patrik Deleaval,[2,1] Christopher W. McIntyre.[1,3] *[1]London Health Sciences Centre, London, ON, Canada; [2]NephroCare Tassin-Charcot, Saint Foy-les-Lyon, France; [3]Lawson Health Research Institute, London, ON, Canada.*

Background: Industrialized 'one size fits all' approaches to care and reliance on single intervention-based strategies results in negative outcomes for many. In response we developed and applied a systematic patient optimization program (POP) applying individualization and complex interventions to support the needs of the most vulnerable patients aiming to improve both the subjective experience and objective tolerability of dialysis.

Methods: Patients (19) with inadequate response to conventional care were identified over a 12-month period. A series of comprehensive baseline objective (physiological, hemodynamic) and subjective assessments were performed and complex foundational/patient-disease specific interventions applied and rigorously evaluated over two weeks. Subjective impact was assessed using dynamic daily patient reported outcome measures. Objective assessments (inclusion and monitoring response) included continuous hemodynamic monitoring, tissue perfusion, vascular ultrasound and intradialytic echocardiography with assessment of HD-induced cardiac injury (myocardial stunning).

Results: Nineteen patients, largely with issues related to hypotension & failure to achieve target weight- in concert with a range of negative symptoms. All patients had multiple components of dialysis altered. POP was associated with a marked improvement in a range of subjective and objective outcomes. QOL improved by 20% (p0.02), recovery time by 86% (p0.005). Reductions in intradialytic systolic BP improved by 19% (p<0.01), interdialytic weight gain 33% (p0.01) and myocardial stunning was significantly reduced (by 63% p0.01) with tight association between changes in BP (p<0.001) and ultrafiltration (p<0.05). At inclusion all patients had been declined transplantation listing, after re-evaluation 3/19 were listed and two successfully received graft.

Conclusions: A complex intervention delivered in a systematic POP improves the subjective wellbeing and objective tolerability of HD in the most challenging patients.



TH-PO300

Improving Treatment Adherence in Patients on In-Center Hemodialysis through Daily Targeted Reporting and Intervention

Sheetal Chaudhuri,[1] Joanna Willetts,[1] Trevor Halliday,[2] Melissa Hosey,[2] Len A. Usvyat,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care AG, Bad Homburg, Germany; [2]Fresenius Medical Care Holdings Inc, Waltham, MA.*

Background: In-center hemodialysis (ICHD) patients who miss prescribed treatments have an increased risk of hospitalization and mortality. We implemented daily targeted reporting (DTR) to identify patients who missed their scheduled treatment the day prior, followed by a tailored intervention to reschedule these missed treatments. Our goal is to describe treatment adherence before and after implementation of DTR and intervention.

Methods: We analyzed clinical data from ICHD patients in the periods before and after introduction of DTR across 16 clinics from a large dialysis organization. Targeted reporting of missed treatments began on 01Mar2024. Missed and ordered treatments, documented in patients' electronic health records, were summarized in the two months before (01Jan2024-29Feb2024) and after (01Mar2024-30Apr2024) initiation of DTR. DTR provided clinic staff with a list of patients who were absent during the scheduled treatment the previous day, enabling staff to reschedule treatments accordingly. Missed treatments were reported as a percent of ordered treatments and as a crude rate per patient per year (ppy). We used Analysis of Variance to test the difference in crude missed treatment rate (ppy) before and after implementation of DTR and intervention.

Results: There were 745 ICHD patients before and 722 ICHD patients after the DTR in the 16 clinics in this analysis. Demographic information for patients before and after DTR showed no significant differences. The percent of documented missed treatments decreased by nearly 6% following introduction of DTR. Crude rate ratio was 0.96 (95% confidence interval 0.80, 1.15) (Table 1).

Conclusions: Although not statistically significant, implementation of DTR suggests a reduction in missed treatments and improvement in treatment adherence in the short term. Future work includes monitoring missed treatments in these clinics to determine if DTR provides sustained reduction in missed treatment rate. Furthermore, conducting a matched analysis could offer insights into the magnitude of the effect.

Funding: Commercial Support - Fresenius Medical Care

Percent of missed treatments and missed treatment rate (ppy) before and after daily targeted reporting/intervention.

	Before (95% CI)	After (95% CI)	% Change	Rate Ratio (95% CI)	P-value
% Missed Treatments	5.34	5.02	-5.99%		
Crude Missed Treatment Rate (ppy, 95% CI)	8.06 (7.12, 9.13)	7.73 (6.79, 8.82)	-4.09%	0.96 (0.80, 1.15)	0.6497

TH-PO301

Self-Management Barriers in Patients on Dialysis: A Potential Target for Improving Clinical and Patient-Reported Outcomes

Esmee Driehuis,[1,2] Yvette Meuleman,[3] Anna A. Bonenkamp,[2] Friedo W. Dekker,[3] Alferso C. Abrahams,[1] Brigit C. van Jaarsveld.[2] DOMESTICO Study Group. *[1]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [2]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands; [3]Leids Universitair Medisch Centrum, Leiden, Netherlands.*

Background: Self-management skills are important to dialysis patients, as they may lead to better health outcomes. However, knowledge is lacking on self-management barriers in these patients, hereby impeding identification of patients in whom self-management may be improved and how these barriers impact health. Thus, we aimed to 1) identify self-management barriers in dialysis patients, 2) assess their relation to patient characteristics and 3) assess their effect on clinical and patient-reported outcomes.

Methods: Patients from the DOMESTICO study, a cohort study in adult incident dialysis, who filled in the Self-Management Screening questionnaire were included. Descriptives of self-management barriers were reported. We determined the barriers' associations with sex, age, educational level, cohabitation, modality (hemodialysis [HD] vs. peritoneal dialysis [PD]) and multimorbidity using point bi-serial correlations. Effects of self-management barriers on health outcomes at 6 and 12 months were investigated using linear and quasi-binomial regression with adjustment for confounding.

Results: In 1518 patients, the presence of self-management barriers varied widely. For instance, most felt confident in their own abilities (self-efficacy; 84.3%), while only 43.6% reported good problem-solving coping skills. Many patient characteristics were related to self-management barriers. For example, age was associated with almost all barriers, PD patients were more willing to perform self-care (r 0.23, 95%CI 0.18;0.28), and patients with more comorbidities were less willing (-0.09, -0.14;-0.04). At 6 months, in patients with more barriers, diastolic blood pressure (DBP) was lower (β -0.51, 95%CI -0.81;-0.20), interdialytic weight gain (IDWG) was higher (0.03, 0.01;0.05), symptom burden was higher (1.99, 1.45;2.55), physical health-related quality of life (HRQoL) was lower (-0.81, -1.04;-0.57) and mental HRQoL was lower (-1.14, -1.38;-0.90). Except for IDWG, these effects persisted at 12 months.

Conclusions: We identified important self-management barriers in incident dialysis patients and their relation to patient characteristics. These barriers impact patients' DBP, IDWG, symptom burden and HRQoL, hence they may be a potential target to improve clinical and patient-reported outcomes.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH, Baxter, Dirinco, AstraZeneca, Cablon Medical, Eurocept Homecare, Novartis, CSL Vifor, Bayer, Alnylam, Government Support - Non-U.S.

TH-PO302

Translation of Interventional Study Findings into Clinical Guidelines for Adults Requiring Maintenance Dialysis

Katherine L. Hull,[1,2] Sherna F. Adenwalla,[1,2] Victoria Cluley,[4] Daniel S. March,[1] Matthew Graham-Brown,[1,2] Rahma Said,[3] James Burton.[1,2] *[1]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [2]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [3]University of Leicester Department of Population Health Sciences, Leicester, United Kingdom; [4]University of Nottingham School of Sociology and Social Policy, Nottingham, United Kingdom.*

Background: There is a substantial gap between the evidence-base from randomised controlled trials (RCTs) and the implementation within clinical care in nephrology. This study aims to understand the factors that influence the utilisation of RCT data in nephrology clinical practice guidelines for the maintenance dialysis population.

Methods: The systematic review was registered prospectively on National Institute for Health Research's International Prospective Register of Systematic Reviews (PROSPERO, CRD42021249460). Searches were completed in MEDLINE, Embase, CINAHL, and CENTRAL. There were no limits on language or location. The search strategy was limited by publication date 01/01/2015 - 31/12/2018. Descriptive statistics are reported as frequencies with percentages and statistical testing included binomial logistic regression.

Results: 7844 records were identified; 268 RCTs with 305 associated reports were eligible. None of the eligible RCTs reported a Patient and Public Involvement and Engagement statement. Twenty-two (8.2%) of the RCTs were utilised in the nephrology clinical guidelines through 24 (7.9%) associated reports. None of the RCTs included in the guidelines were unique to the peritoneal dialysis (PD) population. Binomial logistic regression modelling suggests that RCTs included in the clinical guidelines are more likely to: have clinical effectiveness as their primary purpose; report a clinical trials registration; originate from North America; have a longer follow-up time; and publish adverse event data (Table 1).

Conclusions: Nephrology clinical guidelines are not utilising the full evidence-base of RCTs, with a preference for North American led research. There is an absence of documented patient involvement. The PD population are underrepresented. Poor study design, inconsistent reporting and a lack of external validity appears to impact the utility of RCT data in guidelines.

Variable for RCT characteristic	Co-efficient (β)	Standard Error	Odds Ratio	95% confidence interval
Constant	-4.060	0.686		
Primary purpose of the study	1.899	0.792	6.7	1.4 – 31.5
Clinical trials registration	1.304	0.676	3.7	1.0 – 13.9
Continent	1.604	0.473	5.0	2.0 – 12.6
Variable for report characteristic	**Co-efficient (β)**	**Standard Error**	**Odds Ratio**	**95% confidence interval**
Constant	-3.194	0.422		
Length of follow-up (years)	0.437	0.189	1.5	1.1 – 2.2
Adverse events reporting	0.806	0.471	2.2	0.9 – 5.6

Table 1 - Model of best fit for RCT and publication characteristics predicting presence in nephrology clinical guidelines

TH-PO303

Evaluating Dialysis Decision-Making in Hepatorenal Syndrome

Kunal Bailoor,[1,2] Elliot Tapper,[1] Julie A. Wright Nunes.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Michigan Center for Bioethics and Social Sciences in Medicine, Ann Arbor, MI.*

Background: Hepatorenal syndrome has been traditionally felt to have universally high in-hospital mortality without transplantation. However, the underlying data is uncertain. The question of whether to recommend initiation of hemodialysis for patients with HRS who are not considered candidates for liver transplant is therefore both clinically and emotionally difficult.

Methods: We conducted a vignette-based survey of clinicians across 3 internal medicine sub-specialties (nephrology, critical care, and palliative care) who are involved in decision making regarding dialysis initiation for critically ill patients with hepatorenal syndrome. Our vignette included a case of a critically ill patient with hepatorenal syndrome requiring multiple vasopressors who was not felt to be a candidate for liver transplantation.

Results: 53 clinicians (19 nephrology, 21 critical care, 9 palliative care, 4 trainees) responded; the majority of clinicians (77%) did not recommend hemodialysis. High distress around this decision was reported (Figure 1); this was measured with a validated scale. There were varying degrees of comfort with dialysis-decision making (Figure 2), with nephrologists reporting the lowest comfort (2.6 on 4 point Likert scale) and critical care physicians reporting the highest (2.9/4). Nephrologists reported the highest increase in distress when colleagues disagreed with their decision; all clinicians reported increases in distress with family disagreement.

Conclusions: Decision making about dialysis initiation in the critically ill patient with hepatorenal syndrome provokes distress in all clinicians involved, though distress and comfort with decision making varies among specialties. Further research into what underlies these differences and how best to support clinicians is needed.

Figure 1: Clinician Distress by Specialty

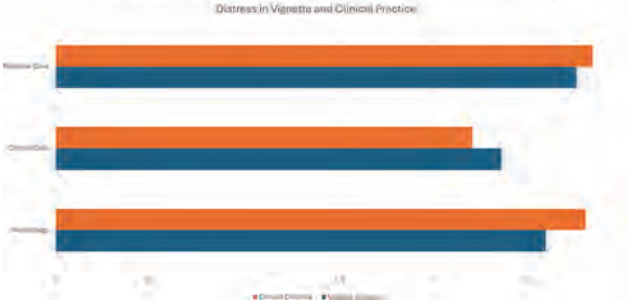
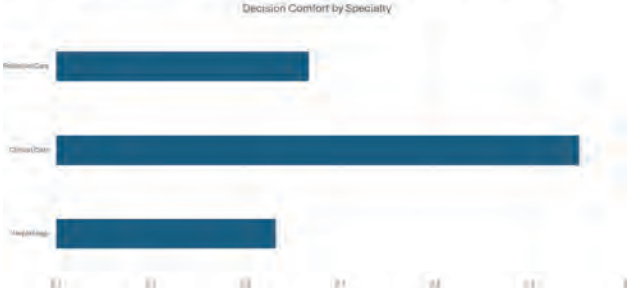


Figure 2: Clinician Comfort by Specialty



TH-PO304

Uncoordinated Care: Decreasing Unnecessary Lab Work in Patients on Dialysis

Jonathan Hall, Sesha Pavan K. Myneni, Nathaniel Leonardi, David A. Mcmillan, Ryan Mullane. *University of Nebraska Medical Center, Omaha, NE.*

Background: The KDOQI clinical practice guidelines recommend avoiding unnecessary venipuncture in patients with end-stage kidney disease (ESKD). Patients on maintenance dialysis have routine blood work. Redundant diagnostics at primary care clinics result in increased frequency of venipuncture, cost of care, and administrative burden. Unfortunately, dialysis unit diagnostics are not consistently available to primary care providers (PCP). We present a quality initiative to identify the extent of this problem and address it through an iterative process of improvement.

Methods: A deidentified analytics report included patients with ESKD based on ICD-10 codes who had lab work ordered at our affiliated primary care clinics. Kidney transplant recipients were excluded. Institutional lab components were used to collect information on ambulatory orders redundant with dialysis labs. This included the number of orders over a specified period and the ordering clinic. PCPs completed surveys regarding how they access dialysis labs, if such access would decrease the number of tests ordered, and their familiarity with what routine dialysis studies entail. Education on access to certain dialysis units' lab results and what labs are routinely ordered was sent by email followed by a repeat survey.

Results: Between February 2023 and January 2024, 191 patients with ESKD underwent at least 1536 venipuncture events for redundant testing. The median number of metabolic panels per patient was 5 (IQR 3-11). Initial surveys were completed by 42 of 113 PCPs (37%). 90% could not access dialysis labs and 92% would order less tests with access to these results. Three months post-education, 3 of 20 clinics decreased the number of metabolic panels ordered on ESKD patients by 16.9-41.7%, but no significant change was noted overall. 27 PCPs (24%) completed repeat surveys. 85% still could not access dialysis labs and 83% were not familiar with what these studies entail.

Conclusions: Dialysis patients frequently undergo unnecessary diagnostics. Access to dialysis studies and familiarity with dialysis lab monitoring could decrease redundant ordering practices. An estimation of the costs of care is underway. Focus groups and in-person provider education will be held at primary care clinics. Further progress will require collaboration with PCPs, dialysis units, and health system informatics.

TH-PO305

Inpatient vs. Outpatient Dialysis Transition and Hospitalization Outcomes in a National Cohort of Patients with Advanced CKD

Ji Hoon Yoon,[1] Kamyar Kalantar-Zadeh,[2] Yoko Narasaki,[1] Amy S. You,[1] John J. Sim,[4] Csaba P. Kovesdy,[3] Alejandra Novoa Vargas,[1] Danh V. Nguyen,[5] Connie Rhee.[1] *[1]University of California Los Angeles, Los Angeles, CA; [2]Harbor-UCLA Medical Center, Torrance, CA; [3]The University of Tennessee Health Science Center, Memphis, TN; [4]Kaiser Permanente Southern California, Pasadena, CA; [5]University of California Irvine, Irvine, CA.*

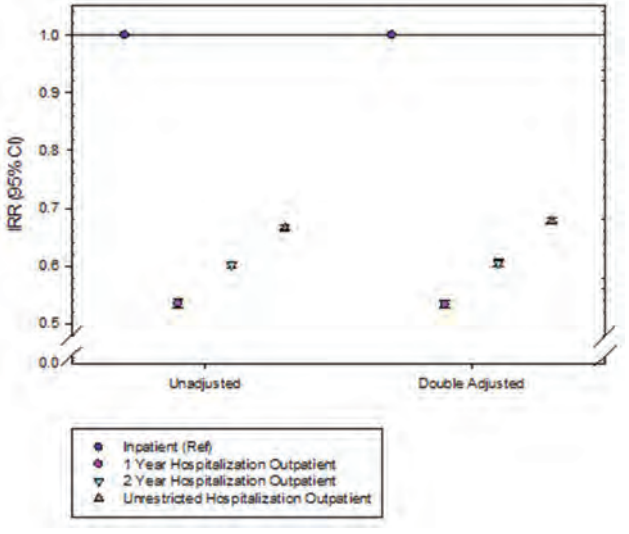
Background: Advanced CKD patients transitioning to ESKD have high morbidity and mortality in the first few months of dialysis initiation. We sought to determine whether transitioning to dialysis in the inpatient vs. outpatient setting is associated with differential hospitalization outcomes among incident ESKD patients.

Methods: We examined advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) who transitioned to dialysis within 2-yrs of their 1st (index) eGFR <25 over 1/1/07-6/30/20 from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical/pharmacy claims and enrollment records for commercial/Medicare enrollees, and EHR data. We compared hospitalization rates among patients who transitioned to dialysis in the inpatient vs. outpatient setting matched by propensity score (PS) in a 1:1 ratio with a caliper distance of ≤0.2 to address confounding by indication in Poisson models.

Results: Among 84,915 advanced CKD patients who transitioned to dialysis, 20,617 patients who transitioned to dialysis in the outpatient setting were PS-matched to 20,617 patients who transitioned to dialysis in the inpatient setting. In PS-matched models, outpatient dialysis transition was associated with lower hospitalization rates vs. inpatient dialysis transition within 1-yr and 2-yrs after the index eGFR date: IRRs (95%CI) 0.54 (0.53-0.54) and 0.60 (0.60, 0.61), respectively. Similar findings were observed in sensitivity analyses doubly-adjusted for PS-score covariates.

Conclusions: In a national cohort of advanced CKD patients transitioning to ESKD, outpatient dialysis was associated with lower hospitalization rates vs. inpatient dialysis transition.

Funding: NIDDK Support



TH-PO306

Association of Primary Care Continuity with Home Dialysis, Transplantation, and Utilization of Medical Services for Patients Starting Hemodialysis

Cole Wyman,[1] Maya Djerboua,[2] Kristin Clemens,[3,2] Manish M. Sood,[4] Samuel A. Silver.[2,5] *[1]Queen's University, Kingston, ON, Canada; [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [3]Division of Endocrinology and Metabolism and Department of Epidemiology and Biostatistics, Western University, London, ON, Canada; [4]University of Ottawa Faculty of Medicine, Ottawa, ON, Canada; [5]Division of Nephrology, Kingston Health Sciences Center, Queen's University, Kingston, ON, Canada.*

Background: Primary care involvement may help patients starting dialysis with care coordination and support. It is unknown whether higher primary care physician (PCP) continuity associates with increased utilization of medical services or helps support patients towards home dialysis and kidney transplantation.

Methods: Using administrative databases in Ontario, Canada, we conducted a population-based study of patients initiating maintenance hemodialysis between 2007 and 2017. We defined PCP continuity as a high usual provider of care index, >75% of PCP visits with the same PCP in the 2 years before dialysis (an established measure of PCP continuity). We used propensity scores to match patients with high and low continuity so that indicators of baseline health were similar. The primary outcomes were time to home dialysis (peritoneal or hemodialysis) and kidney transplantation, adjusted for the competing risk of death. Secondary outcomes included specialist visits, cancer screening, influenza vaccination, and measures of diabetes care.

Results: We identified 9530 matched pairs. High PCP continuity was not associated with increased home dialysis transfer (14.0 events per 100 person-years versus 14.0 events per 100 person-years; hazard ratio 1.00; 95% CI 0.97-1.04) or kidney transplantation (4.3 events per 100 person-years versus 4.5 events per 100 person-years; hazard ratio 0.97; 95% CI 0.90-1.04). There were no differences in utilization of medical services, with the exception of high PCP continuity associated with greater colon cancer screening (hazard ratio 1.07, 95% CI 1.01-1.14), influenza vaccination (hazard ratio 1.33, 95% CI 1.27-1.39), and comprehensive diabetes care (hazard ratio 1.23, 95% CI 1.14-1.33).

Conclusions: High PCP continuity during the transition to dialysis was not associated with increased utilization of home dialysis or transplantation and had only small effects on preventative services outside of influenza vaccination and comprehensive diabetes care. Given the competing health and time demands of patients on maintenance hemodialysis, additional work is needed to clarify how primary care may benefit this patient population.

Funding: Government Support - Non-U.S.

TH-PO307

Review of Hospital Admissions for Urgent Dialysis Initiation among Patients with Stage 5 CKD

Johanna Marie S. Orejo. *Boston Medical Center, Boston, MA.*

Background: Patients with advanced CKD may present to the emergency department with unplanned and urgent indications to start dialysis. Lack of patient preparedness and an urgent start to dialysis are associated with higher morbidity.

Methods: This QI project utilizes EMR for chart review of adult patients who were admitted to our institution from January 2023 to December 2023, and who required hemodialysis initiation. We particularly focused on the review of the CKD stage 5 patients that were followed in the CKD clinic.

Results: There was a total of 146 patients who were admitted for urgent dialysis initiation. 74 patients (51%) had CKD stage 5. Among this cohort, 59 of these patients were followed in our CKD clinic. 42 patients (71%) did not have any vascular access, 11 patients (19%) had mature AVF/ AVG, and 6 patients (10%) either had non-mature or non-functioning AVF/AVG. The average length of hospital stay was 22.5 days. 11 patients (18%) required medical ICU admission for emergent dialysis start. A review of the CKD clinic visits reveals that in 67% of the patients, dialysis education with Kidney Smart (Davita) was offered, however, only half attended and expressed their modality of choice. 21% of the patients had short (<6 months) dialysis planning time due to their advanced presentation and lost to follow-up, and 12% were not interested in GOC discussion, kidney education, and dialysis planning. Other factors that were identified include language barrier, lack of social support, untimely Nephrology and Vascular surgery referral, late initiation of GOC discussion, and unpredictable timing of kidney function decline and symptoms.

Conclusions: Among CKD5 patients, suboptimal dialysis planning leads to urgent and unplanned admission for HD initiation. These patients receive a higher intensity of care, have longer hospital stays, and have higher medical costs. Factors are multifactorial including lack of patient education, untimely Nephrology and Vascular referral, and late initiation of GOC discussion, among others. Optimal dialysis planning should focus on early patient education and GOC discussion and improving pre-dialysis care that involves a multidisciplinary team, timely referral, frequent follow-up, and access to different members of the care team. A risk prediction tool (KFRE) and a dialysis planning list (EPIC smart phrase) may be of utility.

TH-PO308

Association of Heavy Precipitation with In-Center Dialysis Treatment Absenteeism

Adam G. Walker,[1] Carey Colson,[1] Scott Sibbel,[1] Mesbah Ahmad,[2] Francesca Tentori,[1] Steven M. Brunelli.[1] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO.*

Background: Dialysis treatment absenteeism (i.e., skipping a treatment for reasons other than hospitalization) is associated with greater risk for poor clinical outcomes. Adverse weather (e.g., excessive rainfall or snow accumulation) may pose additional challenges to treatment attendance for dialysis patients dependent upon public transportation or ride assistance. We sought to examine the impact of heavy precipitation on absentee rates.

Methods: This study retrospectively compared absentee patterns at 2,780 dialysis clinics at a kidney care organization in the United States on days with and without precipitation during the first half of 2022 (rain or snow, considered separately). Precipitation data was gathered from the Global Historical Climatology Network

(GHCN) for weather stations near all clinics included in the analysis. Weather patterns and absences were considered daily for each clinic during the study periods (excluding Sundays). Associations were estimated using a linear mixed model with a random intercept for clinic using a zero-inflated Poisson distribution adjusted for day of the week, calendar month, and United States census region. The number of absences attributed to precipitation during the study period were estimated using a recycled predictions method based on observed proportion of days above the thresholds for rain or snow.

Results: Average absences were 4.0% relatively greater on days with ≥ 0.5 inches of rain than on days with <0.5 inch of rain (4.2% vs. 3.8%). Absences were 52% relatively greater on days with snow vs. days without snow (6.5% vs. 3.8%). Snow related absentee rates are higher for the Southern region (12.5%) than the Midwestern, Northeastern, or Western regions of the US (6.2%, 4.8%, and 5.4% respectively).

Conclusions: These results suggest that weather patterns are associated with dialysis absences; snow had a greater impact compared to rain. Proactive rescheduling during periods of inclement weather may represent an opportunity to improve clinical outcomes and treatment adherence. Transit authorities that facilitate nonemergent medical transportation should ensure outreach to dialysis patients before arrival of inclement weather.

	Rain <0.50 inches	Rain 0.50+ inches	Did not snow	Snowed
Treatments, n	10,738,565	562,196	6,968,714	467,833
Missed Treatments, n (%)	412,906 (3.8%)	23,470 (4.2%)	265,008 (3.8%)	30,632 (6.5%)
aIRR (95% CI) [a]	-	1.04 (1.03-1.06)	-	1.52 (1.49-1.55)
Estimated missed treatments due to precipitation	-	996	-	14,208

[a] Adjusted for day of the week, calendar month, and US census region

TH-PO309

Cardiac Arrest in Dialysis Units: A National Cross-Sectional Survey Evaluating the Experience of Dialysis Technicians

Benjamin P. Catanese,[1,2] Laura J. Fish,[4] Jeeyon G. Rim,[1,2] Audrey L. Blewer,[3] Margaret Falkovic,[4] Patrick H. Pun.[1,2] *[1]Duke University Health System, Durham, NC; [2]Duke University Duke Clinical Research Institute, Durham, NC; [3]Duke University School of Medicine, Durham, NC; [4]Duke University, Durham, NC.*

Background: Cardiac arrest is the number one cause of death for hemodialysis patients, and often occurs in outpatient dialysis clinics. Immediate cardiopulmonary resuscitation (CPR) decreases mortality, but CPR is not performed during some cardiac arrests in dialysis clinics. Dialysis technicians are the most common first line providers within US outpatient dialysis clinics, but little is known about their training, experience, and preparedness to provide CPR. We conducted a nationwide survey to understand barriers to CPR among dialysis technicians.

Methods: We conducted a cross-sectional survey of National Association of Nephrology Technicians/Technologists members. The survey was distributed via email and at a national conference. Questions included details about current dialysis unit, demographics, basic life support (BLS) training, experience with cardiac arrests, confidence in performing the steps of BLS, and rating of potential barriers to CPR in the dialysis clinic. Data were analyzed using descriptive statistics.

Results: 101 technicians completed the survey, with a median work experience of 10 years. 75% reported BLS training within the past year, 88% had knowledge of a unit-specific CPR protocol and 74% had participated in mock codes. 80% witnessed a dialysis clinic cardiac arrest (median 4 cardiac arrests witnessed). For patients who had an in chair intradialytic cardiac arrest, technicians reported that CPR was performed 53% of the time in the dialysis chair and 47% on the floor (moved from the chair). Respondents reported high levels of confidence for performing each step of BLS (65%±7% selecting the highest level on a 5-point Likert scale), but only 33% reported the same level of confidence that their dialysis team could resuscitate a patient that arrested. The most significant barriers to performing CPR in the dialysis clinic were delay in recognizing the patient had a cardiac arrest (44%) and fear of harming the patient (41%).

Conclusions: Despite a high proportion citing completion of best practice CPR training, 2/3 of dialysis technicians did not feel highly confident that their teams could resuscitate patients. Novel barriers to CPR include delay in cardiac arrest recognition, lack of agreement in positioning of patients for CPR, and fear of harming patients during CPR.

Funding: Clinical Revenue Support

TH-PO310

Is the Preferred Place of Death Met in Patients on Dialysis? A Systematic Review

Marc L. Boereboom,[1] Joost Verbruggen,[1] Maurice Theunissen,[2] Jmh Joosten,[3] Marieke H. van den Beuken-van Everdingen,[2] Marc H. Hemmelder,[4,5] Pim Bouwmans.[4,5] *[1]Universiteit Maastricht Faculty of Health Medicine and Life Sciences, Maastricht, Netherlands; [2]Center of Expertise for Palliative Care, MUMC+, Maastricht, Netherlands; [3]Division of General Medicine, Department of Internal Medicine, Section of Geriatric Medicine, MUMC+, Maastricht, Netherlands; [4]Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Maastricht, Netherlands; [5]CARIM School for Cardiovascular Diseases, University of Maastricht, Maastricht, Netherlands.*

Background: Dialysis patients' palliative care needs are frequently unmet. An important aspect of palliative care is to timely determine the preferred place of death. In this study, we questioned what the preferred place of death is in dialysis patients, and whether this is met at time of death.

Methods: A systematic review was performed searching PubMed for studies on palliative care and preferred place of death in adult dialysis patients. Articles were screened by two observers on title, abstract and full text. Risk-of-bias was assessed with a tool for prevalence studies (Hoy et al.).

Results: We included nine studies that reported a preferred place of death. The majority of patients (67-75%) preferred to die out-of-hospital. Janssen et al. reported the preferred place of death in 206 Dutch patients with end-stage organ failure as being at-home in 51%, in a hospital in 30%, in a nursing home or hospice in 10%, and unknown in 9%. Davison et al. observed similar rates of preferred death out-of-hospital in 238 Canadian predialysis patients, 295 dialysis patients and 51 kidney transplant recipients. Other studies did not specify the preferred out-of-hospital place of death. Four studies reported the actual place of death and observed an out-of-hospital death in between 42 and 80% of cases. Out-of-hospital death was reported more frequently in patients who were receiving palliative care, had advance care planning or opted for dialysis withdrawal. Most out-of-hospital deaths occurred at home. Janssen et al. observed that 39% of patients died at their preferred place of death.

Conclusions: A large majority of dialysis patients prefer to die out-of-hospital, yet their preference is often not met at time of death. Advance care planning, palliative care and dialysis withdrawal emerged as factors that promote an out-of-hospital death. Comprehensive documentation of wants, values and needs for palliative care is warranted to enhance alignment with dialysis patients' preferences.

TH-PO311

A Comparative Study of Health-Related Quality of Life between Patients on Maintenance Hemodialysis and Kidney Transplant Recipients

Bala Waziri,[1] Aishatu M. Nalado.[2] *[1]Ibrahim Badamasi Babangida University, Lapai, Nigeria; [2]Aminu Kano Teaching Hospital, Kano, Nigeria.*

Background: It is generally recommended that patients with end stage kidney disease (ESKD) should be offered kidney transplantation, as this modality of renal replacement therapy (RRT) has been shown to improve health related quality of life (HRQOL) and a better life expectancy.

Methods: This cross-sectional multicenter study included KTRs with functioning grafts and patients on MHD from three major transplant centers and five dialysis units in Nigeria. Quality of life was assessed with the Kidney Disease QOL-SF-36 (version 1.3) questionnaire. Multivariable linear regression was used to assess differences in mean HRQOL scores between KTRs and HD patients.

Results: Four hundred and ninety-nine (293 HD patients, 98 KTRs, and 108 healthy controls) participants were enrolled into the study. Both HD patients (47.2±14.0 years) and KTRs (46.5±11.4 years) were significantly older than the healthy controls (32.2±9.7 years, p<.0001). Higher proportion of KTRs (81.6%) obtained tertiary education as compared with HD patients (66.9%). The distribution of gender was similar between HD patients and KTRs. With the exception of bodily pain, KTRs had significantly higher HRQOL mean scores in the eight subscales of the SF-36 than HD patients: physical functioning (73.8 ±25.3 versus 52.7±27.5;p<.0001), log role-physical (4.4±0.4 versus 3.8±0.6; p<.0001), bodily pain (79.1±25.8 versus72.7±25.5; p=0.10), general health (73.8±23.2;p<.0001), vitality(65.1±15.0 versus 57.2 ;p=0.002), social functioning (62.5±24.6 versus 50.6±25.0; p<.0001), log role emotional (4.3±0.4 versus 4.1±0.5; p=0.01) and mental health (84.7±16.7 versus 72.3±17.9; p<.001). Except for mental health and social functioning, the subscale scores and the two Mental Component Summary (MCS) and Physical Component Summary (PCS) measures for KTRs and healthy controls did not differ. KTRs have higher PCS (46.8±9.1 versus 38.2±8.8; p< .0001) and MCS (50.1±8.1 versus 43.9±9.1; p<.0001) scores than HD patients. Having kidney transplant is significantly associated with higher PCS score (β coefficient: 8.33; 95% confidence interval: 5.08- 11.58; P<.0001) and higher MCS score (β coefficient: 6. 29; 95% confidence interval: 3.11-9.47; P<.0001).

Conclusions: Kidney transplant recipients have a better health related quality of life than hemodialysis patients and comparable HRQOL scores to healthy individuals

Funding: Private Foundation Support

TH-PO312

Usefulness of Central Concentrate Delivery System for Health Care Workers: A Questionnaire Survey

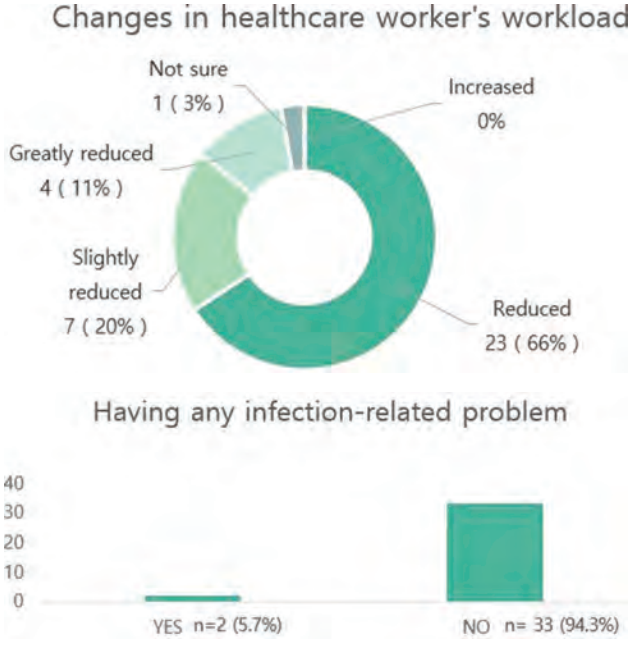
Seokjin Hwang, Sua Lee, Soyoung Lee, Bo Sun Park, Kewon Baik.
Daejeon Eulji University Hospital, Daejeon, Republic of Korea.

Background: In South Korea, the Central Concentrate Delivery System (CCDS), which centralizes the preparation of dialysate with concentrate solutions for multiple patients and distributes it to each dialysis machines, was introduced in the early 2000s. However, there was a lack of research conducted from the perspective of the healthcare workers. Therefore, this study revealed the usefulness of CCDS for healthcare workers.

Methods: Among the dialysis hospitals currently using CCDS, questionnaires were sent to 60 dialysis facilities whose address and contact address were confirmed.

Results: Responses from 35 institutions were received and analyzed. Of the institutions that responded, 21 (60%) were primary healthcare facilities, 4 (11%) were secondary healthcare facilities, and 7 (20%) were tertiary institutions. The average usage period of CCDS across all facilities was 8.1±4.2 years. The most common reasons for introducing CCDS were for reducing healthcare workers' loading and creating a pleasant environment. Economic feasibility was second reason for introducing CCDS. In terms of healthcare workers' workload after the implementation of CCDS, none of the respondents reported an increase. 65% stated that there had been a decrease, and 12% reported a substantial decrease. This indicates that overall, the workload has significantly reduced. When asked if they had ever had an infection-related problem in dialysis system, 2 of the 35 institutions surveyed reported, had an infection problem while using CCDS, and the remaining institutions reported no infection problem.

Conclusions: The CCDS appear to be labor-saving and environmentally friendly in the dialysis facilities without increasing infection-related problem. Further study is needed to determine the effect and safety of CCDS.



TH-PO313

Plastic Neutrality in Green Dialysis: A Pilot Study Exploring Plastoconcrete for Circularity

Ravichandran Palani. *Saveetha Medical College Department of General Medicine, Chennai, India.*

Background: Dialysis treatment generates substantial plastic waste, with 41% constituting the total waste stream. Traditional disposal methods (incineration, pyrolysis) worsen carbon emissions. landfill or recycling are legally restricted. This study investigates plastic neutrality as a solution, focusing on the use of surrogate plastic pebbles in plastoconcrete (PC) for a circular economy.

Methods: We converted 2,000 dialysis-equivalent plastic waste units into pebbles and distributed them to institutions for conversion into PC bricks, planters, and Ganesha idols. After six months, we compared PC products against traditional alternatives (kiln-baked bricks, plastic pots) in terms of strength, durability, and cost-effectiveness. Additionally, we assessed the effectiveness of Ganesha idols in raising awareness.

Results: Our findings demonstrate successful conversion of 4 tonnes of plastic waste into 2.8 tonnes of pebbles. Six polytechnic colleges and four NGOs utilized the pebbles, each processing an average of 250 kg. PC bricks exhibited superior strength, reduced weight, and cost-competitiveness compared to kiln-baked bricks (cost: 50 cents/kg). PC planters offered enhanced durability and aesthetics, effectively replacing plastic pots in college gardens. The distribution of Ganesha idols to healthcare professionals served as impactful awareness tools.

Conclusions: Plastoconcrete is a promising solution for achieving plastic neutrality and fostering a circular economy in green dialysis. Future research will focus on scalability, long-term impact, and the integration of a plastic credit model into green dialysis.

Institution Students making plastoconcrete bricks, pots and finished items

TH-PO314

Canadian Wildfires of 2023 and Risk of Mortality and Hospitalization among ESKD Patients

Hyeonjin Song. *University of Maryland College Park, College Park, MD.*

Background: Climate change driven droughts are increasing frequency and intensity of wildfires, a significant source of air pollution. Smoke plumes from the 2023 Canadian wildfires travelled long distances and negatively impacted air quality across large swaths of eastern US. We investigated the association between exposure to 2023 Canadian wildfire-related air pollutants and risk of mortality and hospitalization among hemodialysis patients in New England, the Mid-Atlantic, and the Midwest U.S.

Methods: The study population includes the end stage kidney disease patients (N=52,995) receiving hemodialysis treatment at Fresenius Kidney Care clinics located in New England, the Mid-Atlantic, and the Midwest U.S. during June-July 2023. Daily number of all-cause deaths, all-cause hospitalizations, respiratory disease hospitalizations, and cardiovascular disease hospitalizations were counted for each hemodialysis clinic. Presence and absence of wildfire smoke plume and wildfire-related fine particulate matter ($PM_{2.5}$) concentration were assessed using both satellite-derived smoke polygons and ground-based $PM_{2.5}$ monitors. We constructed a retrospective observational study using a time-stratified case-crossover analysis with a conditional quasi-Poisson model to investigate the risk of mortality and hospitalization associated with exposures to wildfire-related air pollutants.

Results: Canadian wildfires of 2023 significantly increased air pollution level across the dialysis clinics in the study area, with the highest daily wildfire-related $PM_{2.5}$ concentration reaching 251.1μg/m^3. The presence of wildfire smoke plume was associated with an 18% increase in risk of same day (lag0) all-cause mortality (rate ratio [RR]:1.18; 95% confidence interval [CI], 1.13-1.24) and a 3% increase in risk of all-cause hospitalization (RR:1.03; 95% CI, 1.00-1.07). A 10-μg/m3 increase in wildfire-related $PM_{2.5}$ was associated with a 139% increase in same day all-cause mortality (RR: 2.39; 95% CI, 1.79-3.18), and a 33% increase in all-cause hospitalization (RR:1.33; 95% CI, 1.10-1.62).

Conclusions: Our data suggest that air pollution from the 2023 Canadian wildfires resulted in increased risk of mortality and hospitalization among hemodialysis patients in New England, the Mid-Atlantic, and the Midwest U.S.

TH-PO315

Impact of Comprehensive Predialysis Education (CoPE) on Rural Veterans' Informed Kidney Replacement Therapy (KRT) Selection

Anuradha Wadhwa,[1] Shobha Subhash,[2] Kailyn Pearce,[2] Grant D. Scheiffele,[2] Xiangyang Ye,[3] Adhish Agarwal,[3] Ashutosh M. Shukla.[2,4] *[1]Edward Hines Junior VA Hospital, Hines, IL; [2]VA North Florida South Georgia Veterans Health System, Gainesville, FL; [3]VA Salt Lake City Health Care System, Salt Lake City, UT; [4]University of Florida Health, Gainesville, FL.*

Background: CoPE has a significant impact on patients' informed KRT modality choice; however, the prevalent state of informed dialysis selection patterns and the impact of CoPE among rural Veterans is unknown.

Methods: We conducted a prospective cohort study across five Veteran Healthcare systems in FL, UT, and IL to evaluate the impact of CoPE on rural Veterans' KRT decision-making. Informed modality selection was defined as KRT modality selection with more than 60% confidence on a 0-100%, 5-point Likert scale. Differences in ability to make a modality selection were assessed pre- and post-CoPE by various patient-level characteristics.

Results: Of the 218 Veterans with advanced CKD who received CoPE during fiscal years 2023 and 2024, only 9.0% reported receiving prior CoPE. Pre-CoPE, fewer than half (38.5%) of patients endorsed a hypothetical KRT modality; however, post-CoPE nearly all (94.5%) did. Home dialysis KRT preferences additionally rose significantly from 21% pre-CoPE to 82% post-CoPE (p=0.04, Table 1). Optimal health literacy score, advanced (Stage 5) CKD, and hypertension comorbidity were each independently associated with higher odds of KRT selection pre-intervention; however, post-CoPE KRT modality endorsement differed significantly only by CKD/ESRD awareness measures ($p<0.05$).

Conclusions: Our study shows significant deficits in access to CoPE and poor baseline state of dialysis decision-making among rural Veterans with advanced CKD. Substantial improvement both in Veterans' confidence in modality selection and selection of home dialysis KRT methods were noted after provision of education. Importantly, CoPE appeared to attenuate patient-level differences in ability to endorse a KRT modality preference in our sample. System-wide assessment and implementation of CoPE can improve Veteran confidence in dialysis selection and home dialysis utilization.

Funding: Veterans Affairs Support

KRT selections pre- vs. post-CoPE

Patient Selection	Pre-CoPE	Post-CoPE
Peritoneal dialysis	16 (7.5%)	160 (73.4%)
Home hemodialysis	30 (13.8%)	19 (8.7%)
In-center hemodialysis	17 (7.8%)	18 (8.3%)
Conservative care	21 (10.0%)	9 (4.1%)
Informed KRT Selection		
Yes (61 – 100% confident)	34 (15.6%)	187 (85.8%)
No (0 – 60% confident)	50 (22.9%)	19 (8.7%)

TH-PO316

Towards a Greener Practice: Implementation of Continuous Kidney Replacement Therapy Waste Reduction

Megan M. Moore,[1] Theresa A. Mottes,[3] Jennifer L. Daniel,[4] Gracious Sarasak,[1] Sameer Thadani,[2,1] Kristin J. Dolan,[2,1] Michael C. Braun,[2,1] Ayse Akcan Arikan.[2,1] *[1]Texas Children's Hospital, Houston, TX; [2]Baylor College of Medicine, Houston, TX; [3]Ann and Robert H Lurie Children's Hospital of Chicago Foundation, Chicago, IL; [4]Imagine Pediatrics LLC, Nashville, TN.*

Background: Dialytic therapies are significant contributors to the medical carbon footprint. With the increasing prevalence of continuous renal replacement therapy (CRRT) in pediatric patients, there is a need to implement systematic waste-reduction strategies to mitigate the environmental impact and increase long-term sustainability. We noted 12% of CRRT fluid bags dispensed monthly were wasted for a multitude of reasons within our health system. We utilized implementation science methodology to unpack the complex workflow and identify barriers and facilitators of pharmacy and other system processes to reduce medical waste for our CRRT program.

Methods: We leveraged Expert Recommendations for Implementing Change (ERIC) to assess drivers of CRRT waste and manage change. A multidisciplinary expert panel was assembled to map change objectives and manage change. We identified process problems (incorrectly timed daily dispensing [before daily rounds]), prescriber and pharmacist knowledge gaps, communication barriers between unit pharmacists and prescribers as barriers. Between 2019 and 2022, numerous interventions were implemented to decrease dialysate and replacement fluid bag waste including increasing awareness to the problem through education, process standardization, electronic medical record (EMR) embedded decision aids, and standardization of replacement fluids.

Results: Following the first phase of multidisciplinary team education, monthly fluid waste decreased from 12% to 9.3% over 13-months from July 2019 to July 2020. With EMR optimization and process enhancement in August 2020, monthly waste decreased by another 1.8% to 7.5% by February 2022. With standardization of replacement fluids, our monthly waste decreased by an additional 3.7% to 3.8% by December 2023. Overall, our interventions reduced monthly waste by 8.2% for an annual cost savings of $34,079 (28%).

Conclusions: Identification of systematic processes resulting in waste with structured change management through multidisciplinary team engagement can lead to reductions in overall dialytic therapies related waste. Future studies should continue to evaluate methods to decrease the impact of dialytic therapies on our environment.

TH-PO317

When the Crystals Do Not Align: A Rare Case of Sevelamer-Induced Colonic Ulceration and Crystal Deposition

Uma Mahesh R. Avula, Aun Muhammad, Saleha Aziz, Namrata Paladugu, Mohammad Atari, Mohamed Hassanein. *The University of Mississippi Medical Center, Jackson, MS.*

Introduction: Sevelamer is a commonly used non-calcium-based phosphate-binding agent designed to reduce serum phosphate levels in patients with end-stage kidney disease (ESKD). Severe gastrointestinal injury induced by Sevelamer is uncommon but noteworthy. We present a rare case of Sevelamer-induced colonic ulceration with crystal deposition and colitis.

Case Description: A 64-year-old male with a history of heart failure with reduced ejection fraction, coronary artery disease, ESKD on intermittent hemodialysis, and a previous cerebrovascular accident was admitted for acute hypoxic respiratory failure and septic shock. His hospital course was complicated by atrial flutter, which required a heparin drip that was discontinued after he developed melena with severe anemia. A gastroenterology consultation led to a colonoscopy with biopsy, which revealed a fragment of granulation tissue with ulceration containing Sevelamer crystals consistent with Sevelamer-induced colitis. There were no chronic ischemic changes in the intact colonic mucosa, suggesting the possibility of acute ischemia or Sevelamer-related injury. Consequently, Sevelamer was discontinued. Due to the worsening of his comorbid conditions, the patient was transitioned to comfort care, and dialysis was withdrawn.

Discussion: Crystal deposition by ion-exchange resins like Sevelamer can result in inflammation, mucosal damage, and ulceration. While Sevelamer is generally well tolerated while causing mild gastrointestinal side effects such as nausea, vomiting, constipation, flatulence, and diarrhea, cases of more severe gastrointestinal mucosal injury have been associated with its use. Albeit rare, Sevelamer-induced colitis should be included in the differential diagnosis of gastrointestinal bleeding in patients with ESKD. This case contributes to the growing evidence of significant gastrointestinal complications related to Sevelamer.

TH-PO318

Blood Volume Monitoring in Hospitalized Patients with ESKD and Heart Failure

Christopher El Mouhayyar, Ayman Al Jurdi, Tianqi Ouyang, Mengyao Tang, Sahir Kalim, Sagar U. Nigwekar, Annie Liu. *Massachusetts General Hospital, Boston, MA.*

Background: Heart failure (HF) is the leading cause of hospitalization in people with end-stage kidney disease (ESKD). The co-occurrence of ESKD and HF increases this likelihood. This study assesses the association between blood volume monitoring (BVM) guided hemodialysis (HD) and clinical outcomes in ESKD patients with HF admitted for HF exacerbation.

Methods: This multicenter retrospective cohort study, conducted between January 2017 and January 2020, included 278 hospitalized HD-dependent individuals with HF admitted for HF exacerbation. BVM was either applied or not according to the admitting hospital's protocols. BVM use was confirmed based on manual patient chart review. Data for demographics, comorbidities, and clinical parameters were extracted from the electronic health records.

Results: 278 patients were hospitalized between 2017 and 2020 (mean age: 70 years, 58% males, 62% white) with an average index hospitalization of 7 days [(interquartile range) IQR: 4.00, 11.75]. 168 patients (58%) were dialyzed with BVM while 118 (42%) were dialyzed without BVM during hospitalization. Multivariable adjusted analyses showed that BVM-guided HD was associated with a shorter length of stay (difference of -2.00 days, 95% confidence interval (CI) -3.90 to -0.13), reduced number of readmissions within 90- (adjusted Beta Coefficient= -0.27, 95% CI: -0.48, -0.06) and 180-days post-discharge (adjusted Beta Coefficient= -0.47, 95% CI: -0.48, -0.06) compared to assignment to without BVM guidance. During 2015 and 2017, BVM was not utilized at MGH and BWH, 100 patients dialyzed independent of BVM showed no difference in all endpoints.

Conclusions: BVM use was associated with shorter length of stay and lower number of readmits in patients with ESKD hospitalized for HF.

Table 1. Baseline Characters of participants between 2017 and 2020

	January 2017-January 2020			
Characteristics	Overall (n=278)	Conventional (n=118)	BVM (n=160)	P
Age (years)	70.00 [62.00, 78.00]	69.00 [58.00, 78.00]	71.00 [61.00, 79.00]	0.129
Male Gender	164 (59%)	64 (54%)	97 (61%)	0.345
Race Group (%)				
White	173 (62.23)	66 (55.93)	107 (66.88)	0.111
Black	53 (19.06)	28 (23.73)	25 (15.63)	
Asian	16 (5.76)	5 (4.24)	11 (6.88)	
Hispanic/Other	36 (12.95)	19 (16.10)	17 (10.63)	
Coexisting Conditions				
Hypertension	271 (97.48)	116 (98.31)	155 (96.88)	0.715
Diabetes Mellitus	213(76.62)	94 (79.66)	119 (74.38)	0.376
Coronary Artery Disease	243 (87.41)	103 (87.28)	140(87.50)	0.999
Dialysis related Factors				
Ultrafiltration rate (mL/Kg/h)	9.46 [6.76, 12.78]	9.52 [6.57, 12.50]	9.46 [6.84, 12.74]	0.850
Estimated Dry Weight (Kg)	74.25 [62.33, 89.75]	74.90 [60.10, 87.30]	73.20 [64.58, 92.63]	0.463
Admit Weight (Kg)	77.60 [63.33, 93.53]	77.75 [63.63, 90.35]	77.15 [67.60, 97.23]	0.423
Δ Weight (Kg)	-2.50 [-5.00, -2.20]	-3.40 [-4.93, -2.03]	-2.35 [-5.53, -2.30]	0.175
Dialysis vintage (years)	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	0.364
GWTG-HF Severity (%)				
Low	93(33.45%)	29(24.60%)	49(30.60%)	0.051
Moderate	87(31.30%)	27(22.90%)	49(30.60%)	
Severe	98(35.25%)	62(52.50%)	62(38.80%)	
Labs				
Hematocrit admit (L/L)	31.30 [28.10, 35.35]	31.15 [28.10, 34.40]	31.45 [28.08, 35.53]	0.435
Hematocrit discharge (L/L)	29.80 [27.03, 32.35]	28.95 [26.60, 31.60]	30.40 [27.50, 33.20]	0.009
Δ HCT (discharge-admit)	2.60 [1.20, 4.60]	2.95 [0.90, 4.90]	2.40 [1.20, 4.30]	0.725
NT-proBNP (pg/mL)	32349.50 [14689.00, 64924.50]	35214.50 [15089.00, 70000.00]	31517.00 [14160.30, 56331.50]	0.594

Data summarized as mean (SD) or median (25th, 75th percentile) for continuous variable or n(%) for categorical variable. GWTG-HF: Get with the guidelines heart failure score, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, Δ weight: Admit weight – Estimated dry weight, BVM: Blood Volume Monitoring

TH-PO319

Associations of Blood Water Cleared during a Dialysis Session Scaled to Body Surface Area with Weight-Specific Mortality Risk

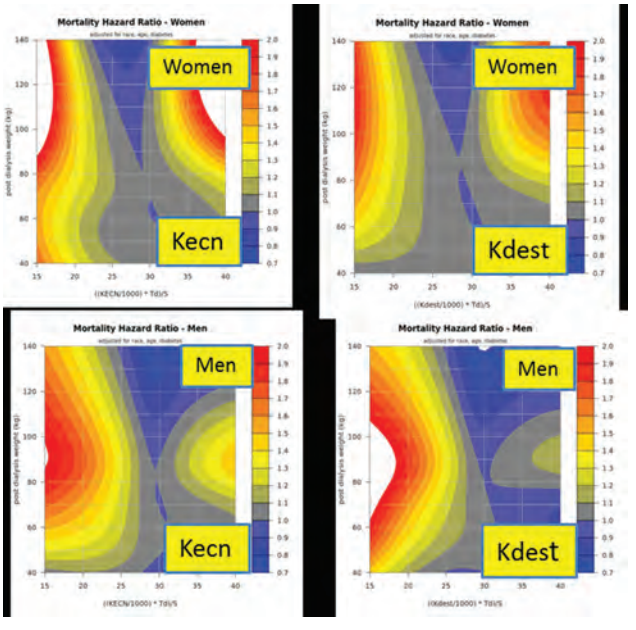
John T. Daugirdas,[1] Ariella E. Mermelstein,[2] Yuedong Wang,[3] Jochen G. Raimann,[2] Peter Kotanko.[2,4] *[1]University of Illinois Chicago College of Medicine, Chicago, IL; [2]Renal Research Institute, New York, NY; [3]University of California Santa Barbara, Santa Barbara, CA; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Lowrie et al (Kidney Int, 2005) suggested using volume of blood water cleared during a dialysis session (K x t) normalized to body surface area (S) for a size-dependent adequacy target.

Methods: We examined associations between estimated K (Kdest, vivo/vitro KoA ratio of 0.43) or measured K (conductivity, Kecn) scaled to S (Dubois equation) and survival for different strata of post-dialysis weights (W). Mean dialysis dose data were analyzed from the US Fresenius Kidney Care database for 1 year after dialysis initiation (baseline) and deaths were counted over the next 2 years. To investigate the joint effect of Kt/V or Kt/S and W on survival, we fit Cox proportional hazards models using bivariate tensor product spline functions and constructed contour plots of W-specific mortality hazard ratios over the entire range of dialysis dose values and W.

Results: In 233,293 patients, mean Kecn x t was 57 ± 7.4 liters/session in men, 53 ± 7.1 in women. Mean Kdest was 57 ± 6.2 liters/session in men, 53 ± 6.3 in women. Contour plots suggested a Kt/S target which decreased risk had somewhat plateaued of 37 – 10/W liters/m^2 for either sex, for both Kecn and Kdest, but mortality risk increased more steeply in men when dose fell below this value. For unknown reasons, mortality risk was higher in heavier patients (>80 kg), especially women, when Kt/S was greater than 32 liters/m^2.

Conclusions: Our findings agreed with Lowrie et al, that a Kt/S adequacy target would need to be scaled to patient size (either as S or W). Increased mortality in patients given very high doses of dialysis was a surprising finding and deserves further study.



TH-PO320

Low-Cardiac Output State in Children and Young Adults on Maintenance Hemodialysis

Golnaz Sadeghiani,[1,4] Sameer Thadani,[1,4] Jessica Geer,[1] Christin N. Silos,[1,4] Alexandra Idrovo,[3] Rinaldo Bellomo,[2] Poyyapakkam Srivaths,[1,4] Ayse Akcan Arikan.[1,4] *[1]Texas Children's Hospital, Houston, TX; [2]Centre for Integrated Critical Care, The University of Melbourne, Melbourne, VIC, Australia; [3]The University of Texas Southwestern Medical Center, Dallas, TX; [4]Baylor College of Medicine, Houston, TX.*

Background: Intermittent hemodialysis (iHD) induces circulatory strain and impairs myocardial dynamics. Maturing cardiovascular system in children may create an additional risk for iHD induced myocardial dysfunction. We used continuous electrocardiometry to measure cardiac index (CI) and stroke volume index (SVI) in children on maintenance iHD.

Methods: Prospective observational study of patients <21 years on 3/week 4-hour maintenance iHD at Texas Children Hospital. We collected hemodynamic data (CI, SVI) with ICON (Berlin Germany Ospky medical) during the first treatment of the week. Baseline CI and SVI were measured at the initiation of iHD and continuously thereafter for 240 minutes.

Results: 14 patients with median iHD vintage 14 months (9-24) were included. The median ultrafiltration rate was 10ml/kg/hr (6-13) The baseline CI was 3.37 +/- 0.69 L/min/m^2 while the nadir CI was 2.60 +/-0.48 L/min/m^2. 3 (21%) patients had a baseline CI <3L/min/m^2. CI decreased in the majority of patients (13/14, 93%). The mean change in CI was - 21%+/- 14% (Figure 1). The baseline SVI was 39.7 +/- 7.3 ml/m^2 and the nadir SVI was 29.7 +/- 5.4 mL/m^2. SVI decreased by 23% +/- 15% (Figure 2). 7 (50%) patients developed a low cardiac output state (CI<2.5).

Conclusions: Asymptomatic children and young adults on maintenance iHD experience >20% decrease in CI and SVI. Despite fewer cardiovascular comorbidities than their adult counterparts, iHD can induce myocardial dysfunction in children. Association of these cardiovascular changes with markers of other end organ injury should be further investigated.

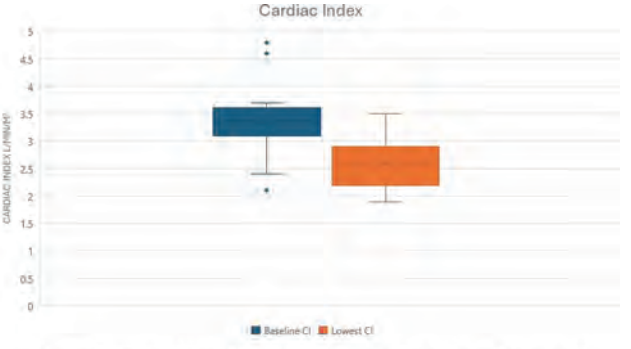


Figure 1: Baseline (blue), Lowest (orange) cardiac index during intermittent hemodialysis.

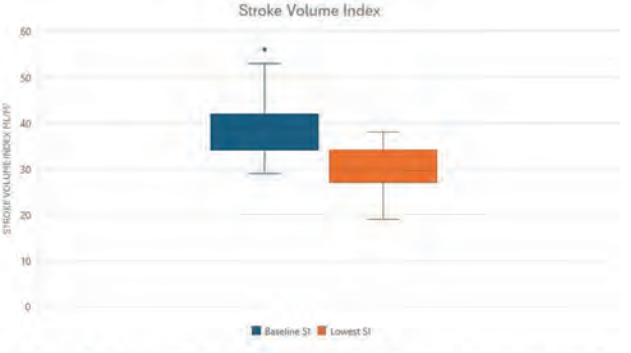


Figure 2: Baseline (blue), lowest (orange) stroke volume index during intermittent hemodialysis.

TH-PO321

Changes in Relative Blood Volume during Hemodialysis: An Extensive US Cohort

Vincent Filardi,[1] Andrea Nandorine Ban,[1] Lin-Chun Wang,[1] Xiaoling Ye,[1] Peter Kotanko,[1,2] Hanjie Zhang.[1] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Specific hourly intradialytic relative blood volume (RBV) ranges are associated with lower all-cause mortality in chronic hemodialysis (HD) patients (Preciado, NDT 2019). However, the intradialytic RBV levels in large US population is unknown. The goal of our research was to fill this knowledge gap by exploring the intradialytic RBV levels at a session level in a large US HD population.

Methods: Hematocrit was measured every 10 seconds during an HD session with the Crit-Line Monitor (CLM; Fresenius Medical Care, Waltham, MA). The CLM then reports the RBV every 10 seconds. Data were uploaded to the cloud in real time. We analyzed CLM data collected from 1/14/2021 to 7/30/2023. We aggregated RBV values into intervals at 30, 60, 90, 120, 150, 180, 210, and 240 minutes into the HD session. To accomplish this, we averaged the RBV data between 20 and 40 minutes as the 30-minute interval, 50 and 70 minutes as the 60-minute interval, and so on. Sessions with less than 1 hour of data or an average RBV value outside the 90% to 110% range during 5 to 20 minutes into the treatment were excluded. Finally, an interval was excluded if it had less than 5 minutes of data or an average value outside 75% to 115%.

Results: We analyzed 71,984 patients from 719 HD clinics. Over the final 4,798,225 treatment sessions, Figure 1A shows the distribution of intradialytic RBV per 30-minute interval. Figure 1B shows the distribution of treatments relative to the favorable RBV ranges by hours into the HD session.

Conclusions: Our findings indicate, at the session level, a slightly higher prevalence within the favorable hourly RBV ranges, lower prevalence above the ranges, and higher prevalence below the ranges when compared to Preciado (NDT, 2019). We hypothesize that this variation may indicate improved fluid management. The clinical correlates of this finding warrants further research. Reference: Preciado P, Zhang H, Thijssen S, Kooman JP, van der Sande FM, Kotanko P. All-cause mortality in relation to changes in relative blood volume during hemodialysis. Nephrol Dial Transplant. 2019 Aug 1;34(8):1401-1408.

Funding: Commercial Support - Renal Research Institute, New York, NY, a wholly owned subsidiary of Fresenius Medical Care.

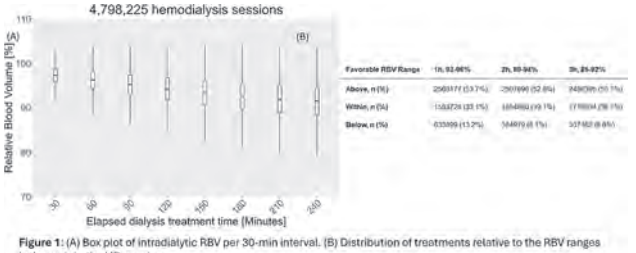


Figure 1: (A) Box plot of intradialytic RBV per 30-min interval. (B) Distribution of treatments relative to the RBV ranges by hours into the HD session.

TH-PO322

Evaluating Microcirculation Changes in Patients with ESKD during Hemodialysis Using Conjunctival Capillaroscopy

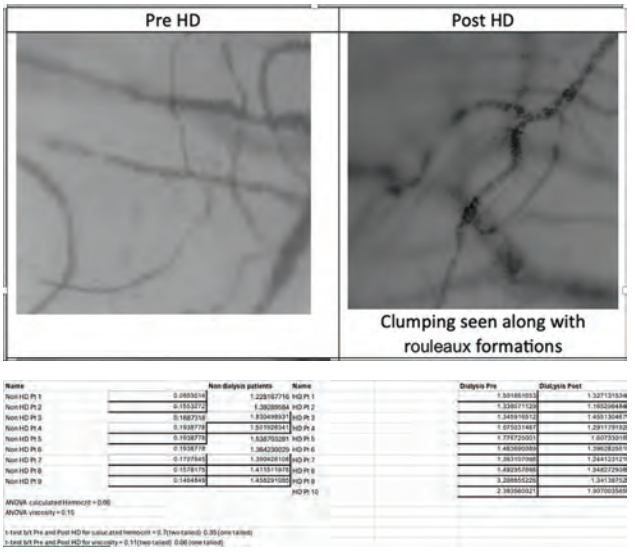
Sylvester Barnes IV,[1,2] Bruce I. Gaynes,[1,2] Abedelkarim M. Murrar.[3] *[1]Loyola University Medical Center, Chicago, IL; [2]Edward Hines Junior VA Hospital, Hines, IL; [3]University of Illinois Chicago, Chicago, IL.*

Background: During hemodialysis, there appears to be an internal viscosity change in RBCs, leading to a decrease in their deformability. This change results in a rouleau formation with concurrent changes in microcirculation viscosity.

Methods: Microcirculation impairment is an independent predictor of organ dysfunction and death. Sublingual capillaroscopy has been utilized to visualize capillary flow; however, microcirculation flow in the eye is more representative of the cerebral circulation. We have adapted a commercial sublingual capillaroscopy for use in the conjunctival tissue bed to obtain vessel diameter and blood flow velocity. From Pries et al. discharge hematocrit (Hd) $v_b / v = H_D + (1 - H_D) * (1 + 1.7e^{(-0.415D)} - 0.6e^{(-0.011D)})$ was obtained, then in-vivo viscosity using $\eta_{vivo} = [1 + (\eta - 1) * ((1 - H_D)^C - 1) / ((1 - 0.45)^C - 1) * (D / (D - 1.1))^2] * (D / (D - 1.1))^2$ where $\eta = 6e^{(-0.085D)} + 3.2 - 2.44e^{(-0.06D^0.445)}$ was calculated. Previously non-physiologic viscosity was reported.

Results: Our previosuly reported findings in ESRD patients appear to demonstrate profound abnormalities in RBC aggregation and RBC density in the microvasculature post-HD (Figure 1). We postulated that this would cause a significant change in in-vivo viscosity. However, there was no statistical difference between calculated hematocrit levels or viscosity levels, although with a p-value of 0.06, the decrease in viscosity is close.

Conclusions: Our sample size limits the power of the study. These results show promise in that measured velocity values using capillaroscopy, with calculated in vivo vessel hematocrit and in-vivo viscosity, are within physiological range and provide a valuable way to measure real-time in-vivo blood flow characteristics pre and post HD. With more patient recruitment the power of sour study should increase.



TH-PO323

Hyponatremia Treatment: Improving the Rate of Overcorrection

Shlomo Greenberg, Sanjeev Gupta, George N. Coritsidis. *Westchester Medical Center, Valhalla, NY.*

Background: Hyponatremia, an electrolyte disorder resulting from impaired free water excretion, requires tailored treatment based on its etiology and severity. The goal of treatment is to raise serum sodium (Na+) levels safely to avoid osmotic demyelination syndrome (ODS). The object of this study was to institute a protocol in the emergency department (ED) that would decrease the incidence of overcorrection.

Methods: A prospective, single-center study was conducted at Westchester Medical Center (WMC) between January and April 2024. Adult patients presenting to the ED with Na+ ≤125 mmol/L were included. A protocol was initiated requiring the ED physician to assess urine Na and osmolality (osm), implement cautious use of intravenous (IV) fluids, and consult nephrology. Overcorrection was defined as a serum Na+ correction exceeding 8 mmol/L within the first 24-hours. Excluded from the study were transfer patients, patients with hyperglycemia induced hyponatremia, and patients who didn't stay a full 24 hrs. Data was collected on patient comorbidities, urine and serum osm, use of IV fluids, and efforts to slow overcorrection. The data was compared to retrospective data of adult patients presenting to the WMC ED between 2019 and 2022 with serum Na+ ≤125 mmol/L.

Results: Between 2019-2022, 89 out of 477 patients (19%) experienced overcorrection. Notably, 42% were on medications associated with hyponatremia (thiazides or psychiatric drugs), and 15% had cirrhosis or congestive heart failure. Most patients (76%) received empiric IV fluids, and 68% had urine osmolality <300 mmol/L. After implementing the protocol (January to April 2024), 11 patients had a Na+ ≤125 mmol/L. Four patients were excluded. Among the remaining 7 patients, 2 (29%) were on hyponatremia-associated medications, and 3 (42%) had cirrhosis or CHF. Only 1 patient (14%) overcorrected, and that patient had received empiric IV fluids and had an initial urine osm<300. This patient corrected by 9 mmol/L, and D5W was administered to rectify the overcorrection.

Conclusions: Our retrospective data highlights a 19% overcorrection rate in hyponatremia, a potentially significant risk for ODS. Early renal intervention, as observed in our prospective study, improved the overcorrection rate through collaboration between the ED and the nephrology division. Further investigation is warranted to further analyze the benefits of the hyponatremia protocol.

TH-PO324

Efficacy of Low-Dosage Tolvaptan for Treatment of Profound Hyponatremia in Syndrome of Inappropriate Antidiuresis: An Open-Label Randomized Controlled Trial

Pajaree Krisanapan, Sutatip Chinpraditsuk, Narongchai Jaiyen, Pichaya Tantiyavarong, Pattharawin Pattharanitima. *Thammasat University Hospital, Khlong Nueng, Thailand.*

Background: It is commonly accepted that the first-line treatment of syndrome of inappropriate antidiuresis (SIAD) is fluid restriction (FR). However, the second-line treatments are still controversial among guidelines. This study investigates whether

tolvaptan is more effective than FR combined with furosemide (FSM) and sodium chloride (NaCl) tablets in treating SIAD patients who likely to fail from FR alone.

Methods: We conducted a 28-day single-center, open-label, randomized controlled trial in patients with profound hyponatremia (serum sodium concentration, [Na+] ≤ 125 mmol/L) who showed signs of FR failure in SIAD. Patients were randomly assigned to either the tolvaptan group (received tolvaptan 7.5 mg/day) or the control group (received FR of 800 ml/day, FSM 20–40 mg/day, and NaCl 3 g/day). The primary endpoint measured the change in [Na+] from baseline to day 4. The protocol was registered on thaiclinicaltrial.gov (TCTR20210628004).

Results: In the analysis of 29 patients (13 on tolvaptan and 16 on control), baseline [Na+] averaged was 120 ± 3 mmol/L in both groups. Tolvaptan significantly increased the change in mean [Na+] on day 4 compared to the control with 12.2±3.4 and 6.3±6.0 mmol/L (p=0.004), respectively. Notable differences persisted days 7 and 14 but not at day 28 (Figure 1A). The actual [Na^+] was shown on Figure 1B. At days 4, the proportion of patients with [Na+] ≥ 130 mmol/L was achieved by 76.9% on tolvaptan and 25% on control (p = 0.009). Median time [IQR] to restore [Na+] ≥ 130 mmol/L was 2 [1, 14] days with tolvaptan and 14 [3, 14] days with control (p=0.059). In terms of safety, tolvaptan showed fewer cases of hypokalemia (p=0.044) than the control. However, 3 tolvaptan patients developed sodium overcorrection without statistical significance (p=0.078).

Conclusions: In profound SIAD with clinical features suggesting failure with fluid restriction alone, tolvaptan significantly increases [Na+] without causing significant sodium overcorrection.

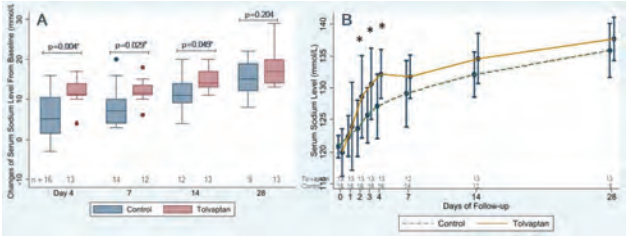


Figure 1A and 1B

TH-PO325

Electronic Alerts (E-alerts) for Electrolyte Disturbances

Miho Murashima,[1,2] Minamo Ono,[1] Masashi Mizuno,[1] Kodai Suzuki,[1] Yuki Miyaguchi,[1] Takahisa Kasugai,[1] Tatsuya Tomonari,[1] Takayuki Hamano.[1]
[1]Nagoya Shiritsu Daigaku, Nagoya, Japan; [2]Kinki Daigaku, Higashiosaka, Japan.

Background: The impacts of e-alerts for acute kidney injury on outcomes have been debated. We implemented e-alerts for electrolyte disturbances, which are common but often overlooked or mismanaged. The study aims to examine the changes introduced by e-alerts for electrolyte disturbances.

Methods: This is a retrospective observational study at Nagoya City University Hospital. E-alerts for electrolyte disturbances were implemented in May 2021. The criteria for e-alerts were serum sodium <125 or >160 mEq/L, potassium <2.5 or >6.0 mEq/L, corrected calcium <7.5 or 11.5 mg/dL, and magnesium <1.0 or >4.0 mg/dL. The following outcomes were compared 1 year before and after the initiation of the e-alerts: nephrology referral for electrolyte disturbances; for those with hyponatremia, the proportion of patients with measurement of urinary sodium concentration and osmolarity, length of stay, the number of falls during hospitalization, and overcorrection of hyponatremia. Descriptive statistics were used except for the number of referrals and falls, which were compared by Poisson and negative binomial regression, respectively.

Results: The number of electrolyte measurements was 185,305 and 19,238 one year before and after the initiation of e-alerts. The nephrology referrals for electrolyte disturbance increased from 5.6 to 9.7 per month (incidence rate ratio [IRR]: 1.75 (1.13-2.76)). Among those with hyponatremia, the proportion of patients with urinary sodium concentration and osmolarity measured increased from 34.9% to 47.2%. The length of stay decreased from 27 (15-47) to 20 (12-36) days for those with hyponatremia, whereas the length of stay did not change for those without hyponatremia. The number of falls was lower after initiating e-alerts (IRR: 0.82 (0.44-1.50)), though not statistically significant. The number of overcorrections of hyponatremia decreased from 22.1% to 15.3%. Eight out of 27 patients referred for hyponatremia within 1 year after the initiation of e-alerts were diagnosed with syndrome of inappropriate antidiuretic hormone secretion and tolvaptan improved hyponatremia in 4 patients.

Conclusions: E-alerts for electrolyte disturbances increased nephrology referral, urinary sodium and osmolarity measurements, decreased length of stay, falls, and the overcorrection of hyponatremia.

TH-PO326

Exploring the Effectiveness of Urea in Hyponatremia Due to Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Comprehensive Systematic Review and Meta-Analysis

Abhi Lohana,[1] Fnu Shivani,[5] Sejal Neel,[4] Subhash Chander,[3] Syed Adil Mir Shah,[2] Neeharika Muddana.[1] *[1]Camden Clark Medical Center, Parkersburg, WV; [2]Dow Medical College, Karachi, Pakistan; [3]Mount Sinai Beth Israel Hospital, New York, NY; [4]Hackensack Meridian Jersey Shore University Medical Center, Neptune, NJ; [5]Ascension Saint Joseph - Chicago, Chicago, IL.*

Background: Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) often leads to hyponatremia, posing significant health risks. Management strategies include urea administration, targeting osmotic diuresis, and Vaptan Receptor Antagonists (VRAs). This study systematically reviews the effectiveness of urea compared to VRAs and other interventions in increasing plasma sodium concentration among SIADH patients.

Methods: A comprehensive search yielded 16 relevant studies on urea treatment for SIADH-related hyponatremia. Meta-analysis assessed serum sodium level changes, considering treatment duration and SIADH severity. Safety profile analysis included adverse events.

Results: Urea significantly increased serum sodium levels (MD = 9.08, 95%CI: 7.64, 10.52, P < 0.01), with enduring efficacy over varying time frames. Subgroup analyses revealed comparable outcomes across different treatment durations and a severity-dependent effect favouring urea in severe SIADH cases. Serum urea levels significantly rose post-treatment (MD = 31.66, 95%CI: 16.05, 47.26, P < 0.01). Urea outperformed fluid restriction in increasing serum sodium (MD = 7.99, 95%CI: 6.25, 9.72, P < 0.01), with similar efficacy to VRAs. Meta-regression indicated urea's efficacy correlated inversely with SIADH severity. Urea was generally tolerable, with distaste as the primary adverse event.

Conclusions: Urea demonstrates consistent efficacy in raising serum sodium levels in SIADH-related hyponatremia, with a safety profile comparable to other treatments. Its enduring impact, even in severe cases, underscores its clinical significance as a management option. However, further randomized controlled trials are warranted to validate these findings and elucidate optimal treatment protocols.

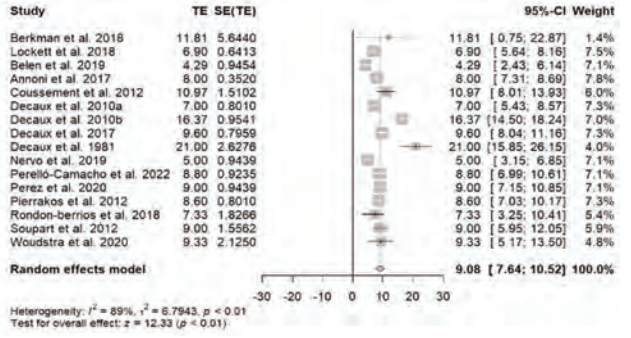


Figure 1. Forest plot shows serum sodium level change from the baseline after urea administration.

TH-PO327

Analysis of Sodium in Inpatients, Outcomes, and Nephrology Engagement (ASIN-ONE): A Study on Nephrology Referral Timing in Hyponatremic Adult Patients at a Tertiary Hospital

Charles Michael T. Herrera, Andrew Timothy Qua, Adrian L. Santos, Janice Jill Lao.
Philippine General Hospital, Manila, Philippines.

Background: Hyponatremia is the most common inpatient electrolyte abnormality. Earlier referral to a nephrologist may shorten hospitalization and improve patient survival.

Methods: This was a 6-month retrospective cohort study of nephrology referrals in a tertiary hospital. We analyzed four groups based on days from admission to referral (<1d, 1-<3d, 3-7d, and >7d) for length of stay, in-hospital mortality, and hyponatremia resolution. Kaplan-Meier curves and Cox proportional hazard regression were done.

Results: Of the 800 patients analyzed, overall mortality was 31.87%. Those referred <1d from admission had significantly shorter hospitalization (median 8.41 vs. 24.57 days) and significantly lower mortality (26.04% vs. 51.35%) than the >7d group. The 3-7d group had a higher risk of death than the <1d group (HR 2.91, 95% CI, 1.94–4.36). Kaplan-Meier curves revealed decreased survival in patients referred >72 hours from admission. There was no significant difference across groups in terms of normonatremia attainment prior to discharge or mortality.

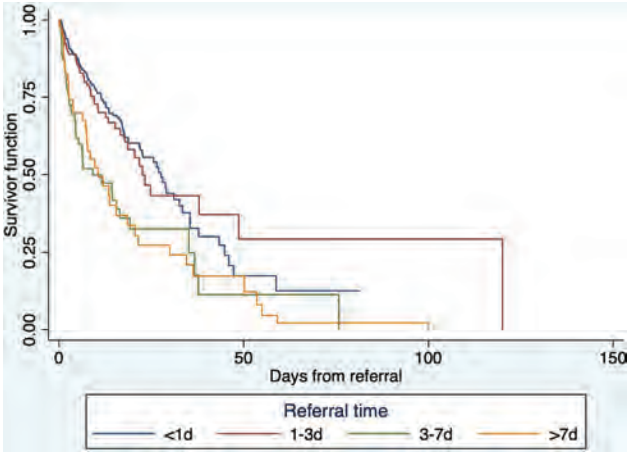
Conclusions: Earlier nephrology referral was associated with decreased hospital stay and mortality. Significant divergence in in-hospital mortality was seen in hyponatremic patients referred more than 72 hours from admission.

Hospital Outcomes	Timing of Referral from Admission (Days)				
	<1 Day	1-<3 Days	3-7 Days	>7 Days	p-value
Length of Stay, Days [Median (IQR)]	8.41 (10.15)	10.55 (10.255)	10.27 (12.82)	24.565 (27.62)	<0.001
In-hospital Mortality [Frequency (%)]	132 (26.04%)	46 (31.94%)	39 (52.00%)	38 (51.35%)	<0.001
Hyponatremia Resolution [Frequency (%)]	215 (42.41%)	64 (44.44%)	39 (52.00%)	39 (52.70%)	0.202

	Full Model			Reduced Model		
	Adj. HR*	95% CI	p-value	Adj. HR*	95% CI	p-value
Referral time						
<1 d	Reference			Reference		
1-<3 d	1.30	0.91, 1.87	0.150	1.24	0.87, 1.77	0.232
3-7 d	2.61	1.74, 3.93	<0.001	2.91	1.94, 4.36	<0.001
>7 d	1.79	1.14, 2.81	0.011	1.82	1.16, 2.84	0.009
Hyponatremia Severity						
Mild (130 – 134 mmol/L)	Reference					
Moderate (120 – 129 mmol/L)	1.39	1.04, 1.87	0.027			
Severe (< 120 mmol/L)	0.68	0.47, 0.98	0.038			

*Model adjusted for confounding effects of area of referral and attending service.

Cox proportional hazards regression between referral timing and in-hospital mortality



Kaplan-Meier survival curve of timing of nephrology referral

TH-PO328

Genotype, Phenotype, and Follow-Up in Taiwanese Patients with Congenital Nephrogenic Diabetes Insipidus

Min-hua Tseng,[1] Shih-Hua P. Lin.[2] *[1]Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan; [2]Tri-Service General Hospital, Taipei, Taiwan.*

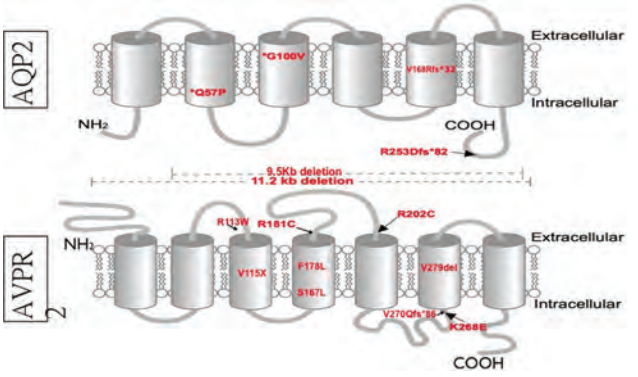
Background: Genotype, phenotype, and follow-up outcome in Taiwanese patients with congenital nephrogenic diabetes insipidus (CNDI) due to arginine vasopressin V2 receptor (*AVPR2*) and the aquaporin 2 (*AQP2*) genetic mutations are not well evaluated. To investigate the phenotypic, genetic characteristics, and outcomes in the Taiwanese families with CNDI.

Methods: Twenty-seven patients (M:F=21:6, age 22 ± 17) with CNDI belonging to eighteen unrelated Taiwanese families were enrolled. Genomic DNA from blood leukocytes was analyzed for *AVPR2* and *AQP2* genes mutations. deamino D-arginine vasopressin (dDAVP) stimulation was administered to separate these two gene mutations. Clinical symptoms and biochemical studies at the first presentation as well as follow-up were examined.

Results: Of the 27 patients with CNDI, 17 have *AVPR2* mutations and 10 have *AQP2* mutations. Eleven mutations, including 6 missense, 3 novel small deletion, and 2 large deletion mutation, and four mutations, including Q57P, G100V, 592InsC, and R253Dfs*82 were identified in *AVPR2* and *AQP2* gene, respectively. Q57P and G100V of *AQP2* were recurrent, and Q57P exerted a founder effect. All patients developed phenotypic polyuria and polydipsia. All patients with *AVPR2* mutations lack of normal hypotensive and coagulation responses to dDAVP. One symptomatic female patient with heterozygous V115X mutation in *AVPR2* gene had inactivated X chromosome in another allele. Three patients who carried same mutation (F178Q) from one family have different phenotypic severity. Seven patients have non-obstructive hydroureteronephrosis. Seven patients, 4 *AVPR2* and 3 *AQP2* mutations, reached chronic kidney disease (CKD, stage III-V) during the follow-up.

Conclusions: Q57P in *AQP2* is the Taiwanese founder mutation. Non-obstructive hydroureteronephrosis is not uncommon complication. Chronic kidney disease should be aware in congenital NDI cases caused by either *AVPR2* or *AQP2* mutations.

Funding: Government Support - Non-U.S.



TH-PO329

X Marks the Salt: A Case of Pseudohyponatremia Due to Lipoprotein X

Madison B. Calder,[1] John M. Duch.[2] *[1]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [2]Audie L Murphy Memorial Veterans' Hospital, San Antonio, TX.*

Introduction: Pseudohyponatremia is a lab artifact produced when *indirect* ion-selective electrode (I-ISE) laboratory instruments, which incorporate a pre-measurement dilution step, measure serum sodium in the presence of abnormally increased non-aqueous components (e.g., protein/lipid). Instruments utilizing *direct* ion-selective electrode (D-ISE) technology are not affected; a marked discrepancy in serum sodium concentrations obtained with I-ISE and D-ISE instruments can be revealing. We present a case of pseudohyponatremia due to lipoprotein X (Lp-X).

Case Description: A 34-year-old man was admitted to the hospital with jaundice and abdominal pain. Examination was notable for normal mentation, scleral icterus, and hepatomegaly. Abdominal ultrasonography demonstrated severe hepatic steatosis. Initial laboratory studies performed using an I-ISE autoanalyzer were notable for severe hyponatremia, mild hyperglycemia, hyperbilirubinemia, and elevated ethanol level. Further diagnostic workup revealed significantly elevated lipids and a sodium value within normal limits obtained using a D-ISE analyzer. Subsequent agarose gel lipid pheresis suggested markedly elevated Lp-X. His clinical status and lab values improved with supportive care, nearly normalizing by six months after ethanol cessation (**Table 1**).

Discussion: Lp-X is an abnormal lipoprotein rich in unesterified cholesterol and phospholipids with similar density to low density lipoprotein molecules. Obstructive cholestasis causes reflux of lipid fractions from bile into plasma and can lead to serum Lp-X elevations. Treatment involves reversing the cholestatic liver disease. Importantly, our patient's triglyceride level of 1252 mg/dL would only be expected to lower his serum sodium by approximately 2 mEq/L using proposed estimating equations, much less than was observed. Until Lp-X levels normalize, accurate serum sodium determination requires *direct* potentiometry analysis. Failure to promptly recognize pseudohyponatremia can lead to inappropriate therapy with disastrous consequences.

	Day 0	Day 1	Day 7	Day 200	Reference
Serum sodium, I-ISE (mEq/L)	112	114	120	140	136-145
Serum sodium, D-ISE (mEq/L)	–	137	137	137	136-145
BUN (mg/dL)	11	8	14	–	8-20
Glucose (mg/dL)	143	128	97	–	70-99
Ethanol (mg/dL)	117	<10	–	–	< 5
Serum osmolality (mOsm/kg H_2O)	285	278	–	–	275-295
Cholesterol (mg/dL)	1862	2004	1620	274	<200
Triglycerides (mg/dL)	1252	880	–	–	<150
Total bilirubin (mg/dL)	17.9	15.0	5.5	0.2	.3-1.0
Alkaline phosphatase (U/L)	637	611	484	89	30-120
Total protein (g/dL)	3.8	3.4	4.2	7.4	5.5-9.0

Table 1. Laboratory value trends throughout the patient's hospitalization managed with supportive care and alcohol cessation. Day 0 represents the date of initial hospital admission. Na, sodium; BUN, blood urea nitrogen; I-ISE, indirect ion sensitive electrode / indirect potentiometry; D-ISE, direct ion sensitive electrode / indirect potentiometry.

TH-PO330

A Case of Acute Symptomatic Hyponatremia from Self-Infusion of D5W into the Abdomen and Scrotum

Nicholas M. Malchione,[1] Benjamin S. Horowitz,[2] Jonathan Lebowitz.[3]
[1]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; [2]Columbia University Irving Medical Center, New York, NY; [3]Princeton Hypertension Nephrology Associates, Princeton Junction, NJ.

Introduction: Hyponatremia can develop when the amount of free water intake is greater than the free water excretory capacity of the kidneys. This is most commonly seen in primary polydipsia, which is characterized by large intake of water typically in patients with psychiatric conditions. Here we present a case of acute symptomatic hyponatremia as a consequence of self-infusion of D5W into the abdominal and scrotal space; such a presentation has not been previously reported.

Case Description: A 24-year-old man with history of depression presented with lightheadedness, dizziness, nausea, vomiting and one episode of loss of consciousness. He was found to have a serum sodium of 123 mEq/L. Upon further investigation it was determined that earlier in the day the patient had self-infused 3-4 liters of D5W into his abdomen and 1 liter into his scrotum for self-pleasure purposes via needles and equipment obtained from a medical supply company. Exam was notable for a non-tender, distended abdomen and swelling of the scrotum. Laboratory results were notable for a serum sodium of 123 mEq/L, serum glucose 122 mg/dL and urinalysis with a specific gravity of 1.005. Repeat serum sodium 1 hour later was further decreased to 121 mEq/L. The patient was started on sodium chloride 3% infusion and placed on a free water fluid restriction. Given the known acute time course and inciting event the patient was allowed to re-equilibrate quickly with a low concern for osmotic demyelination syndrome. Serum sodium corrected to 133 mEq/L over the course of approximately 10 hours. His symptoms resolved and serum sodium remained within normal limits for the remainder of his hospitalization.

Discussion: This practice termed "inflation" has rarely been reported in medical literature and to our knowledge no prior articles have reported hyponatremia as an adverse event. This case highlights the importance of obtaining a detailed history in patients presenting with hyponatremia in order to identify the underlying etiology and appropriate treatment strategy. Additionally, the case emphasizes the importance of interdisciplinary teamwork for patients at high risk of such behaviors, or for primary polydipsia, to try to prevent such behavior from happening, or if it does happen, to have appropriate monitoring and more rapid recognition and treatment of severe complications.

TH-PO331

Polyuria without Thirst: Adipsic Arginine Vasopressin Deficiency as a Sequela of Pituitary Surgery

Nabeel Siddiqui, Kevin Meek, Rupinder Kaur, Muhammad Qureshi, Bhoomi Shah, Nowoghomwenma C. Ibie. *Southeast Health, Dothan, AL.*

Introduction: Arginine vasopressin deficiency (AVP-D) stems from impairment or absence of vasopressinergic neurons in the hypothalamus and posterior pituitary, resulting in an inability to concentrate urine. Patients typically present with polyuria and polydipsia. Acute AVP-D mostly occurs following surgery for pituitary tumors. Here, we present a case of AVP-D following surgical resection of a suprasellar mass and an unusual absence of thirst response indicative of adipsia.

Case Description: 26-year-old female with complaints of headache, nausea, vomiting, loss of appetite, and unintentional weight loss. She had low TSH, ACTH, cortisol, and IGF-1. MRI head showed a large sellar and suprasellar mass abutting her optic chiasm. She underwent a total macroscopic transcranial resection with findings of extensive sellar and suprasellar lesions displacing the optic nerve and compressing the pituitary. Post-surgery, she had polyuria, a sodium level of 183 with decreased density, serum osmolality of 396, and urine osmolality of 182. The maximum urine output recorded was 5.6 liters in 24 hours. She was treated with desmopressin. Despite sodium levels in the 170s, she denied experiencing thirst.

Discussion: Postoperative AVP-D involves disruption of the hypothalamic-pituitary axis during surgery. Classically, patients with AVP-D experience polyuria and compensatory polydipsia. Increased plasma sodium levels typically trigger the thirst response. Adipsic AVP-D is a rare subset that results when injury to the hypothalamus impairs thirst osmoreceptors and ADH-synthesizing neurons, leading to the absence of thirst in response to hypernatremia. AVP-D following pituitary tumor surgery is a challenging complication requiring comprehensive evaluation and management. Early recognition, appropriate fluid and electrolyte replacement, and tailored ADH replacement therapy are crucial for optimal patient outcomes. This case underscores the importance of prompt recognition and tailored management of AVP-D post-surgery, particularly in patients with complications such as adipsia. Further research is needed to refine diagnostic approaches, optimize treatment strategies, and improve long-term outcomes for patients with postoperative AVP-D.

TH-PO332

A Painful Way to Get Hyponatremia: Acute Intermittent Porphyria

Naman Gupta, Jason M. Kidd, Graham T. Gipson. *Virginia Commonwealth University Medical Center, Richmond, VA.*

Introduction: Acute intermittent porphyria (AIP) is a rare metabolic disorder caused by abnormal enzyme activity in the heme biosynthesis pathway. Symptoms can be nonspecific which can make it challenging to diagnose and treat. Hyponatremia is seen in severe cases and thought to be due to syndrome of inappropriate antidiuretic hormone (SIADH). We present a case of AIP in a young woman presenting with SIADH and recurrent hospitalizations for abdominal pain.

Case Description: A 22-year-old female with a history of endometriosis presented with acute abdominal pain. Vital signs revealed a blood pressure of 137/82 mm Hg. Abdominal examination was significant for diffuse tenderness to palpation without rebound or guarding. She reported experiencing similar episodes in the past year and underwent extensive evaluation and prior hospitalization. Initial laboratory results were significant for sodium (Na) level of 143 mmol/L that rapidly decreased to 122 mmol/L the next day. She was aggressively fluid resuscitated, and Na decreased to 118 mmol/L. Serum osmolality was 257 mosm/kg, urine sodium was 149 mosm/L, and urine osmolality was 642 mosm/kg, consistent with SIADH that was attributed to pain. Sodium did not improve despite medical management including 3% saline infusion. Abdominal imaging revealed an ileus. Due to the combination of her symptoms, AIP was considered. Urine porphobilinogen was checked and was found to be elevated 176.8 mg/L consistent with AIP. A Hemin infusion was started and the patient's pain and hyponatremia improved. Genetic testing was done, which later confirmed AIP.

Discussion: AIP is characterized by neurovisceral attacks associated with high accumulation of early porphyrin precursors. This presence of SIADH in AIP is thought to be multifactorial. Firstly, pain because of visceral spasms is a direct stimulator for ADH. Secondly, presence of paralytic ileus, as in our case, accompanying abdominal pain, leads to intestinal sequestration of water and electrolytes. This leads to activation of angiotensin II and subsequent stimulation of ADH. Treatment includes prompt administration of hemin. Delays in recognizing and treating attacks can lead to serious complications including motor axonal neuropathy, seizures, psychosis and severe hyponatremia. This case highlights the importance of considering the diagnosis of AIP in patients presenting with recurrent abdominal pain and hyponatremia.

TH-PO333

Challenges in Identifying and Managing Lithium-Induced Arginine-Vasopressin Resistance

Michelle Neuman, Abigail Bradner, Jennifer Bergeron. *West Virginia University, Morgantown, WV.*

Introduction: Arginine vasopressin resistance (AVP-R), formerly nephrogenic diabetes insipidus, is the inability to concentrate urine due to resistance to AVP. Lithium is a classic cause of AVP-R, but identifying and managing AVP-R is not always textbook. In this case of AVP-R in lithium toxicity, UTI and dysphagia significantly delayed the diagnosis and improvement in symptoms.

Case Description: A 71-year-old female with bipolar disorder on chronic lithium, CKD3, and hypertension was admitted for 1 week of confusion, vomiting, and diarrhea. Labs were remarkable for creatinine 3.3mg/dL and sodium 133mEq/L (1 year ago 1.2 and 141 respectively). UA showed a UTI, which was presumed to be the cause of her symptoms. She was given fluids and her Cr improved to 2.5mg/dL. The case seemed closed. Surprisingly, the next day, her sodium was 154mEq/L with >3.5L urine output. Urine osmolality (UOsm) was 189mOsm/kg consistent with water diuresis, triggering a lithium level to be sent. It was 1.92mEq/L, consistent with lithium toxicity given her symptoms. Lithium was held and Nephrology conducted a desmopressin challenge without improvement in her Uosm, confirming AVP-R. She was given ample free water. Despite 5 days without lithium, her UOsm fell to 79mOsm/kg. With amiloride daily, Uosm rose to 137mOm/kg, but for days her sodium continued to fluctuate. HCTZ did not help. Eventually, we noted that she had a thickened liquids diet. The thickener is 5.5g modified food starch with 15mg of sodium in 4oz water. Once she was cleared for thin liquids, her sodium stabilized at 142mEq/L. Unfortunately, 11 days later she continued to have neuro symptoms, requiring inpatient rehab discharge for Syndrome of Irreversible Lithium-Effectuated NeuroToxicity (SILENT).

Discussion: This case reveals that lithium induced AVP-R can be masked by volume depletion from UTI and gives evidence that AVP-R can manifest quickly and worsen even after lithium is stopped. Furthermore, it demonstrates how lithium neurotoxicity complicates achieving euvolemia and free water and low solute/protein intake. We found that thickeners add tonicity (and aversion) to otherwise good fluid intake. This case demonstrates the importance of prompt diagnosis and multi-faceted management of lithium toxicities to prevent prolonged hospitalization and permanent life-altering neuromuscular symptoms.

TH-PO334

Exploring the Cause of Acute Severe Hyponatremia: Cytarabine vs. Suspected Brain Lesion Due to Acute Myeloid Leukemia

Emily Vazquez Morales, Juan J. Adams Chahin, Ileana E. Ocasio Melendez. *Universidad de Puerto Rico Recinto de Ciencias Medicas, San Juan, Puerto Rico.*

Introduction: Hyponatremia is a serious electrolyte disorder associated with life-threatening neurological complications with a 47% prevalence in cancer patients. This case involves a patient diagnosed with acute myeloid leukemia (AML) and suspected central nervous system involvement, presenting with hyponatremia.

Case Description: A 54-year-old female with a history of AML was admitted to the Oncology ward for suspected AML relapse. A brain MRI revealed a homogenously enhancing lesion, lymphoproliferative in nature. Due to worsening leukocytosis (increasing from 61K to 126K), cytoreductive therapy with Cytarabine was initiated. After therapy was started, the patient developed an acute symptomatic hyponatremia of 120 mEq/L and Nephrology service was consulted. On examination, the patient was disoriented and lethargic with moist oral mucosa and no signs of volume overload. Serum osmolality was 253 mOsm/kg, and TSH levels were within normal limits. Urine spots were ordered, and 3% saline bolus was administered for a stated sodium correction goal of 4-6 mEq/L in 24 hours. The patient's hyponatremia was attributed to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, potentially precipitated her intracranial lesion or Cytarabine infusion. After 3% saline bolus administration, sodium level improved to 123 mEq/L, but case was complicated by spontaneous ICH and fur further workup for the patient's hyponatremia was not able to be ined due to the patient's untimely death.

Discussion: Although laboratory evidence identifying SIADH as the primary cause of patient's hyponatremia was insufficient, clinical suspicion was high. While cytarabine-induced SIADH is a rare occurrence, it has been documented in medical literature. Furthermore, in cases involving an intracranial lesion that may predispose a patient to SIADH, should we avoid the use of alkylating agents such as cytarabine, or should we instead implement closer monitoring if such agents are administered?

TH-PO335

Polyuria-Polydipsia in Pregnancy: A Case Report of Newly Diagnosed Arginine-Vasopressin Deficiency and Cushing Disease

Juan J. Adams Chahin, Janice M. Cuevas Rivera, Ileana E. Ocasio Melendez, Carlos G. Rivera-Bermudez. *Universidad de Puerto Rico Recinto de Ciencias Medicas, San Juan, Puerto Rico*.

Introduction: Polyuria and polydipsia during pregnancy can often present a diagnostic challenge due to the physiological changes inherent to gestation. Persistent, disruptive symptoms necessitate thorough investigation. We report a case of a pregnant woman with polyuria and polydipsia in the second trimester, unveiling arginine vasopressin deficiency and Cushing's disease, rare endocrine disorders.

Case Description: 30-year-old G5P3A1 at 16 weeks gestation with hypertension presented with excessive thirst and urination for about 4 weeks before admission. Vital signs were remarkable for elevated blood pressures. Physical exam revealed round facies, dorsocervical fat pad, facial and chest acne, hirsutism, and diffuse purple striae. A systolic murmur was also noted. Laboratories showed hyperglycemia (305), hypernatremia (154), hypokalemia (2.2), and metabolic alkalosis (34) with a urine output of 11 liters/day. Urine workup indicated low specific gravity: 1.002 and osmolarity: 100 mOsm/kg. Elevated nocturnal salivary cortisol (35 ng/mL) and ACTH levels (132 pg/dL) were noted. Initial treatment involved fluid and potassium replacement, followed by a single dose of IV desmopressin 4mcg, leading to improved hypernatremia and polyuria (3 liters/day, urine osmolarity: 630 mOsm/kg), indicating arginine vasopressin deficiency (previously known as central diabetes insipidus) along with concomitant Cushing's disease. Pregnancy termination did not resolve polyuria. While on intranasal desmopressin (10mcg q8 hours), she developed shortness of breath and pulmonary congestion. Severe mitral regurgitation was detected on 2D-echo, necessitating reduced desmopressin frequency to allow increased diuresis. Abdominopelvic CT was unremarkable, but brain MRI revealed a pituitary macroadenoma, scheduled for neurosurgical removal.

Discussion: This case underscores the diagnostic challenges posed by polyuria-polydipsia symptoms during pregnancy and emphasizes the importance of thorough investigation in such cases. It highlights the intricate interplay between pregnancy and endocrine disorders, which are rare yet significant contributors to polyuria-polydipsia presentations. Prompt recognition and management are crucial to mitigate complications and improve outcomes

TH-PO336

Severe Hyponatremia: An Unconventional Presentation

Philip Fermano, Rija Ahmad, Habib Nazir. *Bayonne Medical Center, Bayonne, NJ*.

Introduction: Hyponatremia management is a time sensitive correction that requires close monitoring. Irreplaceable neurologic damage could be done if not effectively managed. Hyponatremia has many different etiologies, and it is imperative to identify the cause to treat it. We present a case of a patient who presented to the emergency department with severe hyponatremia and able to recover without any neurologic disturbances.

Case Description: A 61 y/o male with history of alcohol abuse presented with melena. Patient was admitted for GI bleed with covid infection, beer potomania and severe hyponatremia. The patient was found to have Na of 104 on presentation. Patient was oriented only to person due to alcohol intoxication. Pt did not present with neurologic symptoms which was unusual for these Na levels. Initially, the patient was thought to be hypervolemic given 3+ pitting edema in his lower extremities. The patient was given Lasix which brought his Na levels further down. Urine studies supported Hypovolemic Hyponatremia as the urine osmolality was not low initially (351) and then decreased further (99) after administration of hypertonic saline indicating that volume reduced ADH release. Pt was given 1L of NS bolus which failed to improve his Na levels. Pt was given 70cc 3% hypertonic saline two separate times with a D5W maintenance fluid which improved the Na over the next week. It was found by the treating Nephrologist that patient never experienced severe neurological disturbances such as nausea, vomiting, seizure activity, or blurred vision because although patients Na was severely depleted, his osmolarity was maintained by his heavy alcohol consumption. The patient's initial serum osmolality was higher than expected (257). The cause of hypovolemia was a lower GI bleed.

Discussion: In this complex case, the Na correction must be maintained at a rate of 8mmol in 24 hours to avoid complications like osmotic demyelination syndrome. Urine and serum osmolarity are vital indicators of volume state. On presentation, the patient's physical exam and history of alcohol abuse suggested a hypervolemic state, but the elevated urine osmolarity along with the acute drop in Na from 126 to 103 in setting of GI bleed indicated volume depletion. Our recommendation is that careful consideration should be taken into account in patients with multiple causes of hyponatremia regardless of neurologic symptoms of the patient on presentation.

TH-PO337

Unusual Presentation of Arginine-Vasopressin Deficiency: Long Story Short, Decades of Polyuria without Proper Diagnosis

Sundus Sardar, Rafael Portela, Aidaliz Llorens, Umar Farooq. *Penn State Health Milton S Hershey Medical Center, Hershey, PA.*

Introduction: Arginine Vasopressin Deficiency (AVP-D), formerly Diabetes Insipidus, is a rare disorder causing polyuria and free water loss. Typical findings include hypernatremia and low urine osmolality. A positive response to desmopressin (DDAVP) indicates central deficiency. This case underscores the importance of thorough history and high suspicion for AVP-D despite normal electrolytes to ensure prompt diagnosis and improvement in quality of life.

Case Description: 33-year-old female with no past medical history who presented to our nephrology clinic by referral from PCP. Chief complaint was decades of polyuria. Since the age of 7, she remembers having trouble with nocturia. She recalls multiple sleepovers at 11 years of age. She had to sneak out multiple times at night to urinate to a point she needed to use 'pull ups" at sleepovers. In her words: " every road trip We had I remember how my family would say we would have gotten there much faster if they didnt have to stop multiple times to pee". To a point she would just use a "pull up" to "get there faster". In school, her teachers would not let her go to the bathroom as often as she needed it, they blamed "you are just going to fix your make-up". At work during her first job, but being so embarrassed of how often she needed to use the bathroom that she went to other floors in the building so her co-workers would not notice. Her first medical appointment at 7yrs old had cystoscopy done which was normal, few years later was reevaluated and was treated for "overactive bladder". During her pregnancy her polyuria was blamed on bladder pressure from the baby and was complicated by polyhydramnios and post-partum hemorrhage. At 30 yrs of age she presented to our nephrology clinic. 24 hour urine with self imposed fluid restriction revealed 5.7L of urine. Brain MRI was normal, genetic testing was unrevealing, no history of head trauma or surgery. Patient was diagnosed with idiopathic AVP-D and started on DDAVP and since then her life changed forever.

Discussion: This case emphasizes the need to consider AVP-D in chronic polyuria cases, even without typical hypernatremia. Delayed diagnosis of AVP-D led to decades of distress for this patient. Early recognition and treatment with DDAVP drastically improved her quality of life, underscoring the necessity for vigilance in cases like this.

TH-PO338

Renal Salt Wasting in Acute Myeloid Leukemia

Martin Brigham, Neev Patel, Adrian P. Sequeira. LSU Health Shreveport Nephrology. *LSU Health Shreveport, Shreveport, LA.*

Introduction: The idea of a salt wasting disease distinct from syndrome of inappropriate antidiuretic hormone (SIADH) has been a point of skepticism among nephrologists for decades. Discernment between hypovolemia and isovolemia easily runs afoul when fewer methods of evaluation are employed. Integrating Point Of Care Ultrasound (POCUS) bolsters confidence for clinicians trying to group patients into specific volume categories; which is demonstrated in the case below.

Case Description: Our patient was a 52 yo caucasian female with cerebral palsy who was diagnosed with Acute Myeloid leukemia (AML) and admitted for platelet transfusion. Prior to her admission she had completed one cycle of azacitidine and ventecolax. She began her second cycle of chemotherapy with this admission. Nephrology was consulted for chronic hypotonic hyponatremia occurring for the past month. She was euvolemic on exam. Her urine output could not be quantified. At the time of consultation her sodium was 125 mmol/L with a serum osmolality of 272 mOsm/kg and a urine osmolality of 599 mOsm/kg. Uric acid was 2.5 g/dL Interestingly, low serum uric acid characterized the entire duration of her hyponatremia. Her urinalysis was significant for a specific gravity > 1.030 with a urine sodium, potassium, and creatinine of 77 mmol/L, 41 mmol/L, and 63 mg/dl. TSH, serum cortisol, and renal functions were normal & BNP was 43. POCUS of the inferior vena cava (IVC) was performed for further clarification of the patient's volume status. The max IVC diameter was 0.5 cm during expiration while being completely collapsed on inspiration. Collectively, these findings painted a picture of hypovolemia, which favored a diagnosis of RSW over SIADH. Recommendations were given to hydrate with IV normal saline. Over the course of 3 days, the patient's hypotonicity resolved and her serum sodium improved to a value of 141 mmol/L.

Discussion: Resolution of our patient's hyponatremia depended on an accurate volume assessment, as overt hypovolemia excluded SIADH as a diagnosis. Improvement in serum sodium with IV fluids confirmed RSW as the cause of hyponatremia. Supplementing physical exam with POCUS was an effective tool for discerning between SIADH and the more rare diagnosis of RSW. Further research is needed into optimal diagnostic strategies for RSW, including the incorporation of POCUS, which may help to address a lack of data on the disorder's prevalence.

TH-PO339

Rapid Correction of Measured Sodium Levels Despite Relatively Stable Corrected Sodium Levels Can Lead to Osmotic Demyelination Syndrome

Dhairya Salvi,[1,2] Pedro A. Pineiro De Jesus.[1,2] *[1]Ascension Providence Rochester Hospital, Rochester, MI; [2]Wayne State University, Detroit, MI.*

Introduction: Hyperglycemia causes osmotic shift of water from the intracellular to the extracellular space, causing a dilutional hyponatremia. We refer to the sodium level corrected for hyperglycemia in such situations. We present a case that stresses the importance of measured sodium levels (Na_M) rather than corrected sodium levels for hyperglycemia(Na_C).

Case Description: A 59-year-old well-nourished, non-alcoholic male presented with polyuria, polydipsia, and generalized weakness for 2 weeks. On admission, he was dry with an unremarkable neurological exam. His labs suggested Hyperosmolar Hyperglycemic state (HHS) with blood glucose 844 mg/dL, Na_M 129 mmol/L (Na_C 141), bicarbonate 24 mmol/L, anion gap 14, blood urea nitrogen 29 mg/dL and a normal beta-hydroxybutyrate level. HbA1c was >14%. He received 2 liters of normal saline bolus and 15 units of regular insulin. Four hours later, glucose improved to 464 mg/dL with Na_M 137 mmol/L (Na_C 143). He was further started on a basal-bolus insulin regimen. Approximately 16 hours from arrival, he had a transient episode of dysarthria and right hemiplegia. Labs then showed glucose 178 mg/dL and Na_M 139 mmol/L (Na_C 140). CT scan of the head did not show any acute findings. MRI brain showed abnormal restricted diffusion and abnormal increased T2 signal intensity in the pons concerning for osmotic demyelination syndrome (ODS). The patient was later discharged safely without any residual neurological deficits.

Discussion: ODS develops as a result of relative hypertonic insult. Patients with HHS are particularly susceptible to a rapid rise in sodium levels, as the relative lack of insulin allows the development of higher glucose and thus lower sodium levels over a longer course as opposed to DKA patients which present more acutely. In this case, the corrected sodium levels were relatively stable, however, there was a rapid rise in the measured sodium levels, which most likely precipitated the event. Rapid lowering of blood glucose has also been proposed as a triggering factor for ODS in HHS. However, it is refutable as it causes a relatively hypotonic insult. This raises the question of whether we are being falsely reassured by relatively stable corrected sodium levels(Na_C) even when the measured sodium levels(Na_M) fluctuate and have the potential to lead to deleterious consequences.

TH-PO340

Low-Dosage Tolvaptan for Refractory Hyponatremia in Fontan-Associated Cardiac Cirrhosis

Prashant N. Bhenswala,[1,2] Pratap Kumar Upadrista,[1,2] Purva D. Sharma.[1,2] *[1]Northwell Health, New Hyde Park, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.*

Introduction: Hyponatremia in cardiac cirrhosis is challenging to manage. Fontan surgery is a palliative procedure for patients with single ventricle congenital heart lesions that diverts blood from the great veins to the pulmonary arteries, bypassing the right ventricle. Patients develop elevated CVP and cardiac cirrhosis with hyponatremia that is typically managed with a combination of loop diuretics and mineralocorticoid receptor antagonists. Our patient had refractory fluid overload and hyponatremia necessitating Tolvaptan use with good results and no adverse events.

Case Description: A 45-year-old male with hx of Fontan procedure complicated by Fontan Associated Liver Disease requiring paracenteses every 3 weeks, came to the ED for a serum Na of 122 mEq/L. He was on 1 L water restriction and maximally tolerated diuretics of Furosemide 40 mg and Spironolactone 25 mg daily but remained hyponatremic needing more frequent paracenteses and hospitalizations. Physical exam revealed a BP of 85/48 mm Hg, thin appearing male, with ascites and anasarca. Serum osmolality was 266 mosmol/kg. Urine studies: sodium 7 mmol/L, potassium 45 mmol/L, osmolality of 628 mosm/kg indicative of ADH mediated hyponatremia. Despite his history of cirrhosis, low dose Tolvaptan (7.5 mg) was given. Serum Na level appropriately increased from 125 mEq/L to 135 mEq/L over 4 days. The patient was discharged on Tolvaptan 7.5 mg once a week in addition to his home diuretics and has remained stable with a serum Na of 130-133 mEq/L with a reduced need for hospitalizations and paracenteses. Serum creatinine has remained stable at 1.2 mg/dL.

Discussion: Tolvaptan is an arginine vasopressor V2 receptor antagonist promoting excretion of free water. While not contraindicated, it is recommended to avoid use of Tolvaptan in patients with cirrhosis due to the risk of liver failure and variceal bleed. However, owing to the refractory nature of this patient's hyponatremia and limited alternative therapies, low dose weekly Tolvaptan was initiated. Treatment led to controlled and sustained correction of serum Na level and reduction in hospitalizations for fluid overload. Tolvaptan should be considered as alternative therapy for refractory hyponatremia in cirrhosis. Altered pharmacokinetics of the drug in cirrhosis may enable use of a lower dose and frequency for the same effect with no appreciable adverse events.

TH-PO341

Navigating Hyponatremia in a Patient with Superior Vena Cava Obstruction from Retained Pacer Wires and Portal Hypertension

George J. Kavalam, Rucci Marcus C. Foo, Solab Chitrakar, Matthias Bergmann, Samer S. Nasser. *Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: Managing hyponatremia proves challenging when multifactorial, involving hypervolemia and continuous total body sodium losses. A 54-year-old male with biopsy-proven nodular regenerative hyperplasia, grade 2 liver fibrosis with portal hypertension, and complete heart block (CHB) attributed to Lyme disease, requiring a pacemaker. Subsequent recovery prompted the removal of the device, resulting in retained pacer wires that precipitated superior vena cava (SVC) obstruction years later. Deemed too risky for extraction, the patient developed recurrent pleural effusions, necessitating management with a Pleur-X catheter. Within two weeks, severe hyponatremia (serum sodium 121 mEq/L) ensued, leading to a prolonged and complex hospitalization.

Case Description: Initially diagnosed with hypovolemic hyponatremia due to sodium losses from frequent pleural fluid drainage, the patient's sodium levels improved with isotonic fluid replacement. However, he developed hypervolemia and respiratory compromise. Despite treatment with fluid restriction, urea packets, salt tablets, intravenous diuretics, and Tolvaptan, limited success was achieved, with progressive renal failure further complicating the clinical picture. SVC recanalization and stent placement were performed; however, hyponatremia persisted, necessitating continuous renal replacement therapy (CRRT) for volume removal. His course was further complicated by SVC stent migration, precipitating cardiogenic shock requiring extracorporeal membrane oxygenation (ECMO). Subsequently, epicardial lead extraction and SVC reconstruction were performed, restoring kidney function and normalizing sodium levels.

Discussion: This case underscores the complexities of managing hyponatremia caused by volume overload and total body sodium depletion. Managing volume status and electrolyte balance required a multidisciplinary approach involving hepatologists, cardiologists, and nephrologists. The successful preoperative use of CRRT to optimize volume status and electrolytes, followed by complex surgical interventions to treat the underlying problem, highlights the potential of advanced therapeutic modalities when conventional treatments fail. Tailored, collaborative care significantly improves outcomes in complex medical conditions like treatment-resistant hyponatremia.

TH-PO342

Critical Importance of Close Monitoring of Sodium and Fluid Balance in Labor and Delivery

Stefani M. Thompson, Sandeep S. Soman. *Henry Ford Health System, Detroit, MI.*

Introduction: Hyponatremia (hypoNa) is the most common electrolyte disorder seen in clinical practice; due to its many causes, it can be difficult to diagnose and manage. In this case report, we present a unique case of rapid hypoNa associated with pregnancy and the concurrent use of oxytocin and ketorolac. Oxytocin exerts antidiuretic effects similar to those of vasopressin, leading to water retention and dilutional hypoNa. The risk of oxytocin-induced hypoNa is heightened by concomitant fluid administration, making it a well-recognized but potentially preventable complication in obstetric practice. Ketorolac has also been associated with hypoNa, due to the inhibition of renal prostaglandin synthesis, which affects renal water handling and sodium (Na) balance. Additionally, while healthy women can typically excrete about 900 ml of water per hour, this ability decreases by about 1/3rd in late pregnancy, further complicating the management of fluid balance and hypoNa.

Case Description: We present a case of a 35-year-old G1P1 female with a past medical history notable for depression and anxiety who presented 32 weeks pregnant with preeclampsia with severe features. She was started on a magnesium infusion and underwent a cesarian section. During the procedure she had 500 ml blood loss, she received 30 units of oxytocin and 900 ml of lactated ringers (LR). Post procedure she was started on LR at 75 ml/hr and ketorolac every 6 hours for pain control. Eight hours later the patient was found to be lethargic. Stat labs showed a Na of 122 mmol/L (Na was 134 mmol/L on admission). LR was changed to normal saline (NS) and Na further dropped to 119 mmol/L. Urine Na and osmols were 123 mmol/L and 629 mOsm/kg respectively. The patient denied excessive fluid intake and pain. NS and ketorolac were discontinued, and water restriction was initiated. The Na improved to 130 mmol/L within 24 hours.

Discussion: This case presents a rare but significant complication of acute hypoNa precipitated by the concurrent administration of oxytocin and ketorolac in a patient population with decreased free water clearance. Prompt recognition and management of hypoNa is vital to prevent serious neurological complications and ensure favorable patient outcomes. This case highlights the need for electrolyte and fluid balance monitoring, particularly in patients receiving medications known to cause hypoNa.

TH-PO343

Unveiling the West Nile Virus's Sodium Surprise: A Unique Case of Hyponatremia

Justin D. Tse, Jackson Wang. *Sutter Health, Roseville, CA.*

Introduction: West Nile virus (WNV) is a vector-borne flavivirus typically transmitted by the Aedes and Anopheles mosquitos. WNV infection typically manifests with symptoms consistent with viral meningitis and is typically self-resolving, lasting anywhere from 3-10 days. Although uncommon, 30% of patients with WNV encephalitis can be afflicted with hyponatremia, although the etiology is unclear. It can be speculated that because of encephalitis, neuroinflammation may be involved in the deterioration of adrenal signalling, leading to salt wasting.

Case Description: We present a 75-year-old man who presented with meningeal signs and viral illness symptoms. He was found to be hyponatremic with a sodium of 117 mmol/L and was started on 3% saline, fluid restriction, and salt tablets. After ruling out more organic causes of hyponatremia, there was ongoing concern for SIADH in the setting of positive WNV titers. CSF analysis was fairly bland. A paraneoplastic panel was negative, copeptin levels were elevated, and an MRI of the brain revealed the absence of the posterior pituitary bright spot, suggesting a SIADH pathology. He continued to do well with IVF resuscitation and salt tablets, and eventually, his sodium returned to normal levels, with the most recent measure at 138 mmol/L.

Discussion: WNV infection typically manifests with symptoms consistent with viral meningitis and encephalitis. Although there have been cases of mosquito-borne infections with subsequent encephalitis, this is the first known reported case of SIADH related to WNV infection reported to date. The association between WNV and SIADH resulting in hyponatremia adds a new dimension to our understanding of the neurological consequences of mosquito-borne illnesses. The negative paraneoplastic panel, elevated copeptin levels, and the established pathophysiology of WNV encephalitis suggest that SIADH occurred because of neuroinflammation and neuroendocrine disruption. These findings, coupled with supporting imaging demonstrating the loss of the pituitary bright spot, which suggests alterations in the posterior pituitary's functional integrity, support our proposed pathophysiology of WNV-induced encephalitis causing SIADH. This case underscores the intricate interplay between WNV encephalitis, neuroinflammation, and hormonal dysregulation, emphasizing the diagnostic complexity and management challenges in this and other similar clinical scenarios.

TH-PO344

Development of Pediatric Hypokalemia Prediction Deep-Learning System Based on Wearable Single-Lead Electrocardiography in Real Time

Naye Choi,[1] Hyun Kyung Lee,[2] Ji hyun Kim,[4] Hee Gyung Kang.[3]
[1]Korea University Anam Hospital, Seoul, Republic of Korea; [2]Chung Ang University Hospital, Seoul, Republic of Korea; [3]Seoul National University Children's Hospital, Seoul, Republic of Korea; [4]Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

Background: Bartter syndrome (BS) is one of the most well-known hereditary tubular disorders, posing significant challenges for patients in maintaining electrolyte and fluid balance. In severe cases, muscle weakness, paralysis, arrhythmias, and even sudden death can occur, emphasizing the importance of continuous potassium level monitoring for appropriate management. While recent studies have explored deep learning models using 12-lead electrocardiograms to predict abnormal potassium levels, research on monitoring serum potassium levels in patients' home settings is lacking. Therefore, this study aims to develop a deep learning model for detecting hypokalemia using wearable devices' electrocardiogram data.

Methods: This study employed oversampling of positive data and utilizing a generative adversarial neural network-based data augmentation process. A classification model is employed to verify the quality of data, ensuring the utilization of high-quality datasets. Subsequently, the study selects ResNet-50, MobileNet-v3, and EfficientNet-B3 models to compare their performance following dataset augmentation.

Results: The performance of hypokalemia prediction models was evaluated by comparing ROC (Receiver Operating Characteristic) curve values. The best AUC (Area Under the Curve) of the hypokalemia detection model was 0.98.

Conclusions: This study developed a deep learning model for hypokalemia detection using data measured by wearable devices, focusing on pediatric patients with BS. Continuous monitoring of potassium levels through wearable devices to predict abnormal potassium concentrations in the bloodstream is expected to aid in the healthcare management of patients with BS and support medical decision-making by healthcare professionals.

Funding: Clinical Revenue Support

TH-PO345

Role of Artificial Intelligence-Enabled Electrocardiography in the Management and Outcome Prediction of Coexisting Hyperkalemia and Bradycardia

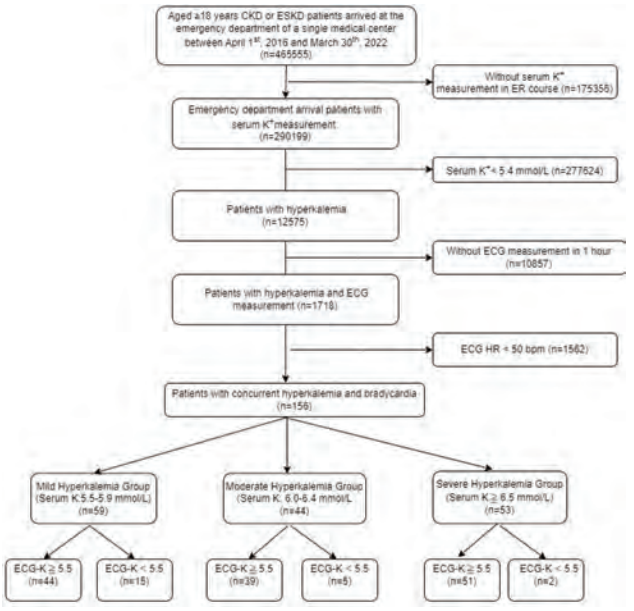
Chien-Chou Chen,[1] Chin Lin,[2] Chi Wei Shih,[3] Ang Lu,[3] Shih-Hua P. Lin.[3]
[1]Tri-Service General Hospital Songshan Branch, Taipei, Taiwan; [2]National Defense Medical Center, Taipei City, Taiwan; [3]Tri-Service General Hospital Department of Medicine, Taipei, Taiwan.

Background: Concomitant hyperkalemia and bradycardia as a life-threatening urgency requires rapid management. Although artificial intelligence-enabled electrocardiography (AI-ECG) has been developed to rapidly detect hyperkalemia and bradycardia, its application in management and outcome prediction has not been evaluated.

Methods: This retrospective study was performed at the emergency department of a single medical center over 8 years. Patients with hyperkalemia≥5.5 mmol/L and ECG showing bradycardia less than 50 bpm were included. Both the cardiologists and nephrologists were consulted for pacemaker placement (PP) and emergent hemodialysis (HD) evaluation. Patients' characteristics, treatment including PP and HD, and outcome were examined. AI-ECG-K^+ quantified by ECG12Net analysis showing ECG-K^+≥5.5 was defined as ECG-K^+ hyperkalemia.

Results: A total of 156 patients who met the inclusion criteria had mild (5.5-5.9 mmol/L, n=59), moderate (6.0-6.4 mmol/L, n=44), and severe hyperkalemia (≥6.5 mmol/L, n=53). Their mean heart rate (HR) was 39.6±8.1 bpm, with atrioventricular block in 68 patients. Most of them had acute kidney injury, chronic kidney disease, or chronic HD. Approximately 50% of them had the drugs affecting HR. The sensitivity for AI-ECG to predict mild, moderate, and severe hyperkalemia was 74.6%, 88.6%, and 96.2%, respectively. Patients with positive ECG-K^+ (ECG-K^+≥5.5) had significantly higher rate of emergent PP (29.9% vs 18.2%), HD (43.3% vs 13.6%), and in-hospital mortality (19.4% vs 9.1%) compared to those with negative ECG-K^+ (ECG-K^+<5.5).

Conclusions: AI-ECG-K^+ may help offer management suggestion and predict the outcomes in the patients with coexisting hyperkalemia and bradycardia, even in the mild to moderate hyperkalemia.



TH-PO346

Safety and Efficacy of WS016 in Patients with Hyperkalemia in China from a Phase 2 Study

Aiyun Song,[1] Li Zuo,[11] Jianrong Zhao,[12] Zhen H. Ji,[7] Qingfeng Peng,[2] Wen C. Xu,[4] N a Tian,[6] Qinghong Zhang,[5] Xianjun Xue,[10] Xinzhong Huang,[8] Changyou Sun,[9] Jianying Niu,[3] Fan Yan,[1] Faming Zhang.[1] WS016 Phase 2 China Study Group. *[1]Waterstone Pharmaceutical (Wuhan) Co., LTD, Wuhan, China; [2]Zhuzhou Central Hospital, Zhuzhou, China; [3]Fifth People's Hospital of Shanghai Fudan University, Shanghai, China; [4]Wuhan Fourth Hospital, Wuhan, China; [5]Taihe Hospital of Shiyan City, Shiyan, China; [6]Affiliated Hospital of Ningxia Medical University, Yinchuan, China; [7]Central Hospital affiliated to Shenyang Medical College, Shenyang, China; [8]Affiliated Hospital of Nantong Medical University, Nantong, China; [9]Tancheng County First People's Hospital, Tancheng, China; [10]Puyang Oilfield General Hospital, Puyang, China; [11]Peking University People's Hospital, Beijing, China; [12]The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China*.

Background: Hyperkalemia is a common electrolyte disorder that is associated with serious cardiac dysrhythmias and increased mortality. WS016 is a highly selective cation exchanger that entraps potassium in the intestinal tract thus could lower serum potassium levels in patients with hyperkalemia.

Methods: 140 patients with hyperkalemia were randomly assigned to receive either WS016(dose of 3g, 6g, 12g) or placebo three times daily for 48 hours(acute phase) in this multicenter, two-stage, double-blind, phase 2 trial. Patients with normokalemia at 48 hour in WS016 group were randomly assigned to receive WS016 or placebo once daily from day 3 to day 14(maintenance phase). The primary endpoint was the exponential rate of change of serum potassium at 48 hour.

Results: At 48 hours, there were absolute mean reduction of 0.58 mmol/L,0.51 mmol/L,0.86 mmol/L in the 3g, 6g, 12g group respectively, and 0.35 mmol/L in placebo group. The reduction at 1 hour after the first 3g dose of WS016 was 0.24mmol/L, while 0.05 mmol/L in the placebo group, respectively. The maxim reduction was 0.98,1.16 mmol/L in 3g and 12g group, 0.50 mmol/L in placebo group at 26 hour. The proportion of patients who reached the normokalemia were 71.4%, 70%,80%,45.7% in 3g, 6g, 12g, and placebo group. At the end of 12-day maintenance treatment, the proportion of patients who maintain normokalemia was 63% in treatment group and 40% in placebo group. The mean increase was 0.27 VS.0.44 mmol/L in 6g and its corresponding placebo group, 0.49 VS.0.68 mmol/L in 12g and its corresponding placebo group. During acute phase adverse events were reported in 26.9% patients in the WS016 group and 20% in the placebo group; and 32.3% patients in the WS016 group and 35.3% in the placebo group during the maintenance phase. Most of AEs were grade 1. There is only 1 SAE found in 12g group, and is not related with WS016. Only 2 patients were reported with hypokalemia graded as 1 in 12g group and recovered without rescue treatment. No patients reported with other abnormal electrolytes and edema.

Conclusions: WS016 can reduce potassium levels during 48 hours rapidly and maintain more patients within the normokalemia duiring 12-day maintenance phase compared with placebo. It was suggested that WS016 is effective and safety for hyperkalemic patients.

Funding: Commercial Support - Waterstone Pharmaceutical (Wuhan) Co., LTD

TH-PO347

Intermittent Sodium Zirconium Cyclosilicate for the Prevention of Hyperkalemia in CKD

Cheuk-Chun Szeto, Winston W. Fung, Jack K. Ng. *The Chinese University of Hong Kong, Hong Kong, Hong Kong*.

Background: Sodium zirconium cyclosilicate emerged as an effective short-term treatment for acute hyperkalemia. Recent evidence supports its use for long-term control of hyperkalemia, but the recommended daily dosage is expensive and may not be well tolerated. We determined the efficacy and safety of intermittent sodium zirconium cyclosilicate therapy for the prevention of hyperkalemia in CKD patients.

Methods: We reviewed 36 patients who received intermittent (1 to 2 doses weekly) sodium zirconium cyclosilicate for more than 3 months. We analyzed plasma potassium levels, episodes of hyperkalemia, emergency room attendance, and hospitalizations before and during sodium zirconium cyclosilicate treatment.

Results: The total duration of observation was 274 patient-months with Lokelma treatment and 216 patient months in the control period; the median duration of Lokelma treatment was 4.4 months (IQR 3.0 – 10.4 months). The median plasma potassium level decreased from 5.10 (IQR 4.91 – 5.40) to 4.73 (IQR 4.50 – 5.10) mmol/l (p = 0.0003). There were 114 episodes of hyperkalemia during the control period and 57 episodes during Lokelma treatment. The median incidene of hyperkalemia reduced from 5.0 (IQR 2.0 – 8.0) to 1.9 (IQR 0.0 – 4.7) episode per patient-year (p = 0.0001). Similarly, the incidence of moderate hyperkalemia reduced from 2.0 (IQR 0.0 – 4.0) to 0.0 (IQR 0.0 – 0.2) episode per patient-year (p = 0.001). There was no significant difference in the total hospitalization or attendance to the Emergency Department.

Conclusions: Intermittent low dose sodium zirconium cyclosilicate is effective for potassium control and enhances the management of hyperkalemia in CKD.

TH-PO348

Updated Design and Status of CONTINUITY: A Phase 4 Study of Continued Postdischarge Sodium Zirconium Cyclosilicate in CKD

James Burton,[1] Alpesh Amin,[8] Maria Jesus Izquierdo,[2] Cecilia Linde,[3] Nicolas R. Robles,[4] Manish M. Sood,[5] Alaster Allum,[6] James M. Eudicone,[7] Katie Mohan.[6] *[1]University of Leicester and University Hospitals of Leicester, Leicester, United Kingdom; [2]Hospital Universitario de Burgos, Burgos, Spain; [3]Karolinska Institutet, Stockholm, Sweden; [4]Universidad de Extremadura, Badajoz, Spain; [5]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [6]AstraZeneca, Cambridge, United Kingdom; [7]AstraZeneca, Wilmington, DE; [8]University of California Irvine, Irvine, CA.*

Background: Patients (pts) hospitalized with hyperkalemia (HK) have increased risk of recurrent HK and re-hospitalization. The ongoing CONTINUITY study (NCT05347693) compares efficacy of continued post-discharge sodium zirconium cyclosilicate (SZC) treatment vs standard of care (SoC) in hospitalized pts with chronic kidney disease (CKD) and HK. We present protocol changes made to clarify eligibility criteria, better align inclusion/exclusion criteria with local practice, and ensure a more clinically relevant main secondary endpoint (Figure).

Methods: CONTINUITY is a randomized, open-label study across 6 European countries. Pts with CKD admitted to hospital with HK will be treated in hospital with SZC. At discharge, pts with normokalemia (NK; serum potassium [sK^+] 3.5–5.0 mmol/L) are randomized 1:1 to SZC:SoC, per local label/practice, for 180 days. The primary endpoint evaluates SZC efficacy as part of discharge medications, vs SoC, in maintaining NK. The main secondary endpoint evaluates the effect of SZC as part of discharge medications, vs SoC, in reducing incidence of the composite outcome of all-cause hospital admissions, or emergency department visits with HK as a contributing factor, or all-cause death, or use of rescue-therapy for HK.

Results: As of May 2024, 179 pts were enrolled and 129 randomized (SZC n=65; SoC n=64) from Belgium (n=2), France (n=6), Italy (n=9), the Netherlands (n=1), Spain (n=109), and the UK (n=2); mean age 72 years, 29% female. Further baseline demographics/characteristics will be presented at Kidney Week 2024.

Conclusions: The CONTINUITY study (estimated completion: Dec 2024) will provide important evidence supporting either SoC or more active sK^+ management with a K^+ binder post discharge for pts with CKD admitted with HK. Protocol changes allow inclusion of a wider pt population and the potential to improve the clinical relevance of the results.

Funding: Commercial Support - AstraZeneca

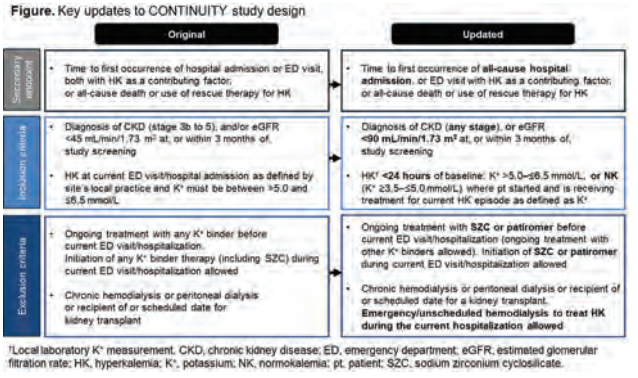


Figure. Key updates to CONTINUITY study design

†Local laboratory K+ measurement. CKD, chronic kidney disease; ED, emergency department; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; K+, potassium; NK, normokalemia; pt, patient; SZC, sodium zirconium cyclosilicate.

TH-PO349

Hyperkalemia-Related Health Care Resource Use (HRU) Associated with Short-Term vs. Long-Term Sodium Zirconium Cyclosilicate (SZC) Therapy in Patients with ESKD: The GALVANIZE Outcomes Study

Arun Malhotra,[1] Abiy Agiro,[1] Erin Cook,[2] Fan Mu,[2] Alexandra Greatsinger,[2] Jingyi Chen,[2] Manasvi Sundar,[2] Ellen Colman,[1] Neela Kumar,[1] Connie Rhee.[3]
[1]AstraZeneca Pharmaceuticals LP, Wilmington, DE; [2]Analysis Group Inc, Boston, MA; [3]University of California Los Angeles, Los Angeles, CA.

Background: Long-term sodium zirconium cyclosilicate (SZC) therapy use has been shown to be associated with lower rates of hyperkalemia (HK)-related healthcare resource use (HRU) than short-term SZC therapy. However, this association has not been evaluated in patients with end-stage kidney disease (ESKD). The GALVANIZE Outcome real-world study compared HRU between long-term and short-term SZC users in patients with ESKD.

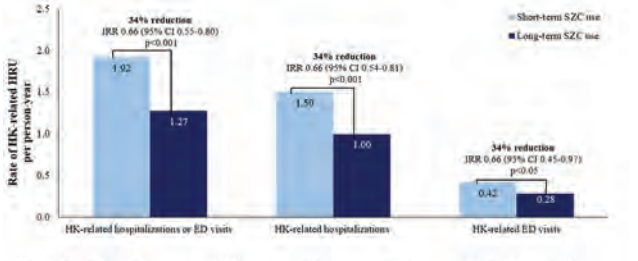
Methods: Adults with a diagnosis of ESKD initiating SZC in the outpatient setting from 7/2018-12/2022 were identified from a large US insurance claims database. Patients with long-term SZC use (>90 days) were exactly and propensity score matched on key baseline characteristics to patients with short-term SZC use (≤30 days). Rates of HK-related hospitalizations and/or emergency department (ED) visits, HK-related hospitalizations, and HK-related ED visits after SZC initiation were compared using generalized estimating equations (also done for all-cause).

Results: Of 1,010 matched pairs with ESKD, 60% were male, the mean age was 57 years. Insurance coverage included 41% of patients with Medicare Advantage, 26% with Medicaid, and 31% with commercial insurance. Hypertension (86%) and diabetes (67%) were the most common comorbidities. Patients with long-term SZC use had a 34% lower rate of HK-related hospitalizations or ED visits (p<0.001), a 34% lower rate of HK-related hospitalizations (p<0.001), and a 34% lower rate of HK-related ED visits (p<0.05) than patients with short-term SZC use.

Conclusions: Long-term SZC use among patients with ESKD was associated with significantly lower rates of HK-related HRU compared to short-term SZC use.

Funding: Commercial Support - AstraZeneca

Figure 1. Rates of HK-related HRU for short-term vs. long-term SZC use in patients with ESKD



Abbreviations: *CI, confidence interval; ED, emergency department; ESKD, end-stage kidney disease; HK, hyperkalemia; HRU, healthcare resource utilization; IP inpatient; IRR, incidence rate ratio; SZC, sodium zirconium cyclosilicate*

Figure 1. Rates of HK-related HRU for short-term vs. long-term SZC use in patients with ESKD

TH-PO350

Effectiveness, Safety, and Treatment Patterns of Sodium Zirconium Cyclosilicate (SZC) for Hyperkalemia (HK) in China: Final Results of the Actualize Study

Hong L. Lin,[1] Nan Shen,[1] Lihong Zhang,[2] Jing Yang,[3] Yongqiang Lin,[19] Xinyu Liu,[4] Xudong Cai,[5] Juan Cao,[6] Qiang Zhu,[7] Xun Luo,[20] Xin Wan,[8] Henglan Wu,[22] Jianming Ye,[9] Chunyan Shan,[15] Hua Xie,[16] Yifan Wu,[17] Yanping Cao,[10] Lin Yang,[11] Xiaoyong Yu,[12] Wang H. Min,[21] Jingdong He,[13] Shaojiang Tian,[14] Fenglei Wu,[18] Yifan Shi.[23]
[1]First Affiliated Hospital of Dalian Medical University, Dalian, China; [2]The First Hospital of Hebei Medical University, Shijiazhuang, China; [3]Hefei First People's Hospital, Hefei, China; [4]Nanyang Central Hospital, Nanyang, China; [5]Ningbo Traditional Chinese Medicine Hospital, Ningbo, China; [6]Taixing People's Hospital, Taixing, China; [7]Xinghua People's Hospital, Taizhou, China; [8]Nanjing First Hospital, Nanjing, China; [9]Kunshan First People's Hospital, Kunshan, China; [10]Handan First Hospital, Handan, China; [11]Linfen Central Hospital, Linfen, China; [12]Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an, China; [13]Nuclear Industry 416 Hospital, Chengdu, China; [14]Shiyan People's Hospital, Shiyan, China; [15]Chu Hsien-I Memorial Hospital of Tianjin Medical University, Tianjin, China; [16]Dalian Ruikaer Renal Disease Hospital, Dalian, China; [17]Guangzhou Hospital of Integrated Traditional Chinese and Western Medicine, Guangzhou, China; [18]Nantong University Affiliated Qidong Hospital, Qidong, China; [19]Wenzhou Integrated Chinese and Western Medicine Hospital, Wenzhou, China; [20]Hunan Provincial People's Hospital, Changsha, China; [21]Liaoning Health Industry Group Bensteel General Hospital, Benxi, China; [22]The First Hospital of Jiaxing, Jiaxing, China; [23]AstraZeneca Investment China Co Ltd, Shanghai, China.

Background: SZC is a non-absorbed cation exchanger approved in China for treating HK (serum potassium level [sK^+] >5.0 mmol/L). Actualize is the first real-world study to assess the effectiveness, safety, and treatment patterns of SZC in Chinese patients (pts) with HK.

Methods: This study included adult HK pts taking/willing to take SZC from 40 sites in China. All pts completed 6- month follow-up. As per Chinese label, treatment was categorized as correction (FAS-P1) and maintenance phase (FAS-P2); treatment was discontinued as per the HK threshold at each site (mostly 5.3 or 5.5 mmol/L). The study evaluated changes in sK^+ and the incidence of adverse events (AEs).

Results: 442 and 878 pts were included in FAS-P1 and FAS-P2, respectively. In FAS-P1, with a mean daily SZC dose of 9.5g, mean sK^+ reduced significantly from 5.8 mmol/L at baseline to 5.0 mmol/L. After correction phase, 51% and 80% of pts had sK^+ between 3.5-5.0 and 3.5-5.5 mmol/L, respectively. In FAS-P2, with a mean daily SZC dose of 4.2 g, the mean sK^+ over 6 months was 5.1 mmol/L. The proportions of normokalaemic pts at 6 months by chronic kidney disease (CKD) stage at enrollment are shown in **Table 1**; in pts with stage 3–4, stage 5/non-hemodialytic and hemodialytic CKD, 59.0%, 63.2% and 51.5%, respectively, had sK^+ between 3.5-5.0 mmol/L. Incidence rate (per 100 person-days) of AEs was 2.9% and 0.5% in FAS-P1 and FAS-P2, respectively, and that of severe AEs was 0.2% in both. There was no AE leading to treatment discontinuation in FAS-P2 and 0.1% in FAS-P1. Overall, 3.8% and 6.5% of pts experienced oedema and hypokalemia, respectively.

Conclusions: SZC was effective and safe in treating HK in CKD pts, and can be considered as standard treatment for acute and chronic HK in China.

Funding: Commercial Support - AstraZeneca China

Table 1. Proportion of normokalaemic pts at 6 months by CKD stage/hemodialysis at enrollment

	CKD stage 1-2 (N=6)	CKD stage 3-4 (N=94)	CKD stage 5/ No haemodialysis (N=115)	CKD stage 5/ Haemodialysis (N=102)
Number of pts with non-missing sK measurements	2	39	57	66
Pts with sK level of [3.5, 5.0] mmol/L				
Number of pts	1	23	36	34
Proportion (95% CI)	50.0 (1.26, 98.74)	59.0 (42.10, 74.43)	63.2 (49.34, 75.55)	51.5 (38.88, 64.01)
Pts with sK level of [3.5, 5.3] mmol/L				
Number of pts	1	25	43	44
Proportion (95% CI)	50.0 (1.26, 98.74)	64.1 (47.18, 78.80)	75.4 (62.24, 85.87)	66.7 (53.99, 77.80)
Pts with sK level of [3.5, 5.5] mmol/L				
Number of pts	1	28	45	52
Proportion (95% CI)	50.0 (1.26, 98.74)	71.8 (55.13, 85.00)	78.9 (66.11, 88.62)	78.8 (66.98, 87.89)

TH-PO351

Prolonged Hypokalemia Long after Causative Factor Elimination in Pseudo-Bartter/Gitelman Syndrome

Atsushi Kondo,[1,2] Tomoko Horinouchi,[1] Yuta Inoki,[1] Yu Tanaka,[1] Hideaki Kitakado,[1] Chika Ueda,[1] Nana Sakakibara,[1] China Nagano,[1] Junya Fujimura,[2] Tomohiko Yamamura,[1] Shingo Ishimori,[1] Kandai Nozu.[1] *[1]Kobe Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Kobe, Japan; [2]Kakogawa Chuo Shimin Byoin, Kakogawa, Japan.*

Background: Pseudo-Bartter/Gitelman syndrome (PBS/PGS) is a medication- and lifestyle-related disorder characterized by hypokalemia and a tendency to renal dysfunction. Treatment involves the elimination of the causative factor and potassium supplementation. However, PBS/PGS symptoms may persist long after the removal of causative factors, and its pathogenesis remains unclear.

Methods: We included 157 cases in which no pathogenic variant was identified despite comprehensive genetic testing, including targeted next-generation sequencing, for suspected inherited salt-losing tubulopathy. Among these, we examined 49 cases with a clear medical history confirming the cause of PBS/PGS. They were categorized into two groups: the current group (n=39), where causative factors persisted, and the past group (n=10), where more than one year had elapsed since the elimination of the causative factors at the time of examination. A retrospective comparative analysis was conducted between these groups.

Results: All patients were female, except for two in the current group. The median age at the time of genetic testing was 44.0 years (range 16–60 years) in the current group and 37.5 years (range 29–58 years) in the past group. The median time since the elimination of causes in the past group was 7.5 years. Blood tests revealed evident hypokalemia in the current and past groups, with a median of 2.4 vs. 2.6 mEq/L (p=0.51), respectively. Renal dysfunction was observed in both groups, with the median estimated glomerular filtration rate 57.6 vs. 60.7 mL/min/1.73 m^2 (p=0.84). Notably, overactivation of the renin-angiotensin system was observed in both groups, as evidenced by a median plasma renin activity of 21.2 vs. 13.2 ng/mL/h (p=0.24) and a median plasma aldosterone concentration of 253 vs. 165 pg/mL (p=0.031).

Conclusions: This study is the first to reveal the possibility of persistent PBS/PGS findings even after removing causative factors. Regarding pathogenesis, we suspect that prolonged hypokalemia may result in a low set point for serum potassium levels being fixed in the renal tubules. While swift removal of the cause of PBS/PGS is crucial, long-term post-removal monitoring is essential to improve renal prognosis.

Funding: Government Support - Non-U.S.

TH-PO352

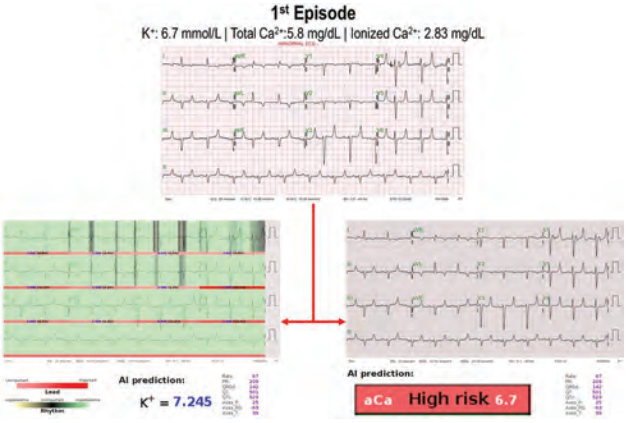
A 57-Year-Old Uremic Man with Recurrent Hyperkalemia following Parathyroidectomy

Ang Lu,[1] Chin Lin,[2] Shih-Hua P. Lin.[2] *[1]Tri-Service General Hospital, Taipei, Taiwan; [2]National Defense Medical Center, Taipei, Taiwan.*

Introduction: Hyperkalemia, associated with an increased mortality risk in hemodialysis (HD) patients, with a higher incidence during the post-parathyroidectomy period, can be divided into shifting causes and non-shifting causes. We present a case of recurrent hyperkalemia associated with severe hypocalcemia following parathyroidectomy rapidly recognized by artificial intelligence electrocardiography (AI-ECG).

Case Description: A 57-year-old uremic male on maintenance HD four times per week presented to the emergency department (ED) at night with muscle twitching and carpopedal spasm. His medication regimen was unchanged, and he had no prior hyperkalemia episode. One week earlier, he underwent parathyroidectomy with autograft implantation for severe secondary hyperparathyroidism, renal osteodystrophy, and pruritus unresponsive to phosphate binder, calcitriol, and calcimimetic. On the 8th postoperative day, he returned to the ED with palpitations and tetany. An AI-ECG alerted hyperkalemia predicting 7.25 mmol/L. Confirmed with hypocalcemia (ionized calcium 2.83 mg/dL) and hyperkalemia (6.7 mmol/L), the tetany resolved within 2 hours following calcium infusion and emergency HD. Despite oral calcium polystyrene sulfonate treatment, he returned to the ED on the 10th postoperative day with the same symptoms and received the same management, leading to symptom resolution.

Discussion: Despite being a known issue, hyperkalemia is often under-managed in HD patients, particularly following parathyroidectomy, where it primarily arises from potassium shifting. A preventive strategy of quantifying calcium supplement dosage postoperatively based on the estimated bone turnover rate is crucial. The risk of HD patients being vulnerable to potassium accumulation and redistribution can be mitigated by advanced AI technology. Increased vigilance and rapid treatment of hyperkalemia in this high-risk population are warranted.



The ECG and AI analysis model from 1st tenancy episode

TH-PO353

Rebound Hyperkalemia in Thyrotoxicosis: A Case Report

Richard Raymund R. Ragasa. *University of the Philippines System, Manila, Philippines.*

Introduction: Thyroid hormones play a significant role in potassium homeostasis through increasing expression of the Na/K ATPase pump. This increases the complexity of repleting potassium in patients with hyperthyroidism. This is a case of unexpected rebound hyperkalemia after potassium repletion in a patient with thyroid storm.

Case Description: A 57-year-old woman with multinodular toxic goiter presented with hematochezia, tachycardia, seizure, and jaundice. Initial workup showed thyrotoxicosis (FT4 55 pmol/L) associated with hypercoagulability (INR 6.0) with subdural hematoma, and cholestatic jaundice. Potassium level on admission was 2.3 mEq/L, which was attributed to intracellular shifting of potassium from thyrotoxicosis and low magnesium at 0.6 mmol/L. Thyroid storm was managed in the ICU with propylthiouracil, hydrocortisone, and potassium iodide. Cryoprecipitate was transfused with resolution of hypercoagulability and bleeding. Patient also underwent hematoma evacuation with neurosurgery. Postoperatively, potassium ranged from 2.6 to 4.7 mEq/L, magnesium at 0.65 to 0.99 mmol/L, and were repleted as necessary. On hospital day 18, potassium was found to be low at 1.8 mEq/L with normal magnesium. EKG showed sinus bradycardia with prominent u waves. Continuous intravenous potassium repletion was started at 8-10 mEq/h on top of oral repletion. Urine K/Crea was found to be <13 mEq/g suggesting intracellular potassium shift. Several hours after around 220 mEq repleted, patient was noted to have wide complex tachycardia and went into cardiopulmonary arrest. Advanced cardiac life support was performed without return of spontaneous circulation. Blood chemistry sent minutes prior to the arrhythmia showed serum potassium of 7.7 mEq/L confirmed by plasma potassium of 7.4 mEq/L. It was unexpected that the repletion resulted in disproportionate and precipitous rise in serum levels.

Discussion: In the thyrotoxic state, intracellular redistribution of potassium decreases serum potassium without changing total body potassium. In about 1 of 4 patients with thyrotoxicosis, paradoxical hypokalemia is observed even with repletion and this was associated with higher thyroxine levels and more pronounced rebound hyperkalemia. This phenomenon makes it difficult to anticipate response to repletion. Potassium repletion in these situations, particularly through the intravenous route, should be done cautiously under close monitoring.

TH-PO354

Primary Hyperaldosteronism with Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Nephrocalcinosis

Misah White, Rob Rope. *Oregon Health & Science University, Portland, OR.*

Introduction: Primary hyperaldosteronism (PA), traditionally characterized by hypertension, sodium retention, and hypokalemic metabolic alkalosis, is often managed effectively with mineralocorticoid receptor antagonists. We present a case of PA management complicated by concurrent SIADH, hypercalciuria, and nephrocalcinosis.

Case Description: Our 39 year-old woman presented in 2019 with hypertension due to primary hyperaldosteronism, without hypokalemia or metabolic alkalosis. Serum aldosterone ranged from 16-70 ng/dL, plasma renin activity 0.1-0.5 ng/mL/hr, with elevated aldosterone:renin ratios of 140-350. Oral salt load did not suppress aldosterone excretion. On CT, adrenals were normal, and adrenal vein sampling showed bilateral disease. Genetic testing was negative for glucocorticoid-remediable aldosteronism. Spironolactone was initiated then discontinued due to a worsening of chronic hyponatremia to 123 mEq/L. Serum sodium on eplerenone ranged from 127-131 mEq/L; hyponatremia did not resolve off MRAs. Hyponatremia workup was consistent with SIADH without

identifiable cause. Her hyponatremia responded well to oral urea, however dosing has been limited by worsening hypercalciuria and noted medullary nephrocalcinosis on CT.

Discussion: PA is typically effectively managed with MRAs, however this strategy can be limited with concurrent SIADH. Hypercalciuria and nephrocalcinosis further complicates management. For example, increasing solute therapy or adding loop diuretics is contraindicated. There are few other case reports of PA associated with nephrocalcinosis. PA has been observed with increased urinary calcium excretion and oxalate crystal formation, though proposed mechanisms including prolonged hypokalemia, hypocitraturia, and urine acidification are not present in our patient. Thus far no unifying etiology has been identified, including tubulopathies (no proteinuria, hematuria) or rheumatic disease, to link these conditions. The next management step for this patient will be repeat eplerenone trial with oral urea for hyponatremia. Amiloride could also be considered.

Serum (S) Aldo	16-70 ng/dL
Renin	0.1-0.5 ng/mL/hr
ARR	140-350
Urine catecholamines	Normal
Cortisol, dexamethasone suppressed	1.3 ug/dL
GRA genetic test	negative
CT abdomen	Normal adrenals, nephrocalcinosis
S Na	123-134 mEq/L
S K	4.0-4.5 mEq/L
S Ca	9.0-9.5 mg/dL
PTH, TSH, ACTH, ACE	normal
24Hr urine (U) Ca	348-592 mg (H)
U Citrate	1304-1414 mg
U Phos	1.07-1.83 mg (H)
U Uric acid	1.03-1.22 mg (H)
U pH	6.32-6.63

Workup summary

TH-PO355

Wasting K, the Ampicillin Way: An Uncommon Cause of Hypokalemia

Isaac Swartzman,[1,2] Jack Luo,[1] Natalie M. Beck.[1] *[1]University of California Davis, Davis, CA; [2]Travis Air Force Base, Travis AFB, CA.*

Introduction: Hypokalemia arises from transcellular shift, reduced intake or increased loss of potassium (K). Elevated urinary K in a hypokalemic individual prompts further workup for renal K loss. We describe a case of renal K-wasting secondary to high dose intravenous (IV) ampicillin use.

Case Description: A 49-year-old male with a history of multidrug resistant disseminated tuberculosis (TB) was hospitalized with abdominal pain and nausea and found to have a small bowel obstruction secondary to an ileal stricture. His home TB regimen was converted to IV linezolid and moxifloxacin. Initial labs revealed normal electrolytes and renal function. On hospital day (HD) 6, he resumed a liquid diet. The following day, he was initiated on ampicillin/sulbactam 3 g TID and meropenem 2 g TID to replace long-acting bedaquiline from his home regimen. On HD 8, he became hypokalemic to 2.8 mmol/L and hypophosphatemic to nadir of 1.2 mg/dL with normal serum magnesium and bicarbonate. Blood pressures were low-normal range. Refeeding syndrome was considered but thought less likely given the persistence of hypokalemia several days after the patient resumed eating, prompting quantification of urinary K. On HD 15, urine studies revealed a spot K:Cr ratio of 155 mEq/g (normal < 13) and a 24-hour K excretion of 143 mmol with a urine anion gap of 110. These findings supported renal K wasting due to nonreabsorbable anions, most likely ampicillin and/or meropenem. He continued on antibiotic therapy and was able to maintain a normal serum K on oral repletion for the remainder of the hospitalization. He resumed his home oral antibiotics upon discharge on HD 22.

Discussion: Workup for renal K loss includes assessing mineralocorticoid activity, acid-base status, and the presence of a urine anion gap if concerned for renal tubular acidosis (RTA). This patient had a low-normal blood pressure and no metabolic alkalosis or acidosis to suggest increased mineralocorticoid activity or RTA, respectively. Hypokalemia associated with antibiotics is a known risk factor, with few cases associated with high dose ampicillin described in the literature. In our case, the high urine anion gap suggests the presence of nonreabsorbable anions. The proposed mechanism is the inability to reabsorb the anion along the nephron, preserving a negative luminal charge and resulting in K secretion at the distal tubule.

TH-PO356

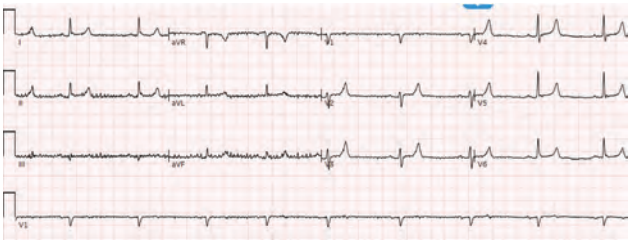
Sea Moss Supplement-Induced Hyperkalemia with Electrocardiographic (EKG) Changes

Marim Zoma,[1] Emma Rochlin,[1] Mohammed A. Abourahma,[2] Agnes R. Libot.[2] *[1]Loyola University Chicago Stritch School of Medicine, Chicago, IL; [2]Loyola University Medical Center, Maywood, IL.*

Introduction: Sea Moss is a widely available herbal supplement, gaining popularity for its supposed health and weight loss benefits. It is high in calcium, magnesium, potassium, and iodine. Sea moss has known risks associated with the excessive iodine, particularly for those with thyroid issues. Our patient experienced hyperkalemia after two weeks on a restrictive sea moss diet, indicating possible additional risks of this supplement.

Case Description: A 72-year-old male with a history of hyperthyroidism, HLD, HTN, CKD stage 3A presented to the emergency department with a one-day history of non-bloody emesis, fatigue and dizziness. In an attempt to lose weight, he was participating in a two-week "sea moss" diet consisting of fruit, water, and sea moss supplements. He continued to take his prescribed medications, including amlodipine and losartan. In the ED, the patient was hypotensive (85/53) and bradycardic (pulse in 40s). Other vital signs remained stable. Physical examination was benign. Labs were notable for: Sodium 130, Potassium 7.1, BUN 54, Cr 4.77 (baseline 1.9), and TSH of 0.26. CBC and troponin levels were within normal limits. The initial EKG displayed peaked T waves and sinus bradycardia, indicative of hyperkalemia. Assessment of renal function showed prerenal AKI, but was otherwise unremarkable. The patient received a 3L IV fluid bolus, calcium gluconate, insulin, and kayexalate to manage hyperkalemia and stabilize cardiac membranes. Antihypertensive medications were stopped, and the patient was continued on maintenance fluids. After a 4-day hospitalization and fluid-resuscitation, the patient's AKI resolved, potassium levels improved to 4.4, and EKG normalized.

Discussion: This report outlines a case of hyperkalemia with associated arrhythmias provoked by excessive sea moss supplementation in a patient taking losartan. This case highlights the growing trend of supplement usage for health management, often without full awareness of their physiological effects and drug interactions. It's crucial for healthcare providers to proactively inquire about patients' supplement use and prioritize discussions on the associated risks.



Abnormal EKG

TH-PO357

Plentiful Peeing in Pregnancy: Could It Be Potassium?

Sruthi Sundaram, Sana Waheed. *Emory University School of Medicine, Atlanta, GA.*

Introduction: In pregnant patients with polyuria, it is important to consider diabetes insipidus (DI). To highlight this, we present a case of complete nephrogenic DI in pregnancy.

Case Description: A 15-year-old G1P0 female with gestational hypertension was admitted at 35 weeks of gestation with polyuria, polydipsia, and in preterm labor. She had persistent hypokalemia during pregnancy which was attributed to vomiting. Ongoing hypokalemia K < 3.0 meq/L and hypernatremia Na > 145 meq/L were noted. Urine output was 5-7 L per day. Plasma renin activity and aldosterone were normal. Urine osmolality was < 100 mosm/L and urine potassium was < 10 mEq/L. Desmopressin (DDAVP) test revealed complete arginine vasopressin-resistance (AVP-R) (Figure 1). Common causes were ruled out, and AVP-R was deemed most likely due to prolonged severe hypokalemia. The patient delivered a healthy preterm infant at 36 weeks, her vomiting resolved, and her serum potassium normalized with supplementation. However, her polyuria persisted, and a thiazide diuretic was initiated until it resolved.

Discussion: The original leading differential was gestational DI caused by placental production of vasopressinase and AVP breakdown; however, this would cause AVP-deficiency and is at odds with the result of the DDAVP test. Hypokalemia causes autophagic degradation of aquaporin-2 and decreased response to AVP causing AVP-R. Typically, the concentrating defect is mild, and symptomatic polydipsia and polyuria is rare. Our patient likely had severe degradation of aquaporin-2 caused by months of persistent hypokalemia resulting in complete AVP-R. Potassium supplementation was unsuccessful until after delivery due to intractable vomiting. Since there is data regarding safety of thiazides while breastfeeding, that was used to treat her persistent AVP-R postpartum. This case

highlights the importance of considering nephrogenic DI in pregnant patients with polyuria and that the DDAVP test can be carried out safely. Fortunately, our patient only required treatment with a thiazide diuretic for 6 weeks postpartum, retained her ability to breastfeed her infant, and was able to be taken off treatment after resolution of AVP-R in a consistently normokalemic state.

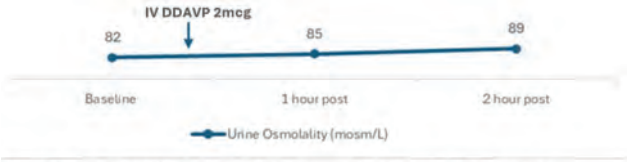


Figure 1: Results of DDAVP challenge. Baseline serum Na 146 meq/L. Baseline serum osmolality 299 mosm/L.

TH-PO358

Unraveling an Uncommon Encounter: Hypokalemic Periodic Paralysis with Brugada Phenocopy Amidst Hypokalemia

Elie El-Charabaty,[1,2] Syed Salman Hamid Hashmi,[1,2] Suzanne E. El Sayegh.[1,2]
[1]Staten Island University Hospital, Staten Island, NY; [2]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY.

Introduction: Hypokalemic Periodic Paralysis (HPP) presents a diagnostic challenge due to its painless muscle weakness, often linked to ion channel dysregulation. This paper discusses Brugada Phenocopies (BrP), showcasing Electrocardiography (ECG) patterns resembling Brugada Syndrome without the genetic condition. The case contributes to understanding BrP induced by hypokalemia alongside HPP, possibly the seventh documented instance.

Case Description: A 43-year-old man with a medical history significant for hypertension and coronary artery disease presented to the emergency department with lower limb weakness. He reported normal muscular strength the day prior but experienced weakness upon waking the next morning. He attributed his symptoms to a substantial meal consumed after breaking his Ramadhan fast, recalling a similar episode following heavy meals in the past. He had a family history of early cardiac-related deaths. The patient was alert and oriented but demonstrated reduced strength in both upper (3/5) and lower (0/5 bilaterally) limbs. ECG revealed a Brugada type 1 pattern. Laboratory analysis revealed hypokalemia (2.5 mmol/L), elevated creatine kinase (326 U/L), and normal thyroid function. Following potassium supplementation, his symptoms resolved, ECG normalized and subsequent tests demonstrated improvement in potassium levels. A neurology evaluation yielded no significant findings. The patient was discharged with plans for outpatient follow-up.

Discussion: HPP occurs in the context of increased carbohydrate intake, potentially leading to rapid insulin release and activation of Na-K ATPase, enhancing cellular potassium absorption and lowering serum potassium levels. Symptoms range from weakness and fatigue to severe neuromuscular weakness and cardiac arrhythmias. Investigating hypokalemia requires excluding hypomagnesemia, thyroid function tests, and metabolic acidosis/alkalosis before considering HPP. Management involves gradual oral potassium repletion to avoid the risk of hyperkalemia associated with intravenous administration. Clinicians should consider including HPP in differential diagnoses of patients presenting with weakness. An electrophysiological evaluation suggested Brugada pattern induced by hypokalemia, which resolved during the hospitalization. In this case, the association with Brugada phenocopies is intriguing.

TH-PO359

How Low Can You Go? Unlocking the Mystery of Persistent Hypokalemia in Pregnancy

Sadhana Gonuguntla, Lakshmi Kattamuri, Lisa A. Hechanova, Adeel Ahmad.
Texas Tech University Health Sciences Center El Paso, El Paso, TX.

Introduction: Geller syndrome is a very uncommon cause of persistent hypokalemia during pregnancy, first described by Geller et al in 2000, which is caused by a gain of function mutation in the mineralocorticoid receptor gene MRS810L which allows progesterone to activate the mineralocorticoid receptor during pregnancy, causing both hypertension and persistent hypokalemia. We present one such case.

Case Description: 29-year-old G2P1 female at 33 weeks of gestation admitted for preeclampsia with a BP 180/100, also noted to have persistent asymptomatic hypokalemia despite adequate repletion (serum potassium 2.5mMol/L). Her 24 hour urine protein was 0.6g/day. Her urine potassium was 20 mmol/L, urine creatinine 68 mg/dl and random urine potassium to creatinine ratio was 3.3, suggesting renal potassium wasting. Serum renin 2.6ng/ml/h, Serum aldosterone 1ng/dl, and aldosterone renin ratio was 0.3 signifying suppressed aldosterone. She was managed conservatively, and subsequently underwent cesarean section at 34 weeks of gestation after failed induction of labor. 24 hours after delivery, her blood pressure and potassium level returned to normal without needing antihypertensive medications or further potassium supplementation.

Discussion: As mentioned above, Geller syndrome is a rare form of monogenic hypertension, which results from a gain of function mutation in the mineralocorticoid receptor gene MRS810L. It typically presents with hypertension and persistent hypokalemia in the third trimester of pregnancy. In humans, progesterone works as an antagonist on mineralocorticoid receptors but in Geller syndrome, this mutation causes progesterone into an agonist of the mineralocorticoid receptors which causes activation of mineralocorticoid receptors during the third trimester of pregnancy due to high progesterone state, causing hypertension and hypokalemia refractory to correction. Amiloride can be used to treat hypokalemia with some benefit. Interestingly it's been noted that Spironolactone, even though a mineralocorticoid receptor antagonist, seems to have an agonist effect on the mutated MR receptor gene worsening the hypokalemia. We must consider Geller syndrome in the differential for hypertension and persistent hypokalemia during pregnancy. Recognition of this entity can prevent unnecessary early delivery, especially if the patient does not actually have preeclampsia.

TH-PO360

Ectopic Adrenocorticotropic Hormone (ACTH) Syndrome Presenting with Hypokalemia in a Patient with Prostate Cancer

Muhammed N. Rehmani,[1] Sreedhar A. Mandayam.[2] *[1]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX.*

Introduction: Cushing's syndrome is a disorder resulting from excess cortisol levels in the body. Most common clinical manifestations are hypertension, weight gain, excess abdominal fat and hirsutism. We present the case of a patient who presented with refractory hypokalemia and was found to have Cushing's syndrome from ectopic ACTH production despite no clinical signs. Ectopic ACTH syndrome (EAS) is most commonly seen in neuroendocrine tumors however it is rarely also seen in those with primary prostate cancer.

Case Description: A 61-year-old-male with metastatic castrate-resistant prostate cancer and hypertension was admitted for severe hypokalemia. Nephrology was consulted for persistent hypokalemia, with serum potassium levels between 2-3 mmol/L despite multiple enteral and parenteral replacements. His blood work was remarkable for serum sodium of 149 mmol/L, serum pH of 7.66 and serum bicarbonate of 30 mmol/L suggestive of metabolic alkalosis. Of note, he had routine labs one month prior, including electrolytes, which were normal. Further work up revealed elevated serum cortisol and ACTH levels. Dexamethasone suppression test was performed which showed ectopic ACTH production. He underwent extensive imaging, but no source of ectopic ACTH production could be identified. He was therefore diagnosed with EAS secondary to prostate cancer and started on daily metyrapone. Due to poor prognosis, he was discharged to hospice.

Discussion: Cushing's syndrome is rare, and diagnosis is frequently delayed due to non-specific symptoms. Our patient had normal labs one month ago and had no clinical manifestations commonly seen in Cushing's syndrome. Prompt workup of refractory hypokalemia led to a timely diagnosis. Had this patient remained outpatient, diagnosis could have been delayed potentially leading to complications from hypokalemia. This patient also had prostate cancer which does not commonly cause ectopic ACTH production. However, there are growing number of cases in patients with castrate-resistant prostate cancer with treatment related neuroendocrine differentiation as a cause of EAS. Key take-away from this case is that it is important for clinicians to have a high index of suspicion for atypical presentations such as electrolyte disturbances as a presenting sign for underlying Cushing's syndrome.

TH-PO361

Potassium of 8? It May Be Okay to Wait

Tammy N. Do, Arash Ataei, Nahida Baigam, Farshid Yazdi, Rajesh Mohandas.
LSU Health New Orleans, New Orleans, LA.

Introduction: Tumor Lysis Syndrome (TLS) can cause renal failure and life-threatening hyperkalemia due to the release of intracellular potassium. We report an unusual cause of severe hyperkalemia, resistant to therapy, in a patient with suspected tumor lysis syndrome.

Case Description: A 69-year old man undergoing chemotherapy with Bendamustine and Rituximab for Chronic Lymphocytic Leukemia (CLL) was admitted for possible tumor lysis syndrome. On admission, his labs were significant for WBC 364,000/uL, Hb 9.1 gm/dL, K 6.9 mmol/L, Cr 1.77 mg/dL (baseline ~1.4-1.6), BUN 22 mg/dL, Phos 3.4 mg/dL, uric acid 9.7 mg/dL, and Ca 7.8 mg/dL. He was started on IV fluids and allopurinol for TLS and given calcium gluconate, albuterol, Lasix, and insulin for hyperkalemia. His renal function improved to a Cr of 1.5 mg/dL and BUN of 18 mg/dL; however, his hyperkalemia persisted, ranging from 5.5 to 6.5 mmol/L, for which he was repeatedly shifted and started on sodium zirconium cyclosilicate TID. On hospital day 3, patient's hyperkalemia acutely worsened to 7.6 mmol/L and nephrology service was consulted. EKG did not show characteristic changes of hyperkalemia. A venous blood gas with electrolytes was performed, which showed a K of 3.8 mmol/L, confirming the diagnosis of pseudo-hyperkalemia.

Discussion: TLS often complicates hematological malignancies and can result in acute renal failure and hyperkalemia. Although TLS was initially suspected because of hyperkalemia and hyperuricemia in this patient with CLL, the stable or worsening WBC counts and lack of hyperphosphatemia or hypocalcemia all raised questions about TLS. The absence of symptoms, EKG changes, response to therapy, and stable renal function pointed to pseudo-hyperkalemia. Hyperkalemia in CLL is thought to be due to lysis of white cells during the centrifugation step necessary for measuring plasma or serum K. Blood gas analyzers use capillary or venous whole blood samples and do not require centrifugation. Timely recognition of pseudo-hyperkalemia is required to avoid unnecessary and potentially hazardous therapy.

TH-PO362

Urine Chemistry: A Valuable Link Binding Kidney Physiology to Patient Care

Anas R. Alshwayat, Nithin Karakala, Joseph H. Holthoff. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: The intricate dance of electrolytes within the human body orchestrates vital physiological functions, particularly within the renal system. Amidst the myriad diagnostic tools available, the analysis of urine electrolytes emerges as a cornerstone in unraveling the mysteries of renal channel dysfunction. By Analyzing the composition of electrolytes excreted in urine, clinicians gain invaluable insights into the renal handling of these essential ions. We delve into the significance of urine electrolyte analysis as a diagnostic modality for identifying dysfunctional renal channels. We explore the physiological principles underpinning electrolyte handling in the kidneys, elucidate the mechanisms of channel dysfunction, and discuss the clinical implications of aberrant urine electrolyte patterns.

Case Description: A 17-year-old African American pregnant female, G1P0 at 34 weeks gestation, presented to triage three times with muscle weakness. During one episode, she fell because her legs gave out and was unable to stand again due to the leg weakness. Her potassium level in the ED was 2 mEq/L. This was her first experience of such weakness. We ordered spot urine potassium and creatinine tests, which revealed a K/Cr ratio of 20 mEq/g and a fractional excretion of potassium (FeK) of 4%. This high FeK in the context of hypokalemia prompted us to proceed with a 24-hour urine collection for electrolytes to confirm renal potassium loss. The 24-hour urine results showed undetectable calcium levels, and elevated levels of sodium, chloride, magnesium, and uric acid in the urine, with normal potassium levels (which are considered high for a patient with hypokalemia). These findings confirmed renal potassium loss and implicated thiazide-sensitive NCC channels as the defective mechanism. Genetic testing revealed a mutation in the NOTCH2 gene of unknown significance, potentially causing NCC channel dysfunction, as NOTCH genes affect the expression of SLC12A3 (the gene responsible for NCC channel function). Additionally, the patient had a mutation in the SCN4A gene, which can cause periodic hypokalemic paralysis.

Discussion: The urine studies are extremely valuable in assessing perturbations in renal physiology that can help in determining the management of patients with electrolyte abnormalities

TH-PO363

A Novel Form of Apparent Hypokalemia

Fiona E. Karet, Elizabeth Norgett. *Dept of Medical Genetics/Cambridge Institute for Medical Research, University of Cambridge, Cambridge, United Kingdom.*

Introduction: In contrast to commonly observed rises in blood potassium levels when sample processing is delayed, pseudohypokalemia (an *ex vivo* fall in plasma potassium level) has previously been reported only rarely. Here we describe pseudohypokalemia as a novel clinical phenomenon in a group of patients with hereditary spherocytosis (HS) and *SLC4A1* mutations.

Case Description: Four patients were referred to our renal clinic for investigation of hypokalemia discovered in primary care. All were male and had HS with general malaise. All lived considerable distances from sites of sample processing. *In vitro* time-course experiments revealed marked falls from normal plasma K in patient samples during the first few hours after phlebotomy that were absent from unselected HS blood or a panel of normal controls. This *ex vivo* finding was most marked (up to 1 mEq/L drop) at 25°C, also observed at 18 and 37°C, but absent at 4°C. Three pseudohypokalemics carried mutations in *SLC4A1* (gene encoding the chloride-bicarbonate exchanger AE1). There was no evidence of renal K wasting and acid-base balance was normal. K supplements were stopped without incident; freshly drawn K levels remained normal. The *in vitro* K falls were abolished by ouabain but not bumetanide, implicating the Na/K-ATPase and excluding NKCC1. Na/K-ATPase activity of patient erythrocyte membranes was increased, concomitant with increased Na/K-ATPase protein levels. In *Xenopus* oocytes, mutant AE1 proteins failed to reach and/or exchange chloride at the cell membrane.

Discussion: Hypokalemia is frequently encountered in biochemistry laboratories and during routine patient management. The differential diagnosis is wide, including whole body K depletion and K redistribution into cells. The latter occurs temporarily with insulin treatment of diabetic ketoacidosis; in alkalosis; catecholamine excess; hypothermia; hypokalemic periodic paralysis and in various leukemias (where K is redistributed into the leukemic cells). An abnormally increased rate of K movement into the cells of whole blood in non-leukemic patients has not been previously documented. Here we have demonstrated this phenomenon *in vitro* in selected individuals with HS, associated with AE1 malfunction. Pseudohypokalemia should be considered in any patient with apparent hypokalemia where there has been a delay in sample processing, particularly in the summer, and a blood film examined, looking for red cell dysmorphology.

TH-PO364

Association of Bartter Syndrome in a Filipino Patient with Overlap Syndrome

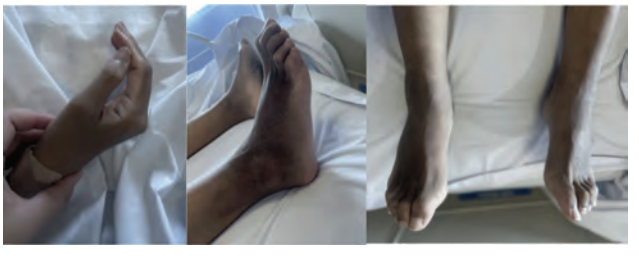
Wilmark N. Gular, Ivy Kathryn A. Ilagan-Asis, Abigail Kristine S. Juat. *St. Luke's Medical Center-Global City, Taguig, Philippines.*

Introduction: Bartter Syndrome is a genetic tubulopathy resulting in hypokalemia and hypochloremic alkalosis. It has been reported to exist with autoimmune diseases. We describe, possibly the first case of an acquired Bartter Syndrome in a patient with Overlap syndrome.

Case Description: We present a 34-year old Filipino woman with two-month history of generalized weakness. Work-up revealed hypokalemia, urine potassium wasting, metabolic alkalosis consistent with Bartter Syndrome. Oral and intravenous potassium were given with return of potassium to normal. However, weakness persisted. EMG-NCV done showed findings of demyelinating polyneuropathy consistent with Guillain-Barre Syndrome. She was treated with Intravenous Immunoglobulin with resolution of the weakness. The patient had recurrence of weakness two months later, this time with dysphagia. Physical exam revealed diffuse skin thickening with sclerodactyly with an mRSS score of 18 for Systemic sclerosis. ANA was at 1:160. Complements were low with high Anti-dsDNA pointing to lupus. Repeat EMG-NCV showed diffuse distal and proximal sensory-motor polyradiculoneuropathy suggestive of myositis. Rheumatoid factor was positive though she had no joint pains. Serum potassium was low at 3.4. Management included oral potassium with Spironolactone and Methylprednisolone Pulse Therapy which led to significant improvement.

Discussion: We presented a case of an acquired Bartter Syndrome with Overlap Syndrome (Systemic Sclerosis, SLE, pre-clinical Rheumatoid Arthritis and Myositis). This case highlighted the temporal evolution of autoimmune disease and its association with a renal tubular disorder. Management involved potassium supplementation and treatment of the underlying disorder.

Serum Chemistry	Result	Reference Range
Crea	0.54	0.55-1.2 mg/dL
BUN	5	9-23 mg/dL
Na	139	136-145 mEqs/L
K	2.6	3.5-5.1 mEqs/L
Ca	9.1	8.3-10.6 mg/dL
Mg	1.9	1.6-2.6 mg/dL
Bicarb	27	20-31 mEqs/L
Urine Electrolytes		
K	9	12-7 mmol/L
Crea	20.24	30-25 mg/dL
K to Crea ratio	45	<13 mmol/g
Cl	41	55-125 mmol/L
Ca	4.9	2-17.5 mg/dL



Flexion contracture and Sclerodactyly of the hand foot. Skin thickening of the legs and feet

TH-PO365

Abiraterone-Induced Hypokalemia Refractory to Exogenous Glucocorticoids Successfully Managed with Amiloride

Natalia R. Nombera,[1] Juan Carlos Q. Velez.[2,3] Ochsner Group. [1]*Universidad Peruana Cayetano Heredia, Lima, Peru;* [2]*UQ-Ochsner Clinical School, Brisbane, QLD, Australia;* [3]*Ochsner Health, New Orleans, LA.*

Introduction: Abiraterone acetate irreversibly inhibits CYP17 blocking androgen synthesis in tumors, testes, and adrenal glands, and is used for prostate cancer treatment. Diversion of this enzymatic pathway leads to increased production of the mineralocorticoid

molecules deoxycorticosterone and corticosterone. By virtue of its enzymatic blockade, abiraterone also decreases cortisol, leading to a compensatory rise in ACTH and further rise in mineralocorticoid production, leading to hypokalemia. These effects can be mitigated by ACTH suppression with prednisone. Herein, we report an unusual case of abiraterone-induced hypokalemia despite glucocorticosteroid coadministration, successfully managed with amiloride.

Case Description: A 70-year-old man with prostate cancer receiving chronic treatment with abiraterone and prednisone, presented with dyspnea, emesis and low back pain. He had recently undergone bronchoscopy due to an abnormal CT scan concerning for a granulomatous lesion. Review of old records revealed several episodes of serum potassium (K) of 2.5 – 3.0 mEq/L for the last 3 years. On arrival, blood pressure was 173/107 mmHg, pulse 109/min. Physical exam was normal. Pertinent serum laboratory data revealed a K level of 2.5 mEq/L, sodium 145 mEq/L, creatinine (Cr) 0.8 mg/dL, and carbon dioxide 20 mEq/L. Despite aggressive oral and intravenous KCl supplementation, hypokalemia persisted. Urine K-to-Cr ratio was 82 mEq/g. Plasma renin activity was 0.6 ng/mL/hr and plasma aldosterone concentration was 21 ng/dL. ACTH was 56 pg/mL (normal range 0-46). Corticosterone level was obtained: 6190 ng/dL (normal range 53-1560). A diagnosis of glucocorticoid-refractory abiraterone-induced hypokalemia was made.

Discussion: Amiloride was initiated, and aggressive repletion of potassium was continued. After discussion with Oncology, abiraterone was discontinued. Serum K normalized to 4.0 mEq/L in 2 days and remained normal 2 weeks post-discharge. Amiloride was discontinued and serum K remained normal therafter. This case exemplifies how abiraterone can lead to severe symptomatic hypokalemia despite chronic glococorticoidsteroid mitigating therapy. Elevated ACTH and corticosterone levels confirm the diagnosis. Direct blockade of the epithelial sodium channel (EnaC) with amiloride is an effective therapy.

TH-PO366

Medullary Thyroid Carcinoma Presenting with Severe Hypokalemia

Areej Zaheer. *Henry Ford Macomb Hospital, Clinton Township, MI.*

Introduction: Medullary thyroid carcinoma (MTC) accounts for about 1-2% of all thyroid malignancies. 70 % of most medullary thyroid carcinomas are sporadic in nature. The typical age at initial presentation ranges between 41 and 55 years. Approximately 0.6% of cases of MTC have ectopic production of ACTH. The objective of this case is to bring attention to the association between ectopic ACTH or CRH causing symptoms in the setting of medullary thyroid carcinoma

Case Description: Thirty-eight-year-old male, presented to the hospital due to left upper extremity swelling, redness, and pain. He was diagnosed with acute cellulitis and started on appropriate antibiotics. At the same time, aggressive replacement of potassium resulted in only minimal improvement and recurrence of severe hypokalemia prompting further workup. Urine electrolyte panel results were suggestive of renal potassium wasting defect. The aldosterone level was normal and direct renin level was normal The random cortisol level was increased. Dexamethasone suppression test was done which showed elevated cortisol levels confirming ACTH production. Brain MRI revealed no pituitary lesions. Due to a lack of improvement in the left arm swelling, the patient underwent a CT scan with IV contrast to look for possible obstruction which showed a mass in the thyroid region with abdominal lymph nodes, and multiple hepatic lesions. A liver biopsy was done which was consistent with medullary thyroid carcinoma. The patient was started on metyrapone with an improvement in cortisol levels. The patient was then started on Selpercatinib 160 mg twice per day, with regular follow-ups with heme/onc, nephrology, and endocrinology. His potassium and glucose were well controlled. However, he developed a recurrence of cancer.

Discussion: The diagnosis of ectopic ACTH production secondary to MTC is based on the presence of hypercortisolism not suppressed by high cortisol, absence of pituitary adenoma, and Cushing syndrome symptoms. MTC can spread to lymph nodes, and the lungs, liver, and brain via blood. Treatment for ACTH production includes adrenolytic agents or suppression of steroidogenesis. In extreme cases, bilateral adrenalectomy may be needed. Tyrosine kinase inhibitors including selpercatinib, sorafenib, vandetanib, and cabozantinib are used for chemotherapy for MTC. Due to the high resistance rates of MTC to tyrosine kinase inhibitors, screening for recurrence is essential.

TH-PO367

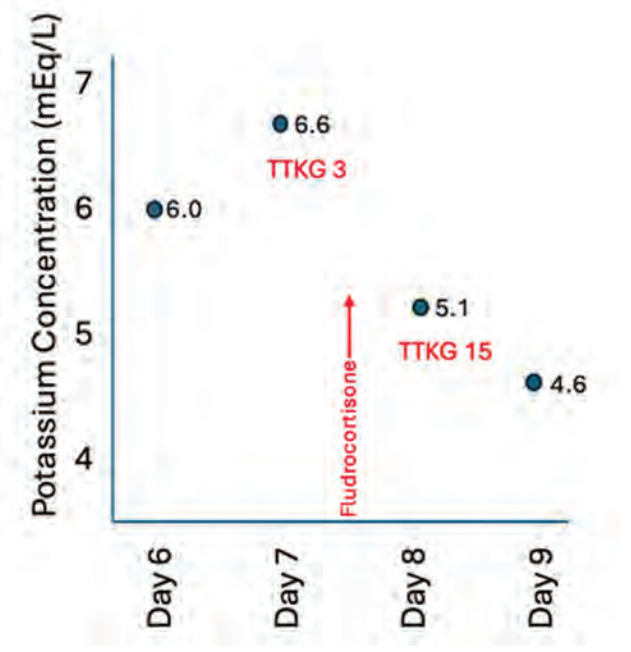
AKI Confounding Heparin-Induced Hyperkalemia

Levan Gakhokidze, Nicole Wyatt, Juan Pablo Arroyo Ornelas. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Heparin induced hypoaldosteronism is an uncommon etiology of hyperkalemia in hospitalized patients. It poses a challenge from diagnostic and management perspectives especially when it occurs in conjunction with other causes of hyperkalemia. We present a a patient with pre-renal acute kidney injury as well as hyperkalemia where transtubular potassium gradient (TTKG) was successfully used for diagnosis and management.

Case Description: A 70 year-old male with an end-ileostomy, CKD3b secondary to recurrent pre-renal acute kidney injury (AKI) from high ostomy output was admitted with atrial fibrillation with a rapid ventricular rate and hypotension. He was started on heparin infusion and cardioverted. The hospital course was complicated with pre-renal non-oliguric AKI thought to be from volume depletion from high ostomy output. Despite improving renal function (creatinine 4.3 - > 2.6 mg/dL) and with appropriate urine output (>1.3L) hyperkalemia progressively worsened (Table 1). There was no evidence of hemolysis or rhabdomyloysis. TTK calculated on day six was 3, suggestive of impaired distal tubular potassium secretion. The patient was initiated on fludrocortisone resulting in prompt improvement of hyperkalemia and increase of TTKG to 15.

Discussion: Heparin induced hyperkalemia is due to decreased renal excretion secondary to decreased aldosterone activity in the distal tubule. Heparin is thought to directly interfere with production of aldosterone. TTKG can assess hypoaldosteronism (cutoff < 5-7). Increase to > 10 after fludrocortisone administration confirmatory. In above case, Fludrocortisone was shown be a successful therapy in addition other conventional treatments of such hyperkalemia. This case highlights that in non-oliguric acute kidney injury with refractory hyperkalemia, heparin must be considered as a potential culprit.



TH-PO368

Semaglutide (S) Completely Reverses the Severe Chronic Myopathy of Hyperkalemic Periodic Paralysis

Kenneth Brand, Daniel L. Landry, Jeffrey Mulhern, Gregory L. Braden. Kidney Care and Transplant Services of New England. *Baystate Medical Center, Springfield, MA.*

Introduction: Hyperkalemic Periodic Paralysis (HPP) is caused by a gene mutation in skeletal muscle Na channel, SCN4a, causing sustained muscle depolarization, hyperkalemia & muscle weakness. After 3 decades most patients develop severe muscle weakness leading to life in a wheelchair. We describe a patient with HPP with severe chronic myopathy & after starting S for weight loss he regained normal strength.

Case Description: A 48 year-male with HPP at age 4 had a Na channel point mutation in the SCN4A gene at 704 with methionine replacing threonine. His father, uncle, sister, & 3 nephews have the same mutation. He was treated with acetazolamide, albuterol, & daranide without success. S was given due to a body mass index greater than 40. We studied the Short Phyicsal Performance Battery (SPPB) pre S & at 4, 7 & 12 months of S. After the third weekly dose sub q of 0.25 mg he noted less weakness. Before the S he could not rise out of a chair without help & his gait was very slow. The table shows his dramatic results & he was normal at 7 months. He stopped S after having GI side effects on 2.4 mg/week & his weakness returned. He is now on 1.7 mg/week with a normal SPPB and muscle strength at 1 year..

Discussion: S is a glucagon like peptide (GLP-1) agonist that inhibits glucagon release, enhances the growth of pancreatic beta cells, and increases their production of insulin. Meals on S increase insulin levels 5 fold which shift K intracellularly. As in animal studies, GLP-1 stimulation of its receptors on skeletal muscle can reverse myopathy by promoting muscle cell growth and inhibiting muscle atrophy. By altering insulin signaling and skeletal muscle physiology, S increases intracellular potassium storage and decreases myopathy in HPP. S is an excellent & novel once weekly option that treats not just the hyperkalemic periodic paralysis but also the skeletal muscle weakness in a multimodal way.

SPPB

SPPB	Pre S	4 mo	7 mo	12 mo
Side by Side Test (sec/ score)	4/0	29/1	>30/1	180/1
Semi Tandem Gait Test (sec/ score)	1/0	15/1	>30/1	45/1
Tandem Gait Test (sec/ score)	0/0	20/2	>20/2	15/2
3 Meter Standard Gait Test (sec/ score)	10.1/0	4.25/3	2.87/4	3.52/4
3 Meter Fast Gait Test (sec/ score)	6.8/0	3.0/4	1.8/4	3.25/4
Repeat Chair Stand Test (sec/ #/ score)	0/0/0	25.1/5/1	15.4/5/2	20.5/5/1
Total Score (normal >12)	0	12	14	13
BMI (kg/m2)	36.5	33.2	31.3	29.2

TH-PO369

Familial Hypokalemic Periodic Paralysis: A Case Induced by Concurrent Hyperthyroidism

Leanne Brown,[1] Zein Alabdin Hannouneh,[2] C. E. Cervantes,[1] John Sperati,[1] Mohamad A. Hanouneh.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]Al Andalus University for Medical Sciences, Tartus, Syrian Arab Republic.*

Introduction: Familial hypokalemic periodic paralysis (HypoPP) is an uncommon genetic channelopathy marked by recurrent episodes of flaccid skeletal muscle paralysis accompanied by hypokalemia.

Case Description: A 40-year-old African American man was admitted with profound muscle weakness after eating high salt diet. He was unable to move his extremities or sit upright. He had a family history of hyperthyroidism and hypokalemia in his brother and mother. Physical examination revealed profound weakness in extremities. Laboratory results are shown in Figure 1. Swift replacement of hypokalemia alleviated his symptoms. Genetic testing revealed a heterozygous pathogenic variant in *CACNA1S* [c.1583 G>A (p. R528H)] and normal sequencing of *SCN4A* and *KCNJ18*. The patient was diagnosed with familial HypoPP and hyperthyroidism due to Graves' disease. He was started on PO methimazole 10 mg three times a day and PO acetazolamide 250 mg twice a day. He was advised to follow a low carbohydrate and low salt diet.

Discussion: The main triggers for HypoPP episodes are vigorous exercise and high carbohydrate diet, with occasional links to viral infections, stress, salt intake, and medications. Familial HypoPP is linked to gene variants: SCN4A in 20% or CACNA1S in 60% of patients, affecting skeletal muscle sodium and calcium channels, respectively. Generally, hyperthyroidism is linked to thyrotoxic periodic paralysis (TPP) in Asian populations. KCNJ18 variants are associated with TPP susceptibility. TPP likelihood is low in this case due to non-Asian ethnicity, a family history of HypoPP, and absence of KCNJ18 variants. Nevertheless, Graves' disease and a high-salt diet are likely the triggers of the HypoPP episode in this case. Treating acute paralytic episodes involves potassium replacements with monitoring for potential post-treatment hyperkalemia. Changing lifestyle and diet to avoid triggers is crucial. Carbonic anhydrase inhibitors and potassium-sparing diuretic have shown effectiveness in decreasing the frequency of familiar HypoPP episodes.

Basic Laboratory Tests

Blood Tests	Reference Range & Units	Results
Sodium	136 - 145 mmol/L	139
Potassium	3.5 - 5.1 mmol/L	<1.5
Chloride	98 - 107 mmol/L	105
CO2 Total	22 - 29 mmol/L	21
Anion Gap	7 - 18	13
BUN	6 - 23 mg/dL	18
Creatinine	0.67 - 1.17 mg/dL	0.91
eGFR	>=60	109
Glucose	70 - 99 mg/dL	142
Calcium	8.6 - 10.2 mg/dL	9.3
Calcium Ionized	1.17 - 1.38 mmol/L	1.32
Magnesium	1.6 - 2.6 mg/dL	1.9
Phosphorus	2.5 - 4.5 mg/dL	2.1
Total Protein	6.6 - 8.7 g/dL	7.2
Albumin	3.5 - 5.2 g/dL	3.9
Globulin	2.5 - 4.0 g/dL	3.3
AST	5 - 40 U/L	64
ALT	5 - 41 U/L	153
Bilirubin Total	0.2 - 1.2 mg/dL	0.3
Alk Phos	40 - 129 U/L	79

Thyroid Hormone Tests

Blood Tests	Reference Range & Units	Results
Thyroid Stimulating Hormone (TSH)	0.270 - 4.200 mcIU/mL	<0.006
Free T3	2.1 - 4.4 pg/mL	13.0
Free T4	0.90 - 1.70 ng/dL	3.04
Thyroid Stimulation Immunoglobulin (TSI)	<=0.54 IU/L	3.43
Thyroid Peroxidase Ab	0.0 - 9.0 IU/mL	62.6

Urine Tests

Urine Tests	Results
Random Creatinine	75.02 mg/dL
Random potassium	8 mmol/L
Random potassium/creatinine ratio mmol/g	10.66 mmol/g

Figure 1: Laboratory results

TH-PO370

Gitelman Syndrome-Related Hypokalemic Nephropathy

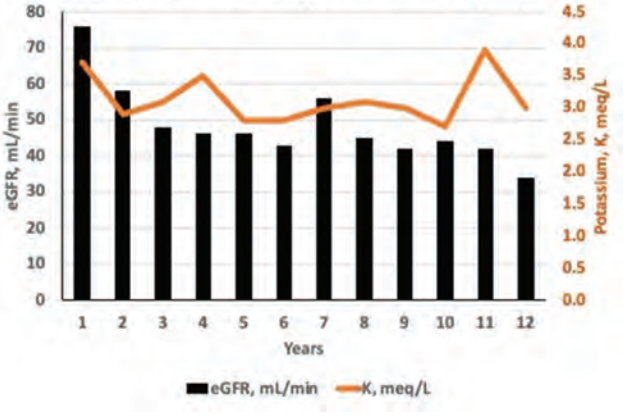
Kamyar Pournazari,[1,2] Maria C. Browne,[1,2] Stephen L. Seliger,[1,2] Abutaleb A. Ejaz.[1,2] *[1]University of Maryland School of Medicine, Baltimore, MD; [2]VA Maryland Health Care System, Baltimore, MD.*

Introduction: Gitelman syndrome (GS) is a rare, inherited renal tubular disorder, usually considered a benign tubulopathy wherein progressive CKD is not a common feature. We present a 56-year-old WF with progressive decline in eGFR related to suspected Gitelman syndrome-associated hypokalemia.

Case Description: PMH of bipolar disorder, presented with asymptomatic, persistent hypokalemia and incidental CT finding of bilateral single kidney stone ~3mm. Current medications include bupropion HCL, Topiramate, diazepam and levothyroxine. Patient declined all K supplementation for years. Exam remarkable for thin body habitus, wt 112lbs, BP 102/59. Labs showed persistent hypokalemia and hyperbicarbonatemia over the past decade, SCR 1.66mg/dL, eGFR 36mL/min, CysC 1.68mg/dL, CysC-eGFR 37mL/min, Ca 10.1mg/dL, Mg 2.2mg/dL, UACR<7, UpH 5.5 and SG 1.021, PTH 34.1. eGFR declined from 76mL/min to 34mL/min over a 12-year period. Serum Aldo 9ng/dL, PRA 10.6ng/mL/hr. Gitelman syndrome was suspected and amiloride started, while 24hr urine studies were pending. (Figure 1)

Discussion: Hypokalemia is associated with interstitial fibrosis related to intrarenal vasoconstriction, increased RAS activation and inflammation, leading to tubular atrophy and dropout. Clinically, our patient had intact urine concentration and acidifying capacity. Reungjui et al have proposed another mechanism that involves decreased renal angiogenesis. Accordingly, macrophage-associated cytokines (IL-1β, IL-6, TNF-α) inhibit VEGF expression that causes progressive capillary loss, reduced EC proliferation and decline in GFR. The decade long direct correlation of persistent hypokalemia and progressive loss of eGFR in our patient substantiates our suspicion of Gitelman syndrome-related hypokalemic nephropathy. Ref: **Reungjui S**, Roncal CA, Sato W, Glushakova OY, Croker BP, Suga S, Ouyang X, Tungsanga K, Nakagawa T, Johnson RJ, Mu W. Hypokalemic nephropathy is associated with impaired angiogenesis. J Am Soc Nephrol. 2008; 19:125-134.

Figure 1: Evolution of hypokalemic nephropathy



TH-PO371

Back to Basics: Multiple Episodes of Hyperkalemia Due to Different Etiologies All Explained by Basic Physiologic Principles

Rafael Portela, Ahmad Matarneh, Sundus Sardar, Aidaliz Llorens, Muhammad Abdulbasit. *Penn State Health Milton S Hershey Medical Center, Hershey, PA.*

Introduction: Potassium handling by the nephron is an important concept taught in medical school but, an intricate understanding of these processes usually develops during nephrology fellowship. Potassium disturbances are greatly influenced by intake, excretion and cellular shifts. We present a case of multiple episodes of hyperkalemia due to different etiologies all explained by basic physiology of potassium handling.

Case Description: 57 year old female with chronic kidney disease stage 3a, MEN 2a syndrome status post right adrenal resection and gastric outlet obstruction with gastrojejunal (GJ) tube who presented for GJ tube dysfunction and stage 1 acute kidney injury. After unclogging the GJ tube, Peptamen 1.0 tube feeds (TF) were started (6 cans per day). After 48 hours, she developed unexplained hypotension. CT Chest revealed partial loculated pleural effusion. Labs showed hyperkalemia of 7.1 meq/L. She was treated medically and nephrology was consulted. At this point, acute kidney injury had resolved, but non anion gap metabolic acidosis (NAGMA) persisted (bicarbonate 20meq/L). Up to this point, hyperkalemia etiology was thought to be multifactorial: excess intake of potassium by TF (11 meq per bottle of Peptamen 1.0), NAGMA and underlying untreated primary adrenal crisis. Morning cortisol was low at 9.9 mcg/dL, consistent with our suspicion of primary adrenal insufficiency. She was treated with IV steroids accordingly and TF potassium content decreased and potassium remained stable at 4-5 meq/L. After 48 hours, had another hyperkalemic episode of 7.7 meq/L with worsening hyperglycemia of 409 mg/dL. Nephrology was reengaged and treatment with insulin was recommended. At this time, the culprit for hyperkalemia was increased insulin resistance in the setting of high dose steroid use, so steroids were tapered. Identifying each etiology of hyperkalemia episode led to prompt management and resolution of severe hyperkalemia.

Discussion: Here we portray multiple etiologies of hyperkalemia that every nephrologist should be aware. Prompt recognition of reversible causes of hyperkalemia such as increased dietary potassium intake, metabolic acidosis, adrenal insufficiency and insulin resistance are life saving and cost effective when managing admitted patients, avoiding invasive procedures, such as hemodialysis.

TH-PO372

Unexpected Discovery: A Case of Adrenocortical Carcinoma

Olamide Olowoyo, Kartik Kalra. *Geisinger Health, Danville, PA.*

Introduction: Adrenocortical carcinoma (ACC) is a rare disease that could present in an unusual pattern. We present a case of a patient with rapid onset, severe hypokalemia and worsening blood pressure (BP) leading to diagnosis of ACC.

Case Description: 67-year-old female, with history of hypertension (well controlled on Amlodipine 5mg daily) presented with gradual onset generalized muscle weakness for 10 days. Her blood pressure (BP) had been poorly controlled over the past 2 weeks and was 180/110 mmHg at presentation. She denied drug abuse, diuretics, or liquorice use. Lab testing (image 1) revealed severe hypokalemia with EKG changes (elongated QT interval and U wave). She was managed medically and discharged on oral potassium supplements in addition to multiple BP medications (Telmisartan 80 mg, Amlodipine 10 mg, Spironolactone 25 mg). Further evaluation in the office revealed elevated Aldosterone/PRA ratio (image 1) raising suspicion for primary hyperaldosteronism (PHA). A CT of the abdomen with adrenal protocol revealed a lobulated right adrenal nodule with adenomatous thickening. Adrenal venous sampling lateralized to the right adrenal gland, and she was referred for a laparoscopic right adrenalectomy. Adrenal gland histology revealed a high grade myxoid ACC. The patient was started on cisplatin, etoposide and mitotane.

Discussion: ACC is a rare and potentially aggressive malignancy. The incidence of ACC worldwide is 0.5 to 2 per 1 million people annually. It could present with hormonal changes from hyperaldosteronism, hyperandrogenism or hypercortisolism, non-specific symptoms or as an incidental finding. It could also be part of some familial cancer syndromes. A high index of suspicion is therefore needed when it presents in an unusual manner such as was seen in our patient with rapid onset hypokalemia and worsening HTN suggestive of hyperaldosteronism. Treatment is with surgery and adjuvant chemotherapy/ radiation therapy. It has a high risk of recurrence.

Parameter	Results at presentation	Normal range	Unit
Serum potassium	1.4	3.5 – 5.1	mmol/L
Creatinine	0.6	0.5 – 1.0	mg/dL
eGFR	>90	>90	mL/min/1.73m²
CO2	34	22-32	mmol/L
Magnesium	2.1	1.5-2.6	mg/dL
Potassium, 24-hour urine	89	25-120	mmol/24 hours
24-hour urine free Cortisol	13.8	4.0 – 50.0	mcg/24 hours

Parameter	Results at presentation	Results after surgery	Normal range	Unit
Aldosterone level	38	2	<28 (Upright)	ng/dL
Plasma renin activity	0.07	0.81	0.25-5.82	ng/ml/h
Aldo/PRA ratio	542.9	2.5	0.9-28.9	mL/min/1.73m²

Image 1

TH-PO373

How Low Can You Go? Abiraterone-Mediated Mineralocorticoid Excess Despite Prednisone Use

Ahmad Al-Tamari, Patricia Khalil, Amr Habbach. *Allegheny Health Network, Pittsburgh, PA.*

Introduction: Abiraterone is approved for the treatment of castration-resistant prostate cancer by inhibiting androgen synthesis. Through this mechanism, however, it also leads to decreased Cortisol synthesis and increased ACTH production. If not given with sufficient dose of oral steroids, this can lead to ACTH mediated mineralocorticoid excess (AME). We present a case of Abiraterone-Induced AME despite glucocorticoid use.

Case Description: 71-year-old male with prostate cancer, presenting with 4 weeks of weakness, and myalgia. Evaluation showed profound hypokalemia with potassium of 1.6 mEq/L and Rhabdomyolysis with a CK level of 7700 U/L, creatinine remained normal. He also had resistant hypertension despite being on multiple oral agents. Further testing suggested potassium wasting with a potassium/Creatinine ratio of 58 mmol/g. Aldosterone level was at less than the detectable range and Renin levels low suggesting a diagnosis of Abiraterone-Induced AME. Abiraterone was discontinued and he was started on Eplerenone with oral potassium supplementation leading to resolution of hypokalemia and hypertension.

Discussion: Profound hypokalemia can lead to life threatening complications, and it is imperative for nephrologists to recognize the presence of AME picture and identify potential rare causes. Abiraterone suppresses androgen production by inhibiting CYP17A1 enzyme. This enzyme is also key in cortisol production pathway. Decreased cortisol levels can lead to increased ACTH secretion causing an increase in Deoxycorticosterone which is a potent mineralocorticoid itself. This leasds to the clinical picture of hypertension, metabolic alkalosis, and hypokalemia. Oral Prednisone is used to suppress ACTH and prevent AME. Close monitoring of potassium levels while on Abiraterone is needed and will likely lead to early identification and need for treatment. However, our case highlights the need for the addition of mineralocorticoid receptor blocker such as Eplerenone to the Prednisone to fully prevent this complication. This case sheds light on Abiraterone as a rare yet significant cause of AME and the need for further investigation of the effective therapy to prevent Abiraterone induced AME.

TH-PO374

Let's Break It Down! A Case of Hypokalemia-Induced Rhabdomyolysis

Shaylor Klein, Gary Sirken, Anna Dymarsky. *Jefferson Health Northeast, Philadelphia, PA.*

Introduction: Severe hypokalemia can result in life-threatening complications such as fatal dysrhythmias and respiratory muscle paralysis. It is the most common, but often unrecognized, electrolyte-induced cause of rhabdomyolysis.

Case Description: A 54-year-old female presented with 6 months of progressive paresthesias, generalized weakness, and fatigue. Her medical history included depression, fibromyalgia, GERD, HLD, IBS, and left breast cancer. Review of systems was positive for anorexia, palpitations, myalgias, and chronic diarrhea. Medications were Anastrozole, Atorvastatin, Cyclobenzaprine, Omeprazole, and Paroxetine. She denied the use of herbal medications, alcohol, or illicit drugs. Vital signs revealed HR 141, BP 150/63, SpO2 98%, T 36.8ºC, and Wt 101 kg. Physical exam revealed a fatigued woman with dry mucous membranes, an irregular cardiac rhythm without murmurs, clear breath sounds, abdomen soft and non-distended, 4/5 strength in the distal bilateral upper extremities, soft compartments, and no dermatological lesions. An ECG revealed frequent PVCs with bigeminy. She was treated with IV fluids, potassium, and magnesium with subsequent ECG normalization. During her hospitalization, her symptoms resolved with electrolyte repletion in conjunction with nephrology input. Her FeNa was 0.1%. Her TTKG was 2.

Discussion: Hypokalemia-induced rhabdomyolysis occurs from cellular potassium depletion, causing vasoconstriction and skeletal muscle ischemia. Our patient had severe hypokalemia causing muscle breakdown and dysrhythmias from chronic diarrhea and anorexia. She had risk factors for other causes of non-traumatic rhabdomyolysis. She was on the lowest dose of Atorvastatin, which has a dose-dependent risk of myotoxicity. Anastrozole and Omeprazole are CYP3A4 inhibitors, however, her Anastrozole dose was reduced and Omeprazole is a weak inhibitor.

Table 1: Laboratory values obtained upon initial evaluation

Laboratory value[1]	Patient value	Laboratory value	Patient value
Sodium (mmol/L) [136-145][2]	142	Urinalysis	Specific gravity: 1.008 [1.005-1.025] pH: 6.5 [5-8.5] Protein: +1 Glucose: negative Bilirubin: negative Ketones: trace Blood: +3 Nitrite: negative Urobilinogen: normal Leukocyte esterase: +3 RBC: 9 [0-3/HPF] WBC: 24 [0-3/HPF] Squamous cells: 3 [0-4/HPF] Bacteria: rare Calcium oxalate crystals: occasional
Potassium (mmol/L) [3.3-4.8]	1.6	Random urine creatinine (mg/dL) [28-217]	118.2
Chloride (mmol/L) [98-107]	87	Urine potassium (mmol/L)	7
Bicarbonate (mmol/L) [21-30]	37	Urine sodium (mmol/L)	23
Anion gap (mmol/L) [6-14]	18	Urine osmolality (mOsmol/kg) [390-1,090]	333
Urea nitrogen (mg/dL) [6-20]	8		
Creatinine (mg/dL) [0.5-0.9]	1.1		
Glucose (mg/dL) [70-100]	116		
Calcium (mg/dL) [8.6-10]	8.6		
Magnesium (mEq/L) [1.3-2.1]	1.1		
Phosphate (mg/dL) [2.5-4.5]	3.2		
Albumin (g/dL) [3.5-5.2]	3.8		
Total bilirubin (mg/dL) [0.1-0.9]	1.4		
Direct bilirubin (mg/dL) [0.0-0.3]	0.2		
Alkaline phosphatase (IU/L) [35-105]	169		
Aspartate aminotransferase (IU/L) [0-32]	349		
Alanine aminotransferase (IU/L) [0-33]	105		
Troponin (ng/L) [<19]	72 – 71		
Creatine kinase (IU/L) [20-180]	19,687		
Thyroid stimulating hormone (uIU/mL) [0.27-4.2]	3.03		
White blood cell count (10^9 cells/L [4.0-11.0)	8.6		
Hemoglobin (g/dL) [12.5-15.0]	13.6		
Red cell distribution width (%) [11.5-14.5]	15.3		
Platelets (10^9 cells/L) [140-400]	297		

[1]Laboratory values are as follows: millimole per liter (mmol/L), milligrams per deciliter (mg/dL), milliequivalents per liter (mEq/L), grams per deciliter (g/dL), international units per liter (IU/L), nanograms per liter (ng/L), micro-international units per milliliter (uIU/mL), high powered field (HPF), milliosmoles per kilogram of water (mOsm/kg)
[2]Reference ranges for units

TH-PO375

Mulethi ("Stick Made Out of Root"): Two Cases of Store-Bought Licorice Toxicity

Brendan L. Ho, Sandeep Aggarwal, Alexander M. Pennekamp, Kirstin Knox. *University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Introduction: There are many OTC supplements and foods with clinically significant adverse effects. One such compound is licorice, which can result in a syndrome similar to apparent mineralocorticoid excess when consumed in excess. The metabolism of licorice produces glycyrrhizic acid, which competitively inhibits 11β-hydroxysteroid dehydrogenase and allows for inappropriate cortisol binding to renal mineralocorticoid receptors. In this case series, we present two cases in which ingestion of store-bought licorice and its derivatives presents with classic and non-classical manifestations.

Case Description: CASE 1: A 77M with neurocognitive disorder, HCV, HTN, recent poor intake and frailty presented with asymptomatic hypokalemia noted on outpatient labs. On admission, K was 2.5, Mg was 2.0, and HCO3 was 30. BP was 160/92, increased from previous. He received IV and PO repletions of KCl with limited improvement to 3.7 by day 3. He denied recent diuretic & laxative use, vomiting, or diarrhea, so his hypokalemia was initially thought to be due to poor intake. However, further questioning uncovered that he had been consuming bags of black licorice from multiple brands. Plasma aldosterone was <1.0. K was gradually repleted to 4.0 and he was discharged on day 5. CASE 2: A 75M with HTN, CAD s/p PCI presented with fatigue and dyspnea on exertion. In the ED, he was hypotensive, bradycardic, and hypokalemic with ST-depressions and U-waves on EKG. Careful history taking revealed that he had been taking licorice root extract for the past three weeks to treat fatigue. Serum K was 1.2, fractional excretion of K was 45%. Licorice was d/c'd, K was corrected, and bradycardia resolved, at which point he was found to be hypertensive.

Discussion: Licorice and its derivatives are among many foods and OTC supplements with documented harmful effects in the appropriate setting. Other examples include tyramine in aged cheese (Hypertensive Emergency), St. John's Wart (CYP-450 induction, Serotonin Syndrome), and gingko biloba (bleeding risk). Unfortunately, many potentially harmful products are easily purchased at grocery stores and pharmacies without warning labels – an issue compounded by an abundance of claims regarding potentially beneficial effects. Improved regulation and preventative measures to increase awareness about adverse effects could prevent potentially significant complications.

TH-PO376

A Case of Decreased Urine Output with Loop Diuretics

Chanwoo Nam, Negiin Pourafshar, Christopher S. Wilcox. *MedStar Georgetown University Hospital Nephrology Services, Washington, DC.*

Introduction: Loop diuretics are used in escalating doses to treat volume overload and to overcome diuretics resistance. We present a case of a patient who had a decreased urine output despite receiving high doses of intravenous loop diuretics.

Case Description: A 65-year-old obese male presented with acute hypoxic/hypercapnic respiratory failure requiring intubation. He had non pitting edema, without other clinical or radiological evidence of pulmonary edema. His Right atrial pressure was elevated 13 mmHg, right ventricular pressure of 85/15 mmHg, and pulmonary artery pressure of 87/27 mmHg with normal ejection fraction. Due to inability to wean the patient off ventilator, he received a trial of high dose furosemide infusion for 4 days. Over the course of diuretic therapy, his blood urea nitrogen (BUN) and Serum Creatinine (Scr) increased from 13 to 38 mg/dl, and from 0.97 to 2.43 mg/dl respectively. He was given furosemide 200-300 mg/day with less than 1 L urine output and urine sodium (UNa) of 10 during diuretic therapy. Following nephrology recommendation, diuretic administration ceased, resulting in a subsequent increase in urine output to 100-150 ml/hr within 4 hours.

Discussion: This case presents a fascinating unusual antidiuretic response to furosemide with the swift and complete reversal upon diuretic withdrawal is particularly noteworthy. The underlying mechanism is likely rooted in an extreme hemodynamic event within the kidney, precipitated by severe pulmonary hypertension, heightened right heart pressure, and cor pulmonale, possibly from obesity related Pickwickian syndrome. Increased right heart pressure with omental fat deposits in a recumbent position elevates systemic and renal venous pressures, exacerbated by positive pressure ventilation. In the above situation, loop diuretics exacerbates tubular fluid accumulation, increasing renal pressures, reducing net filtration pressure, resulting in a decrease in estimated glomerular filtration rate (eGFR) and urine output. Increased interstitial pressure contributes further compresses capillaries, hindering renal blood flow. Discontinuation of diuretics rapidly alleviates tubular pressure, facilitating the renal function recovery. This underscores the importance of tailored interventions in managing patients with such intricate pathophysiological profiles.

TH-PO377

Aquapheresis: An Alternative Method of Controlled Fluid Removal in the Setting of Hypervolemia and Refractory Gout in Sickle Nephropathy

Hatem Najar, Urmiya Rashid, JingJing Zhang, Hasan Arif, Omar H. Maarouf. *Thomas Jefferson University Hospital, Philadelphia, PA.*

Introduction: Gout flares and vaso-occlusive attacks complicate acute diuresis in patients with sickle cell nephropathy and volume overload (VO). Loop diuretics are considered first line therapy in the management of VO. We present a case in which aquapheresis (AQ) was used as an alternative and more effective method of fluid removal in a patient with sickle cell nephropathy and secondary pulmonary hypertension complicated by refractory gout and sickle pains upon IV diuresis.

Case Description: A 48-year-old patient with sickle cell nephropathy, gout, pulmonary hypertension presented with shortness of breath and bone pain. The physical exam was significant for hypoxia, lower extremity edema and bone tenderness. Chest x-ray showed pulmonary edema. The patient was diagnosed with sickle cell crisis and hypoxic respiratory failure secondary to VO. He was initiated on IV furosemide and analgesics. With diuresis, he developed severe right wrist pain consistent with an acute gout attack despite appropriate treatment. His vaso-occlusive attacks worsened. Upon decreasing the IV diuretic dose, he developed hypervolemic respiratory failure. His kidney function remained stable. Aquapheresis (AQ) consists of the extracorporeal extraction of plasma fluid from the vascular space across a semipermeable membrane. In AQ, fluid removal is controlled by specifying an hourly ultrafiltration rate. This modality offers controlled fluid removal. Upon initiating AQ and stopping IV diuresis, the patient's weight dropped by 10 Kg over several days. He had significant improvement in his respiratory status and remission in his gout flare with a drop in his serum uric acid levels (10.6 to 4.9 mg/dL). His vaso-occlusive pains improved.

Discussion: In summary, AQ was successful in treating hypervolemia in a patient with sickle cell nephropathy and a stable renal function. Uncontrolled and excessive fluid removal using IV diuresis can exacerbate vaso-occlusive disease and precipitate gout flares in patients with sickle cell nephropathy. Controlled fluid removal using AQ reversed the acute rise in uric acid mitigating gout flares and alleviating vaso-occlusive

disease with improved pain control. AQ promises to be a superior method for controlled fluid removal in hypervolemia in patients with sickle cell nephropathy complicated by VO and hypoxia.

TH-PO378

Association between Urine Volume, Urine pH, and Urine H+ Excretion

Robert H. Yenchek, Kalani L. Raphael. *University of Utah Health, Salt Lake City, UT.*

Background: Fluid intake is the cornerstone of nephrolithiasis prevention by increasing 24-hour urine volume. Increasing urine volume could raise urine pH through a dilutional effect on urine [H+] yet not impact H+ excretion rate. We evaluated the association between urine volume, pH, and H+ excretion rate in calcium stone formers. Dietary acids and alkali absorption affect the 24-hour urine pH and modulate nephrolithiasis risk. It is unknown whether fluid intake independently affects urine pH via a dilution effect on the urine H+ excretion rate.

Methods: We evaluated cross-sectional associations between 24-hour urine volume, urine pH, and urinary free H+ excretion rate in 165 adult treatment-naïve, calcium stone formers. All urine parameters were measured using laboratory derived 24-hour urine collection data. 24-hour free H+ excretion was calculated based on urine pH and urine volume. Dietary alkali was estimated by calculating GI alkali absorption (GIAA) and urine sulfate was used as an estimate of dietary acid intake. Linear regression models were used to evaluate the association between 24-hour urine volume and 1) urine pH and 2) 24-hour free urine H+ excretion rate. Models were adjusted for GIAA, urine sulfate, age, sex, BMI, urine creatinine, and urine ammonium.

Results: Mean age was 51 years, 49% were female. Mean urine pH was 5.9 and mean 24-hour urine volume was 1.8 L/d. Urine volume was not associated with urine pH in the adjusted model. However, each 1 liter increase in 24-hour urine volume was associated with a 0.42 (0.33, 0.51) increase in log 24 hour H+ excretion rate in the adjusted model, (see Figure 1).

Conclusions: Contrary to our hypothesis, urine volume was not associated with urine pH but was associated with higher free H+ excretion rate, perhaps due to increased urine flow. Increased H+ excretion rate may offset the expected increase in urine pH from dilution alone.

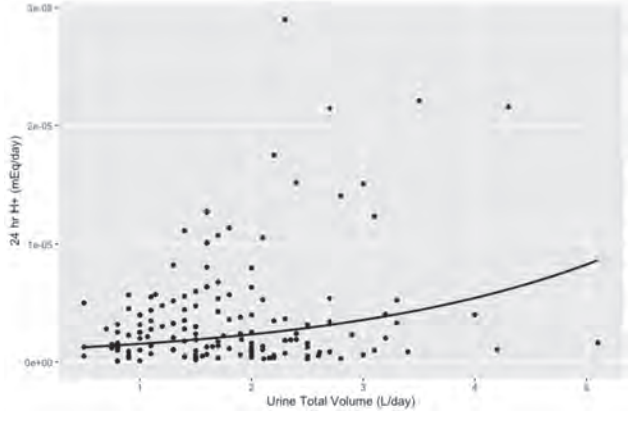


Figure 1.

TH-PO379

Estimating Arterial Bicarbonate (HCO3) from Venous Blood Using the Kidney Electrolyte Panel

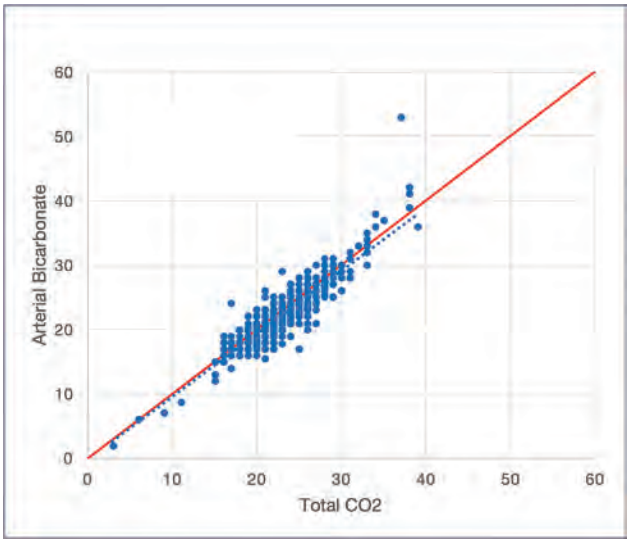
Romy S. Fischer, Crisel I. Rivero Gonzalez, Mohammed Z. Rehman, Carlos A. Rueda Mantilla, Robert M. Rosa, Daniel Batlle. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Arterial blood gas (ABG) analysis remains the gold standard for diagnosis and management of acid-base disorders. Venous blood is much more easily obtainable but there is a need for reliable data to convert venous to arterial data. At last year's ASN meeting we presented results from 7470 samples where blood pCO2 and pH had been measured at the same time for pH and pCO2. We now report on how to best calculate arterial HCO3 from venous blood using a subset of those samples (n=1425) where total venous CO2 had also been obtained at the same time.

Methods: Data were extracted from the medical records of totally de-identified subjects. A total of 1425 samples where it was verified that not only the sampling for venous and arterial blood gas was performed at the same time but that there were also concurrent measurements of total CO2 from an electrolyte panel All measurements were done from samples delivered at the laboratories of Northwestern Medicine over a period of 7 years. The information was provided to us by an independent data analyst and Linear regression and Bland Altman plots were used.

Results: The relationship between venous HCO3 and arterial HCO3 was strong (r=0.89). From the equation defining this relationship venous HCO3 was corrected and plotted against the total CO2 obtained from the venous electrolyte panel. The correlation was also strong (r=0.84) (figure) indicating that the total CO2 can be used to replace arterial bicarbonate in the Henderson Hasselbalch equation.

Conclusions: Using a large database with concurrent measurements of arterial and venous blood accurate estimations of arterial bicarbonate could be made from the venous total CO2 in the renal electrolyte panel. This information has been integrated in an App that allows conversion of venous to arterial blood gas data.



TH-PO380

Pax8 Maintains the Epithelial Phenotype of Proximal Tubule Cells via Distal Regulatory Elements

Jeffrey A. Beamish, Madison C. McElliott, Greg R. Dressler. *University of Michigan, Ann Arbor, MI.*

Background: Pax2 and Pax8 are homologous DNA-binding proteins that orchestrate kidney development, regulate urine concentration in the kidney medulla, and dictate sensitivity to ischemic injury in the kidney cortex. However, the targets of Pax proteins that mediate these functions remain poorly defined. The goal of this project was to identify genes regulated by Pax proteins in the proximal tubule.

Methods: A line of Pax8-conditional, Pax2-null immortalized proximal tubule epithelial cells with a constitutive driver of tamoxifen-dependent Cre (Rosa26-CreER) were derived from adult transgenic mice. A line with spontaneous loss of Pax2 was selected to focus on the effects of Pax8, which is expressed at higher levels in the proximal tubule. Pax8 can be depleted from these cells by addition of 4-OH tamoxifen (4-OHT) to the culture medium. RNA and chromatin samples were collected before and after genetic depletion of Pax8 and submitted for RNA sequencing and chromatin-immunoprecipitation sequencing (ChIP-seq) for Pax8 and histone H3 lysine 4 trimethylation (H3K4me3).

Results: Pax8 protein was depleted by 2 days after 4-OHT exposure. By day 3, cells lost cobblestone epithelial morphology and organization of cell-cell junction proteins. Cell proliferation also slowed. RNA sequencing showed upregulated genes were associated with epithelial-to-mesenchymal transition and inflammatory responses. Downregulated genes were associated with oxidative metabolism. These expression changes mimicked those observed in vivo after proximal-tubule-selective depletion of Pax8. ChIP-seq was used to assess the correlation between gene expression and Pax8 chromatin binding. Promoters bound by Pax8 showed a small but significant reduction in H3K4me3 after Pax8 depletion relative to those lacking Pax8. However, differential gene expression was most strongly enriched with genes associated with distal Pax8 binding sites, between 3-100 kb from the transcription start site. These sites had low H3K4me3 signal.

Conclusions: Pax8 is necessary for the maintenance of differentiated epithelial phenotype in proximal tubule epithelial cells. Differential gene expression induced by Pax8 depletion was strongly associated with Pax8 binding at distal regulatory elements with low H3K4me3. This finding suggests Pax8 maintains gene expression of proximal tubules cells via binding at enhancer elements.

Funding: NIDDK Support

TH-PO381

SLC25A48 Is a Human Mitochondrial Choline Transporter

Suraj Dasharath Patil,[1,2] Oleg Borisov,[3] Nora Scherer,[3,2] Christophe Wirth,[4] Pascal Schlosser,[1] Matthias Wuttke,[3] Luciana Hannibal,[8] Kai-Uwe Eckardt,[5,6] Bjoern Neubauer,[1] Anna Kottgen,[3,7] Michael Kottgen.[1,7] *[1]Department of Medicine IV - Nephrology and Primary Care, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany; [2]Spemann Graduate School of Biology and Medicine (SGBM), University of Freiburg, Freiburg im Breisgau, Germany; [3]Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center–University of Freiburg, Freiburg im Breisgau, Germany; [4]Institute of Biochemistry and Molecular Biology, ZBMZ, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany; [5]Department of Nephrology and Medical Intensive Care, Charité–Universitätsmedizin Berlin, Berlin, Germany; [6]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [7]CIBSS - Centre for Integrative Biological Signalling Studies, University of Freiburg, Freiburg im Breisgau, Germany; [8]Laboratory of Clinical Biochemistry and Metabolism, Department of General Pediatrics, Adolescent Medicine and Neonatology, Faculty of Medicine, Medical Center, University of Freiburg, Freiburg im Breisgau, Germany*.

Background: Choline has important physiological functions as a precursor for essential cell components and signalling molecules including phospholipids and the neurotransmitter acetylcholine. Choline is a water-soluble charged molecule and therefore requires transport proteins to cross biological membranes. Its transport across phospholipid bilayer membranes remains incompletely understood. Using metabolite genome-wide association studies, we uncovered that common variants of human *SLC25A48* are associated with altered choline levels in plasma and urine supporting the hypothesis that the orphan solute carrier SLC25A48 may be a choline transporter.

Methods: We used mGWAS, mitochondrial isolation, radioactive uptake assay, LC/MS, immunofluorescence, western blotting, qPCR, and structural modelling.

Results: Overexpression of SLC25A48 revealed mitochondrial localization and increased choline uptake in human epithelial cells compared to control cells. We identified rare putatively damaging variants in *SLC25A48* in humans, which showed an association with elevated urine and plasma choline levels. These mutations exhibited impaired choline transport into mitochondria. Through the combination of immunofluorescence, western blotting, and structural modelling, we revealed distinct mechanisms causing functional impairment of specific damaging variants in *SLC25A48*.

Conclusions: In summary, we showed that the physiological function of SLC25A48 in humans is choline import into mitochondria. The deorphanization of SLC25A48 defines its molecular function in humans and enables future studies addressing its role in health and disease.

Funding: Government Support - Non-U.S.

TH-PO382

Identifying Molecular Regulators of Kidney Collecting Duct Cell Type Plasticity

Alicia L. Simmons,[1,2] Malini Mukherjee,[1] Oduduabasi Isaiah,[1] Michael S. Kareta,[1,3] Kameswaran Surendran.[1,3] Surendran Lab. *[1]Sanford Research, Sioux Falls, SD; [2]University of South Dakota, Vermillion, SD; [3]University of South Dakota Sanford School of Medicine, Sioux Falls, SD*.

Background: Remodeling of kidney collecting duct segments by altering the cell type composition may underlie adaptive capacity when it occurs in a limited manner but may also be part of pathological states. Deficiencies in the machinery and number of principal cells (PCs) are associated with acquired Nephrogenic Diabetes Insipidus (NDI). Conversion of PCs to intercalated cells (ICs) results in loss of PCs when Notch signaling is blocked in adult mouse kidneys resulting in a NDI-like phenotype. Here we use rodent Notch-signaling deficient kidneys to identify the molecular mediators of PC to IC conversion.

Methods: We profiled the wild type versus littermate mice with inactivation of *Hes1* in adult kidney epithelia for 7 days by total kidney RNA-sequencing and by single cell RNA-sequencing of samples enriched for epithelial cells of the loop of Henle, distal nephron and collecting duct segments. We used the mpkccdc14, a principal cell line, with ectopic Hes1-FLAG expression to identify the genes directly regulated by Hes1 by performing Hes1-FLAG-chromatin immunoprecipitation (ChIP) followed by sequencing and qPCR. The spatial pattern of the differentially expressed genes in Hes1 deficient kidneys versus the control wild type littermates were analyzed by RNAscope, and immunohistochemistry.

Results: Hes1-deficiency altered expression of signaling components of Hedgehog, mTOR, and Wnt pathways. Sub-clustering cells expressing PC and/or IC markers as determined by scRNA-seq revealed two PC clusters, two IC clusters and a fifth transitional cell (TC) cluster with both PC and IC marker expression. Comparison of TC versus PC cluster revealed higher expression of IC specific genes and down-regulation of PC specific genes. Some of the upregulated genes in the TCs, such as irs1, were identified as potential direct targets of Hes1 by Hes1-FLAG-ChIP-qPCR.

Conclusions: Hes1-deficient kidneys are useful to identify transcriptional signature and potential mediators of PC to IC conversion that occurs in adult kidneys. Considering that lithium treatment increased PC to IC conversion as determined by lineage tracing, identifying the molecular mediators of PC to IC conversion will allow us to test if these mechanisms are conserved in different forms of acquired of NDI, such as lithium induced or low K+ diets.

Funding: NIDDK Support

TH-PO383

β-Catenin Phosphorylation at Ser552 Impairs Expression of β-Catenin-TCF/LEF Target Genes in Mouse Collecting Duct

Shuo-Ming Ou, Hiroaki Kikuchi, Lihe Chen, Chung-Lin Chou, Mark A. Knepper. *National Institutes of Health, Bethesda, MD*.

Background: Prior phospho-proteomics studies in both cultured and native collecting duct cells showed that vasopressin strongly increases phosphorylation of β-catenin at Ser552 in a protein kinase A (PKA)-dependent manner. In contrast to the N-terminal sites of β-catenin that are phosphorylated as part of canonical Wnt signaling, little is known about the role of Ser552 phosphorylation.

Methods: To address its role in the mature renal collecting duct, we have inserted an Ser552Ala mutation in mice using CRISPR-Cas9.

Results: The mutation did not affect the abundance of the vasopressin-regulated water channel aquaporin-2 (AQP2), urinary osmolality, serum chemistries, and there were no abnormalities of structure of collecting ducts or kidneys or other organs. RNA-seq in microdissected cortical collecting ducts (CDs) of unstressed mice revealed relatively few transcripts that underwent changes in abundance, and no changes in abundances of mRNAs coding for major collecting duct transport proteins, indicative of sustained collecting-duct differentiation. However, when stressed by vasopressin infusion, RNA-seq in microdissected cortical CDs revealed extensive changes in the transcriptome in response to the Ser552Ala mutation, associated with increases in transcriptional targets of the Wnt/β-catenin/TCF pathway. Enriched *Gene Ontology-Biological Process* terms included “cell development“, “collecting duct development“, “ureteric bud development“ and “Wnt signaling pathway“.

Conclusions: Overall, vasopressin-mediated phosphorylation of β-catenin at S552 appears to serve as an “off-switch” for the Wnt/β-catenin/TCF pathway in the collecting duct in the presence of high levels of vasopressin.

Funding: Other NIH Support - funded by the Division of Intramural Research, National Heart, Lung, and Blood Institute

TH-PO384

Influence of Gravity on Ureteric Bud Branching and Organ Morphology

Miguel A. Rocha,[1,2] Simone Reichelt-Wurm,[3] Morgan Hamon,[2,1] Hsiao-Min Chang,[2,1] Norimoto Yanagawa,[2] Miriam C. Banas,[3] Peter V. Hauser.[2,1] *[1]VA Greater Los Angeles Healthcare System, Los Angeles, CA; [2]University of California Los Angeles, Los Angeles, CA; [3]Universitat Regensburg Fakultat fur Medizin, Regensburg, Germany*.

Background: In vitro organ culture of metanephroi is a standard technique to study renal development and regeneration. While many aspects of the renal anatomy develop normally, the overall morphology of cultured kidneys appears mono-dimensional (pancake-like). We aimed to study the influence of gravity on 3D morphology and branching to grow kidneys with organotypic anatomy.

Methods: E12.5 kidneys obtained from *Hoxb7*^{Venus} mice were cultured in vitro under static, or dynamic conditions for up to 144h. Ureteric bud (UB) branching morphogenesis was imaged by confocal microscopy on kidneys at 72h + 96h. 3D images were used to measure Branching length, diameter, and branching angle, utilizing gradient vector-based software (TreeSurveyor). Micro Computer Tomography (mCT) images were generated from kidneys at 48h, 72h, 96h, and 120h to compare 3D morphology and volume. Microarray analysis, using GeneChip Mouse Gene 2.0 ST arrays, was performed to uncover gene expression of samples at 72h + 144h. Liquid Chromatography tandem mass spectrometry was used to compare protein expression in samples after 96h of static and dynamic culture.

Results: mCT imaging showed that dynamic culture supports organotypic morphology in contrast to static cultured kidneys, which present mono-dimensional. Cell count of kidneys showed no significant differences between the groups from 0h to 144h, demonstrating normal cell growth in both conditions. UB branching showed similar branch lengths and diameters, but the branching angle average was greater in dynamically cultured kidneys compared to static conditions. Microarray analysis displayed that dynamic culture induced significant differential regulation of genes associated with extracellular matrix (ECM) and receptor interaction, down-regulation of apoptotic processes, mechanical stimulation, bone mineralization, blood pressure regulation, cell migration, and others. Proteomic analysis identified >4000 different proteins. Dynamic culture conditions induced changes in the abundance of proteins associated with focal segmental glomerulosclerosis, Wnt signaling, ECM, pluripotency pathways, and more.

Conclusions: We think dynamic in vitro culture of metanephroi supports organotypic morphology of the developing kidney. Studies are under way to delineate the effect on specific pathways associated with mechanical stimulation.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO385

α-Parvin, an Integrin-Related Scaffold Protein, Regulates Actin Dynamics to Facilitate Kidney Ureteric Bud Branching Morphogenesis

Xinyu Dong,[1,2] Fabian Bock,[2] Ambra Pozzi,[2] Roy Zent.[2] *[1]Vanderbilt University, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN.*

Background: The kidney collecting system is developed from the ureteric bud (UB), which undergoes branching and tubule elongation via cell division and movement. Multiple factors, including growth factor-dependent signaling, cell-extracellular matrix (ECM) interactions, and actin dynamics are required. While extensive information exists on how growth factors regulate branching morphogenesis, significantly less is known about the roles of cell-ECM receptors and actin dynamics. Integrins, the major cell-ECM receptors, are crucial for mediating cell adhesion and signaling. Integrin function is partly mediated by the recruitment of scaffold proteins like α-parvin. Our previous research demonstrated that a global knockout of α-parvin results in kidney agenesis. However, the specific role of α-parvin in ureteric bud branching morphogenesis remains unexplored.

Methods: We deleted α-Parvin at the initiation of UB development (E10.5) by crossing the α-Parvin$^{fl/fl}$ with HOXB7^{Cre} mice. To allow *ex vivo* imaging and cell tracking, we utilized membrane-tethered (mTmG) GFP mice. To study the molecular function of α-Parvin, we isolated CD cells from 8-week-old α-parvin mice and deleted the gene *in vitro* using adenovirus-mediated delivery of a Cre recombinase.

Results: In this study, we show that a-parvin, an integrin-associating and actin-binding protein, plays a critical role in UB development by regulating ureteric bud cell movement. We observed that the α-parvin$^{fl/fl}$:HoxB7^{Cre} mice exhibited severely dysmorphic kidneys and died within 2-3 months. Mutant kidneys in different embryonic stages showed a significant decrease in size and branching tips, along with widened tubules. Direct *ex vivo* imaging and cell tracking using the mTmG mice demonstrated that a-parvin regulates neighbor exchanges (cell intercalation) and motion persistence, which are essential for tubule narrowing. Isolated α-parvin-null CD cells had increased cell adhesion and spreading but impaired migration. Surprisingly, a-parvin mediated these effects only by regulating Rho family GTPase-dependent depolymerization of F-actin via cofilin and not by affecting integrin function.

Conclusions: We conclude that the integrin scaffold protein, α-parvin, regulates branching morphogenesis and tubule elongation of the UB by controlling actin dynamics.

Funding: NIDDK Support

TH-PO386

Integrin-Binding Proteins Kindlins Regulate Kidney Branching Morphogenic in Both Integrin β1-Dependent and -Independent Mechanisms

Shensen Li, Fabian Bock, Xinyu Dong, Olga Viquez, Ambra Pozzi, Roy Zent. Zent Lab. *Vanderbilt University Medical Center, Nashville, TN.*

Background: The kidney collecting system derives from the branching of the ureteric bud (UB). This process is dependent on growth factor (GF) signaling and the interactions between integrins and the extracellular matrix. Integrin function requires binding of structural intracelluar proteins such as kindlins to highly conserved NxxY motifs to the β cytoplasmic tails. The kidney contains two Kindlins, namely Kindlin 1 and 2, yet their role in govering β1-mediated UB branching is currently unknown.

Methods: Two mutations in the β1 cytoplasmic tail can abrogate kindlin-β1 binding (TT/AA (amino acids 800-801) and Y795A). We expressed these mutations in the developing mouse UB using the Hoxb7 promoter (Hoxb7:TTAA, and Hoxb7:Y795A) and assessed 3D branching. We compared this phenotype to mice lacking both Kindlin 1 and 2 in the UB (Hoxb7:K1/K2). Furthermore, we generated collecting duct (CD) cells *in vitro* expressing these mutations or lacking kindlins and assessed tubulogenesis, polarity, adhesion, migration, proliferation, and GF-dependent signaling.

Results: Hoxb7:TTAA and Hoxb7:Y795A mice displayed mildly dysplastic collecting systems with a mild branching morphogenesis defect. CD cells expressing TTAA or Y795A mutations had moderate abnormalities in tubulogenesis, cell adhesion, migration, proliferation, and polarity, while matrix-induced and GF-dependent signaling was largely intact. In contrast, mice lacking both kindlins in the UB failed to form kidneys due to a lack of UB budding. In addition, the K1/K2 KO CD cells had severe spreading, and polarity defects, and were unable to adhere or transduce GF signaling.

Conclusions: This study shows that kindlins are essential for UB formation and that they control UB branching through mechanisms that are largely independent of β1 integrin binding.

Funding: NIDDK Support

TH-PO387

Deletion of Notch Signaling in the Developing Mouse Kidney Results in Expanded Expression of Arf6, Reduced Expression of E-cadherin, and Dilation of Collecting Ducts

Greg Vanden Heuvel, Kristi L. Bailey. *Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, MI.*

Background: The Notch pathway is an evolutionary conserved signaling pathway that affects cellular differentiation and proliferation. Notch signaling regulates proximal/distal patterning of the nephron in the mammalian kidney. There are four Notch receptors and five ligands, and during kidney development, Notch receptors are activated by binding to ligands on neighboring cells. This results in a series of proteolytic cleavages that lead to the expression of Notch target genes. Deletion of Notch signaling in the developing collecting duct results in collecting duct dilatations and hydronephrosis. While cells lining the medullary cavity formed from hydronephrosis are highly proliferative, cells lining the cortical dilations do not label with markers of proliferation, and the cell cycle regulator Cux1 is reduced in these cells.

Methods: To determine whether the dilated collecting ducts in Notch mutant kidneys, called RBPJ/k^{CD}, resulted from changes in cell-cell interactions we evaluated the expression of the ADP-ribosylation factor GTPase Arf6 and its target of regulation, E-cadherin. To determine whether reduced Notch signaling had an effect on ciliogenesis, cilia morphology was assessed by immunofluorescence labeling of alpha-tubulin.

Results: Newborn RBPJ/k^{CD} mice exhibited medullary and cortical dilatations. Staining with DBA lectin and cytokeratin confirmed the collecting duct origin of the dilatations. Postnatal day 14 (P14), RBPJ/k^{CD} mice exhibited hydronephrosis and cortical dilatations. Cells lining the dilated collecting ducts exhibited expanded expression of the ADP-ribosylation factor GTPase Arf6, which is normally restricted to the apical membranes. This was associated with a reduction in the expression of E-cadherin in the RBPJ/k^{CD} collecting ducts. However, no differences in N-cadherin expression were observed. In addition, there was no difference in cilia length between wild type and RBPJ/k^{CD} mice.

Conclusions: Taken together, our results suggest that Notch signaling is required for normal kidney collecting duct development, and that reduced Notch signaling may disrupt cell-cell interactions leading to hydronephrosis.

TH-PO388

Transcription Factor Tcf21 Is Required for Specifying Foxd1 Cells to the Juxtaglomerular Cell Lineage

Gal Finer,[1,2] Hina Anjum,[1] George S. Yacu,[1] Silvia Medrano,[3] Roberto Ariel Gomez,[3] Maria Luisa S. Sequeira Lopez,[3] Susan E. Quaggin.[2,4] *[1]Division of Pediatric Nephrology, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [2]Feinberg Cardiovascular and Renal Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL; [3]Department of Pediatrics, Child Health Research Center, University of Virginia, Charlottesville, VA; [4]Division of Nephrology and Hypertension, Northwestern Memorial Hospital, Chicago, IL.*

Background: Renin is crucial for blood pressure regulation and electrolyte balance. Renin expressing cells are known to arise from the Foxd1+ stromal progenitors; however, the factors guiding Foxd1+ cells towards the renin-secreting cell fate remain poorly understood. Tcf21 is a bHLH transcription factor of the metanephric mesenchyme that plays a crucial role in kidney development. We have previously shown that deletion of Tcf21 in Foxd1+ cells (*Foxd1$^{Cre/+}$;Tcf21$^{f/f}$*) results in paucity of vascular mural cells and in disorganized renal arterial tree. Here, we sought to examine the relationship between Tcf21 and renin cells during kidney development and test whether Tcf21 is implicated in juxtaglomerular cell differentiation.

Methods: We performed histological examination of kidney samples from two mouse models and littermate controls: one with conditional inactivation of *Tcf21* in Foxd1+ expressing cells (*Foxd1$^{Cre/+}$ Tcf21$^{f/f}$*) and the other with inactivation of *Tcf21* in renin-expressing cells (*Ren1d$^{Cre/+}$ Tcf21$^{f/f}$*).

Results: Immunostaining for renin demonstrated that kidneys of *Foxd1$^{Cre/+}$;Tcf21$^{f/f}$* have fewer renin-positive spots at E16.5 and E18.5 compared with controls. In-situ hybridization for *renin* mRNA showed reduced expression in *Foxd1$^{Cre/+}$;Tcf21$^{f/f}$* kidneys at E14.5, E16.5, and E18.5. Together, these data suggest that stromal expression of Tcf21 is required for the emergence of renin cells. To dissect the role of Tcf21 in juxtaglomerular (JG) cells, we deleted Tcf21 upon renin promoter activation (*Ren1$^{dCre/+}$;Tcf21$^{f/f}$*). Interestingly, the *Ren1$^{dCre/+}$;Tcf21$^{f/f}$* kidney showed normal arterial tree at E16.5 identical to controls. Furthermore, inactivation of Tcf21 upon renin expression did not alter kidney morphology in two- and four-month-old mice. Finally, expression *renin* mRNA was similar between *Ren1$^{dCre/+}$;Tcf21$^{f/f}$* and controls at 2 months.

Conclusions: Taken together, our findings suggest that Tcf21 expression in Foxd1+ cells is essential for specifying the fate of these cells into juxtaglomerular cells. However, once renin cell identity is assumed, Tcf21 is dispensable.

Funding: NIDDK Support

TH-PO389

Bridging the Gap of Late-Gestation Human Nephrogenesis Using a Nonhuman Primate Model

Kairavee Thakkar,[1] Sunitha Yarlagadda,[1] Lyan Alkhudairy,[1] Andrew Potter,[1] Konrad Thorner,[1] Nathan Salomonis,[1,2] Raphael Kopan,[1,2] Meredith P. Schuh.[1,2] *[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]University of Cincinnati College of Medicine, Cincinnati, OH.*

Background: Prematurity is associated with low nephron endowment and an increased risk of chronic kidney disease. Human nephrogenesis is complete at 34-36 weeks gestation, with 60% of nephrons forming during 3rd trimester through lateral branch nephrogenesis (LBN). To overcome the barriers of studying late-gestation human tissue, we utilized a non-human primate model (rhesus macaque) to study LBN.

Methods: Single-cell RNA-sequencing (scRNA-Seq) was performed on 9 cortically-enriched fetal rhesus kidneys from late second trimester and third trimester during LBN. This data was integrated with publicly available human scRNA-seq datasets from 8-18 weeks gestation kidneys (n=8) using state-of-the-art bioinformatics pipelines. Ligand-receptor interactions were assessed and validated on human and rhesus archival tissue using RNAScope.

Results: scRNA-Seq of 64,782 rhesus cells revealed 37 transcriptionally distinct cell populations, including four nephron progenitor cell (NPC) clusters (7937 cells) (Figure 1). We noted increased *SFRP1*, *FZD4*, *FZD6*, and *TLE2* and decreased *FZD7*, *SHISA2*, *SHISA3*, and *TLE4* within the rhesus late-gestation NPC compared to mid-gestation human NPC, supporting a compositional shift in WNT signaling within the naive NPC population during LBN. We identified changes in constitution of the FGF and Semaphorin (SEMA3) pathways as well.

Conclusions: The rhesus macaque uniquely enables molecular studies of late gestation primate nephrogenesis. Our study supports the hypothesis that a compositional shift in key pathways within the naive NPC population during LBN may underly the switch from branch phase nephrogenesis to lateral branching. Future studies will focus on maintaining this signaling environment to promote nephron formation in preterm infants.

Funding: NIDDK Support

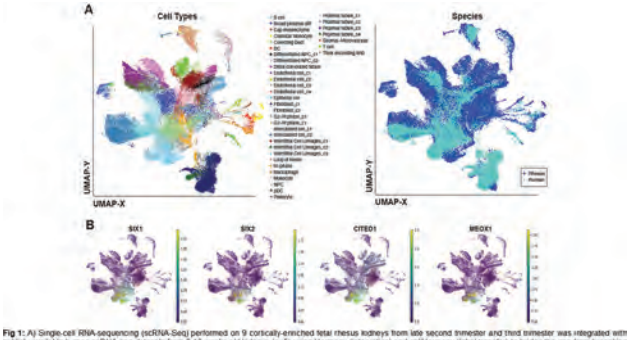


Fig 1: A) Single-cell RNA-sequencing (scRNA-Seq) performed on 9 cortically-enriched fetal rhesus kidneys from late second trimester and third trimester was integrated with publicly available human scRNA-seq datasets from 8-13 weeks old kidneys (n=5) using Harmony (integration) and cellHarmony (label transfer) to bridge the gap from branching phase nephrogenesis (BpN) to Lateral Branch Nephrogenesis. B) Known nephron progenitor cell markers highlight the progenitor clusters for subcluster analyses.

TH-PO390

Regulators of Intermediate Mesoderm Development Impact Neighboring Vessel Progenitor Specification

Elliot Perens,[1,2] Elizabeth Willemijn Stouthart,[1] Matthew Nunes,[1] Deborah Yelon.[1] *[1]University of California San Diego, La Jolla, CA; [2]Rady Children's Hospital San Diego, San Diego, CA.*

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are diagnosed in 1 out of 500 live births, and pathogenic mutations have been identified more than 50 genes. Many of these genes, including the two most frequently mutated genes, *PAX2* and *HNF1β*, have been implicated in early aspects of kidney development. The first step in kidney development is the specification of kidney progenitors within the intermediate mesoderm (IM), a pair of bilateral territories within the posterior mesoderm, flanked by tissues that give rise to vessels, blood, muscle, bone, and peritoneum. Our previous work in the zebrafish model system highlighted a coupling of IM formation with the development of neighboring vessel progenitors (VPs). We demonstrated that the transcription factors Hand2 and Osr1 act in opposition at the lateral border of the IM to balance the specification of IM and VPs (Perens et al., 2016; Perens et al., 2021). More recently we found that the transcription factor Npas4l (Cloche), an early essential regulator of VP formation, is required to inhibit IM formation at both the lateral and medial IM borders (Perens and Yelon, 2024).

Methods: Genetic analyses, molecular anatomical studies, single cell RNA-seq, genetic lineage analysis

Results: First, surprisingly, our genetic analyses suggest that genes expressed in and necessary for IM development – *pax2a* and *pax8* – are required for formation of VPs at the lateral IM border while inhibiting excessive VP formation at the medial border. Second, we observe that lateral VPs co-express genes associated with VP (ie. *etv2*) and IM fates (ie. *pax2a*). Third, our preliminary scRNA-seq data on IM cells (obtained by sorting cells double positive for *pax2a* and *hnf1βa* transgenes) further suggest that the IM is divided into subdomains with unique transcriptional signatures and divergent developmental potentials, including a domain capable of generating IM and VPs.

Conclusions: Together, our data further highlight intriguing genetic and lineage relationships between the IM and neighboring VPs.

Funding: NIDDK Support

TH-PO391

Forming Nephrons Promote Nephron Progenitor Maintenance via Paracrine BMP4 Signaling

Alexander N. Combes, Julie L. Moreau. *Monash University, Melbourne, VIC, Australia.*

Background: Current models propose that interactions between stromal, ureteric, and nephron progenitors are sufficient to drive kidney development. In this study, we aimed to investigate whether the forming nephron is a passive product of the niche, or whether it is an active partner in the signalling interactions required for ongoing progenitor maintenance and branching morphogenesis.

Methods: Kidney size and morphology were assessed in global *Wnt4* knockout (KO, *Wnt4*$^{GCE/GCE}$), and conditional *Wnt4* knockout (cKO, *Six2*TGC-*Wnt4*$^{fl/fl}$) mice using brightfield imaging, histology and immunofluorescence at embryonic day (E) 17.5. Nephron progenitor cell number, dispersal, proliferation and death were examined through wholemount and section immunofluorescence at E14.5 and E17.5. Conditional deletion of *Wnt4* was assessed by ddPCR in sorted *Six2*GFP+ and LTL+ cells. Transcriptional changes were assessed with bulk and single cell RNAseq in KO and cKO kidneys; select results were validated by quantitative hybridisation chain reaction (HCR). Nephron progenitor cell dispersal from the tip was assessed by confocal microscopy in wholemount wildtype and *Wnt4* KO kidneys after culture with or without 100ng/mL BMP4.

Results: Kidney size, branching, and nephron progenitor cell number were severely reduced in *Wnt4* KO kidneys. Conditional deletion of *Wnt4* with *Six2*Cre was incomplete but led to decreased kidney size, lower nephron progenitor cell number, increased cell death and dispersal from the tip, and reduced branching morphogenesis. Single cell RNAseq revealed a downregulation of BMP signalling effectors *Id1* and *Id3* in nephron progenitor cells, implicating *Wnt4* target BMP4 as a paracrine signal mediating feedback from the committing nephron. Reduced expression of *Bmp4, Id1*, and *Id3* was validated by HCR; *Fgf8* was unchanged. Recombinant BMP4 restored nephron progenitor compaction in cultured *Wnt4* mutant kidneys and blocked differentiation in wildtype controls, mirroring the role of BMP7-MAPK signalling in progenitor self-renewal.

Conclusions: This study illustrates a crucial role for developing nephrons in maintaining the nephron progenitor population, partly via paracrine BMP4 signalling. These results suggest an indirect relationship between nephron formation and branching morphogenesis and shed light on the mechanisms of renal hypodysplasia associated with human *WNT4* mutations.

Funding: Government Support - Non-U.S.

TH-PO392

Transcriptional Control of Early Nephrogenesis in Xenopus tropicalis

Paulina Ogar,[1] Maike Getwan,[1] Yuya Sugano,[1] Thomas Naert,[2,1] Soeren S. Lienkamp.[1] *[1]Universitat Zurich, Zurich, Switzerland; [2]Universiteit Gent, Gent, Belgium.*

Background: The transcription factors Pax8, Hnf1b, and Sall1 underpin embryonic kidney development, and are linked to Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). They are localised in distinct regions within the ureteric bud epithelium, and metanephric mesenchyme, which interact to orchestrate kidney formation. Intriguingly, however, these factors are roughly co-expressed within the same developing pronephric region in *Xenopus*. Further understanding of their functions could unveil insights into the transcriptome underlying nephrogenesis.

Methods: We visualised cells in the developing pronephros, by confocal microscopy. Injections were combined with CRISPR/Cas9 knock-out (KO) of *pax8*, *hnf1b*, or *sall1* to analyse effects on kidney morphology. Termed single embryo transcriptomics (seRNA-seq), we performed CRISPR/Cas9 KO of *pax8*, *hnf1b* and *sall1* in individual embryos and bulk RNA-seq at an early stage. To filter for renal genes, seRNA-seq was intersected with a kidney-enriched *X. tropicalis* dataset. Localisation of seRNA-seq targets was performed using *in situ* hybridisation (ISH).

Results: We characterised pronephros development in molecular detail, highlighting key stages, from mesenchyme condensation to epithelialisation. KO of *pax8*, *hnf1b*, or *sall1* disrupted size, cell organisation and the basement membrane, underscoring their importance in proper pronephros formation. Considering this, we explored their roles in the transcriptional network using CRISPR/Cas9 and seRNA-seq. Renal and morphogenetic genes were identified (e.g. *slc12a1* up- and downregulated in *pax8 and hnf1b* KO respectively, *twist1* upregulated in *pax8* and *hnf1b* KO). Extracellular matrix genes (*lama1*, *col4a6*) were downregulated in the *sall1* KO. ISH validation of seRNA-seq revealed expression of several targets within the early and developed pronephros (e.g. *agpat3*, *traf4*, and *epha4*).

Conclusions: Pax8, Hnf1b and Sall1 are key regulators of nephrogenesis, and influence a network of renal and morphogenetic targets in *X. tropicalis*. Clarifying their roles will improve understanding of inherited kidney malformations and disease.

TH-PO393

Alternative Oxidase Expression Restores Kidney Progenitor Differentiation in Mice with Mitochondrial Complex lll Disruption

Ryoichi Bessho, Hanako Kobayashi, Volker H. Haase. *Vanderbilt University School of Medicine, Nashville, TN.*

Background: Oxidative metabolism in mitochondria generates ATP through oxidative phosphorylation, regulates cellular differentiation and gene expression through intermediary metabolism and produces reactive oxygen species (ROS). The specific roles of different mt functions in kidney development and pathogenesis are not well understood. We previously reported that disruption of mitochondrial (mt) complex III in cap mesenchyme resulted in severe kidney dysplasia and perinatal death (Guan N, *et al. Kidney Int* 2022). For the disruption of mt complex III, we targeted ubiquinone binding protein QPC using the *Six2-Cre* transgene (*Six2-Qpc*$^{-/-}$ mutants). This resulted in decreased proliferation of renal progenitors and their complete failure to differentiate into tubular epithelium. QPC inactivation disrupted mt electron flux and oxidative phosphorylation and decreased total kidney tricarboxylic acid (TCA) cycle metabolites and amino acid levels.

Methods: To investigate the contribution of TCA cycle dysfunction to the *Six2-Qpc*$^{-/-}$ phenotype, we generated mice expressing alternative oxidase (AOX) in *Qpc*$^{-/-}$ renal progenitors. AOX is derived from sea squirt and restores mt electron transport and TCA cycle flux. We performed morphological, immunohistochemical, gene expression, as well as targeted and untargeted metabolomic analyses of kidneys at postnatal day 0.

Results: AOX expression in *Qpc*$^{-/-}$ renal progenitors rescued postnatal lethality. Immunohistochemical staining and gene expression analyses of tubular differentiation markers, such as megalin, demonstrated restoration of proximal tubular differentiation. AOX expression, however, did not completely restore kidney weight to normal values and all AOX-expressing *Six2-Qpc*$^{-/-}$ mutants died by postnatal day 14. The results from metabolomic analyses will be presented in detail at the meeting.

Conclusions: Taken together, restoration of TCA cycle flux by AOX induced tubular differentiation in mice with mt electron chain disruption in SIX2 nephron progenitors but did not generate functional adult kidneys. Although, our studies suggest a critical role for TCA cycle flux and TCA cycle-regulated gene expression in nephron progenitor differentiation, other mt functions, such as oxidative phosphorylation and ROS production, are required for cell proliferation and postnatal growth of the kidney.

Funding: NIDDK Support, Other NIH Support - NIA, Private Foundation Support

TH-PO394

Interrogating Progenitor Fate Processes in the Developing Zebrafish Pronephros Using Mathematical Models

Matthew R. Hawkins, Stuart Jones, Hannah M. Wesselman, Cecilia A. Cesa, Rebecca A. Wingert. *University of Notre Dame, Notre Dame, IN.*

Background: A core component of developmental and regenerative nephrology is aimed at determining critical relationships between renal progenitors, cells with stem-like qualities, and their progeny. Zebrafish, a vertebrate model well suited for studies involving nephrogenesis and neonephrogenesis, presents with a unique progenitor-rich environment that allows us to characterize and hypothesize qualities and relationships that these precursors hold. Previously, much of the work using this model has been aimed at better understanding conserved genetic regulators of renal development. While this work has been foundational to our understanding of pronephros development, there is still much to be uncovered with respect to the cellular relationships present in early nephrogenesis. Using mathematical models, we are able to hypothesize and interrogate these properties and relationships that precursor populations hold during zebrafish pronephros development.

Methods: To parameterize our model, we have utilized techniques such as whole-mount and fluorescent in situ hybridization as well as immunohistochemistry. For our mathematical modeling, we have used both ordinary differential equations as well as statistical models to characterize multiple cellular populations present in the zebrafish pronephros. For our algorithmic approaches to model parameterization, we have utilized the Nelder-Mead method.

Results: Using the aforementioned methods, we have constructed models that contain different forms of fate processes during nephrogenesis including asymmetric differentiation as well as division independent differentiation. From these models, we can speculate how and when precursors differentiate during pronephros development in the zebrafish model. Using ordinary differential equations that represent multiple cell populations through time and by using multiple goodness of fit indicators to compare model outcomes to biological data, we can arrive at properties of progenitor populations.

Conclusions: Using this model for pronephric development, we test hypotheses on the necessity for division dependent/ asymmetric fate processes, characterize progenitor activity in the earliest stages of renal development, and demonstrate the need for independent qualities among progenitor populations that exist in nephrogenesis.

TH-PO395

Assembly of a Functionally Mature Synthetic Kidney Organoid with Spatial Patterning from the Self-Organization of Expandable Kidney Progenitors

Pedro Medina, Biao Huang, Chennan Zhang, Megan Schreiber, Nuria M. Pastor-Soler, Andrew P. McMahon, Zhongwei Li. *Keck Medicine of USC, Los Angeles, CA.*

Background: The prospect of utilizing stem cells to rebuild a kidney holds great promise as an alternative organ source for kidney transplantation. During kidney development, nephron progenitor cells (NPCs) give rise to the nephrons, and ureteric progenitor cells (UPCs). We have previously established systems to expand mouse and human NPCs and UPCs. Here we investigate whether we can assemble a functionally mature synthetic kidney organoid with patterned and interconnected nephrons to the collecting ducts from expandable NPCs and UPCs.

Methods: Culture conditions were tested to enhance the natural reciprocal interactions between NPCs and UPCs. The resulting synthetic kidney organoids were characterized in a time-course manner and compared to the native kidney development. Single-cell multiome, and physiological assays were performed to characterize the development and functionality of the synthetic kidney organoids.

Results: Under optimal culture conditions, we assembled synthetic kidney organoids from expandable NPCs and UPCs. Synthetic kidney organoids can recapitulate the major developmental stages of the native kidney *in vitro* as that *in vivo*: NPCs undergo the subsequent stages of nephrogenesis before forming around 150 well-segmented nephrons; UPCs undergo dramatic branching morphogenesis, eventually forming a central collecting duct system interconnected to the distal ends of the nephrons formed from the NPCs. snRNA-seq and snATAC-seq confirmed the formation of all major nephron and collecting duct cell types with a transcriptome comparable to a postnatal kidney. Surprisingly, the major kidney stromal cell types are also formed, in a mechanism that involves the plasticity of a subset of NPCs adopting interstitial progenitor cell fate, the third kidney progenitor cell type that gives rise to the kidney stromal cells. Functional assays validate the renal epithelia's physiological and major endocrine roles similar to the native kidney. Upon transplantation, the synthetic kidney organoids are properly vascularized and produce primitive urine.

Conclusions: The generation of a functionally mature, and spatially organized synthetic kidney organoid model represents a major step toward the development of transplantable synthetic kidneys, and other therapeutic modalities.

Funding: NIDDK Support, Other NIH Support - NIH Directors Award, NIH T32HD060549, Private Foundation Support

TH-PO396

A Scalable Platform for Generating Uniform Human-Induced Pluripotent Stem Cell (hiPSC)-Derived Kidney Organoids Using Micropatterning

Samera Nademi, Benjamin S. Freedman. *University of Washington School of Medicine, Seattle, WA.*

Background: Organoids hold immense potential for modeling complex diseases, drug discovery, and regenerative medicine. However, current methods for generating organoids suffer from limitations in reproducibility and scalability, hindering their use in high-throughput applications. We present a novel approach to overcome these limitations by developing a standardized micropatterned platform for generating human induced pluripotent stem cell (hiPSC)-derived kidney organoids. Micropatterning has shown promise in improving the development and drug screening capabilities of other organoid types, such as neural organoids. However, its application to hiPSC-derived kidney organoids remains unexplored.

Methods: Here, we describe the first-of-its-kind method for generating uniform hiPSC-derived kidney organoids in various micropatterns, including linear, square, and hexagonal shapes, with customizable patterns and sizes.

Results: Our micropatterning method successfully generated hiPSC cultures in various geometries, including linear, square, and hexagonal shapes. We achieved precise control over both the pattern and size of the cultured hiPSCs, enabling customization for specific experimental needs.

Conclusions: In conclusion, our micropatterning method has established a foundation for the development of standardized hiPSC cultures. The precise control over patterning and size paves the way for tailored experiments and potentially unlocks a new era of consistent and scalable hiPSC-derived organoid generation. We now investigate if micropatterned hiPSCs differentiate into more uniform kidney organoids (size and structure) compared to conventional methods. This analysis, involving comparisons between patterned and non-patterned organoids, will determine if our approach enables large-scale production of consistent kidney organoids for disease modeling, drug screening, and potentially, future kidney regeneration.

TH-PO397

Generation of Human Expanded Pluripotent Stem Cell-Derived Kidney Organoids with Patterned Nephron by Regulating Hippo-YAP Pathway

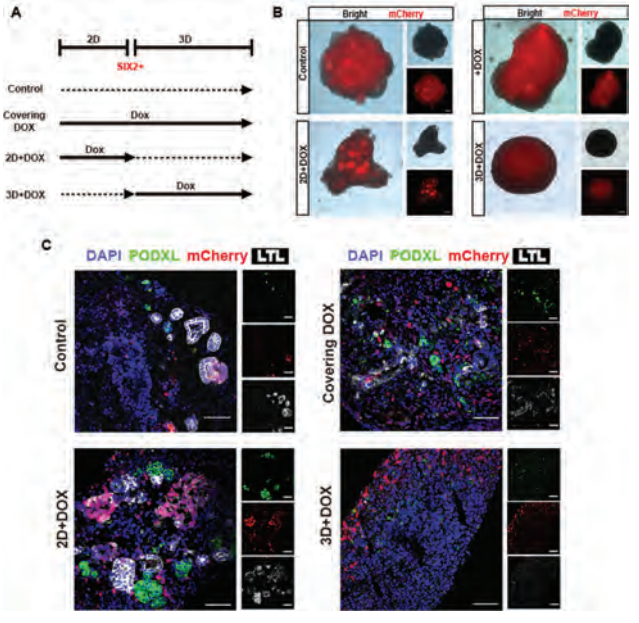
Liangzhong Sun. *Southern Medical University, Guangzhou, China.*

Background: Numerous cultivation protocols for kidney organoids, differentiation efficiency remains generally low. This study aims to investigate the influence of the Hippo-YAP pathway on induced differentiation of kidney organoids and elucidate its molecular mechanisms, thereby providing efficient induction strategies for kidney organoid construction.

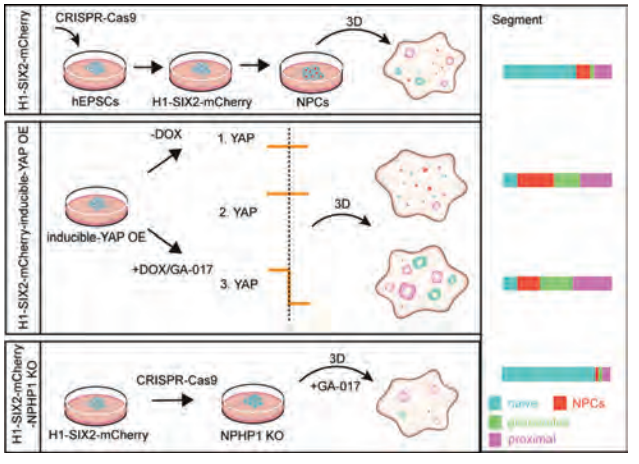
Methods: We used CRISPR-Cas9 technology for a reporter gene cell line was constructed based on human Expanded Pluripotent Stem Cells (hEPSC). Besides, an inducible YAP overexpression cell line and a NPHP1 knock-out cell line were constructed on this basis. The differentiation of kidney organoids under genetic and chemical schemes were compared.

Results: We have developed a methodology to generate kidney organoids with pattern nerphron, differentiated from SIX2-mCherry knock-in reporter hEPSCs, by regulating Hippo-YAP signaling pathway. We find that inhibiting the Hippo-YAP pathway during early differentiation stages effectively increased the number of nephron progenitor cells, resulting in more pattern nerphron.

Conclusions: Regulating the Hippo-YAP pathway during early stages of kidney organoid differentiation facilitates their maturation, offering effective induction strategies to enhance the efficiency of kidney organoid differentiation.



The result for regualting YAP expression



Schematic showing regulating Hippo-YAP pathway for kidney organoids with patterned nephron

TH-PO398

Controlling Proximal Nephron Arrangement and Maturity in Stem Cell-Derived Engineered Kidney Tissue

Jessica M. Vanslambrouck,[1,2] Ker sin Tan,[1] Sophia Ying Yii Mah,[1] Kathleen Dominic,[1] Melissa H. Little.[1,2] Kidney Regeneration, Stem Cell Medicine Theme. *[1]The Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Murdoch Children's Research Institute, Parkville, Melbourne, VIC, Australia; [2]Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, Melbourne, VIC, Australia.*

Background: The proximal tubule (PT) structure is critical to the metabolic, endocrine, immune, and general homeostatic functions of the kidney. However, its acute vulnerability to damage and disease has made the generation of stable and accurate PTs a key objective of kidney disease research and treatment advances. While human pluripotent stem (hPSC)-derived kidney organoids are one approach, their immature PTs and disorganised nephron spatial arrangement remain a barrier to translational applications. We have previously developed PT-enhanced kidney organoids with elongated and functionalised proximal tubules. Here we report a breakthrough in the control of proximal nephron spatial arrangement achieved by exploiting biophysical parameters. This approach supports the formation of physiologically relevant S1/S2/S3 PT segmentation and is transferable to organ-on-a-chip platforms.

Methods: Standard and reporter hPSCs were differentiated to enhanced nephron progenitors prior to organoid formation (Vanslambrouck *et al. Nature Protocols*, 2023). Progenitors and PT-enhanced organoids were generated using standard or extrusion-based 3D cellular bioprinting techniques in combination with novel organ-on-a-chip platforms, metabolic-supportive media, and comprehensive analyses using high-content confocal imaging, transcriptional profiling, and transporter functional assays.

Results: Here we show that stringent control of organoid biophysical parameters can be used to guide the spatial arrangement of nephrons within hPSC-derived PT-enhanced kidney tissue. Using appropriate metabolic support for maturing organoid cells populations, increased levels of transporters and the formation of distinct PT cell subtypes was observed. Finally, the generation of appropriately patterned PT was possible from cryopreserved progenitors, simplifying manufacture and scale up.

Conclusions: The advances to our protocol have founded an improved PT platform likely to provide more accurate disease modelling and drug/toxicity screening opportunities.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO399

Selective Induction of Renal Interstitial Progenitor Cell Lineages from Human-Induced Pluripotent Stem Cells (hiPSCs) for Understanding of Mesangial and Erythropoietin (EPO)-Producing Cell Development and Kidney Regeneration

Hiraku Tsujimoto,[1,2] Azusa Hoshina,[1,3] Shin-ichi Mae,[1] Toshikazu Araoka,[1] Cecilia Graneli,[4] Kevin Woollard,[4] Kenji Osafune.[1] *[1]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan; [2]Rege Nephro Co., Ltd., Kyoto, Japan; [3]Shiga Kenritsu Sogo Byoin, Moriyama, Japan; [4]AstraZeneca PLC, Cambridge, United Kingdom.*

Background: Recent regenerative studies using human pluripotent stem cells (hPSCs) have developed multiple kidney-lineage cells and organoids. To further form functional segments of the kidney, the interactions of epithelial and interstitial cells are required. By selectively generating one lineage, we can detail developmental signals in complex organ development. Renal interstitial progenitor cells (IPCs) are useful for elucidating the function and pathology of renal interstitium. Renin-producing mesangial lineage cells contribute to hypertension and EPO-producing cells are key in kidney fibrosis. We aim to develop a method to selectively induce renal IPCs and their derivatives from human induced pluripotent stem cells (hiPSCs) and reveal the developmental mechanisms of IPC-lineage cells.

Methods: We modified our previously reported induction method for nephron progenitor cells (NPCs) from hiPSCs by modulating developmental signals involved in the transition from primitive streak to renal IPCs, which were identified by single-cell RNA-sequencing (scRNA-seq) analysis of mouse embryos. We established OSR1-GFP/FOXD1-tdTomato double knock-in hiPSC lines.

Results: We developed a method to generate IPC-like cells (IPLCs) over 80% of induction efficiency. Our IPLCs combined with hiPSC-derived NPCs and nephric duct cells form nephrogenic niche- and mesangium-like structures *in vitro*. Furthermore, we successfully induced mesangial and EPO-producing cell lineages *in vitro* by screening differentiation-inducing factors. We confirmed that p38 MAPK and vascular endothelial growth factor (VEGF) signaling pathways are involved in the differentiation of mesangial-lineage cells. Re-analysis of public scRNA-seq data of human embryonic kidneys and an organ culture experiment using mouse embryonic kidneys supports p38 MAPK activation upon the differentiation of mesangial-lineage cells. Furthermore, using small molecules, we revealed that Sonic Hedgehog signaling is involved in the differentiation from IPLCs to EPO-producing cells *in vitro*.

Conclusions: Our IPC-lineage induction method contributes to kidney regeneration and developmental research.

Funding: Commercial Support - Rege Nephro Co., Ltd., AstraZeneca plc

TH-PO400

Amniotic Fluid Organoids as Personalized Real-Time Models of the Fetal Kidney and Lung

Oren Pleniceanu,[1,2] Olga Babosova,[1,2] Boaz Weisz,[1,2] Grace Rabinowitz,[1] Tammir Jubany,[1,2] Hagai Avnet,[1,2] Noam Pardo,[1,2] Iris Barshack,[1,2] Dorit Omer,[1] Zohar A. Dotan,[1,2] Benjamin Dekel,[1,2] Rena Levin-Klein,[1] Pazit Beckerman.[1,2] Kidney Research Lab, Sheba Medical Center. *[1]Sheba Medical Center, Tel Hashomer, Israel; [2]Tel Aviv University, Tel Aviv, Israel.*

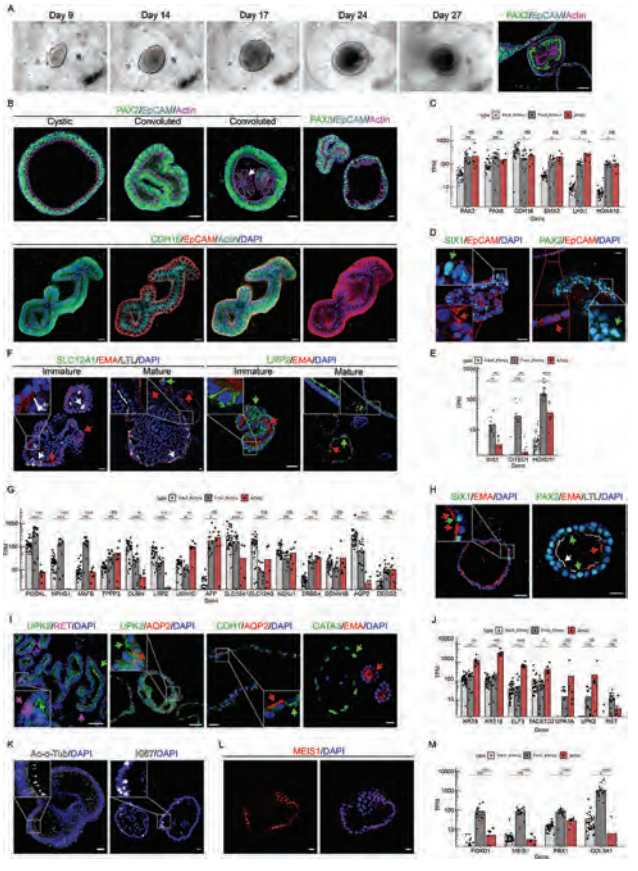
Background: As fetuses are largely inaccessible, human development remains poorly understood, and many developmental disorders, such as kidney anomalies, lack therapy. We aimed to use amniotic fluid (AF), which comprises fetal urine and lung secretions, to model fetal kidneys and lungs.

Methods: AF was seeded in 'kidney' or 'lung' media, which select for the respective progenitors, generating 3D organoids mirroring both organs. These were analyzed by immunostainings, single cell RNA-seq and functional tests.

Results: We established single cell-derived AF kidney (AFKO) and lung organoids (AFLO). AFKO harbor nephrogenic, urothelial and stromal cells, and uptake albumin. Upon injection to human fetal kidney explants, AFKO cells populate the progenitor niche and contribute to nascent tubules. AFLO habor alveolar and airway cells, upregulate surfactant levels upon steroid treatment and show active CFTR channels.

Conclusions: We present a new tool for personalized modeling of fetal organs, applicable to virtually any fetus. This provides accessible means to study normal and abnormal development via bona fide human fetal cells, which until now has been difficult.

Funding: Private Foundation Support, Government Support - Non-U.S.



A-B. AFKO express renal markers. C. Renal gene expression; D. AFKO harbor SIX1$^+$EpCAM$^-$ & PAX2$^+$EpCAM$^-$ nephron progenitors (NP), generating SIX1$^-$EpCAM$^+$ & PAX2$^-$EpCAM$^+$ epithelia. E. NP marker expression. F. AFKO harbor tubules of multiple nephron segments. G. Segment-specific marker expression. H. SIX1$^+$/PAX2$^+$ NP give rise to EpCAM$^+$ epithelia. I. UB lineage differentiation in AFKO: RET$^+$ tip cells alongside AQP2$^+$ collecting duct cells and UPK2$^+$ urothelia. J. UB marker expression. K. AFKO have cilia and proliferate. L. MEIS1$^+$ stromal AFKO. M. Stromal marker expression.

TH-PO401

Development of a Fetal Kidney Failure Model through Nephron Progenitor Cell Ablation via the Intrinsic Apoptosis Pathway

Kenji Matsui, Shuichiro Yamanaka, Kei Matsumoto, Takashi Yokoo. Div of Nephrology and Hypertension, Dept of Internal Medicine. *Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan.*

Background: Fetal organ failure models are promising for xenotransplantation targeting fetuses and developmental and pathological research. Conventional knockout models often result in fetal lethality, while tamoxifen-inducible conditional ablation models are harmful to fetuses and lack both rapidity and completeness. In this study, we introduce inducible caspase 9 (iC9) to mouse fetuses for the first time, creating a viable CKD model with an easily adjustable phenotype.

Methods: We developed Six2-iC9 mice that express iC9 in nephron progenitor cells (NPCs). To generate a congenital CKD model, we administered a chemical inducer of dimerization (CID) to pregnant mothers intraperitoneally, introducing NPC ablation in Six2-iC9$^{+/+}$ offspring. This system's efficiency and speed of cell ablation were verified in the culture of Six2-iC9$^{+/+}$ and Six2-iC9$^{+/-}$ fetal kidneys. Additionally, we developed loxP-iC9 mice and Six2-iC9 rats.

Results: A single intraperitoneal CID administration resulted in complete NPC ablation, with the severity adjustable depending on timing. Offspring treated at E13.5 survived, exhibiting significant increases in BUN and urinary albumin from as early as one month old. Histology demonstrated reduced glomeruli with compensatory hypertrophy, tubular dilation, and interstitial fibrosis. In whole-organ cultures of Six2-iC9$^{+/+}$ fetal kidneys, NPC apoptosis began 6 hours after CID addition, with an ablation efficiency of 94%. Ablation was not induced in Six2-iC9$^{+/-}$, confirming the existence of a threshold for iC9 expression. However, in dissociated and re-aggregated sphere cultures of Six2-iC9$^{+/-}$ kidneys, NPC ablation was achieved. RNA-seq suggested that DNA damage from cell dissociation made cells more susceptible to apoptosis. Even in whole-organ cultures, co-administering XIAP inhibitor with CID facilitated NPC ablation in Six2-iC9$^{+/-}$. NPC ablation was also induced in loxP-iC9 mice crossed with Six2-Cre mice and in Six2-iC9 rats.

Conclusions: We established a congenital CKD model utilizing the intrinsic apoptosis pathway. Our findings indicate that iC9 expression levels and cell conditions influence this system's effectiveness. The successful implementation of the loxP system promises applications in other cell types, and the development of rat models will advance fetal xenotransplantation research.

Funding: Government Support - Non-U.S.

TH-PO402

Hypoxic Injury Triggers Maladaptive Repair in Human Kidney Organoids

Ana B. Nunez Nescolarde,[1] Mehran Piran,[1] Zhengqi Cheng,[3] Christine A. Wells,[3] David J. Nikolic-Paterson,[2,1] Alexander N. Combes.[1] *[1]Monash University, Melbourne, VIC, Australia; [2]Monash Medical Centre, Clayton, VIC, Australia; [3]The University of Melbourne, Melbourne, VIC, Australia.*

Background: Hypoxia is an important driver of AKI. Individuals who survive AKI often develop CKD through a maladaptive repair process characterised by failed epithelial regeneration, fibrosis, inflammation and metabolic dysregulation. Despite detailed knowledge built in rodent models, translational challenges underscore a need for human models.

Methods: Kidney organoids were generated from three independent human induced pluripotent stem cell lines and cultured for 48h in hypoxic (1% O2) or normoxic conditions from day (d) 18 to 20 of differentiation. Organoids were collected at d20 to assess immediate injury, or at d25, after 5d of culture in normoxic conditions, to assess repair. The response was analysed using transcriptomics, proteomics and metabolomics analyses. In addition, the role of the hypoxia regulator, *HIF1A*, was evaluated by exposing to hypoxia CRISPR edited *HIF1A*$^{-/-}$ organoids. Finally, direct co-culture with human induced macrophages was performed and their location and expression signatures were interrogated using immunoassays and spatial transcriptomics.

Results: Kidney organoids exposed to hypoxia upregulated hypoxic response genes (*VEGFA*, *HK1*), tubular injury markers (*JUN*, *TGFB1*, *GDF15*), and transcriptional signatures of AKI-associated cell stress and death pathways (apoptosis, ferroptosis). Deletion of *HIF1A* abrogated most of the hypoxic transcriptional response. However, we found the expression of *GDF15* to be HIF1A-independent. Instead, *GDF15* expression seemed to be mediated by the increase in *DDIT3* due to endoplasmic reticulum stress. At d25, injured organoids had increased ceramide production, elevated levels of maladaptive repair markers (S100A8, S100A9), and genes associated with collagen production, inflammation and fibrotic mediators. Dysregulation of iron metabolism (*HMOX1*, *FTL*) and lipid peroxidation were also lasting effects of the hypoxic injury. Single-cell RNAseq localised expression of maladaptive repair genes, and activation of TNF, NF-κB and JAK-STAT signalling pathways to tubular epithelial cells. Furthermore, co-cultured with macrophages modified the hypoxic response by enhancing TNF-α signalling via NF-kB and TGF-ß signalling pathways.

Conclusions: This multi-omic analysis provides compelling evidence supporting the use of organoids as *in vitro* models of ischemic AKI and maladaptive repair.

Funding: Government Support - Non-U.S.

TH-PO403

Pax2 Mutant Mice Have Dysregulated Nuclear Maintenance, Cell Proliferation, and Motility Associated with Abnormal Glomerular Repair

Joanna Cunanan,[1,2] Jasmeet K. Benepal,[1,2] Vanessa S. De Gregorio,[1,2] Samantha Ricardo,[1,2] Emine B. Caparali,[1] Ana Konvalinka,[1,2] Moumita Barua.[1,2] *[1]Division of Nephrology, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada; [2]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada.*

Background: Focal segmental glomerulosclerosis (FSGS) is characterized by podocyte loss. Parietal epithelial cells (PECs) that express PAX2, a regulator of cellular and morphological changes during glomerular development, can regenerate podocytes after injury. We previously found that pathogenic *PAX2* missense variants account for 4% of adult FSGS, and mutant PAX2+ PECs display impaired podocyte regeneration resulting in worsened FSGS in mice with a *Pax2* missense variant (*Pax2*-MV) (**Figure 1A-B**). In this study, we report the molecular mechanisms of impaired podocyte regeneration in *Pax2*-MV.

Methods: FSGS was induced by Adriamycin (ADR) in *Pax2*-MV and wildtype mice. Isolated glomeruli were subjected to mass spectrometry-based proteomics and analyzed by Gene Ontology (GO) and Reactome pathway enrichment analysis.

Results: Downregulated processes in ADR-injured *Pax2*-MV compared to wildtype glomeruli include decreased metabolic processes and actin cytoskeleton structure regulation (**Figure 1C**), consistent with worsened podocyte loss observed in these mice. Upregulated processes in ADR-injured *Pax2*-MV include those involved in nuclear abnormalities, cell proliferation and motility (**Figure 1D**). These are consistent with the increased glomerular tuft cell proliferation observed in ADR-injured *Pax2*-MV mice. This suggests a maladaptive attempt to regenerate podocytes due to the lack of regeneration from mutant PAX2+ PECs.

Conclusions: In ADR-injured *Pax2*-MV, downregulated metabolism and cytoskeleton structure are typical signatures of podocyte loss. However, our novel findings are the upregulated pathways that are consistent with dysregulated PAX2 signaling, including nuclear abnormalities, cell proliferation and motility.

Funding: Government Support - Non-U.S.

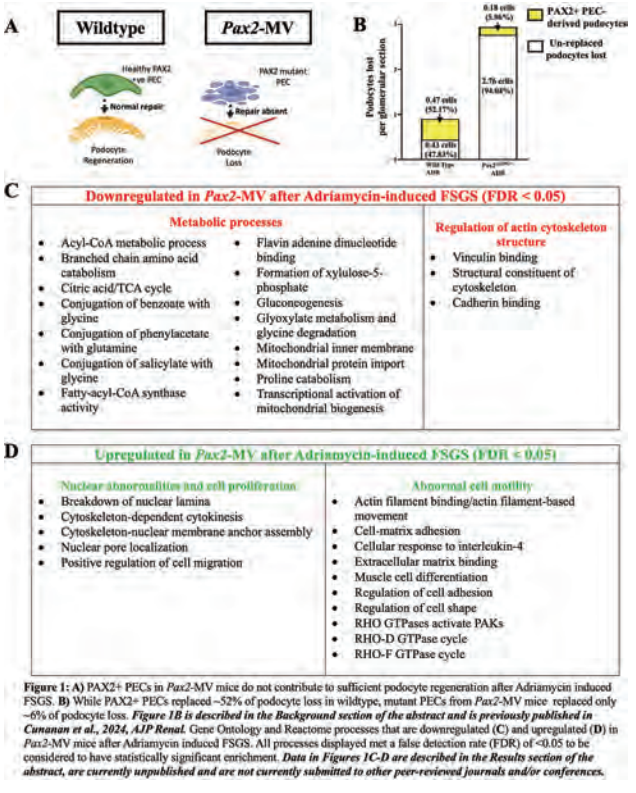


Figure 1: A) PAX2+ PECs in *Pax2*-MV mice do not contribute to sufficient podocyte regeneration after Adriamycin induced FSGS. **B)** While PAX2+ PECs replaced ~52% of podocyte loss in wildtype, mutant PECs from *Pax2*-MV mice replaced only ~6% of podocyte loss. ***Figure 1B is described in the Background section of the abstract and is previously published in Cunanan et al., 2024, AJP Renal.*** Gene Ontology and Reactome processes that are downregulated (**C**) and upregulated (**D**) in *Pax2*-MV mice after Adriamycin induced FSGS. All processes displayed met a false detection rate (FDR) of <0.05 to be considered to have statistically significant enrichment. ***Data in Figures 1C-D are described in the Results section of the abstract, are currently unpublished and are not currently submitted to other peer-reviewed journals and/or conferences.***

TH-PO404

Piezo1 Promotes Podocyte Survival and Regeneration by Regulating F-actin Remodeling

Maria Elena Melica,[1] Giulia Antonelli,[1] Giulia Carangelo,[1] Maria Lucia Angelotti,[1] Elena Lazzeri,[1] Carolina Conte,[1] Anna J. Peired,[1] Letizia De Chiara,[1] Benedetta Mazzinghi,[2] Paola Romagnani,[1,2] Laura Lasagni.[1] *[1]Universita degli Studi di Firenze, Firenze, Italy; [2]Meyer - Azienda Ospedaliera Universitaria, Firenze, Italy.*

Background: Podocytes and podocyte progenitors are interdependent components of the kidney's glomerular structure, with podocytes forming the glomerular filtration barrier and progenitors being key players in podocyte regeneration during pathophysiological processes. Both cell types are subjected to constant mechanical forces, whose alterations can initiate podocytopathy and worsen glomerular injury. Despite this, the specific mechanosensors and mechanotransduction pathways involved in their response to mechanical cues remain partially explored.

Methods: We used transcriptomics, immunofluorescence, and silencing experiments on human primary progenitor cell cultures to demonstrate the expression and function of Piezo1 channels. We generated podocyte- and podocyte progenitor-specific Piezo1 knockout mice and evaluated the effects of Piezo1 loss in the context of Adriamycin nephropathy (ADN) and aging.

Results: Silencing of Piezo1 in progenitors triggered F-actin remodelling, induced cell shape modification and nuclear envelope defects with accumulation of DNA damage that lead to mitotic catastrophe in differentiated podocytes. Podocyte progenitor-specific knockout of Piezo1 in mouse resulted in severe albuminuria following ADN. Podocyte-specific knockout of Piezo1 not only induced higher susceptibility to podocyte injury in ADN but also led to accumulation of DNA damage and albuminuria throughout aging.

Conclusions: These results underline the central role of mechanical force perception and mechanotransduction in the pathogenesis of glomerular disease and identify Piezo1 as a potential target of mechanodrugs in disease conditions.

Funding: Government Support - Non-U.S.

TH-PO405

Impact of Renin on the Migration of Renin-Positive Cells in the Course of CKD

Shila Azizolli,[1] Sagor Halder,[1] Maria Schuster,[1] Florian Gembardt,[1] Jan Sradnick,[1] Ulf Panzer,[2] Christian Hugo.[1] *[1]Universitatsklinikum Carl Gustav Carus, Dresden, Germany; [2]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: Renin-positive juxtaglomerular cells (RPC) have been shown to serve as precursors for various glomerular cell types in models of acute kidney injury. Specifically, we have previously demonstrated their ability to migrate intraglomerularly and differentiate into mesangial cells upon losing their renin-positivity. However, the role of RPC and their mechanisms in chronic injury models remains unknown. Therefore, we aimed to evaluate the role of renin and RPC migration in the chronic disease model of anti-glomerular basement membrane (anti-GBM), using an inducible renin-knockout (RenKO) mouse line.

Methods: Inducible transgenic renin-reporter (WT) and RenKO 8-12 week mice were used. The injury model was initiated by an intraperitoneal (i.p) injection of TNF-α. Two hours later, anti-GBM serum was administered i.p. To examine the effects of the model, a uni-nephrectomy was performed on day 10 after serum injection, followed by the final biopsy on day 21. PAS staining was used to assess the renal damage. RPC migration was analyzed using immunofluorescence staining against tdTomato, a8-Integrin, and renin. The extent of RPC migration was determined by the glomerular tdTomato-positive areas.

Results: PAS staining of the samples from both WT and RenKO groups, revealed substantial glomerular injury upon anti-GBM model induction. The damage was marked by the emergence of tubular casts, high PAS-positivity, and crescent formation. The immunofluorescence staining revealed significant differences between the groups in terms of RPC migration. At day 10, RPC migration was observed in 45% and 13% (p-value < 0.0001) of the overall glomeruli in WT and RenKO after anti-GBM induction, respectively. Additionally, at day 21 RPC migration was observed in 50% and 12% (p-value = 0.0002) of the overall glomeruli in WT and RenKO respectively.

Conclusions: In conclusion, we were able to demonstrate for the first time, RPC migration during a chronically progressive kidney injury model. Since renin depletion leads to significantly reduced migration, renin itself appears to be involved in this process. Next, a thorough analysis of the injury advancement between the groups, and a characterization of the transcriptomic landscape of the RPC under healthy and pathological conditions will provide further clarity on this mechanism.

TH-PO406

Deciphering Cellular Mechanisms in Cells of Renin Lineage-Mediated Kidney Regeneration under SGLT2 Inhibition

Loïs van der Pluijm,[1] Juliette A. de Klerk,[2] Angela Koudijs,[2] Joris I. Rotmans,[2] Kenneth W. Gross,[3] Michael P. Pieper,[4] Anton J. Van Zonneveld,[2] Roel Bijkerk.[2] Einthoven Laboratory for Vascular and Regenerative Medicine. *[1]Leids Universitair Medisch Centrum, Leiden, Netherlands; [2]Leids Universitair Medisch Centrum, Leiden, Netherlands; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany.*

Background: A newly discovered, promising source of renal intrinsic regenerative cells comprise the cells of renin lineage (CoRL). Juxtaglomerular CoRL can repopulate essential glomerular cells like podocytes and mesangial cells post-injury, a process that can be enhanced by inhibiting the sodium glucose co transporter 2 (SGLT2). Despite its potential, the underlying cellular mechanisms remain largely elusive. Our study aims to identify the key genes driving this reparative process.

Methods: We employed a chronic kidney disease (CKD) model of 5/6 nephrectomy (5/6NX) in Ren1cre-tdTomato CoRL-lineage trace mice while daily administering the SGLT2 inhibitor empagliflozin (10mg/kg) for two weeks. Renal CoRL were isolated using fluorescent automated cell sorting (FACS) and subjected to single cell RNA sequencing.

Results: As determined by blood urea levels and GFR measurements throughout the study, we demonstrated enhanced kidney function recovery upon SGLT2 inhibition post kidney injury. In addition, SGLT2 inhibition led to increased numbers of CoRL-derived intraglomerular cells, specifically due to a rise in CoRL-derived podocytes. Single-cell RNA sequencing of CoRL revealed several distinct cell type clusters and confirmed the presence of a CoRL-derived podocyte cluster. Currently, pseudo-time trajectory analyses are being conducted to further elucidate differentiation dynamics of CoRL, particularly under SGLT2 inhibition.

Conclusions: Our findings highlight the potential of SGLT2 inhibition in promoting CoRL-mediated intrinsic kidney regeneration. Ongoing investigations aim to further decode the gene expression patterns during the phenotypic commitment shift of CoRL post-injury under SGLT2 inhibition. These insights may pave the way for novel, targeted approaches to augment the kidney's regenerative capacity.

Funding: Commercial Support - Boehringer Ingelheim

TH-PO407

Targeting MicroRNA-132 Decreases Kidney Fibrosis: A Role for Altered Plasticity of Cells of Renin Lineage?

Loïs van der Pluijm,[1] Angela Koudijs,[1] Joris I. Rotmans,[1] Kenneth W. Gross,[2] Anton J. Van Zonneveld,[1] Roel Bijkerk.[1] *[1]Leids Universitair Medisch Centrum, Leiden, Netherlands; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY.*

Background: Recent research has highlighted the potential of cells of renin lineage (CoRL) in promoting intrinsic kidney regeneration. The juxtaglomerular CoRL can repopulate crucial glomerular cells such as podocytes and mesangial cells following renal injury. Besides beneficial redifferentiation, CoRL can give rise to pericytes and subsequently myofibroblasts, contributing to fibrotic tissue formation. Our recent findings suggest that cellular responses to injury are largely regulated at the post-transcriptional level, with microRNA-132 (miR-132) playing a pivotal role. Induced by high-salt conditions, miR-132 directly stimulates renin release from CoRL, while miR-132 also regulates genes involved in cell proliferation and kidney fibrosis. The current study aims to investigate the role of MiR-132 in CoRL plasticity.

Methods: We employed various experimental kidney injury models in Ren1cre-tdTomato CoRL-lineage trace mice, including 5/6 nephrectomy (5/6NX), uni- and bilateral ischemic reperfusion injury (uIRI and bIRI), while administering locked nucleic acid (LNA) antisense oligonucleotide inhibitor of miR-132 (antimir-132).

Results: Blood urea levels indicated improved kidney function in the loss-of-function models 5/6NX and bIRI upon miR-132 interference. Histological analysis showed a strong trend towards decreased fibrosis with miR-132 inhibition in all models, as well as an association of miR-132 knockdown with altered renin activity (PRA). Upon miR-132 knockdown, we observed a reduction in interstitial tdTomato+ cells, suggesting a decrease in CoRL-derived myofibroblasts. Intraglomerular cell fates of CoRL upon miR-132 modulation in the various injury models are currently explored.

Conclusions: Our study sheds light on the intricate role of miR-132 in kidney fibrosis and modulating the plasticity of CoRL therein. These findings suggest a potential therapeutic opportunity for targeting miR-132 to mitigate renal fibrosis. However, further investigation will be essential to fully elucidate the mechanisms underlying CoRL plasticity and the specific effects of miR-132 inhibition in different injury contexts.

TH-PO408

Heparanase 2 Is an Important Regulator of Glomerular Glycocalyx and Influences Albuminuria in Zebrafish via Vascular Endothelial Growth Factor A (VEGF-A) and Fibroblast Growth Factor (FGF) Signaling

Hermann Haller. *MDIBL, Bar Harbor, ME.*

Background: The endothelial glycocalyx (eGCX) is a glycan-rich layer important for vascular homeostasis. Shedding of heparan sulfates (HS) from the eGCX by heparanase leads to endothelial dysfunction. Heparanase 2 (Hpa2) is known to interact with (HS). We investigated the role of Hpa2 for the vascular system in zebrafish to establish a novel vertebrate model to study of eGCX in renal and vascular disease.

Methods: We use zebrafish larvae as research model. Expression and localization of Hpa2 was examined by *in situ* hybridization and immune fluorescence. *hpse2* loss-of-function (LOF) was induced by CRISPR-Cas9 or morpholino antisense strategies and eGCX was quantified. Endothelial permeability was analyzed in *Tg(l-fabp:VDB-EGFP)* fish. EC morphology, and expression profiles were examined in *Tg(flia1:eGFP)* fish and by transmission electron microscopy. Recombinant Hpa2 was injected into *hpse2* LOF fish and its effect on vascular pathology analyzed. Hpa2 was applied in EC cell cultures to study signal transduction of FGF2 and VEGFA.

Results: *hpse2 was detected* in hepatic tissue of zebrafish from 72 hpf onwards and localized the protein in blood vessels. *hpse2* LOF caused a vascular phenotype. *hpse2* LOF reduces eGCX and causes changes in the endothelial transcriptome characterized by genes involved in ECM-receptor interaction and signal transduction regulation. Recombinant hHpa2 rescued the *hpse2* LOF phenotype in zebrafish. *In vitro* studies showed that Hpa2 competes with heparin-binding growth factors FGF2 and VEGFA for binding on the EC surface and consequently reduces the cellular response these factors cause. Pharmacological inhibition of VEGFR2 and FGFR in alleviated the *hpse2* LOF phenotype in zebrafish.

Conclusions: We conclude that Hpa2 is necessary to maintain EC homeostasis by preventing HS breakdown. Recombinant Hpa2 prevents endothelial dysfunction and reduces proteinuria. Hpa2 induced maintenance of HS glycans strongly regulates growth factor-dependent signaling in EC. These findings may translate into novel treatment strategies with recombinant Hpa2.

Funding: Private Foundation Support

TH-PO409

Podocyte-Specific Partitioning Defective Par1a/b Deletion Increases Susceptibility to Adriamycin Nephropathy

Aparajita Mishra,[1] Zhongfang Du,[2] Selin Kurt,[3] Lanny T. DiFranza,[3] Catherine E. Brennan,[2] Kimberly J. Reidy.[1] *[1]Children's Hospital at Montefiore, New York, NY; [2]Albert Einstein College of Medicine, Bronx, NY; [3]Montefiore Medical Center, Bronx, NY.*

Background: The Partitioning-defective (Par1) proteins are serine threonine kinase members of a family of apico-basal polarity proteins that contribute to nephrocyte and podocyte differentiation and glomerular development in Drosophila and Mus musculus, respectively. However the role of Par1a/b following podocyte injury is not known. We hypothesized Par1a/b (aka Mark2 and Mark3) are protective against podocyte injury.

Methods: We examined correlation of glomerular Par1a/b (MARK2/3) gene expression with proteinuria using publicly available data from Nephroseq. Next, to test our hypothesis, we generated podocyte specific Par1a/b knockout (podocyte Par1a/b cKO): NPHS2-Cre: Mark2flox/flox: Mark3flox/flox which were maintained on a C57BL6 background. To determine the effect on podocyte injury, adult 8-week-old podocyte Par1a/b cKO mice were injected with adriamycin (15mg/kg). Controls included adriamycin injected Mark2flox/flox:Mark3flox/flox mice and vehicle injected mice. Mice were euthanized at 14 weeks to analyze the kidney phenotype. To analyze the severity of adriamycin nephropathy, Periodic-acid Schiff staining and urine albumin creatinine ratio were performed.

Results: Glomerular Par1a/MARK3 and Par1b/MARK2 expression was inversely correlated with proteinuria in multiple human gene expression data sets from subjects with glomerular disease ($p<0.05$). Podocyte Par1a/b cKO mice survive to adulthood, but more adriamycin treated Podocyte Par1a/b cKO died than Adriamycin treated flox/flox mice. Adriamycin treated Podocyte Par1a/b cKO mice had more global sclerosis and segmental sclerosis compared to the Adriamycin treated flox/flox controls ($p<0.05$). Adriamycin treated Podocyte Par1a/b cKO mice showed more albuminuria compared to the adriamycin flox/flox treated controls ($p<0.05$). Serum creatinine measurement showed no statistical difference among the groups.

Conclusions: Decreased Par1a/b (MARK2/3) expression correlates with more proteinuria in human glomerular disease. Podocyte Par1a/b deletion increased susceptibility to Adriamycin nephropathy, suggesting Par1a/b is protective following podocyte injury. Ongoing studies are examining the mechanism(s) by which podocyte Par1a/b deletion affects susceptibility to glomerular injury

Funding: NIDDK Support

TH-PO410

Single-Cell and Spatial Transcriptomics Identify Immediate Early Genes as Central Transcriptomic Factors during Renal Endothelial Regeneration In Vivo

Jan Sradnick, Meike Seitz, Patrick Arndt, Anika Wirth, Maria Schuster, Hannah Weissbach, Christian Hugo. *Universitatsklinikum Carl Gustav Carus, Dresden, Germany*.

Background: Immediate early genes play a central role in the regulation of cell stress, cell proliferation and differentiation. Individual studies indicate that immediate early genes significantly influence vascular repair, of aortic and lung endothelial cells. Less is known about the regenerative mechanisms in renal endothelial cells. To test the relevance of mediated early genes in the kidney, renal endothelial injury was induced. Transcriptomic patterns of the endothelium were evaluated on a single-cell level to uncover potential mechanisms of renal vascular regeneration.

Methods: For single-cell transcriptomics (scRNA), endothelial-specific injury was induced in Tie2 eGFP reporter mice (n=48) by renal arterial perfusion with Concanavalin A (ConA) /anti-ConA. Nineteen mice served as sham-operated controls. Kidneys were harvested 24 hours, 48 hours, 4 days, and 7 days after injury induction. For scRNA transcriptomics, cells were isolated from glomerular and extraglomerular renal tissue. Biopsies from 15 mice were used to perform 10x Xenium spatial transcriptomics. Endothelial cell damage was evaluated using periodic acid–Schiff and endomucin stainings.

Results: Both endothelial cell injury (24h) and remarkable regeneration (d4-d7) were observed using glomerular injury evaluation. Following quality control measurements, 10 glomerular and 7 peritubular endothelial cell subclusters were identified. Based on scRNA transcriptomics, we identified cells which increased significantly with proportions of 6% (d2), 17% (d4), and 20% (d7), along with the detected healing process. Immediate early genes like *Atf3*, *Erg1*, *Fos*, and *Junb* were differentially expressed in these cell population. A similar pattern was observed in peritubular endothelial cells. With the help of spatial transcriptomics, findings were successfully confirmed.

Conclusions: In summary, state-of-the-art transcriptomics allowed us to initially identify endothelial renal subpopulations expressing the immediate early genes, which potentially regulate the subsequent endothelial cell repair mediated by cell differentiation and proliferation. Next, gene expression has to be modified by depletion or overactivation to evaluate the participation of immediate early response genes in renal regenerative processes.

TH-PO411

Endothelial Cells of Afferent Arteriole: Novel Potential Regenerative Niche of Glomerular Endothelial Regeneration?

Meike Seitz, Jan Sradnick, Maria Schuster, Anika Wirth, Hannah Weissbach, Patrick Arndt, Christian Hugo. *Universitatsklinikum Carl Gustav Carus, Dresden, Germany*.

Background: Recent research has demonstrated that endothelial cells (EC) exhibit significant heterogeneity, displaying remarkable plasticity in both normal and pathophysiological conditions. However, the precise cellular responses of renal EC during injury and regeneration remain poorly understood. Therefore, we characterize the process of regeneration of renal EC using single-cell RNA sequencing (SC RNA-seq). This approach enables the identification of differentially expressed genes (DEG) at the single-cell level, which may facilitate the identification of potential regenerative gene patterns or niches within the renal endothelium.

Methods: EC-specific injury was induced in Tie2-eGFP reporter mice (n=48) by renal arterial perfusion with ConcanavalinA (ConA)/anti-ConA serum. Ten mice served as sham-operated controls. Kidneys were harvested at 24h, 48h, 4 days, and 7 days post-injury induction. For SC RNA-seq more than 40,000 glomerular (gEC) and peritubular (pEC) endothelial cells were isolated and further separated using fluorescence-activated cell sorting (FACS). EC damage was evaluated by endomucin staining. Bioinformatic analyses of the SC RNAseq data were conducted using the Seurat, clusterProfiler, and venn. diagram packages for R.

Results: EC injury (24 h) and remarkable regeneration (d4-d7) were observed in histology and SC RNA-seq data. In addition to known glomerular and peritubular endothelial subclusters, Gene Set Enrichment Analyses (GSEA) revealed several clusters with DEG associated with injury, a transition from injury to regeneration, remodeling, regeneration and proliferation. A strong resemblance between the regeneration cluster and the already known afferent arteriole-associated cluster was evident. 29% of the DEG of the regeneration cluster can also be found in the afferent arteriole associated cluster. A lot of these DEG are associated with regenerative processes. In contrast, only 1% of the regenerative cluster DEG can be found in the cluster linked with the EC of the efferent arteriole.

Conclusions: In conclusion, our SC RNA-seq data illuminates the transcriptional changes that occur during injury and regeneration of renal EC. The analyses strongly suggest a role of the EC of afferent arteriole in initiating or transducing regeneration processes in the renal endothelium.

TH-PO412

A New Subtype of Glomerular Capillary Endothelial Cells Was Found in the Human Glomerular Single-Cell Transcriptome

Jinjie Zhong, Qilin Chen, Shuying Li, Wan JunLi, Li Qiu. *Department of Nephrology Children's Hospital of Chongqing Medical University, Chongqing, China*.

Background: Kidney endothelial cells from different sites with different phenotypes coexist in three anatomical and functional compartments of the kidney, namely the glomerulus, the cortex and the medulla, supporting specific renal tasks. However, the heterogeneity of glomerular capillary endothelial cells (EC-GCs) is still poorly addressed and not as widely recognized as the heterogeneity of renal medullary and cortical endothelium.

Methods: We carried out scRNA-seqand spatial transcription sequencing (ST-seq) of children's kidney tissues near the cortex. Human glomeruli were rapidly enriched and human glomerular cell atlas was successfully constructed. The molecular signatures of the identified human EC-GCs were validated at the protein level. Combined scRNA-seq data from mouse glomeruli and bulk RNA-seq data from human renal disease glomeruli were synthesized and deconvoluted to clarify the alterations of different glomerular cell subtypes in disease.

Results: (1) Combined scRNA-seq and ST-seq of human kidney tissues, the human glomerular cell atlas was successfully constructed, which comprehensively demonstrated the molecular features of human glomerular cells. (2) EC-GCs might consist of a group of TOP2A$^+$EC-GCs with proliferative function, a group of EMS1$^+$EC-GCs with high expression of THBS1 and GJA1, a group of THBD$^+$EC-GCs with high expression of PTGS1 and FABP5, and a group of classical EC-GCs. (3) THBD$^+$EC-GCs was associated with shear stress, and the source of differentiation of other cellular subtypes of EC-GCs. And shear stress might be a key factor driving this differentiation. (4) The diversity of human EC-GCs identified in this study is also present in mice. Deconvolutional analysis of bulk RNA-seq of glomeruli in human kidney disease revealed that both cellular proportions and characteristic molecules of glomerular cells are significantly altered in the disease, and that a significant increase in the number of shear stress -associated EC-GCs may be among the characteristic changes.

Conclusions: EC-GCs are composed of multiple subtypes of cells with different molecular characteristics, and that shear stress -related THBD$^+$EC-GCs might be the source of the development of EC-GCs. Shear stress -associated molecular features are significantly altered in glomerular diseases, which may be the key pathological molecular features of EC-GCs.

Funding: Government Support - Non-U.S.

TH-PO413

Development of Novel Cell Therapeutic Strategies for AKI and CKD Using Human Induced Pluripotent Stem Cell (iPSC)-Derived Nephron Progenitor Cells

Toshikazu Araoka, Kosuke Toyohara, Makoto Ryosaka, Maasa Matsuura, Kenji Osafune. *Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan*.

Background: The therapeutic effect of human iPS cell-derived nephron progenitor cells (hiPSC-NPCs) on acute kidney injury (AKI) has been reported in mice but has not been clinically confirmed. No reported studies have examined the therapeutic potential of hiPSC-NPCs on chronic kidney disease (CKD). On the other hand, it was recently reported that the properties of hiPSC-NPCs differ depending on differences in iPSC lines and batches among experiments. Therefore, a large number of uniform hiPSC-NPCs are required to realize cell therapies for AKI and CKD, but effective expansion cultures remain to be developed.

Methods: We screened culture conditions that maintained the function of hiPSC-NPCs by multiple combinations of the low-molecular-weight compounds and growth factors. Furthermore, we transplanted expanded hiPSC-NPCs into the renal subcapsule of cisplatin-induced AKI model (cis-AKI) mice and aristolochic acid-induced CKD model (AA-CKD) mice and evaluated renal function and histological changes. We also administered conditioned medium (CM) produced by expanded hiPSC-NPCs to cis-AKI mice to examine the therapeutic effects, and performed mass spectrometry of CM and RNA-sequencing of hiPSC-NPCs.

Results: We established a novel expansion culture condition (CFY medium) that enables more than 1,000-fold proliferation of hiPSC-NPCs in three passages while maintaining NPC marker expression. We demonstrated that hiPSC-NPCs expanded by CFY medium attenuate kidney injury and improve survival rate in cis-AKI mice. Furthermore, we found that hiPSC-NPCs prevent kidney functional decline, interstitial fibrosis, and senescence in AA-CKD mice. In addition, the contralateral kidneys transplanted with hiPSC-NPCs in AKI and CKD mice were also treated, suggesting that the therapeutic effects of hiPSC-NPCs were due to reno-protective factors. Therefore, we administered CM produced by expanded hiPSC-NPCs to cis-AKI mice, which prevented kidney functional decline and improved survival rate. Furthermore, we identified some reno-protective factors contained in CM and demonstrated that angiogenesis in the injured kidney is involved as part of the mechanisms by which hiPSC-NPCs exert therapeutic effects.

Conclusions: The expanded hiPSC-NPCs are useful for cell therapies for AKI and CKD and will open new avenues in the treatment of kidney diseases.

Funding: Commercial Support - Rege Nephro Co., Ltd, Government Support - Non-U.S.

TH-PO414

Induced Kidney Progenitor Cells Provide a Rapid One-Pot Starting Material for Nephron Regeneration

Thomas Vincent,[1] Michael Namestnikov,[3] Benjamin Dekel,[2] Benjamin S. Freedman.[1] *[1]University of Washington, Seattle, WA; [2]Sheba Medical Center, Tel Hashomer, Israel; [3]Tel Aviv University, Tel Aviv, Israel.*

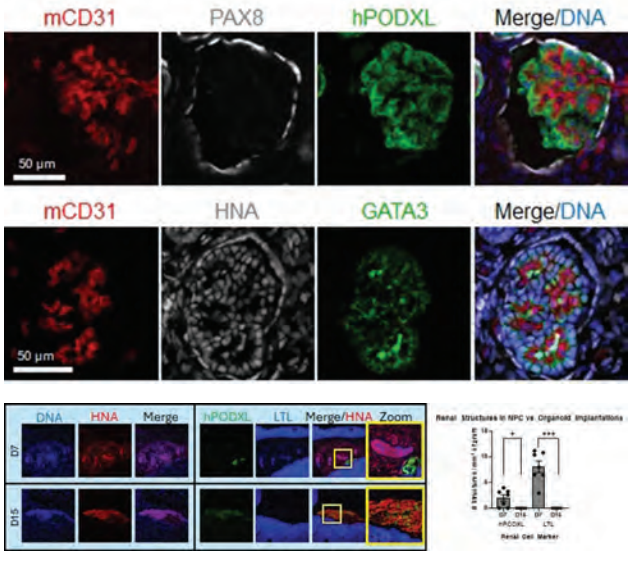
Background: For human kidney embryonic rudiment transplantation, there is an early window of opportunity that promotes enhanced graft formation. Protocols to differentiate kidney organoids from human stem cells mimics *in vivo* organogenesis as cells progress through intermediate mesoderm, metanephric mesenchyme, and progenitor cell stages. This raises the possibility of achieving tissue engineered therapeutics to restore renal function. We therefore tested the impact of early organoids on patterns of *in vivo* engraftment.

Methods: Organoids were differentiated from stem cells using a brief CHIR pulse. Cells were characterized temporally through qPCR and immunofluorescence staining. Implanted material was collected at multiple timepoints (days 4, 7, and 15) by scraping cells from an adherent 24-well plate. These pellets were inserted beneath the kidney capsules of NOD-SCID mice. Kidneys were excised after 3-weeks and analyzed through immunofluorescent staining.

Results: Here we show that 4 days of differentiation generates an induced metanephric mesenchyme-like population. When implanted beneath the kidney capsule, they develop into well-vascularized glomeruli containing human podocytes and GATA3$^+$, PDGFRβ$^+$ mesangial cells contiguous with tubular structures (**Fig 1**). Implanting of d7 cells consistently produced grafts with more PODXL$^+$ and LTL$^+$ structures than d15 late-stage kidney organoid implantations (**Fig 2**).

Conclusions: These results suggest using progenitor cells as starting material may have advantages in the development of future therapeutics over late-stage organoids. We are currently working to use these engraftments to study drug delivery and create novel disease models. In the future, we hope to address challenges related to distal tubule connections in order to achieve successful urine drainage from the graft and begin to assess function.

Funding: NIDDK Support, Other U.S. Government Support



TH-PO415

Phase 3 Clinical Trial Candidate Rilparencel Demonstrates Consistent Phenotypic Characteristics during Ex Vivo Culture Expansion Process

Evan Trudeau, Andrew T. Bruce, Dominic M. Justewicz. Bioanalytical Development. *ProKidney, Morrisville, NC.*

Background: A variety of transitional cell states allow for kidney cell replacement. This regenerative heterogeneity challenges the assessment of renal identity. We characterize rilparencel, a renal autologous cell therapy, to elucidate its cellular dynamics during bioprocessing.

Methods: Banked source material and drug product samples from the manufacture of rilparencel from kidney biopsies of five patients with T2D and CKD (NCT02836574, investigative clinical trial of T2D with stage 3a-4 CKD) were evaluated using reagents specific for canonical renal cell markers associated with tissue healing. Comparison followed with samples from discarded kidneys (n=3; National Disease Research Interchange) and key reference cells (ATCC). Cell composition was evaluated by flow cytometry using BD FACS Lyric and analysis by FlowJo and FlowSOM.

Results: Epithelial cells making up rilparencel maintain their renal identity throughout the manufacturing process, showing colocalization and biological activity of anchored cell markers of the proximal tubule (*e.g.*, GGT, CD13, EpCAM). CD146 expression, a reliable marker of tubular cells, was also confirmed – it is essential for kidney vasculature development (*i.e.*, epithelial and endothelial cell differentiation). This along with data for CD151 and CD156c suggests that rilparencel may play an important role in migration and remodeling within the host tissue. Complementary is the dynamic appearance of an array of key indicators of repair-related biological processes (*e.g.*, self-renewal, regulation of proliferation, cell re-/de-differentiation, and epithelialization, including CD24, CD44, CD90, CD133, CD106, Pax2, and Bmi-1) which may be self-protective against further renal damage in the host patient. Further, there is genomic stability (*e.g.*, cell cycle and DNA content) and absence of cellular senescence (*e.g.*, CD74-negative). Finally, the cell phenotype of rilparencel, manufactured from diseased kidney tissue, resembles that found in batches made from reference control cells.

Conclusions: The autologous cell-based therapeutic rilparencel shows a robust potential for successful kidney restoration, providing a roadmap to unveil mechanisms(s) of action.

Funding: Commercial Support - ProKidney

TH-PO416

Protective Effect of Tonsil-Derived Mesenchymal Stem Cells on Peritoneal Fibrosis by Inhibiting Oxidative Stress

Duk-Hee Kang, Dal-Ah Kim, Chor ho Jo. *Ewha Womans University College of Medicine, Seoul, Republic of Korea.*

Background: Mesenchymal stem cells (MSCs) have regenerative capability and exert paracrine actions on damaged tissues and have recently received a new attention due to its preventive effect on organ fibrosis by inhibiting epithelial-to-mesenchymal transition (EMT). The EMT of mesothelial cells (MCs) is an early mechanism of peritoneal dysfunction in peritoneal dialysis (PD). This study was undertaken to investigate the role of Tonsil-derived MSCs (T-MSCs) in TGFβ-induced EMT of human peritoneal mesothelial cells (HPMCs) and its mechanism.

Methods: Transwell co-culture system was used in which MCs were cultured with T-MSCs or T-MSC-conditioned medium (T-MSC-CM). EMT was evaluated by the changes in morphology and markers of epithelial and mesenchymal cells. ROS generation was assessed by DCF-DA and MitoSox^R staining. Animal model of PD was established by daily infusion of 4.25% glucose-based dialysate with methylglyoxal for 3 weeks via intraperitoneal catheter in Sprague-Dawley rats. T-MSC (1.0 x 10^7cells, i.p.) was injected at 14 days of catheter insertion, and peritoneal tissue was isolated in 7 days of T-MSC injection. Markers of oxidative stress, ER-stress, apoptosis, and NLRP3 inflammasome were evaluated with peritoneal equilibrium test (PET) and histologic analysis.

Results: Co-culture of HPMCs and T-MSC or T-MSC-CM inhibited TGFβ-induced EMT (increased ZO-1 and E-cadherin and decreased αSMA) and oxidative stress (decreased ROS generation). In PD, T-MSCs alleviated EMT and peritoneal fibrosis and reduced Bax, cleaved caspase and increased Bcl-2, and also decreased 8-OHdG with an increase in GSH and SOD2. T-MSC led to a decrease in proteins of ER stress and NLRP3 inflammasome. T-MSCs treated rats had a higher D_2/D_0 glucose and a lower D_2/P_2 creatinine. Anti-human nuclei staining revealed scattered positive staining along peritoneal mesothelial layer.

Conclusions: T-MSCs represent a promising approach to prevent peritoneal fibrosis by providing anti-fibrosis and anti-oxidant effects in the peritoneal cavity and ameliorating the phenotype transition of peritoneal mesothelial cells.

Funding: Government Support - Non-U.S.

TH-PO417

Thrombomodulin-Overexpressing Adipose-Derived Mesenchymal Stem Cells Prevent Thromboembolism and Ameliorate Kidney Fibrosis in Rats

Yoshiki Tanaka,[1] Ayumu Nakashima,[3] Naoki Ishiuchi,[2] Kisho Miyasako,[1] Keisuke Morimoto,[1] Kensuke Sasaki,[2] Takao Masaki.[2] *[1]Hiroshima Daigaku Daigakuin Ikei Kagaku Kenkyuka, Hiroshima, Japan; [2]Hiroshima Daigaku Byoin, Hiroshima, Japan; [3]Yamanashi Daigaku, Kofu, Japan.*

Background: Adipose-derived mesenchymal stem cells (ASCs) exhibit anti-inflammatory and anti-fibrotic effects via their paracrine action, and thereby are expected to be a new therapy for kidney disease. Meanwhile, ASCs reportedly exhibit procoagulant activity compared to other mesenchymal stem cell types, raising concerns about thrombogenic risk. Thrombomodulin (TM) on the cell surface acts as an anticoagulant and antifibrinolytic factor by binding to thrombin, a procoagulant factor. This led us to the hypothesis that ASCs overexpressing TM can be safely used for cell therapy by reducing the risk of thromboembolism.

Methods: ASCs infected with adeno-associated virus (AAV) carrying TM cDNA or an empty AAV were designated as "TM-ASC" or "null-ASC", respectively. To examine the risk of renal infarction induced by ASCs, 5.0×10^5 ASCs were administered via renal artery into rats with unilateral ischemia reperfusion injury (IRI) and contralateral nephrectomy (renal infarction model). To assess the risk of pulmonary embolism caused by ASCs, 7.5×10^6 ASCs were injected into rats via tail vein (pulmonary embolism model). Additionally, we examined the anti-inflammatory and anti-fibrotic effects of TM-ASC using IRI rats treated with TM-ASC and null-ASC.

Results: In the renal infarction model, 36% (n = 4/11) of the rats in the null-ASC group died by day 3, whereas all of rats (n = 11/11) in the TM-ASC group were alive. In the pulmonary embolism model, 40% (n = 3/12) of the rats in the null-ASC group died within 24 hours, while all of rats (n = 12/12) in the TM-ASC group were alive. Intravascular thrombus was identified in 30/120 fields in the null-ASC group and decreased to 3/120 fields in the TM-ASC group in hematoxylin and eosin staining of rat lung tissues. In addition, administration of TM-ASC more potently alleviated renal inflammation and fibrosis induced by IRI compared to that of null-ASC.

Conclusions: These findings indicate that TM-overexpressing ASCs not only increase treatment safety, but also enhance their therapeutic efficacy. Administration of TM-overexpressing ASCs is a promising therapeutic strategy to prevent progression from organ damage to failure.

TH-PO418

Mesenchymal Stem Cells Overexpressing Tumor Necrosis Factor α-Induced Protein 6 Have an Enhanced Inhibitory Effect on Kidney Fibrosis

Keisuke Morimoto,[1] Ayumu Nakashima,[2] Naoki Ishiuchi,[3] Kisho Miyasako,[1] Yoshiki Tanaka,[1] Kensuke Sasaki,[3] Takao Masaki.[3] *[1]Hiroshima Daigaku Daigakuin Ikei Kagaku Kenkyuka, Hiroshima, Japan; [2]Yamanashi Daigaku, Kofu, Japan; [3]Hiroshima Daigaku Byoin, Hiroshima, Japan.*

Background: Acute kidney injury (AKI) is involved in subsequent chronic kidney disease (CKD) development, and effective treatments to prevent AKI to CKD progression are lacking. Mesenchymal stem cells (MSCs) are emerging as a promising cellular therapy to impede such progression. MSCs repair injured tissue through secretion of various humoral factors. Among these factors, tumor necrosis factor-α-induced protein 6 (TSG-6) has a central role in the anti-inflammatory effects of MSCs. However, the mechanisms by which MSCs secrete TSG-6 and exert anti-inflammatory effects are not fully clarified. In this study, we investigated these mechanisms using TSG-6-overexpressing MSCs.

Methods: MSCs infected with an adeno-associated virus carrying TSG-6 cDNA or an empty adeno-associated virus were designed as TSG-6 MSCs and null MSCs, respectively. Extracellular vesicles (EVs) were isolated from MSC culture supernatants by ultracentrifugation. MSCs were injected through the abdominal aorta into rats with ischemia-reperfusion injury (IRI) to evaluate their anti-inflammatory and anti-fibrotic effects. We also examined whether TSG-6 secreted from MSCs affected polarization of monocytic THP-1 cell-derived macrophages to the immunosuppressive M2 phenotype. Additionally, we explored natural compounds that increased TSG-6 expression in MSCs.

Results: Most TSG-6 was immediately secreted in EVs and was not stored intracellularly. Administration of TSG-6 MSCs more strongly suppressed renal fibrosis and inflammation in IRI rats than null MSCs. Although EVs and conditioned medium from TSG-6 MSCs (TSG-6 MSC-CM) strongly promoted polarization of M2 macrophages, TSG-6 MSC-CM after EV depletion promoted it only slightly. Moreover, TSG-6 MSC-CM enhanced regulatory T cell induction. Additionally, MSCs treated with indole-3-carbinol had enhanced TSG-6 expression and markedly suppressed IRI-induced renal fibrosis.

Conclusions: TSG-6 is secreted in EVs from MSCs and exerts potent anti-inflammatory effects by promoting M2 macrophage polarization and regulatory T cell induction. Administration of MSCs with enhanced TSG-6 secretion is a promising therapeutic strategy to impede AKI to CKD progression.

TH-PO419

Efficient and Programmable Particle Delivery for Genome Editing in Human Kidney Organoids

Nicole Vo, Benjamin S. Freedman. *University of Washington, Seattle, WA.*

Background: Kidney organoids are complex structures that resemble nephrons and can be used to develop gene therapy approaches. Gene editing in organoids, much like in tissues, has great potential but currently suffers from inefficiency and lack of specificity. There is a critical need for the development of methods for efficient and precise genome editing.

Methods: We developed CaSh (Calcium Shock), a method that improves transfection and transduction, and CaSh-Pro, a programmable version that targets specific cell types. To enable better detection of genome editing events, we developed a fluorescence-on (tdTomato) reporter system in human iPS cells. Intact kidney organoids were transfected with CRISPR ribonucleoprotein (RNP) complexes. To improve delivery, identified molecular targeting agents (MTAs) specifically recognizing podocytes, proximal tubules, or endothelial cells in live imaging assays, and tethered these to Cas9. Genome editing events or adeno-associated virus (AAV) transduction were detected by changes in fluorescence in specific cell types.

Results: CaSh dramatically improved genome editing by CRISPR-Cas9 ribonucleoprotein from ~ 2% in organoids without CaSh to 15% with CaSh. CaSh-Pro, which incorporates specific MTAs, resulted in substantially enhanced editing in the targeted cell types of podocytes (~12%) (**Figure 1**) or tubules (~5%), as detected by tdTomato co-localization with a specific marker, relative to negative controls including untreated, no MTA, or generic IgG. Finally, CaSh improved transduction of AAV8 encoding a red fluorescent reporter protein into proximal tubular epithelial cells, resulting in ~15% efficiency at 1 x 10^5 genome copies (gc)/cell, compared to negative controls.

Conclusions: CaSh and CaSh-Pro provide versatile protocols for biological discovery, therapeutics development, and genome editing. Our innovative method improves specificity and efficiency enabling a wide variety of potential applications such as testing gene therapies in specific cell types as a surrogate for tissues. Gene editing can be achieved in a clinically effective range (> 10%) and in specific cell types, enabling future studies of phenotypic rescue in human models.

Funding: NIDDK Support

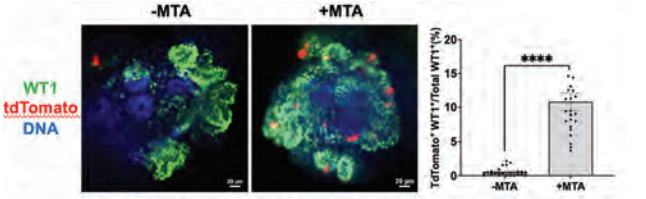


Figure 1: CaSh-Pro enables programmable editing of specific cell types in human organoids.

TH-PO420

Genome Therapy in Kidney Organoids Reveals that Canonical NFκB Signaling Governs Tubular Senescence, Cytotoxicity, and Immunogenicity in Response to Adeno-Associated Viruses (AAV)

Navin R. Gupta,[1] Haruka Oishi,[2] Kenta Inomata,[2] Ryuji Morizane.[2,3] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Massachusetts General Hospital, Boston, MA; [3]Harvard University Wyss Institute for Biologically Inspired Engineering, Boston, MA.*

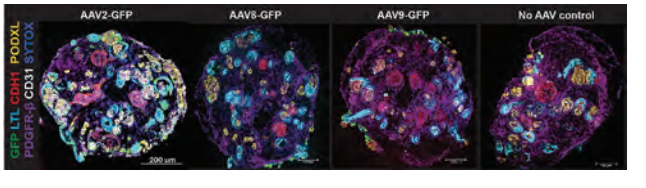
Background: Genome therapy is revolutionizing the treatment of inherited diseases by directly editing the human genome. Due to its potential to irreversibly alter human DNA, systemic gene therapy raises significant concerns, demanding a new approach to preclinical evaluations. These concerns are further illustrated by recent tragedies in clinical trials, which have led to organ failures and patient fatalities. Due to high blood flow, the kidney emerges as a focal point for drug-related toxicity.

Methods: Human stem cell-derived kidney organoids are nephron-rich, highly structured 3-dimensional tissue capable of exocrine and endocrine functions, have modeled human genetic and non-genetic disease, kidney injury and repair, and nephrotoxicity testing. Here we use kidney organoids as a pre-clinical platform for CRISPR genome editing via adeno-associated virus (AAV) delivery, a common genome editing strategy in clinical trials that have raised safety concerns. Although AAV is of limited pathogenesis in humans, clinical use has required supraphysiologic titers often met with toxicity.

Results: Kidney organoids validated the tropism of differing AAV serotypes for human kidney. Applying immunostaining to organoid cryosections and electrochemiluminescence-based mesoscale discovery to their supernatants, we found that AAV drives tubular genotoxicity, cytotoxicity, and immunogenicity. RNA-sequencing identified an association between tubular injury and IL-1β activation of the canonical NFκB pathway. Targeted inhibition of canonical NFκB signaling prevented the fibrotic loss of nephrons by ameliorating $p21^+$ senescence in injured tubules.

Conclusions: Our findings demonstrate the translational utility of kidney organoids as a pre-clinical testing platform for genome therapy, which may inform clinical trials of strategies that limit organ failures and death.

Funding: NIDDK Support



TH-PO421

Metabolic Responses in Human Kidney Organoids to Tumor Necrosis Factor-Alpha Stimulation: Integration of Proteomic and Metabolomic Signatures

Moritz Lassé,[1] Jennifer L. Harder,[3] Sandra D. Laufer,[1] Fabian Braun,[1] Markus M. Rinschen.[1,2] Rinschen Lab. *[1]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Aarhus Universitet, Aarhus, Denmark; [3]University of Michigan Michigan Medicine, Ann Arbor, MI.*

Background: Tumor necrosis factor-alpha (TNF-alpha) is a cytokine involved in systemic inflammation and has a profound impact on metabolic processes within cells. Studying its effects on kidney cells using organoids can reveal insights into renal inflammatory responses and metabolic dysregulation associated with kidney diseases. This study aimed to identify and analyze the metabolic shifts in human kidney organoids following TNF-alpha treatment, focusing on energy metabolism, amino acid metabolism and generation of uremic toxins.

Methods: TNF-alpha exposed Kidney organoids were analyzed using proteomics and targeted metabolomic mass spectrometric analyses. Altered metabolites were integrated with proteome-scale networks. We quantified changes in key catalytic enzymes and metabolites involved in major metabolic pathways including the citric acid cycle, amino acid metabolism, and the production of known uremic toxins.

Results: TNF-alpha stimulation resulted in significant metabolic rewiring of the organoid cells. We observed altered protein expression upon TNF-alpha exposure, particularly in amino acid, energy, and nucleotide metabolism. Top proteins involved were associated with adverse clinical outcomes in proteinuric disease in the NEPTUNE cohort. Enhanced energy demand was evident by an increased production of TCA cycle metabolites. Crucially, we also detected increased metabolite markers of kidney injury, inflammation, amino acid metabolism and apoptosis to be upregulated. Conversely, there was a marked decrease of metabolites related to energy production, nucleotide synthesis, and protein synthesis. These downregulated metabolites highlight a possible reduction in biosynthetic and energy-related processes under inflammatory conditions. Altered metabolites were integrated with proteome-scale networks.

Conclusions: TNF-alpha induces complex metabolic responses in human kidney organoids, characterized by orchestrated response of shifts in critical metabolites across various pathways. The observed metabolic reprogramming may represent an adaptive response to inflammation or a pathogenic mechanism contributing to disease progression. These findings emphasize the importance of renal metabolic responses to inflammation and may guide future therapeutic strategies targeting metabolic disturbances in kidney diseases.

TH-PO422

Neonatal Kidney Stem/Progenitor Cells (nKSPCs) Downregulate Activation of Human Neutrophils In Vitro

Junyu Chen,[1,2] Mieke Gouwy,[2] Paul Proost,[2] Sara Akalay,[2] Hildo C. Lantermans,[1] Lambertus P. Van den Heuvel,[3,2] Fanny O. Arcolino,[1] Elena Levtchenko.[1] Translational Paediatric Nephrology. *[1]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [2]Katholieke Universiteit Leuven, Leuven, Belgium; [3]Radboud Universiteit, Nijmegen, Netherlands.*

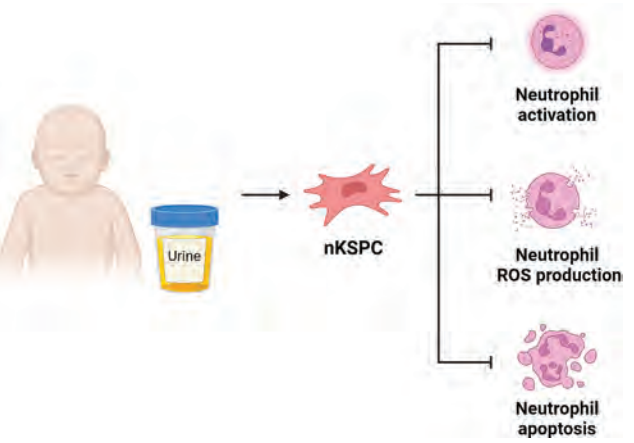
Background: Neonatal Kidney Stem/Progenitor Cells (nKSPC), a novel type of kidney progenitor cell, isolated from urine of preterm neonates, have demonstrated immunoregulatory capacity and can inhibit proliferation of T-lymphocytes in mixed lymphocyte reaction. Our group is testing nKSPC as a potential source of cell therapy in the context of kidney transplantation. Neutrophils play important roles in ischemia-reperfusion injury (IRI), a common occurrence in kidney transplantation. In this study, we examined the capacity of nKSPC to inhibit human neutrophils *in vitro*.

Methods: Freshly isolated neutrophils activated by TNF-α were co-cultured with nKSPC at varying ratios (10:1 to 500:1). CD16 and CD66b as markers related to neutrophil activation were measured by Fluorescence-Activated Cell Sorting (FACS). Apoptosis was analyzed by Annexin V assay in FACS. Assessing neutrophil-produced reactive oxygen species (ROS), we employed a Luminol assay under multiple stimuli (TNF-α, IL-1β, fMLF, PGN). Neutrophil chemotaxis was investigated by Boyden chamber assay.

Results: Neutrophils, stimulated by TNF-α, exhibit increased CD66b and decreased CD16 expression, indicating activation. TNF-α also induced apoptosis of neutrophils. Co-culturing with nKSPC significantly reduced TNF-α-induced neutrophil activation and apoptosis. TNF-α, IL-1β, fMLF, and PGN stimulation promoted ROS production in neutrophils, and a co-culture with nKSPC inhibited this induction. Neutrophil chemotaxis induced by TNF-α was not inhibited by nKSPC.

Conclusions: Our *in vitro* data show the immunomodulatory capacity of nKSPC on neutrophils with decreased activation, reduction of apoptosis and abolishing ROS production.

Funding: Government Support - Non-U.S.



TH-PO423

Progressive Tubulointerstitial Damage through Constitutive Activation of the NF-kB Pathway in Renin Lineage Cells

Irina Simonova,[1] Florian Gembardt,[1] Anne Steglich,[1] Jan Sradnick,[1] Vladimir T. Todorov,[1,2] Christian Hugo.[1] Working Group Hugo, University Clinic Carl Gustav Carus, Dresden. *[1]Universitatsklinikum Carl Gustav Carus, Dresden, Germany; [2]Universitat Witten/Herdecke Institut fur Physiologie und Pathophysiologie, Witten, Germany.*

Background: NF-κB (Nuclear factor κB) is a family of related transcription factors that play a pivotal role in many inflammatory processes including immune mediated kidney disease potentially linking inflammation, injury or regeneration. Various inflammatory signals activate NF-κB through TNF (tumor necrosis factor) and other cyto- and chemokine, B or T cell receptors. Activated IKK (inhibitor of NF-kB kinase) complex plays a major role in degradation of IκBα(NF-kB inhibitor α) after which the NF κB dimer p65/ RelA translocates to the nucleus and activates inflammatory genes. We investigated the impact of NF-κB(IKK) activation specifically in RLC (renin-lineage cells) well known as an important niche involved in regeneration and replacement of damaged mesangial and epithelial cells of the murine kidney. RLC of adult mice make up about 10% of all kidney cells including JGA, mesangial, epithelial and smooth-muscle cells

Methods: We created transgenic mouse line mRen-Cre-IKKca with targeted overexpression of IKK2 in RLCs leading to constitutive activation of the NF-kB pathway. The data were collected at 1, 3 and 6 months of age for IKK2 and WT male and female animals. We analyzed functional parameters, morphological changes (PAS) and the expression of Renin, aSMA,Na+/K+ ATPase, SLC4A4, AQP1, AQP2, AE1, Calb1, serum and 24h urine samples

Results: Data showed in IKK2 mice significant increase of urine volumes (in WT μ=1850ml, in IKK2 μ=5186ml) as well as α1-Microglobulin amounts in 24h urine(in WT μ=1.12μg, in IKK2 μ=14.24μg) already at the age of 3M compared to WT but slight rise of urine albumin amounts only at 6M. PAS stainings demonstrated progressive tubulo-interstitial damage solely in mRen-Cre-IKKca mice starting at 3M of age. IHC staining of AQP2 (principal cells in collecting duct) was significantly reduced at 3M and 6M compared to WT. Other markers will clarify these changes

Conclusions: Our study reveals a profound renal phenotype of mice with NF-kB pathway activation specifically in RLCs linking this inflammation signaling with progressive injury and insufficient regeneration. The transgenic mice developed tubulo-interstitial damage starting at 3M of age(increased α1-Microglobulin, PAS, concomitant reduction of AQP-2) while only slight albumin rise at 6M indicates that glomerular changes appear later and less severe

Funding: Government Support - Non-U.S.

TH-PO424

Renal Progenitor Cells Isolated from Urine of Patients with IgA Nephropathy Formed Renal Spheroids That Can Recapitulate Typical IgA1 Deposition

Fabio Sallustio,[1] Francesca Giannuzzi,[1] Angela Picerno,[1] Silvia Maiullari,[1] Francesca Montenegro,[1] Antonella Cicirelli,[1] Alessandra Stasi,[1] Giuseppe De Palma,[2] Giovanni B. Pertosa,[1] Paola Pontrelli,[1] Michele Rossini,[3] Vincenzo Di leo,[1] Mariella Errede,[1] Roberto Tamma,[1] Domenico Ribatti,[1] Loreto Gesualdo.[1] *[1]Universita degli Studi di Bari Aldo Moro, Bari, Italy; [2]Istituto Tumori Bari Giovanni Paolo II IRCCS, Bari, Italy; [3]Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy*.

Background: The creation of renal spheroids and organoids from stem cells represents a suitable model for drug studies and in the simulation of nephrotoxicity and renal disease. However, it requires the use of sophisticated differentiation protocols and the administration of growth factors with a precise temporal order. Here we show that adult human renal progenitor cells (ARPCs) isolated from the urine of healthy subjects or patients with IgA Nephropathy (IgAN) can form spheroids and long tubular-like structures naturally, recapitulating typical IgA1 deposits.

Methods: Spheroids and tubular-like structures were generated by using an ARPC mixed cell population method and characterized by immunofluorescence and flow cytometry, using CD133, NanoG, Oct3/4, GATA-3, SSEA4, CD249, Aminopeptidase N, ZO-1, Uromodulin, and Lotus antibodies. ELISA;CAM assays; PKH-26 labeling was used for cell tracking.

Results: Spheroids derived from ARPCs without the use of chemokines or growth factors generated very long tubular-like structures that expressed structural and functional markers of renal tubules sharing structural similarities with regions of nephrons, such as the distal convoluted tubule, loop of Henle and the proximal convoluted tubules. Furthermore, the spheroids secreted high levels of renin and exhibited angiogenic properties. To study whether spheroids derived by urinary ARPCs can be used to establish in vitro models recapitulating renal diseases, we generated IgAN patient-specific renal spheroids. ARPCs formed spheroids in which IgA1 deposits could be observed after 4, 8 and 15 days of culture with patient serum (p=0.004, p=0.0029 and p=0.0012, respectively). In contrast, no positive signal was detected either with inactivated IgAN serum or in spheroids derived from the urine of healthy patients cultured with IgAN serum.

Conclusions: The ability of urinary ARPCs to form spheroids and differentiate into tubular-like structures without the need for external chemokines is a significant advancement in the field, opening new avenues in the study of pathological mechanisms and in the for regenerative medicine for kidney diseases.

Funding: Government Support - Non-U.S.

TH-PO425

Study Sex Differences in Genetic Kidney Diseases Using Organoid Xenotransplantation Model

Yun Xia. *Nanyang Technological University, Singapore, Singapore*.

Background: Chronic kidney disease (CKD) affects about 10% global population, with higher prevalence in women but faster progression in men. A deeper understanding of how the interplay between genetic sex and systemic sex hormones modifies human kidney disease constitutes a pivotal advancement toward precision medicine, which promises equitable benefits for women (including pregnant women), men, and transgender individuals alike. Despite mounting evidence that sex disparity must be taken into consideration in studying human kidney diseases and developing therapies, limited progress has been made due to the lack of suitable experimental models.

Methods: In this study, we harness this organoid xenotransplantation methodology to investigate the combined effects of genetic sex and systemic sex hormones on human genetic kidney disease. Single cell RNA-sequencing (scRNAseq), genetic perturbation, and pharmacological interference are employed to dissect the mechanism underlying sex differences manifested in different sex contexts.

Results: Induced pluripotent stem cells (iPSCs) derived from patients with autosomal recessive PKD (ARPKD) and autosomal recessive PKD (ARPKD) can be differentiated into kidney organoids. scRNAseq of kidney organoids detected enriched expression of androgen and estrogen receptors in the proximal tubule. Upon xenotransplantation into immunocompromised mice, kidney organoid grafts grown in male mice exhibited higher cystic index compared with the same patient iPSC derived kidney organoids grafted in female mice. Analyses of kidney organoid grafts revealed increased tubular injury, proliferation, and activation of androgen signalling in kidney organoids grafted in male host mice, compared with those grafted in female host mice. Genetic ablation or pharmacological inhibition of androgen receptor effectively inhibited cyst severity. Comparatively, genetic sex of the kidney organoid itself showed less impact on the severity of cystogenesis.

Conclusions: Organoid xenotransplantation model represents a feasible platform to comprehend sex disparity in human diseases, to distinguish the impact of genetic sex on human diseases from those imparted by systemic sex hormones, as well as to test candidate therapeutics targeting principal sex hormone signalling pathways for treating human diseases.

TH-PO426

Sexual Dimorphism in the Regenerative and Polyploid Response of Kidney Tubule during Aging

Elena Lazzeri, Giulia Antonelli, Giulia Carangelo, Paola Romagnani. *Universita degli Studi di Firenze, Firenze, Italy*.

Background: Kidney function declines with age, leading to chronic kidney disease (CKD). Although a higher prevalence of CKD in females, men experience a faster CKD progression. The cellular mechanisms underlying this difference in CKD development during ageing remain to be clarified. A link has been hypothesized between a regenerative and polyploid response and ageing. Whereas the decline in the regenerative potential of stem cells is associated with tissue ageing, the increase of polyploidy preserves tissue function during ageing. In the kidney, a regenerative and polyploid response takes place after AKI. Whereas renal progenitors (RPC) generate new tubular cells (TC) to recover structural integrity, TC enter alternative type of cell-cycle to become polyploid and to recover kidney function. Here, we aimed to investigate how these two adaptive responses act differently in females and males during ageing.

Methods: Female and male mice were analyzed at 2, 6, 12, 20 months of age. Pax2/Confetti mice were used to study the regenerative response driven by RPC (Pax2+cells). Pax8/FUCCI2aR and h-Pax8/Confetti mice were used to study the polyploid response. In the first one polyploid TC are identified by combining DNA content with FUCCI2aR technology. In the second one polyploid TC are identified as multicolored TC following recombination of Confetti reporter genes. scRNAsequencing was performed in female and male mice at 2 and 20 months of age.

Results: During ageing, male mice experienced an earlier and faster kidney function decline than females. Pax2/Confetti mice revealed that females were endowed with a higher number of RPC, which have a greater capacity to expand clonally, showing a better regenerative capacity than males during ageing. Analysis of the polyploid response in Pax8/FUCCI2aR and in h-Pax8/Confetti mice revealed that whereas the polyploid fraction increased in aged females, it was reduced in aged males. Indeed, polyploid TC in aged males accumulated DNA damage, which resulted in additional rounds of polyploidization, genetic instability and death. scRNAsequencing analysis profiled the ageing-related stress responses of polyploid TC in aged males.

Conclusions: These insights might explain why females are more capable to compensate kidney function decline, whereas males are more susceptible to an earlier and faster progression to CKD during ageing.

TH-PO427

Bowman Capsular Laser Irradiation Induces Parietal Migration of Renin Cells in Longitudinal Three-Dimensional Intravital Microscopy

Patrick Arndt,[1] Jan Sradnick,[1] Shila Azizolli,[1] Sagor Halder,[1] Vladimir T. Todorov,[1,2] Christian Hugo.[1] *[1]Experimental Nephrology, Division of Nephrology, Department of Internal Medicine III, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; [2]Institute of Physiology and Pathophysiology, Center of Biomedical Education and Research (ZBAF), Faculty of Health - School of Medicine, Witten/Herdecke University, Witten, Germany*.

Background: Renin cells reside in the juxtaglomerular apparatus and serve as progenitors capable of migrating into the glomerulus following injury. These glomerular repair processes involve an individual intraglomerular-juxtaglomerular feedback mechanism. Using longitudinal intravital microscopy and a laser injury model to induce localized damage in individual glomeruli allows for controlled observation of repair processes. Laser irradiation of the Bowman capsule provides further insights into the migration processes of renin cells modeling glomerular damage and tubulointerstitial injures similar to Bowman capsule rupture in ANCA-associated GN.

Methods: Renin tdTomato reporter mice were subjected to doxycycline treatment for 3 weeks. Intravital microscopy was performed through an implanted body window using an upright 2-photon microscope for 3 hours on day 1 and after 96 hours. Laser injury was induced by focusing 100% laser power for 5 to 20 seconds at 12x to 48x zoom on one Z-plane. 3D processing was performed with Bitplane Imaris 10.1. Tdtomato+ cells and parietal epithelial cells were identified through immunohistochemistry in PFA-fixed kidney cryosections.

Results: The targeted use of a laser injury model induced reproducible capsular and trans-capsule injuries in murine nephrons. In 39 nephrons with capsular injury, renin cells migrated parietally in 36% and intraglomerularly towards the laser irradiated area in 41% of all cases. In 8 nephrons (20%), the renin cells migrated both parietally and intraglomerularly. No migration occurred in 23% of the nephrons with capsular injury. Migrating renin cells were able to connect to capsular injuries opposite from the juxtaglomerular apparatus with a tdTomato signal chain keeping contact to their niche of origin.

Conclusions: Longitudinal intravital microscopy combined with a capsular-targeted laser injury model and 3D image analysis in transgenic mice revealed an additional pathway for renin cell migration. Besides direct migration towards intraglomerular injuries, renin cells are also capable of parietal migration towards capsular damage linking

them to glomerular-tubulointerstitial regeneration. Further research may investigate the juxtaglomerular feedback system of renin cell recruitment/migration, transdifferentiation and regenerative site-specific responses.

Funding: Government Support - Non-U.S.

TH-PO428

Abstract Withdrawn

TH-PO429

Navigating the Translation of LoAc Compound Efficacy in ADPKD

David J. Henderson,[1] Julia M. Adam,[1] Xiaofang Wang,[2] Claire Whitworth,[1] Susan Macdonald,[1] Li Jiang,[2] Tom Moore,[1] Catherine L. Kelleher,[1] Vicente E. Torres,[2] Adele Rowley.[1] *[1]Mironid Ltd, Glasgow, United Kingdom; [2]Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Elevated cAMP signalling is known to promote cystogenesis in Autosomal Dominant Polycystic Kidney Disease (ADPKD). Phosphodiesterase 4 (PDE4) enzymes degrade cAMP and contribute to its compartmentalized signalling. We have previously described novel small molecules (LoAc®) that allosterically activate long isoforms of PDE4 and lower intracellular cAMP both *in vitro* and *in vivo*. Here we discuss translation of the LoAc® approach from bench to bedside, with an emphasis on differentiation and on biomarker development.

Methods: The effects of LoAc® compound MR-L22 were examined in the *Pkd1*$^{RC/RC}$ mouse model of ADPKD, dosed once daily by oral gavage from post-natal weeks 4-16. Test groups were compared to groups receiving vehicle alone or tolvaptan. Urinary biomarker assays were conducted in Han Wistar rats, where cAMP was measured by either ELISA or LC-MS. *Ex vivo* studies in primary human cells were used to demonstrate efficacy in samples from multiple ADPKD patient donors.

Results: LoAc® treated *Pkd1*$^{RC/RC}$ mice exhibit reduced kidney cystic indices, kidney weight/body weight ratios (Kw/Bw) and MRI measured total kidney volumes (TKV). LoAc® administration protected kidney function and despite delivering similar reductions in renal cAMP, induced less polyuria than tolvaptan. Similarly, LoAc®-driven changes in protein expression and phosphorylation overlap with, but are distinct from, those measured after tolvaptan treatment. Experiments using cells from human ADPKD donors show that LoAc® compounds not only suppress AVP-stimulated cyst expansion but also the endogenous cystic disease drive, further differentiating LoAc® from tolvaptan as well as against a range of other clinical strategies. In rats, reduced cAMP in the urine can be detected after a single oral dose of LoAc® compound and correlate with cystic disease in LoAc® treated *Pkd1*$^{RC/RC}$ mice. Urinary cAMP offers an accessible, mechanism-related, biomarker of LoAc® compound activity *in vivo* and provides important step in managing the translation of the LoAc® approach in ADPKD.

Conclusions: LoAc® compounds suppress cystic disease progression in key translational models of ADPKD and are differentiated from clinically evaluated strategies. Urinary cAMP represents an accessible biomarker of LoAc® compound activity for translation to clinical studies.

Funding: Commercial Support - Mironid Limited

TH-PO430

PYC-003, a Peptide-Conjugated Oligonucleotide for the Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Clarissa Mcdonagh, Anna Mills. PYC-003 Pharmacology Team. *PYC Therapeutics, Nedlands, WA, Australia.*

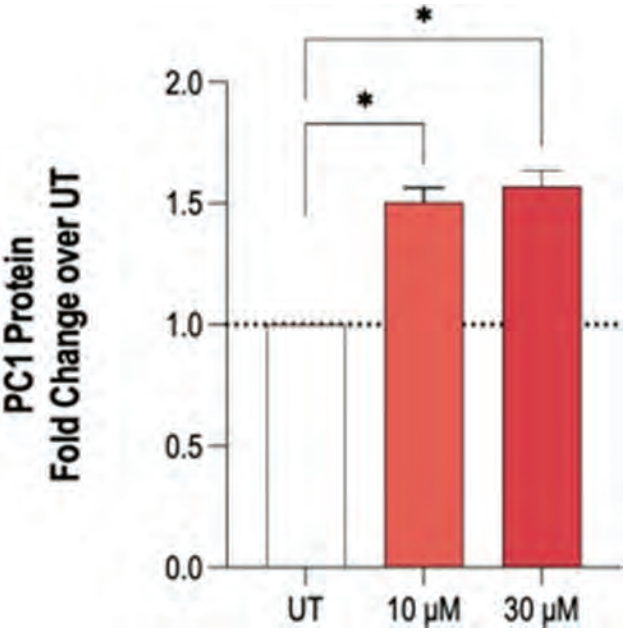
Background: ADPKD is a severe disease that causes kidney failure, affecting 1 in 1,000 people. Roughly 80% of ADPKD cases are caused by mutations in one copy of the *PKD1* gene leading to deficient PC1 protein. Addressing the root cause, PYC-003 is designed to upregulate PC1 expression.

Methods: PYC-003 effects on PC1 protein was determined by western blot and cyst shrinkage tested in 3D patient-derived models. A PYC-003 mouse surrogate molecule was intravenously injected into B6 mice where drug distribution was measured after 3 days using miRNAscope.

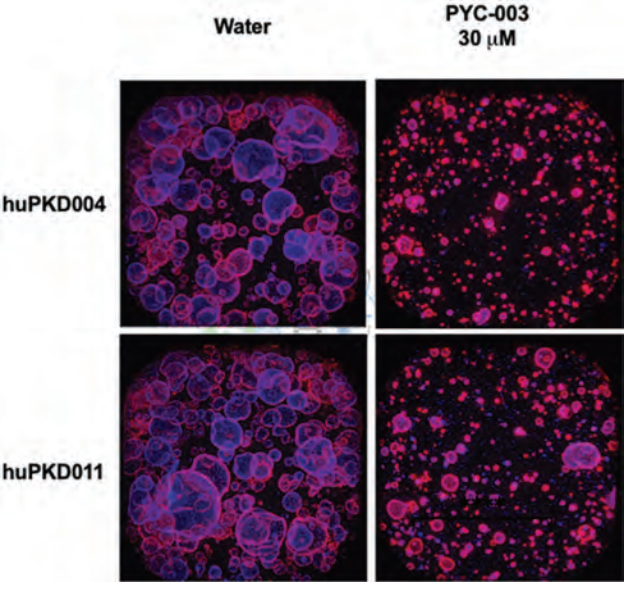
Results: PYC-003 raises PC1 protein in HEK293 cells to 1.6-fold. PYC-003 prevented cyst formation and reduces cyst area. A single dose of the PYC-003 mouse surrogate showed uniform renal distribution.

Conclusions: PYC-003 shows potential to be a treatment for ADPKD by increasing PC1 protein, preventing the formation of cysts *in vitro* and exhibiting enhanced renal delivery. PYC-003 is undergoing IND-enabling studies in preparation for anticipated clinical trials scheduled to begin in Q1 2025.

Funding: Commercial Support - PYC Therapeutics



PC1 fold-change over untreated (normalized to total protein) in HEK293 cells at day 3 following treatment of PYC-003. Mean + S.D (n=2)



ADPKD 3D cyst shrinkage after 2 treatments of PYC-003 in two patients. Nuclei (blue) and cytoskeleton (red), x4 magnification

TH-PO431

Development of a Nonviral Genetic Medicine for ADPKD Administered through Targeted Transcutaneous Ultrasound-Mediated Delivery

Margarita Krivega, Julia Poniatowski, Surabhi Rao, Elizabeth Del Greco, David Kim, Victor Foster, Oliver Chen, Bert J. Frederich, Katie Benthall, Nana Ingram, Glenda Arauz, Celia Ortiz, David Satyadi, Charles S. Levine, Jonathan Chan, Tanaya Ghosh, Belinda Cabriga, Dhruv Bole, Ivan Krivega, Steven Feinstein, Kenneth Greenberg. *SonoThera, South San Francisco, CA.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation and growth of fluid-filled renal cysts, often leading to kidney failure. The most frequent genetic cause of ADPKD are monogenic mutations in the PKD1 gene. Ultrasound mediated gene delivery (UMGD) is an effective approach for noninvasive targeted transgene delivery into renal cells, enabling the development of a nonviral gene replacement therapy for ADPKD.

Methods: Using genetic engineering and screening of next generation DNA payload formats, we developed an optimized DNA construct expressing a full-size PKD1 protein. Transgenic PKD1 expression was assessed in vitro in relevant renal cells. To evaluate

the potential of UMGD as a nonviral ADPKD treatment option, we delivered genetic constructs to the cystic kidney of an ADPKD mouse model using proprietary acoustic energy profiles and FDA-approved ultrasound components.

Results: Testing multiple variants of codon-optimized full-size PKD1 open reading frame sequences along with proximal tubular epithelial cells-specific promoter enabled robust transgenic PKD1 protein expression in ADPKD cystic cells. SonoThera's highly optimized and proprietary acoustic energy profiles has enabled the targeted delivery of optimized genetic constructs to the cells of cystic kidneys of an ADPKD mouse model.

Conclusions: High levels of tissue-specific transgenic full-length PKD1 expression along with the favorable efficacy and safety profile of ultrasound mediated transgene delivery to the cystic cells in ADPKD kidney supports further translation of this approach into clinical development for the treatment of ADPKD.

TH-PO432

Kidney-Targeted Delivery of Nonviral Nucleic Acids Using Noninvasive Transcutaneous Ultrasound Enables Safe, Re-dosable, Titratable, and Durable Gene Expression in Mice and Nonhuman Primates

Bert J. Frederich, Jonathan Chan, Surabhi Rao, Victor Foster, Adel Alonso, Celia Ortiz, Elizabeth Del Greco, Oliver Chen, David Satyadi, David Kim, Dhruv Bole, Nana Ingram, Katie Benthall, Margarita Krivega, Julia Poniatowski, Tanaya Ghosh, Belinda Cabriga, Charles S. Levine, Ivan Krivega, Kenneth Greenberg, Steven Feinstein. *Sonothera, South San Francisco, CA.*

Background: Effective kidney-targeted delivery of genetic medicines has been elusive despite significant research. Transcutaneous ultrasound-mediated gene delivery (UMGD) offers a noninvasive, targeted approach to overcome these challenges

Methods: SonoThera is developing a proprietary ultrasound-guided nonviral gene therapy platform for selective kidney targeting in a safe, redosable, durable, and titratable manner. In vivo bioluminescence imaging of firefly luciferase reporter gene expression was conducted using an IVIS imaging system at various time points in the kidneys of both wild-type and polycystic kidney disease (Nek8JCK) mouse models. Kidney tissue obtained from mice and nonhuman primates was analyzed for reporter gene presence and expression using ddPCR, RNAscope, snRNA-seq, and immunohistochemistry. Multiple clinical and molecular safety assessments were conducted in mice and nonhuman primates using established methods.

Results: SonoThera's UMGD platform enabled robust, durable, redosable, and titratable transgene expression in wild-type mouse kidneys, with durable gene expression observed for over a year following a single treatment. Renal disease-relevant cell types including podocytes, tubular epithelial cells, and endothelial cells were effectively transfected in mice and nonhuman primates. Robust delivery and transgene expression were confirmed in the polycystic kidney mouse model (Nek8JCK). Safety assessments, including clinical observations, blood urea nitrogen, creatinine levels, and a proinflammatory cytokine panel, indicated excellent tolerability and safety following single and repeat treatments in mice and nonhuman primates.

Conclusions: These results provide strong support for the continued development of UMGD for the treatment of renal disease.

Funding: Commercial Support - Sonothera Inc.

TH-PO433

Untapped Potential of the ADPKD Treatment Landscape

Jennifer Lafave, Ellie Mcclatchy, Bridget Bergan, Meghan Weiss. *Spherix Global Insights, Exton, PA*.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is identified by nephrologists as one of the top three renal conditions with the highest unmet need for new treatment options. Tolvaptan is currently the only FDA-approved treatment that is available for ADPKD, underscoring a significant opportunity for new entrants to foster market growth.

Methods: Data was collected in January 2024 in partnership with 101 US nephrologists via an online survey.

Results: Despite the availability of tolvaptan, two-thirds of nephrologists agree that there is a lack of effective treatment options for ADPKD (64%), and half believe that there is little they can do to treat these patients beyond blood pressure control and dietary guidance (49%). Current treatment regimens include ACE inhibitors/ARBs, fluid intake of at least three liters per day, SGLT2 inhibitors, and tolvaptan. Nearly all nephrologists (87%) report that they have prescribed tolvaptan to at least one of their ADPKD patients and express that the REMS program is not a barrier to their use of the drug. However, they also report that they encounter patient resistance to starting therapy with tolvaptan, especially since the most ideal patients often present as asymptomatic, are unable to tolerate the required water intake, and may be hesitant to begin a long-term treatment regimen that has monitoring requirements. Nephrologists report that 17% of their ADPKD patients are currently being treated with tolvaptan and just under one-third (32%) of users report being highly satisfied with the drug. Looking forward, nearly two-thirds of nephrologists anticipate that the biggest change in their management of ADPKD patients will be the introduction of new treatment options. Although their awareness of pipeline agents for ADPKD is low, physicians primarily seek new agents that effectively slow the progression of eGFR decline with no serious adverse events, good long-term safety profiles, and are supported by both clinical and outcomes data.

Conclusions: As new agents for ADPKD advance in their clinical trials, physician education on efficacy and safety data will be key in helping to drive the evolution of ADPKD treatment where significant unmet needs remain.

TH-PO434

Ameliorative Effect of Anti-microRNA-21 Oligonucleotide Synthesized from Serinol Nucleic Acid on Animal and Human Models of Cystic Kidney Disease

Yuhei Noda,[1] Noritoshi Kato,[1] Yuka Sato,[1] Kayaho Maeda,[1] Tamio Yamaguchi,[3,2] Shizuko Nagao,[2] Tomoki Kosugi,[1] Yukiko Kamiya,[5,4] Hiroyuki Asanuma,[4] Shoichi Maruyama.[1] *[1]Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Nagoya, Japan; [2]Fujita Ika Daigaku, Toyoake, Japan; [3]Suzuka Iryo Kagaku Daigaku, Suzuka, Japan; [4]Nagoya Daigaku, Nagoya, Japan; [5]Kobe Yakka Daigaku, Kobe, Japan*.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most frequent single-gene disorders. It is characterized by the prolific emergence of renal cysts originating from the renal tubules, which proliferate within the bilateral kidneys due to the disturbance of manifold cellular processes. These aberrations include abnormal tubular epithelial cell proliferation, anomalous apoptotic events, and perturbations in mitochondrial metabolism. MicroRNAs (miRNAs) are endogenous small RNAs that regulate gene expression at the post-transcriptional level via sequence-specific hybridization. It has been reported that miR-21 is upregulated in ADPKD and is involved in cyst formation. In the present study, we assessed the effect for cystic disease using an anti-miRNA oligonucleotide targeting miR-21 synthesized from serinol.

Methods: In this study, we synthesized anti-miR-21 oligonucleotides from serinol nucleic acid to improve nuclease resistance and affinity to nucleic acid molecules and evaluated renal function and cyst growth in vivo mouse model. In vitro, anti-miR-21 oligonucleotides treatment was evaluated for inhibition of cyst enlargement in primary cultured renal tubular cells derived from ADPKD patient.

Results: In a mouse model of cystic kidney disease, systemically administered anti-miR-21 oligonucleotides accumulated mainly in the kidney, suggesting effective drug delivery to the diseased kidney, in addition to successfully suppressing renal cyst growth and improving renal function in mice. Anti-miR-21 oligonucleotides markedly suppressed miR-21 expression in microRNA in situ hybridization of miR-21 in the cystic kidney tissue. Western blotting of kidney tissue showed that it affected molecules associated with proliferation, mitochondrial metabolism, apoptosis, and fibrosis pathways characteristic in multiple cystic kidneys. In vitro, anti-miR-21 oligonucleotides significantly reduced cyst size and ameliorated the characteristic decrease in Ca2+ concentration in primary cultured human cells derived from ADPKD patient.

Conclusions: The favorable effect of anti-miR-21 oligonucleotide on cystic kidney model animals and human ADPKD cells showed its potential as a clinical therapeutic agent for ADPKD.

TH-PO435

RGLS8429-Mediated miR-17 Inhibition Leads to Acute PKD1/2 De-repression and Ameliorates Preclinical ADPKD

Ronak Lakhia,[1] Jesus A. Alvarez,[1] Harini Ramalingam,[1] Patricia Cobo-Stark,[1] Laurence M. Biggers,[1] Jianfeng Huang,[2] Tania M. Valencia,[2] Edmund C. Lee,[2] Vishal Patel.[1] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]Regulus Therapeutics Inc, San Diego, CA.*

Background: ADPKD is caused by reduced *PKD1/2* gene dosage. However, drugs that improve *PKD1/2* levels are not available. We have shown that microRNA-17 directly represses *PKD1/2* and aggravates ADPKD progression. Thus, our goals were to characterize the next-gen anti-miR-17 drug RGLS8429 and its impact on *PKD1/2* and ADPKD.

Methods: We treated murine and human ADPKD kidney cell lines and mouse models with PBS, control oligo, or RGLS8429 to assess for miR-17 inhibition, *PKD1/2* de-repression, and therapeutic efficacy before or after PKD onset and in synergy with tolvaptan. We used multi-omic analyses to uncover early cellular and molecular events modulated by RGLS8429.

Results: RGLS8429, a 9-nt oligonucleotide, inhibits the miR-17 miRNA family and de-represses direct miR-17 targets, including *PKD1/2*. It reduces 3D cyst size in multiple mouse and human ADPKD cell lines. In the Ksp^{Cre};$Pkd1^{F/RC}$ model, RGLS8429 effectively delivers to kidney cysts, even if administered after significant disease, and leads to a rapid *Pkd1/2* de-repression within just 3 days of starting treatment. Remarkably, early RGLS8429 treatment prevents cyst formation, while treatment initiation at later disease stages stabilizes cyst burden and prolongs survival, with ~50% of mice surviving nearly 1 year and, in some cases, showing disease resolution. Further, we demonstrate therapeutic synergy between RGLS8429 and tolvaptan in the Pcy model. Finally, we produced a high-resolution cellular atlas by profiling >160,000 single nuclear transcriptomes (snRNA-seq),

uncovering 26 kidney cellular clusters. We noted rapid transitions in cellular states within 10 days after treatment initiation, with a reduced abundance of immune cells and principal cells with fibroinflammatory signatures and the emergence of 'healthier' proximal tubule cell types. We used a multi-layered, sequential RNA-seq and proteomics approach to map early molecular events onto these cellular neighborhoods.

Conclusions: RGLS8429-mediated acute pharmaceutical *PKD1/2* de-repression holds the potential for a significant disease-modifying effect in ADPKD. This promising drug is currently being evaluated in Phase 1b ADPKD clinical trials.

Funding: NIDDK Support, Commercial Support - Regulus Therapeutics

TH-PO436

Development of a Pkd1 mRNA Stabilizing Oligonucleotide for the Treatment of ADPKD

Ronak Lakhia, Maggie Zumwalt, Laurence M. Biggers, Harini Ramalingam, Patricia Cobo-Stark, Vishal Patel. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Nearly 80% of individuals with ADPKD harbor a pathogenic mutation in one copy of the *PKD1* gene. We have identified a miR-17 binding motif in the 3′ untranslated region (3′UTR) of *PKD1* that represses mRNA translation emanating from the other remaining allele. Here we have engineered an oligonucleotide directly targeting the *PKD1* 3′UTR to sterically hinder miR-17 interaction with *PKD1* mRNA and enhance its translation.

Methods: We designed a 16-base pair oligonucleotide that specifically binds to the miR-17 binding motif in the *Pkd1*3′-UTR (*Pkd1* oligo). Next, we tested *Pkd1* oligo in *Pkd1*$^{+/+}$ and *Pkd1*$^{RC/-}$ kidney epithelial cells. We used CRISPR-based live-cell imaging and qRT-PCR of *Pkd1* mRNA to quantify the abundance and transcript degradation rates to determine the *Pkd1* mRNA half-life. We performed 3D cystogenesis assays and western blot to assess for phenotypic benefit. Finally, we characterized the effect of our oligo in multiple human ADPKD kidney cell lines. In each experiment, a non-targeting scramble oligonucleotide was used as a control.

Results: Live-cell imaging of endogenous *Pkd1* mRNA and qRT-PCR revealed that *Pkd1* oligo treatment increased *Pkd1* mRNA abundance in both *Pkd1*$^{+/+}$ and *Pkd1*$^{RC/-}$ cells. In addition, *Pkd1* oligo prolonged *Pkd1* mRNA half-life compared to control oligo-treated cells. Moreover, we find that enhancement of *Pkd1* mRNA by *Pkd1* oligo translates to increased PC1 protein in both *Pkd1*$^{+/+}$ and *Pkd1*$^{RC/-}$ cells. Phenotypically we find that *Pkd1* oligo-treatment leads to reduced cyst size, enhanced mitochondrial membrane potential, and reduced pCREB expression in *Pkd1*$^{RC/-}$ cells. Finally, we find that treatment of multiple human ADPKD kidney cell lines with *Pkd1* oligo enhances *PKD1/PC1*, improves mitochondrial metabolism, reduces cyst size and pathogenic marker expression.

Conclusions: Our studies are the first to demonstrate the feasibility of oligonucleotides to raise endogenous *PKD1/PC1*expression. More broadly, our work suggests a novel 3′-UTR-based therapeutic approach for treating other haploinsufficient disorders by amplifying the healthy gene copy.

Funding: NIDDK Support

TH-PO437

Patient Cyst Type Composition Predicts Responsiveness to Therapeutic Intervention in Autosomal Polycystic Kidney Disease

Johannes Roeles,[1] Axel Giesler,[1] Jan H. Braesen,[2] Jessica Schmitz,[2] Frank Friedersdorff,[3,4] Michael Kottgen,[5] E. Wolfgang Kuehn,[5] Roland Schmitt,[1,6] Kai M. Schmidt-Ott,[1] Christian Hinze.[1] Hinze Lab. *[1]Hannover Medical School, Department of Nephrology and Hypertension, Hannover, Germany; [2]Hannover Medical School, Nephropathology Unit, Department of Pathology, Hannover, Germany; [3]Charité Universitätsmedizin Berlin, Department of Urology, Berlin, Germany; [4]Evangelisches Krankenhaus Königin Elisabeth Herzberge, Department of Urology, Berlin, Germany; [5]University of Freiburg Faculty of Medicine, Department of Nephrology and Primary Care, Freiburg, Germany; [6]University Hospital Schleswig-Holstein, Department of Nephrology and Hypertension, Kiel, Germany.*

Background: Autosomal polycystic kidney disease (ADPKD) is the main genetic cause of end stage renal disease. High variability of disease progression and inability of current models to accurately predict clinical efficacy hamper drug development and individualized patient care.

Methods: We analyzed 15 cyst wall samples from 5 ADPKD patients and 3 samples of tumor adjacent normal kidney tissue from 3 patients using single nucleus RNA sequencing (snRNA-seq) and immunofluorescence (IF) imaging. For cysts, the composition of cyst fluids was measured. An additional cohort of ca. 370 cyst from 9 patients was analyzed using machine learning aided IF image analysis to validate results.

Results: Integrated snRNA-seq analysis enabled clear identification of all major kidney cell types. Based on the expression of megalin (LRP2) or aquaporin 2 (AQP2) in the cyst epithelium, cysts could be categorized into proximal tubule-like (LRP2^{+}) and collecting duct-like (AQP2^{+}) cysts. Moreover, multiple cysts contained LRP2^{+} and AQP2^{+} populations within the same cyst (mixed cysts). Our gene expression analysis strongly suggests a differential responsiveness of cyst types to therapeutic interventions, including diet modifications, preclinical compounds, and drugs tested in clinical trials. The mechanistic amenability to drugs targeting epithelial injury and inflammation (MCP-1 inhibitors, Bardoxolone) depended mainly on pure versus mixed cyst identity. By contrast, expression of molecular targets for modulating solute-water transport (Vaptans, CFTR inhibitors) was cell type-specific. Importantly, the analysis of ca. 370 cysts from 9 additional patients revealed highly variable ratios of LRP2^{+} to AQP2^{+} to mixed cysts between patients.

Conclusions: Our study reveals an intra- and inter-individual heterogeneity of cyst types, which predicts the differential responsiveness of patients to treatment. The frequent detection of proximal tubule and mixed cysts calls for critical re-evaluation of current disease models and drug development efforts, which focus mainly on the collecting duct. Future strategies determining the individual cyst type composition are warranted to significantly improve treatment of patients with ADPKD.

TH-PO438

A Ketogenic Diet Alters Liver Cyst Progression in a Rodent Model of Polycystic Kidney Disease and Is Dependent on GPR109A

Jacob A. Torres, Brina A. Aceves, Melina Messing, Nickolas J. Holznecht, Shreya Krishnan, Roxanna Razavi, Anna G. Seligson, Thomas Weimbs. *University of California Santa Barbara, Santa Barbara, CA.*

Background: Polycystic Liver Disease (PLD) often co-occurs alongside Autosomal Dominant Polycystic Kidney Disease (ADPKD), a genetic disorder characterized by the growth of numerous cysts in the kidneys. Our lab has demonstrated that a low-carbohydrate, high-fat ketogenic diet, can slow and partially reverse kidney cyst growth in animal models of PKD in a mechanism involving the ketone beta-hydroxybutyrate (BHB). Furthermore, clinical evidence has found that ketogenic dietary interventions appear to be safe, feasible, and potentially beneficial for ADPKD patients. However, the impact of a ketogenic diet on PLD remains unexplored. This study aims to investigate the effects of a ketogenic diet and the BHB receptor, GPR109A, on PLD using an orthologous rodent model of PKD to build on the existing knowledge of the beneficial effects of such a diet on kidney cyst progression in ADPKD.

Methods: We utilized wild-type and *Gpr109a*-knockout mice with a tamoxifen-inducible *Pkd1*$^{fl/fl}$:ROSA-Cre system. Mice were induced on postnatal day 28 through postnatal day 30. Three days post-induction, the mice were segregated into two groups for a twelve-week dietary intervention: one group was fed a low carbohydrate (~5% of total calories), high-fat (~80% total calories) ketogenic diet, while the other group was maintained on standard chow. Following this period, tissues were harvested and subjected to a comprehensive analysis to assess disease progression, including histological and immunohistochemical analysis.

Results: Our study revealed a marked manifestation of hepatic cysts in the induced animals, as depicted by a significant increase in both the number and size of bile ducts, liver mass, and collagen deposition when compared to uninduced controls. Treatment with a ketogenic diet significantly reduced liver mass and fibrosis and was dependent on *Gpr109a*. Additionally, the localization of immune cells exhibited distinctly different patterns in treated versus untreated cystic animals.

Conclusions: We find that a ketogenic diet significantly blunts the growth of the liver due to PLD and markedly decreases collagen deposition. These findings underscore the potential of ketogenic dietary interventions as a novel therapeutic strategy for PLD and the importance of the receptor GPR109A.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO439

The Receptor GPR109A Modifies Cystic Disease Progression and the Effect of Beta-Hydroxybutyrate in Polycystic Kidney Disease

Jacob A. Torres, Nickolas J. Holznecht, Brina A. Aceves, Elizabeth H. Sharpe, Margaret Schimmel, Maria Shapiro, David A. Asplund, Shagun Agrawal, Bradley C. Kroes, Sebastian Strubl, Thomas Weimbs. *University of California Santa Barbara, Santa Barbara, CA.*

Background: Our lab's research has demonstrated that ketogenic metabolic therapies (KMT) can effectively slow and reverse the progression of polycystic kidney disease (PKD) in multiple rodent models of the disease. Moreover, we have discovered that the beneficial effects of KMT are largely mediated by the action of the metabolite beta-hydroxybutyrate (BHB). This finding opens up the possibility of developing BHB supplementation as a potential treatment for PKD. In addition to its role as an energy substrate, BHB acts as a signaling molecule and binds to the receptor GPR109A. GPR109A is expressed on macrophages and epithelial cells, regulating the activity of adenylate cyclase, a known contributor to PKD progression. Given the integral role GPR109A plays in cellular signaling, it is strongly implicated in mediating the effect of KMT in PKD, highlighting its potential as a therapeutic target.

Methods: Three-week-old Pkd1RC/RC mice with and without concurrent Gpr109a gene inactivation were treated with BHB until 3 months of age and then euthanized for

analysis. Additionally, 4-week-old Pkd1:Nestin-Cre mice with and without Gpr109a were treated with a ketogenic diet for 4 weeks and then euthanized for analysis.

Results: Loss of GPR109A causes a worsening of cystic disease progression in the Nestin-Cre mouse, altering the effect of a ketogenic diet on PKD. Additionally, GPR109A Knockout in the Pkd1RC/RC mouse caused a loss of some of the beneficial effects of BHB supplementation.

Conclusions: We found that loss of GPR109A caused a worsening of disease in the Nestin:Cre mouse and a partial loss of BHB's effect in the Pkd1RC/RC mouse. These results indicate that GPR109A is at least partially involved in slowing the progression of PKD, regulating the endogenous action of BHB as well as the beneficial effect of KMT on PKD progression.

Funding: NIDDK Support

TH-PO440

Real-Life Data from a Ketogenic Metabolic Therapy Program for Autosomal-Dominant Polycystic Kidney Disease Suggests Significant Benefits to Participants

Emily G. Muensterman,[1] Kelly L. Welsh,[2] Diana Bruen,[1,4] Jacob A. Torres,[1,3] Thomas Weimbs,[1,3] Jessianna Saville.[2,1] *[1]Santa Barbara Nutrients, Inc., Santa Barbara, CA; [2]Kidney Nutrition Institute, Titusville, FL; [3]University of California Santa Barbara, Santa Barbara, CA; [4]The PKD Dietitian, Henrico, VA.*

Background: ADPKD, the most common genetic form of chronic kidney disease, lacks pharmacological treatments to halt or reverse its progression. Recent studies indicate that nutrition and lifestyle factors, such as renal microcrystals (calcium oxalate/phosphate/uric acid) and metabolic issues (persistent hyperglycemia/insulin resistance), contribute to ADPKD progression. Dietary interventions aiming to reduce renal microcrystals through citrate supplementation and urine alkalization, and to improve metabolism via ketosis or beta-hydroxybutyrate (BHB) supplementation, have shown promise in animal models. Recent human clinical studies also support the potential benefits of these interventions.

Methods: The Ren.Nu program, developed in 2021 by renal dietitians and PKD-focused scientists, helps patients adopt a plant-focused, kidney-safe, ketogenic lifestyle to improve metabolic health and reduce renal microcrystal burden. It uses KetoCitra®, a medical food with exogenous BHB, citrate, minerals, and alkaline base. Nearly 200 ADPKD patients have completed the personalized medical nutrition therapy group program. The first year of development focused on methodology refinement, and since 2022, clinical and quality of life (QOL) data have been collected. This is not a formal clinical trial but an assessment of a real-life dietary program.

Results: Analysis of outcomes for 103 participants from baseline to program completion revealed significant improvements. Participants adhered well to the diet and lifestyle changes, evidenced by consistently elevated blood BHB levels and reduction in fat weight loss. There was a 6.3% increase in the estimated glomerular filtration rate (eGFR) from 58.4 to 61.6 mL/min/1.73m2 (P<0.001). The program reduced kidney pain, headaches, and hypertensive medication use. Biomarkers (total-, HDL-, LDL-cholesterol, triglycerides, potassium, phosphorus, bicarbonate) remained stable, indicating safety.

Conclusions: Our evaluation and ongoing clinical experience with the Ren.Nu program indicates that its dietary and lifestyle interventions, combined with the medical food, KetoCitra®, are feasible and safe. Several ongoing and planned controlled clinical studies will further assess the long-term effects on metabolic health, lithogenic risk, and renal outcomes.

TH-PO441

Metabolite Changes while Adhering to a Ketogenic Diet in Autosomal Dominant Polycystic Kidney Disease

Martine G. Knol,[1,2] Sita Arjune,[4] Maatje D. van Gastel,[1] Jacob A. Torres,[3] Thomas Weimbs,[3] Roman-Ulrich Mueller,[4] Markus M. Rinschen.[2,5] *[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]Aarhus Universitet, Aarhus, Denmark; [3]University of California Santa Barbara, Santa Barbara, CA; [4]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany; [5]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany*.

Background: A dysregulated metabolism in Autosomal Dominant Polycystic Kidney Disease (ADPKD) contributes to cystogenesis. A ketogenic intervention, currently under investigation, profoundly changes metabolism and may offer protective effects in ADPKD. Various metabolites, including those from one-carbon metabolism, branched-chain amino acids, tryptophan, and glutamine, have been linked to altering disease progression in ADPKD. This study aimed to discover which metabolites change during ketogenic interventions using LC/MS/MS in the KETO-ADPKD trial.

Methods: Targeted metabolomics was performed using LC/MS/MS. Urine and serum samples from the KETO-ADPKD trial (n=63) were used. Participants followed a ketogenic diet (n=23), a 3-day water fast once monthly (n=21), or a control diet (n=19). Additionally, serum and kidney tissue were measured from Han:SPRD PKD rats (n=18) and WT rats (n=18) on a ketogenic or control diet.

Results: The average age was 41±9.6, and 44% were women. Of 21 participants, we had serum samples on baseline and 3 months after the ketogenic diet. 112 metabolites were quantified in the serum. Serum analysis revealed changes in 6 upregulated and 7 downregulated metabolites after a 3-month ketogenic diet. An increase in ketone bodies indicated adherence to a ketogenic diet. Further increases in citric acid and homocysteine, and decreases in hypotaurine, aspartate, and kynurenine were observed. In the spot urine, 89 metabolites were quantified and normalized to urinary creatinine. After 3 months, 9 metabolites were significantly more excreted, out of which 5 were aromatic amino acid metabolites (so-called uremic toxins), and 1 metabolite, tyrosine, was downregulated. We assessed the effect of the ketogenic diet in PKD rats and WT rats in kidney tissue and serum to compare to the human data, providing similar signatures.

Conclusions: Profound changes in ketosis-induced metabolism were observed. Of special interest are the decreased abundance of hypotaurine and kynurenine, which were found in both humans and animals. Elevated kynurenine levels, a uremic toxin, have been described before in ADPKD, and their relevance in cyst progression should be further studied. How hypotaurine is regulated in ADPKD and whether it plays a part in the pathophysiology still need to be unraveled.

TH-PO442

Early Insights from Grease II: Safety and Efficacy of a Ketogenic Diet in ADPKD

Maria Ferri,[1] Carla Pezzuoli,[5] Giulia Ligabue,[2] Silvia Giovanella,[2] Francesca Testa,[1] Marco Ferrarini,[2] Francesca Ciurli,[3] Maria Amicone,[4] Antonio Pisani,[4] Riccardo Magistroni.[2,1] AOU Policlinico di Modena, Nephrology Unit. *[1]AOU Policlinico di Modena, Nephrology Unit, Modena, Italy; [2]University of Modena and Reggio Emilia, Dep. CHIMOMO, Modena, Italy; [3]Nephrology, Dialysis and Kidney Transplant Unit, IRCCS, AOU, Bologna, Italy; [4]AOU Federico II, Nephrology Unit, Napoli, Italy; [5]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy*.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a systemic disorder marked by the progressive formation and enlargement of kidney cysts, ultimately leading to kidney failure. Common extra-renal manifestations include polycystic liver disease, cerebral aneurysms, and cardiac valve abnormalities. The primary genetic causes are mutations in the PKD1 and PKD2 genes. Currently, Tolvaptan, a vasopressin-2 receptor antagonist, is the only approved therapy, which primarily slows kidney function decline without addressing extra-renal complications. Research indicates that cyst-lining epithelial cells in ADPKD are glucose-dependent due to metabolic alterations, including defective glucose metabolism, impaired beta-oxidation, and abnormal mitochondrial activity(Warburg effect). Thus, dietary manipulation to induce ketosis and deprive these cells of glucose is a promising therapeutic strategy.

Methods: The Grease II study is a phase II, 24-month randomized, parallel-group, two-arm superiority trial with a 1:1 allocation. It aims to evaluate the efficacy of a ketogenic diet (Modified Atkins Diet - MAD) compared to a balanced normocaloric diet (BND) in 92 patients with rapidly progressive ADPKD. During the run-in period blood pressure and lipid abnormalities will be normalized, if necessary. The primary outcome is the difference in kidney volume enlargement between the two groups, assessed by MRI at baseline and after 12 months. To mitigate potential biases from glycogen depletion induced by the ketogenic diet, MRIs will be performed after a 30-day switch to the BND diet for both groups. Secondary outcomes include, renal function comparison between the two groups, calculated using the CKD-EPI formula on creatinine and cystatin, at the end of the study(24 months of follow up).

Results: We anticipate achieving three primary endpoints: confirmation of MAD's tolerability through questionnaire data, confirmation of safety monitored via laboratory tests and clinical observations, reduction in Total Kidney Volume, measured by MRI, in the MAD group. Secondary endpoints include improvements in renal function and the impact of MAD on exploratory biomarkers.

Conclusions: The study is on going and 23 patients were recruited. This study was funded by the Italian ministry of Health - RF-2021- 12374522

Funding: Government Support - Non-U.S.

TH-PO443

Dietary Lysine Supplementation Causes Metabolic Dysregulation and Kidney Cyst Growth in Mice with Polycystic Kidney Disease

Randee Sedaka, Jifeng Huang, Shinobu Yamaguchi, Caleb R. Lovelady, Emily Hallit, Aida Moran-Reyna, Sejal Sanjay Shinde, Jung-Shan Hsu, Malgorzata Kasztan, Takamitsu Saigusa. Dept of Medicine/Div of Nephrology, Dept of Pediatrics/Div of Pediatric Hematology Oncology. *The University of Alabama at Birmingham, Birmingham, AL*.

Background: High casein protein diet induces renal hypertrophy, macrophage (MΦ) infiltration, and accelerated cyst growth in polycystic kidney disease (PKD) mice. Early cyst growth during casein protein load is associated with higher expression of glutamine transporter Snat3 and energy metabolism markers prior to increases in kidney MΦ

number. It is unknown whether plant-based protein similarly exacerbates PKD. Here, we determined the effect of wheat- or casein-based diet on cyst growth, as well as how specific amino acids abundant in these respective diets contribute to disease progression in mice lacking *Pkd1*.

Methods: Adult tamoxifen inducible global *Pkd1* knockout (*Pkd1*KO) mice were fed a high protein (60%) casein or wheat-gluten (WG) diet for 6 weeks. Kidneys were harvested for histology, MΦ quantification, and mitochondrial function. The most abundant amino acid in casein and WG diets were Lysine (Lys) and glutamine (Gln), respectively. Thus, *Pkd1*KO mice were gavaged with Lys (6.8g/kg/day), Gln (5.3g/kg/day) or phosphate buffered saline (PBS) for 4 weeks to assess cyst growth, glomerular filtration rate (GFR) and kidney tissue analysis.

Results: WG-fed *Pkd1*KO mice had fewer kidney MΦs, cytokines and cysts versus casein-fed counterparts. Mitochondrial oxygen consumption rate was similar between diets. Although both Lys and Gln gavaged *Pkd1*KO mice had higher GFR compared to PBS treated counterparts, only Lys gavaged mice had increased kidney cysts with higher expression of energy metabolism and fatty acid catabolism markers. Further, Lys treated mice had elevated renal Snat3 expression and urinary ammonia excretion, but lower blood urea nitrogen compared to Gln counterparts. Neither Lys nor Gln supplementation altered inflammatory cytokine expression relative to PBS treated mice.

Conclusions: Plant-based protein retarded the inflammation and cyst growth observed in casein-fed *Pkd1*KO mice. Lys, the most abundant amino acid in casein versus WG diet, increased Gln transport, energy metabolism and cyst growth in early PKD.

Funding: NIDDK Support

TH-PO444

Evaluating the Safety and Effectiveness in Adult Korean Patients Treated with Tolvaptan for Management of Autosomal Dominant Polycystic Kidney Disease (ESSENTIAL): Final Report

Hayne C. Park,[1] Yong Chul Kim,[3] Yeonsoon Jung,[2] Yaerim Kim,[4] Yun Kyu Oh.[5]
[1]Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea; [2]Kosin University, Busan, Republic of Korea; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [5]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea.

Background: Tolvaptan, a selective vasopressin V2 receptor antagonist, was first approved by Korean FDA in 2015 as a treatment option in autosomal dominant polycystic kidney disease (ADPKD). To prescribe Tolvaptan safely and effectively, we designed the phase 4 clinical trial among Korean ADPKD patients with chronic kidney disease (CKD) stage 1-3.

Methods: A total of 117 Korean patients aged 19 to 50 with rapidly progressing ADPKD were enrolled in the study. Tolvaptan was prescribed for 24 months with the maximum tolerable dose up to 120mg per day. The primary outcome was the incidence of treatment emergent adverse events (TEAEs) including hepatic adverse events. The secondary outcomes were the annual mean percent change of total kidney volume (TKV) and the annual mean change of estimated glomerular filtration rate (eGFR).

Results: A total of 489 TEAEs occurred in 106 (90.6%) patients. A total of 17 cases (14.5%) of hepatic adverse events occurred during the study period and mostly within the first 18-month period. However, liver enzymes were normalized after drug discontinuation. Although it was not statistically significant, patients with a previous history of liver disease as well as those with mild elevation of liver enzyme showed higher frequency of hepatic adverse events. Comparing with the predicted value from calculation, Tolvaptan attenuated both TKV growth and eGFR decline rate.

Conclusions: Although the incidence of hepatic adverse events was higher in Korean ADPKD patients compared to the previous studies, Tolvaptan can be prescribed safely and effectively using meticulous titration and 1-month interval monitoring.

Funding: Commercial Support - Korea Otsuka Pharmaceuticals

Comparison of liver injury incidence after Tolvaptan use among clinical trials

Trial	Essential	TEMPO 3:4		REPRISE	
Study duration	2 years	3 years		1 year	
Monitoring interval	1-month interval until 18 months, 3-month interval thereafter	Every 4 months		Every month	
Subjects	Tolvaptan (n=117)	Tolvaptan (n=958)	Placebo (n=484)	Tolvaptan (n=681)	Placebo (n=685)
ALT>3xULN	15 (12.8%)	42 (4.4%)	5 (1.0%)	38 (5.6%)	8 (1.2%)
ALT or AST>3xULN or TB>2xULN	17 (14.5%)	48 (5.0%)	11 (2.3%)	41 (6.0%)	8 (1.2%)
ALT or AST>3xULN & TB>2xULN	1 (0.85%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)
ALT or AST>3xULN & TB>2xULN & ALP<2xULN	1 (0.85%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ULN, upper limit of normal

TH-PO445

Effectiveness of Tolvaptan on Kidney Replacement Therapy in Patients with Autosomal Dominant Polycystic Kidney Disease: A Retrospective Cohort Study from the TriNetX Global Collaborative Network

Ming-Ju Wu,[1,2] Cheng-Hsu Chen.[1,2] *[1]Taichung Veterans General Hospital, Taichung, Taiwan; [2]National Chung Hsing University, Taichung, Taiwan.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a major genetic contributor to end-stage kidney disease (ESKD). Current evidence on tolvaptan primarily focuses on slowing estimated glomerular filtration rate (eGFR) decline and kidney volume growth. However, direct confirmation of its effectiveness in reducing the need for hemodialysis in ESKD remains limited.

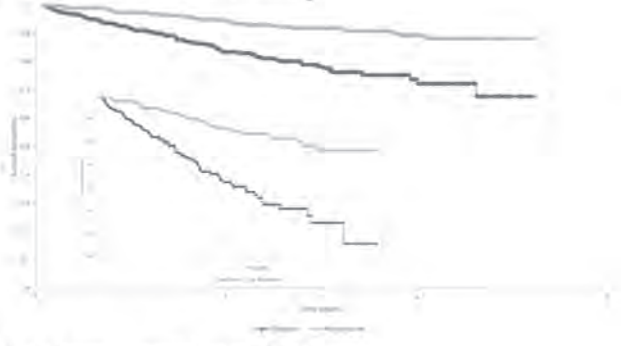
Methods: We enrolled ADPKD patients aged ≥18 years using TriNetx data from Sep 2, 2018, to Sep 3, 2023. Propensity score matching (PSM) ensured baseline comparability (standardized mean difference (SMD) <0.1).

Results: After 1:1 PSM, both groups comprised 673 patients. The average age was 45, with generally good health (3-5% diabetes, 2-3%). Baseline eGFR averaged ~50 ml/min/1.73m^2. Post-matching, all SMDs were <0.1, indicating successful matching. Tolvaptan users exhibited lower eGFR (47.3±26.5 vs. 53.5±34.3, p=0.001) and higher risk of stage 4-CKD (HR: 2.44, 95% CI:1.65, 3.60) compared to non-users. However, tolvaptan users showed significantly reduced chances of initiating hemodialysis (HR:0.362, 95%CI:0.18, 0.75), experiencing urinary tract infections (HR:0.58, 95%CI:0.35, 0.96), and all-cause mortality (HR:0.36, 95CI:0.18, 0.70). Lower eGFR in tolvaptan groups was not observed when refill time was ≥9. Kaplan-Meier curves for hemodialysis initiation indicated higher survival rates among tolvaptan users across age and refill time subgroups.

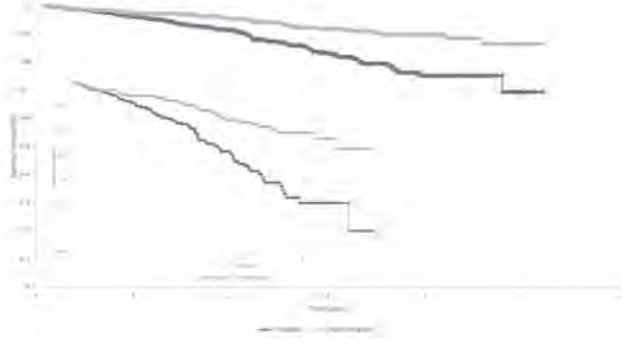
Conclusions: This real-world study, employing precise matching, reveals tolvaptan's role in reducing hemodialysis initiation risk in ADPKD, despite initial hemodynamic-induced lower eGFR. With more frequent refills, differences in subsequent eGFR became statistically insignificant.

Figure 1, In comparison to the non-tolvaptan group, the tolvaptan-treated group showed a higher likelihood of progressing to stage 4 (figure A) and stage 5 CKD (figure B) (both log-rank tests p<0.0001). Two Kaplan-Meier curves were presented per outcome with different scales to highlight the differences) (outcome: one month after the index event)

A. CKD stage 4 (log-rank test p<0.0001)



B. CKD stage 5 (log-rank test p<0.0001)



Kaplan-Meier survival curves

TH-PO446

Combination Treatment of Difelikefalin and Tolvaptan for Late-Stage Polycystic Kidney Disease

Ashlyn Y. Anderson, Daniel R. Kapusta, Kara Johnson, Madison G. Haggard, Jacob K. Meariman, Ian B. Denys, Mihran V. Naljayan, Juan Gao.
LSU Health New Orleans, New Orleans, LA.

Background: We have previously reported that, in the early stages of polycystic kidney disease (PKD), combination treatment of the kappa opioid agonist, difelikefalin, and the V2 vasopressin receptor antagonist, tolvaptan, maintained glomerular filtration rate and ameliorated polyuria and polydipsia associated with tolvaptan monotreatment. This current study tested the hypothesis that combination treatment of difelikefalin and tolvaptan can protect against worsening of PKD in the late stages.

Methods: Six-month old PKD mice were divided into five groups and were treated daily (dose titrated to decrease urine osmolality) for 3-months with either difelikefalin, tolvaptan, a combination of difelikefalin and tolvaptan (D+T), a combination of difelikefalin and half does of tolvaptan (D+1/2T), or vehicle. Metabolic studies were performed monthly to measure 24-hour urine output and water intake during the study period. Glomeruli filtration rate (GFR; beginning, midterm, endpoint) and total kidney volume (TKV, calculated as length, width, and depth of kidneys after mice were sacrificed) were determined in each group. Kidney tissue cAMP levels were also measured after mice were sacrificed.

Results: Treatment of PKD mice with difelikefalin, tolvaptan, D+T, and D+1/2T all prevented a decline in GFR over time. D+1/2T reduced the ratio of kidney weight to body weight by 12% compared to PKD mice treated with vehicle. None of the treatments caused a statistically significant reduction in TKV. Compared to vehicle, treatment with D+1/2T produced increases in 24-hr urine volume and decreases in urine osmolality measured monthly in PKD mice that were greater in magnitude than responses produced by difelikefalin alone, but less than mice treated with tolvaptan or D+T. The combination treatments of D+T and D+1/2T both significantly decreased renal cAMP levels compared with vehicle.

Conclusions: Together, these results suggest that combination treatment of difelikefalin and tolvaptan preserves kidney filtration function, reduces side effects, and decreases necessity of dose escalation of tolvaptan in late stages of PKD. (Funding DoD W81XWH-22-1-0046)

Funding: Other U.S. Government Support

TH-PO447

Investigational New Drug (IND)-Enabling Studies to Support the Development of 2-Deoxy-D-Glucose (2DG) for the Treatment of ADPKD

Matteo Federici,[1] Scott J. Weir,[3] Carolyn J. Vivian,[3] Alan S. Yu,[2] Alessandra Boletta.[1] *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]University of Kansas Medical Center Department of Internal Medicine, Kansas City, KS; [3]University of Kansas Institute for Advancing Medical Innovations, Kansas City, KS.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the growth of fluid-filled cysts due to abnormal epithelial proliferation. We have demonstrated that ADPKD cyst epithelial cells undergo metabolic reprogramming, which can be targeted using 2DG. Our preclinical data indicate that 2DG retards the disease progression in PKD models. Previously tested in >300 individuals, 2DG showed to be safe at 45-63 mg/kg/day. We have designed a Phase 1b clinical trial to evaluate safety/tolerability in ADPKD patients assuming a ceiling dose of 32 mg/kg/day. We now present our development program and the IND-enabling studies required to support this clinical trial

Methods: Our program was discussed in a pre-IND meeting with the FDA. The purpose was to reach agreement on chemistry, manufacturing, and controls (CMC) and nonclinical studies to be completed prior to the IND submission. We manufactured a GMP batch of 2DG drug substance, with ongoing stability testing. Nonclinical GLP studies are being conducted in two species to determine the toxicity/toxicokinetic profile of 2DG when administered by oral gavage. The studies include dose escalation to determine the maximum tolerated dose followed by 7-day repeat-dose to assess tolerance, 28-day repeat-dose toxicity, safety pharmacology on CNS, respiratory, cardiovascular systems, and genotoxicity studies

Results: The FDA generally agreed with our development program and gave helpful recommendations to optimize the nonclinical plans. The GMP batch passed all quality controls for release. Preliminary data showed stability at least up to one year. In the dose escalation study 2DG resulted well tolerated at single dose up to 1,600 mg/kg in the rat and 480 mg/kg in the dog (human equivalent dose of ~256 mg/kg). Transient clinical signs were observed only at 1,600 mg/kg in rats. No major gross findings at necropsy in both species. Bacterial reverse mutation test showed negative mutagenic response.

Conclusions: Our hypothesis is that 2DG will be an effective and safe treatment for ADPKD. The results from current nonclinical studies, along with CMC information and clinical trial plans, will be ultimately included in the IND submission to seek FDA approval for initiating the clinical study. Future efforts will focus on securing funds for the clinical trials.

Funding: Other U.S. Government Support

TH-PO448

Diagnosis and Management of Polycystic Kidney Disease in a Commercially Insured Population

Yun Han,[1] Michael Heung,[1] Areeba Jawed,[1] Jennifer L. Bragg-Gresham,[1] Fang Xu,[2] Yoshihisa Miyamoto,[2] Pranav S. Garimella,[3] Rajiv Saran.[1]
[1]University of Michigan, Ann Arbor, MI; [2]Centers for Disease Control and Prevention, Atlanta, GA; [3]University of California San Diego, La Jolla, CA.

Background: Since the approval of vasopressin V2-receptor antagonist tolvaptan to treat polycystic kidney disease (PKD) in April 2018, there has been an increase in diagnosis of PKD. Generally reserved for younger patients with aggressive disease, tolvaptan is associated with increased healthcare costs in managing PKD. We sought to investigate contemporary diagnostic and management practices among commercially insured patients with newly diagnosed PKD.

Methods: Patients with PKD were identified in Optum Clinformatics™ Data (2016-2020, 38.7 million beneficiaries) by ICD-10 diagnosis codes. A one-year look-back window was utilized to identify newly diagnosed PKD, determined by the initial diagnosis codes on or after January 1, 2017. CPT codes were used to identify kidney imaging: ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT); brain vascular imaging: magnetic resonance angiography (MRA) and computed tomography angiography (CTA); genetic testing; kidney related surgery; and tolvaptan. Utilization of these services were analyzed one year prior to and two years following the PKD diagnosis, except for surgery and tolvaptan (post-diagnosis only).

Results: A total of 15,260 newly diagnosed PKD patients were identified (mean age: 57.9 years). Service utilization included nephrologist visit (59.3%), kidney MRI (10.2%), CT (43.3%), brain MRA or CTA (12.6%), ultrasound (40.9%), genetic consultation (3.4%), kidney-related surgery (0.6%), and tolvaptan (2.2%).

Conclusions: PKD-related health service utilization varied with low use of advanced imaging procedure among a large commercially insured population. Findings may underscore the need for standardized care protocols and enhanced awareness of PKD management strategies to improve disease outcomes.

Funding: Other U.S. Government Support

Table: Baseline Characteristics and Healthcare Utilization of Patients with Newly Diagnosed PKD

N=15,260	N	%
Demographics		
Age (years; Mean, SD)	57.9	19.9
Age group (years)		
<20	632	4.1
20-35	1,646	10.8
35-50	2,462	16.1
50-65	3,420	22.4
65-80	5,176	33.9
≥80	1,925	12.6
Sex		
Female	7,379	48.4
Male	7,881	51.6
Race		
Asian	451	3.0
Non-Hispanic Black	1,594	10.4
Hispanic	1,456	9.5
Unknown	3,698	24.2
Non-Hispanic White	8,062	52.8
Hypertension	9,966	65.3
Diabetes	3,229	21.2
Health Service Utilization		
Nephrologist visit	9,042	59.3
Magnetic Resonance Imaging	1,552	10.2
Computed Tomography	6,614	43.3
Angiographic Imaging Techniques	1,925	12.6
Ultrasound	6,248	40.9
Gene testing	516	3.4
Kidney related surgery	98	0.6
tolvaptan	337	2.2

TH-PO449

Early Treatment with 2-Deoxy-D-Glucose Reduces Proliferative Proteins in the Kidney and Slows Cyst Growth in a Hypomorphic Pkd1 Mouse Model of Autosomal Dominant Polycystic Kidney Disease

Daniel Atwood, Zhibin He, Makoto Miyazaki, Charles L. Edelstein.
University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: There is enhanced aerobic glycolysis (Warburg effect) in the cyst lining epithelial cells in ADPKD that contributes to cyst growth. The glucose mimetic, 2-Deoxy-d-glucose (2-DG) inhibits glycolysis. The effect of early and late administration

of 2-DG on cyst growth and kidney function was determined in Pkd1RC/RC mice, a hypomorphic PKD model orthologous to human disease.

Methods: Mice were treated with 2-DG (100 mg/kg/d IP) from 50-120 (Early treatment) or 150 to 350 days old (Late treatment). An array of mTOR and autophagy proteins was measured in the kidney by immunoblot analysis. Cre-lox technology was used to Pkd1, Rictor double knockout mice. Proliferation measured by PCNA IHC

Results: Early administration of 2-DG decreased cyst indices (See table). 2-DG decreased proliferation of cells lining the cyst. Late administration of 2-DG had no effect on cyst growth (See Table). 2-DG suppressed autophagic flux in kidneys evidenced by no increase in LC3-II 2 hrs after IP injection of bafilomycin and a decrease in autophagy proteins, ATG3, ATG5 and ATG12-5. 2-DG had no effect on p-mTOR or p-S6 (mTORC1). 2-DG decreased both functional p-4E-BP1 isoforms, p-c-Myc and p-ERK that are known to promote proliferation and cyst growth in PKD. 2-DG decreased p-AKTS473, a marker of mTORC2. However, knockout of Rictor (mTORC2) in Pkd1 knockout mice did not change the PKD phenotype.

Conclusions: In summary, 2-DG decreases proliferation in cells lining the cyst and decreases cyst growth by decreasing proteins that are known to promote proliferation. The present study reinforces the therapeutic potential of 2-DG for use in patients with ADPKD.

Funding: Veterans Affairs Support

	VEH	2-DG (50-120)	VEH	2-DG (150-350)
BW (g)	26	26	25	26
KW/BW (%)	2.4	2.0*	2.9	2.7
Index (%)	8.8	4.1*	19	18
Cyst #	211	161*	441	401
BUN (mg/dL)	27	25	35	33
HW/BW (%)	0.5	0.5	0.6	0.5
p/t-ERK (RDU)	0.7	0.3*		
p/t-c-Myc (RDU)	0.5	0.2*		
p/t-4E-BP1 (RDU)	0.5/0.7*	0.2/0.3*		

*P<0.05. RDU=relative densitometry units on immunoblot

TH-PO450

Itaconate Controls the Severity of Autosomal Dominant Polycystic Kidney Disease

Ewud Agborbesong, Shasha Cheng, Peter C. Harris, Xia Zhou, Xiaogang Li. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a genetically inherited disease in which inflammation plays a role in renal cyst growth. Itaconate has emerged as a key immunoregulatory metabolite with diverse roles in inflammation and immunity. However, the role of itaconate in cyst growth and its therapeutic potential in ADPKD is unknown.

Methods: We performed 1) quantitative real-time PCR to examine the expression of aconitate decarboxylase (Acod1) in *Pkd1* mutant renal epithelial cells and tissues, 2) clonogenic assay to assess the effects of itaconate derivative 4-octyl itaconate (4-OI) on *Pkd1* mutant renal epithelial cell growth, and 3) western blot and immunostaining analysis in *Pkd1* homozygous (PN24) renal epithelial and macrophage (RAW264.7) cells treated with 4-OI. Light microscopy was used to assess the effect of 4-OI on RAW264.7 cell activation in a *Pkd1* mutant microenvironment. Furthermore, $Pkd1^{RC/RC}$ mice were treated with 4-OI to evaluate its effect on cyst growth.

Results: We found that the expression of itaconate-synthesizing enzyme, Acod1, was downregulated in PN24 cells compared to *Pkd1* heterozygous (PH2) control cells and in $Pkd1^{RC/RC}$ mouse kidneys compared to wild type kidneys. Treatment with 4-OI decreased 1) PN24 cell proliferation as examined with clonogenic assay, 2) the activation of PKD associated signaling pathways, including Akt, Erk, Stat3, p65, and S6, and 3) the expression of histone modifying enzymes including JMJD2A, a JmjC histone lysine demethylase (KDM), Smyd2 and Smyd3, both histone lysine methyltransferases (KMTs). In addition, we found that treatment with 4-OI altered mitochondrial dynamics by decreasing mitochondrial fission, and increasing mitochondrial fusion as determined by MitoTracker Red staining. Consistent with its immunoregulatory role, 4-OI treatment affected macrophage polarization of RAW264.7 cells stimulated with condition medium from PN24 cells. Importantly, treatment with 4-OI delayed cyst growth in $Pkd1^{RC/RC}$ mice as seen by a decrease in cystic index, kidney weight (KW)/body weight (BW) ratio and blood urea nitrogen (BUN) levels.

Conclusions: Collectively, itaconate contributes to ADPKD by modulating epigenetic reprogramming, cell proliferation, mitochondrial dynamics, and immune response/inflammation, and treatment with itaconate derivatives may be a viable therapeutic strategy for ADPKD.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO451

Increased Urinary Ferritin in Patients with Autosomal Dominant Polycystic Kidney Disease

Madhulika Sharma,[1,2] Nicole Sommer,[1,2] Matthew A. Kavanaugh,[1,2] Pamela V. Tran,[1,2] Alan S. Yu,[1,2] Darren P. Wallace.[1,2] *[1]The University of Kansas School of Medicine, Kansas City, KS; [2]The Jared Grantham Kidney Institute, Kansas, KS.*

Background: Polycystic kidney disease (PKD) is the fourth leading cause of renal failure among adults, yet reliable blood or urine diagnostic and prognostic biomarkers are lacking. Diagnosis is usually made by ultrasound or MRI scanning to estimate height adjusted total kidney volume (htTKV) or PKD mutation analysis, which are expensive. We previously showed that ferritin accumulates in the cystic epithelial cells of PKD kidneys due to loss of ferritinophagy. Here, we evaluate the potential of ferritin as a biomarker of ADPKD progression.

Methods: Cystic fluid from ADPKD patients, urines and urinary extracellular vesicles (UEVs) from normal and ADPKD patients, primary cultures of cyst epithelial cells from ADPKD kidneys and tubule epithelial cells from normal human kidneys (NHK) were obtained from age matched individuals with the assistance of the Kansas Clinical Research Core and Biomaterials and Biospecimens Core at the Kansas PKD Center. ADPKD and NHK cells were grown in low serum, and conditioned media were obtained for the measurement of ferritin by Western blot analysis. Cystic fluid, urine, UEVs and conditioned media were evaluated for ferritin expression via Western blots and ELISA. Urine from normal and PKD ($Pkd^{RC/RC}/Pkd2^{+/-}$) mice was also assessed for ferritin expression.

Results: Ferritin was detected as monomer, dimer, and tetramer units in the cystic fluid of ADPKD patients. Of the urine samples tested, ferritin was detected in one ADPKD patient, and it was not detected in any of the normal individuals. Conditioned media from ADPKD cells had 5 times higher ferritin compared to media from NHK cells. UEVs from ADPKD patients also had significantly more ferritin compared to UEVs from normal age matched individuals. These ferritin levels in UEVs appeared to correlate partially with the Mayo Imaging Classification categories. Moreover, we found that ADPKD mice had increased urinary ferritin compared to WT mice.

Conclusions: Ferritin, secreted by cyst epithelial cells, accumulates in cystic fluid and urine of ADPKD patients and appears to correlate with disease progression. Further studies will test the potential role of ferritin as a diagnostic, prognostic, and a response biomarker for ADPKD.

Funding: Other U.S. Government Support, Private Foundation Support

TH-PO452

Association between Age and Body Mass Index in Patients with End-Stage Autosomal Dominant Polycystic Kidney Disease (ADPKD) in the United States and Japan

Tatsuya Suwabe,[1,2] Vicente E. Torres,[2] Lisa E. Vaughan,[2] Charles D. Madsen,[2] Peter C. Harris,[2] Junichi Hoshino,[3] Saori Nishio.[4] *[1]Toranomon Byoin, Minato-ku, Japan; [2]Mayo Clinic Minnesota, Rochester, MN; [3]Juntendo Daigaku, Bunkyo-ku, Japan; [4]Hokkaido Daigaku, Sapporo, Japan.*

Background: Dietary interventions have been proposed to delay the progression of ADPKD. Body mass index (BMI) has been associated with ADPKD progression. However, the long-term effects of dietary interventions and BMI have not been proven.

Methods: Cross-sectional analysis using data from the United States Renal Data System (USRDS) and the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) to compare the ages and their relation to BMI and other clinical characteristics at initiation of renal replacement therapy (RRT) in these two populations, and their possible association with different dietary habits.

Results: The study included 3,556 patients (1,877 men and 1,679 women; mean age 58.1±13.1 years) who initiated RRT in 2006 and 2007 from the USRDS (2,491) and JRDR (1,065). The mean ages at initiation of RRT were 56.6±13.1 years in the United States and 61.6±12.5 years in Japan (p<0.0001). BMI was 28.2±7.1 kg/m2 in the USRDS and 22.0±3.3 kg/m2 in the JRDR (p<0.0001). Japanese participants were the oldest at time of RRT, followed in descending order by Asian Americans, White Americans, and African Americans. Japanese participants also had the lowest BMI, followed in ascending order by Asian Americans, White Americans, and African Americans. Univariable and multivariable analyses showed that BMI was significantly and inversely associated with age at initiation of RRT in the entire cohort, as well as separately in both the American and Japanese participants. Estimated GFR was not associated with age at initiation of RRT overall and in the USRDS populations, and was significantly, but positively correlated in the JRDR population. As expected, comorbidities were associated with age at initiation of RRT.

Conclusions: BMI is significantly associated with age at initiation of RRT in patients with ADPKD in both the United States and Japan. Japanese had lower BMI and were older than US people of various ethnicities at the initiation of RRT. The lower-calorie diets consumed in Japan are likely associated with lower BMI and a slower progression of ADPKD.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO453

Redefining Overweight and Obesity (OW/OB) in a Large Cohort of Patients with ADPKD

Sol M. Carriazo Julio,[1,3] Taher Dehkharghanian,[1] Mauricio A. Miranda Cam,[1,3] Yasmina Sarie,[3] Xuewen Song,[3] Timothy L. Kline,[2] Saima Khowaja,[1] Korosh Khalili,[1] York Pei.[1,3] *[1]University Health Network, Toronto, ON, Canada; [2]Mayo Clinic Minnesota, Rochester, MN; [3]University of Toronto, Toronto, ON, Canada.*

Background: Emerging data indicate OW/OB are risk factors for accelerated progression in ADPKD patients. Thus, an accurate diagnosis is crucial to implement appropriate therapeutic measures and avoid unnecessary treatments if not indicated. The traditional BMI formula used to define OW/OB does not take into account the excess of weight attributed to large cystic kidney and liver in ADPKD. Here we define the prevalence and clinical characteristics of ADPKD patients with OW/OB in a large cohort using a formula recommended by KDIGO

Methods: Cross-sectional analysis of patients with *PKD1* and *PKD2* mutations from the Toronto PKD Registry who had clinical and MRI measurements of total kidney volume (TKV) and total liver volume (TLV) was performed. BMI was calculated by the formula: weight (kg)/height (m^2)), while estimated BMI (eBMI) was calculated with the formula proposed by KDIGO: adjusted body weight (body weight (kg) - TKV (kg) - TLV (kg) + weight of normal kidneys and liver/ height (m^2)

Results: **Table 1** shows clinical characteristics of the study cohort (n=693) and subgroups defined by eBMI category. The median weight and BMI pre and post adjustment were 73 kg and 25,1 kg/m^2 and 71.8 kg, and 24,3 kg/m^2 respectively. A total of 352 (50.7%) patients were initially classified as OW/OB but the number decreased to 314 (45.3%) post adjustment; 10.7% of those initially classified as OW/OB were reclassified as having normal weight, and 80 (11.5%) of the study cohort were classified into a milder BMI category post adjustment

Conclusions: OW/OB are highly prevalent among patients with ADPKD and are associated with worse prognoses. Using eBMI for an accurate diagnosis of OW/OB can help avoid unnecessary treatment for those previously misclassified

Table 1. Clinical characteristics of the subgroups defined by eBMI category.

Table 1.	Underweight (n=22) <18,5 kg/m^2	Normal weight (n=357) 18.5-25 kg/m^2	Overweight (n=217) 25-30 kg/m^2	Obesity (n=97) >30 kg/m^2
Age, median (Q1,Q3)	30.5 (28.25-56)	41 (32-52)	46 (36-55)	44 (35-53)
Male, n (%)	2 (9.1)	136 (38.1)	94 (43.3)	47 (48.5)
Ethnicity, n (%)				
European	5 (22.7)	214 (59.9)	147 (67.7)	71 (73.2)
East Asian	9 (40.9)	58 (16.2)	11 (5.1)	2 (2.1)
South Asian	4 (18.2)	30 (8.4)	28 (12.9)	5 (5.2)
Other	4 (18.1)	47 (13.1)	26 (11.9)	19 (19.5)
Hypertension, n (%)	7 (31.8)	179 (50.1)	144 (66.4)	64 (66)
Weight, median (Q1,Q3)	47.6 (44.7-53.25)	65.7 (58.9-72.5)	81.6 (75-89.4)	99.7 (89.1-110)
Adjusted weight, median (Q1,Q3)	46.8 (42.8-53.3)	63.4 (56.9-70.7)	80.1 (73.4-87.5)	97.7 (87.9-107.4)
BMI, median (Q1,Q3)	18.1 (17.5-18.6)	22.8 (21.4-24.1)	27.7 (26.6-28.9)	33.7 (31.8-35.6)
eBMI, median (Q1,Q3)	17.6 (16.8-18.2)	22.31 (20,8-23.4)	27 (26,1-28,2)	32.6 (31.2-34.4)
eGFR median (Q1,Q3)	93 (73-113)	82 (57.5-104)	68 (45-89.5)	65 (43-95)
CKD stage n (%)				
1-2	18 (81.8)	260 (72.8)	124 (57.1)	53 (54.6)
3a	3 (13.6)	44 (12.3)	40 (18.4)	18 (18.6)
3b, 4, 5	1 (4.5)	53 (14.8)	54 (24.4)	26 (26.8)
Mutation class, n (%)				
PKD1 PT/Indel	15 (68.2)	180 (50.4)	99 (45.6)	37 (38.5)
PKD1 NT	3 (13.6)	87 (24.4)	43 (19.8)	24 (24.7)
PKD2	4 (18.2)	90 (25.2)	75 (34.6)	36 (37.1)
TLV, median (Q1,Q3)	1361 (905-2899)	1506 (1240-2046)	1696 (1407-2069)	1955 (1504-2276)
TKV, median (Q1,Q3)	932 (622-1383)	1065 (647-1872)	1480 (846-2343)	1707 (933-2804)
TLKV, median (Q1,Q3)	1361 (905-2899)	2844 (2011-4266)	3306 (2561-4372)	3541 (2746-5052)
MCIC, n (%)				
1A-1B	7 (31.8)	138 (38.7)	63 (29)	23 (23.7)
1C-1E	15 (68.2)	219 (61.3)	154 (71)	74 (76.3)

TH-PO454

Prognostic Value of Skeletal Muscle Mass and Body Mass Index in PKD

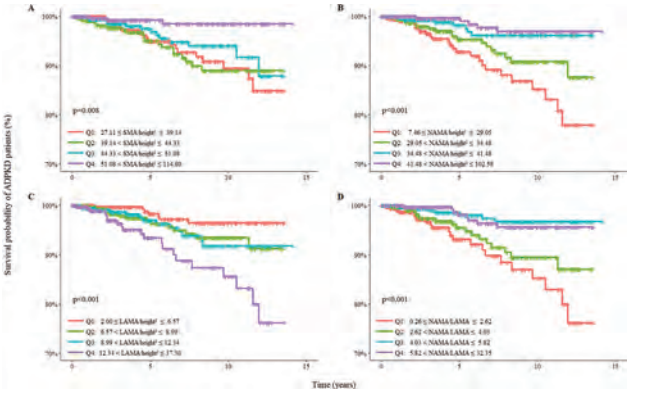
Dha Woon Im,[1] Jiyun Jung,[2] Yon Su Kim,[4] Kook-Hwan Oh,[4] Dong Ki Kim,[4] Hajeong Lee,[4] Seung Seok Han,[4] Eunjeong Kang,[4] Sehoon Park,[4] Sung Joon Shin,[3] Jangwook Lee,[3] Jeongin Song,[3] Jae Yoon Park,[3] Yong Chul Kim.[4] *[1]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [2]Dongguk University College of Medicine, Gyeongju, Gyeongsangbuk-do, Republic of Korea; [3]Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; [4]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: Low muscle mass is a well-established risk factor for the progression of chronic kidney disease (CKD). However, little is known about the impact of muscle mass on mortality in patients with autosomal dominant polycystic kidney disease (ADPKD). This study aimed to investigate the effect of muscle mass on mortality in individuals with ADPKD.

Methods: We collected clinical information on 1273 ADPKD patients from Seoul National University Hospital between 2006 and 2019, and obtained CT image at lumbar 3rd vertebra to measure the skeletal muscle area (SMA) by artificial intelligence. SMA was classified as low attenuation muscle area (LAMA) and normal attenuation muscle area (NAMA) according to muscle quality, and divided by height^2 to adjust the body size. Tracked through 2020, we estimated hazard ratio (HR) and 95% confidence interval (CI) on Cox-proportional hazard model adjusted by sex, age, MAYO classification, serum creatinine, blood urea nitrogen, and glucose.

Results: During the average of 5.14 years, more than half of the patients were female, and the mean (standard deviation) age was 47.2 (12.6) years. We observed 55 deaths, and the average of SMA/height^2, NAMA/height^2, and LAMA/height^2 was 45.4 cm^2/m^2, 35.5 cm^2/m^2, 9.9 cm^2/m^2, respectively. We found significant protective effects of SMA (HR 0.94, 95% CI 0.89–0.98) and NAMA (HR 0.94, 95% CI 0.90–0.97) on mortality while weak adverse effect in LAMA (HR 1.06, 95% CI 1.00–1.12). According to body mass index classification, those who had normal weight (18.5≤BMI<25) showed prominently positive health effects with NAMA increase (HR 0.95, 95% CI 0.91–0.99).

Conclusions: In ADPKD, greater muscle mass, especially high-quality muscle mass, is associated with a reduced risk of mortality.



Survival probability according to quartile of (A) skeletal muscle area (SMA)/height^2, (B) normal attenuation muscle area (NAMA)/height^2, (C) low attenuation muscle area (LAMA) /height^2, and (D) NAMA/LAMA.

TH-PO455

Overweight and Obesity Are Associated with Lower Kidney Blood Flow in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Carissa L. Birznieks, Wei Wang, Cortney Steele, Berenice Y. Gitomer, Michel Chonchol, Kristen L. Nowak. *University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO.*

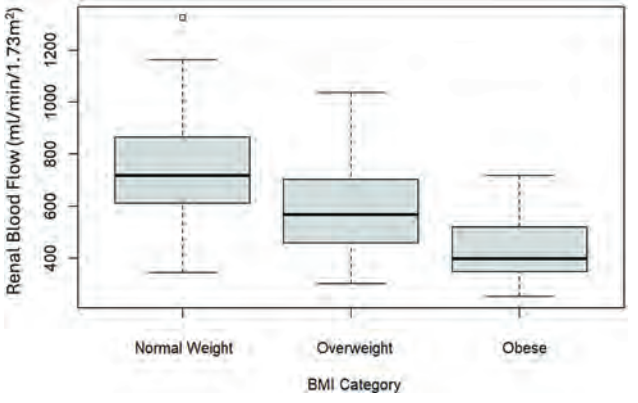
Background: We have previously reported that overweight and obesity are independently associated with more rapid progression in adults with early-stage ADPKD. Renal blood flow (RBF) precedes the decline in eGFR and is associated with faster kidney growth. We now evaluated whether overweight and obesity are also associated with changes in renal blood flow.

Methods: 150 non-diabetic adults (25-60 years of age) with ADPKD and an eGFR ≥60 ml/min/1.73m^2 who participated in a randomized controlled trial of pravastatin therapy were categorized based on baseline body mass index (BMI) as normal weight (n=68 [45%], overweight (n=53 [35%], or obese (n=26 [17%]. RBF was measured by phase contrast MRI, analyzed using Segment for Research (Medviso), and adjusted for body surface area (BSA) prior to analysis. The association of baseline BMI with baseline RBF was assessed using multivariable linear regression.

Results: Participants were 40±10 years (mean±s.d), 65% female, with a baseline RBF of 635±214 ml/min/1.73m^2, and a baseline eGFR of 90±21 ml/min/1.73m^2. BSA-adjusted RBF was lower in a stepwise manner with increasing BMI category (**Figure**). After adjustment for demographics, systolic blood pressure, blood glucose, HDL, eGFR, and height-adjusted total kidney volume, both overweight (β-estimate: -116.8; 95% CI: -168.8 -64.8) and obesity (β-estimate: -289.2; 95% CI: -361.5, -216.9) remained significantly associated with lower RBF as compared to normal weight participants. For every one unit increase in BMI, RBF was 20.6 ml/min/1.73m^2 lower (95% CI: -25.2, -16.1) in the fully adjusted model.

Conclusions: Overweight and obesity are associated with lower RBF in patients with early-stage ADPKD. Prior research in adults without ADPKD have been discordant, reporting both higher and lower RBF with overweight or obesity. Further research is needed to evaluate whether reduced RBF may be a mechanism by which obesity is associated with faster progression in patients with ADPKD.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support, Clinical Revenue Support



TH-PO456

Glucagon-Like Peptide 1 Receptor Agonist (GLP-1 RA) Delays Cyst Growth in ADPKD

Jiao Wu, Shasha Cheng, Yingying Zhang, Xiaoyan Li, Xia Zhou, Xiaogang Li. *Mayo Clinic Minnesota, Rochester, MN.*

Background: ADPKD is the most frequent genetic cause of chronic kidney disease (CKD), accounting for 6-10 % of patients on dialysis in the United States. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of drugs utilized to treat type 2 diabetes mellitus and obesity due to its profound glycemic control effect and weight lowering. In this study, we tested the effect of one of the most popular GLP-1RA, Semaglutide, and the underlying mechanisms on the progression of ADPKD.

Methods: To determine the effect of GLP-1RA in ADPKD, we treated *Pkd1$^{flox/flox}$:Pkhd1-Cre* mice and *Pkd1$^{RC/RC}$* mice with Semaglutide (10 ug/kg) via daily intraperitoneal injection. Kidneys were collected from *Pkd1$^{flox/flox}$:Pkhd1-Cre* mice at PN25 and from *Pkd1$^{RC/RC}$* mice at PN91. Kidneys and renal tubular cells treated with Semaglutide were analyzed by H&E staining, WB, qRT-PCR, as well as immunofluorescence, immunohistochemistry, and TUNEL staining. Additionally, we utilized transmission electron microscopy to identify mitochondrial changes in *Pkd1* mutant cells and kidneys.

Results: We found that the expression of GLP-1R was decreased in *Pkd1* mutant renal epithelial cells and kidneys. Treatment with Semaglutide (10ug/kg) delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and increased cyst lining epithelial cell apoptosis in *Pkd1* mutant mice (all $p < 0.05$). Treatment with Semaglutide could reduce total kidney volumes in living *Pkd1$^{RC/RC}$* mice as examined by ultrosoud, as well as decrease the recruitment of macrophages and the expression of fibrotic markers, including fibronectin and a-SMA, resulting in a decrease of interstitial fibrosis in *Pkd1* mutant kidneys as examined by picrosirius red and a-SMA staining. Notably, we found that treatment with Semaglutide 1) decreased glucose uptake, ATP generation and glycolysis characterized by a decrease of the expression of the key glycolytic enzymes, and 2) normalized the structure of mitochondria and the expression of the genes involved in mitochondrial metabolism, in *Pkd1* mutant renal epithelial cells and kidneys.

Conclusions: This study highlights a role of downregulation of GLP-1R in abnormal glycolysis and mitochondrial metabolism in *Pkd1* mutant kidneys and suggests that GLP-1RA therapy may be a novel therapeutic strategy for ADPKD.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO457

Novel Use of Recombinant Dimeric IgA Monoclonal Antibodies as Cyst-Targeted Therapeutics in Polycystic Kidney Disease

Margaret Schimmel, Thomas Weimbs. *University of California Santa Barbara, Santa Barbara, CA.*

Background: The sole approved treatment for autosomal dominant polycystic kidney disease demonstrates limited efficacy and causes adverse side effects[1]. Urgent development of more effective therapies is imperative. While biological drugs, such as IgG monoclonal antibodies, offer increased target specificity and decreased off-target effects compared to small molecule drugs, they are unable to reach a large portion of target proteins present in cyst lumen due to their structure. Thus, we engineered a human dimeric IgA1 (dIgA) antibody - an isotype that is naturally secreted onto luminal surfaces, to target the cMET receptor on cyst-lining epithelial cells of Pkd kidneys. dIgAs have the unique ability to cross epithelial barriers via binding the polymeric immunoglobulin receptor (pIgR). We previously found pIgR highly upregulated in Pkd cyst-lining cells, giving rise to this novel dIgA targeting approach.

Methods: Human IgA1 chains are co-expressed in HEK293F cells and purified using Ni-NTA and AEX chromatography to obtain dimeric IgA suitable for in vitro functional testing as well as preliminary preclinical studies. Cystic (Bpk) and wildtype (WT) mice were treated once daily for 1 week with vehicle (PBS) or 20mg/kg anti-cMET dIgA.

Results: Our anti-cMET dIgA mAb has shown potent antagonistic function in the nanomolar range in vitro, and the ability to transytose via pIgR. The dIgA accumulated and remained stable for multiple days in cyst lumen after a single injection. 1-week cMET-dIgA treatment slowed cyst growth and improved kidney function in a rapid-onset Pkd mouse model.

Conclusions: We have shown it is feasible to utilize antagonistic mAbs against a number of growth factors/receptors implicated in PKD to slow cyst progression and even ameliorate kidney dysfunction, provided they are in dIgA format. This approach has the potential to eliminate all extra-renal side effects seen with small molecule drugs, and thus, would be tolerable and effective during long-term treatment in PKD clinical trials.

Funding: Other NIH Support - NIH (R01DK109563, R01DK124895), Other U.S. Government Support, Commercial Support - Chinook Therapeutics, Private Foundation Support

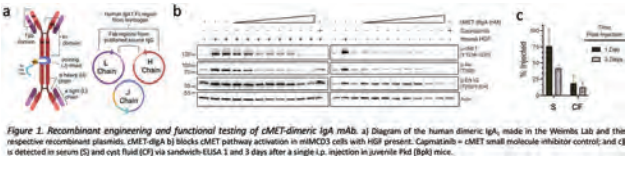


Figure 1. Recombinant engineering and functional testing of cMET-dimeric IgA mAb. a) Diagram of the human dimeric IgA, made in the Weimbs Lab and the respective recombinant plasmids. cMET-dIgA b) blocks cMET pathway activation in mIMCD3 cells with HGF present. Capmatinib = cMET small molecule inhibitor control; and c) is detected in serum (S) and cyst fluid (CF) via sandwich-ELISA 1 and 3 days after a single i.p. injection in juvenile Pkd (Bpk) mice.

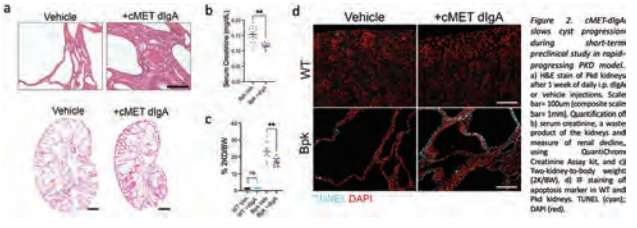


Figure 2. cMET-dIgA slows cyst progression during short-term preclinical study in rapid-progressing PKD model. a) H&E stain of Pkd kidneys after 1 week of daily i.p. dIgA or vehicle injections. Scale bar= 100um (composite scale bar= 1mm). Quantification of b) serum creatinine, a waste product of the kidneys and measure of renal decline, using QuantiChrom Creatinine Assay kit, and c) Two-kidney-to-body weight (2K/BW). d) TUNEL staining of apoptosis marker in WT and Pkd kidneys. TUNEL (cyan); DAPI (red).

TH-PO458

Adeno-Associated Virus 1 (AAV1) CFTR Gene Therapy Successfully Reduces Cysts in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease

Liudmila Cebotaru. *The Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation of multiple large cysts that lead to end-stage renal disease by the sixth decade of life. Current therapies for ADPKD involve treatment of the symptoms associated with kidney disease and/or organ transplantation. Cyst growth involves fluid secretion into the cyst lumen through the action of CFTR, located at the luminal membrane. We showed that CFTR correctors such as VX-809 alter the location of CFTR in cystic epithelia from the apical to the basolateral membrane, thereby reducing cyst formation. Here, we propose the novel hypothesis that a gene therapy based on CFTR can prove effective in reducing kidney damage in ADPKD.

Methods: To provide data showing that kidney transduction via systemic delivery is feasible, approximately 1-month-old, Pkd1$^{R3277C/R3277C}$ mice were injected intraperitonially with 2 × 10^{12} VP/kg of AAV1 containing either GFP or Δ27-264CFTR, a truncated version of CFTR that increases expression of endogenous CFTR via biomolecular interaction with endogenous CFTR defined as transcomplementation. Animals were necropsied 2 months after treatment and the kidney tissue was anaylised by immunoflourescence microscopy and H&E staining. Also the vector genome and DNA expression was quantified by real time PCR.

Results: The cyst area and size were less in the CFTR- compared to GFP-vector treated animals. We detected vector genomes at >4x10^5 vector genomes/ug DNA and mRNA expression at 4-8x10^4 copies/ug DNA after vector instillation. Tissues were co-stained with either NHE3 or ENaC to highlight proximal or collecting duct expression, respectively. Expression of GFP and CFTR above background levels consistent with protein expression were generated by both vectors. We detected more GFP in the vector-treated cystic cells compared to surrounding tissue suggesting that AAV1 is more specific for cysts than the cells surrounding the cysts. We detected more CFTR IF at the basolateral membrane in AAV1-CFTR treated kidneys suggesting that CFTR was restored to its normal location.

Conclusions: These experiments demonstrate convincingly that kidneys of RC/RC animals can be transduced by AAV1 and that phenotypic correction of defective function can be achieved by over expression of CFTR. Also the data suggests that CFTR plays a critical role in ADPKD.

Funding: NIDDK Support

TH-PO459

Effectiveness of MQ232 in an Orthologous ADPKD Mouse Model

Xiaofang Wang,[1] Li Jiang,[1] Jinghua Hu,[1] Nicolas Gilles,[2] Vicente E. Torres.[1]
[1]Mayo Clinic Minnesota, Rochester, MN; [2]Universite Paris-Saclay, Gif-sur-Yvette, France.

Background: The vasopressin V2 receptor (V2R) inverse agonist Tolvaptan ameliorates the development of polycystic kidney disease (PKD) in orthologous *Pkd1* and *Pkd2* mouse models and is the only currently approved drug for the treatment of autosomal dominant PKD (ADPKD). However, its benefits are hindered by the dose limiting aquaretic effect and potential hepatotoxicity. Mambaquaretin-1 (MQ1) is a peptide isolated from the venom of the green mamba snake that selectively blocks V2R. Vasopressin binds tightly to the V2R which can simultaneously activate G protein and β-arrestin signaling. Satavaptan, a Tolvaptan-related V2R inverse agonist, inhibits Gαs signaling and cAMP production while activating β-arrestin signaling. In contrast, MQ1 inhibits both V2R activated pathways.

Methods: To confirm the efficacy of MQ1 in an orthologous *Pkd1* mouse model and its relative potency compared to tolvaptan, we have treated male *Pkd1*$^{RC/RC}$ mice with MQ232 (an optimized modification of MQ1), 4 nanomoles/kg/hr via osmotic minipump, or with tolvaptan, 0.2% in powdered food and vehicle via osmotic minipump, along with control mice, from 4 to 16 weeks of age. Osmotic minipumps were replaced every 4 weeks.

Results: MRI kidney volumes at baseline were the same. Tolvaptan and MQ232 reduced kidney and cyst volumes and cAMP (Table 1). MQ lowered plasma urea. Both reduced the kidney tissue levels of p-Thr202/Tyr204 ERK1/2, p-Ser235/236 S6, p-Ser473 Akt, p-Thr308 Akt, and p-Ser9 GSK3β, more markedly in the MQ232 treated mice (Figure 1).

Conclusions: MQ232 ameliorates PKD in an ADPKD orthologous mouse model and is at least as effective as tolvaptan. Studies to further characterize the dose response effectiveness of MQ232 are in progress.

Funding: Other U.S. Government Support

Table 1

	Control (n=10)	Tolvaptan (n=10)	MQ232 (n=10)
Body wt (g)	30.1±1.4	29.4±1.5	29.0±1.4
Total Kid wt (g)	0.81±0.20	0.65±0.06*	0.60±0.11†
Kidney wt (%BW)	2.71±0.67	2.22±0.21*	2.05±0.33†
Kid Cyst Vol (µl)	214.1±99.3	139.7±41.6*	132.6±57.1*
Renal cAMP (pmol/mg protein)	16.1±7.18	10.8±1.7*	8.5±2.3†
Plasma Urea (mg/dl)	52.8±8.4	57.5±4.2	45.6±5.4*
24 hrs urine (ml)	1.05±0.35	5.24±1.98‡	4.90±0.92‡
End TKV (µl)	1059±234	872±172*	863±122*

ttest p value vs control: *<0.05; †<0.01; ‡ <0.001

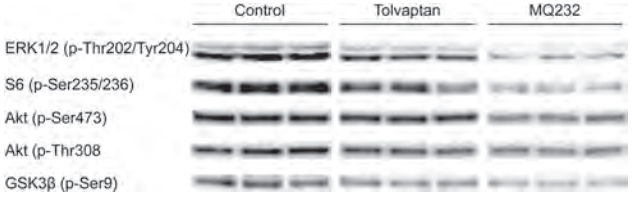


Figure 1

TH-PO460

Enteropeptidase Inhibitor SCO-792 Ameliorates Disease Progression in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease

Takuro Kawamura,[1] Fumihiko Hattanda,[1] Shun Takenaka,[1] Kanako Watanabe-Kusunoki,[1] Jun Sugama,[2] Yusuke Moritoh,[2] Masanori Watanabe,[2] Daigo Nakazawa,[1] Tatsuya Atsumi,[1] Saori Nishio.[3] *[1]Department of Rheumatology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; [2]SCOHIA PHARMA, Inc, Fujisawa, Japan; [3]Department of Hemodialysis and Apheresis, Hokkaido University Hospital, Sapporo, Japan.*

Background: Excess branched-chain amino acids activate the mammalian target of the rapamycin (mTOR) pathway, leading to disease progression of autosomal dominant polycystic kidney disease (ADPKD). Enteropeptidase inhibitor SCO-792 decreases amino acid absorption by inhibiting the digestive enzyme that converts protein to amino acids. This study aims to investigate the effects of SCO-792 on ADPKD model mice.

Methods: *Pkd1* gene conditional knockout mice (*Pkd1$^{flox/flox}$ Mx-1-Cre mice*) were randomly assigned to a vehicle group and a group treated with SCO-792 (SCO group). The vehicle group was fed a normal diet from day 28. The SCO group was fed a diet containing 0.003% (w/w) SCO-792 starting on day 28, and the dose level was increased to 0.01% from day 42. All mice were sacrificed at 98 days of age. We analyzed the phenotype of cystic kidneys by measuring kidney/body weight ratio (KW/BW) and kidney cystic index (CI), defined as the percentage of areas occupied by cysts. Additionally, we performed immunofluorescence staining of Ki-67 for kidney tissue to evaluate cell proliferation. We also conducted western blotting of the signaling pathway of cyst growth by using the whole kidney protein.

Results: Until day 42, there was no significant difference in body weight between the two groups. Following the administration of 0.01% SCO-792, the SCO group exhibited a significant reduction in body weight compared to the vehicle group. KW/BW tended to be lower in the SCO group than in the vehicle group. CI of the SCO group was significantly lower than the vehicle group (28.2 ± 10.8% vs 42.8 ± 13.6%, p=0.037). Serum urea nitrogen levels in the SCO group were significantly lower than the in vehicle group. The SCO group showed a significant decrease in Ki-67-positive cells in kidney compared to the vehicle group. In western blotting, phosphorylated-S6 protein was significantly downregulated in the SCO group compared to the vehicle group.

Conclusions: In the ADPKD mouse model, SCO-792 ameliorates renal cyst growth and kidney function decline by inhibiting the mTOR pathway activation.

Funding: Commercial Support - SCOHIA PHARMA, Inc

TH-PO461

Inhibition of Anoctamin 3 Attenuates Cystogenesis in Autosomal Dominant Polycystic Kidney Disease

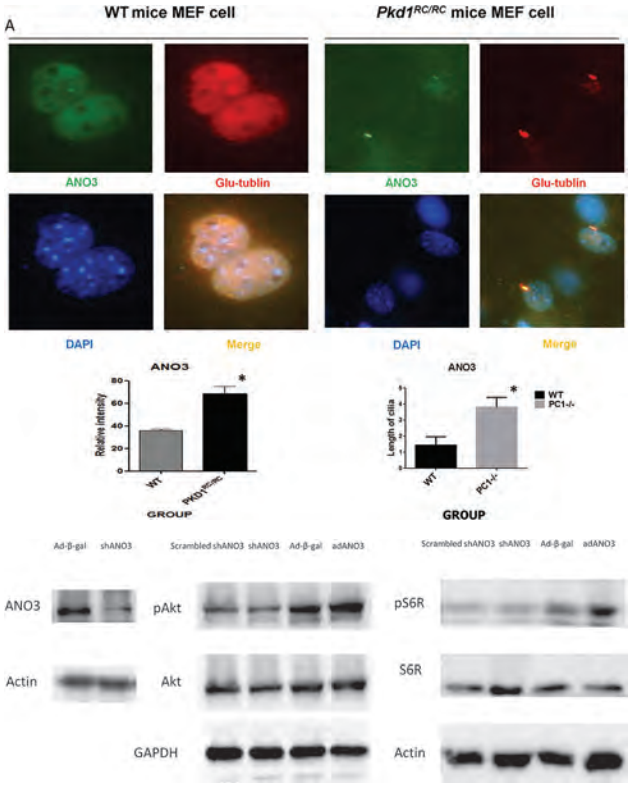
Tao Xu. Shanghai Jiaotong Medical University Affliated Shanghai 6th Hospital. *Shanghai Jiao Tong University, Shanghai, China.*

Background: Autosomal dominant polycystic kidney disease(ADPKD) is the most common inherited kidney disease, which is characterized by progressive growth of renal cysts. As we reported Anoctamin 1, one of chlorine channels family promotes both ciliogenesis and cyst formation in PKDcells. Wherever another member Anoctamin3(ANO3) was recently shown to be involved in ADPKD progression in our research. It seems there is nobody reported.

Methods: 1.RT RCR,WB and Immunohistochemistry to detect ANO3 in kidney tissue of ADPKD patients and normal kidndy tissue. 2.3Dculture to vertify the function of ANO3 in cysts formation in RCTE and IMCD3 cell with siANO3. 3.Co-immunofluorescence to investigate the impact of ANO3 on cilia and PC2 by siANO3. 4.WB to test the effect of ANO3 in proliferation signaling pathways. 5.To measure the kidney cyst index of Ano3$^{-/-}$:Pkd1 $^{flox/flox}$:CAG-creER$^+$mice by HE staining and MRI.

Results: 1.ANO3 located in renal tubules and renal cyst and high expression in human and mouse ADPKD kidneys. 2.shANO3 attenuated cyst formation in 3D culture cells. 3.ANO3 was localization on ciliary body and shANO3 increased the cilia length and the expression of PC2. 4.ShANO3 could attenuated cyst formation by inhibiting phosphorylation of AKT and mTOR signal pathways. 5.Cyst index of *PKD1 $^{flox/flox}$CAG-creER$^+$*mice was significantly decrease than which in PKD1$^{RC/RC}$mice.

Conclusions: Our data indicate inhibition of Anoctamin3 attenuates cystogenesis in ADPKD by decreasing phosphorylation of AKT and mTOR signal pathways.



TH-PO462

Targeting Growth Hormone/JAK2 Signaling as a Novel Therapy for Polycystic Kidney Disease Treatment

Fiona Macleod,[1,2] Maria Fragiadaki.[1,2] Maria Fragiadaki Lab. *[1]Queen Mary University of London Faculty of Medicine and Dentistry, London, United Kingdom; [2]The University of Sheffield Faculty of Medicine Dentistry and Health, Sheffield, United Kingdom.*

Background: PKD is characterized by renal cyst growth, fibrosis, and renal failure due to mutations in PKD1 or PKD2, leading to dysregulated JAK/STAT signaling. Our previous studies have shown elevated Growth Hormone (GH) levels and excessive JAK2/STAT5 activation in ADPKD mouse models. This study explores the therapeutic potential of targeting the GH/JAK/STAT pathway in ADPKD.

Methods: We conducted cystogenesis and proliferation assays in human cells. We employed three strategies to antagonise GH/JAK2 signaling: (i) GH receptor antagonist (GHA), (ii) ruxolitinib (a small molecule JAK2 inhibitor), and (iii) siRNA-mediated silencing of GHR/STAT5. Proliferation was measured by flow cytometry and qPCR. Ruxolitinib or vehicle control was administered to $Pkd1^{nl/nl}$ mice (n=20), and kidney function, fibrosis, inflammation and RNA-seq analyses were performed. GH and IGF-1 levels were measured by ELISA and GH receptor levels determined by immunohistochemistry.

Results: GH levels were elevated (~3-fold, P<0.01) in $Pkd1^{nl/nl}$ mice. GH receptor (GHR) was expressed in renal cyst-derived human cells and murine $Pkd1^{nl/nl}$ kidneys. RNA-seq analysis revealed that GH induces proliferation via mitogenic factors, including a ~4-fold increase in cyclin D1 expression (P<0.0001). GH stimulated significant increases in cell cycle progression and mitosis (P<0.01). Critically, ruxolitinib or GHA effectively countered GH-induced proliferation, inflammation, and STAT5 transcriptional activity (Ruxo-P<0.05; GHA-P<0.001) in renal cells. GH enhanced cyst growth in vitro, an effect fully antagonised by ruxolitinib, GHA, or GHR/STAT5 siRNA. In vivo, ruxolitinib treatment (50mg/kg) significantly reduced phosphorylation and activity of JAK2, which in turn led to improved renal function (P<0.05), reduced kidney size (P<0.05), and decreased fibrosis (P<0.01). Bulk-RNA-seq coupled with spatial transcriptomics revealed the transcriptome changes responsible for the anti-fibrotic and anti-proliferative properties of ruxolitinib treatment.

Conclusions: Our findings demonstrate the therapeutic potential of GH/GHR/JAK2/STAT5 antagonism in experimental ADPKD. Antagonizing JAK2 signaling leads to decreased fibrosis and improved renal function. We propose JAK2 antagonism as a promising strategy to decelerate the progression of ADPKD. These findings have implication for additional renal diseases characterised by fibrosis.

Funding: Government Support - Non-U.S.

TH-PO463

Exploring Therapeutic Potential of Neuropeptide Y in an ADPKD Mouse Model

Xiaobo Sun, Yan Huang, Xiaofang Wang, Li Jiang, Vicente E. Torres, Jinghua Hu. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common form of monogenic cystic kidney disease that often leads to End Stage Renal Disease (ESRD). Addressing the aberrant cAMP-PKA signaling pathway within cyst-lining renal epithelial cells has emerged as a promising therapeutic avenue for ADPKD patients. This study endeavors to delve into the influence of Neuropeptide Y (NPY) and its kidney-specific G_i-coupled receptors on modulating cAMP-PKA signaling and consequent ADPKD progression in the $Pkd1^{RC/RC}$ mouse model.

Methods: $Pkd1^{RC/RC}$ mice, aged 3 weeks and exhibiting similar Total Kidney Volume (TKV), were chosen and allocated randomly into control, Low dose NPY, and High dose NPY groups (n = 10/gender/group). Subsequently, these $Pkd1^{RC/RC}$ mice received intraperitoneal injections of 0.1mg/kg or 0.3mg/kg NPY for a further 12 weeks. Following the study period, magnetic resonance imaging (MRI) was conducted to ascertain Total Kidney Volume (TKV), while kidney samples were harvested for cystic index and cystic volume analysis. Plasma samples were also collected for Blood Urea Nitrogen (BUN) assessment. Statistical analysis was carried out utilizing two-way ANOVA.

Results: A significant reduction in TKV was observed in NPY-treated groups in comparison to the control group. Furthermore, although statistical significance was not attained, a dose-dependent downward trend in cystic index and cystic volume was noted. We observed a statistically significant decrease of BUN levels in low dose NPY group (22.2 ± 4.5 mg/dL) as compared to control (26.4 ± 6.0 mg/dL), while BUN in high dose treatment group also showed a trend of decrease (23.4 ± 5.7 mg/dL).

Conclusions: Our current study underscores the therapeutic potential of NPY in decelerating ADPKD progression within a preclinical mouse model. Future directions will entail 1) optimizing and augmenting NPY dosage for ADPKD mice treatment, 2) delineating and functionally distinguishing kidney-expressed NPY receptors in human and mouse renal epithelial cells, and 3) investigating the molecular interplay between NPY and Polycystin signaling in the context of ADPKD.

Funding: Other U.S. Government Support

TH-PO464

Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) Blockade as New Therapeutic Opportunity for Polycystic Kidney Disease

Laura Nuñez-Gonzalez,[1] Lucia Tejedor,[2] María Pereira Hernández,[1] Ana Barcia de la Iglesia,[1] Adrian Cordido,[1] Miguel A. Garcia-Gonzalez,[1] Marta Ruiz-Ortega.[2] *[1]Instituto de Investigacion Sanitaria de Santiago de Compostela, Santiago de Compostela, Spain; [2]Universidad Autonoma de Madrid, Madrid, Spain.*

Background: Polycystic Kidney Disease (PKD) encompasses a group of genetic disorders characterized by the presence of multiple cysts in the renal parenchyma, alongside extrarenal manifestations such as hepatic cysts, termed Polycystic Liver Disease (PLD). Autosomal Dominant Polycystic Kidney Disease (ADPKD), the dominantly inherited form, arises from mutations in genes *PKD1* and *PKD2*. Despite extensive research efforts, the precise mechanism underlying cystogenesis in PKD remains elusive. This study focuses on investigating the role of NOTCH signaling in ADPKD, given its documented activation in various progressive kidney diseases. Cystogenesis progression is marked by pronounced inflammation, with interstitial fibroblasts and macrophage polarization releasing chemokines, cytokines, and growth factors. Additionally, GREMLIN (one of the key mediators of NOTCH pathway) has emerged as a key mediator of chronic kidney disease in preclinical studies, with urinary levels proposed as potential biomarkers for renal diseases.

Methods: To assess the involvement of the Gremlin-VEGFR2 signaling pathway in cystic disease, we examined the expression of pathway proteins in both human samples and an orthologous murine model of ADPKD. Additionally, we validated the inhibition of VEGFR2 as a potential therapeutic strategy using an orthologous rapid progressive mouse model: B6.*Pkd1 cko/cko TamCre.*

Results: Our findings revealed upregulation of Gremlin/VEGFR2 pathway proteins in ADPKD, evident through transcriptomic and proteomic overexpression in ADPKD mouse kidney tissues, as well as in urine and cystic fluid from ADPKD patients. Treatment with Semaxinib, a specific VEGFR2 inhibitor, yielded beneficial effects in a short term-treatment in a rapid progressive ADPKD mouse model, including significant improvement in renal function (measured by BUN levels) as well as a significant reductions in cystic area.

Conclusions: This study sheds light on the altered role of the Gremlin/VEGFR2 pathway in cystogenesis and cyst growth progression in ADPKD. Moreover, the efficacy of a VEGFR2 inhibitor as demonstrated in a preclinical ADPKD model suggests a promising therapeutic avenue for PKD diseases.

TH-PO465

Role of Advanced Imaging Metrics in Predicting Outcomes in Patients Affected with Polycystic Kidney Disease

Timothy L. Kline,[1] Adriana Gregory,[1] Aaron Cohen,[2] Erin Ables,[2] Fouad T. Chebib,[8] Doug Landsittel,[3] Vicente E. Torres,[1] Peter C. Harris,[1] Frederic F. Rahbari-Oskoui,[4] Arlene B. Chapman,[5] Michal Mrug,[6] Alan S. Yu.[7]
[1]Mayo Foundation for Medical Education and Research, Rochester, MN; [2]Indiana University, Bloomington, IN; [3]University at Buffalo, Buffalo, NY; [4]Emory University, Atlanta, GA; [5]University of Chicago Division of the Biological Sciences, Chicago, IL; [6]The University of Alabama at Birmingham Division of Nephrology, Birmingham, AL; [7]The University of Kansas Medical Center, Kansas City, KS; [8]Mayo Clinic in Florida, Jacksonville, FL.

Background: The CRISP and HALT-A studies have provided significant longitudinal data on patients affected with ADPKD. This study utilized this data to compare advanced imaging metrics with a model built upon clinical information for predicting kidney health outcomes.

Methods: A cohort of 582 patients from the CRISP and HALT-A studies were included, all of whom had complete data for the following 'base model' variables: age, sex, serum creatinine, BMI, diastolic BP, hemoglobin, and CO2. Using the T2-weighted coronal sequences, standard imaging metrics such as total kidney volume (TKV) were measured. Additionally, from these same series, advanced imaging metrics were calculated using a previously developed AI-based tool, including total kidney cyst volume (TKCV), total cyst number (TCN), renal parenchyma volume (RPV), and cyst parenchyma surface area (CPSA). Statistical analyses were performed to compare the predictive power of these advanced imaging metrics with the base model, as well as explore their incorporation into the model.

Results: The analysis demonstrated that individual advanced imaging metrics (TKCV, TCN, RPV, CPSA) were comparable to the base model in predicting kidney health outcomes (see Table). The analysis demonstrated that individual advanced imaging metrics (TKCV, TCN, RPV, CPSA) were 1) comparable to the entire base model for prognosis of kidney failure, 2) were statistically significant and led to improvements in predicted risk when added to the base model.

Conclusions: Advanced imaging metrics offer valuable insights into kidney structure in PKD patients. Their individual predictive power for kidney health outcomes is on par with a multivariable model (i.e. the base model) and also their addition to the base model further improves the model's predictive potential. Further research is needed to explore the potential of these imaging techniques in clinical practice and their ability to predict long-term outcomes in PKD patients.

Funding: NIDDK Support

Comparison of Imaging Biomarkers

	c-index unadj*	c-index adj†	NRI 10 year‡	NRI 15 year‡
Base§	--	0.757 (0.708, 0.807)	--	--
MIC	0.622 (0.566, 0.678)	0.777 (0.729, 0.826)	0.696 (0.265, 1.109)	0.686 (0.41, 0.967)
HtTKV	0.737 (0.686, 0.787)	0.776 (0.726, 0.825)	0.73 (0.269, 1.133)	0.513 (0.22, 0.775)
TKCV	0.723 (0.672, 0.774)	0.765 (0.715, 0.815)	0.683 (0.28, 1.074)	0.577 (0.296, 0.841)
Tot. Cyst Num.	0.774 (0.726, 0.823)	0.81 (0.765, 0.855)	0.847 (0.475, 1.26)	0.655 (0.376, 0.925)
RPV	0.739 (0.685, 0.793)	0.785 (0.737, 0.834)	0.893 (0.408, 1.366)	0.738 (0.443, 1.035)
CPSA	0.779 (0.731, 0.826)	0.804 (0.757, 0.851)	0.782 (0.314, 1.216)	0.725 (0.442, 0.987)

Note:
For all models, N = 582 and N-event = 103
§ Base Model covariates: age, sex, serum creat, bmi, diastol, hemoglob, co2
* Unc c-index for unadjusted models
† Unc c-index for base model plus imaging biomarkers
‡ Continuous Net Reclassification Index at 10 and 15 years, for imaging biomarkers on top of base model

TH-PO466

Automated Segmentation of Individual Kidney Cysts in Routine Abdominal CT Images

Adriana Gregory,[1] Jeeho Im,[1] Muhammed Khalifa,[1] Fouad T. Chebib,[2] Vicente E. Torres,[1] Peter C. Harris,[1] Bradley J. Erickson,[1] Timothy L. Kline.[1]
[1]Mayo Foundation for Medical Education and Research, Rochester, MN; [2]Mayo Clinic in Florida, Jacksonville, FL.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder characterized by the development and growth of many cysts in the kidneys. Total kidney volume (TKV) is the main imaging biomarker used for disease progression prediction; however, advanced biomarkers like total cyst number (TCN) and cyst-parenchyma surface area have been shown to provide complementary information to TKV in MR imaging. Automated methods to segment individual kidney cysts in CT images of patients affected by PKD are still needed.

Methods: A 3D deep learning model using the nnUNet architecture was trained (n=60 CT images) to learn cyst edges and cores. Then, a postprocessing algorithm was applied to convert the semantic edge-core representation to instance (individual) cyst level segmentations. A 5-fold cross-validation was done to improve model robustness. The model was tested on 15 CT images not seen during training. The test set was manually segmented by two blinded readers to establish interobserver variability and the target performance for the model. The similarity between segmentations was assessed by Dice score, Bland Altman, and linear regression.

Results: The automated segmentation approach performed on par with human readers. Table1 shows the assessment metrics results. Significant agreement was observed between the readers and between each reader with the automated model. Figure1 presents an example test case.

Conclusions: This is the first model trained to segment individual cysts in contrast-enhanced CT images of patients affected by ADPKD. The initial results show good agreement between the model and segmentations of two expert readers.

Funding: NIDDK Support

Similarity metrics

	Reader1 vs Reader2	Reader1 vs Auto	Reader2 vs Auto
†Dice Score	0.88 ± 0.07	0.86 ± 0.05	0.88 ± 0.06
TCV Bias% [95% CI]	15.1 [9 to 22]	15.1 [9 to 21]	0.00 [-8 to 8]
TCV correlation (r)	1.00	1.00	1.00
TCN correlation (r)	0.97	0.97	0.96

†Mean ± st. dev.

TCV and TCN: total cyst volume and number

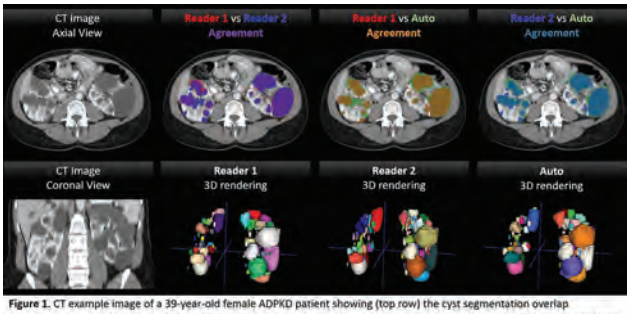


Figure 1. CT example image of a 39-year-old female ADPKD patient showing (top row) the cyst segmentation overlap agreement between the readers (Dice=0.89) and between each reader with the automated segmentation (Dice=0.87 and 0.88, respectively). (Bottom row) the 3D renderings of the readers and automated model segmentations (TCN: Reader1 183 cysts, Reader2 199 cysts, and automated 180 cysts). The cyst colors are not expected to match as they are assigned randomly.

TH-PO467

Phenotypic Characterization of Patients with ADPKD with PKD1 and PKD2 Pathogenic Variants Using Advanced Imaging Biomarkers

Abdul Hamid Borghol,[1] Fadi George Munairdjy Debeh,[1] Ahmad Ghanem,[1] Stefan N. Paul,[1] Bassel Alkhatib,[1] Nay Nader,[1] Adriana Gregory,[2] Hana Yang,[2] Christian Hanna,[2] Neera K. Dahl,[2] Timothy L. Kline,[2] Peter C. Harris,[2] Fouad T. Chebib.[1] *[1]Mayo Clinic in Florida, Jacksonville, FL; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Autosomal dominant polycystic kidney disease (ADPKD), caused by *PKD1* and *PKD2* pathogenic variants, is the fourth leading cause of kidney failure. The aim of this study is to compare the clinical and imaging biomarkers of ADPKD-*PKD1* and ADPKD-*PKD2* patients.

Methods: In this retrospective study, 602 ADPKD patients of the Mayo Clinic database were included based on having a pathogenic variant in *PKD1T* (50%), *PKD1NT1* (15%), *PKD1NT2* (14%), or *PKD2* (21%), and an abdominal imaging prior to any event that could affect kidney volume. Advanced imaging biomarkers were then assessed using an automated cyst segmentation deep learning model as shown in **Figure**.

Results: Of the included ADPKD patients, 408 (64.8%) were female, with a mean (±SD) age of 42.5 (±14.0) years. ADPKD-*PKD1T* and ADPKD-*PKD1NT1* patients had larger height-adjusted total kidney volume (htTKV), cyst-parenchymal surface area (CPSA), and total cyst number (TCN) compared to ADPKD-*PKD1NT2* and ADPKD-*PKD2*, with *PKD1T* showing the highest median htTKV (759.9mL/m), CPSA (1190 cm^2), and TCN (374). Additionally, median cyst index, defined by the fraction of total cyst volume (TCV) over TKV, was the highest in *PKD2* (0.43) and the lowest in *PKD1NT2* (0.28). Detailed analysis of the advanced imaging biomarkers is shown in **Table**.

Conclusions: ADPKD-*PKD1T* and ADPKD-*PKD1NT1* patients have bigger kidneys with more cysts, that occupy a larger total surface area of the parenchyma, compared to ADPKD-*PKD1NT2* and ADPKD-*PKD2* patients.

Table

	PKD1T	*PKD1NT1*	*PKD1NT2*	*PKD2*	p-value
N	303	90	82	126	
Age at imaging (yrs), mean (±SD)	38.5 (12.7)	43.8 (13.7)	44.6 (13.4)	48.9 (14.5)	<0.01
Height-adjusted total kidney volume (htTKV) (mL/m), median (Q1 – Q3)	759.9 (474.6 – 1236.9)	710.1 (461.4 – 1252.1)	538.0 (338.5 – 802.1)	651.0 (357.4 – 1388.3)	0.07
Percentage of patients with MIC-1C (%)	37.1%	23.6%	26.8%	36.9%	0.04
Total cyst volume (TCV) (mL), median (Q1 – Q3)	543.7 (246.9 – 1006.2)	466.2 (203 – 1094.1)	250.2 (96.3 – 563.6)	487.9 (147.2 – 1330.2)	0.02
Renal parenchymal volume (RPV) (mL), median (Q1 – Q3)	738.1 (539.6 – 1067.7)	705.9 (511.8 – 1115.2)	622 (479.7 – 864)	585.6 (422.7 – 937.7)	0.7
Cyst-parenchymal surface area (CPSA) (cm^2), median (Q1 – Q3)	1190 (636.8 – 2128.3)	1119.6 (532.3 – 2155.7)	785.6 (358.6 – 1308.9)	759 (330 – 1709.3)	<0.01
Total cyst number (TCN), median (Q1 – Q3)	374 (217 – 599)	362 (190.7 – 562)	298 (157 – 444)	225 (122.3 – 425.3)	<0.01
Cyst index (TKV/TCV), median (Q1 – Q3)	0.41 (0.29 – 0.49)	0.35 (0.27 – 0.54)	0.28 (0.17 – 0.43)	0.43 (0.24 – 0.57)	<0.01

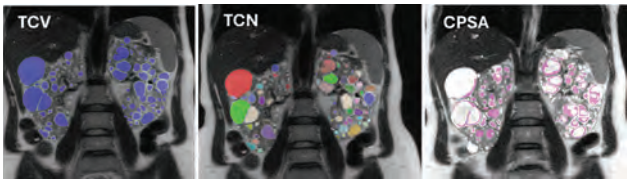


Figure: Advanced imaging biomarkers using deep-learning segmentation tool.

TH-PO468

Long-Term Trajectories of Kidney Function in ADPKD: Follow-Up of CRISP and HALT-PKD-Study A Cohorts

Frederic F. Rahbari-Oskoui,[1] Chelsie Parker,[3] Doug Landsittel,[2] Erin Ables,[3] Lilian Golzarri-Arroyo,[3] Peter C. Harris,[6] Arlene B. Chapman,[9] Vicente E. Torres,[6] Michal Mrug,[4] Fouad T. Chebib,[7] Kyongtae T. Bae,[10] William M. Bennett,[8] Alan S. Yu.[5] Consortium for Radiologic Imaging Studies of Polycystsic kidney disease (CRISP) and The HALT-PKD Trial. *[1]Emory University, Atlanta, GA; [2]University at Buffalo, Buffalo, NY; [3]Indiana University, Bloomington, IN; [4]The University of Alabama at Birmingham, Birmingham, AL; [5]The University of Kansas Medical Center, Kansas City, KS; [6]Mayo Clinic Minnesota, Rochester, MN; [7]Mayo Clinic in Florida, Jacksonville, FL; [8]Legacy Health System, Portland, OR; [9]University of Chicago Pritzker School of Medicine, Chicago, IL; [10]The University of Hong Kong Li Ka Shing Faculty of Medicine, Hong Kong, Hong Kong.*

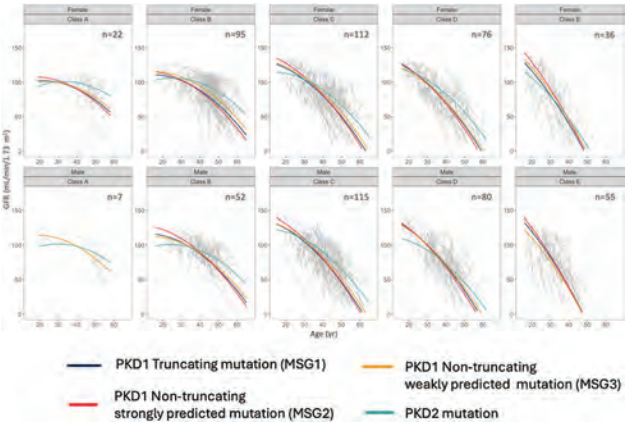
Background: Previously, we reported trajectories of estimated Glomerular filtration rate (eGFR) decline in 241 patients in the CRISP study. However, those reports were limited by the relatively small sample size and lack of external validation in other PKD cohorts. This study aimed to develop long term trajectories in a large PKD cohort that included the observational CRISP study and the HALT-PKD-Study A hypertension trial.

Methods: 721 patients (age 15-49 with baseline eGFR >60 mL/min/1.73 m^2) were included and followed for up to 21.2 years. Routine laboratory and detailed genetic results, and Mayo imaging class (MIC) were used in linear mixed models (including a term for age^2 and interactions with age) by forcing in essential variables and using a forward selection process to select other clinical biomarkers. Polynomial graphics and slopes of eGFR were calculated for each MIC per decade of life. Goodness of fit was assessed by calculating mean differences between observed and predicted eGFRs over 10-year age intervals.

Results: The best gender-specific polynomial trajectory models were developed by including age, sex, serum creatinine, ADPKD genotype mutation strength group, MIC, serum CO_2 and uric acid, and hemoglobin levels, diastolic blood pressure (DBP), race, presence of hypertension, and body mass index. The slopes of decline of eGFR vary widely from -0.39 to -5.89 (from slow to fast progressors) and continuously accelerated in time within each MIC.

Conclusions: We developed more robust, gender-specific, long-term trajectories of eGFR for each MIC category over 21.2 years of follow up, in a well-characterized ADPKD cohort. Serum CO_2, uric acid, hemoglobin, race, presence of hypertension, BMI and DBP were identified as additional parameters of relevance. External validation of these models is underway, on the Mayo PKD registry.

Funding: NIDDK Support



TH-PO469

Predicting the Relationship between Treatment Effects on Total Kidney Volume and eGFR in ADPKD Trials Using a Novel Modeling Approach

Alan S. Yu,[1] Chelsie Parker,[2] Lilian Golzarri-Arroyo,[2] Doug Landsittel,[3] Rekha Garg,[4] Edmund C. Lee.[4] CRISP Consortium. *[1]The University of Kansas Medical Center, Kansas City, KS; [2]Indiana University, Bloomington, IN; [3]University of Buffalo, Buffalo, NY; [4]Regulus Therapeutics Inc, San Diego, CA.*

Background: TKV is accepted by the FDA as a surrogate endpoint that is reasonably likely to predict clinical benefit in ADPKD and the most commonly used response biomarker for proof-of-concept intervention trials. However, the magnitude of treatment effect on TKV that would be predictive of a meaningful improvement in a clinical outcome, such as eGFR, is unknown. Inference of this from observational studies has previously been approached by examining inter-individual variance in the relationship between TKV and GFR slopes over time.

Methods: We developed a novel approach to modeling the intra-individual relationship between TKV and eGFR. Patients from the CRISP IV dataset were stratified by Mayo Imaging Class (MIC). Linear mixed models were fitted to eGFR with a fixed effect of log(TKV) and random intercepts, and the average slope within each MIC was estimated.

Results: We find that within each MIC there is a consistent, linear relationship between log(TKV) and eGFR (Fig. 1). The model predicts that within classes 1C–1E, for each 1% point per year reduction in TKV growth rate, the rate of eGFR decline would be reduced by approximately 0.4 to 0.5 mL/min/1.73 m^2 per year.

Conclusions: We have developed a new model that provides a framework for defining the magnitude of treatment effect on TKV that would support accelerated approval of a drug for ADPKD.

Funding: NIDDK Support

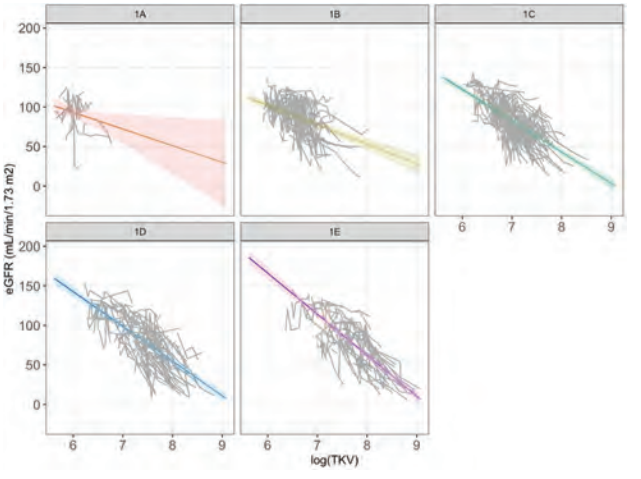


Fig. 1. Relationship between $\log_e$(TKV) and eGFR, subdivided by Mayo Imaging Class. Individual patient trajectories are shown in grey (N=487). Colored lines and shading show the modeled linear relationship and 95% confidence intervals from linear mixed models.

TH-PO470

Correlation of Total Kidney Volume (TKV), Total Liver Volume (TLV), and Combined TKV and TLV with Abdominal Symptoms in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Mauricio A. Miranda Cam,[1] Taher Dehkharghanian,[1] Saima Khowaja,[1] Xuewen Song,[1] Yasmina Sarie,[1] Korosh Khalili,[1] Timothy L. Kline,[2] York Pei.[1]
[1]University Health Network, Toronto, ON, Canada; [2]Mayo Foundation for Medical Education and Research, Rochester, MN.

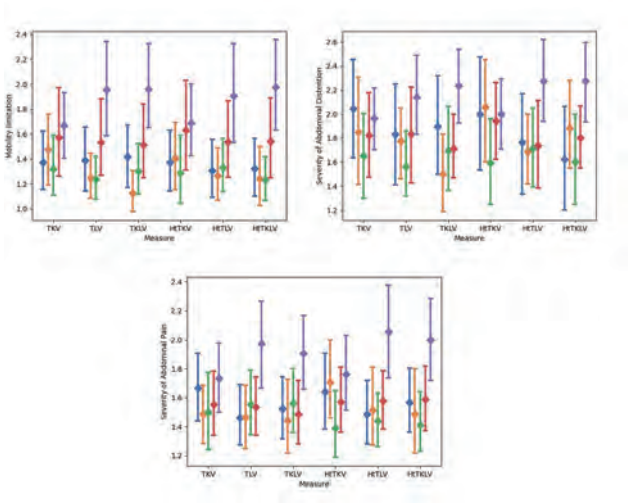
Background: Mass effect (e.g. early satiety, flank pain, abdominal distention and pain) symptoms from polycystic kidney and liver enlargement can result in clinically significant symptoms and complications, and negatively impact the quality of life in patients with ADPKD. Several studies have documented a significant correlation of these symptoms with TKV or TLV. Here we report a single center correlative study of mass effect symptoms with TKV, TLV, and combined TKV+TLV

Methods: Prospective study at the Center of Innovative Management in PKD in Toronto between October 2017-July 2021. All study patients had a clinical diagnosis of ADPKD based on kidney imaging, underwent a research protocol for detailed clinical and laboratory data, genetic testing and MRI measurements of height-adjusted (ht-) TKV, TLV, and combined TKV+TLV. Volume measures were divided by quintiles (Q). Mass-effect symptoms were assessed using a standardized research questionnaire and by review of their medical records

Results: The study cohort comprises 250 patients, with a mean age of 46 years and 56.4% female. Their median htTLV, htTKV, and htTKLV were 1182, 702, and 1884 ml/m, respectively. We found that Q4-Q5 discriminate patients with mobility limitation by all volumetric groups whereas Q5 discriminates the severity of abdominal distention and abdominal pain by htTLV and htTKLV (Figure 1). The lower bound of Q5 in htTKV, htTLV, and htTKLV were 1009, 1337, 2323 ml/m, respectively

Conclusions: Our study suggest specific thresholds that correlate with clinically important "mass effect" symptoms (i.e. mobility limitation, severity of abdominal distention and pain). Multivariate analysis will be performed to further delineate the effects of age, sex, and cystic organ volumetric with "mass effect" symptoms

Funding: Government Support - Non-U.S.



TH-PO471

Multicenter Longitudinal Cohort of Children and Adults with ADPKD: The PKD-Renal Research Consortium (PKD-RRC)

Stephen L. Seliger,[1] Terry J. Watnick,[1] Reem Mustafa,[2] Lisa M. Guay-Woodford,[3] Darren P. Wallace,[2] Alan S. Yu.[2] *[1]University of Maryland School of Medicine, Baltimore, MD; [2]The University of Kansas Medical Center, Kansas City, KS; [3]The Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Further progress in the clinical-translational investigation of ADPKD requires utilization of large, well-phenotyped, longitudinal cohorts of participants with linked biospecimens.

Methods: Patients with ADPKD have been enrolled in longitudinal observational cohorts at 3 sites: Children's National Hospital; Univ of Kansas Medical Center; and Univ of Maryland School of Medicine. In the NIH-supported PKD-RRC, a joint harmonized longitudinal database was created combining data in multiple demographic and clinical domains. Extracts of data and linked biospecimens (blood, urine, DNA) are available to investigators through a standardized request process. Baseline characteristics of study participants are displayed for pediatric ADPKD participants and for adults, the latter subdivided by imaging-based Mayo risk classification.

Results: The joint clinical database includes data on 416 participants with ADPKD and 1,432 individual study visits, and comprises 609 variables across multiple health and clinical domains. The database includes 59 pediatric (age ≤18) and 357 adults with ADPKD (table). Among adults, those at higher risk of progression per Mayo imaging classification had earlier diagnosis and were more likely to be male and to have hypertension and gross hematuria (p<.05)

Conclusions: The PKD-RRC joint clinical database of adults and children with ADPKD, linked to stored biospecimens, provides a robust resource for clinical and translational investigation. Enrollment and follow-up of this cohort remains ongoing.

Funding: NIDDK Support

Table – Characteristics of Participants at Baseline, by Age Group and Mayo Risk Classification

	Pediatric (N=59)	Adult - Mayo Risk Class				
		1A (N=41)	1B (N=74)	1C (N=108)	1D (N=73)	1E (N=61)
Age (years)	10.5 (4.9)	47.7 (15.7)	41.5 (14.5)	45.3 (15.0)	58.6 (12.9)	31.5 (8.4)
Female	33 (55.9%)	27 (65.9%)	50 (67.6%)	74 (68.5%)	38 (52.1%)	24 (39.3%)
White	47 (82.5%)	32 (78.1%)	58 (78.4%)	88 (81.5%)	63 (86.3%)	48 (78.7%)
African-American	3 (5.3%)	7 (17.1%)	12 (16.2%)	13 (12.0%)	8 (11.0%)	6 (9.8%)
Asian	7 (12.3%)	2 (4.9%)	4 (5.4%)	5 (4.6%)	2 (2.7%)	7 (11.5%)
Age at Dx	8.5 (5.3)	34.7 (14.4)	29.4 (12.0)	32.5 (12.2)	25.7 (12.2)	21.7 (9.0)
Family Hx of ADPKD	51 (86.4%)	35 (87.5%)	56 (81.2%)	87 (86.1%)	62 (87.3%)	44 (74.6%)
Hypertension	14 (25.9%)	27 (65.9%)	38 (52.8%)	74 (68.5%)	57 (78.1%)	48 (78.7%)
Gross Hematuria	5 (8.5%)	10 (24.4%)	10 (14.3%)	23 (21.7%)	29 (41.4%)	21 (35.0%)
Flank Pain	15 (25.4%)	21 (51.2%)	33 (46.5%)	53 (49.5%)	46 (63.0%)	30 (49.2%)
Kidney Stone	5 (8.5%)	6 (15.4%)	8 (11.3%)	16 (15.7%)	10 (14.9%)	12 (20.7%)
eGFR (ml/min/1.73m2)	102.6 (14.3)	76.8 (34.7)	88.0 (26.4)	78.6 (34.3)	79.9 (34.4)	84.5 (32.7)

Cell Values represent N(%) or mean (SD)

TH-PO472

Qualitative Analysis and Comparison of Externally Led, Patient-Focused Drug Development (EL-PFDD) Concepts for Autosomal Recessive Polycystic Kidney Disease (ARPKD) against Standardized Outcomes in Nephrology (SONG) Initiatives

Belle A. Soyfer,[1] Sorin V. Fedeles,[1,2] Wendy Vanasco,[1] Ronald D. Perrone,[3] Max C. Liebau,[4] Erum A. Hartung,[5] Katherine M. Dell,[7] Lisa M. Guay-Woodford,[5] Elise Hoover,[8] Dorothee Oberdhan.[6] *[1]Critical Path Institute, Tucson, AZ; [2]Yale University School of Medicine, New Haven, CT; [3]Tufts Medical Center, Boston, MA; [4]Universitatsklinikum Koln Klinische Infektiologie, Koln, Germany; [5]The Children's Hospital of Philadelphia, Philadelphia, PA; [6]Otsuka Seiyaku Kabushiki Kaisha, Chiyoda-ku, Japan; [7]Cleveland Clinic Children's Hospital, Cleveland, OH; [8]PKD Foundation, Kansas City, MO.*

Background: ARPKD is an area of huge unmet need with no approved treatments. An EL-PFDD meeting in 2023 collected patient and caregiver concepts regarding burden of disease and treatment preferences. The Standardized Outcomes in Nephrology (SONG) initiatives previously captured qualitative data from large international cohorts including pediatric CKD, but the EL-PFDD focused specifically on individuals and families with ARPKD.

Methods: A thematic synthesis and comparison among SONG-Transplant (Tx), SONG-Children and Adolescents (SONG-Kids), SONG-Polycystic Kidney Disease (PKD, focused on autosomal dominant PKD), and the ARPKD EL-PFDD was conducted.

Results: All participants from the EL-PFDD and SONG-PKD had a diagnosis of ADPKD, compared to 6% in SONG-Kids and 27% in SONG-Tx. The EL-PFDD represented patients and caregivers while the SONG had additional concepts from healthcare professionals, as well. Common themes included disease inevitability, multi-organ involvement, treatment complications, blood pressure, kidney function, graft function and loss, self-esteem, desire for normality, mental health, and life participation. Exploratory findings between the EL-PFDD and SONG-Kids found disease inevitability and uncertainty, treatment complications and risks, blood pressure, kidney function, life participation, treatment, and failure to thrive. Concepts unique to the EL-PFDD included heterogeneous disease, body image related to extended abdomen and height, deficiencies of currently available treatment options, and goals for future research. Additionally, the EL-PFDD discussed supportive ARPKD therapies, unmet needs of currently available treatment options, and goals for future research.

Conclusions: The EL-PFDD meeting captured patient and caregiver insights that will impact the advancement of biomarkers and drugs whose benefits are aligned with the patient experience. The EL-PFDD highlighted the need for ARPKD-specific standardized outcomes due to its unique pathophysiology distinct from pediatric CKD etiologies. The analysis of combined elements from the SONG initiatives and EL-PFDD will facilitate future development of outcome tools and treatment plan designs.

Funding: Other U.S. Government Support, Commercial Support - Otsuka Pharmaceuticals, Private Foundation Support

TH-PO473

Sex and Aging Influence the Association between Kidney Prognosis and Anemia in Patients with ADPKD: Attribute-Based Medicine (ABM) Insights

Ken Tsuchiya,[1] Hiroshi Kataoka,[1] Shun Manabe,[1] Yusuke Ushio,[1] Momoko Seki,[1] Kosaku Nitta,[1] Toshio Mochizuki,[2] Junichi Hoshino.[1] *[1]Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan; [2]PKD Nephrology Clinic, Tokyo, Japan.*

Background: Although anemia is traditionally considered a marker of poor renal prognosis in CKD, the significance and the prognostic role of anemia in ADPKD remains clearly unexplored. Recently, the significance of ABM has been underscored, and the effects of anemia on CKD progression may differ between young male and elderly female patients with ADPKD. We aimed to examine the effects of sex and aging to CKD progression of ADPKD using various levels of anemia.

Methods: We enrolled 553 ADPKD patients. Renal outcome, defined as a 30% reduction in eGFR or initiation of renal replacement therapy, was assessed using Cox regression analysis. Five thresholds of anemia were considered: 1) Hb <12 g/dL in men and Hb<11 g/dL in women; 2) Hb<13 g/dL in men and Hb<12 g/dL in women; 3) Hb<11 g/dL; 4) Hb<12 g/dL; 5) Hb<13g/dL. For subgroup analyses, cross-classification (4 groups) of sex × 50 years was also used for analyses per attribute.

Results: The cohort's median age was 43 years old, with median eGFR of 55.9 mL/min/1.73 m^2, and a median total kidney volume of 1335.4 ml. Over a median follow-up period was 9.1 years, renal outcomes were observed in 236 patients. Multivariable Cox analyses revealed that anemia (2: Hb<13.0 g/dL in men, Hb<12.0 g/dL in women; HR=1.81, P=0.0004) had the strongest association with kidney disease progression in the entire cohort. Subgroup analyses showed significant associations between kidney disease progression and anemia (5: Hb<13.0 g/dL; HR=3.46 in men <50 years old, HR=3.11 in men ≥50 years old), anemia (4: Hb<12.0 g/dL; HR=2.00 in men <50 years old), and anemia (3: Hb<11.0 g/dL; HR= 2.18 in women ≥50 years old).

Conclusions: In ADPKD patients, a higher threshold for anemia (Hb<13.0 g/dL in men, Hb<12.0 g/dL in women) was associated with kidney prognosis. Furthermore, cross-classification analysis revealed differential associations between higher thresholds of anemia and renal prognosis in male and younger patients, while a lower threshold (Hb<11.0 g/dL) was associated with renal prognosis in elderly women (women ≥50 years old). These findings underscore the utility of ABM care, employing cross-classification, in managing anemia in ADPKD patients.

Funding: Government Support - Non-U.S.

TH-PO474

Long-Term Changes in Liver and Kidney Cyst Volumes following Foam Sclerotherapy

Cassie Howe,[1] Ryan Helland,[1] Lisa E. Vaughan,[2,1] Timothy L. Kline,[1] Adriana Gregory,[1] Vicente E. Torres,[1] Marie C. Hogan.[1] Div of Nephrology, Mayo Clinic. *[1]Mayo Clinic Research Rochester, Rochester, MN; [2]Mayo Quantitative Health Sciences, Rochester, MN.*

Background: This medical center uses sotradecol foam sclerotherapy (SFS) in managing symptomatic kidney/ liver cysts. Using ultrasound & fluoroscopy, kidney/ liver cysts (≥5cm; up to 4/session) are targeted for SFS. A drain is placed into the cyst, contrast injected, aspirated & sclerosant instilled (3% sodium tetradecyl sulfate). We have performed SFS in >200 individuals & evaluated durability in a subset of patients with longerm sequential imaging.

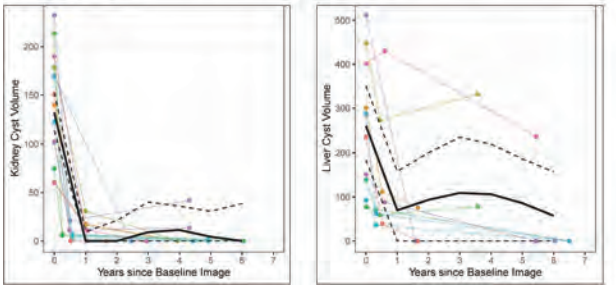
Methods: Cases from 1/2017-12/2021 with available TKCV /TLCV (per Targeted Kidney or Liver or Cyst analysis) and with long-term image follow up were segmented using a deep-learning algorithm and cyst segmentation software (pre, post procedure and last imaging). Median TKCV/ TLCV percent change per patient were evaluated using the 1-sample Wilcoxon signed rank test. Changes in liver and kidney cyst volumes over time were modeled using linear mixed effects regression methods with time modeled as a restricted cubic spline term.

Results: One hundred forty five SFS sessions were performed on 102 unique individuals (62 kidney, 74 liver, 9 combined liver/ kidney cysts). A total of n=78 kidney cysts in 34 patients and n=138 liver cysts in 46 patients with pre and post imaging within 6 mo prior to procedure & at least 2 mo post-procedure, respectively. Median [interquartile range, IQR] % reductions in TKCV were -92.0% [IQR-98.2%, -82.7%]; (p<0.001) & for TLCV -83.1% [IQR -93.5%, -52.9%]; (p <0.001). Among 12 patients with multiple follow-up images available (2 follow-up images for all patients), there were a total of 72 cysts (30 liver & 42 kidney cysts). Both liver & kidney cyst volumes sharply declined to near 0 around 1 year follow-up, and then remained relatively stable several years later (P<0.001 for non-linear associations for both liver & kidney cyst volumes using LRT test). **Figure 1.**

Conclusions: Foam sclerotherapy is durable and is an option for management of individuals with symptomatic large kidney and liver cysts.

Funding: NIDDK Support, Private Foundation Support, Clinical Revenue Support

Change in A) kidney and B) liver cyst volumes over time, among patients with multiple follow-up imaging available. Colored dots and lines denote different cysts. Black solid line denotes estimated average cyst volumes and dotted lines denote estimated 95% confidence interval using a regression linear mixed modeling approach with random intercepts for each patient.



Change in targeted kidney and liver cyst volumes over time.

TH-PO475

Cell-Free and Concentrated Ascites Reinfusion Therapy Is More Effective for Refractory Ascites in Patients with Autosomal Dominant Polycystic Kidney Disease

Shigekazu Kurihara,[1,2] Tatsuya Suwabe,[1] Masayuki Yamanouchi,[1] Yoshifumi Ubara,[1] Yuji Kamijo,[2] Naoki Sawa.[1] *[1]Toranomon Byoin Bunin, Kawasaki, Japan; [2]Shinshu Daigaku, Matsumoto, Japan.*

Background: Refractory ascites is one of frequent complications in patients with autosomal dominant polycystic kidney disease (ADPKD). Cell-free and Concentrated Ascites Reinfusion Therapy (CART) is known to be an effective treatment for refractory ascites. However, its efficacy in patients with ADPKD is unknown.

Methods: In this retrospective cohort study, we enrolled all patients (age > 18 years) with refractory ascites, who were treated with CART or simple abdominal paracentesis between January 2013 and December 2023 at the Toranomon Hospital Kajigaya in Japan. Patients who were diagnosed as liver or kidney cystic infection at the time of CART or paracentesis were excluded. Patients who underwent CART at least once were assigned in the CART group. Patients who had never undergone CART and underwent only paracentesis were assigned in the paracentesis group. We compared clinical characteristics and overall survival between the two groups, and analyzed factors associated with overall survival of the patients.

Results: A total of 42 patients underwent CART or paracentesis. 14 patients were excluded due to diagnosis of cyst infection. We enrolled 18 patients in the CART group (male 4; age 54.3±8.8 years, median observational periods 747 days) and 10 patients in the paracentesis group (3; 58.2±6.3 years, 568 days). There were no significant differences in clinical characteristics of the patients at baseline between two groups. 4 patients died in the CART group, while 6 patients died in the paracentesis group during the observation period. Kaplan-Meier survival curves indicated that patients in CART group had better overall survival(p=0.035). Univariable and multivariable cox proportional hazards regression analyses revealed CART and hemodialysis were significant factors associated with overall survival. The change in serum albumin level was +0.15 g/dL in the CART group and -0.10 g/dL in the paracentesis group (p=0.006). The patients in CART group had significantly more overall adverse events including mild adverse events such as transient fever; however, no serious adverse events were observed.

Conclusions: In patients with ADPKD accompanied by refractory ascites, CART improves overall survival without increasing serious complications compared to abdominal paracentesis.

TH-PO476

Early PKD Observational Cohort (EPOC) Study: Advancing Early Detection of Polycystic Kidney Disease

Vinamratha Rao,[1] Catherine Creed,[1] Rebecca J. Lepping,[1] Arlene B. Chapman,[2] Darren P. Wallace,[1] Reem Mustafa,[1] Alan S. Yu.[1] *[1]The University of Kansas Medical Center, Kansas City, KS; [2]University of Chicago Division of the Biological Sciences, Chicago, IL.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, often leading to renal failure. Early intervention, especially in children, is hindered by the lack of reliable biomarkers to detect and monitor early cyst growth. Longitudinal data, biospecimens and imaging from children and young adults are needed to address this gap.

Methods: EPOC is an observational longitudinal study of individuals aged 4-35 with an eGFR>80ml/min per 1.73m2. Individuals with ADPKD, siblings known to be unaffected and those with uncertain diagnosis ("at-risk" siblings), and healthy unaffected volunteers, were recruited from the University of Kansas, University of Chicago and Children's Mercy Hospital Kansas City. Clinical history, vital signs, serum chemistry, and urine protein were collected at baseline and annually up to 5 years. Urine, urinary

exosomes, plasma, sera and DNA are stored in a biorepository. For ADPKD participants, abdominal MRI scans were performed at baseline and every 2 years to measure height-adjusted total kidney volume(HtTKV).

Results: The EPOC study enrolled 51 healthy controls, 112 individuals with ADPKD, 7 unaffected siblings, and 21 at-risk siblings, with a balanced gender distribution of 56% females. The cohort was predominantly White (80%), with 10% Asian, 8% Black or African American, 1% Native Hawaiian/Pacific Islander, and 6% Hispanic or Latino ethnicity. The median age was 22.2 years (range:4.1-34.7). 82% of those with ADPKD had family history of the disease. Of the 102 genotyped individuals, 88% had PKD1 mutations, 9% PKD2, 2% IFT140, and 1% had both PKD1 and PKD2 mutations. The median baseline HtTKV was 365.6 ml/m (IQR: 267-528.7 ml/m, N=98), with Mayo Imaging Classifications of 10.2% (Class 1A), 22.4% (Class 1B), 26.5% (Class 1C), 20.4% (Class 1D), and 20.4% (Class 1E). Common baseline complications in the ADPKD group included hypertension (39%), flank pain (37%), and urinary tract infection (28%).

Conclusions: We have recruited a cohort of children and young adults with very early ADPKD. This biorepository is uniquely poised to facilitate discovery of novel biomarkers and prognostic models in pediatric ADPKD. The inclusion of unaffected controls and at-risk siblings is novel, providing critical comparative data for understanding early-stage disease.

Funding: NIDDK Support

TH-PO477

Correlation between PKD1 Mutation Type and Height-Adjusted Total Kidney Volume in Chinese Patients with ADPKD: Genotype-Phenotype Analysis

Zhiying Liu, Jiayi Zhang, Shu Qu, Mengshi Li, Yang Li, Hong Zhang, Xu-jie Zhou. *Peking University First Hospital, Beijing, China*.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited kidney disease but with allelic and genetic heterogeneity. This study aims to explore the association between PKD1 mutation types and height-adjusted total kidney volume (htTKV) in Chinese ADPKD patients.

Methods: We evaluated genotype-phenotype correlations in 379 subjects with affected ADPKD between August 25, 2017 and April 2, 2024. Patients with complex genotypes (mosaic, digenic, or diallelic) were excluded. We performed regression analysis to examine the effects of age, sex, and mutation type on htTKV natural log scale.

Results: 90.5% of the patients got molecularly diagnosed with PKD1 (82.3%, n=312) and PKD2 (7.9%, n=30) in the current study. PKD1 truncating mutations accounts for 67.3% of the patients (Figure 1). Men had more severe disease than women with lower eGFR and larger htTKV (Figure 2, A and B). Patients with nonsense and frameshift mutations showed faster eGFR decline compared to missense mutations (Figure 2C). Patients with PKD1 truncating mutations generally have larger htTKV than non-truncating mutations (P<0.005) (Figure 2D). Allelic effect on htTKV was more significant in splicing, frameshift and nonsense mutation classes (Figure 2E).

Conclusions: In Chinese ADPKD patients, we confirmed that kidney cyst severity differs by mutation types in PKD1. Patients with PKD1 truncating mutations have higher TKV and lower eGFR, particularly frameshift and nonsense mutations. Assessment of mutation types may predict renal prognosis and aid in caring for high-risk ADPKD patients.

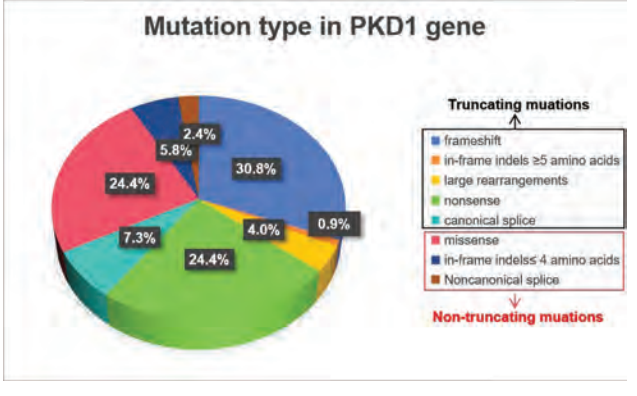


Figure 1. Categories of mutation type in PKD1 population.

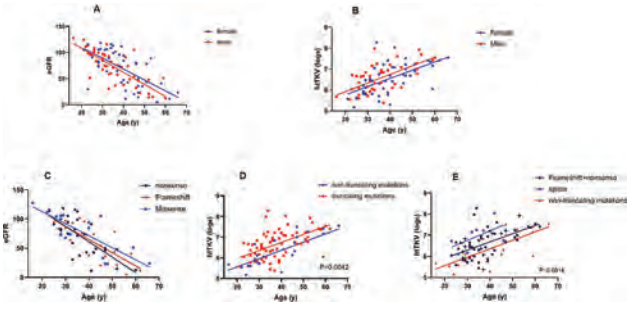


Figure 2. Sex and allelic effects on ADPKD phenotype in PKD1 population.

TH-PO478

Correlation of Genotype with Age at Disease Onset and Hypertension Diagnosis in Autosomal Dominant Polycystic Kidney Disease

Dimitra Gkalitsiou,[1] Eirini Evangelou,[1] Maria Konsta,[2] Kiriaki Vasiliou,[1] Aggeliki Poula,[1] Niki Markou,[1] Tsielestina Poulli,[1] Danai Palaiologou,[3] Konstantina Kanellopoulou,[1] George I. Tsirpanlis.[1] *[1]General Hospital of Athens Georgios Gennimatas, Nephrology Department, Athens, Greece; [2]Department of Rheumatology, Sismanoglion General Hospital, Athens, Greece; [3]Genesis Genoma Lab, Genetics Diagnosis, Clinical Genetics & Research, Athens, Greece*.

Background: Autosomal Dominant Polycystic Kidney Disease is the predominant genetic disease leading to End Stage Kidney Disease. Genetic identity could correlate to disease profile. Correlations between genetic and phenotypic characteristics in a cohort of ADPKD patients are investigated.

Methods: Genetic analysis was conducted in 85 ADPKD patients, using targeted Next Generation (tNGS) or Sanger Sequencing and Multiplex ligation-dependent probe amplification (MLPA). Medical history, clinical and laboratory data, including MRI for Total Kidney Volume (TKV) measurement, were recorded and subsequently correlated to the respective genotypes.

Results: Eighty-five patients (43 females, 42 males, 33±16 years old) were included. The mean age at diagnosis was 21.5±13 (0.6-69) years. Familial history of ADPKD was present in 58 patients (68%). The mean age at which the affected parent reached ESKD was 53.0±9 years. Hypertension was diagnosed in 60 patients (71%) within the study cohort. The mean age at HTN diagnosis was 31±11 years. In the assessment based on height-adjusted TKV and age, Mayo Clinic Imaging Categories revealed that 9% of patients were classified as 1A, 20% as 1B, 29% as 1C, 29% as 1D, and 13% as 1E. Mutations in PKD1 gene were detected in 70 patients (82%), with 61% exhibiting truncating and 39% non-truncating mutations, while PKD2 mutations were identified in 15 patients (18%). The average age of ADPKD diagnosis varied among genetic subgroups. Patients carrying PKD1-truncating mutations were diagnosed at 17.6±11 years, those with PKD1-non-truncating mutations at 24.5±12 years, and those with PKD2 at 27.3±16 years (p = 0.01). Moreover, the mean age at which the affected parent reached ESKD was 50±8 years, 55±10 and 60±7 years in PKD1-truncating, PKD1-non-truncating and PKD2 patients respectively (p = 0.04). Additionally, the mean age of HTN diagnosis was 29±12 years in PKD1-truncating, 30±10 years in PKD1-non-truncating and 40±7 years in PKD2 patients (p = 0.05).

Conclusions: Mutation type correlates with the age of ADPKD diagnosis, renal survival within families and hypertension onset. Patients with PKD1-truncating mutations manifest an earlier onset of both disease and hypertension compared to those with PKD2 mutations.

TH-PO479

Association of Tumor Necrosis Factor Receptor 1 (TNFR1) and TNFR2 with Kidney Volume and Function in Patients with ADPKD

Seyda G. Ozcan,[1] Metin Ergul,[2] Durdane Y. Ersoy,[1] Mevlut T. Dincer,[1] Ibrahim M. Bolayirli,[1] Necmi Eren,[2] Nurhan Seyahi.[1] *[1]Istanbul Universitesi-Cerrahpasa Cerrahpasa Tip Fakultesi, Fatih, Turkey; [2]Kocaeli Universitesi, Kocaeli, Turkey*.

Background: ADPKD is a genetic disorder with numerous kidney cysts, leading to increased kidney volume and compromised kidney function. TNF receptors (TNFR1,TNFR2) mediate the intracellular effects of TNF-α, an inflammatory cytokine that may influence cyst growth in ADPKD. We aimed to investigate the association between TNFR1/TNFR2 levels and kidney function and volume in ADPKD patients.

Methods: We recruited adult ADPKD patients(Mayo Class IC-E). Serum TNFR1/TNFR2 levels were measured using ELISA. Kidney volumes were assessed using MRI.

Kidney function was evaluated using serum creatinine and cystatin C-based eGFR. Statistical analysis was performed to determine correlations between TNFR levels, kidney volumes, and function.

Results: We examined a total of 50 patients. Demographic, clinical, and laboratory data are shown in Table 1. No significant correlations were found between kidney volume and TNFR1/TNFR2 levels. There was a weak negative correlation between eGFR and TNFR1(r=-0.332,p=0.019). TNFR1 and TNFR2 levels were not significantly different between Mayo stages D-E and C.

Conclusions: TNFR1 may be associated with decreased kidney function in ADPKD. Longitudinal studies are needed to determine if a causal relationship exists between TNFR levels and kidney function. Further research is warranted to explore other potential biomarkers influencing kidney enlargement and functional decline in ADPKD patients.

Variables	
Age, years	41.1 ± 9.1
Female, %	52.0
BMI, %	26.2 ± 5.5
Comorbid disease, %	
-Hypertension	87.8
-Coronary heart disease	4.2
-Diabetes mellitus	4.0
Family history, %	76.0
ACEi, ARB use, %	88.0
Mayo Classification, %	
-Class 1C	24.5
-Class 1D	59.2
-Class 1E	16.3
Urea, mg/dL	38.8 ± 22.6
e-GFR, ml/mm/1.73 m^2	30.7 ± 12.8
Sodium, mmol/L	140.5 ± 2.9
Potassium, mmol/L	4.55 ± 0.4
Hemoglobin, g/dL	13.8 ± 1.8

TH-PO480

Association between Nephrolithiasis and Kidney Disease Progression in Patients with Autosomal Dominant Polycystic Kidney Disease from a Single-Center, Prospective Cohort

Hongran Moon, Hyunjin Ryu, Yong Chul Kim, Yun Kyu Oh. *Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Nephrolithiasis is a common complication in Autosomal dominant polycystic kidney disease (ADPKD) patients. A few in vitro and in vivo studies showed that kidney and ureter stone formation could accelerate renal disease progression in ADPKD. However, its association between nephrolithiasis and renal function deterioration remains unknown in ADPKD patients.

Methods: This single-center prospective cohort study, HOPE-PKD, analyzed 410 subjects who underwent abdominal CT scans within a year before enrollment. Subjects were divided into stone (n=80, 19.5%) and no-stone (n=330, 80.5%) groups based on CT findings. The primary outcome was the initiation of renal replacement therapy due to end-stage renal disease, and the secondary outcome was a composite of a 50% decline in eGFR, doubling of serum creatinine, or initiation of renal replacement therapy.

Results: There was no statistical difference in baseline characteristics between the stone and no-stone cohorts. During a median 5.18 [interquartile range 3.41 - 8.03] year of follow-up, the primary and secondary outcomes occurred in 51 (12.4%) and 96 (23.4%) patients, respectively. In the unadjusted Cox regression analysis, there was no significant difference in the survival analysis between the two groups. However, after adjusting possible confounding factors (age, sex, body mass index, eGFR, comorbidity of hypertension and diabetes, serum uric acid, phosphorous, calcium level, results of PKD1 and PKD2 gene analysis, and Mayo classification), the stone group showed an increased risk of the primary and secondary outcome of HR 2.84 (95%CI 1.26 - 6.38; p-value 0.012) and HR 1.83 (95% CI 1.03 - 3.27; p-value 0.041), respectively compared to the no-stone group (Figure 1).

Conclusions: This study demonstrates an association between nethrolithiasis and adverse renal outcome in ADPKD patients, underscoring the need for further clinical studies to enhance renal outcomes.

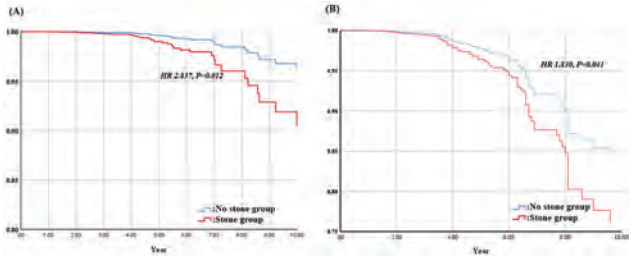


Figure 1. Survival curve for primary outcome (A) and secondary outcome (B) obtained by means of multivariate Cox regression model, in model 4.

TH-PO481

Effect of Oral Antibiotic Exposure on Urine Lithogenic Profile in ADPKD

Wei Wang,[1] Anna Ostrow,[1] Jelena Klawitter,[1] Kristen L. Nowak,[1] Erin R. Coleman,[1] Diana George,[1] Lama Nazzal,[2] Huilin Li,[2] David S. Goldfarb,[3] Berenice Y. Gitomer,[1] Michel Chonchol.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]New York University, New York, NY; [3]New York University Grossman School of Medicine, New York, NY.*

Background: Oral antibiotic use alters the gut microbiome leading to an increase in urine oxalate and risk for nephrolithiasis. However, this novel risk factor has not been explored in ADPKD patients who are frequently treated with oral antibiotics for recurrent urinary tract (UTI) and kidney cyst infections. The high incidence of KSD in patients with ADPKD underscores the importance of understanding this potential risk factor for progression.

Methods: Diagnosis of ADPKD was based on imaging or genetic testing and participants were required to have an eGFR ≥ 45 ml/min/1.73m^2. Subjects were recruited nationally between 2021-2024 and were stratified based on recent antibiotic use within the previous 6 months or no antibiotic use within the previous 3-years (control group). All participants had no history of KSD within the previous 5-years. Diet was assessed by ASA24 dietary intake tool (NCI) on 3-separate occasions and subjects completed a 24-hour urine and stool collection. The urine stone risk profile was assessed by Litholink™ (Labcorp, Itasca, Illinois).

Results: To date 15 participants with a history of antibiotic use (mean age 41±8 years) and 13 participants with no antibiotic use (mean age 41±8 years) have completed the study. All participants are female most likely due to the higher prevalence of UTI in females. Mean eGFR was 80±10 ml/min/1.73m^2 in subjects with recent antibiotic use and 79±12 ml/min/1.73m^2 in control subjects. The mean age 24-hour urine calcium excretion was significantly higher in patients with antibiotic use compared to the control subjects (136.5±63.5 vs. 91.2±52.7 mg/day P= 0.05). The supersaturation of calcium phosphate was also higher in patients with recent exposure to antibiotics compared to controls (0.67±0.69 vs. 0.28±0.22, P=0.06), however it did not reach significance. Urinary oxalate and citrate excretion did not differ between groups.

Conclusions: Patients with recent exposure to antibiotics have higher daily urine calcium excretion levels despite no apparent dietary differences. Analysis of additional subjects and fecal samples will be necessary to fully evaluate the potential effects of antibiotics in this patient population.

Funding: NIDDK Support, Private Foundation Support

TH-PO482

Kidney Stone Incidence Rate in Patients with ADPKD, 2000-2023

Anna Ostrow,[1] Zhiying You,[1] David Turnbull,[2] Tom Belnap,[2] Sanjiv Anand,[2] Lama Nazzal,[3] Huilin Li,[3] David S. Goldfarb,[4] Kristen L. Nowak,[1] Berenice Y. Gitomer,[1] Michel Chonchol.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Intermountain Healthcare, Salt Lake City, UT; [3]New York University, New York, NY; [4]New York University Grossman School of Medicine, New York, NY.*

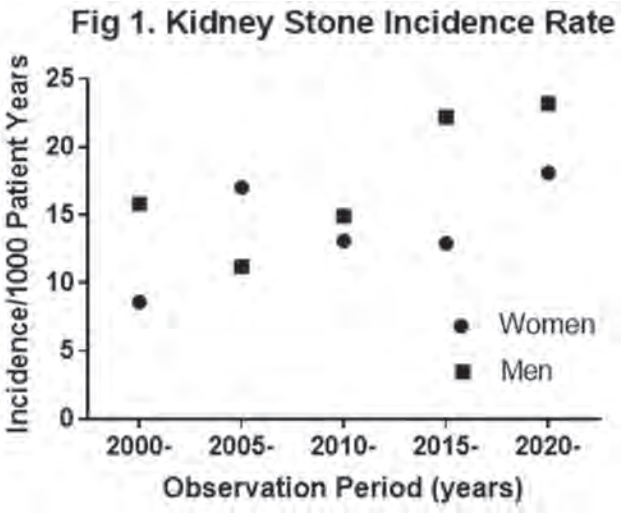
Background: The incidence of kidney stone disease (KSD) has increased in the general population in recent times. However, trends in KSD among patients with autosomal dominant polycystic kidney disease (ADPKD) remain poorly understood. Thus, the goal of the current study is to define the incidence of KSD from 2000-2023 according to sex and age in an ADPKD population.

Methods: De-identified data from Intermountain Healthcare, an integrated healthcare delivery system in Utah, was utilized for the study after approval by the respective Institutional Review Boards. Overall, 976 subjects aged ≥ 18 years with an ADPKD diagnosis were included in the study. Among these, 183 had a diagnosis of KSD based on ICD-9 or ICD-10 codes during the observation period. Incidence rates of KSD were calculated per 1000 patient years and summarized by sex across 5-year intervals and by age.

Results: The overall incidence rate of KSD increased from 11.1/1000 patient years between 2000-2004 to 20.3/1000 patient years between 2020-2023. This increase was observed in both male and female patients with a slightly higher incidence in men (23.2/1000 patient years compared to women (18.1/1000 patient years in women) in the period 2020-2013 (Figure 1). The incidence rate of KSD remained fairly constant across age groups.

Conclusions: Similar to the general population, incidence rate of KSD has increased recently among ADPKD patients. As KSD may contribute to the overall morbidity of ADPKD, periodic monitoring of urine stone risk factors in patients with ADPKD should be considered.

Funding: NIDDK Support, Private Foundation Support



TH-PO483

Kidney Stone Incidence in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Anna Ostrow,[1] Adriana Gregory,[2] Timothy L. Kline,[2] Peter C. Harris,[2] Neera K. Dahl,[2] Bradley J. Erickson,[2] Kristen L. Nowak,[1] Vicente E. Torres,[2] David S. Goldfarb,[3] Berenice Y. Gitomer,[1] Michel Chonchol.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Mayo Clinic Minnesota, Rochester, MN; [3]New York University Grossman School of Medicine, New York, NY.*

Background: Nephrolithiasis, or kidney stone disease (KSD), is a common comorbidity in patients with ADPKD and is associated with an increased risk of more rapid decline in kidney function. However, incident rates of kidney stones within the ADPKD population have not been well examined. This study aimed to characterize the incidence of symptomatic kidney stone disease in an ADPKD patient population.

Methods: We focused on data from the Mayo Clinic repository (Olmstead County, MN). The observation window was defined as January 1st, 1994, to December 31st, 2023. Of 3,428 total ADPKD patients, 2,792 aged ≥ 18 years were included who had a recorded serum creatinine lab measurement between 1994 and 2023. Follow-up time per patient was calculated using the dates of their first and last serum creatinine measurements within the observation window, and initial stone diagnosis was defined as the earliest recorded date of KSD after 1993. Incidence rates were calculated per 1,000 person-years between males and females and across age groups.

Results: Of 2,792 eligible patients (1,256 males and 1,536 females), 545 had evidence of overall KSD (19.5%), while 380 had evidence of an initial diagnosis within this time period. The overall incidence rate was 27.9 per 1,000 person-years. KSD incidence rates remained similar in both males and females with ADPKD between 1994 and 2023 (Figure 1), with the highest overall rate observed in patients aged 18-29. We found the clearest increase in rates between 1994 and 2000, and the highest incidence per 1,000 person-years between 2000 and 2006.

Conclusions: In patients with ADPKD, a high incidence rate of KSD occurs in both males and females. Overall, the incidence rate of KSD has increased between 1994 and 2023.

Funding: NIDDK Support, Private Foundation Support

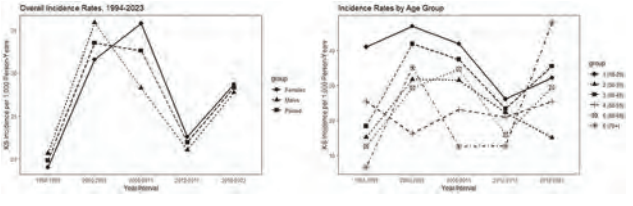


Figure 1. KSD incidence rates by 5-year interval and age group, 1994-2023.

TH-PO484

Xanthine Oxidase in Rats, Mice, and Humans with Polycystic Kidney Disease

Zhibin He,[1] Wei Wang,[1] Daniel Atwood,[1] Berenice Y. Gitomer,[1] Michel Chonchol,[1] Allen Davidoff,[2] Charles L. Edelstein.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Xortx Therapeutics Inc, Calgary, AB, Canada.*

Background: Raising uric acid (UA) worsens PKD in rodents (Edelstein, AJP, 2024). Xanthine oxidase (XO) results in the formation of uric acid and generates reactive oxygen species like H_2O_2. There is increasing evidence that increased XO in addition to UA plays role in disease.

Methods: To gain insight into whether increased XO is associated with cyst growth, XO activity was measured in PCK rats, $Pkd1^{RC/RC}$ (RC) mice and 34 patients at HALT-PKD study 24 month visit. XO in rodents (iU/ug): Fluorometric assay kit that detects H_2O_2. XO in humans (ng/mL): ELISA that directly measures XO. Fast progressors (N=17) defined as increase in height corrected total kidney volume (TKV) of >7%/yr. Fast and slow progressors were matched for clinical characteristics including age, gender, Pkd1 mutation. Values=means

Results: Kidney XO was higher in PCK rats vs. RC mice (19 vs. 6, P<0.05). **PCK rats:** XO was lower in serum (119 vs 145, P<0.01), kidney (19 vs 34, P<0.05) and liver (1505 vs 2173, P<0.01) vs wildtype. Higher cyst index correlated with lower serum (R^2 0.66, P=0.09) and kidney (R^2=0.47, P=0.02) XO. **RC mice:** No correlation between cyst index and serum XO (R^2=0.06, p=NS) or kidney XO (R^2=0.06, NS). Oxypurinol decreased cyst growth (Edelstein et al. AJP, 2024) and decreased both serum UA and serum XO (91 vs. 171, p<0.05). **Patients:** Serum UA was higher with eGFR<60 vs >60 (8.5 vs. 6, P<0.05). Higher TKV correlated with lower eGFR (R^2 0.24, P=0.008). Correlation between higher serum UA and higher total kidney volume (R^2=0.02, P=0.003). Fast progressors had higher TKV (1523 vs 583, P=0.003), lower eGFR (65 vs 91, P=0.005) and higher serum UA (8.1 vs 5.5, P<0.01) than slow progressors. Serum XO activity was the same between eGFR>60 vs <60 (8.5 vs 6.3,NS). Correlation between higher serum XO and lower eGFR showed a trend (R^2=0.08, P=0.07). No correlation between serum XO and TKV (R^2=0.009, NS). XO activity was the same in fast and slow progressors (7.7 vs 9.2, P=NS).

Conclusions: In summary, in rodents with PKD, there was no correlation between increased serum or kidney XO activity and cyst index. In PKD patients there was a trend towards higher serum XO and lower GFR. In conclusion, serum XO needs to be measured in a larger group of patients from the HALT-PKD study.

Funding: Commercial Support - Xortx Therapeutics inc

TH-PO485

Renal Uric Acid Crystals Trigger Cystogenesis and CKD in Polycystic Kidney Disease

Nickolas J. Holznecht,[1] Sebastian Strubl,[1,2] Jacob A. Torres,[1] Peter C. Harris,[3] Roman-Ulrich Mueller,[2] Thomas Weimbs.[1] *[1]University of California Santa Barbara, Santa Barbara, CA; [2]Universitat zu Koln, Koln, Germany; [3]Mayo Clinic Minnesota, Rochester, MN.*

Background: We have reported that renal tubular calcium oxalate crystals trigger transient tubule dilation in normal kidneys facilitating their excretion. In ADPKD kidneys, the same reno-protective mechanism triggers cystogenesis and worsen disease progression. Since hyperuricemia and uric acid (UA) kidneys stones are common in individuals with ADPKD, we investigated the impact of UA crystals on disease progression in a novel, orthologous heterozygous ($Pkd1^{+/-}$) rat model that is genetically identical to human ADPKD.

Methods: $Pkd1^{+/+}$ and $Pkd1^{+/-}$ rats were treated with UA and the uricase inhibitor oxonic acid for 14 days followed by a washout period for 56 days. To investigate the preventative and therapeutic potential, respectively, of treatment with beta-hydroxybutyrate (BHB) and citrate, we treated rats with BHB/citrate either concurrently during UA challenge, or for 28 days at the end of the washout period.

Results: Challenging $Pkd1^{+/-}$ rats with hyperuricemia diet leads to tubular UA crystal deposition which triggers cystogenesis and ongoing, progressive PKD as well as an acute inflammatory response (neutrophils, macrophages) that transitions into chronic inflammation, fibrosis, and cystic progression in $Pkd1^{+/-}$ rats. In contrast, $Pkd1^{+/+}$ rats recover after UA crystal clearance. Concurrent treatment with BHB/citrate prevents UA crystal deposition. Treatment with BHB/citrate after the UA washout leads to regression of inflammation, fibrosis and cystogenesis.

Conclusions: In contrast to all other existing PKD rodent models, our novel, orthologous, heterozygous $Pkd1^{+/-}$ rat model closely resembles human ADPKD patients ($PKD1^{+/-}$). We show that crystal injury triggers de-novo cystogenesis in $Pkd1^{+/-}$ rats that otherwise do not develop PKD. Therefore, a second-hit genetic mutation is not necessary for cystogenesis. Rather, a specific renal injury controlled by diet, such as hyperuricemia-induced

UA crystals, can trigger PKD onset and progression in a heterozygous context. Our results have immediate clinical implications and suggest that avoidance of renal injury triggers is critical for the management of ADPKD. Furthermore, BHB/citrate treatment is promising as a preventative measure and as a disease-modifying therapy.

Funding: Private Foundation Support

TH-PO486

Death-Specific Risk Factors among US Veterans with Autosomal Dominant Polycystic Kidney Disease

Michal Mrug,[1,2] Julia W. Gallini,[2] Christine L. Jasien,[2] Phillip H. Chumley,[1,2] Xiangqin Cui.[3,2] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Veterans Health Administration, Washington, DC; [3]Emory University, Atlanta, GA.*

Background: Identifying and addressing death-specific risk factors in people with autosomal dominant polycystic kidney disease (ADPKD) is critical for improving healthcare outcomes and reducing mortality in this patient population.

Methods: To identify death-specific risk factors for ADPKD, we used a cohort of 12,217 ADPKD patients that we recently established using nationwide VA electronic health record data from 1999-2020. Of these patients, 5,342 were identified as deceased based on the VA death index. We used these data to conduct a survival analysis on the time to death from the first use of ADPKD diagnosis ICD codes in the VA database on the whole cohort.

Results: The multivariable Cox regression analysis yielded the following key findings: 1) A higher hazard for death was associated with older age at diagnosis (hazard ratio [HR] per year 1.056; p<0.001) and a longer delay in the ADPKD diagnosis after the initial encounter (HR per year 1.012; p=0.002). 2) A lower hazard of death was associated with a higher estimated glomerular filtration rate (eGFR) at the time of ADPKD diagnosis (HR 0.981; p<0.001) and female gender (HR 0.733; p=0.001).

Conclusions: While some of the identified death-specific risk factors cannot be modified, others, especially the delay in the ADPKD diagnosis after the initial encounter, are potentially modifiable. Together, these findings suggest that interventions leading to earlier ADPKD diagnosis may delay death in patients with ADPKD. However, it is important to note that this study was conducted on a predominantly male population of US veterans, limiting the generalizability of the results.

Funding: Veterans Affairs Support, Commercial Support - Otsuka

TH-PO487

A Family with Autosomal Dominant Alport Syndrome with Phenotypic Variability

Sadaf Akbari, Meenakshi Sambharia. *The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, IA.*

Introduction: Alport syndrome (AS) is a glomerulopathy, characterized by glomerular hematuria, progressive hearing loss and ocular abnormalities. It is inherited in X-linked, Autosomal Dominant (AD) and Recessive (AR) manner. Mutations in COL4A3 are responsible for ADAS.

Case Description: A 32 YO female with no past history was referred for microscopic hematuria/high blood pressure. She had microscopic hematuria with normal creatinine. Family history was significant for AS in her father who had been on dialysis since the age of 46 years. Father was diagnosed with AS based on a kidney biopsy showing features of AS, progressive hearing loss, lenticonus. Given normal renal function we decided to proceed with genetic testing to confirm AS instead of a kidney biopsy. Results revealed a heterozygous missense mutation in COL4A3 c.3955G>A (p.Gly1319Arg) which was reported as variant of uncertain significance(VUS). Her father was then tested and was found to have the same mutation. It was determined that despite it being reported as VUS it was likely causative of AS in both of them. Upon further history, multiple family members were on dialysis/had kidney disease including paternal and maternal uncle. While the Pt herself did not have any ocular or hearing abnormalities and preserved kidney fucntion, her father had all the classical symptoms by mid-30's.

Discussion: Compared to X-linked and ARAS, ADAS is considered least severe with majority of pts having hematuria and only a few with CKD and needing dialysis. A study found that in ADAS there was no significant difference in males and females in term of kidney survival. Extra-renal features are rare in ADAS, but our Pt's father had classical extra-renal features of lenticonus and early onset progressive sensorineural hearing loss. To the best of our knowledge till date this mutation has not be known to cause ADAS. The complexity of ADAS diagnosis and management is compounded by the broad range of phenotypic expressions observed in patients. In addition, individuals often exhibit a spectrum of symptoms, from severe to completely asymptomatic within families sharing the same genetic mutation. The absence of symptoms and preserved kidney function may suggest genetic modifiers, variable expressivity, incomplete penetrance, or the influence of other protective genetic or environmental factors.

TH-PO488

Resolution of Two Intronic Noncanonical Splicing Variants Located in X-linked Alport COL4A5 Gene

Si Ting Lim,[1,2] Chee Teck Koh,[1,2] Alwin Hwai Liang Loh,[3] Jia Liang Kwek,[4] Jason Choo Chon Jun,[4] Irene Y. Mok,[4] Cynthia C. Lim,[4] Hui-Lin L. Chin,[1,2] Jun Li Ng,[1,2] Hui Kim Yap,[1,2] Kar Hui Ng,[1,2] Yaochun Zhang.[1,2] *[1]National University of Singapore Yong Loo Lin School of Medicine, Singapore, Singapore; [2]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, Singapore; [3]Singapore General Hospital Division of Pathology, Singapore, Singapore; [4]Singapore General Hospital, Singapore, Singapore.*

Introduction: Variants located at intronic non-canonical sites are challenging to interpret due to limited literature. We report two families carrying two different intronic variants at non-canonical splicing sites of the *COL4A5* gene which causes X-linked Alport syndrome.

Case Description: Proband 1 first presented at age 4 with isolated persistent microhematuria with no extrarenal manifestations. She progressed to A3 albuminuria by age 20, but kidney function remained normal at age 41. Her mother developed kidney failure at 60. Her son had persistent microhematuria and proteinuria since age 2, progressing to chronic kidney disease (CKD) by age 9. Proband 2 first presented at age 3 with microhematuria and recurrent gross hematuria and persistent subnephrotic proteinuria. He later developed stage 3 CKD and bilateral kidney cysts by age 14. His 44-year-old mother has microhematuria, persistent proteinuria with FSGS, bilateral renal cysts, but normal renal function. His 28-year-old maternal uncle was diagnosed with Alport syndrome at age 15, progressing to kidney failure and underwent a transplant. He has bilateral sensorineural hearing loss needing hearing aids. In both probands, anti-COL4A5 immunofluorescence staining patterns were abnormal but not characteristic of classic X-lined or autosomal recessive disease. Electron microscopy showed GBM thinning for one case, while the other displayed thin and thick basement membranes with lamina densa multilamination. Whole exome sequencing identified variant c.1032+4A>G in proband 1 and c.1032+3_1032+6delAAGT in proband 2, both located at intron 18 of *COL4A5*. To assess their impact on pre-mRNA splicing, exons 17-19 with introns 17-18 from probands and healthy controls were subcloned and transfected into HEK293 cells. The wild type construct produced a 300 bp band, while the mutant plasmids generated a truncated transcript. Sanger sequencing confirmed a skipping of exon 18.

Discussion: Skipping of exon 18 results in truncation of a critical domain of the protein, hence, both variants can be rendered a "strong" criterion in PVS1 according to the revised ACMG variant interpretation guidelines. This suggested both variants are likely pathogenic.

TH-PO489

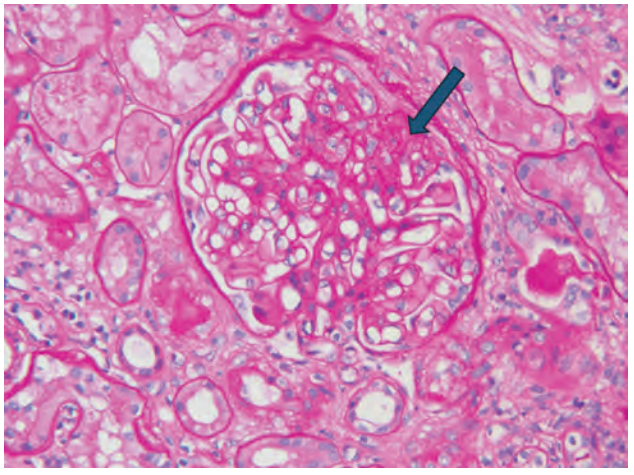
Unveiling X-linked Alport Syndrome: Genetic Testing in FSGS

Nitika Agrawal, Steven T. Heidt, Pravir V. Baxi. *Rush University Medical Center, Chicago, IL.*

Introduction: FSGS is often considered in the evaluation of patients with CKD and proteinuria. As a histopathologic pattern of injury with various causes, investigating the underlying etiology of podocyte injury is crucial, given its potential therapeutic implications. Recent advances in genetic testing have revealed pathogenic variants of Alport's syndrome (AS) in patients presenting with biopsy findings of FSGS. Here, we present a patient with biopsy proven FSGS subsequently found to have X-linked AS.

Case Description: An 18 y/o man with CKD was evaluated for HTN at age 7, at which time he had a normal creatinine (Cr) and microscopic hematuria without proteinuria. He was started on an ACE-i. At age 16, he developed proteinuria, with a biopsy showing FSGS and acute interstitial nephritis (AIN). There was insufficient sample for EM analysis. A course of steroids was prescribed for the AIN. Now, he has developed significant HTN, rising Cr, and worsening proteinuria. He had no history of vision or hearing issues. Further evaluation of his family revealed siblings with microscopic hematuria. Genetic testing was done now 11 yrs after the biopsy and showed a mutation within the COL4A5 gene, consistent with X-linked AS.

Discussion: FSGS of genetic origin can appear at different ages and exhibit varying degrees of proteinuria and foot process effacement. Recent advancements have shed light on the role of COL4A3-5 mutations in the development of FSGS amongst patients diagnosed with primary FSGS or steroid-resistant nephrotic syndrome. AS diagnosis has significant implications not only for the patient but also their family members who are at risk for the spectrum of systemic manifestations of the condition. Early diagnosis also allows for patients to be enrolled in clinical trials to help our therapeutic options. This case underscores the importance of accurately classifying patients with FSGS and highlights the pivotal role of genetic testing in managing CKD.



PAS stain showing segmental scar (arrow)

TH-PO490

A Case of Autosomal Dominant Hereditary Nephritis

Faten Aqeel, John Sperati, Lois J. Arend, Mohamad A. Hanouneh. *Johns Hopkins University, Baltimore, MD.*

Introduction: Alport syndrome, or hereditary nephritis, results from genetic mutations in collagen IV protein genes, leading to a basement membrane disorder. It can be inherited through X-linked (COL4A5 gene defect), autosomal recessive (AR), or autosomal dominant (AD) (COL4A3 or COL4A4 gene defects). This disorder causes a progressive glomerular disease and often involves sensorineural hearing loss and ocular abnormalities.

Case Description: A 47-year-old woman with Crohn's disease, receiving infliximab, is evaluated for CKD stage IIIA and proteinuria (UACR 838 mg/g Cr). No history of hearing or ocular issues is reported. She has a family history of ESRD in two maternal aunts. Serology shows positive ANA (1:640), and anti-histone antibodies. The kidney biopsy showed variable glomerular basement membrane width; areas of thinning alternated with thickened sections having variable lucency (Fig 1A). No immune complex electron-dense deposits were noted. Irregular staining of the glomerular capillary walls for COLIV alpha5 chain was observed (Fig 1B left) compared to the normal control tissue (Fig 1B right). Genetic testing revealed heterozygous pathogenic variant in COL4A4 c.2402G>T (p.Gly801Val). She was diagnosed with AD Alport syndrome. She was referred for ocular and auditory evaluations. She began treatment with losartan and Empagliflozin. After 6 months, her kidney function remained stable, and UACR improved to 397 mg/g Cr.

Discussion: Though her positive serology likely stems from an immunologic effect of infliximab, there's no evidence of immune complex-related kidney disease. The observed GBM abnormalities align with a COL4-related disorder. While variable alpha5 staining hints at COL4A5 gene abnormalities, her family history suggests otherwise; with her maternal grandfather lived longer without ESRD. With a heterozygous genetic mutation, she has AD disease. Her variable COL4A5 staining reflects deficiency of normal A3-A4-A5 trimer formation. AD Alport's is typically less severe than AR and often lacks hearing loss and eye issues (occurs in <10 – 25%).

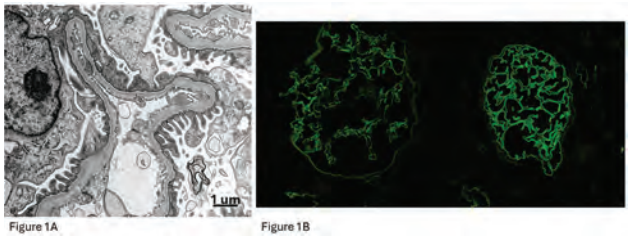


Figure 1A Figure 1B

TH-PO491

Unusual Glomerular Abnormalities in a Patient with Combined COL4A5-NPHS1 Variants

Abdelrahman Alwan,[1] Carol Vincent,[1] Dmitry A. Lyalin,[2] Alexei V. Mikhailov.[1] *[1]Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC; [2]Virginia Commonwealth University, Richmond, VA.*

Introduction: Collagen IV a5 (gene *COL4A5*) isoform is an essential part of the glomerular basement membrane (GBM) *lamina densa.* Pathogenic variants in *COL4A5* are associated with X-linked Alport syndrome. Nephrin (gene *NPHS1*) is a major component of the podocyte slit diaphragm; pathogenic *NPHS1* variants are autosomal recessive and manifest as childhood proteinuria. We present the first case of a patient with combined pathogenic *COL4A5-NPHS1* variants resulting in unique glomerular abnormalities

Case Description: A 5-year old female (proband) presented with recurrent gross hematuria and proteinuria 80 mg albumin/g creatinine. Renal function was normal; no hearing or ocular abnormalities were detected. Her sister (3 y.o.) exhibited similar symptoms; father was diagnosed with Alport syndrome. Panel-based DNA sequencing identified pathogenic heterozygous *COL4A5* c.1633G>A (p.G545S) and *NPHS1* c.2417C>A (p.A806N) variants in the proband, her father and sister. Whole exome sequencing did not identify additional pathogenic/likely pathogenic variants of renal significance. The kidney biopsy revealed immature glomeruli, 5% global glomerulosclerosis, and small foci of interstitial fibrosis and tubular atrophy. Electron microscopy showed the characteristic Alport-like GBM changes. Filamentous slit diaphragms were detected in 39.9% of filtration slits between non-effaced foot processes compared to 74.9% in control (acute tubulointerstitial nephritis). In some glomeruli several, or all, capillary segments were abnormal, displaying thin irregular GBMs with large gaps covered by podocytes forming tight junctions between each other and the underlying cells. Such capillaries never contained red blood cells, and were lined by cells lacking the endothelial morphology, displaying intraluminal cross-bridges with foci of aberrant GBM formation (Figure 1).

Discussion: Two previous reports of combined *COL4A5-NPHS1* variants describe hematuria and moderate proteinuria detected at 2.5-6 years of age. A kidney biopsy done in one patient showed GBM gaps. In our patient, both pathogenic variants lead to a severe mosaic glomerular capillary malformation. We hypothesize that Alport-associated alterations in GBM positioning of extracellular matrix proteins and changes in nephrin-associated signaling combine to affect the developmental cues resulting in this striking phenotype.

TH-PO492

Alport Syndrome in Iceland: Epidemiology and Outcomes

Saga Ingadóttir,[1] Olafur S. Indridason,[2] Sindri Valdimarsson,[2,3] Hjordis Thorsteinsdottir,[3] Vidar O. Edvardsson.[2,1] *[1]School of Health Sciences, University of Iceland, Reykjavik, Iceland; [2]Landspitali, Reykjavik, Iceland; [3]Domus barnalaeknar, Reykjavik, Iceland.*

Background: Alport syndrome (AS) is caused by mutations in the collagen IV genes, COL4A3, COL4A4 and COL4A5. Three types of AS have been described: X-linked AS (XLAS), autosomal recessive AS (ARAS) and autosomal dominant AS (ADAS). The aim of this study was to examine the epidemiology and outcomes of AS in Iceland.

Methods: This was a retrospective study of all Icelandic AS cases in the period 1968-2023. Affected individuals were identified through diagnosis codes, the Icelandic Renal Registry, and family tracing. Medical records were reviewed for the confirmation of diagnosis. End-stage kidney disease (ESKD) was defined as the need for kidney replacement therapy. Clinical characteristics, family history and genetic testing were used for the diagnosis of X-linked AS. The diagnosis of autosomal AS was made in individuals with persistent haematuria in whom a secondary cause had been excluded.

Results: We identified 76 individuals with AS, 52 with XLAS (13 males) and 24 individuals with autosomal AS (8 males). Diagnosis was confirmed with genetic testing in 45 of the 52 XLAS patients and in 2 autosomal AS cases. The mean (±SD) age at XLAS diagnosis was 28.5±22.3 years and 9.4±9.6 years for autosomal AS. The prevalence of AS in January 2024 was 17.7 per 100,000 population. The average yearly incidence of XLAS in the last 10 years was 0.54 individuals per 100,000 population. Five autosomal AS patients (20.8%) had some degree of proteinuria at latest follow-up, but all had normal kidney function. A total of 10 individuals with XLAS developed ESKD, 7 men and 3 women, at the median (range) age of 19 (16-25) and 60 (37-69) years for males and females, respectively.

Conclusions: The prevalence of AS in Iceland appears to be similar to other western countries. A high proportion of males but only a few females with XLAS progress to ESKD. The outcomes of individuals with autosomal AS are excellent.

Funding: Government Support - Non-U.S.

TH-PO493

Ocular Coherence Tomography Unveils Alport Syndrome: A Critical Tool in Detecting Collagen IV Nephropathies

Abdelrahman Ibrahim, Zena Altawallbeh, Monica P. Revelo Penafiel, Martin C. Gregory, Laith Al-Rabadi. *University of Utah Health, Salt Lake City, UT.*

Background: Alport Syndrome (AS) and Focal Segmental Glomerulosclerosis (FSGS) pose diagnostic challenges due to overlapping clinical, histopathological, and genetic features. AS is characterized by mutations in collagen genes (COL4A3, COL4A4, COL4A5), leading to glomerular basement membrane (GBM) abnormalities, while FSGS can be primary, autoimmune mediated, or secondary to systemic causes or to genetic mutations, including mutations in the collagen 4 genes. Optical Coherence Tomography

(OCT) aids in identifying these conditions by demostrating temporal macular thinning in COL4 nephropathies. We describe two cases presenting with proteinuria that were initially diagnosed as primary FSGS and treated with long term steroid therapy. Subsequent genetic testing and OCT imaging were carried out.

Methods: Genetic analysis was conducted using next-generation sequencing (NGS) with copy number variation (CNV) analysis. Mutations were confirmed through polymerase chain reaction (PCR) and Sanger sequencing. Under high-resolution spectral OCT done by ophthalmologists, the Temporal Thinning Index (TTI) was measured using the formula: TTI = {(N1 + N2) – (T1 + T2)} / (N1 + N2) × 100. Severe thinning is defined as TTI exceeding 2 standard deviations above the mean for healthy eyes.

Results: Case 1: We identified a novel deletion in COL4A5 exons 8 and 9. OCT: TTI 8.21 OD and 8.36 OS, indicating severe temporal thinning, consistent with Alport Syndrome. Case 2: We detected two variants in COL4A3: a missense mutation (COL4A3:c.2452G>A; p.Gly818Arg) and a novel nonsense mutation (COL4A3:c.4722G>A; p.Trp1574*). OCT: TTI 10.5 OD and 10.8 OS, suggesting severe temporal thinning, indicative of Alport Syndrome.

Conclusions: OCT assists clinicians when the diagnosis of a COL4 nephropathy is unclear. Earlier use of OCT could have established a precise diagnosis in these cases, thus avoiding unnecessary immune suppression. These findings highlight OCT's vital role in distinguishing COL4A nephropathy from primary FSGS, guiding diagnosis, management, and genetic counseling. In broader contexts, OCT can potentially assist in more accurately assessing the prevalence of COL4 nephropathies, identifying individuals for phenotype studies, and exploring potential therapeutic options.

TH-PO494

Variants Involving Podocyte and Extracellular Matrix Proteins in Alport Syndrome: A Case Series

Stefan N. Lujinschi,[1,2] Bogdan Obrisca,[1,2] Bogdan Sorohan,[1,2] Elena-Emanuela Rusu,[1,2] Roxana A. Jurubita,[1,2] Gener Ismail.[1,2] *[1]Institutul Clinic Fundeni, Bucuresti, Romania; [2]Universitatea de Medicina si Farmacie Carol Davila din Bucuresti, Bucuresti, Romania.*

Background: Caused by mutations of type IV collagen genes (COL4), Alport syndrome (AS) displays a wide phenotype. Recent studies have highlighted AS as one of the leading causes of focal and segmental glomerulosclerosis (FSGS). There is a growing body of evidence favoring the modifier role of variants involving podocyte and extracellular matrix proteins in AS.

Methods: We conducted a retrospective case series study including 6 patients with COL4 mutations and simultaneous variants involving podocyte or non-collagen basement membrane proteins, aiming to describe the influence of such variants on the phenotypic spectrum of AS.

Results: We identified 8 different COL4A3 and COL4A4 variants. Two patients had multiple COL4 variants: one had digenic AS and the other had 2 different COL4A3 variants. There were 5 variants of uncertain significance (VUS), 2 pathogenic and one likely-pathogenic variant. All the variants were heterozygous. There were 7 variants involving podocyte and extracellular matrix proteins, including: LAMA5, LAMB2, NUP107, NPHS2, MYO1E and PLCE1. All the variants were heterozygous VUS. Four patients had nephrotic syndrome or nephrotic range proteinuria, one had nephritic syndrome and one had acute tubulointerstitial nephritis. Only 2 patients had hearing loss. Four patients had a family history of kidney disease. Only 2 subjects developed end-stage kidney disease (at 29 and 39 years old respectively). There were 2 cases of FSGS and one case of thin basement membrane disease on kidney biopsy (3/6 patient). Five patients received renin-angiotensin system inhibitors. Only 2 patients were treated with sodium-glucose transport protein 2 inhibitors. Both experienced an important drop in proteinuria (82% and 88% respectively) when compared to baseline. Three patients received immunosuppression, all having nephrotic syndrome.

Conclusions: Although mutations of podocyte and extracellular matrix proteins do not usually cause genetic nephrotic syndrome in heterozygous form, the presence of such variants influenced the phenotype of patients with AS followed in our clinic, as most of them presented with nephrotic syndrome or nephrotic range proteinuria.

TH-PO495

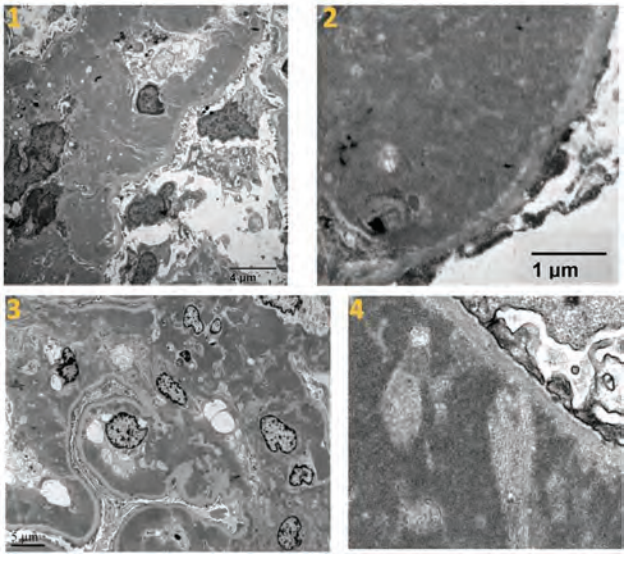
Role of Family History and Genetic Testing in Diagnosing Rare Diseases

Katrina Gonzales, Weixiong Zhong, Tripti Singh. *University of Wisconsin-Madison, Madison, WI.*

Introduction: Fibronectin nephropathy (FN) is an autosomal dominant disease characterized by proteinuria, hematuria, and decline in kidney function [1]. The diagnosis is made with kidney biopsy (KB) showing fibrillary mesangial and subendothelial deposits immunoreactive to fibronectin [1, 2]. There is no treatment and there is a risk of recurrence after transplant [3]. We present two cases of FN that reinforce the need for dedicated family history (FH) and genetic analyses.

Case Description: A 44-year-old female presented for evaluation of proteinuria. Her mother had membranoproliferative glomerulonephritis (MPGN) at age 45, and later ESKD requiring transplant. Physical exam was benign. Urine protein creatinine ratio (UPCR) was 1.26 gm/gm, hepatitis panel, ANA, C3, C4 and kidney ultrasound were normal. Image 1 is the patient's KB results; however, there was insufficient sample, and it did not reveal a diagnosis. Due to the FH of MPGN and to help with her diagnosis, the patient allowed a re-analysis of her deceased mother's KB. There were many similarities between the KBs. A genetic test for the mutation W1925R in the FN1 gene was positive, leading to diagnosis of FN for her, and likely for her mother [4]. She is now on lisinopril, with recent UPCR .65 gm/gm.

Discussion: FN is diagnosed with KB. This patient was unique since she did not have classic findings on KB, but her mother had MPGN and later ESKD. The FH prevented a second KB, and instead received a diagnosis from a genetic test. This case demonstrates the vital role of FH and the benefit of having a multi-disciplinary team, specifically nephrologist, renal pathologist, and genetic counselor.



Patient (1, 2) and mother KB (3, 4) shows large amounts of subendothelial and mesangial electron-dense deposits with vague fibrillary structure under high-power magnification. The mother's KB was post-transplant with recurrent disease.

TH-PO496

Unwrapping the Enigma: A Rare Case of MYH9 Nephropathy

Samiya Yasin, Samina Fazal, Akinwande A. Akinfolarin. *Baylor Scott & White Health, Dallas, TX.*

Introduction: The MYH9 gene encodes the non-muscle myosin heavy chain IIA expressed in various tissues including podocytes and mesangial cells. Mutations in this gene lead to MYH9 related disorders (MYH9-RD) with an autosomal dominant pattern of inheritance characterized by macrothrombocytopenia with variable risk of non-hematologic features including nephropathy, cataracts and hearing loss. Lack of a family history does not rule out disease, as some mutations are sporadic.

Case Description: A 56-year-old Caucasian female with a past medical history of thrombocytopenia in childhood was found to be hypertensive with an elevated creatinine (Cr) 3.23 mg/dl and a reduced eGFR 15 ml/min/1.73m2 during her wellness check which prompted a referral to nephrology. She had no skin rash, hematuria, dysuria, leg swelling or hemoptysis. She denied a history of kidney stones, recurrent urinary tract infections, hearing loss, cataracts or nonsteroidal anti-inflammatory (NSAID) use. Urinalysis showed proteinuria without hematuria, Urine Protein Creatinine ratio (UPCR) 4236 mg/g. Platelet count was 30,000 K/uL. Renal ultrasound revealed bilateral echogenic kidneys with no hydronephrosis, calculi or masses. Work up for proteinuria including antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-double stranded DNA, anti Glomerular basement membrane antibody, HIV, hepatitis panel, complements and immunofixation were negative. A renal biopsy was deferred due to thrombocytopenia. Hematology was consulted and a diagnosis of idiopathic thrombocytopenic purpura (ITP) was made. Genetic testing revealed a pathogenic mutation of c.4270G>A (p. Asp1424Asn) in exon 31 of MYH9 gene. Her blood pressure and antiproteinuric regimen was optimized with subsequent improvement in proteinuria. She was provided counseling by the genetic counselling team.

Discussion: There is great heterogeneity among renal and nonrenal manifestations of MYH9 related disorders including age at presentation, quantity of proteinuria and rate of progression to ESRD. Disease prevalence is underestimated due to misdiagnosis. MYH9-RD should be considered in any patient presenting with renal failure and thrombocytopenia, as early diagnosis and therapy with RAAS blockade may slow progression to ESRD.

TH-PO497

A Boy with Steroid-Resistant Nephrotic Syndrome and Cortical Blindness

Fang Wang, Huijie Xiao, Liuyu Sun, Yali Ren. *Peking University First Hospital, Beijing, China*.

Introduction: Renal involvement in primary mitochondrial disorders may be a dominant or non-dominant feature. Primary mitochondrial disorders should be considered in the etiology of steroid-resistant nephrotic syndrome due to focal segmental glomerulosclerosis. The aim of this study is to describe the prominent extra-neurologic phenotype including steroid-resistant nephrotic syndrome associated with focal segmental glomerulosclerosis characterized by abnormal mitochondria in podocytes, cortical blindness and pancreatitis in a Chinese boy with primary mitochondrial disease.

Case Description: A 5-year-old previously healthy Han ethnicity boy experienced loss of vision after fever and proteinuria 3.5 months before admission to our hospital. Proteinuria did not improve after 5 weeks of prednisolone at 10 mg thrice daily (2mg/kg/d). His personal history indicated he was very prone to fatigue and motor coordination was not good. His past medical history was negative for systemic illness, rash or joint pain. Family history was not remarkable for renal disease. Physical examination showed edema in face and both legs, and less muscle volume of lower extremities. Laboratory findings revealed hypoalbuminaemia (24 g/L), significant proteinuria (2.98 g/24h), normal renal function, and increased level of serum lactate (three times). The serum level of C3 and C4 was normal. The anti-nuclear antibody, anti-DNA antibody, anti-neutrophil cytoplasm antibodies, and anti-hepatitis B virus were all negative. Brain MRI (three times) indicated bilateral parietal occipital lesions and cerebellar atrophy. Visual evoked potentials were absent bilaterally. Renal biopsy revealed focal segmental glomerulosclerosis (collapsing variant). Electron microscope examination revealed mitochondrial abnormality in the renal tissue. Mitochondrial DNA (mtDNA) screening using peripheral blood and urine specimens for common point mutations was negative. Four and a half months after the onset of disease, he was diagnosed with acute pancreatitis with acute peritonitis.

Discussion: The multi-organ impairments of our young patient associated with elevated serum lactate levels and prominent abnormal mitochondria in the podocytes indicated a mitochondrial disease. Screening for the blood lactate level should be included in initial workup for clinically presumed unknown causes of proteinuria or nephrotic syndrome.

TH-PO498

Clinical and Genetic Assessment for the Mechanisms Underlying Phenotypic Diversity in Steroid-Resistant Nephrotic Syndrome Caused by TRPC6 Variants

Hiroyasu Tsukaguchi,[1,2] Huong Quynh Tran Thuy,[1] Mikio Hayashi,[4] Kenji Fukui.[3] Div of Nephrology. *[1]Kansai Medical University, Second Department of Internal Medicine, Hirakata, Japan; [2]Kansai Medical University Hospital, Clinical Genetics Center, Hirakata, Japan; [3]Osaka Medical and Pharmaceutical University, Faculty of Medicine, Department of Biochemistry, Takatsuki, Japan; [4]Kansai Medical University, Department of Physiology, Hirakata, Japan*.

Background: Histologically, 30% of children and 10% of adult individuals with steroid resistant nephrotic syndrome (SRNS) are characterized by Focal Segmental Glomerulosclerosis (FSGS). More than 60 podocyte-related gene mutations have been reported in monogenic SRNS. Among these, *TRPC6* variants account for approximately 6% of familial FSGS and 2% in sporadic cases. Individuals with *TRPC6* variants show a considerable clinical diversity with regards to age onset and disease progression. However, the mechanisms underlying the heterogeneity remain investigated.

Methods: To analyzing the molecular basis of TRPC6 glomerulopathy, we investigated the clinical-genetic features of *TRPC6* variants in our SRNS cohort (*n*=39, average onset of proteinuria 4.6 years, ESRD 7.6 years)

Results: Genetic analysis revealed *TRPC6* variant is the most frequent cause of SRNS (n=8, 21%), followed by *NUP107* (*n*=5), *PLCE1*(*n*=3), *COL4A3,A5*(*n*=2). The eight *TRPC6* variants remarkably clustered into two distinctive cytoplasmic domains: Four in the N-terminal Ankyrin repeat 3 (AR3 163-189 (p.Y173D, R175W, R175G) and the other four C-terminal helix (CH1 and CH2 853-920, p.E875V, 867_868Del, S893N, R895C). Three patients exhibited NS in early childhood around age 3, two manifested in childhood (age 3-12), while the remaining 3 developed NS in adolescence. In familial cases, for example, affected individuals with p.R175W or p.R875V showed discordant age onset and disease severity. The 3D structure analysis with the homo-tetrameric TRPC6 complex revealed that all pathogenic *TRPC6* variants alter the residues composing Ca-permeable pore in the center of the protein complex. Expression studies with HEK293 cells showed that *TRPC6* variants are expressed on the cell surface, supporting that an excessive Ca influx through the gain-of-function of channel may contribute to the podocyte injury.

Conclusions: TRPC6 channelopathy was found to be the most frequent cause in our SRNS cohort. The pathogenic variants likely disrupt the integrity of AR3-CH2 interface, which confers a Ca-binding site for channel inactivation. Remarkable clinical heterogeneity suggests that channel activity may be regulated by other modifying factors. Further studies will be required to address how the excessive Ca influx affect the cytoskeletal organization in the podocytes.

TH-PO499

Combined Genetics and Ultrastructural Examination in Diagnosis and Treatment Decisions of Focal and Segmental Glomerulosclerosis

Roberta Fenoglio, Dario Roccatello. *CMID, Nephrology and Dialysis Unit, San Giovanni Bosco Hospital and University of Turin, Torino, Italy*.

Background: FSGS defines a histologic lesion that represents a pattern of injury associated to different pathologic conditions affecting both children and adults. Better understanding the role of Genetics in FSGS and response to treatment in different forms is of vital importance in this rare and multifaceted condition. We analyzed a cohort of pts with FSGS examined both with EM and genetic testing (GT). Main aims of study were: 1) assessment of GT in primary and secondary forms; 2) analysis of response to therapy according to histologic and genetic classification

Methods: This is a retrospective observational study on patients that received a histological diagnosis of FSGS, including EM, and underwent NGS genetic testing from January 2020 to June 2023. Primary and secondary forms of FSGS were distinguished by degree of pedicle fusion at EM, according to Mayo Clinic classification. Clinical, laboratory, genetic data and used therapies were recorded.

Results: 33 pts receiving a histologic diagnosis of FSGS with EM examination underwent NGS testing. Of these, 25 had available genetic results and were included. Ten patients were females, 15 were males; mean age was 40.8 years; 20 were Caucasian, 4 Black, 1 Asian. Based on EM, 11 were classified as primary forms, 14 as secondary forms. 12 patients presented with nephrotic syndrome (10 had a primary form). 7 had nephrotic range proteinuria, 6 had subnephrotic proteinuria. 6 primary and 8 secondary forms had a positive GT (p=0.78). All primary forms received immunosuppressive therapies (rituximab-based regimens); all secondary forms received support therapy. 9 primary and 9 secondary forms had at least a PR to treatment (4 CR in primary and 1 CR in secondary group) (p=0.33). Among primary forms, 5 of 6 patients with a positive GT had at least a PR with a strong immunosuppressive therapy. In secondary forms group 4 of 8 patients had at least PR with offered support therapy.

Conclusions: Percentage of positive GT did not differ in primary and secondary forms of FSGS as defined by Mayo Clinic classification. Thus a positive GT should not be considered a unique feature of secondary forms. In conclusion, as clinical presentation and light microscopy are not sufficient for an accurate diagnosis, combining EM and GT is of utmost importance in proper classification and management of FSGS.

TH-PO500

May-Hegglin Anomaly-Associated Nephropathy: A Case Series

Matthew D. Nguyen, Marrey Ruby L. Quizon, Vu Q. Nguyen, Ryan E. Fekrat, Arif N. Demirci, Ramy M. Hanna. *University of California Irvine Nephrology Hypertension & Kidney Transplantation, Orange, CA.*

Introduction: May-Hegglin Anomaly (MHA) is a rare autosomal dominant disease associated with a mutation in MYH-9 gene and it is characterized by macrothrombocytopenia, large platelets and neutrophils with abnormal cytoplasmic inclusions. Clinical features of this disease include hearing loss, early cataracts, and renal failure. The MYH-9 gene is associated with MYH-9 Related Disorders (MYH9-RD), such as Fecthner (FTNS) and Sebastian (SBS) syndromes.

Case Description: We present two interesting cases of renal injury attributed to May-Hegglin Anomaly. The first is a 52-year-old Hispanic female with May-Hegglin Anomaly (MHA) associated with nephropathy and thrombocytopenia complicated by stage 3 chronic kidney disease (CKD) and hypothyroidism. She was found to have a pathogenic MYH-9 heterozygous mutation and she met the clinical criteria for May-Hegglin Anomaly. The patient is not a candidate for kidney biopsy due to low platelets secondary to her May-Hegglin Anomaly. She has been treated with SGLT-2 inhibitors, ARBs for managing her CKD and Synthroid® for hypothyroidism. She continues to have low platelets, proteinuria, and her CKD continues to progress. Our second case highlights a 39-year-old white female with MHA associated with focal segmental glomerulosclerosis, diagnosed at the age of 15 on renal biopsy, thrombocytopenia, and mix connective tissue disorder with rheumatoid arthritis and systemic lupus erythematosus clinical features. She is currently on a treatment regimen of methotrexate, Xeljanz, and IVIG for her rheumatological diseases. Her kidney function has remained stable on ACE inhibitors, HCTZ and as needed loop diuretics for her frequent edema.

Discussion: These cases illustrate the challenges with diagnosing and managing the renal complications associated with MHA due to the MYH-9 gene mutation. The chronic thrombocytopenia in both patients restricts the use of invasive diagnostic procedures such as biopsies that is critical for confirming relation between nephropathy and MHA. This further limit the possibility for more targeted treatment. Thus, these cases stress the importance of genetic testing as a factor in diagnosing and stress the challenge of managing patients with suspected MHA with associated nephropathy and thrombocytopenia. Further studies are needed to improve and understand the management of this rare condition.

TH-PO501

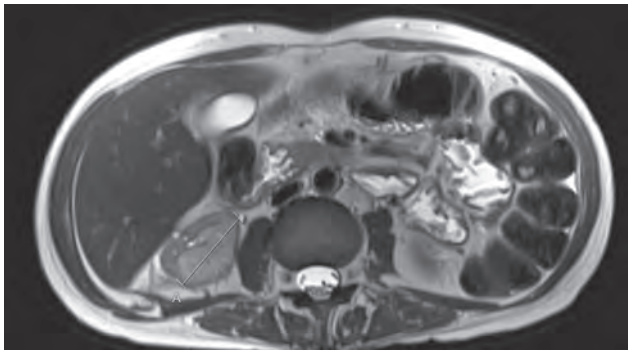
Case Report of a Novel NRIP1 Gene Mutation: Disease Association or Mere Coincidence?

Sabaa Asif, David M. Naimark. *University of Toronto, Toronto, ON, Canada*.

Introduction: Nuclear receptor-interacting protein 1 (NRIP 1) is known for its role in several physiological processes. These include and are not limited to ovulation; mammary gland development; lipid and glucose metabolism in adipose tissue, muscle and liver; regulation of inflammatory processes; maintenance of cognitive function; and cardiac function. Recently, case studies have shown an association between truncating NRIP-1 mutations and CAKUT (Congenital Anomalies of the Kidney and Urinary Tract).

Case Description: A 40-year-old woman presented in 2021, with idiopathic, non-ischemic cardiomyopathy and stage 5 chronic kidney disease (CKD) of unknown etiology. Investigations were inconclusive. Other comorbid conditions included, migraine headaches, anemia and diagnosis of mixed connective tissue disease *versus* fibromyalgia, with positive anti-nuclear antibodies and antinuclear ribonucleoprotein-A antibodies. In late 2023, she was admitted to a hospital with retropharyngeal abscess, and mediastinitis with progression of CKD, requiring initiation of hemodialysis. Prior to admission she had renal imaging as part of kidney transplant evaluation, which showed suspicious renal mass. Magnetic resonance imaging of the kidneys during the admission demonstrated multiple bilateral renal masses. These were confirmed to be lipid-free angiomyolipomas on biopsy. The kidney itself had changes suggestive of chronic hypoperfusion. There were no findings suggestive of any urinary tract abnormalities on imaging. Genetic testing showed a heterozygous c.1203A>C, pArg401Ser, missense mutation of the gene for NRIP1 which is novel.

Discussion: NRIP1 mutations have been associated with different malignant tumors, CAKUT and heart failure. The NRIP1 missense mutation observed in this case could be the etiology of the non-ischemic cardiomyopathy or the first documentation of its association with renal angiomyolipoma. Studies have demonstrated that NRIP1 missense mutations are also present in disease-free controls, hence, further studies are required to validate this association.



Angiomyolipoma of the right kidney.

TH-PO502

Hiding in Plain Sight: The Diagnostic Challenge of Autosomal Dominant Tubulointerstitial Kidney Disease

Luke Barr,[1] Lonnie Thach,[1] James J. Paparello,[1] Susan E. Quaggin,[1] Yashpal S. Kanwar,[1] Anthony J. Bleyer.[2] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Wake Forest University School of Medicine, Winston-Salem, NC*.

Introduction: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of rare inherited disorders characterized by tubular damage and interstitial fibrosis, bland urinary sediment and normal imaging. Mutations in the *MUC1* gene encoding mucin-1 are one cause. A cytosine insertion within *MUC1* leads to formation of MUC1 frameshift proteins. Deposition of these proteins leads to ADTKD, progressive CKD and early onset ESRD.

Case Description: A 33 year old asymptomatic man was admitted after an elevated serum creatinine of 5.1 mg/dl was found on outpatient labs. There was no history of dysuria, hematuria, NSAID exposure, tobacco use, recurrent UTI, kidney stones or prematurity. While the father's clinical history was unknown, a paternal grandmother and three uncles were on renal replacement therapy. He was hypertensive with labs notable for mild hyperkalemia 5.3 mmol/L, serum bicarbonate 19 mmol/L, BUN 68 mg/dl, serum creatinine 5.15 mg/d and uric acid 10.2 mg/dl. Urinalysis was bland. Renal ultrasound showed a R kidney 10.7 cm, L kidney 8.9 cm, few L simple renal cysts, increased echogenicity and no hydronephrosis. Kidney biopsy showed mild to moderate arteriosclerosis, ATN and moderate tubulo-interstitial disease with 40% tubular atrophy and fibrosis. Initial genetic testing was negative. Through the Rare Inherited Kidney Disease Team at Wake Forest and the Broad Institute of Harvard-MIT, advanced genetic testing identified a *MUC1* mutation, confirming a diagnosis of ADTKD. Ultimately, he progressed to ESRD and is currently being evaluated for transplant.

Discussion: Our case demonstrates a classic presentation of ADTKD-*MUC1* as well as the diagnostic challenges – namely the absence of typical hallmarks of kidney disease like proteinuria, hematuria, serum serologies, diagnostic imaging or pathology. This case highlights the limitation of commercially available genetic testing and the need for improved awareness of these disorders and specialized centers which can help establish the diagnosis. Accurate diagnosis is essential for family planning and prognostication, not only with respect to native kidney disease but post-transplant as well. Only with heightened awareness and identification can our understanding of ADTKD grow and lead to the discovery of early treatment options.

TH-PO503

Chronic Benign Tubular Proteinuria from Compound Heterozygous Mutations in CUBN: A Case Report

Adam Pietrobon,[1,2] Mark Elliott.[1,2] *[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]Providence Health Care, Vancouver, BC, Canada*.

Introduction: Proteinuria is a commonly used parameter for predicting decline in renal filtration function. Cubilin, encoded by *CUBN*, is a critical protein involved in low molecular weight protein reabsorption in the proximal tubule. Mutations in *CUBN* lead to Imerslund-Gräsbeck syndrome (IGS), a disorder characterized by vitamin B12 deficiency (and consequences related to that) with or without proteinuria. Recent evidence suggests that C-terminal mutations in *CUBN* may lead to proteinuria without other features of IGS.

Case Description: We report a case of a 47 year-old male with chronic, albumin-predominant, subnephrotic range proteinuria since his teenage years, but preserved eGFR. Neither ACE inhibition nor AT-II receptor blockade reduced his degree of proteinuria. Genetic testing identified three distinct pathogenic mutations in *CUBN* that were confirmed by parental cascade testing to be compound heterozygosity. All mutations were downstream of the vitamin B12-intrinsic factor binding domain of cubilin, two of which conferred stop-gain sequences. The patient had normal vitamin B12 levels and did not exhibit megaloblastic anemia, growth retardation, or any other features of IGS. Renal biopsy was not pursued for this patient as diagnostic clarification was achieved by non-invasive genetic testing alone.

Discussion: This case report presents the first long-term follow-up of a patient with *CUBN* mutations, demonstrating eGFR stability despite chronic proteinuria. We highlight several important lessons. First, not all proteinuria is made equal, and forms of tubular proteinuria can exist without compromising renal filtration function. Second, identifying genetic forms of tubular proteinuria is key to avoiding ineffective interventions (e.g. ACE inhibition, AT-II receptor blockade) and unnecessary invasive procedures (e.g. renal biopsy). Third, the location of *CUBN* mutations dictate phenotypic consequences, with C-terminal mutations leading to proteinuria without vitamin B12 deficiency.

TH-PO504

Cases of Patients with E66Q Mutation Manifesting Zebra Bodies in Various Organs

Hayaki Okamoto, Shunsuke Goto, Keiji Kono, Hideki Fujii. Div of Nephrology, Kobe University Graduate School of Medicine. *Kobe University Graduate School of Medicine, Kobe, Japan*.

Introduction: Fabry disease is a X-linked inherited disorder caused by mutations in the alpha-galactosidase A (GLA) gene, leading to the accumulation of globotriaosylceramide (Gb3) in various organs. The accumulation of Gb3 results in dysfunction of these organs. Although patients with the E66Q mutation have reduced GLA enzyme activity, this mutation is considered a functional polymorphism because Gb3 accumulation is not observed in any organs. We report here cases with the E66Q mutation in which histopathological examination revealed zebra bodies in various organs.

Case Description: A 54-year-old woman was found to have the E66Q mutation from our previous Fabry disease screening study on hemodialysis patients at the age of 46. She initiated hemodialysis therapy at the age of 34, despite her young age, and suffered a cerebral infarction at the age of 44. She also had left ventricular hypertrophy and mild systolic dysfunction. A pathological specimen obtained during cataract surgery showed zebra bodies in the lens epithelial cells. A 34-year-old man, the son of the aforementioned patient, was also found to have the same genetic abnormality (E66Q mutation) at the age of 19 years during a family history survey. He was admitted to our hospital at the age of 33 years for the creation of an arteriovenous (AV) fistula due to progressive deterioration of kidney function. The vascular tissue obtained during the AV fistula surgery showed zebra bodies in both arteries and veins. A myocardial biopsy was performed at the age of 34 years to investigate left ventricular hypertrophy. Optical microscope images showed scattered vacuolar degeneration in cardiomyocytes, and electron microscope images showed zebra bodies in cardiomyocytes. Both patients received enzyme replacement therapy after diagnosis, which improved clinical symptoms such as limb pain and chest pain, as well as laboratory findings such as left ventricular mass and coronary flow reserve.

Discussion: Although known reports suggest that patients with the E66Q mutation do not show tissue Gb3 accumulation, our findings otherwise. These patients exhibited zebra bodies in multiple organs, suggesting Gb3 accumulation. Therefore, we believe there is a possibility that E66Q may not be a functional polymorphism but a pathogenic mutation. Consequently, we suggest that the classification of E66Q should be carefully reconsidered.

TH-PO505

Fishing for Zebras: Catching Fabry Disease with Pretransplant Genetic Testing

Sydney E. Hartsell, Sarah Gilligan, Isaac E. Hall, Duha A. Jweehan, Suayp Oygen, Miklos Z. Molnar, Divya Raghavan. *The University of Utah School of Medicine, Salt Lake City, UT.*

Introduction: Fabry Disease (FD) is a rare X-linked lysosomal storage disorder whose diagnosis can be particularly challenging in women, who often present atypically.

Case Description: A 43-year-old woman with ESRD attributed to hypertension and fibromuscular dysplasia (FMD) presented to renal clinic for pre-transplant evaluation. She had hypertension since age 20, complicated by hemorrhagic stroke at age 33 and an admission for hypertensive urgency at age 34, during which she was told she had FMD based on right renal atrophy and distal right renal artery stenosis, treated with balloon angioplasty. Unfortunately her eGFR declined rapidly over 4 years from 52 to 10 ml/min/1.73m^2 without explanation on serology and "no evidence of fibromuscular dysplasia" or re-stenosis on repeat MRA. She started dialysis in 2019 at age 39. Her medical history was also notable for incidental ischemic strokes seen on imaging, memory impairment, complete heart block in 2022, and systolic heart failure in 2024. Due to the patient's early-onset renal disease (in combination with her cardiac and neurologic history), the transplant nephrologist ordered a kidney gene panel. This revealed a heterozygous, "likely-pathogenic" galactosidase alpha (*GLA*) gene mutation *c.1018T>A (p.Trp340Arg)*, consistent with FD. She was referred to Medical Genetics who elicited a history of hypohidrosis and diarrhea, but no neuropathic pain, skin lesions, vision/hearing impairment, or known family history of FD. However, her son had neuropathy and her brother died young from heart failure. Enzyme levels showed accumulation of globotriaosylsphingosine (LysoGb3) and she subsequently started enzyme replacement therapy. Family testing revealed the same mutation in her daughter.

Discussion: FD demands a high index of suspicion and low threshold for genetic testing in patients with early-onset kidney disease, especially in the setting of cardiac and neurologic manifestations. Panels to identify genetic causes of CKD are now recommended in KDIGO's recent 2024 CKD evaluation guidelines. Patients with FD stand to benefit as more nephrologists gain access to this testing and can cast a wide net to catch heterozygous or atypical cases earlier. Furthermore, ESRD is not too late to test and drastically improve outcomes for patients and their family members.

TH-PO506

Fabry Nephropathy: An Important Phenotype of the Mutation p.R356W (c.1066C>T)

Arquizia M. Albuquerque, Ana Cecília M. Siqueira, Ana Paula Gueiros. *Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil.*

Introduction: Nephropathy is a serious manifestation of Fabry disease. Kidney biopsy (KB) is a valuable tool for diagnosing nephropathy. The aim of this study is to describe renal impairment in three generations of patients with the p.R356W mutation.

Case Description: CASE 1- Male, aged 65, diabetes mellitus for 12 years. Enzyme activity (EA): 0.52 (VR >2.2 umol/L/h); Lyso-GB3: 1.8 (VR < 1.8 ng/mL); Creatinine (Cr) 1.6 mg/dL; proteinuria 2.2 g/24h. KB: Optical microscopy (OM): 4/9 glomeruli with global sclerosis, foamy podocytes, mild tubular atrophy, and interstitial fibrosis, moderate arteriolar hyalinosis, artery with moderate fibrointimal hyperplasia. Electron microscopy (EM): lamellar inclusions in podocytes, thickened capillary loops, podocyte foot process effacement. CASE 2 Female, aged 50. EA: 2.2 (VR1.68-13.3 umol/L/h); Lyso-GB3: 1.6 (VR < 2.0 ng/mL); Cr 0.6 mg/dL; proteinuria 0.2 g/24h; albuminuria 18.5 mg/L. KB OM: segmental sclerosis in 3/47 glomeruli, global sclerosis in 2/47 glomeruli, podocytes with large and vacuolated cytoplasm, interstitial fibrosis (<10%). EM: podocytes with disorganized cytoplasm, foot process effacement containing zebra bodies. CASE 3 Male, aged 31. Lyso-GB3: 2.1 (VR < 0.8 ng/mL); Cr 0.76 mg/dL; proteinuria 0.22 g/24h; urinary albumin/creatinine ratio (ACR) 9.15mg/g. KB: diffuse podocyte vacuolation, preserved tubulointerstitium, arteries with slightly thickened walls. EM: lamellar inclusions in podocytes, with foot process effacement. CASE 4 Female, aged 17. Cr 0.6 mg/dL; ACR 29 mg/g; Lyso-GB3: 0.8 (VR < 1.8 ng/mL). KB OM: Podocyte hypertrophy, artery with mild fibrointimal hyperplasia, tubulointerstitium with no particularities. EM: podocytes with voluminous cytoplasm containing inclusions with myelin figures and zebra bodies and foot process effacement. CASE 5 Male, aged 8. EA: 0.16 (VR 1.68-13.3 umol/L/h), Lyso-GB3: 6.5 (VR < 1.8 ng/mL); Cr 0.4 mg/dL; ACR 4.6 mg/g. KB OM: Discreet podocyte hyperplasia, tubulointerstitial and vascular compartment with no particularities; EM: focal lamellar inclusions in podocytes, endothelium, and tubules; preserved foot process.

Discussion: This study demonstrates the importance of KB in an early diagnosis of Fabry nephropathy and for understanding the phenotypic presentation of the different mutations. This study has demonstrated the tropism of the p.R356W mutation for the kidney.

TH-PO507

MMP1 Levels in Kidney Tissue May Be Related to Kidney Interstitial Fibrosis in Fabry Disease

Aline A. Santana, Regiane S. Cunha, Guilherme Miniskiskosky, Paulo C. Gregório, Rodrigo Hagemann, Fellype Barreto, Andréa M. Stinghen. *Universidade Federal do Parana, Curitiba, Brazil.*

Background: Fabry disease (FD) is a rare disease, linked to the X chromosome and caused by mutations in the *GLA* gene that leads to complete or partial deficiency of the enzyme α-galactosidase (α-GAL). Loss of this enzyme leads to lysosomal accumulation of glycosphingolipids, especially globotriaosylceramide (gb3), with a broad spectrum of clinical manifestations. Matrix metalloproteinase-1 (MMP-1) is a colagenase responsable for insterstitial remodelling, specifically breaking down collagen type I, II, and III. FD patients could have prominent kidney involvement, with progressively worse of renal function caused by fibrosis. Here, we evaluated the MMP-1 presence in renal tissue.

Methods: The study included 6 FD patients diagnosed with the p.G35V missense mutation and 1 control patient. Creatinine and proteinuria levels were evaluated in these patients, and immunohistochemistry for MMP-1 was performed on kidney biopsies.

Results: Female patients (n=5) had creatinine levels 0.78 mg/dL (+- 0.10 mg/dL) and proteinuria 322.0 mg/24h (+- 207.2 mg/24h). Male patient (n=1) shows 0.9 mg/dL of creatinine and proteinuria 400.0 mg/24h. Four of them had stage 1 CKD, while the other two had stage 2 CKD. Analysis of the kidney biopsies showed positive immunostaining for MMP-1 in control patient (Figure 1A) and negative immunostaining for MMP-1 in the glomerular capillary walls for all patients with FD (Figure 1B). MMP-1 interstitial positivity was observed in 4 patients; sparse and discrete form in one, discrete focal form in another one and mild multifocal in 2 patients. Furthermore, 2 patients showed MMP-1 positivity in the tubular epithelium and parietal epithelium. All patients with FD had interstitial fibrosis.

Conclusions: Patients with FD due to the p.G35V mutation have reduced levels of MMP-1, an enzyme related to interstitial kidney fibrosis, even in stages 1 and 2 of CKD.

Funding: Government Support - Non-U.S.

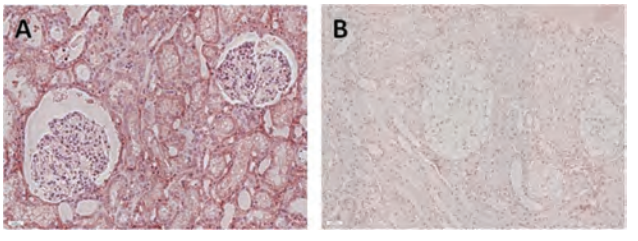


Figure 1 - Images showing MMP-1 immunostaining. (A) Control patient. (B) Male patient with FD. The scale bar indicates 50 μm, magnification 200x.

TH-PO508

Influenza B Triggering Atypical Hemolytic Uremic Syndrome (aHUS) in a Patient with Cobalamin C (CblC) Disease Carrier State and a Complement Factor H (CFH) Mutation

Laura Aponte Becerra, Gilbert W. Moeckel, Deepthi Gunasekaran. *Yale University, New Haven, CT.*

Introduction: AHUS is driven by abnormalities in genes coding for alternative complement pathway regulators triggering increased activity of the membrane attack complex. This causes endothelial damage, platelet adhesion and formation of microthrombi with subsequent thrombocytopenia, intravascular destruction of erythrocytes and acute kidney injury; termed thrombotic microangiopathy (TMA). We report a rare environmental trigger for aHUS in a patient with rare mutations in cobalamin uptake and CFH gene.

Case Description: A 59-year-old woman presented with upper respiratory symptoms and tested positive for Influenza B. Laboratory showed AKI, thrombocytopenia, hemolytic anemia with schistocytes and nephrotic range proteinuria. Creatinine at admission was 2.14mg/dL (from a normal baseline) and peaked at 8.67mg/dL with hyperkalemia requiring hemodialysis. C3 was low. C4, ADAMTS13 activity and Vitamin B12 were normal and methylmalonic acid level was mildly elevated. Acute kidney injury progressed and patient required initiation of hemodialysis. Kidney biopsy showed lobular accentuation of glomeruli, increased matrix deposition, karyorrhectic debris and red blood cell fragments in the mesangium and fibrinoid necrosis of an arteriole. Eculizumab was initiated and six days later renal function recovered, and dialysis was discontinued. Genetic testing revealed heterozygous p. Arg161Gly missense variant in the metabolism

of cobalamin associated C (MMACHC gene) and heterozygous p. Thr724Lys missense variant in the CFH gene classified as a variant of unknown significance.

Discussion: MMACHC gene mutations cause autosomal recessive methylmalonic aciduria and homocystinuria (CblC disease) which rarely presents as aHUS. CblC disease is usually reported in children and none in the carrier state. Additional CFH high-risk haplotype and environmental factors increased the risk for aHUS in this case, with influenza being a known trigger but influenza B being very rare. This case highlights the importance of suspecting aHUS in older adults with identifiable triggers and low threshold to initiate complement blockade.

TH-PO509

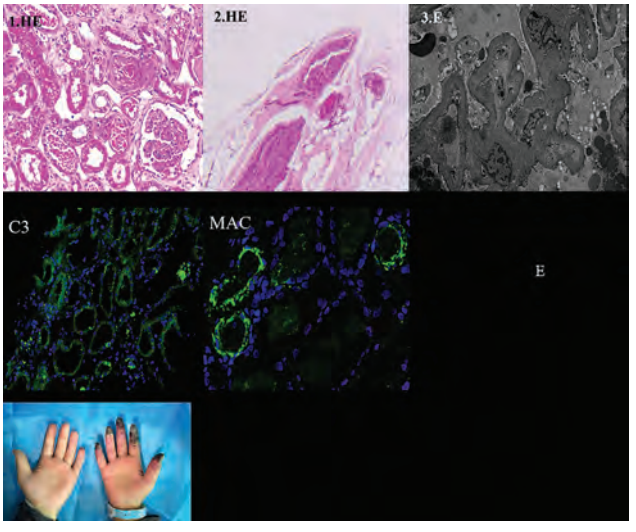
Atypical Hemolytic Uremic Syndrome with Peripheral Gangrene

Ailima Aierken,[1] Gulimire Muhetaer,[1] Shufen Yang,[1] Jing Zhuang,[1] Hong Jiang,[1] Xuefei Tian.[2] *[1]People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China; [2]Yale University School of Medicine, New Haven, CT.*

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a form of complement-mediated thrombotic microangiopathy (TMA). The clinical symptoms of aHUS can involve multiple organ systems. Few aHUS case reports describe peripheral vascular manifestations.

Case Description: A 27-year-old Chinese male was admitted to the hospital with acute renal failure and thrombocytopenia following a fever. Blood pressure was 145/85 mmHg, with 2.5% peripheral broken red blood cells, LDH at 1024 U/L and normal ADAMTS13 activity. He was diagnosed with TMA. Received hemodialysis, plasma exchange, Rituximab and glucocorticoid therapy. The kidney biopsy revealed TMA. After treatment, he was discharged from dialysis. After 1 month he recurrenced of TMA, began maintenance hemodialysis. After 1 year, exposure to cold weather, the fingertips of his right hand turned cyanotic and painful. The symptoms gradually worsened, leading to necrosis. Laboratory results showed normal platelets, no broken red blood cells, low C3, LDH at 308 U/L, and normal ADAMTS13 activity. Within 3 weeks, the right hand progressed to gangrenous. He has a family history, with two uncles died of kidney failure at around 25 years old. Whole-exome genetic testing revealed a C3 gene mutation (C3: c.640C > T, *p*.P214S), which destabilized the overall spatial structure of the protein. We confirmed the diagnosis of aHUS. Eculizumab treatment was initiated, and the affected finger was amputated. Biopsy of the vascular tissue during surgery revealed intravascular thrombosis. After starting eculizumab, the patient's pain decreased, perfusion near the gangrene area improved.

Discussion: We describe a case of skin involvement associated with C3-associated aHUS, demonstrating that aHUS can affect small peripheral vessels. This case highlights that aHUS lesions can be attributed to TMA, even if TMA may not be fully evident in laboratory tests. The skin gangrene, responded well to eculizumab.



TH-PO510

A Case of Atypical Hemolytic Uremic Syndrome with a Complement Factor I Mutation Triggered by a Femoral Neck Fracture in an Elderly Japanese Patient

Hiroyuki Iwasaki,[1] Hiroaki Io,[1] Toshiki Kano,[1,2] Kunimi Maeda,[1] Yusuke Suzuki.[2] *[1]Juntendo University Nerima Hospital, Nephrology & Blood Purification Center, Nerima-ku, Japan; [2]Juntendo University Faculty of Medicine, Bunkyo-ku, Japan.*

Introduction: Regional and racial differences in the genetic variations of aHUS have also been observed. Complement factor I (CFI) mutations are present in 4–8% of European cases. However, few patients with aHUS with CFI mutations have been reported in Asia, and to our knowledge, there have been no reports of these mutations in Japan.

Case Description: An 83-year-old woman fractured her left femoral neck and was admitted to the orthopedic department of another hospital 2 days before she was referred to our hospital. On admission at the other hospital, her serum creatinine level was found to have increased to 7.23 mg/dL, and she was transferred to our department. Laboratory results revealed hemoglobin levels of 9.2 gm/dL, platelet counts at 7,000/μL, creatinine levels of 8.20 mg/dL, and lactate dehydrogenase at 2838 IU/L. A peripheral blood smear revealed occasional schistocytes with reduced platelets at admission, consistent with HUS. Nine hemodialysis and eight plasma exchange sessions were performed, and the patient was weaned. However, the platelets did not return to their previous levels after plasma exchange. ADAMTS13 activity was 46%, and various examinations were negative for thrombotic thrombocytopenic purpura or secondary TMA. Therefore, she was clinically diagnosed with aHUS and received ravulizumab on day 35 of hospitalization. After the initial induction dose of ravulizumab, the patient's platelet level peaked at 170,000/μL, and there was no further decrease in platelets. The genomic gene sequences confirmed that the patient had a novel heterozygous frameshift mutation in the CFI gene.

Discussion: CFI mutation identified in this patient has not been reported from Japan. Notably, aHUS patients with CFI mutations have a low remission rate of 30-40%, a high mortality rate and a high rate of progression to end-stage renal disease. Ravulizumab treatment was continued in this patient on an outpatient basis, and to date, there has been no recurrence or progression of renal dysfunction for 2 years. Early treatment with plasma exchange and ravulizumab resulted in successful treatment in this case.

TH-PO511

Sex-Specific Modulation of Renal Dopamine Receptor Expression by DRD2 Single-Nucleotide Polymorphisms (SNPs) and Hormonal Factors

Raisha L. Campisi Cadme, Shaun C. Moore, Pedro Alves Soares Vaz de Castro, Hewang Lee, Pedro A. Jose, Ines Armando. *The George Washington University School of Medicine and Health Sciences, Washington, DC.*

Background: The involvement of renal dopamine, through the dopamine D2 receptor (D2R), in maintaining water, electrolyte balance, and blood pressure has a critical role in homeostasis in mammals. We have reported that the D2R is essential in preventing inflammation and kidney injury. In humans, the *DRD2* gene has several polymorphisms. The presence of specific single nucleotide polymorphisms (SNPs), such as rs6276 and rs6277 (*DRD2* SNPs), correlates with decreased D2R expression and activity, and is associated with increased blood pressure and susceptibility to hypertension. Human renal proximal tubule cells (hRPTCs) carrying these *DRD2* SNPs show a proinflammatory and profibrotic phenotype, which differs between sexes and is influenced by hormones in the culture medium. Exploring how hormonal factors modulate these responses could provide insights into sex-specific differences in renal physiology and pathophysiology.

Methods: This study was designed to investigate the factors influencing D2R expression in hRPTCs. We used four different hRPTC lines, genotyped for the absence (WT) or presence of SNPs and categorized by sex (male: M WT, M SNPs; female: F WT, F SNPs). We measured D2R expression levels and investigated the involvement of transcription factors Nurr1, ATF4, and Sp1, and the androgen receptor (AR), all known to bind to the *DRD2* promoter.

Results: D2R expression in male and female hRPTCs was greater in WT than SNPs cells. Expression of Nurr1 and Sp1 was similar in all cell lines. However, there were differences in ATF4 expression. While expressions were similar in F WT and F SNPs cells (1.3±0.1 vs 1.0±0.1; n= 3-5; p=0.199), a notable disparity was observed between M WT and M SNPs (1.0±0.1 vs 2.4±0.1; n= 3-5; p<0.001). AR expression was lower in female WT and SNP cells (0.77±0.09 and 0.8±0.1, respectively) than their male counterparts (1.10±0.10 and 1.56±0.04). Dihydrotestosterone (DHT) (5 nM/24 hr) decreased D2R expression in F WT cells (1.2±0.10 vs. 0.72±0.05; n=10-13; p<0.001) and M WT cells, (0.97±0.06 vs. 0.70±0.090; n=10-13, p<0.001), relative to vehicle treatment. DHT had no effect in cells with SNPs, F or M.

Conclusions: These findings highlight the sex-dependent regulation of renal D2R expression and suggest potential importance of SNPs on gene promoter binding sites and responses to hormones.

Funding: NIDDK Support

TH-PO512

Kidney Disease Due to Caudal Regression Syndrome

Bhaktidevi Makadia, Mercedes Malone, Charles W. Heilig, Brian Li, Irtiza Hasan. *University of Florida College of Medicine, Jacksonville, FL.*

Introduction: Embryonic development, influenced by fetal genetics, maternal health, and environmental factors, plays a pivotal role in shaping long-term health outcomes. Among the myriad anomalies that can arise during this process, Caudal Regression Syndrome (CRS) stands out as a rare condition characterized by developmental abnormalities affecting multiple bodily organs. While infrequent, CRS exhibits a higher prevalence among males and has been linked to maternal diabetes, vascular hypoperfusion, and genetic predispositions. Despite its potential to induce various kidney dysfunctions, CRS often evades prompt identification due to its rarity and the lack of familiarity among healthcare providers. Here, we present a compelling case of a patient with CRS who underwent intricate urological surgeries without prior awareness of her congenital condition.

Case Description: A 21-year-old female sought care at our nephrology clinic for chronic kidney disease and congenital urological issues. Born without an anal opening, she required a colostomy bag and a neo bladder to manage her condition. Furthermore, she had a tethered cord, necessitating complex surgical interventions to ensure her survival into adulthood. Currently, she is managed with a neobladder/nephrostomy tube for urinary elimination. Despite these measures, her GFR has remained in the 30s, with a recent creatinine level of 2.16. Urine analysis revealed significant protein. The patient was unaware of any genetic component to her condition until recommended evaluation by a geneticist to gain further insights into her condition.

Discussion: In this case, CRS poses a distinct challenge since the patient lacks maternal diabetes and has survived into adulthood. The complexity of her medical history highlights the challenges in managing CRS-related complications, especially renal dysfunction. It's crucial to recognize CRS and its impact on kidney health to provide the best possible care. The rarity of CRS underscores the importance of understanding and sharing similar cases to develop suitable treatment approaches. CRS remains a significant cause of renal dysfunction, deserving more research and clinical focus.

TH-PO513

AA Amyloidosis Unveiling Familial Mediterranean Fever in a 65-Year-Old Armenian Man with Arthritis and Immunosuppression History

Sofia Yamada,[1,2] Xavier F. Parada,[3,4] Sphoorthy Pasala,[1,2] Rajesh Anumolu,[1,2] Saif A. Alenizi.[1,2] *[1]Brigham and Women's Hospital Department of Medicine, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]UMass Memorial Medical Center, Worcester, MA; [4]University of Massachusetts Chan Medical School, Worcester, MA.*

Introduction: Familial Mediterranean Fever (FMF) affects certain ethnicities with a higher incidence in males. Caused by MEFV gene mutation, leading to recurrent inflammation. Arthritis occurs in 75% of patients with renal amyloidosis as a complication due to elevated protein production. While colchicine is the mainstay treatment, 5 to 10% of patients may be refractory or encounter adverse effects. Biologic agents serve as a secondary therapy but their efficacy can diminish necessitating alternative treatments

Case Description: A 65 year old Armenian man with a 35 year past medical history of psoriatic arthritis treated with extensive immunosuppressive therapies with refractory symptoms, thalassemia minor, hypertension, and coronary artery disease attributed to JAK inhibitors, status post bilateral total knee arthroplasty 25 years ago. Was admitted for pneumonia and prerenal acute kidney injury with nephrotic range proteinuria. An elevated CH50 suggested hyperfunctioning complements and acute inflammation. Differential diagnoses included infection related glomerulonephritis (IRGN), and adalimumab nephrotoxicity. Kidney biopsy revealed secondary amyloidosis and genetic testing identified heterozygosity for FMF (p.Met694Val and p.VAl726Ala) Classic FMF episodes were absent. Family history revealed possible FMF cases (sister's recurrent abdominal and jaw pain, and a daughter with undiagnosed digestive issues) His father had chronic kidney disease requiring hemodialysis. Treatment with colchicine and IL-1β inhibitors normalized CRP levels and reduced proteinuria maintaining stable renal function

Discussion: While there have been rare cases of AA amyloidosis associated with psoriatic arthropathy, AA amyloidosis is a recognized complication of FMF. Our case reveals an autosomal recessive FMF with two pathogenic variants: p.Val726Ala (mild) and p.Met694Val (severe). Vigilance for thrombotic events is essential due to nephrotic syndrome. Early FMF detection prevents organ damage. Secondary amyloidosis prompted an investigation revealing undiagnosed FMF. Management involves colchicine and IL-1β inhibitors like canakinumab. Adalimumab's efficacy in FMF associated arthritis is noted though previous use on this patient's response was poor. Further research is necessary to refine therapeutic strategies in refractory cases

TH-PO514

A Case of Prolonged Glycosuria Secondary to SLC5A2 Receptor Mutation Affecting theSGLT2

Anzal Jangda, Shivangi Patel. *Morristown Medical Center, Morristown, NJ.*

Introduction: Glycosuria most commonly occurs in diabetics patients but can also be seen in pregnancy, multiple myeloma, secondary to SGLT2 inhibitor use or with any medication that causes proximal renal tubular acidosis for e.g. Tenofovir. Here we present a case of glycosuria secondary to a mutation in the SLC5A2 receptor, encoding the sodium-glucose cotransporter 2 (SGLT2).

Case Description: A 38-year-old with a past medical history of hypothyroidism presented with persistent glucosuria despite normoglycemia on routine lab work. The patient was Initially evaluated by urology for recurrent yeast infections. Subsequent workup was unremarkable, and the patient was referred to nephrology for persistent glycosuria. Patient denied any personal history of diabetes (HBA1c of 5.1%) and Levothyroxine was the only home medication for underlying hypothyroidism. Persistent lab work was notable for normal serum glucose and isolated glucosuria on the urine analysis. Subsequent workup for glycosuria was negative for serum protein electrophoresis (SPEP), free light chains, anti-nuclear antibody (ANA), ruling out concerns for multiple myeloma and connective tissue disease. The patient did not have any electrolyte abnormalities for e.g., hyperphosphatemia, hyperuricemia, or acidosis to suggest proximal Renal tubular acidosis (RTA) or Fanconi's syndrome. Renal ultrasound showed normal kidneys without cysts, hydronephrosis or stones. With work up so far negative for any disease process, there was concern for familial renal glycosuria (FRG). For patient reassurance it was decided to go ahead with genetic testing which confirmed an autosomal dominant/recessive mutation of the SLC5A2 gene. Management primarily involved patient reassurance and dietary modifications including a low carb diet as uncontrolled glycosuria would lead to recurrent yeast infections.

Discussion: This case underlines the importance of considering genetic causes of glycosuria in the absence of diabetes mellitus and other common causes. Accurate diagnosis through genetic testing can spare patients from unnecessary treatments and anxiety associated with a potential misdiagnosis. Additionally, it highlights the significance of genetic counseling and screening for affected individuals, allowing patients to understand their carrier status and potential risk.

TH-PO515

Acute Kidney Failure: An Atypical Presentation of Gordon Syndrome

Hatem Najar, Fitsum T. Hailemariam, Anju Yadav. *Thomas Jefferson University Hospital, Philadelphia, PA.*

Introduction: Gordon syndrome is a rare form of genetic hypertension characterized by hyperkalemia and metabolic acidosis. It is usually diagnosed in teenagers or young adults with normal kidney function. We present a case of a young adult with Gordon syndrome presenting with acute renal failure.

Case Description: A 24-year-old Caucasian male with history of hypertension since he was 16 years old, hyperkalemia, non-adherent to thiazide diuretics presented to the hospital with abdominal pain and vomiting. Family history was significant for early onset hypertension in his brother, father, and paternal grandmother. On arrival blood pressure (BP) was 250/160 mmHg. A comprehensive metabolic panel revealed a creatinine of 9.9 mg/dL, potassium of 3.0 mmol/L, sodium of 136 mmol/L, chloride of 91 mmol/L, CO2 of 18 mmol/L. The complete blood count was significant Hb of 10 g/dL, platelet 87/ mcL. A renal ultrasound revealed increased echogenicity of both kidneys. Detailed serologic work-up for glomerulonephritis was negative. BP was managed with intravenous and oral antihypertensives. Due to persistent azotemia, the patient was initiated on hemodialysis and a kidney biopsy was performed. Kidney biopsy revealed findings suggestive of chronic hypertension, severe arteriolar and arterial intimal thickening, and presence of moderate interstitial fibrosis and tubular atrophy (30-35%). Genetic testing was positive for Kelch Like Family Member 3 (KLHL3) gene identified in heterozygous pattern, which is associated with Gordon syndrome, or Pseudo-hypoaldosteronism, type 2b.

Discussion: We describe an atypical presentation of Gordon syndrome in a young adult presenting with hypokalemia (instead of hyperkalemia) and malignant hypertension leading to dialysis dependent acute kidney injury. The pathophysiology of Gordon syndrome is based on an increased activity of the sodium (Na)-potassium chloride channel. Increased Na reabsorption will induce a state of hypoaldosteronism with hyperkalemia and metabolic acidosis. It is associated with pathogenic variants of the WNK1, WNK2, CUL3 or KLHL 3 genes. Higher suspicion, diagnosis, genetic counselling and management of genetic forms of hypertension are crucial in the prevention of severe complications.

TH-PO516

Increased Risk of Kidney Injury and Early Death from Activating Mutations in the Calcium-Sensing Receptor: A Regional Case Series

Deepika Manoharan,[1,2] Shalabh Srivastava,[1,3] John A. Sayer.[1,2]
[1]Newcastle University, Newcastle upon Tyne, United Kingdom; [2]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom; [3]South Tyneside and Sunderland NHS Foundation Trust, Sunderland, United Kingdom.

Introduction: Calcium-sensing receptors (CASR), primarily expressed in the parathyroid glands and kidney tubules, play a key role in calcium homeostasis. Heterozygous activating, or gain-of-function, mutation of the CASR gene causes autosomal dominant hypocalcemia type 1 (ADH1) resulting in severe hypocalcemia associated with inappropriately normal to low parathyroid hormone, hyperphosphatemia, and hypercalciuria. We present 8 patient cases from North East England with this rare condition.

Case Description: Table 1 describes the clinical characteristics including the genetic mutation, biochemistry, and complications in 8 patients with ADH1. All patients were identified to have hypocalcemia at birth or childhood before a formal diagnosis of ADH1 was considered, at which point caution was taken to avoid overcorrection of serum calcium through reduction or complete avoidance of calcium and vitamin D supplementation. However, despite this, 7 out of 8 patients suffered from nephrocalcinosis and/or nephrolithiasis, increasing the risk of recurrent urinary tract infections and renal impairment. 2 out of 8 patients developed kidney failure and suffered from premature death. Other complications such as short stature, dental issues, hypertension, and/or brain calcifications were also noted across all 8 patients.

Discussion: Ectopic calcification, particularly in the kidneys, is a known complication of ADH1. Close monitoring and acceptance of a low serum calcium levels is thought to reduce hypercalciuria and prevent rapid onset of nephrocalcinosis and subsequent renal impairment. However, this case series demonstrates that renal complications in ADH1 is inevitable, despite maintaining 'optimal' serum calcium levels for these patients. Therefore, the use of a novel therapeutic agent, such as a CASR antagonist, may prove to be helpful, and is something we will soon look to offer to these patients as part of a clinical trial.

Table 1: Clinical characteristics of ADH1 patients

Patient	Age, gender, and demographics	CASR gene mutation (heterozygous)	Biochemical profile			Average adjusted Ca2+ (mmol/L)	Renal complications
			Ca2+	PTH	PO4-		
Case 1	57-year-old Caucasian female (deceased)	c.354C>A; p. Asn118Lys	↓	↓	↑	1.83	Nephrocalcinosis Nephrolithiasis UTI ESRF
Case 2	32-year-old Caucasian female (deceased)	c.354C>A; p. Asn118Lys	↓	↓	↑	1.88	Nephrocalcinosis Nephrolithiasis ESRF
Case 3	33-year-old Caucasian female	c.354C>A; p. Asn118Lys	↓	→	↑	1.52	Nephrocalcinosis Nephrolithiasis UTI CKD
Case 4	24-year-old Caucasian female	c.2363T>G; p.Phe788Cys)	↓	↓	↑	1.59	Nephrocalcinosis
Case 5	29-year-old Caucasian male	c.350A>G; p.Gln117Arg	↓	→	↑	1.66	
Case 6	57-year-old Caucasian male	c.2053G>A; p.Gly685Ser	↓	→	→	1.90	Nephrolithiasis
Case 7	36-year-old Caucasian female	c.416T>C; p.Ile139Thr	↓	↓	↑	2.10	Nephrolithiasis
Case 8	38-year-old Caucasian male	c.2495T>C; p.Phe832Ser	↓	→	↑	1.26	Nephrocalcinosis

TH-PO517

OMg! What Links Hypomagnesemia, Kidney Stones, and Arrhythmia

Amara Sarwal, Nirupama Ramkumar, Gurbir S. Sehmbey, Sarah Gilligan.
University of Utah Health, Salt Lake City, UT.

Introduction: Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive disease that usually presents during early childhood and is known to be caused by mutations of claudin-16 and claudin-19. We discuss an atypical presentation of an adult patient with kidney stones and hypomagnesemia with genetic testing remarkable for heterozygous mutation in claudin-16 (c235C>G).

Case Description: 23 year old female with history of kidney stones presented to the ED with ventricular fibrillation cardiac arrest. After successful resuscitation, she recovered quickly with intact neurological function. Initial workup revealed low-normal magnesium of 1.7 mg/dL which dropped to 1.5 mg/dL during hospitalization despite 4g of intravenous magnesium per day in addition to oral supplementation. Admission labs were also significant for a calcium of 7.8 mg/dL, albumin of 3.7 mg/dL and serum creatinine of 1.02 mg/dL, which improved during hospitalization. Laboratory values prior to this admission were not available. Medication history was unrevealing for culprit medications, including loop or thiazide diuretics. Urine studies revealed a fractional excretion of magnesium at 16%. Patient was supplemented with magnesium and discharged. During outpatient follow up, a 24 hour urine collection was obtained. She was found to have hypocitraturia, however with a normal urine calcium. Genetic testing was obtained which was negative for pathogenic variants but positive for a variant of unknown significance; a c235C>G heterozygous mutation in claudin-16. Upon outpatient clinic follow up, she continued to require magnesium oxide supplementation, currently at 400mg twice daily, with a corresponding magnesium level of 1.8 mg/dL.

Discussion: FHHNC has over 50 known mutations in the claudin-16 gene, and presents in early childhood leading to progressive kidney failure. Our adult patient had significant renal magnesium wasting during hospitalization that continued as an outpatient, and required ongoing supplementation. Although clinical history and urine magnesium studies were consistent with FHHNC, she did not have hypercalciuria or family history of kidney stones or kidney failure. As genetic testing has become more common in clinical practice, this case highlights the need to critically assess variants of uncertain significance and monitor for any potential clinical manifestations.

TH-PO518

Ceroid Lipofuscin in Renal Tubular Cells in Hermsky Pudlak Syndrome (HPS): An Unexplored Entity

Benjamin Strickland, Juan J. Cintrón-García, Maria M. Picken, Ewa Borys, Kavitha Vellanki. *Loyola University Chicago, Chicago, IL.*

Introduction: HPS is a rare autosomal recessive disorder of lysosomes and lysosome related organelles (LOR) resulting in defective oculocutaneous pigmentation and bleeding diathesis. 11 clinical subtypes have been identified so far with a relatively higher prevalence reported in Puerto Rico. While pulmonary manifestations are well known, the renal component of HPS remains unstudied and under-reported. Here, we report kidney biopsy findings in HPS.

Case Description: A 53 year old male from Puerto Rico with bilateral lung transplant (12/2020) for pulmonary fibrosis related to type 1 HPS and baseline stage G3bA3 CKD presented with SOB and AKI on CKD (increase in baseline serum creatinine from 1.8-2.1 to 4.4 mg/dl) with 3.9 gm/gm albuminuria (baseline 0.57 gm/gm). Urinalysis revealed glucosuria since 2021 with no h/o DM. Kidney biopsy findings revealed acute tubular injury and ceroid lipofuscin deposition in tubular epithelium as shown in Figure 1, similar to prior lung biopsy findings (Figure 1).

Discussion: Renal involvement in HPS is characterized by ceroid lysosomal deposition, yet the incidence/prevalence of biopsy proven kidney involvement is not known. In a report of 49 patients with HPS, 20% had creatinine clearance lower than 90 ml/min/1.73m2 (9 out of 45 patients with available data), the pathophysiology of such a finding neither explained nor explored. To our knowledge, our case is the first to report ceroid disposition in both lung and renal tissue in the same patient.

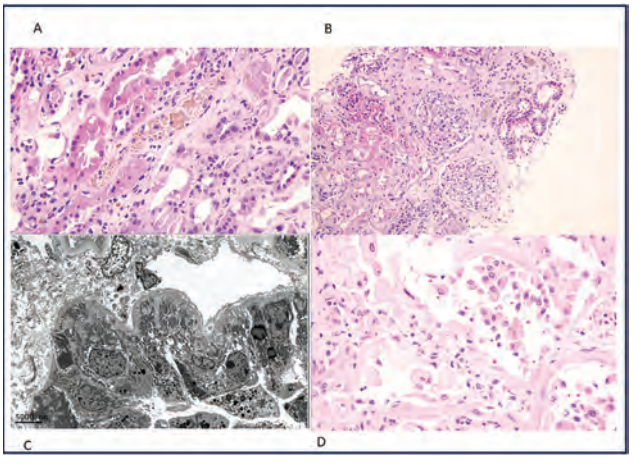


Figure 1: Kidney and lung biopsy findings.
A) H&E section with ceroid tubular deposition.
B) H&E section with mild glomerular mesangial expansion and ceroid tubular deposition.
C) EM section with ceroid tubular deposition.
D) Lung biopsy with ceroid deposition.

TH-PO519

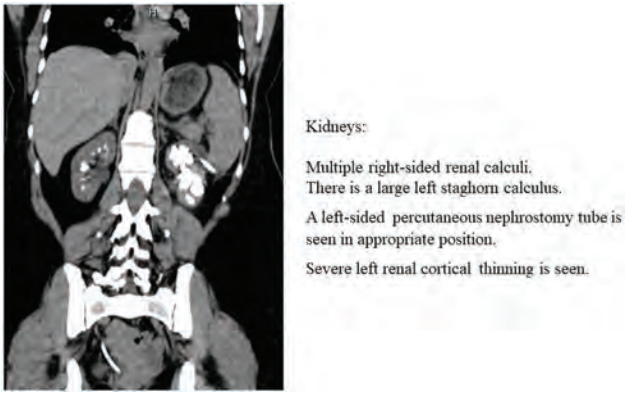
Deafness and Bilateral Staghorn Kidney Stones in a Young Patient

Hoang Anh Nguyen,[1] Sapna Gopal,[1] Anirudh V. Chandra,[1] Anita Kamarzarian,[1] Golriz Jafari,[1] Phuong-Thu T. Pham,[2] Phuong-Chi T. Pham.[1] *[1]UCLA Medical Center Olive View, Sylmar, CA; [2]Ronald Reagan UCLA Medical Center, Los Angeles, CA.*

Introduction: Massive stone formation in a young patient requires a thorough evaluation for the underlying cause. With the advent of genetic testing, rare conditions may be diagnosed.

Case Description: A 36-year-old female is referred for bilateral staghorn calculi and recurrent pyelonephritis. Urological history: lithotripsy and percutaneous nephrolithotomy of left kidney, and cystoscopy with stent placement. Medication: none. Review of systems: deafness since childhood. Family history: noncontributory. Vital signs: blood pressure 126/95 mm Hg, pulse 74, weight 71 Kg, Height 160 cm. Physical examination: within normal limits. Laboratory studies: Serum sodium 134, potassium 3, chloride 111, total CO2 12 mmol/L; blood urea nitrogen 27, creatinine 3.5, glucose 108, calcium 8.6, phosphorus 3.2, magnesium 2.8 mg/dL; total protein 7.9, albumin 3.9 g/dL; parathyroid hormone 82 pg/mL, vitamin D 25 38 ng/mL. Urinalysis: urine pH 7.0 (persistently ≥6.5). Given normal anion gap metabolic acidosis, high urine pH, and hypokalemia, distal renal tubular acidosis (dRTA) type 1 is considered. Serologies for autoimmune disease including ANA, anti-SSA and anti-SSB are negative. Genetic testing reveals homozygous nonsense mutation of ATP6V1B1 gene, encoding H-ATPase, autosomal recessive inheritance.

Discussion: The inherited nonsense mutation of ATP6V1B1 gene is associated with short stature, dRTA, nephrocalcinosis, medullary cysts, hypokalemia, hypokalemic periodic paralysis, and deafness. In the heterozygous state, patients may present with incomplete dRTA, hypercalcemia, and kidney stones. Management includes routine stone management (fluids, potassium supplement as needed). We suspect that the addition of fludrocortisone (in an attempt to acidify the urine) + thiazide diuretic (to both enhenace fludrocortisone efficacy and reduce calciuria) may be beneficial.



TH-PO520

Triple Threat! A Case of Lowe Syndrome with Triple Genetic Mutations

Edward Mwarangu, Uma Mahesh R. Avula, Mohammad Atari, Ramya Krishna Velagapudi, Mohamed Hassanein. *The University of Mississippi Medical Center, Jackson, MS.*

Introduction: Lowe syndrome (LS), also known as Oculocerebrorenal Syndrome of Lowe (OCRL), is an extremely rare multisystem disorder that primarily affects the eyes, brain, and kidneys. It is inherited in an X-linked manner and is caused by a deficiency of inositol biphosphate 5-phosphatase, localized to the Golgi complex. Here, we report a case with a unique combination of genetic variations in the OCRL, Collagen-4 A3 (COL4A3), and Apolipoprotein-1 (APOL1) genes.

Case Description: A 33-year-old male with a history of congenital cataracts, cerebral palsy, significant growth retardation, and proximal kidney tubular dysfunction, including proteinuria was diagnosed with Lowe syndrome between the ages of 7 and 9. During a routine follow-up his urine protein-to-creatinine ratio increased to 2.23 g/g, and his chronic kidney disease (CKD) progressed, as evidenced by a decrease in Cystatin C estimated glomerular filtration rate from 52 ml/min/1.73m^2 to 46 ml/min/1.73m^2. Genetic testing confirmed the presence of a genetic mutation in the OCRL gene, a heterozygous mutation in COL4A3 gene and a high risk APOL1 allele. In light of these findings, a kidney biopsy was performed, revealing extensive global glomerulosclerosis and segmental thinning of the glomerular basement membrane (GBM) up to 168 nm and lamellated thickening of the tubular basement membranes. He continued to follow up in the nephrology clinic with plan to optimize anti-proteinuric therapy.

Discussion: Lowe Syndrome occurs almost exclusively in males due to mutations in the OCRL gene and has an estimated prevalence of approximately 1 in every 500,000 children. Although not pathognomonic, lamellated tubular basement membranes have been reported in patients with OCRL gene abnormalities which may explain proximal tubular dysfunction. The presence of segmental thinning in the GBM could raise the possibility of early changes secondary to his COL4A3 mutation. To our knowledge, this is the first report of a patient with Lowe syndrome presenting with triple genetic variations. The biopsy enhanced our understanding of the etiology of CKD in this patient.

TH-PO521

Unraveling the Mystery: McCune-Albright Syndrome as a Rare Cause of Fanconi Syndrome and Kidney Failure

Geraldine Boh,[1] Hui-Lin L. Chin,[2] Ru Sin Lim.[1] [1]*Tan Tock Seng Hospital, Singapore, Singapore;* [2]*National University Hospital, Singapore, Singapore.*

Introduction: McCune Albright Syndrome (MAS) is a rare sporadic genetic disorder caused by post-zygotic somatic missense mutations of the *GNAS1* gene characterized by polyostotic fibrous dysplasia, café au lait skin pigmentation, and precocious puberty. Here we present a proband with MAS manifesting with Fanconi syndrome (FS) and eventual kidney failure (KF).

Case Description: A 44-year-old female was referred to Nephrology in 2007 for impaired renal function (Creatinine 136 umol/L, eGFR 42ml/min/1.73m^2). Her medical history included right femur osteoid osteoma, hypophosphatemia, osteoporosis, Grave's disease, and congenital primary amenorrhea. Further work up revealed FS with hypophosphatemia, hypokalemia, hyperchloraemic metabolic acidosis, aminoaciduria (24hr urine total protein 1.3g/day), euglycaemic glucosuria, and a low tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) ratio implying impaired tubular phosphate reabsorption. Ultrasound kidneys and secondary work up were unremarkable. Renal biopsy was unyielding with non-specific interstitial fibrosis and tubular atrophy. Her kidney function continued to deteriorate necessitating peritoneal dialysis in 2022. In view of idiopathic KF with FS, primary bone marrow failure of unclear cause and endocrinopathies (thyrotoxicosis and primary ovarian failure), genetic testing (whole exome sequencing) was performed. This identified that the proband was mosaic for pathogenic *GNAS* variant (NM:_000516:c.[602G>A];[=],p.(Arg201His)), diagnostic of MAS.

Discussion: This case marks the first instance of MAS presenting with FS and KF to our knowledge. While renal phosphate wasting due to increased FGF-23 level and proteinuria have been reported in MAS, FS and KF are unprecedented, likely mediated by factors apart from FGF-23. We hypothesize that dysfunction of proximal tubule (PT) transporters in MAS relate to elevated circulating cyclic adenosine monophosphate (cAMP) and selective expression of G protein-coupled receptors (GPCRs) in the PT via a gain-of-function in G-protein alpha subunit (Gαs), induced by the GNAS pathogenic variant. Raised cAMP level following chronic Gαs activation may lead to mesangial cell proliferation and hyperfiltration, potentially contributing to KF in MAS. The role of cAMP leading to FS and KF in MAS requires further investigations.

TH-PO522

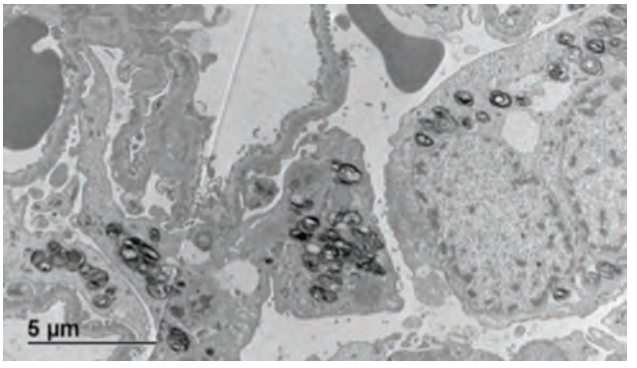
Nail-Patella Syndrome Presenting with Nephrotic Syndrome during Pregnancy

Lucia Facal, Maria Belen Facal, Paula Parnizari, Federico Yandian, Jose Boggia, Gabriela Ottati, Oscar A. Noboa. *Hospital de Clinicas Doctor Manuel Quintela, Montevideo, Uruguay.*

Introduction: We report a rare cause of nephrotic syndrome.

Case Description: A 38-year-old woman with a one-year history of proteinuria, hypoalbuminemia and new headache and blurred vision presented to our clinic at 9 weeks of pregnancy. Physical examination: normotensive, lower limbs edema, Marcus Gunn's sign on right eye, bilateral optic disc edema and serous exudative retinal detachment. Lumbar puncture showed inflammatory CSF. Neoplastic, infectious and systemic autoimmune causes were excluded. A diagnosis of Vogt-Koyanagi-Harada was made and received steroids and azathioprine. Visual acuity slightly improved. She presented with nephrotic syndrome resistant to prednisone, with proteinuria of 8 g/24 hrs., serum albumin 2 g/dl, hypercholesterolemia, Cr 0.3 mg/dl. Renal biopsy revealed non-specific glomerular changes and EM revealed diffuse FPE and myeloid bodies (MBs). *GLA* enzymatic activity was normal and *GLA* sequencing was negative. Exomic sequencing identified a heterozygous pathogenic variant in *LMX1B*. She delivered a healthy baby boy at term. One year after birth: Cr 0.4 mg/dl, serum albumin 4 g/dl and proteinuria 2.6 g/24 hrs. We studied her 22-year-old daughter and found the same variant. She did not show patellar abnormalities but had nail dysplasia.

Discussion: MBs are classically associated but not exclusive of Fabry Disease. The patient had no exposure to silica or drugs. NPS is an autosomal-dominant disease with variable penetrance caused by mutations in *LMX1B*. Our patient presented with patellar hypoplasia, triangular lunulae, reduced sensation to pain and temperature in hands and feet and renal involvement. The risk of preeclampsia in NPS is increased and onset of nephrotic syndrome during pregnancy has been described. This case illustrates the difficulties of diagnosing rare kidney diseases with subtle clinical hints and the importance of EM and sequencing technologies to reach a definitive diagnosis. It is one of the few cases described of NPS and pregnancy.



EM shows MBs in podocytes

TH-PO523

All in the Genes: Chronic Benign Proteinuria Due to CUBN Mutations

Frank Cassavell, Areeba Nayyer, Louis C. Jan, Tanganyika Barnes. *Englewood Hospital and Medical Center, Englewood, NJ*.

Introduction: Proteinuria is common in primary care patients. It can have transient causes such as UTI and heavy exercise or can be persistent. Most forms of persistent proteinuria are caused by damage to the kidney which can be intrinsic as in glomerular diseases or secondary to conditions such as CHF, hypertension, or diabetes. Persistent forms including protein receptor deficiencies can also cause chronic benign proteinuria and do not require treatment. The CUBN gene encodes the cubilin protein which forms a receptor in the proximal renal tubule that plays a key role in blocking excessive protein excretion. Deficiency in the cubilin protein can lead to non-nephrotic range proteinuria without decreased renal function given the lack of associated glomerular disease. We present a case of a patient with chronic, non-nephrotic range proteinuria with normal renal function, found to have the CUBN mutation.

Case Description: A 33-year-old male with a history of mild hypertension treated with 2.5mg lisinopril presented to the nephrology office for evaluation of persistent proteinuria. He had a renal biopsy 15 years prior which showed normal renal cortex by light and electron microscopy. No diagnosis was made or treatment started at that time. His only symptom was slightly foamy urine. Creatinine was 0.99 mg/dl and a 24-hour urine protein collection was significantly elevated at 945 mg/24h, but not nephrotic range. Hepatitis, HIV, and rheumatic disease workup was negative. The patient was started on dapagliflozin for renal protection. At his follow-up visit, a genetic panel showed two very rare heterozygous mutations to the CUBN gene. He was diagnosed with chronic benign proteinuria. Given the low risk for progression to CKD, dapagliflozin and lisinopril were discontinued with plans for one-year follow up.

Discussion: CUBN gene mutations that cause chronic benign proteinuria have been shown to be nondetrimental to kidney function with limited progression to CKD. This case shows the benefit of early genetic testing in cases with isolated, non-nephrotic range proteinuria with normal kidney function through early diagnosis and avoidance of unnecessary treatments or invasive tests such as biopsies. While unlikely, these patients should be followed routinely to screen for worsening renal function.

TH-PO524

Sex Differences in Primary Distal Renal Tubular Acidosis

Viola D'Ambrosio,[1,2] Keith Siew,[2] Rhys Evans,[2] Pietro Manuel Ferraro,[3] Stephen B. Walsh.[2] London Tubular Center. *[1]Universita Cattolica del Sacro Cuore, Rome, Italy; [2]University College London, London, United Kingdom; [3]Universita degli Studi di Verona, Verona, Italy*.

Background: The kidney is one of the most estrogen-responsive organs and an influence of estrogens has been described for several transporters along the renal tubule. Primary distal renal tubular acidosis (dRTA) are rare genetic conditions characterized by impaired urinary acidification in the collecting duct. Our study aimed to investigate phenotypic sex differences in the natural history of primary dRTA.

Methods: We studied 31 genetically confirmed dRTA patients followed at the London Tubular Centre. We undertook a retrospective analysis of prospectively collected clinical, biochemical and radiological data. We used low bone mineral density (BMD) (defined as a Z-score ≤ -2) to assess the severity of osteomalacia.

Results: Baseline characteristics and prevalence of causative mutations are shown in Figure 1. Most patients regardless of sex presented with overt hypercalciuria (60% of women vs 90% of men) but prevalence of nephrolithiasis and nephrocalcinosis was higher in women. Men had a significantly (p value=0.0138) higher decline in annual mean slope of eGFR (-3.3 ± 2.5 mL/min/1.73 m^2) compared to women (-0.5 ± 1.5 mL/min/1.73 m^2) (**Figure 2a**). There was a trend towards higher fractional excretion of phosphate (**Figure2b**) and dyslipidemia in men (**Figure 2c**). Prevalence of low BMD was higher in men (50%) vs women (17%) with low BMD predominantly affecting the lumbar spine.

Conclusions: Men affected by primary dRTA are at increased risk of CKD progression and appear to be more dyslipidemic than women. To our knowledge, this is the first study reporting sex differences in primary dRTA.

	Women n= 19	Men n= 12
Age years	37 ± 17	35 ± 14
Gene		
ATP6V1B1	1 (5)	2 (17)
ATP6V0A4	2 (10)	1 (8)
SLC4A1	13 (70)	7 (58)
FOXi1	1 (5)	0
not available	2 (10)	2 (17)
Nephrolithiasis	16 (89)	7 (58)
Nephrocalcinosis	15 (83)	7 (58)

Figure 1. Baseline characteristics of the study cohort. Continuous variables are reported as medians and interquartile ranges (in brackets) and categorical variables as frequencies and percentages (in brackets).

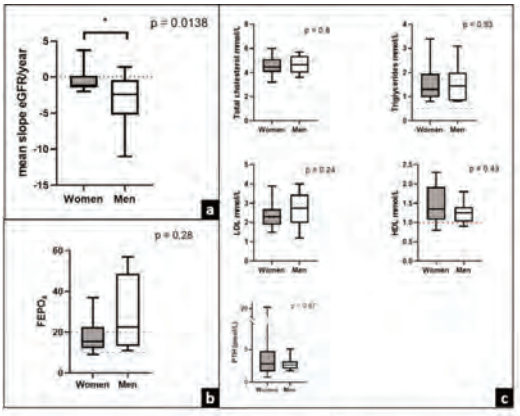


Figure 2. Comparison of annual mean slope of eGFR (a), $FePO_4$ (b) and metabolic parameters (c) between women and men. Grey dotted lines represent upper and lower limit of the clinical normal range. Red dotted line represents the upper clinical threshold.

TH-PO525

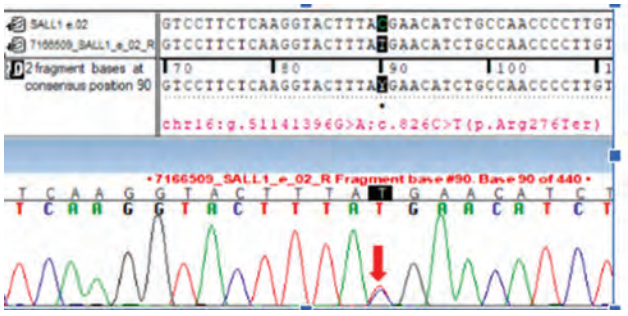
Towne Brocks Syndrome Presenting as ESKD

Aswini P. Patnaik, Nikunj Kishore Rout, Scienthia Sanjeevani, Ashim K. Mahali. *Kalinga Institute of Medical Sciences, Bhubaneswar, India*.

Introduction: Townes Brocks Syndrome (TBS) is rare autosomal dominant disorder with multiple organ involvement with mutation of SALL1 on chromosome 16q12.1. Cardiac and renal abnormalities have been reported infrequently. We present one case with TBS who presented with end stage renal disease. Mutation analysis showed de novo mutation in the SALL1 gene.

Case Description: Proband, 15 years old female presented with anasarca and decreased appetite. She has history of imperforate anus for which operated on 3rd year of life. No significant history in grandparents, parents, siblings. On examination, growth retardation, ear anomaly (overfolding of superior helix of left ear and pre-auricular tag), thumb anomaly (rudimentary Right thumb), flat foot, toe anomaly, atrial septal defect, bilateral sensorineural hearing loss were present. Investigation showed anemia with raised urea and serum creatinine. USG showed both small sized kidneys. Genetic testing confirmed diagnosis with heterozygous nonsense variation of SALL 1gene. Geneting screening of both parents were normal. She was initiated on hemodialysis for renal dysfunction.

Discussion: Malformations related to TBS are usually diagnosed in the neonatal period and less known by adult specialists. Renal anomalies, including functional and structural abnormalities has been resported in 43% of patients. In this case report, typical extra renal manifestations led us to genetic testing and confirming diagnosis of TBS, but uremia was the first symptom to prompt the proband to visit the hospital.



Sanger sequencing

TH-PO526

Patient Satisfaction and Outcomes following a Session with a Genetic Counselor for Kidney Diseases

Megan M. Hager,[1] Quinn P. Stein,[1] Emily Hendricks,[1] Tessa R. Pitman,[1] Mary E. Conway,[1] Cassie Vance,[1] Kelsey Mcqueen,[2] Margaret Westemeyer.[1]
[1]Natera Inc., Austin, TX; [2]PKU foundation, New York, NY.

Background: Limited data exist on patient satisfaction with genetic counseling for kidney disease provided by laboratory genetic counselors (LGCs). Here, we provide survey results designed to examine patient experiences following a Genetic Information Session (GIS) for kidney disease. The survey aimed to understand patient satisfaction and subsequent actions following a GIS. The survey also explored the role of LGCs in improving genetic counseling accessibility to patients, aligning with nephrologists' interest in helping their patients gain access to LGC services to better understand the genetic testing result in the context of their care.

Methods: A 47-question survey was developed based on prior studies and sent to patients via email following a GIS conducted by telephone to review genetic results from the RenasightTM test (a multigene hereditary kidney panel) (Natera, Austin, TX). The collected responses were anonymous and analyzed using simple statistics.

Results: Of 1,667 GIS completed over a 1-year period, 201 responses were recorded. Overall, 95.3% of respondents indicated the GIS was valuable to them. Most respondents (64.7%) felt they had actionable steps to take following the GIS, which included: meeting with a specialist for management of extrarenal problems related to the genetic diagnosis, family planning, seeing a local genetics provider, or sharing results with relatives. Additionally, 78.9% of respondents felt they had the information needed to take additional steps related to their healthcare or family's health following the GIS. 32.9% of respondents indicated they were unable to see a local GC and 52.0% were uncertain if it would be possible to do so.

Conclusions: This is the first study to examine patient satisfaction and outcomes following a GIS for kidney genetics, or to examine LGC service implementation in this context. This study demonstrated that LGCs provided patients with increased access to genetic counseling, valuable information that helped patients and their families navigate their clinical journeys, and acted as a complementary resource/link to providers ordering kidney genetic testing.

TH-PO527

Nephrologists' Views and Experience with Genetic Testing: Developing vs. Developed Countries

Jaison George,[1] Tushar J. Vachharajani,[3] Xiangling Wang.[2] *[1]Kauvery Hospitals, Bangalore, India; [2]Cleveland Clinic, Cleveland, OH; [3]John D. Dingell VA Medical Center & Wayne State University School of Medicine, Detroit, MI.*

Background: Genetic testing has increasingly been utilized in nephrology practice in developed countries, with limited data available on the perspectives of nephrologists from developing countries.

Methods: An online survey was conducted via SurveyMonkey and distributed to practicing nephrologists worldwide through social media, emails, or phone messages.

Results: A total of 297 nephrologists from 28 countries completed the survey, including 230 from developing countries and 67 from developed countries. The majority of respondents from both developing and developed countries reported having ordered genetic testing in their practice (80% vs. 85%, p=0.31). Of those who had ordered genetic testing, 80% from developing countries and 79% from developed countries found it useful (p=0.86). Nephrologists from developing countries expressed more concern about the availability of testing resources compared to colleagues from developed countries (62% vs. 38%, p=0.004). High cost was reported as the leading barrier among nephrologists from both developing and developed countries (64% vs. 61%, p=0.65). Fewer nephrologists from developing countries reported a high level of confidence in interpreting genetic testing results compared to colleagues from developed countries (5% vs. 19%, p=0.00009), while more reported a lack of confidence (47% vs. 22%, p=0.0004).

Conclusions: Renal genetic testing has been considered useful by nephrologists worldwide. There is a pressing need to enhance the availability of testing resources and education in renal genetics, particularly in developing countries. We acknowledge the potential bias of this study, as respondents may have primarily been those interested in genetic testing.

Table 1

Gender Distribution	N (Percentage)
Male	211 (71.04%)
Female	84 (28.28%)
Prefer not to say	2 (0.67%)
Affliation	
Teaching private hospital/medical college	135 (45.45%)
Non teaching private hospital	92 (30.98%)
Government Medical college	60 (20.20%)
Government non teaching institution	10 (3.37%)
Years of practice	N (Percentage)
1-5 years	112 (37.71%)
6-10 years	55 (18.52%)
10-20 years	71 (23.91%)
>20 years	59 (19.87%)
Population catered to	N (Percentage)
Adult patients	210 (70.71%)
Pediatric patients	10 (3.37%)
Both	77 (25.93%)
Area of practice	N (Percentage)
City	254(85.52%)
Town	431(4.48%)
Village	0.00%

TH-PO528

Value of Genetic Testing in a Glomerular Disease Center

Josep Miquel Blasco Pelicano,[1,2] Jordan G. Nestor,[1] Natalie Vena,[1] Kelsie Bogyo,[1] Simone Sanna-Cherchi,[1] Krzysztof Kiryluk,[1] Mariela Navarro Torres,[1] Benjamin Wooden,[1] Andrew S. Bomback,[1] Gerald B. Appel,[1] Jai Radhakrishnan,[1] Pietro A. Canetta.[1] *[1]Columbia University, New York, NY; [2]Hospital Clinic de Barcelona, Barcelona, Spain.*

Background: Integrating genomics into clinical practice is essential for offering high-quality personalized medicine at glomerular disease centers.

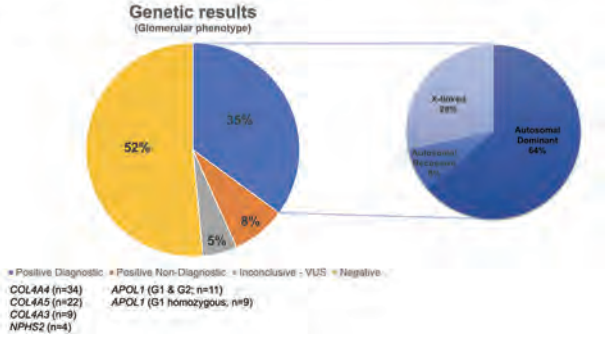
Methods: This observational, retrospective study evaluated the clinical usefulness of genetic studies at Columbia University's Glomerular Kidney Disease Center. Over 40 months (7/2020–11/2023), 231 patients with glomerular phenotypes were referred for genetic evaluation. After a multidisciplinary visit by a genetic counselor and a specialized nephrologist, genetic tests were selected individually based on clinical suspicion.

Results: Of the 231 patients, 142 had a biopsy-confirmed glomerular disease, while 89 had a suspected glomerular disease, who never were biopsied. The average age was 43.5 years±16.8, with 54% female and 37% self-reported as white. Main clinical suspicions were collagenopathies (47%), hereditary focal segmental glomerulosclerosis (25%) and complement dysregulation (8%). The most common genetic tests ordered (71%) were large, multi-gene (100+), next generation sequencing panels. Genetic testing results were positive diagnostic (pathogenic or likely pathogenic variants) in 34% (n=79) and positive non-diagnostic (*APOL1* risk alleles) in 9% (n=20) (Figure 1). Among diagnostic results, the most frequent genes were collagen-related (*COL4A3-5*) with 76%, followed by complement genes (*CFH*, *CFI*, *MCP*) and *NPHS1* & *2* (both 4%). Top benefits and clinical implications included prognostic information (47%), therapeutic guidance (42%), familial testing (42%), establishing a genetic diagnosis (34%) and sub-specialty referral (32%).

Conclusions: Multi-disciplinary care integrating genetic evaluation of a glomerular disease referral population provided important benefits for the patients and their families. It is recommended to integrate this approach more broadly, moving forward to a precision medicine in glomerular disease.

Funding: Government Support - Non-U.S.

Figure 1: Genetic Study Results, Inheritance Patterns, and Most Frequent Genes in Glomerular Phenotype Patients (n=231).



TH-PO529

Genome-Wide Survival Study Identifies Variants Associated with Disease Progression in IgA Nephropathy

Xu Linlin, Xu-jie Zhou, Jicheng Lv, Hong Zhang. Professor Zhang's Research Group. *Peking University First Hospital Department of Nephrology Renal Division, Beijing, China.*

Background: IgA nephropathy (IgAN) has a poor prognosis and recent data suggested that almost all of patients may progress to kidney failure within their lifetime. Genetic variations intricately shape disease risks. However, genetic markers associated with the progression of IgA nephropathy have been quite limited.

Methods: We performed genome-wide survival analyses in two independent cohorts and meta-analysis, the PKU-IgAN follow-up cohort containing 1859 IgAN patients and the TESTING cohort containing 279 patients from China. The primary outcome was end-stage kidney disease (ESKD), and the secondary outcome was the combination of ESKD or ≥40% reduction in estimated glomerular filtration rate (eGFR) after diagnostic kidney biopsy. Genome-wide survival analyses were performed on the two cohorts separately, and variants were selected as candidate variants when they had $P < 1\times10^{-5}$ in one cohort and $P < 0.05$ in the other. Functional annotations of candidate variants, expression quantitative trait loci (eQTL) studies, exploration of epigenetic architecture, differential expression of the candidate genes, and the association between genotype and clinical characteristics were conducted.

Results: For the primary outcome, a variant of *SFMBT2* achieved genome-wide significance in the meta-analysis (HR 3.01, $P = 8.24\times10^{-9}$). Two loci, *SLC8A1* (HR 1.90, $P = 2.06\times10^{-7}$) and *MIR548B* (HR 3.19, $P = 5.04\times10^{-7}$) were considered as the candidate loci. For the secondary outcome, three loci, *ESRRG* (HR 3.68, $P = 7.26\times10^{-8}$), *FAM19A5* (HR 1.76, $P = 4.43\times10^{-7}$), and *LINC00583* (HR 3.43, $P = 6.07\times10^{-7}$) were considered as the candidate loci. *SLC8A1*, *SFMBT2*, and *FAM19A5* variants were also associated with the eGFR slope and time-average proteinuria. In addition, the risk allele of *FAM19A5* was associated with the glomerular sclerosis ($P = 4\times10^{-3}$) and the tubulointerstitial damage ($P = 0.03$).

Conclusions: Six candidate loci were significantly associated with prognosis of IgAN. These findings may help characterize molecular mechanisms of progression of IgAN, contributing to the identification of patients at high risk of progression and the development of new therapeutic targets to slow disease progression.

TH-PO530

Immune Checkpoint Molecule B and T Lymphocyte Attenuator and Induces Anti-inflammatory Dendritic Cells in Experimental GN

Bastian Trinsch,[1,2] Paul Diefenhardt,[1,2] Jasper F. Nies,[1,2] Claudio Sierra Gonzalez,[1,2] Manuel Koch,[2] Paul T. Brinkkoetter,[1,2] Bernhard Schermer,[1] Thomas Benzing,[1,2] Sebastian Braehler.[1,2] *[1]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany; [2]University of Cologne Center for Molecular Medicine Cologne, Cologne, Germany.*

Background: T cell-mediated inflammation can lead to crescentic glomerulonephritis (GN). T cell receptor signaling requires secondary signals (immune checkpoints) for T cell activation and differentiation. Interference with this signaling might represent a treatment option for GN. In a recent study, we have shown that the immune checkpoint molecule B and T Lymphocyte Attenuator (BTLA) attenuates inflammation in experimental GN. The complex signaling networks involving different immune cell subsets and the binding partner Herpesvirus entry mediator (HVEM), however, remained unclear.

Methods: Nephrotoxic nephritis (NTN) was induced in mice with a cell-specific knock out of BTLA on T cells or dendritic cells. For treatment studies, HVEM coupled to a human Fc-tag (HVEM-Fc) was produced and administered i.v. in wild-type (wt) mice after NTN induction. Readouts included albuminuria and BUN concentration and histological damage on PAS-stained tissue. Immunophenotyping of kidney tissue and renal lymph nodes was performed using IHC, IF, and flow cytometry. A scRNA-sequencing of renal immune cells was performed in wt and BTLA knock out mice with and without induction of NTN.

Results: Compared to wt, BTLA deficiency on dendritic cells led to a reduction of protective cDC1 in kidney tissue and increased numbers of pro-inflammatory T effector cells. The T cell-specific knock out of BTLA, however, led to a decrease of T regulatory cells (Treg) and to infiltration of monocytes and neutrophils. Both mouse lines showed a dysregulation of T cell polarization in renal lymph nodes. Administration of HVEM-Fc reversed this T cell composition and resulted in increasing numbers of renal cDC1 as well as a decreasing number of renal B cells. ScRNA sequencing confirmed overactivation of T cell subsets and altered survival-associated signaling in cDC1.

Conclusions: The necessity of BTLA for the suppression of T effector cells by Tregs is well-established. Our research now reveals the central importance of BTLA in the immunosuppressive function of cDC1 in glomerulonephritis. The potential of HVEM-Fc, functioning as a BTLA agonist and decoy molecule to inhibit inflammatory LIGHT-signaling, opens up exciting possibilities for future treatment strategies in renal inflammatory diseases.

Funding: Government Support - Non-U.S.

TH-PO531

Effects of Multilocus Interaction on IgA Nephropathy in the Chinese Han Population

Dianchun Shi,[1] Wu Yuanyuan,[1] Xueqing Yu,[1,2] Li Ming.[1] *[1]Guangdong Provincial People's Hospital, Guangzhou, China; [2]The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Previous genome-wide association studies (GWAS) have identified multiple susceptibility genes for IgAN, including TNFSF13, ITGAX-ITGAM, FCRL3, ST6GAL1 and CARD9. Gene-gene interaction might have more influence on the susceptibility of IgAN and advance our understanding of the genetic pathogenesis of IgAN. This study aims to investigate the correlation between the gene-gene interaction and IgAN susceptibility.

Methods: A total of 63 single-nucleotide polymorphisms (SNPs) were selected for genotyping by using MassARRAY platform in 1,000 IgAN cases and 1,000 healthy controls. Data quality control and filtering were conducted using PLINK 1.90, and the frequency distribution of genotypes and alleles were calculated. Multifactor dimensionality reduction (GMDR) method was used to analyze the multi-step gene-gene interactions.

Results: The GMDR analysis revealed that the interaction of TNFSF13 (rs4968210), FCRL3 (rs11264793), and ST6GAL1 (rs2284750, rs7634389) was significantly associated with the risk of IgAN (*P*=0.01, *OR*=2.88). In addition, the genotype–phenotype association analysis showed that the interaction of TNFSF13 (rs3803800), FCRL3 (rs11264793, rs7528684), ITGAX (rs11150619) and ST6GAL1 (rs6784233, rs7634389) was associated with eGFR in IgAN patients (*P*=0.01, *OR*=14.03). The TNFSF13 (rs3803800), FCRL3 (rs11264793, rs7528684), ITGAX (rs11150614), and ST6GAL1 (rs7634389) had combined effects on the low density lipoprotein in IgAN patients (*P*=0.01, *OR*=4.81). Furthermore, the interaction of TNFSF13 (rs3803800), FCRL3 (rs11264793, rs7528684), ITGAX (rs7190997) and ST6GAL1 (rs6784233, rs7634389) was also associated with hematuria in IgAN patients (*P*=0.001, *OR*=29.66).

Conclusions: The study suggested that the interaction of ITGAX-ITGAM, TNFSF13, FCRL3 and ST6GAL1 genes might have some influence on the susceptibility to IgAN. Additionally, it may also correlate with the lipid levels, hematuria, and the progression of renal function in patients.

TH-PO532

Dissecting Deregulated Multicellular Programs in IgA Nephropathy

Charlotte M. Boys,[1] Phillip J. McCown,[3] Sean Eddy,[3] Matthias Kretzler,[3] Julio Saez-Rodriguez.[2,1] NEPTUNE Consortium. *[1]UniversitatsKlinikum Heidelberg, Heidelberg, Germany; [2]European Bioinformatics Institute, Cambridge, United Kingdom; [3]University of Michigan Michigan Medicine, Ann Arbor, MI.*

Background: Our understanding of IgA nephropathy pathogenesis is rich, but incomplete. Emerging single-cell data offers the opportunity for improving our understanding of the disease. The Omnibus of CElls And Nuclei (OCEAN) comprises single nucleus data from 11 living donors from the Michigan Human Kidney Transplant Transcriptomic Atlas study and 120 FSGS, MCD, IgAN, and other kidney disease patients from the NEPTUNE consortium. We present the results from an unsupervised exploratory analysis of this dataset with the aim of studying transcriptomic alterations in primary proteinuric glomerular diseases, with a focus on IgA nephropathy.

Methods: Pseudobulk profiles were generated from OCEAN 10x single nucleus data for each cell type and sample. Candidate ligand-receptor interactions were computed using LIANA+. Exploratory data analysis was performed on the resulting pseudobulk profiles and ligand-receptor features using the multicellular factor analysis framework, resulting in unsupervised "factors" which describe the transcriptomic heterogeneity across all samples including living donors. Factors were associated post-hoc with clinical metadata and cell type compositional information by ANOVA. Further analysis focused on factors best explaining patient heterogeneity in (but necessarily not exclusive to) IgAN.

Results: Our computational analysis disentangles transcriptomic alterations in the tubular compartment associated with GFR loss (p val < 1e-10) and patients age (p val < 1e-8) from other more specific pathological changes. We identify further patterns of transcriptomic dysregulation and cell-cell communication which account for heterogeneity among IgAN patient samples, including a factor associated with parietal epithelial cell expansion and loss of podocytes, accompanied by downregulation of SLIT-ROBO signalling, which was also observed in FSGS.

Conclusions: Analysis of NEPTUNE OCEAN single nucleus data not only provides a description of patient heterogeneity in IgAN and reveals pathogenic alterations in the IgAN transcriptome but, crucially, places these in the wider context of nephrotic syndrome and glomerular disease.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO533

An Omnibus of Transcripts Integrated from More than One Million Nuclei and Cells of Patients with Kidney Diseases Provides Distinct Insights into Disease Mechanisms

Phillip J. McCown,[1] Edgar A. Otto,[1] Damian Fermin,[1] John R. Hartman,[1] Mathew O. Alaba,[1] Maria Larkina,[1] Michael Arbit,[1] Margaret Helmuth,[1] Brad A. Godfrey,[1] Sean Eddy,[1] Laura H. Mariani,[1] Abhijit S. Naik,[1] Maarten Hoek,[2] Terry Satterfield,[2] Matthias Kretzler.[1] NEPTUNE Consortium. *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]Maze Therapeutics Inc, South San Francisco, CA.*

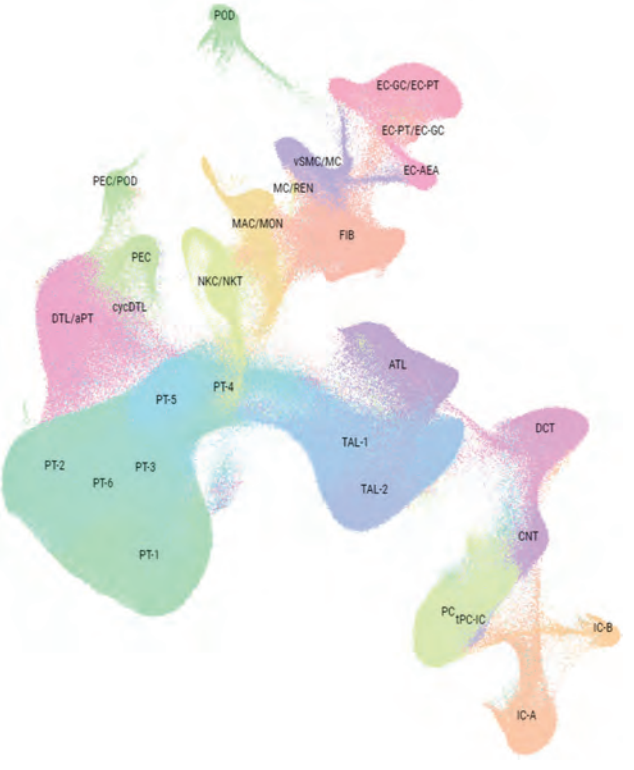
Background: Single nuclear RNA sequencing (snRNAseq) of biopsies affords insight to molecular and cellular pathways in kidneys. In the NEPTUNE consortium, biopsy samples of participants with nephrotic syndrome (NS) have been curated for snRNAseq. While small studies have provided insights using subsets of samples, an omnibus of transcriptional data from numerous samples may aid further discovery and research.

Methods: snRNAseq (n=11) and single cell RNA sequencing (n=47) from kidney biopsies from healthy living donors and transplant recipients in the Michigan HKTTA study were integrated with snRNAseq of 120 biopsies from patients with FSGS, MCD, IgAN, and other kidney diseases enrolled in the NEPTUNE Consortium to identify clusters of cells. Whole genome sequencing data from blood samples of 90 NEPTUNE participants were used to assess APOL1 genotype.

Results: Nuclei and cells (n=1,047,781) resolved into 28 clusters of kidney resident and non-resident cell types, including a novel cluster of transitioning parietal epithelial cells. APOL1 risk alleles were present in 90 participants. Among kidney cell types, we observed the strongest correlation between APOL1 mRNA levels and JAK-STAT activity in podocytes in participants with FSGS with at least one copy of the G1 APOL1 risk allele.

Conclusions: This Omnibus of CElls And Nuclei (OCEAN) from NEPTUNE participants with NS and IgAN is a large set of molecular and clinical data that allows unique analyses that can provide novel insights into mechanisms of kidney diseases

Funding: NIDDK Support, Commercial Support - Maze Therapeutics



A UMAP of over 1 million nuclei and cells in OCEAN

TH-PO534

Analysis of Peripheral Blood Mononuclear Cells Single-Cell RNA Sequencing Shows IFN Signaling Activation Contributes to the Pathogenesis of Childhood Nephrotic Syndrome

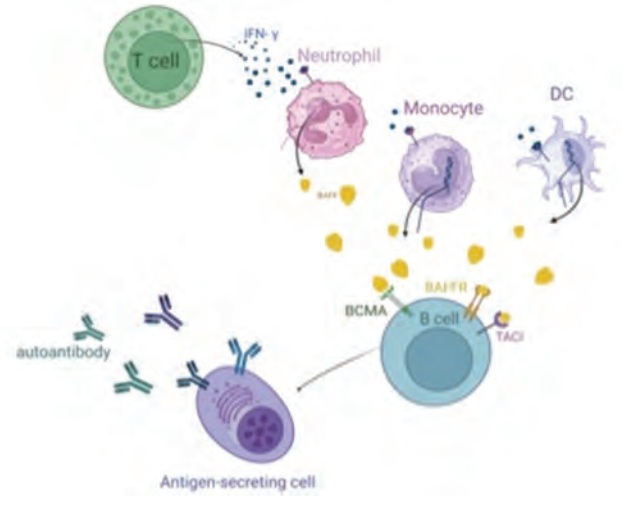
Qiu-yu Li, Fei Liu, Minchao Kang, Linnan Bai, Junnan Wu, Jianhua Mao.
Zhejiang University School of Medicine Children's Hospital, Hangzhou, China.

Background: Idiopathic Nephrotic syndrome (INS) is a prevalent glomerular disease, especially in children. Previous understanding of INS pathogenesis has emphasized T-cell changes and their correlation with cytokine shifts. Accumulating evidence indicates that B-cell dysfunction is also involved in the process. Nevertheless, a gap remains in the comprehensive understanding of the mechanisms and cellular interactions among immune cells in new-onset INS.

Methods: Our study employed single-cell RNA sequencing (scRNA-seq) to characterize immuno-dysfunction in peripheral blood mononuclear cells (PBMCs) obtained from five new-onset INS patients before treatment and post-remission, alongside healthy controls. We identified differentially expressed genes and investigated cell-cell communications across different cell types. We also performed validations.

Results: Through differentially expressed gene analysis across clusters, we observed the activation of interferon-stimulated genes (ISGs) and the enrichment of interferon (IFN)-related pathways. Specifically, we noted increased expression of B-cell activating factor (BAFF) in untreated patients, along with elevated expression of BAFF receptors, particularly B-cell maturation antigen (BCMA) in plasma cells, collaborated by flow cytometry in an independent INS cohort. Furthermore, we identified an increase in the serum level of IFN-γ rather than IFN-α.

Conclusions: Our research provides the first comprehensive exploration of IFN-related pathways in the initiation of INS. These results suggest that IFN-γ activation stimulates the interaction between BAFF and B-cell receptors, triggering autoantibody release and contributing to INS pathogenesis. New insights into the pathogenesis of NS may pave the way for precise therapeutic interventions that target these pathways.



TH-PO535

Single Nucleus Transcriptomic Landscape of Human Glomerular Diseases

Jeong Ho Joo,[1] Sehoon Park,[2] Jeong Seok Lee,[1] Dong Ki Kim.[2]
[1]Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea; [2]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.

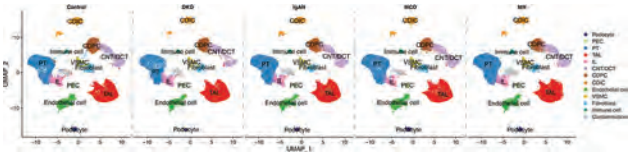
Background: Glomerular diseases, often progress to end-stage kidney disease, with each type following a distinct clinical course despite common features. Single-nucleus RNA-seq (SnRNA seq) enabled researchers to capture the gene expression of rare glomerular cells. In this study, we examined the transcriptomic differences among glomerular diseases in glomerular cells.

Methods: We collected snap-frozen kidney biopsy tissues from 6 cases of IgA nephropathy (IgAN), 6 cases of minimal change disease (MCD), 6 cases of PLA2R-Ab positive membranous nephropathy (MN), 3 cases of diabetic kidney disease (DKD), and 7 cases of adjacent normal tissue in renal cell carcinoma. We conducted snRNA seq using kidney tissue, comparing proportions and differentially expressed genes (DEGs) among various diseases. We also subdivided detailed clusters within each cell type and compared specific cell types with the patients' clinical data to assess correlations.

Results: A total of 262,984 nuclei were obtained from 28 subjects with MCD, MN, IgAN, DKD, as well as the control, and UMAP was drawn. Thirteen clusters were identified including glomerular cells. When k-means clustering was performed on DEGs between each condition within each cell types, upregulated DEGs display patterns common to cell types and specific to diseases, whereas downregulated DEGs exhibit patterns specific to cell types and common across various cell types. After subclustering, we identified podocyte with endocytosis feature associated with proteinuria. The module score of marker genes of this cell type significantly increased with higher levels of proteinuria in patients. The proportion of myofibroblasts were increased in glomerular diseases, compared to control group significantly. Additionally, we found that gene expression of myofibroblast was directly associated with kidney function of glomerular diseases.

Conclusions: To our knowledge, our snRNA-Seq data is the largest datasets of biopsy-confirmed human glomerular disease to date. Our results provided novel insights regarding the kidney indwelling cell-specific or disease- specific transcriptomic alterations. The data serve as valuable asset for future investigations into the development of biomarkers or therapeutic targets for glomerular diseases.

Funding: Government Support - Non-U.S.



TH-PO536

Single-Cell RNA Sequencing Shows How AP-1 Upregulation Affects Different Kidney Cells in the Chronic Progression of Glomerular Diseases

Shuying Li,[1,2] Qilin Chen,[1,2] Li Qiu.[1,2] *[1]Department of Nephrology, Children's Hospital of Chongqing Medical University, Chongqing, China; [2]National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Pediatric Metabolism and Inflammatory Disease, Chongqing, China.*

Background: Podocytopathies, resulting from podocyte injury, can lead to proteinuria and often progresses to end-stage renal disease, significantly impacting patient prognosis. Current studies have found that podocyte injury triggers parietal epithelial cell (PEC) activation, proliferation, migration to the capillary tuft, and acquisition of a podocyte phenotype. This process ultimately leads to global glomerulosclerosis and loss of renal function. However, the molecular mechanism underlying this critical process remains unclear.

Methods: We have established a cellular atlas of human glomeruli and kidney tissue from patients with glomerular disease, including 10 pediatric cases and 3 control children using scRNA-seq. Additionally, we conducted in vivo experiments with the AP-1 inhibitor T-5224 in an ADR mouse model.

Results: By rapidly enriching human glomeruli, we constructed a human glomerular cell atlas and identified podocytes with high expression of *NPHS2* and *PLA2R1*. We discovered a group of podocytes expressing AP-1-related genes (*JUNB*, *JUN*, *FOS*, and *FOSB*), designated as AP-1^{high} podocytes. Their existence was confirmed through immunofluorescence and immunohistochemistry. RNA velocity analysis revealed that AP-1^{high} had differentiation potential. Similarly, AP-1^{high} podocytes were also found in the mouse glomerular cell atlas and validated. Reclustering analysis of renal tissue cell atlas from patients with glomerular diseases revealed a group of AP-1^{high} PECs expressing *CCL2* and *ICAM1*. Remarkably, RNA velocity analysis indicated a tendency for AP-1^{high} PECs transform into AP-1^{high} podocytes. Increased expression of AP-1 was observed in connecting tubules, and endothelial cell subsets exhibiting signatures of inflammatory activation linked to chronic kidney disease progression. The critical role of AP-1 was confirmed by treatment with the AP-1 inhibitor T-5224 in mouse model of ADR-induced nephropathy resulting in significant improvement in proteinuria.

Conclusions: Parietal epithelial cells in glomerular diseases are activated and proliferate due to the up-regulation of AP-1, leading to their migration and differentiation into podocytes. The induction and activation of AP-1-related molecules across various cell subsets likely significantly contribute to chronic kidney injury progression and inflammatory activation.

TH-PO537

Kidney Tissue Single-Nucleus Multiomics Analysis of ANCA-Associated Glomerulonephritis Reveals Key Transcriptional Regulation Networks

Shuo Zhang,[1] Lubin Xu,[1] Zheng Huang,[2] Saifu Yin,[3,4] Yun Li,[2] Yanjie Chen,[2] Xini Meng,[2] Ying Wang,[1] Jiaying Li,[1] Yubing Wen,[1] Xixi Zheng,[1] Turun Song,[3,4] Tao Lin,[3,4] Lan Jiang,[2] Limeng Chen.[1] *[1]Department of Nephrology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China; [2]Beijing Institute of Genomics, Chinese Academy of Sciences and China National Center for Bioinformation, Beijing, China; [3]Department of Urology/Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; [4]Kidney Transplantation Center, West China Hospital, Sichuan University, Chengdu, China.*

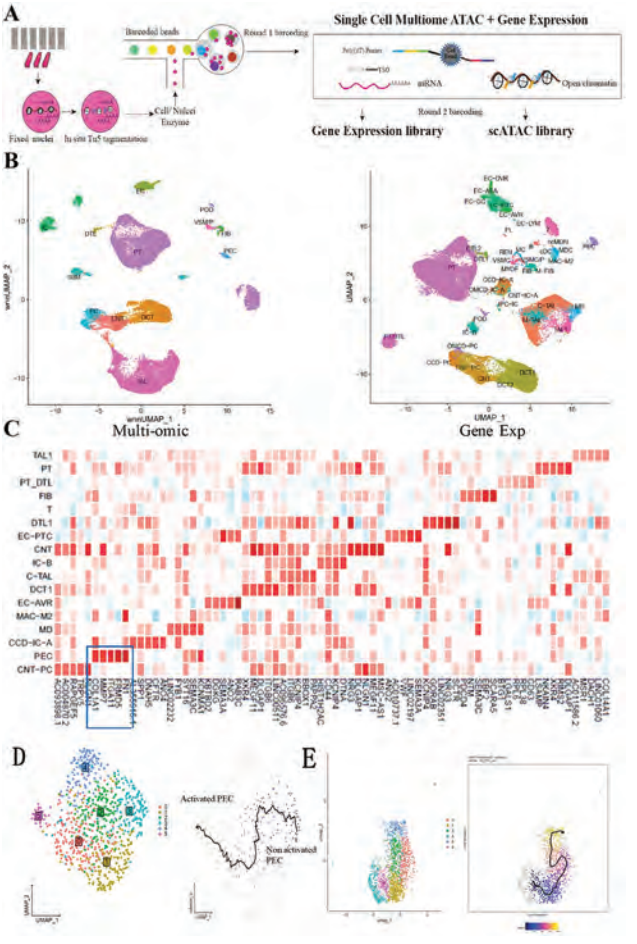
Background: We aimed to use single-cell nuclear RNA and chromatin accessibility (ATAC) sequencing on renal biopsy specimens from ANCA-associated glomerulonephritis (AAGN) patients to identify crucial pathways for further mechanistic studies

Methods: We studied five AAGN patients, ten healthy donors, and seven paraneoplastic renal tissues. SnRNA-Seq and snATAC-Seq performed with Universal Droplet-Based Single-Cell Combinational Indexed Sequencing technique. We used the Weighted Nearest Neighbor method for co-dimensional reduction of the multi-omics data, clustering, and cell type annotation via Seurat's Label Transfer method to identify differentially expressed genes and ATAC

Results: The patient group had an average age of 64±6 years, and the clinical manifestations were glomerulonephritis with acute kidney injury and the pathological manifestations of small-vessel vasculitis with crescent formation. Activated parietal epithelial cells (PECs) with high CD44 expression, up-regulated crescent-forming and development potential genes were enriched in AAGN kidneys. SCENIC+ identified E2F3 and BACH1 as core transcription factors (TF) in the regulatory network of activated PECs. Endothelial cell abnormalities were noted in peritubular capillaries (EC-PTCs) with up-regulated genes related to cell junction assembly and angiogenesis. SMAD1 and BACH1 were identified as key TFs of EC-PTC injury. AAGN patients had increased intercellular communication

Conclusions: Our study applied single-cell multi-omics sequencing to AAGN renal biopsies, revealing cell-specific transcriptomes and epigenetic profiles of PECs and EC-PTCs. This work provides insights into new mechanisms and potential therapeutic targets for AAGN

Funding: Government Support - Non-U.S.



TH-PO538

Integrated Multiomics Analyses and Mendelian Randomization Identify the Macrophage-Endothelial Characteristics of Membranous Nephropathy

Yi Ling, Jianzhong Li. *First Affiliated Hospital of Soochow University, Suzhou, China.*

Background: Membranous nephropathy (MN) is recognized as an autoimmune glomerular disease that may progress to severe end-stage renal disease. In recent years, extensive investigations into molecular characteristics of MN have been conducted at bulk-transcriptome level. However, the single-cell transcriptomic and proteomic features of MN remain to be elucidated. Mendelian randomization (MR) serves as a methodology for establishing causal relationships between exposure factors and outcomes, offering robust evidence to bridge the transition from "associated genes" to "causal genes".

Methods: Transcriptome data of MN glomeruli acquired from GEO databases were analyzed and immune infiltration was delineated. Olink proteomics assessed inflammatory proteins in peripheral blood of MN patients in our cohort. Single-cell analyses were conducted to pinpoint subclusters closely linked to the progression of MN. hdWGCNA was utilized to identify co-expression modules correlated with key subclusters. Finally, bidirectional MR was implemented to select module genes exhibiting causal relationship with MN.

Results: MN patients exhibited an increase in monocyte and M1 macrophage infiltration within glomeruli. scRNA-seq uncovered an increased abundance of pro-inflammatory macrophages expressing *VEGFA* and *CXCL8*, alongside inflammatory endothelial cells (IECs) exhibiting a high level of *CCL2* and *CXCL2* in MN patients with massive proteinuria. The communication between pro-inflammatory macrophages and endothelial cells appeared to be dominated by *VEGFA* and *CXCL8*, while IECs demonstrated an autocrine proclivity for *CCL2* and *CXCL2*. Proteomic analysis showed that inflammatory related proteins, such as MCP1 (CCL2) and IL8 were up-regulated in MN. MR revealed a potential causal relationship between *SLC1A5*, and the occurrence of

MN (OR=1.4, *p*=0.02). Drivers of ferroptosis were significantly enriched in endothelial cells with elevated *SLC1A5*, accompanied by higher expression of *CCL2* and *CXCL2*.

Conclusions: This study elucidated the circulatory and tissue inflammation of MN from a multi-omics perspective and identified pivotal macrophage-endothelial phenotypes and their interactions. MR identified genes with a causal relationship to MN in the phenotype-associated modules, potentially impacted the onset and progression of MN through modulation of endothelial phenotypes.

Funding: Government Support - Non-U.S.

TH-PO539

Single-Nucleus RNA Sequencing (SnRNA-seq) of Biopsy-Confirmed IgA Nephropathy Reveals Cell-Specific Transcriptomic Alteration

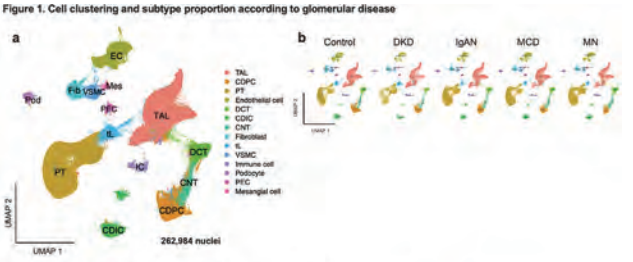
Jeongmin Cho,[1,2] Sehoon Park,[3] Jung Hun Koh,[1] Yaerim Kim,[4] Dong Ki Kim.[3,1]
[1]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [2]Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Gyeonggi-do, Republic of Korea; [3]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [4]Keimyung University School of Medicine, Daegu, Republic of Korea.

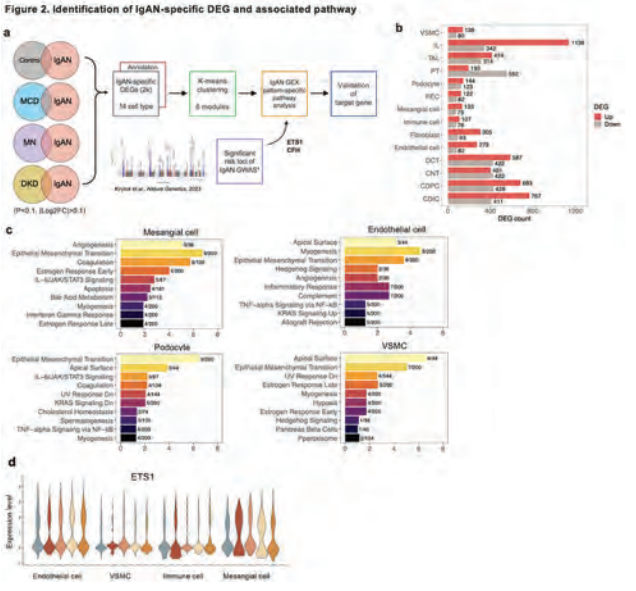
Background: SnRNA-seq is a valuable method for identifying cell-specific transcriptomic alterations in kidney cells. Our objective was to investigate SnRNA-seq data from biopsy-confirmed IgA nephropathy (IgAN) cases and identify cell-specific alterations in the transcriptome.

Methods: We collected snap-frozen kidney biopsy tissues from 6 cases of IgAN and 7 nephrectomy control cases. The disease control group included 3 cases of diabetic kidney disease, 6 cases of minimal change disease, and 6 PLA2R-Ab positive membranous nephropathy cases. SnRNA-seq was performed on the kidney tissues, and kidney cells were identified through UMAP clustering. We investigated differences in the proportion of kidney cell types and identified differentially expressed genes (DEGs). Additionally, we searched for representative gene loci previously reported in a multiethnic genome-wide association study (GWAS).

Results: We identified transcriptomic profiles of > 50,000 cells from IgAN, with a considerable enrichment of intraglomerular cells. The DEG analysis revealed a high number of DEGs in mesangial cells, fibroblasts, and vascular smooth muscle cells in the IgAN transcriptome compared to the nephrectomy and disease control cases. In the gene set enrichment analysis, the epithelial-mesenchymal transition pathway was enriched in the glomerular cells of IgAN. Among various GWAS loci, ETS1 was the gene significantly highly expressed in the mesangial cells of IgAN, consistent across the compared control groups.

Conclusions: This investigation represents the largest SnRNA-Seq profiling of IgAN kidney cells to date. Notable cell-specific pathways in IgAN were identified. ETS1 may be a kidney-indwelling causal factor for IgAN pathophysiology, considering its significance in both previous GWAS and the current SnRNA-Seq data.





TH-PO540

Identification of Cellular Determinants Impacting Mesangial Cells in IgA Nephropathy

Ranjit S. Atwal, Susan E. Quaggin, Hasan H. Munshi, Shana O. Kelley.
Northwestern University, Evanston, IL.

Background: IgA nephropathy is a prevalent glomerulonephritis that frequently develop into end-stage renal disease, impacting over a million patients worldwide. Presently there is no disease-specific therapy, necessitating the development of targeted therapeutic intervention strategies and approaches for early diagnosis. One of the characteristic hallmarks of the disease is the predominant autoimmune complex deposition in the glomerular mesangium. However, the genetic regulators of the preferential accumulation of these IgAN immune complexes on the mesangial cells are not defined.

Methods: Using our magnetic ranking cytometry platform (termed LEAPFROG for large scale phenotypic functional genomics), together with the versatility of genome-scale CRISPR/Cas9 pooled screening across primary mesangial cells and other non-impacted/non-mesangial kidney cell types in parallel, we will identify the cellular surface component(s) driving the predominant accumulation of autoimmune complexes on the mesangial cells. Using our pooled surfaceome libraries, we will systematically profile the impact of individual surface proteins on the sensitivity of galactose-deficient IgA induced IgAN complex deposition. To enrich subpopulation of mesangial cells with either high or low levels of IgAN complex deposit phenotypes, we can functionalize the commercially available monoclonal anti-Gd-IgA1 antibody or the *in vitro* purified IgAN complexes to be useable on our platform. The systematic comparison of next-generation sequencing based guide RNA enrichment of regulators of IgAN complex deposition accumulation on mesangial cells versus the non-mesangial cells is anticipated to enable identification of cellular components regulating the IgAN complex induced proliferation and activation of mesangial cells.

Results: We have completed the lentiviral CRISPR guide RNA library targeting the cellsurfacome. It encompasses 3000 unique surface proteins, with 12,450 unique guides in total. Gererated cosmc knock out DAKIKI cell line for production of galactose-deficient IgA. These reagents, together with the KM55 antibody are being used for phenotypic screening of primary mesangial cells to identify genetic determinants impacting IgA nephropathy.

Conclusions: Use of LEAPFROG-powered CRISPR-cas9 based loss-of-fucnction phenotypic screening is anticipated to identify potentially druggable targets for IgAN.

Funding: NIDDK Support

TH-PO541

Investigation of Molecular Insights into the Disease-Specific Pathophysiology of IgA Nephropathy Using Single-Cell RNA Sequencing

Soojin Lee,[1] Gwanghun Kim,[4] Jung Hun Koh,[2] Sehoon Park,[2] Yaerim Kim,[3] Hang-Rae Kim,[4] Dong Ki Kim.[2,4] *[1]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [3]Keimyung University School of Medicine, Daegu, Republic of Korea; [4]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: IgA nephropathy (IgAN) has difficulty in explaining the heterogeneity of its clinical presentation and prognosis as the pathogenesis is not completely elucidated yet. We performed transcriptome profiling of peripheral immune cells of IgAN to explore their role in the pathogenesis of IgAN.

Methods: Peripheral blood mononuclear cells were obtained from 20 IgAN patients and 9 healthy controls. The cells were sorted into B, CD4 T, and CD8 T subsets. Single cell RNA sequencing was performed with NovaSeq6000. The patients were categorized according to the eGFR and proteinuria value. The differentially expressed genes (DEG) were identified. Then, gene ontology analysis was done with ToppGene Suite.

Results: After quality control, 32,742 B cells, 101,637 CD4 T cells, 63,029 CD8 T cells were retained for analysis. Cell clusters were presented in UMAP. (Figure 1) Ninety five genes were commonly upregulated in all subsets of IgAN, including AKT1, JUN and TGFB1. (Figure 2) Compared to control group, severe IgAN group exhibited significant increase in DEG expression; 40, 148, 132 upregulated and 233, 77, 78 downregulated DEGs in B, CD4 T, CD8 T cell subsets, respectively. Downregulated DEGs in B subset were highly enriched in MHC protein complex and antigen binding pathway.

Conclusions: The present transcriptome profiling showed different gene expression profiles according to the severity of IgAN. The study provides new insights into the role of immune cells in understanding the pathogenesis and it may contribute to the investment of the disease specific biomarkers of IgAN.

Funding: Government Support - Non-U.S.

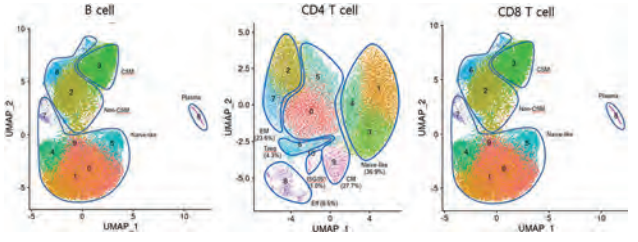


Fig 1. Cell cluster annotation

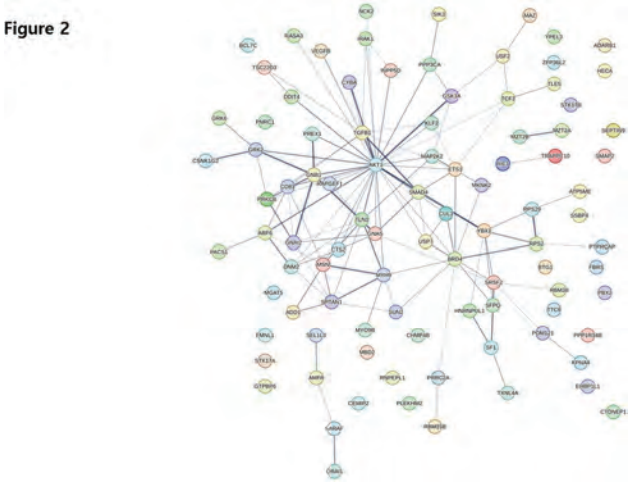


Fig 2. Gene network analysis results

TH-PO542

Unveiling Prognostic Biomarkers in IgA Nephropathy: A Chromatin Accessibility Approach Using Peripheral Immune Cells

Soojin Lee,[1] Gwanghun Kim,[4] Jung Hun Koh,[2] Sehoon Park,[2] Yaerim Kim,[3] Hang-Rae Kim,[4] Dong Ki Kim.[2,4] *[1]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [3]Keimyung University School of Medicine, Daegu, Republic of Korea; [4]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: IgA nephropathy (IgAN), the most prevalent primary glomerulonephritis globally, exhibits heterogeneous clinical presentation and prognosis. The disease's heterogeneity remains enigmatic due to incomplete understanding of pathogenesis. This study employs an epigenetic approach to comprehensively profile peripheral immune cells in IgAN patients, aiming to elucidate their role in disease progression.

Methods: Peripheral blood mononuclear cells were obtained from 57 biopsy-proven IgAN patients and 20 healthy controls and were FACS sorted into B cells, CD4+ T cells, and CD8+ T cells. To explore the role of immune cells in IgAN pathogenesis, we performed Assay for Transposase-Accessible Chromatin (ATAC) Sequencing using NovaSeq 6000. Quality control and normalization process was performed consecutively to identify the differential peaks.

Results: After peak-calling, 65,234 peaks in B cells, 61,007 peaks in CD4+ T cells, and 59,162 peaks in CD8+ T cells, were considered for the differential ATAC-peak selection according to the patient groups. (Figure 1) Differential ATAC-peaks were highest in the CD8+ T cell subset compared to other immune cell populations. Gene ontology analysis showed significant functional differences in CD8+ T cells, when categorized by IgAN progression status. Interestingly, both B and CD4+ T cell subsets displayed significant chromatin accessibility differences, specifically within the ST6GALNAC5 gene locus. (Figure 2)

Conclusions: The present study offers novel insights into the role of immune cells in IgAN pathogenesis. Our findings hold promise for the development of novel, disease-specific biomarkers for improved prognosis assessment in IgAN patients.

Funding: Government Support - Non-U.S.

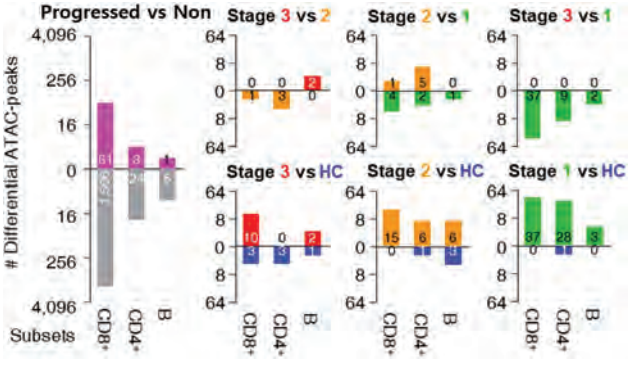


Fig 1. The number of differential peaks.

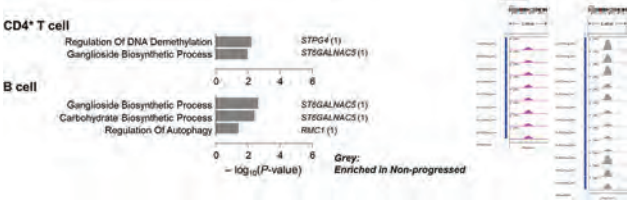


Fig 2. The results of gene ontology analysis

TH-PO543

Multisystem Alterations in the Mesangium of IgA Nephropathy Mice Using Single-Nucleus RNA Sequencing and Single-Nucleus Assay for Transposase-Accessible Chromatin

Soo-Young Yoon,[1] Dae Kyu Kim,[1] Su Woong Jung,[2] Jin Sug Kim,[1] Ju young Moon,[2] Hyeon Seok Hwang,[1] Kyunghwan Jeong.[1] *[1]Kyung Hee University Hospital, Dongdaemun-gu, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea.*

Background: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. One of the most prominent features of IgAN is mesangial proliferation with deposition of immune complexes. The role of the immune response in the development of IgAN is well-established. However, the genetics and pathways involved are not yet fully understood.

Methods: Mesangium from ddY mice (8 weeks gddY mice, n=3) and control mice (8 weeks Balb/c mice, m=3) were analyzed from three different system-level perspectives: genome level by single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq), transcription level by single-nucleus RNA sequencing (snRNA-seq), and metabolic level by in-silico metabolic flux simulation. 'Pdgfrb', 'Pdgfra', 'Fhl2′ and 'Itga8' were selected as mesangium-specific marker genes prior to analysis.

Results: The study found that there was a proliferation of cells in IgAN compared to the control, as determined through spatial deconvolution of single-nuclei RNA-seq. The cells in the mesangium were rearranged into three subgroups, including two IgAN-specific subgroups and one control-specific subgroup, each with system-level-specific alterations. From an epigenomic perspective, one of the IgAN-specific subgroups revealed a 'positive regulation of cell adhesion' and 'epithelial cell proliferation' compared to the control-specific subgroup. In transcription profile alteration, two IgAN-specific subgroups revealed either upregulation of immune-associated pathways or energy-associated pathways. Metabolic flux changes affected various metabolic pathways, including 'alanine and aspartate metabolism' and 'purine catabolism'. Three metabolic pathways, namely 'beta-alanine metabolism', 'nucleotide metabolism', and 'pyrimidine catabolism', showed multiple simultaneous alterations on all three system levels.

Conclusions: This study provides insight into the key molecular changes that occur during the development of IgAN-associated glomerular injury, particularly in the mesangium of mice.

TH-PO544

Glomerular Dissection Allows High-Throughput RNA Sequencing of Single Podocytes

Najeong Kim,[1] Darshan Jadhav,[1] Nestor H. Garcia,[1] Agustin Gonzalez-Vicente.[1,2] Kidney Precision Medicine Project (KPMP). *[1]Case Western Reserve University, Cleveland, OH; [2]Cleveland Clinic Glickman Urological and Kidney Institute, Cleveland, OH.*

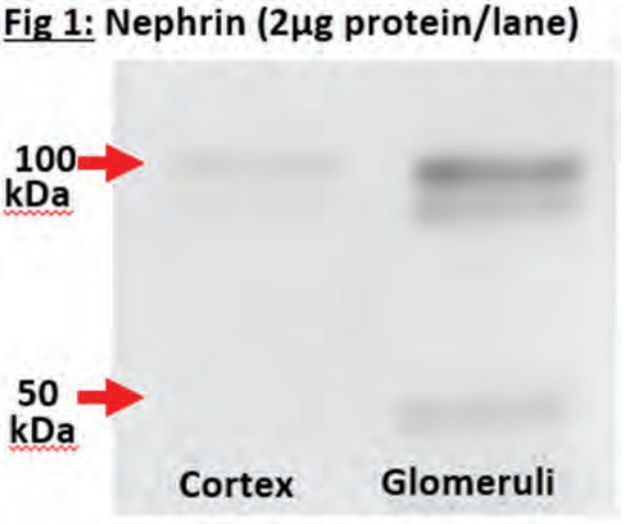
Background: Podocytes (POD) are essential for maintaining the integrity of the glomerular filtration barrier. Persistent insult to POD leads to proteinuria and chronic kidney disease. Single nuclei (sn) RNA sequencing (RNAseq) is an important tool in kidney research. As POD represent a small percentage of cells in kidneys, we developed a method to maximize POD recovery.

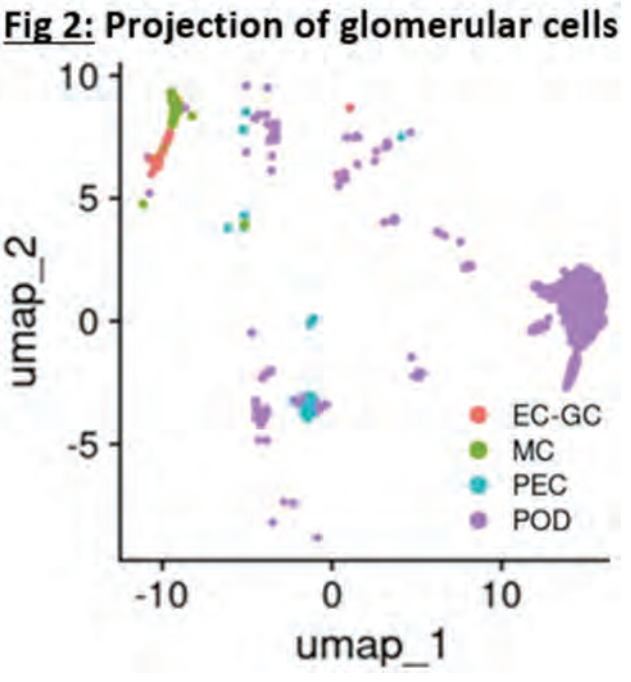
Methods: Rat glomeruli were microdissected and nuclei suspensions obtained by cellular fractionation. Libraries were prepared with 10X Chromium X technology and sequenced on the Illumina NovaSeq X platform.

Results: Western blots (Fig 1) of 77 glomeruli show enrichment for the slit-diaphragm protein nephrin. We also recovered 22.5 ng RNA from 30 glomeruli with a 28S/18S ratio >1.8. We prepared two sn-libraries, using ~180 (Rat1) and ~90 (Rat2) glomeruli, which yielded 6590 and 1022 sn-transcriptomes, respectively. We quality-controlled and clustered cells in Seurat, and used label transfer from a reference human kidney atlas (PMID: 37468583) to assign cell types (Fig 2). The number of glomerular cells recovered was: POD 1534 (22.2%), parietal epithelial cells (PEC) 96 (1.6%), mesangial cells (MC) 61 (0.9%) and glomerular capillary endothelial cells (EC-GC) 36 (0.5%). The reference atlas contains 2.1% POD, 1.1% PEC, 0.4% MC and 1.3% EC-GC. In addition, the reference atlas recovered on average 73 POD/biopsy, while our pilot study recovered 759 POD/sample.

Conclusions: Collectively, these findings show that our protocol enriches POD proteins and yields high-quality RNA suitable for sequencing. Isolated glomeruli also resulted in a more than tenfold increase in sn-POD transcriptomes per sample compared to kidney biopsies. Further development of this methodology will support high-throughput sequencing of POD with small sample sizes.

Funding: NIDDK Support





TH-PO545

Glomerular Transcriptomics Reveal Clinically Relevant Endothelial Disturbances in Idiopathic Nephrotic Syndrome

Sarah K. Nelson-Taylor,[1] Courtney Giannini,[1] Jonathan P. Troost,[4] Tarak Srivastava,[2] Jarcy Zee,[3] Markus Bitzer,[4] Laura Barisoni,[5] Richard J. Johnson,[1] Gabriel M. Cara-Fuentes.[6] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Children's Mercy Kansas City, Kansas City, MO; [3]University of Pennsylvania, Philadelphia, PA; [4]University of Michigan, Ann Arbor, MI; [5]Duke University, Durham, NC; [6]Nationwide Children's Hospital, Columbus, OH.*

Background: There is a growing evidence that the glomerular endothelium is important in podocytopathies presenting as idiopathic nephrotic syndrome (INS). In this study we characterize the expression 10 selected genes associated with glomerular endothelial health and injury in patients with INS.

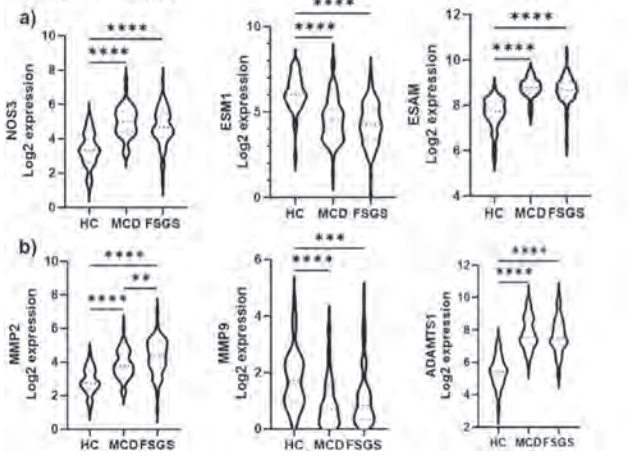
Methods: N=53 healthy controls and N=153 INS NEPTUNE participants with biopsy proven minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) and mRNA expression profiling from micro-dissected human glomeruli were included. Gene expression was analyzed according to the histological diagnosis (MCD vs. FSGS) and disease state (relapse/remission). Correlation between gene expression, clinical features (proteinuria, kidney function -eGFR) and validated ultrastructural endothelial (loss of fenestrations, etc.) and podocyte descriptors (foot process effacement, etc.) was performed. Statistical analyses included two-way ANOVA and Pearson correlation.

Results: Endothelial-specific genes related to endothelial health and barrier integrity (NOS3, ESAM, ESM1), glycocalyx injury (HPSE, HYAL1, MMP2, MMP9, ADAMTS1) and cell activation (ICAM1, CAV1) were significantly altered in INS patients (Fig. 1 shows representative results) compared to controls, independent of the histological pattern and disease state. High ICAM1, CAV1 and HPSE expression associated with low eGFR. NOS3 and CAV1 associated with loss of endothelial cell fenestrations, and MMP2 with loss endothelial cell honeycombing appearance. Analysis of gene expression and podocyte descriptors is in process.

Conclusions: Glomerular expression of genes associated with endothelial health is altered in INS, regardless of histological patterns or disease state, and associates with low eGFR and endothelial ultrastructural injury.

Funding: Private Foundation Support

Figure 1. Glomerular transcriptomics in human INS. a) Endothelial-specific genes. b) Genes related to extracellular remodeling and glycocalyx injury. **p<0.01, ***p<0.001, ****p<0.0001



TH-PO546

Analysis of Glomerular Transcriptomes from Nephrotic Patients Suggests APOL1 Risk Variants Impact Parietal Epithelial Cells

Agustin Gonzalez-Vicente,[1,2] Dana C. Crawford,[1] William S. Bush,[1] Zhenzhen Wu,[2] Leslie A. Bruggeman,[2] Viji Nair,[3] Matthias Kretzler,[3] John F. O'Toole,[2] John R. Sedor.[2] Nephrotic Syndrome Study Network (NEPTUNE) and Kidney Precision Medicine Project (KPMP). *[1]Case Western Reserve University School of Medicine, Cleveland, OH; [2]Cleveland Clinic, Cleveland, OH; [3]University of Michigan, Ann Arbor, MI.*

Background: Two *APOL1* gene variants (G1 and G2), only present in individuals with African ancestry, are linked to increased kidney disease rates. The mechanisms behind this genetic association remain obscure. We hypothesized that individuals with *APOL1* risk alleles have a glomerular transcriptional signature, which could identify candidate disease mechanisms.

Methods: We analyzed glomerular RNASeq transcriptomes from patients with idiopathic nephrotic syndrome, of which 72 had inferred African ancestry (AA) and 152 did not.

Results: Characteristic Direction identified a signature (SIG, 1481 genes), which separated AA patients with *APOL1* risk alleles from those homozygous for reference *APOL1*. Kaplan-Meier (KM) analysis showed that AA patients in the highest tertile of SIG activation scores progressed faster to the composite event of kidney failure or loss of 40% eGFR ($p \leq 0.013$). In addition, we found an association between a gene coexpression metamodule (MM, 437 genes) and the number of *APOL1* risk alleles, which remained significant after adjusting for eGFR and proteinuria. KM analysis showed that AA patients in the highest tertile of MM activation scores were less likely to achieve complete proteinuria remission ($p \leq 0.014$). SIG and MM activation scores did not associate with clinical outcomes in patients without inferred African ancestry. MM and SIG presented 191 common genes, and were both enriched for Epithelial Mesenchymal Transition (EMT) and inflammation terms. Overlap with glomerular cell identity signatures showed that MM predominantly features genes from parietal epithelial cells (PECs) rather than podocytes (PODs).

Conclusions: Concordant with enrichment in EMT genes, PECs could lose their epithelial phenotype while concomitantly driving glomerular scarring. These data suggest *APOL1* nephropathy is mediated by cellular crosstalk, in which PODs expressing G1 or G2 variants have paracrine effects on PECs, perhaps mediated by inflammatory cytokines. Thus, the presence of *APOL1* risk alleles may lead to persistent glomerular inflammation, PEC activation, podocyte loss, and glomerular scarring, thereby accelerating the progression of kidney disease.

Funding: NIDDK Support

TH-PO547

Energy Score Analysis in Immune Cells Linked to Atypical Hemolytic Uremic Syndrome Using Single-Cell Sequencing

I-Ru Chen,[1] Siang-Jyun Tu,[2] Chiu-Ching Huang,[1] Ping chin Lai.[1] *[1]China Medical University Hospital Department of Internal Medicine, Taichung, Taiwan; [2]China Medical University Hospital, Taichung, Taiwan.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA) with complex genetic and immunologic factors. Our single-cell sequencing shows a significant correlation between aHUS and immune cell subsets. Energy metabolism is crucial for immune responses, with cells reprogramming upon activation. We hypothesize that energy metabolism genes play a role in aHUS pathogenesis. This study evaluates energy metabolism-related gene expression (Energy Score, ES) in immune cell subpopulations from aHUS patients, unaffected family members, and healthy controls, enabling detailed comparison of aHUS activity and new research avenues.

Methods: We recruited 13 aHUS patients, three unaffected families, and four healthy controls from a medical center in Taiwan. Peripheral blood samples underwent single-cell RNA sequencing (scRNA-seq). The aHUS patients were classified into stable and unstable groups. ScRNA-seq data were processed with CellRanger and analyzed using Seurat in R. Inflammatory genes from the Molecular Signatures Database (MSigDB) were used to compute the energy score (ES) with Seurat's AddModuleScore, enabling detailed analysis of cellular energy metabolism.

Results: Our study assessed Energy Score (ES) in cell subpopulations among aHUS patients, aHUS nuclear families without the syndrome, and healthy controls via transcriptomic analysis. Intermediate monocytes showed the highest ES in aHUS patients, followed by aHUS families, and then healthy controls, with significant differences ($p < 0.0001$). No significant differences were found between aHUS families and healthy controls. Subclusters 1 and 2 of intermediate monocytes had significantly higher ES in aHUS patients compared to others. ES in intermediate monocytes, naïve CD8 T cells, terminal effector CD8 T cells, and non-V delta 2 gamma delta T cells was highest in unstable aHUS patients, followed by stable aHUS patients, aHUS families, and healthy controls.

Conclusions: Our study reveals a link between energy metabolism genes and aHUS severity through single-cell sequencing energy scores. Intermediate monocytes are significant markers of aHUS activity. This suggests energy metabolism genes play a key role in aHUS, warranting further research. These findings could predict disease stability and inform new therapeutic approaches.

TH-PO548

Spatially Resolved Transcriptomic Signature of Relapsing Minimal Change Disease

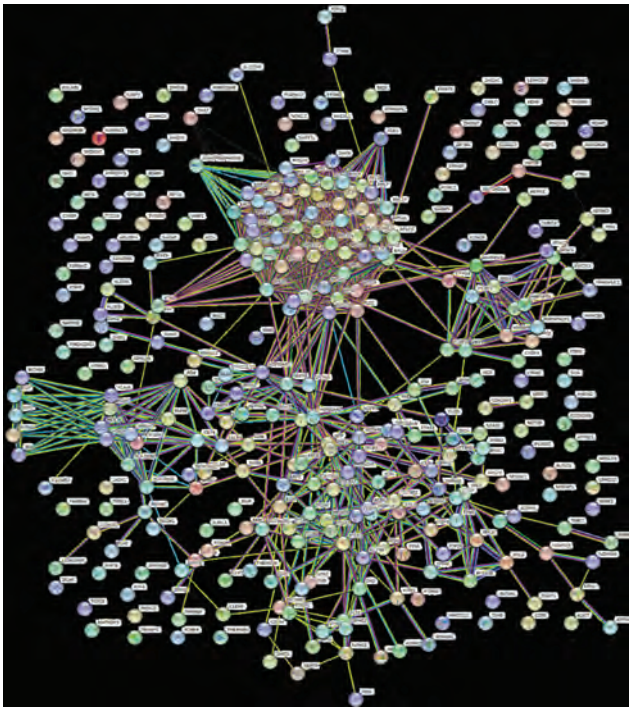
Semin Cho,[1] Jeongmin Cho,[1] Soojin Lee,[2] Sehoon Park,[3] Yaerim Kim,[4] Dong Ki Kim.[3] *[1]Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Gyeonggi-do, Republic of Korea; [2]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [3]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [4]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea.*

Background: Minimal change disease (MCD) is usually responsive to corticosteroid. However, there are few data regarding the frequently relapsing MCD even after complete remission with previous treatment including corticosteroid. We aimed to investigate the molecular mechanisms of relapsing MCD using spatial transcriptomics.

Methods: We performed spatial transcriptomic profiling using GeoMx Digital Spatial Profiler with formalin-fixed paraffin embedded kidney biopsy specimens from four patients with relapsing MCD and various disease controls (MCD without relapse, focal segmental glomerulosclerosis, membranous nephropathy, diabetic nephropathy, and healthy controls). We compared the gene expression levels of relapsing MCD with the various disease controls in both glomeruli and tubules by DeSeq2 method. Differentially expressed genes (DEGs) were identified, and gene ontology (GO) term annotation and pathway analysis were performed.

Results: A total of 320 DEGs were consistently down-regulated in the glomerulus of relapsing MCD compared to all other various disease controls. Among the 320 DEGs, there are previously known genes that related to the pathogenesis of podocyte disease including NPHS1, NPHS2, and PODXL. GO annotation including cell adhesion molecule binding (GO:0050839), protein-containing complex binding (GO:0044877), MHC class II protein complex binding (GO:0023026) were the most notable annotated domain in the glomerulus of relapsing MCD. On the other hand, no DEG showed significance in the tubules between relapsing MCD and other disease controls.

Conclusions: In this study, we discovered consistently down-regulated DEGs in relapsing MCD compared with the various disease controls through spatial transcriptomics.



TH-PO549

Spatial Transcriptomic Profiling of Glomeruli in FSGS and Minimal Change Disease That Appear Normal on Light Microscopy

Hyung Woo Kim,[1,2] Minsun Jung,[1] Chung Lee,[1] Ga Young Heo,[1,2] Cheol Ho Park,[1,2] Hae-Ryong Yun,[1] Jung Tak Park,[1] Tae-Hyun Yoo,[1] Shin-Wook Kang,[1] Beom Jin Lim,[1] Seung Hyeok Han.[1] *[1]Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Republic of Korea.*

Background: Distinguishing between minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) based solely on pathological findings is challenging, with no validated biomarkers available for their discrimination.

Methods: Using the GeoMx Digital Spatial Profiler, spatial transcriptomic profiling was performed on formalin-fixed paraffin-embedded kidney biopsy specimens from five patients with MCD and three patients with FSGS (one tip variant and two NOS variants), all of whom presented with nephrotic syndrome. Additionally, we included four control patients from time zero biopsy of kidney recipients. Glomerular regions of interest were selected and outlined by two kidney pathologists using the web interface. For FSGS, glomeruli with and without sclerosis were selected separately. Differential gene expression (DEGs) analyses were conducted by fitting each gene's Q3 normalized expression level using edgeR. Gene ontology (GO) enrichment analyses of DEGs were performed using clusterProfiler.

Results: After excluding genes exhibiting expression levels below 5% of the ROIs in each sample, a final analysis was conducted on the remaining gene expression levels of 13,929 genes. Compared with glomeruli from MCD, normal glomeruli from FSGS exhibited increased expression of *GPR141*, and *DEFB104A* and decreased expression of *BRD2*, *FAM124A*, and *MYADM*. Sclerotic glomeruli from FSGS showed increased expression of *WIPI1* and *CLCN7* and decreased expression of *PODXL*, *NDNF*, *DCN*, and *HTRA1* compared with glomeruli from MCD. When comparing normal and sclerotic glomeruli from FSGS, normal glomeruli showed increased expression of *NPHS2*, *COL4A3*, *ID1*, and *ADAMTSL5*, whereas sclerotic glomeruli showed increased expression of *RPS23*, *RPL27A*, *EEF1G*, and *CRTAP*. Additionally, GO analyses revealed significant enrichment of genes for genes related to various biologic processes when these three phenotypes were compared with each other.

Conclusions: Utilizing digital spatial profiling identified significant differences in the expression profiles between glomeruli in FSGS and MCD that appear normal on light microscopy. Future studies are warranted to validate our findings and evaluate whether the observed genes could serve as discriminative biomarkers between the two phenotypes.

TH-PO550

High-Resolution Morphometry and Spatial Transcriptomics to Reveal Cellular and Molecular Mechanisms of Podocyte Effacement

Tobias Bohnenpoll,[1] Philipp Skroblin,[1] Johannes Pospiech,[1] Anna Guhl,[1] Nils Liebe,[1] Alexander Lomow,[1] Carolin Wiechers,[1] Britta Seip,[1] Menglin Zheng,[1] Michael Helwig,[1] Rüdiger Fritsch,[1] Olivier Radresa,[1] Kristina Kramer,[2] Florian Grimm,[2] Christian A. Wurm,[2] Gerald Donnert,[2] Uwe Andag.[1] *[1]Evotec International GmbH, Göttingen, Germany; [2]Abberior Instruments GmbH, Göttingen, Germany.*

Background: Podocyte injury and effacement precede proteinuria and result in characteristic glomerular lesions associated with focal segmental glomerulosclerosis (FSGS) and other glomerulopathies. These lesions have long been considered distinct disease entities, but their cellular and molecular features remain poorly characterized. Stimulated emission depletion (STED) is a light microscopy technique which provides a unique opportunity to assess podocyte foot process morphology in unprecedented detail. Here, we combine super-resolution STED morphometry and spatial transcriptomics to unravel the cellular and molecular mechanisms underlying podocyte injury and effacement in kidney biopsies from the NURTuRE patient cohort.

Methods: Adjacent thin sections of formalin-fixed, paraffin-embedded biopsies from 18 NURTuRE patients diagnosed with FSGS and other glomerulopathies and 2 healthy living donors were analyzed using STED microscopy (Facility line, Abberior) and spatial transcriptomics (Visium HD, 10x Genomics). Podocyte foot processes and filtration slits were stained for synaptopodin and nephrin, and super-resolution scans were exported for morphometry.

Results: Clinical-grade biopsies were selected to represent patients with early, intermediate, and end-stage disease, maximizing the range of kidney function and proteinuria. High-resolution spatial transcriptomics allowed identification of tissue niches based on the expression of cell type-specific and mechanistic signatures, representing distinct glomerular and tubulointerstitial microenvironments with different cellular composition. Unbiased clustering of spatially and molecularly defined niches stratified glomeruli along the continuum of podocyte injury and glomerular remodeling. Interestingly, glomerular niches were associated with different slit diaphragm lengths and densities, as determined by podocyte STED morphometry, depending on their position along the disease continuum.

Conclusions: Further integration of molecular, morphometric and clinical data has the potential to reveal cellular and molecular mechanisms of podocyte injury and glomerular remodeling and will aid in mechanistic disease understanding.

Funding: Commercial Support - Evotec International GmbH, Abberior GmbH

TH-PO551

Single-Cell Spatial Atlas of Immune and Kidney Cell States in Human Rapidly Progressive Glomerulonephritis

Zeba Sultana, Robin Khatri, Behnam Yousefi, Nikhat Shaikh, Saskia-L. Jauch-Speer, Varshi Sivayoganathan, Hans-Joachim Paust, Thorsten Wiech, Tobias B. Huber, Ulf Panzer, Stefan Bonn, Christian F. Krebs. *Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: Rapidly progressive glomerulonephritis (RPGN) represents the most aggressive form of autoimmune kidney disease and is characterized by the formation of glomerular crescents and the infiltration of immune cells. However, a detailed definition of leukocyte composition, cellular localization and the interactions of immune cells with renal tissue cells leading to the formation of glomerular crescents and loss of renal function is lacking.

Methods: We employed high-dimensional in situ mRNA detection (10x Xenium) to investigate immune cell infiltration and kidney cell reactions in patients with RPGN (ANCA-GN: n= 32; lupus nephritis: n=19; anti-GBM: n=6) and controls (n=6). Based on single-cell RNA-seq and spatial transcriptomics data from kidney samples from the same cohort, we designed a panel consisting of 480 probes for mRNA detection to cover a broad range of immune cells, parenchymal kidney cells and potential drivers of tissue inflammation. We used manual annotation as well as a graph neural network (GNN)-based clustering algorithm to define kidney niches.

Results: Our analysis resulted in a total of 2,899,179 cells from all disease categories and the panel enabled the definition and localization of all major immune and kidney cell types. Gene-expression-based pseudotime analysis from annotated glomeruli provided a trajectory from healthy glomeruli identified most frequently in control samples to severely damaged glomeruli mainly from anti-GBM patients. Patients with ANCA-GN showed glomeruli with all stages of the pseudotime. These analyses define the sequential recruitment of proinflammatory T cells and macrophages into inflammatory niches causing changes in cellular composition and crosstalk between different cell types and resulting in altered transcriptional profiles of epithelial kidney cells leading to crescent formation.

Conclusions: This integrated high-dimensional spatial immune and kidney cell atlas of healthy and RPGN kidneys represents a comprehensive benchmark of the cellular players with their localization and interactions in glomerular pathology. This is the basis for a better understanding of the cellular and molecular mechanisms required to develop targeted therapies in glomerulonephritis.

Funding: Government Support - Non-U.S.

TH-PO552

Single-Cell Spatial Resolution Transcriptomic Profiling in Lupus Membranous Nephritis

Claire Avillach,[1,2] Alessia Giarraputo,[1,2] Ivy A. Rosales,[1,2] Jeremy M. Marcin,[1,2] Nicole L. Brousaides,[1,2] Robert B. Colvin.[1,2] Immunopathology Research Lab.
[1]Mass General Brigham Inc, Boston, MA; [2]Harvard University, Cambridge, MA.

Background: Understanding the molecular pathways involved in membranous lupus nephritis (classV LN) is crucial for identifying diagnostic biomarkers and potential therapeutic targets.

Methods: Spatial transcriptomic technology with cellular resolution was employed to analyze the expression of 1,000 RNAs in kidney core biopsies from patients with classV LN (n=3) and PLA2R-associated membranous nephropathy (PLA2R-MN, n=3). Spatially resolved cells were classified into cell types and differential gene expression analysis was conducted using a negative binomial model.

Results: Spatial single-cell transcriptomic analysis was conducted on 33,195 cells from class V LN samples and 39,127 cells from PLA2R-MN samples. Gene expression analysis revealed a significant upregulation of multiple type I interferon-stimulated genes (ISGs) in lupus nephritis, including IFIMT1, OAS1, STAT1, and IFI27 (Figure1). Increased ISG expression was observed across the main glomerular cell subtypes (podocytes, glomerular endothelial cells, mesangial cells/fibroblasts) as well as in tubular epithelial cells (Figure2). Notably, there was no significant increased expression of interferon (IFN) alpha, beta, gamma genes nor their receptors in lupus nephritis.

Conclusions: In comparison to PLA2-R-MN, class V LN shows activation of the type I IFN pathway. Further studies are needed to determine the role of interferon pathway activation in kidney injury and its use as a possible diagnostic or prognostic biomarker or therapeutic target for class V lupus nephritis.

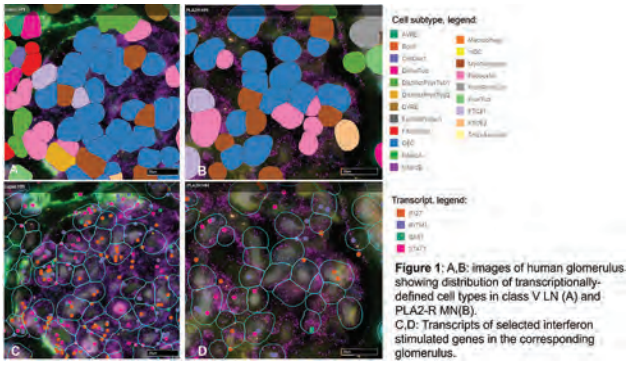


Figure 1: A,B: images of human glomerulus showing distribution of transcriptionally-defined cell types in class V LN (A) and PLA2-R MN(B). C,D: Transcripts of selected interferon stimulated genes in the corresponding glomerulus.

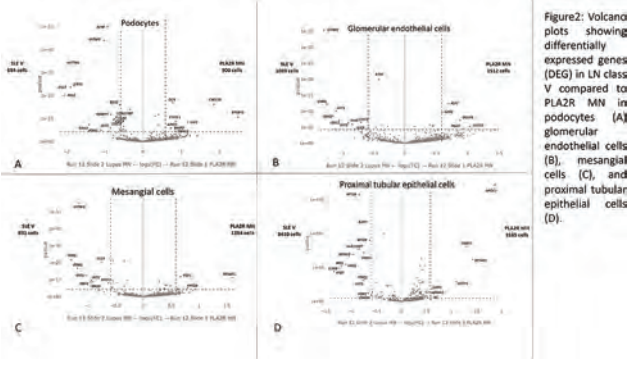


Figure2: Volcano plots showing differentially expressed genes (DEG) in LN class V compared to PLA2R MN in podocytes (A), glomerular endothelial cells (B), mesangial cells (C), and proximal tubular epithelial cells (D).

TH-PO553

Glomerular Proteomic Signature in ANCA-Associated Glomerulonephritis

Ivana Stojkic,[1] John P. Shapiro,[2] Asish Thakkar,[3] Salem Almaani.[2]
[1]Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University Wexner Medical Center, Columbus, OH; [3]VA Central Ohio, Columbus, OH.

Background: Crescentic glomerulonephritis (AAGN) is a common manifestation of ANCA-associated vasculitis (AAV) but does not occur in all patients. It is unclear whether the immune pathways driving systemic AAV are similar to the ones that drive AAGN, or whether there are pathways that are specific to the kidneys. To gain more insight into activated disease pathways in AAGN, we performed an agnostic proteomic analysis of glomeruli in patients with AAGN.

Methods: Kidney biopsies from 10 patients with AAGN and 5 controls (transplant donor biopsies) were used. Glomeruli were isolated using laser-capture microdissection, processed, and submitted for LC-MS/MS. Peptides were analyzed for spectral count quantitation. Spectral counts of each disease were compared to control samples and differential abundance analysis was performed using t-tests of log2 transformed peptide counts. Multiple hypothesis testing correction was performed and false discovery rate (FDR) adjusted p-values were used. Significance was defined as an FDR p value of <0.05 AND an absolute log2 fold change >1. Significantly abundant peptides were used for pathway analysis using Reactome.

Results: 105 peptides were significantly upregulated and 331 peptides were significantly downregulated when comparing AAGN vs control (Figure 1). Pathway analysis revealed upregulation of complement peptides, platelet aggregation, and neutrophil degranulation. In addition, several metabolic pathways were downregulated in kidneys of patients with AAGN.

Conclusions: Proteomic analysis of glomeruli from patients with AAGN reveals upregulation of distinct pathways such as the complement system, and downregulation of many metabolic pathways. These pathways can provide insight into the mechanism of kidney injury in AAGN, and aid in development of kidney targeted therapies.

Funding: Private Foundation Support

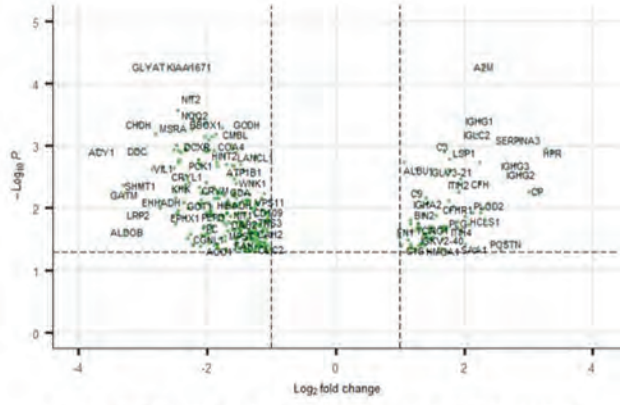


Figure 1. Differentially abundant proteins in AAGN vs control

TH-PO554

Single Glomerular Proteomics of Crescentic and Noncrescentic Glomeruli

Michael Merchant,[1] Laura Biederman,[4] Michelle T. Barati,[1] Joseph Gaut,[2] Julie Dougherty,[3] Daniel W. Wilkey,[1] Adam E. Gaweda,[1] Jon B. Klein,[1] William E. Smoyer.[3] *[1]University of Louisville School of Medicine, Louisville, KY; [2]Washington University in St Louis School of Medicine, St Louis, MO; [3]Nationwide Children's Hospital, Columbus, OH; [4]The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Glomerular crescent formation is characteristic of rapidly progressive glomerulonephritis (RPGN), but the molecular mechanisms of crescent formation are poorly understood. We addressed the hypothesis that proteomic analysis of single crescentic glomeruli compared to unaffected glomerular tissue could reveal differential protein expression and provide mechanistic insight into crescent formation.

Methods: VIPER, a digital imaging platform, was used to annotate and select glomeruli with and without crescents in three different patient biopsies. Single glomeruli were followed through 5µm serial sections on PEN slides for microdissection. Isolated glomerular sections for crescentic and otherwise normal glomeruli (n=3) were analyzed using data independent acquisition (DIA) with a Thermo QE-HF LCMS. DIA data analysis (PeaksX) employed human glomerular and in silico spectral libraries. Single glomerulus datasets (n=6; 3x2) were quantitatively compared by paired and 2-way ttest (unadjusted p<0.05) and functionally characterized by g:Profiler using all proteins to establish differences within (paired) and between (2-way) crescentic and otherwise normal glomeruli.

Results: 1,468 protein groups were detected across all datasets. 21 proteins differentiated crescentic and normal glomeruli with 19 more abundant in crescentic glomeruli. Ontologic analysis of all proteins identified top qualitative terms including cell adhesion (MF), cytoplasmic translation (BP), extracellular space (CC), coronavirus disease (KEGG), and primary focal segmental glomerulosclerosis (Wikipathways enrichment based on the following geneset: CR1, PTPRO, NPHS2, NPHS1, ILK, FYN, MYO1E, PODXL, LIMS1, CD151, MME, ITGA3, SYNPO, TLN1, ITGB1, AGRN, PARVA, DAG1, MYH9, ACTN4,I NF2, COL4A3, LAMA5, UTRN,C OL4A5, VCL, COL4A4, VTN, LAMB2, CD2AP, YWHAQ, PTK2, ITGAV, ITGB3, SCARB2, VIM, KRT8, CTNNB1).

Conclusions: This study demonstrates the ability to get glomerulus specific proteomic data from both crescentic and normal glomeruli from the same biopsy. The proteomic data shows a clear difference between the crescentic glomeruli and the normal glomeruli. Wider application of this technique will allow us to compare different stages of crescent formation as well as crescents in different disease states.

Funding: NIDDK Support, Other NIH Support - DK130294, AA028436, GM113226, ES030283

TH-PO555

Human Kidney Tissue Proteomics Unveils Complement Factor D Involved in the Pathogenesis of Focal Segmental Glomerulosclerosis

Sahomi Yamaguchi,[1,2] Toshiaki Nakano,[1] Daiki Setoyama,[2] Abhijeet Sonawane,[3] Takaki Iwamoto,[1] Sasha Singh,[3] Masanori Aikawa,[3] Yuya Kunisaki,[2] Takanari Kitazono.[1] *[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Clinical Chemistry and Laboratory Medicine, Kyushu University Hospital, Fukuoka, Japan; [3]Brigham and Women's Hospital, Boston, MA.*

Background: Focal segmental glomerulosclerosis (FSGS) is a clinicopathological syndrome manifested with nephrosis resistant to glucocorticoids. Given the fact that FSGS has unfavorable renal prognosis, efficient therapeutic options targeting specific pathways are sought to be developed. The Columbia classification proposed the 5 variants, namely Collapsing, TIP, Cellular, Perihilar and NOS. Differences in their renal prognosis imply distinct underlying molecular mechanisms, which remains unclear. Here, we aimed to explore factors involved in the pathogenesis of FSGS by comprehensive proteomics with human kidney tissues.

Methods: Kidney tissues from a total of 73 individuals including 23 FSGS patients, healthy and disease controls, were subjected to the analysis using LC-MS/MS-enabled proteomics. Immunohistochemistry and the microarray data from the Nephroseq database were used for validation.

Results: Our proteomics platform identified a total of 4,168 proteins from renal tissue specimens. Comparison of FSGS and healthy control groups identified 175 proteins increased in FSGS, which were enriched in the complement pathway and immune responses by Gene Ontology analysis. These results suggest involvement of the complement system as an underlying mechanism. Furthermore, complement factor D (CFD), which activates the alternative complement pathway, was identified to be significantly elevated in the FSGS group compared to disease control groups. Analysis with immunohistochemistry and gene expression from the Nephroseq database confirmed that CFD was produced mainly in glomeruli, where complement cascades are possibly triggered. Next, we extracted proteins specific for the Columbia variants. Gene Ontology analysis with these factors uncovered that complement pathway was enriched in the Cellular and TIP variants, while endoplasmic reticulum, ribosome, and ferroptosis pathways were in the Collapsing variant, suggesting their different pathophysiology.

Conclusions: Our study provided deeper insights into the recently proposed functional association between FSGS and the complement pathway, offering targeted treatment options. Moreover, the variant-specific molecular background in the Columbia classification will enable us to stratify treatments of FSGS.

TH-PO556

The Glomerular Kinome in Health and Disease

Jonathan C. Haydak, Nanditha Anandakrishnan, Evren U. Azeloglu. Kidney Precision Medicine Project (KPMP). *Icahn School of Medicine at Mount Sinai Department of Medicine, New York, NY.*

Background: Pharmacologically targeting the glomerular kinome is an appealing strategy as existing kinase inhibitors could potentially be repurposed for treating kidney diseases. To this end, we investigated alterations in the glomerular kinome signature in rat models of minimal change disease and hypertensive nephropathy in combination with single-nucleus RNA sequencing (snRNA-seq) from biopsies of patients in the Kidney Precision Medicine Project (KPMP).

Methods: Sprague-Dawley rats were injected with a single dose of 100mg/kg puromycin aminonucleoside (PAN) and studied for 4 weeks with tissue collected at post-injection days 7, 14, 21, and 28. 13-week-old spontaneously hypertensive rats and age- and sex-matched Wistar-Kyoto rats were studied for 5 weeks before harvesting kidneys. Quantitative isobaric tandem mass tag proteomics was performed on isolated glomeruli, with differentially abundant proteins (DAPs) identified using the LIMMA statistical package and correlated with functional measurements such as urine albumin-creatinine ratio. Publicly available KPMP snRNA-seq data was analyzed using Seurat. Pathway analyses on DAPs and differentially expressed genes (DEGs) were performed using Enrichr and Molecular-Biology-of-the-Cell Ontology.

Results: Both rat models showed severe and overlapping perturbations to the glomerular kinome. In PAN rats, alterations in glomerular kinome corresponded to the severity of albuminuria (**Figure 1A**). Enrichment of the top up- and down-regulated kinases showed cytoskeletal dynamics, adhesion, and the Hippo pathway to be significantly impacted. Patient snRNA-seq data from KPMP similarly showed dysregulation of Hippo-related transcripts which correlated with levels of albuminuria (**Figure 1B**).

Conclusions: In albuminuric kidney diseases, the altered kinome and dysregulation of the Hippo pathway may represent common underlying disease mechanisms.

Funding: NIDDK Support, Other NIH Support - NIH T32HD075735

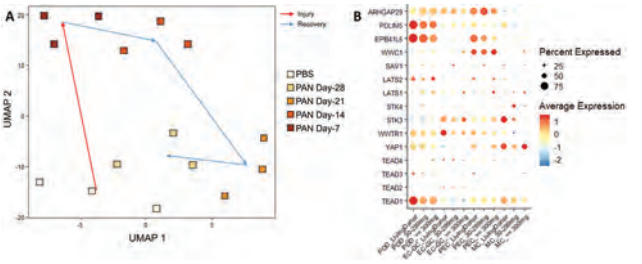


Figure 1: (A) UMAP of glomerular expression levels of detected kinases during transient glomerular dysfunction in PAN rats (red = injury during days 0-7, blue = recovery during days 8-28). **(B)** Expression levels of Hippo-related genes in KPMP glomerular cells split by severity of albuminuria.

TH-PO557

Expanding the Limits Single Glomerulus Measurements by Targeted, Quantitative Proteomics

Chris Hsu, Mariya T. Sweetwyne, Michael Maccoss. *University of Washington, Seattle, WA.*

Background: As age progresses, the kidney glomeruli can undergo heterogeneous structural changes that affect filtration efficiency and cause kidney dysfunction. To capture these structural changes at the proteomics level, single glomerulus measurements need to be performed to see the spatial heterogeneity that would otherwise be lost in aggregated, bulk kidney or glomerular samples. We aim to improve the sensitivity and sample recovery of a single glomerulus to better profile its molecular heterogeneity.

Methods: Single glomerulus samples were individually dissected from a pool for bulk glomerulus samples from a 7 month old mouse. An optimized acid lysis protocol was performed prior to protein aggregate capture (PAC) and clean-up. A targeted proteomics method was generated from a data-independent acquisition (DIA) library of pooled bulk glomerulus samples. Our targeted list includes peptides from podocyte, glomerular and tubule proteins. Proteomics data on all of the samples were acquired using a targeted method measuring 571 peptides from 500 proteins on an EvoSep running a 30 minute liquid chromatography gradient coupled to a Lumos tribrid mass spectrometer.

Results: We applied our optimized targeted protocol to study 30x single mouse glomeruli compared to bulk glomeruli. Podocyte and glomerular proteins, such as Synaptopodin and Podocin, were enriched in protein abundance, and tubule proteins, such as Uromodulin, were highly depleted in the single glomerulus samples compared to the bulk glomerulus control. To assess heterogeneity of the single glomerulus samples, the coefficient of variation was calculated at the peptide level. A higher coefficient of variation (62%) was observed for the single glomerulus samples compared to the bulk glomerulus samples (20%), demonstrating biological variation of individually measured single glomeruli compared to pooled bulk glomerulus samples.

Conclusions: We developed an effective sample preparation strategy to recover peptides down to the single glomerulus level. Using massively parallel targeted proteomics, we can measure 571 peptides from both single glomeruli and bulk samples with robust quantitation and no missing data. This method allows for the capture of robust individual glomerular proteomes and captures the confounding heterogeneity that accompanies glomerular aging.

TH-PO558

Using Laser Capture Microdissection and Proteomics to Identify Key Components of Metabolic Signaling Pathways in Glomerular Diseases

Marie-Kristin Kroll,[1] Linus A. Volker,[2,1] Martin Höhne,[2,1] Bernhard Schermer,[2,1] Martin Kann,[2,1] Thomas Benzing,[2,1] Paul T. Brinkkoetter.[2,1] *[1]University of Cologne Center for Molecular Medicine Cologne, Cologne, Germany; [2]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany.*

Background: Renal biopsies are classified based on descriptive parameters and validated antibodies. This histopathological assessment does not routinely consider molecular parameters. Here, we aim to unravel the key molecular changes in metabolic signaling pathways to establish a set of molecular markers linked to distinct disease states or response to therapy in glomerular diseases, including MCD and FSGS.

Methods: A technical workflow was established for rodent kidney samples. Glomerular sections of genetically modified mouse models and experimentally treated animals, including the induction of nephrotoxic nephritis (NTN) by serum application, as well as a rodent FSGS model, were isolated by Laser capture microdissection (LCM). Isolated glomerular sections were processed and analyzed using mass spectrometry.

Results: We identified proteins with dissenting regulation within a large-scale proteomics approach using genetically modified and experimentally treated mouse models. The expression patterns of significantly regulated proteins revealed reliable clustering of genetically or experimentally affected mice and control samples. Furthermore, some of

the identified proteins correlated with transcriptome data linked to podocyte damage in rodent models.

Conclusions: Our workflow identified significantly regulated proteins and distinct overlaps with transcriptome data in the glomerular sections of mice with renal impairment. Next, this workflow will be applied to human biopsies of FSGS and MCD patients to identify regulated proteins of interest in a large-scale setup. Following, in a targeted proteomics approach key proteins of metabolic signaling pathways will be analyzed in depth. By combining molecular findings with comprehensive clinical background information, including disease state, progression, and responsiveness to therapy, we aim to define a set of marker proteins allowing a precise molecular characterization of patient biopsies and thereby supporting indications for suitable therapies and drug treatment strategies for MCD and FSGS patients.

Funding: Government Support - Non-U.S.

TH-PO559

Proteomic Analysis of Glomerular Extracellular Matrix Suggests a Potential Role of Complement in the Pathogenesis of Idiopathic Collapsing Glomerulopathy Associated with APOL1 High-Risk Genotypes

Precil D. Neves,[1] Talita S. Siqueira,[1] Valkercyo A. Feitosa,[1] Andreia Watanabe,[1] Elieser H. Watanabe,[1] Jussara B. Castelli,[2] Natalia G. Gonçalves,[1] Chin J. Lin,[1] Livia B. Cavalcante,[1] Denise M. Malheiros,[1] Lectícia Jorge,[1] Irene L. Noronha,[1] Valdemir M. Carvalho,[2] Luiz F. Onuchic.[1] *[1]Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil; [2]Fleury Laboratory, São Paulo, Brazil.*

Background: The pathogenesis of collapsing glomerulopathy (CG), a highly aggressive nephropathy, remains largely unclear. While a significant fraction of idiopathic CG (ICG) cases is associated with *APOL1* high-risk genotypes (HRG), the differences in pathogenic processes between ICG associated with HRG (ICG+HRG) and with *APOL1* low-risk genotypes (ICG+LRG) are still poorly characterized.

Methods: To identify novel potential differences in molecular pathogenic pathways between ICG+HRG and ICG+LRG, we performed proteomic analyses of glomerular extracellular matrix (ECM) in 4 groups of patients: ICG+HRG (9 cases); non-Mendelian ICG+LRG (8 cases); FSGS-NOS+LRG (5 cases, a disease profile control); and normal kidney tissue (NK, 6 cases, a baseline control obtained from non-affected areas of nephrectomies secondary to malignancy). Glomerular samples were acquired by laser-microdissection. The relative abundance of proteins was compared between groups.

Results: We identified 931 proteins present in at least 60% of the samples of one group. Two hundred of them were classified as ECM proteins. C1QC, CFHR1, and hornerin were detected exclusively in the ICG+HRG group while laminin alpha 2 was detected only in the ICG+LRG group. Moreover, annexin A4, C5, C9, C4b-binding protein alpha chain (C4BPA), Serpin Family B Member 6 (SERPINB6), SERPINB9, and SERPINC1 stood out as displaying greater abundance in ICG+HRG than NK, and C4BPA, COL4A4, COL4A5, laminin beta 2, and nidogen-1 as presenting more abundance in ICG+HRG than FSGS-NOS+LRG. Annexin A4, annexin A6, SERPINB9 and SERPINH1 stood out as displaying greater abundance in ICG+LRG than NK. No difference in abundance was detected between ICG+HRG and ICG+LRG.

Conclusions: Our data showed that ICG+HRG and ICG+LRG presented patterns of glomerular ECM proteins associated with inflammation, immune activation and fibrosis pathways, and suggested a potential involvement of the complement system in the pathogenesis of ICG+HRG.

TH-PO560

Human Tubulointerstitial Responses to Proteinuria Analysed by Proteomics and Laser Capture Microdissection

Lars Nilges, Moritz Lassé, Felicitas E. Hengel, Elion Hoxha, Tobias B. Huber, Nicola M. Tomas, Markus M. Rinschen. *Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany*.

Background: Proteinuria damages the tubule compartment. Laser capture microdissection (LCM) enables the precise isolation of specific renal tubular segments, allowing for targeted proteomic analysis of the renal tubular interstitium in IgA nephropathy (IgAN) patients. By identifying differentially expressed proteins and molecular pathways associated with tubulointerstitial injury in IgAN, we sought to gain insights into the pathogenesis of this complex renal disease and identify potential therapeutic targets.

Methods: We studied 24 IgAN patients with M1E1 score alongside 10 zero-biopsy controls. Using formalin-fixed paraffin-embedded (FFPE) renal tissue and LCM, we isolated tubular compartments for analysis. Mass spectrometry-based proteomics identified differentially expressed proteins linked to tubulointerstitial injury in IgAN.

Results: Our analysis unveiled a distinct proteomic signature characterized by the upregulation of complement system proteins, including C7, C6, C5, and CFHR1, suggestive of an inflammatory response within the tubular interstitium. This inflammatory milieu is further corroborated by the identification of upregulated IgGs. Our study revealed a profound downregulation of sodium ion transporters, SLC5A1 and SLC4A7, within the tubular interstitium of IgAN patients indicating a significant disruption in tubular function. The marked downregulation of these sodium transporters suggests a pivotal role in the pathogenesis of tubulointerstitial injury, potentially contributing to disease severity and renal dysfunction in IgAN.

Conclusions: Upregulation of proteins associated with the complement system and immune response outside the glomerular compartment indicates a robust inflammatory process. Downregulation of key sodium ion transporters highlights disrupted electrolyte homeostasis and tubular dysfunction. These insights into tubulointerstitial injury in IgAN enhance our understanding of its pathogenesis and identify potential therapeutic targets to improve renal outcomes.

TH-PO561

Analysis of Kidney Biopsies from Patients with Glomerulonephritis Using Imaging Mass Cytometry Reveals Increase in Immune Cells with Associated Dedifferentiation and Injury of Tubular Cells

Marlene Weiss,[1,2] Vijayakumar R. Kakade,[2] Megan L. Baker,[2,4] Tifanny Budiman,[2] Ashish Shelar,[3] Lloyd G. Cantley.[2] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Yale University School of Medicine, New Haven, CT; [3]Yale University, New Haven, CT; [4]Yale University Graduate School of Arts and Sciences, New Haven, CT.*

Background: This study was conducted to characterize and develop mechanistic understanding of the tubulointerstitial impact of acute glomerulonephritis. For both ANCA-associated vasculitis (AAV) and Lupus nephritis (LN), there is a lack of patient-targeted therapies.

Methods: 30 FFPE cortex samples from 15 patients (5 with AAV, 5 with proliferating LN, and 5 tumor-remote nephrectomy samples (reference) were analyzed in a Tissue Microarray with imaging mass cytometry (IMC) after staining it with 37 metal-tagged antibody markers. Analysis was performed using scripts in Python and RStudio. Cells were segmented with mesmer, a deep learning platform. Clustering was performed using the Phenograph algorithm.

Results: Analysis of all 30 samples resulted in identification and segmentation of 106,455 cells (37.2% from reference, 31.2% from AAV, 31.6% from LN) with total analyzed tissue areas of 9.7, 5.1 and 5.8 mm^2, respectively. Thirty-nine cell clusters were identified with annotation revealing 17 different cell types. 95.6% of cells were successfully annotated. Total cell counts per mm^2 tissue area showed that reference kidneys had 3.1±1.8% immune cells whereas AAV and LN kidneys contained 28±17% and 21.9±20% immune cells, respectively, including T cells, B cells and macrophages. Analysis of the resident cell types revealed the expected predominance of proximal tubule (PT) cells (38.4±5.2% in reference, 32.7±8.2% in AAV, 30.9±7.5% in LN). Injury markers analyzed included kidney-injury molecule 1 (KIM-1), vimentin, FACL4 (ferroptosis) and pRIPK3 (necroptosis). Initial clustering resulted in 9 different PT clusters, of which 2 were notable for high expression of injury markers. Cells in cluster iPT were increased in both AAV and LN and had high expression of vimentin, pRIPK3 and KIM-1, while cells in cluster aavPT were found only in AAV and had high expression of KIM-1 and FACL4.

Conclusions: AAV and LN kidney samples reveal a marked increase in interstitial immune cells with associated dedifferentiation and injury of resident tubular cells. The tubular injury is highlighted by increased KIM-1, ferroptosis and necroptosis marker expression in injured PT with concurrent downregulation of resident markers Megalin and Aquaporin 1.

TH-PO562

Isotope-Guided Metabolomics Dissects Arginine Metabolism in Proteinuria

Maria Chrysopoulou,[1] Markus Bleich,[3] Nina Himmerkus,[3] Markus M. Rinschen.[1,2] Laboratory of Kidney Omics and Metabolism. *[1]Aarhus Universitet Institut for Biomedicin, Aarhus, Denmark; [2]III Department of Medicine, University Medical Center Hamburg Eppendorf, Hamburg, Germany; [3]Christian-Albrechts-Universitat zu Kiel, Kiel, Germany.*

Background: Proteinuria is a direct outcome of kidney glomerulus injury and an independent risk factor for cardiovascular disease (CVD). Arginine (Arg) metabolism links protein metabolism to renal function and CVD through urea excretion and nitric oxide generation. Due to the many metabolic fates, signals related to Arg metabolism are uninterpretable and its role in proteinuric kidney disease is not completely understood. The aim of this study is to investigate arginine's metabolic fate and interorgan communication in the healthy kidney and proteinuric kidney disease in a systemic way by comprehensive metabolomics and proteomics approaches.

Methods: Compound-heterozygous $Pod^{R231Q/A286V}$ is a mouse model of human hereditary nephrotic syndrome developing progressive proteinuria and leading to focal segmental glomerulosclerosis. *Ex vivo*, isolated and dissected nephron segments from healthy mice (n=4) and isolated tubule and glomeruli suspension from healthy

and Pod$^{R231Q/A286V}$ mice, (n=8), were incubated with $^{13}C_6$-Arg for 60 minutes. Extracted metabolites were analyzed with UHPLC/QQQ-based mass spectrometry targeting Arg-related metabolic pathways. *In vivo*, healthy and Pod$^{R231Q/A286V}$ mice (n=21) were fed with normal and stable isotope-labeled Arg diet for 2 weeks. Metabolites and proteins extracted from 19 metabolically active organs, urine, and plasma were analyzed accordingly.

Results: *Ex vivo,* Arg-derived glutamate, proline and agmatine were detected along the whole nephron, whereas $^{13}C_5$-ornithine and $^{13}C_1$-guanidineacetic acid were mostly formed in the proximal nephron segments. The same Arg metabolic pathways were also confirmed in the tubules and glomeruli suspensions. Proteinuria did not alter Arg metabolism in glomeruli, however, in proteinuric renal tubules, $^{13}C_5$-glutamate, $^{13}C_5$-proline and $^{13}C_1$-guanidineacetic acid were increased. *In vivo*, in proteinuric animals, Arg was accumulated in the liver. Even though total urea levels showed systemic accumulation in all investigated organs and lower excretion in the urine, the relative abundance of newly synthesized urea was decreased. Arg-derived glutamate was increased mostly in the kidneys, demonstrating significant metabolic rewiring across organ borders.

Conclusions: In proteinuria, arginine metabolism shifts from the liver-focused urea formation towards a more global utilization of arginine in the kidney.

TH-PO563

Clinical Impact of Podometrics and Quantitation of Podocyte Parameters in Patients with IgA Nephropathy (IgAN)

Shoko Ochiai, Masao Kikuchi, Koichi Kaikita, Shouichi Fujimoto.
Miyazaki Daigaku, Miyazaki, Japan.

Background: Podocyte loss and resultant nephron loss are common processes in developing glomerulosclerosis and chronic kidney disease. Podometrics for estimating podocyte number, density, glomerular volume and other parameters in kidney biopsies, can be an important toolbox for monitoring glomerular disease. We validated podometrics in patients with IgAN.

Methods: Biopsy-proven IgAN patients with our hospital from 2019 to 2022 were enrolled in this study (n=44, median age 35.5 years [25-57.5], 45.5% male) and podocyte parameters were measured using the technology of Venkatareddy et al. (JASN 2014). Glomerular volume, mean podocyte volume, and podocyte density were measured and divided into two groups, high and low, respectively, to determine their relationship to clinical characteristics. Podocyte parameters were compared between the groups categorized based on the presence or absence of lesion defined by Oxford MEST-C scores (mesangial hypercellularity: M, endocapillary hypercellularity: E, segmental sclerosis or adhesion: S, interstitial fibrosis and tubular atrophy: T, and crescents: C).

Results: Patients with larger glomerular and podocyte volumes were older and had lower eGFR than those with smaller volumes. Patients with lower podocyte density were older, had lower eGFR, and higher UP/Ucr and urinary NAG/Ucr than those with higher. At the time of kidney biopsy, there were no differences in eGFR and UP/UCr between groups in the M, E, and S categories, nor podocyte parameters. However, T1 and T2 had lower eGFR (36.8 vs. 53.8 mL/min/1.73m^2, p<0.05) and higher urinary NAG/Cre (0.0131 vs. 0.0077 IU/mgCr, p<0.05) versus T0. There was no difference in glomerular volume (2.65 v.s. 2.69 x 10^6 μm^3), but podocyte number and density was lower in T1 and T2 (199 v.s. 218 per glomeruli, 162 v.s. 107 per ×10^6 μm^3, respectively). In addition, urinary NAG/UCr was higher (0.0095 v.s. 0.0061 IU/mgCr, p<0.05) and podocyte volume was smaller in C1 and C2 compared to C0 (2905 v.s. 3395 μm^3).

Conclusions: Podometrics correlated well with clinical characteristics and the Oxford classification at the time of kidney biopsy in IgAN patients. Notably, the association between podometrics (evaluating glomeruli) and the T category (presence or absence of tubular lesions) is intriguing and warrants further investigation, including its relationship to prognosis.

TH-PO564

An Unbiased and Automated Approach: Artificial Intelligence (AI)-Based Pipeline for Glomerulosclerosis Scoring in Rodent Models of CKD

Alex Frias Hernandez, Maria K. Ougaard, Ditte M. Jensen, Michael Christensen.
Gubra AS, Horsholm, Denmark.

Background: Glomerulosclerosis is a kidney disease that involves the formation of scar tissue in the glomeruli in patients with chronic kidney disease (CKD). An accurate histopathological evaluation of glomerulosclerosis plays a crucial role in the diagnosis, prognosis and treatment of people suffering from CKD. Several rodent models mimic glomerulosclerosis and aid in preclinical target identification and drug development for CKD. To accelerate the objective and efficient assessment of glomerulosclerosis, we have designed an AI-powered scoring system using deep learning algorithms, adapted to murine and rat CKD models.

Methods: A deep learning model was trained on a large sample test set (4293 glomeruli images) of mouse and rat PAS-stained kidney sections and compared to expert histopathologist-verified manual glomerulosclerosis scoring. AI model performance was validated using an independent kidney sample set from three different mouse models of CKD (adeno-associated virus-mediated renin overexpression (ReninAAV) in uninephrectomized (UNx) db/db mice as a model of diabetic kidney disease, anti-GBM induced nephritis, and adriamycin-induced nephropathy) as well as 5/6 nephrectomy (Nx)-induced CKD in the rat.

Results: Our AI-based method accurately identify and quantify the severity of glomerulosclerosis (ranging from absence to advanced or global sclerosis, scored from 0 to 4) with exceptional sensitivity and specificity in murine and rat kidney sections. It showed promising efficacy in monitoring the progression of glomerulosclerosis not only in murine models (db/db UNx ReninAAV, anti-GBM and adriamycin mice), but also in nephrectomy 5/6-induced CKD model in rats.

Conclusions: Our AI-based glomerulosclerosis scoring method offers unbiased, accurate and automated glomerulosclerosis assessment in rodent models of CKD. The pipeline is optimized to accommodate both mouse and rat kidney sections, highlighting the applicability to the wide range of rodent models of CKD used in preclinical drug discovery.

Funding: Commercial Support - Gubra

TH-PO565

Urinary Exosomes as Noninvasive Window to Glomerular and Tubular Cells and Their Communication

Sindhu Thiagarajan,[1,2] Janina Kern,[1,2] Nina Sopel,[1,2] Janina Müller-Deile.[1,2]
[1]Universitatsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; [2]Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany.

Background: Although many renal diseases originate in glomerular unit, subsequent damage of tubular cells may lead to alleviate the disease condition. Exosomes are a type of extracellular vesicles, which play a major role in intercellular communication in many diseases. All cells secrete exosomes which carry nucleic acids, proteins, lipids and metabolites to recipient cells. Our previous studies showed the role of microRNAs in intraglomerular communication as well as their disease specific detection in the urine. However, little is known if such communication can be mediated by exosomes and if they also can serve as non-invasive biomarker.

Methods: Characterization of exosomes from the glomerular and tubular cell lines and patients' urines was performed via nanoparticle tracking analysis to identify size and concentration, electron-microscopic imaging to show intact morphology and appropriate size of the exosomes as well as FACS staining and western blotting to detect common exosome markers. Proteome profiling and proteases activity assay of exosomes from cell culture supernatant and respective "mother cells" was used to characterize internal and external exosome cargo. Cell type specific marker in FACS sorting of exosomes was used to identify the cellular origin of urinary exosomes.

Results: Cell culture and urinary derived extracellular vesicles showed typical exosome size, morphology and marker expression (CD63, CD9, CD81). Proteomics of cell culture derived exosomes and mother cells allowed distinct protein cargo characterization of the exosomes. Proteases activity could be detected on exosome surface derived from glomerular cells. Glomerular cell derived exosomes could be detected and isolated via cell sorting from urines of patients with different glomerular diseases giving a non-invasive material for further characterization as potential biomarker.

Conclusions: Podocyte derived exosomes might deliver cargo to tubular cells on their way of being secreted with the urine where they might serve as non-invasive snapshots of their cell of origin. Size wise exosomes should not be able to pass the glomerular basement membrane in vivo. However, the presence of proteases on exosomes might enable the passage of endothelial cell or even systemic exosomes through the GBM to reach podocytes or even tubular cells.

Funding: Government Support - Non-U.S.

TH-PO566

Patients with IgA Nephropathy (IgAN) or IgA Vasculitis (IgAV) Have Significantly Higher Serum Levels of α1-Microglobulin IgA Complexes

Olivier Lardinois,[1] Leesa Deterding,[1] Jason G. Williams,[1] Patrick H. Nachman.[2]
[1]National Institute of Environmental Health Sciences, Mass Spectrometry Research and Support Group, Research Triangle Park, NC; [2]University of Minnesota, Division of Renal Diseases and Hypertension, Minneapolis, MN.

Background: The cause of IgAN and IgAV remains unknown. Patients with IgAN and IgAV who develop nephritis have elevated levels of circulatory IgA1-containing complexes, which contain galactose-deficient IgA1, IgG antibodies and some unidentified proteins. Identification of the key constituents of these protein-protein complexes and the nature of the chemical bonds within the complexes may lead to better understanding of the pathophysiology of IgAN/V.

Methods: Low and high molecular mass IgA forms were isolated from serum of 32 patients with IgAN/V and 12 healthy controls (HC) by affinity-capture on peptide M agarose beads. Various molecular forms of IgA1 were size-separated by gel electrophoresis. Proteins were visualized by Coomassie blue staining or by Western blotting using appropriate antibodies. The relative abundance of each protein within the complexes was estimated by mass spectrometry using a Tandem Mass Tag (TMT)

quantification approach. A sensitive and efficient method for mapping protein disulfide bonds was used to identify the inter-chain disulfide bonds within the complexes.

Results: Immunoblotting demonstrated 1:1 complexes between IgA and albumin, α1-antitrypsin, or α1-microglobulin. Mapping of protein disulfide bonds demonstrated that 1) complexes of albumin and α1-antitrypsin with IgA monomer are disulfide-bound to penultimate C-terminal cysteine on the tailpiece of IgA and 2) α1-microglobulin is linked to IgA by a non-reducible covalent thioether bond to the same cysteine. Of 146 identified proteins, 86 were robustly quantified in the protein complexes using TMT-based quantification, and 15 showed significantly different levels in patients with IgAN/V and healthy controls. The relative abundance of IgA-α1-microglobulin complexes was significantly higher in patients than HC. The association of IgA-α1-microglobulin complexes level and IgAN had an area under the curve (AUC) value of 0.912 (C.I. = 0.840-0.984), significantly higher than other serum candidate diagnostic biomarkers under investigation.

Conclusions: We confirmed the presence of increased levels of IgA-α1-microglobulin complexes in the serum of patients with IgAN compared to HC. The specificity of the complex for IgAN or IgAV is under investigation. IgA-α1-microglobulin complexes could serve as a non-invasive biomarker of IgAN/V.

Funding: Other NIH Support - Intramural Research Program of the National Institute of Environmental Health Sciences

TH-PO567

Identification of Circulating IgA Targeting Chemical Adducts in Patients with IgA Nephropathy

Sara Alibrandi,[1,3] Paolo Molinari,[1,2] Paolo Cravedi,[1] Emmanuel Zorn.[4]
[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Universita degli Studi di Parma Dipartimento di Medicina e Chirurgia, Parma, Italy; [4]Columbia University, New York, NY.

Background: IgA nephropathy (IgAN) is characterized by IgA accumulation in the mesangial area, leading to inflammation and kidney damage. Despite extensive research into its pathophysiology, the trigger for IgA production remains unclear. We hypothesized that the abnormal IgA levels in IgAN may result from a pathological immune response to post-translational protein modifications. To identify potential targets, we used a high-dimensional ELISA platform to assess IgA reactivity patterns in IgAN patients and controls towards post-translational protein modifications, building on our prior research.

Methods: A total of 28 patients with biopsy-proven IgAN and 22 healthy individuals were enrolled. Serum samples were analyzed using a high-dimensional ELISA platform to assess IgA reactivity to 93 natural chemical adducts. Statistical analyses were performed using Boruta algorithm to identify significant targets.

Results: Among the chemical adducts, carboxymethyl lysine (CML) emerged as a prominent target, with significantly higher IgA reactivity in IgAN patients. This reactivity was confirmed in an independent validation cohort of 15 cases and 15 controls and remained significant after adjusting for total IgA levels. IgG reactivity to CML did not differ between groups. Additionally, a positive correlation was observed between IgA reactivity to CML, serum CML levels and albuminuria in IgAN patients.

Conclusions: This study identifies CML as a potential target of IgA in IgAN. These findings highlight the possibility of using IgA reactivity to CML as a diagnostic biomarker for IgAN and provide new insights into the IgAN underlying mechanisms.

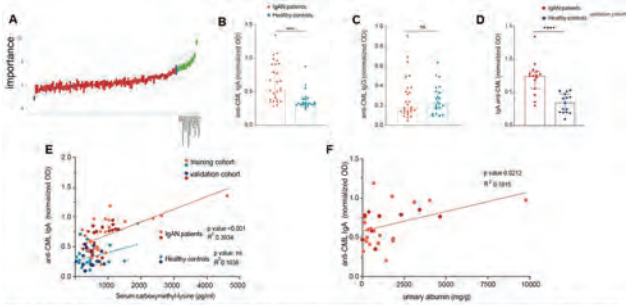


Fig.1: (A) Boxplot of importance distribution of each adduct in Boruta algorithm. Blue boxplots represent a shadow attribute's minimum, average, and maximum Z scores. Z scores of qualities that were rejected and confirmed, respectively, are represented by red and green boxplots. Box plot of IgA (B), IgG (C) and IgA in validation cohort (D) reactivity towards anti CML IgA. OD in IgAN patients and healthy donors. Correlation between urinary albumin and anti CML IgA (E), correlation between urinary albumin and serum CML (F). (ns p > 0.05, * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001)

TH-PO568

Plasma Testican-2 and MGT5A Are Potential Markers of Membranous Nephropathy

Taesoo Kim,[1,2] Aditya L. Surapaneni,[3,4] Insa M. Schmidt,[5,6] Sahir Kalim,[1,2] Anand Srivastava,[7] Ragnar Palsson,[1,2] Isaac E. Stillman,[8] Morgan Grams,[3,4] Sushrut S. Waikar,[5,6] Eugene P. Rhee.[1,2]
[1]Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]NYU Langone Health, New York, NY; [4]New York University Grossman School of Medicine, New York, NY; [5]Boston Medical Center, Boston, MA; [6]Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [7]University of Illinois Chicago College of Medicine, Chicago, IL; [8]Icahn School of Medicine at Mount Sinai, New York, NY.

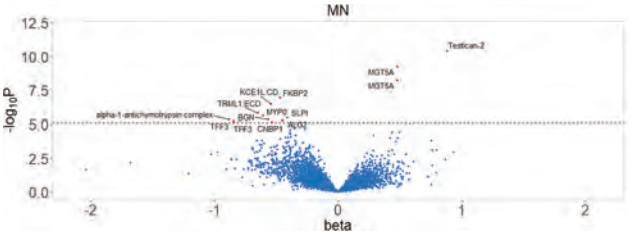
Background: Membranous nephropathy (MN) is a rare cause of chronic kidney disease, most of which require biopsy to diagnose. In select cases, serologic assays such as PLA2R antibodies may help diagnose MN where kidney biopsy is contraindicated, but additional specific markers are needed.

Methods: Among 434 individuals who underwent native kidney biopsy adjudicated by 2 expert pathologists, 39 were diagnosed with MN. We examined the associations between the diagnosis of MN and the 6592 plasma protein levels measured by aptamers using linear regression models adjusted for eGFR, proteinuria and demographic factors. Combined cases of normal kidney and thin basement membrane disease served as a control group (n=26). In sensitivity analysis, we evaluated the associations between each plasma protein level and the diagnosis of MN versus all other diagnoses if the reason for biopsy was proteinuria (n=231). For the proteins identified, we examined the kidney expression of the corresponding genes using publicly available single cell RNA sequencing data from the Kidney Precision Medicine Project (KPMP).

Results: Twelve proteins were associated with the diagnoses of MN. Testican-2 ($P=4.0 \times 10^{-11}$) and MGT5A ($P=5.8 \times 10^{-10}$) were the top 2 proteins with significant associations with MN, higher levels of which were associated with a diagnosis of MN. Both Testican-2 ($P=1.2 \times 10^{-8}$) and MGT5A ($P=3.6 \times 10^{-10}$) remained associated with MN in the sensitivity analysis. In KPMP, *SPOCK2* (encodes Testican-2) and *MGAT5* (encodes MGT5A) showed significant enrichment in podocytes (89% and 71% respectively).

Conclusions: These findings identify Testican-2 and MGT5A as candidate plasma markers of MN, both with literature outlining potential biologic relevance. Additional studies should be directed towards external replication.

Funding: NIDDK Support



Volcano plot of proteins (Log2-transformed) associated MN in linear models adjusted for age, sex, ethnicity, eGFR and proteinuria. Each dot represents an aptamer measuring protein. Some proteins were measured by multiple aptamers. Proteins meeting statistical significance ($P < 0.05/6592$) are labeled

TH-PO569

Unlocking the Role of Transcription Factors in PLCG2 Expression: Implications for Nephrotic Syndrome (NS)

Tarak Srivastava,[1] Daniel P. Heruth,[1] Sean Eddy,[3] Mukut Sharma.[2]
[1]Children's Mercy Kansas City, Kansas City, MO; [2]Kansas City VA Medical Center, Kansas City, MO; [3]University of Michigan, Ann Arbor, MI.

Background: The mechanism of immunopathogenesis of NS in minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) remains unclear. We recently showed elevated expression of a scaffold protein SH3BP2 in MCD and FSGS. SH3BP2 forms a signaling complex with PLCG2, a key enzyme of immune signaling (JCI Insight 2024:e170055) and a candidate gene locus in NS (J Am Soc Nephrol. 2015:1701). To define the role of the SH3BP2/PLCG2 complex in NS we investigated the transcription factors (TFs) regulating PLCG2 expression.

Methods: RNA sequencing data (NEPTUNE consortium) from the glomerular compartment of Control (n=8), biopsy-proven MCD (n=89) and FSGS (n=93) cases were analyzed to (a) identify PLCG2 transcripts and (b) generate a Z-score for each gene for each patient. We used three models to predict TFs regulating PLCG2 expression: JASPAR (jaspar.elixir.no), TFBSpred (michalopoulos.net), and GeneCards (genecards.org). Gene Ontology (GO) analysis was performed using the Panther Knowledgebase (pantherdb.org).

Results: The primary transcript for PLCG2 (ENST00000564138.6; GRCh38.p14) was the most abundant. JASPAR, TFBSpred, and GeneCards predicted 665, 41, and 76

TFs regulating PLCG2, respectively. Data for the 56 TFs identified in more than one dataset were further analyzed. Gene expression for transcription factors IKZF1, MLX, IRF8, POU2F2 and SPI1 increased from Control to MCD to FSGS. Expression of MAX, MEIS2, GLIS2, PKNOX1, ETV2, TFE3, ELF4, SNAI2, ERG, ATF2, NR2C1, KLF9, KLF15, ATF7 and MAZ was significantly different in MCD and FSGS compared to Control. Expression for ETS1, SP1, TFDP1 and MITF was only significantly changed in MCD and that of SMAD5 and GABPA only in FSGS ($p<0.05$ in all comparisons). GO analysis of the 26 transcription factors identified key biological processes including: Developmental (20/26; FDR 8.87E-05), Immune System (11/26; 1.14E-02), Positive Regulation Transcription by RNA PolII (20/26; 6.25E-16) and Negative Regulation of Transcription by RNA PolII (13/26; 2.07E-03).

Conclusions: Identification of these 26 transcriptional regulators of PLCG2 that play a role in Immune System, Regulation of Transcription by RNA PolII and Developmental processes will provide the basis for investigating the role of PLCG2/SH3BP2 complex in the immunopathogenesis of NS and for identifying therapeutic targets.

Funding: Private Foundation Support

TH-PO570

Establishing Methods to Predict Responsiveness to Steroid Therapy at Disease Onset of Idiopathic Nephrotic Syndrome in Children

Chikage Yajima, Yasuko Kobayashi, Yoko Yamasaki, Takumi Takizawa. *Gunma Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Maebashi, Japan.*

Background: Steroid responsiveness is important in predicting the long-term prognosis of kidney function in children with idiopathic nephrotic syndrome. However, there is no method for predicting steroid responsiveness at disease onset in patients with massive proteinuria. Patients require more than 4 weeks of steroid treatment to diagnose steroid-resistant nephrotic syndrome (SRNS); therefore, complications from refractory edema and side effects of steroid therapy could be severe in SRNS patients. There is an urgent need to establish methods that enable the prediction of patient responsiveness to steroid treatment at disease onset.

Methods: We investigated the activation of αvβ3 integrin and Rho GTPases (RhoA, Rac1, and Cdc42), and cell migration activity utilizing healthy human podocyte cell lines (ciPods). Differentiated ciPods were stimulated with serum obtained from patients with steroid sensitive nephrotic syndrome (SSNS, n=14) and SRNS (n=9) at relapse. Activated αvβ3 integrin expressed on the basement membrane of ciPods was measured using the immunofluorescent antibody method with total reflection illumination fluorescence microscopy. Cell lysates were collected after stimulation with serum to quantify active GTPases using enzyme-linked immunosorbent assay. Cell migration was evaluated using scratch assay.

Results: SRNS relapse serum activated αvβ3 integrin in ciPods, whereas SSNS relapse serum did not induce the activation. Relative fluorescence intensity of active αvβ3 integrin was significantly higher with SRNS serum stimulation than with SSNS serum ($p=0.0012$). The area under the receiver operating characteristic curve was 0.8889, and the cut-off point was 0.166, with 78% sensitivity and 93% specificity. The relative absorbance of active Cdc42, which promotes cell motility, showed no significant difference between SSNS and SRNS stimulation ($p=0.3939$); however, in the migration assay, ciPods tended to migrate faster with SRNS serum stimulation than with SSNS serum stimulation ($p=0.0556$).

Conclusions: The αvβ3 integrin activation level on the ciPods basement membrane surface may be useful in differentiating SRNS from SSNS. The ciPods migration assay can be used supplementally to differentiate between SSNS and SRNS. Further investigations using patient serum samples at disease onset are required.

Funding: Government Support - Non-U.S.

TH-PO571

Presence and Intensity of Leptin Expression in the Kidney in Focal Segmental Glomerulosclerosis: Can It Shed Light on the Pathogenesis and Prognosis of the Disease?

Zeynep Ural. *Kirikkale Yüksek Ihtisas Hospital, Kirikkale, Turkey.*

Background: Focal segmental glomerulosclerosis (FSGS) is a primary glomerulopathy often progressing to chronic kidney failure. It can be primary or secondary to factors like drugs, substance use, sickle cell anemia, HIV, parvovirus B19, genetic factors, and obesity. Leptin, a hormone produced by adipose tissue, binds to receptors in endothelial and mesangial cells, inducing cellular proliferation, extracellular matrix accumulation, and type IV collagen production. These effects of leptin are significant in FSGS pathogenesis. This study evaluates the impact of leptin expression in kidney biopsy on renal survival and differentiation between primary and secondary FSGS.

Methods: Patients with FSGS, followed at Gazi University Faculty of Medicine Hospital's Adult Nephrology Clinic for at least two years and who had undergone diagnostic kidney biopsy, were included. Kidney biopsies were stained immunohistochemically with leptin. Demographic characteristics, clinical and laboratory findings, and medical treatments were recorded. The relationship between immunohistochemical staining and clinical findings was evaluated.

Results: A total of 105 patients were evaluated. 23% were Leptin (-), 62% were Leptin (+), and 15% were Leptin (++). Demographic characteristics were similar across groups. There was no relationship between leptin positivity and body weight. Leptin negativity was significantly associated with a good treatment response, while severe leptin positivity was significantly associated with a poor treatment response (both $p<0.05$). Most patients with secondary FSGS showed severe leptin positivity. Among patients with severe leptin positivity, 92% were non-responsive to treatment, compared to 20% in leptin-negative patients.

Conclusions: The role of leptin in kidney diseases has been known, but no prior study demonstrated leptin expression in glomerular diseases. Our study is the first to show leptin expression in the kidneys of FSGS patients and evaluate disease etiology and prognosis based on expression intensity. Leptin can be a guiding biomarker and therapeutic target in terms of renal survival and treatment response in FSGS. Evaluating leptin expression in the kidney can shed light on pathogenesis, assist in individualized treatment, and provide insights into poor renal prognosis, guiding future studies.

Funding: Private Foundation Support

TH-PO572

Translational Strategy to Evaluate Urinary Plasminogen as a Targetable Biomarker of Glomerular Diseases

Marina de Cos, Gohar Mosoyan, Jenny Wong, Justina Ray, Steven G. Coca, Kirk N. Campbell. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Given the heterogeneity of glomerular diseases and necessity of kidney biopsies for predictive purposes, non-invasive biomarkers defining mechanisms underlying progression are needed. Our previous work identified plasminogen as a cause of podocyte injury and established a correlation between plasminogenuria and renal dysfunction. Here, we propose a translational strategy to evaluate the plasminogen as a mediator of podocyte damage and the potential utility of plasminogen inactivation, through urokinase-type plasminogen activator (uPA) inhibition, as a protective strategy.

Methods: To evaluate the predictive value of the basal plasminogen, we performed a multicenter cohort study that included 1010 patients from CureGN with biopsy-proven glomerular disease. The main predictor was urine plasminogen at baseline and Cox regression was used to examine ESKD progression. To test uPA inhibition as a protective strategy, we developed a podocyte surface uPA activity assay in immortalized human podocytes, followed by High-Content Image Analysis of the cytoskeleton and focal adhesions by TIRF-Microscopy of podocytes treated with/without human plasminogen and uPA inhibitors.

Results: In the cohort of patients, adjusted Log_2uPlasminogen/Cr was significantly associated with ESKD (HR per doubling Log_2uPlasminogen/Cr 1.31 (95%CI 1.22-1.40), $P < 0.001$). Comparison of the predictive performance of models including Log2uPlasminogen/Cr, Log_2UPCR or both markers showed plasminogen model superiority. In the cell-surface uPA activity assay, amiloride had a IC50 of 8824 nM (5964-12661), compared to Candidates A and B (amiloride derivatives with computationally predicted increased uPA inhibitory activity), whose IC50 were 334.0 nM (249-397) and 643 (385-955). Quantitative high-content image analysis showed that plasminogen treatment resulted in a reduction in cell area and focal adhesions in plasminogen treated cells. Partial rescue was achieved after amiloride cotreatment whereas Candidates A and B completely reversed the phenotype.

Conclusions: Urinary plasmin(ogen) is independently associated with ESKD in patients with glomerular disease. Plasminogen inactivation by uPA inhibition may be a strategy to reduce podocyte damage. Patients most likely to respond to uPA inhibition could potentially be identified using our urinary biomarker approach.

Funding: NIDDK Support, Other NIH Support - NephCure Kidney International – CureGN Pilot Project Award

TH-PO573

Blood DNA Methylation Is Associated with Histopathological Changes in Patients with Lupus Nephritis

Christine Y. Bakhoum,[1] Patrick C. Demkowicz,[1] Deepika Kumar,[1] Joachim H. Ix,[2] Dennis G. Moledina,[1] Mathieu F. Bakhoum.[1] *[1]Yale University School of Medicine, New Haven, CT; [2]University of California San Diego, La Jolla, CA.*

Background: Approximately 60% of patients with systemic lupus erythematosus (SLE) develop nephritis. Histologically-determined disease classification provides clinically actionable information including administration and intensity of immunosuppression, but requires invasive biopsies. We hypothesized DNA methylation patterns from immune cells would be associated with histopathological changes from kidney biopsy in individuals with lupus nephritis.

Methods: We identified 28 participants from the Yale Kidney Biobank with biopsy-confirmed lupus nephritis. A study renal pathologist graded all kidney biopsies according to the NIH Activity and Chronicity Indices. DNA was extracted from blood buffy coat. DNA methylation was analyzed using Illumina MethylationEPIC V2.0, surveying > 935,000 CpG loci. β-values (percent methylation) were derived using the R Sesame package. We utilized the Bioconductor limma package to determine differentially

methylated loci by overall indices, as well as by each component of disease activity and chronicity. Benjamini-Hochberg method was used for false discovery rate correction.

Results: The cohort was comprised of participants with the following: class I (n=1), class II (n=3), class III (n=5), class III + V (n=3), class IV (n=4), class IV+V (n=1), class V (n=9), and class VI (n=2). The median activity index was 3 (IQR 1, 7). The median chronicity index was 3 (IQR 2, 6.25). In unadjusted analyses, we identified differentially methylated loci ($q < 0.05$) by scores including: fibrinoid necrosis, cellular/fibrocellular crescents, global glomerulosclerosis, fibrous crescents, and total chronicity index (**Table**). After adjustment for age, BMI, sex, and eGFR, loci remained significantly associated with fibrinoid necrosis, cellular/fibrocellular crescents and fibrous crescents.

Conclusions: DNA methylation patterns from immune cells correlate with important histopathologic findings, particularly crescent formation, from kidney biopsy in patients with SLE nephritis.

Funding: NIDDK Support

Table. Differential Methylation Analyses by Histopathological Components of NIH Activity and Chronicity Indices.

Biopsy parameter	Unadjusted Analyses		Analyses adjusted for age, BMI, sex, eGFR	
	Number of CpG loci with q-value < 0.05	Number of CpG loci with p-value < 0.001	Number of CpG loci with q-value < 0.05	Number of CpG loci with p-value < 0.001
Endocapillary hypercellularity	0	496	0	335
Neutrophils/karyorrhexis	0	310	0	260
Fibrinoid necrosis	882	3096	667	2376
Hyaline deposits	0	299	0	245
Cellular/Fibrocellular crescents	3	599	5	744
Interstitial inflammation	0	969	0	2875
Total NIH Activity Index	0	340	0	453
Global glomerulosclerosis	2	1175	0	426
Fibrous crescents	195	1344	176	1029
Tubular atrophy	0	760	0	1512
Interstitial Fibrosis	0	760	0	1512
Total NIH Chronicity Index	2	1149	0	759

TH-PO574

Defining NFκβ-Regulated Biomarkers in Lupus Nephritis Patient Serum

Nicholas A. Shoctor, Makayla Brady, Rebecca Lightman, Shweta Tandon, Dawn J. Caster, David W. Powell. *University of Louisville, Louisville, KY.*

Background: Lupus nephritis (LN) is an autoimmune disease that results from glomerular immune complex deposition and subsequent inflammatory events. Prior studies demonstrate that NF-κβ activation contributes to LN pathogenesis. If NF-κβ-regulated proteins contribute to LN, then we hypothesize that some of these proteins are elevated in LN patients' serum relative to healthy donors (HD).

Methods: The Bio-Plex Pro human immune modulator screening panel was used to measure the contents of serum from 28 LN patients and 8 HD controls. Comparisons of protein concentrations between LN patients and HD were performed using Mann-Whitney tests. Comparisons among HD and the LN genotypes were performed using Kruskal-Wallis tests. Associations between protein concentrations and clinical features were determined using Spearman correlation analyses. All results were corrected for multiple comparisons. Logistic regression models were generated for each independent protein and all possible combinations. Receiver operating characteristic (ROC) curves were used to determine the optimal cutoff concentrations for each protein.

Results: Of the 48 NF-κβ-regulated proteins measured, 25 yielded statistically analyzable results. Three of those 25 proteins, IL-2 receptor alpha (IL-2Rα), macrophage colony stimulating factor (M-CSF), and stem cell factor (SCF), were significantly elevated in active LN patients relative to HD. Moreover, serum from patients who were heterozygous for a previously identified NF-κβ-associated LN risk allele, *TNIP1* rs49958881, contained significantly more of each protein than homozygous LN patients or HD. M-CSF and SCF were positively correlated with UPCR. IL-2Rα and SCF were positively correlated with serum creatinine. SCF was negatively correlated with glomerular filtration rate. The best fitting model included IL-2Rα and M-CSF. The optimal cutoff concentrations were 47.8 pg/mL for IL-2Rα, 12.69 pg/mL for M-CSF, and 64.47 pg/mL for SCF.

Conclusions: The central aim of this project was to characterize immune phenotypes associated with NF-κβ in LN. We've identified three NF-κβ-regulated proteins as candidate markers of LN activity that can be obtained relatively non-invasively. Our findings also further characterize approaches to precision medicine by understanding how genetic profiles influence disease progression and response to available therapies.

Funding: NIDDK Support

TH-PO575

Retinol Binding Protein 4 Is a Marker for Proteinuria in Humans and Zebrafish

Jan René Haak,[1,2] Cathiana Kolb,[1] Lena Pollinger,[1] Melanie Grosch,[1] Iain A. Drummond,[2] Hermann Haller,[2] Friedhelm Hildebrandt,[3] Mario Schiffer,[1,2] Markus M. Rinschen,[4] Tilman Jobst-Schwan.[1,2] *[1]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [2]Mount Desert Island Biological Laboratory, Salsbury Cove, ME; [3]Division of Nephrology, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA; [4]Aarhus Universitet Institut for Biomedicin, Aarhus, Denmark.*

Background: A clinical hallmark of glomerular kidney diseases is proteinuria. In humans, proteinuria is described as the urinary albumin-creatine-ratio. The zebrafish is a widely used model in kidney research. However, up to date proteinuria detection in zebrafish requires transgenic lines, because the zebrafish does not possess an albumin orthologue. Although allowing for proteinuria-related kidney research in zebrafish, these transgenic lines may possess altered physiology and lack direct translational potential to human health.

Methods: We performed proteomics on fish water samples of zebrafish larvae with a described glomerular damage phenotype (*magi2a*^{cl604}). We designed and 3D-printed a custom dot blot plate to subject water samples of zebrafish larvae individually housed for 24 hours on a PVDF membrane. Assessment of proteinuria was performed by detecting Rbp4 on the membrane. To induce glomerular damage, different transgenic lines, a chemical induction model and somatic CRISPR knock-out models were used. Additionally, a fluorescent eye assay using the transgenic line *Tg(lfab:VDBP-eGFP)* was performed to compare the performance of the novel assay to a standard zebrafish proteinuria assay.

Results: Using a proteomics approach, we found high abundance of rbp4 in fish water of edema fish compared to control fish. It has been shown before that RBP4 is proteinuria marker in humans as well. Based on that, we developed a dot blot-based assay where fish water is used to quantify proteinuria in individually housed zebrafish larvae by immunodetection of Rbp4. Using four different established models to induce proteinuria in zebrafish, we validated the dot blot-based assay.

Conclusions: We developed a novel proteinuria assay in zebrafish based on the endogenous orthologue of a known human proteinuria marker. This assay allows for individual proteinuria assessment, independent of transgenic zebrafish lines and with a higher physiological relevance. Thereby, we established a novel translational assay that is useful for drug discovery as it is scalable and suitable for high-throughput procedures.

Funding: Other NIH Support - P20GM103423 and P20GM104318, Government Support - Non-U.S.

TH-PO576

Expanding the Use of Surface Plasmon Resonance (SPR) for Characterizing Nephritic Factors in Patients with C3 Glomerulopathy (C3G)

Christopher Culek, Cecelia F. Fierce, Carla M. Nester. Molecular Otolaryngology and Renal Research Laboratories. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Nephritic factors (Nefs) are convertase-directed autoantibodies present in up to 80% of C3 glomerulopathy patients.[1] Despite this prevalence and the associated complement dysregulation, there remains much to be learned about Nef characteristics. Previous work used SPR to show Nefs drive disease by stabilizing the convertase and amplifying complement activity.[2] However, this work was unable to characterize patients with Nefs sensitive to regulation by DAF or FH (scenarios evident in our patient population). This deficiency limits our understanding of individual patients and opens the possibility that we are missing populations of Nefs all together. We sought to develop a simple regulator-independent SPR technique that can provide a reproducible half-life of the Nef-convertase interaction.

Methods: C3b was immobilized to an SPR microfluidic chip at 1200RUs. Several concentrations of FB, FD, and IgG were co-injected onto the C3b ligand to form convertase-IgG complexes. The complex dissociated at 37C for 600 seconds (~6-7 half-lives of reagent convertase), to allow total decay of unbound convertase complexes. Then the sensorgram was normalized to 100RUs. The estimated half-life was calculated as the time at which the sensorgram reached 50RUs remaining. We evaluated nine replicates of one polyclonal Nef-positive IgG test subject and five Nef-negative test subjects.

Results: Both the Nef-positive and Nef-negative polyclonal IgG show specificity to the convertase, as previously supported.[3] The Nef-positive stabilization half-life ranged from 2072 to 2084 seconds with a mean of 2080, while the Nef-negative stabilization half-lives ranged from 464 to 598 seconds. The Nef-positive sample had low variability with a SD of only 4.609, and a SE of 1.537. The estimated half-life was independent of the concentration of FB or FD.

Conclusions: This data suggests our approach was able to reproducibly provide an estimated half-life for the Nef-convertase complex. Furthermore, it shows distinct

kinetics between the Nef-positive and Nef-negative autoantibodies. The assay expands the scope of current Nef evaluation by removing the requirement of complement regulator proteins in the kinetic analysis and provides valuable kinetic information for evaluating complement dysregulation in Nef-positive C3G patients regardless of regulator sensitivity.
Citations 1. PMC3280037 2. PMC3608896 3. PMC10695638

Funding: NIDDK Support, Private Foundation Support

TH-PO577

Establishment of a Human Hybridoma Cell Line That Produces IgG Autoantibody Involved in the Pathogenesis of IgA Nephropathy

Tzu Yu Liu,[1] Ann Chen,[2,3] Shuk-Man Ka.[4] *[1]Graduate Institute of Life sciences, Department of Medicine, National Defense Medical Center, Taipei, Taiwan; [2]Taiwan Autoantibody Biobank Initiative, Hualien Tzu Chi Hospital, Hualien, Taiwan; [3]Department of Anatomical Pathology, Hualien Tzu Chi Medical Foundation, Hualien, Taiwan; [4]Graduate Institute of Aerospace and Undersea Medicine, Department of Medicine, National Defense Medical Center, Taipei, Taiwan.*

Background: IgA nephropathy (IgAN) is an autoimmune disease, also the most common primary glomerulonephritis. Because the pathogenesis underlying IgAN remains largely known, there is still a lack of disease-specific and effective treatment for the renal disease. Recently, there is a key issue in the pathophysiology of galactose deficiency of *O*-glycans on the hinge region of IgA1, which has been considered as a main autoantigen (auto-Ag) involved in the development and progression of IgAN. However, the mechanistic pathways, including: **(1)** resultant production of IgG autoantibody (auto-Ab) against the galactose-deficient IgA1 (Gd-IgA1) auto-Ag triggered by the a auto-Ag; **(2)** subsequent formation of IgG-IgA1 immune complexes (ICs) and their potential in pathogenicity and clinical implications as well as **(3)** the property of the deposition of the ICs in the microenvironment of the glomeruli, in terms of the levels of intensity and distribution, are warranted further investigation.

Methods: To this end, our lab has successfully established exclusively a human hybridoma production platform suitable for preparing human IgG auto-Ab against Gd-IgA1 auto-Ag and the latter proteins. This strategy and the platform rendered a tremendous advantage for us to unravel the pathogenesis involving human IgG auto-Abs and IgA1 auto-Ags in this autoimmune disease towards the understanding of the immune and molecular pathogenesis of IgAN and further translational and clinical research topics. Our preliminary results show that using a SPYMEG human partner cell system and peripheral blood mononuclear cells from IgAN patients.

Results: We first time developed three human hybridoma cell lines from a single (the same) patient with IgAN namely Teddy71 (IgG auto-Ab) and 71D2 and 71C6 (two different IgA1 auto-Ags). In human macrophages and renal mesangial cells, the ICs formed by the human IgG auto-Ab with either of the two distinct human Gd-IgA1 auto-Ags clearly stimulated these cells to produce IL-1β, TNF-α, and IL-6 in significantly different levels, suggesting the nature of auto-Ags itself may also play a key role in resultant inflammatory responses in IgAN.

Conclusions: In consistence with these effects, the ICs containing human IgG auto-Ab and individual IgA1 auto-Ags was able to activate common pathway of complement system *in vitro*.

Funding: Government Support - Non-U.S.

TH-PO578

Ex Vivo Kidney Perfusion as a Model for Recurrent Focal Segmental Glomerulosclerosis

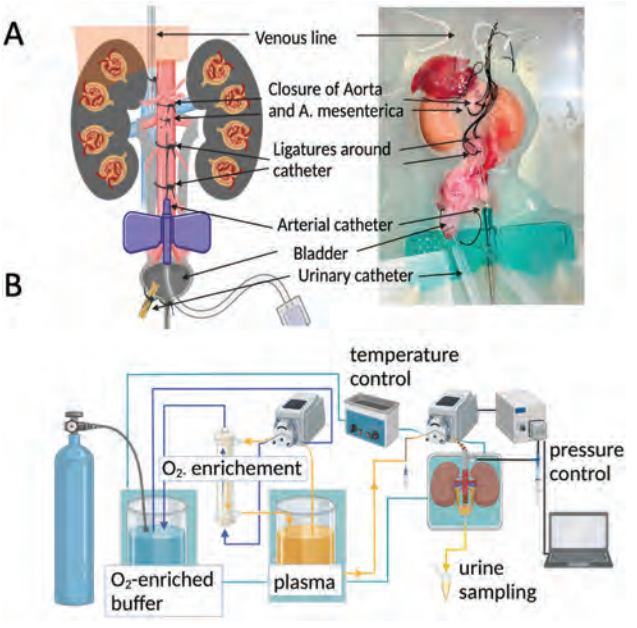
Anne K. Muehlig,[1,2] Fabian Braun,[1,2] Paula F. Rischke,[1] Jun Oh,[1] Sonja Haenzelmann,[3] Manuela Poets,[3] Madelaine Wingerath,[1] Inka C. Homeyer,[1] Oliver Kretz,[1,2] Victor G. Puelles,[1,2] Jan Czogalla,[1,2] Tobias B. Huber.[1,2] *[1]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Hamburg Center for Kidney Health, Hamburg, Germany; [3]Universitatsklinikum Hamburg-Eppendorf Zentrum fur Molekulare Neurobiologie Hamburg, Hamburg, Germany.*

Background: Primary focal segmental glomerulosclerosis (FSGS) recurs in about 40%, indicative of a yet unidentified circulating factor. Recently, we detected several novel pathways in an *in vitro* model of podocytes incubated with recurrent (r)FSGS patient sera. To characterize their importance under conditions of intact glomerular integrity, we used *ex vivo* perfusion of mouse kidneys with plasma from rFSGS-patients.

Methods: Kidneys of transgenic podocyte-reporter mice were perfused with plasma from 5 different rFSGS patients and 3 controls (fig 1) (n=20). The glomerular physiology, ultrastructure, protein- and mRNA expression were analyzed using urinanalysis, immunofluorescence, electron microscopy and mRNA bulk sequencing of isolated glomeruli.

Results: Perfusion with rFSGS plasma resulted in an impairment of the filtration barrier, foot process effacement, downregulation of the podocyte marker synaptopodin, remodeling of podocytes and detection of human albumin in the urine of perfused kidneys. mRNA bulk sequencing of glomeruli revealed 802 differentially regulated genes. In rFSGS plasma perfused kidneys integrin b1 and fibronectin were both strongly regulated in the same direction as in rFSGS serum-incubated podocytes in our previous experiments.

Conclusions: *Ex vivo* perfusion with rFSGS plasma resulted in a disruption of the glomerular filtration barrier and was able to recapitulate our previous *in vitro* findings. This study validates ex vivo perfusion of mouse kidneys with human plasma as a model to study rFSGS in the intact cellular architecture. This model represents a valuable tool to identify and target new FSGS pathomechanisms.



Isolated perfused mouse kidneys (A) and perfusion set up (B)

TH-PO579

Functional Impact of COL4A3/4A4 Variants in Patients with Nephrotic Syndrome

Jennifer Lai Yee,[1] Veronica Glaser,[1] Damian Fermin,[1] Michelle N. Rheault,[2] Alessia Fornoni,[3] Jacob O. Kitzman.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Minnesota Medical School, Minneapolis, MN; [3]University of Miami, Coral Gables, FL.*

Background: The increasing prevalence of genetic testing in patients with kidney disease has led to the frequent identification of variants in *COL4A3/4A4*, which are vital components of the kidney's glomerular basement membrane. However, the diverse clinical manifestations of these variants remain poorly understood, and the lack of specific functional assays hampers the assignment of variant pathogenicity. We aim to investigate the functionality of *COL4A3/4* in a cell-based collagen trimerization assay and study its impact on disease in a longitudinal observational cohort with nephrotic syndrome (NEPTUNE).

Methods: Patients with a heterozygous *COL4A3/4* variant (n=32 heterozygous, n=1 homozygous) have been identified in the NEPTUNE cohort. We employed an established split luciferase assay to test trimerization (intracellular signal) and secretory effect (extracellular signal) of these variants. We created several known pathogenic, benign, and rare *COL4A3/4* variants found in NEPTUNE and cloned them into the corresponding expression constructs. Intracellular and extracellular NanoLuc luciferase activity was then measured in 293T cells. Finally, we compared these in vitro functional activities with the clinical outcomes of the patients by a descriptive analysis.

Results: Low luciferase activity, either intracellularly or extracellularly, corresponded well to the expression constructs bearing the known pathogenic variants. 3 patients' *COL4A3* variants were successfully cloned and suggested to have a trimerization defect (N=1), secretory defect (N=1), and mild abnormality (N=1 with *APOL1* high-risk genotype) based on intracellular and extracellular luciferase activity. The patient with a variant of trimerization defect had a kidney biopsy showing Alport findings. Both patients with a variant of secretory defect and mild abnormality were pediatric patients with progressive kidney disease (eGFR < 60 at baseline or a 40% loss of eGFR during follow-up).

Conclusions: These findings underscore the potential of the split luciferase assay as an effective functional assay for distinguishing benign and pathogenic *COL4A* variants. This paves the way for future development of the split luciferase as a clinical test to inform the variant pathogenicity and prognosis, and can enable more precise disease classification to foster further research development in NEPTUNE.

Funding: Other NIH Support - NETPUNE career development

TH-PO580

Systematic Classification of WT1 Zinc Finger Missense Mutations Using Multiplex Assays of Variant Effect (MAVEs)

Jennifer Lai Yee, Veronica Glaser, Jacob O. Kitzman. *University of Michigan, Ann Arbor, MI.*

Background: Patients with Mendelian nephrotic syndrome (NS) face a high risk of progressing to end-stage kidney disease. Genetic screening is increasingly accessible and can guide clinical decisions. However, it remains challenging to accurately class variant's pathogenicity. MAVEs are a new category of functional assay that can be applied to many variants at one time in a pooled fashion. Here we apply MAVEs to systematically and prospectively test variants in the zinc finger domains of *WT1*, one of the most common genes underyling Mendelian NS.

Methods: We derived clonal *WT*1 knockout (KO) cell lines from KBM7, a myeloid leukemia cell line that normally expresses *WT1*. We then synthesized a saturation mutagenesis library for *WT1* cDNA, encompasing every possible missense mutation across three zinc-finger motifs (exons 7-9, n=1028 mutations). This library was stably integrated into KBM7 *WT1* KO cells using a lentiviral indcuble expression construct, such that each cell expresses a different *WT1* variant. Because *WT1* loss of function is growth-promoting in KBM7 cells, we performed serial outgrowth of the *WT1* library population for four passages to enrich for loss-of-function mutatinos. We then deeply sequenced the *WT1* library from cells at passage 4 v.s. baseline, and calculated an enrichment score of each mutation.

Results: We observed perfect separation between nonsense and synonymous mutations in functional scores. Missense variants were nearly all deleterious to some extent (89%), with nearly a third of these being equivalently deleterious to a nonsense variant, indicating a strong constraint against coding variation in this key DNA-binding domain. Nevertheless, some mutations have relatively mild effects, especially R435Q, which is also present in apparently unaffected individuals in the general population. Mutations at essential residues that coordinate Zn^{2+} ions were particularly deleterious, comparable to truncating mutations.

Conclusions: The completion of a variant-to-effect map for this region validates the feasibility of extending this approach to the full *WT1* protein. The maps will serve as a freely available 'lookup table' of functional evidence to support the clinical interpretation of newly encountered variants. This approach can improve the accuracy of genetic diagnosis for NS and remove one barrier to future genotype-guided therapies.

Funding: Other NIH Support - 5K12HD028820-28:Clinical Scientist Institutional Career Development Program Award

TH-PO581

Ex Vivo-Derived Human-Induced Pluripotent Stem Cell (hiPSC) Podocytes from a Patient with Genetic Focal Segmental Glomerulosclerosis with an INF2 Mutation

Victoria Rose, Denise Fink, René Krüger, Johannes Schödel, Mario Schiffer, Janina Müller-Deile. *Universitatsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany.*

Background: Genetic focal segmental glomerulosclerosis (FSGS) is caused by mutations in podocyte genes related to slit diaphragm formation, actin cytoskeleton or cellular adhesion but knowledge on the consequences of these mutations is limited. Usually genetic FSGS is not responsive to immunosuppression even though partial responses have been documented in some mutations most likely due to direct effects of these agents on podocytes themselves. Patient-specific podocyte models that carry the patient's mutation might help to further characterize the diseased podocyte phenotype and test response to potential treatment options *ex vivo*.

Methods: Human induced pluripotent stem cell (hiPSC)-derived podocytes (hiPSC-Podocytes) were generated by reprogramming dermal fibroblasts, obtained from a human skin punch biopsy, into hiPSCs with subsequent differentiation into podocyte cell type. Healthy donor-derived hiPSC-Podocytes were compared to commonly used conditionally immortalized (ciPodocytes) by bulk RNA sequencing and electron microscopy. Patient-specific hiPSC-Podocytes holding an inverted formin 2 (INF2) mutation were used to assess phenotypical and functional alterations in a personalized manner *ex vivo*.

Results: Compared to ciPodocytes, hiPSC-Podocytes had a higher developed phenotype with better podocyte marker expression, and foot processes. Patient-specific hiPSC-Podocytes showed unbranched and shorter protrusions, loss of podocyte-specific marker and decreased levels of filamentous actin. Furthermore, an increased actin depolymerization rate, altered INF2 cleavage, and other compensatory mechanisms were identified. First treatment experiments with immunosuppressive drugs and actin-modulating agents resulted in improvement of filamentous actin in patient-specific INF2 mutated hiPSC-Podocytes.

Conclusions: Using a patient-specific hiPSC-based model enables investigation of the patient-specific diseased phenotype and response to treatment *in vitro* and allows further studies of podocyte mutations. This will provide valuable insights into patho-mechanisms and may help identify individualized therapeutic strategies. Moreover, patient-derived hiPSCs allow to create patient-specific 3D kidney organoids to study multi-cellular and -structural differences.

Funding: Government Support - Non-U.S.

TH-PO582

Investigating Organoid Characteristics of CoQ10-Deficient Glomerulopathy

Seyoung Yu,[1] Friedhelm Hildebrandt,[2] Heon Yung Gee.[1] *[1]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [2]Boston Children's Hospital, Boston, MA.*

Background: Monogenic causes account for 11-30% of steroid-resistant nephrotic syndrome (SRNS) cases in children. Genes involved in the biosynthesis of coenzyme Q_{10} (CoQ_{10}), such as PDSS2, COQ2, COQ6, and ADCK4, are known to cause SRNS and focal segmental glomerulosclerosis (FSGS). CoQ_{10}, located in the mitochondrial inner membrane, is crucial for supporting the electron transport chain in oxidative phosphorylation and for protecting against oxidative stress. While CoQ_{10}-deficient glomerulopathy can be partially treated with CoQ_{10} supplements, the effectiveness of this treatment varies and has limitations. We developed an in vitro model system of CoQ_{10}-deficient glomerulopathies to study drug effects through detailed manipulations, which facilitates a better understanding of the disease and the creation of more effective treatments

Methods: We generated CoQ_{10}-deficient kidney organoids from human induced pluripotent stem cells (iPSCs) using the well-established in vitro induction protocol. To establish CoQ_{10}-deficient human iPSCs, we used synthetically generated gRNAs targeting PDSS2, COQ2, COQ6, ADCK4 along with Cas9 protein. We performed immunostaining and light microscopy analysis to evaluate the extent of their differentiation. We also observed mitochondrial morphology to investigate the phenotypic characteristics due to CoQ_{10} deficiency.

Results: Gene ablation of CoQ_{10}-deficient iPSCs was confirmed through Sanger sequencing. CoQ_{10}-deficient kidney organoids expressed positive kidney markers and successfully differentiated into nephrons. To model glomerulopathy in these organoids, we verified the expression of podocyte markers and confirmed their development using electron microscopy. The podocytes displayed primary processes and cell-cell junctions, resembling the early stages of foot process formation. There were no significant differences in podocyte development between control and CoQ_{10}-deficient kidney organoids. However, examining the ultrastructure of podocytes in CoQ_{10}-deficient kidney organoids revealed abnormal mitochondria, characterized by hyperproliferation and increased size.

Conclusions: In conclusion, we have generated a model of CoQ_{10}-deficient glomerulopathy using kidney organoids, demonstrating abnormal mitochondrial phenotypes. This system provides a valuable platform for testing potential drug therapies and advancing treatment options for this condition.

TH-PO583

Comparative Analysis of Human Primary Mesangial Cell Clones: Implications for Experimental Design

Kerstin Ebefors, Alva Johansson, Gayathri Narasimhan, Jenny C. Nystrom. *Goteborgs universitet Sahlgrenska Akademin, Gothenburg, Sweden.*

Background: Mesangial cells (MCs) not only form the central stalk of the glomerulus but are of importance for glomerular cross talk and function. The MCs are central in several glomerular diseases such as IgA nephropathy and diabetic kidney disease and are often used in vitro to reveal molecular mechanisms of onset and progression. Human primary MCs (HMCs) are considered the best option for in vitro studies, but over the years we have observed that there are differences between HMCs from different suppliers (and hence donors) in their phenotype and response to stimuli and/or treatment

Methods: Commercially available HMCs from two different suppliers were cultured and characterized by their expression of mesangial markers (qPCR, western blot, immunofluorescence, mass spectrometry), response to PDGF-BB (proliferation assay, mass spectrometry) and angiotensin 2 (contractility assay). In addition to the commonly used MC markers we put together a list of 144 MC markers, compiled based on 12 recent articles containing omics data, and these markers were used combination with the proteomic data set.

Results: Both clones (HMCv1 and HMCv2) expressed the common MC markers and in the proteomic data set, 70 out of the 144 MC markers were found for both. HMCv1 and 2 and responded with increased proliferation in response to stimulation with PDGF-BB. HMCv1 contracted significantly in response to angiotensin 2, but not HMCv2. Proteomic analysis of HMCv1 and 2 after stimulation with PDGF-BB revealed that HMCv1 was much more responsive than HMCv2 in terms of more differentially regulated proteins and pathways.

Conclusions: In conclusion, we found that there were similarities as well as differences between the two clones of HMCs. Both HMCv1 and HMCv2 behaved as MCs in that they expressed the major MC markers and responded to PDGF-BB stimulation. However, HMCv1 was much more responsive to stimulation with PDGF-BB and angiotensin 2 than HMCv2. These differences could have a major impact on the outcome of experiments performed using these cells, and therefore we suggest to carefully examine the response of the chosen HMC clone to relevant stimulants before conducting experiments on HMCs. In addition, out of our list of 144 MC markers, the clones were found to express 70 and we suggest that these markers can be used as a signature for MCs.

Funding: Private Foundation Support

TH-PO584

Discovery of Epigenetic Substances for the Treatment of FSGS Using Zebrafish Larvae as an In Vivo Model

Nicole Endlich, Maximilian Schindler. *Universitatsmedizin Greifswald, Greifswald, Germany*.

Background: Podocytes are essential cells of the glomerulus that maintain the size selectivity of the glomerular filtration barrier. Injury to these postmitotic cells is a major cause of FSGS often resulting in end-stage kidney disease. To date, no specific drugs or compounds have been discovered to protect podocytes, underscoring the significant unmet need for drug development. Our group recently established a high-content *in vivo* screening assay to discover potential drugs and compounds to treat FSGS. For this purpose, we used zebrafish larvae that develop a filtering glomerulus within 4 days and we analyzed the effect of epigenetic substances after the induction of FSGS.

Methods: A transgenic zebrafish screening strain expresses the bacterial enzyme nitroreductase as well as the fluorophore mCherry exclusively in podocytes. Furthermore, the expression of a circulating 78 kDa vitamin-D-binding fusion protein with eGFP provides a readout for the integrity of the glomerular filtration barrier in the vasculature. Addition of the prodrug Nifurpirinol (NFP) to the water results in a specific podocyte injury, a loss of mCherry in the glomerulus and a decreased eGFP fluorescence between 4 and 6 days post fertilization (dpf). After 6 dpf, larvae develop proteinuric edema and classical hallmarks of FSGS due to podocyte injury. These readouts were utilized in a rapid, imaging-based screening of an epigenetic drug library as reported in Schindler et al. 2023. Drugs and compounds that prevent a loss of fluorescence or the development of edema were further validated.

Results: The screening of epigenetic drugs revealed that PTACH as well as the substances MN876 and MN119 showed a high potency to alleviate larval FSGS and exhibited a prolonged protective effect on podocytes.

Conclusions: We have identified three promising new drugs/compounds for the treatment of FSGS in zebrafish larvae that are currently under validation in mammalian FSGS models.

Funding: Private Foundation Support

TH-PO585

Glomerular Disease Caused by Vinyl Carbamate in A/J Inbred Mice: A Novel Model of Membranoproliferative Glomerulonephritis (MPGN)

Athena Y. Gong,[1,2] Lance D. Dworkin,[2] William T. Gunning,[2] Mengxuan Chen.[2] *[1]University of Michigan, Ann Arbor, MI; [2]The University of Toledo Medical Center, Toledo, OH.*

Background: Ethyl carbamate (EC) is a process contaminant in fermented foods and alcoholic beverages. Metabolic conversion of EC generates vinyl carbamate (VC), a carcinogenic metabolite. EC, as a Group 2A probable human carcinogen, and the more potent VC, are known to cause tumors in rodents. However, their effects on the kidney are unknown.

Methods: A/J inbred mice received a single i.p. injection of VC (60 mg/kg). Kidney injury was evaluated. A *post hoc* analysis was performed on a publicly available RNA-Seq transcriptome of kidneys derived from rats treated with fermented wine containing high concentrations of EC.

Results: Beginning 5 weeks post VC injection, mice showed signs of moribund state and were killed. By 12 weeks, a total of 97 of the 240 treated mice had died or were killed. Necropsies of mice revealed evident renal disease, characterized by glomerular lobularization, mesangial hypercellularity and expansion, endocapillary proliferation, and capillary wall thickening by light microscopy. Electron microscopy revealed subendothelial electron-dense deposits, formation of new basement membrane between the interposed cell and endothelium, and extensive podocyte foot process effacement. On immunofluorescent staining, abundant granular mesangial C3 staining was noted along with coarse linear capillary staining, whilst immunoglobulin staining was negative. These changes were highly reminiscent of the pathology of MPGN. In addition, Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed on differentially expressed genes between high EC-treated and control rats, and showed that complement and coagulation cascades are top predicted biological processes implicated. Furthermore, pathway-based data integration and visualization using Pathview demonstrated that key regulators of complement activation pathways were altered by high EC treatment. Among these, complement factor (CF) D and H, critical positive and negative regulators of the alternative pathway, respectively, were the most affected, with CFD induced by 3.49-fold and CFH repressed by 5.88-fold, underscoring a hyperactive alternative pathway.

Conclusions: VC, a metabolite of EC, induces complement fixation in glomeruli and MPGN in mice. Complement overactivation due to CFD induction and CFH repression may be an underlying pathomechanism.

TH-PO586

Belimumab and Rituximab for the Treatment of Primary Membranous Nephropathy: Initial REBOOT Results

Patrick H. Nachman,[1] Lia Stelzig,[2] Matthew A. Sherman,[3] William T. Barry,[2] Sharon Chung.[4] On behalf of the REBOOT Study Investigators. *[1]University of Minnesota Medical School, Minneapolis, MN; [2]Rho Inc., Durham, NC; [3]National Institute of Allergy and Infectious Diseases, Bethesda, MD; [4]University of California San Francisco, San Francisco, CA.*

Background: Primary membranous nephropathy (PMN) is caused by glomerular immune complex deposition, and 70% of patients produce anti-phospholipase A_2 receptor (PLA_2R) autoantibodies. We hypothesize that treatment with belimumab (BEL) and rituximab (RTX) will enhance memory B cell depletion, curb the re-emergence of autoreactive B cells, and lead to better clinical responses compared to RTX alone.

Methods: REBOOT (NCT03949855) is a two-part, phase 2, multicenter, clinical trial examining the effectiveness of BEL with RTX for the treatment of PMN. Participants (18-75 years) must have detectable serum anti-PLA2R and proteinuria ≥ 4 g/d. Part A is a single arm, open-label, pharmacokinetic study, where all participants receive BEL 200 mg weekly for 52 weeks and RTX 1000 mg at weeks 4 and 6. Participants are followed for complete (CR, proteinuria ≤ 0.3 g/d with serum albumin ≥ 3.5 g/dL) or partial remission (PR, proteinuria < 3.5 g/d with ≥50% reduction from baseline) to week 156. We present the initial clinical results for Part A.

Results: 17 participants (mean age 56 years) started BEL and RTX; 5 stopped BEL prior to week 52 (COVID-19 [n=2]; infection, mood swings, worsening kidney function [1 each]). 9 participants have completed BEL and reached week 104 so far. Table 1 presents baseline characteristics and clinical outcomes. 89% (8/9) achieved CR or PR by week 104. The proteinuria decline, anti-PLA_2R reduction, and serum albumin normalization persisted for 1 year after stopping BEL without additional RTX or other immunotherapy.

Conclusions: A large proportion of evaluable participants have attained PR or CR with BEL and RTX so far. A rapid decline in anti-PLA2R and normalization of serum albumin also occurs. Part A followup continues, and Part B, a randomized, double-blind, placebo-controlled trial comparing BEL with RTX to RTX alone, is enrolling to assess the effectiveness of this treatment strategy.

Funding: Other NIH Support - REBOOT is conducted by the Immune Tolerance Network, which is supported by the National Institute of Allergy and Infectious Diseases (UM1-AI-109565), Commercial Support - Belimumab was provided by GSK plc.

Clinical Outcomes for REBOOT Part A.

Timepoint (# evaluable participants)	Baseline (n=17)	Week 24 (n=13)	Week 52 (n=12)	Week 104 (n=9)
CR or PR (% achieved)	0	23	67	89
Anti-PLA_2R (% detectable)	100	15	17	0
Proteinuria (g/d), median (interquartile range)	11.2 (8.2-16.7)	5.5 (3.7-9.3)	2.1 (1.1-4.9)	1.0 (0.5-2.7)
Serum albumin (g/dL), median (interquartile range)	2.6 (2.3-2.9)	3.6 (3.3-3.7)	4.1 (3.8-4.3)	4.3 (4.2-4.5)
Serum creatinine (mg/dL), mean (standard deviation)	1.2 (0.3)	1.3 (0.4)	1.1 (0.4)	1.2 (0.2)

Anti-PLA2R = anti-phospholipase A2 receptor autoantibody, CR = complete remission, PR = partial remission

TH-PO587

A Phase 1b, Single-Arm, Open-Label Study of Budoprutug, an Anti-CD19 Monoclonal Antibody with Enhanced Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC), in Primary Membranous Nephropathy

Frank B. Cortazar,[1] William Bonificio,[2] Naveen Daryani,[2] Stephen B. Thomas.[2] *[1]New York Nephrology, Vasculitis and Glomerular Center, Albany, NY; [2]Tenet Medicines, Scotch Plains, NJ.*

Background: Membranous nephropathy (MN) is characterized by a histologic pattern of injury caused by autoantibodies directed against podocyte antigens. Targeting B lymphocytes with anti-CD20 monoclonal antibodies has become a preferred therapy for primary MN, but this strategy fails to induce complete remission (CR) in most patients. Budoprutug is an anti-CD19 monoclonal antibody with a broader spectrum of B-cell depletion, including activity against CD19-positive plasmablasts and plasma cells. Here, we present the results of a Phase 1b, open label, dose escalation study of budoprutug in patients with primary MN.

Methods: Eligible patients had primary MN with a history of nephrotic syndrome, received maximally tolerated therapy with a renin-angiotensin system inhibitor for 6 months, and had a urine protein to creatinine ratio (UPCR) of > 2 g/g on two measurements during screening. Budoprutug was administered as 2 bi-weekly doses of 100 or 200 mg six months apart on Days 1,15,169, and 183. The primary objective was safety. Secondary objectives included B-cell levels, anti-phospholipase A2 receptor (anti-PLA2R) antibody (Ab) levels, and changes in proteinuria. The analysis was restricted to patients with at least 48 weeks of follow-up.

Results: Five patients met inclusion criteria, 3 of which were PLA2R Ab positive. All patients achieved complete B cell depletion, with 2 patients reconstituting B-cells before Week 24. Serologic remission was achieved in all anti-PLA2R Ab positive patients over a range of 5 to 18 weeks. Median baseline proteinuria was 4.2 g/g. Three patients achieved complete remission (UPCR ≤ 0.3 g/g, range, 40 to 48 weeks), with a fourth patient achieving a UPCR of 0.33 at week 48. All patients achieved a UPCR < 1 g/g and partial remission. Two patients with 72 week follow up achieved durable CRs ~18 months from initial dosing. Budoprutug was well tolerated with no drug-related serious or Grade ≥3 adverse events.

Conclusions: Treatment with budoprutug resulted in high rates of serologic and clinical remission, suggesting that CD19-targeted B-cell depletion may be a promising approach to the treatment of primary MN. These findings warrant larger studies to confirm the efficacy of budoprutug in MN.

Funding: Commercial Support - ValenzaBio, Acelyrin, Tenet Medicines

TH-PO588

Randomized Controlled Trial Comparing Rituximab to Mycophenolate Mofetil in Children and Young Adults with Steroid-Dependent Idiopathic Nephrotic Syndrome

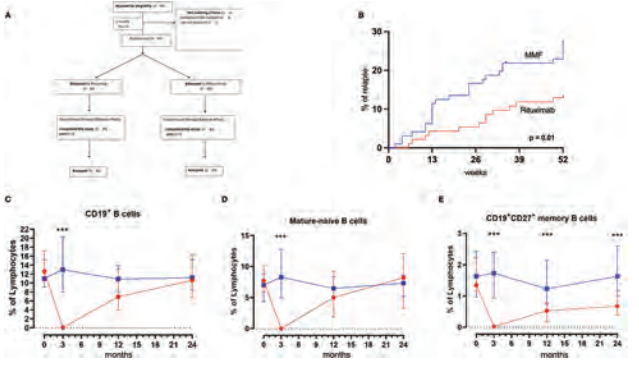
Andrea Angeletti,[1] Gianluca Caridi,[1] Francesca Lugani,[1] Marina Vivarelli,[2] Francesco Emma,[2] Gian Marco Ghiggeri,[1] Manuela Colucci,[2] Antonio Gargiulo,[2] Paolo Cravedi.[3] *[1]Istituto Giannina Gaslini, Genova, Italy; [2]Ospedale Pediatrico Bambino Gesu, Roma, Italy; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Steroids induce remission in 90% of children with idiopathic nephrotic syndrome (INS). Some become steroid-dependent (SD) and require the addition of drugs such as calcineurin-inhibitors (CNI), to maintain remission. Considering the toxicity of these drugs, alternative interventions are needed. The anti-CD20 antibody rituximab was effective as a steroid-sparing agent. Mycophenolate mofetil (MMF) is effective in maintaining free-steroid remission, however, studies are limited to a few uncontrolled trials with different doses of MMF.

Methods: This open-label, two-parallel-arm, multi-center, superiority-controlled randomized clinical trial will enroll children with SD-INS maintained in remission with oral glucocorticoids or CNI. Subjects will be randomized to either MMF (1.200 mg/m2) or rituximab (375 mg/m2) infusion. Glucocorticoids will be tapered until complete withdrawal. The primary end-point is to detect as significant at the two-sided p-value of 0.01 with a power >0.8 a reduction in the risk of 1-year relapse. In a sub-cohort of 39 patients (rituximab, n=19; MMF, n=20), we characterized the circulating levels of the B-cell subsets by flow cytometry.

Results: We randomized 160 children and young adults (aged 2–24 years) (**Fig1A**). At 1 year, 12 of 80 (15%) participants who received rituximab experienced relapse versus 30 of 80 (37%) who received rituximab (odds ratio [OR], 2.27; 95% confidence interval [95% CI], 1.20 to 4.29) (**Fig1B**). As expected, there were no significant differences in B-cell subsets between the two arms at baseline. MMF treatment had no significant effect on B cells, while RTX depleted all B-cell subsets. By 1yr, total, transitional and mature-naïve B cells were restored to levels similar to the MMF arm (**Fig.1A-B-C**).

Conclusions: A single dose of rituximab was superior to a single MMF in maintaining remission in children with steroid-dependent and CNI–dependent nephrotic syndrome.



TH-PO589

Updated Results with Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in Primary Membranous Nephropathy (RUBY-3 Study)

Arvind Madan,[1] Rajesh Yalavarthy,[2] Dong Ki Kim,[3] Ju young Moon,[4] Inwhee Park,[5] Sreedhar A. Mandayam,[6] Frank B. Cortazar,[7] Sung Gyun Kim,[8] Rupert H. Davies,[9] Amanda M. Enstrom,[9] Heather Thomas,[9] Jiahua Li,[9] Stanford L. Peng,[9] James A. Tumlin.[10,11] *[1]Central Florida Kidney Specialists, Orlando, FL; [2]Western Nephrology, Arvada, CO; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [5]Ajou University School of Medicine, Suwon-Si, Gyeonggi-do, Republic of Korea; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]New York Nephrology Vasculitis and Glomerular Center, Albany, NY; [8]Hallym University Sacred Heart Hospital, Anyang-Si, Gyeonggi-do, Republic of Korea; [9]Alpine Immune Sciences, Inc., Seattle, WA; [10]NephroNet Clinical Trials Consortium, Atlanta, GA; [11]Emory University School of Medicine, Atlanta, GA.*

Background: Inhibition of BAFF and/or APRIL has shown promise in IgA nephropathy (IgAN), lupus, lupus nephritis (LN), and primary membranous nephropathy (pMN), and has the potential to exert a disease-modifying effect. Povetacicept (ALPN-303) is an Fc fusion protein of a variant TACI domain engineered for more potent dual BAFF/APRIL inhibition vs WT TACI or anti-BAFF/-APRIL antibodies. Povetacicept has been associated with on-target reductions in Ig levels and antibody-secreting cells in healthy volunteers. In an initial case report of pMN from the ongoing RUBY-3 study of povetacicept (NCT05732402), immunological remission was achieved at 22 wk, with anti-PLA2R1 levels reduced to below the limit of detection (Tumlin J, et al. Poster TH-PO1125 presented at ASN 2023).

Methods: RUBY-3 is an open-label, multiple ascending dose, ph 1b/2a study of povetacicept 80 or 240 mg SC Q4W for 24 wk, followed by a 28-wk extension; participants meeting prespecified criteria at 48 wk may enter an optional 52-wk extension. Eligible participants are aged ≥18 y with IgAN, pMN, LN, or ANCA-associated vasculitis (biopsy-confirmed diagnosis required for IgAN, pMN, and LN). Participants must be on maximally tolerated ACEi/ARB therapy, with well-controlled BP, and disease-specific immunosuppressive therapy where applicable. Primary objective is safety; secondary objectives include PK, PD, immunogenicity, biomarkers, and efficacy.

Results: As of 1 Mar 2024, 3 participants with pMN have enrolled at the povetacicept dose level of 80 mg SC Q4W; 1 has completed ≥40 wk and 2 have completed <4 wk. Povetacicept has been well tolerated with multiple dosing, with no serious or severe adverse events. In the participant with the longest follow-up, significant reduction in anti-PLA2R1 has continued to be observed following achievement of immunological remission at 22 wk, with levels remaining below the limit of detection. Updated safety, efficacy, PK, and PD findings will be reported at the time of presentation.

Conclusions: In these initial findings, povetacicept demonstrates promising activity in pMN, strongly supporting its further development in autoantibody-associated glomerulonephritis.

Funding: Commercial Support - Alpine Immune Sciences, Inc.

TH-PO590

CD19 Repopulation and Anti-phospholipase A2 Receptor (PLA2R) following Rituximab in Membranous Nephropathy

Durga Anil K Kanigicherla, Patrick Hamilton, Meshaal M. Shukkur, May K. Thet, Omar S. Ragy. *Manchester Institute of Nephrology and Transplantation, Manchester, United Kingdom.*

Background: Rituximab is used for treatment in PMN. However, remission rates remain modest, and optimal dosing remains uncertain.

Methods: 29 consecutive patients were followed prospectively after rituximab treatment. Clinical markers, Anti-PLA2R, CD19 count (cells/μL) were analysed at 1-week, 2-3-week, 4-6-week, 2-3-month, 4-6-month, 8-10-month, and 12-month.

Results: Features and outcomes are in Table. Remission at 1-year was seen in 15 (52%) patients. All patients had CD19 depletion (<5) between 1-3 weeks. CD19 reconstitution was seen in 6% patients at 4-6 weeks, 25% at 2-3 months, and 60% at 4-6 months. Anti-PLA2R levels reduced at 3 months from baseline but remained at similar level until 12 months. There was significant correlation between CD19 and anti-PLA2R (R=0.89, p= 0.075). Notably, CD19 repopulation preceded rise in anti-PLA2R.

Conclusions: Following rituximab treatment, CD19 levels correlate with anti-PLA2R, repopulation occurs in majority of patients by 4-6 months, and precedes emergence of antiPLA2R. This may explain the modest remission rates in PMN with rituximab and additional dosing at 4-6 months may improve remission.

Baseline & Outcomes

		N	29		
			2019-2023		
		Males	66%		
		Age	56		
		Biopsy	29 (100%)		
			Incident-14 Relapse-15		
		PLA2R-ab +ve	90%		
		Follow-up	13.5 mon		
		Remission	15 (52%)		
		Refractory	14 (48%)		
	Time0	3 mon	6 mon	9 mon	12 mon
Rescue Rs	NA	0	0	6	0
eGFR	43	43	44	46	44
uPCR	893	582	485	407	177
Alb	23	26	27	30	31
CD19	155	2	13	22	69
Anti-PLA2R	88	22	27	18	27
Remission	NA	14%	21%	33%	56%

Values are median, median & %

TH-PO591

A Comparative Analysis of Efficacy of Rituximab in Patients with Primary Membranous Nephropathy

Qianwei Zhang, Liyi Xie. *The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: The efficacy of rituximab in patients with primary membranous nephropathy(PMN) has been confirmed. The study was conducted to analyze the efficacy of rituximab in PMN patients by comparing with supportive and immunotherapy therapy. The optimal treatment strategies for membranous nephropathy were proposed.

Methods: Patients diagnosed with PMN by clinical manifestations of nephrotic syndrome and began initial treatment were divided into four treatment groups: rituximab(RTX); low-dose glucocorticoid with tacrolimus or cyclophosphamide (CTX);supportive treatment. Collecte the data consecutively for 30 months to conduct a single-center retrospective study.

Results: 161 patients underwent the study totally, 93 were male(57.76%) and 68 were female(42.24%). The mean age was 50.50 years old. The mean follow-up time was 17.61 months. The main pathologic types were stage I-II of MN(71.4%). The PLA_2R positive rate in kidney tissue was 78.9%, and it was 62.66% in serum (defined as the PLA_2R titer<20RU/ml). There were no significant differences in age, sex, baseline UTP and eGFR among the four groups(P>0.05). Compared with supportive treatment, remissionin of immunotherapy groups occurred earlier. The decline rate of UTP in the rituximab group was higher than tacrolimus group from 6 months, and the difference was significant at 30 month(μ_{RTX}=91.52%,$\mu_{tacrolimus}$=75.52%,P<0.001). At 12 month and before, the increase rate of ALB was higher in the tacrolimus group. It had a significant difference in the two group at 18 month(μRTX=87.96%,$\mu_{tacrolimus}$=66.98%,P<0.05). The decline rate of UTP in RTX group was lower than that in CTX group at 12 month and before. After 12 month, it was gradually higher in RTX group and showed a significant difference at 24 month(μ_{RTX}=93.45%,μ_{CTX}=64.48%,P<0.001). After 18 month, the eGFR in RTX group decreased by 0.63 ml/min.1.73m^2 compared with baseline data, while it decreased by 8.85, 7.78, 8.55 ml/min.1.73m^2 in tacrolimus, CTX, supportive group respectively.

Conclusions: Rituximab and tacrolimus, cyclophosphamide were all eutherapeutic. Tacrolimus group has better adherence. The efficacy of rituximab had no significant different with other regiments in short term, but the long-term efficacy was better and the kidney function was better protected. In addition, the incidence of adverse events was lower. Therefore, rituximab can be considered as one of the first options for the treatment of the PMN.

TH-PO592

Long-Term Outcome of Adult Patients with Membranous Nephropathy Treated with Rituximab

Maria Jose Vargas-Brochero,[1] Yeshwanter Radhakrishnan,[1] Elisabeth P. Lafaut,[2] Nancy Daniela Valencia-Morales,[1] Miriam Machado,[1] Ladan Zand,[1] Sanjeev Sethi,[1] Maria Jose Soler,[3] Fernando C. Fervenza.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Universiteit Gent Faculteit Geneeskunde en Gezondheidswetenschappen, Gent, Belgium; [3]Hospital Universitari Vall d'Hebron, Barcelona, Spain.*

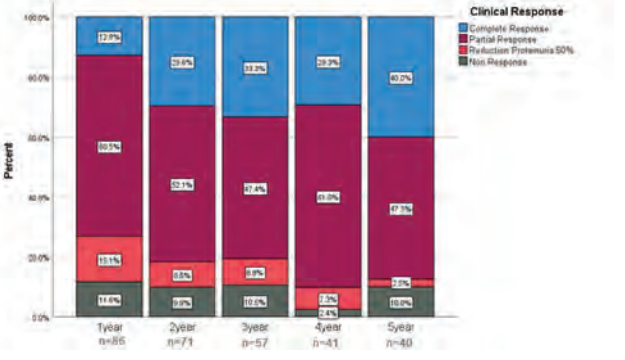
Background: Rituximab (RTX) has become the cornerstone treatment of membranous nephropathy (MN). However, data on hard outcome such as eGFR and progression to end-stage kidney disease (ESKD) are lacking.

Methods: Retrospective cohort study was conducted on MN patients and treated with RTX from January 2000 through December 2022. Clinical outcome were complete remission (CR) [proteinuria ≤0.3 g/24h and serum albumin ≥3.5 g/dl], partial remission (PR)[baseline proteinuria reduction≥50% and proteinuria ≤3.5 g/24h], reduction proteinuria (RP)[baselineproteinuria reduction≥50%], and development of ESKD. Immunological remission (IR) was defined as negative serum PLA2R-Ab.

Results: 90 patients included, 72(80%) were male, and 81(90%) white, with a mean (SD) age of 56.5(14.2) years at RTX initiation. Previous immunosuppression used in 45(50%). Baseline median[IQR]serum creatinine was 1.4 mg/dl [1.09-1.90], albumin 2.8 g/dl [2.2-3.4], and proteinuria 9 g/24h [6.2-11.2]. Nephrotic syndrome was present in 78.9%(71) patients. PLA2R Ab status in serum and/or kidney biopsy was available in 80 (88.9%) and positive in 61 (76.3%) patients. Mean (SE) survival was 17(0.72) years. 87 patients reached clinical response (CR, PR or RP) after a median [IQR] of 6.3 [4.8, 14.8] months. Median [IQR] time to first CR and PR was 21.6[11.8, 41.8] and 6.1[4.3, 13.8] months. Median time to IR was 4.79[95% CI 3.78, 6.34]months. ESKD developed in 3(3.3%) patients. Estimated ESKD-free survival was 100% at 5 years and 96.9% at 10 years.

Conclusions: RTX on MN patients is associated with an excellent long-term renal survival, that compares favorably with historical survival rates using the cyclic corticosteroids/cyclophosphamide regimen.

Figure 1. Proportion of complete remission, partial remission, and reduction of proteinuria ≥50% over time.



TH-PO593

Obinutuzumab Is Effective and Safe for Membranous Nephropathy with Very High Risk: A Retrospective Study from China

Duqun Chen,[1] Hui Li,[2] Yuanmao Tu,[1] Youliang Wang,[1] Dandan Qiu,[1] Ke Zuo,[1] Zhen Cheng.[1] *[1]National Clinical Research Center of Kidney Diseases, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China; [2]National Clinical Research Center of Kidney Diseases, Jinling Hospital, Affiliated Hospital of Nanjing medical University, Nanjing, China.*

Background: Membranous nephropathy (MN) is a common cause of nephrotic syndrome (NS) in adults. Factors considered to place a patient at very high risk for progression include life-threatening complications related to NS and severe renal dysfunction. The present study aimed to explore the efficiency and safety of Obinutuzumab for MN with very high risk in a retrospectively cohort.

Methods: MN patients with serum anti-phospholipase A2 receptor antibody (aPLA2Rab) ≥14RU/ml with very high risk (venous thromboembolic events, n=10, serum creatinine≥1.5mg/dl, n=16) received Obinutuzumab treatment (1g×2) in the National Clinical Medical Research Center for Renal Diseases at Jinling Hospital from October 2022 to November 2023 were retrospectively analyzed. Immunological complete remission is defined as aPLA2Rab<2RU/ml. B cell depletion is defined as CD20+cells<5/ul. All patients were followed more than 6 months.

Results: 26 MN patients including 23 males and 3 females was enrolled in the present study, with a mean proteinuria of 11g/24h at baseline. Complete (proteinuria <0.5g/24h) or partial (proteinuria <3.5g/24h with ≥50% reduction vs baseline) remission was achieved in 35% and 61.5% patients at month 3 and 6 respectively. B cell depletion rate was 100% and 88%, and immunological complete remission was 77% and 85% at month 3 and 6 respectively. aPLA2Rab titers progressively decreased by medians of 99% at month 6 compared to baseline. Obinutuzumab significantly reduced 24-hour proteinuria and increased serum albumin, and immunoglobulin G levels. Estimated glomerular filtration rate was significantly increased by an average of 32% in patients with serum creatinine ≥1.5mg/dl. Venous thrombosis was disappeared in 9 (90%) patients. 16 patients were followed more than 9 months and only one patient failed to response, a remission rate of 94% was achieved at month 9. Infusion-related adverse event was mostly mild. No patients died or progression into end stage kidney disease.

Conclusions: Obinutuzumab is safe and effective in the treatment of membranous nephropathy with very high risk. Large prospective studies are needed to validate these preliminary findings.

Funding: Clinical Revenue Support

TH-PO594

Outcomes in Membranous Nephropathy Treated with Intravenous Cyclophosphamide and Oral Prednisolone (Modification of the Modified Ponticelli Regimen): A Single-Centre Experience

David W. Ritter, Jacob A. Lange, David Makanjuola, Nicholas Cole. *Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.*

Background: The Modified Ponticelli regime (MPR) is established treatment for membranous nephropathy (MN). We modified this at our centre to use oral Prednisolone 40mg daily (months 1, 3, 5) and intravenous Cyclophosphamide (CP) (single dose at start of months 2, 4, 6). This reduces CP and corticosteroid (CS) exposure as compared to the MPR. We analysed our data to see whether our approach negatively impacted remission and relapse rates.

Methods: Individuals treated with our modified regimen between 2005 and 2024 were identified. Follow-up continued until the most recent clinic visit at our centre, change in immunosuppressive therapy, or death (whichever happened first). Primary outcomes were: partial remission (PR), defined as > 50% drop in proteinuria from baseline AND urine PCR (uPCR) of 30-350 g/mol; complete remission (CR), defined as uPCR <30 g/mol; relapse, defined as recurrence of uPCR >350 g/mol. All were confirmed on at least 2 consecutive samples. An adverse renal outcome was included as a secondary outcome, defined as dialysis-dependence or a >50% decline in GFR from baseline.

Results: 44 individuals commenced our MPR at a median of 4.5 months from diagnosis: 80% were male, 81% were of white ethnicity and the median age was 65 (IQR 58-69) years. 55% were serum PLA2R antibody positive. 39 (87%) completed the full course with a mean total CP dose of 3.1 g (range 1.3-4.5g). The median follow-up period was 1.8 years (IQR.1.0-4.1). 25 (64.1%) achieved remission, and 8 (20.51%) had CR. 7/25 (28%) experienced a relapse during the follow-up period. An adverse renal outcome occurred in 4/14 (29%) of those who did not attain remission, compared to 1/25 (4%) in those who achieved at least PR. The mean rate of eGFR change in those who achieved remission was 2.0 mL/min/year and -9.7 mL/min/year in those who did not ($P < 0.01$).

Conclusions: Our modified MPR achieved comparable remission rates, relapse rates and renal outcomes to those reported with the standard MPR and other regimes that use much higher doses of CP and CS.

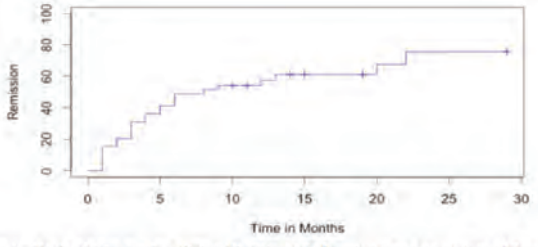


Figure 1 – Kaplan-Meier graph outlining 1st attainment of remission as a percentage of the sample

TH-PO595

Assessing the Rates of Complications in Patients with Membranous Nephropathy Treated with Cyclical Intravenous Cyclophosphamide and Oral Prednisolone: A Single-Centre Experience

Jacob A. Lange, David W. Ritter, David Makanjuola, Nicholas Cole. *Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.*

Background: The Modified Ponticelli Regimen (MPR) is an established treatment option for membranous nephropathy (MN). We use a modified MPR at our centre, administering intravenous (IV) Cyclophosphamide (CP) at the start of months 2,4 and 6. Oral Prednisolone 40mg is prescribed daily during months 1,3 and 5 without the use of IV Methylprednisolone. We reviewed whether minimising the dosage of CP and steroids reduces complication rates without compromising on remission rates.

Methods: All patients treated with the modified MPR at our centre were included for analysis. Patients were followed up till either their most recent clinic visit, until they switched immunosuppressive treatment, died or left our locality. We looked at the complications during follow-up, defined as either: leucopenia; severe infection requiring hospitalisation; or hyperglycaemia requiring hospitalisation or insulin initiation.

Results: 44 individuals were identified: 35 (80%) were male; 36 (81%) were of white ethnicity; the median age was 65 (IQR 58-69) years; 2 (5%) had diabetes mellitus. 39 (87%) completed the full course and the mean total CP dose was 3.1 g (range 1.3-4.5g). The median follow-up was 1.8 years (IQR.1.0-4.1). 25/39 (64.1%) achieved remission, 8 of whom (20.51%) reached CR. None became leucopenic, 10 (22.7%) sustained serious infections requiring hospitalisation and 1 (2.3%) needed admission with a hyperglycaemia (blood glucose of 74mmol/L or 1333mg/dL). The infections individuals were admitted with are summarised below, with some patients admitted more than once or with more than one source.

Conclusions: Our modified MPR regime resulted in a comparable remission rate to other studies using a standard MPR (66% for Jha et al. (2007) and 71% for Rao et al. (2019)) but demonstrated a marked reduction in complication rates, particularly in relation to leucopenia and diabetes-related complications: comparative studies using a standard MPR show leucopenia rates of 8.5-42%, infection rates of 25.7-35.7% and hyperglycaemia-related complications of 1.5-40%. Our data suggests that our modified MPR maintains efficacy and reduces treatment-related toxicity.

Infection Type	Respiratory	Gastrointestinal	Urine	Line	Unknown
Number of Patients	8	2	1	1	1

TH-PO596

Effect of Phospholipase A2 Receptor (PLA2R) Antibody and Inflammatory Factors on Cardiovascular and Thromboembolic Events in Patients with Primary Membranous Nephropathy

Hong Cheng, Nan Ye, Lei Yang, Guo-qin Wang. *Beijing Anzhen Hospital Affiliated to Capital Medical University, Chaoyang-qu, China.*

Background: Primary membranous nephropathy (pMN) is the most likely cause of venous thromboembolic complications in all pathological types of NS, as well as arterial thrombotic events, especially cardiovascular events. What are the high-risk groups for arterial and venous thromboembolic events in patients with pMN? Why are arterial and venous thromboembolic events likely to occur in this population?

Methods: Patients with pMN diagnosed by renal biopsy in our hospital from June 1, 2010 to March 3, 2023 were included. The study outcome was set as a composite of ACS, HF, stroke, arrhythmia, VTE, pulmonary embolism and all-cause mortality.

Results: A total of 433 patients were included, with a median follow-up of 75 months. The proportion of composite endpoint was 8.1%. Univariate analysis showed that the event group had a higher proportion of males, smokers, with hypertension, a previous history of venous thromboembolism, a higher amount of urinary protein, a higher blood PLA2R antibody titer, a higher hsCRP level, and a higher D-dimer and FDP level than the non-event group. Cox proportional hazards model results showed that both high blood PLA2R antibody titer (OR 1.045, 95%CI 1.013-1.078, P=0.006) and high hsCRP levels were independent risk factors for the occurrence of endpoint events (OR 1.057, 95%CI 1.002-1.115, P=0.041). The results of correlation analysis showed that there was a correlation between blood PLA2R antibody titer and hsCRP level (r=0.185, P<0.001), so we inferred that blood PLA2R antibody may lead to endothelial cell injury through an inflammatory mechanism, causing cardiovascular events or thromboembolic events. We initially detected IL-6 levels in the enrolled patients, and the results showed that IL-6 levels were 5.58±4.44pg/ml in the cardiovascular and thromboembolic event groups and 2.95±1.22pg/ml in the non-event group, and the difference between the two groups was statistically significant (p=0.015).

Conclusions: Both high serum PLA2R antibody titer and high hsCRP level are independent risk factors for cardiovascular events or thromboembolic events in patients with pMN, and IL-6 level is significantly increased in the event group, which may suggest that serum PLA2R antibody and inflammation play a role in the mechanism of pMN and provide a basis for our subsequent basic experiments.

TH-PO597

Comparability of Two Anti-phospholipase A2 Receptor (PLA2R) Enzyme-Linked Immunosorbent Assays (ELISAs) in Patients with Primary Membranous Nephropathy

Sean Barbour,[1] Holly Clarke,[2] Eriola Berisha,[3] Audrey Arjomandi,[2] Debbie Chen,[2] William Riboulet,[3] Heather Boston,[3] Sylvie Prot,[3] Daniel C. Cattran,[4] David E. Place.[2] *[1]The University of British Columbia, Vancouver, BC, Canada; [2]Genentech Inc, South San Francisco, CA; [3]F Hoffmann-La Roche AG, Basel, Switzerland; [4]Toronto General Research Institute, University of Toronto, Toronto, ON, Canada.*

Background: In patients with primary membranous nephropathy (pMN), 70-80% have circulating anti-M-type phospholipase A2 receptor (PLA2R) autoantibodies. The EuroImmun (EI) anti-PLA2R (αPLA2R) ELISA is a diagnostic test for pMN used in the ongoing, Phase III MAJESTY clinical trial (NCT04629248), which evaluates the safety and efficacy of obinutuzumab versus tacrolimus in patients with pMN. In the Phase III MEmbranous Nephropathy Trial of Rituximab (MENTOR, NCT01180036), an ELISA developed by Paul Brenchley was used prior to the development of a commercial ELISA. The comparability of the two αPLA2R assays is unknown. Measurement of MENTOR αPLA2R titers using EI-ELISA allows for comparison of outcomes between these B cell depletion clinical trials and informs the MAJESTY protocol design, which uses EI-ELISA.

Methods: Baseline serum samples obtained from MENTOR were analyzed by EI-ELISA. Spearman's rank correlation was used to assess comparability of the EI-ELISA results. For EI-ELISA, αPLA2R+ was defined as ≥14 RU/mL; αPLA2R+ was defined as >40 U/mL by Brenchley ELISA. The median EI-ELISA αPLA2R titer among αPLA2R+ MENTOR study participants was determined and used for stratification of study participants in MAJESTY.

Results: At baseline, αPLA2R titers in MENTOR were highly concordant (r=0.91, P=1.26x10^{-49}) (**Fig 1**). At baseline, 93/130 (71.5%) were αPLA2R+ by the EI-ELISA (≥14 RU/mL) and 96/130 (73.8%) were αPLA2R+ (>40 U/mL) by the Brenchley ELISA, with 96.2% agreement. Among patients who were αPLA2R+ as assessed by the EI-ELISA, the median titer was 175 RU/mL (IQR, 58-394).

Conclusions: The EI-ELISA used in the ongoing MAJESTY study is highly concordant with the Brenchley ELISA. To ensure the two arms in MAJESTY have a comparable proportion of participants who are αPLA2R+, the median EI-ELISA αPLA2R+ titer (175 RU/mL) was used for stratification.

Funding: Commercial Support - Genentech, Inc., and F. Hoffmann-La Roche Ltd, Private Foundation Support

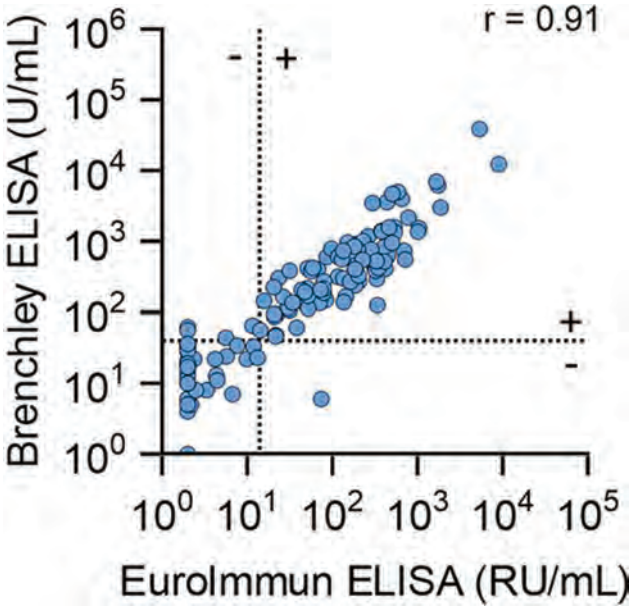


Fig 1. Concordance Between Anti-PLA2R ELISA Titers in MENTOR

TH-PO598

Noninvasive Diagnostic Strategies for Membranous Nephropathy in the NEPTUNE Study

Jarcy Zee,[1,2] Jonathan Hogan,[5] Ahmed Abdullah,[4] Lili Liu,[3] Krzysztof Kiryluk,[3] Laurence H. Beck.[4] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]The Children's Hospital of Philadelphia Research Institute, Philadelphia, PA; [3]Columbia University Vagelos College of Physicians and Surgeons, New York, NY; [4]Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [5]Cabaletta Bio Inc, Philadelphia, PA.*

Background: Clinical practice guidelines recommend that a kidney biopsy is no longer required to confirm a diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome and a positive test for anti-phospholipase A2 receptor antibodies (PLA2R-Ab). However, the optimal diagnostic strategy for using the different PLA2R-Ab tests and their optimal thresholds for positivity among incident patients with proteinuria is still unknown.

Methods: We used serum samples at or before the first kidney biopsy from NEPTUNE study participants to analyze diagnostic test performance using different combinations and cut-offs of the PLA2R-Ab enzyme-linked immunosorbent assay (ELISA), PLA2R-Ab indirect immunofluorescence (IIF) test, and genetic risk score for diagnosing MN. Secondary analyses included serum samples within 6 months after biopsy but before any immunosuppression use.

Results: N=325 study participants had serum samples on or before the day of kidney biopsy and an additional N=143 had samples within 6 months after biopsy but before any immunosuppression use. N=85 had biopsy-confirmed MN. The combination of ELISA ≥2 RU/mL and positive IIF was the optimal approach, with sensitivity of 0.600, specificity of 1.000, negative predictive value of 0.925, and positive predictive value of 1.000 (Table). Using IIF to confirm only borderline ELISA titers between 2 and 20 resulted in similar sensitivity but specificity of 0.996. In our multiethnic study sample, we did not find improved diagnostic performance with the addition of genetic risk scores.

Conclusions: Given the possibility of false positives by ELISA alone, both ELISA and IIF testing should be performed to establish PLA2R-Ab seropositivity before making a non-invasive diagnosis of PLA2R-associated MN among patients with proteinuria. Further studies in multiethnic populations are needed to assess whether genetic data can augment this approach.

PLA2R-Ab ELISA and IIF diagnostic test characteristics

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
ELISA ≥2	0.636	0.837	0.443	0.919
ELISA ≥14	0.564	0.996	0.969	0.918
ELISA ≥20	0.527	0.996	0.967	0.912
ELISA ≥2 and IIF+	0.600	1.000	1.000	0.925
ELISA >20 or (20≥ELISA≥2 and IIF+)	0.600	0.996	0.971	0.924
ELISA >20 or (20≥ELISA≥14 and IIF+)	0.564	0.996	0.969	0.918
ELISA >20 and IIF+	0.527	1.000	1.000	0.912

TH-PO599

Assessment of Endothelial Dysfunction in Patient with Phospholipase A2 Receptor (PLA2R)-Positive Primary Membranous Nephropathy in Remission

Rishab R. Prabhu,[1,2] Nikhil Vojjala,[1,2] Arun Prabhahar,[5] Joyita Bharati,[4] Ujjwal Gorsi,[5] Pratyaksha Rana,[3] Sunil K. Arora,[5] Raja Ramachandran.[5] *[1]Trinity Health Oakland Hospital, Pontiac, MI; [2]Wayne State University School of Medicine, Detroit, MI; [3]UN Mehta Institute of Cardiology and Research Centre, Ahmedabad, India; [4]Boston Medical Center, Boston, MA; [5]Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

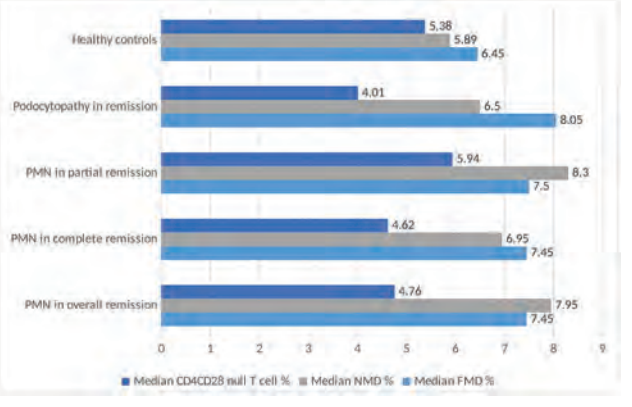
Background: Primary membranous nephropathy (PMN) is associated with endothelial dysfunction. Emerging evidence suggests that this dysfunction persists even after clinical remission. Therefore, we aimed to study the level of endothelial dysfunction in patients with PMN in remission and compare it with healthy controls (HC) and adult podocytopathy patients in remission.

Methods: This prospective cohort study included 60 patients with Phospholipase A2 receptor (PLA2R) positive PMN in remission, all of whom had received immunosuppressive therapy at least six months prior. Endothelial dysfunction was assessed using flow-mediated vasodilation (FMD), nitroglycerin-mediated vasodilation (NMD), and CD4+CD28null T cell levels. These values were then compared with those of healthy controls.

Results: Total of 60 patients with PMN in remission were included in the study. Mean age of the patients was 43.4 years (range: 20-68). Of these, 70% (n=42) were male, and 50% (n=30) had PMN in complete remission. Mean serum creatinine level was 0.873 mg/dl (SD ± 0.2248), the mean 24-hour urinary protein was 0.873 gm/TV (SD ± 0.2248), and the mean serum albumin level was 4.152 mg/dl (SD ± 0.6473). Median FMD in PMN cases, analysed with an FDA-approved brachial analyser, was 7.45% (IQR: 2.925-12.525) (vs 6.45% (IQR=4.525-10.2) in HC (p=0.654), and the median NMD was 7.95% (IQR: 4.5-12.875) in PMN cases versus 5.89% (IQR=3.153-11.88) in HC (p=0.850). Median percentage of CD4+CD28null T cells in the PMN patients was 4.76% (IQR: 2.36-12.18) versus 5.38% (IQR: 2.26-13.09) in HC (p=0.901).

Conclusions: Patients with PMN in proteinuric and serological remission exhibit endothelial dysfunction comparable to that of healthy individuals.

Figure 1: Bar diagram depicting FMD, NMD, and CD4CD28 null T cells among various study groups



TH-PO600

Assessing the Utility and Accuracy of Phospholipase A2 Receptor (PLA2R) Antibody in Membranous Nephropathy: A Systematic Review and Meta-Analysis

Omar S. Ragy,[1] Wessam Abass,[2] Durga Anil K Kanigicherla,[1] Bethany Shinkins,[3] Janine Bestall,[2] Natalie V. King,[2] Paul E. Brenchley,[1] Alison F. Smith,[2] Patrick Hamilton.[1] *[1]Manchester University NHS Foundation Trust, Manchester, United Kingdom; [2]University of Leeds Leeds Institute of Health Sciences, Leeds, United Kingdom; [3]University of Warwick Medical School, Coventry, United Kingdom.*

Background: If used as a first-line triage test to diagnose primary membranous nephropathy, the PLA2R antibody (PLA2R-Ab) test could reduce the proportion of people with nephrotic syndrome needing a kidney biopsy. Evidence to determine an appropriate PLA2R-Ab test threshold, however, is lacking.

Methods: A systematic review of diagnostic accuracy studies was conducted to evaluate serum- or urine-based biomarkers to distinguish primary and secondary membranous nephropathy (MN). We searched for relevant articles in Medline, Embase, Cochrane Library, Scopus, Web of Science, INAHTA, and ClinicalTrials.gov. Cochrane-recommended systematic review and meta-analysis methodology was implemented. QUADAS-2 was used to assess the risk of bias.

Results: Eighty-one studies were eligible for inclusion, and 50 were meta-analyzed stratified by PLA2R-Ab test method using either EUROIMMUN Enzyme-linked immunosorbent assay (ELISA) in 44 studies or EUROIMMUN immunofluorescence test (IF) in 29 studies. The pooled sensitivity and specificity of EUROIMMUN ELISA at a cut-off value of 20 RU/ml were 0.631 (95% CI: 0.546, 0.709) and 0.955 (95% CI: 0.914, 0.977), respectively. The pooled sensitivity and specificity of EUROIMMUN IF at a threshold of 1:10 were 0.705 (95% CI: 0.653 – 0.752) and 0.986 (95% CI: 0.925 – 0.998), respectively. The risk of bias was higher for studies evaluating EUROIMMUN IF compared to the ELISA test. We also explored whether the timing of the index test had an impact on the pooled diagnostic accuracy results; no significant differences were found.

Conclusions: By comprehensively considering the specificity and sensitivity of EUROIMMUN ELISA PLA2R-Ab, we show that 20 RU/mL could be used as an optimal cut-off value to confirm a diagnosis of MN without the need for kidney biopsy.

Funding: Government Support - Non-U.S.

TH-PO601

Type II Glycoengineered Anti-CD20 Antibody MIL62 or Cyclosporine in Chinese Primary Membranous Nephropathy: A Multicenter, Randomized, Open-Label Phase 1b/2 Trial

Zhao Cui,[1] Zhang Yimiao,[1] Heng Li,[3] Hua Zhou,[4] Hong L. Lin,[6] Guangqun Xing,[7] Wei Chen,[8] Wei Liang,[9] Ping Luo,[10] Chen X. Lan,[11] Hui Xu,[12] Yan Zha,[18] Yue Wang,[13] Xing Chen,[14] Zhaohui Ni,[15] Junjun Zhang,[16] Wanhong Lu,[17] Li Hua Zhang,[5] Ming-Hui Zhao,[1] Min Wei,[2] Song Meng,[2] Liang Jinjin,[2] Feng Li.[2] *[1]Peking University First Hospital Department of Nephrology, Beijing, China; [2]Beijing Mabworks Biotech Co Ltd, Beijing, China; [3]The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [4]Shengjing Hospital of China Medical University, Shenyang, China; [5]General Hospital of Eastern Theatre Command, Nanjing, China; [6]The First Affiliated Hospital of Dalian Medical University, Dalian, China; [7]The Affiliated Hospital of Qingdao University, Qingdao, China; [8]The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [9]Wuhan University Renmin Hospital, Wuhan, China; [10]The Second Hospital of Jilin University, Changchun, China; [11]Affiliated Hospital of Nantong University, Nantong, China; [12]Xiangya Hospital Central South University, Changsha, China; [13]Peking University Third Hospital, Beijing, China; [14]The First Affiliated Hospital of Xiamen University, Xiamen, China; [15]Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, China; [16]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [17]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [18]Guizhou Provincial People's Hospital, Guiyang, China.*

Background: A novel glycoengineered type II anti-CD20 antibody, MIL62 with a nearly completely afucosylated N-glycans in Fc region, has demonstrated superior activity compared with rituximab and obinutuzumab in vitro and in vivo, respectively. Last year, we we announced that the 12-week immunological remission rate and 24-week overall remmision rate (ORR) of MIL62 was significantly higher than CsA, meeting the primary endpiont of this study. Here we will update the follow-up data for week 76.

Methods: Eligible patients with pMN diagnosed by kidney biopsy, proteinuria of at least 3.5 g per 24 hours received intravenous MIL62 (two infusions, 600 or 1000 mg each, administered 14 days apart; repeated at 6 months) or Cyclosporine (CsA, starting at a dose of 3.5 mg per kilogram of body weight per day for 12 months). Patients were followed up for up to 104 weeks after initial administration. The primary efficacy outcome was a composite of complete or partial remission of proteinuria and stable eGFR. Safety and anti-PLA2R antibodies were also assessed.

Results: From Feb. 23th, 2022 to Jan. 13th, 2023, a total of 87 patients were randomly enrolled from 19 centers in China. One patient in the MIL62 group discontinued the intervention. As of Apr. 22th, 2024, all the 86 patients had evaluable data at 52 weeks and 75 patients had data at 76 weeks. The complete remission rates (CRR) of MIL62 group and cyclosporine group were 20/60 (33.3%) and 1/26 (3.8%) at 52 weeks (risk difference, 29.5%; 95% CI, 15.5 to 43.5; P=0.003 for superiority), and 23/49 (46.9%) and 0/26 (0.0%) (P<0.001) at 76 weeks. The ORR of MIL62 group and cyclosporine group were 48/60 (80.0%) and 3/26 (11.5%) at 52 weeks (risk difference, 68.5%; 95% CI, 52.5 to 84.4; P<0.001 for superiority), and 35/49 (71.4%) and 2/26 (7.7%) (P<0.001) at 76 weeks. Treatment-related adverse events occurred in 76.7%, 80.6% and 88.5% of MIL62 600mg, MIL62 1000mg and cyclosporine group respectively. No treatment-related death occurred.

Conclusions: MIL62 was superior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months. A phase 3 clinical trial of MIL62 in pMN is ongoing (NCT05862233).

TH-PO602

Characterization of the Immune-Dominant Region on the CysR Domain of Phospholipase A2 Receptor 1 (PLA2R1) Targeted by Autoreactive Memory B Cells

Linda Reinhard,[1] Sara Montagner,[2] Martine Marchant,[2] Zheng Zhou,[2] Marco Catalano,[2] Mariavittoria Iazeolla,[2] Alexandra Lavoisier,[2] Elisabetta Traggiai,[2] Elion Hoxha.[1] *[1]III. Department of Medicine, University Medical Center Hamburg Eppendorf, Hamburg, Germany; [2]Novartis AG, Basel, Switzerland.*

Background: Membranous nephropathy (MN) is caused by PLA2R1-ab in 70-80% of patients. The mechanisms how this highly specific and persistent autoreactive memory response is generated in these patients, remain unclear and all current treatment options for MN are unspecific.

Methods: Using ELISA and Western Blot, the isotypes, affinity and amount of PLA2R1-ab in patients with MN were studied. Circulating memory PLA2R1-specific B cells were isolated from patients with PLA2R1-induced MN and after cloning of the B cell receptors, monoclonal human PLA2R1-ab (PLA2R1-mAb) were produced and used to dissect the epitope binding site. Using inhibition assays, we studied the relevance of this epitope for ab binding and complement activation.

Results: In a cohort of 105 patients with PLA2R1-induced MN, we detected a high affinity IgG4-dominated immune response with expansion of IgG4 memory B cells and plasma blasts. In ca. 1/3 of patients, the PLA2R1 immune response was IgG1-dominant. Four of the five produced human PLA2R1-mAb recognized an overlapping epitope patch on the CysR domain, while the last mAb bound to the CTLD1 domain. PLA2R1-mAb show high affinity (0.2 pM), used different heavy- and light-chain variable region genes and carried high levels of somatic mutations in complementary-determining regions, consistent with antigenic selection. PLA2R1-mAb showed a strong inhibition of serum PLA2R1-ab binding from patients with PLA2R1-induced MN both in vitro and in vivo in a transgenic PLA2R1-specific rat model. In patients with circulating CTLD1-ab, the combination of CysR- and CTLD1-mAb showed an additive inhibitory effect of 85% in vitro and 75% in vivo. PLA2R1-ab positive sera from patients with PLA2R1-induced MN showed strong complement activation in an in vitro complement activity assay. In a competition assay, the PLA2R1-mAb led to abrogation of complement activation by the patients' sera, pointing toward a key functional role for the identified PLA2R1 epitopes in patients with MN.

Conclusions: The detailed characterization of the immune dominant epitope patch on the CysR domain of PLA2R1 targeted by PLA2R1 autoreactive memory B cells will facilitate the development of treatment strategies aimed at depletion of PLA2R1 specific memory B cells and plasma blasts.

Funding: Clinical Revenue Support

TH-PO603

Laser Microdissection and Mass Spectrometry: A Reliable Clinical Test for Detection of Membranous Nephropathy (MN) Antigens

Sanjeev Sethi, Jason D. Theis, Benjamin J. Madden, Fernando C. Fervenza, Julie A. Vrana. *Mayo Clinic Minnesota, Rochester, MN.*

Background: MN results from accumulation of antigen (Ag)-antibody (Ab) immune-complexes along the GBM. 13 target Ag have been discovered and include PLA2R, THSD7A, EXT1/EXT2, NELL1, SEMA3B, NCAM1, CNTN1, HTRA1, FAT1, PCDH7, NTNG1, PCSK6 and NDNF, accounting for ~80% of Ag. MN associated with many Ag have distinctive clinicopathologic finding and tissue/serum Ab have been described in all except EXT1/EXT2. As such, it is crucial to accurately identify the Ag in MN. Currently, IHC/IF methods are used to detect PLA2R, THSD7A, NELL1 and EXT1/EXT2. IHC/IF methods do not exist and are not practical for the remaining Ag. We have developed laser microdissection-mass spectrometry methodology (LMD/MS) as a one-stop clinical test for the detection of Ag using paraffin-embedded (FFPE) kidney biopsy tissue.

Methods: For each case, 6 μM thick FFPE sections were mounted on Director slides and H&E stained. Using a Leica Laser Microdissection microscope, the glomeruli were dissected to reach ~250,000 μM² per sample. Proteins were extracted using heat and sonication. Extracted proteins were reduced, alkylated and digested by incubating with trypsin. Resulting peptides were analyzed using an Exploris mass spectrometer connected to a liquid-chromatography system. Resulting MS/MS spectra were processed using three search engines to match the spectra against SwissProt human protein sequence database.

Results: The LMD/MS test was validated in 2 steps: 1) LMD/MS was used to detect the Ag in 75 cases of MN with known Ag. LMD/MS correctly identified the Ag in all 75 cases (100%). 2) LMD/MS was used to identify the Ag in 61 MN cases where the Ag was unknown. LMD/MS identified one of the above Ag in 40 of 61 cases (65.5%) including less common Ag. In 21 cases (34.5%), none of the above Ag were detected. None of the negative controls were positive for any Ag.

Conclusions: LMD/MS is an extremely useful and reliable method for the detection of MN Ag in the clinical laboratory.

LMD/MS showing total spectral counts of MN Ag. Each column represents one MN case; 2 samples from each case are shown. Also shown in the bottom rows are housekeeping proteins actin and vimentin.

TH-PO604

Overview of the Characteristics of a Phospholipase A2 Receptor (PLA2R)-Negative Membranous Nephropathy Cohort

António d. Inácio,[1] Patrícia A. Domingues,[1] Ana D. Piedade,[1] Beatriz B. Mendes,[1] Francisca G. da Fonseca,[1] Julie A. Vrana,[2] Jason D. Theis,[2] Fernando C. Fervenza,[2] Karina Soto,[1] Sanjeev Sethi.[2] *[1]Centro Hospitalar de Setubal EPE, Setubal, Portugal; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Recent insights into target antigens involved in Membranous Nephropathy's (MN) pathophysiology have propelled towards its antigen-based classification. While most are PLA2R-positive, a subset involves a variety of proteins. Antigen identification provides valuable clues regarding underlying disease or exposure, influencing clinical investigation and management. We aimed to characterize a single-center cohort of PLA2R-negative MN through antigen identification.

Methods: Retrospective analysis of all MN cases diagnosed at our Center with negative serum PLA2R titer between 2013-2023. Glomerular laser capture microdissection (LMD) was performed on paraffin-embedded kidney biopsy samples, followed by tandem mass spectrometry (MS) for antigen identification. Clinical data was included for comprehensive analysis.

Results: Of 26 biopsy-proven MN, 14 had negative serum PLA2R. Of those, 11 cases had available tissue sample for LMD/MS. LMD/MS identified a MN antigen in 8 (72.7%) cases. These included: 3 PLA2R (one case with paraproteinemia, other with syphilis and other with no underlying disease); 2 NELL-1 (one with paraproteinemia and other with lung cancer); 1 EXT1/2 (with mixed connective tissue disease and multiple myeloma); 1 HTRA1 (with multiple myeloma and uncharacterized autoimmune disease); 1 NDNF (with thyroid cancer); and 1 THSD7A (had no underlying diagnosis). In 3 (27.3%) cases no antigen was identified by MS. The diagnosis of NELL1, EXT1/EXT2 and THSD7A was confirmed by immunohistochemistry. Time from MN diagnosis to underlying disease diagnosis ranged from >2 years before up to >5 years after. Clinical course and outcomes were widely variable from spontaneous remission to ESKD progression.

Conclusions: More than half of MN cases had negative serum anti-PLA2R antibodies. Our analysis revealed diverse target-antigens involved, reflecting various underlying diseases, and exhibiting different clinical courses. The antigens detected on LMD/MS correlated with the clinical and pathologic findings. We also highlight the sensitivity of LMD/MS in identifying PLA2R, particularly in cases with negative serum measurements. We observed that negative PLA2R IHC staining can be misleading, underlining the need for caution in its interpretation.

TH-PO605

Sparsentan (SPAR) in Pediatric Patients with Rare Proteinuric Kidney Disease: Preliminary Findings from the EPPIK Study

Howard Trachtman,[1] Rosanna Coppo,[2] Nuhira Ahmed Masthan Ahmed,[3] Kenneth V. Lieberman,[4] Alex Mercer,[5] Michelle N. Rheault,[6] Moin A. Saleem,[7] Radko Komers.[3] *[1]University of Michigan, Ann Arbor, MI; [2]Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy; [3]Travere Therapeutics, Inc., San Diego, CA; [4]Joseph M. Sanzari Children's Hospital of the Hackensack Meridian Health, Hackensack, NJ; [5]JAMCO Pharma Consulting, Stockholm, Sweden; [6]University of Minnesota Medical School, Minneapolis, MN; [7]University of Bristol & Bristol Royal Hospital for Children, Bristol, United Kingdom.*

Background: SPAR is a nonimmunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA) approved (US and EU) for adults with IgA nephropathy (IgAN) at risk of rapid disease progression and is being investigated for focal segmental glomerulosclerosis (FSGS). The phase 2 EPPIK study (NCT05003986) evaluates safety and long-term antiproteinuric and nephroprotective effects of SPAR in pediatric patients (pts) with FSGS, minimal change disease (MCD), IgAN, IgA vasculitis (IgAV), and Alport syndrome (AS). We report preliminary findings per individual diagnoses.

Methods: This open-label, single-arm trial examines SPAR safety, efficacy, and pharmacokinetics in ≈30 pts 1-<18 y with FSGS and/or MCD histological patterns (population 1) and ≈27 pts 2-<18 y with IgAN, IgAV, or AS (population 2) over 108 wk and 4-wk safety follow-up. SPAR is given once daily (liquid form, dose adjusted for weight); pts on a renin-angiotensin system inhibitor undergo 2-wk washout before study medication (baseline [BL]). Primary endpoints include safety and efficacy (change in urine protein/creatinine ratio [UP/C]).

Results: At data cutoff (2/15/2024), 34 pts received ≥1 SPAR dose (BL characteristics in **Table**). Over 12 wk, proteinuria (UP/C) decreased by 51% and 27% in pts with MCD and FSGS and 54% and 61% in pts with IgAN/IgAV and AS (**Figure**). SPAR was safe and generally well tolerated.

Conclusions: SPAR is well tolerated in pediatric pts with various glomerular diseases, consistent with adult trials in FSGS and IgAN. Proteinuria decreased in each indication, even in those not previously studied, with about 50% overall reduction over 12 wk of treatment.

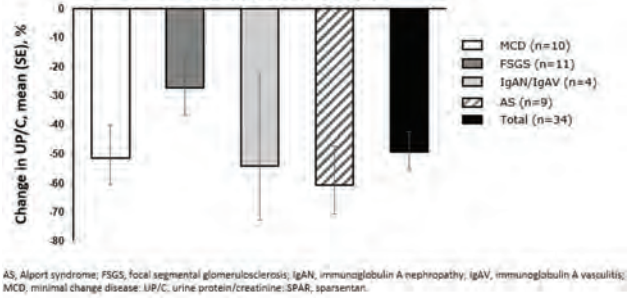
Funding: Commercial Support - Travere Therapeutics, Inc.

Table. BL Characteristics

	Population 1 MCD* (n=10)	Population 1 FSGS* (n=11)	Population 2 IgAN/IgAV†,‡ (n=4)	Population 2 AS‡ (n=9)	Total (n=34)
Age at screening, median (IQR), years	7.5 (6.0-11.0)	5.0 (3.0-14.0)	13.0 (9.5-13.5)	12.0 (11.0-14.0)	8.5 (6.0-13.0)
UP/C, median (IQR), g/g	2.75 (2.13-3.61)	4.9 (4.33-11.28)	2.27 (0.67-3.18)	2.61 (2.30-3.74)	3.08 (2.36-4.98)
Nephrotic-range proteinuria, UP/C >2 g/g, n (%)	8 (80.0)	10 (90.9)	2 (50.0)	8 (88.9)	28 (82.4)
eGFR, mean (SD), mL/min/1.73 m²	149.2 (47.29)	73.9 (20.38)	127.0 (45.31)	89.3 (31.26)	106.4 (46.87)
Immunosuppression at baseline, n (%)	5 (50.0)	6 (54.5)	2 (50.0)	0 (0.0)	13 (38.2)

AS, Alport syndrome; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; MCD, minimal change disease; UP/C, urine protein/creatinine ratio.
*UP/C ≥ 1.5 g/g at screening. †UP/C ≥0.6 g/g at screening. ‡One pt with IgAV.

Figure. Geometric Mean Percent Change in Baseline UP/C at 12 Wk of SPAR Treatment



AS, Alport syndrome; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; MCD, minimal change disease; UP/C, urine protein/creatinine; SPAR, sparsentan.

TH-PO606

"RESULT" Umbrella Trial in Primary Focal Segmental Glomerulosclerosis/ Minimal Change Disease

Julie Lin,[1,2] An-Qi Hu,[1] Shiguang Liu,[1] Karen Ocwieja,[1] Madhurima Uppara Kowthalam,[1] Arjun S. Channi,[1] Tara C. Hastings,[1] Celine Luscan,[1] Sandrine Turpault,[1] Sagar U. Nigwekar,[3] Manish Maski.[1] *[1]Sanofi, Cambridge, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Massachusetts General Hospital, Boston, MA.*

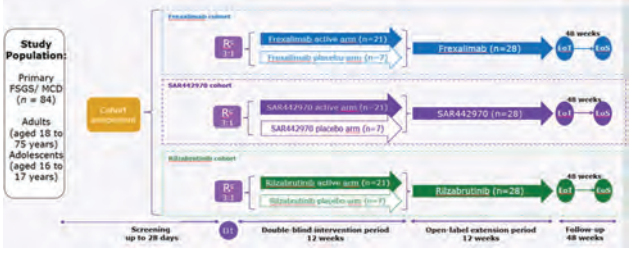
Background: Primary focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) continuum is a major cause of nephrotic syndrome among adult and pediatric patients. There is a lack of safe and effective therapies for FSGS/MCD, which is considered to be immune-mediated. We describe the protocol and operational feasibility for the Renal Efficacy Signaling UmbrelLa Trial (RESULT).

Methods: RESULT is an innovative global Phase 2a randomized, placebo-controlled umbrella trial that simultaneously evaluates the safety and efficacy of 3 novel therapies targeting immunological pathways implicated in primary FSGS/MCD: frexalimab (anti-CD40L monoclonal antibody), SAR442970 (anti-OX40L and anti-TNFα bispecific), and rilzabrutinib (BTK-inhibitor). Pts 16-75 years with biopsy-confirmed primary FSGS/MCD, eGFR ≥45 mL/min/1.73 m² and UPCR ≥3 g/g will enter a 12-wk double blind period followed by a 12-wk open-label extension (Fig). Primary endpoint is UPCR reduction from baseline to Wk 12 for each IMP vs pooled placebo. Operational feasibility has been conducted in 132 study sites across 23 countries.

Results: Majority (83%) of investigator responders expressed high interest in the trial, with top reasons being scientific importance (62%) and medical interest for patients (67%). Overall, 79% viewed burden of study procedures as appropriate, and 87% perceived remote study visits as safe. Interviews conducted with 11 affected adults, adolescents, and caregivers confirmed the high burden of disease, need for better therapies, and suitability of trial protocol.

Conclusions: This global RESULT Phase 2a trial utilizes an innovative efficacy signal-seeking master protocol to simultaneously evaluate 3 immunologically active therapies in FSGS/MCD and is the first umbrella trial in nephrology. Operational feasibility and stakeholder feedback demonstrate high scientific and medical interest, as well as appropriateness of trial design and assessments.

Funding: Commercial Support - Sanofi



TH-PO607

Patient-Reported Outcomes in Adults with FSGS: Sparsentan vs. Irbesartan

Isabelle Ayoub,[1] Mark E. Bensink,[2] Xiaolei Zhou,[3] Jinyi Wang,[3] Wu Gong,[2] Priscila Preciado,[2] Radko Komers,[2] Jula K. Inrig,[2] Michelle N. Rheault,[4] Howard Trachtman.[5] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]Travere Therapeutics Inc, San Diego, CA; [3]RTI Health Solutions Research Triangle Park, Research Triangle Park, NC; [4]University of Minnesota Medical School, Minneapolis, MN; [5]University of Michigan, Ann Arbor, MI.*

Background: In the randomized, phase 3 DUPLEX trial (NCT03493685), sparsentan (SPAR), a dual endothelin and angiotensin II receptor antagonist (DEARA), demonstrated a greater sustained antiproteinuric effect compared with irbesartan (IRB), with a favorable safety profile similar to IRB in patients with FSGS. This analysis aimed to evaluate the effect of SPAR compared with IRB on patient-reported outcomes (PROs) in adults with FSGS.

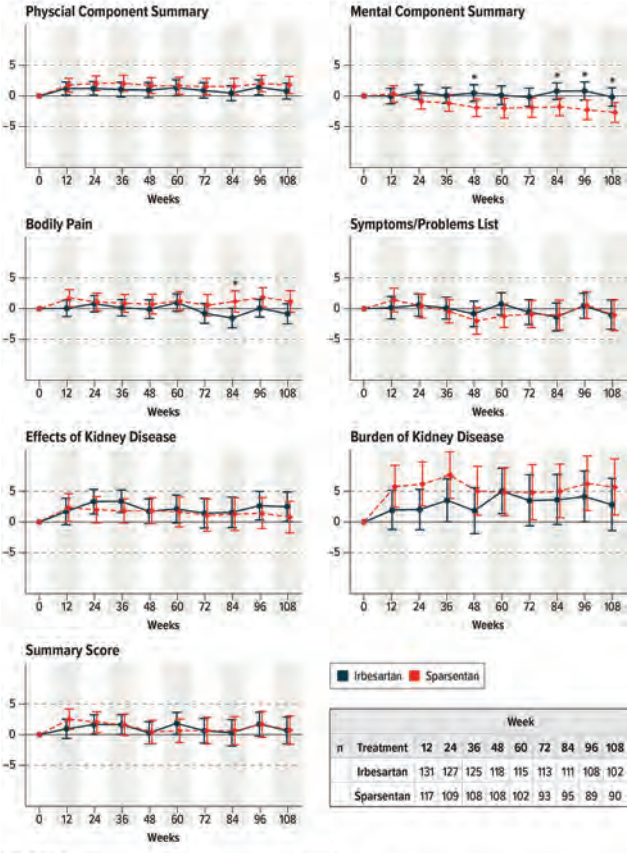
Methods: In the DUPLEX trial, the Kidney Disease Quality of Life-36 (KDQOL-36) questionnaire was administered to adults at baseline and every 12 weeks. Least squares mean changes from baseline in physical component summary, mental component summary, bodily pain, and kidney-targeted subscales were estimated using mixed models for repeated measures. A prespecified threshold change of 5 points was considered clinically meaningful.

Results: Burden of kidney disease scores were clinically meaningfully improved compared with baseline in the SPAR group but not in the IRB group (Figure). Least squares mean changes from baseline scores were stable, if not improved, throughout the 2-year treatment period for SPAR with the exception of mental component summary, which appeared slightly worsened at some timepoints compared with baseline and with IRB.

Conclusions: For adult patients with FSGS, our analysis of PROs from the DUPLEX trial suggests that health-related quality of life was relatively stable over the 2-year treatment period and comparable between SPAR and maximized angiotensin II receptor inhibition with IRB. Further work is needed to better understand the association between PROs and clinical endpoints in FSGS.

Funding: Commercial Support - Travere Therapeutics

Figure. Least Squares Mean Change From Baseline for KDQOL-36 Scores by Treatment and Visit



* $P < 0.05$ for differences between sparsentan and irbesartan.

Note: Summary score is the average of items from the symptoms and problems of kidney disease, effects of kidney disease, and burden of kidney disease scales.

Note: The vertical bars indicate 95% confidence intervals. The dotted lines indicate meaningful changes thresholds. A higher score indicates better HRQOL/functioning.

TH-PO608

Primary FSGS Patient Response to Immunosuppression (IS) and Risk of ESKD

John J. Sim,[1] Mercedes A. Munis,[1] Qiaoling Chen,[1] T. M. Hill,[2] Min Zhuo,[3] Benjamin Lewing,[2] Teresa N. Harrison,[1] Ancilla Fernandes,[2] Asher D. Schachter.[3] *[1]Kaiser Permanente Southern California, Pasadena, CA; [2]Otsuka America Pharmaceutical Inc, Rockville, MD; [3]Visterra Inc, Waltham, MA.*

Background: Primary FSGS is a podocytopathy with variability in response to IS which may affect subsequent outcomes. We compared ESKD outcomes between IS responsive vs non-responsive pts with primary FSGS.

Methods: Retrospective cohort study of Kaiser Permanente Southern California pts (≥18yo) with biopsy confirmed primary FSGS and treated with IS (2010-2021). Treatment response within 8-months was categorized as IS responsive (urine protein to creatinine ratio [UPCR] decline of >50% from baseline AND UPCR ≤3.5g/g) or IS non-responsive. ESKD was defined as treatment with kidney transplant or dialysis. Multivariable Cox proportional hazard models used to estimate hazard ratios (HR) for ESKD. IS was implemented as a time-dependent covariate and Fine-Gray method utilized for the competing risk of mortality.

Results: Among 230 patients treated with IS, 125 (54%) responded to IS. Characteristics of responders vs non-responders were: age 57.4 yrs (vs 57.6), 56% male (vs 51%), 39% White (vs 25%), 30% Hispanic/Latino (vs 30%), 17% Asian/Pacific Islander (vs 24%), 13% Black (vs 22%), mean eGFR 53 (vs 40 mL/min/1.73m²), serum albumin 2.7 (vs 2.9 g/dL), and median UPCR 5.8 (vs 5.3 g/g). Over median follow up of

2.5yrs, 88 patients (38%) progressed to ESKD of which 58pts were IS non-responders. Median time to ESKD was1.8 yrs. Median age at ESKD was 69 yrs. ESKD HR (95% CI) was 0.45 (0.28, 0.73) for IS responders vs non responders. Asian/Pacific Islanders (HR 2.01 [1.05, 3.83]) had the highest risk for ESKD.

Conclusions: We observed a high rate of ESKD within a relatively short time among primary FSGS pts treated with IS. IS non-responders compared to responders had over twice the risk for progression to ESKD.

Figure 1. Cumulative Incidence Curve for ESKD in Treated Primary FSGS

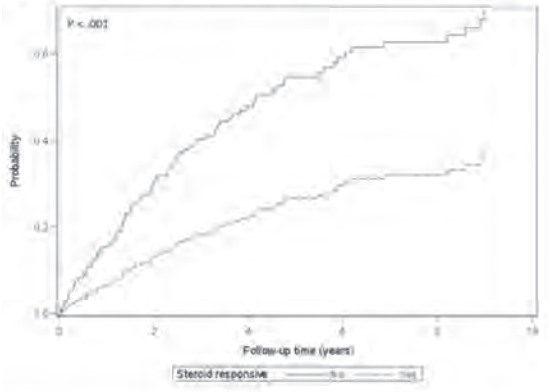


Table 1. Adjusted Hazard Ratio for ESKD among Treated Primary FSGS

ESKD	Adjusted Hazard Ratios (95%CI)	P-Value
Treatment response (yes vs. no)	0.45 (0.28, 0.73)	<0.01
Age (10-year increment)	0.87 (0.75, 1.01)	0.06
Race/ethnicity (ref=White)		0.11
Asian/Pacific Islander	2.01 (1.05, 3.83)	
Black	0.91 (0.46, 1.80)	
Hispanic	1.31 (0.73, 2.35)	
Elixhauser comorbidity index*	1.12 (0.99, 1.27)	0.06
Diabetes (yes vs. no)	1.11 (0.66, 1.87)	0.69
Hypertension (yes vs. no)	0.84 (0.41, 1.72)	0.62
Baseline eGFR (ref=30 or below)		<0.01
30-59	0.69 (0.41, 1.17)	
60+	0.21 (0.10, 0.45)	
Baseline UPCR (mg/mg)	1.02 (0.96, 1.09)	0.51

*Excluded diabetes and hypertension

TH-PO609

Long-Term Outcomes of Patients with FSGS: A Multicenter Real-World Evidence (RWE) Study

Ali Poyan-Mehr,[1] Alice J. Drozd,[1] Tingting Li,[2] Raymond K. Hsu,[3] Tripti Singh,[4] Nidia C. Messias,[2] Nasim Wiegley,[5] Kuang-Yu Jen,[5] Stewart H. Lecker,[6] Swati Arora,[7] Dia R. Waguespack,[8] Amanda Tchakarov,[8] Nancy D. Mendelssohn,[1] Iyad S. Mansour,[9] Tejwinder S. Sandhu,[1] Jose D. Mena,[6] Gabriela Sanchez,[1] Jennifer Yip,[1] Mythili Sivaswarupan,[1] Andrew Avins.[1]
[1]The Permanente Medical Group Inc, Oakland, CA; [2]Washington University in St Louis, St Louis, MO; [3]University of California San Francisco, San Francisco, CA; [4]University of Wisconsin-Madison, Madison, WI; [5]University of California Davis, Davis, CA; [6]Beth Israel Deaconess Medical Center, Boston, MA; [7]Allegheny Health Network, Pittsburgh, PA; [8]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX; [9]Banner - University Medical Center Tucson, Tucson, AZ.

Background: FSGS is a common histopathologic lesion in adult patients with nephrotic syndrome. We report on one of the most extensive observational studies of FSGS to identify predictors of long-term outcomes.

Methods: Nine centers enrolled 723 patients with FSGS of primary, genetic, or unknown etiology between 01/01/2000 and 08/01/2021. The GlomCon Research Consortium developed data definitions, collection instruments and study protocol.

Results: Clinical and biopsy characteristics (Table 1) were evaluated based on treatment history. Figure 1 and Table 2 show outcomes at 1, 3, and 5 years and time to events. Several statistically and clinically significant differences exist between immunosuppressive therapy (IST) and no IST groups.

Conclusions: The overall risk of ESKD and death is substantial. Additional analysis is being conducted to identify independent factors (clinical, treatment, and biopsy characteristics) associated with patient outcomes, predictors of IST response, and those most at risk for CKD progression, ESKD, and death.

Funding: Commercial Support - Travere Therapeutics

Baseline Characteristics

	Total	IST	No IST	*p*-value
Clinical Characteristics				
Total, n (%)	723 (100%)	176 (24.3%)	547 (75.7%)	
Age* [years], n (%)				
Mean (SD)	49.9 (17.6)	48.0 (16.8)	50.5 (17.8)	0.10
Median (Q1, Q3)	50.0 (35.0, 65.0)	46.0 (35.0, 62.0)	51.0 (35.0, 65.0)	0.10
Sex Assigned at Birth, n (%)				0.18
Female, n (%)	297 (41.1%)	80 (45.5%)	217 (39.7%)	0.18
Ethnicity, n (%)				<0.001
Native Hawaiian / Pacific Islander	6 (0.8%)	0 (0.0%)	6 (1.1%)	
American Indian / Alaskan Native	6 (0.8%)	1 (0.6%)	5 (0.9%)	
Asian	119 (16.6%)	19 (10.9%)	100 (18.4%)	
African-American / Black	128 (17.8%)	28 (16.0%)	99 (18.2%)	
White	242 (33.7%)	65 (37.1%)	177 (32.5%)	
Hispanic	129 (17.8%)	22 (12.6%)	107 (19.7%)	
Multiple ethnicities	5 (0.7%)	2 (1.1%)	3 (0.6%)	
Unknown or not reported	84 (11.7%)	37 (21.1%)	47 (8.6%)	
BMI* [kg/m²], n (%)				
Mean (SD)	31.1 (7.1)	30.6 (7.6)	31.1 (6.9)	0.75
Median (Q1, Q3)	30.1 (26.2, 34.7)	29.9 (25.6, 34.6)	30.2 (26.3, 34.8)	0.49
Serum Creatinine* [mg/dl], n (%)				
Mean (SD)	2.1 (2.0)	1.8 (1.3)	2.2 (2.2)	0.03
Median (Q1, Q3)	1.7 (1.1, 2.5)	1.4 (0.9, 2.2)	1.7 (1.1, 2.6)	<0.001
Serum Albumin* [g/dL], n (%)				
Mean (SD)	3.2 (1.0)	2.8 (1.0)	3.3 (0.9)	<0.001
Median (Q1, Q3)	3.4 (2.4, 3.9)	2.8 (1.9, 3.5)	3.6 (2.7, 4.0)	<0.001
Cholesterol* [mg/dL], n (%)				
Mean (SD)	262.2 (113.6)	299.9 (128.4)	248.7 (105.3)	0.004
Median (Q1, Q3)	233 (180, 308)	261 (217, 361)	213.5 (176, 295)	0.003
Proteinuria* [g/24hr], n (%)				
Mean (SD)	7.8 (8.7)	9.0 (6.6)	7.4 (9.1)	0.07
Median (Q1, Q3)	5.8 (2.9, 9.9)	7.2 (4.4, 12.0)	5.4 (2.6, 9.1)	<0.001
Comorbidities, n (%)				
Hypertension	556 (76.9%)	121 (68.8%)	435 (79.5%)	0.003
Diabetes	180 (24.9%)	31 (17.6%)	149 (27.2%)	0.01
Coronary Artery Disease	127 (17.6%)	16 (9.1%)	111 (20.3%)	0.001
Heart Failure	84 (11.6%)	10 (5.7%)	74 (13.5%)	0.005
Stroke	43 (6.0%)	7 (4.0%)	36 (6.7%)	0.20
Malignancy	78 (10.8%)	12 (6.8%)	66 (12.1%)	0.05
Peripheral Vascular Disease	25 (2.6%)	5 (2.8%)	20 (3.7%)	0.61
Preeclampsia (% of all female patients)	13 (4.4%)	1 (1.3%)	12 (5.5%)	0.11
Deep Vein Thrombosis	22 (3.0%)	5 (2.8%)	17 (3.1%)	0.86
Dyslipidemia	152 (21.0%)	22 (12.5%)	130 (23.8%)	0.001
Autoimmune disease	25 (3.8%)	5 (2.8%)	20 (3.7%)	0.61
Family History, n (%)				0.92
No Family History	430 (59.5%)	94 (53.4%)	336 (61.4%)	
1 Family Member	84 (11.6%)	19 (10.8%)	65 (11.9%)	
2 Family Members	25 (3.5%)	6 (3.4%)	19 (3.5%)	
3+ Family Members	8 (1.1%)	1 (0.6%)	7 (1.3%)	
Unknown	176 (24.3%)	56 (31.8%)	120 (21.9%)	
Biopsy Characteristics				
Total Glomeruli, Mean (SD)	21.8 (13.5)	22.2 (13.5)	21.7 (13.5)	0.68
GSG, %, Mean (SD)	29.9 (23.5)	23.5 (23.4)	31.9 (23.2)	<0.001
SSG, %, Mean (SD)	17.7 (18.6)	17.1 (15.3)	17.9 (19.6)	0.62
IFTA				
None/not significant (0%–5%), n (%)	83 (11.5)	27	56	0.07
Mild (6%–25%), n (%)	236 (32.6)	72	164	0.0025
Moderate (26%–50%), n (%)	176 (24.3)	35	141	0.12
Severe (>50%), n (%)	118 (16.3)	15	103	0.0008
Unknown, n (%)	110 (15.2)	27	83	——
Collapsing FSGS, n (%)	122 (16.9)	21 (12.0)	101 (18.5)	<0.05
Podocyte Foot Process Effacement				
Segmental, n (%)	241 (33.3%)	42 (23.9%)	199 (36.4%)	<0.001
Diffuse, widespread, or complete, n (%)	367 (50.8%)	116 (65.9%)	251 (45.9%)	<0.0001
None, n (%)	30 (4.2%)	3 (1.7%)	27 (4.9%)	0.17
Unknown, n (%)	85 (11.8%)	15 (8.5%)	70 (12.8%)	——

Table 1. Baseline clinical and biopsy characteristics. The total number of patients stratified according to any history of immunosuppressive therapy (IST). GSG: Globally Sclerosed Glomeruli. SSG: Segmentally sclerosed glomeruli. IFTA: Interstitial fibrosis and tubular atrophy. *Values at time of diagnosis. P values were computed using parametric test (t test), non-parametric test (Wilcoxon rank test), Kruskal Wallis for group differences, and Chi-square and Fisher's exact test for categorical variables.

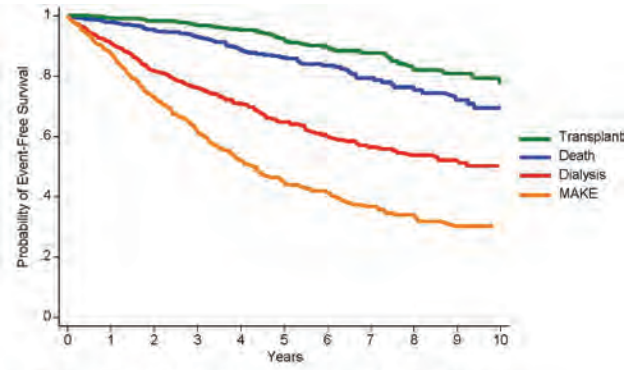


Figure 1. Event-free survival of patients with a biopsy diagnosis of FSGS. Major Adverse Kidney Event (MAKE) is defined as a 40% decline in eGFR, end-stage kidney disease (initiation of kidney replacement therapy, kidney transplantation, or eGFR<15 ml/min/1.73m²) or death.

Probability of Event-Free Survival

Outcome	Probability (95% CI)		
	7 year	9 years	0 years
Dialysis	91% (89% - 93%)	76% (68% - 80%)	65% (60% - 69%)
Transplant	99% (98% - 99.7%)	97% (95% - 98%)	92% (89% - 95%)
Death	98% (97% - 99%)	93% (90% - 95%)	86% (82% - 89%)
MAKE	88% (85% - 90%)	62% (57% - 66%)	45% (40% - 49%)

Table 2. Probability of event-free survival at years 1, 3, and 5 of patients with a biopsy diagnosis of FSGS. Major Adverse Kidney Event (MAKE) is defined as a 40% decline in eGFR, end-stage kidney disease (initiation of kidney replacement therapy, kidney transplantation, or eGFR<15 ml/min/1.73m²) or death.

TH-PO610

Clinicopathologic Prognostic Factors to Estimate ESKD in Patients with FSGS

Eun Mi You,[1] Ho Jun Chin.[2,1] *[1]Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [2]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: FSGS can be caused by heterogenous aetiologies with subdivided by primary, secondary, and genetical forms. However, the classification may not provide future outcomes of FSGS. We searched for prognostic markers of any form of FSGS.

Methods: We enrolled a total of 20,404 adult patients who underwent native renal biopsy from 1979 to 2018 in 18 hospitals in Korea. We selected patients with definite segmental sclerosis by light microscopic examination including ≥10 glomeruli and without electron dense deposits by electron microscopic examination. We excluded patients with other forms of pathologic diagnosis except FSGS, with diabetes mellitus, or with follow-up period < 6 months after renal biopsy. We evaluated prognostic factors to estimate the risk of ESRD.

Results: Among 511 patients, GFR <60 ml/min/1.73 m2 was found in 41.5 % of patients and UPCR ≥ 3.0 g/g creatinine in 41.1% of patients. During 117.5 ± 100.1 months of follow-up period, there were 97 (19.0%) patients with incident ESRD. The prognostic factors to incident ESRD were estimated GFR, diastolic blood pressure, year of renal biopsy, glomerular size, amount of global sclerosis (GS) and segmental sclerosis (SS), severity of increase in glomerular matrix, interstitial fibrosis, interstitial inflammation, and tubular atrophy (TA), and presence of artherosclerosis of intrarenal vessels. Adjusted with clinicopathologic factors related to incident ESRD, only pathologic findings of GS, SS, and TA were the independent prognostic factors. AUC by ROC to estimate the event of ESRD by percentage of GS was 0.601 (range; 0.538-0.663, p=0.002) and, by percentage of SS, 0.679 (range; 0.616-0.743, p<0.001). We grouped patients with three pathology categorical variables of a criterion of GS 30.9 %, SS 10.5 %, and moderate degree in severity of TA into 4 groups according to the relative risk to develop ESRD. UPCR was a significant risk factor to estimate ESRD only in a Group 4 with the criterion of 2 g/g creatinine by the Kaplan-Meier test (p=0.034). GFR was not a prognostic factor in any pathology subgroup.

Conclusions: Important prognostic factors to estimate incident ESRD were pathologic findings of GS, SS and TA. Significance of UPCR and GFR as prognostic factors was varied according to pathologic findings. We need to reconsider the criterion of UPCR to initiate immunosuppressive treatment according to pathologic findings at renal biopsy.

TH-PO611

Longitudinal Analysis of 100 Biopsy-Confirmed Focal Segmental Glomerulosclerosis: Incidence and Treatment Outcomes of a 10-Year, Single-Center Experience in Saudi Arabia

Sultan Al Dalbhi,[1] Asma M. Alotaibi,[1] Manal E. Alotaibi.[2] *[1]Prince Sultan Military Medical City, Riyadh, Saudi Arabia; [2]Umm Al-Qura University, Makkah, Saudi Arabia.*

Background: This study analyzes trends in biopsy-confirmed Focal Segmental Glomerulosclerosis (FSGS) over a ten-year period and evaluates outcomes of various treatment protocols and amins to identify factors influencing disease progression and disease prognosis.

Methods: A retrospective study of 100 biopsy-confirmed FSGS cases from 2013 to 2022 were analyzed. Hypothetical individual patient data were generated for treatment response, renal function, proteinuria, and quality of life. Statistical methods included trend analysis, survival analysis, and comparative analysis.

Results: The incidence rate of FSGS showed variability over the years, ranging from 2.86% to 21.67%. Notably, the highest incidence rate was observed in 2016 (21.67%). Immunosuppressive therapy and supportive care had higher complete remission rates (33.33% and 48.39%, respectively) compared to steroids (16.67%). All treatment groups experienced a decline in eGFR, with steroids showing the highest mean decline (-14.85 mL/min/1.73 m). Proteinuria reduction was most significant with steroids (-1.83 g/g). Quality of life scores were highest for patients on steroids (mean: 72.64).

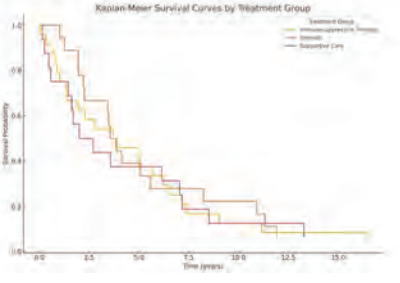
Conclusions: This study emphasizes the necessity of individualized treatment strategies for FSGS and highlights the significance of long-term monitoring of patient outcomes.

Table 1: Annual Incidence Rate of FSGS

Year	FSGS Cases	Total Biopsies (Hypothetical)	Incidence Rate (%)
2013	2	70	2.86
2014	3	80	3.75
2015	9	55	16.36
2016	13	60	21.67
2017	8	95	8.42
2018	5	85	5.88
2019	6	90	6.67
2020	2	50	4.00
2021	6	75	8.00
2022	3	60	5.00

Figure 1: Kaplan-Meier Survival Curves

Survival probability over time for different treatment groups (Immunosuppressive, Steroids, Supportive Care).



TH-PO612

Machine Learning-Derived Predictors of Clinical Outcomes in CureGN Participants with FSGS

Mark Elliott,[1] Margaret Helmuth,[2] Abigail R. Smith,[3] Vivette D. D'Agati,[4] Laura Barisoni,[5] Simone Sanna-Cherchi,[4] Daniel C. Cattran.[6] CureGN. *[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]University of Michigan, Ann Arbor, MI; [3]Northwestern University, Evanston, IL; [4]Columbia University Irving Medical Center, New York, NY; [5]Duke University, Durham, NC; [6]Toronto General Hospital, Toronto, ON, Canada.*

Background: Focal segmental glomerulosclerosis (FSGS) is a common disease pattern with variable clinical presentations, outcomes, and etiologies, including immune-mediated, adaptive, and genetic. Much of the clinical heterogeneity remains unexplained.

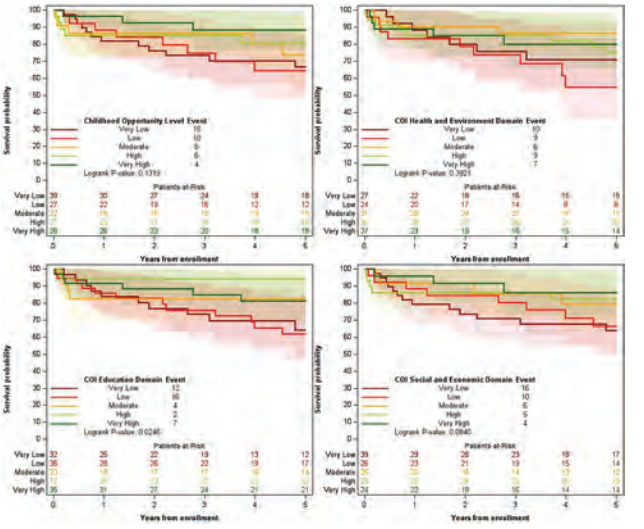
Methods: 722 participants with FSGS have been enrolled with 512 having whole genome sequencing (WGS) data, 276 with centralized biopsy scoring for conventional morphologic parameters, and 226 having both WGS and pathology scoring. Sequential

ridge regression models were performed using: 1) baseline demographic, 2) social determinants of health, clinical, and genetic, 3) pathology morphologic features to predict time to kidney failure defined as two eGFR measurements <15mL/min, dialysis, or kidney transplantation. Ridge regression allows complex modelling while avoiding overfitting. Missing variables were imputed where possible. Discrimination was assessed using integrated area under the curve (iAUC) and variables were ranked by absolute value of standardized coefficients.

Results: Among participants with WGS data, 92 had a high-risk *APOL1* genotype and 32 had monogenic kidney disorders. Model discrimination improved with the stepwise addition of features from model 1 to 3 (iAUC = 0.86, 0.93, 0.95 respectively). Among the 31 most predictive features 14 were protective (1 demographic, 6 clinical, 7 morphologic) and 17 were risk factors (2 demographic, 7 clinical, 1 genetic, 7 morphologic). The top ranked protective factors included high eGFR, high serum albumin, low rates of interstitial fibrosis and tubular atrophy (IFTA), high calcium, diffuse mesangial hypercellularity, high hemoglobin and sodium, tip variant FSGS, and no inflammation in areas of IFTA. Top ranked risk factors included high levels of IFTA, high proteinuria, tubular microcystic changes, hypertension, collapsing variant FSGS, inflammation in areas of IFTA, high levels of segmental and globally sclerosed glomeruli, thrombotic diagnosis, high potassium, edema, high-risk *APOL1* genotype, private health insurance, high levels of arteriosclerosis, black race, use of RAAS inhibitors, and young age at onset.

Conclusions: Machine learning methodologies that integrate a broad range of clinical, genetic, and pathology data allow for the identification of parameters that are predictive of clinical outcome in FSGS.

Funding: NIDDK Support



Time to composite endpoint by COI levels (FSGS only)

TH-PO613

Role of Neighborhood Disadvantage in Patient Outcomes in Childhood Nephrotic Syndrome in the CureGN Cohort

Elizabeth A. Onugha,[1,7] Abigail R. Smith,[4] Margaret Helmuth,[2] Jill Krissberg,[3] Susan F. Massengill,[5] Chia-Shi Wang,[6] Paul R. Brakeman,[9] Rulan S. Parekh,[10] Sangeeta R. Hingorani.[8] *[1]Baylor College of Medicine, Houston, TX; [2]University of Michigan, Ann Arbor, MI; [3]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [4]Northwestern University Feinberg School of Medicine, Chicago, IL; [5]Wake Forest University School of Medicine, Winston-Salem, NC; [6]Emory University, Atlanta, GA; [7]Texas Children's Hospital, Houston, TX; [8]Seattle Children's Hospital, Seattle, WA; [9]University of California San Francisco, San Francisco, CA; [10]Women's College Hospital, Toronto, ON, Canada.*

Background: Disparities in clinical outcomes in childhood nephrotic syndrome are not completely explained by race and genetics. We aim to examine the influence of residential neighborhood on disease activity and progression in childhood nephrotic syndrome using the Child Opportunity Index (COI).

Methods: CureGN is a prospective cohort study of patients with glomerular diseases diagnosed by biopsy within 5 years prior to enrollment. CureGN pediatric participants with minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) with census tract data were included. COI composite score and subdomain scores in education, health and environment, and social and economic were categorized into quintiles and examined for associations with development of ESKD or 40% decline in eGFR using Kaplan-Meier estimates and log-rank tests.

Results: 371 children (228 MCD; 143 FSGS) with a median follow-up of 5.8 years (IQR 3.4-7.2) were included. Median age at biopsy was 8 years (IQR 4-7); 58% were White, 26% Black, and 12% Hispanic. In the subset of children with FSGS, the probability of progression to kidney failure or 40% decline differed across quintiles of the education domain COI (p=0.02).

Conclusions: In a national cohort of children with nephrotic syndrome, children with FSGS who resided in areas with lower education opportunities had a higher probability of disease progression. Future work will assess potential ways to mitigate the effects of neighborhood opportunities on outcomes.

Funding: NIDDK Support

TH-PO614

Clinical Significance of Immune Deposits and Complement System Activation in Patients with FSGS: Findings from the CureGN Study

Yasar Caliskan,[1] Virginie Royal,[2] Stephan Troyanov,[3] Arnaud Bonnefoy,[4] Clémence Merlen,[4] Mark Schnitzler,[1] John C. Edwards,[1] Krista L. Lentine,[1] Louis-Philippe Laurin.[5] *[1]Saint Louis University, St Louis, MO; [2]Division of Pathology, Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, QC, Canada; [3]Division of Nephrology, Hôpital du Sacré-Cœur-de-Montréal, University of Montreal, Montreal, QC, Canada; [4]Division of Hematology, Centre Hospitalier Universitaire Sainte-Justine, University of Montreal, Montreal, QC, Canada; [5]Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada.*

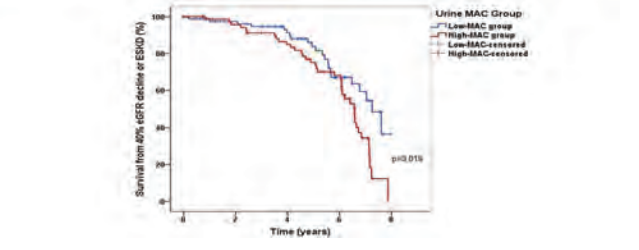
Background: Glomerular IgM and C3 deposits are commonly found in FSGS and assumed to be the result of passive trapping rather than immune mechanisms. The clinical significance of IgM and C3 immunostaining, and their association with complement system activation have not been elucidated yet. We sought to assess the value of immunofluorescence (IF) findings and urinary complement fragments in defining disease activity and progression.

Methods: FSGS patients with available pathology assessment from the CureGN cohort were reviewed and we tested associations of glomerular Igs and C3 staining intensity by IF with the urinary membrane attack complex (sC5b9), proteinuria and time to a composite outcome, defined by kidney failure or 40% eGFR decline. We compared urinary levels of sC5b9 expressed as creatinine and protein ratios.

Results: We analyzed 175 FSGS patients, including 63(36%) incident subjects enrolled within 6 months of pathology review. Glomerular IgM, C3 and IgG deposits were found in 88(50%), 48(27.4%) and 27(15.4%) patients, respectively. 44(91%) and 20(48%) of patients with C3 deposition presented with accompanying IgM and IgG deposition, respectively. C3 deposition was correlated with global sclerosis (r=0.27,p<0.001), interstitial fibrosis and tubular atrophy (IFTA) (r=0.17,p=0.028). In incident patients, urinary sC5b9 levels correlated with total segmental sclerosis (r=0.35,p=0.006) and IFTA (r=0.35,p=0.007). There was no correlation between urinary sC5b9 and the intensity of C3, IgM and IgG staining. IFTA and urinary sC5b9 level at enrollment were independent risk factors for composite outcome (HR 1.92, 95%CI 1.45-2.53,p<0.001 and HR 2.15, 95%CI 1.39-3.33,p<0.001, respectively).(Fig. 1)

Conclusions: In patients with FSGS, a higher urinary level of sC5b9 appears to be associated with eGFR loss independently of proteinuria level. Glomerular C3 deposition was associated with fibrotic lesions which was a predictor of disease progression.

Figure 1. Kaplan Meier survival plot for high urinary membrane attack complex (MAC) group (> median sC5b9 level of 0.075 per proteinuria) versus low MAC group (< median sC5b9 level of 0.075 per proteinuria) (p=0.019).



TH-PO615

Interplay between Immune Deposits, Complement Activation, and APOL1 Renal Risk Variants in Patients with FSGS

Yasar Caliskan,[1] Virginie Royal,[2] Stephan Troyanov,[3] Arnaud Bonnefoy,[4] Clémence Merlen,[4] Mark Schnitzler,[1] John C. Edwards,[1] Louis-Philippe Laurin,[2] Krista L. Lentine.[1] *[1]Saint Louis University, St Louis, MO; [2]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [3]Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada; [4]Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada*.

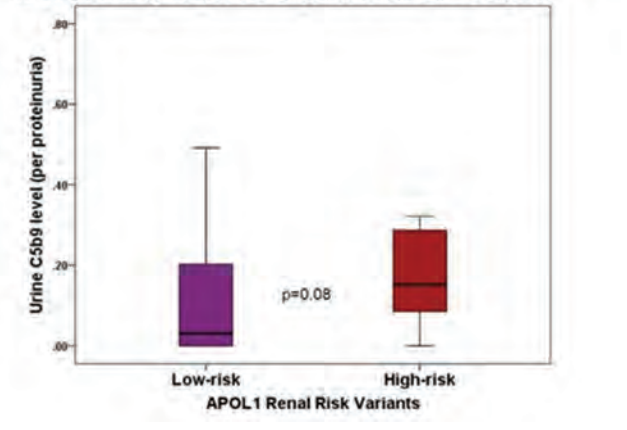
Background: The mechanisms by which *APOL1* renal risk variants (RRVs) carry a worse prognosis in FSGS is debated. Whether glomerular immune deposits and complement activation participate in *APOL1* mediated FSGS is unknown. Using the large CureGN cohort, we evaluated the association *APOL1* RRVs and immunofluorescence (IF) findings and urinary complement fragment measurements (sC5b9).

Methods: We studied the associations of glomerular IgG, IgM and C3 localization and intensity, biopsy findings, urinary sC5b9 and clinical data in CureGN FSGS cohort, regardless of self-reported race. Patients were categorized by two *APOL1* RRVs [high risk (HR)] versus zero to one risk alleles [low risk (LR)] groups. The association between histopathological findings, urinary sC5b9 levels and *APOL1* RRVs were analyzed.

Results: Of 175 participants, 148 (85%) had genetic testing, among whom 31 were HR and 117 were LR participants. The percentage of patients with active disease (UPCR>1 g/g) at enrollment was higher in HR patients compared to LR patients (74% vs 51%, p=0.07). Collapsing FSGS is the dominant type in HR group (45% vs 11%, p<0.001). Mesangial IgG deposition was significantly more frequent in HR group compared to LR group [10 (32%) vs 4 (3%), p<0.001]. Interstitial fibrosis/tubular atrophy and tubular microcystic changes were found at a significantly higher rate in HR group (84% vs 64%, p=0.033; 29% vs 12%, p<0.001, respectively). Urinary sC5b9 levels (median, IQR) were higher in HR patients enrolled within 6 months of biopsy compared to LR group [0.15 (0.08-0.31) vs 0.03 (0-0.20) µg/g, p=0.08] (Fig.1). Proteinuria levels were similar in both groups (p=0.79).

Conclusions: Patients with FSGS and high-risk *APOL1* genotype have more frequent mesangial IgG deposition and a trend towards higher urinary membrane attack complex levels compared to patients with non-risk genotype.

Figure 1. Urine levels of membrane attack complex (sC5b9) per proteinuria were higher in high-risk patients compared to low-risk *APOL1* group.



TH-PO616

Identification of Urinary Biomarkers for Outcome-Associated Digital Pathology Descriptors in Patients with Nephrotic Syndrome

Viji Nair,[1] Jeffrey B. Hodgin,[1] Damian Fermin,[1] Edmond Lee,[1] Laura Barisoni,[2] Matthias Kretzler,[1] Wenjun Ju.[1] *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]Duke University, Durham, NC.*

Background: Interstitial fibrosis (IF), tubular atrophy (TA) and Mononuclear white blood cells (MWBC) have been shown to be strongly associated with kidney disease outcome in patients with nephrotic syndrome. However, due to the invasive nature of kidney biopsy process, it is impractical to perform repeated assessments hence potentially missing crucial periods for early prognosis and intervention. There is an unmet need to develop non-invasive biomarkers that can represent underlying disease mechanisms and can serve as surrogates for outcome-associated digital pathology descriptors (DPD)s.

Methods: Urine proteomics data (SomaScan assay v4.1), kidney transcriptomic profiles, and DPD including IF, TA, and MWBC of 64 patients with nephrotic syndrome from the NEPTUNE cohort, were integrated to identify urinary protein markers. Statstical methods employed included pearson correlation, linear regression with signifcance set at p ≤0.05. Significance was adjusted for multiple testing. Ingenuity pathway analysis was used to identify enriched canonical pathways. Cox model was used to determine the association of markers with kidney composite endpoint of kidney failure and 40% reduction of GFR.

Results: 274 urine proteins and 2,031 tubulointerstitial genes were identified showing significant correlation with IF (adj. p ≤0.05). Pathway enrichment analysis of IF-correlated genes identified 480 significantly enriched canonical pathways, including interleukin signaling pathways, axonal guidance, STAT3 pathway that have been known as associated with kidney disease progression were among top pathways. Integrating the urine markers and the pathway representing genes, we identified urine protein signatures that predict IF (linear regression, p ≤ 0.05) and a subset of these markers (n=27) also predicted the composite outcome. Similarly, we also identified TA and MWBC associated urinary biomarkers.

Conclusions: We identified pathway representing urine biomarkers that can predict IF and clinical outcomes in patients with NS. Such biomarkers would enable frequent non-invasive pathway-specific disease monitoring, offering the possibility for timely prognosis and targeted treatment. Our finding warrants further validation in larger and independent cohorts.

Funding: NIDDK Support

TH-PO617

A Phase 1 Study in Healthy Adults of the Safety, Tolerability, and Pharmacokinetics of MZE829, an APOL1 Inhibitor, for the Treatment of APOL1-Mediated Kidney Disease (AMKD)

Susan Limb, Victoria Assimon, Janet M. Leeds, Ryan Dick, Cecile Yu, David T. Beattie, Sarah Bronner, Angela Octaviani, Maarten Hoek, Harold S. Bernstein. *Maze Therapeutics Inc, South San Francisco, CA.*

Background: Genetic variants of apolipoprotein L1 (APOL1) are associated with an increased risk of chronic kidney disease and disease progression in individuals of West African ancestry. MZE829 is a highly potent, small molecule inhibitor of APOL1 currently under investigation for the treatment of APOL1-mediated kidney disease (AMKD). We conducted a first-in-human trial to assess the safety, tolerability, and pharmacokinetics of MZE829 in healthy participants.

Methods: The randomized, blinded, placebo-controlled Phase 1 trial evaluated single and multiple ascending doses of MZE829 in healthy participants ages 18 years and older. Assessment of potency and selection of the Phase 1 clinical starting dose were based on the efficacy of MZE829 for reducing albuminuria in a transgenic mouse model of AMKD, where mice homozygous for the APOL1 G2 ($G2_{HOM}$) variant were administered an IFN-γ challenge to elevate APOL1 levels and induce albuminuria. An exposure-response curve from this in vivo pharmacology model was used to assess the minimum anticipated biological effect level and target efficacious exposure range (~EC_{50-98}). Safety and tolerability were evaluated through the assessment of multiple primary endpoints including, the incidence and severity of adverse events, clinically significant abnormalities in laboratory assessments, physical examinations, vital signs, and 12-lead ECGs. Noncompartmental analysis and population pharmacokinetic analysis were used to estimate doses for subsequent patient studies. Selected probes for potential drug-drug interactions were performed to inform use of MZE829 with other medications used in patients with proteinuric kidney disease.

Results: The study is in progress. Final safety and pharmacokinetic results will be presented.

Conclusions: MZE829 is a potent, selective, small molecule APOL1 inhibitor. Phase 1 evaluation in healthy participants demonstrated that safe and well-tolerated doses of MZE829 achieve exposures through the target efficacious range. Trials in patients with AMKD will be conducted to demonstrate clinical proof of concept for proteinuria reduction

Funding: Commercial Support - Maze Therapeutics

TH-PO618

Complement Activation Products in Kidneys of Patients with Primary Focal Segmental Glomerulosclerosis

Xiaojie Gong, Jing Huang, Zhao Cui, Ming-Hui Zhao. *Peking University First Hospital Department of Nephrology, Beijing, China*.

Background: Plasma and urinary complement profile of patients with primary focal segmental glomerulosclerosis (FSGS) have provided compelling evidence indicating the participation of complement system in FSGS pathogenesis. However, the profile of complement activation in glomeruli of primary FSGS requires clarification.

Methods: Fifty-four patients with primary FSGS were enrolled. Kidney deposition of complement C1q, MBL, C4d, Bb, C3d and C5b-9 was detected by immunohistochemistry. The correlations between clinical features and glomerular complement deposits were analyzed.

Results: The percentages of glomeruli with positive staining of C1q, C4d, Bb, C3d and C5b-9, and the IOD of MBL were significantly higher in patients with primary FSGS than those in healthy controls (all *P*<0.001). Among FSGS patients in comparison with tip variant, the percentages of C4d positive glomeruli were significantly higher in NOS variant (*P*=0.03), cellular variant (*P*=0.003), and perilihar variant (*P*=0.007); the

percentage of Bb positive glomeruli was significantly higher in cellular variant (*P*=0.02); the percentages of C5b-9 positive glomeruli were significantly higher in NOS variant (*P*=0.001) and cellular variant (*P*=0.001). The percentage of C4d positive glomeruli exhibited positive correlation with the percentage of segmental glomerulosclerosis (r=0.33, *P*=0.02). The percentage of C5b-9 positive glomeruli exhibited negative correlation with eGFR (r=-0.29, *P*=0.04) and positive correlation with the percentage of segmental glomerulosclerosis (r=0.37, *P*=0.008). The percentage of C3d positive glomeruli was significantly higher in the relapse cases than the non-relapse ones (*P*=0.02). The patients with a higher percentage of C5b-9 positive glomeruli had worse kidney prognosis during follow-up (Log-rank, *P*=0.02).

Conclusions: The complement system is activated in primary FSGS, via the classical pathway and alternative pathway. The complement activation was closely related to the pathogenesis of NOS and cellular variant, and correlated with the severity of nephrotic syndrome and kidney outcome. These findings indicate that complement system may actively participate in the mechanism of FSGS.

Funding: Government Support - Non-U.S.

TH-PO619

Efficacy and Safety of Rituximab in Patients with Focal Segmental Glomerulosclerosis (FSGS): A Single-Center Retrospective Cohort

Amnah T. Kashkari,[1] Nahlah A. Alagla,[1] Hanin S. Aldalham,[1] Gamal Mohamed,[1] Turki Al Hussain,[1] Abeer A. Alkhawlani,[2] Rojina F. Mohamed,[2] Bushra S. Khan,[2] Fawzy M. Abodahab,[2] Ahmed F. Elfar.[1] *[1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [2]Alfaisal University College of Medicine, Riyadh, Saudi Arabia.*

Background: FSGS is a pattern of glomerular lesion which can be primary or secondary. Current therapy is based on FSGS category, avoiding immunosuppressive therapy in non primary-FSGS. Rituximab may be useful in the management, however clinical evidence in adults is limited. Our study assessed the efficacy of Rituximab in adolescents and adults with FSGS.

Methods: We retrospectively reviewed all biopsy proven FSGS from 2010 to 2021. Patients aged ≥ 14 years who received at least one dose of Rituximab were included. Primary outcome was response rate at 3, 6 and 12 months. It was classified as complete or partial remission according to KDIGO criteria.

Results: A total of 30 patients were included. Baseline characteristics are shown in table 1. Response rate (combined complete and partial) at 3, 6 and 12 months was 67 %, 70%, and 69% respectively as in figure 1. At 6 months, 65% of responded patients had B cell depletion. A better response was observed with steroid dependent patients. Median time to first relapse from last Rituximab dose was 11 months with relapse rate of 53%. Regarding safety, mild reactions were reported consistent with the known safety profile of Rituximab.

Conclusions: Our data suggests that Rituximab is effective in FSGS especially those who are steroid dependent. However relapse rate is significant once Rituximab is stopped. To support our result, further studies are needed with larger volume of patients.

Table 1: Baseline Characteristics of 30 Patients with FSGS

	At Diagnosis	At Rituximab Administration
Age (group)	Adolescent 9 (30) Adult 21 (70)	
Age (yrs)	20 (13)	23.5 (14)
Gender	Male 16 (53.3) Female 14 (46.6)	
FSGS classification	Primary 28 (93) Secondary 2 (7)	
Steroid dependent	Dependent 20 (66.6) Resistant 10 (33.3)	
Serum Creatinine (umol/L)	65 (40)	75 (99)
Serum Albumin (g/L)	20 (15)	25 (16)
Urine protein creatinine ratio (mg/mmol)	478.4 (265)	511 (582)

Table 1: results are expressed in N (%) for categorical variables and median (interquartile range) for continues variables

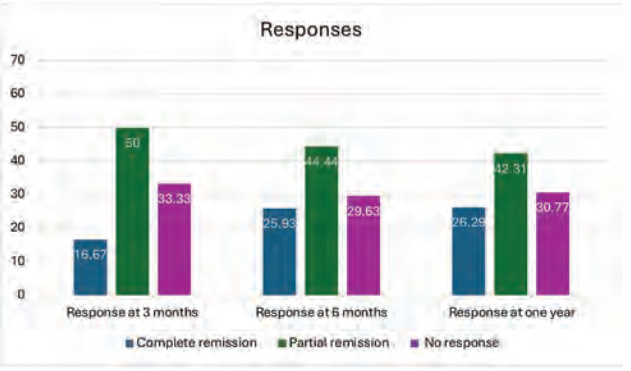


Figure 1

TH-PO620

A Pilot Study on the Efficacy and Safety of Rituximab in the Maintenance of Remission in Adults with Minimal Change Disease

Wang Ling, Xiao Fei, Dai H. Zi. *Department of Rheumatology and Clinical Immunology, Daping Hospital, Army Medical University (Third Military Medical University), Chongqing, China.*

Background: Minimal change disease (MCD) is a common etiology of nephrotic syndrome (NS). Steroid therapy is usually effective, but frequent relapses / steroid-dependent are therapeutic challenges. Rituximab (RTX) has shown promising results in inducing remission of relapsed and refractory MCD in adults, reducing the recurrence rate of the disease and prolonging the recurrence-free time. However, the efficacy and safety of RTX in maintaining the remission of adult-onset MCD have not been reported.

Methods: 12 patients were confirmed by renal biopsy as MCD and received intravenous methylprednisolone (500mg/d, for 3 days) followed by oral methylprednisolone (0.8mg / kg / day). All patients achieved complete remission(CR) within 8 weeks,and then were randomised 1:1 to receive methylprednisolone(n=6) and RTX (n=6, 375mg/m2, intravenous, once weekly, 2 times in total). The methylprednisolone maintenance remission group(MMRG) continued oral methylprednisolone alone, with a reduction of 4 mg every 2-4 weeks. In the RTX maintenance remission group(RMRG), the methylprednisolone was reduced from the 9th week to discontinuation. The total exposure time of methylprednisolone was no more than 9 weeks.

Results: All patients presented with NS with a median urine protein quantification of 10.89 g/24h (5.9, 13.8 g/24h) and a median serum albumin level of 16.7 g/l (13.43, 19.85g/l). Their renal function was normal when MCD was diagnosed. Of the 6 patients with MCD in MMRG, there were three patients of relapsed during glucocorticoid reduction, 1 patient relapsed 1 month after glucocorticoid withdrawal, and 2 patients relapsed 2 months after glucocorticoid withdrawal. The Median duration of sustained remission was 7 months (4.75, 8 months, inter quartile range (IQR)). 6 patients in RMRG during a follow-up of 18.5 months (17, 20.5 months) had no relapse. Compared with the MMRG, the RMRG had significantly longer recurrence-free time (*P*<0.001) and less glucocorticoid exposure(*P*<0.001). No adverse events occurred in all patients.

Conclusions: RTX maybe an effective and safe treatment option for adult patients with first-episode MCD in maintaining disease remission and minimizing glucocorticoid exposure. However, high-quality clinical studies are needed to confirm the efficacy of rituximab in the maintenance of remission in first-episode MCD.

Funding: Government Support - Non-U.S.

TH-PO621

Plasma Exchange and Rituximab for Prevention of Recurrent FSGS after Previous Graft Loss

Sophie Gharaei,[1,2] Durga Anil K Kanigicherla,[2] Hashim Abbas.[2] *[1]The University of Manchester Faculty of Biology Medicine and Health, Manchester, United Kingdom; [2]Manchester Royal Infirmary, Manchester, United Kingdom.*

Background: Primary focal segmental glomerulosclerosis (FSGS) commonly recurs after transplantation, significantly increasing the risk of graft dysfunction, especially in patients with prior graft loss due to recurrent FSGS (rFSGS). Even though therapeutic plasma exchange and rituximab have found increasing use in the treatment of post-transplant recurrence, there is no clear consensus on pre-transplant interventions to prevent recurrence in this patient cohort.

Methods: We conducted a systematic review on the role of prophylactic use of rituximab and plasma exchange to prevent the recurrence of FSGS in patients with prior graft loss due to rFSGS. We analysed the outcomes of 32 patients who had a diagnosis of primary FSGS in their native kidneys, lost one or two prior transplants due to recurrence of FSGS, and received prophylactic treatment with plasma exchange, rituximab or a combination of both.

Results: Table 1 summarises the recurrence rates after different prophylactic treatments, encompassing 32 patients across 11 studies with prior graft loss and re-recurrence. Plasma exchange in isolation (62.5%) was the more common intervention used in these patients, rituximab was used in combination in 25%, and in isolation in 12.5% of patients. Recurrence rates were similar across the three interventions. Overall, 47% experienced recurrence, either immediately or within the first three months after transplantation. 53% remained free of FSGS in the index transplant, with a minimum follow-up of 8 months.

Conclusions: Pre-transplant measures may have a role in the prevention of recurrence of post-transplant FSGS in high-risk patients. The paucity of reliable data available in the literature calls for larger prospective controlled studies to further investigate the effectiveness of pre-emptive plasma exchange and rituximab in preventing this devastating complication in patients with rFSGS.

Prophylaxis (n)	Recurrence (%)	No Recurrence (%)
PE only (20)	9 (45)	11 (55)
RTX only (4)	1 (25)	3 (75)
PE + RTX (8)	5 (63)	3 (37)
Total (32)	15 (47)	17 (53)

Table 1. Rates of rFSGS following prophylactic use of plasma exchange (PE) or rituximab (RTX).

TH-PO622

Obinutuzumab in Children with Kidney Diseases: A Single-Center Experience

Shefali Vyas,[1] Ursula Nath,[2] Benjamin Steinman,[1] Isabel Roberti.[1]
[1]RWJBarnabas Health, West Orange, NJ; [2]University of Delaware, Newark, DE.

Background: Chart review of children with refractory kidney diseases treated with Obinutuzumab. Obinutuzumab an antiCD20 monoclonal antibody developed to overcome rituximab resistance in B-cell malignancies, has demonstrated superior outcomes. Obinutuzumab is proven to be effective in the treatment of active lupus nephritis and membranous nephropathy. There are only 2 peds studies reporting its use in SDNS and MN.

Methods: Chart review was done of children who received Obinutuzumab between 2020 and 2024. All received Obinutuzumab (1000 mg/1.73 m2/dose) and one received Ofatumumab (300 mg/1.73 m2/dose). Indications: adverse reaction or disease relapse after Rituximab; refractory nephropathies to standard therapy (abnormal eGFR or severe proteinuria). Demographic data, etiology of kidney disease, kidney biopsy results, therapies used, eGFR, Urine pr/cr, follow-up time & side effects were collected. Improvement in the degree of proteinuria and/or eGFR changes were reviewed

Results: Total of 46 infusions in 29 patients. Male 52%, Hisp 52%, AA= 27%, C= 7% and other =14%. **Median age** at presentation = 5 yrs. **Etiology**: NS= 22 (76%) [SDNS=13 (59%), SRNS= 41%]; 2 pts post Txp NS (1 FSGS recurrence; 1 de novo MCNS); chronic GN = 5 (17%) (C3GN, SLE, IgAN, C1Q); AIN with AKI=2 (7%). **Biopsy** =25 (96%). **Initial therapy:** All received steroids; Ritx= 20 (69%), CNI (tacro/CSA) = 19 (66%), MMF= 17 (59%), Cytx =7 (30%). **Median age at time** of med =13 yrs, **Median time to respond** = 25 days**. Time of obinutuzumab from diagnosis** 2m-14 years (median 4 yrs). 6 patients received > 2 doses **Proteinuria**: 34 infusions at the time of relapse. Pre-tx no proteinuria =1, mild proteinuria (<2.5 g/g Cr) = 6 ; nephrotic proteinuria (>2.5g/g Cr) = 27. **AKI/CKD** =6 (20%) **ACEi/ARBs**: 48%(14/29) HTN= 24% (7/29) **Post-tx** = 6 patients had mild proteinuria and 1 nephrotic range. (pvalue <0.001) Complete remission of proteinuria was achieved in 75%. **At last follow up:** CKD=5; in all eGFR improved with average 33% post tx. 1 death **Follow up time** (3 to 44 mos; median= 10). Post tx: all patients off steroids and 24% (7/29) off all immunosuppressive therapy

Conclusions: Obinutuzumab was well tolerated in children with various refractory nephropathies. We noted significant reduction in proteinuria and 33% improvement in eGFR. All patients were able to be weaned off the steroids, 75% had complete remission and 24% were off all medications.

TH-PO623

Successful Treatment of Primary FSGS with LDL Apheresis

Anjali B. Nayak,[1] German A. Lozano-Guzman,[1] Raja Dandamudi,[2] Joshua Zaritsky.[1] *[1]Phoenix Children's Hospital, Phoenix, AZ; [2]Washington University in St Louis, St Louis, MO.*

Background: Focal Segmental Glomerulosclerosis (FSGS) remains one of the most common causes of pediatric end stage kidney disease (ESKD). Its treatment remains empiric and is often unsuccessful with significant treatment morbidity. Additionally, recurrence of FSGS is quite common in renal allograft recipients. Therefore we wanted to describe the efficacy and safety of LDL-A in 4 patients with primary FSGS resistant to multi-drug therapy

Methods: Retrospective, single center study. LDL-A was done using the Liposorber LA-15 system, with 12 treatments over 9 weeks. Patients received IV methylprednisolone with the last 6 treatments (Table 1).

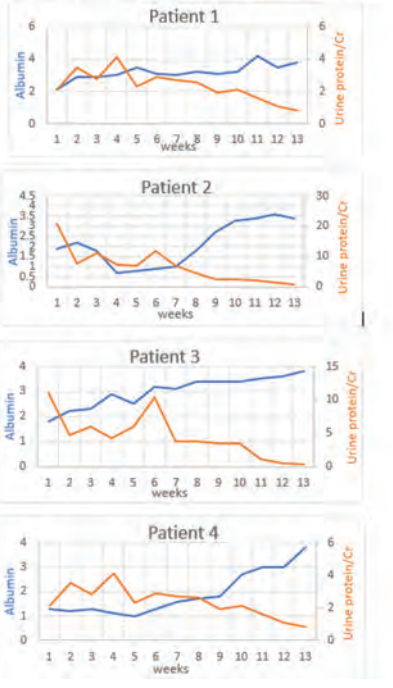
Results: Primary outcomes were measured by either complete remission (CR), or partial remission (PR). CR was a urine protein to creatinine (UPC) of less than 0.5 mg/mg. PR was a UPC between 0.5 mg/mg to 2 mg/mg, and greater than or equal to 50% reduction on proteinuria. Secondary outcomes included improvement in serum albumin. We treated 4 patients with FSGS resistant to multi-drug therapy. All 4 patients responded and went into complete remission. (Pic 1).

Conclusions: All 4 of our patients were able to achieve complete remission of primary FSGS despite a lengthy history of multi-drug resistance. This builds on existing evidence demonstrating the utility of LDL-A in recurrent disease. Although future studies are needed to determine its mechanism of action, LDL-A is a well-tolerated treatment that may become a standard of care in both primary and recurrent FSGS.

Clinical characteristics of patients at baseline

	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis(years)	3	3	5	2
Age at LDL-A treatment	4.5	4.5	5.5	14
Initial treatment course	Steroids, mycophenolate, tacrolimus and rituximab	Steroids, mycophenolate, tacrolimus and rituximab	Steroids, mycophenolate, tacrolimus and rituximab	Steroids, mycophenolate, tacrolimus and rituximab
Post LDL-A course	Went into CR	Went into CR	Went into CR	Went into CR

Figure 1. UPC trend and albumin trend of patients with SRNS during LDL-A treatment and follow up



TH-PO624

Characteristics of Dyslipidemia in Primary Nephrotic Syndromes

Sulaiman M. Alhumaid,[1,2] Hamzah A. Alhamzah,[3] Ali S. Almagooshi,[1] Ahmad M. Samman,[1] Ali M. Alqaraishi,[1] Muhannad Alqudsi.[1]
[1]King Abdulaziz Medical City, Riyadh, Saudi Arabia; [2]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [3]Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia.

Background: Although it is not a criterion for diagnosis, dyslipidemia is frequently found in nephrotic syndrome (NS). Cholesterol, triglyceride, and low-density lipoprotein (LDL) are usually elevated in NS, while high-density lipoprotein (HDL) can be normal or minimally decreased. Mechanisms, treatments, and related medical outcomes of dyslipidemia in NS have been studied in isolation of the underlying disease, hence the comparison of lipid values between primary membranous nephropathy (MN), minimal change disease (MCD), and primary focal segmental glomerulosclerosis (FSGS), is not well recognized.

Methods: Retrospective chart review of patients with NS from 2010-2022. Only patients with primary MN, MCD, and primary FSGS were included. Lipid profile was reported at the time of NS diagnosis and twelve months later. We compared lipid values between three primary NS using Kruskal-Wallis and Mann-Whitney U tests.

Results: There were 409 patients diagnosed with NS. 284 patients were excluded due to insufficient data, secondary NS, or uncontrolled DMII (glycated hemoglobin A1C>8). 125 patients with primary FSGS, MN, or MCD were included. 52=FSGS (41%), 31=MCD (25%), 42=MN (34%). Average age was 32 years, 55=Females (44%), 25=Diabetes Mellitus (DM) (20%), 79=received statin (56%), there was no statistical difference in baseline characteristics between NS groups. After adjustment to serum albumin and urine protein/creatinine ratio, initial cholesterol and triglyceride were similar

in three NS groups (P>0.05), LDL was 216 mg/dL, 201 mg/dL, and 178 mg/dL in FSGS, MCD, and MN respectively p= 0.04 (statistical difference was only in FSGS vs MN group p=0.04), initial HDL was 58 mg/dL, 77 mg/dL, and 50 mg/dL in FSGS, MCD, and MN respectively p=<0.001 (statistical differences were in MCD vs FSGS, and MCD vs MN groups p=0.001, and p=<0.001 respectively). After 12 months follow up, all lipid values were similar in three NS groups regardless of statin use.

Conclusions: After adjustment to primary NS severity, cholesterol and triglyceride values are not significantly different at presentation of MN, MCD, and FSGS. HDL is significantly higher in MCD compared to MN, and FSGS. LDL is significantly higher in FSGS compared to MN. At 12 months follow up, use of statin did not change lipid values in MN, MCD, or FSGS.

TH-PO625

Lipidomics Analysis Reveals Biomarkers for Proteinuria Remission and Disease Progression in FSGS/Minimal Change Disease (MCD) from the NEPTUNE Cohort

Takaya Ozeki,[1,2] Fadhl Alakwaa,[1] Anna V. Mathew,[1] Matthias Kretzler,[1] Laura H. Mariani.[1] NEPTUNE (Nephrotic Syndrome Study Network).
[1]University of Michigan, Ann Arbor, MI; [2]Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: FSGS/MCD exhibits significant heterogeneity, presenting a challenge for effective treatment. Assessment of the systemic metabolic changes reflected in circulating lipids and capture of lipid signaling molecules can illuminate this complexity.

Methods: We examined 131 participants with FSGS/MCD from the NEPTUNE cohort, analyzing plasma samples collected within 45 days of kidney biopsy. Lipidomics profiles were obtained through liquid chromatography-mass spectrometry (LC-MS), utilizing in silico tandem mass spectral databases for identification and established normalization method. Rigorous data filtration included the removal of low variance and high missing rate features, missing value imputation, log transformation, and scaling. A Cox-Elastic Net model with 5-fold cross-validation was employed to identify lipids associated with complete remission of proteinuria (CR, UPCR<0.3) and disease progression (40% decline of eGFR or ESKD).

Results: Among the 131 participants, 59.5% had FSGS, 64.1% were adults, and 62.6% were male. Median UPCR level was 1.65, and 31.3% had nephrotic range proteinuria (UPCR>3.5). Median eGFR levels was 84.1 at the sample collection. Over a median follow-up of 51.0 months, 50.0% achieved CR, while 26.2% reached to the composite renal outcomes. We measured 984 plasma lipids, of which 732 met our stringent quality criteria for further analysis. Among these, 37 lipids were associated with CR and 69 with disease progression. Notably, five of them were linked to both outcomes and belong to the Glycerophospholipids, Sphingolipids, and Glycerolipids lipid categories (Table 1).

Conclusions: This lipidomics analysis of FSGS/MCD patients identified specific lipid classes, including Glycerophospholipids, Sphingolipids, and Glycerolipids, as potential biomarkers for proteinuria remission and disease progression. These findings can offer insights into the heterogeneity in FSGS/MCD and suggest avenues for personalized therapeutic interventions. Further mechanistic studies are needed to elucidate the specific roles of these lipid categories in remission of proteinuria and disease progression.

Funding: NIDDK Support, Other NIH Support - NCATS

Table1. Lipids Associated with both Complete Remission and Disease Progression

		Complete Remission					Disease Progression				
Name	Categories	Rank	Importance	HR	IQR	P-value	Rank	Importance	HR	IQR	P-value
PC O-36:3	Glycerophospholipids	20	0.079241	1.43	[1.04-1.97]	0.026	60	0.021174	0.62	[0.43-0.90]	0.012
SM 42:2;2O	Sphingolipids	36	0.010863	0.76	[0.59-0.99]	0.046	57	0.024742	1.46	[1.00-2.12]	0.048
Cer 40:1;2O	Sphingolipids	16	0.038780	0.76	[0.55-1.05]	0.099	16	0.116832	1.94	[1.29-2.97]	0.002
LNAPE N-39:5	Glycerophospholipids	18	0.086659	0.65	[0.49-0.87]	0.003	43	0.150235	1.61	[1.10-2.37]	0.015
MGDG O-28:0	Glycerolipids	4	0.157394	0.67	[0.49-0.92]	0.013	19	0.114708	1.68	[1.07-2.65]	0.025

PC, phosphatidylcholine; SM, sphingomyelin; Cer, ceramides; LNAPE, N-acyl lysophosphatidylethanolamine; MGDG, monogalactosyldiacylglycerol
Rank, rank of variable importance through Cox-Elastic Net algorithm; Importance, magnitude of the variable importance assigned by Cox-Elastic Net
HR, hazard ratio from the univariate Cox proportional hazards model; IQR, interquartile range from the Cox proportional hazards model

TH-PO626

Association of Proteinuria Remission and Its Timing with Kidney Outcomes in Patients with Focal Segmental Glomerulosclerosis

Takehiko Kawaguchi,[1] Toshiyuki Imasawa,[1] Moritoshi Kadomura,[1] Hiroshi Kitamura,[1] Takaya Ozeki,[2] Ritsuko Katafuchi,[3] Kazamasa Oka,[3] Kengo Furuichi,[3] Yoshitaka Isaka,[3] Hiroshii Sato,[3] Hitoshi Sugiyama,[3] Shoichi Maruyama.[2,3] *[1]National Hospital Organization Chibahigashi National Hospital, Chiba, Japan; [2]Nagoya University, Nagoya, Japan; [3]Ippan Shadan Hojin Nihon Jinzo Gakkai, Bunkyo-ku, Japan.*

Background: Focal Segmental Glomerulosclerosis (FSGS) is a leading cause of end-stage kidney disease (ESKD), and proteinuria remission (PR) is associated with improved renal prognosis in patients with FSGS. However, it is unclear whether the timing of PR affects renal outcome.

Methods: Data on 304 patients with biopsy-confirmed FSGS of Japan Renal Biopsy Registry from 2010 to 2013 were analyzed [median age: 52 years; female: 37%; median eGFR: 58 ml/min/1.73m^2; nephrotic proteinuria: 54%; histologic variant: not otherwise specified (NOS) 48%, tip 19%, perihilar 15%, cellular 13%, collapsing 5%]. Patients were divided into 4 groups based on timing of PR (<0.3 g/day) from biopsy: ≦2 months, 2 to 12 months, >12 months, and no PR during follow-up. The primary outcome was a composite of progression to ESKD or all-cause death 5 years after biopsy. Kaplan-Meier curves and multivariable Cox models were used to compare the outcomes among these groups.

Results: One hundred thirty-six patients (45%) achieved PR, with a median time to PR of 4 (interquartile range 2, 13) months (Figure 1). During the median follow-up period of 4.8 years, outcome events occurred in 37 patients (12%). Overall, PR was associated with the primary outcome (adjusted hazard ratio [aHR]: 0.08 [95% confidence interval (CI), 0.02-0.30]). However, no significant difference in the outcome was found among the three groups achieving PR (Figure 2); compared with PR ≦2 months, the aHR for the outcome was 0.87 [95% CI, 0.05-14.2] for PR between 2 and 12 months, 1.04 [95% CI, 0.06-17.6] for PR ≧12 months, and 11.1 [95% CI, 1.38-93.5] for no PR.

Conclusions: Although PR itself has an impact on renal outcomes of FSGS during 5 years, the timing of PR may not predict improved renal prognosis. Specific strategies and interventions to achieve PR should be implemented for better renal outcomes at any clinical stage of FSGS.

Funding: Government Support - Non-U.S.

Figure 1.
Distribution of the timing of proteinuria remission (n=136)

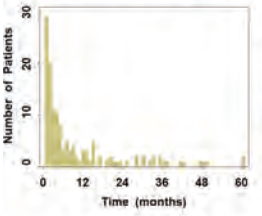
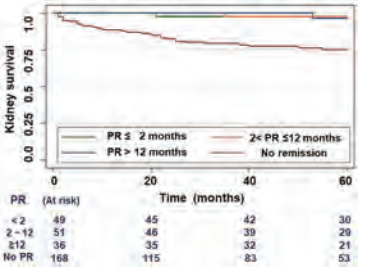


Figure 2.
Association of the timing of proteinuria remission (PR) with the primary outcome (n=304)



PR	(At risk)			
<2	49	45	42	30
2 - 12	51	46	39	29
≥12	36	35	32	21
No PR	168	115	83	53

TH-PO627

Frequency of Adverse Events and Relapses after SARS-CoV-2 Vaccination in Patients with Podocytopathies

Sophia Lionaki,[1,2] Angeliki Sardeli,[1] Marios Papasotiriou,[7] Evangelia Dounousi,[6] Smaragdi Marinaki,[2,8] Kriki Pelagia,[3] Dimitra Gkalitsiou,[4] Vassilios Liakopoulos,[5] Eva P. Andronikidi,[2] Giannakopoulos Panagiotis,[1] Stylianos A. Panagoutsos.[3] *[1]Panepistemiako Geniko Nosokomeio Attikon, Athens, Greece; [2]Ethniko kai Kapodistriako Panepistemio Athenon, Athens, Greece; [3]Demokriteio Panepistemio Thrakes, Komotini, Greece; [4]Geniko Nosokomeio Athenon Giorgos Gennematas, Athens, Greece; [5]Aristoteleio Panepistemio Thessalonikes, Thessalonike, Greece; [6]Panepistemio Ioanninon, Ioannina, Greece; [7]Panepistemio Patron, Patra, Greece; [8]Laiko General Hospital, Athens, Greece.*

Background: To evaluate the impact, if any, of SARS-CoV-2 vaccination in the clinical course of patients with biopsy-proven podocytopathies.

Methods: This is a multicenter retrospective study of patients with histologically proven minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), who were vaccinated against SARS-CoV-2. Patients who had developed ESKD prior to vaccine were excluded. Recorded data included adverse events, immunosuppressive regimens and relapses of the primary disease.

Results: Included patients (N=77) patients were 46.1(±17.8) years old and 38(49.3%) were males. Of these, 68(88.3%) patients had received immunosuppression at diagnosis and 80.5% had achieved remission. The time interval from kidney biopsy to vaccination was 69.2(±75.8) months and received 2.9(±0.76) doses. 37.3% of patients were on immunosuppressive therapy at vaccination. 25.3% of patients reported systemic and 31.8% local adverse events associated with vaccination. Among patients on remission at vaccination, 8(10.4%) experienced a relapse of nephrotic syndrome within 3.5 (±2.7) months. Among relapsers, 5 (71.4%%) had MCD.

Conclusions: Patients with podocytopathies in this cohort had a good vaccine safety profile. Among patientson remission 8(10.4%) experienced a relapse of the primary disease after vaccination.

TH-PO628

Prediction of Response to Intensified Immunosuppression in Childhood Steroid-Resistant Nephrotic Syndrome by Multimodal Machine Learning

Franz Schaefer,[1] William Morello,[7] Huy Q. Vo,[6] Anibal Pedraza,[3] Nicola Altini,[4] Moin A. Saleem,[5] Chandra Mohan,[6] Jan U. Becker.[2] *[1]Universitat Heidelberg, Heidelberg, Germany; [2]Universitat zu Koln, Cologne, Germany; [3]Universidad de Castilla-La Mancha, Ciudad Real, Spain; [4]Politecnico di Bari, Bari, Italy; [5]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom; [6]University of Houston, Houston, TX; [7]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.*

Background: There are no established models to predict the varied response to intensified immunosuppression in steroid-resistant nephrotic syndrome (SRNS). Multimodal machine learning, integrating clinical and genetic data with nephropathology imaging holds great promise to deliver such classifiers with perfect reproducibility. Here, we present such a theranostic classifier based on a multi-centric dataset obtained from the PodoNet registry cohort.

Methods: Data from 201 SRNS patients with available clinical data and whole slide images of kidney biopsies were collected from 14 European pediatric nephrology centres. The clinical input data contained 19 parameters including genetic mutation (yes/no) and eGFR at biopsy; the ground truth theranostic endpoint was treatment response as no (n=114), partial (n=42) and complete remission (n=45) within 6 months as defined by serum albumin and proteinuria changes. We trained our proprietary multimodal MorphSet++ architecture in a weakly supervised fashion. MorphSet++ integrates the clinical data vector from a shallow network at various stages with the transformer-based deep network analysis of the histopathology imaging data. Results are given as means after 5-fold internal cross-validation.

Results: Mean AUC was 80% for complete, 77% for partial and and 81% for no remission. The mean positive predictive value was 89.7, 89.8, 89.3 % and the mean negative predictive value 94.8, 93.4 and 97.6%. Mean sensitivity was 84.2, 67.1, and 98.5% and mean specificity 96.8, 98.4, and 83.9%. Mean balanced accuracy was 90.5%, 82.8%, and 91.2% for no, partial and complete remission, respectively. Adding the results of image analysis improved model performance as compared to clinical/genetic data input alone.t of SRNS.

Conclusions: Our MorphSet++ architecture shows promising results as a theranostic tool to predict response to immunosuppression in SRNS. MorphSet++ allows for rapid up-scaling with additional, larger datasets for even better and more robust performance. This might lead to a re-appraisal of nephropathology in the clinical management of SRNS.

Funding: Government Support - Non-U.S.

TH-PO629

Anti-slit Antibodies on Kidney Biopsy Identify Patients with Steroid-Resistant Nephrotic Syndrome Responsive to Second-Line Immunosuppressant and Hence Have a Good Prognosis

Valentina Raglianti,[1,2] Maria Lucia Angelotti,[2] Luigi Cirillo,[1] Samuela Landini,[1] Viviana Palazzo,[1] Maria Elena Melica,[2] Giulia Antonelli,[2] Carolina Conte,[1] Benedetta Mazzinghi,[1] Francesca Becherucci,[2,1] Paola Romagnani.[1,2] *[1]Azienda Ospedaliero Universitaria Meyer, Firenze, Italy; [2]Universita degli Studi di Firenze, Firenze, Italy.*

Background: Anti-nephrin antibodies have been recently reported in patients with Minimal Change and steroid-sensitive Nephrotic Syndrome (NS), as well as in post-transplant recurrence of Focal Segmental Glomerulosclerosis, supporting an autoimmune etiology in a subset of podocytopathies. We hypothesized that the presence of autoantibodies against slit diaphragm antigens would identify also a subset of patients with steroid resistant NS (SRNS) and explain response to second-line immunosuppressant and hence prognosis

Methods: We evaluated 45 patients with SRNS out of 128 patients with available kidney biopsy samples followed up at Meyer University Hospital IRCCS. By using high-resolution confocal microscopy, we assessed the colocalization between IgG and nephrin staining. To further determine the specificity of the IgG deposition STED microscopy and two different ELISA for anti-nephrin antibodies have been performed

Results: STED microscopy and anti-nephrin ELISA assays suggest that a subset of patients with podocytopathies showed antibodies against either nephrin or non-nephrin slit antigens, i.e. slit antibodies. We observed anti-slit antibodies in 48.5% of non-genetic patients and only in 8.3% of genetic one with SRSN, irrespective of histology lesion patterns. Almost all anti-slit positive patients (92.3%) showed response to second-line immunosuppressive therapy. The only multidrug-resistant anti-slit positive patient reached kidney failure was a diagnosed case of Nail-Patella syndorme. He experienced recurrence after kidney transplantation and anti-slit antibodies have been detected on graft biopsy. Kaplan Meier analysis confirm anti-slit positive patients had a favourable outcome. On the contrary, genetic patient, independently of anti-slit status, and non-genetic anti-slit negative patients, showed poor prognosis at 10 years, both achieving chronic kidney disease and kidney failure

Conclusions: Detection of anti-slit antibodies represents a novel tool for personalized management, by allowing identification of patients more likely to responds to second-line immunosuppressive therapy and have better long term kidney prognosis, i.e. autoimmune podocytopathies

TH-PO630

Soluble Angiopoietins in Idiopathic Nephrotic Syndrome

Sarah K. Nelson-Taylor,[1] Colin D. Bauer,[1] Courtney Giannini,[1] Richard J. Johnson,[1] Gabriel M. Cara-Fuentes.[2] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Nationwide Children's Hospital, Columbus, OH.*

Background: Idiopathic nephrotic syndrome (INS) is associated with endothelial injury, but its involvement is poorly understood. To gain more insights, we measured soluble (serum) angiopoietins (Ang) 1 and 2 and soluble Tie2, as markers of blood vessel homeostasis, in children with INS.

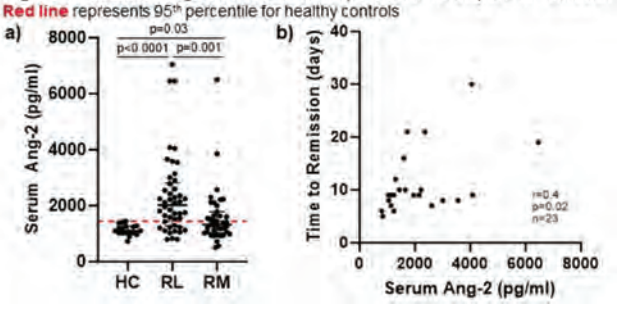
Methods: We included 17 healthy children, 46 children with steroid sensitive INS (either unbiopsied or with minimal change disease pattern on histology) during relapse and 39 during remission. We measured soluble levels of Ang1, Ang2, and Tie2 in serum using commercially available ELISA kits. Currently, we are analyzing additional patients' samples and estimated total of 70 patients/group by november. Non-parametric tests were used to assess differences among groups and correlation between soluble levels in serum and time to achieve remission in those patients studied during remission. In vitro studies involving immortalized human glomerular cells exposed to healthy and disease sera are in process to test whether INS sera may directly stimulate glomerular endothelial cells to release these soluble biomarkers.

Results: Soluble Ang2 (**Fig. 1a**) and Ang1 levels were higher in patients in relapse and remission than in controls, and higher in those in relapse compared to remission. No differences were found in soluble Tie2 levels between healthy controls and patients. In patients studied during relapse (and with documented time in days to achieve remission), higher soluble Ang2 was associated with slower time to achieve remission (**Fig. 1b**).

Conclusions: INS is associated with alterations of markers of blood vessel homeostasis.

Funding: Private Foundation Support

Figure 1. Soluble Ang2 in INS. HC healthy controls, RL relapse, RM remission
Red line represents 95th percentile for healthy controls



TH-PO631

Peripheral Blood Cell DNA Methylation Can Predict Steroid Response in Nephrotic Syndrome

Samantha J. Hayward, Matthew Suderman, Gavin I. Welsh, Moin A. Saleem. *University of Bristol, Bristol, United Kingdom.*

Background: The majority of children with idiopathic nephrotic syndrome (INS) and adults with Focal Segmental Glomerulosclerosis (FSGS) and Minimal Change Disease (MCD) receive glucocorticoid treatment at diagnosis. Overall, about 10% will not respond to steroid treatment and we have no reliable way of prospectively identifying these patients. DNA methylation (DNAm) is an epigenetic mechanism meaning that it can induce stable but reversible changes in gene expression without any change in underlying DNA sequence. DNAm has shown great potential as a treatment stratification tool in other disease settings. We investigated whether DNAm can predict initial response to steroids in children and young adults with INS.

Methods: Two hundred and eighty one INS patients recruited to the NephroS and NURTuRE cohorts were selected. All patients had been diagnosed with INS ≤ 30 years of age and those who underwent a renal biopsy had a histological diagnosis of FSGS or MCD. Peripheral blood DNAm measurements were generated using the Illumina MethylationEPIC Beadchip (>850,000 CpG sites). Clinical data was used to label patients by their initial response to steroids. Machine learning models were created to predict steroid response from the DNAm data. Models were generated using elastic net following feature filtering, and model hyperparameters were tuned and performance measured within the context of cross validation.

Results: The 281 INS patients had a median age at diagnosis of 5 years (IQR 2-10) and the majority were white (n=198, 71%). The median time between diagnosis and DNAm sample collection was 4 years (IQR 1-10). One hundred and thirty five patients

were sensitive to their first course of steroids and 146 were resistant. The steroid resistant group included patients with known monogenic disease (n=46, 31%). Using the DNAm data, initial response to steroid treatment could be predicted with 70% accuracy and an area under the curve (AUC) of 0.76, (sensitivity 0.79, specificity of 0.60, Figure 1). The final steroid response prediction model contained 14 CpG sites.

Conclusions: We have demonstrated that peripheral blood cell DNAm profiles are a promising predictor of steroid response in INS. Further work to incorporate genetic data into the prediction models is underway and external validation of the results in a separate cohort of patients is required.

TH-PO632

Qualitative Findings for Preparing a Clinical Outcomes Assessment Set (COA) for Nephrotic Syndrome (Prepare-NS)

Eloise Salmon,[1] Somayeh Hashemi,[1] Tina Creguer,[1] Courtney N. Hurt,[2] Rebecca Scherr,[1] Yan Zhai,[1] Noelle E. Carlozzi,[1] Jin-Shei Lai,[2] Shikha Wadhwani,[2] John D. Peipert.[2] *[1]University of Michigan, Ann Arbor, MI; [2]Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Fluid overload (FO) in nephrotic syndrome (NS) impacts health-related quality of life (HRQOL). Partnering with Food and Drug Administration (FDA), Prepare-NS aims to create and validate COA of FO in NS for use in drug trials over the lifespan. Prepare-NS has developed and debriefed survey items capturing key aspects of FO and its impact on function.

Methods: Individuals with (or caregivers of young children with) focal segmental glomerulosclerosis, minimal change disease, IgM nephropathy, membranous nephropathy, or childhood-onset NS (no biopsy) who had NS edema within 3 months volunteered for interviews on study website. Concept elicitation (CE) by Zoom or phone discussed how FO impacts functioning and other symptoms. Transcripts were coded in NVivo by two independent raters. Recurring themes informed conceptual model development and draft survey items. Additional participants provided feedback on draft items by cognitive debriefing (CogDe).

Results: 32 individuals with NS and 26 caregivers of children with NS completed CE. 6 CogDe interviews analyzed to date. Figure 1 shows demographics. CE themes overall consistent across the lifespan, and among sex, race, and diagnosis groups. Figure 2 shows quotations from CE (by conceptual model domain) and CogDe.

Conclusions: FO in NS over the lifespan impacts multiple HRQOL domains. Validation of survey instruments as COAs in a larger quantitative study is the next phase of Prepare-NS.

Funding: Other U.S. Government Support

	Parents/Guardians of Children Ages 2 - 11 (n = 26)	Children and Adults Ages 9+ (n = 32)	Cognitive Debriefing Participants (n = 6)
Sex at birth – n (%)			
Female	14 (54)	20 (65)	5 (83)
Age – Range	2 - 11	13 - 72	7 - 54
Race – n (%)			
White	21 (65)	22 (69)	3 (50)
Black	3 (12)	3 (9)	2 (33)
Asian	1 (4)	4 (13)	
Multiple	1 (4)		
Did Not Respond		3 (9)	
Ethnicity – n (%)			
Hispanic/Latino	4 (15)	4 (13)	1 (17)
Diagnosis – n (%)			
Focal Segmental Glomerulosclerosis	4 (15)	12 (37)	3 (50)
Minimal Change Disease	5 (19)	10 (31)	2 (33)
Childhood Onset Not Biopsied	14 (54)	1 (3)	
Membranous Nephropathy	1 (4)	8 (26)	
IgM Nephropathy	2 (8)	1 (3)	1 (17)

*Note: Where caregivers responding for young children, demographic data for child with NS.

	Representative Quotations from Parents/Guardians of Children Ages 2 - 11	Representative Quotations from Individuals Ages 9+
Concept Elicitation		
Physical Function		
Upper Extremity Function	And he couldn't even hold the crayon because his hands were too puffy.	It almost feels like there's something at the bottom of my - like the base of my fingers, like preventing me to like move my hands.
Activities of Daily Living	Putting his shirt on is tough. Putting his socks and shoes on is tough. Bending down to just, like, reach his toes is tough because of the belly.	Sometimes when I swell too much it's for me to put my clothes on because it's hard for me to move
Mobility or Walking	Sometimes she waddles because she gets so big, like a little penguin, like she just waddles around.	Sometimes the swelling would feel like it's getting pushed into my toes and hurt. Enough that I couldn't really walk
Physical Symptom		
Appetite, Thirst, Dietary	She wasn't eating as much. She would say she was full. She would take like one bite, and then, be like "I'm full," you know, "I don't want anything else."...like whenever she swells up.	I didn't really have an appetite at all. I felt like my stomach was full all the time, because of the swelling.
Fatigue	He had very, very low energy, and he would just want to lay around all day.	I just felt like I was drained of energy.
Sleep	He tosses and turns until he's able to find something comfortable sometimes. There are nights where he's moving around so much where he doesn't get the adequate sleep that he needs.	I do get like super tired where I'll stay in bed all day.
Gastrointestinal Diseases	Yeah, when he begins to relapse, he'll have more diarrhea, and then it will quickly turn into constipation.	I go through a lot of times where I am nauseous, and it doesn't really it kind of comes in waves, and I don't really understand where it's coming from, because I don't I don't vomit
Pain, Aches, Cramps, Discomfort	When she was swollen, like all over her body, she was having, like, a pain from every touch on the worst day.	I think the only thing that swelling caused was pain in my feet when I walked. If I was putting weight on my feet, then there was pain
Essential Function		
Breathing	When she was the most swollen that it did seem like her breathing was a little labored because her belly, and everything was so tight.	I just couldn't breathe in all the way because I felt like my stomach was sort of suppressing my lungs.
Urination	[Going]to the bathroom is a big one when he's swollen. He has a really hard time with that because his groin gets so swollen	Just I physically can't pee, because all the swelling
Vision	And her little eyes are so swollen that she can't see very well.	Then I would wake up with my eyes -- my eyes would be swollen out of my face. I mean I couldn't even – I could barely even open my eyes, it was that bad
Cognitive Debriefing		
	When it's at her worst all of these are relevant, every single thing.	I understand the question. It's not repetitive of any of your other questions so far
	That was easy to answer, too, and easy to understand.	All of those questions, all of them. Hitting the nail on the head.
	I can see the relevance of the question. It doesn't necessarily affect my child. But I can see the relevance of the question. I understood the question.	That's a good question. It helps, That helps give you an idea of severity.

TH-PO633

Clinical Characteristics of Young and Elderly Patients with Minimal Change Nephrotic Syndrome

Kodai Furukawa, Shinya Yamamoto, Naoko Yasugi, Hideki Yokoi, Motoko Yanagita. *Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.*

Background: The clinical features and favorable response to treatment in young patients with minimal change nephrotic syndrome (MCNS) have been reported. However, clinical differences between young and elderly patients remain unclear.

Methods: We evaluated 17 patients diagnosed with MCNS by renal biopsy between January 2019 and December 2023 at our hospital and divided them into two groups: younger (< 65 years) and elderly (≥ 65 years) patients. We collected clinical deta retrospectively.

Results: Of the 17 patients diagnosed with MCNS on renal biopsy, 8 were elderly and 9 were young, with mean ages of 71.7 (median 71.5) and 36.7 (median 34.0) years, respectively. The number of patients diagnosed with acute kidney injury (AKI) at the time of biopsy was higher in the elderly group (7 in the elderly group (87.5%) and 5 in the young group (55.5%)), of whom 6 (75%) in the elderly group had more severe AKI (> stage 2) and 2 (22.2%) in the young group. There was a significant difference between the young and elderly groups ($p < 0.05$). All patients received high doses of steroids (> 0.50 mg/kg body weight/day) as initial treatment, and all patients who responded to treatment achieved complete remission, 6 patients (75%) in the elderly group, and all in the young group. The median time to achieve complete remission was significantly longer in the elderly group (28.0 vs. 9.0 days, $p < 0.05$). In patients who achieved complete remission, there was no significant difference in the following oral steroid doses (0.69 vs. 0.75 mg/kg body weight/day) and the mean urine protein-to-creatinine ratio (10.1 vs. 12.3 g/gCr) at the time of biopsy between the young and elderly groups. The ratios were not significantly different after 12 months of treatment among the 11 patients, excluding 2 elderly patients who underwent dialysis and 3 elderly patients who died during the period due to myocardial infarction, lung cancer, and myelodysplastic syndromes.

Conclusions: We reveal clinical differences between young and elderly patients with MCNS. MCNS in the elderly is associated with more severe AKI and a longer time to achieve complete remission than MCNS in younger patients. When treating elderly patients with MCNS, we should be alert to the complications of steroids and nephrotic syndrome with severe renal impairment, induced by prolonged time to remission.

TH-PO634

Distinctions between C1q Nephropathy and Other Glomerular Diseases with Overlapping Clinical and Pathologic Features

Vanessa Moreno, Yichun Hu, Volker Nickeleit, Harsharan K. Singh, J. Charles Jennette. *The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.*

Background: C1q nephropathy (C1qN) has prominent mesangial C1q immunostaining with varying staining for immunoglobulins. C1qN has overlapping clinical and pathologic features with minimal change disease (MCD), IgM nephropathy (IgMN), focal segmental glomerulosclerosis (FSGS), and class I/II (mesangiopathic) lupus nephritis (MLN). The distinctiveness of C1qN is controversial. C1qN is often considered a variant of MCD and FSGS, or seronegative LN. We compared C1qN demographic, clinical and pathologic features to IgMN, MLN, FSGS and MCD.

Methods: Using data from the UNC Glomerular Disease Collaborative Network, demographic, clinical, and kidney biopsy light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) data were analyzed from 150 C1qN, 34 IgMN, 104 MLN, 279 FSGS and 115 MCD patients. Diagnosis of C1q nephropathy required C1q staining ≥2+ (scale of 0-4+) with no clinical SLE. Pathology data was prospectively scored at diagnosis. Statistically significant distinctions between C1qN and other glomerular diseases were identified.

Results: As shown in the Table, IF and other pathologic features of C1qN, IgMN, FSGS and MCD are different. Compared to C1qN, these patterns of injury have different LM, EM, demographic and clinical features supporting the possibility of different etiologies and pathogenic mechanisms. C1qN has overlapping IF features with MLN and IgMN but demographic and serologic parameters are different. C1qN has pathologic features overlapping with FSGS and MCD but demographic profile is different.

Conclusions: Compared to IgMN, MLN, FSGS and MCD, C1q nephropathy has different pathologic, demographic and clinical features suggesting different etiology and pathogenesis, and different outcome and response to treatment. The next step with these cohorts is analysis of clinical outcomes and responses to therapy.

Variables	C1qN	IgMN	I/II Lupus	FSGS	MCD	P value*			
	N=150	N=34	N=104	N=279	N=115	C1qN vs IgMN	C1qN vs lupus	C1qN vs FSGS	C1qN vs MCD
Age median(IQR)	26.0 (17.0, 36.0)	35.0 (19.0, 53.0)	29.0 (17.0, 39.5)	45.0 (32.0, 60.0)	40.0 (25.0, 57.0)	0.0212	0.2196	<.0001	<.0001
Age at bx						0.3098	0.3376	<.0001	<.0001
% ≤18 yo	34.00%	23.50%	27.90%	9.00%	13.00%				
% >18 yo	66.00%	76.50%	72.10%	91.00%	87.00%				
Sex						0.1811	0.0012	0.0064	0.3834
Male	42.00%	55.90%	22.10%	55.90%	47.80%				
Femal	58.00%	44.10%	77.90%	44.10%	52.20%				
Race						0.0723	0.9736	0.0008	<.0001
W	25%	48.00%	26.60%	43.40%	56.40%				
B	65.50%	48.00%	64.60%	44.60%	30.90%				
O	9.50%	4.00%	8.90%	12.00%	2.70%				
% with hematuria	38.10%	88.20%	81.30%	57.10%	47.00%	0.0035	<.0001	0.001	0.1254
% with proteinuria	99.20%	93.30%	91.80%	99.10%	99.10%	0.0972	0.0111	1	1
gm/24hr, median	3.2	0.9	0.3	3.7	8	0.0006	<.0001	0.0989	<.0001
creatinine, median	1.1	1	0.9	1.6	1.1	0.4733	0.0221	<.0001	0.7585
% +ANA	6.90%	20.60%	94.70%	22.20%	8.70%	0.0278	<.0001	0.0077	0.7861
% low complement	0.00%	80.00%	64.40%	10.00%	2.60%	<.0001	<.0001	0.0139	0.552
Glom	53.10%	73.50%	91.40%	2.90%	3.50%	0.034	<.0001	<.0001	<.0001
Glom sclerosis	85.20%	8.80%	0.00%	100.00%	13.90%	<.0001	<.0001	<.0001	<.0001
IgG, median	1	0	2	0	0	<.0001	<.0001	<.0001	<.0001
IgA, median	0.5	0.5	1	0	0	0.2167	<.0001	<.0001	<.0001
IgM, median	0.5	2	1	0.5	0.5	<.0001	<.0001	<.0001	<.0001
k LC, median	1	0.5	2	0	0	0.7812	<.0001	<.0001	<.0001
λ LC, median	0.5	0.5	2	0	0	<.0001	<.0001	<.0001	<.0001
C3, median	0.5	0.5	2	0	0	0.3531	<.0001	<.0001	<.0001
C1q, median	2	0	1	0	0	0.6276	<.0001	<.0001	<.0001
IgG (>0)	93.30%	44.10%	94.20%	15.00%	11.30%	<.0001	1.000	<.0001	<.0001
IgA (>0)	55.00%	64.70%	89.40%	31.20%	12.20%	0.3419	<.0001	<.0001	<.0001
IgM (>0)	78.70%	100.00%	95.20%	55.80%	50.40%	0.0009	0.0002	<.0001	<.0001
k LC (>0)	89.90%	94.10%	97.10%	28.60%	18.30%	0.743	0.0441	<.0001	<.0001
λ LC (>0)	90.60%	85.30%	95.20%	32.70%	14.80%	0.357	0.2274	<.0001	<.0001
C3 (>0)	83.20%	70.60%	93.30%	43.10%	31.30%	0.0968	0.0207	<.0001	<.0001
C1q (>0)	100.00%	38.20%	91.40%	20.80%	24.40%	<.0001	0.0003	<.0001	<.0001
Mesangial dd	92.00%	84.90%	98.10%	8.50%	3.50%	0.1972	0.0487	<.0001	<.0001
Subendothelial dd	14.00%	18.20%	49.00%	1.10%	0.00%	0.5882	<.0001	<.0001	<.0001
Subepithelial dd	14.00%	8.10%	35.90%	1.40%	0.00%	0.2613	<.0001	<.0001	<.0001
TR inclusions	3.30%	12.10%	62.50%	1.10%	0.00%	0.0571	<.0001	0.1345	0.0711

TH-PO635

Efficacy and Safety of Belimumab in Refractory and Newly Diagnosed Patients with Active Lupus Nephritis: A Real-World Retrospective Observational Study

Ying Ma, Wanhong Lu, Jiping Sun. *Nephrology Hospital of the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: Lupus nephritis (LN), the common manifestation of SLE, continues to be a principal cause of morbidity and mortality. According to 2024 KDIGO guideline, belimumab is recommended as adjunct therapy for active LN. However, the differences in its efficacy and safety between refractory and newly diagnosed active LN are unknown.

Methods: We enrolled active LN patients who initiated belimumab as adjunct therapy in our center between June 2021 and January 2024, and divided them into refractory group and newly diagnosed group according to previous immunosuppressive therapy. Patients were followed up for more than 3 months. Renal manifestation, serologic features, SLEDAI score and steroid dosage were recorded. Efficacy endpoints were complete renal response(CRR) and primary efficacy renal response(PERR)(see BLISS-LN).

Results: A total of 89 active LN patients were selected from 116 LN patients receiving belimumab in our database, among which 42 were in refractory group. At the initiation of belimumab, there is no statistical difference of age, gender, SLEDAI score, renal related markers(proteinuria, serum albumin, eGFR, renal histological classification), and serologic features(positive anti-dsDNA, C3, C4, etc.) between the two groups. Compared with newly diagnosed patients, refractory patients had significantly longer LN duration (P<0.001), lower B-lymphocyte count(P=0.001), and lower dosage of steroids(p=0.003). During the follow-up period, serum albumin, eGFR, C3 and C4 increased, while SLEDAI score, proteinuria and steroids dosage decreased in both groups. The decrease in dosage of steroids were more prominent in newly diagnosed group, with the proportion of patients receiving>7.5 mg/d (prednisone-equivalent dose) steroids reduced from 97.8%(45/46) at initiation to 34.8%(16/46) at last visit. For the refractory active LN patients, the estimated probability of CRR at 3 months was 39.0% and the estimated probability of PERR at 3 months was 48.8%. They were all comparable to newly diagnosed patients by Log Rank test(p=0.137,p=0.623). No difference was found in adverse events rates(p=0.183), time to first renal flare(p=0.792) or RRE(p=0.701).

Conclusions: The add-on treatment with belimumab showed comparable efficacy and safety in refractory and newly diagnosed active LN patients.

TH-PO636

Abstract Withdrawn

TH-PO637

Efficacy and Safety of Belimumab in Severe Lupus Nephritis: A Retrospective Single-Center Study

Ailima Aierken,[1] Jing Zhuang,[1] Shufen Yang,[1] Dilina Yalikun,[1] Chengren Xu,[1] Changrong Zhang,[1] Xuefei Tian,[2] Hong Jiang.[1] *[1]People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China; [2]Yale University School of Medicine, New Haven, CT.*

Background: Belimumab is a novel biological agent approved for the treatment of active lupus nephritis (LN), but its efficacy in severe LN has not been fully clarified. This study aimed to evaluate the efficacy and safety of belimumab combined with standard therapy in adult patients with severe active LN compared to standard therapy alone.

Methods: This observational and retrospective single-center study included 36 adult patients with severe active LN. Among them, 18 patients received belimumab combined with standard treatment, while another 18 patients received standard treatment. Demographic, clinical, laboratory, efficacy, and safety variables were collected. Effectiveness was evaluated based on changes from baseline in SLEDAI scores and disease activity markers. Safety data included any adverse event (AE) due to any cause.

Results: The baseline demographic and clinical characteristics of the two groups were similar, with no statistical differences. At week 24, the complete remission rate of renal involvement was significantly higher in the belimumab group compared to the control group (55.6% vs. 33.3%, P = 0.01). The proportion of partial remission of renal involvement was higher in the belimumab group (44.4% vs. 27.8%, P = 0.01). Seven cases of renal involvement in the control group did not reach remission. At week 24, the average SLEDAI score in the belimumab group decreased from 21.67 ± 3.69 at baseline to 6.11 ± 2.423, and the proportion of patients with SLEDAI scores ≤ 4 was higher in the belimumab group than in the control group (38.9% vs. 0%, P = 0.008). At week 24, patients treated with belimumab had a lower proportion of average daily hormone doses (≤ 5 mg/d: 0% vs. 61.6%) compared to the control group. Five patients in the belimumab group required dialysis initially; after treatment, though 2 remained in stage 4 chronic kidney disease, all 5 were off dialysis. The belimumab group was well-tolerated, with an incidence of adverse events similar to the control group. Belimumab did not significantly increase the risk of infection, even during the induction period of LN treatment.

Conclusions: The results of this study indicate that belimumab combined with standard treatment can improve the overall remission rate of severe LN, reduce disease activity, and decrease hormone exposure time while maintaining safety.

TH-PO638

Obinutuzumab for Treatment of Refractory Lupus Nephritis

Tripti Singh,[1] Shelby Gomez,[2] Sarah E. Panzer,[1] Sancia K. Ferguson,[1] Shivani Garg.[1] *[1]University of Wisconsin-Madison, Madison, WI; [2]UW Health, Madison, WI.*

Background: Despite advances, the rates of complete and partial remission remain low in LN. B cell depletion with rituximab has been shown to be effective and is recommended by KDIGO for treatment of refractory LN after verifying adherence to treatment. Obinutuzumab has shown efficacy in addition to mycophenolate mofetil (MMF) in LN. However, the role of Obinutuzumab in refractory LN remains elusive. We studied the efficacy of Obinutuzumab in refractory LN.

Methods: 8 patients with refractory LN were included in the study. Patients received Obinutuzumab 1000 mg, 2 doses, two weeks apart.

Results: Patients included in the study had kidney biopsy with class IV LN (25%), class IV and V LN (25%), class III and V LN (25%) and class II and V LN (25%). Mean age of patients was 29.6 years, 75% were females, 50% were of white race, 13% were Asian race and 38% were Hispanic ethnicity. All patients were on angiotensin convertase inhibitor (ACE-i) or angiotensin receptor blocker (ARB), and 87.5% of patients were on MMF and hydroxychloroquine, 62% were on tacrolimus, and 12.5% on azathioprine. Among this cohort, 75% had been on cyclophosphamide, 50% had been on rituximab, 50% on voclosporin and 37.5% had been on belimumab. Mean duration of follow up was 118 days. After treatment with Obinutuzumab, there was a significant decrease in proteinuria (mean protein: creatinine ratio 2.6 gm/gm vs 1.2 gm/gm, p-value = 0.01, Table 1). There was also significant improvement in mean serum albumin (2.9 gm/dL vs 3.2 gm/dL, p-value 0.03) and serum C4 levels (14 mg/dL vs 17 mg/dL, p-value= 0.02). Additionally, there was a trend in improvement in eGFR (62 ml/min/1.73m^2 vs 71 ml/min/1.73m^2, p-value= 0.19) and serum C3 levels (78 mg/dL vs 87 mg/dL, p-value= 0.23) (Table 1). One patient had shingles 2 months after the Obinutuzumab infusion.

Conclusions: Obinutuzumab therapy along with MMF, HCQ and ACE-i was associated with significant improvement in proteinuria, serum albumin and serum C4 levels in patients with refractory LN. Obinutuzumab could be considered as a treatment option for refractory LN.

Table: Paired t-test to compare Lupus Nephritis parameters pre- and post-Obinutuzumab (8 patients, Median follow-up duration = 118 days)

	Urine Protein Creatinine Ratio		Serum Albumin		eGFR		Creatinine		Complement 3		Complement 4	
Patient Number	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Patient 1	7.26	3.22	2.2	3	36	45	2.48	2.09	113.00	104	23.00	23
Patient 2	6.09	2.51	2.7	3.1	63	48	1.17	1.46	144	164	26	32
Patient 3	7.55	1.4	3	3.1	56	89	1.22	0.83	74	80	10	15
Patient 4	0.68	0.4	3.1	3	77	79	1	0.98	52	51	6	7
Patient 5	5	1.7	3.1	3.5	61	55	1.27	1.37	81	147	16	23
Patient 6	2.87	1.89	2.7	2.9	75	123	1.35	0.88	74	74.00	12	13.00
Patient 7	1.43	0.33	2.2	3.4	71	68	1.05	1.09	85	82	25	26
Patient 8	1.1	0.7	3.2	3.4	68	87	1.16	0.93	41	51	8	10
Mean Difference (95% CIs)	-2.48 (-0.72, -4.24)		0.4 (0.05, 0.79)		10.9 (-6.9, 28.70)		-0.13 (-0.36, 0.10)		11.13 (-8.84, 31)		2.88 (0.62, 5.13)	
P-value	0.0127		0.03		0.191		0.212		0.229		0.0195	

TH-PO639

Safety and Efficacy of Anifrolumab Therapy to Reduce Proteinuria in APOL1-Associated Lupus Nephritis

James A. Tumlin,[1,2] Lorin M. Sanchez,[1,2] Sharad Virmani,[1,2] Brad H. Rovin.[3,2] NephroNet Clinical Trials Group. *[1]Emory University, Atlanta, GA; [2]NephroNet Clinical Trials Group, Atlanta, GA; [3]The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disorder that leads to Lupus nephritis (LN) in up to 40% of patients. High type I interferon gene signatures (IFNGS) are present in approximately 80% of patients with LN and are associated with higher rates of treatment failure. Previous studies using the interferon alpha receptor antagonist Anifrolumab to treat Lupus nephritis failed to demonstrate a reduction in UP/Cr at 52 weeks. Because dual expression of APOL-1 "at-risk" alleles in LN is associated with progressive disease, we examined the efficacy of Anifrolumab in LN with varying APOL-1 gene expression.

Methods: Prospective, open-labeled study of 11 patients with confirmed Lupus nephritis with UP/Cr > 500 mg/gm after 6 months of induction immunosuppressive therapy. All patients were maintained on mycophenolate and RAAS therapy for 4 weeks prior to Anifrolumab. All patients were screened for APOL-1 status. Serial UP/Cr and eGFR measurements were collected and reported as Means ± SEM. **Study Inclusion Criteria** 1) APOL-1 testing prior to Anifrolumab infusion; 3) UP/Cr > 500 mg/gm; 5) CKD-Epi eGFR >30 mls/min/1.73M^2 4) and active immunosuppression. **Definitions:** A complete response was defined as UP/Cr < 500 mg/gm after 6 months. A partial response was defined as > 50% reduction from pre-study UP/Cr.

Results: Data from this study are presented in Table-1. Of the 11 enrolled patients 3 had dual APOL-1 at risk alleles and 3 with a single allele. Five patients had no at risk alleles. A six month course of Anifrolumab (300 mg) induced a complete or partial remission in 73% of the total and 66% among dual or single allele LN patients. Both single and dual APOL-1 patients had higher baseline UP/CR compared to wild-type patients. There were no major infections or hospitalizations

Conclusions: Anifrolumab significantly reduced UP/Cr in LN patients with dual, single or no APOL-1 "at risk alleles. Over 60% of dual or single allele LN patients achieved a complete or partial response. Larger studies in this high risk population will be needed to confirm these results.

Funding: NIDDK Support

Table-1

Table-1	% Lupus FSGS	Baseline UP/Cr	Post UP/Cr	Baseline eGFR	Post eGFR
Total Population	64%	5091 mg/gm	1317 mg/gm *	59 mls/min	50 mls/min
APOL 2 Alleles	100%	8788 mg/gm	1847 mg/gm	46 mls/mi	50 mls/min
APOL 1 Allele	80%	6243 mg/gm	2146 mg/gm ^	50 mls/min	51 mls/min
APOL 0 allele	20%	1463 mg/gm	531 mg/gm	63 mls/min	56 mls/min

* P<0.028 ^P<0.032

TH-PO640

Comparison between Standard of Care Treatment and Dapagliflozin Added to Standard of Care in Patients with Lupus Nephritis: A Randomized Controlled Trial

Manish Rathi, Niranjan A V, Smita S. Divyaveer, Aman Sharma. *Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

Background: The exploration of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) presents a novel avenue in treating Lupus Nephritis (LN). This study investigates the potential role of adding Dapagliflozin to the SOC treatment in management of LN patients.

Methods: We conducted a randomised controlled open-label study by enrolling 32 newly diagnosed LN patients. Among them, 17 received Dapagliflozin in addition to SOC, while 15 received SOC alone. The patients were followed up monthly for 6 months. The primary outcome was the treatment response at 6 months as per the KDIGO guidelines.

Results: Baseline characteristics revealed no significant demographic differences between the two groups. While both groups exhibited prevalent lupus-related symptoms, the intervention group demonstrated significantly lower mean systolic blood pressure and total protein levels at baseline. At the 6-month follow-up, the clinical response rate in the intervention group was 81.8%, with a trend toward better outcomes compared to the standard of care group (60%) (p 0.425). Frequency of urinary tract infections was higher in the dapagliflozin arm (p 0.31). No significant differences were observed in other parameters between the groups at the 6 months.

Conclusions: In conclusion, this pilot study suggests that the addition of Dapagliflozin to standard care may improve clinical responses in LN with acceptable adverse effects.

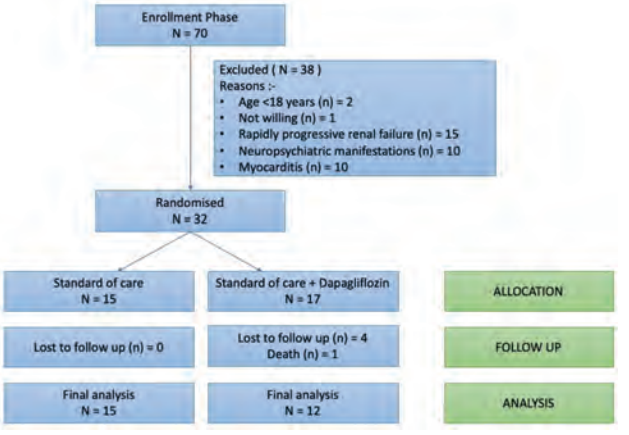


Figure 1: Consort Diagram

Characteristic	Intervention group (MMF + steroids + Dapagliflozin) n = 17	Standard of care treatment (MMF + steroids) n = 15	P-value
Demographic characteristics			
Mean Age (in years)	35.71±10.90	33.53±9.16	0.549
M/F (n)	2/15	3/12	0.645
Renal biopsy			
• Class III LN	2 (11.8%)	2 (13.3%)	1.000
• Class IV LN	3 (17.6 %)	5 (33.3%)	0.423
• Class V LN	7 (41.2 %)	2 (13.3%)	0.122
• Class III + V LN	4 (23.5%)	3 (20%)	1.000
• Class IV + V LN	2 (11.8%)	3 (20%)	0.645
Estimated GFR			
≥60 ml per minute per 1.73 m2	14 (82.3%)	12 (80%)	
≥90 ml per minute per 1.73 m2	11 (64.7%)	9 (60%)	
SLEDAI-2K score (mean)	24.47±6.93	24.40±6.26	0.976
Biomarkers			
• Antinuclear antibodies	17 (100%)	15(100%)	
• Low C3 and C4	12 (70.6%)	13 (86.7%)	0.402
• Anti ds DNA	12 (70.6%)	12 (80%)	0.691
Proteinuria (g/day) (median)	3.9 (2.25 – 6.75)	2.80 (1.53 – 4.7)	0.50
Serum Albumin (g/dl) (mean)	2.67(1.88-3.03)	2.92(2.30-3.37)	0.093
Serum Creatinine(mg/dl) (median)	0.79(0.60-1.14)	0.80(0.70-1.17)	0.705

Abbreviations – MMF – mycophenolate mofetil , M -males , F- females , n – number , LN -Lupus nephritis , SLEDAI -SLE disease activity index

Table 1: Baseline characteristics

TH-PO641

Dapagliflozin in Inactive Lupus Nephritis: Preliminary Results of a Cross-Over Trial

Gisele Vajgel, Carlos R. Silva Miranda Filho, Braziliano M. da Silva Júnior, Camila B. Oliveira, Denise M. Costa, Camilla A. de Lima, Paula S. Sandrin-Garcia. *Universidade Federal de Pernambuco, Recife, Brazil*.

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors slow the progression of chronic kidney disease (CKD). Lupus nephritis (LN) patients were excluded from the main trials with SGLT2 inhibitors. This trial aims to assess the effect and safety of dapagliflozin in inactive LN patients with residual proteinuria.

Methods: For this cross-over randomized trial, we include adult patients with LN class III, IV (+/-V) without active nephritis but with proteinuria >500mg/24h and ≥ 20ml/min, in the maintenance treatment with a RAAS and MMF<2g/day in stable a dose for at least 4 weeks. We excluded patients with other etiologies of CKD, those with active LN lesions on the recent biopsy (AI>2), use of induction therapy in the last 12 mo. Those included were randomized to receive dapagliflozin 10mg on top of standard of care therapy (SoC) or not. After 24 weeks the groups were switched and those without dapagliflozin received it for the next 24 weeks. Primary endpoint is reduction of proteinuria compared to baseline at 6 and 12 mo. The sample size was calculated for 28 patients enrolled providing 80% power to detect a 25% relative risk reduction in proteinuria (α 0.05).

Results: From 97 screened class III, IV (+/- V) LN patients, we excluded 67 due to active LN, low proteinuria or low eGFR. We included 30 patients that were randomized 14 to start the treatment with dapagliflozin on top of SoC and 16 to remain with the usual therapy for 24 weeks. Eight patients were excluded from the analysis due to new LN flare or lost to f/u. We analyzed the data of 10 patients in the initial dapa+SoC and 12 patients in the initial SoC group after 3 (n=21), 6 (n=21), 9 (n=19) and 12 (n=17) mo. Patients in initial dapa group had a significant decrease in proteinuria after 6 months (1018 to 609mg/day; p=0.017) but increased to 1060mg/day 6 months after the drug withdrawal. This preliminary analysis shows a significant reduction in the proteinuria of –37.3% (+/-38) in patients after 6mo of dapagliflozin as opposed to a 0% (+/-54) for those in the SoC therapy at the end of a 6mo period, p=0.026.

Conclusions: Preliminary results show a significant reduction in residual proteinuria in patients with inactive LN with dapagliflozin without an increase in infections.

Funding: Government Support - Non-U.S.

TH-PO642

Disease Targeting Properties of Voclosporin in Kidney Transplant and Lupus Nephritis Patients

Simon Zhou,[1] Linda M. Rehaume,[1] Ernie Yap,[1] Henry Leher,[1] Lucy S. Hodge,[1] Robert B. Huizinga.[2] *[1]Aurinia Pharmaceuticals Inc, Edmonton, AB, Canada; [2]Reformation Consulting Services Inc, Victoria, BC, Canada*.

Background: Voclosporin (VCS), a second generation calcineurin inhibitor, is approved in the United States and Europe for the treatment lupus nephritis (LN) in combination with background immunosuppressive therapy. VCS does not require therapeutic drug monitoring, and is associated with improved glucose, lipid and electrolyte profiles compared to tacrolimus and cyclosporine. VCS demonstrates non-linear selective tissue disposition in animal models, and in renal transplant and LN clinical trials. Pharmacometric modeling was conducted to assess the selective tissue drug disposition relative to systemic drug exposure in patients with renal transplant or LN, comparing with healthy volunteers.

Methods: Individual VCS blood concentration-time measurements were pooled from single and multiple dose ascending studies in healthy volunteers, the Phase IIb PROMISE study in renal transplant patients, and the Phase II AURA-LV and Phase III AURORA 1 studies in LN patients. The VCS blood exposure data were pharmacometrically modelled using a two-compartment model.

Results: In healthy subjects, VCS has comparable central and peripheral volume of distribution (Vc/Vp of 242/272 L/L) and higher elimination than distribution clearance (CL/Q of 43/16 [L/hr]/[L/h]). In transplant patients, VCS has larger peripheral than central volume of distribution (Vc/Vp of 62/2140 L/L), comparable elimination versus distribution clearance (CL/Q of 58/54 [L/hr]/[L/h]) In LN patients, VCS also has larger peripheral than central volume of distribution (Vc/Vp of 34/2120 L/L), slower distribution than elimination clearance (CL/Q of 41/6 [L/hr]/[L/h]).

Conclusions: The larger peripheral volume of distribution indicates selective peripheral tissue uptake of VCS in patients with renal transplant and LN. This is consistent with immunosuppressive activity of VCS in targeted organs relative to blood circulation. The low blood levels of VCS are consistent with the safety profile of VCS compared to other calcineurin inhibitors. Overall, the higher concentration of VCS in affected tissues may account for the efficacy and safety profiles reported in renal transplant and LN patients.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

TH-PO643

Antiproteinuric Effect and Transient Reduction in Kidney Function of Calcineurin Inhibitors in Hispanic Patients with Lupus Nephritis

Irving G. Ramirez, Mario Alamilla-Sanchez, Valeria Yanez Salguero, Enrique F. Morales Lopez, Martin B. Yama Estrella, Carolina Gonzalez-Fuentes, Karen Hopf, Fani G. Ruiz Rivera, Juan D. Diaz Garcia. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico*.

Background: Systemic lupus erythematosus is an autoimmune disease with common renal involvement. Although current remission inital therapies are effective, a high portion of patients suffer flares or are treatment resistant. Combining immunosuppressants with ICNs may improve clinical response, but scarce data exists for the Hispanic population.

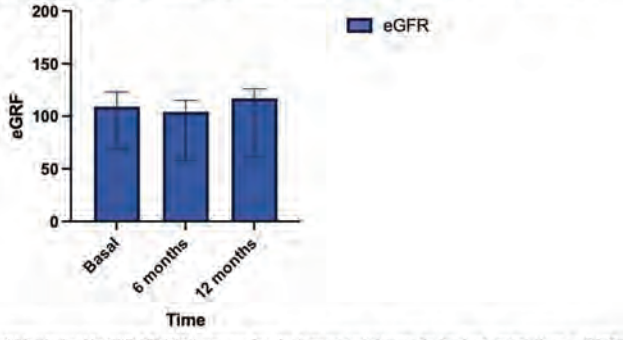
Methods: Patients with SLE and (LN) with persistent proteinuria despite previous immunosuppression and who began a combined regimen, including CNI, were included. 24-hour proteinuria and eGFR by CKD-EPI were assess at 6 and 12 months.

Results: 239 records from patients with LN diagnosis were evaluated, and 42 met inclusion criteria. At 6 months, 40% of the patients obtained complete (CR), and partial response (PR) was reached by 26% of patients. At 12 months, CR and PR were reached by 44% and 32% of patients respectively. A notable reduction in proteinuria was seen at 6 and 12 months compared to baseline (2.89 vs 1.21 g/d, p < 0.001; vs 0.78 g/d, p< 0.001). A transient reduction in eGFR was detected at 6 months (109 vs 104 ml/min/1.73 m^2, p= 0.005), which improved significantly at 12 months (109 vs 117 ml/min/1.73 m^2, p=0.002).

Conclusions: In Hispanic patients with lupus nephritis who previously used immunosuppressor regimes with partial or no response, the addition of a calcineurin inhibitor can be effective. It attains optimal biochemical response rates despite a brief reduction in eGFR that improves without treatment withdrawal.

Women, n (%)	36 (85%)
Age, years [± SD]	35 ± 12
ISN/RPS histological classes, n (%) Class V Class III / IV Class III / IV + V	 15 (38.5) 14 (35.9) 10 (25.6)
CNI prescribed, n (%) Tacrolimus Cyclosporine A	 34 (81) 8 (19)
Concomitant immunosuppressor, n (%) Mycophenolate Azathioprine Prednisone	 37 (88) 5 (12) 42 (100)
Proteinuria 24 h(g/24h) Basal 6 months 12 months	 2.8 (0.45-13.5) 1.2 (0.03-11.1) 0.78 (0.04-4.8)
Response Combined No response	 14 (66%) 28 (33%)

Figure 1. Comparison of change Estimated glomerular filtration rate over time



eGFR calculated by CKD-EPI (2021) equation. *p value between periods using the Friedman statistical test p= 0.005

TH-PO644

Therapeutic Effect of Arsenic Trioxide in Human Lupus Nephritis: Results from Network Pharmacology and Ex Vivo Studies

Ruiyan Xie. *The University of Hong Kong Li Ka Shing Faculty of Medicine, Hong Kong, Hong Kong*.

Background: The renal response to standard treatments of lupus nephritis (LN) often remains suboptimal. Preliminary studies showed efficacy of low-dose arsenic trioxide (ATO) in active systemic lupus erythematosus (SLE), but the mechanisms of action are poorly understood.

Methods: Three machine learning approaches and network pharmacology were applied to screen out the predictive targets of differentially expressed genes (DEGs) from human SLE and LN peripheral blood mononuclear cells (PBMCs) and kidney biopsy datasets. Functional enrichment analysis was conducted. The relationship between characteristic genes and inflammatory cell infiltration was further analyzed and validated in ex-vivo experiments.

Results: Twelve predictive intersected DEGs in SLE patients were selected. Functional enrichment analysis showed a strong association between IL-17 signaling pathway and ATO in SLE (p =1.67E-18). Amongst these DEGs, five immunoregulatory genes were further identified by machine learning models, with MMP9 showing the highest AUC (0.942) by ROC curve analysis. Similar results were validated in kidney biopsy and PBMCs from different LN datasets. Our in vitro experiments showed that ATO could downregulate MMP9 and IL17 expression in PBMCs isolated from LN patients (n=5). Ex-vivo studies suggested that ATO may induce apoptosis and inhibit proliferation of CpG-stimulated CD19+ B cells from LN patients.

Conclusions: ATO shows promising effects on B lymphocyte inhibition via downregulation of MMP9, and hence has good potential to be repurposed for the treatment of SLE and LN.

Funding: Other NIH Support - Wai Im Charitable Foundation, Chan Sui Kau Family Benefits and Charitable Foundation, So Ka Wing and Lee Sau Ying Charitable Foundation

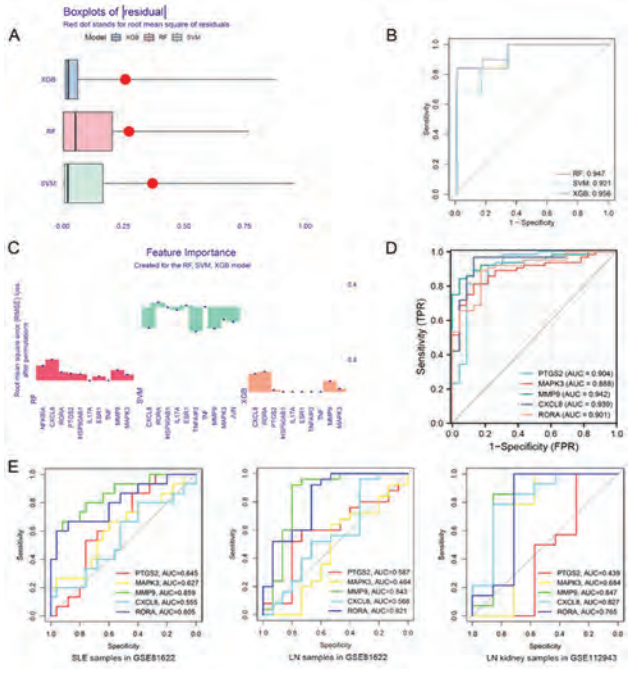


Fig1

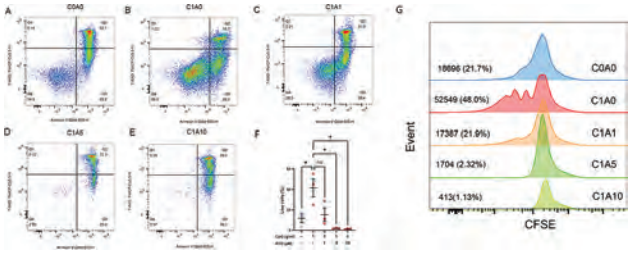


Fig2

TH-PO645

How Global Are the New Lupus Nephritis Guidelines? Evidence Gaps and Underrepresented Groups

Alberto Nordmann-Gomes,[1] Gabriel Cojuc,[2] Adriana Hernández Andrade,[1] Valeria Navarro Sanchez,[1] Juan Carlos Ramirez-Sandoval,[1] Juan M. Mejia-Vilet,[1] Brad H. Rovin.[3] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Recent recommendations for managing lupus nephritis (LN) are based on randomized clinical trials (RCTs). However, these RCTs vary greatly in design and population characteristics. This study aimed to summarize LN RCT data to identify evidence gaps and underrepresented populations.

Methods: We performed a literature review using MEDLINE, CENTRAL, Scopus, and Web of Science to identify all LN RCTs evaluating pharmacologic interventions performed between January 2000 and February 2024. The collected information included variables of study design, selection criteria, studied populations, and study outcomes. Data is summarized by descriptive statistics.

Results: The search strategy identified 1,335 studies of which 71 were selected, with a total population of 8,281 participants. Cyclophosphamide-based regimens were studied in 39 (31.4%) treatment arms, mycophenolic acid analogs (MPAA) in 33 (26.6%), calcineurin inhibitors (CNI) plus standard of care (SoC) in 6 (4.8%), and belimumab plus SoC in 1 (0.8%). The majority of RCTs were multicenter (n=36, 59%), of which 19 (31.1%) were multinational. Most studies were performed in East Asia and the Pacific region (54.1%), followed by North America (24.6%), Europe and Central Asia (26.2%), and Latin America and the Caribbean (22.9%). Tacrolimus plus SoC was exclusively evaluated in Asia while other interventions such as oral cyclophosphamide and belimumab did not include patients from Africa and South Asia. Globally, 86.5% of participants were female. Most participants (55.2%) were Asian, followed by white (28.4%), and only 7.2% were black. ISN/RPS LN classes II and V were evaluated in <10% of RCTs. The definition of the primary efficacy outcome was not standardized among RCTs and only 29 (47.5%) reported severe adverse events. Most guideline-recommended regimens have not been compared against each other.

Conclusions: In light of new recommendations for the management of LN, we make a call to broaden inclusion of underrepresented populations, improve and homogenize study design, and assess unexplored treatment comparisons.

TH-PO646

Urine Epidermal Growth Factor as a Biomarker for Kidney Function Recovery and Prognosis in Glomerulonephritis with Severe Kidney Failure

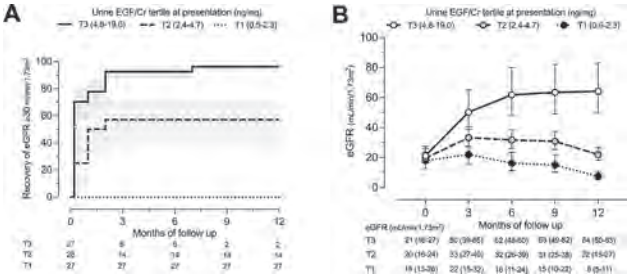
Alberto Nordmann-Gomes, Adriana Hernández Andrade, Bernardo Juarez Cuevas, María F. Zavala Miranda, Cristino Cruz Rivera, Juan M. Mejia-Vilet.
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.

Background: Prognostication in glomerulonephritis (GN) with severe kidney failure is critical to evaluate the benefit-to-risk ratio of immunosuppression. This study aimed to evaluate the role of urine epidermal growth factor (uEGF) levels as predictor of kidney function recovery.

Methods: We included 82 subjects with GN and severe kidney failure defined as eGFR ≤30ml/min/1.73m^2 at presentation. Fifty-eight had lupus nephritis (LN) and 24 ANCA-associated vasculitis (AAV). Thirty-five subjects had initial kidney replacement therapy (KRT) requirement. Urine EGF was measured by ELISA and corrected by urine creatinine. The outcomes included time to persistent recovery of eGFR≥30ml/min/1.73m2 and time to recovery of kidney function with dialysis independence in those with initial KRT.

Results: Forty-four (54%) subjects recovered their eGFR ≥30ml/min/1.73m2 with 6-month recovery rates of 93%, 57%, and 0% for subjects in the highest, middle, and lowest uEGF tertile, respectively. Recovery of kidney function was faster and to a higher eGFR in the highest uEGF tertile. The area under the curve (AUC) of uEGF as predictor of recovery was 0.92 (95%CI 0.87-0.98) with a cutoff of 2.60ng/mg having 100% sensitivity to detect all subjects who recovered kidney function above 30ml/min. In the subgroup of subjects with initial KRT, admission uEGF had an AUC of 0.96 (95%CI 0.92-0.99) to detect all subjects who recovered from KRT by 6 months. A uEGF cut-off of 2.0 ng/mg demonstrated 100% sensitivity in detecting all subjects who recovered from KRT within this period.

Conclusions: Urine EGF is a promising biomarker to aid in the prediction of recovery of kidney function in glomerulonephritis with severe kidney function. The addition of uEGF to clinical and histopathological variables may aid therapeutic decisions in these patients.



TH-PO647

Early Adoption of Advanced Systemic Therapies in Lupus Nephritis: A Retrospective Analysis

Meghan Weiss, Sawyer A. May. *Spherix Global Insights, Exton, PA*.

Background: Recently, KDIGO and EULAR have issued updated guidelines concerning the management of SLE and LN. These updates advocate for the early use of belimumab and CNIs in the treatment of active LN. Our study delves into US rheumatologists' and nephrologists' strategies for using advanced systemic therapies in LN.

Methods: 1,043 ISN Class III or IV (+/-V) and Class V adult LN patient records were collected in collaboration with 107 US rheumatologists and 90 US nephrologists via an online survey from September to November 2023. These patients had to be in the maintenance phase of treatment and have an eGFR greater than 15 mL/min/1.73m2. This retrospective analysis focuses on the subset of 669 LN patients diagnosed in 2021 or later.

Results: Nearly half (48%) of patients were on an advanced systemic agent during their latest specialist visit, with belimumab being the most commonly prescribed (32%), followed by voclosporin at 12% and rituximab at 4%. Notably, 61% of patients were on oral steroids. About one-third of patients treated with advanced systemic agents for LN received such treatment either before or at the time of diagnosis. Moreover, the majority of patients initiated advanced systemic therapy within six months of diagnosis. There was no discernible difference in the timing of initiation between belimumab, voclosporin, and rituximab by specialists. Upon initiation of belimumab or voclosporin, patients were prescribed an average of 20mg of oral steroids daily. A notable distinction between patient groups was observed in proteinuria levels, with those receiving voclosporin exhibiting higher levels compared to belimumab.

Conclusions: These results underscore a growing emphasis on initiating systemic treatments earlier in the treatment trajectory, yet high doses of steroids remain prevalent. Despite the earlier adoption of advanced systemic therapies, there persists an unmet need for steroid-sparing agents to mitigate the continued reliance on high-dose steroids.

Key Patient Characteristics at Initiation (Means)

Drug	Time from Diagnosis to Initiation	Steroid dose	UPCR	eGFR
Belimumab	Pre-LN diagnosis (n=37)	16.9mg	1.6g	60.4
	Within 6 months of LN diagnosis (n=149)	23.3mg	2.1g	56.2
	>6 months past LN diagnosis (n=113)	12.3mg	1.9g	54.0
	Total	***18.4mg***	***2.0g***	***55.9***
Voclosporin	Pre-LN diagnosis (n=11)	24.5mg	2.9g	50.5
	Within 6 months of LN diagnosis (n=47)	20.0mg	2.3g	54.1
	>6 months past LN diagnosis (n=56)	17.3mg	3.0g	56.5
	Total	***19.1mg***	***2.7g***	***54.9***

TH-PO648

Modeling Chronic Damage in Lupus Nephritis Kidneys Noninvasively

Jorge E. Rojas-Rivera,[1] John P. Shapiro,[1] Juan M. Mejia-Vilet,[2] Valeria Navarro Sanchez,[2] Brad H. Rovin.[1] [1]*The Ohio State University Wexner Medical Center, Columbus, OH;* [2]*Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico*.

Background: Chronic kidney damage in lupus nephritis (LN) occurs during cycles of inflammation, and healing after treatment. Urine epidermal growth factor (uEGF) correlates well with the histologic chronicity index (CI) and reflects functional tubular mass. We tested models combining uEGF with clinical variables and other putative urine biomarkers to determine whether various levels of chronic damage could be distinguished non-invasively.

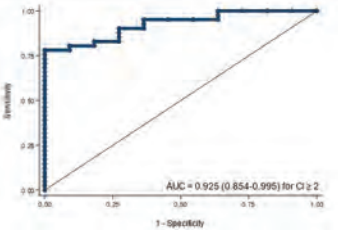
Methods: Urine collected at the time of kidney biopsy for LN (n=119) was assessed by ELISAs specific for EGF, complement activation products (C5a, C5b-9, factor Ba) and macrophage-derived CD163, a biomarker of histologic activity in LN. Clinical laboratory tests for serum creatinine (SCr), proteinuria, and complement components C3 and C4 were done. Predictive models to distinguish between no (CI=0) and increasing levels of chronic damage were built by combining urine and clinical markers and were tested using the area under (AUC) the receiver operating characteristic (ROC) curve.

Results: The best models to differentiate between no chronic damage and increasingly higher levels of chronic damage are shown in the Table. The model to predict a CI of 2 or more has the best performance (Figure below Table), but the ability to identify most patients (>80%) with a CI of 4 or greater is still very good (AUC = 0.877, sensitivity = 82%, specificity = 80%). uEGF, serum C3, and uC5b-9 are common to all models.

Conclusions: At LN flare the CI of the kidney can be estimated noninvasively by urine and serum markers. These biomarkers include measures of chronic damage and disease activity consistent with active lesions healing with scarring. Identifying patients with a CI≥4 is important as this level of damage is associated with poor long-term kidney outcome and should prompt treatment with immunosuppressives and nephro-protective therapies. Interestingly, these equations suggest that intra-renal and systemic complement activation may contribute to chronic kidney damage in LN.

Funding: Other NIH Support - NIAMS

Multivariable model	Predictive performance (%) AUC (95%CI)	Sensitivity	Specificity	PPV	NPV	Correctly Classified
Outcome CI ≥ 1: SCr + C3 + uEGF + uC5b9 + uBa	0.903 (0.815-0.992)	93.6	81.3	88.0	50.0	83.9
Outcome CI ≥ 2: SCr + C3 + C4 + uCD163 + uEGF + uC5b9 + uBa	0.925 (0.854-0.995)	95.1	63.6	90.7	77.8	88.5
Outcome CI ≥ 3: C3 + C4 + uCD163 + uEGF + uC5b9	0.852 (0.731-0.973)	92.3	53.9	85.7	70.0	82.7
Outcome CI ≥ 4: C3 + C4 + uEGF + uC5a + uC5b9	0.877 (0.783-0.971)	81.5	80.0	81.5	80.0	80.8
Outcome CI ≥ 5: C3 + uEGF + uC5b9	0.818 (0.706-0.929)	57.1	80.0	63.2	75.7	71.4
Outcome CI ≥ 6: C3 + uEGF + uC5a + uC5b9	0.881 (0.793-0.969)	50.0	87.5	81.3	81.4	76.8
Outcome CI ≥ 7: SCr + C3 + uCD163 + uEGF	0.719 (0.619-0.820)	40.0	91.3	50.0	87.5	82.1



TH-PO649

AZD1152: Repurposing for Treatment of Lupus Nephritis Driven by the Results of Clinical Trials

Yue Zhao, Shaoshan Liang, Changming Zhang, Ming-chao Zhang, Lang Yue, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing, China*.

Background: Lupus nephritis(LN) is one of the most common and serious complications of systemic lupus erythematosus(SLE). About 20% of LN patients will progress to ESRD within 15 years. The complete remission(CR) rate of LN is not satisfactory. Combination therapy consisting of mycophenolate mofetil, tacrolimus and glucocorticoid achieved a 20% higher CR than conventional therapy. Intrigued by its excellent clinical efficacy, we attempted to discover a new drug which is comparable to combination therapy.

Methods: The Connectivity Map(CMap) database was used for drug repurposing based on the "signature" of combination therapy. And the aurora kinase B(AURKB) inhibitor, AZD1152, was predicted to have similar efficacy as combination regime. The efficacy verification was conducted with MRL/lpr mice. Transcriptome sequencing and functional experiments were performed to reveal and verify the mechanism of AZD1152, respectively. The expression and clinical significance of AURKB were evaluated with lupus-prone mice model and LN patients.

Results: AZD1152 treatment significantly alleviated systemic immune activation and renal injury in MRL/lpr mice. And the efficacy of AZD1152 was comparable to combination therapy. Transcriptome profile demonstrated that AZD1152 could affect local immune-inflammatory pathway in kidney, similar to the combination regime. AURKB, the direct target of AZD1152, was upregulated and expressed in LN renal interstitial infiltrated T cells. The expression levels of AURKB was positively correlated with the activity index(AI) and serum creatinine(Scr) of LN patients. Mechanistic studies indicated that AZD1152 exerts its curative effects mainly through inhibiting AURKB-mediated T-cell proliferation.

Conclusions: This is the first study to illustrate the therapeutic effect of AZD1152 in SLE and renal injury. The comparable efficacy of AZD1152 to combination regime means it is able to further reduce the side effects of drug combination. Our study also revealed the potential of AURKB as a biomarker to predict LN disease activity. In summary, our work proposed a new paradigm for drug discovery which is based on clinical trial proved therapy and approaches of drug repurposing. This strategy is able to accelerate clinical translation process as well as to build bridges between basic scientists and clinical researchers.

Funding: Government Support - Non-U.S.

TH-PO650

7000-Plex Proteomic Screen of Urine for Flare Monitoring and Treatment Response Biomarkers in Active Lupus Nephritis

Chandra Mohan,[1] Kamala Vanarsa,[1] Yewei Ma,[1] Mohammad Daouk,[1] Vinaika Maruvada,[1] Ramesh Saxena.[2] *[1]University of Houston, Houston, TX; [2]The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with lupus. Since the kidney biopsy is invasive, better, more predictive biomarkers of kidney injury are warranted.

Methods: Clarified urine samples from biopsy proven LN patients with differing degrees of disease activity, and healthy controls, were subjected to a 7000-plex aptamer based proteomic screen. The screening cohort included 15 LN patients with active LN, 6 with inactive LN, 9 healthy controls, and 6 LN patients with serial pre-flare and post-flare urine collections, at an average interval of 3 mo.

Results: Compared to inactive lupus, 605 proteins were significantly differentially expressed in active LN urine (Fig. 1A), with 279 proteins elevated >2-fold at ROC AUC≥0.80. Gene enrichment analysis implicated several functional pathways including receptor-mediated endocytosis, regulation of immune response, GTPase activity, among others. Following treatment, post-flare samples compared to flare samples exhibited 2817 proteins significantly reduced ≥50% (Fig. 1B). Comparing renal flare to pre-flare samples. 398 urine proteins were elevated during flare, with ROC AUC >0.90 and WRS test p-≤ 0.125 (Fig. 1A). A flare response index (FRI) was computed for each urine biomarker, reflecting its fold-change across pre-flare, through flare, to post-flare intervals. Compared to the FRI of urine albumin (6.5), the top 22 urine biomarkers exhibited FRI > 100 (with the highest reaching ~2000).

Conclusions: These studies have identified several novel urine biomarkers of active LN that are highly responsive to renal flares, compared to albuminuria. Further validation studies are warranted.

Funding: Other NIH Support - 1R01AR074096

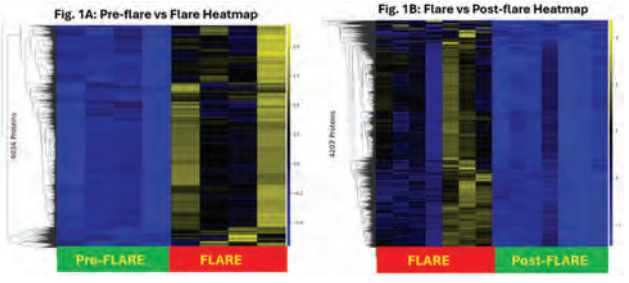


Figure 1. Heatmap representation of urine proteins differentially expressed in lupus nephritis during renal flares compared to pre-flare (A) and renal flare versus post flare following treatment (B), based on hierarchical clustering.

TH-PO651

Genetic Regulation of Exhausted and Classic Memory B Cells in Lupus Nephritis: Results from In Vitro Studies and Bioinformatic Analyses

Litong Zhu, Yat Hin Desmond Yap. *Queen Mary Hospital, Hong Kong, Hong Kong.*

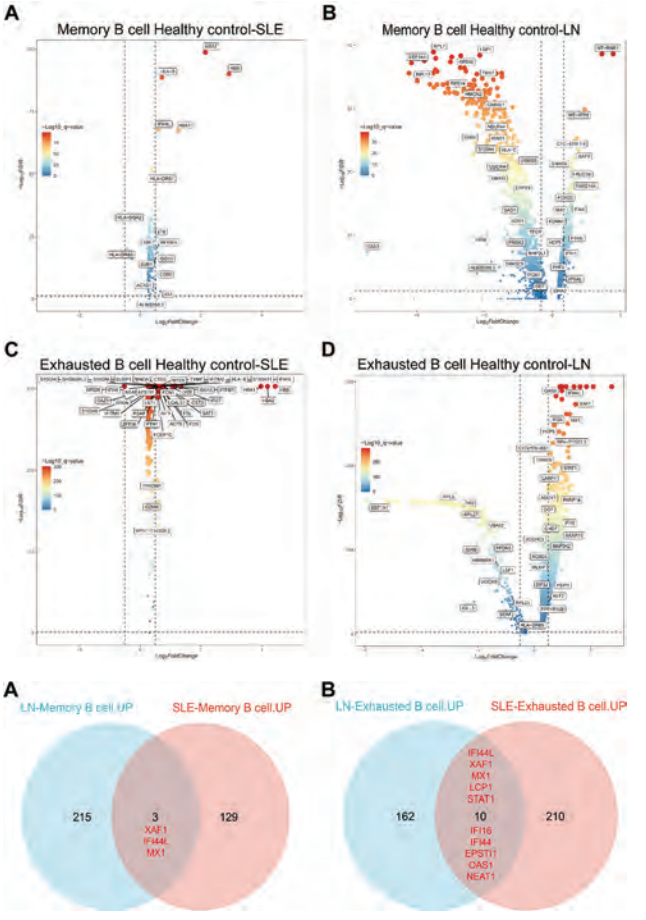
Background: Disturbances in exhausted and classical memory B cells are crucial B lymphocyte abnormalities. Genetic dysregulation of exhausted and memory B cells in lupus nephritis remains unclear.

Methods: We analyzed the single cell RNA-seq data of peripheral mononuclear blood cells from the NIH LN dataset (GSE135779) and another published LN single-cell RNA-seq dataset(dbGAP database accession code phs001457.v1.p1). Overlapping differentially expressed genes in exhausted and classical memory B cells from SLE and LN patients were identified, and their expression was validated in B cells obtained from LN patients and healthy controls. GO and KEGG analyses were used to analyze associated pathways. The circulating immune cells in SLE patients were analyzed and their relationship with candidate genes were examined.

Results: IFI44L, XAF1, and MX1 were detected in both exhausted and classical memory B cells, and their increased expression were verified in classical and exhausted memory B cells were obtained from LN patients during remission. Protein protein interaction network of DEGs suggested that STAT1 showed the highest eigenvector centrality. GO and KEGG analyses also suggested that IFI44L, XAF1 and MX1 were involved in distinct biological processes and immune pathways related to SLE and LN. Circulating immune cell analysis revealed significant links between exhausted B cell, neutrophil, and immature B cell.

Conclusions: Altered IFI44L, XAF1 and MX1 expression in exhausted and classical memory B cells may be related to the pathogenesis of SLE and LN.

Funding: Government Support - Non-U.S.



TH-PO652

Proteolytic Rewiring and Signaling through the Human Complement System

Markus M. Rinschen,[1,2] Moritz Lassé,[2] Steffen Thiel,[1] Elion Hoxha,[2] Simon Melderis,[2] Moin A. Saleem,[3] Fatih Demir.[1] *[1]Aarhus Universitet, Aarhus, Denmark; [2]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [3]University of Bristol Bristol Renal, Bristol, United Kingdom.*

Background: Proteolysis is substantially involved during the manifestation of damage in the kidney in multiple diseases and is pivotal for exacerbation and resolution of inflammatory processes. The human complement system is a prime example for a clinically relevant proteolytic cascade. Systematic lupus erythematosus (SLE) is a severe chronic, inflammatory disease with renal complications, which affects mostly women (>80%).

Methods: We developed a high-throughput, automated analytical workflow for enrichment of N-termini from human EDTA-plasma through negative selection with the mass spectrometry-based "High-sensitivity Undecanal N-TERmini enrichment" (HUNTER) method. We mapped the enriched protease cleavage sites in a variety of clinically relevant populations, including complement inhibitor-treated individuals, SLE and lupus nephritis patients (cross-sectional and longitudinal). Furthermore, in vitro assays for selected proteases and specific activity assays for the human complement system were performed. In addition, we performed serum N-termini enrichment from stable-isotope labeled mice sera to identify proteolytic fragments, which have a lower turnover rate.

Results: We identified > 11 500 protease-generated N-termini in human plasma from more than 150 patients. Most of those N-termini did not correspond to already known fragments and a considerable fraction displayed a substantial alteration in SLE. Additionally, we could identify specific substrates for four central proteases of the human complement system and link this information to our identified N-termini from the human SLE cohorts. We also discovered GFR and proteinuria-associated cleavage products. Some of the identified protein N-termini were clearly linked to renal function, but also to the global activity of the human complement system and could pave the way for potential interventions in the future.

Conclusions: We could identify proteolytic processing events and determine functions of proteolytic modulation in SLE, with implications for lupus nephritis. The data suggest an unanticipated complexity of proteolytic processing throughout the human complement system.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO653

Enlight-LN Registry: Baseline Demographics and Clinical Characteristics of an Initial Cohort of Patients Treated with Voclosporin for Lupus Nephritis in the United States

Niloofar Nobakht,[1] Laura B. Geraldino-Pardilla,[2] Leanna M. Wise,[3] Mohammad Kamgar,[1] Lily Cipolla,[4] Lucy S. Hodge,[4] Keelin Dahl.[4]
[1]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [2]Columbia University Irving Medical Center, New York, NY; [3]University of Southern California Keck School of Medicine, Los Angeles, CA; [4]Aurinia Pharmaceuticals Inc, Edmonton, AB, Canada.

Background: Voclosporin is approved for adults with active lupus nephritis (LN). In the AURORA 1 and AURORA 2 studies, adding voclosporin to MMF and low-dose glucocorticoids led to significantly earlier and greater reductions in proteinuria while maintaining stable eGFR for up to 3 years. The Enlight-LN registry is designed to characterize the real-world effectiveness and usage patterns of voclosporin in the United States (US). We describe baseline demographics and clinical characteristics of patients currently enrolled in this ongoing, prospective, observational registry.

Methods: The registry is enrolling patients ≥18 years with biopsy-confirmed LN who are initiating or have already initiated treatment with commercial voclosporin within 12 months prior to study consent. Patients receive standard of care according to usual clinical practice. Data are extracted from patient records ~every 3 months up to 36 months and include demographics, disease characteristics, response to therapy and treatment patterns.

Results: Data are available on 123 patients enrolled prior to or on December 31, 2023. Patients ranged in age from 18 to 72 years (median, 33 years); 82.9% were female. Most patients self-identified as White (43.1%) or Black/African American (35.8%); 7.3% were Asian. A total of 35.8% were Hispanic/Latino. Median (range) time since first LN diagnosis was 1.1 (0-26.2) years. The majority of patients (62.6%) had Class III or IV +/- V disease; 32.5% had Class V disease. Median (range) eGFR and SCr were 90 (20-143) mL/min/1.73 m^2 and 0.9 (0-66) mg/dL, respectively. Median (range) UPCR was 2.0 (0-16.8) g/g. A total of 107 patients were on concomitant immunosuppression at voclosporin initiation (most commonly, antimalarials, 72.4%; MMF/mycophenolate sodium, 70.7%; belimumab, 13%). In addition, 58.5% of patients were on steroids and 40.7% on RAAS agents. Three patients were on SGLT-2 inhibitors.

Conclusions: Baseline data on this initial cohort of patients are reflective of the larger LN population in the US, including high percentages of Black and Hispanic and/or Latino patients. Enrollment of additional patients and ongoing data collection will provide valuable insight into the real-world utilization of voclosporin.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

TH-PO654

Incidence of Adverse Events from SARS-CoV-2 Vaccination and Its Potential Effect on the Outcome of Lupus Nephritis

Angeliki Sardeli,[1] Smaragdi Marinaki,[2,6] Sofia Flouda,[5] Kriki Pelagia,[3] Aliki I. Venetsanopoulou,[4] Evangelia Pantzopoulou,[1] Stylianos A. Panagoutsos,[3] Sophia Lionaki.[1,2] *[1]Panepistemiako Geniko Nosokomeio Attikon, Athens, Greece; [2]Ethniko kai Kapodistriako Panepistemio Athenon, Athens, Greece; [3]Panepistemiako Geniko Nosokomeio Alexandroupoles, Alexandroupoli, Greece; [4]Panepistemio Ioanninon Reumatologike Klinike, Ioannina, Greece; [5]Panepistemiako Geniko Nosokomeio Attikon, Athens, Greece; [6]Laiko General Hospital, Athens, Greece*.

Background: To investigate the incidence of adverse events associated with SARS-CoV-2 vaccination in patients with lupus nephritis (LN).

Methods: Patients with biopsy-proven LN, who were vaccinated against SARS-CoV-2, were retrospectively studied. Patients who reached ESKD prior to vaccination were excluded. Histopathological class of LN, immunosuppressive regimens for LN, outcome of LN as a result of treatment, the time interval form the diagnostic biopsy to vaccination, the number of vaccine doses, adverse events associated with the vaccine, including systemic and local adverse events were recorded. We also explored the potential of LN relapse after vaccination among patients in remission.

Results: Ninety patients with SLE and renal involvement were included with age of 31(±18) years, of whom 80% were women. Proliferative LN was present in the diagnostic kidney biopsy in 68(77.2%) cases and 91.8% of patients had achieved remission with treatment prior to vaccination. 86.7% of patients were vaccinated with 3(2.75, 3) doses. The median time from diagnosis to vaccination was 59(32-137) months and 70.5% of patients were on immunosuppression at vaccination. 30.5% of patients reported systemic and 36.1% local adverse reactions at the site of administration. Among patients in remission, who were vaccinated, only 1(1.2%) experienced a relapse of LN within 3 weeks of the 1st dose. Three (3.4%) patients who had treatment-resistant disease experienced a worsening of SLE activity after vaccine administration.

Conclusions: In this cohort of patients with a history of LN, SARS-CoV-2 vaccination appears safe, with no effect on the likelihood of disease recurrence among patients who have achieved remission.

TH-PO655

Kidney and Patients Outcomes of Pure Lupus Nephritis: A Nationwide Analysis in Japan

Hidekazu Ikeuchi,[1] Yoichi Imai,[1] Shoichi Maruyama,[2] Hitoshi Sugiyama,[3] Hiroshii Sato,[4] Hitoshi Yokoyama,[5] Keiju Hiromura.[1] *[1]Gunma Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Maebashi, Japan; [2]Nagoya Daigaku, Nagoya, Japan; [3]Kawasaki Ika Daigaku, Kurashiki, Japan; [4]Tohoku Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Sendai, Japan; [5]Kanazawa Daigaku, Kanazawa, Japan*.

Background: Pure membranous lupus nephritis (MLN) generally exhibits a more favorable renal prognosis compared to proliferative lupus nephritis (LN). However, clinical data on pure MLN are limited. This study aims to clarify the renal and patient outcomes, as well as the associated risk factors, of pure MLN in Japan.

Methods: Among 489 adult patients who underwent renal biopsy and were registered as having LN in the Japan Renal Biopsy Registry (J-RBR) from 2007 to 2012, 90 patients with pure MLN were examined in this study. Renal endpoint was defined as a 50% increase in serum creatinine. Risk factors were determined using univariate and multivariate Cox proportional hazards analysis.

Results: The average age at the time of renal biopsy was 43.7±15.1 years, with females comprising 87.8% of the cohort. The average eGFR and urinary protein levels were 90.2±32.7 mL/min/1.73m^2 and 3.36±0.16 g/gCr, respectively. Nephrotic syndrome (NS) was observed in 42.2% of patients. Glucocorticoids (GC) were administered to 84 patients (93.3%), with an average initial dose of 33.5 ± 18.1 mg/day, and 27 patients (30.3%) were treated with GC alone. Tacrolimus was used in 38 patients (42.2%), and cyclosporin A in 14 patients (15.6%). During the median observation period of 62.4 months (IQR, 50.5–81.8), 11 patients (12.2%) reached a renal endpoint and 7 patients (7.8%) died. The 5-year renal and patient survival rates were 90.3% (95% CI, 81.3–95.0) and 93.8% (95% CI, 85.6–97.4), respectively. Univariate analysis showed that eGFR <45 and NS were associated with poor renal outcomes (HR 6.810, P=0.005 and HR 3.789, P=0.049, respectively). Univariate analysis also showed that age ≥45 and eGFR <45 were associated with patient death (HR 6.584, P=0.081 and HR 13.05, P=0.001, respectively). Multivariate analysis revealed that eGFR <45 was an independent risk factor for both poor renal outcomes (HR 5.686, P=0.015) and patient death (HR 8.633, P=0.008).

Conclusions: During a median 5-year observation period, some patients with pure MLN experienced a decline in renal function or death. An eGFR <45 at the time of renal biopsy was identified as a risk factor for both poor renal outcomes and decreased patient survival.

Funding: Private Foundation Support

TH-PO656

CKD in Lupus Nephritis: Prevalence and Risk Factors in a Single-Centre Chinese Cohort

Selene Tse Yen Teoh, Yat Hin Desmond Yap, Becky M. Ma, Tak Mao D. Chan. *Queen Mary Hospital, Hong Kong, Hong Kong*.

Background: Despite treatment advances, 10-20% of patients with lupus nephritis (LN) progress to end stage kidney disease (ESKD). Understanding the burden and risk factors of developing chronic kidney disease (CKD) is pivotal in preventing ESKD. We aim to study the prevalence of CKD, defined as estimated glomerular filtration rate (eGFR) <60ml/min/m^2, its evolution over time, and associated risk factors.

Methods: Patients with an incident episode of biopsy-proven LN diagnosed from January 1981 to December 2014 were included, with follow-up censor date February 15 2017. Patients with <2 years of follow-up were excluded. Data were obtained from retrospective review of medical records.

Results: 149 patients with a mean follow up of 15.8±8.5 years were studied; 90% were female and 70.5% had Class III/IV±V LN. Remission (partial or complete) occurred in 83.9% of patients; 56.4% had disease relapse at a median of 3.73 (0.5-27) years after remission. 29.5% developed CKD and 7.4% progressed to ESKD during the study period. Older age, presence of hypertension, an eGFR of <60ml/min, lower C3 and higher dsDNA levels at time of incident biopsy were risk factors for CKD. 24.8% of patients had an eGFR of <60ml/min at the time of incident biopsy, and kidney function improved in over half after treatment, with percentages decreased to 11.7% and 10.7% at 6 months and 1 year respectively. The percentage with eGFR of <60ml/min then increased to 14.1% at 2 years and 14.5% at 5 years. Non-response to treatment, a higher number of flares (2.2±2 vs 1±1.3, p<0.01) and having ≥2 flares were associated with incident CKD during follow-up. Use of mycophenolate mofetil as induction therapy (and continued as maintenance treatment) was associated with reduced risk of CKD development (adjusted OR 0.18, p=0.01). Calcineurin inhibitor use did not differ significantly between those who had or had not developed CKD during follow up (34.1% vs 21.9%, p=0.12). Renin-angiotensin blockers were more commonly used in those with CKD (81.8% vs 61.9%, p=0.02).

Conclusions: CKD is common in patients with LN. Renal impairment at LN flare often improves with treatment, but CKD progresses over time. Efforts to prevent ESKD should focus on modifiable risk factors including optimizing immunosuppressive treatment, prevention of flares, and renoprotective measures.

TH-PO657

Induction Therapy and Kidney Outcomes in Pediatric Lupus Nephritis: A Prospective Study from the Pediatric Nephrology Research Consortium

Melonie A. Phillips,[1] Mahmoud Kallash,[1] Hancong Tang,[1] Steve Rust,[1] Scott E. Wenderfer,[2,3] Tetyana L. Vasylyeva,[4] Jerome C. Lane.[5] *[1]Nationwide Children's Hospital, Columbus, OH; [2]Texas Children's Hospital, Houston, TX; [3]BC Children's Hospital, Vancouver, BC, Canada; [4]Texas Tech University Health Sciences Center, Lubbock, TX; [5]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL.*

Background: Pediatric lupus nephritis (pLN) occurs in 30-50% of children with SLE and is usually more severe compared to adults. Despite that, treatment protocols and outcome data have been limited, mostly constructed using adult studies. In this study, we aim to evaluate the management and outcome of pLN in a large prospective observational multi-center study.

Methods: Patients <21 years of age with new diagnosis of pLN were enrolled at 8 sites across the United States between 2011 and 2019. Induction therapy was determined by the treating practioner. We evaluated 6, 12, and 24-month remission rates, using the American College of Rheumatology guidelines, and kidney outcomes based on induction therapy with Mycophenolate Mofetil (MMF) or Cyclophosphamide (CYC).

Results: Study included 107 patients. The median age at diagnosis was 14 years (range 7-19 years), and 81% of patients were female. Induction treatment varied significantly across institutions, but most patients received MMF (38%) or CYC (21%). 48 patients with proliferative pLN (III, IV, and V + III or IV) received either MMF or CYC. Combined complete and partial remission rates at 6, 12, and 24 months in proliferative pLN with MMF vs CYC induction therapies are listed in table 1. There were no differences in eGFR, proteinuria, or infection rate between CYC vs MMF at 6, 12, or 24 months. Propensity analysis showed that patients with pLN class IV and lower albumin were more likely to receive CYC.

Conclusions: Remission rates and kidney outcomes were similar between children who received induction MMF vs CYC in proliferative pLN. There were significant variations in induction therapy used to manage pLN, which highlights the need for pediatric-focused LN studies to develop standardized treatment regimens and provide equitable care to patients.

Table 1 Combined complete and partial remission rates at 6, 12, and 24 months in proliferative pLN with MMF vs CYC induction therapies

		Combined complete + partial remission rates		
LN class	Induction therapy	6 months	12 months	24 months
III + IV	MMF	54.5% *	80%	71.4%
	CYC	100% *	84.6%	71.4%
Class V mixed	MMF	62.5%	66.7%	33.3%
	CYC	50%	75.0%	66.7%

*p = 0.0297

TH-PO658

Single-Center Experience with Exostosin-2 Immunohistochemical Staining in Lupus Membranous Nephropathy

Raghunandan Konda, Vijaya Chelikani, Huma Fatima, Dana V. Rizk, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: In lupus membranous nephropathy (LMN), Exostosin-2 (EXT2) is a potential disease antigen. Compared with EXT2-negative cases, EXT2-positive LMN likely represents a subgroup with favorable kidney biopsy findings with respect to chronicity indices and are less likely to progress to kidney failure. We describe a single center experience of LMN stratified by EXT2 status at initial presentation.

Methods: We conducted a retrospective cohort study of patients with MLN and performed an immunohistochemistry (IHC) study on the kidney biopsy specimen against EXT2. Clinicopathological features in LMN patients with EXT2- positive versus negative IHC staining were compared.

Results: Among 10 LMN patients at initial presentation, 4 were EXT2-positive (40%) and 6 were EXT2-negative (Table 1). Those with EXT2 positivity were all Black females, younger, and had a higher baseline serum creatinine. They all had hematuria and higher proteinuria (including nephrotic-range) at baseline. All EXT2-positive patients had lower chronicity features although 50% had additional proliferative lesions associated with lupus. Electron microscopy revealed a higher rate of subendothelial, mesangial, subepithelial, and intramembranous deposits in EXT2-positive cases.

Conclusions: At our center, 40% of LMN patients had EXT2 positivity comparable to that described in the medical literature. Interestingly, our patients had a higher baseline creatinine, proteinuria, and additional proliferative lesions. However, despite this, their kidney biopsies demonstrated lesser scarring and chronicity features which aligns with the current notion that in EXT positive LMN, the increased secretion of EXT into the glomerular basement membrane (GBM) likely results in increased local synthesis of heparan sulfates which adds to their stability and may offer protection from downstream damaging events.

Table 1: Clinicopathological Features of Exostosin2-Positive and Exostosin2-Negative Lupus Membranous Nephritis at Initial Presentation at UAB

	Exostosin2-Positive (N = 4)	Exostosin2-Negative (N = 6)
Mean age (yr.)	26.5	43
Race		
Black	100%	83.33 %
Hispanic	0%	16.66 %
White	0%	0%
Sex		
Female	100%	83.33 %
Male	0%	16.66 %
Mean serum creatinine (mg/dL)	1.25	0.87
Mean proteinuria (g/g)	6.75	3.70
Proteinuria ≥ 3.5 g/d	75%	66.66%
Hematuria	100%	83.33%
Other autoimmune disease	0%	33% (MCTD, Raynaud's)
Sclerosed glomeruli, %	0-7%	0-30%
IFTA %	5-10%	5-20%
Proliferative features	50%	16.66%
Electron microscopy		
Subepithelial deposits	100%	100%
Intramembranous deposits	100%	83%
Mesangial deposits	0%	17%
Subendothelial deposits	75%	17%
Tubuloreticular inclusion	25%	33%

Abbreviations: UAB, University of Alabama at Birmingham; MCTD, Mixed Connective Tissue Disease; IFTA, Interstitial Fibrosis and Tubular Atrophy

TH-PO659

Clinical and Outcomes Correlations with Exostosin 1 Positivity Lupus Nephritis

Luiza L. Assis, Luis Yu, Denise M. Malheiros. *Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Recently, exostosin 1 (EXT1) and exostosin 2 (EXT2), were identified in patients with lupus membranous nephropathy (LMN). Immunohistochemical studies revealed positivity rates from 32.6% to 46%, and these patients present lower chronicity indexes and reduced chronic kidney disease (CKD) progression but are more likely to disclose massive proteinuria at diagnosis. Follow-up results are conflicting, but patients with positive EXT1/EXT2 LMN had a lower incidence of end-stage kidney disease (ESKD) compared to those with negative EXT1/EXT2 LMN. The aim of this study was to assess the prevalence of EXT1/EXT2 in renal biopsies of patients with LMN (class V) and LMN with proliferative component (class III/IV + V), comparing clinicopathologic features at diagnosis and outcomes in patients followed for at least 2 years.

Methods: A retrospective cohort study of patients with membranous lupus nephritis was performed and EXT 1 immunohistochemistry studies on the kidney biopsy specimens were evaluated. (Picture 1). Clinicopathologic features and outcomes of EXT1 positive versus EXT1 negative patients were compared.

Results: Our cohort included 94 patients, of which 34 (36%) were EXT1 positive. According to histological classification, 13 out of 31 (41.94%) patients with LMN were EXT1 positive and 21 out of 63 (33%) patients with LNM associated with proliferation were EXT 1 positive (Picture 2). There were not significant differences between EXT 1 positive and negative groups at the time of renal biopsy, regarding proteinuria and serum creatinine levels, and also activity or chronicity indices on kidney biopsy. A total of 85 patients were followed for a median of 50 months. Patients with EXT1 positive showed significantly higher rates of complete or partial treatment response (p=0.035) and negative anti-DNA antibodies (p=0.01).

Conclusions: The prevalence of EXT1 positivity in LMN was 36% in our cohort. No differences were observed at diagnosis presentation, however, patients with positive EXT1 had better treatment response rates and lower anti-DNA antibodies levels, suggesting a more favorable prognosis for these patients.

TH-PO660

Role of Surveillance Kidney Biopsy in Management of Lupus Nephritis

Mikayla Burrell, Katherine A. Vandenheuvel, Francisco X. Flores, Elif Erkan. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematous. The benefit of early surveillance biopsies to prevent future relapses and to monitor treatment response is not established. In our institution, we implemented surveillance biopsies 6 months after induction therapy. This study aims to assess the value of surveillance biopsies in concordance with the clinical findings in medical management.

Methods: Patients diagnosed with Class III or IV LN on initial kidney biopsy and who had a surveillance biopsy were included in this retrospective chart review. Patients received monthly cyclophosphamide infusions based on NIH protocol or mycophenolate mofetil (MMF) as induction therapy. The clinical history, treatment course, pathology results, and biochemical results were assessed. Proteinuria was determined by urine protein/creatinine mg:mg (UPC) ratio. Estimated glomerular filtration rate (eGFR) was

assessed by the CKiD U25 calculation. LN classification and activity index (AI) was determined by pathology on initial and surveillance biopsies.

Results: Nineteen patients fulfilled inclusion criteria. Seven and 12 patients were initially diagnosed with Class III and Class IV respectively. AI was 8.4±5.6, UPC was 2.57±2.1, and eGFR was 79.09±35 at presentation. LN classification improved in 15 (79%) patients on surveillance biopsy. 16 (84%) patients changed from cyclophosphamide to MMF after the surveillance biopsy, and the other 3 received additional cyclophosphamide or rituximab infusions. Six patients experienced a relapse. Of the patients who switched to MMF, 3 (16%) relapsed. The AI improved in 14 (74%) patients, and mean AI on surveillance biopsy was 1.56. The mean AI on surveillance biopsy was 4.8 and 0.43 between relapsers and non-relapsers respectively ($p<0.05$). Patients who relapsed had a higher LN class (Class III vs Class I/II) on surveillance biopsy in comparison to non-relapsers ($p<0.05$). UPC and eGFR at the time of surveillance biopsy did not predict patient relapse.

Conclusions: The results of surveillance biopsies often guided treatment for patients with LN. The AI and degree of improvement in classification on LN on the surveillance biopsy may be a useful tool in predicting likelihood of LN relapse. We propose that surveillance biopsies should be considered as part of standard care in management of patients with LN.

TH-PO661

Role of Repeat Kidney Biopsy in Lupus Nephritis in a Uruguayan Cohort

Paula Parnizari, Jose Boggia, Leonella Luzardo, Gabriela Ottati, Oscar A. Noboa. *Hospital de Clinicas Doctor Manuel Quintela, Montevideo, Uruguay*.

Background: There is no biomarker that substitutes renal biopsy in assessment of histopathological class, activity, or chronicity in lupus nephritis (LN). We aim to characterize clinical and histological features of repeat biopsies by clinical indication in LN.

Methods: We reviewed the clinical charts and pathology reports of patients with LN and two renal biopsies from a University Hospital in Uruguay.

Results: A total of 20 patients, 18 women were analyzed. Clinical characteristics are shown in Table 1. In 5/9 patients biopsied because of mild clinical changes (hematuria and/or sub-nephrotic proteinuria), pathology revealed severe proliferative forms. Repeat biopsy showed a change in LN class in 80% of the sample, 18.2% to a lower class, 35% to a higher class and 30% had an additional membranous pattern (Class IV+V). There was also an increase in interstitial fibrosis and tubular atrophy (IFTA), 5 vs 20% (p 0.019) and the presence of moderate-severe IFTA was associated with lower eGFR after initial treatment (p 0.009). After repeat biopsy immunosuppression was intensified in 17 patients (85%).

Conclusions: Change in LN class was frequent in this cohort and there was a significant increase in chronic changes in repeat biopsies with a negative impact in renal function. Repeat biopsy by clinical indication is a valuable tool in LN management.

Baseline characteristics according to first and second biopsy

	First biopsy	Second biopsy	p value
Age at time of the biopsy (y), mean (SD)	26.2±11.5	33.1±11.7	<0.0001
Microscopic hematuria and/or proteinuria, n(%)	5 (25)	4 (20)	0.705
Nephrotic syndrome, n (%)	10 (50)	12 (60)	0.525
Nephritic syndrome, n (%)	1 (5)	0	—
RPGN, n (%)	3 (15)	3 (15)	—
LN Class I/II, n (%)	3 (15)	3 (15)	—
LN Class III, n (%)	4 (20)	1 (5)	—
LN Class IV, n (%)	11 (55)	8 (40)	—
LN Class V, n (%)	2 (10)	2 (10)	—
LN Class III/IV+V, n (%)	0	6 (30)	—
Creatinine (mg/dl), median (IQR)	1.08 (0.70-1.45)	1.00 (0.70-1.40)	0.730
eGFR (ml/min/1.73m2), median (IQR)	72.7 (51.7-111.8)	73.7 (46.6-118.5)	0.988
Proteinuria (g/24hs), median (IQR)	3.94 (2.35-6.40)	4.29 (2.56-6.25)	0.883
Initial treatment			
Corticosteroids	20 (100)	19 (100)	—
Cyclophosphamide	11 (55)	10 (52.6)	—
Mycophenolate	2 (10.1)	10 (52.6)	0.001
Azathioprine	6 (30)	1 (5)	0.001

TH-PO662

Predictive Value of Chronic Histologic Changes in Lupus Nephritis

Maria C. Cuellar-Gutierrez,[1,2] Jaime Flores-Gouyonnet,[1] Gabriel Figueroa-Parra,[1] Marta I. Casal Moura,[1] Fernando C. Fervenza,[1] Cynthia S. Crowson,[1] Ali Duarte-Garcia,[1] Sanjeev Sethi.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Hospital Del Salvador, Santiago, Chile*.

Background: We aimed to assess the predictive value of the individual components of the NIH chronicity score and the Mayo Clinic Chronicity Score (MCCS) in lupus nephritis (LN).

Methods: LN patients from Mayo Clinic between 1992 and 2023 were included. The earliest kidney biopsy was index date. Follow-up was until July 2023, death or loss follow-up. Biopsy reports were reviewed by a nephropathologist (SS) and chronic lesions reclassified (glomerulosclerosis [GS], interstitial fibrosis [IF], tubular atrophy [TA], arteriosclerosis [AE], and fibrous crescents [FC]). The outcomes were proteinuria <500 mg/day and complete renal response (CRR) within 1-year, end-stage kidney disease (ESKD), and death. We used stratified multivariable proportional hazards regression adjusted for sex and age. P-values <0.05 were statistically significant.

Results: We included 307 patients (median age, 34 years; 75% female; median follow-up, 11 years). The majority had Class III, IV. FC were in 4.9%, AE in 12%. At one year, 47.5% had proteinuria <500 mg/day and 43.4% CRR. Those with grade 2-3 of GS (HR 0.21 [0.09, 0.48] and grade 2-3 IFTA (HR 0.14 [0.05, 0.39] were less likely to achieve proteinuria <500 mg/day. Grade 2-3 of GS (HR 0.19 [0.08, 0.48]) and grade 2-3 IFTA (HR 0.16 [0.06, 0.44] were also less likely to achieve CRR. Similarly, AE (HR 0.44 [0.21, 0.91], for proteinuria <500 mg/day, HR 0.37 [0.16, 0.84], for CRR) was associated with a reduced likelihood of achieving the outcomes. During follow-up, 33 patients died, and 60 developed ESKD. No variables were associated with mortality. Grade 2-3 GS (HR 9.28 [4.91, 17.54], grade 2-3 IFTA (HR 20.10 [10.08, 40.08]), were associated with an increased ESKD (table).

Conclusions: GS, IFTA, AE are independently associated with outcomes in LN. FC is a rare finding. The MCCS included all the chronic histologic elements associated with outcomes in LN.

Table. Hazard ratios of proteinuria<500mg/day, CRR, ESRD, and death for variables.

Element	Prot <500 HR (95%CI)	CRR HR (95%CI)	ESKD HR (95%CI)	Death HR (95%CI)
GS grade 1	0.68 (0.43, 1.08)	0.68 (0.42, 1.10)	1.94 (0.91, 4.13)	1.47 (0.57, 3.77)
GS grade 2-3	**0.21 (0.09, 0.48)***	**0.19 (0.08, 0.48)***	**9.28 (4.91, 17.54)***	2.15 (0.93, 4.98)
IFTA grade 1	**0.57 (0.37, 0.88)***	**0.54 (0.34, 0.86)***	**3.44 (1.70, 6.96)***	1.26 (0.51, 3.12)
IFTA grade 2-3	**0.14 (0.05, 0.39)***	**0.16 (0.06, 0.44)***	**20.10 (10.08, 40.08)***	1.89 (0.79, 4.52)
FC grade 1-3	0.87 (0.38, 1.98)	1.02 (0.44, 2.34)	1.05 (0.25, 4.34)	0.00 (0.00, Inf)
AE score 1	**0.44 (0.21, 0.91)***	**0.37 (0.16, 0.84)***	**3.56 (1.87, 6.78)***	1.10 (0.41, 2.90)
NIH chronicity (1 unit increase)	**0.76 (0.68, 0.85)***	**0.76 (0.67, 0.86)***	**1.53 (1.39, 1.68)***	1.11 (0.98, 1.25)
MCCS grade (1 unit increase)	**0.77 (0.69, 0.86)***	**0.77 (0.69, 0.87)***	**1.45 (1.33, 1.58)***	1.09 (0.98, 1.21)

Prot <500: Proteinuria <500mg/day, **CRR**: Complete renal response, **ESKD**: End Stage kidney disease, **HR**: Hazard ratio, **GS**: Glomerulosclerosis, **IFTA**: Interstitial fibrosis and tubular atrophy, **FC**: Fibrous crescent, **AE**: Arteriosclerosis, **NIH**: National Institutes of health, **MCCS**: Mayo Clinic Chronicity score. ***=p<0.05.**

TH-PO663

Clinical and Histological Characterization of Several Patients with Lupus Nephritis in Colombia

Maite Hurtado Uriarte, Daniel H. Ducuara, Wilson Suarez, Javier M. Mora Mendez, Andres F. Forero, Maria A. Gomez, Diana C. Sanchez, Angie K. Gonzalez ortiz. *Hospital Clinica San Rafael, Bogotá, D.C., Colombia.*

Background: Lupus Nephritis (LN) is a common and severe manifestation of Systemic Lupus Erythematosus (SLE). The study aims to describe the clinical and histological symptoms and response to treatment in a low-income population.

Methods: Descriptive cross-sectional observational study of patients with LN between 2015 and 2021 at a level 4 hospital in Colombia with renal biopsies.

Results: Ninety-nine patients were described, 72.2% of whom were female with an average age of 32 years. The main presenting syndrome was nephrotic/nephritic (43.4%) and nephrotic (25.3%). The mean SLEDAI was 17. Regarding treatment: The induction regimen included cyclophosphamide (62.4%) and Mycophenolate (34,4%). As for histological classification, 49.5% were class IV and 22.2% IV/V. Crescents were presented in 7%. The median index activity was 2 and a chronicity index was 6. Concerning de outcomes: 5% died during hospitalization and 11.7% within the next year. 29,3% of the patients required treatment at the ICU due to severe malfunction. 18,2% continued with dialysis after discharge from the hospital; of these, 37.5% and 28% continued with dialysis at 6 and 12 months, respectively. Remission at 6 months was 44.1% and 51.6% at 12 months.

Conclusions: A low socioeconomic status population is described with severe clinical and histological LN presentation with infectious and administrative complications that have limited treatment which directly affect mortality and further need of dialysis. This requires the development of public policies in this population to improve short- and long-term outcomes.

Funding: Clinical Revenue Support

TH-PO664

Histologic Predictors of Response and Prognosis in Lupus Nephritis: Why Segmental Sclerosis Should Not Be Part of the Chronicity Index

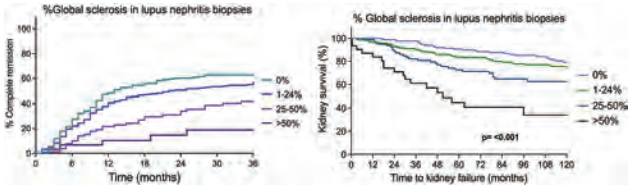
Denisse N. Tinajero Sánchez, Erick Y. Zuñiga Gonzalez, Adriana Hernández Andrade, Valeria Navarro Sanchez, Alberto Nordmann-Gomes, María F. Zavala Miranda, Norma O. Uribe-uribe, Juan M. Mejia-Vilet. *Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico*.

Background: The current histological chronicity index (CI) is calculated by summing the percentages of glomeruli with global sclerosis (GS) and segmental sclerosis (SS), fibrous crescents (FC), and the percentages of interstitial fibrosis (IF) and tubular atrophy (TA). The study aimed to evaluate the prognostic value of individual histological items in predicting complete response to treatment (CR) and progression to kidney failure (KF)

Methods: This retrospective cohort study included all biopsy-proven LN patients diagnosed between 2008 and 2021 with follow-up ≥36 months. Demographic, laboratory, and histopathological variables were recorded at presentation. The study outcomes were evaluated through time-to-event analyses, including time to CR and time to KF. The best predictive models for CR and KF were constructed using Cox regression analysis and evaluated through Harrell's C statistic

Results: We studied 492 patients with a median follow-up of 99 months (IQR 66-129). The median age was 28 years (IQR 22-37), and 94% were female. Creatinine at presentation was 0.96 mg/dL (IQR 0.67-1.49), proteinuria was 3.4 g/g (IQR 2.0-5.7). Median activity and CI were 4 points (IQR 2-8) and 4 points (IQR 2-6), respectively. Individual items of the CI, except SS, were associated with the time to CR in the univariate analysis, while only interstitial inflammation was associated with time to CR (Figure 1). All activity and chronicity items were associated with time to KF. The best predictive model for KF included GS, FC, IF, and TA (C-statistic 0.74 [0.69-0.78]). The model did not improve with the addition of SS (C-statistic 0.73 [0.69-0.78]). The calculated CI did not improve with the addition of SS (C-statistic 0.72 [0.67-0.76] and 0.71 [0.68-0.76], respectively)

Conclusions: Individual histological items of the activity and CI are variably associated with time to CR and KF. SS is not associated with time to KF, and its inclusion in the calculation of the CI does not improve its predictive value for this outcome



TH-PO665

Assessing Chronicity Index on Kidney Biopsies of Patients with Lupus Nephritis and Its Correlation with Creatinine and Proteinuria at 1-Year Follow-Up

Liliana M. Kassar, Felipe Carvalho Barros Sousa, Karoline W. Silva, Vinícius S. Silveira, José Guilherme R. Gonçalves, Viktoria Woronik, Luis Yu, Cristiane B. Dias, Lectícia Jorge. *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil*.

Background: Lupus nephritis is a common manifestation of sistemic lupus erithematous and is associated with higher mortality, specially on those who progress to end-stage kidney disease. This study aims to assess chronicity index on initial kidney biopsy as a prognostic factor in lupus nephritis by correlating it to creatinine and proteinuria after 1-year follow-up.

Methods: Patients diagnosed with lupus nephritis between January 2012 and December 2018 were included. Study variables comprised age, gender, creatinine, estimated glomerular filtration rate (eGFR) by CKD-EPI, proteinuria, histological class and chronicity index on renal biopsy.

Results: A total of 253 renal biopsies were performed on the studied period, 86% in women. Mean age was 31 years old (13-70), initial serum creatinine 1.3 mg/dL (0.3-8.0) and final 1.47mg/dL (0.4-13.2). Average eGFR was 58 mL/min (4-156) at the time of kidney biopsy and 82mL/min (4-156) a year later, with average proteinuria going from 1.9g (0.1-10.7) on initial measure to 0.37g (0.04-6.9) after 1 year. Median chronicity index on kidney biopsy was 3 (0-10). Spearman correlation between chronicity index and creatinine after 1 year was 0.538 with $p < 0.001$, and with proteinuria was 0.144 with p 0.047. Chronicity index ≤ 4 was associated with lower proteinuria (p 0.02) and lower creatinine ($p < 0.001$) at 1 year of follow-up.

Conclusions: Patients with high chronicity indices at diagnosis present worse renal function and higher levels of proteinuria during follow-up. Supportive care and degree of immunosuppression in the setting of chronic and irreversible histologic lesions are topics that need more attention in such scenarios.

TH-PO666

Lupus Nephritis Histopathological Classification System: A Questionnaire-Based Survey of the Renal Pathology Society (RPS)

Martina Uzzo,[1,2] Mark Haas,[3] David R. Jayne,[4] Liz Lightstone,[5] Ioannis Parodis,[9] Brad H. Rovin,[6] Surya V. Seshan,[10] Shreeram Akilesh,[7] Agnes B. Fogo,[8] Ingeborg M. Bajema.[2] *[1]Universita degli Studi di Milano-Bicocca Scuole di Specializzazione, Milano, Italy; [2]Universitair Medisch Centrum Groningen Pathologie en Medische Biologie, Groningen, Netherlands; [3]Cedars-Sinai Medical Center, Los Angeles, CA; [4]University of Cambridge, Cambridge, United Kingdom; [5]Imperial College London Faculty of Medicine, London, United Kingdom; [6]The Ohio State University, Columbus, OH; [7]University of Washington School of Medicine, Seattle, WA; [8]Vanderbilt University Medical Center, Nashville, TN; [9]Karolinska Institutet, Stockholm, Sweden; [10]Weill Cornell Medicine, New York, NY*.

Background: The updated 2018ISN/RPS histopathological classification on kidney biopsy is widely used for prognosis and treatment decisions in lupus nephritis (LN). Due to the success of new targeted agents, there is ongoing discussion about the need for updating existing classification systems. A survey to assess the current use of the 2018ISN/RPS classification system in everyday practice was conducted on behalf of the RPS.

Methods: An online survey was sent between September 27th and October 24th 2023 to active members of the RPS. The survey contained multiple-choice and open-ended questions; results were analyzed anonymously.

Results: 185 of 562 RPS members replied to the questionnaire, mostly pathologists (97%). 120(65%) participants encounter >20 LN biopsies per year, while 13% <10. Nearly 90% discuss biopsy results in multidisciplinary meetings, involving both pathologists and clinicians. The 2018ISN/RPS classification is used in most cases(92%) and 90% of the pathologists include NIH activity/chronicity indices in biopsy reports, although concerns about workload, reproducibility and clinical utility were raised. The average grade on the utility of the 2018ISN/RPS classification and activity/chronicity indexes were 8(IQR 7-9) and 7(IQR-9) on a scale from 0(not useful) to 10(extremely useful). Pathologists rated clinicians' understanding of kidney biopsy reports with an average score of 8(IQR 7-9) on a scale from 0(no understanding) to 10(complete understanding). Suggested improvements of the 2018ISN/RPS classification involved the introduction of new parameters (focus on extraglomerular involvement, laboratory, clinical features), biomarkers (CD68+ staining for endocapillary hypercellularity, EXT1/2 immunostaining), standardization and simplicity. Clearer definitions were requested for class III vs IV, segmental sclerosis vs fibrous crescents, the role of globally sclerosed glomeruli and lupus-like entities.

Conclusions: Our survey shows the 2018ISN/RPS classification is widely used in everyday practice by pathologists, and well known by clinicians. The results obtained by the RPS survey acknowledge the need for ongoing refinement to facilitate targeted treatment decisions, particularly considering evolving phenotypes and therapeutic advancements in LN.

TH-PO667

Lupus Navigator Program: Pilot

Abdallah Sassine Geara, Patricia Nogueira De Sa, Stephanie Wirtshafter, Aylin Ergin, Pranav S. Kancherla, Faith Ryu, Himanshi Verma, Kimberly Dequattro. *University of Pennsylvania, Philadelphia, PA.*

Background: SLE disproportionally affects individuals from racial and ethnic minority groups with more than 95% of patients reporting social determinants of health (SDOH) challenges

Methods: We developed a Lupus Navigator Program in an outpatient clinic with 3 phases: 1. Referral: patients identified by the treating physician as having high SDOH challenges based on medical history, compliance, social setting 2. Screening: SDOH survey by volunteer college students 3. Intervention: Medical team implemented an patient-tailored plan

Results: Patients were mainly young black women The top 3 SDOH: visit copays, help with adherence and transportation. The primary SDOH were: transportation, visit copays, and health system navigation. The table summarise the different interventions

Conclusions: This pilot Lupus Navigator Program demonstrated high SODH challenges among individuals with SLE/LN. the next step is to administer this program by a dedicated SLE social worker

Funding: Commercial Support - Aurinia

SODH surveys

Demographics (N=28)		
Age (years)	33 (19-56)	
Gender	Female	24
Ethnicity	Black Hispanic	25 2
Disease Status	LN LN Acute flare	24 14
SODH	Reported	The Primary Need
Visit Copay	15	4
Compliance	15	1
Medication Copay	12	1
Transportation	13	4
Support group	10	1
Medical Supplies	10	0
Health system Navigation	8	4
Housing	7	2
Social Services	7	0
Disease Education	7	1
Mental health	7	0
Food Insecurity	3	1
	Interventions	
Direct financial help	20	
Referral to social services	19	
Medical supplies	12	
Referral for SLE education or support group	10	

TH-PO668

Global and National Public Awareness and Interest in Glomerular Diseases, 2004-2024

Suryanarayanan Balakrishnan,[1] Charat Thongprayoon,[2] Iasmina Craici,[1] Wisit Cheungpasitporn,[1] Jing Miao.[2] [1]*Mayo Clinic Minnesota, Rochester, MN;* [2]*Mayo Clinic Health System, Mankato, MN.*

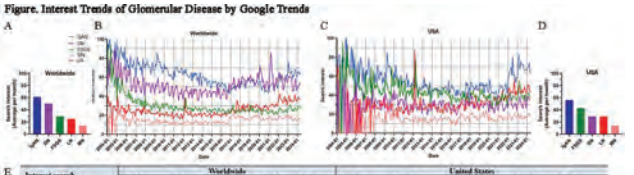
Background: Glomerular diseases (GD) significantly impact global health, and public awareness of these conditions is crucial, especially in recent years, as emerging treatments and clinical trials offer patients new opportunities for care. This study investigated public interest in 5 common GD based on Internet search queries.

Methods: We conducted a Google Trends™ search for the terms IgA nephropathy (IgAN), membranous glomerulonephritis (MN), focal segmental glomerulosclerosis (FSGS), lupus nephritis (LN), and diabetic nephropathy (DN) between 1/1/2004 and 5/13/2024. Searching trends were analyzed in both worldwide and the United States.

Results: Over a 20-year review, IgAN showed the most global attention on Google Trends™, whereas MN attracted the least (**Fig. A**). LN demonstrated a rise in interest, peaking at 43 in Mar 2022. In contrast, 4 other diseases, including IgAN, DN, FSGS and MN, experienced noticeable declines in interest (**Fig. B**). Their peak interest search recorded in Apr 2004 for IgAN (100), Jan 2004 for DN (95), May 2004 for FSGS (94) and Feb 2005 for MN (26) (**Fig. E**). Each GD's interest varied across the top 5 countries (**Fig. E**). In the United States, search trends paralleled global pattern, with various search activity across states (**Fig. C-E**).

Conclusions: Despite new treatments and more clinical trials for GD, public interest remains low and unincreased, especially in conditions like MN. This underscores the necessity for heightened awareness to ensure patients benefit from these advancements. The differing interest levels across countries indicate the need for specific public health strategies. There is a crucial need to enhance the availability of accurate information on these diseases through social media and websites to encourage appropriate patient engagement and care.

Figure. Interest Trends of Glomerular Disease by Google Trends



E

Interest search	Worldwide					United States				
	IgAN	DN	LN	FSGS	MN	IgAN	DN	LN	FSGS	MN
Average interest per month Peak interest and date	61 100; 4/04	50 95; 1/04	25 43; 3/22	29 94; 3/04	14 26; 2/05	56 100, 12/04	39 71; 11/04	29 88; 3/22	43 96; 8/04	34 38; 12/05
Lowest interest and date Most recent (May 13, 2024) interest	43; 12/16 65	35; 7/11 58	0; 7/04 86	20; 4/20 27	0; 3/04 96	0; 6/04 63	0; 7/06 29	0; 7/07 43	0; 7/04 37	0; 11/07 18
Interest by region (top 5 countries or States)	Japan	Congo - Kinshasa	Cuba	Tunisia	Sudan	North Dakota	West Virginia	Connecticut	Minnesota	West Virginia
	Argentina	Japan	Nicaragua	Nepal	Nepal	West Virginia	Massachusetts	Delaware	Maryland	Vermont
	China	Bolivia	Bolivia	USA	Jordan	South Dakota	Connecticut	Massachusetts	Missouri	Connecticut
	Nepal	Nicaragua	Nepal	Jordan	Bolivia	Minnesota	Pennsylvania	Mississippi	Massachusetts	Nebraska
	Philippines	Kyrgyzstan	Jamaica	Lebanon	Japan	Iowa	Mississippi	West Virginia	Rhode Island	Pennsylvania

: The data contains several zero values, and the most recent date has been provided.

TH-PO669

Podocytic Infolding Glomerulopathy: A Systematic Report of 44 Cases

Zhirang Shen,[1] Changrong Zhang,[1] Jing Zhuang,[1] Yue Qu,[1] Xuefei Tian,[2] Hong Jiang.[1] [1]*People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China;* [2]*Yale University School of Medicine, New Haven, CT.*

Background: Podocytic infolding glomerulopathy (PIG), a newly recognized rare disease entity with unique histopathological features characterized by podocytic cytoplasmic invagination into the glomerular basement membrane (GBM) and presenting as "microsphere" or "microtubule"-like structures visualized under a transmission electron microscope, has attracted increasing attention in recent years. Since PIG was first reported in 1965, the clinical features and pathogenesis of PIG are still poorly understood. Delving into the understanding of PIG, elucidating its etiology, clinical implications, and optimal treatment strategies is needed.

Methods: A total of 1713 kidney biopsies from January 2020 to April 2024 in our kidney center were retrospectively analyzed for PIG screening. The diagnostic criteria for PIG are as follows: Electron microscopy shows microspheres or microtubules associated with podocyte cytoplasm folded into the GBM, along with a complete medical record. Forty-four patients were enrolled in the study.

Results: We reviewed 44 PIG patients, of whom 16 were female (36.4%) and 28 were male (63.6%), with an average age of 40±15.9 years. The median [Min, Max] of 24-hour urine protein quantitation was 2.14[0.0280,8.32]g/24h. The median [Min, Max] of Serum creatinine was 84.0[41.6,688]μmol/l. 43.2% of PIG patients had IgA nephropathy. The pathological results of all patients were consistent with PIG features.

Conclusions: Most PIG patients are complicated with immune system-mediated kidney diseases, such as IgA nephropathy, IgA vasculitis associated nephritis, ANCA-associated glomerulonephritis, etc. However, the pathogenic mechanism of PIG is unknown and needs further study.

Funding: Government Support - Non-U.S.

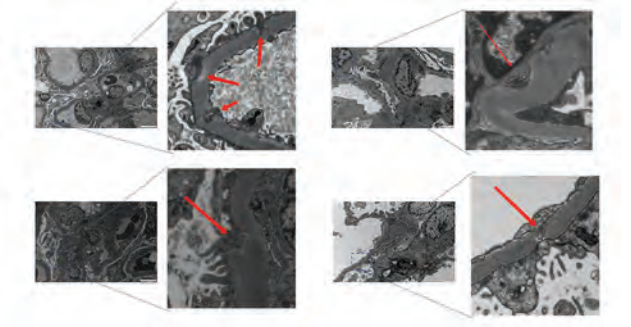
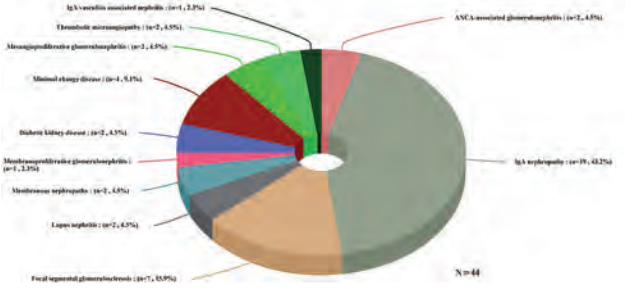


FIGURE 1. Ultrastructure changes of PIG (Arrow: Microspheres in the GBM (→) and podocytes components trapped in the GBM)

FIGURE 2. Percentage of Distribution of etiologies of 44 patients with PIG



TH-PO670

Alpha Lipoic Acid-Associated NELL1-Positive Membranous Nephropathy

Mohammed O. Ali,[1] Jignesh Shah,[1,2] Ehsan Shaban.[1] *[1]University of Missouri-Kansas City, Kansas City, MO; [2]University Health Truman Medical Center, Kansas City, MO.*

Introduction: Membranous nephropathy (MN) is one of the leading causes of nephrotic syndrome in adults and involves an autoimmune response against various antigens, such as PLA2R, THSD7A, NELL1, Sema3B, and NCAM1. Notably, there are increased cases of MN triggered by antibodies against NELL1 following exposure to alpha-lipoic acid (ALA) supplements, which are over-the-counter antioxidant supplements for multiple sclerosis, diabetic neuropathy, and schizophrenia. This report presents a case of NELL1-positive MN nephropathy likely caused by exposure to ALA, emphasizing early recognition and good outcomes without immunosuppression.

Case Description: 70-year-old male with diabetes mellitus and hypertension was referred due to concerns about nephrotic syndrome with leg swelling, foamy urine and neuropathic pain. He had been taking 2400 mg of alpha-lipoic acid daily for a year to help with his diabetic neuropathy. Physical examination was notable for bilateral severe pedal edema. Laboratory investigations revealed normal complete blood counts, creatinine, urea, and basic electrolytes. His hemoglobin A1C level was 7%, His albumin level was low at 2.4 g/dl and his cholesterol was elevated at 224 mg/dl, with LDL cholesterol at 120 mg/dl. Urine protein-to-creatinine ratio increased to 6.4 g/g. Additional tests, including serologies for ANA, ANCA, Hepatitis B surface Ag, Hepatitis C Ab, urine protein electrophoresis and serum PLA2R antibodies levels were negative. The kidney biopsy revealed NELL-1 positive Membranous Nephropathy-. Patient underwent age-appropriate malignancy screening with CT chest, abdomen and pelvis which showed no remarkable findings, normal PSA level and a screening colonoscopy was unremarkable. The Patient's NELL-1 positive MN is related to Alpha lipoic acid use, hence it was discontinued, he was on ARB and diuretic at tolerated dose. Three months later, the patient reported resolution of his edema and he is in partial remission of his proteinuria with levels of 2.5 g/g without any immunosupressive agents.

Discussion: ALA has the most substantial evidence of the therapeutic effect in diabetic neuropathy and oxidative stress conditions. Growing data suggests a correlation between MN and (ALA) supplements. The limited literature consists of a few case reports that note the association between lipoic acid and MN and more areas to investigate the pathogenesis behind such correlation.

TH-PO671

Alpha Lipoic Acid- and NELL1-Associated Membranous Nephropathy

William L. Vaughn, Ryan A. Parrish, Indira Chervu. *Wellstar Kennestone Regional Medical Center, Marietta, GA.*

Introduction: Membranous nephropathy (MN) is a leading cause of nephrotic syndrome, representing a spectrum of diseases with a common histological pattern of Immunoglobulin and complement-containing immune deposits in the subepithelial position. 75% of cases are primary to some response to a normal podocyte antigen antigen (of which PLA2R is most common) whereas the other cases are secondary to a systemic process. Neural Epidermal Growth Factor-Like 1 (NELL-1) has been implicated as a target antigen in MN. Alpha Lipoic Acid (ALA), a common over the counter supplement, is often recommended for diabetic neuropathy. We describe a rare case of ALA associated NELL-1 positive MN with complete resolution of proteinuria when the drug was stopped.

Case Description: A 69 year-old female with prediabetes and controlled hypertension presented to clinic for proteinuria in 2022. The patient had no history of CKD. She was prescribed 1200 mg of ALA in October 2020 for peripheral neuropathy. Urinalysis in 2017 was normal. UA in January 2022 revealed an Albumin:Cr 1774 and Serum Creatinine 0.70. 24 hour total protein excretion was 1,625 mg, albumin 1,160 mg and Creatinine clearance of 79. SPEP, UPEP, and Serum Immunofixation were normal. Although the patient had a positive ANA (1:1280), further workup was negative, and rheumatology evaluated the positive lab value to not be clinically significant. Hepatitis panel was negative. Renal biopsy showed segmental membranous nephropathy with diffuse staining for IgG3 and NELL-1. ALA was stopped in June 2022, and in June 2023 there was complete resolution of proteinuria (135 mg 24 hour total protein). She was up to date with all age-appropriate cancer-related screening exams.

Discussion: Recent advances in serologic testing have allowed for a biopsy-sparing approach in diagnosis and treatment of PLA2R associated MN. NELL-1 is the second most common antigen identified in MN. There is an opportunity to expand upon this diagnostic approach to include other target antigens such as NELL-1. ALA associated NELL-1 MN is rarely reported upon in literature. Furthermore, there is only one retrospective review of this association. The growing recognition of the interplay between ALA and NELL-1 MN should prompt research into the unclear mechanism behind how this association occurs. Understanding this relationship will guide intervention to both treat and prevent ALA associated MN.

TH-PO672

What the NELL-1 Does α-Lipoic Acid Have to Do with It?

Khateeb Raza,[1] Andrew Dorst,[2] Salar Alam,[1] Katherine W. Kwon.[1] *[1]Corewell Health Southwest Michigan, Saint Joseph, MI; [2]Michigan State University College of Osteopathic Medicine, East Lansing, MI.*

Introduction: Membranous nephropathy, a common cause of nephrotic syndrome, is characterized by the widespread autoantibody targeting of the glomerular basement membrane and subsequent subepithelial immune complex deposition causing renal impairment. Primary Membranous Nephropathy (PMN) arises from autoantibodies against glomerular podocytes. Phospholipase A2 receptor (PLA2R) remains a predominant target, followed by Thrombospondin type-1 domain containing 7A (THSD7A). Recent studies indicate autoantibodies to Neural Epidermal Growth Factor-like 1 (NELL-1), a non-podocyte target, as a significant emerging cause of PMN. Furthermore, an association between NELL-1-associated PMN and α-lipoic acid (ALA), a common over-the-counter (OTC) antioxidant, is suggested. Herein, a case of NELL-1-positive PMN caused by ALA is described.

Case Description: An 84-year-old male with chronic kidney disease 3b/A3 and type 2 diabetes with peripheral neuropathy was evaluated by nephrology for nephrotic range proteinuria. He notably had a 15-month increase in microalbumin/creatinine ratio from 15 mg/g to 5,410 mg/g, despite therapy with SGLT2i, ARB, and GLP-1. Serum creatinine showed mild fluctuations; his exam remained without stigmata of nephrotic syndrome. Work-up for infectious, autoimmune, or malignant etiologies was unremarkable. Renal biopsy was positive for NELL-1 and negative for PLA2R or THSD7A. An in-depth review revealed an undocumented start of ALA 18 months prior by the patient in attempts to treat neuropathy refractory to maximum gabapentin dosage. Prompt discontinuation of ALA led to improved proteinuria in subsequent labs.

Discussion: NELL-1 PMN induced by ALA supplementation is a rare phenomenon seldom described in literature. Its mechanism, though not fully understood, has been proposed through the activation of autoantibodies. Classically, PMN is treated with immunosuppressive agents. In NELL-1 PMN linked to ALA use, recent literature suggests discontinuation of ALA as sufficient treatment. Contemporary trends have led to the increased use of understudied and under-recognized OTC supplements such as ALA in the treatment of neuropathy. These trends have thus necessitated heightened awareness of potential adverse effects and medication interactions. Timely recognition of adverse effects due to supplements is essential to prevent unnecessary treatment and prompt discontinuation of offending agents.

TH-PO673

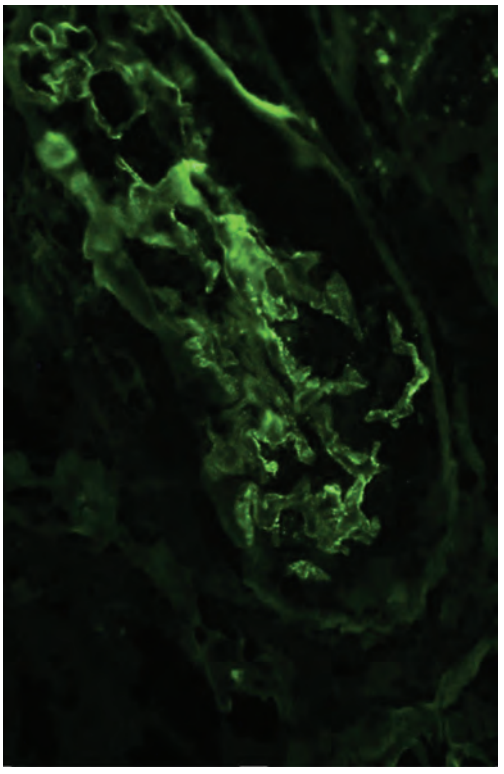
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Associated with NELL1-Positive Membranous Glomerulopathy

Ravi K. Thimmisetty, Karla G. Carias Martinez, George Vasquez-Rios. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

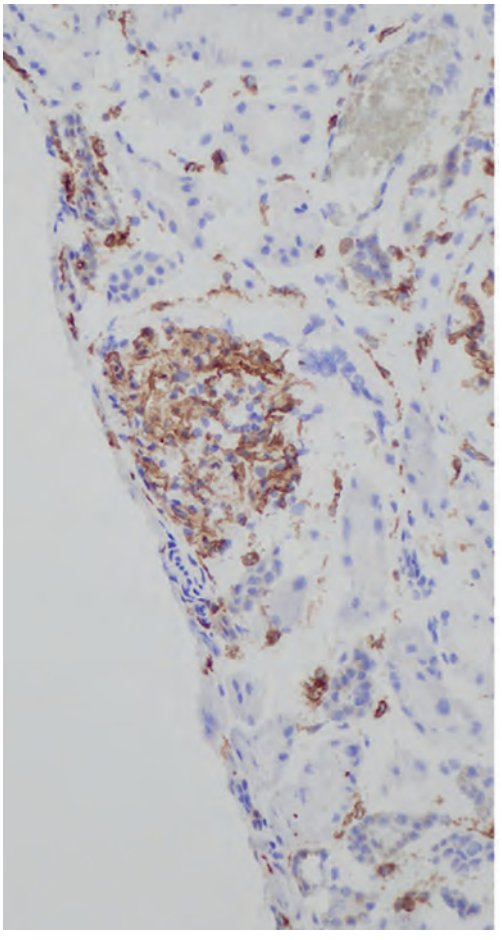
Introduction: Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in adults. We are presenting a rare case of neural epidermal growth factor-like 1 (NELL-1) caused by NSAIDs.

Case Description: A 49-year-old male with history of hyperlipidemia, DJD and on chronic NSAIDs admitted with complaints of periorbital swelling and generalized body swelling since 2 weeks. Also weight gain of 10 pounds over the last few weeks. h/o recent URI symptoms that resolved quickly. he is taking meloxicam for chronic foot pain and also started taking Artri King for last 2 weeks. vitals were with in acceptable range. on room air. exam shows 1-2+ edema. Labs showed serum Cr of 1.68, nephrotic range proteinuria with random UP/UC ratio 9.52, COVID-19 positive. rest of the labs were acceptable. Biopsy showed Membranous Glomerulopathy, NELL1-Positive. With supportive care, creatinine was 1.05 mg/dl and up/uc is 0.06.

Discussion: NELL1-associated MN is commonly described with malignancy. Our case showed that NSAIDs also contribute for this target antigen associated MN. With in 1-2 months, patient better significantly with supportive care. There is an FDA alert on this Over the counter drug. Need to educate all providers in community not to use Artri King.



Ig G1-2 +



TH-PO674

Anti-phospholipase A2 Receptor (PLA2R)-Positive Membranous Nephropathy Triggered by Sunitinib in Patients with Gastrointestinal Stromal Tumor (GIST): A New Association?

Mateus Pascoal, Antony J. Tors, Juliana Hickmann de Moura, Cassiano de Mattos Marques, Elvino J. Guardao barros, Francisco V. Veronese, Luciano Wolffenbuttel. *Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil.*

Introduction: Tyrosine Kinase Inhibitors are classically associated with hypertension and proteinuria due to thrombotic microangiopathy. We report the second case of Membranous Nephropathy associated with anti-PLA2R antibody in the literature, developed shortly after starting Sunitinib, in patients with metastatic GIST.

Case Description: A 55-year-old female was diagnosed with metastatic duodenal GIST in May 2018, and treated with Imatinib 400 mg/day. Oral Sunitinib was started in September 2023 due to disease progression. She developed proteinuria (1450 mg/24 hours) after two doses, leading to treatment discontinuation. Despite that, proteinuria increased to nephrotic levels with urine protein/creatinine ratio (UPCR) of 11 g/g of creatinine. A renal biopsy revealed Membranous Nephropathy and serum anti-PLA2R was positive at 259 UR/ml (<14). The patient was treated with Rituximab, with serologic remission and a marked improvement in proteinuria (UPCR 2.6 g/g of creatinine) shortly after (1 week) completion of treatment.

Discussion: In 2021, Zonoozi et al (BMJ Case Rep 2021;14:e243567) reported a very similar case: proteinuria developed after a few weeks of treatment with Sunitinib in a patient with metastatic GIST that progressed on Imatinib. As in the case reported here, renal biopsy revealed Membranous Nephropathy with serology and tissue IF positive for anti-PLA2R. Both patients were treated with Rituximab, with complete serologic remission. To our knowledge, this is the second case reported of anti-PLA2R Membranous Nephropathy associated with Sunitinib in the literature, coincidentally or not, in patients with GIST. Since there is no known association between Membranous Nephropathy and GIST, and anti-PLA2R antibodies are usually associated with “primary” Membranous Nephropathy, we hypothesize that the Tyrosine Kinase Inhibitor Sunitinib elicited the production of anti-PLA2R antibodies in both cases

TH-PO675

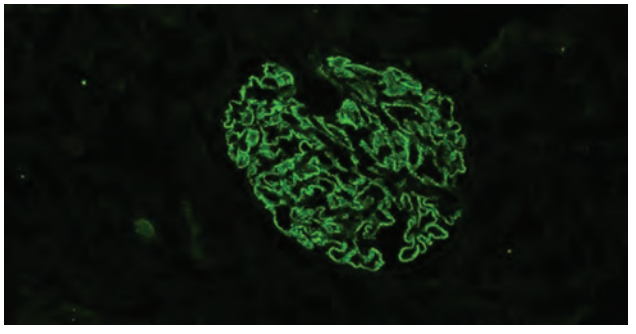
A Case of Primary and Secondary Membranous Nephropathy Associated with a Neuroendocrine Tumor

Wardah Zoha, Maen M. Talib, Ramesh Soundararajan, Mohammed Sadique Hussain, Hasnoor K. Sandhu, Amani Masoud. *Franciscan Health Olympia Fields, Olympia Fields, IL.*

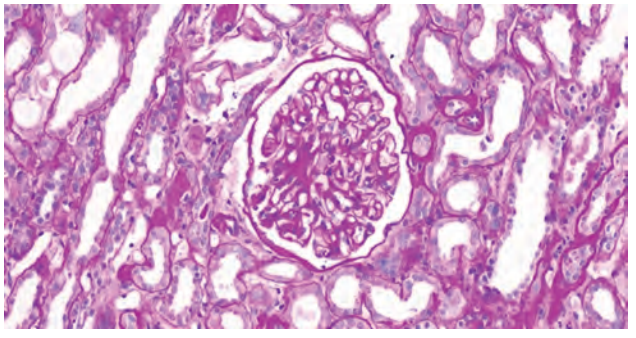
Introduction: Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults. 80% of MN cases are of primary MN, while 20% are secondary. Primary MN involves a positive antibody for anti-phospholipase A2 receptor (PLA2R). Secondary MN is commonly a result of malignancy, infection or drugs. In this case, we present a patient with biopsy proven PLA2R MN and a new diagnosis of neuroendocrine tumor (NET) yielding a mixed primary and secondary MN diagnosis.

Case Description: A 65 year old man with a medical history of congestive heart failure, chronic kidney disease and tobacco use presented with dark stools and altered mental status. His labs showed hemoglobin 6.4, potassium 8.4, BUN 194 and creatinine 8.9. A computed tomography of the abdomen and pelvis showed multiple enlarged lymph nodes concerning for malignancy. He underwent HD line placement and emergent dialysis was initiated. His mentation improved however his dark stools persisted. He underwent an esophagogastroduodenoscopy which showed an actively bleeding duodenal ulcer that was biopsied. Biopsy results showed a large-cell neuroendocrine tumor (NET). A renal biopsy was then performed which revealed PLA2R positive MN and severe acute tubular injury.

Discussion: The simultaneous occurrence of primary and secondary MN in the setting of NET is rare with only a few cases reported in literature. This unusual presentation does not fit previously accepted classifications of primary versus secondary, but rather shows a combination. Therefore, concurrent workup for age appropriate cancer screening and serum PLA2R levels could be of benefit in patients with a new diagnosis of MN.



IF staining of PLA2R



Thick basement membrane in MN

TH-PO676

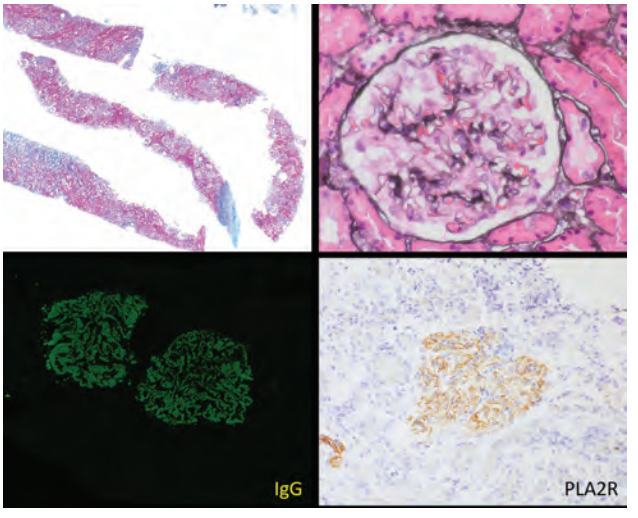
Phospholipase A2 Receptor (PLA2R)-Positive Membranous Nephropathy in a Patient with Negative PLA2R Serology

Irmaris R. Quinones Vargas,[1] Paul B. Avila,[2] J. Pedro Teixeira,[1] Tiffany Caza,[3] Pablo Garcia.[1] *[1]University of New Mexico Health Sciences Center, Albuquerque, NM; [2]Universidad de San Carlos de Guatemala, Ciudad de Guatemala, Guatemala; [3]Arkana Laboratories, Little Rock, AR.*

Introduction: Recent advances in the understanding of the pathogenesis of membranous nephropathy (MN) led to the identification of several target antigens, including phospholipase A2 receptor (PLA2R). PLA2R antibodies are present in the majority of primary MN cases and have important implications for diagnosis, prognosis, and treatment. Here we present a case of MN negative for PLA2R antibodies but with positive biopsy staining for PLA2R.

Case Description: A 51-year-old man presented to clinic with nephrotic syndrome (NS) with lower extremity edema, serum creatinine 1.1 mg/dL, albumin 0.4 g/dL, 24-h urine protein of 13.2 g, and urine protein-creatinine ratio (UPCR) of 14 g/g. He was recently diagnosed with pulmonary embolism which was felt to be secondary to NS. All serologies, including HIV, hepatitis panel, C3, C4, ANCA, ANA, dsDNA, SPEP, UPEP, free light chains, and PLA2R by immunofluorescence assay (IFA), were negative. A kidney biopsy showed MN with glomerular PLA2R deposition by immunohistochemistry (Figure). He was treated with rituximab 1 g x 2 doses 2 weeks apart. A month later UPCR decreased to 7 g/g and serum albumin increased to 1.4 g/dL.

Discussion: Prior studies have suggested that negative PLA2R serology in patients with previously diagnosed PLA2R-positive MN indicates disease inactivity. However, this case suggests this is not always true. In particular, early in the course of MN PLA2R may be detected on biopsy despite a lack of circulating PLA2R antibodies. For scenarios highly suspicious for MN despite negative initial PLA2R serology, clinicians may consider alternative PLA2R antibody assays (e.g., enzyme-linked immunosorbent assay rather than IFA) as well as definitive biopsy diagnosis.



TH-PO677

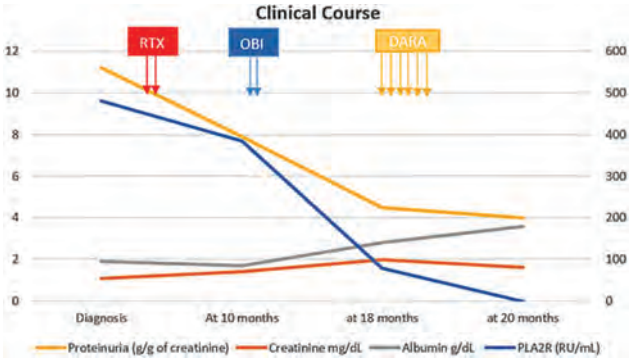
Daratumumab for Anti-CD20-Refractory Membranous Nephropathy

Tammy Yu, Abdallah Sassine Geara. *Penn Medicine, Philadelphia, PA.*

Introduction: Rituximab (RTX) is a cornerstone of therapy for primary membranous nephropathy (MN). However, up to 35-40% of patients do not achieve remission despite depletion of circulating B cells. We discuss a patient with refractory MN who was successfully treated with daratumumab, a plasma cell-directed anti-CD38 monoclonal antibody (mAb).

Case Description: An 80-year-old man presented with anasarca, creatinine (Cr) 1.1 mg/dL, 24-hour urine protein 11.2g, and anti-phospholipase A2 receptor (PLA2R) level 481 relative units (RU)/mL. Kidney biopsy showed subepithelial deposits with basement membrane spikes and diffuse IgG, C3, and PLA2R staining, confirming PLA2R+ MN. He began therapy with RTX 1gx2 in addition to supportive care. At 8 months, he had persistent edema with urine protein to creatinine ratio (UPCR) 11.65 g/g and anti-PLA2R 383 RU/mL. Due to his frailty and age, we elected against treatment with cyclophosphamide (CYC). He was treated with tacrolimus followed by obinutuzumab (OBI) 1gx2. However, despite total depletion of CD19+ B cells, he achieved only partial remission with Cr 2.04 mg/dL, UPCR 7.033 g/g, and anti-PLA2R 78 RU/mL at 6 months. We arranged for daratumumab (DARA) 1800mg weekly injections. At 6 weeks, his edema had resolved, with undetectable PLA2R level, Cr 1.68 mg/dL, and UPCR 4.49 g/g. At 4 months, PLA2R remained undetectable with UPCR 4.03 g/g (Figure 1)

Discussion: Treatment of patients with RTX-resistant MN who are unable to tolerate CYC remains a challenge. Recent reports have demonstrated the potential of newer anti-CD20 mAbs such as OBI for patients with refractory disease. Plasma cell-directed agents like bortezomib or DARA, first approved for B cell malignancies, are now being investigated for autoimmune disease. For our patient, more than 18 months of B cell-depleting therapy led to only partial improvement in PLA2R titers and failed to produce clinical improvement. DARA was able to achieve rapid serologic remission and reversal of his Cr trend, suggesting that anti-CD38 therapy holds promise for multidrug-resistant MN.



Clinical course

TH-PO678

Double Trouble in the Basement! A Case of Phospholipase A2 Receptor (PLA2R)-Associated Membranous Nephropathy with Atypical Anti-glomerular Basement Membrane Disease

Renuka Tolani,[1] Theresa Thurston,[2] Steffi Sathiyaraj,[1] David Lyu,[1] Ziad M. El-Zaatari,[1] Luan D. Truong,[1] Angelina Edwards,[1] Tariq Shafi,[1] Shane A. Bobart.[1] *[1]Houston Methodist, Houston, TX; [2]Texas A&M University System, College Station, TX.*

Introduction: Only a few cases have been reported of concurrent atypical anti-glomerular basement membrane (anti-GBM) disease with membranous nephropathy. Compared to typical anti GBM disease, atypical anti GBM disease is often seronegative, with a mild disease presentation and course. We present a case of concomitant of PLA2R associated membranous nephropathy and atypical anti-GBM disease in a patient with cholangiocarcinoma.

Case Description: A 66-year-old male with type 2 diabetes, hypertension, hyperlipidemia, viral hepatitis C, cirrhosis, and cholangiocarcinoma presented with nephrotic range proteinuria, and worsening bilateral lower extremity edema. Urine studies showed 3+ protein and 13 red blood cells per high powered field and 24-hour urine proteinuria of 14 grams with serum albumin of 2.1 g/dL, and serum creatinine 0.8 mg/dL. (nephrotic syndrome). Serological work-up was negative for ANA, anti-dsDNA, PLA2R, ANCA, rheumatoid factor, and anti-GBM, with normal complements, and no monoclonal gammopathy. A kidney biopsy showed membranous nephropathy with typical light microscopic, immunofluorescent, and electron microscopic changes. In addition, there was atypical anti-GBM disease characterized by a non-circumferential cellular crescent in 1 out of 12 glomeruli, and 2-3+ linear staining for IgG along glomerular basement membrane with 2+ C3, kappa and lambda light chain. There was no tubular basement membrane staining for IgG. The glomeruli demonstrated strong staining for PLA2R, but negative for THSD7A and NELL-1. The patient received rituximab infusion, dapagliflozin, and lisinopril, resulting in remission of proteinuria. Despite intense chemotherapy with cisplatin, gemcitabine and immunotherapy, the malignancy progressed, and he transitioned to hospice care.

Discussion: For our patient, rituximab resulted in remission of proteinuria, but malignancy had progressed. The lack of temporal association is consistent with the biopsy findings of PLA2R -associated membranous nephropathy. While there is not an established guideline, our case demonstrates the utility of rituximab for the management of concurrent atypical anti-GBM disease with membranous nephropathy.

TH-PO679

Unveiling the Enigma: Primary Membranous Nephropathy with Crescent Formation, a Puzzling Rarity

Joy Kumar, Cleris N. Christian, Raafat F. Makary, Irtiza Hasan. *University of Florida College of Medicine - Jacksonville, Jacksonville, FL.*

Introduction: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. Development of crescents in MN is extremely rare (<1%) & is usually associated with a rapidly progressive course to renal failure. We report a case of crescents in primary MN, characterized by positive anti-phospholipase A2 receptor (PLA2R) antibodies with a negative ANCA profile & anti-GBM assay.

Case Description: A 38-year-old male with essential hypertension presented in 2018 with anasarca & hypertensive emergency. Labs showed creatinine (Cr) of 1.1 mg/dl, hypoalbuminemia (serum albumin of 1.4 g/dl), & massive proteinuria (37.13 g/24 hrs). Serum ANCA, ANA, anti-dsDNA, & anti-GBM were negative. Anti-PLA2R was highly positive (280.3 RU/ml). A kidney biopsy with immunofluorescence (IF) & electron microscopy (EM) were consistent with Primary MN (stage 3). IF showed diffuse granular deposits of IgG, C3 & C1q. EM showed subepithelial immune deposits with extensive foot process effacement. No endocapillary proliferation, fibrinoid necrosis, or crescent were seen. Received immunosuppressant (IS) therapy per Dutch protocol, achieving partial remission. In the next 4 years, there were multiple admissions with AKI (Cr ranging between 1.9-3.5 mg/dl), as well as a COVID-19 infection in 2020. A repeat renal biopsy was performed during subsequent readmission with a Cr of 10.6 mg/dl in 2022, which revealed MN with focal crescents (7 cellular/fibro cellular & one fibrous), global sclerosis of 46%, tubular atrophy, & chronic interstitial inflammation. Anti-PLA2R was lower but still elevated (45 RU/ml). No meaningful recovery despite IS therapy, and he progressed to End-Stage Kidney Disease & started on dialysis.

Discussion: The presence of crescents raised suspicion of secondary MN due to infections, neoplasms, etc. However, the lack of secondary MN indicators, negative ANA, anti-dsDNA, ANCA, anti-GBM antibodies, & highly positive anti-PLA2R ab confirmed the diagnosis. Primary idiopathic crescentic MN is rare, with crescent formation likely due to PLA2R immune complex deposition, suggesting MN progression. Although rare, the crescents could also be linked to COVID-19 infection, with no documented cases. Another possibility is the coincidental occurrence of two separate diseases. Recognizing crescents in primary MN is crucial for early & accurate management to prevent progression.

TH-PO680

Rare Coincidence or Secondary Process: Membranous Nephropathy with ANCA-Associated Vasculitis

Leen Al-yacoub, Leal C. Herlitz, Ali Mehdi. *Cleveland Clinic, Cleveland, OH.*

Introduction: Membranous nephropathy (MN) is reported to occur in ANCA-associated vasculitis (AAV) and is usually thought of as secondary. We hereby contrast two cases with AAV both with membranous features one being PLA2R positive suggesting a primary disease process.

Case Description: Case 1: A 70-year-old man with hypertension and chronic sinusitis presented with worsening nasal symptoms, fatigue, poor appetite, and arthralgias. He had severe acute kidney injury requiring dialysis. He had positive C-ANCA/ PR3 antibodies with hematuria and nephrotic-range proteinuria on urinalysis. Kidney biopsy confirmed pauci-immune necrotizing crescentic glomerulonephritis but also showed prominent membranous nephropathy features. Serologic PLA2R testing was negative along with negative tissue PLA2R and Exostosin 1/2 staining. Patient was treated with pulse steroids, plasmapheresis, and oral cyclophosphamide and was able to be liberated from dialysis (Creatinine nadir: 1.2 mg/dL). Proteinuria also trended down from UPCR 7.9 to 3.9 g/g. Due to concern for relapse 3 months into treatment, he was switched over to Rituximab. Remission was achieved after 7 months. Now 2 years after starting rituximab, patient remains in remission (creatinine 1.17mg/dL, UPCR 0.3g/g). Case 2: A 68-year-old female with hypertension and type 2 diabetes presented with generalized edema. She was found to have hematuria, proteinuria, and AKI (creatinine 1.1 mg/dL, baseline 0.7mg/dL). Albumin was 0.9 g/dL with proteinuria of 5.1 g/day. P-ANCA/MPO was positive with kidney biopsy showing pauci-immune crescentic glomerulonephritis along with prominent membranous features. Serologic PLA2R was positive. Patients was treated with pulse steroids and rituximab with serologic and clinical remission within 8 weeks. 5 years after diagnosis patient remains in complete remission (creatinine: 0.68 mg/dL, no hematuria or proteinuria).

Discussion: These cases highlight that MN can occur in the context of AAV. Whether the MN is secondary to AAV is not clear but the PLA2R positive case suggests a seperate primary disease. This patient's presentation with a primarily florid nephrotic syndrome with a mild AKI also suggests that. Rituximab based therapy resulted in remission of both diseases in both cases.

TH-PO681

Thrombotic Microangiopathy and Membranous Nephropathy: A Complicated Paraneoplastic Disorder

Leen Al-yacoub, Jagmeet S. Dhingra, Corey J. Cavanaugh, Leal C. Herlitz, Ali Mehdi. *Cleveland Clinic, Cleveland, OH.*

Introduction: Hematologic malignancies are associated with a myriad of paraneoplastic glomerular pathologies. Various lesions have been described with Mantle cell lymphoma (MCL). We hereby describe a case of concomitant membranous nephropathy (MN) and thrombotic microangiopathy (TMA) in the context of relapsed MCL.

Case Description: A 68-year-old male with history of MCL previously in remission presented with generalized edema. MCL had recently relapsed and patient was set to start Zanubrutinib. He had AKI (Creatinine 2 mg/dL, baseline 1.2), hypoalbuminemia

(1.8 g/dL), nephrotic range proteinuria (13 g/day), normocytic anemia and mild thrombocytopenia. Complements were depleted with a negative serologic workup including PLA2R and THSD7A. Kidney biopsy showed subacute/chronic TMA along with MN. Tissue PLA2R staining was negative. Pathologies were felt to be paraneoplastic and as such lymphoma directed therapy was intensified. Two months later, worsening AKI and anasarca prompted dialysis initiation. Microangiopathic hemolytic anemia and thrombocytopenia were noted along with depleted haptoglobin. Complements remained depleted with elevated sC5b-9 (>2130ng/ml; ref <244ng/ml). Imaging suggested lack of lymphoma response. Along with changing lymphoma therapy, decision was made to initiate eculizumab. This led to liberalization from dialysis (creatinine nadir 1.9 mg/dL) and stabilization of hematologic parameters. Haptoglobin and sC5b-9 also normalized. Attempt at stopping eculizumab after 8 weeks resulted in worsening of kidney and hematologic parameters. Upon restarting eculizumab, things stabilized again. Four months after resuming therapy, kidney function remains stable with improving proteinuria (creatinine 1.9 mg/dL; albumin 3.8g/dL). MCL remains stable.

Discussion: We present a complex paraneoplastic renal pathology of MN and TMA in the context of relapsed MCL. While addressing the underlying malignancy remains the cornerstone of management, given the severity of the presentation eculizumab was successfully used here to stabilize the situation until meaningful hematologic response is achieved. This case highlights that management of these ever-challenging cases needs to be individualized and requires an interdisciplinary approach

TH-PO682

A Case of Membranous Nephropathy Secondary to ANCA-Associated Vasculitis

Chiharu Aizawa,[1] Takuya Fujimaru,[1,2] Futoshi Iwata,[1] Nozomi Kadota,[1] Risa Ishikawa,[1] Yugo Ito,[1] Masahiko Nagahama,[1] Fumika Taki,[1] Motoko Chiga,[2] Eisei Sohara,[2] Shinichi Uchida,[2] Michiko Suzuki.[1] *[1]Sei Roka Kokusai Byoin, Chuo-ku, Japan; [2]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan.*

Introduction: ANCA-associated vasculitis (AAV) is sometimes associated with secondary membranous nephropathy (MN). Avacopan, a complement C5a receptor inhibitor, is a drug that can minimize or discontinue corticosteroid doses for AAV. It is unclear whether avacopan, which exerts anti-inflammatory effects through selective C5a receptor antagonism, is useful in the treatment of secondary MN due to AAV.

Case Description: An 80-year-old woman had tested positive for anti-Mycobacterium avium complex antibodies 6 years earlier. She was followed up without treatment because she had no respiratory symptoms. She had been P-ANCA positive for 3 years, but there were no findings suggestive of vasculitis and she was followed up without treatment. She presented to our department with increasing serum creatinine from 0.6 mg/dL to 1.2 mg/dL, severe proteinuria (10 g/gCr), hematuria, and hypoalbuminemia (Alb 2.3 g/dL). Clinically, she was diagnosed with rapid progressive glomerulonephritis with nephrotic syndrome. A renal biopsy was performed and revealed findings of necrotizing crescentic nephritis and MN. Immunofluorescence (IF) staining showed positive IgG4 and MPO-ANCA in the glomerular basement membrane (GBM) but negative anti-PLA2R and anti-THSD7A antibodies. We diagnosed AAV and secondary MN due to MPO-ANCA. We started treatment with prednisolone, rituximab, and avacopan. Prednisolone decreased early. Serum P-ANCA became negative after 1 month of treatment. Seven months later, serum creatinine improved to 1.0 mg/dL, urine protein was 2.8 g/g Cr and serum Alb was 3.9 g/dL.

Discussion: Secondary MN associated with AAV often shows positive MPO-ANCA in the GBM and is negative for IgG4 and anti-PLA2R antibodies in IF staining. However, there have been several case reports of IgG4 predominance. In this case, MPO-ANCA was positive for GBM and was considered secondary MN due to AAV. Avacopan in combination with rituximab and early dose reduction of prednisolone resulted in resolution of P-ANCA, improvement of renal dysfunction, and resolution of proteinuria in this patient. Steroid-sparing therapy with avacopan and rituximab may be effective in secondary MN due to ANCA.

TH-PO683

Anti-brush Border Antibody Disease with Segmental Membranous Nephropathy and Acute Tubular Injury in a Patient with Severe Diabetic Nephropathy

Devansh H. Patel, Deepak Chandramohan, Huma Fatima, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Autoantibody directed to the low-density lipoprotein receptor related protein 2 (LRP2), also known as megalin, is a newly recognized cause of human autoimmune tubular injury. This entity has been termed antibrush border antibody (ABBA) disease or anti-LRP2 nephropathy. LRP2 plays an important role in proximal tubular endocytosis of albumin and other molecules.

Case Description: A 64-year-old male with longstanding diabetes and recurrent AKIs on CKD4A3 presented with symptomatic volume overload and oliguric AKI. He was hypoalbuminemic [Sr albumin 1.5 g/dL] and had high grade proteinuria [UPCR ~ 12.5 g/g] on admission. Extensive serological workup was negative. Kidney biopsy revealed severe diabetes related kidney injury including mesangiolysis and microaneurysmal ruptures, segmental membranous nephropathy [IgG and light chains being 2+], and moderate acute tubular injury. Diffuse, homogenous appearing electron-dense deposits were noted along the TBMs. NELL-1 staining was negative along the GBM; LRP2 staining was positive along the TBM as well as segmentally in the glomeruli [membranous pattern] and along the Bowman's capsule. Patient continues to be dialysis dependent as of now. Immunosuppression was not started given his tenous overall condition.

Discussion: ABBA disease is extremely rare seen in 0.05% of all kidney biopsies. It most commonly afflicts elderly White males; 41% cases have concomitant monoclonal gammopathies. Its co-occurance with severe diabetic nephroapthy is not well ascribed. Acute tubular injury, granular TBM deposits in the proximal tubule, and segmental deposits in the subepithelial region and Bowman's capsule [seen in 80%] are charecteristic. Confirmation warrants positive IF staining for LRP2 within TBM deposits or serologic confirmation of anti-LRP2 antibodies by indirect IF performed on normal human kidney. Prognosis is guarded with 53% progressing to ESKD. Immunosuppression may be warranted in most cases. Our case highlights the importance of considering ABBA disease in the differential when diffuse TBM injury is noted.

TH-PO684

Autologous Stem-Cell Transplant Inducing Autoimmunity Leading to Membranous Nephropathy

Joshua A. Larrazolo, Koyal Jain. *The University of North Carolina at Chapel Hill Department of Medicine, Chapel Hill, NC.*

Introduction: We present a rare case of amyloidosis and autologous stem cell transplant (auto-SCT) two years prior presenting with new nephrotic range proteinuria due to secondary immune complex vasculopathy and membranous nephropathy.

Case Description: A 67-year-old woman with HTN, HLD, AL amyloidosis (diagnosed 4 years ago, treated with CyBorD-Daratumaumab for 1.5 years) presented with worsening proteinuria. Peak proteinuria was 800mg. Auto-SCT was 2.5 years earlier with severe engraftment syndrome (fever, rash, diarrhea) diagnosed by colon biopsy consistent with autologous GVHD treated with prednisone for 2 years, compared to typical 1-2 week therapy, given recurrence of diarrhea with cessation of steroids. Repeat colonoscopy negative for GVHD but inflammatory cecal mass noted while on 5mg Prednisone daily. Prednisone was stopped 4 months prior and patient then noted foamy urine, increased fatigue, mild nausea, intermittent water stools. Lab work showed ACR 3.4g up from 15mg one year ago and UPC 6.4g, moderate hematuria, urine sediment with 1 dysmorphic RBC, stable creatinine 0.97, albumin 2.8, negative ANA, negative anti-PLA2R, positive hepatitis B surface antibody (vaccinated), and negative hepatitis C and CMV. Amyloid noted to be in remission on blood work. Renal biopsy showed membranous nephropathy (stage I-II) and glomerular and arteriolar IgG, IgA, C3, and C1q immune deposits by IF. 40% global and 10% FSGS, minimal glomerular and vascular amyloid deposits, moderate-severe interstitial fibrosis, and tubular atrophy noted. Diagnosis of autoimmune IC type disease with secondary membranous in auto-SCT was made and treatment started with Rituximab and steroids.

Discussion: Autologous GVHD is thought to be similar to autoimmune syndrome and has been documented in the GI tract and skin. Studies have detected autoantibodies after SCT with chronic GVHD, providing evidence for B-cell involvement. Here the proteinuria is driven by membranous nephropathy with polyclonal immune complex deposits. Autoimmunity is likely from ASCT (can happen with infections, e.g. hepatitis B, but it was negative). Steroids and Rituximab can be used to treat auto-SCT-associated antibody mediated autoimmune MN. This case highlights not only a rare presentation but also the importance of repeat biopsy for diagnosing another cause, especially if other markers of amyloidosis are negative and history doesn't support amyloidosis.

TH-PO685

Breaking Barriers: Unconventional Therapy Treats a Challenging Case of Primary Membranous Nephropathy

Md R. Hasan,[1] Ahmed Abdallah,[2] John M. Arthur,[2] Joseph H. Holthoff.[2] *[1]Arkansas College of Osteopathic Medicine, Fort Smith, AR; [2]University of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Membranous nephropathy (MN) is a common cause of nephrotic syndrome, occurring either as primary or secondary. Notably, primary MN is linked to specific antigens, such as phospholipase A2 receptor (PLA2R), which is associated with lower rates of spontaneous remission and a progressive decline in kidney function. Approximately 30% of PLA2R-positive cases may exhibit resistance to conventional treatments like rituximab and cyclophosphamide, prompting the need for innovative therapeutic approaches. We hereby, present a case of treatment-resistant primary MN managed using bortezomib, a medication typically used in myeloma therapy.

Case Description: 44 y.o. male with past medical history of essential hypertension presented to the emergency department with complains of anasarca for 3 weeks. On presentation, he had generalized edema on physical exam. Initial laboratory work up revealed a serum creatinine of 2.5 mg/dl (baseline 1.2 mg/dl), serum albumin of <1 g/dl and a urine protein creatinine ratio (UPCR) showed proteinuria of 12.9 g which was later quantified on

a 24 hour urinary sample as 15 g. We ordered an anti-PLA2R antibody (IgG) titer which was significantly elevated consistent with primary MN. MN was also evident on renal biopsy that was done prior to the antibody results. He was subsequently started on rituximab infusion but unfortunately failed to respond and had persistently elevated anti PLA2R antibodies. Serum CD-19 was undetectable, however, despite achieving complete B-cell depletion he retained high anti-PLA2R antibody levels. We, therefore anticipated plasma cells lacking CD-19 to be the likely source for persistent production of the culprit antibodies and decided to target plasma cells with bortezumab. After two doses of bortezumab, he achieved a gradual reduction in proteinuria as well as anti PLA2R antibodies.

Discussion: For patients with primary MN who do not attain immunologic remission despite B-cell depletion, another hypothesis proposes the existence of long-lived plasma cells that generate anti-PLA2R antibodies. This rationale led to the administration of the proteasome inhibitor, bortezomib, to our patient with PLA2R-positive MN resistant to rituximab. We suggest targeting plasma cells in specific MN cases that remain immunologically active despite successful B-cell depletion with conventional therapies.

TH-PO686

A Case of Severe Membranous Nephropathy Complicated by Chylothorax

Jack Luo, Michael T. Sim, Nasim Wiegley. *UC Davis Medical Center, Sacramento, CA.*

Introduction: Membranous nephropathy (MN) is one of the most common causes of adult-onset nephrotic syndrome (NS). Development of chylothorax is a very rare complication of MN. We present a patient with severe MN, refractory to two first-line immunosuppressive therapy regimens, who developed a chylous pleural effusion, which eventually resolved after the use of cyclophosphamide-based Ponticelli protocol.

Case Description: A 61-year-old White man without any known medical history presented with profound peripheral edema, hypertension, hyperlipidemia, >10 grams per day on 24-hour urine collection, and normal kidney function. Kidney biopsy showed MN with negative PLA2R on tissue staining and serum. A thorough age-appropriate malignancy workup was negative. He was initially treated with rituximab (RTX) infusion 1g x2, followed by initiation of tacrolimus, given minimal response to RTX. He developed progressively worsening shortness of breath, found to have moderate to large right pleural effusion on chest x-ray requiring thoracentesis, with the removal of 1.5L of cloudy white/yellow fluid, with triglyceride (TG) levels of 143 mg/dL. He continued to require monthly thoracentesis. After transitioning to a cyclophosphamide-based regimen with the Ponticelli protocol, he had complete resolution of pleural effusions with partial remission of NS.

Discussion: Chylothorax occurs when the thoracic duct or its tributaries are disrupted, leading to chyle leakage and accumulation into the pleural cavity. The pathophysiology of chylothorax in the setting of MN is not well understood. Proposed theories include increased permeability due to hypoproteinemia or increased lymphatic vessel pressure from severe tissue edema. Immune-mediated damage to lymphatic vessels related to the MN disease process is also a possibility. Further research is needed to elucidate the precise mechanisms underlying this association. Our case underscores the challenges in managing MN and highlights a rare complication of this disease.

Figure 1. A and B) Thoracentesis done prior to Cytoxan; C) Thoracentesis done after Cytoxan

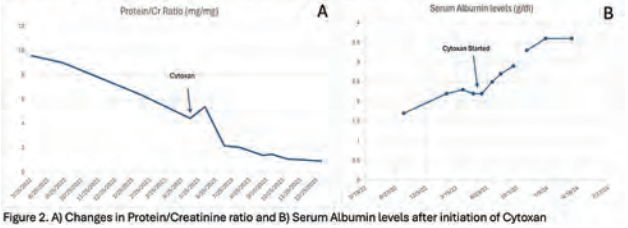


Figure 2. A) Changes in Protein/Creatinine ratio and B) Serum Albumin levels after initiation of Cytoxan

TH-PO687

A Rare Convergence: Suspected Secondary IgA Nephropathy Associated with Dermatomyositis

Jack Luo, Andrea Broka, Kuang-Yu Jen, Nasim Wiegley. *UC Davis Medical Center, Sacramento, CA.*

Introduction: IgA nephropathy (IgAN) is characterized by the accumulation of circulating immune complexes of immunoglobulins and galactose-deficient IgA antibodies in the glomeruli, leading to inflammation and tissue injury. Dermatomyositis, an autoimmune disorder affecting skin and muscles, is rarely linked to kidney manifestations. We present a patient with dermatomyositis who developed sub-nephrotic range proteinuria and microscopic hematuria and was found to have secondary IgAN while on immunosuppressive therapy.

Case Description: A 58-year-old White man with a known history of hypertension, dermatomyositis on Methotrexate 17.5 mg weekly, Tocilizumab 162 mg once a week, and erosive arthritis, presented for evaluation of sub-nephrotic range proteinuria (UPRC 2.5 g/g) with normal kidney function. Initial workup, including ultrasound, complements C3 and C4, and serologic workup for autoimmune disease and chronic infection was negative. Fat pad biopsy was negative for amyloid. Kidney biopsy showed IgAN with the presence of tubuloreticular inclusions on electron microscopy, suggesting a secondary autoimmune nature. He was started on Dapagliflozin, Olmesartan, and Spironolactone with a marked reduction in proteinuria.

Discussion: This case highlights the rare occurrence of secondary IgAN in a patient with dermatomyositis under immunosuppressive therapy. IgAN has been associated with other autoimmune diseases, such as inflammatory bowel disease, celiac disease, and Sjogren's syndrome, but is rarely associated with idiopathic inflammatory myopathies, such as dermatomyositis. Our findings contribute insights into the diverse clinical presentations of idiopathic inflammatory myopathy-associated complications and highlight the need for further studies to evaluate the relationship between idiopathic inflammatory myopathies, such as dermatomyositis, and IgAN.

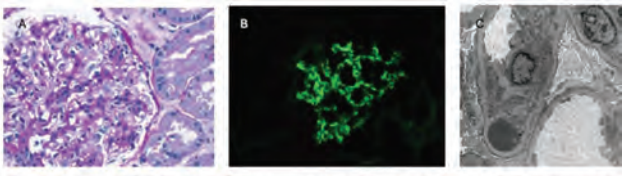


Figure 1: A) Glomerulus with mesangial widening/hypercellularity (PAS, 400X); B) IgA immunofluorescence showing IgA-dominant immune deposits predominantly in the mesangium (200X); C) Electron microscopy reveals paramesangial/mesangial immune deposits (6000X).

TH-PO688

Hypereosinophilic Syndrome with Skin Lesions and Secondary Membranous Nephropathy

Mohamad Bakro, Jee H. Kim, Nitzy N. Munoz Casablanca, Hameeda T. Khan, Aaron S. Stern, Maritza Brown, Hyun Joon Cho. *Mount Sinai Health System, New York, NY.*

Introduction: Hypereosinophilic syndrome (HES) is a rare disorder characterized by persistently high absolute eosinophil count (AEC) (>1500 cells/μL), which leads to organ damage due to cell infiltration. Clinical presentations encompass diverse organ systems, including skin, heart, lungs, and gastrointestinal tract. While uncommon, HES can have renal involvement. Approximately 25-30% of cases of membranous nephropathy (MN) are secondary in nature, with HES being a possible but infrequent cause.

Case Description: A 63-year-old undomiciled male, with a history of alcohol use disorder and evolving hypereosinophilia for over a year, presented for generalized pruritus and a widespread scaly erythematous rash with excoriations. Extensive infectious workup was unremarkable. A bone marrow biopsy ruled out neoplasm, and a skin biopsy showed no evidence of scabies. Despite empiric treatment for scabies and strongyloides, the patient's AEC continued to rise, reaching 13,000 cells/microL. **Laboratory evaluation revealed rising serum creatinine to 5.0 mg/dL and a urine protein-to-creatinine ratio of 3.3.** These findings prompted a kidney biopsy, which demonstrated severe interstitial fibrosis, tubular damage, patchy lymphoplasmacytic interstitial infiltrates, and rare eosinophils. **Electron microscopy** showed mesangial, subepithelial, and intramembranous immune-type deposits. **Immunofluorescence studies revealed IgG and C3 deposits along the glomerular basement membrane, with additional mesangial IgG, IgM, and C3 deposits. Findings were consistent with a diagnosis of secondary MN.** The patient initially showed improvement in kidney function with methylprednisolone followed by a tapering regimen of prednisone. However, during the steroid tapering phase, the patient's renal impairment progressed, ultimately necessitating hemodialysis initiation.

Discussion: HES is a heterogeneous disorder with diverse clinical presentations. Renal involvement, as exemplified by this case, is uncommon but poses significant morbidity with delayed identification and treatment. While the patient initially responded to steroid therapy, kidney disease progression underscores the complexities of managing HES-related renal complications. A review of the literature identified limited case reports of MN associated with HES, highlighting the rarity of this presentation.

TH-PO689

A Child with Exostosin 2-Associated Membranous Nephropathy

Nicole Vegh,[1] Ihor V. Yosypiv.[2] *[1]Louisiana State University, Baton Rouge, LA; [2]Tulane University School of Medicine, New Orleans, LA.*

Introduction: Unlike adults, membranous nephropathy (MN) comprises only 1-2% of childhood nephrotic syndrome. Primary MN is driven by the formation of immune complexes formed by specific antibodies targeting antigens along the subepithelial region of the glomerular basement membrane (GBM). Exostosin 1 and exostosin 2 (EXT1/EXT2) antigens identify a unique form of MN associated with autoimmune disease, such as lupus.

Case Description: A healthy 9-year-old African American boy presented to emergency department for thoughts of suicidal ideation and self harm due to bullying at school. Vital signs and physical examination were normal. Family history was positive for lupus nephritis requiring kidney transplantation. Labs showed normal eGFR, reduced serum albumin (2.5 g/dL), negative ANA, normal C3/C4 complement levels, negative HIV, hepatitis panel, RPR, TB QuantiFERON gold and TSH. Urinalysis (UA) was negative except increased protein to creatinine ratio (5.061 mg/mg). Nephrology started prednisone (2mg/kg/day) treatment of nephrotic syndrome. Lack of remission triggered renal biopsy which showed diffuse global holes and spikes along the thickened GBM, +4 IgG, trace IgA, 3+ C3, 3+ kappa, +3 lambda, EXT2+, global subepithelial and intramembranous electron dense deposits with severe epithelial foot process effacement. Renasight gene panel was negative. A diagnosis of primary EXT2-positive membranous nephropathy was made. *EXT2* encodes glycosyltransferase involved in the chain elongation step of heparan sulfate biosynthesis. Prednisone was stopped and lisinopril was started for nephroprotection. Proteinuria resolved within ~2 months and lisinopril was stopped.

Discussion: This case illustrates that EXT2-positive MN is associated with good short-term clinical outcomes in children. Given that kidney EXT2-positivity is associated with autoimmune diseases, most commonly lupus nephritis, long-term monitoring is required. This case highlights that through identifying specific podocyte antigens, we can tailor individuals' care. Knowledge of the association of EXT2 with lupus nephritis allows for better anticipatory guidance to families.

TH-PO690

THSD7A-Associated Membranous Nephropathy in a Patient with IgA Lambda Myeloma

Saeed Razaq, Khudija Nayab, Frida Rosenblum, Arun Rajasekaran.
The University of Alabama at Birmingham, Birmingham, AL.

Introduction: Membranous nephropathy (MN) is a pattern of glomerular injury caused by autoantibodies binding to specific target antigens, with accumulation of immune complexes along the subepithelial region of glomerular basement membranes. At least 14 target antigens have been identified, accounting for 80%–90% of cases of MN. Thrombospondin type-I domain-containing 7A (THSD7A) was discovered in 2014, but is seen in only 2% cases of MN (both primary and associated with neoplasms). We describe a rare case of THSD7A mediated MN in a patient with concomitant IgA lambda multiple myeloma

Case Description: A 77-year-old male with history of hypertension was admitted with nephrotic syndrome. Cr 1 mg/dL, Sr albumin 1.9 g/dL, and 24 hour urinary protein 6604 mg. SPEP and SIFE revealed 1 IgA lambda monoclonal protein 0.19 mg/dL. Serum PLA2R was negative and serum THSD7A was positive [Mayo Clinic based, titer not available]. Kidney biopsy revealed a membranous pattern of GN with IFTA < 10%. IF: IgG (4+), IgA (4+), IgM (1+), C3 (2+), C1q (trace), kappa LC (3+) and lambda LC (4+) along the capillary loops. Pronase IF was negative. Electron microscopy revealed subepithelial and intramembranous electron dense deposits which were finely granular. Diffuse foot process effacement was noted. PLA2R was negative in the glomeruli while THSD7A IF was positive in the glomeruli. Congo red staining was in kidney biopsy. BM biopsy showed 15% IgA lambda restricted plasma cells. Extensive workup for AL amyloid was negative. A diagnosis of IgA lambda smoldering multiple myeloma was made. Clone based therapy was not initiated and a wait-and-watch approach was implemented. Conservative management including ARBs were started. Patient has now attained complete remission of proteinuria with negative serum THSD7A levels.

Discussion: THSD7A associated MN, in the majority of cases, is a prototypical example of a primary MN, with anti-THSD7A antibodies, predominantly of the IgG4 subclass, directed against THSD7A that is endogenously expressed on podocytes. Disease activity correlates with the titer and trajectory of antibodies and responds to immunosuppression. 16% have a concurrent malignancy; circulating anti-THSD7A antibodies have been reported as a consequence of THSD7A expression by a malignant tumor. Co-occurance with underlying IgA Lambda Smoldering Myeloma has not been reported thus far.

TH-PO691

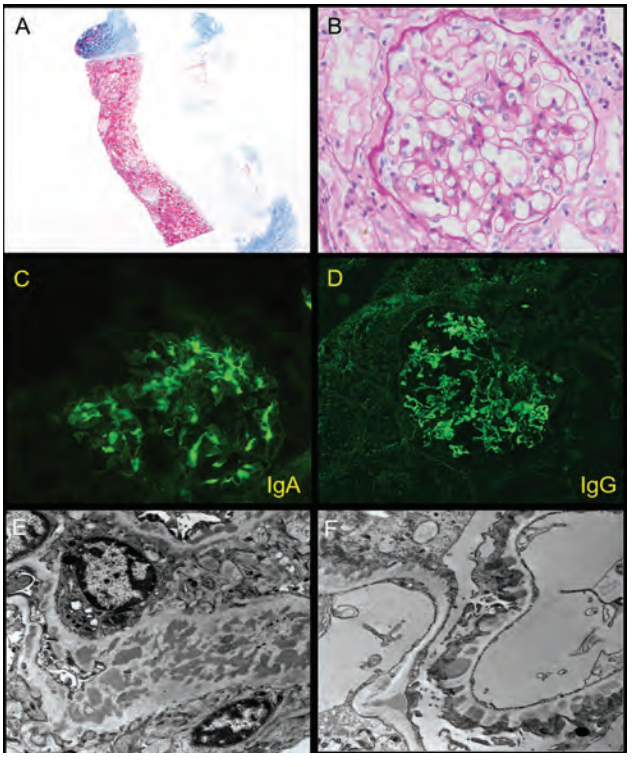
A Postkidney Transplant Patient with Membranous-Like Glomerulopathy with Masked IgG-Kappa Deposits

Paul B. Avila,[1] Ulises Rodriguez Medina,[2] Pooja P. Singh,[2] Namita Singh,[2] Tiffany Caza,[3] Pablo Garcia.[2] *[1]Universidad de San Carlos de Guatemala, Ciudad de Guatemala, Guatemala; [2]University of New Mexico Health Sciences Center, Albuquerque, NM; [3]Arkana Laboratories, Little Rock, AR.*

Introduction: Membranous-like glomerulopathy with masked IgG kappa deposits (MGMIDs) is a novel glomerulonephritis —44% of patients experience worsening kidney disease or ESKD. There is no data on long-term post-kidney transplant (KT) outcomes in patients with MGMID. Here, we present a patient with MGMIDs after KT with four years follow-up after diagnosis.

Case Description: A 47 y/o Hispanic male with ESKD due to membranous nephropathy received DDKT without post-KT complications. He developed worsening proteinuria four years after the KT (2.8 g/g). Thus, he underwent a kidney biopsy, which showed MGMID with concurrent IgA nephropathy (M1 E0 S0 T0 C0). No malignancy, no clones and no bone marrow abnormalities were found. After a multidisciplinary team discussion with the patient, he was started on an ACEi and continued immunosuppressive (IS) therapy (tacrolimus, MMF, and prednisone) with no adjustment to his IS therapy. Four years after his diagnosis, his allograft function remains stable, with an eGFR of 109 ml/min and UPCR of 0.2 g/g.

Discussion: MGMID is a complex disease with no easily identifiable clone, lacks established treatment, and has unclear outcomes. Limited data exists for post-KT MGMIDs. This case highlights the disease remission after ACEi and continuation of his IS therapy, indicating that ACEi, MMF and tacrolimus could play a role in the therapeutic approach. Further studies are needed to understand the disease process and guide our management.



A. No significant interstitial fibrosis
B. Glomerulus with mild mesangial expansion
C. Mesangial IgA staining
D. Capillary loop IgG1 staining
E. Mesangial electron dense deposits.
F. Subepithelial electron dense deposits.

TH-PO692

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits in a Patient with Recent Deceased Donor Kidney Transplant Successfully Treated with Rituximab Monotherapy

Nicholas S. Thorneloe, Alexandra Stewart. *Brooke Army Medical Center, Fort Sam Houston, TX.*

Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMIDs) is a poorly understood monoclonal gammopathy of renal significance. The pathophysiology of this disease remains elusive; though is generally characterized by altered renal function, proteinuria and monoclonal immunoglobulin granular glomerular deposits. Prognosis is poor and treatment without consensus.

Case Description: Patient is a 40-year-old male with history of end stage renal disease due to presumed post infectious C3 glomerular nephritis with secondary focal segmental glomerular sclerosis positive for APOL1; resistant to prolonged steroids. Patient is status post deceased donor kidney transplant in 2022 complicated by delayed graft function with hyperkalemia, hypertension, and secondary polycythemia. Post-transplant patient's creatinine (Cr) nadir was 2.3 with uptrend to 2.8 without proteinuria. Serum immunofixation demonstrated IgA monoclonal protein with kappa light chain specificity, prompting biopsy. Immunofluorescence revealed mesangial deposits of 3+ C3, 1+ C1q, 3+ lambda light chains, 3+ IgG3. Bone marrow biopsy showed hypocellularity without evidence of malignancy. He completed seven of eight doses of Rituximab monotherapy complicated by neutropenia. Renal function improved (Cr 1.9-2.2) and he remained without proteinuria. His recovery course was complicated by severe clostridium difficile infection with acute kidney injury (peak Cr 5.0) one month after completion of Rituximab; likely interfering with optimal renal recovery.

Discussion: Currently therapy for PGNMIDs is without established best practice. Data are from small heterogenous populations with varying intra study combinations of chemotherapy and immunosuppression. The literature supports targeted clonal approach with treatment of underlying hematologic malignancies when relevant. Empiric therapy with some combination of agents such as rituximab, cyclophosphamide, steroids and bortezomib shows promise in those without identifiable clones. It is notable that this patient is without identifiable clonal target and was able to achieve clinical remission with empiric Rituximab monotherapy.

TH-PO693

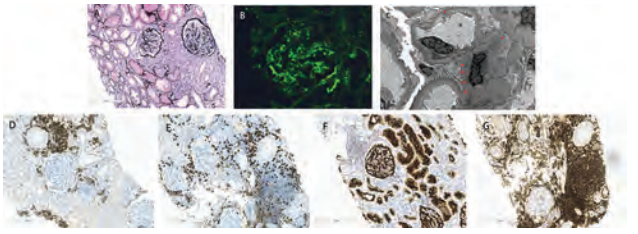
Monoclonal Gammopathy-Associated C3 Glomerulonephritis Secondary to Follicular Lymphoma: A Case Report

Wenjing Cai, Qingying Shi, Chenyu Lei, Xinyi Fu, Anning Xu, Linlin Yuan, Xinling Liang, Zhiming Ye, Zhilian Li. *Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China.*

Introduction: C3 glomerulopathy (C3G) is defined by dominant complement component C3 deposition on kidney biopsy. Monoclonal immunoglobulin-associated C3G (MIg-C3G) is a unique subtype, and lymphoma-associated C3G is rare.

Case Description: A 38-year-old male with a history of hepatitis B virus infection and follicular lymphoma presented with proteinuria, acute kidney injury, and a left neck mass. Renal biopsy revealed C3 glomerulonephritis (C3GN) with lymphoma cell infiltration in the interstitium. Kidney immunohistochemistry showed positive lymphoma (CD19 and CD20) and its subtype follicular lymphoma biomarkers (CD10 and Bcl2). Serum electrophoresis revealed a monoclonal IgM kappa M-spike. Positive autoantibodies to complement C3 convertase and complement factor H indicated complement dysregulation. Treatment with CD20 and CD79b monoclonal antibodies, Zebutinib, and Lenalidomide resolved proteinuria and restored renal function to normal.

Discussion: This case underscores the rarity of follicular lymphoma-associated C3G, with only one previous report in the literature. The patient's diagnosis at a relatively young age without evidence of multiple myeloma or other forms of monoclonal gammopathy of renal significance (MGRS) emphasizes the need for a broad differential diagnosis in glomerulopathies with monoclonal immunoglobulins. The presence of lymphoma cells in the kidney interstitium represents a previously unreported occurrence in patients diagnosed with MIg-C3GN. The patient treated with lymphoma-directed therapy, resolving proteinuria and normalizing renal function, indicating effective B-cell clone treatment.



Kidney histology and immunohistochemistry for general lymphoma and its subtype follicular lymphoma markers. (A) Light microscopy showed a mesangial proliferative pattern of injury with multifocal numerous lymphoma cells infiltration in the interstitium. (B) Immunofluorescence staining showed bright C3 staining along capillary walls and within mesangial areas. (C) Electron Microscopy showed electron-dense deposits in mesangial and endothelial regions (red arrows). (D) CD19. (E) CD 20. (F) CD 10. (G) Bcl2.

TH-PO694

Renal Crystal-Storing Histiocytosis: Transition from Monoclonal Gammopathy of Unknown Significance to Monoclonal Gammopathy of Renal Significance

Kamonluk Rodsom,[1,2] Chutawat Kookanok,[1,3] Wanprapit Noree,[1] Vitchapong Prasitsumrit,[1,2] Tatchaya Kanthajan,[1,4] Ekamol Tantisattamo,[1] Natnicha Jakramonpreeya,[1] Nicha Wareesawetsuwan.[1] *[1]University of California Irvine, Irvine, CA; [2]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [3]Phramongkutklao College of Medicine, Bangkok, Thailand; [4]Srinakharinwirot University Faculty of Medicine, Bangkok, Thailand.*

Introduction: Crystal-storing histiocytosis (CSH) is a rare condition where immunoglobulins accumulate in histiocytes, causing a variety of manifestations depending on the affected organ systems. We present a case of a man with MGUS which transitioned to MGRS evidenced by renal CSH.

Case Description: A 71-year-old man was diagnosed with MGUS from the workup of normocytic anemia 10 years ago. Urine protein electrophoresis showed a monoclonal spike, serum-free kappa level was 563 mg/dL, and immunofixation showed a κ light chain without corresponding heavy chain and faint IgG κ monoclonal protein. Bone marrow revealed 5-10% of plasma cells. Urinary protein: creatinine ratio (UPCR) had been stable at 400 mg/g of creatinine (Cr). Six years later, he presented with non-nephrotic-range proteinuria. A 24-hour-urine protein was 1,436 mg/day with a stable creatinine of 1.1-1.3 mg/dL. Given the increase in proteinuria with an increase in levels of IgG, kappa light chain, and M-protein and worsening anemia, a kidney biopsy was performed which showed kappa light chain proximal tubulopathy, crystallin type, crystal storing histiocytosis. Segmental glomerulosclerosis**,** with podocyte crystalline inclusions. Low-grade segmental lambda light chain mesangial deposits. Mildly thickened glomerular basement membranes, mild global glomerulosclerosis, arterial and mild arteriolar sclerosis. He has been treated with bortezomib and dexamethasone. His serum Cr is stable at 1.1-1.2 mg/dL and a 24-hour-urine protein decreased to 257 mg/day over 4 years despite without antiproteinuric agents.

Discussion: Our patient had MGUS for 4 years before developing MGRS secondary to renal CSH. Renal involvement in MGUS is usually due to AL amyloidosis, light-chain deposition disease, or chronic kidney disease secondary to paraproteinemia. Nephropathy associated with CSH is extremely rare. Patients diagnosed with MGUS can develop multiple myeloma or other related diseases including MGRS which increases the risk for morbidity and mortality. Therefore, surveillance for transition from MGUS to MGRS is warranted to to early detect and promptly treat for evolving kidney diseases.

TH-PO695

Surviving Fluid Excess: A Rare Case of Collapsing Glomerulopathy with IgM Kappa Monoclonal Gammopathy of Renal Significance

Hira Tahir, Fatima D. Sheikh, Randolph A. Hennigar, Katherine Andrade, Henry Yip. *Stony Brook University Hospital, Stony Brook, NY.*

Introduction: Collapsing glomerulopathy (CG) consists of rapid kidney failure and nephrotic syndrome (NS) which can occur with malignancy. Similarly, monoclonal gammopathy of renal significance (MGRS) is a rare renal failure characterized by clonal plasma or B-cells leading to NS from nephrotoxic monoclonal immunoglobulin deposits in the kidney. Our unique case describes collapsing glomerulopathy in IgM kappa deposition disease causing MGRS.

Case Description: A 78-year-old Haitian male with type II diabetes, hypertension, hyperlipidemia and cerebrovascular attack (2019) was referred for poorly controlled hypertension and rising creatinine. Family history included diabetes but no contributing medications or social history. Initial serum creatinine (SCr) of 0.8 mg/dL trended from 1.4 to 4.4 within four months. Urinalysis revealed 100+ protein without hematuria and elevated spot urine microalbumin/Cr of 3484 mg/g and urine protein/Cr of 4.4g. Serum

protein electrophoresis (SPEP) with immunofixation (IFE) had peak in gamma region with IgM kappa but normal kappa/lambda ratio. Otherwise hepatitis B/C, HIV, parvovirus, ANCA, and ANA were negative. Albumin trended 3.7 g/dL to 3.2 g/dL, Hgb 12 g/dL to 8.5 g/dL, cholesterol 145 mg/dL to 216 mg/dL and LDL 66 mg/dL to 135 mg/dL. On subsequent appointments, SBP ranged 150s to 220s mmHg with progression of lower extremity edema. Renal biopsy revealed collapsing glomerulopathy with concurrent IgM Kappa deposits. Hematology evaluation with peripheral blood cytology, bone marrow biopsy and PET/CT imaging diagnosed low-grade monoclonal B-cell lymphocytosis CLL type or B- cell clone causing MGRS. He was treated with rituximab however required dialysis initiation.

Discussion: MGRS is a disease of the kidney, secondary to plasma or B-cell clonal proliferation, requiring treatment to eradicate the offending clone. When plasma or B-cell clones cannot be identified by lab work and bone marrow testing, kidney biopsy can direct treatment. The rapid progression of these diseases warrants prompt diagnosis and treatment to prevent dialysis and furthermore improve prognosis and mortality in this patient population. The rare occurrence of collapsing glomerulopathy simultaneously with IgM Kappa deposition disease warrants further investigation into MGRS treatment protocols.

TH-PO696

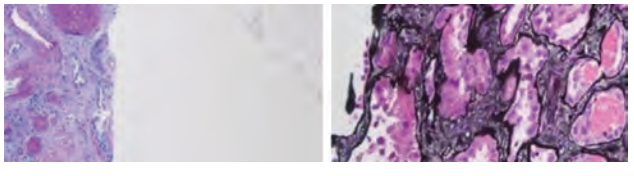
Unveiling the Uncommon: ANCA-Positive IgA Nephropathy

Anvitha Rangan, Mariana Vanoye Tamez, Michael J. Monsour, Syeda M. Sayeed. *Landmark Medical Center, Woonsocket, RI.*

Introduction: Occurrence of antineutrophilic cytoplasmic autoantibodies (ANCA) associated vasculitis (AAV) with immunoglobulin A nephropathy (IgAN) is infrequent. Circulating ANCAs have an underlying role in pathogenesis of this combined entity. We report a rare case of new-onset AAV in a 68-year-old male with IgAN, presenting years after the initial diagnosis of IgAN.

Case Description: A 68-year-old male with stable IgAN was evaluated for epistaxis, hematuria, and purpuric rash over lower extremities occurring over two months. Workup revealed dysmorphic urinary red blood cells, proteinuria, and elevated creatinine (Cr) to 2.62 mg/dl. He also had significantly elevated inflammatory markers and ANCA titers. A repeat kidney biopsy showed fibrinoid necrosis with cellular crescents. Immunofluorescence demonstrated 3+ mesangial IgA deposits. This combination of positive ANCA titers, systemic symptoms, and fibrinoid necrosis provided compelling evidence for a new ANCA-mediated vasculitic process superimposed on IgAN. Intensive corticosteroid therapy was initiated. He then developed an acute diarrheal illness leading to worsening renal failure (BUN/Cr: 243/8.4). Due to rapidly progressive renal failure, cyclophosphamide was started. Plasmapheresis and hemodialysis were eventually required due to minimal renal recovery.

Discussion: Hallmark of ANCA-associated glomerulonephritis is fibrinoid necrosis of the small vessels. ANCA-positive IgAN patients commonly present with extrarenal symptoms as compared to the ANCA-negative IgAN group. Immunotherapy improves renal outcomes and vasculitic symptoms and lowers ANCA titers. It does not reduce the risk of progression to dialysis. Severe proteinuria, advanced age, and low initial eGFR are markers of poor prognosis. IgAN requires regular monitoring of Cr, proteinuria, and changes in symptoms. ANCAs are reported in less than 2% of IgAN patients and may be present during active disease or appear later. ANCAs are pathogenic and not merely biomarkers of AAV. Epitope specificity influences their pathogenicity. These patients have a challenging clinical course. To prevent diagnostic pitfalls, it is essential to repeat kidney biopsy for prompt diagnosis and treatment of ANCA-positive IgAN.



TH-PO697

Triad of Troubles: Rare Confluence of Three Glomerular Diseases

Jessica Boldridge,[1] Ankur Shah,[1] Anthony Chang.[2] *[1]Brown University, Providence, RI; [2]University of Chicago Division of the Biological Sciences, Chicago, IL.*

Introduction: Glomerulonephritis (GN) is an important cause of ESKD contributing to 10-15% of all cases in the United States. IgA nephropathy is the most common cause of GN. Detection is important as delay in treatment can cause significant morbidity with progression to dialysis.

Case Description: A 61 yo female with a PMH of Grave's disease, Sjogren's, Raynauds, extranodal marginal zone lymphoma of the lung treated with rituximab presented initially with hematuria, proteinuria. She had a previous history of IgA vasculitis with renal and skin manifestations including bilateral purpura, hematuria and 0.3g/g proteinuria with preserved GFR. Renal biopsy had shown mild to moderate mesangial expansion, focal endocapillary hypercellularity with fine granular 2+ IgA staining on IF consistent with mesangioproliferative IgAN. She was started on steroids but due to worsening proteinuria and rising Cr she was switched to mycophenolate (MMF) in 2017. This was held in 2021 due to pneumonia. In 2023, she had worsening proteinuria with re-initiation of steroids and MMF. Reiniation of MMF caused anemia, gastrointestinal and infectious complications. A repeat kidney biopsy was performed to assess disease activity and prognosis desmonstrating a single fibrocellular crescent, diffuse mesangial hypercellularity and vacuolated capillary loops with a subepithelial spike formation. There was no significant glomerular staining for IgA. EM demonstrated sub-epithelial electron dense deposits. She was started on rituximab for concomitant membranous glomerulopathy and ANCA vasculitis and avacopan due to her prior steroid complications.

Discussion: We present a rare case of 3 coexisting biopsy proven glomerulopathies in one patient. This is a classic example of Hickam's dictum, an aphorism that notes that the desire to find a single diagnosis for a patients ailments ignores the possibility of multiple co-existing disease states. In this case, the propensity for auto-immunity with her prior sjogrens, graves, and raynauds prompted consideration of multiple syndromes, which was found on biopsy. Treatment of multiple co-existing glomerulopathies is not well described, and our medical decision making was to attempt to apply occam's razor to treatment, using a single treatment strategy that would treat all the co-existing glomerulopathies. This case demonstrates a wide range of medical decision making, highlighting its educational merit.

TH-PO698

Insidious Presentation of IgA Fibrillary Glomerulonephritis

Ayesha Shah, Amna Anees. *Charleston Area Medical Center, Charleston, WV.*

Introduction: Fibrillary glomerulonephritis (FGN) is a rare diagnosis, present in 0.5 to 1.4% of native kidney biopsies. Symptoms include proteinuria, hematuria, kidney function impairment, hypertension (HTN), and monoclonal gammopathy. Positive DNAJB9 stain and large, non-branching overlapping fibrils on kidney biopsy confirm the diagnosis. We present a case of FGN in a patient with known chronic kidney disease (CKD).

Case Description: An 80-year-old male with history of CKD stage 3b, HTN, benign prostatic hyperplasia, bladder calculi with obstructive uropathy status post transurethral resection of the prostate, atrial fibrillation on apixaban, and coronary artery disease presented for outpatient nephrology evaluation of elevated creatinine (Cr). He also had proteinuria and microscopic hematuria, ongoing for the past four years. Initially, hematuria was thought to be non-glomerular in nature due to prior urologic history. Patient also had new-onset bilateral lower extremity edema but denied urinary symptoms. His Cr was 1.7 mg/dL (eGFR 39 mL/min), compared to Cr 1.4mg/dL (eGFR 49 mL/min) eight months prior. Urinalysis showed proteinuria, hematuria, and red blood cell casts. Workup was significant for elevated free kappa and lambda light chains without apparent M-spike on protein electrophoresis; urine studies were positive for albumin and alpha-1, alpha-2, beta, and gamma globulins. CT abdomen/pelvis completed six months prior showed only small renal cysts; retroperitoneal ultrasound was significant for bilateral echogenic kidneys. Over the next five months, the patient continued to have lower extremity swelling; Cr at follow-up was 3.2mg/dL. He developed hypocalcemia and hyperphosphatemia. Urological evaluation for post-renal causes, including cystoscopy, was unrevealing. Kidney biopsy was significant for negative Congo red stain and positive DNAJB9 stain. Electron microscopy confirmed FGN, and immunofluorescence was significant for mesangial IgA, IgM, C3, kappa, and lambda staining. The patient was started on systemic steroids and rituximab treatment; he completed two doses of rituximab treatment with improvement in Cr.

Discussion: Our patient had common manifestations of FGN years prior to initial nephrology evaluation, at which point his FGN rapidly progressed prior to rituximab treatment. This case highlights the importance of consideration and timely diagnosis of glomerulonephritis and emphasizes avoiding anchor bias.

TH-PO699

A Unique Case of IgA Nephropathy Associated with Both Immune Thrombocytopenia and Erythrocytosis

Parker Lehmann,[1] Udayan Y. Bhatt,[2] Asish Thakkar.[3] *[1]Idaho College of Osteopathic Medicine, Meridian, ID; [2]The Ohio State University Wexner Medical Center, Columbus, OH; [3]VA Health Care System, Columbus, OH.*

Introduction: Erythrocytosis is characterized by an elevation in hemoglobin and may be primary (typically associated with a mutation in the JAK2 gene) or it may be secondary. Many renal diseases have been associated with erythrocytosis. One association that has become increasingly reported is the association between IgA nephropathy and erythrocytosis. In addition, there have been a few case reports of IgA nephropathy associated with immune thrombocytopenia (ITP). We describe a novel presentation of both erythrocytosis and immune thrombocytopenia associated with IgA nephropathy.

Case Description: A 26yo African American male presented to the Hematology clinic for mild thrombocytopenia. The patient had a positive platelet associated antibody. This resulted in the diagnosis of ITP. The patient was coincidentally noted to have chronic

kidney disease with eGFR of 65cc/min at that time. He subsequently had a climbing hemoglobin and began requiring therapeutic phlebotomy. His erythrocytosis showed no evidence of a JAK2 mutation and a bone marrow biopsy showing a normocellular marrow with an erythroid predominant hematopoiesis but normal megakaryocytes. The diagnosis was idiopathic erythrocytosis. At 36yo, repeat chemistries showed an eGFR of 33cc/min. Because of that, he was referred to nephrology and underwent a renal biopsy that showed IgA nephropathy with moderate interstitial fibrosis and tubular atrophy but without active injury or thrombotic microangiopathy. The patient continued to receive phlebotomy. He was noted to have a normal to occasionally elevated erythropoietin level. Imaging did not show evidence of intrabdominal or renal neoplasms. The patient has not manifested any hemorrhagic complications and his platelet count has continued to be mildly suppressed.

Discussion: IgA nephropathy is the most common primary glomerular disease worldwide. It is diagnosed via biopsy and there are no exact immune markers that definitively suggest IgA nephropathy. However, the presence of hematologic disorders such as ITP and erythrocytosis may also indicate the presence of underlying IgA nephropathy. Our unique case describes IgA nephropathy associated with both ITP and erythrocytosis. Further work is warranted in exploring the pathogenesis of these connected disorders.

TH-PO700

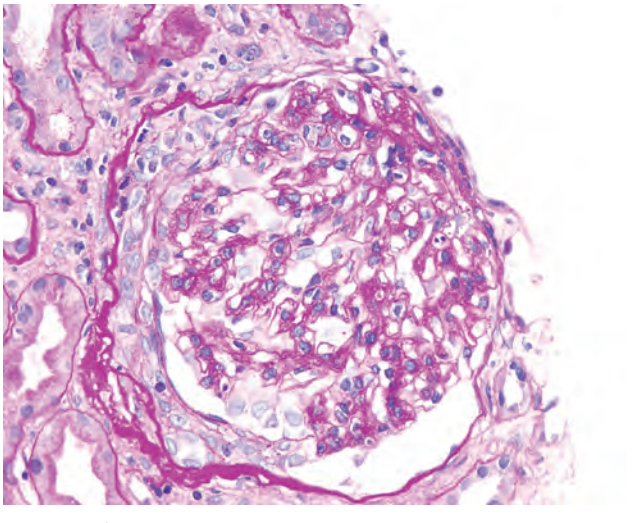
Infliximab-Induced Secondary IgA Nephropathy in a Patient with Rheumatoid Arthritis

Prachi Gajjar,[1] Parth Parmar,[1] Hetvi Gajjar,[2] Sepiya Shrestha,[1] Dhruvil K. Shah,[1] Kashish Magnani.[3] *[1]Trumbull Regional Medical Center, Warren, OH; [2]Pramukhswami Medical College, Karamsad, India; [3]Surat Municipal Institute of Medical Education and Research, Surat, India.*

Introduction: IgA Nephropathy is the most common primary glomerular disease in the world, characterized by the antibody formation against Galactose-deficient IgA1, which gets deposited in the glomerulus. It can be primary or secondary. Secondary causes associated are liver disease, celiac disease, HIV infection and medications like anti-tumour Necrosis Factor α therapy.

Case Description: A 69-year-old male with polyarticular erosive rheumatoid arthritis, atrial fibrillation, hypertension, chronic kidney disease stage 3a with baseline creatinine of 1.5 mg/dL came with a complaint of fatigue and dark urine for a month. His rheumatoid arthritis was well controlled with Infliximab infusions eight weekly for last 10 years. On admission, he had acute kidney injury with five fold rise in creatinine without oliguria. Urinalysis showed microscopic hematuria and moderate proteinuria. Renal biopsy suggested IgA Nephropathy with mesangial proliferation with IgA deposits. Infliximab was stopped, and the patient was given a tapering dose of steroids. After around two months of stable renal function with steroids, rheumatologist resumed Infliximab, which resulted in a similar episode of acute kidney injury, which was again resolved by stopping the medicine. This made it more evident that Infliximab was the culprit behind secondary IgA nephropathy.

Discussion: There have been case reports on Infliximab and other TNFα inhibitors causing secondary IgA Nephropathy. The overall aetiology of medication-induced IgA Nephropathy, along with the underlying autoimmune conditions, is not well understood. One hypothesis suggests antibodies against the glycan structure of TNFα inhibitors lead to interaction with the presence of aberrant IgA1 molecules in the serum, forming large polymeric IgA complexes. More molecular-level studies are needed to get more robust evidence of such an association.



Mesangial Proliferation on PAS stain

TH-PO701

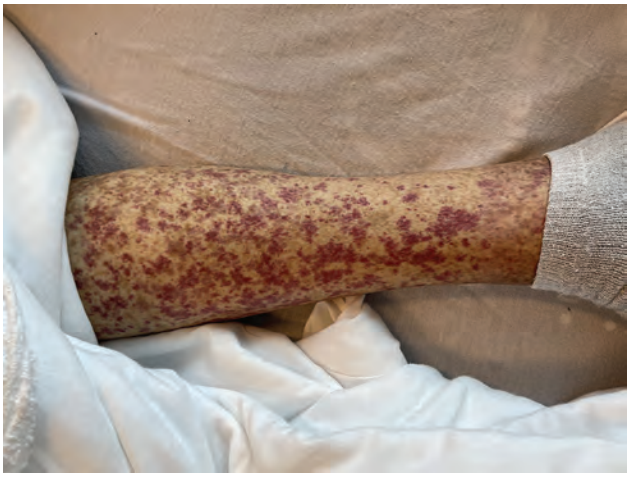
A Rare Case of IgA Vasculitis and Crescentic Glomerulonephritis in a Patient with Cirrhosis

Kevin Zhang, Raphael J. Rosen. Stamford Health Nephrology. *Stamford Hospital, Stamford, CT.*

Introduction: Rapidly progressing glomerulonephritis (RPGN), also known as crescentic glomerulonephritis, is a condition characterized by rapid decline in kidney function over days to weeks. RPGN is characterized by the presence of glomerular crescents seen on kidney biopsy. While most cases of RPGN are pauci-immune glomerulonephritis, less common causes must also be considered. We present an unusual case of RPGN from IgA vasculitis associated with cirrhosis.

Case Description: A 37-year-old man with cirrhosis from alcohol use disorder presented to the emergency department with thrombocytopenia, anemia, and creatinine elevation to 6.1 mg/dL (from a prior baseline of 0.7). Urinalysis demonstrated +4 proteinuria and 3+ hematuria. Of note, he had been diagnosed with leukocytoclastic vasculitis with IgA deposits 4 months prior. On this current admission, his rash had worsened (image 1). He was given pulse dose steroids and renal biopsy was performed, which demonstrated diffuse mesangial and focal endocapillary proliferative and sclerosing glomerulonephritis with membranoproliferative features, focal crescents, and focal necrotizing features. Immunofluorescence demonstrated IgA dominant staining, confirming the diagnosis of crescentic IgA vasculitis. He was treated with cyclophosphamide for RPGN, and his creatinine stabilized.

Discussion: Though IgA nephropathy is the most common glomerulonephritis, crescentic IgA and IgA vasculitis are relatively uncommon. Most patients with cirrhosis who are found to have IgA nephropathy have a mild, secondary form of IgAN. Our patient, in contrast, had extremely severe features of the spectrum of IgA related disorders, including both generalized IgA vasculitis and RPGN from IgAN. In a patient with cirrhosis and acute kidney injury, glomerulonephritis remains on the differential and may be responsive to immunosuppression.



TH-PO702

Sinister Synergy: IgA Nephropathy and Apixaban

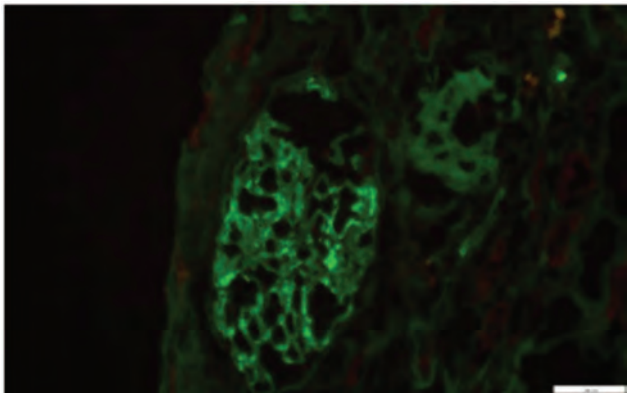
Atlee Baker, Gonzalo Matzumura Umemoto. *Washington University in St Louis, St Louis, MO.*

Introduction: IgA nephropathy is the most common glomerulonephritis worldwide, divided into primary and secondary types. Oral anticoagulants have been associated with acute kidney injury, although less well defined. We present a case of IgAN made more severe with the addition of Apixaban.

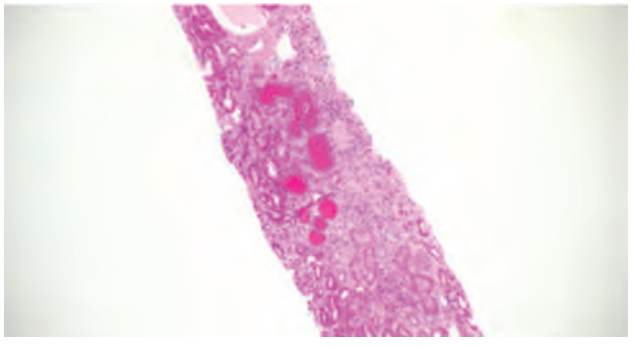
Case Description: A 75-year-old male with history of recently diagnosed atrial fibrillation on Apixaban, systolic heart failure, and prior EtOH abuse who presented for evaluation of lower extremity edema. He developed rapid onset of stage 3 AKI (sCr 4mg/dL, baseline 1mg/mL) over one month and gross hematuria 1 week prior to presentation. Urinalysis revealed >50 RBCs; UPCR 1.8g/g. Urine microscopy revealed mixed cellular casts. Broad serological work up was negative. C3/C4 levels normal. Infectious work up was negative. US revealed mild liver contour changes concerning for mild cirrhosis. Renal biopsy with findings of IgAN (3+ IgA/C3 in the mesangium and tubular lumen, low mesangial expansion and endocapillary proliferation, no crescents), and numerous RBC casts. Findings were attributed to secondary IgAN with cirrhosis, with other findings suggestive of anticoagulant-related nephropathy. Given the rapid progression of his disease, patient was started on high-dose steroids. Apixaban was held with resolution of hematuria. Patient's renal function subsequently improved and Apixaban was restarted.

Discussion: We present a case of sIgAN complicated by the addition of anticoagulation. Our case is unique as the patient presented with rapidly progressive and

severe renal injury, without characteristic findings of aggressive disease on biopsy. Our case highlights the role that anticoagulation can have worsening glomerular disease.



IgA Mesangial Staining



RBC Casts

TH-PO703

Apixaban-Induced IgA Vasculitis with Nephritis

Tahir A. Jatoi,[1,2] Sandeep R. Sasidharan,[1,2] Rabiya Akram,[1] Mohammad W. Abushawer,[2,1] Fnu Pariya,[1] Arfa Amjad,[1] Subodh J. Saggi,[1] Susan Grossman,[2] Marie-Alex Michel,[2] Moro O. Salifu.[1] *[1]SUNY Downstate Health Sciences University, New York City, NY; [2]VA New York Harbor Healthcare System, New York, NY.*

Introduction: Leukocytoclastic vasculitis (LCV), previously called Henoch-Schönlein purpura, is characterized by IgA-dominant immune deposits affecting small vessels and often involves the skin, gastrointestinal tract, joints, and kidneys. Direct oral anticoagulants are an emerging cause of LCV. This is a diagnosis of exclusion. In cases of drug-induced LCV, discontinuation of offending agent is the mainstay of treatment. Steroids may have a role in treating cases with widespread skin involvement. We are presenting a rare case of Apixaban induced leukocytoclastic vasculitis (LCV) with Nephritis

Case Description: 71 y.o. male with PMH of CKD3b, DM, CAD, COPD, HTN, LE DVT with B/L bilateral leg swelling for 6 months, admitted with c/o extensive pruritic rash after being started on Apixaban for 2 weeks. Vital signs and system review were otherwise unremarkable. On PE, he had open skin lesions with draining clear fluid and LE swelling. Labs showed BUN/Creat of 54/2.1, from baseline of 1.6, HGB 11 mg/dl, UA had proteinuria with significant microhematuria, Upcr of 3.7 g/g from 0.5 g/g, IgE levels were elevated 1020, rest of the nephrotic work up was negative. Skin biopsy revealed leukocytoclastic vasculitis. Due to worsening creatinine and proteinuria, renal biopsy was performed, and it showed globally sclerotic glomeruli with moderate interstitial fibrosis and tubular atrophy on light microscopy, IgA staining positive on immunofluorescence with dense deposits in mesangium on electron microscopy. The patient was switched from apixaban to warfarin, and started on prednisone and Mycophenolate Mofetil with a diagnosis of IgA vasculitis and nephritis. Renal function and proteinuria improved.

Discussion: Apixaban is a rare cause of leukocytoclastic vasculitis (LCV). To our knowledge, there are only a few reported cases of LCV due to apixaban in the literature. Our case is the only case of apixaban associated LCV with Nephritis. LCV is a diagnosis of exclusion after infectious, autoimmune, and inflammatory conditions have been excluded. Almost 30% of all cases of LCV are drug-induced. However, anticoagulants are a rare cause of LCV. Our case of apixaban-induced LCV with nephritis highlights a rare complication of a common medication, which is important for physicians to be aware of.

TH-PO704

A Novel Case of IgA Nephropathy and Tubulointerstitial Nephritis in Patients with Crohn Disease Treated with Adalimumab: What Is the Culprit?

Shota Obata,[1] Martine Pollack-Zollman.[2] *[1]Mount Sinai Beth Israel Hospital, New York, NY; [2]Mount Sinai Morningside Hospital, New York, NY.*

Introduction: IgA nephropathy (IgAN) is associated with Crohn's disease (CD) and the use of tumor necrosis factor-alpha inhibitor (TNF-αi). Tubulointerstitial nephritis (TIN) is noted as an extra-intestinal manifestation of CD but is also reported to be caused by the use of TNF-αi. Thus, it is challenging to underpin the culprit of IgAN and TIN among patients with CD treated with TNF-αi. We present a case of IgAN concomitant with TIN in a patient with CD on adalimumab, a TNF- αi.

Case Description: A 21-year-old man with a history of CD treated with adalimumab for six years presented with a sore throat, fever, gross hematuria, and AKI (Cr 3.0 mg/dL from 0.8 mg/dL). Urinalysis revealed numerous WBCs and RBCs, rare eosinophils, negative leukocyte esterase and nitrite, and a urine protein-creatinine ratio of 3.74 g/gCr. Kidney ultrasound showed normal size and echogenicity without hydronephrosis. Immunologic and infectious workups were negative. After hydration, Cr improved to 1.8 mg/dL on discharge. He was referred for kidney biopsy, which revealed IgAN and acute tubular necrosis with acute and chronic interstitial nephritis. Adalimumab was switched to Skyrizi, an interleukin-23 (IL-23) antagonist, and losartan and prednisone 40 mg were initiated. At the last follow-up, Cr improved to 1.32 mg/dL with mild proteinuria of 0.251 g/gCr while on a slow prednisone taper.

Discussion: It is challenging to determine whether CD or TNF-αi induces IgAN and TIN. In our case, extra-intestinal manifestation is unlikely to develop, given the remission of CD. Thus, TNF-αi was switched to IL-23 antagonists in addition to administration of steroids, resulting in improved renal function and resolution of proteinuria. The mechanism of action how TNF-αi causes IgAN and TIN is unknown but may be due to an underlying predisposition to defective IgA1 structure along with altered immune regulation, auto-drug and antibody formation, and/or molecular mimicry, which together leads to immune-complex deposits in the glomeruli. Whether this is a TNF-αi class effect or specific to adalimumab needs to be determined along with the possibility of future research to determine who is at risk. It is important for gastroenterologists treating patients with CD to be aware of this risk, check baseline Cr and urinalysis, and perform regular monitoring.

TH-PO705

Unusual Suspect: Apixaban as a Cause of ANCA-Associated Vasculitis

Navya Reddy Perkit,[1] Mithil Gowda Suresh,[1] Jassimran Singh,[1] Aviraag Vijayaprakash,[1] Helmut G. Rennke,[2] Suzanne G. Martin.[1] *[1]Saint Vincent Hospital, Worcester, MA; [2]Brigham and Women's Hospital, Boston, MA.*

Introduction: Antineutrophilic cytoplasmic antibody (ANCA) vasculitis is a common cause of acute glomerulonephritis in adults, with drug-induced ANCA vasculitis (DIAV) being relatively rare.

Case Description: An 85-year-old female with stage IV chronic kidney disease (CKD), on apixaban for atrial fibrillation, presented with fatigue, weakness, and dyspnea. Exam showed clear lungs and new trace bilateral pitting pedal edema. She had proteinuria, hematuria, and creatinine of 5.41 mg/dL, up from baseline 2.5 mg/dL. Urine protein-creatinine ratio was elevated at 4.5 g/gCr. Renal biopsy indicated chronic-active focal proliferative, necrotizing, and crescentic glomerulonephritis with immune deposits. Serologies showed a high anti-MPO titer of 1:1997, with other autoantibodies negative. Given the elevated anti-MPO titer and biopsy findings, drug-induced ANCA vasculitis was considered. The patient was not on known causative medications. The temporal relationship with apixaban led to its discontinuation and transition to warfain. She received steroids along with two biweekly doses of rituximab which reduced the anti-MPO titer to 1:32 and proteinuria improved to 3 g/gCr.

Discussion: DIAV is a diagnosis of exclusion suggested by high anti-MPO titers, as seen in this case. The rapid improvement after discontinuation of apixaban and two doses of rituximab suggest her ANCA vasculitis was likely due to an offending agent, rather than spontaneous ANCA disease. Apixaban-induced ANCA vasculitis has not been previously reported, though apixaban-induced cutaneous leukocytoclastic vasculitis and drug-induced lupus suggest its potential for autoimmune phenomena. Prompt identification and treatment, including drug discontinuation and immunosuppressive therapy, are crucial for managing DIAV and preventing disease progression. Increased awareness and further research into apixaban-induced DIAV are essential due to its expanding use in CKD patients.

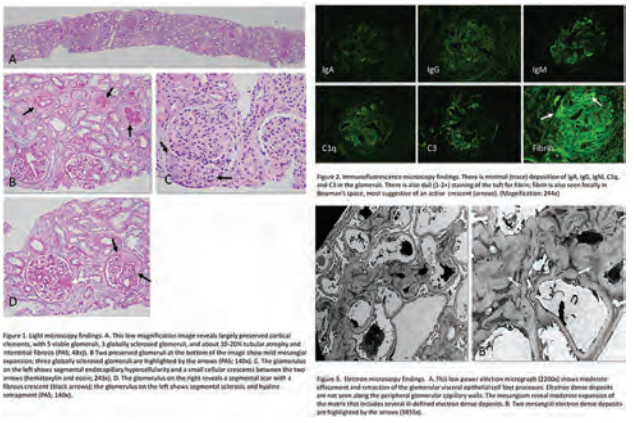


Figure 1. Light microscopy findings. A. This low magnification image reveals largely preserved cortical elements, with 5 viable glomeruli, 3 globally sclerosed glomeruli, and about 10-20% tubular atrophy and interstitial fibrosis (PAS; 40x). B Two preserved glomeruli at the bottom of the image show mild mesangial expansion; three globally sclerosed glomeruli are highlighted by the arrows (PAS; 140x). C. The glomerulus on the left shows segmental endocapillary hypercellularity and a small cellular crescents between the two arrows (hematoxylin and eosin; 240x). D. The glomerulus on the right reveals a segmental scar with a fibrous crescent (black arrows); the glomerulus on the left shows segmental sclerosis and hyaline entrapment (PAS; 140x).

Figure 2. Immunofluorescence microscopy findings. There is minimal (trace) deposition of IgA, IgG, IgM, C1q, and C3 in the glomeruli. There is also dull (1-2+) staining of the tuft for fibrin; fibrin is also seen focally in Bowman's space, most suggestive of an active crescent (arrows). (Magnification: 244x)

Figure 3. Electron microscopy findings. A. This low power electron micrograph (2200x) shows moderate effacement and retraction of the glomerular visceral epithelial cell foot processes. Electron dense deposits are not seen along the peripheral glomerular capillary walls. The mesangium reveal moderate expansion of the matrix that includes several ill-defined electron dense deposits. B. Two mesangial electron dense deposits are highlighted by the arrows (5855x).

TH-PO706

IgA Nephropathy Due to Polycythemia Vera

Sharmilee Vuyyuru, Rajib K. Gupta, Nandakishor Kapa. *University of California Davis, Sacramento, CA.*

Introduction: Polycythemia Vera (PV) can manifest with mutations in the JAK2 gene and affects bone marrow, spleen, and liver. Kidney involvement is rare, but when it occurs, over 50% of cases have glomerular hyperfiltration. We present an unusual instance of PV associated with IgA nephropathy.

Case Description: A 41-year-old male with hypertension (HTN) and PV presented with 24-hour urine protein level of 3.6g and microscopic hematuria. His hemoglobin level was 17.1g/dL, red blood cell count was 6.23m/mm3, and serum erythropoietin level was 8U/l (normal). JAK2-V617F mutation, CALR and MPL were negative. Kidney biopsy showed IgA nephropathy with secondary features like thrombotic microangiopathy (see image 1), segmental fibrinoid necrosis and segmental sclerosis. Serum complements 3 and 4, hepatitis panel, and antibody serologies tested negative. With concern for PV associated IgA nephropathy, bone marrow biopsy and next generation sequencing (NGS) was recommended. Given benefit of sodium glucose co-transporter 2 inhibitors in IgA Nephropathy, and proteinuria, empagliflozin 10mg daily was added to his regimen of losartan 100mg for HTN. On follow up, spot urine protein/creatinine ratio was 1.4g/g, with continued microscopic hematuria.

Discussion: PV associated IgA Nephropathy is rare. A thorough work up should be done for new-onset proteinuria, and kidney biopsy is often indicated. As kidney dysfunction is a later complication and has guarded prognosis, early diagnosis and more awareness is needed to help establish defined therapies.

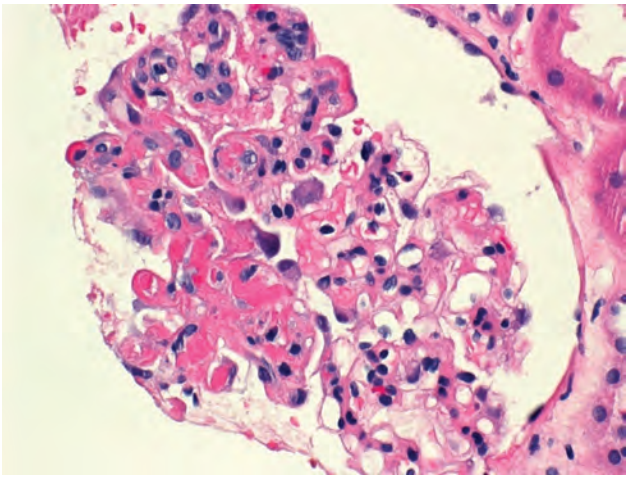
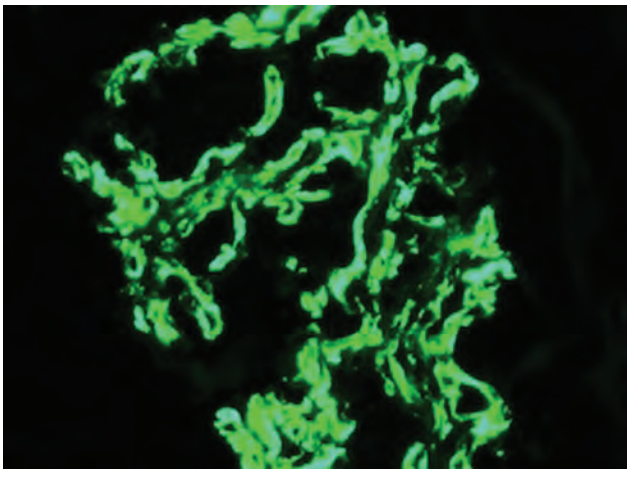


Image 1



IgA on IF

TH-PO707

Severe IgA Vasculitis Nephritis in Adults: Two Challenging Cases

Assaf Potruch, Momen Abbasi, Roy Abel, Ittamar Gork. *Hadassah University Medical Center, Jerusalem, Israel.*

Introduction: Immunoglobulin A vasculitis (IgAV) in adults is characterized by the combination of skin, gastrointestinal, joint and renal involvement. Yearly incidence is 1-1.8 per 1 million. IgAV nephritis occurs in 45-85% of adults with IgAV, manifesting as acute kidney injury (AKI), active urine sediment and proteinuria. Treatment protocols for severe cases of IgAV nephritis presenting with AKI, nephrotic range proteinuria and crescentic glomerulonephritis (GN) are not validated. We present two cases of severe IgAV nephritis over the span of 2 months.

Case Description: Case I – A previously healthy 54-year-old female presented with a lower limb purpuric rash. A skin biopsy was consistent with IgA vasculitis. Severe terminal ileitis developed, and prednisone 40 mg/d led to symptomatic improvement. Shortly after, proteinuria was noted and increased up to protein/creatinine ratio (UPCR) 6.7 g/g and serum creatinine rose from 0.68 mg/dL to 1.78 mg/dL. Kidney biopsy demonstrated proliferative necrotizing GN with >50% crescents and dominant IgA immune deposits (Figure 1). Methylprednisolone 500 mg/d for 3 days followed by prednisone 60 mg daily and IV cyclophosphamide were started; Proteinuria peaked at a UPCR of 14 g/g Therefore, Rituximab was added, total dose of 2 grams, leading to significant improvement (UPCR 0.5 g/g, creatinine 1.3 mg/dL). **Case II –** A 58-year-old male, with past medical history of diabetes, hypertension and peripheral vascular disease presented with a lower limb purpuric rash. Skin biopsy was consistent with IgAV. Nephrotic syndrome with proteinuria of 6 g/D, leg edema, albumin of 2.6 g/dL and a rise in serum creatinine 0.6 mg/dL to 1.5 mg/dL were observed. Kidney biopsy demonstrated proliferative necrotizing GN with >25% crescents and dominant IgA immune deposits.3 grams IV solumedrol followed by 60 mg/d prednisone, and a total of 6 grams of IV cyclophosphamide were given, with improvement (creatinine to 1.2 mg/dL and UACR below 500 mg/g).

Discussion: Evidence is lacking regarding the optimal treatment of severe IgAV nephritis. The above-described cases presented with severe findings clinically and histologically and responded well to aggressive immunosuppression. Case 1 highlights that Rituximab could be added to our 2nd line treatment options and emphasizes the need for studies in IgAV nephritis treatment.

TH-PO708

CTLA-4 Haploinsufficiency Presenting with IgA Nephropathy

Andrea Broka, Brian Y. Young, Hiba Hamdan, Victoria R. Dimitriades, Kuang-Yu Jen, Nasim Wiegley. *UC Davis Health, Sacramento, CA.*

Introduction: The regulatory mechanisms governing activation and inhibition of the immune response are orchestrated by key molecules. Derangements in CTLA-4 activity can lead to loss of T cell suppression with a resulting hyperinflammatory state, with manifestations of recurrent infections, lymphoproliferation, cytopenias, and liver/lung infiltration.

Case Description: A 25yr South Asian Woman with CTLA4 immune dysregulation syndrome, managed with monthly abatacept (anti CD80/CD86) and IVIg infusions for 5 years, presented with new onset cytopenia, hypertension, acute kidney injury, Cr 3 mg/dL (baseline 1 mg/dl), proteinuria of 1 g/g and an active urine sediment with acanthocytes, red blood cell casts. Serologic workup and cultures were negative. Kidney biopsy showed IgA Nephropathy (IgAN) with 25% crescentic lesions. The etiology of the IgAN was

most likely secondary to her immune dysregulation syndrome, given the concomitant cytopenias and profound upregulation of inflammatory markers, rather than the effect of drug-induced IgAN. Therefore the immunosuppression was escalated. Kidney function initially stabilized, but worsened again, progressing to oliguric AKI-D. She was started on pulse steroids and IV cyclophosphamide. She continues to be dialysis dependent despite these therapies.

Discussion: CTLA-4 haploinsufficiency has been rarely linked with kidney disease, with only a few reports of interstitial nephritis. Our case is the first report of CTLA-4 immune dysregulation associated with glomerulonephritis (GN). Studies have shown that CTLA-4 polymorphisms have a predisposition for GN. This patient's presentation with other autoimmune diseases (cytopenias) and upregulation of systemic inflammatory markers such as CD19 and IL2, it was thought to be more an escape from the abatacept immune regulation, rather than caused by it. This case highlights the first reported IgAN associated with CTLA-4 immune dysregulation syndrome.

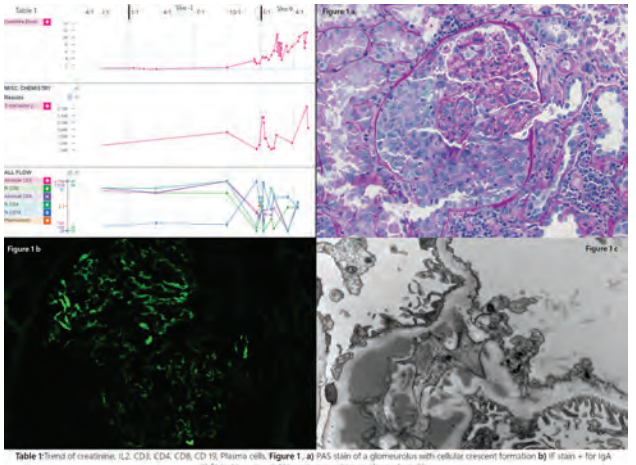


Table 1: Trend of creatinine, IL2, CD3, CD4, CD8, CD 19, Plasma cells. **Figure 1 . a)** PAS stain of a glomerulus with cellular crescent formation **b)** IF stain + for IgA **c)** EM with mesangial immune-type electron-dense deposits

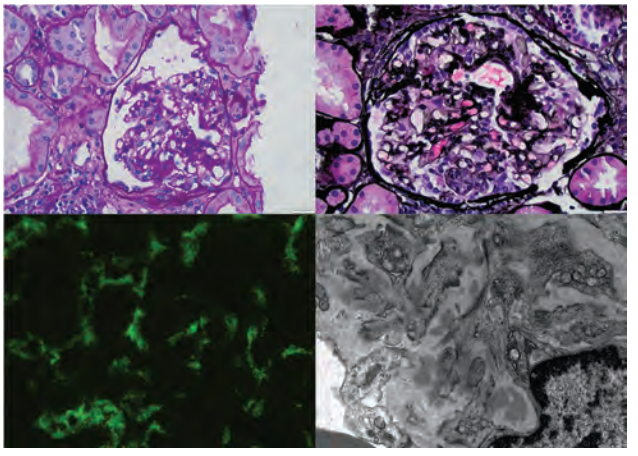


Figure 1. Kidney biopsy revealed recurrent IgAN

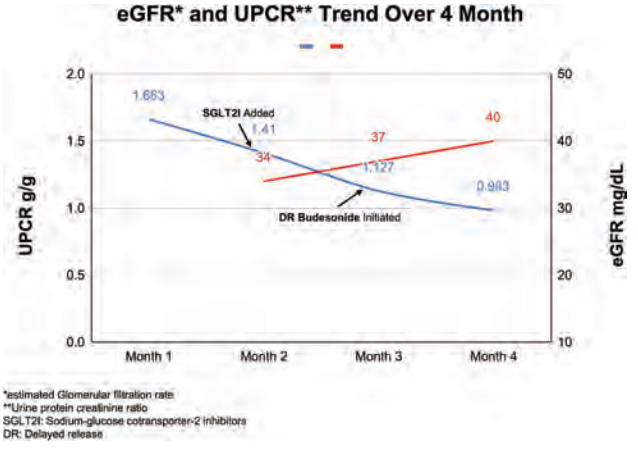


Figure 2. eGFR and UPCR Trend

TH-PO709

Treatment of Recurrent IgA Nephropathy after Kidney Transplant with Delayed-Release Budesonide

Niloufar Ebrahimi, Yan Chen Wongworawat, Amir Abdi Pour, Sayna Norouzi.
Loma Linda University Medical Center, Loma Linda, CA.

Introduction: IgA nephropathy (IgAN), the most prevalent form of glomerulonephritis worldwide, is characterized by hematuria, proteinuria, and progressive kidney function decline. Currently, there are no clear guidelines on the treatment of recurrent IgAN post-transplant.

Case Description: A 22-year-old Caucasian male with a history of end-stage kidney disease secondary to IgAN status post-kidney transplant two years ago on maintenance therapy with tacrolimus, mycophenolate mofetil, and low-dose steroids presented with hematuria, proteinuria, and declining kidney function. A follow-up biopsy on the transplanted kidney revealed recurrent IgAN with secondary focal and segmental glomerulosclerosis but without signs of acute rejection (Figure 1). Delayed release (DR) budesonide was initiated, and he tolerated the medication well. Figure 2 shows his eGFR and UPCR improvement three months after starting the treatment.

Discussion: The FDA has approved DR budesonide for managing adults with primary IgAN at risk of rapid disease progression. However, transplant patients were excluded from the NefIgArd trial. Our case report suggests future studies on the effects of DR budesonide for treating recurrent IgAN post-transplant.

TH-PO710

Secondary IgA Nephropathy Due to Ketamine-Induced Cirrhosis: A Rare Cause of ESKD in Ketamine Users

Prashant N. Bhenswala,[1,2] Purva D. Sharma.[1,2] *[1]Northwell Health, New Hyde Park, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, NY.*

Introduction: Ketamine abuse is a known cause of hepatobiliary injury and cirrhosis as well as urologic injury possibly resulting from irritation of the urologic system. Chronic ketamine use is also known to cause cystitis, bladder dysfunction, and hydronephrosis. The relationship between cirrhosis and IgA nephropathy is well known and is due to the liver's inability to clear circulating IgA immune complexes. However, little to no reports linking Ketamine-Induced-Cirrhosis (KIC) to IgA nephropathy resulting in kidney failure and end-stage kidney disease needing dialysis have been reported.

Case Description: Our case involves a 26-year-old female with history of ketamine abuse (since age 16), with biopsy proven ketamine-induced liver injury with F1 fibrosis. She presented to the hospital with advanced kidney disease with a serum creatinine of 9 mg/dL, hematuria, and 1gm of proteinuria. Serologic workup was negative. Kidney biopsy was performed that showed focal crescentic and diffuse sclerosing glomerulonephritis consistent with IgA nephropathy with mild activity and severe chronicity. There was severe tubular atrophy and interstitial fibrosis. She was initiated on dialysis and remained dialysis dependent. As a result of her continued ketamine abuse, she was deemed to be ineligible for liver/kidney transplant.

Discussion: Ketamine is a known cause of urologic injury including decreased bladder compliance and volume, hematuria and rarely hydronephrosis and papillary injury. Our patient who was a chronic ketamine user developed progressive IgA nephropathy with crescentic and diffuse sclerosing glomerulonephritis with severe tubular atrophy, causing her to develop end stage kidney disease. This was thought to be secondary to ketamine induced cirrhosis. To the best of our knowledge, this cause of ESRD in ketamine users has not been reported. There should be a low threshold to perform kidney biopsy in ketamine misusers at the earliest onset of kidney disease. Treatment of secondary IgA nephropathy in ketamine users would include cessation of the drug and control of BP and proteinuria. Unfortunately, our patient continued to misuse ketamine and ended up with liver cirrhosis and end stage kidney disease.

TH-PO711

A Rare Clinical Entity: Anti-tubular Basement Membrane Disease

Ubaid Naeem, Vishwajeeth Pasham, Natalie T. Freidin. *Medical University of South Carolina, Charleston, SC.*

Introduction: Acute kidney injury (AKI) is well reported after developing auto antibodies against glomerular basement membrane however very little is published about anti-tubular basement membrane disease (Anti-TBM), an entirely different and rare disease entity, as a cause of AKI.

Case Description: 83-year-old male with a history of Sjogren's syndrome and monoclonal B-cell lymphocytosis was admitted with AKI with a previously normal serum Creatinine(0.9 mg/dl). Urine analysis was significant for microscopic hematuria. His serological workup was positive for ANA, SSA/SSB, MPO with indeterminate ANCA and negative for anti-GBM, IgG4 and Cryoglobulins. He had normal C3, C4 and miniscule population of B-cells on flow cytometry. Rapidly declining kidney function prompted a kidney biopsy and initiation of renal replacement therapy (RRT). His biopsy yielded a diagnosis of anti-TBM, culminating in the initiation of high dose steroids. No anti-TBM antibody levels were sent due to unavailability at our institution. Plasma exchange was also commenced but discontinued due to inconclusive evidence of lung involvement. His renal function recovered without further RRT after two weeks of prednisone 60 mg, followed by a taper to 40 mg along with initiation of Cyclophosphamide 100mg daily.

Discussion: The overall histologic findings of tubulointerstitial nephritis with strong linear proximal tubular basement membrane deposition of IgG and C3 with sparing of glomeruli was diagnostic of anti-TBM disease. Anti-TBM can be of primary or secondary origin. Secondary cases have been reported in association with membranous nephropathy, transplant rejection and urinary infections. Current literature is devoid of any guidelines to monitor disease activity with any markers or treat with any specific immunosuppressive agents. However, anecdotal evidence suggests that plasma exchange, steroids, steroid sparing Immunosuppressive agents and rituximab may have role in the management of anti -TBM. We recommend sending anti -TBM titers, if possible, to monitor the response and to tailor the therapy based on literature review.

A comparison of Anti-TBM vs Anti- GBM vs Anti - ABBA

	Anti-TBM	Anti-GBM	Anti-brush border tubular antibodies disease (ABBA)
Antigen	58-kDA Non collagenous protein	Collagen Type 4a3	LDL-receptor protein-2
Tubular Involvement	+	+	+
Glomerular Involvement	-	+	+
Target Renal Site	Basement membrane of Proximal tubule	Basement membrane of glomeruli	Brush border of tubules
Extra-Renal Involvement	-	+	+/-
IF	Strong Linear IgG/kappa/lambda staining with distal tubules sparing	Linear IgG staining of GBM with focal linear distal tubular staining	Granular staining of brush border of Proximal tubules
EM	No Deposits	Non-specific features of crescentric GN	Segmental sub-epithelial deposits

TH-PO712

Fibrillary Glomerulonephritis Associated with Eosinophilic Esophagitis

Ana Paula Gueiros, Janielma S. Laudelino, Denise M. Costa, Italo R. Alves, Thais O. Santos. *Hospital das Clinicas, Recife, Brazil.*

Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease, whose pathophysiology is relatively unclear, and is associated with neoplasms, infectious and autoimmune diseases. Discovering the DNAJ homolog subfamily B member 9 (DNAJB9) has contributed to a better understanding of the pathophysiology and diagnosis of FGN. We report a case of FGN associated with eosinophilic esophagitis (EE), with a challenging diagnosis.

Case Description: A 41-year-old woman, with progressive dysphagia, was diagnosed with EE in 2020. Despite treatment with corticosteroids, her condition worsened, requiring a gastrostomy. She developed renal dysfunction associated with nephrotic syndrome. Tests: creatinine 2.3 mg/dL; serum albumin 2.4 g/dL; proteinuria 7.6g/24h; microscopic hematuria; ANA 1/320; C3 76 mg/dL (normal: 88-165 mg/dL); Other tests were negative, including anti-DNA, anti-Sm, ANCA, serology for hepatitis B and C, HIV and syphilis. Lupus nephritis was suspected and a kidney biopsy was performed. Light microscopy (LM): 3/7 global glomerulosclerosis, 4/7 segmental glomerulosclerosis, discrete mesangial expansion with preserved cellularity and mild interstitial fibrosis and tubular atrophy (IFTA). Positive immunofluorescence (IF) for IgG, C3, kappa and lambda in mesangium and capillary loops. Electron microscopy (EM) was not performed. Treatment was initiated with methylprednisolone and cyclophosphamide. In December 2023, continuing with nephrotic syndrome and renal dysfunction, a new biopsy was performed: LM 35/45 global glomerulosclerosis, discrete, diffuse mesangial matrix expansion and cellularity, severe IFTA; positive IF for the same previous pattern; ME: diffuse thickening of the basement membrane and frequent structured deposits arranged diffusely in the subepithelial, subendothelial, intramembranous and mesangial regions. Deposits averaged 15.6 nm. Immunohistochemistry was performed and was strongly positive for DNAJB9 throughout the glomerular compartment

Discussion: Around 10%-30% of FGN are associated with autoimmune diseases. To our knowledge, this is the first report of FGN associated with EE. We emphasize the importance of EM for the correct diagnosis of glomerulopathies, including FGN. Currently, DNAJB9 is considered an excellent biomarker for FGN and probably a new gold standard for diagnosis

TH-PO713

Rare Case of Fibrillary Glomerulonephritis with Concomitant Acute Interstitial Nephritis Related to Cemiplimab Use

Paras A. Abro, Sheeraz G. Abro, Huma Fatima, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Immune checkpoint inhibitors (ICPI) can cause immune-related kidney injury. Acute tubulointerstitial nephritis (AIN) is commonly caused by ICPIs, although rarely, glomerular injury may also be seen. Fibrillary glomerulonephritis (FGN) is a rare glomerular disorder characterized by the presence of Congo red (CR) negative, non-amyloid fibrillary deposits in the glomeruli. DnaJ homolog subfamily B member 9 (DNAJB9) is a highly sensitive and specific biomarker for FGN. We describe a unique case of FGN accompanied by AIN, hypothesized to be attributable to cemiplimab use.

Case Description: A 63-year-old male with recurrent SCC of the skin treated with cemiplimab (PD-1 inhibitor) presented with non-oliguric AKI. On admission, Sr 13 mg/dL, Sr albumin 4 g/dL, UACR 52 mg/g, and UPCR 513 mg/g. Urinalysis revealed acanthocyturia and RBC casts. The patient had no underlying hypertension or diabetes. Comprehensive serological workup was negative. Kidney biopsy revealed AIN with moderate to severe acute tubular injury and 5-10% IFTA. IF: Trace to 1+ smudgy segmental mesangial staining for IgG, C3, kappa, and lambda. EM revealed mesangial matrix expansion containing segmental nonbranching, randomly arranged fibrillary deposits, ranging in size from 11-17nm in diameter. No usual immune complex deposits or fibrillary deposits were identified along the tubular basement membranes. CR staining was negative. DNAJB9 immunohistochemical staining was positive in the glomeruli. Cemiplimab was discontinued and high-dose glucocorticoids tapered over 6 weeks were given. After 9 weeks, Sr Cr was 2.5 mg/dL with a bland urinalysis.

Discussion: FGN has been associated with malignancy in approximately 9% cases. Given this association, it is recommended to screen patients with FGN for malignancy. Our patient's history of recurrent squamous cell carcinoma may have predisposed him to FGN. Additionally, treatment with cemiplimab, an ICPI, adds complexity due to its potential for drug-induced AIN. While ICPIs are known to cause widespread organ inflammation, isolated AIN are rare, but have been reported. This case underscores the complexity of diagnosing and managing FGN, particularly when present concomitantly with AIN potentially induced by cemiplimab. It also highlights the importance of personalized treatment strategies in managing complex clinical scenarios.

TH-PO714

Rituximab Responsive Relapsing Fibrillary Glomerulonephritis

Sheeraz G. Abro, Paras A. Abro, Huma Fatima, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Fibrillary glomerulonephritis (FGN) is seen in 1% of kidney biopsies and is characterized by glomerular deposition of infiltrative fibrils larger than amyloid composed of polytypic IgG lacking Congo red (CR) reactivity. DnaJ homolog subfamily B member 9 (DNAJB9) also known as endoplasmic reticulum-localized DnaJ 4 was discovered is a highly sensitive and specific biomarker. Upto 50% progress to ESKD within a few years of biopsy but the disease course remains highly variable as some patients with sub-nephrotic proteinuria and well-preserved kidney function can have more of a chronic, smoldering course over time.

Case Description: 63-year-old female with past medical history significant for arterial hypertension, morbid obesity, & prediabetes presented with microscopic hematuria & proteinuria. Cr 1.5 mg/dL, eGFR 39 mL/min, Sr albumin 4 g/dl, UPCR 8962 mg/g. Urine microscopy: acanthocyturia & RBC casts. Comprehensive serological workup negative. Kidney biopsy - LM: Moderately expanded mesangium with mild hypercellularity. Capillary basement membranes showed focal & segmental splitting due to the extension of similar material along the capillary loops; 5% IFTA. IF: 2+ smudgy, predominantly mesangial and rare capillary loop staining for IgG, C3 [1-2+], kappa = lambda = 2-3+. EM: Moderately increased mesangial matrix with segmental nodularity, containing randomly arranged, nonbranching, fibrillary deposits, 9-18 nm in diameter. No immune complex deposits or punctate amorphous deposits were identified. CR stain was negative. DNAJB9 IHC stain positive in glomeruli. Patient received 2 courses of Rituximab [each course with 2 doses of 1g spread 14 days apart]. During last follow up, Sr Cr and albumin were normal with UPCR having reduced to 2638 mg/dL. Further Rituximab administration is being based on B-cell reconstitution.

Discussion: There is no standard-of-care treatment for FGN. Rituximab may be the most promising treatment for progressive FGN. In the first prospective clinical trial of rituximab in 11 patients with FGN, investigators observed no significant change in the

eGFR at 12 months. At 1 year, there was an overall ~50% reduction in proteinuria; 3 patients experienced a partial response. Neither treatment nor disease remission status affected DNAJB9 serum levels. Our case highlights the utility of considering use of repeated doses of Rituximab for a select subset of FGN patients.

TH-PO715

Fibrillary Glomerulonephritis with Concurrent Anti-glomerular Basement Membrane Leading to Rapidly Progressive Glomerulonephritis: A Diagnostic Conundrum

Abraham Bell,[1] Gautam Maddineni,[1] Stefan Milutinovic,[1] Isaac Bell,[2] Ibrahim Khambati.[1] [1]*Florida State University, Tallahassee, FL;* [2]*Nova Southeastern University, Fort Lauderdale, FL.*

Introduction: Anti–glomerular basement membrane (anti-GBM) disease is a rare small vessel vasculitis that affects the capillary beds of the kidneys and lungs. It is a well-known significant cause of rapidly progressive glomerulonephritis (RPGN). Conversely, fibrillary glomerulonephritis (FGN) typically presents proteinuria, hematuria and more gradual decline in renal function as compared to a rapid one. Herein, we report a case of anti-GBM disease with finding of FGN on renal biopsy; a rare presentation of both entities existing concurrently.

Case Description: 57-year-old male with a previous medical history significant for hypertension, hyperlipidemia, recently diagnosed CKD stage 3A with previous reported Creatinine of 1.54 a month before admission who presented with complaints of dyspnea, worsening fatigue, sleepiness, and approximately 20-pound weight gain along with decreased urine output. After initial evaluation, the patient was noted to have acute renal failure, evidenced by a creatinine of 13.08 and a BUN of 109. Chest X-ray did not reveal any acute cardiopulmonary findings. The patient subsequently underwent renal biopsy, which revealed glomeruli demonstrating necrosis or cellular/fibrocellular crescent formation. In addition, many glomeruli demonstrated Bowman's capsule disruption and extensive glomerular deposition of DNA JB 9 positive fibrils. As well as having positive anti-GBM antibodies. The patient received treatment with IV Solu-Medrol, which was then transitioned to oral Prednisone 80 mg in conjunction with oral Cyclophosphamide 100 mg. Furthermore, the patient underwent five sessions of plasmapheresis and required initiation on Hemodialysis in the hospital with plans to continue treatment after discharge.

Discussion: Standard of care treatment of anti-GBM disease usually involves the use of prednisone and cyclophosphamide in conjunction with plasmapheresis however, renal prognosis is poor with patient usually requiring initiation of hemodialysis. Similar treatment modalities are used to treat FGN with the clinical presentation of RPGN however, this is largely anectodal with similar renal outcomes. Our case highlights the rare coexistence of these two GNs and the importance of renal biopsy to aid in diagnostic/therapeutic intervention.

TH-PO716

Fibrillary Glomerulonephritis: A Rare Glomerulonephritis with No Definitive Treatment

Htun H. Naing, Daniele Rios Leite. *University of Florida, Gainesville, FL.*

Introduction: Fibrillary glomerulonephritis (FGN) is an uncommon disorder, present in 0.5-1.4% of kidney biopsies. It is mostly seen in Caucasians of 50-60 years of age. It was initially thought to be idiopathic; however, an association with autoimmune disease, malignancy, and HCV infection has been proposed based on recent studies. It typically presents with hematuria, proteinuria, renal function impairment, HTN, and monoclonal gammopathy. For the diagnosis it is required the demonstration of randomly oriented, straight, non-branching, fibrillary deposits with a mean diameter of 20 nm in the mesangium and glomerular capillary walls without microtubule formation and Congo red stain negative. The specific biomarker DNAJB9 can be detected through immunohistochemical stain.

Case Description: A 65-year-old man with medical history significant for lymphoma, tonsillar cancer, prostate cancer, treated HCV, and alcohol use disorder was admitted to the ICU due to alcohol intoxication and pneumonia. He was found to have AKI with microscopic hematuria. His renal function had some improvement initially, with gradual worsening posteriorly, and persistent microscopic hematuria with grade A3 microalbuminuria. He tested negative for ANA, MPO, PR3, anti-GBM, Syphilis, HIV, hepatitis B; C3 and C4 levels were normal. The renal pathology results showed moderate IFTA of 40%, mesangial IgM-dominant immune complex deposition, positive staining for DNAJB9, negative Congo red staining, and haphazardly arranged fibrils within mesangial regions, focally infiltrating the entire width of the GBM, with texture suggestive of fibrillary glomerulonephritis, which was more prominent than the IgM deposition. These results were consistent with FGN. He was found to have a biclonal IgG spike on SPEP, which did not correlate with the findings of IgM deposition. Bone marrow biopsy was normocellular. Cryoglobulin screening was positive. The patient was started on prednisone and ACE-i. His renal function improved but did not return to baseline.

Discussion: Currently, there are no definite treatment guidelines for FGN, and the efficacy of antiproteinuric therapy is unclear. The majority of patients still progress to ESKD, being 40-50% of cases within 2-6 years. Due to the rarity of this condition, further research isneeded for better understanding of the disease process and improvement of treatment outcomes.

TH-PO717

Case of Crescentic Fibrillary Glomerulonephritis with Linear IgG Mimicking Anti-glomerular Basement Membrane Nephritis with Good Response to Treatment

Gedaliah May, Andrew Chandler, Andrew A. Moses, Jordan L. Rosenstock. *Lenox Hill Hospital, New York, NY.*

Introduction: Fibrillary glomerulonephritis (FGN) is an uncommon glomerular disease whose diagnosis depends on electron microscopy (EM) showing fibrillary immune deposits and immunohistochemistry (IH) with DNAJB9 deposits in glomeruli. Light microscopy of FGN can have variable histological patterns, and can rarely present with diffuse crescentic disease which has a very poor prognosis. The deposits on immunofluorescence (IF) are typically described as "smudgy" but can sometimes be pseudo-linear mimicking anti GBM disease. Here we describe a patient with FGN mimicking anti- GBM disease who had a good response to immunosuppressive therapy.

Case Description: The patient is a 31-year-old female with obesity who presented with three weeks of foamy urine, fatigue, and poor appetite. On presentation serum creatinine was 3.0 mg/dL (was 0.5 mg/dl three months prior). Urinalysis showed hematuria and proteinuria and a urine protein/creatinine ratio was 17.3. A kidney biopsy showed diffusely crescentic proliferative glomerulonephritis with fibrinoid necrosis on light microscopy and IF was reported as linear IgG along the glomerular capillaries suspicious for anti-GBM disease. Anti- GBM antibody was negative and the diagnosis of atypical anti- GBM disease was considered. Subsequently, EM revealed diffuse organized fibrillary deposits and later IH showed DNAJB9 positivity in glomeruli. The patient was treated with steroids and intravenous cyclophosphamide. Her creatinine was 1.0 at 6 months follow-up.

Discussion: This case touches on clinical challenges related to crescentic FGN. There can be a challenge in distinguishing crescentic FGN and anti-GBM disease if EM and IH are not immediately available. In our case, atypical anti-GBM disease was considered when her anti-GBM antibody was negative, though this is usually a more indolent disease than typical anti-GBM with either no or only focal crescents. Once a diagnosis was established by EM and IH the optimal treatment regimen remained unclear as there is no clear therapy for crescentic FGN and it has been observed that the prognosis of diffusely crescentic FGN is very poor despite immunosuppression. However, this patient responded well to a course of steroids and cyclophosphamide with a significantly improved creatinine.

TH-PO718

A Cat and a "Full House"

Neha B. Patel, Alana Dasgupta, Isabelle Ayoub, Madeline S. Chung. *The Ohio State University Wexner Medical Center, Columbus, OH.*

Introduction: In a patient with constitutional symptoms, positive ANA serologies, and hypocomplementemia, immune complex glomerulonephritis (GN) often suggests lupus nephritis. However, Bartonella endocarditis can mimic this presentation. We detail the case of a 34-year-old man with history of pulmonary valve replacement and cat bite with acute kidney injury (AKI) due to Bartonella endocarditis-related GN.

Case Description: The patient initially presented with upper respiratory symptoms, diarrhea, and AKI, attributed to hypovolemia and NSAID use. AKI worsened despite resolution of symptoms. Further workup revealed elevated rheumatoid factor, positive Epstein-Barr Virus (EBV) IgM, normal complement levels, and negative infectious workup. Kidney biopsy was consistent with IgA nephropathy. Post-discharge, he developed a pruritic rash, assumed to be IgA vasculitis. Twelve days later, he returned with a new pulmonic regurgitation murmur, weight loss, nocturnal fevers, and heart failure symptoms. Both transthoracic and transesophageal echocardiograms were negative for vegetations, but Bartonella IgG titers were elevated. Glucocorticoids resolved symptoms and AKI temporarily, but they recurred post-tapering, prompting transfer to our institution. Repeat serologies showed positive ANCA, low C3 and C4, and high Bartonella titers. Repeat kidney biopsy revealed mesangioproliferative GN with full-house immune complex deposition in the mesangium and also in the subendothelial, subepithelial and intramembranous spaces. Bartonella DNA was detected, leading to hospital readmission for bacteremia and pulmonic valve vegetation. He was treated with antibiotics leading to and then following valve replacement.

Discussion: The differential diagnosis for immune complex glomerulonephritis includes autoimmune disease, malignancy and infection which may often be missed at the time of acute infection due to mild symptoms and a negative infectious workup due to a fastidious and/or slow-growing microbe. Bartonella is most often diagnosed in the later stages of infection with elevated IgG titers rather than IgM and PCR as it is a facultative intracellular bacterium, rarely isolated in culture and only fleetingly found in the blood. When the kidney biopsy shows an immune complex glomerulonephritis, always consider smoldering infections, especially if the patient is immunocompromised or has a history of cardiac valve surgery.

TH-PO719

Diagnosis of Alport Syndrome Requires One More Step after Kidney Biopsy

Dhairya Salvi,[1,2] Pedro A. Pineiro De Jesus.[1,2] *[1]Ascension Providence Rochester Hospital, Rochester, MI; [2]Wayne State University, Detroit, MI.*

Introduction: Alport syndrome is an inherited disorder heterogeneously affecting the basement membrane of the kidney, eyes, and inner ear. It is a diagnostic challenge as symptoms are non-specific, with hematuria being the only evident sign in many cases. The age at presentation and genetic modes of transmission also show significant variation. A kidney biopsy may show non-specific findings making further diagnostic tests necessary.

Case Description: We present a case of a 66-year-old female with a history of long-standing hypertension and WHO class II obesity who was referred to our clinic for CKD stage G2A3 with a baseline creatinine of 0.9 mg/dL. She had microscopic hematuria with 5-9 RBCs on urinalysis and subnephrotic proteinuria with urine protein creatinine ratio of 1.8 g/g. Serological workup for glomerulonephritis was negative. Decision was taken to investigate further with a kidney biopsy which showed epithelial foot process effacement, moderate arteriosclerosis, and glomerulomegaly. thin glomerular basement membrane without any lamellation; Immunofluorescence was negative for antibody or complement deposition. An Alport immunofluorescence showed a normal uninterrupted staining for alpha 5 chain of collagen type IV. Given a family history of CKD, there was still some suspicion of a hereditary disorder. Genetic testing revealed COL4A4 variant suggestive of autosomal dominant Alport syndrome.

Discussion: This patient had hematuria, subnephrotic proteinuria, and CKD which can be attributed to a combination of thin basement membrane nephropathy and hypertensive arteriosclerosis, which was evident on kidney biopsy. The patient did not have eye or ear involvement seen in Alport syndrome. Furthermore, the kidney biopsy did not show any lamellation or splitting of glomerular basement membrane. Despite this, the patient was found to have Alport syndrome based on genetic analysis. This case demonstrates the importance of genetic testing for Alport syndrome despite non-specific findings on kidney biopsy in case of hematuria, progressive kidney disease, and a positive family history.

TH-PO720

Factor B: The "It" Factor in Infection-Related Glomerulonephritis

Jennifer L. Grigsby,[1] Eric Magliulo,[1] David A. Mcmillan,[1] Kirk W. Foster,[2] Prasanth Ravipati.[1] *[1]University of Nebraska Medical Center Department of Internal Medicine, Omaha, NE; [2]University of Nebraska Medical Center Department of Pathology and Microbiology, Omaha, NE.*

Introduction: Infection-Related Glomerulonephritis (IRGN) and C3 Glomerulopathy (C3G) demonstrate considerable clinicopathologic overlap, presenting a diagnostic challenge to clinicians and making selection of an appropriate treatment regimen difficult. We present a case of IRGN which highlights this diagnostic conundrum.

Case Description: A 43-year-old man presented with volume overload, acute kidney injury, 2 grams of proteinuria, and hypocomplementemia without a history or clinical signs of recent infection. Kidney biopsy demonstrated proliferative glomerulonephritis with immune complex deposition with co-dominant staining of C3 and IgG by immunofluorescence. These findings appeared most consistent with a diagnosis of IRGN; however, with primarily subendothelial and mesangial deposits on electron microscopy, lack of infectious history, and a family history notable for chronic kidney disease in multiple relatives, there was concern for familial hypocomplementemia or C3G. His renal function continued to worsen, requiring intermittent hemodialysis and initiation of empiric pulse solumedrol followed by daily prednisone and mycophenolate mofetil. After being discharged, autoantibody testing returned positive for Factor B autoantibodies. Genetic testing otherwise was negative. Given the previously described strong association of Factor B autoantibodies and IRGN, immune suppression was discontinued. Ten weeks after his initial presentation, repeat labs demonstrated resolution of his hypocomplementemia, near resolution of his proteinuria, and return of serum creatinine to normal (0.9 mg/dL).

Discussion: This patient was ultimately diagnosed with IRGN; however, features of his presentation raised concern for C3G. Factor B autoantibodies have been shown to contribute to transient dysregulation of the alternative complement pathway and have been found in a significantly higher proportion of patients with IRGN compared to C3G. This case highlights the utility of diagnostic complement testing, as the positive Factor B autoantibody helped inform the decision to discontinue immune suppression and limit potential related toxicities. Improvement in timeliness and availability of complement testing is needed to aid clinicians faced with diagnostic uncertainty in the realm of C3G.

TH-PO721

Kidney Involvement in Cryoglobulinemia: Not Always Crystal Clear

Raja S. Boddepalli,[1] Vishnupriya Alavala,[1] Lynn D. Cornell,[2] Jason M. Kidd.[1] Virginia Commonwealth University. *[1]Virginia Commonwealth University, Richmond, VA; [2]Mayo Foundation for Medical Education and Research, Rochester, MN.*

Introduction: Cryocrystalglobulinemia (CCG) is a rare variant of type 1 cryoglobulinemia. Renal involvement is rare and associated with plasma cell dyscrasias. In CCG, monoclonal immunoglobulins assemble into crystalline arrays inciting inflammation and causing vasculopathy from pseudo thrombi in renal glomerular capillaries. We present a case of CCG due to monotypic IgG deposits with negative immunofixation (IFE).

Case Description: A 67-year-old male was referred for edema and proteinuria. On presentation, blood pressure was 136/87 mmHg and physical exam was significant for lower extremity edema. Laboratory studies revealed a creatinine of 2.5 mg/dl with no antecedent history of renal failure and spot urine protein to creatinine ratio (UPCR) was 2.5 g/g. Serum and urine IFE were negative. Kidney biopsy showed endocapillary proliferative macrophage-rich glomerulonephritis with intracapillary pseudo-thrombi, intracellular crystals, and monotypic IgG2 Kappa deposits. On electron microscopy, crystals were noted within infiltrating macrophages in glomerular capillary lumens consistent with CCG. (Figure 1) Bone marrow biopsy was unremarkable. He was treated with cyclophosphamide, bortezomib and dexamethasone. Proteinuria persisted and daratunamab was added and serum creatinine improved to 1.8 mg/dl and proteinuria completely resolved 8 months after his initial presentation

Discussion: Our case describes a rare variant of monoclonal gammopathy with renal significance (MGRS) without a detectable circulating monoclonal protein that responded to clone-directed therapy. Kidney biopsy should be pursued in patients with renal insufficiency and proteinuria without abnormal serologies.

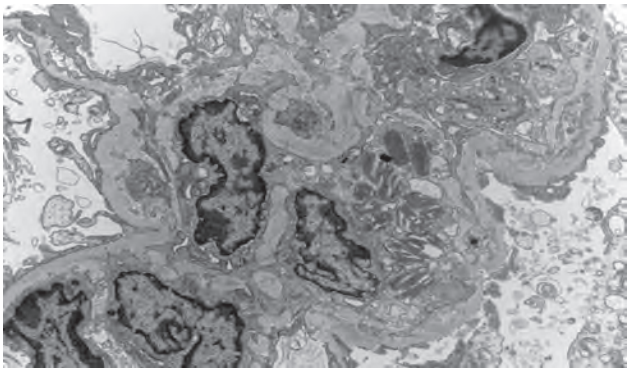


Figure 1: Crystals noted within infiltrating macrophages in glomerular capillary lumens.

TH-PO722

A Periodic Curveball: Collagenofibrotic Glomerulopathy

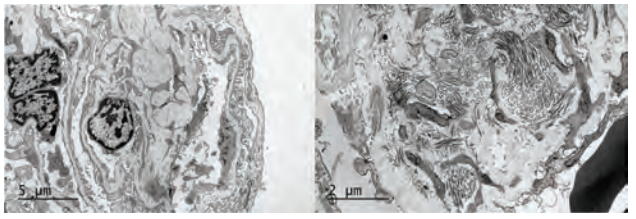
Sydney E. Hartsell, Monica P. Revelo Penafiel, Sarah Gilligan, Gurbir S. Sehmbey, Nirupama Ramkumar. *The University of Utah School of Medicine, Salt Lake City, UT.*

Introduction: Collagenofibrotic Glomerulopathy is a rare idiopathic disease with unknown pathogenesis and no treatment.

Case Description: A 65-year-old man with hypertension and tobacco use disorder was hospitalized after 5 months of fevers, rigors, weight loss, malaise and one week of heavy acetaminophen and ibuprofen use. He was treated for acetaminophen toxicity and received extensive infectious and hematologic workup, which revealed multiple hypermetabolic lymph nodes on PET CT with necrotizing lymphadenitis on biopsy and prostatomegaly with intermittent bleeding on cystoscopy. Nephrology was consulted for microscopic hematuria, spot urine protein:creatinine ratio 524 mg/g, and 117 mg/g albuminuria. Creatinine was 0.9 mg/dL with estimated glomerular filtration rate 90 ml/min/1.73m^2. Serologic workup was negative aside from antinuclear antibody titer of 1:80. Urine microscopy showed acanthocytes. Subsequent renal biopsy showed mesangial and subendothelial deposits of curved fibrils with frayed edges and transverse banding at 60 nm periodicity, consistent with collagenofibrotic glomerulopathy (Figure). Two years later, renal function remains preserved with mild proteinuria and microscopic hematuria. The etiology of his B-symptoms remains unconfirmed. He has been treated with valsartan and dapagliflozin. Rheumatology initiated methotrexate for suspected systemic autoimmune inflammatory syndrome. A recent repeat bone marrow biopsy revealed chronic monomyelocytic leukemia stage 0.

Discussion: Collagenofibrotic glomerulopathy is identified by atypical type III collagen deposition in the mesangium and subendothelium. Limited case reports note hypertension, mild proteinuria, microscopic hematuria and typically preserved renal

function, consistent with this case. Interestingly, this mysterious disease was found amid a mysterious constellation of symptoms. It is classically not linked with extrarenal symptoms at diagnosis, but re-evaluation of known cases should be considered for later development of hematologic or rheumatologic disease.



Electron Microscopy

TH-PO723

An Unusual Presentation of Poststreptococcal Glomerulonephritis (PSGN) in a Patient with Alcoholic Liver Cirrhosis

Aseel Zghayer, Maria M. Picken, David J. Leehey. *Loyola University Chicago Stritch School of Medicine, Chicago, IL.*

Introduction: Post-infectious glomerulonephritis (PIGN) is commonly triggered by streptococcal skin or throat infections and is well-recognized to manifest in childhood. A characteristic feature of PIGN is the activation of the alternate complement pathway, leading to complement overactivation. The typical immunofluorescence pattern seen in PIGN is IgG and C3 deposition. Here, we present an unusual presentation of PIGN in a patient with liver cirrhosis following a recent streptococcal infection.

Case Description: A 54-year-old man, recently diagnosed with alcoholic liver cirrhosis, presented with abdominal pain attributed to an umbilical hernia. He developed oliguric acute kidney injury (AKI) necessitating hemodialysis. During further evaluation, the patient disclosed a history of sore throat, headache, and fever 2 weeks prior to admission. The workup is detailed in Table 1. Kidney biopsy demonstrated PIGN with prominent IgA as well as IgG deposition (Figure 1). After the biopsy, serology for anti-DNAse B was strongly positive, confirming a diagnosis of PSGN. Four weeks later, the C3 level had increased from < 15 to 56 mg/dL, and the patient is off dialysis with a serum creatinine of 2.0 mg/dL.

Discussion: Our patient's very low C3 and normal C4 levels make it highly unlikely that hypocomplementemia was due to a synthetic defect from hepatic cirrhosis. Given that patients with alcoholic liver disease are known to be at increased risk of PIGN, we hypothesize the possibility that our patient had an acute PSGN superimposed on a pre-existing IgA hepatic glomerulopathy. This case underscores the theory that patients with liver cirrhosis may have an impaired ability to clear immune complexes during bacterial infections.

Lab (reference range)	Patient values	Lab (reference range)	Patient values
Na (136-144 mmol/L)	134 mmol/L	Calcium (8.9-10.3 mg/dL)	8.7 mg/dL
K (3.3-5.1 mmol/L)	5.8 mmol/L	WBC (4.0-11.0 k/uL)	4.5 k/uL
Urea Nitrogen (7-22 mg/dL)	104 mg/dL	Hemoglobin (13-17 g/dL)	8.7 g/dL
Creatinine (0.6-1.4 mg/dL)	7.8 mg/dL	Platelets (130-400 k/uL)	69 k/uL
Urinalysis: yellow, pH 5.0, specific gravity 1.017, 2+ protein, RBC 37/HPF, WBC 10/HPF			
Urine protein/creatinine (0-200 mg/g): 1340 mg/g			
Serology			
ANTI STREPTOLYSIN O (<200 IU/ml) : 59	**C3 (90-180 mg/dL): <15**	ANA 1:320	ANCA neg
DNASE-B Ab (<301 U/ml) : **858**	**C4 (10-40 mg/dL): 23**	dsDNA neg	HIV,HBV,HCV non-reactive

Table 1. Work up

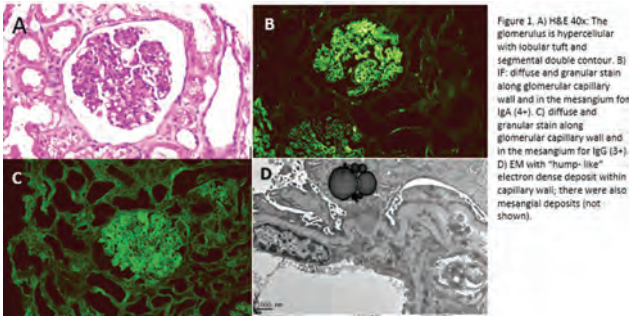


Figure 1.

TH-PO724

Oligomeganephronia in a 29-Year-Old Pregnant Woman

Nada Youssef, Prerna Rastogi, Abdullah Thayyil. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Introduction: Oligomeganephronia (OMN) is a congenital anomaly characterized by reduced nephron number, glomerulomegaly and tubulomegaly. It is a pediatric disease, while late-onset OMN is very rare. We present a case of adult onset OMN at our institute with kidney disease during pregnancy.

Case Description: A 29-year-old female with unexplained stage IV chronic kidney disease (CKD) was referred to us for kidney biopsy. Her clinical history dates to 2019, during a pregnancy, when she was noted to have a creatinine of 1.9 with sub-nephrotic proteinuria. Workup done including complement levels, anti-nuclear and anti-neutrophil cytoplasmic antibodies, myeloperoxidase and proteinase-3 antibody were negative. On physical exam, she had height 64", weight 174 lbs, BMI 29.87 kg/m^2, blood pressure 116/78 mmHg. Cardiac and pulmonary auscultation were normal. She had no edema. She was started on angiotensin receptor blocker. Her kidney function gradually worsened and a kidney biopsy was done in February 2023 showing moderate chronicity with no evidence of an immune complex-mediated process. Supportive measures were continued. As kidney function continued to decline 1 year later, repeat biopsy was done in March 2024 showing findings consistent with histological diagnosis of OMN (images below).

Discussion: OMN is a congenital anomaly characterized by reduced nephron number due to arrested development of metanephric blastema at 14-20-week gestation. Patients are usually born with low birth weight. Early-onset type present at a young age with polyuria, polydipsia, or proteinuria and usually progress to ESRD early in life. Late-onset type is rare; and usually present as asymptomatic proteinuria. Disease pathophysiology is unclear. OMN does not cause any phenotypic characteristics, thus, renal biopsy is crucial for diagnosis. Histologically, OMN is characterized by a reduced number of glomeruli, glomerulomegaly, and tubulomegaly. Over time, histologic changes of fibrosis will be seen. There is no effective treatment for OMN at present. The focus is on supportive measures to reduce glomerular hyperfiltration and delay disease progression.

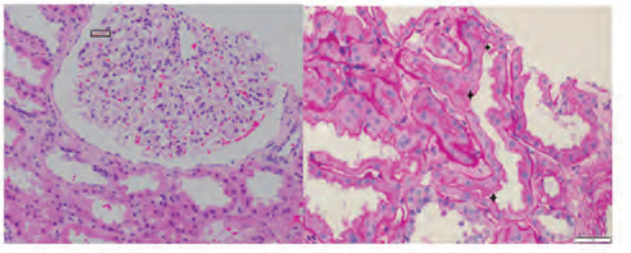


Figure 1 (Left panel): H+E-stained image of the glomerulus. Measurement 315.30 µm. (Right panel): PAS-stained image of a tubule with multiple branch points (Black asterisk). The brush borders are intact and there is no cell exfoliation into the lumen.

TH-PO725

Cryoglobulinemic Glomerulonephritis Masquerading as IgA Nephropathy in a Patient with Crohn Disease

Saad A. Alshihri, Gabriel B. Lerner, Adrian Llama, William S. Asch. *Yale University School of Medicine, New Haven, CT.*

Introduction: We report a case of a patient with long standing history of Crohn's presenting with anemia, acute renal failure requiring initiation of dialysis and lower extremity painful rash. Renal biopsy initially suggested IgA nephropathy given history of Crohn's and codominant IgA and IgM, but EM features and serological markers made cryoglobulinemic GN a favorable diagnosis. In this case, we address the diagnostic complexity we came across.

Case Description: This is a 48-year-old Caucasian female who was admitted with anemia, acute kidney injury, and purpuric rash of the lower extremities. Urinalysis revealed red blood cells and nephrotic range proteinuria. Urine sediment showed RBC casts. Renal function rapidly deteriorated requiring initiation of dialysis. Physical exam revealed painful LE purpuric rash, levido reticularis and dorsal foot ulcers. Imaging showed ground glass opacities. Given the rapid decline in renal function and findings suggestive of systemic vasculitis, a renal biopsy was expedited. Biopsy showed focal necrotizing and crescentic glomerulonephritis on LM, IF staining with +1 IgA, IgM and +2 C3 staining. However, there were rare subendothelial and mesangial electron dense deposits with curvilinear substructure on EM suggesting cryoglobulinemic GN. Serological markers came back positive for rheumatoid, borderline low C3 with normal C4 and serum cryoglobulin was positive, with immunofixation showing type 2 mixed cryoglobulins. Broad work up was done to identify an infectious or lymphoproliferative etiology of cryogenesis revealing a positive respiratory culture growing Klebsiella pneumonia on BAL, and pleural nodule biopsy showed organizing pneumonia. The patient was promptly started on pulse steroids, IVIG and PLEX with improvement in skin rash. She continued to require dialysis on discharge, and Rituximab was deferred to the outpatient setting due to active infection.

Discussion: Cryoglobulinemic glomerulonephritis (GN) is a disorder characterized by the deposition of cryoglobulins. Cryoglobulinemic and IgA vasculitis can have multiple similarities in clinical and pathological features. In this case we encountered multiple overlapping clinical and histological findings, but ultimate diagnosis was favorable for cryoglobulinemic vasculitis. The positive rheumatoid and EM findings helped in making the distinction.

TH-PO726

The Cat Scratch That Leaves a Renal Mark: A Bartonella-Associated Glomerulonephritis

David A. Mcmillan, Prasanth Ravipati, Kirk W. Foster, Nathaniel Leonardi, Kathleen Borghoff, Nicolas Cortes-Penfield, Ketki K. Tendulkar.
University of Nebraska Medical Center, Omaha, NE.

Introduction: Chronic infections such as infective endocarditis (IE) and infected implanted devices are known causes of glomerulonephritis (GN). *Bartonella* spp are a leading cause of blood culture-negative IE (BCNE). Due to this a high clinical suspicion is required to make the diagnosis. We present a case of *Bartonella* aortic graft infection related GN.

Case Description: A 63-year-old man with a history of type A aortic dissection with graft repair, was undergoing treatment with cyclophosphamide, bortezomib, and dexamethasone for monoclonal gammopathy of renal significance induced C3 GN. After three months of therapy the patient developed sudden onset shortness of breath. A CT scan showed pseudoaneurysm at the suture line of his previous graft site. Subsequent PET CT scan was concerning for infection corresponding to the small pseudoaneurysm, but blood cultures were negative. TEE showed no vegetations on this prosthetic aortic valve. *Bartonella henselae* serology was positive with IgG >1:1024. His immunosuppression was discontinued and he was initiated on doxycycline 100mg BID and rifampin 300mg BID. Rifampin was discontinued due to poor tolerance. He developed shoulder pain and imaging showed increased size of pseudoaneurysm and surrounding hematoma needing immediate repair. During recovery, he had worsening renal function with creatinine rise from 1.2 mg/dL to 1.7 mg/dL; urine protein to creatinine (PCR) level was elevated at 1.2 mg/mg, and he had microscopic hematuria (>50 RBC/HPF). He underwent kidney biopsy which showed co-dominance of IgM, C3, and C1q with kappa staining. This led to diagnosis of *Bartonella* associated GN and he was initiated on rifabutin along with doxycycline, leading to reduction of PCR to 0.3 mg/mg and Cr to 1.37 mg/dL.

Discussion: *Bartonella* IE and infected implanted devices, as seen in this case, may result in an infection related GN. *Bartonella* IE has been suggested to have clinicopathological differences from IE caused by other bacteria. This includes a higher frequency of crescents along with full-house staining patterns especially IgM and C1q. When diagnosis is uncertain following biopsy physicians should consider obtaining a targeted history of animal exposure and serological workup for *Bartonella* spp. especially in patients with a history of implanted devices or BCNE.

TH-PO727

Cognitive Bias in the Diagnosis of Acute Nephritis: A Case of Complementary Details

Sarah Rokaw,[1] Benjamin A. Wagner,[1] Kavita Mistry,[1] Seymour Rosen,[1] Kambiz Zandi-Nejad,[1] Sylvia E. Rosas,[2,1] Stewart H. Lecker.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Joslin Diabetes Center, Boston, MA.*

Introduction: The etiologies of acute nephritis are characterized by complement levels and systemic versus renal-limited diseases. Both pauci-immune glomerulonephritis (GN) and anti-GBM disease have normal complements and systemic involvement, while lupus nephritis is classically associated with low complements. Nonetheless, studies demonstrating diagnostic sensitivity of complement levels are small and variable.

Case Description: A 33-year-old woman with asthma and prior tobacco use presented with subacute hemoptysis and was found to have acute hypoxic respiratory failure and anemia. Prior to admission, her respiratory symptoms had initially improved with steroids and antibiotics. On presentation, vital signs were remarkable for hypertension and new hypoxia requiring high flow nasal cannula. Physical exam revealed bibasilar rales and 2+ lower extremity edema. Creatinine was at baseline of 0.8 mg/dL with albumin of 3.4 g/dL. Hemolysis labs were positive. Urinalysis revealed 3+ blood and 4+ protein quantified at 3.3 g/g, and sediment demonstrated innumerous RBC casts, WBC casts, and acanthocytes. Bronchoscopy revealed diffuse alveolar hemorrhage. ANA was positive at 1:320 in nuclear homogenous pattern with negative dsDNA and anti-Sm. C3 was slightly low at 83 mg/dL, and C4 was normal. Pulse-dose steroids were initiated, and she received three sessions of plasmapheresis for presumed pauci-immune GN or anti-GBM disease. Additional workup then returned as follows: positive p-ANCA 1:320 with negative MPO and PR3, positive SS-A, negative HIV and hepatitis B/C, negative lupus anticoagulant, and negative antibodies for GBM, anti-PLA2R IgG, cardiolipin, beta-2-glycoprotein, RNP and SS-B. Renal biopsy was delayed for one week due to antecedent NSAID use, though ultimately revealed endocapillary proliferative GN with limited crescent formation and very focal necrosis and immunofluorescence consistent with lupus nephritis.

Discussion: The mildly low C3 was an important diagnostic clue - overlooked due to data mismatch with diagnostic schema. However, the patient met criteria for SLE, which includes a score for low C3 or C4. This case illustrates that a simplified framework of classifying GN must be contextualized both with the sensitivity of available tests and the clinical picture to avoid cognitive bias and diagnostic inaccuracy.

TH-PO728

Does Race Impact Outcomes in Kidney Transplant Recipients with Obesity? A Mate Kidney Analysis

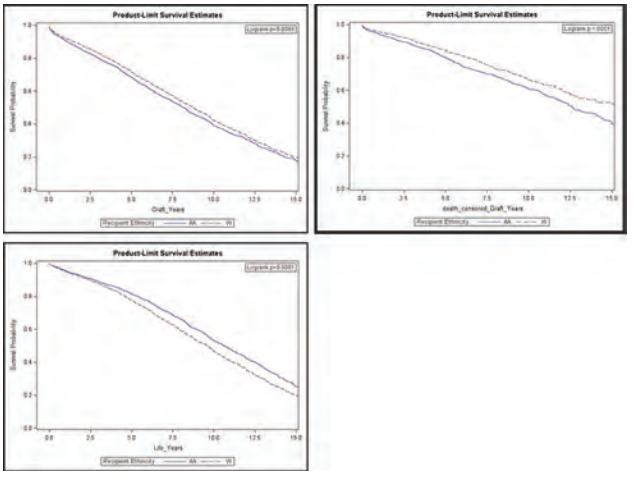
Kalathil K. Sureshkumar,[1] Reem Daloul,[1] Bhavna Chopra,[3] Rita L. McGill.[2] *[1]Allegheny Health Network, Pittsburgh, PA; [2]University of Chicago Pritzker School of Medicine, Chicago, IL; [3]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Epidemiological studies have shown favorable impacts of both high body mass index (BMI) and African American (AA) race on the outcomes in patients on long-term dialysis. A mate-kidney model was used to examine the differential impact of recipient race on the outcomes of obese kidney transplant recipients (KTRs).

Methods: Using OPTN/UNOS database from 2000 to 2023, we identified deceased donors with two adult first-time KTRs who were discordant for recipient race. AA recipients were compared to white recipients for outcomes including transplant hospital length of stay (LOS), delayed graft function (DGF; dialysis in the first post-transplant week), overall graft failure (GF), death-censored GF and patient death. Findings were evaluated with Kaplan-Meier survival plots and McNemar tests.

Results: During the study period, there were 6052 obese recipients who received mate-kidneys from 3026 donors in which one recipient was AA and the other was white. Median hospital LOS did not differ by race. The incidence of DGF was higher in AA KTRs (57.6% vs. 42.5%, p<0.001). Kaplan-Meier analysis showed increased GF and death-censored GF in AA compared to white KTRs but AA recipients had lower patient deaths (figure).

Conclusions: Despite increased risk for DGF and inferior graft outcomes, obese AA recipients had enhanced patient survival compared to their white counterparts. Further work is warranted to investigate the factors that affect the interaction of race and obesity on graft and patient survival.



TH-PO729

Kidney Allograft Nephrectomy Is Associated with Lower Mortality and Improved Repeat Kidney Transplant Rates

Steven Achinger,[1,2] Juan Carlos Ayus,[3] Ambuj Kumar,[1] Athanasios Tsalatsanis.[1] *[1]University of South Florida Morsani College of Medicine, Tampa, FL; [2]Watson Clinic LLP, Lakeland, FL; [3]University of California Irvine, Irvine, CA.*

Background: It has been shown that surgical removal of failed allografts leads to both reduced inflammatory markers and improved patient survival. However, the potential impact of allograft nephrectomy on repeat transplantation is unknown.

Methods: We performed a retrospective cohort study using USRDS data where adult patients with Medicare coverage returning to dialysis after failed kidney transplant between January 1, 1995, and December 31, 2018 were eligible. The index event for the analysis in the comparison group was the date of failure of the first renal allograft. The index event for the analysis in the nephrectomy group was the date of nephrectomy. The primary outcome was time to second transplant. We extracted data on demographics, insurance status and Charlson comorbidity index (using 3 years of hospital claims preceding index event). All analyses were performed using R 4.0.3 package.

Results: Overall, 48,094 patients met the inclusion criteria and 10,117 patients had an allograft nephrectomy. After propensity score matching, 10,117 patients each remained in

the nephrectomy and comparison cohorts **(Table 1)**. Patients in the nephrectomy cohort were more likely to receive a second transplant than patients in the comparison group (HR 1.13; 95% CI:1.07, 1.20; p<0.001) **(Figure 1)**. At 2, 5 and 10 years follow-up, the nephrectomy group had a reduced likelihood of death and a higher likelihood of being alive and having a functional kidney allograft than the comparison group.

Conclusions: Allograft nephrectomy is associated with higher likelihood of repeat kidney transplantation and long term survival with a functioning kidney allograft compared with propensity score matched patients without allograft nephrectomy.

Figure 1

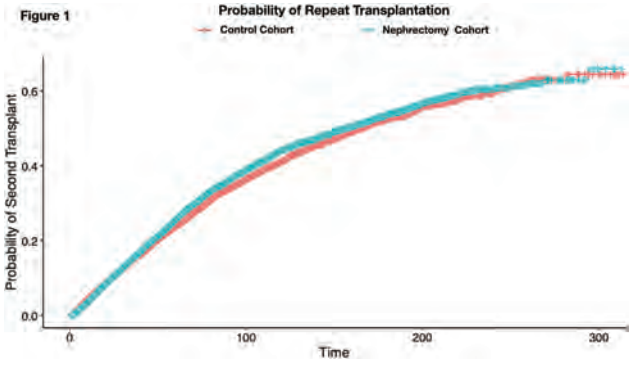


Table 1

	Control (N=10117)	Nephrectomy (N=10117)	All (N=20234)
Donor Age			
Mean (SD)	36.5 (15.5)	37.7 (16.0)	37.1 (15.8)
Median [Min, Max]	37.1 [0.083, 83.8]	38.7 [0.17, 82.5]	37.8 [0.083, 83.8]
Missing	716 (7.1%)	388 (3.8%)	1104 (5.5%)
Donor Sex			
Female	4261 (45.3%)	4303 (44.2%)	8564 (44.8%)
Male	5145 (54.7%)	5428 (55.8%)	10573 (55.2%)
Missing	711 (7.0%)	386 (3.8%)	1097 (5.4%)
Donor Race			
White	7228 (75.3%)	7646 (77.4%)	14874 (76.4%)
Black or African American	1917 (20.0%)	1833 (18.6%)	3750 (19.2%)
American Indian/Alaskan Native	40 (0.4%)	32 (0.3%)	72 (0.4%)
Asian	152 (1.6%)	154 (1.6%)	306 (1.6%)
Native Hawaiian or Other Pacific Islander	38 (0.4%)	36 (0.4%)	74 (0.4%)
Mid-East/Arabian	15 (0.2%)	12 (0.1%)	27 (0.1%)
Unknown	215 (2.2%)	163 (1.7%)	378 (1.9%)
Missing	512 (5.1%)	241 (2.4%)	753 (3.7%)
Donor Ethnicity			
Hispanic	1081 (11.3%)	1077 (10.9%)	2158 (11.1%)
Non-Hispanic	8524 (88.7%)	8799 (89.1%)	17323 (88.9%)
Missing	512 (5.1%)	241 (2.4%)	753 (3.7%)
Dialysis prior to transplant			
No	638 (8.6%)	519 (6.8%)	1157 (7.7%)
Yes	6812 (91.4%)	7140 (93.2%)	13952 (92.3%)
Missing	2667 (26.4%)	2458 (24.3%)	5125 (25.3%)

TH-PO730

Long-Term Outcomes of BK Viremia in Kidney Transplant Recipients

Sneha Chandrashekar, Srijan Tandukar, Divyash V. Shah, Roy D. Bloom.
University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

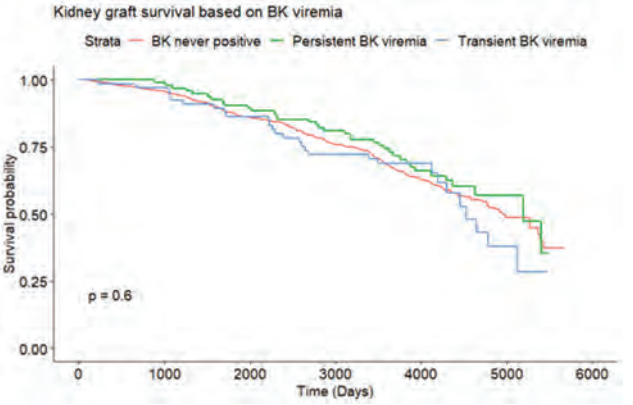
Background: BK viremia (BKV) occurs in 10-30% of kidney transplant (KT) recipients. It has not been shown to adversely impact short and intermediate term graft and patient outcomes, but long term impact is unknown.

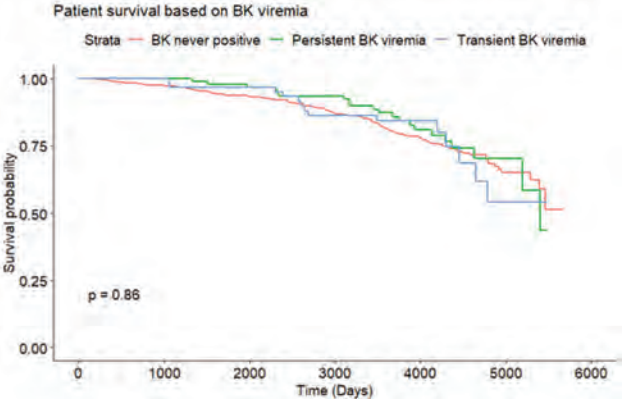
Methods: We included KT alone recipients between 2008 and 2013 without prior history of KT and those who were alive with a functioning graft beyond 90 days of KT. We split the cohort into BK never positive, transient BKV (<140 days) and persistent BKV (≥140 days). Outcomes were graft and patient survival, kidney function, de novo DSA and acute rejection over 10 years of follow up. Survival analysis was performed using Kaplan Meier (KM) analysis.

Results: Among 762 patients, there were 596, 68 and 98 patients in BK never positive, transient BKV and persistent BKV groups respectively. There was no difference in GFR at 10 years (p=0.29), acute rejection (p=0.15) and de novo class I DSA development (p=0.75). De novo class II DSA developed more often in persistent BKV group (p=0.03). On KM analysis, there was no difference in graft (p=0.6) and patient survival (p=0.86).

Conclusions: BKV does not impact long-term outcomes in KT recipients although there is a higher risk of de novo class II DSA development.

Category	BK never positive (N=596)	Transient BK viremia (N=68)	Persistent BK viremia (N=98)	p value
Recipient ethnicity: Black	26 (38.2%)	202 (33.9%)	51 (52%)	0.53
Recipient age	53 (11)	51 (13)	52 (12)	0.004
Recipient gender: Female	35 (51.5%)	300 (50.3%)	43 (43.9%)	0.47
Donor age	37 (15)	39 (15)	39 (14)	0.68
Donor gender: Female	35 (51.5%)	300 (50.3%)	43 (43.9%)	0.47
Peak PRA: Class I	30 (36)	42 (31)	55 (35)	0.1
Peak PRA: Class II	61 (29)	49 (30)	67 (29)	0.18





TH-PO731

Variation in Quality of Life in Frail, Older Transplant Recipients: Mixed-Methods Results from the Kidney Transplantation in Older People (KTOP) Study

Amarpreet K. Thind,[1,2] Lina Johansson,[2] Michelle Willicombe,[1,2] Edwina A. Brown.[2,1] Kidney Transplantation in Older People Study Investigator Group.
[1]Imperial College London Faculty of Medicine, London, United Kingdom; [2]Hammersmith Hospital, London, United Kingdom.

Background: Demand for kidney transplantation (KT) in older people is increasing. Frailty predicts poorer medical outcomes, but little is known about quality of life (QoL) and lived experiences of KT in frail older people.

Methods: KTOP is a 2-year observational study of patients aged >60 years on the KT waitlist. The mixed methods design used questionnaires and semi-structured interviews to explore QoL experiences. Descriptive and mixed-effect analysis was used for the questionnaires and thematic analysis for the interviews. The qualitative data enabled richer understanding of trends identified from questionnaires.

Results: 210 patients were recruited. 68 were vulnerable/frail of whom 35 underwent KT. 21 were recruited into the qualitative study, 10 of whom underwent KT. After KT, vulnerable/frail participants experienced stabilising of physical QoL (figure), with 81.3% reporting improved treatment satisfaction and less illness intrusion (68.8%). However, mental QoL declined (figure) and 58.8% reported worse symptom burden after KT. Qualitative themes revealed KT as physically and emotionally demanding (table). Time free from dialysis was valued yet challenged by unchanging frailty and unexpected burdens of KT. Family/social networks, spiritual beliefs, and positive mindset enabled coping with KT.

Conclusions: Vulnerable/frail older people have mixed QoL changes after KT. Determining expectations of KT and individual personal and socio-cultural resources, are integral to discussions and decision making around KT listing.

Figure. Predicted quality of life changes in vulnerable/frail participants on the waitlist and following transplantation.

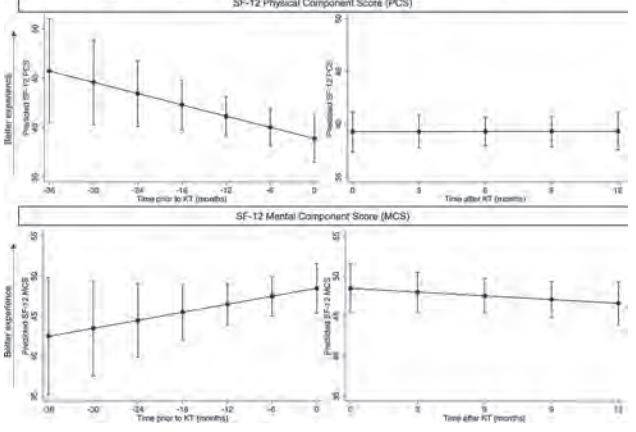


Table 1. Qualitative themes and subthemes encompassing quality of life.

Time point	Themes: subthemes		
Waitlist on dialysis	**Burden of dialysis** • *Physical impact* • *Emotional impact* • *Compromised quality of life*	**Living with frailty** • *Physical impact* • *Emotional impact*	**Personal & socio-cultural resources** • *Coping mindset* • *Faith as a source of resilience* • *Family involvement*
3 months post-transplant	**Burden of transplant procedure** • *Physical impact* • *Emotional impact* • *Returning to normal living* • *Misleading expectations*	**Living with frailty** • *Physical impact* • *Emotional impact* • *Lack of mobility*	
12 months post-transplant	**Living with a transplant** • *Physical impact* • *Emotional/stress impact* • *Compromised quality of life* • *Returning to normal living*	**Living with frailty** • *Physical impact* • *Emotional impact* • *Limited mobility*	

TH-PO732

A Multimodal Aftercare Intervention Improves Outcome after Kidney Transplantation: Results of the KTx360° Aftercare Program Using Claims Data

Lars Pape,[1] Mario Schiffer.[2] The KTx360° Research Group. *[1]Universitatsklinikum Essen, Essen, Germany; [2]Universitatsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany*.

Background: The after-care treatment project KTx360° aimed to reduce graft failure and mortality after kidney transplantation (KTx).

Methods: The study was conducted in the study centers Hannover, Erlangen and Hannoversch Muenden from May 2017 to October 2020 under the trial registration ISRCTN29416382. The program provided a multimodal aftercare program including specialized case management, telemedicine support, psychological and exercise assessments, and interventions. For the analysis of graft failure, which was defined as death, re-transplantation or start of long-term dialysis, we used longitudinal claims data from participating statutory health insurances (SHI) which enabled us to compare participants with controls. To balance covariate distributions between these nonrandomized groups we used propensity score methodology, in particular the inverse probability of treatment weighting (IPTW) approach.

Results: In total, 930 adult participants were recruited at three different transplant centres in Germany, of whom 320 were incident (enrolled within the first year after KTx) and 610 prevalent (enrolled >1 year after KTx) patients. Due to differences in the availability of the claims data, the claims data of 411 participants and 418 controls could be used for the analyses. In the prevalent group we detected a significantly lower risk for graft failure in the study participants compared to the matched controls (HR=0.13, 95% CI=0.04-0.39, p=0.005, n=389), whereas this difference could not be detected in the incident group (HR=0.92, 95% CI=0.54-1.56, p=0.837, n=440).

Conclusions: Our findings suggest that a multimodal and multidisciplinary aftercare intervention can significantly improve outcome after KTx, specifically in patients later after KTx. For evaluation of effects on these outcome parameters in patients enrolled within the first year after transplantation longer observation times are necessary.

Funding: Government Support - Non-U.S.

TH-PO733

Pain Interference and Social Participation among Kidney Transplant Recipients

Maria G. Pucci,[1] Sambea Cochrane,[1] Janine Farragher,[2] Susan J. Bartlett,[3,4] Doris Howell,[5] Madeline Li,[6] John D. Peipert,[7,8] Istvan Mucsi.[1] *[1]Multi-Organ Transplant Program, University Health Network and University of Toronto, Toronto, ON, Canada; [2]Department of Occupational Science and Occupational Therapy, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [3]Centre for Outcomes Research and Evaluation, McGill University Health Centre, Montreal, QC, Canada; [4]Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, QC, Canada; [5]Princess Margaret Cancer Research Institute, Toronto, ON, Canada; [6]Psychosocial Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [7]Department of Medical Social Sciences, Northwestern University, Feinberg School of Medicine, Chicago, IL; [8]Northwestern University Transplant Outcomes Research Collaborative, Comprehensive Transplant Center, Feinberg School of Medicine, Chicago, IL.*

Background: Bodily pain can be linked to poor quality of life (QOL) and limited social participation. Social participation, defined as the ability to perform one's usual social roles and activities, is a patient-valued QOL domain often restricted in kidney transplant recipients (KTRs). Our objective was to explore the association between pain interference (PI) and social participation (SP) among KTRs.

Methods: We analyzed cross-sectional data from a convenience sample of adult KTRs at Toronto General Hospital. PI and SP were assessed using Patient-Reported Outcome Measurement Information System (PROMIS) computer adaptive testing (CAT). We defined moderate/severe PI as a T-score > 60 and low SP as a T-score < 45. We used Spearman correlation analysis to explore the relationship between SP and PI and employed multivariable linear and logistic regression to further examine the association, after adjusting for covariables (age, sex, marital status, racialized status, comorbidity, hemoglobin, albumin, eGFR, months since transplant, depression, and fatigue). Multiple imputation was used to address missing data.

Results: The mean (SD) age of the 282 participants was 52 (14) years, 62% were male, 59% were white. The median (IQR) months since transplant was 37 (120). The mean (SD) SP and PI scores were 52 (9) and 50 (10), respectively. A moderate negative correlation existed between SP and PI (rho= -0.55, p<0.001). This association remained significant in multivariable linear regression analysis after adjusting for covariables (ß= -.253, p<0.001; 95% CI: -.340 – -.165). Participants with moderate/severe PI were more likely to report low SP compared to those with no or mild PI in multivariable logistic regression analysis after adjusting for covariables (OR= 5.16, p= 0.001; 95% CI: 1.93 – 13.8).

Conclusions: KTRs experiencing significant PI reported more limited SP than those with low PI. Future studies should assess the impact of pain and pain management on social health following transplantation.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO734

Symptom Recovery after Kidney Transplantation

Ana M. Samudio,[1] Crystal Huang,[1] Katalin Groe,[1] Nolan J. Marblestone,[1] Susan J. Bartlett,[2,3] Doris Howell,[4] Madeline Li,[4] John D. Peipert,[5,6] Istvan Mucsi.[1] *[1]University Health Network, Toronto, ON, Canada; [2]McGill University Health Centre, Montreal, QC, Canada; [3]McGill University, Montreal, QC, Canada; [4]Princess Margaret Hospital Cancer Centre, Toronto, ON, Canada; [5]Northwestern University Department of Medical Social Sciences, Chicago, IL; [6]Northwestern University Comprehensive Transplant Center, Chicago, IL.*

Background: We report physical and psychological symptom severity and frequency among incident kidney transplant (KT) recipients using Patient Reported Outcomes Measurement Information System (PROMIS) computer adaptive tests (CAT).

Methods: Longitudinal convenience sample of incident (<30 days post-transplant) adult KT recipients, recruited 2021-2024. Participants completed PROMIS CATs at baseline, biweekly for 3 months, and monthly thereafter. PROMIS T are standardized to a mean of 50 and standard deviation (SD) of 10, corresponding to the U.S. general population mean. Scores > 60 or <= 40 indicate moderate-severe symptom severity or function impairment, respectively.

Results: Of 133 participants, 84(63%) were male, 69(58%) were white, 43(35%) had diabetes, and mean(SD) age was 51(15) years. Median (interquartile range) time after transplant at enrolment was 5(3,8) days. At baseline, all domain T-scores were worse than the U.S. population mean and improved significantly by week 12. At week 12, domain T-scores neared the U.S. population mean (Table 1). Mean T-scores at week 24 were similar to week 12, except physical function and pain interference, which showed significant further improvement. At week 0, the proportion of patients scoring moderate-severe symptom severity or function impairment: fatigue 36%, sleep disturbance 32%, physical function 52%, pain interference 48%, anxiety 36%, and depression 18%. At week 12, the proportion of patients scoring moderate-severe symptom severity or

function impairment: fatigue 7%, sleep disturbance 14%, physical function 12%, pain interference 10%, anxiety 11%, and depression 10%. All proportions were significantly lower at week 12 vs week 0, except for depression.

Conclusions: A majority of KT recipients will experience moderate-severe symptom severity or function impairment immediately post-transplant. By week 12, most improve significantly and near levels seen in the U.S. general population. Findings highlight need for systematic symptom screening and support early after kidney transplant.

Funding: Private Foundation Support, Government Support - Non-U.S.

	Mean T-scores (SD) [p-value]	
Assessment Week (n)	0	12
PROMIS Domain		
Fatigue	56 (9)	46 (10)
	<0.001	
Sleep Disturbance	56 (10)	49 (10)
	<0.001	
Physical Function	40(10)	47(6)
	<0.001	
Pain Interference	58(10)	49(10)
	<0.001	
Anxiety	56(9)	47(10)
	<0.001	
Depression	51(11)	45(10)
	0.005	

Table 1. PROMIS domain mean T-scores (SD) [p-value] for KT recipients at weeks 0 and 12.

TH-PO735

Inflammatory Markers in Patients with ESKD on Maintenance Hemodialysis, Hemodiafiltration (HDF), and Early Postkidney Transplant Patients and Their Relation to Quality of Life (SGA Score)

Magdy ElSharkawy, Hesham M. Elsayed, Aber H. Baki, Abdelrahman A. Elbraky, Mohamed A. Abd El-Mohsen, Meryhan O. El-Rayes. Dept of Internal Medicine and Nephrology. *Ain Shams University Faculty of Medicine, Cairo, Egypt*.

Background: Patients with end-stage renal disease (ESRD) needing renal replacement therapy is estimated about 7 million worldwide. Hemodiafiltration (HDF) yields an increased overall solute clearance compared with hemodialysis (HD). Kidney transplantation offers an improved quality of life in comparison to dialysis. In ESRD, inflammation has become recognized. High-sensitivity C-reactive protein (Hs-CRP) is a biomarker of inflammation which plays a key role in atherosclerosis.A growing amount of information is emerging about MicroRNAs in the regulation of renal fibrosis. We studied inflammatory markers and quality of life (QOL) in different renal replacement modalities.

Methods: A cross-sectional study was conducted on 75 patients;25 patients with ESRD on HD,25 patients with ESRD on HDF and 25 early post-renal transplant patients. Moreover, 10 healthy controls were added to get to the normal gene expression of the studied MicroRNA 'serum miR-223'.Inflammatory biomarkers (Hs-CRP, serum miR-223) were withdrawn and subjective global assessment (SGA) was applied.

Results: Hs-CRP was significantly higher in HD patients; median 14.2 (7.4 - 16.9 mg/L) than HDF; median 6.3 (4.1 - 14.3 mg/L) and post renal transplant patients median 5.2 (3.3 - 8.6 mg/L) **(P= 0.003)**. Serum miR-223 showed down-regulation in dialysis patients; HD and HDF. This down-regulation improved in post renal transplant patients (approaching readings of the healthy control group) with highly significant differences between dialysis and post-transplant groups **(P= 0.000)**. Post renal transplant patients had better quality of life;SGA score A (normal)= 100%, in comparison with dialysis groups of patients. Moreover, when comparing SGA in both dialysis modalities, HDF group of patients had better quality of life as 76% of them had normal nutritional status (SGA score A) in comparison with the HD group who had only 32% patients with SGA score A (normal) with highly significant statistical differences between the 3 groups **(P= 0.000).**

Conclusions: Kidney transplantation offers improved quality of life for ESRD patients in comparison to dialysis. Moreover, for patients on dialysis, HDF modality demonstrates a beneficial effect on QOL in comparison to HD.

TH-PO736

Effect of a Lifestyle Intervention on Sleep and Fatigue in Kidney Transplant Recipients: A Predefined Analysis of the Active Care after Transplantation (ACT) Randomized Clinical Trial

Tim J. Knobbe,[1,2] Daan Kremer,[1,2] Frederike J. Bemelman,[3] Stefan P. Berger,[1,2] Gerjan Navis,[1,2] Stephan J. Bakker,[1,2] Eva Corpeleijn.[1,2] *[1]Rijksuniversiteit Groningen, Groningen, Netherlands; [2]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [3]Amsterdam Universitair Medische Centra, Amsterdam, Netherlands*.

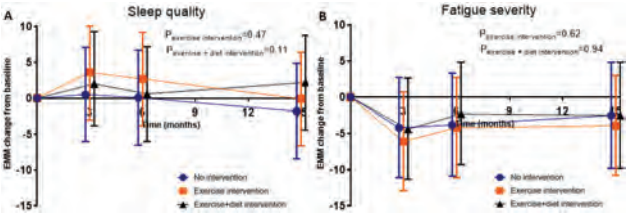
Background: Improving lifestyle may be a promising target to improve sleep quality and reduce fatigue among kidney transplant recipients (KTR). We assessed whether a lifestyle intervention, proven to enhance physical functioning, improves sleep and reduces fatigue among KTR.

Methods: We performed a predefined analysis of the Dutch multicenter randomized controlled Active Care after Transplantation (ACT) study (NCT01047410). KTR were randomized into exercise intervention, exercise + diet intervention, or usual care. Exercise intervention included three months supervised exercise with 15 months lifestyle coaching. For the exercise + diet group, this was supplemented with 15 months dietary counselling. Sleep and fatigue were assessed by KDQOL-SF and CIS20R questionnaires. Multilevel general linear mixed model analyses were performed.

Results: We included 146 KTR (36% female, mean age 54±13 years); 57 received exercise intervention, 45 exercise + diet intervention and 44 usual care. At 15 months, both arms showed no statistically significant effect on sleep quality (**Figure 1a**), with a mean difference in estimated marginal means (EMM) from baseline, compared with control, of +1.7 (95%CI -2.8, +6.2) for the exercise intervention group (P=0.47) and +4.0 (95%CI -0.9, +8.8) for the exercise + diet group (P=0.11). Regarding fatigue severity, no statistically significant effect was observed at 15-months (**Figure 1b**), with a mean difference in EMM from baseline, compared to the control, of -1.4 (95%CI -7.0, +4.2) for the exercise intervention group (P=0.62) and -0.2 (95%CI -6.2, +5.8) for the exercise + diet intervention group (P=0.94).

Conclusions: Although the lifestyle intervention had previously been shown to improve physical functioning, there was neither a significant treatment effect on sleep nor on fatigue. Improving lifestyle – important as it may be – may not be a panacea for KTR. Addressing sleep and fatigue in this population requires a specific, dedicated approach.

Funding: Clinical Revenue Support



TH-PO737

Primary Care Utilization by Kidney Transplant Recipients

Long Qian,[1] Sophia Faulkner,[1] Yu Yamamoto,[1] Sarthak Virmani,[2] Francis P. Wilson,[1] Sherry Mansour.[1] *[1]Yale University, New Haven, CT; [2]University of Virginia, Charlottesville, VA*.

Background: While most kidney transplant recipients (KTRs) receive consistent outpatient care from nephrologists, the extent to which they access primary care providers (PCPs) is unknown, as is whether receiving primary care affects clinical outcomes.

Methods: We used the electronic medical record data of Yale New Haven Hospital from 2016 to 2020 to investigate patterns of PCP exposure among KTRs and factors associated with PCP exposure. We used a multivariable cox regression analysis adjusting for demographics and clinical factors to assess the association between seeing a PCP and all-cause mortality.

Results: A total of 844 KTRs were included with a median follow-up time of 3.16 (IQR:1.55, 4.84) years. Median age was 54 (IQR: 42, 63) years; 311 (37%) were female; 244 (29%) identified as Black and 125 (15%) identified as Hispanic. 33% of KTRs had at least one PCP visit after transplantation during our study period but within 1 year after transplantation, only 15% saw a PCP. Those seen by a PCP were slightly older [56 (47, 64) vs. 53 (42, 63) years, p=0.08], and more likely to be female (61 (47%) vs. 250 (35%), p=0.01] and diabetic [75 (57%) vs. 56(43%), p=0.01]. Additionally, being female and diabetic were independently associated with, respectively, a 66% and 69% higher odds of seeing a PCP (aOR: 1.66 (95%CI:1.13-2.42 and aOR:1.69 (95%CI: 1.15-2.49)]. During our study follow up, 98 (12%) of KTRs died. Seeing a PCP within the first year was not significantly associated with all-cause mortality (aHR 0.74 (95%CI: 0.17-3.19).

Conclusions: Only a small proportion of KTRs are seen by a PCP post-transplant. There were certain factors associated with higher odds of PCP exposure, but overall PCP exposure was not associated with all-cause mortality. Further investigations are needed to evaluate if PCP exposure may improve outcomes in KTRs.

TH-PO738

Impact of Diabetes on Physical Function Recovery following Kidney Transplantation

Jad Fadlallah, Eliana Barbuzzi, Fabiha Razzak, Caroline Carruthers, Christina Commisso, Nishat F. Syeda, Nathaniel Edwards, Heather Ford, Istvan Mucsi. Kidney Health Education and Research Group. *University Health Network, Toronto, ON, Canada*.

Background: Diabetes mellitus (DM) can impair post-operative recovery. We assess the association of DM with recovery of physical function over time among incident kidney transplant (KT) recipients using the Patient Reported Outcome Measurement Information System (PROMIS) physical function computer adaptive test (PF-CAT).

Methods: Longitudinal convenience sample of incident (<30 days post-transplant) adult KT recipients recruited in 2021-2024. Demographic information was self-reported, clinical data extracted from health records. Participants completed PROMIS PF-CAT at baseline, biweekly for 3 months, and then every four weeks up to 6 months on an electronic data capture platform. PROMIS PF-CAT is scored on a T-score metric (20-80, higher scores=better physical function). Linear mixed-effect models with random intercepts were used to compare PF recovery between DM and non-DM (NDM) KT recipients. The model included the interaction between time and diabetes status, representing the average difference in PF over time, adjusting for age, sex, education, socioeconomic status, BMI and significant anxiety or depression symptoms at baseline. Individual clinically significant improvement in PF was assessed in a time-to-event analysis, with the use of log-rank tests and Cox proportional-hazards model adjusting for mentioned covariates. The primary event was defined as reaching a T-score ≥50.

Results: Of 110 participants, 71(65%) were male, 62(56%) were white, 36(33%) had DM, mean(SD) age was 51(15) years and median[IQR] time since transplantation at enrollment was 4[3; 7] days. DM had significantly lower PROMIS PF over time (ref:NDM, coeff, -0.19; 95%CI, -0.33 to -0.05). At baseline, mean(SD) scores in DM(n=36) vs NDM(n=74) were 39(10) vs 39(8). At 12w, scores in DM(n=11) vs NDM(n=33) were 45(6) vs 47(6). At 24w, scores in DM(n=11) vs NDM(n=30) were 48(5) vs 51(6). The cumulative incidence of the event was 25 in NDM vs 5 in DM, p=0.02. This association remained significant after adjusting for covariates (ref: NDM, HR, 0.33; 95%CI 0.11 to 0.95, p=0.04).

Conclusions: KT recipients with DM demonstrated less significant improvements in PF over 6 months compared to NDM. KT with DM may need extra support for their PF, such as prehabilitation or post-transplant rehabilitation.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO739

Diabetes Distress Is High and Negatively Affects Diabetes Control in Kidney Transplant Recipients (KTR): A Prospective Study

Aleksandra Kukla, Sukhdeep S. Sahi, Aleksandar Denic, Corey Kurek, Ravinder Jeet Kaur, Afsana Ansari Shaik, Byron H. Smith, Tayyab S. Diwan, Mark D. Stegall, Yogish C. Kudva. *Mayo Clinic Minnesota, Rochester, MN*.

Background: Impact of diabetes distress (DDS) on type 2 diabetes (T2D) control in KTR is unknown. Validated T2D DDS questionnaire includes emotional, physician-related, management related, and interpersonal distress components (17 points). Total scores>2 and ≥3 in each component indicate moderate and severe DDS, respectively.

Methods: We prospectively assessed DDS in 21 KTR at mean time of 2.1 (1.5) y post KT. Glucose control was assessed by Continuous glucose monitoring (CGM) metrics (Dexcom G6) worn for ten days and HbA1C.

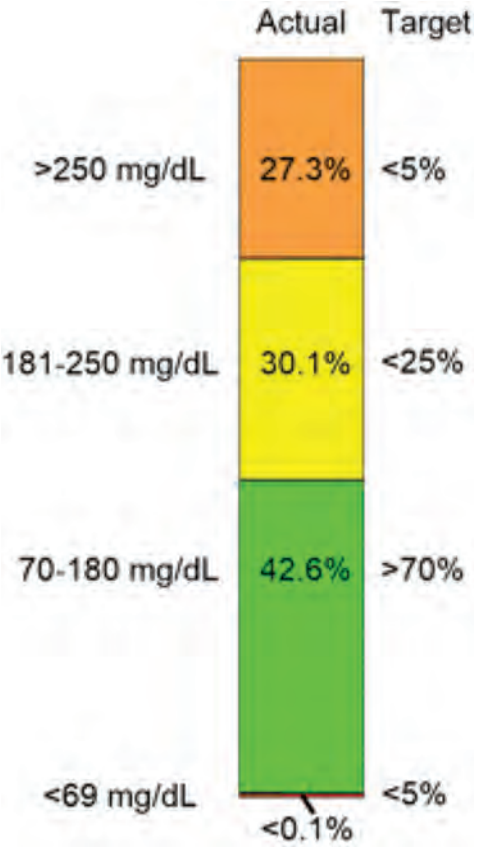
Results: Table 1 depicts demographics and Figure 1 glucose metrics. Treatment regimens: Median DDS scores were 7 (IQR 5,13), 4 (IQR4,4), 8 (IQR 5,11), and 3 (IQR 3,5) for emotional, physician, treatment regimen, and interpersonal subscale, respectively. CGM metrics showed mean time in range (TIR; goal>70%) of 42.6 (25.2) %, and mean time in hyperglycemia of 57.4 (25.2) %. Treatment distress correlated with higher mean glucose (rs=0.44; p=0.04) and lower TIR (rs=-0.45; p=0.04) and higher HbA1c (latter in pts with no anemia) (rs=0.62; p=0.003). No correlation was found between HbA1c and CGM metrics.

Conclusions: KTR with T2D experience high DDS, which negatively impact glucose control. Efforts should be focused on reducing treatment burden.

Funding: Commercial Support - DEXCOM, Private Foundation Support

Demographics

Mean age (yrs)	61.7 (9.1)
BMI(Kg/m2)	32.4 (3.9)
Mean glucose (mg/dL)*	212 (64.4)
Hb (%)	7.8 (1.4)
Normal Hb (N)	16 (69.5%)
On Insulin (N)	8 (34.7%)
On Insulin + other anti-hyperglycemic (N)	13 (56.5%)
On non-insulin (N)	2 (8.7%)



TH-PO740

SGLT2 Inhibitors in Kidney Transplant Recipients: A Pharmacist-Led Clinic in a Predominantly Hispanic and American Indian Population

Raja Ravender, Ngoc-Yen Pham, Namita Singh, Pablo Garcia, Christos Argyropoulos, Pooja P. Singh. *University of New Mexico Health Sciences Center, Albuquerque, NM*.

Background: SGLT2 inhibitors have been shown to help modify disease progression for diabetes and CKD. Kidney transplant recipients (KTRs) were excluded from major RCTs utilizing these drugs. Here we describe kidney outcomes and adverse events among KT recipients in New Mexico (NM).

Methods: This is a single-center retrospective chart review of KTRs in NM who were started on SGLT2 inhibitors from May 2019 through June 2023, and followed for one year after initiation of therapy. Diabetes management was done primarily by a clinician pharmacist-run clinic. The primary objective reviewed adverse events in immunocompromised people and the secondary objectives reviewed eGFR, proteinuria, HCT, and HgA1C.

Results: We included 49 KTRs in this cohort, 24% American Indian, 16.3% non-Hispanic White, 46.9% Hispanic White, 4% Asian, 2% Black, 2% Native Hawaiian, and 4.8% unreported. 81.6% of patients were started on Empagliflozin, with 84.8% started on SGLT2 inhibitors for diabetes management and 27.1% for other causes. In one year 8.9% of patients had a urinary tract infection (UTI), with 4% having two UTIs and one requiring IV antibiotics to treat the UTI twice. One patient had a metatarsal amputation and the SGLT2 inhibitor was discontinued. Only 6% of patients were taken off the medications due to either adverse events or other reasons. No patients experienced ketoacidosis or a thrombotic event such as DVT. After adjusting for age, gender, and ethnicity there was a reduction of UACR (6mg/g per month) and UPCR (15 mg/g) per month of therapy. At 12 months there was an estimated 35% reduction in proteinuria with no significant change in the eGFR or HCT.

Conclusions: SGLT2 inhibitors are a safe therapy among immunocompromised transplant recipients. A few patients in our study were taken off therapy due to an adverse event. The reduction in proteinuria was similar to what was seen in major RCTs. Using an interdisciplinary approach with the help of clinical pharmacists, quality of care delivered is greatly improved in this vulnerable population of patients who require comprehensive care due to their multiple comorbidities.

	EGFR	HCT	UPCR
Change in the lab per month of therapy	0.15 +/- 0.16 ml/min/1.73m2/month	0.08 +/- 0.18 %/month	-14.6 +/- 5.8 mg/mg/month
P Value	0.38	0.66	0.0127

TH-PO741

A Prospective Observational Study to Assess the Efficacy of a SGLT2 Inhibitor (Dapagliflozin) in Kidney Allograft Recipients with Diabetes Mellitus

Avishek Naskar. *Kolkata Kidney Institute, Kolkata, India.*

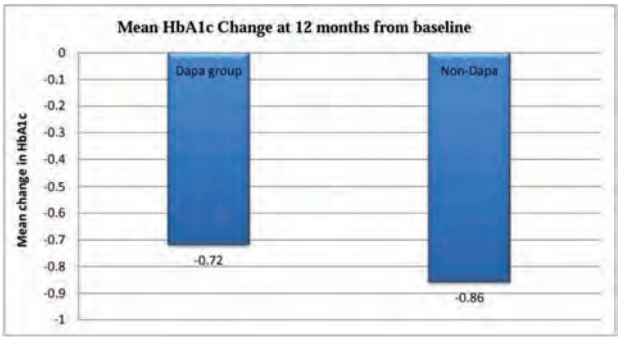
Background: Cardiovascular disease is a major cause of graft loss and mortality in renal transplant patients, who may be benefited from SGLT2 inhibitors. But, they are not routinely recommended and few studies of their use in renal transplant patients have been published.

Methods: In this 12 months study, 100 renal transplant patients with both pre-existing and post transplant diabetes mellitus, visiting out patient department, were included. Half of them received dapagliflozin 10mg along with their ongoing anti-diabetic medicines and the others continued their already ongoing medicines, with dose adjustment according to HbA1c. Fasting and post-prandial blood glucose, glycated hemoglobin (HbA1c) and creatinine and urine for routine examination and albumin-creatinine ratio (ACR) were tested at baseline and at 3, 6 and 12 months during routine follow-up visit.

Results: There was no significant statistical difference in the mean reduction of HbA1c (0.72% in dapa group, 0.86% in non-dapa group), as well as mean reduction of urine ACR between the 2 groups. No significant change in eGFR was found at 12 months. There was no episode of acute kidney injury observed, other than in patients requiring hospitalization. The frequency of urinary tract infection (UTI) (12% in both the groups) as well as genital infections were not statistically different (8% in dapa group, 6% in non-dapa group). Dapagliflozin was discontinued in 4% patients with UTI, for recurrence, but none in those with genital infections. No patient suffered rejection, ketoacidosis or hypotension.

Conclusions: Dapagliflozin lead to a modest reduction of HbA1c, but had less potent anti-proteinuric action. It was not associated with significant allograft dysfunction, and had similar frequency of adverse effects like that of other anti-diabetic medications.

Funding: Clinical Revenue Support



TH-PO742

SGLT2 Inhibitors Reduce the Rate of Decline in the Estimated Glomerular Filtration Rate of Kidney Transplant Patients with Recurrent or De Novo Glomerulonephritis

Hyuk yong Kwon, Sung Hyun Son, Jin M. Kong. *Nephrology, Department of Internal medicine, BHS-Hanseo Hospital, Busan, Republic of Korea.*

Background: Although recurrent or de novo glomerulonephritis (GN) after kidney transplantation (KT) is one of the main causes of renal allograft failure, no effective treatment is currently available. Recent evidences indicate the beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in delaying the progression of a broad range of chronic kidney diseases, including GN.

Methods: Twenty-seven patients with biopsy-proven GN of the renal allograft were treated with SGLT2i at a median of 16.3±8.4 years post-transplant and were prospectively followed. IgA nephropathy was the most common (n=18), followed by focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease (n=2 each), and others (n=3). The baseline mean eGFR was 57±26 mL/min/1.73 m^2. The baseline mean urine protein-creatinine ratio (U-PCR) was 689±536 mg/g. The primary outcomes were the changes in proteinuria from baseline to 6 and 12 months, and the change in the eGFR slope before (-12 to 0 months) and after (3 to 15 months) the initiation of SGLT2i. The secondary outcomes were changes in body weight (BW), systolic blood pressure (SBP), and doses of antihypertensives. Adverse reactions were closely monitored.

Results: The post-SGLT2i follow-up period was 23.9 (median) ±15.0 months. The eGFR slope improved from -5.67±7.77 ml/min/1.73 m^2/year [before SGLT2i] to -0.38±17.19 [after SGLT2i] (P=0.006, paired t-test). The U-PCR did not change significantly. BW decreased significantly at 3 months and was maintained thereafter. SBP did not change significantly, but the number of antihypertensives decreased. There were no cases of acute pyelonephritis, acute kidney injury, or other adverse reactions attributable to SGLT2i.

Conclusions: SGLT2i slowed the decline in eGFR in patients with GN of the renal allograft and was well-tolerated. Our preliminary results warrant confirmation by further studies with a larger number of patients and prolonged follow-up.

TH-PO743

Benefits of Glucagon-Like Peptide 1 Receptor Agonists in Kidney Transplant Recipients

Oscar A. Garcia Valencia,[1] Sukhdeep S. Sahi,[1] Jie Na_,[1] Byron H. Smith,[1] Pooja Budhiraja,[2] Tayyab S. Diwan,[1] Naim S. Issa,[1] Aleksandar Denic,[1] Ahmed Abdelrheem,[1] Hani Wadei,[3] Yogish C. Kudva,[1] Aleksandra Kukla.[1]
[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic Arizona, Scottsdale, AZ; [3]Mayo Clinic in Florida, Jacksonville, FL.

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) showed improved outcomes in patients with type 2 diabetes (DM2), however limited studies exist in kidney transplant recipients (KTR).

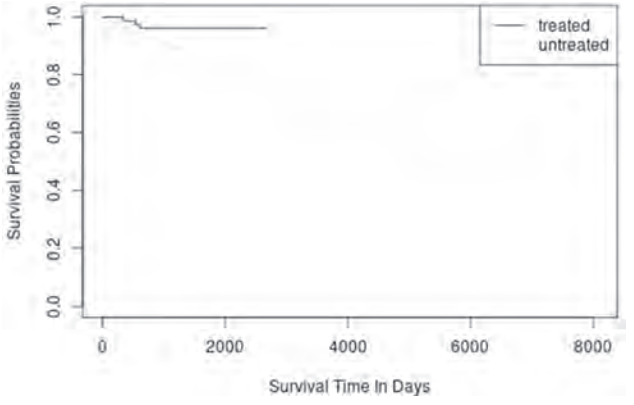
Methods: We retrospectively studied patient and allograft outcomes in KTR treated with GLP-1 RA for at least 12 months vs a reference group (DM2 with not treated with GLP-1 RA).

Results: Demographics of both cohorts are presented in Table 1. The mean (SD) follow-up for GLP-1 RA and reference group was 6.9 (4.4) and 6.8 (4.2) years, respectively. The use of GLP-1 RA was associated with significantly better survival (p=0.03); Fig. 1, improved mean urine albumin/creatinine ratio (decreased by 31 mg/g/year vs increased by 20.47 mg/g/year; p <.001), eGFR (increased by 0.52 mL/min/BSA/y vs decreased by 1.56 mL/min/BSA/y, p= 0.044) and triglycerides (decreased by 2.17 mg/dl/y and decreased by 2.3 mg/dl/y; p=.04) in GLP1RA treated patients versus not, respectively.

Conclusions: GLP1RA may potentially improve survival and may positively impact kidney endpoints. Limitations include the retrospective study design and potential bias related to patient selection for GLP-1 RA therapy. Prospective studies with patient survival and renal endpoints are needed.

Table 1: Baseline characteristics for treatment and reference group

Baseline Characteristics	GLP-1 RA treatment group (n=77)	Reference group (N=2094)	p-value
Female sex, N (%)	30 (39)	711 (34)	0.39
Age at transplant, years	57.9 (9.5)	60.8 (9.5)	0.015
BMI at transplant, kg/m2/BSA	32.1 (4.3)	30.1 (5.1)	0.002
Race, N (%)			0.02
Black	18 (23.4)	332 (15.9)	
White	42 (54.5)	924 (44.1)	
American Indian/Alaskan Native	2 (2.6)	175 (8.4)	
Asian	3 (3.9)	98 (4.7)	
Other	12 (15.6)	565 (27)	
Age at GLP-1 RA start, years	62.0 (9.4)	NA	NA
Baseline MACE events			NA
Heart Failure, N (%)	22 (28.5)	NA	
Myocardial Infarction, N (%)	7 (9.1)	NA	
Stroke, N (%)	7 (9.1)	NA	
Time between transplant and GLP-1 RA start, years	4.1 (4.3)	NA	NA
Serum creatinine at transplant, years	1.4 (0.4)	1.5 (0.7)	0.21
eGFR at transplant, mL/min/1.73 m^2	41.9 (14.4)	40.9 (15.2)	0.59
Albumin/creatinine ratio at transplant, mg/gm,	187.6 (226.2)	93.8 (161.4)	0.03
Hba1c at transplant, %	7.2 (1.5)	7.0 (1.4)	0.56
Triglycerides at transplant, mg/dl	165.6 (118.8)	171.6 (116.6)	0.71



TH-PO744

Evaluating the Impact of Multiple Kidney Retransplants on Post-transplant Outcomes: An Analysis of the OPTN/UNOS Database

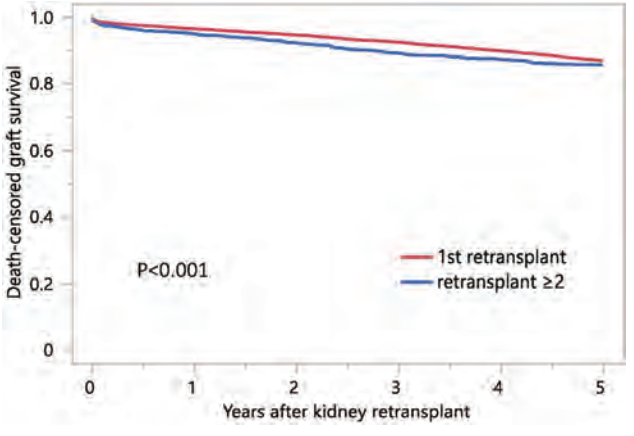
Oscar A. Garcia Valencia,[1] Charat Thongprayoon,[1] Jing Miao,[1] Iasmina Craici,[1] Napat Leeaphorn,[2] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic in Florida, Jacksonville, FL.*

Background: Kidney transplantation offers a valuable therapeutic option for patients esperiencing graft failure after their initial transplant. There is a increasing trend of patients undergoing multiple retransplants however the impact of these subsequent procedures remains understudied. This study evaluated the assocaition between the number of kidney retransplants and patient outcomes.

Methods: Using the OPTN/UNOS database, we identified all kidney-only retransplants in the United States from 2010 to 2019. We categorized them into two groups: those with a first kidney retransplant and those with two or more. The study analyzed the association between multiple retransplants and outcomes such as death-censored graft failure, patient mortality, and acute rejection through Cox proportional hazard and logistic regression analyses.

Results: Of the 17,433 recipients of kidney retransplants included, 15,821 (91%) received one retransplant, while 1,612 (9%) underwent two or more. The latter group tended to be younger, more frequently white, had higher PRA levels, used public insurance, and attained higher education levels. However, they had a lower prevalence of DM and total HLA mismatch compared to individuals with a single kidney retransplant. Multivariate analysis revealed that multiple retransplants significantly increased the risk of death-censored graft failure and acute rejection, albeit it did not significantly impact patient mortality.

Conclusions: Patients undergoing multiple kidney retransplants face a higher risk of graft failure and rejection compared to those with a single retransplant. These findings highlight the need for tailored management and surveillance strategies to improve outcomes for patients receiving multiple kidney retransplants.



TH-PO745

Treatment with Cinacalcet Post Kidney Transplant Does Not Confer Clinically Meaningful PTH Suppression Compared with No Treatment

Emily K. O'Leary, Erin Biggs, Michele Mccloskey, Jorge C. Garces, Juan Carlos Q. Velez, Terrance J. Wickman. *Ochsner Health, New Orleans, LA.*

Background: Cinacalcet is a calcimimetic used to treat secondary hyperparathyroidism (SHP) of end-stage kidney disease (ESKD) that fails to achieve adequate parathyroid hormone (PTH) suppression with calcitriol or other vitamin D analogs. However, their role to control persistent PTH after kidney lacks supporting evidence. We hypothesized that the use of calcimimetics provides no meaningful difference in PTH level after kidney transplant when compared with calcitriol or other vitamin D analogs or no therapy at all.

Methods: A retrospective chart review was performed searching for adults with a diagnosis of SHP who received a kidney transplant at Ochsner Health between 2018 and 2022. SHP was defined by ICD code. We excluded those with parathyroidectomy, dual organ transplant or missing data. We compared 6-month post-transplant PTH amongst patients being treated with cinacalcet, cinacalcet and calcitriol, calcitriol, or no treatment, by linear regression.

Results: 226 patients were included, mean age was 51 (20-78), mean BMI was 30 (19-47), 43% women, and 56% Black. 93% had hypertension, 39% had diabetes. All treatment groups showed a statistically significant decrease in PTH 6 months after transplant, as expected. Mean post-transplant PTH for those on cinacalcet, cinacalcet and calcitriol, calcitriol, and no treatment were 272, 208, 320, and 277 pg/mL, respectively. Adjusting for age, pre-transplant PTH, type of donor, delayed graft function, and dialysis before transplant, we observed no difference in mean PTH after transplant in patients treated with cinacalcet alone compared to the no treatment group (p=0.21); however, we observed a lower mean post-transplant PTH with those treated with calcitriol alone (p=0.0007).

Conclusions: Use of cinacalcet after kidney transplant was not associated with a clinically significant difference in PTH suppression when compared to cinacalcet and calcitriol, calcitriol, or no treatment. Our findings suggest that calcimimetics may not be beneficial for the treatment of SHP after kidney transplant.

TH-PO746

Nonadherence to Immunosuppressive Medications in Kidney Transplant Recipients: A Systematic Scoping Review

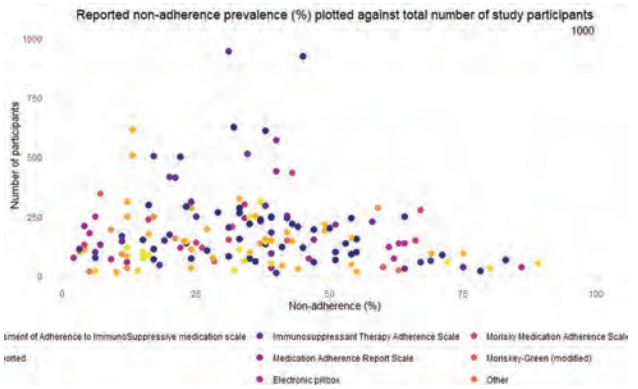
Michael Corr,[1] Andrew I. Walker,[2] Alexander P. Maxwell,[1] Gareth J. McKay.[1] *[1]Queen's University Belfast, Belfast, United Kingdom; [2]Northern Ireland Foundation Programme, Belfast, United Kingdom.*

Background: Rejection and graft failure remain common in transplant recipients. Non-adherence to immunosuppressive medications is considered a major contributor to reduced long-term graft survival, particularly in younger people. Improved clinical practice based on adherence studies has been minimal. Our aim was to increase understanding of non-adherence to immunosuppressive medications following kidney transplantation and identify research gaps to inform future studies.

Methods: Joanna Briggs' Institute Methodology used. MedlineALL, Embase, Web of Science Core Collection and Scopus databases searched January 2000 through December 2023. Abstract and full text review undertaken independently by two reviewers. Data collated using a pre-designed extraction tool.

Results: 359 articles met the inclusion criteria. Non-adherence was commonly defined using self-reported questionnaires. Prevalence of non-adherence varied widely. There was little correlation between method of measurement and reported rates of non-adherence (Figure 1). Despite younger age being identified as a risk factor for non-adherence, reported prevalence did not differ significantly in studies reporting prevalence in children, adolescents, or young adults vs. older adults (33.5% vs. 34.0%). Interventional studies to improve adherence are heterogenous, often report small effects and limited by the lack of gold-standard methods to measure adherence.

Conclusions: Despite increasing research in the field, evidence to support measures to improve non-adherence in kidney transplant recipients remains weak. Future studies should consider a common definition of non-adherence to enable robust comparisons to be made e.g. using the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS). We recommend validation of existing tools and interventions in larger cohorts rather than further single-centre studies to improve the evidence-base to address this important clinical problem.



TH-PO747

Using Artificial Intelligence to Improve Tacrolimus Dosing in Kidney Transplant Patients

Sean A. Perez,[1] Mingjia Huo,[4] Linda Awdishu,[3] Hayden H. Pour,[2] Janice Kerr,[3] Pengtao Xie,[4] Adnan A. Khan,[2] Kristin Mekeel,[1] Shamim Nemati.[2]
[1]University of California San Diego Department of Surgery, La Jolla, CA; [2]University of California San Diego Department of Medicine, La Jolla, CA; [3]University of California San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences, San Diego, CA; [4]University of California San Diego Department of Electrical and Computer Engineering, La Jolla, CA.

Background: Tacrolimus (FK) is a mainstay of post-transplant immunosuppression with a narrow therapeutic window. Achieving therapeutic FK trough concentrations in the immediate post-operative period is challenging due to changing perioperative physiology and pharmacokinetics resulting in variable day to day exposures. We developed a machine learning (ML) model to predict the next day FK concentration and guide dosing to prevent persistent over- or under-dosing.

Methods: Retrospective data was extracted for adult kidney and/or liver transplant recipients from January 2016 to December 2023. Patient demographics, vital signs, laboratory values, diet, and medications were utilized to build the model. Data was randomly split 70%/15%/15% for training, validation, and test sets. XGBoost, traditional Recurrent Neural Network, and Long Short-Term Memory models were evaluated for best fit given the complexity of relationships and time dependency.

Results: 1126 (706 kidney, 420 liver) transplant recipients were included in the study with a median (IQR) age of 58 (47-65) years, 51% white race, with FK daily dose of 4.0 (1.5 – 8.0) mg and concentration of 8.38 (5.9-10.3) ng/mL. The XGBoost model achieved a Mean Absolute Error (MAE) of 1.916 when predicting the next day's FK concentrations. Figure 1 depicts the model's ability to predict underdosage or overdosage—using a target concentration of 10-13 ng/mL, via 3-class classification task. Overall, the model achieved accuracy of 0.73 with average F1-score of 0.58, F1-score 0.85 for predicting underdosing, and area under the curve of 0.67.

Conclusions: Machine learning accurately predicts next day FK concentrations which may improve precision dosing. Future directions include clinical implementation and evaluation and development of decision support for dosing recommendations.

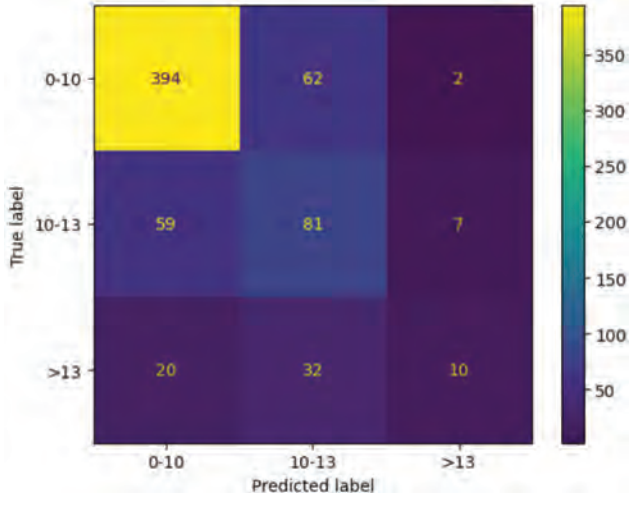


Figure 1. XGBoost 3-class classification task.

TH-PO748

Real-World Data of Tacrolimus Drug Levels in Ultra-long Kidney Transplant Survivors

Chung Hee Baek, Hyosang Kim. *Asan Medical Center, Songpa-gu, Seoul, Republic of Korea.*

Background: Maintaining tacrolimus trough drug levels of more than 5ng/ml decreases the risk of de novo donor-specific antibodies. However, for ultra-long kidney transplant survivors, the evidence of appropriate tacrolimus levels is rare. Therefore, we investigated real-world data on tacrolimus drug levels of ultra-long kidney transplant survivors in a high-volume medical center.

Methods: Our center started kidney transplantation in 1990. Among 1375 patients who received kidney transplants in our center from 1990 to 2002, 606 kidney allografts survived more than 20 years. We identified 155 kidney transplant recipients who administered tacrolimus continuously from 15 to 20 years after kidney transplantation and analyzed tacrolimus drug levels and clinical outcomes.

Results: The mean tacrolimus trough drug levels between 15 and 20 years after kidney transplantation was 3.94 ng/mL ± 1.52 (range 1.13 – 7.70, median 3.61). After 20 years of kidney transplantation, 11 cases of rejection and 19 cases of graft failure occurred. When analyzing three groups according to the tacrolimus drug levels (<3ng/ml, 3-5ng/ml, >5ng/ml), there were no significant differences in the incidence of rejection (10.2% in <3ng/ml group, 7.4% in 3-5ng/ml group and 2.6% in >5ng/ml group, P = 0.392) and graft failure (16.4% in <3ng/ml group, 11.8% in 3-5ng/ml group and 7.9% in <5ng/ml group, P = 0.486). However, the >5ng/ml group showed the lowest rejection and graft failure incidence without statistical significance. When analyzing two groups according to the tacrolimus drug levels (<5ng/ml group and ≥5ng/ml group), there were also no significant differences in rejection and graft failure.

Conclusions: Very low and high tacrolimus drug levels did not show different graft outcomes in ultra-long kidney transplant survivors. However, it seems that tacrolimus drug levels >5ng/ml are not related to poor outcomes compared to physicians' worries about calcineurin inhibitor toxicities. Well-designed, randomized prospective studies are necessary for more appropriate use of tacrolimus in ultra-long kidney transplant survivors.

TH-PO749

Comparison of Extended-Release and Immediate-Release Tacrolimus for Preventing De Novo Human Leukocyte Antigen (HLA) Sensitisation in Patients with Failed Allografts

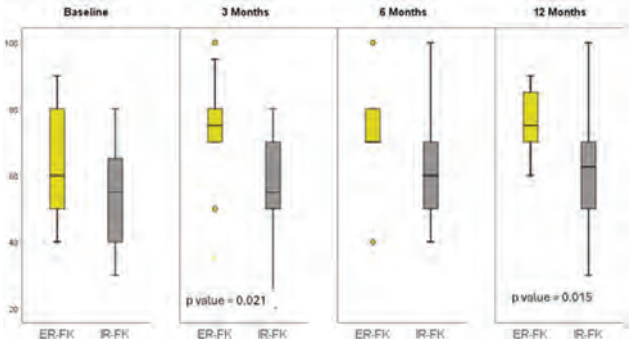
Tina E. Thomson, Michelle Willicombe. *Imperial College London, London, United Kingdom.*

Background: No consensus exists for maintenance immunosuppression in patients returning to dialysis following allograft failure. De novo HLA is undesirable for those suitable for retransplantation. Continuation of low dose tacrolimus may provide protection against broadening sensitisation, but it has a narrow therapeutic index. The use of extended release (ER-FK) preparations may enable better adherence less complications.

Methods: This is an interim analysis of a prospective study, randomising patients to either receive ER-FK or immediate release IR-FK to achieve a trough level of 3-5ng/ml. The primary end point was dnHLA development at 2 yr post-failure. Additional clinical variables, included screening for medication adherence (BAASIS©) and quality of life measures (QoL) (ED-5D-5L) at baseline, 3,6,12,18,24 months.

Results: There was no difference in baseline characteristics of 35 patients with at least 1yr follow-up. At 6 months, 42% of patients had developed dnHLA which increased to 54% by 1yr, with the corresponding number of DSA being 23% and 34%; no differences were seen between the ER-FK and IR-FK groups. Adherence scores were low overall, and significantly lower in IR-FK group at 3 months (p=0.02). 25% of the IR-FK group had a trough level <3 at any time point compared with 8% of the ER-FK (p=0.26). Despite randomisation, baseline QoL measures were lower in the IR-FK, which were reflected in the self-reported health visual analogue scale Figure 1. IR-FK group had significantly worse diabetic control (p=0.009) and also higher CRP (p=0.026). Infection-related admissions were significantly higher with IR-FK(p=0.05). 4 patients died. 5 have been retransplanted.

Conclusions: We found no difference in dnHLA by FK preparation, but 'sub-therapeutic' levels were more frequent with IR-FK. There was a significant burden of poor QoL measures, which correlated with co-morbidity and may confound both HLA responses and adherence. Multiple considerations are likely required to reduce dnHLA in patients with failed allografts.



TH-PO750

Incidence of Thrombotic Microangiopathy in Kidney Transplant Recipients Who Received Tacrolimus: A Multicenter Retrospective Study

Ahmad Matarneh, Sundus Sardar, Rafael Portela, Gurwant Kaur, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Background: Thrombotic microangiopathy (TMA) is a severe condition characterized by thrombocytopenia, hemolytic anemia, and acute kidney failure. TMA can be triggered by infections, medications such as calcineurin inhibitors, and genetic complement defects. In kidney transplant recipients, TMA can lead to graft failure, morbidity, and mortality. Our study aims to identify the incidence of TMA in kidney transplant recipients on tacrolimus versus those not on tacrolimus, and to assess outcomes including transplant rejection, graft failure, and mortality risk.

Methods: We conducted a retrospective multi-center cohort study using TriNetX. We identified 1,252 post-renal transplant recipients on tacrolimus and 290 not on tacrolimus. Survival rates after developing TMA were analyzed over 5 years. Secondary endpoints included the incidence of kidney transplant failure in recipients who developed TMA on tacrolimus compared to those not on tacrolimus, and the risk of graft failure, mortality, and TMA incidence over 5 years.

Results: TMA occurred in 40.3% of kidney transplant recipients on tacrolimus, compared to 24.4% in the non-tacrolimus group (RR=0.613, 95% CI 0.495-0.760). The 5-year risk of developing TMA was higher in patients on tacrolimus (0.7% vs. 0.2%, P=0.0). Survival probability was 36.1% in tacrolimus patients with TMA, compared to 77.3% in non-tacrolimus patients (RR=0.379, 95% CI 0.291-0.495). The risk of graft rejection over 5 years was higher in patients on tacrolimus with TMA (43.1% vs. 16.95%). The risk of kidney graft failure over 5 years was higher in tacrolimus patients with TMA (38.6% vs. 24.1%, RR=0.624). Kidney transplant recipients on tacrolimus with TMA had a survival rate of 98.4% compared to 99.2% in the other group (Hazard ratio 0.387, 95% CI 0.329-0.453). Our study shows a significant difference in TMA incidence in kidney transplant recipients on tacrolimus compared to those not on tacrolimus (P=0.053). There is a higher risk of graft rejection in patients on tacrolimus who develop TMA.

Conclusions: 1. Tacrolimus appears to be an independent risk factor for TMA in kidney transplant recipients. 2. The risk of graft rejection is higher in patients on tacrolimus who develop TMA. 3. The survival rate in kidney transplant recipients who developed TMA was less in those who recieved tacrolimus.

TH-PO751

Safety and Efficacy of Weight-Based MMF (Cellcept) Dosing in Kidney Transplant Recipients: A Quality Improvement Study

Aidan Gangji,[1,2] Wilma M. Hopman,[1] Jessy Donelle,[1] Melana Felske,[1] David C. Holland,[1,3] M. Khaled Shamseddin.[1,3] *[1]Kingston Health Sciences Centre, Kingston, ON, Canada; [2]Queen's University Faculty of Health Sciences, Kingston, ON, Canada; [3]Queen's University, Kingston, ON, Canada.*

Background: Mycophenolate mofetil (MMF) reduces the risk of acute rejection (AR) in kidney transplant recipients (KTRs) and improves post-transplant graft survival. MMF is usually prescribed in fixed doses (2 gm/day). Due to its side effects, MMF doses often require reduction. Weight-based MMF dosing (10-16 mg/kg/day) was correlated with therapeutic level in Asian KTRs. We are aiming to evaluate the safety and efficacy of weight-based MMF dosing at 15 mg/kg/day, adopted by our program in September 2021.

Methods: This is a single center retrospective quality improvement study evaluating the safety and efficacy of weight-based MMF dosing at 15 mg/kg/day, compared with non-weight-based doses (≤ 2 gm/day), to reduce the risk of MMF-associated side effects including leukopenia (WBC ≤ 3.5), BK- and/or CMV-viremia, while monitoring the risk of AR associated with reduced MMF doses. All KTRs followed in our kidney transplant clinic at Queen's University between September 1, 2021, and August 31, 2023, were included.

Results: 230 KTRs [Age 56.9±14.4 years, Female (36.1%), Caucasian (87.8%)] were included. By August 31, 2023, 112 (48.7%) patients were on MMF. 18 patients were on weight-based doses (15.9 (14.9-18.1) mg/kg/day). 17 patients were on fixed doses (20.7 (17.2-26.2) mg/kg/day). 68.8% of MMF patients were on reduced doses (14.4 (10.4-14.4) mg/kg/day) due to adverse effects, most notably leukopenia (25%) and BK-viremia (18%). At the end of the study, leukopenia, BK- and CMV-viremia were active in 4 (1.7%), 7 (3%) and 1 (0.4%) of all patients, respectively and none of them were on weight-based MMF doses. Median eGFR of MMF patients was higher than non-MMF patients (58 vs. 53 ml/min per 1.73 sm; P 0.37), and it was better among patients on weight-based MMF doses compared with fixed (68.5 vs. 51; P 0.035) and reduced doses (58; P 0.26).

Conclusions: Snapshot data showed a low rate of leukopenia, BK- and CMV-viremia/infection, likely due to effective MMF dose reduction. Further analysis will be done through our next retrospective cohort study to evaluate the outcomes of weight-based dosing.

Funding: Private Foundation Support

TH-PO752

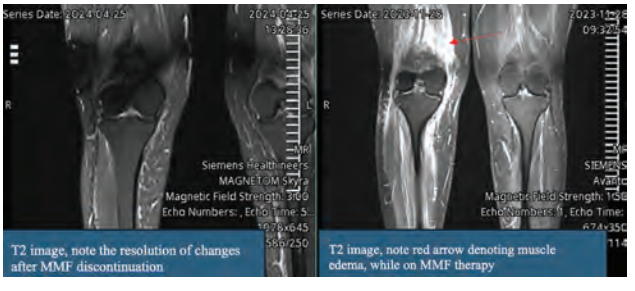
Sickle Cell Pain Crisis or Something Else? A Painful Journey of a Kidney Transplant Patient

Waseem Umer, Essa Abuhelaiqa, Mohamad M. Alkadi. *Hamad Medical Corporation, Doha, Qatar.*

Introduction: Mycophenolate (MMF) is an essential medication in transplant care, yet one should be vigilant of the uncommon adverse effects of such agents. We describe a rare side effect of migratory arthralgias and myalgia related to MMF in a post-renal transplant patient.

Case Description: A 44-year-old lady with past medical history of sickle cell trait, type I diabetes mellitus complicated by diabetic nephropathy, status post preemtive live-related kidney transplant in October 2023. She was maintained on a steroid-free regimen with MMF and tacrolimus. Following discharge, she visited the emergency room multiple times with joint pain and swelling at different sites, including the left shoulder and wrist, right thigh and knee. Each time she was diagnosed with sickle cell pain crisis and discharged after symptoms improvement. Tacrolimus levels were within target range, and extensive workup including workup for rheumatological and infectious causes, was unremarkable. An MRI of the leg was performed, which showed extensive muscular edema of distal right thigh, knee, and leg regions with no evidence of avascular necrosis or osteomyelitis (Figure1). These findings prompt us to investigate medication-related adverse effects; hence, MMF was discontinued. Surprisingly, two days later, the patient's symptoms improved significantly. Upon follow-up, three months later, a repeat MRI of the leg showed near total resolution of the right lower limb muscular oedema, with no recurrence of symptoms.

Discussion: Migratory polyarthritis with myalgias is a rare and usually forgotten side effect of MMF. In 2002, Bart et al. first described an inflammatory reaction in two patients with Wegner's granulomatosis treated with MMF, characterized by fever, arthralgia and myalgia, these symptom resolved within 48hrs of MMF discontinuation 1. This was followed by several other reports, all of which described a pro-inflammatory reaction in the form of migratory polyarthralgia related to MMF. 2 3,4,5,6 In conclusion, a nephrologist should be informed about rare MMF-related side effects, and early intervention should be considered to prevent long-term complications.



TH-PO753

Alfalfa-Induced Acute Cellular Rejection in a Kidney Allograft

Ryan Cullen, Asif A. Sharfuddin. *Indiana University School of Medicine, Indianapolis, IN.*

Introduction: Tacrolimus is an immunosuppressant used in solid organ transplants. Tacrolimus has known drug-drug interactions with a variety of prescripation medications, as well as foods, food extracts, and over the counter supplements. These interactions can cause subtherapeutic or supratherapeutic levels of tacrolimus resulting in suboptimal immunosuppression or nephrotoxicity. We present a case of acute cellular rejection in a renal allograft caused by a drug-drug interaction between tacrolimus and an alfalfa supplement.

Case Description: 56 year old female with history of ESKD secondary to IgA nephropathy, s/p LDKT 1997, DDKT 2015 who presented with subacute cough, poor appetite, and fatigue. She recently returned from a four week trip to Mexico, prior to this she started taking an alfalfa supplement. She denied missing doses of her immunosuppressants tacrolimus and mycophenolic acid. Physical exam was unremarkable. Labs notable for Cr 3.09mg/dL (baseline 0.70-0.80mg/dL), CK normal, UA with bland sediment, UPCR 0.45g/g, Ur Na 29mmol/L, FENA 3.4%. Retroperitoneal US showed increased cortical thickness and mild hydronephrosis of left renal allograft. CT abdomen/pelvis showed perinephric inflammation and mild collecting system dilatation of left renal allograft. She was started on IV fluids but no change in Cr after 24 hours. Further studies showed a tacrolimus level < 1.5 ng/mL, negative CMV DNA, and negative BK DNA. Foley catheter was placed, repeat renal allograft US showed improved hydrouerteronephrosis but no change in Cr. Renal allograft biopsy showed Banff 1B acute cellular rejection, C4D staining negative. Patient was treated with a 3 day course of pulse-dose steroids followed by prednisone taper. She was resumed on her tacrolimus and mycophenolic acid. The alfalfa supplement was discontinued. She was counseled to avoid OTC supplements in the future.

Discussion: Adverse interactions between tacrolimus and other medications have been previously reported, as well as interactions between tacrolimus and foods including grapefruit juice, clementine, tumeric, and cranberry extract. To our knowledge, this is the first reported case of an alfalfa supplement interfering with the metabolism of tacrolimus, resulting in subtherapeutic levels and acute cellular rejection in a kidney allograft. This case demonstrates the importance of counseling patients on the potential harms of over the counter supplements.

TH-PO754

Importance of the Use of Omeprazole and Famotidine in the Development of Chronic Dysfunction of the Kidney Transplant

Milosz Miedziaszczyk, Ilona Idasiak-Piechocka. *Uniwersytet Medyczny im Karola Marcinkowskiego w Poznaniu, Poznan, Poland.*

Background: Tacrolimus is metabolized in the liver with the participation of the CYP3A4 and CYP3A5 enzymes. Proton pump inhibitors are used in kidney transplant patients to prevent duodenal and gastric ulcer disease due to glucocorticoids. Omeprazole, unlike famotidine, is a substrate and inhibitor of the CYP2C19, CYP3A4, CYP3A5 enzymes. The aim of the study is to compare the effect of omeprazole and famotidine on the tacrolimus concentration and risk of developing chronic dysfunction of the kidney transplant.

Methods: A randomized, non-blinded study was conducted in 24 adult patients with stable kidney transplant function who received a standard triple immunosuppression regimen. Patients were assigned to the study group (n=12) additionally receiving omeprazole (20 mg) or the control group (n=12) receiving famotidine (20 mg). At the time of qualification and during follow-up visits, tacrolimus blood concentration and selected laboratory tests were performed. Statistical analysis was performed using the MedCalc system.

Results: A single administration of omeprazole increased tacrolimus concentrations. AUC0-6 amounted to 63.07±19.46 ng×h/mL (day 2) vs 54.23±10.48 ng×h/mL (day 1), (p=0.0295). Conversely, no significant changes were observed for famotidine. The value of creatinine concentration did not change significantly after three years in the study group (1.53±0.50 vs 1.70±0.72, p=0.5071) and in the control group (1.54±0.25 vs 1.50±0.49, p=0.1953). The difference in creatinine concentration values between the groups after three years was not significant (1.70±0.72 vs 1.50±0.49, p=0.6891). The value of tacrolimus concentration in the blood increased after a year in the study group (3.41±1.36 vs. 2.44±1.30, p=0.0101). A reduction in tacrolimus dosage was observed after three years in the study group (3.56±1.75 vs 2.78±1.00, p=0.0440) and in the control group (2.72±0.84 vs 2.10± 0.48, p=0.0051). In one patient in the study group and in the control group, the kidney transplant was rejected due to infection. Both patients are treated with hemodialysis.

Conclusions: Omeprazole significantly increases blood exposure of tacrolimus after single administration and after one year from administration the drug. There was no effect of famotidine or omeprazole on the function of the kidney transplant. ClinicalTrials.gov identifier: NCT05061303.

TH-PO755

Impact of Probiotic Supplementation on Kidney Transplantation Outcomes

Yookyung Jang, Young Eun Choi, Tai yeon Koo, Sewon Oh, Sang-Kyung Jo, Ko Yoon Sook, Lee Hee Young, Myung-Gyu Kim. *Korea University Anam Hospital, Seoul, Republic of Korea.*

Background: The effect of probiotic supplementation on kidney transplantation (KT) outcomes has limited evidence, leading to an unclear understanding of the potential advantages and disadvantages in KT recipients. This study aims to explore the effects of probiotic supplementation on KT outcomes.

Methods: We conducted a retrospective analysis of medical records from 354 KT recipients at Korea University Anam Hospital between January 2010 and December 2020. Only patients who had taken probiotics within 1 year post-KT were included, and transplant outcomes, including graft function, infections, and cardiovascular events, were evaluated 1-3 years after KT.

Results: Of the 354 recipients (mean age: 48.03 years; 31.64% female), 97 received probiotics during the study period, with 36 taking them for >3 months. Probiotic types included Lactobacillus spp. (45.4%), Bacillus subtilis (14.4%), and others (40.2%). The average duration of supplementation was 104.8 days. The probiotics group showed no significant difference in eGFR at 1 and 3 years compared with the non-probiotics group. CMV viremia occurred in 80 patients, with a higher incidence in the probiotics group (35.1 vs. 14.0%). No significant differences were reported in BK viremia or COVID-19 infection. During the study period, 116 patients received antibiotics for >1 week, and the prevalence of bacterial infection was no significantly difference between the two groups. In addition, 15 patients experienced new-onset cardiovascular disease, with no significant difference between the groups. Propensity score matching, employed to address baseline differences between groups also revealed that probiotic supplementation was only significantly associated with the development of CMV viremia, suggesting a potential immunomodulatory effect of probiotics on T-cell function and CMV infection.

Conclusions: This study identified a notable association between probiotic use and CMV viremia after KT. Large-scale prospective studies are needed to comprehensively understand the impact of probiotics on immunocompromised patients and to obtain sufficient evidence for both their safety and effectiveness.

TH-PO756

Recurrence of Anti-nephrin Antibodies Associated Nephrotic Syndrome after Kidney Transplantation

Iman W. Chaudhry, Tariku T. Gudura, Emilio D. Poggio, Kristen Tomaszewski, Itunu O. Owoyemi. Cleveland Clinic Foundation. *Cleveland Clinic, Cleveland, OH.*

Introduction: Minimal change disease (MCD) and focal segmental glomerulosclerosis are podocytopathies characterized by damage to the glomerular basement membrane, leading to nephrotic syndrome. Anti-podocyte antibodies have been proposed as potential circulating factors damaging nephrin, a component of the slit diaphragm. We report a case of recurrent MCD after kidney transplantation associated with anti-nephrin antibodies.

Case Description: A man in his 50s with end stage kidney disease (ESKD) secondary to biopsy proven minimal change disease, treated with steroids, received a deceased donor kidney transplant. He presented eight weeks post-transplant with complaints of shortness of breath and decreased urine output. Labs at presentation were significant for BUN 56 mg/dL, creatinine 1.97 mg/dL (baseline 1.3–1.5 mg/dL), total protein 3.9 g/dL, serum albumin 1.8 g/dL, and urine protein to creatinine ratio (UPCR) of 8.65 mg/mg. Secondary work up for nephrotic range proteinuria was done and was negative. His hospital course was complicated by hemorrhagic shock due to gastrointestinal bleed from an ulcer. He tested positive for H. pylori and was treated. He clinically improved with bleed resolution however nephrotic syndrome persisted prompting a transplant kidney biopsy. Biopsy showed diffuse podocyte foot process effacement with finely granular podocyte staining for IgG. IgG/nephrin immunofluorescence showed overlap of clustered nephrin with punctate IgG, indicative of anti-nephrin antibodies. He received two doses of rituximab 1000 mg with significant reduction in UPCR to 0.95 and serum albumin increase to 3.3 g/dL. Kidney function improved to baseline.

Discussion: In kidney transplant patients, with recurrence of nephrotic syndrome, anti-nephrin antibodies should be considered as a possible contributing etiology. Response to rituximab in this case suggests that B cell targeted therapy may be a reasonable approach of treatment for patients with anti-nephrin associated MCD post-transplant. Interestingly, MCD has been associated with chronic infections. Our patient had H. Pylori infection which was treated prior to B cell therapy. It is unclear how significant that may have been. The role of underlying cause of MCD and anti-nephrin antibodies still needs further exploration.

TH-PO757

Preemptive Kidney Transplantation Trends in Lupus

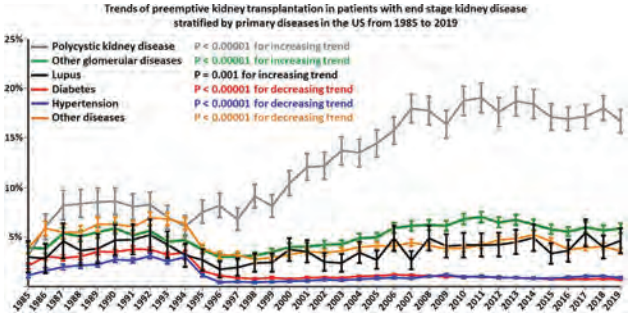
Gabriel Contreras,[1] Javier Pagan,[1] Tali Elfassy,[1] Miguel A. Bandes,[1] Nicolas Bustamante,[2] Mariella O. Goggins,[1] Laura Aponte Becerra,[3] Jair Munoz Mendoza,[1] Yelena Drexler,[1] Shawn Alonso,[1] David Roth.[1] *[1]University of Miami Miller School of Medicine, Miami, FL; [2]Universidad de Ciencias Medicas, San Jose, Costa Rica; [3]Yale University School of Medicine, New Haven, CT.*

Background: The proportion of patients with lupus approaching end-stage kidney disease (ESKD) and undergoing preemptive kidney transplantation (PKT) is <5%, due to concern for poor outcomes. In this study, we describe PKT trends in lupus versus non-lupus patients from 1985 to 2019. We also describe all-cause mortality rate in lupus and non-lupus patients undergoing PKT.

Methods: We included 3,035,161 incident ESKD patients with adequate records in the USRDS. Patients were stratified by their primary diagnosis of ESKD into 6 groups: lupus, polycystic kidney disease (PKD), glomerular diseases excluding lupus (GD), diabetes mellitus (DM), hypertension (HTN), and other diseases (OD). PKT trends were assessed with the Cochran-Armitage test.

Results: Of 33,415 lupus and 3,001,746 non-lupus incident ESKD patients, 1,234 (3.69%) and 68,326 (2.28%) underwent PKT. Lupus versus non-lupus patients undergoing PKT were younger (41 vs. 49 years), more often women (82% vs. 42%), and more frequently received living donor kidneys (64% vs. 52%). PKT trends increased from 1985 to 2019 in the lupus (3.02% to 4.65%, p=0.001), PKD (3.14 to 16.71%, p<0.001), and GD (3.94% to 5.90%, p<0.001) groups and decreased in the DM (2.11% to 0.71%, p<0.001), HTN (1.15% to 0.92%, p<0.001) and OD (3.89% to 3.60%, p<0.001) groups. Among lupus patients, PKT trends increased in those ≥ 50 years of age (1.18% to % 6.73, p<0.001), women (3.11% to 4.83%, p=0.002), Caucasian-Americans (3.78% to 5.26%, p<0.001), and Asian-Americans (0% to 10.61%, p<0.001). Among PKT patients, the mortality rate (per 100 patient-years) was similarly low in lupus (2.59), GD (2.62), PKD (2.20) and OD (2.99) patients, but significantly higher in HTN (6.39) and DM (6.49) patients.

Conclusions: In patients approaching ESKD, PKT trends have increased from 1985 to 2019 in patients with lupus, PKD and GD, most notably in PKD patients. Mortality rates are similarly low in lupus, GD, and PKD patients undergoing PKT.



TH-PO758

Outcomes after Kidney Transplantation in ANCA-Associated Vasculitis

Benoit Brilland,[1] Marine Dekervel,[1] Priscille Traversat,[1] Antoine Thierry,[11] Leonard Golbin,[3] Dominique Bertrand,[12] Emilie Cornec-Le Gall,[4] Giorgina B. Piccoli,[5] Assia Ilham Djema,[6] Nicolas Henry,[7] Agnes Duveau,[1] Dany Anglicheau,[8] Valerie Chatelet Pouliquen,[9] Sophie Caillard,[10] Fabien Duthe,[11] Philippe Gatault,[2] Jean Francois Augusto.[11] Spiesser Group. *[1]CHU Angers, Angers, France; [2]CHU Tours, Tours, France; [3]CHU Rennes, Rennes, France; [4]CHU Brest, Brest, France; [5]Centre Hospitalier du Mans, Le Mans, France; [6]Centre Hospitalier de Cholet, Cholet, France; [7]CH Laval, Laval, France; [8]Assistance Publique - Hopitaux de Paris, Paris, France; [9]Centre Hospitalier Universitaire de Caen Normandie, Caen, France; [10]CHU Strasbourg, Strasbourg, France; [11]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [12]CHU Rouen, Rouen, France*.

Background: ANCA-associated glomerulonephritis (AAV-GN) frequently leads to end-stage kidney disease (ESKD), requiring replacement therapy with dialysis or kidney transplant (KT). Few large studies evaluated the outcome of these patients after KT. Our aim was to describe, in comparison with a control group, the occurrence of delayed graft function, graft failure, relapse, acute rejection, death; and to study the risk factors associated with these events.

Methods: This was a retrospective, multicenter (8 French centers), observational study including patients who received a KT between 2005 and 2023 for ESKD secondary to AAV-GN. Each vasculitis case receiving a KT was matched with 2 controls, matched on gender, center, recipient age (± 5 years) and transplant period (± 1 year). Event-free survival and the associated risk factors were analyzed.

Results: 474 patients were included, including 158 with AAV-GN and 316 control patients. The median post-KT follow-up for vasculitis patients was 5.3 years. There was no difference in the occurrence of DGF between the groups (17.9 vs 18.3 %, p = 1.0). In multivariable analysis, graft survival tended to be lower in the AAV-GN group compared to the controls (76% vs 81% at 10 years, p = 0.057, **Figure 1A**). 11 patients experienced a relapse after KT. ANCA positivity at the time of transplantation appeared to be correlated with relapse. There was no difference in the incidence of acute rejection between the groups (p = 0.4). In multivariable analysis, overall survival was not significantly lower in AAV-GN patients compared to controls (60% vs 72% at 10 years, p = 0.13, **Figure 1B**).

Conclusions: Kidney transplantation is a valuable option for patients with AAV-GN: the relapse rate is low, and the occurrence of acute rejection is comparable to a population of control patients. However, in AAV-GN, graft survival appears to be poorer when compared to control patients.

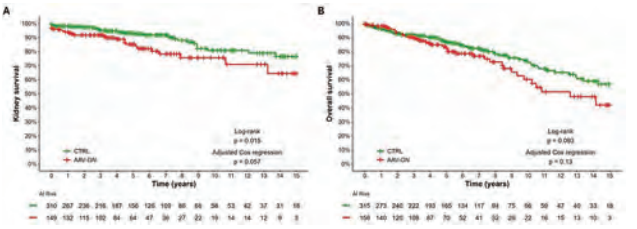


Figure 1. Kidney (A) and overall (B) survival after kidney transplantation.

TH-PO759

Outcomes after Kidney Transplantation in Anti-glomerular Basement Membrane Disease

Benoit Brilland,[1] Priscille Traversat,[1] Marine Dekervel,[1] Philippe Gatault,[11] Antoine Thierry,[10] Emilie Cornec-Le Gall,[3] Leonard Golbin,[2] Agnes Duveau,[1] Giorgina B. Piccoli,[4] Assia Ilham Djema,[5] Nicolas Henry,[6] Dany Anglicheau,[7] Valerie Chatelet Pouliquen,[8] Sophie Caillard,[9] Fabien Duthe,[10] Dominique Bertrand,[12] Jean Francois Augusto.[1] Spiesser Group. *[1]CHU Angers, Angers, France; [2]CHU Rennes, Rennes, France; [3]Centre Hospitalier Regional et Universitaire de Brest, Brest, France; [4]Centre Hospitalier du Mans, Le Mans, France; [5]Centre Hospitalier de Cholet, Cholet, France; [6]CH Laval, Laval, France; [7]Assistance Publique - Hopitaux de Paris, Paris, France; [8]Centre Hospitalier Universitaire de Caen Normandie, Caen, France; [9]CHU Strasbourg, Strasbourg, France; [10]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [11]CHU Tours, Tours, France; [12]CHU Rouen, Rouen, France*.

Background: Anti-glomerular basement membrane antibody disease-associated glomerulonephritis (GBM-GN) frequently leads to end-stage kidney disease (ESKD), requiring replacement therapy with dialysis or kidney transplant (KT). Few studies evaluated the outcome of these patients after KT. Our aim was to describe, in comparison with a control group, the occurrence of the following events: delayed graft function recovery, graft survival, relapse, acute rejection, overall survival; and to study the risk factors associated with these events.

Methods: This was a retrospective, multicenter (8 French centers), observational study including patients who received a KT between 2005 and 2023 for ESKD secondary to GBM-GN. Each vasculitis case receiving a KT was matched with 2 controls, matched on gender, center, recipient age (± 5 years) and transplant period (± 1 year). Event-free survival and the associated risk factors were analyzed.

Results: 165 patients were included, including 55 with GBM-GN and 110 control patients. The median post-KT follow-up for vasculitis patients was 8.3 years. There was no difference in the occurrence of DGF between the groups (22.2 vs 18.3%, p = 0.61). In multivariable analysis, there was no difference in graft survival when comparing both groups (80% vs 81% at 10 years, p = 0.7) (**Figure 1A**). Only one patient experienced a relapse after KT (being anti-GBM negative at the time of transplantation). There was no difference in the incidence of acute rejection between the groups (p = 0.3). In multivariable analysis, there was no difference in overall survival when comparing both groups (87% vs 85% at 10 years, p = 0.3) (**Figure 1B**).

Conclusions: Kidney transplantation is a valuable option for patients with GBM-GN: outcomes are similar to those of a matched population with similar occurrence of acute rejection, graft loss or death.

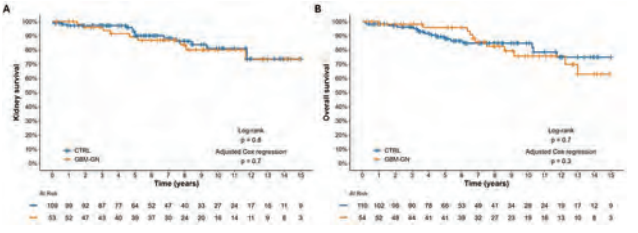


Figure 1. Kidney (A) and overall (B) survival after kidney transplantation.

TH-PO760

Acute Rejection and Relapse of Native Disease in Kidney Transplant Recipients with ESKD from ANCA-Associated Vasculitis: Insights from a Single-Center Study

Nada Youssef, Melissa L. Swee, Sarat C. Kuppachi. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare systemic autoimmune disease characterized by necrotizing inflammation of small blood vessels leading to end-organ damage. Up to 40% of AAV patients progress to end-stage kidney disease (ESKD), necessitating renal replacement therapy. The long-term outcomes of patients with AAV after renal transplantation are not well described. Our study aims to evaluate biopsy proven acute rejection (BPAR) and relapse of AAV following transplantation at our center.

Methods: We retrospectively reviewed all patients with ESKD secondary to AAV who underwent a kidney transplant at the University of Iowa between January 2000 and October 2023. 33 kidney transplants were completed in 30 patients.

Results: Among the 33 transplant episodes, 18 grafts were from deceased donors, 3 from living unrelated donors, and 12 from living related donors, including an identical twin. 3 patients (9%) developed AAV relapse between 4 and 117 months after transplantation and, all had p-ANCA sub-type of AAV. None required dialysis or lost their graft. 9 patients (27%) developed BPAR between 2 and 178 months after transplant. Of these, 5 had p-ANCA, 2 c-ANCA, and 2 had unknown sub-types. 5 of the 9 developed graft failure requiring dialysis (15%). 3 patients died with functioning graft, 1 after rejection treatment, 1 after relapse of AAV and one of non AAV disease (42, 92 and 120 months after transplant).

Conclusions: Our data indicates transplant and overall survival rates in patients with ESKD secondary to AAV are comparable to those receiving kidney transplants for ESKD due to other causes. AAV relapse after kidney transplantation is uncommon but appeared exclusively in patients with the p-ANCA subtype and those who received IL-2RA or no induction. Kidney transplantation remains a viable and effective treatment option for these patients and larger database analysis are necessary to better characterize those at risk for disease relapse and BPAR.

	All Patients (n=30)	Patients with Relapse (n=3)
Age at Time of Transplant	45.15 (± 21.77) years	62.3 years
Female Gender	17 (56.7%)	2 (66.7%)
Male Gender	13 (43.3%)	1 (33.3%)
AAV p-ANCA Pattern	19 (63.3%)	3 (100%)
AAV c-ANCA Pattern	10 (33.3%)	0 (0%)
AAV Unknown ANCA Pattern	1 (3.3%)	0 (0%)
AAV MPO+ Disease Subtype	17 (56.7%)	2 (66.7%)
AAV PR3+ Disease Subtype	7 (23.3%)	0 (0%)
AAV Unknown Disease Subtype	6 (20%)	1 (33.3%)
Induction agents		
IL-2 Receptor Antibody (IL-2RA)	12 (36.37%)	2 (66.7%)
Thymoglobulin	10 (30.3%)	0 (0%)
Alemtuzumab	5 (15.15%)	0 (0%)
Steroids	1 (3.03%)	1 (33.3%)
Unknown	5 (15.15%)	0 (0%)

TH-PO761

Two Cases of Recurrence Immediately after Living Donor Kidney Transplantation for ANCA-Associated Vasculitis (AAV)

Yusuke Shimanaka, Aya Kaito, Tetsuro Takeda. *Dokkyo Medical University Saitama Medical Center Department of Nephrology, Saitama, Japan.*

Introduction: Rituximab, the standard treatment for AAV, reduces B cells and suppresses antibody production, thus contributing to the prevention of AAV recurrence. The two cases presented here are precious cases of recurrent AAV immediately after kidney transplantation (KT).

Case Description: [Case 1] A 24-year-old woman diagnosed with AAV 7 years ago, was treated with steroid pulse therapy, plasma exchange, and rituximab, but her renal function declined, and she was introduced to hemodialysis four years ago. MPO-ANCA remained positive, and a blood group-mismatched living donor KT was performed with her aunt as donor. On postoperative day 8, serum creatinine worsened to 2.16 mg/dL and kidney biopsy revealed tuft necrosis. She was considered to have recurrent AAV and creatinine improved to 1.57 mg/dL with steroid pulse and plasma exchange. Repeat biopsy after KT showed still tuft necrosis and fibrocellular crescents. After administration of avacopan, creatinine remained at 1.5-1.7 mg/dl. [Case 2] A 23-year-old woman diagnosed with AAV 18 months ago, was treated with steroid pulse therapy and rituximab, but kidney biopsy showed devastated glomeruli and fibrous crescents, and hemodialysis was introduced. MPO-ANCA remained positive, and a blood group-matched living donor KT was performed with her mother as donor. On postoperative day 4, creatinine deteriorated to 3.34 mg/dL and biopsy showed focal fibrinoid necrosis and cellular crescents. She was diagnosed to have recurrent AAV and was treated with steroid pulse, plasma exchange, cyclophosphamide pulse, and abacopan. Proteinuria and hematuria resolved, and creatinine improved to 1.49 mg /dL.

Discussion: The recurrence rate of AAV after KT is reported to be about 10%, and even if recurrence occurs, treatment is successful with intensified immunosuppressive therapy, making KT highly beneficial. ANCA antibody titer before KT does not affect the recurrence rate, so KT should not be postponed because of ANCA positivity. However, KT within one year of remission is associated with increased mortality. Among cases presenting with RPGN, relapse is reported to be more common in ANCA-positive cases than in non-positive cases. The fact that AAV recurred immediately after administration of rituximab, also used in KT, suggests that the MPO-ANCA-producing cells may have already changed from B cells to plasma cells.

TH-PO762

Changing the Tides in Hawaii: Recurrent IgA Nephropathy in an Isograft on the 70th Anniversary of the First Successful Twin Transplantation

Chinnawat Arayangkool, Akiko Tokunaga, Lisa Kim. *University of Hawai'i System, Honolulu, HI.*

Introduction: IgA nephropathy (IgAN) is the most common primary glomerulopathy globally and also most common to recur after transplantation. While a pediatric screening program for IgAN is not standard in the United States, it is routine in several Asian countries. We report a case of presumed recurrent IgAN in a monozygotic twin and question the status quo for screening in Hawaii.

Case Description: A 36-year-old Asian male with history of living related renal transplant (LRRT) from twin brother underwent allograft biopsy for increasing proteinuria and hematuria. Serum creatinine (SCr) and eGFR were stable (Chart 1). Four years prior he presented to his PCP with tension headaches and found hypertensive 191/99 mmHg, SCr 6.0 mg/dL with eGFR 11 mL/min/1.73m(2). His brother was confirmed as a monozygous twin without hypertension, proteinuria or hematuria. LRRT was performed 18 months after initial presentation. He received basiliximab induction and tacrolimus with immediate graft function and discharged on post op day 4. One year post transplant immunosuppression was weaned off. The allograft biopsy showed no evidence of acute cellular or antibody-mediated rejection but was consistent with recurrent IgAN (MEST-C score M1, E0, S0, T0, C0). Mycophenolate mofetil was started with decrease in proteinuria. Two years post donation his brother continued without proteinuria or hematuria.

Discussion: In 1954, the first twin transplantation or "isograft" was considered a success after 8 year graft survival. Yet, in the following 70 years there remain uncertainties about prevention of recurrent disease, especially IgAN. Our case exemplifies the need for earlier detection and prevention of end stage kidney disease in early adulthood. Further studies are warranted in a high multi-ethnic Asian population like Hawaii to assess the benefit of a screening program for IgAN.

Chart 1

Events	Months	ACR mg/g creatinine		Serum Creatinine mg/dL		eGFR mL/min/1.73m(2)		Urine RBC
		RT	DT	RT	DT	RT	DT	RT
Pre-op	-2			12.8	0.8	5	117	
	0			1.2	1.7	72	60	
	6		<7.8	1.2	1.3	81	74	
	12		None	1.1	1.0	90	101	0-2
	24	28.6		1.1	1.5	90	62	3-5
	28	117.9		1.1		89		6-20
Bx	30			1.2		80		
MMF 500mg BID	34	103.8		1.0		100		0-2

TH-PO763

Successful Kidney Transplantation in Dent Disease

Adnan Barazi, Kalathil K. Sureshkumar. *Allegheny Health Network Graduate Medical Education, Pittsburgh, PA.*

Introduction: Dent disease is a rare X-linked recessive condition due to inactivating mutation in CLCN5 or OCRL1 gene resulting in proximal tubular dysfunction that primarily affects young men characterized by low molecular weight (LMW) proteinuria, hypercalciuria, recurrent kidney stones, nephrocalcinosis and progressive kidney failure. Only ~ 250 families have been identified with these mutations. We present a patient with Dent disease from CLCN5 mutation and kidney failure who underwent successful kidney transplantation from a living donor.

Case Description: A 51-year-old male with long-standing proteinuria, recurrent kidney stones, progressive chronic kidney disease (CKD) on peritoneal dialysis for 2 years with kidney biopsy evidence for secondary focal segmental glomerulosclerosis was evaluated for kidney transplantation. His brother also was experiencing recurrent kidney stones and CKD. Genetic test on the patient revealed mutation in CLCN5 gene consistent with Dent disease type 1. Patient was not sensitized, IgG negative for CMV but positive for EBV and underwent living unrelated kidney transplantation from a 4 HLA mismatched donor who was IgG negative for CMV and positive for EBV. Thymoglobulin was used for induction followed by tacrolimus/mycophenolic acid maintenance. Patient received infection prophylaxis with acyclovir, nystatin and trimethoprim-sulfamethoxazole. There was prompt allograft function (figure1).

Discussion: Our case illustrates the importance of genetic testing especially in young patients with family history of kidney disease. This will help in arriving at correct diagnosis and to advise genetic screening of immediate family members. Since end-organ damage in Dent disease is renal-limited, kidney transplantation is curative. Female family members are carriers, can have low grade LMW proteinuria and could develop future mild kidney failure. Caution should be used while evaluating female family members as potential living donors.

TH-PO764

Typical! Atypical Hemolytic Uremic Syndrome (aHUS) Overlooked in Malignant Hypertension and Thrombotic Microangiopathy: Case Reports and Clinical Implications

Norhan Elsayed, Michael Allevato, Brian R. Stephany, Raviprasenna K. Parasuraman. *University of Michigan, Ann Arbor, MI.*

Introduction: Thrombotic microangiopathy (TMA) is a clinicopathologic manifestation of atypical HUS (aHUS) and often overlooked in patients with malignant hypertension (MH) leading to a delay in diagnosis. Prompt diagnosis of aHUS can significantly improve patient outcomes, especially in the setting of kidney transplantation where recurrent disease can occur rapidly in the allograft. Here we describe two cases of patients with severe HTN and TMA: one where aHUS was diagnosed and managed with eculizumab prior to kidney transplantation and one where the diagnosis was masked by other clinical features and ultimately resulted in recurrence after transplant.

Case Description: Case 1: A 34 y/o woman with CKD due to Class IV lupus nephritis presented with hypertensive emergency with native kidney biopsy also showing features of TMA. Genetic testing for aHUS revealed variants of unknown significance in CD46 (membrane co-factor protein). She later underwent a renal transplant with immediate graft function, but soon after developed allograft dysfunction with hematological features of TMA confirmed by biopsy. Other causes of TMA were ruled out leading to a diagnosis of aHUS. She was treated with eculizumab emergently and had normalization of allograft function. Case 2: A 32 y/o woman presented with hypertensive emergency and cardiomyopathy during the postpartum period and was found on biopsy to have chronic TMA. Genetic testing revealed a homozygous variant in the CFI gene, a variant of unknown significance in the THED gene, and a homozygous deletion of CFHR3-CFHRI. She was treated with eculizumab prior to transplantation and had a stable post-transplant course without recurrent disease.

Discussion: It can be challenging to determine whether TMA is due to MH or underlying aHUS caused by derangement in the alternative complement pathway. It has been estimated that 20% of MH patients who require hospital admission have TMA features and 60% of these patients may have underlying aHUS when genetic testing was performed. We believe it is crucial to obtain genetic testing for aHUS in patients with severe HTN and TMA to help distinguish these conditions and improve patient outcomes by making the diagnosis of aHUS, guiding treatment options, facilitating genetic counseling and preventing recurrence of TMA in renal allografts.

TH-PO765

Successful Use of Eculizumab for Prevention of Atypical Hemolytic Uremic Syndrome Recurrence in a Pregnant Kidney Transplant Recipient with CFH Gene Mutation: A Case Report and Literature Review

Somaya Zahran,[1] Thomas Nodzynski,[2] Catherine Matte,[3] Shaifali Sandal,[1] Tiina Podymow,[1] Marcelo Cantarovich.[1] [1]*McGill University, Montreal, QC, Canada;* [2]*Hopital general du Lakeshore, Pointe-Claire, QC, Canada;* [3]*Anna Laberge Hospital, Montreal, QC, Canada.*

Introduction: Eculizumab is a humanized monoclonal antibody targeting C5, used in the treatment of atypical hemolytic uremic syndrome (aHUS). It is accepted as maintenance therapy for the prevention of recurrent aHUS post kidney transplant (KTx), however, clinical experience with its use during pregnancy is limited.

Case Description: 36-year-old woman with history of end stage renal disease secondary to aHUS with confirmed complement factor H gene mutation was treated with hemodialysis, plasmapheresis, rituximab and vincristine. She received a standard-criteria deceased donor KTx in 2013. Eculizumab was administered in the perioperative period at a dose of 1200 mg IV, followed by 1200 mg Q1W for 2 weeks, and then Q2W thereafter as maintenance therapy. In 2016, she had a planned pregnancy during which eculizumab was continued. Biomarkers of hemolysis and kidney function were closely monitored. Despite the development of pre-eclampsia resulting in preterm delivery at 33W, the patient delivered a healthy infant and had well-preserved allograft function with no aHUS recurrence. 8 years later, no complications are observed and her child is developing normally. Pubmed search was conducted for reports of prophylactic use of eculizumab in aHUS pregnant KTx recipients between 1993 and 2024. 35 articles were found, of which, three fulfilled our criteria (table 1).

Discussion: Although eculizumab is considered safe during pregnancy, its use in pregnant KTx recipients is rare given the lack of relevant pharmacological data and unknown long-term effects on the offspring. We report for the first time, 8-year follow up favorable maternal and fetal outcomes and provide a literature review of similar cases. We conclude that maintenance eculizumab is a plausible option for prevention of aHUS recurrence in pregnant women who received KTx. Close monitoring of hemolytic markers and kidney function is recommended to ensure early detection and management of complications.

Article	# of cases	Patient characteristics	Genetic testing	Pre-conception immunosuppression	Eculizumab dose			Monitoring during pregnancy	Pregnancy complications	Pregnancy outcome
					Pre-conception	During pregnancy	Postpartum			
Duval et al. 2019	1	IgAN, preemptive DCD complicated with severe postoperative TMA	Negative	Cyclosporin A, azathioprine and steroids	900mg Q2W	Increased to 1200mg Q2W at W32 gestation	Decreased back to 900mg Q2W then stopped after 6 months	Biweekly hemolytic markers and monthly complement activity	Moderate pre-eclampsia at [illegible]	C-section at [illegible]
Cheong et al. 2013	1	[illegible]	Not reported	Tacrolimus + azathioprine	1200 mg Q2W	Increased to 1500mg Q2W (16-27w gestation) then 900mg Q1W (28W until delivery)	An extra infusion of 900mg was given within 24h of delivery then 1200mg 1W postpartum then back to 1200mg Q2W	Hemolytic markers and complement activity (C3, C4, C5, CH50, AH50 assays) every 2 weeks	Placental biopsy proven pre-eclampsia at 29 weeks +5/d	Preterm delivery (30w gestation) of an infant with [illegible]
Haninger-Vacariu et al. 2020	1	cTMA patient received DCD KTx	1.Rare CFH variant (p.C1032X, heterozygous) 2.CD46ggaac risk haplotype (homozygous) 3.CFH H3 haplotype (heterozygous)	Cyclosporine A (75 mg twice daily [trough level, 50-80 ng/mL]), azathioprine 25 mg once daily, and prednisolone at 5 mg once daily	1200 mg Q2W	Increased to 900mg Q1W (at 17W gestation)	Not reported	Hemolytic markers and complement activity (C3, C4, C5, CFH, CFI, CFB assays), eculizumab level Q12W	Slight increase in BP and proteinuria at 38W gestation	[illegible] delivery at 37W

TH-PO766

The Secret Ingredient for Isolated Kidney Transplantation with Primary Hyperoxaluria: A Case Report

Sarah Hryzak,[1] Christopher R. Showers,[1] Zahra Ahmad,[2] Olivia Atlas,[1] Katie Hummel,[1] Samir Abu Gazala,[1] Sabiha M. Hussain.[1] [1]*Hospital of the University of Pennsylvania, Philadelphia, PA;* [2]*University of Pennsylvania, Philadelphia, PA.*

Introduction: Primary hyperoxaluria is defined by a group of autosomal recessive conditions that cause alteration of oxalate metabolism leading to complications such as kidney failure. Simultaneous liver-kidney transplantation (SLKT) has been the treatment of choice for primary hyperoxaluria however newer therapies with RNA interference (RNAi) may offer alternative options. Here we outline both the utilization of RNAi therapy as well as specifics of perioperative kidney replacement therapies for successful isolated kidney transplant (KT).

Case Description: 25-year-old with hypertension diagnosed with primary hyperoxaluria at nine months old experienced multiple kidney stones and eventually progressed to advanced kidney disease. She was treated with pyridoxine with reduction in nephrolithiasis. She then received Lumasiran injections for 23 months prior to receiving KT. Plasma oxalate levels were monitored and a level of ≤20umol/L was targeted prior to KT. To achieve this, one week prior to KT, patient underwent daily four-hour hemodialysis sessions for five consecutive days to optimize oxalate clearance. She then underwent isolated living-unrelated KT with immediate graft function followed by three consecutive days of hemodialysis (Figure1). Patient was induced with thymoglobulin and maintained on tacrolimus, mycophenolate and prednisone. She required no further treatments and continues to have excellent allograft function with creatinine of 1.2mg/dL seven months post KT.

Discussion: Primary hyperoxaluria is a devastating disease that for decades has been treated with SLKT. This case highlights the ability to avoid dual organ transplantation and provides granular details of perioperative renal replacement management utilized for a successful KT. By continuing to expand our knowledge on treatment for primary hyperoxaluria, we can reduce risks associated with multi-organ transplantation as well as increase organ availability worldwide.

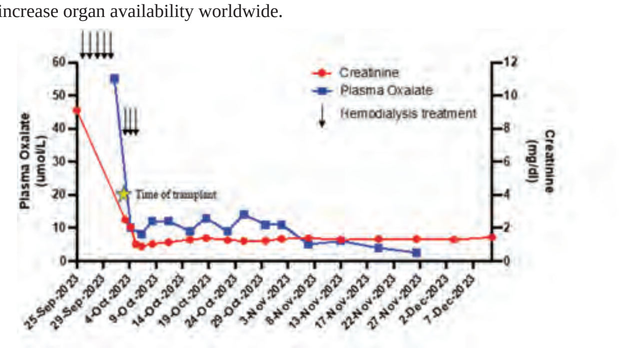


Figure 1 Measured serum creatinine levels (mg/dl) and plasma oxalate levels (umol/L) before, during, and after time of isolated kidney transplantation with timing of dialysis treatments outlined.

TH-PO767

Less Is More: A Case of Isolated Kidney Transplantation with Lumasiran in Primary Hyperoxaluria Type 1

Alissa A. Ice, Muhammad J. Azam, Anthony J. Langone. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disorder of hepatic glyoxylate metabolism. Consequently, it results in the overproduction of oxalate causing nephrolithiasis, nephrocalcinosis, and CKD. In the setting of kidney failure, generally simultaneous liver and kidney transplantation is recommended. Given the pathophysiology with high risk for recurrent allograft involvement and previous lack of effective therapies, there are very few cases of kidney-only transplantations in these patients. We present an exceedingly rare case illustrating the essential role of lumasiran, a small interfering RNA agent, in PH1 kidney-only transplantation.

Case Description: A 41 year old male with PH1 and subsequent ESRD, HTN, developmental delay, and history of a resected paraganglioma underwent a deceased kidney donor transplantation. Notably, he developed nephrolithiasis at the age of 13 and underwent lithotripsy at age 26 prior to his PH1 diagnosis. Hemodialysis and lumasiran were initiated three years prior to his transplantation, with plasma oxalate levels ranging between 13-65 mcmol/L during this timeframe. He received alemtuzumab and solumedrol induction with immediate graft function followed by maintenance tacrolimus, mycophenolate, and prednisone. In addition to hyperhydration, low oxalate diet, and pyridoxine, he was continued on his lumasiran injections. Within the first month posttransplantation, his plasma oxalate level became undetectable and creatinine was 0.9.

Discussion: PH1 is characterized by a mutation in the alanine glyoxylate aminotransferase gene, which encodes for the hepatic peroxisomal enzyme AGT and results in increased glyoxylate production and thus oxalate. The first drug to treat PH1, lumasiran, was FDA approved in 2020, targeting glycolate oxidase and thereby decreasing oxalate synthesis. Although it does not affect the systemically stored oxalate release, this case highlights the favorable decline in plasma oxalate levels even without prophylactic posttransplantation dialysis that a few cases have employed. This clinical vignette illustrates that patients with PH1 can receive a successful kidney transplant without a concomitant liver transplant in the setting of aggressive medical management, including the novel agent, lumasiran.

TH-PO768

Clinical Characteristics and Outcomes of Kidney Transplantation in Patients with Autosomal Dominant Polycystic Kidney Disease

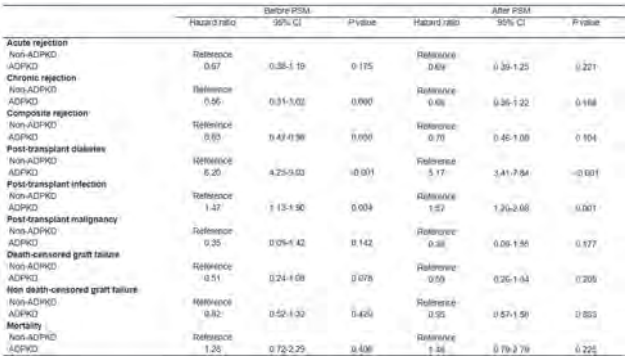
Jin Hyeog Lee, Sung Jin Moon. *Catholic Kwandong University International Saint Mary's Hospital, Incheon, Republic of Korea.*

Background: Kidney transplantation (KT) is the best treatment for autosomal dominant polycystic kidney disease (ADPKD). We aimed to investigate clinical characteristics and outcomes of KT in ADPKD patients compared to those in non-ADPKD patients.

Methods: We retrospectively analyzed KT recipients in two Korean transplantation centers A propensity score-mactching and Cox regression analysis were used to assess the clinical outcomes of ADPKD compared to non-ADPKD and prognostic factors influencing outcomes in ADPKD.

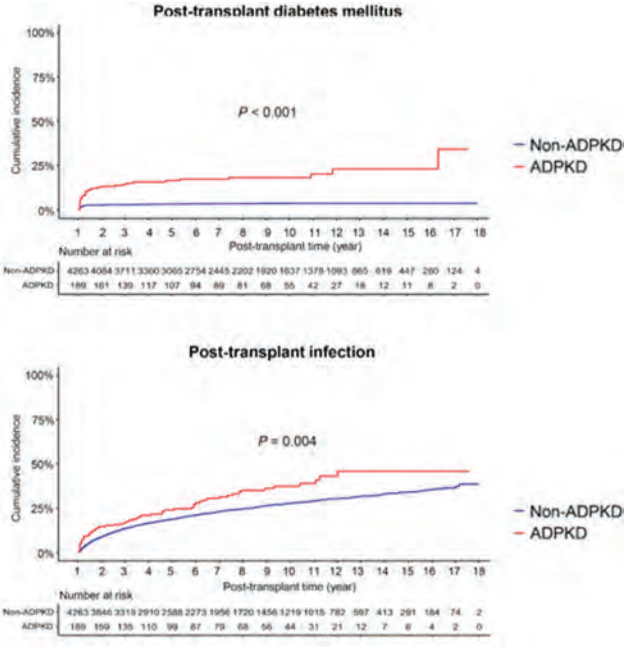
Results: Among a total of 4,452 KT patients, 189 (4.2%) were ADPKD patients. In both groups, living-donor KT were more common than deceased-donor KT. The ADPKD group had a 4.09-fold higher risk of post-transplant diabetes mellitus and a 1.65-fold higher risk of post-transplant infection compared to the non-ADPKD group; however, it had similar risk of rejection, graft failure, and mortality. In the ADPKD group, kidney volume decreased after KT irrespective of kidney volume status, while size of hepatic cyst increased. Either kidney volume or nephrectomy of native kidneys was not associated with risk of infection, graft failure, or mortality in the ADPKD group.

Conclusions: ADPKD patients have a higher risk of post-transplant diabetes mellitus and infection than non-ADPKD patients without a significant impact of kidney volume or nephrectomy on post-transplant outcomes.



	Before PSM			After PSM		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Acute rejection						
Non-ADPKD	Reference			Reference		
ADPKD	0.67	0.38-1.19	0.175	0.69	0.39-1.25	0.221
Chronic rejection						
Non-ADPKD	Reference			Reference		
ADPKD	0.56	0.31-1.02	0.060	0.65	0.36-1.22	0.168
Composite rejection						
Non-ADPKD	Reference			Reference		
ADPKD	0.63	0.47-0.86	0.003	0.70	0.48-1.00	0.104
Post-transplant diabetes						
Non-ADPKD	Reference			Reference		
ADPKD	5.20	4.25-9.03	<0.001	5.17	3.41-7.84	<0.001
Post-transplant infection						
Non-ADPKD	Reference			Reference		
ADPKD	1.47	1.13-1.90	0.004	1.57	1.20-2.06	0.001
Post-transplant malignancy						
Non-ADPKD	Reference			Reference		
ADPKD	0.35	0.05-1.42	0.142	0.38	0.06-1.56	0.177
Death-censored graft failure						
Non-ADPKD	Reference			Reference		
ADPKD	0.51	0.24-1.08	0.078	0.59	0.26-1.34	0.208
Non death-censored graft failure						
Non-ADPKD	Reference			Reference		
ADPKD	0.82	0.52-1.30	0.409	0.95	0.57-1.58	0.853
Mortality						
Non-ADPKD	Reference			Reference		
ADPKD	1.26	0.72-2.29	0.406	1.46	0.79-2.79	0.225

Comparative post-transplant outcomes



Cumulative incidence of post-transplant complications

TH-PO769

A Case of Omeprazole-Associated Tubular Disease with Subsequent Kidney Transplant

Christopher B. Gitter, Badi Rawashdeh, Anna R. Gaddy. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Anti-tubular basement membrane (anti-TBM) antibody disease is an extremely rare disease characterized by the direct exposure of the renal tubular cell basement membrane, focused in the proximal tubule. Diagnosis is one of exclusion and treatment is generally similar to that of anti-glomerular basement membrane disease. Only one case of anti-TBM disease undergoing transplant has been reported.

Case Description: A 50 year old male presented to a tertiary care center for orthostatic hypotension and was found to have worsening of prior AKI. In the year prior to presentation, patient underwent extensive workup for esophageal dysmotility and was started on omeprazole three months prior to admission. One month prior to admission, patient presented to outside hospital for rash and AKI and was diagnosed with acute interstitial nephritis (AIN) with "unusual linear C3 deposition along basement membrane" attributed to omeprazole therapy. Physical exam showed diffuse macular rash and purpuric lesions on lips. Urinalysis demonstrated mild proteinuria, without hematuria or casts. Patient underwent native kidney biopsy which demonstrated extensive acute interstitial nephritis with linear IgG and C3 immunofluorescence staining of the tubular basement membranes. The patient underwent plasma exchange and was started on cyclophosphamide plus glucocorticoids. Clearance remained poor and the patient required maintenance dialysis. Due to polyuria, glucosuria, and orthostasis, the patient required high dose fludrocortisone and salt tablets and ultimately underwent bilateral renal artery glue embolization in an attempt to minimize wasting. Ultimately, the patient underwent uncomplicated deceased brain death kidney transplant, where graft biopsy was performed prior to anastomoses. Methylprednisone and anti-thymocyte were used

for induction, with maintenance regimen of tacrolimus, mycophenylate mofetil, and prednisone started prior to discharge.

Discussion: Initial patient presentation remained consistent with AIN, however his continued polyuria likely was a result of extensive proximal tubular damage as demonstrated on biopsy. This case may represent the second case of successful kidney transplant in a patient with this disease presentation. Repeat graft biopsy as follow-up for kidney transplant may be beneficial in understanding further disease presentation and progression.

TH-PO770

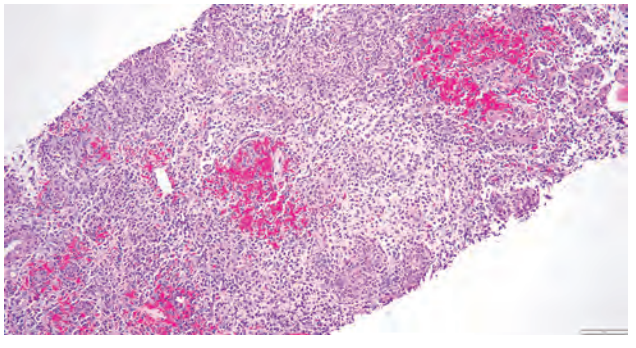
Post-transplant Granulomatous Tubulointerstitial Nephritis (GIN)

Fausto R. Cabezas, Andrea Roche-Recinos, Subodh J. Saggi, Yihe Yang.
SUNY The State University of New York, Albany, NY.

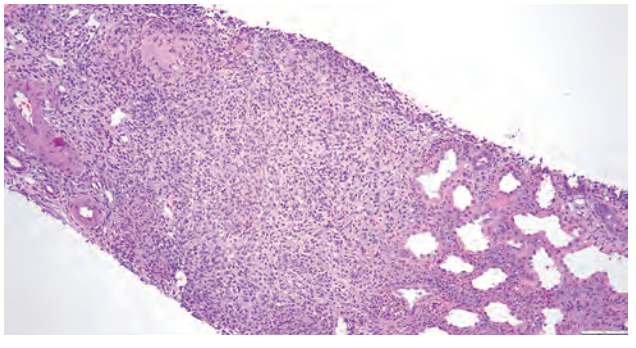
Introduction: GIN is identified in less than 1% of allograft biopsies. We describe a case of GIN contributing to graft failure.

Case Description: A 69-year-old man with ESKD of unknown etiology & liver failure from concomitant hepatitis B/C infection received a Simultaneous Liver-Kidney Transplant in 2017. He previously underwent a Living Unrelated Kidney Transplant in 2007. Recently, Serum creatinine (sCr) increased from 2.9 mg/dl to 4.3 mg/d with nephrotic range proteinuria (UPCR 6.0 GR/GR) and urinalysis showing pyuria (WBC 49) with no hematuria. He required hemodialysis given declining allograft function. An allograft biopsy (Images) showed acute pyelonephritis with non-necrotizing granulomata and negative AFB stain. Occasional collapsing lesions are identified in the glomeruli. And recurrent diabetic nephrosclerosis was also identified. We were unable to prove active tuberculosis infection.

Discussion: GIN is commonly associated infectious agents in up to 60% of cases. The etiology GIN in this patient is likely multifactorial. His second post-transplant course was complicated with recurrent urinary tract infections, antibody mediated rejection, and most recently, an episode of cellular mediated rejection treated with corticosteroids and thymoglobulin. However, granulomata in the interstitium rarely cause nephrotic range proteinuria. The observed proteinuria is attributed to collapsing lesions and concurrent diabetic kidney disease. De novo collapsing lesions, which can appear in 10-20% of kidney allografts, are linked to several risk factors including: high-risk ApoL1 genotype, viral infections such as HIV, SARS-CoV-2, CMV, EBV and BK virus, recent or active rejection, and acute vaso-occlusion.



Allograft biopsy. H&E stain, 200x magnification.



TH-PO771

Trends in 1-Year Outcomes among Kidney Transplant Recipients, by Time since Transplant

David T. Gilbertson,[1,2] James B. Wetmore,[1,2] Jiannong Liu,[1] Nicholas S. Roetker,[1] Kirsten L. Johansen.[1,2] *[1]Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN; [2]University of Minnesota Twin Cities, Minneapolis, MN.*

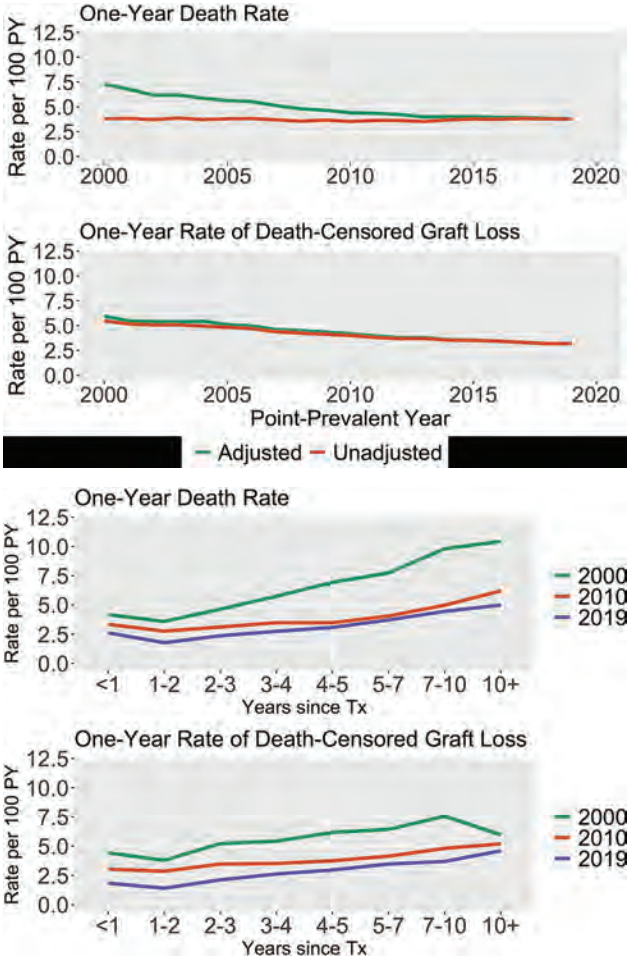
Background: Trends in 1- and 5-year outcomes after kidney transplant (KTx) have improved over the last 20 years, trends that could be driven in part by increasing prevalence of long-term KTx survivors over time. We examined trends in rates of 1-year death and graft loss among KTx recipients, overall and by time since KTx.

Methods: We selected point prevalent deceased-donor KTx recipients on Jan 1 of each year, 2000-2019. In each cohort, we examined 1-year death and death-censored graft loss rates. We estimated unadjusted and adjusted rates overall and by time since KTx. Adjustors were age, sex, race, ESKD cause and pre-KTx dialysis vintage.

Results: Before adjustment, patient survival showed little change over time, whereas adjusted analyses show improvement (Fig 1). Death-censored graft loss improved over time, regardless of adjustment. Fig 2 shows adjusted 1-year death (top) and graft loss (bottom) rates by time since KTx, for 2000, 2010 and 2019. After 2 years post-KTx, death and graft loss rates increased by time since transplant, as expected. However, rates of both outcomes were lower in 2010 and 2019 relative to 2000, irrespective of the years since transplant.

Conclusions: Adjusted rates of death and death-censored graft loss in the year following KTx have improved over time, an important finding given that older patients and those with more comorbidities are now more likely to receive a KTx than in the past. Adjusted outcomes are better in 2019 than in 2000, irrespective of the time since KTx.

Funding: NIDDK Support



TH-PO772

Comparative Survival Outcomes of Kidney Transplantation vs. Ongoing Dialysis in Extremely Elderly Patients: A Matched-Pair Study

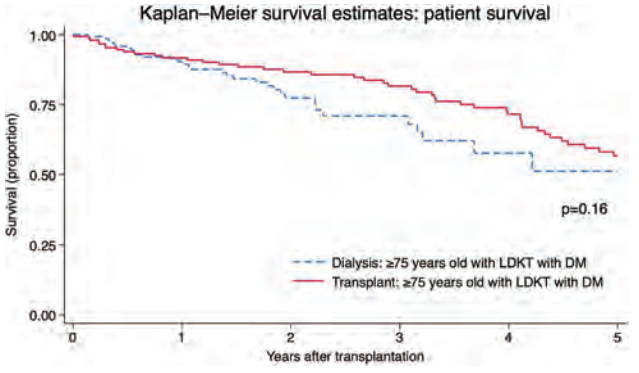
Napat Leeaphorn,[1] Rose Mary Attieh,[1] Oscar A. Garcia Valencia,[2] Wisit Cheungpasitporn,[2] Tambi Jarmi.[1] *[1]Mayo Clinic Florida, Jacksonville, FL; [2]Mayo Clinic Minnesota, Rochester, MN.*

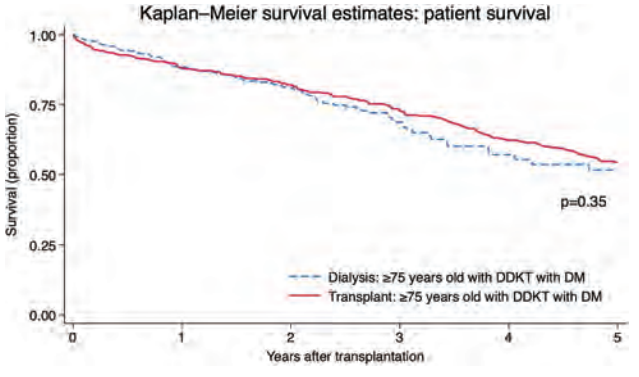
Background: Limited data exists on the outcomes of kidney transplantation (KT) in extremely elderly patients.

Methods: Using the OPTN database between 2005 and 2019, elderly recipients who were on dialysis before KT were stratified into two groups: 70-74 and ≥75 years old. These recipients were then exactly matched to waitlisted dialysis patients by age at the start of dialysis, race, diabetes status, functional status, and duration on inactive status while on the waitlist (WL). Propensity matching was used for the remaining variables.

Results: Recipients aged 70-74 had a 37% lower risk of death compared with WL candidates of the same age (HR=0.63, p<0.001). This age group benefited from KT regardless of their diabetes status and transplant type. Recipients aged ≥75 had an overall 20% lower risk of death compared with WL candidates (HR=0.80, p=0.001). However, no significant difference in mortality risk was observed in diabetic patients within this age group (HR=0.85, p=0.15). When analyzed by transplant type, there was a trend towards reduced mortality in diabetic living donor KT recipients aged ≥75, though it did not reach statistical significance (HR=0.72, p=0.16). No difference in mortality was found for diabetic deceased donor KT recipients aged ≥75 compared to those on the WL (HR=0.89, p=0.35).

Conclusions: KT provides a significant decrease in mortality risk compared to dialysis among individuals aged 70-74 with ESRD on the WL, as well as non-diabetic patients aged ≥75. However, the advantage of KT becomes less evident in diabetic patients aged ≥75, particularly those without living donors.





TH-PO773

Kidney Transplant Outcomes in Patients with BMI of 35 or Greater: Should We Be Doing More? A Single-Center Experience

Arjun Sabharwal, Arif Khwaja, Jacob W. Whatmore. *Northern General Hospital Sheffield Kidney Institute, Sheffield, United Kingdom.*

Background: Obesity remains a key barrier to access to kidney transplantation. Large registry data shows that whilst obese patients have poorer graft survival compared to those with a normal BMI, they still have a survival advantage when compared to outcomes on dialysis. However, it is not clear whether there are similar outcomes in smaller transplant centers. We therefore conducted a single-center audit evaluating transplant outcomes in patients with BMI ≥ 35 at the time of transplant at the Sheffield Kidney Institute, UK from 2010-2023.

Methods: This single center, retrospective study looked at death censored graft survival, medical and surgical complications for a total of 53 patients who were transplanted from 2010 to 2023 with a BMI ≥ 35 kg/m2 at the time of transplant.

Results: A total of 53 transplants were done in the time period in patients with a BMI ≥ 35. The recipient mean age was 58 years (SD 10.7) with a mean BMI of 36.8 kg/m2 (Range: 35-40.9) at the time of transplant. Most common primary disease was IgA Nephropathy(n=11) followed by Diabetic Nephropathy (n=8). Graft failure was observed in 10 patients (18.8%) and 13 (24.6%) died with a functioning graft out of a total 53 transplants. In the 38 patients who had at least 5 years follow up, 23 (60.6%) had a functioning graft and there were 6 graft failures (15.8%) over a median follow up of 6.29 years. Average eGFR for those with functioning grafts were 53.9 ml/min/1.73m2 with a mean graft survival age of 6.8 years. In terms of medical complications 6 (11.3%) had a biopsy proved rejection, 28 (52.8%) had a delayed graft function, post-transplant CMV was seen in 3 patients. New onset diabetes after transplant was observed in 11(28.9%) patients. Six % of grafts failed in the first 3 months. Wound infection was the most common surgical complication n=8 (15.1%) and the average length of stay in hospital was 7.8 days. Readmission rates within 30 days were n=11(20.7%).

Conclusions: Patients with BMI ≥ 35 do have increased medical and surgical complications including NODAT, delayed graft function and wound infection but can be successfully transplanted. Careful patient selection and optimisation may further improve transplant in obese recipients. Patients in smaller centres should not be denied transplantation based on BMI alone and a thorough assessment by the surgeon should be done for them.

TH-PO774

Outcomes among Hispanic Kidney Transplant Recipients Including Non-US Citizens

Sixto G. Giusti, Susana Arrigain, Rocio Lopez, Marco Ramos, Marko A. Karakadze, Lilia Cervantes, Jesse D. Schold, Elizabeth A. Pomfret. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

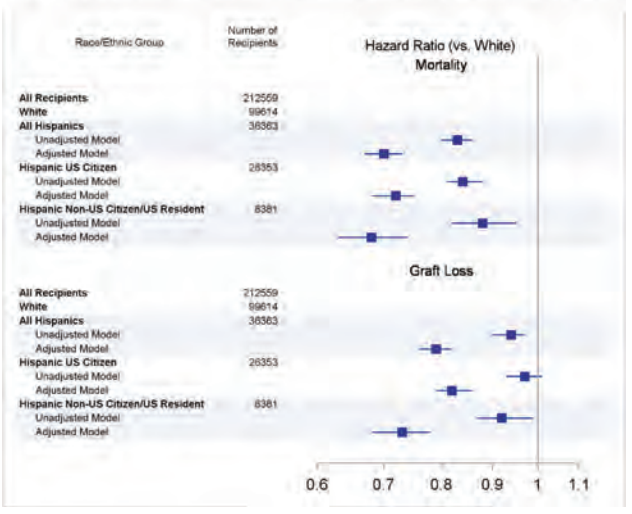
Background: Hispanics experience a faster progression of CKD to kidney failure compared to non-Hispanic Whites (NHW). They are also less likely to receive pre-dialysis nephrology care, be referred for transplant evaluation, be listed for transplant, and receive a transplant. This study compares transplant outcomes between Hispanic individuals and NHW, to demonstrate the benefit of increasing access to transplantation to this patient population.

Methods: We evaluated kidney transplant recipients from 2010-2021 using the SRTR data. For the main outcomes we compared time to post-transplant patient mortality and graft failure between Hispanic and NHW recipients using Cox proportional models adjusted for donor and recipient characteristics.

Results: Among 212,559 kidney recipients, 17% were Hispanic and 47% were NHW. Among Hispanics, 27.5% were non-US citizens. Hispanic recipients were younger than NHW recipients (mean age 48.8+14.1 vs. 53.5+14.0). The average wait list months for Hispanics was 18.4 compared to 12.7 for NHW recipients. 28% of Hispanics had private health insurance compared to 42% of NHW. In adjusted models, Hispanics had a lower HR of death and graft failure compared to NHW recipients (HR=0.70, 95 % CI: 0.67, 0.73, and HR=0.79, 95% CI: 0.76, 0.82, respectively). We found similar results when comparing Hispanic non-US citizens to NHW recipients (HR=0.68, 95 % CI: 0.63, 0.74, and HR=0.73, 95% CI: 0.68, 0.78; Figure 1).

Conclusions: Despite many social and economic challenges and irrespective of citizenship status, Hispanic transplant recipients had a lower HR of death and better graft survival compared to NHW transplant recipients. Future studies that focus on reducing disparities throughout the transplant process and improve access to transplantation in this population are warranted.

Figure 1. Unadjusted and Adjusted Hazard Ratios of Mortality and Graft Failure



TH-PO775

Death and Kidney Failure in 3-Year Survivors of Kidney Transplantation: Influence of Prior Changes in eGFR

Finnian R. McCausland,[1,2] Martina M. McGrath,[1,2] Brian Claggett,[1,2] Edgar L. Milford,[1,2] Andrew S. Levey,[3] Marc A. Pfeffer.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Tufts Medical Center, Boston, MA.*

Background: Kidney transplant recipients (KTRs) continue to experience high rates of allograft failure and death. We explored if changes in eGFR between the first and third year post-transplant could identify patients at higher risk for subsequent allograft failure and death.

Methods: From 149,058 adult KTRs in the UNOS database who received a first kidney transplant from 2009-2019, we included 109,198 who survived to 3 years post-transplant with a functioning allograft and available baseline and follow-up (1- and 3-year post-transplant) serum creatinine. We calculated eGFR using the 2021 CKD-EPI equation and used Cox models, landmarked at 3-year post-transplant, to explore the association of eGFR decline (<0, 0-<5, and ≥5 mL/min/1.73m^2/year) with subsequent development of the composite of allograft failure or death (median follow-up 3.5 yrs). Models were adjusted for age, sex, race, diabetes, BMI, baseline eGFR, graft vintage, and donor status (living/cadaveric).

Results: During the two-year exposure period, 50,796 (44%), 33,611 (31%), and 24,791 (23%) experienced eGFR decline <0, 0-<5, and ≥5 mL/min/1.73m^2/year, respectively. Patients in the highest category of eGFR decline were more likely to be younger, female, Black, diabetic, received a cadaveric donor, have lower BMI, yet higher baseline eGFR. Overall, beginning 3 years post-transplant, 31,302 (23%) of patients developed allograft failure or death. Compared with eGFR decline <0, patients experiencing an annual decline >5 mL/min/1.73m^2 had a 2.6-fold (HR 2.62; 95%CI 2.55, 2.70) higher adjusted risk of allograft failure or death (Table 1).

Conclusions: In a contemporary cohort of KTRs, who survived at least 3 years post-transplant, rates of subsequent allograft failure and death remain unacceptably high. An eGFR decline >5 mL/min/1.73m^2/year in the prior two years is an easily calculable metric and identifies patients at markedly higher risk of future allograft failure and death.

	Category of annualized eGFR decline		
	<0 ml/min/1.73m^2	0-<5 ml/min/1.73m^2	≥5 ml/min/1.73m^2
	n=50,796 (44%)	n=33,611 (31%)	n=24,791 (23%)
Age, years	53 ± 13	54 ± 13	52 ± 14
Female, n(%)	18274 (36.0%)	13347 (39.7%)	11731 (47.3%)
Black, n(%)	13014 (25.6%)	8939 (26.6%)	6701 (27.0%)
History of Diabetes, n(%)	16283 (32.1%)	11239 (33.4%)	8985 (36.2%)
Body mass index, kg/m2	28.0 [24.4 , 32.1]	27.8 [24.2 , 31.9]	27.4 [23.7 , 31.7]
eGFR, ml/min/1.73m^2 at yr 1	59 ± 19	62 ± 21	72 ± 21
Living Donor, n(%)	18554 (36.5%)	12274 (36.5%)	8458 (34.1%)
Kidney failure or death			
Rate (95%CI) per 100 pt yrs	20.8 (20.5, 21.2)	25.6 (25.1, 26.1)	39.2 (38.4, 40.0)
No. Events (%)	11,869 (23%)	9,622 (29%)	9,811 (40%)
Unadjusted Hazard Ratio (95%CI)	Ref	1.22 (1.19, 1.26)	1.92 (1.87, 1.97)
Adjusted Hazard Ratio (95%CI)	Ref	1.32 (1.29, 1.36)	2.62 (2.55, 2.70)

TH-PO776

Model-Based Inference of the Living-to-Deceased-Donor Ratio among Living Kidney Transplant Patients in the United States

David J. Joerg,[1] Doris H. Fuertinger,[1] Benjamin E. Hippen,[2] Peter Kotanko.[3,4] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Global Medical Office, Fresenius Medical Care, Waltham, MA; [3]Renal Research Institute, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: In the United States, statistics on the proportions of incident kidney-transplant patients with living-donor (LD) or deceased-donor (DD) kidneys are available via the Organ Procurement & Transplantation Network (OPTN) database. However, data on the prevalent patient population with an LD/DD kidney transplant is not widely available, as longer-term follow-up and outcomes reporting is not uniform. As DD kidney transplants are more common than LD transplants but also result in inferior mean long-term patient and graft survival, the prevalent population of patients with a functioning transplant by donor-type is likely different from the incident transplant population.

Methods: Using a two-compartment modeling approach capturing transplantation, graft failure and mortality by donor-type, we inferred a range for the LD proportion in 2020. Rates for modelled processes were sourced from the US Renal Data System's Annual Data Report 2023. A multitude of model simulations (N = 100,000) were performed, initialized with LD proportions ranging between 0% and 100% in 2001, reflecting the uncertainty about past prevalent proportions (Fig. 1a,b). The model then simulated kidney-transplant patient numbers by donor type until 2020.

Results: Model simulations converged towards an LD proportion of 44% ± 3% (mean ± sd.) in 2020 (Fig. 1c), a relatively narrow band compared to the wide range of initial proportions. This is because of mean patient and graft survival times being shorter than the simulation period (19 y). Thus, final proportions are dominated by the balance of incidence, graft failure and mortality in the preceding years.

Conclusions: Modeling results suggest that the proportion of prevalent patients in the U.S. with a functioning graft from a living donor is 45%. Based on these results, the long-term care workforce might be faced with both (a) "long-graft-survivor" living donor recipients disproportionately represented in the prevalent transplant population, and (b) a higher volume of patients with earlier graft failure after deceased donor transplants.

Funding: Commercial Support - Fresenius Medical Care

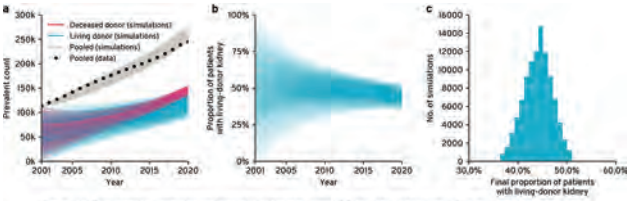


Figure 1: (a) Total counts of transplant patients with a deceased-donor (DD, red) and living-donor (LD, blue) kidney transplant according to the simulation model; different simulation curves correspond to different initial conditions with varying initial LD proportion (see panel b). Pooled (LD+DD) counts shown for simulations (gray), compared against data (dots) from the USRDS Annual Data Report 2023 (Reference Table D.9). (b) Living-donor proportion for the model simulations shown in panel a. Panels a and b show 1,000 simulations for visual clarity. (c) Distribution of final (2020) living-donor proportions in model simulations. (N = 100,000 simulations)

TH-PO777

Impact of Donor Sex on Graft Outcome in Deceased Donor Kidney Transplantation

Thei S. Steenvoorden, Liffert Vogt, Marc Hilhorst, Frederike J. Bemelman, Jesper Kers, Hessel Peters-Sengers. *Amsterdam UMC Locatie AMC, Amsterdam, Netherlands.*

Background: Clinically relevant differences between human sexes have been made apparent in many diseases, but studies in kidney transplantation have been producing varying results. Because of recent insight in the possibly fundamental differences between grafts donated after brain death (DBD) and after circulatory death (DCD), we postulated that it is important to look at the effects of donor and recipient sex for donor types individually.

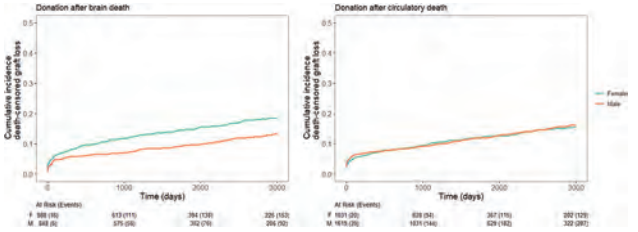
Methods: We requested data from the national renal replacement registry of the Netherlands and the Scientific Registry of Transplant Recipients (SRTR, United States). We used cumulative incidence competing risk (CICR) analyses treating recipient death as competing event, and confounder-adjusted cause-specific cox-regression analyses to determine the association of donor sex and donor-recipient sex matching with death-censored graft loss (DCGL) in DBD and DCD.

Results: In the Dutch cohort (2010-2024), there were 988 female DBD and 848 male DBD donors, CICR showed that DCGL was more common in grafts from female donors than in male donors (Figure A). Cerebrovascular accident was more common in female donors and donor age was higher than in male donors. After covariate adjustment, the adjusted hazard ratio (aHR) for female DBD donors was 1.43 (95% CI: 1.08–1.88; reference male DBD donors, p=0.013). This association was independent of recipient sex and weight mismatching. There were no differences in DCGL between the grafts from 1031 female and 1619 male DCD donors (Figure B). In a preliminary external validation of these findings in data from the SRTR (DBD N = 112,873, DCD N = 38,289), female

donor sex also had a differential impact on DCGL in DBD and DCD. Driving factors explaining these between-sex differences will be analyzed in both cohorts together with kidney biopsy data.

Conclusions: Donor sex has a differential impact on outcome specific to donor type.

Funding: Commercial Support - Health Holland B.V.



Incidence of death-censored graft loss with competing risk recipient death.

TH-PO778

Patient and Graft Survival Rates at 5 Years following Kidney Transplant at the National Transplantation Center in Ethiopia

Solomon T. Amade. *Saint Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia.*

Background: In Ethiopia living donor kidney transplantation was started in September 2015 at the National Transplantation Center. The center was established in Saint Paul Hospital Millennium Medical College (SPHMMC) in collaboration with the Ethiopian Federal Ministry of Health and Michigan University. One year death censored graft survival rate was 98.5%. This study was conducted to determine five-year patient and graft survival among the cohort of recipients operated from September1 2015 to November 15 2018.

Methods: A retrospective study of the cohort was conducted. Recipient and donor data were collected from the medical records using a structured printed tool. The collected data were entered and analyzed using IBM SPSS statistics version 29.0.2.0. Five-year graft and patient survival rates were determined. Predictors of five year patient and graft survival were identified using logistic regression. Ethical clearance was obtained from the institutional review board of SPHMMC. Data collection took place from November 15 to December 12 2023.

Results: Ninety two recipients were included. Mean ± SD age was 34.07 ± 11.26 years. Sixty-four (68.8%) were male. Mean ± SD age of donors was 34.9 ± 11.9 years. All except 9 (9.8%) were related to the recipient. Basiliximab was the induction regimen for 93.5%. Tacrolimus, MMF and prednisolone were maintenance immunosuppressive for 95% of recipients. Five year patient survival was 83.7%. Age ≥ 40 years, longer duration of post-op admission, serious infection during follow-up, graft rejection and graft biopsy predicted significantly reduced five year patient survival. OR (95% CI) were 0.19 (0.05-0.77), 0.92 (0.86 - 0.99), 0.06 (0.01 - 0.47), 0.14(0.03-0.64) and 0.21(0.06 - 0.74) respectively. Tertiary education predicted better five year patient survival OR (95% CI) 6.73(1.16-39.09). Five year death censored graft survival was 90%. Donor 24 hour urinary protein level, record of graft rejection and number of hospital admissions predicted reduced five-year death censored graft survival with OR (95% CI) of 0.98 (0.96 – 0.99), 0.01(0.001-0.1) and 0.39 (0.22 – 0.71) respectively.

Conclusions: Five year survival rate of recipients at the National Transplantation Center of Ethiopia is acceptable. The death censored graft survival rate at five years is comparable to those in developed regions.

Funding: Government Support - Non-U.S.

TH-PO779

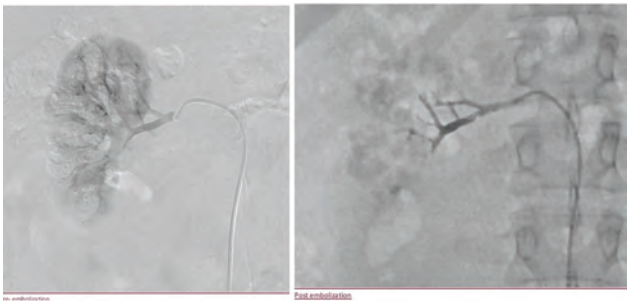
Residual Native Kidney Function after Kidney Transplant (KT): Unusual Complications

Abdallah Abdelrazeq, Swati Rao, Ziv J. Haskal, Jeanne Kamal. *University of Virginia, Charlottesville, VA.*

Introduction: Bartter syndrome, affects 1 in 1,000,000, presents challenges in KT recipients with residual native renal function. We present the clinical course of a KT recipient with suspected Bartter syndrome.

Case Description: 26-year-old man with CKD V underwent a preemptive deceased donor KT. Kidney biopsy (bx) 7 years ago revealed interstitial nephritis with moderate fibrosis and tubular atrophy, attributed to prolonged NSAID use. He had persistent hypokalemia requiring supplementation. Post-transplant, he experienced slow graft function (SGF), serial allograft bx showed acute tubular injury. He received thymoglobulin induction and a calcineurin-inhibitor (CNI)-based maintenance immunosuppression regimen. Due to ongoing SGF with nadir creatinine (Cr) of 4, he was switched to a CNI-free regimen with Belatacept. His electrolyte profile showed hypokalemia, and a significant urine output of 3-5 L/day, requiring scheduled fluid administration after which Cr improved but plateaued at 3. Technetium-99m mercaptoacetyltriglycine perfusion scan (MAG3) with split function analysis showed a 32.6% contribution from native kidneys. raising suspicion of Bartter syndrome, with preserved native output leading to chronic hypovolemia and allograft dysfunction. Following multidisciplinary discussion, including the patient's input, native right renal artery embolization with 10 mL of Visipaque 270 was performed 9 months post-transplant. Procedure was tolerated well. Cr, 1 month after, improved to 2.9, with long term follow-up awaited.

Discussion: Residual kidney function in tubulointerstitial, salt-wasting diseases can challenge KT, impending allograft function. In such disease, timing of KT is crucial. Delaying until no residual renal function or considering preemptive native nephrectomy may minimize allograft failure risk. Native kidney embolization is a minimally invasive alternative to nephrectomy, though its efficacy remains unproven in KT. We plan to update MAG3 to assess left native kidney function and consider contralateral embolization.



Selective Native Renal Artery Embolization:Radiological Procedure

TH-PO780

Fistula Ligation after Kidney Transplant: Yes or No?

Farah M. Ahmed,[1] Rosa M. Montero.[2,1] *[1]St George's University of London, London, United Kingdom; [2]St George's University Hospitals NHS Foundation Trust, London, United Kingdom.*

Background: Cardiovascular disease (CVD) accounts for 30-35% of all-cause mortality in kidney transplant recipients (KTR) causing 25% of deaths 1-year post-transplant. Arteriovenous Fistulas(avf) have been shown to contribute to CVD progression with up to 42% of ESRD patients on dialysis developing Heart Failure and Pulmonary Hypertension. We report our experience with avf ligation in KTR.

Methods: A single centre retrospective observational study of all KTR with existing avf at the time of their transplant between 1983-2023 were included. Demographic and clinical outcome data was collected from electronic patient records including dates of avf formation and ligation, echocardiogram (echo) details at baseline and post-transplant. All KTR were categorised into 4 groups according to EF; group 1 <35%, group 2 36-49%, group 3 50-54%, group 4 ≥55% according to British Society of Echocardiography classification. Paired t-tests and ANOVA were used to perform statistical analysis with a $p<0.05$ significant level.

Results: 340 KTR from 1983- 2023 had avf in our centre. 214 Male, 126 female with a median age 63yrs (25-88yrs). 122 White, 80 Black, 97 Asian, 6 Chinese, 24 Other, 11 Unknown. 142 (42%) had avf ligation of which 17 KTR previously had >1 avf ligated leaving 116 KTR with avf ligated in total (73Male, 43Female). 20% (23/116) died unrelated to the procedure. Median time avf duration 9yrs (1-41yrs), median time post-KT avf ligation 5yrs (0-21yrs). 52% (61/116) had pre-KT echo classified according to EF: Group 1 had 1 KTR, Group 2: 5, Group 3: 8 Group 4 47. 20 KTR had a subsequent echo post ligation. 55% (11/20) had pre and post echo with 6 KTR showing an improvement moving from group 3 to 4(5) and group 2 to 4(1) in this small sample ($p=0.06$). Creatinine significantly improved pre-post KT ($p<0.001$). The changes were not related to the type of avf.

Conclusions: Many KTR did not meet the criteria for echo pre- transplant work-up leading to a smaller cohort. 11 KTR had an echo after avf ligation. An insignificant trend towards improvement in EF was seen despite the small sample size. Given the lack of guidance in this area consideration should be given to performing an echo 1 year after ligation to determine whether there is any improvement in cardiac function given the high cardiovascular morbidity and mortality of KTR.

TH-PO781

Venous Outflow Obstruction: A Rare Cause of Shock in a Recent Kidney Transplant Patient

David Wilhelm, Saed Shawar. *Vanderbilt University, Nashville, TN.*

Introduction: There are four recognized types of shock: distributive, cardiogenic, hypovolemic, and obstructive. Septic shock is the most common among ICU patients, while obstructive shock is rare. We present a case of venous outflow obstruction causing shock in a recent kidney transplant patient.

Case Description: A 64-year-old female with end-stage kidney disease (ESKD) secondary to diabetes and hypertension, who had undergone a living-related kidney transplant with immediate graft function, was readmitted one week later with fatigue, lightheadedness, significant right greater than left lower extremity swelling, acute kidney injury, and shock. A full workup for shock revealed no evidence of infectious, cardiologic, or endocrinologic causes. A CT scan of the chest, abdomen, and pelvis without contrast showed no acute chest abnormality but identified a hyperdense area in the right external iliac vein, raising concerns for deep vein thrombosis. Additionally, it showed a narrowed right common iliac vein and inferior vena cava (IVC). A CTA of the pelvis with bilateral lower extremity runoff revealed right greater than left edema and no venous enhancement in the right iliac vein. Interventional radiology performed venography and found an atretic right common iliac vein and IVC with multiple collaterals. Venoplasty and stent placement were performed, extending from the IVC to the right external iliac vein. The patient's hypotension resolved upon relief of the venous obstruction, and she experienced significant improvement in lower extremity swelling.

Discussion: This case represents a rare cause of shock. Although the patient was treated with broad-spectrum antibiotics, a thorough infectious workup was negative. Further evaluation for other causes of shock was also unremarkable. The patient's shock resolved with relief of the obstruction, indicating this as the primary etiology. The cause of venous obstruction in this patient was unknown. Risk factors for venous stenosis include thrombotic and non-thrombotic etiologies. Non-thrombotic causes include extrinsic vein compression or obstruction related to an intraluminal device. For ESKD patients, vein stenosis related to the presence of a dialysis catheter is a specific etiology to consider. In summary, this case of venous outflow obstruction highlights the importance of maintaining a broad differential diagnosis in patients presenting with shock.

TH-PO782

Patient Review of Informed Consent Form as Best Practice in Clinical Trial Design

Devra Densmore. *Elevate Advocacy, Chicago, IL.*

Background: The informed consent form (ICF) is one of the most important documents in a clinical trial, because it contains all essential and relevant information on both what will happen within a study and what is expected and provided to a study participant. However, rigorous reviews by members of the patient population being studied are not done consistently in the study design and development process. Our objective was to optimize readability and understandability of patient-facing clinical study materials for kidney transplant-related interventional clinical trial by facilitating asynchronous review of informed consent form (ICF) by global panel of kidney transplant patients and advocates.

Methods: Three separate asynchronous 10-day reviews of draft ICF were provided to individual (3) global patient reviewers via a secure online platform in August, October, and December 2023.

Results: Elevate Advocacy, in partnership with one of its sponsor clients, facilitated three separate reviews by three global patients and advocates who had experience with post-kidney transplant complications. Although the three reviewers were from different countries, racial and ethnic backgrounds, trial experience (e.g., naive vs experienced), sexes, and ages, 68% of their comments and suggestions were independently aligned. In total, 183 comments, questions and suggestions were provided on a 19-page draft ICF. An in-depth review of all comments was conducted to understand what feedback should be incorporated into the ICF (50%). Recommendations included: ● A schematic design of the study visits, dosing schedule, and timeline ● A pronunciation guide for the study drug ● Language that was universally understood by global audiences ● Formatting changes of dense text into sections and bulleted lists

Conclusions: Patients and advocates can provide valuable insights and feedback on patient-facing study materials to make them more understandable for clinical trial participants. Patient-facing study materials review can be a safe, low-cost, and highly valuable exercise that benefits both the study and the study participants. To be most successful, reviews should be iterative and allow enough time for patient reviewers to provide feedback (7-10 days), internal program teams to analyze and discuss the incorporation of comments into the ICF, and internal review committees to determine if template changes should be made.

Funding: Commercial Support - argenx

TH-PO783

Unique Case of Hemosiderosis-Induced Ascites in Kidney Transplant Recipient

Mansoor Ahmed, Sakil A. Bhuiyan, Navdeep Kaur, Rula A. Abdulrahman, Farah Daccueil. *Stony Brook University, Stony Brook, NY.*

Introduction: Iron overload or hemosiderosis is often a frequent complication from intermittent blood transfusions. Anemia of end stage kidney disease (ESKD) is managed with IV iron and erythropoietin stimulating agents (ESAs) and these patients are at risk of iron overload, especially those with increased dialysis vintage. Here we describe a unique case of recurrent ascites caused by secondary hemosiderosis in a kidney transplant recipient who was on Peritoneal Dialysis (PD) for 12 years.

Case Description: A 61-year-old female with ESKD secondary to presumed Hypertension underwent 2nd deceased donor renal transplant(DDRT) in 2023. She was on PD from 2011 to 2023. She required 8 units of PRBC's peri-operatively. Nadir creatinine 0.77 mg/dl. Post-transplant course complicated with COVID PNA, transplant renal artery stenosis requiring stent placement. She developed ascites three months post-transplant requiring frequent large volume paracentesis which was contributed to hepatic congestion in setting of heart failure with preserved ejection fraction (HFpEF). Seven months post-transplant she developed AKI in setting of E.coli bacteremia, CMV viremia and a transplant renal biopsy was performed showing focal endothelialitis, suggesting T cell mediated rejection, CMV nephritis and renal hemosiderosis and about 40% IFTA. Labs also showed iron levels of 15, Ferritin of 1400, TSAT 27%, AST/ALT normal, with elevated ALP 130. MRI liver was done which showed mild diffuse gain of signal in liver and spleen. A liver Biopsy was also performed which showed nodular regenerative hyperplasia and 1-2+ iron staining in Kupffer's cells + hepatocytes and no evidence of fibrosis. Given liver biopsy findings and multiple transfusion history, it can be hypothesized that recurrent ascites was likely to secondary hemosiderosis rather than HFpEF. Patient's AKI recovered with treatment of underlying infection. Of recent, she has not required paracentesis.

Discussion: Here we describe an interesting case of a transplant patient with high dialysis vintage who developed recurrent ascites due to renal hemosiderosis. It is possible that long term IV iron exposure and multiple transfusions immediately post-transplant lead to secondary hemosiderosis. Long term PD could be contributing to development of ascites as well.

TH-PO784

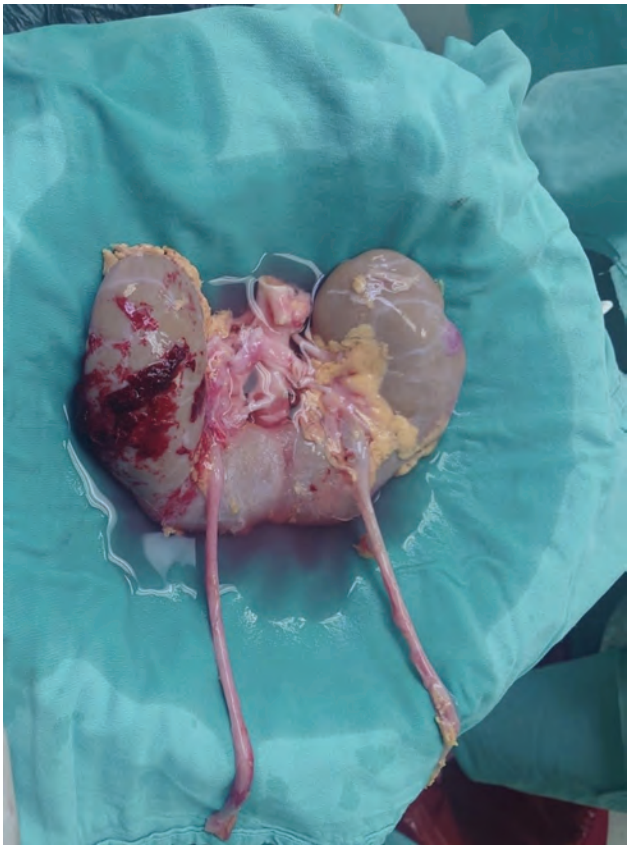
Case Report of First Kidney Transplant in Mexico Using Horseshoe Kidney from a Cadaveric Donor in a Single Recipient

Joary Vargas Santana, Asdrubal Guevara-Charles, Marco A Hernández-Guedea, Mara C. Olivo Gutierrez, Allina P. Flores Mendoza. *Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico.*

Introduction: Horseshoe kidneys are the most common fusion defect of the kidneys, with a reported frequency of approximately 1:500. They are characterized by anomalies in the position, rotation and vascular supply of the kidney.

Case Description: The recipient was a 51-year-old female patient, with a history of chronic kidney disease of unknown etiology diagnosed in 2012, she received a first kidney transplant from a deceased donor in 2014. She entered to transplant protocol for a 2nd kidney transplant in 2019 with eGFR CKD EPI 13 ml/min/1.73m^2. A horseshoe kidney transplant with 2 arteries and 2 veins per kidney, a infraumbilical laparotomy approach was performed, bloc implant with arterial anastomosis to the right common iliac artery and venous anastomosis to the infrarrenal cava, induction immunosuppression was with thymoglobulin and methylprednisolone. She presented spontaneous uresis after graft reperfusion, she was discharged on March 12, 2024, with creatinine 0.4 mg/dl.

Discussion: There is little evidence of related cases of kidney transplant associated with horseshoe kidney, there are case reports that show en bloc transplantation to 2 recipients, unlike our case that includes a single recipient. Currently considered technically and biochemically successful, long-term surveillance continues to assess graft survival and whether there are complications associated with using this type of graft with anatomical variant, since they have been associated with associated syndromes and subsequent malignancy.



TH-PO785

Prevalence and Correlates of Hepatic Steatosis and Fibrosis in Patients with CKD before Kidney Transplantation: A Retrospective Cohort Study

Carlo Alfieri,[1,2] Rosa Lombardi,[1,2] Anna Regalia,[1] Simona Verdesca,[1] Mariarosaria Campise,[1] Emilietta Brigati,[1] Margherita Di Naro,[1] Anna Sikharulidze,[1] Giuseppe Castellano,[1,2] Paolo Molinari.[1] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Universita degli Studi di Milano, Milano, Italy.*

Background: Metabolic dysfunction associated steatotic liver disease (MASLD), is closely linked to CKD and increases the risk of hepatic fibrosis and cardiovascular damage. MASLD is common in the general population but data on dialysis patients is limited. We aim to assess the prevalence of MASLD and related factors in kidney transplant patients at the time of list admission.

Methods: We studied 531 kidney transplant patients (age 49±13, 59% male) from 2010-2020. We noted their data at admission. Hepatic steatosis (HS) was gauged by hepatic steatosis index (HSI), with >36 as pathological (HSI+). Advanced fibrosis (>F3) was assessed by Fibrosis-4 index (FIB4), with >1.3 and >2.66 as borderline and pathological (FIB4+), and the NAFLD Fibrosis Score (NFS), with >-1.455 and >0.676 as borderline and pathological (NFS+).

Results: In our study, 67.2% of patients had hemodialysis. At evaluation, 8.8% had diabetes, 15% were obese, and 37.5% had steroid treatment history. Glomerulonephritis and polycystic kidney disease caused nephropathy in 20% and 18% of cases, respectively. HSI, FIB4, and NFS averages were 32.9±6.01, 1.25±1.07, and -1.75±1.5. FIB-4 and NFS correlated strongly (r=0.65, p<0.0001). HS by HSI+ was in 27.5% of patients, while hepatic fibrosis by FIB4+ and NFS+ was in 32.8% and 39.3% of patients. HSI+ patients were older with higher BMI, glucose, and urea levels. FIB4+ and NFS+ patients were older with higher glucose and CRP levels. NFS+ patients had higher BMI. These results confirm the concordance between the two fibrosis markers. In multivariate analysis, BMI and urea were independent risk factors for hepatic steatosis by HSI, while age and CRP were independent risk factors for hepatic fibrosis by both FIB4+ and NFS+.

Conclusions: Our data reveals a high occurrence of MASLD in patients awaiting kidney transplants, particularly in older, overweight individuals. Inflammatory parameters independently predicted hepatic fibrosis, suggesting their potential role. FIB4 and NFS showed a strong correlation, validating their use as fibrosis markers. Future research could shed light on the causes, risk factors, and impacts of HS and fibrosis on kidney transplant outcomes.

TH-PO786

Association between Noninvasive Liver Biomarkers and Graft Outcomes in Kidney Transplant Recipients

Jaeyun Lee, Chung Hee Baek, Hyosang Kim, Chan-Young Jung. *Asan Medical Center, Songpa-gu, Seoul, Republic of Korea.*

Background: Though studies have suggested that metabolic risk profiles may be prognostic factors in kidney transplant recipients (KTRs), the prognostic significance of fatty liver severity, a known surrogate of metabolic risk, in KTRs has not been previously investigated. This study aimed to evaluate the association between non-invasive liver biomarkers and graft outcomes in KTRs.

Methods: Patients who underwent deceased or living donor kidney transplantation (KT) between January 2000 and December 2022 were collected. Hepatic fibrosis burdens of KTRs were assessed using the Fibrosis-4 (FIB-4) score and the non-alcoholic fatty liver disease fibrosis score (NFS), one month after KT. The primary outcome was a composite of 50% estimated glomerular filtration rate (eGFR) decline and graft failure. Secondary outcomes included individual outcomes of 50% eGFR decline, graft failure, and acute rejection including both cellular and antibody-mediated rejection.

Results: A total of 3,092 patients were grouped into three categories according to FIB-4 scores. During a mean follow-up of 6.0 years, the composite outcome occurred in 519 (2.8/100 person-years) patients. For the secondary outcomes, incidence rates for 50% eGFR decline, acute rejection, and graft failure were 2.3, 2.3, and 1.5 per 100 person-years, respectively. The cumulative incidences of all outcomes were higher in patients with higher FIB-4 scores (all P <0.05; Fig 1). In multivariate Cox models, the highest score group (FIB-4≥2.67) had a 2.05-fold (95% confidence interval [CI], 1.44-2.91; P<0.001) higher risk of the composite outcome compared to the lowest score group (FIB-4<1.30). The highest score group showed higher risk of the secondary outcomes compared to the lowest score group, with risk ratios of 1.75 (95% CI, 1.16-2.66), 1.62 (95% CI, 1.06-2.46), 2.23 (95% CI, 1.43-3.46). Similar findings were observed for NFS.

Conclusions: Higher liver fibrosis scores were associated with unfavorable graft outcomes in KTRs.

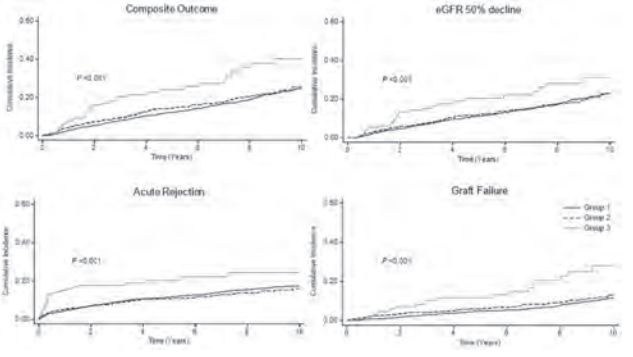


Figure 1. Cumulative incidence of graft outcomes according to FIB-4 score

TH-PO787

Association between Kidney Allograft Fibrosis and Magnetic Resonance Elastography-Derived Stiffness in Kidney Transplant Recipients

Pantipa Tonsawan, Kattareeya Jandaboot, Ubonrat Toimamueang, Pakorn Kiatsopit, Ukrit Rompsaithong, Julaluck Promsorn. *Khon Kaen University, Nai Mueang, Thailand.*

Background: Kidney biopsy remains the gold standard for assessing fibrosis. However, it is an invasive procedure and leads to significant complications. Magnetic resonance elastography (MRE) has been evaluated as an alternative method for evaluating fibrosis, but the results are still inconclusive. Herein, we aimed to determine the association between MRE-derived whole stiffness and interstitial fibrosis and tubular atrophy and urinary transforming growth factor (TGF) beta.

Methods: We conducted a cross-sectional study involving adult kidney transplant patients who required kidney biopsy. Enrolled patients underwent evaluation using two-dimensional gradient-echo MRE within 2 days prior to biopsy, enabling the determination of MRE-derived whole kidney stiffness through computer-assisted techniques. Urinary TGF beta was collected at the biopsy date and measured by ELISA. Pathological results were classified according to the Banff classification system. Correlations between MRE-derived whole kidney stiffness, histologic fibrosis, and urinary TGF beta were analyze.

Results: 21 patients were calculated for interim analysis. Majority were deceased donor kidney transplant patients (90.5%). Median transplant vintage was 8.6 years (interquartile range [IQR] 3.8-11.1 years) with a median estimated glomerular filtration rate of 36.6 ml/min/1.73 m^2 ([IQR] 24.3-49.6 ml/min/1.73 m^2). Most common biopsy indication was allograft dysfunction. We found that mean MRE-derived whole kidney stiffness was a significant negative correlation to the overall nephron fibrosis and ct scores

(*Rho* = -0.48, p=0.03, *Rho* = -0.47, p=0.03, respectively). In addition, there was a trend to negatively associate ci and cv scores and whole kidney stiffness. However, MRE-derived kidney stiffness did not show a significant correlation with urine TGF beta.

Conclusions: MRE-derived whole kidney stiffness correlates with nephron fibrosis, suggesting that MRE could offer a promising alternative for fibrosis evaluation in kidney transplant recipients.

Funding: Government Support - Non-U.S.

TH-PO788

Radiomic Texture Features in CT Images of Kidneys in Ventilated Deceased Donors Predict Delayed Graft Function

Fayzan Ali,[1] Edwin Baldelomar,[2] Jennifer R. Charlton,[3] Richard L. Wahl,[2] Gary F. Marklin,[4] Kevin M. Bennett.[2] *[1]Saint Louis University School of Medicine, St Louis, MO; [2]Washington University in St Louis School of Medicine Mallinckrodt Institute of Radiology, Saint Louis, MO; [3]University of Virginia Department of Pediatrics, Charlottesville, VA; [4]Mid-America Transplant, St. Louis, MO.*

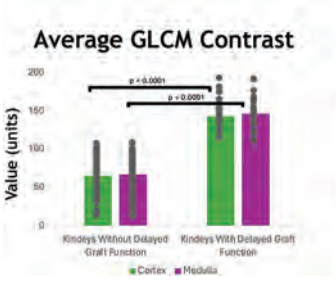
Background: Kidney transplants are a life-saving resource for ~25,000 patients each year. 80% of allografts come from deceased donors. The success of kidney transplants is affected by variable organ quality and recipient factors. However, there is no method to reliably predict which kidneys will be successful. We investigated the use of contrast-enhanced Xray-CT images of the kidneys in ventilated deceased donors, acquired during assessment for cardiovascular function. We hypothesized that radiomic features from CT images of deceased donors under ventilation, scanned before the kidneys are removed, associate with transplant outcomes measured by delayed graft function (DGF) after transplant in recipients.

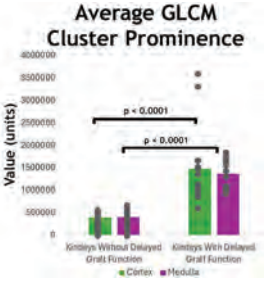
Methods: We acquired CT images of 102 (65M, 37F) ventilated, brain-dead donors at a single organ procurement organization (1/2019-6/2019). Scans were acquired with a Siemens 64-slice Somatom and Optiray 350 contrast. The primary outcome was DGF defined as need for dialysis within a week after transplant, obtained from the Scientific Registry of Transplant Recipients. Donors of all transplanted kidneys were included. Donors whose kidneys were not transplanted were excluded. Texture features (n=64) were extracted from three image slices of each kidney using Lifex. ANOVA was performed with a Bonferroni correction to determine significant prediction of DGF (p<0.01).

Results: Two image texture features, Grey Level Co-occurrence Matrix (GLCM) Contrast and GLCM Cluster Prominence, predicted DGF. These features measure heterogeneity and may reflect microvascular ischemia. Significantly higher GLCM Contrast and Cluster Prominence were observed in both cortex and medulla in kidneys with DGF (p<0.01).

Conclusions: Two radiomic features in CT images of kidneys in ventilated deceased donors were highly predictive of DGF. With further validation, this approach could provide a sensitive, individualized measure of deceased donor kidneys to improve functional assessment resulting in transplantation. It could also enable studies of optimal donor management to improve allograft function.

Funding: Private Foundation Support





TH-PO789

Relationship between Parenchymal Stiffness and Kidney Fibrosis in Kidney Transplant Recipients

Kohei Unagami,[1,2] Ayaka Saitoh,[1,2] Toshihito Hirai,[1] Kazuya Omoto,[1,2] Tomokazu Shimizu,[1,2] Junichi Hoshino,[1] Toshio Takagi,[1] Hideki Ishida.[1,2] *[1]Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan; [2]Yochomachi Clinic, Shinjuku-ku, Japan.*

Background: Transplant kidney biopsy has been the method for evaluating interstitial fibrosis and tubular atrophy (IF/TA) of renal allografts. However, its invasiveness, limited sequency and quantitation are shortcomings. Transient elastography (TE) is a device primarily used for measuring liver cirrhosis under ultrasound. TE may have shown promise for assessing transplanted kidney located in the iliac fossa unlike own kidneys, which are located deep from the body surface. We investigated the parenchymal stiffness of renal allografts in kidney transplant recipients and its correlation with renal allograft fibrosis and renal function.

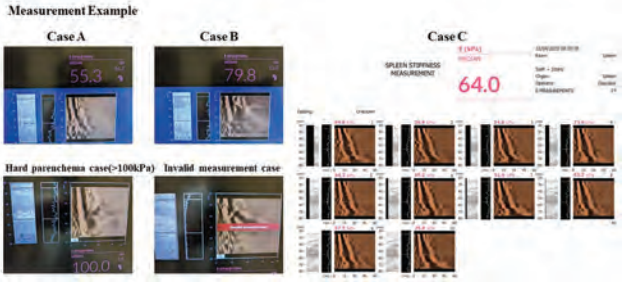
Methods: A total of 455 recipients who underwent kidney transplantation between 2001 and 2023 were included in this study. All recipients underwent TE using FibroScan®expert630 (Echosense Paris, France) (Figure1). TE measured parenchymal stiffness in a volume approximating a cylinder of 25-55 mm in length.

Results: Parenchymal stiffness measurement was successful in 450 of 455 patients (98.9%). The median stiffness of renal allograft parenchyma was 46.7 kPa. Correlations with TE median values, recipients' serum creatinine levels, eGFR, and IFTA showed statistically significant differences (p <0.01 in each). Further division into two groups (eGFR >40 and ≦40) revealed significant differences in allograft kidney age, renal allograft parenchyma, and recipients' hemoglobin levels (p <0.01).

Conclusions: Renal function deterioration and IF/TA progression exhibited a robust correlation with renal allograft parenchyma by TE. TE is non-invasive, exhibits excellent reproducibility and rapidity, and is considered highly valuable for quantitative evaluation of IF/TA.

Funding: Private Foundation Support

Figure1.



Correlation with renal allograft parenchyma

	Spearman's rank correlation coefficient(ρ)	P value
eGFR	0.26	<.01
Cre (mg/dL)	-0.29	<.01
Hb (g/dL)	0.16	.07
Age at Kidney Transplantation (Y)	0.09	.45
Years elapsed since transplantation (Y)	-0.24	.03
IFTA (%)	-0.39	<.01

Confounding factors in assessment

	eGFR<40 (N=245)	eGFR≧40 (N=210)	p
allograft kidney age (Y)	68.8 ± 12.2	60.7 ± 9.4	<.01
Recipient age (Y)	54.2 ± 13.2	55.1 ± 9.6	.78
renal allograft parenchyma (kPa)	55.4 (32.6, 91.2)	43.3 (20.9, 55.9)	<.01
Hb (g/dL)	13.6 (12.8, 14.2)	12.8 (11.8, 13.8)	<.01

TH-PO790

Venous Excess Ultrasound (VExUS) and Lung Ultrasound (LUS) in Post-transplant (PosKTx) Volume Assessment (VA): Is There a Place for Them?

Haridian Sosa Barrios,[1,2] Irene Minguez,[1] Victor Burguera,[1] Cristina Galeano,[1] Sandra Elias,[1] Miriam Roncal Redin,[1] Jorge Sánchez,[1] Raquel Moreno Garcia,[1] Milagros Fernandez-Lucas,[1,2] Maite Rivera Gorrin.[1,2] Grupo de Nefrología Diagnóstica e Intervencionista de la Sociedad Española de Nefrología (GNDI). *[1]Hospital Universitario Ramon y Cajal, Madrid, Spain; [2]Universidad de Alcala, Alcala de Henares, Spain.*

Background: VA in the posKTx period reduces morbidity and mortality, saving resources.LUS, VExUS and bioimpedance (BIA) are volume evaluation methods on the rise.

Methods: Prospective single-center study (4-12/23):31 pts (Group1) VA days+1 and +7 (LUS, VExUS, BIA and physical examination (PE) vs 40 previous KTx (Group 2) assessed clinically.

Results: Characteristics in table 1. No differences at baseline or evolution (delayed function, RRT, hospitalization or cardiovascular events (CVE) nor weight gain day+1, although there were 6 acute pulmonary edema in group 2 (post-KTx) and only 2 post-discharge in group 1. BIA not correlated with PE (p 0.022). VExUS score and BIA did not correlate. BNP and Ca125: 88% with CVE had elevated BNP and 22% high Ca125. Of those requiring HDx, 85.7% had elevated BNP and 14.2% risen Ca125. VExUS score: Day+1 VExUS1 (3): 50% elevated BNP but normal Ca125. VExUS 2 (1) elevated Ca125 + BNP. VExUS 3 none. Day+7 VExUS1 (4): 75% elevated BNP and 25% elevated Ca125. VExUS+LUS detected hypervolemia with normal PE (3 mild edema

and VExUS 1-2, 9 pathological LUS without clinical edema or only mild), although not significantly. VExUS modified treatment in 77.6% day+1 and 30% day+7: **day 1-->** *No* 7 (22.6%), *reducing iv fluids 71%*; *reducing iv fluids+diuretics* 1, *lower limb edema due to lymphocele* 1.D**ay 7-->** *No* 19 (70.1%), *reducing iv fluids* 2, *stopping iv fluids* 2, HDx 1, *other findings* 3 (2 *retroperitoneal bleedings and 1 perirrenal haematoma).*

Conclusions: LUS+VExUS outperformed PE for accurate management of posKTx volume, detecting hypervolemia early and modifying the therapeutic attitude up to almost 78% of cases. BIA correlated poorly with volume status in these patients.

Table 1. Group characteristics

	COHORT	Group 1 Prospective	Group 2 Retrospective	p
N		31	40	
Sex M/F %		58 / 42	65 / 35	
Age (years)		60.9±10.7	58.8±10.8	
CKD %	Glomerular	12.9	32.5	
	Diabetes	12.9	2.5	
	Polycystic	29	7.5	
	Tubulointerstitial	12.9	5	
HTN/2DM %		93.5/20	90 / 27.5	
Residual renal function %	>1 L	58.1	52.5	
	< 500 ml	35.5	40	
Referral HDx/PD %		61.3 / 29	67.5 / 30	
RRT (median months)		33	24	
Previous KTx %	1	64.5	50	
	2	25.8	45	
	>2	6.	5	
Donor type %	DCD	51.6	75	
	ACD	42	20	
	Vivo	6.5	5	
Cold ischaemia time (mean-range)		13 (0.5 -23)	16.3 (8-26)	
Induction Basiliximab %		67.7	50	
PRA %	0	74.2	60	
	50-90	6.5	15	
	>90	19.3	15	
BNP pg/mL		259±519	NA	
Ca125 UI/mL	(mean±SD)	17±14	NA	
Evolución posTR				
Fluids postKTx %	Diuresis+100	93.5	92.5	NS
	Diuresis+50	3.3	2.5	
	Diuresis	3.3	5	
Delayed graft function %		45.5	15	
HDx postKTx %		25.8	25	0.268
Hospitalization (days)		27.5±33	19.7±22.1	
CVE %		30	27.5	0.602
Weight gain (kg)	range	3.3±3.6	2.8±4.1	NS

TH-PO791

Carboxyhemoglobin and Smoking Status in Kidney Transplant Recipients

Sovia Salamah,[1] Antonio W. Gomes Neto,[1] Firas F. Alkaff,[1,2] Jenny E. Kootstra-Ros,[1] Daniel J. Touw,[1] Casper F. Franssen,[1] Stephan J. Bakker.[1]
[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]Universitas Airlangga Fakultas Kedokteran, Surabaya, Indonesia.

Background: Smoking is a risk factor for graft failure and death in kidney transplant recipients (KTRs). Nicotine addiction complicates quitting and self-reported smoking status is unreliable. Urinary cotinine is the gold standard for identifying active smokers, but is costly, infrequently measured, and prone to false positivity in nicotine patch or gum users. We aimed to investigate carboxyhemoglobin (COHb) as a potential biomarker for assessing smoking in KTRs.

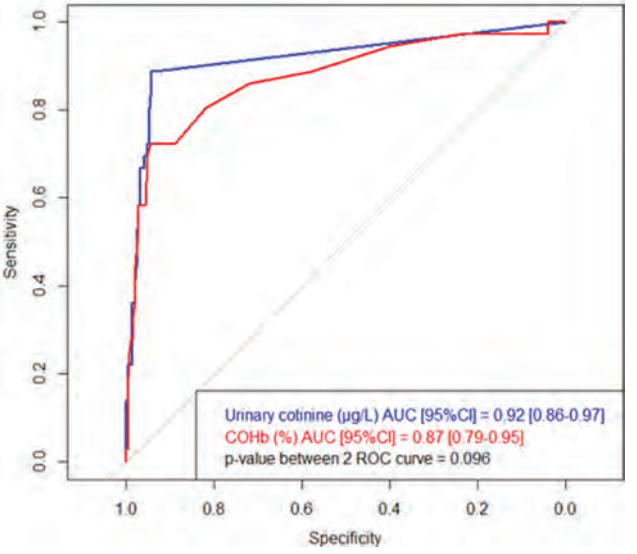
Methods: We used data from KTRs in the TransplantLines Biobank and Cohort. Smoking status was determined by a questionnaire. Urinary cotinine was measured with Enzyme Multiplied Immunoassay Technique (LLQ 100 µg/L) and plasma COHb was obtained from blood gas analysis. The ROC curve evaluated the diagnostic performance.

Results: Among 404 KTRs (mean age 56 ± 13 years, 43% female, median time post-transplant 89 months [interquartile range (IQR) 36-157]), the prevalence of KTRs with urinary cotinine > 100 µg/L was 15.1%, and the median COHb was 0.92% [IQR 0.82-1.14%] **(Table)**. COHb was strongly correlated with urinary cotinine (R=0.61; P<0.001). The area under the curve (AUC) of urinary cotinine and COHb was comparable **(Figure)**. Using the Youden index, the COHb cut-off was 1.5%. With this cut-off, the specificity and sensitivity of COHb were 94% and 72%, respectively.

Conclusions: Carboxyhemoglobin, which is more accessible than urinary cotinine, is just as effective in identifying smoking in KTRs.

Urinary cotinine and COHb of KTRs according to their answer on smoking questionnaire.

	Total N=404	Non-smoker N=107	Ex-smoker N=153	Smoker N=36	Unknown N=28	P-value
Detectable urinary cotinine concentration, n (%)	61 (15.1%)	3 (1.6%)	19 (12.4%)	32 (88.9%)	7 (25%)	<0.001
Detectable Urinary cotinine, µg/L [IQR]	660 [434-1009]	395 [305-921]	564 [388-829]	705 [484-994]	952 [766-1433]	<0.001
COHb, % [IQR]	0.92 [0.82-1.14]	0.92 [0.72-1.11]	0.92 [0.82-1.11]	2.27 [1.21-3.84]	0.96 [0.82-1.36]	<0.001



ROC curve of urinary cotinine and COHb to identify active smokers in KTRs.

TH-PO792

Serum Metalloproteinase-8 (MMP-8) and Tissue Inhibition of Metalloproteinase-1 (TIMP-1) Pretransplant Levels Predict Early Graft Function after Kidney Transplantation

Kadri Hendrikson,[1,2] Ilkka Helanterä,[1] Seppo Meri,[2] Timo Sorsa,[2] Fernanda Ortiz.[1] *[1]Helsingin Seudun Yliopistollinen Keskussairaala, Helsinki, Finland; [2]Helsingin Yliopisto, Helsinki, Finland.*

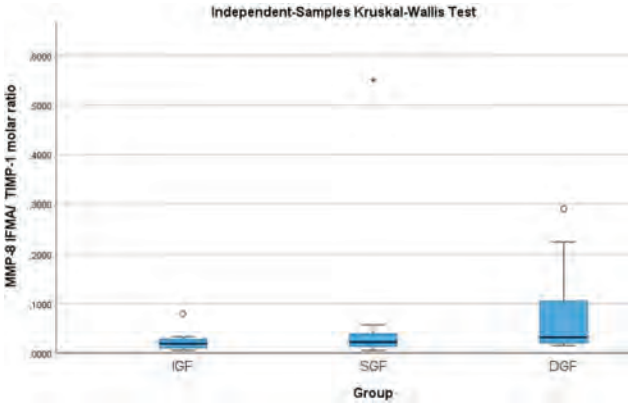
Background: Matrix metalloproteinases (MMPs) have a major role in the degradation of components of the extracellular matrix, which results in tissue remodeling. Particularly MMP-8, released by polymorphonuclear neutrophils, has a role in mediating inflammation and kidney fibrosis. Tissue inhibitor of metalloproteinase-1 (TIMP-1) is a natural inhibitor of MMP-8. MMPs have been suggested as a possible common pathway for chronic allograft nephropathy. MMP-8 role in renal transplantation has not been described.

Methods: We prospectively recruited 60 patients waitlisted for kidney transplantation. Patients were divided into 3 groups based on the graft function after surgery: delayed graft function (DGF: need of dialysis), immediate (IGF), and slow graft function (SGF: creatinine concentration over 2,2 mg/dl after 7 d pop). Follow-up data was obtained from the Finnish Transplant Registry. MMP-8 and TIMP-1 were measured in the serum from 59 patients obtained before transplant surgery. MMP-8 levels were determined by time-resolved immunofluorometric assay (IFMA), and TIMP-1 levels by ELISA. Mann-Whitney-U test was used to investigate differences across groups.

Results: MMP-8 concentration was highest and TIMP-1 the lowest in DGF, although not statistically different across DGF, SGF, and IFG (p=0.072 and p=0.060 respectively), but the MMP-8/TIMP-1 ratio was the highest in DGF group (p=0.029). We identified four outlier values, particularly in patients over 70 years old, without any other distinct characteristics explaining the high values. After removing outliers, MMP8 was statistically significantly higher in DGF than IGF (p=0.029). TIPM-1 concentration was lower in DGF (p=0.075) and MMP-8/TIPM-1 ratio was the highest in DGF vs IGF (p=0.014).

Conclusions: High pre-transplant concentrations of pro-inflammatory marker MMP-8 and lower TIMP-1 are related to delayed graft function.

Funding: Private Foundation Support



TH-PO793

Urine Epidermal Growth Factor as a Potential Biomarker of Functional Kidney Mass for the Evaluation of Kidney Transplant Donors and Recipients

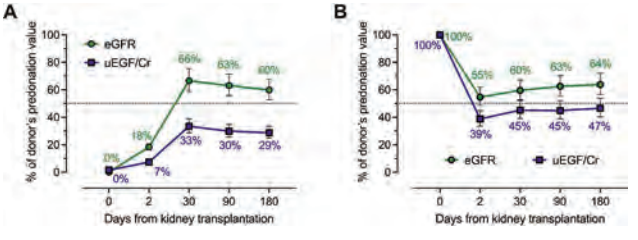
Adriana Hernández Andrade, Bernardo Juarez Cuevas, Valeria Navarro Sanchez, Jesus A. Sanchez Ramirez, Alberto Nordmann-Gomes, María F. Zavala Miranda, Cristino Cruz Rivera, Luis E. Morales-Buenrostro, Juan M. Mejia-Vilet.
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico.

Background: Serum creatinine (SCr) and the estimated glomerular filtration rate (eGFR) are limited biomarkers of kidney function. A kidney donor "loses" approximately 50% of the kidney mass, still, post-procedure SCr and eGFR recover to a value ≥60-70% baseline. The study aimed to evaluate urine epidermal growth factor (uEGF) as a better biomarker of kidney mass.

Methods: We recruited 32 donor/receptor pairs and obtained their pre-donation/pre-transplantation demographics, and kidney function tests. After the kidney donation/transplantation procedure, we collected blood and urine samples on days 2, 30, 90, and 180. The course of uEGF and eGFR were evaluated by linear mixed models and expressed as a percentage of the baseline kidney donor values.

Results: Kidney donors had a median age of 38 years (IQR 32-54), and 24 (75%) were female. Kidney recipients' median age was 36 years (IQR 29-46), 18 (56%) were male, 18 (56%) had kidney failure from an unknown cause, and 8 (25%) from glomerular disease. 27 (84%) corresponded to a first transplant and 5 (16%) to a second transplant. The baseline eGFR in kidney donors decreased immediately post-donation and then stabilized at 60-64% of their baseline eGFR from day 30. Conversely, uEGF decreased post-donation and stabilized at 45-47% of their baseline uEGF (closer to the theoretically 50% decrease after donation) (Figure 1B). In kidney recipients, the eGFR increased to a peak of 66% of the baseline eGFR of their kidney donor and remained at 60-63% over follow-up. Interestingly, uEGF in the kidney recipient remained at 29-33% of the baseline level of the kidney donor. Urine EGF (but not eGFR) in the recipient correlated with the allograft volume estimated by CT scan.

Conclusions: Urine EGF is a potential biomarker of functional kidney mass to be used for the evaluation of kidney donors and kidney recipients. uEGF levels are better approximate to the theoretical 50% "loss" of kidney mass that occurs after donation.



TH-PO794

Urinary Podocin as a Noninvasive Marker of Kidney Injury in New-Onset Diabetes after Kidney Transplantation

Adriana A. Rezende,[1] Ony A. Galdino,[1] Mabelle A. De Lima,[2] Mauricio G. Pereira,[2] Jose B. Almeida,[1] Marcela Ururahy,[1] Karla Souza.[1] *[1]Universidade Federal do Rio Grande do Norte, Natal, Brazil; [2]Universidade Potiguar, Natal, Brazil.*

Background: New-onset diabetes after transplantation (NODAT) is a serious metabolic complication that leads to decreased survival of renal allograft transplantation. However, currently, there is no early marker to assess kidney injury in NODAT. Given that podocytes are the primary targets of kidney injury, proteins from these cells are potential early markers of kidney dysfunction in NODAT. Among these podocyte proteins, podocin is an important molecule that maintains the integrity of the glomerular filtration barrier, which is negatively regulated in the case of kidney injury. Therefore, the aim of the study was to evaluate the potential of urinary podocin as a non-invasive marker of kidney injury in NODAT.

Methods: Thirty-eight kidney transplant (KTx) patients, who were 6 months post-KTx and aged above 19 years, without a history of segmental and focal glomerulosclerosis or *Diabetes mellitus*, were recruited. Patients were divided into 2 groups according to the diagnosis of NODAT [non-NODAT (n=20) and NODAT (n=18) groups]. Fasting blood glucose, glycated hemoglobin, serum creatinine, urinary albumin/creatinine ratio (ACR), and estimated glomerular filtration rate (eGFR) were determined. Podocin was measured by western blot from urinary extracellular vesicles, previously isolated by ultracentrifugation. Podocin band density was normalized by urinary creatinine.

Results: An increase in fasting blood glucose ($p < 0.001$) and HbA1c levels ($p < 0.001$) was observed in the NODAT group. Additionally, ACR and serum creatinine levels were elevated in the NODAT group compared to the non-NODAT group ($p < 0.001$, for both). In contrast, eGFR values decreased in the NODAT group compared to the non-NODAT group ($p = 0.003$). Increased urinary podocin was found in the NODAT group compared to the non-NODAT group ($p < 0.001$). Furthermore, urinary podocin was observed to be a predictor of low eGFR <60 mL/min/1.73 m² [Area Under the Receiver Operating Characteristic (AUROC) = 0.844; p = 0.032].

Conclusions: This study is the pioneer to show an increase in urinary podocin in NODAT patients. These results associated with the ones obtained in the AUROC analysis and for the eGFR suggest that urinary podocin can become a potential marker in the early detection of kidney injury in the NODAT.

Funding: Government Support - Non-U.S.

TH-PO795

Urinary Nephrin and Podocin Levels as Potential Predictors of Reduced Glomerular Filtration Rate after Kidney Transplantation

Karla Souza,[1] Ony A. Galdino,[1] Mabelle A. De Lima,[2] Mauricio G. Pereira,[2] Jose B. Almeida,[1] Marcela Ururahy,[1] Adriana A. Rezende.[1]
[1]Universidade Federal do Rio Grande do Norte, Natal, Brazil; [2]Universidade Potiguar, Natal, Brazil.

Background: Nephrin and podocin could be associated with early podocyte injury, leading to alterations in the glomerular filtration barrier that may result in a reduced glomerular filtration rate (GFR) after kidney transplantation (KTx). Therefore, the aim of this study was to investigate whether the increase in urinary levels of nephrin and podocin is associated with low GFR post-KTx.

Methods: Forty KTx patients aged above 19 years, without a history of segmental and focal glomerulosclerosis or *Diabetes mellitus* were recruited. Urinary albumin/creatinine ratio (ACR), estimated GFR (eGFR), and serum creatinine were determined. Nephrin and podocin were measured by western blot from urinary extracellular vesicles isolated by ultracentrifugation. All analyses were performed in patients at 3, 6, 9, and 12 months post-KTx.

Results: An increase in ACR and a decrease in eGFR were observed at 12 months compared to 3 months post-KTx. No differences were found in serum creatinine levels. A linear mixed effects model was employed to investigate the association between urinary nephrin and podocin levels with low GFR post-KTx, using eGFR as the dependent variable. The model considered the 12-month follow-up as the fixed effect and included nephrin and podocin as covariates. This analysis indicated an association between urinary nephrin [3 months ($p<0.001$), 6 months ($p=0.031$), 9 months ($p=0.029$), and 12 months ($p=0.006$)] and podocin [3 months ($p<0.001$), 6 months ($p=0.001$), 9 months ($p=0.012$), and 12 months ($p=0.014$)] with the reduction of eGFR. To determine if urinary nephrin and podocin could predict low GFR post-KTx, an Area Under the receiver operating Characteristic (AUC) analysis was performed. It was observed that urinary nephrin [3 months (AUC=0.984,$p=0.001$), 6 months (AUC=0.999,$p<0.001$), 9 months (AUC=0.929,$p=0.001$), and 12 months (AUC=0.857,$p=0.005$)] and podocin [3 months (AUC=0.900,$p=0.005$), 6 months (AUC=0.999,$p<0.001$), 9 months (AUC=0.999,$p<0.001$), and 12 months (AUC=0.913,$p=0.001$)] were predictors of low eGFR.

Conclusions: The results demonstrate an association between urinary nephrin and podocin and low GFR. Moreover, the high AUC values found during patient follow-up indicate that these urinary proteins are potential predictors of low GFR post-KTx.

Funding: Government Support - Non-U.S.

TH-PO796

Next-Level Approach to Antibody-Mediated Rejection and T Cell-Mediated Rejection Diagnosis in Kidney Transplantation: Dynamic Duo of Urine CXCL10 and Donor-Derived Cell-Free DNA

Daniel Fantus,[1,2] Sílvia Casas,[5] Narin S. Tangprasertchai,[5] Thierry Viard,[5] Justin Belair,[2] Chee Loong Saw,[4] Claude Daniel,[4] Julie Ho.[3] *[1]Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [3]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [4]McGill University Health Centre, Montreal, QC, Canada; [5]CareDx Inc, Brisbane, CA.*

Background: Biopsies are required to diagnose rejection but they are invasive and difficult to use for monitoring. While there is evidence that donor derived cell free DNA (dd-cfDNA) performs well as a biomarker of antibody-mediated rejection (AMR), its ability to identify T cell mediated rejection (TCMR) remains unclear. In contrast, urine CXCL10 is a well-characterised biomarker of tubulitis. Due to these complementary properties, we hypothesized that use of these 2 biomarkers together would improve the diagnosis of rejection phenotypes marked predominantly by tubulitis, particularly TCMR.

Methods: A single center exploratory study was conducted whereby 126 transplant biopsies (with paired plasma and urine) were selected. Banff criteria were followed to generate the following diagnostic categories: AMR (n=20), low and high grade TCMR (n=17) and normal histology (n=43). Urine CXCL10 was measured using the Meso Scale V-Plex assay. Cell free DNA was extracted from EDTA plasma samples and percent donor derived cell free DNA calculated using the CareDx AlloSeq cfDNA kit.

Results: The AUC for AMR (versus normal) was 0.952 (0.893-1000) using dd-cfDNA. In contrast, the AUC for AMR was 0.595 (0.469-0.722) using urine CXCL10 and increased to 0.969 (0.923-1.000) when dd-cfDNA was added ($p=1.71X10^{-8}$). For high grade TCMR, AUC using dd-cfDNA was 0.762 (0.562-0.963). AUC using urine CXCL10 was 0.681 (0.474-0.888) and increased to 0.792 (0.585-1.000) when dd-cfDNA was added (p=0.16). For low grade TCMR, AUC was 0.577 (0.442-0.711) using dd-cfDNA. AUC was 0.595 (0.424-0.767) using urine CXCL10 and increased to 0.652 (0.473-0.832) (p=0.32) when dd-cfDNA was added.

Conclusions: Urine CXCL10 is a weaker diagnostic biomarker of AMR compared to dd-cfDNA. In contrast, when evaluating TCMR, there was no clear advantage of one biomarker over the other, though their combination may improve diagnosis. These findings require prospective multi-center studies.

Funding: Private Foundation Support

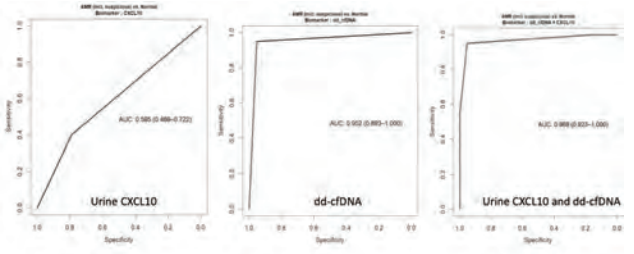


Figure 1: AUC curves for AMR comparing urine CXCL10 alone, dd-cfDNA alone and combined urine CXCL10 and dd-cfDNA

TH-PO797

Urinary Basigin/CD147 Is a Useful Marker of Acute T Cell-Mediated Rejection in Kidney Transplant Recipients

Makoto Tsujita. *Masuko Kinen Byoin, Nagoya, Japan.*

Background: Acute T cell-mediated rejection (ATCMR) is one of the severe problems following kidney transplantation. However, no reliable marker of it is currently available in Japan.

Methods: This cross-sectional study was performed at Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital to determine whether serum or urinary Basigin/CD147 worked as an effective marker of ATCMR from 2016 to 2018. Serum and urinary samples were obtained when episode graft biopsies were done.

Results: A total of 46 kidney transplant recipients received graft biopsies. Three of them missed serum and urinary samples and three in ATCMR were on post-rejection treatment. Graft biopsy results revealed ATCMR in 12 of them, calcineurin inhibitor nephrotoxicity (CNIN) in 9, chronic active antibody-mediated rejection (CAAMR) in 9, BK nephropathy, recurrence IgA nephropathy, necrotic glomerulonephritis, and infection-related glomerulonephritis in one each, and others in 6. Urinary Basigin/CD147 levels in patients with ATCMR group (690.1 ± 247.0 pg/gCre) were notably greater than those in patients with CAAMR (242.2 ± 86.1 pg/ gCre) and CNIN groups (351.6 ± 117.0 pg/ gCre). ($P < 0.001$)(Figure1) No statistical difference in serum Basigin/CD147 levels was observed between those groups. At an urinary Basigin/CD147 of 631.5 pg/gCre, sensitivity, and specificity of 75% and 84%, respectively, were reached for diagnosing acute rejection with an area under the curve of 0.80.(Figure2)

Conclusions: Urinary Basigin/CD147 was correlated with tubulointerstitial damage and might be a potential marker for ATCMR in kidney transplant recipients. Further study will be needed to clarify the effectiveness of Basigin/CD147.

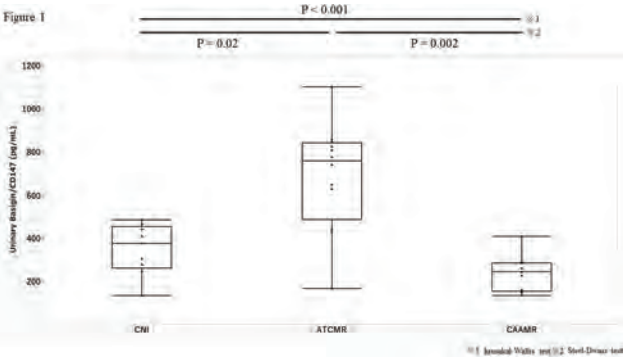
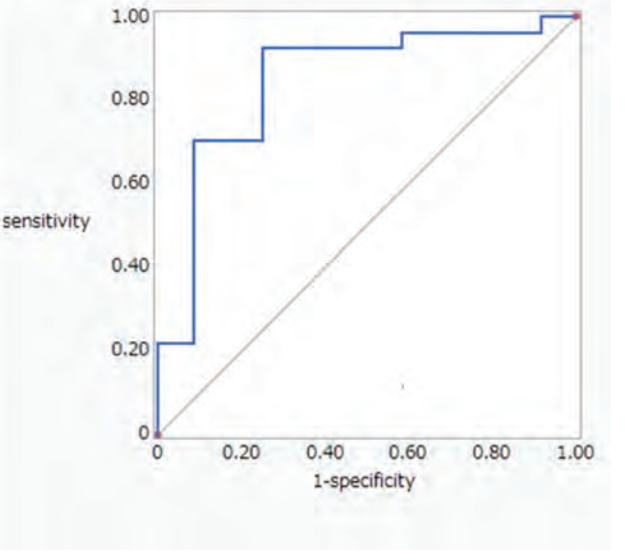


Figure 2



TH-PO798

Noninvasive Urine Epigenomics Identifies Allograft Pathology in Kidney Allografts

Essa Abuhelaiqa,[1,2] Mohamad M. Alkadi,[1,2] Aziz Belkadi,[2] Gaurav Thareja,[2] Thangamani Muthukumar,[3] Hassan A. Al-Malki,[1,2] Manikkam Suthanthiran.[3] *[1]Hamad Medical Corporation, Doha, Qatar; [2]Weill Cornell Medicine - Qatar, Doha, Qatar; [3]Weill Cornell Medicine, New York, NY.*

Background: Development of noninvasive assay as a diagnostic alternative to allograft biopsy in kidney transplantation is critical and has the potential of prompt diagnosis and treatment of allograft dysfunction. We aim to detect kidney pathology via recognition of associated methylation signatures and cellular profiles in urine, hypothesizing that different disease states lead to unique and measurable epigenetic and cellular changes.

Methods: Urine samples were obtained at time of for-cause kidney allograft biopsy of 138 kidney allograft recipients. Urinary pellet DNA was processed with the Infinium MethylationEPIC kit and categorized into "phenotypes" from biopsy findings. The resulting methylation data was filtered with the "ewastools" package in R. Average cellular composition for each phenotype was generated through a reference atlas and deconvolution algorithm from the literature. Differentially methylated regions (DMR) were compared between non-rejection (NR) and acute rejection (AR) specimens via the chip analysis methylation pipeline package.

Results: From a total of 138 unique samples and 11 technical replicates, methylation data for 650,719 CpG sites per analyte was available after filtering. Deconvolution analysis demonstrated immune cell predominance in AR and micro-vascular injury, particularly neutrophils, with only BKVN samples showing relative renal cell prevalence. Borderline samples showed a cellular profile intermediate between NR and AR. DMR analysis yielded a panel of 197 genes containing differentially methylated CpG sites between AR and NR samples.

Conclusions: Epigenomic analysis of urine is a feasible modality to assess graft health, with cellular composition and DMRs acting as surrogate biomarkers.

Funding: Government Support - Non-U.S.

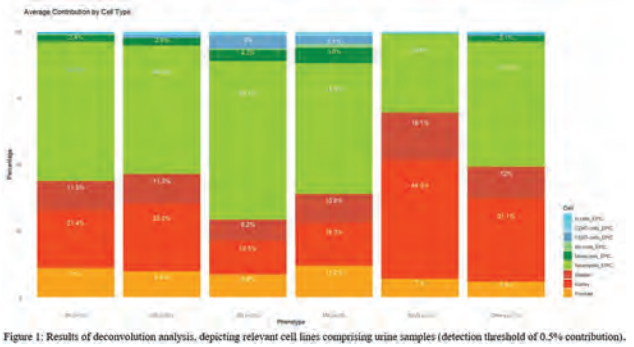


Figure 1: Results of deconvolution analysis, depicting relevant cell lines comprising urine samples (detection threshold of 0.5% contribution).

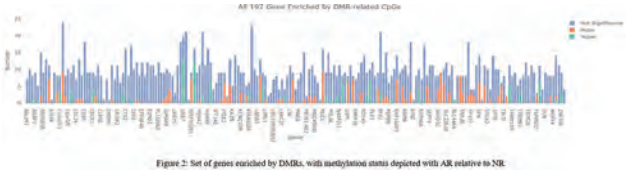


Figure 2: Set of genes enriched by DMRs, with methylation status depicted with AR relative to NR

TH-PO799

Urinary Metabolite Constellation Also Detects Very Early Post-transplant Rejection in Living Donor Kidney Recipients

Miriam C. Banas,[1] Katharina Wiesner,[1,3] Bernhard Banas,[1] Andrew Robertson,[2] Amauri Schwäble Santamaría,[2] Simone Mark,[2] Eric Schiffer.[2]
[1]Universitatsklinikum Regensburg, Regensburg, Germany; [2]Numares AG, Regensburg, Germany; [3]Barmherzige Brüder, Regensburg, Germany.

Background: Kidney transplantation is the preferred treatment for end stage kidney disease, offering improved survival rates and quality of life compared to dialysis. However, acute allograft rejection remains a significant complication, necessitating accurate diagnosis for timely intervention. Standard serum creatinine monitoring lacks specificity, leading to unnecessary biopsies and missed subclinical rejection. Previously we published a novel metabolom-based urinary non-invasive test for the detection of renal allograft rejection (Banas M et al., EBioMedicine, 2019).

Methods: In this study, conducted as part of the UMBRELLA study, n=682 urine samples from 109 transplant recipients were analyzed using a recently introduced urine metabolite constellation of alanine, citrate, lactate, and urea. Parameters (n=29) such as induction therapy, warm ischemia time, and donor type were examined for their impact on the test's performance to identify biopsy confirmed rejection in the first 14 days post-transplant.

Results: Univariate analysis identified 10 significant confounders, particularly the influence of deceased organ donation on metabolic urine profiles. Multivariate analysis confirmed the relevance of parameters related to living donation and highlighted warm ischemia time as an independent factor affecting metabolite profiles. Subgroup analysis directly testing the performance of the rejection score revealed living donor recipients as the most accurately discriminated subgroup with an AUC of 0.720 (95% CI 0.62-0.82), followed by those with short (<30 min) warm ischemia times 0.702 (95% CI 0.61-0.79). Clinical observations supported these findings, with anomalies in the urine metabolite test often correlating with clinical complications.

Conclusions: The study underscores the importance of considering donor type and ischemia times when interpreting metabolomics data for rejection monitoring in kidney transplant recipients. Understanding these factors could enhance the accuracy of non-invasive rejection detection methods, facilitating timely intervention and improving patient outcomes.

Funding: Commercial Support - Numares AG, Regensburg, Germany

TH-PO800

Time Course of Glycolytic Control Protein Expression in Urinary Extracellular Vesicles (UEV) of Deceased Donor Kidney Transplant Recipients

Po Yee Mia Leung,[1,2] Alison S. Graver,[1,2] Marina Katerelos,[2] John B. Whitlam,[1,2] David A. Power,[1,2] Peter F. Mount.[1,2] *[1]Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia; [2]Department of Nephrology, Austin Health, Melbourne, VIC, Australia.*

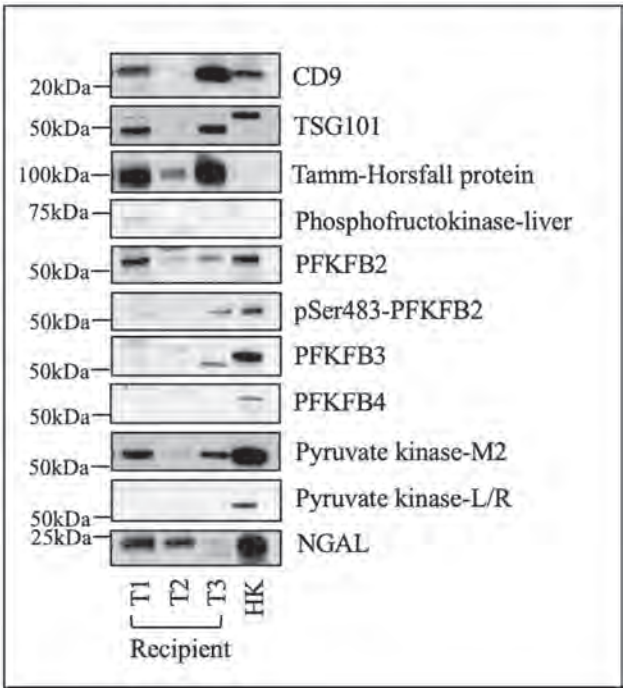
Background: An important switch to increased glycolysis has been demonstrated in experimental ischaemia-reperfusion injury. We aimed to measure expression of glycolytic control proteins contained in UEV as a marker for changes in renal glycolysis following deceased donor kidney transplantation.

Methods: In this prospective observational study, urine samples were collected from deceased donor kidney transplant recipients prior to (T0) and after transplant at days 1-3 (T1), 5-10 (T2) and 70-100 (T3). UEV were separated by differential ultracentrifugation and characterized by expression of CD9, TSG101 and THP. Proteins were analysed by immunoblotting and included PFK-L, PFKFB2, pSer483-PFKFB2, PFKFB3, PFKFB4, PK-LR, PK-M2 and NGAL. Densitometry was normalized to urine creatinine, then compared via repeated measures one-way ANOVA.

Results: 29 urine samples from 8 subjects were included. Three were anuric at T0. PFK-L was not detected. There were no statistically significant changes in expression of PFKFB2, pSer483-PFKFB2, PFKFB3, PFKFB4 and PK-M2 over time. Expression of PFKFB2 and PK-M2, however, was seen in 8/8 subjects at T1 and persisted in 7/8 subjects at T3. PK-LR was detected in 4/5 samples at T0 and not thereafter (p=0.0010). NGAL was detected in 4/5 subjects at T0 and in 8/8 at T1-3, with expression measured by densitometry reducing over time (p=0.043).

Conclusions: Regulation of glycolytic control in the early post-transplant period is poorly understood. We identified changes in PFKFB2 and PK-M2 immediately post-transplant, which persists over time. PFKFB2 and PK-M2 have been associated with increased glycolysis, including aerobic glycolysis. Future studies will focus on the way this can be used to monitor kidney transplants.

Figure 1 - Representative Western blots of one recipient with UEV at time points T1, T2 and T3 (anuric at T0). Human kidney lysate (HK) was the positive control.



TH-PO801

Single-Center Observational Study of Torque Teno Virus in Mainly Steroid-Free Adult and Pediatric Kidney Transplant Recipients

Ann-Maria Gramkow,[1] Helle C. Thiesson,[1,2] Maja Nørgaard,[3] Pernille Koefoed-Nielsen,[3] Randi Berg.[3] *[1]Odense Universitetshospital, Odense, Denmark; [2]Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Odense, Denmark; [3]Aarhus Universitetshospital, Aarhus, Denmark.*

Background: Torque Teno Virus (TTV), an apathogenic single-stranded anellovirus, is prevalent in solid organ transplant recipients. Evidence suggests that its replication varies with immunosuppression after transplantation. This study investigates TTV correlations with rejection and infections in kidney transplant recipients and assesses the impact of steroid-free versus steroid-containing therapy. It explores individual TTV trajectories over time and compares TTV dynamics and levels between adult and pediatric recipients.

Methods: We prospectively collected 1704 samples from 310 adults and 20 pediatric recipients after transplantation. All recipients received tacrolimus and mycophenolate mofetil; 27% also received prednisolone, while the remainder were steroid-free. TTV was quantified with an in-house rtPCR assay. Cox regression models assessed TTV's association with rejection and infections, while mixed effects linear regression models analyzed other outcomes.

Results: We observed a decreased hazard ratio for rejection (HR 0.90, 95% CI: 0.82-0.99) with increasing TTV load but no association with infections (HR 1.00, 95% CI: 0.97-1.03). TTV levels were 0.66 (95% CI: 0.42-0.90) log10 copies/ml higher in recipients receiving prednisolone than those not receiving prednisolone ($p<0.001$). Stratification by TTV levels at transplantation revealed significant differences in levels over time: 2.51 (95% CI: 2.32-2.69) log10 copies/ml in the first tertile, 4.32 (95% CI: 4.02-4.62) in the second, and 5.02 (95% CI: 4.77-5.26) in the third. TTV peaked three months post-transplantation, then declined to stabilize, with no significant differences between adult and pediatric recipients.

Conclusions: We observed decreasing TTV levels correlated with increased rejection risk, but no association with infections. Notably, steroid use increased TTV levels, suggesting caution extrapolating TTV thresholds established from steroid-based regimens on steroid-free populations. Recipients with low TTV levels at transplantation maintained this trend over time. Further research is warranted to explore individual TTV trajectories. No differences in TTV level or dynamic were observed between adult and pediatric recipients, supporting the applicability of TTV in pediatric recipients.

Funding: Private Foundation Support

TH-PO802

Assessing Stability of Donor-Specific Antibodies (DSA) in Relation to Changes in Donor-Derived Cell-Free DNA: A Retrospective Cohort Study

Bradley Hyman. *Memorial Hermann Texas Medical Center, Houston, TX.*

Background: Focus of renal transplant recipients has turned toward prolonging the life of the graft. Donor-derived cell-free DNA (dd-cfDNA), is now validated for the assessment of allograft injury in transplant recipients. Given the relatively new use, the relevance of persistently elevated levels of dd-cfDNA remains unknown. In this study, we compare patients with and without sustained elevation above 1% for more than 12 months and their relationship with transplant biomarkers.

Methods: This retrospective cohort study included all patients managed at UTHealth, University of Texas at Houston. In routine clinical care, post-transplant patients are seen in clinic every 3 months after the acute post-transplant period. At each visit, blood and urine tests were performed. Estimated glomular filtration rate (eGFR) was calculated using the Chronic Kidney Disease in Children Under 25 (CKiD U25) equation. Data were de-identified prior to analysis.

Results: From 2017 to 2023, a total of unique 61 pediatric renal transplant recipients were followed at the UTHealth transplant clinic. We excluded patients who had undergone combined visceral organ transplant (n=4) and those with less than 4 dd-cfDNA values reported by the end of the study period (n=14). Among the 43 patients included in the analysis, 10 patients experienced persistently elevated dd-cfDNA levels, >=1.0% for at least 12 months. No differences were noted when comparing baseline characteristics, cause of ESRD, or transplant source between the two groups. Comparing between the two groups, for those with dd-cfDNA level >1.0% for more than one year, there was a difference in DSA data. For those who met the defined threshold, DSA presence was increased (OR 4.03, 95% CI, 0.81 to 20.0, p value 0.088). Further analysis of DSA classes showed increased presence of Type A and B (OR 22.2 and 55.7, respectively, p-value <0.001). After controlling for months from transplant, sustained elevation of dd-cfDNA levels was an independent risk factor for presence of DSA.

Conclusions: To our knowledge, this is the first pediatric study evaluating sustained elevation of dd-cfDNA levels and its association with DSA. Obtaining dd-cfDNA levels during these visits can easily be performed and could provide supplemental information for the continued monitoring and management of renal transplant recipients.

TH-PO803

Discovery and Validation of a Kidney Rejection Prediction Model Using Urinary CXCL9 and CXCL10

Kenny W. Chen,[1] Lihui Zhao,[1] Sookhyeon Park,[1] Sujay D. Paudel,[1] Ronnie Lacombe,[2] Steven Kleiboeker,[2] John J. Friedewald.[1] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Eurofins Viracor BioPharma Services, Lenexa, KS.*

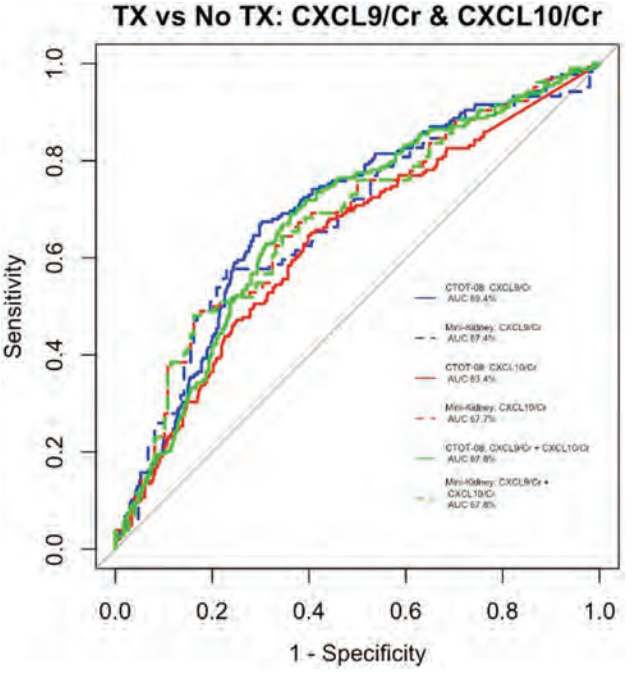
Background: Urinary chemokines (CXCL9 + CXCL10) have shown to be non-invasive biomarkers in diagnosing kidney rejection. We aim to discover and validate a rejection prediction model combining the two by assessing the diagnostic performance in two independent cohorts.

Methods: We analyzed 638 biopsy paired urine samples paired from the CTOT-08 trial for discovery and then samples from an internal study cohort as a validation. We fit univariate logistic regression models using urine CXCL9 and CXCL10 normalized to urine creatinine and a logistic regression model with both to predict kidney rejection. AUC was used to evaluate the model's diagnostic performance.

Results: The univariate logistic model with CXCL9 had an AUC of 0.694 while the univariate model with CXCL10 had an AUC of 0.634. In the logistic model with both CXCL9 and CXCL10, the AUC was 0.678. In the validation cohort, the univariate model with CXCL9 had an AUC of 0.674, the univariate model with CXCL10 had an AUC of 0.677 and the model with both had an AUC of 0.678.

Conclusions: Incorporating urinary biomarkers CXCL9 and CXCL10 into prediction models to monitor kidney rejection resulted in moderately high diagnostic value (AUC: 0.63 – 0.68). This performance held in the external validation cohort. The combination of both biomarkers did not significantly improve model performance.

Funding: Other NIH Support - NIAID, Commercial Support - Eurofins - Viracor



TH-PO804

Impact of Donor-Derived Cell-Free DNA Testing on Patient and Graft Outcomes

Fawad Shuaib,[1] Ana L. Castellanos,[1] Sravanthi Paluri,[1] Lauren Schumacher,[1] Olivia Philippart,[1] Jesica Yau,[2] Hasan Fattah.[1] *[1]University of Kentucky, Lexington, KY; [2]CareDx Inc, Brisbane, CA.*

Background: The objective of this study was to compare outcomes in cohorts of patients with and without donor-derived cell-free DNA (dd-cfDNA) testing.

Methods: This is a single center retrospective cohort study of kidney transplant recipients (KTRs) comparing a historical cohort of patients transplanted from 2015-2017 without dd-cfDNA testing and cohort of patients transplanted from 2019-2022 with dd-cfDNA testing. Outcomes included BPAR, DSAs, death censored graft loss, death, and renal function at 1 year.

Results: 408 KTRs were included in the analysis. There were significantly more patients with DGF and DCD donor type in the dd-cfDNA cohort (Table 1). At 1-year post-transplant, there was no significant difference in DSAs (7.4% vs 8.3%; p=0.75) or BPAR (6.5% vs 7.8%, p=0.621) between the two groups. Statistical analysis on death-censored graft loss and patient death was not performed due to few KTRs reaching these

outcomes (Table 2). Serum creatinine and eGFR at 1-year was not significantly different between the two cohorts, whereas there was significantly less proteinuria in the historical cohort (7.5% vs 13.6%, p=0.044). When stratifying the dd-cfDNA cohort by results ≥ 0.5% vs <0.5% at 3 months and 1 year, there was significantly more BPAR seen in the ≥ 0.5% dd-cfDNA cohort.

Conclusions: There was no difference in most outcomes between the two cohorts, except for more proteinuria in the dd-cfDNA cohort. This result is limited due to higher proportion of KTRs with DGF and DCD donor type in the dd-cfDNA cohort. Assessing effectiveness of dd-cfDNA monitoring was limited to 1 year follow up period in our study. The impact of dd-cfDNA testing frequency on patient-centered outcomes remains unknown. Further studies are needed to study the ideal testing frequency impact on such outcomes.

Table 1. Baseline Demographics and Transplant Characteristics

	Pre-dd-cfDNA N=215	dd-cfDNA N=193	P-Value
Age at time of transplant (years), median [IQR]	49 [39, 58]	51 [40, 61.5]	0.177
Race, n (%)			0.509
Caucasian	168 (78.1)	158 (81.9)	
African American	36 (16.7)	29 (15.0)	
Other	11 (5.1)	6 (3.1)	
Male, n (%)	135 (62.8)	119 (61.7)	0.814
Etiology of renal disease, n (%)			0.355
Diabetes	51 (23.7)	54 (28.0)	
Hypertension	36 (16.7)	22 (11.4)	
Glomerulonephritis	48 (22.3)	39 (20.2)	
Polycystic Kidney Disease	24 (11.2)	26 (13.5)	
Congenital	10 (4.7)	9 (4.7)	
Retransplant	26 (12.1)	19 (9.8)	
Other/Unknown	20 (9.3)	24 (12.4)	
Induction agent, n (%)			0.608
Rabbit anti-thymocyte globulin	202 (94.0)	183 (94.8)	
Basiliximab	12 (5.6)	7 (3.6)	
Other	1 (0.5)	3 (1.6)	
cPRA (%), median [IQR]	0 [0, 39]	3 [0, 43.5]	0.386
Delayed graft function*, n (%)	22 (10.2)	38 (19.8)	**0.007**
Donor type, n (%)			**0.009**
Deceased, brain death	130 (60.5)	96 (49.7)	
Deceased, cardiac death	19 (8.8)	36 (18.7)	
Living donor	66 (30.7)	61 (31.6)	
Donor type, n (%)			0.843
Deceased	149 (69.3)	132 (68.4)	
Living	66 (30.7)	61 (31.6)	

*Defined as requiring dialysis within 7 days of transplant

Table 2. Patient and Allograft Outcomes

	Pre-dd-cfDNA N=215	dd-cfDNA N=193	P-Value
DSA, n (%)			
Time to DSA, median [IQR]	334.5 [127.5, 529.5]	215.5 [74.75, 569]	
DSA at 1 yr	16 (7.4)	16 (8.3)	0.750
Biopsy-proven acute rejection, n (%)			
Time to BPAR, median [IQR]	315 [113, 825]	247.5 [130.75, 570.25]	
BPAR at 1 yr	14 (6.5)	15 (7.8)	0.621
Death-censored graft loss, n (%)			
Time to DCGL (days), median [IQR]	844 [503.5, 1029.5]	667 [513, 970]	
DCGL at 1 yr	0	0	--
Patient Death, n (%)			
Time to death (days), median [IQR]	822 [554, 925.5]	797.5 [528.25, 909.25]	
Death at 1 yr	0	0	--

Table 3. Allograft Function

	Pre-dd-cfDNA N=215	dd-cfDNA N=192	P-Value
Serum creatinine, mean ± SD			
SCr at 1 yr (n = 215 vs 184)	1.35 ± 0.53	1.40 ± 0.49	0.323
Proteinuria*, n (%)			
Proteinuria at 1 yr (n = 215 vs 184)	16 (7.5)	25 (13.6)	**0.044**
eGFR (mL/min/1.73m²) at 1 year			0.316
≥ 60	89 (41.4)	76 (39.6)	
45 – 59	82 (38.1)	61 (31.8)	
30 – 44	39 (18.1)	46 (24.0)	
15 – 29	4 (1.9)	8 (4.2)	
< 15	1 (0.5)	1 (0.5)	

*Proteinuria is defined as >30 mg/dL

Table 4. dd-cfDNA data

	dd-cfDNA < 0.5% N=99	dd-cfDNA ≥ 0.5% N=26	P-Value
Biopsy-proven acute rejection, n (%)			
BPAR at 1 yr	12 (12.1%)	10 (38.5%)	0.004
eGFR (mL/min/1.73m²) at 1 year			
	dd-cfDNA < 0.5% N=58	dd-cfDNA ≥ 0.5% N=20	P-Value
≥ 60	35	8	0.078
45 – 59	12	5	
30 – 44	6	4	
15 – 29	5	1	
< 15	0	2	

TH-PO805

Selective Implementation of Belatacept (Bela) Every Other Month as a Standard Care Option with the Use of Donor-Derived Cell-Free DNA (dd-cfDNA) Testing

Jae H. Son, Ryan Fields, Geeta Karadkhele, Michael Hurtik, Payaswini Vasanth, Christian Larsen. *Emory University, Atlanta, GA.*

Background: The goal of this study is to safely transition selected kidney transplant recipients who are 24 months post-transplant to an every-other-month Bela regimen using dd-cfDNA monitoring.

Methods: A cohort of 13 patients was included. Inclusion criteria were at least 24 months post-transplant, off calcineurin inhibitors for a minimum of 6 months, free from acute cellular rejection or donor-specific antibodies, and stable renal function for ten months. Increased monitoring for q2 months Bela included dd-cfDNA approximately monthly for six months, then every month until one year after the transition, followed by every six months.

Results: dd-cfDNA was used to detect cell death, which is not rejection-specific. Creatinine values from 180 days before the beginning of cfDNA were used to help establish a baseline. In the study, the Subjects' creatinine (Cr) was stable. Two subjects experienced a concerning increase in cfDNA that was not associated with increased Cr. cfDNA levels and returned to baseline. Two subjects had a short interval of noncompliance with MMF without overt signs of rejection. One was advised to return to the standard regimen but refused. Cr remained at baseline.

Conclusions: Bela preserves renal function, reduces DSA formation, and improves long-term survival. Standard monthly infusions lead to significant costs, monthly travel, and frequent healthcare encounters for life. In the current climate, the institution that provides this service facilitates crucial care coordination (recurrent scheduling, extensive tracking, etc.) with a strained infusion capacity for an ever-growing population. We have found that q2 monthly Bela with cfDNA monitoring is a safe alternative to monthly infusions. This regimen mitigates the risk of rejecting futile biopsies, improves compliance, and decreases the financial burden of healthcare.

TH-PO806

Use of Donor-Derived Cell-Free DNA and Gene Expression Profiling to Facilitate Belatacept Monotherapy in Kidney Transplant Recipients

David Wojciechowski,[1] Juan D. Salcedo Betancourt,[1] Morgan Marsh,[1] Cyrus Feizpour,[3] Hwarang S. Han,[2] Laila S. Lakhani,[1] Swee-Ling Levea,[1] Lee E. Anderson.[1] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]The University of Texas at Austin, Austin, TX; [3]Indiana University School of Medicine, Indianapolis, IN.*

Background: Donor-derived cell-free DNA (AlloSure) levels <1.0 % and gene expression profiling (AlloMap) score <11.5 help discriminate immune quiescence from acute rejection. We investigated their utility in weaning to belatacept monotherapy.

Methods: Between December 2022 and April 2024, we enrolled adult kidney recipients on belatacept immunosuppression with stable renal function (eGFR >40 mL/min/1.73m2) and absent Donor-Specific Antibodies (DSA) into a 12-month prospective, single-center, interventional pilot study. AlloSure, AlloMap, serum creatinine, spot urine protein, and DSA were measured at monthly infusion visits. Patients deemed clinically stable (eGFR <20% lower than baseline, absence of biopsy-proven rejection) and immune quiescent (absence of de novo DSA, AlloMap <11.5, AlloSure <1.0 % or >0.5% without a change >61% from baseline) underwent immunosuppression tapering. Outcomes included biopsy-proven rejection, allograft/patient survival, change in eGFR, proteinuria or de-novo DSA development, and percentage of patients weaned to belatacept monotherapy.

Results: We analyzed the first 19 patients who completed at least 6 months of follow-up. Subjects were predominantly male (n=14) with a mean age of 56 years. Mean eGFR in mL/min/1.73m2 was 72.84 ± 19.04 SD at enrollment and 70.47 ± 18.59 SD at 6 months. The most common agents used with belatacept were prednisone + mycophenolate (n = 16), prednisone + everolimus (n = 2) or sirolimus (n=1). Mean AlloSure and AlloMap throughout were 0.27% ± 0.25 and 11.29 ± 1.99 respectively. 5 patients (26%) were weaned off prednisone, and 2 were weaned entirely off prednisone and mycophenolate. There was 100% patient and graft survival, with no biopsy-proven rejection, nephrotic proteinuria, or DSA development.

Conclusions: Despite having AlloSure <1%, the mean AlloMap score was above the reported threshold shown to discriminate rejection from quiescence. We hypothesize that patients on belatacept-based immunosuppression have higher AlloMap scores even if immune quiescent, as prior studies primarily included patients on tacrolimus-based immunosuppression. Higher cutoffs may be necessary for this population. Investigation is ongoing to test this hypothesis in our cohort.

Funding: Commercial Support - CareDx

TH-PO807

Histopathological Discordance with Sequentially Rising Donor-Derived Cell-Free DNA

Andrew Slater, William L. Clapp, Alfonso Santos, Amer A. Belal. *University of Florida, Gainesville, FL.*

Introduction: Plasma donor-derived cell-free DNA (dd-cfDNA) fraction is a promising, non-invasive predictive tool for allograft kidney rejection. An elevated dd-cfDNA fraction when combined with HLA de novo donor-specific antibody (dnDSA) can further be used to predict ABMR. We discuss a case where the dd-cfDNA and dnDSA inform decisions to seek a biopsy that is ultimately inconsistent with the predictive models for ABMR.

Case Description: A 73-year-old male with ESKD due to Type 2 diabetes had a living, unrelated kidney transplant (KT). There were no pre-formed anti-HLA antibodies, and HLA A-B-DR mismatch was 2-2-1. Induction was with basiliximab. He started tacrolimus (TAC), mycophenolate (MMF) 750 mg BID and prednisone. Two months post KT, MMF was reduced to 500 mg BID due to leukopenia. Three months post KT, MMF was paused for neutropenic fever and then resumed at 250 mg BID. He developed low titer BK viremia. TAC trough goal was reduced to 4-6 mcg/L. The prednisone dose was reduced from 10 mg to 5 mg daily. The patient began serial checks of dd-cfDNA, with a dd-cfDNA fraction of 0.19%. 13 months post KT, the repeated dd-cfDNA fraction increased to 0.28% with a new finding of a single dnDSA, DQ2 (8000MFI). Although he had stable creatinine without proteinuria, there was concern for subclinical acute rejection. An allograft biopsy showed mild glomerulitis without evidence of acute rejection but with findings of mild glomerulitis. There was concern for microvascular injury of immunologic causes, so serial measurement of dd-cfDNA and dnDSA continued. 16 months post-KT, the dd-cfDNA rose to 2.1%. Although creatinine remained stable without proteinuria, a second kidney biopsy was done. There was focal, minimal peritubular capillary staining for C4d without morphological evidence of rejection. 28 months post-KT, creatinine has remained stable without proteinuria.

Discussion: Although novel tools exist in predicting allograft kidney rejection, they are imperfect and require careful interpretation and application. There was marked discordance between the probability of active rejection, as indicated by the combination of elevated and sequentially rising fractions of dd-cfDNA and dnDSA, and the absence of histological, immunofluorescence, and electron microscopic evidence of rejection on two kidney allograft biopsies 4 months apart.

TH-PO808

Transcriptomic Analysis of Kidney Allograft Biopsies May Allow Early Detection of Rejection, Precise Rejection Typing, and Dynamic Treatment Monitoring

Thomas Schachtner, Vila S. Angheloiu, Lukas Weidmann, Dusan Harmacek, Britta George, Elena Rho, Ariana Gaspert, Seraina C. Von Moos. *UniversitatsSpital Zurich, Zurich, Switzerland.*

Background: The 2022 Banff Meeting Report suggests that biopsy-based transcripts related to antibody-mediated rejection (AMR) could substitute for microvascular inflammation (MVI). In addition, transcriptomic analysis may (1) detect molecular signatures associated with rejection earlier than traditional histopathologic methods, (2) distinguish between different types of rejection more accurately, and (3) provide more quantifiable measures of treatment responses. Studies with follow-up biopsies, however, are needed to test the performance of biopsy-based transcript analysis for these aims.

Methods: From 2018 to 2023, we examined 62 kidney transplant recipients and 139 kidney allograft biopsies evaluated by histology and the Molecular Microscope Diagnostic System (MMDx). The 62 biopsy series were analyzed regarding (1) the time of rejection diagnosis, (2) the type of rejection, and (3) the response to treatment.

Results: 20, 5, 8, and 29 of the initial biopsies showed histologic AMR/DSA-negative MVI, TCMR, mixed AMR/TCMR, and no AMR/TCMR (including 8 probable AMR cases), respectively. Molecular AMR, TCMR, and mixed AMR/TCMR were detected in 17, 4, and 8 of the initial biopsies, respectively. Follow-up biopsies were obtained at a median of 9 months (IQR 4,18) after the initial biopsy. With the MMDx, AMR was detected sooner in 8 cases (including 3 probable AMR cases by histology), which was verified histologically by the follow-up biopsy. There were 3 cases of histologic TCMR with mixed molecular AMR/TCMR and 2 cases of histologic AMR with mixed molecular AMR/TCMR. Follow-up biopsies verified the presence of mixed AMR/TCMR in all 5 cases by histology. Using transcriptomic analyses, treatment responses were observed in 1 early active AMR and 3 mixed AMR/TCMR cases (by rejection classifier scores) but not by histology. 5 of 20 histologic AMR cases (25%) showed no molecular AMR signature throughout the biopsy series.

Conclusions: Biopsy-based transcript diagnostics can help detect rejection sooner and identify rejection types more precisely, which might reduce the need for repeat biopsies and support treatment decisions. Molecular diagnostics may also allow clinicians to measure treatment outcomes more comprehensively through follow-up biopsies.

Funding: Private Foundation Support

TH-PO809

Pretransplant Inflammatory Biomarkers Predict Death-Censored Graft Failure after Kidney Transplantation

Elizabeth C. Lorenz,[1] Byron H. Smith,[2] Amanda L. Tapia,[2] Walter Park,[2] Mark D. Stegall.[2] *[1]Baylor College of Medicine, Houston, TX; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Pre-transplant inflammatory biomarkers have previously been associated with adverse kidney transplant (KT) outcomes, including delayed graft function and acute rejection. The goal of this study was to determine if pre-KT inflammatory biomarkers are also associated with graft failure after KT.

Methods: We retrospectively measured inflammatory biomarker levels in serum collected up to 1 year prior to KT in recipients transplanted at Mayo Clinic in Rochester, Minnesota between 1/2006-12/2018. The following biomarkers were chosen based on their association with medical risk across multiple patient populations: interleukin-15 (IL-15), IL-1β, monocyte chemoattractant protein-1 (MCP-1), growth differentiation factor-15 (GDF-15), IL-6, monokine induced by gamma interferon/chemokine (C-X-C motif) ligand 9 (MIG/CXCL9), soluble FAS (sFAS), soluble tumor necrosis factor receptor-1 (sTNF-R1), and TNFα. Biomarker levels were normalized with Z-transformation. Kaplan-Meier estimation and Cox regression were used to examine the relationship between biomarkers and death-censored graft failure.

Results: Our cohort consisted of 1,595 KT recipients with a mean age of 52.0 ± 14.2 years; 62.9% were male and 83.2% were White. Over a mean follow-up of 7.4 ± 3.9 years, 10.4% of patients (n=166) experienced death-censored graft failure. Higher pre-KT levels of soluble tumor necrosis factor receptor-1 (sTNF-R1) were significantly associated with death-censored graft failure after adjusting for other biomarkers (HR 1.4 per standardized log-value, 95% CI 1.2-1.7, p=0.0006).

Conclusions: Pre-KT activation of TNF pathways may contribute to graft failure following KT. Measuring pre-KT serum concentrations of sTNF-R1 may help to risk stratify and manage patients undergoing KT.

Funding: NIDDK Support

TH-PO810

Pediatric Transplantations: Clinical and Training Perspectives Based on a Survey of Pediatric Transplant Fellows

Nikhil Nair,[1] Mignon McCulloch,[2] Rupesh Raina.[3,4] *[1]Case Western Reserve University School of Medicine, Cleveland, OH; [2]Red Cross War Memorial Children's Hospital, Rondebosch, South Africa; [3]Cleveland Clinic Akron General, Akron, OH; [4]Akron Children's Hospital, Akron, OH.*

Background: The aim of this survey was to identify the satisfaction and shortcomings that pediatric transplantation fellows have with their education. Additional aims included the identification of strategies and modalities to better improve transplant education during fellowship.

Methods: An online Qualtrics survey composed of 29 questions available in Enlgish and Spainish was distributed to pediatric transplant fellows through various international pediatric and transplant associations. The responses of the online survey was entered into the Microsoft Excel and analysis was performed using SPSS version 22.

Results: A total of 237 physicians responded to the survey with a diverse distribution participants from Europe(38.4%), Asia(30%), the Americas(27.2%), Africa(2.1%) and Ocenaina(2.1%). In regard to overall education, most patients felt they were adequately educated on the important aspects of pre and post transplant care. Content areas fellows felt they were more lacking in education included transition protocols from paediatrics to adult care post transplantation(12.2%), immuno-suppression regimens post-transplantation(10.6%), and side-effects of different immunosuppression regimens post-transplantation(10.6%). In regards to improving the fellow education process, the formats fellows felts were most likely to help included, discussions of fellow's cases(88.8%), short presentations with open questions(69.2%) and Pro/con discussions(57.0%). Overarching competencies that warranted inclusion and emphasis according to fellows included critical thinking(80.6%), problem solving(76.6%) and leadership skills(69.6%).

Conclusions: This survey provides valuable information in regard to the quality of training and knowledge base from a diverse group current/former pediatric fellows from around the world. The majority of fellows are getting good to above average education for the majority of content areas they are expected to know over the course of their fellowship. Despite this there are still key foundational areas in immunosuppression and post transplant management that can use investigation for new methods for delivery information. The fellows who responded to this survey identified several promising methods for developing new educational content to serve as the foundation for discussion for the development of updated training guidelines.

TH-PO811

Pediatric Kidney Transplant and BK Viral Infection: A Single-Center Retrospective Analysis of Interventions and Outcomes

Raja Dandamudi,[1,2] Kevin T. Barton,[1,2] Vikas R. Dharnidharka.[1,2]
[1]Washington University in St Louis, St Louis, MO; [2]St. Louis Children's Hospital, St Louis, MO.

Background: In a single-center cohort of pediatric renal transplant patients, we investigated BK virus-associated nephropathy (BKVN) incidence, management strategies, and clinical outcomes.

Methods: We analyzed kidney transplant patients from Jan 2009 to Dec 2022. Ureteral stents placed during transplantation removed in 4-6 weeks. Recipients had monthly urine and plasma PCR screening for BK virus for the first 12 months and during rejection treatment.

Results: Among 101 patients, 17 (16.8%) had BK viruria, 15 (14.9%) had presumptive BKVN (DNAemia >10,000 copies/mL), and 15 (14.9%) had probable BKVN (DNAemia 1,000-10,000 copies/mL), with 4 showing blip DNAemia. Median time to BK viruria was 48 days post-transplant and 141 days for BK viremia. Of the 15 patients with presumptive BKVN, 11 (73.3%) were male; 10 (66.6%) were white, 4 (26.7%) African American, and 1 (6.7%) other. Mean age at transplantation was 11.6 years (range 2.4-18.4); 11 (73.3%) received kidneys from deceased donors. 10 patients had IVIg monthly at 500 mg/kg for 6 months. Before IVIg, mean urinary BKV DNA was 232 million ± 574 million copies/mL, and plasma load was 171,945 ± 428,810 copies/mL. At diagnosis, mean serum creatinine peaked at 1.3 mg/dL (baseline 0.85 mg/dL). Post-treatment, mean serum creatinine improved to 0.95 mg/dL, and plasma BKV DNA load decreased to 312 ± 788 copies/mL. 7/10 had non-quantifiable plasma loads. One IVIg-allergic patient received leflunomide alone, clearing BK viremia from 160,000 to non-quantifiable levels, with creatinine improving from 1.6 to 1 mg/dL. 4 patients received 10 monthly doses of IVIg but did not clear DNAemia and then received leflunomide. Two cleared BK virus (mean 27,900 copies/mL to undetected) with creatinine improving (2.02 to 1.14 mg/dL). Two non-responsive patients received low-dose IV cidofovir (0.5-0.75 mg/kg/dose) for six doses. Despite BK viral level improvements (28,000 to 15,000 copies/mL), viremia clearance was unsuccessful, with minimal creatinine improvement (1.45 to 1.2 mg/dL).

Conclusions: At our center, IVIg seems to be an effective treatment for persistent BKVN after failed reduction in immunosuppression. IVIG was effective in 70% of cases, while leflunomide alone or following IVIG was effective in 60%. The addition of cidofovir for those resistant to IVIG and leflunomide was not successful.

TH-PO812

Probability of Kidney Transplant in the Pediatric ESKD Population by Residence Type

Lucas Barrett, Morgan B. Swanson, David Axelrod, Lyndsay Harshman.
University of Iowa Health Care, Iowa City, IA.

Background: Rurality is a commonly cited barrier to care in pediatric nephrology. Utilization of healthcare by pediatric chronic kidney disease (CKD) patients has been shown to be largely centralized, with more than 86.6% of hospitalized pediatric CKD patients being cared for in urban teaching hospitals in one study. Access to care is a particular problem in CKD as it is a progressive disease that often leads to end-stage kidney disease (ESKD) requiring dialysis and/or kidney transplantation (KT). The goal of this study is to estimate the effect of rural or micropolitan residence, compared to urban residence, on probability of KT in patients with pediatric ESKD in the United States (US).

Methods: We performed an observational cohort study using the US Renal Data System (USRDS) to identify pediatric (< 18 years) ESKD patients who have their first ESKD service between 2000 and 2019 and classify them using ZIP codes to rural, micropolitan, or urban residence at time of first ESKD service. Stabilized inverse probability of treatment weighting (IPTW) was used to balance rural, micropolitan, and urban groups based on their baseline covariates. Weighted Cox regression was used to calculate the hazard ratio of experiencing KT for rural and micropolitan patients compared to urban. Sensitivity analyses were run using time-varying residential status, mean and median imputation for missing calculated panel reactive antibody percentage and competing risks regression.

Results: The final cohort of 14,404 pediatric (<18 years old) patients had 12,390 patients (86.0%) with urban residence, 1,095 patients (7.6%) with micropolitan residence, and 919 patients (6.4%) with rural residence. Of the cohort, 13,316 patients underwent kidney transplantation and 369 died prior to transplantation. Cox regression showed a non-significant decrease in probability of transplantation for patients who had rural (HR = 0.95, 95% CI = 0.86, 1.06) and micropolitan (HR = 0.99, 95% CI = 0.91, 1.07) residence compared to urban residence. Sensitivity analyses had similar results.

Conclusions: Despite differences in healthcare resources between rural, micropolitan, urban areas in the US, once children receive their first ESKD service we did not identify a difference in probability of receiving KT based on rurality of residence.

TH-PO813

Linear Growth after Pediatric Kidney Transplant: Factors Influencing Catch-Up Growth in a Retrospective Cohort

Patrick Ribeiro, Paula S. Campelo, João Victor R. Borges, Leonardo P. Stakonski, Marcos K. Hesler, Marco A. De Barros, Lucimary D. Sylvestre, Maria H. Peralta, Andrea N. Moreno-Amaral. *Pontificia Universidade Catolica do Parana, Curitiba, Brazil.*

Background: Children with chronic kidney disease often face growth deficits due to electrolyte, nutritional, and hormonal issues. Kidney transplantation (KT) can enhance growth, but catch-up growth (CUG) to expected height for age is not always achieved. Understanding post-transplant (PT) growth is vital for optimizing interventions, such as growth hormone (GH) use, which is limited in Brazil. Therefore, this study aims to identify the prevalence and factors associated with sufficient CUG in children who underwent KT.

Methods: This retrospective cohort study at a tertiary pediatric nephrology center in Brazil included patients under 18 who had KTs between 2010 and 2023. Data were collected from medical records. Sufficient CUG was defined as an increase in height standard deviation score (SDS) ≥ 0.5 SD from pre-transplant to 2 years PT. Weight, height SDS and BMI-for-height-age SDS were compared using ANOVA for repeated measures, followed by Bonferroni post hoc tests for normally distributed variables, and the Friedman test with Bonferroni-adjusted significance level post hoc analysis for non-normal variables. Logistic regression was used to identify pre-transplant factors associated with CUG, with significance set at 5%.

Results: The sample included 27 patients (mean age 9.4 years, 81.5% male). Dialysis modalities included peritoneal (44.4%), hemodialysis (29.6%), and both (18.5%). Uropathy was the main etiology (51.9%). None used GH during follow-up. Preemptive transplants accounted for 7.4%. KT significantly improved weight ($p<0.001$), height SDS ($p<0.024$), and BMI-for-height-age ($p<0.002$), with more pronounced gains in the first 6 months. Improvements stabilized between 6 months and 1 year. Among the 22 patients who followed up to 2 years, sufficient CUG was observed in 18.2%. Univariate and multivariate analyses found no significant associations between the pre-transplant characteristics and CUG.

Conclusions: KT significantly improved height and weight, though only a small proportion achieved sufficient CUG after 2 years. Larger studies are needed to identify factors involved in CUG and optimize interventions.

TH-PO814

BMI in Pediatric Kidney Transplant Candidates: Association with Neurodevelopmental Outcomes

Lidan Gu,[1] Danielle M. Glad,[2] Christopher J. Anzalone,[3] Finola E. Kane-Grade,[4] Michael D. Evans,[1] Sarah J. Kizilbash.[1] *[1]University of Minnesota Medical School, Minneapolis, MN; [2]Medical College of Wisconsin, Milwaukee, WI; [3]Boston Children's Hospital, Boston, MA; [4]University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Recent studies indicated that both low and high body mass index (BMI) in pediatric kidney transplant patients is linked to higher graft failure and mortality risk (al Tamimi et al., 2023; Bonthuis et al., 2023; Winnicki et al., 2018). However, the interaction of BMI, neurocognitive outcomes, and transplant outcomes has not been explored. This study aimed to evaluate the association between BMI, neurocognitive outcomes, and transplant outcomes.

Methods: A retrospective study was completed for 75 patients aged 3 to 17 years who completed pre-transplant neuropsychological evaluations at University of Minnesota Medical Center between 2010 and 2022. Neurocognitive outcome variables include Full Scale IQ, Verbal Comprehension, Nonverbal Reasoning, Working Memory, and Processing Speed. Medical (i.e., pre-transplant BMI, eGFR 1 year and 5 years post-transplant) and demographic variables were retrieved from the electronic medical records. Based on the CDC guideline, patients were categorized to underweight, normal, overweight, and obese groups. Analysis of Variance was used to exam the effect of BMI category on neurocognitive outcomes. Spearman correlations examined the correlation between BMI z scores, neurocognitive performance, and eGFR at 1 and 5 years.

Results: The mean age at the time of neuropsychological evaluation was 11.7 years (SD=3.6). The mean age at kidney transplant was 13.3 (SD=3.6). The mean BMI z score was 0.2 (SD=1.2). Within the 75 patients, 7 (9.3%) were underweight, 45 (60.0%) were normal, 12 (16%) were overweight, and 11 (14.7%) were obese. There was a significant effect of BMI category on Working Memory performance ($F(3)=2.82$, $p=0.045$). Patients with normal BMI had higher Working Memory performance than patients who were underweight or overweight. There was no significant effect of BMI category on other neurocognitive outcomes (p values ranged from 0.197 to 0.60). Pre-transplant BMI z scores were not significantly associated with eGFR at 1 year or 5 years post-transplant.

Conclusions: Our study found that pre-transplant body mass index (BMI) was associated with pre-transplant working memory in pediatric kidney transplant candidates. The findings highlight the importance of a multidisciplinary approach to managing medical and neurocognitive factors to ensure optimal outcomes in this population.

TH-PO815

Decreasing Trends in Pediatric Kidney Transplantation in Mexico, 2007-2023

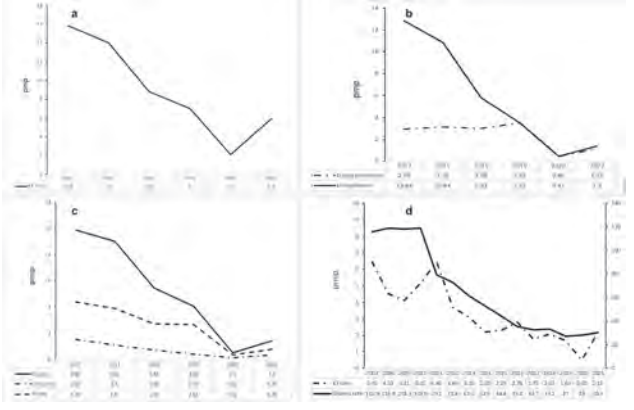
Ana E. Oliva,[1] Jochen G. Raimann,[2] Ariella E. Mermelstein,[2] Andrea Nandorine Ban,[2] Yuridia Plascencia,[3] Mara Medeiros,[4] Araceli Cisneros,[5] Jonathan Chavez,[1,6] Guillermo Garcia-Garcia.[6] *[1]Hospital Civil de Guadalajara Unidad Hospitalaria Fray Antonio Alcalde, Guadalajara, Mexico; [2]Renal Research Institute, New York, NY; [3]Hospital de Pediatria Centro Medico Nacional de Occidente, Guadalajara, Mexico; [4]Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico; [5]Hospital San Javier, Guadalajara, Mexico; [6]Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Guadalajara, Mexico*.

Background: Kidney transplantation (KT) is the most preferable therapy for children with end-stage kidney disease (ESKD). There is a paucity of information on temporal trends of KT in children in Mexico. We analyzed data of KT in children < 18 years between 2007-2023, to determine the presence of inequalities in access to KT.

Methods: In this retrospective study of pediatric ESKD patients receiving KT, we analyzed data from the national transplant center database between 2007- 2023. Transplant rates are presented by insurance status and donor type and standardized to the general population in the respective age segment as per million population (pmp). In the absence of a national dialysis registry, we estimated trends of dialysis prevalence based on data from the Jalisco state registry.

Results: We analyzed a total of 5,123 KT patients. The median age was 14 years (IQR 12 to 16), 57% males, and 71% were recipients from living donors. 32% were uninsured, 61% had public and 8% private insurance. Annual KT rates decreased steadily from 15.8 pmp in 2007 to 7.0 pmp in 2019, and further to 2.1 pmp during the COVID-19 pandemic, mainly in those with living donors (12.8 pmp to 3.5 pmp). The decrease was independent of health insurance status (**Fig a to c**). Consistently, in Jalisco KT rates dropped from 6.45 pmp in 2007 to 1.66 pmp in 2019 accompanied by a decrease in dialysis prevalence from 115.9 pmp in 2008 to 27.0 pmp in 2019 (**Fig d**).

Conclusions: Pediatric kidney transplant rates in Mexico have consistently decreased over the last 17 years, independent of health insurance status. Based on the results from Jalisco the drop is accompanied by a decrease in the number of dialysis patients. It remains to be evaluated if the decrease is caused by limited access to dialysis treatment or due to decreases in the prevalence of ESKD.



Pediatric kidney transplantation rates

TH-PO816

Safety and Efficacy of Selective Plasma Exchange vs. Conventional Plasma Exchange in Pretransplant Desensitization of ABO-Incompatible Kidney Transplantation

Takahiro Inoue,[1,2] Norio Hanafusa,[1] Yuki Kawaguchi,[1] Kohei Unagami,[1] Junichi Hoshino,[1] Hideki Ishida,[1] Toshio Takagi,[1] Ken Tsuchiya.[1] *[1]Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan; [2]Tsukuba Kidney Clinic, Tsukuba, Japan*.

Background: Selective Plasma Exchange (SePE) is a new simple PE modality that uses a membrane plasma separator with a smaller pore size compared to conventional plasma separators and enables removal of small and medium-sized molecules without removing larger substances such as coagulation factors. Conventional PE (CPE) supplemented with fresh frozen plasma (FFP) is performed preoperatively to reduce the risk of bleeding, but adverse events associated with FFP are common. Since July 2022, our institution has started SePE as a desensitization method before ABO-incompatible kidney transplantation.

Methods: This is a single-center, retrospective cohort study of patients undergoing ABO-incompatible kidney transplantation from January 2020 to April 2024. Seventy-five patients underwent apheresis for antibody removal prior to kidney transplantation and were divided into two groups: one undergoing CPE with FFP and the other undergoing SePE. The safety and efficacy of both groups were compared.

Results: In the CPE group, adverse events were observed in 17 cases, including four instances of anaphylactic shock. In the SePE group, hypotension was observed in five cases, but no serious adverse events were reported. Except for one case, preoperative antibody levels in both groups were reduced to less than 32 times the target. Although the surgical time was longer for the CPE group, there was no significant difference in intraoperative blood loss between the two groups.

Conclusions: Both groups showed adequate antibody removal, whereas the incidence of adverse events in the pretransplant desensitization of ABO-incompatible kidney transplantation was lower in the SePE group compared to the CPE group.

Clinical features and Outcome between SePE group and CPE group

Patients undergoing kidney transplantation(N = 75)	SePE(N = 48)	CPE(N = 27)	P value
Age, years.	51.1 ± 13.1	49.2 ± 13.8	0.568
IgM (initial titers at admission)	16.0 (8.0-16.0)	16.0 (8.0-32.0)	0.152
IgM(titers at transplantation)	2.0 (2.0-4.0)	1.0 (1.0-2.0)	0.006
IgG (initial titers at admission)	8.0 (2.0-16.0)	64.0 (32.0-128.0)	0.017
IgG(titers at transplantation)	2.0 (2.0-4.0)	4.0 (2.0-16.0)	0.007
Surgical operating time, min.	234.5 (213.0-280.0)	274.0 (243.0-316.0)	0.015
Total blood loss, ml.	200.0 (93.8-298.0)	150.0 (80.5-292.5)	0.811
Patients experiencing adverse events during PE, n.%	5 (10.4)	17 (63.0)	<0.001
Anaphylactic shock, n. %	0 (0)	4 (14.8)	0.027

TH-PO817

Effects of Desensitization Therapy on Acute Rejection and Graft Function in Patients Who Are Hyperimmunized after Receiving a Living-Donor Kidney Transplant

Caren D. Castro,[1,2] Jorge Andrade-Sierra,[3,1] Hugo L. Reynoso de la Torre,[1,2] Enrique Rojas-Campos,[1,2] Luis Alberto Evangelista-Carrillo,[1,2] Mauricio Carvallo Venegas,[1,2] Adriana Banda Lopez,[1,2] Jose Ignacio Cerrillos,[1,2] Miguel Medina Perez,[1,2] Diana Laura Muñoz.[1,2] *[1]Instituto Mexicano del Seguro Social. UMAE-Centro Medico Nacional de Occidente. Depto Nefrologia y Trasplantes, Guadalajara, Mexico; [2]Instituto Mexicano del Seguro Social Delegacion Jalisco, Guadalajara, Mexico; [3]Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Guadalajara, Mexico*.

Background: Desensitization therapy may enhance the probability of successful kidney transplantation (KT) and ensure long-term survival for hyperimmunized patients.

Methods: A retrospective cohort included 38 patients ≥18 years with a positive DSA flow crossmatch test. (January 2018 to December 2022). All patients received pre-transplant desensitization using plasmapheresis (PF), immunoglobulins (IG), rituximab (RTX) and maintenance immunosuppressive consisting of mycophenolic acid, prednisone, tacrolimus (TAC) and thymoglobulin. The occurrences of infectious and acute rejection (AR) episodes were registered.

Results: The function of the graft at 12 months was 80 ± 28.5 ml/min/1.73m2 and AR rate was 18.4% (7 patients). The MFI class I of the patients who developed AR was 7001 ± 1269 (p= 0.17), and MFI class II 7083 ± 3264 (p=0.58). Two patients developed hyperacute rejection, both positive in DSA flow crossmatch class II, with a MFI DSA class I 6782 ± 1639 and class II of 8958 ± 5828. The first patient with positive antigen B and DR, and the second patient with positive antigen for C and DR. 36.5% patients had urinary tract infection (UTI), with a cumulative number of UTI events of 27. Four patients developed respiratory tract infections (10.5%), death was reported in 2 of them due to the infection.

Conclusions: The main risk factors were the number of match class II antigens and serum tacrolimus levels at 6 months. The hyperimmunized patients can have an opportunity and access a high-risk transplant, with successful results.

Demographic Characteristics of the Population

Age (years)	31 (IQR, 28-35)
Male-gender (%)	23 (60.5%)
Dialysis Time, (years)	3 (IQR, 1-6)
DSA, MFI (SD)	
Class I	6725 ± 4763
Class II	9764 ± 4473
Transplant n (%)	
First	11 (28.9%)
Second	27 (71.1%)
Acute rejection n (%)	7 (18.4%)
Rejection type n (%)	
Antibody-mediated rejection	7 (100%)
Acute T-cell–mediated rejection	0 (0%)
Crs at discharge (mg/dL)	1.06 ± 0.69
CrS at 3 months (mg/dL)	1.18 ± 0.51
CrS at 12 months (mg/dL)	1.33 ± 0.69
Infections	
UTI	15 (39.4%)
CMV	0
Respiratory tract infection	4 (10.5%)
BK virus	0

DSA: Donor specific antibody, CrS: serum creatinine, UTI: urinary tract infection, CMV: cytomegalovirus.

TH-PO818

Successful Eculizumab-Based Desensitization in ABO-Incompatible Living Donor Kidney Transplantation

Ga Young Heo, Minsun Jung, Honglin Piao, Hyun-Jeong Kim, Hyung Woo Kim, Juhan Lee, Kyu ha Huh, Beom Seok Kim, Jaeseok Yang. *Yonsei University, Seoul, Republic of Korea*.

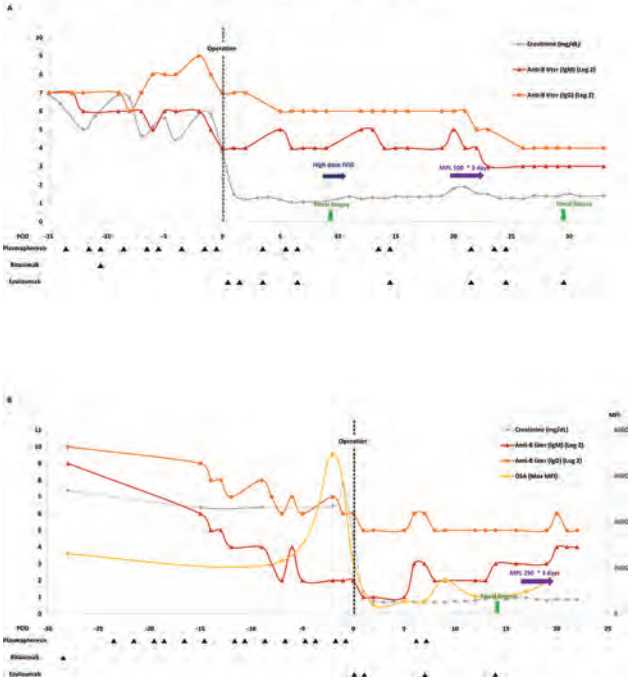
Background: High titers of anti-ABO antibodies in some patients are refractory to standard desensitization, leading to loss of KT opportunities or AMR.

Methods: Eculizumab-based desensitization was used to rescue high-titer ABOi KT patients refractory to plasmapheresis/rituximab-based desensitization.

Results: Initial titers of anti-ABO IgG antibodies in the two patients were 1:512 and >1:1024; the final pre-transplant titers after desensitization were 1:128 and 1:64. Both patients received eculizumab from the day of KT to two or four weeks post-KT and maintained stable renal function up to one-year without overt complications, despite early episodes of suspicious AMR or borderline TCMR. Molecular phenotype analysis of allograft biopsies using the B-HOT gene panel revealed that gene expression patterns in the ABOi KT with eculizumab group overlapped with those in the ABOi KT with AMR group more than in the ABOi KT without AMR group, except for complement pathway-related gene expression.

Conclusions: Short-term eculizumab-based desensitization therapy is promising for rescuing ABOi KT recipients with unacceptably high anti-ABO antibody titers refractory to plasmapheresis-based desensitization therapy.

Figure 1. Clinical courses of patients in the eculizumab group. **(A)** Case 1 and **(B)** Case 2.



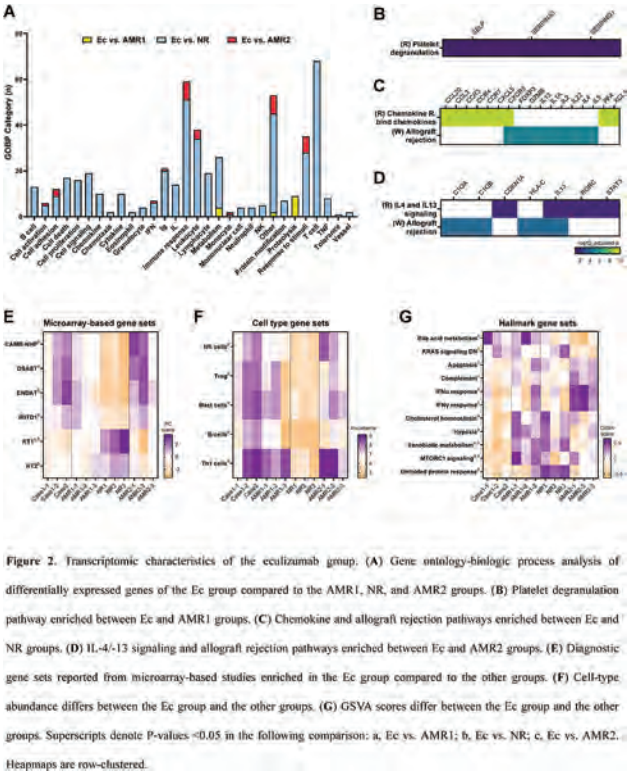


Figure 2. Transcriptomic characteristics of the eculizumab group. **(A)** Gene ontology-biologic process analysis of differentially expressed genes of the Ec group compared to the AMR1, NR, and AMR2 groups. **(B)** Platelet degranulation pathway enriched between Ec and AMR1 groups. **(C)** Chemokine and allograft rejection pathways enriched between Ec and NR groups. **(D)** IL-4/-13 signaling and allograft rejection pathways enriched between Ec and AMR2 groups. **(E)** Diagnostic gene sets reported from microarray-based studies enriched in the Ec group compared to the other groups. **(F)** Cell-type abundance differs between the Ec group and the other groups. **(G)** GSVA scores differ between the Ec group and the other groups. Superscripts denote P-values <0.05 in the following comparison: a, Ec vs. AMR1; b, Ec vs. NR; c, Ec vs. AMR2. Heapmaps are row-clustered.

TH-PO819

Is Induction Therapy with Basiliximab Mandatory in Kidney Transplant Recipients with a Low Immunological-Risk Profile?

Florian Lacave, Arnaud Devresse, Christophe de Terwangne, Guillaume Fernandes, Tom Darius, Antoine Buemi, Eric Goffin, Nada Kanaan. *Cliniques universitaires Saint-Luc, Bruxelles, Belgium*.

Background: Induction therapy with basiliximab is recommended in kidney transplant (KT) recipients with a low immunological risk (LIR) profile. Whether basiliximab is associated with a decreased risk of acute rejection (AR) and graft loss is controversial.

Methods: In our institution, LIR patients (absence of anti-HLA antibodies before KT) are inducted with basiliximab in case of living-donor KT (LDKT) while deceased-donor KT recipients (DDKT) receive no induction. Maintenance immunosuppression is similar, including a combination of tacrolimus, mycophenolate and steroids. In this single-center retrospective study, all adult LIR patients who underwent KT between 01/01/2015 and 12/31/2022 (excluding ABO-incompatible and multiorgan transplantations) have been included.

Results: Of the 471 patients included, 354 received a DDKT (DDKT group) and 117 a LDKT (LDKT group). Patients from the DDKT group were more frequently male, older and received fewer preemptive KT compared to those from the LDKT group. The median (IQR) number of HLA A-B-DR mismatches was 3 (2-3) and 2 (2-4) in the DDKT group and the LDKT group, respectively. Survival free from treated AR was similar in both groups at 6 months, 1 year and 5 years (Figure 1), as was 5-year survival without reaching a composite endpoint of treated AR or graft loss. At 5 years, the incidences of graft loss (p= 0.074) and death (p=0.6) were similar in the DDKT group vs LDKT group.

Conclusions: Induction therapy with basiliximab showed no benefit regarding the risk of treated AR or graft loss within 5 years post-KT compared with a strategy without induction therapy in patients with a LIR profile.

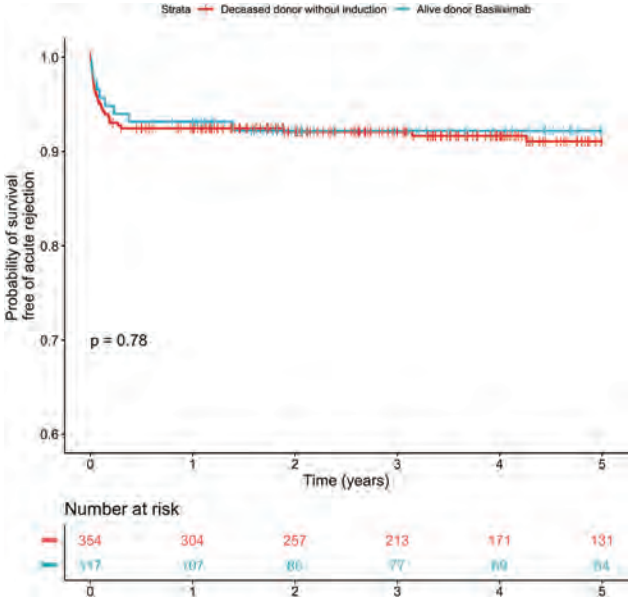


Figure 1 : Treated acute rejection-free survival in the 5 years after kidney transplantation.

TH-PO820

Rabbit Anti-thymocyte Globulin Induction (rATG) in Older Adult Kidney Transplant Recipients

Brandon L. Trollinger,[1] Rachel Cartus,[3] Nada Alachkar,[2] Heather Carberry,[2] Divyanshu Malhotra,[2] Laura Lees,[1] Benjamin Philosophe,[2] Sara Strout,[1] Daniel C. Brennan.[2] *[1]The Johns Hopkins Hospital, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD; [3]Keck Medicine of USC, Los Angeles, CA.*

Background: Deceased donor kidney transplants are increasingly performed in older patients. There are limited published efficacy and safety data of rATG use in this population, particularly in those ≥75 years old.

Methods: This is a single center, real-world retrospective cohort study of 445 first-time kidney-only DDKT recipients ≥40 yo who received rATG induction. Patients were age-stratified: 40-64 yo (middle age, MA), 65-74 yo (older, O), ≥75 yo (oldest old, OO). Dosing, baseline characteristics, efficacy and safety outcomes were analyzed using Kruskal-Wallis or Fisher's exact tests.

Results: The cohorts (MA: n=284, O: n=133, OO: n=28) showed imbalances in baseline characteristics: race, sensitization, weight and estimated posttransplant survival/ kidney donor profile indices (Figure 1). Median rATG dose (mg/kg) decreased with increasing age (MA: 5.0, O: 4.5, OO: 3.1, p<0.01) with lower rejection rates. Death, early cytomegalovirus viremia, cardiovascular events and cancer rates were higher in the older cohorts, but death-censored graft failure and infection were not (Figure 2).

Conclusions: Lower rATG doses effectively prevented rejection with similar graft survival rates in older patients. However, adverse event rates remain higher in these cohorts.

Baseline Recipient and Transplant Characteristics

Characteristic	Middle Age (n=284)	Older (n=133)	Older Old (n=28)
Age, median years, (IQR)*	**55 (48-59)**	**69 (67-71)**	**77.5 (76-79)**
Female sex, n (%)	122 (43.0)	54 (40.6)	8 (28.6)
Race, n (%)†	**Black: 160 (56.3) White: 71 (25.0) Other: 53 (18.7)**	**Black: 51 (38.4) White: 66 (49.6) Other: 16 (12.0)**	**Black: 5 (17.9) White: 17 (60.7) Other: 6 (16.9)**
Native kidney disease, n (%)†	**DM-HTN: 182 (64.1) FSGS: 36 (12.7) Other: 66 (23.2)**	**DM-HTN: 87 (65.4) FSGS: 3 (2.3) Other: 43 (32.3)**	**DM-HTN: 19 (67.9) FSGS: 0 Other: 9 (32.1)**
Weight, median kg (IQR)*	**88.4 (73.6-103.7)**	**82.9 (71.7-96.2)**	**77 (65.8-86.4)**
EPTS at transplant, median % (IQR)*	**41 (27.5-53.5)**	**77 (70-82)**	**94 (91-96.5)**
cPRA <20%, n (%)†	**209 (54.9)**	**105 (60.7)**	**26 (78.8)**
DCD donor, n (%)	91 (33.9)	43 (24.9)	8 (24.2)
Donor age, median years (IQR)*	**34 (27-45)**	**35 (27.5-47)**	**47 (32-57)**
KDPI, median % (IQR)*	**41 (25-61.5)**	**50 (33-70)**	**72.5 (43.5-89.5)**
HLA-A, -B, -DR mismatches, n (IQR)	4 (3-5)	4 (4-5)	4 (4-5)
Cold ischemia time, median hours (IQR)*	**21.0 (15.1-25.8)**	**23.5 (18.2-28.0)**	**22.5 (16.8-28.3)**
CMV D+/R-, n (%)	44 (15.5)	22 (16.5)	4 (14.3)

*p≤0.0221 Kruskal-Wallis, †p<0.001 Fisher's Exact
Abbreviations: CMV: cytomegalovirus, cPRA: calculated panel reactive antibody, DCD: donation after cardiac death, DM-HTN: diabetic nephropathy and/or hypertensive nephrosclerosis, EPTS: estimated posttransplant survival, FSGS: focal segmental glomerulosclerosis, HLA: human leukocyte antigen, IQR: interquartile range, KDPI: kidney donor profile index

Patient Outcomes

Characteristic	Middle Age (n=284)	Older (n=133)	Older Old (n=28)
rATG dose, median mg/kg (IQR)*	**5.0 (4.6-5.9)**	**4.5 (3.6-5.1)**	**3.1 (2.9-4.0)**
Length of stay, median days (IQR)*	**7.7 (6.2-9.9)**	**8.2 (6.8-11.0)**	**9.7 (6.5-12.6)**
DGF, n (%)	98 (34.5)	51 (38.4)	8 (28.9)
SCr at discharge, median mg/dL (IQR)	2.9 (1.5-5.8)	3.2 (1.7-5.3)	2.2 (1.5-4.3)
Duration follow-up, median months (IQR)*	**57 (43-72)**	**50 (38-62)**	**52 (42.5-61)**
Death 1 year, n (%)†	**6 (2.1)**	**10 (7.5)**	**0**
Death 3 years, n (%)†	**17 (6.0)**	**20 (15.0)**	**2 (7.1)**
Death-censored graft failure (3 years), n (%)	18 (6.3)	4 (3.0)	1 (3.6)
CMV viremia (>50,000 IU/mL) (6 months), n (%)†	**1 (0.4)**	**5 (3.8)**	**1 (3.6)**
CMV viremia (>50,000 IU/mL) (3 years), n (%)	6 (2.11)	8 (6.0)	1 (3.6)
BKV ≥10,000 IU/mL (3 years), n (%)	32 (11.3)	14 (10.5)	3 (10.7)
EBV viremia at 3 years, n (%)	22 (7.8)	8 (6.0)	1 (3.6)
TCMR at 3 years, n (%)†	**19 (6.7)**	**2 (1.5)**	**0**
Infection, n (%)	165 (58.1)	80 (60.2)	16 (57.1)
UTI, n (%)	66 (23.2)	31 (23.3)	6 (21.4)
Recurrent UTI, n (%)	23 (8.1)	9 (6.8)	1 (3.6)
MACE total, n (%)†	**23 (8.1)**	**24 (18.1)**	**7 (25)**
MACE: CV, n (%)†	**9 (3.2)**	**14 (10.5)**	**3 (10.7)**
MACE: CVA or TIA, n (%)†	**16 (5.6)**	**13 (9.8)**	**5 (17.9)**
MACE: cardiac death, n (%)	3 (1.1)	1 (0.8)	0
Cancer, n (%)†	**23 (8.1)**	**26 (19.6)**	**4 (14.3)**

*p≤0.0369 Kruskal-Wallis, †p≤0.035 Fisher's Exact
Abbreviations: IQR: interquartile range, CV: cardiovascular, CVA: cerebrovascular accident, DGF: delayed graft function, CMV: cytomegalovirus, EBV: Epstein-Barr virus, MACE: major cardiovascular adverse event, rATG: rabbit anti-thymocyte globulin, TIA: transient ischemic attack, TCMR: T-cell mediated rejection, UTI: urinary tract infection, USA: unstable angina

TH-PO821

Anti-thymocyte Globulin (ATG) vs. Interleukin-2 Receptor Antagonist (IL-2 RA) in Low Immunologic-Risk Kidney Transplant Recipients

Pamela M. Prado Lozano, Jose H. Cano Cervantes, Mayra M. Matias Carmona, Citlali Fernandez Vivar, Carolina Gonzalez-Fuentes, Jose L. Torres Cuevas, Martin B. Yama Estrella, Nicte Alaide R. García, Martin O. Carbajal, Ydris Z. Rosillo-Salgado. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico*.

Background: KDIGO recommends IL2-RA as first line induction therapy and a lymphocyte-depleting agent for kidney transplant recipients (KTR) at high immunologic risk. Although, depleting agents reduce acute rejection they also increase the risk of infections and malignancies. However, the evidence is controversial.

Methods: Patients were allocated to receive IL2-RA or rATG as induction in a 1:1 ratio. Inclusion criteria: ≥18 years old, LIR – KTR. LIR was defined as PRA <30%,1st kidney transplant from living donor with ABO compatibility. PBL subsets, C3 and IgG determinations were obtained pre-transplant, 7 days and 3 months after. CMV and BK viral loads obtained as per protocol and allograft biopsies performed at 3 and 12 months. All received maintenance with Mycophenolic Acid, Tacrolimus and prednisone. Prophylaxis with Trimethoprim – Sulfamethoxazole was given to all and Valganciclovir to those with moderate-high risk for CMV. Primary outcome: measure the effect of rATG compared to IL2-RA as induction for LIR-KTR in PBL subsets, C3 an IgG levels at 7 days and 3 months after transplant. Secondary outcomes: evaluate the incidence of BPAR and infections.

Results: 24 patients were analyzed, 14 received IL2-RA. There was a significant decrease in PBL subsets at 7 days post-transplant in the rATG group. CD4 418 cel/µl (285 – 788 cel/µl) vs 30 cel/µl (2 – 58 cel/µl) p = 0.0002, CD8 58 cel/µl (3 – 108 cel/µl) vs 291 cel/µl (116 – 483 cel/µl) p=0.011; CD4/CD8 ratio 1.8 (1.48 – 2.82) vs 0.76 (0.36 – 0.76) p=0.0002, and NK cells 85 cel/µl (74 – 113.5 cel/µl) vs 34 cel/µl (8 – 65 cel/µl p=0.045). This difference was sustained by month 3 in the CD4 count (935 ± 440 cel/µl vs 228 ± 136 cel /µl, p= 0.002) and CD4/CD8 ratio (0.96 ± 0.65 cel/µl vs 1.79 ± 0.33 cel/µl, p = 0.008); with no difference in CD8, NK cells, C3 and IgG at this point. The IL2-RA group showed significant decrease in CD4 and NK cells by day 7; sustained until month 3 for CD4. During follow up, 1 patient in the IL2-RA group presented an ITU and 1 in the rATG early CMV infection. There was 1 BPAR in IL2-RA vs none in the rATG.

Conclusions: rATG is associated with prolonged CD4 suppression but no CD8, what probably lessens the adverse effects, while improving allograft survival.

TH-PO822

Impact of Delayed Graft Function on Kidney Transplant Outcomes

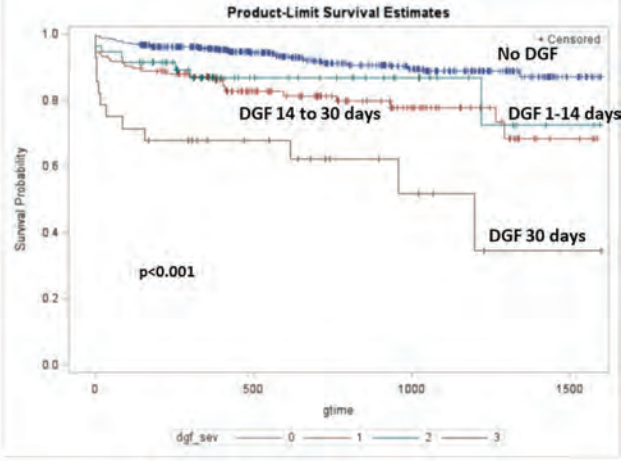
Mary Show, Mona D. Doshi. *University of Michigan Michigan Medicine, Ann Arbor, MI.*

Background: Delayed graft function (DGF) is a frequent complication following deceased donor kidney transplant. The revised allocation policy mandates a wider geographical distribution of kidneys from deceased donors resulting in prolonged cold time and higher rates of DGF. Our study explores the impact of duration of DGF on graft function and survival.

Methods: We reviewed records of 687 patients who received deceased donor kidney transplant (DDKT) from 2020 to 2023 at the University of Michigan Transplant Center. Patients were grouped based on occurrence of DGF (need for dialysis within 7 days of transplant) and duration (0-14, 15-30, and >30 days). We compared donor, and recipient characteristics across 4 groups. Graft outcomes across 4 groups were compared via serum creatinine at last follow-up and also via Kaplan-Meier Survival Curves. Cox proportional hazard models were constructed to account for donor and recipient factors for graft loss.

Results: Of the 687 DDKT, 466 (68%) had no DGF and 221 (32%) developed DGF. Of 221 patients with DGF, 135 (61%) required dialysis for <14 days, 58 (26%) for 15-30 days, and 28 (13%) for more than 30 days. Donor risk factors that were associated with severe DGF include donation after cardiac death, death by anoxia, history of hypertension, and diabetes mellitus (p<0.05). Recipient risk factors for severe DGF include usage of anticoagulation, and Midodrine, African American race, and history of diabetes (p<0.05). Serum creatinine varied across 4 groups and was lowest among patients with no DGF and highest among patients with most severe DGF (1.1±0.6, 1.7±0.6, 2.3±0.9 and 2.4±1.4 mg/dL; p<0.001). Graft survival varied across 4 groups and was lowest among recipients requiring dialysis for more than 30 days (see Figure 1, p<0.001). On multi-variate analyses, severity of DGF, donor age and donor history of diabetes were associated with graft loss.

Conclusions: Duration of DGF has a negative impact on graft function and survival. New strategies are needed to improve organ preservation and manage patients after transplant to reduce the duration of DGF and subsequently graft loss.



TH-PO823

Single-Center Short-Term Outcomes in Recipients of Deceased Donor Kidneys with AKI

Barbara A. Greco, Kenneth Brand, Boonyanuth N. Maturostrakul. *Baystate Medical Center, Springfield, MA.*

Background: Previous reports suggest that long term outcomes in recipients of deceased donor kidneys (DDKT) from donors with acute kidney injury (AKI) are comparable to those without AKI. We report short term outcomes in 20 recipients of AKI donor kidneys compared to 20 recipients of kidneys without AKI to provide insight into optimal deceased donor acceptance criteria.

Methods: We reviewed data on 40 consecutive recipients of DDKT done at the Baystate Transplant Program between October 2023 and March of 2024. Twenty of these were from donors with AKI defined as terminal creatinine (Cr)> 1.5 times admission Cr. We used UNET data to collect demographics, KDPI, DCD criteria, terminal creatinine and urine output, and pre-implantation biopsy findings. Cold ischemia time (CIT) was obtained from the OPO. Recipient outcomes were evaluated as part of quality review.

Results: The mean age and KDPI of recipients of AKI vs. standard kidneys was 58.2 vs.59.7 years and 70.15 (43-98) vs. 76.2 (49-98), respectively. AKI kidney donor age was higher, 61.8 vs. 51.1 years, with a similar number of DCD donors in each group (9 vs. 10). CIT was higher in the AKI donor group: 1436 vs. 1215 min. LOS was comparable between groups: 8 vs. 8.5 days (excluding 1 recipient of an AKI kidney who remains hospitalized). More than twice as many recipients of AKI kidneys had DGF (13/20) vs. nonAKI (6/20). Mean Cr at 3 months for recipients of AKI vs. nonAKI kidneys were 2.42 and 2.26 mg/dl, respectively, and 45% vs. 44% had Cr>2 mg/dl at 3 months. Two recipients of AKI donors remained dialysis-dependent at 3 months post-transplant. These patients had significant post-transplant complications. For-cause allograft biopsies in 2/8 AKI recipients and 4/12 recipients of nonAKI donors revealed acute rejection. At 4 months post-transplant, 4 recipients of AKI donor kidneys vs none from nonAKI donors have been referred for retransplantation due to poor allograft function.

Conclusions: Our single-center, short-term outcomes in 40 DDKT recipients are concordant with prior reports that kidneys from donors with AKI have similar allograft functional outcomes with no increase in rejection rate. Accepting kidneys from deceased donors with AKI can increase rates of transplantation but at the cost of more DGF and graft failures.

Funding: Clinical Revenue Support

TH-PO824

Risk Factors for Death-Censored Graft Loss and Death in Kidney Transplant Recipients with Delayed Graft Function

Krutika P. Chauhan, Qingyuan Tan, Siobhan Sutcliffe, Su-Hsin Chang, Tarek Alhamad, Massini Merzkani. *Washington University in St Louis, St Louis, MO.*

Background: Delayed Graft Function (DGF) independently causes a significant reduction in graft survival. Very few studies have analyzed the risk factors for graft loss and death in recipients.

Methods: We used the Organ Procurement and Transplantation Network (OPTN) data for solitary kidney transplants from 1/1/2000 to 12/31/2023. We included adults with solitary ABO-compatible kidney transplants who were on dialysis before the transplant. We limited the study population to people who had delayed graft function, defined as requiring dialysis during the first week after transplantation. Our outcomes were death-censored graft loss (DCGL) and death with functioning graft. Multivariable Cox regression was done to evaluate the association of risk factors and adjusted for recipient, donor, and transplant characteristics.

Results: There were 72,992 solitary deceased kidney transplants with DCGL 23% and death 20.1%. Risk factors for increased DCGL were younger age (aHR=0.79 95% CI 0.78-0.80), lower donor BMI (aHR=0.94 95%CI 0.93-0.95), African American recipient (aHR=1.25 95%CI 1.20-1.29), and donor (aHR=1.09 95%CI 1.04-1.15), history of smoking (aHR=1.19 95% CI 1.15-1.23), and extended criteria donor (aHR=1.25; 95% CI 1.19-132) (Fig 1A) Risk factors for increased risk for death with functional graft were higher recipient age (aHR=1.56 95% CI 1.54–1.59), recipient gender male (aHR=1.06 95% CI 1.02-1.10), higher recipient BMI (aHR=1.03 95% CI 1.01–1.04), history of smoking (aHR=1.16 95% CI 1.12-1.21), and ECD (aHR=1.14 95% CI (1.07–1.20) (Fig 1B)

Conclusions: Recipients of DGF have unique risk factors for DCGL and death, emphasizing the need for closer follow-up and monitoring of this group. Additional prospective studies are essential for patient and graft survival.

Death censored Graft Failure	Haz. ratio	Low CI	High CI	Pvz
Recipient age	0.80	0.78	0.81	0.00
Donor age	1.01	0.99	1.02	0.39
Recipient gender				
Male	3.04	0.91	0.97	0.00
Donor gender				
Male	0.87	0.84	0.90	0.00
Donor BMI	0.96	0.93	0.96	0.00
KDPI (tertiles)				
34-59	1.19	1.14	1.25	0.20
>=60	1.44	1.35	1.54	0.00
History of diabetes				
Yes	0.81	0.76	0.86	0.30
missing	0.77	0.53	1.15	0.20
Recipient race				
African American	1.25	1.21	1.29	0.30
Donor race				
African American	1.10	1.05	1.15	0.00
Cause of death				
anoxia	0.71	0.68	0.73	0.30
History of hypertension				
yes	1.04	1.00	1.08	0.04
missing	0.49	0.33	0.72	0.00
Donation after cardiac death				
Yes	0.68	0.65	0.71	0.00
Donor creatinine				
1-1.5	1.13	1.10	1.19	0.00
>1.5	0.88	0.81	0.89	0.00
History of smoking				
Yes	1.19	1.15	1.24	0.00
Missing	0.84	0.72	0.98	0.03
HLA mismatch				
1 to 2	0.98	0.89	1.07	0.61
3 to 6	1.04	0.97	1.11	0.30
Missing	1.58	1.01	2.51	0.05
Cold ischemia time				
12 to 24	1.01	0.97	1.06	0.56
>24	1.07	1.01	1.12	0.01
Missing	1.72	1.38	1.87	0.00
ECD				
Yes	1.26	1.19	1.33	0.00

Figure 1A- Multivariable cox regression for death censored graft failure in the DGF population

Death with Functional Graft	Haz. ratio	Low CI	High CI	Pvz
Recipient age	1.57	1.54	1.59	0.00
Donor age	0.99	0.97	1.01	0.13
Recipient gender				
Male	1.36	1.02	1.10	0.00
Donor gender				
Male	0.89	0.86	0.93	0.00
Recipient BMI	1.10	1.12	1.08	0.00
Donor BMI	0.98	0.95	0.97	0.00
KDPI (tertiles)				
34-59	0.93	0.86	0.99	0.00
>=60	0.84	0.79	0.90	0.00
PRA	1.00	1.00	1.00	0.02
History of diabetes				
Yes	0.93	0.86	0.99	0.03
missing	0.60	0.41	0.88	0.01
Recipient race				
African American	0.91	0.88	0.94	0.00
Donor race				
African American	0.72	0.69	0.75	0.00
History of hypertension				
yes	1.03	0.99	1.07	0.10
missing	0.69	0.63	1.34	5.47
Donor creatinine				
1-1.5	1.14	1.10	1.19	0.00
>1.5	0.92	0.88	0.96	0.00
History of smoking				
Yes	1.17	1.12	1.21	0.00
Missing	0.96	0.83	1.11	5.68
HLA mismatch				
1 to 2	0.90	0.83	0.99	0.03
3 to 6	0.83	0.77	0.89	5.00
Missing	0.39	0.16	2.36	0.48
Cold ischemia time				
12 to 24	0.97	0.93	1.02	5.24
>24	0.94	0.88	0.99	0.02
Missing	1.67	1.52	1.83	0.00
ECD				
Yes	1.14	1.08	1.21	0.00

Figure 1B- Multivariable cox regression for death with functional graft in the DGF population

TH-PO825

Delayed Graft Function Equally Worsens Early Outcomes in Kidney Recipients from Donation after Circulatory Death vs. Brain Death Donors

Angela L. Zhou, Suseela A. Raj, Ekaterina Fedorova, Jacqueline Garonzik Wang, Didier A. Mandelbrot, Brad C. Astor, Sandesh Parajuli. *University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI.*

Background: While delayed graft function (DGF) is more common after donation after circulatory death (DCD) vs donation after brain death (DBD) kidney transplantation, we sought to determine if risk factors for DGF and post-transplant outcomes differ across donor type.

Methods: We studied all adult kidney deceased donor recipients (DDKTR) transplanted between 2005-2019 at UW Health Transplant Center, stratified by donor type (DBD vs. DCD). DGF was defined as dialysis within the first week after transplantation. Outcomes of interest included DGF, acute rejection (AR), one-year uncensored (GF) and death-censored graft failure (DCGF).

Results: Among 2543 DDKTs, 804 (31%) were DCD. In DBD recipients, older donor age, higher terminal creatinine, higher KDPI, right kidney, prolonged cold ischemia time (CIT), higher recipient BMI, and depleting induction agent were associated with higher risk for DGF, while female recipient and preemptive transplant were protective. Similarly, among DCD, older donor age, female donor, higher donor and recipient BMI, and depleting induction were associated with increased risk, while female recipient and preemptive transplant were protective. While DGF was significantly associated with higher risk for AR and GF, these associations did not differ significantly between DBD and DCD in adjusted models: AR (HR: 2.22 in DBD vs 2.37 in DCD; p-interaction=0.65); GF (3.04 vs 2.56; p-interaction=0.47). There were no adjusted DCGF to compare.

Conclusions: Several factors differ between DBD and DCD for risk of DGF. However, early outcomes were similarly worsened in both groups.

TH-PO826

Delayed Graft Function among Simultaneous Pancreas-Kidney Transplant Recipients Is Associated with an Increased Risk of Urinary Tract Infections and Kidney Rejections

Sofia Nehring Firmino, Ekaterina Fedorova, Eman Alshaikh, Dixon Kaufman, Jon S. Odorico, Didier A. Mandelbrot, Brad C. Astor, Sandesh Parajuli. *University of Wisconsin-Madison, Madison, WI.*

Background: Kidney delayed graft function (K-DGF) is associated with various detrimental outcomes among simultaneous pancreas and kidney (SPK) recipients. However, its potential risk associated with infection and rejection remains unclear.

Methods: We compared recipients with K-DGF to those without K-DGF among all adult SPK recipients transplanted at our center between 01/2010 and 12/2022 who had pancreas graft survival of more than 2 weeks. Outcomes of interest included urinary tract infections (UTI) and pneumonia, along with pancreas and kidney graft rejections, within one-year post-transplant.

Results: 543 SPK recipients were included, of whom 47 (9.5%) developed K-DGF. A total of 89 recipients had UTI, 33 had pneumonia, 77 had pancreas rejection and 21 had kidney rejection within one-year post-transplant. Recipients with K-DGF experienced a higher incidence of UTI. This association remained after adjustment for baseline characteristics (adjusted Hazard Ratio [aHR]: 3.06; 95% CI: 1.46-6.42; p=0.003). Similarly, K-DGF was associated with increased risk for kidney rejection in an unadjusted and adjusted models (aHR: 5.47; 95% CI: 1.98-15.1, p=0.001). K-DGF was not associated with pneumonia or pancreas rejection.

Conclusions: K-DGF among SPK recipients is associated with an increased risk for UTI and kidney allograft rejection, likely related to dysregulation of the immune system. Close monitoring and appropriate management are warranted in these unique patient populations.

Funding: Private Foundation Support

TH-PO827

Impact of Modified Delayed Graft Function (DGF) Biopsy Protocol on Patient and Allograft Outcomes: A Retrospective, Single-Center Study

Swarna laxmi Umapathy,[1] Jae H. Son,[1] Jayden Eccleston,[1] Karthiga Vasudevan,[2] Abinaya Rajendran,[4] Ryan Demartino,[3] Payaswini Vasanth.[1] *[1]Emory University, Atlanta, GA; [2]Georgia Department of Public Health, Atlanta, GA; [3]Emory Healthcare, Atlanta, GA; [4]Pondicherry Institute of Medical Sciences, Pondicherry, India.*

Background: The traditional DGF biopsy protocol (defined as weekly biopsy until resolution of DGF) was modified by delaying the first biopsy until two weeks post-transplantation, with subsequent biopsies performed only if indicated. Our Study seeks to evaluate the impact of implementing a modified DGF biopsy protocol on patient and allograft outcomes.

Methods: We conducted a retrospective analysis of kidney transplant recipients with DGF 2021-2023, comparing outcomes between those managed under the traditional and modified protocols

Results: 450 patients who had DGF in 2021-2023 were included in this Study. Results are outlined in Table 1. In 2021, under the traditional biopsy protocol, 19 patients (14%) experienced rejection, with the majority having borderline results, and some showing v1 lesions that were not treated due to DGF recovery. In 2022 and 2023, with the new biopsy protocols, 23 (14%) and 13 (8%) experienced rejection, with the majority having borderline results and only a few needing clinically significant treatment. Technical, vascular issues and recurrent disease resulted in graft failure and was unrelated to DGF.

Conclusions: Implementing the new protocol significantly reduced early DGF biopsies without negatively impacting patient and allograft outcomes. Moreover, this change led to significant cost savings, with each biopsy costing approximately $3000, alongside reductions in length of stay and readmission rates associated with biopsy procedures. These findings underscore the efficacy of protocol adjustment in enhancing both the clinical and economic aspects of post-transplant care.

	2021	2022	2023
DGF rate	137/383(35%)	154/378(41%)	159/365(44%)
Week 1 biopsy	84/137(61%)	18/154(12%)	7/159(4%)
Rejection	19/84(22%)	6/18(33%)	4/7(57%)
No rejection	65/84(77%)	12/18(67%)	3/7(43%)
Week 2 biopsy		54/154(35%)	23/159(14%)
Rejection		17/54(31%)	9/23(39%)
No rejection		37/54(69%)	14/23(61%)
Allograft function 1 year post transplant			
creatinine <1	14(15%)	17(11%)	27(17%)
creatinine 1 -2	97(70%)	101(65%)	96(60%)
creatinine 2 - 2.5	10(7%)	13(8%)	16(10%)
creatinine > 2.5	9(6%)	16(10%)	11(7%)
Failed (including non DGF causes)	3(2%)	7(4%)	9(5%)

TH-PO828

Does Early Belatacept Conversion in Delayed Graft Function Preserve Allograft Function?

Jasmine Zahid, Rehan Ansari, Ronald Michael Hofmann. *Trinity Health Michigan, Grand Rapids, MI.*

Background: Calcineurin inhibitors (CNIs) remain the cornerstone of immunosuppression in renal transplantation. However, there remain concerns regarding CNI induced nephrotoxicity. Belatacept is an alternative to nephrotoxic CNIs and has been FDA approved for immunosuppression in renal transplantation since 2011. The purpose of this case series is to identify short-term outcomes of early belatacept conversion in prolonged delayed graft function (DGF).

Methods: DGF includes patients who required dialysis within the first 2 weeks post-transplant. Early Belatacept conversion occurs within the first 6 months post-transplant. Charts were individually audited for data collection. Demographic data included age, gender, race, BMI, history of diabetes, and new onset diabetes after transplantation,

HLA mismatch, KDPI, cPRA, EBV, CMV, BK virus, donor type, prior transplants, pre-transplant dialysis dependence, dialysis length, biopsy, steroid use, neutropenia. Outcomes included creatinine, GFR, PTLD, infections and withdrawal from dialysis. SPSS was used for statistical analysis.

Results: This case series included 19 patients. Transplantation occurred from 2012-2023. Patient demographics are Figure 1. Patients had a statistically significant improvement in creatinine and GFR in 6 months. Additional complications included new onset diabetes after transplantation and acute cellular mediated rejection in 1 patient each. All patients were weaned off dialysis except one. No patients developed PTLD.

Conclusions: This case series suggests early conversion to Belatacept in DGF results in preserved short-term graft function. This case series adds to the current literature suggesting that the long term outcomes of Belatacept warrants further study.

Pre and Post-conversion GFR

	Pre-conversion GFR	Post-conversion GFR
Median [25th, 75th percentile]	13.5 [6.0, 25.5]	35.5 [26, 42.5]
Mean ± SD	16.4 ± 10.7	34.3 ± 11.0

Wilcoxon Signed Rank Test used to determine statistical significance (P<0.001).

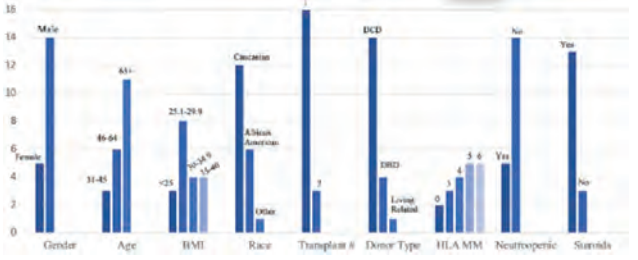


Fig 1. Demographics. (DCD = death after cardiac death; DBD = donation after brain death; HLA MM = Human Leukocyte Antigen Mismatch; Neutropenia: WBC <2.1).

TH-PO829

Extended Experience of Belatacept Conversion in Kidney Transplant Patients with Chronic Active Antibody-Mediated Rejection

Dhiren Kumar, Louiza Azzouz, Irfan A. Moinuddin, Gaurav Gupta.
Virginia Commonwealth University, Richmond, VA.

Background: Chronic active antibody mediated rejection (cABMR) is a major cause of kidney transplant (KT) loss. Current therapies have unclear efficacy and side effects. We have previously presented our experience with belatacept conversion with an improved eGFR compared to propensity matched controls (Kumar et al, Transplantation 2021). Here we present our extended experience with clinical outcomes and graft survival.

Methods: 55 patients with biopsy-proven cABMR were converted to belatacept with a modified tacrolimus taper performed over 12 weeks. 46/55 (84%) patients underwent biopsies between 6-12 months post-conversion and 32/55 (58%) also underwent paired transcriptome analysis using the molecular microscope (MMDx; ATAGC). We followed eGFR, graft survival and evaluated predictors of graft survival.

Results: Patients (mean age: 44years) were converted from tacrolimus to belatacept at a median of 29 months post-KT. At conversion, the cohort had low mean GFR of 44.6±22ml/min/1.73m2 and high mean chronicity scores (CI+CT) of 2.55±1.31. The mean decline in eGFR for the 12 months prior to conversion was -0.89±2.5ml/min/1.73m2 which then stabilized/improved to 1.37±2.9 ml/min/1.73m2 (p=0.002) 12 months after conversion. 53/55 (96%) of patients had less than 30% decline in GFR at 12-months. A paired histologic and MMDx comparison of pre and post-biopsies showed no worsening in microvascular inflammation (G+PTC), chronicity scores (CI+CT) and molecular ABMR scores. Overall, at a median follow up of 58 months (IQR:39-66), death censored graft survival was 67% and patient survival was 87%. Those with graft loss had a significantly lower GFR at conversion (36±16ml/min/1.73m2 vs 49±23ml/min/1.73m2; p=0.03). The area under the curve (AUC) for GFR at conversion was 0.69 (95% [CI] 0.55 to 0.80; p=0.01) for predicting graft failure. A GFR cutoff value of less than 30ml/min/1.73m2 had a specificity of 76% and sensitivity of 55%.

Conclusions: In this largest and extended report on belatacept conversion for cABMR with associated low GFR and high chronicity in patients who were otherwise not candidates for additional intensive immunosuppressive therapies, showed both short and long-term stability in renal function. Extended graft survival was seen in patients who had higher GFR at the time of conversion.

TH-PO830

Human Leukocyte Antigen (HLA)-Incompatible Kidney Transplantation Shows Similar Outcomes Compared with HLA-Compatible Kidney Transplantation after Early Rejection

Youn sik Oh,[1] Ji Won Min,[4] Sik Lee,[3] Jaeseok Yang,[2] Myoung soo Kim,[2] Mingyu Kim,[1] Jeong-Hoon Lim,[1] Hee-Yeon Jung,[1] Sun-Hee Park,[1] Chan-Duck Kim,[1] Yong-Lim Kim,[1] Jang-Hee Cho.[1] KOTRY Study Group.
[1]Kyungpook National University School of Medicine, Daegu, Republic of Korea; [2]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [3]Jeonbuk National University Hospital, Jeonju, Jeollabuk-do, Republic of Korea; [4]The Catholic University of Korea Seoul St Mary's Hospital, Seocho-gu, Seoul, Republic of Korea.

Background: HLA-incompatible (HLA-i) kidney transplantation (KT) constitutes a high-risk group with an increased risk of rejection and graft failure. We investigated the differences in short- and long-term outcomes of HLA-i KT compared to HLA-compatible (HLA-c) KT.

Methods: Patients with living donor KT were enrolled from a prospective nationwide cohort in Korea. HLA-i KT was defined as a desensitized transplantation with complement-dependent cytotoxicity (CDC) or flow-cytometric (FCM) crossmatch positivity. The primary outcome was a composite of acute rejection, graft failure, and patient death. The association between acute rejection and HLA types was analyzed. The trough levels of tacrolimus compared between HLA-i and HLA-c KT groups.

Results: A total of 3692 KT recipients were enrolled and 466 (12.6%) patients received HLA-i KT. Kaplan-Meier curve revealed that HLA-i KT showed higher acute rejection, graft failure, and the composite than HLA-c KT (P<0.05). The HLA-i group is associated with a higher risk of the composite (adjusted HR [aHR] 1.57; 95% CI 1.34-1.79; *P*<0.001) (Table 1) and acute rejection (aHR 1.56; 95% CI 1.37-2.88; *P*<0.001) (Table 2) than the HLA-c group during the 1st year after KT. However, 1 year after KT, all the transplant outcomes did not differ between the two groups. Logistic regression analysis showed that antibodies against HLA-DR were significantly associated with an increased risk of acute rejection (OR 1.93; 95% CI 1.14-3.28; P=0.015). Tacrolimus trough levels of the HLA-i and HLA-c groups showed no difference at 1 year after KT (6.3±2.2 vs. 6.4±2.3 ng/mL, respectively) and thereafter.

Conclusions: HLA-i KT showed worse transplant outcomes until 1 year after transplantation. However, HLA-i KT after the early period had non-inferior graft and patient survival results compared to HLA-c KT.

Funding: Government Support - Non-U.S.

Table 1. Cox regression of composite outcome

	HR	p-value	aHR*	p-value
1-12mo	1.57 (1.17-2.12)	0.003	1.93 (1.34-1.79)	<0.001
12-24mo	1.02 (0.58-1.80)	0.934	1.05 (0.53-2.11)	0.883
>24mo	0.90 (0.39-2.07)	0.798	1.02 (0.36-2.84)	0.977

*: adjusted with age, sex, BMI, comorbidity DM, cold ischemic time, HLA mismatch number, and donor's sex

Table 2. Cox regression of acute rejection

	HR	p-value	aHR*	p-value
1-12mo	1.56 (1.15-2.12)	0.004	1.98 (1.37-2.88)	<0.001
12-24mo	1.07 (0.61-1.88)	0.812	1.10 (0.55-2.23)	0.781
>24mo	1.04 (0.37-2.91)	0.946	1.24 (0.37-4.10)	0.730

*: adjusted with age, sex, BMI, comorbidity DM, cold ischemic time, HLA mismatch number, and donor's sex

TH-PO831

Tocilizumab in the Treatment of Allograft Rejection in an HIV-Positive Kidney Transplant Recipient

Kavindya Wickramasinghe,[1] Joseph D. Nguyen,[1] Joel D. Murphy,[2] William F. Glass,[3] Swati Rao.[4] *[1]University of Virginia School of Medicine, Charlottesville, VA; [2]Arkana Laboratories, Little Rock, AR; [3]University of Virginia Department of Pathology, Charlottesville, VA; [4]University of Virginia, Charlottesville, VA.*

Introduction: Chronic active antibody-mediated rejection (CAAbMR) in kidney transplant recipients (KTRs) is a major cause of late graft loss and responds poorly to standard-of-care (SOC) immunosuppression (steroids, IVIG, plasmapheresis). Recently, tocilizumab (TCZ), an IL-6 receptor antagonist affecting multiple pathways involved in B-, T-, and plasma cell activity, has been utilized in the treatment of CAAbMR. However, escalating immunosuppression in patients with chronic infections, such as HIV and HBV, can increase the risk of viral reactivation. We report a successful case of TCZ used to treat refractory allograft rejection in a KTR with chronic HIV and HBV.

Case Description: A 56-year-old male with well-controlled HIV and HBV, with ESKD from HIV nephropathy, received a deceased donor kidney transplant in 2016. After enjoying good allograft function for 5 years, he developed proteinuria (1 g/d) with low-level donor specific antibodies. Kidney biopsy demonstrated CAAbMR (fig. 1a/b). As the patient demonstrated no response to SOC treatment (fig. 1c/d), he was started on TCZ. During the 1-year treatment course, serial monitoring of HIV and HBV was conducted. He did not develop viremia and CD4 count remained over 200 cells/mm^3. One episode of cellulitis was treated with IV antibiotics. The Cr remains 1 mg/dl, proteinuria has improved (0.3 g/d), and the allograft biopsy shows improvement in CAAbMR (fig. 1e/f).

Discussion: As with all immunosuppressive medications, TCZ use in KTRs has been associated with infections. Extrapolating from the safety of short-term TCZ in HIV patients during the COVID-19 pandemic, we opted for long-term TCZ for treatment of refractory CAAbMR in our patient, with serial viral load monitoring. To the authors' knowledge, this is the first case report demonstrating the successful use of TCZ in a KTR with HIV and HBV.

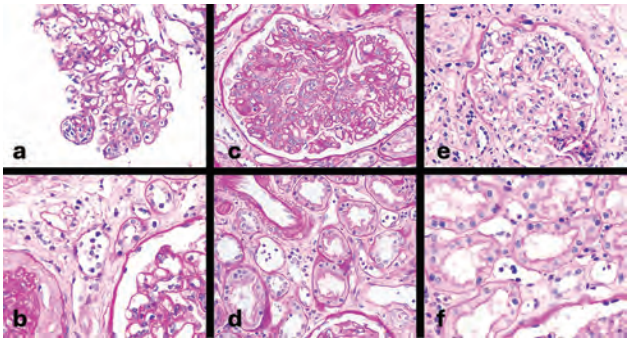


Figure 1. Biopsy after SOC therapy for CAAbMR showing lack of efficacy (g3,ptc3,cg1). Biopsy after 6 months (c/d) and 12 months (e/f) of TCZ showing improvement (g2,ptc2,cg1b) and minimal IFTA.

TH-PO832

Systemic Thrombotic Microangiopathy Induced by Antibody-Mediated Rejection in a Highly Sensitized Kidney Transplant Recipient

Gilad S. Guez, Beatrice P. Concepcion, Michelle A. Josephson, Sambhavi Krishnamoorthy, Patrick Cunningham, Yousuf Kyeso. *University of Chicago Pritzker School of Medicine, Chicago, IL.*

Introduction: Atypical HUS (aHUS) is a form of thrombotic microangiopathy (TMA), which is defined by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. aHUS is caused by uncontrolled activation of the alternative pathway of the complement cascade, and can be due to a variety of causes, such as genetic defects in complement related factors or acquired autoantibodies to complement regulators. Here we present a unique case of aHUS post kidney transplant in a highly sensitized recipient.

Case Description: A 38 year old female with history of ESRD secondary to bilateral ureteral reflux disease, presented for deceased donor kidney transplantation. The patient was highly sensitized with panel reactive antibody of 100% due to history of blood transfusions and pregnancy. She underwent desensitization while on the waiting list with eight sessions of plasmapheresis and replacement IVIG. This resulted in a flow negative T and B cell crossmatch kidney transplant offer with pre-existing class I and II donor specific HLA antibodies (DSAs). On post-operative day 1, she developed acute kidney injury, acute anemia, thrombocytopenia, and schistocytes were found on the blood smear. Additional labs showed low C3, elevated LDH, and undetectable haptoglobin level. ADAMTS13 functional assay was 54%. aHUS was suspected, and patient was immediately started on eculizumab. Subsequent kidney biopsy showed evidence of microangiopathy with focal C4d positivity. Hematologic markers improved within 24-48 hours after initiation of eculizumab, as did renal function. Follow up genetic testing revealed homozygous CFHR1 deletion.

Discussion: This case illustrates an early development of acute antibody mediated rejection manifested as systemic TMA post kidney transplantation. This process was likely triggered by the presence of DSAs in the setting of homozygous CFHR1 deletion, and promptly responded to eculizumab. This case supports the use of pre-transplant genetic testing to stratify patients who are at high risk for developing post-transplant TMA, and such can help guide the decision-making process of peri-operative use of eculizumab.

TH-PO833

Clinical Outcomes of Antibody-Mediated Rejection with or without Anti-human Leukocyte Antigen (HLA) Donor-Specific Antibody

Byounghwi Ko, Minsun Jung, Juhan Lee, Jaeseok Yang. *Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.*

Background: Antibody-mediated rejection (ABMR) is a major cause of late kidney allograft loss. It is increasingly recognized that histologic ABMRs without detectable donor-specific antibodies (DSA) can occur. Several studies have examined the prognosis of DSA-negative ABMR; however, there remains a need for further evidence.

Methods: From a single-center, retrospective study conducted from 2006 to 2021, 2,498 kidney transplant patients were screened, and 1,483 were available for at least one renal biopsy. Of these, 290 patients with biopsy-proven T-cell mediated rejection (TCMR) or ABMR were included in the study. The patients were categorized into TCMR, DSA-positive ABMR, and DSA-negative ABMR groups. DSAs were measured between the six months before and after the biopsies. The primary outcome was death-censored graft failure, and the secondary outcome was death-uncensored graft failure.

Results: The incidences for death-censored graft failure of TCMR, DSA-positive ABMR, and DSA-negative ABMR were 4.56, 4.98, and 6.23 per 100 patient-years. Over a median follow-up period of 5 years, death-censored graft failure occurred in 94 (32.4%) patients, with an incidence of 5.87 per 100 person-years. Compared with the TCMR group, the fully adjusted hazard ratios (HR) with 95% confidence intervals (CI) for death-censored graft failure were 1.28 (0.74-2.23) for the DSA-positive ABMR group and 1.67 (0.89-3.11) for the DSA-negative ABMR group. Furthermore, for death-uncensored graft failure, the DSA-negative group had a significantly higher risk compared with the TCMR group (HR, 1.88; 95% CI, 1.06-3.32), whereas the risk did not differ between the DSA-negative and DSA-positive group.

Conclusions: DSA-negative ABMR showed a significantly higher risk for death-uncensored graft failure compared with TCMR, with a similar risk as DSA-positive ABMR. Validation study using a Korean nationwide kidney transplant cohort is ongoing together with exploration of specific causes of DSA-negative ABMR.

TH-PO834

A Descriptive Study of a New Mexico-Based Kidney-Allograft Biopsy Registry

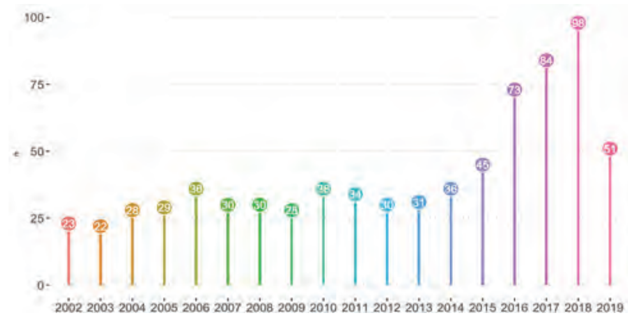
Saeed K. Shaffi. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: A kidney biopsy provides crucial information regarding allograft health. The diagnoses encountered on kidney allograft biopsies at the University of New Mexico Health Sciences Center have not been systematically studied. Additionally, the frequency of multiple pathologies in a single biopsy report is unknown. Therefore, we performed a retrospective review of the allograft biopsies to describe the frequency of diagnoses from this allograft biopsy registry.

Methods: The kidney biopsy registry was established using natural language processing (NLP) to extract diagnoses from biopsy reports, covering the period from January 2002 to June 2019. We identified kidney allograft biopsies, described the frequency of diagnoses, and, for common diagnoses, explored the presence of other pathologies. Results were reported as n (%) or Median (IQR), as appropriate.

Results: A total of 742 allograft biopsies were performed. The number of biopsies increased over the years (Fig. 1). The median biopsy age was 43 years (IQR 22–58). The most frequent diagnoses were acute T-cell mediated rejection (acute-TCMR), transplant glomerulopathy, and acute tubular necrosis (Fig. 2a). Acute tubular necrosis was the most common accompanying diagnosis in patients with acute TCMR and transplant glomerulopathy, respectively.

Conclusions: We analyzed a large number of allograft biopsies using NLP and described the diagnoses encountered in this population.



The number of biopsies performed each year.

Figure 2a. Biopsy Diagnoses Ranking

RANK	DIAGNOSIS	N (%)	RANK	DIAGNOSIS	N (%)	RANK	DIAGNOSIS	N (%)
19	Acute TCMR	339 (45.6)	7	Membranous GN	9 (1.2)	2	MIDD	2 (0.3)
18	Transplant glomerulopathy	105 (14.1)	6	No diagnostic abn	7 (0.9)	2	Pigmented casts	2 (0.3)
17	ATN	91 (12.2)	6	Oxalate nephropathy	7 (0.9)	1	PIGN	
16	Borderline acute TCMR	78 (10.5)	5	ANCA associated GN	6 (0.8)	1	Primary FSGS	1 (0.1)
15	CNI toxicity	69 (9.3)	4	Collapsing FSGS	5 (0.7)	1	MPGN-complement mediated	1 (0.1)
14	Diabetic glomerulosclerosis	64 (8.6)	4	C1Q nephropathy	5 (0.7)	1	CIN	1 (0.1)
13	Active ABMR	48 (6.5)	4	Polyomavirus nephropathy	5 (0.7)	1	Amyloidosis-AA	1 (0.1)
12	Secondary glomerulosclerosis	36 (4.8)	4	PTLD	5 (0.7)	1	MCD	1 (0.1)
11	IgAN/HSP	30 (4)	4	TMA	5 (0.7)	1	TBMD/Alport	1 (0.1)
10	Chronic active ABMR	28 (3.8)	4	Chronic active TCMR	5 (0.7)	1	Immune-complex mediated GN	1 (0.1)
9	Calcium phosphate deposition	13 (1.7)	3	Non-diagnostic sample	4 (0.5)	1	Focal cortical scarring	1 (0.1)
8	No rejection	10 (1.3)	3	Acute pyelonephritis	4 (0.5)	1	Infarcted kidney	1 (0.1)
8	AIN	10 (1.3)	3	Lupus nephritis	4 (0.5)	1	Occlusive thrombosis	1 (0.1)
			3	Acute cortical necrosis	4 (0.5)	1	Coagulative necrosis	1 (0.1)

Figure 2b. Accompanying Diagnoses for the Two Most Common Primary Diagnoses

ACUTE TCMR (N = 339)

DIAGNOSIS	N (%)
ATN	175 (52.1)
Transplant Glomerulopathy	37 (11)
CNI Toxicity	29 (8.6)
Diabetic Glomerulosclerosis	23 (6.8)
Active ABMR	23 (6.8)

TRANSPLANT GLOMERULOPATHY (N = 105)

DIAGNOSIS	N (%)
ATN	41 (26.1)
Acute TCRM	37 (23.6)
Chronic active ABMR	24 (15.3)
CNI Toxicity	12 (7.6)
Borderline Acute TCMR	9 (5.7)
Active ABMR	8 (5.1)

Legend: Figure 2a: The same rank is assigned to a diagnosis in case of a tie. Figure 2b: Diagnoses with a frequency >5% are shown. Abbreviations: TCMR, T-Cell Mediated Rejection; ATN, Acute Tubular Necrosis; CNI, Calcineurin inhibitor; IgAN/HSP, IgA Nephropathy/Henoch Schoenlein's Purpura; ABMR, Antibody Mediated Rejection; AIN, Acute Interstitial Nephritis; MIDD, Monoclonal Immunoglobulin Deposition Disease; PIGN, Post-Infectious Glomerulonephritis; FSGS, Focal-Segmental Glomerulosclerosis; MPGN, Membranoproliferative Glomerulonephritis; CIN, Chronic Interstitial Nephritis; Amyloidosis-AA, Amyloidosis – Amyloid Associated; MCD, Minimal Change Disease; TBMD, Thin Basement Membrane Disease

Population description.

TH-PO835

Intestinal Microbiome and Acute Rejection of the Transplanted Kidney: Results of Single-Center, Case-Control Study

Marcin Adamczak,[1] Patrycja Pokora,[1] Mariusz Kaczmarczyk,[2] Damian Gojowy,[1] Anna Wierzbicka-Wos,[2] Danuta Cembrowska-Lech,[2] Aureliusz Kolonko,[1] Igor I. Loniewski,[3,2] Andrzej Wiecek.[1] [1]*Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland;* [2]*Sanprobi sp. z o.o, Szczecin, Poland;* [3]*Department of Biochemical Science, Faculty of Health Sciences, Pomeranian Medical University, Szczecin, Poland.*

Background: Kidney transplantation (KTx) is the preferred form of renal replacement therapy. Acute rejection of transplanted kidney (AR) shortly after KTx may impair long-term survival of the kidney graft and the recipients. The relationship between gut microbiota and kidney rejection remains underexplored. This study aimed to investigate the relationship between gut microbiome and the risk of AR shortly after KTx.

Methods: In this single-center, retrospective case-control study, 10 patients with biopsy proved AR shortly after KTx (mean age 44.7 ± 12.3 years; 8M/2F) were matched by sex and age with 20 patients without AR during one year follow up after KTx (mean age 43.7 ± 10.7 years; 16M/4F). Stool samples were collected 4-7 days after KTx for microbiome analysis using Illumina shallow shotgun sequencing. Bioinformatic analysis included taxonomic and functional profiling, with predictive modeling performed using a random forest model. Model performance was evaluated using receiver operating characteristic (ROC) curves and area under the curve (AUC).

Results: No significant differences in clinical characteristics or microbiota diversity were observed between two groups. Differential abundance analysis identified *Bacteroides dorei/vulgatus* and *Clostridium* as differentially abundant in AR patients, but no consistent taxonomic markers were found. Predictive models varied in performance, with functional KEGG pathway profiles showing the highest predictive value (AUC = 0.740). Key metabolic pathways implicated included lipid metabolism (e.g., sphingolipid metabolism, glycerophospholipid metabolism, and secondary bile acid biosynthesis), glycan biosynthesis, and terpenoid and polyketide metabolism.

Conclusions: 1. No universal taxonomic gut microbiota marker of AR was identified. 2. Functional profile of the gut microbiome may be related with AR, with specific metabolic pathways 3. These findings suggest a role for immunomodulation, inflammation, and metabolic regulation in AR, highlighting the need for further research to understand these associations and their impact on kidney transplant outcomes.

Funding: Government Support - Non-U.S.

TH-PO836

Gender Inequities Persist in National Institutes of Health Funding for Nephrology Research

Karima Wehbe,[1] Wafaa M. Khaled,[1] Hay Me Me,[2] Kenar D. Jhaveri,[3] Rose Mary Attieh.[3,4] [1]*American University of Beirut, Beirut, Lebanon;* [2]*Mayo Clinic Arizona, Scottsdale, AZ;* [3]*Northwell Health, Great Neck, NY;* [4]*Mayo Clinic in Florida, Jacksonville, FL.*

Background: Gender inequity remains pervasive in the medical community, with women significantly underrepresented in access to extramural funding opportunities. We aimed to assess gender disparities in National Institutes of Health (NIH) awards for nephrology research within the 40 highest-funded academic university hospitals in the United States between 2017 and 2020.

Methods: Data on funding for nephrology research were retrieved from the NIH Principal Investigator (PI) database records. Only new awards were considered. Grants were identified by specifying the corresponding fiscal year (2017-2020), award type "new", and NIH spending category "kidney disease". For each grant, the type, amount of funds, and gender of the PI were recorded.

Results: Between 2017 and 2020, the NIH awarded 1472 new grants for research on kidney disease. 40 academic medical centers received the majority of grants (776 grants, 52.7% of total). Within these institutions, male PIs were awarded 475 grants (61.2%), totaling $193,787,257. Female PIs received 301 grants (38.8%), totaling $108,102,109 (**Table 1**). The difference in NIH funding between male and female PIs across all grant types was statistically significant, favoring male PIs (95% CI: [-89,812; -24,258]; p-value < 0.001). However, this imbalance was not observed across the 10 most commonly awarded grant types (p-value >0.05 for all).

Conclusions: Gender inequities in NIH funding remain in nephrology. Further research is warranted to understand their root cause and to explore strategies aimed at empowering women in the field to successfully secure funding.

Funding: Private Foundation Support

		Total Funds (in USD)		Median funds (in USD)		Median difference in funds (range)*	95% Confidence Interval**	P-value**
	Number of grants (% female PIs)	Male PIs	Female PIs	Male PIs	Female PIs			
All grant types	775 (38.8)	193,787,257	108,102,109	240,545	222,500	-50,340 (-4,922,340; 5,487,815)	[-89,812; -24,258]	<0.001
Stratification across the 10 most awarded grant types								
R01	342 (32.1)	118,829,478	46,919,757	487,726	485,481	2,500 (-4,876,974; 783,280)	[-88,809; 43,214]	0.87
R21	73 (48.2)	8,924,677	9,000,754	230,131	227,720	-4,433 (-184,796; 308,825)	[-10,400; 15,750]	0.54
F32	38 (39.5)	1,268,882	1,022,300	45,310	54,528	384 (-30,384; 60,760)	[-6,120; 8,564]	0.82
K23	35 (54.3)	2,545,851	3,637,886	190,102	186,256	-448 (-45,066; 192,347)	[-12,061; 11,273]	0.91
F31	35 (60.7)	324,259	924,398	30,375.5	44,044	1,869 (-48,613; 15,417)	[-2,902; 8,296]	0.33
K08	35 (45.7)	2,184,584	4,177,344	160,264	188,080	-548.5 (-54,247; 1,538,903)	[-6,800; 5,849]	0.90
U01	34 (32.35)	23,870,428	19,291,265	747,860	621,378	118,211 (-2,600,430; 5,487,815)	[-484,360; 1,860,213]	0.58
R03	29 (41.4)	1,602,126	3,119,577	99,599	104,749.5	0 (-155,270; 152,822)	[-17,209; 28,885]	1
K01	24 (70.8)	991,600	2,456,165	153,791	150,526	1,750 (-69,604; 51,765)	[-8,547; 28,350]	0.86
U19	18 (44.4)	45,441,008	3,042,884	483,237	230,980.5	-151,297.5 (-1,910,046; 697,909)	[-819,296; 115,280]	0.37
Stratification by Year								
2017	215 (35.3)	58,788,270	28,504,345	234,125	240,078.3	-9,559 (-4,027,480; 1,577,987)	[-75,215; 55,816]	0.75
2018	172 (45.3)	34,972,761	23,957,072	227,427	254,065	-72,759.5 (-1,173,072; 2,428,453)	[-148,719; -9,415]	0.02
2019	177 (36.7)	47,989,844	2,4086,314	345,918.5	173,852	-63,329.5 (-2,552,614; 2,863,266)	[-147,268; 0]	0.54
2020	212 (35.7)	54,716,400	34,354,318	395,025	227,544	-71,600 (-2,328,862; 5,455,938)	[-168,417; -12,900]	0.31

Table 1: Gender differences in National Institutes of Health new grant allocations to principal investigators (PIs) for research on kidney disease from 2017 to 2020. * Hodges-Lehmann method (a negative median value indicates that women were allocated less funding compared to men). ** Mann-Whitney 2-sided test.

TH-PO837

Women as Leaders in Nephrology Research: Have We Bridged the Gender Gap?

Darshil K. Jhaveri,[1] Kiran Munir,[2] Kenar D. Jhaveri,[2] Rose Mary Attieh.[2,3] [1]*Herricks Union Free School District, New Hyde Park, NY;* [2]*Northwell Health, Great Neck, NY;* [3]*Mayo Clinic in Florida, Jacksonville, FL.*

Background: Significant efforts have been made in the field of nephrology to advocate for the professional development and inclusion of women. However, it remains unclear whether these efforts have materialized. We aimed to assess the current state of research leadership among women in nephrology by analyzing gender disparities in original research output and in number of citations per article across key nephrology subspecialties.

Methods: Abstracts accepted for oral presentation at the American Society of Nephrology (ASN) Kidney Week meetings 2017-2020 were reviewed to capture impactful nephrology research. A subset focusing on glomerular diseases (GN), transplant, and onconephrology was selected. The gender of the first or last author (FLA) was recorded. Public databases (PubMed, Web of Science, and Google Scholar) were interrogated to find corresponding articles. The number of citations per article was analyzed for academic influence.

Results: 336 abstracts were screened. 50.6% (N=170) had male-only FLA and 49.4% (N=166) had at least 1 female FLA (**table 1**). 75.9% of abstracts (N=129) with male-only FLAs were eventually developed into full articles vs 84.9% (N=140) of abstracts with at least 1 female FLA. There was a very strong correlation between FLA gender groups on the abstract and on the full article (p-value<0.001), and no significant inter-group difference in any of the following: average number of abstracts having corresponding articles with FLAs of same gender group (p=0.32), average number of abstracts having corresponding articles with FLAs of the opposite gender group (p=0.85), average number of abstracts which did not result in a full article (p=0.35). In addition, we found no statistically significant difference in the median number of citations per article between FLA gender groups (95% confidence interval [CI] [-5;5]; p-value 0.97) (**table 2**).

Conclusions: This is the first report to demonstrate that male and female researchers in nephrology now exhibit comparable academic performance and influence. While our findings are encouraging, women in the field still face numerous obstacles, and the road to true and sustainable gender equity remains long.

Funding: Private Foundation Support

TH-PO838

Gender and Geographical Differences in International Nephrology Guideline Authorship: A Comparison of the US, UK, and International Nephrology Guidelines, 2009-2024

Ohm S. Tripathi. *University of Connecticut, Storrs, CT.*

Background: In Nephrology, there is an underrepresentation of women as first and senior authors as well as in leadership positions. We evaluated the trends in gender and geographical differences in the guideline writing groups of the KDIGO, KDOQI, Renal association, UKKA, and ISPD from 2009 to 2024.

Methods: We extracted all guidelines authors from 2009 to 2024, assessed their gender from publicly available profiles, and compared differences based on chair position, workgroup, and specific societies. Stratified and trend analyses were performed using $\chi 2$ and average annual percentage change. We analyzed various countries' representation among different guidelines.

Results: A total of 14 KDIGO, 22 KDOQI, 12 Renal Association, 22 UKKA, and 9 ISPD guidelines were analyzed. There were 831 authors (37.3% women vs 62.8% men, p<0.05), KDIGO (203 authors [26.1% women vs 73.9% men, p <0.05]), KDOQI (185 authors [34.1% women vs 65.9% men, p <0.05]), Renal Association (91 authors [41.8% women vs 58.2% men, p=0.54]), UKKA (278 authors [42.5% women vs 57.5% men, p<0.05]) and ISPD(74 authors [41.9% women vs 58.1% men, p=0.39]). There were 23 women chairs KDIGO (3 authors [10.7 % women vs 89.3% men, p <0.05]), KDOQI (15 authors [42.9% women vs 57.1% men, p =0.30]), Renal Association (3 authors [50% women vs 50% men, p=1]), and UKKA (2 authors [25% women vs 75% men, p=0.13]). The US had the highest numbers of authors in KDIGO (72) and KDOQI (174) while the UK (23) had the highest authors contribution in ISPD.

Conclusions: There is a significant disparity in the inclusion of women on all the international nephrology guidelines as chair and as authors. Further advocacy is required to promote equity, diversity, and inclusion in our nephrology guidelines globally. The US and UK contribute most to the guidelines. KDIGO had the most diverse country representation.

TH-PO839

Assessing Diversity and Inclusion in Nephrology Journal Editorial Leadership: EDI-N Study

Jingyao Zhang,[1] Rhea Gandhi,[1] Tushar Chopra,[2] Vineet Gupta,[1] Rakesh Malhotra.[1] *[1]University of California San Diego, La Jolla, CA; [2]University of Virginia, Charlottesville, VA.*

Background: Understanding and promoting diversity within editorial boards is crucial for advancing equity, fostering scholarly inclusivity and addressing bias in academic publishing. Here, we investigated the self-identified gender and race/ethnicity diversity within the editorial boards of nephrology journals.

Methods: A brief survey consisting of ten questions was electronically disseminated to editors, including editors in chief, deputy, associate, assistant, and section editors, as well as editorial board members, across 23 nephrology journals via REDCap. The survey aimed to gather self-reported demographic details such as gender, age, ethnicity, geographical location, editorial board position, and educational background. A follow-up reminder email was sent twice, each with a one-week gap to enhance response rates. Summary statistics were used for data analysis.

Results: Out of 1095 members, 367 (34%) respondents completed the survey. Among these, 58% were male, and 42 % were female. There were significant differences among gender representation (P<0.01) in journals leadership position with only 8.3% of Editor-in-Chief positions held by women. Regarding race/ethnicity, a majority of editorial board members were White (66.7%), followed by those identifying as Asian (10.7%) and South Asian (10.7%). Blacks and Hispanics constitute only 2.2% and 4.9% of editorial members, respectively. Editorial-in-Chief positions were predominantly held by White individuals (71%) followed by South Asians (17%). There was no reported Black and Hispanic individuals in Editor-in-Chief positions. Only 10 % of early career investigators with age less than 40 and 19% with degree outside of medicine were part of the editorial board.

Conclusions: This analysis reveals a significant underrepresentation of women and minorities in leadership positions within nephrology editorial boards. Journal should implement strategies for greater diversity and representation in editorial boards.

Funding: Other U.S. Government Support

TH-PO840

Modeling Diversity in Diabetic Kidney Disease Clinical Trials Using Real-World Data

Andrew M. Bevan,[1] Davide Garrisi,[2] Sarah D. Stump,[3] Carmichael Angeles.[3] *[1]PPD, Part of Thermo Fisher Scientific, Cambridge, United Kingdom; [2]PPD, Part of Thermo Fisher Scientific, Milan, Italy; [3]PPD, Part of Thermo Fisher Scientific, Wilmington, NC.*

Background: The FDA places emphasis on studying clinically relevant trial populations but does not address how to define these. The authors previously reported underrepresentation of people of African descent in lupus nephritis trials, but this has not been investigated in more common renal disorders such as diabetic kidney disease (DKD). The study aims to compare demographics of individuals with DKD from a large electronic health record (EHR) database with completed US-only DKD trials and propose statistical parameters for cohort sizes to support DKD trial planning.

Methods: Data was obtained from the TriNetX Analytics Network containing EHRs from >150 million individuals in the US. Demographics (gender, race, ethnicity) were assessed for those with an ICD-10-CM code E11.22 Type 2 Diabetes Mellitus with DKD in the last 5 years that did not also have an ICD-10-CM code N18.6 ESRD. Binomial confidence intervals were calculated to define demographic cohort sample sizes for clinical trials. Data were compared to average proportions of demographic cohorts in completed US-only DKD trials reported in clinicaltrials.gov.

Results: Real-world Data: 583,660 individuals met eligibility, gender distribution (50.2% Male, 45.4% Female, 4.4% Unknown), race distribution (62.8% White, 19.8% Black or African American, 4.0% Asian, 13.4% Other/Unknown), ethnic distribution (73.5% Non-Hispanic or Latino, 6.9% Hispanic or Latino, 19.6% Unknown). **Clinical Trials:** 9 DKD clinical trials were evaluated (956 subjects). Gender was reported for 9 trials (Male 64.8%, Female 35.2%). Race was reported for 6 trials (813 subjects), 77.4.% White, 18.2% Black or African American, 2.0% Asian, 2.3% Other/Unknown. Ethnicity was reported for 3 trials (549 subjects), 64.4.% Non-Hispanic/Latino, 35.6% Hispanic/Latino. **Cohort Modelling:** Based on an analysis of binomial confidence intervals, a US DKD trial of 100 subjects would be considered statistically representative ($p < 0.05$) of the TriNetX population if it included a range of 40-60 Male, 35-55 Female, 53-72 White, 13-29 Black or African American and 13-29 Hispanic/Latino patients.

Conclusions: Our data shows underrepresentation of non-white and female patients in US-only DKD trials compared to the TriNetX DKD population. Large EHR databases are one method to determine "real-world" demographics to support the planning of "representative" trial cohorts.

TH-PO841

Designing Equitable Care for Kidneys (DECK): Community-Based Interventions for Addressing Social Determinants of Health and Kidney Disease Risk Factors

Amber Paulus. *Virginia Commonwealth University School of Medicine, Richmond, VA.*

Background: Health disparities in kidney disease are often attributed to higher rates of risk factors such as diabetes and hypertension among minority groups. While research has extensively focused on clinical risk factors, little is known about the intersection of chronic kidney disease (CKD) risk and unmet social determinants of health (SDOH) needs.

Methods: The DECK Pilot Study, guided by the Equitable Diagnosis Pathway (EDP) model for chronic kidney disease, selected Richmond's East End for community-based screenings. The EDP model informed our intervention to address the silent nature of CKD, as 9 in 10 individuals are unaware of their condition until it is advanced. Using the CDC's Social Vulnerability Index (SVI) and HOLC ratings, we identified the East End for its high social vulnerability and history of redlining. This data-driven approach aims to identify and address CKD risk and unmet social needs to slow disease progression.

Results: Based on U.S. Census data, Richmond, VA has over 225,000 residents, of which 54.8% are non-White. Analysis revealed the East End has a high burden of CKD risk factors, including diabetes, hypertension, and obesity. The Dialysis Facility Report indicated 75% of dialysis patients in Richmond are Black, compared to 22% White. Additionally, 19% of individuals with ESRD in Richmond did not receive pre-dialysis nephrology care, and 5% to 12% of those starting dialysis lacked medical coverage, compared to 3% to 7% statewide. Diabetes is the major cause of kidney disease in Richmond, emphasizing the need for early detection and intervention.

Conclusions: The DECK Pilot Study demonstrates the critical need for integrating community-based interventions to address both medical and social determinants of kidney health. DECK serves as a model for enhancing kidney health equity and can be replicated in other underserved communities to reduce health disparities and improve care quality.

Funding: Private Foundation Support

Disease and Health Burden of East End Richmond, VA

Location	HOLC Grade	Percent Minority	SVI	Diabetes	Hypertension	Obesity	Kidney Disease
Creighton Court	D5	98.9	0.840	22.1	48.0	50.5	5.7
Fairmount	D5	87.2	0.796	22.5	50.8	45.0	5.4
Church Hill North	D6	77.5	0.731	23.3	50.6	46.6	5.6
Oakwood	D6	84.6	0.723	20.3	47.8	43.4	4.8
Rocketts	C13	78.5	0.818	14.6	37.6	42.5	3.8
Lower Rocketts	C12	82.3	0.733	18.0	44.3	42.7	4.4

TH-PO842

Promoting Kidney Health Equity through Kidney Disease Screening and Awareness Program at University of Virginia

Morgan Greig,[1] Joseph D. Nguyen,[1,2] Monarch Shah,[1] Rakesh Malhotra,[3] Tushar Chopra.[1] *[1]UVA Health, Charlottesville, VA; [2]University of Virginia School of Medicine, Charlottesville, VA; [3]University of California San Diego Department of Medicine, La Jolla, CA.*

Background: Kidney Disease Screening and Awareness Program (KDSAP) at University of Virginia (UVA) aims to promote kidney health awareness and improve outcomes among vulnerable populations. Our community health events employed questionnaires and screening tests to assess community prevalence and awareness of hypertension (HTN), diabetes (DM), and isolated proteinuria among participants based on self-reported race and gender.

Methods: Self-reported race, gender, and screening results were obtained from the KDSAP at UVA database from 2022 to 2024. Reported race was White, Black, Asian, Hispanic, or Latin(o). Reported gender was male, female, or other. Positive HTN screen was defined as blood pressure above 130/80 mm Hg, positive DM screen was defined as fasting blood glucose ≥126 mg/dL, and positive proteinuria screen was defined as urine albumin creatinine ratio (UACR) above 30 mg/g. A patient-reported screening questionnaire obtained the percentage of participants unaware of their condition.

Results: Of the 92 patients in the KDSAP database, the frequency of a positive screening test was 48.9% for HTN, 10.1% for DM, and 32.2% for proteinuria. Positive HTN screening rate was particularly prevalent among self-reported males (52.8%), Blacks (64%), and Asians (64.7%), with unawareness rates of 67.9%, 25%, and 81%, respectively (Table 1). Positive proteinuria screen rate was 30-40% amongst males, females, whites, and blacks, and approximately 80-100% of total participants were unaware of proteinuria.

Conclusions: In summary, the majority of patients screened positive on at least one test, and many of these patients were unaware of their condition. Our data suggests that there are significant cultural and socioeconomic barriers to care that prevent vulnerable populations from taking advantage of preventive interventions, both medical and educational, for chronic conditions such as HTN, DM, and CKD. We improved patient awareness and provided educational materials with the goal of leading to positive behavioral changes. Our study highlights the need for long-term primary care and nephrology follow-up for patients who screened positive.

	Male		Female		White		Black		Asian		Hispanic/Latin(o)	
	% Pos Screen	% Pos Unaware of Cond.	% Pos Screen	% Pos Unaware of Cond.	% Pos Screen	% Pos Unaware of Cond.	% Pos Screen	% Pos Unaware of Cond.	% Pos Screen	% Pos Unaware of Cond.	% Pos Screen	% Pos Unaware of Cond.
HTN	53	68	46	56	36	75	64	25	65	82	40	90
Proteinuria	30	88	31	83	36	100	40	80	12	100	28	100
DM	11	17	8	67	14	0	4	33	18	33	4	100

TH-PO843

Supporting the Participation of Latinx Individuals in Dialysis Research

Katherine M. Rizzolo,[1] Jennifer E. Flythe,[2] Lilia Cervantes.[3] *[1]Boston Medical Center, Boston, MA; [2]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Despite their disproportionate burden of kidney disease, the Latinx population is underrepresented in kidney research. Culturally concordant community health workers (CHWs) with shared lived experience have increased Latinx patient representation in cancer research, but less is known about enhancing Latinx representation in kidney research. Our study aims to fill the knowledge gap about optimal strategies for supporting the participation of Latinx individuals in kidney research, through the lived experience of adult Latinx people with kidney disease and CHWs who are involved in the recruitment of Latinx individuals for research.

Methods: We conducted a qualitative study with adult Latinx dialysis recipients and CHWs via semi-structured interviews assessing barriers/ facilitators to research participation. Interview transcripts were analyzed inductively for themes, coding followed thematic analysis and consensus on themes and sub-themes was reached.

Results: Patient participants (n=6) had a mean age of 56.2 years, 50% were women with 6.3 year average dialysis vintage. CHW participants (n= 9) had a mean age of 44.5 years, 77.8% were women, and 66.7% identified as Latinx. Participants described four themes (table): 1) Community relationships are key to trust building 2) Key elements to building rapport 3) Motivations to participate in a research study and 4) Barriers to participation and retention. Key areas to enhance recruitment and retention are researcher accountability (i.e. returning research findings to the community), valuing the patient voice and lived experience, and addressing social needs and language barriers that may de incentivize participation.

Conclusions: Our study indicates that relationship building and establishing trust in a community is critical for Latinx research participants. The strategies identified in this study will generate insights into augmenting diversity in future kidney research, an essential step toward achieving health equity.

Funding: Private Foundation Support

Theme and sub-themes	Patient illustrative quote	CHW illustrative quote
Community relationships are key to trust building		
Language/culture concordance Improve connection Equal footing/lack of power dynamic Community partnership Understanding lived experience	Before talking about the study, before talking about the protocols and everything, you make a connection …So that the person feels that they are important to you, not that you arrive and impose on them like, "Oh, I am the worker." No, feel that they are above you, that you are there because you need them in the research, not them needing you. (PT4)	I think a lot of people rightly so have hesitations about research. And so, I think the more that we can get involved in the community in a way that is genuine and not like, hey, here's our study like do it. But just really making genuine connections is a really important first step. (CHW15)
Key elements to building rapport		
Warmth and curiosity of interviewer Sincerity and caring about the individual In-person preferred over phone Interviewers encourage active participation and confidence	The sincerity regarding the person who is going to invite you, or honesty is what matters most because I think that if you invite me, you're not going to invite me to something where I'm going to get harmed, because someone aware that there will be some harm would automatically reject participation. (PT2)	When you're doing a program specifically for Latinos, and you can connect with them and teach them that it's important what they have to say, I noticed that it would make them more willing to talk, and they felt more comfortable, too. So, a person who is outgoing, friendly, obviously, and curious to learn from people. (CHW2)
Motivations to participate in a research study		
Research helping community Learning about disease Personal health benefit Compensation	It wasn't even about the money. It's just the knowledge. I'm a mother, I'm a sister, I'm a daughter, I'm a pet owner and I'm needed… I wanna live, I wanna be able to see my grandkids. (PT9)	I would say the biggest thing that has helped me get Latinos to respond is by being sincere about the fact that their information is going to help someone. (CHW6)
Barriers to participation and retention		
Not feeling heard or valued Social needs and language barriers Lack of clarity of the study expectations Lack of study team accountability or follow up	Information on any topic or any information or study, that's very important to be well informed to know what you're doing, what you're going to receive, or what you're going to share with the next patients, what you can give them in your case. (PT4)	I think it is very important that we are clear that sometimes there are no benefits for the patient or that it will not impact the care they are receiving from the hospital…I think sometimes there is no direct connection and there is no trust either, that they don't know exactly what their participation involves and why we are interested in knowing anything about their experience. (CHW13)

TH-PO844

A Qualitative Study of Chinese American Knowledge and Perceptions about Kidneys and Kidney Diseases

Michelle M. Richardson,[1,2] Abigail Lebovitz,[2] Klemens B. Meyer,[3,2] Tamara Vesel.[3,2] *[1]Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, NJ; [2]Tufts University School of Medicine, Boston, MA; [3]Tufts Medical Center, Boston, MA.*

Background: Asian Americans have a higher risk of early chronic kidney disease (CKD) compared to other racial groups in the United States (US) and were the only group without a decrease in end-stage renal disease prevalence from 2019-2021 [USRDS 2023 Annual Report, United States Renal Data System]. Timely identification and treatment of CKD is crucial to prevent or delay disease progression. Evaluating kidney health and disease knowledge can shape culturally sensitive education to reduce disease prevalence.

Methods: Our community partner conducted semi-structured, 1:1 interviews of elders without kidney disease from 12/2023-2/ 2024. Iterative multi-stage thematic analyses identified key concepts and themes.

Results: Of nine participants, 89% were female, all were born in China, lived in the US an average of 19 years, and over half had at least a high school education. Eight interviews were in Cantonese and one in Taishanese. Half of participants knew someone with kidney disease. Baseline knowledge was high and included: knowing the importance of kidneys for overall health and survival; the role of kidneys in hormone regulation,

fluid balance, and detoxification; the relationship between kidneys and the urinary system; and recognizing "silent" disease progression. Additional themes arose at the intersection and divergence of traditional Chinese medicine and western medicine concepts of CKD including: relationship of kidney disease with sexual health, the term "kidney deficiency", and the consideration of mood and mindset when understanding disease. Lastly, concern over lack of individual and population knowledge surrounding kidney health and CKD was prevalent and many were curious and enthusiastic to learn more about the kidneys and identifying CKD.

Conclusions: Overall, our participants' knowledge of the kidneys was advanced. There are important cultural considerations within Eastern and Western medicine that clinicians should be aware of when providing CKD education and care. Chinese American individuals have distinctive perspectives and understanding of kidney health and disease that should be acknowledged to provide high quality, culturally respectful disease education and health care.

Funding: Other NIH Support - National Center for Advancing Translational Sciences, National Institutes of Health, Award Number UL1TR002544

TH-PO845

Creating a Bilingual Community Advisory Board to Promote Kidney Research and Academic-Community Collaborations

Michelle M. Osuna-Diaz, Tessa K. Novick. *The University of Texas at Austin Dell Medical School, Austin, TX.*

Background: Little is known about best practices for establishing a bilingual community advisory board to promote academic-community collaborations.

Methods: We created a community advisory board composed of nephrology providers, researchers, people with kidney disease, and community-based organizations representing Hispanic/Latine and Black/African American populations. We held ten virtual board meetings in Spanish with live interpretation, then conducted a focus group to assess (1) strengths and challenges, and (2) recommendations for improvement and sustainability. We described the process of board creation, meeting agenda items, and thematic analysis of focus group content.

Results: The board included 17 members with diverse representation. Agenda items included: establishment of mission and member responsibilities, selection of leadership, review of a grant proposal, and provision of small grants to members to conduct research that promoted the board's mission. Live virtual interpretation increased sense of inclusivity and connection. Challenges included incomplete understanding of the purpose of collaboration, lack of trust, and lack of sustainable funding. Recommendations included community fiscal sponsorship and teambuilding activities to promote trust.

Conclusions: Bilingual community advisory boards promote academic-community collaboration.

Funding: Private Foundation Support

TH-PO846

Associations of Risk and Protective Factors with Kidney Outcomes among American Indians: The Strong Heart Family Study

Reya H. Mokiao,[1,2] Kristen E. Carlin,[2] Jason F. Deen,[1] Jason G. Umans,[3,4] Bessie A. Young,[1] Amanda M. Fretts.[5] *[1]University of Washington School of Medicine, Seattle, WA; [2]Seattle Children's Research Institute, Seattle, WA; [3]MedStar Health Research Institute, Hyattsville, MD; [4]Georgetown University, Washington, DC; [5]University of Washington School of Public Health, Seattle, WA.*

Background: Kidney disease disproportionately affects American Indians (AI) compared to White individuals, and it is important to explore modifiable risk factors as potential areas for intervention. The objective of this study was to explore the associations of kidney disease risk factors, achievement of the American Heart Association's (AHA) Life's Essential 8 (LE8), and social support with low estimated glomerular filtration rate (eGFR) and albuminuria among AI in the Strong Heart Family Study (SHFS).

Methods: The study population included participants from the SHFS, a longitudinal study of cardiovascular disease (CVD) among AIs from 12 tribes (n=1956, age 39 ± 16 years, 61% female, 13% with diabetes (DM)). Participants completed baseline (2001-2003) and follow-up (2007-2009) exams. The primary exposures were prevalent DM, obesity, hypertension, dyslipidemia, CVD, smoking, diet, physical activity, a modified LE8 score (smoking, body mass index (BMI), lipids, glucose, blood pressure, physical activity, and diet), and social support as risk/ protective factors. The primary outcomes were: 1) incident albuminuria (albumin to creatinine ratio 30mg/g or greater); 2) incident low eGFR (eGFR < 90 ml/min/1.73m^2 using the 2021 CKD-EPI Creatinine equation). Generalized estimating equations were used to examine the association of all exposures with outcomes.

Results: In this relatively young cohort of AI, kidney disease risk factors were common. Based on LE8 scores, 14%, 71% and 15% had low, moderate, and optimal CVD health respectively. At follow up, 10% had incident albuminuria and 8% had incident low eGFR. Higher BMI (OR 1.04, 95%CI 1.01, 1.07, p<0.01) and DM (OR 2.94, 95%CI 1.84, 4.67, p< 0.0001) were associated with incident albuminuria. Those with moderate (0.57, 95%CI 0.39, 0.84, p<0.01) and high (OR 0.30, 95%CI 0.16, 0.58, p<0.001) compared to those with low CVD health based on LE8 scores had decreasing odds of incident albuminuria. None of the exposures were associated with incident low eGFR.

Conclusions: Although kidney disease risk factors were prevalent among the SHFS cohort, adherence to the AHA's LE8 was associated with lower odds of incident albuminuria. Preventative interventions that promote and facilitate adherence to healthy behaviors, like LE8, may improve cardiovascular and kidney health among AIs.

Funding: Other NIH Support - The Strong Heart Study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institute of Health, Department of Health and Human Services, under contract numbers 75N92019D00027, 75N92019D00028, 75N92019D00029, & 75N92019D00030. The study was previously supported by research grants: R01HL109315, R01HL109301, R01HL109284, R01HL109282, and R01HL109319 and by cooperative agreements: U01HL41642, U01HL41652, U01HL41654, U01HL65520, and U01HL65521. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Indian Health Service (IHS).

TH-PO847

APOL1 Genotyping, Knowledge, and Attitudes among African American Patients: Building a Cohort in a Midwestern US Urban Community

Krista L. Lentine,[1] Marie D. Philipneri,[1] Aliza Anwar Memon,[1] John C. Edwards,[1] Amy Mosman,[1] Kana Miyata,[1] Fadee Abu Al Rub,[1] Amber Carriker,[4] Barry I. Freedman,[2] Rengin Elsurer Afsar,[1] Baris Afsar,[1] Anthony N. Muiru,[3] Chi-yuan Hsu,[3] Yasar Caliskan.[1] *[1]Saint Louis Univ, St. Louis, MO; [2]Wake Forest, Winston Salem, NC; [3]UCSF, San Francisco, CA; [4]Mid-America Transplant, St. Louis, MO.*

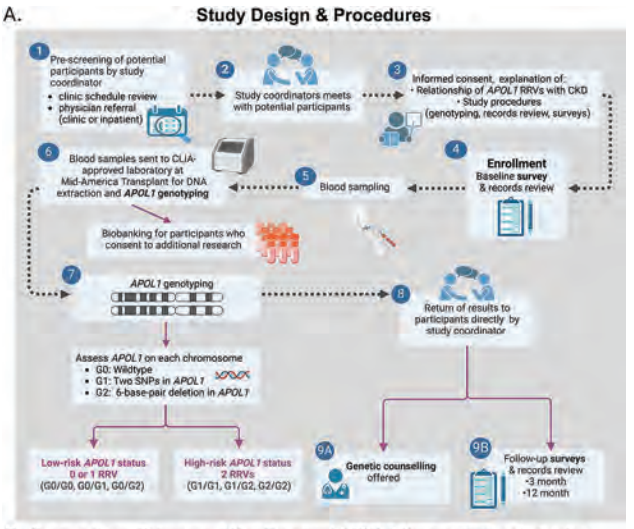
Background: While some past studies assessed interest in apolipoprotein L1 (*APOL1)* genotyping among focus groups, few studies examine attitudes and knowledge combined with the opportunity to receive individual genotyping.

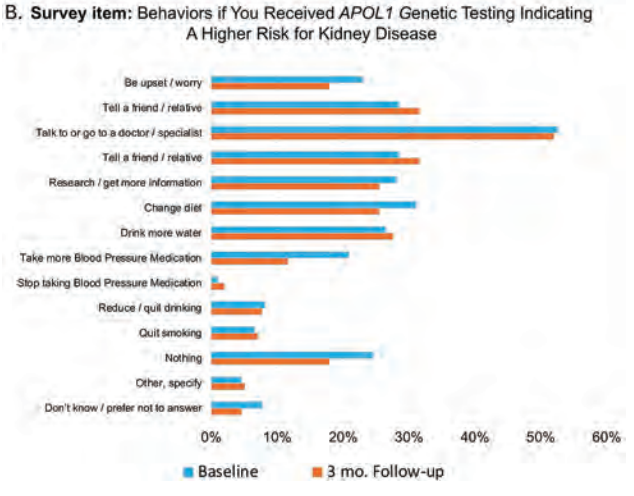
Methods: We offered *APOL1* genetic testing and surveyed knowledge, attitudes and concerns related to *APOL1* testing and kidney risk management among self-identified African American patients (NCT05656261) including 3 mo. follow-up (**Fig 1A**).

Results: Among 263 participants with genotyping results to date (Jan 2019–March 2024), 16% had high-risk genotypes (2 *APOL1* RRVs) and 84% were low-risk (0/1 RRV). Median $eGFR_{2021}$ was 47.7 in *APOL1* low-risk vs. 42.2 ml/min/1.73 m^2 in high-risk groups. 50.7% of low-risk and 54.8% of high-risk groups reported family members with kidney problems. 24% of the 2 RRV group rated their overall health as poor to very poor, vs. 10% of the 0/1 RRV group. At baseline, 86% reported they would want *APOL1* testing for their family members. However, only 9.5% accepted formal genetic counseling beyond study-related education. Participants reported a variety of behavior changes may follow genotyping information (**Fig 1B**). The proportion who might worry about a high-risk genotype was lower at 3 mo. (18% vs 23%). 90% agreed to future research.

Conclusions: Self-identified African American patients at a Midwestern medical center report a high family history of kidney disease and were receptive to individual *APOL1* genetic testing, not only in theory, but by participating in testing. Ongoing research is needed to define the interplay of genetic and environmental factors underlying kidney risk in this population.

Funding: Private Foundation Support





TH-PO848

Who Receives Kidney Disease Education? An Analysis of Patients with ESKD

Ron Preblick,[1] Praveen Kumar Potukuchi,[1] Jessica Voss,[1] Cynthia Gutierrez,[2] Danielle Acquaviva,[2] Mona Kelkar,[2] Yu Hong,[2] Amy D. Waterman.[3]
[1]Genzyme Corporation, Cambridge, MA; [2]Genesis Research LLC, Hoboken, NJ; [3]Houston Methodist Hospital, Houston, TX.

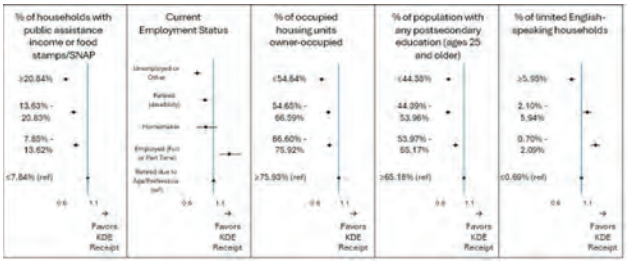
Background: While kidney disease education (KDE) is linked to improved outcomes for ESRD patients, disparities in uptake exist. We evaluated the association of KDE with social determinants of health (SDOH) among 519,902 patients with ESRD.

Methods: This retrospective cohort study was conducted using data from Medicare-linked US Renal Data System (USRDS), the Agency for Healthcare Research and Quality (AHRQ) SDOH database, and the Robert Graham Center's calculated social deprivation index (SDI). Included patients had a CMS2728 fill date between Jun 30, 2011 and Sept 30, 2019, an ESRD diagnosis ±30 days of the fill date, and ≥1-year pre-index activity. KDE status was assessed in the 2-year pre-index period. Baseline characteristics were assessed using CMS2728 and Medicare claims. Neighborhood variables were linked at the zip code level. Post-index ESRD treatments were assessed during a variable follow-up period. Univariate logistic regression was used to test SDOH differences between KDE and non-KDE patients.

Results: Of the patients identified, 7,838 received KDE (1.5%). Most received individual KDE (75.6% vs group [23.1%] or both [1.3%]), with mean of 1.6 sessions (SD 1.2). Most received KDE in stage 4 (85.6%), followed by stages 5 (13.1%) and 3 (1.3%). Black patients were less likely to receive KDE (Odds Ratio [OR] 0.92 vs White patients [95% confidence interval 0.87-0.97]), as were Hispanic patients (OR 0.72 vs non-Hispanics [0.67-0.79]). Patients who were in the most vulnerable quartile of the SDI were less likely to receive KDE than those in higher quartiles (OR 0.68; 95% CI, 0.64-0.79). Similar results were seen across SDOH factors (**Figure**). Throughout the post-index period, patients in the KDE group were more likely than non-KDE patients to receive peritoneal dialysis (28.1% vs 17.3%) and/or kidney transplants (4.4% vs 2.4%).

Conclusions: Identifying factors associated with KDE disparities may provide opportunities to increase utilization and improve outcomes.

Funding: Commercial Support - Sanofi



TH-PO849

Long-Term Effects of Structural Racism on Kidney Health: Redlining in Atlanta

Jennifer L. Bragg-Gresham,[1] Linda Fraunhofer,[2] Ana Laura Licon,[1] Tiffany C. Veinot,[3] Jennifer L. Ennis,[2] Rajiv Saran.[1] *[1]University of Michigan Medical School, Ann Arbor, MI; [2]Laboratory Corporation of America Holdings, Burlington, NC; [3]University of Michigan School of Information, Ann Arbor, MI.*

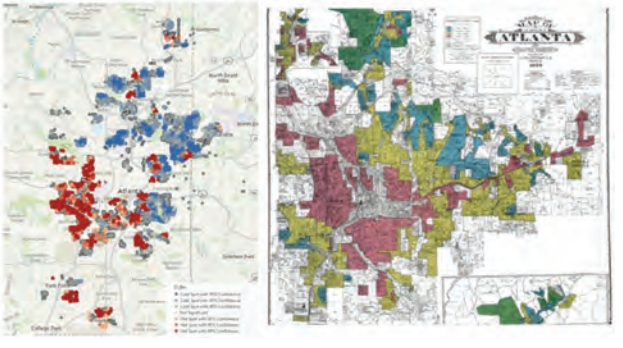
Background: In 1938, the Home Owners' Loan Corporation (HOLC) produced a map of Alanta, GA, as a safety investment guide for mortgage lenders. Areas labeled "hazardous" reinforced racial residential segregation with lasting patterns of continuing inequality. We hypothesize that individuals residing in "less desirable" neighborhoods continue to face challenges contributing to the risk of kidney disease.

Methods: Using Labcorp's most recent kidney disease laboratory tests (~25K, 2021-2024) from individuals residing in previously mapped HOLC districts in Atlanta, GA, we spatially joined results to each grade (A: Best [Blue], B: Desirable [Green], C: Declining [Yellow], and D: Hazardous [Red]). Kidney disease was defined by either an eGFR <60 ml/min/1.73m^2 or a UACR ≥30 mg/g. Hot spot analysis was conducted employing the Getis-Ord Gi*. Logistic regression assessed the odds of kidney disease by HOLC grade, adjusted for age, sex, and current Area Deprivation Index (ADI).

Results: Individuals living in HOLC-A & B neighborhoods were older with a higher proportion of females than those in HOLC-C & D. The prevalence of CKD and current ADI were higher within each successively worse HOLC grade (CKD from 5.3%-13.2% and ADI from 1-3.6). The odds of kidney disease was significantly higher for all HOLC grades compared to grade A (B: OR=1.9, C: OR=2.9, and D: OR=3.7, all p<0.0001). Current day ADI was associated with 13% higher odds of CKD per 1 higher ADI score, p<0.0001.

Conclusions: Significant positive associations were seen between historically redlined areas of Atlanta and the odds of kidney disease. It is imperative to determine the mechanisms underlying these observations and to develop place/person-centered intervention programs to mitigate the effects of these disparities. Future work will assess the causal impact of current day social determinants of health in these geographic areas, including measures of housing, food insecurity, access to healthcare, climate/temperature, and air pollution.

Figure: Current Day Hotspot Map of CKD Compared to 1938 Redlining Map of Atlanta



TH-PO850

Navigating the Distinct Needs of English- and Spanish-Speaking Patients with Kidney Diseases

Kimberly Vasquez, Brittany S. Christian, Jenny I. Shen. *Harbor-UCLA Medical Center, Torrance, CA.*

Background: Latinx patients have a high burden of chronic kidney disease (CKD) and face barriers such as limited health literacy, mistrust of health providers, and communication issues. Patients of lower socioeconomic status face similar barriers,

regardless of their ethnicity. We sought to explore the experiences of patients with CKD who receive care at a US safety-net hospital as well as the potential challenges of introducing a peer mentoring program to support these patients.

Methods: We conducted 8 focus groups of 33 adult patients and 27 caregivers who receive CKD care at a safety-net hospital in California. Patients either spoke English or Spanish. Transcripts were analyzed thematically.

Results: The median age of participants was 50. 60% were women; 40% Spanish-speaking. All had low enough income to qualify for Medicaid. The themes identfied were 1) the need for more information and better communication, 2) the emotional toll of CKD, and 3) lack of trust (Table). To increase awareness of exisiting peer mentoring programs, patients suggested direct text messages, personalized calls, interactive introductory videos, and having doctors introduce the program during clinic visits.

Conclusions: Participants described their kidney disease journey as a labyrinth with emotional distress for themselves and their caregivers. Peer mentors can address barriers of lack of emotional support, communication, and health literacy. Multi-faceted approaches to raising awareness of peer mentoring programs are needed to encourage participation in peer mentoring programs.

Illustrative Quotes

Theme	Quote
Lack of clear information and communication	"You come [to clinic] and you ask, what happened, something is going on...because you don't know the reason why. It has to be from something."
	"I did know [about living with dialysis], not until now [at this focus group] that I talked to the woman explaining about her situation, I am like wow, she has [been on dialysis] a long time and has been surviving."
Emotional toll of CKD	"Your body is fighting against you, and you don't know why, you don't know what to do, and nobody knows what to do with you. I am living in an underlying fear because I don't know what is going to happen... so abruptly my life changed."
	"Every time I wake up, I am grateful to God I am not dead because I was feeling really bad."
Lack of trust	"The doctor told me why you are taking this medicine? its damaging more your kidneys. You were not supposed to be taking this medicine, when he gave me those pills... He told me the contrary."
	"Every time I come in clinic it's a different doctor and they tell me something different. Do they really know what's going on?"

TH-PO851

Sex- and Age-Related Differences in the Prevalence of the Cardiovascular-Kidney-Metabolic Syndrome among US Adults, 1999-2020: An Analysis of the NHANES Survey

Bernhard M. Schmidt, Samira Soltani, Johann Bauersachs, Kai M. Schmidt-Ott, Anette Melk, Zhejia Tian. *Medizinische Hochschule Hannover, Hannover, Germany*.

Background: The cardiovascular-kidney-metabolic (CKM) syndrome is defined as the intricate interplay among metabolic risks, chronic kidney disease (CKD) and the cardiovascular system. The deteriorating CKM syndrome contributes to untimely morbidity and mortality. We aim to characterize sex and age related differences in the prevalence of CKM syndrome.

Methods: We used cross-sectional data provided by National Health and Nutrition Examination Survey (NHANES), representative of the non-institutionalized civilian population of the United States. We included non-pregnant participants aged 18 or older between 1999 and 2020 in our analysis. Prevalence was analyzed overall and by population subgroup (including age, sex, and race/ethnicity), and was weighted to be nationally representative.

Results: A total of 32848 US adults were included in our study from 1999 to 2020 (weighted mean age, 47.3 years; women, 51.3%). 7.9% of US adults were at stage 0 without any CKM risk factors, with the majority being female, comprising 64% of this subgroup. A higher percentage of younger participants were categorized in this group, with 74.9% being under the age of 45. 18.3% of US adults encountered issues related to excess or dysfunctional adiposity without other metabolic risk factors or CKD (stage 1). The distribution between sexes was similar. Over half of the US adult population (56.5%) exhibited either metabolic risk factors, CKD, or a combination of both (stage 2). Older individuals were more prevalent in stage 2, with 41.1% between the ages of 45-64 and 20.4% aged 65 or older. Females aged 65 or older showed a significantly higher prevalence across almost all metabolic risk factors and CKD compared to men. Between 1999 and 2020, the CKM features increased with decreasing prevalence of CKM stage 0 (*P* for trends =0.0018) in females (*P* for trends =0.0039) and to a leser extent in males (*P* for trends =0.031).

Conclusions: Our findings illustrate an exceptionally high and increasing prevalence of CKM syndrome among US adults. Especially elderly women are overrepresented in the high risk group of stage 2 patients. Intense preventive measures should explicitly focus on this group of female patients

TH-PO852

Association and Contribution of Gender-Related Characteristics to Prevalence of CKD in Women and Men in a Multiethnic Population

Taryn G. Vosters,[1] Vianda S. Stel,[1] Liffert Vogt,[1] Kitty J. Jager,[1] Frans J. van Ittersum,[2] Bert-Jan Van den Born,[1] Irene van Valkengoed.[1] *[1]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [2]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands*.

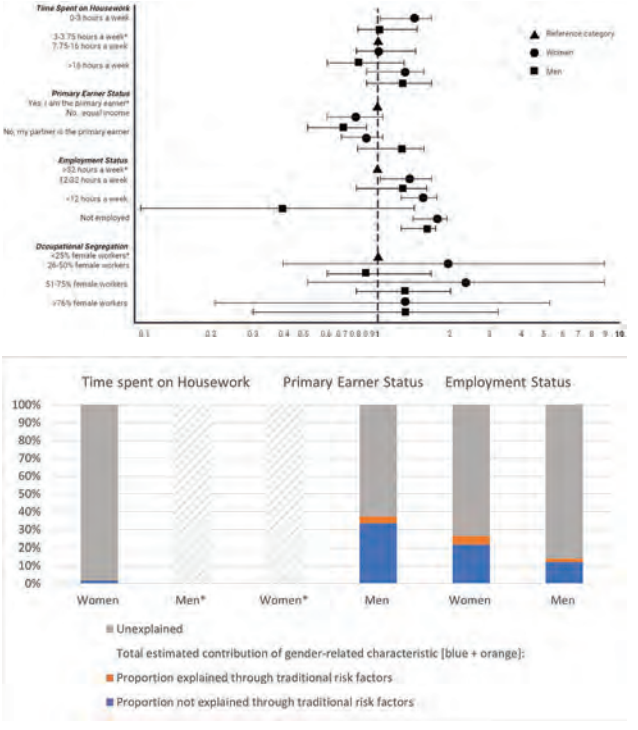
Background: In chronic kidney disease (CKD), prevalence differences between sexes have been reported. While biological factors have been investigated, research on sociocultural factors is scarce. We explore the extent gender-related characteristics associate with, and contribute to, CKD prevalence in women and men in a multi-ethnic population.

Methods: Cross-sectional analyses were performed on data of 12,221 women and 8,930 men aged 18-70 years across six ethnic groups from the HELIUS Study. Using age-, education-, and ethnicity adjusted Poisson regression, we determined associations between time spent on housework; primary earner status; employment status; and occupational segregation, and CKD. Population Attributable Fractions estimated the contribution to CKD and the extent traditional CKD risk factors explained these contributions.

Results: In women, associations with CKD were found for doing little housework, part-time work, and unemployment. In men, primary-earnership and unemployment were associated. Associations aligned across ethnic groups. Estimated contributions ranged from 1.8% for women doing little housework to 26.5% for part-time employment and 12.1% for unemployment to 37.5% for primary-earnership in men, and were hardly explained by risk factors.

Conclusions: In our study, gender-related characteristics are associated with CKD in women and men across ethnic groups. Contributions to population prevalence may hardly be explained by CKD risk factors.

Funding: Private Foundation Support



TH-PO853

Intersection of Race, Age, and Mortality in Young Adults in the United States Renal Data System

Neha D. Pottanat,[1,2] Marciana Laster,[1,2] Jaya S. Parulekar,[1] Mengyu Di,[3] Jade Buford,[3] Rachel E. Patzer.[1,3] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Riley Hospital for Children at Indiana University Health, Indianapolis, IN; [3]Regenstrief Institute Inc, Indianapolis, IN*.

Background: Adults 18-44 years with end-stage kidney disease (ESKD) demonstrate heterogeneity in mortality and transplant waitlist access when categorized by race-ethnicity. Young adults have intensified disparities, but the age cut-off is unknown. Patients between 18-26 years experience changes in insurance status and executive functioning, as it relates to health self-management and transitioning to adult care. Our goal is to compare racial-ethnic disparities in adults <26 years to 26-44 years.

Methods: Incident patients receiving dialysis were identified using USRDS data from 2015-2020. Cox proportional hazard models adjusted for covariates were used to examine the relationship between race-ethnicity and mortality within each age category.

Results: Baseline characteristics of ESKD patients are described for each age category (**Table 1**). Non-Hispanic Black, non-Hispanic Asian, and Hispanic patients had a lower risk of mortality when compared to the reference group of non-Hispanic White patients in crude and adjusted analyses (**Table 2**). When stratified by age, these findings persisted amongst all racial-ethnic categories in patients 26-44 years old. However, in those <26 years, non-Hispanic Black patients had increased risk of mortality in crude analysis (HR 1.41, 95% CI 1.22-1.63) with attenuation upon adjustment. The lower risk of mortality noted in Hispanic and non-Hispanic Asian patients remained within this age group.

Conclusions: This study emphasizes that disparities in mortality within the non-Hispanic Black dialysis population are age dependent. This is consistent with prior research suggesting a "survival advantage" may not be present in younger non-Hispanic Black adults. Further research is needed to define critical ages when disparities in outcomes become apparent.

Table 1: Baseline characteristics of ESKD patients (2015-2020) by age category

Variable	Level	Age 18-25 N =8277 (9.47)	Age 26-44 N = 79134 (90.53)
Sex	Female	3835 (46.33)	32099 (40.56)
	Male	4442 (53.67)	47035 (59.44)
Race/Ethnicity Group	Non-Hispanic White	2825 (34.25)	26943 (34.17)
	Non-Hispanic Black	2463 (29.87)	28011 (35.53)
	Hispanic	2363 (28.65)	17679 (22.42)
	Non-Hispanic Asian	357 (4.33)	3480 (4.41)
	Non-Hispanic Other	239 (2.9)	2728 (3.45)
Attributed Cause of ESKD	Diabetes	815 (10.01)	31240 (40.06)
	Hypertension	1743 (21.4)	22271 (28.56)
	Glomerulonephritis	3530 (43.34)	12563 (16.11)
	Cystic Kidney	569 (6.99)	3081 (3.95)
	Other	1488 (18.27)	8824 (11.32)
Insurance Status	Medicaid	3463 (42.51)	32773 (42.02)
	Medicare	200 (2.46)	6033 (7.74)
	Employer	2254 (27.67)	20653 (26.48)
	Other	1082 (13.28)	7932 (10.17)
	None	1147 (14.08)	10605 (13.6)

Table 2: The association between race-ethnicity and mortality by age category

Race/Ethnicity Group	Overall		Age < 26		Age 26-44	
	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*
Non-Hispanic White	Reference		Reference		Reference	
Non-Hispanic Black	0.87 (0.84-0.90)	0.81 (0.77-0.84)	1.41 (1.22-1.63)	1.10 (0.91-1.32)	0.84 (0.81-0.87)	0.79 (0.76-0.83)
Hispanic	0.60 (0.58-0.63)	0.60 (0.57-0.63)	0.42 (0.34-0.52)	0.43 (0.33-0.54)	0.62 (0.60-0.65)	0.61 (0.58-0.65)
Non-Hispanic Asian	0.38 (0.34-0.42)	0.49 (0.44-0.55)	0.33 (0.19-0.56)	0.25 (0.13-0.47)	0.38 (0.34-0.42)	0.51 (0.45-0.57)

* Adjusted for patient variables: sex, attributed cause of ESKD, pre-ESKD nephrology care, informed of kidney transplant options, insurance status, patient neighborhood variables: average % female, average % black, average % high school graduates, average % renters, average % with no vehicle; and dialysis facility variables: for-profit facility, freestanding facility, facility size/number of patients, and patient-to-social worker ratio

TH-PO854

Sex-Free Estimation of eGFR Preferentially Reclassifies Women as Having Better Kidney Function

Inga Steinbrenner,[1] Anna Kottgen,[1] Elke Schaeffner,[2] Kai-Uwe Eckardt,[3,4] Ulla T. Schultheiss.[1,5] *[1]Institute of Genetic Epidemiology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [2]Institute of Public Health, Charité – Universitätsmedizin Berlin, Berlin, Germany; [3]Department of Nephrology and Hypertension, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen-Nürnberg, Germany; [4]Department of Nephrology and Medical Intensive Care, Charité, Berlin, Germany; [5]Department of Medicine IV, Nephrology and Primary Care, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany.*

Background: Chronic kidney disease (CKD) is staged based on estimated glomerular filtration rate (eGFR, G categories) and urinary-creatinine-to-albumin-ratio (UACR; A categories). Using the cystatin-C based CKD-EPI equation (CKD-EPI) to estimate GFR, women are more likely to be diagnosed with CKD, while men have higher incidence of kidney replacement therapy (KRT). This discrepancy could stem from an overestimation of CKD prevalence and severity on eGFR equations in women, or a slower CKD progression in women compared to men. Pottel et al. introduced a cystatin C-based eGFR equation (EKFC) no longer requiring sex information showing less bias compared to measured GFR than previous equations. We therefore assessed reclassification of CKD stages in >5,000 participants diagnosed with CKD in the German CKD (GCKD) study with the EKFC compared to the CKD-EPI equation in a sex-specific manner.

Methods: The GCKD study's main inclusion criteria were an eGFR between 30-60 or >60 mL/min/1.73m² in the presence of a UACR >300 mg/g. Of 5,217 participants, 91.5% fulfilled the criteria of decreased eGFR, while 8.5% were enrolled based on UACR. Cystatin C was measured from baseline serum samples using a particle-enhanced turbidimetric immunoassay (Tina-quant, Roche). The CKD-EPI and EKFC equations were used to estimate GFR. Reclassification of proportions by sex using the KDIGO G stages was done by comparing the CKD-EPI equation with the EKFC equation.

Results: Among 5,161 participants (60% men), clear sex-specific differences were detected when applying the EKFC equation: compared to the CKD-EPI equation, women in G3a/b were 2-4.5 times more likely to be reclassified to a "milder" G category of CKD (**Table**).

Conclusions: The observed reclassification of women is consistent with the lower incidence of KRT in women and may help to resolve the apparent discrepancy of higher CKD prevalence yet lower KRT incidence observed with previous equations. Future studies should assess the relationship between EKFC estimates and CKD progression.

CKD-EPI \ EKFC		normal or high (G1)	mildly decreased (G2)	mildly to moderately decreased (G3a)	moderately to severely decreased (G3b)	severely decreased (G4)	kidney failure (G5)	N	reclassified N (%)
Men									
G3a	mildly to moderately	0	6.1%	93.9%	0	0	0	902	55 (6.1%)
G3b	moderately to severely	0	0	19.9%	80.1%	0	0	988	197 (19.9%)
Women									
G3a	mildly to moderately	0	27.5%	72.5%	0	0	0	556	153 (27.5%)
G3b	moderately to severely	0	0	39.8%	60.2%	0	0	646	257 (39.8%)

Excerpt: Reclassification of G categories by sex in GCKD study participants in G3a/b by the cystatin C-based EKFC eGFR equation without sex and cystatin C-based CKD-EPI eGFR equation including sex.

TH-PO855

High Prevalence and Inequities in Unmet Social Risk in Diverse Urban Patients on Hemodialysis

Wenchy Tan,[1] Huei Hsun Wen,[1] Lin-Chun Wang,[2] Zijun Dong,[2] Lela Tisdale,[2] Stephan Thijssen,[2] Peter Kotanko,[2] Girish N. Nadkarni,[1] Lili Chan.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Renal Research Institute, New York, NY.*

Background: Health-related social risks (SR) are associated with adverse health outcomes amongst patients with kidney disease. We aimed to identify and analyze SR in a diverse population of hemodialysis (HD) patients.

Methods: We prospectively surveyed SR related to insecurity of housing, food, transportation, and utilities in HD patients from five New York centers, using the AHC Health-Related Social Needs Screening Tool (AHC-HRSN). The presence of unmet SR was compared across self-reported race/ethnicity. Patient demographics (age, gender, education level, employment status, marital status, and income) were assessed for their association with the odds of having any unmet SR using logistic regression. A two-tailed p-value <0.05 was considered statistically significant.

Results: Among 324 consented patients, 144 (44%) had at least one unmet SR (Fig. 1A). Food insecurity differed significantly across race/ethnicity groups ($p = 0.017$). While lower proportions of Whites reported experiencing any unmet SR (35%) compared to Hispanics (63%), Blacks (59%), and Asians (43%), this difference was not statistically significant ($p = 0.097$). Having a college degree or above (OR: 0.64, 95% CI: 0.410 – 0.996) and older age (OR: 0.98, 95% CI: 0.967 – 0.996) were each associated with significantly lower odds of having any SR (Fig. 1B). No significant association was observed between SR and gender, employment status, and marital status after adjusting for patient demographics (Fig. 1C).

Conclusions: This study uncovered disparities in SR factors across different demographic categories, including race/ethnicity and education levels. The overall high burden of unmet SR indicates a need for improved screening and referrals.

Funding: NIDDK Support

TH-PO856

"Life Is Either You're Going into a Storm, Going through a Storm, or Coming out of One": Narrative Interviews with Younger Adults on Dialysis in Baltimore City

Yordanos Tesfai,[1] Deirdre Petkiewicz,[2] Kennedy A. Brown,[2] Deidra C. Crews,[3] Kathryn Taylor.[2] *[1]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD; [3]Johns Hopkins Medicine, Baltimore, MD.*

Background: Racial disparities in survival with kidney failure are most pronounced among younger adults on dialysis, particularly those living in disinvested urban communities. We lack understanding of how younger Black adults on dialysis living in these communities frame their own narratives, navigate their environment to preserve functioning, or the role of dialysis in that work. Narratives can inform interventions to advance health equity in dialysis.

Methods: We are conducting narrative (unstructured) interviews with younger adults on dialysis in Baltimore City to explore their lived experience on and off dialysis. We are recruiting a purposive sample of adults age 18 to 45 years who are receiving dialysis from a facility in Baltimore City, excluding adults who initiated dialysis before age 18. We aim to enroll 15 participants and complete data analysis by October 2024. We will conduct member checking via focus groups when enrollment is complete. We present preliminary analysis of interviews with the 8 participants we have enrolled to date. Interviews were audiorecorded and transcribed, and we used F4Analyze to code qualitative data. Three study members independently conducted reflexive thematic analysis of study interviews and discussed preliminary codes and themes.

Results: All participants self-identified their race as Black or African American and their ethnicity as non-Hispanic; 6 (75%) identified as male. Preliminary codes and supporting quotes (Table 1) illuminate how participants creatively leveraged psychological and available social resources to navigate life as a person on dialysis.

Conclusions: Multiple targets exist for interventions to eliminate racial survival inequities among younger adults on dialysis in disinvested urban communities.

Funding: Other NIH Support - NIH/NIMHD P50MD0173XX

Preliminary Codes	Supporting Quotes
Trying to process	The physical is draining. But depression is real....just kind of realizing this is my life now. Where I'm going to in-center three days a week, and I'm sitting in a room with mostly older folks, because I'm 35 at this time...Trying to process all that's going through, what does it mean for your life? What does it mean going forward? (Participant 6)
Strategies: Prioritizing multiple responsibilities and tasks/ adjusting to fluctuating energy levels	Really the biggest transition was trying to find time for everything. And then also managing that along with energy levels...when I get out of dialysis on a Tuesday and a Thursday, I'm wiped. I've woken up at 7:00, went to work, worked all day...Trying to figure out what are the important priorities for getting things done. For me, it's making sure that there's food in my house, dinner is made, making sure that it's not in shambles completely. And then making sure that my mom's okay, because she is needing a lot more help now than previously. (Participant 1)
Strategies: Negotiating with clinicians for person-centered care	...every year they have this yearly action plan they're supposed to give to the patients and I told my doctor that we're not going to do this on the floor. I don't feel comfortable. I've always said that. So he goes and says, well, he didn't want to do telehealth...And then he goes and says, "Well, you can come up here on Tuesday." Well, in my head I'm like, I live in West Baltimore. I'm not coming across town just to meet with you for 15 minutes for you to tell me the same thing you told me last year...So I didn't show up. Time went by..."Well, I'm going to start the paperwork to have you discharged." So you're going to discharge me because I don't want to meet with you– So it took for me to say something to call the, you know, 1-800 number for them to come back and say, "Hey, won't you just do it in the observation room," which nobody else is in there but one person. (Participant 5)
Survival resources: People try to take advantage of you	So it's like I found myself, here recently, I found myself getting this young lady to come. I thought she was going be here to help me. That's not the case. It's like she's taking advantage of me, and you run into that at times. Not all dialysis patients, because some people have their family and friends and things like that, but for some reason, I ran into this brick wall and I can't get her to move out...Or when we talk, it turns into a argument on her part, and the one day she jumped up in my face and I felt threatened. So now, I have sleep with a butcher knife underneath my pillow and a empty soda bottle, glass bottle, by my bedside. (Participant 7)
Survival resources: I didn't have anyone to guide me	I spent a month in the hospital and then two months in [a skilled nursing and rehabilitation facility]...So that's three months altogether. I got kicked out of the house where I was living too, at the time, because I didn't have no rent and had no money. I wasn't getting disability yet. So, I was working part time on dialysis, not on disability or nothing. Again, I didn't have anybody to guide me, like "Hey, man, you're on disability. Let me take you to Social Security." Because I was on my own on the street. (Participant 2)
Reframing the situation: You have to see the world as it is	It just doesn't make sense to keep perceiving the world and the way that you think it should be. You have to deal with things the way it is and then work from there. Somebody told me, I remember who it was, I'll never forget this, "Life is either you're going into a storm, going through a storm or coming out of one."...Like, that's life. And you're going to have to learn how to put on your raincoat, put on your boots and just deal with it. And I mean, I just had to deal with it. I mean, is it resilience? I guess. (Participant 2)
Reframing the situation: You have to have some kind of hope	My uncle just passed, and the one thing that I believe that why he passed is that he didn't have something to look forward for...You have to have some kind of hope, something that you want to strive for...You got to have something to go for to keep you moving because if not, you just sit still and just, you just die. (Participant 8)

TH-PO857

Motivation Associates with Dialysis Treatment Adherence in African American Patients

Marylou Wallace,[1] Julianna Forbess,[1] Meaghan S. Roche,[2] Heather L. Prigmore,[1] Robert Greevy,[1] Marquetta L. Faulkner,[3] Hilary A. Tindle,[1] Devika Nair,[1] Rachel B. Fissell,[1] Kerri L. Cavanaugh,[1] Ebele M. Umeukeje.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Henry Ford Health System, Detroit, MI; [3]Meharry Medical College, Nashville, TN.*

Background: African Americans (AA) comprise 33% of end-stage kidney disease (ESKD) patients, and are more likely to be nonadherent to in-center hemodialysis (HD) compared to Whites. Motivation-based factors informed by self-determination theory (SDT) associate with medication adherence. However, the association with HD treatment adherence in AA is unknown.

Methods: In a multi-site prospective study, motivation was assessed via SDT surveys: Autonomous Regulation [(AR) range: 1-7], Health Care Climate Questionnaire [(HCCQ) range: 1-7], and Perceived Kidney Disease Self-Management Scale [(PKDSMS) range: 8-40] Higher scores indicate better 'attitudes', perception of autonomy support from providers, and self-efficacy, respectively. Nonadherence was reported as mean proportion of missed HD minutes and shortened (i.e.,>15 minutes less than prescribed HD) and missed HD sessions over 3-month post-baseline survey period. Mean number of sessions was standardized to 36.

Results: Among 210 AAs on HD for at least 90 days (56.2% male; mean age 56 (±13.8), about one-third had a high school education or less, an annual income of $10,000 or less, and lived alone. Mean number of missed and shortened HD sessions per 36 sessions was 1.8 (±3.24) and 3.24(±5.04) respectively. All SDT scores significantly associated with shortened HD sessions; AR being the strongest. Higher PKDSMS scores were inversely and significantly associated with all measures of HD non-adherence **(Table 1).**

Conclusions: SDT measures were associated with HD adherence. Optimizing patients' attitudes may be most effective for improving nonadherence due to shortened HD. Enhancing patients' self-efficacy may significantly impact nonadherence for shortened and/or missed HD. Future research will target better understanding of underlying factors affecting patients' attitudes and self-efficacy to inform motivational strategies for improving HD adherence and kidney health equity.

Funding: NIDDK Support

Table 1

	Missed minutes	Missed minutes	Missed HD sessions	Missed HD sessions	Shortened HD sessions	Shortened HD sessions
Variables	Spearman Rho	p-value	Spearman Rho	p-value	Spearman Rho	p-value
AR	-0.16	0.024	-0.04	0.554	-0.31	<0.001
HCCQ	0.01	0.962	0.08	0.261	-0.19	0.005
PKDSMS	-0.35	<0.001	-0.30	<0.001	-0.23	0.001

TH-PO858

Apathy, Depression, and Hemodialysis Adherence in African American Patients

Meaghan S. Roche,[1] Marcus G. Wild,[2] Ratib T. Mahfouz,[1] Amulya Rajagopal,[1] Luis G. Osorio,[1] Javad Najjar Mojarrab,[1] Queen Henry-Okafor,[3] Toddra Liddell,[2] Rachel B. Fissell,[2] Devika Nair,[2] Heather L. Prigmore,[2] Robert Greevy,[2] Kerri L. Cavanaugh,[2] Hilary A. Tindle,[2] Ebele M. Umeukeje.[2] *[1]Henry Ford Health System, Detroit, MI; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Vanderbilt University School of Nursing, Nashville, TN.*

Background: African Americans (AAs) have a four-fold higher prevalence of end-stage kidney disease (ESKD), high depression risk, and poor adherence to in-center hemodialysis (HD) compared to Whites. Depression and Apathy, and their association with HD adherence, are greatly understudied in AAs.

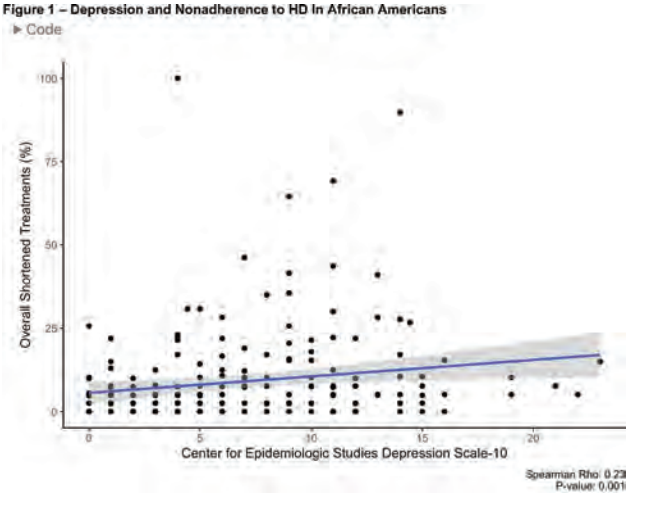
Methods: Validated surveys assessing depressive symptoms (Center for Epidemiologic Studies Depression scale, [range:0-30], higher scores indicating more depressive symptoms) and trait apathy (Apathy Evaluation Scale, [range:7-28], higher scores indicating less apathy), were administered to a multi-site cohort of AAs at 3 HD clinics. Nonadherence was defined as mean proportion of shortened HD sessions (i.e.,>15 minutes less than prescribed HD), and missed HD sessions over the 3-month post-baseline survey period; and mean number of missed/shortened sessions standardized to 36 sessions.

Results: AAs (N = 210; mean age 56; 56% male) had been on HD for at least 90 days. About one-third had a high school education or less; earned $10,000 /year or less; and lived alone. Mean number of missed and shortened HD sessions per 36 sessions was 1.8(±3.24) and 3.24(±5.04) respectively. Prevalence of significant depressive symptoms was 29.0%. Higher depressive symptoms (Fig.1) (r= 0.23; p = 0.001) and more apathy (r= -0.15; p = 0.029) correlated with shortened HD but not missed HD sessions.

Conclusions: Higher depressive symptoms and more apathy correlated with more shortened sessions in AAs on HD. Motivational strategies to reduce depressive symptoms and apathy, may be a novel way to improve adherence to HD among AAs, curb racial disparities, and promote kidney health equity.

Funding: NIDDK Support

Figure 1 – Depression and Nonadherence to HD in African Americans



TH-PO859

MoVE TRIAL Protocol: MotiVational Strategies to Empower African American Patients to Improve Dialysis Adherence

Anita Medepalli,[1] Marylou Wallace,[2] Zuri N. St. Julien,[3] Julianna Forbess,[2] Heather L. Prigmore,[2] Robert Greevy,[2] Sarah J. Schrauben,[4] Devika Nair,[2] Rachel B. Fissell,[2] Julia Lewis,[2] Kerri L. Cavanaugh,[2] Kenneth A. Resnicow,[5] Ruth Q. Wolever,[2] Ebele M. Umeukeje.[2] *[1]Mercer University, Macon, GA; [2]Vanderbilt University Medical Center, Nashville, TN; [3]University of Missouri-St Louis, St Louis, MO; [4]University of Pennsylvania, Philadelphia, PA; [5]University of Michigan, Ann Arbor, MI.*

Background: Compared to Whites, African Americans (AA) have a four-fold higher prevalence of end-stage kidney disease (ESKD) and higher hemodialysis (HD) treatment non-adherence rates. We pilot-tested (NCT05003115) and confirmed *feasibility* of culturally tailored motivational interviewing (MI) to improve HD adherence in AA. We describe our efficacy trial protocol (NCT05735743) and hypothesize that the intervention improves HD adherence.

Methods: Multi-site, 2-arm, parallel group (MI vs. Usual Care) RCT of ≥ 18 years old, AA HD patients (n=150, 2:4:2 stratified block randomization), who missed or shortened ≥1 session by ≥15 minutes/2 months before enrollment. Trained health coaches (HC) conduct MI sessions. Intervention fidelity is assessed pre-enrollment and mid-RCT, via MI Treatment Integrity Scale. MI patients receive 6 sessions in 8 weeks, culturally tailored to prioritize AA patient-identified contributors to nonadherence, including racial identity (Fig 1). Survey completion and EMR abstraction occur at baseline, 8, and 24 weeks; adherence data is abstracted to week 24. Primary and secondary outcomes are proportions of missed HD minutes at 8 and 24 weeks, respectively.

Results: IRB approval was obtained. Manual of procedures, intervention manual, and study charter were developed. HC received protocol, logistics, and further MI training. Enrollment was launched upon DSMB and site approval. RCT activities are ongoing.

Conclusions: Findings will determine *efficacy* of culturally tailored MI on improving HD adherence in AA. Improved HD adherence will reduce morbidity, mortality, healthcare costs, and racial disparities in ESKD.

Funding: NIDDK Support

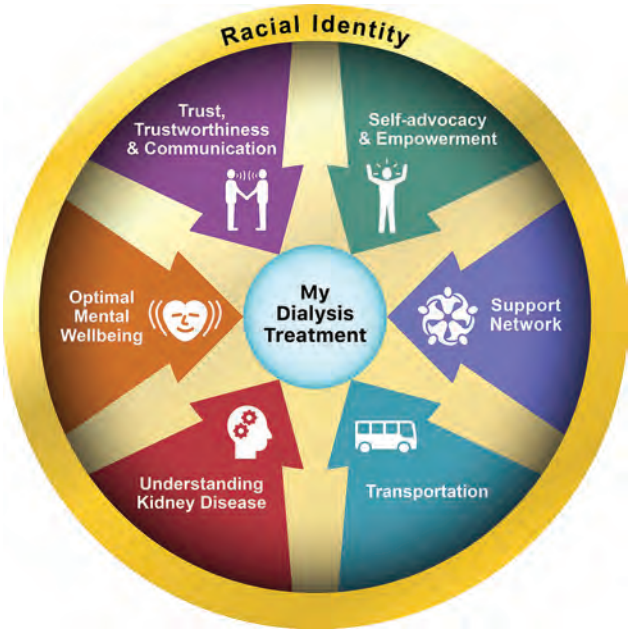


Figure 1

TH-PO860

The Lived Experiences of African American and Latinx Individuals with CKD Using Photo Elicitation

Sadia Anjum Ashrafi,[1] Norman A. Hernandez,[2] Laura Quintero Silva,[2] Katherine Hopkins,[2] Michelle Martinez,[2] Maya Ordaz,[2] Minakshi Raj,[2] Andiara Schwingel.[2] *[1]University of Illinois Chicago College of Medicine, Chicago, IL; [2]University of Illinois Urbana-Champaign, Urbana, IL.*

Background: Chronic Kidney Disease (CKD) disproportionately affects the lives of African Americans and Latinx, but there remains a knowledge gap about their lived experiences. Therefore, the US healthcare system struggles to address their needs, leading to poorer health outcomes among these populations. This study aims to uncover the lived experiences of African American and Latinx individuals with CKD using a participatory approach to guide the delivery of optimal health care.

Methods: This study employed the photo elicitation technique with 20 individuals with CKD (African Americans = 15 and Latinx = 5). Each participant shared five photos that symbolized their CKD journeys and subsequently discussed these photos during individual Zoom interviews, either in English or Spanish, based on their preferences. The interviews were transcribed verbatim, cleaned, coded, and subjected to reflexive thematic analysis.

Results: The analysis of both photos and interview transcripts revealed four key themes. Theme 1 explored "*The Burden of CKD: Physical Challenges, Limited Lifestyle, and Emotional Stress*," revealing the profound impact of CKD on patients' physical, social, and emotional well-being throughout their journey. Theme 2, "*Navigating CKD with Positivity and Support*," investigated how participants maintained psychological resilience and received support from their surroundings despite the challenges they faced. Theme 3, "*Systemic Challenges in the Journey*," addressed the systemic barriers encountered by participants, such as financial constraints, communication barriers, systemic racism within the kidney care system, and limited access to care. Lastly, Theme 4, "*Building Bridges in the Kidney Community*," underscored participants' endeavors to combat CKD within their communities through advocacy and outreach efforts.

Conclusions: These findings emphasize the requirement for a healthcare approach that is more inclusive and equitable, addressing the specific needs and obstacles encountered by these populations. This will lead to improved health outcomes for African American and Latinx individuals with CKD.

Funding: Private Foundation Support

TH-PO861

Historical and Contemporary Burden of ESKD among Torres Strait Islander People of Australia, 1963-2022

Jaquelyne T. Hughes, Katie Cundale, Shahid Ullah, Karla J. Canuto. *Flinders University College of Medicine and Public Health, Adelaide, SA, Australia.*

Background: Zenadh (Torres Strait Islander) people are the First Peoples of the lands and waterways of the Torres Strait in Australia. Zenadh people have been oppressed by colonisation and systemic racism for many years, experiencing sustained barriers to healthcare and optimal health outcomes. Today, Zenadh people live with inequitable rates of advanced diabetes and kidney disease. To best advocate for health equity change, Tribal Elders sought to describe the patterns, modality, and outcomes of kidney replacement therapy (KRT) among Zenadh people to inform health-improving actions.

Methods: Data was extracted from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry that included demographic details (age, sex, location), primary disease, comorbidities, and treatment modality. Adults (≥18 years) who commenced KRT in Australia between 1963 and 2022 were included, and we describe patients with the ethnicity identifier of "Torres Strait Islander". The research and its conduct was approval by Maluilgal Tribal Governance and an Indigenous Health Ethics Committee.

Results: A total of 453 Zenadh adults received KRT during 1963-2022, with an average commencement age of 54 (SD=12.3) years and 55% were female. The most recent decade accounted for 42% (190/453) of KRT initiation, and the majority of patients overall were resident of Queensland (92%, 418/453). Diabetic kidney disease was the primary kidney disease in most patients (75%, 341/453). Forty-seven (10%) transplants occurred since 1978. For Zenadh patients still alive at 31 December 2022, satellite and hospital haemodialysis were the two most common KRT modalities (51% and 26%, respectively), and transplantation was 9%.

Conclusions: This analysis presents, for the first time, data specific to the treatment of kidney failure for Zenadh people who have lived across Australia during 1963-2022. This first look into the historical and contemporary burden of kidney disease establishes baseline health statistics from which health improving actions can be progressed and health systems held accountable for equity and change.

TH-PO862

Improving Transplantation Equity in Australia: The National Indigenous Kidney Transplantation Taskforce

Jaquelyne T. Hughes,[1,2] Katie Cundale,[3,4] Stephen P. McDonald.[3,5] *[1]Flinders University College of Medicine and Public Health, Adelaide, SA, Australia; [2]Royal Darwin Hospital Division of Medicine, Darwin, NT, Australia; [3]Australia and New Zealand Dialysis and Transplant Registry, Adelaide, SA, Australia; [4]South Australian Health and Medical Research Institute Limited, Adelaide, SA, Australia; [5]The University of Adelaide Adelaide Medical School, Adelaide, SA, Australia.*

Background: In Australia, Aboriginal and Torres Strait Islander people experience inequitably high rates of kidney failure yet significantly lower rates of transplantation. The Australian Government recognised this disparity and funded the establishment of the National Indigenous Kidney Transplantation Taskforce (NIKTT). The NIKTT is the

first of its kind: in Australia, and other colonised countries, little coordinated effort has been made from government-led initiatives to truly change transplantation access and outcomes for Indigenous peoples.

Methods: The NIKTT was created to drive the development and implementation of initiatives that targeted gaps in access to care for Aboriginal and Torres Strait Islander kidney patients, facilitating improved transplant waitlisting. The NIKTT did this by: (1) implementing enhanced clinical data collection on waitlisting; (2) trialling a range of locally developed and led service models; and (3) evaluating cultural bias initiatives in Australia. To best inform Taskforce action, the NIKTT created a national network of Aboriginal and Torres Strait Islander consumers and established Indigenous Reference Groups at transplant units around the country.

Results: Over three years, the NIKTT found that: (1) While there was an increase in the number of Aboriginal and Torres Strait Islander people activated on the waitlist, waitlisting and transplantation remain inequitable in Australia. Data suggests that late initiation of work up, along with clinician-perceived barriers such as obesity and non-adherence, could contribute to this disparity; (2) Models of care that work best to increase the rate of placement on the waitlist include outreach assessment clinics, patient navigator programs, Indigenous Reference Groups, and context-specific educational resources; and (3) Increasing the Aboriginal and Torres Strait Islander renal workforce, tailoring models of care to local contexts, and improving institutional safety through policies and funding could meaningfully improve the safety of services.

Conclusions: The development of a national Taskforce was critical to provide a focal point to drive real change in Australia. Targeted clinical, policy, and consumer activity within the NIKTT has confirmed increased waitlisting, but further time and funding is needed to appreciate the impact on transplantation and outcomes.

Funding: Government Support - Non-U.S.

TH-PO863

Responses from Arabic-Speaking Caregivers of Youth with Chronic Conditions to the Health Care Transition Readiness Starx Questionnaire

Peter Said, Yara Abumohsen, Maria E. Ferris. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Successful healthcare transition (HCT) is vital for youths with chronic conditions shifting from pediatric to adult care. A USA cohort revealed a preference among youths for health information from caregivers. Assessments of HCT readiness using the STARx Questionnaire inform customized interventions. However, there is a lack of studies on Arabic-speaking dyads. Our hypothesis explores potential differences in HCT readiness scores among youth with chronic conditions.

Methods: The STARx Questionnaire underwent translation/back-translation into Arabic. Ethics approval was obtained from the University of North Carolina at Chapel Hill and Zagazig University, Egypt. We enrolled youths with chronic conditions and their caregivers.

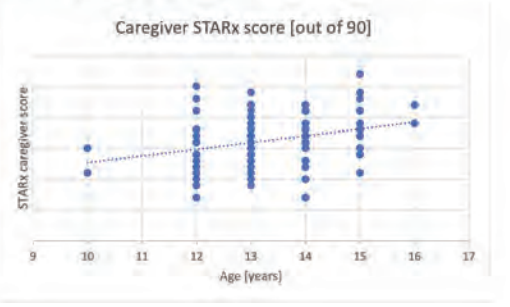
Results: We included 107 youth/caregiver dyads, with 60% male youths, averaging 13.3±1.2 years. Diagnoses comprised 24% Kidney disease, 33% thalassemia, and 43% diabetes mellitus. The median medication count was 2 (range 0-4). Total Caregiver STARx scores positively correlated significantly with youth's age (Pearson r=0.31, Figure 1). While total STARx scores significantly correlated between caregivers and youths (Pearson r=0.18, Figure 1), caregivers scored substantially lower (51±5) than youths (54±5, p=1.35E-07, paired t-test). Lower caregiver scores were observed in disease knowledge and self-management domains, with caregivers outperforming youths in provider communication (Table 1).

Conclusions: Arabic-speaking caregivers scored lower in HCT readiness (total, disease knowledge, and self-management), while youths scored lower in healthcare communication. Ambiguity exists whether youths overestimate their skills in disease knowledge and self-management. Further investigation of the caregiver-youth gap in provider communication is needed to enhance youths' skills and perceptions.

Table 1: Total and 3 sub-domain STARx Questionnaire scores of youths and caregivers and paired t-test

	Youth		Caregiver		p-value
Parameter	Average	St. Dev	Average	St. Dev	
Total (90 points)	54	5	51	4	<0.0001
Disease knowledge (20 points)	15	1	10	2	<0.0001
Self-management (25 points)	15	2	13	2	<0.0001
Provider communication (20 points)	12	2	15	2	<0.0001

Figure 1: The relationship between youth age and caregiver total STARx healthcare transition readiness score of 107 youth/caregiver dyads.



TH-PO864

Equity in Kidney Transplant Allocation: Graft Survival Outcomes for Blood Group B Recipients from A2/A2B- and ABO-Compatible Donors

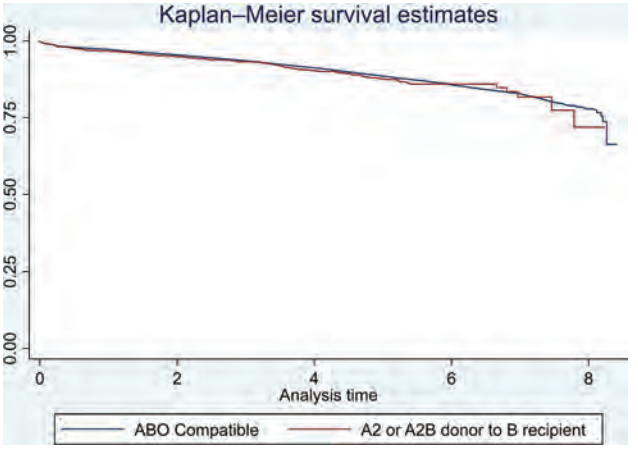
Hatem Ali,[1] Ahmed Daoud,[2,3] Tibor Fulop.[2] *[1]University Hospitals North Midlands, Stoke on Trent, United Kingdom; [2]Medical University of South Carolina, Charleston, SC; [3]Cairo University Medical School, Cairo, Egypt.*

Background: Disparities in kidney transplant allocations affect blood group B candidates, who are predominantly from minority groups. Prior studies have indicated successful outcomes from transplanting kidneys from donors with non-A1/non-A1B (A2/A2B) subtypes to blood group B recipients.

Methods: This retrospective cohort study utilized the United Network for Organ Sharing (UNOS) database, covering the period from January 1, 2015, to June 1, 2022, with follow-up data until June 1, 2023. The study included 110,826 adult deceased kidney donor transplant recipients, of which 109,353 (98.24%) received ABO-compatible transplants. We compared graft survival between blood group B recipients receiving kidneys from A2B or B group donors (incompatible group) and those receiving ABO-compatible kidneys. Covariates such as donor age, sex, ethnicity, BMI, hypertension, diabetes, transplant factors (PRA, HLA mismatch, cold ischemia time), and recipient factors (age, sex, ethnicity, cause of renal failure, BMI, dialysis prior to transplant, number of previous transplants) were adjusted for in the analysis.

Results: Our findings show no significant difference in graft survival between the ABO-compatible and incompatible groups, with a hazard ratio of 1.08 (95% CI: 0.91-1.27; p=0.345). This suggests equivalent outcomes in both groups, supporting the viability of expanding donor eligibility criteria to include A2/A2B donors for blood group B recipients.

Conclusions: The study supports the ongoing efforts to improve equity in kidney transplant allocations through broader use of A2/A2B donors for blood group B recipients, particularly benefiting minority populations. This could potentially mitigate disparities in transplant access and outcomes for this group, aligning with changes implemented in the kidney allocation system (KAS). Further research is needed to explore the long-term impacts of these policy changes on transplant equity.



TH-PO865

Tears of the Nile: Unraveling the Tragedy of Kidney Transplant Recipients in Sudan during Wartime

Lina Alatta,[1,2] Amira Mohamed,[2,3] Anmar Homeida.[2,4] *[1]New York Presbyterian Queens, Flushing, NY; [2]Sudanese American Physicians Association (SAPA), Plano, TX; [3]Montefiore Medical Center, New York, NY; [4]New York University, School of Global Public Health, New York, NY.*

Background: In 1974, Sudan achieved its first renal transplantation, but progress stalled for twenty-five years. However, in 2000, a transformative initiative led by Sudanese expatriate surgeons and local nephrologists, with support from visiting teams from England, revitalized kidney transplantation in Sudan. Currently, Sudan has four functioning transplant centers, including a specialized pediatric unit in Khartoum. Despite challenges like political instability and healthcare underinvestment, studies are shedding light on obstacles faced by transplant patients, such as financial constraints and limited post-transplant care Following the onset of the conflict in Sudan on April 15, 2023, the healthcare system experienced considerable strain and depletion of already limited resources. Prior to the outbreak of war in Sudan, the estimated population of living transplant recipients stood at approximately 4500. Kidney transplant recipients rely on immunosuppressive medication to sustain graft viability. However, interruptions in medication availability and follow-up care markedly increase vulnerability to infections and the risk of transplant rejection

Methods: Data were collected from published research, social media, and medical personnels

Results: Kidney transplant recipients faced a disruption in access to immunosuppressive medications, as the primary pharmacy serving these patients was in Ahmed Gassim Hospital. There is a lack of clear data regarding the incidence of infections or transplant rejection cases, as well as the number of patients requiring hospitalization or dialysis.

Conclusions: The findings highlight the severe impact of wartime conditions on kidney transplant recipients in Sudan, emphasizing disruptions in accessing vital medications and follow-up care. To assist kidney transplant patients in conflict zones like Sudan, the international community should prioritize strengthening health infrastructure, providing training programs for healthcare professionals, and establishing financial aid mechanisms. Additionally, promoting robust organ donation initiatives, fostering research and data collection, building collaborative networks, and utilizing telemedicine for remote support are essential steps. These efforts aim to improve the resilience and sustainability of kidney transplant programs, ultimately enhancing patient outcomes and quality of life.

TH-PO866

Barriers to Familial Consent in Deceased Organ Donation among Racialized and Indigenous Communities in Canada: A Qualitative Study

Simran Sandhu,[1] Jagbir Gill,[1,3] Reetinder Kaur.[2] *[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]Providence Research, Vancouver, BC, Canada; [3]Division of Nephrology, The University of British Columbia, Vancouver, BC, Canada.*

Background: In Canada, over 3700 people are on the organ transplant list, with deceased donor kidney transplants making the majority of transplants completed annually. Despite the increasing numbers of transplants, populations marginalized by race and ethnicity have lower rates of organ donation registration and are less likely to consent to donation. Gaining insight into barriers to providing consent is critical in developing strategies to address disparities. This study aimed to identify barriers to familial consent among members of racialized and Indigenous communities.

Methods: 48 participants were recruited through community-based organizations in British Columbia (BC) and included BC residents, aged over 19, who spoke English. 31 participants completed interviews and 17 completed focus groups. Participants were oversampled for members of racialized and Indigenous communities. A case vignette was used to collect data with data analyzed using summative content analysis.

Results: Four overarching barriers were identified: 1) system-level; 2) community-based; 3) related to decision-making; and 4) informational. System-level barriers highlighted mistrust of Canadian healthcare institutions, perceived coercion, and the role of language in consent. Community-based barriers involved ideas around the deceased body, funeral, afterlife, and general perceptions of organ donation. Decision-making was affected by family dynamics and donor and recipient identity. Informational barriers such as age eligibility also influenced consent. Facilitators to address barriers include culturally diverse resources, increasing community knowledge, and providing language, cultural, and religious support to build trust and facilitate discussions.

Conclusions: This study highlights barriers and modifiable determinants to familial consent in deceased organ donation among members of racialized and Indigenous communities. Although it examines barriers to familial consent for all organ donation, findings are of significant relevance to kidney care, as patients waiting for kidney transplants constitute the majority of patients on transplant waitlists. Education and engagement initiatives must be targeted at the health system and community levels to fully address barriers to consent and reduce racial and ethnic disparities in organ transplantation.

TH-PO867

Kidney Transplantation and Health Equity in ESKD Survival

Paul T. Williams. *E O Lawrence Berkeley National Laboratory, Berkeley, CA.*

Background: Recently, the OPTN mandated race-neutral equations to estimate kidney function, and to retroactively apply the results to credit Blacks for the wait time that would have been accrued. This will likely decrease the proportion of White ESRD patients receiving deceased donor kidneys. Because the risks for mortality and ineligibility due to deteriorating health are greater in Whites than non-Whites, the OPTN policy changes could increase racial health disparities in ESRD survival.

Methods: Age- and sex-adjusted 2-year, 5-year, and 10-year survival rates from the 2021 United States Renal Data System ESRD cohort were used to estimate the effects of deceased donor kidney re-assignment on racial health equity in ESRD patients. Overall survival calculated as the weighted average of 2-year survival for dialysis, deceased donor, and live-donor transplant patients.

Results: Two-year survival was substantially lower in White than Black ESRD patients as originally allocated (70.6% vs. 77.1%). Each 10% in deceased donor kidneys diverted from non-Black to Black recipients increased Black survival by 0.518% whilst decreasing White survival by 0.194%, further increasing Black-White health inequity. Conversely, re-allocating most of the 8853 deceased donor transplants originally allocated to non-White to White dialysis patients would theoretically eliminate White-Black inequity in 2-year survival (73.4% vs. 74.8%). Although this would decrease 2-year survival in non-Whites, all would continue to survive better than Whites.

Conclusions: Increasing deceased donor kidney transplants to Blacks from non-Blacks is projected to increase Black-White survival disparities, contrary to the pursuit of health equity. Alternatively, deceased donor kidneys could be assigned by treating patients equally regardless of race, as has been the American ideal.

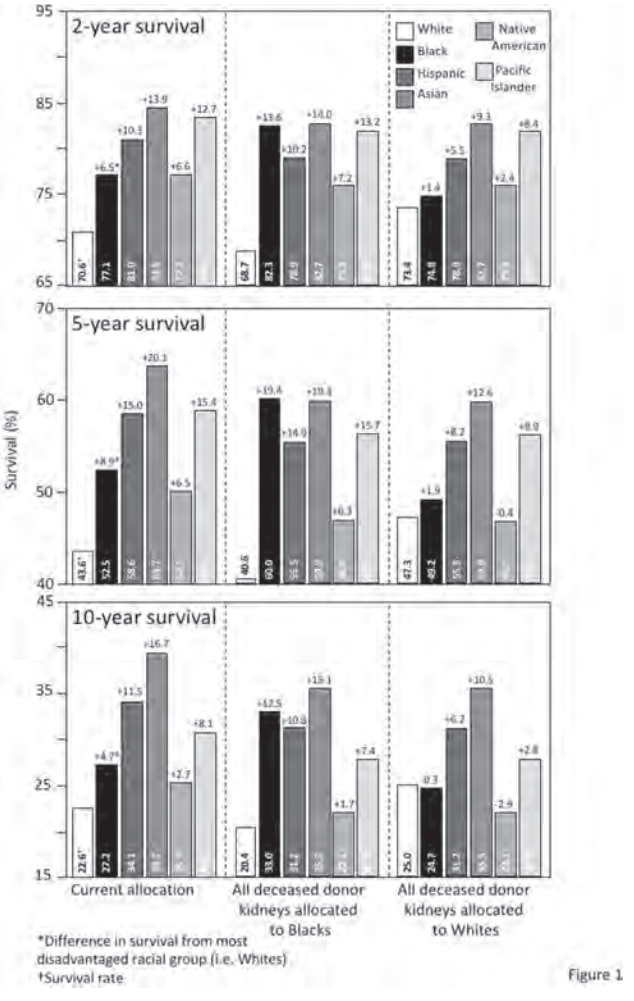


Figure 1

TH-PO868

Medical Mistrust Predicts Lower Likelihood of Wait-Listing in Kidney Transplant Candidates

Miriam E. Velez-Bermudez,[1] Yuridia Leyva,[1] Chethan M. Puttarajappa,[3] Arjun L. Kalaria,[3] Yiliang Zhu,[1] Yue-Harn Ng,[2] Amit D. Tevar,[3] Mary Amanda Dew,[3] Larissa Myaskovsky.[1] *[1]University of New Mexico Health Sciences Center, Albuquerque, NM; [2]University of Washington School of Medicine, Seattle, WA; [3]UPMC, Pittsburgh, PA.*

Background: The kidney transplant fast track (KTFT) program was implemented within a large, single-center urban transplant center to reduce patient burden and streamline the kidney transplant (KT) evaluation process. KTFT aimed to improve the KT evaluation process for all patients, regardless of socioeconomic resources, and reduce the waitlisting disparity between White and Black patients. In this prospective cohort study of patients who underwent KTFT, we examined whether sociocultural factors (e.g., medical mistrust; discrimination & racism in healthcare; trust in physician) predicted the likelihood of KT waitlisting.

Methods: Patients who were referred to KT evaluation were recruited into KTFT starting in 2015. Baseline characteristics were collected during a pre-KT evaluation interview. Participants' medical records were reviewed through 08/2022 for waitlist status. We used Fine-Gray proportional hazards models to examine how sociocultural factors uniquely predicted likelihood of waitlisting, controlling for demographics and clinical factors.

Results: The final sample of KTFT patients included 1107 participants (782 Non-Hispanic White, 243 Non-Hispanic Black, 82 Other). We found that medical mistrust (subdistribution hazard ratio [SHR] = 0.79, 95% CI: 0.70, 0.90) and Black race (SHR = 0.70, 95% CI: 0.55, 0.90) lowered likelihood of waitlisting. After controlling for demographic and clinical factors, the effect of Black race on waitlisting went away, but the influence of medical mistrust on waitlisting was maintained (SHR = 0.86, 95% CI: 0.75, 0.99).

Conclusions: In a cohort of patients who underwent a clinic-level intervention that streamlined the KT evaluation process, we found that medical mistrust, not race, was associated with reduced likelihood of KT waitlisting. These findings suggest that working to reduce KT disparities may involve targeting sociocultural factors that explain race differences, rather than targeting race itself. Such interventions may need to involve targeting multiple levels within the healthcare system (e.g., clinic-level and provider-level intervention) instead of exclusively focusing on a single level.

Funding: NIDDK Support

TH-PO869

Racial Disparities in Inpatient Outcomes for Patients with Renal Cell Carcinoma

Iskandar Berbari, Fayaz A. Khan, M Kenan Rahima, Madelyn Durhman. *TriHealth Inc, Cincinnati, OH.*

Background: Healthcare disparities persist, reflecting variations in health outcomes, access, and quality among racial groups. Understanding these disparities is essential for improving healthcare equity.

Methods: We queried the National Inpatient Sample 2017-2020 for adult patients of different races hospitalized with Renal cell carcinoma (RCC) using ICD-10 codes. The primary outcome was inpatient mortality. The secondary outcomes were intubation, length of stay (LOS), and hospital cost. Multivariable logistic, linear, and Poisson regression analyses were used to estimate clinical outcomes with a p-value < 0.05 was significant.

Results: Total 361060 RCC hospitalizations, mean age 65.6 years, 64.7% male. Caucasians were the largest group, followed by Blacks. Blacks had the highest rates of AKI, CKD, dialysis indicating more severe renal impairment. Clinical characteristics are listed in Figure 1. Blacks have the highest rates of intubation, LOS, and inpatient mortality. Hispanics incurred the highest total costs. Clinical outcomes are shown in Figure 2.

Conclusions: Data suggest significant racial disparities in inpatient admissions and outcomes of RCC. A lower rate of hospitalization among Blacks, despite higher incidence may be due to decrease access to healthcare, poor awareness, socioeconomic factors, reporting biases. Targeted interventions are needed to address these disparities, including improved access to healthcare, better management of comorbid conditions, and aggressive follow-up care, particularly for high-risk groups like Blacks.

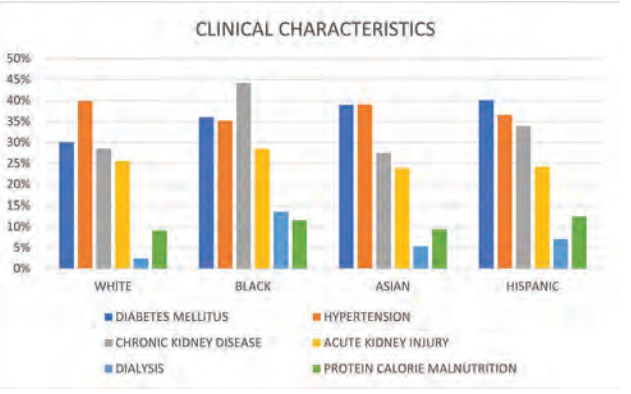


Figure 1

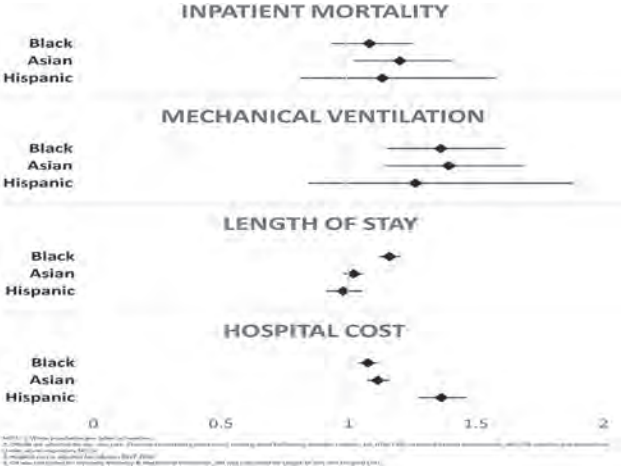


Figure 2

TH-PO870

Racial Disparities in Adverse Cardiovascular and Cerebrovascular Events among Patients with Renal Cell Carcinoma

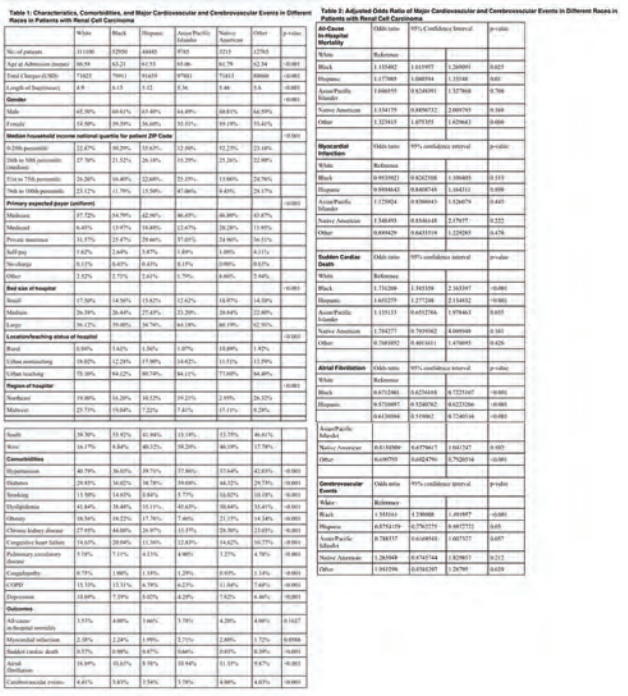
Sobia Mansoor,[1] Kanishka Uttam Chandani,[1] Siddharth P. Agrawal,[1] Sahil Bhargava,[2] Maharshi Raval,[1] Sajid Siddiq,[1] Ahmed Nadeem,[1] Michael J. Monsour.[1] *[1]Landmark Medical Center, Woonsocket, RI; [2]Smt NHL Municipal Medical College, Ahmedabad, India.*

Background: Renal cell carcinoma (RCC) is the most prevalent urogenital malignancy and the 13th leading cause of cancer-related mortality. Treatment advances, including ICIs, have improved overall survival (OS). We aim to study racial disparities in major cardiovascular and cerebrovascular events (MACCE) among RCC patients.

Methods: ICD-10 codes were used to identify RCC patients from the NIS 2016–2020 database. MACCE included all-cause in-hospital mortality (ACIHM), acute myocardial infarction (AMI), atrial fibrillation (AF), cerebral events, and sudden cardiac death (SCD). Baseline characteristics and MACCE were compared using chi-square for categorical or ANOVA for continuous data (statistical significance determined p-value<0.05), with results stratified by patient's race.

Results: 434,260 patients were identified: 71.65% (311,100) White, 12.19% (52,950) Black, 10.23% (44,445) Hispanic, 2.25% (9,785) Asian/Pacific Islander, 0.74% (3,215) Native American, and 2.93% (12,765) were of other races. When compared to White patients, ACIHM and SCD were significantly higher in Black patients with an adjusted odds ratio (aOR) of 1.13 (95% CI 1.01-1.26, p=0.025) and Hispanics (aOR of 1.17, 95% CI 1.04-1.33, p=0.01). Cerebral events were higher in Black patients (aOR of 1.35, 95%CI 1.23-1.49, p<0.001) and lower in Hispanics (aOR 0.87, 95%CI 0.77-0.98, p=0.03). Most racial groups were noted to have lower aORs of AF as compared to white patients.

Conclusions: The study noted that cerebral events were higher in black patients, and ACIHM and SCD were considerably higher in black and Hispanic patients. The findings underscore the need for equitable access to healthcare and further research regarding the epigenomic factors involved.



TH-PO871

Demographics and Trends of Uropathy-Associated Mortality in the United States, 1999-2020

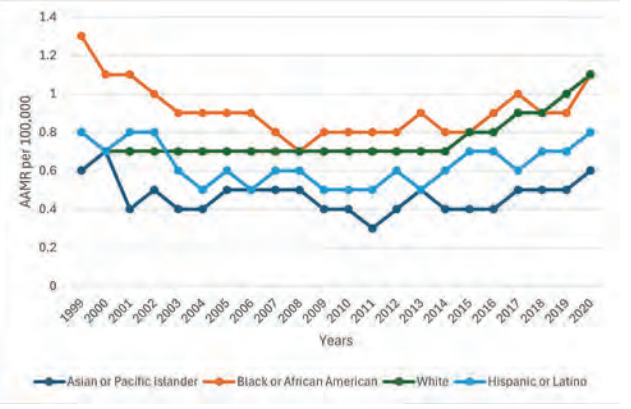
Badar U Din Shah,[1] Muhammad Talha Shaukat,[2] Wania Rehman,[2] Malik S. Hayat,[2] Muhammad Imaz Bhatti,[2] Aleenah Mohsin,[3] Aqeeb Ur Rehman.[4]
[1]Geisinger Medical Center, Danville, PA; [2]King Edward Medical University, Lahore, Pakistan; [3]Brown University, Providence, RI; [4]The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.

Background: Uropathy/ obstructive uropathy is a progressively growing cause of mortality and morbidity in the United States. In this study, we aimed to analyze trends of uropathy-related mortality in the US from 1999-2020. Understanding the epidemiology and trends would help guide in better management and consequently improve outcomes.

Methods: Data was extracted from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research (CDC WONDER) database from 1999-2020. Age-adjusted mortality rate (AAMR) per 100,000 individuals and annual percent changes (APC) with 95% Confidence Intervals (CI) were calculated using Joinpoint regression analysis. Data were also stratified to account for gender, race, locale and patient population.

Results: A total of 56,521 uropathy-related deaths were identified from 1999-2020. There was an overall decline in the AAMR from 1990 to 2011 followed by a gradual rise from 2011 to 2020 with an APC of -1.7457 and 5.6503 respectively. The analysis revealed significant disparities in mortality rates among different demographic groups. The mortality rates were found to be higher in male patients (AAPC:0.08% (95% CI -0.63 to 0.79)) and white/non-Hispanic patients (AAPC:1.5% (95 % CI 0.84 to 2.26)). There was no statistically significant difference between the mortality rates of metropolitan (AAPC:1.24% (95% CI 0.5845 to 1.8938) and non-metropolitan areas (AAPC: 1.29% (95% CI 0.33 to 2.45)). A higher proportion of uropathy-related mortality occurred in the Southern regions of the country and most deaths occurred among the in-patient population.

Conclusions: Though there has been an overall decline in mortality associated with uropathy from 1999-2011, a progressively rising trend from 2011 highlights the need for targeted research and interventions to address demographic disparities and regional healthcare inequities.



Uropathy associated mortality trends across different races

TH-PO872

Association of Intravenous vs. Oral Iron Therapy with Risk of Infectious Outcomes in Patients with CKD

Prabin Shrestha,[1] Keiichi Sumida,[1] Fridtjof Thomas,[1] Satya Surbhi,[1] Abu Mohd Naser,[2] Elani Streja,[3] Connie Rhee,[3] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[1,4] *[1]The University of Tennessee Health Science Center, Memphis, TN; [2]The University of Memphis, Memphis, TN; [3]University of California Irvine, Irvine, CA; [4]VA Memphis Healthcare System, Memphis, TN.*

Background: Iron replacement therapy (IRT) is a core component of anemia management in chronic kidney disease (CKD), but its long-term safety remains unclear. Intravenous (IV) IRT has been linked to increased risk of bacterial infections, but the evidence is inconclusive. We investigated the association of IV vs oral IRT with infectious hospitalization and infectious mortality.

Methods: In a national cohort of US Veterans, we identified 18,307 incident new users of IRT with eGFR <60 mL/min/1.73m^2 at baseline (N=17,428 on oral and 879 on IV iron). We used propensity score overlap weighting to account for differences in baseline characteristics associated with the use of IV vs oral iron. We examined the association of IV vs oral IRT with the incidence of the composite outcome of infectious hospitalization or infectious mortality in competing risk regression models, with non-infectious mortality as the competing event.

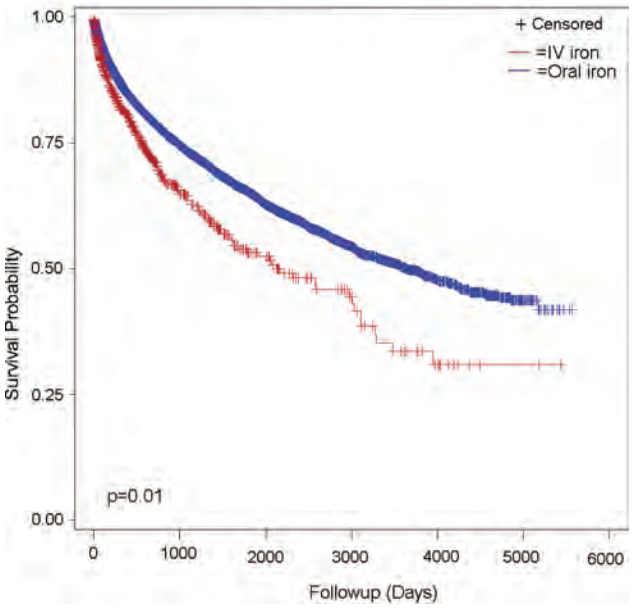
Results: The overall mean (SD) age was 73±10 years, 97% were male, 75% were white, and the baseline eGFR, hemoglobin and ferritin levels were 43±13 ml/min/1.73m^2, 10.6±1.8 gm/dL and 78 mcg/l (25th-75th pctl: 26-212), respectively. There were 4,580 cases of the composite infectious outcome (event rate **98.41**/1000PY; 95% CI **95.56-101.27**) over a median follow up of **2.12** years. IV IRT (vs oral IRT) was associated with higher crude risk of infection (Figure 1), but the association became statistically non-significant after PS weighting (subhazard ratio, 1.09; 95% CI 0.90-1.32; p-value 0.4) (Figure 1).

Conclusions: In this comparative effectiveness study, IV IRT was associated with similar risk of infectious outcomes as oral IRT.

Funding: Veterans Affairs Support

Composite outcome of infectious hospitalization or infectious mortality

Iron Therapy		PS overlap Weighting	
	Event rate per 1000PY (95% CI)	SHR (95% CI)	P-value
IV (N=879)	152.39 (133.39, 171.40)	1.09 (0.90, 1.32)	0.4
Oral (N=17,428)	94.47 (93.60, 99.34)	Referent	



TH-PO873

IHOPE: A Randomized, Open-Label, Positive-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Oral Iron Polysaccharide Complex in Patients on Hemodialysis

Renhua Lu,[1] Haijiao Jin,[1] Juan Cao,[2] Hua Li,[3] Xiaoxia Wang,[4] Yinghui Qi,[5] Qiu Li,[6] Xudong Cai,[7] Bin Song,[8] Na Li,[9] Lianglan Shen,[10] Lili Wang,[11] Xiaoping Wang,[12] Zhaohui Ni.[1] *[1]Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, China; [2]Taixing People's Hospital, Taixing, China; [3]Shaw Hospital Affiliated to Zhejiang University School of Medicine, Hangzhou, China; [4]Tongren Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [5]Shanghai Punan Hospital of Pudong NEW District, Shanghai, China; [6]The First People's Hospital of Shuangliu District, Chengdu, Chengdu, China; [7]Ningbo Traditional Chinese Medicine Hospital, Ningbo, China; [8]Deyang People's Hospital, Deyang, China; [9]Jinan Zhangqiu District People's Hospital, Jinan, China; [10]Nantong First People's Hospital, Nantong, China; [11]Shandong Province Qianfoshan Hospital, Jinan, China; [12]Central Hospital Affiliated to Shandong First Medical University, Jinan, China.*

Background: The IHOPE study (ChiCTR 2000031166) evaluated the efficacy and safety of iron polysaccharide complex (a novel oral trivalent iron preparation) in individuals receiving hemodialysis (HD) in China.

Methods: IHOPE was a randomized, open-label, positive-controlled, non-inferiority, multicenter study conducted at 12 sites across China. Participants aged 18-75 years who were receiving HD ≥3 months with hemoglobin (Hb) levels ≥100–<130g/L, transferrin saturation (TSAT) ≥20–≤50% or serum ferritin (SF) ≥100–≤500 μg/L, and who had received recombinant human erythropoietin or iron therapy within 12 weeks prior to enrollment, were recruited. Following a 4-week screening period, patients were randomized 1:1 to the experimental group (iron polysaccharide complex 150 mg twice daily orally) or a control group (iron sucrose injection 100 mg 2-weekly IV) for 24 weeks. The primary outcome was the TSAT at 12 weeks of treatment. Secondary outcomes included the TSAT and Hb after 24 weeks of treatment. Safety outcomes included recorded adverse events (AEs) and severe adverse events (SAEs). Non-inferiority for TSAT was assessed using confidence interval methods, with a non-inferiority margin of 7%.

Results: 193 adults of mean (SD) age 55.3 (11.66) years were randomized to the experimental group (n = 96) or control group (n = 97); 62.2% were male. At 12 weeks, TSAT in the expertimental group was 32.3% (95% CI 29.39–35.19%) demonstrating non-inferiority to the control group – in whom TSAT was 33.4% (95% CI 30.95–35.77%). At 24 weeks, TSAT values were 29.4% (95% CI 26.71–32.18%) in the experimental group and 32.6% (95% CI 29.68–35.45%) in the control group, again showing non-inferiority. Hb levels at 24 weeks were also comparable between the experimental and control groups (114.6 ± 11.81 g/L vs 117.4 ± 13.89 g/L; *P* = 0.166). AEs and SAEs were reported in 56.3% and 15.6% of patients, respectively in the experimental arm, and 47.4% and 13.4%, respectively in the control arm, with no new safety concerns identified.

Conclusions: Orally administered iron polysaccharide complex is an effective, well-tolerated treatment, demonstrating non-inferiority to intravenous iron sucrose in managing anemia among Chinese individuals receiving HD.

TH-PO874

Overexpression of the Iron Regulatory Hormone Erythroferrone Mitigates Anemia and Enhances Kidney Function in a Mouse Model of CKD

Brian Czaya, Elizabeta Nemeth, Tomas Ganz. *Center for Iron Disorders, David Geffin School of Medicine, University of California Los Angeles, Los Angeles, CA.*

Background: Most CKD patients develop anemia because of combined effects of relative erythropoietin deficiency, iron restriction caused by increased levels of the iron-regulatory hormone hepcidin, as well as absolute iron deficiency. Erythropoietin-stimulating agents (ESAs) and iron supplementation mitigate anemia in CKD, but patients often become hyporesponsive to the treatment, requiring higher doses of these drugs. Increasing ESA doses may heighten risks of thrombosis and cardiovascular mortality, highlighting the need for alternative strategies. Erythroferrone (ERFE) is a hormone produced by erythroblasts in response to EPO, and functions as a physiological suppressor of hepcidin to facilitate iron mobilization for erythropoiesis. In CKD, diminished marrow erythroblasts and inadequate EPO concentrations contribute to decreased ERFE production, likely further increasing hepcidin. Exploring the potential therapeutic use of ERFE in CKD, we tested the impact of augmented ERFE on systemic iron homeostasis, hypoxia, inflammation, and kidney function.

Methods: Transgenic mice with erythroid overexpression of ERFE (ERFE-Tg) have similar iron stores to wild-type littermates (WT) at weaning but become iron-overloaded as they age. To prevent early iron overload prior to CKD, we placed ERFE-Tg at weaning on low iron (4 ppm) diet for 4 weeks. WT mice were fed iron-replete diet. At 8 weeks of age, male ERFE-Tg and WT were then fed identical 0.2% adenine-rich diet containing 100 ppm iron for 8 weeks to induce CKD.

Results: At 16 weeks, both WT and ERFE-Tg developed CKD and anemia, but ERFE-Tg had higher hemoglobin, MCV and serum iron, as well as a lower ratio of serum hepcidin to liver iron content, indicating effective suppression of hepcidin by ERFE even in the setting of CKD. Systemic hypoxia as reflected by serum VEGF levels was also reduced in ERFE-Tg, indicating improved tissue oxygenation. Furthermore, although systemic and kidney inflammation (TNFa, IL1b, IL6) were similar between WT and ERFE-Tg, kidney function (BUN and serum creatinine) was less impaired in ERFE-Tg.

Conclusions: Our study demonstrates that despite chronic inflammation, ERFE overexpression in adenine-induced nephropathy improves CKD-associated anemia, hypoxia and kidney function. These data indicate that therapeutic augmentation of ERFE could provide multiple benefits in CKD.

Funding: NIDDK Support

TH-PO875

Effects of Interleukin-6 Inhibition with Clazakizumab on Anemia and Iron Parameters in Patients with Kidney Failure

Brendon L. Neuen,[1] Myles Wolf,[2] Benjamin P. Catanese,[2] Mark A. Heise,[4] Pierluigi Tricoci,[4] Anna Marie Chang,[4] Glenn M. Chertow.[3] *[1]The George Institute for Global Health, Sydney, NSW, Australia; [2]Duke University School of Medicine, Durham, NC; [3]Stanford University School of Medicine, Stanford, CA; [4]CSL Behring LLC, King of Prussia, PA.*

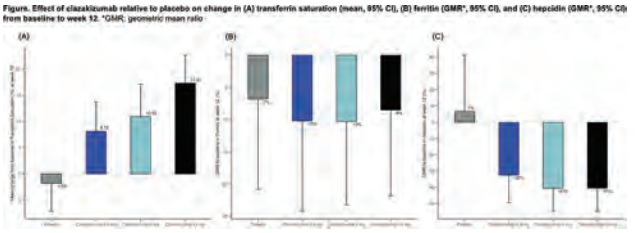
Background: Inflammation contributes to anemia and erythropoietin stimulating agent resistance in patients with kidney failure. Clazakizumab is a high affinity humanized monoclonal antibody that targets the interleukin-6 (IL-6) ligand and inhibits downstream IL-6 function. We recently reported an approximate 90% reduction in high-sensitivity C-reactive protein (hs-CRP) in patients receiving dialysis with a history of cardiovascular disease and/or diabetes. We sought to evaluate the effect of clazakizumab on anemia and iron parameters.

Methods: The Phase 2b component of the POSIBIL$_6$ESKD Phase 2b/3 trial evaluated the effect of clazakizumab (2.5mg, 5mg, 10mg) or placebo administered every 4 weeks. The primary efficacy endpoint was the placebo-adjusted change in hs-CRP at 12 weeks. We prespecified as secondary endpoints the effects of clazakizumab on hemoglobin (Hb), iron parameters, and hepcidin, using mixed effects models for repeated measures.

Results: Among 127 participants, overall mean ± SD Hb and TSAT, median (25%, 75% range) ferritin and hepcidin were 10.7 ± 1.4 g/dL, 31 ± 11.7%, 1267 (735, 1598) μg/L and 232 (150, 306) ng/mL, respectively. The mean increase in Hb was 0.6 ± 1.5, 1.0 ± 1.3, 1.0 ± 1.4 g/dL at 12 weeks relative to baseline in the 2.5, 5, and 10 mg clazakizumab groups, respectively, compared with 0.4 ± 1.3 g/dL with placebo. These differences were not statistically significant. Clazakizumab significantly increased transferrin saturation and reduced hepcidin across all studied doses versus placebo, and had no clear effect on ferritin (**Figure**).

Conclusions: Through anti-IL6 effects, clazakizumab may improve iron utilization and contribute to anemia correction in patients receiving dialysis. Larger and longer-term data from the ongoing Phase 3 study will provide additional insights.

Funding: Commercial Support - CSL Behring



TH-PO876

Impact of Changes in Hemoglobin on Health-Related Quality of Life in Dialysis Patients

Thomas S. van Lieshout,[1,2] Esmee Driehuis,[1,3] Osman Mahic,[3,4] Brigit C. van Jaarsveld,[1] Alferso C. Abrahams.[3] DOMESTICO Study Group.
[1]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands; [2]Noordwest Ziekenhuisgroep, Alkmaar, Netherlands; [3]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [4]Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde, Utrecht, Netherlands.

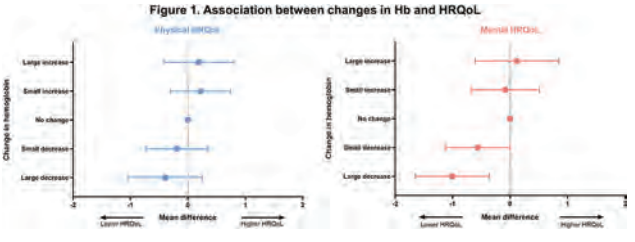
Background: Anemia is a common complication among dialysis patients and has a negative impact on health-related quality of life (HRQoL). Higher levels of hemoglobin (Hb) are associated with better HRQoL but also with an increased risk of adverse events like stroke. The optimal target level for Hb remains subject of debate and an individual approach is proposed. To develop this, changes in Hb are of additional importance. However, the impact of changes in Hb levels on HRQoL are unclear. Therefore, we investigate the impact of changes in Hb on HRQoL during the first 24 months of dialysis.

Methods: Dialysis patients (n=1718), included in the prospective Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO), were studied. Change in Hb was categorized into no change (-0.5; 0.5 g/dL), small increase (0.5; 2.0 g/dL), large increase (> 2.0 g/dL), small decrease (-2.0; -0.5 g/dL), and large decrease (<-2.0 g/dL). HRQoL was measured with the 12-item Short Form Health Survey (SF-12), containing two summary scores, reflecting physical and mental HRQoL. Data were analyzed using linear mixed models and generalized linear models, both adjusted for confounders.

Results: Mean age at initiation was 63.8 years (SD 14.5) and 75.3% of the patients started with hemodialysis. The mean Hb level during the first 24 months of dialysis was 10.8 g/dL (SD 1.6). Patients with an increase or decrease in Hb showed no difference in physical HRQoL compared to patients with stable Hb over time (Figure 1). A large decrease in Hb was associated with lower mental HRQoL over time, with a mean difference of -1.01 (95% CI -1.65;-0.36). An increase of Hb did not impact mental HRQoL (Figure 1).

Conclusions: This study shows that a decrease in Hb has a negative impact on mental HRQoL compared to no change in Hb. Hb changes were not associated with physical HRQoL. These findings indicate that physicians should not focus on increasing Hb levels but rather on preventing a decrease when it comes to HRQoL. Such an approach could help in adjusting present guidelines with the goal to induce less adverse events and improve cost-effectiveness.

Figure 1. Association between changes in Hb and HRQoL



TH-PO877

Associations of Anemia and Iron Parameters with Fatigue in Persons with and without Kidney Diseases

Lucile Parker Gregg,[1,2] Christine Vu,[3] Aaron R. Perkins,[3] Hui Yang,[3] Sankar D. Navaneethan,[1,4] Carlos A. Alvarez.[3] *[1]Baylor College of Medicine, Houston, TX; [2]VA Center for Innovations in Quality Effectiveness and Safety, Houston, TX; [3]Texas Tech University Health Sciences Center, Dallas, TX; [4]Michael E DeBakey VA Medical Center, Houston, TX.*

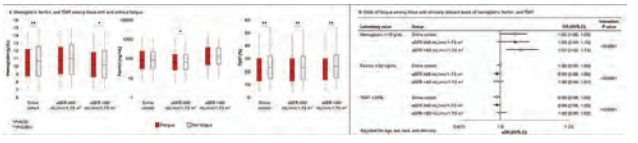
Background: Low estimated glomerular filtration rate (eGFR) is associated with anemia and absolute and functional iron deficiency. Hemoglobin and biomarkers of iron stores are associated with fatigue, but it is unclear if an eGFR <60 mL/min/1.73 m^2 modifies these relationships.

Methods: Using data from the National Institutes of Health All of Us cohort, we identified individuals who answered the self-reported fatigue item over the last 7 days at cohort enrollment, with fatigue defined as any fatigue (*i.e.*, mild, moderate, severe, or very severe) *vs.* none. We limited the sample to individuals who had a hemoglobin, ferritin, and/or transferrin saturation (TSAT) level within 1 year of cohort enrollment. Ferritin <30 ng/mL (consistent with KDIGO guidelines) or TSAT <20% identified patients with likely absolute iron deficiency. Multivariable logistic regression evaluated the associations of hemoglobin, ferritin, and TSAT levels with fatigue, adjusting for age, sex, race, and ethnicity, with multiplicative interaction terms to assess if an eGFR <60 mL/min/1.73 m^2 modified these associations.

Results: Of 19,310 individuals included in the cohort, fatigue was present in 16,587 (86%). Compared to those without fatigue, patients with fatigue had lower median (IQR) hemoglobin, 10.5 (8.8, 12.2) *vs.* 10.7 (8.8, 12.6) g/dL, *P*<.0001, and lower TSAT, 21 (13, 30) *vs.* 23 (15, 32), *P*<.0001 (**Figure A**). Those with fatigue were also more likely to have hemoglobin <10 g/dL (40% *vs.* 31%, *P*<.0001), ferritin <30 ng/mL (32% *vs.* 29%, *P*=.003), and TSAT <20% (56% *vs.* 48%, *P*<.0001). Fatigue was present in 7,164 (85%) of those with an eGFR ≥60 and 5,243 (86%) with an eGFR <60 mL/min/1.73 m^2. Hemoglobin <10 g/dL was associated with higher odds of fatigue in those with an eGFR <60 but not in those with an eGFR ≥60 mL/min/1.73 m^2, interaction *P*<.0001 (**Figure B**).

Conclusions: Hemoglobin <10 g/dL was associated with fatigue in those with an eGFR<60 but not ≥60 mL/min/1.73 m^2, possibly related to differences in the physiology of oxygen delivery and utilization in kidney disease. The presence of kidney disease limits the use of ferritin and TSAT levels to identify iron deficiency and may affect these associations.

Funding: Veterans Affairs Support



TH-PO878

Exploring the Interplay of Inflammation, Eryptosis, and Anemia in ESKD

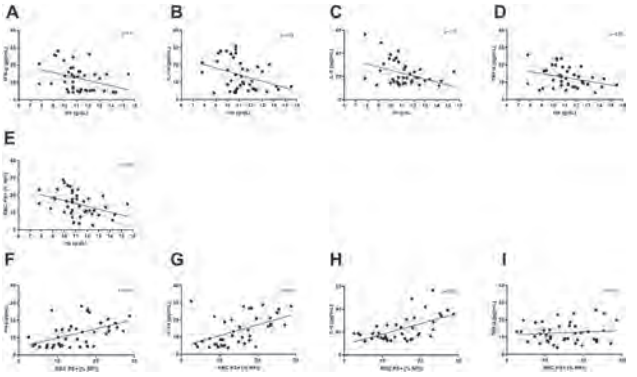
Andrea N. Moreno-Amaral,[1] Erika S. Dias,[1] Júlia B. Monte-Alegre,[1] Beatriz Akemi K. Van Spitzenbergen,[1] Gabriela B. Andrade,[1] Vitor A. Brugnolo-Santos,[1] Yuri D. Ozogovski,[1] Gabriela Ferreira Dias,[2] Nadja Grobe,[2] Peter Kotanko,[2] Thyago P. Moraes.[1,3] *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Renal Research Institute, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Most ESKD patients have some degree of chronic inflammation, which heightens infection risk, elevates pro-inflammatory cytokines, and augments uremic solute accumulation. These events could exacerbate anemia by premature death (eryptosis) of red blood cells (RBC). This study aimed to explore the link between eryptosis, cytokines, and hemoglobin levels (HB) in ESKD dialytic patients.

Methods: Serum from 41 ESKD dialytic patients was analyzed using ELISA for IL-6, IFN-g, TNF-a, and IL-1b. RBC from peripheral blood were annexin-V labeled to assess phosphatidylserine (PS) expression. A nonparametric Spearman test was used to analyze the correlation between the variables, while simple linear regression was employed to quantify the slope and intercept of these relationships.

Results: Figure 1 – As expected, Hb levels correlated inversely with the cytokines INF-g (A, p<0.01) and IL-1b (B, p<0.03) but not with IL-6 (C, p<0.07) and TNF-a (D, p<0.06). Higher PS expression was correlated with lower Hb levels (E, p<0.001). Additionally, significant inverse correlations were observed between PS expression and IFN-g (F, p<0.001), IL-1b (G, p<0.001), and IL-6 (H, p<0.001). However, no significant correlation was found between PS exposure and TNF-a (I, p<0.55).

Conclusions: The results showed a link between low Hb levels and high cytokine concentrations, connecting inflammation with anemia. A significant inverse correlation was also seen between high PS expression and low Hb levels and between PS expression and the cytokines INF-g, IL-1b, and IL-6. These findings imply an association between eryptosis, renal anemia, and inflammation in these patients. This underscores the importance of addressing inflammation and eryptosis to manage anemia, potentially reshaping clinical approaches.



TH-PO879

Association of Erythropoietin Resistance with Sleep Apnea Syndrome and Prognosis in Patients on Maintenance Hemodialysis

Yasuhiro Mochida, Kunihiro Ishioka, Machiko Oka, Hidekazu Moriya, Takayasu Ohtake, Yusuke Tsukamoto, Sumi Hidaka. *Shonan Kamakura Sogo Byoin, Kamakura, Japan.*

Background: Nocturnal intermitted hypoxia with sleep apnea syndrome (SAS) is known to stimulate erythropoietin (EPO) production and is associated with prognosis in populations without kidney dysfunction. However, it remains unresolved whether SAS severity is related to EPO production, EPO resistance, and cardiovascular events in patients with end stage kidney disease. In this study, we investigated the association between SAS severity and EPO resistance in hemodialysis patients.

Methods: We investigated the association between the nocturnal 3% oxygen desaturation index (3%ODI) and the EPO resistance index (ERI) in 134 hemodialysis patients who underwent overnight pulse oximetry at Shonan Kamakura General Hospital from December 2012 to April 2013. After evaluating overnight pulse oximetry, these patients were divided into 4 groups (low or high 3% ODI and ERI levels) and followed up to investigate major adverse cardiovascular events (MACEs) for about 8 years until April 2021. MACEs included cardiac events, cerebrovascular events, peripheral artery disease events, and cardiovascular death. The association between 3% ODI and ERI was investigated by multiple linear regression analysis with covariants: age, sex, duration of hemodialysis, history of diabetes mellitus, systolic blood pressure, and serum of albumin, c-reactive protein, beta-2 microglobulin, phosphate, and parathyroid hormone. The cumulative incidence of MACEs across the groups was assessed using the log-rank test for trend with Kaplan-Meier curve.

Results: The baseline characteristics of 134 patients were as follows: the median age was 67 years, 37.3% were diabetic, and the median duration of HD was 69 months, median 3% ODI was 11.3 %, median ERI was 8.94. 3% ODI was independently associated with ERI (beta co-efficient = -1.2%, p=0.002) by multiple linear regression analysis. The Highest incidence of MACE was shown in the group with high 3% ODI and high ERI compared with low 3% ODI and low ERI (p for trend=0.01, hazard ratio=2.43).

Conclusions: Hemodialysis patients with hypoxemia were associated with lower ERI than patients without hypoxemia. However, it should be noted that patients with nocturnal hypoxemia had a higher likelihood of developing cardiovascular disorders, especially in those with high EPO resistance.

TH-PO880

Reduced Flippase Activity in the Early Life of Mature Erythrocytes Is Associated with Their Shortened Lifespan in Renal Anemia

Momoko Seki, Nobuto Arashiki, Shun Manabe, Hiroshi Kataoka, Ken Tsuchiya, Junichi Hoshino, Fumio Nakamura. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Background: The lifespan of mature erythrocytes in renal anemia patients is shortened (approximately 70 days) compared to that of healthy individuals (120 days), but its pathogenesis is unclear. Previously, we reported that in healthy senescent erythrocytes decreased intracellular K^+ and ATP levels, and flippase molecule ATP11C, lead to decreased flippase activity, resulting in increased phosphatidylserine (PS) exposure, a removal sign for macrophages (Seki M, 2020). Our recent investigations have revealed that senescent erythrocytes from renal anemia patients also exhibited decreased flippase activity, leading to PS exposure, mainly due to K^+ loss. This study demonstrated that senescent erythrocytes in patients were younger than the senescent erythrocytes in healthy individuals. We additionally conducted a quantitative proteome analysis of the membrane proteins obtained from young and senescent erythrocytes of patients to identify candidates involved in K^+ loss.

Methods: Erythrocytes from patients undergoing maintenance hemodialysis and from healthy volunteers were fractionated into young (light) and senescent (heavy) populations using a Percoll-density gradient according to our previous report. HbA1c was measured in fractionated erythrocytes as a marker of their age. We conducted a quantitative MS/MS using the Tandem Mass Tagging labeling system on membrane proteins from young and senescent erythrocytes of renal anemia patients (n=3).

Results: Although the number of senescent erythrocytes in patients bore a similarity to that of healthy humans, HbA1c levels in the heavy fractions of patients were lower than levels in healthy individuals. The proteomic analysis of patients' membranes presented oxidation-modified Transient Receptor Potential Melastatin 2 (TRPM2), an oxidation-sensitive calcium channel, and a sufficient amount of Piezo1, a mechanosensitive calcium channel. Both are potent contributors to activate calcium-dependent K^+ leakage (Gardos effect).

Conclusions: In the early life of mature erythrocytes in renal anemia patients, reduced flippase activity causes PS exposure due to K^+ loss. We identified two responsible candidates for K^+ leakage, TRPM2 and Piezo1, which could serve as novel therapeutic targets for renal anemia.

Funding: Other NIH Support - Japan society for the promotion of science

TH-PO881

Mitochondrial Dysfunction in FOXD1 Lineage Cells Has a Key Role in the Development of Anemia Associated with CKD

Hanako Kobayashi,[1,2] Volker H. Haase.[1,2] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]VA Tennessee Valley Healthcare System, Nashville, TN.*

Background: Anemia is one of the common complications of chronic kidney disease (CKD) diminishing quality of life and increasing cardiovascular mobility and mortality in affected patients. Inadequate production of renal erythropoietin (EPO) is the main cause of CKD-associated anemia. EPO is produced in perivascular fibroblast-like cells which are derived from FOXD1 lineage cells and are regulated by hypoxia-inducible factor-2 (HIF-2). Despite recent advances in understanding EPO regulation, the mechanisms for the loss of EPO production are ill-defined. Perivascular fibroblast-like cells are viewed as quiescent; however, they can rapidly proliferate, migrate, and produce extracellular matrix in kidney disease. The role of metabolic regulation in this process is only incompletely understood. Mitochondria (mt) are essential for cellular metabolism, and mt dysfunction is a common feature of acute and chronic kidney diseases. However, the function of mt in perivascular fibroblast-like cells is largely unknown.

Methods: To investigate mt function in renal stroma, we generated and analyzed mice with interstitial cell-specific deficiency of mt transcription factor A (TFAM) using *FoxD1-cre* transgenic mice (*FoxD1-Tfam*$^{-/-}$). TFAM is required for the transcription of mt genes and mt DNA replication and is thus essential for the maintenance of mt mass and function.

Results: We demonstrate that suppression of mt mass in renal stroma results in progressive renal failure, characterized by elevated BUN, tubulointerstitial fibrosis, and glomerulosclerosis. Single cell RNA sequencing of *FoxD1-Tfam*$^{-/-}$ interstitial cells demonstrated increased expression of genes involved in amino acid metabolism and ATF4-mediated stress responses. Furthermore, *FoxD1-Tfam*$^{-/-}$ mice developed anemia, characterized by relative EPO deficiency in response to hypoxia or treatment with HIF stabilizing agents. This was due to the inability to stabilize HIF-2α in *Tfam*$^{-/-}$ stroma.

Conclusions: In summary, we have developed a novel genetic mouse model of slowly progressive CKD-associated anemia that mimics human disease. Our data suggest that mt in renal stroma play a critical role for the maintenance of normal kidney function and homeostasis.

Funding: NIDDK Support

TH-PO882

Protein-Bound Uremic Solute 3-Carboxy-4-Methyl-5-Propyl-2-Furanpropanoic Acid (CMPF) Induces Eryptosis through a Piezo1-Dependent Pathway

Beatriz Akemi K. Van Spitzenbergen,[1] Erika S. Dias,[1] Júlia B. Monte-Alegre,[1] Gabriela B. Andrade,[1] Vitor A. Brugnolo-Santos,[1] Yuri D. Ozogovski,[1] Gabriela Ferreira Dias,[2] Nadja Grobe,[2] Peter Kotanko,[2,3] Andrea N. Moreno-Amaral.[1] *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Renal Research Institute, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The uremic solute 3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF) exhibits structural resemblances with Jedi1, a known chemical activator of the mechanosensitive ion channel Piezo1. Therefore, we hypothesized that activation of Piezo1 on red blood cells (RBC) may promote eryptosis, i.e., premature RBC death in uremia (Kotanko, FASEB Bioadv. 2022). Our aim was to further probe into that hypothesis.

Methods: Isolated RBC from six healthy individuals were either pre-treated or left untreated with the Piezo1 inhibitor GsMTx-4 (5 min). This step was followed by 30 min incubation with CMPF or Jedi1 (both 87 mM). Subsequently, we stimulated

Piezo1 by challenging RBC for 5 min with either hypotonic (NaCl 6g/L) or isotonic (9 g/L) saline. After centrifugation, RBC pellets were stained with Annexin-V to assess phosphatidylserine (PS) exposure on the RBC membrane and with Fluo-4AM to quantify intracellular calcium (icCa2+). Both signals report eryptosis pathways were measured by flow cytometry.

Results: Table 1: When challenged with hypotonic saline, both Jedi1 and CMPF increased PS exposure and $icCa^{2+}$. In contrast, in the presence of isotonic saline, CMPF, but not Jedi1, increased PS and $icCa^{2+}$. These effects were prevented by 5-min pre-incubation with GsMTx-4.

Conclusions: Our results support the notion that CMPF, a uremic toxin, activates Piezo1 on RBC and, through that pathway, promotes eryptosis. Further investigation is warranted to determine whether and to what extent this effect aggravates anemia in kidney patients.

Experimental Condition	NaCl 6 g/L		NaCl 9 g/L	
	% PS exposure (MFI)	% icCa2+ (MFI)	% PS exposure (MFI)	% icCa2+ (MFI)
Control (DMSO 0.12% in PBS+4% HSA)	5.3 ± 1.4	21.1 ± 1.8	3.8 ± 1.1	14.1 ± 3.1
Jedi 1 (87 µM)	12.4 ± 4.4**	37.2 ± 8.2**	6.8 ± 1.2	21.8 ± 5.2
GsMTx-4 (2 µM) + Jedi 1 (87 µM)	5.6 ± 1.2	21.4 ± 6.3	5 ± 1.1	14.1 ± 3.3
CMPF (87 µM)	17.8 ± 5.7***	40.5 ± 8.1***	13.2 ± 3.3**	24.2 ± 4.7**
GsMTx-4 (2 µM) + CMPF (87 µM)	5.5 ± 1.2	19.1 ± 6.5	4.8 ± 1.3	15.4 ± 3.4

MFI = Mean Fluorescence Intensity; HAS = Human Albumin Serum, **p<0.01 versus Control. ***p<0.001 versus Control.

TH-PO883

Prescribing Practices of Erythropoiesis-Stimulating Agents in Dialysis-Dependent and Nondialysis-Dependent CKD

Rammdeep Saini,[1,2] Keigan More,[1,2] Jo-Anne S. Wilson,[1,2] David Clark,[1,2] Amanda J. Vinson,[1,2] Karthik K. Tennankore.[1,2] *[1]Dalhousie University, Halifax, NS, Canada; [2]Nova Scotia Health Authority, Halifax, NS, Canada.*

Background: Anemia is a common complication of CKD. Erythropoiesis-stimulating agents (ESAs) have been used to treat CKD-associated anemia but are associated with increased risk of stroke, cancer progression and recurrence. There are no clear guidelines on ESA use for CKD patients with stroke, active or prior malignancy. Our objective was to assess the practice patterns and hemoglobin targets of Canadian Nephrologists and other Nephrology prescribers for ESA use in CKD patients with stroke or malignancy.

Methods: We developed a cross-sectional, online survey to assess the anemia practice patterns of Canadian nephrologists, nephrology trainees, pharmacists and nurse practitioners. Survey design was done using a modified-Delphi process. The survey was nationally disseminated to members of the Canadian Society of Nephrology from March to May, 2024. Descriptive statistics were used to characterize hemoglobin targets and perceptions of "comfort" in prescribing across practitioners.

Results: Survey response rate is 16.3% (88/540). In general CKD patients, a hemoglobin target of 95-115 g/L was most common (50.0%). In CKD patients with history of stroke, 90-105 g/L and 95-115 g/L were the most common targets (both 27.3%). In CKD patients with active or previous malignancy, 90-105 g/L was the most common target (27.3% and 25.0%, respectively). Figure-1 shows Likert scale ratings for ESA prescribing comfort in different CKD populations. Differences were observed for comfort in prescribing. Final survey results will be available in June 2024.

Conclusions: This study highlights that there are a wide range of hemoglobin targets that are used, especially among those with active or prior malignancy and informs the need for better evidence for hemoglobin targets among CKD patients with malignancy or stroke.

Question	Median Rating	Interquartile Range	P
I am comfortable with prescribing ESAs in patients with dialysis dependent or non-dialysis dependent CKD	5	4-5	–
I am comfortable with prescribing ESAs in dialysis dependent or non-dialysis dependent CKD patients with history of stroke	4	3-4	<0.001
I am comfortable with prescribing ESAs in dialysis dependent or non-dialysis dependent CKD patients with an active malignancy	3	2-4	<0.001
I am comfortable with prescribing ESAs in dialysis dependent or non-dialysis dependent CKD patients with history of previous cancer	4	3-4	<0.001

Figure-1: Likert Scale Ratings for ESA Prescriber Comfort in CKD Populations. Likert Rating: 1-Strongly Disagree, 2-Disagree, 3-Neither Agree nor Disagree, 4-Agree, 5-Strongly Agree. Comfort levels between general CKD patients versus other populations were compared.

TH-PO884

Association of Erythropoietin Resistance Index with Interleukin-6 among Patients Undergoing Conventional and Extended-Hours Haemodialysis

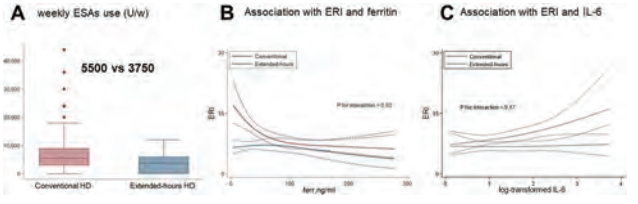
Nobuhiro Nishibori, Takumi Yamada, Masaki Okazaki, Takahiro Imaizumi, Shoichi Maruyama. *Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Nagoya, Japan.*

Background: Extended-hours hemodialysis (HD) has better clinical outcomes than conventional HD. In patients with maintenance HD, high level of the erythropoietin resistance index (ERI) is known as the factor of high mortality. Previous studies have reported that Extended-hours HD is associated with lower ERI levels, but the mechanism is unkouwn.

Methods: We performed a cross-sectional study of patients with extended-hours HD or conventional HD between January and March 2020. ERI was calculated by dividing weekly erythropoiesis-stimulating agents (ESAs) use by body weight (BW, kg) and hemoglobin (Hb, g/dL). Blood interleukin-6 (IL-6) levels were measured by ELISA kit (HS600C, R&D). Linear and non-linear associations between ERI, ferritin and IL-6 levels were examined across dialysis modalities.

Results: A total of 364 participants (176 with extended-hours HD and 188 with conventional HD) were included in the analysis. The mean age was 66 vs 72 years, percentage of men was 68 vs 62%, and the mean Hb was 11.1 vs 11.2 g/dL. Extended-hours HD was associated with lower weekly ESAs use (FigureA). Multivariable linear regression analysis showed that extended-hours HD was associated with lower weekly ESAs use; -3800 U/week (95% confidence interval (CI); -5300 to -2300). In Figure B, restricted cubic spline (RCS) function indicated that extended-hours HD was associated with lower ERI, especially in hypoferritinic conditions (*P* for interaction <0.01). In conventional HD group, ERI is increased with elevation of IL-6 levels, on the other hans, in extended-hours HD group, ERI appears to remain unchanged despite increased IL-6 levels (FigureC).

Conclusions: The patients with extended-hours HD had lower ERI than those with the conventional HD group, especially in hypoferritinic conditions. In extended-hours HD group, higher IL-6 levels tended not to be associated with higher ERIs, which may contribute to better clinical outcomes in patients on extended-hours HD.



TH-PO885

Role of Iron Sequestration in the Development of Anemia of CKD: Implications for Treatment Resistance

Chantalle A. Campbell, Jade Matthews balcombe, Hannah G. Federman, Heba Elsayed, Kanza Baqai, Edwin Patiño, Mary E. Choi, Oleh M. Akchurin. *Weill Cornell Medicine, New York, NY.*

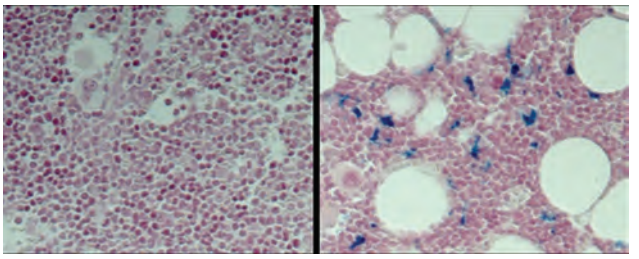
Background: Anemia is a common complication of CKD, and iron supplementation is the recommended first line of therapy. The efficacy of oral iron therapy in CKD is unsatisfactory, likely owing, at least in part, to elevated hepcidin. Hepcidin induction might limit iron availability for erythropoiesis through either reduced intestinal absorption or by enhanced sequestration. However, the relative contribution of iron malabsorption vs. sequestration to anemia of CKD remains unclear.

Methods: CKD was induced in 8-week old wild type (WT) and macrophage-specific (*LysM*-Cre) ferroportin (*Fpt*) knockout (KO) mice using a 0.2% adenine diet for 8 weeks. We used oral carbonyl iron, iron sulfate, and iron citrate in doses comparable to those used in CKD patients. Iron content was quantified in the bone marrow, spleen, and liver by staining, a bathophenanthroline-based colorimetric method, and by MRI. Tissue ferritin was assessed by immunoblotting.

Results: WT CKD mice developed anemia and their serum hepcidin was 3-fold higher than in healthy mice. There was a marked increase in the number of iron-positive cells in the bone marrow (Fig.) and a 2-fold increase in the spleen of WT CKD mice compared to healthy mice. Liver ferritin was induced in untreated WT CKD mice. Macrophage-specific *Fpt* KO CKD mice had more severe anemia and further increase of iron stores in the bone marrow, spleen, and liver, compared to WT CKD mice. Oral iron supplementation improved hemoglobin in WT CKD mice by 20.8% but increased hepcidin by 1.5-fold, spleen iron content by 74.8% and liver iron content by 12.5-fold compared to untreated CKD mice.

Conclusions: In this model of CKD, we observed iron sequestration in the bone marrow, spleen, and liver in the absence of iron therapy. Oral iron supplementation further enhanced iron sequestration, disproportionate to the alleviation of anemia in CKD mice. Sequestered iron remained partially mobilizable via incompletely suppressed ferroportin.

Funding: NIDDK Support, Private Foundation Support



Bone marrow iron staining by Perls Prussian blue in healthy mice and in mice with untreated CKD after 8 weeks of control or adenine diet.

TH-PO886

Iron Sequestration in Kidney Macrophages Is Essential for Protecting Proximal Tubules from Iron Overload during Iron Therapy in CKD

Hannah G. Federman,[1] Chantalle A. Campbell,[1] Heba Elsayed,[1] Divya Bhatia,[1] Mary E. Choi,[1] Francesca Vinchi,[2] Oleh M. Akchurin.[1] *[1]Weill Cornell Medicine, New York, NY; [2]New York Blood Center, New York, NY.*

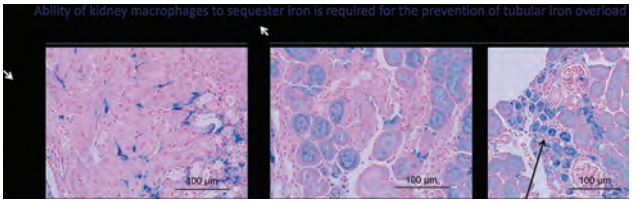
Background: Chronic kidney disease (CKD) affects 10-15% of the adult U.S. population. Iron supplementation is very common in patients with CKD, and may lead to organ iron overload, rising concerns about nephrotoxic effects of iron. However, intrarenal iron trafficking during iron supplementation in CKD has not been delineated, making it difficult to account for renal effects of iron in CKD patients.

Methods: CKD was induced in 8-week old wild type (WT) and myeloid-specific (*LysM*-Cre) ferritin heavy chain knockout mice (*Fth1*$^{M\phi}$-KO) by 8 weeks of adenine diet. Iron dextran was administered intraperitoneally once a week, 500 mg/kg/dose. Kidney tissues were assessed by histology as well as processed for single cell suspensions via collagenase digestion immediately upon harvest, and analyzed by flow cytometry. Furthermore, proximal tubular epithelial cells (pTEC) and kidney macrophages were isolated using CD133 and CD11b magnetic microbeads.

Results: In pTEC of untreated WT CKD mice, ferritin heavy and light chain proteins were induced while labile iron pool was reduced, compared to healthy WT mice. Expression of transferrin receptor 1 (TfR1), a major iron importer, was reduced in pTEC of untreated CKD mice compared to controls. Iron suppementation resulted in iron accumulation within kidney macrophages in WT CKD mice while sparing pTEC, as assessed by Perls iron stain of kidney tissues and sorted kidney macrophages. In *Fth1*$^{M\phi}$-KO CKD mice supplementaed with iron, the distribution of iron within the kidney was vastly different from the WT: iron was accumulating primarily in pTEC, with especially massive iron content seen within atrophic tubulues in the areas of fibrosis (Figure).

Conclusions: Kidney macrophages are indespensable for preventing tubular iron overload during iron supplementation in CKD. Modifying iron-scavenging ability of kidney macrophages may represent a novel renoprotective strategy in CKD.

Funding: NIDDK Support



Iron accumulation in wild type and myeloid-specific ferritin heavy chain knockout mice with adenine-induced CKD treated with iron dextran supplementation.

TH-PO887

Safety and Effectiveness of Erythropoietin vs. Roxadustat for Anemia in Hemodialysis-Dependent Peridialytic CKD Patients: An Observational, Retrospective, Matched, Real-World Study

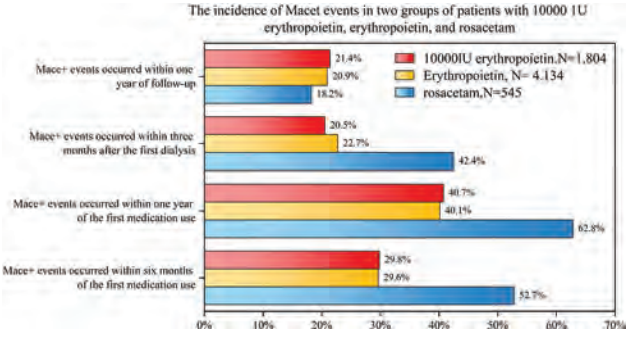
Li H. Wang. *The Second Hospital of Tianjin Medical University, Tianjin, China.*

Background: Current evidence remains elusive about the efficacy and safety of erythropoietin *versus* roxadustat for anemia treatment in the peridialytic period.

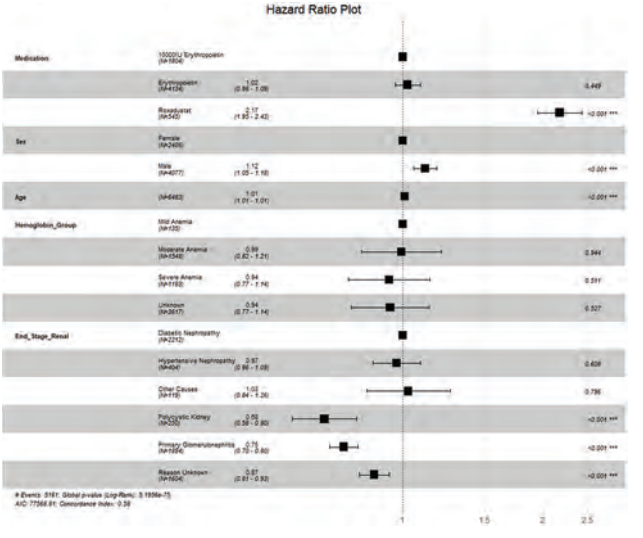
Methods: This study extracted longitudinal data from a metropolis-wide hospitals-based database Tianjin Healthcare and Medical Big Data Platform. Subjects with CKD stage G5 and anemia (hemoglobin <100 g/L) who had received treatment with erythropoietin or roxadustat between January 1, 2015 and December 31, 2021.

Results: Of 40,324 patients who were included and treated with erythropoietin and erythropoietin 10,000 IU were matched to 545 patients treated with roxadustat. Significant differences were observed in the rates of MACE+ events as well as cardiocerebrovascular events.

Conclusions: Erythropoietin, particularly erythropoietin 10,000 IU, improved hemoglobin response and exhibited better cardiovascular safety, as compared with roxadustat, in patients with anemia who had hemodialysis-dependent CKD in the peridialytic period.



The rates of MACE+ events within 6 and 12 months of treatment initiation, within 3 months of hemodialysis initiation and during 12 months of follow-up among patients who were treated with roxadustat, erythropoietin, or erythropoietin 10,000 IU



COX regression analysis showed that receipt of roxadustat was associated with an approximately two-fold increase in the risk of MACE+ *versus* erythropoietin 10,000 IU (HR=2.17, 95% CI 1.95-2.43; *P*<0.001).

TH-PO888

Pegmolesatide for the Treatment of Anemia in Patients with CKD Undergoing Dialysis: Insights from a Randomized Active-Controlled Phase 3 Study

Jianghua Chen,[1] Linghui Zhou,[2] Minghao Guo,[3] Hongguang Zheng,[4] Deqiong Xie,[5] Zhizhen Hu,[6] Weili Luo.[6] *[1]The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [2]The First Affiliated Hospital of Xiamen University, Xiamen, China; [3]The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China; [4]General Hospital of Northern Theater Command, Shenyang, China; [5]Second People's Hospital of Yibin, Yibin, China; [6]Jiangsu Hansoh Pharmaceutical Co Ltd, Lianyungang, China.*

Background: Pegmolesatide, a novel long-acting pegylated erythropoietin mimetic peptide, has proved comparable efficacy and safety with epoetin alfa based on a randomized, multicenter, open-label, non-inferiority phase 3 study (NCT03902691). This post-hoc analysis aims to explore further benefits of pegmolesatide for the treatment of anemia patients on dialysis.

Methods: A total of 372 chronic kidney disease (CKD) patients undergoing dialysis were randomized (2:1) to receive pegmolesatide or epoetin alfa for 52 weeks. Post-hoc analysis was conducted to assess the proportions of patients across various hemoglobin (Hb) ranges during the efficacy evaluation period.

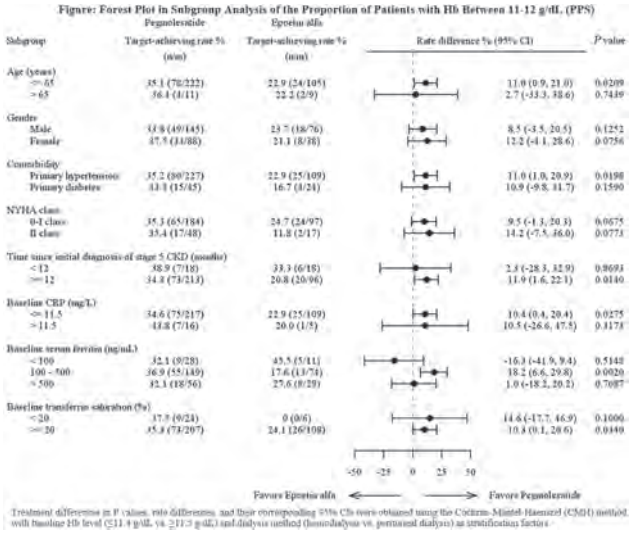
Results: A larger proportion of patients on pegmolesatide achieved mean Hb≥11 g/dL compared to those on epoetin alfa (63.9% vs. 44.7%, *P*=0.0003). More patients receiving

pegmolesatide maintained their Hb levels within the target ranges of 11-12 g/dL (35.2% vs. 22.8%, *P*=0.0164) and 11-13 g/dL (57.5% vs. 36.8%, *P*=0.0002) compared to those receiving epoetin alfa. In subgroups of baseline characteristics with age ≤65 yrs., primary hypertension, stage 5 CKD≥12 months, CRP≤11.5 mg/L, serum ferritin between 100-500 ng/mL, and transferrin saturation≥20%, pegmolesatide also showed greater effect in maintaining Hb levels between 11-12 g/dL (Figure). Similar findings were observed in these subgroups for the target range of 11-13 g/dL. The incidences of treatment related adverse events of particular interest, including hypertension (4.5% vs. 6.5%), hepatotoxicity (0.8% vs. 2.4%) and hyperkalaemia (2.4% vs. 4.0%), were numerically lower in the pegmolesatide group.

Conclusions: Pegmolesatide demonstrated a stronger likelihood of maintaining Hb levels within guideline-recommended ranges and potentially provided a more favorable safety profile compared to epoetin alfa.

Funding: Commercial Support - Jiangsu Hansoh Pharmaceutical Co Ltd

Figure: Forest Plot in Subgroup Analysis of the Proportion of Patients with Hb Between 11-12 g/dL (PPS)



Treatment difference in P values, rate differences, and their corresponding 95% CIs were obtained using the Cochran-Mantel-Haenszel (CMH) method with baseline Hb level (≤11.4 g/dL vs. ≥11.5 g/dL) and dialysis method (hemodialysis vs. peritoneal dialysis) as stratification factors.

TH-PO889

Hepcidin Is a Potential Predictor Marker for Anemia Progression in Patients on Hemodialysis

Hiroki Uchida, Ryo Kurimoto, Miho Suzuki, Akiko Kudo, Takeshi Nakata, Akihiro Fukuda, Hirotaka Shibata. *Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan*.

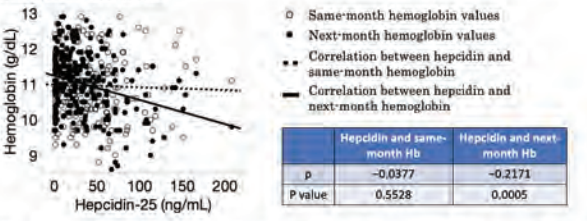
Background: Higher hepcidin levels observed in patients on hemodialysis cause functional iron deficiency and erythropoiesis-stimulating agent hyporesponsiveness, which may result in anemia; however, the impact of hepcidin elevation on anemia in patients on hemodialysis remains unclear. This study assessed the association between hepcidin-25 and hemoglobin (Hb) levels in patients on hemodialysis.

Methods: This observational study included 44 outpatients on hemodialysis with 251 available blood test results between April and November 2023. Erythropoiesis-stimulating agents and hypoxia-inducible factor prolyl hydroxylase inhibitors were administered in 40 and 2 patients, respectively, whereas 2 patients did not receive anemia treatment. Transferrin saturation and Hb, ferritin, and serum hepcidin-25 levels were measured every month, and the association of same-month hepcidin-25 and Hb levels were assessed. Whether the hepcidin-25 levels predicted future anemia and changes in Hb levels was determined by assessing the associations of hepcidin-25 with the next-month Hb level and the changes in Hb level after 1 month.

Results: Hepcidin-25 levels, although not associated with the same-month Hb levels ($\rho = -0.0377$, $P = 0.5528$; Fig. 1), exhibited significant negative association with the next-month Hb levels ($\rho = -0.2171$, $P = 0.0005$; Fig. 1) and the changes in Hb levels ($\rho = -0.1349$, $P = 0.0326$; Fig. 2). Furthermore, Hb levels in the next month declined in patients with hepcidin-25 levels of >70 ng/mL (Fig. 3).

Conclusions: Our analyses demonstrated that hepcidin levels were useful in predicting anemia progression within a month in patients on hemodialysis. A hepcidin level of >70 ng/mL predicted anemia progression, suggesting the requirement for intensified anemia treatment in these patients on hemodialysis.

Fig. 1 Association of hepcidin-25 levels with the same-month and next-month hemoglobin (Hb) levels



	Hepcidin and same-month Hb	Hepcidin and next-month Hb
ρ	−0.0377	−0.2171
P value	0.5528	0.0005

Fig. 2 Correlation between hepcidin-25 levels and changes in Hb levels one month later

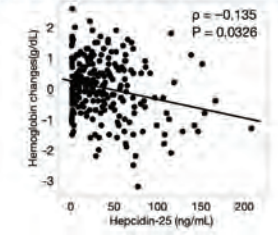
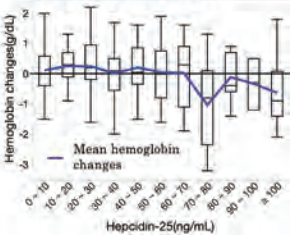


Fig. 3 Changes in Hb levels stratified according to hepcidin-25 levels



TH-PO890

Recombinant Human Erythropoietin (rhEPO)-Fc for Renal Anaemia in Chinese Patients on Haemodialysis: A Multicentre, Randomised, Open-Label, Phase 3 Study

Liangying Gan,[1] Ling Tong,[2] Chun Yang,[2] Li Zuo.[1] Fc-Acts Study Group. *[1]Peking University People's Hospital, Beijing, China; [2]Sichuan Luzhou Buchang BIO-Pharmaceutical Co., Ltd., Beijing, China*.

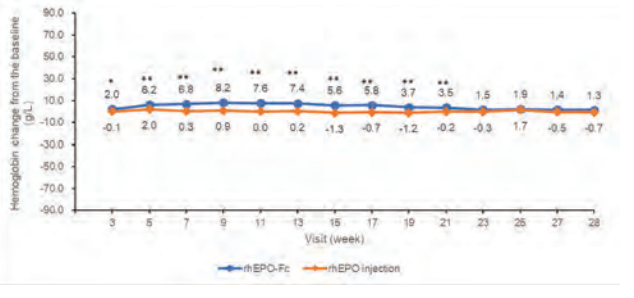
Background: Recombinant human erythropoietin (rhEPO) Fc fusion protein (rhEPO-Fc) has been developed to prolong the plasma half-life and improve the biological activity of EPO. The efficacy and safety characteristics of rhEPO-Fc have not been investigated in renal anaemia patients.

Methods: This was a multicentre, randomised, open, positive drug controlled, phase 3 trial conducted at 45 hospitals in China (NCT05359068). After a 6-week screening period, eligible patients were randomised (2:1) to receive rhEPO-Fc initiated at 18 μg/kg once a week or rhEPO initiated at 1500 IU two to three times a week or 3000 IU twice a week for 28 weeks. Eligible patients were enrolled to the consecutive 24-week extended treatment period. The primary outcome was the change in mean haemoglobin (Hb) from baseline between week 21 and week 28. Efficacy was analysed in full analysis set (FAS) and per protocol set (PPS). Safety was assessed in all patients who received at least one dose of the investigational drugs.

Results: Between 31 May 2021 and 27 June 2023, 356 patients received rhEPO-Fc and 178 received rhEPO injection. The rhEPO-Fc treatment group resulted in a significantly greater least-square mean (LSM) of the mean Hb changes between week 21 and week 28 from baseline in the FAS and PPS populations: inter-group LSM difference of 3.96 (95% CI 3.02 to 4.89; P<0.001) and 2.27 (0.60, 3.95; P=0.008), respectively. The incidence of adverse drug reaction (ADR) in the rhEPO-Fc group was slightly lower compared with the rhEPO group (39.2% vs 40.2%). The percentage of patients with dose adjustment due to treatment emergent adverse events (TEAEs) in the rhEPO-Fc group was statistically significantly lower compared with that of the rhEPO group (0.0% vs 2.2%; P<0.05). Two patients in the rhEPO-Fc group and 4 patients in the rhEPO group died due to TEAEs that were considered not related to the investigational drugs.

Conclusions: The efficacy of rhEPO-Fc was not inferior to that of rhEPO in maintaining Hb in Chinese hemodialysis patients with anaemia and was generally well tolerated.

Funding: Commercial Support - Sichuan Luzhou Buchang BIO-Pharmaceutical Co.,Ltd.



TH-PO891

Association of Anemia (Hemoglobin <13 g/dL in Men and <12 g/dL in Women) with Long-Term Kidney Prognosis in Patients with ADPKD: Insights from Time Series Analyses

Hiroshi Kataoka, Toshio Mochizuki, Shun Manabe, Yusuke Ushio, Momoko Seki, Ken Tsuchiya, Kosaku Nitta, Junichi Hoshino. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan*.

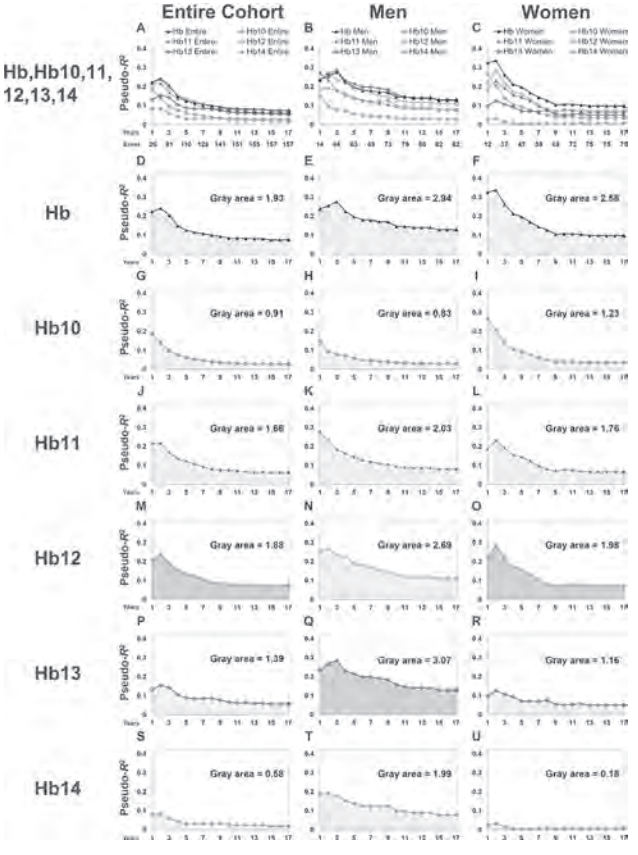
Background: Hemoglobin (Hb) levels are generally higher in autosomal dominant polycystic kidney disease (ADPKD) compared to other kidney diseases, but the prognostic role of anemia in ADPKD is not well understood. Prognostic factors for kidney outcomes can vary with the length of follow-up periods, making it crucial to understand the time-series changes and integrals of pseudo-R^2 values for kidney risk factors.

Methods: We enrolled 553 ADPKD patients. Renal outcome was defined as a 50% reduction in estimated glomerular filtration rate or initiation of renal replacement therapy. Survival analyses and logistic regression analyses for generating time-series pseudo-R^2 values were conducted. The integrated values of the pseudo-R^2 values from the 1st year to the 17th year (1Y–17Y Integrals) were calculated to determine the optimal Hb cut-off points for long-term renal prognosis.

Results: Multivariable Cox analyses indicated that anemia (Hb 1 g/L decrease, P=0.0004) was associated with kidney disease progression. To determine the anemia cut-off for kidney prognosis, pseudo-R^2 values for Hb <12 g/dL showed the highest 1Y–17Y integrals of 1.88 among all anemia cut-offs. These values peaked at 0.2401 two years after baseline and had the highest end value of 0.0721 at 17 years. Therefore, Hb <12 g/dL was identified as a key indicator of long-term kidney prognosis in ADPKD patients. Similar sex-specific analyses revealed different anemia cut-offs: Hb <13 g/dL in men and Hb <12 g/dL in women.

Conclusions: The 1Y–17Y Integrals of the pseudo-R^2 values for kidney prognosis contributed to determining the cut-off points of the anemia according to the sex difference.

Funding: Government Support - Non-U.S.



TH-PO892

A Randomized Controlled Trial to Evaluate the Efficacy of Roxadustat Dosing Regimens in Patients with CKD and Anemia on Dialysis

Yan Tu,[1] Bi-Cheng Liu,[1] Cuihua Huang,[3] Zhang Yuchen,[3] Shuting Pan,[2] Wei Niu.[4] *[1]Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine, Nanjing, China; [2]Clinical Biometrics, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China; [3]Medical Affairs, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China; [4]Clinical Development, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China*.

Background: It is unknown how roxadustat dose frequency reduction impacts hemoglobin (Hb) maintenance in patients with CKD anemia. We report here on Part 2 of a Phase 4 study (NCT04059913) which evaluated efficacy (Hb maintenance) and safety of three roxadustat dosing frequencies (once weekly [QW], twice a week [BIW], thrice a week [TIW]) in Chinese CKD anemia patients on dialysis after Hb correction in Part 1 (2023 ASN TH-PO981).

Methods: Eligible patients from Part 1 (Weeks 19 and 21 Hb ≥105 g/L and 4-week change in Hb >−10 g/L) were randomized to roxadustat QW, BIW or TIW. Frequency increases were permitted if needed. Non-inferiority testing was used for full analysis set (FAS) and per protocol set (PPS) analyses: 1) BIW vs. TIW and 2) QW vs. TIW (non-inferiority margin [NIM]=10 g/L). The primary endpoint was least-squares mean (LSM) Hb averaged at Weeks 33–37.

Results: A total of 178 patients were included: 175 patients in FAS (TIW: 61; BIW: 59; QW: 55) and 169 patients in PPS (TIW: 60; BIW: 57; QW: 52). Demographics were comparable across arms. Mean (SD) baseline Hb were 115.0 (6.1) g/L (TIW), 115.4 (6.5) g/L (BIW) and 114.4 (5.7) g/L (QW). In the PPS, the Hb LSMs [95% CI] at weeks 33-37 were 108.3 [105.7, 110.9] g/L (TIW), 107.1[104.4, 109.7] g/L (BIW), and 106.3 [103.6, 108.9] g/L (QW) (differences: −1.2 [95% CI: −4.4, 1.9] g/L [BIW vs. TIW]; −2.0 [95% CI: −5.3, 1.2] g/L [QW vs. TIW]). The lower 95% CI limit was >−10 g/L (NIM margin) for each comparison. FAS and PPS results were consistent. Around 90–95% TIW patients maintained TIW dosing, while 69.5–76.3% BIW and only 30.9–32.7% QW patients maintained their dose frequency. TEAEs occurred in 81.1% (TIW), 78.3% (BIW), and 63.4% (QW) of patients.

Conclusions: Non-inferiority was established between roxadustat BIW vs. TIW and QW vs. TIW. However, a proportion of patients in QW and BIW arms required dose frequency increases to maintain Hb. The clinical benefit of reducing roxadustat dose frequency is limited and should be carefully evaluated.

Funding: Commercial Support - FibroGen (China) sponsored this study

TH-PO893

Single-Centre Prospective Study of Indigenously Developed Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI) (Desidustat) for Treatment of Renal Anemia

Krishnaswamy Sampathkumar, Krishna Priya, Biju Dennis. *Meenakshi Mission Hospital and Research Centre, Madurai, India*.

Background: Anemia in dialysis patients impairs quality of life and leads to adverse cardiovascular outcomes. Standard treatments for CKD-associated anemia include EPO analogues and iron supplementation. Desidustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), was recently approved in India for treating anemia in CKD patients. This study aims to evaluate the efficacy and safety of Desidustat in patients with dialysis-dependent CKD anemia.

Methods: This single-center, prospective study enrolled 68 dialysis-dependent CKD patients with anemia. Patients received Desidustat (Oxemia®) either twice or thrice weekly, depending on their hemoglobin (Hb) levels, and were monitored monthly. Supplemental treatments included iron, vitamin B12, and folic acid as needed. The primary endpoint was the efficacy of Desidustat in increasing Hb levels, while the secondary endpoint assessed its safety profile.

Results: The study cohort consisted of 68 patients, 47 (69.11%) male, with a mean age of 56 ± 11.5 years. The majority, 66 (97%), were on maintenance hemodialysis (MHD) twice weekly, while 2 (3%) were on thrice weekly schedules. Desidustat was administered to 35 (51.4%) patients thrice weekly and to 31 (45.6%) patients twice weekly. Among the participants, 40 (58.8%) were EPO-naïve, and 28 (42.8%) had switched from EPO therapy. Significant improvements in Hb levels were observed following Desidustat treatment ($p<0.05$). Pre-treatment Hb was 7.78 gm/dl, increasing to 8.27 gm/dl after 1 month, 8.71 gm/dl after 2 months, 9.22 gm/dl after 3 months, and 9.94 gm/dl after more than 3 months, with a mean treatment duration of 11.8 ± 6.7 months. Both EPO-naïve patients and those who switched from EPO showed comparable increases in Hb levels. Background therapy included oral iron for 12 (17.6%) patients, intravenous (IV) iron for 52 (76.4%) patients, and vitamin B12 supplementation. Adverse events included mild hyperkalemia in 6 patients and vomiting in 2 patients, both managed appropriately.

Conclusions: This study demonstrates that Desidustat is an effective and safe alternative for treating anemia in dialysis-dependent CKD patients. Given its oral administration Desidustat offers a convenient alternative to injectable EPO therapies

Funding: Commercial Support - Zydus Pharmaceutical, India

TH-PO894

Evaluating Therapeutic Potential and Safety Profile of Desidustat for Anaemia Management in Patients with CKD: A Prospective, Open-Label, Single-Centre Study

Dinesh Khullar, Abhishek Singh, Deepak Kumar, Sahil Bagai, Kulwant Singh, Rahul Grover. *Max Super Speciality Hospital, Saket, Delhi, India*.

Background: Anemia is one of the common, most prevalent and challenging complications of chronic kidney disease (CKD). Desidustat (Oxemia®), a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), is a promising oral alternative to injectable erythropoiesis-stimulating agents (ESAs) for the treatment of anaemia in patients with CKD. Desidustat is approved in India for adults with CKD who are either not on dialysis or on dialysis. Here we aim to evaluate the real life effectiveness and safety profile of Desidustat in managing anemia among patients with chronic kidney disease (CKD).

Methods: This is a prospective single center analysis of Patient suffering from CKD –Anemia treated with Newer HIF PHIv-Desidustat. In this study Patients were on 100 mg Desidustat three times in a week. Primary end point was to observe rise in Hb from baseline to 24 weeks. Other secondary were safety and rise of Hb between different subgroup. Dose adjustments based on the haemoglobin levels at each follow up.

Results: Sixty four (n=64) patients median (IQR) age 60(18.5) years, n=37(57.8%) were female. Majority of the patients were suffering from CIN (21, 32.8%), DKD (15, 23.4%) and CGN (13, 20.3%). 33 (51.5%) were on HD, one patients on PD and 30 (46.8%) were Pre Dialysis patients. Out of 64 Patients, 43(67.2%) patients were EpO switched and 21(32.8%) were EpO naïve patients. There was statistically significant improvement in mean Hb (figure 1). In different category of EpO naïve Switched from EpO, DD vs ND rise of Hb was comparable. Among the safety parameters, the change in serum potassium value from baseline to the end of 24 weeks was within the normal range, with minimal change (p=0.856). The adverse events were observed in (n=5, 7.8%) patients; including VA stenosis(n= 1,1.6%), MGUS(n= 1,1.6%), Vascular Thrombosis(n= 1,1.6%), IE(n= 1,1.6%), and MACE death(n= 1,1.6%).

Conclusions: The study shows desidustat is significantly effective in improvement of Hb levels in both EPO exposed and naïve patients with CKD anaemia. The oral administration further improves the compliance of the patients.

TH-PO895

Real-World Experience of Hypoxia-Inducing Factor-Prolyl Hydroxylase Inhibitor Desidustat for Anemia in Dialysis-Dependent CKD

Aswini P. Patnaik, Nikunj Kishore Rout, Ashim K. Mahali, Scienthia Sanjeevani. *Kalinga Institute of Medical Sciences, Bhubaneswar, India*.

Background: Anemia poses a significant challenge in the management of End-stage kidney disease (ESKD), leading to a diminished quality of life in affected individuals. Patients with ESKD have a relative deficiency of Eryhtopoetin (EpO) andErythropoetin analogues are a standard of care for such patients. Desidustat is a of Hypoxia Inducing Factor Prolyl Hydroxylase Inhibitor (HIF –PHI) thatendogenously increases the EpO production. We studied the real world effectiveness of Desidustat, in ameliorating anemia among ESKD patients undergoing maintenance hemodialysis.

Methods: Observational cohort data were collected data of 65 ESKD patients, aged >18 years on maintenance hemodialysis with hemoglobin levels <10g/dL. Patients with iron deficiency anemia, known bleeding disorders, recent red blood cell transfusions, or concurrent cancer were excluded. Initially, all patients received 100 mg of Desidustat thrice weekly, with subsequent dose adjustments based on individual responses.

Results: The patients had a mean age of 50.35±12.94 years with 45 being male. Of all patients, 41 (63%) were EpO naïve and others were switched from EpO. After 3 months, only 6 patients exhibited a positive response to the initial Desidustat regimen, necessitating a dose escalation to 150 mg. thrice weekly. Following this, 47 out of 65 patients showed significant improvements in hemoglobin levels after 3 months. However, 18 patients (27.6%) did not respond to Desidustat treatment. The mean hemoglobin level before Desidustat initiation was 8.13±0.77 g/dl and after 24 weeks of Desidustat therapy, the mean hemoglobin level rose to 8.73±0.97 g/dl, with a statistically significant p-value of <0.001. There were no major adverse events during the follow-up duration.

Conclusions: Desidustat demonstrated effectiveness in increasing Hb levels in around 3/4th of ESKD patients undergoing MHD. However, starting at 150mg thrice weekly seems to be more beneficial in our population

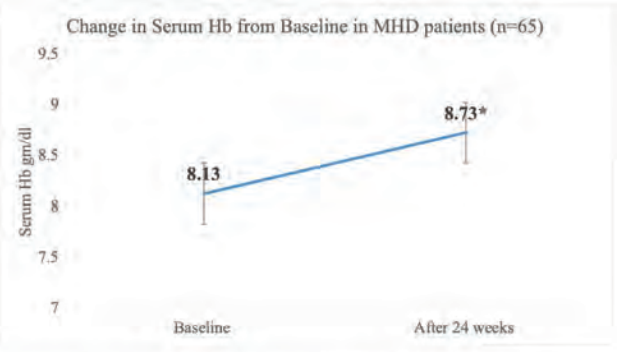


Figure 1: Change in Serum Hb from baseline to 24 weeks (* p<0.01)

TH-PO896

First-in-Human Study of Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI) AND017 in Healthy Participants

Yusha Zhu, Ping Du, Qi Zhu. *Kind Pharmaceuticals LLC, Redwood City, CA.*

Background: AND017 is a novel oral HIF-PHI independently developed by Kind Pharmaceuticals LLC. The first-in-human study of AND017 was performed among healthy subjects in Australia to evaluate the safety, pharmacokinetics, and pharmacodynamics of AND017 (NCT04751539).

Methods: This Phase I, randomized, double-blinded, placebo-controlled study consisted of two parts: a single ascending dose (SAD) part followed by a multiple ascending dose (MAD) part. In the SAD part, doses of 1, 4, 10, 20, 30, and 50 mg AND017 or placebo were assessed in 6 consecutive cohorts; In the MAD part, doses of 4, 10, 20 and 30 mg AND017 or placebo were administered daily for 10 days and assessed in 4 consecutive cohorts. After each cohort, a Safety Review Committee (SRC) reviewed blinded cumulative safety data to determine the safety of the study dose before proceeding to the next dose cohort.

Results: A total of 78 subjects were enrolled in the study- 46 subjects in the SAD part and 32 subjects in the MAD part. All subjects were included in the PD and safety analysis set; all 58 subjects dosed with AND017 were included in PK analysis set. Subjects in all treatment groups were of similar demographic and baseline characteristics. AND017 was absorbed quickly with a median T_{max} of 2-4.5 h after single and multiple dose administration. There was no tendency toward a change in T_{max}, half-life, volume of distribution and clearance across the dose range investigated. AND017 steady state reached by 6 days dosing, with an approximate 1.2 to 1.6-fold accumulation after 10 days of administration. Dose proportionality in AND017 exposure was observed after single (1 to 50 mg) and multiple (4 to 30 mg) dosing. In the PD analysis, $E_{max,EPO}$, baseline-corrected $E_{max,EPO}$, $AUEC_{0\text{-}24,EPO}$, and baseline-corrected $AUEC_{0\text{-}24,EPO}$ of erythropoietin (EPO) showed obvious dose dependence. The increase in EPO was significantly associated with the PK exposure. The most frequently reported treatment related adverse events in the SAD part were dizziness, headache, and fatigue occurred in 2 subjects of AND017 cohorts each; in the MAD part, headache occurred in 2 subjects of AND017 cohorts and 1 subjects of placebo cohort.

Conclusions: AND017 appeared to be safe and well tolerated when administered to healthy adult subjects at oral doses ranging from 1 mg up to 50 mg in the SAD part and 4 mg up to 30 mg in the MAD part.

TH-PO897

Effect of Food on the Pharmacokinetics of AND017 in a Phase I Study

Yusha Zhu,[1] Hua Zhang,[2] Ping Du,[1] Qi Zhu,[1] Liyan Miao.[2]
[1]Kind Pharmaceuticals LLC, Redwood City, CA; [2]The First Affiliated Hospital of Soochow University, Suzhou, China.

Background: AND017 is a novel hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) independently developed by Kind Pharmaceuticals LLC and is an emerging new option of treatment for anemia due to chronic kidney disease (CKD). The effect of food on the pharmacokinetics (PKs) of AND017 was investigated in a Phase I study (NCT04712500).

Methods: This is a Phase I, randomized, open-labeled, two-sequence, two-period, crossover study conducted among healthy non-elderly volunteers in China. The primary objective was to evaluate the effect of food on the PKs of a single oral dose of 10 mg of AND017. The study consisted of two periods with a 5-day washout in between. Healthy volunteers were randomized at 1:1 to receive a single dose of 10 mg AND017 under fasted (sequence A) or fed conditions (sequence B) in the first study period. After a 5-day washout, volunteers received another single dose of 10 mg of AND017 under fed (sequence A) or fasted (sequence B) conditions in the second study period. PK samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 h post-dose

after each dose. Safety was assessed by monitoring adverse events (AEs), clinical laboratory tests (hematology, chemistry, urinalysis, and coagulation), vital signs, 12-lead ECGs, and physical examinations.

Results: In the study, a total of 14 healthy volunteers were enrolled with similar demographics and baseline characteristics. There were no significant differences in the PK parameters when AND017 was administered under fed and fasted conditions, except for a 20% reduction of C_{max} under fed condition compared to the fasted condition; the geometric mean ratio (fed/fasted) and 90% CI for C_{max} and $AUC_{0\text{-}inf}$ were 79.61% (73.40,86.34) and 99.93% (96.31,103.68) respectively. In the safety analysis, a total of 7 volunteers reported 12 TEAEs, among which 4 TEAEs reported by 3 volunteers were determined to be treatment-related, which were alanine aminotransferase increased, diastolic pressure decreased, triglycerides high, and creatine kinase increased, with each reported once and CTCAE grade ≤2. No AE leading to discontinuation or SAE occurred in the study.

Conclusions: In summary, a single dose of AND017 at 10 mg administered alone or in combination with food was generally safe and well-tolerated in healthy non-elderly volunteers. The study supports the safe use of AND017 under fed or fasted conditions.

TH-PO898

Safety and Efficacy of AND017, a Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI), in Patients with Nondialysis-Dependent CKD (NDD-CKD)

Yusha Zhu,[1] Li Zuo,[4] Xiaoqiang Ding,[5] Suzanne Wilson,[1] Ping Du,[1] Qi Zhu,[1] Geoffrey A. Block,[3] Pablo E. Pergola.[2] *[1]Kind Pharmaceuticals LLC, Redwood City, CA; [2]Renal Associates PA, San Antonio, TX; [3]US Renal Care, Dallas, TX; [4]Peking University People's Hospital, Beijing, China; [5]Zhongshan Hospital Fudan University, Shanghai, China.*

Background: AND017, a novel HIF-PHI, was investigated in a Phase II study in patients with NDD-CKD in the US and China (NCT05035641).

Methods: Patients with NDD-CKD and hemoglobin (Hb) ≥7.5 and <10.0 g/dL were randomized at a 1:1:1:1 ratio to AND017 8 mg, 12 mg, 16 mg or placebo three times weekly (TIW) during the first 5-weeks treatment (Fixed-dose Period, no dose adjustment allowed). At the end of the Fixed-dose period (Week 6), patients who met the pre-defined criteria were re-randomized at a ratio of 1:1 to continue the TIW dosing schedule or switch to a once-weekly (QW) dosing schedule and entered the 8-week Titration Period. During this period, the doses of the study drug were adjusted to maintain Hb within the range of 10.0-11.0 g/dL inclusive. The primary objectives were to evaluate the safety and efficacy of AND017 by assessing the rate of rise in Hb at Week 6.

Results: A total of 113 patients were enrolled: placebo (28), 8 mg (28), 12 mg (29), and 16 mg (28). Treatment-emergent adverse events occurred in 69.41% in the pooled AND017 group versus 64.29% in the placebo group while treatment-related adverse events occurred in 11.76% in the pooled AND017 group versus 3.57% in the placebo group. A total of 6 patients from AND017 dose groups experienced serious adverse events (SAEs), none of which were assessed as related to the study drug. Compared to the placebo group, the mean rate of rise in Hb (g/dL/week) from baseline to Week 6 was significantly higher in all the AND017 dose groups ($p<0.0001$). Change from baseline in Hb at Week 6 was 1.44 g/dL, 2.03 g/dL, 2.51 g/dL in AND017 8 mg, 12 mg, and 16 mg group, respectively, and -0.21 g/dL in the placebo. The cumulative response rates (Hb ≥10.0 g/dL and increase from baseline ≥1.0 g/dL during the entire treatment period) were higher in all AND017 dose and dosing frequency groups, 100% and 90% for the pooled AND017 TIW group and QW group, respectively, compared to 40% in the placebo.

Conclusions: AND017 was safe and well tolerated in patients with NDD-CKD and anemia. AND017 effectively increased Hb level in a dose-dependent manner starting at 8 mg TIW within the first 5-week Fixed-dose period and maintained Hb within 10.0-11.0 g/dL at both TIW and QW dosing frequency in the following 8-week Titration period.

TH-PO899

Real-World Evidence of Vadadustat in Patients with Anemia and CKD: Interim Results from Postmarketing Surveillance (VIOLET Survey) in Japan

Kiichiro Ueta,[1] Kenichi Nishimura,[1] Kazuyo Sasaki,[1] Jing Bi,[1] Takafumi Hashimoto,[1] Yuki Seto,[1] Masaomi Nangaku.[2] *[1]Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; [2]The University of Tokyo, Tokyo, Japan.*

Background: Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor. We report the interim results of ongoing post-marketing surveillance (PMS) in Japanese patients with anemia in CKD receiving vadadustat.

Methods: This 2-year, prospective, observational, multicenter PMS evaluated the safety and effectiveness of vadadustat in clinical practice. Patients with anemia in CKD who had not been treated with vadadustat were enrolled. The occurrence of adverse drug reactions (ADRs) and hemoglobin levels, etc., were evaluated for the interim analysis up to June 2023. ADRs of special interest included hepatic impairment, thromboembolism, hypertension, cardiovascular events excluding thromboembolism, malignant tumor, retinal hemorrhage, and progression of autosomal dominant polycystic kidney disease.

Results: A total of 1847 patients (non-dialysis (ND): 1233; peritoneal dialysis (PD): 142; hemodialysis (HD): 472) were included in safety analysis. The proportion of patients switched from erythropoiesis-stimulating agents was ND: 12.08%, PD: 33.80% and HD: 42.16%, respectively. The median duration for vadadustat treatment was ND: 182 days, PD: 182 and HD: 138 days. ADRs and serious ADRs occurred in 10.94% and 3.41% (overall), 10.30% and 2.92% (ND), 12.68% and 5.63% (PD) and 12.08% and 4.03% (HD), respectively. The most common ADR were ND: diarrhea (0.89%), PD: diarrhea (2.11%) and decreased appetite (2.11%), and HD: nausea (2.54%), respectively. There were no ADRs of special interest with incidence > 2%. The hemoglobin values (g/dL, mean ±SD [n]) at baseline and 1 year after the treatment were 10.10±1.16 [1198] and 11.23±1.39 [434] (ND), 10.57±1.32 [142] and 11.17±1.36 [40] (PD), and 10.10±1.38 [471] and 10.83±1.30 [109] (HD), respectively. The mean dose of vadadustat (mg/day) 1 year after the treatment were 321.7 (ND), 373.1 (PD) and 386.9 (HD). The latest interim results up to June 2024 will be presented at Kidney Week 2024.

Conclusions: Any new safety concerns beyond those already described in the package inserts were not identified in the interim analysis of PMS.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

TH-PO900

Framework to Assess the Benefits and Risks of Treatments and Dosing Regimens for Anemia of CKD

Kevin Dykstra, Todd E. Minga, Bryce S. Foote, Zhiqun Zhang, Pamela C. Navarro Gonzales, Steven K. Burke. *Akebia Therapeutics Inc, Cambridge, MA.*

Background: Vadadustat (VADA) is an oral HIF prolyl hydroxylase inhibitor approved for treating anemia in adults with CKD on dialysis. VADA stabilizes HIF, stimulates endogenous EPO production, increases iron mobilization and RBC production. It is approved for use in 38 countries. The recommended starting dose for VADA is 300mg QD, with dose adjustments between 150-600mg to maintain Hb levels within target range. Alternative dosing regimens may be beneficial based on patient characteristics or preferences. We developed a framework to balance benefits and risks of VADA treatment with different treatment regimens.

Methods: The framework was developed by first identifying and ranking treatment attributes associated with any treatment for CKD-related anemia including efficacy, safety, and tolerability outcomes. An importance value (0-100) was assigned to each attribute. Specific outcome measures and relevant responses associated with each attribute were identified. Weights for each response within an attribute were elicited. The result was the benefit-risk framework in which a given treatment regimen could be assigned a net benefit or clinical utility score based on its performance in the benefit-risk framework, with the utility scores ranging from 0-100 after normalization.

Results: We identified and ranked 7 attributes (1 efficacy, 4 safety, and 2 tolerability/convenience) that contribute to the overall utility of a treatment for CKD anemia. Overall, efficacy (transfusion avoidance) contributed 25% to the utility score, while safety attributes (incidence of MACE, thromboembolic events, hospitalization for HF, and vascular access thromboses) contributed 60% of the net benefit; tolerability and convenience contributed the remaining 15% of utility. When combined with mathematical models predicting the probability of a given response for each attribute, the expected benefit-risk tradeoff for that regimen could be calculated and compared against alternative treatments or dosing regimens.

Conclusions: This benefit-risk framework will be used to identify and optimize treatment regimens for VADA in comparison to the standard of care (ESAs).

Funding: Commercial Support - Akebia Therapeutics, Inc.

Figure: Building a Benefit-Risk Framework

TH-PO901

On-Treatment Analyses of Cardiovascular Safety in the Vadadustat Phase 3 Program

Wolfgang C. Winkelmayer,[1] Steven K. Burke,[2] Glenn M. Chertow,[3] Kevin Dykstra,[2] Kai-Uwe Eckardt,[4] Mark Koury,[5] Wenli Luo,[2] Todd E. Minga,[2] Eldrin F. Lewis.[3] *[1]Baylor College of Medicine Margaret M and Albert B Alkek Department of Medicine, Houston, TX; [2]Akebia Therapeutics Inc, Cambridge, MA; [3]Stanford University School of Medicine, Stanford, CA; [4]Charité–Universitätsmedizin Berlin, Berlin, Germany; [5]Vanderbilt University Medical Center, Nashville, TN.*

Background: Vadadustat (VADA) is an oral HIF-PHI for treating anemia in CKD. In the Phase 3 clinical program ($INNO_2VATE$: incident dialysis-dependent [DD]-CKD or prevalent DD-CKD; PRO_2TECT: ESA-untreated and ESA-treated non-DD [NDD]-CKD), VADA demonstrated noninferiority (HR=1.25 threshold) to darbepoetin alfa (DA) for MACE risk in DD-CKD (HR: 0.96, 95% CI, 0.83 to 1.11) but not NDD-CKD (HR: 1.17, 95% CI, 1.01 to 1.36) in primary ITT analyses. We conducted on-treatment analyses taking PK/PD profiles into account to better understand MACE risk.

Methods: The primary safety endpoint was time to first MACE (all-cause mortality, nonfatal MI, nonfatal stroke). Secondary safety endpoints were time to expanded MACE (MACE plus hospitalization for either heart failure or major thromboembolic event), CV MACE, CV mortality, and all-cause mortality. We adjusted on-treatment time at risk to include time to last treatment drug administration plus 28 days plus dosing frequency to account for PK/PD differences (VADA vs DA). For considering dosing frequency, we added 1 day for VADA and variable days (7-28 days) for DA.

Results: INNO$_2$VATE trials randomized 3902 patients (VADA=1947, DA=1955); PRO$_2$TECT trials randomized 3476 patients (VADA=1739, DA=1732). In the on-treatment analysis of DD-CKD, the risk of MACE was similar between treatment groups, consistent with results from ITT analyses (**Figure**). In the on-treatment analysis of NDD-CKD, the risk of MACE was similar between groups, and similar to results derived from the ITT analyses, inclusive of crossing the non-inferiority threshold. On-treatment analyses of secondary safety endpoints for DD-CKD and NDD-CKD populations were similar to their respective ITT analyses.

Conclusions: On-treatment dose-frequency-adjusted analyses address imbalances in PK/PD profiles and effective treatment duration between comparators and can complement results derived from ITT analyses.

Funding: Commercial Support - Akebia Therapeutics, Inc.

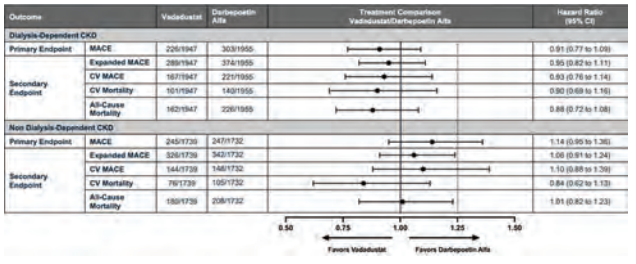


Figure. On-treatment Safety Endpoints

TH-PO902

Major Adverse Cardiovascular Events (MACE) in Patients Randomly Assigned to Vadadustat vs. Darbepoetin Alfa during the 3 Months after Dialysis Initiation

Wolfgang C. Winkelmayer,[1] Steven K. Burke,[2] Glenn M. Chertow,[3] Kai-Uwe Eckardt,[4] Eldrin F. Lewis,[3] Wenli Luo,[2] Todd E. Minga,[2] Mark J. Sarnak.[5]
[1]Baylor College of Medicine, Houston, TX; [2]Akebia Therapeutics Inc, Cambridge, MA; [3]Stanford University School of Medicine, Stanford, CA; [4]Charite Universitatsmedizin Berlin, Berlin, Germany; [5]Tufts University School of Medicine, Boston, MA.

Background: Trials and registries usually do not capture events during the weeks following dialysis initiation, when cardiovascular event rates and mortality are particularly high. The PRO$_2$TECT trials compared vadadustat (VADA), an oral HIF-PHI, and the ESA darbepoetin alfa (DA), in patients with non–dialysis-dependent (NDD)-CKD (ESA-untreated [NCT02648347] and ESA-treated [NCT02680574]). Many PRO$_2$TECT patients progressed to kidney failure and initiated dialysis, thus providing an opportunity to study this vulnerable incident dialysis period.

Methods: The PRO$_2$TECT Ph 3 trials randomized 3476 patients with anemia and NDD-CKD 1:1 to VADA or DA. This post-hoc analysis anchored baseline at dialysis initiation and followed patients for up to 90 days. We estimated cumulative incidences and rate ratios (RR) with 95% confidence intervals (CI) of MACE (all-cause mortality, nonfatal MI, nonfatal stroke) and expanded MACE (MACE plus hospitalizations for either heart failure or a thromboembolic event). We also described event rates in 30-day intervals for 90 days after dialysis initiation.

Results: 527 patients randomized to VADA and 539 patients randomized to DA initiated dialysis. The median [25th, 75th percentile] time since trial enrolment was 255 [122, 448] days in the VADA and 268 [142, 483] days in the DA group. In the first 90 days after dialysis initiation, 50 patients (9.5%) in the VADA group and 55 patients (10.2%) in the DA group had a MACE (RR=0.93; 95% CI: 0.65-1.34]). During the same time, 57 patients (10.8%) in the VADA group and 67 patients (12.4%) in the DA group had an expanded MACE (RR=0.87; 95% CI, 0.62-1.21). Incidence of expanded MACE was highest in the 30 days after dialysis initiation (Table), where most events were deaths.

Conclusions: Rates of MACE and expanded MACE within the first 90 days of dialysis initiation were similar among patients randomized to VADA vs. DA. The majority of these events occurred in the first 30 days after dialysis initiation.

Funding: Commercial Support - Akebia Therapeutics, Inc.

Expanded MACE After Dialysis Initiation

	Vadadustat N=527 n (%)	Darbepoetin alfa N=539 n (%)
1-30 days after dialysis initiation	36 (6.8)	40 (7.4)
>30-60 days after dialysis initiation	8 (1.51	14 (2.6)
>60-90 days after dialysis initiation	6 (1.1)	8 (1.5)

TH-PO903

Projected Long-Term Cost Savings with Roxadustat, a Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI), among Patients on Hemodialysis: Insights from a 100-Week Longitudinal Study

Satoshi Funakoshi, Jyunichiro Hashiguchi, Shinichi Abe, Kenji Sawase, Mayu Iwata. *Nagasaki Kidney Center, Nagasaki, Japan.*

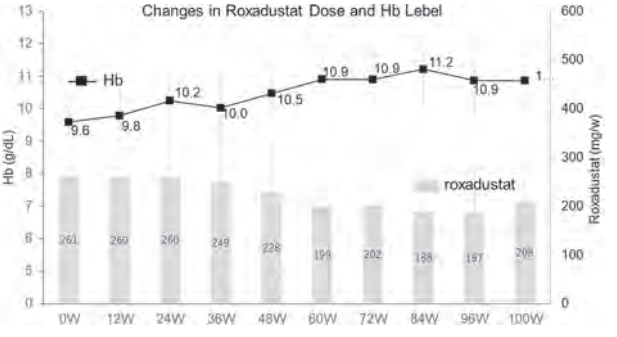
Background: HIF-PH inhibitors are attracting attention for their novel mechanisms of action. However, the cost of the starting dose of HIF-PH inhibitors is considerably higher than biosimilar ESA, and it may limit the use of them. Nevertheless, HIF-PH inhibitors demonstrate targeting capabilities across numerous genes, hinting at potential advantages extending beyond just anemia alleviation.

Methods: Seventy-two hemodialysis (HD) patients receiving 9000 U/week of EPO were transitioned to roxadustat thrice weekly at 100 mg doses, titrated to maintain hemoglobin (Hb) levels between 10 to 12 g/dL. During the titration of roxadustat dosage, we carefully observed ferrokinetic and administered iron supplementation as necessary.

Results: The initial dose of roxadustat was approximately 261 mg/week, equivalent to about 4,000 yen/week, well above EPO's cost of about 2,600 yen/week. Over time, the dose of roxadustat gradually decreased, and as shown in the figure, after 60 weeks, the cost of roxadustat was almost equal to that of EPO. during 100 weeks, the dose/cost of roxadustat decreased to about 60% from the initial dose. At the same time, GNRI decreased slightly from 92 ± 12.4 to 87 ± 8.9 and CRP increased from 0.3 ± 0.14 mg/dL to 0.8 ± 0.14 mg/dL, but without statistical significance. No serious adverse reactions were reported.

Conclusions: Roxadustat, HIF-PH inhibitors, demonstrated the dose / cost reductions over long-term use. Given their reported cost-sparing advantages, HIF-PH inhibitors emerge as effective alternatives to ESA for managing anemia in HD patients. The observed reduction in cost over time subsequent to switching from EPO to roxadustat suggests underlying factors beyond nutritional and inflammatory statuses. Hence, further investigation into this phenomenon is warranted.

Funding: Private Foundation Support



TH-PO904

A Prospective Single-Center Study on Desidustat, a Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI), in the Management of Anemia in Dialysis-Dependent CKD

Arun Kumar Narayana. *Apollo Hospital Seshadripuram, Bengaluru, India.*

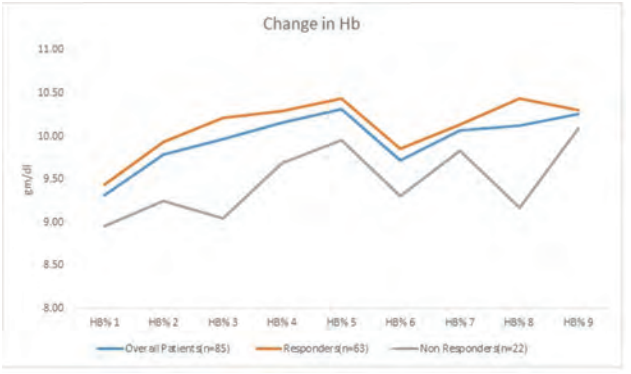
Background: Erythropoietin analogous is the backbone of the treatment of dialysis-dependent CKD –Anemia. Recently in India, Desidustat (Oxemia®) a HIF PHI approved by DCGI in dialysis-dependent and Non dialysis-dependent CKD Anemia. The current study enroutes the outcome of the usage of desidustat in DD-CKD Anemia patients.

Methods: We analyzed data of patients who were receiving Desidustat 100 mg thrice weekly for correction of Anemia at our center. Patients were followed up regularly for Anemia parameters.

Results: In the current study, we enrolled data from 85 patients at our center. The majority of 61 (71.7%) were male, and 24 (28.2%) were female. The mean age of participants was 51.27±14 years. The majority, 66 (77.6%), belong to the middle socioeconomic background. All the patients analyzed received three-time maintenance hemodialysis at our center. Patients with ESRD 71 (83.5%), hypertension 83 (97.6%), diabetic nephropathy 42 (49.4%), PVD 3 (3.5%), Alport syndrome 1 (1.1%), and CVD 1 (1.1%). The baseline serum creatinine of the patients was 6.4±1.5 mg/dl. Serum Iron 29.51±7.94, TSAT 25.06 ± 6.9, and Serum Ferritin 89.34 ± 39.19. In the present study, out of 85 patients, 63 (74.1%) responded with the treatment of anemia, while 22 (25.6%)

showed a low rise in Hb with desidustat treatment, as shown in figure 1. In the present study, out of 85 patients, 10 (11.7%) underwent renal transplantation and 3 (3.5%) expired. The reason for low Hb in 22 patients can be due to iron depletion. Gastrointestinal ADRs were observed with Desidustat therapy, which was treated appropriately.

Conclusions: The treatment of dialysis-dependent CKD anemia with Desidustat showed a promising response rate. Ensuring adequate iron repletion is crucial for optimizing the response to HIF-PHI treatment



TH-PO905

Impact of Roxadustat Kinetic Pharmacodynamics on Starting Dosage for Anemia in Dialysis-Dependent (DD) and Nondialysis-Dependent (NDD) Patients with CKD

Chenhui Deng,[1] Ping Liu,[1] Yiqing Wu.[2] *[1]Clinical Pharmacology Department, Linking Truth Technology Co., Ltd, Beijing, China; [2]Medical Affairs, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China.*

Background: We evaluated the impacting factors on roxadustat pharmacodynamics, and simulated relevant dosing regimens based on the established kinetic-pharmacodynamic (K-PD) model to support the starting dose optimization in Chinese CKD anemia patients.

Methods: The analysis included 9964 hemoglobin (Hb) data from 992 Chinese patients in 6 Phase 2/3/4 clinical studies. Based on the established K-PD model, Hb levels in these patients at standard or 1–step lower starting dosing regimen were simulated following 52 weeks of three times weekly administration. Dose adjustment was allowed based on Hb levels at Week 4 and later to maintain Hb levels within 10.5-12.0 g/dL.

Results: The Hb profiles in CKD anemia patients were well described with a cell lifespan model. Body weight, subject type (DD/NDD), and prior erythropoietin (EPO) dose (≥ or <10,000 IU/wk) were significant covariates for roxadustat dose at half of the maximum stimulation (ED_{50}); the effect of CKD stage (3&4) on ED_{50} in 1 Phase 4 study (NDD) was also included in the final model. For NDD CKD stage 3&4 patients, erythropoiesis-stimulating agent (ESA)-naïve DD patients, and ESA-treated DD patients with prior EPO dose <10,000 IU/wk, following the 1–step lower starting dose, adequate efficacy (10.5 g/dL≤ Hb <12.0 g/dL) could still be maintained and proportions of patients with high Hb levels (Hb ≥13.0 & Hb ≥12.0 g/dL) could be further reduced compared to the standard starting dose. For NDD CKD stage 5 patients, at the standard starting dose, a higher proportion of patients had an increase in Hb levels of 1-2 g/dL within the first 4 weeks without obvious increase in proportions of patients with high Hb levels, compared to the 1–step lower starting dose. For ESA-treated DD patients with prior EPO dose ≥10,000 IU/wk, at the standard starting dose, a higher proportion of patients maintained adequate efficacy for the first 8 weeks without obvious increase in proportions of patients with high Hb levels, compared to the 1–step lower starting dose.

Conclusions: For NDD CKD stage 5 patients and ESA-treated DD patients with prior EPO dose ≥10,000 IU/wk, the standard starting dose can be maintained. For NDD CKD stage 3&4 patients, ESA-naïve DD patients, and ESA-treated DD patients with prior EPO dose <10,000 IU/wk, the 1–step lower starting dose may be considered.

Funding: Commercial Support - FibroGen (China) sponsored this analysis

TH-PO906

Efficacy of Desidustat in Increasing and Maintaining Hemoglobin Levels in Anemic Patients with CKD

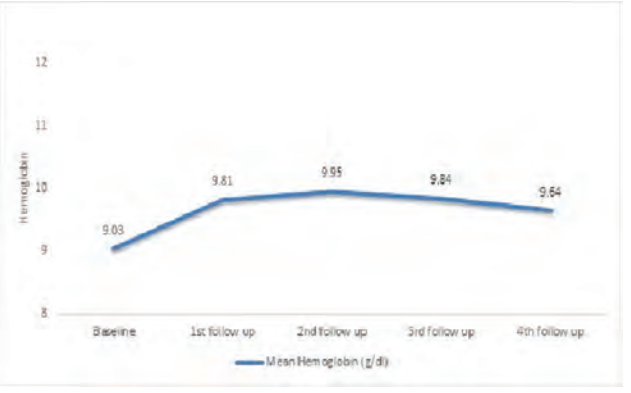
Manish R. Balwani. *Saraswati Kidney Care Center, Nagpur, India.*

Background: Desidustat, a novel hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor, offers a promising therapeutic approach by stimulating endogenous erythropoietin production and promoting red blood cell production. The study aims to contribute valuable insights into the potential therapeutic role of Desidustat in improving hemoglobin parameter in anemic - CKD patients.

Methods: This is a retrospective single centre, open label interventional study. Patients diagnosed with anemic CKD were enrolled into this study. The patients underwent desidustat therapy at a dosage of 100 mg thrice a week for the management of anemia associated with CKD. Regular follow -ups were conducted to monitor anemia and to ensure safety. In addition to anemia management, patients received standard treatment as per naive cause of CKD. Difference in hemoglobin parameter was analysed comparing the measurement at baseline to 4th follow up visit.

Results: Total of 79 patients were included into study, 43(54.4%) male and 36(45.6%) female (Mean age 54.62 ± 13.99). In these 79 patients, 42(53.2%) were having diabetes mellitus, 67(84.8%) were having hypertension, 21(26.5%) were having glomerulonephritis, 19(24.1%) were having diabetic retinopathy and 28(35.4%) were having diabetic nephropathy as a concomitant disease. 28(35.4%) patients were on regular maintenance haemodylasis and 51(64.5%) were on iron supplement as per their requirement. Following treatment with desidustat, significant improvements in mean hemoglobin levels were observed at each follow-up visit (P value <0.05). There were no any reported adverse events during the treatment follow-up period.

Conclusions: This study demonstrates the effectiveness of desidustat in improving significant hemoglobin levels in anemic CKD in both dialysis dependent and independent patients. A well designed, long duration, randomized controlled trial will further help in establishing this concept.



Mean rise in Hb($p<0.05$)

TH-PO907

Safety and Efficacy of Vadadustat in Erythropoiesis-Stimulating Agent-Naïve Patients New to Dialysis Who Have CKD-Related Anemia

Glenn M. Chertow,[1] Steven K. Burke,[2] Eldrin F. Lewis,[1] Wenli Luo,[2] Todd E. Minga,[2] Mark J. Sarnak,[3] Kai-Uwe Eckardt.[4] *[1]Stanford University School of Medicine, Stanford, CA; [2]Akebia Therapeutics Inc, Cambridge, MA; [3]Tufts Medical Center, Boston, MA; [4]Charite Universitatsmedizin Berlin, Berlin, Germany.*

Background: Vadadustat (VADA) is an oral HIF-PHI for treating anemia in CKD. In the phase 3 incident $INNO_2VATE$ trial in patients new to dialysis, VADA was noninferior to the ESA darbepoetin alfa (DA) for hemoglobin (Hb) efficacy, with a similar safety profile. Since this trial enrolled patients with and without prior ESA use, post hoc analyses of patients previously naïve to ESAs were conducted to better understand efficacy and safety of VADA in this subgroup.

Methods: A post hoc analysis of the incident $INNO_2VATE$ trial (N=369; NCT02865850) assessed the efficacy and safety of VADA compared to DA in ESA-naïve patients. Primary and secondary efficacy endpoints were mean change in Hb from baseline to the primary (PEP, weeks 24-36) and secondary (SEP, weeks 40-52) evaluation periods, respectively (noninferiority margin [lower bound of the 95% CI] of –0.75 g/dL). Other endpoints included the proportion of patients requiring ESA rescue and those with Hb levels >12g/dL and <9g/dL. Treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and TEAEs leading to death were reported as safety endpoints.

Results: In the incident $INNO_2VATE$ trial, 192 patients were ESA naïve (VADA, n=89; DA, n=103). A majority (VADA, n=58 [65.2%]; DA, n=66 [64.1%]) had Hb <9.5 g/dL. In ESA-naïve patients, VADA was noninferior to DA for Hb efficacy during the PEP (LS mean treatment difference, -0.13; 95% CI, -0.44 to 0.18) and SEP (LS mean treatment difference, 0.05; 95% CI, -0.30 to 0.40). ESA rescue therapy was similar, with 9.0% and 10.6% (PEP) and 6.2% and 7.2% (SEP) of patients receiving it in the VADA and DA groups, respectively. Hb excursions >12.0 g/dL were more common in the VADA group (PEP, 25.6%; SEP, 30.4%) than the DA group (PEP, 18.9%; SEP, 21.2%). Hb concentrations <9.0 g/dL were seen with similar frequency in the VADA and DA groups during the PEP (VADA, 23.1%; DA, 18.9%) and SEP (VADA, 24.6%; DA, 28.2%). Safety endpoints were seen with similar frequency between treatment groups: TEAEs (VADA, 79.5%; DA, 86.3%), SAEs (VADA, 51.1%; DA, 57.8%), TEAEs leading to death (VADA, 11.4%; DA, 9.8%).

Conclusions: In this post hoc analysis of ESA-naïve patients new to dialysis with CKD-related anemia, VADA was noninferior to DA for efficacy and had a similar safety profile.

Funding: Commercial Support - Akebia Therapeutics, Inc.

TH-PO908

Long-Term Safety of Vadadustat for Treatment of Anemia-Related CKD in Phase 3 Trials

Glenn M. Chertow,[1] Steven K. Burke,[2] Kai-Uwe Eckardt,[3] Mark Koury,[4] Wenli Luo,[2] Todd E. Minga,[2] Eldrin F. Lewis.[1] *[1]Stanford University Department of Medicine, Stanford, CA; [2]Akebia Therapeutics Inc, Cambridge, MA; [3]Charite Universitatsmedizin Berlin, Berlin, Germany; [4]Vanderbilt University Medical Center, Nashville, TN.*

Background: Vadadustat (VADA) is an oral HIF-PHI for treating anemia in CKD. In a safety analysis from the VADA phase 3 clinical program, VADA had a similar safety profile to darbepoetin alfa (DA) over the course of treatment with respect to treatment-emergent adverse events (TEAEs) and TEAEs of special interest (TEAESIs), including cardiovascular, hepatic, retinal, and neoplasm-related AEs. The present analysis evaluated the long-term safety of VADA compared with DA in patients from the phase 3 VADA clinical program.

Methods: Safety data were pooled from four global phase 3 trials that compared the safety and efficacy of VADA and DA in patients with CKD ($INNO_2VATE$: incident dialysis-dependent [DD]-CKD [NCT02865850] or prevalent DD-CKD [NCT02892149]; PRO_2TECT: ESA-untreated [NCT02648347] or ESA-treated [NCT02680574] with non-DD [NDD]-CKD). We compared the long-term (≥2 years) risk of TEAESIs and serious TEAESIs for each treatment arm. TEAESIs were grouped by medical topic. Rate ratios and 95% CIs were calculated for each TEAESI to evaluate potential differences between treatment arms.

Results: In the global phase 3 program, 2634 patients had ≥2 years of treatment and follow-up (VADA, n=1305, total patient years [PY]=3426.7; DA, n=1329, total PY=3512.4). Baseline characteristics were similar. TEAESIs were observed in 625 (47.9%; 42.2 events per 100 PY) and 696 (52.4%; 46.2 events per 100 PY) patients treated with VADA and DA, respectively (**Figure**). The frequency of serious TEAESIs was similar between VADA (259 patients [19.8%]; 12.3 events per 100 PY) and DA (292 patients [22.0%]; 14.5 events per 100 PY).

Conclusions: The long-term (≥2 years) safety profile of VADA was similar to DA in a pooled population of patients with DD- or NDD-CKD-related anemia.

Funding: Commercial Support - Akebia Therapeutics, Inc.

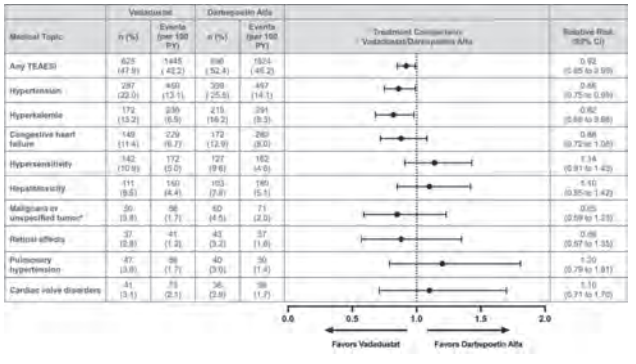


Figure. TEAESIs During Long-term Treatment. *Clear cell renal carcinomas were reported in 2 (0.2%) patients in the VADA group and 2 (0.2%) patients in the DA group.

TH-PO909

Single-Center 1-Year Experience with the Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor Desidustat (Oxemia) in Dialysis- and Nondialysis-Dependent Patients with CKD and Anemia

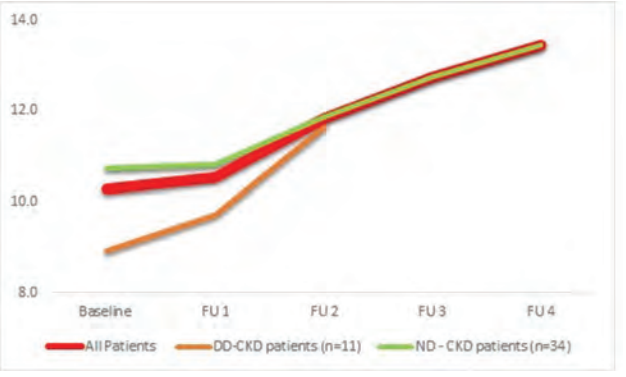
Vishal Saxena. *BLK Max Hospital, New Delhi, India.*

Background: Chronic Kidney Disease (CKD)-induced anemia results from a deficiency of erythropoietin. Recently, Desidustat, a HIF-PHI, approved in India, has shown promise in correcting anemia in both dialysis-dependent and non-dialysis-dependent CKD patients. This study presents a retrospective analysis of Desidustat usage in CKD anemia patients.

Methods: This retrospective analysis was conducted at BLK Max Hospital, New Delhi. Patients diagnosed with CKD received Desidustat at doses of 100 mg, thrice weekly, with regular monitoring of hemoglobin levels. Subjects with diabetic nephropathy, ADPKD, and a history of malignancy were excluded. The Desidustat dose was adjusted to maintain hemoglobin levels of 11-12 gm/dL.

Results: We enrolled 45 patients: 17 (37.7%) with CKD stage 3, 5 (11.1%) with CKD stage 4, 12 (26.6%) with CKD stage 5, and 11 (24.4%). Of these, 24 (53.4%) were male and 21 (46.6%) female. The majority (34, 75.5%) were non-dialysis-dependent, while 11 (24.4%) were dialysis-dependent. Hypertension was present in 40 (88.8%), diabetes in 11 (24.4%), hypothyroidism in 8 (17.7%), and hyperthyroidism in one patient. All patients received Desidustat thrice weekly with intravenous iron supplementation. Most patients (43, 95.5%) received 100 mg, one patient received 125 mg (2.2%), and another 150 mg (2.2%). The mean serum creatinine was 4.48 ± 1.28 mg/dL, eGFR was 23.17 ± 8.13 mL/min/1.73m2, and mean transferrin saturation (TSAT) was 21.21 ± 9.65%. The mean baseline hemoglobin was 10.28 ± 1.8 g/dL, which increased to 13.5 ± 1.7 g/dL by the end of the study ($p<0.05$, one-way ANOVA). Compliance with Desidustat was high, and no thrombosis, fistula failure, treatment failure, or hyperkalemia associated with HIF-PHI treatment was observed. Mild adverse events such as decreased appetite, vomiting, and generalized body weakness were transient and self-resolved.

Conclusions: Desidustat showed promising outcomes in improving hemoglobin levels in CKD-related anemia. Long-term data suggest that Desidustat is a safe alternative to erythropoietin analogues.



$p<0.05$

TH-PO910

Pharmacovigilance Analysis of the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) Events for Belzutifan

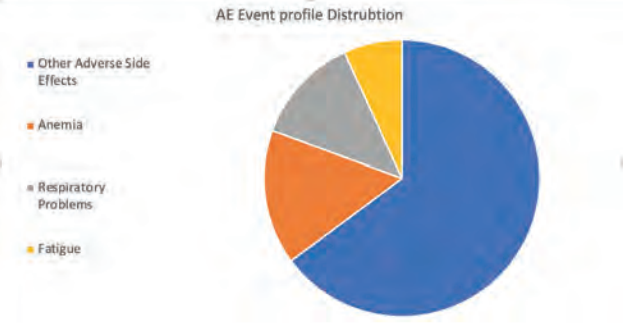
Abraham Bell, Stefan Milutinovic, Gautam Maddineni, Meloney Oliveira. *Florida State University, Tallahassee, FL.*

Background: Belzutifan is an anti-cancer medication used for the treatment of on Von Hippel–Lindau (VHL) disease-associated renal cell carcinoma. Belzutifan is a hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor. The adverse effects reported with belzutifan use include, but not limited to, fatigue, anemia, dyspnea and acute kidney injury (AKI).

Methods: We explored belzutifan's reported adverse events using the FDA Adverse Reporting System (FAERS). We analyzed data that was used in the initial study to approve belzutifan from late 2021 until May 2024.

Results: A total of 731 adverse events were reviewed. The most common side effect reported was anemia in 115 cases (14.9%). The second most common side effect were respiratory problems (both hypoxia and dyspnea) reported in over 92 cases (12.6%). The third most common side effect was fatigue, which was present in over 50 cases (6.8%). Among all adverse effects, over 543 (24.3%) were classified as severe cases that required hospitalization. Of those 543 cases, over 62 (8.5%) resulted in death.

Conclusions: The side effects of belzutifan that were commonly reported in FAERS include fatigue, anemia and respiratory complaints. According to the LiteSpark study (1), the most common side effect was anemia, reported in over 25 percent of the patient cohort. According to our results that was also present amongst the most common side effects as well. With the new approval of this drug for the treatment of advanced RCC in the setting of VHL disease, it is crucial that there is ongoing monitoring and reporting of adverse events and safety monitoring as it is used to treat patients.



Adverse event profile distrubution by cases of FAERS

TH-PO911

Pharmacovigilance Analysis of the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) Events for Daprodustat

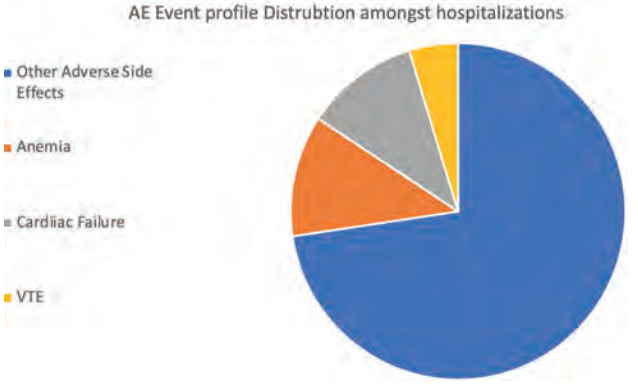
Abraham Bell,[1] Gautam Maddineni,[1] Stefan Milutinovic,[1] Isaac Bell,[2] Meloney Oliveira.[1] *[1]Florida State University, Tallahassee, FL; [2]Nova Southeastern University, Fort Lauderdale, FL.*

Background: Daprodustat was granted approval by the U.S. Food and Drug Administration on February 1st, 2023, marking it as the inaugural oral therapy for anemia induced by chronic kidney disease in adult patients undergoing dialysis for a minimum of four months. Notably, daprodustat carries a black box warning due to the heightened risk of thrombotic vascular events, myocardial infarction, cerebral vascular events, and mortality.

Methods: The adverse events associated with daprodustat were examined by utilizing the FDA Adverse Event Reporting System (FAERS). Our analysis encompassed data spanning from February 2023 to March 31st, 2024.

Results: A comprehensive review of 575 reported cases revealed that 318 cases necessitated hospitalization due to the severity of the adverse effects, with 147 reported fatalities. Notably, the most frequently reported event among hospitalized patients was a reduction in hemoglobin levels subsequent to the initiation of daprodustat (37 cases). The second most commonly reported event was cardiac failure, encompassing both new onset and acute exacerbation of chronic heart failure (35 cases). Additionally, venous thromboembolism (VTE) was reported in 15 cases.

Conclusions: FAERS analysis has highlighted anemia, acute exacerbation of heart failure, and venous thromboembolism as noteworthy adverse effects associated with daprodustat. Given its status as a novel medication, it is imperative to conduct further research and implement vigilant monitoring whilst on treatment with daprodustat.



FAERS Adverse event proflie amongst hospitalizations (severe cases)

TH-PO912

Reversible Central Hypothyroidism Associated with Roxadustat in Patients Undergoing Hemodialysis

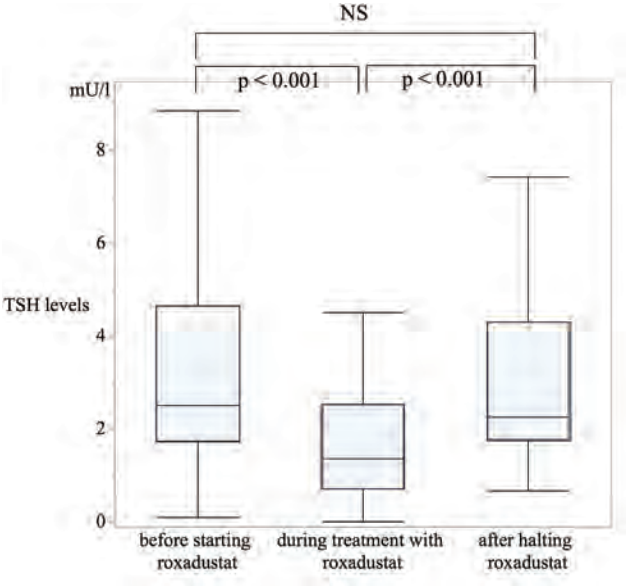
Emiko Otsuka,[1] Mineaki Kitamura,[1] Shinichi Abe,[2] Satoshi Funakoshi,[2] Tomoya Nishino.[1] *[1]Nagasaki Daigaku Byoin, Nagasaki, Japan; [2]Nagasaki Kidney Center, Nagasaki, Japan.*

Background: More than 90% of patients undergoing hemodialysis suffer from anemia. The conventional treatments involve the use of erythropoiesis-stimulating agents (ESAs) and iron supplementation. Recently, hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) have emerged as an alternative therapy for renal anemia. As roxadustat, one of HIF-PHIs, has been widely used, there have been several reports on central hypothyroidism associated with roxadustat. However, the prevalence and reversibility of roxadustat-associated central hypothyroidism in patients undergoing hemodialysis remain unclear.

Methods: We conducted a retrospective study at a single center. We included patients undergoing hemodialysis who were initially administered with roxadustat but later transitioned to ESA, and measured TSH, FT4, FT3 before, during, and after halting roxadustat treatment at the Nagasaki Renal Center from February 2020 to August 2023. We analyzed TSH, FT4, and FT3 levels in three periods: before starting roxadustat, during treatment with roxadustat, and after the discontinuation of roxadustat treatment. The Friedman test and the Bonferroni post hoc test were used to analyze.

Results: We analyzed 51 patients (mean age: 72.3 ± 10.7 years and 58.8% male). During the treatment, TSH significantly decreased from 2.46 (1.60–4.51) mU/l to 1.36 (0.72–2.41) mU/l(P<0.001) and FT4 decreased from 1.11 (0.97–1.24) mU/l to 0.92 (0.71–1.03) mU/l (P<0.001). After cessation, TSH and FT4 subsequently recovered to 2.56 (1.78–4.63) mU/l(P<0.001) and 1.05 (0.93–1.17) mU/l (P<0.001) (Figure). There were no significant differences in FT3 at the three points.

Conclusions: Roxadustat causes reversible central hypothyroidism in patients undergoing hemodialysis.



TH-PO913

Cutoff Value of Erythropoiesis-Stimulating Agent Resistance Index at Which Iron Replacement Therapy Is Expected to Be Effective

Chie Ogawa,[1,2] Ken Tsuchiya,[3,2] Taku Morito,[1] Hiroaki Io,[4] Kunimi Maeda.[1,2] *[1]Maeda Institute of Renal Research, Kawasaki, Japan; [2]Biomarker Society, INC, Kawasaki, Japan; [3]Department of Blood Purification, Tokyo Women's Medical University, Tokyo, Japan; [4]Juntendo Nerima Hospital, Tokyo, Japan.*

Background: Erythropoiesis stimulating agents (ESAs) in the treatment of renal anemia have provided tremendous long-term success, but the current problem is resistance to them. A number of causative factors can be cited, but the biggest concern is the issue of iron supply for iron deficiency and the lack of a useful iron indicator. Therefore, we investigated ESA resistance index (ERI) levels and the effects of oral iron replacement therapy (OIRT) in hemodialysis (HD) patients.

Methods: This study involved 81 courses in 67 HD patients with CRP< 0.3mg/dL who received OIRT. OIRT was performed for patients with serum ferritin <60 ng/mL and Hb <12 g/dL and continued for at least seven months(M7). The dose of darbepoetin alfa (DA) was adjusted to a target Hb level of 10–12 g/dL in accordance with the Japanese guidelines. The relationship of efficacy to changes in erythrocyte- and iron-related factors as well as baseline (M0) data was examined. Effective group was when (1) Hb increased by ≥1 g/dL or to >12 g/dL without an increase in DA, and (2) the DA dose was decreased. ERI = Weekly DA dose (μg) x 200/Hb level (g/dL)/body weight(kg).

Results: There were no significant differences in erythrocyte- and iron-related factors between the effective and ineffective groups at M0, and only the ERI was significantly higher in the effective group (9.0±7.6 vs 4.0±2.5, p=0.01). ROC curve analysis with efficacy as the endpoint showed a ERI cut-point value of ≥7.8 (sensitivity; 51.5%, specificity; 93.3%, AUC; 0.78, 95% CI; 0.66–0.90). In patients with an ERI ≥ 7.8, there were only 1 invalid cases. ERI showed significant monthly decreases down from M1 to 4 and maintained a constant value thereafter in effective group, whereas no significant change in ineffective group, and ERI was no significant difference between the groups at M7(4.9±3.8vs 3.8±2.8, p=0.32,). In effective group, red blood cell (RBC) counts and mean hemoglobin content (MCH) showed a significant increase. Serum ferritin significantly elevated at similar levels in both groups.

Conclusions: This study showed a decrease in ERI, and an increase in RBC and MCH in the effective group, suggesting that the proliferation of RBC and the production of hemoglobin were suppressed due to iron deficiency. Thus, iron replacement therapy may be effective in HD patients with CRP<0.3mg/dL and ERI≥7.8.

Funding: Private Foundation Support

TH-PO914

Hemoglobin Rate of Rise during Initial Treatment in Nondialysis-Dependent Patients with CKD and Anemia: Secondary Analysis of a Randomized Controlled Study

Ping Li,[1] Cuihua Huang,[2] Xiaoyan Xia,[2] Shuting Pan,[3] Guangyan Cai,[1] Xiangmei Chen.[1] *[1]Department of Nephrology, First Medical Center of Chinese PLA General Hospital, Nephrology Institute of the Chinese People's Liberation Army, National Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Disease, Beijing, China; [2]Medical Affairs, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China; [3]Clinical Biometrics, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China.*

Background: Clinical guidelines recommend a rate of rise (RoR) in hemoglobin (Hb) for chronic kidney disease (CKD) patients with anemia of 10-20 g/L/month, not exceeding 20 g/L/month during correction phase. We conducted a secondary analysis of a randomized study (ChiCTR2100045359) to evaluate RoR in Hb during the initial 8 weeks'treatment in non-dialysis CKD patients with anemia receiving a weight-based standard (<60/≥60 kg: 70/100 mg three times per week [TIW]) or lower (<60/≥60 kg: 50/70 mg TIW) starting dose of roxadustat.

Methods: This secondary analysis used existing data of a previous randomized study (primary results presented at ASN 2023 TH-PO1157). Patients treated with roxadustat who had at least one post-baseline Hb value were included. RoRs in Hb every 4 weeks and its distribution (ideal: 2.5-5 g/L/week; high: >5 g/L/week) during initial treatment (weeks 0–8) were evaluated.

Results: A total of 249 patients (126 in lower starting-dose and 123 in standard starting-dose arms) were included. Overall baseline Hb was 89.9±6.9 g/L. Patients in the lower-dose arm experienced slower ROR (g/L/week) in Hb during weeks 0–4 (3.3 [3.0] vs. 4.7 [3.2], P=0.0003) and weeks 0–8 (2.6 [1.9] vs. 3.3 [1.7], P=0.0024) compared to the standard-dose arm (Table). In the lower-dose arm, there were fewer patients with Hb RoR >5 g/L/week (4.8% [6/124] vs. 11.6% [14/121], P=0.0278), more patients with Hb RoR <2.5 g/L/week (45.2% [56/124] vs. 28.1% [34/121], P=0.0029), and a similar patients with Hb RoR 2.5–5 g/L/week during weeks 0-8 (50.0% [62/124] vs. 60.3% [73/121], P=0.0996) compared to the standard-dose group.

Conclusions: Both lower and standard starting doses of roxadustat corrected anemia with an ideal RoR in Hb for non-dialysis CKD patients during initial treatment. Patients receiving the lower starting dose had a slower RoR and fewer patients with high RoR.

Funding: Commercial Support - FibroGen (China) sponsored this study

Rate of rise in Hb during initial treatment

Statistic	Overall		CKD Stage 3-4		CKD Stage 5	
	Lower (n=126)	Standard (n=123)	Lower (n=77)	Standard (n=72)	Lower (n=49)	Standard (n=51)
Weeks 0-4, Mean (SD)	3.3 (3.0)	4.7 (3.2)	3.5 (3.0)	5.3 (3.1)	2.9 (2.9)	3.9 (3.1)
Difference, 95% CI	-1.4 (-2.2, -0.7)		-1.9 (-2.9, -0.8)		-0.9 (-2.2, 0.3)	
Weeks 4-8, Mean (SD)	2.1 (2.7)	1.6 (3.4)	2.1 (2.7)	1.0 (3.5)	2.0 (2.8)	2.6 (3.1)
Difference, 95% CI	0.4 (-0.4, 1.2)		1.0 (-0.0, 2.1)		-0.5 (-1.7, 0.7)	
Weeks 0-8, Mean (SD)	2.6 (1.9)	3.3 (1.7)	2.8 (1.8)	3.3 (1.8)	2.3 (2.1)	3.2 (1.7)
Difference, 95% CI	-0.7 (-1.2, -0.3)		-0.6 (-1.2, -0.1)		-0.8 (-1.6, -0.1)	

CI, confidence interval; CKD, chronic kidney disease; Hb, hemoglobin; SD, standard deviation.
Rate of Rise is defined as a slope from a linear regression model estimated using Hb values in the given time period.
Treatment comparisons were performed using Analysis of Covariance, taking baseline Hb and baseline estimate glomerular filtration rate as covariates.

TH-PO915

Hemoglobin Variability in Nondialysis-Dependent Patients with CKD and Anemia: Secondary Analysis of a Randomized Controlled Study

Ping Li,[1] Cuihua Huang,[2] Shirui Tang,[2] Shuting Pan,[3] Guangyan Cai,[1] Xiangmei Chen.[1] *[1]Department of Nephrology, First Medical Center of Chinese PLA General Hospital, Nephrology Institute of the Chinese People's Liberation Army, National Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Disease Research, Beijing, China; [2]Medical Affairs, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China; [3]Clinical Biometrics, FibroGen (China) Medical Technology Development Co., Ltd., Beijing, China.*

Background: In a previous randomized study, a smaller absolute value of the rate of hemoglobin (Hb) change was seen during 16-weeks' treatment for non-dialysis patients with chronic kidney disease (CKD) and anemia receiving a lower roxadustat starting dose (<60/≥60 kg: 50/70 mg three times per week [TIW]) compared to the standard starting dose (<60/≥60 kg: 70/100 mg TIW), indicating less temporal Hb variability with a lower starting dose of roxadustat (previously published, ASN 2023 TH-PO1157). We conducted a secondary analysis of this study to evaluate Hb variability in both arms by non-temporal methods.

Methods: This was a secondary analysis of study ChiCTR2100045359. Patients treated with roxadustat and with at least one non-missing post-baseline Hb value were included. Hb variability was measured throughout the entire treatment period (16 weeks) by typical non-temporal methods: standard deviation (SD), coefficient variation (CV), and residual SD of Hb. The proportion of patients who achieved Hb treatment targets of 110–130 and 100–130 g/L averaged over weeks 12-16 was counted.

Results: A total of 249 patients were included (126 in lower starting-dose and 123 in standard starting-dose arms). Overall baseline Hb was 89.9±6.9 g/L. More patients in the standard-dose arm achieved the Hb treatment targets of 110–130 g/L (lower, 50.8% [64/126]; standard, 68.3% [84/123]; odds ratio [OR] [95%CI]: 0.54 [0.31, 0.94], P=0.0293), and 100–130 g/L (lower, 69.8% [88/126]; standard, 86.2% [106/123]; OR [95%CI]: 0.42 [0.20, 0.88], P=0.0217) averaged over weeks 12–16. Patients in the lower-dose arm had significantly less SD of Hb (lower, 11.1 [4.2] g/L; standard, 12.4 [4.1] g/L; difference [95%CI]: -1.4 [-2.4, -0.4] g/L, P=0.0078), and less residual SD of Hb (lower, 7.9 [4.0] g/L; standard, 9.1 [4.1] g/L; difference [95%CI]: -1.2 [-2.3, -0.2] g/L, P=0.0195). The CV of Hb was also less for the lower-dose arm, but the difference was not significant (lower, 10.8% [4.0%]; standard 11.4% [3.7%]; difference [95%CI]: -0.8% [-1.7%, 0.1%], P=0.0651).

Conclusions: More patients treated with the standard starting dose of roxadustat achieved Hb treatment targets at weeks 12–16. However, Hb variability during the 16-week treatment period was less for patients receiving the lower starting dose.

Funding: Commercial Support - FibroGen (China) sponsored this study

TH-PO916

Association of Hemoglobin Level with Mortality and Its Effect Modifiers in Patients Undergoing Maintenance Hemodialysis: A Nationwide Cohort Study

Takaaki Kosugi,[1] Takeshi Hasegawa,[2] Takahiro Imaizumi,[3] Hiroki Nishiwaki,[4] Hirokazu Honda,[5] Yasuhiko Ito,[6] Kazuhiko Tsuruya,[1] Masanori Abe,[7] Norio Hanafusa,[9] Takahiro Kuragano.[8] *[1]Department of Nephrology, Nara Medical University, Kashihara, Japan; [2]Institute of Clinical Epidemiology, Showa University, Tokyo, Japan; [3]Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan; [4]Division of Nephrology, Department of Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [5]Division of Nephrology, Department of Medicine, School of Medicine, Showa University, Tokyo, Japan; [6]Department of Nephrology and Rheumatology, Aichi Medical University, Nagakute, Japan; [7]Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan; [8]Division of Kidney and Dialysis, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan; [9]Department of Blood Purification, Tokyo Women's Medical University, Tokyo, Japan.*

Background: The optimal range of hemoglobin (Hb) levels in patients on hemodialysis (HD) remains controversial. This study aimed to investigate the association between Hb levels and mortality in patients on HD, and to explore the potential factors modifying this association using the latest nationwide database in Japan.

Methods: This observational study utilized a nationwide database from the Japanese Renal Data Registry spanning from 2019 to 2021. This study included 265,779 patients who underwent HD thrice a week. The exposure of interest was the Hb level, which was categorized into six groups: <9.0, 9.0–9.9, 10.0–10.9, 11.0–11.9, 12.0–12.9, and ≥13.0 g/dL. The primary outcome was all-cause mortality. A multivariable Cox regression analysis was performed. The nonlinear relationship between Hb levels and outcomes was investigated using restricted cubic spline analysis. Subgroup analysis was performed to explore the potential factors modifying the association between Hb levels and all-cause mortality. Missing values were imputed using multiple imputations by chained equations.

Results: During a median follow-up period of 24 months, 45,734 patients died. Compared to the reference Hb category of 10–10.9 g/dL, the risk of all-cause mortality was higher in the Hb categories of <9.0, 9.0–9.9, and ≥13 g/dL with the adjusted hazard ratios (95% confidence intervals) of 1.24 (1.20–1.29), 1.09 (1.06–1.12), and 1.19 (1.14–1.25), respectively. Restricted cubic spline analysis also showed a U-shaped relationship between Hb level and mortality. The subgroup analysis indicated that the Hb category of 12.0–12.9 g/dL was associated with increased mortality risk in patients on dialysis for ≥10 years and those with a history of cerebral infarction.

Conclusions: Hb levels of <10.0 and ≥13.0 g/dL were significantly associated with an increased risk of mortality compared with an Hb level of 10.0–10.9 g/dL in patients undergoing HD. An Hb level of ≥12.0 g/dL was also associated with an increased risk in patients on dialysis for ≥10 years and those with a history of cerebral infarction.

TH-PO917

Treatment of Clinically Meaningful Anemia by Prescriber Type in Nondialysis-Dependent CKD Patients in the United States

Jeffrey Petersen,[1] Junjie Ma,[1] Carol Moore,[1] Matthew R. Weir,[2] Jeffrey S. Berns,[3] Robert D. Toto.[4] *[1]Amgen Inc, Thousand Oaks, CA; [2]University of Maryland School of Medicine, Baltimore, MD; [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [4]The University of Texas Southwestern Medical Center, Dallas, TX.*

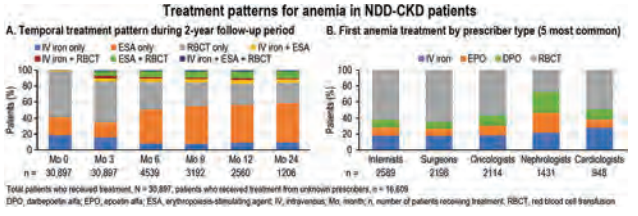
Background: Anemia management in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) remains suboptimal due to a lack of data to further understand the potential barriers. This study investigated anemia treatment patterns by prescriber type in NDD-CKD patients with clinically meaningful anemia (hemoglobin [Hb] < 10 g/dL).

Methods: This retrospective cohort study used the Optum electronic health record database (Jan 2015–Dec 2022) to describe the treatment of NDD-CKD anemia with red blood cell transfusion (RBCT), intravenous (IV) iron, or erythropoiesis stimulating agents (ESAs). Inclusion criteria included: age ≥ 18 years at CKD diagnosis, stage 3–5 CKD, ≥ 2 Hb measurements < 10 g/dL, and treatment-naïve for anemia. The date of first Hb result < 10 g/dL was the index date for anemia diagnosis. Temporal trends of anemia treatment patterns were analyzed and stratified by prescriber type.

Results: Overall, 88,917 NDD-CKD patients (mean [SD]: age, 73.9 [10.5] years; baseline Hb, 9.1 [0.6] g/dL) were included. During the follow-up (median [25th–75th percentile], 1.34 [0.50–2.94] person years), two-thirds of patients received no treatment. Among patients prescribed treatment at the index date, 20% received RBCT, 7% IV iron, and 8% an ESA; after index, 23% received RBCT, 9% IV iron, and 13% ESAs, alone or in combination. Among patients treated at index, 8% and 4% continued to receive treatment at 1- and 2-year follow-up, respectively. At 3 months, 61% and 30% of patients received RBCT or ESAs, versus 39% and 62%, respectively, at 1 year (Fig A). Among the 5 most common prescriber types, internists, surgeons, and oncologists prescribed RBCT to ~60% and nephrologists to 28% of patients (Fig B). ESAs (epoetin alfa and darbepoetin alfa combined) were prescribed to 25% and 50% of patients by oncologists and nephrologists, respectively.

Conclusions: A large proportion of NDD-CKD patients with clinically meaningful anemia remained untreated. RBCT was the most common initial treatment versus ESAs which increased with longer follow-up. Treatment patterns varied by prescriber type with nephrologists prescribing ESAs most frequently.

Funding: Commercial Support - Amgen Inc.



TH-PO918

Clinical Implementation Framework of Anemia Control Model in Singapore

Jasmine Ion Titapiccolo,[1] Milind Nikam,[2] Nandakumar Mooppil,[2] Tripti Singh,[2] Andrea Gualdoni,[3] Jeffrey L. Hymes,[4] John W. Larkin,[4] Len A. Usvyat,[4] Francesco Bellocchio,[1] Luca Neri,[1] Julianna Yeung.[3] *[1]Fresenius Medical Care AG, Bad Homburg, Germany; [2]Fresenius Medical Care AG, Singapore, Singapore; [3]Fresenius Medical Care AG, Hong Kong, China; [4]Fresenius Medical Care AG, Boston, MA.*

Background: The efficacy and safety of the Anemia Control Model (ACM) in Europe is well documented. Since 2021, ACM was piloted and implemented in Singapore. We sought to report the uptake and outcomes of ACM in the first two years of clinical implementation.

Methods: Our clinical implementation framework was based on incremental piloting and expanding the use of ACM progressively in additional clinics (Fig 1). We evaluated hemoglobin (Hb) target achievement over 12-months follow up.

Results: In a preclinical feasibility analysis ACM accurately predicted Hb levels (mean absolute error=0.66). We piloted ACM in three clinics for usability and clinical performance and gradually expanded in the full network over two years. Doctors assessed 6597 suggestions generated by ACM (52% were accepted). ACM target achievement was higher in patients treated according to ACM suggestion (p<0.05) (Fig 2).

Conclusions: Despite improved target achievement, the uptake of ACM suggestions in clinical practice is still partial. More research should be conducted in advancing clinical implementation framework of artificial intelligence so that this technology can be more effectively utilized in clinical practice.

Funding: Commercial Support - Fresenius Medical Care, Private Foundation Support

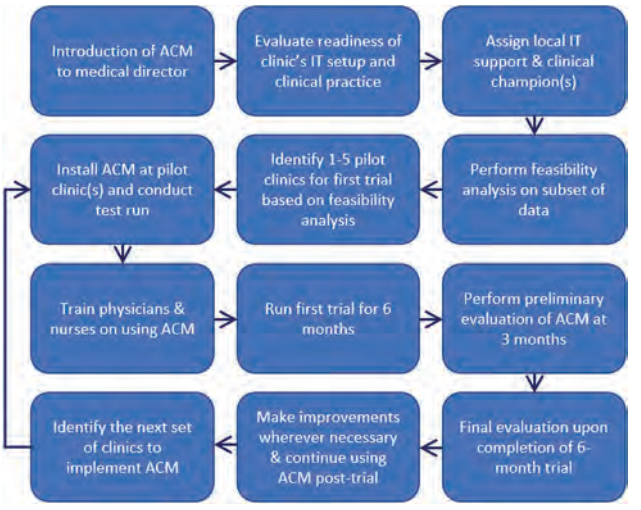


Figure1. ACM clinical implementation framework.

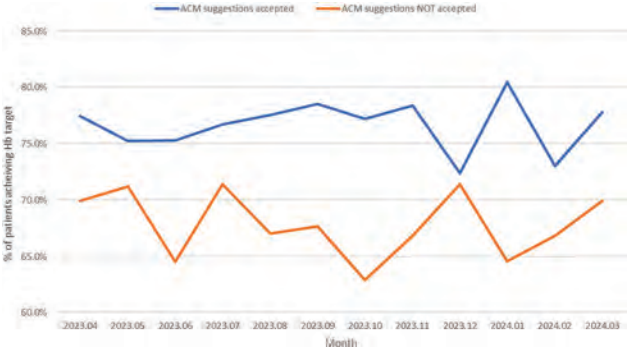


Figure 2: Percentages of patient achieving Hb target.

TH-PO919

Association of CKD with Sarcopenia: A Population-Wide Study

Mackenzie R. Alexiuk,[1,2] Silvia J. Leon Mantilla,[3] Hailey V. Hildebrand,[4] Clara Bohm,[4,3] William Leslie,[4,5] Navdeep Tangri.[4,3] *[1]University of Manitoba Department of Community Health Sciences, Winnipeg, MB, Canada; [2]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [3]Chronic Disease Innovation Centre, Winnipeg, MB, Canada; [4]University of Manitoba Department of Internal Medicine, Winnipeg, MB, Canada; [5]St Boniface General Hospital, Winnipeg, MB, Canada.*

Background: Sarcopenia, defined as the loss of muscle mass, is a growing public health concern and is an underrecognized problem in adults with Chronic Kidney Disease (CKD). The diagnosis of sarcopenia can be made via measurement of appendicular lean mass index (ALMi, indexed to height by m^2), traditionally obtained through whole-body dual-energy X-ray absorptiometry (DXA) scans, however these are not frequently performed. As a result, large population-based studies examining the relationship between CKD and sarcopenia are lacking.

Methods: Using Manitoba longitudinal administrative health data, we identified adults who had at least one DXA scan linkable to serum creatinine values within 365 days, between 2007 and 2022. Serum creatinine was used to calculate estimated glomerular filtration rate, and estimated ALMi (eALMi) was calculated through central DXA scans via a previously developed algorithm. Linear, logistic, and Cox proportional hazards models were executed to examine the relationship between CKD, sarcopenia, and adverse clinical outcomes.

Results: Our cohort contained 24,660 individuals (64.4 ± 12.5 years, 84.4% female), with 3,204 individuals (13.0%) having eALMi indicating sarcopenia. 22,648 individuals (91.8%) had eGFR ≥ 60, and 2,012 (8.2%) had eGFR < 60. After adjustment for age, sex, estimated central mass index, and comorbid conditions, the presence of eGFR < 60 was associated with higher odds of sarcopenia (OR: 1.39; 95% CI: 1.16–1.67). In individuals with two DXA scans (n=2,985), eGFR < 60 at baseline was associated with a larger decline in eALMi compared to individuals with preserved eGFR (OR: 1.61; 95% CI: 1.05–2.45). Both sarcopenia and declining eALMi were also associated with adverse clinical outcomes including hospitalization and emergency room visits, home care use, long-term care use, and all-cause mortality.

Conclusions: Our results show that CKD is associated with sarcopenia and leads to more rapid declines in appendicular lean mass over time. These findings further validate our central DXA based measurement of eALMi and sarcopenia and highlight the importance preservation of muscle mass in individuals with CKD, especially in those with reduced eGFR.

Funding: Government Support - Non-U.S.

TH-PO920

Low Skeletal Muscle Area Measured by CT Is Associated with Osteoporosis in Patients on Hemodialysis

Hwajin Park. *The Catholic University of Korea Daejeon St Mary's Hospital, Daejeon, Republic of Korea.*

Background: There are few studies to address the association of muscle and bone in dialysis patients and most of the previous studies assessed skeletal muscle mass with BIA and DXA. Whereas, we selected abdominal CT scans as assement tools for SMA because of an advantage of guaranteeing high accuracy and reproducibility. Thus, the purpose of this study is to examine the association between SMA measured by abdominal CT and BMD, and to investigate the risk of occurrence of osteoporosis with low measured SMA values.

Methods: We included 87 patients who underwent abdominal CT and BMD within 3 months after initial HD date at Daejeon St. Mary's hospital between January 2018 and September 2021. We used an abdominal CT image exported at the upper endplate of L3 transverse section and SMA was calculated by the open-source software program developed by Samsung Medical center of Korea in 2018. The BMD was measured by DEXA. All patients were divided into four SMA groups according to the interquartile ranges of measured SMA values to compare the impact of SMA groups on the osteoporosis occurrence.

Results: The mean SMA in all patients was 122.92 cm^2, and significantly higher in men (137.22 ± 26.48) than in women (106.88 ± 22.98). The positively correlated factors with both BMD were Sex(male), BMI, SMA, VFA. In multivariate regression analysis, the independent factor that most significantly affected with each BMD was the SMA ($\beta = 0.314$, $\beta = 0.974$). The risk for osteoporosis more increased as the subjects belong to the lower SMA groups (Very low SMA group; OR = 40.11, $p < 0.001$).

Conclusions: Low skeletal muscle area assessed by abdominal CT independently increases risk of osteoporosis occurrence in hemodialysis patients.

Figure 1. Correlation between SMA and lumbar spine BMD. (B) Correlation between SMA and proximal femur BMD.

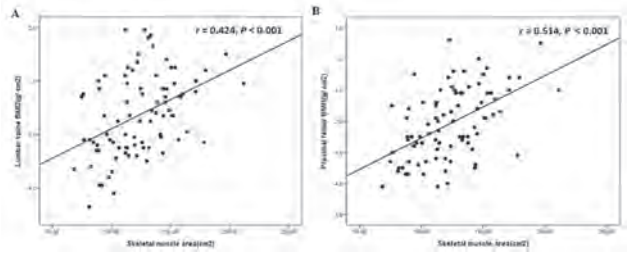


Table 4. Comparison of baseline clinical parameters among four SMA groups based on the interquartile ranges of measured SMA values.

	High SMA	Moderate SMA	Low SMA	Very low SMA	
	SMA ≥ 75 percentile (N = 22)	50 percentile ≤ SMA < 75 percentile (N = 22)	25 percentile ≤ SMA < 50 percentile (N= 21)	SMA < 25 percentile (N=22)	*p*-value
Age(years)	59.91 ± 10.98	67.14 ± 16.90	66.76 ± 12.38	67.73 ± 13.47	0.197
Sex Male, n(%)	18(81.8)	17(77.3)	8(17.4)	3(13.6)	< 0.001
BMI(kg/m^2)	27.58 ± 4.22	24.40 ± 3.12	22.78 ± 2.81	22.88 ± 6.97	0.003
Lumbar spine BMD (g/cm^2)	-0.65 ± 1.03	-0.77 ± 1.51	-1.51 ± 1.56	-2.26 ± 1.36	0.001
Proximal femur BMD(g/cm^2)	-1.39 ± 1.04	-1.69 ± 1.02	-2.46 ± 1.00	-2.81 ± 0.88	< 0.001

TH-PO921

Creatinine Filtration as an Indicator of Muscle Mass and Functional Status in Older Adults

Jacquelyn Ferguson,[1] Andrew S. Levey,[4] Lesley A. Inker,[4] Pranav S. Garimella,[3] Shoshana Ballew,[6] Tatsufumi Oka,[5,4] O. Alison Potok.[3,2] *[1]University of Vermont The Robert Larner MD College of Medicine, Burlington, VT; [2]San Diego Veterans Affairs Healthcare system, La Jolla, CA; [3]University of California San Diego, La Jolla, CA; [4]Tufts Medical Center, Boston, MA; [5]Osaka Daigaku, Suita, Osaka, Japan; [6]NYU Langone Health, New York, NY.*

Background: Low muscle mass is associated with frailty and mortality in older adults. Estimated creatinine (Cr) filtration, defined as the product of serum Cr by cystatin C-based glomerular filtration rate (eGFRCys) in mg/day/1.73m^2, has been associated with frailty and mortality. We hypothesized that lower Cr filtration would be associated with poor functional status and decreased muscle mass on imaging, in both men and women.

Methods: In the Health Aging Body Composition study, 2804 (91% of HABC) well-functioning community-living elders (aged 70-79) had serum Cr, cystatin C, functional status defined by the HABC physical performance battery HABCPPB (score 0=worst; 4=best), and appendicular lean mass (aLM) and fat free mass (FFM) on dual-energy X-ray absorptiometry (DXA). CKD-EPI 2012 and 2021 equations were used to calculate eGFRCys and eGFRCr-Cys respectively. Participants were stratified by sex and divided into Cr filtration tertiles. The association of Cr filtration with outcomes was assessed by linear regression.

Results: Mean(SD) age was 74(3) years, eGFRCr-Cys was 74(17) mL/min/1.73m^2, Cr filtration was 1049(246) mg/day/1.73m^2. Mean HABCPPB score, aLM and FFM were 2.3(0.5)points, 24(4) and 57(7)kg in men, and 2.1(0.5)points, 17(3) and 41(6)kg in women, respectively. Men and women in the highest vs lowest Cr filtration tertile walked faster (1.1(0.4) vs. 1.0(0.5)m/s for men; 1.0(0.4) vs. 0.8(0.5)m/s for women), and had stronger grip (40(8) vs. 35(7)kg for men; 24(6) vs. 21(5)kg for women). Higher Cr filtration (per SD) was associated with significantly better HABCPPB performance, higher aLM and FFM in both sexes (Table).

Conclusions: Higher Cr filtration was associated with better functional status, higher aLM and FFM in both men and women. These findings suggest it might be used clinically as a measure of muscle mass and function in older adults.

Funding: NIDDK Support

Association of Cr filtration (per SD) with functional status and with body composition, stratified by sex.

Outcome	β [95% CI] in Men	p-value	β [95% CI] in Women	p-value
HABCPPB	0.07 [0.04; 0.10]	p<.0001	0.11 [0.07; 0.14]	p<.0001
aLM	0.43 [0.27; 0.58]	p<.0001	0.30 [0.16; 0.43]	p<.0001
FFM	0.53 [0.23; 0.83]	p<.001	0.57 [0.30; 0.83]	p<.0001

adjusted for age, race, body mass index, study site, education, smoking, hypertension, diabetes, statin medication use, serum albumin, log(C-reactive protein)

TH-PO922

Clinical and Nutritional Variables Associated with Hospital Stay Days in Older Adults with CKD

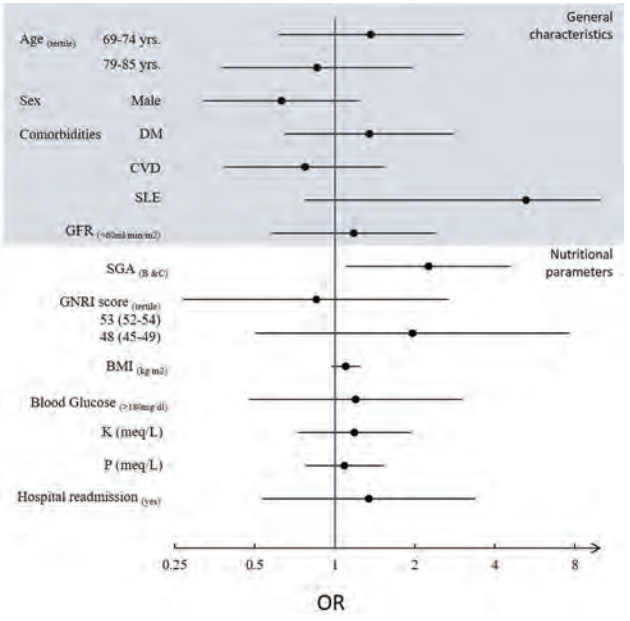
Sonia Lopez-Cisneros,[1] Samuel Ramos-Acevedo,[2] Ailema Janeth G. Ortiz,[3] Angeles Espinosa-Cuevas.[4] *[1]Instituto Nacional de Geriatria, Ciudad de Mexico, Mexico; [2]Mc Master University, Hamilton, ON, Canada; [3]Instituto Nacional de Pediatria, Mexico City, Mexico; [4]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: Malnutrition in hospitalized patients with chronic kidney disease (CKD) is a prevalent condition that is related to mortality, higher costs, and prolonged hospital stays, as well as higher hospital readmissions. The relationship between specific nutritional parameters and the days of hospital stay in our population with chronic kidney disease (CKD) has been little explored. We aimed to evaluate the association of days of hospital stay with different nutritional parameters and determine their relationship with hospital readmission.

Methods: Data was analyzed from the database of a retrospective cohort from 2007 to 2021 of patients with CKD who received nutritional care from our service. We included patients >60 years, both sexes, with at least one serum albumin, weight, and height record. Patients with terminal cancer, treatment with some renal replacement therapy, or with missing data were excluded.

Results: 419 patients were analyzed; those with longer days of hospital stay (>seven days) decreased serum albumin concentrations, and so did those with CKD stages 3Gb – 5, as well as lower scores in geriatric nutritional risk index (GNRI). Any degree of malnutrition assessed with the subjective global assessment was associated with a greater probability of prolonged stays (Table 1). No significant associations with hospital readmission were observed.

Conclusions: the detection and classification of malnutrition were related to longer days of hospital stay in patients with CKD.



TH-PO923

Creatinine Filtration as a Novel Index of Muscle Mass and Adverse Outcomes among Older Adults

Tatsufumi Oka,[1,2] Juan J. Carrero,[3] Shoshana Ballew,[4,7] Edouard Fu,[5] Yingying Sang,[4] Marie Evans,[3] Junichi Ishigami,[6] Lesley A. Inker,[2] Morgan Grams,[4] Josef Coresh,[4,7] Andrew S. Levey.[2] *[1]Osaka University Graduate School of Medicine, Suita, Japan; [2]Tufts Medical Center, Boston, MA; [3]Karolinska Institutet, Stockholm, Sweden; [4]New York University Grossman School of Medicine, New York, NY; [5]Leids Universitair Medisch Centrum, Leiden, Netherlands; [6]Johns Hopkins University Center for Health Security, Baltimore, MD; [7]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

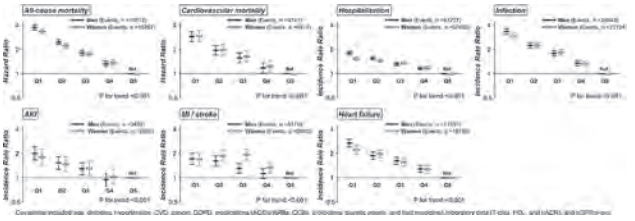
Background: Low muscle mass is common among older adults and associated with poor prognosis. Quantifying muscle mass is challenging in routine clinical practice. We previously proposed estimated glomerular filtration of creatinine (eGFcr), the product of serum creatinine (Scr) times estimated GFR using serum cystatin C (Scys) (eGFRcys), as a practical index of muscle mass in older adults, and showed an inverse association with all-cause mortality (Ballew SH, et al. *JASN* 2023). The association of eGFcr with other clinical outcomes remains uncertain.

Methods: Using data from the SCREAM (Stockholm CREAtinine Measurements) project, a health care utilization cohort in Stockholm, we analyzed 82,154 adults aged ≥65 years who had same-day tests for Scr and Scys. We examined the associations of eGFcr with all-cause and cardiovascular mortality using sex-specific Cox regression models. The associations with recurrent outcomes (hospitalizations, infection, acute kidney injury, myocardial infarction or stroke, and heart failure) were examined using sex-specific negative binomial regression.

Results: At baseline, mean (SD) age and eGFRcys were 75 (8) years and 55 (24) mL/min/1.73 m^2 in men and 78 (9) years and 53 (23) mL/min/1.73 m^2 in women, respectively. During follow-up (median, 3.9 years), a lower quintile of eGFcr was significantly associated with a higher risk of all-cause mortality in men (hazard ratio [HR] in the lowest quintile [vs. the highest quintile], 3.74; 95% confidence interval [CI], 3.48–4.03) and in women (HR, 3.34; 95% CI, 3.09–3.60), and cardiovascular mortality in men (HR, 2.88; 95% CI, 2.50–3.32) and in women (HR, 2.92; 95% CI, 2.50–3.41) in multivariable models. A consistent monotonic association was observed in each recurrent outcome (P_{trend} <0.001) (Figure).

Conclusions: Lower eGFcr was associated with a higher risk of multiple adverse outcomes among community-based older adults. We suggest evaluating the clinical utility of assessing eGFcr in clinical and research settings.

Funding: NIDDK Support



Sex-specific adjusted hazard ratios and incidence rate ratios by quintiles of eGFcr.

TH-PO924

Risk Factors of CKD Progression in Elderly Patients by Stratified Analysis from 60s to 80s

Takahito Moriyama, Yuta Kimura, Rie Suzuki, Yoshitaka Miyaoka, Yoshihiko Kanno. *Tokyo Ika Daigaku, Shinjuku-ku, Japan.*

Background: The recent high care and the managements for elderly patients have been improving their problems about the lower quality of life with malnutrition, frail, cognitive dysfunction, and others. Those approaches might also change the CKD progression and risk factors. This study analyzed 7 years renal prognosis and the risk factors for progression by the stratified analysis from 60s to 80s of CKD patients.

Methods: The 328 elderly CKD out-patients who were visited our institution in January 2017 were divided into three groups according to the age of 60s, 70s, and 80s. The clinical and laboratory findings, and medication [renin angiotensin systems (RAS) inhibitors, statins, and any diuretics] were compared among these three groups, and the renal survival until end stage kidney disease (ESKD) and/or 50 % decrease of eGFR was analyzed by the Kaplan-Meier method and log-rank test. The risk factors for CKD progressions were analyzed by the univariate and multivariate Cox regression analysis in each 60s, 70s, and 80s.

Results: The sex distributions, mean arterial pressure (MAP), and body mass index (BMI) were similar among three groups (60s/70s/80s; MAP: 94.8/92.7/93.2 mmHg, p=0.196, BMI: 24.8/23.8/23.8 kg/m^2, p=0.054). Hemoglobin (Hb) and serum albumin were significant lower according to the ages (Hb: 12.6/12.0/11.7 g/dL, p<0.001, albumin: 3.9/3.8/3.7 mf/dL, p=0.005), but the eGFR (31.3/31.1/31.8 mL/min/1.73m^2, p=0.106) and other laboratory factors were similar among three groups. The administrations of RAS inhibitors and statins were similar, but any diuretics were significantly higher according to the age (28.0/31.6/47.7 %, p=0.01). The renal survival rates were similar among three groups (68.0/58.6/59.1%, p=0.149). The univariate and multivariate analysis indicated that CKD stage and the amount of proteinuria was the significant risk factors in any ages, and the other risk factors were higher BMI in 60s [hazard ratio (HR): 1.47, 95% confidence interval (CI): 1.07-2.02, p=0.017], and lower Hb in 70's (HR: 1.68, 95% CI: 1.28-2.21, p<0.001), but any medications were not related.

Conclusions: These results indicated that we should pay attention to CKD stage and the amount of proteinuria in any elderly CKD patients. Moreover, we should also pay attention to obesity in 60s and anemia in 70s to prevent form progression of CKD.

TH-PO925

Impact of the Kidney-Metabolic Pattern on Multimorbidity and Mortality among Elderly Inpatients in China

Mengjing Wang, Jing Chen. *Huashan Hospital Fudan University, Shanghai, China.*

Background: As populations age globally, multimorbidity has emerged as a significant challenge, complicating medical decision-making and deteriorating health outcomes. Chronic kidney disease (CKD) is a common condition among the aging population, yet its role and influence on elderly multimorbidity are seldom reported. This study aims to enhance the management and standardization of medical data and chronic disease diagnoses among elderly inpatients in China, investigating the prevalence and patterns of multimorbidity, with a specific focus on CKD-associated multimorbidity patterns and their prognosis.

Methods: Our study conducted a cross-sectional analysis using a large dataset from a single center, maintained by the comprehensive hospital at Fudan University, Shanghai, China. Data were collected from the electronic medical records system for patients aged over 60 years at Huashan Hospital, Fudan University, between January 1, 2013, and January 1, 2019.

Results: Our database included 163,626 elderly inpatients with a mean age of 69.8±0.1 years. The number of morbidities was positively associated with mortality. 80.7% of patients with CKD had other comorbidities. Factor analysis revealed four multimorbidity patterns in the elderly inpatients, named the "Kidney-metabolic" pattern, "Cerebro-vascular" pattern, "Cardio-pulmonary" pattern, and "Thyroid-digestive" pattern. The "Kidney-metabolic" pattern, characterized by CKD, Hypertension, Diabetes, and Lipid disorders, exhibited the highest prevalence at 13.3%. All four multimorbidity patterns were significantly positively associated with increased mortality. However, the

impact of the "Kidney-metabolic" pattern on mortality was the only one that significantly increased with age. Among patients with the "Kidney-metabolic" pattern, the odds ratios (OR) for mortality in those aged 80-89 and ≥90 years were 11.469 (95% CI: 9.066-14.508) and 49.237 (95% CI: 37.455-64.724), respectively, compared to those aged 60-69 years.

Conclusions: CKD plays a critical role in the multimorbidity of the elderly. The "Kidney-metabolic" pattern, the most prevalent among the elderly, significantly heightened mortality risk, particularly in the oldest cohorts. Clinical practices should prioritize the management of CKD and associated metabolic diseases within multimorbid contexts to reduce mortality and promote healthy aging.

TH-PO926

Aortic Valve Alterations in Dialysis-Initiating Patients: Patient Background and Prognosis

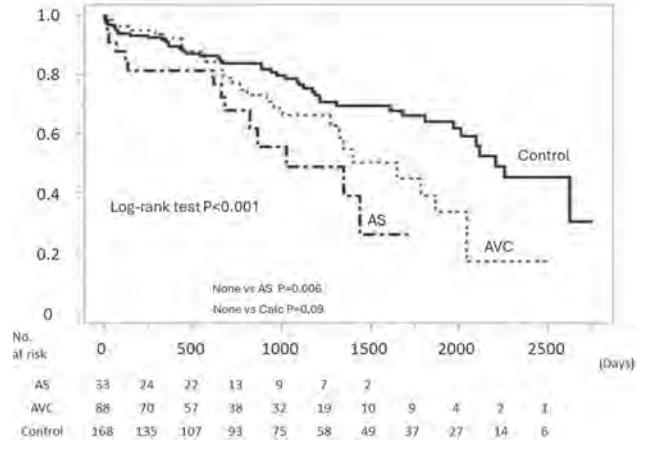
Mineaki Kitamura,[1,2] Tomoya Nishino.[1] *[1]Nagasaki Daigaku Byoin, Nagasaki, Japan; [2]Nagasaki Minato Medical Center Shimin Byoin, Nagasaki, Japan.*

Background: Aortic stenosis (AS) is a critical complication in patients undergoing, and aortic valve calcification (AVC) is considered a culprit lesion. However, little is known regarding aortic valve changes in dialysis-initiating patients, as past studies focused on those undergoing maintenance dialysis. We aimed to elucidate the relationship between AVC, AS, and patient survival following dialysis initiation.

Methods: Patients initiating dialysis between 2016 and 2023 were included. Echocardiograms assessed aortic valve changes, defining AS with a maximum trans-aortic velocity > 2.0 m/s. Patients were categorized into AS, AVC only, and control groups and followed up until February 2024. Multivariable logistic regression and Cox regression were used.

Results: We included 289 patients (mean age: 71.8 ± 12.2 years, 65.3% male, HD: PD=275:14). Aortic valve changes were identified in 121 patients (42%), with 33 patients (11%) meeting AS criteria. The mean ages for the AS, AVC only, and control groups were 79.1±8.9, 75.9±9.2, and 68.3±12.9, respectively (P<0.001). Multivariable logistic regression identified age as the sole factor associated with aortic valve changes (P<0.001). During a median follow-up of 718 (interquartile range 307-1353) days, 88 patients died. The log-rank test revealed significantly worse outcomes in the AS group. Even adjusted multivariable Cox regression indicated that AS was an independent death risk factor post-dialysis initiation (HR: 1.95, 95% CI: 1.06–3.59, P=0.04). However, aortic valve changes (AS + AVC only) were not a significant death risk (HR: 1.51, 95% CI: 0.95–2.39, P=0.08).

Conclusions: AS and AVC are associated with age in patients initiating dialysis. However, AVC only was not a risk factor for death, suggesting that risk factors related to AS, such as serum phosphate levels, should be strictly controlled following dialysis initiation.



Kaplan–Meier curves for aortic stenosis (AS), aortic valve calcification (AVC), and Control groups.

TH-PO927

Effect Modification of Familial Longevity on the Association between Cardiovascular Disease and Kidney Dysfunction

Laith Alzyood,[1,2] Tina Gao,[2] Sanish Sathyan,[2] Sandra Aleksic,[2] Sofiya Milman,[2] Michal L. Melamed,[3] Wei Chen.[2] *[1]Montefiore Medical Center, New York, NY; [2]Albert Einstein College of Medicine, Bronx, NY; [3]New York University, New York, NY.*

Background: Chronic kidney disease (CKD) is among the strongest risk factors for cardiovascular disease (CVD) and mortality. Familial longevity may protect from age-related diseases. We hypothesized that familial longevity modified the association between CKD and CVD in older adults.

Methods: LonGenity is a cohort study of community dwelling Ashkenazi Jewish adults aged 65-94 years that aims to identify genetic determinants of familial longevity by comparing offspring of parents with exceptional longevity (OPEL, n=427) with offspring of parents with usual survival (OPUS, n=404). Exceptional longevity was defined as living past the age of 95 years. GFR was estimated using serum creatinine and CKD-EPI equation. Prevalent CVD was defined as a composite of myocardial infarction, coronary artery bypass graft, percutaneous intervention, or stroke. Multiple logistic regression was used to examine the cross-sectional association between eGFR and CVD. Effect modification with familial longevity (OPEL vs. OPUS) was tested using a first-order interaction term and stratified analyses.

Results: Mean age was 76±7 years, 57% were women, 9% had diabetes, 44.5% had hypertension, and 14.6% had CVD. Mean eGFR was 73 and 69 ml/min/1.73m2 in OPEL and OPUS, respectively. Familial longevity did not significantly modify the association between eGFR and CVD (p for interaction=0.99). In stratified analyses, after adjusting for age, sex, physical activity, hypertension, diabetes, and body mass index, the odds ratio for having CVD was 0.94 (95% CI: 0.84-1.04) for every 5 mL/min/1.73m2 higher eGFR among OPEL and 0.94 (95% CI: 0.86-1.02) for OPUS.

Conclusions: In this unique cohort, we found that familial longevity did not significantly modify the association between eGFR and CVD prevalence. Further studies are needed to examine whether kidney disease predicts the incidence or progression of CVD.

Funding: NIDDK Support, Other NIH Support - N/A

Multiple Logistic Regression Analysis Stratified by Familial Longevity

	Odds Ratio (95%CI)	P-value
OPEL (n=427)	CVD events=41	
eGFR, 5mL/min/1.73m2	0.94 (0.84-1.05)	0.25
Age, 5 years	1.41 (1.05-1.90)	0.02
Female	0.12 (0.05-0.29)	<0.01
Walking endurance>30 min	0.43 (0.19-0.99)	0.05
Hypertension	1.94 (0.93-4.03)	0.08
Diabetes	1.22 (0.39-3.84)	0.73
Obese, BMI>30	1.05 (0.46-2.36)	0.92
OPUS(n=404)	CVD events=75	
eGFR, 5mL/min/1.73m2	0.94 (0.86-1.02)	0.14
Age, 5 years	1.46 (1.14-1.87)	<0.01
Female	0.11 (0.06-0.23)	<0.01
Walking endurance>30 min	0.59 (0.30,1.15)	0.12
Hypertension	1.88 (1.01-3.51)	0.05
Diabetes	1.55 (0.66-3.64)	0.31
Obese, BMI>30	1.39 (0.72-2.71)	0.33

TH-PO928

Development of a Prognostic Risk Score to Predict Early Mortality in Incident Elderly Japanese Patients on Hemodialysis

Hirokazu Okada,[1] Ken Sakai,[2] Ichiei Narita,[6] Toshiki Moriyama,[5] Yoshitaka Isaka,[5] Kei Fukami,[3] Eiichiro Kanda,[4] Naoki Kashihara.[4] *[1]Saitama Ika Daigaku, Iruma-gun, Japan; [2]Toho Daigaku, Ota-ku, Japan; [3]Kurume Daigaku Igakubu Daigakuin Igaku Kenkyuka, Kurume, Japan; [4]Kawasaki Ika Daigaku, Kurashiki, Japan; [5]Osaka Daigaku, Suita, Japan; [6]Niigata Daigaku, Niigata, Japan.*

Background: Information of short-term prognosis after hemodialysis (HD) introduction is important for elderly patients with chronic kidney disease (CKD) and their families choosing a modality of renal replacement therapy. Therefore, we developed a risk score to predict early mortality in incident elderly Japanese hemodialysis patients.

Methods: We analyzed data of incident elderly HD patients from a nationwide cohort study of the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) to develop a prognostic risk score. Candidate risk factors for early death within 1 year was evaluated using multivariate logistic regression analysis. The risk score was developed by summing up points derived from parameter estimate values of independent risk factors. The association between risk score and early death was tested using Cox proportional hazards models. This risk score was validated twice by using an internal validation cohort derived from the JRDR and an external validation cohort collected for this study.

Results: Using the development cohort (n=2,000), nine risk factors were retained in the risk score: older age (>85), yes=2, no=0; sex, male=2, female=0; lower body mass index (<20), yes=2, no=0; cancer, yes=1, no=0; dementia, yes=3, no=0; lower creatinine (<6.5 mg/dL), yes=1, no=0; lower albumin (<3.0 g/dL), yes=3, no=0; normal or high calcium (≥8.5 mg/dL), yes=1, no=0; and higher C reactive protein (>2.0 mg/dL), yes=2, no=0. In the internal and external validation cohorts (n=739, 140, respectively), the medium- and high-risk groups (total score, 6 to 10 and 11 or more, respectively) showed significantly higher risk of early death than the low-risk group (total score, 0 to 5) (p<0.001).

Conclusions: We developed a prognostic risk score predicting early death within 1 year in incident elderly Japanese HD patients, which may help detect elderly patients with a high-risk of early death after HD introduction.

Funding: Government Support - Non-U.S.

TH-PO929

Serum Uric Acid and the Risk of Cardiovascular and All-Cause Mortality in Community-Dwelling Older Adults

Antonios Douros, Muhammad Barghouth, Nina Mielke, Natalie Ebert, Elke Schaeffner. *Charite Universitatsmedizin Berlin, Berlin, Germany.*

Background: Several observational studies have shown moderate-to-strong associations between serum uric acid (SUA) and the risk of adverse cardiovascular outcomes and death. However, data on these associations among older adults are scarce. This is an important knowledge gap given the common use of SUA lowering drugs in this group, which are associated with several toxicities. Thus, we conducted a preliminary assessment of the association between SUA and the risk of cardiovascular and all-cause mortality among older adults.

Methods: We conducted a population-based prospective cohort study using data from the Berlin Initiative Study (BIS) linked to administrative healthcare data. Participants were followed from cohort entry until the occurrence of a study outcome or two years after their last individual visit, whichever occurred first. We created four exposure groups based on quartiles of SUA distribution at cohort entry – from low to high in mg/dL: Q1 [1.7,4.8], Q2 (4.8,5.8], Q3 (5.8,6.8], Q4 (6.8,13.0] – and used an intention-to-treat exposure definition (Q2 as reference group). Cox proportional hazards model estimated age- and sex-adjusted hazard ratios and 95% confidence intervals of cardiovascular and all-cause mortality.

Results: Overall, 2058 of the 2069 BIS participants were included. Mean age was 80 years, 53% were female, and the mean eGFR was 58 mL/min/1.73m^2. BIS participants with high SUA levels (Q4) were more likely to be male, obese, smokers, and to have prior cardiovascular or chronic kidney disease than those with lower SUA levels (Q1-Q3). During a median follow-up of 8 years, Q1 and Q3 were not associated with the risk of either outcome, when compared to Q2 (Table). Q4 was associated with a numerical, statistically non-significant increase in the risk of cardiovascular mortality and with a 30% increased risk of all-cause mortality, compared to Q2.

Conclusions: Our prospective cohort study suggests that high SUA is associated with the risk of all-cause, but not with cardiovascular mortality in older adults.

Funding: Private Foundation Support

	N Patients	N Events (%)	N Person-years	Incidence rate per 1000 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)
Cardiovascular Mortality						
SUA Quartiles (mg/dL)						
Q1 [1.7,4.8]	517	13 (2.5%)	3802	3.4	0.63 (0.31 – 1.26)	0.72 (0.36 – 1.45)
Q2 (4.8,5.8]	519	20 (3.9%)	3724	5.4	Reference	Reference
Q3 (5.8,6.8]	507	32 (6.3%)	3429	9.3	1.76 (1.01 – 3.08)	1.37 (0.90 – 2.75)
Q4 [6.8,13.0]	515	33 (6.4%)	3404	9.7	1.85 (1.06 – 3.22)	1.49 (0.85 – 2.61)
All-cause Mortality						
SUA Quartiles (mg/dL)						
Q1 [1.7,4.8]	517	125 (24.2%)	3802	32.9	0.76 (0.60 – 0.96)	0.84 (0.67 – 1.07)
Q2 (4.8,5.8]	519	160 (30.8%)	3724	43.0	Reference	Reference
Q3 (5.8,6.8]	507	180 (35.5%)	3429	52.5	1.23 (1.00 – 1.53)	1.10 (0.89 – 1.36)
Q4 (6.8,13.0]	515	228 (44.3%)	3404	67.0	1.59 (1.30 – 1.95)	1.30 (1.06 – 1.59)

* HR: Hazard ratio
* CI: Confidence Interval
* SUA: Serum uric acid
* Models are adjusted for age and sex

TH-PO930

Patient Activation Impacts Physical Activity in Older Adults with CKD

Karan K. Mirpuri,[1] Christopher N. Roach,[2] Emily M. Woodall,[2] Heather L. Prigmore,[2] Robert Greevy,[2] Daniel Cukor,[3] Warren D. Taylor,[2] Ebele M. Umeukeje,[2] Rachel B. Fissell,[2] Kerri L. Cavanaugh,[2] Devika Nair.[2] *[1]Washington University in St Louis, St Louis, MO; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Rogosin Institute, New York, NY.*

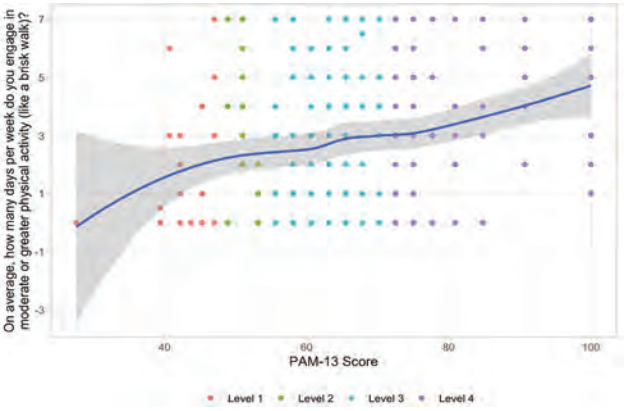
Background: Older adults with Stage 3B-5 chronic kidney disease (CKD) experience high mortality due to cardiovascular disease. Though physical activity reduces cardiovascular risk, most older adults with CKD are sedentary. The few physical activity interventions for this group face high drop-out, potentially because they do not target factors that strongly impact activity. We tested whether Patient Activation, a modifiable psychological construct of knowledge, confidence, and skill, associates with physical activity frequency in older adults with CKD to explore its utility as an intervention target.

Methods: In a cross-sectional multi-site study, we collected validated psychological (including Patient Activation Measure-13 (PAM-13); 0-100, Levels 1-4) and physiologic (including Montreal Cognitive Assessment, Physical Frailty Phenotype) factors. Physical activity was measured with the first question of the validated Exercise Vital Sign, a report of the average days/week of moderate-to-vigorous physical activity. Comorbidities were obtained from the medical record.

Results: In 231 older adults with Stage 3B-5 CKD (median age 69, 46% women, 26% Black), median PAM-13 was 65.50 (Interquartile Range (IQR) [55.60, 75]). Higher Activation associated with more frequent days of moderate-to-vigorous physical activity. Adjusting for demographics, hemoglobin, body mass index, cognition, comorbidities, instrumental support, depression, anxiety, literacy, pain, and fatigue, a 19.4 point, or 1 IQR difference in PAM-13 associated with a 0.83 (95% Confidence Interval (CI) [0.36, 1.31]; p<0.001) increase in activity days. On average, frailty associated with fewer activity days, -1.89 (95% CI [-3.07, -0.71]); p<0.01).

Conclusions: Older adults with CKD reporting higher Activation also reported more frequent moderate-to-vigorous physical activity, independent of many conceptually relevant covariates.

Funding: NIDDK Support



TH-PO931

Concentric vs. Eccentric Cycling: Effects of Progressive Training in Older Patients with CKD: A Randomized Trial

Chien Yao Sun,[1,3] Chia-Ter Chao,[2] Yu T. Chang.[1] *[1]National Cheng Kung University, Tainan, Taiwan; [2]National Taiwan University Hospital, Taipei, Taiwan; [3]University of California San Francisco Department of Medicine, San Francisco, CA.*

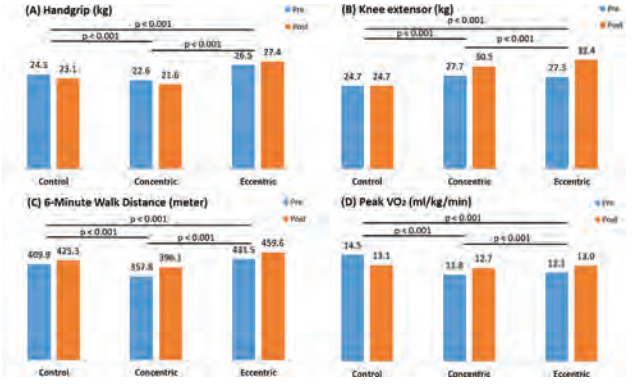
Background: Sarcopenia is common in CKD patients and leads to negative clinical outcomes. Eccentric cycling, which involves muscle lengthening under load, offers benefits like lower energy cost and perceived exertion, enabling higher intensity training. This study evaluates the effectiveness of a novel eccentric cycling (ECCcyc) intervention to reverse sarcopenia in older CKD patients.

Methods: Patients over 55 years with confirmed CKD were randomized into three groups: ECCcyc exercise, concentric cycling (CONcyc), or exercise education control. They completed 24 sessions over eight weeks, three times per week, for 20-30 minutes each on a stationary bike. Training was at RPE 13, starting at 50% of maximal cardiopulmonary output, with weekly increases of 5-10%. Efficacy (body composition, performance, cardiopulmonary fitness) was assessed at baseline and after intervention using the GEE statistical method.

Results: Thirty-one CKD patients were assigned to ECCcyc (11), CONcyc (10), and control (10) groups. Post-24 sessions, significant improvements were seen in the ECCcyc group in physical function, cardiopulmonary capacity, and quality of life. Skeletal muscle percentage increased by 3.4% in ECCcyc, while CONcyc and control groups declined by 4.4% and 4.1%, respectively (group-time interaction P<0.001). Knee strength rose from 26.2 to 30.1 kg (+14.9%) in ECCcyc, compared to 22.5 to 24.3 kg (+8.0%) in CONcyc, and decreased from 23.6 to 23.5 kg (-0.4%) in the control group. Peak oxygen consumption increased by 16.8% in ECCcyc and 15.7% in CONcyc, but decreased by 11.2% in the control group (P<0.001). The 6-minute walking distance increased by 6.5% in ECCcyc, 10.7% in CONcyc, and 3.8% in the control group (P<0.001).

Conclusions: This study provides promising evidence for the feasibility of a novel cycling modality to reverse sarcopenia in older CKD patients.

Funding: Other NIH Support - Ministry of Science and Technology (MOST) 111-2314-B-006 -034 (Taiwan)



Effects of different exercise modalities on physical outcomes in older CKD patients (between-group by time interaction analyzed using the Generalized Estimating Equations method).

TH-PO932

Evaluating Decision-Making Capacity in Elderly Patients with ESKD on Hemodialysis

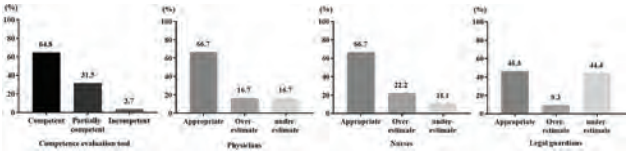
Byung chul Yu, Soo Jeong Choi, Moo Yong Park, Jin kuk Kim. *Soonchunhyang University Hospital Bucheon, Bucheon, Gyeonggi-do, Republic of Korea.*

Background: Although the act on decisions on life-sustaining treatment including hemodialysis (HD) came into force in Korea, there is no specific mention to the assessment of the patient's decision-making capacity (DMC). We compared assessments of DMC of elderly patients with end-stage kidney disease (ESKD) on HD as provided by attending physicians, nurses, legal guardians, and a competence assessment tool.

Methods: The DMC of the 94 elderly patients aged 65 and more with ESKD on HD were assessed by physicians (n = 5), nurses (n = 18), legal guardians (n = 94), and the Korean version of the Capacity-to-Consent Screen (K-CCS) as an assessment tool. We analyzed the agreement between intuitive assessments by participants and objective assessments using K-CCS for patients' DMC.

Results: The mean age and dialysis vintage of the patients were 70.2 years and 15.1 years, respectively. The concordance with capacity assessed using the K-CCS was higher in physicians- and nurses- compared with legal guardians-rated capacity (64.8% both vs. 46.3%, p = 0.003). Compared to the capacity assessed by K-CCS, legal guardians tended to underestimate the capacity (Figure 1). While physician-rated capacity showed a good agreement (α = 0.634) with the assessments using the K-CCS, assessments by nurses and legal guardians showed a moderate agreement (α = 0.580 and 0.479, respectively). A good agreement between the competence assessments of the nurses versus those of the physicians (α = 0.768), but a moderate agreement between the assessments of the physicians and nurses versus those of the patients' legal guardians (α = 0.452 and 0.447, respectively), was observed.

Conclusions: Although the intuitive assessments by nephrologists showed a good agreement with the objective evaluation using assessment tools, one-third of their assessments were inaccurate. Particularly, the tendency of legal guardians to underestimate patients' DMC raises concerns about limiting patients' autonomy. Actively utilizing competence assessment tools may help in accurately evaluating DMC of elderly patients with ESKD on HD.



Comparison of the decision-making capacity of patients assessed by the competence evaluation tool with intuitive assessments by participants

TH-PO933

Clinical Outcomes between Planned and Unplanned Hemodialysis in Elderly Patients

Woo Yeong Park,[1] Jang-Hee Cho,[2] Byung chul Yu,[3] Sang Heon Song,[4] Jae Won Yang,[5] Sungjin Chung,[6] Young Youl Hyun,[7] Eunjin Bae,[8] In O Sun,[9] Hyunsuk Kim,[10] Won Min Hwang,[11] Sung Joon Shin,[12] Soon hyo Kwon,[13] Kyung Don Yoo,[14] Yu Ah Hong.[15] The Korean Society of Geriatric Nephrology (KSGN). *[1]Division of Nephrology, Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Division of Nephrology, Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; [3]Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea; [4]Division of Nephrology, Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea; [5]Division of Nephrology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [6]Division of Nephrology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Seoul, Republic of Korea; [7]Division of Nephrology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [8]Division of Nephrology, Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea; [9]Division of Nephrology, Department of Internal Medicine, Presbyterian Medical Center, Jeonju, Republic of Korea; [10]Division of Nephrology, Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Republic of Korea; [11]Division of Nephrology, Department of Internal Medicine, Konyang University Hospital, Daejeon, Republic of Korea; [12]Division of Nephrology, Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University School of Medicine, Goyang, Republic of Korea; [13]Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea; [14]Division of Nephrology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea; [15]Division of Nephrology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Daejeon, Republic of Korea.*

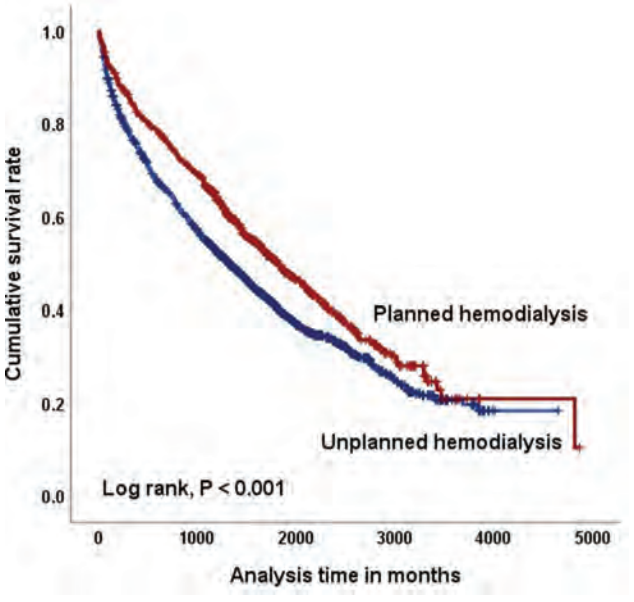
Background: The initial mortality rate of hemodialysis (HD) is high in elderly patients with end-stage renal disease (ESRD). However, the clinical outcomes between unplanned and planned HD treatment among them and prognostic factors are not clear.

Methods: We analyzed 2,373 patients aged ≥70 years starting HD. We investigated patient survivals between unplanned and planned HD in elderly ESRD patients and risk factors for mortality.

Results: Unplanned HD patients were older, had a higher dementia, congestive heart failure (CHF) and activities of daily living dependency, lower BMI, hemoglobin, albumin, hypertension and diabetes. However, there were no significant differences in the proportion of ischemic heart disease, cerebrovascular accident, in the hospitalization history prior to HD initiation between planned and unplanned HD. The proportions of catheter use at dialysis initiation and maintenance vascular access were significantly higher in the unplanned HD patients than in the planned HD patients. In Kaplan-Meier analysis, unplanned HD patients showed significantly lower patient survival rate than planned HD patients. In multivariate cox regression analysis, male, older age at dialysis initiation, lower BMI, CHF, uncontrolled malignancy, lower activities of daily living dependency, hospitalization prior to HD, catheter use as a maintenance vascular access and lower serum albumin level were significantly associated with a higher risk of all-cause mortality.

Conclusions: In elderly ESRD patients, unplanned HD using catheter as maintenance dialysis has a poor prognosis, so it is necessary to plan the appropriate vascular access in elderly patients.

Funding: Government Support - Non-U.S.



Patient survival between planned and unplanned hemodialysis

TH-PO934

Comparison of the Expression Levels of Senescence Genes between Human Normal Kidney Cells and Kidney Tumor Cells According to Age

Woo Yeong Park, Yaerim Kim, Jin hyuk Paek, Kyubok Jin, Seungyeup Han. *Division of Nephrology, Department of Internal Medicine, Keimyung University School of Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea.*

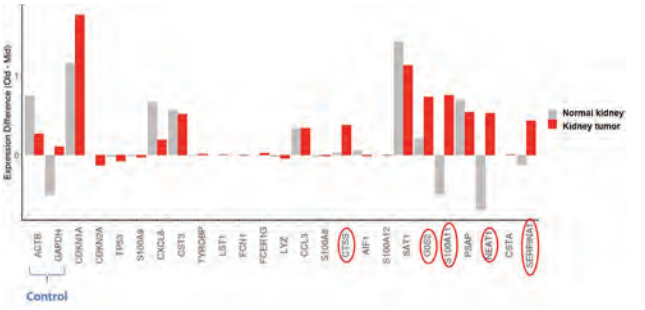
Background: Although most carcinogenic mutations induce senescence, senescence-induced cell-cycle arrest can prevent mutations, resulting in the suppression of tumorigenesis. On the contrary, the senescence-associated secretory phenotype also contributes to a pro-inflammatory and growth-stimulatory microenvironment that can promote tumor development. Despite their potential correlation, the relationship between tumor- and aging-related transcriptional changes is largely unknown.

Methods: We integrated three datasets in publicly available bulk and single-cell RNA-seq: Gene Expression Omibus (GSE207493, GSE159115, GSE131685), and applied new senescent gene set in CellAge and SenMayo to our dataset. We classified them into younger and older age groups to compare senescent gene expression patterns in normal kidney and kidney tumor cells based on the age. The study aims to investigate the differences in expression patterns of senescence genes between them.

Results: We clustered normal kidney and kidney tumor cells in the UMAP plot. Kidney tumor was located on the proximal tubule. We compared senescent gene expression levels between normal kidney and kidney tumor cells, focusing on differences between younger and older age groups. ACTB and GAPDH were in the control group, and the expression of representative senescent genes p21 (CDKN1A), p16 (CDKN2A), and p53 (TP53) was confirmed. Among them, the expression difference in CDKN1A was found to be greater in kidney tumor cells than in normal kidney cells. I applied the new senescent gene set, and CTSS, G0S2, S100A11, NEAT1, and SERPINA1 showed similar patterns. This suggests that in kidney tumors, the difference in expression of senescent genes becomes greater with older age.

Conclusions: Kidney tumorigenesis might be associated with senescent genes. This result can serve as a basis for future studies on the role of aging and senescence in human kidney malignancies.

Funding: Government Support - Non-U.S.



The difference of senescent gene expression between younger and older age in normal kidney cells and kidney tumor cells

TH-PO935

Integrating Palliative Care Consultation into a Hemodialysis Unit: A Pilot Study

Natanong Thamcharoen,[1] Pagaporn Asavapujanamanee,[2] Jeerath Phannajit,[1] Paweena Susantitaphong,[1,3] Kearkiat Praditpornsilpa.[1,3] *[1]King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [2]Benchakitti Park Hospital, Bangkok, Thailand; [3]Chulalongkorn University, Bangkok, Thailand.*

Background: Patients on hemodialysis(HD) are rarely engaged in advance care planning(ACP), resulting in frequent use of invasive treatments that are futile at the end of life. This study aims to assess the impact of integrating palliative care consultations on ACP in a HD unit.

Methods: This single-center, prospective cohort study was conducted at Benchakitti Park General Hospital HD Unit in Bangkok, Thailand. Patients on chronic HD were screened, those who met any of the following criteria were enrolled:Older than 80 years, advanced organ failure, metastatic cancer, and Palliative Performance Score ≤ 40. The enrolled patients were referred to a palliative care specialist if the primary nephrologist agreed (palliative care group, PC); otherwise, they received routine care(routine care group,RC). The study compares these 2 groups for the number of ACP or code status discussions and treatments received at the end of life.

Results: One hundred and twenty-two patients were screened, 45 patients(36.9%) were enrolled and followed for 18 months. Mean age was 81.5±9.3 years. As shown in Table1, 10 out of 45 patients (22.2%) were referred to a palliative care specialist, while 35 patients received routine care. ACP was discussed in all patients in PC group, while none in the RC group had the discussion. Seven patients(70%) in PC group chose DNR/DNI. During the follow-up, 10 out of 45 patients(22.2%) died. Of those who died, 5 out of 8 patients(62.5%) in the PC group received comfort care at the end of life, while 1 out of 2 patients in the RC who died received comfort care. One patient in PC group who chose DNR/DNI initially had full resuscitation and died. Three patients in the PC group had planned HD withdrawal and died at home.

Conclusions: Significant numbers of patients on chronic HD require palliative care. Integrating palliative care to HD unit can assist patient with ACP. Patients who had palliative care consult had code status addressed more and received less aggressive care at the end of life.

Outcomes	Palliative care, PC group (N = 10)	Routine care, RC group (N = 35)
Advance Care Planning	10	0
Code status		
Full code	2	-
DNR/DNI	7	-
Undecided	1	-
Death	8	2
Care received at end-of-life		
Comfort	5	1
Intubation	2	0
Full code	1	1
Place of death		
Home or nursing home	4	0
Hospital	4	2
Hemodialysis withdrawal	3	0

Table 1 Comparison of outcomes between 2 groups

TH-PO936

Prognostic Awareness among Patients with ESKD and Care Partners: Preliminary Themes from Semistructured Interviews

Annie Liu,[1,2] Amanda J. Reich,[3,2] Joshua R. Lakin,[4,2] Sahir Kalim.[1,2]
[1]Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Brigham and Women's Hospital, Boston, MA; [4]Dana-Farber Cancer Institute, Boston, MA.

Background: End stage kidney disease (ESKD) patients have shown limited prognostic awareness and less is known about their care partners. With older adults on dialysis and care partners being a crucial support source, we aimed to characterize various domains of prognostic awareness among patient-care partner dyads to inform the future delivery of goal concordant care.

Methods: We conducted 12 initial semi-structured interviews with ESKD patients on hemodialysis at a Boston hospital and their care partners using an interview guide developed by our research team (comprised of nephrologists, palliative care physician, and qualitative researcher). Qualitative analysis of audio-recorded, de-identified, transcribed interviews was performed. Inductive codes were identified based on Antonovsky's sense of coherence model.

Results: Analysis of 12 interviews (7 patients and 5 care partners) with a median duration of 33 minutes (19-40 minutes) revealed two preliminary themes: (1) Prognosis perception: Care partners viewed patient prognosis as time before death and shorter in duration than the patients. (2) Prognostic information preferences: Patients preferred prognostic information focused on changes in physical function, whereas care partners sought information on time remaining and expected end of life symptoms.

Conclusions: Preliminary data from this exploratory study suggest differing prognostic information needs within the dyads, possibly due to their distinct roles and responsibilities.

Participant sociodemographic and clinical characteristics

	Patient (n=7)	Care partner (n=5)
Age (years)	M=74 (67-84)	M=53 (38-65)
Female	2 (29%)	4 (80%)
Education		
High school or below	2 (29%)	1 (20%)
College or above	5 (71%)	4 (80%)
Employed	2 (29%)	3 (60%)
Married/partnered	1 (14%)	3 (60%)
Completion of Instrumental Activities of Daily Living		
All	2 (29%)	
Partial	3 (43%)	
None	2 (29%)	
Transplant Status		
Active	1 (14%)	
Temporarily inactive	1 (14%)	
Ineligible	5 (71%)	
Dialysis vintage (years)	M=3 (0.7-8)	

TH-PO937

Kidney Palliative Care in the Outpatient Setting

Samantha L. Gelfand,[1,2] Kate Sciacca.[1] *[1]Brigham and Women's Hospital, Boston, MA; [2]Dana-Farber Cancer Institute, Boston, MA.*

Background: Patients with advanced kidney disease have notable unmet palliative care needs that can affect quality of life, coping, and caregiver distress. In the United States, most outpatient specialty palliative care is devoted to patients with cancer. Few patients with advanced kidney disease have access to outpatient longitudinal palliative care. At our tertiary academic medical center, an interprofessional specialty palliative care team called KidneyPal has operated in the inpatient setting since 2019. KidneyPal developed the KidneyPal Outpatient Program (KPOP) to define and meet the palliative care needs of seriously ill outpatients with kidney disease.

Methods: We conducted a manual chart review of electronic medical records of patients seen in KPOP from October 2022-October 2023. We maintained a panel that lists all patients who have received care from KidneyPal in both inpatient and outpatient settings.

Results: Over one year, we convened 48 half-day KPOP clinic sessions. Half of these clinic sessions were staffed by a physician and nurse practitioner together, and half by the nurse practitioner alone. An average of 2.8 patients were seen per clinic session (range 0-6). A total of 138 visits occurred for a total of 63 unique patients. Mean patient age was 71.1 (range 23-91 years). Nineteen patients (30%) died during this period. Thirty-one patients (49%) were also cared for during hospitalization by the inpatient branch of the KidneyPal team. Thirteen patients (20%) elected conservative kidney management over dialysis for the treatment of kidney failure. Eleven patients (17%) received > 1 opioid prescription for the treatment of severe refractory pain.

Conclusions: Outpatient kidney palliative encompasses symptom management and decision support regarding treatment options for kidney failure. The patient population was seen in outpatient kidney palliative care is older and experiences high mortality rates. A substantial proportion may opt for conservative kidney management over dialysis if offered the choice. Approximately half of patients who received outpatient longitudinal palliative care in the clinic experienced hospitalizations during which they required inpatient palliative care consultation as well. Models of kidney palliative care should consider including outpatient resources to enhance care continuity and longitudinal relationships.

TH-PO938

Comprehensive Geriatric Assessment (CGA) and Optimisation Services before Kidney Transplantation in Older Potential Recipients: Results from the First UK-Wide Transplant Centre Survey Study

John Holland,[1,2] Judith S. Partridge,[1,2] Antonia Cronin.[1,2] *[1]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]King's College London, London, United Kingdom.*

Background: In the UK, as elsewhere, chronic kidney disease (CKD) is more prevalent in older people. Kidney transplant is the treatment of choice for End-Stage-Kidney Disease (ESKD). As the number of patients aged over 60 with advanced CKD increases, the demand for transplants in this cohort will inevitably increase. Frailty, multimorbidity and cognitive impairment are seen frequently in old age and are associated with poorer transplant outcomes. CGA is a multidimensional multidisciplinary methodology that has demonstrated benefit at systematic review level in modifying outcomes relating to these factors. This national survey aims to describe availability of CGA and optimisation services across the UK, assess attitudes and beliefs on CGA among transplant clinicians and investigate practice relating to assessment and documentation of mental capacity prior to transplant listing.

Methods: A 21-question electronic survey was developed on the SurveyMonkey platform using established healthcare survey methodology including focus groups, piloting, and research-specific question design. Lead transplant clinicians at each of the UK's 23 transplant centres were contacted by email and invited to participate using a protected survey link between 24/04/24-15/05/24

Results: A 100% response rate was obtained (23/23). Most respondents reported that frailty (13/19) and cognitive impairment (9/18) in potential transplant recipients over 60 were not adequately addressed by current NHS services.17/19 (89%) of respondents were in favour of using CGA in this population though only 3 units offered CGA. Lack of funding (13/18) and clinical evidence (12/18) were reported as key barriers to implementing CGA services. Most respondents reported their unit lacked robust methods of assessing (10/18) and documenting (10/18) mental capacity of potential transplant recipients prior to listing.

Conclusions: Our nationwide survey shows that at present frailty, multimorbidity and cognitive impairment in older potential kidney transplant recipients are not being adequately addressed in the UK. An overwhelming majority of respondents were in favour of making CGA accessible to this group. Research is underway to develop a transplant-specific CGA to improve access to and outcomes from kidney transplant in this patient cohort.

TH-PO939

Polypharmacy and Potentially Inappropriate Medications among Elderly Patients with Advanced Stage G5 CKD

Masahiko Yazawa,[1] Hiroki Nishiwaki,[2,3] Minoru Murakami,[9] Yosuke Saka,[11] Kenichiro Koitabashi,[8] Masahide Furusho,[10] Yoshihiko Raita,[6] Hiroo Kawarazaki,[4] Hideaki Shimizu,[7] Takeshi Hasegawa,[5] Yugo Shibagaki,[1] Sho Sasaki.[12] Japanese InvestigatOrs with Innovative NeTwork about Kidney Disease (JOINT-KD). *[1]St. Marianna University School of Medicine, Kawasaki, Japan; [2]Showa Daigaku Fujigaoka Byoin, Yokohama, Japan; [3]University of Illinois at Chigo Division of Nephrology, Chicago, IL; [4]Teikyo University Hospital, Mizonokuchi, Kawasaki, Japan; [5]Showa Daigaku, Shinagawa-ku, Japan; [6]Okinawa Chubu Hospital, Naha, Japan; [7]Daido Byoin, Nagoya, Japan; [8]Inagi Shiritsu Byoin, Inagi, Japan; [9]Saku General Hospital, Saku, Japan; [10]Kagoshima Medical Center, Kagoshima, Japan; [11]Kasugai Shimin Byoin, Kasugai, Japan; [12]Kyoto Daigaku Igakubu Fuzoku Byoin, Kyoto, Japan.*

Background: The American Geriatrics Society identifies Beers Criteria and potentially inappropriate medications as medication use–related issues among the elderly. Patients with chronic kidney disease (CKD) experience polypharmacy when managing multiple conditions according to clinical practice guidelines. However, a standardized description of polypharmacy and Beers Criteria–listed medications (BCLM) among elderly patients with non-dialysis-dependent CKD stage G5, defined as an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m², is lacking.

Methods: This multicenter cross-sectional study of eight teaching hospitals in Japan included elderly (≥65 years old) and non-elderly patients with non-dialysis-dependent CKD stage G5. Study candidates were enrolled from April to June 2013, and their total daily number of regular oral medications was recorded. Super-polypharmacy was defined as ≥10 medications. Medication issues, including BCLM, were compared between groups. A multivariable logistic regression analysis was done to analyze factors related to super-pharmacy and BCLM use.

Results: Of the 600 participants, 412 were elderly. The mean age and eGFR of the elderly group were 76.8±7.0 years and 10.8 mL/min/1.73 m^2, respectively. Total medications were significantly higher in the elderly versus non-elderly group (9.2±3.8 and 8.4±3.6, respectively; p=0.001). Super-polypharmacy was more prevalent in the elderly versus non-elderly group (47% vs. 37%, respectively; p=0.042). Regarding BCLM, fewer elderly participants used insulin and potassium-sparing agents, whereas significantly more elderly participants took proton pump inhibitors and hypnotics. The logistic regression analysis revealed that age, welfare public assistance, hypertension, cardiovascular disease, and diabetes were significantly associated with super-polypharmacy. The BCLM analysis identified age as negatively associated with BCLM use.

Conclusions: Almost half of elderly patients with non-dialysis-dependent CKD stage G5 had super-polypharmacy. Age was significantly associated with polypharmacy but less associated with BCLM use. Although this vulnerable population requires many medications, nephrologists might pay attention to using PIMs.

TH-PO940

Age-Related Changes in Nephrons and Podocytes: A Morphometric Study of Japanese Autopsy Kidneys

Eisuke Kubo,[1] Kotaro Haruhara,[1] Takaya Sasaki,[1] Yusuke Okabayashi,[1] Go Kanzaki,[1] John F. Bertram,[3] Akira Shimizu,[2] Nobuo Tsuboi,[1] Takashi Yokoo.[1] *[1]Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan; [2]Nihon Ika Daigaku, Bunkyo-ku, Japan; [3]Monash University, Melbourne, VIC, Australia.*

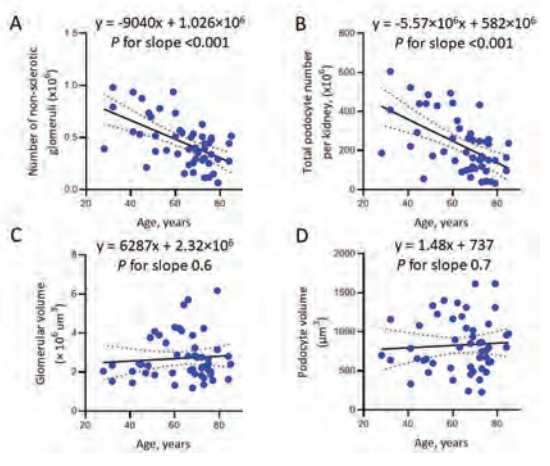
Background: Glomerular filtration rate (GFR) declines with age. However, how the number and size of nephrons and podocytes changes with age or age-related GFR decline is not fully elucidated.

Methods: Fifty autopsy kidneys without apparent kidney disease were studied. Subject age ranged from 28 to 85 years. The total number of non-sclerotic glomeruli (NSG) per kidney was estimated using design-based stereology. Podocyte number per glomerulus and glomerular and podocyte volumes were estimated using model-based stereology. Correlations between these parameters, age and estimated GFR without adjustment for body surface area (eGFR) were assessed using linear regression analysis.

Results: The median number of NSG was 421,547 per kidney and median podocyte number per glomerulus was 492. The loss of NSG averaged 9,040 per year (Fig A), and the total number of podocytes per kidney declined at a rate of 5.57 million per year (Fig B). Given that an average of 9,040 NSG were lost each year, the glomerulosclerosis-associated podocyte loss was estimated as a median of 4.4 million (IQR, 3.5×106–5.0×106) per kidney per year. The number of podocytes lost in each NSG per year was 2.7 (median, IQR 1.2–6.8). Both the number of NSG and total podocyte number per kidney were positively correlated with eGFR. Interestingly, despite the fact that both glomerular and podocyte numbers decreased with aging or eGFR decline, neither glomerular volume nor podocyte volume changed with age (Fig C and D) or eGFR.

Conclusions: This study is the first to quantitatively estimate nephron and podocyte morphometric indices associated with age and age-related GFR decline in the same population. These results suggest that a reduced number of nephrons and podocytes, and a lack of size compensation for these decreases, are characteristic morphological features of aging kidneys.

Figure



TH-PO941

Age-Related Downregulation of TFEB Activity in Proximal Tubules Affects Systemic Lipid Metabolism and Causes Apolipoprotein A4-Related Amyloidosis

Jun Nakamura, Takeshi Yamamoto, Tomoko Namba-Hamano, Atsushi Takahashi, Jun Matsuda, Satoshi Minami, Shinsuke Sakai, Sho Matsui, Hideaki Kawai, Takuya Kubota, Yoshitaka Isaka. *Osaka Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Suita, Japan.*

Background: Transcription factor EB (TFEB) is important for longevity in *Caenorhabditis elegans* and age-related deterioration of several organs in mice. However, the role of TFEB in proximal tubules remains unknown.

Methods: We investigated TFEB nuclear translocation in mouse kidneys and human kidney biopsy samples. We generated TFEB proximal tubular epithelial cell (PTEC)-conditional knockout mice (TFEB cKO mice). Wild-type mice and TFEB cKO mice were bred for up to 24 months to elucidate the role of TFEB in PTECs of aged mice.

Results: TFEB nuclear translocation in PTECs was decreased in aged mice and older patients. Surprisingly, amyloid fibrils were prominently deposited in the glomeruli and the interstitium of several aged TFEB cKO mice. To identify amyloidogenic proteins, we isolated glomeruli by laser-capture microdissection and subject the sample to proteomics. Proteomic analyses indicated that apolipoprotein A4 (ApoA4) was the primary candidate. Indeed, ApoA4 was highly positive, corresponding to the distribution of amyloid deposits, and the hepatic *Apoa4* mRNA was increased. We found that hepatic steatosis was more severe in aged TFEB cKO mice, which may upregulate hepatic ApoA4, as previously reported. In addition, we verified white adipose tissue hypertrophy and increased circulating free fatty acids in aged TFEB cKO mice. These indicate that TFEB deficiency in PTECs of aged mice causes metabolic disorders. To further elucidate the role of TFEB in PTECs, we performed scRNA-seq analyses of the kidneys. The scRNA-seq analyses showed that both oxidative phosphorylation (OXPHOS) and lysosome pathways were downregulated in the PTECs of aged TFEB cKO mice. Electron microscopy revealed that the number of mitochondria-lysosome-related organelles, which are involved in mitochondrial quality control dependent on lysosomal function, was increased in the PTECs of aged TFEB cKO mice. Reflecting these results, succinate dehydrogenase staining, indicative of mitochondrial function, was also deteriorated in the PTECs of aged TFEB cKO mice.

Conclusions: TFEB deficiency in PTECs of aged mice induces metabolic disorder due to dysfunction of both OXPHOS and lysosome pathways, likely contributing to ApoA4-related amyloidosis.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO942

PRDM16 Attenuates Glomerular Aging by Upregulating Autophagy of Podocytes

Ben Tang, Qian Yuan, Chun Zhang. *Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.*

Background: Aging leads to age-related glomerulosclerosis and a decline in GFR, manifested by the loss and reduced density of podocytes. As terminally differentiated cells, podocytes have high autophagic activity to maintain cellular homeostasis. Reduced autophagy in podocytes results in their damage and accelerates aging. Previous research by our group found that PR domain-containing 16 (PRDM16) expression decreases in damaged podocytes; however, the role of PRDM16 in podocyte aging and its relationship with autophagy levels remain unclear.

Methods: We investigated the function and mechanism of PRDM16 in natural aging animal models and immortalized human podocytes cell line models to provide a theoretical basis for targeted delay of podocyte aging. The mouse models included 24-month-old wild-type mice with PRDM16 lenti-virus injected into the renal cortexand and naturally aging mice withSelective knockout of PRDM16 in podocytes($PRDM16^{Flox}$/$NPHS2^{Cre}$) mice, supplemented by various morphological and molecular biology tests. The cellular model used an immortalized human podocyte line treated with adriamycin and X-ray irradiation, supplemented by various morphological and molecular biology tests, to confirm that PRDM16 regulates autophagy levels and thereby affects podocyte aging.

Results: In aged mice kidney, podocyte damage and sclerosis worsen, and PRDM16 expression decreases in podocytes. In podocytes aged by adriamycin or X-ray irradiation, both transcription and translation levels of PRDM16 are reduced. In vivo, localized overexpression of PRDM16 in the renal cortex significantly reduces proteinuria levels in aged mice, improves autophagic flux, and protects podocyte function. Conversely, Specific knockdown of PRDM16 in podocytes in vivo further reduces autophagy and exacerbates podocyte damage, sclerosis, and aging in elderly mice. In vitro, overexpression of PRDM16 effectively restores autophagic flux stimulated by radiotherapy and alleviates podocyte aging while knocking down PRDM16 impairs autophagic function and exacerbates aging in podocytes. In podocytes, overexpression of PRDM16 increases the expression of the key autophagy gene ATG4A, while knocking down PRDM16 reduces ATG4A expression levels.

Conclusions: Upregulating PRDM16 can restore autophagic flux by increasing ATG4A expression, thereby delaying podocyte aging and improving glomerulosclerosis.

TH-PO943

Loss of Kidney Microvasculature during Aging Is Dependent on Several Pathways: A Study in African Turquoise Killifish

Anastasia Paulmann,[1,2] Matthew Cox,[1] Laura L. Beverly-Staggs,[1] Cory P. Johnson,[1] Hannah Somers,[1] Hermann Haller.[1,2] Haller Lab. *[1]Mount Desert Island Biological Laboratory, Salsbury Cove, ME; [2]Medizinische Hochschule Hannover, Hannover, Germany*.

Background: It has been proposed that age-related kidney dysfunction and chronic kidney disease are closely associated with the loss of microvasculature, microvascular rarefaction. However, microvascular rarefaction has not been studied in an aging model and the underlying mechanisms are unclear.

Methods: We analyzed vascular density of aging kidneys in a novel aging model, African turquoise killifish (Nothobranchius furzeri), with natural lifespan of 4-6 months and phenotypical signs of aging. We tested the effects of aging on microvascular structure in different organs (kidney as well as heart and liver). Microvascular density was analyzed by histology, immunostaining and in-situ hybridization. We further used single nuclei RNA sequencing (snucRNAseq).

Results: We were able to observe a significant reduction of the kidney microvasculature in aged kidneys. The loss of vascular density was most prominent in the kidney (63.3%), followed by heart (53.35%) and liver (49.2%). We observed a significant change in gene expression in molecular pathways of endothelial cell differentiation and metabolism.

Conclusions: Our results provide a better understanding of microvascular loss and allow the identification of novel treatment targets to prevent microvascular loss in aging kidneys.

TH-PO944

Cross-Talk of Tet2 and Autophagy Promotes Senescence and Kidney Aging

Xinyue Mao,[1,2] Lu Li,[1,2] Xiaoyan Li,[1,2] Xia Zhou,[1,2] Xiaogang Li.[1,2] *[1]Mayo Clinic Department of Internal Medicine, Rochester, MN; [2]Mayo Clinic Department of Biochemistry and Molecular Biology, Rochester, MN*.

Background: Kidneys are highly susceptible to the aging process. In renal aging, a complex interplay of genetics, epigenetics, and cellular dysfunction leads to a decline in renal function. Dysregulation of DNA methylation is a prominent feature of aging. However, the role of the ten eleven translocation (Tet) enzymes, which oxidize 5-methylcytosines (5mCs) and promote locus-specific reversal of DNA methylation, in senescence and kidney aging is largely unknown.

Methods: We performed Western blot, qRT-PCR, immunoprecipitation (IP), GST pull-down assay, reduced representation bisulfite sequencing (RRBS) and methylation-specific PCR (MSP) to investigate a crosstalk of Tets and autophagy in renal tubular cells upon induction of senescence and aged kidneys upon treatment with autophagy inhibitor or Tets activator.

Results: The proteins of Tets family members (Tet1, Tet2 and Tet3) were decreased in senescent renal tubular cells and in aged kidneys, but not their mRNAs, compared to the controls. Treatment with the autophagy inhibitor (lys05) but not the proteasome inhibitor (MG132) only blocked the downregulation of Tet2 protein but not Tet1/3 upon induction of senescence. Treatment with lys05 also increased the Tet2 protein levels in aged kidneys. We found that Tet2 interacts with ATG7, but not other autophagy proteins. Knockdown of ATG7 with siRNA also blocked senescence mediated Tet2 downregulation. Tet2 directly binds to ATG7 as examined with purified GST pull-down assay. We defined the domain of Tet2 that interacts with ATG7 with Tet2 truncated constructs. We further found that AMPK mediated Tet2 phosphorylation could decrease the interaction between Tet2 and ATG7, blocking autophagy mediated Tet2 downregulation in senescent renal tubular cells. By performing RRBS, we identified three autophagy-related genes (PIK3C2B, PIK3C3 and PIK3CA), which were hypermethylated in senescent renal tubular cells as examined by MSP. Treatment with Tet2 activator AA increased the expression of PIK3C2B, PIK3C3 and PIK3CA but decreased two senescence markers, p16 and p21, supporting a direct role of Tet2 in the regulation of autophagy and senescence.

Conclusions: Tet2 is recognized as a substrate of autophagy, and is subjected to autophagy protein ATG7 mediated degradation. The downregulation of Tet2 increased the methylation of autophagy-related genes in senescent renal tubular cells and aged kidney.

TH-PO945

Role of Podocyte Ceramide Synthase 6 and C16 Ceramide in Aging-Related Kidney Changes in Marmosets

Yihan Yuan,[1] Qinyue Wang,[1,2] Qingwei Zhao,[1] Hak Joo Lee,[1,3] Ian M. Tamayo,[1] Esmeralda Trevino,[1] Balakuntalam S. Kasinath,[1] Daohong Zhou,[1] Kumar Sharma,[1,3] Guanshi Zhang.[1,3] *[1]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [2]Columbia University, New York, NY; [3]Audie L Murphy Memorial Veterans' Hospital, San Antonio, TX*.

Background: The marmoset, a nonhuman primate, has been established as a valuable model for studying the aging kidney. Aged marmosets' kidneys exhibit glomerulosclerosis, tubular fibrosis, and an increased urinary albumin to creatinine ratio. Signaling pathways related to protein synthesis and fibrosis were activated in the kidneys of these aged marmosets. Matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) analysis has revealed alterations in lipid profiles within the glomeruli of aging mouse kidneys, with a particular accumulation of ceramides (Cer) in the aging kidney. However, the role of Cer metabolism in the progression of aging-related renal changes in marmosets remains unclear.

Methods: We investigated the lipid profile in glomeruli *in situ* using MALDI-MSI-based spatial metabolomics (spatial resolution: 20 μm). The study included young male and female (around 3 years; n=4/gender), aged male and female (around 16 years; n=5/gender) marmosets from the Southwest National Primate Research Center. A targeted list of lipids involved in ceramide metabolism was extracted from the glomeruli of young and aged marmosets for comparisons. The protein level of Cer synthase 6 (CERS6) in kidney cortical tissues was measured using western blotting. Given that CERS6 is specifically expressed in podocytes of human kidneys according to single-cell transcriptomics, immunofluorescence (IF) staining was employed using anti-synaptopodin (a podocyte marker) and anti-CERS6 antibodies.

Results: Univariate and multivariate analyses revealed significant changes in lipid species involved in Cer metabolism within the glomeruli of aging marmosets. Notably, C16 Cer accumulated in the glomeruli of aged marmosets. The enzyme CERS6, which biosynthesizes C16 Cer, was significantly elevated in the kidney cortex of aging marmosets compared to young controls. IF demonstrated that CERS6 was specifically expressed in podocytes of marmoset kidneys and its expression increased with age.

Conclusions: These findings indicate dysregulation of Cer metabolism in the glomeruli (e.g., podocytes) of aging marmoset kidneys. This provides valuable insights into potential therapeutic targets and enhances our understanding of the pathological and metabolic changes associated with renal aging.

Funding: Other NIH Support - San Antonio Claude D. Pepper Older Americans Independence Center, Other U.S. Government Support

TH-PO946

Characterization of Aging-Associated Renal Phenotypes in Renal Tubular Cell-Specific NFAT5 Knockout Mice

Kosuke Maruyama, Yuichiro Izumi, Makoto Ono, Yutaka Kakizoe, Takashige Kuwabara, Masashi Mukoyama. *Department of Nephrology, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan*.

Background: The number of patients with chronic kidney disease (CKD) and hypertension is increased with age; however, it is not clearly defined why and how aging causes renal dysfunction and hypertension. Nuclear factor of activated T-cells 5 (NFAT5) is a transcription factor that is activated upon hypertonic conditions as observed in the renal medulla. Genome-wide association study has suggested that NFAT5 variants are associated with the elevation of blood pressure. We have shown that the renal tubular cell-specific NFAT5 conditional knockout (KO) mice exhibit salt-sensitive hypertension, while the mice exhibit impaired urine concentrating ability and are susceptible to renal fibrosis. These phenotypes resemble aging-associated renal dysfunction, i.e., urine concentrating disorder, salt-sensitive hypertension, and renal fibrosis. We therefore investigated the possible involvement of NFAT5 in aging-related changes of the kidney.

Methods: Aged NFAT5 KO mice (18 months old) were characterized in terms of aging-related renal phenotypes and compared with wild type (WT) mice. Kidney function was evaluated by serum creatinine. Gene expressions of senescence-associated secretory phenotype (SASP)-related factors (IL-6, IFNγ, TGF-β1, CDKN1A (p21), CDKN2A (p16), COL1A1, PAI-1, MMP3) were examined by real-time PCR. Renal fibrosis was evaluated by AZAN staining.

Results: Gene expressions of SASP-related factors were significantly increased in KO mice compared with WT mice. KO mice exhibited renal atrophy and fibrosis in the medulla. Serum creatinine was significantly higher in KO mice than in WT mice.

Conclusions: These results suggest that renal tubular NFAT5 protects against the progression of aging-associated chronic kidney disease.

TH-PO947

Vitamin D Receptor Deficiency Promotes Premature Aging by Inducing Pericytes and Microvessel Loss

Xujiao Chen. *Huashan Hospital Fudan University, Shanghai, China.*

Background: Aging is a complex process influenced by a variety of factors and demonstrates organ-specific characteristics. A common hallmark of pathological changes across various organs is the decline in microvascular density. However, the molecular mechanisms governing organ-specific microvascular decline and aging are still not well understood. Vitamin D receptor (VDR) plays a crucial role in maintaining vascular health, and its deficiency is associated with numerous age-related diseases. Nonetheless, whether VDR regulates the aging process via microvascular pathways remains unreported.

Methods: We extracted data in the Tabula Muris Senis database, and analyzed the changes in the expression of VDR with age. The VDR knockout mice was established and the changes of kidney, bone, heart, liver, lung, muscle, skin, spleen, and other tissues and organs at the age of 3 to 12 months in aging related indicators at the functional, histological and molecular biological levels were obeserved. Single cell RNA sequencing was performed in the kidneys of 6-month-old wild type and VDR knockout mice, while RNA velocity and pseudo-time analysis were used to simulate the dynamic changes of cell. adeno-associated virus (AAV) transfection technology was mainly used to carry out in vivo research in mice. Kidney pericyte-specific VDR knockdown and overexpress model were established to validate the function of pericyte in kidney aging. Finally, the effect of VDR on pericytes angiogenesis was investigated through 3D co-culture of pericytes and endothelial cells.

Results: In this study, we demonstrate that VDR deficiency leads to premature aging, prominently affecting the kidneys. Using single-cell RNA sequencing, we identified pericytes as the most significantly altered cell subtype within the kidney in VDR knockout mice. Further analysis revealed a marked decrease in pericytes and microvessels in both VDR knockout and kidney pericyte-specific VDR knockdown mice. Notably, an augmented pericyte-myofibroblast differentiation was observed, suggesting a potential mechanism underlying the observed microvascular dysfunction in the absence of VDR, which contributed to the aging process.

Conclusions: Our investigation into the role of VDR in the decline of pericytes and microvessels throughout the aging process holds the potential to unveil novel therapeutic strategies for delaying multi-organ aging.

Funding: Government Support - Non-U.S.

TH-PO948

ZFYVE21 Sustains Akt-Endothelial Nitric Oxide Synthase (ENOS) Signaling to Promote Vascular Barrier Function in the Kidneys during Aging

Dan Jane-wit. *Yale University School of Medicine, New Haven, CT.*

Background: We previously identified ZFYVE21 as a Rab5 effector in ECs. ZFYVE21 is a zinc finger-containing protein implicated in cell motility whose functions *in vivo* are unknown. In cultured human endothelial cells (ECs), we previously observed that ZFYVE21 localized to Rab5+ vesicles where it modulated PI(3,4,5)P3 content to enable Akt activation. As part of these studies, we incidentally observed that ZFYVE21 was highly expressed in glomerular ECs as well as peritubular capillaries. These observations prompted us to examine ZFYVE21 in Akt-mediated ENOS activity, a pathway critical for homeostasis of vascular barriers.

Methods: We used gene targeting to generate endothelial cell (EC)-specific ZFYVE21 KO reporter mice where ECs were labeled with GFP while other cells expressed RFP. We performed whole blood chemistries and inulin clearance measurements in mice. We analyzed human and mouse kidney tissues using I.F., in situ hybridization, Western blots, co-immunoprecipitations, and electron microscopy. We performed live cell imaging studies using mutant reporter constructs.

Results: We found that ZFYVE21 levels significantly decline in ECs in aged human and mouse kidneys. To investigate attendant effects, we analyzed EC-specific ZFVYE21$^{-/-}$ reporter mice. ZFYVE21 EC$^{-/-}$ mice developed accelerated aging phenotypes including reduced ENOS activity, failure to thrive, and renal insufficiency; and kidneys from ZFYVE21 EC$^{-/-}$ mice showed interstitial edema and glomerular EC injury. ZFYVE21-mediated phenotypes were not programmed developmentally as loss of ZFYVE21 in ECs during adulthood phenocopied its loss prenatally, and a nitric oxide donor normalized kidney function in adult hosts. Using live cell imaging and human kidney organ cultures, we found that, in a Rab5- and Akt-dependent manner, ZFYVE21 reduced vesicular levels of inhibitory caveolin-1 and promoted transfer of Golgi-derived ENOS to a perinuclear Rab5+ vesicular population to functionally sustain ENOS activity.

Conclusions: Our work defines a ZFYVE21-mediated trafficking mechanism sustaining ENOS activity and demonstrates the relevance of this pathway for maintaining kidney function with aging.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO949

Relationship between Psychological Resilience and Health Outcomes in Older Adults with Advanced CKD

Brett Burrows,[1] Anika Lucas,[1,2] C. Barrett Bowling,[1,2] Rasheeda K. Hall.[1,2]
[1]Duke University School of Medicine, Durham, NC; [2]Durham VA Health Care System, Durham, NC.

Background: Resilience, defined as the ability to recover from stressful events, is important for healthy aging. However, resilience has not been well studied in older adults with advanced chronic kidney disease (CKD), a subpopulation at high risk of stress due to wavering health status. Towards a goal of improving or maintaining resilience in older adults with advanced CKD, there is a need to identify factors related to resilience. We aimed to examine the association of depressive symptoms, physical activity (PA), and community mobility with psychological resilience.

Methods: This cross-sectional study surveyed 30 older adults (≥55 years of age) with advanced CKD (eGFR<30 ml/min/1.73m^2) seen at a routine nephrology visit to assess the potential correlation (Pearson's correlation coefficient) between psychological resilience and depressive symptoms, PA levels, and community mobility. Psychological resilience was assessed by the Resilience Scale (scores range 25 to 175, cut-offs: ≤120= low resilience, 121-145= moderate resilience, ≥146= high resilience). Depressive symptoms were assessed by the Center for Epidemiological Studies Depression (CESD) (higher scores indicate greater depressive symptoms). PA was measured by the PA Scale for the Elderly (PASE) (higher scores indicate increased PA) and community mobility was measured by the Life-space Assessment (LSA) score (higher scores reflect greater mobility).

Results: Mean (SD) age was 73.0 (9.8) years, 56.7% were female, 56.7% were Black race, and participation rate was 85.7%. The majority reported low to moderate levels of resilience (60%), with a mean (SD) of 138.0 (21.4). Participants also reported low levels of PA (mean= 71.2, SD= 72.8) and community mobility (mean= 58.6, SD= 26.7), and elevated depressive symptoms (mean= 13.9, SD= 9.9). The CESD had the strongest correlation (r= -.82 (p< 0.001)) to psychological resilience, with both the PASE and the LSA displaying moderate strength correlations (r= .38, p= 0.04; r= .47, p< 0.01, respectively).

Conclusions: The majority of participants had low to moderate levels of resilience. We found that depressive symptoms had a strong inverse correlation with psychological resilience. Future studies should examine the underlying mechanisms of this relationship and potential therapies to promote resilience among older adults with advanced CKD.

Funding: Other NIH Support - NIA

TH-PO950

Impact of Frailty on Performance of the Kidney Failure Risk Equation Using Creatinine- and Cystatin C-Based eGFR

Heather Walker, Michael K. Sullivan, Bhautesh D. Jani, Katie I. Gallacher, Patrick B. Mark. *University of Glasgow College of Medical Veterinary and Life Sciences, Glasgow, United Kingdom.*

Background: There is a high prevalence of frailty in people with chronic kidney disease (CKD). Frailty is associated with increased risk of mortality. Risk predictions equations, such as the kidney failure risk equation (KFRE) can guide management. Consideration of the competing risk of mortality on risk of future need for kidney replacement therapy is important. Decline in muscle mass in frail people may impact accuracy of creatinine-based eGFR. Using Cystatin C based eGFR (eGFRcys) or combined creatinine and Cystatin C eGFR (eGFRcrcys), may improve risk stratification of future kidney failure. We assessed the impact of frailty on performance of KFRE using eGFRcr, eGFRcys and eGFRcrcys in the UK Biobank research cohort.

Methods: Adults with CKD G3-5 (eGFR<60mL/min/1.73m^2 by any of eGFRcr, eGFRcys and eGFRcrcys) were studied. Frailty was assessed by the Fried, Rockwood and laboratory frailty indices. The outcome was kidney failure, i.e.long-term dialysis or kidney transplantation. KFRE performance at 2- and 5-years was assessed.

Results: 24,489 participants were studied; 8,533 (34.8%) had frailty by at least one frailty measure. The frail group had a mean age of 62.4 years (SD 5.7), 57% were female and mean eGFRcr 67.7ml/min/1.73m^2 (SD 17.7) compared to mean age 63.1 years (SD 5.6), 52% female and mean eGFRcr 64.5 ml/min/1.73m^2 (SD 14.8) in the non-frail group (all p<0.001). The frail group had higher discrepancy between eGFRcys and eGFRcr compared to the non-frail (-15.8 vs -6.9 ml/min/1.73m^2, p<0.001). There were 312 (1.27%) kidney failure and 1,471 (6.01%) death events within 5-years. Discrimination power of KFRE was good in individuals with and without frailty (AUC ≥0.87 across all frailty measures and eGFR equations). A higher risk of kidney failure was demonstrated in frail compared to non-frail groups with increased divergence between Kaplan-Meier and Aalen-Johansen cumulative incidence curves suggesting greater impact of the competing risk of death in the frail group.

Conclusions: KFRE adequately predicts kidney failure risk in individuals with frailty. GFR estimated using equations containing Cystatin C does not impact performance. Further work developing models considering competing risk of death may refine the risk of kidney failure in individuals with frailty.

Funding: Private Foundation Support

TH-PO951

Association between Urine Albumin and Estimated Glomerular Filtration Rate with Incident Frailty in Healthy Older Adults: Secondary Analysis of the ASPREE Trial Cohort

Elisa K. Bongetti,[1,2] Anna Wilkinson,[3,4] James B. Wetmore,[5] Anne M. Murray,[6] Robyn L. Woods,[3] Sara E. Espinoza,[7] Michael E. Ernst,[8] Michelle A. Fravel,[8] Suzanne G. Orchard,[3] Le T. Thao,[3] Joanne Ryan,[3] Rory Wolfe,[3] Kevan Polkinghorne.[1,2] *[1]Department of Nephrology, Monash Health, Melbourne, VIC, Australia; [2]Monash University Department of Medicine, Clayton, VIC, Australia; [3]School of Public Heath and Preventative Medicine, Monash University, Melbourne, VIC, Australia; [4]Disease Elimination, Burnet Institute, Melbourne, VIC, Australia; [5]Division of Nephrology, Hennepin Healthcare, Minneapolis, MN; [6]Berman Center for Outcomes and Clinical Research and Department of Medicine, Hennepin Healthcare Research Institute, and Department of Medicine, Geriatrics Division, Hennepin Healthcare Minneapolis, Minneapolis, MN; [7]Center for Translational Geroscience, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA; [8]Department of Pharmacy Practice and Science, College of Pharmacy; and, Department of Family Medicine, Carver College of Medicine. The University of Iowa, Iowa City, IA.*

Background: Identifying risk factors for frailty may facilitate early diagnosis and intervention to preserve functional status. The association between estimated glomerular filtration rate (eGFR) and albuminuria (spot urine albumin to creatinine ratio, UACR) with incident frailty in generally healthy older individuals is unclear. This study aimed to investigate whether abnormal kidney function is associated with incident frailty assessed by the modified Fried frailty phenotype (FP), and, separately, a deficit accumulation frailty index (FI).

Methods: This was a secondary analysis of 16,965 non-frail older adults aged ≥65 years in the ASPirin in Reducing Events in the Elderly (ASPREE) randomised trial cohort. Primary exposures were UACR, and eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration 2021 equation. Missing data in the FP was managed with multiple imputation. The primary outcome was time to incident frailty, analysed using multivariable adjusted discrete time survival analyses.

Results: The mean age was 75.0 ± 4.5 years, median eGFR 78.5mL/min/1.73m^2 (IQR 67.5, 89.3), and the median UACR was 0.80 mg/mmol (IQR 0.50, 1.50). In analyses using the FP, 950 people developed frailty over a median follow-up of 4.7 years (IQR 3.0, 5.0). Using the FI, 2,338 developed frailty over a median of 4.0 years (IQR 3.0, 5.0). The relationships between eGFR and both incident FP and FI was non-linear, such that an eGFR <45 or ≥75mL/min/1.73m^2 was significantly associated with an increased risk of incident frailty. For every doubling of baseline UACR, risk of incident frailty increased by 4% using the FP (HR: 1.04, 95%CI:1.02-1.07) and the FI (HR: 1.04, 95%CI:1.01-1.07).

Conclusions: In older adults, doubling of UACR, even at very low levels, was independently associated with incident frailty. Both low and high eGFR were associated with increased risk of incident frailty.

Funding: Other NIH Support - NIA, NCI, NEI, Government Support - Non-U.S.

TH-PO952

Impact of Y-Chromosome Loss on Age-Related Gene Expression

Jose L. Agraz, Parker C. Wilson. Wilson Lab. *University of Pennsylvania, Philadelphia, PA.*

Background: Loss of Y chromosome (LOY) is associated with compromised DNA repair, increased inflammation, and diminished immune surveillance. Single-cell RNA sequencing (scRNA-seq) elucidates the impact of LOY in the kidney, which may provide insight into how LOY heightens susceptibility to chronic kidney disease (CKD), acute kidney injury (AKI) and renal cancer. This study analyzes a large scRNA-seq dataset from the Kidney Precision Medicine Project (KPMP) to examine the effects of aging and LOY in different kidney cell types.

Methods: The KPMP dataset comprised 174 participants: 87 males, 85 females, and 2 individuals with an unspecified sex, aged 20 to 89. These data include samples from healthy individuals (n=55) and patients with CKD (n=82), AKI (n=33), and diabetes mellitus without CKD (n=3). scRNA-seq raw data was realigned, preprocessed to remove doublets, and integrated using scvi-tools. LOY cells were genotyped based on the lack of Y chromosome transcripts in cells meeting prespecified filters. Differential expression was compared between groups using scanpy.

Results: We observed significant age-related changes in gene expression among multiple kidney cell types. In aged men, *TTTY14* and *USP9Y* (Y chromosome transcripts) were significantly decreased in healthy proximal tubule (PT) and injured PT subsets, parietal epithelial cells, and distal nephron cell types. Cell types with the highest proportion of LOY were injured subsets of proximal tubule: PT_MT (22%), PT_PROM1 (17%), and PT_VCAM1 (13%). LOY in PT was associated with enrichment of multiple pathways, including calcium reabsorption, immune response, and metabolic pathways.

Conclusions: LOY significantly impacts gene expression in PT of aging males. Elevated LOY in PT cell types correlates with enrichment of pathways linked to calcium reabsorption, immune response and metabolic pathways. These data suggest LOY contributes to cellular dysfunction and may predispose men to kidney disease.

Funding: Other NIH Support - DK126847

TH-PO953

Exploring the Therapeutic Strategy of Low-Intensity Pulsed Ultrasonography in Age-Related CKD

Shing-Hwa Liu,[1] Chih-Kang Chiang,[1] Ting-Yu Chang,[1] Cheng-Tien Wu.[2] *[1]National Taiwan University, Taipei, Taiwan; [2]China Medical University, Taichung, Taiwan.*

Background: The global population is entering an aging stage. The prevalence of chronic kidney disease (CKD) in people ≥65 years old is much higher than that of people under 65 years old. Ultrasound has been a useful diagnostic tool for a long time. Non-invasive low-intensity pulsed ultrasound (LIPUS) has been found to be a method for treating diseases, such as neurological or bone diseases. Our team's studies also found that LIPUS could effectively alleviate the renal dysfunction in AKI and CKD mouse models. The preventive or therapeutic strategies for age-related CKD still need to be clarified or developed. Here, we evaluated the interventional potential of LIPUS on CKD progression in a naturally aging mouse model.

Methods: Male C57BL/6 mice with the age of 3 (young control), 12, and 24 months (human age equivalent: about 20, 42.5, and 69 years, respectively) were tested. LIPUS with condition of 3 MHz, 0.1 W/cm^2, 20 min daily was applied to the kidney of aged mice for one month. The biochemical analysis in the serum, histological examination in the kidney, and protein expression for senescence-related signaling molecules in the kidney were determined.

Results: In naturally aged mice, the serum creatinine and cystatin C, but not BUN, levels were significantly increased in mice with 24-month-old ($p<0.05$, n=6), but not 12-month-old ($p>0.05$, n=6), compared to the young control mice (3-month-old), which could be significantly reversed by LIPUS stimulation ($p<0.05$, n=6). The periodic acid-Schiff stain and Masson's trichrome stain showed that there were histological changes and collagen deposition, respectively, in aged mice with 24-month-old ($p<0.05$, n=6), which could be significantly reversed by LIPUS stimulation ($p<0.05$, n=6). The protein expression levels of senescence markers including senescence-associated secretory phenotype (SASP)-related signals (p53, p21, GATA-4, NFκB, TGFβ, IGFBP3, and PAI-1) increased in the kidneys of aged mice ($p<0.05$, n=6). LIPUS treatment significantly prevented the increased senescence signals in the kidney of aged mice ($p<0.05$, n=6).

Conclusions: These findings suggest that cell senescence in the kidney may contribute to the CKD progression in naturally aged mice. LIPUS is capable of inhibiting the renal cell senescence in the aging kidney and may have potential for treating age-related CKD.

Funding: Government Support - Non-U.S.

TH-PO954

Mary1 Increases Adenosine Triphosphate and Decreases Collagen-1 in Renal Cortices of Aged Mice

Kai W. Mcalister,[1] Jaroslav Janda,[1] Paul Victor Santiago Raj,[1] Austin D. Thompson,[1,2] Rick G. Schnellmann.[1,3] *[1]The University of Arizona College of Pharmacy, Tucson, AZ; [2]Southwestern Environmental Health Sciences Center, Tucson, AZ; [3]Southern Arizona VA Health Care System, Tucson, AZ.*

Background: Kidney disease remains a leading cause of death in the United States and its prevalence is on the rise. One of the greatest risk factors for the development of kidney disease is aging. Unfortunately, little is known regarding prevention of the debilitating effects of renal aging. Renal aging is characterized by increased mitochondrial dysfunction and fibrogenic mediators, which have been linked to various metabolic and renal impairments, such as diabetes, obesity, cardiovascular disease, and chronic inflammation. Mary1 is an experimental therapeutic that induces mitochondrial biogenesis (MB) and restores renal function in a mouse model of AKI. We hypothesized that treatment with Mary1 may decrease markers of renal dysfunction during aging.

Methods: Mice were divided into three groups: 1) young (10-week-old) mice treated with vehicle control [saline + 0.1% DMSO], 2) aged (25-month-old) mice treated with vehicle control, and 3) aged mice treated with Mary1 [0.3 mg/kg] (n=6-8/group). Each group was further divided into subgroups and treated for 1) 3 weeks or 2) 16 weeks. Following treatment, kidneys were harvested, and cortical tissue was used for immunoblotting and RT-PCR.

Results: For the 3-week treatment group, Mary1-treated aged mice exhibited a 35% reduction in renal cortical collagen-1 mRNA, and a 61% reduction in collagen-1 protein

compared to vehicle-treated aged mice. For the 16-week group, Mary1-treated aged mice exhibited a 46% reduction in renal cortical collagen-1 mRNA, and a 35% reduction in collagen-1 protein compared to vehicle-treated aged mice. Additionally, Mary1 treatment increased renal cortical ATP by 73% compared to aged mice that received vehicle, reaching levels comparable to that in young mice in the 3-week treatment group. While Mary1-treated aged mice exhibited a 33% increase in renal cortical collagen-1 mRNA, there was a persistent 35% reduction in collagen-1 protein compared to vehicle-treated aged mice in the 16-week group.

Conclusions: These results show the therapeutic potential of Mary1 in ameliorating age-related renal cortical mitochondrial dysfunction and fibrosis. Further research is needed to determine the mechanism by which Mary1 achieves these therapeutic effects.

Funding: Veterans Affairs Support

TH-PO955

Decrements in Lower-Body Muscle Power Are Associated with Impaired Physical Function in Patients on Hemodialysis

Natalie A. Macheret,[1] Drake Dillman,[2] Sharon M. Moe,[2] Sharon L. Karp,[2] Kenneth Lim,[2] Eliott Arroyo.[1] *[1]Wake Forest University, Winston-Salem, NC; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: Patients with chronic kidney disease (CKD) commonly suffer from poor physical function and decreased quality of life. Muscular power—the product of force and velocity of contraction—is a significant predictor of physical function in healthy older adults. However, the role of muscle power in regulating physical function in CKD is unclear. Herein, we sought to examine the relationship between muscular power and physical function in individuals with advanced CKD on hemodialysis (HD).

Methods: This cross-sectional study used data from the Musculoskeletal Function, Imaging and Tissue Resource Core (FIT Core) study cohort at the Indiana Center for Musculoskeletal Health. Participants completed a comprehensive battery of objective and self-reported physical function assessments. Muscle power was estimated from the sit-to-stand test using a validated equation and adjusted for body mass (relative power) and leg muscle mass (specific power). Multiple linear regression analysis was used to assess the association between relative muscle power and physical function outcomes.

Results: Group comparisons between patients on HD (n=44, 54.5% men, age=50±14 y) and healthy controls (n=50, 62% men, age=52±14 y) showed that the HD group had a greater prevalence of diabetes (p<0.001), but no significant differences in age, sex, or race. Patients on HD exhibited significant decrements in both relative (3.0 [0.8] W/kg versus 3.9 [1.2] W/kg in controls; p<0.001) and specific (14.5 [3.4] W/kg versus 17.8 [5.3]; p<0.001) muscle power, even after adjusting for age, sex, diabetes, smoking status, cardiovascular disease, and race. Relative muscle power in patients on HD was significantly associated with the short physical performance battery (SPPB) score (β=1.5, p<0.001) and with the physical function subscale of the Short Form 36 Health Survey (SF36 PF-10) score (β=13.0,p=0.006) after adjusting for covariates.

Conclusions: Patients on HD exhibit significant decrements in both relative and specific lower body muscle power, which indicates that these decrements are not a result of muscle atrophy alone. The decline in muscle power is independently associated with both objective and self-reported measures of physical function. Further research is needed to validate the prognostic utility of muscle power in patients on HD.

Funding: Other NIH Support - NIH P30P30 AR072581-06

TH-PO956

Association between Electrical Impedance Vectors and Sarcopenia in Patients with CKD

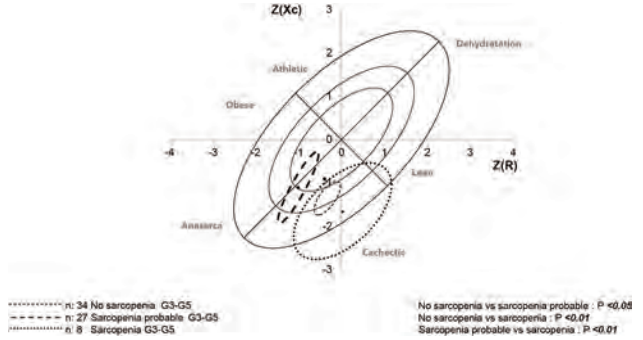
Ailema Janeth G. Ortiz,[1] Laura F. Rosales Arreola,[2] Ana Callejas,[2] Paola V. Miranda,[2] Sonia Lopez-Cisneros,[3] Angeles Espinosa-Cuevas.[2] *[1]Instituto Nacional de Pediatria, Mexico City, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [3]Instituto Nacional de Geriatria, Ciudad de Mexico, Mexico.*

Background: Sarcopenia, characterized by the progressive loss of muscle quality and quantity, affecting quality of life, commonly occurs in patients with Chronic Kidney Disease. Bioelectric Impedance (IBE) and IBE Vectors (VIBE) allow the identification of decreased muscle mass and might identify patients with sarcopenia. We aimed to identify the association between VIBE and sarcopenia in patients with CKD (G3-G5) and HD.

Methods: This cross-sectional study included adult patients over 18 years with ESRD and replacement treatment. Bioelectrical impedance measurements were performed, and body composition was evaluated. The EWGSOP2 criteria were used to diagnose sarcopenia.

Results: The prevalence of sarcopenia was 11.6% in CKD (G3-G5) and 14.8% in HD. VIBE patterns indicated that sarcopenia was located outside the tolerance ellipses in the right quadrant in both groups ($p < 0.05$). In the HD population, the phase angle and Impedance Ratio (IR) were lower in patients with CKD on HD (p 0.03). In CKD (G3-G5), age was higher in the sarcopenia group ($p < 0.05$), and they had DM (p 0.03) and lower creatinine concentration (p 0.02).

Conclusions: The results suggest that VIBE, phase angle, and IR could be helpful tools for identifying sarcopenia in patients with CKD and HD. These measurements could provide valuable information for the early detection and management of sarcopenia in this population.



TH-PO957

Nutritional Status and Sleep Quality in Adult Patients with CKD

Ailema Janeth G. Ortiz,[1] Norberto Rodriguez Gonzalez,[5] Ingrid Mendoza Mayorga,[4] Samuel Ramos-Acevedo,[3] Sonia Lopez-Cisneros,[2] Angeles Espinosa-Cuevas.[4] *[1]Instituto Nacional de Pediatria, Mexico City, Mexico; [2]Instituto Nacional de Geriatria, Ciudad de Mexico, Mexico; [3]McMaster University, Hamilton, ON, Canada; [4]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [5]Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico.*

Background: Sleep and appetite disorders share common mechanisms and have been shown to impact metabolic disorders in the general population. Patients with chronic kidney disease (CKD) often experience sleep disturbances, but whether these are associated with their nutritional status is unknown. We aimed to determine the relationship between measures of nutritional status and sleep quality in adult patients with non-dialysis-dependent CKD.

Methods: Cross-sectional cohort study including adult patients with estimated glomerular filtration rate (eGFR)<60 ml/min/1.73m2 attending nephrologist consultations. Patients with amputations or metallic plates, diagnosed psychiatric disorders, and using medications with a direct effect on sleep were excluded. All patients responded to the Pittsburgh sleep quality questionnaire (PSQI) and underwent a full nutritional assessment including subjective global assessment (SGA), bioelectrical impedance, anthropometry, and 24-hour recall. Multivariate regression was used to analyze the associations between measures of nutritional status and sleep quality (Odd Ratios with 95% confidence intervals).

Results: A total of 106 participants, median age 52 (38-66) years. Hypertension was present in 62% of participants and diabetes in 46%. The majority (75%) of participants presented poor sleep quality (PSQI ≥5), and a total of 35% were considered malnourished (SGA>1). Compared to well-nourished patients, malnourished patients were more likely higher systolic blood pressure, lower serum albumin, and lower eGFR, ($p<0.05$ for all). No significant differences in age, gender, comorbidities, or dietary energy intake were observed. Malnourished patients also reported higher PSQI scores (worse sleep quality, median score 10 vs 7, $p <0.01$). In multivariable logistic regression adjusting for age, sex, eGFR, energy intake, and comorbidities, the Odds of malnutrition increased by 18% (OR 1.18, 95% CI 1.04 to 1.33) for unit increase in PSQI).

Conclusions: Most patients with non-dialysis dependent CKD reported poor sleep quality, and its severity was associated with the presence of malnutrition as assessed by SGA.

TH-PO958

Sarcopenia in Patients on Hemodialysis in Brazil: Results of the SARC-HD Study

Heitor S. Ribeiro,[1] Marvery P. Duarte,[1] Otavio Nobrega,[1] Fábio A. Vieira,[1] Maryanne Silva,[2] Dário R. Mondini,[11] Bruna Maggi Sant'Helena,[12] Henrique S. Disessa,[3] Angélica N. Adamoli,[10] Daiana C. Bundchen,[7] Rodrigo d. Krug,[4] Antonio Jose Inda-Filho,[9] Carla M. Avesani,[5] Barbara P. Vogt,[8] Maycon M. Reboredo.[6] SARC-HD Study Group. *[1]Universidade de Brasilia Faculdade de Ciencias da Saude, Brasilia, Brazil; [2]Universidade Estadual Paulista Julio de Mesquita Filho, Botucatu, Brazil; [3]Universidade Estadual Paulista Julio de Mesquita Filho, Bauru, Brazil; [4]Universidade de Cruz Alta, Cruz Alta, Brazil; [5]Karolinska Institutet, Stockholm, Sweden; [6]Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil; [7]Universidade Federal de Santa Catarina, Ararangua, Brazil; [8]Universidade Federal de Uberlandia, Uberlandia, Brazil; [9]Centro Universitario ICESP, Brasilia, Brazil; [10]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [11]Universidade Estadual de Campinas, Campinas, Brazil; [12]Faculdade IELUSC, Joinville, Brazil.*

Background: Sarcopenia is a common feature of patients on hemodialysis and is strongly associated with adverse clinical outcomes, but its epidemiology in middle-income countries remains underexplored. We described the prevalence and risk factors for sarcopenia in patients on hemodialysis in Brazil.

Methods: Baseline data from the SARC-HD multicenter study was analyzed. Muscle strength was assessed by handgrip; muscle mass by calf circumference; and physical performance by gait speed. Sarcopenia diagnosis and staging were based on the revised EWGSOP2 as probable, confirmed, and severe sarcopenia. Prevalence rates were compared among clinical and sociodemographic characteristics and risk factors analyzed.

Results: 983 patients (median 59 years; 40% female) from 19 Brazilian dialysis centers were enrolled. Prevalences of probable, confirmed, and severe sarcopenia were 12%, 9%, and 5%, respectively. The prevalence of sarcopenia increased with advancing age groups, ranging from 7% to 45% in males and from 4% to 21% in females. After adjustment for confounders, male sex (odds ratio [OR]:1.7, 95% confidence interval [CI]:1.1–2.7), older age (OR:3.4, 95%CI:2.2–5.4), white ethnicity (OR:1.8, 95%CI:1.2–2.8), hemodiafiltration treatment (OR:1.6, 95%CI:1.1–2.4), and catheter access (OR:1.6, 95%CI:1.0–2.4) were the main risk factor for sarcopenia; however, overweight (body mass index ≥25.0 kg/m^2) was a protective factor (OR:0.3, 95%CI:0.2–0.4).

Conclusions: Any stage of sarcopenia was found in one out of four patients on hemodialysis. Male sex, older age, white ethnicity, hemodiafiltration treatment, and catheter access were risk factors for presenting sarcopenia. Our findings enhance the understanding of sarcopenia in patients on hemodialysis in Brazil.

Funding: Government Support - Non-U.S.

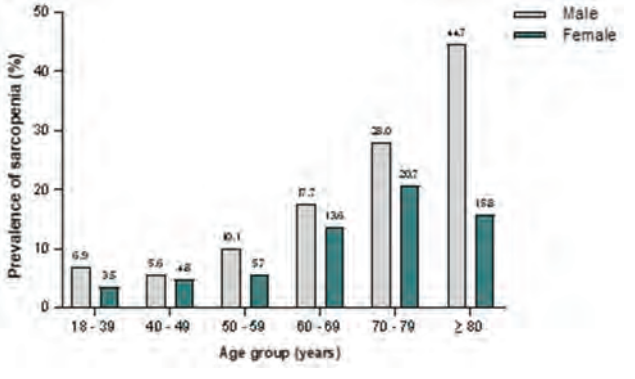


Figure 1. Prevalence of sarcopenia stratified by age groups and sex.

TH-PO959

Association of Phase Angle with Cardiorespiratory Fitness and Physical Function in Patients on Maintenance Hemodialysis

Robbie L. Grace,[1] Drake Dillman,[2] Nolan Groninger,[2] Sharon M. Moe,[2] Sharon L. Karp,[2] Kenneth Lim,[2] Eliott Arroyo.[1] *[1]Wake Forest University, Winston-Salem, NC; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: Phase angle (PhA) is a surrogate measure of cellular health and integrity of the cell membrane derived via bioelectrical impedance analysis. PhA has been shown to be predictive of muscle strength and physical function in healthy older adults. Herein, we sought to examine the relationship of PhA with cardiorespiratory fitness and physical function in patients on maintenance hemodialysis (HD).

Methods: This exploratory cross-sectional study used pooled data taken from previous trials conducted in the Division of Nephrology & Hypertension at the Indiana University School of Medicine. Participants completed a comprehensive battery of physical function assessments and a cardiopulmonary exercise test. Body composition and PhA were measured using bioelectrical impendence spectroscopy at a current frequency of 50 kHz. Multiple linear regression analyses were used to assess the association of PhA with peak oxygen uptake (VO_2Peak) and physical function outcomes.

Results: Group comparisons between patients on HD (n=27, 59% men, age=52 [12] y) and healthy controls (n=13, 38.5% men, age=53 [9] y) showed differences in race (p<0.001), however no differences in age, sex, or BMI. Patients on HD had a lower PhA (5.0 [1.4]°) compared with the controls (5.9 [0.6]°, p=0.005), even after adjusting for age, sex, and race (p=0.002). The HD group also had a lower short physical performance battery (SPPB) score (11 [8.3-12] versus 12 [12-12], p=0.002) and lower VO_2Peak (13.4 [3.7] mL*kg^{-1}*min^{-1} versus 30.7 [0.6] mL*kg^{-1}*min^{-1}; p<0.001) compared with the controls. PhA in patients on HD was significantly associated with VO_2Peak (β=1.18, p=0.022) and SPPB score (β=0.92, p=0.006) on univariate regression. After adjusting for age, PhA remained significantly associated with SPPB score (β=0.71, p=0.032); however, it was no longer associated with VO_2Peak (β=1.01, p=0.055).

Conclusions: Patients on HD exhibit significant declines in PhA that are comparable with those observed in older (65+ years) adults and are associated with impaired physical function. Further prospective studies are needed to determine whether changes in PhA as kidney function declines are predictive of physical function decline in this vulnerable population.

Funding: Private Foundation Support

TH-PO960

Exercise and Physical Activity for People with CKD: A National Survey of Nephrologist Practice Patterns in Saudi Arabia

Enad A. Alsolami, Sami A. Alobaidi. *University of Jeddah, Jeddah, Saudi Arabia.*

Background: A variety of health benefits are associated with physical activity in individuals with chronic kidney disease. The aim of this study was to examine nephrologist practice patterns concerning exercise and physical activity (PA) in CKD patients.

Methods: This is an online cross-sectional survey study that was conducted between June 2023 and May 2024 in Saudi Arabia. Nephrology fellow, specialists, and consultants in Saudi Arabia formed the study population.

Results: A total of 96 physicians participated in this study. Only 9.4% of renal units have exercise programs available to patients. These programs are available mainly for advanced CKD (pre-dialysis) and in-center hemodialysis patients. The major barriers to initiating or expanding exercise programs at their centers are a lack of motivation/interest from front-line staff (55.2%), lack of interest from management (48.3%), and no funding (47.1). Around 56.2% of respondents ask patients about their level of physical activity. Additionally, 64.6% give patients specific advice on how to increase their level of physical activity. For the types of exercise most beneficial for people with CKD, 90.6% recommend walking. Around 34.4% of respondents believe that physiotherapists should take ownership in providing exercise counselling and resources to people with CKD. The majority agreed or strongly agreed to recommend exercise in patients with CKD (76.0%). The mean attitude score for the study participants was 32.1 (SD: 3.9) out of 40 (equal to 80.3%); which demonstrates positive attitude towards recommending exercise for CKD patients.

Conclusions: This study highlights a critical gap in the availability of exercise programs for CKD patients. Key barriers include lack of interest by staff and management and funding issues. In spite of these barriers, a majority of physicians acknowledge the role of exercise in CKD patients and advice regarding physical activity on a frequent basis. It suggests recommendations in order to expand the programs, including increasing staff motivation, securing management support, and getting funding for exercise programs and identifying the role of physiotherapists in exercise counselling for CKD patients.

TH-PO961

Sarcopenia Index Is Associated with the Risk of Stroke in Middle-Aged and Older Chinese Adults: A Retrospective Cohort Study from the China Health and Retirement Longitudinal Study

Haofei Hu,[1,2] Zhiming Ye.[1] *[1]Guangdong Provincial People's Hospital, Guangzhou, China; [2]Shenzhen Second People's Hospital, Shenzhen, China.*

Background: The sarcopenia index (SI), calculated as the serum creatinine divided by the serum cystatin C, multiplied by 100, is recommended for predicting sarcopenia. However, limited evidence exists regarding its association with incident stroke. The aim of this study was to assess the relationship between SI and the risk of stroke in middle-aged and older adults.

Methods: This study utilized a retrospective cohort design, enrolling a total of 7842 participants who met the inclusion criteria from the China Health and Retirement Longitudinal Study (CHARLS) between 2011 and 2012. The study utilized the Cox proportional-hazards regression model to investigate the correlation between baseline SI and the risk of stroke. To identify the non-linear relationship between SI and stroke, a Cox proportional hazards regression with cubic spline function and smooth curve fitting technique was employed. Additionally, various sensitivity and subgroup analyses were performed.

Results: The mean age of the participants was 59.97 ± 10.06 years, with 3607 (46.0%) being male. The average baseline SI was 78.53 ± 17.43. Over a median follow-up period of 7.0 years, 938 (11.96%) individuals experienced a stroke. The multivariate Cox proportional hazards regression model revealed a negative association between SI and stroke risk (HR=0.995, 95% CI: 0.991-0.999). A non-linear relationship between SI and incident stroke was identified, with an inflection point at 70.0 for SI. Each 1 unit increase in SI to the right of the inflection point corresponded to a 0.9% decrease in stroke risk (HR=0.991, 95% CI: 0.985-0.997). However, when the SI was lower than 70.0, the connection was not significant (HR: 1.006, 95% CI: 0.994-1.017). The robustness of our results was confirmed through sensitivity and subgroup analyses.

Conclusions: This study provides evidence of a negative and non-linear correlation between SI and stroke risk in middle-aged and older adults in China. When the SI exceeded 70.0, a significant negative association with stroke risk was observed. Maintaining an SI level above 70.0 may contribute to a notable reduction in the risk of stroke.

Funding: Other NIH Support - National Key Research and Development Project of China (2021YFC2501302)

TH-PO962

Determining the Feasibility and Acceptability of a Culturally Tailored Lifestyle Intervention to Improve the Health of Hispanic and Native American Kidney Transplant Recipients

Miriam E. Velez-Bermudez, Claudia M. Rice, Shoshana Adler Jaffe, Yuridia Leyva, Elizabeth Y. Jimenez, Yiliang Zhu, Pooja P. Singh, Christos Argyropoulos, Mark L. Unruh, Larissa Myaskovsky. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Our team conducted a culturally-tailored diet and exercise clinical pilot trial with kidney transplant (KT) recipients, integrating lifestyle changes into post-KT care prior to discharge from KT surgery. We purposely recruited a diverse sample of KT recipients to test the pilot study's feasibility and acceptability.

Methods: Patients were randomized into usual care (UC) or the intervention arm 2-5 days after KT surgery and prior to discharge. Physical activity for all participants was measured with an activPAL accelerometer. Participants were instructed to wear the activPAL for one week, at four time points throughout the 12-month study period. Intervention participants received a customized exercise and nutrition plan tailored by a physical therapist (PT) and registered dietitian nutritionist (RDN). Feasibility was determined by recruitment/retention rates and intervention activity adherence. Acceptability was assessed by satisfaction ratings (3-month follow-up) and interviews (6-month follow-up).

Results: Forty-nine patients were approached, 23 (47%) agreed to participate, and three (13%) subsequently withdrew from the study. The final sample consisted of 20 patients (11 Intervention, 9 UC; 9 Hispanic, 7 Native American, 4 Other). Eighty-two percent of the intervention participants wore the activPAL at all four follow-ups versus 67% of the UC participants. Among intervention arm participants, per-protocol adherence to the PT and RDN visits was 78% and 82%, respectively. Intervention arm participants' responses to surveys and interviews demonstrated intervention acceptability, ease of participation, and overall satisfaction with the intervention.

Conclusions: This pilot effectively delivered a lifestyle intervention to a diverse sample of KT recipients, demonstrating good retention and adherence to the intervention and activity monitoring components. The PT and RDN components were well-received by participants, who also reported satisfaction with the intervention. This study is a vital step to creating a large-scale lifestyle intervention that addresses the post-KT diet and exercise needs of Hispanic and Native American recipients.

Funding: Other NIH Support - NCATS grant #UL1TR001449, Clinical Revenue Support

TH-PO963

Distribution of Sedentary Time during the 24-Hour Day in Adults with CKD

Mary Hannan,[1] Arissara Sawatpanich,[1] Emily Kringle,[2] Eleanor Rivera,[1] Ardith Z. Doorenbos,[1] James P. Lash.[1] *[1]University of Illinois Chicago, Chicago, IL; [2]University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Adults with CKD spend over 60% of their waking time sedentary, but less is known about when during the 24-hour day most sedentary time occurs. We examined distribution of within-day sedentary time among adults with CKD and explored differences by demographic and health characteristics.

Methods: This is a secondary analysis of baseline data (n=21) from a feasibility study evaluating a sedentary-reducing intervention in adults with CKD. Sedentary behavior was evaluated with the activPAL inclinometer. Waking sedentary time (sleep time removed) was examined during four time periods, and distribution was explored by gender, employment status, and CKD Stage with independent samples t-tests.

Results: Mean age was 59.7 yrs., 76% were women, 57% were employed, and 86% had CKD Stage 3. Mean waking sedentary time was 11.75 hours/day. Most sedentary time occurred in the afternoon and evening. Men, those who were retired, and those with CKD Stage 4 each had the highest amount of sedentary time occur in the evening. Women, those who were employed, and those with CKD Stage 3 each had the highest amount of sedentary time occur in the afternoon.

Conclusions: Adults with CKD tend to accumulate their sedentary time during the afternoon and evening. These exploratory findings support that sedentary-reducing interventions for those with CKD should focus on reallocating sedentary time to non-sedentary activities that are feasible during the afternoon and evening. Funding for this research was provided through a research grant from the American Nephrology Nurses Association (ANNA). Findings of the study do not necessarily reflect the opinions of ANNA. The views expressed herein are those of the authors and no official endorsement by ANNA is intended or should be inferred.

Funding: Private Foundation Support

Distribution of Sedentary Time

	Morning (06:00-11:59)	Afternoon (12:00-17:59)	Evening (18:00-23:59)	Overnight (00:00-5:59)
Overall (n=21)	24.7%	33.9%	32.5%	8.9%
Women (n=16)	26.2%	34.1%	31.9%	7.8%
Men (n=5)	19.8%	33.5%	34.2%	12.5%
p+	0.10	0.83	0.59	0.38
Employed (n=12)	26.3%	35.0%	30.8%	7.8%
Retired (n=9)	22.5%	32.5%	34.7%	10.3%
p+	0.19	0.25	0.26	0.41
CKD Stage 3 (n=18)	24.4%	34.6%	32.1%	9.6%
CKD Stage 4 (n=3)	26.4%	33.8%	35.0%	4.8%
p+	0.69	0.92	0.61	0.03

+t-test

TH-PO964

Sleep Quality and Symptom Experience in CKD

Roseanne E. Billany,[1] Ella C. Ford,[2] Gurneet K. Sohansoha,[1] Courtney J. Lightfoot,[1] Alice C. Smith.[1] *[1]University of Leicester College of Life Sciences, Leicester, United Kingdom; [2]Leeds Beckett University, Leeds, United Kingdom.*

Background: Poor sleep quality is common in chronic kidney disease (CKD). Understanding how symptoms (Sx) relate to sleep could help identify people who experience, or are at risk of experiencing, poor sleep quality. We explored the relationship between sleep quality and Sx experienced in people with living with CKD and their significant others (SO).

Methods: People living with CKD and their SO were invited from nine hospital sites in England to complete an online survey including the Pittsburgh Sleep Quality Index (PSQI) and the Kidney Symptom Questionnaire (KSQ). Data were analysed using multiple regression (adjusted for age and sex), χ^2, and Mann-Whitney U as appropriate.

Results: 291 CKD (age 60±14 years; 54% male; 173 (59%) non-dialysis; 66 (23%) kidney transplant; 52 (18%) dialysis [haemo and peritoneal]), and 47 SO (age 63±11 years; 32% male) had complete data. The proportion of participants with poor sleep was greater in CKD than in SO (60% vs 45%, respectively; p=.046). The median number of Sx experienced by people with CKD was higher than in SO (5 vs 2; p=.001). There was a significant association between sleep quality and number of Sx in CKD in univariate analysis and after adjustment (both p<.001). In a multivariable model, loss of appetite, pain, weakness, restless legs syndrome, and feeling cold were significantly associated with poorer sleep quality (Table 1).

Conclusions: We found relationships between experiencing CKD-related Sx and poorer sleep quality in CKD. Optimal CKD management should include assessment of both Sx burden and sleep quality; a bi-directional relationship is likely. Multi-disciplinary teams and sleep services should work together to provide relevant information, and/or referrals to optimise sleep and Sx management and improve quality of life.

Table 1: Multivariable model exploring the contribution of symptoms experienced to sleep quality measured by the PSQI in people living with CKD

Symptom Experienced	B	CI	β	p
Itching	0.26	(-0.65, 1.17)	0.03	0.571
Loss of appetite	1.69**	(0.71, 2.67)	0.20**	0.001
Pain in bones/joints	1.06*	(0.07, 2.06)	0.14*	0.036
Poor concentration/alertness	0.78	(-0.23, 1.79)	0.10	0.129
Loss of libido	0.13	(-0.79, 1.05)	0.02	0.777
Loss of muscle strength/power	1.42*	(0.39, 2.45)	0.18*	0.007
Shortness of breath	-0.45	(-1.40, 0.49)	-0.06	0.345
Cramp/muscle stiffness	-0.26	(-1.24, 0.71)	-0.03	0.598
Restless legs	0.96*	(0.03, 1.88)	0.12*	0.043
Feeling cold	1.02*	(0.07, 1.96)	0.13*	0.036
Need to urinate more often	0.80	(-0.06, 1.67)	0.10	0.069

B and β represent the difference in PSQI score of participants who experience the symptom compared to participants who do not
Model adjusted for age and sex
Significance (*) p < 0.050 (**) p < 0.001

TH-PO965

Association between Sleep Hours and Incidence of Kidney Failure: Findings from the National Health and Nutrition Examination Survey, 2005-2018

Yoshihisa Miyamoto, Alain K. Koyama, Ryan Saelee, Fang Xu, Ibrahim Zaganjor, Stephen J. Onufrak, Meda E. Pavkov. *Centers for Disease Control and Prevention, Atlanta, GA.*

Background: Sleep duration may be associated with chronic kidney disease (CKD) and its progression. However, few studies have examined the association between sleep duration and kidney failure incidence.

Methods: We used data from the National Health and Nutrition Examination Surveys (2005–2006 through 2017–2018) linked to the United States Renal Data System to assess the association between self-reported sleep duration and three outcomes: incidence of kidney failure, all-cause death, and the composite of the two. We followed adults aged ≥20 years from the interview date until the date of kidney failure, death, or December 31st, 2018, whichever occurred first. We used multivariable Cox regression models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) to adjust for demographics, eGFR, log of urine albumin creatinine ratio, diabetes, and hypertension.

Results: Among 27,498 adults who met the inclusion criteria, 1,544 (4.4%) reported a sleep duration of <5 hours, 2,497 (7.8%) reported ≥5 to <6 hours, 5,828 (20.7%) reported ≥ 6 to <7 hours, 14,202 (55.4%) reported ≥ 7 to <9 hours and 3,427 (11.6%) reported ≥ 9 hours. The mean age was 47 years; 48% were men and 66.7% were non-Hispanic White, 11.4% were non-Hispanic Black. The median observational period was 6.2 years. Compared to ≥7 to <9 hours of sleep, sleep durations < 5 hours, ≥ 5 to <6 hours and ≥9 hours were associated with higher risk of the composite events (adjusted hazard ratio, 1.67 [95% CI, 1.34-2.08], 1.34 [1.14-1.56], and 1.50 [1.31-1.71], respectively). Similarly, sleep durations < 5 hours and ≥ 9 hours were associated with higher risk of kidney failure (adjusted hazard ratio, 1.44 [95% CI, 0.85-2.42] and 1.64 [0.83-3.21], respectively) although not statistically significant due to low number of events.

Conclusions: Both shorter and longer sleep duration may be associated with higher risk of kidney failure and death.

Funding: Other U.S. Government Support

TH-PO966

Effect of a Low-Protein Diet Supplemented with Ketoanalogues on Body Composition and Hand Grip Strength of Elderly Mexican Patients with CKD Attending a Nutritional Care Center

Nadia I. Aldana Solis,[1] Abril G. Espinoza,[2] Julia Nava,[1] Adriana Salinas Rico,[1] Araceli Aguilar Gamiño,[1] Sara De La Rosa Diez,[1] Joel D. Kopple.[3] *[1]Fresenius Kabi Mexico SA de CV, CDMX, Mexico; [2]Fresenius Kabi Mexico SA de CV, Tijuana, Mexico; [3]The Lundquist Institute, Torrance, CA.*

Background: Chronic kidney disease has become one of the significant causes of mortality in the world. Nutritional therapy is one of the cornerstones of conservative management. Elderly subjects with CKD are considered a frail population. An LPD supplemented with keto analogs and adequate energy supply could be an option for treatment to avoid or differ dialysis and maintain a good nutritional status and muscle strength.

Methods: This was a retrospective analysis of 60 patients with CKD stages 3b-5. The data were collected from the database of one Fresenius Kabi CEAN center in Mexico City. The study included nondiabetic and diabetic patients who were ≥65 years old. Each patient was prescribed a sk-LPD individualized according to the patients GFR level, nutritional status, and specific tastes. Biochemical, body composition, HGS, and nutritional screening parameters were compared between baseline and at a six-month interval.

Results: The patient population was 41.7% female and 43.3% diabetic. At the onset of dietary treatment, according to the BMI criteria, 41.7% were normal weight; 43.3% were overweight, and 15% obese. After six month's treatment, 45% were normal weight, 38.3% were overweight, and 16.7% obese (change in weight status: p=NS). Fat mass tended to decrease from 37.2±10.0 to 35.5±8.9% p=0.32; lean body mass did not change, 47.5±16.1% to 48.4±17.0% p=0.76; and phase angle tended to decrease although not significantly, 4.49±2.37 to 4.02±0.73, p=0.080. HGS was maintained 21.6 ±7.6 to 21.7 ±8.0 kg p=0.109. Serum urea nitrogen (SUN) decreased at six months from 47.9±21.8 to 33.7±17.2 mg/dL, p<0.001. Serum albumin was maintained, 4.14±0.40 to 4.14±0.40 g/dL, p=0.722, eGFR increased from 25.0±10.3 to 29.4±13.0 ml/min/1.73 m^2 p=0.042.

Conclusions: The major decrease in SUN during the study suggests at least fair to good adherence to the prescribed diets. No significant changes were noticed in anthropometric, biochemical, HGS and other nutritional characteristics during this six-month interval, suggesting that the sk-LPD treatment maintained nutritional status in these older stage 3b-5 CKD patients.

TH-PO967

Maternal Ketosis during Gestation: Implications for Fetal Kidney Development and Long-Term Kidney Health

Oded Volovelsky, Yaniv Makayes, Morris Nechama. *Hadassah University Medical Center, Jerusalem, Israel.*

Background: Maternal ketosis is a metabolic state that can be encountered during normal pregnancy, gestational diabetes, and due to the growing popularity of ketogenic diets. While ketone bodies in the physiological range facilitate energy supply to the fetus, emerging data suggest potential adverse fetal outcomes of increased ketosis. This study investigates the impact of maternal ketosis during gestation on fetal kidney development and nephrogenesis, a critical determinant of lifelong renal health.

Methods: Two murine models evaluated the effects of maternal ketosis on kidney development: a ketogenic diet regimen and exogenous beta-hydroxybutyrate (BHB) supplementation in drinking water. Nephron endowment was quantified in adulthood, and renal function was assessed by blood urea levels. Nephron progenitor cells were isolated via fluorescence-activated cell sorting from transgenic reporter mice, and RNA-sequencing analyzed transcriptomic profiles. Alterations in gene expression pathways were validated through immunofluorescence, western blot, and qPCR.

Results: Both maternal ketosis models exhibited significantly reduced nephron endowment at birth and adulthood compared to the control group, indicative of impaired nephrogenesis. The reduction in nephron number in the ketogenic group was associated with compromised long-term renal function in adulthood, as was measured by elevated blood urea levels. Transcriptomic analyses revealed decreased proliferative capacity of nephron progenitors, with downregulation of the MYC pathway and concomitant upregulation of inflammatory response genes. These findings were consistently validated across multiple complementary techniques.

Conclusions: This study provides compelling evidence that maternal ketosis during gestation adversely impacts fetal kidney development and long-term renal function. Reduced nephron progenitor proliferation, decrease MYC expression and heightened inflammatory signaling, emerges as an underlying mechanism. These findings underscore the importance of monitoring and managing maternal ketosis to protect fetal nephrogenesis and lifelong kidney health.

TH-PO968

Patient Self-Management of Kidney Diseases: A Health Care Staff Perspective

Naeema A. Patel, Matthew Graham-Brown, Alice C. Smith, Courtney J. Lightfoot. *University of Leicester College of Life Sciences, Leicester, United Kingdom.*

Background: Self-management is an important component of care for people with chronic kidney disease (CKD). Effective self-management has the potential to improve health outcomes, but evidence-based resources to support people with non-dialysis CKD to self-manage are lacking. Healthcare professionals (HCPs) are critical for the uptake and adoption of self-management resources in clinical practice. This qualitative study explored professional stakeholders' views on current practices of self-management education and support and the requirements for effective resources to be used in routine care

Methods: Semi-structured interviews with kidney HCPs and service managers were conducted to explore CKD education and self-management support. Interviews were audio recorded and transcribed verbatim. Data were analysed using thematic analysis.

Results: 42 participants, including 20 nephrologists, 6 kidney nurses, 10 allied health professionals, and 6 service managers in kidney care and quality improvement were interviewed. Four overarching themes were identified: **Lack of prioritisation of self-management education and practices** (perceived that self-management is overlooked in CKD and lacks priority in current practices) **Personalised and responsive approach to CKD** (considering the need to take a patient-centred approach to care and understanding self-management in CKD to other multiple long-term conditions) **Perceived features of successful self-management** (identifying key effective strategies for self-management resources and support) **Considerations around health equity** (Adapting interventions to improve equity and accessibility for underserved groups)

Conclusions: The findings highlight the need for patient education and evidence-based self-management resources. HCPs should prioritise patient knowledge and understanding of kidney disease, tailor resources to individual needs, and improve equity for underserved groups. These findings can be used to support the design and delivery of healthcare resources to optimise and increase uptake.

TH-PO969

Depressive Symptoms and RANKL/OPG in Hemodialysis

Heejeong Kim, Dong-Young Lee. *Department of Internal Medicine, Veterans Healthcare Service (VHS) Medical Center, Seoul, Republic of Korea.*

Background: Depression and osteoporosis are prevalent in dialysis patients. Denosumab and romosozumab similarly block RANKL. While RANKL causes bone resorption after binding RANKL, binding with OPG inhibits bone resorption. A recent

mice study, denosumab improved depressive-like phenotype by inhibiting RANKL. OPG was linked to depression. This study aimed to explore the association of depressive symptoms with RANKL/OPG in HD patients.

Methods: We conducted a cross-sectional study involving 172 HD patients, measuring plasma RANKL, OPG levels. Logistic regression analysis was performed to evaluate the effect of RANKL and OPG on the depressive symptoms.

Results: The depressive symptoms were observed in 90(52.3%) subjects. RANKL tertile 3 had negative association with BDI score(β-4.527, 95% CI -8.310~-0.743) in univariate analysis. This association persisted after multivariate adjustments(β-5.603, 95% CI -9.715~-1.491) in linear regression. In logistic regression between RANKL tertiles and depressive symptoms, RANKL tertile 3 had significantly lower unadjusted OR (0.40, 95% CI 0.19~0.86), and multivariate-adjusted OR (0.31, 95% CI 0.12~0.82) for depressive symptoms.

Conclusions: OPG wasn't significantly associated with depressive symptoms. Higher plasma RANKL levels were associated with lower depressive symptoms in HD patients.

Odds ratios of plasma RANKL, OPG, and RANKL/OPG ratio for depressive symptoms

	OR (95% CI) Unadjusted	P value	OR (95% CI) Adjusted	P Value
RANKL tertile 1	Reference		Reference	
RANKL tertile 2	0.51 (0.24-1.09)	0.080	0.42 (0.16-1.09)	0.074
RANKL tertile 3	0.40 (0.19-0.86)	0.018	0.31 (0.12-0.82)	0.018
OPG tertile 1	Reference		Reference	
OPG tertile 2	1.64 (0.78-3.44)	0.191	0.59 (0.20-1.69)	0.326
OPG tertile 3	1.37 (0.66-2.85)	0.401	0.29 (0.08-1.02)	0.165
RANKL/OPG tertile 1	Reference		Reference	
RANKL/OPG tertile 2	0.48 (0.23-1.03)	0.059	0.51 (0.20-1.32)	0.041
RANKL/OPG tertile 3	0.35 (0.17-0.75)	0.007	0.55 (0.21-1.42)	0.256

RANKL receptor activator of nuclear factor-κB ligand, OPG Osteoprotegerin, OR Odds Ratio, CI Confidential Interval

Multivariate, adjusted for age, sex, BMI, Diabetes mellitus, cardiovascular diseases, HD vintage, spKt/V, hsCRP

Table 1 The baseline characteristics of all subjects and with or without depressive symptoms

	Total (N=172)	No depressive symptoms (n=82)	Depressive symptoms (N=90)	P value
Age, years, Mean ± SD	61.2 ± 11.7	58.5 ± 13.1	64.1 ± 9.8	0.002
Men, n (%)	118 (68.6)	52 (63.4)	67 (74.4)	0.163
Body Mass Index, Kg/m², Mean ± SD	23.2 ± 4.1	22.3 ± 4.0	23.9 ± 3.9	0.006
Diabetes Mellitus, n (%)	101 (58.7)	46 (56.1)	55 (61.1)	0.609
Cardiovascular diseases, n (%)	90 (52.3)	37 (45.1)	53 (58.9)	0.068
Charlson comorbidity index, Mean ± SD	4.09 ± 1.47	3.84 ± 1.43	4.32 ± 1.48	0.040
Pre-hemodialysis SBP, mmHg, Mean ± SD	140.2 ± 19.1	141.5 ± 19.4	141.0 ± 19.0	0.871
BDI score, Mean ± SD	17.5 ± 10.3	8.8 ± 4.1	25.0 ± 7.9	<0.001
Hemodialysis vintage (months), Mean ± SD	70.6 ± 78.8	63.3 ± 80.4	77.5 ± 75.9	0.314
spKt/V, Mean ± SD	1.58 ± 0.31	1.57 ± 0.30	1.59 ± 0.32	0.564
Presence of AVF, n (%)	77 (59.7)	42 (66.7)	35 (53.0)	0.162
hs-CRP, mg/dL, Mean ± SD	5.16 ± 8.88	2.76 ± 8.61	7.35 ± 10.24	0.001
Calcium, mg/dL, Mean ± SD	8.5 ± 0.8	8.4 ± 0.9	8.5 ± 0.7	0.370
Phosphorus, mg/dL, Mean ± SD	4.6 ± 0.8	5.6 ± 1.3	4.6 ± 1.2	0.273
Bone-specific ALP, μ/L, Mean ± SD	17.4 ± 9.9	18.6 ± 11.4	16.4 ± 8.4	0.173
Parathyroid hormone, pg/mL, Mean ± SD	290.0 ± 227.1	303.5 ± 229.2	277.9 ± 229.4	0.465
25(OH)Vitamin D, ng/mL, Mean ± SD	15.7 ± 10.1	15.6 ± 10.1	15.7 ± 10.1	0.897
RANKL, pg/mL, Median (IQR)	6.11 (2.99, 22.61)	12.72 (2.99, 24.14)	6.07 (2.62, 17.90)	0.021
OPG, pg/mL, Median (IQR)	2982.6 (2065.4, 3998.6)	3607.7 (3825.8, 3941.4)	3034.6 (2314.7, 4013.6)	0.188
RANKL/OPG ratio, Mean ± SD	0.0131 ± 0.0044	0.0225 ± 0.1215	0.0059 ± 0.0092	0.166

SBP Systolic Blood Pressure, BDI Beck's Depression Inventory, IQR Interquartile Range, RRF Residual Renal Function, hs-CRP high-sensitivity C-reactive protein, ALP Alkaline Phosphate, RANKL receptor activator of nuclear factor-κB ligand, OPG Osteoprotegerin

TH-PO970

Association of Cardiovascular-Kidney-Metabolic Syndrome with Cognitive Decline and Dementia: The ARIC Study Insights

Peichen Xie, Yiqin Wang, Wei Chen. *The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*.

Background: Cardiovascular-kidney-metabolic(CKM) syndrome is a prevalent health concern, while its impact on cognitive function has not been extensively studied.

Methods: We conducted a prospective analysis with Atherosclerosis Risk in Communities (ARIC) study data. CKM risk was assessed with the PREVENT™ Calculator and cognitive function was evaluated using *z* score from different cognitive function tests at Visit 2 and Visit 4. Dementia cases were identified through a combination of assessments and hospital records, with analyses adjusted for demographics and vascular risks during Visit 5.

Results: Our study included 10,960 participants with a mean age of 56.9±5.7 years. A robust inverse relationship was observed between cognitive function and CKM risk, with the inflection point at 6.381% CKM risk for the global *z* score. The risk of dementia increased with higher CKM risk (HR 1.14, 95% CI 1.13-1.16). Notably, male participants exhibited a comparatively reduced risk of dementia (HR 0.72, 95% CI 0.63-0.82). A subsequent sensitivity analysis, utilizing baseline data from Visit 4 (n=4644), confirmed these results.

Conclusions: Our findings indicate a significant link between CKM risk and cognitive decline, suggesting the importance of CKM syndrome management in preventing cognitive impairment and dementia.

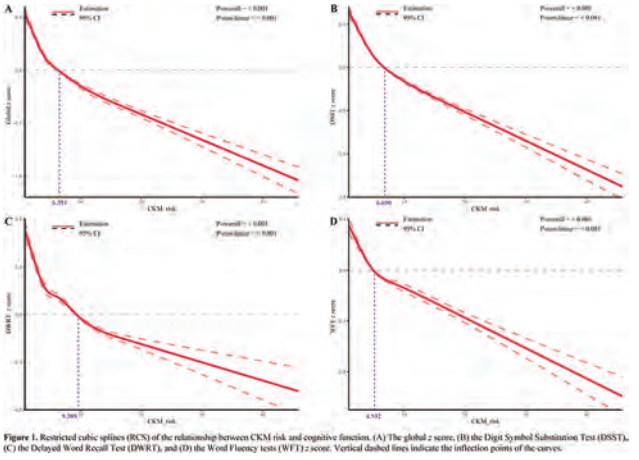


Figure 1. Restricted cubic splines (RCS) of the relationship between CKM risk and cognitive function. (A) The global *z* score, (B) the Digit Symbol Substitution Test (DSST), (C) the Delayed Word Recall Test (DWRT), and (D) the Word Fluency tests (WFT) *z* score. Vertical dashed lines indicate the inflection points of the curves.

RCS of CKM risk and cognitive scores

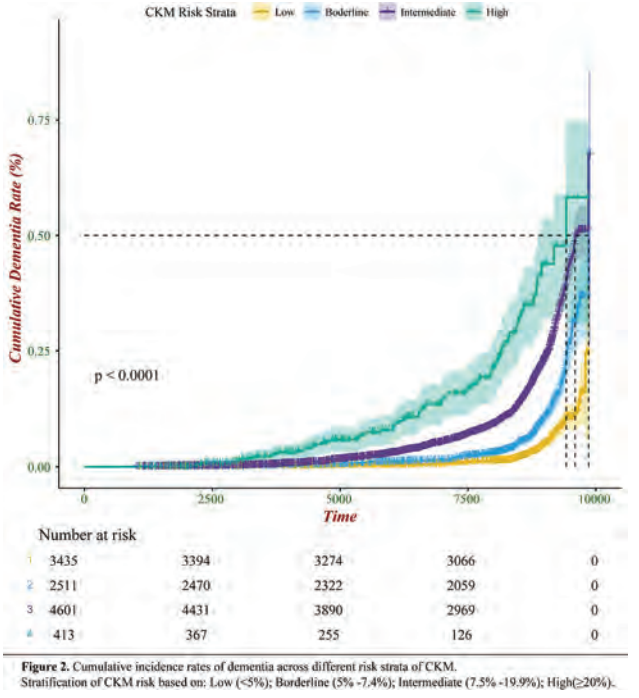


Figure 2. Cumulative incidence rates of dementia across different risk strata of CKM. Stratification of CKM risk based on: Low (<5%); Borderline (5% -7.4%); Intermediate (7.5% -19.9%); High(≥20%).

Cumulative dementia rates across different risk strata of CKM

TH-PO971

Age-Specific Relationship between Insulin Resistance and Obesity: A Machine Learning-Based Interpretation

Sewon Oh, Yookyung Jang, Young Eun Choi, Tai yeon Koo, Myung-Gyu Kim, Sang-Kyung Jo. *Korea University, Seongbuk-gu, Republic of Korea*.

Background: There has been a threefold surge in the global prevalence of obesity over the last four decades. Obesity is related to the increased risk of cardiovascular and kidney disease. Obesity in the elderly exhibits distinct features, such as sarcopenia and an increased visceral fat mass. We investigate the risk factors for obesity according to age by developing machine learning (ML) model.

Methods: We performed ML analysis on 3768 individuals whose age was over 18 from the 2021 Korea National Health and Nutrition Examination Survey dataset. ML predicted individual body mass index (BMI) values, and the predictive values were labeled into normal (BMI<25 kg/m^2) and obese (BMI>25 kg/m^2). Through 5-fold cross-validation, the performance and SHapley Additive exPlanations (SHAP) values, representing the feature importance in each sample, were calculated in the test set of every fold and collected.

Results: The Light Gradient Boosting Machine demonstrated reliable prediction, yielding an area under ROC curve of 0.813 (higher than other ML algorithms) and an error of 2.199±1.654. SHAP analysis revealed high importance for Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and fasting insulin, displaying an

increasing trend with higher BMI (Figure 1.a). Important indicators were followed by, systolic blood pressure, alanine-transaminase, uric acid, HDL-cholesterol, hypertension, age and occupation. Age showed the highest interaction with the impact of HOMA-IR. A dependence plot (Figure 1.b) illustrated that the impact of high HOMA-IR on BMI was higher in younger adults compared to older adults. A significant disparity in obesity ratio between HOMA-IR>5 and HOMA-IR<5 was observed, particularly pronounced in individuals under 50 years.

Conclusions: While HOMA-IR is recognized for its significance in BMI and diabetic diseases, this study highlights its prominence over other known BMI-related features. The analysis showed that younger ages with high insulin resistance is more vulnerable to obesity compared to older adults.

TH-PO972

Combination of Hyperuricemia and Obesity Is an Independent Risk for CKD in the Young Population

Akihiro Kuma, Yasuyuki Mimura, Masayoshi Nanami, Takahiro Kuragano. *Department of Cardiovascular and Renal Medicine, Hyogo Medical University, Nishinomiya, Japan.*

Background: Recent studies have shown a significant relationship between hyperuricemia and kidney disease. However, managing serum uric acid (SUA) levels in incident chronic kidney disease (CKD) remains challenging. This study investigated the appropriate SUA management in incident CKD to prevent kidney dysfunction in the general population.

Methods: This retrospective observational study included Japanese aged 20–60 years who underwent a health examination during 2009–2014. Participants with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or proteinuria ≥1+ in 2009 were excluded. Incident CKD was defined as eGFR <60 mL/min/1.73 m^2 or proteinuria 5 years later. Receiver operating characteristic (ROC) curve analysis was performed to determine the SUA cutoff value for incident CKD. The risk of incident CKD (odds ratio [OR] and confidence interval [CI]) was analyzed using logistic regression analysis. Propensity score matching based on the SUA cutoff value was performed to exclude biases related to participant covariances.

Results: Of 16,708 recruited participants, 8,702 were eligible. Mean age, eGFR, and SUA were 41.4 years, 81.1 mL/min/1.73 m^2, and 6.0 mg/dL, respectively. A total of 728 (8.4%) participants developed CKD. Based on the ROC analysis, the SUA cutoff value for incident CKD was 6.6 mg/dL. High SUA level (≥6.6 mg/dL) combined with obesity (body mass index ≥25 kg/m^2) was a significant risk for incident CKD in participants aged <40 years (OR=2.18, 95% CI 1.10–4.31) but not if without obesity (OR=0.69, 95% CI 0.40–1.18). SUA level was significantly associated with obesity status (P=0.009). In participants aged ≥40 years, high SUA level was a risk factor for incident CKD, regardless of obesity status (OR 1.32, 95% CI 1.07–1.63). In participants aged <40 years with obesity and high SUA level, the difference in 5-year eGFR slope between participants with <6.6 mg/dl of SUA and those with ≥6.6 mg/dL (5-year later) was +0.80 mL/min/year (P=0.0002).

Conclusions: In the population aged <40 years, SUA of ≥6.6 mg/dL combined with obesity was an independent risk for incident CKD 5 years later. Lowering SUA to <6.6 mg/dL may attenuate eGFR decline.

TH-PO973

Role of Normal Protein Catabolic Rate (nPCR) in Predicting Weight Loss among Patients on Hemodialysis Treated with Tirzepatide

Jyunichiro Hashiguchi, Shinichi Abe, Satoshi Funakoshi, Mayu Iwata, Kenji Sawase. *Nagasaki Kidney Center, Nagasaki, Japan.*

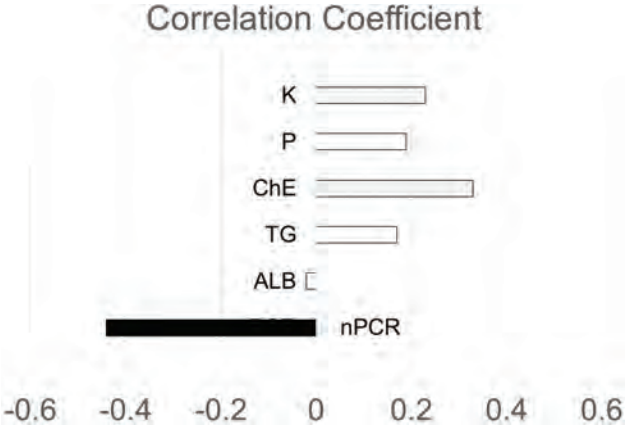
Background: Tirzepatide, a novel dual GLP-1/GIP receptor combination, shows promising potential for treating type 2 diabetes mellitus (T2DM) by inducing weight loss, albeit with variable efficacy among individuals. In HD patients, establishing appropriate dry weight (DW) parameters is crucial, as spontaneous weight fluctuations are uncommon. This study aims to identify optimal parameters for setting DW in patients undergoing HD on tirzepatide treatment.

Methods: Twenty-three stable type 2 diabetic patients undergoing outpatient maintenance HD, already on existing GLP-1 receptor agonists, were enrolled. Mean age was 63.8 years, with 18 males and 5 females, and mean dialysis history of 5.6 years. Patients transitioned from existing GLP-1 receptor agonists to tirzepatide, with the correlation between the rate of DW reduction, clinical symptoms, and changes in various nutritional indices assessed over a 6-month period.

Results: Mean DW decreased significantly from 72.7kg to 70.3kg over 6 months, with an average weight loss of -2.6kg (-3.9%). Notably, a considerable variation in weight change was observed (standard deviation: 2.28; coefficient of variation: -0.851). Among nutritional indices, only nPCR demonstrated a significant correlation with weight loss (r=-0.44, p=0.04), indicating greater weight loss in patients with decreased nPCR (Figure).

Conclusions: While serum phosphorus and potassium levels are commonly used to estimate appetite and food intake in hemodialysis patients, they did not exhibit significant correlation with changes in body weight. Conversely, nPCR, reflecting dietary protein intake, showed the strongest correlation with weight changes during tirzepatide administration. Monitoring nPCR can enable early detection of appetite loss and facilitate adjustments in DW, potentially mitigating complications like pulmonary congestion and pleural effusion associated with tirzepatide use in HD patients.

Funding: NIDDK Support, Private Foundation Support



TH-PO974

Causal Effect of Kidney Function on Lipid Metabolism: An Integrated Population-Scale Observational Analysis and Mendelian Randomization Study

Minsang Kim, Jeongmin Cho, Sehoon Park. *Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.*

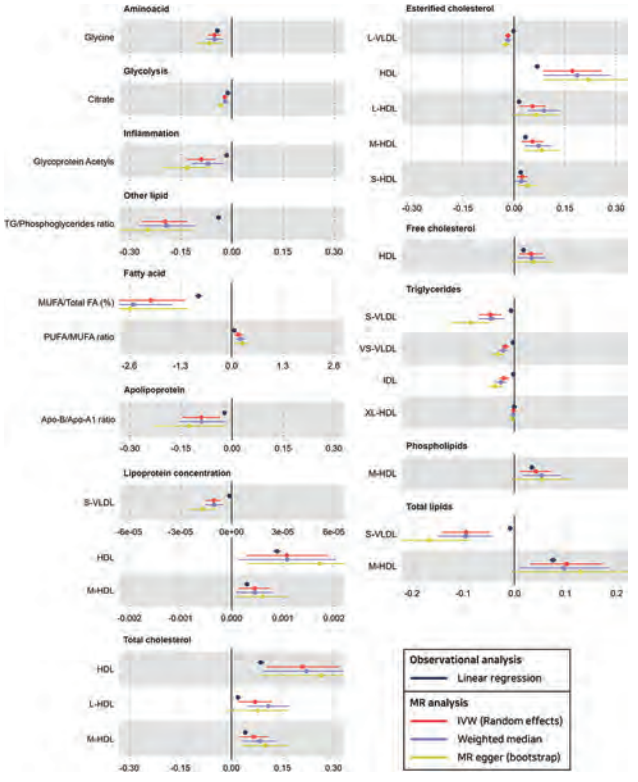
Background: Additional investigations into the causal effects of kidney function on various metabolites, particularly lipoprotein lipids in detailed subfractions of lipoprotein particles, in the general population are warranted.

Methods: This study included cross-sectional observational and Mendelian randomization (MR) analyses. For both analyses, 157,541 participants aged 40–69 years from the UK Biobank cohort were included. The estimated glomerular filtration rate (eGFR) was the exposure, and the outcome was each of the 178 metabolites from recently updated metabolomics data, including detailed lipoprotein components within 14 subclasses of lipoproteins. Observational analysis was performed using multivariable linear regression analysis. Genetic instruments for eGFR were developed from the Chronic Kidney Disease Genetics genome-wide association study meta-analysis results, which comprised 567,460 individuals of European ancestry. A two-sample MR analysis was performed using the random-effects inverse variance weighted method as the main MR method.

Results: In the integrated results of the observational and MR analyses, 26 metabolites were causally associated with eGFR (Figure 1). A lower eGFR causally decreased lipoprotein components of high-density lipoprotein (HDL) and several of its subclasses, particularly medium HDL. Conversely, a lower eGFR causally increased triglycerides (TG) levels in smaller-sized very low-density lipoprotein (VLDL) and intermediate-density lipoprotein, as well as increased lipoprotein particle concentrations and total lipids in small VLDL.

Conclusions: Decreased kidney function causally aggravates lipoprotein lipid profiles; therefore, clinicians should closely monitor the lipid profiles of individuals with impaired kidney function.

Funding: Government Support - Non-U.S.



TH-PO975

Weight-Loss Interventions in Patients with Overweight/Obesity and CKD

Ryan Chang, Livia A. Frost, Sankar D. Navaneethan. *Baylor College of Medicine, Houston, TX.*

Background: Obesity is an independent risk factor for progression of chronic kidney disease (CKD). We conducted a systematic review and meta-analysis to evaluate the effects of weight loss interventions in patients with non-dialysis-dependent CKD.

Methods: We searched Embase, Web of Science, Cochrane, and MEDLINE for randomized controlled trials (RCTs) and pre-specified and post-hoc analyses of RCTs that examined surgical, lifestyle, and pharmacologic interventions in adult patients with CKD and overweight or obesity. We used Cochrane RevMan to perform a random-effects meta-analysis comparing each intervention to its respective control. Weighted mean differences (with 95% confidence intervals) were calculated for various kidney outcome measures.

Results: We included 32 studies (from a total of 12,175 studies identified during search). 3 examined surgical interventions, 15 examined lifestyle interventions, and 14 examined pharmacologic interventions (9 of which were GLP-1 agonists). Lifestyle changes were associated with improvements in eGFR, rate of eGFR change, BMI, and weight (Figure). Surgery was associated with significant reductions in weight, BMI, and HbA1c, but no improvements in kidney parameters. Both GLP-1 agonists and other medications were associated with weight loss, but only GLP-1 agonists improved eGFR, rate of eGFR change, and HbA1c. Surgical and lifestyle interventions also improved proteinuria, while some GLP-1 agonist trials demonstrated improvements in urine albumin-creatinine ratio.

Conclusions: Weight loss interventions, particularly lifestyle-based and GLP-1 agonists, may confer improvements in kidney function. Larger trials examining kidney outcomes in patients with obesity and CKD are needed to fully elucidate the benefits of such interventions.

Intervention Type	Outcome	Number of Trials; Patients	Effect Size	95% Confidence Interval	I-squared
Lifestyle	Change in eGFR	9; 6462	0.55 mL/min/1.73 m^2	0.12, 0.97	0%
	Rate of eGFR change	1; 16	7.8 mL/min/1.73 m^2/year	1.92, 13.68	N/A
	BMI	8; 427	-1.36 kg/m^2	-1.93, -0.78	40%
	Weight	9; 1729	-2.94 kg	-5.06, -0.81	86%
	HbA1c	3; 103	-0.25%	-1.12, 0.62	28%
	Systolic blood pressure	7; 458	2.98 mm Hg	-2.76, 8.71	0%
Surgical	Change in eGFR	2; 111	2.93 mL/min/1.73 m^2	-2.03, 7.89	0%
	BMI	2; 111	-8.42 kg/m^2	-12.91, -3.92	59%
	Weight	1; 11	-29.00 kg	-35.11, -22.89	N/A
	HbA1c	1; 100	-1.20%	-1.77, -0.75	N/A
	Systolic blood pressure	1; 100	-8.81 mm Hg	-11.80, 2.18	N/A
GLP-1 agonist	Change in eGFR	4; 5402	0.89 mL/min/1.73 m^2	0.87, 0.91	0%
	Rate of eGFR change	1; 1995	2.20 mL/min/1.73 m^2/year	1.60, 2.80	N/A
	BMI	1; 3388	-0.92 kg/m^2	-0.92, -0.92	N/A
	Weight	5; 4399	-2.66 kg	-3.76, -1.55	108%
	HbA1c	5; 4205	-1.15%	-1.66, -0.64	98%
	Systolic blood pressure	2; 3503	-4.09 mm Hg	-9.50, 1.31	95%
Non-GLP-1 agonist agents	Change in eGFR	2; 13739	-3.08 mL/min/1.73 m^2	-11.51, 5.35	92%
	BMI	1; 53	-2.41 kg/m^2	-2.70, -2.12	N/A
	Weight	2; 704	-5.72 kg	-6.06, -5.37	N/A
	HbA1c	1; 511	-0.25%	-2.46, 1.96	N/A

Figure: Outcomes by Intervention Type. All interventions led to significant reductions in BMI and/or weight. Improvements in eGFR were observed only in lifestyle and GLP-1 agonist trials.

TH-PO976

Health Trajectories of Adults with ESKD and Obesity Who Are Trying to Lose Weight

Dahlia Stott,[1] Bengucan Gunen,[1] Stephen Chien,[1] Brandy-Joe Milliron,[1] Ann C. Klassen,[1] Lucy Robinson,[1] Jason Cobb,[2] Alden M. Doyle,[3] Meera N. Harhay.[1] *[1]Drexel University, Philadelphia, PA; [2]Emory University, Atlanta, GA; [3]University of Virginia, Charlottesville, VA.*

Background: Adults with ESKD and obesity (i.e., body mass index ≥30 kg/m^2) have reported numerous barriers to healthy weight loss, limiting access to transplantation. Weight loss in ESKD patients may also indicate frailty or sarcopenia. Knowledge gaps persist about predictors of healthy weight loss in adults with ESKD and obesity.

Methods: In our longitudinal cohort study, we are assessing predictors of weight, body composition (using bioimpedance spectroscopy), anthropometry, and functional trajectories among adults with ESKD and obesity who are trying to lose weight. In this preliminary analysis, we compare dietary quality, health literacy, and 3-month changes in fat free mass, waist circumference, and physical function of participants who did and did not achieve weight loss using t-tests and Mann-Whitney U tests, as appropriate.

Results: Among 34 participants with longitudinal data to date, 41% lost weight at 3 months (mean loss 2 kg, SD 1.74 kg). Mean participant age was 57 years; 47% were female, and 94% identified as non-Hispanic Black. No participants were taking weight loss medication at baseline. Participant characteristics, dietary intake, and health literacy were similar between those with and without weight loss. Participants who lost weight were more likely to lose waist circumference but had similar changes in fat free mass and physical function as those without weight loss (Table).

Conclusions: Less than half of participants achieved desired weight loss at 3 months. Those who lost weight had similar baseline dietary quality and health literacy but were more likely to lose waist circumference than those who did not lose weight. Fat free mass and functional status changes were observed with and without weight loss.

Funding: NIDDK Support

	Participants with weight loss (n=14)		Participants without weight loss (n=20)		
	Mean	Standard Deviation	Mean	Standard Deviation	p
Baseline age	56.64	13.98	57.75	11.30	.800
Baseline body mass index (kg/m^2)	36.47	5.35	37.96	7.51	.717
Baseline calories/day	1369.86	246.14	1685.11	695.17	.323
Baseline protein/day, grams	63.27	13.59	75.13	24.16	.107
Baseline dietary quality (0-100)	48.41	8.19	48.92	7.74	.854
Baseline health literacy (0-18)	15.50	3.59	14.55	4.97	.500
3-month fat free mass change, kg	.38	4.65	5.03	6.55	.156
3-month waist circumference change, in	-.66	2.47	2.22	2.30	.001
3-month timed gait change, sec	0.00	1.03	-.06	1.61	.911
3-month grip strength change, kg	-.88	9.12	-.91	7.59	.959

TH-PO977

Impact of Bariatric Surgery on Metabolic and Lithogenic Risk Factors in Patients with Morbid Obesity

Sofia San Román, Gustavo Bruno, Lucía Fernández Talice, Gabriela Ottati, Pilar Portas, Mariela Garau, Oscar A. Noboa. *Universidad de la Republica Uruguay, Montevideo, Uruguay.*

Background: Obesity and metabolic syndrome are risk factors for kidney stones. Bariatric surgeries, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), are options for the management of obesity. Despite the many positive metabolic outcomes, RYGB is also associated with higher risk of kidney stones after surgery. The aim of this study is to determine the modification of lithiasis risk factors in obese patients post-bariatric surgery.

Methods: Descriptive, observational and prospective study analyzing lithogenic factors before and 6 months after bariatric surgery. Wilcoxon signed-rank test was used to assess median differences. Ethical approval was obtained

Results: 25 patients (24 womens), mean age was 43.3 (±10.6) years. RYGB was performed in 16 and SG in 9. The initial BMI was 47 kg/m ^{2} (38.0 - 70.4 kg/m^2). The post BMI was 30.6 kg/m^2 (22 - 50 kg/m^2). In the pre-bariatric study, 10 patients had oxaluria higher than 40 mg/day, with a mean of 37.1 ± 17.5 mg/day, 7 had calciuria higher than 250 mg/day, with a mean of 195.7 ± 148.9 mg/day, 15 had uricosuria higher than 600mg/day, with a mean of 706.9 ± 290.7 mg/day, 10 had citraturia less than 300mg/day, with a mean of 514.8 ± 408.5 mg/day, and 10 had magnesiuria less than 73mg/day with a mean of 88.7 ± 46.2 mg/day. 15 had parathyroid hormone (PTH) levels higher than 68pg/mL, with a mean of 83.8 ± 38.4 pg/mL with normocalcemia, 11/15 with hypovitaminosis D. Postoperatively, significant reductions were seen in hyperuricosuria present in 6/25 patients, with a mean of 498.9 ± 194.2 mg/day, p: 0.005, and hypomagnesuria present in 5/25, with a mean of 120.8 ± 68.8 mg/day, p: 0.021. Mean oxaluria was 33.9 ± 25.6mg/day, decreasing in 6/10 patients with preoperative hyperoxaluria and new onset in 3 patients, with no differences based on the type of surgery. Citraturia and calciuria showed a non-significant decrease. Among the 15 patients with elevated (PTH) levels preoperatively, only 6 remained elevated postoperatively, 4 with persistent hypovitaminosis D. Additionally, 3 patients developed postoperative hyperparathyroidism.

Conclusions: Morbid obesity presents significant lithogenic risk factors. Bariatric surgery modifies these factors, particularly reducing hyperuricosuria and increasing hypomagnesiuria

Funding: Government Support - Non-U.S.

TH-PO978

Dynamics of Changing Nutritional Status following Kidney Transplantation

Diana Sukackiene,[1,2] Marius Miglinas.[1,2] *[1]Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2]Center of Nephrology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania.*

Background: Kidney transplantation (KTx) is the optimal treatment for end-stage renal disease (ESRD) which improving patient survival, yet nutritional and metabolic disorders in patients both before and after KTx are an important clinical and scientific problem. Our study aimed to assess the nutritional status and body composition of candidates for kidney transplantation before the surgery and 12 months after it, to analyse the changes.

Methods: Prospective, observational study was conducted in a tertiary reference hospital. The nutritional status of the patients was assessed by performing laboratory tests, anthropometric measurements, and body composition analysis by using the Bioelectrical Impedance Analysis (BIA), measuring the handgrip strength (HGS), and filling out malnutrition (MN) screening tools on the day of KTx, 6 and 12 months after it.

Results: A total of 98-kidney transplant patients (mean age of 43 [20;60] years, 55 % male, 10 % with diabetes) were included. 52 % of the subjects were overweight or obese before KTx and only 4 % had BMI less than 18.5 kg/m^2 . The baseline screening showed the prevalence of malnutrition prior to the KTx ranged from 7 to 40 %, depending on the screening questionnaire. When assessing the nutritional risk after KTx - the frequency of a low or mild risk of MN is reduced, and more patients achieve a good nutritional status and subsequently lose the risk of MN (87–98%). In the female population, HGS significantly decreased when assessed before KTx and after 6 months (26.2 ± 6 kg and 24.1 ± 6 kg, $p < 0.01$), as well as after 12 months (26.2 ± 6 kg and 24.2 ± 6.7 kg, $p < 0.01$). In men, a significant decline in HGS was observed only after 6 months (46.3 vs 44.1 kg, $p < 0.01$) A decrease in the muscle mass was found in 8% of males 6 months after the surgery, and in 4% of females 12 months after the surgery. This reduction in the muscle mass leads to a significant loss of fat free mass. During the 1-year follow up period we observed a significant increase in body weight (77.6 ± 17.6 kg vs 79.1 ± 18.3 kg), waist circumference (92.6 ± 15 cm vs 96.7 ± 16.2 cm), fat mass (14.4 [1.8-56.9] kg vs 17.3 [2-51.8] kg).

Conclusions: Kidney transplantation leads to changes in body composition that favor increasing body weight driven by fat mass accumulation, increased waist circumference and lean body mass loss.

TH-PO979

Clenbuterol-Associated Rhabdomyolysis: A Rare Case Report

Parth Parmar,[1] Prachi Gajjar,[1] Hetvi Gajjar,[2] Dhruvil K. Shah,[1] Pratik Gyawali,[1] Sepiya Shrestha,[1] Kashish Magnani.[3] *[1]Trumbull Regional Medical Center, Warren, OH; [2]Pramukhswami Medical College, Karamsad, India; [3]Surat Municipal Institute of Medical Education and Research, Surat, India.*

Introduction: Clenbuterol is a beta-2 agonist medication used by fitness enthusiasts for anabolic and lipolytic effects. It has been obtained from illegal markets since it was banned by the US FDA. It carries the risk of severe adverse effects such as myocardial infarction, death and others.

Case Description: We present a case of a 43-year-old male who was involved in bodybuilding. He presented to the hospital with complaints of red urine for a day after using Clenbuterol in higher doses and an extensive workout session at the gym. On admission, laboratory findings showed serum creatine kinase levels of 66,000 U/L and red urine without red blood cells in urinalysis, suggesting the diagnosis of rhabdomyolysis. He survived no fractures or muscle injuries recently. He maintained adequate urine output and normal serum creatinine levels throughout his hospital stay. With intravenous hydration, laboratory serum creatine kinase values trended down to normal. The patient was discharged and advised that the US FDA does not recommend Clenbuterol in the United States for any use in humans or animals.

Discussion: Clenbuterol is an illegally available illicit drug used by fitness enthusiasts. Case reports regarding rhabdomyolysis in humans after illicit use are limited. Proper education regarding Clenbuterol and its serious adverse effects, including death, is needed among fitness enthusiasts. Physicians must also keep a differential diagnosis of rhabdomyolysis due to Clenbuterol in young athletes.

TH-PO980

Effects of Intradialytic Aerobic Exercises on Mitochondrial Biogenesis Markers in Patients Undergoing Hemodialysis

Denise Mafra,[1,2] Livia D. Alvarenga,[2] Ludmila F. Cardozo,[1] Marcelo Ribeiro-Alves,[3] Jessyca S. Brito.[2] *[1]Universidade Federal Fluminense, Niteroi, Brazil; [2]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [3]Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil.*

Background: Chronic kidney disease (CKD) patients commonly have impaired mitochondrial biogenesis and antioxidant defenses. Therefore, gene transcription factors involved with mitochondrial function, such as the peroxisome proliferator-activated receptor gamma 1 alpha coactivator (PGC-1α), the nuclear respiratory factor-1 gene (NRF1) and the mitochondrial transcription A (TFAM), may have its expression modified in patients with CKD. Furthermore, nuclear factor erythroid 2-related factor 2 (Nrf2), an important antioxidant transcription factor, and antioxidant enzymes such as NQO1: NAD(P)H: quinone oxidoreductase-1 (NQO1) are downregulated in CKD patients contributing to oxidative stress. Thus, the study aimed to evaluate the effects of an aerobic intradialytic exercise program on the expression of mitochondrial function markers and antioxidant function in hemodialysis (HD) patients.

Methods: This was a longitudinal crossover clinical trial that included 18 HD patients [61.1% men; 44 (12.2) years; 23.7 (3.9) kg/m^2; dialysis vintage = 17.2 (20.2) months]. Patients were randomized into 2 groups: exercise and control (usual care). The physical exercise program was individualized and performed on an adapted stationary bicycle, consisting of heating (5 minutes), 35 minutes of aerobic training at target heart rate, and cool down (load reduction for 5 minutes), monitored thrice weekly for 3 months. After this, there was one month of washout, crossover, and another 3 months of intervention. Peripheral blood mononuclear cells were isolated and processed to evaluate PGC-1α, NRF1, TFAM, Nrf2, and NQO1 mRNA expression by RT-qPCR.

Results: After the intradialytic exercise program intervention, there was no significant change in the mitochondrial parameters evaluated (PGC-1α, TFAM, and NFR1) nor in the parameters related to antioxidant defenses (Nrf2 and NQO1). Interestingly, a positive correlation was found between PGC-1α and Nrf2 mRNA expression ($r=0.38$ $p=0.04$) and between TFAM and NRF1 ($r=0.45$, $p=0.00$) at baseline.

Conclusions: Three months of interdialytic aerobic exercise was insufficient to modulate significantly mitochondrial biogenesis markers or increase antioxidant defenses.

Funding: Government Support - Non-U.S.

TH-PO981

Association between Kidney Function and Comprehensive Frailty in Elderly Japanese Community-Dwelling Adults

Tatsunori Toida, Akiko Kamimura, Toshiyuki Atsumi, Yasuyuki Kourogi. *Kyushu University of Medical Science, Nobeoka, Japan.*

Background: The Japanese government has implemented a new screening program to prevent the worsening of comprehensive frailty in older adults, and a new frailty assessment questionnaire for medical check-ups of old-old adults aged ≥75 years (QMCOO) has been developed starting in 2020. Few detailed studies have investigated renal function as a risk factor for comprehensive frailty. Therefore, this study examined the association between renal function and comprehensive frailty using the QMCOO score in Japanese community-dwelling elderly.

Methods: Between April 2020 and March 2021, 4621 participants (mean age: 80.1 years; 39.5% male) underwent annual health check-ups in Nobeoka City, Miyazaki Prefecture, Japan. Subjects were divided into four groups based on their estimated glomerular filtration rate (eGFR): G4+5 (<30 mL/min/1.73m^2, n=106), G3b (30–44 mL/min/1.73m^2, n=473), G3a (45-59 mL/min/1.73m^2, n=1477), and G1+2 (≥60 mL/min/1.73m^2, n=2526). Associations between the eGFR groups and comprehensive frailty assessed using a cutoff score of 3/4 for the QMCOO (Geriatr Gerontol Int. 2023, 23,437) were examined. Physical, oral, nutritional, cognitive, and social frailty subdomains were also investigated. In a longitudinal analysis, the G1+2 group served as a reference to

investigate the incidence of comprehensive frailty during the following year among participants without frailty at baseline (n=2398) using logistic regression models to examine odds ratios adjusted for potential confounders.

Results: In this cross-sectional study, the frequency of comprehensive frailty increased with worsening renal function (G1+2: 21.5%; G3a: 23.2%; G3b: 32.8%, G4+5: 38.7%). The results were similar for the physical, oral, nutritional, and cognitive subdomains though no association between renal function and social frailty was identified. In the longitudinal study, a G4+5 eGFR was significantly associated with new-onset comprehensive frailty (G3a: odds ratio (OR): 0.83, 95% confidence interval (CI): 0.62–1.10; G3b: OR: 0.69, 95% CI: 0.43–1.09; G4+5: OR: 2.37, 95% CI: 1.10-5.20).

Conclusions: A decline in renal function in older adults may be a risk factor for comprehensive frailty.

TH-PO982

Estimating Glomerular Filtration Rate: Is There Any Role of Including Lipids and Hemoglobin A1c (Hb A1c) in Patients with Cardiovascular Disease?

Madhab Ray.[1,2] Healthy Heart Initiative Study Group. *[1]University of California Davis, Davis, CA; [2]Tufts Medical Center, Boston, MA.*

Background: Estimation of Glomerular Filtration Rate (GFR) is a cornerstone in practice of nephrology and modern medicine. Over the last few decades, the estimation process has gone through multiple iterations with combinations of different potential predictor variables. Most commonly used CKD-Epi formula incorporates five variables: age, sex, race, body surface area and serum creatinine levels. However, there are potentially some unmeasured variables which, in a given clinical context may add predictive accuracy.

Methods: Four thousand schoolteachers were recruited in Calcutta, India for cardiovascular disease (CVD) risk assessment and evaluation of kidney function with joint approval from Tufts University IRB, Boston, and the local Ethics Committee, Calcutta. GFR was estimated with CKD-Epi model. To explore any potential unmeasured variables for GFR regression analyses were performed with traditional CVD risk factors: lipid panel for dyslipidemia and Hb A1c for diabetes mellitus.

Results: The mean age of the participants was 44 years with 41% male. Estimation of renal function with eGFR revealed most of the study population had CKD G2 (n = 125, 52%) followed by G1 and G3 (n = 53, 22% each). Six participants had CKD G3B while number of participants in G4 and G5 were one in each category. Univariate analyses showed considerable association of GFR with total cholesterol, HDL, triglycerides and Hb A1C. A multivariable regression model showed significant association with HDL and Hb A1 C when adjusted for total cholesterol and triglycerides.

Conclusions: In patients with CVD and diabetes mellitus incorporating Hb A1 C level may potentially improve accuracy of estimated GFR by CKD-Epi model. It is important for the clinicians to remain cognizant of the possibility of inflated GFR in presence of diabetes mellitus with high Hb A1C. Similar adjustment, although to a lesser extent, may be necessary for HDL level. While elevated HB A1 C level may increase GFR by its glycosuric effect the mechanism by which HDL may influence GFR is not entirely clear at this point.

Multivariable linear regression model with HDL and Hb A1C for eGFR

	Estimate	95% CI	P value
Intercept	88.6	72.52 — 104.66	<0.001
Cholesterol	-0.03	-0.11 — 0.05	0.5
HDL	-0.55	-0.81 — - 0.28	<0.001
Triglycerides	0.03	-0.02 — 0.08	0.18
HB A1C	1.99	0.17 — 3.81	0.03

TH-PO983

Association between Potential Renal Acid Load and 10-Year Mortality in Patients on Hemodialysis

Mai Tanaka, Hideyuki Kabasawa, Michihiro Hosojima. *Department of Clinical Nutrition Science, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: Dietary intake has long been known to influence acid-base balance. Recently, higher dietary acid load (DAL) has been reported to be associated with increased risk of incidence and progression of chronic kidney disease. However, the association between DAL and mortality in patients on maintenance hemodialysis (MHD) has not been evaluated. In this study, we investigated the association between DAL and mortality and analyzed the kinds of food that affect DAL in Japanese patients on MHD.

Methods: We retrospectively analyzed baseline laboratory data, self-administered diet history questionnaire results, and 10-year mortality rates in 44 patients (26 men, 67.9±10.4 years) on MHD who participated in a randomized, double-blind, crossover pilot trial of rice endosperm protein supplementation which was conducted in 2013. DAL was estimated from nutrition intake using potential renal acid load (PRAL). Patients were divided into tertiles according to PRAL score to explore its association with all-cause mortality. Cox proportional hazards regression with adjustment for age and sex was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. In addition, multivariable logistic regression was performed to estimate odds ratios (ORs) for the kinds of food that significantly affected PRAL score.

Results: During the 10-year observation period, a total of 19 patients (43%) died. Mean PRAL score was 11.0 mEq/L. A higher PRAL score was significantly associated with higher all-cause mortality. The multivariable-adjusted HR for all-cause mortality in the highest tertile compared with the lowest tertile of PRAL score was 3.88 (95% CI, 1.10-13.61). Multiple logistic regression analysis showed a significant association between higher PRAL score and lower intake of green and yellow vegetables (OR, 5.40; 95%CI, 1.37-21.26) and fruits (OR, 4.76; 95% CI, 1.30-16.76).

Conclusions: Our findings suggested that high PRAL score is positively associated with all-cause mortality in patients on MHD. Low intake of fruits and vegetables would increase PRAL score and might affect the risk of mortality in Japanese patients on MHD. Further studies, including prospective ones, are needed to confirm whether DAL affects mortality in patients on MHD.

TH-PO984

Prevalence of Visual Impairment and Effects on Quality of Life (QoL) in a Population of Inner-City Patients with ESKD

Wen Huang, Sasha E. Gerard, Mariana S. Markell. *SUNY Downstate Health Sciences University College of Medicine, Brooklyn, NY.*

Background: Kidney disease is often associated with eye disease. We investigated the prevalence of visual impairment and impact on QOL in an inner city population of pts with ESKD.

Methods: A random convenience sample of 13 hemodialysis and 13 kidney transplant pts were surveyed face to face regarding their visual ability utilizing general vision-related questions and the National Eye Institute Visual Function Questionnaire (NEI VFQ-25).

Results: Mean age was 61.8±2.5yrs, 15 male (58%), 22 (85%) identified as Black, 59% (13) made <$40K/yr. 41% (10/24) rated their vision as fair to poor. Higher income was associated with better vision related mental health (r=0.6, p=0.005), despite no association with personal vision rating. Mean HbA1c was 6.2±0.2, range 4.7-8.8. Higher HbA1c was associated with eye discomfort (r=0.68, p<0.001), difficulty seeing at night (r=0.44, p=0.03), inability to accomplish tasks (r=-0.45, p=0.03), limitation due to optic pain or discomfort (r=-0.63, p=0.01), being more likely to stay home (r=-0.51, p=0.01) and feeling less control (r=-0.59, p=0.002). Pts who stayed home were also more likely to report no longer reading the newspaper or doing close activities (r=-0.61, p=0.002), being unable to read street signs (r=-0.59, p=0.002), find things (r=-0.77, p<0.001) or use stairs (r=-0.77, p=0.001). They also reported difficulty judging facial reactions (-0.69, p<0.001), frustration (r=0.85, p<0.001), inability to work (r=0.74, p<0.001), increased dependency (r=-0.78, p<0.001), decreased mental health (r=0.84, p<0.001) and decreased social interactions (r=0.78, p<0.001). There was no difference between dialysis and txp pts or males and females.

Conclusions: In our population: 1. Almost half of pts rated their vision as fair to poor 2. Pts with higher income had better adjustment to visual limitations. 3. Higher HbA1c was associated with more symptoms, decreased social interaction, and feeling less control. 3. Limited vision patients reported stopping normal daily activities, inability to work, decreased mental health and increased dependency. 4. Visual impairment has far reaching impact on QoL in pts with ESKD and may be overlooked given other medical issues. Decreased visual function should be recognized and addressed early in the course of kidney disease, with targeted support provided for the already visually impaired.

TH-PO985

Impact of Fatty Acid Desaturase 1 on CKD via Very Low-Density Lipoprotein-Associated Metabolites: A Drug Target-Related Mediation Mendelian Randomization Study

Lei Chen, Wanxin Tang. *West China Hospital of Sichuan University, Chengdu, China.*

Background: Metabolic dysregulation plays a crucial role in chronic kidney disease (CKD). Identifying new targets for CKD through metabolites and their regulatory genes requires further investigation.

Methods: A total of 233 metabolites from GWAS Catalog with $P < 5 \times 10^{-8}$ were utilized for Mendelian randomization with CKD. External validation was conducted from UK Biobank. Cis-eQTL of genes related to VLDL were selected for Mendelian randomization with CKD and metabolites. The total effect of the fatty acid desaturase 1 gene (*FADS1*) on CKD and metabolite-mediated effects were calculated. Bulk RNA-seq were used to validate *FADS1* expression in the kidney tissues of patients with CKD.

Results: The cholesteryl esters to total lipids ratio in medium VLDL (OR = 0.84 [0.77–0.92]; P.adj = 0.039) and total cholesterol to total lipids ratio in small VLDL (OR = 0.84 [0.77–0.91]; P.adj = 0.003) were protective factors for CKD, whereas the triglycerides to total lipids ratio in small VLDL (OR = 1.18 [1.09–1.27]; P.adj = 0.009) and the triglycerides to total lipids in very small VLDL (OR = 1.19 [1.10–1.27]; P.adj < 0.001) were risk factors. They mediated the risk of CKD by *FADS1* (OR = 1.11 [1.06–1.17]; P.adj = 0.001), and mediation effects of 21.17%, 10.43%, 23.52%, and 29.96% were obtained. The differential expression of *FADS1* was observed in the kidney tissues of patients with CKD.

Conclusions: *FADS1* is a risk factor for CKD and a novel therapeutic target. Four metabolites mediate the detrimental effect of *FADS1* in CKD.

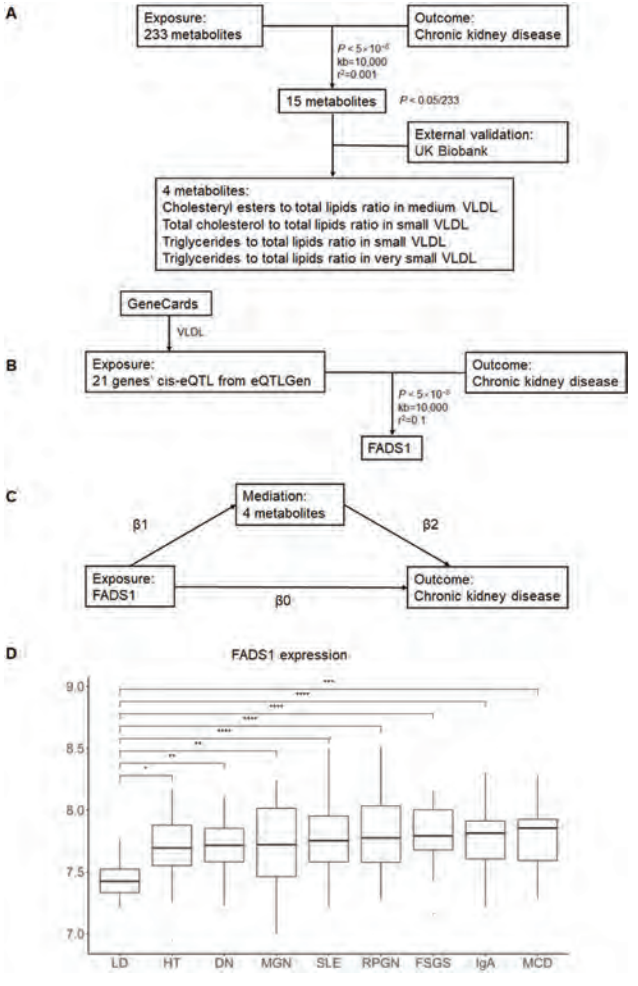


Figure 1: Overview Diagram of Drug Target MR and Mediation MR Analysis

TH-PO986

Lipoprotein (a) and Kidney Function: A Correlation Study

Xinyi Fu, Chenyu Lei, Anning Xu, Linlin Yuan, Wenjing Cai, Qingying Shi, Xinling Liang, Zhiming Ye, Zhilian Li. *Department of Nephrology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China.*

Background: Recent evidence implicates Lipoprotein(a) [Lp(a)] as a potent atherogenic factor, surpassing LDL in its cardiovascular risk. Despite this, the dynamics of plasma Lp(a) levels across varying stages of renal function, as defined by estimated Glomerular Filtration Rate (eGFR), remain inadequately explored. This retrospective study aims to investigate the relationship between plasma Lp(a) concentrations and renal function, utilizing a large patient cohort.

Methods: Between January 2019 and December 2022, data from 141,376 patients at Guangdong Provincial People's Hospital, including renal function parameters and lipid profiles, were analyzed. Lipid markers studied encompassed Lp(a), triglycerides (TG), total cholesterol (TC), HDL-C, LDL-C, Apo A1, and Apo B. Patients were stratified into five groups per eGFR levels aligning with chronic kidney disease stages (KDIGO guidelines). Plasma Lp(a) levels were compared across these groups through the Kruskal-Wallis test, with statistical analyses performed using SPSS version 22.0.

Results: The median plasma Lp(a) concentration in the study population was 166.0 mg/L (IQR: 91.0 - 346.0 mg/L). Importantly, the median plasma Lp(a) levels (IQR) showed a progressive increase across the five eGFR groups, as follows: eGFR ≥ 90 mL/min/1.73 m^2 : 153.0 (85.0, 313.0) mg/L;eGFR 60-89 mL/min/1.73 m^2: 172.0 (95.0, 351.0) mg/L;eGFR 30-59 mL/min/1.73 m^2: 203.0 (107.0, 422.0) mg/L;eGFR 15-29 mL/min/1.73 m^2: 235.0 (125.0, 469.0) mg/L;eGFR < 15 mL/min/1.73 m^2 : 260.5 (148.0, 460.0) mg/L. Statistical analysis revealed a highly significant difference in Lp(a) levels among the groups (p< 0.01), with pairwise comparisons also demonstrating statistically significant differences between each group (p < 0.01). Notably, this trend was not observed for other lipid markers including LDL-C and ApoB.

Conclusions: Our findings underscore a clear association between plasma Lp(a) concentrations and renal function decline. As eGFR decreases, there is a discernible rise in plasma Lp(a) levels, highlighting its potential role in renal dysfunction progression.

TH-PO987

Trend Analysis of Kidney Failure and Metabolic Syndrome-Related Mortality, 1999-2020

Mohammad Ammar ur Rahman,[1] Ahmed J. Chaudhary,[2] Jawad Ahmad,[2] Saleha Azeem,[1] Luqman Munir,[1] Amna Khalid.[1] *[1]King Edward Medical University, Lahore, Pakistan; [2]Detroit Medical Center, Detroit, MI.*

Background: End-stage renal disease which manifests as renal failure is one of the leading causes of death in America and when combined with a comorbidity like metabolic syndromes, has reasonable prevalence. Minor metabolic syndromes including lipomatosis, lipodystrophy, and tumor lysis syndrome increase the complications of renal failure by interfering with the function of the already diseased kidney to a greater extent which is often the underlying pathology. The goal of this study is to explore the trends of mortality due to renal failure when combined with various minor metabolic syndromes like lipomatosis, lipodystrophy, and tumor lysis syndrome from 1999 to 2020 using the age-adjusted mortality rates to target inconsistencies in various epidemiological groups. These metabolic syndromes affect the overall survival outcome of patients with end-stage renal disease leading to worse outcomes.

Methods: We analyzed Death Certificates from the Centers for Disease Control and Prevention (CDC) Wide Ranging Online Data for Epidemiological Research (WONDER) database from 1999-2020. AAMR per 1,000,000 people and annual percent change (APC) with a 95% confidence interval were determined. We then used the Joinpoint Regression Program to obtain trends amongst demographic (race, ethnicity, gender, age) groups.

Results: There has been a steady rise in mortality from 1999 to 2015 with an annual percent change (APC) of 4.47 but from 2015 onward, a steep rise in mortality with an APC of 17.67 has been observed. Overall mortality for males has been higher and steady but APC for females followed an interesting trend as it declined from 2003 to 2007 but has risen since. African Americans have consistently had worse outcomes as APC since 1999 has been in the high 20s with it dropping down in the early to mid-2000s. South census region has crept up to be the region most affected which until 2012 was the Midwest.

Conclusions: Renal failure and metabolic syndromes-related mortality have experienced an uprise in the United States in recent years. Persistent demographic and geographic disparities in renal failure and associated metabolic syndromes' mortality underscore the need for further investigation and intervention.

TH-PO988

Prevalence of Hyperuricemia and Its Correlation with Metabolic Syndrome in Young Adults: A Cross-Sectional Study in Eastern China

Bohan Lu.[1,2] Dept of Nephrology, Renji Hospital, Shanghai Jiaotong University School of Medicine. *[1]Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Ningbo Hangzhou Bay Hospital, Ningbo, China.*

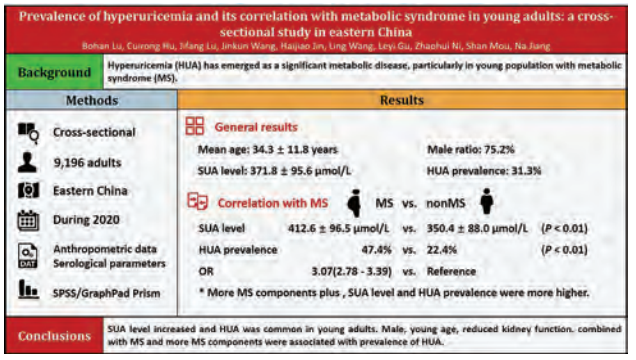
Background: Hyperuricemia (HUA) has emerged as a significant metabolic disease, particularly in young population with metabolic syndrome (MS). The purpose of this study was to study the prevalence of HUA and its correlation with metabolic syndrome among young adults in a coastal city of eastern China.

Methods: It was a cross-sectional study conducted in adults undergoing routine healthy checkup. Anthropometric data and serological parameters were collected and in related to serum uric acid (SUA) concentration and prevalence of HUA.

Results: A total of 9,196 adults with mean age of 34.3 ± 11.8 years old and 75.2% of males were recruited. Mean SUA level was 371.8 ± 95.6 mmol/l and overall HUA prevalence was 31.3%. SUA level was higher and HUA was more common in younger males, as well as in those with MS (OR: 3.07; 95% CI: 2.78 - 3.39) demonstrated by using the univariable binary logistic regression analysis model. The multivariable binary logistic regression analysis revealed that male (OR: 3.74; 95% CI: 3.12 - 4.48), young age (OR: 1.22; 95% CI: 1.19 - 1.26), low estimated-glomerular filtration rate (OR: 2.45; 95% CI: 2.11 - 2.84), high body mass index (OR: 2.31; 95%CI: 2.06 - 2.60), hypertension (OR: 1.18; 95% CI: 1.04 - 1.32), high serum triglyceride (OR: 2.08; 95%CI: 1.81 - 2.37), and low serum high-density lipoprotein cholesterol (OR: 1.33; 95% CI: 1.15 - 1.55) were independent risk factors associated with HUA prevalence.

Conclusions: SUA level increased and HUA was common in young adults. Male, young age, reduced kidney function, combined with MS and more MS components were associated with prevalence of HUA.

Funding: Other NIH Support - National Natural Scientific Foundation of China (No. 81970574 and 82170685)



TH-PO989

Association of Zinc Deficiency with Abdominal Fat and Muscle Mass Areas in Patients on Hemodialysis

Junko Ishida,[1] Nao Muramoto,[1] Masako Tanaka,[1] Yoshiteru Yamada,[2] Mayumi Yamada,[2] Ai Asano,[2] Teppei Matsuoka,[2] Akihiko Kato.[3]
[1]Kinjo Gakuin University, Nagoya, Japan; [2]Taiseikai Medical Corporation, Ogaki, Japan; [3]Hamamatsu University Hospital, Hamamatsu, Japan.

Background: Zinc (Zn) deficiency is highly prevalent in hemodialysis (HD) patients. However, the relationship between Zn deficiency and body muscle and fat masses remains to be clarified in HD patients. So, we aimed this study to examine the relationship between serum Zn levels and anthropometric parameters in HD patients in a cross-sectional design.

Methods: We measured abdominal muscle area (AMA), subcutaneous fat area (ASFA) and visceral fat area (AVFA) on transverse slice of computed tomography (CT) at L3 to L4 of vertebral bodies in 287 patients who had been undergoing regular HD for more than 2 years (median age: 69.0 years old, M/F = 200/87, diabetes (DM)/non-DM = 87/200). We adjusted these parameters by height square. This study was approved by the Institutional Ethics Committee of Kinjo Gakuin University and supported by JSPS KAKENHI(JP20K10391).

Results: Serum Zn was lower than the reference range (80~130 μg/dL) in almost of the patients (97%). Median Zn level was significantly lower in non-DM patients (56.0 [51.0-62.0] μg/dL) when compared with DM patients (58.0 [53.0-66.0] μg/dL) (p<0.05). Zn deficiency (<60 μg/dL) was found in 64.5% of non-DM patients and 54.0% of DM patients, respectively. AMA, ASFA, AVFA were significantly lower in non-DM than in DM patients (p<0.05) (Table). There was a significant and positive correlation between serum Zn and AMA in non-DM patients (r=0.185, p<0.01), but not in DM patients. Serum Zn was also significantly and negatively correlated with ASFA, but not with AVFA in DM and non-DM groups. Multiple regression analyses revealed that serum Zn was a significant determinant of AMA and ASFA.

Conclusions: Our findings suggested that Zn deficiency is associated with abdominal muscle wasting, while with accumulation of subcutaneous fat mass in non-DM HD patients.

Funding: Other NIH Support - This work was supported by Grant-in-Aid for Scientific Research "JSPS KAKENHI" Grant Number JP 20K10391

Abdominal anthropometric parameters in non-DM and DM patients

Primary disease	Non-DM	DM	P value
N	200	87	
Age (years)	70.0 (59.0 - 78.0)	68.0 (55.0-73.0)	N.S.
HD vintage (years)	10.6 (4.9 - 19.7)	5.9 (2.9-9.0)	< 0.05
AMA (cm2/m2)	33.09 (27.66 - 39.23)	35.31 (30.11 - 41.54)	< 0.05
ASFA (cm2/m2)	35.17 (22.09 - 56.14)	43.60 (32.40 - 61.19)	< 0.01
AVFA (cm2/m2)	51.33 (37.59 - 70.29)	64.24 (42.73 - 87.99)	< 0.01

Mann Whitney U test. All variables were expressed as the median and interquartile range (25th to 75th percentiles).

TH-PO990

Early Evidence of Tendon Dysfunction in a Rat Model of CKD

Christopher Hayden,[1] Natalie K. Gilmore,[1] Baback Roshanravan,[2] Keith Baar.[1] *[1]University of California Davis, Davis, CA; [2]University of California Davis School of Medicine, Sacramento, CA.*

Background: Spontaneous tendon ruptures are debilitating injuries that are disproportionately high in individuals with chronic kidney disease (CKD). Despite this, almost no data exists regarding CKD-related tendon pathology. Thus, we used a rat model of CKD to determine whether tendon mechanics are altered by CKD.

Methods: Sprague-Dawley rats (n=32, 50% female, age=8wk) were equally divided into a control group (CON) and a group fed chow with 0.25% adenine to induce CKD. After 8wk, blood markers for CKD were evaluated, and Achilles and tibialis anterior (TA) tendons were collected. Tendons were then tested in tension to failure using a single-column tensile tester with a 100N load cell. Maximum tensile load (MTL), failure stress, Young's modulus, and cross-sectional area (CSA) were determined. The strongest of each tendon for every animal was used in analysis. The effect of CKD was evaluated for each tendon by two-way ANOVA (main and interaction effects: CKD and sex).

Results: CKD was confirmed through elevated creatinine (1.99 vs 0.61mg/dL, CKD vs CON, P=0.001), blood urea nitrogen (93.4 vs 21.4mg/dL, P<0.001), kidney mass (2.7 vs 1.25g, P<0.001), and lower hematocrit levels (34 vs 47%, P<0.001). Final body weight did not differ for the females (282 vs 284g, P=0.9), but the CKD males were lighter than controls (438 vs 585g, P<0.001). The failure stress of TA tendons was significantly lower in CKD vs CON (18.8 vs 24.8 mPa, P=0.039). There were no statistically significant differences in MTL, modulus, or CSA (p>0.097) or for any parameter for the Achilles (P=0.73). Sex did not modify the effects of CKD (P=0.86).

Conclusions: We demonstrate that, early in the development of CKD in rats, TA tendons failed at a lower stress. These results along with the finding that there were no differences in CSA between groups suggest that CKD diminishes tendon material properties. To our knowledge, this is the first direct evidence of changes in tendon mechanics caused by kidney disease, providing a model for further evaluating mechanisms and interventions.

Funding: NIDDK Support

TH-PO991

Gut Microbe-Derived Metabolite Phenylacetylglutamine and Risk of CKD Progression

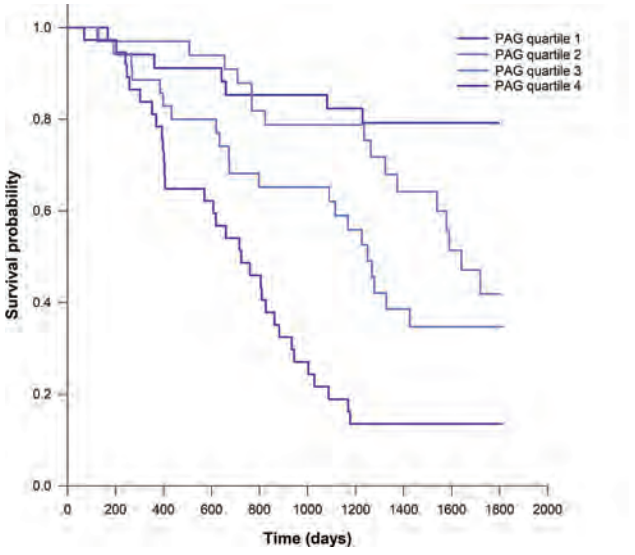
Evelyn Cheng,[1] Ting-yun Lin,[2] Szu-Chun Hung.[2] *[1]University of Washington, Seattle, WA; [2]Taipei Tzu Chi Hospital, Taipei, Taiwan.*

Background: Phenylacetylglutamine (PAG) is a gut microbe-derived metabolite from dietary phenylalanine. High PAG levels have been associated with overall mortality and cardiovascular disease in patients with CKD. However, potential associations of PAG with the risk of progression to kidney failure in patients with CKD remains unclear.

Methods: We prospectively followed 152 non-dialysis patients with CKD stages 3–5 and a measurement of plasma PAG. The primary outcome was a composite of progression of kidney disease (defined as a sustained decrease in eGFR of ≥40% from baseline, initiation of maintenance dialysis, kidney transplantation, or death from renal causes).

Results: Participants had a mean age of 66 years; 41.4% were women; 39.5% had diabetes; and the median eGFR was 23 mL/min/1.73 m2. Participants with higher PAG were more likely to have a significantly lower eGFR (P <0.001). During a median follow-up of 3.3 years, progression of kidney disease occurred in 76 (50%) participants. Higher PAG was associated with a significantly increased risk of the composite outcome after controlling for demographics, comorbidities, and proteinuria (hazard ratio, 1.79; 95% CI, 1.27–2.54). However, the association was attenuated and statistically insignificant after adjustment for eGFR.

Conclusions: Our findings suggest the relevance of PAG in the progression of kidney disease. Whether PAG is simply a marker of kidney dysfunction or, in contrast, whether PAG actively alters the course of CKD needs to be investigated.



PAG and CKD progression. Kaplan–Meier survival curve. Quartiles of serum PAG.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PAG (Ln)	2.47 (1.86–3.29)	<0.001	1.79 (1.27–2.54)	0.001	1.25 (0.86–1.93)	0.229
Indoxyl sulfate (Ln)	1.73 (1.35–2.22)	<0.001	1.34 (0.96–1.86)	0.082	1.17 (0.85–1.63)	0.333
p-cresyl sulfate (Ln)	1.77 (1.32–2.39)	<0.001	1.36 (0.98–1.89)	0.066	0.99 (0.69–1.41)	0.946

Cox proportional hazard survival analysis

TH-PO992

Gut Microbe-Derived Metabolite Trimethylamine N-oxide and Risk of CKD Progression

Evelyn Cheng,[1] Ting-yun Lin,[2] Szu-Chun Hung.[2] *[1]University of Washington, Seattle, WA; [2]Taipei Tzu Chi Hospital, Taipei, Taiwan.*

Background: Trimethylamine N-oxide (TMAO) is derived from gut microbial metabolism of dietary L-carnitine, phosphatidylcholine, and choline. Higher TMAO have been associated with increased risk of cardiovascular diseases. However, the potential relevance between TMAO and kidney function decline in patients with CKD remains unclear.

Methods: We prospectively followed 152 participants with CKD stages 3–5. Measurement of plasma TMAO was done by liquid chromatography-mass spectrometry at baseline. The primary outcome was defined as a composite of progression of kidney disease (sustained decline in eGFR of ≥40% from baseline, initiation of dialysis, or death from renal causes). Additionally, we performed logistic regression to determine the probability of slow and fast eGFR decline (≤3 versus >3 ml/min/year) with plasma TMAO as the main predictor.

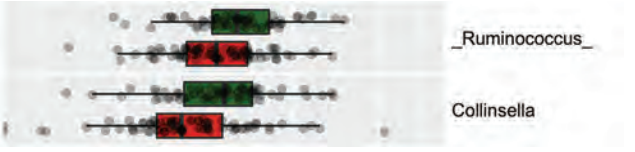
Results: Participants with higher TMAO were more likely to have a significantly lower eGFR. Higher TMAO was significantly associated with an increased risk of the composite outcome after adjustment for demographics, comorbidities, proteinuria, and the use of ACEI/ARB (hazard ratio, 1.48; 95% CI, 1.21–1.97). However, the association was attenuated and statistically insignificant after adjustment for eGFR. Higher TMAO was significantly associated with increased odds of fast eGFR decline after adjustment for eGFR, proteinuria, and other confounding characteristics (odds ratio, 2.35; 95% CI, 1.31–4.22). In addition, gut microbial analyses showed that compared to slow eGFR decliners, fast eGFR decliners had a significantly higher abundance of *Ruminococcus* and *Collinsella*, which have been implicated as TMA-producing bacteria in previous studies.

Conclusions: TMAO is associated with fast eGFR decline in patients with CKD. Whether the gut microbiota contributes to the progression of CKD needs further investigations.

Cox proportional hazard survival analysis

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
TMAO	1.74 (1.37-2.21)	<0.001	1.48 (1.12-1.97)	0.007	1.18 (0.86-1.63)	0.306

HR per 1-SD increase.
Model 1 adjusted for age and sex.
Model 2 additionally adjusted for DM, use of ACEI/ARB, BMI, urine protein, and phosphate.
Model 3 additionally adjusted for eGFR.



Higher abundance of *Ruminococcus* and *Collinsella* (fast vs. slow eGFR decliners)

TH-PO993

Metabolome Biomarkers of CKD Progression in SPRINT Participants

Yunus Ozekin,[1] Zhiying You,[1] Kristen L. Nowak,[1] Berenice Y. Gitomer,[1] Anna Jovanovich,[2] Michel Chonchol.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Bozeman Health, Bozeman, MT.*

Background: Understanding circulating metabolome patterns in relation to kidney disease progression may facilitate the identification of novel biomarkers and development of targeted interventions for CKD progression.

Methods: Untargeted metabolomics of baseline plasma samples from 700 Systolic Blood Pressure Interventional Trial (SPRINT) participants with CKD was performed using UPLC-MS/MS. Bioinformatic analysis was performed using the MetaboAnalyst 6.0 workflow. The association between 35 metabolites and the primary kidney outcome in SPRINT (≥50% decrease in eGFR or development of ESKD requiring dialysis or kidney transplantation) was assessed using Cox proportional hazards models.

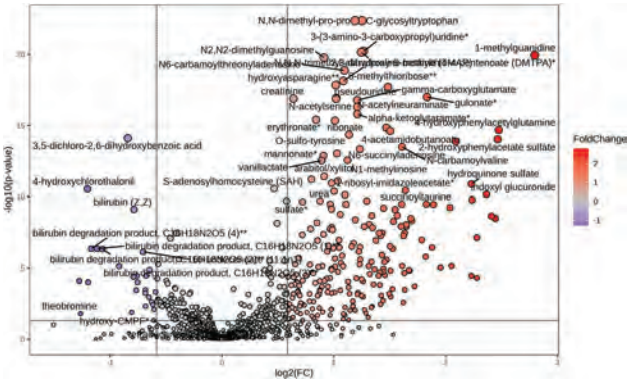
Results: Baseline characteristics are summarized in Table 1. There were 1686 metabolites with standardized measurements at baseline. 234 compounds were upregulated and 27 were downregulated (p<0.05, abs(fold change) >1.5) (Fig. 1). The associations of the top 35 metabolites with the CKD composite outcome in SPRINT are shown in Fig. 2.

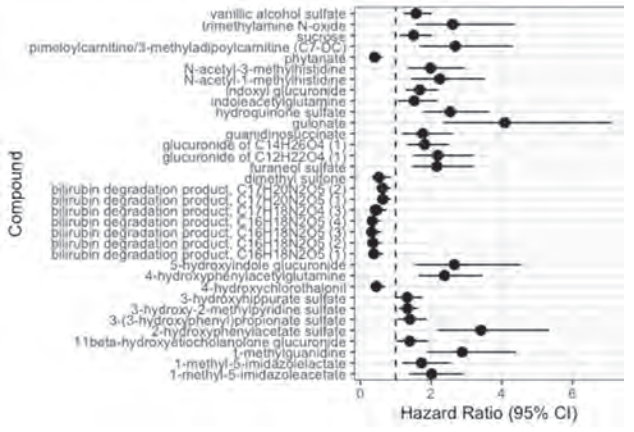
Conclusions: Among patients with CKD, novel metabolites derived from untargeted metabolomic profiling were independently associated with kidney disease progression outcomes.

Funding: Veterans Affairs Support

Baseline Characteristics of Study Patients

Characteristic	Standard Treatment n=342	Intensive Treatment n=358
Age	73.46 +/- 9.06	74.03 +/- 9.53
Female sex-no. (%)	141 (39.39)	135 (39.47)
eGFR	45.14 +/- 9.82	45.23 +/- 9.76
Body mass index	29.35 +/- 6.82	29.12 +/- 6.27
Composite Renal Outcome-no. (%)	13 (3.63)	10 (2.92)





TH-PO994

Metabolites Associated with Inflammatory Proteins in the AASK Study

Teresa K. Chen,[1,2] Aditya L. Surapaneni,[3] Michelle M. Estrella,[1,2] Lawrence J. Appel,[4] Wassim Obeid,[4] Chirag R. Parikh,[4] Morgan Grams.[3]
[1]University of California San Francisco, San Francisco, CA; [2]San Francisco VA Health Care System, San Francisco, CA; [3]New York University, New York, NY; [4]Johns Hopkins University, Baltimore, MD.

Background: Inflammation is associated with greater risk of adverse outcomes, including CKD progression, CVD, and mortality, and may also be impacted by the metabolic milieu. Using an untargeted metabolomics approach, we identified metabolites associated with 9 inflammatory proteins (TNFR1, TNFR2, TNF-α, IFN-γ, IL-6, IL-8, IL-10, UMOD, EGF) in the African American Study of Kidney Disease and Hypertension (AASK).

Methods: Among 491 AASK participants (37% female, mean age 54 y and GFR 45 mL/min/1.73m^2, median UPCR 91 mg/g), we measured 812 serum metabolites by untargeted mass spectrometry (Metabolon) at study baseline and serum proteins by targeted immunoassays (MesoScale Discovery) at baseline, 12- and 24-months. Using multivariable linear regression, linear mixed-effects, and Cox PH models, we evaluated associations of metabolites with proteins at baseline, over time, and with ESKD risk, respectively. We used Metaboanalyst to identify enriched metabolomic pathways for each protein.

Results: At baseline, 367 associations between metabolites and inflammatory proteins were significant after Bonferroni correction: with more positive associations for TNFR1 (97%), TNFR2 (97%), IL-8 (77%), and IL-10 (100%); more negative associations for UMOD (80%) and EGF (97%); and variable for TNF-α, IFN-γ, and IL-6. Enriched pathways differed across inflammatory proteins (**Table**). For TNFR1 and TNFR2, these included inositol phosphate metabolism, ascorbate and aldarate metabolism, and tryptophan metabolism. Several metabolites were associated with changes in TNFR1, TNFR2, TNF-α, IL-8, UMOD, or EGF. Higher levels of tigylcarnitine and N2,N5 diacetylornithine were associated with 2-year increases in TNFR1 and/or TNFR2, and notably of ESKD (**Figure**).

Conclusions: Using an untargeted approach, multiple metabolites were cross-sectionally and longitudinally associated with inflammatory proteins.

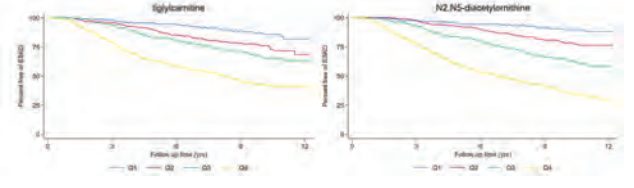
Funding: NIDDK Support

Table: Pathways upregulated by metabolites associated with inflammatory proteins at baseline.

	TNFR1	TNFR2	TNF-α	IFN-γ	IL-6	IL-8	IL-10	UMOD	EGF
Inositol phosphate metabolism	X	X							X
Ascorbate and aldarate metabolism	X	X							
Tryptophan metabolism		X							
Beta-alanine metabolism			X			X			
Pyrimidine metabolism				X					
Nitrogen metabolism				X					
Glycoxylate and dicarboxylate metabolism				X					
Arginine biosynthesis				X					
Alanine, aspartate, and glutamate metabolism				X		X			
Glycerophospholipid metabolism					X				
Glycosylphosphatidylinositol-anchor biosynthesis					X				
Retinol metabolism					X				
Pyruvate metabolism						X			
Cysteine and methionine metabolism						X			
Citrate cycle (TCA cycle)						X			
Sphingolipid metabolism						X			
Taurine and hypotaurine metabolism						X			

*Significant pathways defined as p<0.05.

Figure: Kaplan-Meier curves for ESKD, by quartiles of baseline tiglylcarnitine and N2,N5-diacetylornithine.



TH-PO995

Urine Metabolome and CKD Progression in African American Patients

Changwei Li,[1] Ruiyuan Zhang,[1] Morgan Grams,[2] Tanika Kelly,[3] Jing Chen,[4,1] Jiang He.[1]
[1]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; [2]New York University Grossman School of Medicine, New York, NY; [3]University of Illinois System, Urbana, IL; [4]Tulane University School of Medicine, New Orleans, LA.

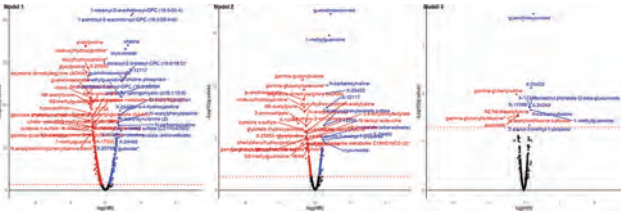
Background: Urine samples of chronic kidney disease (CKD) patients may contain unique metabolite profiles for CKD progression. However, urinary metabolomic study of CKD progression, particularly among African American (AA) patients, has not been well studied. We aimed to identify novel urinary metabolites associated with CKD progression in AA participants of the Chronic Renal Insufficiency Cohort (CRIC).

Methods: Metabolites were measured from baseline 24-hour urine samples of 1,513 AA participants of the CRIC, using an untargeted approach. After quality control, 1,350 metabolites were analyzed. CKD progression was defined as the onset of end-stage renal disease or a 50% reduction in estimated glomerular filtration rate (eGFR). Associations of metabolites with CKD progression were examined by a base model adjusting for age, sex, study site, smoking, drinking, body mass index, systolic blood pressure, diabetes, cardiovascular disease, and APOL1 risk alleles, and two models sequentially adding urine protein creatinine ratio and eGFR. Metabolites with a false discovery rate corrected q <0.05 were deemed significant. For metabolites with unknown identities, we performed genome-wide analyses to identify genes associated with them.

Results: A total of 569, 287, and 14 metabolites were significantly associated with the risk of CKD progression in the three models, respectively (**Figure**). Among the 14 metabolites identified in the fully adjusted model, *guanidinosuccinate*, a uremic toxin, was most significant, with one standard deviation increase associated with 1.31 (95% confidence interval: 1.18-1.45, q=2.25×10^{-4}) times higher risk of CKD progression. While many known metabolites were previously linked to eGFR, two metabolites, *2-amino-2-methyl-1-propanol (AMP)* and *N2,N6-diacetyllysine*, showed novel associations with CKD progression. Moreover, unknown metabolite X-25422 showed significant associations with *ASNS* and *ASPG*, two genes involved in asparagine synthesis and metabolism.

Conclusions: We identified 14 urinary metabolites associated with CKD progression among African Americans.

Funding: Other NIH Support - NIGMS



TH-PO996

Genome-Wide DNA Methylation Association Study Identifies DNA Methylation Associated with ESKD

Xiaohong Zhou. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: End stage renal disease (ESRD) is a leading cause of morbidity and mortality worldwide. It has been increasingly appreciated that epigenetic changes, such as DNA methylation, play an important role in kidney disease.

Methods: Here, using Illumina Infinium EPIC arrays, we performed an epigenome-wide association study (EWAS) of DNA methylation in two ESRD cohorts from China (460 ESRD cases and 196 controls with CKD) and Singapore (229 ESRD cases and 508 controls with T2D).

Results: Through a meta-analysis of the association evidences from the two cohorts, we discovered 2400 differentially methylated probes or CpG sites (DMP) whose DNA methylation levels were associated with ESRD at genome wide significance (P < 1.29e-8), with 39% ~ 72% of which were found to be associated with estimated glomerular filtration rate (eGFR) by several EWAS analyses of eGFR. The 2400 DMPs were mostly located in transcriptionally active enhancers, and 42.7% of them were found to be associated with transcriptomic changes according to published eQTM datasets. By interrogating these 2400 DMPs with the genomic functional information for blood, kidney and muscle tissue, we identified 3788 target genes whose transcriptions may be influenced by these DMPs. The enrichment analysis of these target genes revealed the pathways and GO terms related to immunity and inflammation, endocrinology and metabolism, particularly autophagy process, B cell receptor signaling and insulin resistance.

Conclusions: Our findings have not only discovered ESRD associated DNA methylation variations that can be used as biomarkers for ESRD, but also highlighted certain biological processes that are involved in kidney disease progression to ESRD.

Funding: Government Support - Non-U.S.

Clinical characteristics of the subjects in the GDPH and the KTPH cohort.

	GDPH cohort			AHPL cohort		
	ESRD	CKD	P value	ESRD	CKD	P value
Characteristics						
Subjects number	457	196	-	229	508	-
Age	48.33(±14.29)	42.77(±15.57)	<0.0001	61.23 ± 9.94	57.68 ± 10.36	<0.0001
Male cases	246(53.83%)	82(41.83%)	0.11	154 (67.2%)	286 (56.3%)	0.005
Complications						
Diabetes	36(11.25%)	10(8.98%)	0.5743	-	-	
Hypertension	226(70.63%)	45(24.86%)	<0.0001	158 (71.2%)	330 (65.7%)	0.15
Cardiovascular disease	108(33.43%)	5(2.82%)	<0.0001	3 (18.8%)	31 (13.0%)	0.515
Blood biochemistry						
CRP(mg/L)	6.72(2.75,22.64)	3.20(2.07,6.20)	<0.0001	-	-	-
Hb A1c%	5.45(4.90,6.13)	5.60(5.20,5.90)	0.475	7.05 (6.23,8.20)	7.80 (6.90,9.00)	<0.0001
Uric acid (umol/L)	432(361,520)	367(305,445)	<0.0001	445 (377,523)	454 (386,534)	0.304
LDL-C (mmol/L)	2.18(1.50,2.83)	2.92(1.95,4.00)	<0.0001	2.63 (1.97,3.32)	2.52 (2.11,2.97)	0.223

TH-PO997

Mendelian Randomization Reveals a Causal Relationship between the Effects of Gut Microbiota and Progression of CKD

Chiehlun Yang. *Xiamen Chang Gung Hospital, Xiamen, China.*

Background: To reveal the causal relationship between gut microbiota and the progression of Chronic Kidney Disease (CKD) using Mendelian Randomization (MR).

Methods: A two-sample MR Analysis combined with Genome-Wide Association Studies (GWAS) data was used to evaluate the potential impact of 195 bacterial groups on CKD progression. Inverse Variance Weighted (IVW) method was used as the main analysis tool. Robustness was verified by weighted median, MR-Egger regression, MR-PRESSO detection and Model-Based Estimation (MBE). The Bonferroni correction method was used to adjust the risk of false positives in multiple comparisons.

Results: MR Analysis showed that *Desulfovibrionales, Eubacterium eligens, Desulfovibrionaceae, Mucoraceae UCG-002, Proteobacteria, and Clostridium* increased significantly with CKD risk ($P<0.05$). Sensitivity analysis showed that the main MR Analysis results were robust.

Conclusions: This study provides evidence of a causal relationship between the gut microbiota and the progression of CKD, and in particular an increased abundance of *Desulfovibrionales* is associated with an increased risk of CKD. These findings reinforce the important role of gut microbes in the pathogenesis of CKD and provide directions for future research and potential clinical interventions.

TH-PO998

Identification of Modifiable Risk Factors for Incident CKD via an Exposome-Wide Association Study

Yang Gyun Kim,[1,2] Sanghyuk Jung,[2] Su Woong Jung,[1] Ju young Moon,[1] Sangho Lee,[1] Dokyoon Kim.[2,3] *[1]Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [3]Biomedical Informatics, University of Pennsylvania, Philadelphia, PA.*

Background: Chronic kidney disease (CKD) has no specific treatment, making the control of modifiable risk factors crucial in mitigating kidney disease and related complications. This study aimed to clarify the variable modifiable factors associated with incident CKD.

Methods: We analyzed 351,123 European participants from the UK Biobank who had not been diagnosed with CKD. An exposome-wide association study was conducted with 271 modifiable factors to find associations with incident CKD. Genetically high-risk patients were defined as those having a high polygenic risk score for CKD stage 3 or higher, based on a large-scale genome-wide association study from CKDGen Consortium.

Results: The mean age of subjects was 57.33±7.94 years. CKD occurred in 12,259 cases over a median follow-up period of 11.85 years. Of the 271 risk factors, 155 were significantly associated with incident CKD: 63 factors were protective, while 92 factors had detrimental effect on disease development (Figure 1). When dividing the factors into five main domains- lifestyle, environmental, psychological, socio-economic status, and physical components- 66.24%, 27.27%, 61.76%, 85.19%, and 72.41% significantly contributed to developing CKD in each domain, respectively. Higher physical activity, better pulmonary function, and more coffee intake were the strongest protective factors against the development of CKD, whereas frequent chest pain, physical restriction, and low satisfaction were the highest risk factors. This pattern was consistent across the different CKD genetic risk groups.

Conclusions: This study identified critical modifiable risk factors for incident CKD development. Even for individuals with a high genetic risk, managing these risk factors can effectively reduce the likelihood of developing CKD.

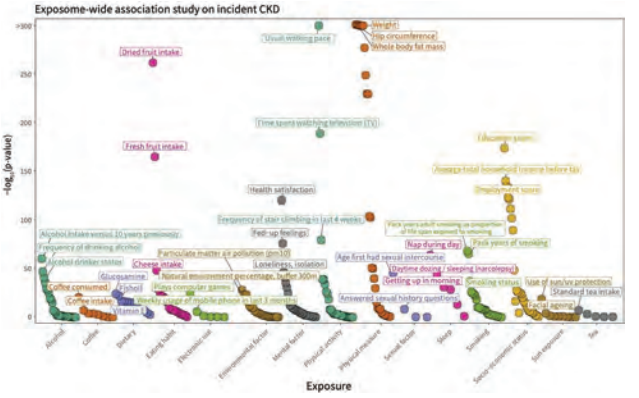


Figure 1

TH-PO999

Effects of Body Mass Index on Rapid Kidney Function Decline: A Two-Sample Mendelian Randomization Study

Haofei Hu,[1,2] Zhiming Ye.[1] *[1]Guangdong Provincial People's Hospital, Guangzhou, China; [2]Shenzhen Second People's Hospital, Shenzhen, China.*

Background: Observational studies have reported an association between body mass index (BMI) and a decline in renal function, but the causal relationship between BMI and renal function decline has not been established. The objective of the study was to use the two-sample Mendelian randomization (MR) approach to evaluate the causal impact of BMI on rapid renal function decline.

Methods: We obtained the instrumental variables for BMI from a meta-analysis of genome-wide association studies (GWAS) that included approximately 700,000 individuals of European descent. To obtain summary statistics data for rapid renal function decline, we used data from a previously published meta-analysis of GWAS that included over 270,000 individuals. Two criteria were used to determine the rapid renal function decline: a decline of 3 mL/min/1.73m^2/year or more in estimated glomerular filtration rate (eGFR) ("Rapid3"), and a drop of 25% or more in eGFR and an eGFR below 60 mL/min/1.73m^2 at follow-up among individuals with eGFR of 60 mL/min/1.73m^2 or more at baseline ("CKDi25). We employed several filtering steps to select robust genetic instruments associated with BMI. Our primary analysis utilized the inverse variance weighted (IVW) method, with additional MR methods including weighted median, MR-Egger, and MR Pleiotropy RESidual Sum and Outlier test.

Results: We utilized a set of 491 single nucleotide polymorphisms (SNPs) as instrumental variables in this MR study. Our findings showed that genetically predicted higher BMI was significantly associated with an elevated risk of rapid renal function decline, as determined by the IVW method for CKDi25 [OR = 1.33, 95% CI = 1.22-1.44, $P = 1.54 \times 10^{-11}$] and Rapid3 [OR = 1.15, 95% CI = 1.09-1.22, $P = 7.99 \times 10^{-7}$]. The results of both the MR Egger regression analysis and the weighted median method were consistent with the primary analysis. In addition, the effect estimate remained stable even after eliminating SNPs that were connected to confounding factors, and the "Leave-one-out" analysis validated the consistency of our findings. Notably, the absence of heterogeneity and directional pleiotropy was suggested by our results.

Conclusions: The results of the MR analysis suggest that there may be a causal relationship between BMI and a higher risk of renal function decline.

Funding: Other NIH Support - National Key Research and Development Project of China (2021YFC2501302)

TH-PO1000

CKD as a Mediator of the Associations between Adiposity and Cardiovascular Diseases

Killian Donovan, Rebecca J. Sardell, William G. Herrington, Natalie Staplin. Renal Studies Group. *University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom.*

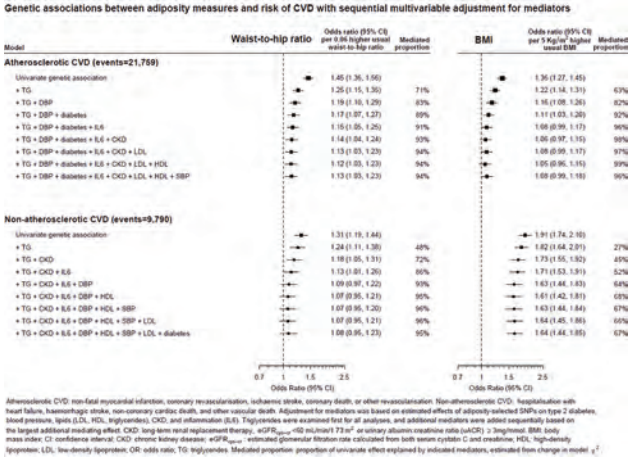
Background: Adiposity is associated with atherosclerotic and non-atherosclerotic cardiovascular diseases (CVDs). These associations are not fully explained by traditional cardiovascular risk factors. Genetic epidemiological methods can be used to estimate the mediating effects of risk factors including chronic kidney disease (CKD) on cardiovascular outcomes.

Methods: Data from 288,984 UK Biobank participants were used to estimate the relevance of genetically-predicted waist-to-hip ratio (WHR, central adiposity) and body-mass index (BMI, general adiposity) to risk of CVDs, both atherosclerotic (aCVD) and non-atherosclerotic (nCVD). Genetic analyses employed Mendelian Randomisation (MR) and data from 394 WHR and 773 BMI-associated loci. To explore how adiposity causes

CVDs, multivariable MR models were constructed adjusting for the genetic associations between these loci and mediators including blood pressure (BP), lipids, diabetes status (DM), inflammatory markers and CKD.

Results: 21,759 (7.5%) participants had aCVD and 9,790 (3.4%) participants had nCVD. Genotype-predicted WHR and BMI were both associated with increased risk of aCVD and nCVD (Fig 1). TGs, diastolic BP, and DM were the top mediators for aCVD explaining ~90% of both BMI and WHR associations (Fig 1). Adding CKD to this model did not significantly increase the explained effect. TGs, CKD and inflammation (IL-6) were the top mediators for nCVD, together explaining 86% of WHR associations and 52% of BMI associations (Fig 1).

Conclusions: MR suggests that any mediating effect of CKD on the effects of adiposity on risk of aCVD is small (particularly when compared to the mediating effects of TGs, BP and DM). Conversely, CKD is likely to be an important mediator of effects of central adiposity (WHR) on risk of nCVD. The effects of general adiposity (BMI) on nCVD appear to be only partly explained by CKD, inflammation, BP and lipids.



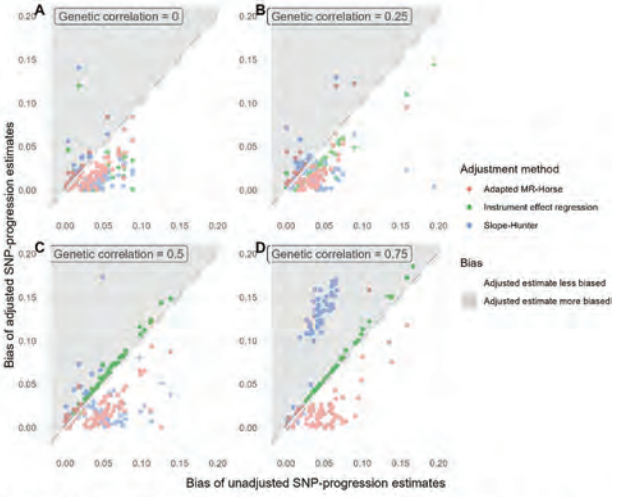


Figure 1: Bias of estimated SNP effects on CKD progression in simulated GWAS of CKD progression, with and without adjustment, in scenarios with increasing correlation between SNP effects on CKD incidence and CKD progression. With increasing genetic correlation, existing adjustment methods yield more biased results (gray shaded areas). MR-Horse adjusted estimates are consistently less biased than unadjusted estimates.

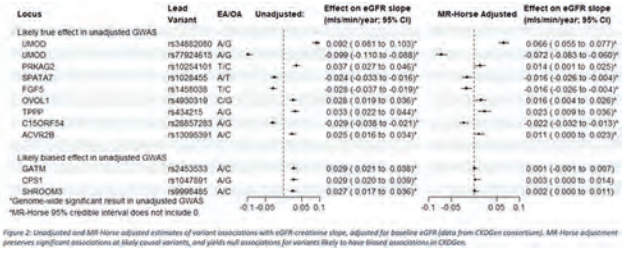


Figure 2: Unadjusted and MR-Horse adjusted estimates of variant associations with eGFR-creatinine slope, adjusted for baseline eGFR (data from CKDGen consortium). MR-Horse adjustment preserves significant associations at likely causal variants, and yields null associations for variants likely to have biased associations in CKDGen.

TH-PO1001

A Bayesian Method to Reduce Selection Bias in Genetic Association Studies of CKD Progression

Killian Donovan. Renal Studies Group. *University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom.*

Background: The rate of progression of CKD has high inter-patient variability. Genetic differences are responsible for some of this variation, but GWAS results have been inconsistent. This may be due to selection bias arising when GWAS participants are selected based on kidney function. Such bias is apparent in the results of existing studies. Current methods to address this bias are predicted to fail in the setting of CKD due to high genetic correlation between incident CKD and rate of CKD progression.

Methods: We adapted a Mendelian Randomization method (MR-Horse) for unbiased estimation of SNP associations with CKD progression in the setting of correlated SNP effects on disease incidence and progression (the hypothesized genetic architecture of CKD). We applied this method and others to simulated GWAS of traits with different genetic architectures. We then applied these methods to GWAS results from the CKDGen Consortium, and evaluated their effects on SNP-progression estimates at loci with known significant effects on progression and at loci with likely biased associations.

Results: Our method reduced the bias of simulated SNP-progression effect estimates, including in situations with high genetic correlation where other methods failed (Fig 1). Power and type 1 error rate were comparable to other methods. In CKDGen data (Fig 2), our method attenuated associations at loci with likely biased associations with CKD progression, whilst preserving associations at loci with likely real direct effects on progression.

Conclusions: GWAS of CKD progression are affected by selection bias, and this can be reduced by an adaptation of the MR-Horse method.

Funding: Private Foundation Support

TH-PO1002

Differential DNA Methylation in CKD with Particular Reference to APOL1

Suri Guga,[1] Dalvir Kular,[1] Samantha J. Hayward,[4] Moin A. Saleem,[4] Kate Bramham,[1,3] Ania B. Koziell.[1,2] *[1]King's College London, London, United Kingdom; [2]Evelina London Children's Hospital, London, United Kingdom; [3]King's College Hospital NHS Foundation Trust, London, United Kingdom; [4]University of Bristol, Bristol, United Kingdom.*

Background: Individuals of African descent are generally at increased risk of CKD and specific variants of the *APOL1* gene play a significant role. However, not all high risk cases progress to CKD suggesting other factors such as co-variants and environmental/ epigenetic modifiers may contribute. The study examined the role of whole genome DNA methylation (DNAm) on CKD, including its impact on both baseline glomerular filtration rate (eGFR) and rate of change in eGFR. Additionally, the study explored whether differntial DNAm might also explain the differing phenotypes associated with high-risk *APOL1* genotypes with no protective allele detected.

Methods: Genome-wide DNAm data from the Genetic Epidemiology Network of Arteriopathy (GENOA) was analysed. Phenotypic evaluation including CKD status together with *APOL1* risk variant genotype identified 1,394 cases suitable for study. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2 and urine albumin-creatinine ratio (uACR) > 30 ug/mg. Bioinformatics tools were used for DNA methylation (DNAm) analysis controlling for age, cell type, BMI, gender and smoking. EWAS and linear regression analysis was performed on CKD and non-CKD cases. The relationship between *APOL1* DNAm on baseline eGFR was analysed used linear regression and a mixed-effects model used to analyse the association between DNAm with change in eGFR.

Results: Analysis DNAm in CKD vs non-CKD showed significant differences at 3 CpG islands ($p < 0.05$). Whole genome DNAm analysis of high risk *APOL1* CKD *vs.* high risk non-CKD cases identified a unique CpG signal as significantly differentially methylated ($p < 0.05$).. Mixed-effect model analysis detected an association between DNAm and longitudinal eGFR change ($p < 0.05$). Lastly, linear regression analyses, adjusted for age and the interval between examinations, identified differential DNAm at another unique CpG. No difference in DNAm was detected in high risk genotype *vs.* low risk APOL1 genotype cases with or without CKD.

Conclusions: The findings suggest that differential DNAm may contribute to CKD. Additionally, APOL1 DNAm appears associated with CKD development. It might also in part explain why some high risk APOL1 genotype cases develop CKD and others do not. Epigenetic markers could aid in understanding the pathogenesis of CKD and suggest novel avenues for targeted interventions.

TH-PO1003

SLC6A19 (BOAT1) Allelic Series: Loss of Function Is Associated with Improved Kidney Function

Sahar V. Mozaffari, Yannan Xi, Laura Sanman, Julie Ullman, Susan Limb, Maarten Hoek, Karol Estrada, Robert R. Graham. *Maze Therapeutics Inc, South San Francisco, CA.*

Background: Chronic kidney disease (CKD) remains a significant health burden despite recent advances in care, including development of inhibitors of the sodium-dependent glucose transporter SLC5A2 (SGLT2). A burden test incorporating predicted loss of function (pLOF) and rare missense variants (MAF <1%) identified SLC6A19 as among the strongest effects in the genome for improved kidney function (UK biobank: serum creatinine, beta = -0.13, p = 4.58e-35). The gene SLC6A19 encodes the protein BoAT1, a sodium-dependent neutral amino acid transporter involved in the uptake of free amino acids from the diet and minimizing loss of amino acids via the urin

Methods: Here, we built an allelic series of variants that impact SLC6A19 function or expression levels composed of aggregated pLOF and rare predicted damaging missense variants, a known hypomorphic missense variant (D173N, rs121434346), and an eQTL variant (rs11133665). We then tested these variants for an association to biomarkers of kidney function and disease risk across multiple biobanks.

Results: A meta-analysis for serum creatinine, a marker of kidney function, was performed across multiple large-scale datasets (UK Biobank, deCODE, CKDGen: > 600,000 individuals). The hypomorphic variant D173N (rs121434346) is associated with decreased serum creatinine (beta: -0.15, p: 7.2e-24) in deCODE and UK Biobank meta-analysis. Aggregated UK Biobank pLOF variants (beta: -0.15, p: 1.02e-04) and missense variants (MAF<0.001) (beta: -0.08, p-value: 3e-13) are associated with decreased serum creatinine. Consistent results for the SLC6A19 allelic series were obtained for estimated glomerular filtration rate (eGFR) and serum cystatin C, suggesting loss of function of SLC6A19 is associated with improved markers of kidney function.

Conclusions: An allelic series of functional SLC6A19 variants is robustly associated with serum and urine markers related to kidney function, with loss of function of SLC6A19 conferring reno-protection, and suggests inhibition of SLC6A19 is a potential therapeutic approach for CKD.

Funding: Commercial Support - Maze Therapuetics

TH-PO1004

Genome-Wide Association Study on Creatinine Clearance in the Lifelines Cohort Study

Anna D. Argoty-Pantoja, Peter J. Van der Most, Amarens van der Vaart, Harold Snieder, Martin H. De Borst. *University of Groningen, University Medical Center Groningen, Groningen, Netherlands.*

Background: Genome-wide association studies (GWAS) for kidney function have mainly focused on creatinine-based glomerular filtration rate (eGFR). However, variation in muscle mass reduces the accuracy of the eGFR. Creatinine clearance is able to assess kidney function independently of muscle mass. Our aim was to identify genes influencing creatinine clearance as an alternative phenotype of kidney function. In addition, we aimed to analyse overlap of creatinine clearance loci with eGFR loci.

Methods: We performed a GWAS on creatinine clearance and eGFR (creatinine-based CKD-EPI 2009) in 58,976 individuals of European descent from the Lifelines Cohort Study. Genetic correlation between phenotypes and heritability was estimated using linkage disequilibrium score regression. In addition, we performed expression Quantitative Trait Loci (eQTL) analyses.

Results: We identified 16 independent loci for creatinine clearance with 21 genome-wide significant lead single nucleotide polymorphism (SNPs) ($P < 5x10^{-8}$). In addition, we found 65 loci for eGFR with 95 lead SNPs. Two new SNPs, not previously related to eGFR in CKDGen were discovered (rs146465192: EAF = 0.01, $P = 3.38x10^{-09}$; rs117014836: EAF = 0.02, $P = 5.42x10^{-09}$). Both SNPs were also associated with eGFR (rs146465192: $P = 1.34x10^{-08}$; rs117014836: $P = 3.64x10^{-07}$) in our analysis. The variant rs117014836 was associated with expression levels of *AGPAT4* gene in blood (eQTL $P = 6.54x10^{-6}$). The common SNP heritability of creatinine clearance was 12%. We observed a high genetic correlation between creatinine clearance and eGFR (rg = 0.77).

Conclusions: We found two new SNPs, one of which influenced blood expression of *AGPAT4* gene, which plays a crucial role in modulating the diversity of fatty acid chains. This supports the role of lysophospholipid metabolism in impaired kidney function.

TH-PO1005

A Comprehensive Report on Patients with CKD in the CDC NHANES Cohort, 2001-2020

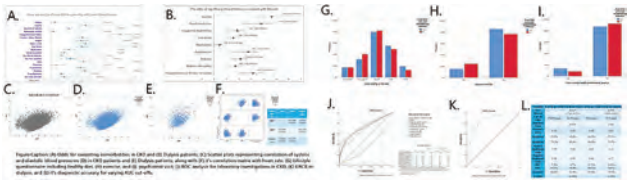
Muhammad Sohaib Asghar.[1,2] Chad K. Brands (AdventHealth Sebring Internal Medicine Residency Program). *[1]AdventHealth Sebring, Sebring, FL; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: This study is a comprehensive review of the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination (NHANES) databases. The primary objectives were to ascertain patterns of demographic and clinical data among chronic kidney disease (CKD) and dialysis patients.

Methods: This study examines participants from the CDC NHANES database to identify the population diagnosed with chronic kidney disease or dialysis patients in the past 12 months. The total cohort of 51,743 patients were included in each group, i.e., CKD group included 1509 patients (out of which 173 patients have received dialysis in the past 12 months), while non-CKD group included 50,234 patients.d. Exclusion criteria included age ≥85 years of age (n=624), pregnancy (n=1375), and history of malignancy (n=5575).

Results: The mean age of study participants (n=51,743) was 48.50 ±17.43 years. Age is significantly higher in CKD group but there was no difference in dialysis versus non-dialysis patients (P=0.833). There is no gender predisposition in CKD patients however, males were more likely to undergo dialysis with 13.3% vs 9.8% in females (P=0.032). Among racial differences, Non-hispanic whites are predominantly affected by CKD (37.0%) followed by non-hispanic blacks (29.3%) but non-hispanic blacks are mostly undergoing dialysis (48.6% vs 17.3%). BMI (kg/m^2) was significantly higher in CKD group (P<0.001), but lower in dialysis group (P=0.039). Among urinary complaints, history of kidney stones is prevalent in CKD patients (7.7% vs 2.6%, P<0.001). Frequent coexisting comorbidities were congestive heart failure (OR: 9.8), diabetes (OR: 5.4), Coronary artery disease (OR: 5.0), and hypertension (OR: 4.7). UACR (>30 mg/g) is able to categorize CKD patients (**AUC**: 0.73), at a sensitivity of *44.9%* and a specificity of *88.8%*.

Conclusions: Certain clinical factors were identified as highly associated with CKD, as disseminated by the NHANES database findings.



TH-PO1006

Patient-Centered Outcomes of Advanced CKD Treated with Conservative Management vs. Dialysis: A Substudy of the Prospective NIH OPTIMAL Cohort

Amy S. You,[1] Yoko Narasaki,[1] Alejandra Novoa Vargas,[1] Lisa Le,[1] Danh V. Nguyen,[2] Kamyar Kalantar-Zadeh,[3] Connie Rhee.[1] *[1]University of California Los Angeles, Los Angeles, CA; [2]University of California Irvine, Irvine, CA; [3]Harbor-UCLA Medical Center, Torrance, CA.*

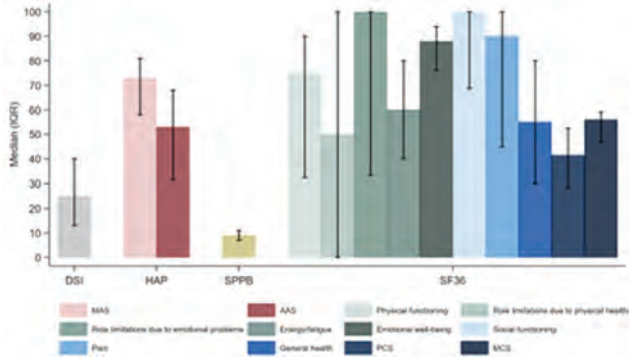
Background: While dialysis has been the treatment paradigm among advanced CKD patients ineligible for/unlikely to receive transplantation, it may not improve HRQOL among certain subgroups (elderly, multi-morbid), which has motivated interest in conservative management (CM) as an alternative patient-centered treatment option.

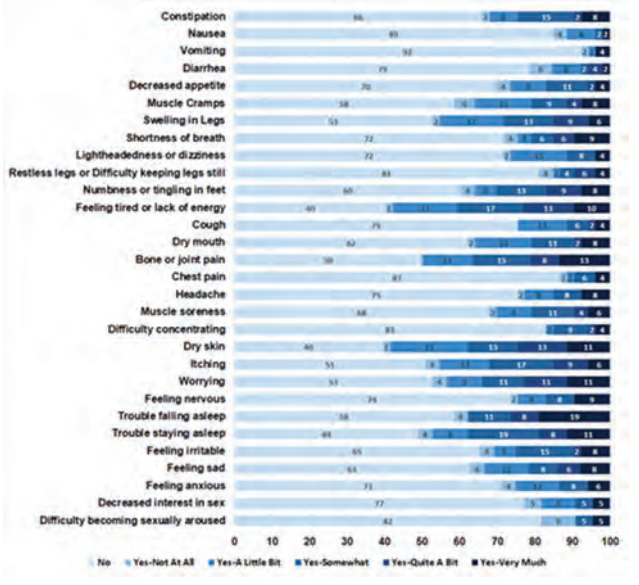
Methods: In a subcohort of 53 participants from the ongoing multicenter prospective NIH OPTIMAL study comparing CM vs. dialysis preparation on the longitudinal trajectory of HRQOL, physical performance/activity, symptom burden, and nutrition in stage 4-5 CKD patients, we examined baseline patient-centered outcomes data collected using validated instruments.

Results: Short Form 36 data showed low (worse) PCS (median [IQR] 41 [28, 52]) and MCS (median [IQR] 56 [47, 59]) scores. Short Physical Performance Battery data showed relatively low physical performance (median [IQR] 9 [7, 11]). Human Activity Profile data showed low self-reported activity (50% with low Adjusted Activity Score <53). Dialysis Symptom Index data showed high symptom burden (median [IQR] 25 [15, 30]). The most prevalent symptoms included feeling tired/lack of energy (60%), dry skin (60%), and trouble staying asleep (51%).

Conclusions: Baseline data from the NIH OPTIMAL cohort showed low HRQOL, low physical performance/activity, and high symptom burden in advanced CKD patients undergoing CM vs. dialysis preparation.

Funding: NIDDK Support





TH-PO1007

Assessing the Quality of Care for People with CKD: A Systematic Review and Meta-Analysis

Daniel B. Ketema,[1,2] Hannah Wallace,[1,3] Brendon L. Neuen,[1] Sradha S. Kotwal,[1] Paul E. Ronksley,[4] Sunil Badve,[1] Vlado Perkovic,[2] Martin P. Gallagher,[1,2] Rohina Joshi,[5,1] Min Jun.[1,2] *[1]The George Institute for Global Health, Sydney, NSW, Australia; [2]University of New South Wales Medicine & Health, Sydney, NSW, Australia; [3]Western Health, Footscray, VIC, Australia; [4]University of Calgary Department of Community Health Sciences, Calgary, AB, Canada; [5]University of New South Wales Medicine & Health, Sydney, NSW, Australia.*

Background: Effective strategies for managing CKD are available, but the extent to which implementation of these strategies is consistent with guideline recommendations is uncertain. We aimed to synthesize available data on the quality of CKD care globally.

Methods: EMBASE, PubMed, and CINAHL were systematically searched (inception–2023) for observational studies reporting on the quality of CKD care across domains related to patient monitoring (eGFR, albuminuria), appropriate medication use (ACEIs, ARBs, statins, NSAIDs), and treatment targets (BP, HbA1c) according to management recommendations in international CKD guidelines. Pooled estimates (95% CI) of the percentage of patients who met the quality indicators for CKD care were obtained using random effects meta-analysis.

Results: 58 studies across 22 countries, including a total of 2,969,039 patients with CKD, were included. The reporting of and adherence to quality indicators for CKD care varied substantially across the included studies (Figure 1). Summary estimates of the percentage of CKD patients who met key indicators showed that (1) eGFR was monitored in 81% (75–87%) of patients, albuminuria in 47% (40–54%) and BP in 90% (84–95%); (2) ACEIs/ARBs were prescribed in 56% (51–62%), statins in 56% (48–64%), and NSAIDs withheld in 81% (77–86%) and (3) a BP target of ≤140/90 mmHg was achieved in 56% (48–64%) patients.

Conclusions: Current evidence suggests substantial variation in the reporting and quality of CKD care. Concordance with guideline recommendations varied across quality indicators and patient groups, with opportunities for considerable improvement, particularly albuminuria testing. Effective quality improvement strategies to address gaps in CKD care, along with systematic approaches for monitoring care quality, are needed.

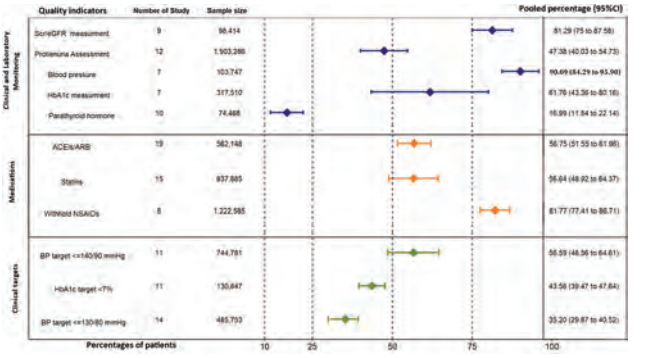


Figure 1: Forest plot summarising the percentage of patients with CKD who met the quality indicators for CKD care

TH-PO1008

Health Insurance Status since the Affordable Care Act among US Adults with and without CKD

Jenna Kiryakos,[1] Tiffany C. Veinot,[2] Yun Han,[1] William H. Herman,[1] Hal Morgenstern,[4] Yoshihisa Miyamoto,[3] Rajiv Saran,[1] Jennifer L. Bragg-Gresham.[1] *[1]University of Michigan Department of Internal Medicine, Ann Arbor, MI; [2]University of Michigan School of Information, Ann Arbor, MI; [3]Centers for Disease Control and Prevention, Atlanta, GA; [4]University of Michigan School of Public Health, Ann Arbor, MI.*

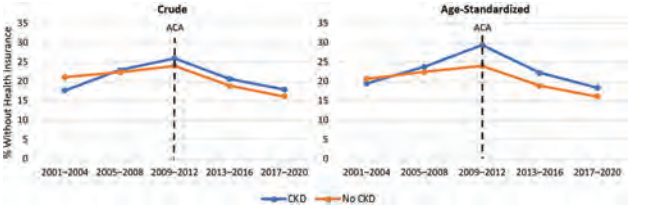
Background: Adults without health insurance are more likely to delay care due to costs, including preventive care and services for acute and chronic illnesses. In 2010, the Affordable Care Act (ACA) was implemented to reduce the number of uninsured individuals under age 65 through health insurance exchanges, the dependent coverage provision, Medicaid expansion, and other policy changes. As health care coverage is important for optimal management of chronic kidney disease (CKD), we sought to examine the proportion of adults who lack health care coverage by CKD status.

Methods: We included 38,119 participants from the National Health and Nutrition Examination Survey (NHANES, 2001–March 2020) aged 18–64 years. CKD was defined by the presence of albuminuria (urine albumin to creatinine ratio – UACR ≥30 mg/g) or estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2. Lack of health care coverage was defined by a response of "No" to the NHANES question "Are you covered by health insurance or some other kind of health care plan?". The proportion of adults without health insurance by CKD status was age-standardized to the 2010 U.S. Census population for adults ages 18–24, 25–44, and 45–64.

Results: The sample included 3,967 participants with CKD and 34,152 participants without CKD. The mean age of the entire sample was 40.7 and 50% were male. For both those with and without CKD, prevalence of lack of health insurance increased from 2001-2004 to 2009-2012 (p=0.01), then declined (p<0.001). The decline corresponded with the implementation of the ACA (Figure). Age-standardized trends were similar to crude rates.

Conclusions: Since 2009-2012, coinciding with the ACA implementation, there has been a decrease in the proportion of US adults without health insurance. This trend was present in adults with or without CKD; however, the percentage of persons lacking health insurance tended to be higher among those with CKD.

Funding: Other U.S. Government Support



TH-PO1009

Health-Related Social Needs and CKD in Medicare Advantage Beneficiaries

Lindsay Bengtson,[2] Anny C. Wong,[2] Alexandra Rothenburger,[2] Zackery R. White,[1] Amanda Terry,[1] Halima Ahmadi-Montecalvo,[1] Bonnie M. Donato.[2]
[1]Unite Us, New York, NY; [2]Boehringer Ingelheim International GmbH, Ingelheim, Germany.

Background: The impact of health-related social needs (HRSNs) on patient outcomes has been established; however, there is limited research regarding HRSNs and chronic kidney disease (CKD). This study addresses this gap by identifying HRSN predictors of CKD diagnosis at stage 3 vs. stages 1 or 2 and examining the association between HRSNs and concordance with guideline-recommended CKD management in the year following diagnosis.

Methods: A retrospective database analysis was conducted of Medicare Advantage beneficiaries newly diagnosed with CKD stages 1-3 from January 2020 to October 2022. Patients' HRSNs were identified using Unite Us' Social Needs System (SNS), a proprietary index leveraging public and consumer data to identify individual-level social risk. Logistic regression assessed the effect of HRSNs on the likelihood of diagnosis at stage 3 vs. stages 1 or 2. Logistic and linear regression examined the effect of HRSNs on healthcare utilization (HCU) and CKD management in the year following diagnosis, adjusted for CKD stage. Analyses were adjusted for age, sex, race/ethnicity, urbanity, comorbidities, and baseline HCU.

Results: A total of 6,053 individuals with CKD were included (median age 76 years; 97% English-speaking; 54% female; 84% White, non-Hispanic). CKD stage at diagnosis varied: stage 1 (2%), stage 2 (18%), and stage 3 (80%). Identified HRSNs included a lack of internet access (15%), food insecurity (10%), and financial insecurity (8%). While individuals with HRSNs tended to be diagnosed at stage 3 vs stage 1 or 2, differences were not statistically significant. Women (OR: 1.34; CI: 1.17-1.54, p<0.01) and older individuals (OR: 1.04; CI: 1.02-1.65, p<0.01) were more likely to be diagnosed at stage 3 than stages 1 or 2, while those with proteinuria (OR: 0.49; CI: 0.35-0.68, p<0.01) or living in rural counties (OR: 0.72; CI: 0.61-0.84, p<0.01) were less likely. In the year following diagnosis, patients with financial insecurity, versus those without, had an increased number of ER visits (β: 0.15; CI: 0.01-0.29, p=0.01) and were less likely to receive diabetes education (OR: 0.40; CI: 0.16-0.97, p=0.04).

Conclusions: These findings emphasize that specific HRSNs impact CKD management and present opportunities for targeted interventions to address HRSN barriers to care for individuals with CKD.

Funding: Commercial Support - Boehringer Ingelheim

TH-PO1010

Evaluating the Clinical, Socioeconomic, and Environmental Impact of Guideline-Directed Therapy in the United States: An IMPACT CKD Analysis

Navdeep Tangri,[1] Cole Wyman,[2] Naveen Rao,[2] Jieling Chen,[3] Stacey Priest,[4] Stephen Brown,[4] Aleix Cases,[5] Steven J. Chadban.[6] *[1]University of Manitoba, Winnipeg, MB, Canada; [2]BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom; [3]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD; [4]EVERSANA, Burlington, ON, Canada; [5]Hospital Clinic de Barcelona, Barcelona, Spain; [6]Royal Prince Alfred Hospital, Camperdown, NSW, Australia.*

Background: Chronic kidney disease (CKD) is underdiagnosed and undertreated in the United States (US) despite evidence that therapies can delay disease progression and reduce clinical events. This study aims to illustrate the impact of improved adherence to therapies recommended for patients with CKD (i.e., guideline-directed medical therapy [GDMT]) on clinical, socioeconomic, and environmental outcomes to inform policy decisions.

Methods: The US population was simulated for 25-years (baseline: 2022; simulated years: 2023-2047) using the IMPACT CKD model. Two scenarios were compared: 75% adherence to GDMT vs. current practice as observed. GDMT included glucose and lipid lowering, antihypertensive, and lifestyle interventions. It was assumed that patients diagnosed with CKD could be treated with multiple therapies per guideline eligibility and that there would be no changes to guidelines or CKD detection rate over the time horizon. Treatment effects on estimated glomerular filtration rate (eGFR) decline, cardiovascular events, and acute kidney injury (AKI) events were assumed to be multiplicative.

Results: Improved adherence to GDMT was associated with a 32% decrease in dialysis due to delayed disease progression. Reductions were projected in myocardial infarction, stroke, hospitalized heart failure, AKI, and death by 21%, 17%, 24%, 9%, and 5%, respectively. Renal replacement therapy (RRT) and total CKD costs were projected to decrease by 25% and 5%, respectively. Freshwater consumption, fossil fuel depletion, and carbon emissions due to RRT were also projected to decrease by 28%. Furthermore, reductions in disease progression and death also contributed to improvements in projected net workdays, gross domestic product, full-time equivalents, and tax revenue among employed patients and caregivers. The benefits of improved adherence to GDMT were seen after six years. Similar trends were observed with a 10-year time horizon but with smaller magnitude.

Conclusions: This study predicted significant clinical, socioeconomic, and environmental benefits with improved adherence to GDMT. These findings underscore the importance of policy action to improve adherence and actualize the potential of effective therapies to mitigate CKD burden.

Funding: Commercial Support - AstraZeneca

TH-PO1011

Comorbidity Prevalence among Patients with CKD: Insights from the National Health and Nutrition Examination Survey (NHANES)

Doris H. Fuertinger,[1] David J. Joerg,[1] Felix J. Meigel,[1] Peter Kotanko.[2,3]
[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Renal Research Institute, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.

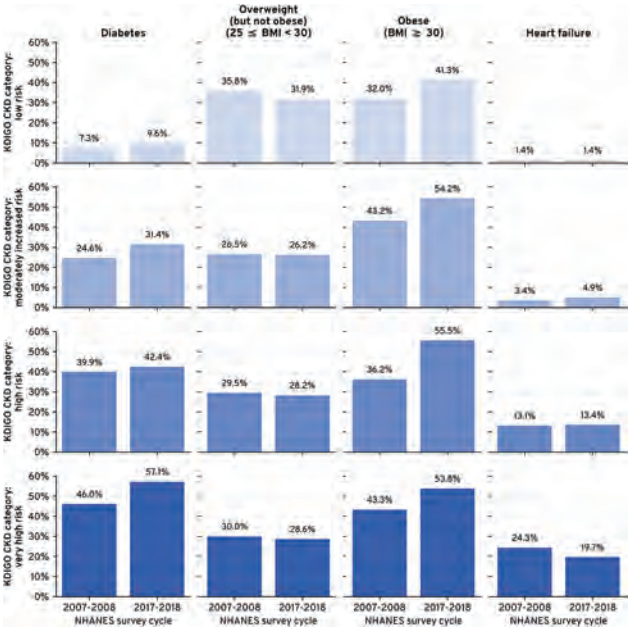
Background: In the past decade, obesity and various other conditions that can cause chronic kidney disease (CKD) were on the rise. We used data from the National Health and Nutrition Examination Survey (NHANES) cycles 2007-2008 and 2017-2018 to quantitate the changes in diabetes mellitus (DM), overweight, obesity and heart failure (HF) in different CKD risk categories.

Methods: We stratify the NHANES population into KDIGO risk categories based on albuminuria and creatinine measurements (both serum and urine). Additionally, we assess the prevalence of obesity, HF, and DM by stratifying the NHANES population by body mass index (overweight: BMI 25-30, obesity: BMI >30 kg/m^2), self-reported diagnosis of DM as well as fasting glucose or HbA1c levels and HF. We analyze patients for whom complete information on CKD and DM, obesity, and HF was reported.

Results: The percentage of CKD patients that are overweight has slightly declined for all CKD risk categories during the considered decade 2007/2008-2017/2018 (very high risk: 30% to 29%). This is contrasted by a pronounced increase in obesity over all CKD risk categories (very high risk: 43% to 54%), see Fig. 1. The proportion of CKD patients having DM markedly increased in the very high risk group (46% to 57%), but showed only a slight increase in the high risk category (40% to 42%). HF among CKD patients showed a stagnant or declining trend in the high risk categories (13% to 13% and 24% to 20%).

Conclusions: NHANES data suggest a pronounced upward trend in the proportion of CKD patients suffering from DM and obesity and a stagnant trend in CKD patients suffering from HF and overweight. The analysis is limited by the fact that CKD measurements and self-reported diagnoses are not available for all NHANES participants.

Funding: Commercial Support - Fresenius Medical Care



TH-PO1012

Evaluation of the SGLT2 Inhibitor Dapagliflozin as an Alternative Treatment of Kidney Impairment in a 5/6 Nephrectomy Model Associated with Obesity

Desiree R. Bernardo,[1] Daniele Canale,[1] Mariana M. Nascimento,[1] Maria H. Shimizu,[1] Antonio C. Seguro,[1] Ana Carolina de Braganca,[3] Rildo A. Volpini.[3,2]
[1]Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil; [2]Universidade de Sao Paulo Faculdade de Medicina de Ribeirao Preto, Ribeirao Preto, Brazil; [3]Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.

Background: Chronic kidney disease is a global health burden, characterized by functional and structural renal changes as decreased GFR, inflammation and fibrosis. Obesity is a chronic disease directly related to diabetes mellitus and hypertension, the main disorders responsible for the progression to end-stage kidney disease. Lately, the alternative use of SGLT2 inhibitors has been offering new perspectives for the treatment of kidney diseases, regardless their glucosuric effects. We evaluated the effects of dapagliflozin (DAPA) as an alternative treatment on renal impairment in an obesity-associated 5/6 nephrectomy (Nx) model.

Methods: We followed male wistar rats during a 100-day protocol. On day 40, all the rats were submitted to Nx surgery and followed up until the end of the protocol. The animals were divided into four groups according to the diet: standard (N); hyperlipidic (N+H); standard+DAPA (N+D); and hyperlipidic+DAPA (N+H+D). DAPA (50 mg/kg diet) was offered from the 1st day after Nx surgery. We evaluated anthropometric data, biochemical parameters, GFR, renal protein expression of SGLT1 and GLUT2, as well as renal tissue levels of SGLT2, TGF-β, collagen 3 (COL-3) and MCP-1 by ELISA.

Results: N+H animals presented a lower GFR, increased anthropometrical and metabolic parameters, and enhanced renal tissue levels of TGF-β, COL-3 and MCP-1. N+H+D showed improved renal function, metabolic parameters, and a restoration of plasma glucose levels. Most importantly, treatment with dapagliflozin prevented the renal expression of TGF-β, COL-3 and MCP-1 in this obesity-associated Nx model. The results are described in Figure 1 (Table 1).

Conclusions: The use of dapagliflozin prevented the renal fibrosis formation and inflamation observed in our 5/6 nephrectomy model associated with obesity. Financial support: FAPESP 2022/07409-0, 2023/06387-6.

Funding: Government Support - Non-U.S.

TABLE 1

	N	N+D	N+H	N+H+D
C_{in} (mL/min/100g BW)	0.53±0.02	0.64±0.04[c]	0.36±0.04[bd]	0.61±0.04[g]
Body Mass Index (g/cm²)	0.59±0.08	0.55±0.01	0.65±0.02 [ad]	0.64±0.01[bd]
AC (cm)	17.2±0.1	16.5±0.1	19.9±0.5 [ad]	18.7±0.3[adgh]
Triglycerides (mg/dL)	131±27	129±33	139±14[ad]	109±17
Cholesterol (mg/dL)	68±5	65±5	94±7[cf]	85±7
Glucose (mg/dL)	166±8	160±15	191±6	161±12
Glycosuria (mg/dL)	1.5±0.4	212.3±4.9[a]	1.5±0.3[a]	214.2±13.4[ag]
GLUT2 (%)	101.0±4.7	125.9±8.0	203.1±27.5	341.1±49.1
SGLT1 (%)	99.7±3.6	117.2±7.2	85.7±7.7[f]	99.8±5.8[f]
SGLT2 (ng/µg)	0.073±0.009	0.076±0.006	0.085±0.010	0.084±0.006
MCP-1 (ng/µg)	0.063±0.006	0.061±0.002[a]	0.092±0.006[abc]	0.070±0.003[f]
TGF-β (ng/µg)	0.65±0.05	0.55±0.05	0.76±0.07[f]	0.57±0.03[c]
COL-3 (ng/µg)	82.54±5.95	59.13±6.79	94.33±9.55[a]	69.42±5.63[c]

Data are expressed as mean±SEM. C_{in}: inulin clearance; BW: body weight; AC: abdominal circumference. [a]p<0.001, [b]p<0.01, [c]p<0.05 vs N; [d]p<0.001, [e]p<0.01, [f]p<0.05 vs N+D; [g]p<0.001, [h]p<0.01, [i]p<0.05 vs N+H.

TH-PO1013

Racial Disparities in SGLT2 Inhibitor (SGLT2i) and Glucagon-Like Peptide 1 Receptor Agonist (GLP-1 RA) Use in the US Military Health System (MHS)

James D. Oliver,[1] Robert Nee,[1,2] Hava Marneweck,[4] Amanda Banaag,[4] Fang Xu,[3] Alain K. Koyama,[3] Yoshihisa Miyamoto,[3] Meda E. Pavkov,[3] Tracey L. Koehlmoos.[1] *[1]Uniformed Services University of the Health Sciences, Bethesda, MD; [2]Walter Reed National Military Medical Center, Bethesda, MD; [3]Centers for Disease Control and Prevention, Atlanta, GA; [4]Henry M Jackson Foundation for the Advancement of Military Medicine Inc, Bethesda, MD.*

Background: Recent studies have indicated racial disparities in the use of SGLT2i and GLP-1 RA, novel diabetes mellitus (DM) therapies that have been shown to reduce chronic kidney disease (CKD) progression and cardiovascular morbidity and mortality. We evaluated whether such disparities exist in the MHS, a universal payer system with fewer barriers to health care access.

Methods: We extracted data for 2,989,368 non-pregnant adults in 2019. Diagnoses of type 2 DM and CKD were based on ICD-10 codes, labs, and medications. Adjusted odds ratios (aOR) for medication use were calculated by multivariable logistic regression.

Results: The DM population was 180,625 (6.0%), of whom 68,747 (38.1%) had CKD (median age 60 years, 47.2% female; 32.5% White, 17.7% Black, 5.1% Asian/Pacific Islander, 0.5% Native American/Alaska Native [NA/AN], 3.1% Other, 11.4% Unknown, and 29.7% Missing). Use of an SGLT2i or GLP-1 RA was 13.1% and 12.5%, respectively (Table) and was higher in White adults than in other races except NA/AN. After adjustment for age, sex, socioeconomic status, and comorbidities (CKD, hypertension, heart disease, heart failure, obesity), aOR of using either medication was significantly lower in all racial groups except NA/AN compared to White adults.

Conclusions: In the MHS, a universal payer system with minimal barriers to access, use of an SGLT2i or GLP-1 RA was significantly lower in most non-White adults. Further investigation may be required to determine the factors behind the prescription differences and possible mitigation strategies. *The views expressed in this abstract are those of the authors and do not reflect the official position of the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense, the Department of Health and Human Services, or the U.S. government.*

Funding: Other U.S. Government Support

	SGLT2i		GLP-1 RA	
	Use (%)	aOR (95% CI)	Use (%)	aOR (95% CI)
Overall	13.1	n/a	12.5	n/a
White	16.4	Reference	13.8	Reference
Asian/Pacific Islander	11.9	0.77[a] (0.72, 0.82)	8.8	0.62[a] (0.58, 0.67)
Black	12.3	0.70[a] (0.67, 0.73)	11.5	0.76[a] (0.73, 0.79)
Native American/Alaska Native	17.0	1.11 (0.93, 1.31)	13.8	0.99 (0.82, 1.19)
Other	14.9	0.90[a] [b] (0.84, 0.98)	11.7	0.82[a] (0.76, 0.90
Unknown	9.4	0.75[a] (0.71, 0.79)	10.6	0.78[a] (0.74, 0.83)

*p < .0001 **p < .01 vs. reference. CI, confidence interval

TH-PO1014

SGLT2 Inhibitors and Mortality Risk in Individuals with Advanced CKD

Rochell Issa,[1] Mirela A. Dobre,[2] Mohamed Makhlouf,[2] Lavinia A. Negrea,[2] Andrei Brateanu.[1] *[1]Cleveland Clinic, Cleveland, OH; [2]University Hospitals, Cleveland, OH.*

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown to reduce all-cause mortality in type 2 diabetes. It is unknown whether this beneficial effect is maintained in advanced CKD stages 4-5D, irrespective of diabetes status.

Methods: In this retrospective cohort study of electronic health records from the TriNetX Analytics Network, we aimed to assess the associations of SGLT2i with all-cause mortality compared to usual care without SGLT2i medications in patients >65 years with CKD 4-5D. The hazard ratios (HRs) and 95% confidence intervals (CIs) of all cause mortality were calculated for the 6-month, 1 and 5 year follow-up by comparing propensity score-matched patient groups.

Results: The study population included 40,000 patients with CKD stages 4-5D who were prescribed SGLT2i or usual care without SGLT2i. Compared with non-SGLT2i users, patients with CKD 4 or 5 pre-dialysis (mean age 74.8± 6.2 years, 48% female), or CKD 5D (mean age 73.3±5.8 years, 42% female) taking SGLT2i had lower risk for all-cause mortality, consistent across CKD stages and time points (Table).

Conclusions: The use of SGLT2i was associated with a significant lower all-cause mortality risk in patients with advanced CKD stages 4, 5, or 5D.

Funding: Other NIH Support - NHLBI

	Mortality at 6 months n (%)	Hazard Ratio (95% CI)	Mortality at 1 year n (%)	Hazard Ratio (95% CI)	Mortality at 5 years n (%)	Hazard Ratio (95% CI)
CKD 4 and 5						
SGLT2i + n=12,112	785 (6.4)	0.67 (0.61-0.73)	1,111 (9.2)	0.68 (0.63-0.73)	1,580 (13.0)	0.67 (0.62-0.71)
SGLT2i – n=12,112	1,113 (9.2)		1,532 (12.6)		2,168 (17.9)	
CKD - 5D						
SGLT2i + n=7,888	545 (6.9)	0.59 (0.53-0.66)	730 (9.3)	0.59 (0.54-0.65)	1,158 (14.7)	0.61 (0.59-0.66)
SGLT2i – n=7,888	862 (10.9)		1,127 (14.3)		1,667 (21.1)	

Mortality risk at 6 months, 1 year, and 5 years by CKD stage in SGLT2i users (+) vs non-users (-)

TH-PO1015

Cost-Effectiveness of Empagliflozin in CKD in a Real-World US Population

Satabdi Chatterjee,[1] Neda Al Rawashdh,[2] Pablo Anaya,[2] Anastasia Uster,[4] Anna R. Aguirre Mazo,[4] Mafalda Ramos,[3] Laetitia Gerlier,[5] Mark Lamotte.[3]
[1]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; [2]IQVIA Inc, Falls Church, VA; [3]Th(is)2modeling, Asse, Belgium; [4]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [5]IQVIA Belgium, Zaventem, Belgium.

Background: Studies have established the cost-effectiveness of empagliflozin (EMPA) on top of standard of care (SoC) in patients similar to the EMPA-KIDNEY population (wide range of patients with CKD, with or without diabetes) and have shown benefits of timely EMPA initiation from a US payer perspective. In the current study the cost-effectiveness of EMPA and the consequences of delaying EMPA, in a real-world population of patients with CKD was assessed.

Methods: Using a patient-level state transition model that defined health states by KDIGO categories, simulated patients were tracked over a lifetime horizon. 2020 US Renal Data System data were used to populate demographics, CKD stages (40.3% G1, 19.8% G2, 28.6% G3a, 7.9% G3b, 2.4% G4, 1.0% G5), and comorbidities (e.g., 51.7% diabetes, 61.2% cardiovascular disease). The model used published cohort studies to predict disease progression, complications, and death; EMPA-KIDNEY trial data for treatment effects; and literature for drug costs, complication, and adverse events management costs and utilities. Life years (LY), quality-adjusted LY (QALY), and incremental cost-effectiveness ratios (ICERs) were estimated at a willingness to pay (WTP) threshold of $150,000/QALY. Scenario analyses compared delaying initiation of EMPA by 1, 3, and 5 years vs. SoC alone with the base case (no EMPA delay).

Results: In base case analyses, use of EMPA+SoC delayed disease progression to ESKD or death by 1.21 years, and resulted in 0.50 LYs and 0.47 QALYs gained vs. SoC only. The increased effectiveness came with higher costs for both payers ($20,393 for commercial payers and $42,152 for Medicare), however, ICERs ($43,898/QALY for commercial and $90,737/QALY for Medicare) were cost-effective at the WTP threshold. Delaying EMPA initiation reduced the clinical benefits and increased the incidence of progression to ESKD and the need to initiate kidney replacement therapy; a longer delay in initiation further reduced benefits. Additionally, delaying EMPA therapy did not result in significant savings to either commercial or Medicare payers.

Conclusions: Findings confirm the cost-effectiveness of EMPA in a real-world population of individuals with CKD for US commercial and Medicare payers, and provide evidence of benefits with timely initiation of EMPA.

Funding: Commercial Support - Boehringer Ingelheim Pharmaceuticals

TH-PO1016

Association between Environmental Factors and Kidney Diseases: A Nationwide Population-Based Study

Semin Cho,[1] Jeongmin Cho,[1] Soojin Lee,[3] Sehoon Park,[2] Kyungdo Han,[5] Dong Ki Kim,[2] Yaerim Kim.[4] *[1]Chung-Ang University Gwangmyeong Hospital, Gyeonggi-do, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [3]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [4]Keimyung University Daegu Dongsan Hospital, Daegu, Republic of Korea; [5]Soongsil University, Dongjak-gu, Seoul, Republic of Korea.*

Background: It is well known that various environmental factors including air pollution increase the risk of kidney disease. We aimed to elucidate the risk of chronic kidney disease according to the indoor air quality and urinary volatile organic compounds (VOCs) using data from the Korea National Health and Nutrition Examination Survey (KNHANES).

Methods: The ratio of indoor and ambient PM2.5 and urine creatinine-corrected VOCs concentration were extracted from the KNHANES VIII (2019-2021) dataset. CKD was defined as estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2, and the association between environmental factors and CKD was analyzed through multiple linear regression model.

Results: A total of 1,319 participants was analyzed in this study. The highest quartile of indoor and ambient PM2.5 ratio was associated with increased risk of CKD (odds ratio(OR), 4.28; 95% confidence interval(95% CI), 1.43-12.75) after adjustment of age, sex, comorbidities, and window opening status. The urinary concentration of several VOCs (3,4MHA [3,4-Methylhexanoic Acid], PGA [Phenylglyoxylic Acid], MA [Maleic Acid], DHBMA [Dihydroxybenzene Mercapturic Acid]) have been found to have statistically significant association with reduced kidney function. ([3,4MHA] OR, 5.86; 95% CI, 1.30-26.45; [PGA] OR, 14.30; 95% CI, 1.53-133.78; [MA] OR, 5.38; 95% CI, 1.03-28.12; [DHBMA] OR, 4.14; 95% CI, 0.77-22.21).

Conclusions: In this cross-sectional study, the indoor air quality of PM2.5 relative to the concentration of PM2.5 in the ambient air was associated with the deterioration of kidney function and urinary VOCs concentration showed the association with declined kidney function which could be used to be a predictive marker of CKD.

Table 2. The risk of the deterioration of eGFR according to indoor and ambient PM2.5 concentration

		N (%)	Model 1	Model 2	Model 3	Model 4
Indoor PM2.5	Tertile 1	0.75 (0.35)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.40 (0.57)	1.89 (0.55, 6.52)	1.82 (0.51, 6.54)	1.93 (0.52, 7.23)	1.52 (0.41, 5.60)
	Tertile 3	3.01 (0.97)	4.13 (1.40, 12.19)	4.62 (1.50, 14.23)	5.28 (1.71, 16.31)	4.28 (1.43, 12.75)
	P for trend		0.010	0.009	0.005	0.009
Indoor PM2.5	Tertile 1	1.92 (0.73)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	0.71 (0.39)	0.37 (0.09, 1.44)	0.37 (0.09, 1.50)	0.38 (0.08, 1.76)	0.34 (0.08, 1.59)
	Tertile 3	2.65 (0.87)	1.39 (0.52, 3.74)	1.09 (0.39, 3.02)	1.04 (0.38, 2.88)	0.97 (0.37, 2.50)
	P for trend		0.489	0.773	0.839	0.925
Ambient PM2.5	Tertile 1	1.71 (0.77)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.68 (0.64)	0.98 (0.30, 3.23)	0.64 (0.18, 2.29)	0.50 (0.14, 1.85)	0.72 (0.20, 2.54)
	Tertile 3	1.82 (0.72)	1.067 (0.33, 3.46)	0.85 (0.26, 2.85)	0.72 (0.23, 2.26)	0.88 (0.30, 2.61)
	P for trend		0.914	0.842	0.678	0.873

Abbreviations: eGFR, estimated glomerular filtration rate; PM2.5, particulate matter 2.5
Model 1 was non-adjusted.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for variables in model 2 and BMI, smoking history, alcohol consumption, hypertension and diabetes mellitus
Model 4 was adjusted for variables in model 3 and window opening status

Table 2. The risk of declined kidney function according to urinary VOCs concentration

		N (%)	Model 1	Model 2	Model 3	Model 4	Model 5
BMA	Tertile 1	1.06 (0.32)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.91 (0.72)	1.81 (0.67, 4.90)	1.06 (0.35, 3.17)	1.14 (0.39, 3.33)	1.25 (0.43, 3.64)	1.27 (0.43, 3.76)
	Tertile 3	1.26 (0.65)	1.18 (0.28, 4.99)	0.44 (0.11, 1.76)	0.475 (0.12, 1.95)	0.44 (0.10, 1.94)	0.45 (0.10, 2.01)
	P for trend		0.737	0.173	0.235	0.206	0.272
2MHA	Tertile 1	1.52 (0.89)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.07 (0.38)	0.70 (0.17, 2.93)	0.55 (0.14, 2.17)	0.62 (0.16, 2.48)	0.59 (0.13, 2.28)	0.59 (0.13, 2.30)
	Tertile 3	3.6 (0.61)	1.05 (0.39, 2.86)	1.04 (0.38, 2.81)	1.06 (0.27, 4.08)	1.33 (0.34, 5.12)	1.37 (0.36, 5.31)
	P for trend		0.892	0.898	0.952	0.709	0.709
3,4MHA	Tertile 1	0.41 (0.21)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.97 (0.78)	4.88 (1.38, 17.29)	4.70 (1.35, 16.39)	4.27 (1.27, 14.42)	3.57 (1.05, 12.11)	3.68 (1.08, 12.59)
	Tertile 3	1.67 (0.62)	4.11 (1.13, 14.88)	4.82 (1.31, 17.70)	5.49 (1.34, 26.33)	5.48 (1.20, 25.00)	5.86 (1.30, 26.45)
	P for trend		0.062	0.031	0.034	0.032	0.023
PGA	Tertile 1	0.08 (0.08)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.46 (0.62)	17.83 (1.94, 155.10)	14.10 (1.58, 125.79)	13.88 (1.36, 140.58)	12.56 (1.35, 116.55)	13.00 (1.39, 121.71)
	Tertile 3	3.05 (0.97)	38.16 (4.77, 305.54)	15.757 (1.91, 130.16)	14.13 (1.58, 126.71)	16.38 (1.65, 162.92)	14.38 (1.51, 133.78)
	P for trend		<0.001	0.006	0.011	0.0188	0.014
MA	Tertile 1	0.23 (0.2)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	2.31 (1.07)	10.07 (1.44, 70.50)	6.70 (0.92, 48.73)	8.52 (1.31, 55.49)	8.29 (1.44, 47.94)	8.43 (1.33, 54.08)
	Tertile 3	1.87 (0.62)	8.09 (1.32, 49.62)	4.19 (0.63, 28.92)	4.43 (0.77, 25.55)	5.42 (1.09, 26.85)	5.38 (1.01, 28.12)
	P for trend		0.007	0.204	0.172	0.037	0.040
SPMA	Tertile 1	0.51 (0.3)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	0.84 (0.43)	1.43 (0.31, 7.59)	0.58 (0.11, 3.11)	0.89 (0.09, 2.65)	0.47 (0.08, 2.50)	0.22 (0.04, 4.29)
	Tertile 3	3.2 (1.03)	6.39 (1.80, 22.67)	1.65 (0.37, 7.38)	1.40 (0.25, 7.85)	1.16 (0.27, 4.90)	1.164 (0.30, 33.22)
	P for trend		0.001	0.271	0.395	0.423	0.252
HPMA	Tertile 1	0.78 (0.34)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.29 (0.66)	3.66 (0.44, 6.32)	0.78 (0.10, 3.21)	0.78 (0.20, 3.12)	0.74 (0.19, 2.91)	0.69 (0.17, 2.73)
	Tertile 3	2.2 (0.81)	2.85 (0.93, 8.70)	1.13 (0.33, 3.90)	1.01 (0.32, 3.12)	0.90 (0.29, 2.81)	0.86 (0.26, 2.81)
	P for trend		0.074	0.733	0.907	0.851	0.917
BPMA	Tertile 1	1.7 (0.83)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.33 (0.51)	0.78 (0.23, 2.67)	0.46 (0.12, 1.71)	0.59 (0.18, 1.93)	0.56 (0.16, 1.93)	0.45 (0.13, 1.61)
	Tertile 3	1.11 (0.61)	0.65 (0.16, 2.71)	0.24 (0.06, 0.95)	0.24 (0.06, 0.92)	0.20 (0.06, 0.70)	0.20 (0.06, 0.70)
	P for trend		0.549	0.048	0.052	0.010	0.013
DHBMA	Tertile 1	0.24 (0.17)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Tertile 2	1.17 (0.57)	4.83 (0.83, 28.28)	2.38 (0.36, 15.73)	2.33 (0.37, 14.63)	1.79 (0.28, 11.62)	1.67 (0.28, 9.49)
	Tertile 3	3.11 (1.18)	13.89 (2.73, 63.77)	5.19 (0.94, 28.53)	5.32 (1.02, 27.85)	4.44 (0.83, 23.26)	4.14 (0.77, 22.21)
	P for trend		0.001	0.043	0.0363	0.043	0.054

Abbreviations: VOCs, volatile organic compounds; BMA, Benzene Metabolites Acetate; 2MHA, 2-Methylhippuric Acid; 3,4MHA, 3,4-Methylhexanoic Acid; PGA, Phenylglyoxylic Acid; MA, Maleic Acid; SPMA, S-Phenylmercapturic Acid; HPMA, 3-Hydroxypropylmercapturic Acid; BPMA, Benzylmercapturic Acid; DHBMA, Dihydroxybenzene Mercapturic Acid
Model 1 was non-adjusted.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for variables in model 2 and BMI, smoking history, alcohol consumption, hypertension and diabetes mellitus
Model 4 was adjusted for variables in model 3 and window opening status
Model 4 was adjusted for variables in model 4 and indoor air quality

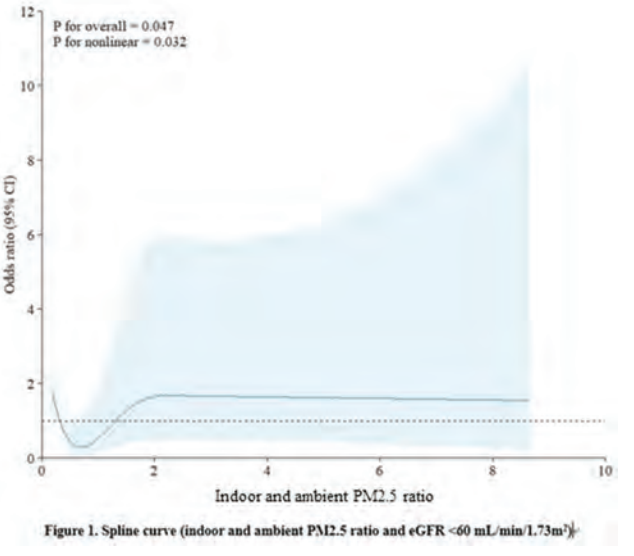


Figure 1. Spline curve (indoor and ambient PM2.5 ratio and eGFR <60 mL/min/1.73m^2)

TH-PO1017

International Patterns of Low eGFR in Population-Based Surveys of Working-Age Adults: Disadvantaged Populations eGFR Epidemiology (DEGREE) Study

Ben Caplin,[1] Charlotte E. Rutter,[2] Neil Pearce.[2] DEGREE Study Group.
[1]University College London Research Department of Renal Medicine, London, United Kingdom; [2]London School of Hygiene & Tropical Medicine, London, United Kingdom.

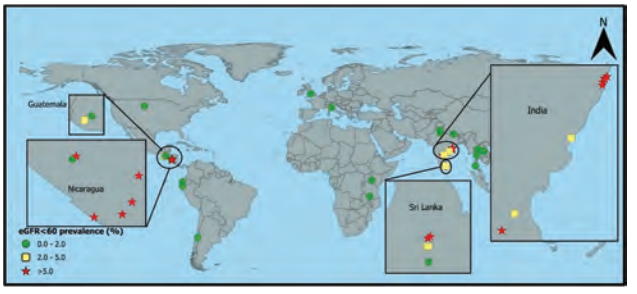
Background: The Disadvantaged Populations eGFR Epidemiology study was designed to gain insight into the burden of chronic kidney disease (CKD) of undetermined cause (CKDu) by using standard protocols to estimate the general-population prevalence of low estimated glomerular filtration rate (eGFR).

Methods: We estimated the age-standardised prevalence of eGFR<60mL/min/1.73m^2 not due to common, known causes of CKD (eGFR<60$_{[absent\ HT,\ DM,\ high\ ACR]}$) by excluding participants with self-reported or measured hypertension or diabetes, or an ACR>300mg/g or equivalent in population-representative surveys of working-age adults, stratified by sex and rural-urban classification. Included studies either were designed to estimate CKDu burden or were re-analyses of regional or national surveys and were conducted either in areas where CKDu was reported to be endemic or in areas with proposed CKDu risk factors, alongside two high-income reference datasets.

Results: There were 61306 participants from 43 areas across 14 countries. A high prevalence (>5%) of eGFR<60$_{[absent HT, DM, high ACR]}$ was generally only observed in rural men. Rates were highest in Andhra Pradesh, India, and Northwest Nicaragua. Of the areas considered, prevalence in rural men was low outside of Central America and South Asia; including areas of Kenya, Italy, Malawi, Peru, Chile, Ecuador, and Thailand (as well as England and the USA).

Conclusions: Although there are limitations in terms of comparability of study populations, study timing, lack of individual-level exposures, and absent data in many regions, this work is the first attempt to estimate the burden of CKDu around the world. Clusters of disease may exist elsewhere, but to date there is evidence consistent with a high general-population burden of CKDu in Central America and South Asia.

Funding: Government Support - Non-U.S.



eGFR<60: Age-standardised rural male prevalence of eGFR<60$_{[absent HT, DM, high ACR]}$ in mL/min/1.73m^2. NB: USA includes both rural and urban. The authors take a neutral position with respect to territorial clams on the map.

TH-PO1018

Time-Updated eGFR Variability Is Associated with Mortality, Cardiovascular Disease, and ESKD in Patients with CKD: The CRIC Study

Hiroki Nishiwaki,[1,3] Celestin Missikpode,[1] Ana C. Ricardo,[1] Wei Yang,[4] Amanda H. Anderson,[2] James P. Lash,[1] Tanika Kelly.[1] CRIC Study Investigators. *[1]University of Illinois Chicago, Chicago, IL; [2]Tulane University, New Orleans, LA; [3]Showa University Fujigaoka Hospital, Yokohama, Japan; [4]University of Pennsylvania, Philadelphia, PA.*

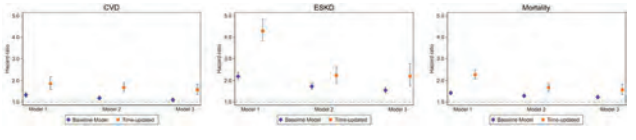
Background: Previous reports have identified increased estimated glomerular filtration rate (eGFR) variability, measured during a single ascertainment window, as a risk factor for CVD and all-cause mortality. We hypothesized that repeated measures of eGFR variability over multiple ascertainment windows would display stronger associations with common CKD sequelae when compared to analysis methods investigating only a single measure.

Methods: To test our hypothesis, we leveraged longitudinal data from 4,224 participants of the Chronic Renal Insufficiency Cohort (CRIC). eGFR variability was estimated as the coefficient of variation of eGFR measured at 3 consecutive annual follow-up visits, starting at baseline and estimated repeatedly in one-year sliding windows. Associations of eGFR variability with all-cause mortality, CVD, and CKD were tested using two statistical models: Cox proportional hazards models that included baseline covariables and eGFR variability measured during the first ascertainment window (baseline model) and marginal structural models that included repeated measures of eGFR variability and covariables (time-updated model).

Results: The 4,224 CKD patients contributed a total of 39,024 person-years of follow-up time, with a median participant follow-up time of 5.9, 6.1, and 8.3 years for CVD, ESKD and all-cause mortality, respectively. In the baseline and time-updated multivariable adjusted analyses, each standard deviation increase in eGFR variability was associated with respective, 1.04-fold (95%CI:0.96-1.13) and 1.78-fold (95%CI:1.50-2.11) increased risks of CVD, 1.08-fold (95%CI:0.99-1.18) and 2.20-fold (95%CI:1.76-2.75) increased risks of ESKD, and 1.15-fold (95%CI:1.08-1.23) and 1.56-fold (95%CI:1.35-1.81) increased risks of all-cause mortality.

Conclusions: Time-updated analyses revealed markedly larger effect sizes compared to the baseline model, highlighting the potentially important role of this measure in common CKD sequelae.

Funding: NIDDK Support



Forrest plots for the association between continuous eGFR variabilities and CVD, ESKD and mortality with baseline and time-updated models.

TH-PO1019

GFR Estimation Errors and Association with Outcomes in CKD

Maria Clarissa Tio,[1] Xiaoqian Zhu,[1] Yoshitsugu Obi,[1] Timothy E. Yen,[1] Michael E. Hall,[1] Neville R. Dossabhoy,[1] Tariq Shafi.[2] *[1]The University of Mississippi Medical Center, Jackson, MS; [2]Houston Methodist, Houston, TX.*

Background: Estimated GFR (eGFR) can often be significantly different from measured (mGFR). The clinical implications of large errors in eGFR on risks of outcomes in CKD are unknown.

Methods: Using the Chronic Renal Insufficiency Cohort, a multi-center, prospective cohort of persons with CKD, we analyzed 1,423 participants with mGFR (urinary clearance of iothalamate). We calculated eGFR using the CKD-EPI 2021 creatinine equation. We defined large errors as eGFR that was 15% higher or lower than mGFR. We evaluated the association of large errors, compared to no errors, with outcomes using Fine-Gray subdistribution hazard models for kidney failure with death as a competing risk and Cox proportional hazards models for death, and first occurrence of hyperkalemia, hyperphosphatemia, and anemia. All models were adjusted for age, sex, and race/ethnicity. Data were provided by NIDDK CR, a program of the NIDDK.

Results: Mean age was 56 years, 44% were women, and 37% were Black participants. 776 (55%) participants had large errors: 428 (30%) had mGFR > eGFR and 242 (17%) had mGFR < eGFR. Those with mGFR < eGFR tended to be of White or Hispanic race/ethnicity, have diabetes, and have a higher systolic blood pressure and body mass index. mGFR > eGFR (underestimation) was associated with lower risk of death (HR=0.73; 95%CI: 0.65-0.82), hyperphosphatemia (HR=0.68; 95%CI: 0.49-0.94), and anemia (HR=0.84; 95%CI: 0.73-0.97), with trends toward lower risk of kidney failure and hyperkalemia (Table 1). Conversely, mGFR < eGFR (overestimation) was associated with increased risk of kidney failure (HR=1.22; 95%CI: 1.11-1.35) and anemia (HR=1.39; 95%CI: 1.16-1.66), with trends toward increased risk of death, hyperkalemia, and hyperphosphatemia (Table). Every 10 mL/min/1.73 m^2 increase in bias (eGFR-mGFR) was significantly associated with an increased 22% risk of death, 19% risk of kidney failure, 20% risk of hyperkalemia, 18% risk of hyperphosphatemia, and 18% risk of anemia (Table).

Conclusions: Among persons with CKD who have large differences between mGFR and eGFR, risks of adverse outcomes track closer to mGFR than eGFR.

Funding: Other NIH Support - U54GM11542

Table 1

Exposure		All-Cause Death	Kidney Failure	Hyperkalemia	Hyperphosphatemia	Anemia
Large Error	No large error	ref	ref	ref	ref	ref
	mGFR >eGFR	0.73 (0.65, 0.82)*	0.88 (0.74, 1.04)	0.89 (0.69, 1.13)	0.68 (0.49, 0.94)**	0.84 (0.73, 0.97)**
	mGFR < eGFR	1.37 (0.99, 1.88)	1.22 (1.11, 1.35)*	1.25 (0.99, 1.58)	1.08 (0.87, 1.34)	1.39 (1.16, 1.66)*
Bias (eGFR-mGFR)		1.22 (1.12, 1.34)*	1.19 (1.09, 1.31)*	1.20 (1.11, 1.29)*	1.18 (1.09, 1.28)*	1.18 (1.12, 1.24)*

mGFR > eGFR is defined as mGFR > 1.15*eGFR.
mGFR < eGFR is defined as mGFR < 0.85*eGFR.
eGFR-mGFR is the absolute difference between a participant's eGFR and mGFR divided by 10. Sample interpretation: each 10 unit increase in the difference between eGFR and mGFR is associated with a 22% increased risk of death.
*p<0.001
**p<0.05

TH-PO1020

Outcomes and Risk Factors of Widened Difference in Estimated Glomerular Filtration Rate by Creatinine or Cystatin C: Adjust Model Development with More than 300,000 UK Biobank Participants

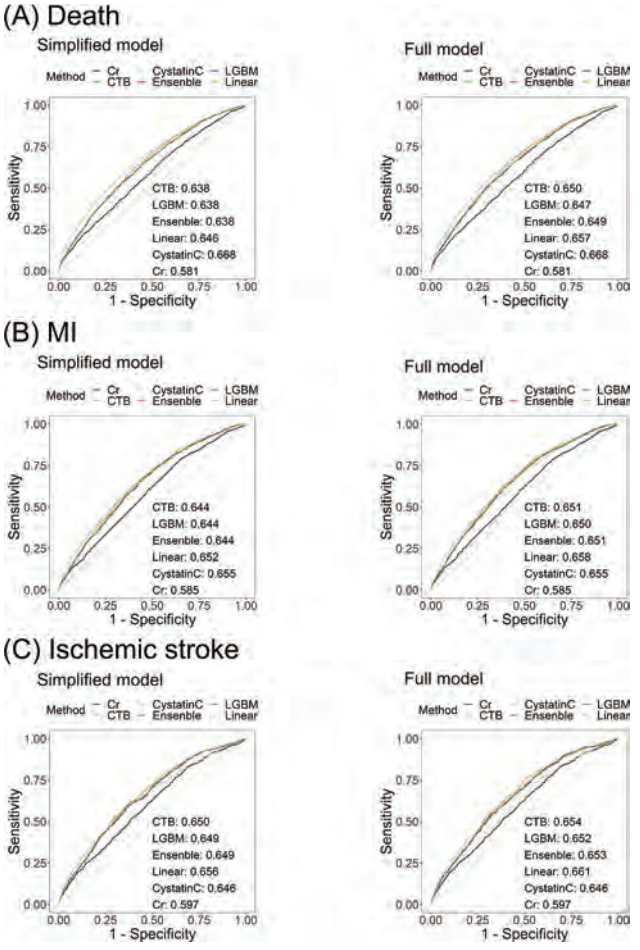
Min Woo Kang, Yong Chul Kim, Kook-Hwan Oh, Dong Ki Kim, Sehoon Park. *Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: Recent studies have highlighted the significance of discrepancies between cystatin C-based(eGFRcys) and creatinine-based(eGFRcr) CKD-EPI eGFR. This study explores the implications of differences between eGFRcys and eGFRcr(eGFRdiff) on clinical outcomes and develops an adjusted model using eGFRcr and variables.

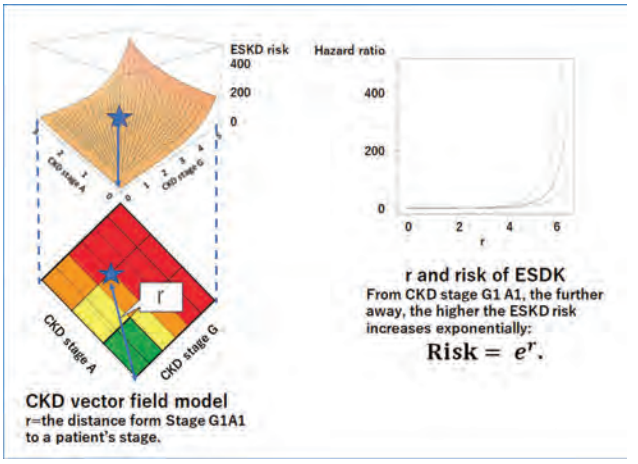
Methods: Using data from the UK Biobank cohort of 343,854 participants, we stratified them into three groups based on eGFRdiff: lower(eGFRcys-eGFRcr<-15), middle(-15≤eGFRcys-eGFRcr≤15), and upper(eGFRcys-eGFRcr>15). We analyzed the risks of death, MI, and ischemic stroke in the eGFRdiff<-15 and eGFRdiff>15 groups using Cox regression models. Logistic regression identified variables associated with eGFRdiff. And we developed and validated a regression model using eGFRcr and associated variables to approximate eGFRcys.

Results: Individuals with eGFRdiff<-15 had increased risks of death (HR:1.37[1.30-1.44]), MI (HR:1.23[1.15-1.33]), and ischemic stroke (HR:1.19[1.08-1.31]). Variables associated with eGFRdiff<-15 included high waist/hip circumference, high body weight, low fat-free mass, high total food intake, low protein intake, diabetes, and larger kidney volumes. A regression model was developed using eGFRcr, sex, age, height, weight, and BMI. In the validation set, this model achieved an adjusted R^2 of 0.47, improved from the initial R^2 of 0.32 between eGFRcys and eGFRcr. The adjusted model improved clinical outcome prediction.

Conclusions: This study confirmed that eGFRdiff<-15 is associated with increased risks of clinical outcomes and identified factors associated with eGFRdiff. We developed an adjusted model, demonstrating superior clinical outcome association.



ROC and AUROC of adjust models.



TH-PO1021

Vector Field Model of CKD Stage and Its Directional Derivative Mathematically Enable Accurate Kidney Prognosis Prediction

Eiichiro Kanda,[1] Bogdan I. Epureanu,[2] Taiji Adachi,[3] Tamaki Sasaki,[1] Naoki Kashihara.[1] *[1]Kawasaki Ika Daigaku, Kurashiki, Japan; [2]University of Michigan, Ann Arbor, MI; [3]Kyoto Daigaku, Kyoto, Japan.*

Background: Chronic kidney disease (CKD) is the cause of end-stage kidney disease (ESKD), cardiovascular disease, and death, and is categorized into 18 stages on the basis of the estimated glomerular filtration rate (eGFR) and proteinuria. It is difficult to accurately predict CKD progression, because CKD stage cannot be mathematically analyzed in terms of scale and cut-off values. In this study, we determined whether CKD stage transformed into a vector field accurately predicts ESKD risk (CKD vector field model).

Methods: The distance from stage G1 A1 to a patient's current stage in terms of on eGFR and proteinuria was defined, r. The model was constructed to reflect ESKD risk on the basis of systematic review of large cohort studies: ESKD risk=exp(r). Then, the model was validated using data from a cohort study of CKD patients in Japan followed up for three years (n=1,564). Moreover, the directional derivative of the model was developed as an index of CKD progression velocity.

Results: Cox proportional hazards models showed the exponential association between r and ESKD risk (p<0.0001). The CKD potential model more accurately predicted ESKD with the areas under the receiver operating characteristic curves adjusted for baseline characteristics 0.81 (95% CI 0.76, 0.87) than CKD stage 0.59 (95% CI 0.54, 0.63) (p<0.0001). Moreover, the directional derivative of the model better predicted the ESKD risk 0.77 (95% CI 0.71, 0.83) than eGFR slope 0.53 (95% CI 0.47, 0.60) (p<0.0001).

Conclusions: Those results indicated that the vector field model mathematically unifies CKD stage and eGFR slope and enables the accurate estimation of CKD progression.

TH-PO1022

Impact of the CKD-EPI 2021 Equation on the Classification of CKD in Older Australian Adults

Elisa K. Bongetti,[1,2] Rory Wolfe,[3] James B. Wetmore,[4] Anne M. Murray,[5] Robyn L. Woods,[3] Michelle A. Fravel,[6] Mark Nelson,[7] Nigel Stocks,[8] Suzanne G. Orchard,[3] Kevan Polkinghorne.[2,1] *[1]Monash University Department of Medicine, Clayton, VIC, Australia; [2]Department of Nephrology, Monash Health, Melbourne, VIC, Australia; [3]Monash University, School of Public Health and Preventative Medicine, Melbourne, VIC, Australia; [4]Division of Nephrology, Hennepin Healthcare, Minneapolis, MN; [5]Berman Center for Outcomes and Clinical Research and Department of Medicine, Hennepin Healthcare Research Institute, and Department of Medicine, Geriatrics Division, Hennepin Healthcare, Minneapolis, MN; [6]Department of Pharmacy Practice and Science, College of Pharmacy; The University of Iowa, Minneapolis, MN; [7]University of Tasmania Menzies Institute for Medical Research, Hobart, TAS, Australia; [8]Adelaide Medical School, Discipline of General Practice, Adelaide, SA, Australia.*

Background: A recalibrated version of CKD-EPI$_{2009}$, without a race coefficient, was released in 2021 (CKD-EPI$_{2021}$). This updated equation, implemented in the US, can result in the reclassification of chronic kidney disease (CKD) stage in a significant proportion of individuals. The aim of this study was to investigate the clinical impact of transitioning from the 2009 CKD-EPI (CKD-EPI$_{2009}$) to the 2021 CKD-EPI (CKD-EPI$_{2021}$) estimated glomerular filtration rate (eGFR) equation in generally healthy older Australians.

Methods: This was a prospective cohort study using data from 16,244 Australian community-dwelling adults aged ≥70 years, in the ASPirin in Reducing events in the Elderly (ASPREE) study cohort. Baseline characteristics and long-term health outcomes were compared in participants who were reclassified to a different chronic kidney disease (CKD) stage with CKD-EPI$_{2021}$ versus those with unchanged classification.

Results: With CKD-EPI$_{2021}$, baseline eGFR increased by a median of 3.8 mL/min/1.73m^2 (interquartile range [IQR] 3.3, 4.4) resulting in the reclassification of 3,106 (20%) participants to a less advanced CKD stage and the reduction in the prevalence of CKD from 17% to 12%. Over a median follow-up period of 6.5 years (IQR 5.4, 7.9), there was no difference in disability-free survival (HR: 0.94, 95%CI:0.84-1.05), mortality (HR: 0.90, 95%CI:0.78-1.03), major cardiac events (HR: 0.94, 95%CI:0.79-1.13), or hospitalisations for heart failure (HR: 1.00, 95%CI:0.67-1.49) in reclassified, versus non-reclassified, participants.

Conclusions: Implementing CKD-EPI$_{2021}$ would raise eGFR by a median of nearly 4 ml/min/1.73m^2, substantially reducing the proportion of older Australian adults classified as having CKD with no difference in long-term health outcomes among reclassified people. Transitioning to using the CKD-EPI$_{2021}$ may result in a significant reduction in nephrology referrals in generally healthy, older adults.

Funding: Other NIH Support - NIA, NCI, NEI, Government Support - Non-U.S.

TH-PO1023

Associations of Epigenetic Age Acceleration and Kidney Function in the Bogalusa Heart Study

Brenna J. Kirkpatrick,[1] Tanika Kelly,[1] Changwei Li,[2] James P. Lash.[1]
[1]University of Illinois Chicago College of Medicine, Chicago, IL; [2]Tulane University, New Orleans, LA.

Background: Chronic kidney disease (CKD) is an age-related condition associated with significant morbidity and mortality that affects approximately 14% of the US population. As the average age in the US increases, it is critical to identify factors that may predispose individuals to heightened risk of kidney dysfunction. Epigenetic age acceleration (EAA), defined as the difference between chronological age and a composite DNA methylation-derived age, has emerged as a robust predictor of numerous health conditions. Multiple EAA measures have been validated, each with its own physiologic implications. We hypothesized that accelerated epigenetic aging is associated with baseline kidney function and its prospective decline in the Bogalusa Heart Study (BHS).

Methods: We examined associations between four EAA measures (intrinsic EAA [IEAA], extrinsic EAA [EEAA], PhenoAA, and GrimAA) and kidney function in BHS, a longitudinal, prospective study aimed at characterizing cardiometabolic risk factors across the lifespan. Kidney function was assessed as estimated glomerular filtration rate (eGFR), calculated using the race-free CKD-EPI creatinine-based equation. Multiple logistic regression was used to examine cross-sectional associations of EAA with the discrete reduced kidney function outcome (eGFR < 60 mL/min/1.73 m^2) at the most recent study visit (N=1,249). For participants with repeated kidney function measurements, multiple logistic mixed effects models were used to assess associations of baseline EAA and progression to the reduced kidney function outcome (N=965). Cross-lagged panel models were constructed to examine directionality of associations between EAA and kidney function at two time points (N=676).

Results: At baseline, each standard deviation increase in EEAA, GrimAA, and PhenoAA conferred significant 1.73, 1.55, and 1.46 increased odds of reduced kidney function, respectively (P=2.11 X 10-3, 0.04, 0.03, respectively). Likewise baseline EEAA and GrimAA were prospectively associated with 2.03 and 3.50 increased odds of incident kidney function decline (P=0.02 and 2.88 X 10-3, respectively). Path coefficients from baseline EEAA and GrimAA to follow-up eGFR were statistically significant.

Conclusions: Our findings implicate accelerated epigenetic aging as a novel predictor of kidney function decline.

Funding: Other NIH Support - TL1DK132769

TH-PO1024

Associations of Proteinuria Trajectories with Kidney Failure and Death in Patients with CKD

Avi G. Aronov,[1] Ashish Verma,[2] Ana C. Ricardo,[1] Tanika Kelly,[1] Sushrut S. Waikar,[2] James P. Lash,[1] Anand Srivastava.[1] CRIC Study. *[1]University of Illinois Chicago, Chicago, IL; [2]Boston Medical Center, Boston, MA.*

Background: Despite repeating proteinuria measurements multiple times during the clinical course of a patient with chronic kidney disease (CKD), clinicians may overlook the significance of temporal patterns of proteinuria. In addition, it is unclear whether proteinuria trajectories identify sub-populations with varying risks of adverse clinical outcomes.

Methods: We used group-based trajectory modeling to identify proteinuria trajectories based on annual urine protein-to-creatinine ratio (UPCR) measurements in 3209 participants of the Chronic Renal Insufficiency Cohort Study who were alive and did not reach end-stage kidney disease (ESKD) within 3 years of study entry. Multivariable-adjusted Cox proportional hazards models tested the associations of UPCR trajectories with ESKD and death in those who survived beyond the 3rd annual visit.

Results: Trajectory analyses identified 4 discrete groups based on annual UPCR measurements: low-slowly rising (n=1528), high-slowly rising (n=1363), regressing (n=114), and rapidly rising (n=204) (**Figure 1A**). Compared to the low-slowly rising proteinuria trajectory group, participants in the other proteinuria trajectory groups had lower socioeconomic status, a greater prevalence of comorbid conditions, and lower eGFR. During a median follow-up of 8.6 years, 547 participants progressed to ESKD, and 836 participants died. Compared to the low-slowly rising group, all proteinuria trajectory groups were associated with higher risks of subsequent ESKD, but only the high-slowly rising group was associated with a higher risk of death (**Figure 1B**).

Conclusions: Trajectories of repeated proteinuria measurements identify subgroups of patients with CKD that have increased risks of ESKD and death independent of known risk factors.

Funding: NIDDK Support, Other NIH Support - NHLBI

Figure 1A. Trajectory modeling identified four distinct proteinuria trajectory groups

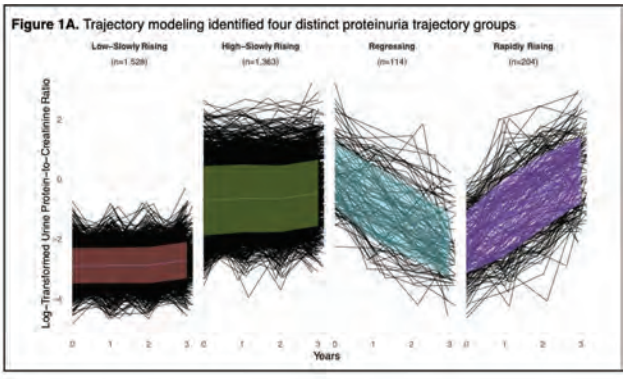


Figure 1B. Association of proteinuria trajectory groups with risks of ESKD and all-cause mortality

Trajectory Groups	No. of events	Events per 1000 person-years	Model 1* Hazard Ratio (95% Confidence Interval)	Model 1* P Value	Model 2† Hazard Ratio (95% Confidence Interval)	Model 2† P Value	Model 3‡ Hazard Ratio (95% Confidence Interval)	Model 3‡ P Value
ESKD								
Low-slowly Rising	69	5.60	Reference	—	Reference	—	Reference	—
High-slowly Rising	381	59.8	8.07 (6.30 – 10.3)	<0.001	4.59 (3.56 – 5.90)	<0.001	1.55 (1.13 – 2.11)	<0.001
Regressing	29	48.9	5.35 (3.54 – 8.06)	<0.001	2.67 (1.77 – 4.04)	<0.001	2.23 (1.46 – 3.40)	<0.001
Rapidly rising	68	85.9	9.59 (6.97 – 13.2)	<0.001	6.77 (4.89 – 9.38)	<0.001	1.54 (1.03 – 2.31)	0.036
All-cause mortality								
Low-slowly Rising	332	26.5	Reference	—	Reference	—	Reference	—
High-slowly Rising	400	47.7	1.59 (1.38 – 1.84)	<0.001	1.51 (1.30 – 1.75)	<0.001	1.24 (1.02 – 1.51)	0.030
Regressing	27	37.7	1.48 (1.04 – 2.10)	0.029	1.39 (0.98 – 1.99)	0.066	1.33 (0.93 – 1.91)	0.110
Rapidly rising	77	64.3	1.80 (1.43 – 2.28)	<0.001	1.71 (1.25 – 2.17)	<0.001	1.30 (0.97 – 1.75)	0.083

All covariables in models were obtained at the year 3 visit.
*Model 1: stratified by clinical centers and adjusted for age, sex, race/ethnicity, household income, education, systolic blood pressure, diabetes, history of cardiovascular disease, body mass index, current smoking, hemoglobin, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers, beta-blockers, diuretics, lipid-lowering agents, and antiplatelet agents.
†Model 2: Model 1 and further adjusted for eGFR.
‡Model 3: Model 2 and further adjusted for natural log-transformed UPCR.

TH-PO1025

Panel Estimated Glomerular Filtration Rate: Statistical Considerations for Maximizing Accuracy in Diverse Clinical Populations

Nora F. Fino. CKD-EPI. *University of Utah Health, Salt Lake City, UT.*

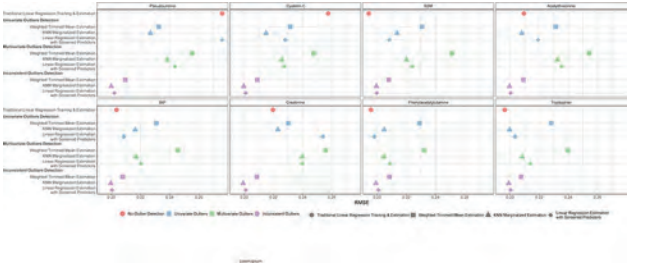
Background: Accuracy of eGFR is limited by non-GFR determinants that affect creatine or cystatin C. We hypothesized that a panel eGFR that incorporates multiple filtration markers with unrelated non-GFR determinants could further improve eGFR accuracy, but methods for robust estimation that can accommodate anomalous values of some filtration markers are required for optimal accuracy. Here, we evaluated methods for estimating GFR based on multiple markers in applications with higher rates of anomalous predictors.

Methods: We detected anomalous predictors in the application data using 3 approaches: univariate outliers, multivariate outliers, and inconsistencies among predictor markers. After removing anomalous predictors, we also compared 3 approaches for robust estimation: weighted trimmed mean prediction, linear model with K-nearest neighbors (KNN) marginalized estimation, and linear regression with screened predictors estimation. Using statistical simulation to emulate applications with increased anomalous predictors, we compared these approaches using Root Mean Square Error (RMSE). As proof of concept, we evaluated these methods in an initial panel of 8 markers (5 metabolites and 3 low molecular weight proteins) in 3,554 participants from 9 diverse studies.

Results: Figure displays RMSE for each strategy. For example, when 10% of pseudouridine values were anomalous using the univariate and multivariable outliers perspective and applying the three robust estimation approaches, RMSEs were 0.227 - 0.276 and 0.238-0.255, respectively. However, when considering inconsistent outliers with linear regression with screened predictors estimation, the RMSE was 0.196. Results using other markers are similar.

Conclusions: We found that focusing on markers with consistent predictors yields robust GFR estimates in application populations with substantial levels of anomalous predictors. Our findings demonstrate that even in cases where a subset of markers appears to be anomalous for a particular patient, accurate and unbiased estimates remain feasible.

Funding: NIDDK Support



TH-PO1026

Intraindividual Difference between Cystatin C- and Creatinine-Based eGFR Is Associated with All-Cause and Cardiovascular Mortality: The Fukuoka Kidney disease Registry (FKR) Study

Hiromasa Kitamura,[1,2] Shigeru Tanaka,[1] Hiroto Hiyamuta,[3] Hiroaki Ooboshi,[1] Kazuhiko Tsuruya,[4] Takanari Kitazono,[2] Toshiaki Nakano.[2] *[1]Fukuoka Shika Daigaku, Fukuoka, Japan; [2]Kyushu Daigaku, Fukuoka, Japan; [3]Shakai Iryo Hojin Seitetsu Kinen Yawata Byoin, Kitakyushu, Japan; [4]Nara Kenritsu Ika Daigaku, Kashihara, Japan.*

Background: Estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcr) and serum cystatin C (eGFRcys) are widely used to evaluate kidney function in patients with chronic kidney disease (CKD). Discrepancies between these measurements are not uncommon and have been linked to adverse outcomes such as death and cardiovascular events. Despite this, research on these discrepancies and their association with outcomes in Japanese patients with CKD is limited, highlighting a major gap in the collective understanding within this community.

Methods: We examined 4,244 patients with non-dialysis-dependent CKD who participated in the Fukuoka Kidney disease Registry (FKR) Study, a multicenter prospective cohort study. Patients were categorized into three groups based on eGFRdiff (calculated as eGFRcys – eGFRcr, mL/min/1.73m^2): G1 (<0), G2 (0–10), and G3 (>10). The associations between eGFRdiff and both all-cause and cardiovascular mortality were investigated using Cox proportional hazards models.

Results: During the 5-year follow-up period, 418 patients (9.8%) died from all causes, and 101 patients (2.4%) died from cardiovascular causes. Compared to G3, the multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for all-cause mortality were 2.67 (1.98–3.59) for G1 and 1.71 (1.25–2.33) for G2. For cardiovascular mortality, the HRs (95% CIs) were 2.48 (1.38–4.46) for G1 and 1.20 (0.63–2.30) for G2.

Conclusions: Lower eGFRdiff values are associated with poor outcomes in terms of both all-cause and cardiovascular mortality in patients with non-dialysis-dependent CKD.

TH-PO1027

Kidney Function Variability Independently Predicts CKD Progression

Richard L. Amdur,[1,2] Mark J. Butler,[1,2] Jia Hwei Ng.[1,2] *[1]Northwell Health, New Hyde Park, NY; [2]Feinstein Institutes for Medical Research, New Hyde Park, NY.*

Background: Kidney function variability (KFV) was an independent predictor of renal and cardiovascular outcomes in 15 prior studies since 2009. Here, we test three measures of KFV in a large patient sample in a US healthcare system to determine the optimal definition of KFV for predicting renal outcomes.

Methods: Using EHR data from 2016-2023 in a large hospital system in the northeastern US, we selected patients who had an inpatient admission and at least 4 serum creatinine (Scr) measurements over 18 months (baseline) and baseline eGFR > 30 ml/min/1.73 m2. We calculated eGFR slope and variability during this baseline period and examined renal outcomes for patients with 3 or more Scr measures over at least 6 and up to 80 months of follow-up. Renal outcomes included 25% eGFR decrease from baseline mean and entry into stage 4 CKD. We used quintiles of KFV as measured by standard deviation (SD), coefficient of variation (CV), and non-linearity (NL; deviation from the individual patient's regression line of monthly minimum eGFR x year). We used Cox proportional hazard models with covariates age, race, sex, baseline mean eGFR, baseline slope of eGFR, baseline comorbidities and baseline anti-diabetic or anti-hypertensive medication class, to examine the independent predictive value of each KFV measure on renal outcomes, with censoring at death or the end of the study period.

Results: 99,964 patients qualified for inclusion (mean age 62, mean baseline eGFR 82, 57% female, 17% Black, 6% Asian, 13% Hispanic, 28% with DM). 15.1% of patients had 25% eGFR drop, and 5.5% reached CKD stage 4. In Cox models adjusted for demographics, comorbidities, medications, and baseline eGFR slope and mean, all three KFV measures were significant independent predictors of both renal outcomes (all p<.0001), but the strongest effect was for CV. After adjusting for covariates, each 1-quintile increase in baseline eGFR-CV was associated with a 12% increase in hazard of 25% eGFR decline (95% ci 10-13%, p<.0001) and a 15% increase in hazard of reaching stage 4 CKD (95% ci 13-18%, p<.0001) during follow-up.

Conclusions: KFV is a powerful independent predictor of CKD progression even after accounting for baseline level and slope of eGFR and other covariates, and since it is easily obtainable, it should be considered for use in future risk stratification algorithms. CV appears to be the best measure of KFV.

TH-PO1028

Impact of Adoption of European Kidney Consortium Equation (EKFC) on CKD Prevalence and CKD Staging in Older Irish Adults

Meera Tandan,[1] Leonard Browne,[1] Austin G. Stack.[1,2] National Kidney Disease Surveillance System and Quality Assurance Programme. *[1]University of Limerick, Limerick, Ireland; [2]Health Service Executive, Dublin, Ireland.*

Background: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation tends to overestimate glomerular filtration rate (GFR) and has limitation in younger and older age groups, while the European Kidney Function Consortium (EKFC) full-age spectrum (FAS) correct for these problems and provide better performance in estimating GFR. We compared the 2017 EKFC- FAS(Scr-CysC) equation with 2012 CKD-EPI(Scr-CysC) for estimating CKD prevalence and staging in a national representative sample of older Irish adults.

Methods: We utilised data from The Irish Longitudinal Study on Ageing (2009-2011), for participants aged 50 to 79 years with complete measurement of serum creatinine (Scr) and Cystatin-C (CysC). Using 2017 EKFC- $FAS_{(Scr\text{-}CysC)}$ and 2012 CKD-$EPI_{(Scr\text{-}CysC)}$, equations eGFR was calculated. CKD was defined as eGFR below 60 ml/min/1.73m^2. Median eGFR, CKD prevalence, concordance correlation coefficient (CCC), and impact of EKFC equation on GFR category reclassification was examined.

Results: A total of 5,092 participants (53.3% women), median age 61 years were included. CKD prevalence varied significantly from 10.8% (9.9% – 11.8%) using 2021 CKD-$EPI_{(Scr\text{-}CysC)}$ to 16.7 % (15.5 - 17.9%) with the 2017 EKFC- $FAS_{(Scr\text{-}CysC)}$ equation. The corresponding numbers of CKD increased from 114,867 to 176,439 individuals respectively. The median eGFR for 2021 CKD-$EPI_{(Scr\text{-}CysC)}$ was 82.1 ml/min/1.73m^2 and 2017 EKFC- $FAS_{(Scr\text{-}CysC)}$ was 74.5 ml/min/1.73m^2, P<0.001). The net reclassification was 23.1 % based on 2017 EKFC- $FAS_{(Scr\text{-}CysC)}$ equation compared to CKD-EPI 2012 $_{(Scr\text{-}CysC)}$ and was towards more worsening CKD stage. The CCC between 2012 CKD-$EPI_{(Scr\text{-}CysC)}$ and 2017 EKFC- $FAS_{(Scr\text{-}CysC)}$ was 0.88 (95% CI, 0.88 - 0.89).

Conclusions: CKD prevalence varies according to eGFR equation with substantially higher numbers of CKD predicted by the European Kidney Function Consortium than CKD-EPI equations. This has direct implications on healthcare planning, resource allocation, and rates of referral to specialist nephrology services in Ireland.

Funding: Government Support - Non-U.S.

TH-PO1029

Circulating Very Long-Chain Saturated Fatty Acids and Incident CKD: A Meta-Analysis of Prospective Cohort Studies

Benjamin Lidgard, Amanda M. Fretts, Rozenn Lemaitre. Fatty Acids Outcomes Research Consortium. *University of Washington, Seattle, WA.*

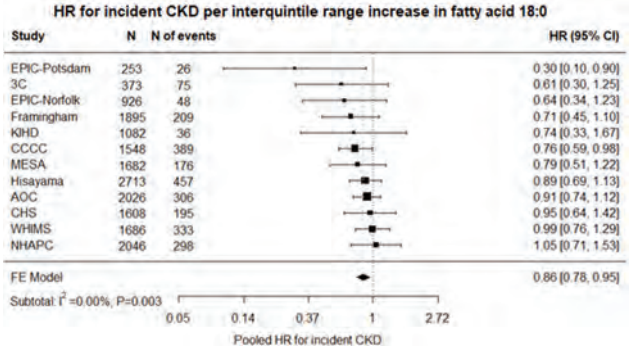
Background: Chronic kidney disease (CKD) is a global health problem whose prevalence is expected to increase. Identification of novel risk factors for CKD may lead to improved outcomes. Saturated fatty acids (SFAs) have been posited as contributors to CKD risk. We performed a meta-analysis of de-novo analyses which were undertaken in 12 contributing cohorts using a harmonized protocol to evaluate the associations of SFA with incident CKD.

Methods: SFAs were measured in 12 cohorts in the Fatty Acids Outcomes Research Consortium (FORCE), yielding a sample size of 17,838 participants with eGFR >60 mL/min/1.73 m2 across 9 countries. Associations between each SFA (16:0, 18:0, 20:0, 22:0, and 24:0) and incident CKD (defined as an eGFR <60 mL/min/1.73 m2 and ≥25% decrease from baseline) were assessed by Cox or Poisson regressions, adjusted for multiple potential covariates. Results were pooled using inverse variance weighted meta-analysis.

Results: In total, 2,548 participants across the 12 cohorts developed CKD during follow-up. After adjustment for multiple covariates, higher concentrations of SFA 18:0 were associated with significantly decreased risk of incident CKD (RR per interquintile range of SFA 18:0 0.86, 95% CI 0.78 to 0.95, P=0.003, I2=0.00%) (Figure). SFA 18:0 was associated with slower annual decline in eGFR and less risk for ≥40% decline in eGFR from baseline in sensitivity analyses.

Conclusions: In this meta-analysis of harmonized de-novo analyses among 12 cohorts across 9 countries (including 17,838 participants without baseline CKD), higher circulating levels of SFA 18:0 were consistently associated with decreased risk for incident CKD. Future work may be indicated to assess mechanisms by which SFA 18:0 may exert kidney-protective effects, and how circulating SFA 18:0 levels may be altered.

Funding: Other NIH Support - NCATS KL2TR002317



TH-PO1030

Patients with CKD with Wide Fluctuations in Plasma Uric Acid Levels Are Prone to Have Faster Decline in eGFR and High Chance of Orthopedic Admissions

Hiroshi Tanaka. *Mihara Red Cross Hospital, Mihara, Japan.*

Background: Plasma uric acid level is known to be associated not only with gouty attacks and urolithiasis but also with CKD progression and higher cardiovascular mortality. In some CKD patients, plasma uric acid levels are occasionally found to be widely fluctuated; the clinical significance of those fluctuations has not been extensively studied. In the era of growing numbers of elderly population, this fluctuation might be associated with unfavorable patient prognosis such as orthopedic admissions.

Methods: A hospital-wide study with all the laboratory data for a period of 4 years and 2 months was conducted. Non-dialysis patients with an age 18 or more in whom the eGFR slope was calculated over 731 days or more, with a median eGFR < 60 mL/min/1.73m^2, and with at least 3 uric acid measurements, were included in the study. Uric acid level fluctuations were analyzed by 3 parameters: standard deviation (SD), coefficient of variation (CV) and interquartile range (IQR). Hospital admission records were retrieved over 52 months following the above survey period of uric acid fluctuations.

Results: A total of 1,103 patients met the inclusion criteria. Those with wide fluctuations in plasma uric acid (i.e., those who had the widest quartile in CV) had faster eGFR decline than patients in the narrower 3 quartiles (-2.67 +- 5.74 vs -1.01 +- 2.55 mL/min/1.73m^2/yr, P<0.0001; Because a virtually identical trend was confirmed also in analyses with SD and IQR, CV will be used thereafter). Hyperuricemic patients (i.e., patients with higher-than-median plasma uric acid level) had faster eGFR decline compared with normouricemic patients (-2.61+- 6.30 vs -1.02 +- 3.31 mL/min/1.73m^2/yr, P=0.0015). The eGFR decline was even faster in widely-fluctuated hyperuricemic patients compared with the rest (eGFR decline: -3.65 +- 6.30 vs -1.66 +- 4.99 mL/min/1.73m^2/yr, P<0.0001). Interestingly those who had wide fluctuations in uric acid level were found to have significantly higher risk of orthopedic admissions in the following 52 months compared with those with narrow fluctuation (14.9% vs 9.1%; chi-squared test, P=0.020).

Conclusions: Wide fluctuation in plasma uric acid level is associated with faster eGFR decline and risk of orthopedic admissions.

TH-PO1031

Prediction of Medication Therapy Problems in Patients with Moderate-to High-Risk CKD

Melanie R. Weltman,[1,2] Alaa A. Alghwiri,[2] Zhuoheng Han,[2] Linda-Marie U. Lavenburg,[2] Thomas D. Nolin,[1,2] Jonathan G. Yabes,[3,4] Yi-Fan Chen,[3] Manisha Jhamb.[2] *[1]University of Pittsburgh School of Pharmacy, Pittsburgh, PA; [2]University of Pittsburgh Division of Renal-Electrolyte, Pittsburgh, PA; [3]University of Pittsburgh Department of Medicine, Pittsburgh, PA; [4]University of Pittsburgh Department of Biostatistics, Pittsburgh, PA.*

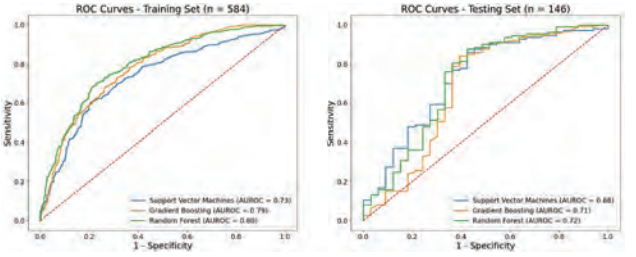
Background: Patients with chronic kidney disease (CKD) are at risk of medication therapy problems (MTP) due to high comorbidity and medication burden. Using data from the Kidney Coordinated HeAlth Management Partnership (K-CHAMP) trial, we used machine learning to build a predictive model to identify MTP high-risk patients with CKD in the primary care setting.

Methods: We used baseline data from patients enrolled in the intervention arm of the K-CHAMP trial, completed May 2019 to July 2022, which tested a population health management strategy, including medication management, for improving CKD care. The dataset was divided into 80% training and 20% testing subsets. The area under the ROC curve (AUROC) was used to assess classification accuracy in distinguishing between patients with and without MTP. Eight candidate models were considered, and the top three performing models (Random Forest, Support Vector Machines, and Gradient Boosting), based on cross-validated AUROC on training data, underwent further refinement. The model with the highest AUROC in the testing set, while considering the bias/variance trade-off, was selected as the best-performing model.

Results: Among 730 patients who received medication review at baseline, 566 (77.5%) had at least 1 MTP. Key demographics were mean age 74 years, 55% females, 92% White, 64% with diabetes, and the mean number of medications was 5.8 at baseline. The Random Forest model had the best performance on the testing set with AUROC 0.72, sensitivity 0.80, and specificity 0.64. The five most influential variables, ranked in descending order of importance for predicting individuals with MTP, were diabetes status (yes/no), HbA1C level, UACR level, age, and number of comorbidities.

Conclusions: The Random Forest model provided the highest performance in predicting MTP for patients with moderate-to high-risk CKD. Future work will focus on developing a user-friendly online tool aimed at identifying patients who may benefit most from pharmacist-led medication management.

Funding: NIDDK Support



TH-PO1032

Long-Term Use of Proton-Pump Inhibitors Is Associated with Rapid Progression to ESKD in Patients with CKD: A Korean Nationwide Study

Harin Rhee. *Pusan National University School of Medicine, Busan, Republic of Korea.*

Background: Proton pump inhibitors (PPIs) are one of the most widely used drugs worldwide. Nevertheless, it has long been debated whether PPIs are associated with disease progression in patients with chronic kidney disease (CKD).

Methods: Using the Korean Health Insurance Review and Assessment (HIRA) database encoded in the Observational Medical Outcomes Partnership – Common Data Model (OMOP-CDM) version 5.3, a total of 34,656 patients with CKD stage 3 or 4 initiating PPIs or H2 receptor antagonists (H2RAs) for more than 90 days were assembled from 2012 through 2021. ESKD progression was defined as the initiation of kidney replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation) for more than three months. The observation period was three years, and we calculated the incidence rate (IR) as 100 person-years (PYs) in the 1:1 propensity score-matched model.

Results: After 1:1 propensity score matching, we retrieved a total of 19,438 CKD stage 3 or 4 patients initiated PPIs or H2RA for more than three months. In all, 66.3% were CKD stage 3, 44.5% were aged over 75 years, 59.8% were male, and 68.3% had diabetes. During the mean follow-up of 1.2 years, ESKD progression was observed in 2,327 patients, and it was more frequent in PPI users (IR, 10.5/100PYs) compared to H2RA users (IR, 9.2/100PYs; incidence rate ratio (IRR), 1.19(1.07-1.32)). In the subgroup analysis, ESKD progression was more prominent in CKD stage 3 patients (PPI, 5.7 /100 PYs; H2RA 4.2/ 100 PYs; IRR 1.40(1.12-1.69)) than in CKD stage 4 (PPI, 19.8/100 PYs; H2RA 19.34 /100 PYs; IRR 1.03(0.91-1.18)), and non-diabetic CKD 3 or 4 patients (PPI, 7.7/100PYs; H2RA, 6.3/100 PYs; IRR, 1.32(1.07-1.64)) than in diabetic CKD 3 or 4 patients (PPI, 11.7/100PYs; H2RA, 10.80/100 PYs; IRR, 1.12(0.99-1.26)).

Conclusions: In CKD stage 3 or 4 patients, the use of PPIs for more than three months is associated with a 19% higher risk of ESKD progression, and the risk is more prominent in non-diabetic and earlier-staged CKD patients.

TH-PO1033

Association of Glucose Variability with Coronary Artery Calcium Score in Patients with Nondialysis-Dependent CKD: Findings from KNOW-CKD

Dong Hoon Kang, Jong Hyun Jhee, Byounghwi Ko, Cheol Ho Park, Ga Young Heo, Hyung Woo Kim, Jung Tak Park, Seung Hyeok Han, Shin-Wook Kang, Tae-Hyun Yoo. *Yonsei University College of Medicine, Seoul, Republic of Korea.*

Background: Coronary artery calcification (CAC) is common in patients with chronic kidney disease (CKD) and predicts the risk of cardiovascular disease. Glucose variability has been implicated as an independent risk factor for adverse cardiovascular outcomes in various populations. We investigated whether glucose variability is associated with CAC prevalence and progression in patients with non-dialysis CKD.

Methods: We used a prospective cohort of Korean patients with CKD. CAC score was measured at baseline and 4-year with Agatston units and fasting blood glucose was measured at baseline, 6-month, and 1-year. Glucose variability was defined as the standard deviation of three fasting blood glucose measurements. CAC prevalence was

defined as a baseline CAC score greater than zero and CAC progression was defined as an annual CAC percentage change of 15% or greater.

Results: Of the total of 1,518 patients, mean age was 53.5 years and 39.9% were men. According to four glucose variability group stratified by quartile, the prevalence of CAC was 37.6%, 38.9%, 52.0% and 76.3% for each group (Q1 vs Q4, prevalence ratio 1.35, 95% CI 1.08–1.69, *p*=0.009). In overall patients, higher glucose variability was associated with a higher risk of CAC progression (Q1 vs Q4, relative risk 1.85, 95% CI 1.20–2.87, *p*=0.005). In a subgroup analysis stratified according to the presence of diabetes, association was only observed in non-diabetic CKD patients (non-diabetic Q1 vs Q4, relative risk 2.01, 95% CI 1.12–3.62, *p*=0.02; diabetic CKD Q1 vs Q4, relative risk 1.31 (0.37–4.64), *p*=0.68).

Conclusions: In non-dialysis CKD patients, higher glucose variability was associated with a higher prevalence of CAC, and in non-diabetic CKD patients, higher glucose variability was associated with CAC progression.

Funding: Government Support - Non-U.S.

	Prevalence of Coronary artery calcification (N=1518)			Progression of Coronary artery calcification (N=959)		
Glucose variability group	No. of events (%)	Prevalence ratio (95% CI)	P value	No. of events (%)	Odds ratio (95% CI)	P value
Q1	143 (37.6%)	1.0	–	71 (29.6%)	1.0	–
Q2	148 (38.9%)	0.97 (0.77-1.22)	0.807	82 (34.2%)	1.15 (0.77-1.72)	0.496
Q3	197 (52.0%)	1.08 (0.87-1.35)	0.486	94 (39.2%)	1.32 (0.88-1.98)	0.186
Q4	289 (76.3%)	1.35 (1.08-1.69)	0.009	127 (53.1%)	1.85 (1.20-2.87)	0.005

Model was adjusted for age, sex, educational level, smoking status, charlson's comorbidity index, body mass index, systolic BP, statin use, eGFR category, and natural log-transformed urinary protein-to-creatinine ratio.

TH-PO1034

Association between Weight Change and Estimated Glomerular Filtration Rate Decline in a Middle-Aged Population

Niloofar Deravi,[1] Azra Ramezankhani,[1] Mohammad Rahmanian,[1] Parto Hadaegh,[1] Alireza Esteghamati,[2] Fereidoun Azizi,[1] Farzad Hadaegh.[1]
[1]Shahid Beheshti University of Medical Sciences Research Institute for Endocrine Sciences, Tehran, Tehran, Islamic Republic of Iran; [2]Tehran University of Medical Sciences, Tehran, Tehran, Islamic Republic of Iran.

Background: Little is known about the impact of weight change on the estimated glomerular filtration rate (eGFR) decline. We examined the association between weight changes and eGFR decline risk among middle-aged Iranians, participating in the Tehran Lipid and Glucose Study cohort.

Methods: A total of 4,748 individuals aged ≥30 years were selected. We defined weight change as difference in body weight during 3 years. The outcome was an eGFR decline of ≥30% and ≥40%. Cox regression models were utilized to calculate multivariable hazard ratios (HRs, 95% confidence interval (CI)) for different body weight changes (>10% weight loss; 5% to 10% weight loss; -5% to 5% weight change (reference group); 5% to10% weight gain; >10% weight gain).

Results: After a median follow-up of 9.4 years, there were 498 and 144 cases of eGFR decline of ≥30% and ≥40%, respectively. Individuals with a weight gain of ≥10% had a 71% higher risk (1.71, 1.15-2.55) for eGFR decline of ≥30%; the comparable value for eGFR decline of ≥40% was 2.85 (1.46-5.57). Those with a 5%-10% weight loss had higher risk for eGFR decline of ≥30% [(1.30 (0.98-1.72), P=0.06]; and an 86% (1.86, 1.18-2.93) higher risk for ≥40% eGFR decline. The impact of weight gain was more prominent among hypertensive individuals for eGFR decline of ≥30% (P for interaction=0.007). In a sensitivity analysis, among those with eGFR>60 ml/min per 1.73 m2 and without eGFR decline during weight change period, weight gain of >10% was associated with a 53% higher risk of eGFR decline ≥30% (1.53 (0.99-2.37).

Conclusions: Among the middle-aged Iranian population, there was significant association between both weight gain and weight loss with subsequent eGFR decline. Our results underscore the clinical importance of monitoring weight as a factor in renal risk assessment.

A. Incidence rates and hazard ratios (95% CI) for eGFR decline (≥30%) according to the weight change categories

Weight change	Number	eGFR decline	Incidence rate, per 1000 person years	Model 1	Model 2	Model 3	Model 4	Model 5
≤-10%	126	9	9.0 (4.2-15.8)	0.69 (0.35-1.34)	0.69 (0.35-1.34)	0.71 (0.37-1.42)	0.69 (0.35-1.35)	0.85 (0.44-1.64)
-10% to -5%	148	16	17.2 (13.5-32.0)	**1.48 (1.13-1.94)**	**1.48 (1.00-1.84)**	**1.44 (1.10-1.89)**	**1.37 (1.05-1.81)**	1.10 (0.98-1.72)*
-5% to 5%	3310	360	11.7 (10.5-13.0)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
5% to 10%	665	58	10.4 (7.8-13.0)	0.85 (0.65-1.13)	1.00 (0.76-1.33)	0.95 (0.73-1.31)	1.00 (0.75-1.32)	1.06 (0.79-1.40)
≥10%	221	37	14.0 (9.6-20.6)	1.20 (0.81-1.77)	**1.66 (1.08-2.38)**	**1.58 (1.06-2.34)**	**1.67 (1.12-2.48)**	**1.78 (1.15-2.55)**

B. Incidence rates and hazard ratios (95% CI) for eGFR decline (≥40%) according to the weight change categories

Weight change	Number	eGFR decline	Incidence rate, per 1000 person years	Model 1	Model 2	Model 3	Model 4	Model 5
≤-10%	126	5	4.8 (1.8-10.6)	1.48 (0.69-3.65)	1.45 (0.59-3.58)	1.46 (0.72-4.87)	1.69 (0.64-4.60)	1.97 (0.79-4.91)
-10% to -5%	148	25	8.6 (4.5-9.5)	**2.14 (1.37-3.33)**	**1.93 (1.23-3.00)**	**2.06 (1.33-3.22)**	**1.88 (1.19-2.98)**	**1.86 (1.15-2.93)**
-5% to 5%	3310	90	3.0 (2.4-3.7)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
5% to 10%	665	14	2.3 (1.4-3.9)	0.78 (0.44-1.37)	0.99 (0.56-1.74)	0.91 (0.51-1.60)	0.94 (0.53-1.66)	0.90 (0.54-1.71)
≥10%	221	10	5.6 (2.7-9.3)	1.67 (0.87-3.22)	**2.75 (1.45-5.32)**	**2.52 (1.30-4.90)**	**2.80 (1.43-5.48)**	**2.85 (1.46-5.57)**

*Model 1: Unadjusted
Model 2: Adjusted for sex and age
Model 3: Adjusted for model 2+ physical activity level+ smoking+waist circumference+education
Model 4: Adjusted for model 3+ hypertension+ diabetes+ hypercholesterolemia
Model 5: Adjusted for model 4+ eGFR baseline
eGFR: estimated glomerular filtration rate; **CI:** confidence interval

Incidence rates and hazard ratios (95% CI) for eGFR decline (A.≥30% and B.≥40%) according to the weight change categories

TH-PO1035

Analysis of the Relationship between Body Mass Index and Kidney Function Decline in a Middle-Aged Japanese Population

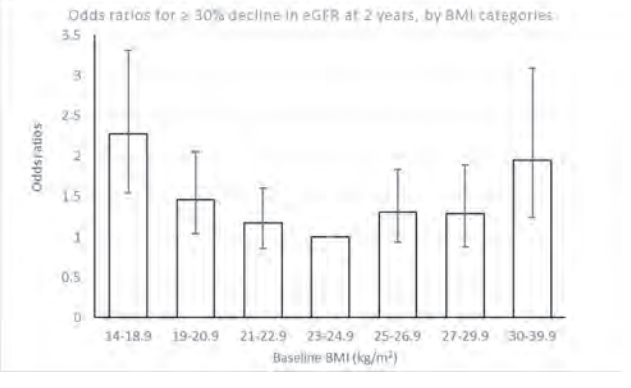
Miki Nakamura, Chiho Yamazaki, Keiju Hiromura, Kei Hamazaki.
Gunma Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Maebashi, Japan.

Background: The number of dialysis patients in Japan is increasing every year. In patients with chronic kidney disease, both obesity and underweight are reported to be risks for renal function decline. On the other hand, in the general population, obesity is a risk factor, but the relationship between underweight and renal function decline has not been well studied. Therefore, we aimed to analyze the relationship between body mass index (BMI), especially underweight, and renal function decline using health checkup data from Gunma prefecture, Japan.

Methods: We studied National Health Insurance beneficiaries aged 40 to 74 in Gunma who underwent health checkups in FY 2018 and 2020 and had usable estimated glomerular filtration rate (eGFR) and BMI data. We excluded those who self-reported receiving dialysis or had a BMI < 14 kg/m^2 or ≥ 40 kg/m^2. The outcome was defined as an eGFR decline rate of ≥ 30% over 2 years. Baseline BMI was classified into 7 categories, and odds ratios (OR) and 95% confidence intervals (95% CI) were calculated by logistic regression analysis.

Results: 64,970 individuals were included in the analysis. In a model adjusted for age, sex, smoking, alcohol consumption, blood pressure, hemoglobin A1c, and lipid profile, BMI and renal function decline showed an inverse J-shaped relationship, with underweight (BMI = 14.0-18.9 kg/m^2, OR [95% CI] 2.27 [1.55-3.31]) posing a higher risk of renal function decline compared to obesity (BMI = 30.0-39.9 kg/m^2, OR [95% CI] 1.95 [1.24-3.09]). Similar trends were seen across subgroups by sex, age, urinary protein presence, baseline eGFR, and diabetes, especially among those with negative urinary protein and non-diabetic status.

Conclusions: In the middle-aged and elderly general population, both obesity and underweight were shown to be risk factors for renal function decline. To prevent the need for dialysis, intervention is necessary for underweight groups who are not targeted for health guidance.



TH-PO1036

Periodontal Disease, Its Treatment, and the Risk of Kidney Failure among US Veterans

Nilang G. Patel,[1,2] Scott Silvey,[2,1] Jasmohan S. Bajaj.[1,2] *[1]VA Richmond Medical Center, Richmond, VA; [2]Virginia Commonwealth University Department of Internal Medicine, Richmond, VA.*

Background: Association of periodontal disease(PD) on incidence and progression of CKD is unknown.

Methods: Retrospective study conducted on veterans eligible for continuous and comprehensive dental care from 2009-2014. Veterans with a baseline eGFR > 60 ml/min/1.73m^2 were followed from the date of their initial comprehensive dental exam until the end of 2019. Patients divided into three groups: Periodontal disease (PD), Periodontal disease with treatment (PT) and no periodontal disease (no-PD). The composite outcome included: incident CKD, a 40% drop in eGFR, transplant/dialysis, or death.

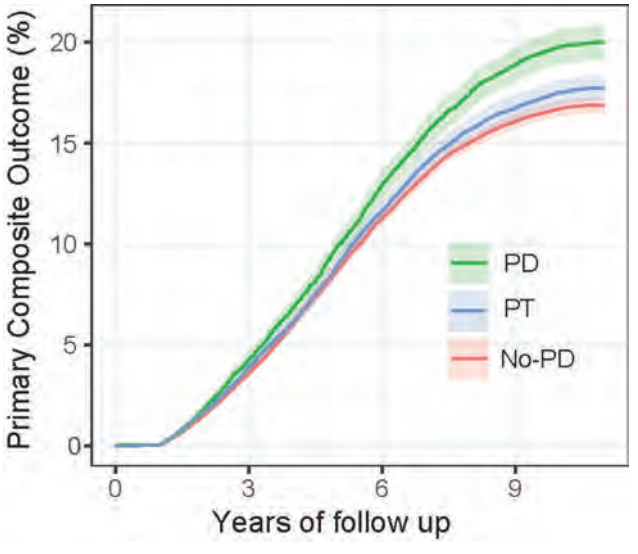
Results: 86,376 veterans (age 57.17±12.59, 91.4% male) were included in the final cohort. 12,172(14.1%) had untreated PD, 20,283 (23.5%) had PT and 53,921 (62.4%) had No-PD. The median follow-up was 7.39 yrs. Table 1 shows baseline characteristics and outcomes. Upon analyzing the primary composite outcome, PD patients had significantly increased risk over time(HR,1.18 [1.12-1.24], p<0.001), as did PT patients (HR:1.05 [1.01-1.09], p=0.02) (Fig. 1). After adjusting all covariates, PD associated with higher rates of the composite outcome (aHR:1.08 [1.01-1.15], *p*=0.025), while the PT was no longer statistically significant.

Conclusions: Untreated periodontal disease is linked to an increased Incident CKD and CKD progression. Treated PD associated with better outcomes.

Funding: Veterans Affairs Support

Table 1 (*n* = 86,376) : Baseline Characteristics and Outcomes

	Periodontal Disease + No Treatment (*n* = 12,172, 14.1%)	Periodontal Disease + Treatment (*n* = 20,283, 23.5%)	No Periodontal Disease (*n* = 53,921, 62.4%)	*p*-value
Variable, Mean ± SD or n (%)				
Age (> 65)	3199 (26.3%)	5042 (24.9%)	13142 (24.4%)	<0.001
Male Gender	11363 (93.4%)	19178 (94.6%)	48435 (89.8%)	<0.001
White Race	8607 (78.6%)	13751 (74.3%)	39123 (79.0%)	<0.001
BMI (> 30)	6263 (51.5%)	10967 (54.1%)	27737 (51.4%)	<0.001
Hispanic Ethnicity	870 (7.3%)	1841 (9.3%)	3931 (7.5%)	<0.001
Median Household Income	51513.93 (±18188.04)	52380.55 (±10885.36)	51898.87 (±17912.48)	<0.001
Urban Residence	5821 (59.9%)	10094 (62.8%)	24994 (58.2%)	<0.001
% w/Bachelor's Degree	23.49 (±12.30)	23.77 (±12.22)	23.80 (±12.32)	0.085
Current Smoker	3849 (39.4%)	5749 (37.7%)	13516 (33.6%)	<0.001
Alcohol Use Disorder	1935 (15.9%)	3662 (18.1%)	8080 (15.0%)	<0.001
Baseline eGFR	87.65 (±14.01)	87.85 (±14.16)	89.38 (±15.16)	<0.001
ACE/ARB	4589 (37.7%)	7490 (36.9%)	17713 (32.8%)	<0.001
Statin	2803 (23.0%)	4534 (22.4%)	11251 (20.9%)	<0.001
PPI	1794 (14.7%)	2872 (14.2%)	8230 (15.2%)	<0.001
NSAIDs	1883 (15.5%)	3056 (15.1%)	8352 (15.5%)	0.351
CCI (> 3)	1000 (8.2%)	1447 (7.1%)	3804 (7.1%)	<0.001
Diabetes	4018 (33.0%)	6835 (33.7%)	15667 (29.1%)	<0.001
CAD	2678 (22.0%)	3760 (18.5%)	9924 (18.4%)	<0.001
Hypertension	8006 (65.8%)	13208 (65.1%)	31742 (58.9%)	<0.001
Outcomes				
New CKD	2174 (17.9%)	3241 (16.0%)	8223 (15.3%)	<0.001
≥40% eGFR decline	1111 (9.1%)	1664 (8.2%)	4194 (7.7%)	<0.001
Dialysis/Transplant	141 (1.2%)	282 (1.4%)	670 (1.2%)	0.114
Death	5 (<0.1%)	7 (<0.1%)	18 (<0.1%)	0.919
Primary Composite Outcome	2283 (18.8%)	3443 (17.0%)	8723 (16.2%)	<0.001



TH-PO1037

CKD and Infection Risk: A CKD Prognosis Consortium Study

Junichi Ishigami, Keiichi Sumida. CKD Prognosis Consortium.
CKD Prognosis Consortium, New York, NY.

Background: Infectious disease is a major cause of hospitalization in people with CKD yet it has not been systematically studied across stages of CKD.

Methods: We analyzed data on 2,958,633 individuals (mean age 49 yrs, 59% female, 19% diabetes, mean eGFRcr (CKD-EPI 2021), 93 ml/min/1.73m^2) from 45 cohorts in the CKD Prognosis Consortium to examine the association of eGFRcr and ACR with the risk of hospitalization with infection. Outcomes were ascertained through ICD-9 and 10 codes on hospital discharge records relevant to acute infections (i.e., upper and lower respiratory tract, urinary tract, skin and soft tissue, musculoskeletal, gastrointestinal tract, genital, nervous system, cardiovascular system infections, and sepsis). Follow-up was censored at December 31, 2019, and therefore COVID-19 infection was not assessed. Multivariable Cox models were used to estimate HRs.

Results: During follow-up, 195,040 had a hospitalization with infection (IR, 140.3 [89.4-202.5] per 10,000 person-yrs). In Cox models, compared to eGFRcr 90-105 and ACR <10, lower eGFRcr and higher ACR were each incrementally associated with an increased risk of infection, including in eGFRcr 45-59 and ACR 10-29 (adjusted HRs [95% CI], 1.46 [1.41-1.51] and 1.41 [1.35-1.47], respectively; far right column and bottom row in **Figure**). High eGFRcr ≥105 was also associated with the risk of hospitalization with infection (1.33 [1.27-1.39]). The cross-category analysis revealed that the association of eGFRcr and ACR was independent of each other, with the highest risk observed in eGFRcr <30 and ACR ≥300 (5.92 [5.37-6.53] vs. eGFRcr 90-105 and ACR <10). These findings were consistent across infection subtypes.

Conclusions: Lower kidney function and higher albuminuria were independently associated with a higher risk of infection. The risk was substantially elevated even in mild to moderate CKD, with the highest risk seen in the most advanced stage of CKD. Infection prevention measures should target individuals across all CKD stages, and are particularly important for those with low eGFR and elevated ACR.

Funding: NIDDK Support, Private Foundation Support

Figure: The association of eGFR and ACR with risk of hospitalization with infection

CKD Stage		By ACR, mg/g				Combined
		<10	10-29	30-299	≥300	
By eGFRcr, ml/min/1.73m^2	≥105	1.09 (1.03 - 1.16)	1.59 (1.47 - 1.71)	2.09 (1.93 - 2.27)	3.45 (3.04 - 3.91)	1.33 (1.27 - 1.39)
	90-104	REF	1.42 (1.33 - 1.51)	1.80 (1.66 - 1.96)	2.77 (2.52 - 3.04)	REF
	60-89	1.07 (1.02 - 1.12)	1.52 (1.43 - 1.61)	1.95 (1.80 - 2.11)	3.26 (2.96 - 3.58)	1.06 (1.04 - 1.09)
	45-59	1.54 (1.43 - 1.66)	1.98 (1.85 - 2.12)	2.65 (2.44 - 2.89)	3.74 (3.36 - 4.16)	1.46 (1.41 - 1.51)
	30-44	1.94 (1.75 - 2.14)	2.48 (2.22 - 2.76)	3.00 (2.75 - 3.27)	4.54 (4.09 - 5.03)	1.72 (1.64 - 1.80)
	<30	3.65 (3.03 - 4.39)	3.80 (3.26 - 4.44)	4.08 (3.60 - 4.63)	5.92 (5.37 - 6.53)	2.14 (2.01 - 2.28)
Combined		REF	1.41 (1.35 - 1.47)	1.82 (1.72 - 1.93)	2.71 (2.54 - 2.90)	

*The models were adjusted for age, sex, Black race, smoking, hypertension, diabetes, BMI, total cholesterol, history of CVD, aspirin use, COPD, use of glucocorticoid or immunosuppressant, log ACR (for eGFRcr analysis) and eGFR (for ACR analysis). In the cross-category analysis, cells are colored in green if HR <1.1; yellow if HR <2.0, orange if HR <3.0, and red if HR ≥3.0.

TH-PO1038

Association of Water Intake with Incident CKD in the UK Biobank Study

Hyung Woo Kim,[1,2] Ga Young Heo,[1,2] Cheol Ho Park,[1,2] Jung Tak Park,[1] Seung Hyeok Han,[1] Tae-Hyun Yoo,[1] Shin-Wook Kang.[1] *[1]Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Republic of Korea.*

Background: Water intake has been suggested as a preventive strategy for chronic kidney disease (CKD). Nevertheless, there is a lack of evidence to suggest that higher water intake may be beneficial in the prevention of CKD.

Methods: This prospective, population-based cohort study enrolled participants without a history of CKD from the UK Biobank. Participants with heart failure, valvular heart disease, or a history of diuretic use were excluded. The main exposure was total daily fluid intake including water, tea, and coffee. Inverse probability of treatment weighting (IPTW) based on propensity scores was used to build groups with different amount of daily fluid intake. The primary outcome was the newly diagnosed CKD and the risks were estimated by Cox regression models.

Results: Among 286,139 participants (median age, 57 years; men, 48.2%; median estimated glomerular filtration rate, 97.9 ml/min/1.73 m^2), 6,816 (2.4%) cases of incident CKD occurred. Participants were categorized into five groups according to the amount of daily fluid intake: <1.5 L/d (n=117,555), 1.5 to 2.0 L/d (n=87,613), 2.0 to 2.5 L/d (n=48,845), 2.5 to 3.0 L/d (n=19,026), and ≥3.0 L/d (n=13,100). Compared with participants who intake 1.5 to 2.0 L/d of fluid, the respective hazard ratios (95% confidence intervals) for those with <1.5 L/d, 2.0 to 2.5 L/d, 2.5 to 3.0 L/d, and ≥3.0 L/d were 1.06 (1.01-1.13), 1.06 (0.98-1.14), 1.04 (0.93-1.16), and 1.26 (1.11-1.43), respectively.

Conclusions: The relationship between fluid intake and the development of CKD appears to be non-linear. The findings of this study indicate that consuming a high volume of fluid may not be associated with a reduced risk of incident CKD.

TH-PO1039

Subclinical Liver Fibrosis and Associated Risk Factors and Clinical Outcomes in CKD: The CRIC Study

Jing Chen, L. Lee Hamm, Cong Zhao, Siyi Geng, Lucy Van Dyke, Sydney L. Richardson, Layla H. Wright, Grace S. Morley, Rebecca J. Owens, Geetika Gorrepati, Allison N. Marshall, Vecihi Batuman, Jiang He. *Tulane University, New Orleans, LA.*

Background: Metabolic abnormalities associated with CKD may lead to liver fibrosis. We studied the incidence, risk factors, ASCVD, and mortality associated with subclinical liver fibrosis in CKD patients.

Methods: This analysis included 3,485 CKD patients from the Chronic Renal Insufficiency Cohort (CRIC) Study, excluding those with missing values. The mean follow-up was 8.2 years. The validated FIB-4 index (age × AST / (PLT × $\sqrt{}$ALT) evaluated subclinical liver fibrosis (defined as a FIB-4 >3.25). CVD and death events were adjudicated by two physicians. Cox proportional hazards models with backward selection examined risk factors for incident liver fibrosis, including CVD risk factors, eGFR, uACR, and biomarkers (inflammation, mineral bone disorder, fibrosis, and NT-proBNP). The models also assessed the link of FIB-4 with ASCVD and all-cause mortality.

Results: The average age was 62 for those with FIB-4 > 3.25 and 57 for those with FIB-4 ≤ 3.25. The age-adjusted incidence was 14.0 per 1000 person-years (17.5 for men and 10.1 for women). Multivariable-adjusted hazard ratios (HR) and 95% CI for liver fibrosis and risk factors are shown in **Table**. HR (95% CI) for one SD higher FIB-4 were 1.06 (1.02, 1.11) for ASCVD and 1.07 (1.03, 1.10) for all-cause mortality, adjusted for confounders including eGFR and uACR.

Conclusions: This study indicates that age, male, mineral bone disorder, inflammation, fibrotic factors, and volume overload are independently associated with risk of subclinical liver fibrosis. Additionally, liver fibrosis was associated with ASCVD and all-cause mortality. Further studies are needed to assess liver fibrosis and related interventions in CKD.

Funding: NIDDK Support, Other NIH Support - Tulane COBRE for Clinical and Translational Research in Cardiometabolic Diseases P20 GM109036

Significant Multivariable-Adjusted Hazard Ratios of Liver Fibrosis Associated with Risk Factors

	Multivariable-adjusted	
Variables	Hazard ratio (95% CI)	P-value
Age, (per SD, 11 years)	1.97 (1.68, 2.31)	<.0001
Male	2.15 (1.64, 2.81)	<.0001
Alkaline phosphatase (per 1 SD, 33.91, u/L)	1.14(1.01, 1.28)	0.03
Log (TGF-β) (per 1SD, 0.78 ng/mL)	0.86 (0.77, 0.96)	0.006
Log (hsCRP) (per 1SD, 1.25 mg/L)	0.79 (0.69, 0.90)	0.001
Log (IL-6) (per 1SD, 0.89 pg/mL)	1.16 (1.01, 1.33)	0.04
Galectin-3 (per 1SD, 7.09 ng/mL)	1.27 (1.12, 1.44)	0.0002
Log (NT-proBNP) (per 1SD, 1.41 ng/mL)	1.16 (1.01, 1.34)	0.04

TH-PO1040

Association of Pancreas Fat Fraction with Adverse Kidney and Cardiovascular Outcomes

Philip K. Thomas,[1] Celestin Missikpode,[1] Ashish Verma,[2] Runqi Zhao,[2] Sophie E. Claudel,[2] Insa M. Schmidt,[2] Petter Bjornstad,[3] Brian Layden,[1] James P. Lash,[1] Sushrut S. Waikar,[2] Anand Srivastava.[1] *[1]University of Illinois Chicago, Chicago, IL; [2]Boston University, Boston, MA; [3]University of Washington, Seattle, WA.*

Background: Pancreas fat accumulation has been associated with impaired glucose metabolism and stimulation of inflammation. The associations of pancreatic fat fraction (PFF) with adverse outcomes remain understudied.

Methods: We estimated baseline predicted PFF (pPFF) from abdominal MRI in 29464 participants of the UK Biobank. Since the initial imaging visit occurred 9.3 [IQR 8.2,10.2] years after the baseline visit, we calculated annual change in PFF using linear regression in 337 participants who underwent repeat imaging 2.8 [IQR 2.2,4.8] years after the initial scan. We back-calculated pPFF by adding this change to each participant based on the time between the baseline visit and initial MRI visit assuming linear change in PFF over time. Multivariable-adjusted proportional hazards models tested associations of pPFF with incident chronic kidney disease (CKD), cardiovascular disease (CVD), and death.

Results: Participants had a mean ± SD age of 56 ± 8 years, mean eGFR of 98 ± 13 mL/min/1.73m^2, median [IQR] albuminuria of 5.7 [3.5,9.2] mg/g, and median pPFF of 4.7 [1.6,10.3]%. During a median follow-up of 13.8 years, there were 573 incident CKD events, 1049 incident CVD events, and 471 deaths. In fully adjusted models, participants in the 2nd and 3rd tertiles of pPFF each had a 1.58-fold increased risk of incident CKD compared to the 1st tertile, respectively (**Figure 1A**). The association of pPFF with incident CKD was non-linear (Non-linear P<0.001, **Figure 1B)**. pPFF was not associated with incident CVD or death.

Conclusions: Higher pPFF levels are associated with increased risk of incident CKD but not CVD or death. Future studies should investigate whether reducing pancreas fat decreases the risk of incident CKD.

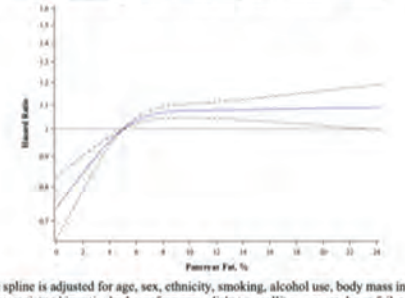
Funding: NIDDK Support

[A] Association of pPFF with incident CKD, incident CVD, and death

pPFF (%)	Tertile 1	Tertile 2	Tertile 3
CKD			
N	8593	8593	8593
Events	89	197	287
Model 1	Reference	2.26 (1.76 – 2.90)	3.30 (2.60 – 4.19)
Model 2	Reference	1.66 (1.28 – 2.15)	1.84 (1.41 – 2.40)
Model 3	Reference	1.58 (1.22 – 2.05)	1.58 (1.21 – 2.07)
CVD			
N	9630	9631	9630
Events	181	345	523
Model 1	Reference	1.94 (1.62 – 2.32)	2.97 (2.51 – 3.51)
Model 2	Reference	1.17 (0.97 – 1.41)	1.22 (1.00 – 1.47)
Model 3	Reference	1.14 (0.94 – 1.37)	1.19 (0.98 – 1.44)
Death			
N	9,821	9,822	9,821
Events	106	141	224
Model 1	Reference	1.37 (1.07 – 1.77)	2.18 (1.73 – 2.75)
Model 2	Reference	0.85 (0.65 – 1.10)	0.92 (0.70 – 1.20)
Model 3	Reference	0.85 (0.65 – 1.11)	0.91 (0.69 – 1.19)

Model 1: Unadjusted
Model 2: adjusted for age, sex, ethnicity, smoking, alcohol use, body mass index, Townsend deprivation index, waist to hip ratio, body surface area
Model 3: includes model 2 and further adjusted for diabetes mellitus, cancer, heart failure, myocardial infarction, stroke, systolic blood pressure, blood pressure medications, serum albumin, hemoglobin A1c, C-reactive protein, eGFR, log base 2 transformed albuminuria

[B] Restricted cubic spline analysis for association of pPFF with incident CKD



Restricted cubic spline is adjusted for age, sex, ethnicity, smoking, alcohol use, body mass index, Townsend deprivation index, waist to hip ratio, body surface area, diabetes mellitus, cancer, heart failure, myocardial infarction, stroke, systolic blood pressure, blood pressure medications, serum albumin, hemoglobin A1c, C-reactive protein, eGFR, and log base 2 transformed albuminuria.

TH-PO1041

Association of IgG Glycosylation with Kidney Markers and CKD Progression

Ulla T. Schultheiss,[1,2] Elena Butz,[1] Ivan Gudelj,[3,4] Barbara Radovani,[3] Anna Kottgen,[1] Peggy Sekula.[1] GCKD Study Investigators. *[1]Universitatsklinikum Freiburg, Freiburg, Germany; [2]Synlab MVZ Humangenetik Freiburg GmbH, Freiburg, Germany; [3]University of Rijeka, Faculty of Biotechnology and Drug Development, Rijeka, Croatia; [4]Genos Glycoscience Research Laboratory, Zagreb, Croatia.*

Background: Glycosylation profiles of immunoglobulin G (IgG) has been associated with kidney function and chronic kidney disease (CKD) in the general population but has not been explored in CKD cohorts. Glycans, like galactose, modulate immune responses and may impact kidney diseases. Our aim was to identify glycosylation patterns associated with kidney function markers and CKD progression to kidney failure (KF) and mortality among CKD patients.

Methods: Plasma samples from 4819 German CKD (GCKD) study participants were analyzed for 24 IgG glycans. This abstract focuses on 12 traits derived from these measurements, related to either complete or partial glycosylation patterns. Linear and Cox regression models, adjusted for confounders, evaluated associations with eGFR, UACR, KF, and mortality. A significance threshold of p=0.0021 (0.05/24) was used.

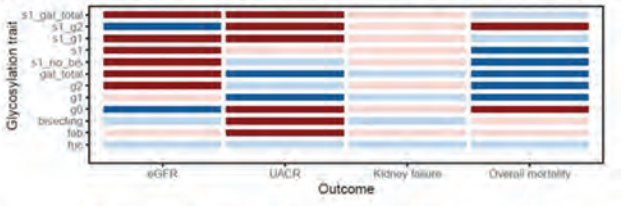
Results: The study included 460 participants reaching KF and 607 died during 6.5-years follow-up. Mean age was 60.1 years, with 39.8% females, median UACR of 50.8 mg/g, and median eGFR of 49.4 mL/min/1.73m^2. Most glycosylation patterns showed significant results, none were associated with KF, e.g. an increase of one standard deviation total galactosylated IgG (gal_total) was significantly associated with a 0.045 mL/min/1.73m^2 increase in eGFR and a 0.11 mg/g decrease in UACR. Higher levels of gal_total were linked to a lower risk of mortality (Hazard Ratio 0.72), indicating a protective effect. Similar protective effects were observed for s1, s1_no_bis, g2, and g1, while harmful associations were found for s1_g2 and g0.

Conclusions: Our study shows that certain patterns of glycosylation in IgG N-glycans are associated with kidney function and mortality. Galactosylation and specific sialylation patterns are linked to better kidney function and lower mortality, while agalactosylation

and specific ratios of sialylation are associated with poorer kidney function and higher mortality. Ongoing analyses will further explore these associations.

Funding: Government Support - Non-U.S.

Figure: Association of the 12 derived IgG glycans with eGFR, UACR, kidney failure, and mortality.



Legend: s1_gal_total=monosialylated and total galactosylated IgG, s1_g2=monosialylated and digalactosylated IgG, s1_g1= monosialylated and monogalactosylated IgG, s1=monosialylated IgG, s1_no_bis=monosialylated IgG without bisecting N-acetylglucosamine in IgG N-glycome, gal_total=total galactosylated IgG, g2=digalactosylated IgG, g1=monogalactosylated IgG, g0=agalactosylated IgG, bisecting=bisecting N-acetylglucosamine in IgG N-glycome, fab=Fab glycosylated IgG, fuc=fucosylated IgG. g0, g1, g2, gal_total, s1, s1_no_bis, bisecting, and fuc levels are derived in relation to the total IgG N-glycome. s1_g1, s1_g2, s1_gal_total, and fab levels are derived in relation to g1, g2, and gal_total respectively.

TH-PO1042

Empagliflozin Dosage and Albuminuria Reduction in CKD

C. E. Cervantes, Dustin Le, Mohamad A. Hanouneh. *Johns Hopkins University, Baltimore, MD.*

Background: Exploratory analysis from EMPA-REG trial revealed empagliflozin significantly reduces albuminuria compared to placebo. Yet, no study has examined if there's a correlation between albuminuria reduction and varying dosage.

Methods: We conducted a retrospective study on CKD patients with UACR > 30 mg/g, dividing them into two groups: group one received empagliflozin 10 mg daily and group 2 received empagliflozin 25 mg daily, with primary goal of assessing the proportion of patients achieving >50% reduction in UACR from baseline.

Results: 163 patients were included, 94 (58%) were on group 1 with mean eGFR 43.2 ml/min per 1.73m2 and median UACR 399 mg/g, and 69 (42%) were on group 2 with mean eGFR 51.0 ml/min per 1.73m2 and median UACR 666 mg/g. At baseline, 126 (77.3.%) were on RAAS blockade, and 131 (80.3%) had type 2 diabetes. After 6 months, a reduction of > 50% in albuminuria was noted in 46% of patients in group 1, while in group 2, this figure rose to 68% [with a p-value of 0.01 and an OR of 2.46 (95% CI: 1.24 to 4.9)] (Figure 1A). When we looked at percent albuminuria reduction adjusted for baseline covariates, despite noting a greater reduction in group 2 (54%, 95% CI 41 to 67) compared to group 1 (45%, 95% CI 36 to 55), the difference was 9.2% (95% CI: -0.16 to 22.7) and was not statistically significant (Figure 1B). At 6-months, the mean difference in eGFR was –2 ml/min per 1.73m2 (SD 5.7) in group 1 and -2.7 ml/min per 1.73m2 (SD 7.7) in group 2, with no discernible variance between the two groups following adjustment for baseline eGFR and baseline covariates [the difference was -0.38 (95% CI: -2.49 to 1.74)]. At 6-months, the average difference in serum potassium was –0.1 mmol/L (SD 0.4) in both groups with no difference between the two groups after adjustment for baseline serum potassium level and baseline covariates [0.00 (95% Cl: -0.11 to 0.11].

Conclusions: Higher dose of empagliflozin led to more reduction in albuminuria among CKD patients, without a significant change in eGFR or serum potassium levels compared to the lower dose.

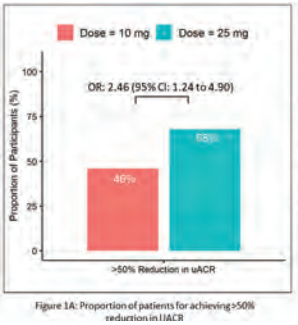


Figure 1A: Proportion of patients for achieving >50% reduction in UACR

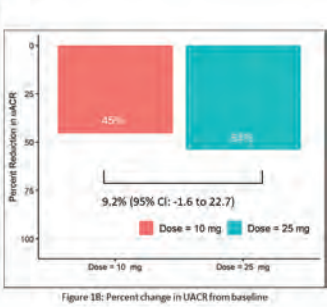


Figure 1B: Percent change in UACR from baseline

TH-PO1043

Effects of Empagliflozin on Health Care Use and Quality of Life in CKD in the United Kingdom: Results from EMPA-KIDNEY

Junwen Zhou, Borislava N. Mihaylova. On behalf of the EMPA-KIDNEY Collaborative Group. *Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom.*

Background: In EMPA-KIDNEY, empagliflozin reduced the risk of the primary composite outcome of kidney disease progression or cardiovascular death in patients with chronic kidney disease at risk of progression. We aimed to estimate the effects on within-trial healthcare use and health-related quality of life (QoL).

Methods: 6609 participants were randomly assigned to empagliflozin 10 mg daily or placebo and followed for a median of 2.0 (IQR 1.5-2.4) years. We estimated the effects of allocation to empagliflozin on healthcare use and costs (2022 UK£), including hospital admissions, concomitant medications, and kidney replacement therapy, and on QoL using shared parameter (analyzing outcomes together with time to death) or negative binomial models. These models informed estimates of the net effects of empagliflozin on healthcare use and costs and quality-adjusted life years (QALYs) over 2.5 years using 3.5%/year discount rate.

Results: Allocation to empagliflozin resulted in fewer hospital admissions (hazard ratio 0.86, 95% confidence interval 0.78-0.95). There were fewer days on (rate ratio (RR) 0.98, 0.95-1.00) and lower cost of (RR 0.90, 0.85-0.96) concomitant medications. Only a small number of participants initiated kidney replacement therapy and there was no statistically significant difference in these costs (RR 0.74, 0.33-1.69). Overall over 2.5 years, the estimated net cost of healthcare use was £353 (8-698) and additional QALYs were 0.016 (0.001-0.032) per participant allocated empagliflozin (Table).

Conclusions: In EMPA-KIDNEY and based on UK costs, allocation to empagliflozin over 2.5 years reduced other healthcare related costs, offsetting about two-thirds of empagliflozin costs. Ongoing post-trial follow-up will provide useful information on longer-term effects.

Funding: Commercial Support - EMPA-KIDNEY was funded by a grant to the University of Oxford from Boehringer Ingelheim and Eli Lilly.

Effects of empagliflozin on healthcare use and quality-adjusted life years (QALYs) over 2.5 years in EMPA-KIDNEY

	Days per person over 2.5 years, Mean (95%CIs)			Costs or QALY per person over 2.5 years, Mean (95% CIs)		
	Empagliflozin	Placebo	Difference	Empagliflozin	Placebo	Difference
Total healthcare use (including empagliflozin)	-	-	-	**£4438 (4215, 4660)**	**£4084 (3834, 4335)**	**£353 (8, 698)**
Hospital admissions	5.22 (4.61, 5.83)	6.24 (5.46, 7.01)	-1.01 (-2.09, 0.07)	£1222 (1088, 1357)	£1490 (1326, 1655)	-£268 (-499, -37)
Individual concomitant medications*	4312 (4228, 4396)	4396 (4309, 4483)	-84 (-216, 47)	£1505 (1434, 1576)	£1663 (1584, 1741)	-£158 (-258, -57)
Kidney replacement therapy	9.78 (7.52, 12.00)	12.60 (10.29, 14.92)	-2.82 (-6.04, 0.40)	£694 (532, 856)	£931 (759, 1104)	-£237 (-472, -2)
Study empagliflozin	790 (765, 815)	-	790 (765, 815)	£1016 (1006, 1026)	-	£1016 (1006, 1026)
Quality-adjusted life years (QALYs)	-	-	-	**2.014 (2.000, 2.029)**	**1.998 (1.983, 2.013)**	**0.016 (0.001, 0.032)**

*Each day on individual medication contributes a 'medication day' (e.g. a person on 5 medications/day accumulates 5 medication days).

TH-PO1044

Validation of Impact Using SGLT2 Inhibitor in Changes of Body Weight and Serum Albumin for Elderly Patients with CKD: A Retrospective Observational Study

Honami Honjoh, Takahito Moriyama. *Tokyo Ika Daigaku, Shinjuku-ku, Japan.*

Background: Elderly Chronic Kidney Disease (CKD) patients have a high frequency of frailty. These definitions include body weight (BW) loss and decreasing serum albumin, perceived as critical changes suspecting nutrition disorder. Although recent studies have shown that Sodium-glucose cotransporter 2 inhibitors (SGLT2Is) have improved renal surviva, the impact of SGLT2Is on nutrition status in elderly CKD patients is not well understood.

Methods: This retrospective observational study was conducted on CKD patients who were treated with SGLT2I at our department from 2020 to 2023. From these 207 patients, 94 patients whose serum creatinine (Cr), serum albumin, and BW had been fully measured at the three time points (baseline and at one year before and after treatment) were included. eGFR slopes and the % change of serum alb and BW were calculated from a one-year period before baseline and a one-year period after treatment, respectively.

Results: The characteristics of 94 patients) were mean age 65.1±15.6 (≥65 years old: 58.5%), female 21 (22.3%), diabetes 37 (39.4%), hypertension 86 (91.5%), ischemic heart disease 19 (14.7%), mean eGFR 40.9±23.1 mL/min/1.73 m 2. Overall, eGFR slope was not changed between before and after treatment (before treatment -0.173 mL/min/

1.73m2/month, after treatment -0.22 mL/min/1.73m 2 /month, p=0.83). % BW was significantly decreased after administration [-0.0 (-0.28 to 2.1) %/year vs -2.0 (-0.43 to 0.0) %/year, p < 0.001], though serum albumin was not changed (p=0.13). Elderly pstients had more severe CKD, lower BMI, more frequent ischemic heart disease, less use of inhibitors of renin angiotensin-aldosterone systems, and lower baseline eGFR compared with not elderly patients. In high-risk group, which had the decreasing changes in both % BW and % albumin between before and after treatment, the eGFR was significantly lower (p=0.016). The predictors for BW loss and decreasing serum alb were baseline lower albumin level [odd ratio (OR) 7.22 (1.17- 44.7), p = 0.033 and more severe CKD stage 2.44 (1.05-5.67), p = 0.037].

Conclusions: It was suggested that the lower the serum albumin level and the more severe CKD stage, the more likely BW and serum albumin will decrease in this study. Further evaluation is required to determine whether these changes are associated with malnutrition.

TH-PO1045

Increasing Use of SGLT2 Inhibitors in Patients with CKD and Heart Failure through Physician Education and Outreach Reduces Inpatient Admissions in a Value-Based Care Model

Katherine W. Kwon, Roy G. Marcus, Douglas Eckhardt, Jie Pu, Robert Pardini, Nirav Vakharia. *Panoramic Health, Tempe, AZ.*

Background: We developed a quality improvement project to increase the uptake of SGLT2i therapy in patients with comorbid chronic kidney disease and heart failure (CKD/HF) participating in a value-based care model with Panoramic Health.

Methods: Patients with CKD/HF and SGLT2i penetration were identified using data from both claims and electronic medical records (EMR). A prescription was defined as at least one prescription written within the past year, or an SGLT2i on the EMR medication list. We then undertook several interventions to increase appropriate prescribing rates. After executing a physician survey to gauge baseline knowledge, we conducted physician education about the efficacy and safety of SGLT2i medications. The Panoramic Health pharmacy team identified patient candidates and notified physicians prior to their next scheduled appointment. Practice-level SGLT2i prescribing rates were reported monthly to practice leaders. Outcomes metrics included SGLT2i prescriptions and inpatient admissions, expressed as admissions per 1000 patients (IP/1K).

Results: The initial rate of SGLT2i utilization in the target population was 16.1%. After five months of the described interventions, rates increased to 24.5% across participating Panoramic Heath partner practices, with some practices achieving rates as high as 50%. All-cause hospital admissions remained, on average, 11% lower (IP/1K of 964 vs. 1070) in patients prescribed an SGLT2i compared to those who were not. This trend persisted as the proportion of patients receiving SGLT2i increased. We also tracked physician responses to pharmacist outreach. 19.7% of messages led to a new prescription. The most common reasons given for not prescribing were “defer to PCP,” “frequent UTIs” and “does not meet criteria.”

Conclusions: SGLT2i prescribing rates are an important metric in any value-based program. While this simple intervention has a near-immediate impact on inpatient admissions, uptake has been slow. Our physician partners responded to education delivered by peers and directed outreach on individual patients. However, therapeutic inertia and concern for potential side effects continue to pose challenges to increased adoption.

Funding: Commercial Support - AstraZeneca

TH-PO1046

Targeted Clinician Emails to Promote SGLT2 Inhibitor Re-initiation after Discontinuation for Remediable Side Effects

Sarah F. Sanghavi,[1,2] Neha Deval,[3] Ethan Nguyen.[1] *[1]VA Puget Sound Health Care System Seattle Division, Seattle, WA; [2]University of Washington, Seattle, WA; [3]Sea Mar Community Health Centers, Seattle, WA.*

Background: Despite well-established efficacy in decreasing progression of kidney disease, SGLT2i therapy is discontinued in up to 60% of patients at 2 years. The purpose of this study was to identify veterans who had indications for SGLT2i reinitiation and remediable side effects. We then performed an intervention designed to educate the discontinuing clinician and resume therapy.

Methods: We identified patients from the VA Puget Sound Healthcare System who had a prescription for an SGLT2i discontinued between 1/1/2019 and 2/1/2023. Charts were manually reviewed to determine the reason for discontinuation and indications for therapy. Indications were defined as CAD or CHF, albuminuria > 30 mg/g, and eGFR < 60 ml/min. If the reason for discontinuation was remediable, patient specific e-mails were sent to the primary care provider or the discontinuing clinician outlining the reason for discontinuation and rationale for a second trial of the medication.

Results: The medical records of 805 veterans who discontinued therapy within the 4-year period were reviewed. After removal of records for discontinuation due to death or transfer to another VA, 435 records remained. The most common causes for discontinuation were genital infection (62), urinary frequency (60), volume depletion (53), decline in eGFR (30), and GI symptoms (23). We identified 99 patients with an indication to resume SGLT2i therapy and remediable side effects. Within 3 to 9 months of clinician e-mail notification, 26/99 veterans had resumed treatment.

Conclusions: We found that 23% of veterans who discontinued SGLT2i therapy had an indication for treatment and remediable side effects. Targeted e-mails to clinicians resulted in resumption of medication in 26% of veterans within 3-9 months of notification suggesting benefit of the intervention. Longterm data are needed to determine if this effect is durable.

Funding: Veterans Affairs Support

Most Common Side Effects	Discontinued N=435	E-mail Sent N=99	Reinitiation N=26
Genital Infections (Suspected or Confirmed)	62	6	0
Urinary Frequency	60	22	5
Volume Depletion	53	15	6
Decline in eGFR	30	12	4
GI Symptoms	23	6	2
Urinary Tract Infection (Suspected or Confirmed)	21	2	0
Improved HbA1c	20	4	1
Suspected ketoacidosis	16	3	1
Hospitalization	6	3	2

TH-PO1047

Effects of Empagliflozin on Serum Uric Acid and Gout in CKD

Kaitlin J. Mayne. The EMPA-KIDNEY Collaborative Group. *University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom.*

Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce serum uric acid and may reduce the risk of gout in patients with diabetes and/or heart failure, but randomized evidence in patients with CKD is lacking.

Methods: EMPA-KIDNEY compared empagliflozin 10 mg daily with placebo in 6609 patients with CKD (Clinicaltrials.gov: NCT03594110). Eligible patients had an eGFR of 20 to <45; or 45 to <90 mL/min/1.73m^2 with ≥200 mg/g albuminuria. Serum uric acid measured at randomization, 2 and 18 months was analyzed using a mixed model repeated measures approach including interaction terms to estimate subgroup-specific effects with calculation of heterogeneity or trend statistics. In exploratory analyses, first and total gout events were analyzed in Cox regression models with the Andersen-Gill extension for total events. All models were adjusted for age, sex, region, eGFR, uACR and diabetes status.

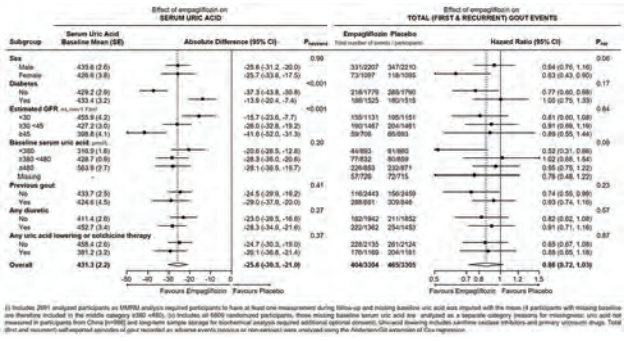
Results: Mean±SD baseline serum uric acid was 431.3±113.5 μmol/L. Empagliflozin reduced serum uric acid (study average between-group difference [95% CI] -25.6 [-30.3, -21.0] μmol/L). Uric acid lowering was greater in participants without diabetes (heterogeneity P<0.001) and at higher eGFR (trend P<0.001; Figure). During 2 years’ median follow-up, there was no significant effect of empagliflozin on risk of gout events alone (whether analyzing first or all occurrences, Table) which was consistent across subgroups including by baseline diabetes, eGFR and uric acid concentration (heterogeneity P all >0.1).

Conclusions: In EMPA-KIDNEY, empagliflozin modestly reduced serum uric acid with greater effects at higher eGFR and in those without diabetes, but did not significantly reduce episodes of gout.

Funding: Commercial Support - EMPA-KIDNEY trial funding from Boehringer Ingelheim & Eli Lilly

Effects of empagliflozin versus placebo on gout

	Empagliflozin n/N	Empagliflozin Rate per 1000 patient-years	Placebo n/N	Placebo Rate per 1000 patient-years	Hazard Ratio (95% CI)
First occurrence of gout	278/3304	45.7	317/3305	52.3	0.87 (0.74-1.02)
All occurrences of gout	404/3304	62.2	465/3305	71.7	0.86 (0.72-1.03)
First occurrence of gout or new initiation of xanthine oxidase inhibitor, primary uricosuric agent or colchicine in participants not on such therapy at randomization	261/2135	66.3	314/2124	81.8	0.81 (0.69-0.96)



Effects of empagliflozin versus placebo on serum uric acid and gout in subgroups defined by baseline characteristics

TH-PO1048

Patient-Level Factors Associated with the Prescription of SGLT2 Inhibitors in Patients with CKD

Angela M. Victoria Castro, Lisa Chan, Bashar A. Kadhim, Justin A. Dower, Rema Elmostafa, Sherry Mansour. *Yale University School of Medicine, New Haven, CT.*

Background: Sodium/glucose cotransporter 2 inhibitors (SGLT2i) are a valuable therapy in patients with chronic kidney disease (CKD). However, since approval by the Food and Drug Administration, they have not gained widespread use in CKD patients. In this study, we aimed to evaluate the patient-level factors associated with SGLT2i prescription within the Yale New Haven Health System.

Methods: This is a retrospective study of patients with CKD and eGFR ≥20mL/min/1.73m2, treated in the inpatient or outpatient setting from 2021 to 2024. We used a multivariable logistic regression model to estimate the adjusted odds ratios (aOR) to identify factors associated with SGLT2i perscription. We adjusted for sociodemographic and clinical factors.

Results: Out of a total of 352,408 eligible patients with CKD, 5,728 (1.6%) were prescribed SGLT2i. Patients who received a prescription were more likely older (median (IQR) 70 (60-78) vs. 62 (48-73) years, p<0.001), male (61% vs. 42%, p<0.001), Black (19% vs.12%, p<0.001) and retired (50% vs. 33%, p<0.001) as compared to those who did not receive an SGLT2i. The most frequent specialties prescribing SGLT2is were Internal Medicine (35%) and Cardiology (31%), with only 3% of perscriptions by Endocrinologists and 1% by Nephrologists. Among Hispanic and Black CKD patients, only 1% and 2% respectively were prescribed SGLT2is. Native American (aOR 0.36, 95%CI 0.26-0.52), Black (aOR 0.49, 95%CI 0.45-0.52), and Asian (aOR 0.62, 95%CI 0.52-0.73) patients were 64%, 51%, and 38% less likely to get prescribed SGLT2is as compared to White CKD patients, respectively. Similarly, patients with Medicaid (OR 0.81, 95%CI 0.75-0.88) were 19% less likely to be perscribed as compared to the ones with comercial insurance. Patients unable to work due to disability (OR 0.36, 95%CI 0.33-0.40) and unemployed (OR 0.62, 95%CI 0.57-0.68) were also 64% and 38% less likely to be prescribed an SGLT2i, respectively, when compared with employed patients.

Conclusions: In this preliminary analysis of patient-level factors, we found that there is suboptimal use of SGLT2is in the CKD population and that social determinants of health impact the prescription of these medications. There is a need for further evaluation of interventions to promote the use of SGLT2is in CKD patients with emphasis on health equity for all.

TH-PO1049

Benefits of Dapagliflozin in Slowing eGFR Decline in Patients with Different Rates of eGFR Loss

Niels Jongs,[1] Peter Rossing,[2,3] David Sjostrom,[4] Glenn M. Chertow,[5] Robert D. Toto,[6] David C. Wheeler,[7] Hiddo J. Heerspink.[1,8] *[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [2]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [4]Late-stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [5]Departments of Medicine and Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA; [6]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX; [7]Department of Renal Medicine, University College London, London, United Kingdom; [8]The George Institute for Global Health, Sydney, NSW, Australia.*

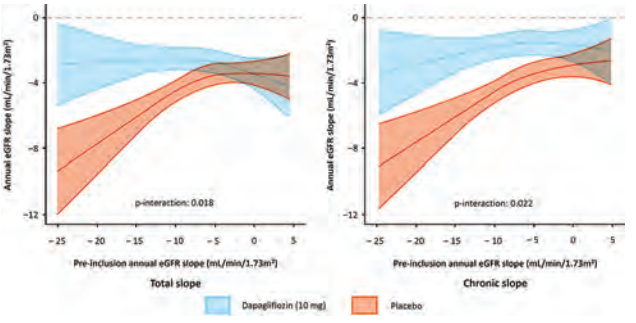
Background: Inclusion of patients likely to experience a loss of estimated glomerular filtration rate (eGFR) is required to detect a kidney protective treatment effect in clinical trials. This is usually achieved by enrolling patients with high levels of albuminuria. However, not all patients with elevated albuminuria show a progressive loss of kidney function. eGFR slope before the trial may better predict whether patients experience a loss in eGFR during a clinical trial. We assessed the effect of dapagliflozin on eGFR slope according to patient eGFR slope prior to inclusion in the DAPA-CKD trial (pre-inclusion eGFR slope).

Methods: We recorded eGFR data for ≤2 years from electronic medical records for 4304 patients with CKD before enrollment in DAPA-CKD, a randomized, placebo-controlled trial of dapagliflozin. We used linear regression to estimate within-patient pre-inclusion eGFR slopes. We evaluated the association of pre-inclusion eGFR slope with total (randomization to end-of-treatment) and chronic (Week 2 to end-of-treatment) eGFR slopes using a two-slope linear mixed-effects model. The composite kidney endpoint was defined as sustained ≥50% eGFR decline, end-stage kidney disease, or death from kidney causes.

Results: In total, 870 (20.2%) patients with ≥3 historical eGFR measurements were evaluated (mean pre-inclusion eGFR slope [SD]: −6.15 [6.1]). The benefit of dapagliflozin in reducing the total (p-interaction: 0.018) and chronic (p-interaction: 0.022) eGFR slopes was more pronounced in patients with steeper pre-inclusion eGFR slopes (rapid progressors; **Figure**). The effect of dapagliflozin compared to placebo on the composite kidney endpoint was also more pronounced in rapid progressors (p-interaction: 0.023).

Conclusions: Determination of pre-trial eGFR slope may help to identify patients with CKD at higher and lower risks of progression and those more or less likely to benefit from a targeted intervention to slow kidney function loss.

Funding: Commercial Support - AstraZeneca



TH-PO1050

Implications of Acute GFR Change for the Effect of SGLT2 Inhibitors on Long-Term End Points

Ransmond O. Berchie,[1] Lesley A. Inker,[2] Hiddo J. Heerspink,[3] Tom Greene.[1] *[1]University of Utah Health, Salt Lake City, UT; [2]Tufts University, Medford, MA; [3]Universiteit Groningen Afdeling Gezondheidswetenschappen, Groningen, Netherlands.*

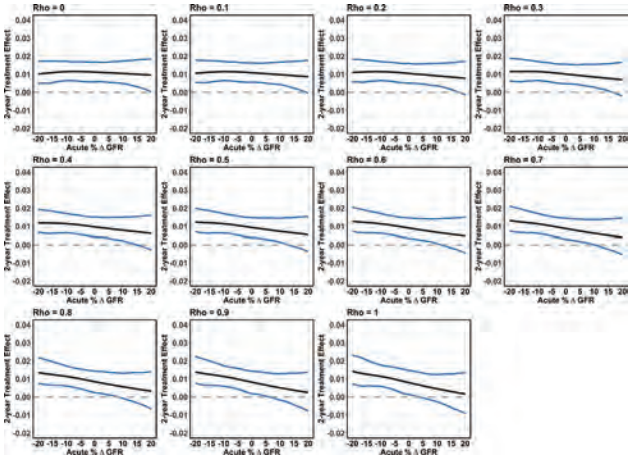
Background: Several studies have reported that chronic kidney disease (CKD) patients often experience a substantial decline in glomerular filtration rate (GFR) within 1 month after initiating treatment with sodium-glucose cotransporter-2 inhibitors (SGLT2i). Our goal is to determine, to the extent possible from the data, how the expected effect of SGLT2i on the time to kidney failure is modified by knowledge of the acute GFR change (ΔGFR) after starting SGLT2i.

Methods: We used a Johnson SU model for the distribution of ΔGFR within the SGLT2i and control groups and a Fine-Grey model with cubic splines to relate ΔGFR to the time to kidney failure with death as a competing risk for 3 clinical trials: DAPA-CKD, EMPA-REG, and CREDENCE. Then, using the modern causal inference framework of principal stratification, we specified the unobservable correlation ρ between ΔGFR under the SGLT2i and control treatments as a sensitivity parameter. This allowed us to define the distribution of ΔGFR under the control consistent with an observed ΔGFR with the SGLT2i and thereby estimate the effects of SGLT2i on the time to kidney failure conditional on ΔGFR across different possible values for ρ.

Results: Across all values of ρ, we find no evidence that negative acute GFR changes after SGLT2i initiation indicate an adverse effect or reduction in the benefit of SGLT2i on kidney failure. Moreover, for ρ≥0.7, we observe a trend suggesting that more negative acute changes signify a greater benefit of SGLT2i on the time to kidney failure.

Conclusions: The findings suggest that larger than average GFR reductions 1 month after initiating SGLT2i do not signify reduced benefit on kidney failure and may indicate therapeutic effectiveness.

Funding: Private Foundation Support



The Figure shows the impact of ΔGFR on the estimated effect of SGLT2i treatment on the probability of kidney failure by 2 years.

TH-PO1051

Real-Life Experience on the Effect of SGLT2 Inhibitors vs. Finerenone vs. Combination on Albuminuria in CKD

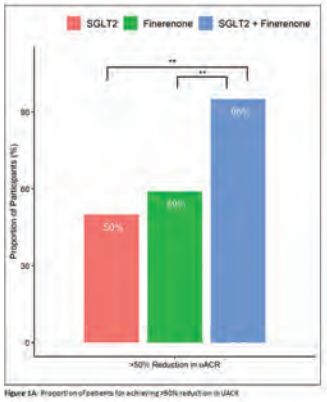
Mohamad A. Hanouneh, Dustin Le, Christina L. Tamargo, Bernard G. Jaar, C. E. Cervantes. *Johns Hopkins University, Baltimore, MD.*

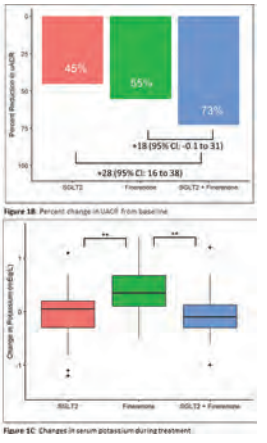
Background: Recent progress in treating CKD include utilizing SGLT2 inhibitors and selective mineralocorticoid receptor antagonists, finerenone. This real-world experience retrospective study examines the effects of these treatments, individually and in combination on CKD patients.

Methods: 98 adults patients with CKD, an eGFR 25 to 90 ml/min per 1.73 m2 and a urine albumin/creatinine ratio (UACR) > 30 mg/g were included. The patients were divided into 3 groups with 8 months follow-up: group one (N=52) treated with SGLT2 inhibitors, group two (N=22) treated with finerenone, and group three (N=24) treated with combination therapy- SGLT2i inhibitors for the first 4 months then finerenone was subsequently added. The primary outcome was the percentage of patients achieving >50% reduction in UACR from baseline.

Results: For all patients, the mean eGFR was 51.0 ml/min per 1.73m2, and median UACR was 580 mg/g. After 8 months, >50% decrease in albuminuria was achieved in 96% of patients in group 3, compared to 50% in group 1 and 59% in group 2 (P-values <0.01 and <0.01 respectively) (Fig 1A). When we assessed percent albuminuria reduction adjusted for baseline covariates, there was a significant difference comparing group 1 (45%, 95% CI [32,58]) to group 3 (73%, 95% CI [53,92]) with difference reduction of 28% (95% Cl [16,38], p-value < 0.01) (Fig 1B). Despite observing a substantial reduction in albuminuria in group 3 compared to group 2, the difference was 18% (95% Cl: [-0.1,31]) and did not reach statistical significance (p-value 0.07) (Fig 1B). There was a significant change in mean potassium levels in group 2 (+0.4 mmol/L) compared to either group 1 (0.0 mmol/L, p-value: < 0.01) or group 3 (-0.01 mmol/L, p-value: < 0.01) (Fig 1C). However, there was no difference comparing group 1 and 3 (Fig 1C).

Conclusions: In this real-world experience, the combination of SGLT2 inhibitors and finerenone in CKD patients was associated with a significant reduction in UACR, without an increased risk of hyperkalemia.





TH-PO1052

Effects of Zibotentan Alone and in Combination with Dapagliflozin on Fluid Retention in Patients with CKD

Johannes D. Smeijer,[1] Magnus Åstrand,[2] Anne-Kristina Mercier,[2] Peter J. Greasley,[3] Philip D. Ambery,[4] Hiddo J. Heerspink.[1,5] Investigators of ZENITH-CDK Clinical Trial. *[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden; [3]Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [4]Clinical Late Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [5]The George Institute for Global Health, Sydney, NSW, Australia.*

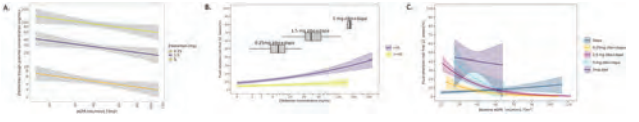
Background: Endothelin receptor antagonists (ERAs) effectively reduce albuminuria but are limited by fluid retention risk, particularly in patients with chronic kidney disease (CKD). Combining ERAs with sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have diuretic effects, offers a promising strategy to mitigate fluid retention. In this post-hoc analysis of the ZENITH-CKD trial, we assessed fluid dynamics in patients with CKD treated with the ERA zibotentan alone, and in combination with the SGLT2 inhibitor dapagliflozin

Methods: In ZENITH-CKD, 508 patients with CKD (eGFR ≥ 20 mL/min/1.73 m2 and a urinary albumin-to-creatinine ratio (UACR) of 150–5000 mg/g) were randomized to treatment with placebo, dapagliflozin 10 mg plus placebo, zibotentan (0.25, 1.5 or 5 mg) plus dapagliflozin 10 mg and zibotentan 5 mg plus placebo. We evaluated correlations between changes in fluid retention markers and bioimpedance-measured extracellular fluid (ECF) in response to zibotentan treatment. We used Cox proportional hazards regression to assess the association between zibotentan/dapagliflozin treatment, baseline characteristics, and fluid retention, as well as the relationship between zibotentan plasma exposure and fluid retention.

Results: After 3 weeks of treatment with zibotentan 0.25, 1.5 or 5 mg plus dapagliflozin 10 mg, changes in body weight, BNP, and hemoglobin were independently associated with changes in ECF. Higher doses of zibotentan significantly increased the risk of fluid retention compared to dapagliflozin alone (zibotentan 5 mg HR 9.13 [95%CI 3.40, 24.49]). The hazard ratio attenuated when zibotentan was combined with dapagliflozin (HR zibotentan/dapagliflozin 5/10 mg 3.61 (95%CI 1.26,10.33) and zibotentan/dapagliflozin 0.25/10 mg HR 0.99 (95%CI 0.37, 2.63). The risk of fluid retention increased with higher zibotentan exposure and lower eGFR.

Conclusions: High doses of zibotentan increased the risk of fluid retention which could be reduced with lower doses and addition of dapagliflozin. This risk was more pronounced at lower eGFR which highlights the need for combined use of low zibotentan doses and dapagliflozin in advanced CKD.

Funding: Commercial Support - The ZENITH-CKD trial was sponsored by AstraZeneca



TH-PO1053

Cumulative Effects of Aldosterone Synthase and SGLT2 Inhibition on Albuminuria in People with CKD

Peter Rossing,[1] Sibylle J. Hauske,[2] Lisa Cronin,[3] Hiddo J. Heerspink,[4,5] Juliane Meyerhoff,[2] Shimoli Shah,[3] Zhichao Sun,[3] Dick de Zeeuw,[4] Katherine R. Tuttle.[6] On behalf of the ASi in CKD Group. *[1]Steno Diabetes Center Copenhagen, Herlev, Denmark; [2]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [3]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; [4]University Medical Centre Groningen, Groningen, Netherlands; [5]The George Institute for Global Health, Sydney, NSW, Australia; [6]Providence Inland Northwest Health, Spokane, WA.*

Background: A phase II trial reported efficacy and safety of the aldosterone synthase inhibitor (ASi) BI 690517 in chronic kidney disease (CKD) showing significant albuminuria reduction with or without empagliflozin (EMPA) in the background. This *post hoc* analysis estimates the cumulative effects of ASi and EMPA 10mg on urine albumin:creatinine ratio (UACR) vs ASi alone.

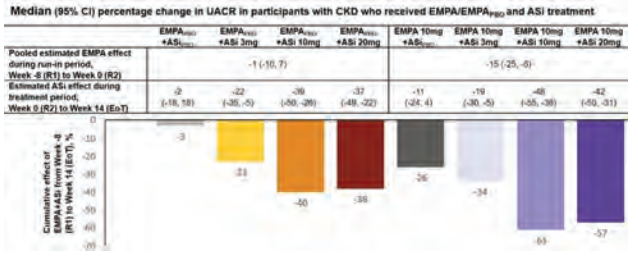
Methods: Participants receiving a maximally tolerated dose of a renin-angiotensin system inhibitor were first randomized (R1) to an 8-week run-in period to receive EMPA 10mg daily or $EMPA_{PBO}$, followed by a second randomization (R2) to a 14-week treatment period to receive ASi (3, 10, or 20mg daily) or ASi_{PBO}. For the run-in period, EMPA effects were assessed by pooling participants into EMPA vs $EMPA_{PBO}$ groups, regardless of ASi dose levels at R2. Randomized ASi dose groups on top of EMPA/$EMPA_{PBO}$ were assessed from R2 to 14 weeks. R2 served as the baseline reference time point and mixed-effect model for repeated measures (MMRM) was used to assess change in UACR. Cumulative

effects of both ASi and EMPA were calculated by adding UACR changes from R1 to R2 and R2 to the end of treatment period.

Results: UACR data were available from 249 participants who were randomized at R1 to receive EMPA 10mg and 254 who received $EMPA_{PBO}$. Estimated cumulative effects on UACR reduction from R1 to week 14 were larger with EMPA+ASi 10mg (-61%) compared to ASi 10mg alone (-40%) and vs $EMPA_{PBO}$+ASi_{PBO} (-3%) (**Table**).

Conclusions: Meaningfully larger UACR reductions across all ASi doses were achieved in participants with CKD who received both active components of EMPA+ASi compared to treatment with either ASi or EMPA alone. Combination of ASi with SGLT2 inhibitors is a promising, novel therapy strategy that may afford superior benefits over AS or SGLT2 inhibition alone and will be tested further in a phase III clinical trial.

Funding: Commercial Support - Boehringer Ingelheim



TH-PO1054

Insulin Glargine and SGLT2 Inhibitors Have Higher Risk of Major Adverse Cardiovascular Events (MACE) Compared with Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) in a National Cohort of Veterans with Type 2 Diabetes (T2D) and CKD

Niharika Katkam,[1,2] Amara Sarwal,[1,2] Sydney E. Hartsell,[1,2] Ravinder Singh,[1,2] Guo Wei,[1,2] Robert E. Boucher,[1,2] Akhil Ramanujam Chakravartula,[1,2] Jincheng Shen,[1,2] Mckenna R. Nevers,[1,2] Stavros Drakos,[1,2] Tom Greene,[1] Srinivasan Beddhu.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

Background: Insulin glargine(IG) is commonly used for glycemic control in persons with T2D and CKD. However, there is limited data on direct comparisons between IG and newer agents like GLP1-RA and SGLT2i on MACE in CKD.

Methods: We used an active comparator, new user design to compare the effects of initiating IG, GLP1-RA, or SGLT2i on MACE between 1/1/18 to 12/31/21 in veterans with T2D on metformin. Prescriptions for these agents between 1/1/08 to 1/1/18 was an exclusion. Follow-up was until 3/31/23. Application of inverse probability weighting(IPW) for each of the pairwise comparisons resulted in balance of baseline variables including demographics, comorbidity, duration of T2D, BP, BMI, A1C, eGFR and meds. MACE was defined as ER visit/ hospitalization for MI, stroke or HF. IPW Cox models with further adjustment for baseline covariates, were used to related the three drug initiation groups to MACE, all-cause mortality(ACM) or composite of MACE/ACM in those without and with CKD (eGFR < 60).

Results: 33.7% were initiated on IG, 13.7% on GLP1-RA, and 52.6% on SGLT2i. 16.5% had CKD. We observed 15461 MACE events/ 352837person-years in non-CKD and 5304 events/ 61578person-years in CKD.11325 deaths/ 377116person-years in non-CKD and 3943 deaths/70343person-years in CKD. IPW Cox model results are summarized in Table.

Conclusions: In CKD, initiation of IG was associated with higher risk of MACE and ACM compared to GLP1-RA and higher risk of ACM compared to SGLT2i. Compared to GLP1-RA, SGLT2i had higher risk of MACE in CKD. Randomized controlled trials comparing SGLT2i and GLP1-RA in CKD are warranted.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support

MACE	Non-CKD HR (95% CI)	CKD HR (95% CI)
IG vs GLP1-RA	1.27 (1.19, 1.34)	1.14 (1.04, 1.25)
IG vs SGLT2i	1.10 (1.05, 1.14)	1.03 (0.96, 1.11)
SGLT2i vs GLP1-RA	1.16 (1.09, 1.23)	1.13 (1.03, 1.24)
MACE/ ACM		
IG vs GLP1-RA	1.44 (1.37, 1.51)	1.25 (1.16, 1.36)
IG vs SGLT2i	1.28 (1.24, 1.32)	1.18 (1.11, 1.25)
SGLT2i vs GLP1-RA	1.13 (1.07, 1.19)	1.08 (1.00, 1.18)
ACM		
IG vs GLP1-RA	1.72 (1.60, 1.85)	1.42 (1.27, 1.58)
IG vs SGLT2i	1.59 (1.51, 1.67)	1.43 (1.32, 1.56)
SGLT2i vs GLP1-RA	1.11 (1.03, 1.19)	1.01 (0.89, 1.13)

TH-PO1055

Insulin Glargine Compared with Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) or SGLT2 Inhibitors Is Associated with Higher Risk of Alzheimer Disease and Alzheimer Disease-Related Dementias (AD/ADRD) in CKD

Amara Sarwal,[1,2] Guo Wei,[1,2] Ravinder Singh,[1,2] Sydney E. Hartsell,[1,2] Adam Bress,[1,2] Catherine G. Derington,[1,2] Robert E. Boucher,[1,2] Mckenna R. Nevers,[1,2] Niharika Katkam,[1,2] Augustine Takyi,[1,2] Akhil Ramanujam Chakravartula,[1,2] Jincheng Shen,[1,2] Tom Greene,[1] Srinivasan Beddhu.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

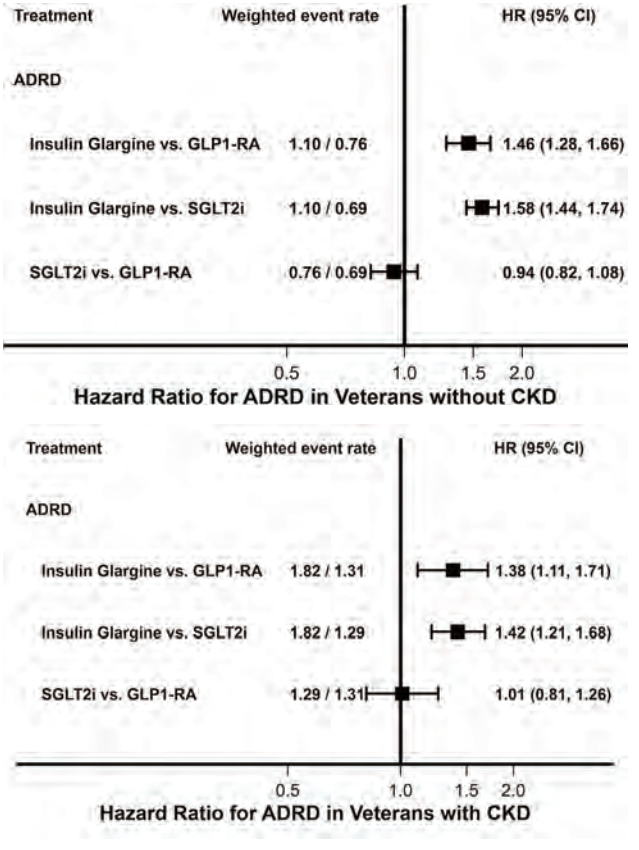
Background: It is unknown whether the risk of AD/ADRD is related to the use of insulin glargine (IG), GLP1-RA or SGLT2i in persons with T2D and CKD.

Methods: Using VA Informatics and Computing Infrastructure (VINCI) platform, we conducted an active comparator, new user design study to compare the effects of initiating IG, GLP1-RA, or SGLT2i on AD/ADRD between 1/1/18 to 12/31/21 in veterans with T2D on metformin and without AD/ADRD at baseline (N= 155,481). Prescriptions for these agents anytime between 1/1/08 to 1/1/18 was an exclusion. Follow-up was until 3/31/2023. Generalized propensity score based inverse probability weighting (IPW) was employed to control confounding in the observational data and facilitate comparisons among the three drug classes. In IPW Cox models, drug classes were related to time to the first diagnosis of AD/ADRD (defined by ICD-10) in those without and with CKD (eGFR <60).

Results: 33.2% were initiated on IG, 12.8% on GLP1-RA and 53.0% on SGLT2i. 16% had CKD. There were 2970 AD/ADRD events over 361410 patient-years in non-CKD and 3946 AD/ADRD events over 64806 patient-years in CKD patients. In IPW Cox regression, IG had higher risk of AD/ADRD when compared to GLP1-RA and SGLT2i (Figures).

Conclusions: In both non-CKD and CKD subgroups, IG is associated with higher AD/ADRD risk when compared to SGLT2i and GLP1-RA whereas SGLT2i and GLP1-RA had similar risk.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support



TH-PO1056

Comparative Effectiveness of Semaglutide, Liraglutide, and Dulaglutide for All-Cause Mortality in Type 2 Diabetes (T2D) with and without CKD: An Emulated Clinical Trial Observational Study

Amara Sarwal,[1,2] Guo Wei,[1,2] Sydney E. Hartsell,[1,2] Ravinder Singh,[1,2] Mckenna R. Nevers,[1,2] Niharika Katkam,[1,2] Augustine Takyi,[2] Akhil Ramanujam Chakravartula,[2] Jincheng Shen,[1,2] Srinivasan Beddhu.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

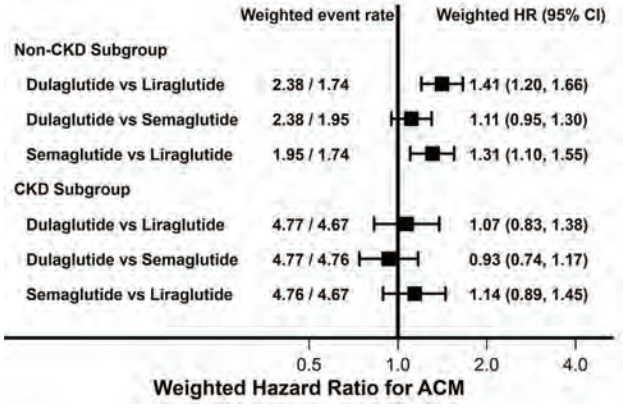
Background: Compared to placebo, semaglutide, liraglutide and dulaglutide reduced the risk of CV events and CV death. However, there is a paucity of data on comparative effectiveness of these agents versus each other. Therefore, we examined the comparive risk of all-cause mortality (ACM) of these agents in a national cohort of veterans with T2D.

Methods: We used the active comparator, new user study design to compare the effect of initiating on semaglutide, liraglutide or dulaglutide on ACM in veterans with T2D on metformin who initiated any one of these three between 01/01/2018 to 12/31/2021 (N=22145). Those with previous use of these agents were excluded. Administrative censor date was 03/31/2023. ACM data were obtained from VA CDW which is also updated with national vital statistics. Generalized propensity score based inverse probability weighting (IPW) was employed to balance baseline variables across the three classes. In IPW Cox models, the study drug classes were related to the risk of mortality in those without and with CKD (eGFR < 60).

Results: 49.1% were initiated on semaglutide, 24.6% on liraglutide and 25.0% on dulaglutide. Mean age was 64 ±11 years, 9% were female and 16.5% were Black. Mean eGFR 81 ± 20. 17.2% had CKD. There were 1081 deaths/54727 years of follow-up in non-CKD and 489 deaths/10606 years in CKD subgroups. In non-CKD subgroup, both dulaglutide and semaglutide had higher hazard of ACM compared to liraglutide whereas dulaglutide and semaglutide had similar hazard (Figure). In CKD subgroup, hazard of ACM was similar across the three pairwise comparisons.

Conclusions: In the non-CKD subgroup, liraglutide had lower hazard of mortality compared to either dulaglutide or semaglutide. However, in the CKD subgroup, all three agents had similar risk of mortality.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support



TH-PO1057

Risk of Gastroparesis Is Higher with Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) but Risk of Death Is Higher with Insulin Glargine in Veterans with Type 2 Diabetes and CKD

Amara Sarwal,[1,2] Ravinder Singh,[1,2] Guo Wei,[1,2] Sydney E. Hartsell,[1,2] Robert E. Boucher,[1,2] Mckenna R. Nevers,[1,2] Niharika Katkam,[1,2] Augustine Takyi,[1,2] Akhil Ramanujam Chakravartula,[1,2] Jincheng Shen,[1,2] Srinivasan Beddhu.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

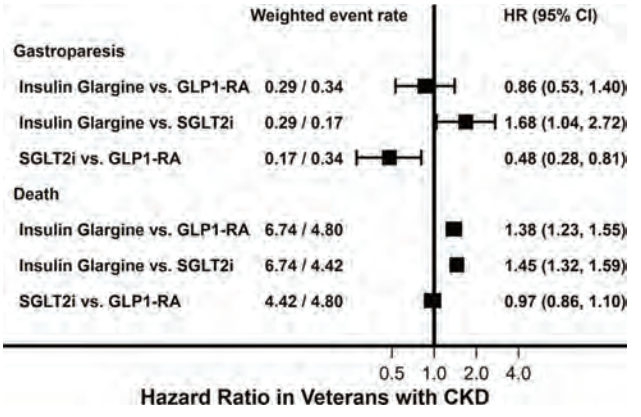
Background: There is a paucity of data on the risk of gastroparesis risk with GLP1-RA compared to insulin glargine (IG) or SGLT2i in T2D with CKD.

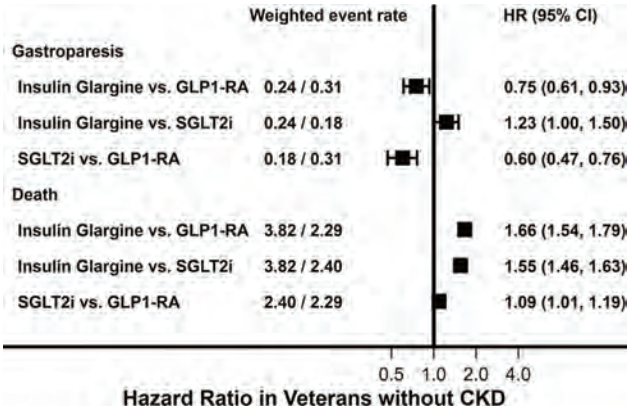
Methods: We used the active comparator, new user design to emulate a trial to compare the effects of IG, GLP1-RA or SGLT2i in veterans with T2D on metformin without baseline GI comorbidities who initiated one of these three agents for the first time between 01/01/18 to 12/31/21. Administrative censor date was 03/31/23. Generalized propensity score based inverse probability weighting (IPW) was employed to control confounding and facilitate comparisons among the drug classes. In IPW Cox models, the study drug classes were related to the risk of gastroparesis and death in those without (N=119945) and with CKD (eGFR < 60, N=23027).

Results: In the CKD cohort, 36% were initiated on IG, 15% on GLP1-RA and 49% on SGLT2i. In IPW Cox regression, IG had a decreased risk of gastroparesis although had a higher risk of death when compared to GLP1-RA (Figures). IG was associated with increased risk of both outcomes when compared to SGLT2i. SGLT2i had a lower risk of gastroparesis and similar risk of death compared to GLP1-RA. Similar trend was seen in the non-CKD subgroup, although SGLT2i was had a higher risk of death compared to GLP1-RA.

Conclusions: As the risk of death with IG is higher, concern for gastroparesis should not prohibit prescription of GLP1-RA over IG in people with T2D and CKD.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support





TH-PO1058

SGLT2 Inhibitors, Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists, and the Risk of Hypokalemia and Hyperkalemia in a National Cohort of Veterans with Type 2 Diabetes

Akhil Ramanujam Chakravartula,[1,2] Sydney E. Hartsell,[1,2] Amara Sarwal,[1,2] Guo Wei,[1,2] Mckenna R. Nevers,[1,2] Robert E. Boucher,[1,2] Niharika Katkam,[1,2] Augustine Takyi,[1,2] Jincheng Shen,[1,2] Tom Greene,[1,2] Srinivasan Beddhu.[1,2] *[1]The University of Utah School of Medicine, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

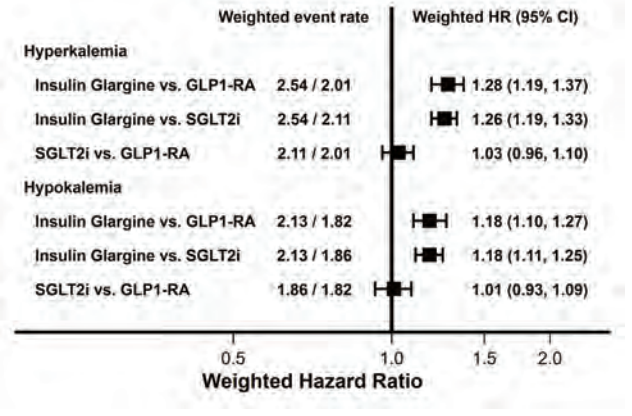
Background: As SGLT2i are osmotic diuretics, they might increase the risk of hypokalemia and decrease the risk of hyperkalemia compared to other glycemic agents such as GLP1-RA or insulin glargine (IG).

Methods: Using the VA Informatics and Computing Infrastructure (VINCI) platform, in an active comparator new user design study, we compared the effects of IG, GLP1-RA, or SGLT2i on the risk of hypo and hyperkalemia. We identified veterans with T2D on metformin who initiated one of these 3 agents of interest for the first time between 1/1/18 to 12/31/21. We excluded those with prior prescriptions for these agents between 1/1/08 to 1/1/18. Index date was defined as the first date one of these agents were prescribed. Baseline demographics, BP, BMI, comorbidity, medications, lab data including eGFR and A1C were extracted. Follow-up was until 3/31/2023. Hyperkalemia and hypokalemia were identified using diagnostic codes. We used generalized propensity score based inverse probability weighting (IPW) to balance baseline variables across the study drug classes. IPW cox regression models related study drug class to outcomes.

Results: The study included 161,405 participants who were 64.9±10.8 years old, 94.6% male, 18.6% black at baseline with mean eGFR of 80± 20ml/min/1.73m^2 and 16.5% with baseline eGFR <60 ml/min/1.73m^2. There were 9,745 hyperkalemic events over 430,841 years of follow up, and 8,455 hypokalemic events over 433,548 years of follow up. The figure shows weighted cox model results of event rates and hazard ratio by pairwise drug comparison.

Conclusions: In veterans with T2D, IG is associated with a higher risk of both hyper- and hypokalemia compared to GLP1-RA or SGLT2i. Both SGLT2i and GLP1-RAs had similar risk of hypo or hyperkalemia.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support



TH-PO1059

Does CKD Modify the Effects of Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) and SGLT2 Inhibitors on Weight Loss?

Shalini Kasera,[1] Sydney E. Hartsell,[1,2] Guo Wei,[1,2] Ravinder Singh,[1,2] Mckenna R. Nevers,[1,2] Amara Sarwal,[1,2] Akhil Ramanujam Chakravartula,[1] Niharika Katkam,[1] Srinivasan Beddhu.[1,2] *[1]The University of Utah School of Medicine, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

Background: It is unknown whether weight loss resulting from a GLP1-RA or SGLT2i is modified by the presence of CKD.

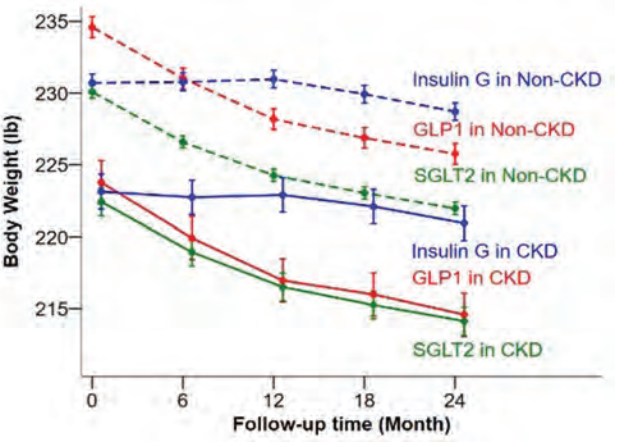
Methods: In an active comparator, new user study, we examined the effects of CKD status on weight loss in veterans with T2D on metformin who began insulin glargine (IG), SGLT2i or GLP1-RA from 1/1/18 to 12/31/21. Index date was the date of initial drug prescription. Outpatient weight closest to the index date and within 1 year prior was defined as baseline weight. Weight change after drug initiation was defined as the difference between baseline weight and an average of all outpatient weights across 6 month intervals after the index date up to 24 months. Follow-up was until 3/31/2023 or 24 months after index date, whichever was earlier. Inverse probability weights (IPW) for each pairwise drug comparison resulted in balance of baseline variables across the drug classes. In IPW mixed effects models, study drug classes were related to weight change at 24 months in pairwise comparisons in non-CKD and CKD (eGFR <60) subgroups. Effect modification was tested by comparing the regression coefficients for each of the pairwise comparisons in non-CKD and CKD subgroups.

Results: Out of 148,920 included veterans, 5.4% were female, 76.1% were white with mean age 64.9±10.7 years, baseline eGFR 80±20 and 16.7% with CKD. The figure shows weight loss at 6 month intervals by drug class and CKD status and the table shows mixed effects model results.

Conclusions: Patients lost significantly more weight on GLP1-RA or SGLT2i compared to insulin glargine, but there was minimal difference in weight change at 2 years between SGLT2i and GLP1-RA. CKD status did not modify weight loss on SGLT2i or GLP1-RA.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support

Pairwise Comparison	Weight Difference at 24 Months (pounds) in Non-CKD Subgroup	Weight Difference at 24 Months (pounds) in CKD subgroup	Interaction P-Value for CKD Status on Drug-Based Weight Change
IG v. GLP1-RA	6.82(6.41, 7.22)	6.98(6.10, 7.87)	0.74
IG v. SGLT2i	6.13(5.80, 6.46)	6.09(5.40, 6.79)	0.93
SGLT2i v. GLP1-RA	0.69(0.32, 1.06)	0.89(0.09, 1.70)	0.65



TH-PO1060

Effects of Glucagon-Like Peptide 1 Agonists (GLP-1 RAs) on Ectopic Fat Deposition in CKD: A Pilot and Feasibility Study (GLIMP)

Ragibe Gulsah Dilaver,[1] Rachelle Crescenzi,[3] Rengin Elsurer Afsar,[2] Jorge Gamboa,[1] Talat Alp Ikizler.[1] *[1]Vanderbilt University Medical Center, Department of Medicine, Nashville, TN; [2]Saint Louis University Department of Internal Medicine, St Louis, MO; [3]Vanderbilt University Medical Center, Nashville, TN.*

Background: Ectopic fat deposition, including intermuscular adipose tissue (IMAT), is associated with metabolic derangements such as insulin resistance (IR) and inflammation in patients with CKD. GLP-1RA reduces ectopic fat deposition in patients with type 2 diabetes and obesity. In a pilot and feasibility study, we aimed to test whether dulaglutide administration decreases IMAT accumulation and improves physical performance in patients with stage 3-4 CKD.

Methods: We prospectively enrolled 7 patients with stage 3-4 CKD serving as their own controls. Dulaglutide (1.5 mg/week) was administered for 12 weeks. IMAT accumulation in the quadriceps muscle using magnetic resonance imaging, biochemical markers including markers of inflammation and insulin resistance, and physical performance were measured before and after administration.

Results: Participant demographics were as follows: age 59 ± 8 years, BMI 31.4 ± 4.1 kg/m2, 57.1% female, and baseline eGFR 31.7 ± 9.0 mL/min/1.73m2. Two patients had type 2 diabetes. IMAT accumulation was 0.104 ± 0.041 before treatment and 0.095 ± 0.033 after treatment (p = 0.69), **(Figure 1)**. BMI levels were significantly lower after the treatment (p < 0.001). There were no statistically significant differences in HbA1c, Hs-CRP, total cholesterol, triglyceride concentrations, short physical performance battery test scores before and after treatment **(Table 1).** Medication was well tolerated except one participant stopped early due to nausea and one due to injection site drug reaction.

Conclusions: In this pilot and feasibility study in patients with stage 3-4 CKD, 12 weeks of dulaglutide administration decreased IMAT accumulation numerically but the difference did not reach statistical significance. The medication was well tolerated. Larger studies are needed to examine the metabolic effects GLP-1RAs in patients with CKD.

Funding: NIDDK Support, Veterans Affairs Support

Figure 1. Comparison of IMAT Before and After Treatment

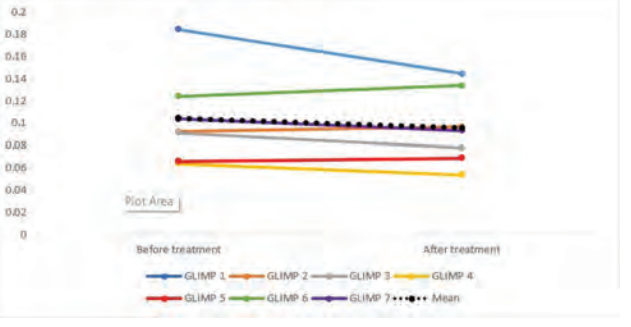


Table 1. Study parameters before and after treatment

Parameters	Before treatment	After treatment	p-value
BMI (kg/m2)	35.4 ± 4.1	32.3 ± 3.9	< 0.001
Hba1c (%)	6.2 ± 1.2	5.6 ± 0.7	0.27
SPPB test score	9.1 ± 1.4	9.1 ± 1.9	0.93
Hs-CRP (mg/L)	12.3 ± 6.9	10.6 ± 7.1	0.65
TNF-α (pg/mL)	5.54 ± 3.39	5.33 ± 4	0.86
IL-6 (pg/mL)	4.01 (3.185 – 5.87)	3.37 (1.65 – 6.56)	0.71
Total cholesterol (mg/dL)	183.5 ± 29.8	161.4 ± 32.8	0.21
Triglyceride (mg/dL)	186.9 ± 61.2	168.1 ± 60.6	0.57

TH-PO1061

Trial Design and Baseline Characteristics from REMODEL: A Mechanistic Study of Semaglutide vs. Placebo in People with Type 2 Diabetes and CKD

David Cherney,[1] Petter Bjornstad,[2,3] Milenta M. Chacko,[4] Thomas P. Gunnarsson,[5] Jeffrey B. Hodgin,[6] Matthias Kretzler,[6] Nicolas Belmar,[5] Menno Pruijm,[7] Philip A. Schytz,[5] Katherine R. Tuttle.[2] *[1]University Health Network, Toronto, ON, Canada; [2]University of Washington, Seattle, WA; [3]University of Colorado Anschutz Medical Campus, Aurora, CO; [4]Novo Nordisk GBS India, Bangalore, India; [5]Novo Nordisk A/S, Bagsvaerd, Denmark; [6]University of Michigan Michigan Medicine, Ann Arbor, MI; [7]Universite de Lausanne, Lausanne, Switzerland.*

Background: Type 2 diabetes (T2D) is the leading cause of chronic kidney disease (CKD) and kidney failure globally. Semaglutide, a glucagon-like peptide-1 receptor agonist, reduces risks of major kidney, cardiovascular, and mortality outcomes in people with T2D and CKD as shown in the FLOW trial. Despite the clinical benefits, the precise kidney-specific mode-of-action (MoA) of semaglutide remains unclear.

Methods: REMODEL is a 52-week phase 3b trial investigating the kidney-specific MoA for semaglutide (once-weekly subcutaneous 1.0 mg) vs. placebo in people with T2D and CKD (Figure 1). Primary endpoints are magnetic-resonance imaging (MRI)-based measures of changes in kidney oxygenation, global kidney perfusion, inflammation and fibrosis. A subset of participants opted to undergo sequential kidney biopsies both at baseline and at the end of treatment for tissue-based interrogation including single nucleus transcriptomics, pathology, and morphometric examination.

Results: REMODEL enrolled 106 participants across 8 countries (Table 1). All participants were prescribed concomitant medications at baseline with 98.1% using RAAS inhibition, and 38.7% using SGLT2i. Baseline kidney biopsies were performed in 33 participants with characteristics similar to the entire cohort.

Conclusions: REMODEL will comprehensively assess multiple proposed physiological pathways for the kidney-specific MoA of semaglutide and will help elucidate kidney-specific benefits seen in the FLOW trial. The REMODEL trial has successfully enrolled a representative population of people with T2D and CKD, ensuring the generalizability and clinical relevance of the findings.

Funding: Commercial Support - NOVO NORDISK AS

Variable	Full population N=106	Biopsy sub-group N=33
Age, years (SD)	65.3 (9.9)	65.4 (10.3)
Male participants, N (%)	81 (76.4)	29 (87.9)
Body weight, kg (SD)	89.6 (18.9)	92.9 (15.2)
BMI, kg/m² (SD)	30.8 (5.7)	30.7 (6.4)
HbA_{1c}, % (SD)	7.1 (0.9)	7.1 (1.0)
Duration of diabetes, years (SD)	14.7 (8.2)	15.3 (8.4)
Creatinine-based eGFR, mL/min/1.73 m² (SD)	51.1 (10.4)	53.5 (9.9)
Cystatin C-based eGFR, mL/min/1.73 m² (SD)	42.3 (12.3)	43.7 (13.6)
Median UACR, mg/gram (IQR)	187.6 (60.2 ; 546.0)	150.4 (54.0 ; 463.7)
RAAS blocker use, N (%)	104 (98.1)	33 (100)
SGLT2i use, N (%)	41 (38.7)	19 (57.6)

Table 1. Summary of baseline characteristics reported in REMODEL for all participants and the biopsy sub-group. Creatinine-based and Cystatin C-based eGFR were calculated per CKD-EPI 2009 equation. Data reported with standard deviation (SD), inter-quartile range (IQR) or percentage (%).

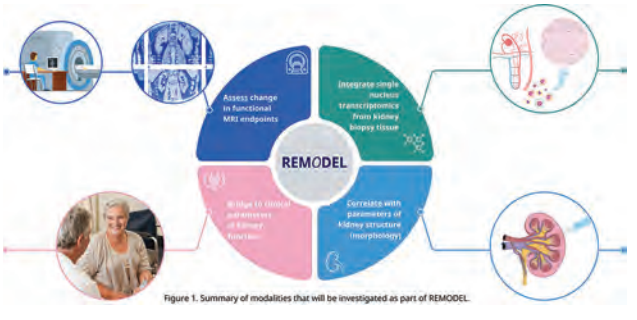


Figure 1. Summary of modalities that will be investigated as part of REMODEL.

TH-PO1062

Effect of Spironolactone on Long-Term Outcomes in Patients with CKD

Tz-Heng Chen,[1,2] Shuo-ming Ou,[1,3] Yuan-Chia Chu,[1] Der-Cherng Tarng.[1] *[1]Taipei Veterans General Hospital, Taipei, Taiwan; [2]National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan; [3]National Institutes of Health, Bethesda, MD.*

Background: Steroidal mineralocorticoid receptor antagonists (MRAs) have been shown to reduce mortality in patients with heart failure with reduced ejection fraction, while also effectively treating resistant hypertension and lowering proteinuria. However, the effects of steroidal MRAs on patients with chronic kidney disease (CKD) remain uncertain. This study aimed to investigate the impact of spironolactone on long-term outcomes among CKD patients.

Methods: In a retrospective cohort study, we identified patients with CKD stage 3–5 from January 1, 2011, to June 30, 2023. The patients were divided into spironolactone user and nonuser groups. We matched each spironolactone user to two nonusers according to propensity scores. The outcomes of interest included end-stage renal disease (ESRD), major adverse cardiovascular events (MACEs), all-cause mortality, and severe hyperkalemia. MACEs were defined as a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death.

Results: After propensity score matching, 2,711 spironolactone users and 5,422 nonusers were included in the analyses. Compared with nonusers, the spironolactone users exhibited higher risks of all-cause mortality (adjusted hazard ratio [aHR], 1.23; 95% confidence interval [CI], 1.10–1.37) and severe hyperkalemia (aHR, 1.44; 95% CI, 1.23–1.68). However, there was a lower risk of MACEs (aHR, 0.89; 95% CI, 0.81–0.98), primarily due to a significant reduction in stroke risk (aHR, 0.78; 95% CI, 0.70–0.87). The risk of ESRD was similar between the two groups (aHR, 1.07; 95% CI, 0.84–1.37).

Conclusions: In patients with CKD, spironolactone use was associated with increased risks of all-cause mortality and severe hyperkalemia, and a reduced risk of MACE, primarily driven by a decrease in stroke risk. The risk of ESRD remained unchanged.

Risks of end-stage renal disease, major adverse cardiovascular events, all-cause mortality and severe hyperkalemia between spironolactone users versus matched nonusers

	Spironolactone users			Spironolactone nonusers						
Outcomes	No. of Events	Person-years	Incidence Rate*	No. of Events	Person-years	Incidence Rate*	HR (95% CI)	p value	adjusted HR† (95% CI)	p value
End-stage renal disease‡	113	10483	1.08	182	20898	0.87	1.23 (0.97-1.56)	0.081	1.07 (0.84-1.37)	0.581
MACE	663	8620	7.69	1341	17089	7.85	0.98 (0.89-1.08)	0.678	0.89 (0.81-0.98)	0.018
Myocardial infarction	192	10268	1.87	227	20855	1.09	1.71 (1.41-2.07)	<0.001	1.49 (1.22-1.82)	<0.001
Stroke	507	9039	5.61	1172	17582	6.67	0.85 (0.76-0.94)	0.002	0.78 (0.70-0.87)	<0.001
Cardiovascular death	178	10758	1.65	278	21447	1.30	1.27 (1.06-1.54)	0.011	1.01 (0.83-1.23)	0.920
All-cause mortality	613	10758	5.70	878	21447	4.09	1.39 (1.25-1.54)	<0.001	1.23 (1.10-1.37)	<0.001
Severe hyperkalemia	329	10656	3.09	381	21468	1.77	1.75 (1.51-2.03)	<0.001	1.44 (1.23-1.68)	<0.001

TH-PO1063

Effect of the RAS Inhibitors on Kidney Outcomes in Patients with Advanced CKD: A Systematic Review and Meta-Analysis

Kavita Jintanapramote, Rathanon Leevongsakorn, Anan Chuasuwan. *Bhumibol Adulyadej Hospital, Bangkok, Thailand.*

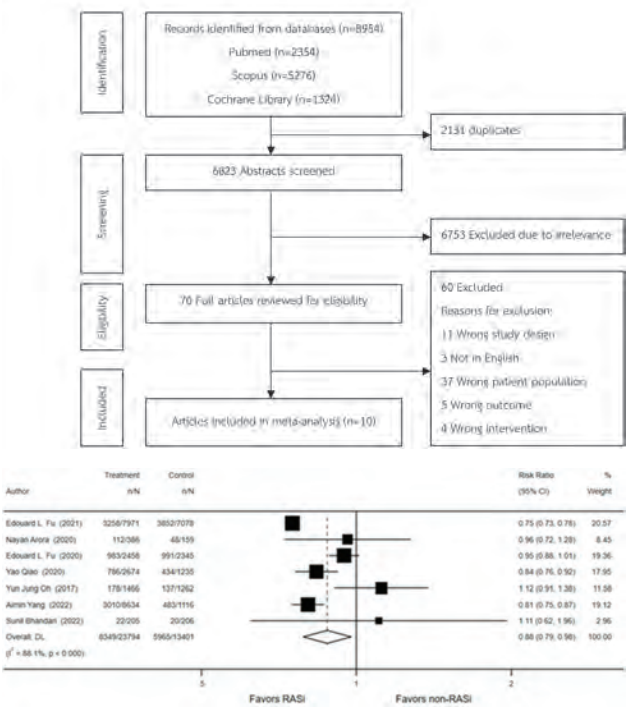
Background: Chronic kidney disease (CKD) is a global health concern, with Renin-Angiotensin System inhibitors (RASi) playing a crucial role in slowing CKD progression. However, the efficacy and safety of advanced CKD (eGFR <30 ml/min per 1.73 m^2) are still controversial. This study aims to evaluate the impact of RASi on kidney function and outcomes in this specific population.

Methods: We conducted a literature search in MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials until September 2023 in search of studies comparing the effects of receiving RASi versus non-receiving RASi in advanced CKD patients on kidney progression, all-cause mortality, major adverse cardiovascular events (MACEs), hyperkalemia, and heart failure.

Results: A total of ten studies, including 60,212 participants, were included. Analysis revealed no statistically significant difference in kidney progression [risk ratio (RR) 1.08 (95% CI: 0.95-1.23)] or MACEs [RR 0.95 (95% CI: 0.81–1.0)] between receiving RASi and non-receiving RASi. However, a significant decrease in all-cause mortality was observed in patients receiving RASi [RR 0.88 (95% CI: 0.79–0.98)]. Conversely, the analysis indicated a significant increase in adverse events in RASi usage, including hyperkalemia [RR 1.29 (95% CI: 1.15–1.43)] and heart failure [RR 1.35 (95% CI: 1.16–1.56)].

Conclusions: The use of RASi in advanced CKD has shown benefits in reducing all-cause mortality without exacerbating kidney disease progression. However, employing RASi may also lead to complications such as hyperkalemia and potential heart failure, necessitating caution and diligent monitoring.

Figure 1 PRISMA flow diagram



TH-PO1064

Impact of Renin-Angiotensin-Aldosterone-System Inhibition on Advanced CKD: A Retrospective Observational Study

Lukas Westermann,[1] Janis M. Nolde,[1] Frederic Arnold,[1,2] Thomas Welte.[1]
[1]Department of Medicine IV, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [2]Institute for Microbiology and Hygiene, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany.

Background: Therapeutic renin-angiotensin-aldosterone system inhibition (RAASi) slows chronic kidney disease (CKD) progression in mild and moderate CKD, but was thought to be unfavorable in advanced CKD. In contrast, recent data from a randomized controlled trial demonstrated that RAASi does not modulate kidney function decline in advanced CKD. Due to limited real-world data, this study investigates effects of RAASi on kidney function decline in advanced CKD in a comparably large cohort.

Methods: This single-center retrospective observational study presents data from 951 individuals with advanced CKD (estimated glomerular filtration rate [eGFR] 15-30 ml/min/1.73 m^2) treated with or without RAASi, incorporating 1.298 treatment intervals over a median follow-up period of 19 months (interquartile range: 8-44). The primary endpoint was defined as time to manifestation of ESRD (eGFR <15 ml/min/1.73 m^2) and was analyzed using interval- and right-censored datasets. Patients receiving RAASi were compared to those not receiving RAASi using univariate and covariate-adjusted time-to-event analysis. Covariate-adjusted hazard ratios (HR) were estimated for covariates comprised of several discrete (sex, CKD diagnosis) and continuous variables (year of inclusion, age, eGFR, urin-protein-creatinine-ratio [UPCR], BMI, mean arterial pressure, hemoglobin and serum potassium), applying multivariate parametric regression models.

Results: Univariate time-to-event analysis revealed a statistically significant yet clinically negligible difference in the median time to ESRD between the RAASi vs. non-RAASi group (p<0.001), with 7.0 years [95% CI: 4-NA] vs. 7.19 years [95% CI: 5.62-NA], respectively. Covariate adjusted analysis did not confirm an association of RAASi and kidney function decline (HR 0.90 [95% CI: 0.65-1.24], p=0.506). Higher eGFR (HR 0.75 [95% CI: 0.72-0.78], p<0.001) was associated with slower kidney function decline. Increased UPCR (HR 1.18 [95% CI: 1.12-1.24], p<0.001) was associated with faster kidney function decline.

Conclusions: RAAS inhibition is not associated with slower kidney function decline in advanced CKD. This study supports the continuation of therapeutic RAAS inhibition in advanced CKD, if clinically indicated. **FA and TW contributed equally.*

Funding: Government Support - Non-U.S.

TH-PO1065

Mineralocorticoid Receptor Antagonist (MRA) Use Patterns following Potassium Binder Initiation: Insights from the DEMONSTRATE Database

Hans Furuland,[1] Anders Larsson,[1] Milica Uhde,[2] Matilda Almstedt,[2] Thomas Cars,[2] Maria K. Svensson.[1] *[1]Uppsala Universitet, Uppsala, Sweden; [2]CLS Vifor, Uppsala, Sweden.*

Background: Hyperkalemia (HK) is a common in chronic kidney disease (CKD). Mineralocorticoid receptor antagonists (MRAs) provide significant cardiovascular and renal benefits but can exacerbate HK. HK often leads to the reduction or discontinuation of MRA therapy. This study aims to investigate the treatment pattern of MRA following initiation of treatment with potassium binders.

Methods: From the DEMONSTRATE database (six regions in mid-Sweden) patients with at least one pharmacy dispensation of first (sodium polystyrene sulfonate, SPS) or second-generation (patiromer or sodium zirconium cyclosilicate, SZC) potassium binders between 2005 and 2022 were selected, prescriptions were estimated and treatment episodes were established.

Results: 2,146 and 280 patients were treated with MRA and initiated first and second-generation K+ binders. The second-generation users tended to have a higher comorbidity profile. 26% had an overlapping comorbid profile of hypertension, heart failure, diabetes mellitus and CKD. Persistence to potassium binder treatment was higher among second generation users; median persistence was 87.5 and 112.5 days for first and second generation respectively. After 120 days 33% had discontinued MRA and after 240 days more than 50% (Figure 1).

Conclusions: MRA-treated patients had a high comorbidity profile and compared to the first-generation potassium binders, patients initiating second generation potassium binders had more comorbidities and longer K+ binder treatment duration. Overall, potassium binder users still dose reduced MRA to a large degree. Whether second generation binders lead to more persistent MRA use remains to be elucidated.

Funding: Commercial Support - CLS Vifor

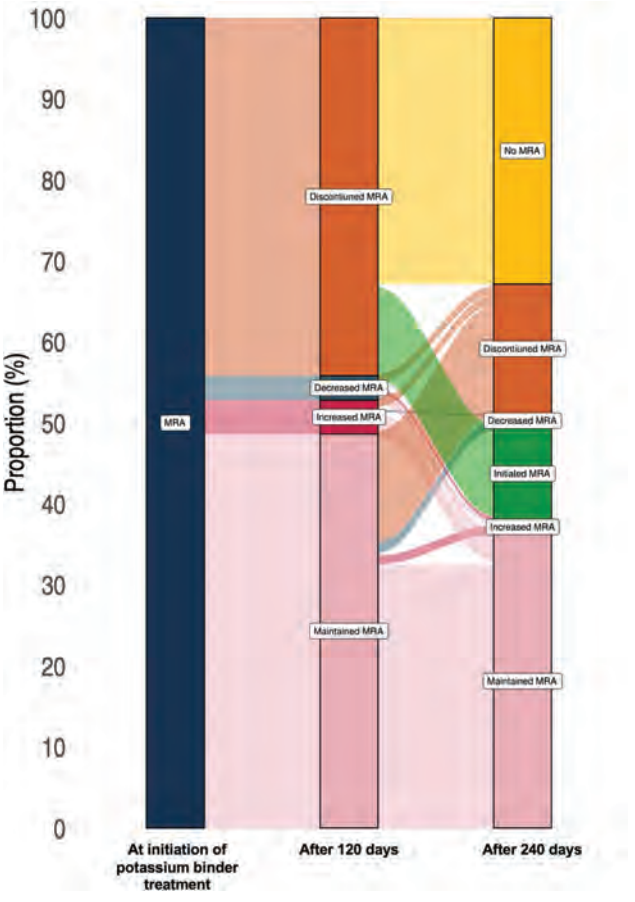


Figure 1 – Treatment pattern of MRA after initiation of potassium binder treatment

TH-PO1066

Effect of Ultrasound Renal Denervation in Patients with CKD: A Matched-Controlled Analysis of the RADIANCE Clinical Trial Program

Roland E. Schmieder,[1] Michel Azizi,[2] Debbie L. Cohen,[3] Samantha Rogers,[4] Maureen Mcguire,[4] Candace Mcclure,[5] Ajay J. Kirtane.[6] *[1]University Hospital Erlangen, Erlangen, Germany; [2]Universite Paris-Descartes, Paris, France; [3]University of Pennsylvania, Philadelphia, PA; [4]Recor Medical, Palo Alto, CA; [5]North American Science Associates Inc, Minneapolis, MN; [6]Columbia University Irving Medical Center, New York, NY.*

Background: In CKD patients, hyperactivation of the sympathetic nervous activity exacerbates hypertension. Ultrasound renal denervation (uRDN), known to decrease SNS activity, has been shown to lower blood pressure (BP) in hypertension patients. In addition, pilot studies indicate that uRDN could lower BP among CKD patients.

Methods: The RADIANCE clinical program included 3 randomized controlled studies that compared uRDN to sham control in 506 mild-to-moderate and resistant hypertensive patients. Patients were eligible for randomization if daytime ambulatory BP (dABP) was ≥135/85 mmHg after a 4-week stabilization/washout period and eGFR was ≥40 ml/min/1.73m^2. In a matched analysis, the BP response 2 months after uRDN or sham was compared between patients with eGFR<60 (CKD n=28: 16 uRDN and 12 sham) and patients with eGFR ≥60 (non-CKD n=28: 16 uRDN and 12 sham) who were matched on cohort, treatment arm, sex, race, age (± 8 years), and baseline daytime ambulatory systolic BP (dASBP) (±15mmHg).

Results: In this cohort, 79% were men; 21% were black; and average age was 59 years. At baseline, dABP was 150.8/93.5±10.4/7.0 mmHg vs. 153.4/94.0±9.9/7.8 mmHg (p=0.333), median antihypertensive medications defined daily dose was 2.0 vs 2.5 (p=0.565), and eGFR was 53.2±4.9 vs. 77.6±12.2 ml/min/1.73m^2 (p<0.001) in CKD vs. non-CKD patients, respectively. At 2-months, there were no differences in changes in dASBP from baseline -7.7±18.7 mmHg vs. -8.7±11.3 or office systolic BP -7.6±19.4 vs. -5.1±17.9 in CKD vs. non-CKD, respectively. Changes in eGFR at 2 months were CKD: +7.4±11.0 vs. non-CKD + 2.2±9.6 (baseline-adj p=0.804). Results were similar when comparing the patients with uRDN only: neither dASBP nor office BP differed between CKD and non-CKD patients. Among CKD only patients, the mean difference in dASBP reduction between uRDN and sham at 2-months was -11.1 mmHg (95% CI: -25.3, 3.1; p adj=0.119) and diastolic ambulatory BP -8.0 mmHg (95% CI: -16.4, 0.3; p adj=0.007).

Conclusions: Among patients with mild CKD in the RADIANCE trials, uRDN reduces BP to the same magnitude in both CKD and non-CKD patients while eGFR was not adversely affected. This analysis supports the use of uRDN in patients with uncontrolled RDN who have stage 3 CKD (40-60 ml/min/1.73m^2).

Funding: Commercial Support - Recor Medical

TH-PO1067

The Acute Kidney Function Change with Fenofibrate Is Not Damaging: A Post Hoc Analysis of the FIELD Trial

Alexandra Gallagher,[1,2] Rachel L. O'Connell,[2] George Mangos,[1,4] Brendan Smyth,[1,2] Anthony C. Keech,[5,2] Meg Jardine.[3,2] The FIELD Investigators. *[1]St George Hospital Department of Renal Medicine, Kogarah, NSW, Australia; [2]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [3]Concord Repatriation General Hospital, Concord, NSW, Australia; [4]University of New South Wales Medicine & Health, Sydney, NSW, Australia; [5]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia.*

Background: Several agents known to protect against chronic kidney disease have been associated with an initial decline in the estimated Glomerular Filtration Rate (eGFR). Studies on sodium-glucose cotransporter-2 inhibitors have shown that these initial eGFR dips are not harmful, although the analyses were conducted after randomization. Fenofibrate, on the other hand, leads to an acute, reversible eGFR decline through non-glomerular mechanisms. In a trial where the acute eGFR response to fenofibrate was assessed before randomization, the aim was to test whether this initial acute eGFR decline could predict potential benefits.

Methods: The FIELD trial randomised adults to fenofibrate or placebo. All participants were exposed to an active run-in. The Acute Fenofibrate Response (AFR) was measured and categorised as nil, mild, moderate, or large (increase/no change, 0-10%, 10-20%, >20% eGFR decline). Subgroup analyses were conducted for several cardiovascular outcomes, mortality, a clinical kidney endpoint (doubling serum creatinine, eGFR <15ml/min/1.73m^2, renal related death, or kidney replacement therapy), and total (baseline to study close) and chronic (4 months post-randomisation to study close) eGFR slopes, with heterogeneity assessed using a test of trend.

Results: In 9777 participants, fenofibrate therapy did not reduce coronary events with no evidence of treatment modification by acute eGFR decline category (overall HR 0.89 [95% CI 0.75 to 1.05]); nil, mild, moderate, and large acute decline: 1.08, 0.77, 1.02 and 0.82 respectively, p-trend 0.997). AFR category did not predict harm for clinical kidney, total cardiovascular events (Figure 1) nor for total microvascular events, or all-cause mortality (p-trend 0.46 and 0.95, respectively). Subgroups of greater AFR experienced more improvement on chronic eGFR slope, and the reverse trend for total slope (p-trend <0.0001 and 0.01, respectively).

Conclusions: There was no evidence that greater acute eGFR decline leads to fenofibrate-associated harm for a range of clinically meaningful endpoints.

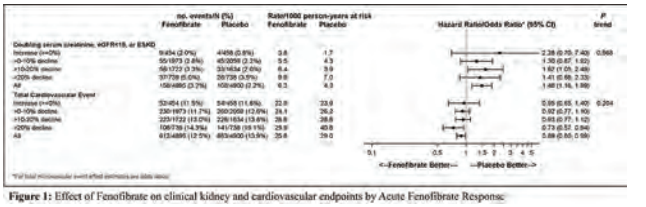


Figure 1: Effect of Fenofibrate on clinical kidney and cardiovascular endpoints by Acute Fenofibrate Response

TH-PO1068

Association of Fibrate Use with Greater Survival Independent of Baseline Kidney Function and Albuminuria

Rina Takahashi,[1] Jenny I. Shen,[1] Diana Tran,[1] Ibrahim Elali,[1] Tiane Dai,[1] Keiichi Sumida,[2] Fridtjof Thomas,[2] Connie Rhee,[3] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]The Lundquist Institute, Torrance, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]University of California Los Angeles, Los Angeles, CA.*

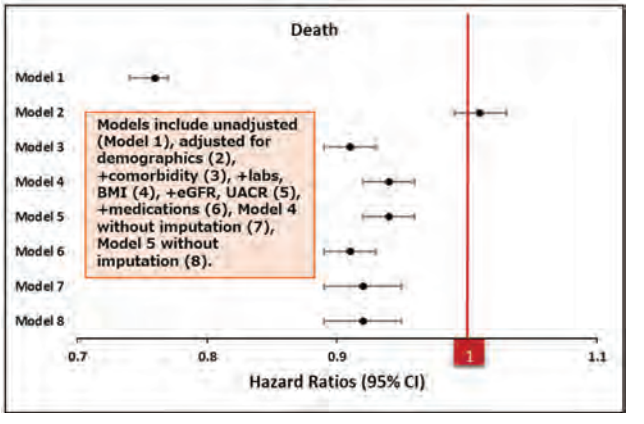
Background: Fibrate use can result in an acute increase in serum creatinine, making assessing long-term outcomes associated with fibrates difficult. Additionally, some studies reported no change, and others showed improved mortality with fibrate use. This study aims to examine the association of fibrate use with death independent of changes in serum creatinine levels in a large national cohort of United States (US) Veterans with long follow-ups.

Methods: A retrospective cohort study was conducted to examine the association of de novo prescription of fibrate medications during the baseline period with death over 14 years. Patients (n=688,382) were selected from Veterans Administration (VA) research databases if they had data on albuminuria from 2004 to 2006. Associations were examined in Cox proportional hazard models adjusted for demographics, major comorbidities, and laboratory data, including baseline estimated glomerular filtration rate (eGFR), albuminuria, and medications.

Results: We identified 58,773 incident new fibrate users. The overall mean (SD) age was 59 (13) years, with 6.6% female, 17.9% Black, and 7.0% Hispanic, and baseline triglycerides of 119 (81, 181) mg/dl (users 334 (228, 497), non-users 112 (79, 163)) mg/dl. Fibrate users were more likely to be male, White, current smokers, and had higher frequencies of comorbidities. Fibrate use (vs. non-use) was associated with a lower risk of death (Hazard ratio (HR): 0.91, 95% confidential interval [CI]: 0.89-0.93).

Conclusions: In this large national cohort of US Veterans with long follow-up, fibrate use was associated with a lower risk of death independent of baseline renal function and albuminuria. Further studies are needed to corroborate the potential benefits of fibrate on survival.

Funding: Veterans Affairs Support



TH-PO1069

Kidney Safety of Prescribed Oral Fibrates in Veterans without CKD

Rina Takahashi,[1] Jenny I. Shen,[1] Diana Tran,[1] Ibrahim Elali,[1] Tiane Dai,[1] Keiichi Sumida,[2] Fridtjof Thomas,[2] Connie Rhee,[3] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]The Lundquist Institute, Torrance, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]University of California Los Angeles, Los Angeles, CA.*

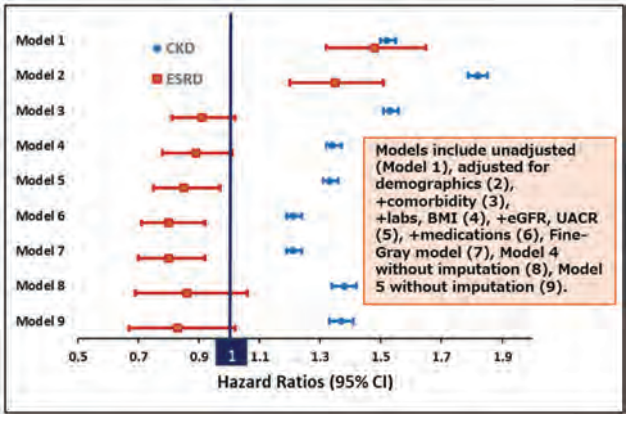
Background: Prescribing fibrate medications can result in an acute increase in serum creatinine, making assessing renal outcomes associated with fibrates difficult. There is limited research on certain renal outcomes, and past studies have mixed results. This study aims to examine the association of fibrate use with incident chronic kidney disease (CKD) and incident end-stage renal disease (ESRD) in a large national cohort of veterans of the United States (US) who have long follow-ups.

Methods: A retrospective cohort study examined the association of de novo prescription of fibrate medications during the baseline period with incident CKD and ESRD over 14 years. Patients (n=688,382) were selected from VA databases if they had albuminuria data from 2004 to 2006. Cox proportional hazard models (Model 2-6) and Fine-Gray competitive risk models (Model 7, competing events: ESRD, death) were used and adjusted for demographics, major comorbidities, labs, baseline estimated glomerular filtration rate (eGFR), albuminuria, and medications.

Results: We identified 58,773 incident new fibrate users. The overall mean (SD) age was 59 (13) years, with 6.6% female, 17.9% Black, and 7.0% Hispanic, and baseline triglycerides of 119 (81, 181) mg/dl (users 334 (228, 497), non-users 112 (79, 163)) mg/dl. Fibrate users were more likely to be male, White, current smokers, and had higher frequencies of comorbidities. Fibrate use (vs. non-use) was associated with a higher risk of CKD (Model 6, Hazard ratio (HR): 1.21, 95% confidential interval [CI]: 1.19-1.24) but with a lower risk of ESRD (Model 6, HR: 0.80, 95% CI: 0.71-0.92). Fine-gray models showed similar results (Model 7).

Conclusions: In this large national cohort of US Veterans with long follow-up, fibrate use was associated with a higher risk of incident CKD but a lower risk of ESRD. Further studies are warranted to corroborate the potential benefits of fibrate on kidney function.

Funding: Veterans Affairs Support



TH-PO1070

Examining the Associations between Incident Niacin Therapy and Kidney Outcomes

Rina Takahashi,[1] Thuy-Anh Bui,[4] Ibrahim Elali,[1] Diana Tran,[1] Keiichi Sumida,[2] Fridtjof Thomas,[2] Ramanath B. Dukkipati,[1] Anuja P. Shah,[1] Connie Rhee,[3] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]The Lundquist Institute, Torrance, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]University of California Los Angeles, Los Angeles, CA; [4]University of California Irvine, Irvine, CA.*

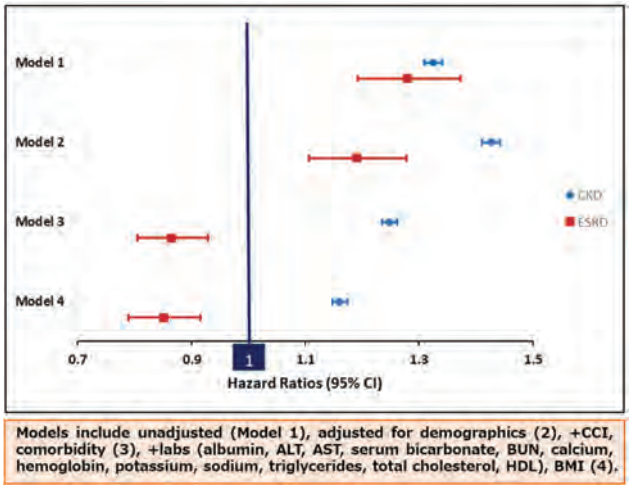
Background: Despite the favorable data shown in studies of niacin, a lipid-lowering medication that can lower triglycerides and improve other risk factors for renal outcomes, its effect on long-term outcomes remains to be determined. This study aims to examine the associations of niacin therapy with incident chronic kidney disease (CKD) and end-stage renal disease (ESRD) in patients with normal renal function.

Methods: In a nationwide historical cohort of 1,139,630 US Veterans with normal baseline eGFR, we examined the association of de novo prescription of niacin from 2004 to 2006 with incident CKD (defined as eGFR <60 ml/min/1.73m2 on two occasions, separated by ≥90 days) and ESRD during the 14-year follow-up. Associations were examined in Cox proportional hazard models adjusted for demographics, major comorbidities, and laboratory measurements. Prescription time-distribution matching was used to control for survival bias.

Results: We identified 133,450 new users of niacin. Overall, patients (n=1,139,630) had a mean (standard deviation; SD) age of 60 (13) years, with 6% female, 78% White, 16% Black, and 6% Hispanic. Niacin users were more likely to be male, White, current, or former smokers, with higher frequencies of comorbidities. Niacin use (vs. non-use) was associated with a higher risk of CKD (Hazard ratio [HR]: 1.16, 95% confidential interval [CI]: 1.15-1.17) but a lower risk of ESRD (HR: 0.85, 95% CI: 0.79-0.92).

Conclusions: In a large national cohort of US Veterans with normal kidney function, niacin use was associated with a higher risk of incident CKD but a lower risk of ESRD. Additional studies are warranted to examine the potential effect of niacin on renal function.

Funding: Veterans Affairs Support



TH-PO1071

Association of Prescribed Bicarbonate Therapy with Incident Kidney Failure in Veterans with CKD

Diana Tran,[1] Rina Takahashi,[1] Ibrahim Elali,[1] Jenny I. Shen,[1] Ramanath B. Dukkipati,[1] Anuja P. Shah,[1] Prabin Shrestha,[2] Fridtjof Thomas,[2] Keiichi Sumida,[2] Connie Rhee,[3] Kamyar Kalantar-Zadeh,[1] Csaba P. Kovesdy.[2] *[1]The Lundquist Institute, Torrance, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]University of California Los Angeles, Los Angeles, CA.*

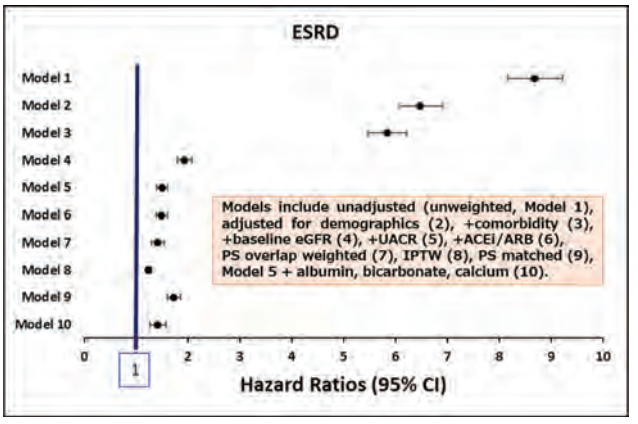
Background: Treatment of metabolic acidosis may delay the renal function decline in patients with chronic kidney disease (CKD), but the effects of bicarbonate on CKD progression to end-stage renal disease (ESRD) in unselected populations with all stages of CKD remain unclear. We examined the association of bicarbonate use with incident ESRD in a large national cohort of United States (US) Veterans.

Methods: In a cohort of 50,540 patients with incident CKD (eGFR <60 mL/min/1.73m^2), we examined the association of de novo bicarbonate prescription with incident ESRD (defined as initiation of renal replacement therapy) during the 14-year follow-up using Cox proportional hazard models adjusted for demographics, major comorbidities, baseline eGFR, urine albumin-creatinine ratio (UACR), and use of renin angiotensin-system inhibitors. Additionally, propensity score (PS) overlap weighting, inverse probability of treatment weighting (IPTW), and PS matching were used to reduce confounding.

Results: We identified 11,896 incident bicarbonate users. Overall mean age was 65, with 3.0% female, 15.3% Black, and 5.5% Hispanic, baseline serum bicarbonate of 24.2±4.4 (users 20.2±3.7, non-users 26.1±3.4) mEq/L, and eGFR of 35.5±11 mL/min/1.73m^2. Bicarbonate users were more likely to be male, Black, current smokers, had higher frequencies of diabetes and liver disease, and lower eGFR compared to non-users. Bicarbonate use (vs. non-use) was associated with a higher risk of incident ESRD in the fully adjusted model (HR: 1.48, 95% CI: 1.38-1.60), PS overlap weighting (1.41, 1.29-1.55), IPTW (1.24, 1.19-1.29), and PS matching (1.72, 1.61-1.85).

Conclusions: In this large national cohort of US Veterans with long follow-up, bicarbonate use was associated with a higher risk of incident ESRD. Further studies are needed to test the effects of bicarbonate replacement on CKD progression.

Funding: Veterans Affairs Support



TH-PO1072

Effect of Sodium Bicarbonate on Blood N-terminal Pro B-type Natriuretic Peptide (NT-proBNP) and Fetuin Levels: A Secondary Analysis of the VA-Bicarb Trial

Paola Gudino,[1] Seiji Koike,[2] Jodi A. Lapidus,[2] Daniela A. Arrieta-Asmadt,[3] Mirela A. Dobre,[4] Matthew K. Abramowitz,[5] Thomas H. Hostetter,[6] Alfred K. Cheung,[3] Wei Chen,[5] Michal L. Melamed,[7] Kalani L. Raphael.[3]
[1]New York City Health and Hospitals Corporation, New York, NY; [2]Oregon Health & Science University, Portland, OR; [3]University of Utah Health, Salt Lake City, UT; [4]University Hospitals, Cleveland, OH; [5]Albert Einstein College of Medicine, Bronx, NY; [6]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [7]New York University, New York, NY.

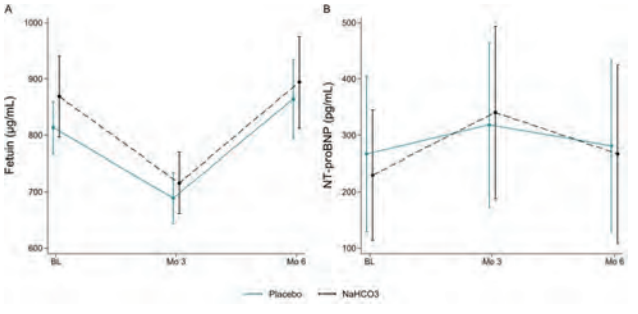
Background: NaHCO3 is often used to treat metabolic acidosis in chronic kidney disease (CKD). However, NaHCO3 has been hypothesized to cause fluid retention and increase risk of vascular calcification. We conducted a secondary analysis of the VA-Bicarb Trial to determine the effect of NaHCO3 on blood N-terminal pro-b-type natriuretic peptide (NT-proBNP) and fetuin levels.

Methods: NT-proBNP and fetuin were measured from stored samples of participants in the VA-Bicarb Trial, a six-month, double-blind, randomized, placebo-controlled NaHCO3 trial of 74 US Veterans with stage 2-4 CKD attributed to diabetes. Measurements were performed at baseline, month-3, and month-6. Generalized linear mixed effects models were fit and a series of hypothesis tests were performed to globally asses differences in biomarker trajectory between treatment groups as well as intergroup differences at each visit. Additionally, we analyzed intragroup biomarker variations at each visit relative to the group baseline values.

Results: The mean (SD) age was 72 (8) years, 72 (97%) male, and 64 (87%) non-Hispanic White. Mean (SD) eGFR was 56 (20) ml/min/1.73m^2 and median (IQR) urinary ACR was 121 (58, 370) mg/g. Median (IQR) NT-proBNP was 81 (48, 219) pg/mL and mean (SD) fetuin was 840 (187) µg/mL. Fetuin decreased in both the NaHCO3 and placebo groups at month-3; month-6 values returned to near baseline levels in both groups (Figure 1A). There was no significant change in NT-proBNP levels in either group during follow-up (Figure 1B). Overall, there was no statistically significant difference in NT-proBNP or fetuin between the groups.

Conclusions: Among US Veterans with stage 2-4 CKD attributed to diabetes, treatment with NaHCO3 had no effect on blood NT-proBNP or fetuin levels.

Funding: NIDDK Support, Veterans Affairs Support



Blood fetuin (A) and NT-proBNP (B) levels during follow-up by treatment group.

TH-PO1073

Proteinuria Outcomes of Tenofovir Alafenamide Fumarate (TAF) vs. Tenofovir Disoproxil Fumarate (TDF) Regimens for Treatment of HIV, HBV, and HIV PrEP: A Systematic Literature Review and Meta-Analysis

Xi Liang,[1] Kyu Yun Park,[1] Haeseon Lee,[1] Nathorn Chaiyakunapruk,[1] Tara Dhippayom,[3] Rachel Rogers,[2] Amy R. Weinberg,[2] Julia Green,[2] Aileen Chi,[2] Connor W. Willis.[1] *[1]University of Utah Health, Salt Lake City, UT; [2]Gilead Sciences Inc, Foster City, CA; [3]The Prince Royal's College, Chiang Mai, Thailand.*

Background: TDF and TAF are tenofovir's prodrugs. TAF has improved renal safety and comparable efficacy to TDF. Monitoring proteinuria biomarkers is crucial for early kidney damage detection. We aimed to comprehensively synthesize evidence on proteinuria outcomes of TDF and TAF regimens.

Methods: We systematically reviewed RCTs comparing TDF vs. TAF for pre-exposure prophylaxis (PrEP), treatment of human immunodeficiency virus (HIV-1), hepatitis B virus (HBV), and HIV/HBV. We searched PubMed, EMBASE, Web of Science, and Cochrane Trial Registry from inception to 12/6/2023. The outcomes were pooled using mean % change differences with 95% CI. The heterogeneity was assessed using I^2 test. Subgroup analyses were based on baseline eGFR and prior treatment.

Results: Out of 9,014 studies, 10 RCTs reported urine protein to creatinine ratio (UPCR), 12 RCTs reported urine albumin to creatinine ratio (UACR), 15 RCTs reported retinol-binding protein to creatinine ratio (RBPCR), and 16 RCTs reported β_2-macroglobulin to creatinine ratio (β_2MCR). TAF showed improved proteinuria compared to TDF, with a magnitude of improvement increasing over time. This trend was consistent across all subgroup analyses.

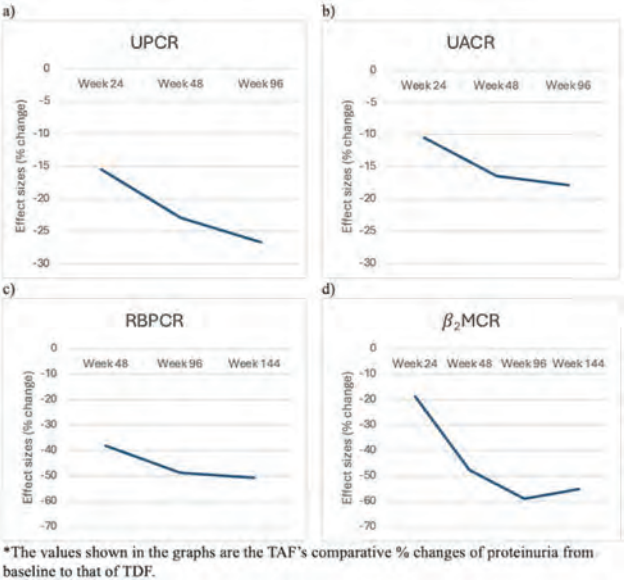
Conclusions: Proteinuria outcomes significantly improved with TAF compared to TDF, which became more pronounced over time. This supports using TAF regimens across indications.

Funding: Commercial Support - Gilead Sciences, Inc.

Effect Sizes and Heterogeneity of Changes in Proteinuria Biomarkers of TAF Compared to TDF

	Effect sizes† (95% CI)				I^2			
Proteinuria (no. participants in TAF, TDF)	Week 24	Week 48	Week 96	Week 144	Week 24	Week 48	Week 96	Week 144
UPCR (3730, 2991)	-15.48 (-40.90 to -9.93)	-22.91 (-31.26 to -14.55)	-26.55 (-35.54 to -17.56)	N/A	83.58%	67.93%	0%	N/A
UACR (4458, 3729)	-10.50 (-24.99 to 5.99)	-16.42 (-21.99 to -10.84)	-17.84 (-27.14 to -8.55)	N/A	N/A*	38.78%	74.76%	N/A
RBPCR (7177, 6653)	N/A	-38.09 (-47.14 to -29.03)	-48.94 (-69.52 to -28.35)	-50.78 (-90.03 to -11.53)	N/A	42.82%	68.26%	60.21%
β_2MCR (7372, 6889)	-19.70 (-33.09 to -4.31)	-47.69 (-60.30 to -35.07)	-59.11 (-85.49 to -32.73)	-55.31 (-83.10 to -27.52)	N/A*	55.54%	64.71%	23.52%

† TAF's comparative % change from baseline to that of TDF
*Only 1 study included. Thus, heterogeneity is not available.



*The values shown in the graphs are the TAF's comparative % changes of proteinuria from baseline to that of TDF.

Comparative Reduction of Proteinuria Biomarkers of TAF to TDF

TH-PO1074

Association between Urate-Lowering Therapy and Kidney Failure in Patients with CKD

Agathe Mouheb,[1,5] Oriane Lambert,[2] Natalia Alencar de Pinho,[2] Christian Jacquelinet,[3] Maurice Laville,[9] Christian Combe,[4,8] Denis Fouque,[10,9] Luc Frimat,[6,11] Ziad Massy,[7,12] Solene M. Laville,[1,5] Sophie Liabeuf.[1,5]
[1]Centre Hospitalier Universitaire Amiens-Picardie, Amiens, France; [2]Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; [3]Agence de la biomedecine, La Plaine Saint-Denis, France; [4]Centre Hospitalier Universitaire de Bordeaux Groupe hospitalier Sud, Bordeaux, France; [5]Universite de Picardie Jules Verne, Amiens, France; [6]Centre Hospitalier Regional Universitaire de Nancy, Nancy, France; [7]Association pour l'Utilisation du Rein Artificiel dans la région parisienne (AURA), Paris, France; [8]INSERM, U1026, Université Bordeaux Segalen, Bordeaux, France; [9]Université de Lyon, CarMeN INSERM1060, Lyon, France; [10]Nephrology department, Lyon South Medical Center, Lyon, France; [11]Universite de Lorraine Laboratoire Adaptation Mesure et Evaluation en Sante Approches Interdisciplinaires, Vandoeuvre-les-Nancy, France; [12]Ambroise Paré University Hospital, APHP, Boulogne-Billancourt, France.

Background: Hyperuricemia is a hallmark of gout and a suspected risk factor for the progression of chronic kidney disease (CKD). However, the impact of urate-lowering therapy (ULT) on CKD progression is subject to debate. The objective of the present study was to evaluate the association between ULT prescription and the progression of kidney disease in patients with CKD.

Methods: CKD-REIN is a French, nationwide, prospective cohort of 3,033 nephrology outpatients with a confirmed diagnosis of CKD (eGFR<60 mL/min/1.73 m²). Prescriptions of ULT drugs (allopurinol or febuxostat), and patient's characteristics were recorded prospectively during follow-up. Propensity score-matched, cause-specific Cox proportional hazards regression models were used to assess the association between incident ULT use and CKD progression (defined primarily as the initiation of kidney replacement therapy (KRT) but also in other ways).

Results: Among the patients included in the cohort, 337 started ULT and were matched with a ULT non-user. The characteristics of the matched patients were balanced. The median age of the patients was 71 years, the mean eGFR was 30 mL/min/1.73 m², the mean uricemia was 494 µmol/L, and 65% were receiving diuretics. Over a median follow-up of 3.2 [1.9-4.2] years, 136 patients started KRT (incidence rate [95% confidence interval (CI)]: 7.6 [6.3–8.8] per 100 person-years), among whom 66 patients initiated ULT. Our analysis did not reveal a significant association between ULT prescription and the occurrence of KRT (HR [95%CI]: 0.89 [0.67 – 1.20]). Regardless of the definition considered, CKD progression was not significantly associated with ULT prescription.

Conclusions: Real-world data from the CKD-REIN cohort show that ULTs do not slow the progression of CKD. Thus, in patients with asymptomatic hyperuricemia, ULT should not be prescribed for the purpose of slowing down CKD progression.

TH-PO1075

Efficacy and Safety of SEL-212 in Patients with Refractory Gout and CKD: A Post Hoc Analysis from the Two Phase 3 DISSOLVE Studies

Puja Khanna,[1] Richard J. Johnson,[2] Rehan Azeem,[3] Aletta Falk,[4] Bhavisha Desai,[3] Hugues Santin-Janin,[5] Herbert Baraf,[6,7] Alan J. Kivitz.[8] *[1]Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; [2]Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, CO; [3]Sobi, Waltham, MA; [4]Sobi, Stockholm, Sweden; [5]Sobi, Basel, Switzerland; [6]The Center for Rheumatology and Bone Research, Rheumatology, Wheaton, MD; [7]The George Washington University, Rheumatology, Washington, DC; [8]Department of Rheumatology, Altoona Center for Clinical Research, Duncansville, PA.*

Background: Chronic kidney disease (CKD) is common in patients with gout, especially in patients with chronic refractory gout (CRG), but evidence on the management of gout in these patients is limited (Stamp LK, et al. *Nat Rev Rheumatol* 2021;17:633). Here, we present Phase 3 efficacy and safety data on the investigational uricase-based therapy SEL-212 in patients with CRG and CKD.

Methods: DISSOLVE I (NCT04513366) and DISSOLVE II (NCT04596540) investigated the efficacy and safety of SEL-212, a two-component infusion therapy of pegadricase (a pegylated uricase) and immune-tolerizing nanoparticles containing sirolimus in the treatment of CRG. Two doses of SEL-212 or placebo were administered every 28 days for up to 6 treatment periods (TPs) in DISSOLVE II, or up to 12 TPs in DISSOLVE I. The primary endpoint was serum uric acid reduction below 6 mg/dL for at least 80% of the time during TP6. Secondary endpoints assessed sUA reduction and related outcomes. In this *post hoc* analysis, efficacy and safety data from both studies were pooled and outcomes in patients with CKD stage 3 at baseline were analyzed using the Mantel-Haenszel test with randomization of tophus presence (yes/no) with a two-sided error rate of α=2.5% to account for the two comparisons of study drug against placebo.

Results: Among 265 patients in DISSOLVE I and II, 61 had CKD stage 3. The proportion of patients with CKD stage 3 who met the primary endpoint was broadly comparable to the overall population: 52% vs 51% in the high dose treatment arm, 61% vs 43% in the low dose arm, and 10% vs 8% in the placebo arm. Mean glomerular filtration rates were stable in both arms from baseline to TP6 (Fig. 1).

Conclusions: Data from DISSOLVE I and II endorsed the efficacy and safety of SEL-212 in patients with gout refractory to conventional therapy with CKD stage 3. Further studies are needed to establish the use of this novel combination product in refractory gout with end-stage kidney damage.

Funding: Commercial Support - Sobi and Selecta Biosciences, Inc

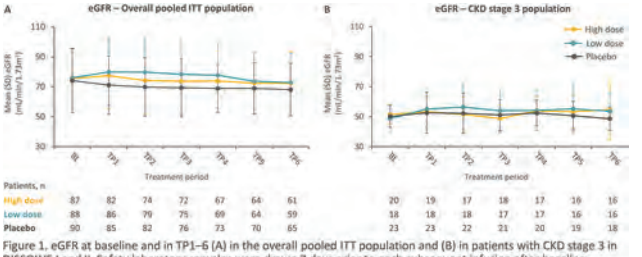


Figure 1. eGFR at baseline and in TP1–6 (A) in the overall pooled ITT population and (B) in patients with CKD stage 3 in DISSOLVE I and II. Safety laboratory samples were drawn 7 days prior to each subsequent infusion after baseline.
BL, baseline; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; SD, standard deviation; TP, treatment period.

TH-PO1076

Effect of Different Erythropoiesis-Stimulating Agents on Mortality and Kidney Disease Progression among Nondialysis-Dependent Patients with CKD

Sungjin Chung, Eun Sil Koh. *The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: Erythropoiesis-stimulating agents (ESAs) are commonly prescribed to treat anemia in both dialysis-independent and -dependent chronic kidney disease (CKD) patients. However, the clinical outcomes, particularly mortality, associated with short- and long-acting ESAs remain debated. This study investigates the prognostic implications of ESA type in a large cohort of non-dialysis CKD patients.

Methods: Using the Korean National Health Insurance Service cohort database, we analyzed data from 166,673 subjects treated with epoetin α, darbepoetin, or methoxy polyethylene glycol-epoetin β (MPGB) between 2002 and 2021, with follow-up until December 31, 2022. The primary outcomes were all-cause mortality, a decline of over 40% in estimated glomerular filtration rate (eGFR), or initiation of dialysis.

Results: During the follow-up period, patients receiving darbepoetin or MPGB had a significantly lower risk of renal composite outcomes compared to those receiving epoetin α (HR 0.523, 95% CI 0.489-0.561 and HR 0.266, 95% CI 0.246-0.288, respectively). However, darbepoetin use was associated with a significantly higher risk of all-cause death (HR 1.119, 95% CI 1.053-1.190), while MPGB use showed a significantly lower risk (HR 0.928, 95% CI 0.873-0.986) compared to epoetin α. Excluding subjects with missing hemoglobin data, those treated with MPGB who achieved optimal hemoglobin levels (10.0-10.9 g/dL) demonstrated a higher risk of all-cause death compared to those treated with epoetin α.

Conclusions: The use of longer-acting ESAs in non-dialysis CKD patients may be associated with a reduced risk of kidney disease progression compared to short-acting ESAs. However, longer-acting ESAs may also be linked to an increased mortality rate, particularly among patients achieving optimal hemoglobin levels with MPGB.

TH-PO1077

Health Effects (Renal) of Extra Strength Avmacol (HEROES) Study: Interim Update from the Phase 2 Randomized Double-Blind Placebo-Controlled Trial

Yves T. Wang, Sharvari A. Sonawane, Allison J. Stewart, Rita Ghimirey, Timothy J. Beane, Thu H. Le. *University of Rochester Medical Center, Rochester, NY.*

Background: Progression of chronic kidney disease (CKD) is associated with increased oxidative stress (OS). The common null allele of the glutathione S-transferase µ-1 (*GSTM1*) gene, which encodes an antioxidant enzyme and is a downstream target of nuclear factor erythroid 2-related factor 2 (Nrf2), has been shown to be associated with elevated oxidative stress and increased risk of CKD progression in clinical studies. We hypothesize that upregulating antioxidant enzymes by activating the Nrf2 pathway via supplementation with sulforaphane (SFN) would decrease markers of OS and inflammation and slow CKD progression. We are testing this hypothesis using Avmacol Extra Strength (ES) in a Phase 2 randomized double-blind placebo-controlled safety and feasibility trial.

Methods: Adult subjects with CKD Stage 3-4 (eGFR 15-60 mL/min/1.73m^2) and progressive GFR decline are recruited from the Kidney Clinic at the University of Rochester Medical Center. Subjects are randomized to take 4 tablets daily of either Avmacol ES or a matching placebo for 6 months. Blood and urine are obtained for markers of OS and inflammation at baseline, and at 1, 3, and 6 months, in addition to standard of care clinical labs. *GSTM1* genotype is also determined.

Results: As of May 1, 2024, 59 subjects have enrolled and completed a baseline visit, of which 28 have completed the 6-month study. By RT-PCR genotyping, 27 have at least 1 active *Gstm1* allele (1/0 or 1/1, 45.8%). In total, there have been 149 reported side effects (SEs), including 101 related to the gastrointestinal (GI) system, and 3 serious adverse events (SAEs), all GI-related. While 1 arm of the study has a slightly higher proportion of subjects without any SEs (21.2% vs. 12.0%), the number of SEs per subject with at least 1 SE is similar (2.5 vs 2.7). One subject with a GI SAE was discontinued from the study due to safety concerns, while another 7 subjects have voluntarily withdrawn from the study.

Conclusions: As of this interim report, there is no significant difference in SE or SAE rate between the arms of the study, with most being relatively mild. The *GSTM1* genotypes of the study participants are within the expected proportions. This study is on pace to complete recruitment (100 subjects total) in ~6 months.

Funding: NIDDK Support, Commercial Support - Nutramax

TH-PO1078

Hyperkalemia Treatment Strategies by Specialty in the TRACK Study: Interim Analysis

Meredith S. Bishop,[1] Judith Hsia,[2] Linda F. Fried,[3] Jordi Bover,[5] Javed Butler,[6] Pietro Manuel Ferraro,[7] Markus P. Schneider,[8] Navdeep Tangri,[9] Wolfgang C. Winkelmayer,[4] Nitin Shivappa,[1] Anna-Karin Sundin,[1] Hungta (Tony) Chen,[1] Marc P. Bonaca.[2] *[1]AstraZeneca Pharmaceuticals LP, Wilmington, DE; [2]University of Colorado System, Denver, CO; [3]University of Pittsburgh, Pittsburgh, PA; [4]Baylor College of Medicine, Houston, TX; [5]Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [6]Baylor Scott & White Health, Dallas, TX; [7]Universita degli Studi di Verona, Verona, Italy; [8]Friedrich-Alexander-Universitat Erlangen-Nurnberg Medizinische Fakultat, Erlangen, Germany; [9]University of Manitoba, Winnipeg, MB, Canada.*

Background: We compared baseline treatment strategies by healthcare provider (HCP) specialty from TRACK, a prospective, observational study designed to address the evidence gap regarding HCP decision making in patients with hyperkalemia (HK).

Methods: TRACK enrolled adults with serum potassium (sK^+) >5.0 mmol/L and recorded HCP management decisions for 12 months. HCPs were asked, but not required, to record their specialty. An interim analysis was conducted when 600 enrolled participants had completed 6 months. Initial treatment strategy by specialty was compared using Fisher's exact or Pearson's Chi-squared tests. Treatment objectives and planned treatment duration were analyzed descriptively.

Results: Participants (N=1330) were enrolled (July 2022–December 2023) in the USA and Europe (mean age, 68±14 years; female, 31%; mean sK^+, 5.6±0.5 mmol/L; estimated glomerular filtration rate, 28±21 mL/min/1.73 m^2). In total, 55% had chronic kidney disease (CKD) without heart failure (HF), 29% had CKD and HF, and 6% had HF without CKD. Overall, nephrologists managed 597 (45%) participants, 327 (25%) had another specified specialty (237 cardiologists), and the HCP specialty was not specified for 30%. Nephrologists were more likely to plan for indefinite treatment, cite CKD guideline compliance as an objective, and prescribe a low K^+ diet (Table; P<0.0001); less likely to manage renin-angiotensin-aldosterone system inhibitor therapy as an initial strategy and more likely to manage K^+ binder therapy (both P<0.0001).

Conclusions: HCP specialty affected HK management approaches, possibly reflecting differences in specialty guidelines.

Funding: Commercial Support - AstraZeneca

Table. Initial management strategy for index HK event by provider specialty

	Nephrologists	Non-nephrologists	P-value[a]
N	597	327	
HK treatment objective:[b]			
Ease of treatment, n (%)	196 (35)	145 (46)	
Safety, n (%)	170 (31)	97 (31)	
HF guidelines, n (%)	18 (3)	72 (23)	
CKD guidelines, n (%)	285 (52)	26 (8)	
Adjust RAASi, n (%)	50 (9)	36 (12)	
Planned treatment duration,[b] n	579	326	
Until sK[+] normalizes, n (%)	330 (57)	200 (61)	
As long as patient takes RAASi, n (%)	53 (9)	29 (9)	
Indefinitely,[c] n (%)	113 (79)	75 (23)	
Initial management strategy reported, n	588	327	
Low K[+] diet, n (%)	400 (68)	71 (22)	<0.0001
ACEi/ARB/ARNI, n (%)	265 (45)	194 (59)	<0.0001
Discontinued, n (%)	12 (4.5)	8 (4.1)	
Dose reduced, n (%)	8 (3.0)	5 (2.5)	
Dose maintained, n (%)	237 (88.4)	170 (87.6)	
Dose increased, n (%)	4 (1.5)	6 (3.1)	
Started, n (%)	7 (2.6)	8 (4.1)	
MRA, n (%)	26 (4.0)	99 (30.0)	<0.0001
Discontinued, n (%)	5 (19.2)	17 (17.2)	
Dose reduced, n (%)	2 (7.7)	13 (13.1)	
Dose maintained, n (%)	18 (69.2)	65 (65.7)	
Dose increased, n (%)	1 (3.8)	1 (1.0)	
Started, n (%)	0	5 (5.1)	
K[+] binder, n (%)	152 (26)	45 (14)	<0.0001
Discontinued, n (%)	1 (0.7)	0	
Dose reduced, n (%)	1 (0.7)	0	
Dose maintained, n (%)	58 (38.2)	10 (22.2)	
Dose increased, n (%)	21 (13.8)	2 (4.4)	
Started, n (%)	71 (46.7)	33 (73.3)	
Dialysis, n (%)	24 (4.0)	0	<0.0001[a]
Unscheduled, n (%)	1 (4.2)	0	
Changed prescription, n (%)	5 (20.8)	0	
Started, n (%)	19 (79.2)	0	

Dialysis was not a management strategy for non-nephrologists. Dose adjustments did not differ by specialty. For medication and dialysis, the denominator for the percentage is the number of participants with an initial management strategy reported. [a]P-value calculated by Fisher's exact test for dialysis comparisons, and by Pearson's Chi-squared test for other comparisons. [b]Participants could appear in >1 row. Not all response options are shown. [c]Denominator for the percentage is the number responding. Specific period of time to Planned treatment duration.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalemia; K+, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; sK+, serum potassium.

TH-PO1079

Weight-Based Sliding Scale vs. Fixed-Dose Loop Diuretics for Fluid Overload in CKD: A Retrospective Analysis

Sameen Aamer,[1] Katelin Gardonis,[1] Andrey Vavrenyuk,[2] Randa Abd Algayoum,[3] Swati Arora.[1] *[1]Allegheny General Hospital, Pittsburgh, PA; [2]University of Wisconsin-Madison, Madison, WI; [3]Garden City Hospital, Garden City, MI.*

Background: Managing fluid overload in chronic kidney disease (CKD) patients is challenging. Fixed doses of loop diuretics often lead to complications such as frequent hospitalizations due to volume overload or pre-renal acute kidney injury (AKI). While weight-based loop diuretic adjustments have reduced hospitalizations in heart failure patients, this approach has not been specifically studied in CKD patients.

Methods: A single-center retrospective study (n=80) from June 2020 to July 2022 compared clinical outcomes between forty patients on fixed-dose loop diuretics (FDD) and forty on weight-based sliding scale loop diuretics (SSD).

Results: The demographics of both groups were similar, except that SSD patients were older (mean age 64.15 vs. 56.28, p = 0.04) and predominantly white (81%), while FDD patients were more likely to be Black (30%, p = 0.03). Linear modeling revealed that SSD significantly predicted better blood pressure (BP) control, with FDD patients having 7.95 mmHg higher BP (β = 7.95, t(246) = 2.19, p = 0.03). Hierarchical generalized linear modeling showed a 57% variance in volume between groups, with SSD patients being 46% less likely to develop hypervolemia over time (OR = 0.54, 95% CI [0.37, 0.80], p = 0.03) compared to FDD patients, who were 8% less likely to develop hypervolemia over time (OR = 0.92, 95% CI [0.71, 1.20], p = 0.03). Patients on FDD had higher hospitalization rates (43.4%) compared to 18.5% for those on SSD (p = 0.03). Clinical outcomes are shown in Table 1.

Conclusions: This study highlights the benefits of sliding scale loop diuretics for managing fluid overload in CKD patients, leading to fewer hospitalizations and improved volume control over time. Further research is needed to validate and expand upon these findings.

Table 1. Comparison of Clinical Outcomes Between Sliding Scale and Fixed-Dose Diuretic Groups

Variable	Sliding Scale: No n(%)	Sliding Scale: Yes n(%)	P Value
Hospitalizations			.0274
No	30 (56.60%)	22 (81.48%)	
Yes	23 (43.40%)	5 (18.52%)	
Pre-renal AKI			.4806
No	27 (50.94%)	16 (59.26%)	
Yes	26 (49.06%)	11 (40.74%)	
Volume overload			.7418
No	44 (83.02%)	24 (88.89%)	
Yes	9 (16.98%)	3 (11.11%)	
HTN urgency			.2943
No	49 (92.45%)	27 (100%)	
Yes	4 (7.55%)	0 (0%)	
Hypotension			.1116
No	50 (94.34%)	22 (81.48%)	
Yes	3 (5.66%)	5 (18.52%)	
Outpatient creatinine elevation to hold diuretics			.0916
No	47 (88.68%)	27 (100%)	
Yes	6 (11.32%)	0 (0%)	

TH-PO1080

Effects of Pediococcus acidilactici GKA4 Supplementation on Proinflammatory Cytokines in Early-Stage CKD

Wen-Ching Yang, Hui-Min Hsieh, Jun-Peng Chen, Yun-Yu Chen, Po-Hsin Pai, Cheng-Hsu Chen. *Taichung Veterans General Hospital, Taichung, Taiwan.*

Background: Chronic kidney disease (CKD) commonly results in elevated levels of proinflammatory cytokines such as TNF-α and IL-6. Although probiotics may modulate these markers in advanced CKD, their effects on early-stage CKD (ECKD) are unclear. This study explored the impact of a specific probiotic on these cytokines in patients with ECKD.

Methods: In this randomized, double-blinded, placebo-controlled trial, individuals with CKD stages G2–3a (eGFR 45–89 mL/min/1.73 m^2; ages 20–90 years) were enrolled. Participants were randomly allocated to a probiotic group (Pediococcus acidilactici GKA4) or a control group (placebo) for a six-month treatment period. TNF-α and IL-6 levels were measured in the serum and urine by ELISA, with urinary values adjusted for urine creatinine. Differences between groups were assessed using generalized estimating equations (GEEs).

Results: Eighty patients (median age 57 years; median eGFR 64.1 mL/min/1.73 m^2) were included in the intention-to-treat analysis, with 40 patients in each group. No significant differences between the groups in serum and urinary IL-6 or serum TNF-α levels were observed. However, there was a significant decrease in urinary TNF-α levels adjusted for urine creatinine (TNF-α/Cr) in the probiotic group compared to the control group ($p = 0.017$).

Conclusions: Although probiotic supplementation did not alter serum TNF-α or IL-6 levels, it modulated urinary TNF-α excretion in ECKD patients. Further studies with a larger population are required to confirm the findings.

Table 1. Generalized estimating equation (GEE) analysis of cytokines between the two groups

	β	SD	95% Confidence interval	p value
Serum measurement				
IL-6 (pg/mL)	-0.061	0.303	(-0.654, 0.532)	0.841
TNF-α (pg/mL)	-0.283	0.389	(-1.045, 0.480)	0.467
Urinary measurement				
IL-6/Cr (pg/mg)	0.001	0.003	(-0.006, 0.007)	0.866
TNF-α/Cr (pg/mg)	-0.007	0.003	(-0.013, -0.001)	0.017*

β: Coefficient estimate. SD: Standard deviation of the estimate. * $p < 0.05$

TH-PO1081

Prognostic Enrichment Using the Klinrisk Model: Insights from Landmark Kidney Disease Clinical Trials

Brendon L. Neuen,[1,2] Thomas W. Ferguson,[3,4] Meg Jardine,[5,2] Bruce Neal,[6,2] Vlado Perkovic,[7,2] George L. Bakris,[8,9] Rajiv Agarwal,[10] Patrick Schloemer,[11] Alfredo E. Farjat,[11] Niels Jongs,[12,13] Hiddo J. Heerspink,[12] David C. Wheeler,[14,15] Glenn M. Chertow,[16] Navdeep Tangri.[3,4] *[1]Royal North Shore Hospital, St Leonards, NSW, Australia; [2]The George Institute for Global Health, Sydney, NSW, Australia; [3]University of Manitoba Department of Internal Medicine, Winnipeg, MB, Canada; [4]Chronic Disease Innovation Centre, Winnipeg, MB, Canada; [5]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [6]University of New South Wales Medicine & Health, Sydney, NSW, Australia; [7]University of New South Wales, Sydney, NSW, Australia; [8]University of Chicago Pritzker School of Medicine, Chicago, IL; [9]University of Chicago Division of the Biological Sciences, Chicago, IL; [10]Indiana University School of Medicine, Indianapolis, IN; [11]Bayer AG, Leverkusen, Germany; [12]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [13]Rijksuniversiteit Groningen, Groningen, Netherlands; [14]University College London, London, United Kingdom; [15]National Institute for Health and Care Research, London, United Kingdom; [16]Stanford University School of Medicine, Stanford, CA.*

Background: Patients with macroalbuminuria (KDIGO stage A3) experience high rates of CKD progression and cardiovascular events. Identifying patients with lesser degrees of albuminuria who also experience high kidney and cardiovascular event rates could enhance access to, and improve efficiency of, CKD-focused clinical trials.

Methods: We applied the Klinrisk model, a validated machine learning model incorporating routinely collected laboratory data, to patients with uACR ≥30 mg/g who were evaluated for participation in the CANVAS Program, CREDENCE, FIDELIO, FIGARO and DAPA-CKD trials but who failed screening due to albuminuria levels below the randomization threshold. We examined 2-year incidence of CKD progression (40% decline in eGFR or kidney failure) in different uACR categories, stratified by Klinrisk score (low, intermediate, and high risk indicating <2%, 2–10%, and >10% 2-year risk of CKD progression, respectively). We subsequently reviewed screen failure data from the CREDENCE, FIDELIO and DAPA-CKD trials to determine what proportion of individuals with uACR 30–300 mg/g could have been enrolled using a Klinrisk-informed approach.

Results: Across the included trials, the incidence of CKD progression among participants with uACR 30–300mg/g (KDIGO stage A2) was highly variable across risk categories, ranging from 1.1 to 9.7% in those classified as low vs. high risk by the Klinrisk model, respectively. Compared to participants with uACR 300-1000 mg/g, event rates were similar or higher for participants with uACR 30-300mg/g classified as high-risk based on the Klinrisk model. 24 to 36% of participants who screen failed due to A2 albuminuria in the CREDENCE, FIDELIO and DAPA-CKD trials were classified as high risk with the Klinrisk model.

Conclusions: Extending recruitment to patients with uACR 30-300mg/g at high-risk based on the Klinrisk algorithm could facilitate recruitment for CKD progression trials without affecting event rates. Prognostic enrichment using Klinrisk has the potential to accelerate drug development in CKD by enabling more inclusive and efficient clinical trials.

TH-PO1082

Composite Primary Outcome Variables in Nephrology Clinical Trials

Steven Fishbane, Pratap Kumar Upadrista, Hitesh H. Shah. *Northwell Health Division of Nephrology, Great Neck, NY.*

Background: Clinical trials use one or more primary outcome variables to assess results. The type of outcome selected can affect sample size needed and interpretation of results. Composite endpoints have been increasingly popular in nephrology trials. Although potentially beneficial, composites have also been criticized for leading to potentially misleading results. In this analysis we studied nephrology trials with a special emphasis on composite outcomes and the component variables from which the composites were constructed.

Methods: We searched nephrology trials published in major medical and nephrology journals between 1/1/2019 – 12/31/2023. Only articles based on primary trials were used; post hoc or other secondary analyses were excluded. For each publication a reviewer assessed the primary outcome as well as study characteristics and results. For each study that used composite primary outcomes (CPO), the individual component results were analyzed.

Results: 183 studies were analyzed, of which the primary endpoint was a single outcome variable in 123 (67.2%), co-primary variables in 28 (15.4%) and CPO in 32 (17.4%) (Table). With CPOs, the mean number of individual component variables was 3.4±1.6. Studies with CPOs had larger sample sizes (<0.0001) and were significantly more likely to have positive study results (p=0.03, Table), with 50% of the CPO component variables having positive results. We found no association between the

number of component variables and likelihood of positivity of the overall CPO. Trials with CPO were more likely to be published in medical than nephrology journals 25/70 (35.7%) vs. 7/113 (6.2%), p<0.0001. Reporting of CPO was frequently associated with failure to provide results for the composite's individual component variables (42.9%).

Conclusions: Nephrology trials commonly utilize composite primary endpoints. In this study we describe the impact on study results, the quality of reporting of CPOs and note how these endpoints can alter the interpretation of studies.

Funding: Clinical Revenue Support

	Composite (17.4%)	Single or Co-Primary (82.6%)	P Value
Journal Type			
Medical	25/70 (35.7%)	45/70 (64.3%)	0.0001
Nephrology	7/113 (6.2%)	106/113 (93.8%)	<0.0001
	<0.0001		
Mean # Patients	2,957.3±5765.4	494.2±1070.6	<0.0001
Positive Study Results	20/32 (62.5%)	62/151 (41.1%)	0.03
Composite Outcomes			
Mean # of Components		3.4±1.6	
Positive Studies with 3 or less Components		13/21 (61.9%)	
Studies with Insufficient Description of Composite Components		9/21 (42.9%)	

TH-PO1083

Examining the Association between Quality of Life and Functional Status in African American Adults with CKD in Southeast Wisconsin: A Cross-Sectional Study

Mukoso N. Ozieh,[1,2] Aprill Dawson,[1] Leonard E. Egede.[1] *[1]Medical College of Wisconsin Department of Medicine, Milwaukee, WI; [2]VA Milwaukee Healthcare System, Milwaukee, WI.*

Background: CKD is a burdensome disease and quality of life (QOL) independently predicts morbidity and mortality in patients with CKD. The aim of this study was to examine the association between quality of life and functional status in African American adults with chronic kidney disease in southeast Wisconsin.

Methods: Three hundred African American adults were recruited from southeast Wisconsin, United States in 2020. Individuals aged 21 and older with a diagnosis of chronic kidney disease were eligible to participate. CKD diagnosis was based on self-report and laboratory diagnosis based on estimated glomerular filtration rate (eGFR) in ml/min/1.73m2 using CKD-EPI 2021. Quality of life was based on the physical component score (PCS) and mental component score (MCS) and functional status was based on the EQ-5D-3L which comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and the EQ visual analog scale (VAS) scores which range from 0 to 100, where 100 is the best possible health state. Unadjusted and adjusted models were performed using the QOL components and the five dimensions of functional status as the dependent variables adjusting for relevant covariates.

Results: In this cross-sectional study of 300 African American adults, the mean age was 51.9 ± 12.5 for CKD on dialysis (CKD-D) and 60.3 ± 11.4 non-dialysis dependent CKD (CKD-ND). Mean eGFR for CKD-D was 7.8 ± 6.7 and 50.8 ± 22.6 for CKD-ND. We found significant associations for CKD-ND status and EQ pain/discomfort (β = 0.52, p < 0.01). BMI was an independent correlate for PCS (β = 0.25, p <0.01), EQ VAS (β = -7.5, p <0.01), EQ mobility (β = 0.41, p <0.01), EQ self-care (β = 0.37, p <0.01), EQ usual activities (β = 0.35, p <0.01), and EQ anxiety/depression (β = 0.41, p <0.01). Employment was an independent correlate for EQ VAS (β = 9.69, p <0.01), EQ self-care (β = -0.48, p <0.01), EQ usual activities (β = -0.67, p <0.01), and EQ anxiety/depression (β = -0.49, p <0.01). We did not significant associations for CKD-ND status and mcs (β = -0.61, p 0.07).

Conclusions: Future studies exploring the direct and indirect pathways to understand the relationship between functional status and CKD-ND are needed in order to develop novel interventions to address and improve QOL and functional status in adults with CKD.

Funding: NIDDK Support, Other NIH Support - NIMHD, CTSI KL2

TH-PO1084

Calcineurin Inhibitors Cause Kidney Fibrosis by Inactivating Pyruvate Dehydrogenase and Disrupting Energy Metabolism in Proximal Tubule Cells

Yasuhiro Oda,[1] Hiroshi Nishi,[1] Teruhiko Yoshida,[2] Jeffrey B. Kopp,[2] Masaomi Nangaku.[1] *[1]The University of Tokyo Graduate School of Medicine, Bunkyo, Japan; [2]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.*

Background: Arteriolopathy is regarded as a hallmark of chronic calcineurin inhibitor (CNI) nephrotoxicity, but whether tubular cells play a causative role in the development of chronic CNI nephrotoxicity is not fully understood. Calcineurin was recently shown to directly dephosphorylate and activate pyruvate dehydrogenase (PDH), a gatekeeper of the TCA cycle. We hypothesized that 1) CNIs disrupt mitochondrial energy metabolism by decreasing the activity of PDH in energy-demanding proximal tubule cells (PTCs) in the kidneys and 2) the dysregulated mitochondrial metabolism causes cellular senescence, thereby contributing to kidney fibrosis.

Methods: Primary human renal proximal tubule epithelial cells (RPTECs) were cultured with cyclosporin A (CsA) or tacrolimus. Chronic CNI nephrotoxicity mouse model was created by feeding low-salt diet and administering 30 mg/kg/day CsA to ICR mice for up to 4 weeks.

Results: Single-nucleus RNA-seq showed that genes associated with oxidative phosphorylation were significantly downregulated in PTCs of chronic CNI mouse model compared to PTCs of its control mouse (FDR < 0.001, gene set enrichment analysis). CsA administration increased the ratio of KIM-1+ PTCs with an upregulated expression of genes associated with cellular senescence and TGF-β signaling. In primary human RPTECs cultured with CsA or tacrolimus, the amount of phosphorylated, inactivated PDH was increased, and PDH activity was decreased. Mitochondrial oxygen consumption was decreased in primary human RPTECs cultured with CsA or tacrolimus, and this decrease was ameliorated by lentiviral overexpression of PDP1, an endogenous phosphatase and activator of PDH. The level of senescence-associated β-galactosidase and senescence-associated gene expression was increased in primary human RPTECs cultured with CsA. Administering dichloroacetic acid, an activator of PDH, to chronic CNI nephrotoxicity mouse model alleviated the increase in both immunohistochemical staining of type I collagen in the kidneys and the upregulated expression of senescence-associated genes caused by CsA administration.

Conclusions: To our knowledge, this is the first study to show that CNIs disrupt energy metabolism by inactivating PDH in PTCs and that activating PDH ameliorates dysregulated energy metabolism as well as kidney fibrosis.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO1085

Renal Tubule-Specific Deletion of Aldosterone Synthase CYP11B2 Improves 2-Kidney, 1-Clip-Induced Ischemic Nephropathy, and Renovascular Hypertension in Mice

Ziwei Fu,[1,2] Changjiang Zou,[1,2] Tianxin Yang.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

Background: Although the intrarenal renin-angiotensin system (RAS) has been well established, evidence for intrarenal generation of aldosterone (Aldo) is scarce and therefore Aldo is often omitted in the intrarenal RAS. The co-expression of renin and its receptor (pro)renin receptor (PRR) in the collecting duct (CD) constitutes a key component of the intrarenal RAS.

Methods: In the present study, mice carrying inducible Pax8-rtTA-LC1-Cre were crossed with CYP11B2 floxed mice to generate a novel mouse model of renal tubules-specific deletion of CYP11B2 (RT CYP11B2 KO), born at the expected Mendelian ratio without noticeable developmental abnormalities. CD-specific deletion of PRR (CD PRR KO) or renin (CD renin KO), RT CYP11B2 KO mice and related floxed mice were subjected to sham or 2K1C procedure, followed by radiotelemetry analysis of blood pressure (BP), renal injury, and indices of the Aldo, as well as the expression of subunits of ENaC.

Results: Clipping-induced hypertension and renal injury were both attenuated in RT CYP11B2 KO mice as compared with floxed controls (MAP on day 24: Floxed/2K1C 151.2±4.9 mmHg vs. RT CYP11B2 KO/2K1C 135.3±3.6 mmHg, n=7, p < 0.05) (urinary albumin/creatinine:Floxed/2K1C69.7±4.8mg/gvs.RTCYP11B2KO/2K1C34.2±3.8mg/g, n=7, p < 0.01). Clipping-induced upregulation of renal fibronectin and α-SMA was blunted in RT CYP11B2 KO mice by 54% and 50%, respectively. Similarly, clipping induced paralleled increases in renal mRNA expression of IL-1β, TNF-α, MCP-1 and TGF-β1 were all blunted in RT CYP11B2 KO mice. The protective phenotype of RT CYP11B2 KO mice were paralleled with suppressed urinary Aldo level (urinary Aldo excretion: Floxed/2K1C 9.8±0.7 ng/24h vs. RT CYP11B2 KO/2K1C 2.2±0.3 ng/24h, n=7, p < 0.01). In contrast, clipping-induced enhancement of circulating Aldo remained unchanged between the genotypes. Moreover, renal medullary α-ENaC mRNA expression was elevated by clipping in floxed mice, which was blunted by 51% in RT CYP11B2 KO mice. CD PRR KO mice and CD renin KO mice exhibited similar improvements in renal injury and hypertension, which was paralleled with suppressed intrarenal Aldo levels.

Conclusions: Together, these results provide genetic evidence for pathogenic role of intrarenal Aldo in renovascular hypertension and ischemic nephropathy.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

TH-PO1086

Cell-Specific Role of Platelet-Derived Growth Factor Subunit B (PDGF-B) in Kidney Fibrosis

Barbara M. Klinkhammer,[1] Eva M. Buhl,[2] Tim Caspers,[1] Dickson W. Wong,[1] Michaël Goedertier,[3] David Laurin Hölscher,[4] Roman D. Bülow,[1] Peter Boor.[1,2]
[1]Institute of Pathology, RWTH Aachen University Hospital, Aachen, Germany; [2]Electron Microscopy Facility, RWTH Aachen University Hospital, Aachen, Germany; [3]Institute for Computational Genomics, RWTH Aachen University Hospital, Aachen, Germany; [4]Division of Nephrology and Immunology, RWTH Aachen University Hospital, Aachen, Germany.

Background: Kidney fibrosis is a critical pathological process in progressive kidney diseases. Platelet-derived growth factor (PDGF) has been implicated in the development and progression of kidney fibrosis, yet the exact cellular origins remain unclear.

Methods: Three transgenic mouse lines were generated with cell-specific *Pdgfb* deletion in platelets, fibroblasts or epithelial cells. Spontaneous phenotypes were analyzed in young and aged male and female animals. Kidney fibrosis was induced by unilateral ureteral obstruction, ischemia-reperfusion injury or 0.2% adenine diet. Kidney function was analyzed by blood and urine analysis and perfused kidneys were investigated with histological, immunohistochemical, and immunofluorescence stainings, molecular biology and protein biochemical analyses.

Results: Mice with megakaryocyte- and platelet-specific *Pdgfb* deletion exhibited neither a spontaneous kidney phenotype nor altered fibrosis development in disease models, challenging the conventional understanding of fibrosis as wound healing, in which "platelet-derived" growth factors play a major role. PDGF-B, and its receptor PDGFR-β, are expressed by mesenchymal cells in the kidneys, and some studies suggested potential autocrine effects. Deletion of *Pdgfb* in mesenchymal cells had no effects on normal development, aging or disease model progression, suggesting negligible effects of autocrine signaling in the kidney. In contrast, mice with *Pdgfb* deletion in kidney tubular epithelial cells exhibited smaller kidneys with reduced interstitium, particularly in the medulla, without compromising overall development or physiological kidney function, even at advanced ages. Furthermore, in three distinct models featuring tubular injury from various causes, mice lacking *Pdgfb* in tubular cells displayed significantly reduced fibrosis. The diminished paracrine PDGF-B/PDGFR-β signaling between tubules and peritubular fibroblasts led to decreased activation and proliferation of peritubular PDGFR-β+ cells, ultimately altering the profibrotic niche in the interstitium.

Conclusions: Our findings unveil a PDGF-driven molecular mechanism of paracrine cellular crosstalk mediating the transition from tubular injury to interstitial fibrosis.

TH-PO1087

ADAMTS12 Promotes Fibrosis by Cleaving HMCN1, Enabling the Activation and Migration of Injury-Responsive Fibroblasts

Lars Koch,[1] Konrad Hoeft,[1] David Schumacher,[1] Ling Zhang,[1] Maria Tanzer,[2] Felix Schreibing,[1] Qingqing Long,[1] Barbara M. Klinkhammer,[3] Carla S. Schikarski,[1] Sidrah Maryam,[1] Sarah Krieg,[4] Fabian Peisker,[1] Gideon J. Schaefer,[1] Sylvia Menzel,[1] Benjamin D. Humphreys,[5] Peter Boor,[3] Rafael Kramann.[1,6] Dept of Medicine 2 (Nephrology, Rheumatology, Clinical Immunology, Hypertension), RWTH Aachen University. *[1]Department of Medicine 2 (Nephrology, Rheumatology, Clinical Immunology and Hypertension), RWTH Aachen University, Aachen, Germany; [2]The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia; [3]Department of Pathology, RWTH Aachen University, Aachen, Germany; [4]Institute of Biochemistry and Molecular Biology, RWTH Aachen University, Aachen, Germany; [5]Institute of Biochemistry and Molecular Biology, RWTH Aachen University, St. Louis, MO; [6]Department of Internal Medicine, Nephrology and Transplantation, Erasmus Medical Center, Rotterdam, Netherlands.*

Background: Fibrosis is the uncontrolled replacement of parenchymal tissue with extracellular matrix (ECM) following tissue injury, which impairs organ function. Myofibroblast, which mainly originate from a small perivascular progenitor population marked by Gli1, are considered the major source of ECM deposition. Following injury, they proliferate, migrate to the interstitium, and differentiate into myofibroblasts.

Methods: We conducted genetic fate-tracing to analyze gene expression in Gli1+ cells after unilateral ureteral obstruction (UUO). *Adamts12*$^{-/-}$ and wild-type (WT) mice were subjected to UUO and myocardial infarction (MI) surgeries to assess fibrosis, ejection fraction, and spatial gene expression using 10X Visium spatial transcriptomics. *In vitro*, human renal PDGFRB+ fibroblast cell lines with CRISPR-mediated ADAMTS12 knockout (KO) and lentiviral overexpression of catalytically active and inactive ADAMTS12 were analyzed using bulk RNA sequencing and live-cell imaging. ECM expression of WT and ADAMTS12-KO fibroblasts was characterized by mass spectrometry. Digestion assays and siRNA knockdown assessed the interaction of ADAMTS12 and HMCN1.

Results: *Adamts12* was identified as top upregulated gene in Gli1+ fibroblast progenitor cells following UUO. In UUO and MI models, *Adamts12*$^{-/-}$ mice exhibited reduced fibrosis and preserved left ventricular ejection fraction post-MI. Spatial transcriptomics post-MI confirmed depletion of injury-response fibroblasts in *Adamts12*$^{-/-}$ mice. *In vitro*, PDGFRb+ fibroblasts expressing catalytically active ADAMTS12 showed a distinct injury-response fibroblast signature and increased migration-associated genes. Live-cell imaging confirmed accelerated cell migration by active ADAMTS12. Mass spectrometry revealed accumulation of HMCN1 in ADAMTS12-KO cell ECM. Digestion assays confirmed HMCN1 cleavage by ADAMTS12, a hitherto unknown ADAMTS12 substrate. Enhanced fibroblast migration with cleaved HMCN1 was validated by siRNA knockdown and live-cell imaging.

Conclusions: We identified ADAMTS12 as a critical checkpoint in fibrosis, that controls fibroblast migration and activation via cleavage of a hitherto unknown substrate, HMCN1.

Funding: Government Support - Non-U.S.

TH-PO1088

CAPG as a Novel Therapeutic Target in Kidney Fibrosis via Transforming Growth Factor (TGF)-β Signaling by Mediating Smad4 and CBP Interaction in Fibroblasts

Sixiu Chen,[1] Meng Zhang,[1] Tao Zhang,[2] Joseph V. Bonventre,[3] Wei Chen.[1]
[1]The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [2]Sun Yat-sen University Zhongshan School of Medicine, Guangzhou, China; [3]Brigham and Women's Hospital, Boston, MA.

Background: Fibroblast-to-myofibroblast transition is a key event in renal fibrosis (RF). However, the mechanisms remain unclear. Using single-cell RNA sequencing (scRNA-seq) from a public dataset (GSE180420), we identified that elevated expression of CAPG, a member of the gelsolin family, is associated with fibroblast activation. This study aims to investigate the role and mechanism of CAPG in RF.

Methods: We generated *Capg* knockout (*Capg*$^{-/-}$) and heterozygous (*Capg*$^{+/-}$) mice and utilized folic acid (FA) and unilateral ischemia-reperfusion injury with contralateral nephrectomy (uIRIx) models. scRNA-seq was performed on the FA model. Renal fibroblasts (NRK-49F) were transfected with CAPG-siRNA and CAPG-overexpressing (CAPG-OE) lentivirus. CUT&Tag sequencing identified CAPG-regulated pathways while immunoblotting, immunofluorescence (IF), immunoprecipitation (IP), and chromatin immunoprecipitation (ChIP) were conducted for further analysis.

Results: CAPG expression was significantly elevated in CKD patient kidney tissues compared to healthy controls and correlated with the degree of fibrosis. CAPG levels progressively increased post-FA injection. CAPG deficiency significantly reduced renal fibrosis, as evidenced by histological analysis, and reduced expression of extracellular matrix (Figure 1). scRNA-seq revealed CAPG expression predominantly in fibroblasts in fibrotic kidneys, with IF confirming nuclear localization in fibroblasts. CUT&Tag sequencing indicated CAPG-binding genes are enriched in TGF-β signaling, sharing similar binding sites with Smad proteins. IP confirmed CAPG and CBP interactions with Smad4 in NRK-49F cells. Quantitative IP demonstrated TGF-β-induced interaction between Smad4 and CBP, which was inhibited by CAPG knockdown. ChIP confirmed co-localization of CAPG and Smad4 at *Col1a1* promoter region, with ChIP-qPCR showing increased CBP enrichment at *Col1a1* promoter in CAPG-OE cells compared to controls.

Conclusions: CAPG is upregulated following kidney injury and promotes the interaction between Smad4 and CBP, thereby activating the TGF-β pathway. This leads to fibroblast activation and progression of RF, suggesting CAPG as a potential therapeutic target for RF.

Funding: Government Support - Non-U.S.

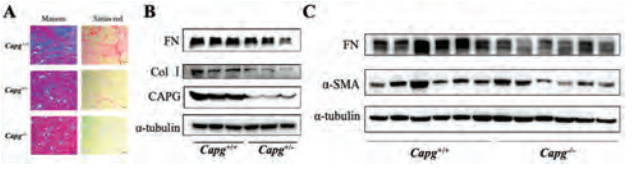


Figure 1

TH-PO1089

Targeting Long Noncoding RNA MALAT1 Preserves Endothelial Cell Integrity and Protects against Kidney Fibrosis

Qiao Zhao,[1] Loïs van der Pluijm,[1] Daniel Peled,[2] Juliette A. de Klerk,[1] Roderick Slieker,[1] Leen M. 't Hart,[1] Wendy Stam,[1] Jacques Duijs,[1] Angela Koudijs,[1] Joris I. Rotmans,[1] Anton J. Van Zonneveld,[1] Coen van Solingen,[2] Roel Bijkerk.[1] *[1]Leids Universitair Medisch Centrum, Leiden, Netherlands; [2]NYU Langone Health, New York, NY.*

Background: Loss of integrity of the peritubular capillary network is directly associated with the development of kidney fibrosis and chronic kidney disease. Here, we aimed to identify long non-coding RNAs (lncRNAs) that could serve as a target to maintain vascular integrity and decrease kidney fibrosis.

Methods: We induced vascular injury and kidney fibrosis by ischemia-reperfusion injury (IRI) and unilateral ureteral obstruction (UUO) in VE-cadherin-ERT2;tdTomato mice to label and trace endothelial cells (ECs). Subsequently, we sorted Tomato-positive ECs by FACS and profiled for differentially expressed lncRNAs. We reprocessed transcriptomic datasets to assess kidney and circulating *MALAT1* levels in patients with kidney fibrosis.

Results: In IRI and UUO, we found 417 and 587 lncRNAs differentially expressed (>2-fold, $p<0.05$) in the VE-cadherin-derived tomato-positive ECs, respectively. We identified the conserved lncRNA *MALAT1* to be increased in ECs in both UUO (7.42-fold) and IRI (2.38 fold). Subsequent gapmer-mediated knockdown of *MALAT1* in the UUO model protected against the development of kidney fibrosis, as illustrated by a ~50% decrease in collagen deposition and a concomitant decrease in interstitial α-SMA positive cells. This protective effect was associated with an increase in capillary density and reduced endothelial to mesenchymal transition. Transcriptomic analysis of kidney ECs isolated using FACS from gapmer-*MALAT1* treated animals demonstrated that *MALAT1* knockdown increased ECM-receptor and cell-cell interaction. Indeed, using the microvessel-on-a-chip platform and transendothelial electric resistance assays, we demonstrated that silencing *MALAT1* resulted in increased barrier function, less vascular leakage and a decreased angiogenic response. In addition, *MALAT1* knockdown in ECs decreased focal adherens junctions and maintained normal VE-cadherin distribution. Lastly, we found both kidney and circulating *MALAT1* levels to be increased in patients with fibrotic kidney disease compared to healthy controls.

Conclusions: Taken together, we demonstrated that targeting *MALAT1* preserves endothelial cell function and kidney health and may provide novel strategies to counteract the development of fibrosis.

Funding: Private Foundation Support

TH-PO1090

Repression of Frmd6 Expression by miR-17/-20a in the Renal Epithelium Mitigates Interstitial Fibrosis

Debora Malta C.S Santos,[1] Maliha Tayeb,[1] Andrew J. Bodnar,[1] Christopher L. O'Connor,[2] Huanqing Zhang,[2] Corynn Appolonia,[1] Brittney M. Rush,[1] Roderick J. Tan,[1,3] Arohan R. Subramanya,[1] David L. Turner,[2] Markus Bitzer,[2] Jacqueline Ho.[1] *[1]University of Pittsburgh, Pittsburgh, PA; [2]University of Michigan, Ann Arbor, MI; [3]Pittsburgh Center for Kidney Research, Pittsburgh, PA.*

Background: Chronic kidney disease (CKD) is characterized by a progressive decline in kidney function, and renal fibrosis is an essential part of the pathophysiological mechanism underlying disease progression. In this study, we investigated the role of the *miR-17~92* microRNA (miRNA) cluster in renal fibrosis. This cluster generates a single polycistronic primary transcript that yields six mature miRNAs (*miR-17*, *-18a*, *-19a*, *-19b*, *-20a*, and *-92a*).

Methods: Unilateral ureteral obstruction (UUO) and acute kidney injury (AKI) to CKD model were used as models of renal fibrosis. To investigate the potential role of *miR-17~92* as an anti-fibrotic molecule, genetic mouse models of inducible Pax8 lineage-specific deletion (*imiR-17~92*^{EpiLOF}) and gain-of-function (*imiR-17~92*^{EpiGOF}) of *miR-17~92* were generated. Protein expression was assessed by immunostaining in mouse kidneys and human nephrectomy samples from the PRECISE cohort, which includes patients with CKD stages 1 and 2. PAR-CLIP was performed in the human proximal tubular epithelial cell line HK2 treated or not with TGFβ1 to identify potential *miR-17~92* targets, which were then validated by dual luciferase reporter assays in HEK293 cells. HK2 cells were transfected with either an empty vector or a vector containing the *Frmd6 cDNA*.

Results: *miRs-17*, *-18a*, and *-20a* were upregulated in UUO and the AKI to CKD model. Interestingly, UUO-induced fibrosis was exacerbated in *imiR-17~92*^{EpiLOF} mice but ameliorated in *imiR-17~92*^{EpiGOF} mice. *Frmd6*, an activator of Hippo signaling, was identified as a novel *miR-17/-20a* target. Frmd6 was increased in the tubular epithelium of obstructed *imiR-17~92*^{EpiLOF} kidneys compared to controls. Furthermore, augmented Frmd6 was associated with regions of human nephrectomy samples with increased collagen III deposition. Finally, overexpression of Frmd6 in HK2 cells resulted in increased expression of the COPII secretory pathway component, Sec31, and was accompanied by elevated secretion of collagen III in conditioned media.

Conclusions: Together, our findings indicate that the epithelial-derived *miR-17~92* limits collagen deposition during renal fibrosis by regulating Frmd6 expression.

Funding: NIDDK Support

TH-PO1091

ACSM3 Protects Kidney Aging and Fibrosis by Cellular Senescence via Histone Acetylation

Yiting Wu,[1,2] Liang Ma,[1,2] Ping Fu.[1,2] *[1]Sichuan University, Chengdu, China; [2]Kidney Research Institute, Division of Nephrology, West China Hospital of Sichuan Univeristy, Chengdu, China.*

Background: Cellular senescence is associated with renal disease progression. Accelerated tubular cell senescence promotes the pathogenesis of renal fibrosis caused by natural aging and disease.

Methods: Proteomic analysis and IHC staining were made to show Acsm3 expression. Acsm3 KO and overexpressed(AAV) mice were performed UUO surgeries. Renal fibrosis was measured by qPCR and Western Blot. SA-β-gal staining and γH2AX IHC staining was used to check senescence. IF staining was to locate Acsm3.

Results: Cellular senescence happened in both elderly mice and UUO mice. Acsm3 is the No.1 increased protein in elderly mice via proteomic sequencing. ACSM3 was positively correlated with age and eGFR. The KO of Acsm3 could induce renal fibrosis with increased α-SMA etc. Senescence was increased with growth SA-β-gal and γH2AX. Overexpressing Acsm3 by AAV, the fibrosis and senescence became less. H3K27AC was the most significant histone modification among others. Locating ACSM3 in cell mitochondria, there was an ACSM3 nuclear translocation treated with TGF-β. Overexpression of ACSM3 can reduce acetyl-CoA in the nucleus.

Conclusions: Acsm3 may be a protector for renal fibrosis by inhibiting cellular senescence of tubular epithelial cells. The underlying mechanism may be the histone acetylation modification.

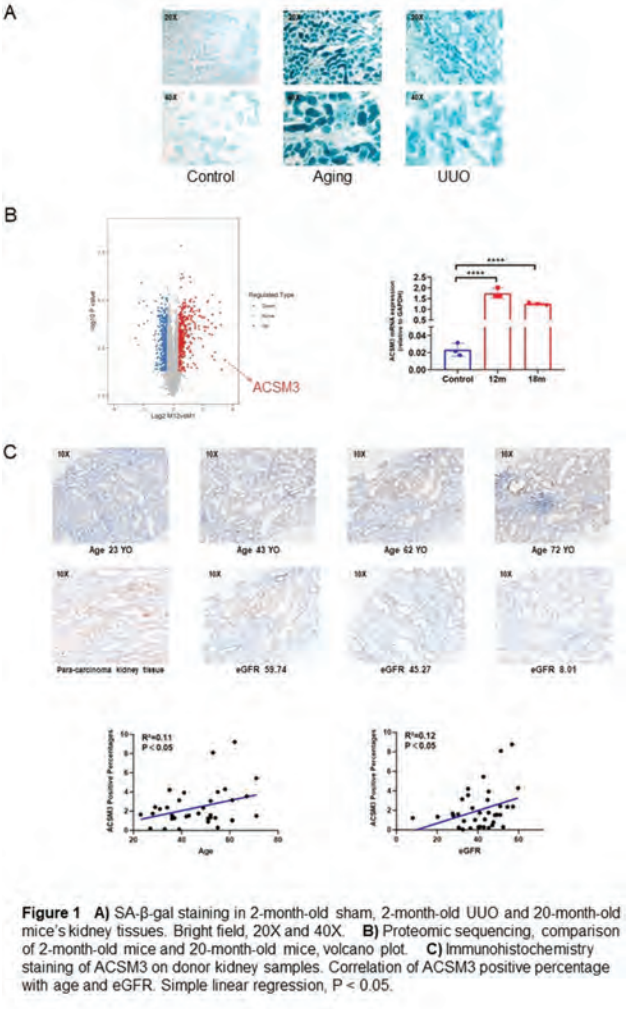


Figure 1 **A)** SA-β-gal staining in 2-month-old sham, 2-month-old UUO and 20-month-old mice's kidney tissues. Bright field, 20X and 40X. **B)** Proteomic sequencing, comparison of 2-month-old mice and 20-month-old mice, volcano plot. **C)** Immunohistochemistry staining of ACSM3 on donor kidney samples. Correlation of ACSM3 positive percentage with age and eGFR. Simple linear regression, $P < 0.05$.

Figure 1

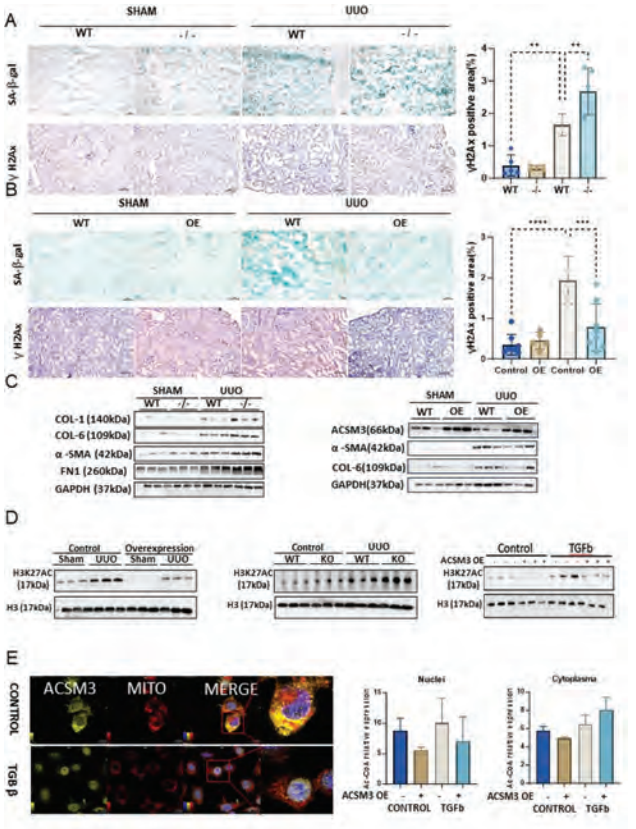


Figure 2 **A)** Sham and UUO surgeries performed on WT and ACSM3-KO mice. SA-β-gal staining and gammaH2AX IHC staining on OCT and FFPE. **B)** Overexpress ACSM3 with AAV2/9-Ksp-ACSM3 on sham and UUO mice. SA-β-gal staining and gammaH2AX IHC staining on OCT and FFPE. **C)** Western Blot of Col1a1, Col6, α-SMA and FN1 on ACSM3 KO mice; Western Blot of Col6 and FN1 on ACSM3 OE mice. **D)** H3K27AC protein expression in vivo and vitro models. Western Blot. **E)** overexpress ACSM3 on HK-2 cell line and treated with 5ng/ml TGF-β. Images taken on 0 and 48 hrs. Blue channel: DAPI; Red channel: mitochondrial; Yellow channel: ACSM3. Acetyl-Coa test on HK-2 nuclei and cytoplasm separately.

Figure 2

TH-PO1092

Transient DNA Damage in Proximal Tubules Accelerates Kidney Aging

Masanobu Takasu,[1] Seiji Kishi,[1] Yuhei Kirita,[2] Kengo Kidokoro,[1] Tamaki Sasaki,[1] Naoki Kashihara,[1] Motoshi Hayano.[3] *[1]Kawasaki Ika Daigaku, Kurashiki, Japan; [2]Kyoto-fu, Kyoto, Japan; [3]Keio Gijuku Daigaku, Minato-ku, Japan.*

Background: As global aging, it is crucial to investigate how aging impacts organ functions. CKD is increasingly prevalent among older populations. Research shows that kidney function gradually declines until age 40, after which the deterioration accelerates (J Am Geriatr Soc, 1985; Nephrol Dial Transplant, 2006). This underscores the role of aging in elevating kidney disease risk. However, the reasons behind the rapid decline in kidney function post-40 and the impact of early adult lifestyle choices on later kidney health remain unclear. Our previous studies with ICE (Inducible Changes in Epigenome) mice (Hayano et al, Cell, 2023), motivate this investigation into how DNA stress contributes to kidney aging.

Methods: We developed ICE mice by crossing I-PpoI$^{STOP/+}$ mice with Cre$^{ERT2/+}$ mice. The enzyme I-PpoI only causes DNA double-strand breaks during tamoxifen administration, which are repaired via the DNA damage repair pathway. We fed 4 to 6 month-old ICE mice a tamoxifen-enriched diet for three weeks and euthanized them at 14 months. We then conducted a thorough examination of their kidney function, including histology, snRNA sequencing, qPCR, and WB analysis.

Results: Histological evaluation showed no significant changes in interstitial fibrosis between ICE and control mice. However, snRNA sequencing revealed an increase in the proximal tubules of ICE mice expressing Kim-1 and Vcam-1, markers of failed repair. Increased expression of VCAM-1 at the protein level was also confirmed by WB and immunostaining. We also observed heightened expression of p21 and upregulation of the DNA repair gene Mgmt, indicating genomic instability and progressive cellular senescence in the proximal tubules. Assessments of whole kidneys showed no changes in mitochondrial number, and single-cell analysis indicated no significant differences in mitochondrial function.

Conclusions: Our findings suggest that even brief, transient DNA damage, though repaired, can have long-term effects on kidney health, particularly in the proximal tubules. These tubules exhibit signs of DNA instability and accelerated cellular senescence, which may increase their vulnerability to external damage. This vulnerability underscores the susceptibility of the proximal tubules to DNA damage and could explain the diminished recovery from acute kidney injury observed in older individuals.

TH-PO1093

Glycolysis-Induced Advanced Glycation End Products Promote Tubular Senescence and Maladaptive Kidney Repair after Ischemic Injury

Qingqing Wei,[1] Zheng Dong.[1,2] *[1]Augusta University Department of Cellular Biology and Anatomy, Augusta, GA; [2]Charlie Norwood Department of Veterans Affairs Medical Center, Augusta, GA.*

Background: Maladaptive kidney repair is accompanied by the metabolic switch to glycolysis. In our study, specific knockout of renal tubule PKM2 (PKM2-KO), a key enzyme in glycolysis, ameliorated maladaptive kidney repair after ischemic injury.

Methods: In PKM2-KO mouse kidneys, we observed higher levels of GSH, likely due to the metabolic flux shift to the pentose phosphate pathway (PPP), a branched pathway producing NADPH and GSH. One consequence of this metabolic shifting could be the neutralization of methylglyoxal (MG, a major by-product of glycolysis) by PPP-derived GSH. MG is a reactive carbonyl species, which binds to various biomolecules (e.g. proteins, nucleic acids, and lipids) to form advanced glycation endproducts (AGEs), causing cellular dysfunction such as senescence in renal tubular cells.

Results: Consistently, we found that senescence was significantly induced in kidneys after 30 minutes ischemia and 2 weeks of reperfusion, showing higher SA-b-Gal staining and P16 expression (senescence markers). Meanwhile, there was dramatic AGEs induction, as demonstrated by the immunoblots and immunohistochemical staining in kidneys. PKM2-KO significantly suppressed the induction of P16 and AGEs. In cultured renal proximal tubular cells, MG induced P16 and promoted the expression of fibronectin after TGF-b1 treatment. Furthermore, AG1, an activator of the key enzyme glucose 6 phosphate dehydrogenase in PPP, enhanced wound healing in a scratch wound model of cultured renal proximal tubular cells.

Conclusions: In conclusion, these data suggest that metabolic switch to glycolysis may induce MG/AGEs in proximal tubule cells, exacerbating the senescence to promote maladaptive kidney repair.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO1094

p38 Phosphorylation in Proximal Tubular Cells Induces Quiescence-to-Senescence Transition and Kidney Fibrosis

Yohei Iwashige,[1] Ryo Yamada,[1] Takuya Morinishi,[1] Koji Muro,[1] Shigenori Yamamoto,[1] Yasuhiro Yamada,[2] Motoko Yanagita.[1] *[1]Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu, Kyoto, Japan; [2]Tokyo Daigaku, Bunkyo-ku, Japan.*

Background: Phosphorylation of p38 (p-p38) has been reported in kidney injury models and is known to induce cellular senescence *in vitro*. However, how p-p38 contributes to kidney injury has not been fully elucidated.

Methods: We established transgenic mice (PT-MKK6EE mice) and cell lines (MKK6EE HK-2) that can induce doxycycline (Dox)-induced constitutive p38 phosphorylation in proximal tubular cells (PTCs). The contribution of p-p38 in the induction of cellular senescence and fibrosis was examined in these mice and cell lines.

Results: Wild-type mice showed p-p38 expression in injured PTCs in ischemia-reperfusion (IR) and ureteral obstruction models. Ki67 expression was suppressed in p-p38 positive PTCs, suggesting a link between p-p38 and cell cycle arrest *in vivo*. In PT-MKK6EE mice, Dox treatment induced p38 phosphorylation in PTCs, where Cyclin D1 expression was completely suppressed and Kim-1 expression was strongly induced. When IR injury model was induced in PT-MKK6EE mice, Ki67-positive cells in PTCs was significantly decreased, supporting the hypothesis that p-p38 induces cell cycle arrest *in vivo*. Furthermore, after long-term observation without injury, a subpopulation of p-p38-induced PTCs exhibited cytoplasmic lysosomal accumulation and a pro-inflammatory phenotype, indicating a phenotype similar to cellular senescence. Additionally, αSMA-positive myofibroblasts appeared around p-p38-induced PTCs, suggesting that p-p38 in PTCs induces kidney fibrosis. In MKK6EE HK-2 cells, Dox treatment induced p38 phosphorylation and inhibited cell proliferation. At the same time, Dox treatment decreased Cyclin D1 expression and increased p21 and p27 expression, together with the reduction of Skp2, an E3 ligase of p21 and p27, consistent with cellular quiescence, known as the G0 phase. Long-term observations revealed cytoplasmic lysosomal accumulation and a pro-inflammatory phenotype in p-p38 induced cells *in vitro*.

Conclusions: We revealed a novel mechanism by which p-p38 induces G0 cell cycle arrest by increasing p21 and p27 expression and decreasing Skp2 expression *in vitro*. Furthermore, prolonged p-p38 expression induces quiescence-to-senescence transition both *in vivo* and *in vitro*. In addition, p-p38-induced senescent PTCs *in vivo* affect the surrounding microenvironment and induce kidney fibrosis.

TH-PO1095

TEAD1 Regulates Tubular Epithelial-Cell Dedifferentiation and Kidney Fibrosis

Melanie Tran, Baihai Jiao, Hao Du, Yanlin Wang. *University of Connecticut School of Medicine, Farmington, CT.*

Background: A prominent pathological feature of chronic kidney disease (CKD) is renal fibrosis, which is characterized by excessive accumulation of extracellular matrix (ECM). In fibrosis, tubular epithelial cells (TECs) undergo dedifferentiation leading to reduced expression of characteristic epithelial markers and increased expression of mesenchymal markers. Despite recent advances in our understanding of the mechanisms of renal fibrosis, the molecular mechanisms remain poorly understood. In this study, we examined the role of TEA domain family member 1 (TEAD1) in regulating TEC dedifferentiation during the development of CKD.

Methods: Cultured TECs were used to examine the role of TEAD1 in regulating TEC dedifferentiation, G2/M cycle arrest, and cellular senescence. Proximal tubule-specific TEAD1 knockout ($TEAD1^{PKO}$) mice were generated by crossing TEAD1 floxed mice with PEPCK-Cre mice. Ten-week-old male $TEAD1^{PKO}$ mice and $TEAD1^{f/f}$ ($TEAD1^{CON}$) mice were intraperitoneally injected with folic acid (250 mg/kg) or vehicle (0.3mM $NaHCO_3$) to induce renal fibrosis. Blood and kidneys were collected at 14 days for analysis of kidney function, TEC dedifferentiation, inflammation, fibroblast activation, collagen deposition and fibrosis.

Results: In cultured TECs, knockdown of TEAD1 using shRNA promoted TEC dedifferentiation and ECM protein production. Additionally, knockdown of TEAD1 markedly induced p-H3 and p21 levels indicating G2/M cycle arrest which was associated with increased senescence-associated β-galactosidase activity. In contrast, overexpression of TEAD1 prevented tubular cell dedifferentiation and ECM protein production, and markedly reduced p-H3 and p21 expression. *In vivo*, TEAD1 expression was significantly induced in kidneys of mice with folic acid injury. Following folic acid injury, $TEAD1^{PKO}$ mice exhibited kidney dysfunction as reflected by higher BUN levels compared with $TEAD1^{CON}$ mice. Moreover, $TEAD1^{PKO}$ mice had increased inflammatory cytokines, enhanced fibroblast activation and upregulated total collagen deposition and ECM proteins, which was associated with p-H3 and p21 induction compared with $TEAD1^{CON}$ mice.

Conclusions: Taken together, our results indicate that TEAD1 plays an important role in regulating TEC dedifferentiation and fibrosis. Therefore, targeting TEAD1 could represent a novel therapeutic approach for attenuating CKD progression.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO1096

ELF4 in NK Cells Is an Important Mediator of Fibroinflammation in Mice and Patients

Chenyu Li, Katalin Susztak. *University of Pennsylvania, Philadelphia, PA.*

Background: Inflammation plays a key role in tissue fibrosis. However, the pathways that orchestrate the inflammatory response are poorly understood. Using genome-wide comparative transcriptomics, we identified ELF4 as a conserved transcription factor upregulated in mouse kidney fibrosis models and human chronic kidney disease (CKD) samples.

Methods: We analyzed gene expression profiles of kidneys from five mouse fibrosis models and human CKD samples to identify conserved transcriptional regulators. The functional role of the identified transcription factor ELF4 was studied using genetic modified mice, single cell RNA-seq, chromatin immunoprecipitation and in vivo antibody mediated cell-depletion and cytokine neutralization.

Results: Overlap analysis of differentially expressed genes identified ELF4 as a conserved upregulated transcription factor in kidney fibrosis. Mice with genetic deletion of ELF4 were protected from folic acid induced kidney fibrosis, showing reduced collagen accumulation and expression of pro-fibrotic genes. Single cell RNA-seq and immunofluorescence indicated that ELF4 was primarily expressed by NK cells in the mouse kidney. ChIP-seq and scRNA-seq revealed that ELF4 directly regulates IFNG expression in NK cells. In vivo, loss of ELF4 reduced IFNG expression by NK cells and altered macrophage polarization in an IFNG dependent manner, which further confirmed by NK cell depletion and IFNG neutralization experiments. Antisense oligonucleotide mediated ELF4 knockdown also protected mice from kidney fibrosis, recapitulating the genetic deletion phenotype. Moreover, in vitro studies showed that ELF4 knock out macrophages had normal IFNG response, indicating an indirect regulation of macrophages by ELF4 in vivo.

Conclusions: We identified ELF4 as a conserved transcription factor induced in kidney fibrosis. ELF4 expressed by NK cells directly regulates IFNG expression and indirectly alters macrophage polarization and fibrogenesis. Inhibiting ELF4 expression might provide new therapeutic opportunities for kidney fibrosis.

Funding: NIDDK Support

TH-PO1097

Itaconate Serves as a Urinary Biomarker and an Inhibitor of Chronic Kidney Inflammation

Qian Yuan, Xie Yaru, Chun Zhang. *Huazhong University of Science and Technology Tongji Medical College Union Hospital, Wuhan, China.*

Background: Inflammation plays a pivotal role in the pathogenesis of chronic kidney diseases (CKD), serving as a predominant pathological alteration and a key driving force. The identification of a noninvasive biomarker for renal inflammation holds significant implications for elevating the progression of CKD. Notably, the correlation between phenotypes and metabolite levels surpasses that observed for proteins and genes, highlighting the growing attention towards exploring metabolites as biomarkers for human diseases. Therefore, this study aims to investigate noninvasive metabolic biomarkers of renal inflammation.

Methods: Metabonomics analysis was used to identify key differential metabolites in urine samples from CKD patients and healthy individuals. The correlation between urinary itaconate levels measured by LC-MS/MS and renal inflammation was investigated. Furthermore, the mechanism underlying the upregulation of itaconate was explored using single-cell sequencing, Western Blot, qRT-PCR, and ChIP assays. To explore the role of itaconate in the progression of CKD, *IRG1* global knockout mice and macrophage specific *IRG1* deletion mice were generated, and were subjected to bilateral ischemia reperfusion (bIRI) surgery.

Results: Through metabonomics and LC-MS/MS analysis, we found that urinary itaconate was elevated in patients and mice with CKD, and positively correlated to renal inflammation and the decline of renal function. Mechanistically, the IL-1β signaling pathway activates the transcription factor AP-1, thereby upregulating the expression of IRG1, which encodes the enzyme responsible for catalyzing itaconate production through direct binding to its promoter in macrophages. Furthermore, renal cytokines and alternative M2 macrophages accumulation, as well as the development of renal fibrosis induced by bIRI were aggravated by global *Irg1* knockout and macrophage specific *Irg1* knockout.

Conclusions: Our findings not only provide a noninvasive biomarker of chronic renal inflammation but also elucidate the role and mechanism of itaconate in CKD.

Funding: Government Support - Non-U.S.

TH-PO1098

Identification of Gut Microbiota Involved in the Production of Uremic Toxins in Patients with CKD

Takafumi Toyohara,[1] Shun Watanabe,[1] Koichi Kikuchi,[1] Takehiro Suzuki,[1] Tetsuhiro Tanaka,[1] Takaaki Abe.[1,2] *[1]Tohoku University Graduate School of Medicine, Sendai, Japan; [2]Tohoku University Graduate School of Biomedical Engineering, Sendai, Japan.*

Background: Modulating the gut microbiota is a promising therapeutic strategy for chronic kidney disease (CKD) because uremic toxins derived from gut microbiota accumulate in CKD patients and worsen their prognosis. However, the specific gut bacterial species involved in the production of uremic toxins in CKD patients have not been sufficiently elucidated. This study aimed to identify gut bacteria that either produce or inhibit uremic toxins.

Methods: Serum levels of gut microbiota-derived uremic toxins (Indoxyl sulfate (IS), Phenyl sulfate (PS), *p*-Cresyl sulfate (*p*CS), trimethylamine N-oxide (TMAO)) were measured in 101 CKD patients attending Tohoku University Hospital. Additionally, the gut microbiota composition was analyzed by 16S rRNA gene sequencing. Multiple regression analysis was conducted with the uremic toxins as dependent variables and bacterial composition and eGFR as explanatory variables to identify significant bacteria independent of kidney function as a confounder.

Results: Analysis of patient stool samples identified 585 bacterial species at the genus level. Multiple regression analysis revealed significant correlations between uremic toxins and gut microbiota in 21 combinations. Notably, two species showed a strong positive correlation with *p*CS, and two showed a strong negative correlation. At the species level, *Clostridium fessum*, *Veillonella parvula*, and *Enterocloster bolteae* were negatively correlated with *p*CS. When these three species were administered to adenine-induced renal failure mice, only *Veillonella parvula* significantly reduced *p*CS levels ($P = 0.0079$).

Conclusions: This study identified bacterial species correlated with blood *p*CS levels in renal failure patients. Among these species, *Veillonella parvula* significantly reduced the *p*CS level in a renal failure mouse model. These findings suggest that modulating specific bacterial species could lead to new therapeutic strategies for CKD, improving patient outcomes through gut microbiota or dietary intervention.

Funding: Government Support - Non-U.S.

TH-PO1099

Small Molecule Inhibitor of Gut Microbial Choline Trimethylamine Lyase Reduces Serum Trimethylamine N-oxide and Slows the Loss of Kidney Function in a Rat Model of CKD

Jerry Buysse, Jun Shao, Robert Matunas, Camilla V. Simpson.
Zehna Therapeutics, Inc., Los Altos, CA.

Background: Gut microbial choline trimethylamine (TMA) lyase (CutC) plays a key role in the formation of TMA, a precursor of trimethylamine *N*-oxide (TMAO) that is both a cause and driver of CKD. Here we describe the pharmacological effects of small molecule CutC inhibitor ZTx102 on serum TMAO level and kidney function in an adenine-induced rat model of CKD.

Methods: CKD was induced and maintained in rats by adding 0.25% adenine to a standard chow diet supplemented with 0.5% choline in the drinking water. The small molecule CutC inhibitor, ZTx102, an orally administered colon directed formulation, was administered at doses of 1.25 and 12.5 mg/kg of body weight, once a day, during the maintenance phase. The controls received matching placebo, once a day. Serum TMAO was quantified using LC-MS/MS. Kidney function was assessed by serum levels of creatinine and eGFR.

Results: Adenine and choline supplementation increased serum levels of TMAO and creatinine in rats. Oral administration of ZTx102 as a colon directed formulation resulted in rapid and sustained reduction of serum TMAO to the normal range during the maintenance phase of the study. ZTx102 significantly reduced serum levels of creatinine (0.8 mg/dL in 12.5 mg/kg ZTx102 vs. 1.5 mg/dL in placebo; P<0.001). ZTx102 significantly slowed eGFR decline (0.96 mL/min in 12.5 mg/kg ZTx102 vs. 0.64 mL/min in placebo; P<0.05). In addition, ZTx102 reduced serum N-terminal prohormone of brain natriuretic peptide (5.6 pg/mL in 12.5 mg/kg ZTx102 vs. 112.2 pg/mL in placebo; P<0.0001), a biomarker of myocardial stress and early heart failure.

Conclusions: The small molecule CutC inhibitor ZTx102 is effective in normalizing elevated serum levels of TMAO and slowing the loss of kidney function in a rat model of CKD when administered as a colon directed formulation. Reduction of serum TMAO level by the CutC inhibitor ZTx102 may provide a potential new approach to slow disease progression in persons with CKD.

Funding: Commercial Support - Zehna Therapeutics, Inc., Private Foundation Support

TH-PO1100

Depletion of the Gut Microbiota Modulates Metabolome and Immune Profiles in Experimental CKD

Alex Yarritu,[1] Wibke Anders,[1] Sakshi Kamboj,[2] Sara A. Hassan,[1] Carina Hoffmann,[1] Ariana Rauch,[1] Franziska Fuckert,[1] Johannes Holle,[1] Hendrik Bartolomaeus,[1] Wolfram Gronwald,[2] Nicola Wilck.[1] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Universitat Regensburg, Regensburg, Germany.*

Background: Chronic Kidney Disease (CKD) disrupts the gut microbiome, leading to the production of uremic toxins that impaired kidneys fail to excrete. These toxins potentially increase immune cell activation and senescence, promoting chronic inflammation and exacerbating CKD progression. The exact mechanisms by which gut-derived uremic toxins modulate these alterations remain poorly understood. We hypothesize that microbiome depletion reduces uremic toxin accumulation and immune activation, thereby slowing CKD progression.

Methods: Experimental CKD was induced in 129Sv mice by 5/6 nephrectomy (STNx). Mice were given a non-absorptive antibiotic (Abx) cocktail in drinking water for microbiota depletion or control (Ctrl) throughout the 13-week study period. Plasma, feces, and urine were collected longitudinally to explore metabolite dynamics and CKD progression using untargeted Nuclear Magnetic Resonance (NMR), followed by a targeted approach.

Results: Measurement of 16S gene abundance confirmed the suppression of intestinal microbial load in Abx groups. 16S sequencing of fecal samples showed alterations of bacterial taxa by STNx, with some taxa being reminiscent of human CKD. Abx-STNx mice showed improved kidney function compared to STNx (FITC-sinistrin GFR 113.2 ± 57.21 µl/min vs. 53.32 ± 41.05 µl/min; p = 0.0028). Abx-STNx mice exhibited reduced systemic inflammation, with lower plasma C-reactive protein levels (56.88 ± 16.21 µg/L vs. 78.57 ± 16.57 µg/L; p = 0.0024). Untargeted NMR analysis identified a unique metabolite profile, with higher accumulation of 36.8% the detected metabolome in STNx (p = 0.05) compared to only 18.2% in Abx-STNx (p = 0.05), suggetsing that half of the metabolite accumulation in CKD is microbiome-dependent. To further explore the mechanistic link between metabolite accumulation and inflammation, we assessed the aryl hydrocarbon receptor (AhR)-activating potential. Moreover, organ-specific (blood, spleen, heart, intestine) immune cell composition was analyzed.

Conclusions: Microbiome depletion in experimental CKD improves kidney function. Abx impacted plasma metabolite profiles, leading to reduced inflammation. These proof-of-concept experiments underscore the microbiome as treatment target for in CKD.

TH-PO1101

Proximal Tubular Function Is Independent of Glomerular Filtration Rate

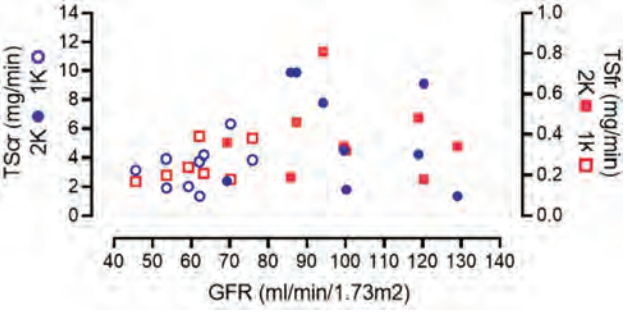
Magdalena Madero,[1] Ana K. Fernandez Yepez,[1] Guadalupe M. Montesinos Ojeda,[1] Alan J. Guzmán Portillo,[1] Aurora I. Estrada Escamilla,[1] Francisco Perez Allende Perez,[1] Bernardo Rodriguez-Iturbe.[1,2] *[1]Instituto Nacional de Cardiologia Ignacio Chavez, Ciudad de Mexico, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: Tubular function is not routinely evaluated in kidney donors in the assumption that glomerular filtration rate (GFR) offers adequate representation of overall kidney health

Methods: We studied in kidney donors the response of cationic organic transporters (COT) with an oral dose of 5g of creatinine (cr) and anionic organic transporters (AOT) with an intravenous dose of 1mg/kg of furosemide (fr). Previous studies had shown that these doses resulted in maximal stimulation of CAT and AOT, respectively, without significant changes in GFR. Studies were done in 10 kidney donors (age 20-51 years; 3 females) before (2 kidneys or 2K) and 3 months after nephrectomy (1 kidney or 1K). GFR (iohexol), serum and urine cr (autoanalyzer) and urinary fr (HPLC) concentrations were determined in hourly blood and urine collections obtained 5 hours after the administration of cr and fr. Water diuresis was maintained during the studies and complete bladder emptying was determined by ultrasound. Tubular secretion of cr (TScr) was estimated as the subtraction of filtered creatinine (GFR x serum cr) from the urinary creatinine excretion (Ucr x Uvolume) and tubular secretion of furosemide (TSfr) = Ufr x Uvol. Data given are mean±95%CI

Results: First hour TScr and TSfr in the first hour (2K-TScr= 5.47±2.57 mg/min; 2K-TSfr= 0.39±0.123 mg/min) were 3-4 fold higher (p<0.01) than in subsequent hours when they remained essentially stable. The 1K responses were lower than the 2K responses, but also maximal in the first hour, (1K-TScr 3.38±0.981; 1K-TSfr 0.25±0.068) and stable afterwards. As There were no correlations between TScr or TSfr with the GFR in 2K or 1K studies (Figure 1) and no consistent changes between 2K and 1K studies in the relation between GFR and TScr or TSfr

Conclusions: The data show that stimulated functional responses of OCT and OAT in kidney donors, neither pre nor post-nephrectomy, are related to GFR and deserve evaluation of their prognostic relevance.



TH-PO1102

Cell Cycle Arrest and CCN2 Expression in Proximal Tubular Epithelial Cells in a Mouse CKD Model

Wakako Kosakai,[1] Tetsuya Sato,[2] Tsutomu Inoue,[1] Daichi Fukaya,[1] Hiroaki Amano,[1] Hirokazu Okada.[1] *[1]Saitama Ika Daigaku, Iruma-gun, Japan; [2]Saitama Ika Daigaku, Hidaka-shi, Japan.*

Background: Proximal tubular epithelial cells (PTECs) enter the M phase in response to injury, after which a subset of the cells undergo G2/M arrest and acquire a pro-fibrotic phenotype (PFP), expressing CCN2 and TGF-β. Alternatively, other reports indicate G1/S arrest resulting in a PFP. To investigate the relationship between the cell cycle of PTECs and the PFP, we used a unilateral renal ischemia-reperfusion injury (IRI) model.

Methods: We reanalyzed the publicly available data for scRNA-seq from IRI, extracting only the PTEC data (cont. 7,315 cells; IRI 1, 3, 14 days; 2,689 cells: Nat. Commun. 13 (1): 4018). Furthermore, we performed studies in IRI model established using F1 mice generated by crossing Fucci2aR mice with γ-glutamyltransferase-Cre mice, allowing visualization of the cell cycle by fluorescence (G1 = Cherry, S/G2/M = mVenus). We also used cultured renal tubular epithelial cells (HK-2 cells).

Results: Reanalysis of scRNA-seq data revealed that the proportion of PTECs in the G2/M phase in fibrotic kidneys was similar to that in normal kidneys, with a minor increase in the acute phase (10.3% normal vs. 12.2% at 3 days, 8.7% at 14 days post-fibrosis). In F1 mice, mVenus-positive cells increased sharply after IRI, but declined from a peak at 3 days (2.3 ± 2.1%) to less than 1% by day 7 (0.8 ± 1.1%) with no further increase observed, despite progressive fibrosis. Mimicking IRI in HK-2 cells by transiently inducing G1/G0 arrest via a hypoxia/glucose-free medium followed by re-oxygenation and the addition of growth media led to transient cyclin-dependent kinase 1 upregulation and progression into the S/G2 phase. However, as the cell density increased,

p21/p27 expression increased, with the proportion of G1/G0 PTECs increasing again by 72 h. These re-arrested G1/G0 cells exhibited increased TGF-β and CCN2 expression. Higher cell densities tended to further enhance CCN2 expression.

Conclusions: While G2/M arrest has been highlighted in the PFP, our findings suggest that G1/G0-arrested PTECs can also acquire this phenotype. In injured kidneys, the proportion of G1/G0-arrested PTECs exceeded that observed in the G2/M phase. Although the importance of PTECs in chronic kidney disease progression is undisputed, further studies should consider cells in all cell cycle states rather than limiting their focus to particular phases.

Funding: Government Support - Non-U.S.

TH-PO1103

Inhibition of Hyaluronan Synthesis or Hyaluronan-CD44 Interaction Attenuates Kidney Inflammation and Fibrosis in NZB/W F1 Mice

Tak Mao D. Chan, Cheuk Yin Wong, Yuesong Xu, Susan Yung. *Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong, Hong Kong.*

Background: Lupus nephritis (LN) is characterized by immune-mediated kidney injury, and it is an important cause of acute kidney injury and chronic kidney disease. Hyaluronan (HA) is a non-sulfated glycosaminoglycan implicated in tissue inflammation and fibrosis through binding to its cell surface receptor, CD44. We previously demonstrated that in patients with LN the circulating HA level correlated with the severity of chronic kidney damage as demonstrated in kidney biopsies. This study investigated the effect of 4-methylumbelliferone (4-MU), a specific inhibitor of HA synthesis, and anti-CD44 antibody, on disease manifestations and kidney fibrosis in an animal LN model of NZB/W F1 mice.

Methods: HA expression was investigated in female NZB/W F1 mice showing proteinuria. In the first study, mice were randomized to receive either vehicle (Arabic Gum) or 4-MU in Arabic Gum for 12 weeks. In the second study, mice were randomized to receive either anti-CD44 antibody or Control IgG for 4 weeks and parameters related to kidney inflammation and fibrosis were assessed in both studies.

Results: As disease progressed, mice treated with Arabic Gum or Control IgG showed glomerulosclerosis and neighboring glomerular hypertrophy, tubular dilation with flattening of epithelial cells, tubular protein casts and periglomerular and tubulo-interstitial mononuclear cell infiltration that included $CD3^+$ and $CD4^+$ T cells, $CD19^+$ B cells and macrophages. Also, HA expression increased in the interstitium and periglomerular area, accompanied by increased CD44, TGF-β1, IL-1β, MCP-1, α-smooth muscle actin, fibronectin, collagen, VCAM-1, and NGAL expression. Treatment of mice with either 4-MU or anti-CD44 antibody preserved normal kidney histological structure, which was associated with reduced expression of mediators of tubulo-interstitial fibrosis and mononuclear inflammatory cell infiltration.

Conclusions: The findings suggest that HA plays a key role in the pathogenesis of inflammation and fibrosis in LN, and suppression of HA synthesis or its interaction with CD44 may have therapeutic implications.

Funding: Government Support - Non-U.S.

TH-PO1104

Inhibition of Hyaluronan Synthesis Attenuates Tubulointerstitial Inflammation and Fibrosis in Murine Unilateral Ureteral Obstruction Model of CKD

Yuesong Xu, Susan Yung, Tak Mao D. Chan. *Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong SAR, Hong Kong.*

Background: Chronic kidney disease (CKD) is a major global issue resulting in considerable morbidity and mortality. Irrespective of the primary etiology, tubulo-interstitial fibrosis is the predominant pathogenic process in CKD progression to end-stage kidney disease, but the underlying mechanism remains obscure. Hyaluronan (HA) is a ubiquitous component of the extracellular matrix and is implicated in tissue inflammation and fibrosis. HA is synthesized by three enzymes, namely HA synthase (HAS), I, II and III. We investigated the roles of HAS I, II and III in tubulo-interstitial inflammation and fibrosis in a murine model of unilateral ureteral obstruction (UUO).

Methods: UUO or Sham operation (Control group) was performed on 10-week old male wild-type (WT) and HAS I, III or I/III knockout (KO) mice, and sacrificed 14 days after UUO and the kidneys were harvested to investigate histopathology and expression of mediators relating to inflammation, fibrosis and tubular injury.

Results: Compared to WT Sham mice, WT mice with UUO showed increased tubulo-interstitial HA expression, and HAS I, II and III gene expression was increased by 360.70±82.95-fold, 91.91±14.6-fold and 3.96±0.37-fold respectively (p = 0.0020, <0.0001 and 0.0022 respectively). Increased HA expression was accompanied by tubular atrophy, immune cell infiltration, and increased expression of KIM-1, TNF-α, CCL-2, α-smooth muscle actin, fibronectin and collagen III (p<0.05, for all). HAS I, III and I/III KO mice with UUO showed reduced immune cell infiltration, tubular atrophy and mediators of renal tubular injury, inflammation and fibrosis, and reduced HA expression, compared to WT UUO mice. HAS I KO was associated with more marked reduction in the expression of inflammatory and fibrotic mediators.

Conclusions: Our findings suggest that HA and HAS I, II, and III may have distinct roles in mediating tubulo-interstitial inflammation and fibrosis in murine UUO CKD model.

Funding: Government Support - Non-U.S.

TH-PO1105

TGFBR1 Inhibition Attenuates Expansion of Maladaptive Tubule Cells and Ameliorates Kidney Function Decline in the Adenine Nephropathy Mouse Model of CKD

Shawn S. Badal,[1] Jay Kuo,[1] Seamus Ragan,[1] Mark McConnell,[1] Reza Amirzadeh,[1] Mariam O. Oyinlola,[1] Charles Nieh,[1] Ralph Gruber,[3] Johannes Nordlohne,[2] Tobias Bohnenpoll,[2] N. Eric Olson.[1] *[1]Chinook Therapeutics Canada Inc, Vancouver, BC, Canada; [2]Evotec SE, Hamburg, Germany; [3]Novartis AG, Basel, Switzerland.*

Background: CKD is increasing worldwide and there is an urgent need for new therapies designed against molecular endotypes of CKD. Recently, a distinct population of maladaptive tubule (MT) cells with a unique molecular phenotype have been linked to more rapid ESRD progression and fibrosis, inflammation and tissue injury in CKD. Here, we characterize an in vivo model of renal impairment and evaluate if inhibition of TGF-β1 signaling attenuates MT cell accumulation, fibrosis, and renal function loss.

Methods: CD1 mice were randomized to control, 0.15% adenine diet or adenine diet with ALK5 inhibitor (ALK5i, SB-525334) equivalent to 60mg/kg in chow. Mice were sacrificed 4 weeks after diet initiation for endpoint analysis. Plasma and serum were collected for creatinine and blood urea nitrogen (BUN) analysis. Kidneys were harvested for assessment of fibrosis (PSR), tubular atrophy (LTL), MT marker (VCAM1) and tubular injury (PAS). Nuclei extracted from flash frozen kidneys were fixed, and barcoded libraries were prepared for single nucleus RNA-Seq.

Results: Creatinine (0.30±0.03 vs. 0.20±.01 mg/dL, p<0.05) and BUN (46.6±8.9 vs. 28.3±5.4, p<0.001) were elevated in adenine and attenuated in ALK5i animals. PSR stain (28.3±5.49 vs 4.5±2.08 %, p<0.0001) and tubular injury (20.7±3.9 vs 9.1±4.0 a.u., p<0.0001) increased following adenine diet and attenuated in ALK5i group. LTL+/VCAM1- (healthy PT), decreased in adenine diet and restored following ALK5i inhibition (13.8±6.0 vs 29.8±5.6 %, p<0.0001). LTL-/VCAM+ cells (MT cells), increased in adenine diet, and decreased after ALK5 inhibition (32.9±4.4 vs 19.3±4.5 %, p<0.0001). snRNA-Seq revealed significant expansion of MT cells with adenine diet and failed repair cells were dominant in the adenine samples compared to control (33% FR vs 0.9% FR).

Conclusions: Inhibition of TGF-β1 pathway attenuates MT cell accumulation in adenine model determined by sn-RNA-Seq and tubular staining for VCAM1 and LTL. ALK5i prevented adenine-induced tubular injury and atrophy, reduced fibrosis and kidney function loss. This study confirms induction of MT cells in the adenine model and as proof of concept that pharmacological intervention can impact accumulation of MT cells in a model of CKD.

Funding: Commercial Support - Chinook Therapeutics, a Novartis Company

TH-PO1106

Histone Demethylase Inhibitor, GSK-J4, Suppresses Tubulointerstitial Fibrosis in CKD

Imari Mimura, Fumiaki Tanemoto, Masaomi Nangaku. *Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Bunkyo-ku, Japan.*

Background: Epigenetic modifications including histone modifications in the kidney have recently been reported to contribute to the progression of renal fibrosis. We have previously reported that one of histone modification inhibitors suppressed renal fibrosis by decreasing open chromatin region. Another histone modifier inhibitor, GSK-J4, is known to inhibit KDM6b (lysine demethylase 6b) which demethylates H3K27me3, resulting in the increase in H3K27me3, a repressive mark of histone modification. We investigated how GSK-J4 affected renal fibrosis.

Methods: We performed in vitro experiments using normal rat kidney interstitial fibroblast cells (NRK49F) stimulated by transforming growth factor-beta (TGF-β) with or without exposure to GSK-J4. To identify the downstream target genes of GSK-J4, we performed comprehensive RNA-seq under normal condition and TGF-β stimulation with and without GSK-J4. In addition, we also performed RNA-seq using siRNA of KDM6b to identify the downstream targets of KDM6b because GSK-J4 inhibited KDM6b.

Results: We confirmed that fibrosis-promoting genes including Ccn2 (cellular communication network factor2), also known as Ctgf (connective tissue growth factor), were inhibited by GSK-J4 in NRK49F under TGF-β stimulation. As a result of RNA-seq, we identified 113 downstream target genes of GSK-J4 that were upregulated by TGF-β and downregulated by GSK-J4. After siRNA knockdown of KDM6b with TGF-β stimulation, we identified 26 genes whose expression was upregulated by TGF-β but downregulated by knockdown of KDM6b. We compared the downstream genes of GSK-J4 to those with siRNA of KDM6b, and we identified seven genes commonly. Among them, Acta2 (alpha SMA; alpha smooth muscle actin), a fibrotic marker whose expression increases as renal

fibrosis progresses, was suppressed by GSK-J4 treatment, which prevented KDM6b from demethylating H3K27me3 and increases H3K27me3, resulting in the reduction of renal fibrosis.

Conclusions: GSK-J4 inhibited renal fibrosis by modulating H3K27me3 via KDM6b on fibrosis-related genes including Acta2. It is important to elucidate the epigenetic molecular mechanisms that accompany the progression of renal fibrosis, as this will lead to the discovery of new therapeutic targets in CKD.

Funding: Government Support - Non-U.S.

TH-PO1107

Characterization of the Mouse Adenine Nephropathy Model: Kidney Proteomic Profiling

Srinath Jagarlapudi, Simone Romoli, Chang J. Zou, Rose A. Keenan, Charles Halsey, Jeffrey A. Culver, Jeffrey Morin, Dinesh K. Hirenallur-Shanthappa, Denis Feliers. *Pfizer Cambridge, Cambridge, MA*.

Background: Most models of chronic kidney disease in mice do not show a robust inflammation/fibrosis response. In this study, we sought renal injury and function in mice fed an adenine-rich diet.

Methods: Ten weeks-old C57Bl/6 mice were fed an adenine-rich diet (0.15%) for 6 weeks. Noninvasive renal oxygen content, renal stiffness and transcutaneous glomerular filtration rate (GFR) were determined at the end of the experiment. Tubular integrity was measured using the furosemide test and correlated with histology and expression of tubular injury biomarkers. The remaining kidneys were harvested, and proteomics analysis was performed on the cortical fraction.

Results: In adenine-fed mice, we observed a progressive reduction in GFR, which reached ~30% of the initial value at 6 weeks. Renal oxygenation was reduced, and renal stiffness was increased in the adenine-fed mice. Histology showed a significant increase in tubular degeneration, inflammation and fibrosis, the latter correlating well with renal stiffness. Adenine-fed mice had an impaired response to furosemide, suggesting a disruption of tubular integrity. Nephron segment-specific injury marker analysis showed that the proximal tubules, cortical thick limb of the loop of Henle and distal tubules were injured in this model. Proteomic analysis showed a massive increase in pathways associated with extracellular matrix expansion, inflammation and complement cascade, while pathways associated with TCA cycle and respiration, transport activity, amino acid metabolism and peroxisomal lipid metabolism were downregulated.

Conclusions: An adenine-rich diet causes a progressive loss of renal function that is associated with a significant increase in tubular injury, fibrosis and inflammation, and a reduction in tubular transport activity and energy metabolism. Therefore, adenine causes chronic renal failure in mice, which manifests as progressive renal insufficiency and metabolic abnormalities that are similar to those seen in patients with chronic kidney disease.

TH-PO1108

Adenine-Induced Mouse Model of CKD Shows Rapid Development of Impaired Kidney Function, Anaemia, Muscle Wasting, and Persistent Kidney Fibrosis following Diet Reversal

Maria K. Ougaard, Frederikke E. Sembach, Michael Christensen. *Gubra, Hørsholm, Denmark.*

Background: Translational rodent models are essential to identify more efficacious treatment options for patients with chronic kidney disease (CKD). However, most preclinical CKD models do not demonstrate impaired kidney function as determined by decreased glomerular filtration rate (GFR). Here, we characterized the adenine diet-induced (ADI) mouse model of CKD for functional, biochemical and histological hallmarks of CKD.

Methods: Male C57BL/6j mice (11 wks. old) were randomized into study groups (n=8-10/group) based on body weight. ADI mice received a control (ctrl) diet from study day -2 and a CKD-inducing diet 0.2% adenine for up to 5 weeks, while control mice received a ctrl diet served as healthy controls (CTRL mice). All groups received oral vehicle dosing once daily from day 1 until termination. Transdermal GFR (tGFR), urine albumin-to-creatinine ratio (uACR), and plasma cystatin C (pCyC) were evaluated at week 3 and 5. Blood was collected for haemoglobin analysis, and gastrocnemius muscle and kidney tissue were sampled and weighed. Kidneys were processed for histological evaluation of markers of macrophage infiltration (F4/80) and fibrosis (Col1a1). In parallel study, ADI mice (3 weeks on ADI diet) were switched to control diet for 2 weeks (diet reversal) to test for spontaneous regression of kidney biomarker and histological changes (uACR, pCyC, F4/80, Col1a1).

Results: Compared to controls, ADI mice showed a significant tGFR decline correlating with increased pCyC levels and marked albuminuria at 3 and 5 weeks after adenine diet-induction. At termination, ADI mice showed significantly decreased haemoglobin and gastrocnemius muscle weight compared to CTRL mice. Furthermore, Quantitative histomorphometric analyses revealed development of renal fibrosis and macrophage infiltration in ADI mice. While diet reversal improved uACR, pCyC, renal fibrosis and macrophage infiltration remained significantly increased in ADI mice.

Conclusions: ADI mice rapidly develop functional, biochemical, and histological hallmarks of CKD complicated by anaemia and muscle wasting. Collectively, the ADI mouse model is highly applicable in preclinical target and drug discovery for CKD.

Funding: Commercial Support - Gubra

TH-PO1109

Cluster of Differentiation-14 Contributes to Tubulointerstitial Inflammation in a Murine Model of CKD

Vivian Wei, Jing Yu. *The University of Hong Kong Li Ka Shing Faculty of Medicine, Hong Kong, Hong Kong*.

Background: Chronic kidney disease (CKD) is characterized by progressive tubulo-interstitial fibrosis and tubular atrophy leading to irreversible deterioration of kidney function. Low-grade persistent inflammation drives CKD progression, but the underlying mechanism remains obscure. CD14 is a GPI-anchored glycoprotein that is predominantly expressed on myeloid cells. Secretion of pro-inflammatory cytokines by macrophages is CD14-dependent. We previously demonstrated that CD14 expression was increased in proximal tubular epithelial cells (PTEC) and interstitium in kidney biopsies of patients with CKD. This study investigated the role of CD14 in kidney inflammation in a murine model of CKD.

Methods: CKD was induced in male wild-type (WT) and CD14 knockout (KO) mice by feeding with casein-based chow containing 0.2% adenine for 8 weeks, after which time kidneys were harvested to assess the expression of mediators of inflammation and kidney injury. Mice fed casein-based chow served as non-CKD controls. The role of CD14 in inflammatory processes was investigated in HK-2 cells that either overexpressed CD14 or were deficient in CD14 expression.

Results: CD14 gene expression increased by 17.66 ± 5.64-fold in WT CKD mice compared to non-CKD WT mice, and was predominantly localized to PTEC and the interstitium. Increased CD14 expression was accompanied by proteinuria and increased mediators of inflammation and tubular injury including IL-6, TNF-α, MCP-1, TGF-β1, NGAL and KIM-1. CD14 KO mice with CKD showed significantly reduced expression of pro-inflammatory and pro-fibrotic cytokines and markers of tubular injury, accompanied by reduced proteinuria ($p<0.05$, for all). HK-2 cells overexpressing CD14 showed increased IL-6, IL-8 and MCP-1 secretion compared to non-transfected cells, and LPS stimulation further augmented cytokine secretion. CD14-deficient HK-2 cells showed significantly reduced IL-6, IL-8 and MCP-1 secretion compared to non-transfected cells.

Conclusions: Our data suggest that CD14 contributes to tubulo-interstitial inflammation in murine adenine-induced CKD and may regulate pro-inflammatory cytokine secretion in PTEC.

Funding: Government Support - Non-U.S.

TH-PO1110

Single-Nucleus RNA Sequencing of AKI to CKD Transition: Novel Perspectives on Leptospirosis Kidney Disease

Yuehan Lu,[1,3] Li-Fang Chou,[1,2] Huang-Yu Yang,[1,3] Chih-Wei Yang.[1,3]
[1]Kidney Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan; [2]Graduate Institute of Biomedical Sciences, Department of Microbiology and Immunology, Department of Biochemistry, Chang Gung University, Taoyuan, Taiwan; [3]Department of Nephrology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

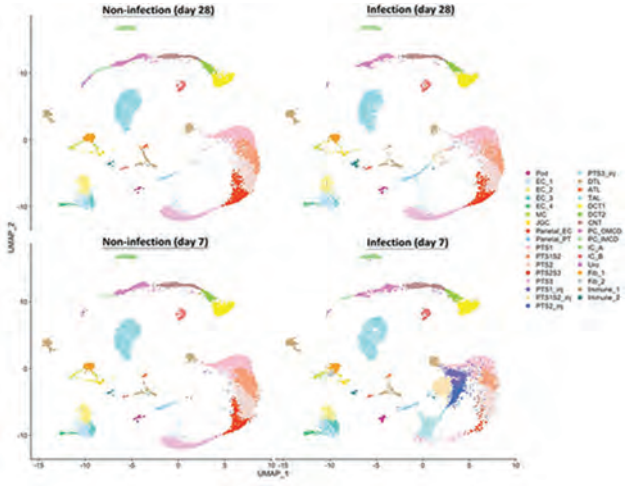
Background: Leptospirosis is a widespread zoonotic disease. Prior cohort studies highlight that acute *Leptospira* infection leads to chronic kidney disease(CKD). This study investigates the transition from acute kidney injury (AKI) to CKD due to *Leptospira* infection.

Methods: 1. Mouse model for leptospiral kidney disease. 2.Transcriptome-wide changes and single-nucleus RNA sequencing(snRNA-seq) in infected kidneys.

Results: The study examined the pathogenic mechanisms from acute to chronic phases during leptospirosis progression. Infected mice showed kidney injury and bacterial adherence to the renal tubules by day 28 post-infection. Renal pathology revealed tubular degeneration, inflammation, and fibrosis characteristic of CKD. Transcriptome profiling identified 714 and 1089 differentially expressed genes at days 7 and 28 postinfection, respectively, which enriched in pathways related to cell activation and innate immune response. Hierarchical clustering identified immune-related genes like *LBP*, *FCGR1*, *SYK*, *IL33*, *COLLA1*, *IRF7*, *NCF1*, and *TLR2*, highlighting roles in immune response regulation and fibrogenesis. SnRNA-seq characterized renal cell states to identify 33 distinct clusters, including various renal cell types. Normal proximal tubular cells (PTCs) decreased on the 7th day postinfection, with an increment of injured PTCs with a potential marker Kynu. Initially, fibroblast numbers increased in the infected group, suggesting early fibrosis development. By day 28, immune cell populations grew, indicating their role in chronic *Leptospira* kidney disease.

Conclusions: *Leptospira* infection disrupts normal kidney cell composition, particularly affecting proximal tubules. Early infection stages revealed a rise in fibroblasts. As infection progresses, immune cell populations increase, indicating their involvement in CKD pathophysiology.

Funding: Government Support - Non-U.S.



UMAP visualization by experimental condition

TH-PO1111

Emx2 Regulates Ciliogenesis by Controlling Prostaglandin Production

Thanh Khoa Nguyen, Rebecca A. Wingert. *University of Notre Dame, Notre Dame, IN.*

Background: Cilia serve important homeostasis roles in fluid flow and sensing to maintain a healthy kidney, and cilia defects have been linked to chronic kidney diseases. Renal multiciliated cells (MCCs) are an aberrant ciliated cell type found in several human kidney pathological states.

Methods: Here, we hypothesized *empty spiracles homeobox gene 2 (emx2)* is important for cilia development in monociliated cells and MCCs. Utilizing several *emx2* deficient models, we performed *in situ* hybridization, renal clearance assays and immunohistochemistry to assess cilia development and function. We studied the relationship between *emx2* and known regulators of the prostaglandin biosynthesis in the kidney such as *ppargc1a*, its downstream targets *ptgs1* and the prostaglandin molecule PGE_2 through a series of qualitative, quantitative and rescue experiments. Finally, we assessed renal basal body functions and performed rescue experiments with PGE_2 in *emx2* deficient models.

Results: We discovered that *emx2* is expressed across ciliated tissues, such as the otic vesicle, nasal placode and renal MCCs. Our *emx2* deficient models displayed reduced cilia development in nephrons, Kupffer's vesicle, neuromasts and the ear. Furthermore, *emx2* deficient embryos displayed a significant reduction in the number of renal MCCs and kidney functional defects including delayed renal clearance, which was associated with pericardial edema. Interestingly, *emx2* deficiency reduced *ppargc1a* and *ptgs1* expression, and the provision of transcripts encoding *ppargc1a* or *ptgs1*, or the supplement of endogenous PGE_2, was sufficient to partially rescue cilia length, intensity and number of ciliated basal bodies. Lastly, we discovered that *emx2* deficiency led to aberrantly positioned basal bodies in the nephron tubule epithelium, which was successfully rescued with PGE_2.

Conclusions: Taken together, our study revealed that *emx2* is an essential regulator of cilia development across tissues through the modulation of prostaglandin biosynthesis.

TH-PO1112

Complement C5aR-Mediated Tubular Mitochondrial Dysregulation in Kidney Ischemia-Reperfusion Injury-Induced AKI to CKD

Jingyuan Ma, Wai Han Yiu, Yuchen Feng, Kar Neng Lai, Sydney Tang. *The University of Hong Kong, Hong Kong, Hong Kong.*

Background: Activation of C5a/C5aR axis contributes to the progression of kidney ischemia-reperfusion injury (IRI), but the mechanisms remain unclear. Potential harm to mitochondrial homeostasis can cause biological disturbances, the production of reactive oxygen species and ultimately cell death and kidney dysfunction. In this study, we aim to explore the role of tubular C5aR1 on mitochondrial homeostasis during IRI-induced acute kidney injury (AKI) to chronic kidney disease (CKD).

Methods: Tubule-specific C5aR1 knockout mice ($C5aR1^{lox/lox}$, KspCre; KO) and their littermates without Cre allele ($C5aR1^{lox/lox}$; WT) were subjected to kidney bilateral ischemia/reperfusion injury (BIRI) and sacrificed 7 days later. Kidney damage was assessed by evaluating kidney function, histopathological changes and expression levels of pro-inflammatory, fibrotic, oxidative stress, apoptotic and mitochondrial function related markers.

Results: C5aR1 KO mice exhibited significant decrease in serum BUN and creatinine levels and showed a markedly reduction in the expression levels of kidney injury marker Kim1 and NGAL in the 7-day BIRI model compared to WT controls. Along with the improvement in kidney function, the number of apoptotic tubular cells and cleaved caspase-3 expression were reduced, resulting in less tubular injury in KO mice. The expression levels of inflammation and fibrosis markers were significantly decreased in kidney tissues of KO mice after BIRI. Mitochondrial function was improved with a decrease in oxidative stress markers (NOX2 and 8-OHdG) and an increase in mitochondrial DNA copy number (ND1) and biogenesis (PGC1α) in KO mice after BIRI.

Conclusions: Tubular deficiency of C5aR1 mitigates IRI-induced kidney damage and apoptosis by reducing mitochondrial dysfunction and oxidative stress. Funding: Research Grants Council of Hong Kong (General Research Fund, grant no. 17108222), Hong Kong Society of Nephrology Research Grant (2021)

TH-PO1113

Purinergic Calcium Signaling Drives Tubulointerstitial Cross-Talk in Kidney Diseases

Andreja Figurek,[1] Nevena Jankovic,[1] Sarah Kollar,[1] Andrew Hall.[1,2] *[1]Insitute of Anatomy, University of Zurich, Zurich, Switzerland; [2]Department of Nephrology, University Hospital Zurich, Zurich, Switzerland.*

Background: Chronic kidney disease (CKD) is a major global health problem with limited treatment options. In response to injury proximal tubules (PTs) release factors that activate surrounding fibroblasts to a pro-fibrotic phenotype, which then drives progressive organ damage. Identifying signaling mechanisms between PTs and fibroblasts could reveal new targets for therapeutic intervention. Calcium is a vital intracellular second messenger that regulates many processes, but the nature of calcium signaling in renal fibroblasts was previously not well understood.

Methods: Multiphoton imaging of the kidney *ex vivo* and *in vivo* in transgenic mice expressing a calcium reporter in renal fibroblasts; confocal imaging of calcium activity in normal rat kidney fibroblasts *in vitro*; histological analysis in fixed tissue.

Results: Interstitial fibroblasts in the kidney display spontaneous calcium transients that originate in processes before spreading across the cell, and which markedly increase in frequency in models of acute tubular injury (cisplatin toxicity) and CKD/renal fibrosis (unilateral ureteric obstruction – UUO). Exposing fibroblasts to UDP or synthetic agonists of its target receptor P2Y6 produced acute rises in intracellular calcium. P2Y6R activation also stimulated fibroblast proliferation and migration, and expression of pro-fibrotic markers *in vitro*. In mice exposed to UUO, affected kidneys showed P2Y6R transcriptional up-regulation and knock out or pharmacological inhibition of the P2Y6R decreased fibroblast proliferation, myofibroblast activation, macrophage proliferation, and collagen 1 expression. Moreover, blocking the P2Y6R decreased fibroblast and macrophage proliferation, and myofibroblast activation in another well-established model of CKD (folic acid nephropathy).

Conclusions: We provide evidence that purinergic mediated calcium signaling mediates tubulo-interstitial cross-talk in CKD and that the P2Y6R could represent a therapeutic target.

TH-PO1114

Kidney Phenotype of Fosl2 Knockout Mice

Marta Ribagorda Bermejo,[1,2] Aranzazu Pintor Chocano,[3] Maria Dolores Sanchez-Nino,[1,2] Alberto Ortiz.[1,2] Group of Nephrology, Vascular Pathology, and Hypertension. *[1]Instituto de Investigacion Sanitaria de la Fundacion Jimenez Diaz, Madrid, Spain; [2]Universidad Autonoma de Madrid Facultad de Medicina, Madrid, Spain; [3]Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain.*

Background: Fosl2 is a member of the AP-1 transcription factor family that plays a role in processes such as fibrosis and inflammation. Fosl2 overexpression induced fibrosis and inflammation in multiple organs, being used as a spontaneous model of systemic sclerosis. Fosl2 deficiency decreased the severity of fibrotic and inflammatory processes. However, the role of Fosl2 in kidney disease is unknown.

Methods: In kidney transcriptomics analyses, we found Fosl2 to be upregulated in a murine cisplatin and folic acid-induced acute kidney injury models. To characterize the role of Fosl2 in kidney injury, we generated renal proximal tubule-specific Fosl2 knock-out mice ($Fosl2^{\Delta tub}$). The kidney phenotype of $Fosl2^{\Delta tub}$ mice was characterized by real-time qPCR, immunohistochemistry and Western blotting and primary cell culture.

Results: Contrary to expectations, deletion of Fosl2 in proximal tubular cells led to a pathological kidney phenotype in 3-month-old mice. While serum creatinine and urea levels were similar to WT mice, $Fosl2^{\Delta tub}$ mice displayed an increased kidney expression of Ngal, an early marker of kidney injury and of pro-inflammatory cytokines in association with higher immune cell infiltration. Moreover, there was evidence of an early fibrotic phenotype (*fibronectin 1* and *cpt1a* mRNA and Sirius Red staining) and of decreased nephroprotective factor (e.g., *klotho*) expression. In concordance with these results, in primary renal tubular cell culture, there was an increase in pro-inflammatory cytokines and fibrotic markers and a decrease in nephroprotective factors.

Conclusions: Fosl2 deficiency in mouse proximal tubular kidney cells causes subclinical kidney injury. These results highlight the versatility of Fosl2 roles in different tissues and cell types and open a new range of investigation lines for the treatment of kidney disease.

Funding: Government Support - Non-U.S.

TH-PO1115

Vitamin C Alleviates Kidney Interstitial Fibrosis by Reducing TET2-Mediated SOCS3 m5C Modification

Junjun Luan, Yonghe Zhang, Feifei Miao, Hua Zhou. *Shengjing Hospital of China Medical University, Shenyang, China*.

Background: Methylcytosine dimethoxygenase-2 (TET2) has recently been identified as an 'eraser' of 5-methylcytosine (m^5C) to participate in RNA methylation and chronic kidneyn diseases. Studies have shown that Vitamin C (VC) can directly enhance the catalytic activity of TET enzyme. However, the role of TET2 in renal interstitial fibrosis remains unknown. This study we aimed to clarify whether upregulated TET2 by VC alleviates renal interstitial fibrosis and explore its underlying mechanism.

Methods: ICR mice were randomly divided into 4 groups: normal control (NC), folic acid (FA, FA was peritoneally injected to mice), FA+ early VC (prophylactic VC treatment once a day and 4 days before folic acid injection for 34 days, and FA+ late VC (delayed VC treatment after AKI induction for 28 days). Serum creatinine (Scr), and blood urea nitrogen (BUN) were examined. Histological damages were evaluated. TET2, suppressor of cytokine signaling 3(SOCS3), profibrotic proteins α-smooth muscle actin (α-SMA), and fibronectin (FN) were also analyzed. The m^5C level of SOCS3 mRNA was detected by MeRIP-qPCR. *In vitro* study, the HK2 cells were transfected with TET2 siRNA, VC and hTGF-β1 to repeat the associated tests in vivo. The m^5C% of total RNA from different groups of HK2 cells was determined using the m^5C ELISA kit.

Results: In FA mice, Scr and BUN were increased on day 2 and returned to the baseline by day 30; tubular injuries and interstitial fibrosis were seen on PAS and Masson staining; α-SMA and FN were overproduced. Renal TET2 was decreased and SOCS3 was increased. The m^5C level of SOCS3 mRNA was increased. In FA+ early VC mice and FA+ late VC mice, the level of SOCS3 and profibrotic α-SMA and FN were reverted by activating TET2. Importantly, the m^5C level of SOCS3 mRNA was decreased. The same change directions to FA mice of SOCS3 and profibrotic proteins were seen in HK2 cells transfected with TET2 siRNA and cells stimulated by hTGF-β1; total m^5C level in those cells was increased. Another side, the upon changes in HK2 cells by hTGF-β1 stimulation were reverted by VC treatment.

Conclusions: Vitamin C agonism of TET2 can alleviate renal interstitial fibrosis by reducing SOCS3 expression through m^5C methylation modification.

Funding: Government Support - Non-U.S.

TH-PO1116

Niraparib, an FDA-Approved Poly-(ADP-Ribose) Polymerase (PARP) Inhibitor Is Renoprotective against Cisplatin Nephrotoxicity in Ovarian Tumor-Bearing Mice

Mira Noh, Amritha Kannan, Babu J. Padanilam. *Icahn School of Medicine at Mount Sinai, New York, NY*.

Background: Cisplatin is one of the most commonly used drugs for the treatment of many solid cancers. However, its dose-limiting side effect is nephrotoxicity, leading to acute kidney injury and chronic kidney disease. We previously demonstrated that genetic or pharmacological suppression of poly(ADP-ribose) polymerase 1 (PARP1) protects against cisplatin nephrotoxicity. PARP1 inhibitors such as olaparib, niraparib, and rucaparib are currently FDA-approved for the treatment of ovarian cancer. In this study, we investigated the effect of niraparib on cisplatin nephrotoxicity in an ovarian tumor-bearing model.

Methods: OVCAR3, ovarian cancer cell line cells, bearing mice were established in athymic nude mice and the animals were treated with saline (vehicle), 8 mg/kg cisplatin (once a week), or cisplatin plus 10 mg/kg niraparib (daily).

Results: We found that PARP1 inhibition attenuated kidney cell death and tissue damage, preserving renal function during cisplatin treatment in ovarian tumor bearing mice. Furthermore, inhibition of PARP1 attenuated cisplatin-induced inflammation and renal interstitial fibrogenesis.

Conclusions: Taken together, these results demonstrate that the FDA-approved PARP inhibitor, niraparib can protect efficaciously against renal tubular cell death during cisplatin nephrotoxicity in tumor bearing mice and could be developed as potential therapeutic agents to improve cisplatin nephrotoxicity.

TH-PO1117

Regulation of Kidney Fibroblast Functions by Palladin-MRTF Circuit in Response to TGF-β1

Naoki Yamamoto, Norihiko Sakai, Yuta Yamamura, Ichiro Mizushima, Shinji Kitajima, Akinori Hara, Miho Shimizu, Takashi Wada, Yasunori Iwata. *Kanazawa Daigaku, Kanazawa, Japan*.

Background: Kidney fibrosis is the common mechanism resulting in chronic kidney disease. We previously clarified myocardin-related transcription factor (MRTF) – serum response factor (SRF) signaling drives renal fibroblast activation and focal adhesion formation consisting of integrins through actin cytoskeleton reorganization. Thus far, it has been reported that actin-associated proteins (AAPs) regulate actin filament assembly and disassembly. However, it has yet to be understood whether AAPs relates to the pathogenesis of the fibrosis. Here, we investigated whether AAPs contributed to the renal fibroblasts (RFBs) activation and focal adhesion formation through actin cytoskeleton reorganization.

Methods: Cultured renal fibroblasts were used to examine transforming growth factor (TGF)-β_1-dependent AAPs. Of these AAPs, palladin was selected for further investigation. The effects of palladin on actin polymerization and MRTF-SRF signaling were evaluated in TGF-β_1-stimulated renal fibroblasts (RFBs) treated with paladin siRNA. In addition, palladin expression was evaluated with siRNA targeting MRTF-A/-B. Furthermore, expressions of α1 chain of type I procollagen (COLIAI), α-smooth muscle actin (αSMA), and integrin α11/β1 were explored with siRNA targeting palladin.

Results: Palladin was significantly upregulated in RFBs with TGF-β_1 stimulation. Palladin knockdown suppressed actin polymerization and MRTF-SRF signaling induced by TGF-β_1 whereas palladin expression was suppressed by siRNA targeting MRTF-A/-B. These results suggested that the amplification loop was created between palladin and MRTF-SRF signaling. In addition, the treatment of RFBs with siRNA targeting palladin attenuated COLIAI and αSMA. In addition, integrin α11/β1 expression induced by the stimulation with TGF-β_1 was also suppressed by palladin knockdown. Finally, the inhibition of integrin α11/β1 expression reduced MRTF-SRF signaling and expressions of COLIAI and αSMA.

Conclusions: TGF-β_1-induced amplification loop between palladin and MRTF-SRF signaling mediates renal fibroblast activation and focal adhesion formation, resulting in the upregulation of extracellular matrix expression.

TH-PO1118

Protective Effect of Targeted Inhibition of Cathepsin S Activity on CKD

Jiayi Zhou, Haiyan Fu. *State Key Laboratory of Organ Failure Research, National Clinical Research Center of Kidney Disease, Renal Division, Nanfang Hospital, Southern Medical University, Guangzhou, China*.

Background: Chronic kidney disease (CKD) is a public health issue characterized by vascular rarefaction, marked by reduced capillary density. The molecular mechanisms underlying endothelial cell injury and loss remain unclear. Cathepsin S (CTSS), a lysosomal protease involved in degrading damaged proteins, has been linked to various diseases. However, its role in vascular rarefaction in CKD is not understood. Previous research indicated that limonin, a compound known for its protective effects against acute kidney injury, might also protect against CKD.

Methods: We used a bilateral ischemia-reperfusion injury (IRI) model to induce CKD in mice and generated CTSS knockout mice. LY3000328, a specific CTSS inhibitor, was administered three days before IRI. We conducted molecular pathology studies on human umbilical vein endothelial cells (HUVECs) in vitro and screened small molecule inhibitors of CTSS from a natural product library. Molecular docking studies assessed the binding affinity between CTSS and limonin, which was validated by microscale thermophoresis (MST) and cellular thermal shift assays (CETSA). Both in vivo and in vitro studies were performed.

Results: CTSS expression and enzyme activity were significantly upregulated in CKD animal models. CTSS knockout and inhibition of CTSS in vivo restored capillary density and reduced renal fibrosis after IRI. Pathologically, CTSS in renal vascular endothelial cells translocated into the nucleus and targeted the degradation of the MCM 2-7 complex, inhibiting the G1/S transition in endothelial cells. This impaired repair mechanisms and worsened CKD progression. Limonin was identified as a natural inhibitor of CTSS. Molecular docking showed a strong binding affinity between CTSS and limonin, confirmed by MST and CETSA. In vitro, limonin bound to CTSS's active center, inhibiting MCM 2-7 complex degradation and promoting the G1/S transition in endothelial cells. In vivo, limonin significantly reduced vascular rarefaction and renal fibrosis.

Conclusions: CTSS plays a critical role in CKD by inhibiting HUVEC cell cycle progression through enzymatic hydrolysis of the MCM 2-7 complex. Targeting CTSS activity offers a novel therapeutic strategy for CKD. Limonin effectively inhibits CTSS, promotes the G1/S transition in HUVECs, alleviates renal fibrosis, and shows promise for clinical application in CKD treatment.

Funding: Government Support - Non-U.S.

TH-PO1119

Elucidation of the Renoprotective Effects of SGLT2 Inhibitors in Nondiabetic CKD

Akira Hirano, Kengo Kidokoro, Seiji Kishi, Hajime Nagasu, Tamaki Sasaki, Naoki Kashihara. *Kawasaki Ika Daigaku, Kurashiki, Japan.*

Background: In the DAPA-CKD trial, dapagliflozin, an inhibitor of Sodium Glucose Cotransporter 2 (SGLT2), has shown the renoprotective effects in patients with chronic kidney disease (CKD), regardless of type 2 diabetes status. Previously, we demonstrated that the involvement of the tubuloglomerular glomerular feedback (TGF) mechanism mediated by the adenosine/adenosine A1 receptor pathway in the pathogenesis of glomerular hyperfiltration in type 1 diabetic mice (Circulation 2019), and observed that SGLT2 inhibition alleviated glomerular hyperfiltration in those mice. However, the renoprotective mechanisms of SGLT2 inhibitor in non-diabetic CKD remain unclear. The aim of this study is to verify the contribution of SGLT2 as an important factor in compensatory glomerular filtration, throughing mechanisms such as increased glucose load to the remnant nephrons due to a decrease in the number of nephrons, enhanced Na^+ reabsorption through SGLT2 and reduced Na^+ delivery to the macula densa.

Methods: Male C57BL/6 mice were subjected to infarction-inducing 5/6 nephrectomy (Nx) to establish a CKD model. The experimental groups comprised a control group, a 5/6Nx group, and a 5/6Nx group treated with an SGLT2 inhibitor for one week. Single Nephron Glomerular Filtration Rate (SNGFR) was measured using in vivo imaging techniques. Additionally, Proximal tubular reabsorption of 2-NDBG (2-deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]-D-glucose) injected transarterially via catheter was also evaluated in vivo. The urinary excretion of adenosine, which is a vasoconstrictive factor of TGF, was quantified.

Results: SNGFR was significantly increased in 5/6Nx group compared to the control group. Additionally, the 5/6Nx group exhibited increase in the uptake of 2-NBDG relative to the control group, whereas the group receiving SGLT2 inhibitor treatment displayed reduction in uptake. Moreover, the SGLT2 inhibitor treatment group exhibited augmentation in the urinary excretion of adenosine in comparison to the 5/6Nx group. Adenosine A1 receptor antagonist administration cancelled the inhibitory effect of SGLT2 inhibitors on hyperfiltration.

Conclusions: Increased glucose uptake via SGLT in the proximal tubule initiates the TGF that leads to hyperfiltration of residual nephrons in non-diabetic CKD.

TH-PO1120

Sabizabulin Ameliorates Kidney Fibrosis by Inhibition of Myofibroblast-Specific Beta Tubulin 3

Yoichiro Ikeda, Masaomi Nangaku. *Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Bunkyo-ku, Japan.*

Background: Tubulointerstitial fibrosis is the hallmark of pathological changes found in the kidneys of CKD patients irrespective of the etiologies. A variety of investigations have been conducted to elucidate the mechanisms of progression to CKD to end-stage kidney diseases so far, but still substantially effective remedies to prevent CKD are limited and not clinically applied. Beta tubulin3 (TUBB3) is specifically expressed in neurons in normal settings, but we found that it is expressed specifically in interstitial cells in kidneys with tubulointerstitial fibrosis. Then we investigated if the intervention of expression of TUBB3 affects the tubulointerstitial fibrosis in kidney in the setting of CKD by using TUBB3-specific inhibitor sabizabulin.

Methods: 10T1/2 cells and mouse primary fibroblasts were used for the fibrogenic assays in vitro by an addition of TGF-beta. Standard C57BL/6 mice were used for the analysis in vivo by doing unilateral ureteral obstruction (UUO) under treatments with TUBB3 inhibitor sabizabulin or vehicle.

Results: Mouse primary fibroblasts, considered as a model of fibroblasts or pericytes, expressing low levels of TUBB3 at baseline, increase fibrogenic responses when stimulated by TGFb, and TUBB3 inhibitor significantly reduced their responses. (aSMA reduction by 40%) Knockdown of TUBB3 by siRNA also showed its significant reduction. (aSMA reduction by 60%) 10T1/2 cells, considered as a model of myofibroblasts, express high levels of TUBB3 at base line, and show strong fibrogenic phenotypes. Sabizabulin reduces fibrogenic responses significantly in a dose dependent manner. (aSMA reduction by up to 70%) UUO mice develop kidney fibrosis in the kidney with a ligation in a time dependent manner. TUBB3 expression is significantly elevated accordingly by UUO, and TUBB3 inhibitor successfully reduced the total TUBB3 expression in UUO kidney in a dose dependent manner. (up to 70%) Surprisingly, histological changes in UUO were significantly suppressed by sabizabulin. Fibrogenic responses were also attenuated by sabizabulin (aSMA reduction by 50%)

Conclusions: Sabizabulin was shown to be effective to ameliorate kidney fibrosis in virto and in vivo. It could be a potential treatment option for CKD.

Funding: Government Support - Non-U.S.

TH-PO1121

Dicarboxylic Acids Protect against CKD

Rebecca M. Uhlean, Katherine Pfister, Sunder Sims-Lucas, Debora Malta C.S Santos. *University of Pittsburgh, Pittsburgh, PA.*

Background: Chronic kidney disease (CKD) affects 30 million people in the US and over 800 million people worldwide. Treatment for end-stage renal failure is largely limited to renal transplant or lifelong dialysis, creating an urgent need for new therapies. We have shown that dicarboxylic acids are protective against acute kidney injury (AKI) in the proximal tubule via hypersuccinylation of mitochondrial and peroxisomal proteins, thereby bolstering peroxisomal fatty acid oxidation over mitochondrial FAO. In this study we aimed to determine whether this mechanism could be leveraged to protect against fibrotic damage due to chronic kidney injury, which we model using Unilateral Ureteral Obstruction (UUO) surgery.

Methods: Wild-type male B6/129 mice were procured from Jackson Laboratories and the experimental group fed with an 10% 8-chain dicarboxylic acid (DC_8, suberic acid) diet. Both the experimental and the control groups underwent UUO surgery, whereby the ureter of one kidney was obstructed for three days before both kidneys were harvested. Each kidney was split into four pieces as follows – 1. histological and immunohistochemical staining; 2. fatty acid oxidation analysis; 3. succinylome analysis using targeted mass spec; 4. snap-frozen for validation and downstream analysis of fibrosis, as well as peroxisomal and mitochondrial signaling.

Results: As previously shown, there was hypersuccinylation in the DC_8-treated animals compared to control fed animals. This was accompanied with corresponding upregulation of peroxisomal FAO specifically in the collecting ducts, which was confirmed by targeted mass spec. Supplementation of DC_8 showed marked protection in the collecting ducts, with decreased dilation and tubular epithelial shedding compared to controls. There was also a decrease in the dilation of the renal pelvis in DC_8 treated animals. Further to this immunohistochemical staining showed a decrease in fibrotic markers in the kidneys of DC_8-fed animals

Conclusions: Taken together this suggests that DC_8 is protective against collecting duct damage and fibrotic changes that occur in CKD. This expands the utilization of DC8 therapy beyond the acute setting and into fibrosis and chronic kidney disease.

Funding: NIDDK Support

TH-PO1122

Gain-of-Function Mutation in PDE3A Limits Renal Signs of CKD

Olena Potapenko,[1,2] Theda U. Bartolomaeus,[2] Fiona Spindler,[1] Michael Bader,[2] Anastasiia Sholokh,[2] Reika Langanki,[2] Eremire Vila,[1] Sofia K. Forslund,[2] Enno Klussmann,[2] Lajos Marko.[2] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Max-Delbruck-Centrum fur Molekulare Medizin in der Helmholtz-Gemeinschaft, Buch, Germany.*

Background: Hypertension is a major risk factor for the development of chronic kidney disease (CKD). Hypertension and brachydactyly syndrome is caused by gain of function mutations in the phosphodiesterase 3a (*PDE3A*) gene and leads – if untreated – to stroke and premature death. However, patients hardly develop end-organ damage. Here, we investigated the effect of the *PDE3A* gene mutations on renal manifestation in a rat model of CKD.

Methods: PDE3A-activating (Δ3aa), litter-mate wild-type (WT) and PDE3A-deleted (functional DEL) rats were generated and CKD was induced by bilateral renal ischemia through clamping renal arteries for 45 minutes. Four weeks after surgery kidneys were harvested for histological and gene expression analyses. Blood pressure was continuously measured by telemetry for 1 week before and 3 weeks after renal ischemia.

Results: Serum creatinine and cystatin C levels were elevated 4 weeks after CKD induction in all 3 groups of rats which underwent CKD-inducing surgery in comparison to values before surgery or values of sham-operated animals. However, no difference could be observed between the groups. Δ3aa rats had significantly higher, and functional DEL significantly lower systolic blood pressure than WT rats (142 vs 121 and 115 mmHg, respectively) which was not affected by the CKD induction. CKD induction led to a reduction of the area of the Bowman's capsule ($p<0.05$) and the glomerular capsule area ($p=0.0536$) in WT but not in the Δ3aa rats. CKD induction led to increased media-to lumen ratio of renal arteries in WT rats but not in Δ3aa rats. Additionally, induction of CKD led to significant renal fibrosis in the kidneys of both WT and Δ3aa rats. However, the fibrotic area in kidneys of Δ3aa rats was less than that of the WT rats. The expression of genes involved in fibrosis showed similar trends in WT and Δ3aa rats.

Conclusions: Our data show that gain-of-function mutation of *PDE3A* limit the development of CKD-induced renal changes arguing that PDE3A modulation can be a useful approach for prevention of hypertension-associated CKD.

Funding: Government Support - Non-U.S.

TH-PO1123

Involvement of Calcium (Ca)-Sensing Receptor in the Development of Interstitial Fibrosis

Akira Kurosawa, Kaori Takayanagi, Masaaki Terao, Shunsuke Takahashi, Akito Maeshima, Hajime Hasegawa. Dept of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical University. *Saitama Ika Daigaku Sogo Iryo Center, Kawagoe, Japan.*

Background: The function of the calcium-sensing receptor (CaSR) in the kidney have not been well understood. We previously reported that the expression of CaSR significantly decreases with the progression of renal interstitial fibrosis. In this study, we administered etelcalcetide (ETL), a CaSR agonist, to a renal fibrosis model to analyze the relationship between CaSR and renal fibrosis.

Methods: We created a renal fibrosis model using 8-week-old Sprague-Dawley rats with unilateral ureteral obstruction (UUO). The rats were sacrificed on the seventh day after ureteral ligation, and samples were collected. Some UUO rats were subcutaneously administered ETL at a dose of 0.5 mg/kg/day. The rats were divided into three groups: Sham (n=8), UUO (n=9), and UUO+ETL (n=10). We conducted blood biochemical tests, evaluated fibrosis using ED-1 staining, αSMA staining, Azan staining, and Picro-Sirius Red (PSR) staining, and compared mRNA expression levels of molecules related to fibrosis, repair, and regeneration using RT-PCR.

Results: CaSR expression significantly decreased due to UUO, but immunohistochemistry and mRNA expression analysis confirmed partial recovery of CaSR expression with ETL administration. Azan staining and PSR staining demonstrated a significant reduction in fibrosis with ETL treatment in UUO rats. ED-1 and αSMA staining revealed a significant decrease in positive areas with ETL administration. Furthermore, ETL treatment significantly increased BMP-7 mRNA expression compared to the UUO group.

Conclusions: ETL partially restored reduced CaSR expression in the kidney, improved renal fibrosis, and inhibited the accumulation of extracellular matrix. The involvement of BMP-7 suggests that CaSR agonists could be a novel therapeutic approach for inhibiting renal fibrosis.

TH-PO1124

Effects of Particulate Matter on CKD: Inflammation, Oxidative Stress, and Fibrosis in Animal Model

Duk-Hee Kang, Chor ho Jo, Dal-Ah Kim. *Ewha Womans University College of Medicine, Seoul, Republic of Korea.*

Background: The exposure to particulate matter (PM) is regarded to be associated with respiratory, cardiovascular, and kidney diseases based on epidemiological analysis. However, there are no studies investigating the causative role of PM in the kidney disease. The activation of endoplasmic reticulum (ER) stress, NLRP3 inflammasome, and oxidative stress are the key mechanisms of renal injury. This study is undertaken to explore the effects of artificially manufactured PM (APM) on the kidneys of animal model of CKD, unilateral ureteral obstruction (UUO).

Methods: Male Sprague-Dawley rats were divided into four groups: Normal control, APM (5 mg/kg, administration for 3 or 5 times via Intratracheal instillation), UUO, and UUO+APM. BUN, proteinuria, renal histology including macrophage marker ED-1 expression, and the markers of ER stress (GRP78, ATF4, CHOP, and cleaved caspase-1), NLRP3 inflammasome (NLRP3 and ASC), oxidative stress (nitrotyrosine, SOD2, catalase, and GPx1) and renal fibrosis (F4/80, α-SMA, and osteopontin) in the kidneys were analyzed at 9 or 14 days of APM exposure.

Results: UUO increased BUN, tubulointerstitial fibrosis, and expression of GRP78, ATF4, CHOP, and NLRP3, ASC, cleaved caspase-1. Markers of renal fibrosis are upregulated with an increased nitrotyrosine and reduced SOD2, catalase, and GPx1 in UUO group. In APM+UUO group, ED-1, GRP78, CHOP expression was increased in 9 and 14 days, and NLRP3, cleaved caspase-1, F4/80, and osteopontin were upregulated in 14 days. In normal rats, APM also increased the expression of ATF4, cleaved caspase-1 and NLRP3 with an imbalance of oxidative stress and increased expression of F4/80 and osteopontin.

Conclusions: Exposure to APM resulted in an enhanced expression of markers of renal inflammation, ER stress, oxidative stress, NLRP3 inflammasome, and fibrosis in both normal and UUO rat models. These findings suggest a potential causative role of PM in kidney disease in subject with normal renal function and CKD.

Funding: Government Support - Non-U.S.

TH-PO1125

Effects of Long-Term Electronic-Cigarette (E-cig) Aerosol Exposure and Kidney Health in Mice

Amna Raja,[1] Morgan E. Poindexter,[2] Christina Awada,[1] Judith T. Zelikoff,[1] Edgar A. Jaimes.[3] *[1]New York University Grossman School of Medicine, New York, NY; [2]University of California Davis, Davis, CA; [3]Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: The link between nicotine/cigarette smoke and chronic kidney disease (CKD) is well-established. In contrast, the relationship between E-cigarette (e-cig) use and kidney injury, is relatively unknown. The aim of this toxicological study was to examine whether inhalation exposure of healthy adult mice to e-cig aerosols, with and without nicotine, produces gene expression changes linked to kidney injury.

Methods: 7-8-week-old FVB/NJ mice were exposed to either: 1) filtered air (control); 2) PG/VG (1:1); or 3) PG/VG (1:1) + Nicotine (24 mg/ml) for 3-mo (5d/wk). RNA was extracted from the kidney and bulk RNAseq was performed, followed by RNAseq libraries preparation with TruSeq Stranded Total RNA kit (Illumina). Libraries were sequenced and aligned against the mouse genome. Differential gene expression analysis was performed with DESeq2 R/Bioconductor package. Ingenuity Pathway Analyses (IPA) was then used to comprehensively analyze the differentially expressed genes (DEGs) in order to infer the underlying causes of the observed fold-changes and predict downstream health events.

Results: Inhalation exposure of mice to PG/VG + nicotine resulted in gene expression changes in 61 genes, compared to the air control group; only 7 genes were differently expressed in the PG/VG group, compared to control. Changes in kidney injury-related genes (i.e., *Adrb3, Ca4, Ca3, Lep, Mfsd2a, Adipoq, Angptl4, Cd1d*) were observed in the kidneys of mice exposed to PG/VG + Nic aerosol, compared to filtered air controls. IPA analysis revealed that gene expression changes observed in PG/VG + Nic exposed mice are related to transcription regulation, adipogenesis and circadian rhythm signaling pathways. Organismal injury, nutritional disease and connective tissue disorders were the top diseases based on gene expression changes. In contrast, mice exposed to PG/VG aerosol, without nicotine demonstrated an upregulation of kidney-injury related genes (i.e., *Upk2*, and *Myc*), compared to the control group.

Conclusions: This study indicates that long-term, repeated exposure of adult male mice to e-cig aerosols alters the expression of kidney-injury related genes. This groundbreaking study and overlooked research area demonstrates the kidney as a target of e-cig use, and opens the door for further research concerning the impact of e-cig use on kidney health.

Funding: Other NIH Support - RO1DK129299

TH-PO1126

Sex-Dependent Effects of Whole-Life Arsenic Exposure and High-Fat Diet on the Kidney Proteome

Timothy Cummins,[1] Joshua S. Carty,[2] Michelle T. Barati,[1] Adam E. Gaweda,[1] Daniel W. Wilkey,[1] J. C. States,[1] Jon B. Klein,[1] Michael Merchant.[1] *[1]University of Louisville School of Medicine, Louisville, KY; [2]Vanderbilt University Medical Center, Nashville, TN.*

Background: The Agency for Toxic Substances and Disease Registry (ATSDR) Substance Priority List ranks Arsenic (As) the number one priority. Environmental exposure to As as well as western high fat diets are global concerns for developed and developing nations. High-fat diet co-morbidities including diabetes, kidney disease, hypertension and cardiovascular disease likely modify pathologic mechanisms of As renal toxicity. We addressed the hypothesis that a proteomic approach to study whole life exposure to sodium arsenite (As_i) in male and female mice fed a high fat diet could reveal proteins and mechanistic pathways important to understanding As_i toxicity.

Methods: Cortical kidney lysates from four groups of male and female mice (n=3/group) were compared using a proteomic approach. Groups included (A) mice exposed to 0 or (B) 100 ppb As_i in drinking water from conception, and fed (C) normal or (D) high-fat chow diet for 21 weeks post weaning at 3 weeks. Univariate and multivariate methods were used to compare protein abundances ($q<0.05$) and identify As_i, sex-based or diet-induced effects on the kidney. Immunohistochemistry and immunoblot confirmation assays indicated potential proteins associated with kidney dysregulation as a function of As_i exposure, sex-based differences and diet.

Results: 2931 kidney proteins were identified, 107 were increased and 94 were decreased (log2FC1) in females vs males after multiple testing correction. Multivariate PLSDA and clustering methods defined differences dominated by sex>diet>>As_i. 2-way ANOVA identified As-exposure regulation of glomerular proteins important for podocyte function, and proximal and distal tubular proteins including As_i up-regulation of aquaporin-3 in females only. Histologic analysis identified arsenic-associated focal degenerative tubule cell toxicity in males and female. Overall, informatics analyses indicated sex, diet, and As_i proteome differences appear to impact multiple biological components such as RNA binding, mitochondria function, and energy metabolism.

Conclusions: Renal proteome studies of sexual dimorphic responses in As_i and high-fat diet exposures indicate potential for sex- and As_i-dependent markers of diet induced kidney damage.

Funding: NIDDK Support, Other NIH Support - DK130294, AA028436, GM113226, ES030283, Other U.S. Government Support

TH-PO1127

Male Mice Have Increased Expression of Renal Genes Linked to Kidney Disease Compared with Gene Expression in Female Mice

G. R. Crislip, Michelle L. Gumz. *University of Florida, Gainesville, FL.*

Background: Men are at increased risk of reaching kidney failure sooner than women, even though less men have chronic kidney disease (CKD) compared to women. Gene expression profiles have linked inflammaiton and fibrosis as contributors to CKD on a molecular level. Kidney function is influenced by circadian rhythms, therefore, consideration of the time of day is warranted. Both humans and mice are diurnal, however, mice are nocturnal and are active during the night. We hypothesized that male young adult mice will have up-regulated expression of genes that are linked to CKD progression compared to female mice.

Methods: We used six-month-old male and female control mice on a C57BL/6 background. Kidneys were harvested at zeitgeber time (ZT) 0 or ZT12, at the beginning of the inactive and active periods for mice. RNA was isolated from the renal medulla and prepared for RNA sequencing (5-9 pooled samples for males, 4-8 for females). Differential gene expression was analyzed using DESeq2 (abs(log2(FC)) ≥ 1.0 and FDR-corrected P-value ≤ 0.05). Qiagen ingenuity pathway analysis was performed.

Results: At ZT0, there were 469 differentially expressed genes between males and females. There were 525 differentially expressed genes at ZT12. Interestingly, genes linked to kidney damage are down-regulated in females at both time points compared to males. The kidney injury molecule, Havcr1, was down-regulated in females compared to males only at ZT0 (log2(FC)=-2.4; P=0.04). However, renal inflammation pathways were up-regulated in females. Cxcr4 was one of the contributors to this finding, which is a gene that promotes infiltration of inflammatory cell to the inflammation site. Cxcr4 was only found to be up-regulated in female mice at ZT0 (log2(FC)=1.3; P=0.01). The anti-aging protein Klotho (Kl) was surprisingly down-regulated in females compared to age-matched males at both time points (log2(FC)=1-1.2; P<0.001).

Conclusions: In conclusion, female mice have down-regulated expression of genes that are linked to the development of CKD compared to males. More of these CKD-related genes were found to be differentially expressed at the beginning of the inactive period vs. active period of the mice. There is evidence that females have up-regulation of genes that promotoe renal inflammation. This finding is interesting as women are more likely to develop immune-related kidney diseases compared to men.

Funding: NIDDK Support

TH-PO1128

Sodium Bicarbonate Treatment Promotes Hypoxia and Insulin Resistance in Rats

Paul O'Connor, Elinor Mannon. *Augusta University, Augusta, GA.*

Background: The Use of Bicarbonate in Chronic Renal Insufficiency (UBI) study, found that the relationship between serum bicarbonate and HOMA-IR in patients treated with sodium bicarbonate is non-linear. That is, while HOMA-IR decreased in patients with serum bicarbonate between 24-28mmol, HOMA-IR increased in patients with levels above 28mmol/L. The mechanisms underlying the divergent responses in the UBI study remain unclear. Chronic intermittent hypoxia has been reported to promote loss of insulin sensitivity. As metabolic alkalosis from high serum bicarbonate may slow respiratory rate, in the current study we hypothesized that sodium bicarbonate treatment may promote hypoxia and insulin resistance in rats with CKD

Methods: Male Sprague Dawley rats were used (n=9-3 per group). Rats underwent either surgical incision 5/6 nephrectomy surgery or sham surgery and were allowed to recover for 8 weeks before performing a baseline insulin tolerance test (ITT). Rats were then randomly divided into treatment groups to receive either 0.1M $NaHCO_3$ in the drinking water (Bicarbonate treatment) or tap water 2 weeks. At the end of the treatment period, blood was collected from the tail vein for analysis (PrimeVet blood gas analyzer) and a repeat ITT performed

Results: Rats in the CKD group had significantly higher plasma creatinine and BUN when compared to rats in the sham group (p<0.01). Plasma HCO_3- was significantly elevated in both sham and CKD bicarbonate treated rats compared to rats receiving tap water (P=0.02). Consistent with bicarbonate treatment promoting hypoxemia and tissue hypoxia, plasma lactate was significantly elevated in both sham and CKD bicarbonate treated rats when compared to rats receiving tap water (p=0.02). Hematocrit and total hemoglobin also tended to be elevated following bicarbonate treatment. Fasted glucose levels were significantly elevated in both sham and 5/6 Nx rats following bicarbonate treatment (p=0.01). ITT identified reduced insulin sensitivity in both sham and 5/6 Nx rats following 2 weeks of bicarbonate, but not tap water treatment.

Conclusions: Our data indicate that bicarbonate loading can promote both hypoxia and worsen insulin sensitivity in rats. We speculate that increases in HOMA-IR in CKD patients receiving bicarbonate with plasma HCO_3- above 28mmol/L may be due to insulin resistance secondary to pH mediated decreases in respiratory rate and intermittent hypoxemia.

Funding: NIDDK Support, Private Foundation Support

TH-PO1129

Kidney Protection during the AKI to CKD Transition: Post-translational Modifications Drive Peroxisome Activity and Cytoskeletal Rearrangements

Katherine Pfister.[1,2] [1]*University of Pittsburgh, Pittsburgh, PA;* [2]*UPMC, Pittsburgh, PA.*

Background: Acute Kidney injury (AKI) is an unfortunately frequent disease without an effective treatment. In many cases, AKI can progress to Chronic Kidney Disease (CKD) and in the worst-case scenario, End Stage Renal Disease (ESRD). To attenuate these transitions, we need a better understanding of the cellular mechanisms underlying damage and physiological changes as disease progresses. The most pronounced effect of AKI is on the Proximal Tubule Epithelial Cells (PTECs) which have the highest metabolic activity and are therefore most susceptible to damage after ischemia, sepsis, or transplant stress. This damage causes not only an increase in radical oxygen species and genetic reprogramming but also a significant change in the landscape of posttranslational modifications (PTMs).

Methods: With our collaborators, we performed targeted mass spectrometry and data-mining to understand the progressive changes in untreated AKI to CKD in murine kidneys. Following our recently published study on the protective effects of upregulated peroxisomal fatty acid oxidation (FAO) through dicarboxylic acid diet supplementation, we analyzed the long-term effects of Suberic Acid (DC8) on the AKI to CKD transition. Large classes of proteins can be modulated rapidly and reversibly through the activity of enzymes that ligate Posttranslational Modifications (PTMs) and we developed a list of candidate proteins that are significantly altered in DC8-fed mice exposed to a CKD model of injury.

Results: We chose to focus on the relationship between peroxisomal FAO enzymes and the resulting cytoskeletal changes that drive the fibrotic phenotype indicative of CKD. We identified a list of actin-binding proteins that are specifically succinylated at key residues when the DC8 treated mice are subjected to an *in vivo* model for CKD and we propose that the increased peroxisomal FAO has long-term protective effects maintaining the epithelial profile of PTECs after injury, preventing cell shedding, tubular collapse, and increased fibrotic scarring that are signs of worsening CKD and ESRD.

Conclusions: By understanding the cellular mechanisms of the AKI to CKD transition we can promote directed clinical trials to lessen the number of patients on lifetime dialysis and those requiring kidney transplants worldwide.

Funding: NIDDK Support

TH-PO1130

Extra Domain A-Spliced Fibronectin Variant Contributes to Tubulointerstitial Fibrosis in CKD

Susan Yung, Yuesong Xu, Max Tung, Rafter Y. Wu, Tak Mao D. Chan. *Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong, Hong Kong.*

Background: Chronic kidney disease (CKD) is characterized by progressive tubulo-interstitial fibrosis and tubular atrophy, leading to kidney failure. There is no effective treatment for kidney fibrosis. Fibronectin (native FN) is a large glycoprotein present in all tissues, and its accumulation in the tubulo-interstitium is a feature in progressive tubulo-interstitial fibrosis. Also, the extra domain A-spliced variant of FN isoform (EDA-FN) is enriched in fibrotic lesions. This study investigated the role of EDA-FN in the pathogenesis of tubulo-interstitial fibrosis in CKD.

Methods: CKD was induced in wild-type (WT) and EDA-FN knockout (KO) mice by feeding with casein-based chow containing 0.2% adenine for 12 weeks, and mice fed casein-based chow served as controls. Mice were sacrificed and kidneys were harvested to assess histopathological changes and expression of mediators of inflammation and fibrosis. In vitro studies were performed on proximal renal tubular epithelial cells (PTEC).

Results: Compared with WT casein-fed mice, WT CKD mice showed proteinuria, tubular atrophy, increased EDA-FN expression, and increased gene and protein expression of native FN, collagen type I and III, and α-smooth muscle actin ($p < 0.05$, for all). EDA-FN KO CKD mice showed comparable proteinuria as WT CKD mice, but less severe kidney histopathological features with reduced immune cell infiltration and decreased expression of fibrosis mediators. Under physiological condition, EDA-FN was not expressed by PTEC. Exposure to TGF-β1, IL-1β, but not IL-6, IL-8 or MCP-1, induced EDA-FN in PTEC, which was mediated in part through PI3K and p38 MAPK phosphorylation. Incubation of PTEC with EDA-peptide increased native FN, collagen I and SNAIL expression and IL-6, IL-8 and MCP-1 secretion.

Conclusions: Our data showed that murine adenine-induced CKD had increased tubulo-interstitial EDA-FN expression, which participated in the pathogenesis of chronic tubulo-interstitial inflammation and fibrosis.

Funding: Government Support - Non-U.S.

TH-PO1131

The Actin and Microtubule Network Regulator WHAMM Is Identified as a Key Kidney Disease Risk Gene

Dhanunjay Mukhi,[1] Kolligundla L. Prasanna,[1] Tomohito Doke,[1] Magaiver A. Silva,[1] Hongbo Liu,[1,2] Matthew Palmer,[1] Katalin Susztak.[1] Susztak Group.
[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of Rochester Medical Center, Rochester, NY.

Background: Nearly 850 million people suffer from kidney disease across the globe, yet the molecular mechanisms remain elusive. Recent genome-wide association studies identified genetic variants at more than 800 loci responsible for kidney dysfunction, however, target genes, target cell types, and underlying pathways remain poorly understood.

Methods: We utilized a comprehensive gene prioritization strategy involving multiple genetic evidence (kidney expression and methylation quantitative trait (eQTL & meQTL), allele-specific expression, snATAC-seq, Bayesian colocalization, and SMR, etc.) to identify the Wasp homolog associated with actin, membranes, and microtubules (*WHAMM*) as a causal gene for kidney dysfunction on chromosome 15. We obtained WHAMM genetic knockout mice and analyzed at baseline and after induction of acute kidney injury, chronic kidney disease by folic acid injection, and unilateral ureter obstruction (UUO). Serum creatinine, BUN, and cystatin C levels were measured. Gene expression and protein levels were measured by real-time PCR, western blotting, and immunofluorescence. Primary kidney tubule epithelial cells were analyzed for cytoskeleton changes, ASC-speckle formation, and cell death by confocal microscopy imaging. Autophagy was assessed by LC3 turnover at baseline and after induction of starvation, and cisplatin. We employed cytoskeletal inhibitors in both in vitro and in vivo studies to demonstrate the role of WHAMM in kidney disease.

Results: Here we show that nucleotide variants on chromosome 15 are not only associated with kidney dysfunction but also regulate the expression of *WHAMM*. *WHAMM* expression is higher in mice and patients with chronic and acute kidney disease. Genetic knockout of *Whamm* appeared healthy at baseline but showed less injury following cisplatin, folic acid, and unilateral ureteral obstruction. In vitro cell studies indicated that WHAMM controls cell death by regulating actin-mediated cytochrome c release from mitochondria and the formation of ASC-speckles. Pharmacological inhibition of actin dynamics was able to mitigate kidney disease development in experimental models.

Conclusions: Our study identifies a key role of *WHAMM* in the kidney disease development and the pharmacological modulation of this pathway as a potential therapeutic approach.

Funding: NIDDK Support

TH-PO1132

Abstract Withdrawn

TH-PO1133

Eculizumab Therapy and Kidney Recovery in SARS-CoV-2-Induced Complement-Mediated Thrombotic Microangiopathy (CM-TMA)

Zeyad J. Rifai, Heather Rowe, Nirali B. Ramani. *Southern Illinois University School of Medicine, Springfield, IL.*

Introduction: Thrombotic Microangiopathies (TMA) have a diverse pathogenesis, featuring microangiopathic hemolytic anemia, thrombocytopenia, end-organ injury, affecting renal microvasculature via microthrombi formation. Advancements in complement biology have introduced targeted therapies like Eculizumab, interrupting the terminal complement pathway mitigating microvascular thrombotic endothelial damage.

Case Description: 60-year-old male, hospitalized for chest pain secondary to uncontrolled hypertension with a negative cardiac workup, and incidental SARS-CoV-2 infection, returned three weeks later with a two-week history of malaise and reduced urine output. He denied infectious, or gastrointestinal symptoms. Investigation revealed a creatinine of 4.09 mg/dL (baseline 0.9 mg/dL). UA with proteinuria and 50 RBC/HPF. Paraproteinemia and autoimmune workup including anti-GBM, ANCA, Lupus serology, Lupus Anticoagulant, Antiphospholipid antibody, C3/C4/CH50 complement, Factor H level and Factor H autoantibody were unremarkable. ADAMSTS-13 activity was not supportive of TTP, Coombs Test was negative. Given a negative stool culture and deteriorating renal function (peak creatinine 5.32 mg/dL), suspicion for CM-TMA increased, prompting pursuit of a renal biopsy to guide management. Light microscopy revealed acute to subacute TMA with secondary acute tubular injury confirming our suspicion of CM-TMA. He was established with an outpatient dialysis center and hematology for Eculizumab infusions. The patient suffered cardiac arrest during a dialysis session requiring hospitalization delaying his Eculizumab infusions. The cardiac arrest was attributed to an anaphylactic reaction to intradialytic iron infusion. He eventually began his Eculizumab regimen; clinical course is highlighted by discontinuation of dialysis four months after renal insult. He maintains routine follow-up with nephrology and hematology clinic for maintenance Eculizumab infusions.

Discussion: Although genetic analysis was inconclusive, a 'first-hit' mutation predisposing to complement dysregulation coupled with SARS-CoV-2 as a 'second-hit' remains a likely pathogenesis. There are no current guidelines describing the length of Eculizumab therapy in this particular case. Our aim is to emphasize the importance of standardizing the duration of Eculizumab therapy, particularly in the absence of autoantibodies or familial history.

TH-PO1134

Mortality among Patients on Hemodialysis Who Received Heterologous and Homologous COVID-19 Vaccine Regimens in Thailand

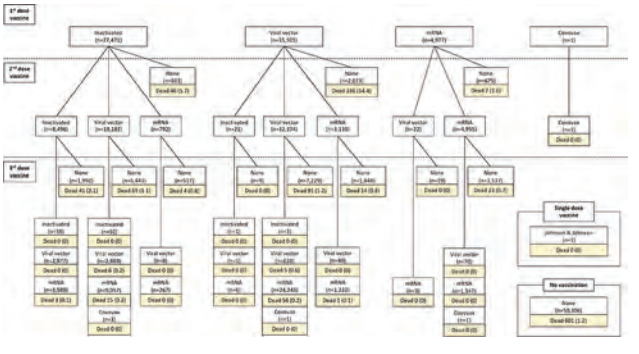
Pattharawin Pattharanitima,[1] Suthiya A. Anumas,[1] Manoch Rattanasompattikul,[2] Thatsaphan Srithongkul,[3] Sukit Raksasuk,[3] Suchai Sritippayawan.[3]
[1]Thammasat University Hospital, Khlong Nueng, Thailand; [2]Golden Jubilee Medical Center, Nakorn Pathom, Thailand; [3]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.

Background: Although studies showed the effectiveness of a 2-dose homologous regimen, it was impractical in Thailand due to limited vaccine supply. Consequently, heterologous vaccine regimens were implemented. This study aims to evaluate the mortality rate and risk factors for mortality in maintenance hemodialysis (HD) patients who received various vaccine regimens.

Methods: We retrospectively reviewed the data of patients receiving HD in Thailand from January 2021 to December 2022. The demographic, vaccination history, SARS-CoV-2 test results, and other laboratory data were retrieved from the Department of Medical Sciences and Thailand RRT registry. Mortality was defined as death within 30 days after a positive RT-PCR or rapid antigen test for SARS-CoV-2.

Results: Among 121,761 HD patients, 71,455 (58.7%), 67,953 (55.8%), and 46,288 (38.0%) patients received 1,2 and 3 vaccine doses, respectively (Figure 1). Of these, 8,836 (40.9%) and 44,900 (97.0%) patients received heterologous vaccines for their first 2 and 3 doses. The most common regimens were viral vector (VV)-VV-mRNA (33.9%), inactivated (IA)-VV-mRNA (12.7%), and VV-VV (10.2%), with mortality rates of 0.2%, 0.2%, and 1.3%, respectively. The mortality was 601 (1.2%) and 667 (0.9%) among unvaccinated and vaccinated patients (P <0.001), and 0.7% and 6.0% among who tested negative and positive for SARS-CoV-2 (P <0.001). Multivariate analysis showed that female, age ≥50 years, no vaccination, single-dose VV and IA vaccination, high BMI, admission to advanced care wards, and requirement for high oxygen therapy were risk factors for mortality. The VV-VV-mRNA regimen was a protective factor.

Conclusions: This study showed that a single dose of VV and IA vaccines was associated with higher mortality compared to the mRNA-mRNA regimen, while the VV-VV-mRNA vaccine was a protective factor. The mortality in patients who received other vaccine regimens was comparable to those who received the mRNA-mRNA regimen.



TH-PO1135

Circulating ACE2 Activity and Gas6 Are Increased in Patients Diagnosed with COVID-19

Irene Martínez Díaz,[1] Ander Vergara,[1] Antonio Cano Camara,[1] José T. Ortiz Pérez,[3] Adria Fernandez Diaz,[3] Carmen Llorens Cebrià,[1] Sara Nunez-Delgado,[1] Jordi Vilardell,[1] Pablo García de Frutos,[2] Albert Morales,[2] Conxita Jacobs Cachá,[1] Maria Jose Soler.[1] Nephrology and Transplantation Group. *[1]Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus,. Nephrology and Transplantation Research Group, Barcelona, Spain; [2]Instituto de Investigaciones Biomédicas de Barcelona (IIBB)-Consejo Superior de Investigaciones Científicas (CSIC), Barcelona, Spain; [3]Department of Cardiology, Cardiovascular Institute, Hospital Clínic de Barcelona, Fundació Clinic per la Recerca Biomédica, Universitat de Barcelona, Barcelona, Spain*.

Background: The angiotensin converting enzyme 2 (ACE2) is the cell entry receptor for SARS-CoV-2. SARS-CoV2 participates in ACE2 shedding from cell membrane, increasing soluble ACE2. ACE2 has been shown to cooperate with the receptor AXL, internalizing SARS-CoV-2. The present study aims to evaluate if the circulating ACE2 activity and the serum levels of AXL and its ligand Gas6 are related with the disease prognosis.

Methods: During the first wave of COVID-19 pandemic, first emergency attendance serum samples were collected from 1519 COVID-19 patients diagnosed at two centers. Age, sex, comorbidities and clinical and analytical variables were collected from the patient's records. Patients that were admitted to intensive care unit, required mechanical ventilation or died due to COVID-19 were considered severe patients. Serum ACE2 activity was measured by fluorescence enzymatic activity assay while Gas6 and sAXL by ELISA.

Results: Patients with severe COVID-19 were older and presented more comorbidities (Table 1). Circulating ACE2 activity and Gas6 levels were increased in 0.43ng/µL and in 5ng/mL respectively (95%IC:0.32–0.54, p<0.001; 95%IC:3.44–6.56, p<0.001) in patients that afterwards developed severe COVID-19 (Table 1). However, we found no differences in levels of sAXL between patients with severe and non-severe COVID-19. A logistic regression model adjusted by age, sex, diabetes, hypertension, obesity, cardiovascular disease and chronic kidney disease identified that high circulating ACE2 activity and high Gas6 levels were independently associated with worse SARS-CoV2 disease (OR:2.5, 95%CI:2.02–3.25, p<0.001; OR:1.0, 95%CI:1.01–1.04, p<0,001, respectively).

Conclusions: Elevated circulating ACE2 activity and GAS6 at admission to the Emergency Department are a risk factor for severe COVID-19 disease. In contrast, sAXL levels are not related to the severity of the disease.

Funding: Private Foundation Support, Government Support - Non-U.S.

Table 1. Comparison of demographic, clinical features and circulating ACE2 activity, Gas6 and AXL between non-severe and severe COVID-19 patients. *a Cardiovascular disease is defined as a history of heart disease, pericarditis, cardiac arrhythmia, heart failure, stroke or peripheral arterial disease. b: circulating ACE2 activity was measured in relative fluorescence units (RFU/s) adjusted using a standard curve with known ACE2 concentrations. $ Mann Whitney Test # Chi² Test*

Variable	Non severe COVID-19 (n=1162)	Severe COVID-19 (n=357)	p Value
Age (years)	59 (RIC: 47 – 74)	67 (RIC: 55 – 78)	<0.001$
Men	577 (49.7%)	220 (61.6%)	<0.001#
Smoker	301 (25.9%)	116 (32.5%)	0.015#
Diabetes	192(18.2%)	98 (29.1%)	<0.001#
Hypertension	447 (41.0%)	185 (53.3%)	<0.001#
Obesity (bmi ≥30)	165 (14.2%)	101 (28.3%)	<0.001#
Cardiovascular disease a	189 (17.9%)	86(26.0%)	0.001#
Chronic kidney disease	69 (6.6%)	34(10.3%)	0.027#
ACEIs	191 (16.4%)	81 (22.7%)	0.007#
ARBs	130 (11.2%)	53 (14.8%)	0.063#
Circulating ACE2 activity (ng/µL) b	0.54 (RIC: 0.29 – 0.66)	0.97 (RIC: 0.43 – 1.05)	<0.001$
sAXL (ng/ml)	49.8 (RIC: 35.7 – 58.6)	48.5 (RIC: 33.6 – 57.2)	0.177$
Gas6 (ng/ml)	20.6 (RIC: 13.7 – 25.1)	25.6 (RIC: 17.8 – 31.2)	<0.001$

TH-PO1136

Kidney Function in Children and Adults Hospitalized with Coronavirus Disease in 2019: Relationship with Urinary Biomarkers and Genetic Polymorphisms

Elba O. Medina Hernandez,[1] Enrique J. Robiou Vivero,[1] Rafael Valdez-Ortiz,[1] Mara Medeiros.[2] *[1]Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico; [2]Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico*.

Background: The kidneys are commonly affected in COVID-19; we can see abnormal dipstick or acute kidney injury; NGAL and Cystatin C increase after kidney injury. Recognition of AKI is sometimes late; identification would help to improve the outcome

Methods: Prospective cohort study (July-September 2020), patients of any age hospitalized for COVID-19. Upon admission and discharge, blood chemistry, urianalysis, NGAL, Cystatin C and APOL1 gene were evaluated

Results: 159 patients were included. In children initial vs final cystatin C; median 26.88vs8.45, regarding initial vs final NGAL, median 7.48vs2.38. In adults Cystatin C initial vs final had a median 79.57vs32.97, NGAL initial vs final 31.74vs17.23. APOL1 variant was found in two adults and one child

Conclusions: Children had lower AKI and mortality than adults. Urinary cystatin C was higher at the admission, but the change was significant only in adults. We found no relationship between genetic variants of APOL1 and the severity of kidney damage

Funding: Government Support - Non-U.S.

Demographic characteristics and Kidney Function

	Children n=40	Adults n=149	p<0.05*
Age (years) x±SD	8.49±5.09	54.55±14	0.0001*
man: woman	18:22	62:57	0.419
DM n(%)	2 (5)	45 (37.8)	0.001*
HTA n(%)	0	39 (32.8)	----
Obesity n(%)	1(4)	59 (49.6)	0.001
Cancer n(%)	10 (25)	0	----
genetic alteration/malformations n(%)	17 (42)	17 (42.5)	----
Dyspnea n(%)	14 (35)	87 (73.1)	0.001*
Fever n(%)	24 (60)	86 (72.3)	0.074
PIMS n(%)	6 (15)	----	----
Days to arrive at the Hospital (median, min-max)	6 (0-32)	8 (0-39)	0.022*
Days of hospital stay (median, min-max)	10 (0-178)	10 (1-100)	0.602
ICU admission n(%)	14 (35)	33 (27.7)	0.234
Death n(%)	1 (2.5)	37 (31.1)	0.044*
APOL1 Homozygous n(%)	31 (96.87)	52 (94.54)	0.044
APOL1 Heterozygous n(%)	1 (3.12)	3(5.45)	0.249
eGFR Admission (median, min-max)	91.71 (17-189)	97 (11-145)	0.588
eGFR Follow-up (median, min-max)	145.73 (41.3-225.27)	106 (13-140)	0.008*
Hematuria Admission n(%)	11 (27.5)	55 (46,2)	0.076
Hematuria Follow-up n(%)	7 (17.5)#	11 (9.3)#	0.263
Proteinuria Admission n(%)	22 (55)	85 (71.4)	0.194
Proteinuria Follow-up n(%)	13 (32.5)#	9 (6.7)#	0.002*
AKI n(%)	9 (22.5)	54 (45.4)	0.003*
Hemodialysis requirement n(%)	1 (2.5)	7 (5.9)	----

TH-PO1137

Impact of the COVID-19 Pandemic on Health Care for People with Rare Diseases in Germany (SCOPE-RD)

Lukas Völkel,[1,4] Lucas R. Fahrenschon,[2] Julia Fleck,[2] Martin Mücke,[2] Melanie May,[3] Immo Zech,[3] Annette D. Wagner.[1] *[1]Medizinische Hochschule Hannover, Hannover, Germany; [2]Universitatsklinikum Aachen, Aachen, Germany; [3]Kyowa Kirin Niederlassung Deutschland, Dusseldorf, Germany; [4]Boehringer Ingelheim International GmbH, Ingelheim, Germany*.

Background: The Covid-19 pandemic has profoundly impacted healthcare worldwide, affecting vulnerable groups such as patients with rare diseases. This study aims to analyze the influence of the Covid-19 pandemic on the healthcare of patients with rare diseases in Germany.

Methods: In order to assess the impact of the pandemic on people with rare diseases in Germany, a retrospective cross-sectional study was conducted using performance data from the statutory health insurance (SHI). The study was conducted in a stepwise approach, comprising 1) a systematic literature review, 2) expert discussions, 3) feasibility analyses and 4) a main analysis. The anonymized SHI claims data set with information on around 9 million people insured was used in this study. Observation period was 2017 to 2022. All 16 indications to be analysed were compared with each other in terms of successful annual diagnoses and other key figures collected. The dataset provided information on feasibility, demographics, work ability, healthcare resource utilisation, burden of disease, top 50 outpatient-, inpatient-, DRG-, OPS-, EBM- and ATC-codes and costs incurred.

Results: The sample drawn from the database contains almost 5 million individuals. In total 14,912 patients were identified within six years with an average age of 59.9. Patient numbers increased over time, but showed a decline in 2020 (2%). 10 of 16 diseases showed less documented patients compared to 2019. The annual diagnoses of all summarised indications showed an increasing trend. The absolute number of diagnoses only fell between 2019 and 2020, before rising sharply again in 2021. The annual mortality rates were between 5.6 and 7.1 per cent. An increase of one percentage point from 2020 was observable. Total patient counts and prevalence rates could be a hint to underline the assumption that less cases were identified due to the pandemic situation and less contacts of healthcare providers. In 7 subgroups the prevalence rates were in ranges as expected, in 5 subgroups the prevalence rates were over- or underestimated.

Conclusions: This study focuses on methodology's complexity and provides insights into the epidemiology and patient characteristics of 16 rare diseases. Initial results indicate that these vulnerable groups were significantly affected by the Covid-19 pandemic.

Funding: Commercial Support - Kyowa Kirin GmbH

TH-PO1138

Survival of COVID-19 Infection after Integrated Resource Planning Vaccination among Thai Patients on Hemodialysis: An Observational Cohort Study

Manoch Rattanasompattikul,[1,2] Suchai Sritippayawan,[2,3] Sukit Raksasuk,[2] Pattharawin Pattharanitima,[4] Thatsaphan Srithongkul.[2,3] *[1]Golden Jubilee Medical Center, Faculty of Medicine Siriraj Hospital, Phutthamonthon District, Thailand; [2]Nephrology Division, Department of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [3]The Nephrology Society of Thailand, Bangkok, Thailand; [4]Nephrology Unit, Department of Medicine, Faculty of Medicine, Thammasat University, Pathumtani, Thailand.*

Background: In response to the pressing issue of limited vaccine supply and initial vaccine source acceptance, heterologous vaccination schedules were adopted, and integrated resource planning (IRP) and management were implemented. This study aims to estimate the change in odds of COVID-19 death following the Thai-IRP vaccination model in maintenance hemodialysis (MHD) patients.

Methods: An authorized committee thoroughly reviewed the data of patients receiving MHD admitted due to COVID-19 from January 2020 to December 2021. The sources of the databases for analysis are described in **Figure 1**. Conditional logistic regression was a fully adjusted model for mortality by dose and each type of vaccine.

Results: In total, 5824 MHD patients were identified with COVID-19 infection (53% male; mean age 58± 14 years). The mortality rate was 7% (N =409), with the underlying disease of diabetes and hypertension (17%), only diabetes (21%), and only hypertension (42%). Covariates associated with mortality in subgroups of the population at risk were significant with age ≥ 60 years, highest BMI and lowest nPNA, crude odds ratio (ORs) [95% CI] were 1.90 [1.54, 2.34], 1.65 [1.29, 2.13] and 1.77 [1.22, 2.56], respectively. The ORs focusing on the mortality outcome of various vaccinations showed that two doses of each vaccine type decreased mortality. The single dose of inactive SARSCoV-2 virus vaccines and ChAdOx1 nCoV-19 vaccine demonstrated increased ORs in the fully adjusted model (2.15 [0.82, 5.67] and 2.22 [1.17, 4.20]).

Conclusions: Our study underscores that age (≥ 60 years old), highest BMI, and lowest nPNA are associated with death in severe acute respiratory syndrome coronavirus two infections. Notably, the Thai-IRP model vaccination demonstrates a clear benefit from the first vaccination dose compared with no vaccine group in each type of vaccine, except the ChAdOx1 nCoV-19 vaccine, which showed an adverse outcome from the first vaccination dose.

Funding: Government Support - Non-U.S.

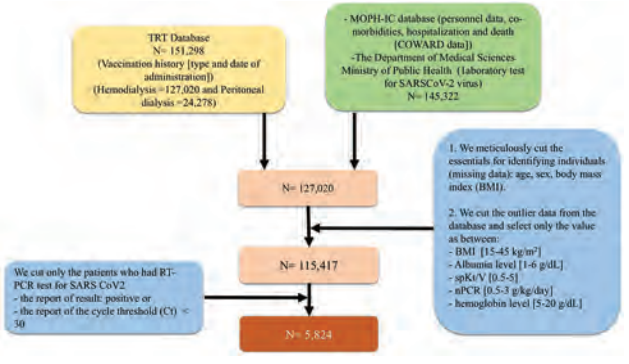


Figure 1

TH-PO1139

Fear of COVID-19 after Vaccination Dissemination and Its Relationship with Multidimensional Health Literacy among Patients on Maintenance Hemodialysis

Atsuro Kawaji,[1] Ryohei Inanaga,[2,4] Takumi Toishi,[1] Masatoshi Matsunami,[1] Tomo Suzuki,[2,1] Tatsunori Toida,[2,3] Noriaki Kurita.[2] *[1]Kameda Medical Center, Kamogawa, Japan; [2]Fukushima Kenritsu Ika Daigaku, Fukushima, Japan; [3]Kyusyu University of Medical Science, Nobeoka, Japan; [4]Shinyurigaoka Sogo Byoin, Kawasaki, Japan.*

Background: A worldwide increase in anxiety due to the COVID-19 pandemic has been suggested to contribute to unhealthy lifestyle habits and depression among patients undergoing hemodialysis (HD). However, the degree of fear of COVID-19 after vaccination dissemination remains to be quantified. In addition, the independent impact of high-order health literacy (HL) on fear of COVID-19 has not been adequately investigated.

Methods: This was a multicenter cross-sectional study conducted in 2022 after the vaccination against COVID-19 became widely available in Japan. The subjects were adults receiving in-center HD. The exposure was multidimensional HL measured by the 14-item Functional, Communicative, and Critical Health Literacy scale. The outcome was the fear of COVID-19 measured by the 7-item Japanese version of the Fear of COVID-19 scale (FCV-19S; total score range 7-35 pts: higher scores indicate stronger fear). Differences in FCV-19S scores among the HD patients and those among Japanese adults in April 2020 (i.e., the beginning of the endemic) reported in the development paper were compared using the unpaired t-test. The association between multidimensional HL and FCV-19S scores was estimated using a multivariable-adjusted general linear model.

Results: In total, 446 HD patients were analyzed. Of these, 431 (96%) and 9 (2%) had received three and two doses of vaccination, respectively. Their FCV-19S scores were significantly lower than those of the general population at the beginning of the endemic ($P < 0.001$; mean difference -4.4 [95% confidence interval (CI): -5.1 to -3.7]; standardized effect size [ES] 0.77). Higher functional HL was associated with less fear (per 1-pt higher: -1.0 [95% CI: -1.7 to -0.3]; standardized ES -0.18). In contrast, higher critical HL was associated with stronger fear (per 1-pt higher: 2.0 [95% CI: 0.9 to 3.2]; standardized ES 0.36). Communicative HL was not associated with fear.

Conclusions: Even after widespread of vaccination, patients' fear due to low functional HL can be reduced by providing health information in an easy-to-understand manner. For patients with skepticism to correct information and strong fear due to excessive critical HL, honest explanations by healthcare providers may be important.

TH-PO1140

Proenkephalin in Critically Ill Patients with COVID-19

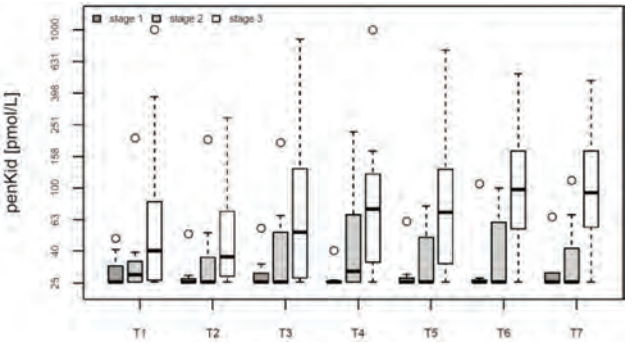
Marlies Ostermann,[1] Oliver Hartmann,[3] Janin Schulte,[3] Fabiola D'Amato,[1] Kyma M. Vas,[1] Shelley Lorah,[1] Gillian Radcliffe,[1] Nuttha Lumlertgul.[2] Sphingotec Penkid and GSST Research Team. *[1]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [3]SphingoTec GmbH, Hennigsdorf, Germany.*

Background: There is growing evidence for proenkephalin A 119-159 (penKid) as an accurate biomarker to estimate kidney function and detect acute kidney injury (AKI) in various patient cohorts but its role in critically ill patients with COVID-19 has not been described.

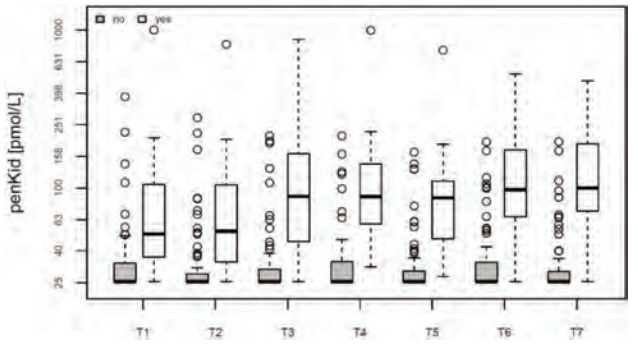
Methods: We recruited critically ill adult patients with COVID-19 admitted to the intensive care unit (ICU) in a University Hospital in London, UK, between August 2020 and January 2022 and measured plasma penKid levels daily for up to seven days. PenKid was compared in patients with and without AKI according to Kidney Disease Improving Global Outcomes (KDIGO) criteria and analyzed for prediction of need for renal replacement therapy (RRT).

Results: Ninety-one critically ill adult patients (34 females, 57 males; mean age 51 years; mean SOFA score 6) were admitted to the ICU. Sixty patients (66%) required mechanical ventilation, 36 patients (40%) had AKI at enrolment of whom 21 received RRT. Twenty-eight day mortality was 15.4%. Among the survivors, six patients (8%) were RRT dependent on day 28. During the first week after enrolment, plasma penKid was increased with stages of AKI and highest penKid levels were observed in patients receiving RRT (Figure 1). Plasma penKid on day 1 at ICU identified patients who were RRT dependent on day 28 (Figure 2).

Conclusions: In critically ill adults with COVID-19, penKid is a measure of kidney function, diagnoses AKI and predicts RRT dependence at 28 days.



penKid by AKI stage



penKid by RRT dependency on day 28

TH-PO1141

AKI in COVID-19 Associated Respiratory Failure (C-19RF) and Other Etiologies: Implications for Distinction in Clinical Characteristics, a Retrospective Analysis of the NU SCRIPTS Study

Jackson Rajendran, Carlos Valladares, Song Peng Ang, Bryan D. Gregory, Jose I. Iglesias, Maya Iglesias. *RWJBarnabas Health, Toms River, NJ.*

Background: Differences in the development of AKI in patients with C-19RF and other causes of severe respiratory failure (RF) may exist, which could have implications for clinical management. We retrospectively analyzed the NU SCRIPTS data to compare AKI's clinical characteristics and outcomes in C-19RF patients and RF attributable to other causes.

Methods: We evaluated 368 mechanically ventilated patients (pts.) from the NU SCRIPT study. AKI was defined as a ≥ 0.3mg/dl increase in serum creatinine within 48 hrs. Clinical and laboratory values obtained on admission were analyzed. We employed stepwise forward logistic analysis (LR) to determine those variables associated with C-19RF. In addition, we used logistic regression analysis LR to compare independent predictors of mortality in C-19RF and RF pts. Those variables found to be statistically significant in univariate analysis ($p < 0.05$) were included in the LR analysis.

Results: A total of 250 pts developed AKI, consisting of 81 patients with C-19RF and 169 RF pts. There was no significant difference in mortality between C-19RF and RF groups (43 vs 47%). Likewise, there was no difference between groups in the need for renal replacement therapy. Stepwise LR demonstrated that increased days on mechanical ventilation, non-Caucasian race, hemoglobin, and increased platelet white blood cell ratio (Plt./WBC) were associated with C-19RF. LR demonstrated that SOFA score, higher O2 saturation and a higher Plt./WBC were associated with increased mortality in C-19RF patients. In contrast, in the RF pts. increased age, Sofa score, vasopressor requirement, and the need for renal replacement therapy were independently associated with mortality.

Conclusions: There are significant differences in clinical outcomes between C-19RF and RF pts developing AKI. These findings suggest a different clinical course and phenotype in the groups. These findings emphasize tailored management strategies based on respiratory failure etiology for better outcomes in C19RF and RF populations. Reference: Markov, N., Gao and SCRIPT researchers (2023) SCRIPT CarpeDiem Dataset: PhysioNet. https://doi.org/10.13026/5phr-4r89. This Work Does Not Reflect the Opinions of the NU-Script Investigators.

TH-PO1142

Barriers from COVID-19 in Home Dialysis Use among Patients with ESKD and Disability

Caroline Williams, Dylan C. Davis, Shalini Parekh, Emily Belowich, Jack Fagan. *Avalere Health LLC, Washington, DC.*

Background: Home dialysis offers numerous patient-centered and economic benefits for patients with ESRD. Despite advancements in federal policy initiatives, only 13.4% of patients with ESRD dialyze at home in the US. Home dialysis is an optimal treatment modality for ESRD patients with disabilities who have increased challenges in activities of daily living. As COVID-19 exacerbated access challenges across healthcare settings, we hypothesized that disabled ESRD patients may utilize home dialysis to a lesser degree post-pandemic compared to prior to the pandemic.

Methods: We used 100% Medicare Fee-For-Service (FFS) claims data to identify patients with ESRD who initiated in-center renal replacement therapy (hemodialysis) between July 1, 2017 and September 30, 2017 (Pre-Pandemic Cohort) or between July 1, 2021 and September 30, 2021 (Post-Pandemic Cohort) and maintained in-center hemodialysis for at least three months from their initial visit. Among these patients, we identified those who transitioned to home peritoneal dialysis within 18 months following the 3-month period of in-center hemodialysis. We stratified beneficiaries by their original reason for Medicare entitlement.

Results: After COVID-19, the relative proportion of disabled Medicare FFS beneficiaries who initiated home hemodialysis decreased from 34.5% in the Pre-Pandemic Cohort to 25.9% in the Post-Pandemic Cohort ($p<0.001$). There were no statistically significant differences between the cohorts in age, dual status, race, sex, or beneficiary state.

Conclusions: Findings suggest that COVID-19 exposed a multi-layered disparity, exacerbating access barriers in the healthcare delivery system for patients with both ESRD and disabilities. Future research and policy should focus on increased support for dialysis patients with disabilities, ensuring equitable access to treatment modalities.

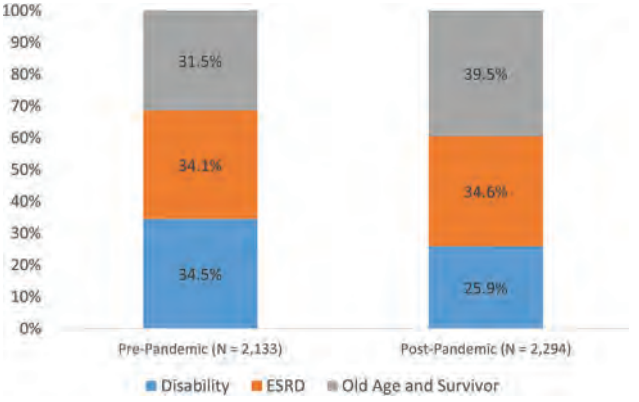


Figure 1: Distribution of Original Reason for Medicare Entitlement among Medicare FFS ESRD Patients Initiating Home Dialysis Service

TH-PO1143

Short- and Long-Term Outcomes in Critically Ill Patients with COVID-19 and AKI

Juliana A. Andrade,[1,2] Gisele Meinerz,[1,2] Eduardo L. Rech,[2] Raphael H. Palma,[1,2] Marco Antônio V. Dall Agnese,[1] Elizete Keitel.[1,2] *[1]Universidade Federal de Ciencias da Saude de Porto Alegre, Porto Alegre, Brazil; [2]Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil.*

Background: Acute kidney injury (AKI) in the setting of COVID-19 infection is associated with worse outcomes. The aim of this study was to follow-up a sample of critically ill patients with COVID-19 and AKI analyzing AKI stages, kidney replacement therapy (KRT), and outcomes at 90 days and at 365 days after hospitalization.

Methods: Observational, prospective cohort study of hospitalized adults (> 18 years old) with severe COVID-19 admitted to the Intensive Care Units (ICUs) in a tertiary hospital in south of Brazil. Patients with nephrological assessment for AKI were included from May 1st, 2020, and April 30th, 2021. Outcomes within 3 months after the COVID-19 included death and kidney function recovery. Survived patients had the glomerular filtration estimated (eGFR) at baseline, discharge and at 12 months. Kaplan-Meier method was used to survivals and ANOVA to compare means. Risk factors for death was analyzed by Cox regression.

Results: 360 patients were enrolled in the study, among them 60.6% were male, the mean age was 63.9 ± 12.5 years, 38.1% had diabetes, 68.6% had hypertension, 44.2% were obese, and 17.1% had ischemic cardiopathy. Median BMI was 29.0 (IQR 25.0-33.2). 98% required mechanical ventilation. AKI stage 1, 2 and 3 was detected in 3.6%, 5.6% and 90.8% of patients, respectively. KRT was indicated in 89.0% of patients. At 90 days follow-up, 317 (88.1%) of patients died before discharge, 7 (1.9%) remained on KRT, and 36 (10.0%) had kidney function recovered. Age (each 10 years increased risk 18%), requirement of KRT, and mechanical ventilation were associated with death within 90 days. Forty-three (43) patients (11.9% of the whole sample) survived beyond 90 days. Of those, 8 (18.6 %) patients died between 90 and 365 days and 5 (11.6 %) remained on KRT at 365 days. Thirty (30) patients (69.7%) were alive and free of KRT. The eGFR was not different between baseline (85.5 ± 23.6ml/min) and at discharge (81.7 ± 29.5ml/min). However, the mean eGFR at 365 days (65.9 ± 24.8ml/min) was lower ($p=0.003$).

Conclusions: Severe COVID-19 infected patients that developed AKI in ICU environment presented high mortality at 90 days (88,1%). Among survived patients 87% were free of dialysis. However, survivors at one year had a lower renal function compared to baseline.

TH-PO1144

AKI in Intensive Care Unit (ICU) Patients in the Omicron Surge: Insights from a Multinational Study

Pedro H. Gois,[1,2] Danyang Dai,[1] Sally Shrapnel,[1] Marina Wainstein,[1] Moji Ghadimi,[1] Nicholas S. Spyrison,[1] Rolando Claure-Del Granado,[3] Jason D. Pole.[1] ISARIC Characterization Group. *[1]The University of Queensland, Brisbane, QLD, Australia; [2]John Hunter Hospital, New Lambton Heights, NSW, Australia; [3]Universidad Mayor de San Simon, Cochabamba, Bolivia, Plurinational State of.*

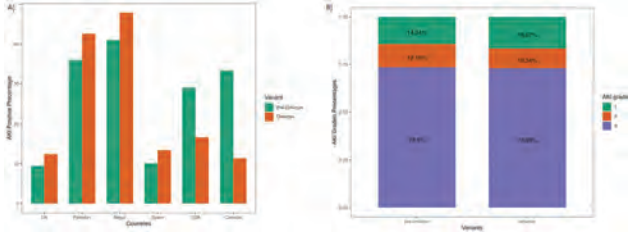
Background: Acute kidney injury (AKI) is a common and serious complication of COVID-19. Few studies have investigated the prevalence of AKI in patients admitted to Intensive Care Units (ICU) during the Omicron surge. We aim to examine the relationship between AKI and the Omicron variant in critically ill patients using the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 global dataset.

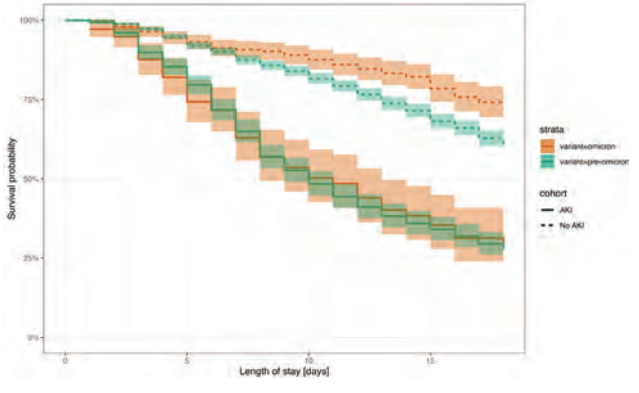
Methods: This is a prospective observational study of COVID-19 patients admitted to ICU across 6 countries between June 2021 and October 2022. AKI was defined as per KDIGO serum creatinine (sCr) criteria within 7 days of hospitalization, using the first available sCr as baseline. Patients were categorized into “Pre-Omicron” (before Dec 1, 2021) and “Omicron” (after Jan 1, 2022). Multivariable logistic regression was used to analyze the association between Omicron and AKI.

Results: The analysis included 3,908 patients (3,203 pre-Omicron, 705 Omicron). AKI distribution by countries/variants is shown in Figure 1A. AKI prevalence and dialysis were not different between Omicron and prior variants (24.7% vs 22.9%, p=0.32; and 45% vs. 52%, p=0.15, respectively). Most patients had stage 3 AKI (Figure 1B). Patients in the Omicron wave were older and had more comorbidities. After adjusting for confounders, Omicron patients were ~40% less likely to develop AKI compared to prior variants. Survival curves for AKI patients showed no significant differences between Omicron and prior variants (Figure 2).

Conclusions: Patients hospitalized during the Omicron wave were less likely to develop AKI compared to previous eras, highlighting the importance of continued research to elucidate the evolving characteristics of the disease.

Funding: Government Support - Non-U.S.





TH-PO1145

Persistent Increase in the Blood Urea Nitrogen/Creatinine Index (PI-BUN/Cr) Phenotypes the Clinical Course of Patients with Severe COVID-19

Gustavo A. Casas-Aparicio,[1] Rolando Claure-Del Granado.[2] *[1]Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico; [2]Hospital Obrero No 2, Division de Nefrologia, Cochabamba, Bolivia, Plurinational State of.*

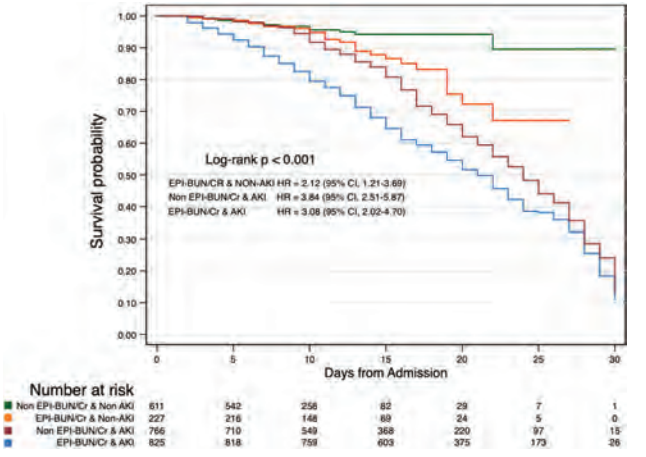
Background: PI-BUN/Cr in patients with COVID-19 is an important clinical marker that extends beyond simple prerenal injury, reflecting more complex underlying pathophysiological processes. Understanding and interpreting PI-BUN/Cr in this context is crucial due to its potential implications for mortality.

Methods: We analyzed a retrospective and longitudinal cohort of patients admitted to a single center in Mexico City. Between March 5, 2020, and August 25, 2021, patients with confirmed positive diagnosis for SARS-CoV-2, age >18 years, and a ratio of partial oxygen pressure to inspired oxygen fraction <300 mmHg on admission were included. Data was obtained from electronic medical records. PI-BUN/Cr was defined as an increase in the BUN/Cr ratio >30 in more than 60% of the measurements recorded during hospitalization. AKI was defined based on the K-DIGO guidelines. The primary objective was to analyze the risk factors for mortality.

Results: The cohort included 3,007 patients, with a median age of 54.6 ±14.5 years. Thirty-five percent of patients died; 44.6% developed PI-BUN/Cr ratio and 71.4% AKI. Mortality was associated with older age >60 years [Hazard ratio (HR)]=1.45, 95%CI:1.28-1.65; p<0.001); male (HR=1.25, 95% CI: 1.09-1.44; p=0.002); and AKI (HR=3.29, 95% CI: 2.42-4.46; p<0.001). PI-BUN/Cr was not associated with mortality (HR=0.95, 95% CI:0.83-1.07; p=0.417). According to the PI-BUN/Cr and AKI status, mortality was higher in the groups with PI-BUN/CR & Non-AKI (HR=2.82, 95% CI: 1.61-4.93; p<0.001); Non-PI-BUN/CR & AKI (HR=5.47, 95% CI: 3.54-8.44; p<0.001); and PI-BUN/CR & AKI (HR=4.26, 95% CI: 2.75-6.62, p<0.001). Survival analysis is shown in Figure 1.

Conclusions: While PI-BUN/Cr alone may not directly associate with mortality, its capacity to phenotype patients according to their AKI status holds significant promise in offering valuable insights into patient prognosis and outcomes.

Funding: Government Support - Non-U.S.



TH-PO1146

Humoral Response to SARS-CoV-2 Vaccination in Lupus Nephritis

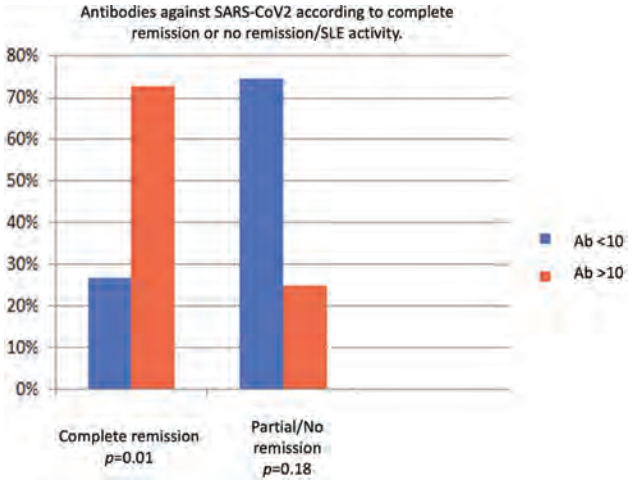
Ana S. Fernandez, Agustin Noboa, Jose Boggia, Gabriela Ottati. *Hospital de Clinicas Doctor Manuel Quintela, Montevideo, Uruguay.*

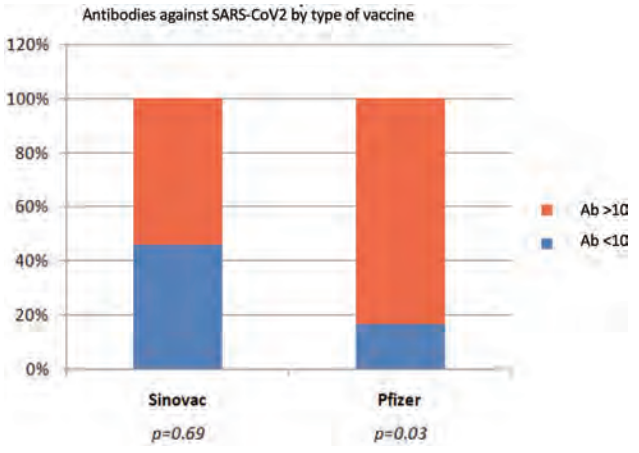
Background: Vaccine development has been the best control measure for the SARS-CoV-2 pandemic. However, patients with lupus nephritis (LN) have not been included in studies assessing vaccine efficacy. The objective is to analyze LN patients’ ability to generate antibodies against SARS-CoV-2 after vaccination while under immunosuppressive treatment.

Methods: A prospective study was conducted on patients with LN. One month after receiving the second SARS-CoV-2 vaccine, a blood sample was taken to test for the presence of antibodies using an ELISA test sensitized with the Receptor Binding Domain (RBD) fragment of the SARS-CoV-2 Spike protein. Adverse effects and changes in the SLEDAI score were documented following the vaccine administration.

Results: We recruited 19 patients, with a median age of 35.5 years and 89% female. The overall seroconversion rate was 63% (p=0.11). Patients in complete remission (CR) exhibited a significantly higher antibody response. The antibody production rate was higher for Pfizer® at 83% (p=0.03) compared to Sinovac at 54% (p=0.69). Patients who initially received Cyclophosphamide treatment showed a significant reduction in antibody production after vaccination (p=0.009).

Conclusions: Patients vaccinated with Pfizer or in complete remission showed higher anti-SARS-CoV-2 seroconversion rates.





TH-PO1147

Humoral and Cellular Immunity following Bivalent mRNA Boosters in Patients on Hemodialysis

Tsai-chieh Ling, Jia-Ling Wu, Chien Yao Sun, Wei-Ren Lin, Chieh-Hsin Huang, Yu T. Chang. *National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: Dialysis patients are at high risk of SARS-CoV-2 related morbidity and mortality. Although bivalent vaccines targeting Omicron subvariants were recommended, data on the immunogenicity in the hemodialysis (HD) population remain limited.

Methods: In this prospective observational study, we enrolled patients on maintenance HD scheduled to receive bivalent mRNA vaccines. Immune responses were assessed before, and one and three months after vaccination (baseline, M1 and M3), and also at M1 and M3 after breakthrough infection. Age-matched healthy adults served as controls. Humoral immunity outcomes included anti-SARS-CoV-2-S antibody, surrogate viral neutralization tests (sVNT) against the ancestral virus, Omicron BA.1, BA.2 and BA.4/5, and pseudovirus neutralization tests against Omicron BF.7, B.2.75, BQ.1.1 and XBB.1.5. Cellular immunity was evaluated with interferon-γ release assay (IGRA) targeting spike proteins from various variants.

Results: A total of 106 HD patients (median age 66) received Spikevax Original/Omicron BA.1 (89.6%) or BA.4-5 (10.4%) from October 2022 to February 2023. Of these, 25.5% had prior infection, and 93.4% had received four doses of vaccines including two AZD1222 and two mRNA vaccines. Anti-SARS-CoV-2-S antibody levels increased by 4.2-fold and subsequently halved at M3. sVNT showed increased neutralization against Omicron subvariants peaked at M1 and positive rates remained high(75.3~96%) at M3. Pseudovirus neutralizing capacity against Omicron BF.7, B.2.75, BQ.1.1 and XBB.1.5 increased by 2-to-9.9 times. However, only 58.1% of patients showed a positive IGRA response at M1, with no correlation to humoral outcomes. No significant differences in humoral and cellular immunity were demonstrated between HD patients and health controls. In those with 5 immunizations, Anti-SARS-CoV-2-S antibody and sVNT against BA.4/5 at M3 were higher following hybrid immunity than pure vaccinations. In multivariate linear mixed effect model, previous SARS-CoV2 infection attenuated neutralization against the ancestral virus.

Conclusions: Bivalent mRNA vaccines boosted antibody titers and broaden neutralization against new Omicron subvariants in HD patients. However, cellular immunity was suboptimal despite multiple immunizations including bivalent vaccines and infection, highlighting a potential area for further investigation.

Funding: Government Support - Non-U.S.

TH-PO1148

Mild COVID-19 Infection Does Not Affect CKD Indices

Avital Angel-Korman,[1,2] Adi Leiba,[1,2] Tal Brosh-Nissimov,[1,2] Ori Mayer.[3] *[1]Assuta Ashdod University Hospital, Ashdod, Israel; [2]Ben-Gurion University of the Negev, Beer-Sheva, Israel; [3]Tel Aviv University Faculty of Medicine, Tel Aviv, Israel.*

Background: COVID-19 in hospitalized patients has been implicated in the deterioration of several indices associated with chronic kidney disease (CKD), including new onset hypertension, and worsening of proteinuria and kidney function. Nevertheless, the influence of COVID-19 on these parameters in patients with CKD has not been fully elucidated. We aimed to study the effect of COVID-19 on blood pressure (BP), proteinuria, and eGFR in a community-based cohort of patients with CKD

Methods: A retrospective cohort study using data obtained from Maccabi Healthcare Services (MHS) during COVID-19 pandemic. MHS, is a nationwide payer-provider healthcare system, with an extended database including laboratory information, vital signs documentation and a well validated CKD registry. Included in the study were all adults (over 18 years of age) with CKD stages I-V insured in MHS, who had a first documented mild-moderate laboratory-confirmed COVID-19, not requiring hospitalization. All reported BP clinic measurements within one year prior to and following COVID-19, were averaged, and so were urine albumin and serum creatinine (sCr) measurements

Results: 43,875 patients were registered as having CKD in MHS and had a documented 1st COVID-19 infection between 2020-2022. Mean age was 69.3 (±12.9) years and 21,775 (49.6%) were males. Following COVID-19, systolic BP was 1 mmHg lower and diastolic BP was 0.6 lower compared with pre-COVID-19 values (P-value 0.03 and 0.004, respectively). 8918 patients had at least 2 documented urine albumin to creatinine ratio (UACR) measurements. The mean UACR was 64mg (±233) before and 93mg (±322) after COVID-19, accounting for an absolute difference of 29mg (±294), p<0.001. Patients with baseline albuminuria >300mg had a mean decrease in albumin level of 263mg (±676) following COVID-19. In 37,923 patients who were tested for sCr, eGFR was 73.2ml/min (±19.8) and 72.2ml/min (±20) before and after COVID-19, respectively - an absolute difference of 1ml/min (±8.9), p<0.001. Adjustment for changes in medications including ACE INH, ARBs, diuretics MRAs and SGLT2 inhibitors did not significantly affect the results

Conclusions: Although some differences in CKD indices were statistically significant given the large cohort size, none were clinically significant. Mild-moderate COVID-19 did not affect indices of CKD and is therefore unlikely to be associated with CKD progression

Funding: Private Foundation Support

TH-PO1149

Vaccination Strategies in Patients Receiving Dialysis: Should We Watch the Clock?

Nivetha Subramanian,[1] Xue Yu,[1] Meri Varkila,[1] Geoffrey A. Block,[2] Julie Parsonnet,[1] Glenn M. Chertow,[1] Shuchi Anand,[1] Maria E. Montez-Rath.[1] *[1]Stanford Medicine, Stanford, CA; [2]US Renal Care Inc, Decatur, GA.*

Background: Previous studies reported that early morning vaccination was associated with a more robust antibody response than late afternoon or evening vaccination. Circadian changes in the immune system may yield better immunogenicity in the morning than later in the day. We examined peak and longitudinal SARS-CoV-2 antibody response by vaccine timing in a nationwide cohort of patients on hemodialysis.

Methods: Patients were documented in the electronic medical record to have received at least 1 dose of mRNA vaccine at the dialysis facility during their assigned shift and had available data on antibody indices after 1st dose (n=1229). Using a semiquantiative Siemens RBD IgG assay and quantile regression, we estimated unadjusted and adjusted median RBD IgG indices over time by dialysis shift.

Results: The mean age of patients receiving vaccine in the early morning (~530 am) shift was younger than those in the mid-day (~10 am) or late afternoon (~2 pm) shifts: 60(SD 13), versus 66(13) and 62(15) years, respectively. Patients in the early morning shift were more likely to receive the BNT162b.2 vaccine than those who dialyzed in mid-day or late afternoon shifts (57% versus 52% and 42%, respectively). A larger proportion of patients who dialyzed in early morning (19%) had detectable RBD IgG indices prior to vaccine compared with patients in mid-day (12%) and late afternoon (14%) shifts. In unadjusted analyses, the early morning cohort had higher RBD IgG indices 30-60 days post-vaccine. Adjusting for age, diabetes, years on dialysis, type of vaccine, and baseline IgG eliminated difference by shift (Fig1).

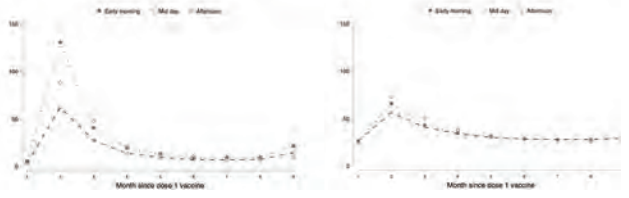
Conclusions: In this nationwide cohort of patients receiving dialysis and mRNA vaccines, we found that early morning vaccination did not yield a better immunogenicity as measured by antibody response. Prior analyses reporting an association of vaccine timing with immune response may not have accounted for prior SARS-CoV-2 infection or other relevant differences in patient characteristics.

Funding: Other NIH Support - NIH U01AI169477

Figure 1: Median RBD Ig by dialysis shift when vaccine was administered

1a. Unadjusted

1b. Adjusted for age, diabetes, vaccine type, dialysis vintage, and baseline RBD Ig levels



TH-PO1150

Wunderlich Syndrome in a Patient with ESKD Diagnosed with COVID-19: A Case Report

Maricar Mae A. Marquez, Annabelle S. Lim, Abigayle Therese R. Guiritan. *St. Luke's Medical Center, Quezon City, Quezon City, Philippines.*

Introduction: Wunderlich syndrome is a rare clinical syndrome characterized by an acute onset of spontaneous renal hemorrhage into the subcapsular, perirenal, and/or pararenal spaces, without a history of antecedent trauma. Patients may present with a multitude of symptoms ranging from abdominal pain to serious manifestations such as hypovolemic shock. In this case report, we presented an end stage renal disease patient diagnosed with Covid 19 who developed Wunderlich syndrome.

Case Description: This is a case of 68-year-old female, with known chronic kidney disease stage 5 on hemodialysis, presented with abdominal pain and hypotension. On the day of admission, patient was scheduled for over-the-wire IJ catheter exchange. Post-procedure, patient developed hypotension and abdominal pain localized to the right upper and lower quadrant. Despite fluid resuscitation, she remained hypotensive. Significant physical examination revealed bibasal crackles. On work up, there was anemia (Hgb: 8.5g/dL, dropping to 6.6g/dL in 6 hours), and bilateral lower lung densities on chest X-ray. COVID RT PCR was positive. Other work up such as 12Lead ECG, 2D echo, Procalcitonin, Urinalysis, Liver Function Test were unremarkable. CT scan thoraco-abdominal aortogram was done which revealed right renal subcapsular acute hemorrhage. Since the patient was hemodynamically unstable, patient underwent renal angiogram with renal artery embolization. She was eventually weaned off inotropic support, anemia was corrected via blood transfusion and adequate antibiotic coverage was given for the pneumonia. Hemodialysis was continued. Following stabilization and completion of isolation, she was discharged. Follow-up imaging showed resolution of the renal subcapsular hemorrhage.

Discussion: Wunderlich syndrome is a life threatening condition with high morbidity and can be fatal if not treated promptly and aggressively. End stage renal disease is a rare cause for Wunderlich syndrome. Patients with ESRD are predisposed to bleeding diathesis. Another rare but possible cause is the presence of COVID-19 infection in the patient. Studies have suggested that COVID-19 can cause a spontaneous hemorrhage and can increase incidence of bleeding. Both of these in combination can cause endothelial dysfunction which could lead to increased bleeding events.

TH-PO1151

Unplanned Initiation of Maintenance Hemodialysis: Patient Background and Survival in Pre- and Post-COVID-19 Emerging

Mineaki Kitamura,[1,2] Tomoya Nishino.[1] [1]*Nagasaki Daigaku Byoin, Nagasaki, Japan;* [2]*Nagasaki Minato Medical Center Shimin Byoin, Nagasaki, Japan.*

Background: The initiation of hemodialysis, especially when unplanned, often leads to a decline in functional status and an increased risk of cardiovascular diseases, malnutrition, and infections. Several factors associated with unplanned dialysis have been reported; however, patient background differences between pre-and post-COVID-19 emerging have not been elucidated. We aimed to identify factors contributing to unplanned hemodialysis and evaluate patient prognosis in collaboration with maintenance hemodialysis centers.

Methods: We analyzed patients initiating hemodialysis at our facility between 2016 and 2023, stratified by pre-April 2020 and post-April 2020 periods based on the declaration of a state of emergency from the Japanese Government. Unplanned hemodialysis was defined as initiation during emergency admission, regardless of arteriovenous fistula presence. Data on patient demographics, comorbidities, and clinical course were collected. Multivariable logistic and Cox regression models assessed factors associated with unplanned hemodialysis initiation and patient mortality, respectively.

Results: We included 290 patients (age:71±12 years old, 64% male) and divided them into the groups pre-(n=149) and post-April 2020 (n=141). Unplanned hemodialysis was initiated in 77 (55%), and 69 (46%) patients in both periods. The prevalence of any infections was higher in patients initiating unplanned dialysis (P<0.001). Multivariable logistic regression analysis indicated that unplanned dialysis initiation throughout the entire period was significantly associated with infections (OR: 15.79, 95% CI: 5.45-45.75, P<0.001). This trend was almost similar in pre- and post-April 2020. Notably, the prevalence of pneumonia in the post-April 2020 group was lower (n=13, 8%) than that in the pre-April 2020 group (n=25, 17%) (P=0.02). During the follow-up period (median 766 days), 89 patients died, and infections were the most prevalent cause of death (34%). Unplanned hemodialysis was an independent risk factor of death (HR:1.96, 95%CI:1.20-3.18, P=0.007)

Conclusions: As patients with renal failure are susceptible to infections, special attention should be paid even after the post-COVID-19 pandemic. Increased awareness of hygiene practices can improve prognosis in patients with renal failure.

TH-PO1152

Incident Obstructive Sleep Apnea in Patients with Primary Aldosteronism following COVID-19 Infection

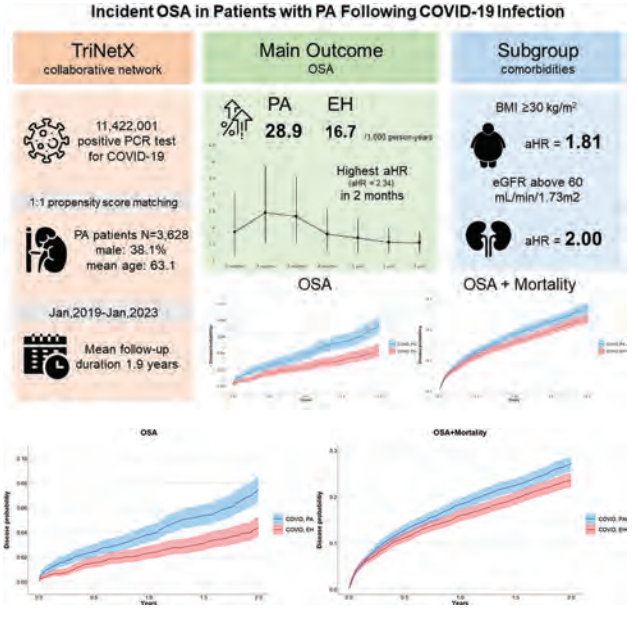
Wen-Kai Chu, Vincent Wu. *National Taiwan University Hospital, Taipei, Taiwan.*

Background: In the context of the COVID-19 pandemic, there is growing concern about the virus's effects on individuals with existing endocrine disorders such as primary aldosteronism (PA). This study explores the potential relationship between PA and the risk of developing obstructive sleep apnea (OSA) after a COVID-19 infection.

Methods: In this retrospective cohort study, we utilized data from the TriNetX database, covering the period from January 2019 to January 2023. We identified essential hypertension (EH) patients as the control group, employing 1:1 propensity score matching. The endpoints included incident OSA and all-cause mortality.

Results: Among 11,422,001 patients with PCR positive COVID-19, we identified 3,628 PA patients (mean 63.1 years old, male 38.1 %). After a medium follow up of 1.9 years, the rate of OSA was 28.9 per 1,000 person-years in PA patients compared to EH with 16.7. We showed a significant increase in incident OSA (adjusted hazard ratio [aHR] 1.58, p < 0.001) and mortality (aHR 1.12, p = 0.04) in PA patients than EH post-COVID-19. The horizon plot revealed that patients with pre-existing PA had the highest risk of OSA at 2 months (aHR = 2.34) post COVID-19. In subgroup analysis, PA patients with a high body mass index (≥30 kg/m^2) (aHR 1.81, p=0.001) or preserved kidney function (aHR 2.00, p<0.001) had increased OSA incidences post-COVID-19.

Conclusions: Our study underscores a notable rise in incident OSA among PA patients post-COVID-19, highlighting the imperative for diligent OSA screening, particularly among individuals with obesity or preserved kidney function.



TH-PO1153

COVID-19 Pandemic and Peritonitis in Patients with ESKD on Peritoneal Dialysis

Hye Soon Shin, Sun Moon Kim, Hyunjeong Cho, Ji Hye Kim, Mi Ran Park, Hye-Young Kim. *Chungbuk National University Hospital, Cheongju, Chungcheongbuk-do, Republic of Korea.*

Background: Coronavirus disease 2019 (COVID-19) pandemic has changed patients' behaviors and social relationships. However, the influence of COVID-19 pandemic on the peritonitis in patients on peritoneal dialysis (PD) remains to be elucidated. Thus, we investigated the impact of COVID-19 pandemic on the incidence and clinical outcome of peritonitis in end-stage kidney disease (ESKD) patients on PD.

Methods: A single-center retrospective study was conducted. Medical records of all the ESKD patients on maintenance PD were reviewed from Jan 2017 to Dec 2022: clinical characteristics, prescription of PD, pathogens, hospitalization, and clinical outcome of peritonitis. We compared the incidence and clinical outcome of peritonitis three years before (2017-2019) and after COVID-19 pandemic (2020-2022).

Results: A total of 572 medical records were analyzed. The incidence of PD-related peritonitis decreased after COVID-19 outbreak. The incidence of peritonitis was 0.187/patient-year in 2017-2019 and 0.120/patient-year in 2020-2022. The microbiologic features were not different. The most common pathogen of peritonitis were gram-positive bacteria. The proportion of peritonitis-related hospitalization and catheter removal associated with treatment failure did not differ between before and after COVID-19 pandemic.

Conclusions: This study suggests that during the COVID-19 pandemic the incidence of PD-related peritonitis was decreased whereas pathogens and hospitalization did not change.

TH-PO1154

Effect of RAAS Inhibitors in People with COVID-19: An Independent Participant Data Meta-Analysis

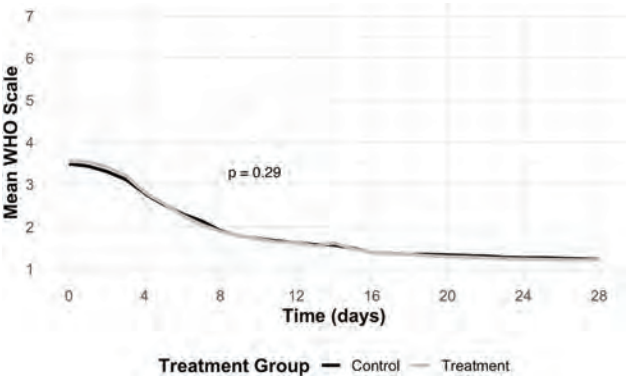
Tae won Yi,[1,2] Kylie-Ann Mallitt,[3] Arlen Wilcox,[2] Michael A. Puskarich,[4] Daniel Freilich,[5] Matthew Geriak,[6] Cecilia M. Shikuma,[7] Meg Jardine.[2] *[1]The University of British Columbia, Vancouver, BC, Canada; [2]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [3]University of Sydney, Camperdown, NSW, Australia; [4]University of Minnesota Twin Cities, Minneapolis, MN; [5]Bassett Medical Center, Cooperstown, NY; [6]Sharp Healthcare, San Diego, CA; [7]University of Hawai'i at Manoa, Honolulu, HI.*

Background: SARS-CoV-2 infection is mediated by angiotensin-converting enzyme 2 receptors. Trials in different settings were initiated to test whether renin-angiotensin-aldosterone system inhibitors (RAASi) improved clinical outcomes in people with COVID-19.

Methods: We performed an individual participant data (IPD) meta-analysis of randomized controlled trials (RCTs) evaluating the effects of RAASi in people with COVID-19. The primary outcome of WHO Clinical Progression scale over 28 days was evaluated using a linear mixed model. All-cause mortality was evaluated with Cox proportional hazards.

Results: Six trials evaluating losartan, telmisartan, and candesartan were included, with sample sizes ranging from 12 to 787. Trials were conducted in the USA, Australia, and India; four were completed as planned, and 5 were placebo controlled. The 1,130 participants had a median age of 50 years and 38% were female. The majority of the cohort was Asian (73%) and Caucasian (16%). The median BMI was 25 kg/m^2, 29% had hypertension, 21% had diabetes, and 17% had a smoking history. The baseline mean WHO score was 3.6 in the RAASi arm and 3.5 in the control arm. Most participants resolved with a mean WHO score of 1.2 in the RAASi arm and 1.2 in the control arm at day 28, with no significant difference in WHO scale progression (Figure 1, p=0.29). RAASi did not affect overall mortality (26 deaths, event rate 0.04 and 18 deaths, event rate 0.03 in the RAASi and control arms respectively: HR 1.42 [0.77-2.64], p=0.261).

Conclusions: This IPD meta-analysis presents the largest randomized report of the effects of commencing RAASi for acute COVID-19. There is no evidence supporting a benefit for RAASi in COVID-19 patients.



TH-PO1155

Impact of COVID-19 Vaccination on Racial Disparity in COVID-19 Mortality from a National US Dialysis Provider

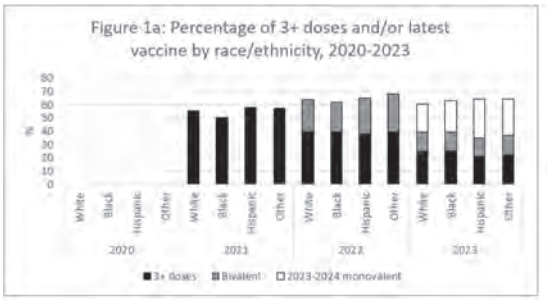
Monica Shieu,[1] Austin Gibson,[1] Nien Chen Li,[1] Harold Manley,[1] Antonia Harford,[1] Caroline M. Hsu,[2] Daniel E. Weiner,[2] Dana Miskulin,[2] Doug Johnson,[1] Eduardo K. Lacson.[1,2] *[1]Dialysis Clinic Inc, Nashville, TN; [2]Tufts Medical Center, Boston, MA.*

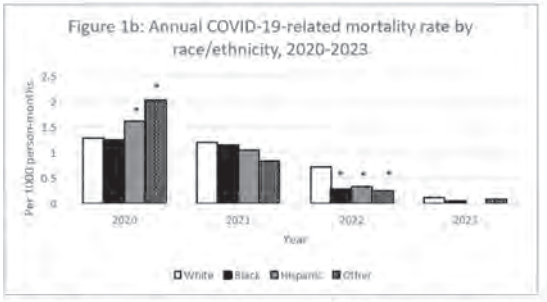
Background: The pandemic has negatively affected vulnerable dialysis patients especially minorities. We examined the impact of providing universal access to COVID-19 vaccines in dialysis clinics on COVID-19 mortality by racial/ethnicity (RE) group from a national provider.

Methods: Adult maintenance dialysis patients at Dialysis Clinic, Inc. from 2020-2023 were included. The percentage of 3+ doses and/or latest updated vaccine at the end of each year was examined. The outcome of interest was death with COVID as the primary cause within 90 days of diagnosis. Distribution of vaccine status among RE groups was analyzed with ANOVA. Change in mortality rate over the years and by RE groups were both assessed by linear regression.

Results: The cohort included 41,257 patients of White (42%), Black (37%), Hispanic (7%), and Other (14%) race. In 2020, White had the lowest mortality rates (1.3 per 1000 person-months) while Other (2.0) and Hispanic (1.6) had the highest rates (p<.001). All RE groups had similar percentages of 3+ doses and/or latest vaccine: 50-58% in 2021 to 60-64% in 2023 (p>0.08) (Fig 1a). Since COVID vaccines became available in 2021, mortality rates among all RE groups have decreased significantly (b=-0.45, p<.001) (Fig 1b). In 2022, mortality rate declined the least among Whites but was similar again in 2023.

Conclusions: With universal access to vaccines provided in the dialysis clinics, more than 50% of dialysis patients were vaccinated with 3+ doses and/or the latest vaccine. Mortality rate among all RE dropped significantly after the availability of COVID vaccines in 2021. Availability of vaccination in the dialysis clinics may have improved racial disparity in COVID-19. Maintaining equal access to vaccines may enable better outcomes and reduce disparities in this high-risk population, even beyond the COVID-19 pandemic.





White is the reference group within each year. *p<0.05. Since COVID vaccines became available in 2021, mortality rates among all RE groups have decreased significantly (b=-0.45, p <.001).

TH-PO1156

Four-Year Impact of the COVID-19 Pandemic on Mortality and Hospitalization Trends among Patients on Maintenance Dialysis from a National US Dialysis Provider

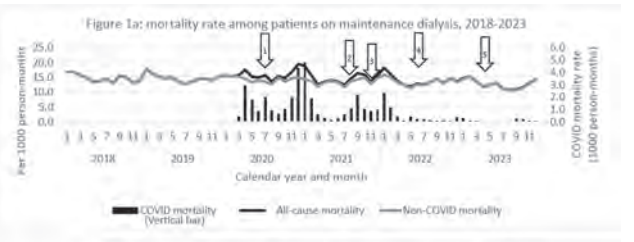
Monica Shieu,[1] Nien Chen Li,[1] Harold Manley,[1] Antonia Harford,[1] Caroline M. Hsu,[2] Daniel E. Weiner,[2] Dana Miskulin,[2] Doug Johnson,[1] Eduardo K. Lacson.[1,2] *[1]Dialysis Clinic Inc, Nashville, TN; [2]Tufts Medical Center, Boston, MA.*

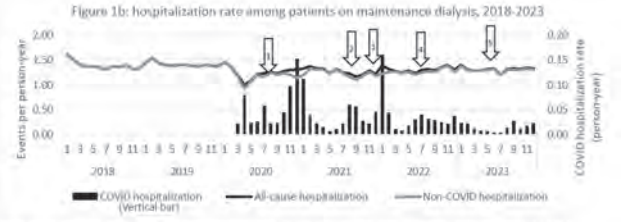
Background: Longitudinal trends in mortality and hospitalization rates during the COVID-19 pandemic period (2020-2023) vs. prior two years (2018-2019) among patients receiving maintenance dialysis from a national provider were described.

Methods: Adult maintenance dialysis patients at Dialysis Clinic, Inc. between 1/1/2018 to 12/31/2023 were included. Hospitalization stays over two midnights and death events were obtained from electronic medical record. COVID-19 hospitalization and death were defined as within 30 days and 90 days of a COVID-19 diagnosis, respectively.

Results: The study included 41,257 patients. All-cause mortality among prevalent patients receiving dialysis decreased by 15.4%, from 16.9 to 14.3 (per 1000 person-months) between 2018-2023, with a spike in 03/2020 when the pandemic started. Mortality peaked that winter (19.4 per 1000 person-months) until the availability of COVID-19 vaccines in early 2021 (Fig 1a). All-cause hospitalization rates decreased between 2018-2023. There was a sudden drop in hospitalization rates when the pandemic began (1.61 from 01/2018 to 1.18 03/2020 and 1.01 from 04/2020 per person-year); these rates never recovered to the overall rates observed prior to the pandemic (Fig 1b).

Conclusions: The pandemic has impacted mortality and hospitalization rates among patients on maintenance dialysis, with a drastic increase in all-cause mortality vs. a sudden drop in all-cause hospitalization when the pandemic started. All-cause mortality and hospitalization rates, 2018-2021, are lower than the rates in 2023 USRDS. The profound impact of vaccination in reducing severe outcomes from COVID-19 is evident. Strategies to maintain updated vaccination status to prevent COVID-19-related hospitalization and death in this high-risk population are warranted.





Numbered arrows indicate pandemic timepoints: 1 (pandemic started, national lockdown), 2 (COVID vaccines became available), 3 (Delta variant dominance period started), 4 (Omicron variant dominance period started), 5 (updated bivalent vaccine recommendation).

TH-PO1157

Tixagevimab-Cilgavimab for Breakthrough COVID-19 Prevention in Dialysis Patients: A Prospective Study

Suchai Sritippayawan,[1] Sarinya Boongird,[2] Thatsaphan Srithongkul,[1] Sethanant Sethakarun,[3] Jackrapong Bruminhent,[4] Sasisopin Kiertiburanakul,[4] Arkom Nongnuch,[2] Chagriya Kitiyakara.[2] *[1]Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2]Division of Nephrology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [3]Bhumirajanagarindra Kidney Institute, Bangkok, Thailand; [4]Division of Infectious diseases, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand.*

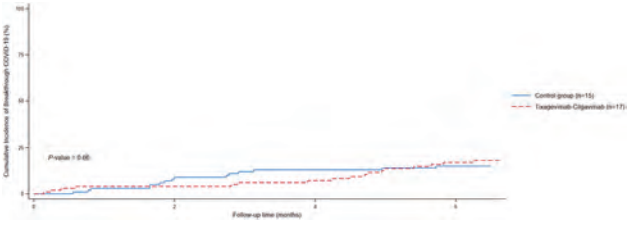
Background: Tixagevimab-cilgavimab (T/C), a monoclonal antibody for pre-exposure prophylaxis (PrEP), holds promise among immunocompromised individuals for preventing COVID-19. However, data on T/C effectiveness in the dialysis population is limited.

Methods: This multi-center, prospective study evaluated the impact of T/C as PrEP for breakthrough COVID-19 in vaccinated dialysis patients during the Omicron BA.2.75 and XBB variant surge. Patients were assigned to either the T/C group, receiving a single 150 mg/150 mg intramuscular dose, or an age-matched control group not receiving T/C. All participants were followed for a period of 6 months. The primary outcome was breakthrough COVID-19 rate. Secondary outcomes included COVID-19 related hospitalization, ICU admission, and mortality. Safety of T/C was assessed in the intervention group.

Results: A total of 200 participants (100 in the T/C and 100 in the control group) were enrolled. The mean age of participants was 66 years old, with over 80% on hemodialysis. At 6 months, the cumulative incidence of breakthrough infection did not differ significantly between groups (17% T/C vs. 15% control; p = 0.66). However, among those who developed breakthrough infections, the median (IQR) time to diagnosis tended to be longer in the T/C group compared to controls [4.9 (2.81–4.98) months vs. 1.96 (1.65–2.91) months; p = 0.08]. T/C administration significantly reduced COVID-19 related hospitalization rates (5.9% vs. 40.0%; p = 0.02) among participants with breakthrough infections. No significant differences were observed in ICU admission, intubation, or death rates from COVID-19. All reported T/C-related adverse events were mild and resolved within 7 days.

Conclusions: Breakthrough COVID-19 can occur in vaccinated dialysis patients receiving T/C during the Omicron surge; however, these patients are likely to experience fewer hospitalizations. Further research on other investigational monoclonal antibody or alternative prevention strategies is needed for this population.

Funding: Clinical Revenue Support, Government Support - Non-U.S.



Cumulative incidence of breakthrough COVID-19

TH-PO1158

RescuE pLAsma eXchange in Severe COVID-19 (RELAX Trial): A Multicenter Randomized Controlled Trial

Christian Nusshag,[1] Christian Morath,[1] Florian Kälble,[1] Claudius Speer,[1] Jan Meis,[2] Vedat Schwenger,[3] Thorsten Brenner,[4] Martin G. Zeier,[1] David Czock,[5] Markus A. Weigand,[6] Uta Merle.[7] *[1]Heidelberg University Hospital, Department of Nephrology, Heidelberg, Germany; [2]University of Heidelberg, Institute of Medical Biometry, Heidelberg, Germany; [3]Klinikum Stuttgart Katharinenhospital, Department of Nephrology, Hypertension and Autoimmune Disorders, Heidelberg, Germany; [4]University Hospital Essen, Department of Anesthesiology and Intensive Care Medicine, Heidelberg, Germany; [5]Heidelberg University Hospital, Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany; [6]Heidelberg University Hospital, Department of Anesthesiology, Heidelberg, Germany; [7]Heidelberg University Hospital, Department of Gastroenterology, Heidelberg, Germany*.

Background: Evidence suggests a multi-level inflammatory syndrome in critically ill COVID-19 patients, resembling inflammatory, coagulopathic and autoimmune diseases. Plasma exchange (PE) is controversially discussed as a potential therapy. Here we report the first results of a multicenter, randomized controlled trial evaluating PE versus standard of care (SOC) in severe COVID-19.

Methods: Critically ill COVID-19 patients were enrolled in the RELAX trial (SOC n=33, SOC+PE n=34). Inclusion criteria were SARS-CoV-2-induced ARDS requiring mechanical ventilation, fever ≥ 38.5°C, D-dimer ≥ 2mg/dL, and dexamethasone therapy for at least two days. Patients received either SOC or SOC plus at least three PE treatments. The primary endpoint was 30-day mortality. Secondary endpoints included 60-, 90-, and 365-day mortality and procedure-related complications.

Results: The PE group underwent a median of 4 PE procedures (Interquartile range [IQR] 3-6), exchanging a plasma volume of 3.9L per treatment (IQR 3.7-3.9L). Hemodynamics and vasopressor support improved after PE treatments. Kaplan-Meier analysis showed no significant survival benefit at 30 days, but a significantly improved 90- and 365-day survival in the PE group (Figure 1). No severe complications occurred. Complications included allergic reactions (1.7%), hypertensive episodes (17.9%), hypocalcemia (75.7%), cardiac arrhythmia (0.6%), and catheter dysfunctions (1.7%). Allergic reactions were limited to skin rash, hypocalcemia was mild (1.1 mmol/L [IQR 1.0-1.1 mmol/L]), and arrhythmia occurred in one patient with prior episodes of atrial fibrillation.

Conclusions: Plasma exchange significnatly improved long-term survival in critically ill COVID-19 patients. Exploring potential mechanisms of PE on inflammation and coagulopathic drivers may have large clinical implications for other viral diseases and sepsis

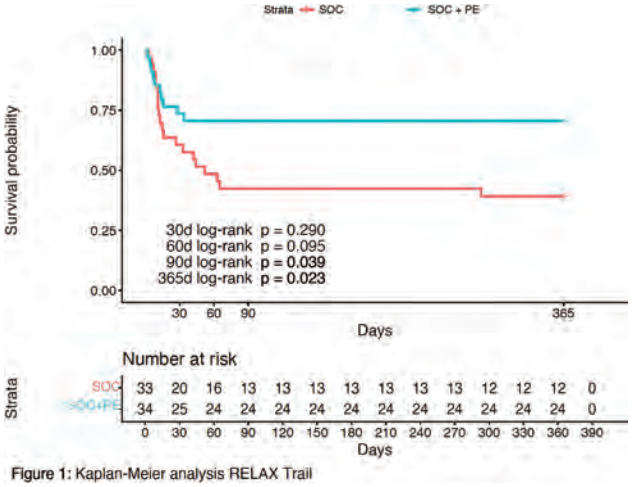


Figure 1: Kaplan-Meier analysis RELAX Trail

TH-PO1159

Rebound and Protracted COVID-19 in Patients Receiving Rituximab for Autoimmune and Glomerular Diseases

Orhan Efe, Gabriel Sauvage, James L. Chung, Anushya Jeyabalan, Ayman Al Jurdi, Harish Shanthanu Seethapathy, Katherine M. Cosgrove, Karen A. Laliberte, John Niles. Vasculitis and Glomerulonephritis Center at Massachusetts General Hospital. *Massachusetts General Hospital, Boston, MA.*

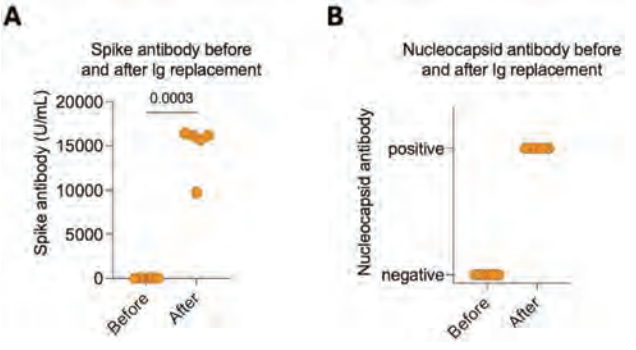
Background: B cell depletion with rituximab abrogates antibody responses against SARS-CoV-2 and is associated with severe COVID-19. The risk and best treatment of rebound COVID-19 with recent strains of SARS-CoV-2 in patients using rituximab is unknown.

Methods: We conducted a retrospective study of patients who developed COVID-19 between 5/25/23-3/1/24 while receiving rituximab at Vasculitis and Glomerulonephritis Center at Massachusetts General Hospital. Patient characteristics, treatments, and outcomes of COVID-19 were evaluated.

Results: A total of 48 patients were included. The median age was 62 (IQR 47–72). 63% (30/48) had ANCA-associated vasculitis. Patients received a median of 5 (IQR 3–6) vaccinations and had 1 (IQR 0–1) prior infection. The median time from the last rituximab dose to COVID-19 was 4.2 (IQR 1.5–11.1) months, and 88% (42/48) had B cell depletion. 19% (9/48) had moderate, severe, or critical disease per NIH symptom scale and required hospitalization. 85% (41/48) received treatment, including nirmatrelvir/ritonavir (56%), remdesivir (21%), and IVIG (4%) (**Table 1**). One patient died. 38% (18/48) developed rebound or protracted (>30 days) COVID-19, of whom all had full B cell depletion, 56% (10/18) developed at least moderate COVID-19, and 67% (12/18) received treatment (**Table 1**). 50% (9/18) were treated with IVIG adjunctive to antivirals, which raised serum anti-SARS-CoV-2 antibodies (**Fig.1**) and improved all except one who died.

Conclusions: COVID-19 in B cell-depleted patients is associated with high rates of rebounding disease and hospitalization despite available treatments and vaccines. IVIG is effective as an adjunct strategy.

Table 1. Treatments and outcomes of COVID-19 infections (n=48)	Median (IQR) or n (%)
Initial disease severity	
Mild	39 (81)
Moderate	7 (15)
Severe	1 (2)
Death	1 (4)
Initial treatment	40 (83)
Nirmatrelvir/ritonavir	27 (56)
Remdesivir	10 (21)
Ig replacement	2 (4)
Steroids	7 (15)
Tocilizumab	1 (2)
Rebound or protracted COVID-19	18 (38)
Disease severity of rebound or protracted COVID-19	
Mild	8 (44)
Moderate	7 (39)
Severe or critical	2 (12)
Death	1 (6)
Treatment of rebound or protracted COVID-19	12 (67)
IVIG	9 (50)
Remdesivir	8 (44)
Nirmatrelvir/ritonavir	2 (11)
Steroids	11 (61)
Tocilizumab	1 (6)
Outcome of rebound or protracted COVID-19	
Full recovery	16 (89)
Second rebound after improvement	1 (6)
Death	1 (6)



TH-PO1160

Population-Level Trends in Kidney Function before and during the COVID-19 Pandemic: A Province-Wide Retrospective Study from Alberta, Canada

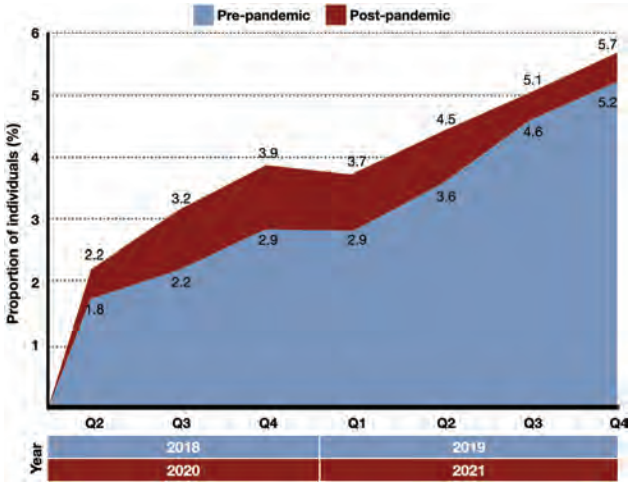
Somkanya Tungsanga, Aminu K. Bello, Gavin Oudit, Ikechi G. Okpechi. *University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada.*

Background: COVID19 infection is linked to the development of kidney-related adverse consequences via direct and indirect kidney injury. We explored changes in kidney function pre and during COVID-19 pandemic at population-level in Alberta, Canada.

Methods: This retrospective study using a province-wide administrative health data from Alberta, Canada, between 2018 and 2021. We included all adults residing in Alberta who had ≥1 annual visit to general practitioner and underwent outpatient serum creatinine tests. Data from each quarter of 2018-2019 was considered as pre-pandemic, while data from each quarter of 2020-2021 was considered during pandemic. Primary outcome was the proportion of individuals with eGFR decline, defined by sustained drop of ≥25% from baseline ≥3 months apart. Secondary outcome was the proportion of individuals with reduced eGFR who progressed to advanced stages of kidney dysfunction (eGFR <30 ml/min/m^2).

Results: A total of 214,496 and 214,103 individuals were included in the study, pre-pandemic and during pandemic, respectively. The mean age was 58.3±17 years and 43% were male. At baseline, 16.5% and 17.3% of individuals had a reduced eGFR of <60 ml/min/m^2 pre and during pandemic. The proportion of individuals with eGFR decline was higher during compared to pre pandemic era, particularly in the third and fourth quarter of 2020 (Q3: 3.2% vs 2.2%, Q4: 3.9% vs 2.9%) (Figure 1). Of those with reduced baseline eGFR, the proportion of individuals who progressed to advanced stages of kidney dysfunction was higher during the pandemic era.

Conclusions: This population-based, province-wide retrospective cohort showed a significant trend in the trajectory of kidney function decline with COVID-19 at the population level. These findings highlight the impact of the COVID-19 pandemic on kidney function, and a need for close monitoring of kidney function (particularly for the high-risk group) at the population level.



Proportion of individuals with eGFR decline in each quarter pre and during pandemic

TH-PO1161

Long-Term Kidney Function of COVID-19 Survivors: A Prospective Cohort Study

Heitor S. Ribeiro, Marcella M. Frediani, Geraldo F. Busatto, Carlos R. Carvalho, Lia J. Marçal, Guilherme P. Santa Catharina, Luis Yu, Emmanuel A. Burdmann. HCFMUSP COVID-19 Study Group. *Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil*.

Background: Long COVID encompasses symptoms that persist >2 months. Its effects on kidney function remain poorly understood. We aimed to investigate the long-term kidney function of COVID-19 survivors.

Methods: A prospective cohort of moderate and severe COVID-19 surviving patients was analyzed. Eligible patients were contacted at 6–9 months after hospital discharge. Kidney function at hospital admission, discharge, and follow-up was assessed by estimated glomerular filtration rate (eGFR; CKD-EPI serum creatinine race-free equation). Urinary albumin was evaluated at follow-up. Major Adverse Kidney Events (MAKE) at follow-up was defined as eGFR <60 ml/min/1.73 m^2, eGFR decline ≥40% from discharge, or albuminuria (>30 mg/L). MAKE-associated factors were investigated by binary logistic regression.

Results: We assessed 655 patients (55±14 years, 45% ≥60 years, 46% female, 50% black). At hospital admission, eGFR was 82.2 ml/min/1.73 m^2 (IQR:49.3–103.5). During hospital stay (median 15 days), peak SCr was 1.52 (IQR:1.02–3.26), 67% were admitted to intensive care units, 46% required intubation, 79% had acute kidney injury (35% at admission; 43% during hospitalization), and 14% needed dialysis. At hospital discharge, eGFR was 92.3 (IQR:64.3–107.4). After 7.8±1.6 months of follow-up, 14% of the patients showed eGFR decline >40% (median -5.4%; IQR:-26.7 – 30.2), and 16% of the patients showed eGFR <60 ml/min/1.73 m^2. MAKE was found in 39% of the patients. The factors independently associated with MAKE were older age (odds ratio [OR]=1.54, 95%CI:1.11–2.14) and peak SCr (OR=1.20, 95%CI:1.10–1.32).

Conclusions: Long-term kidney dysfunction was found in a large proportion of COVID-19 survivors, suggesting that kidney long COVID might be a significant health problem. Older age and peak SCr during hospitalization were independent risk factors associated with MAKE.

Funding: Government Support - Non-U.S.

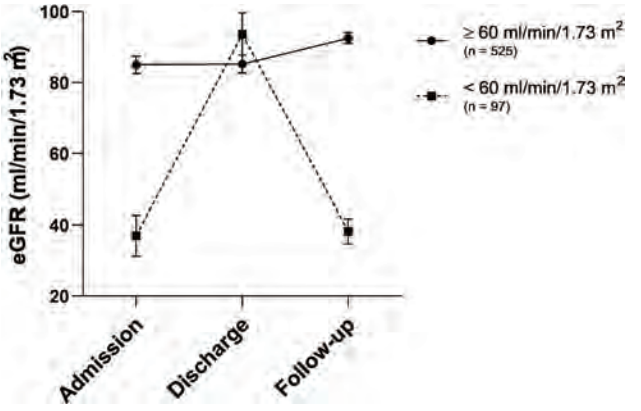


Figure 1. eGFR overtime stratified by follow-up kidney function

TH-PO1162

Impact of Gross Hematuria after COVID-19 mRNA Vaccination on Renal Outcome in Patients with IgAN

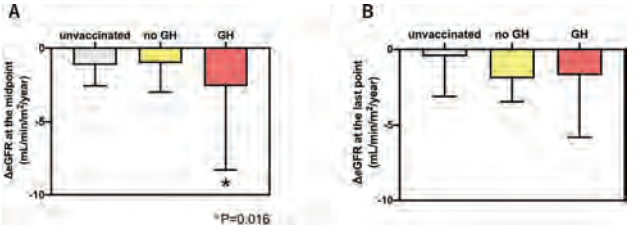
Shinya Yokote,[1,2] Nobuo Tsuboi,[1] Akihiro Shimizu,[1] Masahiro Okabe,[1] Kotaro Haruhara,[1] Saeko Hatanaka,[1] Takaya Sasaki,[1] Hiroyuki Ueda,[1] Takashi Yokoo.[1] *[1]Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan; [2]Kawaguchi Shiritsu Iryo Center, Kawaguchi, Japan*.

Background: The long-term renal prognosis of patients with immunoglobulin A nephropathy (IgAN) presenting with gross hematuria (GH) after COVID-19 mRNA vaccination is unknown. In this study, we aimed to determine whether the post-vaccination GH was associated with long-term renal prognosis of patients already diagnosed with IgAN.

Methods: Japanese patients with biopsy-proven IgAN who visited four Jikei university-affiliated hospitals between 1 February 2021 and 20 September 2021 were recruited. The change in estimated glomerular filtration rate (eGFR) was calculated from the change in eGFR between the baseline and the observation point, divided by the number of days in the outpatient visit period and converted to 365 days. We investigated the relationship between post-vaccination GH and the change in eGFR (ΔeGFR). The factors associated with ΔeGFR were also assessed.

Results: A total of 442 Japanese patients with IgAN (median age, 51 years; 56% female; eGFR, 57.4 mL/min/1.73 m^2) were included. Patients were divided into three groups: unvaccinated group (n=25), post-vaccination GH group (n=25) and post-vaccination no GH group (n=392). ΔeGFR (ml/min/1.73m^2/year) at the midpoint, measured at a median of 597 days from the baseline, was lowest in the GH group at -2.61, compared with -1.16 in the unvaccinated group and -1.03 in the no GH group (Figure 1A, P=0.02). In a multivariable analysis, the presence of post-vaccination GH was associated with ΔeGFR at the midpoint observation (OR 3.01, P=0.04). However, at the last observation, measured at a median of 756 days from the base line, there was no difference in ΔeGFR between groups (-0.45 in the unvaccinated group, -1.93 in the no GH group and -1.72 in the GH group, Figure 1B) and no association between the presence of post-vaccination GH and ΔeGFR at the last observation.

Conclusions: This study suggests that the rate of decline in renal function over about 2 years was similar in IgAN patients with and without post-vaccination GH.



TH-PO1163

Metabolomics Profile of Hemodialysis Patients during the COVID-19 Putative Incubation Period

Gabriela Ferreira Dias,[1] Chenxi Fan,[2] Maggie Han,[1] Xin Wang,[1] Xiaoling Wang,[1] Hanjie Zhang,[1] Nadja Grobe,[1] Wensheng Guo,[3] Peter Kotanko,[1,4] Yuedong Wang.[2] Renal Research Institute's Laboratory Research. *[1]Renal Research Institute, New York, NY; [2]University of California Santa Barbara, Santa Barbara, CA; [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Hemodialysis (HD) patients are at high risk of developing serious complications from COVID-19. To the best of our knowledge, metabolic alterations occurring before COVID-19 diagnosis in the HD population have not been studied. Using untargeted metabolomics, we aimed to (a) identify early alterations in the metabolome of HD patients within the putative incubation period (PIP, defined for the purpose of this research as two weeks before COVID-19 diagnosis) and (b) evaluate their longitudinal metabolic profiles.

Methods: We analyzed routinely collected serum samples from HD patients from 60 days before and 60 days after a positive SARS-CoV-2 RT-PCR. Metabolites were extracted using cold methanol and subjected to reverse phase liquid chromatography/mass spectrometry (LC/MS). Metabolite identification was achieved with library matching (mass, retention time and MS/MS fragmentation spectra). A linear mixed-effects model was fitted to evaluate the change in metabolic feature levels from baseline phase (days -60 to -15) to the PIP (days -14 to 0). False Discovery Rate (FDR) adjusted p-value cutoff was 0.05.

Results: We analyzed 201 serum samples from a cohort of 30 HD patients (59.2 ± 13.3 years, 57% male). Untargeted analysis of these samples revealed 422 metabolic features, 15 of which showed alterations between baseline and the PIP (**Fig.1a**). Notably, α-guanidinoglutaric acid and sialic acid levels increased between baseline and PIP. (**Fig.1b**).

Conclusions: The metabolomics profile of HD patients is altered in the PIP of COVID-19. These molecular fingerprints - as well as α-guanidinoglutaric acid and sialic acid as potential biomarkers - could contribute to the development of predictive models for early COVID-19 detection in HD patients.

Funding: NIDDK Support

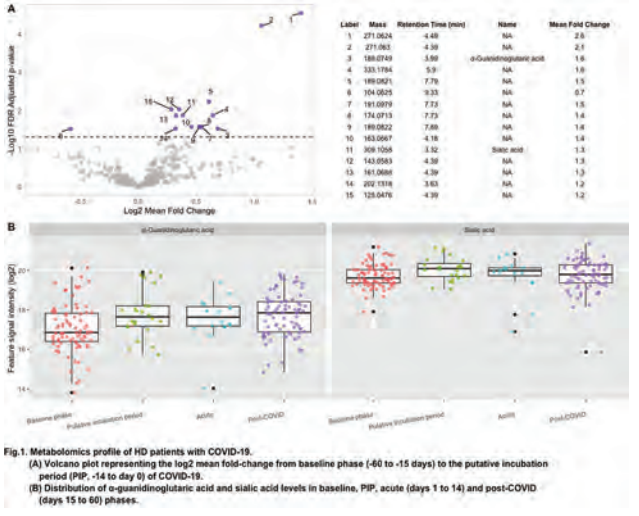


Fig.1. Metabolomics profile of HD patients with COVID-19.
(A) Volcano plot representing the log2 mean fold-change from baseline phase (-60 to -15 days) to the putative incubation period (PIP, -14 to day 0) of COVID-19.
(B) Distribution of α-guanidinoglutaric acid and sialic acid levels in baseline, PIP, acute (days 1 to 14) and post-COVID (days 15 to 60) phases.

TH-PO1164

Oral Biguanide Use Is Associated with Lower Incidence of AKI and Mortality in COVID-19 Patients: A Nationwide Study Using the Diagnosis Procedure Combination System in Japan

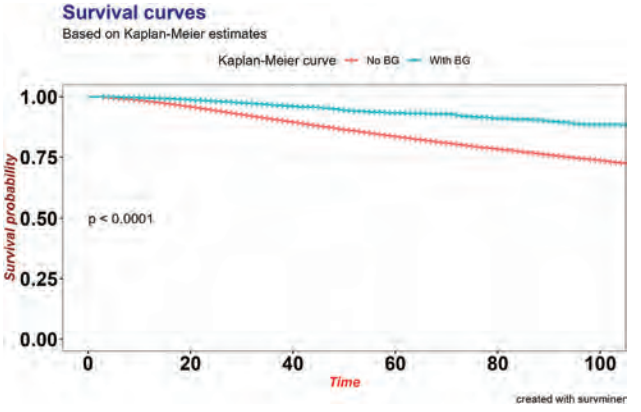
Mari Sugimoto, Hiroaki Kikuchi, Akihiro Hirakawa, Risako Mikami, Koji Mizutani, Eisei Sohara, Shinichi Uchida. Translational Systems Biology Center. *Tokyo Ika Shika Daigaku Daigakin Ishigaku Sogo Kenkyuka, Bunkyo-ku, Japan.*

Background: Recent studies have reported renoprotective effects of biguanides (BG), but their effectiveness in COVID-19 patients remains unclear.

Methods: From the 2021 and 2022 DPC inpatient databases, which cover the era following the development of COVID-19 vaccines, we extracted data on 106,161 COVID-19 patients aged 20 to under 70 years who also had diabetes treated with oral antidiabetic agents including biguanides, dipeptidyl peptidase-4 inhibitors (DPP-4), sodium-glucose cotransporter type 2 inhibitors (SGLT2), sulfonylureas (SU), alpha-glucosidase inhibitors (aGI), glucagon-like peptide-1 (GLP-1) analogs, thiazolidinediones (TZD). Using propensity score matching, based on variables such as age, sex, BMI, and chronic kidney disease stage, we compared two groups: those taking BG medications (n = 7997) and those not taking BG medications (non-BG group, n = 7997). The primary outcome was in-hospital mortality, and the secondary outcome was the incidence of acute kidney injury (AKI) during hospitalization. Logistic regression analysis and Cox proportional hazards models were used for analysis.

Results: The incidence of in-hospital mortality was significantly lower in the BG group (0.7%) compared to the non-BG group (1.2%) (p = 0.002). Similarly, the incidence of AKI during hospitalization was significantly lower in the BG group (0.7%) compared to the non-BG group (1.1%) (p = 0.025). Kaplan-Meier analysis showed a significantly better survival rate in the BG group (hazard ratio 0.675, 95% confidence interval 0.484-0.941, p < 0.0001).

Conclusions: In COVID-19 patients, oral biguanide use may be associated with a reduced risk of AKI and in-hospital mortality.



Kaplan–Meier estimates of all-cause mortality for COVID 19 patients with DM stratified by biguanide medication usage

FR-PO001

The Duke Paired Undergraduate Mentoring Program in Uronephrology: PUMPing Up the Research Workforce

Jennifer D. Varner,[1] Loryn W. Dass,[1] Matthew A. Sparks,[2] Anna E. Williams,[1] Rasheed A. Gbadegesin.[1] *[1]Duke Children's Hospital and Health Center, Durham, NC; [2]Duke Health, Durham, NC.*

Background: There is a looming nephrology clinical and research and urology research workforce crisis. Attrition is high in the STEM career pipeline, especially among students from underrepresented minority backgrounds and women. Feelings of self-efficacy are important determinants for motivating a student for a career in science, and scientic identify formation is important for persistence in the field. We developed a pipeline program designed to instill feelings of self-efficacy and demonstrate the potential for students to become scientists in STEM fields through triangular mentorship. We describe short term outcomes from Duke PUMP in uronephrology.

Methods: PUMP is an R25 funded by the NIDDK that uses a triangular mentorship model with a named junior mentor providing day-to-day oversight coupled to a senior investigator providing overall mentorship. After the summer in person research, participants have professional development and networking sessions throughout the year and are invited to return for a second summer for project continuation. We used anonymously collected pre and post surveys to assess feelings of self-efficacy, identification as a scientist, and mentor support among the first set of participants. We conducted structured interviews to add additional insight to survey responses.

Results: We recruited students through partnership with STEM undergraduate and minority-serving institutions throughout the Southeastern U.S. Eleven students applied and four were invited to participate. All four participants are female, three are from underrepresented groups, and two are from HBCUs. The most common reasons for choosing to participate were "to gain practical experience for a future career" and "it sounded interesting." The largest positive change was seen in "I have a strong sense of belonging to the community of scientists." The largest decline in confidence was seen in "I am able to work through obstacles or challenges." The areas of largest reported benefit gain were in learning laboratory techniques and understanding how scientist work on real problems.

Conclusions: Short-term data from the inaugural cohort of Duke PUMP participants exhibited an increase in participant feelings of belonging to the scientific community which is predictive of persistence in scientific research.

Funding: NIDDK Support

FR-PO002

ESCAPE! A Nephrology Themed Escape Room Curriculum for Internal Medicine Residents

Lauren Haggerty,[1] Tyler Woodell,[2] Nayan Arora.[1] *[1]University of Washington, Seattle, WA; [2]University of California San Diego, La Jolla, CA.*

Background: New generations of learners are increasingly utilizing non-traditional resources for educational purposes. In a survey of US Nephrology fellows, gamification demonstrated the greatest growth of any resource type. Escape rooms are team-based games in which players solve clues to "escape" a room within a time limit. We created a nephrology escape room curriculum (NERC) at the University of Washington, designed to engage internal medicine residents in nephrology topics and encourage interest in nephrology as a career.

Methods: We designed a NERC to accommodate approximately 50 internal medicine residents, divided into groups of 6-8, who completed each escape room simultaneously. We created two escape room sessions to teach acid-base disturbances and hyponatremia, topics identified in an internal survey as particularly challenging for incoming residents. Each session consisted of 30 minutes of content related lecture, followed by 1 hour of game play and debrief. We analyzed post-game survey results using descriptive statistics and thematic analysis of open-ended response questions.

Results: A summary of post-game survey responses is displayed in Table 1. Sample responses from the open-ended questions are shown in Figure 1. Thematic analysis revealed that residents learned and enjoyed the innovative design and team building. Constructive feedback included a request for more lecture time prior to the game.

Conclusions: Gamification, such as medical escape rooms, are gaining popularity and acceptance as effective teaching tools. Grounded in adult learning theory, our escape room curriculum can be utilized to disseminate Nephrology themed content in an active and enjoyable atmosphere, while promoting Nephrology as a subspecialty. Future iterations will include additional topics and employ more rigorous evaluation methods to determine effective content retention.

Table 1: Post game survey results

Question	Yes N (%)	No N (%)
Did this activity increase your understanding of the subject?	48 (87)	7 (13)
Was this an enjoyable experience?	53 (96)	2 (4)
Would you like to do this again with other topics?	54 (98)	1 (2)
Did this increase your interest in Nephrology as a career?	10 (40)	15 (60)

"MORE ESCAPE ROOMS"

"Great experience! This was a fun way to work through acid base disorders and definitely enhanced my understanding."

"The questions were appropriately difficult and the clues were so well hidden!!"

"Great interactive experience. I would want to do it again."

"Helpful exercise. Working through the various hyponatremia labs was particularly helpful learning."

"Definitely a good use of in person time."

"This was the best academic half day ever!!!"

"Super engaging and I felt appropriately challenged with the difficulty level."

FR-PO003

A Qualitative Study of Trainee Experiences with Home Dialysis Education in US Nephrology Fellowship Programs

Wen Qing Wendy Ye,[1] Anjali B. Saxena,[2,3] Kerry Leigh,[4] Yuvaram N. Reddy.[5,6] *[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]Stanford University School of Medicine, Stanford, CA; [3]Santa Clara Valley Medical Center, San Jose, CA; [4]American Society of Nephrology, Washington, DC; [5]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [6]Corporal Michael J Crescenz VA Medical Center, Philadelphia, PA.*

Background: Home dialysis has clinical benefits over in-center hemodialysis (HD) yet its use remains low. One barrier is a lack of comfort in clinical management among graduating nephrology fellows. Prior surveys suggest that fellows desire more training in home dialysis, yet little is known about the best approach to systematically enhance training. To identify opportunities to enhance in-person trainee experiences, we sought to better understand current home dialysis training experiences in US nephrology fellowship programs.

Methods: Using a qualitative approach, we conducted one-on-one semi structured interviews with nephrology trainees who attended Home Dialysis University (HDU) and the American Society of Nephrology Home Dialysis Virtual Education Program (ASN-HDU). Using a constant comparison approach, we developed and refined a codebook to identify themes describing participant's interest and exposure to home dialysis during training, and their comfort with managing patients on home dialysis.

Results: 10 semi-structured interviews were completed between Dec 2023 – Mar 2024. 5 of 10 participants attended the ASN-HDU program. Participants were from a variety of training programs and locations. We identified 3 main themes: (1) Home dialysis education during training is serendipitous rather than systematically built into existing curriculum. Opportunities to increase exposure to home dialysis exist, but trainees must be internally motivated to seek out these opportunities due to their serendipitous nature. (2) There is limited exposure to outpatient management of PD, resulting in a spectrum of comfort levels, which causes concern as trainees envision transitioning to independent practice. (3) Home HD exposure is sparse leading to an overwhelming lack of comfort.

Conclusions: Home dialysis training during nephrology fellowship remains serendipitous, suggesting the need for systematic efforts. There is limited exposure to outpatient PD and home HD resulting in a lack of comfort. Although the American Board of Internal Medicine requires 8 PD clinics to graduate, trainee experiences suggest that fellowship programs may not be able to meet this requirement. The results of our study should inform curriculum changes, while fellowship programs identify new opportunities to enhance trainee comfort in home dialysis.

Funding: Other U.S. Government Support

FR-PO004

Kidney Point-of-Care Ultrasonography (POCUS): Development and Evaluation of a Training Program for Nephrology Fellows

Tony Fang,[1] Sara S. Jdiaa,[2] Mohammad Azfar Qureshi,[3] Alireza Zahirieh,[3] Ann Young,[2] Darren A. Yuen.[2] *[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Background: Insonation is now considered the 5th pillar in physical examination. Despite its exciting potential, the uptake of POCUS in nephrology training curricula is slow. Our study aims to evaluate a locally developed program to train nephrology fellows to accurately perform a kidney POCUS scan to answer two important questions in the workup of kidney dysfunction in hospitalized patients: 1) is there urinary tract obstruction? and 2) are there small kidneys?

Methods: The program consisted of two workshops that included a didactic session and hands-on training session. Trainees identified the presence or absence of urinary tract obstruction in each native kidney or kidney allograft. They also performed a measurement of kidney length. POCUS findings were compared with the abdominal ultrasound exams performed in the medical imaging department. All nephrology fellows participating in the workshop completed pre- and post-workshop surveys to document self-reported comfort level with the use of renal POCUS. Patients were asked to complete a patient satisfaction questionnaire.

Results: A total of 56 native kidneys were assessed. Assessment of hydronephrosis compared to radiology-read kidney imaging reports revealed a specificity of 0.96. Assessment of small right and left kidney size showed a specificity of 0.81 and 0.75, respectively. A total of 32 transplant kidneys were assessed. Assessment of hydronephrosis and kidney allograft size revealed a specificity of 0.96 and 0.97, respectively. Post-workshop, 10 out of 11 trainees had an overall comfort level of 5 or greater out of 7 using POCUS for kidney assessment, in ruling out urinary tract obstruction and measuring kidney size. A total of 51 patients were surveyed. Most patients (71%) strongly agreed that their interaction with their doctors was improved with POCUS.

Conclusions: Our study shows that training programs can provide trainees with the confidence to acquire and apply skills in POCUS and the downstream benefits from patient satisfaction.

FR-PO005

Shared Decision-Making and Enhancement of Patient Autonomy in the Selection of Kidney Replacement Therapy: A Retrospective Study at a Single Center, Seoul National University Bundang Hospital

Julee You,[1] Eun-Jeong Kwon,[1] Ho Jun Chin,[1,2] Sejoong Kim,[1,2] Seokwoo Park.[1,2] *[1]Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [2]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: In patients with CKD approaching end-stage kidney disease(ESKD), effective shared decision-making(SDM) plays a crucial role in selecting the most suitable renal replacement therapy(RRT). We examined the impact of the SDM program on the preference for kidney transplantation or peritoneal dialysis(KT/PD) over hemodialysis(HD), and its potential to reduce unplanned dialysis.

Methods: The SDM program commenced at Seoul National University Bundang Hospital, South Korea, in March 2021, as part of the SDM-ART trial. Adult patients predicted to reach ESKD within a year, were enrolled in the SDM. Participants received extensive education using materials and videos, followed by in-depth discussions with physicians based on self-assessment items at months 0 and 2, in contrast to standard brief consultations. Data were collected in a single center from CKD patients with an eGFR of less than 15 ml/min/1.73m^2 over 3 months, during March 2018 to March 2023, excluding those with contraindication for PD. Logistic regressions were used to compare the likelihood of selecting KT/PD over HD and the occurrence of unplanned dialysis before and after the SDM program. Physicians were categorized based on their involvement in the SDM, and the interaction between SDM implementation and physicians' participation was analyzed.

Results: Among 556 patients starting RRT, 34.0% chose KT/PD, while 41.7% underwent unplanned HD with central venous catheters before long-term RRT. Before SDM, there was no significant difference in the preference for KT/PD vs HD between physicians who participated in SDM and those who did not. However, post-SDM, patients under SDM-participating physicians significantly favored KT/PD (OR, 4.24; 95% CI, 1.29-14.50), unlike those under non-participating physicians(Table 1). SDM could not significantly reduce unplanned dialysis in this cohort.

Conclusions: Our SDM program demonstrated a significant shift in the preference for RRT modality towards KT/PD, highlighting the critical importance of overcoming informational barriers.

Table 1. Impact of SDM on choosing KT/PD over HD, by physician participation, before and after SDM implementation.

		Model 1*		Model 2†		Model 3‡	
SDM	Participation	Odds ratios (95% CI)	*P*-value	Odds ratios (95% CI)	*P*-value	Odds ratios (95% CI)	*P*-value
Before	No	1 (ref)		1 (ref)		1 (ref)	
	Yes	1.05 (0.69-1.57)	0.830	1.08 (0.66-1.77)	0.755	1.34 (0.73-2.46)	0.337
After	No	0.53 (0.26-1.02)	0.070	0.41 (0.10-1.65)	0.203	0.32 (0.07-1.40)	0.127
	Yes	4.09 (1.71-10.19)	0.002§	5.41 (1.87-16.39)	0.002§	4.24 (1.29-14.50)	0.019§

Abbreviations. SDM, shared-decision making; CI, confidence interval.

*Model 1: unadjusted logistic regression including the interaction term between SDM implementation and attending physicians' participation.

†Model 2: Model 1 + adjustments for demographic factors, including age, gender, cardiovascular disease, dementia, hemiplegia, any malignancy, diabetes mellitus, glomerulonephritis, year of the index date, and modified Charlson Comorbidity Index.

‡Model 3: Model 2 + adjustments for laboratory factors, including serum levels of creatinine, hemoglobin, potassium, total bicarbonate, and phosphorus.

§$P < 0.05$

FR-PO006

Innovating Nephrology Point-of-Care Ultrasonography Education: Artificial Intelligence-Assisted Curriculum Integration with Human Expert Feedback Loops

M. Salman Sheikh, Kianoush Kashani, Charat Thongprayoon, James R. Gregoire, Iasmina Craici, Wisit Cheungpasitporn, Fawad Qureshi. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Point-of-care ultrasound (POCUS) education is crucial for nephrology fellowship programs to enhance timely diagnostic accuracy, procedural guidance, and patient management. Integrating a comprehensive POCUS curriculum is essential for advancing educational quality and preparing fellows for effective clinical practice in a timely manner. This quality improvement project involved experts using AI tools to develop a Nephrology POCUS curriculum.

Methods: An AI-assisted curriculum development process was conducted at the Mayo Clinic Minnesota Nephrology Fellowship Program in April 2024. The process involved multiple stages of feedback and refinement using several AI models, including GPT-4.0, Claude 3.0 Opus, Gemini Advanced, and Meta AI with Llama 3. GPT-4.0 generated initial curriculum drafts, while other AI agents provided iterative feedback for improvement. Finally, blinded Nephrology POCUS experts provided insights and expertise to refine the AI-generated curriculum further.

Results: The refinement process included 12 ChatGPT-4.0 revisions and a 29 communications across four AI tools, encompassing initial feedback, subsequent revisions, and final approvals from the AI tools. It yielded in a curriculum with broadened core topics, educational methods, assessment mechanisms, and integration into rotations. POCUS experts provided positive and constructive feedback, expressing satisfaction with the overall curriculum while offering suggestions for improvement. These suggestions included placing more emphasis on using POCUS for assessing fistulas and grafts, making volume assessment open-ended, structuring training to progress fellows from novice to expert, and utilizing Qpath software for mentored scans. Experts also questioned the inclusion of specific procedures and suggested pursuing certification through ASDIN.

Conclusions: The AI-assisted project effectively developed a comprehensive Nephrology POCUS curriculum at the Mayo Clinic Minnesota, significantly enhancing the educational offerings of the fellowship program. Integrating expert feedback, the curriculum emphasizes core POCUS applications, educational diversity, and robust assessment techniques. This innovative approach melds expert insights with AI capabilities, promising substantial improvements in POCUS education.

FR-PO007

A Multicenter Survey on Artificial Intelligence in Nephrology Education: Insights from Mayo Clinic Fellows

M. Salman Sheikh,[1] Charat Thongprayoon,[1] Iasmina Craici,[1] Fawad Qureshi,[1] Michael A. Mao,[2] Musab S. Hommos,[3] Mary B. Prendergast,[2] Sumi Sukumaran Nair,[3] Kianoush Kashani,[1] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic in Florida, Jacksonville, FL; [3]Mayo Clinic Arizona, Scottsdale, AZ.*

Background: Artificial Intelligence (AI) has the potential to support clinical practice, medical education, and research. This study aimed to describe current perceptions and utilization of AI among nephrology fellows in three programs, and perform needs assessment for an educational intervention focused on AI learning.

Methods: An online survey was sent to 23 learners including fellows in general nephrology, kidney transplant, and onco-nephrology at the Mayo Clinic's three sites: Minnesota, Arizona, and Florida. The survey evaluated the current state of AI perceptions, utilization, and integration in practice. It also identified attitudes toward AI training, and perceived barriers to AI adoption in nephrology fellowship education.

Results: Of the 23 trainees, 21 completed the survey (response rate of 91%). The survey revealed that 76% of respondents have never or rarely used AI in their clinical or research activities, and none had formal AI education. However, respondents expressed a strong acknowledgment of AI's significance within nephrology, with 76% of respondents rating AI's current relevance as moderately to highly relevant to the field and 76% of fellows expressed moderate to high interest in receiving targeted AI. The majority of trainees identified interactive workshops as the preferred method of delivering AI training. The majority of fellows identified limited knowledge as the primary barrier to AI adoption. Optimism about AI's potential in nephrology was pronounced, especially for predictive modeling (86%) and diagnostic imaging (81%). However, confidence in AI for clinical decision-making remained cautious, with 33% neutral and 48% uncertain.

Conclusions: The findings underscore a significant interest among nephrology fellows in AI education, along with a critical need for formal education and training. The enthusiasm for AI's potential contrasts with a cautious perspective towards its current use in clinical decision-making, highlighting the necessity for educational initiatives that bridge the knowledge gap and foster confidence in AI technologies in Nephrology fellowship.

FR-PO008

How Education Affects Treatment Decision-Making: Novel Mechanistic Insights into Patients' Knowledge-Seeking and Psychological Changes

Rebecca Campbell-Montalvo,[1] Darin Ftouni,[1,2] Popy Shell,[1] Shobha Subhash,[1] Kailyn Pearce,[1] Ashutosh M. Shukla.[1,2] *[1]VA North Florida South Georgia Veterans Health System, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: KRT-directed comprehensive pre-kidney failure education (CoPE) is a basic necessity to increase informed home dialysis use. Existing cognitive behavior theories and patient-level data suggest that CoPE may enhance knowledge, behavioral capacity, and self-efficacy to improve self-management and health outcomes. However, mechanistic effects of CoPE on these intermediate and patient outcomes have not been articulated.

Methods: To inform on these mechanistic effects, we draw on data from 42 of 511 Veterans participants of TEACH-VET, a randomized trial aimed to assess the effects of CoPE on a variety of outcomes including informed dialysis decision-making. These qualitative interviews were designed under Theoretical Domains Framework (TDF) – a metatheory involving a range of factors impacting health behavior and focused on participants' perspectives on educational content of CoPE and treatment decisions about home dialysis (HoD). Interviews were thematically analyzed, grounded in the TDF as well as Cultural Model Theory. Key social-psychological mechanisms involved in decision making were elucidated through qualitative modeling.

Results: We found novel mechanistic insights into how people understand and think about illness and treatment in ways that motivate their decisions. Specifically, we found that CoPE impacted HoD selection by prompting participants to seek additional knowledge and spurring a range of psychological changes (Figure 1). These changes include new feelings of optimism about treatment, belief in one's treatment capabilities, increased confidence in decision making, and feelings of security with care provided by the VA. Knowledge seeking and psychological changes ushered participants to plan for the future and make treatment decisions, supporting better management of CKD and kidney health outcomes.

Conclusions: This complex modeling identifies new aspects of how education impacts patient decision making which enhances our understanding and informs the design of patient education programs and informs future research.

Funding: Veterans Affairs Support

FR-PO009

Development of Entrustable Professional Activities in Adult Nephrology Fellowship Training

Maria-Eleni Roumelioti, Namita Singh, J. Pedro Teixeira, Christos Argyropoulos, Hayley Israel, Raja Ravender, Zan Shareef. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Entrustable Professional Activities (EPAs) are units of observable work that a competent healthcare professional does in everyday practice. EPAs explicitly build on the principles of competency-based training and assessment and serve as means to translate competencies into clinical practice. To our knowledge there are no established EPAs for US nephrology training programs. We aim to develop a list of EPAs that represent the scope of nephrology practice.

Methods: An initial list of EPAs was developed and refined by the research group using a modified Delphi method. The panel (study participants) included 9 nephrologists (8 faculty, 1 fellow). Responses were given on a 5-point Likert scale and agreement was reached if (A) and (B) were met: (A) mean ≥4 with a SD<1; (B) >75% of respondents rated the item ≥4. After agreement EPAs that scored poorly were excluded from the next Delphi round. The panel provided additional comments and feedback on which EPAs to prioritize and how to proceed with implementation.

Results: Our research group (4 attendings, 1 researcher, 2 fellows) met 3 times and developed an initial list of 25 EPAs covering 10 fields in everyday nephrology practice. After 3 Delphi rounds and revisions, 22 remaining items were established as final EPAs. These EPAs will be linked to target competencies and will serve as a list of training goals to be reached by renal fellows during the implementation and evaluation phase of the study. All panel members had prior experience with clinical work and renal fellowship training (**Table**). Most members believed that renal fellows should have increased exposure to chronic kidney disease and dialysis clinics, should use lay medical terminology, and should treat patients holistically.

Conclusions: Graduating renal fellows must be prepared to meet specific standards, including cultural competence, safety, leadership, and professional development. The EPAs represent the scope of nephrology practice and will facilitate future educational research and curriculum development.

Participants' Characteristics (n=9)

Age (mean ±SD)	47.2 (±8.7)
Females (%)	44.4
Attendings (%)	88.9
Years of clinical experience (academic and/or private) (mean ±SD)	13.7 (±9.97)
Fellows (%)	11.1

FR-PO010

Nephrology Program Director and Fellow Home Hemodialysis (HHD) Curriculum Survey

Nupur Gupta,[1] Andrew J. Howard,[2] Christina M. Yuan.[2] [1]*Indiana University School of Medicine, Indianapolis, IN;* [2]*Walter Reed National Military Medical Center, Bethesda, MD.*

Background: Home hemodialysis (HHD) patients are a minority of those receiving chronic dialysis, and unevenly distributed geographically. Nephrology fellows may not encounter many (if any) HHD patients. The Accreditation Council for Graduate Medical Education (ACGME) requires fellows receive enough HHD training to achieve competence. We performed a survey of US Nephrology program directors and their fellows regarding their HHD curriculum.

Methods: Anonymous on-line survey (12/4/2023-2/4/2024) of 150 US nephrology program directors, who were asked to forward a survey link to their fellows, and indicate the number of fellows to whom they forwarded the link.

Results: 55 program directors responded (37%), 80% completed the survey. 37 forwarded the survey to their fellows (25% of US programs). Respondent program directors and fellows were from programs of similar size and geographic distribution to those nationally. 93% (42/45) of programs had an HHD curriculum or were developing one. 86% (37/43) reported that fellows attend a longitudinal HHD clinic either routinely or during a block rotation. The predominant barrier to incorporating HHD into the curriculum was lack of HHD patients in the area (50%). 237 fellows were forwarded the survey link; 53 (22%) responded and 50/53 completed the survey (94%). 80% (40/50) reported receiving HHD training and of those 24/50 (48%) had followed HHD outpatients. Those who saw HHD outpatients (n=24) were more likely than those who did not (n=26) to be confident in managing specific HHD tasks, and perceived a significantly greater degree of preparation to care for HHD patients after graduation (p=0.0003. Fisher exact test).

Conclusions: The majority of nephrology programs have or are developing an HHD curriculum, but the greatest barrier was lack of HHD patients available to the program. Fellows who had experience following HHD outpatients were significantly more likely to be feel prepared and confident in their ability to care for HHD patients. Disclaimer: The views expressed are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. government.

FR-PO011

A Survey of Pregnancy and Parenthood among Physician Trainees: How Do Nephrology Fellowships Compare?

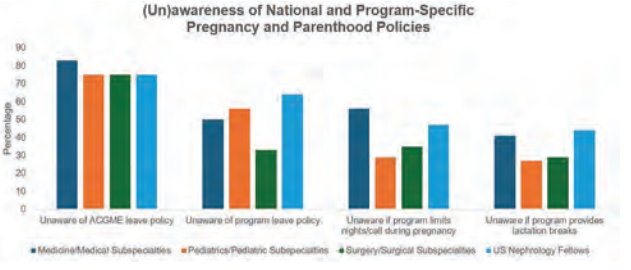
Angelina M. Dixon, Allison H. Martin, Braidie L. Campbell, Anna Ostrow, Jessica B. Kendrick. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: National policies outlining parental leave for physician trainees are inconsistent. We recently demonstrated that most US nephrology fellows are unaware of national and program-specific parental leave policies and pregnancy and lactation accommodations. Here, we examine awareness of current policies in physician trainees across all fields at the University of Colorado (CU) to determine how their perspectives compare to those of US nephrology trainees.

Methods: An anonymous, on-line survey of CU physician trainees (residents and fellows) was undertaken from February to May 2024.

Results: 223 physician trainees submitted the survey (23% male, 76% female, 0.5% nonbinary). The majority of fellow respondents were unaware of individual program specific (47%) or ACGME (78%) mandated parental leave policies. 41% of trainee respondents were unsure if their program limited night shifts or shifts greater than 24 hours for pregnant trainees and 33% reported they were unsure if their program provided lactation accommodations. Almost 70% of trainees agreed or strongly agreed that they would avoid a pregnancy during residency/fellowship due to concern that they would have to extend their training. Still, 59 trainees had children during training. When asked about the duration of parental leave taken during training, trainees most frequently responded (30%) that they received 6-8 weeks of family leave. 80% of trainees who had children prior to or during training reported their career plans did not change as a result of pregnancy or parenthood. These results were similar to what was seen in US nephrology fellows (Figure).

Conclusions: Most physician trainees report that they would avoid pregnancy during training and are unaware of parental leave policies and pregnancy/lactation accommodations that would support pregnancy and parenthood. This lack of awareness is consistent across all training programs, including nephrology programs.



(Un) awareness of national and program-specific policies for pregnancy/parental leave among physician trainees at CU and nephrology fellows across the US

FR-PO012

Improved Management of Nephrological Emergencies through Immersive Technology

Philipp G. Russ, Muriel L. Morgenschweis, Jonas Einloft, Hendrik L. Meyer, Simon Bedenbender, Ivica Grgic. *Philipps-Universitat Marburg Fachbereich Medizin, Marburg, Germany.*

Background: Medical emergencies require rapid initial assessment and immediate action. Many medical students and young physicians often feel overwhelmed in such situations and report inadequate preparation for real-world emergencies. Immersive technologies, such as Virtual Reality (VR), offer new opportunities for realistic simulation training with significant potential in practice-based medical education, including emergency management. To investigate its effectiveness in the field of nephrology, we selected rapidly progressive glomerulonephritis (RPGN) as a well-known prototypical nephrological emergency, which requires swift action to avert life-threatening complications.

Methods: Using an innovative approach, we conducted a single-center study employing a self-designed, 3D virtual, interactive RPGN case represented by an avatar patient on the VR simulation platform STEP-VR, which we recently developed and validated in partnership with ThreeDee. We compared the competencies of third-year medical students before and after VR training with those of a control group. Additionally, we evaluated the impact of synchronous tutorial support during the training on learning outcomes.

Results: A total of 275 medical students participated in the study, with an average age of 25.4 years; 64% of the participants identified as female (n=176). The VR training group showed significantly improved outcomes in the diagnosis of RPGN, based on clinical presentation, laboratory diagnostics, urine dipstick, and urine sediment analysis (p<0.0001 for all comparisons). The VR group also significantly outperformed the control

group in managing RPGN-associated complications, such as severe hyperkalemia and metabolic acidosis ($p < 0.0001$). Additional guidance by a human tutor led to further improvements in diagnosis and treatment performance.

Conclusions: Our findings highlight the potential of immersive technology as an effective medium for enhancing clinical nephrological knowledge and skills. Specifically, the use of realistic and practice-oriented VR simulation training in medical education and training could lead to improved competence in handling nephrological emergencies and, consequently, enhance the quality of patient care. Taken together, VR may be an effective, cost-efficient, and scalable alternative to traditional simulation methods.

FR-PO013

Is Artificial Intelligence (AI) the Missing Member of the Fellowship Interview Panel?

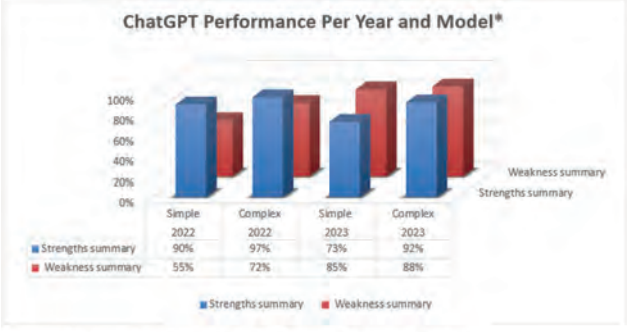
Musab S. Hommos, Bhavna Bhasin-Chhabra, Mira T. Keddis. Mayo Clinic Arizona Nephrology Fellowship. *Mayo Clinic Arizona, Scottsdale, AZ.*

Background: Creating an objective summary of the interviewers' feedback to rank fellowship applicants is a challenging task that can be adversely affected by implicit bias. In this study, we examined the performance of ChatGPT (CGPT) in summarizing interviewers' evaluations of the applicants and compared the CGPT-generated ranking to our rank list.

Methods: For each applicant, 4 faculty independently generated evaluation narratives, each about 100 words. PD use these narratives to create a list of strengths & weaknesses for the ranking meetings. In this study, we provided de-identified narratives to CGPT4.0. We compared the performance of two prompts: a simple prompt that requested CGPT to summarize the strengths and weaknesses and rank applicants without program-specific details and a complex prompt that described our program's mission, aims, and desired applicant attributes. We used data from the 2022 & 2023 seasons. Spearman rank correlation coefficient was used to compare CGPT rank list to the final rank list by the program. The study was deemed exempt by IRB.

Results: There were 29 applicants from 2022 and 26 from 2023. Narratives from 2022 were about 50% shorter. The performance of the complex CGPT prompt was superior to the simple prompt in detecting strengths and weaknesses and in the final ranking. **The complex prompt-generated rank list had a correlation coefficient with our rank list of 0.95 ($p<0.001$) for 2022 and 0.99 ($p<0.001$) for 2023. The simple prompt correlation was 0.85 ($p<0.001$) and 0.83 ($p<0.001$).** See Figure 1

Conclusions: A longer evaluation narrative and more complex prompt that included the program-specific information resulted in an excellent performance by CGPT in summarizing the applicants' strengths & weaknesses, which resulted in a final rank that correlated very closely with the program's rank list. AI limitations included missing subtle applicant attributes that a program may consider necessary but not defined in the prompt. Future research is needed to study the effect of AI-assisted ranking on implicit bias during ranking.



*compared to manual summary of evaluation forms by the program director

FR-PO014

Enhancing Trainee Orientation with Artificial Intelligence (AI)-Powered Gamification

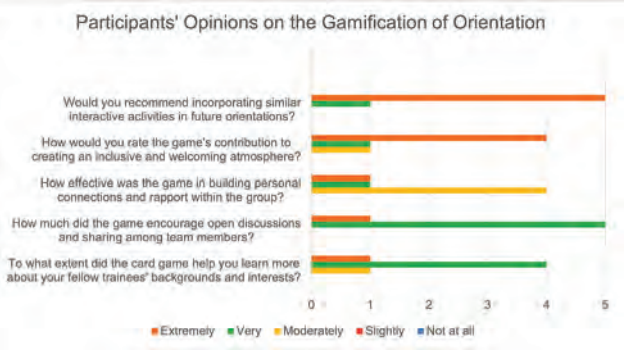
Paavana Varanasi, Musab S. Hommos. *Mayo Clinic Arizona, Scottsdale, AZ.*

Background: Every summer, training programs welcome new trainees and complete their onboarding process, which serves multiple purposes: equipping trainees with valuable information like program expectations, delivering mandated knowledge, and fostering camaraderie. However, orientation can often be overwhelming, with information overload and numerous online modules. This educational study explores the use of conversational AI in building cohesive teams and streamlining the orientation process.

Methods: The authors developed a customized game using ChatGPT. Two sets of cards were created: one with questions regarding the fellowship program, the institution, training expectations, medical knowledge concepts, and historical facts from the field of nephrology and one with "getting to know you" questions. The ChatGPT prompt was designed to generate both sets of cards after being provided with program information available in the training handbook. The game was first trialed with incoming general and transplant nephrology fellows and the respective program leadership. Game content and rules were refined to include more desired information and ensure trainees answered questions from both card decks.

Results: An anonymous online survey was administered to the participants with a 67% response rate. The survey revealed that 100% of respondents thought the game fostered a stronger sense of belonging and teamwork among the participants. The game was also highly effective, based on high ratings, in facilitating learning about trainees' backgrounds and interests, encouraging open discussions among team members, building rapport within the group, creating an inclusive and welcoming atmosphere, and was strongly recommended for future orientations.

Conclusions: This case demonstrates the potential of conversational AI to enhance medical education by creating interactive orientation tools. Developing this game took approximately 30 minutes over three sessions and was well-received by both trainees and program leadership. AI can improve various aspects of training program orientations and further integration is encouraged.



FR-PO015

Interdisciplinary Point-of-Care Ultrasonography (POCUS) Program Led by Nephrology

Eduardo Pino Domenech, Maria V. DeVita, Andrew A. Moses. *Lenox Hill Hospital, New York, NY.*

Background: POCUS has been touted as the fifth pillar of the physical exam: inspection, palpation, percussion, auscultation and insonation. The use of POCUS in nephrology has been growing throughout the country, and now Nephrology has a unique position to increase the use of POCUS in both nephrology and medicine. We describe the POCUS program at our institution unifying various programs under one umbrella.

Methods: One lead nephrologist has developed a curriculum and POCUS has been taught as part of the nephrology training curriculum since 2021. Bi-weekly hour-long sessions with a combination of didactics, hands on sessions, and image reviews to ensure both technical proficiency and diagnostic capability has been created. This is in concordance with ASDIN guidelines for certification. Our target is that Nephrology fellows will become certified 12-18 months into their fellowship and subsequently become superusers and help teach the rising first years and internal medicine residents.

Results: In order to teach the residents, a bimodal approach was used with the critical care faculty teaching weeklong boot camps for interested and available residents. Alternatively, interested residents who were unable to attend the weeklong program, were given similar didactics and hands on teaching spaced out over the year by nephrology POCUS faculty. This increased the total number of residents who had POCUS exposure and improved usage of POCUS. At present, we have 32 house-staff involved. We have also started a parallel program with several hospitalists, with the same intention of establishing 1-3 super users. Presently we are using 8 Phillips Lumify devices, expanded from only a single POCUS device outside of the ICU in 2020. As we have more users, utilizing the resource effectively becomes even more important.

Conclusions: We feel that Nephrology led POCUS initiatives are important because it puts the probe in the hands of users who need to optimize the tools used to master volume status and are most familiar with the physiology of many hospitalized patients. By leading POCUS initiatives throughout the hospital nephrologists can be leaders in guiding internists into the future. With nephrology championing the education of house-staff our objective to expand the program so that all of our nephrology fellows with be superusers, and expand the training to other departments.

FR-PO016

Kahoot Is a Hoot: Gamification of Ambulatory CKD Lectures for Internal Medicine Residents

Kevin Labagnara,[1] Gary Tan,[1] Farhana Begum,[1] Aarika Mehrishi,[2] Kenar D. Jhaveri.[1] *[1]Northwell Health, New Hyde Park, NY; [2]Jericho High School, Jericho, NY.*

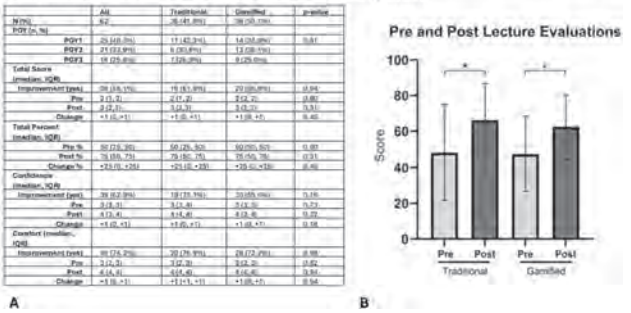
Background: The time constraints of medical residency make it challenging to keep learners engaged while covering essential topics. Emerging literature suggests gamification may be an effective supplement, and in some cases an alternative, to the traditional lecture. We aimed to study how game-based lectures affect resident content mastery by utilizing the online trivia-based platform Kahoot.

Methods: A single-center, prospective study was conducted on categorical internal medical residents during their ambulatory CKD lecture series. Residents received either a traditional in-person lecture or a similar version gamified with the Kahoot platform, followed by pre- and post-lecture surveys including board-style questions on CKD management. Those who completed both pre- and post-lecture surveys were included in the final sample. Statistical analysis utilized the Mann Whitney U and Chi-Square tests, along with logistic regression to control for the training year.

Results: 62 residents completed both surveys, of which 36 (58%) received the gamified lecture. 40% (n=25) were in their first year of training, while 2nd and 3rd years comprised 34% (n=21) and 26% (n=16) of respondents respectively. 58% (n=36) scored higher on the post-survey, while the majority reported higher confidence (n=39, 63%) and comfort (n=46, 74%) in managing CKD. When analyzing changes in pre- and post-lecture survey metrics, no significant differences were noted between traditional and gamified groups in total score and percent (p=0.45), confidence (p=0.18), or comfort (p=0.54) (Table 1). Furthermore, no differences were noted when controlling for the PGY training year (OR=0.84, 95% CI: 0.28-2.49, p=0.74).

Conclusions: Our study shows that when used as a supplement, Kahoot may be an effective method to engage learners while maintaining lecture content and quality. Further studies are needed to assess its effectiveness in a virtual setting.

Figure 1: Baseline characteristics between traditional and gamified cohorts (A) with associated bar graph comparing mean pre- and post-survey total score (B). Chi-square used for categorical variable analysis and Mann-Whitney U for Score, Percent, and Likert-Scale response analysis. P value of <0.05 used to indicate statistical significance



A

B

FR-PO017

Development, Implementation, and Assessment of an Innovative Kidney Pathology Curriculum

Douglas R. Farrell, Layla Fattah, Samira S. Farouk. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: 33% of nephrology fellows indicated an interest in additional pathology education on a 2016 education needs assessment performed by ASN. Fellows at our institution expressed this interest despite scoring higher than the national median on the 2023 In-Training Exam pathology section. WhatsApp®, a free messaging application for mobile devices, has been shown to be an effective educational tool. We designed and implemented a WhatsApp®-based pathology curriculum and hypothesized that it would be well-received and increase confidence in pathology skills.

Methods: A pre-survey of 18 questions was administered to nephrology fellows prior to initiation of the WhatsApp® curriculum. It included questions addressing the quality of their perception of pathology education, interest in supplemental education, confidence in the subject, and brief knowledge assessment.17 nephrology fellows at Mount Sinai Hospital were invited to join a WhatsApp® group. The chat was designed to be used only for pathology education. Once the curriculum began, the peer educator presented a pathology image weekly, followed by a multiple-choice question (MCQ). Participants submitted answers to the MCQ via an anonymous online submission form. On Friday of each week, a comprehensive slide was shared with pathology educational content which included the answer to the MCQ. A post-survey was sent to all nephrology fellows after the 24-week curriculum.

Results: 5/17 responded to the pre-survey (29%), of which all were senior fellows. All expressed an interest in additional pathology education. On average, 13/14 fellows read the content, and 5/14 submitted MCQ questions weekly. 36% responded to the post-survey. All respondents strongly agreed that content was relevant. All respondents strongly agreed/agreed that WhatsApp® was an effective learning platform and reported higher confidence in pathology skills. The mean rating of the program was 8.2/10. All respondents answered that they would recommend the curriculum to other fellows.

Conclusions: Nephrology fellows want more pathology education and are not confident in their pathology skills. A supplemental pathology course is feasible utilizing WhatsApp®. Nephrology fellows rated WhatsApp® as an effective medium for kidney pathology education, report high satisfaction with its curriculum, and report higher confidence in pathology because of the curriculum.

FR-PO018

Curricular Innovation to Improve Performance on Internal Medicine In-Training Exam Nephrology Items

Gauri Bhutani,[1] Samantha J. Strennen,[2] Sarah L. Floden,[1] Andrew Coyle,[1] Suzanne M. Norby.[1] *[1]University of Wisconsin System, Madison, WI; [2]University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Performance on the Internal Medicine In-Training Exam (IM-ITE) is one method by which both resident knowledge and residency program effectiveness is measured. In 2020, our program's aggregate score for all post-graduate years (PGYs) on Nephrology (Neph) specific items was <50th percentile (%ile). Since Nephrology is not a required rotation in our program, a curricular innovation (CI) was developed to be available to all residents to help improve residents' Nephrology specific knowledge.

Methods: Case scenarios based on Nephrology topics with lower % correct score with 3- tier questions for knowledge and difficulty level were disseminated bimonthly to IM residents via e-mail and Twitter (*X*) as free open access meducation (FOAMed). The questions were also open to any interested online viewers. Answers were submitted via a Qualtrics survey tool with options for anonymity and feedback. A robust in-person didactic curriculum was present in all years, though the delivery of this curriculum changed with a transition to an X+Y model in academic year (AY) '22-23 which did lead to a decrease in the number of unique Nephrology sessions from 16 in AY '21-22 to 7 in '22-23. Additionally, PGY1s did not take the IM-ITE after 2021 as part of IM residency program changes.

Results: Over AYs '20-21 to '22-23, a total of 17 CI sessions were disseminated with average resident engagement of 25 (19-31) per question and a class size of 25-32 PGY per year. Most participants (94%) felt they learnt new information. Percent of Nephrology IM-ITE questions answered correctly (% correct) and %ile over time are reported in Table.

Conclusions: Aggregate performance for all PGYs improved on the 2021 examination. 2022 and 2023 data by PGY level shows inconsistent trends, with higher percentiles in 2022 as compared to 2020, and higher percent correct in 2023. These changes occurred in the background of other curricular and ITE utilization changes in the IM residency program and thus, direct correlations between CI implementation and IM-ITE performance cannot be made presently and a longer observation period is needed.

	2020 (% correct [%ile])	2021	2022	2023
PGY1	58% (37th)	64% (51st)	NA	NA
PGY2	68% (53rd)	76% (88th)	57% (64th)	74% (60th)
PGY3	72% (67th)	74% (55th)	64% (80th)	74% (41st)
All PGYs	65% (48th)	71% (67th)	60% (89th)	74% (73rd)

FR-PO019

Empowering Future Nephrologists: Crafting a Leadership Curriculum for Nephrology Trainees

Fahad Aziz, Ali I. Gardezi, Tripti Singh. *University of Wisconsin System, Madison, WI.*

Background: Leadership skills are increasingly recognized as crucial for medical professionals to navigate the complexities of healthcare and improve patient outcomes. Traditional medical training often lacks formal leadership development, leaving a gap in preparing trainees for real-world leadership challenges.

Methods: We developed a leadership curriculum for our nephrology trainees and junior faculty. The proposed curriculum aims to fill this gap by equipping medical trainees with essential leadership competencies, such as communication, teamwork, conflict resolution, and giving and receiving feedback. Participants completed surveys before and after the curriculum to evaluate their comprehension of leadership topics.

Results: The curriculum had 16 participants with a mean age of 33 ± 4 years. Of the participants, 67% were male, 80% were white, and 75% were US medical graduates. Before the curriculum, 44% of participants considered themselves leaders at the workplace; post-curriculum, this number increased to 76% (p=0.06). Initially, 72% of participants understood the difference between leadership and a position, which improved to 100% after the curriculum (p=0.02). Before the curriculum, 42% felt well-equipped to handle workplace conflicts; this improved to 90% after (p=0.004). Comfort in giving feedback increased from 60% before the curriculum to 92% after (p=0.04).

Conclusions: Medical trainees and junior faculty often lack the necessary knowledge and skills in leadership. However, these skills can be taught, as evidenced by the significant

improvement in understanding and confidence among participants. We suggest that such a curriculum be integrated into nephrology training to develop better leaders in the field.

FR-PO020

Impact of Continuing Medical Education/Continuing Education (CME/CE) Course on Primary Care Provider's Understanding of Kidney Diseases and Genetic Testing

Jemetra Collins,[1] Michael Spigler,[1] Lucia Kim,[2] Melanie Paris.[1]
[1]American Kidney Fund, Rockville, MD; [2]Pri-Med LLC, Boston, MA.

Introduction: Genetic conditions as an underlying cause of certain types of kidney disease (KD) have garnered increased attention in nephrology. Although genetic testing has led to more accurate diagnoses and targeted treatment plans for KD patients, identification of potential genetic-based KDs by primary care providers (PCPs) for referral to nephrologists poses barriers to timely and appropriate intervention. Because PCPs often manage earlier stages of CKD independently, limitations in detecting possible genetic KD and understanding of genetic testing may result in missed opportunities to slow progression toward kidney failure. As a remedy, a one-credit, PCP-targeted continuing medical education (CME/CE) webinar was created to educate PCPs on nephrology referral.

Case Description: CME/CE was delivered by a nephrologist and a PCP initially as a live webinar, then posted as an enduring activity, December, 2022-2023. One of four learning objectives was introducing genetic testing options (GTO) and benefits. Faculty discussed screening and diagnosis of CKD, how to recognize which patients may have genetic causes of kidney disease requiring a nephrologist and the role of genetic testing in diagnosis. Pre/post-activity polling measured learner (n=4,540) knowledge competence, confidence along 5 levels, ranging from misinformed to mastery with two questions. Data were analyzed in aggregate.

Discussion: Analysis showed low baseline, with performance moderately better in the live setting than the enduring. Learner mastery increased from <5% pre to >30% post, with a decrease in learners guessing from ~60% to ~1/5. Analysis suggests effectiveness in educating PCPs via a CME/CE course on genetic testing and targeted treatments. PCP education should highlight genetic testing and other CKD diagnostic procedures, especially for patients with KD family history and those with traits consistent with APOL1 gene mutation. PCP-targeted KD CME/CEs can enhance understanding of CKD, referral criteria, and the benefits of timely specialist involvement.

FR-PO021

American Kidney Fund's Kidney Health Coach Online Course Improved Confidence, Knowledge, and Practice Intentions among Health Care Professionals

Rhea Suarez, Sana Siddique, Ryan Woolley, Melanie Paris, Michael Spigler.
American Kidney Fund, Rockville, MD.

Background: People at-risk for or living with chronic kidney disease (CKD) have unique care needs that health care professionals (HCPs) must be prepared to meet. However, there is limited HCP training and education on CKD prevention and management, especially among allied health care. To address this need, the American Kidney Fund (AKF) created Kidney Health Coach (KHC) a community health education program that trains HCPs and lay audiences to educate their patients and the community about preventing and managing CKD. KHC includes a 2-hour online training course discussing disparities and burden of CKD, diagnosis and treatment options, prevention strategies, and best practices to tailor health information for specific audiences.

Methods: AKF analyzed online course self-reported pre- and post-evaluation data to assess differences in HCP coaches' (n=2,160) confidence (4-5 on 6-point Likert scale), knowledge, and intention to make practice changes in their role or clinical setting. Data were stratified by provider type to assess for differences.

Results: Most HCP coaches are nurses (26%), dialysis technicians (DT) (15%), and social workers (SW) (14%). Pre- and post-evaluation comparisons revealed HCP confidence in knowledge about CKD increased 57% to 95% and confidence in ability to educate others about CKD increased 54% to 91%. Nurses had the highest average increase in confidence (61%) compared to DTs (45%) and SWs (51%). Post only evaluation data revealed 89% of HCPs are confident KHC improved their ability to better function as a member of the health care team and 64% indicated they would make changes in their practice or role. Compared to DTs (61%) and SWs (57%), nurses (68%) were most likely to make changes in their practice or role.

Conclusions: Findings support the need for CKD education and training of HCPs across practice settings. KHC is an effective tool that provides HCPs with up-to-date clinical content and best practices in plain language and health literacy. KHC enhanced HCP confidence and knowledge in CKD prevention and management, which leads to HCPs who are better equipped to meet the needs of their patients. Further outreach is needed to build capacity among HCPs to be responsive to the needs of people at-risk for or living with CKD.

FR-PO022

Developing a Participant-Focused Educational Podcast to Enhance Engagement in the Cure Glomerulopathy (CureGN) Study Cohort

Myda Khalid,[1] Tina Creguer,[2] Laura H. Mariani,[2] Shannon Mulroy,[3] Keisha L. Gibson,[4] Sherry L. Wilson,[1] Zubin J. Modi,[2] Caroline J. Poulton.[4]
[1]Riley Hospital for Children at Indiana University Health, Indianapolis, IN; [2]University of Michigan, Ann Arbor, MI; [3]Kidney Solutions, Kerrville, TX; [4]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.

Background: CureGN is an NIH-funded longitudinal cohort study that has enrolled over 2,000 research participants. Engagement is fundamental to encourage retention and to provide value and education to participants. Previous initiatives including newsletters and online "fireside chats" had low participation rates.

Methods: An audio podcast was trialed and evaluated to enhance participant education and engagement. Kidney Chats by CureGN, developed by CureGN's Recruitment and Retention workgroup, launched October 2023. The educational series on glomerular disease topics is accessed on multiple platforms (Spotify, Apple, Amazon, web search); themed episodes are clearly titled by topic. A study participant interviews an expert on a topic suggested by participants. Initial topics included nutrition and prednisone. Newsletters introduce a topic and point readers to the podcast for more in-depth information via a QR code. Social media promotes the podcast.

Results: Three episodes have launched ranging from 16 to 31 minutes long, with new episodes planned at a two-to-three-month cadence. 86 downloads/listens have been logged, surpassing performance of fireside chats in a much shorter amount of time. The podcast reaches participants across all age ranges, with particular strength in ages 28 to 34 and over 60. Listenership by gender is 52% female, 41% male, and the remaining non-binary or not specified. Listeners hail largely from the US, with 77% located in the US. Another 12% tuned in from Germany, 7% from Canada, and 4% from other locations.

Conclusions: For CureGN, an integrated communications strategy that incorporates a highly accessible medium as its centerpiece effectively disseminates relevant research to participants, as well as topics addressing lifestyle topics and helping participants find community by hearing others' lived experiences with kidney disease.

Funding: NIDDK Support

Fireside chat attendance vs podcast listenership

	#1	#2	#3	#4	Total to date
Fireside chat attendance*	8	9	9	10	36
Podcast downloads/listens**	47	28	11	(to come)	86

*estimated
**continues to grow weekly

FR-PO023

Clinical Impact of Kidney Educational Program on Elderly Nocturnal Hypertensive Patients with CKD

Akira Ishii,[1] Ryo Sato,[1] Kosuke Mochizuki,[1] Kansei Otsuka,[1] Kyoka Fujita,[1] Satoshi Kurahashi,[1] Jun Takeoka,[1] Hisako Hirashima,[1] Naohiro Toda,[1] Toshiyuki Komiya,[2] Eri Muso.[1] *[1]Kansai Denryoku Igaku Kenkyujo, Osaka, Japan; [2]Otsu Red Cross Hospital, Shiga, Japan.*

Background: It has been reported that hypertension progresses with age and the rhythm of blood pressure variability is disrupted in the elderly due to autonomic dysfunction and arterial stiffness, which can easily induce nocturnal hypertension. Furthermore, elderly patients with nocturnal hypertension are recognized as being at higher risk of cardiovascular events and chronic kidney disease (CKD) exacerbation. We aimed to elucidate the clinical impact of renal educational program on elderly nocturnal hypertensive CKD patients.

Methods: We reviewed 60 Japanese CKD patients who participated in our one-week CKD educational program from April 2019 to March 2023. All patients took low-salt diet (6 g/day) and were carried out 24-hour urine testing twice and 24-hour ambulatory blood pressure monitoring (ABPM) during the program.

Results: The mean age on admission was 71.6 ± 8.5 years, body mass index (BMI) was 25.6 ± 3.6, and eGFR was 19.2 ± 10.3. Diabetic kidney disease was the most common diagnosis (38% [22 of 58]), followed by nephrosclerosis (19% [11 of 58]), IgA nephropathy (3.4% [2 of 58]) and so on. Of the patients, 25 (43.1%) were non-dipper type and 12 (20.7%) were riser type (these two types (63.8%) were combined into the non-dipper group). During one-week program, the mean body weight decreased from 68.4 to 66.9 kg (2.2% reduction), systolic blood pressure during daytime decreased from

136.9 to 129.9 mmHg (5.1% reduction), urinary protein decreased from 4.10 to 3.93 g/day (4.1% reduction) and the 24-hour urinary sodium excretion decreased from 121.7 mEq/day to 106.1 mEq/day (12.8% reduction). The non-dipper group had a higher BMI but had similar daytime systolic blood pressure and diabetes mellitus complication rates compared with the dipper group. Furthermore, while the non-dipper group showed a decrease in the slope of the pressure-natriuresis curve, there was no obvious difference in the rate of eGFR decrease after one year of hospitalization between two groups.

Conclusions: While the non-dipper group showed increased salt sensitivity compared to the dipper group, there was no obvious difference in the degree of renal function decline after one year of intervention, which was considered by multifaceted intervention effect of CKD education, such as salt reduction instruction.

FR-PO024

Abstract Withdrawn

FR-PO025

Sex-Related Differences in Incidence and Prevalence and Outcomes of AKI

Ruqiyya Bano, Sian E. Piret, Henry Yip, Andreas P. Kalogeropoulos, Sandeep K. Mallipattu. *Stony Brook University, Stony Brook, NY.*

Background: Acute kidney injury (AKI) is a common condition affecting hospitalized patients. While male sex has been correlated as a risk factor for AKI, our aim was to evaluate if age-related sex disparities exist in AKI development and post-AKI outcomes.

Methods: Using the Stony Brook University (SBU) and US Collaborative TriNetX Networks, inpatient encounters for both male and female sex between January 2014 and December 2023 were queried for individuals 0-89 years of age. Outcomes of AKI were assessed using ICD-10 billing codes. Short- and long-term outcomes were defined as having AKI within 90 days and 1 year of inpatient encounter, respectively. Mortality was assessed for within 1 year of reaching the short-term or long-term outcome. Propensity score matching was utilized to match SBU cohorts based on race, ethnicity, and comorbidities (HTN, DM, CVD, Obesity). Hormone replacement therapy (HRT) was defined as use of estrogens, progestins, gonadotropins, or ICD-10 code for HRT. Absolute risk difference (RD), risk ratio (RR), and hazard ratio (HR) comparing risk of AKI/mortality were measured.

Results: The overall risk of developing AKI was greater in males vs females in both SBU (short term RD: 2.063%, $p < 0.0001$; long term RD: 2.332% $p < 0.0001$) and US (short term RD: 1.538% $p < 0.0001$; long term RD: 1.749% $p < 0.0001$) cohorts. In age-related analyses, the RR of AKI was highest in the 30-39 decade of age in the SBU cohort for both short-term (RR: 3.316) and long-term (RR: 2.778) outcomes, while US cohort showed highest risk ratio at 20-29 in short term (RR: 2.518) and 30-39 in long-term (RR: 2.498). AKI risk increased per decade of year in both males and females. In the SBU cohort, females exhibited higher risk of death within 1 year of AKI diagnosis, regardless of short-term (HR: 0.890, $p = 0.006$) or long-term (HR: 0.886, $p = 0.001$) AKI outcome. Females not on HRT also showed lower risk of developing AKI as compared to females on HRT both short-term (HR= 0.613, $p <0.0001$) and long-term (HR = 0.571, $p <0.0001$).

Conclusions: Incidence and prevalence of AKI diagnosis is higher in males as compared to females across all age groups, with a peak in risk ratio noted at 30-39. However, females with AKI had higher risk of death as compared to males with AKI. The use of HRT did not mitigate the risk of AKI in females.

FR-PO026

Age-Dependent Sex Differences in the Incidence of AKI among Patients with CKD: The OCKR Study

Yuki Kawano, Tatsufumi Oka, Yusuke Sakaguchi, Takayuki Kawaoka, Yuta Asahina, Isao Matsui, Masayuki Mizui, Jun-Ya Kaimori, Yoshitaka Isaka. *Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Japan.*

Background: While basic studies revealed a protective effect of female hormones against acute kidney injury (AKI), the Kidney Disease Improving Global Outcomes (KDIGO) guideline states that females have a higher risk of AKI. A meta-analysis of observational studies reported an inconsistent sex difference in AKI with a considerable degree of heterogeneity. Sex differences in AKI have not been studied in the chronic kidney disease (CKD) population. We investigated whether sex affects the incidence of AKI and its impact on the risk of kidney failure among patients with CKD.

Methods: The Osaka Consortium for Kidney Disease Research (OCKR) is a retrospective, multicenter cohort study that includes patients who attended the outpatient departments of nephrology at five hospitals in Osaka, Japan, from January 2005 to December 2021. In the present study, 15,220 patients with an estimated glomerular filtration rate (eGFR) of 15-60 mL/min/1.73 m^2 were included. AKI was defined as a ≥1.5 times increase in a serum creatinine level from its median value over the past year, according to the National Health Service England AKI algorithm. The association of sex with AKI and sex-specific relations of time-dependent AKI with kidney failure with replacement therapy (KFRT) were examined using time-dependent Cox proportional hazards models.

Results: The mean (standard deviation) age and eGFR at baseline were 69 (14) years and 37 (13) mL/min/1.73 m^2, respectively, and 62% were male. Over a median follow-up of 2.9 years, 1,974 (13.0%) patients developed AKI and 1,316 (8.6%) experienced KFRT. Males had a significantly higher hazard of AKI (hazard ratio [HR] 1.20; 95% confidence interval [CI], 1.07-1.33) after adjustment for potential confounders. This association was stronger in patients aged <50 (HR 1.51; 95% CI, 1.05-2.17) than in those aged 50 or older (HR 1.16; 1.03-1.30) (P for interaction=0.04). Males also had an 85%-higher hazard of KFRT (95% CI, 1.58-2.18) than females. In contrast, the hazard of KFRT associated with time-dependent AKI was similar between sexes (P for interaction =0.87). Similar trends were observed when analyzed according to AKI stages.

Conclusions: Females had a lower incidence of AKI, especially in the younger population, but a similar hazard of KFRT after AKI, compared to males.

FR-PO027

Sex Disparities in the Risk of Urgent Dialysis following Acute Aortic Dissections in Japan: A Real-World, Nationwide Study

Yuta Nakano,[1,2] Shintaro Mandai,[2] Daiei Takahashi,[3] Ken Ikenouchi,[2] Yutaro Mori,[2] Fumiaki Ando,[2] Koichiro Susa,[2] Takayasu Mori,[2] Soichiro Iimori,[2] Shotaro Naito,[2] Eisei Sohara,[2] Kiyohide Fushimi,[2] Shinichi Uchida.[2] *[1]Ome Medical Center, Ome, Japan; [2]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan; [3]Musashino Sekijuji Byoin, Musashino, Japan.*

Background: The global outcome of acute aortic dissection (AD) remains poor, with a high risk of acute kidney injury (AKI) and the need for urgent dialysis. This study aimed to clarify the association between sex and the requirement for urgent dialysis within 30 days after admission among patients with AD.

Methods: This study included 83,297 cases who were hospitalized due to AD in Japan from 2010 to 2020 using an administrative claims database. The association between the risk of urgent dialysis within 30 days after admission and sex was investigated using cumulative incidence functions and the Fine and Gray model.

Results: There were 5,640 events of urgent dialysis. Patients were classified into two groups based on the Stanford classification: type A AD (TAAD) and type B AD (TBAD). In TAAD, the cumulative incidence of urgent dialysis at 30 days was 8.6% [95% confidence interval (CI): 8.1–9.0] in women and 15.2% (95% CI: 14.7–15.8) in men ($p < 0.001$) (Figure 1). In TBAD, the cumulative incidence was 1.6% (95% CI: 1.4–1.8) in women and 3.5% (95% CI: 3.3–3.7) in men ($p < 0.001$) (Figure 1). In adjusted models, lower subdistribution hazard ratios (SHRs) in women were observed in both groups: TAAD (SHR: 0.62, 95% CI: 0.58–0.67); TBAD (SHR: 0.59, 95% CI: 0.52–0.68).

Conclusions: Our study revealed that women had a lower risk of requiring urgent dialysis than men in TAAD and TBAD. Further research is needed to clarify the underlying role of sex in AKI in patients with AD.

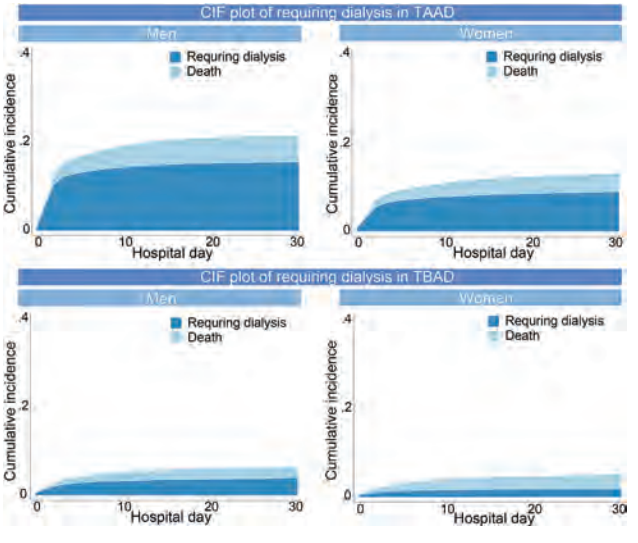


Figure1

FR-PO028

More Hospitalized Pregnant Women in the United States Are Dying with AKI

Chyng-Wen Fwu,[1] Susan R. Mendley,[2] Christine Maric-Bilkan,[2] Shannon S. Givens-Bradley,[2] Paul L. Kimmel,[2] Raquel C. Greer,[2] Kevin L. Chan,[2] Kenneth J. Wilkins,[2] Ivonne H. Schulman.[2] *[1]Social and Scientific Systems, Inc., a DLH Holdings Corp (DLH) company, Silver Spring, MD; [2]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.*

Background: Recent national trends for death occurring in hospitalized pregnant women who have acute kidney injury (AKI) have not been reported. Increased delivery-related hospitalizations with AKI were reported between 2006-2015 but did not include all pregnancy-related hospitalizations.

Methods: The 2019-2021 Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) was analyzed to 1) describe the in-hospital rate of AKI, as primary or secondary diagnosis, and death; 2) evaluate associations of all-cause death with AKI after adjustment of pre-defined predictors; and 3) estimate the number needed to harm (NNH), a death due to AKI, in women ages 12-49 years with pregnancy-related hospitalizations, including delivery or non-delivery, and excluding hospitalizations with end-stage renal disease diagnosis. ICD-10-CM codes and/or the Clinical Classifications Software Refined diagnostic categories were used. Mortality trend and association between in-hospital AKI diagnosis and death were examined using multivariate logistic regression.

Results: Table shows the number of pregnancy hospitalizations recorded in the HCUP-NIS during 2019-2021, the increased rate of in-hospital AKI and death, and the increased number and rate of deaths among hospitalizations with AKI. AKI was one of the major comorbid conditions in pregnant women who died (40%). Deaths with AKI as a percentage of total deaths increased from 35% to 41%. Overall mortality difference between hospitalizations with and without AKI was 2.52%. The NNH with AKI was 40. Adjusted for age, race/ethnicity, CVD, cancer, infection, hemorrhage, and pregnancy-related complications, the odds of death increased annually by 40% per year (Adjusted Odds Ratio (AOR), 1.40; 95% confidence interval (CI), 1.23 to 1.60). AKI was significantly associated with death (AOR 26.33, 95% CI 20.61 to 33.65).

Conclusions: From 2019-2021, increased numbers of hospitalized pregnant women died with AKI. Additionally, deaths with AKI are increasing faster than total deaths.

Funding: NIDDK Support

Table. Number of AKI and number of deaths in hospital stay per 100,000 hospitalizations, HCUP-NIS 2019-2021

Year (Number of hospitalizations)	2019 (N=780,844)	2020 (N=748,706)	2021 (N=759,532)	Percent increase From 2019 to 2021
Hospitalizations with AKI diagnosis				
Number of hospitalizations with AKI diagnosis	1,763	2,012	2,319	32%
Number of hospitalizations with AKI diagnosis, per 100,000 hospitalizations	226	269	305	
Died in hospital stay				
Number of deaths in hospital stay	83	123	184	122%
Number of deaths in hospital stay, per 100,000 hospitalizations	11	16	24	
Died in hospital stay among hospitalizations with AKI				
Number of deaths in hospital stay	29	50	75	159%
Number of deaths in hospital stay, per 100,000 hospitalizations	1645	2485	3234	
Died in hospital stay among hospitalizations without AKI				
Number of deaths in hospital stay	54	73	109	102%
Number of deaths in hospital stay, per 100,000 hospitalizations	7	10	14	

FR-PO029

Clinical Features and Outcomes of Pregnancy-Related AKI: A Single Tertiary Center Study

Tarek A. Ghonimi, Islam A. Elsayed, Ayman R. Abd El-Hameed. *Zagazig University Faculty of Human Medicine, Zagazig, Egypt.*

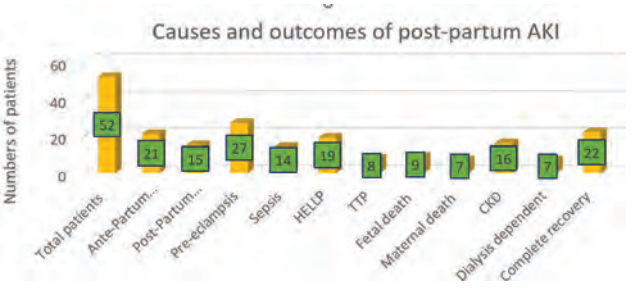
Background: Pregnancy-related acute kidney injury (Pr-AKI) is a major cause of maternal and fetal morbidity and mortality in developing countries. The aim of our study was to study the clinical characteristics and outcomes of patients with Pr-AKI at our center.

Methods: This prospective study at Zagazig University Hospital, Egypt, from October 1, 2023, to March 1, 2024, included patients with post-partum AKI. These women were compared to a matched cohort of healthy pregnant women without pre-existing AKI. Multivariate analysis is used to identify risk factors.

Results: Out of 900 pregnant patients who delivered during the study period, 52 patients developed post-partum AKI with incident of 5.7%. The majority were multiparous(59.6%), and most delivered by cesarean section (67.3%). The most common cause of AKI is preeclampsia (51.9%), followed by ante-partum hemorrhage (40.4%) and HEELP syndrome (36.5%). Stage 3 AKI (KDIGO classification) was the most prevalent occurring in 23% of cases. Maternal death occurred in 13.5% of cases, while fetal death was 17.3%. Follow- up showed that 42.3% had complete recovery, 30.7% CKD and 13.4% remained dialysis-dependent. Risk factors for AKI included high WBC, low Hb, low platelets, and high bilirubin levels, with p-values of 0.004, <0.0001, and 0.031, respectively. Additionally, nulliparous women had significantly lower odds of developing AKI (0.248, p = 0.017). However, the significance of these risk factors disappeared in multivariate analysis.

Conclusions: Post-partum AKI is a relatively common pregnancy complication with significant maternal and fetal mortality risks. Preeclampsia and ante-partum hemorrhage are major risk factors. Larger, long-term follow-up studies are recommended to confirm these findings.

Funding: Private Foundation Support



	Univariate analysis			Multivariate analysis		
	odds	95%CI	p	odds	95%CI	P
Primiparous	0.248	0.079-0.779	0.017	0.029	0.001-0.14	0.076
High WBC	1.562	1.155-2.211	0.004	4.330	0.878-21.35	0.072
Low platelets	0.983	0.974-0.992	0.000	0.936	0.876-1.000	0.052
Low HB	0.545	0.314-0.945	0.031	0.131	0.013-1.30	0.083

FR-PO030

Incidence, Risk Factors, and Outcomes Associated with Pregnancy-Related AKI in Northwest Nigeria

Aishatu M. Nalado. *Aminu Kano Teaching Hospital, Kano, Nigeria.*

Background: Although largely preventable, pregnancy-related acute kidney (PRAKI) continues to be a significant contributor to maternal and perinatal mortality in low- and middle-income countries. Data are scarce on the incidence and impact of PRAKI in Nigeria. Thus, this study aimed to evaluate the incidence, risk factors, and maternal-fetal outcomes of patients with

Methods: This is a prospective multicenter study conducted among 841 women at the Obstetrics and Gynecology units of two large referral hospitals in urban Kano, Nigeria, between 1st October 2022 and 30th March 2023. We employed multivariate logistic regression analysis to determine independent predictors of PRAKI in this resource-constrained setting.

Results: The mean age ± standard deviation (SD) of respondents was 27.8 ± 6.7 years. The prevalence of PRAKI was 11.4%, with the majority (55.2%) being in KDIGO stage 1. The most common risk factors for PRAKI were pre-eclampsia (24%), postpartum hemorrhage (16.7%), sepsis (15.6%), and eclampsia (14.6%). The overall maternal and perinatal mortality rates were 7.4 % and 21.9 %, respectively. PRAKI was independently associated with the use of traditional medications (adjusted odds ratio, aOR =1.94; 95% CI: 1.18, 3.18), history of pregnancy-induced hypertension (aOR = 2.61; 95% CI: 1.49-4.59), an established diagnosis of hypertension (aOR = 2.53; 95% CI: 1.42, 4.50), and advanced maternal age (aOR=0.50; 95% CI: 0.27-0.92, ≥35 years vs. 18-24 years).

Conclusions: PRAKI is common in women presenting for care in our setting and is associated with significant maternal and perinatal mortality. The important risk factors for development of PRAKI in our study population include hypertensive disorders of pregnancy, established diagnosis of hypertension, postpartum hemorrhage, and sepsis.

Funding: Government Support - Non-U.S.

FR-PO031

Atypical Abruptio Placentae with AKI: Interventional Dilemma

Muhammad Yasir Baloch, Ignacio A. Portales Castillo, Benjamin D. Humphreys. *Washington University in St Louis, St Louis, MO.*

Introduction: Alterations in the complement cascade can affect many organs and lead to renal, hematological, or obstetric complications. Here, we present a case of pregnancy complicated by abruptio placentae and severe acute kidney injury (AKI) requiring dialysis, where we identified a genetic predisposition to complement dysregulation.

Case Description: A 37-year-old female G5P3 at 36 weeks pregnancy, presented to the ER with abdominal pain. Fetal bradycardia was detected, prompting an urgent C-section. During surgery, placental abruption was diagnosed, she became hypotensive, requiring 2 liters of blood products. Post-surgery, she was anuric despite intravenous fluids and resolution of hypotension. Laboratory results were notable for AKI (Cr 2.2), transaminitis, anemia (Hb 7.6), thrombocytopenia (Plt 80), low haptoglobin, fibrinogen of 422md/dl and very elevated lactate dehydrogenase (LDH) at 3080U/L. The peripheral blood smear showed few schistocytes. Complement levels and ADAMTS13 were unremarkable. Hemodialysis was initiated on day 2. The clinical diagnosis was thrombotic microangiopathy (TMA) secondary to either HELLP syndrome vs atypical hemolytic uremic syndrome (aHUS). Eculizumab was considered but not given as her hematologic parameters rapidly improved. Two weeks later, she remained dialysis dependent. Three

weeks after admission results of genetic testing for complement pathway related genes, revealed homozygous bi-allelic loss of Complement Factor H (CFHR3 – CFHR1) genes, which has been recently categorized as pathogenic. Eculizumab was then started. Her renal function improved, and she successfully transitioned off dialysis.

Discussion: Despite carrying pathogenic variants associated with complement dysregulation, many patients remain asymptomatic for most of their lives. Several conditions, including pregnancy, can precipitate episodes of TMAs, which can be mistaken for preeclampsia. Advances in complement genetics have transformed our understanding of TMAs, but interpreting complement genetics is complex and often requires expertise from geneticists and complement biology specialists. This case illustrates the need to remain vigilant about atypical obstetric complications, as adequate treatment of aHUS can prevent irreversible renal injury.

FR-PO032

Improving AKI Diagnosis: Estimating Baseline Serum Creatinine Using Kidney Volume Regression Equation

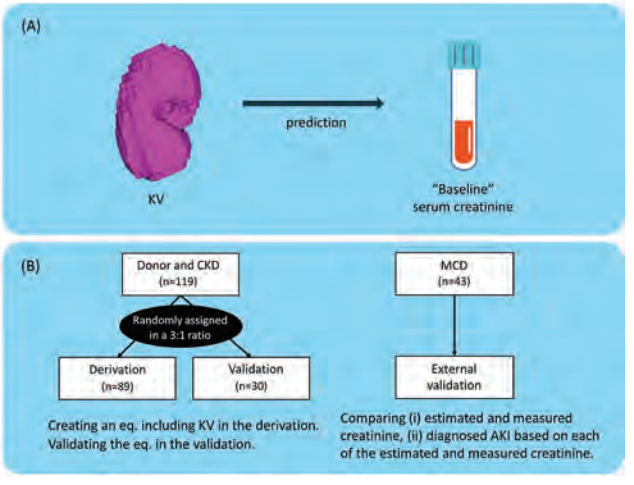
Takaya Sasaki, Takeshi Tosaki, Hideaki Kuno, Hirokazu Marumoto, Yusuke Okabayashi, Kotaro Haruhara, Go Kanzaki, Kentaro Koike, Akimitsu Kobayashi, Izumi Yamamoto, Nobuo Tsuboi, Takashi Yokoo.
Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.

Background: Diagnosing acute kidney injury (AKI) relies on baseline serum creatinine (Cr) levels, which are often unavailable. As shown in **Figure A**, our study aimed to create a regression equation linking kidney volume to function in kidney donors and chronic kidney disease patients, and also sought to estimate baseline Cr in minimal change disease (MCD) patients, which is a common AKI-predisposing condition.

Methods: Kidney donors and patients with chronic kidney disease (CKD) were selected for our study (n = 119, 40% donors, mean age 60 years, 50% male), and randomly divided into derivation and validation groups (**Figure B**). An equation based on kidney volume (KV) was developed in the derivation group and validated in the validation group. We also estimated baseline Cr in MCD patients (n = 43, mean age 45 years, 61% male) using the KV-based equation and compared with their 6-month post-MCD onset Cr values.

Results: The created equation for the estimated glomerular filtration rate (eGFR) was as follows: eGFR (mL/min/1.73m^2) = 0.38 x KV (cm^3) + (-0.40) x age (years) + (-2.9) x male sex + (-13) x hypertension + (-14) x diabetes + (-0.21) x height (cm) + 82 (intercept). In the validation group, the eGFR and estimated Cr values correlated well with the measured values (r = 0.46, p = 0.01 and r = 0.51, p = 0.004, respectively). In the MCD group, the baseline Cr values were significantly correlated with the estimated baseline Cr values (r = 0.52, p <0.001), effectively diagnosing AKI (kappa = 0.76, p <0.001).

Conclusions: The regression equation including KV established in the present study holds promise for estimating baseline Cr values and diagnosing AKI in patients with MCD. Further validation in diverse populations with AKI is necessary.



FR-PO033

A Population-Based Imputation Approach for Missing Baseline Serum Creatinine Values

David R. Chang,[1] Hsiu-Yin Chiang,[2] Yi-Ching Chang,[2] Tomonori Takeuchi,[3,4] Che-Chen Lin,[2] Jin Chen,[3] Javier A. Neyra,[3] Chin-Chi Kuo.[2,1] *[1]China Medical University Hospital Department of Internal Medicine, Taichung, Taiwan; [2]Big Data Center, China Medical University Hospital, Taichung, Taiwan; [3]The University of Alabama at Birmingham, Birmingham, AL; [4]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan.*

Background: Diagnosing acute kidney injury (AKI) requires a baseline serum creatinine (S-Cre), which is often missing in the real world. We aimed to develop and validate a new method for estimating baseline S-Cre and compare it to existing methods

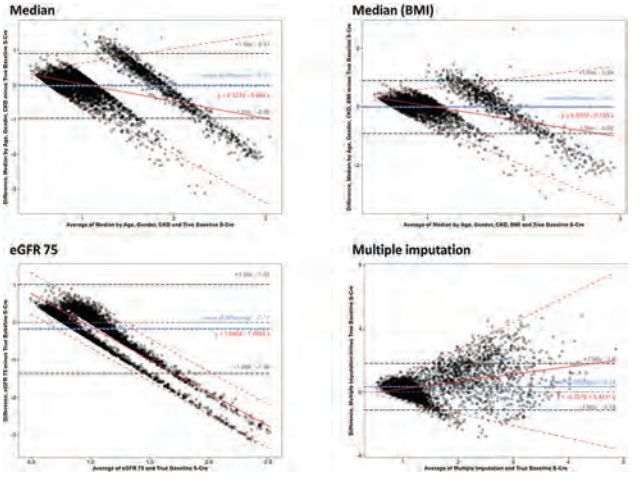
Methods: From all S-Cre measurements collected from adult outpatients at CMUH in 19 years, we excluded those were 1) <0.3 or >30 mg/dL, 2) from patients with end-stage kidney disease or nephrectomy, 3) within 72 hours following dialysis or cardiopulmonary resuscitation, or 4) within 24 hours after massive transfusion, resulting in 3403528 measurements for baseline S-Cre reference. We developed the "median" imputation methods that utilized the median S-Cre within subgroups stratified by age, gender, and chronic kidney disease (median A), or in combination with body mass index (median B). A sepsis cohort meeting Sepsis-3 was used to assess the performance of 4 imputation methods (median A, median B, eGFR 75, and multiple imputation [MI]) in discriminating AKI according to KDIGO criteria. Bland-Altman plot was used to visualize bias between measured and imputed S-Cre.

Results: In the sepsis cohort, median A and B method had a smaller mean of difference, compared to eGFR 75 and MI method. Median A method demonstrated the highest agreement for AKI (84%; Kappa 0.68), compared with eGFR 75 (82%; 0.63) and MI method (81%; 0.62). eGFR 75 had superior sensitivity (85% vs 82%), while MI showed higher specificity compared to median A method (92% vs 86%).

Conclusions: The median methods showed satisfactory agreement in AKI detection comparable to eGFR 75 and MI approaches, offering a simple and intuitive approach for real-world application for baseline S-Cre estimation. External validation in the US population is underway.

Imputation Methods	Pearson's r (p-value)	Mean of Difference (imputed - true)	Kappa	AKI Classification				
				Sensitivity	Specificity	PPV	NPV	Agreement
Median by age (1 year), gender, CKD	0.61 (p < 0.001)	-0.02 (-0.96, 0.91)	0.68	81.7%	85.9%	83.4%	84.4%	83.9%
Median by age (1 year), gender, CKD, BMI	0.61 (p < 0.001)	-0.01 (-0.92, 0.89)	0.60	68.0%	90.1%	86.3%	76.7%	80.2%
eGFR 75 (converted by MDRD formula)	0.05 (p < 0.001)	-0.17 (-1.36, 1.02)	0.63	85.0%	78.5%	77.4%	85.8%	81.5%
Multiple imputation	0.52 (p < 0.001)	0.34 (-1.13, 1.80)	0.62	69.4%	91.6%	87.7%	77.5%	81.3%

Performance of baseline S-Cre imputation methods using sepsis AKI cohort.



Bland-Altman plots of true and imputed baseline S-Cre using different imputation methods.

FR-PO034

ePidEmiology, Risk FactORs, and outcoMes of AKI (PERFORM-AKI)

Amanda Y Wang,[1,2] Johnathan Ngo,[3,4] Praveen S. Perera,[1] Kathryn Higgins,[1] Natashja Eyles,[1] Zoltan Endre,[5,6] Shaundeep Sen,[7,8] Muh Geot Wong,[7,8] Lucinda A. Wynter,[8,9] John P. Killen,[2,10] Séverine Bompoint,[1] Rinaldo Bellomo,[11] Martin P. Gallagher.[6] *[1]The George Institute for Global Health, Sydney, NSW, Australia; [2]Macquarie University Faculty of Medicine Health and Human Sciences, Sydney, NSW, Australia; [3]Department of Renal Medicine, Liverpool Hospital, Liverpool, NSW, Australia; [4]Western Sydney University School of Medicine, Sydney, NSW, Australia; [5]Department of Nephrology, Prince of Wales Hospital, Randwick, NSW, Australia; [6]School of Clinical Medicine, Faculty of Medicine and Health, UNSW, Sydney, NSW, Australia; [7]Department of Renal Medicine, Concord Repatriation General Hospital, Concord, NSW, Australia; [8]Faculty of Medicine and Health, University of Sydney, Camperdown, NSW, Australia; [9]Department of Medicine, Canterbury Hospital, Campsie, NSW, Australia; [10]Department of Renal Medicine, Northern Beaches Hospital, Frenchs Forest, NSW, Australia; [11]Austin Hospital, Heidelberg, VIC, Australia.*

Background: Acute kidney injury (AKI) is common in hospitalised patients and associated with significant morbidity and mortality. Many AKI studies focus upon Intensive Care Unit (ICU) patients, while literature on non-ICU patients with AKI is often limited by retrospectively defined cohorts with varying definitions. The PERFORM-AKI study aims to assess epidemiological and clinical characteristics of hospitalised non-ICU patients with AKI.

Methods: PERFORM-AKI is a multicentre prospective cohort study across 5 centres in Australia. The KDIGO criteria for AKI were used for diagnosing and staging. Baseline data at initial renal consult and follow up data at day 14 or at discharge (whichever occurred first) were collected. Partial renal recovery was defined as the serum creatinine level at the time of follow up has returned to within 50% of baseline levels.

Results: The study included 639 hospitalised patients with AKI diagnosed outside ICU from February 2021 to October 2023. The mean age was 75 years (SD 14.6 years) with a male predominance (57%). The top three pre-existing comorbidities were hypertension (77.3%), cardiovascular disease (58.1%) and diabetes (43.7%). The most common causes of AKI were hypovolaemia (57.0%), sepsis (43.0%) and drug-induced nephrotoxicity (26.6%). Treatments used for AKI were intravenous fluids (57.6%), cessation of nephrotoxic agents (47.3%), and administration of antibiotics (37.2%). There was no significant difference in diagnosis and management of AKI between the initial and follow up renal consultation. AKI was graded as stage 1 in 51.1%, stage 2 in 25.1% and stage 3 in 23.8 % of patients. Mortality across the cohort was 5.6%, few patients (1.7%) required renal replacement therapy, and 75 patients (11.8%) met the definition for partial renal recovery.

Conclusions: Epidemiology and outcomes of AKI in non-ICU patients are distinct to their ICU requiring counterparts. Hypovolaemia is the most common cause of AKI in this cohort, and most patients had incomplete renal recovery by day 14. Since persistent AKI is associated with higher mortality, this study suggests early nephrology follow-up should be encouraged or even mandated in these patients.

Funding: Private Foundation Support

FR-PO035

Predicting Early AKI in Two Large Multicenter Pediatric Critical Care Datasets

Adam Dziorny,[1] Stephen C. Drury,[2] Alex Clark,[2] Martin S. Zand,[2] L. Nelson N. Sanchez-Pinto.[3] *[1]Golisano Children's Hospital, Rochester, NY; [2]University of Rochester Medical Center, Rochester, NY; [3]Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Machine learning (ML) can predict adverse events such as acute kidney injury (AKI) in critically ill children, allowing for proactive care strategies. Most models for pediatric AKI prediction are developed on single-center data which limits generalizability. In this study we externally validate an existing single-center-derived AKI prediction model, recalibrate, and add features on two of the largest multicenter pediatric critical care datasets available.

Methods: Retrospective cohort study within two datasets: (1) a 5-center dataset linking Virtual Pediatric Systems with the PEDSnet (VPS-PN) using probabilistic methods, and (2) the 8-center PICU Data Collaborative (PDC) dataset. We predict AKI within 72 hours of admission, defined by KDIGO serum creatinine criteria. We applied standard ML techniques, including data splitting, imputation, feature selection, and model training, to develop and cross-train a new model. We evaluated prediction score effectiveness with multiple standard measures (area under ROC, AUROC; area under precision-recall curve, AUPRC; and PPV [precision] at two sensitivity thresholds).

Results: Our two datasets included a combined 190,054 ICU encounters, of which 4,797 (2.5%) had AKI within 72 hours of ICU admission. We first applied the existing single-center model and found lower AUROC (0.59 and 0.60) and lower PPV at the 90th percent cut point (0.08 and 0.07) compared to the published single-center results. We developed and tested a new multicenter logistic regression model with 12 features on dataset (1) and recalibrated this model to dataset (2) [**Table 1**]. We evaluated multiple models, feature selection routines, and imputation methods. Optimal performance was targeted to AUPRC and PPV based on goal implementation without excessive false alarms.

Conclusions: We externally validated and subsequently developed a new optimal AKI prediction model within two of the largest pediatric critical care datasets. We specifically identified features that are relevant and available at the time of prediction. Ongoing work is applying this model using FHIR resources within a silent implementation to monitor performance.

Funding: NIDDK Support

Performance characteristics of the two developed models

	Total, N	Test Set, N	AKI at 72 hrs, N (%)	AUROC	AUPRC	50th Percent PPV	90th Percent PPV
VPS-PN (1)	59,330	14,264	1,240 (2.2%)	0.81	0.16	0.04	0.11
PDC (2)	130,724	26,758	3,557 (2.7%)	0.88	0.27	0.05	0.18

FR-PO036

Performance of an Artificial Intelligence-Generated Risk Score for AKI Prediction

Rolando Claure-Del Granado,[1,2] Juan C. Moya-Mamani,[2] Rakesh Malhotra,[3] Subhasis Dasgupta.[4] *[1]Division of Nephrology, Hospital Obrero No 2 - Caja Nacional de Salud, Cochabamba, Bolivia, Plurinational State of; [2]Universidad Mayor de San Simon, Cochabamba, Bolivia, Plurinational State of; [3]University of California San Diego School of Medicine, La Jolla, CA; [4]University of California San Diego, La Jolla, CA.*

Background: Acute kidney injury (AKI) is a frequent complication in hospitalized patients and is associated with worse short—and long-term outcomes. Recent advancements in Generative AI have facilitated the development of a model that enhances risk management and decision-making processes across different acute kidney disease (AKD) cohorts. Through collaboration with OpenAI and prompt engineering, we have created a promising algorithm for assessing the risk of a group of AKD patients.

Methods: We included 303 consecutive hospitalized patients who were at moderate to high risk of AKI using the AKI Risk Assessment algorithm (**Figure 1**). The LLM model score was calculated at admission. Renal function was followed up daily for seven days. AKI was defined and classified by KDIGO sCr criteria. We analyzed the predictive value of this score for the subsequent development of AKI, the need for kidney replacement therapy (KRT), and mortality.

Results: The incidence of AKI was 28% (n=84) most of cases (84.5%) were mild (KDIGO stage 1), with 53.5% of cases secondary to the use of nephrotoxins. The risk score performance was assessed with the area under the curve receiver operating characteristics (AUC ROC). The AUC ROC for AKI was 0.705 (95% CI 0.638 – 0.771; p = 0.001). The performance of the risk prediction score for AKI generated by ChatGPT showed a sensitivity of 85.71%, specificity of 36.07%, with a positive predictive value of 96.2%, a negative predictive value of 11.73%, and an odds ratio of 3.39 (95% CI of 1.7317 to 6.6197; p = 0.0004).

Conclusions: This parsimonious model, encompassing readily available clinical features, displayed acceptable efficacy in predicting AKI. Furthermore, the parsimonious model's integration into clinical practice could support patient risk stratification and inform treatment decisions.

	Risk Factors	Points
Demographic	Age	
	<40 year	0
	40-59 years	1
	60-79 years	2
	≥80 years	3
Co-morbidities	CHF	1
	Chronic hepatic disease	1
	Chronic pulmonary disease	1
	Hypertension	1
	Cancer	1
	Diabetes Mellitus	1
	Presence of 2 or more comorbidities	2
CKD stage	KDIGO stage 1-2	1
	KDIGO stage 3-4	2
Exposures	Nephrotoxins	1
	Sepsis	2
	Hypotension (SBP <90 mmHg or MAP <65 mmHg)	2
	Surgery within 30 days	1
	Dehydration	1
Low risk 0 points Moderate risk 1-3 points High risk ≥ 4 points		

Figure 1. OpenAI-Developed Acute Kidney Injury Risk Score

FR-PO037

Higher Spot Urinary Sodium Concentration Is Associated with Better Decongestion and Lower Risk of AKI in Acute Heart Failure

Rolando Claure-Del Granado,[1,2] Noelia B. Miranda-Velásquez,[2,3] Sergio Villarroel-Espinoza,[3] Edward J. Garcia-Peñaloza,[3] Israel D. Rivas Salazar.[1,2] *[1]Division of Nephrology, Hospital Obrero No 2 - Caja Nacional de Salud, Cochabamba, Bolivia, Plurinational State of; [2]Universidad Mayor de San Simon, Cochabamba, Bolivia, Plurinational State of; [3]Division of Cardiology, Hospital Obrero No 2 - Caja Nacional de Salud, Cochabamba, Bolivia, Plurinational State of.*

Background: Spot urinary sodium concentration (UNa) is recommended in guidelines for assessing diuretic response and adjusting dosage in acute heart failure (AHF) based solely on expert opinion. This study aims to investigate spot UNa levels in patients admitted with decompensated AHF and evaluate its relationship with acute kidney injury (AKI), its efficacy in guiding decongestion, and its impact on short-term outcomes.

Methods: Fifty consecutive AHF patients were included in the study, all of whom received standard care, including the AKI/STOP protocol for patients with AKI. Spot urinary sodium (UNa) levels were measured six hours after the initiation of diuretic therapy, with diuretic insufficiency defined as a UNa <70 mmol/L. Kidney function was monitored daily for up to 7 days. AKI was defined and classified according to the KDIGO serum creatinine criteria.

Results: The mean age of the patients was 70.84 ± 11.19 years, with 62% being women, and the average left ventricular ejection fraction (LVEF) was 43 ± 14%. Patients who received a lower total furosemide dose within 24 hours (37.86 ± 11.34 mg vs. 43.64 ± 7.90 mg; p=0.014) had a UNa ≤ 70 mmol/L. Twenty-four patients (48%) developed AKI within 48 hours of admission. The risk of AKI was lower in patients with a UNa ≥ 50 mmol/L, with an odds ratio (OR) of 0.02 (95% CI 0.0005-0.130; p < 0.0001). Patients with complete or incomplete recovery from AKI had higher UNa values compared to patients with non-recovery (73.2 ± 29.5 vs. 76.6 ± 22.3 vs. 52.6 ± 26.4; p=0.377). There were no significant differences in terms of signs and/or symptoms of clinical congestion or weight loss (9.7 ± 3.3 kg vs. 10.3 ± 2.4 kg; p=0.445). Patients with a UNa > 70 mmol/L had a lower 30-day mortality rate (2% vs. 10%; p=0.0203) and readmission rate (10% vs. 26%; p=0.0142). Additionally, the length of stay was shorter in patients with a UNa > 70 mmol/L (median LOS 6.2 ± 1.6 days vs. 8.5 ± 2.9 days; p=0.002).

Conclusions: Our findings suggest that UNa is a valuable tool for assessing diuretic response and guiding dosage titration in patients AHF. A UNa threshold of ≥70 mmol/L was associated with improved clinical outcomes. Conversely, a lower UNa was indicative of diuretic insufficiency and higher risk of AKI.

FR-PO038

Global Risk of AKI and Tubulointerstitial Nephritis following Anticancer Drug Administration, 1967-2023: Long-Term Pharmacovigilance Analysis

Soo-Young Yoon,[1] Dae Kyu Kim,[1] Su Woong Jung,[2] Jin Sug Kim,[1] Ju young Moon,[2] Hyeon Seok Hwang,[1] Kyunghwan Jeong.[1] *[1]Kyung Hee University Hospital, Dongdaemun-gu, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea.*

Background: Various anticancer drugs are being used worldwide with the advancement of anticancer drugs. Anticancer agents may be nephrotoxic and the aim of this study was to analyze the global risk of renal adverse reactions based on different types of anticancer drugs.

Methods: Between December 1967 to July 2023, we analysed the association between different types of anticancer drugs and the risk of acute kidney injury (AKI) or tubulointerstitial nephritis (TIN) using the World Health Organization pharmacovigilance database. The effect size was assessed using the reporting odds ratio (ROR) through disproportionate Bayesian reporting method. The 306 anticancer drugs were classified into four groups: cytotoxic therapy, hormone therapy, immunotherapy, and targeted therapy.

Results: We identified 32,722 cases of AKI and 2,056 cases of TIN that were reported as renal adverse reactions related to anticancer drugs. Cytotoxic therapies consistently accounted for 13,925 cases, while AKI cases related to targeted therapies and immunotherapies increased to 14,236 and 3,816 cases, respectively, over three decades. The use of immunotherapy between 2015 and 2020 led to a significant increase in TIN, surpassing other categories of anticancer drugs. The highest disproportionality signal for AKI was associated with immunotherapies (ROR, 8.92; confidence interval [CI], 8.63–9.21, followed by cytotoxic therapies (ROR, 7.14; 95% CI, 7.01–7.26), targeted therapies (ROR, 5.83; 95% CI, 5.73–5.93), and hormone therapies (ROR, 2.59; 95% CI, 2.41–2.79). The analysis showed a significantly higher disproportionality signal for immunotherapies (ROR, 21.74; 95% CI, 20.39–23.18) in the case of TIN, followed by cytotoxic therapies (ROR, 2.60; 95% CI, 2.40–2.82), and targeted therapies (ROR, 1.54; 95% CI, 1.40–1.69).

Conclusions: AKI and TIN were observed significantly after administering anticancer drugs. It is crucial to note that renal adverse reactions were more prominent with immunotherapy, which is increasingly used, compared to other types of anticancer drugs.

FR-PO039

Using Machine Learning to Predict AKI in Trauma Patients: A Single Trauma Center Study with Temporal Validation

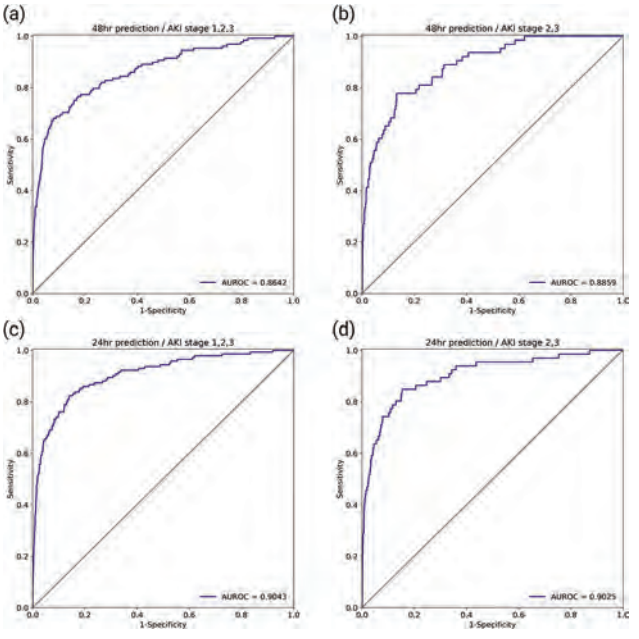
Sunggyul Lim, Yongjin Yi. *Dankook University Hospital, Cheonan, Chungcheongnam-do, Republic of Korea.*

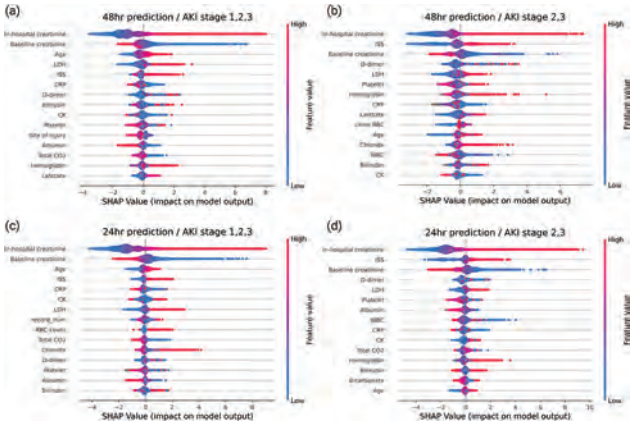
Background: Acute kidney injury (AKI) is a common and serious complication among trauma patients, associated with increased mortality and longer hospital stays. Early identification of AKI in this population is difficult due to its complex causes and the unique characteristics of trauma patients.

Methods: We conducted a retrospective study using electronic health records (EHRs) from a trauma center to develop and validate with extreme gradient boosting (XGBoost) predictive model for predicting AKI. The model was trained on data from Jan 2015 to Jul 2021 and validated on data from Aug 2021 to Jul 2023, internally. Model performance was assessed using the AUROC, and feature importance was evaluated using SHapley Additive exPlanations values.

Results: A total of 11,687 patients (9,063 in the development set and 2,624 in the validation set) were included. The incidence of AKI was 6.6% in the development and 5.4% in the validation group. The models showed AUROCs of 0.864 and 0.886 for predicting AKI stages 1-3 and stages 2-3 at 48 hours, and AUROCs of 0.904 and 0.903 for predicting AKI stages 1-3 and stages 2-3 at 24 hours. Important features influencing model predictions included in-hospital creatinine, age, and laboratory markers such as lactate dehydrogenase.

Conclusions: The machine learning models effectively predict AKI in trauma patients up to 48 hours in advance using readily available EHR data. The performance of this approach highlights the potential for machine learning to enhance predictive capabilities in trauma care.





FR-PO040

Epidemiologic Investigation of Contrast-Induced AKI Based on an In-Hospital Electronic Monitoring System

Xingyue Zheng, Youjun Xu, Fangfang Zhou, Qun Luo. *Ningbo No 2 Hospital, Ningbo, China.*

Background: With the gradual promotion of cardiovascular disease interventions, contrast-induced acute kidney injury (CI-AKI) has become the third most common cause of medically induced kidney injury. Patients with CI-AKI have a poor prognosis, which increases the incidence of end-stage renal disease and the risk of death, and the 2-year survival rate for patients with CI-AKI requiring dialysis is only 18.8%. AKI alerts and corresponding interventions based on electronic surveillance system data have been shown in selected studies to improve AKI patient regression, reduce AKI-related mortality, and decrease hospital length of stay.

Methods: 11,874 adult inpatients who underwent angiography with contrast agents at Ningbo No. 2 Hospital from June 1, 2019 to April 30, 2024 were included, and patients with CI-AKI were screened by an in-hospital electronic monitoring system according to the Kidney Disease Improvement Global Prognosis Organization (KDIGO) criteria.

Results: Of the 11,874 hospitalized patients, 63.36% were male, with an age distribution of 2.08% between 18 and 40 years old, 39.49% between 41 and 65 years old, and 58.43% 66 years old and over. The electronic monitoring system detection rate was 10.49% (1245/11874), of which only 7.47% (93/1245) patients with CI-AKI were invited to nephrologists for consultation, and only 5.30% (66/1245) patients with CI-AKI were discharged with a diagnosis that included an AKI-related diagnosis (acute renal insufficiency/acute renal failure/acute renal damage/acute kidney injury). Of the CI-AKI patients, 46.67% (581/1245) were medical patients, 22.41% (279/1245) were surgical patients, and 30.12% (375/1245) were in intensive care medicine.

Conclusions: The majority of physicians have insufficient knowledge of CI-AKI, serious underdiagnosis, and low consultation rate in nephrology. The establishment of an in-hospital electronic monitoring system is extremely important for improving the prevention and diagnosis of AKI and improving the prognosis of patients.

Funding: Government Support - Non-U.S.

FR-PO041

Relationship of Surgical Type and Fluid Balance with Noncardiac, Perioperative AKI in Neonates

Morgan E. Beebe,[1] Brett Klamer,[3,1] Rain Miller,[2,1] Jonathan L. Slaughter,[1,3] Tahagod Mohamed.[1,3] *[1]Nationwide Children's Hospital, Columbus, OH; [2]The University of Toledo College of Medicine and Life Sciences, Toledo, OH; [3]The Ohio State University College of Medicine, Columbus, OH.*

Background: Few studies examine the relationship between noncardiac surgeries and neonatal acute kidney injury (AKI), with fewer focusing on the effects of fluid balance. Our study aims to evaluate the odds of noncardiac, peri-operative AKI development in neonates based on surgery class and fluid balance at our institution.

Methods: This is a retrospective review of neonates admitted to the neonatal intensive care unit at a single center from Nov 14-Jan 22. Neonates who required a major, minor, or procedural noncardiac surgery in the first 28 days of life were included for analysis. Neonates requiring cardiac surgery, ECMO, lethal chromosomal abnormality, or with significant underlying renal disease were excluded from analysis. Data were evaluated for the development of AKI in the 72 hours following intervention according to revised neonatal Kidney Disease: Improving Global Outcomes (nm:KDIGO) criteria for serum creatinine and urine output. We also reviewed the relationship between peri-operative fluid balance and AKI. Descriptive statistics were used to summarize patient characteristics. Statistical significance was set at an alpha level of 0.05.

Results: 764 neonates were included for final analysis. Following intervention, 715(94%) of neonates did not develop AKI, while 49(6%) did. A more positive fluid balance in the peri-operative period was associated with AKI development on POD 1,2, and 3 (p=0.003,0.002,0.023, respectively). In multivariate logistic regression, the odds of perioperative AKI were significantly higher in neonates undergoing minor surgeries compared procedures. Statistical significance was achieved between the odds of developing AKI in neonates undergoing minor surgery vs procedures [OR 0.52(0.15-1.36);OR 0.19(0.01-0.94), respectively], with a higher odds ratio of AKI after a minor surgery.

Conclusions: In this single-center retrospective analysis, we seek to evaluate associations between AKI and other variables within 72 hours of surgery. Significant factors associated with AKI include a more positive fluid balance, with a higher odds of AKI development in neonates undergoing minor surgery compared to a procedure. AKI surveillance should be undertaken in neonates undergoing noncardiac surgeries, with special attention to fluid balance peri-operatively to further reduce risk of AKI development.

FR-PO042

Rates of AKI with ACE Inhibitor and Angiotensin-Receptor Blocker Use

Michael I. Tabet, Mary V. Sarrazin, Diana I. Jalal, Jason Misurac, Benjamin R. Griffin. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Nephrotoxic medications are a substantial contributor to in-hospital acute kidney injury (AKI). Studies suggest that angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACEi/ARB) are often stopped in the setting of AKI and not resumed on discharge or follow-up, but whether ACEi/ARB should be treated as nephrotoxins is a matter of debate. We hypothesized that among hospitalized patients with high nephrotoxin exposure, receipt of ACEi/ARB would result in similar rates of AKI development as other nephrotoxins.

Methods: Adult patients with ≥1 day of high nephrotoxin exposure from 2014-2022 were included. High nephrotoxin exposure was defined according to Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) criteria as ≥3 nephrotoxins on one day or ≥3 days of intravenous vancomycin or aminoglycoside. The primary outcomes were time to any-stage AKI, AKI stage 1b, and AKI stage 2+3. A Cox proportional hazards model accounted for age, race, sex, BMI, comorbidities, baseline creatinine, vancomycin use, ICU care, and clinical parameters (selected lab values and vital signs) on the day of initial high nephrotoxin exposure.

Results: A total of 13,826 patients had ≥1 day of high nephrotoxin exposure, of which 2,916 (21%) received an ACEi or ARB as part of their nephrotoxin exposure. The ACEi/ARB group was significantly older (64±14 vs 58±15 years) and more likely to have congestive heart failure (16% vs 9%) and diabetes (22% vs 13%), but less likely to be in the ICU (18% vs 25%) and less likely to receive vancomycin (40% vs 67%). All-stage AKI occurred in 31% in both groups (p=0.6); stage 1b AKI occurred in 18% for ACEi/ARB compared to 21% (p<0.001); stage 2+3 AKI occurred in 5.5% vs 7.8% for non-ACEi/ARB (p<0.001). Adjusted hazard ratios for ACEi/ARB exposure were 0.98 (95% CI 0.90-1.09, p=0.6) for any-stage AKI, 0.90 (95% CI 0.81-1.00, p=0.04) for AKI stage 1b, and 0.83 (95% CI 0.69-0.99, p=0.04) for AKI stage 2+3.

Conclusions: Patients receiving two nephrotoxic medications + ACEi/ARB were as likely to develop any-stage AKI as those receiving three nephrotoxic medications (without ACEi/ARB), but had 17% lower hazards for AKI stage 2+3 development.

FR-PO043

Perioperative Kidney Function and AKI in Noncardiac Surgery: A Retrospective Cohort Study in Brasília, Brazil

Petherson M. dos Santos,[1,2] Kirliane D. Rodrigues Lacerda,[3] Rafael F. Rodrigues De Lacerda,[4] Yvve P. Gatto,[4] Gleidson T. Lima,[5] Débora C. Lara,[6] Lucas A. Pinheiro,[7] Priscila de Matos B. Oliveira,[4] Glayson C. Verner,[4] Carolina S. Garcia,[1] Jessica L. Andrade,[1] Lucyana Bertoso de Vasconcelos Freire,[2,6] Cassiane D. da Fonseca,[9] Miguel Angelo Goes.[1,8] Postgraduate Program in Nephrology at the Paulista School of Medicine at the Federal University of São Paulo. *[1]Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil; [2]Escola Superior de Ciencias da Saude, Brasilia, Brazil; [3]Centro Universitario Unieuro, Brasilia, Brazil; [4]Secretaria de Estado da Saude do Distrito Federal, Brasilia, Brazil; [5]Hospital da Crianca de Brasilia Jose Alencar, Brasília, Brazil; [6]Hospital Universitario de Brasilia, Brasilia, Brazil; [7]Universidade de Brasilia Faculdade de Medicina, Brasilia, Brazil; [8]Sociedade Beneficente Israelita Brasileira Albert Einstein, Sao Paulo, Brazil; [9]Universidade Federal de Sao Paulo Escola Paulista de Enfermagem, Sao Paulo, Brazil.*

Background: Acute Kidney Injury (AKI) remains a significant complication in the perioperative period, associated with increased morbidity and mortality. This study aimed to evaluate the frequency and clinical factors associated with perioperative AKI in patients undergoing noncardiac surgery and to assess the predictive value of the SPARK – Simple Postoperative AKI Risk.

Methods: A retrospective study with 172 noncardiac surgery patients from 2021 to 2022 at a teaching hospital in Brasilia, Brazil. The study population included patients of various ages, genders, and comorbidities who underwent a range of noncardiac surgeries. Demographic and clinical data, such as kidney function (measured by creatinine levels), American Society of Anesthesiologists (ASA) score pre-surgery, and outcomes (including length of hospital stay and need for kidney replacement therapy), were compared between AKI and non-AKI groups. Finally, we performed a multivariate analysis and analyzed SPARK's index discrimination with the ROC curve.

Results: 60 (34.9%) patients developed AKI. Older age and higher ASA scores were significantly associated with AKI (p<0.001), and RDW was identified as a predictor of AKI (IRR 1.28%, 95% CI: 1.04-1.57, p= 0.017). Patients with AKI had more extended surgery. Exposure to nephrotoxic agents and blood transfusion requirements were also higher in the AKI group. The SPARK index showed the AUC of 0.72 (95% CI, 0.65-0.80).

Conclusions: Preoperative RDW levels, in addition to age and ASA score, were independently associated with AKI in noncardiac surgeries. The SPARK score, with its AUC of 0.72, is a valuable tool for preoperative risk assessment. These results underscore the complexity of risk factors associated with AKI in the perioperative setting of noncardiac surgeries. Further research is needed to validate the findings and enhance AKI prevention strategies.

FR-PO044

Evaluation of Scoring Tools to Predict AKI Postpercutaneous Coronary Intervention

Joanna Q. Hudson,[1,2] Tara Parnacott,[1,2] Anna R. Jacobs,[2,1] Carolyn Cummings,[2,1] Margaret C. Hastings,[1,2] Benjamin Duhart.[1,2] *[1]The University of Tennessee Health Science Center, Memphis, TN; [2]Methodist Le Bonheur Healthcare, Memphis, TN.*

Background: Radiocontrast-associated acute kidney injury (CA-AKI) is a common cause of in-hospital acute kidney injury (AKI) and other causes of morbidity and mortality. The original Mehran score was developed to predict risk of developing CA-AKI after percutaneous coronary intervention (PCI); however, it requires intraprocedural variables such as contrast volume and cannot proactively identify high-risk patients. The modified Mehran 2 (MM2) score and the CHA_2DS_2-VASc score overcome this limitation, but validation in the clinical setting is limited. This study evaluated the MM2 and CHA_2DS_2-VASc score for prediction of AKI in patients receiving iodinated contrast for PCI.

Methods: A retrospective chart review was conducted of adults (≥ 18 years) admitted to Methodist LeBonheur Hospitals in Memphis, Tennessee between July 2019 and July 2023 who received contrast for PCI. Patients with end-stage kidney disease, AKI prior to receipt of contrast, or with a documented contrast allergy were excluded. MM2 and CHA_2DS_2-VASc scores were evaluated in patients with and without CA-AKI using previously proposed thresholds for high risk (MM2 ≥ 8; CHA_2DS_2-VASc ≥ 4). Predictive ability was analyzed using receiver operating characteristic (ROC) curves for comparison of area under the curve (AUC); p-value < 0.05 considered statistically significant. Other factors associated with AKI not included in the MM2 and CHA_2DS_2-VASc were also evaluated.

Results: One hundred seventy-seven patients were included: 128 without CA-AKI (72.3%), 49 with CA-AKI (27.7%). The MM2 and CHA_2DS_2-VASc scores performed similarly for predicting CA-AKI (ROC AUC 0.68 and 0.67, respectively). The proportion of patients with a high/very high-risk MM2 score was greater in the CA-AKI group (55% vs. 32%; p=0.005). Similarly, more patients in the CA-AKI group had a high-risk CHA_2DS_2-VASc score (51% vs. 31%; p=0.011). The CA-AKI group had a higher rate of hypotension within 48 hours of PCI (41% vs. 12%; p<0.001) and was less likely to have received pre-procedure IV fluids (35% vs. 52%; p=0.035). Patients with CA-AKI had longer hospital length-of-stay (5.3 vs. 3.1 days; p<0.001).

Conclusions: The MM2 and CHA_2DS_2-VASc scores had similar predictive value for CA-AKI after PCI and may provide a practical advantage over the original Mehran score.

FR-PO045

Triglyceride-Glucose Index and Triglyceride-to-High-Density Lipoprotein Cholesterol Ratio as Novel Predictors of AKI: A Large-Scale Prospective Study

Fangfang Zhou, Youjun Xu, Qun Luo. *Ningbo No 2 Hospital, Ningbo, China.*

Background: Our study aimed to comprehensively investigate the associations of the Triglyceride-glucose (TyG) index and triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio with the risk of AKI, based on the data from the UK Biobank.

Methods: A total of 427,659 individuals remained for the final analysis. According to the TyG index levels, patient data were divided into 5 quartiles. The primary outcome of this study was incident AKI, defined based on the International Classification of Diseases edition 10. Participant follow-up started at inclusion in the UK Biobank and was censored on December 31, 2022 or on the date of the first AKI. The analysis involved the utilization of Cox proportional hazard models, log-rank tests, and Kaplan-Meier cumulative incidence graphs. Mediation analyses were carried out to examine the impact of hypertension, diabetes, and dyslipidemia on the relationships between the risk of AKI, the the TyG index, and TG/HDL-C ratio.

Results: Of 427,659 included participants, 22,447 (5.25%) participants developed incident AKI. The median TyG index and TG/HDL-C ratio were 8.68 (IQR 8.31–9.08) and 2.43 (IQR 1.51–3.96), respectively. The risk of AKI elevated progressively with the increased quartiles of both the TyG index and TG/HDL-C ratio, as indicated by Kaplan-Meier curves. Elevated quartiles of the TyG index or TG/HDL-C ratio exhibited strong associations with AKI risk in comparison to lower quartiles, demonstrating respective hazard ratios (95% CI) of 1.16 (1.11-1.22) and 1.05 (1.00-1.10) (p<0.001). After full covariate adjustment, the adjusted smoothed plots displayed U-shaped associations between TyG index and incident AKI, and the relation between TG/HDL-C ratio and the hazard of incident AKI followed a reverse J-shape (p for nonlinearity < 0.001). The results did not change by the sensitivity analysis. In mediation analyses, variables like hypertension, type-2 diabetes, and dyslipidemia emerged as notable intermediaries in the connections between the incident AKI, the TyG index, and the TG/HDL-C ratio (intermediation proportions: 83.5%,74.5%).

Conclusions: Association was detected between the increased TyG index or ratio of TG to HDL-C and increased AKI risks. These associations were mainly influenced by a higher incidence of hypertension, type-2 diabetes, and dyslipidemia.

Funding: Government Support - Non-U.S.

FR-PO046

Preoperative Fasting Time Is Not Associated with Development of AKI after Cardiac Surgery

Moritz Schanz,[1] Carmen Heidrich,[2] Schmid Nico,[2] Nora Goebel,[1] Tina Oberacker,[1] Severin Schricker,[1] Micha Christ,[2] Joerg Latus.[1] *[1]Robert-Bosch-Krankenhaus GmbH, Stuttgart, Germany; [2]Bosch Health Campus, Stuttgart, Germany.*

Background: Acute kidney injury (AKI) is associated with high morbidity and mortality, therefore prevention is important. The aim of this study was to systematically assess AKI incidence after cardiac surgery depending on the preoperative fasting time.

Methods: This single-center study included n = 8423 patients who had cardiac surgery at Robert Bosch Hospital, Stuttgart (Germany) between 2017 and 2024. All patients scheduled for surgery the next day stop eating and drinking at midnight, irrespective the time of surgery. AKI was classified according to the full definition of Kidney Disease: Improving Global Outcomes (KDIGO), including urinary output.

Results: In our cohort, overall postoperative AKI incidence was 71% during hospital stay. Interestingly, patients with AKI stage 1-3 had significant longer preoperative fasting time compared to patients without AKI (p=0.036; OR 1.15 (IQR 1.05-1.27)). However, after adjusting for important confounding factors e. g. urgency of surgery, age, pre-existing conditions such as CKD, heart failure, obesity, as well as aortic clamping time, duration of surgery, the association was no longer evident (p=0.39; OR 1.07 (0.92-1.25)).

Conclusions: Although preoperative fasting time seems to be a plausible risk factor for AKI development, this study provides evidence that preoperative fasting time is not a risk factor for the development of AKI after cardiac surgery after adjustment for potential confounders.

FR-PO047

Utility of Cystatin C as a Predictor for Postoperative AKI in Noncardiac Surgeries

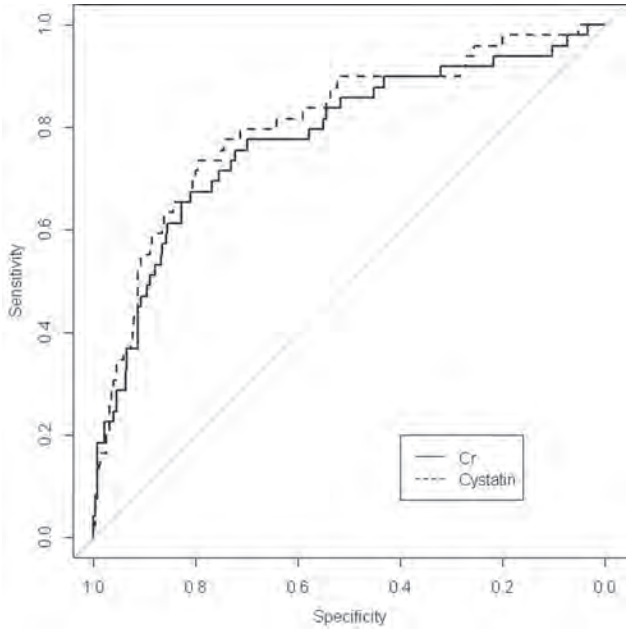
Hae Eun Jeon, Soie Kwon. *Chung Ang University Hospital, Seoul, Republic of Korea.*

Background: Serum creatinine has been widely utilized to estimate glomerular filtration rate (eGFR), although various biomarkers have been developed to address its limitations. Among these biomarkers, the clinical use of Cystatin C is increasingly gaining recognition. However, there is a lack of evaluation regarding the utility of cystatin C in predicting the risk of postoperative acute kidney injury (PO-AKI) in non-cardiac surgeries.

Methods: A retrospective cohort study was conducted on patients who underwent non-cardiac surgeries lasting over 1 hour in five departments. PO-AKI was defined as per KDIGO-AKI criteria occurring within 7 days after surgery. Logistic regression was used to develop a prediction model, and C-statistics and the Delong test were used to compare the performance of each model.

Results: 339 patients were enrolled, with 49 (14.5%) developed PO-AKI. Patients who developed AKI had a higher prevalence of diabetes and prescription of RAS blockers, longer operation duration, and lower eGFR of all types (Table 1). No statistical differences were observed in other laboratory findings between the two groups. The model with eGFR-Cystatin C demonstrated the highest area under the curve (AUC) among the three models (eGFR-Cr: AUC 0.78, 95% CI 0.702-0.857; eGFR-Cystatin C: AUC 0.81, 95% CI 0.735-0.877; eGFR-Cr/Cystatin C: AUC 0.80, 95% CI 0.724-0.871). Only the eGFR-Cystatin C-based model showed significant improvement in prediction compared to the eGFR-Cr-based model in the Delong test (eGFR-Cystatin C vs eGFR-Cr: p-value 0.033; eGFR-Cr/Cystatin C vs eGFR-Cr: p-value 0.055, Figure 1).

Conclusions: Our findings suggest the potential usefulness of cystatin C in predicting the risk of PO-AKI in non-cardiac surgery. Further studies involving larger and external cohorts are essential for validation.



FR-PO048

Validation of Renal Angina Indices in Critically Ill Patients and Assessment of Urinary Biomarker Incorporation for AKI Prediction

Erick Y. Zuñiga Gonzalez,[1] Juan M. Villegas,[1] Noemi Del Toro-Cisneros,[1] Rosario Guadalupe H. Ortega,[2] Pablo E. Galindo,[2] Cristino Cruz Rivera,[1] Olynka Vega.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico*.

Background: The renal angina index (RAI) helps to predict acute kidney injury (AKI) in critically ill patients. Moreover, whether incorporation of urinary biomarkers into RAI may enhance severe AKI prediction is not kown.

Methods: This was a prospective cohort of patients admitted in two intensive care units (ICU) at third-level hospitals in Mexico City. Demographic, laboratory data and urinary samples were collected at ICU admission. RAI score was calculated using three methods at Day0: Matsuura, Ortiz-Soriano and Del Toro-Cisneros methods. AKI was defined according to KDIGO guidelines. The study aimed to evaluate RAI's predictive ability for severe AKI (stage 2 or 3) at 24 and 72 hours post-admission.

Results: Of the 134 patients analyzed, nineteen presented a stage 2 or 3 AKI over 72 hr follow-up. After evaluating all indices, RAI Matsuura presented the best performance in receiver-operating characteristics (ROC) analysis (cutoff of 10p) at 24hr (AUC 0.74, 95% IC 0.57-0.90) and 72hr (AUC 0.70, 95% IC 0.56-0.84). Neither urinary neutrophil gelatinase-associated lipocalin (uNGAL) nor urinary heat shock protein-72 (uHsp72) incorporation into RAIs improved ROC curve and discrimination for RAIs. [Table 1]

Conclusions: Our study highlights RAIs as a practical and useful tool for assessment of AKI risk in ICU adult patients. Urinary biomarkers incorporation does not improve accuracy for prediction of severe AKI, promoting RAIs' seamless integration into routine clinical assessments

Performance of different renal angina indices with and w/o addition of uNGAL

	AUC	Sensitivity	Specificity	PPV	NPV
RAI Matsuura [cut-off 10p] 24hr 72hr	0.74 (0.57-0.90) 0.70 (0.56-0.84)	66% 57%	81% 82%	26% 35%	96% 92%
RAI +/ NGAL +* 24hr 72hr	0.66 (0.47-0.84) 0.65 (0.49-0.80)	60% 56%	72% 73%	17% 25%	95% 91%
RAI del Toro [cut-off 10p] 24hr 72hr	0.68 (0.53-0.83) 0.69 (0.56-0.81)	75% 73%	61% 63%	16% 25%	96% 94%
RAI +/ NGAL +* 24hr 72hr	0.70 (0.54-0.86) 0.68 (0.54-0.82)	60% 75%	72% 68%	16% 24%	95% 94%
RAI Ortiz-Soriano [cut-off 10p] 24hr 72hr	0.62 (0.47-0.77) 0.60 (0.55-0.81)	79% 83%	43% 41%	18% 12%	92% 96%
RAI +/ NGAL +* 24hr 72hr	0.66 (0.50-0.80) 0.65 (0.52-0.78)	90% 88%	42% 44%	13% 19%	98% 96%

Predictive performance of RAIs for severe AKI (stage 2/3) at 24 and 72 hr. uNGAL cutoff based on Youden's optimal index: NGAL >152 ng/ml. *Patients included in the analysis n=118.

FR-PO049

Saliva Urea Nitrogen Improves Mortality Prediction in Children with Malnutrition and AKI

Anthony Batte,[1] Quique Bassat,[2] Peter Kotanko,[3] Jochen G. Raimann,[3] Andrea L. Conroy.[4] *[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]Fundacion Privada Instituto de Salud Global Barcelona, Barcelona, Spain; [3]Renal Research Institute, New York, NY; [4]Indiana University School of Medicine, Indianapolis, IN*.

Background: Acute malnutrition is a leading cause of pediatric mortality and a risk for acute kidney injury (AKI). We evaluated the utility of saliva urea nitrogen (SUN) test strips and AKI to predict mortality in children hospitalized with acute malnutrition.

Methods: This study prospectively enrolled 185 children 6 months to 10 years of age hospitalized with acute malnutrition at Mulago National Referral hospital, Uganda from September 2020 to February 2021. Creatinine was measured using the modified Jaffe method that is IDMS-traceable. AKI was defined using a modified Kidney Disease: Improving Global Outcomes AKI definition (mKDIGO) using serial creatinine measures over hospitalization. Of 574 creatinine measures, 193 (33.6%) were below the assay limit of detection and assigned a value of 0.16mg/dL. Children required a maximum creatinine value ≥0.4mg/dL to be classified as having AKI. SUN was measured at bedside using semi-quantitative point of care strips. Enrolled children had weight-for-age or heigh-for-age z-scores <-2 SD. We used the modified Poisson regression and receiver operating curve (ROC) analysis.

Results: A total of 185 children were enrolled (36.2% female) and 25 children died (13.5%). Overall, 43 children (23.2%) met the definition for mKDIGO AKI and a positive SUN test (SUN ≥11mg/dL) was found in 105 children (56.8%). A positive SUN test was associated with a risk ratio (RR) of AKI of 2.88 (95% CI 1.46, 5.66) and severe AKI (AKI stage 2 & 3) RR 4.1 (95% CI 1.7 to 10.2). mKDIGO AKI (RR 3.58 95% CI 1.76 to 7.27) and a positive SUN test (RR 8.76 95% CI 2.12 to 36.22) were associated with mortality. The area under the ROC for AKI and a positive SUN test to predict mortality were 0.67 (95% CI 0.56 to 0.77) and 0.76 (95% CI 0.64 to 0.77), respectively. Incorporating both SUN and AKI significantly improved mortality prediction compared to either marker alone with an area under the ROC of 0.77 (95% CI 0.69 to 0.84).

Conclusions: SUN is a non-invasive tool that is associated with acute kidney injury and mortality in children with acute malnutrition. This point of care tool may provide additional benefit in risk stratification and prognostication of hospitalized children at risk of death when used in combination with creatinine based AKI definitions.

Funding: Other NIH Support - K43TW012586

FR-PO050

Kidney and Endothelial Injury Biomarkers among Crossfit Athletes

Renan G. Diniz,[1,2] Júlio C. Nunes Filho,[2] Daniel V. Pinto,[2] Robson S. Matos,[2] Gdayllon C. Meneses,[2] Geraldo B. Silva Junior,[2] Elizabeth D. Daher.[2] *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Universidade Federal do Ceara, Fortaleza, Brazil*.

Background: Crossfit® (CF) is a high intensive functional trained sport created in 2000. It is not recognized as an official sport by international sports federations. It has attracted many practitioners due to its quick results in muscle mass increase and weight loss. In Brazil, there was a 5900% increase in CF centers between 2012 and 2019, and there are currently more than 15000 centers worldwide. Given this emerging and intense sport, the purpose of this study was to evaluate markers of kidney and endothelial injuries among CF® athletes.

Methods: The study was conducted in two phases: Phase 1 involved proteinuria analysis from urine samples collected before work-out and results comparing recreational athletes (RAs) with competitive athletes (CAs). Phase 2 study compared levels of

endothelial and kidney injury biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), creatine kinase (CK), albumin, creatinine, and estimated glomerular filtration rate (eGFR) among CAs before and after activity.

Results: In Phase 1, 99 participants were involved. Results showed that 44.4% of CAs had proteinuria levels between 300 and 1000 mg/dL, and 14.8% had levels exceeding -1000 mg/dL. Only 2.8% of RAs had proteinuria levels above 300 mg/dL (p=0.001). In Phase 2, only 10 athletes had completed all the phases. This phase 2 comparing results between and after work out revealed creatinine 1.03 + 0.24 vs. 1.36 + 0.34, mg/dL(p=0.001) and CK 302.40 vs. 2048.80 U/L ; (p 0.005) 24h after the activity, and reduced eGFR (91.55 + 21.15 vs. 66.45 + 20.6, mL/min/1.73m2 p=0.000). ICAM-1, VCAM-1, Syndecan-1, and NGAL did not show statistically significant changes. There was a strong positive correlation between Syndecan-1 and CK (p=0.000, r=0.953).

Conclusions: Despite some limitations (such as not accounting for testosterone use and the small sample size in Phase 2), this is the only study that evaluated proteinuria, endothelial and kidney biomarkers among CF® Athletes. The findings suggest a possible risk of kidney disease in CF® athletes. Further research is warranted with larger sample sizes and more comprehensive risk factors to clarify whether these findings are directly linked to the sport or other confounding factors.

FR-PO051

Construction of a Predictive Model of Risk Factors for Kidney Replacement Therapy after Heart Transplantation

Dinglin Liu, Haofei Hu, Zhiming Ye. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: Acute kidney injury (AKI) is one of the common complications after heart transplantation (HT), which seriously affects the quality of life and survival rate of patients after heart transplantation. Severe acute kidney injury requires renal replacement therapy (RRT), and early identification and intervention of risk factors can improve the prognosis, survival and quality of life of heart transplant patients.

Methods: The study enrolled 288 heart failure patients who underwent HT at Guangdong Provincial People's Hospital (Jan 2010-Feb 2023) and Zhongshan City People's Hospital (Jul 2017-Mar 2023). Risk factors were screened using machine learning and one-way analysis, the optimal coefficients were determined using Lasso regression model combined with cross-validation, non-zero coefficient variables were selected to construct a column-line graph prediction model, and prediction equations were established by multifactor logistic regression. The differentiation of the prediction model was assessed by the Area under Curve, the accuracy of the model was tested by the calibration curve, and the clinical applicability was analyzed by the Decision Curve Analysis.

Results: The incidence of severe acute kidney injury requiring RRT after HT was 28.13%. Six risk factors were identified and integrated into a column-line diagram: history of intra-aortic balloon counterpulsation use, preoperative serum albumin, preoperative blood creatinine, intraoperative red blood cell transfusion volume, duration of HT surgery, and intraoperative mechanical circulatory support. The area under the ROC curve for the predictive model was 0.765, and the calibration curve for the column-line diagram model was close to the ideal curve. The clinical decision curve showed that the column-line diagram prediction model performed optimally in the 0.1-0.6 probability interval. Internal validation was performed using Bootstrap method with 500 repetitive samples, yielding a mean AUC of 0.757.

Conclusions: In this study, we analyzed the risk factors for severe acute kidney injury requiring RRT after HT, and established a column-line graph prediction model and its equations. Internal validation proved that the model was stable and effective in predicting the risk of needing RRT after HT, which can help early intervention and improve prognosis.

FR-PO052

Intrarenal Vein Congestion Score but Not Venous Excess Ultrasonography Is Associated with Kidney Perfusion and Etiology of AKI

Arkadiusz Lubas, Adam Rytel, Ewelina Jedrych, Anna Grzywacz, Stanislaw Niemczyk. *Wojskowy Instytut Medyczny - Panstwowy Instytut Badawczy, Warszawa, Poland.*

Background: Proper diagnosis of acute kidney injury (AKI) etiology contributes to adequate treatment and a more favorable renal prognosis. Recently, a 4-point Venous Excess Ultrasound (VExUS) was introduced for AKI prediction. Due to the poor diagnostic performance of Vena Cava Inferior (VCI) maximal diameter in congestion assessment, interlobular renal vein Doppler flow patterns evaluation expressed as IntraRenal Vein Congestion Score (IRVCS) can be more appropriate for AKI etiology diagnosis. The study aimed to investigate the usefulness of IRVCS in predicting AKI etiology.

Methods: Twenty-four patients (10F, 14M; age 64 ±11) hospitalized due to AKI of unknown origin were evaluated in duplex Doppler ultrasound with the assessment of VExUS (grade 0-3): VCI; Hepatic Veins Systolic to Diastolic ratio, Portal Vein Pulsatility Index (PVPI), Real Vein Doppler. Moreover, Peak Systolic (PSV) and End-Diastolic Velocities (EDV) in interlobar renal arteries and IRVCS (stage 0-3) were investigated. Serum blood NT-proBNP and creatinine with eGFR-CKD-EPI calculation were tested. At discharge, the more probable etiology of AKI was identified as hypovolemia, hypervolemia, and inflammation.

Results: Mean creatinine was 3.48 ±1.82 mg/dL (CKD-EPI 22.97 ± 13.15 mL/min/1.73m^2) and NT-proBNP 9169.1 (IQR 5667.2) pg/mL. Abnormal IRVCS was found in 7 (29%) patients (2 – stage 1, 4 – stage 2, and 1 – stage 3), but VExUS revealed congestion in 12 (50%) patients (11 - grade 1, 1 - grade 3); p< 0.001. IRVSC significantly correlated with NT-proBNP (r=0.573; p=0.010), PSV (r= -0.557; p=0.011), EDV (r= -0.442; p=0.045), PVPI (0.485; p=0.026), and VExUS (r= 0.461; p=0.035). However, VExUS correlated only with VCI (r=0.753; p< 0.001) and IRVSC. Hypovolemic AKI etiology was recognized in 8 patients, hypervolemic in 7, and inflammation in 9. Logistic regression revealed that only IRVSC could substantially predict the hypervolemic etiology of AKI (OR 2.763; 95%CI: 1.008-7.570; p= 0.048). VExUS had no corresponding predictive properties (OR 2.070; 95%CI: 0.580-7.388; p= 0.262).

Conclusions: IntraRenal Vein Congestion Score is significantly associated with renal perfusion and can help predict the hypervolemic etiology of AKI. The presented data suggest that IRVCS is more appropriate than VExUS in diagnosing the etiology of AKI.

Funding: Government Support - Non-U.S.

FR-PO053

Development of Urinalysis Screening Criteria for Electronic Health Alerts for Rhabdomyolysis

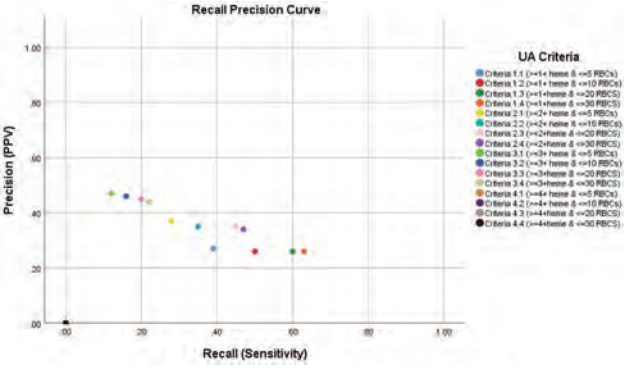
Farah Yasmin,[1,2] Sophia Faulkner,[1,2] Abinet M. Aklilu,[1,2] Yu Yamamoto,[1,2] Dennis G. Moledina,[1,2] Francis P. Wilson.[1,2] Clinical and Translational Research Accelerator (CTRA). *[1]Yale University School of Medicine, New Haven, CT; [2]Clinical and Translational Research Accelerator, Yale University School of Medicine, New Haven, CT.*

Background: Acute kidney injury (AKI) is present in 7-10% of rhabdomyolysis (rhabdo) cases and early intervention can improve outcomes. A discrepancy between heme on dipstick and RBC on microscopy on UA can potentially aid in early rhabdo diagnosis.

Methods: We did a retrospective electronic chart review of adult inpatients hospitalized between Jan 2020-Dec 2022 who met KDIGO-creatinine criteria for AKI, had UA within the same hospitalization pre-AKI, no rhabdo suspicion (i.e., no creatine kinase (CK) test pre-AKI), and no lab evidence of hemolysis.16 screening criteria were formulated to identify individuals at elevated likelihood of rhabdo using combinations of heme ≥1+, ≥ 2+, ≥ 3+, ≥ 4+ and RBC ≤5, ≤10, ≤20, ≤30 thresholds whose accuracy was assessed using post-AKI CK>500 U/L as the definition of rhabdo diagnosis.

Results: A total of 12,284 patients were included of which 20.5% had serum CK levels checked. Of those, 17.4% (440) met the diagnostic criteria for rhabdo. Rhabdo patients had significantly higher incidence of mortality, dialysis, and AKI progression. The median (IQR) time between UA and AKI was 1.97 (4.55-0.84) days. UA criteria of ≥1 heme + ≤30 RBCs (met by 35.1% of patients) had the highest sensitivity for rhabdo (63.4%). Within this criterion, a quarter (1079/4308) had their CK checked, of whom a quarter (279/1079) had CK levels consistent with rhabdo. The UA criteria of ≥ 3+ heme + ≤5 RBCs (met by 2.0% (246) patients) had a specificity of 97.2% and sensitivity of 11.2%. This criterion included the highest proportion of patients with CK measurement (111/246, 45.1%), and nearly half of those tested (52/111) had levels consistent with rhabdo (Fig. 1).

Conclusions: CK testing was overall uncommon under all definitions, suggesting missed rhabdo cases. As UA is obtained frequently in AKI workup (and other conditions) automated electronic screening of UA parameters with clinical decision support to order CK may be a viable mechanism to increase the diagnosis of rhabdo.



FR-PO054

Chloride Variation as an Independent Risk Factor for AKI Development and In-Hospital Mortality in Patients with Rhabdomyolysis

Lucas Araujo, Tania d. Spada, Bruna F. Silva, Heitor S. Ribeiro, Lucia Andrade, Emmanuel A. Burdmann, Jose M. Vieira Jr.. *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Rhabdomyolysis (RB) is considered as an important cause for acute kidney injury (AKI) and mortality. Studies have suggested that acidosis is a risk factor for AKI. We alternatively hypothesized that serum chloride variation (SCV) might be associated with AKI and mortality in RB patients.

Methods: We studied a retrospective cohort of RB (>5x reference values of CPK) patients admitted in a tertiary hospital during a year. Demographic, clinical and laboratorial data were assessed and a regression analysis (RA) was performed in order to identify the independent variables associated with AKI and 28d mortality, including SCV.

Results: We included 291 patients admitted with RB due to diverse causes, from which 67% developed AKI. AKI patients were older, had more comorbidities and were sicker during admission (shock 35 vs 13%; $p < 0.0001$, mechanical ventilation, MV 49 vs 29%; p= 0.0015; sepsis 11 vs 3%; p=0.03). Peak CPK levels were higher in the AKI group (4218 IQR 2316-8968 vs 3221 IQR 1940-6206 U/L; p=0.04). Serum bicarbonate (SBic) and chloride did not differ between AKI and non-AKI at admission (21.0 IQR 18-24 vs 21.5 IQR 20-24 mEq/L, p=0.3; and 107 IQR 102-111 vs 107 IQR 113-111 mEq/L, p=0.5, respectively). During hospitalization, SCV was higher in the AKI group (2 IQR 0-10 vs 0 IQR 0-10 mEq/L, p=0.0003), and SBic was lower (18 IQR 14-21 vs 21 IQR 19-24 mEq/L, p< 0.0001). After RA, SCV remained as an independent variable associated with AKI (OR 1.09 CI 1.01-1.16, p=0.020), along with baseline hypertension (p=0.024) and SBic (p<0.001). AKI patients had higher mortality (39 vs 3.5%, p<0.0001) and RA showed that SCV was associated with mortality in the entire cohort (OR 1.082 CI 1.006-1.163, p=0.035), along with increased age, use of MV, AKI, use of renal replacement therapy, trauma and higher serum lactate.

Conclusions: Higher serum chloride variation was an independent risk factor for AKI and death in hospitalized patients with RB.

FR-PO055

AKI in Patients with Babesiosis: Incidence, Risk Factors, Clinical Features, and Outcomes

Audrey E. Monson,[1] Julio Baigorri,[1] Ahmad Jaser,[1] Sarah A. Kaunfer,[1] Shobana Krishnamurthy,[1] Guillermo Socorro Matos,[1] Peter J. Krause,[2] David E. Leaf.[1] *[1]Mass General Brigham Inc, Boston, MA; [2]Yale New Haven Health System, New Haven, CT.*

Background: Babesiosis is an emerging tickborne illness caused by the intraerythrocytic parasite, *Babesia microti*, which is endemic in the northeastern U.S. Complications have been observed in >20% of hospitalized patients, though AKI remains poorly described, with most data derived from case reports and small case series.

Methods: We reviewed the records of 1317 patients at Mass General Brigham with an ICD code or positive test result for *Babesia* between 2015-2023, of whom 272 (20.7%) were hospitalized. Among those hospitalized, we collected detailed data by manual chart review on demographics, comorbidities, medications, labs, and outcomes. We sought to characterize the incidence, severity, clinical features, risk factors, and outcomes of AKI, defined as a ≥50% increase in serum creatinine above baseline or receipt of kidney replacement therapy (KRT). We used multivariable logistic regression to identify independent risk factors for AKI.

Results: A total of 93 patients (34.2%) developed AKI, including 52 (55.9%), 23 (24.7%), and 18 (19.4%) with stages 1, 2, and 3 (**Fig. 1A**), 7 of whom (7.5%) received KRT. The most common etiologies of AKI were ATN, pre-renal azotemia, and hemolysis (**Fig. 1B**). Independent risk factors for AKI included older age, smoking, higher LDH, higher parasitemia load, and hematuria (**Fig. 1C**). Eight of 50 patients (16%) with data available had persistent kidney dysfunction at day 90.

Conclusions: In the largest study to date, we found that more than one third of hospitalized patients with babesiosis developed AKI, nearly half of which was stage 2 or 3. We identified five independent risk factors for AKI, including markers of hemolysis and severity of parasitemia.

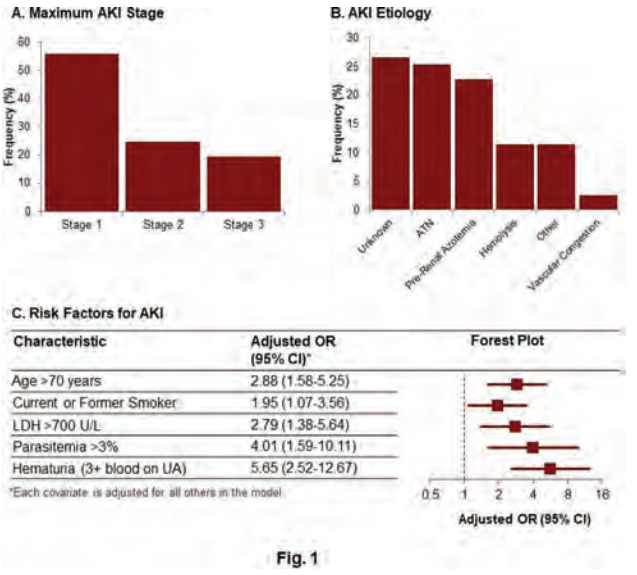


Fig. 1

FR-PO056

University of California Irvine Supported Vascular Endothelial Growth Factor Inhibitor (Intravitreal) Systemic and Renal Toxicity Registry: 24-Month Update

Matthew D. Nguyen,[1,2] Ryan E. Fekrat,[3] Vu Q. Nguyen,[3] Samir D. Patel,[2] Tai Truong,[2] Rebecca S. Ahdoot,[2] Ira Kurtz,[4] Ramy M. Hanna.[2] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]University of California Irvine Nephrology Hypertension & Kidney Transplantation, Orange, CA; [3]University of California, Irvine - Department of Medicine, Irvine, CA; [4]University of California Los Angeles - Division of Nephrology, Los Angeles, CA.*

Background: Intravitreal Vascular Endothelial Growth Factor inhibitors (IVEGFi) are used in treatment of diabetic retinopathy. As we have previously reported there increasing number of cases documenting IVEGFi with renal injury and increased concentrations in the serum. To assess this claim, UCI Dept. of Nephrology has developed a novel reporting system through an electronic registry for cases of suspected VEGFi injury.

Methods: A website with data protection sets was organized to educate, promote awareness, and record cases of suspected intravitreal VEGFi toxicity. The website focused on displaying the biology of VEGF signaling, the process of absorption into the bloodstream, and the reporting of studies showing risks on case, cohort, and epidemiologic levels. A HIPAA compliant patient intake form was designed to collect renal, cardiovascular, cerebrovascular, renal biopsy and function data along with drug type, indication, and frequency of administration.

Results: In our updated cohort we added 17 total cases from the literature showing signs of renal injury from the patient population receiving VEGFi. In current literature, 46 cases of VEGFi related renal injury have been documented. To them we add our 17 cases for a total of 63 cases.

Conclusions: The current database for VEGFi related nephrotoxicity constitutes the largest case series presented for this condition. This study suggests future studies to evaluate what subgroups experience AKI, proteinuria and HTN exacerbations. Additionally, we may expand on our database to include timeline markers for symptomatic-correlative VEGFi usage and, in time, predictive measures in larger scale to correlate comorbidity/drug use with drug effect and mechanism of action.

Patient Number	Age	Gender	Comorbidities	Reason for the Intravitreal macular degeneration, diabetes, and central retinal vein obstruction	IVEGF/i Drug frequency	Drug	Drug Effects (Renal+systemic)
1	30	Male	Chronic Kidney Disease Diabetes Hypertension	DME	Daily	Bevacizumab	sCr 1.4-->2-->3 since starting avastin 2022-->2024 upcr 6g max 1.3 g-->4 g 2022-->2024 htn worsening +DR DM/DN
2	36	Male	Chronic Kidney Disease Diabetes Hypertension	DME	Monthly	Bevacizumab	sCr 1.3-->1.5-->2.5 over last 2 years proteinuria 1g-->2. 7-->3.5 g over last 2 years
3	65	Female	Chronic Kidney Disease Diabetes Hypertension	DME	Daily	Bevacizumab	avastin likely drug sCr increase 0.7 to 1.2
4	62	Male	Chronic Kidney Disease Diabetes Dialysis Heart Attack Hypertension	every 3 months new VEGFi valysimo (q 3 mos - faricimab)	Bi-monthly or less often	Other	proteinuria in allograft of transplant patient 1 g--> 4.3g over last period post 1st injection allograft biopsy planned 1.3 sCr --> 1.5. mg/dL
5	61	Male	Chronic Kidney Disease Diabetes Heart Attack Hypertension	DME	Monthly	Bevacizumab	sCr worsening from 1.9-2 up to 3.7 mg/dl. and rua showing 500+ proteinuria (nephrotic range) no macr or upcr
6	53	Female	Chronic Kidney Disease	DR	Monthly	Bevacizumab	from time of initiation sCr increased to 7 to 10 grams proteinuria rapid progression of CKD
7	47	Female	Chronic Kidney Disease Diabetes Heart Attack Hypertension	Diabetes	Monthly	Ranibizumab	After intravitreal ranibizumab injection, existing proteinuria raised to a nephrotic level in multiple occurence. Renal biopsy performed when proteinuria was 14gr/day and serum albumin 2.9 g/dl. It showed diabetic nephropathy and acute TIN eosinophil dominant inflammation and tubulitis). The patient has a Class 3 obesity, as well.
8	79	Male	Chronic Kidney Disease Diabetes	AMD	Monthly	Aflibercept	new onset proteinuria from 1+ to 3+* 140 mg/day uACR to 1g/day
9	47	Male	Anemia Chronic Kidney Disease Diabetes Hypertension	DR got 6 weeks before injury per pt (last known well kidney function 1.5 --> 3.6)	Weekly	Bevacizumab	Nephrotic range proteinuria 10g of protein. biopsy suggested.
10	43	Female	Chronic Kidney Disease Hypertension	VEGFi for DME	Monthly	Bevacizumab	2000mg/g of proteinuria (albuminuria) initially in 2017 when started intravitreal vegf --> increase to 10 g/day of proteinuria.
11	67	Female	Chronic Kidney Disease Diabetes Heart Attack Hypertension	DME	Monthly	Bevacizumab	patient with worsening renal function (accelerated DM and DN)
12	63	Male	Chronic Kidney Disease Diabetes Heart Attack Hypertension Stroke	Diabetic macular edema	Monthly	Bevacizumab	microalbumin/creatinine ratio of 70
13	75	Male	Hypertension	AMD	Bi-monthly or less often	Aflibercept	no proteinuria or hematuria
14	74	Male	Chronic Kidney Disease Hypertension	Macular degeneration	Monthly	Aflibercept	no proteinuria noted, but accelerated hypertension, with swings. HTN diagnosis normal to start around time of starting intravitreal VEGFi.
15	53	Male	Chronic Kidney Disease Diabetes Hypertension	DR	Bi-monthly or less often	Bevacizumab	nephrotic range proteinuria
16	58	Male	Chronic Kidney Disease	Diabetes	Bi-monthly or less often	Bevacizumab	Yes, ACi went from 1.3 -> 5 gram in span of 5 months. UPCr 4.7 grams.
17	47	Female	Hypertension	Proliferative diabetic retinopathy	Monthly	Other	worsening hypertension and worsening proteinuria.

FR-PO057

AKI after Vancomycin Treatment: Need for Kidney Biopsy

Anjali A. Satoskar,[1] Laura Biederman,[1] Mineaki Kitamura.[2] [1]*The Ohio State University, Columbus, OH;* [2]*Nagasaki Daigaku Daigakuin Ishiyakugaku Sogo Kenkyuka, Nagasaki, Japan.*

Background: Vancomycin is the antibiotic of choice for methicillin-resistant Staphylococcus aureus infections, often given empirically, even before culture results become available. However it is known for its nephrotoxic effect. Acute tubular necrosis (ATN) and mild acute interstitial nephritis (AIN) are the morphologic correlates in the kidney. But a substantial number of kidney biopsies performed for AKI following Vancomycin treatment instead show infection-related glomerulonephritis (IRGN). It is difficult to predict one versus the other. Analysis was performed to see if significant differences in demographic features exist that might help.

Methods: We searched our Pathology files for kidney biopsies with the term "vancomycin" in the clinical history. We retrieved a total of 354 biopsies between 2004 and 2017. Three broad diagnostic categories emerged: Group I- ATN with or without AIN (n=200); Group II - infection-related glomerulonephritis (IRGN) (n=94); and Group III (n=60) - other glomerular or vascular disease (n=60). Statistical comparison was performed for patient age, sex and ethnicity between these groups.

Results: Groups II and III comprised 44% of this cohort. In Group II, 23/94 showed resolving IRGN with mild IgA deposits and 67/94 also showed active proliferative glomerular lesions. Group III contained cases of ANCA-associated GN, cryoglobulinemic GN, proliferative GN with monoclonal IgG deposits (PGNMID), a few lupus nephritis, fibrillary GN and thrombotic microangiopathy (TMA). No significant differences in age or sex were identified between the three groups. Average age was 55.7, 57.7 and 56.8 years respectively. African American ethnicity was more represented in Group III (Pearson Chi-square test p = 0.0005).

Conclusions: AKI in patients receiving Vancomycin may not always be due to drug-induced ATN/AIN alone. Other concomitant pathologies may be present. IRGN can develop despite ongoing antibiotic treatment, in some but not all patients with infection, but is difficult to predict. Although, IRGN is reported to show predilection for older age, male sex and Caucasian background, these demograpic features did not help predict IRGN vesus Vancomycin-induced ATN in this cohort. Urinalysis may offer clues in non-oliguric patients. But kidney biopsy assumes importance. Further studies with urinalysis findings, Vancomycin trough levels, nature of infection are needed.

FR-PO058

Comparison of Clinical Characteristics of AKI between Glufosinate and Glyphosate Poisoning

Ju hwan Oh, A young Cho, Haeun Lee, In O Sun. *Presbyterian Medical Center, Jeonju, Jeollabuk-do, Republic of Korea.*

Background: There are few studies comparing the clinical characteristics of acute kidney injury (AKI) between glufoinate and glyphosate poisoning. In this study, we investigated the clinical characteristics of AKI in patients with glufosinate and glyphosate poisoning, and compared the clinical features of AKI between two groups.

Methods: This study performed between 2008 and 2021 included 76 patients with glufosinate poisoning and 184 patients with glyphosate poisoning. This study included 76 patients with glufosinate poisoning and 184 patients with glyphosate poisoning in the period from 2008 to 2021. Based on Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease classification, we investigated the incidence, clinical characteristics, and severity of AKI between two groups [(glufosinate-induced AKI (Glu-AKI, n=54) and glyphosate-induced AKI (Gly-AKI, n=82)].

Results: The incidence of AKI in patients with glufosinate poisoining is higher than that of glyphosate poisoning (57.5% vs 44.5%, P<0.05). However, there is no difference of AKI severity between two groups (Glu-AKI; Risk 56.2%, Injury 36.9%, Failure 6.9% vs Gly-AKI; Risk 56.2%, Injury 14.6%, Failure 29.2%, P=NS). Comparing two groups, there is also no difference in age (62.6±14.2 years vs. 63.3±16.2 years, *P*=NS) and renal function on admission (63.9±25.2 mL/min/1.73 m^2 vs. 62.2±22.9 mL/min/1.73 m^2, *P*=NS). The length of hospitalization was longer (17.2±17.2 days vs. 10.7±12.1 days, *P*<0.05) in Glu-AKI group than that of Gly-AKI group. The mortality rate was higher in the Gly-AKI group than Glu-AKI (11.1% vs. 18.3%, *P*=NS). Multivariate logistic regression analysis showed that serum bicarbonate concentration on admission was a significant predictors of AKI in patients with AKI after glyphosate and glufosinate intoxication

Conclusions: Although there is a higher incidence of AKI in glufosinate poisoning, there is no difference in clinical characteristics between the two types of intoxication.

FR-PO059

AKI Associated with Intestinal Ostomies

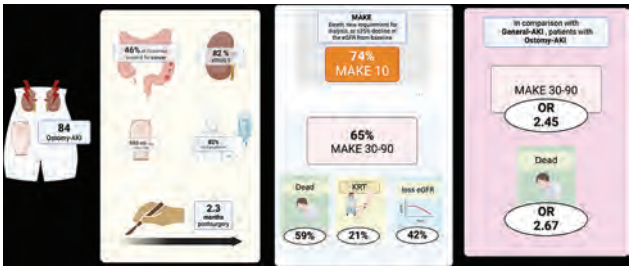
Jonathan Chavez,[1,2] Karla Hernandez Morales,[1] Guillermo Garcia-Garcia,[1] Ramon Medina,[1,2] Jahir R. Camacho,[1] Edgar J. Carmona,[1] Alexa N. Oseguera Gonzalez,[1] César Murguía Soto,[1] Alejandro Martínez Gallardo González.[2] [1]*Universidad de Guadalajara, Guadalajara, Mexico;* [2]*Hospital Civil de Guadalajara, Guadalajara, Mexico.*

Background: People with ostomies can have high output and be complicated by acute kidney injury (AKI). The clinical description of these patients and their association with the composite of major adverse kidney events (MAKE) has not been explored in depth.

Methods: In a retrospective cohort conducted at the Hospital Civil of Guadalajara Fray Antonio Alcalde. We included patients with AKI associated with ostomies (Ostomy-AKI) and compared them with AKI of other etiologies (General-AKI), with the objectives of describing and differentiating their clinical presentation and their association with early MAKE (MAKE10) and after 30 -90 days (MAKE 30-90), in addition to its individual components as death, new requirement for dialysis, or ≥25% decline in the eGFR from baseline. Analyzed the risk by logistic regression model and a multivariate Cox proportional hazard.

Results: During the period from February 2020 to October 2023, 84 patients in Ostomy-AKI were included and compared with 348 in General-AKI. The total cohort is composed mostly of men (59.3%), with an mean age of 55 years (41-67). In AKI-Ostomy patients were largely males (78.7 vs 56.2%), the output through the ostomy was 980 ml /day (760-1700), 82.9% required fluid adjustment; the cause of the ostomy was cancer in 46% and they had an average of 2.3 months with it. The etiology of AKI frequently due to hypovolemia (48.9 vs 24.5%) and they had more frequently AKI KDIGO stage 3 (82.9 vs 63.9%). Both groups had the same frequency of MAKE10 (94%), as were its individual components. The MAKE30-90 occurred more frequently in Ostomy-AKI (65.9 vs 49.3%), increasing more than two-fold the risk (OR 2.459, CI 1.134-5.332, p = 0.023), and it was very similar to its individual component of death (59.5 vs 37%) (OR 2.678, CI 1.260-5.689, p = 0.010).

Conclusions: In comparison with General-AKI, patients with Ostomy-AKI present with more hypovolemia and higher mortality during the 30-90 day follow-up, and a 2.5-fold increase risk of MAKE, especially that of mortality.



FR-PO060

AKI with Proximal Tubular Epithelium Vacuolization following SGLT2 Inhibitor Overdose

Makoto Araki, Yayoi Ogawa, Mitsuru Yanai. *Sapporo Tokushukai Hospital, Sapporo, Japan.*

Introduction: Sodium-glucose cotransporter-2 inhibitors (SGLT2i), commonly used to treat diabetes, heart failure, and chronic kidney disease, have been occasionally linked to acute kidney injury (AKI). Although osmotic renal injury is suspected to be one of the causes due to the drug's pharmacological effects, there are few histological studies on this issue.

Case Description: A 76-year-old woman with a history of two prior suicide attempts through drug overdose was admitted to our hospital after ingesting a large dose of her husband's medications an hour before arrival. The medications included 160 mg of esomeprazole, 1740 mg of azosemide, 725 mg of eplerenone, and 290 mg of dapagliflozin. She had diabetes, an HbA1c level of 8.1%, and bipolar disorder, but her family carefully managed her medications to prevent overdose. Following admission, diuretic-induced polyuria exceeded 150 mL/h. Ten hours later, a drop in blood pressure and signs of dehydration prompted an increase in fluid infusion. On the second day, her urine output increased to 5 liters per day, but then decreased sharply. By the fourth day, she became anuric. Subsequently, she remained anuric with her creatinine level rising to 4.12 mg/dl, leading to a diagnosis of stage 3 AKI and the initiation of dialysis. A renal biopsy conducted the following day revealed significant vacuolization and swelling in the proximal tubular cells, confirming osmotic tubular damage likely caused by SGLT2i, given the absence of hyperosmotic agents or severe potassium imbalance. Fortunately, her urine output gradually improved from the sixth day, allowing for the cessation of dialysis. Her renal function normalized by the twelfth day, and she was subsequently transferred for psychiatric care on the eighteenth day.

Discussion: Osmotic tubular injury, characterized by diffuse vacuolization and swelling of proximal tubular cells and traditionally associated with hyperosmotic agents, is now also sporadically reported with the use of SGLT2i. Risk factors include chronic kidney disease, advanced age, dehydration, and diuretic use. In this case, a combination of uncontrolled hyperglycemia, diuretic-induced dehydration, and high-dose SGLT2i likely caused the tubular injury. The prognosis for SGLT2i-induced damage remains uncertain, though it was favorable here.

FR-PO061

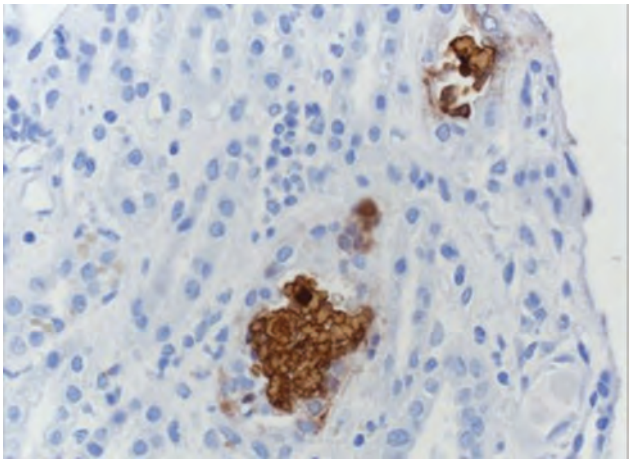
A Rare Case of Herpes Simplex Virus (HSV)-Associated Rhabdomyolysis

Cameron T. Lawson. *East Carolina University, Greenville, NC.*

Introduction: Viral myopathy is an important cause of massive rhabdomyolysis leading to acute renal failure. Many cases involving influenza A and B, Epstein Barr virus, and adenovirus have been reported. To my knowledge, this is only the second case of rhabdomyolysis secondary to herpes virus in a previously healthy patient that has been reported in the English literature.

Case Description: A 23-year-old female without significant past medical history presented to the ER for muscle aches, fevers, and hematuria. No recent trauma, increased exercise, or drug use was reported. The exam was notable only for genital ulceration. Labs were notable for BUN of 52 mg/dL, creatinine of 6.09 mg/dL, AST of 2,126 U/L, and ALT of 424 U/L. Creatine kinase elevated to 426,700 U/L. Ethanol < 10 mg/dL. Viral testing for HIV, Parvovirus B19, RSV, Influenza A, Influenza B, and COVID were all negative. Anti-JO-1 antibodies and complete myositis-specific autoantibody were both negative. Urine analysis showed no active sediment but urine protein: creatine ratio was 3.7 g/day. A kidney biopsy showed 1) diffuse acute tubular injury with extensive myoglobin casts and 2) mild acute interstitial nephritis. HSV-2 serum PCR was positive and valacyclovir was started. She remained anuric and hemodialysis was initiated. A muscle biopsy was performed to rule out autoimmune myositis. Creatinine was 5.6 mg/dL on discharge. Repeat creatinine at two weeks post-discharge was 1.9 mg/dL. The patient remained off dialysis and the muscle biopsy was read as necrotizing myopathy. No morphologic evidence of glycolysis, lipidosis, or mitochondrial myopathy was seen.

Discussion: Herpes virus is a rare cause of rhabdomyolysis leading to acute renal failure. As with other viral myopathies, muscle weakness accompanies this condition and can range from myalgias to myolysis. Rhabdomyolysis can be life-threatening and early recognition and treatment can prevent renal dysfunction. Evaluation for HSV should be included in the workup for viral myopathy.



Myoglobin cast

FR-PO062

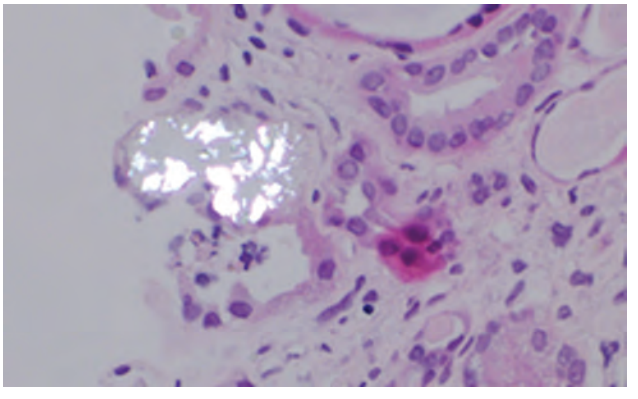
Hyperoxaluria: The Diet before the Riot

Aman Pal, Emmanuel A. Aydin-Ghormoz, Andrea R. Lightle, Geovani Faddoul. *Albany Medical Center, Albany, NY.*

Introduction: Oxalate nephropathy is a rare condition involving the accumulation of oxalate crystals within the nephrons. Primary hyperoxaluria involves enzymatic defects in the metabolism of glyoxylate, while secondary hyperoxaluria includes dietary and malabsorption related etiologies. Our case highlights the early diagnosis of oxalate nephropathy secondary to excessive intake of nuts and vitamin C.

Case Description: A Caucasian male in his 80s presented to the hospital with an AKI on CKD stage 4 in the setting of a new antibiotic prescription. Creatinine had increased to 4.2mg/dL from a baseline of 2.2mg/dL, with no etiology identified on urinalysis or renal ultrasound. Renal biopsy revealed an acute tubular injury with intraluminal calcium oxalate crystals deposits, confirming a diagnosis of oxalate nephropathy (Fig. 1). A detailed history revealed excessive dietary intake of oxalate-rich foods, including nuts, and daily ingestion of 2g of vitamin C. The patient was counselled on adjusting his diet and stopping vitamin C supplementation which led his creatinine to return close to baseline 2-months post-discharge.

Discussion: Dietary oxalate varies in individuals ranging from 44-351mg/day with there being a non-linear association between dietary and urinary oxalate content. The addition of 1000mg of vitamin C has also been shown to increase urinary oxalate up to 13mg/day. Consuming excessive amounts of oxalate can result in urinary levels above the threshold of 44mg/day for association with calcium oxalate stones. Our case emphasizes the possibility of excessive consumption of almonds, walnuts, peanuts, pine nuts and vitamin C as etiologies. The patient consumed approximately 30g of these nuts several times a day, which approximates 242mg of oxalate per serving. Additionally, our patient consumed 2000mg of Vitamin C daily. These factors played an integral part in the development of his AKI, highlighting the importance of collecting a thorough dietary history and keeping a low threshold to performing a kidney biopsy to prevent progression into ESKD.



FR-PO063

Epidemiological and Clinical Characteristics of Atypical Hemolytic Uremic Syndrome in China

Hua Zheng, Limeng Chen. *Peking Union Medical College Hospital Department of Nephrology, Beijing, China.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare thrombotic microangiopathic disease that can lead to acute renal failure and hemolysis. Nevertheless, there is lack of nationwide data in China. This study intended to review and summarize the epidemiological characteristics and outcome of aHUS in China.

Methods: In this observational cohort study, we collected data from the Hospital Quality Monitoring System of China, a direct reporting system of medical data that covers abstract medical records from 5800 public hospitals in 31 provinces and municipalities from 2018 to 2022. All patients diagnosed with aHUS based on ICD-10 coding were enrolled. Patients missing unique identifier number or basic demographic information were excluded.

Results: 372 unique aHUS patients were identified, 45.6% of whom were male. Age distribution showed double peaks: children and women at thirties (Figure 1). Prevalence rates varied greatly among provinces, with the top 5 provinces being Inner Mongolia, Chongqing, Xinjiang, Guangxi, and Xizang, four of which were minority autonomous regions. The incidence of aHUS increased from 0.038 (2018) to 2.996 per million hospital admission (2022). 81% of the patients were first diagnosed in tertiary hospitals, with an average length of stay of 17.6 days. The top five admitting departments were nephrology, intensive care unit, pediatrics, hematology and general internal medicine. 37.5% of patients received dialysis, 20.3% received plasma exchange, 5.1% of patients underwent renal biopsy. The proportion of plasma exchange increased from 14.3% (2018) to 25.8% (2022), while intensive care unit support increased from 9.5% (2019) to 29.6% (2022). The combined proportion of discharges against medical advices and in-hospital deaths dropped from 33.3% (2019) to 16.9% (2022).

Conclusions: AHUS manifested with age and gender preference. With intensive support and treatment being increasing common, the proportion of adverse outcomes decreased through years in China.

Funding: Government Support - Non-U.S.

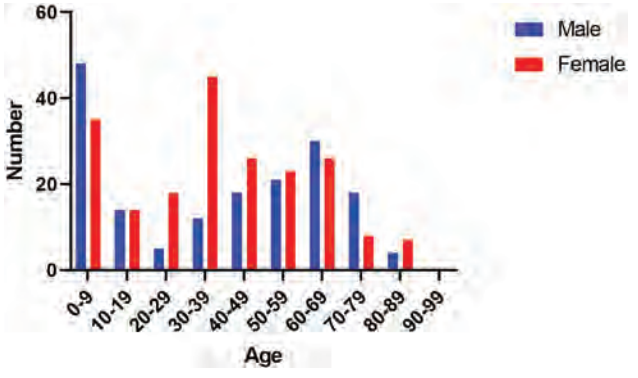


Figure 1. Age and sex distribution of aHUS patients.

FR-PO064

Thrombotic Microangiopathy Due to Liposomal Daunorubicin/ Cytarabine

Luke Webster, Dinna Cruz. *University of California San Diego, La Jolla, CA.*

Introduction: Thrombotic Microangiopathy (TMA) is a syndrome defined by microangiopathic hemolytic anemia, thrombocytopenia and end organ damage. With the rise of new chemotherapy regimens, drug induced TMA (DITMA) represents an important and growing cause of TMA. While DITMA has been occasionally reported with conventional daunorubicin/cytarabine we present the first case report of liposomal daunorubicin/cytarabine (lipo-dau/cyt) as a cause of TMA and Acute Kidney Injury (AKI).

Case Description: A 70F was admitted for management of Acute Myeloid Leukemia with lipo-dau/cyt. Patient with PMHx of well controlled HTN and Stage 2 carcinoma of left breast s/p bilateral mastectomy and adjuvant chemotherapy. One month after initiating lipo-dau/cyt, creatinine (Cr) rose from 0.94 to 1.68 with peak Cr 2.2. Patient reported worsening lower extremity edema and denied any skin rashes, lesions, or hematuria. Vitals showed worsening HTN with BP 165/107 despite previously being well controlled on outpatient antihypertensives, along with 14lb weight gain. Exam showed new 3mm pitting edema bilaterally to the knees. Labs showed Plt 8, Hgb 6.4, LDH 800, AST 52, ALT 37, UA with new 3+ proteinuria and 1+ urobilinogen. A 24h urine showed 4.9gm proteinuria. Complement activity Sc5-9: 633 ng/ml (h), haptoglobin was <10, ADAM-TS13 normal (74), and other serologic workup negative (SSA/SSB, ANA, ANCA, Anti-Sm, PLA2R, Shiga Toxin, SPEP). A peripheral smear showed numerous schistocytes. A kidney biopsy was performed which showed TMA with acute tubular injury. Lipo-dau/cyt was discontinued. Two months post withdrawal of medication Cr improved to 1.3 and LDH, platelets and haptoglobin normalized.

Discussion: This case illustrates the potential for liposomal daunorubicin/cytarabine to cause drug induced TMA. While older non-liposomal formulations have been associated with TMA in the past, this would be first report of its occurrence with the liposomal formulation. Early recognition of liposomal dauno/cyta-associated TMA is important for treatment modification and to help preserve kidney function.

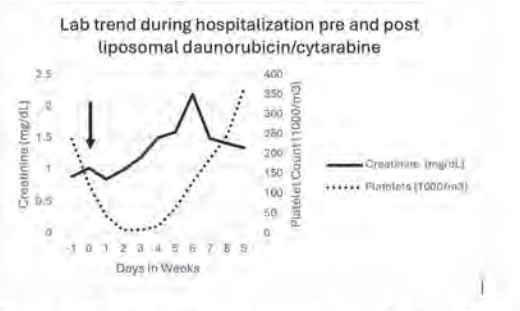


Figure 1: Creatinine trend pre and post exposure to liposomal daunorubicin/cytarabine with time zero representing initiation of therapy (indicated by arrow).

FR-PO065

Rifampin-Induced Hemolytic Anemia and Pigment Nephropathy Requiring Dialysis in an Adolescent

Lana Bridi,[1] Nadine M. Benador,[1,2] Natalie Ellington,[2] Caitlin E. Carter.[1,2]
[1]University of California San Diego, La Jolla, CA; [2]Rady Children's Hospital San Diego, San Diego, CA.

Introduction: Rifampin (RIF) is a commonly used anti-microbial and rarely causes acute kidney injury (AKI). We report a pediatric patient with dialysis dependent AKI due to hemoglobin cast nephropathy from hemolysis while taking RIF for latent tuberculosis (TB).

Case Description: 14 yo with latent TB on RIF with intermittent medication adherence presented with acute onset abdominal pain and intractable emesis. Labs revealed serum creatinine (Cr) 4.2 mg/dL, BUN 62 mg/dL, hemoglobin12.3 g/dL, platelet 77 × 10^9/L, LDH 3107 U/L, haptoglobin 10 mg/dL. Schistocytes were not observed. There was also a pattern of hepatocellular injury with elevated AST, ALT, bilirubin, aPTT and INR. Urine revealed microscopic hematuria, proteinuria (UPCR 4.2 g/gm), and muddy brown casts. Kidneys were both large and echogenic on ultrasound. He developed oliguria and required intermittent hemodialysis (iHD) for 10 days. Kidney biopsy revealed acute tubular injury secondary to hemoglobin casts and moderate interstitial inflammation. Two weeks after last iHD treatment, Cr remains elevated 1.09 mg/dL, eGFR 63 mL/min/1.73m^2.

Discussion: RIF associated AKI is caused by several pathologic patterns: interstitial nephritis and tubular necrosis are most common. Rifampin induced immune hemolytic anemia and thrombocytopenia with kidney injury has been described in adults. Kidney biopsy in this child showed an overlapping pattern of heme pigment nephropathy and interstitial nephritis leading to severe AKI. Sporadic rifampin administration has been associated with this phenomenon in adults. Discontinuation of RIF often results in resolution of hemolysis and AKI although can recurr if re-exposed to RIF. RIF induced AKI secondary to hemoglobin-cast nephropathy has not been reported in children. Adolescents, in whom medication adherence is often inconsistent, may be at higher risk and should be monitored for renal dysfunction.

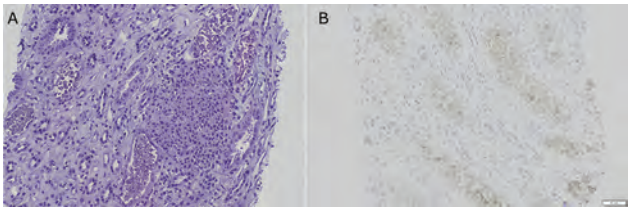


Figure 1. (A) Hemoglobin (Hgb) casts were granular, globular or rope-like in appearance. Focal tubular rupture is seen with adjacent non-necrotizing granulomatous response. (Hematoxylin and eosin). (B) Immunohistochemistry for Hgb showed positive staining within casts.

FR-PO066

A Late and Delayed Case of Rhabdomyolysis with Trabectedin Use

Adnan Barazi, Patricia Khalil, Amr Habbach. *Allegheny Health Network Graduate Medical Education, Pittsburgh, PA.*

Introduction: Trabectedin, a marine-derived alkylating agent, is used in treating Liposarcoma by disrupting the cell cycle and inducing cancer cell death. It, however, has been associated with rhabdomyolysis. What sets this case apart is the delayed onset of Trabectedin-induced rhabdomyolysis, manifesting approximately 3 weeks after the patient's last dose.

Case Description: 38-year-old female with a history of liposarcoma of the left femur with disease progression despite surgery and chemotherapy, has been undergoing palliative chemotherapy with trabectedin. She presents with fever and generalized weakness and laboratory evaluation showed a Creatinine Kinase (CK) level of 2751 U/L. She developed an acute kidney injury with a creatinine of 5.09 mg/dL. CK levels peaked on day 20 from the last dose at 10915 U/L. Trabectedin induced rhabdomyolysis was diagnosed and patient was started on hemodialysis. On outpatient follow-up, her renal function improved leading to discontinuation of hemodialysis with complete resolution of rhabdomyolysis.

Discussion: Trabectedin is an effective drug in treating advanced sarcoma. One of the rare side effects associated with its use is rhabdomyolysis. Its etiology is not completely clear. The most reported cases of rhabdomyolysis associated with Trabectedin occurred on average 2 weeks following the administration of Trabectedin. Most of the cases reported toxicity in the first few cycles of Trabectedin. In our case, rhabdomyolysis occurred 3 weeks after the 5th cycle. Therefore, one should remain vigilant about late and delayed cases of rhabdomyolysis with Trabectedin use. To note, the CK level was elevated after the third cycle at 1,124 U/L. The current recommendation is to check CK after each cycle and to adjust therapy with no discontinuation of therapy unless rhabdomyolysis occurs. This case highlights the need to explore if more stringent CK criteria and monitoring need to be placed to prevent rhabdomyolysis cases.

FR-PO067

Acute Interstitial Nephritis in the Setting of Ipilimumab and Nivolumab Therapy

Rupinder Kaur,[1] Somesh Singh,[2] Nabeel Siddiqui,[1] Bhoomi Shah,[1] Olawale M. Osunsanya.[1] *[1]Southeast Health, Dothan, AL; [2]Alabama College of Osteopathic Medicine, Dothan, AL.*

Introduction: Certainly, immune checkpoint inhibitors (ICIs) like Ipilimumab and Nivolumab, have become an important strategy in cancer therapy; however, the incidence of renal complications arising from the widespread use of ICIs may be underestimated. A less-known adverse reaction from checkpoint inhibitors is acute interstitial nephritis (AIN), and there are only a few case reports demonstrating AIN related to checkpoint inhibitors.

Case Description: A 74- year-old-male with a recent diagnosis of squamous cell lung carcinoma, on combination therapy with nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) for almost 2 months, presented to us with nausea, vomiting, and associated generalized weakness. On presentation vitals were unremarkable. Creatinine 5.2 mg/dl(baseline 0.8- 0.9 mg/dL), Urine microscopy revealed >100 white blood cells, 1+ protein and 1+ bacteria, urine protein creatinine ratio 926 mg/g, and urine culture resulted negative. Renal ultrasound was unremarkable for any acute findings. He was started on IV fluids. On the next day, his creatinine worsened to 5.5mg/dl, and urine output was noted to be decreased. A urine Hansel stain was performed which showed increased eosinophils. Eventually, he started on oral prednisone 60mg PO daily for possible drug-related AIN. A renal biopsy revealed acute tubulointerstitial nephritis. Immunotherapy was discontinued. His creatinine subsequently improved, and he was discharged on 4-week taper of oral prednisone.

Discussion: The significant ICI-induced renal adverse event known as AIN is brought to light in this case, emphasizing the need for careful monitoring of renal function in patients undergoing immunotherapy with these drugs. AIN can occur days to several months after initiation of an offending agent. Although AIN is typically associated with medications such as non-steroidal inflammatory agents, proton pump inhibitors, or antibiotics, checkpoint inhibitors related to AIN have been reported. A brief course of corticosteroid therapy is a viable therapeutic strategy to attain full or partial remission. The true incidence of renal complications from ICIs is underestimated. Early recognition of this rare nephrotoxic reaction by healthcare providers may be important for the subsequent clinical course and recovery from AKI.

FR-PO068

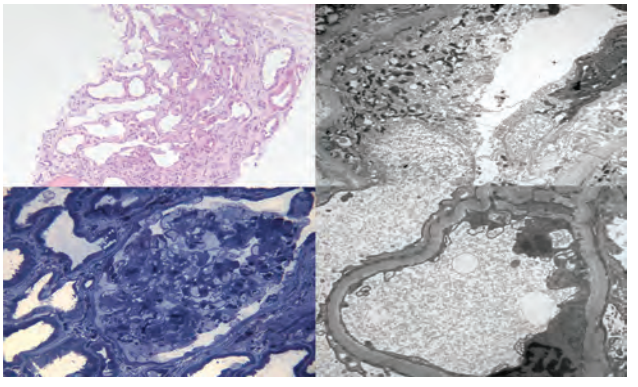
Dengue-Associated Tubulopathy with Resultant AKI and Dialysis Dependence

James Allen, Madhia B. Ahmad, Joshua Kaplan, Smita Mahendrakar. *Rutgers University Newark, Newark, NJ.*

Introduction: Dengue disease remains a prevalent mosquito transmitted viral infection worldwide. The incidence of dengue has increased 30-fold in the past 50 years. Acute kidney injury (AKI) is a serious complication of dengue with high morbidity and mortality. The available data regarding AKI in dengue is sparse and mostly originates from case series and case reports. We present a case of acute tubular injury secondary to dengue.

Case Description: A 59-year-old male presented with AKI on CKD with proteinuria, shortness of breath and lower extremity swelling. He was diagnosed with dengue fever and thrombocytopenia 1 month prior to admission in Brazil, where nephrotic range proteinuria was also found. Labs were significant for a creatinine of 10.1mg/dL and albumin of 1.9gm/dL. Protein to creatinine ratio was 12g/day. Proteinuria work up included C3, C4, Hepatitis B, C panel, HIV screen, anti-PLA2R, P-ANCA, C-ANCA, kappa/lambda ratio, free kappa light chains, and free lambda light chains was non-diagnostic. With worsening renal function and development of volume overload, hemodialysis was initiated, and renal biopsy was obtained. Biopsy demonstrated acute tubular injury denoted by markedly dilated tubules lined by flattened epithelium. Ultrastructural findings support acute tubular injury with loss of brush border. Methylene blue stained section revealed increase in mesangial matrix and protein resorption vacuoles in podocytes with acute tubular injury noted in surrounding tubules. With no signs of renal recovery, patient was discharged on scheduled dialysis and follow up with renal function monitoring.

Discussion: This case illustrates the potential long-term complications with dialysis dependence resulting from tubular injury caused by dengue infection. Dengue is an emerging source of global disease burden with limited data regarding cases complicated by AKI. Earlier recognition and management may lead to a significant reduction in dengue related renal complications in endemic areas.



FR-PO069

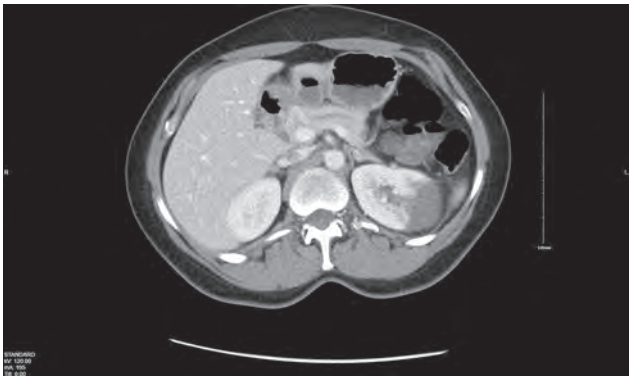
Rare Presentation of Renal Infarction Due to Protein S Deficiency

Thin Thin Soe,[1,2] Arfa Amjad,[1,2] Isha Puri,[1,2] Muhammad Azhar,[1,2] Mary C. Mallappallil.[1,2] *[1]New York City Health and Hospitals Corporation, New York, NY; [2]SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Protein S deficiency is a rare hematologic disorder which can be hereditary or acquired. Protein S deficiency is associated with increased risk of venous thromboembolism. However, there is no clear evidence of PS deficiency and arterial thromboembolic.

Case Description: We present the case of a 55-year-old female patient with no significant medical history who presented with 3 days of left sided flank pain, nausea and vomiting. She had mild leukocytosis, normal hemoglobin, unremarkable metabolic profile and with RBCs in urine microscopy, but no pyuria or bacteria. CAT scan of abdomen and pelvis with intravenous contrast revealed large well demarcated hypodensity in the upper pole of the left kidney, read as renal infarct (see image). CT angiogram of abdomen and pelvis was done to confirm thromboembolism, which revealed the occlusion of peripheral distal segmental branch of the distal left renal artery supplying upper pole of the kidney. She has 2 children, no history of spontaneous fetal losses. There is no family history of blood clotting disorders. She is a smoker 1 pack of cigarette for more than 30 years (>30 pack years). Hypercoagulable work up revealed very Low protein S levels – 26%, normal protein C, antithrombin III assay, Factor V Leiden mutation, Lupus anticoagulants, Cardiolipin, Beta 2 Glycoprotein 1 ab, no PNH clone, or JAK 2 mutation. We ruled out cardiac embolic source by echocardiogram and electrocardiogram did not show any Atrial fibrillation, flutter or other arrhythmias. She was treated with oral Apixaban for 6 months, and counseled about smoking cessation.

Discussion: In literature reviews, smoking nicotine can increase risk of thrombotic events such as stroke and myocardial infarction. There are studies that prove free protein S is significantly lower in smokers, and it contributes to thrombotic complications.



FR-PO070

Incidence and Clinical Outcomes of Sepsis-Associated AKI: A Multicenter Contemporary Cohort Study

Tomonori Takeuchi,[1,2] Alexander H. Flannery,[3] Lucas J. Liu,[4] Augusto Cama-Olivares,[5] Jin Chen,[6] Sarah C. Huen,[7] Ashita J. Tolwani,[1] Javier A. Neyra.[1] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan; [3]University of Kentucky, Lexington, KY; [4]Fred Hutchinson Cancer Center, Seattle, WA; [5]Brookwood Baptist Health, Birmingham, AL; [6]The University of Alabama at Birmingham, Birmingham, AL; [7]The University of Texas Southwestern Medical Center, Dallas, TX.*

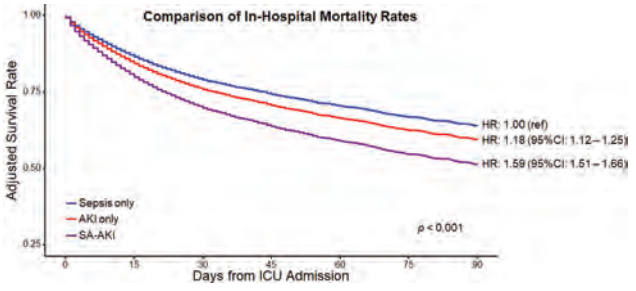
Background: The Acute Dialysis Quality Initiative defines sepsis-associated acute kidney injury (SA-AKI) as meeting both Sepsis-3 and KDIGO criteria within 7 days of sepsis diagnosis. We aim to evaluate the epidemiology of SA-AKI based on this contemporary definition.

Methods: This multicenter retrospective cohort study used EHR data from two academic hospitals, focusing on ICU admissions for individuals aged ≥18 from 2/2010 to 6/2022. Patients with ESKD or kidney transplant were excluded. Using culture and antibiotic timestamps, we identified infection occurrence and classified sepsis if the SOFA score reached 2 or more during the same period. AKI was identified using KDIGO serum creatinine (SCr) and urine output criteria. We compared patients with SA-AKI to those who developed AKI without sepsis (AKI only) and those who developed sepsis without AKI (sepsis only). Clinical outcomes included in-hospital mortality and major adverse kidney events at discharge (MAKE), evaluated by multivariable Cox regression and logistic regression models, respectively.

Results: Among 187,888 identified ICU patients, 63,621 developed sepsis, and 70,692 developed AKI. Of these, 29,615 met the SA-AKI criteria. The median age of ICU patients was 59 [IQR: 47, 70] years, with 43.3% being women. The prevalence of diabetes, cardiovascular disease, and chronic kidney disease was 21.6, 30.4, and 13.7%, respectively. In-hospital mortality was 11.2 for sepsis only, 11.8 for AKI only, and 25.0% for SA-AKI, and the HRs were 1.18 (95% CI: 1.12-1.25) for AKI only and 1.59 (1.51-1.66) for SA-AKI, with sepsis only as the reference group (Figure). The incidence of MAKE was 12.9 for sepsis only, 18.6 for AKI only, and 37.7% for SA-AKI, and the ORs were 1.58 (1.50-1.66) for AKI only and 3.35 (3.19-3.51) for SA-AKI, with sepsis only as the reference group.

Conclusions: In critically ill adults, SA-AKI is a frequent condition that is associated with increased mortality and a higher incidence of MAKE compared to sepsis only and AKI only.

Funding: NIDDK Support



FR-PO071

Acute Kidney Disease Staging Based on Estimated Glomerular Filtration Rate Predicts Outcomes Better than Staging Based on Serum Creatinine in Patients with Dialysis-Requiring AKI

Szu-Yu Pan,[1] Naichi Teng,[2] Likwang Chen,[2] Vincent Wu.[1] *[1]National Taiwan University Hospital, Taipei, Taiwan; [2]National Health Research Institutes, Zhunan, Taiwan.*

Background: The comparative performance of two staging systems for acute kidney disease (AKD), designated AKD_{eGFR} and AKD_{sCr}, remains uncertain. Our objective is to assess the predictive ability of these staging systems concerning outcomes.

Methods: This population-based retrospective observational cohort study identified 71,289 hospitalized patients with acute kidney injury requiring dialysis between July 1, 2015, and June 30, 2022, in the Taiwan National Health Insurance Research Database. AKD stages were defined according to the ADQI 16 Workgroup (AKD_{sCr}) and 2021 KDIGO Consensus (AKD_{eGFR}). Cox proportional hazard models were constructed to examine associations between AKD stages and outcomes including mortality and sustained renal recovery.

Results: The AKD_{eGFR} staging system predicted both outcomes better than the AKD_{sCr} staging system (**Figure 1**). Hazard ratios and 95% confidence intervals for mortality across increasing AKD_{eGFR} stages were 1.27 (1.18 - 1.36), 1.70 (1.59 - 1.82), 2.49 (2.35 - 2.64), 2.96 (2.78 - 3.15), and 5.22 (5.02 - 5.43). Conversely, within the AKD_{sCr} staging system, hazard ratios and 95% confidence intervals for mortality across ascending stages were 1.00 (0.93 - 1.07), 1.00 (0.91 - 1.10), 0.93 (0.81 - 1.07), and 3.37 (3.27 - 3.46). Subgroup and sensitivity analyses yielded consistent results.

Conclusions: The AKD_{eGFR} staging system performs better than the AKD_{sCr} staging system in patients with acute kidney injury requiring dialysis regarding all-cause mortality and kidney recovery.

Funding: Government Support - Non-U.S.

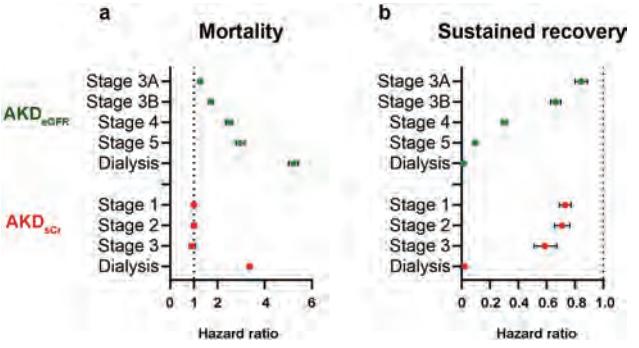


Figure 1. The adjusted hazard ratios (HRs) for mortality (Figure 1a) and sustained renal recovery (Figure 1b) across AKD stages in the AKD_{eGFR} (up) and AKD_{sCr} (down) staging systems were shown. AKD stage 0 served as the reference. Dots and error bars represented the point estimates and the 95% confidence intervals of the HRs.

FR-PO072

Machine Learning-Derived Personalized Fluid Intake Strategy in Sepsis-Associated AKI

Wonsuk Oh, Kullaya Takkavatakarn, Roopa D. Kohli-Seth, Girish N. Nadkarni, Ankit Sakhuja. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Sepsis associated acute kidney injury (SA-AKI) is common and associated with poor outcomes. While intravenous fluids are mainstay of therapy for these patients, recent literature suggests that restrictive fluid administration may be beneficial in certain patients with SA-AKI. This study aims to identify SA-AKI patients who would benefit from restrictive fluid administration.

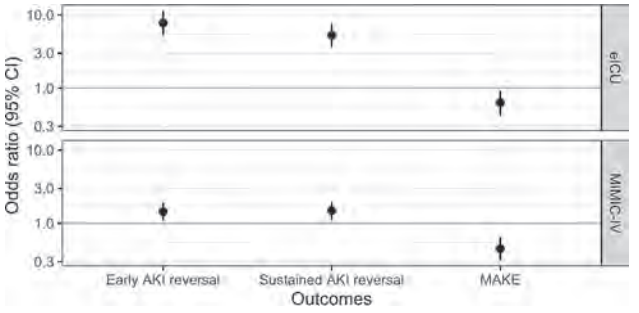
Methods: This retrospective study used eICU database for development and MIMIC-IV for external validation. We identified 2,086 SA-AKI patients in eICU and 6,532 patients in MIMIC-IV using KDIGO criteria for AKI. We defined restrictive fluid as administration of <500mL of fluid in 24 hours after SA-AKI. Primary outcome was early AKI reversal within 48 hours of AKI onset. Secondary outcomes included sustained AKI reversal for at least additional 48 hours after early AKI reversal and Major Adverse Kidney Events (MAKE) by discharge (defined as death, need for new dialysis, or discharge creatinine>=200% of baseline). We used causal tree and policy tree algorithms to estimate individual treatment effects and identify patients benefiting most from fluid restriction, and multivariable logistic regression to assess its impact on outcomes.

Results: 38% patients in the eICU and 43% patients in MIMIC-IV were recommended restrictive fluids. Among those recommended, only 26% patients in eICU and 8% patients in MIMIC-IV received restrictive fluids. Among patients that were recommended restrictive fluids, those that received had higher rates of early AKI reversal (eICU: 73% vs 27%, p<.01; MIMIC-IV: 53% vs 44%, p<.01) and sustained AKI reversal (eICU: 52%

vs 18%, p<.01; MIMIC-IV: 36% vs 29%, p<.01), and lower rates of MAKE at discharge (eICU: 26% vs 38%, p<.01 ; MIMIC-IV: 20% vs 32%, p<.01) in both eICU and MIMIC-IV (validation set). These effects were similar after adjustment of confounders (Fig 1).

Conclusions: In this study using a novel, machine learning approach we have developed and validated a strategy to identify SA-AKI patients who would benefit from a restrictive fluid administration.

Funding: NIDDK Support



FR-PO073

Multisystemic Support Therapies for AKI in Latin America: Current Status and Preliminary Report

Lilia M. Rizo Topete,[1] Dario Xavier Jimenez Acosta,[2] Rolando Claure-Del Granado,[3] Olynka Vega,[4] Alejandra Molano-Triviño,[5] Daniela Ponce,[6] David A. Ballesteros Castro.[7] SLANH AKI and Blood Purification Committee. *[1]Hospital Universitario "Jose Eleuterio Gonzalez", Universidad Autonoma de Nuevo Leon, Monterrey, Mexico; [2]Hospital Enrique Garces, Quito, Ecuador; [3]Universidad Mayor de San Simon, Cochabamba, Bolivia, Plurinational State of; [4]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [5]Fundacion Cardioinfantil Instituto de Cardiologia, Bogota, Colombia; [6]Universidade de Sao Paulo Instituto de Ciencias Biomedicas, Sao Paulo, Brazil; [7]Universidad del Cauca, Popayan, Colombia.*

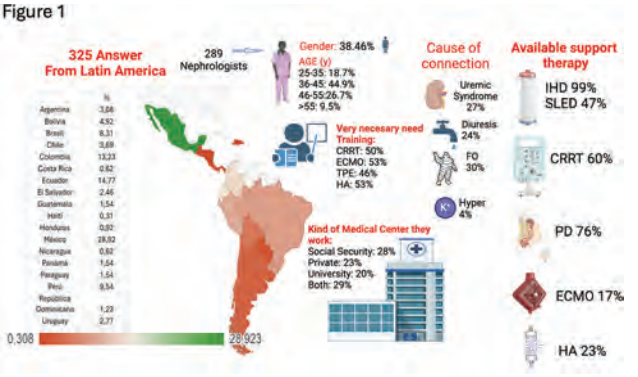
Background: Kidney replacement therapy (KRT), including extracorporeal organ support (ECOS), is vital for treating acute kidney injury (AKI). Understanding available resources is crucial. Therefore, the Acute Kidney Injury Committee of the Latin American Society of Nephrology and Hypertension (SLANH) surveyed to gather information on human resources and equipment for KRT/ECOS treatment of AKI in Latin America.

Methods: A 30-question survey form was created to assess KRT/ECOS characteristics, including human resources, equipment, and types of procedures. Conducted online using Google Forms®, the survey was available for four months.

Results: 325 responses were collected, 89% from nephrologists. Among the nephrologists, 38% were women, and the main age group was 35-45 years. Participants were from 18 countries, with the highest responses from Mexico (29%), Ecuador (15%), and Colombia (13%). The survey highlighted the need for more training in CRRT (50%), ECMO (53%), ECCO2R (47.6%), TPE (46%), and HA (53%). Notably, 80% of participants' hospitals lacked ECMO. The most available therapies were IHD, CRRT, and PD, with the most common machines being IHD, PD, and CRRT. Only 42% could perform TPE, and 28% could provide other liver support therapies, with hemoadsorption available to only 23%. Nephrologists were responsible for prescribing therapies in 80% of cases, with joint decisions in 15%. The most frequent indication was fluid overload (30%), followed by uremic syndrome (26%) and oliguria (24%). Heparin was the most used anticoagulant for CRRT in Latin America (72%).

Conclusions: The lack of statistics in our region is a reality, but the shortage of technologies, equipment, and opportunities for patients and trainees is overwhelming. The new era of renal replacement therapies, like CRRT as a platform for other ECOS therapies, is in the hands of young nephrologists who need support and training.

Figure 1



FR-PO074

Hemodialysis Factors Associated with Kidney Function Recovery in Patients with AKI Receiving Outpatient Dialysis

Seda Babroudi,[1] Hocine Tighiouart,[2,1] Daniel E. Weiner,[1] Javier A. Neyra,[3] Ronald Sanders,[4] Harold Manley,[4] Eduardo K. Lacson,[4,1] David A. Drew.[1] *[1]Tufts Medical Center, Boston, MA; [2]Tufts Medical Center Institute for Clinical Research and Health Policy Studies, Boston, MA; [3]UAB Hospital, Birmingham, AL; [4]Dialysis Clinic Inc, Nashville, TN.*

Background: Patients with acute kidney injury receiving outpatient dialysis (AKI-D) represent 10% or more of annual new hemodialysis starts in the United States, of whom approximately one-third recover kidney function. We examined the relationship of novel hemodialysis prescription factors with kidney function recovery in patients with AKI-D.

Methods: Using a multi-center retrospective cohort design, we evaluated the association of hemodialysis treatment frequency, treatment duration, ultrafiltration rate, net ultrafiltration, intradialytic hypotension, and dialysate temperature and electrolyte concentrations at baseline with kidney function recovery to dialysis independence among patients with AKI-D who initiated dialysis between 2017 and 2021 at a medium-sized dialysis provider. We used Cox proportional hazard models adjusting for demographic and clinical factors.

Results: 2,544 adults with AKI-D treated across 238 dialysis facilities were analyzed. The mean (SD) age was 65 (14.2) years, 58% were men, and 19% were Black. A total of 857 (34%) patients recovered kidney function, with a median (IQR) time-to-kidney function recovery of 29 (17,54) days. Fewer than three hemodialysis treatments per week significantly positively associated with kidney function recovery as compared to three or more treatments per week in the first thirty days. Longer treatment duration, higher net ultrafiltration, and higher ultrafiltration rate significantly negatively associated with kidney function recovery after multivariable adjustment (Table 1). Intradialytic hypotension and hemodialysate characteristics did not associate with kidney function recovery.

Conclusions: Among patients with AKI-D, longer treatment duration, higher net ultrafiltration, and higher ultrafiltration rate significantly negatively associated with kidney function recovery. Fewer than three hemodialysis treatments per week, however, significantly positively associated with kidney function recovery. These results support further study of ultrafiltration rate thresholds and dialysis deprescribing to promote kidney recovery.

Funding: Other NIH Support - National Center for Advancing Translational Sciences, National Institutes of Health, Award Number TL1TR002546

Table 1. Association of hemodialysis factors at baseline with kidney function recovery

	Univariate HR (95% CI)	Adjusted HR (95% CI)
Treatment frequency (before 30 days)		
≥3 sessions/week	*ref*	*ref*
<3 sessions/week	3.51 (2.92, 4.23)	2.88 (2.38, 3.49)
Treatment duration (for every 15min increase)	0.91 (0.87, 0.94)	0.94 (0.90, 0.98)
Net ultrafiltration (for every 1kg increase)	0.55 (0.51, 0.60)	0.72 (0.62, 0.84)
Ultrafiltration rate (for every 1mL/kg/hr increase)	0.83 (0.81, 0.85)	0.92 (0.89, 0.96)

Adjusted for age, sex, body mass index, diabetes mellitus, hypertension, cardiovascular disease, congestive heart failure, cirrhosis, albumin, hemoglobin, inter-dialytic weight gain (proxy for urine output), and nadir pre-treatment SBP systolic blood pressure

FR-PO075

Cumulative Detrimental Effect of Hypotension during Intermittent Hemodialysis on Kidney Recovery in Critically Ill Patients with AKI Requiring Dialysis

Joonhee Yoon, Kipyo Kim. *Inha University, Incheon, Republic of Korea.*

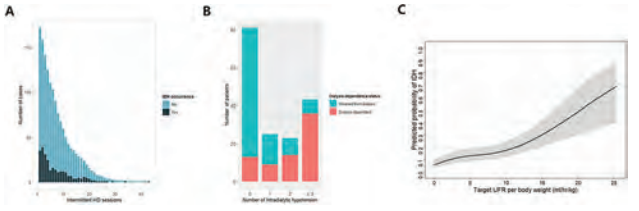
Background: Acute kidney injury requiring dialysis (AKI-D) severely affects the mortality and kidney outcomes of critically ill patients. Intermittent hemodialysis (IHD) is commonly implemented throughout the entire period of kidney replacement therapy

(KRT) in AKI-D patients, irrespective of initial modality of KRT. There remain concerns about hemodynamic instability during IHD, but the impact of intradialytic hypotension (IDH) during IHD on kidney recovery remains undetermined.

Methods: We retrospectively enrolled individuals who were diagnosed with AKI and received IHD at intensive care units of Inha University from January 2018 to February 2024. IDH was defined as having a nadir systolic blood pressure < 90 mmHg, newly starting vasopressors or increasing the dose during IHD sessions, or early termination of dialysis due to hemodynamic instability. We ascertained IDH occurrences and dialysis dependence at discharge in survivors from AKI-D.

Results: Of a total of 1,473 patients received kidney replacement therapy due to AKI, 765 patients died, and 276 patients did not undergo IHD. Therefore, 172 patients receiving IHD were included in the main analysis. Median number of IHD sessions were 7.0 (IQR 3-11.5), and the proportion of IDH per patient was approximately 14%. Of these, 67 patients (45.9%) were dialysis-dependent at discharge. Multivariable logistic regression analyses revealed the number of IHD (as a continuous variable) was a significant predictor for dialysis dependence (OR, 1.71; 95% CI, 1.17-2.64). When the number of IHD was categorized (0, 1-2, and ≥3), the risk of dialysis dependence was substantially higher for individuals with the number of IDH ≥3 compared to those without IDH (OR, 10.41; 95% CI, 2.22-58.93). In the per-session analysis, target UFR was the independent risk factor for IDH occurrence.

Conclusions: Our study revealed that IHD-related hypotension during hospitalization has the cumulative adverse impact on kidney recovery in AKI-D survivors. To improve kidney outcomes following AKI-D, the prevention for hemodynamic instability during IHD might be crucial.



FR-PO076

Predicting Which Newborns Will Benefit from Early Peritoneal Dialysis following Cardiac Surgery: A Quest for Precision Medicine with Comparative Outcomes

Ali Mirza Onder. *Nemours Children's Hospital Delaware, Wilmington, DE.*

Background: This retrospective single center study was conducted to investigate the accuracy of a clinical strategy in predicting newborns who will benefit from early peritoneal dialysis (PD) following cardiac surgery (post-op). Comparative outcomes are reported.

Methods: There were forty-nine newborns. PD catheters were placed for all in the operating room (OR) following cardiopulmonary bypass (CPB). Those with longer CPB times, post-op oligo-anuria and worsening fluid overload were selected for early PD start (PD +). All PD + were started within the first post-op 24 hours. The primary outcomes were 5% fluid overload at post-op 48 hours and severe AKI at post-op day 5.

Results: Twenty-nine subjects were started on early PD (PD +) and twenty used the PD catheter as abdominal drain (PD -). Baseline demographic data were indifferent. Both groups were oliguric during post-op first 8 hours (p= 0.906). The Early PD (+) group produced significantly less urine output during post-op day 1 (0.98 vs 3.02 ml/kg/hour; p= 0.001). At post-op 48 hours, early PD (+) group had similar prevalence of 5% fluid overload as early PD (-) group, (p= 0.427). Severe AKI incidence at post-op day 5 was low and similar between the groups (17.3% vs 5.0%; p=0.204).

Conclusions: Persisting oliguria during post-op 24 hours may successfully identify those who will benefit from early PD. The first post-op 8 hours was indiscriminative for this decision. Placing the PD catheter in the OR may be an advantage. Early PD start may ameliorate the disadvantage for the designated group.

FR-PO077

Patterns of Readmission and Death after Admission with AKI: A Data-Linkage Study

Zena Barakat, Timothy J. Pianta. *Northern Centre for Health Education & Research, Epping, VIC, Australia.*

Background: Despite episode-level data, and health-service level studies, patient-level incidence of AKI across Australia or its major jurisdictions has not been characterized to date. Important outcomes including discharge to residential aged care, hospital readmission, and mortality remain undefined. Data linkage allows clarification of patient-level outcomes across a jurisdiction to permit system-level policy and planning and potentially refine resource allocation.

Methods: Data linkage analysis of jurisdiction-wide administrative data in Victoria, Australia. The study linked the Victorian Admitted Episodes Dataset (VAED), Victorian Death Index (VDI), Victorian Integrated Non-admitted Health (VINAH), and Victorian Cancer Registry (VCR) in July 2016 to June 2017. Index admissions with AKI were defined with follow up to 36 months.

Results: 2,817,000 admissions were complicated by AKI in 198,966 (7.1%) episodes of care in Victorian hospitals. 38,033 individual adult patients accounted for the 96,549 AKI episodes identified in adults admitted overnight to acute care. AKI incidence was greatest amongst elderly (age ≥75 years; 57.6%), overseas-born, and comorbid patients, but paradoxically less amongst socioeconomically disadvantaged patients. Inpatient mortality complicated 1,984 (5.2%) of the index admissions. Most AKI survivors were readmitted [23,757 (65.9%)] at least once (median 3, range 0 – 33), and a majority [20,244 (85.2%)] experienced recurrent AKI within 12 months. At 12-months, overall mortality was 27.2%, and 22.9% amongst survivors of the index episode with 28.0% of these deaths within 30 days. At 3 years, overall mortality was 46.2%. Cancer was the leading cause of death followed by cardiovascular disease, sepsis, dementia, and kidney failure.

Conclusions: Despite likely underreporting of AKI in Victoria, AKI was a commonly reported and relapsing condition of predominantly elderly patients. An index episode of AKI was associated with recurrent admission and recurrent AKI in most patients. Discharge to a residential aged care facility was common. AKI was associated with high mortality, most commonly attributable to cancer rather than cardiovascular disease. Education, interventional studies, and policy can better reflect the epidemiology of AKI. Further analysis should clarify previously unexplored interactions between AKI, cancer, residential aged care, avoidable readmission, and mortality.

FR-PO078

Value of Post-AKI Protein-to-Creatinine Ratio (PCR) in Discriminating Risk of Kidney Disease Progression: Insights from the CRIC Study

Yuenting D. Kwong,[1] Kathleen D. Liu,[1] Alan S. Go,[6] Ian E. McCoy,[1] Anthony N. Muiru,[1] Matthew R. Weir,[2] Mark L. Unruh,[3] Hernan Rincon-Choles,[4] L. Lee Hamm,[5] Jing Chen,[5] Jesse Y. Hsu,[7] Xiaoming Zhang,[7] Chi-yuan Hsu.[1] *[1]UCSF Medical Center, San Francisco, CA; [2]University of Maryland Medical System, Baltimore, MD; [3]University of New Mexico Health System, Albuquerque, NM; [4]Cleveland Clinic, Cleveland, OH; [5]Tulane University, New Orleans, LA; [6]Kaiser Permanente, Oakland, CA; [7]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: Proteinuria after AKI quantified by albumin-to-creatinine ratio (ACR) measured 3 months after AKI is a strong discriminator for rapid loss of kidney function (c-statistic 0.82 in Hsu JAMA 2020). Measuring proteinuria by protein-to-creatinine ratio (PCR) after AKI is less expensive and expanding the timing for collection beyond 3 months may increase flexibility in processes of care. Limited knowledge exists on the implications of using post AKI PCR collected within 1 year in discriminating risks of kidney disease progression in patients with pre-existing CKD.

Methods: We followed participants who had AKI between 7/1/2013-12/1/2021 in the Chronic Renal Insufficiency Cohort (CRIC) cohort from the time of first post AKI PCR within 1 year of AKI discharge to the primary outcome of kidney disease progression defined by halving of eGFR or progression to ESKD. Cox proportional hazards modeling was applied to evaluate the association of log-transformed post AKI proteinuria with kidney disease progression. Analysis was repeated after adjusting for demographic variables, diabetes status, BMI, eGFR, AKI stage, systolic blood pressure, and use of ACEi and ARBs.

Results: 554 CRIC participants had PCR measured a median of 147 [IQR 79-233] days after AKI discharge. Their mean age was 67 years, 43% were female and 51% were non-Hispanic Black. Mean initial post AKI eGFR was 43 mL/min/1.73m^2 and PCR was 0.3 g/g. 82% had AKI stage 1, 15% had AKI stage 2, and 3% had AKI stage 3. Over the mean follow-up of 2.6 years, 124 had kidney disease progression. Higher post AKI PCR was associated with increased risk of kidney disease progression (hazard ratio 2.01 for each doubling of proteinuria 95% CI 1.63-2.49). Post AKI PCR was a strong discriminator of kidney disease progression (c-statistic 0.80 in the unadjusted model, 0.86 in the adjusted model with clinical risk factors). AKI severity was not associated with kidney disease progression.

Conclusions: Proteinuria evaluation by PCR obtained any time up to 1 year after AKI was independently associated with subsequent kidney disease progression in patients with CKD and may be a low cost, flexible alternative to ACR at 3 months for detecting those at risk of kidney disease progression after AKI.

Funding: NIDDK Support

FR-PO079

Quantifying Change in Proteinuria after AKI among Patients with CKD from the CRIC Study

Yuenting D. Kwong,[1] Kathleen D. Liu,[1] Alan S. Go,[2] Anthony N. Muiru,[1] Ian E. McCoy,[1] Matthew R. Weir,[3] Mark L. Unruh,[4] Hernan Rincon-Choles,[5] L. Lee Hamm,[6] Jing Chen,[6] Jesse Y. Hsu,[7] Xiaoming Zhang,[7] Chi-yuan Hsu.[1]
[1]UCSF Medical Center, San Francisco, CA; [2]Kaiser Permanente, Oakland, CA; [3]University of Maryland Medical System, Baltimore, MD; [4]University of New Mexico Health System, Albuquerque, NM; [5]Cleveland Clinic, Cleveland, OH; [6]Tulane University School of Medicine, New Orleans, LA; [7]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Background: Few studies have rigorously investigated if increased proteinuria is an important pathway by which AKI contributes to development or progression of CKD. Numerous published studies lacked appropriate non-AKI controls; Parr et al (KI 2018) relied on semiquantitative dipstick measurements obtained as part of clinical care and Hsu (JASN 2019) included only participants hospitalized shortly before enrollment. Neither study focused exclusively on patients with CKD, who are particularly vulnerable to AKI. To fill this knowledge gap, we analyzed data from the multicenter, prospective Chronic Renal Insufficiency Cohort (CRIC) study.

Methods: We analyzed CRIC study data from 7/1/2013-12/1/2021. Hospitalized AKI was defined as ≥1.5 peak to nadir inpatient serum creatinine (SCr). Mixed effects regression was applied to examine the association between AKI and natural log-transformed urine protein creatinine ratio (uPCR) ascertained at yearly CRIC research study visits. We adjusted for sex, race, clinical center as well as time-updated age, eGFR, SBP, diabetes, number of anti-hypertensive medicines, and use of ACEi or ARB.

Results: The final cohort included 3,197 participants with mean age of 65 years, 44% were female, and 42% self-identified as non-Hispanic Black. The median baseline eGFR was 52 mL/min/1.73m2 and uPCR was 0.14g/g. During a median follow-up time of 6 years, 560 patients experienced AKI and 2637 did not. Most AKI episodes were stage 1 (65%) rather than stage 2 (28%) and stage 3 (7%). We quantified a 4% increase in uPCR (relative change ratio of 1.04, [95% CI 1.02-1.06, p<0.01) after an AKI episode in the multivariable adjusted model. More severe AKI was associated with a greater change in uPCR, with stage 3 AKI being associated with a 10% increase in uPCR (relative change ratio of 1.10, [95% CI 1.02-1.19], p=0.01).

Conclusions: Episodes of AKI may result in residual structural damage to the kidneys as reflected by worsening proteinuria. However, most of the proteinuria observed among AKI survivors was already present prior to AKI.

Funding: NIDDK Support

FR-PO080

Defining Key Elements of Communication after AKI: A Modified Delphi Process by the AKINow Workgroup

Yuenting D. Kwong,[1] Samuel A. Silver,[2] Javier A. Neyra,[3] Ian E. McCoy,[1] Jia Hwei Ng,[4] Emaad M. Abdel-Rahman,[5] Leslie S. Gewin,[6] Erin F. Barreto,[7] Bonnie L. Freshly,[8] Anitha Vijayan.[9] *[1]UCSF Medical Center, San Francisco, CA; [2]Queen's University, Kingston, ON, Canada; [3]The University of Alabama at Birmingham, Birmingham, AL; [4]Northwell Health, New Hyde Park, NY; [5]University of Virginia, Charlottesville, VA; [6]Washington University in St Louis, St Louis, MO; [7]Mayo Clinic Minnesota, Rochester, MN; [8]American Society of Nephrology, Washington, DC; [9]Intermountain Medical Center, Murray, UT.*

Background: Lack of consensus exists on the key elements of communication about an AKI event between inpatient and outpatient care teams and the information that should be provided to patients and their care partners. We aim to develop and refine standardized communication tools that promote AKI awareness and management based on consensus stakeholder feedback.

Methods: We conducted the first of three semi-structured sessions using the modified Delphi process. We recruited stakeholders through purposive and snowball sampling and surveyed them on a 5-point Likert scale (1-strongly disagree to 5-strongly agree) the population that should receive AKI education and the key elements of post-AKI communication. We then conducted virtual discussions to gather additional insights.

Results: The first session had 36 stakeholders from 7 countries, including 22 physicians (18 nephrologists), 4 nurses, 3 pharmacists, 2 physician assistants, 1 physical therapist, 3 patients with history of AKI, and 1 caregiver. The stakeholders strongly agreed (median rating 5) that AKI education should be provided to patients with AKI stage 2-3, AKI requiring dialysis (AKI-D), AKI with only partial recovery by discharge, and AKI in the setting of CKD stage 3-5. On communication between inpatient and outpatient care teams, the most strongly agreed upon elements were medications to be resumed (94%), baseline creatinine (88%) and discharge creatinine (85%). For patients on dialysis, last dialysis date (94%) and dialysis initiation date (91%) were important. On communication between care teams and AKI survivors, the most strongly agreed upon elements were medication changes (91%) and nephrotoxins to avoid (91%). For patients on dialysis, dialysis appointment (94%), AKI-D education (88%), and catheter care (85%) were important. Qualitative evaluation showed the need to further define who provides post-AKI education and care, preferred communication methods and timing, and actionable guidance on managing post AKI sequelae, especially medications and diet.

Conclusions: In the first of three sessions, stakeholders showed consensus on many key elements of AKI communication for care teams and patients. Subsequent sessions will refine standardized communication tools for clinical use.

Funding: NIDDK Support

FR-PO081

Multistate Modeling Patient Transitions from AKI to CKD or Death Using Electronic Health Records (EHR)

Jordan G. Nestor, Yilu Fang, Chunhua Weng. *Columbia University, New York, NY.*

Background: Patients with AKI are at high risk for CKD and death. The epidemiology of these transitions is poorly understood. This study aims to characterize patient health trajectories from the initial AKI episode to CKD or all-cause mortality using EHR data from NewYork-Presbyterian/Columbia University.

Methods: This retrospective study included 20,699 patients. Clinical states were identified by clustering patient vectors derived from temporal medical codes and serum creatinine (SCr) time series using natural language processing models. Transition probabilities between clinical states and to outcomes (CKD or death) were estimated using multi-state modeling.

Results: In the AKI cohort, 17% developed CKD and 19% died. We identified 15 clinical states with varying disease burdens. Each state had unique transition probabilities over 5 years (Figure). Risk factors for each outcome were identified within different AKI subpopulations based on clinical state trajectories (Table).

Conclusions: This study enhances our understanding of patient trajectories from an initial AKI episode to CKD diagnosis or death by tracking the progression of medical conditions, interventions, treatments, and SCr levels over time.

Funding: Other NIH Support - The project was supported by grants from the NIH (grants R01LM012895, R01HG013031, and UL1TR001873). Funding was also provided by the ASN KidneyCure-Harold Amos Medical Faculty Development Program (ASN-AMFDP) Grant (JGN)., Private Foundation Support

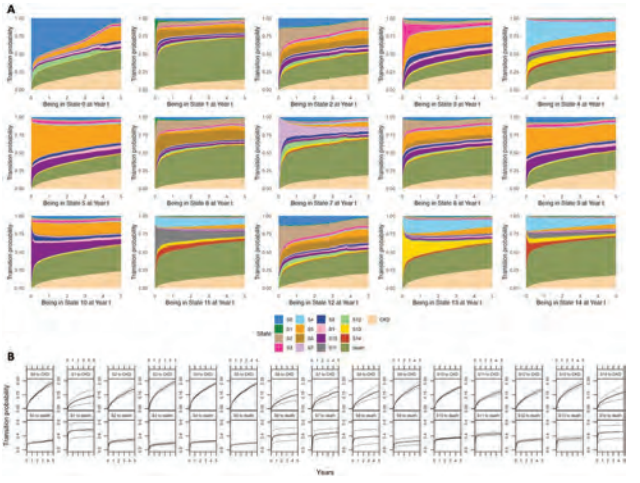


Figure: Transition Probabilities Between Clinical States Over a 5-Year Period

Outcome	First two states	Variable		All patients with identical first two states		
		Descriptor	Attribute	Average hazard ratio (95% CI)	Corrected p-value	N
CKD	S0->S1	Avg. Value (Day 1)	Albumin	0.517 (0.363, 0.735)	0.004	1416
	S0->S12	Pre-existing	DM	2.562 (1.489, 4.406)	0.015	1271
			NSAIDs	2.838 (1.509, 5.338)	0.015	
		Avg. Value (Day 1)	Body Temp.	2.503 (1.386, 4.519)	0.019	
	S4->S1	Pre-existing	Heart Failure	1.552 (1.213, 1.986)	0.008	2853
			Liver Disease	1.361 (1.082, 1.713)	0.046	
		Baseline	eGFR	0.991 (0.985, 0.997)	0.032	
		At encounter	Age	0.986 (0.980, 0.993)	0.001	
		Avg. Value (Day 1)	Body Temp.	2.343 (1.241, 4.422)	0.046	
			Systolic BP	1.023 (1.010, 1.037)	0.006	
			Sodium	0.979 (0.963, 0.995)	0.048	
	S4->S13	Pre-existing	Heart Failure	1.684 (1.181, 2.401)	0.041	1317
		At encounter	Age	0.987 (0.980, 0.995)	0.02	
		Avg. Value (Day 1)	Systolic BP	1.039 (1.019, 1.059)	0.003	
All-cause mortality	S0->S1	Pre-existing	NSAIDs	2.705 (1.672, 4.377)	0.001	1416
		At encounter	Age	1.017 (1.008, 1.027)	0.005	
		Avg. Value (Day 1)	Calcium	1.208 (1.076, 1.355)	0.01	
			Albumin	0.627 (0.499, 0.788)	0.001	
	S0->S12	At encounter	Age	1.021 (1.012, 1.030)	0	1271
		Avg. Value (Day 1)	Calcium	1.190 (1.062, 1.334)	0.045	
	S4->S1	At birth	Sex (male)	0.770 (0.632, 0.939)	0.045	2853
		Pre-existing	Liver Disease	0.706 (0.546, 0.913)	0.043	
		Avg. Value (Day 1)	Body Temp.	0.653 (0.519, 0.822)	0.009	
			Systolic BP	0.967 (0.946, 0.990)	0.042	
			Diastolyic BP	1.049 (1.014, 1.085)	0.042	
			Resp. Rate	1.082 (1.031, 1.135)	0.022	
			AST	1.000 (1.000, 1.000)	0.042	
	S5->S1	At encounter	Age	1.014 (1.007, 1.021)	0.001	1913
		Avg. Value (Day 1)	Body Temp.	0.707 (0.627, 0.797)	0	
			Total Bili	1.035 (1.016, 1.054)	0.003	
		Day 1	Sepsis	1.360 (1.099, 1.684)	0.037	
	S5->S10	At encounter	Age	1.015 (1.008, 1.022)	0.001	1909
		Avg. Value (Day 1)	Body Temp.	0.703 (0.624, 0.793)	0	
			Total Bili	1.036 (1.017, 1.055)	0.002	

Table: Risk Factors for CKD and All-Cause Mortality for Each Initial State Transition

FR-PO082

Predicting Persistent AKI Using Machine Learning: A Multicenter External Validation Study

Kianoush Kashani,[1] Simone Zappalà,[2] Francesca Alfieri,[2] Andrea Ancona.[2]
[1]*Mayo Clinic Minnesota, Rochester, MN;* [2]*U-Care Medical srl, Torino, Italy.*

Background: Acute Kidney Injury (AKI) correlates with higher morbidity and mortality, and its longer duration leads to acute and chronic kidney disease progression. Prompt interventions with externally validated prediction models for those at increased risk of AKI could change its course. We aim to validate the Persistent Electronic Alert (PersEA), a machine learning model, using routinely collected medical data in intensive care units, in predicting Persistent AKI.

Methods: Acute Kidney Injury (AKI) was defined and staged using Kidney Disease Improving Global Outcomes guidelines. Persistent AKI was defined as AKI stage 3 lasting for ≥72 hours or leading to death or necessitating renal replacement therapy. This retrospective study included Adult (≥18 years old) admissions at the Mayo Clinic exhibiting at least AKI stage 2. Model performance was assessed using a specific metric that penalizes late alarms, measuring the area under the receiver operating characteristic (auROC) and the area under the Precision-Recall (auPR) curves. The generalizability of the alerting system was measured through sensitivity, specificity, precision, and lead time under different cutoff criteria. The dataset was stratified into subpopulations according to the reason for admission, comorbidities, and demographics to measure possible biases.

Results: Among the ICU admissions at the Mayo Clinic, a cohort comprising 5,589 cases met the selection criteria and were subsequently included in the conclusive analyses. While the internal validation cohort demonstrated an 11% incidence of persistent AKI, the Mayo Clinic cohort exhibited a lower incidence of 5%. The PersEA model achieved an auROC of 0.98 (95% CI, 0.97-0.98) and an auPR of 0.67 (95% CI, 0.60-0.73). By selecting the threshold that reached 0.80 sensitivity in the internal cohort, PersEA achieved 0.88 sensitivity, 0.94 specificity, and 0.47 precision on Mayo Clinic data.

Conclusions: PersEA model exceptionally performed on an external cohort, showing that the model is scalable on high-quality data with little to no tuning once a noisy training set is chosen.

Funding: Commercial Support - U-Care Medical srl

FR-PO083

Six-Year Prospective Study of Kidney Outcomes after Withdrawal of Concurrent RAAS Blockade in Patients Presenting with New, Progressive, Otherwise Inexplicable AKI

Macaulay A. Onuigbo. *The University of Vermont Medical Center, Burlington, VT.*

Background: We described the new syndrome of late onset renal failure from angiotensin blockade (LORFFAB) in 2005 – this was new progressive AKI defined by >25% increase in baseline creatinine in patients on concurrent stable RAAS blockade in the absence of known traditional precipitating risk factors. We present a 6-year prospective follow-up in our previously reported Vermont cohort following withdrawal of RAAS blockade in the face of new progressive otherwise inexplicable AKI.

Methods: We conducted an ongoing interim prospective cohort analysis of patients enrolled between February 2018 and May 2021 in an outpatient Academic Nephrology Clinic in Vermont. Kidney function was monitored after elective withdrawal of long-term RAAS blockade in CKD patients presenting with new-onset otherwise inexplicable progressive AKI, defined by a >25% increase in baseline serum creatinine.

Results: In 2022, there were 51 surviving patients from the original Vermont cohort of 71 patients - baseline serum creatinine (SC) was 1.30 ± 0.42 (0.66-2.70) mg/dL, peak enrollment SC was 2.17 ± 1.06 (1.1-8.3) mg/dL, and SC after four years was 1.58 ± 0.54 (0.84-3.3) mg/dL. By May 2024, there were 9 deaths, 5 ESRD, and 8 were restarted on RAAS blockade. 30 patients were available for this analysis - M:F=12:18, age 74.4 ± 9.1 (64-99), latest SC 1.59 ± 0.6 mg/dL (0.71 – 3.63); latest eGFR 45.2 ± 20.4 (16-101). Of the 9 patients that died, cause of death was mostly cardiac, and the majority died despite improved or stable renal function. SC trajectory of one of these patients following withdrawal of Olmesartan in January 2020 is demonstrative (Figure).

Conclusions: There remains controversy as to the impacts of continuing versus discontinuing RAAS blockade in advanced CKD. Our report is peculiar since RAAS blockade was electively withdrawn in patients presenting with de novo progressive and otherwise inexplicable AKI. We believe that this specific group of patients unequivocally benefit from withdrawal of RAAS blockade (Figure).

↑- Olmesartan 40 mg daily since February 2024 was discontinued in January 2020 due to AKI

FR-PO084

Primary Care Perspectives (PCPs) on Monitoring and Follow-Up after Hospitalization with AKI

Saniya Kaushal,[1] Matthew T. James,[4] Samuel A. Silver,[2] Adeera Levin,[3,5] Peter C. Birks.[3] *[1]University College Cork School of Medicine, Cork, Ireland; [2]Queen's University, Kingston, ON, Canada; [3]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [4]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [5]BC Provincial Renal Agency, Vancouver, BC, Canada.*

Background: AKI is associated with an increased risk of chronic kidney disease (CKD), cardiovascular disease, and mortality. KDIGO guidelines recommend at minimum rechecking creatinine and urine albumin to creatinine ratio (ACR) within 3 months of AKI. Furthermore, nephrology referral after AKI remains low despite an association with improved patient outcomes. The objective of this study was to analyze perspectives of PCPs on monitoring and follow-up of AKI following hospitalization.

Methods: We surveyed Canadian PCPs using clinical vignettes about choices of laboratory monitoring and nephrology referral, following patient hospitalizations with AKI. The vignettes described various demographic and clinical factors, as well as different severities of AKI and degrees of AKI recovery.

Results: 53 PCPs participated, completing at least one question. 90% of PCPs would 'definitely' or "probably" suggest a follow-up creatinine within 3 months of patient hospitalization with AKI, irrespective of patient variables. Participants were more likely to 'definitely' or 'probably' suggest follow up creatinine in patients with less recovery of kidney function (98%), for those receiving dialysis (98%), and for those with comorbidities (100%). 80% or more of PCPs would 'definitely' or "probably" suggest a follow-up measurement of urine ACR within 3 months of AKI and were more likely to recommend proteinuria monitoring in those with pre-existing CKD (90%). Less than 50% of PCPs would 'definitely' refer to a nephrologist following a patient's AKI, unless they required acute dialysis during hospitalization (54%). Factors associated with increased referrals to nephrology included severe AKI (e.g. stage 3 AKI), less renal recovery, and comorbidities. Less than 25% of PCPs would 'definitely' or 'probably' seek specialist input prior to restarting a patient's ramipril, metformin, and empagliflozin post-AKI if the creatinine improved to 100 μmol/L.

Conclusions: Most PCPs suggest monitoring their patient's creatinine within 3 months of hospitalization with AKI. PCPs often would not refer to nephrology for follow up or medication advice after cases of moderate or severe AKI. Education and quality improvement initiatives warrant further testing to help PCPs optimally monitor and manage patients after a hospitalization with AKI.

FR-PO085

AKI Outcomes among Hospitalized Patients with Acute Myeloid Leukemia and Sepsis

Udit Nangia,[1] Prathap Simhadri,[3,4] Tomonori Takeuchi,[2] Hari Naga Garapati,[6] Sreekant Avula,[7] Nihar K. Jena,[8,9] Devansh H. Patel,[2] Prabhat Singh,[5] Deepak Chandramohan.[2] *[1]UH Parma Medical Center, Parma, OH; [2]The University of Alabama at Birmingham, Birmingham, AL; [3]AdventHealth East Florida, Daytona Beach, FL; [4]Florida State University, Tallahassee, FL; [5]Christus Spohn Health System, Corpus Christi, TX; [6]Baptist Medical Center South, Montgomery, AL; [7]University of Minnesota Twin Cities, Minneapolis, MN; [8]Trinity Health Oakland Hospital, Pontiac, MI; [9]Wayne State University, Detroit, MI.*

Background: Sepsis in patients with Acute Myeloid leukemia (AML) is a common cause of Acute kidney injury (AKI). Data on the outcomes of these patients is lacking.

Methods: We queried the 2016-2020 National Inpatient Sample (NIS) database to collect data on hospitalized adults with sepsis and AML. A multivariable logistic regression was performed while adjusting for potential confounders to generate adjusted odds ratios for the outcomes of interest. The outcomes assessed were inpatient mortality, length of stay (LOS), total hospital charges, fluid and electrolyte disorders, septic shock, vasopressor support, and the requirement for mechanical ventilation.

Results: Out of 288,435 hospital admissions of patients with sepsis and AML, 61,955 (21.4%) had AKI. Patients with AKI were older (mean age 66.1 vs. 60.4 years), more likely to be males (63.1% vs. 52.8%), more blacks were affected (12% vs. 9.2%) and overall had more comorbidities. Tumor lysis syndrome was present in 11.1%. Compared to patients without AKI, patients with AKI had higher LOS days (15.4±18 vs. 10.8±13.1, p<0.001 and hospital charges (229425.2 $ vs. 134930.3 $, p<0.001). Multivariable analysis showed that the patients with AKI had higher odds of mortality (OR: 3.8, 95% CI: 3.6-4.1, p<0.001). They also had a higher risk for electrolyte disorders (OR: 2.2, 95% CI: 2.1-2.4, p<0.001), septic shock (OR: 6.3, 95% CI: 5.7-6.9, p<0.001), vasopressor requirement (OR: 5, 95% CI: 4.3-5.8, p<0.001) and mechanical ventilation (OR: 5.2, 95% CI: 4.7-5.7, p<0.001).

Conclusions: AKI in patients with sepsis and AML was associated with higher mortality than sepsis alone. Further large studies are required to identify factors that could improve outcomes.

Variable	Sepsis in AML without AKI, n = 226480	Sepsis and AML with AKI, n = 61955	p-Value
Patient and hospital characteristics			
Age years, mean±SD	60.4±16.8	66.15±14.47	<0.001
Gender, n(%)			<0.001
Female	106915(47.2)	22910(36.9)	
Male	119565(52.8)	39045(63.1)	
Race, n(%)			<0.001
White	158825(70.1)	43605(70.3)	
African American	20965(9.2)	7455(12)	
Hispanic	21275(9.4)	4270(6.8)	
Hospital size, n(%)			<0.001
Small	26895(11.9)	7605(12.3)	
Medium	45030(19.9)	12055(19.4)	
Large	154555(68.2)	42295(68.3)	
Hospital location and teaching status, n(%)			<0.001
Rural	7075(3.2)	1475(2.3)	
Urban non teaching	22505(9.9)	6540(10.6)	
Urban teaching	196900(86.9)	53940(87.1)	
Medical insurance, n(%)			<0.001
Medicare	107380(47.4)	37215(60)	
Medicaid	28700(12.7)	5415(8.7)	
Private	78385(34.6)	16580(26.8)	
No insurance	4495(1.9)	935(1.5)	
Elixhauser comorbidity index, n(%)			<0.001
1	39205(17.3)	3480(5.6)	
2	47160(20.8)	7345(11.8)	
3-4	43195(19.1)	22435(36.2)	
>5	74600(33)	27790(36.7)	
AML status, n(%)			
AML, not in remission	153500(67.6)	44920(72.4)	<0.001
AML, relapse	32465(14.3)	9140(14.5)	0.241
AML, in remission	41405(18.1)	8175(13.1)	<0.001
Comorbidities, *n(%)*			
Hypertension	95585(42.2)	23190(37.4)	<0.001
Diabetes mellitus with complications	12035(5.3)	8435(13.6)	<0.001
Hyperlipidemia	63045(27.8)	20280(32.7)	<0.001
Congestive Heart Failure	28545(12.6)	16525(26.6)	<0.001
Coronary artery disease	31365(13.8)	12115(19.5)	<0.001
Cardiac arrhythmias	46645(20.6)	20710(33.4)	<0.001
Cerebrovascular disease	8235(3.6)	4310(6.9)	<0.001
Chronic kidney disease	19824(8.7)	19230(31)	<0.001
Tumor lysis syndrome	3220(1.4)	6915(11.1)	<0.001
Chronic obstructive pulmonary disease	35015(15.4)	10750(17.3)	<0.001
Moderate/severe liver disease	1420(0.6)	1145(1.8)	<0.001
Rheumatological disorders	5930(2.6)	1715(2.7)	0.401
Anemia	7525(3.3)	2725(4.4)	<0.001
Dementia	3765(1.6)	1655(2.7)	<0.001
Obesity	21990(9.7)	6910(11.1)	<0.001
Smoking	19060(8.4)	4020(6.4)	<0.001
Length of stay (LOS)	10.8±13.1	15.41±18	<0.001
Total charges	134930.3±234461.8	229425.2±368322.8	<0.001
Outcomes	**With AKI, n (%)**	**Adjusted OR (95% CI)**	***p*-Value**
All-cause mortality	14100(22.7)	3.87(3.60-4.16)	<0.001
Fluid and electrolyte disorders	36335(58.6)	2.29(2.18-2.41)	<0.001
Septic shock	11575(18.6)	6.31(5.77-6.90)	<0.001
Vasopressor support	34995(56.4)	5.0(4.32-5.85)	<0.001
Mechanical ventilation	9485(15.3)	5.29(4.79-5.79)	<0.001

AKI – Acute kidney injury, AML – Acute myeloid leukemia, CI – Confidence intervals, OR – Odds ratio, SD – Standard deviation

Multivariable analysis was performed by adjusting for age, gender, race, median household income for zipcode, Elixhauser comorbidity index, hospital region, hospital bedsize, hospital location and teaching status, insurance, staphylococcus infections, enterococcus infections, gram negative infections, hypertension, diabetes mellitus, diabetes mellitus with complications, hyperlipidemia, congestive heart failure, peripheral vascular disease, coronary artery disease, cardiac arrhythmias, cerebrovascular disease, chronic kidney disease, fluid and electrolyte disorders, chronic obstructive pulmonary disease, moderate/severe liver disease, rheumatological disorders, anemia, obesity, smoking status

FR-PO086

Outcomes of AKI among Hospitalized Patients with Infective Endocarditis

Deepak Chandramohan,[1] Prathap Simhadri,[9,2] Nihar K. Jena,[3,4] Sreekant Avula,[5] Prabhat Singh,[6] Renish Contractor,[2] Michael R. Filoramo,[2] Devansh H. Patel,[1] Boney J. Lapsiwala,[8] Divya Chandramohan.[7] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Florida State University, Tallahassee, FL; [3]Trinity Health Oakland Hospital, Pontiac, MI; [4]Wayne State University School of Medicine, Detroit, MI; [5]University of Minnesota Twin Cities, Minneapolis, MN; [6]Christus Spohn Hospital Corpus Christi Memorial, Corpus Christi, TX; [7]The University of Texas at San Antonio, San Antonio, TX; [8]Government Medical College Surat, Surat, India; [9]AdventHealth Daytona Beach, Daytona Beach, FL.*

Background: Patients with infective endocarditis (IE) are more susceptible to acute kidney injury (AKI). We aimed to assess the characteristics and outcomes of patients with AKI and IE.

Methods: The 2016-2020 National Inpatient Sample (NIS) database was utilized to include adult admissions with AKI and IE. A multivariable logistic regression was performed while adjusting for potential confounders to generate adjusted odds ratios for the outcomes of interest. The primary outcome was inpatient mortality. Secondary outcomes included length of stay (LOS), total hospital charges, septic shock, cardiogenic shock, vasopressor support, and requirement of mechanical ventilation.

Results: Of 63,725 admissions with IE, 16,295 (25.5%) had AKI. When compared with patients without AKI, patients with AKI were more likely to be male (63% vs. 57.6%, p<0.001), had higher Elixhauser Comorbidity Index >5 (73% vs. 44%, p<0.001), diabetes with complications (18.1% vs. 9.9%, p<0.001), congestive heart

failure (50.5% vs. 28.1%, p<0.001), cardiac arrhythmias (45.5% vs. 31.6%, p<0.001) and chronic kidney disease (36.2% vs. 13.6%, p<0.001). They also had higher LOS of 17±16.1 days and mean hospital charges of 239046.8 ± 303977.3 $. Multivariable analysis showed higher odds of mortality (OR: 2.22, 95% CI: 1.81-2.73, p<0.001), septic shock (OR: 3.78, 95% CI: 2.97-4.82, p<0.001), cardiogenic shock (OR: 3.37, 95% CI: 2.65-4.28, p<0.001), vasopressor requirement (OR: 1.99, 95% CI: 1.52-2.60, p<0.001) and mechanical ventilation (OR: 2.75, 95% CI: 2.33-3.24, p<0.001).

Conclusions: Our analysis demonstrated that patients with AKI and infective endocarditis had adverse hospital outcomes, increased mortality, LOS, and hospital costs.

Variable	Infective endocarditis without AKI, n = 47430	Infective endocarditis with AKI, n = 16295	p-Value
Age years, mean±SD	50.46±19.08	55.81±18.48	<0.001
Gender			<0.001
Female	20075(42.4)	6,040(37)	
Male	27340(57.6)	10,255(63)	
Race			0.0875
White	35340(74.5)	12100(74.2)	
African American	4810(10.1)	1610(9.8)	
Hispanic	3630(7.6)	1200(7.3)	
Hospital size			<0.001
Small	8620(18.1)	2360(14.4)	
Medium	12600(26.6)	4045(24.8)	
Large	26210(55.3)	9890(60.6)	
Hospital location and teaching status			<0.001
Rural	3385(7.1)	725(4.4)	
Urban non teaching	8460(17.9)	2220(13.6)	
Urban teaching	35585(75)	13350(81.9)	
Medical insurance			<0.001
Medicare	15985(33.7)	6715(41.2)	
Medicaid	15960(33.6)	4735(29)	
Private	9750(20.5)	3140(19.2)	
No insurance	1715(3.6)	1130(6.9)	
Elixhauser comorbidity index			<0.001
3-4	16515(34.9)	3585(22)	
>5	20900(44)	11896(73)	
Comorbidities			
Hypertension	15710(33.1))	4700(28.8)	<0.001
Diabetes mellitus with complications	4720(9.9)	2950(18.1)	<0.001
Hyperlipidemia	11730(24.7)	4429(27.1)	0.006
Congestive Heart Failure	13360(28.1)	8240(50.5)	<0.001
Coronary artery disease	9005(18.9)	4185(25.6)	<0.001
Cardiac arrhythmias	14995(31.6)	7425(45.5)	<0.001
Prosthetic valve	1840(3.8)	810(4.9)	0.008
Cerebrovascular disease	6545(13.7)	3265(20)	<0.001
Chronic kidney disease	6455(13.6)	5900(36.2)	<0.001
Chronic obstructive pulmonary disease	8365(17.6)	3325(20.4)	<0.001
Moderate/severe liver disease	685(1.4)	550(3.3)	<0.001
Rheumatological disorders	1260(2.6)	505(3)	0.193
Anemia	5145(10.8)	2130(13)	<0.001
Dementia	1340(2.8)	615(3.7)	0.006
Cancer	1165(2.4)	575(3.5)	0.001
Obesity	4905(10.3)	2460(15)	<0.001
Smoking	17355(36.5)	4364(26.7)	<0.001
Length of stay (LOS)	11.32±11.74	17±16.11	<0.001
Total charges	124857.6±192883.5	239046.8±303977.3	<0.001

Outcomes	With AKI, N	Multivariable Adjusted OR (95% CI)	*p*-Value
Mortality	1430	2.22(1.81-2.73)	<0.001
Septic shock	1375	3.78(2.97-4.82)	<0.001
Cardiogenic shock	1385	3.37(2.65-4.28)	<0.001
Vasopressor support	800	1.99(1.52-2.60)	<0.001
Mechanical ventilation	2580	2.75(2.33-3.24)	<0.001

AKI – Acute kidney injury, CI – Confidence intervals, SD – Standard deviation

Multivariable analysis was performed by adjusting for age, sex, race, hospital bedsize, hospital location and teaching status, insurance, hypertension, diabetes, hyperlipidemia, peripheral vascular disease, cerebrovascular disease, chronic kidney disease, fluid and electrolyte disorders, chronic obstructive pulmonary disease, moderate-severe liver disease, smoking

FR-PO087

Prognosis of Community-Acquired Kidney Injury in the Emergency Department

Telma H. Ragnarsdóttir,[1,2] Margret Kristjansdottir,[1] Gisli Gislason,[1,2] Runolfur Palsson,[1,2] Olafur S. Indridason.[1] *[1]Landspitali, Reykjavik, Iceland; [2]Heilbrigdisvisindasvid - Haskoli Island, Reykjavik, Iceland.*

Background: Acute kidney injury (AKI) is a common and serious complication of acute illness, significantly affecting outcomes. While the course and prognosis of hospital-acquired AKI has been thoroughly studied, the outcome of community-acquired AKI has not been well characterized. The aim of this study was to prospectively examine the outcome of patients with community-acquired AKI.

Methods: This was a prospective comparative cohort study in which serum creatinine (SCr) of all individuals presenting to the emergency department (ED) of Landspitali University Hospital were examined for the presence of AKI. All patients who met the SCr component of the KDIGO criteria for AKI were invited to participate. Randomly selected control cases (1:2) were paired according to age, sex, and date of ED admission. Participants answered questions about their medical history and use of medications. Past medical history was also obtained from medical records. Hospital admissions, re-admissions and survival rates were explored over a one-year follow-up period. Groups were compared using the $\chi 2$ test for categorical variables and t-test for continuous variables.

Results: During the study period, AKI was identified in 574 persons, 488 of whom participated in the study (512 cases). The mean (±SD) age of AKI cases and controls was 67.1±16.6 years and 67.2 ±16.2 years, respectively; 48% of cases and controls were female. AKI cases were significantly more likely than controls to be admitted to the hospital following the ED visit (77.1% vs 59.9%, p<0.001), and had longer hospital stays (8.0 ± 10.9 days vs 4.9 ± 15.4 days, p<0.001). Compared with the control group, in-hospital mortality was higher among AKI cases (6.3% vs. 2.4%, p<0.001), as was 90-day mortality (11.1% vs 4.9%, p<0.001) and one-year mortality (17.4% vs 11.2%, p<0.001). No significant difference in readmission rates within one month (14.9% vs 12.4%) or one year (40.8% vs 38.6%)- was observed.

Conclusions: Patients presenting to the ED with community-acquired AKI are significantly more likely to require hospitalization and experienced longer hospital stays, and higher mortality rates than those without AKI. However, the readmission rate is similar to controls.

Funding: Government Support - Non-U.S.

FR-PO088

Adverse Long-Term Outcomes following AKI in Hospitalized Children: A Meta-Analysis

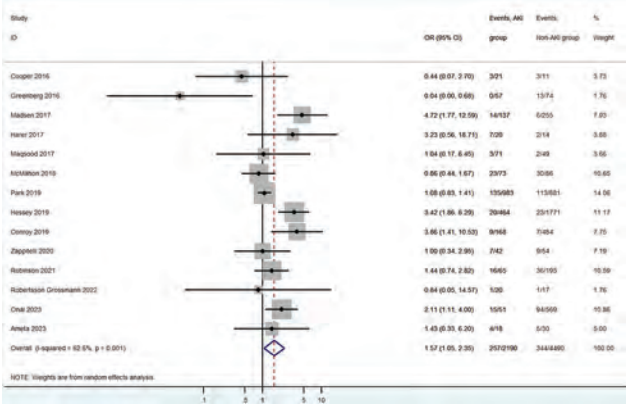
Jitendra Meena,[1] Shanzey Ali,[2] Dua Kamran,[5] Dima Sabeeh,[6] Heather M. Ajoy,[4] Jason H. Greenberg,[3] Cal Robinson,[7] Joginder Kumar Yadav,[8] Rahul Chanchlani.[2] *[1]All India Institute of Medical Sciences, New Delhi, India; [2]McMaster Children's Hospital, Hamilton, ON, Canada; [3]Yale University School of Medicine, New Haven, CT; [4]Toronto Metropolitan University Faculty of Science, Toronto, ON, Canada; [5]University of Waterloo Faculty of Science, Waterloo, ON, Canada; [6]McMaster University Faculty of Science, Hamilton, ON, Canada; [7]The Hospital for Sick Children, Toronto, ON, Canada; [8]Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

Background: Acute kidney injury (AKI) is common during pediatric hospitalizations and is associated with adverse short-term outcomes. However, long-term outcomes among survivors of pediatric AKI remain uncertain. We performed a systematic review to determine the risk of long-term outcomes following an episode of AKI.

Methods: We conducted a systematic literature search in EMBASE, PubMed, and Web of Science for studies reporting adverse events at least three months following AKI defined using standardized definitions in participants aged <18 year. We excluded studies if they reported outcomes in children with obstructive lesions, renal vascular disorder (i.e HUS), or solid organ transplantations. Random effect meta-analyses were performed to calculate pooled estimates.

Results: Of 12817 records identified through our initial search, 38 studies (14892 participants) were included in the final analysis. Pooled cumulative incidence of participants with CKD, mortality, proteinuria, and hypertension was 16% (95% CI: 12 to 19), 6% (3 to 8), 19% (11 to 26) and 13% (10 to 17) respectively, following an episode of AKI. Only 24 studies with follow up period ranging from 6 months to 15 years included a comparator group of patients without AKI. The odds of developing CKD was higher among children with AKI as compared to those without AKI (OR: 1.57, 95% CI: 1.05 to 2.35; Figure 1). Mortality was also higher after AKI (OR: 1.84, 95% CI: 1.28 to 2.63). There was no significant association between AKI and proteinuria (OR: 1.13, 0.63 to 2.03) or hypertension (OR: 1.27, 0.75 to 2.15) at follow up.

Conclusions: Children with AKI are at a higher risk of developing long-term CKD and mortality. These findings support enhanced surveillance of kidney function after an episode of AKI, with the aim of improving long-term kidney and patient survival.



Pooled odds ratio of chronic kidney disease

FR-PO089

Outcomes of AKI Hospitalization among Patients with Protein-Calorie Malnutrition: A Nationwide Analysis

Iskandar Berbari, M Kenan Rahima, Fayaz A. Khan. *TriHealth Inc, Cincinnati, OH.*

Background: AKI can lead to malnutrition due to reduced appetite, dietary restrictions and increased protein breakdown. Pre-existing malnutrition can also exacerbate AKI by impairing the body's ability to recover from kidney injury. Our objective is to examine outcomes among patients presenting with both AKI and protein-calorie malnutrition (PCM).

Methods: We accessed the National Inpatient Sample from 2017-2020 to identify adult patients with PCM hospitalized due to AKI. The primary outcome was inpatient mortality. The secondary outcomes included cardiac arrest, gastrointestinal bleeding (GIB), intubation, length of stay (LOS), and total hospital charges. We utilized multivariable logistic regression analysis to estimate clinical outcomes, considering a significance threshold of $P < 0.05$.

Results: We identified 19,300,000 hospitalizations with AKI, among which 1,687,445 (8.7%) presented with PCM. Patients with AKI and PCM exhibited higher rates of PVD and anemia, but lower occurrences of obesity, AFIB, DM, PVD, HF, dyslipidemia, CKD and HTN. Clinical outcomes revealed stark differences between PCM and Non-PCM cohorts: in-hospital mortality rates were 13% vs 7.3 % (OR 1.67, CI 1.6-1.7); cardiac arrest rates were not significantly different, GIB rates were 12.2% vs 5.8% (OR 2.1, CI 2.09-2.16), need for intensive care was 13.3% vs 7.8% (OR 1.55, CI 1.52-1.58); LOS was 12.2 days vs 6.9 days (IRR 1.71, CI 1.69-1.172); and hospital charges were $36,910 vs $20,164 (IRR 1.76, CI 1.72-1.78). All data demonstrated a p-value < 0.001 and were adjusted for various factors including age, sex, race, obesity, atrial fibrillation, diabetes mellitus, hypertension, peripheral vascular disease, acute kidney injury, chronic kidney disease, alcohol use, stroke, and inflation during 2017-2020.

Conclusions: Despite having lower rates of comorbidities, the PCM group showed significantly worse clinical outcomes, including substantially higher mortality rates, adverse events (GIB), prolonged hospital stays, and increased resource utilization. Clinicians should consider PCM as a negative predictor when managing patients with AKI. Improved patient safety and outcome can be achieved by optimizing inpatient nutrition.

FR-PO090

Impact of Kidney Replacement Therapy during Extracorporeal Membrane Oxygenation Support in Terms of Mortality: A Systematic Review and Meta-Analysis

Pramod K. Guru. *Mayo Clinic, Jacksonville, FL.*

Background: Renal replacement therapy (RRT) is frequently administered to patients receiving extracorporeal membrane oxygenation (ECMO). RRT helps to manage the fluid and electrolyte imbalances in ECMO-supported patients with or without evidence of advanced kidney failure. The use of RRT on ECMO has been linked to higher fatality rates in both adult and pediatric patients. There are many controversies concerning the timing, type, and temporal relationship of combined RRT and ECMO in patient outcomes. We aimed to analyze the impact on mortalities from the available studies in the use of a combination of these two extracorporeal systems.

Methods: We searched PubMed, EMBASE, and google scholar databases until February 2024 for case–control, cross-sectional, or cohort studies investigating the mortality of RRT on ECMO. We followed PRISMA guidelines to conduct the study. We filtered the study based on title and abstract followed by the full text. Data extraction was done in MS Excel and statistical analysis was done using RevMan v5.4. Relative risk (RR) and 95% confidence intervals (95% CIs) were pooled in the meta-analysis.

Results: We evaluated a total of 22 studies which included a total number of 6,117 patients who were on ECMO support. All the studies were of high quality, ranging from 7 to 9. The presence of RRT was associated with a significant increase in mortality (22 studies, Relative Risk (RR): 1.83, 95% CI: 1.61–2.07, $p < 0.001$ **Figure 1**, I2= 64%) when compared to patients on ECMO support alone.

Conclusions: Combination of simulatenous extracorpreal therapies by RRT & ECMO is associated with significantly high patient mortalites. Future studies ought to concentrate on reducing renal dysfunction in individuals on ECMO support, and determining the ideal time for initiation as well as form RRT in these patient population.

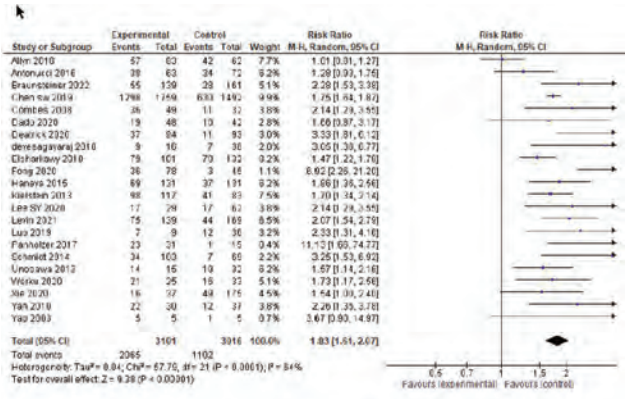


Figure 1: Forest plot showing increased risk of mortality in patients receiving combined therapies (ECMO: extracorporeal membrane oxygenation, RRT: renal replacement therapy).

Forest plot showing increased risk of mortality in patients receiving combined therapies (ECMO and RRT).

FR-PO091

Timing of Acute eGFR Declines in Acute Heart Failure and Their Association with Cardiovascular and Kidney Outcomes

Wendy I. McCallum,[1] Hocine Tighiouart,[1,3] Marcelle Tuttle,[1,3] Anuradha Lala-Trindade,[4] Maria Rosa Costanzo,[5] Isabel V. Bautista,[2] Tatsufumi Oka,[1] Jeffrey M. Testani,[2] Marvin Konstam,[1] Mark J. Sarnak.[1] *[1]Tufts Medical Center, Boston, MA; [2]Yale University School of Medicine, New Haven, CT; [3]Tufts Clinical and Translational Science Institute, Boston, MA; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]Midwest Cardiovascular Institute, Naperville, IL.*

Background: The association of declines in estimated glomerular filtration rate (eGFR) with cardiovascular and kidney outcomes in patients with acute heart failure (AHF) have been inconsistent, perhaps due to differences in assessment of timing of the decline.

Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, we used multivariable Cox regression models to evaluate the association between declines in eGFR at 48-hours after randomization, at hospital discharge and at 14-days after randomization with all-cause mortality, a composite of cardiovascular (CV) mortality and heart failure (HF) hospitalization, as well as with longer term kidney outcomes including eGFR decline by >40% and incident chronic kidney disease (CKD) Stage ≥4.

Results: Among 3931 patients over a median follow-up of 9.9 months, eGFR decline at 48-hours was not associated with mortality (aHR=0.96 [95% CI 0.85, 1.10] per 30% eGFR decline) or with the composite outcome of CV mortality or HF hospitalization (HR=0.95 [0.86, 1.06]), with similar results for eGFR decline at discharge. In contrast, eGFR decline at 14-days was associated with higher risk of mortality (aHR=1.32 [1.20, 1.46] per 30% eGFR decline) and the composite outcome (HR=1.19 [1.10, 1.29]). eGFR declines at the 48-hour, discharge and 14-day time points were associated with significantly higher risk of eGFR decline by >40% and incident CKD Stage ≥4 (Figure).

Conclusions: Among patients admitted for AHF, incorporating timing of acute declines in eGFR is pivotal for interpreting prognostic importance from the cardiovascular standpoint. In contrast, declines in eGFR at all time points are associated with worse longer term kidney function.

Funding: NIDDK Support

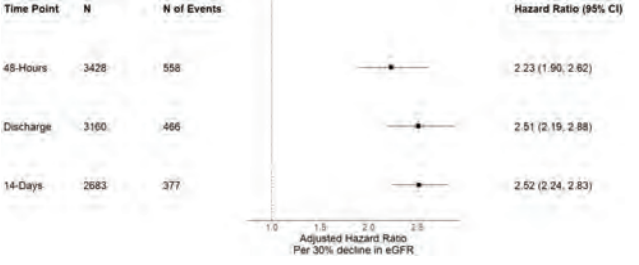


Figure. Adjusted hazard ratios for incident CKD Stage ≥4 based on three different time points of acute decline in eGFR: 48-hours after randomization, at the time of discharge, and 14-days following randomization. Hazard ratios displayed per 30% decline in eGFR.

FR-PO092

Evaluation of the Glomerular Filtration Rate in AKI by Kinetic Estimated Glomerular Filtration Rate in a Tertiary Referral Hospital in Mexico

Carolina Gonzalez-Fuentes, Pamela M. Prado Lozano, Martin B. Yama Estrella, Francisco J. Hernandez Copca, Nicte Alaide R. García, Fani G. Ruiz Rivera, Juana C. De La Torre, Victor M. Ulloa Galvan, Mario Alamilla-Sanchez, Martin O. Carbajal. *Centro Medico Nacional 20 de Noviembre ISSSTE, Mexico City, Mexico*.

Background: Estimating glomerular filtration rate (GFR) in acute kidney injury (AKI) is problematic as plasma creatinine changes rapidly. There is no widely accepted method for estimating renal function in AKI. Kinetic estimated GFR formula and creatinine clearance is an estimate of immediate biomarker clearance derived from two discrete measurements that may better represent the acute function. However, neither the kinetic GFR formula nor the four-hour creatinine clearance have been evaluated in the Mexican population.

Methods: Prospective, analytical study, in patients with acute kidney injury outside of critical care unit. Urinary creatinine clearance was performed along with the calculation of GFR using the kinetic estimated GFR formula and the 2021 CKD-EPI formula with creatinine-cystatin C.

Results: Data were analyzed for 68 patients with a mean age of 67.21 years, 61% were male, and 47% of patients had chronic kidney disease. The mean baseline creatinine was 1.4 mg/dl and the mean GFR was 65.85 mg/dl. The main aetiological factor for AKI was sepsis (33%), followed by cardiorenal syndrome. A Pearson correlation of 0.80 (p= 3.19e-16 CI 95 0.70-0.87) was found between the kinetic estimated GFR formula and four-hour creatinine clearance; concordance was analyzed by the Bland-Altman method with a mean difference of -0.14 with upper LoA of 21.10 (CI 95 16.4-25.7) and lower LoA -21.40 (CI 95 -26.0 -16.7). However, the concordance for the formula kinetic estimated GFR and 2021 CKD-EPI cystatin formula was 0.33.

Conclusions: In Mexican patients with AKI, there is no standardization for GFR calculation. However, with creatinine determinations, GFR can be estimated using the kinetic estimated GFR formula, although it can also be evaluated by 4-hour creatinine clearance, which showed statistical concordance. Evaluation of GFR in AKI with cystatin did not correlate well with either the kinetic estimated GFR formula or the 4-hour creatinine clearance.

FR-PO093

Impact of Baseline Kidney Function in Determining the Efficacy of Terlipressin in Patients with Hepatorenal Syndrome

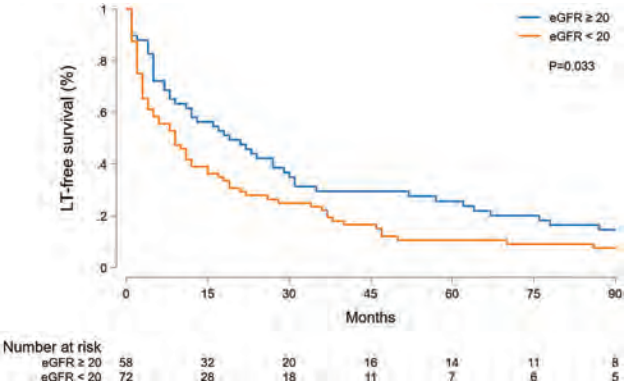
Seung Yun Chae,[1] Young soo Kim,[2] Yaeni Kim.[1] [1]*The Catholic University of Korea Seoul St Mary's Hospital, Seoul, Seo-cho gu, Republic of Korea;* [2]*The Catholic University of Korea Uijeongbu St Mary's Hospital, Uijeongbu, Gyeonggi-do, Republic of Korea*.

Background: We examined the influence of estimated glomerular filtration rate (eGFR) on survival outcomes in patients with hepatorenal syndrome undergoing treatment with terlipressin and albumin. This therapeutic strategy, acknowledged for its ability to improve survival rates and extend the waiting period for liver transplantation, is constrained by korean reimbursement policies. These policies necessitate a diagnosis of HRS-acute kidney injury (AKI) based on serum creatinine levels, thereby restricting the treatment to patients with markedly advanced conditions.

Methods: We performed a retrospective analysis of 130 patients diagnosed with hepatorenal syndrome who were treated with terlipressin and albumin. Our investigation focused on identifying factors linked to liver transplantation-free survival.

Results: In our study, which included patients with an average age of 56 and predominantly male (92%), liver failure was mainly caused by alcohol (71.5%), followed by hepatitis B (14.6%), non-alcoholic fatty liver disease (8.5%), hepatitis C (3.1%), and autoimmune hepatitis (2.3%). The median liver transplantation-free survival was 12 days. Patients with a MELD score greater than 30 had worse survival rates compared to those with a score less than 30. Additionally, individuals with an eGFR above 20 ml/min/1.73 m^2 showed better survival rates than those with an eGFR below 20. Logistic regression analysis identified eGFR below 20 and MELD scores above 30 as significant risk factors for reduced survival in both univariate and multivariate analyses.

Conclusions: Our study found that an increase in eGFR above 20 ml/min/1.73 m^2, along with a lower MELD score, correlated with better liver transplantation-free survival. This suggests that using eGFR rather than creatinine (Cr) as a criterion for terlipressin treatment may result in greater improvements in eGFR and thereby enhance survival outcomes.



LT-Free Survival Curves of Groups Divided by the eGFR cutoff of 20 ml/min/1.73 m^2

FR-PO094

In Vitro Assessment of Proenkephalin a 119-159 (PenKid) Removal in Hemofiltration, Hemodialysis, and Hemoadsorption

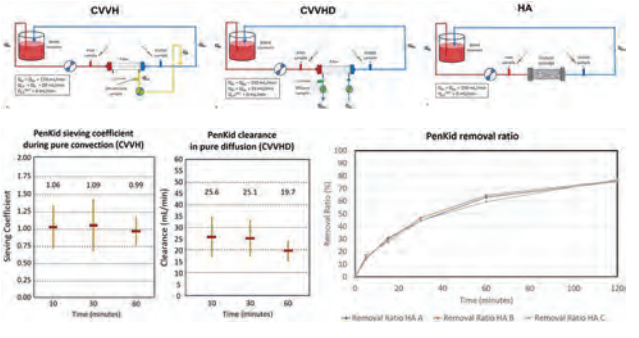
Anna Lorenzin,[1,2] Natascha Perin,[1,2] Massimo de Cal,[1,2] Alessandra Brendolan,[2] Paolo Lentini,[3] Monica Zanella,[1] Claudio Ronco.[2] [1]*Department of Nephrology, Dialysis and Transplantation, St. Bortolo Hospital, Vicenza, Italy;* [2]*International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy;* [3]*Department of Nephrology and Dialysis, St. Bassiano Hospital, Bassano del Grappa (Vicenza), Italy*.

Background: PenKid is a stable surrogate marker for enkephalins (endogenous opioids regulating kidney function). PenKid plasma concentration correlates to glomerular filtration rate and increases in acute kidney injury (AKI), therefore it can be used for prediction and diagnosis of AKI, need of renal replacement therapy (RRT), and prediction of the successful weaning. Whether the penKid concentration is affected by RRT, is a controversial point. To address the issue, we simulated *in vitro* different conditions of RRT: continuous veno-venous hemofiltration (CVVH) to determine the sieving coefficient, continuous veno-venous hemodialysis (CVVHD) to determine diffusive clearance, and hemoadsorption (HA) to define the penKid removal ratio.

Methods: Blood was spiked with lyophilized synthetic penKid to achieve target concentrations: 150 and 500 pmol/L in both CVVH and CVVHD, and 700 pmol/L in HA. For each experiment, a blood batch of 1L was utilized, at 37° and stirred. Circuits and flow rate set-up is shown in Figure 1. AV1000 dialyzer (Fresenius) was utilized for CVVH and CVVHD and samples were taken after 10, 30, 60 minutes from the initiation of circulation. A minimodule of HA380 cartridge (Jafron) was used for HA and samples were taken after 5, 15, 30, 60 and 120 minutes. All the experiments were conducted in triplicate.

Results: Initial penKid concentrations in blood corresponded to the desired targets in all the experiments. Significant removal of PenKid was observed (Figure 2): in CVVH sieving coefficients remained stable over time (1.04±0.27) in CVVHD clearance values decreased over time (23.08±0.89) in HA removal ratio displayed high values (76.1±1% after 120 minutes) Remarkable consistency in measured values was observed confirming a consistent interaction between the sorbent and penKid.

Conclusions: Significant removal of penKid was obtained by the extracorporeal modalities tested. Further investigation is needed to assess if these findings are confirmed during *in vivo* treatments.



FR-PO095

Urine Output at Continuous Kidney Replacement Therapy Discontinuation Predicts 1-Year Mortality and Kidney Outcome in Critically Ill Patients with AKI

Sungmi Kim,[1] Ji Won Min,[2] Eun jeong Ko,[2] Eun Sil Koh,[3] Hyung Duk Kim,[1] Byung ha Chung,[4] Yu Ah Hong.[5] *[1]The Catholic University of Korea Eunpyeong St Mary's Hospital, Eunpyeong-gu, Seoul, Republic of Korea; [2]The Catholic University of Korea Bucheon St Mary's Hospital, Bucheon, Gyeonggi-do, Republic of Korea; [3]The Catholic University of Korea Yeouido Saint Mary's Hospital, Yeongdeungpo-gu, Seoul, Republic of Korea; [4]The Catholic University of Korea Seoul St Mary's Hospital, Seocho-gu, Seoul, Republic of Korea; [5]The Catholic University of Korea Daejeon St Mary's Hospital, Daejeon, Republic of Korea.*

Background: Continuous renal replacement therapy (CRRT) is crucial for managing critically ill patients with acute kidney injury (AKI). However, the prognostic indicators for long-term prognosis after CRRT, especially present in the early stage of AKI, remain unclear. This study aimed to identify predictors of long-term clinical outcomes in patients with severe AKI, focusing on urine output (UO) at CRRT discontinuation.

Methods: This retrospective study included 851 AKI patients undergoing CRRT at three tertiary hospitals. Patients were categorized into four groups based on 24-hour UO at CRRT discontinuation. We analyzed one-year all-cause mortality and the development of end-stage kidney disease (ESKD).

Results: During one year after CRRT discontinuation, 333 (39.1%) of 851 patients died, and 150 (30.1%) of 499 patients progressed to ESKD. In multivariable analysis, UO was inversely associated with the risks of all-cause mortality (UO <100 ml/day: hazard ratio [HR] 3.08, 95% confidence interval [CI] 2.23–4.26, $P < 0.01$; UO 100–499.9 ml/day: HR 2.25, 95% CI 1.58–3.19, $P < 0.01$; UO 500–1499.9 ml/day: HR 1.71, 95% CI 1.18–2.47, $P < 0.01$), and the development of ESKD (UO <100 ml/day: odd ratio [OR] 16.17, 95% CI 7.67–34.09, $P < 0.01$; UO 100–499.9 ml/day: OR 7.50, 95% CI 3.48–16.18, $P < 0.01$; UO 500–1499.9 ml/day: OR 3.40, 95% CI 1.54–7.48, $P < 0.01$) when using UO ≥1500 ml/day as the reference category. There were linear relationships between UO and the risks of ESKD (P for nonlinearity = 0.07) and mortality (P for nonlinearity = 0.22) throughout a wide range of UO. Though diuretics use was not associated with ESKD risk and did not affect the association between UO and ESKD risk, UO remained significantly predictive of the risk of ESKD irrespective of diuretics use.

Conclusions: This study underscores the importance of monitoring UO in predicting long-term risks of ESKD and mortality in critically ill AKI patients undergoing CRRT.

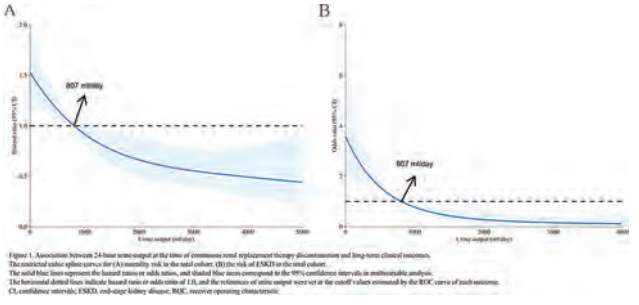


Figure 1. Association between 24-hour urine output at the time of continuous renal replacement therapy discontinuation and long-term clinical outcomes.
The restricted cubic spline curves for (A) mortality risk in the total cohort, (B) the risk of ESKD in the total cohort.
The solid blue lines represent the hazard ratios or odds ratios, and shaded blue areas correspond to the 95% confidence intervals in multivariable analysis.
The horizontal dotted lines indicate hazard ratio or odds ratio of 1.0, and the references of urine output were set at the cutoff values estimated by the ROC curve of each outcome.
CI, confidence intervals; ESKD, end-stage kidney disease; ROC, receiver operating characteristic

FR-PO096

Lower Fractional Excretion of Urinary Sodium among Patients with Muddy Brown Granular Casts Does Not Portend Lesser AKI Severity

Pooja A. Punukollu,[1] Vipin Varghese,[2] Joshua Baguley,[1] Conor Kiely,[1] Jaclyn R. Gerschultz,[1] Stephanie K. Lewis,[1] Rami N. Muhtaseb,[1] Dustin R. Chalmers,[4] Juan Carlos Q. Velez.[1,3] Ochsner Group. *[1]UQ-Ochsner Clinical School, New Orleans, LA; [2]University of Michigan Division of Nephrology, Ann Arbor, MI; [3]Ochsner Health, New Orleans, LA; [4]Louisiana State University, Baton Rouge, LA.*

Background: We previously reported poor concordance between fractional excretion of urinary sodium (FENa) and presence of muddy brown granular casts (MBGCs) by microscopic examination of the urinary sediment (uSEDI) in that patients with acute tubular injury (ATI) can present with abundant MBGC and yet have a low FENa (<1%) [suggesting prerenal acute kidney injury (AKI)]. It has been hypothesized that cases with MBGC and low FENa may reflect early ATI whereas those with high FENa (>1%) reflect advanced ATI. To probe for this, we examined AKI outcomes stratified by uSEDI and FENa.

Methods: We conducted a prospective observational study of patients with AKI seen in inpatient nephrology consultation over 6-yrs in whom uSEDI was performed and a FENa was simultaneously obtained. Outcomes examined included: need for dialysis (AKI-RRT) and acute kidney disease (AKD) (increase in serum creatinine (sCr) >1.5 times baseline sCr) at discharge.

Results: FENa and uSEDI were completed in 489 patients, 44% women, median age 59. Median sCr was 3.4 mg/dL. Main etiologies of AKI were ischemic ATI (41%) and toxic ATI (12%). Greater than 10% low power fields with MBGCs (MBGC+) were found in 180 patients (37%). MBGC+ with FENa <1% were found in 78 (43%) whereas MBGC+ with FENa ≥1% were found in 102 (57%). Thus, uSEDI/FENa concordance for ATI was 59% (kappa 0.17, slight agreement). When concordance assessment was restricted to oliguric patients (urine volume <500 mL/day), it modestly improved to 68% (kappa 0.29, fair). AKI-RRT occurred in 41% of the MBGC+/FENa≥1% group and in 46% of the MBGC+/FENa<1% group (p=0.50). AKD occurred in 38% of the MBGC+/FENa≥1% group and in 29% of the MBGC+/FENa<1% group (p=0.20). Peak sCr was slightly greater in the MBGC+/ FENa≥1% group [5.1 (IQR 4.0-7.8) vs 4.6 (IQR 3.4-6.5) mg/dL], p=0.04 (statistically significant, not clinically significant).

Conclusions: Our findings do not support the hypothesis that in cases with MBGC+, a low FENa may reflect earlier stage of ATI or a less severe insult. In addition, our findings confirm poor concordance between uSEDI and FENa in ATI but do support prior contention that FENa performs slightly better during oliguria.

FR-PO097

Flow-Cytometric Quantification of Urine Kidney Epithelial Cells Specifically Reflects Tubular Damage and Extent of Injury in Acute Kidney Diseases

Leonie F. Wagner,[1,2] Jacob Kujat,[1] Valerie S. Langhans,[1] Luka Prskalo,[2,1] Nina Goerlich,[1,2] Emil Grothgar,[2] Diana Metzke,[2] Sabine Baumgart,[2] Matthias Ochs,[1] Sara Timm,[1] Adrian Schreiber,[1] Philipp Enghard,[1,2] Jan Klocke.[1,2] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Deutsches Rheuma-Forschungszentrum Berlin, Berlin, Germany.*

Background: Despite tubular injury being one of the main mechanisms driving acute kidney injury (AKI), clinicians still have a limited diagnostic repertoire to precisely monitor damage to tubular epithelial cells (TEC). In our previous work we used single cell sequencing to identify TEC subsets as main component of the urine signature in AKI. The aim of this study was to establish TEC as a clinical marker for tubular damage.

Methods: In total, 195 patients were analyzed. To compare mRNA with protein expression, we collected urine samples of 7 patients with AKI and glomerular disease. By aligning single-cell transcriptomes and TEC-surface proteins using CITE-Seq (Cellular Indexing of Transcriptomes and Epitopes by Sequencing), we developed a protocol for flow cytometric quantification of CD10/CD13+ proximal and CD227/CD326+ distal TEC in urine. The marker combinations were confirmed in healthy kidney biopsies. We validated our approach across 3 cohorts with 188 patients, including patients with AKI (n=63), ANCA-associated vasculitis with active disease and stable remission (AAV, n=110) and healthy and in-patient controls (n=15).

Results: Our findings demonstrate that CD10/CD13 and CD227/CD326 adequately identify proximal and distal urinary TEC respectively. Both proximal and distal urinary TEC counts correlate with the severity of AKI based on KDIGO stage (each $p < 0.001$) and can successfully discriminate AKI from healthy controls (AUROC = 0.938/0.919) as well as glomerular disease (AUROC = 0.818/0.821). Patients with AAV also present with elevated amounts of urinary TEC compared to healthy controls ($p < 0.05$), albeit to a lesser extent.

Conclusions: We propose urinary CD10/CD13+ and CD227/CD326+ TEC counts as a specific, non-invasive marker for tubular injury in AKI. Our protocol provides the basis for a deeper phenotypic analysis of urinary TEC.

FR-PO098

Urinary Protein-to-Creatinine Ratios during Hospitalization Are Not Invalidated by AKI

Ian E. McCoy, Aris Oates, Chi-yuan Hsu. *University of California San Francisco, San Francisco, CA.*

Background: Experts have warned that urine protein to creatinine ratio (UPCR) measurement is invalid during acute kidney injury (AKI) because creatinine levels in the blood and urine are rapidly changing. The theoretical concern is that the UPCR will be falsely elevated when the serum creatinine is rising since the urine creatinine in the denominator of the UPCR will be lower during this period. While some anecdotal experiences seem to corroborate this theoretical concern, the issue has not been systematically investigated using real-world clinical data.

Methods: We examined adults hospitalized with stage 2 or 3 AKI (defined as peak:nadir serum creatinine during hospitalization ≥2) at the University of California, San Francisco 1/1/2014 to 12/31/2021. Between a pair of UPCRs measured in the same patient, we used linear regression to look for associations between the difference in UPCR values and the difference in serum creatinine slopes at the time of UPCR collection. We also calculated test characteristics of inpatient UPCR cutoffs to predict outpatient UPCR cutoffs.

Results: At least one UPCR was measured during hospitalization in 19% of the AKI patients in our cohort. Among 329 patients with multiple UPCRs measured during AKI hospitalization (median difference in serum creatinine slopes 0.37 mg/dL per day), the UPCR value with the steepest upward serum creatinine at the time of measurement was similar to the UPCR value with the steepest downward serum creatinine (median difference in UPCRs 0.06 g/g, 95% CI -0.26 to 0.50 g/g). There was no association between the difference in serum creatinine slopes when the UPCRs were collected and the difference in UPCR values (UPCR 0.05 g/g higher per mg/dL/day serum creatinine slope, 95% CI -0.36 to 0.47, p=0.80). This remained true in a subset analysis of those with serum creatinine slope differences > 1 mg/dL per day. An inpatient UPCR ≤ 3.0 g/g ruled out outpatient nephrotic-range proteinuria (> 3.0 g/g) more than 90% of the time (inpatient UPCR ≤ 0.15 g/g ruled out outpatient proteinuria >0.15 g/g > 79% of the time).

Conclusions: UPCRs were commonly measured during an episode of AKI and were not systematically affected by the serum creatinine slope at the time of UPCR collection. UPCRs measured during an episode of AKI remain informative despite non-steady state serum creatinine at the time of collection and should not be wholly disregarded.

Funding: NIDDK Support

FR-PO099

Nonalbumin Proteinuria (NAP): An Accessible, Affordable, and Easy-to-Use Biomarker for Predicting AKI in Patients with Acute Heart Failure (NAP-AHF Study)

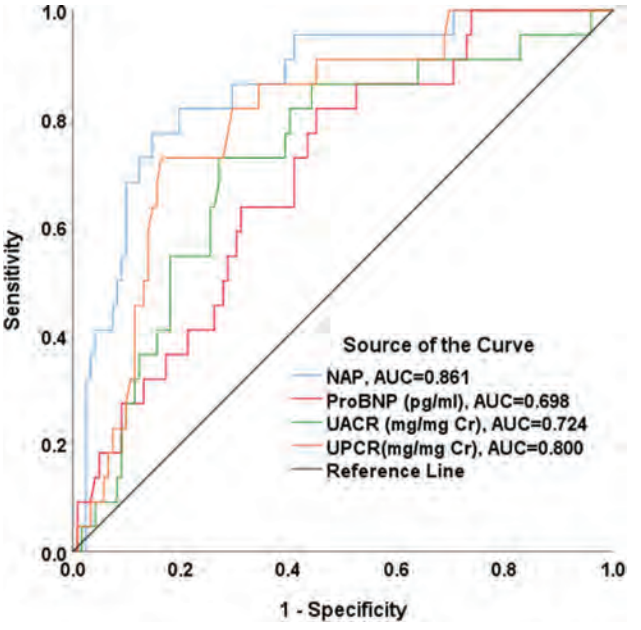
Solos Jaturapisanukul,[1] Khageephan Jaiprasart,[1] Kavee Limbutara,[1] Peerapat Thanapongsatorn,[2] Punnawit Laungchuaychok,[1] Tanun Ngamvichchukorn,[1] Wanjak Pongsitisak.[1] *[1]Navamindradhiraj University, Bangkok, Thailand; [2]Thammasat University Hospital, Khlong Nueng, Thailand.*

Background: Early identification of AKI in patients with acute heart failure (AHF) is challenging in low- to middle-income countries, due to the high costs and limited access to many biomarkers. This study evaluates the effectiveness of non-albumin proteinuria (NAP), as measured by the difference between the Urine Protein-to-Creatinine Ratio (PCR) and the Urine Albumin-to-Creatinine Ratio (ACR), in predicting AKI among AHF patients.

Methods: This prospective study was conducted in a single center in Thailand, from August 2023 to April 2024. We assessed patients admitted with AHF to determine whether NAP at the time of AHF diagnosis could predict the development of AKI within 7 days. Serum creatinine were monitored at baseline, day 2, day 7, and day 28. Exclusion criteria included a PCR ≥ 3 g/gCr, presence of pyuria or hematuria, CKD stage 5, or AKI stage 2-3 or need of KRT.

Results: 144 AHF patients studied, 15.28% developed AKI. The levels of NAP at admission were significantly higher in patients who developed AKI (0.51 vs 0.23, $p < 0.001$). A NAP value ≥ 0.3 g/gCr was significantly associated with the development of AKI by day 2 (30.2% vs 4.3%, $p = 0.022$), by day 7 (34% vs 4.4%, $p < 0.001$), and with acute kidney disease (AKD) by day 28 (15.1% vs 3.3%, $p < 0.01$). Multivariate analysis identified a NAP value ≥ 0.3 g/gCr as a significant predictor of AKI in AHF patients, with a sensitivity of 81.8% and a specificity of 73.0%. Furthermore, the AUROC for NAP was 0.861, demonstrating better predictive ability than PCR, ACR, or pro-BNP for AKI in AHF patients.

Conclusions: An increase in NAP, indicative of tubular protein damage, correlates with the development of AKI in AHF patients. Thus, NAP presents as a promising tool for predicting AKI in this patient population.



AUROC to evaluate the parameters' predictive capability for AKI in acute heart failure patients

FR-PO100

Urinary Proteomics Profiles Classify AKI Subphenotypes

Ian B. Stanaway,[1] Leila R. Zelnick,[1] Frances L. Mabrey,[1] Neha A. Sathe,[1] Zoie A. Bailey,[1] Jordan J. Lo,[1] Jonathan Himmelfarb,[1] Carmen Mikacenic,[2] Laura Evans,[1] Mark M. Wurfel,[1] Eric D. Morrell,[1] Pavan K. Bhatraju.[1] *[1]University of Washington School of Medicine, Seattle, WA; [2]Benaroya Research Institute at Virginia Mason, Seattle, WA.*

Background: Acute kidney injury (AKI) is a common form of organ failure in the intensive care unit. AKI has two distinct sub-phenotypes (SP1 and SP2) that differ in clinical outcomes and response to treatment, with SP2 having worse outcomes. Identification of AKI sub-phenotypes using urine biomarkers could overcome invasive blood sampling and highlight kidney specific pathology.

Methods: We prospectively enrolled 173 ICU patients admitted with a suspected respiratory infection. Of these, 86 patients had AKI and 66 were classified as SP1 and 20 as SP2 using plasma markers of endothelial dysfunction (ANGPT1, ANGPT2) and inflammation (TNFR1). We modeled risk of renal replacement therapy (RRT) adjusting for sex, age, BMI, diabetes, CKD, and COVID-19. Somalogic aptamers assessed 5,212 urine protein abundances collected on admission. We developed urinary proteomic models to predict AKI sub-phenotypes by randomly splitting the data into training (75%) and test sets (25%) and sampling 1000 bootstrap data splits. LASSO 10-fold cross validation was applied to top proteins associated with AKI sub-phenotype (FDR<0.2) in training sets with sex and age as covariates. Iterations over 1000 random data splits obtained a mean area under the curve (mAUC) in test sets. We predicted patients with SP2 among all patients, and predicted SP2 versus SP1 among patients with AKI. We combined training and test sets for final models of selected proteins. For comparison, we also tested a clinical model, which included age, sex, and plasma creatinine.

Results: SP2 patients were more likely to develop incident RRT (OR=12.5 (95% CI 1.9-82.4)). Among all patients, a 32 urinary protein model predicted SP2: mAUC=0.86 (95% CI 0.69-0.99). Among the subset of patients with AKI, a 26 urinary protein model predicted SP2 from SP1: mAUC=0.79 (95% CI 0.58-0.98). The clinical model predicted SP2 from all patients: mAUC=0.77 (95% CI 0.53-0.94) and SP2 from SP1: mAUC=0.68 (95% CI 0.46-0.89).

Conclusions: These results suggest that urinary proteomics can detect AKI SP2 with clinically useful accuracy. Urine tests for AKI sub-phenotypes may be developed for use in hospitals for bedside diagnostics and in low resource settings such as low-middle income countries, military field hospitals, rural and remote regions.

Funding: NIDDK Support, Other NIH Support - CDC, Private Foundation Support

FR-PO101

Urinary Waxy Casts Are Associated with Glomerular Etiology of AKI and Greater Risk for AKI Severity and Post-AKI Chronicity

Stephanie K. Lewis,[1] Vipin Varghese,[2] Pooja A. Punukollu,[1] Joshua Baguley,[1] Conor Kiely,[1] Jaclyn R. Gerschultz,[1] Rami N. Muhtaseb,[1] Dustin R. Chalmers,[3] Juan Carlos Q. Velez.[4] Ochsner Group. *[1]UQ-Ochsner Clinical School, New Orleans, LA; [2]University of Michigan Division of Nephrology, Ann Arbor, MI; [3]Louisiana State University, Baton Rouge, LA; [4]Ochsner Health, New Orleans, LA.*

Background: Identification of muddy brown granular casts (MBGC) by microscopic examination of the urinary sediment (uSEDI) has been reported to predict increased acute tubular injury (ATI) severity. Waxy casts have been traditionally linked to chronic kidney disease (CKD). Recent preliminary observations unveiled diagnostic and prognostic value of WxC in acute kidney injury (AKI). We aimed to explore the relationship of AKI phenotype and outcome with identification of WxC, isolated or in combination with MBGC, in an expanded prospectively-generated AKI cohort.

Methods: We conducted a prospective observational study in patients seen for inpatient nephrology consultation with AKI who had uSEDI performed, over a 6-yr period. Presence of >10% of low power fields with MBGC or WxCs was recorded. Outcomes included need for dialysis (AKI-RRT) and acute kidney disease (AKD) [serum creatinine (sCr) >1.5 times baseline sCr] at discharge and at 6 months.

Results: 801 patients [median age 60, 42% women] were included. Median sCr was 3.4 (IQR 2.3-4.7) mg/dL. The most common etiology of AKI was ischemic ATI (45%). MBGCs and WxCs were found in 45% and 36%, respectively. In those with WxC, 57% had *de novo* AKI (no preexisting CKD). Glomerular etiology of AKI accounted for only 4% of cases with MBGC but 13% of those with WxC (p=0.0003). MBGC were associated with increased risk for AKI-RRT [OR: 1.8 (1.4-2.6, p=0.0001)] but not for AKD [OR: 1.3 (0.8-2.0, p=0.28)]. WxCs were associated with increased risk for AKI-RRT [OR: 1.9 (CI 1.4-2.7, p=0.0001)] and AKD [OR: 2.5 (CI 1.4-4.4, p=0.002)]. Presence of both MBGC and WxC was associated with even greater risk for AKI-RRT [OR: 2.6 (1.7-3.9, p=0.0001)] and AKI-RRT at 6 months [OR: 4.8 (1.9-11.9, p=0.0008)].

Conclusions: WxC can be identified in AKI without pre-exisiting CKD and are more commonly found in glomerular disease compared to MBGC. Prognostically, WxC are associated with increased AKD risk, and co-identification of MBGC and WxC are strongly associated with greater risk for AKI-RRT during hospitalization and at 6 months. Further validation of these clinically relevant observations is warranted

FR-PO102

Adjudication Methodology to Assess Novel Urine Biomarkers Panel Detection of Nephrotoxicant Exposure in Presence or Absence of KDIGO-Defined AKI to Support Biomarker Qualification

Nicholas M. King,[1] Steven G. Coca,[2] Steven C. Hoffmann,[5] Patrick T. Murray,[3] Jai Radhakrishnan,[4] Katrina J. Peron,[1] Gary S. Friedman.[1] PSTC and FNIH BC Kidney Safety Project. *[1]Critical Path Institute, Tucson, AZ; [2]Yale University School of Medicine, New Haven, CT; [3]University College Dublin, Dublin, Ireland; [4]Columbia University Irving Medical Center, New York, NY; [5]Foundation for the National Institutes of Health, North Bethesda, MD.*

Background: Critical Path Institute (C-Path) convened 6 expert nephrologist adjudicators (ENAs) to interpret blinded standard & novel clinical and biomarker (SBM & NBM, respectively) data from 2 prospective studies (N=195 patients) to assess NBM sensitivity for detecting drug-induced kidney injury (DIKI) in KDIGO AKI positive & negative participants. Provided SBM and/or NBM baseline (BL) and post-baseline (PBL) patient-level data packets, each ENA determined presence/absence of KDIGO AKI and presence/absence of PBL increase in NBMs-Clusterin, Cystatin C, KIM-1, Osteopontin, NAG, NGAL. In parallel, presence/absence of AKI and DIKI were programmatically quantified using a NBM geometric mean composite measure (GMCM).

Methods: ENAs assessed patient-level electronic case report forms (eCRFs) (N=195). C-Path programmatically generated CDISC SDTM formatted tables to compare programmatic and "human-in-the-loop" adjudication decisions using SBM only [serum creatinine, serum cystatin C, eGFR, Urine Albumin & Protein-Creatinine Ratio (UACR, UPCR)]; NBM only; or combined SBM+NBM (see two 3-member adjudication panels 3-step process).

Results: ENAs unanimity or consensus was achieved in 100% of cases (N=195). Correlation between "human-in-the-loop" NBM adjudication & programmatic NBM GMCM quantitation are primary endpoints within the FDA Qualification Plan submitted to FDA.

Conclusions: NBM panel full qualification is contingent upon demonstration that NBM PBL change is more sensitive than KDIGO AKI criteria for adjudicating nephrotoxicant exposure. If qualified, academic, clinical, pharma NBM PBL and GMCM utilization will drive global clinical nephrology consensus of NBM panel implementation. Periodic re-interrogation of cumulative SBM+NBM data & NBM GMCM under pre-specified statistical analysis plans (SAP) may be a post-qualification commitment to FDA. C-Path's Biomarker Data Repository (BmDR) housing adjudicated participants' deidentified data (n=195 patients) & patient-level SBM+NBM data from Pharma trials + SAFE-T Consortium trials (~700 participants) may address post-qualification requirements.

Funding: Other U.S. Government Support, Commercial Support - Pfizer, Lilly, Merck, AstraZeneca, Amgen, JnJ

Case Adjudication

Step 1	Step 2	Step 3
PERIOD 1: Adjudication of 50% of cases by 3 Panel A members (individual adjudication decision using SBM+eCRFs, only).	PERIOD 1: Adjudication of 50% of cases by 3 Panel A members (individual adjudication decision using NBM, only.)	PERIOD 1: Adjudication of 50% of cases by 3 Panel B members (individual adjudication decision using COMBINED NBM + SBM + select eCRFs.)
PERIOD 2: Adjudication of 50% of cases by 3 Panel B members (individual adjudication decision using SBM+eCRFs, only).	PERIOD 2: Adjudication of 50% of cases by 3 Panel B members (individual adjudication decision using NBM, only.)	PERIOD 2: Adjudication of 50% of cases by 3 Panel A members (individual) adjudication decision using COMBINED NBM + SBM + select eCRFs.)

FR-PO103

Impact of Biomarkers in the Eligibility Criteria of AKI Randomized Controlled Trials: A Systematic Review with Meta-Analysis

Fella Chennou,[1] Michael Strader,[2] William Beaubien-Souligny,[1,3] Jean Maxime Cote.[1,3] *[1]Universite de Montreal, Montreal, QC, Canada; [2]University College Dublin, Dublin, Ireland; [3]Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada.*

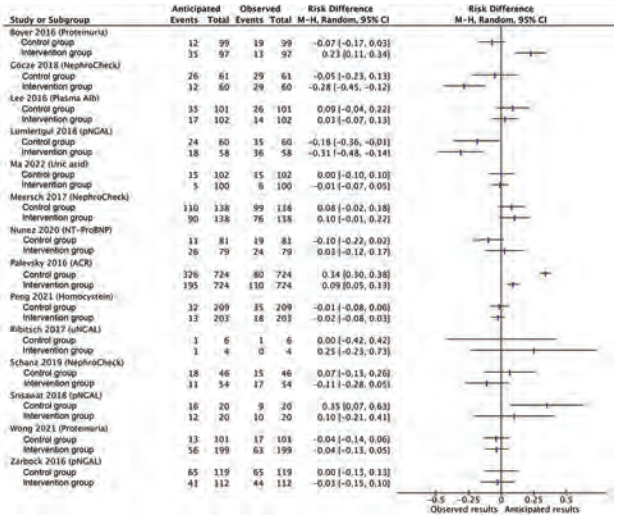
Background: There is a growing interest around novel approaches for assessing acute kidney injury (AKI). Some clinical trials have used kidney biomarkers as part of their eligibility criteria to better select participants. This might cause a selection bias, as the expected event rate used to measure the sample size is based on prior studies without such criteria.

Methods: We searched for studies published after 2010 in MEDLINE, EMBASE, GOOGLE Scholar, EBM Reviews, MedRxiv and PROSPERO. We included RCTs with biomarkers as eligibility criteria that assess kidney outcomes, defined as the incidence or composite of acute kidney injury, major adverse renal or cardiac events, initiation of dialysis or death. The main aim of this review was to quantify the discrepancy between the anticipated (used in sample size estimation) and the observed event rates for control and intervention groups.

Results: A total of 14 RCTs involving 3817 patients were included. Biomarkers of interest were NGAL (4 studies), TIMP-2*IGFBP7 (3 studies), proteinuria (3 studies), albumin, NT-pro-BNP, homocysteine and uric acid. The mean risk difference between the anticipated and observed event rates was 0.098 (SD±0.115, p=0.58) for control groups and 0.116 (SD±0.106, p<0.01) for intervention groups. For RCTs with tubular damage biomarkers (NGAL, TIMP-2*IGFBP7 and proteinuria), the mean risk differences were 0.118 (SD±0.130, p=0.46) and 0.154 (SD±0.103, p=0.008) for the control and intervention groups respectively.

Conclusions: The use of biomarkers as an enrichment method for selecting participants in AKI RCTs is associated with a difference between expected and observed incidence rates. Investigators must consider the implications of integrating such criteria on the event rate of RCTs.

Funding: Clinical Revenue Support



FR-PO104

Uridine Diphosphate (UDP) Sugars Predict AKI in Cardiac Surgery Patients

Christine Legare,[1] Patrick Caron,[1] Chantal Guillemette,[1,4] Siamak Mohammadi,[2,3] Sylvie Breton.[1,3] *[1]Centre Hospitalier Universitaire de Quebec-Universite Laval, Quebec, QC, Canada; [2]Institut Universitaire de Cardiologie et de Pneumologie de Quebec - Universite Laval, Quebec, QC, Canada; [3]Universite Laval Faculte de Medecine, Quebec, QC, Canada; [4]Universite Laval Faculte de Pharmacie, Quebec, QC, Canada.*

Background: UDP-sugars including UDP-glucose (UDP-Glc), UDP-galactose (UDP-Gal), UDP-N-acetylgalactosamine (UDP-GalNAc), UDP-N-acetylglucosamine (UDP-GlcNAc), and UDP-glucuronic acid (UDP-GlcA) activate the pro-inflammatory P2Y14 receptor. Previously, we showed elevated urine UDP-Glc in intensive care unit patients with AKI compared to those without AKI. In addition, renal ischemia reperfusion injury in mice led to an increase in UDP-Glc urine concentration, followed by activation of P2Y14 in intercalated cells (ICs), initiating an inflammatory cascade that worsened AKI. Ischemic-AKI is prevalent among cardiac surgery patients. Here we investigated whether UDP-sugars serve as early markers of AKI in these patients.

Methods: Urine and plasma samples were collected from 53 cardiac surgery patients: prior to initiation of cardio-pulmonary bypass (CPB), at the end of CPB, and 4h, 12h, 24h, 48h, and 72h post-CPB. The concentration of UDP-sugars was quantified using mass spectrometry. The ROC-AUC was used to evaluate the association between urinary and plasma UDP-sugars and AKI. Correlation analysis was performed with urinary kidney injury molecule -1 (KIM-1), measured by electroluminescence.

Results: Compared to patients without AKI, urinary concentration of UDP-Glc (P=0.002), UDP-Gal (P=0.001) and UDP-GalNAc/GlcNAc (P= 0.0001) increased 12h post-CPB, followed by a return to reference levels in patients diagnosed with AKI 24h after surgery. Urinary UDP-GlcA and plasma UDP-sugars did not vary with AKI. Optimal threshold values of UDP-Glc, UDP-Gal, UDP-GalNAc/GlcNAc, and their sum, predicted AKI with AUC values of 0.71, 0.72, 0.75 and 0.76, respectively. Urinary levels of UDP-Glc and UDP-Gal correlated with KIM-1 at 12h post-CPB (R > 0.43).

Conclusions: Our findings indicate that UDP-Glc, UDP-Gal and UDP-GalNAc/GlcNAc measured in urine are predictors of AKI. Given the correlation observed between KIM-1 - a marker indicative of proximal tubule (PT) injury - and UDP-Glc and UDP-Gal, we suggest that these UDP-sugars are actively released by damaged PT during CPB. Following their release, they are eliminated in the urine, where they trigger the activation of the P2Y14 receptor in ICs. This study, thus, identifies P2Y14 as a key driver in AKI.

Funding: Government Support - Non-U.S.

FR-PO105

Exploring the Plasma and Urine Extracellular Vesicles in Sepsis-Induced AKI

Chih-chin Kao, Tanyu Chang, Isabel I-Lin Tsai. *Taipei Medical University, Taipei, Taiwan.*

Background: Half of critical-ill patients with sepsis develop acute kidney injury (AKI), while these patients are associated with poor outcomes. Early recognition of AKI in sepsis is important for optimal treatment and avoiding further kidney injury. The serum creatinine is a late biomarker due to its delayed elevation post-kidney damage. Therefore, we aimed to investigate the plasma and urine extracellular vesicles (EVs) to identify potential biomarkers for early detection of sepsis-induced AKI (S-AKI) by proteomics analysis.

Methods: In this study, 30 sepsis patients were examined, including 19 with S-AKI and 11 with sepsis only. EVs from plasma and urine were isolated using size exclusion chromatography (SEC) and confirmed by using western blot, nano-particle tracking analysis (NTA), and transmission electron microscopy (TEM). EVs were precipitated with acetone and digested with urea, dithiothreitol (DTT), iodoacetamide (IAA), and trypsin before liquid chromatography-mass spectrometry (LC-MS) analysis. Metabolomics analysis was conducted on the soluble portion post-acetone precipitation. MaxQuant processed MS data for identification and label-free quantification. Volcano plot analysis via MetaboAnalyst 6.0 identified differentially expressed proteins (DEPs). Gene enrichment was performed using FunRich software (v3.1.3), and pathway analysis was executed using the Kyoto Encyclopedia of Genes and Genomes (KEGG).

Results: We discovered 38 DEPs in the urine EV dataset and 28 DEPs in the plasma EV dataset. For the gene enrichment study, the DEPs from both datasets mainly come from extracellular, exosome, and extracellular regions. Meanwhile, the molecular function and biological processes of the DEPs in both datasets showed a great relationship with complement activity. Further, the pathway analysis showed these were enriched in complement and coagulation cascades, and Staphylococcus aureus infection. For metabolomics analysis in urineEV dataset, differentially expressed metabolites are enriched in tyrosine metabolism. As for the plasmaEV dataset, differentially expressed metabolites are enriched in nicotinate and nicotinamide metabolism.

Conclusions: These findings underscore the potential of EVs as biomarkers and therapeutic targets in S-AKI, offering new insights into the pathophysiology and potential treatment strategies for this critical condition.

FR-PO106

Clinical Utility and Performance of Urinary L-FABP as a Potentially Suitable Biomarker for Early Detection of Contrast-Induced AKI among Adult Filipino In-Patients Undergoing Coronary Angiography

Anne Laurene Tayo, Donnah Franceska De Leon. *Manila Doctors Hospital, Manila, Philippines.*

Background: Contrast-induced AKI (CI-AKI) is now considered the third most common cause of AKI in hospitalized patients and is recognized as a frequent complication of percutaneous cardiovascular procedures. One significant barrier to improving clinical outcomes in patients with AKI is the delayed administration of potentially beneficial therapies. This delay is compounded by the unreliability of serum creatinine as a marker of GFR in acutely ill patients. Urinary levels of L-FABP have been shown to increase earlier than serum creatinine in patients who develop AKI and is particularly linked with tubular dysfunction. This biomarker could be valuable for assessing a patient's risk, and for the early diagnosis of CI-AKI.

Methods: This analytic prospective cohort study was conducted to determine diagnostic utility of urinary L-FABP in the early detection of CI-AKI among adult Filipino in-patients who underwent coronary angiography from December 2023 to April 2024. Baseline and 4-6 hour post-procedure urinary L-FABP levels were measured using point-of-care kits and compared between patients who developed CI-AKI (diagnosed using KDIGO criteria) and those who did not develop the disease.

Results: The final analysis included 86 patients, 3 of whom were diagnosed with CI-AKI during the study period. ROC analysis showed that baseline urinary L-FABP exhibited 100% sensitivity and 73.49% specificity at a cut-off value of 2.71 ng/ml, while the 4-6 hour urinary L-FABP had 100% sensitivity and 98.8% specificity at a cut-off value of 10.99 ng/ml. The AUC for the baseline urinary L-FABP was 0.89 representing a good test, and 1.0 for the 4-6 hour urinary L-FABP indicating an excellent test in CI-AKI diagnosis.

Conclusions: This study demonstrates that urinary L-FABP could serve as a clinically useful predictive biomarker to detect CI-AKI onset even before contrast media exposure. This biomarker, which has high sensitivity and good negative predictive value in the detection rate of AKI, may enable and improve timely initiation of preventive strategies and potentially beneficial therapies for CI-AKI.

FR-PO107

Renal Tubular Injury Biomarkers (BMs) in the Identification of Subclinical AKI and Drug-Induced Kidney Injury: IMI/SAFE-T/TransBioLine

Michael Strader,[1] Xavier Benain,[3] Nunzio Camerlingo,[2] Gary S. Friedman,[2] Stefan Sultana,[4] Patrick T. Murray.[1] *[1]University College Dublin, Dublin, Ireland; [2]Pfizer Inc, New York, NY; [3]Sanofi SA, Paris, France; [4]AstraZeneca PLC, Cambridge, United Kingdom.*

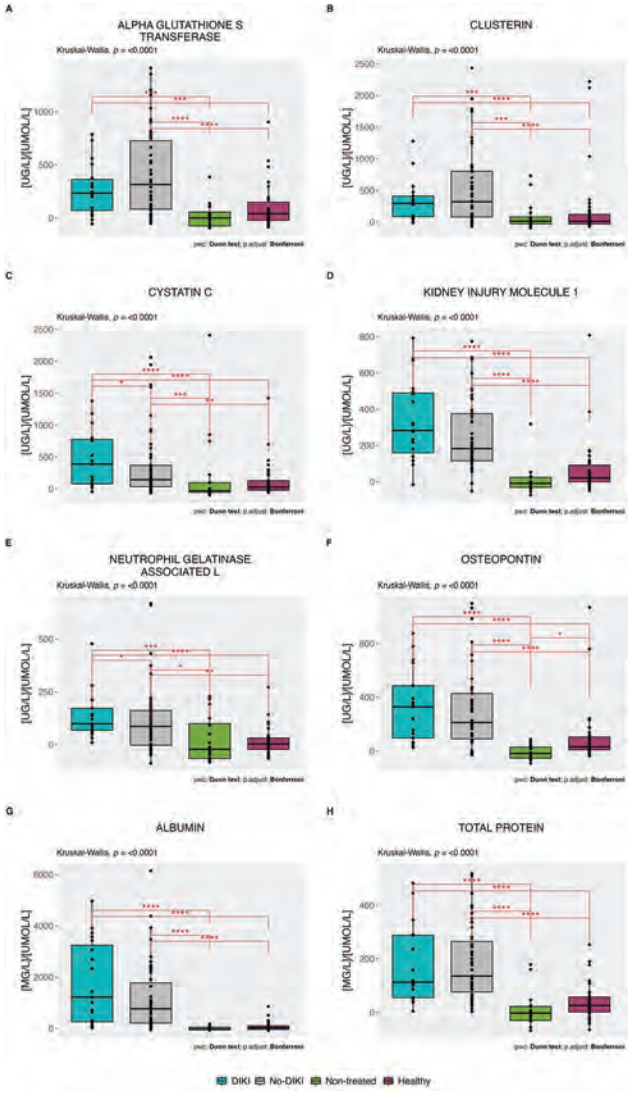
Background: Drug-induced kidney injury (DIKI), a subphenotype of AKI, is a side effect of cisplatin chemotherapy. Current AKI functional BMs are limited and therefore at the 23rd ADQI consensus conference proposed using novel BMs to enhance AKI criteria.

Methods: In this prospective study, 105 cisplatin-treated patients (Treated), 20 non-cisplatin-treated cancer controls (Non-Treated), and 34 Healthy controls were enrolled. Blood and urine samples from the Treated group were collected at specified timepoints. Standard BMs and novel BMs (eight urinary, one serum) were assessed. Three blinded nephrologists determined the presence or absence of DIKI in cisplatin-treated patients. BM accuracy was defined by sensitivity, specificity, AUROC, and changes (absolute and percentage) from baseline were compared between groups, with median time to peaks calculated.

Results: All biomarkers showed significant changes from baseline in the Treated group versus Non-Treated group. Most urinary BMs effectively detected cisplatin exposure (AUROC > 0.8). Novel BMs peaked earlier, with α-GST peaking first (Day 1), followed by serum CYSC and KIM-1 (Day 2). Treated group were adjudicated into DIKI (N = 24) and No-DIKI (N = 71) groups. Significant differences were observed in all BMs between both DIKI and No-DIKI groups compared to controls. No significant differences were found in urinary BMs, except for neutrophil gelatinase-associated lipocalin and cystatin-C, between DIKI and No-DIKI groups.

Conclusions: Novel BMs detected DIKI more sensitively and timely than standard BMs. A panel of BMs is likely superior for comprehensive nephrotoxicity assessment, which aligns with FDA's 2018 qualification letter supporting novel BMs with standard BMs in phase 1 drug development.

Funding: Commercial Support - EFPIA, Government Support - Non-U.S.



FR-PO108

Clinical Impact of Wnt5a Expression on the Persistence of AKI in Patients with Urosepsis

Yoonho Kim, Dong-jin Oh, Hye Min Choi, Young Eun Kwon, Song in Baeg.
Myongji Hospital, Goyang, Gyeonggi-do, Republic of Korea.

Background: This study aimed to investigate the association between Wnt5a values and organ alterations in urosepsis patients.

Methods: Serum creatinine (Cr) and Wnt5a levels were measured in 28 healthy volunteers and on day 1, 5, and discharge day in 87 urosepsis patients. The patients were classified into an improving AKI group and a worsening AKI one by comparing the stages of AKI on day 1 and 5. The impacts of Wnt5a values on major adverse kidney events (MAKE), stage 3 AKI, new renal replacement therapy (RRT), and death. Logistic regression analysis was performed to determine the probability of clinical outcomes. Reversal patterns after AKI were also evaluated.

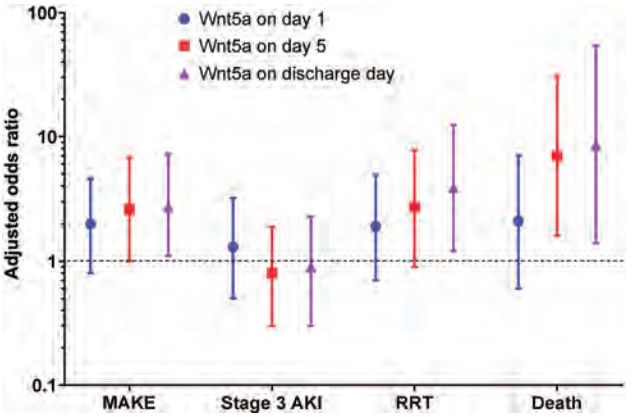
Results: Wnt5a levels were significantly elevated in urosepsis patients compared to healthy volunteers (P=0.009). There were 28 (32.2%) in the worsening AKI and their levels of Wnt5a were consistently higher than those in the improving AKI (Table 1). The association between Wnt5a values and worsening AKI persisted after the adjustment for age, sex, baseline serum Cr, and disease severity (P=0.044, 0.005, and 0.001, at respect time point). Elevated Wnt5a level was related to the raising risk of MAKE (P=0.119 on day 1, 0.060 on day 5, and 0.039 on discharge day), increased RRT needs or 30-day death (P=0.109, 0.003, and 0.004, respectively). (Fig 1). This study identified the patterns that high Wnt5a values on discharge day was associated with unrecovered AKI, irrespective of the confounders. The trajectory of Wnt5a over time differed according to the pattern and discharge renal function (P=0.004 and 0.003).

Conclusions: Wnt5a measurment may serve as a valuable biomarker for identifying at-risk individuals with urosepsis.

Baseline Wnt5a values

Wnt5a, ng/mL	Improving AKI (N=58)	Persistent or worsening AKI (N=29)	P value
On day 1	2.0 (1.8, 2.3)	2.3 (2.0, 2.6)	0.012
On day 5	1.9 (1.7, 2.3)	2.3 (1.9, 2.7)	0.009
On discharge day	2.0 (1.7, 2.3)	2.5 (2.1, 2.7)	0.001

Data are expressed as median (interquartile range).



The adjusted likelyhood of Wnt5a for each component in urosepsis patients.

FR-PO109

Dynamic Changes of SERPINA3 in the Serum of Patients after Cardiac Surgery and Mouse Kidneys Post Ischemia-Reperfusion Injury

Wenli Sai,[1] Yun Jiang,[1] Yanan Wang,[1] Fei Chen,[1] Lili Huang,[1] Fenfen Xiong,[1] Jun Zhu,[1] Yuanyuan Wu,[2] Jiahai Shi,[1] Bin Yang.[3] *[1]Affiliated Hospital of Nantong University, Nantong, China; [2]Nantong University, Nantong, China; [3]University of Leicester College of Life Sciences, Leicester, United Kingdom.*

Background: Serine proteinase inhibitor class A member 3 (SERPINA3) plays crucial roles in regulating serine proteases and various biological processes, but its involvement in acute kidney injury (AKI) remains unclear. Herein, the dynamic change of SERPINA3 in the serum of AKI patients and kidneys of AKI mice were evaluated.

Methods: The serum level of SERPINA3 was analyzed by enzyme-linked immunosorbent assay (ELISA) in patients underwent cardiopulmonary bypass at pre- and post-cardiac surgery at 0, 6, 12 hours (h) and 1,2,3 and 7day(s). In addition, amouse bilateral renal ischemia-reperfusion (IR) model was established by 30-min ischemia and followed by reperfusion for 6 h to 7 days. The expression of SERPINA3 and its localization in kidneys were also evaluated.

Results: Compared with pre-operation, SERPINA3in serum was upregulated from 6 and 12 h, and reached a statistical significance at Day 1,2,3 and 7 after operation in patients without AKI and with AKI stage II/II, and significantly increased at Day1,2 and 3 in patients with AKI stage I. Most interestingly, the level of serum SERPINA3 was peaked at Day 1 or Day 2, and decreased afterwards in both patients without AKI and AKI stage I, but remained high at Day 3 and Day 7 in patients with AKI stage II/III, which may indicate a potential of chronic progression. In addition, the expression of SERPINA3 was significantly raised in kidneys at 24 and 72 h, but gradually decreased afterwards. The immunostaining of SERPINA3 was mainly in interstitial areas and the cytoplasm and nucleus of tubular cells in IR kidneys. The staining in interstitial areas was increased at 6 h post IR, while that intubular areas was remained over 6-24 h. The level of SERPINA3 protein in IR kidneys was positively correlated with the score of tubulointerstitial damage, but was not related with serum creatinine.

Conclusions: SERPINA3 may be a potential early biomarker for IR-AKI, as well as an indicator for its chronic transition. The role of SERPINA3 in AKI and underlying mechanisms need to be further investigated.

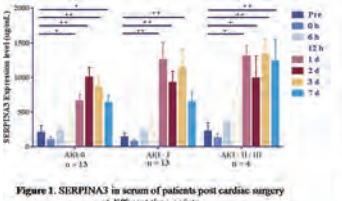


Figure 1. SERPINA3 in serum of patients post cardiac surgery at different time points

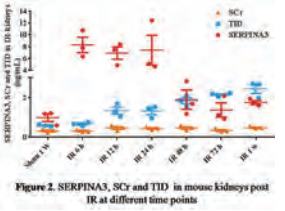


Figure 2. SERPINA3, SCr and TID in mouse kidneys post IR at different time points

FR-PO110

SLPI and Serpin E1 Differentiate between and Can Be Used as AKI Biomarkers in Patients with and without Obesity

Naomi A. Brown,[1] Marcin Wozniak,[1] Haiyan Pan,[2] Barbara Horley,[3,4] Lathishia Joel David,[1] Hardeep Aujla,[1] Gavin J. Murphy,[1] Bin Yang.[3,5] *[1]Department of Cardiovascular Sciences and NIHR Cardiovascular Biomedical Research Unit, University of Leicester, Leicester, United Kingdom; [2]Affiliated Hospital of Nantong University Department of Cardiology, Nantong, China; [3]Department of Cardiovascular Sciences, College of Life Sciences, University of Leicester, Leicester, United Kingdom; [4]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [5]Nantong-Leicester Joint Institute of Kidney Science, Department of Nephrology, Affiliated Hospital of Nantong University, Nantong, China.*

Background: Acute kidney injury (AKI) is among the most common complications after cardiac surgery, with an 18% prevalence and is associated with an increased risk of death. Cardiopulmonary bypass surgery generates danger-associated molecular patterns that trigger a release of proinflammatory molecules that can lead to AKI. Obesity is also associated with chronic low-grade inflammation and an increased risk for AKI. We investigated the utility of inflammatory molecules in the diagnosis of AKI in obese and non-obese cardiac surgery patients.

Methods: A panel of 13 circulating plasma molecules, including CXCL1, CXCL10, CXCL13, CCL22, IL-5,6,8,10,16, SLPI, TIM1, Properdin, Serpins E1 and A3, was measured using MAGPIX. The samples were collected from 95 MaRACAS patients (NCT02315183) before and 6-72 hours (h) after surgery. Obesity was defined as BMI>=32, based on our previous study.

Results: There was no significant difference in the incidence of AKI between obese (46%) and non-obese patients (58%). The levels of the selected molecules were compared between AKI and non-AKI groups in patients with and without obesity. In obese patients with AKI, the levels of serpin E1 were lower before surgery (22.16 vs 40.94ng/mL, q=0.03) and higher 6h post-surgery (49.26 vs 21.65ng/mL, q=0.02), while properdin was lower 72h post-surgery (11.12 vs 14.35ng/mL, q=0.01). In the non-obese group, CXCL10 was higher in the AKI group 6-48h post-surgery, peaking at 6h (218.5pg/mL vs 131.38pg/mL, q=0.02); CXCL13 was higher at 6h (435.78 vs 291.0pg/mL, q=0.04) and 24h (215.18 vs 157.49pg/mL, q=0.04); IL-16 was higher at 6h (256.01 vs 174.44, q=0.04) and 24h (344.94 vs 174.02, q=0.02); and SLPI was higher 6-72h post-surgery, peaking at 6h (50.44 vs 33.53 at 6h, q<0.01). ROC AUC analyses showed that Serpin E1 had a diagnostic value for AKI in obese patients pre (75.6%, 58.3%-92.8%) and 6h post-surgery (80%, 64.6%-95.4%); while SLPI had a diagnostic value in non-obese patients 6h after surgery (75.0%, 62.2%-87.8%).

Conclusions: AKI leads to different expression levels of proinflammatory molecules in obese and non-obese patients undergoing cardiac surgery. SLPI and Serpin E1 have diagnostic potential as biomarkers, but should be validated in larger cohorts.

Funding: Private Foundation Support

FR-PO111

Urinary Follistatin-Like 3 Is Increased in Patients with AKI and Reflects Severity of Tubular Injury

Mari Okada, Izumi Nagayama, Shunsuke Takahashi, Kaori Takayanagi, Hajime Hasegawa, Akito Maeshima. *Saitama Medical Center, Saitama Medical University, Kawagoe, Japan.*

Background: Follistatin is an essential physiological regulator of activin and other members of the TGFβ superfamily. In animal models of acute kidney injury (AKI), blockade of activin A by exogenous follistatin has been shown to attenuate renal injury and improve renal function. This suggests that endogenous activin A negatively modulates tubular repair following AKI. Follistatin serves as a local regulator of activin A in numerous tissues. In addition, urinary follistatin, which is undetectable in normal rats, was significantly increased in ischemic rats. Conversely, follistatin-like 3 (FSTL3) exhibits substantial structural and functional similarity to follistatin, albeit with some notable differences, including its prominent nuclear localization. Nonetheless, the precise role of FSTL3 remains unclear.

Methods: To address this issue, we investigated the localization of FSTL3 in normal human kidneys and measured urinary FSTL3 in patients with AKI to evaluate its potential as a marker for AKI. A total of 127 patients with AKI and 19 healthy adults participated in this study. Serum and urinary FSTL3 levels were quantified using ELISA. We analyzed the correlations between urinary FSTL3 and other clinical parameters.

Results: FSTL3 was localized in renal tubules of normal kidney. FSTL3-producing cells were positive for Na-Cl co-transporter and uromodulin but were negative for aquaporin 1, megalin and aquaporin 2. Urinary FSTL3, undetectable in healthy adults, was significantly increased in patients with AKI (0.00 ± 0.00 vs. 18.09 ± 17.66 ng/mL, p <0.0001). This increase was most pronounced in cases of sepsis (37.65 ± 17.56 ng/mL). In stages of the KDIGO classification, urinary FSTL3 was positively correlated with the severity of AKI (stage I, 7.34 ± 8.75 ng/mL, p<0.05; stage II 9.02 ± 7.60 ng/mL, p<0.01; stage III 25.62 ± 18.66 ng/mL, p<0.0001). There was a significant correlation of urinary FSTL3 with urinary protein, urinary NAG, urinary alpha1-microglobulin, urinary beta2-microglobulin, urinary NGAL, KIM-1 and serum FSTL3. Meanwhile, FSTL3 did not correlate with L-FABP and urinary serum creatinine.

Conclusions: FSTL3 is localized in the distal tubules of normal kidneys. Urinary FSTL3 increases in AKI patients and serve as a valuable marker for monitoring the severity of acute tubular damage in AKI.

Funding: Government Support - Non-U.S.

FR-PO112

Fibroblast Growth Factor 23 and Klotho in Cardiac Surgery-Associated AKI

Cheng chia Lee, Ming-Jen Chan, Chih-Hsiang Chang. *Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan.*

Background: Acute kidney injury (AKI) frequently occurs as a complication following cardiac surgery, leading to increased mortality and prolonged hospital stays. Elevated serum FGF23 levels have been suggested to be associated with a greater degree of systemic inflammation in critical ill patients. This study aims to evaluate the roles of serum FGF23 and klotho levels post-cardiac surgery, and to determine their impact on the occurrence of severe AKI in these patients.

Methods: We included adult patients who underwent on-pump cardiac surgery in a tertiary care university hospital. All prospective clinical and laboratory data were evaluated as predictors of AKI. Serum FGF23 and klotho level were measured within 6 hours after cardiac surgery. The discriminative power for predicting severe AKI (stage 2 or 3) was assessed using the area under the receiver operator characteristic curve (AUROC).

Results: We investigated 214 adult patients with a mean age of 59.9 year. Severe AKI was diagnosed in 32 patients (15.0%). Patients with severe AKI had longer bypass time. Higher FGF23 level and lower klotho level were independent risk factors for severe AKI, even after adjustment for clinical risk factors. The clinical prediction model for severe AKI had an AUROC of 0.71. Adding FGF23 to the clinical model increased the AUROC for predicting severe AKI to 0.76, while combining FGF23 and klotho increased it further to 0.79. The optimal cutoff values for FGF23 and klotho is 2264 pg/ml and 100 pg/ml, respectively. We also performed ROC analysis of the single serum FGF23/klotho ratio, which revealed an AUROC value of 0.71, with a sensitivity of 62.5% and a specificity of 80.2% for predicting severe AKI at a threshold value of 29.5.

Conclusions: The combination of elevated FGF23 level and reduced klotho level could serve as a potential biomarker for the predicting severe AKI.

Table. Baseline characteristics and postoperative biomarkers among the study patients (n = 214)

Characteristics	Non-AKI (n = 122)	Mild AKI (n = 60)	Severe AKI (n = 32)	p for trend
Age (years)	60.3 ± 12.0	58.2 ± 12.4	61.7 ± 12.5	0.568
Men [n (%)]	76 (62.3%)	44 (73.3%)	23 (71.9%)	0.160
Diabetes mellitus [n (%)]	34 (27.9%)	13 (21.7%)	11 (34.4%)	0.772
Body mass index	25.3 ± 4.5	25.3 ± 3.9	26.3 ± 5.0	0.279
Ejection fraction (%)	61.0 ± 14.3	59.8 ± 14.7	58.4 ± 15.4	0.414
Preoperative Cr (mg/dl)	0.78 ± 0.20	0.82 ± 0.21	0.80 ± 0.24	0.710
Euroscore II	2.1 [1.1, 3.6]	2.0 [1.2, 4.0]	2.7 [1.6, 4.4]	0.171
Surgical type [n (%)]				0.135
CABG	39 (32.0%)	14 (23.3%)	4 (12.5%)	
Valve	51 (41.8%)	30 (50.0%)	18 (56.3%)	
Aorta	25 (20.5%)	13 (21.7%)	6 (18.8%)	
Bypass time (hrs)	2.6 ± 1.1	2.9 ± 1.1	3.4 ± 1.4	<0.001
Postoperative biomarkers				
FGF23 (pg/ml)	2083 [1104, 3648]	3167 [1352, 5452]	3731 [2309, 15976]	<0.001
Klotho (pg/ml)	142 [110, 215]	127 [87, 201]	103 [80, 202]	0.007

Continuous data are presented as means ± SDs or medians [interquartile range]

FR-PO113

Concordance of Prebiopsy and Postbiopsy Diagnosis in Patients with Suspected Acute Interstitial Nephritis or Acute Tubular Injury

Steven Menez,[1] David Hu,[1] Heather Thiessen Philbrook,[1] Celia P. Corona Villalobos,[1] Yumeng Wen,[1] Dennis G. Moledina,[3] Steven G. Coca,[2] Chirag R. Parikh.[1] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Yale University School of Medicine, New Haven, CT.*

Background: Percutaneous kidney biopsy remains the gold standard for evaluation of acute kidney injury (AKI), given that clinicians' pre-biopsy clinical impression of AKI, based on history, exam, and non-invasive testing may often be inaccurate. In this study, we evaluated the concordance of pre-biopsy clinical diagnosis with post-biopsy final diagnosis among patients with AKI.

Methods: We leveraged data collected through the Novel Approaches in the Investigation of Kidney Disease (NAIKiD) Study between 2020 and 2023, in which adult patients admitted to the Johns Hopkins Hospital and scheduled for clinical kidney biopsies consented to provide biosamples (blood, urine, and kidney tissue) and data collection. Up to 3 pre-biopsy clinical diagnoses were recorded for each patient, along with up to 3 final diagnoses, adjudicated by a study nephrologist post-biopsy. We investigated the

concordance of pre and post-biopsy diagnoses among patients with suspected acute interstitial nephritis (AIN) or acute tubular injury (ATI).

Results: Among 164 total patients, 29 patients had supsected AIN and 47 had supsected ATI pre-biopsy. Among the patients with suspected AIN, only 7 (24%) had AIN confirmed on biopsy. Of the 22 other biopsies, alternative diagnoses noted on histology included focal segmental glomerulosclerosis (FSGS), ATI, and various glomerular diseases. Out of 47 patients with suspected ATI, ATI was confirmed on biopsy in 27 (57%) patients. In the 20 biopsies without ATI, alternative diagnoses also included glomerular diseases, diabetic nephropathy, and FSGS predominantly.

Conclusions: Patients with suspected ATI or AIN who undergo percutaneous kidney biopsy are often found to have alternative, significant findings present on histology. Among inpatients without relative or absolute contraindications, kidney biopsy remains an essential part of clinical evaluation.

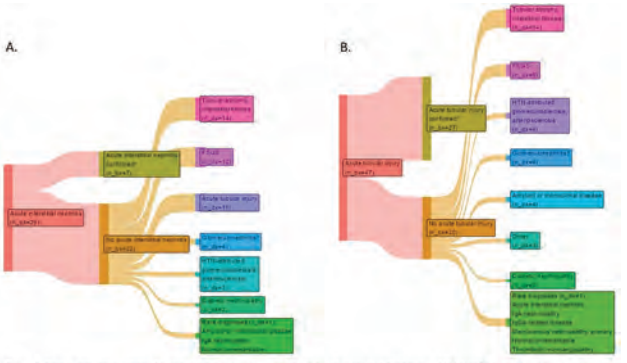


Figure 1. Sankey plots demonstrating final adjudicated diagnoses among patients with suspected diagnoses of AIN (A) and ATI (B) prior to kidney biopsy.
n_bx refers to the number of biopsies in this category, while n_dx refers to the number of diagnoses in this category
*Among the 7 confirmed cases of AIN and 27 confirmed cases of ATI, up to 2 additional diagnoses may be present (not displayed)

FR-PO114

Point-of-Care Ultrasonography for the Diagnosis of Hydronephrosis: A Systematic Review and Meta-Analysis

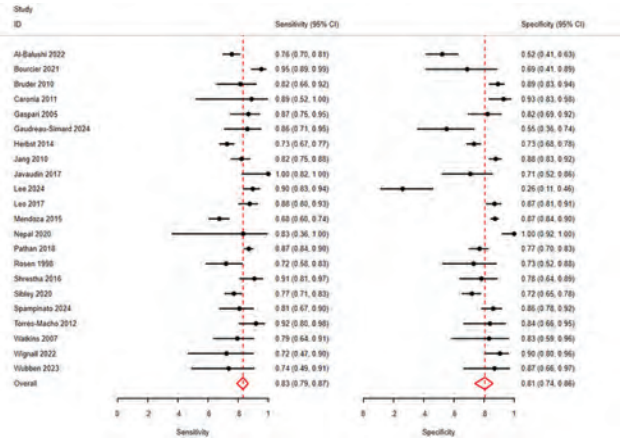
Dominic Wang,[1] Michael K. Wang.[2] *[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]McMaster University, Hamilton, ON, Canada.*

Background: Hydronephrosis is a common sign of urinary tract obstruction detected on imaging. The diagnostic test accuracy of point-of-care ultrasound (POCUS) for hydronephrosis is uncertain.

Methods: We searched MEDLINE, EMBASE, and CENTRAL for observational studies and randomized controlled trials without language restrictions from inception until April 2024. We included studies reporting the diagnostic accuracy of POCUS for hydronephrosis compared to formal radiographic imaging as the reference standard (i.e., ultrasound, computed tomography, and/or intravenous pyelogram performed by a radiology technician or radiologist). We pooled sensitivity and specificity using random-effects models and reported their corresponding 95% confidence intervals (CIs).

Results: We included 22 observational studies (n=4893). The pooled population included patients presenting with flank pain (13 studies), acute kidney injury (AKI) (2 studies), either flank pain or AKI (2 studies), or were unspecified (5 studies). Twenty studies were conducted in the emergency department, 1 study was conducted in hospital wards, and the remaining study was conducted in both an intensive care unit and hospital wards. POCUS had a pooled sensitivity of 0.83 (95% CI 0.79-0.87) and specificity of 0.80 (95% CI 0.74-0.86) for the diagnosis of hydronephrosis when compared to formal imaging. In a subgroup analysis of 3 studies (n=1078), the diagnosis of any severity of hydronephrosis on formal imaging based on moderate to severe hydronephrosis on POCUS demonstrated a pooled sensitivity of 0.32 (95% CI 0.28-0.37) and specificity of 0.96 (95% CI 0.93-0.98).

Conclusions: POCUS has moderate sensitivity and specificity for hydronephrosis and may be used to rule out urinary tract obstruction in patients with a low pre-test probability. Moderate to severe hydronephrosis on POCUS is highly specific for hydronephrosis detected on formal imaging.



Sensitivity and specificity forest plot

FR-PO115

Back to Bedside: Kidney Point-of-Care Ultrasonography (POCUS) by Resident Physicians for Identification of Hydronephrosis in Patients with AKI

Sundus Sardar,[1,5] Rohit Sharma,[2] Abdullah Mohammad Arshad,[3] Mohammed Alamin,[3] Bashar Tanous,[4] Jaweria Akram,[3] Fateen Ata,[3] Rawand Jebril,[3] Abdulrahman Al-Mashdali,[3] Zohaib Yousaf,[6] Muhammad Zahid.[3] *[1]Penn State Health Milton S Hershey Medical Center, Hershey, PA; [2]Department of Internal Medicine, Geisinger Health System, Wilkes-Barre, PA; [3]Hamad Medical Corporation, Doha, Qatar; [4]Department of Internal Medicine, UCSF Fresno, San Francisco, CA; [5]Pennsylvania State University College of Medicine, Hershey, Pennsylvania, Hershey, PA; [6]Tower Health, West Reading, PA.*

Background: POCUS has emerged as a valuable adjunct to bedside clinical examinations. In context of acute kidney injury (AKI), bedside POCUS may facilitate early identification of hydronephrosis indicative of obstructive uropathy as the underlying etiology, thereby enabling timely diagnosis, expediting therapeutic management and decreasing fragmentation of care. Incorporating renal POCUS training in the internal medicine residency program allows residents to develop new skills for day-to-day clinical practice and enhance bedside assessment of patients with AKI.

Methods: We conducted a prospective observational study at Hamad General Hospital, Qatar. Patients were selected from a convenience sample in the Acute Medical Assessment Unit (AMAU) and medical wards for AKI evaluation. Internal Medicine residents underwent mandatory training, including a 30-minute didactic session by a certified physician and performing ten supervised bilateral renal POCUS scans to ensure proper technique. Residents performed bedside renal POCUS to assess hydronephrosis, with findings compared to blinded departmental scans using a common grading system.

Results: Fifty patients with provisional AKI diagnoses based on clinical presentation and renal parameters were included, all pending official renal ultrasound scans. Bedside POCUS identified hydronephrosis in nine patients (one bilateral, eight unilateral). Of these, five were confirmed by departmental ultrasound, and one additional patient with hydronephrosis was missed by POCUS but identified on the formal scan.

Conclusions: This project demonstrated that using POCUS for diagnosing and managing AKI to identify hydronephrosis had a sensitivity of 83.3%, specificity of 93%, positive predictive value of 55.6%, and negative predictive value of 98%. The strength of our study is utilization of senior clinical physicians for POCUS training to guide junior residents in enhancing their skills and bedside assessment of patients with AKI. POCUS-enhanced bedside exams allow residents to identify hydronephrosis in a sensitive and time-efficient manner, facilitating timely diagnosis of obstructive uropathy and appropriate patient management.

FR-PO116

Provider-Performed Point-of-Care Ultrasonography Evaluation of the Kidneys after Kidney Biopsy

Kanza Haq, Nityasree Srialluri, Steven Menez, John Sperati. *Johns Hopkins University, Baltimore, MD.*

Background: Real-time ultrasonographic guidance is standard practice for performing kidney biopsies and is also used to identify post-biopsy bleeding complications. In this study, we aimed to evaluate the accuracy of provider-performed Point-of-Care Ultrasound (POCUS) in identifying post-biopsy bleeding complications.

Methods: Adult patients undergoing outpatient ultrasound (U/S)-guided native kidney biopsy at the Johns Hopkins Hospital between August 2022 – June 2023 were included in the study. Immediate post-biopsy and 4-hour post-biopsy U/S imaging were performed by U/S technicians. POCUS assessments by the nephrology provider were conducted

upon patient arrival to the recovery bay and 4 hours post-biopsy. The nephrology provider was blinded to the findings of the U/S technician. Presence of hematoma, hematoma size, presence of vascular jet, and presence of intra-renal arteriovenous fistula were documented. The prevalence of each complication and sensitivity and specificity of POCUS were calculated.

Results: A total of 82 patients were enrolled. Average age of participants was 55.2 years (SD: 16.5), BMI 28.8 (SD: 6.1), 54.9% were male, 37.8% were Black, and a nephrology attending performed most biopsies (86.6%). Formal radiology U/S detected hematoma and AV fistula in 20.7% (17) and 3.7% (3) immediately post-biopsy and in 40.2 % (33) and 13.4% (11) at 4-hours. By POCUS, hematoma was detected in 19.5% (16) and AV fistula in 2.4% (2) of patients immediately post-biopsy and in 32.9% (27) and 4.9% (4) of patients at 4 hours. When compared with the formal radiology performed U/S, the sensitivity of POCUS for hematoma detection immediately post-biopsy and at 4 hours was 82.4% (95%CI 56.5-96.2) and 75.8% (95%CI 57.7-88.9), respectively. The specificity was 96.2% (95%CI 89.2-99.6) immediately post-biopsy and 95.9% (95%CI 86.0-99.5) at 4 hours. Inter-rater agreement between POCUS and formal radiology U/S for hematoma detection was 93.9 % (κ 0.81) immediately post-biopsy and 87.8 % (κ 0.74) at 4 hours.

Conclusions: Provider-performed POCUS was able to detect post-biopsy bleeding complications with high sensitivity and specificity. This valuable, easily accessible tool should be considered for immediate assessment post-biopsy to expedite decision-making at the bedside. Additional studies are needed to evaluate the utility of POCUS to determine appropriateness for discharge after kidney biopsy.

FR-PO117

Computed Tomography-Measured Subcutaneous Adipose Tissue as a Protective Factor in Patients with Sepsis-Associated AKI Undergoing Continuous Kidney Replacement Therapy

Haeun Lee, Dong Min Kang, Ju hwan Oh, A young Cho, In O Sun.
Presbyterian Medical Center, Jeonju, Jeollabuk-do, Republic of Korea.

Background: The obesity paradox, a phenomenon in which obese patients exhibit improved survival compared to normal weight patients, has been observed in sepsis. However, body mass index does not adequately reflect adipose tissue mass and distribution. We investigated the association between abdominal adiposity and mortality among patients with sepsis-associated acute kidney injury (SA-AKI) undergoing continuous renal replacement therapy (CRRT).

Methods: Between 2011 and 2022, 1,390 adult patients with SA-AKI required CRRT at Presbyterian Medical Center. After excluding those on chronic dialysis, those who died within 24 hours of CRRT initiation, and those with missing data, 330 patients were included in the study. Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) areas were quantified at the L4-L5 level from abdominal CT scans (**Figure 1**). Patients were divided into tertiles based on VAT or SAT values. The second tertile served as the reference, with the first and third tertiles as low and high groups, respectively. The primary outcome was 28-day mortality.

Results: In the high SAT group, 28-day survival was superior compared to the reference group, with no such difference in the low SAT group (**Figure 2A**). In contrast, no significant difference in 28-day survival was observed between the groups based on VAT (**Figure 2B**). Adjusted Cox model analysis indicated high SAT reduced 28-day mortality risk (hazard ratio: 0.675, confidence interval: 0.460 – 0.990).

Conclusions: SAT, but not VAT, may provide a protective effect in patients with SA-AKI requiring CRRT.

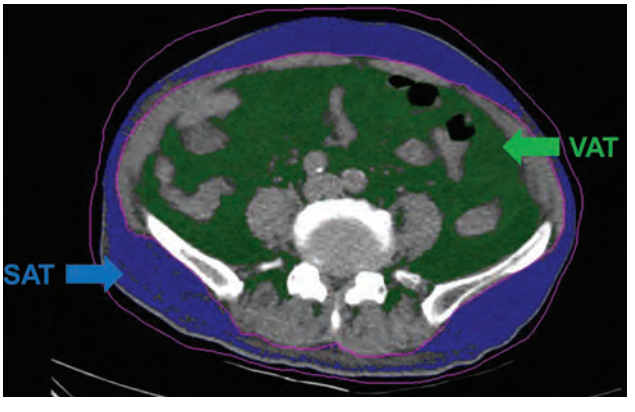
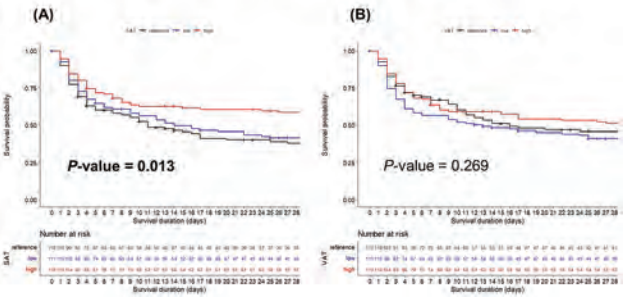


Figure 1. Adipose tissue area quantification

Figure 2. Kaplan-Meier curves according to the SAT and VAT



FR-PO118

Total Kidney Volume and Recovery of Kidney Function in AKI Patients with Kidney Replacement Therapy

Nozomi Kadota, Takuya Fujimaru, Chiharu Aizawa, Kasumi Konishi, Yugo Ito, Masahiko Nagahama, Fumika Taki, Masaaki Nakayama, Michiko Suzuki.
St.Luke's International Hospital, Tokyo, Japan.

Background: Among patients with acute kidney injury (AKI), 10% require renal replacement therapy (RRT), and 15% progress to end-stage renal disease (ESRD) with higher in-hospital mortality. While preexisting chronic kidney disease (CKD) is a risk factor for progression from AKI to ESRD, assessing preexisting CKD at AKI onset is challenging. Total kidney volume (TKV) is known to decrease in CKD. The aim of this study is to investigate whether TKV can predict kidney function recovery in AKI patients.

Methods: We retrospectively investigated AKI patients who required more than three times of RRT from April 2003 to November 2023. Exclusions criterion were the patients with post-kidney transplantation, with polycystic kidney disease, without CT imaging six months before admission, with unmeasurable TKV on CT, or with vascular access for maintenance hemodialysis. The primary outcome was RRT discontinuation within 90 days and no need for RRT for two weeks after discontinuation. TKV was measured using SYNAPSE VINCENT(R) from CT images. Clinical characteristics and laboratory data at RRT initiation were extracted.

Results: Among 446 patients (71.7% male, mean age 68.3 years, mean hospital stay 90.0 days), 179 (40.1%) discontinued RRT within 90 days. In-hospital mortality was significantly lower in the discontinuation group (64.0% vs 17.9%, p<0.001). In multivariate Cox regression analysis with age, sex, TKV, suppressor use, diabetes mellitus (DM), cancer, AKI after surgery, AKI due to acute tubular necrosis, serum albumin and hemoglobin as independent variables, TKV [ml], DM and hemoglobin [g/dl] were significantly associated with dialysis discontinuation (hazard ratio 1.00, 0.70 and 1.11, respectively; 95% confidence interval 1.001 to 1.004, 0.51 to 0.97 and 1.04 to 1.18, respectively).

Conclusions: TKV may predict renal function recovery, offering broader management strategies.

Factors	Hazard Ratio	95% CI for Hazard Ratio	Significance (p value)
Age [yo]	1.00	0.99 to 1.02	0.44
Female	0.76	0.52 to 1.11	0.16
TKV [ml]	1.00	1.00 to 1.00	<0.001
DM	0.70	0.51 to 0.97	0.029
Cancer	0.77	0.53 to 1.11	0.16
Surgery	1.09	0.78 to 1.52	0.62
Suppressor use	0.83	0.61 to 1.13	0.25
AKI due to ATN	1.27	0.80 to 2.02	0.32
Operation	1.09	0.78 to 1.52	0.62
Alb [g/dl]	1.08	0.86 to 1.36	0.49
Hb [g/dl]	1.11	1.04 to 1.18	<0.001

FR-PO119

Serial Multiparametric Kidney Magnetic Resonance Imaging in a Prospective Cohort of Patients with AKI

Rebecca A. Noble,[1,2] Eleanor F. Cox,[2] Maarten W. Taal,[1,2] Nicholas M. Selby,[1,2] Susan Francis.[2] *[1]University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom; [2]University of Nottingham, Nottingham, United Kingdom.*

Background: Recovery from acute kidney injury (AKI) is traditionally measured using serum creatinine but this often over-estimates the degree of renal recovery. Magnetic resonance imaging (MRI) is an imaging modality with promise to improve the understanding and characterisation of renal pathophysiology. In a single renal multiparametric MRI (mpMRI) scan, measures can assess renal morphology, tissue microstructure, oxygenation, perfusion and blood flow. This study aimed to assess the degree of change between 30- and 90-days post AKI, as the first 90 days after AKI appear to be the important in terms of determining outcomes.

Methods: Prospective observational study of 10 participants with AKI of all stages recruited at the time of AKI and followed up with monthly blood and urine samples. MRI scans collected on a Philips 3T Ingenia at Visit 1 (V1, 30-60 day) and Visit 2 (V2, day 90). The MRI protocol included: T2-weighted scans for total kidney volume (TKV), T1 and T2 mapping, DWI, ASL, phase contrast MRI, TRUST-MRI and BOLD $T2^*$.

Results: Participants (5M:5F, median age 64y (IQR 54–68)) had predominantly severe AKI (n=5 stage 3, n=4 stage 2, n=1 stage 1, with median baseline eGFR 82ml/min/1.73m^2 (60-89)) and were heterogeneous in terms of AKI aetiology and subsequent recovery. At V1, 7/10 participants had elevated cortex T1 compared to the healthy range (mean group T1 at V1: 1606±89ms), 3 of these 7 participants returned to the healthy range by V2 (group T1 at V2: 1551±83ms). 3 participants had reduced T2 at V1 compared to the healthy range (group average 99.7±8ms at V1, and group average 100±5ms at V2). Those participants who did not recover renal function at V2 typically had higher T1 and lower T2 at V1, with a trend towards the healthy range at V2.

Conclusions: We observed different patterns of MRI parameter change after AKI which appear to relate to the degree of kidney damage: high T1 suggesting more inflammation and/or oedema and a low T2 suggesting a greater degree of hypoxia. Further analysis will explore how these MRI changes are related to other markers of kidney damage.

FR-PO120

Early Clinical Indicators of ESKD Transition or Kidney Recovery in Patients with AKI on Dialysis

Scott Sibbel,[1] Claire Ryan,[1] Carey Colson,[1] Cicely N. Gibson,[2] Irina Goykhman,[2] Francesca Tentori,[1] Steven M. Brunelli.[1] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO.*

Background: Previous studies reporting factors impacting renal recovery in acute kidney injury (AKI) patients were limited to the inpatient setting. With the 2017 changes to Medicare Reimbursement, patients with AKI that dialyze in the outpatient setting (AKI-D) are increasing in number. We sought to investigate which early indicators in AKI-D patients, those preceding or captured during the hospitalization, predict the likelihood of transition to ESKD or recovery.

Methods: For this analysis, we used the Optum® de-identified Integrated Claims-Clinical Dataset that links administrative claims and clinical data from providers across the continuum of care.[1] Patients included in the study (n=760) were >18 years old, had a claim from 2017-2023 for in-hospital dialysis and an AKI diagnosis and began outpatient dialysis within 3 days of discharge; patients with a previous dialysis treatment or ESKD diagnosis were excluded. We employed a case control study among those that recovered vs. those yet to have recovered.

Results: Those that recovered were younger (63 vs. 68 years old), were more likely to have AKI attributed to acute tubular necrosis (ATN) and/or sepsis during hospitalization; and less likely to have prior diagnoses of CKD 4/5 or cardiovascular disease (PVD, CAD, CVD, and CHF). A heuristic developed from the integrated data set segregates patients into two groups: high likelihood of recovery (64%) vs. a low/medium likelihood of recovery (30% and 45%, respectively).

Conclusions: When considered together, these attributes of patient's medical history and diagnoses can be used to reasonably predict the AKI patients that will recover in the outpatient setting. However, better data collection strategies, testing, and validation are necessary to ensure validity. [1] Optum's de-identified Integrated Claims-Clinical dataset (2007-2021)

	Percent of patients	Likelihood of Recovery
Absence of ATN Or Prior history of CKD 4/5	55%	Low (30%)
+ATN; No prior history CKD 4/5 With History of PVD	16%	Medium (45%)
+ATN; No prior history CKD 4/5 And History of PVD	29%	High (64%)

FR-PO121

Derivation and Validation of Clinical Subphenotypes of AKI with Prognostic Implications in Critically Ill Children

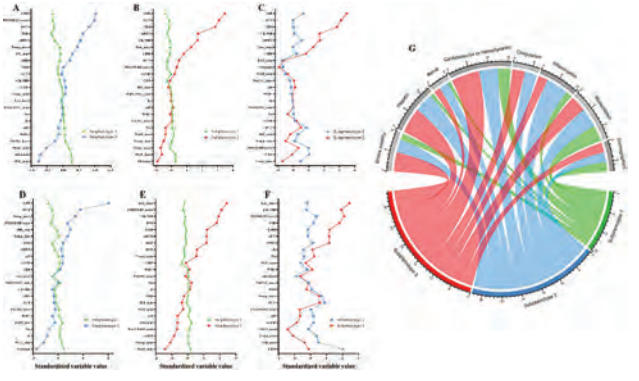
Yanhong Li, Junlong Hu. *Soochow University, Suzhou, China.*

Background: AKI is a heterogeneous syndrome. Identification of distinct clinical subphenotypes (SPs) may allow more precise therapy and improve care. We aim to derive and validate AKI SPs and determine whether the SPs were relevant with respect to outcomes in critically ill children.

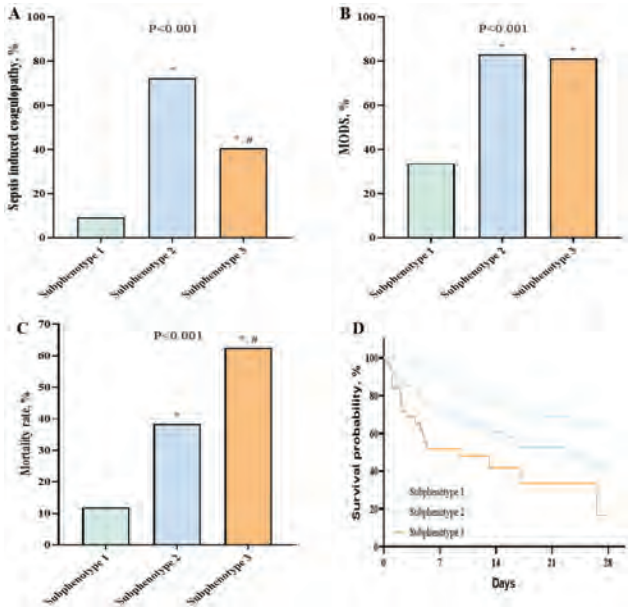
Methods: This is a secondary analysis of our prospective multicenter cohort study, including AKI children met KDIGO criteria or predicted by our prediction model. Medical characteristics easily obtained within the first 24h after PICU admission were employed to select features using the SHapley Additive exPlanation. Latent profile analysis (LPA) was used to identify distinct SPs in derivation cohort and validated in external cohort.

Results: Three SPs were derived among 332 children and validated in 242 using LPA applied to 23 features. Children in SP1 (74.9%) exhibited the least severe illness and organ injury and responded well to milrinone; those in SP2 (19.5%) suffered severe inflammatory response and homeostatic imbalance; those in SP3 (5.6%) suffered more severe hepatic and cardiovascular dysfunction and the highest risk of mortality.

Conclusions: Three SPs were identified in critically ill children with AKI that correlated with outcomes. Further research is needed to determine the utility of the SPs in clinical care and trial design.



Comparison of variables contributing to SPs. Chord diagrams showing abnormal variables by SPs



Comparison of the incidence rate. Kaplan-Meier curves

FR-PO122

A Global Data Approach to Prediction of 30-Day Readmission among Patients with Heart Failure and AKI

Meredith C. McAdams,[1,2] Yaser Elnakieb,[1] Samir M. Parikh.[1] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]Veterans Affairs North Texas Health Care System, Dallas, TX.*

Background: Heart failure (HF) is the leading hospitalization diagnosis in the US. Acute kidney injury (AKI) affects between 10-43% of individuals admitted with HF. Published outcomes models for HF complicated by AKI have poor predictive performance due to small patient numbers, single center data, and variable definitions of AKI.

Methods: The global healthcare database *TriNetX Research* was used to identify patients hospitalized with HF and AKI. Electronic health record (EHR) data including diagnoses, procedures, demographics, vital signs, medications, and laboratory values were obtained. Variables were encoded and pre-processed and the data was split into training and testing cohorts. Various machine learning models were used to build preliminary risk prediction models for 30-day readmission with 5-fold cross-validation. Initial models included only information available during the index hospitalization, no historical data was used. Model performance was evaluated on the hold-out test sets, assessing accuracy, sensitivity, specificity, area under the ROC curve (AUC), and balanced accuracy to comprehensively measure each model's predictive power.

Results: Of 250 million unique patients in *TriNetx*, 271,388 patients hospitalized with HF and AKI were identified. Of these individuals, 78,806 (29%) were readmitted within 30 days. A preliminary logistic regression model for 30-day readmission had an area under the curve (AUC) of 0.63. An initial random forest model had an AUC of 0.65. Adding different feature selection techniques to the models did not improve the AUC. Variables with high importance in both the logistic and random forest models included elements of the complete blood count, blood gas, metabolic profile, urinalysis, and electrocardiogram.

Conclusions: We have identified a large cohort of patients hospitalized with HF who have concurrent AKI. Importantly, this group has a high rate of 30-day readmission. Both models performed poorly for the prediction of 30-day readmission despite converging on variables that routinely inform clinical care in this morbid population. A unique opportunity therefore exists to develop a well-powered and robust risk prediction model by adding machine learning techniques, including deep learning and transformers, and including historical and dynamic EHR data elements.

FR-PO123

Acute Kidney Cortical Necrosis following Cardiac Catheterization: A Diagnostic Challenge

Johanna Marie S. Orejo, Aala Jabero. *Boston Medical Center, Boston, MA.*

Introduction: Atheroembolic renal disease is a rare but serious cause of renal failure among patients who underwent cardiac catheterization. It can lead to ischemic renal cortical necrosis due to microvascular injury. Renal biopsy is the gold standard for the definitive diagnosis, however, this is not possible for patients who are at high risk of bleeding. We present a case of a patient who developed severe acute kidney injury (AKI) following cardiac catheterization. He was diagnosed with renal cortical necrosis using a nuclear dimercaptosuccinic acid (DMSA) renal scan.

Case Description: A 61-year-old male with a past medical history of hypertension and coronary artery disease was sent to the emergency department after a routine Cardiology follow-up for evaluation and management of AKI. His laboratory test showed elevated BUN of 57 mg/dL and serum creatinine of 15.14 mg/dL from a baseline of 1 mg/dL. 3 weeks prior, the patient underwent left heart catheterization and drug-eluting stent (DES) placement for NSTEMI. His hospital course was uncomplicated and he was discharged with a stable renal function. On presentation, the patient reported decreased urine output, otherwise the history and physical examination were unremarkable. His work-ups including a renal ultrasound were unrevealing. A renal biopsy was planned, however, the patient was at high risk for bleeding due to his dual antiplatelet therapy for a recent coronary DES placement. Upon discussion with the Nuclear Medicine department, a DMSA renal scan was obtained to assess the kidney function and to help in the diagnosis of possible cortical infarction. The patient's results showed heterogeneity of uptake compatible with suspected cortical necrosis. The patient had a good renal recovery after undergoing a few treatments with hemodialysis.

Discussion: The diagnosis of atheroembolic renal disease following cardiac catheterization is challenging as the patients may present with non-specific symptoms and unrevealing AKI workups. Renal biopsy is the gold standard to confirm the diagnosis, however, this is a diagnostic challenge as there is a high risk of bleeding for patients who are receiving dual anti-platelet therapy following DES. DMSA, a renal nuclide scan, can provide both functional and anatomic information. This case highlights that radionuclide studies may be utilized in such cases when kidney biopsy is not possible.

FR-PO124

Markers for Cell Death and Purine Metabolites in Patients with and without Delayed Graft Function after Kidney Transplantation

Max Warncke,[1] Armelle Lafont,[1] Laurent Klein,[1] Monica R. Nakamura,[2] Helio T. Silva,[2] Karl Welzenbach.[1] *[1]Novartis AG, Basel, Switzerland; [2]Hospital do Rim, Goionia, Brazil.*

Background: Delayed graft function (DGF) is defined as the dysfunction of the kidney after transplantation (TX) and manifestation of acute tubular necrosis (ATN). Tubular necrosis is one hallmark of DGF, but there is still an incomplete understanding about the trajectories of biomarkers of tissue injury post transplantation. Markers to identify patients at risk for DGF would support the development of novel therapeutic treatments to ameliorate or reduce DGF in the globally growing number of transplanted patients.

Methods: Plasma and urine samples of 41 patients receiving grafts of living donors (10), or grafts from deceased donors with standard criteria (16) or expanded criteria donors (15) were prospectively collected over 28 days after TX. Markers of tissue injury (plasma LDH, Cystatin C (CycC), AST, ALT, CK), NGAL and urinary purine metabolites (ATP, adenosine) were assessed. The association of markers early post TX with DGF diagnosis was evaluated.

Results: Among the 31 patients who received a deceased donor graft, 19 developed DGF, while the remaining 11 did not experience DGF. The incidence of DGF in patients receiving a cadaveric graft was 61%. The 10 patients with grafts from living donors did not develop DGF. Markers of tissue damage were modulated in plasma of patients following TX. Patients receiving living donor organs showed significantly lower TX-induced modulation of biomarkers suggesting a milder insult on grafts and recipients. Urinary adenosine was significantly lower in the 28 days after transplantation in patients with DGF correlating well with increased plasma CysC and NGAL levels. All markers normalized 3-4 weeks after TX. The relative elevation of LDH and AST at 4h after surgery preceded the development of DGF in ~40% of patients who received a graft of a deceased donor.

Conclusions: This study provides a comprehensive trajectory of established and more recent markers of kidney function, potentially graft quality and the relationship to DGF after kidney transplantation in kidney TX patients. The early induction of tissue damage markers shows the importance to start therapies to protect from DGF as early as possible. The observed decrease of urinary adenosine in patients with DGF point to an important function of the purinergic pathway in this patient population.

FR-PO125

Decrease in Platelet Count in Patients with AKI and Its Association with Major Adverse Kidney Events

Jonathan Chavez,[1,2] Guillermo Garcia-Garcia,[1] Ramon Medina,[1,2] Zarahi Andrade,[1] Juárez Correa de León,[1] Eduardo M. Hernández,[1] Jorge L. Padilla Armas,[1] Rebeca L. Ornelas Ruvalcaba,[1] Jose S. Cabrera Aguilar,[1] Alejandro Martínez Gallardo González,[1] Maria de la Luz Alcantar Vallin,[1] Guillermo Navarro Blackaller.[1] *[1]Universidad de Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico.*

Background: A reduction in platelet count in critically ill patients is a marker of severity of the clinical condition. However, whether this association holds true in acute kidney injury (AKI) is unknown. We analyzed the association between platelet reduction in patients with AKI and major adverse kidney events (MAKE).

Methods: In this retrospective cohort, we included AKI patients at the Hospital Civil of Guadalajara, in Jalisco, Mexico. Patients were divided according to whether their platelet count fell >21% during the first 10 days. Our objectives were to analyze the associations between a platelet reduction >21% and MAKE at 10 days (MAKE10) or at 30-90 days (MAKE30-90) and death.

Results: From 2017 to 2023, 400 AKI patients were included, 134 of whom had a >21% reduction in platelet count. The mean age was 54 years, 60% were male, and 44% had sepsis. The mean baseline platelet count was 194 x 103 cells/mL, and 65% of the KDIGO3 patients met these criteria. Those who underwent hemodialysis (HD) had lower platelet counts. After multiple adjustments, a platelet reduction >21% was associated with MAKE10 (OR 4.2, CI 2.1-8.5) but not with MAKE30-90. The mortality risk increased 3-fold (OR 2.9, CI 1.1-7.7, p= 0.02) with a greater decrease in the platelets (<90 x 103 cells/mL). As the platelets decreased, the incidence of MAKE was more likely to increase. These associations lost significance when accounting for starting HD.

Conclusions: In our retrospective cohort of patients with AKI, a >21% reduction in platelet count was associated with MAKE. Our results are useful for generating hypotheses and motivating us to continue studying this association with a more robust design.

FR-PO126

Procalcitonin (PCT) Levels in Septic and Nonseptic Participants with AKI before and during Continuous Kidney Replacement Therapy (CKRT)

North Foulon, Kayo Okamura, Zhibin He, Matt R. Kennis, James F. Colbert, Sarah Faubel. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: PCT is a 14.5 kDa protein and biomarker of bacterial infection. PCT is increased in ESKD and plasma levels decline after hemodialysis, suggesting clearance by the kidney and KRT. Herein, we measured plasma PCT in septic and non-septic patients with AKI and tested the hypothesis that PCT would be increased in AKI without sepsis and cleared by CKRT.

Methods: Plasma and effluent PCT were determined in septic and non-septic subjects with AKI that were selected from a prospective observational cohort of 126 patients who received CKRT at a single center. Plasma was collected prior to CKRT initiation, and plasma and effluent were collected on days 1, 2, and 3 of CKRT. Inclusion criteria for sepsis subjects were: 1) AKI without CKD, and 2) clinical diagnosis of sepsis and 2/2 positive blood cultures. Inclusion criteria for non-septic subjects were: 1) AKI without CKD, and 2) no clinical diagnosis of sepsis and no positive blood cultures. The sepsis cohort contained 9 patients, and the non-septic cohort contained 27 patients. 9 healthy control (HC) subjects with neither kidney disease nor sepsis were also studied.

Results: Plasma PCT was significantly increased in non-septic subjects with AKI vs. healthy controls. Plasma PCT was significantly increased in septic AKI subjects compared to non-septic (Figure 1). No significant difference existed in serum PCT of septic or non-septic AKI patients after 3 days of CKRT compared to pre-CKRT samples (Figure 2A and 2B). The average sieving coefficient for procalcitonin was 0.27 (Figure 3A). The average procalcitonin clearance was 7.05 L on day 1, 12.84 L on day 2, and 10.94 on day 3 of CKRT (Figure 3B).

Conclusions: Plasma PCT is significantly increased in non-septic patients with AKI suggesting that acute kidney function decline affects plasma PCT levels. Although some level of PCT clearance by CKRT was observed, changes in serum PCT were unpredictable during CKRT in both septic and non-septic patients. Our data suggest PCT results should be interpreted cautiously in patients with AKI prior to and during CKRT.

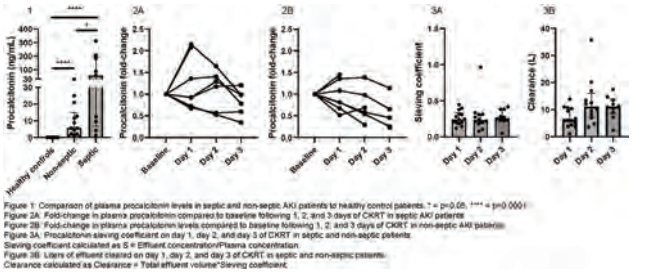


Figure 1: Comparison of plasma procalcitonin levels in septic and non-septic AKI patients to healthy control patients. * = p<0.05, **** = p<0.0001
Figure 2A: Fold-change in plasma procalcitonin compared to baseline following 1, 2, and 3 days of CKRT in septic AKI patients
Figure 2B: Fold-change in plasma procalcitonin levels compared to baseline following 1, 2, and 3 days of CKRT in non-septic AKI patients
Figure 3A: Procalcitonin sieving coefficient on day 1, day 2, and day 3 of CKRT in septic and non-septic patients.
Sieving coefficient calculated as S = Effluent concentration/Plasma concentration
Figure 3B: Liters of effluent cleared on day 1, day 2, and day 3 of CKRT in septic and non-septic patients.
Clearance calculated as Clearance = Total effluent volume*Sieving coefficient

FR-PO127

Magnesium Levels and Mortality in Critically Ill Patients with AKI

Supawadee Suppadungsuk,[1,2] Charat Thongprayoon,[1] Waryaam Singh,[1] Wisit Cheungpasitporn,[1] Kianoush Kashani.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Chakri Naruebodin Medical Institute, Bang Phli, Thailand.*

Background: Magnesium derangement affects endothelial function and inflammation. It also associated with a declines in renal function and increases the risk of death in chronic kidney disease (CKD) and hemodialysis patients. This study aims to assess the significance of serum magnesium derangements in short—and long-term outcomes among critically ill patients with acute kidney injury.

Methods: This cohort study was conducted among patients with AKI admitted to the intensive care units at Mayo Clinic from January 2007 to December 2017. Serum magnesium levels at AKI onset were categorized into five groups of <1.7, 1.7-1.9, 1.9-2.1, 2.1-2.3, and ≧2.3 mg/dL, with 1.9-2.1 mg/dL as the reference group for outcome comparison. Multivariable logistic regression was used to evaluate the association between serum magnesium levels and mortality.

Results: Among 20,198 critically ill patients with AKI, the mean age was 66±16 years, and 57% were male. The mean serum magnesium at AKI onset was 1.9±0.4 mg/dl. The overall incidence of in-hospital and 1-year mortality were 11.6% and 31%, respectively. In multivariable analysis, hypermagnesemia (>2.3 mg/dl) was associated with increased risk of in-hospital and 1-year mortality with the odds ratio of 1.4 (95% CI 1.22-1.65) and 1.48 (95% CI 1.33-1.65), respectively.

Conclusions: Hypermagnesemia (Mg ≧2.3 mg/dL) was associated with increased in-hospital and 1-year mortality in critically ill AKI patients. Serum magnesium monitoring and proper magnesium level correction in critically ill patients with AKI should be considered. Further studies that evaluated the magnesium treatment effect are recommended.

FR-PO128

Comparative Efficacy of Frailty and Barthel Index in Predicting AKI in Critically Ill Geriatric Patients

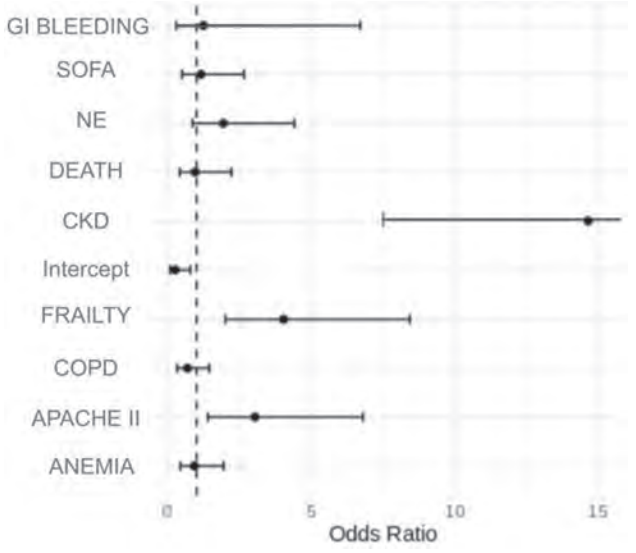
José A. Novoa Burquez. *Hospital Civil de Guadalajara Unidad Hospitalaria Fray Antonio Alcalde, Guadalajara, Mexico.*

Background: The Barthel Index describes functional independence and the FRAIL questionnare predicts fragility in theelderly, this comorbidity is a risk factor to develop acute kidney injury (AKI). Thisstudy, aimed to explore the association between Barthel Index, Fraility and AKI in a geriatric ICU population.

Methods: In a retrospective cohort in the Hospital Civil of Guadalajara, elderly ICU patientswere recluted. Frailty was measured CFS and FRAIL questionnare, functional independence by Barthel Index and AKI by KDIGOguideline. We test the predictive capability of Barthel Index and Fraility to develop AKI by logistic regression analysis and predictive accuracy.

Results: In a total of 207 geriatric ICU patients with mean age of 78 years, 48% being classified as frail and 60% developed AKI. AKI presented in 59.5% in the frailgroup, and in 30.9% of non-frail. The mean Barthel Index was 67, it has nocorrelation with the risk of AKI (p = 0.9). Frailty has a positive correlation with thedevelopment of AKI (adjusted odds ratio = 4.04, p < 0.001). ROC curve analysis 0.6432, further indicated that frailty predicts better the occurrence of AKI than the Barthel Index.

Conclusions: Frailty is a good predictor of AKI in ICU elderly patients, and is better than the Barthel Index.



FR-PO129

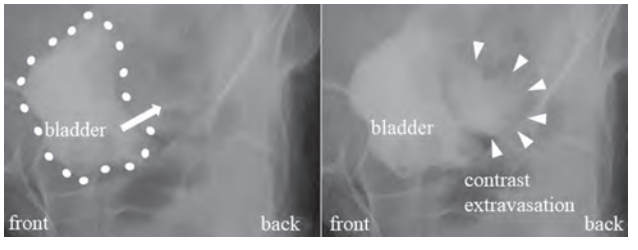
An Overlooked Cause of Pseudo-Kidney Failure Due to Spontaneous Bladder Rupture 8 Years after Radiation Therapy

Makoto Ando, Akiko Kudo, Hiroki Uchida, Takeshi Nakata, Akihiro Fukuda, Hirotaka Shibata. *Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan.*

Introduction: Pseudo-renal failure is characterized by acute renal failure-like abnormalities despite normal renal function. The most common cause is bladder rupture. Pseudo-renal failure occurs secondary to reverse peritoneal dialysis. The initial diagnosis rate of bladder rupture is low; it is often misdiagnosed as peritonitis or acute renal failure. We report a case of pseudo-renal failure due to spontaneous bladder rupture and discuss its diagnostic challenges.

Case Description: A 55-year-old woman underwent total hysterectomy and chemoradiotherapy for cervical cancer 8 years previously. She visited her family hospital because of abdominal pain and diarrhea, and ascitic effusion and elevated serum creatinine (S-Cr) were found. Fluid therapy was given for dehydration due to diarrhea, and antibiotic therapy was given for peritonitis due to enteritis. However, she was admitted to our hospital because of her high S-Cr level (9.7 mg/dL) and increased ascites. She had oliguria and uremic symptoms, and we performed diagnostics while initiating hemodialysis. We suspected urinary ascites because the serum cystatin C level (1.2 mg/dL) was inconsistent with the S-Cr level, and both the urea nitrogen (125.8 mg/dL) and creatinine (27.5 mg/dL) levels in the ascites were extremely high. Cystography showed leakage of contrast medium into the abdominal cavity (Figure), indicating pseudo-renal failure due to spontaneous bladder rupture. The S-Cr level normalized 2 days after urethral catheter insertion, and the ascites disappeared.

Discussion: The incidence of spontaneous bladder rupture is approximately 0.002%, and pelvic radiation and alcohol intoxication are the most common causes. The initial misdiagnosis rate is 64% because of the nonspecific symptoms, and delayed diagnosis is common. Cystography is useful for definitive diagnosis. In this case, the increased ratios of S-Cr to cystatin C and ascites creatinine to S-Cr assisted the diagnosis, as reported in previous studies. The differential diagnosis of pseudo-renal failure is important when acute renal failure with ascites effusion occurs after pelvic radiation.



FR-PO130

Inflammation and Infection: An AKI Diagnostic Dilemma

Hailey V. Hildebrand,[1,2] Emily G. Jeon,[1] Lisa M. Miller.[1] *[1]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [2]Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, MB, Canada.*

Introduction: Glomerular full-house immune complex deposition is a characteristic finding of lupus nephritis; however, in rare cases it can occur with other glomerulopathies. We present a case of non-lupus glomerulonephritis leading to full-house immunostaining on renal biopsy.

Case Description: A 50-year-old gentleman presents with a one-month history of rash and a 20-kilogram weight loss over the past year. He denied infectious symptoms, arthralgias, or other constitutional symptoms. His examination was remarkable for palpable purpura on his legs. Initial investigations revealed an elevated creatinine 114 mmol/L, proteinuria (72mg/mmol) and hematuria. Further work-up showed low serum complements, but normal antinuclear antibodies and anti-double stranded DNA. CT imaging of the abdomen showed splenic infarcts and normal kidneys. He was started on empiric prednisone due to suspicion for an autoimmune process, but on further assessment, he was found to have poor dentition concerning for infectious endocarditis. Prednisone was stopped, and blood cultures returned positive for streptococcus mutans. He was hospitalized and started on ceftriaxone. A transesophageal echocardiogram showed vegetations on the mitral and aortic valves. A kidney biopsy was performed which showed moderate endocapillary hypercellularity with no significant tubular atrophy or interstitial fibrosis. Immunofluorescence was positive for IgG, IgA, IgM, C3, and C1q consistent with full-house immunostaining, suggesting a diagnosis of diffuse proliferative lupus nephritis. However, based on the lack of clinical manifestations and the negative lupus serology, it was suspected that this was a rare biopsy finding associated with infection-related glomerulonephritis (IRGN). He underwent CABG with atrial and mitral valve repair. Following completion of antibiotics his creatinine had normalized consistent with a resolved IRGN.

Discussion: Glomerular full-house immunostaining typically occurs in lupus nephritis; however, it can occur in other diseases including IgA nephropathy, membranoproliferative glomerulonephritis, and IRGN. It is speculated that this deposition may occur in more severe forms of IRGN due to superantigen formation. This case emphasizes the importance of clinical presentation when interpreting renal biopsy findings as rarely patients with full-house immunostaining may have a diagnosis other than lupus nephritis.

FR-PO131

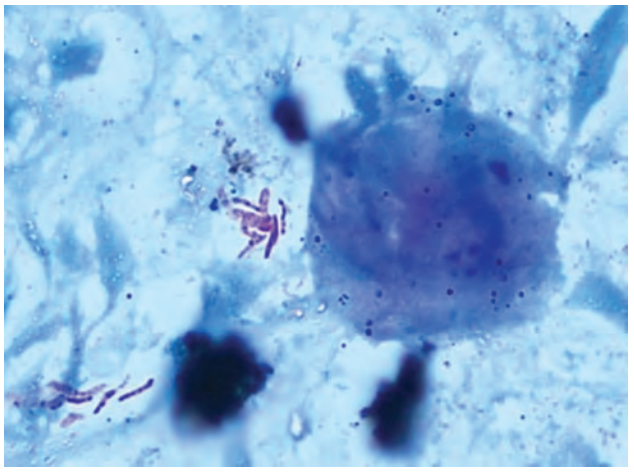
Importance of Kidney Biopsy in Interstitial Nephritis Caused by Mycobacterium Tuberculosis: A Case with Negative Noninvasive Test Results

Itzel A. Martinez,[1] Ana S. Vargas,[1] Victor M. Muñoz,[1] Maria J. Sanchez Perez,[1] Cristopher C. Sanchez Rodriguez,[1] John Hernandez Flores.[1,2] *[1]Operadora de Hospitales Angeles SA de CV, Ciudad de Mexico, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Introduction: Mycobacterium tuberculosis (MTB) is an intracellular pathogen with a wide range of clinical manifestations, including interstitial nephritis (IN). Diagnosing IN due to MTB can be challenging, as non-invasive tests like QuantiFERON and GeneXpert may yield negative in some cases. Renal biopsy (Rb) remains the gold standard.

Case Description: A 61-year-old man with a urothelial cancer treated with lymphadenectomy and bladder resection with robotic neo-bladder creation in March 2023. He finished at july 2023 gemcitabine and cisplatin with a GFR of 80, free tumor activity. Four months after, he presented weakness and weight loss. His creatinine up over two months along with leukocyturia, hematuria, glycosuria, and proteinuria. He presented at hospital with hemodialysis emergency and severe anemia (normal transferrin receptor/ elevated ferritin levels). US reported a small right kidney and an enlarged left one, indicating a high risk for Rb. Infectious and autoimmune tests were performed (Figure 1). He recieved 3x methylprednisolone boluses and rapid tapering. The Rb showed granulomas, severe tubular damage, and ZN positive bacilli, 50% fibrosis and tubular atrophy. The patient started third-line anti-MTB: rifampicin, isoniazid, clarithromycin, levofloxacin, linezolid, and amoxiclav for two months induction. The last GFR is 30 and continue improving since he discontinued hemodialysis in the first month.

Discussion: Rb remains the gold standard for diagnosing MTB-induced IN, even in patients with negative non-invasive test results. Early diagnosis and treatment are essential for improving the prognosis of patients with this disease.



Etiology	Tests				
Infectious (All Negative)	CMV, HSV, HBV, HCV, HIV.	Galactomannan urine antigen.	Brucella.	Chlamydia, Neisseria, Ureaplasma, Mycoplasma, Trichomonas.	QuantiFERON Gene-Xpert Bacilloscopy.
Autoinmmune (All Negative)	C3, C4, ANAs.	Subclasses IgG4.	Anti SSA / Ro, Anti SSB / La.	MPO/ PR3.	Angiotensin converting enzyme.
Inflamatory	Ferritin >2000mg/dl.	ESR >150mm/h.	CRP > 100 mg/dl.	IL-2 alfa receptor >1584 U/mL	

FR-PO132

Brewing Trouble: Tea Consumption and AKI in a Patient on Immune Checkpoint Inhibitor Therapy

Renata Vallecillo, Carl S. Dernell, Paul Hanna. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Acute interstitial nephritis (AIN) is a well-recognized immune related adverse effect (irAE) of immune checkpoint inhibitors (ICIs). AIN can also be secondary to other drugs such as proton pump inhibitors (PPIs), and less commonly, hyperoxaluria – which may result from malabsorption or excessive dietary intake of oxalate-rich foods. Thus, AIN poses a diagnostic challenge in patients with multiple risk factors, often necessitating a kidney biopsy to identify the underlying cause.

Case Description: A 70-year-old female with chronic kidney disease, gastric bypass, and lung adenocarcinoma on immunotherapy was evaluated for acute kidney injury (AKI). The patient had recently started ICI and PPI therapies and had an increase in serum creatinine from a baseline of 1.7 mg/dL to 2.9 mg/dL seven days post-initiation of ICI therapy. Urinalysis was negative for hematuria and proteinuria. ICI-induced nephritis was considered unlikely due to the timing of AKI onset and absence of other irAEs. The patient reported substantial tea consumption preceding the AKI. A kidney biopsy revealed AIN with scattered tubulointerstitial calcium oxalate crystal deposition (**Fig 1**). Discontinuation of her tea and initiation of a prolonged steroid taper led to a return of renal function to baseline.

Discussion: This case highlights the diagnostic challenge of AKI in the context of multiple potential AIN culprits, including ICI therapy in CKD, PPI use, and dietary consumption of tea in gastric bypass patients. AKI in patients on ICI therapy warrants a broad differential diagnosis, including a full assessment of irAEs, past medical and surgical history and dietary habits. This case highlights the value of kidney biopsy in distinguishing between potential etiologies and guiding appropriate management without interrupting lifesaving cancer treatment.

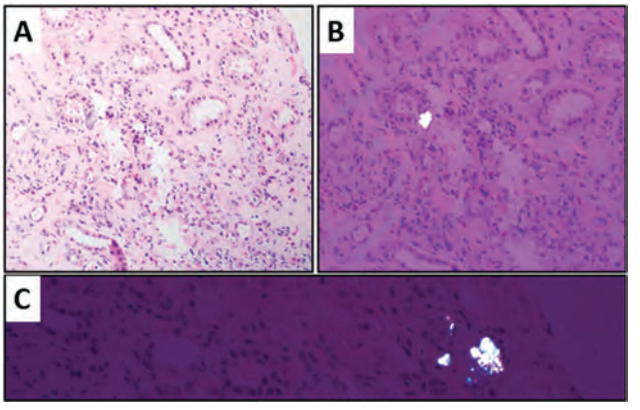


Figure 1: Kidney biopsy. (A) Medullary tubulointerstitial inflammation with eosinophils (arrows). Scatted medullary **(B)** and cortical **(C)** calcium oxalate crystals under polarized light.

FR-PO133

Idiopathic Hypocomplementemia and Interstitial Nephritis: A Case Report

Rucci Marcus C. Foo, Shimontini Mitra, George J. Kavalam, Jeffrey H. William. *Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: Interstitial nephritis is a significant cause of renal failure in patients with autoimmune disease. Typically, this condition is associated with IgG4-related disease or systemic lupus erythematosus, often presenting with low complement levels. Here, we present a case of idiopathic hypocomplementemia with interstitial nephritis without evidence of IgG4-related disease.

Case Description: A 64-year-old woman with a history of right-sided pulmonary embolism, a large exudative pleural effusion in October 2023, moderate pulmonary hypertension, hypertension, and sarcoidosis presented in November 2023 with elevated creatinine levels of 2.8 mg/dL. On exam, she exhibited severe edema. During her hospitalization, her creatinine subsequently rose to 5.4 mg/dL. She was given pulse-dose steroids for three days, without improvement in the acute kidney injury. Her C3 was 30 mg/dL; her C4 was 3 mg/dL. ANA and dsDNA were positive. The renal biopsy showed immune complex-mediated glomerulonephritis with mesangial deposits immunoreactive for C3 and C1q, with weak reactivity for polyclonal IgG and IgA. Immunofluorescence revealed extensive, diffuse immune complexes within the tubular basement membranes, interstitium, and vasculature. There were no cellular crescents, fibrinoid necrosis, or endocapillary hypercellularity observed. Additionally, no plasma cells were identified, making IgG4-related disease less likely. Importantly, there was severe acute interstitial nephritis with associated acute tubular injury, likely a response to the numerous tubulointerstitial deposits. Frequent finely granular electron-dense deposits were present in the mesangium. The patient eventually succumbed to acute kidney injury, complicated by septic shock in the setting of immunosuppression and extent of illness. Autopsy reaffirmed the diagnosis of an autoimmune process most consistent with idiopathic hypocomplementemia and interstitial nephritis.

Discussion: Idiopathic hypocomplementemia and interstitial nephritis is a rare entity that can cause renal failure and death if not identified promptly. Over the past few decades, many cases initially considered idiopathic have been recategorized under IgG4-related disease. This case illustrates the continued utility of renal biopsy in diagnosing undifferentiated renal failure and identifying the underlying disease process.

FR-PO134

Scleroderma Renal Crisis as First Manifestation of Systemic Sclerosis

Buadi K. Tandoh, Milagros Yunes. *Montefiore Medical Center, Bronx, NY.*

Introduction: Scleroderma renal crisis (SRC) is a rare life-threatening complication of scleroderma typically characterized by abrupt onset of severe hypertension and progressive kidney failure. Most cases occur in patients with diffuse scleroderma compared to individuals with limited cutaneous disease. SRC mostly occurs in the first four years of diagnosis of scleroderma but may rarely, be the herald sign of underlying scleroderma. Here, we describe a patient with no prior diagnosis of scleroderma presenting with SRC.

Case Description: 51-year-old female with normal renal function, right ventricular dysfunction, severe pulmonary hypertension on home oxygen, who presented to the emergency room with one-week of shortness of breath and orthopnea. She also had a two-year history of intermittent painful ulcers on fingertips. At home, she was on furosemide 20mg daily and recently prescribed a 14-day course of prednisone 40mg daily. On presentation, blood pressure was 171/119, lung with rales, extremities with sclerodactyly and tender ischemic ulcers on fingertips. Laboratory data with serum creatinine (Scr) of

2.7 mg/dl (from baseline of 0.6 mg/dl). Urinalysis with moderate blood, 100 red blood cells, microalbumin-creatinine ratio of 478mcg/mg and total urine protein-creatinine ratio of 1.7g. Given clinical features of sclerodactyly, hypertension, and renal failure, SRC was considered. Oral captopril was started. Serologies with positive Anti-Nuclear-Antibody titer >1:1280 in a speckled pattern, positive ribonucleic (RNA) polymerase III antibody, negative topoisomerase I antibody and 61% ADAMTS13 activity. Scr continued to rise, and a renal biopsy was done. Light microscopy showed subacute thrombotic microangiopathy with predominant involvement of the blood vessels, diffuse ischemic glomerular changes and moderate tubulointerstitial scarring consistent with SRC. A skin punch biopsy showed fibrosing dermopathy consistent with scleroderma. She required hemodialysis due to worsening renal function. The patient's hospital course was complicated by seizure, superior sagittal sinus thrombosis and then cardiac arrest for which she was pronounced dead.

Discussion: SRC has a high mortality rate and prompt aggressive care is warranted. Although being a rare presentation, SRC should be considered in clinical situations where patients present with suspected skin features despite no established diagnosis of scleroderma.

FR-PO135

Two Cases of Atypical Sarcoidosis Presenting with AKI: Clinical Significance of Sequential Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/CT Images

Yui Mohri,[1] Shinya Yamamoto,[1] Yoko Shimizu,[1] Sho Koyasu,[2] Motoko Yanagita.[1]
[1]Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [2]Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University, Kyoto, Japan.

Introduction: Refractory hypercalcemia can be caused by sarcoidosis, which can induce severe and irreversible renal impairment without appropriate therapy. Therefore, clinicians must correctly diagnose sarcoidosis using serological, radiological, and pathological evaluation.

Case Description: **Case1**: A 76-year-old female was admitted to our hospital with general fatigue. Laboratory tests revealed renal dysfunction (sCre: 2.77 mg/dL), hypercalcemia (12.9 mg/dL). The levels of activated vitamin D was elevated. No respiratory, skin or eye lesions were observed. Renal biopsy revealed no granulomatous lesions. PET/CT showed accumulation in the muscles of the whole body with Tiger-man sign. Muscle biopsy showed granuloma with multinucleated giant cells. The patient was finally diagnosed with muscular sarcoidosis. After starting oral prednisolone 0.7 mg/kg/day, hypercalcemia and renal dysfunction improved. Three months later, PET/CT showed that the accumulation had disappeared. **Case 2**: A 74-year-old male was referred to our hospital with swallowing pain and diagnosed with esophageal cancer. PET/CT showed accumulation in the hilar and mediastinal lymph nodes and bilateral thigh muscles. The patient started chemotherapy. Two months later, repeated PET/CT showed reduced accumulation in the lymph nodes, but new accumulations in the lower leg. Blood tests revealed renal dysfunction (sCre: 3.5 mg/dL) and hypercalcemia (14.3 mg/dL). Muscle biopsy revealed a non-caseating epithelioid cell granuloma. The patient was finally diagnosed with sarcoidosis. Renal biopsy showed lymphocytic infiltration of interstitial and necrotizing vasculitis. Anti-neutrophil cytoplasmic antibodies were negative. After starting oral prednisolone 0.8 mg/kg/day, hypercalcemia and renal dysfunction improved.

Discussion: PET/CT is useful for diagnosis of sarcoidosis, especially in patients without typical organ lesions and in cancer patients with hypercalcemia and lymphadenopathy. While sequential PET/CT in Case 1 clearly showed a good response to treatment, that in Case 2 suggested that emerging muscle lesions contributed to vitamin D activation. In addition, renal biopsy of Case 2 revealed vasculitis, which is a rare complication in patients with sarcoidosis. As previously reported, cancer may trigger sarcoidosis and vasculitis via immune or macrophage abnormalities.

FR-PO136

Granulomatosis with Polyangiitis (GPA) Presenting with Granulomatous Nephritis but No Glomerulonephritis

Mohamed Abdali,[3,1] Praveena Koneru,[1,2] Mili J. Shah,[1,2] Madhumita J. Mohanty.[1,2] *[1]John D Dingell VA Medical Center, Detroit, MI; [2]Wayne State University, Detroit, MI; [3]Detroit Medical Center, Detroit, MI.*

Introduction: We report a patient with worsening renal function and positive ANCA antibody with atypical clinical and histological findings

Case Description: A 83-year-old male with a history of hypertension and working diagnosis of sarcoidosis with recurrent uveitis, skin lesions with biopsy consistent with possible sarcoidosis, and pulmonary nodules, was being treated with mycophenolate mofetil (He was previously on methotrexate). He had an increase in plasma creatinine from 2.2 mg/dl in December 2023 to 4.5 mg/dl in March 2024. His blood pressure was normal, and his examination was unremarkable. He had no proteinuria, hematuria, or urinary casts. Renal ultrasound showed normal sized kidneys with no hydronephrosis. Plasma calcium and complement C3 and C4 were normal. ANA, dsDNA, rheumatoid factor, hepatitis C antibody, hepatitis B surface antigen and QuantiFERON TB Gold Plus were negative. Angiotensin converting enzyme was not high. ANCA immunofluorescence titer was negative but serine protease 3, IgG was elevated at 47 AU/ml (normal: 0-14). He had a kidney biopsy in March 2024 which showed granulomatous nephritis with non-caseating granulomas in the interstitium with possible small artery /arteriole disrupted by granulomatous inflammation. Granulomas were somewhat loose and not clearly defined. There was no definitive glomerulonephritis, glomerular necrosis or crescents. There were occasional neutrophil casts. There was patchy interstitial infiltrate in 40% of cortex with mononuclear and plasma cells in some regions and neutrophil and eosinophils in some regions. There was no evidence of histoplasmosis or AFB in the biopsy. The differential included GPA and sarcoidosis. Loose organization of granulomas, neutrophil casts, interstitial infiltrate with neutrophils and eosinophils and possible destructive arteriolitis all favored GPA over sarcoidosis. The patient was treated with prednisone and rituximab with improvement of plasma creatinine to 2.1 mg/dl.

Discussion: ANCA vasculitis may lead to worsening renal function without glomerular involvement. Renal involvement of ANCA vasculitis should be considered in patients with positive ANCA even in the absence of hematuria, proteinuria or urinary casts and early renal biopsy should be considered in these patients so that treatment may be started before the onset of irreversible renal injury

FR-PO137

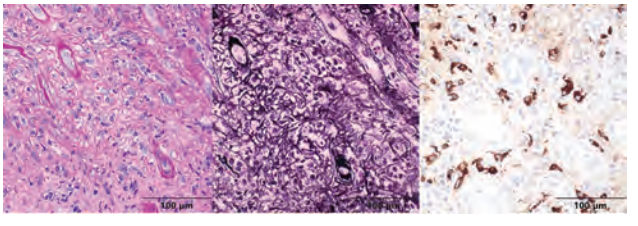
Breakthrough IgG4 Disease-Related Tubulointerstitial Nephritis Treated with Rituximab as Maintenance Therapy

Jill Nehrbas, Joseph D. Nguyen, Monarch Shah, William F. Glass, Tushar Chopra. *University of Virginia, Charlottesville, VA.*

Introduction: IgG4-related disease (IgG4-RD) is a systemic immune-mediated condition that can affect almost any organ system. In the kidneys, the most common manifestation is IgG4-related tubulointerstitial nephritis (IgG4-TIN), characterized by fibrosis and IgG4-positive plasma cell infiltrates in the interstitium. IgG4-RD is typically treated with immunosuppressives, including steroids and rituximab (RTX), which have demonstrated efficacy in achieving disease remission. We present a case of a patient with recurrent IgG4-RD manifesting as IgG4-TIN despite successful treatment of autoimmune pancreatitis and cholangitis.

Case Description: A 69-year-old male with a history of IgG4-RD treated with two courses of prednisone and four infusions of RTX for flares presented with non-oliguric acute kidney injury (AKI) (serum creatinine (sCr) of 2.1 mg/dL (baseline 1.1 mg/dL)). AKI was associated with hypertension, proteinuria (urine protein/creatinine ratio of 0.41 g/g), and hypocomplementemia consistent with IgG4-TIN. Kidney biopsy was also consistent and demonstrated diffuse "bird's eye" fibrosis in the cortex and medulla, extensive tubular destruction, and numerous IgG4-positive plasma cells (Fig 1). IgG4-TIN was treated with pulsed steroids and maintenance remission therapy of RTX 1 gm every 14 days for two doses every six months. At one year, sCr improved to 1.1 mg/dL and urine protein/creatinine ratio improved to 0.08g/g (normal ≤ 0.15g/g), and he remained relapse free.

Discussion: This case has three main teaching points: 1) It is important to maintain a high index of suspicion for IgG4-TIN when AKI is superimposed on IgG4-RD and ensure close follow-up for refractory cases. 2) IgG4-TIN can develop despite appropriate steroid therapy and remission in other involved organs with RTX. 3) Maintenance therapy with RTX retreatment was associated with longer relapse-free survival at 12 months of follow up in this case. Our patient had no severe infections or hypogammaglobulinemia ≤5 g/l with RTX, confirming RTX's safety and efficacy in maintenance remission therapy for recurrent IgG4-TIN.



FR-PO138

Lupus, the Great Mimicker: Unmasked by Urine Microscopy

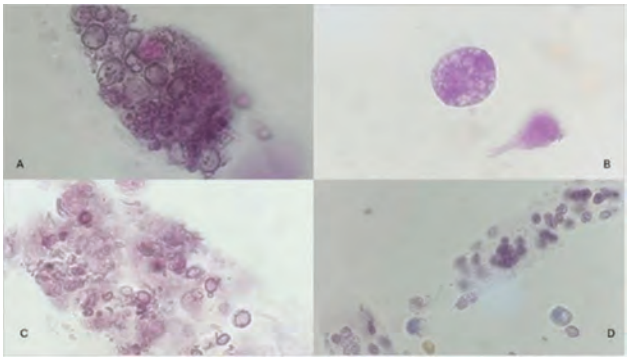
Zach Kisley, Veronica Zamora-Olivencia. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Introduction: Systemic Lupus Erythematosus (SLE) can present in a variety of ways, making it difficult to diagnose. By analyzing the urine microscopy of a critically ill patient, a complex case of SLE was identified and effectively treated.

Case Description: A 75 year old female with a history of chronic L staghorn calculus, recurrent pyelonephritis, and L kidney atrophy presented with dizziness and difficulty ambulating and was found to have multifocal strokes. She developed acute hypoxic respiratory failure with bilateral infiltrates, thought to be multifocal pneumonia. ICU team noted bloody endotracheal secretions. Nephrology was consulted for acute

kidney injury (AKI). Serum creatinine: 1.5-2.0mg/dL (baseline 0.9-1.0 mg/dL). Urinalysis showed persistent hematuria, long attributed to staghorn calculus, with new proteinuria. Urine microscopy revealed RBC casts, acanthocytes, and oval fat bodies seen in figure 1. Serologies revealed ANA >1:1280, elevated dsDNA, anti-smith, RNP, SSA Ro antibodies, low C3/C4, but otherwise negative. Urine protein creatinine ratio: 2.42mg/mg. Given the urine sediment, nephrology recommended bronchoalveolar lavage, revealing diffuse alveolar hemorrhage. Biopsy was deferred given her acute illness and solitary kidney, but data was strong enough to presume class III/V or IV/V lupus nephritis as well as pulmonary and CNS lupus vasculitis. She promptly received a steroid pulse and cyclophosphamide. She was ultimately extubated, had complete resolution of her AKI, had less active urine sediment, and is making a neurologic recovery.

Discussion: The novelty of our case includes the simultaneous presentation of three severe manifestations of SLE, but more importantly highlights the pivotal role of urine microscopy in the evaluation of AKI with an "active" UA. Although not a replacement for biopsy, urine microscopy allowed for prompt treatment, multi-disciplinary agreement, and identification of the unifying diagnosis, lupus vasculitis.



A. RBC cast B. Oval fat body C. folded RBC cast with embedded acanthocyte D. mixed cellular, predominant RBC cast

FR-PO139

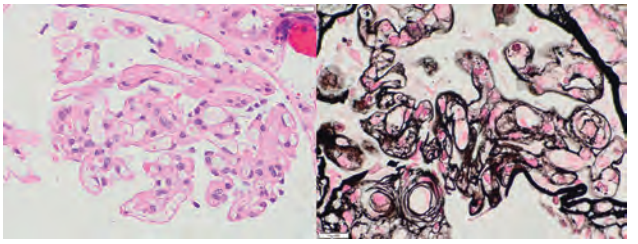
Navigating Atypical Hemolytic Uremic Syndrome (aHUS) in Pregnancy

Mayssaa Hoteit,[1] Hala M. KFoury,[2] Ali K. Abu-Alfa.[2,3] *[1]Bridgeport Hospital Internal Medicine, Bridgeport, CT; [2]American University of Beirut, Beirut, Lebanon; [3]Yale New Haven Hospital, New Haven, CT.*

Introduction: AKI during pregnancy can stem from various causes. Notably, conditions like preeclampsia, HELLP syndrome, TTP, and aHUS present diagnostic challenges due to overlapping symptoms. Understanding these diverse etiologies is crucial for accurate diagnosis and appropriate management strategies. We describe a case of AKI during pregnancy, diagnosed as aHUS.

Case Description: A 21-year-old female with a history of CKD presented during pregnancy with worsening Cr. At age 5, her kidney biopsy showed MPGN with C3 deposition on IF. Her Cr remained stable over the years, around 1.2-1.5 mg/dl, but increased during her pregnancy to 1.6-1.7 with worsening proteinuria. At 36 weeks GA, she was admitted for elevated BP. Laboratory investigations showed Hb of 10.7 g/dl, Plt of 221,000/mcL, Cr of 2.1 mg/dl, LDH of 425 IU/L, and haptoglobin of 0.25 g/L. She was started on magnesium, and labor was induced. Six weeks postpartum, she presented with tonic-clonic seizures, diffuse body edema, elevated Cr, and hemolytic anemia. Further investigations, including CT chest-abdomen-pelvis and CT brain, revealed fluid overload and no acute changes in the brain. An echocardiogram showed a hyperdynamic LV. Initially diagnosed with postpartum eclampsia, she received magnesium but developed severe hypermagnesemia, requiring urgent dialysis. Subsequently, her Cr continued to rise with associated anemia and thrombocytopenia.

Discussion: A suspicion for TMA was raised, leading to further investigations: ADAMTS13 activity returned as 67%, and kidney biopsy showed swelling of the endothelial cells, extensive double contour formation, and one glomerulus showed a thrombus, with non-specific fibrinogen staining on IF. Despite treatment with 10 plasma exchange sessions, her Cr continued to rise, necessitating the initiation of chronic dialysis. The possibility of aHUS was raised, but unfortunately, eculizumab was unavailable. It was eventually secured four months later, but its intermittent administration failed to improve her condition, and she remained dialysis-dependent. As part of her pre-transplantation workup, genetic testing for aHUS revealed a class 3 variant in the C3 gene and another variant of unknown significance in the CFHR5 gene.



Kidney biopsy

FR-PO140

A Case of Thrombotic Thrombocytopenic Purpura Initially Suspected as Shiga Toxin-Producing Escherichia coli Hemolytic Uremic Syndrome Due to the Preceding Symptoms of Hemolytic Anemia with Vomiting, Hematochezia, and AKI

Sonoka Niida, Masaaki Terao, Tomonari Ogawa, Hajime Hasegawa, Akito Maeshima. *Saitama Medical Center, Saitama Medical University, Kawagoe, Japan.*

Introduction: Thrombotic Thrombocytopenic Purpura (TTP) should be suspected in patients presenting with microangiopathic hemolytic anemia and severe thrombocytopenia. Additional findings indicative of TTP include significantly elevated lactate dehydrogenase, elevated indirect bilirubin and negative Coombs testing. Creatinine levels may be normal or slightly elevated, with levels exceeding 2 mg/dL being uncommon. Here, we report a case of TTP with features resembling hemolytic uremic syndrome (HUS), including vomiting, hematochezia, and acute kidney injury.

Case Description: A 59-year-old man developed vomiting, hematochezia, and gross hematuria after eating sashimi. After receiving intravenous therapy at a local clinic without improvement, the patient was transferred to our hospital. At admission, the patient's temperature was 37.2°C. Urinalysis showed proteinuria 2+, and hematuria 3+. The blood test revealed hemoglobin 7.3 g/dL, reticulocytes 4.1%, schistocytes 3‰, platelet count 5,000/μL, serum creatinine 2.41 mg/dL, C-reactive protein 0.89 mg/dL, lactate dehydrogenase 1,160 U/L, indirect bilirubin 2.6 mg/dL, and haptoglobin 2 mg/dL. Based on the clinical symptoms and laboratory findings, HUS caused by Shiga toxin-producing Escherichia coli (STEC) was suspected. The patient received continuous fluid therapy but developed oliguria, leading to initiation of hemodialysis on the second day. On the third day, seizures and confusion occurred. We diagnosed TTP and initiated steroid pulse therapy and plasma exchange. On the fifth day, ADAMTS13 activity was confirmed to have dropped to 1%, along with the detection of an ADAMTS13 inhibitor. The stool culture was negative. Thrombocytopenia, consciousness disorders, and renal dysfunction gradually improved. Dialysis ended successfully on the 7th day. Subsequently, rituximab was given, and the patient was discharged on the 38th day with no recurrence.

Discussion: The classic pentad of TTP symptoms comprises thrombocytopenia, microangiopathic hemolytic anemia, neurological issues, kidney dysfunction, and fever. However, these symptoms and lab findings may not occur simultaneously. It is crucial to maintain a high level of suspicion for TTP during management, even when atypical symptoms or laboratory values are present.

FR-PO141

Acute Kidney Failure and Nephromegaly as Initial Presentation of Recurrent Hematologic Malignancy

Alison Nguyen, Sahil Patel, Renu Regunathan-Shenk. *Inova Fairfax Hospital, Falls Church, VA.*

Introduction: Acute Lymphoblastic Leukemia (ALL) is most commonly diagnosed and monitored for recurrence based on laboratory findings such as leukopenia, anemia, and thrombocytopenia. It rarely presents as acute kidney injury (AKI) due to infiltration of leukemia cells into kidney tissue. Only a few cases have been reported in the literature thus far.

Case Description: We present a case of a 27 year old male with a history of Philadelphia negative B Cell ALL who achieved remission after chemotherapy and matched unrelated peripheral stem cell transplant in 2022 who then presents to the hospital with fatigue one year after remission. His fatigue was initially attributed to recently diagnosed atrial flutter that persisted despite outpatient medical management. Labs on admission revealed white blood cell count 4 X 10 3/uL, hemoglobin 9 g/dL, platelet count 200 x103/uL, creatinine 6.9 mg/dL, blood urea nitrogen 98 mg/dL, bicarbonate 9 mEq/L, and with an anion gap of 15. Renal ultrasound showed enlarged bilateral kidneys measuring at 18 cm for the right kidney and 19.5 cm for the left kidney with diffuse abnormal renal cortical parenchymal texture. Due to concern for infiltrative disease, he underwent a kidney biopsy. His biopsy revealed renal cortical tissue diffusely infiltrated by a densely cellular neoplasm composed by atypical lymphoid cells. Patient was started on chemotherapy and eventually underwent Chimeric Antigen Receptor T- cell therapy to treat his ALL

recurrence. With treatment, his kidney function improved and has remained stable at a new baseline of Creatinine of 2 mg/dL. Our case highlights AKI and nephromegaly as a sign of recurrent ALL.

Discussion: Renal dysfunction is an uncommon presentation of recurrent ALL especially in absence of leukopenia, anemia, and thrombocytopenia. Nephromegaly can be caused by several diseases such as diabetes mellitus, HIV associated nephropathy, interstitial nephritis, and infiltrative diseases such as hematologic malignancies and amyloid. Renal biopsy was crucial in diagnosing the cause of our patient's AKI as well as his recurrent malignancy as he did not have hematologic signs of recurrence. This case report highlights the importance of renal biopsy in patients who present with nephromegaly, especially in patients with known cancer history.

FR-PO142

Delayed Diagnosis of Multiple Myeloma and Amyloidosis Due to Anchoring and Availability Biases Attached to Cardiorenal Syndrome

Alexandra E. Conway,[1] Clay A. Block,[2] Charles W. Hopley.[2] *[1]Dartmouth College Geisel School of Medicine, Hanover, NH; [2]Dartmouth Hitchcock Medical Center, Lebanon, NH.*

Introduction: Anchoring bias (excess reliance on initial information) and availability bias (shortcuts based on prior/recent experience) are among the most common types of cognitive biases resulting in diagnostic errors. We present a case of a 75-year-old man with CKD and episodic AKI in the context of heart failure with preserved ejection fraction (HFpEF). The patient's history and the prevalence of cardiorenal syndrome (CRS) resulted in adoption of this diagnosis without additional investigation until work up for frank hypercalcemia revealed plasma cell dyscrasia.

Case Description: A 75-year-old man with a history of afib, HFpEF, tricuspid and mitral regurgitation, pulmonary hypertension, hypertension, macrocytic anemia, monoclonal gammopathy of undetermined significance (MGUS), and two prior episodes of dyspnea and AKI attributed to CRS, presented with altered mental status, bradycardia, complete heart block, hyperkalemia (7 mmol/L), hyponatremia, AKI (creatinine 4.82 mg/dL vs 2.1 baseline), and hypercalcemia requiring renal replacement therapy and insertion of a permanent pacemaker. Echocardiography demonstrated preserved ejection fraction without specific amyloidosis features. Due to hypercalcemia, the patient's previously known paraprotein was reevaluated and found to have increased (0.8 to 1.6 g/dL). The kappa-to-lambda free light chain ratio was increased to 10.8 (normal 0.4 to 2.6). Bone marrow biopsy demonstrated a plasma cell infiltrate diagnostic of IgG-kappa multiple myeloma as well as kappa light chain (AL) amyloidosis.

Discussion: The patient's CKD and episodic AKI were previously attributed to CRS due to the availability of and anchoring on this common diagnosis. Multiple myeloma/amyloidosis were not considered until hypercalcemia occurred despite clues such as macrocytic anemia, proteinuria, and prior MGUS diagnosis. Clinicians also relied on the absence of amyloidosis echocardiographic stigmata (e.g. relative apical sparing of longitudinal strain), although these features are insensitive and amyloidosis is underdiagnosed in patients with HFpEF. The absence of such findings should not dissuade clinicians from further investigation, and index of suspicion should remain high when signs are not explained by HFpEF. This case highlights the power of availability and anchoring biases to delay diagnosis.

FR-PO143

Sex-Dependent Dynamic Transcriptional Responses in AKI in Mice

Jiakang Wang, Tej Bahadur, Robert Bronstein, Sian E. Piret, Nehaben A. Gujarati, Yiqing Guo, Sandeep K. Mallipattu. *Stony Brook University Renaissance School of Medicine, Stony Brook, NY.*

Background: Previous studies demonstrated the role of sex differences in protection from acute kidney injury (AKI). However, the mechanism(s) that increase the susceptibility to AKI in males vs females remains unclear. We aim to investigate the sex-specific transcriptomic differences with single nucleus multiome sequencing data to identify mediators that increases the susceptibility to AKI in males vs females post-aristolochic acid I (AAI) injury in mice.

Methods: Male and female mice were injected with one dose of DMSO or AAI (2mg/kg) and perfused after 72 hours. Using 10X Genomics, single nuclear multiome (scRNA and scATAC) sequencing on the kidney samples was performed. CellRanger-ARC aligned the sequencing data and proceeded through the ArchR pipeline for data mining. Alevin-fry generated splice counts on the original data and scVelo performed RNA velocity analysis. Kidneys were stained for FOSL1 and JUNB by immunofluorescence.

Results: Compare to females, 4 unique PT clusters formed in males after AAI. Two of these were similar to uninjured PT clusters, but the other two showed increased expression of injury markers, including AP-1 transcription factors(TF) (Fosl1, Junb; injury cluster), NF-kB signaling pathway (Rela, Relb, Nfkb1, Nfkb2; intermediate cluster). Immunostaining validated expression of these unique proteins in injured PT clusters in male mice vs female mice post-AAI. The injury cluster demonstrated high expression of Junb, as well as motif enrichment and footprinting bias. Consistent with its role as an early response gene, RNA velocity showed that Junb was already fully spliced, suggesting earlier upregulation. By contrast Fosl1, had lower expression, but a higher RNA velocity, suggesting ongoing upregulation. Fosl1 motifs were already open, suggesting that chromatin in these cells was already primed for Fosl1 binding. In the intermediate cluster, NFKB pathway genes showed less well defined dynamics, but enrichment for open motifs and footprinting analysis suggested active transcription. Analysis of downstream target genes showed high expression and dynamics of Plau, Tnfaip3, and Vcam1. Expression, motifs, and footprinting analyses for these TFs in female PT clusters after AAI were all negative.

Conclusions: AKI induced dynamic AP-1 and NFKB transcriptional activity in two distinct injured PT clusters in male, but not female mice.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO144

Resistance to Aristolochic Acid-Induced AKI in Female Mice

Asha Rath, Samaneh DiMartino, Sian E. Piret. *Stony Brook University, Stony Brook, NY.*

Background: Females are less susceptible to acute kidney injury (AKI) compared to males, in both humans and mice. The resistance of female mice to developing AKI poses a significant barrier to pre-clinical therapeutic studies, and many studies only use male mice. Our aim was to establish a protocol to induce AKI in female mice using the proximal tubule (PT)-specific nephrotoxin, aristolochic acid I (AAI).

Methods: Male and female C57Bl/6 mice aged 12 weeks were injected intraperitoneally with 2 doses of 3mg/kg AAI, and female mice were also given 2 doses of 4mg/kg – 6.5mg/kg AAI. All doses were given 72 hours apart, followed by euthanasia 24 hours after the last injection. Body and kidney weights were recorded and serum collected for creatinine and urea nitrogen measurements. Kidneys were analyzed using hematoxylin and eosin (H&E) and periodic acid Schiff staining, and immunofluorescence for cytokeratin-20 (KRT-20; injured PT) and Lotus lectin (LL; uninjured PT). Liver morphology was assessed using H&E.

Results: Female mice given the standard male AKI dose of 3mg/kg AAI did not show any histological injury, whereas male mice had extensive PT death. Female mice given 4-6.5mg/kg AAI lost weight, but there was no difference between different doses, and kidney weights did not change. Serum creatinine and urea nitrogen concentrations were not elevated in response to any of the AAI doses. Histologically, kidneys showed minimal injury at 4mg/kg and 5mg/kg, and only small areas of PT cell death and mild loss of brush border at 6mg/kg and 6.5mg/kg AAI. LL and KRT-20 staining showed a linear trend towards reduced LL across increasing AAI doses (one-way ANOVA test for trend), and minimal, non-significant increases in KRT-20. AAI is activated in the liver and H&E showed significant liver vacuolization in mice treated with 6mg/kg AAI, despite only mild kidney injury.

Conclusions: Female mice had mild kidney injury and no loss of kidney function at AAI doses double that needed to cause AKI in male mice. Furthermore, high doses caused liver injury, thus limiting their utility. Studies using high doses of AAI should be interpreted with caution due to the likelihood of liver injury. Further studies are needed to identify a protocol to induce robust AKI in female mice without liver injury, to facilitate future pre-clinical therapeutic studies.

Funding: NIDDK Support

FR-PO145

Endothelin-1 Derived from Failed-Repair Proximal Tubular Cells Exacerbates Fibrosis after Kidney Injury

Yasuto Sunahara, Yuhei Kirita, Tomohiro Nakata, Tetsuro Kusaba, Keiichi Tamagaki. *Department of Nephrology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan.*

Background: Endothelin signaling contributes to the progression of chronic kidney disease across multiple etiology including acute kidney injury (AKI). Previously, single-cell transcriptomic analysis of mouse AKI kidney revealed that a distinct failed repair proximal tubular cell (FR-PTC) state drives fibrosis after injury and endothelin-1 (Edn1) signaling between FR-PTCs and fibroblasts were significantly upregulated (PNAS. 2020). However, the mechanistic link between FR-PTC derived Edn1 and renal fibrosis remains unclear.

Methods: Tamoxifen-inducible proximal tubule-specific Edn1 knockout mice (*Edn1*$^{flox/flox}$::*Slc34a1*$^{CreERT2/+}$) underwent unilateral ischemia-reperfusion injury(IRI) surgery or administration of aristolochic acid (AA), following vehicle or tamoxifen treatment. Mice were sacrificed at 4 weeks after IRI or 2 weeks after AA-induced injury for phenotypic assessment. Immortalized tubular epithelial cells (NRK52E) and fibroblasts (NRK49F) were used in vitro. Furthermore, RNA sequencing (RNA-seq) was performed on Edn1-treated fibroblasts.

Results: Proximal tubule-specific Edn1 deletion decreased the expression levels of profibrotic and proinflammatory genes (e.g. *Tgfb1, Acta2, Ccl2 and Cd68*) after injury. Moreover, immunofluorescence staining showed decrease of αSMA positive myofibroblasts around FR-PTCs. In vitro, RNA-seq revealed that profibrotic and proinflammatory pathways, also NFkB and ERK signaling were upregulated in Edn1-treated

NRK49F. Western blotting revealed that Edn1 activated the phosphorylation of ERK in NRK49F. Edn1 expedited the proliferation and migration of NRK49F, which was attenuated by an ERK inhibitor. Conditioned medium (CM) from AA-treated NRK52E in which Edn1 was upregulated expedited the proliferation and migration of NRK49F. The enhanced fibroblast proliferation and migration was nullified by CM from AA-treated NRK52E with CRISPR-mediated Edn1 knockout.

Conclusions: In this study, we clarified the important role of the proximal tubule-derived Edn1 on pERK-mediated fibroblast proliferation and migration in renal fibrosis. Our results also suggested that Edn1 induced NFkB-mediated profibrotic and proinflammatory signals on fibroblasts which may exacerbate renal fibrosis. Inhibition of Edn1 may be a therapeutic target for preventing renal fibrosis.

FR-PO146

Using Imaging Mass Cytometry to Define Cell Identities in AKI and CKD in Humans

Tifanny Budiman,[1] Ashish Shelar,[2] Megan L. Baker,[1,3] Marlene Weiss,[1,4] Lloyd G. Cantley,[1] Vijayakumar R. Kakade.[1] Kidney Precision Medicine Project (KPMP). *[1]Yale University School of Medicine, New Haven, CT; [2]Yale University, New Haven, CT; [3]Yale University Graduate School of Arts and Sciences, New Haven, CT; [4]Charite Universitatsmedizin Berlin, Berlin, Germany*.

Background: Acute kidney injury (AKI) is a complex clinical syndrome that arises in patients in response to many etiologies, with up to 50% of critically ill patients developing AKI. An episode of AKI is associated with an increased risk of developing chronic kidney disease (CKD), leading to risks of both short- and long-term mortality. Though we have made significant progress in our understanding of many kidney diseases, less attention has been focused on the pathogenesis and treatment of human AKI. Imaging mass cytometry (IMC), allows staining of up to 40 proteins on a formalin fixed paraffin embedded (FFPE) section and provides semiquantitative expression data of each protein with a one square micron resolution. In this study, we applied IMC to define cell types, their activation states, and cell-cell interactions with spatial context in human reference, AKI, and CKD samples from KPMP participants.

Methods: IMC with a validated panel of 34 antibodies was performed on healthy reference tissue (HRT n=6), AKI (n=8), CKD (n=9) and QC tissues. Cell segmentation was performed using the deep learning Mesmer segmentation algorithm and the data was analyzed by imcRtools.

Results: 391,738 cells were identified across 23 KPMP biopsies, with 42 distinct cell clusters generated using Rphenograph clustering. Analysis of tubule cell type marker expression in proximal tubule and thick ascending limb clusters showed that megalin expression per proximal tubule cell is significantly reduced in both AKI (1.641 ± 1.078, $p<0.0001$) and CKD (2.633 ± 2.283, $p<0.0001$) as compared to HRT (6.793 ± 8.442, a.u.), and is significantly lower in AKI as compared to CKD ($p<0.0001$). Similarly, the expression of uromodulin in thick ascending limb cells is significantly decreased in both AKI (2.503 ± 1.552, $p<0.0001$) and CKD (6.300 ± 5.171, $p<0.0001$) as compared to HRT (12.48 ± 11.56, a.u.), and significantly lower in AKI compared to CKD ($p<0.0001$).

Conclusions: We applied quantitative high-dimensional imaging analysis to human reference, AKI and CKD biopsies. This analysis shows a significant reduction in the expression of the tubular cell proteins megalin and UMOD in injured kidneys as compared to healthy reference tissue, with greatest reduction detected in samples from patients with AKI.

Funding: NIDDK Support

FR-PO147

Single-Nucleus RNA Sequencing Identifies Transcriptional Differences in Sepsis- and Ischemia-Induced AKI in Mice

Francis N. Forbi, Nelli Shushakova, Hermann Haller, Kai M. Schmidt-Ott, Heiko J. Schenk, Robert Greite, Christian Hinze. Research Group Hinze. *Medizinische Hochschule Hannover, Hannover, Germany*.

Background: Acute kidney injury (AKI) is frequently observed in hospitalized patients and associated with increased mortality. Two of the most common causes of AKI are sepsis and conditions with kidney ischemia. However, whether and how these two AKI causes differ at the molecular level is incompletely understood. Here, we aimed to identify gene sets that are specific for sepsis or kidney ischemia associated AKI using well-defined mouse models.

Methods: Septic AKI was induced by cecal ligation and puncture (CLP) in adult male C57BL/6 mice (n=6) with sham operated mice as controls (n=3). Kidneys were harvested at 4 and 20 hours after CLP (n=3 each and subjected to single nucleus RNA sequencing (snRNA-seq). Unbiased clustering and marker gene expression analysis enabled the identification of major renal cell types. To account for molecular differences with ischemia-reperfusion injury (IRI)-induced AKI, we integrated our data with two published IRI datasets. To derive sepsis- and IRI-specific gene sets, we systematically searched for genes that are exclusively up- or downregulated in sepsis when compared to IRI in each major cell type and vice versa.

Results: Our analysis resulted in lists of sepsis- and IRI-specific gene sets for each cell type. Sepsis-specific genes (specifically up- or downregulated in CLP kidneys but not in IRI) showed cell type-specific gene expression patterns with little overlap between the cell types. Sepsis-specific genes were mostly present in collecting duct principal cells, endothelial and interstitial cells at 20 hours post-CLP. These genes were enriched in pathways associated with cytoskeletal remodeling (collecting duct principal cells), endothelial activation (endothelial cells) and extracellular matrix production (interstitial cells). In contrast, genes specifically upregulated in IRI were mostly restricted to the proximal tubules. These genes were strongly enriched in pathways associated with cell cycling and DNA damage repair.

Conclusions: Our analyses provide a comprehensive set of cell type-specific marker genes specific for sepsis- and IRI-induced AKI. We highlight strong transcriptional differences between sepsis- and IRI-induced AKI, which involve different cell types.

FR-PO148

Spatial Transcriptomics Define Injury-Specific Microenvironments in the Adult Mouse Kidney and Novel Cellular Interactions in Regeneration and Disease

Louisa M. Gerhardt,[1,2] Michal Polonsky,[3] Jina Yun,[3] Kari A. Koppitch,[1] Long Cai,[3] Andrew P. McMahon.[1] *[1]Keck School of Medicine of the University of Southern California, Los Angeles, CA; [2]University Medical Center Mannheim, Mannheim, Germany; [3]California Institute of Technology, Pasadena, CA.*

Background: Acute kidney injury (AKI) disrupts the highly complex architecture of the kidney resulting in reduced kidney function and triggering intrinsic repair processes. These repair processes can lead to functional recovery of the kidney, but AKI can also invoke inflammation and fibrosis resulting in chronic kidney disease (CKD). Development of targeted treatment strategies to halt disease progression after AKI is still hampered by an incomplete understanding of the underlying pathophysiologic processes. Deciphering molecular and cellular interactions driving injury-invoked inflammation and fibrosis is challenging due to the intricate renal architecture.

Methods: We leveraged sequential Fluorescence In Situ Hybridization (seqFISH) to quantify the expression of 1300 genes within the spatial context at single cell resolution in the mouse kidney during the AKI to CKD transition at day 28 after ischemia-reperfusion injury (n=3). Kidneys from non-surgery mice (n=3) were used as controls.

Results: Clustering 220,753 high-quality cells based on gene expression identified all major cell types in the kidney and revealed changes in the kidneys' cellular composition at 4 weeks post AKI: While immune cells, fibroblasts and injured proximal tubule cells were abundant in the injured kidney, cortical vasculature and proximal tubule segment 3 cells were reduced. Clustering the cells based on the neighborhood cell type composition revealed injury-specific and spatially-dependent gene expression patterns in distinct cellular microenvironments within the kidney. This analysis also predicted novel cell interactions, such as a molecular interplay between persistently injured proximal tubule cells and neighboring fibroblasts via *Clcf1-Crfl1*. Immune cell types play a critical role in organ repair and the spatial analysis revealed cellular microenvironments resembling early tertiary lymphoid structures.

Conclusions: Collectively, this study provides a high-resolution characterization of injury-invoked changes in the kidney, highlighting injury-specific cellular microenvironments and cell-cell interactions relevant to inflammation and fibrosis development after AKI.

Funding: NIDDK Support, Private Foundation Support, Government Support - Non-U.S.

FR-PO149

Optogenetic Stimulation of Kidney Sympathetic Nerves as a New Protective Approach to AKI

Ryusuke Umene,[1,2] Chia-Hsien Wu,[1] Norito Washimine,[2] Sayumi Matsuo,[2] Tomoya Nishino,[2] Tsuyoshi Inoue.[1] *[1]Department of Physiology of Visceral Function and Body Fluid, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan; [2]Department of Nephrology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan.*

Background: Acute kidney injury (AKI) is a life-threatening condition with a poor prognosis. Once AKI develops, there is a high risk of developing chronic kidney disease (CKD), a condition that carries a high risk of cardiovascular disease and death. Even though the number of patients with AKI is increasing every year, there is currently no curative treatment for kidney disease, highlighting the need for innovative therapies. Recent research suggests that renal sympathetic nerve modulation may offer protective effects. Traditional methods lack specificity, so this study employs optogenetics, a minimally invasive technique for precise neural activation, to investigate the renal protective mechanisms of sympathetic nerve stimulation.

Methods: Using optogenetics, we specifically stimulated renal sympathetic nerves in transgenic mice expressing channelrhodopsin-2 in sympathetic neurons (DbHCre-ChR2). Blue light was directed at the kidneys to stimulate these nerves. We optimized stimulation

parameters (duration, frequency, intensity) by monitoring blood pressure, heart rate, and renal norepinephrine levels. To assess protective effects, we induced AKI with bilateral renal ischemia-reperfusion injury (IRI) and LPS-induced sepsis models. Single-cell RNA sequencing (scRNA-seq) on renal tissues identified cells receiving sympathetic signals and their interactions.

Results: Optogenetic stimulation of renal sympathetic nerves significantly reduced renal injury in acute kidney injury models. Protection was observed against bilateral renal IRI following nerve stimulation. scRNA-seq revealed that tubular epithelial cells responded to sympathetic stimulation, with upregulated expression of protective factors, indicating direct renal protection via the sympathetic nervous system, independent of systemic immune modulation.

Conclusions: This study introduces a novel optogenetics-based method for specific stimulation of renal sympathetic nerves, demonstrating its potential to reduce renal injury. The identification of specific cellular responses and protective mechanisms advances our understanding of the renal protective role of sympathetic nerves. These findings pave the way for developing new therapeutic devices and drugs targeting renal sympathetic modulation, offering promising prospects for kidney disease treatment.

Funding: Private Foundation Support

FR-PO150

Mechanistic Representation of Clusterin, a Damage Biomarker for Early Detection of Drug-Induced AKI

Nader Hamzavi, Jeffrey Woodhead. *Simulations Plus Inc, Lancaster, CA.*

Background: Biomarkers have the potential to address several challenges in acute kidney injury (AKI). Novel biomarkers such as clusterin have emerged as promising candidates to address limitations of conventional biomarkers in early detection of acute kidney injury (AKI). To fully leverage the clinical potential of these biomarkers, a mechanistic understanding of the biochemical processes that lead to biomarker release is essential.

Methods: We developed a mechanistic model of clusterin release within the framework of RENAsym, a QST model of drug-induced AKI that incorporates key cellular injury mechanisms and renal hemodynamics. After tubular injury, clusterin starts to upregulate on dedifferentiated tubular epithelial cells and appear in the urine. The clusterin model in RENAsym was used to predict urinary clusterin following cisplatin administration to rats in connection with proximal tubular cell necrosis and regeneration.

Results: The clusterin submodel parameters were calibrated using urinary clusterin data following cisplatin administration into rats: 3 mg/kg and 6 mg/kg single dose, and 1 mg/kg daily dose for two weeks. Clusterin release was modeled to be linked with cellular necrosis to capture timing of observed peak. Simulated urinary clusterin peaked on day 5 matching the peak of necrotic flux and remained elevated for a few more days, in accordance with preclinical data. Representing clusterin during regeneration to replicate the observed delayed clusterin resolution was required to accurately represent clusterin dynamics.

Conclusions: A mechanistic submodel of clusterin was developed in RENAsym that captures the kinetics of urinary clusterin in rats dosed with cisplatin. This modeling effort informed us that signals from necrotic tubular cells predicted the peak timing of urinary clusterin, and clusterin release during regeneration was required to capture clusterin delayed resolution observed in cisplatin-treated rats. This effort demonstrates the ability of QST modeling to provide mechanistic insight into the behavior of novel kidney injury biomarkers.

Funding: Private Foundation Support

FR-PO151

SALL1 Is Essential for Histone H3K27 Methyltransferase EZH2 to Regulate Apoptotic Responses in Kidney Ischemia-Reperfusion Injury

Shuqin Mei. *Department of Nephrology, Shanghai Changzheng Hospital, Shanghai, China.*

Background: The role of histone methylation modifications in renal disease, particularly in ischemia/reperfusion-induced acute kidney injury (AKI), remains unclear. This study aims to investigate the potential involvement of the histone methyltransferase zeste homolog 2 (EZH2) in ischemia/reperfusion-induced AKI and its impact on apoptosis.

Methods: We first examined the expression of EZH2 in the kidney of ischemia/reperfusion-induced AKI mice and hypoxia-stimulated tubular epithelial cells. We next constructed the EZH2 knockout mice to further confirm the effects of EZH2 on apoptosis response in AKI. Subsequently, we constructed the EZH2 knocked-down cells again and performed Chromatin Immunoprecipitation sequencing to screen out the target genes regulated by EZH2 and the enrichment pathway. Then we confirmed the EZH2 target gene and its regulatory pathway in vivo and in vitro experiments.

Results: The study found that EZH2 was upregulated in ischemia/reperfusion-induced AKI and that silencing EZH2 could reduce renal tubular injury by decreasing apoptosis response of tubular epithelial cells. Chromatin immunoprecipitation sequencing and polymerase chain reaction identified SALL1 as a target of EZH2. EZH2 was found to be enriched on the promoter of SALL1. Silencing EZH2 resulted in a significant increase in the transcriptional level of SALL1 and activation of the Wnt/β-catenin signaling pathway. The study further reversed the effects of EZH2 silencing by silencing SALL1 or administering the Wnt/β-catenin inhibitor icg001. It was also found that SALL1 positively regulated the expression of Wnt/β-catenin pathway-related genes. Finally, the study showed that the EZH2 inhibitor GSK-126 significantly alleviated ischemia/reperfusion-induced AKI.

Conclusions: Our results indicate that silencing EZH2 can protect renal function by relieving transcriptional inhibition of SALL1, activating the Wnt/β-catenin pathway, and attenuating tubular epithelial apoptosis response. These results highlight the potential therapeutic value of targeting EZH2 in ischemia/reperfusion-induced AKI.

FR-PO152

Inhibition of Histone Lysine Demethylases 5 Attenuates AKI but Does Not Impact Acute Kidney Disease or CKD

Sungjin Chung, Eun Sil Koh. *The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: Histone lysine demethylases 5 (KDM5) are part of the Jumonji C domain-containing family of histone demethylases, which catalyze the removal of di- and tri-methyl groups from the fourth lysine of histone 3 (H3K4me2/3). The KDM5 family is implicated in various physiological and pathological processes, including cell differentiation, motility, senescence, and epithelial-mesenchymal transition (EMT), through both demethylase-dependent and independent mechanisms in homeostasis and disease. This study investigated the role of KDM5 in renal fibrosis development and progression in acute kidney injury (AKI), chronic kidney disease (CKD), and the transition from AKI to CKD (acute kidney disease, AKD).

Methods: The therapeutic effects of KDM5 inhibition were evaluated in three mouse models: AKI induced by unilateral nephrectomy plus contralateral ischemia-reperfusion (IR) injury, AKD induced by unilateral IR injury followed by removal of the contralateral uninjured kidney 8 days post-IR injury, and CKD induced by unilateral ureteral obstruction (UUO).

Results: The KDM5 inhibitor C70 prevented increases in blood urea nitrogen and reduced areas stained by trichrome, Sirius red, F4/80, and α-smooth muscle actin in kidneys 7 days post-IR injury. Significant reductions in renal mRNA levels of pro-inflammatory cytokines/chemokines, EMT, and pro-fibrotic markers (IL-1β, IL-6, TNF-α, CCL2, CCL3, GM-CSF, MMP9, fibronectin, vimentin, TGF-β1, COL4A1) were observed, along with decreased mRNA levels of KDM5a-c. Additionally, renal protein levels of antioxidants such as catalase, SOD1, and SOD2 were increased in KDM5 inhibitor-treated mice. However, no significant differences in renal fibrosis and inflammation parameters were found between treated and untreated mice in both the AKD and CKD models.

Conclusions: Inhibition of KDM5 can prevent renal inflammation and fibrosis following acute severe IR injury, suggesting that KDM5 activation may be an early step in the development of renal fibrosis after AKI.

Funding: Government Support - Non-U.S.

FR-PO153

N6 Methyladenosine-Modified CircNfix Attenuates Sepsis-Induced AKI by Facilitating the Ubiquitination of YTHDF2 and Increasing DAPK2 mRNA Stability

Peng Wang. *Affiliated Hospital of Guangdong Medical University, Zhanjiang, China.*

Background: Increasing evidence shows that circRNAs play an important role in sepsis-induced acute kidney injury (SAKI). However, the mechanisms of circRNAs in SAKI have not been reported except the way of miRNA sponges. Notably, the function of N^6-methyladenosine (m^6A)-modified circRNA in SAKI remains undiscovered. Therefore, global profiles of circRNAs in kidneys with SAKI are needed, which will contribute to uncovering novel mechanisms underlying circRNAs in pathophysiology of SAKI.

Methods: SAKI-associated circRNAs were screened via circRNA microarray and examined using in situ hybridization (ISH) in mouse renal tissue. The role of circNfix in YTHDF2-induced pro-inflammatory or pro-apoptotic response of tubular epithelial cells (TECs) was assessed by luciferase reporter assay and Annexin V/ PI staining assay in vitro. Adeno-associated virus was used to deliver circNfix to the kidneys of SAKI mice to study the function of circNfix in vivo. The mechanism underlying circNfix-mediated activation of NF-κB signaling was examined by Mass spectrometry, RNA pull-down, MeRIP-qPCR and ISH. To evaluate the biomarker potential of circNfix to predict SAKI, expression level of circNfix in the urine and plasma of 52 sepsis patient was examined using qPCR.

Results: circNfix expression was downregulated in TECs following SAKI, leading to apoptosis and inflammatory injury in TECs in vitro and in vivo. Mechanistically, circNfix was found to provide a scaffold for the interaction between YTHDF2 and HECTD1, which was augmented by circNfix m^6A modification, facilitating YTHDF2 ubiquitination and degradation. By decreasing the expression of YTHDF2, circNfix promoted the

stabilization of DAPK2 mRNA, a negative regulator of NF-κB signaling, to protect LPS-induced TECs injury. Restoring circNfix in an experimentally-induced mouse SAKI model suppressed the activation of NF-κB signaling, thereby improving renal function and ameliorating tubular injury. Spearman's test demonstrated a remarkable negative correlation between urinary circNfix and serum creatinine in sepsis patients.

Conclusions: Collectively, m^{6}A modified-circNfix suppresses NF-κB-driven renal inflammation via a YTHDF2-dependent mechanism during SAKI, and restoring circNfix might represent a therapeutic strategy for SAKI.

Funding: Government Support - Non-U.S.

FR-PO154

Dietary Fiber-Derived Microbial Metabolites Prevent Acute and Chronic Kidney Ischemia-Reperfusion Injury (IRI) through G Protein-Coupled Receptor GPR43

Alexander Gilbert,[1,2] Anita Chitsaz,[1] Guozhen Zhu,[1] Julian J. Singer,[1,2] Steven J. Chadban,[1,2] Huiling Wu.[1,2] *[1]The University of Sydney Charles Perkins Centre, Sydney, NSW, Australia; [2]Royal Prince Alfred Hospital, Camperdown, NSW, Australia*.

Background: Short-chain fatty acids (SCFAs) derived from gut microbial fermentation of fiber exert anti-inflammatory effects and have been found to attenuate the development of inflammatory diseases. We investigated the impact of dietary fiber on kidney IRI in a murine model.

Methods: C57BL/6 mice were fed a high fiber diet (HFD) and controls received normal chow (NC). Kidney ischemia was induced for 22 min followed by reperfusion. Samples were collected 24 hours and 28 days after reperfusion. Kidney histology and gene expression was examined. Stool was assessed by 16S rRNA sequencing (gut microbiome) and ^{1}H NMR spectroscopy (SCFAs).

Results: HFD mice were protected against acute and chronic kidney IRI, with lower serum creatinine, less tubular damage, and tubulo-interstitial infiltrate accumulation compared with NC controls ($p<0.05$). HFD mice had less proteinuria and interstitial fibrosis at 28 days. HFD significantly reduced pro-inflammatory cytokines, chemokines and fibrosis-related gene expression within IRI-kidney compared with NC controls ($p<0.05$-0.01). Kidney IRI-associated dysbiosis and significant expansion of pathobionts was evident in NC-IRI mice compared to NC sham-operated controls ($p<0.05$-0.001), however this was attenuated in HFD-IRI mice ($p<0.05$-0.001). HFD-IRI mice also exhibited significant expansion of SCFA-producing bacteria compared to NC controls. Pearson correlation analyses showed that at a family level, Enterobacteriaceae and Clostridia_vadinBB60_ group were most strongly associated with kidney injury. In contrast, SCFA producers were associated with better kidney histology and function. Consistent with changes in the gut microbiome, HFD mice had significantly higher serum acetate and fecal SCFA concentrations. HFD provided significantly less protection in GPR43-/- mice compared to wild type HFD-IRI-mice, though HFD remained protective in GPR109A$^{-/-}$ mice.

Conclusions: Dietary fiber protects against acute and chronic kidney IRI through modulation of the gut microbiota, enrichment of SCFA-producing bacteria, and increased SCFA production, ameliorating IRI-associated dysbiosis. This protection is partially mediated through GPR43.

Funding: Government Support - Non-U.S.

FR-PO155

Intravenous UNI-494 Slows the Progression or Halts/Reverses AKI When Administered after Ischemia-Reperfusion in Rats

Satya Medicherla, Guru Reddy, Shalabh Gupta. *Unicycive Therapeutics Inc, Los Altos, CA*.

Background: There are no effective treatments approved for acute kidney injury (AKI). Inflammation and reactive oxygen species driven mitochondrial permeability transition pore (mPTP) opening causes mitochondrial dysfunction/swelling and cell death. This is implicated in acute diseases originating from ischemia-reperfusion (I/R) injury or delayed graft function (DGF). Unresolved inflammation exacerbates sustained mPTP opening, evident in chronic kidney diseases. UNI-494, a selective mitochondrial ATP-sensitive potassium channel activator, reverses mitochondrial dysfunction by closing the mPTP. We evaluated in vivo efficacy of intravenous (IV) UNI-494 administered therapeutically after unilateral I/R in AKI rat model.

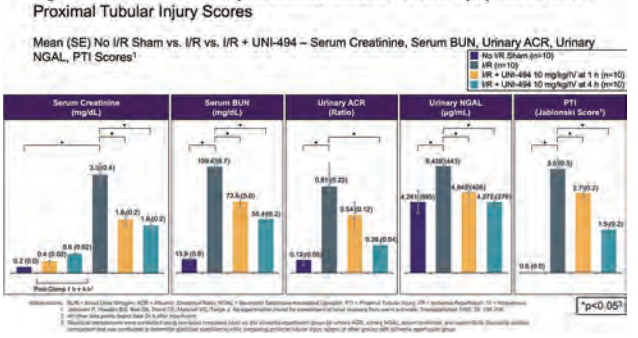
Methods: Rats were anesthetized, right kidney removed, I/R induced by clamping renal vessels in left kidney (30 minutes). After 1 or 4 hours of reperfusion with established renal injury confirmed by elevated serum creatinine (sCr), 10 mg/kg of UNI-494 was administered IV. After 24 hours reperfusion in metabolic cages, blood samples were collected for sCr and blood urea nitrogen (sBUN) levels, and urinary samples collected for albumin-creatinine ratio (uACR) and neutrophil gelatinase-associated lipocalin (uNGAL). At necropsy, clamped left kidney was collected and processed for histology for tubular injury scores.

Results: I/R induced significant increases of sCr, sBUN, uACR, uNGAL, and proximal convoluted tubular injury scores in vehicle treated I/R group vs No I/R sham group. A single IV dose of 10 mg/kg of UNI-494 improved kidney functional markers sCr, sBUN, uACR, uNGAL, and proximal tubular injury scores (Figure 1).

Conclusions: Single IV doses of 10 mg/kg of UNI-494 administered after I/R significantly reduced serum and urinary AKI markers and improved proximal tubular injury scores. These data indicate therapeutic administration of UNI-494 slows down, or even halts/reverses, AKI progression. UNI-494 is a potential candidate for prevention of DGF and other AKI clinical conditions.

Funding: Commercial Support - Unicycive Therapeutics, Inc.

Figure 1. Reduction of Kidney Functional Markers, Tubular Injury Marker, and Proximal Tubular Injury Scores



FR-PO156

DNase-1 Exerts Protective Effects after Severe Kidney Ischemia-Reperfusion Injury

Elena Tutunea-Fatan, Shabitha Arumugarajah, Lakshman Gunaratnam. *Western University, London, ON, Canada*.

Background: Kidney Injury Molecule-1 (KIM-1) is a transmembrane receptor expressed by proximal tubular epithelial cells during injury. KIM-1 recognizes phosphatidylserine, an "eat me" signal that marks apoptotic cells for phagocytic clearance. Notwithstanding that, severe acute injury (AKI) leads to persistent KIM-1 expression and drives fibrosis. Herein, we design a study to evaluate whether DNase1 contribute to the pathogenesis of KIM-1- mediated renal fibrosis.

Methods: To assess the functional role of KIM-1 expression, KIM-1+/+, KIM-1-/-, and Tim1fl/fl SLC34a1 C57BL/6 mice were subjected to both moderate (25 minutes) and severe (45 minutes) unilateral ischemia reperfusion injury (UIRI). Kidneys were isolated after 3, 7, 28, and 42 days of reperfusion to assess histology and markers of injury and fibrosis. To examine gene expression profile, RNA sequencing of kidneys from KIM-1+/+ and KIM-1-/- mice after 45 min UIRI was performed. DNase1 expression and activity was assessed by using in situ and in vitro analyses of kidneys and sera. To test the therapeutic potential of DNase1 after severe UIRI, mice received repeated doses of DNase1 (2 mg/kg) or vehicle-solution (NaCl 0.9%).

Results: Our data indicate that by clamping the renal pedicle for 45 min and following the mice for 42 days, the injured KIM-1+/+ kidneys were markedly reduced in size and fibrotic compared with control kidneys. By contrast, the injured KIM-1-/- kidney recovered completely. The fibrotic phenotype was not observed with the moderate injury model. Also, a strong upregulation of mRNA encoding a panel of cytokines and growth factors was observed at both 7 and 42 days after injury in KIM-1+/+ kidney compared with KIM-1-/-. This highlights the possibility that KIM-1 might directly regulate epithelial cytokine and fibrotic marker expression. In addition, DNase1 was among the top downregulated genes in the KIM-1+/+ kidney exposed to severe injury. Renal DNase1 expression was completely abrogated in KIM-1+/+ kidney compared to KIM-1-/- kidney at all time points analysed. Early decline of DNase1 activity directly correlated with lower injury score and fibrosis. DNase-1 treatment significantly reduced the pro-inflammatory response and histopathological changes observed in KIM-1+/+ kidney after severe AKI.

Conclusions: DNase1 therapy is protective following severe AKI and attenuates murine kidney fibrosis.

Funding: Government Support - Non-U.S.

FR-PO157

DNA-Binding Protein-A Promotes Kidney Ischemia-Reperfusion Injury and Participates in Mitochondrial Function

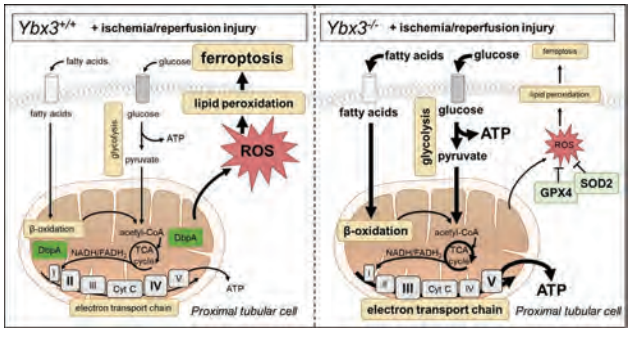
Charlotte Reichardt,[1,2] Sabine Brandt,[1] Anna Krause,[1] Jonathan A. Lindquist,[1] Robert Geffers,[4] Tobias Franz,[1] Sascha Kahlfuß,[1] Akash Mathew,[3] Rajiv Rana,[3] Peter R. Mertens.[1] *[1]Otto-von-Guericke-Universitat Magdeburg, Magdeburg, Germany; [2]Universitatsklinikum Jena, Jena, Germany; [3]Universitat Leipzig, Leipzig, Germany; [4]Helmholtz-Zentrum fur Infektionsforschung GmbH, Braunschweig, Germany*.

Background: DNA binding protein A (DbpA), encoded by the *Ybx3* gene, is a member of the cold shock protein family and is involved in cell cycling, transcription, translation, and tight junction communication. While DbpA is known to be upregulated in chronic nephritis, its functions in acute injury models, such as renal ischemia/reperfusion injury (IRI), remain unclear.

Methods: Mice with *Ybx3*$^{+/+}$, *Ybx3*$^{+/-}$, or *Ybx3*$^{-/-}$ genotypes were characterized over a period of 24 months and following experimental renal IRI. Metabolic processes such as mitochondrial function, number and integrity were analyzed by mito/glycolysis stress tests, MitoTracker staining, Western blotting and electron microscopy. Additionally, RNA sequencing, immunohistochemistry, Western blotting, and flow cytometry were performed to measure tubular cell damage, tissue scarring, and immune cell infiltration.

Results: DbpA is dispensable for kidney development and tissue homeostasis under healthy conditions. Notably, the endogenous DbpA protein is localized within the mitochondria of primary tubular epithelial cells (TECs). However, genetic deletion of *Ybx3* leads to notable changes in TECs, including increased mitochondrial membrane potential, enhanced lipid uptake and metabolism, elevated oxygen consumption rates (OCR), and glycolytic activities. In mice lacking *Ybx3*, protection against IRI is observed, characterized by reduced immune cell infiltration, diminished endoplasmic reticulum (ER) stress, less tubular cell damage, and decreased fibrosis. A putative protective mechanism is identified via upregulated antioxidant activities and reduced ferroptosis, when *Ybx3* is deleted.

Conclusions: Here, experimental evidence shows that DbpA acts as a mitochondrial protein and has significant negative effects on cell metabolism. Moreover, the genetic deletion of *Ybx3* reveals a protective effect against IRI.



FR-PO158

Global but Not Tubule Cell-Specific Knockout of STING Attenuates Kidney Injury in Mice with Unilateral Ureteral Obstruction

Emily S. Yeung, Madiha Zahra Syeda, Duc Tin Tran, Suzanne L. Advani, Youan Liu, Sri nagarjun Batchu, Andrew Advani. *Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, ON, Canada.*

Background: Recent studies have identified a key role for the inflammatory mediator STING in kidney injury. Because it is activated by the cellular response to displaced DNA, it has been proposed that STING mediates kidney injury when mitochondrial DNA leaks into the cytosol of damaged tubule epithelial cells. However, STING is not specific to tubule cells, also having an important regulatory function in other cell-types, amongst them immune cells. Here, we compared the effects of deletion of STING from tubule cells with the effects of global STING deletion in mice with kidney injury caused by unilateral ureteral obstruction (UUO).

Methods: Experiments were performed in wildtype mice, Sting$^{fl/fl}$ mice, Pax8Cre^{+}Sting$^{fl/fl}$ mice (tubule cell-specific STING knockout mice; STING^{TubKO}) and global STING knockout mice (STING^{KO}) 14 days after sham surgery or UUO.

Results: mRNA and protein levels of STING were both increased >5-fold in mice after UUO. In situ hybridization and immunostaining confirmed presence of STING in damaged tubule cells, occasional glomerular cells and notably in infiltrating interstitial cells in UUO kidneys. Knockout of STING was confirmed in STING^{KO} mice by immunoblotting; and in STING^{TubKO} mice by immunohistochemistry 24h after ischemia reperfusion injury. Kidney injury was then determined by measuring mRNA levels of *Havcr1*, the gene encoding KIM-1, in control (Sting$^{fl/fl}$) mice, STING^{TubKO} mice and STING^{KO} mice 14 days after UUO or sham surgery. *Havcr1* mRNA levels were increased >120-fold in Sting$^{fl/fl}$ mice after UUO and they were unaffected by tubule-cell specific STING knockout. In contrast, *Havcr1* mRNA levels after UUO, while increased >60-fold in global STING knockout mice, and were significantly lower than in Sting$^{fl/fl}$ and STING^{TubKO} mice after UUO (P<0.01).

Conclusions: Kidney injury in UUO mice, as assessed by *Havcr1* mRNA levels, is attenuated by global STING deficiency rather than tubule cell-specific STING deficiency. These findings indicate that the actions of STING in kidney disease extend beyond mediating the response to mitochondrial damage in tubule cells. The effects of STING may be primarily due to its actions in other cell-types, especially in infiltrating immune cells.

Funding: Government Support - Non-U.S.

FR-PO159

Wnt5a Promotes AKI to CKD Transition via p-JNK/Snai1 Signaling

Sijie Gu, Haoran Feng, Xiaomei Li, Ying Fan, Niansong Wang. *Shanghai 6th Peoples Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China.*

Background: The transition from acute kidney injury(AKI) to chronic kidney disease(CKD) is the major obstacle in the clinical treatment of AKI. In our previous study, we found Wnt5a-induced noncanonical signaling is a contributing mechanism for renal tubular inflammation in diabetic nephropathy. However, its role of Wnt5a in AKI to CKD transition still remains unknown.

Methods: Renal biopsy sample of 10 AKI patients and their clinical data were collected to analyze the correlation of Wnt5a with renal function and pathological characteristics. Wnt5a knockdown mice (Wnt5a$^{+/-}$) was generated, and two animal models of AKI by inducing renal ischemia-reperfusion (IRI) or unilateral ureteral obstruction (UUO) were established with the observation of 2 weeks post-surgery. *In vitro*, HK-2 cells were treated with transforming growth factor-β (TGF-β) or oxygen-glucose deprivation (OGD). RNA-sequencing was introduced to detect the downstream mechanism of Wnt5a signaling.

Results: The expression of Wnt5a in the kidney section of AKI patients was significantly increased mainly in the renal proximal tubules, and was associated with the decline in kidney function and interstitial fibrosis. In mice with IRI or UUO, Wnt5a elevation promoted the phosphorylation of JNK (p-JNK), increased the expression of Snai1, a transcription factor well known for inducing renal fibrogenesis. In a global Wnt5a knockdown (Wnt5a$^{+/-}$) mouse model subjected to IRI or UUO, reduction of Wnt5a alleviated renal tubule injury and interstitial fibrosis, attenuated the progression from AKI to CKD. *in vitro*, inhibition of Wnt5a in OGD induced HK-2 cells suppressed expression of p-JNK and Snai1, suggesting a strong association between Wnt5a/p-JNK and Snai1. Conversely, overexpression of Wnt5a in HK-2 cells increased the expression of p-JNK and Snai1, thus aggravated renal fibrosis. We further found a direct binding between p-JNK and Snai1 by Co-IP and mutation of JNK phosphorylation site (T183A) reduced the expression of Snai1, indicating a p-JNK/Snai1 pathway downstream of Wnt5a.

Conclusions: Our data revealed that Wnt5a is a key molecule mediating the progression from AKI to CKD, which shed light on the new Wnt5a/p-JNK/Snai1 pathway in AKI to CKD transition.

FR-PO160

Time-Restricted Feeding Protects against Kidney Ischemia-Reperfusion Injury in Mice

Yoonjoo Jang, Byung Min Ye, Seo Rin Kim, Il Young Kim, Dong Won Lee, Soo Bong Lee. *Pusan National University Yangsan Hospital, Yangsan, Republic of Korea.*

Background: Ischemia–reperfusion injury (IRI) in the kidneys stands as a significant contributor to acute kidney injury (AKI). Time-restricted feeding (TRF), known for its metabolic health benefits and alleviation of various chronic diseases without calorie restriction, was investigated for its potential protective effects against IRI-induced AKI.

Methods: C57BL/6 male mice underwent unilateral IRI, and their kidneys were harvested after 2 days. Mice assigned to the TRF group had unrestricted access to standard chow daily but were restricted to an 8-hour feeding window during the dark cycle for two weeks prior to IRI induction. The mice were categorized into four groups: Control, TRF, IRI, and TRF + IRI.

Results: In the TRF + IRI mice, there was a significant reduction observed in the tubular damage score compared to the IRI group. Additionally, the TRF + IRI mice displayed decreased levels of phosphorylated NF-κB and F4/80-positive macrophages relative to the IRI mice. Moreover, markers denoting oxidative stress for protein, lipid and DNA were notably diminished in the TRF + IRI mice in comparison to the IRI mice. Furthermore, TUNEL-positive tubular cells and cleaved caspase-3 expression were observed at lower levels in the TRF + IRI group than in the IRI group.

Conclusions: TRF, without the imposition of calorie restriction, effectively mitigated renal damage by attenuating inflammatory reactions, oxidative stress, and tubular apoptosis in an experimental model of renal IRI. This underscores TRF's potential as an innovative dietary strategy for averting IRI-induced AKI.

FR-PO161

Noncontrast Resting State Magnetic Resonance Imaging Measures Tubuloglomerular Feedback Function and Detects Functional Changes after AKI

Edwin Baldelomar,[1] Jennifer R. Charlton,[2] Kevin M. Bennett.[1] *[1]Washington University in St Louis School of Medicine, St Louis, MO; [2]University of Virginia School of Medicine, Charlottesville, VA.*

Background: The tubuloglomerular feedback (TGF) is a critical autoregulatory mechanism that plays a significant role in modulating single nephron filtration and hyperfiltration in response to acute kidney injury (AKI). There are no clinical tools to measure TGF. Noncontrast resting state magnetic resonance imaging (rsMRI) has

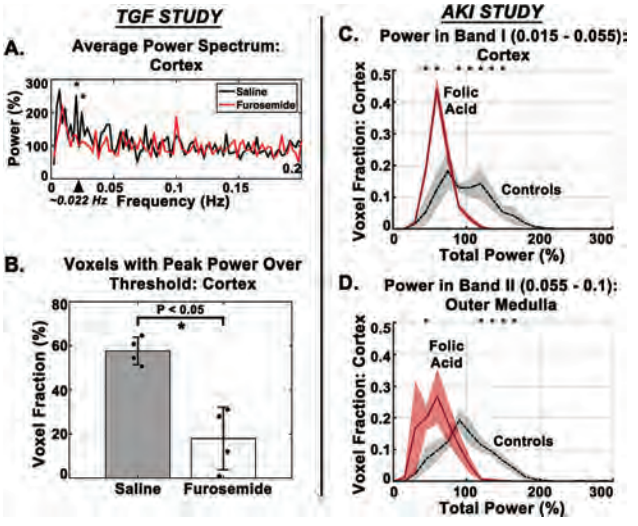
recently been used to detect hemodynamic fluctuations in the kidney, potentially linked with autogregulation. Here, we investigated if fluctuations (0.02-0.05 Hz) measured by rsMRI reflect TGF. We further tested if rsMRI detects changes in fluctuations, reflecting function, after AKI that are not detected by standard metrics.

Methods: *TGF study* – rsMRI was performed during saline infusion (20µl/min, 30min, baseline) and furosemide infusions (20µg/mL, ~45min) on male Sprague Dawley (SD) rats (N=4). *AKI study* – For AKI injury, female SD rats were stratified to folic acid (FA, 200 mg/kg) or sodium bicarbonate(N = 9). rsMRI was performed prior to AKI and again at 10, and 36 day after FA. Transcutaneous GFR, sCr, and BUN were measured days 3 and 59. rsMRI spectra were computed as published. Significance (t-test) at $p<0.05$.

Results: *TGF study, Figure 1A-B* - Furosemide attenuated the rsMRI spectral peaks at 0.015-0.05Hz in cortex. Power in this band was ~60% lower after furosemide, and 70% fewer voxels had a peak in that band. *AKI Study, Fig1C-D* - AKI was confirmed on day 3 after AKI. On day 36, the distribution of power between 0.015-0.055Hz in cortex, and distribution of power between 0.055-0.1 Hz in outer medulla were lower in the FA group. There was no difference in GFR, or BUN and creatinine 3 and 59 days after AKI.

Conclusions: TGF can be measured using noncontrasted rsMRI. Changes in TGF after AKI remain present despite normalization of renal function. This suggests rsMRI could be a translatable tool to understand the role of TGF in disease progression after AKI or in response to therapies.

Funding: NIDDK Support, Private Foundation Support



FR-PO162

Trap1 Lactylation Promotes Tubular Regeneration after AKI through Modulation of PIF1 Transcription

Jinhua Li,[1] Hongjie Zhuang,[2] Jiayi Yang,[2] Shuhan Zeng,[2] Xiaoyan Bai,[1] Zhiming Ye,[1] Xueqing Yu.[1] *[1]Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; [2]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China.*

Background: Recent studies have identified that the modification of histone protein lysine (K) residues by lactylation (La) promotes a wound healing gene transcription profile in macrophages, suggesting that lysine lactylation (KLa) may have a broader role in regulating the tissue repair response. Aim of the study is to identify which KLa has potential to enhance regeneration after acute kidney injury (AKI) and investigate the mechanism by which the identified KLa drives the repair process.

Methods: AKI model was established by a peritoneal injection of folic acid (FA). Mass spectrometry was performed to identify the KLa as a potential regeneration driver after AKI from 5-day FA nephropathy. The biological function of the identified KLa was corroborated with wild type and mutant mice in which lysine was replaced with T to mimic persistent KLa or replaced with R to mimic blockade of lactylation of lysine. Renal function was assessed by histology and biochemical parameters.

Results: Four KLa sites were identified through mass spectrometryand bioinformatic analysis. They were individually overexpressed in the mouse renal tubular epithelial cells (MTEC) via a retroviral vector. The cell proliferation assay clearly demonstrated that Trap1 K126T significantly enhanced MTEC proliferation with the proliferative capability K126T > WT > K126R under both normoxia and hypoxia conditions. Confocal microscopy demonstrated that the number of Pax8+/Ki67+/K126La+ cells were significantly higher than that of Pax8+/Ki67-/K126La+ in human chronic kidney disease (CKD) and FA nephropathy. There were no differences in serum creatinine levels at day 2 after FA administration; but at days 5 and 7 the serum creatinine levels declined faster in Trap1 K126T mice and reduced fibrosis on day 28 compared with WT and Trap1 K126R mice. RNA seq and IP/WB identified that Trap1 K126T upregulates transcription of PIF1 through interaction with Nat14, while PIF1, a DNA-dependent ATPase and 5′-3′ DNA helicase can efficiently unwind G-quadruplex (G4) DNA structures and forked RNA-DNA hybrids and resolve G4 structures, preventing replication pausing and double-strand breaks (DSBs) at G4 motifs.

Conclusions: Trap1 K126La promotes tubular regeneration after AKI through modulation of PIF1 expression. Trap1 K126La may be a therapeutic target in AKI-CKD transition.

Funding: Government Support - Non-U.S.

FR-PO163

Gut Microbiome and Olfactory Receptor 78 in Experimental AKI

Shishir K. Patel, Qisen Guo, Radhika Kapoor, Mahta F. Gooya, Mackenzie Kui, Lois J. Arend, Sanjeev Noel, Jennifer L. Pluznick, Hamid Rabb. *Johns Hopkins Medicine, Baltimore, MD.*

Background: Olfactory receptor 78 (Olfr78) is a short-chain fatty acid (SCFA) receptor activated by gut microbiome-derived acetate and propionate. Olfr78 is expressed in the afferent arteriole, vascular smooth muscle cells, and immune cells. SCFAs are hypothesized to mediate gut microbiome effects in AKI and CKD. We studied the role of Olfr78 in ischemic and cisplatin induced AKI in mice.

Methods: Male and female, wild-type **(**WT) and Olfr78 knockout (KO) C57BL6 mice were subjected to bilateral ischemic or cisplatin AKI. Mice were also studied long-term after severe unilateral ischemic AKI (UIRI). Endpoints included survival, kidney function (SCr, GFR by FITC-sinistrin clearance), histology and kidney immune cell phenotyping (FACS).

Results: In moderate bilateral ischemic AKI, Olfr78 KO mice had worse survival at 72 hrs than WT mice ($P<0.01$). However, no changes were found in kidney function or structure. Cisplatin induced AKI was comparable in KO and WT mice. Female mice were more susceptible to cisplatin, while males more susceptible to ischemic AKI. In the UIRI model, KO had lower GFR than WT at baseline (1369.9±106.4 vs 1170.7±196.5, $P\leq0.05$), 24h after UIRI (959.4±8 vs 837.0±7, $P< 0.05$) and after 21d (1166.1±54.5vs 807.6±11, $P< 0.0001$). After severe UIRI KO mice showed a decrease in double negative (DN) (9.6±1.6 vs 4.0±1.6%, $P<0.001$) and increase in double-positive cells (DP) T cells (0.2±0.1 vs 0.5±0.3%, $P<0.001$). In the CD4 subset, activation marker CD69 (32.6±4.0 vs 74.8±7.6%, $P< 0.0001$), effector cells ($CD44^{+}CD62L^{-}$) (93.1±1.2 vs 94.6 ±0.93%, $P<0.05$), and immune checkpoint molecule TIGIT (12.8±4.5 vs 21.9±3.9%, $P<0.01$) increased in KO vs. WT. In CD8 cells, there was an increase in CD69 (40.8±8.8 vs 55.8±8.6%, $P<0.01$), TIGIT (7.9±2.4 vs 17.4±11.3 %, $P<0.01$) and CTLA4 (0.1±0.14 vs 0.7 ±0.5%, $P<0.01$); There was a decrease in B cells (25.5±2.4 vs 15.7±2.2, $P<0.001$) and an increase in NKT cells (1.0±0.3 vs 2.4±0.70, $P<0.001$) and dendritic cells (2.0±2.2 vs 5.4±6.3, $P<0.001$) in Olfr78 KO vs. WT.

Conclusions: Absence of Olfr78 reduced short-term survival after moderate AKI, but with minimal effects on renal function/structure. However, GFR and kidney immunophenotypes were modified by Olfr78 after severe UIRI. Olfr78 has subtle effects during AKI but is likely not a major mechanism by which gut microbiome influences outcomes in AKI.

Funding: NIDDK Support

FR-PO164

Long-Term Maladaptive Repair of the Kidney Medulla after Reversal of Ureteric Obstruction

Thitinee Vanichapol,[1] Alan J. Davidson,[1] Mark P. de Caestecker.[2] *[1]The University of Auckland, Auckland, New Zealand; [2]Vanderbilt University Medical Center, Nashville, TN.*

Background: There is a long-term decrease in urinary concentrating capacity (UCC) after urinary tract obstruction. UCC is dependent on the correct cellular organization and function of the inner medulla (IM), but little is known about the regenerative potential of the IM, nor the long-term structural and functional effects after reversal of urinary tract obstruction.

Methods: Ureteric clamps were placed in mice for 5 to 8 days to induce reversible unilateral ureteric obstruction (R-UUO), with contralateral nephrectomies to assess renal function. GFR and urine osmolality were measured, and kidneys harvested at Day 28 and 84. Renal histology (PAS), immunostaining, and genetic lineage analysis performed using Six2 and HoxB7 Cre; tdTomato Cre reporter mice. scRNA-Seq was performed using FLEX on isolated renal medullas.

Results: Survivable R-UUO clamp times varied between mouse strains, but all showed a marked decrease in UCC 84 days after R-UUO. Renal histology showed IM damage with papillary necrosis, followed by active tubular repair. Most tubular structures were repopulated by day 28, and the IM appeared indistinguishable from controls by day 84. Unsupervised clustering of scRNA-Seq data identified multiple clusters of loop of Henle (LOH), collecting duct (CD), and endothelial cell (EC) subtypes, likely reflecting their spatial location in the IM. There was a reduction in subsets of these cells and appearance of "injured" clusters at day 28 post R-UUO, with a loss of vasa recta ECs and persistence of injured CD and LOH cells at day 84. Inflammation and fibrosis genes were also increased in "non-injured" CD and LOH populations, suggestive of a persistent

inflammatory state. Immunostaining confirmed a reduction in IM capillary density (CD31) and LOH (AQP1). However, CD markers recovered and expanded in the distal IM by day 84. Since dedifferentiation may affect cell identification, we confirmed these findings independently by genetic lineage labelling studies using Six2-Cre and HoxB7-Cre mice, respectively.

Conclusions: These data indicate that despite robust repair, there is a persistent defect in UCC associated with incomplete repair of vasa recta and LOH cell types in the IM, and persistence of "injured" LOH-derived cells. The CD recovers and expands but also retains populations of injured and inflammatory cells, suggestive of a persistent maladaptive repair state.

Funding: NIDDK Support

FR-PO165

Investigation of the Vulnerability of the Remaining Kidney Postunilateral Nephrectomy under Crystalline Nephropathy Conditions

Neydiana B. Lopes, Maria Oliveira-Souza. *Universidade de Sao Paulo Instituto de Ciencias Biomedicas, Sao Paulo, Brazil.*

Background: The loss of a kidney is a common outcome of single kidney transplantation, renal trauma, and renal cancer. Despite many studies showing stable function after unilateral nephrectomy (UNx), it can lead to overload of the remaining kidney. This overload may become a relevant factor in the development of Acute Kidney Injury and increase the vulnerability of the remaining kidney to Chronic Kidney Disease (CKD). Therefore, the present study aims to investigate the function of the remaining kidney after UNx, its response to crystalline nephropathy, and the potential factors and mechanisms involved in its vulnerability state.

Methods: Eight-week-old male C57BL/6J mice (n=23) were divided into four groups: sham, subjected to UNx, sodium oxalate (intraperitoneal injection of 9 mg/100 g of NaOx to induce crystalline nephropathy), and UNx treated with sodium oxalate (UNx/NaOx). Six days after the sham or UNx surgery and twenty-four hours before the euthanasia, mice were treated according to their group and placed in metabolic cages for metabolic parameters and kidney function track. At the end of twenty-four hours, the animals underwent isoflurane anesthesia (0.8 L/min/rate 5%), blood and urine collection, removal of the left kidney and euthanasia by exsanguination.

Results: One week after the surgery, the UNx animals showed a significant increase in urinary flow (p< 0,04), kidney weight/body weight ratio (p<0,003) and in plasma creatinine(p<0,004) when compared to sham animals. They also showed a significant increase in mRNA expression for *Mki-67* (p<0,02), a biomarker to measure tubular regeneration and renal repair. Still in this group, we observed an increase in mRNA expression for *Col1a1*(p<0,05) and *Col4a1*(p<0,05) and in the protein expression of a specific macrophage marker, F4/80(p<0,004). Faced with NaOx insult, UNx/NaOx animals showed more pronounced renal hypertrophy (p<0,02), greater accumulation of creatinine in plasma (p<0,003) and greater expression of mRNA for tubular injury factors such as *Havcr1* (Kim-1) (p<0,006) and *LCN2* (NGAL) (p<0,0006) and protein expression of Kim-1(p<0,003), when compared to NaOx animals.

Conclusions: Our findings indicate that the remaining kidney has vulnerability, which affected its response to the insult, and can potentially hindering improvement and contributing to the development of CKD.

Funding: Government Support - Non-U.S.

FR-PO166

CD146 Deletion Protects against Kidney and Heart Damage after AKI

Louis Boutin,[1,3] Stefanny M. Figueroa,[1] Safia Hadjadj,[1] Mouhamed Amar,[1] Elena Roger,[1] Nadia Elganfoud,[3] Marcel Blot-Chabaud,[2] François Depret,[3] Jane Lise Samuel,[3] Feriel Azibani,[3] Christos E. Chadjichristos.[1] *[1]UMR_S 1155, Common and Rare Kidney Diseases, Tenon Hospital, Paris, France; [2]Aix-Marseille Univ, INSERM INRA, C2VN, Marseille, France; [3]UMR-942, MASCOT, Cardiovascular Markers in Stress Condition, University Paris Cité, Paris, France.*

Background: AKI is linked to a higher risk of mortality and has been shown to increase heart failure, in months or years following the injury. CD146, an adhesion molecule mainly expressed in vascular endothelial cells, is elevated in patients with both renal and heart diseases. Recent findings show that CD146 increased expression within renal damaged endothelium exacerbates kidney inflammation and promotes tissue fibrosis in experimental nephropathy. Furthermore, mechanisms underlying AKI-induced cardiovascular damage remain poorly understood, including the role of CD146 in this process. Thus, this study assessed the role of CD146 in the progression of renal-cardio damage after renal ischemia-reperfusion (rIR).

Methods: Wild type (WT) and CD146 knock-out (KO) (2-3m) male mice, underwent a unilateral rIR of the left kidney after nephrectomy, with 25min of ischemia followed by 24h, 48h, and 28d of reperfusion. Sham group was submitted to a procedure without nephrectomy and rIR. Renal function was assessed by measuring creatininemia. Histological damage was evaluated by PAS or Sirius Red. Echocardiography was used to analyze heart function, and proinflammatory cytokines were studied by qPCR.

Results: CD146 was highly increased within renal endothelium at 24h (P<0.05) and 48h (P<0.01) in WT mice after rIR, and in the heart at 28d (P<0.05). As expected, after rIR renal function was temporarily altered as shown by plasma creatinine, increased at 24h (24.3±4.7 *vs.* 10.1±0.6μM in Sham), and 48h (20.0±3.1 *vs.* 6.3±0.4μM in Sham) and decreased over time. Interestingly, this increase was not observed in KO mice. In accordance, PAS showed preserved renal damage at 48h in KO mice compared to WT (P<0.05). In addition, increased expression of mRNA for proinflammatory cytokines, such as CCL2 and IL-1β, after 24 and 48h of rIR within damaged kidneys, and CCL2 in the heart at 28d, was blunted in KO (P<0.05). Furthermore, collagen deposition at 28d post-rIR in both kidney and heart was prevented in KO compared to WT mice (0.6 and 0.5 times, respectively). Finally, the absence of CD146 prevented the reduction in fractional shortening caused by rIR at 28d (46% in WT *vs.* 65% in KO mice).

Conclusions: Our results suggest that CD146 deletion protects against AKI and further heart damage after rIR in mice.

Funding: Government Support - Non-U.S.

FR-PO167

Pathophysiology of Cardiorenal Syndrome in an Experimental Model Due to Isolated Right Ventricle Failure: Beyond Systemic Congestion

Firoozeh Farahmand. *Saint Louis University, St Louis, MO.*

Background: Cardiorenal syndrome (CRS) and right heart failure (RHF) have complex and interrelated pathophysiology that involve mechanisms beyond isolated dysfunction of the heart and kidneys. This study investigates changes in antioxidants and oxidative stress in the right ventricle(RV) and the kidney as well as systemic congestion in CRS. This will shed light on pathophysiology based new therapeutic targets and preventive measures in CRS in addition to symptomatic relief with diuretics.

Methods: CRS due to isolated RVF was produced in rats by a single injection of ALK. Animals were observed daily for any clinical signs of dyspnea, cyanosis, subcutaneous edema and ascites. At 1 week post injection serial echocardiography was performed to monitor cardiac function. RV systolic pressure (RVSP), RV hypertrophy (RVH), and RV function, RV and kidney levels of superoxide dismutase (SOD), catalase, glutathione peroxidase (GSHPx) and lipid peroxidation (LPX) were measured. After sacrificing animals, hearts and kidneys were removed for histopathology. Lung and liver wet to dry weight ratio were measured to investigate pulmonary edema and liver congestion.

Results: At 1 week post ALK injection renal histopathology was consistent with CRS. There was no clinical sign of fluid overload. Antioxidant enzymes activities including SOD and GSHPx were decreased in the kidney and the RV. There was LPX in the kidney and the RV. RV pressure overload and RV hypertrophy with no RV dysfunction were observed. There was no lung or liver congestion.

Conclusions: New & noteworthy: This experimental model of CRS due to isolated RV dysfunction provides novel data that oxidative stress is the key contributor to pathophysiology of RV-Kidney deleterious cross talk and systemic congestion develops in later stage. Thus, antioxidants may have a crucial role in management of CRS.

FR-PO168

Abstrac Withdrawn

FR-PO169

Computational Workflow for Spatiotemporal Transcriptomics Analysis of Cold vs. Warm Ischemic Kidney Injury

Srujan Singh, Sanjeev Noel, Shishir K. Patel, Zhaoli Sun, Hamid Rabb, Jean Fan. *Johns Hopkins University, Baltimore, MD.*

Background: Increasing cold ischemia (CI) time leads to AKI, limits lifespan of transplanted organs and increases organ discard. However, there is limited comparison of the molecular pathogenesis between CI and warm ischemia (WI) injury. We performed full-transcriptome characterization in a CI murine model using the 10X Visium spatial transcriptomics (ST) platform for comparison with previously published WI data.

Methods: We induced CI in murine kidneys in UW solution at 4°C (0, 12, 24 and 48 hours), then generated ST datasets (n=1 per timepoint), containing 12530 spatial spots with 19465 shared gene species profiled per kidney tissue section. We developed a computational workflow which facilitates batch correction (via Harmony) to identify shared cell types across all datasets. We segmented kidney tissues into three different compartments, namely the cortex, medulla, and corticomedullary junction based on cell types and their anatomical location. We identified differentially expressed genes (DEGs) across time points unique to each compartment using DESeq2, clustered DEGs into different temporal trends, and further characterized enriched pathways per compartment per trend using ClusterProfiler. We implemented a similar workflow on WI injury kidneys.

Results: We integrated 0, 12, 24 and 48 hours CI kidney ST datasets and identified shared cell types across all timepoints that demarcated similar anatomical locations. We identified shared temporal trends affecting distinct genes and pathways within different kidney compartments. In particular, autophagy-related pathways were uniquely

upregulated in the cortex of CI kidney at an early timepoint (12 hours) whereas upregulation of immune-related pathways emerged in the medulla at a later timepoint (48 hours). Comparisons between CI and WI further elucidated molecular differences within corresponding kidney compartments. For example, the *Fosb* gene was upregulated early in the cortex of the CI kidneys while it was confined to the medulla of WI kidneys.

Conclusions: CI and WI induce pleiotropic transcriptional effects in a spatially and temporally distinct manner. Developing strategy for spatiotemporal molecular characterization can enhance our understanding of CI to improve outcomes and reduce organ discard.

Funding: NIDDK Support

FR-PO170

Role of CDKL1-SOX11 Signaling Axis in AKI

Josie A. Silvaroli, Ji Young Kim. *The Ohio State University, Columbus, OH.*

Background: The biology of CDKL (Cyclin-Dependent Kinase-Like) kinase family remains enigmatic. Contrary to their nomenclature, CDKLs do not rely on cyclins for activation and are not involved in cell cycle regulation. Instead, they share structural similarities with MAPKs (Mitogen-Activated Protein Kinases) and GSK3 (glycogen synthase kinase 3), though their specific functions and associated signaling pathways are still unknown. Previous studies have shown that the activation of CDKL5 kinase contributes to the development of acute kidney injury (AKI) by suppressing the protective SOX9-dependent transcriptional program in tubular epithelial cells. The role of other CDKL family members in kidney biology and disease remains unknown.

Methods: Mouse models of renal ischemia reperfusion, and rhabdomyolysis were used to assess the effect or germline CDKL1 and tubular specific SOX11 conditional knockout mice in the severity of AKI.

Results: In the current study, we measured the functional activity of all the five CDKL kinases and discovered that, in addition to CDKL5, CDKL1 is also activated in tubular epithelial cells during AKI. To explore the role of CDKL1, we generated a germline knockout mouse which exhibited no abnormalities under normal conditions. Notably, when these mice were challenged with bilateral ischemia reperfusion and rhabdomyolysis, they were found to be protected from AKI. Further mechanistic investigations revealed that CDKL1 phosphorylates and destabilizes SOX11, contributing to tubular dysfunction. In summary, these studies have unveiled a previously unknown CDKL1-SOX11 axis that drives tubular dysfunction during AKI.

Conclusions: This study underscores the importance of CDKL1 kinase in kidney injury and supports the development of targeted small-molecule inhibitors as potential therapeutics.

Funding: Other NIH Support - NCATS

FR-PO171

Bilirubin Nanoparticles Protect against Kidney Ischemia-Reperfusion Injury through Antioxidant Activity

Honglin Piao, Jaeseok Yang. *Yonsei University, Seoul, Republic of Korea.*

Background: Renal ischemia-reperfusion injury (IRI) is a common complication but there was no definite treatment, except supportive care. Basic mechanisms of renal IRI is acute inflammation, where oxidative stress plays an important role. Despite potent reactive oxygen species (ROS)-scavenging effects, free bilirubin has an important limitation of water-insolubility, interfering with clinical application. Recently, Brixelle, a PEGylated bilirubin nanoparticle has been developed to improve water solubility.

Methods: This study aimed to assess renoprotective effects of bilirubin nanoparticles against renal IRI. We injected bilirubin nanoparticles intravenously 1 h before and 1.5 h after mouse renal IRI and assessed their renoprotective effects on renal IRI on day 1, 3, and 28, compared to free bilirubin.

Results: Bilirubin nanoparticles suppressed *in vitro* ROS generation and secretion of TNF-α and IL-1β from activated neutrophil-like cells and macrophages, whereas free bilirubin did not show any suppressive effect. Moreover, Bilirubin nanoparticles increased *in vitro* cellular viability of renal tubular epithelial cells against ROS. Intravenous administration of bilirubin nanoparticles led to an increased uptake in the kidney with minimal migration to brain after renal IRI. Peri-IRI administration of bilirubin nanoparticles improved renal function and attenuated renal tissue injury as well as renal tubular apoptosis on day 1 after IRI to greater extent than free bilirubin. Renal infiltration of neutrophils and expression of TNF-α and MCP-1 were also suppressed by bilirubin nanoparticles. Furthermore, bilirubin nanoparticles increased renal tubular regeneration (Ki67) on day 3 and suppressed renal fibrosis as well as renal expression of αSMA, fibronectin, and type IV collagen on day 28 after IRI to greater extent than free bilirubin. Bilirubin nanoparticles suppressed expression of nicotinamide adenine dinucleotide phosphate oxidase (NOX) and iNOS, increased expression of nuclear factor erythroid-2-related factor 2 (Nrf2) and HO-1, and attenuated ROS generation after IRI to greater extent than free bilirubin.

Conclusions: Bilirubin nanoparticles effectively attenuates ROS generation and acute renal injury, facilitates subacute renal recovery, and suppressed chronic fibrosis after renal IRI, having a potential as a new therapy for renal IRI.

Funding: Government Support - Non-U.S.

FR-PO172

Inhibition of RNA-Binding Protein Hu Antigen R (HuR) Prevents AKI-to-CKD Transition in Aristolochic Acid-Induced Nephropathy

Zhou Wang, Lili Zhuang, Yufeng Huang. *University of Utah Health, Salt Lake City, UT.*

Background: Acute kidney injury (AKI) is a significant risk factor for developing chronic kidney disease (CKD). The RNA-binding protein HuR is known to critically influence the progression of CKD, primarily by upregulating inflammation and facilitating fibrosis. We hypothesized that HuR might also play a pivotal role in the transition from AKI-to-CKD and inhibition of HuR could potentially mitigate persistent kidney damage.

Methods: We utilized a model of aristolochic acid nephropathy, induced by the administration of aristolochic acid (AA), which is characterized by tubular atrophy and interstitial fibrosis, mirroring the AKI-to-CKD transition observed in humans. After optimizing the AA dosage, male mice aged at 10 weeks received AA injections of 1.5mg/kg BW daily for 4 consecutive days. Concurrently, these mice were treated either without or with HuR inhibitor KH3 (adminstered at 40mg/kg-BW daily) for 14 days. Normal mice recevied saline injections.

Results: Repeated AA injections significantly increased HuR expression in the kidneys, particularly in tubular cells, which was effectively suppressed by KH3 treatment. AA-induced kidney injury was evidenced by elevated plasma levels of blood urea nitrogen and creatinine, along with decreased glomerular filtration rate and increased urinary albuminuria. Histological analyses revealed markedly tubular atrophy, apoptosis, capillary rarefaction, inflammatory cell infiltration and fibrosis. These findings were determined using periodic acid-Schiff and Masson's trichrome staining, alongside immunofluorescent staining for markers including Tunel+, CD31+, alpha-smooth muscle actin, fibronectin, collagen III, and F4/80+. Treatment with KH3 mitigated these pathological changes in AA-injured mice. Additionally, the increased renal expression of NF-kBp65 and phosphorylated Akt- molecules implicated in AA-induced tubular cell DNA damage, apoptosis, and necrosis- along with gamma-H2AX, cleaved caspase-3, and PARP expression, were inhibited by KH3 treatment.

Conclusions: Our findings demonstrate that elevated HuR levels in renal tubular cells, stimulated by AA, critically contribute to the progression from AKI-to-CKD. This effect is likely mediated through the HuR-cellular DNA signaling pathway. These results highlight the therapeutic potential of HuR inhibitors in treating AKI-to-CKD transition.

Funding: NIDDK Support

FR-PO173

Atypical Protein Kinase C Zeta Is Indispensable for Calcium Oxalate Crystal Clearance in a Dietary-Induced Mouse Model of Kidney Injury

Melina Messing,[1] Nickolas J. Holznecht,[1] Sebastian Strubl,[2,1] Jacob A. Torres,[1] Brina A. Aceves,[1] Margaret Schimmel,[1] Rachel Wong,[1] Thomas Weimbs.[1] *[1]University of California Santa Barbara, Santa Barbara, CA; [2]Universitat zu Koln, Koln, Germany.*

Background: Previously, we showed that renal calcium oxalate (CaOx) crystal deposition triggers reversible tubular dilation to expel crystals from normal kidneys and accelerates disease progression in polycystic kidney disease (PKD) rodent models. Given our previous report that atypical protein kinase C zeta (PKCζ) expression is downregulated in patients with autosomal dominant polycystic kidney disease (ADPKD) and that restoration of PKCζ improves the condition, we investigated the role of PKCζ in the kidneys during and after CaOx deposition.

Methods: To explore reversible tubular dilation and signaling activity in PKCζ-knockout (KO) kidneys following CaOx deposition, we administered a 0.67% sodium oxalate (NaOx) diet to P56 male wild-type and PKCζ-KO mice for up to 14 days, followed by a recovery period of up to 28 days after cessation of NaOx treatment.

Results: Both groups demonstrated substantial renal crystal deposition; however, wild-type mice remained healthy throughout the dietary intervention. In contrast, PKCζ-KO mice showed increased susceptibility to injury, leading to mortality around day 10. Further investigation revealed significantly higher crystal accumulation in PKCζ-KO mice compared to wild-type. Notably, reintroduction of a normal diet after 3 days on NaOx allowed for crystal clearance in wild-type mice, but not in PKCζ-KO mice, where crystals persisted. Additionally, PKCζ-KO mice displayed enduring renal damage characterized by significant collagen deposition and inflammation, even after a 28-day washout period.

Conclusions: These findings underscore the critical role of PKCζ in managing CaOx crystal deposition and suggest its potential as a therapeutic target for preventing chronic kidney disease progression following crystal-induced injury.

Funding: Private Foundation Support

FR-PO174

Exploring the Role of ELMO1 in AKI

Blandine Baffert. *University of Virginia School of Medicine, Charlottesville, VA.*

Background: Acute kidney injury (AKI) is a sudden episode of kidney failure linked to a wide range of health conditions. High mortality in AKI highlights the need to identify new therapeutic approaches. Recent studies revealed the association of ELMO1 gene polymorphisms with diabetic nephropathy and lowering *Elmo1* expression was protective against severe disease. ELMO1 is a cytoplasmic protein that promotes cytoskeletal reorganization during apoptotic cell clearance and cell migration. We have previously shown that loss of ELMO1 in neutrophils reduces neutrophil recruitment in inflammatory arthritis, without affecting bacterial recruitment or killing. Since immune cell recruitment and renal cell death directly affect AKI outcomes, we examined the role of ELMO1 in mouse models of AKI.

Methods: We subjected wild type and *Elmo1*$^{-/-}$ mice to two different models of AKI: 1. Renal ischemia-reperfusion (IRI), a model of traumatic or post-operative kidney injury and 2. Cisplatin-induced nephrotoxicity.

Results: In the bilateral renal IRI model, Elmo1$^{-/-}$ mice reduced expression of the kidney injury marker NGAL and local and global levels of inflammatory cytokines IL-6 and TNFα, as well as a significant decrease in remodeling gene expression. ELMO1-deficient mice also showed a reduction in neutrophils (Ly6G^{+}) and apoptotic cells in renal tissue. Surprisingly, *Elmo1*$^{-/-}$ mice subjected to cisplatin-induced AKI displayed accelerated loss of kidney function and trends toward increased kidney injury marker NGAL and histological damage. We also noted elevated levels of apoptotic cells (cleaved caspase-3 stained) in the kidneys of cisplatin-injected *Elmo1*$^{-/-}$ mice, indicating potential for ELMO1 function in clearance of dying cells during cisplatin nephrotoxicity.

Conclusions: Collectively, our data suggest distinct roles of ELMO1 in acute kidney injury induced by different damage trigger. Our ongoing studies are focused on cells involved in the phagocytosis of apoptotic cells (efferocytosis), having shown that the efferocytosis capacity of macrophages and renal tubular epithelial cells (RTEC) is not altered by loss of ELMO1. Our hypothesis is that ELMO1 could represent an attractive therapeutic target in ischemic injury, while potentially detrimental in the context of chemotherapy.

Funding: Other NIH Support - NIAID

FR-PO175

Role for Actin Organization vs. Tight Junction Membrane Protein Cross-Linking in Regulation of Renal Paracellular Permeability to Macromolecules

Kurt Amsler. *NYIT College of Osteopathic Medicine, Old Westbury, NY.*

Background: The Leak Pathway mediates macromolecule paracellular permeability across the tight junctions of epithelia. Changes in Leak Pathway permeability have been associated with many renal and other epithelial diseases states. The basic cellular processes and regulation of the Leak Pathway are poorly understood. The cytoplasmic ZO-1 protein provides a scaffold for crosslinking tight junction membrane proteins and for linking these proteins to the actin cytoskeleton. It also shuttles TOCA-1 protein, which facilitates formation of branching actin networks, to the tight junction. In MDCK II cells, knockdown of ZO-1 (ZO-1 KD) and knockout of TOCA-1 (TOCA-1 KO) increase Leak Pathway permeability.

Methods: The flux rates of a size panel of fluorescein-dextran molecules (FD) were determined across monolayers of wild type MDCK II cells, ZO-1 KD cells, and TOCA-1 KO cells.

Results: We hypothesized that depletion of these two proteins would similarly affect the Leak Pathway properties, opening number and opening size. Both TOCA-1 KO and wild type MDCK II cells exhibited similar proportional decreases in flux rate with increasing FD molecular size. ZO-1 KD cells exhibited a diminishing difference from wild type cells with increasing FD size. Plotting apparent permeability (P_{app}) versus solute Stokes radius on semilog plots demonstrated that the rate of decrease in P_{app} as a function of FD size was similar for wild type MDCK II and TOCA-1 KO cell monolayers. In contrast, ZO-1 KD cells exhibited a more rapid decline in P_{app} as solute size increased such that a large FD molecular size exhibited a similar P_{app} in wild type and ZO-1 KD MDCK II cells.

Conclusions: Based on theoretical considerations, opening number should not affect P_{app} as a function of solute size. Opening size, however, should affect P_{app} as a function of solute size. Our results support the conclusion that depletion of TOCA-1 increases opening number without significantly affecting opening size. In contrast, ZO-1 depletion increases opening number and decreases opening size. These results suggest that crosslinking of tight junction membrane proteins, a property of ZO-1 but not TOCA-1, may be important for determining the size of the Leak Pathway openings, whereas, interaction of the tight junction with actin structures may affect preferentially opening number.

FR-PO176

Role of Versican in Cisplatin-Induced AKI to CKD Transition

Dan Wang,[1] Juan P. Arango Velasquez,[2] Diana Zepeda-Orozco,[3] Sethu M. Madhavan,[1] Samir V. Parikh,[1] Navjot Pabla,[2] Nicholas J. Ferrell.[1] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]The Ohio State University, Columbus, OH; [3]Nationwide Children's Hospital, Columbus, OH.*

Background: Versican is an extracellular matrix (ECM) proteoglycan with five isoforms (V0-V4) that impacts immunity and inflammation. Studies have shown that versican is upregulated following injury in lung, heart and liver, and versican deficiency protects from acute lung injury. However, the role of versican in regulating renal response in AKI and AKI-CKD transition has not been studied. We hypothesize that versican plays a role in response to AKI and primes ECM for fibrosis in the setting of AKI-CKD transition.

Methods: Mass spectrometry data on human CKD biopsy samples were used to analyze the correlation between versican expression and interstitial fibrosis. We use two cisplatin-induced mouse models: AKI with single high-dose cisplatin (25mg/kg), and AKI-CKD where acute injury transitions to chronic injury and fibrosis with 2 low-doses (10 mg/kg) of cisplatin. C57BL/6J male mice (8-10 weeks) were euthanized 3 days, 2wks, or 1 month post-injection. Kidney tissues were collected and processed for histological analysis, immunofluorescence staining, and immunoblot and qPCR analysis of isoform specific versican expression. Marker of kidney injury (KIM-1 and NGAL) and fibrosis (tenacin C, periostin, aSMA, ACTA2, and col1a1) were evaluated by qPCR.

Results: Versican expression is upregulated in chronic injury and correlates strongly with the degree of interstitial fibrosis in human CKD. Gene expression for all kidney expressed isoforms of versican (V0, V1, V3, Vtotal) and protein expression are upregulated at 72 hours after AKI. In the setting of AKI-CKD transition, versican gene expression increases initially, peaks at 2wks, and then decreases but remains upregulated at 1 month after treatment. This indicates the kidney injury persists and transitions to chronic kidney damage. Gene expressions of fibrosis markers are upregulated in AKI-CKD model. This study shows that versican is rapidly upregulated following acute injury and persists during transition to CKD.

Conclusions: We show upregulation of versican mRNA and protein expression during AKI and AKI-CKD transition. Versican may play a role in ECM remodeling and progressive fibrosis during AKI-CKD transition. Future studies aim to determine the role of versican in promoting fibrogenesis during AKI-CKD transition.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO177

Excess Dietary Sodium Partially Corrects Salt and Water Homeostasis Caused by Loss of the Endoplasmic Reticulum Molecular Chaperone, GRP170, in the Mouse Nephron

Aidan W. Porter,[1,2] Hannah E. Vorndran,[3] Allison L. Marciszyn,[3] Stephanie Mutchler,[3] Arohan R. Subramanya,[1] Thomas R. Kleyman,[3,1] Jeffrey L. Brodsky,[3] Teresa M. Buck.[3] *[1]University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Children's Hospital of Pittsburgh of UPMC Department of Pediatrics, Pittsburgh, PA; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: Correct folding and trafficking of ion channels and transporters by renal tubular epithelial cells is essential to maintain fluid and electrolyte homeostasis. These processes rely on proteins termed molecular chaperones to sustain protein biogenesis and coordinate the repair and recycling of misfolded proteins. We previously found that conditional loss of one such HSP70-like chaperone, GRP170, which resides in the endoplasmic reticulum (ER) of murine tubular epithelial cells leads to hypovolemia, electrolyte imbalance, and an AKI-like phenotype evidenced by tubular injury and elevated kidney injury markers. GRP170 deletion also compromises protein homeostasis and activates an ER quality control mechanism known as the Unfolded Protein Response (UPR). Based on these data, we hypothesized that UPR induction underlies hyponatremia, volume depletion, and AKI in rodents, but that these features might be rectified by intervention to maintain intravascular volume and, hence, renal perfusion.

Methods: Male and female inducible, nephron-specific GRP170 knockout (KO) mice were fed a control or an 8% sodium chloride diet. Serum and urine chemistries and concentration were measured. AKI markers and UPR induction was monitored by qPCR, western blot, and imaging. Renal histology and ER morphology were also assessed.

Results: Sodium supplementation improved electrolyte balance, intravascular volume, and AKI markers but failed to prevent weight loss or restore tubule integrity and function in GRP170 KO mice. UPR induction and ER morphology were also unaffected by excess sodium. Compared to males, female mice had milder kidney dysfunction, which was better ameliorated by sodium. However, GRP170 deletion produced a unique, sodium-independent UPR profile in both sexes.

Conclusions: An aberrant UPR contributes to kidney dysfunction in an inducible nephron-specific GR170 knockout mouse model. Moreover, GRP170 expression in the murine tubule is indispensable for protein homeostasis, cell integrity, and electrolyte balance. The distinct sex-specific phenotypes also indicate that the UPR may contribute to the relative susceptibility of each sex to kidney injury, highlighting the need to account for sex in AKI studies.

Funding: NIDDK Support

FR-PO178

Changes of Kidney and Urinary Klotho Reflect the Involvement of Distal Convoluted Tubules in Lipopolysaccharide (LPS)-Induced AKI in Rats

Weiwan Wang,[1] Mingzhuo Zhang,[1,2] Anni Xie,[1,2] Mingda Liu,[1] Yutao Jia,[1,2] Haonan Duan,[1,2] Xiaoyan Wang.[1,2] *[1]The Core Laboratory, Nanjing BenQ Medical Center, Nanjing, China; [2]The Affiliated BenQ Hospital of Nanjing Medical University, Nanjing, China.*

Background: Sepsis is one of the common causes for acute kidney injuries (AKI).

Methods: To seek a noninvasive but early biomarker, we determined klotho, an anti-aging protein secreted by renal distal convoluted tubules, in kidneys and urines from sepsis-like AKI rats at 6, 12, 24-h respectively after a single intraperitoneal injection of LPS at 5 mg/kg.

Results: The LPS-rats exhibited similar appearances, body weights and urine volumes as the controls. Serum creatinine concentration was not altered at 6, and 12-h but elevated at 24h (51.0±5.0 vs 31.0±1.6, mmol/L??? n=5/group, p<0.05). Compared with baseline (28.8±1.7, ng/ml), serum klotho declined in the rats at 12 (18.5±3.4) and 24h (19.6±3) but not 6h while serum kidney-injury-molecular-1,cystatin C were not changed at all time points. Klotho was detected in rat renal distal convoluted tubules and colocalized with positive staining of NCC at apical membranes. Renal klotho was lowered at 6 (66.8±6.4, % of controls, same as below), 12 (38±1.6) and 24-h (40.5±6.2) in LPS rats than controls. Klotho mRNA expressions were decreased at 6 (27.9±4.6), 12 (36.2±10.7) and 24-h (22.2±3.8). Furthermore, klotho in urinary exosomes was much enriched relative to original urines. Urinary exosomal klotho excretions, corrected by corresponding creatinine concentrations, were elevated at 6 (245.2±56.2), 12-h (246±53), not 24h in LPS rats relative to vehicle controls. NCC in kidneys was unchanged but increased in urinary exosomes at 6 (394.01±137.57) and 12-h (658.83±220.56).

Conclusions: Thus, LPS impaired renal functions including synthesis and production of klotho from distal convoluted tubules while the decrease of klotho in kidney is followed by its decrease in serum. However, the rises of urinary exosomal klotho and NCC may reflect their leakages from kidney into urines during the AKI process and could be considered as early biomarkers for the septic AKI.

FR-PO179

Severity of Kidney Dysfunction in Obstructing Tubulopathy Is Associated with the Number of Renal Tubular Obstructing Foci by Light Microscopy

Ping L. Zhang, Hassan D. Kanaan, Wei Li. *Corewell Health, Royal Oak, MI.*

Background: Etiologies of renal failure due to renal tubular injury may result from either ischemic/toxic injury of proximal tubules (ATN), variants of interstitial nephritis or obstructing tubulopathy by the luminal blocking of either monoclonal casts, uric acid or calcified deposits. We hypothesized that the serum creatinine (SCr) levels and the number of tubular obstructing deposits such as calcium oxalate deposits in proximal tubules, and uric acid or monoclonal cast depoists in distal tubules were correlated so that the pathologic identification of obstructing foci can be predictable for the extent of renal dysfunction.

Methods: Eight controls with mild to moderate acute tubular injury and 11 cases with calcium oxalate nephropathy (calcium group) were selected for the study. Other type of tubular obstructing diseases by uric acid and monoclonal casts were also evaluated. The patient's SCr values were obtained from electronic medical records and the number of polarizable calcium oxalate crystal deposits in the lumina of proximal tubules seen on Hematoxylin & Eosin stained slides at 400x high power field were recorded for each biopsy. Umpired student T-test was used to compare the two groups. Linear regression analysis was used to correlate SCr and the number of calcium oxalate deposits.

Results: Mean ages were not significantly different between two groups (49 ± 8 years in controls and 64 ± 6 years in calcium group). SCr was significantly higher in the calcium group (5.97 ± 0.68 mg/dl*) than in the control group (2.59 ± 0.37 mg/dl). No calcium oxalate deposits were seen in any of the controls, but the number of calcium oxalate deposits ranged from 3 to 7 in the calcium group. In our study, there was a significant linear correlation between SCr and the number of calcium oxalte deposits /high power field, when all cases were taken together (r value = 0.783, p value = 0.0002*). Additional pilot data also showed the similar correlation between the SCr levels and either uric acid deposits or monoclonal cast foci.

Conclusions: Our data indicate that the severity of renal dysfunction in obstructing tubulopathy, calcium oxalate variant, was significantly linked to deposit foci seen microscopically. Identifying the foci of obstructing tubulopathy may be a simple but reliable microscopic method to correlate with patients' SCr levels.

Funding: Clinical Revenue Support

FR-PO180

Evaluation of Urinary NKCC2 and NCC in Rats with AKI Induced by Candesartan Plus Low-Salt Diet in Rats

Anni Xie,[1,2] Leijuan Xiao,[1] Mingzhuo Zhang,[1,2] Haonan Duan,[1,2] Zhiyun Ren,[2] Ping Wang,[2] Yutao Jia,[1,2] Mingda Liu,[2] Jizhuang Lou,[1] Xiaoyan Wang.[1,2] *[1]The Department of Nephrology, The Affiliated BenQ Hospital of Nanjing Medical University, the Fourth Clinical Medical College, Nanjing, China; [2]The Core Laboratory for Clinical Research, The Affiliated BenQ Hospital of Nanjing Medical University, the Fourth Clinical Medical College, Nanjing, China.*

Background: Dietary-salt-restriction and angiotensin-II-receptor-1-blockade are often suggested to the patients with renal and cardiovascular diseases.

Methods: We studied the dietary effects of low-salt(LS, 0.01%NaCl), normal-salt(NS,0.8%NaCl) and high-salt(NS, 2%NaCl) on renal functions and urinary exosomal renal sodium-potassium-chloride-cotransporter-2(NKCC2) and sodium-chloride-cotransporter(NCC) in rats treated with candesartan(1mg/kg/day,IP), a common angiotensin-II-receptor-1-blocker, to determine if the combination of the two strategies were beneficial and how to detect renal dysfunction early. All rats were treated with candesartan. Model I: LS, NS and HS were fed rats respectively for 7 days. Model II: NS was pretreated for 4 days before switching to LS for 3 days in experimental group. Model III: similar as model II, but the diet was switched back to HS for extra 3 days.

Results: Serum creatinine (SCr) increased on day 7(55.83±6.46) of model I and on day 3 of model II(56.56±8.28). Urinary exosomal NKCC2(905.76±127.59, % of day0) and NCC(637.51±87.35) increased on day 7 in Model I. In model II, urinary exosomal NKCC2(908.12±227.46, % of day 0) started to increase on day 1, which was 2 days earlier than increased SCr, and kept high for 3 days. NCC(160.6±23.85) was increased only at day 1. In model III, switching diet back to HS reversed the increases of SCr(39.40±2.56 vs 34.80±1.28,umol/L, day3 vs day+3, p<0.05) and urinary exosomal NKCC2(43.54±17.75,% of day3) and NCC(3.60±0.87,% of day3). NKCC2 was located in the renal apical membranes of rat outer medullary tubules while NCC was in the apical side of certain cortical tubules next to glomeruli, in agreement with their respective distribution in kidney. Their protein expressions were not affected in whole kidney homogenates except an increase of NKCC2 in model I.

Conclusions: Thus, low salt diet induces acute kidney injury in candesartan-treated rats which can be reversed by a moderate salt load. Urinary exosomal NKCC2 and NCC may be considered as early biomarkers for detection of AKI accordingly.

Funding: Government Support - Non-U.S.

FR-PO181

Primary Cultures from Injured and Healthy Mouse Kidneys: A Comparative Transcriptomic Analysis

Karen I. López-Cayuqueo,[1] Arnold Tsamo Tetou,[1,2] Dorothee Günzel,[2] Kai M. Schmidt-Ott.[1] *[1]Medizinische Hochschule Hannover, Hannover, Germany; [2]Charite Universitatsmedizin Berlin, Berlin, Germany.*

Background: Primary cell cultures from mouse kidneys are widely used to investigate kidney physiology and pathophysiology. It is known culture systems are far from being an ideal model but there is still a need for *in vitro* systems to validate different hypotheses. Here, we prepared primary cell cultures of renal cortex from both healthy and injured kidneys, and we compare their transcriptomics landscape intending to determine whether cultured kidney cells from an injured kidney are representative of *in vivo* injury states.

Methods: Unilateral Ischemia-Reperfusion Injury was performed in C57BL/6N mice. After 21 days of reperfusion primary cell cultures were prepared from the renal cortex of both contralateral and injured kidneys. The cells were kept in culture for 6 days before being analyzed using bulk RNAseq and single-cell sequencing. Additionally, cell cultures were compared to uncultured kidney cells from contralateral and injured kidneys (from the same mouse).

Results: Cell cultures only partially resemble *in vivo* conditions. During culturing, the differences between cells from injured kidneys and those from healthy kidneys become less pronounced. Surprisingly, cultured renal cells from healthy kidneys adopt an injured kidney phenotype, detonated by the upregulation of kidney injury markers such as Havcr1 and Vcam1. Despite the similarities between healthy and injured cultured cells, it is possible to identify key differences at the single-cell level, such as the identification of additional clusters represented by monocyte and macrophage markers.

Conclusions: We demonstrated that primary cell cultures from healthy mouse renal cortex could be a suitable model to investigate injury-associated pathways since the culturing step induces in the cells a kidney injury-associated phenotype. However, culturing cells from an injured kidney potentially offers additional information, such as the presence of immune cells.

Funding: Government Support - Non-U.S.

FR-PO182

Proximal Tubule-Specific Knockout of G3bp1 Enhances Kidney Injury after Cisplatin Administration and Kidney Ischemia-Reperfusion

Shixuan Wang,[1] Zheng Dong.[1,2] *[1]Augusta University Medical College of Georgia, Augusta, GA; [2]Charlie Norwood Department of Veterans Affairs Medical Center, Augusta, GA.*

Background: Stress granule, mainly containing RNA-binding proteins (RBPs) and RNAs, is one type of cytoplasmic membraneless structure formed upon stress in eukaryotic cells. G3bp1 is a core protein in stress granule. The role of G3bp1 and associated stress granules in renal pathophysiology is largely unknown.

Methods: To study the function of stress granule and G3bp1 in the kidney, we established a kidney proximal tubule-specific G3bp1 knockout (PT-G3bp1-KO) mouse model by crossing G3bp1-floxed mice with PEPCK-Cre mice. PT-G3bp1-KO mice and their wild-type (WT) littermates were subjected to cisplatin nephrotoxicity or renal ischemia/reperfusion to induce acute kidney injury.

Results: Compared with WT mice, PT-G3bp1-KO mice had more severe kidney injury after cisplatin or ischemia/reperfusion treatment in histological analysis. Consistently, KO mice showed significantly higher levels of serum creatinine after AKI challenge. By TUNEL staining, more apoptotic cells were found in KO mice than in the wild-type. Immunoblotting also detected higher level of caspase-3 cleavage or activation in KO mice kidneys than in wild-type tissues. Additionally, more Ki-67-positive cells were found in KO mice kidney tissues than in the wild-type.

Conclusions: Our data indicate that G3bp1 and associated stress granules play a protective role in proximal tubule cells during acute kidney injury, suggesting a new strategy for the prevention and treatment of this devastating renal diseases.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO183

Trauma of Origin: The Impact of Maternal AKI on Progeny

Rose Odom,[1] Danielle E. Soranno,[1,2] Andrew L. Schwaderer,[1,2] Michelle C. Starr,[1,2] David P. Basile.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Riley Hospital for Children at Indiana University Health, Indianapolis, IN.*

Background: Acute Kidney Injury (AKI) results in both short- and long-term systemic sequelae. The impact of AKI on future generations, however, has not been studied. Here, we investigate the impact AKI has on female mice and their progeny.

Methods: Wild-type, C57 female mice underwent bilateral ischemia-reperfusion AKI. Control groups included sham operated mice (no pedicle clamping) and unmanipulated controls. To confirm AKI had been obtained, serum BUN values were measured 24hrs post procedure. Two weeks after recovery, all mice underwent testing via transcutaneous Glomerular Filtration Rate (tGFR) to assess kidney function. They were then bred and allowed to deliver naturally. Serial measurements of progeny weight and length occurred at birth and then weekly through 42 days of age.

Results: Litter Size: For dams with AKI, we found a correlation between higher 24hr BUN to subsequent litter size produced. Dams with BUN's of 90-115 produced 7 pups in a litter whereas dams with BUN's between 140-175 produced 6 or 3 pups respectively. [SAL1] Weight: At birth, male pups from AKI dams had lower weights than males born to control dams (p=0.02); whereas female pups had no significant changes across all groups. By day 7, all animals' weights had "caught up" to their counterparts in other groups. By day 35, males from AKI dams had weights that surpassed those in control and sham groups (p=0.04). Length: At birth, males from AKI dams were significantly shorter than males from control dams (p=0.005) while females from AKI-dams were significantly shorter than those from sham dams (p=0.01). Like the weight data, all animals "caught up" to their counterparts by day 7 of life, lasting through day 35. At day 42, however, both males and females born to AKI-dams surpassed animals in other groups in length (p=0.0002 in males and p=0.04 in females).

Conclusions: Litter size was significantly reduced post-AKI compared to sham and control animals, and the anthropometrics of the progeny were also significantly impacted at the time of birth. Growth was more impacted in males than females. Throughout the study, progeny from post-AKI dams did obtain "catch up" growth with sham and control progeny. Testing of neurocognitive status and nephron endowment is currently underway to elucidate any other sequelae in the progeny.

FR-PO184

Low Birthweight Impacts the Ability to Recover from Childhood AKI in Mice

Sage Timberline,[1] Kimberly Deronde,[1] Wyatt Johnson,[1] Kevin M. Bennett,[2] Jennifer R. Charlton.[1] *[1]University of Virginia, Charlottesville, VA; [2]Washington University in St Louis, St Louis, MO.*

Background: Low birthweight is a risk factor for the development of chronic kidney disease (CKD). Birth weight and nephron number are highly correlated. In rodents, maternal protein restriction during gestation results in low birthweight offspring with fewer nephrons. Acute kidney injury (AKI) independently increases the risk of CKD. However, the impact of low birthweight on the ability to recover from AKI is unknown.

Methods: Pregnant CD-1 dams were fed a normal protein (NP, 18%) or low protein (LP, 8%) diet from conception through weaning. NP and LP offspring were stratified to receive vancomycin (400 mg/kg intraperitoneal on days 7 and 8, n=6-12/group) or no injection, creating four groups – NP^{V}, LP^{V}, NP^{0}, LP^{0}. At 6 weeks, glomerular filtration rate (GFR) was measured transcutaneously. Kidneys were prepared for histologic evaluation of atubular glomeruli percentage (ATG) using Amira (Thermo Fisher Scientific software). Data were analyzed using Prism 9 (GraphPad software) with significance set at $p<0.05$. Groups were stratified by sex *a priori*.

Results: LP^{0} males had lower GFRs and more ATG compared to NP^{0} males (Table). After AKI, all LP^{V} animals had lower GFRs and more ATG compared to same-sex NP^{V} animals. When compared to LP^{0}, LP^{V} animals had more ATG. LP^{V} animals had lower GFRs than NP^{V} animals. LP^{V} males had lower GFRs compared to LP^{0} males, while LP^{V} and LP^{0} females were similar.

Conclusions: Changes in kidney structure and function after AKI were more severe in LP animals. LP animals exposed to vancomycin AKI had more ATGs, suggesting that AKI is an additional risk factor for development of non-functional glomeruli in low birthweight animals. LP animals exposed to vancomycin AKI also had lower GFRs compared to NP^{V} animals, but only LP^{V} males had lower GFRs than LP^{0} counterparts. This suggests that the degree of impact on kidney function from AKI on low birthweight animals may be sex-specific.

Funding: NIDDK Support

Outcomes for Diet/AKI/Sex Groups

Diet/Sex/AKI groups	NP-V		LP-0		LP-V		NP-V vs. LP-V		LP-0 vs LP-V	
Sex	M	F	M	F	M	F	M	F	M	F
Outcomes	Median (IQR)						P value			
Body weight (grams)	35 (29-37)	28 (27-31)	29 (28-31)	23 (21-24)	24 (22-30)	21 (20-24)	***	***	**	--
Kidney weight/body weight (%)	1.3 (1.2-1.4)	0.9 (0.8-1.0)	1.7 (1.6-1.9)	1.4 (1.3-1.5)	1.1 (1.0-1.4)	0.9 (0.8-1.1)	--	--	**	***
GFR (uL/min)	311 (221-351)	297 (202-394)	201 (195-254)	198 (188-271)	154 (32-171)	170 (77-243)	***	**	*	--
Atubular glomeruli (%)	54 (37-65)	55 (49-63)	32 (31-36)	54 (49-59)	76 (69-79)	82 (74-85)	**	***	***	***

NP: normal protein. LP: low protein. V: vancomycin. 0: no injection. M: male. F: female. ***: $p<0.001$. **: $p<0.01$. *: $p<0.05$. --: $p>0.05$.

FR-PO185

Functional Role of a Novel Renal Protective Protein TMEM52B in Kidney Fibrosis

Rui Xue, Qijun Wan. *Shenzhen Second People's Hospital, Shenzhen, China.*

Background: Renal fibrosis, especially tubulointerstitial fibrosis, is the primary pathological hallmark of renal injury and signifies the progression of end-stage renal disease. Through exome sequencing of various human organs and tissues, our study has identified significant enrichment of transmembrane protein 52B (TMEM52B) expression in the kidney, highlighting its close correlation with renal function. Consequently, our upcoming studies aim to elucidate more deeply the exact role and underlying mechanisms of TMEM52B in renal tubular injury, specifically in tubulointerstitial fibrosis.

Methods: We employed *CRISPR-Cas9* technology to construct TMEM52B gene system knockout C57BL/6 mice. Subsequently, we performed unilateral ureteral obstruction (UUO) surgery to induce renal injury and tubulointerstitial fibrosis. Following the surgery, we then conducted a series of analyses and proteomics testing to investigate the changes after TMEM52B knockout. Finally, we conducted additional *in vitro* experiments to further validate the molecular mechanism of TMEM52B in renal fibrosis.

Results: TMEM52B expression was decreased significantly in UUO mice and nearly absent in the kidneys of TMEM52B knockout mice. Tubular injury and fibrosis markers in UUO mice were aggravated by TMEM52B knockout which was preserved with more tubular injury and fibrosis compared to control mice. Proteomic analysis showed Myeloid-Derived Growth Factor (MYDGF) expression was significantly decreased in the kidney tissue of UUO model mice, and further markedly decreased in TMEM52B system knockout UUO model mice. *In vitro*, TMEM52B expression significantly decreased under TGF-β1 stimulation, and altering TMEM52B levels correspondingly changed MYDGF expression.

Conclusions: Knock-out of TMEM52B could exacerbate tubular injury and alleviate tubulointerstitial fibrosis in UUO mouse model. This process is a cascade coordinated by the regulation of MYDGF. Our findings suggest a critical role of TMEM52B in the pathogenesis of tubular injury and further provide a potential novel therapeutic target for renal fibrosis.

FR-PO186

Induction of Podocyte-Specific SMPDL3b Mitigates Radiation-Induced Kidney Damage

Anis Ahmad,[1] Shamroop Kumar Mallela,[2] Saba Ansari,[1] Mohammed Alnukhali,[1] Sandra M. Merscher,[2] Youssef Zeidan,[3] Alessia Fornoni,[2] Brian Marples.[4]
[1]Department of Radiation Oncology, University of Miami, Miller School of Medicine, Miami, FL; [2]Peggy and Harold Katz Family Drug Discovery Center and Division of Nephrology, Department of Medicine, University of Miami, Miami, FL; [3]Dept of Radiation Oncology, Lynn Cancer Institute, Baptist Health South Florida, Boca Raton, FL; [4]Department of Radiation Oncology, University of Rochester, Rochester, NY.

Background: The kidneys' high sensitivity to radiation limits the dose used in radiotherapy (RT) for abdominal and paraspinal tumors, leading to radiation nephropathy (RN). This study investigates the role of the lipid-modifying enzyme sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b) in renal podocyte response to radiation or cisplatin-induced injury.

Methods: 10-14-week-old WT received 4 Gy bilateral kidney irradiation with or without cisplatin (3 mg/kg). 20 weeks post-RT, urine, and serum samples were analyzed for ACR, BUN, and creatinine levels, and glomerular basement membrane (GBM) ultrastructure was assessed via TEM. Another group of mice with podocyte-specific doxycycline-inducible SMPDL3b expression (SMPDL3b transgenic mice (SMP Tg)) kidney received 14 Gy. 20 weeks post-RT, kidney sections were stained with H&E, Periodic Acid-Schiff, and Picro Sirius Red. Kidney cortex samples were analyzed for ceramide-1-phosphate (C1P) levels using mass spectrometry.

Results: 20 weeks post-4Gy or cisplatin treatment: i) RT or cisplatin significantly reduced podocyte number and SMPDL3b expression ($p < 0.001$), with no further change observed with combined treatment; ii) RT or cisplatin significantly increased GBM thickness and foot process width ($p < 0.05$), which further increased with combined treatment ($p = 0.0005$ and 0.002); iii) RT or cisplatin significantly increased serum BUN levels ($p < 0.05$), with no further increase observed with combined treatment; iv) RT or cisplatin significantly increased serum creatinine levels ($p < 0.05$), which further increased with combined treatment ($p < 0.002$); v) RT did not significantly increase urine ACR, while cisplatin did ($p = 0.03$), but there was no significant difference with combined treatment; vi) RT did not increase C1P levels, but combined treatment did. 20 weeks post-14 Gy irradiation: i) RT significantly decreased podocyte number in WT mice ($p = 0.006$), but not in SMP Tg mice; ii) RT significantly increased the mesangial expansion score in WT mice, but not in SMP Tg mice; iii) RT did not significantly affect serum BUN, creatinine, urine ACR, and C1P levels in SMP Tg mice.

Conclusions: Induction of SMPDL3b reduces radiation-induced podocyte injury and restores C1P levels, suggesting that SMPDL3b is a potential therapeutic target for mitigating RN.

Funding: Other NIH Support - NIH/NCI PQ12 1R01CA227493, Live Like Bella # 23L12, DOD # KC210133, UM SJG 2023-01, TB-INTRA-2024-03, SSC, Other U.S. Government Support

FR-PO187

Adenosine Triphosphate Coincubation with Alkaline Phosphatase Reduces H2O2-Induced Endothelial Barrier Disruption

Thei S. Steenvoorden,[1] Fabienne Podieh,[2] Juan Miguel Tellez Garcia,[1] Frederike J. Bemelman,[1] Peter Hordijk,[2] Liffert Vogt.[1] *[1]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [2]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands.*

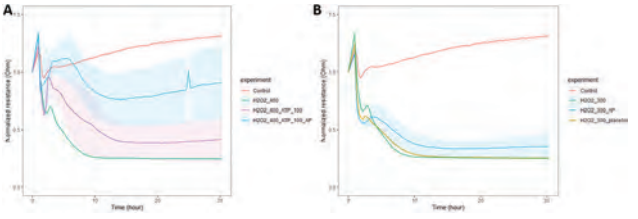
Background: Endothelial damage mediated by oxygen radicals is a key part of ischemia-reperfusion-induced acute kidney injury (IRI-AKI). Nucleotides e.g., adenosine triphosphate (ATP), are released from cells in response to IRI and can cause endothelial barrier disruption. ATP's base, adenosine (ADO), however, might improve barrier function. Alkaline phosphatase (ALP) can dephosphorylate ATP to form ADO. ALP treatment has been shown to protect mice against IRI-AKI. It is unknow if ALP can protect endothelium against IRI.

Methods: We exposed quiescent monolayers of human umbilical vein endothelial cells (HUVECs) to H_2O_2 (300μM and 400μM) and measured the trans-endothelial electrical resistance with Electric Cell-Substrate Impedance Sensing (ECIS). Confocal imaging was used to assess VE-cadherin. HUVECs were co-incubated with either ALP (10IU/ml bovine intestinal ALP), placebo, 100μM ATP, or 100μM ATP with ALP.

Results: Exposure of HUVECs to H_2O_2 led to strong reduction of elctrical resistance, indicating loss of barrier function. Co-treatment with 100 μM of ATP alleviated some of the induced damage. This effect was enhanced by the addition of ALP (Figure A). In the low H_2O_2 concentration, ALP addition resulted in partial rescue of endothelial barrier function (Figure B), however, there were large inter-experimental differences. Partial recovery of endothelial barrier function could be confirmed by immunofluorescent staining of VE-cadherin.

Conclusions: Co-incubation of ATP with ALP reduces H_2O_2 -induced barrier disruption. ALP may protect HUVECs against high levels of oxygen radicals, however, it is unlikely that HUVECs release enough substrate to guarantee stable protection during reperfusion. To determine if ADO generated from ATP dephosphorylation is responsible for the observed barrier protection, endothelial barrier function measurements will be repeated with ADO receptor inhibition.

Funding: Commercial Support - Health Holland B.V. and Alloksys Life Sciences B.V.



Normalized resistance over endothelial monolayer. Red: untreated. Green: H2O2 only. Blue: AP treated with H2O2 with (A) or without (B) ATP. Gold: placebo and H2O2.

FR-PO188

Long Noncoding RNA GSTM3P1/gstm2-ps1 Mediates Sepsis-Associated AKI

Jing Huang,[1,2] Zheng Dong,[1,3] Qingqing Wei.[1] *[1]Augusta University Department of Cellular Biology and Anatomy, Augusta, GA; [2]Department of nephrology, Renmin Hospital of Wuhan University, Wuhan, China; [3]Charlie Norwood Department of Veterans Affairs Medical Center, Augusta, GA.*

Background: Long non-coding RNAs (lncRNAs) are important regulators in various kidney injuries. Our previous study has identified a pro-injurious lncRNA, GSTM3P1 (human orthologue)/gstm2-ps1 (mouse orthologue) in ischemic acute kidney injury (AKI). However, its role in other AKI conditions is unclear.

Methods: More recently, we examined the role of GSTM3P1/gstm2-ps1 in cultured renal proximal tubular cells and in mice with/without proximal tubular specific gstm2-ps1 knockout.

Results: We found that this lncRNA exacerbated sepsis-induced AKI. Overexpression of GSTM3P1 significantly increased the renal proximal tubular cell death induced by LPS treatment, evidenced by the lower cell viability by MTT assay. GSTM3P1 is a lncRNA derived from pseudogene of glutathione S-transferase Mu 3 (GSTM3), which is a protein belonging to GST family and responsible for oxidative stress detoxification by GSH conjugation. We found that GSTM3P1 regulated its parent gene GSTM3 expression, by reducing GSTM3 protein and mRNA level. A lower GSH:GSSG ratio was detected in GSTM3P1 overexpressed cells. Furthermore, the proximal tubular specific gstm2-ps1 knockout mice were protected from LPS induced AKI, showing better renal function and less tubular apoptosis in kidney.

Conclusions: In conclusion, lncRNA GSTM3P1/gstm2-ps1 contributes to renal proximal tubular cell death in sepsis AKI, potentially through the regulation of GSTM3 and enhancement of oxidative stress relief and detoxification.

Funding: NIDDK Support

FR-PO189

Nano-carrier Based Approach to Target the Inflamed Kidney Endothelium

Boaz Y. Bishop,[1,2] Swagat H. Sharma,[1] Simseok A. Yuk,[1] Sultan Almunif,[1] Susan E. Quaggin,[1] Ratnakar Tiwari,[1] Evan Scott,[1] Pinelopi P. Kapitsinou.[1]
[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Rambam Health Care Campus, Haifa, Israel.

Background: Previous studies have demonstrated that endothelial cell (EC) derived mechanisms are sufficient to suppress EC activation of leukocyte adhesion molecules and subsequent inflammation promoting repair from acute kidney injury (AKI). Nevertheless, there are significant challenges for the translation of these findings into the clinical domain, in part because drugs and drug carriers have no natural endothelial affinity. Therefore, precise EC drug delivery is a potential strategy to advance the development of novel therapeutics in AKI. Here, we developed nanocarriers for enhanced drug delivery to inflamed kidney endothelium.

Methods: PEG-b-PPS micelles (MC) were decorated with two different high affinity peptides selected for targeting of inflamed kidney endothelium. The first peptide (CYNTTTHRC) was reported to bind specifically to inflamed endothelial cells (IEC) and is homologue to Scube 1 & 2, previously associated with ischemia reperfusion injury (IRI). The second peptide, (CLPVASC), was reported to bind specifically to kidneys. Average MC diameter (25nm) with PDI<0.1 were assessed by DLS. MC morphology, characterized by MALDI-TOF MS, cryoTEM and by SAX, remained consistent when dual peptides were added. For in vivo studies, we used a unilateral IRI rodent model induced by 30 minutes clamping of renal pedicle.

Results: Using imaging with In vivo imaging system (IVIS) analysis showed a significantly increased uptake of the targeted MC to the ischemic kidney compared to contralateral (non-inflamed) kidney (by 3.4-fold, $p<0.0001$). The uptake was also significantly increased compared to non-targeted MC while at the same time, there was significantly reduced off-target uptake by other major organs such as liver, heart and lungs ($n=8$, $p<0.0001$).

Conclusions: Our work has shown that peptide-based targeting can enhance the delivery of MCs to the post-ischemic kidney. This represents a significant technological advance enabling improved targeted delivery of novel kidney therapeutics.

Funding: NIDDK Support

FR-PO190

Characterization of a Novel Macrocyclic Molecular Glue That Selectively Inhibits the Nucleoside Transporter ENT1 and Demonstrates Tissue Protection in Ischemic-Reperfusion AKI In Vivo

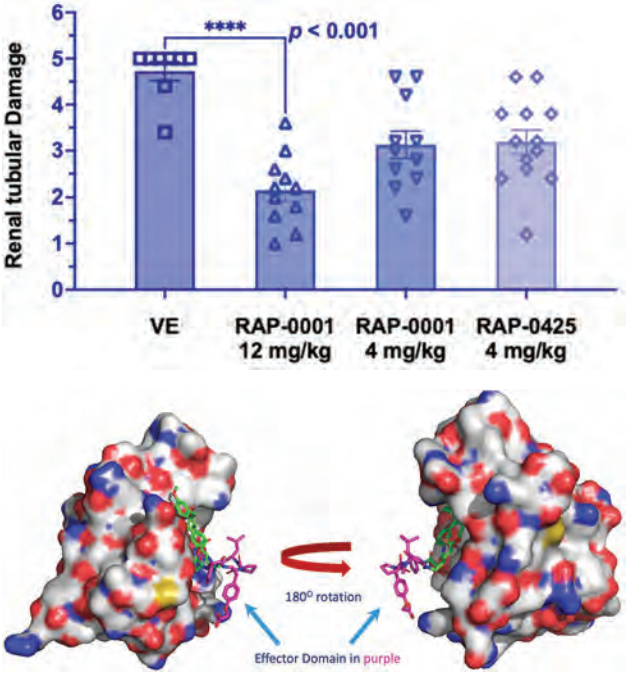
Matthew W. Olson. *Rapafusyn Pharmaceuticals, Baltimore, MD.*

Background: Acute kidney injury (AKI) from renal ischemia and reperfusion (IR) is a major clinical issue, particularly during the perioperative period, and lacks effective therapy. AKI is characterized by a sudden decline in renal function over hours to days from injuries within renal tissue architecture. We report the in-vitro and in-vivo profile of a novel macrocyclic molecular glue (RAP-0001) that exhibits potent and selective inhibition of equilibrative nucleoside transporter 1 (ENT1). These results and our mechanism of action provide a novel therapeutic strategy to mitigate renal damage following ischemic-reperfusion events that occur in cardiovasclar surgeries (CABG and TAVR). Preclinical molecular genetics (1-4), preclinical and human pharmacological evidence via a novel mechanism of action (5-12), and human clinical genetics (13-14) suggest that inhibition of ENT1 would be an effective approach.

Methods: Functional cell-based assays, Biophysical binding assays, X-ray crystallography, In vivo PK and efficacy studies.

Results: RAP-001 forms a ternary complex with FKPB12::RAP-0001::ENT1 on the intracellular side of the cell membrane. RAP-0001 is a potent and selective inhibitor of ENT1 forming molecular glue via the formation of a FKPB12::RAP-0001::ENT1 complex. Our X-ray structure of RAP-0001 bound to FKBP-12 shows the contacts RAP-0001 with FKBP12 where the solvent exposed region can contact ENT1. The efficacy of RAP-0001 was demonstrated in a rat ischemic-reperfusion acute kidney injury model where the compound conferred tissue protection as measured by biomarkers and histological data.

Conclusions: The data presented support the pusuit of IND enabling studies.



FR-PO191

Antifibrotic Effects of Caffeic Acid in a Kidney Ischemia-Reperfusion Injured Mouse Model

Giovambattista Capasso,[1,2] Anna Iervolino,[2,1] Mario Zevola,[2,1] Antonio Miele,[2,1] Antonella Iannaccone,[2,1] Benedetta Sasso,[3,1] Francesco Trepiccione,[2,1] Alessandra Perna.[2] *[1]Biogem, Biology and Molecular Genetics Institute, Ariano Irpino, Italy; [2]University of Campania "L. Vanvitelli", Naples, Italy; [3]University of Naples Federico II, Naples, Italy.*

Background: Acute kidney disease due to renal ischemia/reperfusion (I/R) is a major clinical problem without effective therapies. The injured tubular epithelial cells may undergo epithelial–mesenchymal transition (EMT). The formation of scar tissue in the interstitial space during renal remodeling is caused by the excessive accumulation of extracellular matrix components and induced fibrosis. One of the primary causes of end-stage renal illness is renal tubulointerstitial fibrosis. In this work, we examined the effects of a natural phenolic antifibrotic drug, caffeic acid, on a mouse model of renal fibrosis.

Methods: I/R was induced by clamping bilaterally the renal artery and vein for 30 minutes. A single daily oral gavage of caffeic acid (40 mg/kg) was administered following the procedure. Renal fibrosis and kidney function were assessed 14 days later.

Results: The I/R treated with caffeic acid showed a recovery of renal function as compared to the other I/R groups analyzed. This was proven by a significant rise in urinary creatinine and urea excretion, along with a significant decrease in urine volume, serum creatinine, and proteinuria. Histological analysis, using Masson's trichrome and Picrosirius red staining, revealed that renal interstitial fibrosis and collagen deposition were elevated in I/R and significantly decreased in response to caffeic acid treatment, indicating the inhibitory role of caffeic acid on EMT. Then we investigated the effect of caffeic acid on myofibroblast activation markers, such a-SMA. After I/R, immunofluorescence showed a significant increase in a-SMA expression, which drastically decreased with the administration of caffeic acid. Moreover, using DHE, a fluorescent probe for the detection of Ros, specific for superoxide and hydrogen peroxide, we observed a reduction in Ros generation due to the caffeic acid treatment in the I/R group.

Conclusions: In conclusion, our study demonstrates that caffeic acid attenuates renal injury in an I/R animal model, preventing myofibroblast activation, ECM deposition, Ros generation, and renal interstitial fibrosis deposition.

FR-PO192

Evaluating Proteomics in a Rat Model of AKI

Denise L. Schwabauer,[1] Jeannie M. Camarillo,[2] Toni L. Richards,[1] Daniel C. Liebler,[2] Kenneth H. Minor.[1] *[1]Inotiv, Inc., Westminster, CO; [2]Inotiv, Inc., Nashville, TN.*

Background: Acute kidney injury (AKI) secondary to acute renal ischemia is associated with high mortality and morbidity, few effective treatments, and risk of chronic kidney disease. AKI therapeutics can be advanced with well characterized disease models, which inform early therapeutic development. Here we describe the proteomic landscape of a rat model of AKI and describe characteristic injury pathways and potential therapeutic targets.

Methods: Rats were subjected to sham or warm, bilateral renal ischemia (40′) using proprietary vascular clamps. Rats were housed in metabolic cages for 24 or 48 hours post-reperfusion. In 24 hour intervals, blood and urine samples were collected and evaluated for progression of kidney injury biomarkers. At each endpoint, renal tissue was harvested and subjected to global proteomic analysis using tandem mass tags (TMT) and high resolution mass spectrometry (MS) to define quantitative changes in the kidney proteome following renal ischemia/reperfusion (I/R). Gene set enrichment analysis (GSEA) was utilized to identify cellular pathways significantly altered between sham and I/R timepoints.

Results: Proteomic analysis identified 3,084 proteins that were altered across the I/R time course. GSEA identified several protein networks and pathways that displayed time-dependent alteration with development of AKI. Pathways significantly upregulated with injury include complement and coagulation cascades, cell adhesion and metabolic pathways, and kidney inflammation/injury-associated pathways. Proteomic alterations were correlated with data from orthogonal approaches including gene expression profiling and immunohistochemistry.

Conclusions: Proteomic profiling captures both well-characterized and novel molecular alterations underlying renal injury. Global proteomics enables quantitative assessment of changes in the kidney proteome in the progression of AKI. GSEA with rich proteome data enables rapid identification of cellular pathways significantly altered following renal I/R and represents all the features of the injury phenotype. Variations of the protocol may enable nuanced dissection of injury. Moreover, targeted MS provides robust biomarker assays for any protein, without antibodies. Distinct biomarker expression profiles of varying durations of renal I/R can identify potential therapeutic targets and possible new AKI diagnostic markers.

Funding: Commercial Support - Inotiv

FR-PO193

Role of HTRA1 in an Ischemia-Reperfusion (I/R)-Induced AKI-Mice Model

Naruemon Wikan,[1] Laurence H. Beck,[3] Laith Al-Rabadi,[1] Chio Oka.[2]
[1]The University of Utah School of Medicine, Salt Lake City, UT; [2]Nara Sentan Kagaku Gijutsu Daigakuin Daigaku Sentan Kagaku Gijutsu Kenkyuka Bioscience Ryoiki, Ikoma, Japan; [3]Boston University, Boston, MA.

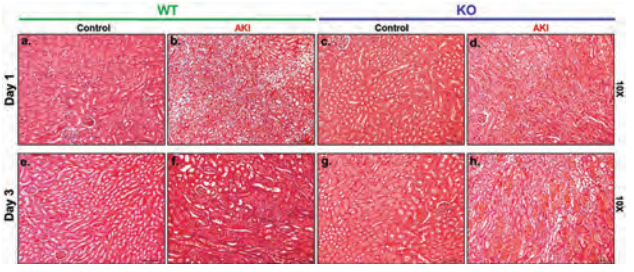
Background: Ischemia-Reperfusion (I/R), commonly observed in surgical settings, heightens risks of acute kidney injury (AKI), mainly attributed to sudden decreases in blood flow, which cause deoxygenation and increases in reactive oxygen radicals. An important member of the heat-shock-induced serine protease group, HTRA1 plays a role in extracellular matrix's homeostasis, by cleaving numerous substrates.

Methods: As HTRA1's role in kidney functions has yet to be elucidated, the research group opted to investigate its function in the AKI I/R setting. HTRA1-knockout (KO) and wild type (WT) mice (C57BL/6) underwent unilateral renal pedicle clamping, thereby replicating AKI I/R injury with a flank incision with 30 m occlusion time until nephrectomy and after 24 h and 72 h reperfusion.

Results: Renal tubular injury was observed in WT and KO mice, after 24 hours. However, it was prolonged and persistent in the HTRA1 KO mice, and still evident after 72 hours. This was supported by the presence of the kidney injury molecule-1 (KIM-1), an AKI marker. Regarding AKI I/R-KO there were significantly increased inflammatory cascade and oxidative stress, along with decreased levels of anti-oxidant and autophagy activation.

Conclusions: HTRA1 could play an efficacious role in kidney recovery, given the impact of AKI I/R's role in causing renal tubular injury.

Funding: NIDDK Support



Kidney histopathological assessments (H&E stainig)

FR-PO194

Angiotensin-Converting Enzyme 2 in AKI Was Attenuated by Uremia Toxin Indoxyl Sulfate and Restored by Renin-Angiotensin-Aldosterone System Inhibitors

Guang-huar Young,[1,3] Vincent Wu.[2] The Consortium for Acute Kidney Injury and Renal Diseases (CAKs). *[1]Department of Biomedical Sciences, Chang Gung University, Taoyuan, Taiwan; [2]National Taiwan University Hospital, Taipei, Taiwan; [3]Kidney Research Center and Department of Nephrology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.*

Background: The accumulation of uremic toxins in patients after acute kidney injury (AKI) is harmful to long-term adverse outcome, but their effects on the severity of AKI by affecting intra-renal renin-angiotensin-aldosterone-system (RAAS) remain uncertain. Indoxyl sulfate (IS) as a representative uremic toxin, causes well-known detrimental effects during kidney injury.

Methods: Human renal proximal renal cells (HK2) were provoked with cobalt chloride to induce hypoxia injury and then supplied with indoxyl sulfate (IS) for the designated time peroids. Cell proliferation was mwasured by MTT assay and cellular ROS was evakuated by DCFDA methods. Male w/t (C57BL6) and homozygous angiotensin-converting enzyme 2 (ACE2)-knockout mice were used for animal model of AKI with uremia. Mice were randomly assigned to six groups: (1) Negative control group; (2) AKI group, unilaterial renal ischemia/reperfusion (I/R) injury to induce AKI; (3) AKI/IS group, AKI mice received IS injection; AKI/IS mice administrated with (4) direct renin inhibitor (DRI), (5) angiotensin II receptor blocker (ARB), and (6) alpha-1-adrenergic blocker, respectively.

Results: Cell study examined the expressions of ACE2 and related downstream metabolites under hypoxia/IS-induced injury. HK2 exposed to cobalt chloride/IS raised cellular oxidative stress and reduced ACE2 levels. These effects were mitigated by DRI or ARB treatment. Similarly, IS activated the ACE/angiotensin II axis of RAAS in mice after renal I/R injury and caused the reduction of ACE2 in mice kidneys. RAASi administration restored the renal ACE2 expression and Angiotensin1–7 (Ang1-7) levels and reduced neutrophil gelatinase-associated lipocalin expression and reactive oxygen species production in IS-enhanced AKI mice. Yet, these effects were absent in ACE2-knockout mice, even after RAASi therapy. Renal microcirculation analysis also showed that RAASi therapy improved the renal hypoperfusion, especially in AKI/IS mice. In hypertensive CKD patients, both DRI and ARB attenuated oxidative stress and increased serum Ang1-7 levels. ARBs, but not DRI, further restored patients' serum ACE2 levels.

Conclusions: Our study revealed that IS enhanced the suppression of the ACE2/Ang1-7 axis in intrarenal RAAS after I/R injury, whereas RAASi restored ACE2 expression and decreased oxidative stress.

Funding: Government Support - Non-U.S.

FR-PO195

Expression and Functional Effect of ACE2 in Heme Protein-Mediated AKI (HP-AKI) in Rodents

Anthony J. Croatt, Raman D. Singh, Allan W. Ackerman, Karl A. Nath.
Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN.

Background: Our prior study demonstrated that ACE2 expression is markedly reduced following acute renal ischemia (IRI-AKI) [Kidney360 2(7):p 1095-1106, 2021]. As ACE2 has previously been shown to be protective in IRI, we now investigate whether a similar expression profile exists in HP-AKI, and the functional significance of ACE2 in this model.

Methods: The glycerol model of HP-AKI was induced in Sprague Dawley rats and C57BL/6J mice by intramuscular injection (6 and 5 mL/kg, respectively). $ACE2^{+/+}$ and $ACE2^{-/-}$ mice were also subjected to HP-AKI (6 mL/kg). Assessments of ACE2 mRNA and protein expression were performed, as well as measurements of renal ACE2 activity. Assessments of renal functional markers (serum creatinine and BUN) were also undertaken.

Results: In the rat, ACE2 mRNA and protein were both reduced significantly at 1 day after induction of HP-AKI. At 2 days after HP-AKI, ACE2 protein expression and activity were both markedly reduced (by approximately 50% and 36%, respectively). In the mouse, ACE2 mRNA expression was reduced at 1 day post HP-AKI induction (8.4±1.0 vs 4.2±0.4, P=0.0013), but was not significantly altered at 8 hours after HP-AKI induction. Serum creatinine following HP-AKI was significantly lower in $ACE2^{-/-}$ mice, compared with $ACE2^{+/+}$ mice (2.2±0.1 vs 2.7±0.1 mg/dL, P=0.0096). BUN levels, however, were not significantly different between $ACE2^{+/+}$ and $ACE2^{-/-}$ mice subjected to HP-AKI at this time point.

Conclusions: As in our previous IRI-AKI studies, the present rat and mouse studies show that ACE2 mRNA, protein, and activity levels are all significantly reduced after HP-AKI induction (as early as 1 day and through at least 2 days). In contrast to prior studies showing that ACE2 deficiency exacerbates the IRI-AKI model, our studies failed to show a similar exacerbation in $ACE2^{-/-}$ mice subjected to HP-AKI. Indeed, as assessed by 1 of 2 functional markers (serum creatinine), we observe a mild protective effect of ACE2 deficiency. These findings point to significant differences between IRI-AKI and HP-AKI as regards the functional roles of ACE2. Further study is required to delineate the basis for the reduced expression of ACE2 in HP-AKI and the functional significance of ACE2 in this model.

Funding: NIDDK Support

FR-PO196

Deficiency of Leucine-Rich α2-Glycoprotein 1 Suppresses Kidney Fibrosis Caused by Ischemia-Reperfusion Injury

Naohito Okami, Hiromichi Wakui, Kengo Azushima, Shinya Taguchi, Tomohiko Kanaoka, Kouichi Tamura. *Yokohama Shiritsu Daigaku, Yokohama, Japan.*

Background: Acute kidney injury (AKI) is recognized for its potential to progress into chronic kidney disease (CKD), a transition known as AKI to CKD. Developing strategies to manage this progression is crucial. Ischemia-reperfusion injury (IRI) serves as a model for AKI and is known to lead to renal fibrosis over time, primarily through the TGF-β pathway. Leucine-rich alpha-2-glycoprotein 1 (LRG1) is endogenously expressed in renal tubular epithelial cells and regulates renal fibrosis by modulating the TGF-β/Smad3 signaling pathway (Kidney Int, 2022). Additionally, LRG1 silencing attenuates AKI following IRI by regulating autophagy and apoptosis via the TGFβ1-Smad1/5 signaling pathway (Arch Biochem Biophys, 2024). However, the role of LRG1 during the remodeling phase of IRI remains unclear. This study investigates the functional role of LRG1 in the AKI to CKD transition using the IRI model in systemic LRG1 knockout (KO) mice.

Methods: *Experiment 1*: Unilateral IRI was performed on wild-type (WT) 6- to 8-week-old male C57BL/6 mice. Ischemia was induced by a retroperitoneal approach to the left kidney using an atraumatic vascular clip for 30 minutes. Mice were sacrificed at 2, 7, 14, and 28 days after surgery to evaluate renal histological findings and LRG1 expression. *Experiment 2*: Male LRG1 KO mice and their littermate control (LC) mice, aged 6-8 weeks, underwent unilateral IRI. They were sacrificed on days 2, 7, and 28 post-surgery for renal histological comparison.

Results: *Experiment 1*:LRG1 mRNA expression in the kidney was significantly higher on the operated side than on the sham side throughout the period, peaking on day 7 and then gradually decreasing. *Experiment 2*: LRG1 KO mice exhibited significantly

reduced renal fibrosis area compared to LC mice on day 28. Furthermore, renal mRNA expression levels of collagen type 1 and type 3, as well as TGFβ, were lower in LRG1 KO mice than in LC mice on day 28 postoperatively, concomitant with the suppression of TGF-β signaling pathway.

Conclusions: Renal LRG1 expression was persistently upregulated until the remodeling phase after IRI. LRG1 knockout mice showed suppression of chronic fibrosis post-IRI and a reduction in TGF-β signaling. Therefore, LRG1 is implicated in the pathogenesis of the AKI to CKD transition and represents a potential therapeutic target.

Funding: Government Support - Non-U.S.

FR-PO197

Histologic and Immunologic Phenotypes of Immune Checkpoint Inhibitor-Mediated Nephrotoxicity in a Novel Humanized Immune System Mouse Model

Sarah C. Asby,[1] Lauren E. Thompson,[1] Michael J. Goedken,[2] Jordi Lanis,[1] Zander C. Kostka-Newman,[1] Roberta Pelanda,[1] Julie Lang,[1] Lauren Aleksunes,[2] Melanie S. Joy.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Rutgers The State University of New Jersey, Piscataway, NJ.*

Background: Kidney immune-related adverse events (irAEs) following cancer treatment with immune checkpoint inhibitors (ICIs) have been observed in 5-25% of patients, with approximately 20% developing new onset chronic kidney disease within 5 years. Humanized immune systems (HIS) mouse models, as opposed to conventional syngeneic pre-clinical mouse models, represent a promising avenue for detecting and evaluating irAEs. The purpose of this study was to characterize the histologic and immunologic phenotypes of ICI-mediated kidney toxicity in humanized immune system (HIS) mice.

Methods: At 17-21 weeks of age, non-humanized (BRGS) and humanized (HIS-BRGS) mice were implanted s.c. with MDA-MB-231 cancer cells and treated with vehicle (PBS) or a combination of ipilimumab and nivolumab (ipi/nivo 10 mg/kg each 1x/wk) i.p. for 4 weeks. H&E-stained sections of kidneys were analyzed for histomorphological evidence of injury with incidence and severity scores (0=none, 1=mild, 2=moderate, and 3=severe), rank ordered and assessed by two-way ANOVA. Tissue sections from formalin-fixed kidneys were co-stained for molecular markers of human immune cell populations and single cell spatial proteomics performed using ChipCytometry (Canopy Biosciences). Flow cytometry was performed on collected tissues and assessed using Welch and Brown-Forsythe ANOVA. $P<0.05$ was considered statistically significant.

Results: Ipi/nivo treatment significantly reduced tumor weight compared to vehicle in HIS-BRGS mice ($p<0.01$). Histological evaluation from ipi/nivo treated HIS-BRGS mice showed increased incidence and severity of renal pathologies including vasculitis/periarteritis ($p<0.001$) and interstitial nephritis ($p<0.05$) compared to vehicle-treated HIS-BRGS mice and non-humanized BRGS mice ($p<0.001$). Ipi/nivo-treated HIS-BRGS mice showed reductions in the % CD8+ T cells and CD4+ T reg cells ($p<0.05$, $p<0.06$) and increase in % TNFα+ CD4+ T cells in the kidneys ($p<0.05$). Single cell proteomics showed a majority of CD4+ T helper vs. CD8+ cytotoxic T cells of total CD45+ cells in the region of kidney injury.

Conclusions: This study demonstrated the utility of a novel HIS mouse model as a translational tool to study the histological and immunological phenotype of ICI-mediated kidney injury.

Funding: Other NIH Support - R01CA277313, P30CA046934, P30CA072720, Other U.S. Government Support, Private Foundation Support

FR-PO198

Impact of Immune Checkpoint Inhibitors on AKI Incidence and Mortality in Patients with Bladder Cancer: A Single-Center Experience

Shina Lee, Seung-Jung Kim. *Ewha Womens University Mokdong Hospital, Seoul, Republic of Korea.*

Background: Immune checkpoint inhibitors (ICPi) have increasingly become a therapeutic option for bladder cancer. Among bladder cancer patients, ICPi-associated acute kidney injury (AKI) has emerged as a significant toxicity. This study aims to describe the incidence, risk factors, renal outcomes, and mortality of AKI in patients receiving ICPi.

Methods: Patients who received ICPi between January 2021 and December 2021 at a single institution were retrospectively identified using the electronic medical database. AKI was defined as an increase in serum creatinine of ≥1.5 times the baseline value, based on the Kidney Disease: Improving Global Outcomes criteria. Cox proportional hazard regression analysis was used to assess risk factors for AKI and to evaluate the relationship between AKI and mortality.

Results: Among 108 patients with bladder cancer receiving checkpoint inhibitors, the overall incidence of AKI was 55.6%. Half of all AKI cases were associated with checkpoint inhibitors. Checkpoint inhibitor-associated AKI was mostly low-grade and occurred a median of 2 months after initiating the checkpoint inhibitors. AKI stage, the period from ICPi initiation to AKI occurrence, and the use of H2 blockers differed significantly between the non-ICPi AKI group and the ICPi-AKI group. However, the presence of all-cause AKI or checkpoint inhibitor-associated AKI did not lead to increased mortality.

Conclusions: This study shows that AKI frequently occurs in bladder cancer patients receiving ICPi. However, the presence of all-cause AKI and AKI related to ICPi toxicity did not increase mortality in these patients.

Cox proportional hazard regression analysis of relationship between AKI group and mortality.

	Crude	Adjusted
	HR (95%CI)	HR (95%CI)
No AKI	Reference	Reference
AKI development	55.2(0.25 - 4217)	0.91 (0.80-1.04)
ICPi related AKI	2.52 (0.67 - 9.39)	0.27 (0.05 - 1.42)
Non ICPi related AKI	2.94 (0.79 - 11.0)	3.06 (0.70 - 18.5)

FR-PO199

Infliximab for Immune Checkpoint Inhibitor-Associated Acute Interstitial Nephritis: A Biomarker-Guided Approach

Elena-Bianca Barbir, Priscilla Koirala, Luis E. Gutierrez, Sandra Herrmann. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Immune checkpoint inhibitor associated acute interstitial nephritis (ICI-AIN) occurs in 3-5% of patients receiving ICI therapy, and is typically steroid responsive. A minority of cases are steroid dependent. We review the outcomes of patients with steroid-dependent ICI-AIN treated with Infliximab at our center, as well as the relationship between several non-invasive biomarkers and response to therapy.

Methods: We describe 3 cases of biopsy-proven ICI-AIN for which Infliximab was used as a steroid sparing agent. We followed several biomarkers including: urine CXCL9, urine TNF-α, urine RBP -- all normalized to creatinine, serum IL2r and CRP at varying time points in the disease course. Serum TNF-α was measured to monitor Infliximab response.

Results: Clinical characteristics are described in Table 1. Figure 1 depicts biomarker trends over time as a function of therapy. All 3 patients had relapse of their ICI-AIN with prednisone taper ≤ 20 mg. Post 1 infliximab infusion, patient 2 was tapered off steroids. Patient 1 and 3 remained on Prednisone 10 mg post 2 doses of Infliximab for other indications. Serum TNF-α was suppressed with Infliximab in all cases. All patients had elevated urine TNF-α/Cr, CXCL9/Cr, RBP/Cr, and serum IL2r at initial diagnosis which decreased with therapy. When measured around the time of ICI-AIN relapse, urine RBP/Cr, CRP, urine TNF-α/Cr, and urine CXCL9/Cr all rose.

Conclusions: In all cases, Infliximab facilitated steroid taper and biomarker trends helped determine the number of Infliximab doses before significant rises in creatinine occurred. Controlled studies are needed to clinically validate these biomarkers for ICI AIN diagnosis and relapse.

Table 1

	Patient 1	Patient 2	Patient 3
Age (y) and Sex	63, Male	90, Female	74, Male
Cancer Type and ICI Therapy	Renal Cell Carcinoma, on Ipilimumab and Nivolumab	Breast Cancer, on Pembrolizumab	Non-Small Cell Lung Cancer, on Pembrolizumab
Preceding Immune Related Adverse Events	Pneumonitis, Hypophysitis	Myocarditis	Myocarditis
ICI Re-Challenge	Yes, on Prednisone 10 mg daily	No, cancer remains in remission	Yes, on Prednisone 10 mg daily

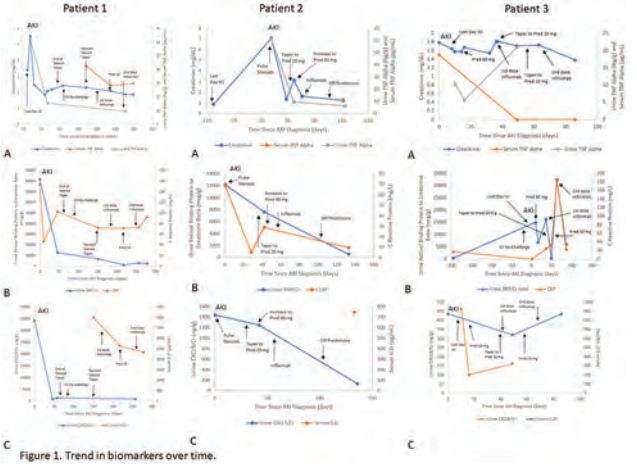


Figure 1. Trend in biomarkers over time.

FR-PO200

Hidden Kidney Impact of Immunotherapy in Patients with Metastatic Kidney and Bladder Cancer: "Nothing Is What It Seems"

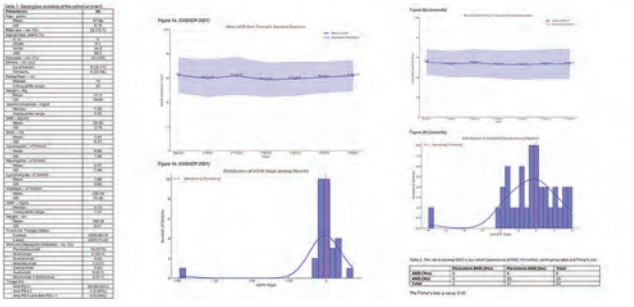
Francesco Trevisani,[1] Andrea Angioi,[2] Matteo Floris,[2] Mariadelina Simeoni,[3] Barbara Galassi,[4] Fiorella Ruatta,[4] Ornella Garrone,[4] Michele Ghidini.[4]
[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Azienda Ospedaliera Brotzu, Cagliari, Italy; [3]Universita degli Studi della Campania Luigi Vanvitelli, Caserta, Italy; [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Background: Immunotherapy has emerged as a pivotal treatment for metastatic renal and bladder cancer. Hovewer, its impact on renal function in term of Acute Kidney Disease (AKD), remains a critical concern. In addiction, the role of nephrologist in this asset of patients remains ancillary and only related to AKI events. Therefore, our aim was to elucidate the incidence and persistence of the insidious and dangerous AKD condition in a cohort of 33 consecutive urological metastatic pts subjected to immunotherapy.

Methods: We conducted a retrospective analysis of 33 patients receiving first-line immunotherapy for metastatic renal and bladder cancer. Patient demographics, clinical characteristics, and treatment details were extracted. Labs were done monthly and kidney function was assessed with eGFR (CKD-EPI 2021; Janowitz formula). AKD was defined as an increase in serum creatinine by ≥0.3 mg/dL or an increase to ≥1.5 times the baseline, persisting for ≥7 days post-exposure and < 3 months in line with K-DIGO 2023 guidelines.

Results: Descriptive analysis is shown in table 1. The incidence of AKD in 6 months of treatment was 24.24%, observed in 8 patients; among these, 6.06% (2 patients) exhibited persistence of AKD over three consecutive months, which was significant at Fisher's test (p=0.05). The slope of eGFR from baseline to six months showed that most patients had minimal changes in kidney function, with a mean slope of 0.634 mL/min/1.73m^2 per month (Figures 1a, 2a,1b,2b). Notably, some patients experienced significant declines, with slopes as steep as -40 mL/min/1.73m^2 per month.

Conclusions: This innovative study highlights for the first time a significant and unexpected incidence (24%) of AKD in patients treated with immunotherapy for metastatic renal and bladder cancer. Because AKD can often evolve in CKD, an onco-nephrological counseling able to reduce the incidence of AKD is mandatory



FR-PO201

Measured GFR Using Renal Scan Improves Preoperative Clinical Decision in Patients with Kidney Cancer Who Are Surgical Candidates

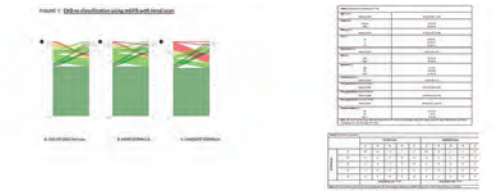
Francesco Trevisani, Giuseppe Rosiello, Pietro Scilipoti, Giacomo Musso, Chiara Re, Francesco Cei, Federico Belladelli, Francesco De Cobelli, Arturo Chiti, Fabrizia Gelardi, Francesco Montorsi, Andrea Salonia, Roberto Bertini, Umberto Capitanio. *IRCCS Ospedale San Raffaele, Milano, Italy.*

Background: Measured GFR (mGFR) using Renal scan before renal surgery represents a precise tool able to better define the "real" renal status of oncological patients candidate to partial or radical nephrectomy. Moreover, Renal scan can also show the split renal contribution of kidneys. Nevertheless, its use in the preoperative workflow is controversial. Thus, we aimed at evaluating the role of renal scan in patients undergoing renal surgery comparing the mGFR with the most used eGFR formulas.

Methods: We prospectively performed renal scan in 94 patients undergoing kidney surgery for cT1-2 renal mass between 2019 and 2022. Renal scan GFR measurement was compared with the most used eGFR formulas (MDRD, CKD-EPI 2021, JANOWITZ). CKD stages were defined according to the KDIGO 2023 classification. Sankey diagram was used to depict concordance between the different GFR estimates.

Results: Descriptive analysis is shown in table 1. The agreement between eGFR formulas and measured GFR using renal scan is represented in table 2. Using the mGFR via renal scan, the baseline pre-operative reclassification of patients was greater than 35% with each type of eGFR formulas. (Figure 1).

Conclusions: If renal scan is routinely used before kidney surgery, patient reclassification is observed in a non-negligible proportion of patients. Moreover, renal scan can identify patients with different split renal function, which does represent a key information for surgical planning and nephrological counseling.



FR-PO202

National Audit of Immune Checkpoint Inhibitor Use in Kidney Transplants

Blathnaid O'Connell,[1] Cliona Cowhig,[2] Jennifer B. Hanko,[3] Michael Clarkson,[2] Peter J. Conlon.[1] *[1]Beaumont Hospital, Dublin, Ireland; [2]Cork University Hospital, Cork, Ireland; [3]HCS Belfast Health and Social Care Trust, Belfast, United Kingdom.*

Background: Cancer is one of the leading causes of death in kidney transplant patients. The incidence of skin cancers among solid organ transplant recipients (SOTR) is markedly higher than general population. Immune checkpoint inhibitors (ICPIs) have revolutionized cancer treatment and have become standard of care for many cancers, including cutaneous malignancies. However, SOTR have been excluded from trials due to risk of allograft rejection, and because immunosuppression may compromise the anti-tumour effect of ICPIs. To date, this is the first case series looking at outcomes of this patient cohort in Ireland.

Methods: This was a multicentre retrospective study assessing kidney transplant recipients treated with ICPIs in Ireland. Cases were identified by members of the Irish Nephrology Society. Data collection included demographics, history of the transplantation, tumour type, ICPI use, changes to immunosuppression and outcomes.

Results: Five patients were included (4 male, 1 female), aged 54–72 years. Three patients received DBD transplants + 2 received living related transplants. 80% had metastatic melanoma, 20% had metastatic squamous cell carcinoma. Four patients were maintained on calcineurin inhibitors (CNI), mycophenolate mofetil (MMF) & prednisolone prior to diagnosis. One was on a CNI & prednisolone alone. Three patients commenced pembrolizumab, one commenced nivolumab and one commenced ipilimumab/nivolumab. None had systemic cancer treatments. MMF was stopped in all relevant cases, and prednisolone dose increased in one case. The majority weaned/stopped their CNI at ICPI initiation, but one switched from tacrolimus to sirolimus. One patient had a transplant biopsy, showing borderline T-Cell mediated rejection. Three patients (two on pembrolizumab, one on nivolumab) had reduction in metastatic burden and showed no evidence of disease progression at 25, 44 and 32 months, respectively and are currently maintained on treatment. All 3 returned to haemodialysis within 42-79 days of ICPI initiation. Two patients died at 53 days & 67 days post ICPI initiation.

Conclusions: The efficacy of ICPIs in kidney transplant patients appears promising, warranting prospective clinical trials. There are currently no guidelines on the use of ICPIs in SOTR, but ultimately, when the question becomes of life versus graft, discussion between the patient & physician is crucial.

FR-PO203

Delayed Immune Checkpoint Inhibitor-Induced Acute Tubulointerstitial Nephritis (ICI-ATIN) Relapse with Proton-Pump Inhibitor Re-exposure Despite ICI Discontinuation: A Case Report

Julia G. Andres,[1] Joycelyn Jie Xin Lee,[2] Hui Zhuan Tan.[1] *[1]Singapore General Hospital, Singapore, Singapore; [2]National Cancer Center Singapore, Singapore, Singapore.*

Introduction: While immune-related adverse events (irAEs) usually occur during active use of immune checkpoint inhibitors (ICI), their sporadic development after ICI discontinuation has been rarely described. We report a case of delayed ICI-acute tubulo-interstitial nephritis (ICI-ATIN) relapse occurring in context of proton pump inhibitor (PPI) re-exposure despite ICI cessation.

Case Description: An 84-year-old Chinese female with colorectal cancer was referred for KDIGO Stage 2, non-oliguric acute kidney injury (AKI) [baseline sCr 84μmol/L, peak sCr 162μmol/L] 4 months after initiation of pembrolizumab. Urinalysis showed hematuria (28 RBC/μL), pyuria (85 WBC/μL) and minimal proteinuria (uPCR 0.35g/g). Only ANA was borderline detected (titre 1:160), while the remaining autoimmune markers were negative. PPI use, but not NSAIDs or antibiotics, was noted. As ICI-ATIN was highly suspected, she received a 10-week tapering course of empiric prednisolone (0.7mg/kg starting dose) with clinical improvement (recovery sCr 112μmol/L). She remained off immunotherapy over the next 5 months, but was inadvertently restarted on PPI for dyspepsia. AKI was observed 4 weeks later (peak sCr of 190μmol/L). ATIN was confirmed on kidney biopsy. Prednisolone at 1mg/kg was recommenced, with improvement of sCr to 124μmol/L after 7 weeks. Vonaprazan was started for dyspepsia. PPI was permanently stopped and recorded as an adverse drug reaction.

Discussion: Our case highlights important observations concerning the use of PPI in ICI-treated patients. The temporal correlation of PPI re-exposure and ATIN relapse supports the postulation that PPI potentiates the development of ICI-ATIN. While PPI avoidance is recommended in ICI rechallenge, it is unknown if and when PPI can be safely resumed after ICI is permanently withdrawn. Long-lasting effects of ICIs surpassing their pharmacokinetic half-lives have been described, with resultant implications for their related immune-related toxicities. We advise continued caution with PPI use in all patients with a history of ICI-ATIN, even when ICI is stopped. Awareness of this association amongst healthcare providers (HCPs) is necessary as PPI use is common. Systematic documentation of irAEs with disease-specific codes, as well as implementation of EHR alerts to identify and inform HCPs of potential irAE triggers are additionally required.

FR-PO204

Sequential Development of Immune Checkpoint Inhibitor-Induced Acute Tubulointerstitial Nephritis (ICI-ATIN) following Stevens-Johnson Syndrome (SJS)-Like Reaction in Patient on Pembrolizumab and Meropenem: A Common Drug Trigger?

Julia G. Andres,[1] Joycelyn Jie Xin Lee,[2] Hui Zhuan Tan.[1] *[1]Singapore General Hospital, Singapore, Singapore; [2]National Cancer Center Singapore, Singapore, Singapore.*

Introduction: Multisystem immune-related adverse events can occur with immunotherapy but their predictors and implications remain unknown. We report a case of immune checkpoint-related acute tubulo-interstitial nephritis (ICI-ATIN) occurring successively after progressive immunotherapy-related mucocutaneous eruption (PIRME), an ICI-related Steven Johnson syndrome (SJS)-like reaction, in the context of meropenem exposure.

Case Description: A 71-year-old Chinese Male receiving pembrolizumab therapy for Stage IV bronchial squamous cell carcinoma, was referred for evaluation of KDIGO Stage 3, non-oliguric AKI [baseline sCr 76 μmol/L, peak sCr 353 μmol/L], occurring one week after the development of biopsy-proven PIRME. Notably, patient received meropenem in the last two weeks for treatment of lung abscess. There was no exposure to PPIs or NSAIDs. First and last dose of ICI were given 9 weeks and 3 weeks prior to AKI, respectively. Evaluation showed mild pyuria (urinary WBC 10/μL) and sub-nephrotic range proteinuria (uPCR 0.90 g/g). Serum C-reactive protein was elevated at 90.5 mg/L. Autoimmune markers and virologies were negative. Prednisolone at 60mg OD (1mg/kg) was started empirically. Kidney biopsy performed subsequently confirmed ATIN. Rebound of AKI observed after 4 weeks, and mycophenolic acid 360mg BD was added. Partial renal remission was observed after 3 months (sCr 107μmol/L).

Discussion: Our case supports the hypothesis that multisystem irAEs may represent a combination of irAEs that share common pathobiology such as HLA genotypes, autoantibody formation or external triggers such as co-medications (PPIs, NSAIDs and antibiotics). Co-medications have been increasingly implicated in the development of ICI-ATIN, which is postulated to be a result of drug-mediated, kidney-specific immune responses occurring unchecked in the setting of lowered immune tolerance during ICI use. A similar phenomenon has been proposed in the development of PIRME. It is probable that meropenem triggered both cutaneous and renal irAEs in our patient. Patients with PIRME should receive close monitoring of renal function during and after the event. ICI-ATIN occurring together with PIRME may warrant extended or additional immunosuppression, although more research is required to confirm our findings.

FR-PO205

IgG4-Tubulointerstitial Nephritis Due to Pembrolizumab

Alice H. Won,[2,1] Steven Salvatore,[1] Insara Jaffer Sathick.[2] *[1]Weill Cornell Medicine, New York, NY; [2]Memorial Sloan Kettering Cancer Center, New York, NY.*

Introduction: Immune checkpoint inhibitors (ICIs) such as pembrolizumab have revolutionized cancer treatment by promoting T cell-mediated antitumor response. There have been increasing reports of ICI-related renal toxicity such as acute tubulointerstitial nephritis (ATIN). Here we describe a case of IgG4 tubulointerstitial nephritis (IgG4-TIN) associated with pembrolizumab in a patient with metastatic serous endometrial carcinoma.

Case Description: The patient is a 71-year-old woman with history of hypertension, diabetes mellitus, and serous endometrial carcinoma who had undergone surgical removal, radiation, and chemotherapy (carpoplatin-taxol) with metastatic recurrence to the peritoneum. She was started on pembrolizumab 200 mg every 3 weeks and received 23 doses when she was hospitalized for recurrent acute kidney injury in the setting of urinary tract infection complicated by hydronephrosis. Laboratory findings showed elevated serum creatinine (sCr) of 4.1 mg/dL (from 1.0 mg/dL) with microscopic hematuria, pyuria, and proteinuria (urine protein-creatinine ratio 1.2 g/g). Kidney biopsy was performed due to persistent AKI despite successful stent placement, revealing diffuse tubulointerstitial inflammation with lymphoplasmacytic cell infiltration stained positive for IgG4. Immunoglobulin levels showed elevated IgG (2,347 g/L) and IgG4 (207 g/L) levels. She was started on prednisone 60 mg daily with subsequent improvement in sCr to 2.1 mg/dL, transitioned to a slow taper. At 18-month follow-up, sCr was 1.1mg/dL without any new symptoms. After discontinuing pembrolizumab she was treated with trastuzumab with continued tumor response.

Discussion: Here, we report a novel toxicity of ICIs in the form of IgG4-TIN, which is characterized by rich IgG4-positive plasma cell infiltration as well as serologic abnormalities including elevated serum IgG, IgG4, and IgE. We hypothesize that immune dysregulation induced by ICIs can manifest as IgG4-TIN in rare cases, as observed in our patient. Prompt discontinuation of ICI and initiation of steroid therapy are effective in the management of this complication.

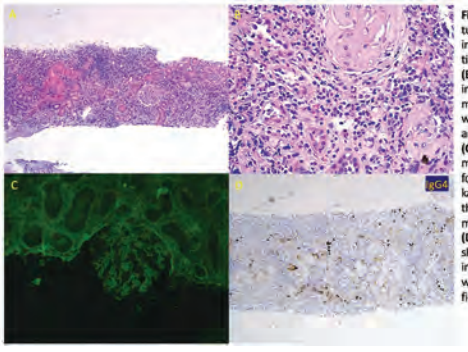


Figure 1: (A) Diffuse active tubulo-interstitial inflammation involving >90% of the cortical tissue (PAS). **(B)** Interstitial inflammatory infiltrates are composed of mainly plasma cells admixed with lymphocytes, eosinophils, and some macrophages (PAS). **(C)** Immunofluorescence microscopy reveals no staining for IgG, IgA, complements, kappa or lambda light chains – there are no immune-complex mediated lesions. **(D)** Immuno-peroxidase stain shows positive staining for IgG in all infiltrating plasma cells, with >8-10 cells per high-power field positive for IgG4.

FR-PO206

Rituximab in Treatment of Glomerulonephritis Induced after Immune Checkpoint Inhibitors

Yazen Alasadi,[1] Naszrin Arani,[1,2] Amanda Tchakarov,[3] Ala Abudayyeh.[1] *[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Baylor College of Medicine, Houston, TX; [3]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.*

Introduction: Immune checkpoint inhibitors have been shown to induce and exacerbate autoimmune side effects especially in those patients with underlying autoimmune disease. Although glomerular disease is a rare entity (less than 1%), it adds further complexity to the cancer patients care. In this report we describe 4 cases of glomerulonephritis successfully treated with rituximab and resumed ICI with continued renal response.

Case Description: A 64-year-old with diagnosis of mesothelioma and treated with nivolumab, after two cycles he developed nephrotic range proteinuria with biopsy confirmation of membranous nephropathy with positive antibody to PLA2R. The patient was initiated on rituximab 1 g IV on Day 1 and 15 and achieved complete renal response while continuing therapy on nivolumab for 3 years and PET/CT imaging ccancer remission and serum Anti-PLA2R negative. Another patient is a 71 y.o with diagnosis of squamous cell cancer of the anal canal who did not respond to cisplatin and 5 FU and was started on nivolumab. After fourth cycle she developed 15g proteinuria. Biopsy confirmed minimal change disease and treated with a short dose of steroids and rituximab. She achieved complete remission of her proteinuria and tumor response with continued ICI treatment. The third case is a 65 y.o male with primary membranous nephropathy 20 years ago with reactivation after Stage IV Melanoma diagnosis and exacerbated ICI treatment. Rituximab achieved excellent response and resolution of proteinuria after one cycle which was maintained on ICI for over 2 years with no exacerbation of his membranous nephropathy and complete tumor response. Our final case is a 65 y.o. male with diagnosis of anaplastic thyroid carcinoma, treated with dabrafenib, trametinib, and pembrolizumab. 2 weeks after pembrolizumab patient developed AKI creatinine increase 3.5mg/dl, nephrotic range proteinuria. Kidney biopsy attained confirmed minimal change disease. He was treated with rituximab and proteinuria improved from 20grams to 0.5 grams. Patient was restarted on pembrolizumab and after 2 doses creatinine is less than 0.9mg/dl and proteinuria less than 1gram.

Discussion: In this report we have presented four unique cases of membranous nephropathy and minimal change disease in a cancer patient after ICI exposure successfully treated and re-challenged on ICI with continued renal and tumor response.

FR-PO207

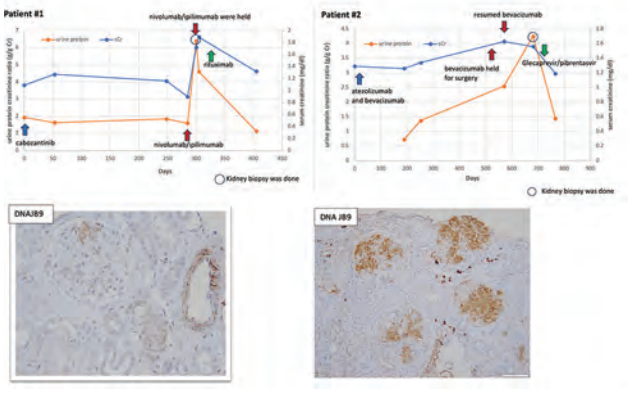
Fibrillary Glomerulonephritis in a Patient on Dual Immune Checkpoint Inhibitor and Tyrosine Kinase Inhibitor Therapy

Api Chewcharat, Raad B. Chowdhury, Romela Petrosyan, Sujal I. Shah, Shruti Gupta. *Brigham and Women's Hospital, Boston, MA.*

Introduction: Fibrillary glomerulonephritis (FGN) is a glomerular disease characterized by nonbranching, randomly arranged 20 nm fibrils which usually stain positive for DNAJB9. The pathogenesis of FGN remains unclear, but recent studies reported an association with autoimmune diseases and hepatitis C infection. Here, we report 2 cases of FGN occurring after dual treatment with an immune checkpoint inhibitor (ICI) and a tyrosine kinase inhibitor (TKI).

Case Description: Patient #1 is a 69-year-old man with a history of metastatic thyroid cancer treated with cabozantinib for nine months. This was stopped due to diarrhea, and he was switched to nivolumab/ipilimumab. After the first cycle, the patient developed AKI, with serum creatinine (sCr) 1.9 mg/dL from a baseline of 1.1 mg/dL and UPCR 2g/g Cr. A kidney biopsy was performed and showed FGN along with chronic TMA. Further ICI was held, and rituximab was started. sCr decreased to 1.2 mg/dL, with UPCR 0.18 g/g Cr after two doses of rituximab. **Patient #2** is a 77-year-old man with a history of untreated hepatitis C viral (HCV) infection and hepatocellular carcinoma treated with atezolizumab and bevacizumab. After two years of treatment, the patient developed AKI, with sCr 1.6 mg/dL from a baseline of 1.3 mg/dL and UPCR 4.2g/g Cr. A kidney biopsy was performed and revealed FGN. Bevacizumab was held due to significant proteinuria and Glecaprevir/pibrentasvir was started for HCV. Follow-up sCr fluctuated between 1.2-1.4 mg/dL, with 24h urine protein 1.4 g.

Discussion: These cases highlight 2 patients treated with dual immunotherapy and targeted therapy who presented with FGN. In the second case, the patient had HCV, which could be implicated; however, glomerular diseases have been described with both ICIs and TKIs. This potential association with FGN warrants further study, particularly given FGN's poor prognosis and the implications it has for holding potentially life-saving cancer treatments.



FR-PO208

The Intersection between Chimeric Antigen Receptor T Cell (CAR-T) Therapy and the Kidneys: A Multicenter Study of Outcomes

Ahmad Matarneh, Sundus Sardar, Rafael Portela, Muhammad Abdulbasit, Navin Verma, Naman Trivedi, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Background: Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized the treatment of refractory hematologic malignancies. Despite its remarkable efficacy, CAR-T therapy is associated with serious adverse effects, including electrolyte abnormalities and acute kidney injury (AKI).

Methods: This study aims to determine the incidence of electrolyte abnormalities and AKI in patients receiving CAR-T therapy. Additionally, we assessed survival outcomes following these events and compared risk differences in patients with and without AKI. We conducted a retrospective multi-center cohort study using the TriNetX database. We identified 3,537 patients who received CAR-T therapy and subsequently developed electrolyte abnormalities or AKI. Survival following these events was also evaluated

Results: The incidences of abnormalities and respective survival properties were as follows: - Hyponatremia:16.5%, survival probability: 78.9%. - Hypernatremia: 3.8%, survival probability: 94.9%. - Hypocalcemia: 7%, survival probability: 90.4% - Hypercalcemia: 6.6%, survival probability: 91.2%. - Hypophosphatemia: 14.7%, survival probability: 80.7%. - Hyperphosphatemia: 1.5%, survival probability: 80.5%. - AKI: 22.4%, survival probability: 70.4%. Compared with the non-AKI cohort, the AKI group had a higher incidence of: - Hyponatremia (24% vs. 14%), associated with lower survival (67.7% vs. 83.1%); - Hypernatremia (8.7% vs. 1.3%), associated with lower survival (88.2% vs. 98.2%); - Hypocalcemia (11.7% vs. 5.8%), associated with lower survival (84.2% vs. 93.2%); - Hypercalcemia (11.6% vs. 3.6%), associated with lower survival (84.5% vs. 95.2%). - Hypophosphatemia (25% vs. 12.2%), associated with lower survival (66% vs. 85.1%); - Hyperphosphatemia (25.5% vs. 12.2%), with similar survival Mortality was higher in patients with AKI following CAR-T therapy, with a risk of 39.5% compared to 18.2% in patients without AKI (RR 0.461, 95% CI 0.415-0.512).

Conclusions: CAR-T therapy is associated with multiple electrolyte derangements and a significant incidence of AKI. These imbalances correlate with increased mortality risk. Patients who develop AKI are at higher risk of electrolyte abnormalities and have lower survival probabilities. Overall, careful monitoring and management of electrolyte disturbances in patients undergoing CAR-T therapy are crucial.

FR-PO209

Clinical Characteristics of AKI Associated with Chimeric Antigen Receptor T Cell (CAR-T) Therapy in Kyoto University Hospital

Tatsuaki Kosaka, Shinya Yamamoto, Yasuyuki Arai, Hideki Yokoi, Motoko Yanagita. *Kyoto Daigaku Igakubu Fuzoku Byoin, Kyoto, Japan.*

Background: CAR-T therapy was approved in 2017 for the treatment of several refractory hematologic tumors and is expected to be expanded to other hematologic and solid tumors in the future. Side effects include cytokine release syndrome (CRS) and, in severe cases, multiple organ failure. However, evidence of AKI associated with CAR-T cell therapy is limited.

Methods: We investigated the incidence of CRS and AKI, cause of AKI, background factors of patients, and renal prognosis in 131 patients treated with CAR-T therapy between December 2019 and December 2023 at our hospital. A two-sample *t*-test was performed for continuous variables, and the chi-square test for categorical variables. In addition, the renal pathology of two autopsies after AKI due to CRS was examined to reveal the pathogenesis of AKI due to CRS.

Results: CRS occurred in 121 cases (92.4%), and AKI occurred in 7 cases (5.3%, Stage 1: 1 case, Stage 2: 1 case, Stage 3: 5 cases). The causes of AKI were CRS (6 cases) and tumor lysis syndrome (1 case). The number of previous chemotherapy regimens, poor response to primary disease, CRS severity, poor response after CAR-T therapy, and higher basal lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin levels were significantly associated with AKI development. Four patients recovered to baseline renal function after AKI, one patient remained with renal impairment, and two patients died. Renal pathology of autopsy cases showed glomerular and peritubular capillary congestion, interstitial edema, and acute tubular necrosis without glomerular nephritis.

Conclusions: In our study, higher tumor volume was considered a risk factor for AKI. Evaluation of tumor volume in the primary disease, such as measurement of serum markers or tumor size on a CT scan, may be useful in predicting the development of AKI after CAR-T therapy. Approximately 70% of AKI cases were stage 3, but about half of the patients recovered to baseline renal function, suggesting that renal prognosis is relatively good when the patient survives. The main pathological features of AKI associated with CRS are interstitial edema, and acute tubular necrosis, indicating that hemodynamic changes could induce AKI associated with CAR-T therapy.

FR-PO210

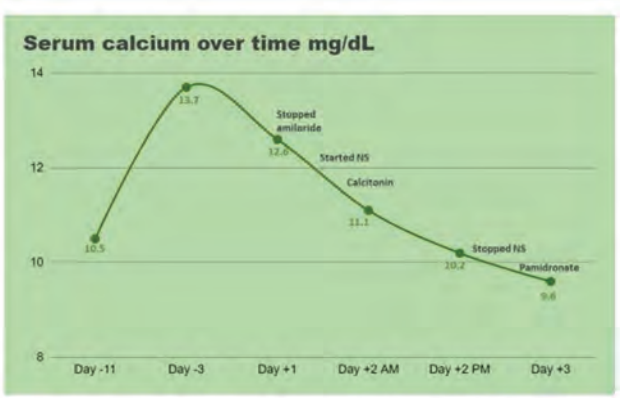
Hypercalcemia in a Patient with Cancer on an Immune Checkpoint Inhibitor, a Tyrosine Kinase Inhibitor, and Amiloride: Which Is the Culprit?

Carolina Saldanha Neves Horta Lima,[1] Meghan E. Sise,[3] Shruti Gupta.[2] *[1]Mass General Brigham Salem Hospital, Salem, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Massachusetts General Hospital, Boston, MA.*

Introduction: Hypercalcemia in oncologic patients can be malignancy-related, but can occur after immune checkpoint inhibitors (ICIs) and amiloride use.

Case Description: A 64-year-old patient with a history of stage IV renal cancer presents with fatigue, weakness and constipation. She was found to have AKI (creatine of 1.77 mg/dL from a prior of 0.9 mg/dL) and hypercalcemia of 13.7 mg/dL. She had been recently started on pembrolizumab, an ICI, and Lenvatinib (a tyrosine kinase inhibitor [TKI]). Within 24 hours of starting Lenvatinib, she had developed hypertension, requiring escalating doses of lisinopril, amlodipine, and metoprolol; amiloride was added for yet uncontrolled blood pressure. She denied use of excessive vitamin D supplements or antacids. Workup showed a 25 (OH) vitamin D of 71 ng/mL, a PTH of 8 pg/mL, a PTHrp of 0.7 pmol/L and a vitamin D 1,25 OH of 67 pg/mL. There was no disease progression or metastasis, pointing to a hypercalcemia not mediated by calcitriol and not cancer-related. Upon admission, amiloride was discontinued and patient received normal saline, calcitonin and pamidronate (Figure). There was normalization of calcium and creatinine.

Discussion: This case highlights, first, how TKI-related hypertension can present so quickly and severly. Thus, the need for further understanding of optimal anti-hypertensive therapies for these patients. And second, how the start of amiloride unmasked a hypercalcemia under ICI use. Amiloride acts by blocking sodium reabsorption through epithelial sodium channels. Amiloride-associated hypercalcemia is an entity mostly theoretical. It is thought to occur due to membrane hyperpolarization in the setting of sodium reabsorption, thereby promoting calcium entry. It is also possible that concurrent treatment with ICIs exacerbated the hypercalcemia, as ICIs have been reported to cause hypercalcemia by endocrinopathies, sarcoid-like granuloma, humoral hypercalcemia due to parathyroid-related hormone and hyperprogressive disease following ICI initiation.



FR-PO211

Chimeric Antigen Receptor T Cell Therapy-Induced Hypophosphatemia (HypoPhos) Due to Renal Phosphate Wasting

Marco Ramos, Brock Gilsdorf, Isaac Teitelbaum. *University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO.*

Introduction: Chimeric antigen receptor T cell (CAR-T) therapy for refractory malignancies has been a major advance in the field of oncology. Several electrolyte abnormalities related to CAR-T therapy have been reported including hyponatremia, hypokalemia, and hypoPhos. The role of phosphaturia in the pathogenesis of CAR-T related hypoPhos has not been well defined.

Case Description: A 36-year-old male with relapsed B-acute lymphoblastic leukemia underwent CAR-T therapy. The patient developed grade 1 cytokine release syndrome (CRS) which was treated with single dose tocilizumab. He developed severe hypoPhos (<1.0 mg/dl) one week later. His fractional excretion of phosphate (FePO4) was initially 36.64% (nl < 20%) and peaked at 116.46%. Fibroblast growth factor 23 (FGF23) was measured daily with initial value <14 pg/ml and peak 31 pg/ml at day 4 day. Markers for CRS are depicted below with serologies in table 1. Oral sodium or potassium phosphate replacement started at day 2, twice or thrice daily (at the discretion of the treating team). While the patient did develop hyponatremia, he did not develop glucosuria, AKI or metabolic acidosis.

Discussion: The mechanism of CAR-T induced hypoPhos has not been well defined. It has been speculated that it might be related to increased metabolic consumption of extracellular phosphorus by CAR-T cells, but the potential role of increased renal wasting has not been examined. While animal models of AKI or CKD have shown a relationship between IL-6 induction of FGF23 and subsequent hypoPhos, this has not been shown in CAR-T cell models. We demonstrated that increased renal excretion does play a significant role. Though FGF23 levels increased, they remained within the normal range. Nevertheless, the FEPO4 greater than 100% indicates addition of phosphate to the urine beyond the amount filtered, i.e. tubular secretion, which might be mediated by FGF23. The absence of glucosuria and acidosis suggests that this was not due to diffuse proximal tubular dysfunction. Further study is necessary to define the mechanism(s) underlying renal phosphate wasting with CAR-T therapy.

Table 1

	Day 1	Day 2	Day 3	Day 4
Sodium (mmol/L)	127.6	122.6	129.6	132.3
Phosphorus (mg/dl)	2.6	0.9	1.6	2.2
Serum IL-6 (pg/ml)	12.1	49.6	9.5	10.4
Serum iFGF23 (pg/ml)	13	13	17	31
FePO4 (%)	36	38	116	40.33
CRP (mg/L)	74.5	183	159	65.5

FR-PO212

Remote Organ Cancer Adversely Alters Kidney Physiology and Induces Kidney Injury and Inflammation

Dana Hammouri, Andrew Orwick, Dianet Sanchez Vega, Levi J. Beverly, Leah J. Siskind. *University of Louisville School of Medicine, Louisville, KY.*

Background: Approximately 30% of cancer patients experience kidney complications, which hinder optimal cancer management, imposing a burden on patients' quality of life and the healthcare system. The etiology of kidney complications in cancer patients is often attributed to nephrotoxic oncological therapies. However, the direct impact of cancer on kidney health is underestimated, as most nephrotoxic oncological therapies have been studied in animal models that do not have cancer. Our previous study demonstrated that lung cancer adversely alters kidney physiology and function, and chemotherapy-induced nephrotoxicity is exacerbated, indicating cancer-kidney crosstalk. This study examines whether this phenomenon is specific to the employed cancer model.

Methods: Mice of various strains were injected with different cell lines representing human and mouse lung cancer, breast cancer, and melanoma. Mice were euthanized upon reaching IACUC protocol endpoints. Kidney tissues were analyzed for toxicity and compared to controls.

Results: The impact of cancer on the kidney varied by cancer type. Breast cancer and specific subtypes of lung cancer, including KRAS- and EGFR-mutant cancer, pathologically altered kidney physiology and function in a stage-dependent manner. This was independent of mouse strain, sex, cancer cell delivery route, and cell line origin. Moreover, tumor DNA was not detected in the kidney tissue. Lewis lung carcinoma and melanoma did not cause nephrotoxicity, regardless of the tumor stage.

Conclusions: Our results confirm cancer-kidney crosstalk in specific cancer types and highlight gaps in understanding renal complication risk in cancer patients. In the era of precision medicine, further research is essential to identify at-risk oncology populations, enabling early detection and management of renal complications.

Funding: NIDDK Support

FR-PO213

Fibroblast Growth Factor Receptor Inhibitor-Induced Hyperphosphatemia: A Case Series from a Tertiary Care Center and Literature Review

Rose Mary Attieh, Kenar D. Jhaveri, Pratap Kumar Upadrista. *Northwell Health, New Hyde Park, NY.*

Background: Fibroblast Growth Factor Receptor Inhibitors (FGFRi) are promising cancer drugs, effective against FGFR2-rearranged cholangiocarcinoma and advanced urothelial carcinoma. Despite their efficacy, they are frequently associated with side effects, notably hyperphosphatemia (hyperP), a significant on-target off-tumor adverse event (AE).

Methods: We conducted a search of the electronic health records system at Northwell Health, a large tertiary healthcare system in New York, to identify patients who received treatment with any FGFRi between January 2020 and December 2023. We collected data on the duration of cancer therapy, the incidence and grade of hyperP, time-to-onset of hyperP, and changes in therapy due to hyperP. Additionally, we scrutinized data from landmark clinical trials and the FDA Adverse Event Reporting System (FAERS) database regarding hyperP as an AE associated with FGFRi.

Results: In our series, 13 patients were treated with erdafitinib, 2 patients received futibatinib, and 1 patient received pemigatinib. 15 out of the 16 patients (94%) developed hyperP with a median time-to-onset of 12 days with futibatinib, 29 days with erdafitinib, and 90 days with pemigatinib. Most hyperP AEs were grade 2 in patients exposed to erdafitinib. Treatment with phosphate binders was required in all patients on futibatinib and pemigatinib, as well as in 58% of patients on erdafitinib. 4 (33%) of patients treated with erdafitinib required FGFRi dose reduction and 1 (8%) required therapy interruption due to hyperP. **Table 1** summarizes the main findings from our cohort, contrasting them with those from large FGFRi randomized clinical trials. Review of the FAERS database showed that hyperP occurred with all FGFRi and constituted 5-15% of all AEs reported with these drugs.

Conclusions: Nephrologists should be aware of hyperP as a possible complication of FGFRi therapy. Collaboration with oncologists is essential to maximize treatment benefits and mitigate AEs without therapy interruption.

	Fibroblast Growth Factor Receptor Inhibitor					
	Futibatinib		Erdafitinib		Pemigatinib	
	Northwell Data	Landmark Clinical Trial (FOENIX-CCA2) [1]	Northwell Data	Landmark Clinical Trial (BLC2001) [2]	Northwell Data	Landmark Clinical Trial [4]
Number of patients (N)	2	103	13	99	1	146
Mean duration of treatment with FGFRi (in months)	4	9.7	9.7	5.3	9	7.2
Incidence of hyperP, N (%)	2(100)	88 (85)	12 (92)	76 (77)	1 (100)	81 (55)
HyperP grade, N (%)	Grade 1: 1 (50) Grade 2: 1(50)	Grade 1: 10(10) Grade 2: 47(46) ≥Grade 3: 31(30)	Grade 1: 1 (8) Grade 2: 9 (69) ≥Grade 3:1(8) Missing: 1 (8)	Grade 1: 53(54) Grade 2: 21(21) ≥Grade 3: 2(2)	Grade 1: 1(100)	Grade 1 or 2: 81(55) ≥Grade 3: 0(0)
Median time-to-onset of hyperP (in days)	12	5	29	14	90	15
Patients requiring phosphate binders for treatment of hyperP, N (%)	2(100)	80(78)	7(58)	-	1(100)	27(18)
Patients requiring dose reduction of FGFRi due to hyperP, N (%)	0(0)	21(20)	4(33)	9(9)	0(0)	1(1)
Patients requiring therapy interruption due to hyperP, N (%)	0(0)	18(17)	1(8)	-	0(0)	2(1)
Incidence of AKI during course of therapy, N (%)	1(50)	-	6 (46)	8(8)	0(0)	4(3)

Table 1: Incidence and characteristics of hyperphosphatemia in the Northwell series and in landmark clinical trials. FGFRi: fibroblast growth factor inhibitor, hyperP: hyperphosphatemia, AKI: acute kidney injury. Hyperphosphatemia was graded as follows: grade 1 = serum phosphate ≥4.5 mg/dL and <5.5mg/dL, grade 2 = serum phosphate ≥5.5mg/dL and <7.0mg/dL, grade 3 = serum phosphate ≥7.0mg/dL and <10.0mg/dL, and grade 4 = serum phosphate ≥10mg/dL.

FR-PO214

Accuracy of Glomerular Filtration Rate Estimates among Patients with Cancer

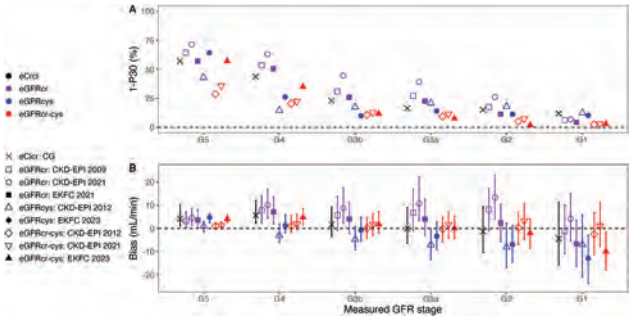
Jennifer S. Lees,[1,3] Edouard Fu,[2] Anne-Laure Faucon,[3] Benjamin M. Elyan,[1] Lesley A. Inker,[4] Andrew S. Levey,[4] Patrick B. Mark,[1] Juan J. Carrero.[3]
[1]University of Glasgow, Glasgow, United Kingdom; [2]Leids Universitair Medisch Centrum, Leiden, Netherlands; [3]Karolinska Institutet, Stockholm, Sweden; [4]Tufts University School of Medicine, Boston, MA.

Background: Little is known about the accuracy of glomerular filtration rate (GFR) assessment among people with cancer. Most cancer guidelines and trials recommend estimated creatinine clearance (eClcr) using the Cockcroft-Gault (CG) equation. Accuracy is key to determine cancer prognosis, treatment eligibility and correct dosing of treatments with narrow therapeutic index.

Methods: We performed a cross-sectional study including 1,781 adults with incident cancer referred for 1,989 determinations of measured GFR (mGFR) using single-point plasma clearance of iohexol in Stockholm, Sweden, with concurrent measurements of creatinine and cystatin C. We assessed the performance of eClcr, estimated GFR based on creatinine (eGFRcr: CKD-EPI 2009/2021, EKFC 2021), cystatin C (eGFRcys: CKD-EPI 2012, EKFC 2023) and the combination (eGFRcr-cys: CKD-EPI 2012/2021, EKFC 2023) equations against mGFR. Values were non-indexed to body surface area and reported in mL/min. Accuracy was reported as % of patients with estimated values that differed by more than 30% of mGFR (1-P30). Bias was estimated as median (interquartile range; IQR) difference between mGFR and eCrcl or eGFR.

Results: Mean age was 64 (SD 14) years, 36% were female with mean mGFR 76 (SD 31) mL/min. The most common cancers were bladder (41%), lung (15%) and colorectal (13%); 13% had metastatic disease. 1-P30 was best for eGFRcr-cys (6-8%). eClcr (1-P30: 17%) had similar accuracy to eGFRcr (1-P30: 13-26%) and eGFRcys (1-P30: 12-17%). Accuracy varied by mGFR (Figure A). Median bias was lowest for eGFRcr-cys CKD-EPI 2012 (-0.5, IQR -6.2 to 6.4 mL/min) and highest for eGFRcr CKD-EPI 2021 (9.8, IQR 0.9 to 19.7 mL/min). Across mGFR categories, eGFRcr-cys equations were the least biased (Figure B).

Conclusions: Non-indexed eGFRcr-cys with CKD-EPI and EKFC equations provide the most accurate estimates of mGFR in patients with cancer, with potential to improve dosing and classification across treatment thresholds compared to eClcr and eGFRcr.



FR-PO215

Performance of a Score for Stratifying the Risk of CKD in Patients with Renal Cell Carcinoma Undergoing Nephrectomy

Liliana M. Kassar,[1,2] Veronica T. Costa e Silva,[1] Benedito J. Pereira,[2,3] Luciana G. Lutf,[1] Francisco Z. Mattedi,[1] Karoline W. Silva,[2] Mauricio D. Cordeiro,[1] Dirce M. Zanetta,[4] Emmanuel A. Burdmann.[4]
[1]Universidade de Sao Paulo Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [2]Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; [3]A C Camargo Cancer Center Centro Internacional de Pesquisa, Sao Paulo, Brazil; [4]Universidade de Sao Paulo, Sao Paulo, Brazil.

Background: Nephrectomy to treat patients with kidney cancer increases the risk of chronic kidney disease (CKD) in the middle and long term. Although new clinical tools have been developed to identify patients at higher risk and promote appropriate follow-up, these instruments have not been externally validated. We aim to assess the performance of the Australian risk stratification score for CKD (ARSC) after nephrectomy in patients with renal cell carcinoma (RCC).

Methods: We screened all adult patients with histology-confirmed RCC submitted to partial or total nephrectomy between 2010 and 2021 at the São Paulo State Cancer Institute – University of São Paulo (Brazil). Patients with a pre-operative (baseline) estimated glomerular filtration rate (eGFR) > 60ml/min/1.73m^2 and with at least one eGFR between 12 and 15 months after surgery were included. The ARSC score was calculated based on baseline characteristics (age, eGFR, diabetes mellitus [DM]) and type of nephrectomy. The primary outcome was eGFR ≤ 45 m/min/1.73m^2 (stage 3b CKD) one year after nephrectomy. eGFR was calculated using the race-free CKD-EPI equation based on the serum creatinine level.

Results: We enrolled 349 patients. The mean age was 58±10 y, 61% were male; 60% and 27% had hypertension and DM, respectively. Median baseline eGFR was 91 (63-123) mL/min/1.73m^2; nephrectomy was radical in 49% of patients. The ARSC score presented satisfactory discrimination; the area under the receiver operation characteristic curve was 0.70 (0.57 – 0.80, p=0.01). However, the score overestimated the outcome in patients at moderate and high risk (≥ 7 points) (Table).

Conclusions: The ARSC score presented satisfactory discrimination but overestimated the outcome of stage 3b CKD in this Brazilian cohort of patients with RCC.

Risk level (ARSC Score)	Predicted risk of stage 3b CKD	Observed outcome (stage 3b CKD)
Negligible (0-3)	<2%	3.7%
Low (4-6)	3-14%	7.2%
Moderate (7-8)	21-26%	14%
High (9-10)	46-69%	21%

ARSC: Australian risk stratification score for CKD; CKD: chronic kidney disease

FR-PO216

Impact of Conventional Antitumoral Therapy on Estimated Glomerular Filtration Rate in Patients with Cancer Using Serum Creatinine and Cystatin C: A Prospective Cohort Study

Renato A. Caires,[1] Lesley A. Inker,[2] Andrew S. Levey,[2] Emmanuel A. Burdmann,[3] Veronica T. Costa e Silva.[1]
[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Tufts Medical Center, Boston, MA; [3]Universidade de Sao Paulo Laboratorios de Investigacao Medica, Sao Paulo, Brazil.

Background: The effects of chemotherapy on the estimated glomerular filtration rate (eGFR) are largely based on retrospective data, relying on serum creatinine (SCr). We aim to sequentially assess the impact of antitumoral conventional therapy on eGFR equations based on SCr and cystatin C (SCysC).

Methods: This is a prospective cohort of adult patients with solid tumors exposed to conventional antitumoral treatment at the São Paulo State Cancer Institute. eGFR was calculated through race-free CKD-EPI equations based on SCr (eGFRcr), on SCysC (eGFRcys), and the combined version (eGFRcrcys) in three moments: before the initiation of treatment (T0), during treatment (TM) and after the end of antitumoral therapy (TF). SCr and SCysC were measured through certified reference materials at the University of Minnesota.

Results: 485 adult patients with solid tumors were recruited between Oct 2017 and Jan 2019. Patients were 53±15y, 62.3% female. The most frequently prescribed drugs were platinum compounds (cisplatin, carboplatin, oxaliplatin) (53.7%), paclitaxel (39.8%), and doxorubicin (27.4%). Patients received a median of 4(3-6) cycles during 105(63-148) days of chemotherapy. Median follow-up was 28(21-32) months. TM was collected 98 (84-119) days after T0, and TF was collected 124(44-204) days after the end of treatment. A significant decline in eGFR over time was observed in elderly patients, those with eGFRcrcys<60mL/min/1.73m2, reduced performance status, and exposed to cisplatin (Table).

Conclusions: Groups at higher risk of eGFR decline should be closely monitored and might be suitable candidates for prophylactic measures to minimize the impact of cancer treatment on GFR.

Funding: Government Support - Non-U.S.

Overall (N=485)	**T0**	**TM**	**TF**
eGFRcr	97 ± 18	96 ± 18	93 ± 20†¥
eGFRcys	89 ± 23	87 ± 23*	88 ± 24¥
eGFRcrcys	96 ± 20	95 ± 22*	94 ± 22†
Age > 65 years (N=96)			
eGFRcr	83 ± 15	81 ± 16	75 ± 19†¥
eGFRcys	70 ± 18	67 ± 21*	65 ± 22†
eGFRcrcys	80 ± 17	77 ± 21*	73 ± 21†¥
eGFRcrcys<60 (N=47)			
eGFRcr	71 ± 21	63 ± 19*	58 ± 17†¥
eGFRcys	57 ± 19	45 ± 15*	44 ± 10†
eGFRcrcys	65 ± 19	53 ± 15*	51 ± 11†
ECOG 2 or 3 (N=32)			
eGFRcr	89 ± 21	89 ± 23	76 ± 24†¥
eGFRcys	69 ± 23	68 ± 21	64 ± 21
eGFRcrcys	81 ± 22	80 ± 23	71 ± 21†¥
Platin (N=244)			
eGFRcr	96 ± 17	95 ± 18	91 ± 18†¥
eGFRcys	87 ± 22	83 ± 23*	85 ± 21
eGFRcrcys	94 ± 19	91 ± 21*	91 ± 19†
Cisplatin (N=94)			
eGFRcr	99 ± 16	95 ± 18*	92 ± 20†
eGFRcys	93 ± 21	82 ± 24*	84 ± 22†
eGFRcrcys	99 ± 18	90 ± 22*	90 ± 21†

eGFR: estimated glomerular filtration rate expressed in mL/min/1.73m^2; cr: creatinine; cys: cystatin C; crcys: creatinine and cystatin C; T0: sample collected before the start of antitumoral therapy; TM: sample collected in middle of treatment; TF: sample collected after the end of antitumoral treatment; ECOG: Eastern Cooperative Oncology Group performance score. Values expressed as mean ± standard deviation. Paired t-test: *p<0.05 between TM and T0; †p<0.05 between TF and T0; ¥p<0.05 between TF and TM.

FR-PO217

CT-Defined Sarcopenia and Performance of GFR-Estimating Equations in Patients with Cancer

Veronica T. Costa e Silva,[1] Meghan E. Sise,[3] Lesley A. Inker,[2] Fernando L. Strufaldi,[1] Lea Mantz,[3] Tianqi Ouyang,[3] Renato A. Caires,[1] Marcelo T. Sapienza,[1] Emmanuel A. Burdmann.[1] *[1]University of São Paulo, São Paulo, Brazil; [2]Tufts Medical Center, Boston, MA; [3]Massachusetts General Hospital, Boston, MA.*

Background: Estimated glomerular filtration rate (eGFR) equations based on serum creatinine (Scr)(eGFRcr) combined or not with serum cystatin C (Scys) present worse accuracy in patients with low body mass index (BMI). This analysis aims to evaluate the impact of sarcopenia, defined by computed tomography (CT), on the performance of the CKD-EPI equations without race based on Scr and Scys in patients with cancer.

Methods: We included adult patients undergoing treatment for solid tumors between May 2017 and October 2017 and an abdominal CT scan within 90 days of measured GFR (mGFR) using the plasma clearance of ^{51}Cr-EDTA. Body composition on an axial image at the third lumbar vertebral body level was performed using a previously validated machine-learning pipeline. Skeletal muscle index was defined as cross-sectional skeletal muscle area [cm^2] divided by the square of the patient's height [m^2]. Sarcopenia was defined using independently established cutoffs of skeletal muscle index (< 39 cm^2/m^2 for women, < 55 cm^2/m^2 for men).

Results: Of 465 included patients (50% women, mean age 58 [14] y), 34% had sarcopenia. Mean (SD) mGFR was 78.0 (22.5) ml/min/1.73 m^2. The table shows the performance of eGFR equations by sarcopenia and BMI categories. Even in patients with high BMI, those with sarcopenia had large eGFRcr overestimation (median bias: -14.7 [-18.1, -11.6] ml/min/1.73 m^2), and poor accuracy (1-P30: 41.7 [29.2, 52.8] %).

Conclusions: This is the first study to demonstrate large bias and poor accuracy for eGFRcr and eGFRcrcys in patients with CT-defined sarcopenia, demanding other instruments such as Scys or mGFR to assess GFR more accurately in this population. Overweight and obese patients might benefit from body composition analysis to unveil underlying sarcopenia.

		Bias (median) (ml/min/1.73 m^2)						
	eGFR	Overall	Sarcopenia		BMI (Kg/m^2)		BMI ≥ 25 Kg/m^2	
	Overall Group	Group	Yes	No	< 25	≥ 25	Sarcopenia: Yes	Sarcopenia: No
N (%)	465 (100%)	465 (100%)	157 (33.7%)	308 (66.3%)	157 (33.8%)	308 (66.2%)	72 (23.4%)	236 (76.6%)
eGFRcr	89.3 (21.7)	-11.5 (-12.7, -9.8)	-14.4 (-17.8, -13.2)	-8.3 (-11.0, -5.9)	-14.4 (-17.1, -12.8)	-8.0 (-10.6, -5.9)	-14.7 (-18.1, -11.6)	-5.3 (-8.0, -3.1)
eGFRcys	73.6 (25.5)	5.5 (3.6, 6.4)	4.1 (2.5, 6.5)	5.7 (3.7, 7.4)	2.4 (-1.0, 4.8)	6.3 (4.9, 8.6)	5.8 (3.1, 9.5)	6.5 (4.9, 8.8)
eGFRcrcys	82.5 (23.8)	-3.8 (-5.4, -2.6)	-5.0 (-7.5, -2.6)	-3.2 (-5.3, -1.6)	-8.1 (-11.0, -6.6)	-2.1 (-3.3, -0.7)	-2.3 (-5.5, -0.3)	-1.9 (-3.6, -0.1)
		Accuracy (1-P$_{30}$) (%)						
	eGFR	Overall	Sarcopenia		BMI (Kg/m^2)		BMI ≥ 25 Kg/m^2	
	Overall Group	Group	Yes	No	< 25	≥ 25	Sarcopenia: Yes	Sarcopenia: No
N (%)	465 (100%)	465 (100%)	157 (33.7%)	308 (66.3%)	157 (33.8%)	308 (66.2%)	72 (23.4%)	236 (76.6%)
eGFRcr	89.3 (21.7)	26.5 (22.2, 30.1)	42.0 (34.4, 49.6)	18.5 (14.3, 23.1)	35.7 (27.4, 42.7)	21.8 (17.2, 26.3)	41.7 (29.2, 52.8)	15.7 (10.6, 19.9)
eGFRcys	73.6 (25.5)	15.3 (11.8, 18.5)	20.4 (14.0, 26.8)	12.7 (8.8, 16.2)	15.9 (9.6, 21.7)	14.9 (10.7, 18.8)	20.8 (11.1, 29.2)	13.1 (8.9, 17.3)
eGFRcrcys	82.5 (23.8)	11.0 (8.0, 13.8)	14.0 (8.3, 19.1)	9.4 (6.2, 12.3)	15.3 (9.6, 20.4)	8.8 (5.5, 11.7)	12.5 (4.2, 19.4)	7.6 (3.8, 10.6)

Data are presented with 95% confidence intervals. Bias was calculated as the median value of (mGFR-eGFR). 1-P$_{30}$ is the percentage of estimates that differed by more than 30% from the measured GFR. Non-overlapping confidence intervals indicate statistical significance. eGFR: estimated glomerular filtration rate using the race-free CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, eGFRcr: eGFR based on the serum level of creatinine (SCr); eGFRcys: based on the serum level of cystatin C (SCys); eGFRcrcys: eGFR based on SCr combined with Scys. SCr and SCys were measured through certified reference materials. Sarcopenia: SMI < 39 39 cm^2/m^2 for men and < 55 cm^2/m^2 for women; SMI: skeletal muscle index, calculated by dividing the skeletal muscle cross-sectional area by the patient's height squared. BMI: body mass index.

FR-PO218

Cystatin C as a Superior Biomarker for Melphalan Dosing in Patients with Multiple Myeloma Undergoing Autologous Stem-Cell Transplant: A Single-Center Retrospective Analysis

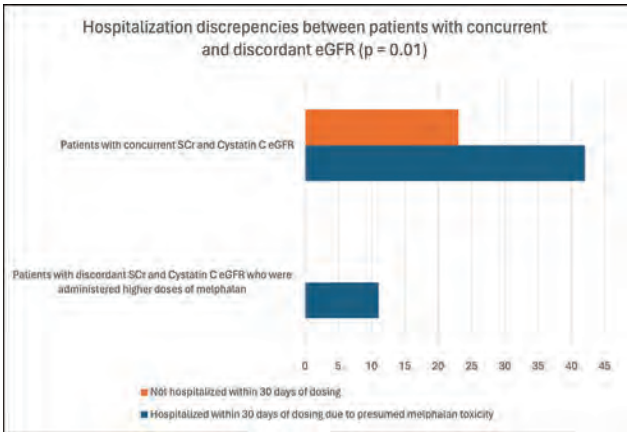
Benjamin R. Teruel, Elaine Park, Blaithin A. McMahon. *Medical University of South Carolina, Charleston, SC.*

Background: Accurate dosing of melphalan is critical for patients with multiple myeloma undergoing autologous stem cell transplant (ASCT). Traditionally, serum creatinine (SCr) is used to estimate glomerular filtration rate (GFR) for melphalan dosing calculations. This study seeks to evaluate the effectiveness of Cystatin C in predicting appropriate melphalan induction doses compared to SCr in patients with multiple myeloma undergoing ASCT.

Methods: A retrospective cohort study was conducted on 76 patients diagnosed with multiple myeloma who received melphalan conditioning before ASCT. Melphalan dosing in all patients was based on pre-transplant eGFR calculated from SCr. This dosing is 200 mg for eGFR >50 mL/min/1.73m^2, 140 mg for eGFR <50. Patient GFR was estimated using Cystatin C levels immediately prior to transplantation. The primary outcome was the incidence of melphalan overdosing, defined as those cases that exceeded the therapeutic dose, due to GFR estimation discrepancies between the two biomarkers and the presence of a hospitalization related to melphalan toxicity within 30 days of Melphalan therapy.

Results: Of the 76 patients, 11 (14.5%) were identified as having received a higher dose of melphalan than anticipated when GFR was estimated using SCr compared to Cystatin C. These patients exhibited higher incidences of treatment-related toxicity due to diarrhea, mucositis, and/or fever and resulted in hospitalization in 100% of patients with melphalan overdose. Of note, 23 patients (35%) of patients with appropriate melphalan dosing as per SCr eGFR and Cystatin C eGFR did not experience toxicity (p = 0.01).

Conclusions: While melphalan is associated with a high baseline toxicity, use of Cystatin C in place of SCr to estimate GFR could significantly decrease the incidence of melphalan toxicity. Further prospective studies are warranted.



FR-PO219

Impact of CKD Stages Based on Measured vs. Estimated Glomerular Filtration Rate on the Overall Survival of Patients with Cancer

Rayra G. Ribeiro,[1] Abhijat Kitchlu,[2] Lesley A. Inker,[3] Veronica T. Costa e Silva,[1] Renato A. Caires,[1] Elerson Costalonga,[1] Marcelo T. Sapienza,[1] Emmanuel A. Burdmann.[1] *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]University of Toronto, Toronto, ON, Canada; [3]Tufts University, Medford, MA.*

Background: Data assessing the impact of chronic kidney disease (CKD) stages on the overall survival (OS) of cancer patients are largely retrospective and rely on the serum level of creatinine (SCr) to estimate the glomerular filtration rate (eGFR). We aimed to evaluate the impact of different CKD stages on the OS of patients with cancer admitted for treatment using measured GFR (mGFR) and eGFR.

Methods: This is a prospective cohort of adult patients with solid tumors (diagnosed in the last 90 days) initiating treatment at the Sao Paulo State Cancer Institute. mGFR was determined by plasma clearance of ^{51}Cr-EDTA. eGFR was calculated using the 2021 CKD-EPI equations, based on SCr (eGFrcr), Scys (eGFRcys), and the combined version (eGFRcrcys). CKD stages were classified according to the KDIGO guidelines using mGFR, eGFRcr, eGFRcys, and eGFRcrcys.

Results: A group of 1,011 patients recruited from April 2015 to September 2017 were included for analysis and censored in March 2023. Patients were 50.6 ±13 y, 50.7% female. The most common cancer sites were breast (22.4%), gastrointestinal (21.9%), and male genital (21.2%); 15.5% had metastasis. ECOG 0, 1, and 2&3 comprised 64%, 32%, and 6% of patients, respectively. Time of follow-up was 5.7 (2.5-6.5) y; overall mortality was 27.4%. In the adjusted Cox regression model, stage 3b CKD based on mGFR and eGFRcys and stages 3a and 3b based on eGFRcys were associated with worse OS. CKD stages based on eGFRcr were not associated with OS (Table).

Conclusions: This is the first study assessing the impact of CKD stages on the OS of patients with solid tumors incorporating mGFR and SCys. Our results endorse the utility of eGFRcys and mGFR as valuable instruments in the kidney care of cancer patients.

Table

Variables	P value	Hazard Ratio (95% Confidence interval)
CKD stage based on mGFR		
Stage 2 or greater *	0.042**	1.51 (1.09 – 2.11)
Stage 3a	0.014	1.24 (0.77 – 2.00)
Stage 3b	0.38	
CKD stage based on eGFRcr		
Stage 2 or greater*	0.67**	1.13 (0.69 – 1,84)
Stage 3a	0.62	1.34 (0.65 – 2.77)
Stage 3b	0.43	
CKD stage based on eGFRcys		
Stage 2 or greater *	< 0.001**	
Stage 3a	<0.001	1.63 (1.22 – 2.18)
Stage 3b	0.008	1.63 (1.13 – 2.34)
CKD stage based on eGFRcr-cys		
Stage 2 or greater *	0.10**	
Stage 3a	0.03	1.50 (1.03 – 2.17)
Stage 3b	0.53	1.18 (0.71 – 1.95)

Models were adjusted for age, sex, cancer site, metastasis, ECOG, and C-reactive protein. *Reference group. **p value for the overall group. CKD: chronic kidney disease; GFR: glomerular filtration rate; eGFR: estimated GFR using the race-free CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation; eGFRcr: eGFR based on the serum level of creatinine (SCr); eGFRcys: based on the serum level of cystatin C (SCys); eGFRcr-cys: eGFR based on SCr combined with SCys. SCr and SCys were measured through certified reference materials. CKD Stage 2 or greater: GFR>60ml/min/1.73m²; CKD stage 3a: GFR 59-45ml/min/1.73m²; CKD stage 3b: GFR <45ml/min/1.73m².

FR-PO220

Temporal and Apparent Decrease of Creatinine-Derived eGFR in the Patients with Cancer Treated with Poly ADP-Ribose Polymerase Inhibitors

Shiho Morimoto,[1,3] Yasuhiro Onishi,[1] Saori Ariki,[2] Hiroshi Morinaga,[1] Katsuyuki Tanabe,[1] Haruhito A. Uchida,[1] Yoshito Zamami,[2] Hisashi Masuyama,[5] Motoo Araki,[4] Jun Wada.[1] *[1]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [2]Department of Pharmacy, Okayama University Hospital, Okayama, Japan; [3]Department of internal medicine, Tsuyama Chuo Hospital, Tsuyama, Japan; [4]Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [5]Department of Obsterics and Gynecology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: Poly ADP-ribose polymerase (PARP) inhibitors, novel molecular targeted drugs used mainly for Breast cancer gene (BRCA) mutation-positive tumors, have been reported to cause an increase in serum creatinine (Cr). It has been reported that PARP inhibitors, which are molecularly targeted drugs, have an off-target effect on tubular transporters (MCT2, MATE1) and suppress Cr secretion into the urine, leading to an increase in serum Cr independent of glomerular filtration rate. With this study, we aimed to assess the relationship between renal function and PARP inhibitors.

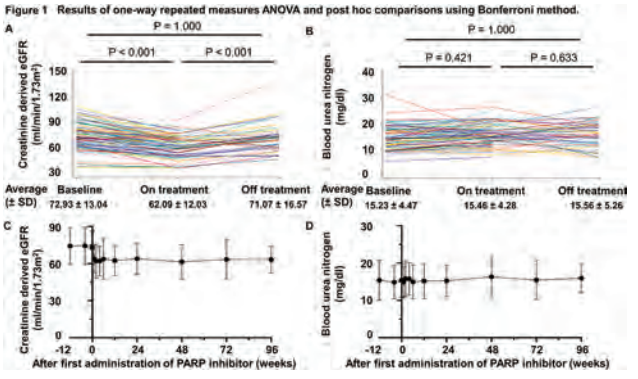
Methods: We retrospectively recruited the patients attending Okayama University Hospital who received PARP inhibitors for the first time from April 2018 to December 2022. We compared the levels of BUN, serum Cr, and Cr-derived eGFR at baseline, on treatment, and off treatment using one-way repeated measures ANOVA and post-hoc analyses.

Results: Of 85 patients, with an average age of 60.7±12.5 years and 96.5% female, the mean eGFR was calculated as 72.9±13.1 ml/min/1.73m². eGFR significantly decreased to 62.6±12.3 one month after starting PARP inhibitor (P<0.001), but improved to 71.6±16.6 one month after discontinuation (P<0.001) and there was no significant increase in BUN (Figure 1A, B). Until 96 weeks, creatinine-derived-eGFR remained unchanged from one month after initiation of PARP inhibitor (Figure1C). Multiple regression analysis showed a negative correlation between post-treatment eGFR decline and starting eGFR (P<0.001).

Conclusions: The present study showed that the increase in serum Cr after the PARP inhibitor was temporary and did not increase BUN, suggesting the apparent change in eGFR.

Funding: Government Support - Non-U.S.

Figure 1 Results of one-way repeated measures ANOVA and post hoc comparisons using Bonferroni method.



FR-PO221

Aberrant SIX2 Expression in Neonatal Kidney Stem Progenitor Cells Is Sufficient to Drive Malignant Transformation

Hildo C. Lantermans,[1] Willem Kraan,[1] Lambertus P. Van den Heuvel,[2] Fanny O. Arcolino,[1] Elena Levtchenko.[1] Paediatric Nephrology. *[1]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [2]Radboud Universitair Medisch Centrum, Nijmegen, Netherlands.*

Background: Wilms tumor (WT) is the most common paediatric renal tumor with an annual incidence of 4 to 10 per million children. WT is thought to arise in renal progenitor cells as it resembles nephrogenic cells both morphologically and transcriptionally. Although the underlying genetic causes of WT are diverse, *in vitro* models to study WT are largely restricted to a few WT cell lines which do not fully represent the diversity observed in patients. In order to expand the *in vitro* models of WT and improve the knowledge on its molecular pathogenesis we investigated whether we could induce malignant transformation of healthy non-immortalized neonatal kidney stem progenitor cells.

Methods: We have previously isolated and characterized kidney stem progenitor cells from the urine of preterm neonates (nKSPC). We transduced nKSPC with retroviral particles encoding for *SIX2*, a transcription factor that is crucial during nephrogenesis and aberrantly upregulated in most WT cases. We monitored changes in cell growth and viability by flow cytometric analysis and investigated molecular reprogramming on both the RNA and protein level.

Results: Intriguingly, overexpression of solely SIX2 in a minor fraction of nKSPC (~5 %) provided the overexpressing cells with a growth advantage that was sufficient to outcompete most non-transduced cells within two weeks. Moreover, the growth of SIX2 overexpressing nKSPC is no longer contact-inhibited and their cellular morphology resembles that of primary WT cells. Whereas the parental nKSPC maintain self-renewing for more than 20 passages, SIX2 overexpressing nKSPCs grow rapidly up to more than 30 passages. On both protein and RNA level we show that SIX2 overexpression results in downregulation of Wnt signaling with concurrent strong upregulation of the oncogene Myc and the cell cycle regulator cyclin D1, which have both been implied in WT pathogenesis.

Conclusions: We show that nKSPCs can serve as a valuable tool to establish *in vitro* WT models and to study WT pathogenesis. As proof of principle we show that overexpression of a single gene involved in WT pathogenesis, *SIX2*, is sufficient to drive malignant transformation and immortalization of nKSPCs.

Funding: Government Support - Non-U.S.

FR-PO222

Influence of the Extracellular Matrix on the Tumor Microenvironment and Cancer Progression

Astgik Petrosyan,[1,2] David S. Koos,[2] Matthew E. Thornton,[1] Paola Aguiari,[2] Valentina Villani,[2] G. Esteban Fernandez,[2] Brendan Grubbs,[1] Roger E. De Filippo,[2] Laura Perin.[1,2] *[1]University of Southern California, Los Angeles, CA; [2]Children's Hospital Los Angeles, Los Angeles, CA.*

Background: This study explores how the extracellular matrix (ECM) in the tumor microenvironment influences cell behavior in Wilms Tumor (WT), a pediatric kidney cancer. We compare the effects of 2D cultures and cancerous versus normal kidney ECM on cellular activities using decellularization techniques, two-photon excited fluorescence (TPEF) microscopy, and transcriptomics.

Methods: We optimized the decellularization technique for normal kidney and WT samples and characterized the decellularized matrices (dECM) with second-harmonic generation (SHG) microscopy (up to 700um in depth) and immunohistochemistry. Protein expression in WT dECM was compared to normal kidney dECM using Oncology Arrays. Bulk transcriptomics was performed on WT and normal human kidney (hFK) nephron progenitors cultured in 2D and on normal kidney and WT dECM scaffolds for 21 days.

Results: Imaging of tumor ECM revealed structural differences, with denser, elongated fibers in the outer layers and mesh-like structures deeper inside. Tumor ECM showed higher expression of oncoproteins (e.g., CEA, PSA-ACT), receptors (e.g., IGF 1R, IGF-II), and markers of cell adhesion and migration (e.g., PDGFR alpha). Cells cultured on tumor dECM exhibited upregulation of genes related to immune response, cancer progression, and metastasis, whereas 2D cultures primarily showed genes involved in basic cellular processes. Cellular behavior and transcriptomic profiles were significantly altered when cultured on tumor versus normal ECM, with tumor ECM promoting proliferation pathways and inhibiting differentiation pathways. Normal cells seeded on tumor ECM activated cancer development pathways and inhibited apoptotic pathways.

Conclusions: This study underscores the critical role of the ECM in influencing cancer cell behavior. These findings are crucial for developing physiologically relevant in vitro tumor models and identifying new therapeutic targets that focus on the ECM in cancer treatment.

Funding: Private Foundation Support

FR-PO223

P-cresyl Sulfate and Indoxyl Sulfate: Uremic Toxins Implicated in the Progression of Colorectal Cancer in Individuals with CKD

Mariadelina Simeoni,[1,2] Rossella Di Paola,[1] Francesco Trevisani,[3] Marianna Abate,[1] Alessandra Perna,[1] Silvia Zappavigna,[1] Alessia M. Cossu,[1] Marco Bocchetti,[1] Federica Melisi,[4] Clara Iannarone,[4] Lucia S. Pasquale,[1] Marianna Scrima,[4] Michele Caraglia.[1,4] *[1]Universita degli Studi della Campania Luigi Vanvitelli, Caserta, Italy; [2]IRCCS Ospedale San Raffaele, Milano, Italy; [3]San Raffaele Scientific Institute, Milan, Italy; [4]Biogem Scarl, Ariano Irpino, Italy.*

Background: Patients with chronic kidney disease (CKD) have a higher incidence of colorectal cancer (CRC) and a significantly poorer prognosis compared to the general population. The reasons for this are not yet understood. One common issue in CKD patients is gut dysbiosis, which is marked by an excess of aerobic bacteria in the gut microbiota. Their metabolic activity results mainly in two metabolites: P-cresyl sulfate (P-cs) and Indoxyl sulfate (IS). Many studies indicate that these metabolites are instrumental in triggering various cancer-causing processes, such as chronic intestinal inflammation and oxidative stress. Given the cancer-promoting effects of P-cs and IS in CKD patients, it appears plausible that these toxins could play a significant role in the advancement of CRC in these individuals.

Methods: To assess the impact of IS and P-cs on three CRC cell lines (Hct116, LoVo, and HT-29), we conducted a range of in vitro experiments. We examined various concentrations of IS and P-cs and used a WST 8 to measure their influence on cancer cell proliferation. We subsequently applied the Wound Healing Assay and invasion assay to evaluate the migratory and invasive abilities of CRC cells after exposure to the toxins. To identify the pathways altered by the toxins, we performed qPCR and ROS assay experiments to assess the inflammatory pathway and the production of ROS.

Results: We noted an enhancement in cell growth following the treatment with toxins. Moreover, the concentrations of IS and P-cs triggered a significant escalation in cell migration and invasion. An examination of the expression of genes linked to the inflammatory process (INOS and IL-6) revealed an increased regulation of the latter across all cell lines. Lastly, a rise in oxidative stress was also detected in the cells treated with toxins when compared to the control group.

Conclusions: From our findings, it seems that IS and P-cs significantly contribute in vitro to the advancement of CRC. Future investigations in translational studies are needed to explore whether these conclusions can be extended to CKD patients with CRC, also exploring potential new target therapies and diagnostic tools

Funding: Government Support - Non-U.S.

FR-PO224

SGLT2 Inhibitor Use and Kidney Outcomes in Persons Receiving Cisplatin

Abiodun B. Idowu,[1] Kevin Bryan Lo,[4] Roy O. Mathew,[5,6] Pranav S. Garimella,[2] Janani Rangaswami.[3,7] *[1]Jefferson Einstein Philadelphia Hospital, Philadelphia, PA; [2]University of California San Diego Division of Nephrology-Hypertension, La Jolla, CA; [3]Division of Nephrology, Veterans Affairs Medical Center, Washington, DC; [4]Brigham and Women's Hospital Division of Cardiovascular Medicine, Boston, MA; [5]Loma Linda University, Loma Linda, CA; [6]Loma Linda VA Healthcare System, Loma Linda, CA; [7]The George Washington University, Washington, DC.*

Background: SGLT2i are protective against progressive kidney function loss, yet their role in preventing drug toxicity is unknown. We sought to determine safety of concurrent SGLT2i use with cisplatin, a chemotherapy with significant nephrotoxicity

Methods: A Retrospective analysis of patients ages 18–65 years treated with cisplatin from 1st January 2000 to 31st May 2023 in TriNetX database. Patients were divided into 2 groups based on SGLT2i use (first-time exposure to SGLT2i within 3 months before or up to 3 months after first cisplatin administration). Cohorts were balanced via nearest-neighbor 1:1 propensity-score matching (PSM). Survival analysis was done via Kaplan-Meier curves with log-rank tests over a 1-year follow-up

Results: After PSM, we identified 150 patients per cohort (Fig 1). At 1 year, there was a significant decline of eGFR by 17.1±4.16 mL/min/1.73m^2 in the SGLT2i group and 16.3±3.61 mL/min/1.73m^2 in the non-SGLT2i group. There were fewer MAKE event rates, as well as its components (AKI, RRT, and mortality) in the SGLT2i group vs non SGLT2i, but the differences were not statistically significant (HR 0.88, 95%CI: 0.58-1.34, p=0.553) (Fig 2)

Conclusions: SGLT2i use during cisplatin therapy was not associated with increased AKI or MAKE risk. Prospective studies are needed to assess the nephroprotective potential of SGLT2i while on cisplatin therapy

Figure 2: Characteristics of cisplatin-treated cancer patients before and after propensity matching

	Before PSM			After PSM		
	SGLT2i (n = 154)	Non-SGLT2i (n = 25016)	Std. Diff.	SGLT2i (n = 150)	Non-SGLT2i (n = 150)	Std. Diff.
Demographics						
Age (in years)	54.7 ± 6.6	45.9 ± 12.5	0.885	54.6 ± 6.7	54.9 ± 5.9	0.038
Male	114 (74.0%)	13678 (55.0%)	0.406	112 (74.7%)	110 (73.3%)	0.030
White	74 (48.1%)	13523 (54.4%)	0.117	73 (48.7%)	66 (44.0%)	0.094
Black/African American	10 (6.5%)	2063 (8.3%)	0.069	10 (6.7%)	10 (6.7%)	0.000
Asian	21 (13.6%)	1516 (6.1%)	0.255	21 (14.0%)	22 (14.7%)	0.019
Co-morbidities						
Cerebrovascular accident	10 (6.5%)	154 (0.6%)	0.321	10 (6.7%)	10 (6.7%)	0.000
COPD	10 (6.5%)	966 (3.9%)	0.118	10 (6.7%)	10 (6.7%)	0.000
Atrial Fibrillation	10 (6.5%)	330 (1.3%)	0.269	10 (6.7%)	10 (6.7%)	0.000
History of myocardial infarction	10 (6.5%)	216 (0.9%)	0.302	10 (6.7%)	10 (6.7%)	0.000
Tobacco smoking	31 (20.1%)	3034 (12.2%)	0.217	30 (20.0%)	22 (14.7%)	0.141
Prior CABG	10 (6.5%)	158 (0.6%)	0.320	10 (6.7%)	10 (6.7%)	0.000
Type 2 Diabetes mellitus	118 (76.6%)	1640 (6.6%)	2.019	114 (76.0%)	122 (81.3%)	0.130
Connective tissue disease	10 (6.5%)	150 (0.6%)	0.323	10 (6.7%)	10 (6.7%)	0.000
Hypertension	83 (53.9%)	4693 (18.9%)	0.782	80 (53.3%)	78 (52.0%)	0.027
Malignancy types						
Lung cancer	31 (20.1%)	2371 (9.5%)	0.302	29 (19.3%)	27 (18.0%)	0.034
Gastric cancer	10 (6.5%)	259 (1.0%)	0.289	10 (6.7%)	0 (0)	0.378
Pancreatic cancer	10 (6.5%)	257 (1.0%)	0.290	10 (6.7%)	10 (6.7%)	0.000
Bladder cancer	10 (6.5%)	1159 (4.7%)	0.080	10 (6.7%)	10 (6.7%)	0.000
Breast cancer	10 (6.5%)	440 (1.8%)	0.239	10 (6.7%)	10 (6.7%)	0.000
Ovarian cancer	10 (6.5%)	932 (3.7%)	0.125	10 (6.7%)	10 (6.7%)	0.000
Testicular cancer	10 (6.5%)	2693 (10.8%)	0.155	10 (6.7%)	10 (6.7%)	0.000
Lymphoproliferative cancer	10 (6.5%)	1169 (4.7%)	0.078	10 (6.7%)	10 (6.7%)	0.000
Skin cancer	10 (6.5%)	1165 (4.7%)	0.079	10 (6.7%)	13 (8.7%)	0.075
Radiation therapy	57 (37.0%)	8454 (34.0%)	0.063	55 (36.7%)	63 (42.0%)	0.109
Medications						
Antiarrhythmics	81 (52.6%)	11811 (47.5%)	0.102	79 (52.7%)	74 (49.3%)	0.067
Anticoagulants	71 (46.1%)	9674 (38.9%)	0.146	67 (44.7%)	70 (46.7%)	0.040
Aspirin	32 (20.8%)	1564 (6.3%)	0.433	31 (20.7%)	20 (20.0%)	0.017
Angiotensin II inhibitor	44 (28.6%)	945 (3.8%)	0.714	40 (26.7%)	35 (23.3%)	0.077
Metformin	94 (61.0%)	691 (2.8%)	1.601	90 (60.0%)	90 (60.0%)	0.000
GLP1 analogue	10 (6.5%)	50 (0.2%)	0.355	10 (6.7%)	10 (6.7%)	0.000
Diuretics	49 (31.8%)	2845 (11.4%)	0.511	48 (32.0%)	42 (28.0%)	0.087
Proton pump inhibitors	65 (42.2%)	5105 (20.5%)	0.481	63 (42.0%)	61 (40.7%)	0.027
HMG-CoA reductase inhibitors	88 (57.1%)	1706 (6.9%)	1.280	84 (56.0%)	85 (56.7%)	0.015
Insulin	73 (48.8%)	1967 (7.9%)	0.988	70 (46.7%)	71 (47.3%)	0.013
DPP-4 inhibitors	28 (18.2%)	127 (0.5%)	0.637	27 (18.0%)	25 (16.7%)	0.035
Laboratory						
LVEF (%)	52.9 ± 10.5	58.8 ± 9.9	0.580	52.9 ± 10.5	52.0 ± 7.8	0.097
Hemoglobin A1c (%)	7.9 ± 1.6	6.4 ± 1.9	0.843	7.9 ± 1.6	8.2 ± 2.2	0.172
Creatinine (mg/dL)	0.8 ± 0.3	0.8 ± 1.4	0.008	0.8 ± 0.3	0.8 ± 0.2	0.042
eGFR (mL/min/1.73m^2)	102.1 ± 36.9	96.9 ± 29.5	0.155	104 ± 37.7	97 ± 26.6	0.201
LDL (mg/dL)	96.1 ± 34.5	104.3 ± 40.4	0.218	95.0 ± 34.5	92.1 ± 33.5	0.085
Hemoglobin (g/dl)	12.7 ± 2.4	12.5 ± 2.9	0.085	12.7 ± 2.4	12.5 ± 2.0	0.096
BMI (kg/m^2)	28.1 ± 6.2	27.2 ± 6.8	0.154	28.1 ± 6.2	28.4 ± 5.4	0.049

GLP1 = Glucagon-like peptide-1, DPP4 = Dipeptidyl-peptidase 4 inhibitors, COPD = Chronic Obstructive Pulmonary Disease, LVEF = Left ventricular ejection fraction, eGFR = estimated Glomerular Filtration Rate, CABG = Coronary Artery Bypass Graft surgery

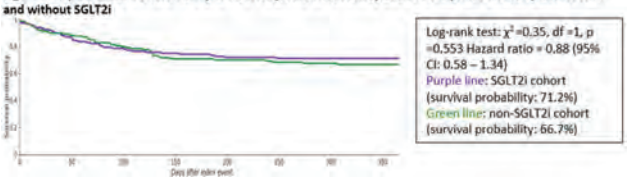
Patient characteristics

Table 1: Comparison of outcomes in cisplatin-treated cancer patients with and without SGLT2 inhibitors

	Cisplatin + SGLT2i (n/N)	Cisplatin - SGLT2i (n/N)	aOR (95% CI)	p
Acute kidney injury	19 / 135 (14.1%)	22 / 133 (16.5%)	0.83 (0.42 – 1.61)	0.575
Renal Replacement Therapy	19 / 130 (14.6%)	24 / 126 (19.0%)	0.73 (0.38 – 1.41)	0.343
All-cause mortality	10 / 150 (6.7%)	10 / 150 (6.7%)	1.0 (0.40 – 2.48)	1.000
MAKE	41 / 150 (27.3%)	46 / 150 (30.7%)	0.85 (0.52 – 1.40)	0.525

*n indicates the number of events; N indicates the total population at risk (patients with outcomes before cisplatin administration not included)

Figure 1: Kaplan-Meier Survival Analysis from Major Adverse Kidney Events in cisplatin-treated patients with and without SGLT2i



Kidney Outcomes of concurrent SGLT2i and Cisplatin use

FR-PO225

Incidence of Cancer in People with CKD: A Systematic Review

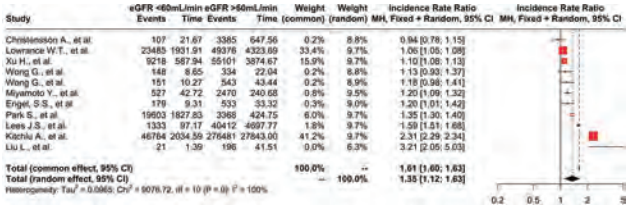
Benjamin M. Elyan,[1,2] Beatrix Tan,[3] Emilie Lambourg,[4] Robert J. Jones,[5,1] David A. Mcallister,[6] Ninian N. Lang,[1,2] Patrick B. Mark,[1,2] Jennifer S. Lees,[1,2] Samira Bell.[3,4] *[1]University of Glasgow College of Medical Veterinary and Life Sciences, Glasgow, United Kingdom; [2]Queen Elizabeth University Hospital, Glasgow, United Kingdom; [3]Ninewells Hospital and Medical School, Dundee, United Kingdom; [4]University of Dundee Division of Population Health and Genomics, Dundee, United Kingdom; [5]Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; [6]University of Glasgow School of Health and Wellbeing, Glasgow, United Kingdom.*

Background: Cancer incidence in people with chronic kidney disease (CKD) who do not require kidney replacement therapy remains inadequately characterised. This systematic review aimed to estimate cancer risk in people with CKD.

Methods: A systematic search of three online bibliographic databases until January 17, 2023, identified studies reporting cancer incidence in CKD cohorts (PROSPERO CRD42022359690). Meta-analyses using inverse variance method compared incidence rates in individuals with low eGFR (<60mL/min/1.73m2) with available cohorts with normal eGFR (≥60mL/min/1.73m2 or both 60-89 and ≥90mL/min/1.73m^2) for all cancers and site-specific cancers. Multiple meta-regression analyses explored associations of eGFR and age.

Results: In 27 studies (5,519,778 people with CKD), from 10 countries spanning 2009-2022, incidence rates of cancer were associated with worse CKD severity. Incidence rate ratio (IRR) comparing people with an eGFR <60mL/min/1.73m2 to ≥60mL/min/1.73m2 was 1.35 [95% CI:1.12-1.63, p=0.002, I^2=99.9%]. People with eGFR <60mL/min/1.73m2 were at elevated rate of cancer compared with eGFR ≥90mL/min/1.73m^2 (IRR 1.48 [95% CI:1.04-2.10, p=0.03, I^2=100%]) and those with eGFR 60-89mL/min/1.73m^2 (IRR 1.21 [95% CI:1.11-1.33, p<0.01, I^2=92%]). Age was associated with increased cancer incidence (β=0.31, p=0.02) on multiple meta-regression analysis. There was no association between site-specific cancer incidence in CKD patients, but these had wide confidence intervals.

Conclusions: Individuals with CKD have an elevated incidence of cancer, with increasing age contributing to this association. These findings emphasise the importance of investigating whether CKD independently elevates cancer risk, building evidence for tailored cancer screening into CKD patient care.



Forest plot showing the pooled incidence rate ratios for people with eGFR <60mL/min/1.73m2 vs ≥60mL/min/1.73m2

FR-PO226

Liquid Silicone Injections: An Infrequent Cause of CKD and Kidney Stones

Ivette Gomez, Anu Sharma, Olesya Ilkun. *University of Florida, Gainesville, FL.*

Introduction: The use of body-modifying cosmetic injections have increased over the last decades. Here we present an infrequent case of severe kidney-related complications due to hypercalcemia arising years after silicone injections.

Case Description: A 44-year-old man with stage 4 chronic kidney disease, hypertension and human immunodeficiency virus on antiretroviral therapy, was found to have acute kidney injury (AKI). The patient's creatinine rose to 3.72 mg/dL from baseline of 2.5 mg/dL. Serum calcium was elevated at 13.5 mg/dL and ionized calcium at 1.79 mmol/L. Parathyroid hormone was at 20 pg/mL, relatively suppressed for CKD4. CT of abdomen and pelvis showed bilateral kidney stones, some larger than 2 cm, and extensive subcutaneous calcifications in the bilateral flanks, proximal thighs and buttocks (Figure 1). The patient disclosed that he had multiple silicone injections in those areas in 2001. His AKI and hypercalcemia improved with intravenous fluid, denosumab, and calcitonin. 25-hydroxyvitamin D, QuantiFERON gold, serum free light chain ratio, and SPEP were unremarkable. 1,25-dihydroxyvitamin D was at the upper limit of normal at 69.2 pg/mL and PTH-r peptide was mildly elevated at 5.8 pmol/L. PET-CT whole body was negative for occult malignancy. Unfortunately, the patient did not follow-up for confirmatory tissue biopsy or to receive outpatient denosumab.

Discussion: We present a rare case of advanced CKD and extensive nephrolithiasis in the setting of hypercalcemia due to likely silicone injection-induced granulomatosis. Cosmetic silicone injections are not approved by the U.S. Food and Drug Administration for any anatomic site, and have been associated with 0.2 to 1% risk of granuloma formation, typically associated with 1,25 vitamin D mediated hypercalcemia. Although tissue biopsy was not obtained, the work-up for other causes of hypercalcemia was negative. There is no effective treatment to date. If silicone cannot be removed, the treatment focuses on reduction of hypercalcemia and removal of kidney stones.

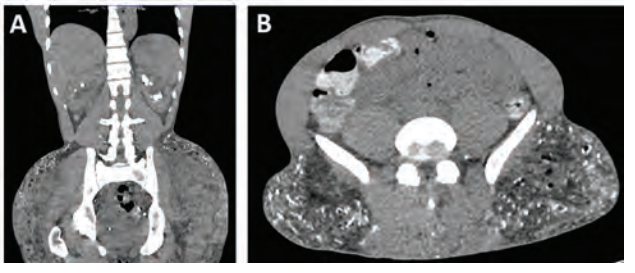


Figure 1. CT scan abdomen and pelvis (A) showing kidney stones and axial view (B) showing extensive bilateral calcifications of the buttocks

FR-PO227

Renal Tubular Calcium Oxalate Crystals Induce Mitochondrial Damage and cGAS-STING Activation

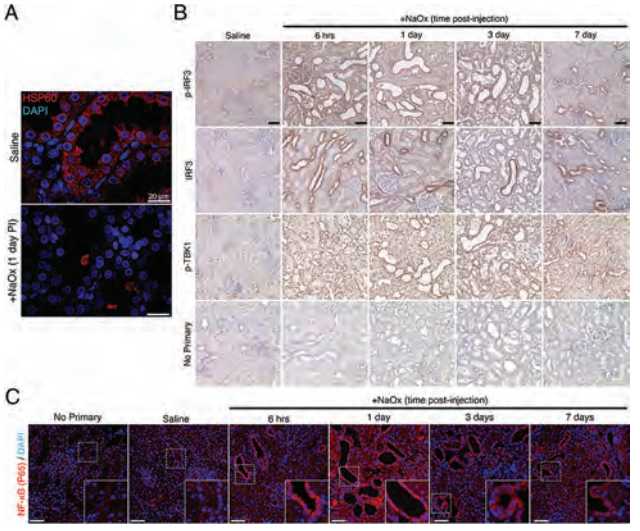
Elizabeth H. Sharpe, Shaina M. Sharma, Jacob A. Torres, Thomas Weimbs. *University of California Santa Barbara, Santa Barbara, CA.*

Background: The kidney is subject to the formation of microscopic calcium oxalate (CaOx) crystals which can cause damage. Previous *in vitro* studies indicate that CaOx-induced damage involves mitochondrial dysfunction, but the specific pathways have yet to be elucidated. The cGAS-STING pathway is a key regulator of the inflammatory response and fibrosis in acute kidney injury (AKI), and activation by cytosolic dsDNA leads to the production of pro-inflammatory cytokines. Activated STING recruits kinases TBK1 and IKK, resulting in activation of transcription factors IRF3 and NF-κB. Activation is triggered by both foreign and self-DNA, including mitochondrial DNA released after mitochondrial damage. Here, we found that mitochondrial damage and activation of the cGAS-STING pathways occurs following acute CaOx crystal deposition in wild type (WT) rats.

Methods: WT S.D. rats received 1 mg/kg sodium oxalate (NaOx) by intraperitoneal injection to induce acute CaOx crystal formation. Immunohistochemical and immunofluorescence staining was used to visualize protein localization in kidney sections at various time points post-injection.

Results: NaOx administration led to decreased mitochondrial HSP60 in renal epithelial cells (**Figure 1A**), indicative of mitochondrial damage. NaOx also promoted activation of downstream STING targets, including an increase in p-TBK1 and p-IRF3 (**Figure 1B**), as well as nuclear translocation of NF-κB (**Figure 1C**).

Conclusions: CaOx crystals promote mitochondrial damage and subsequent activation of the cGAS-STING pathway. Persistent CaOx crystal deposition as a form of subclinical AKI throughout life may drive renal functional decline.



Staining of kidneys from WT S.D. rats at indicated timepoints post-injection with NaOx or saline control (**A**) IF staining of HSP60 (**B**) IHC staining of p-IRF3, IRF3, and p-TBK1 (**C**) IF staining of of NF-κB

FR-PO228

Genotyping Patients with Medullary Sponge Kidney (MSK)

Ahmed E. Ali,[1] Andrea G. Cogal,[1] Barbara M. Seide,[1] David J. Sas,[1] Peter C. Harris,[1] John C. Lieske,[1] David S. Goldfarb.[2] Rare Kidney Stone Consortium. *[1]Mayo Clinic Minnesota, Rochester, MN; [2]New York University, New York, NY.*

Background: The underlying genetics of MSK risk are uncertain, with evidence of increased prevalence of radiologic abnormalities in first-degree relatives of affected patients, *GDNF* was suggested as causative in a few cases. MSK has a characteristic appearance on excretory urogram, but this imaging is now rarely used; ultrasounds and CT scans are often read as "suggestive of MSK" when nephrocalcinosis is observed. We genetically screened a cohort of patients with a clinical diagnosis of MSK to determine if any had a possible monogenic cause.

Methods: We solicited research participants from a Facebook page (~3000 members): "Medullary Sponge Kidney Awareness, Support, and Research". Participants self-identify as having MSK; we did not require radiologic confirmation. 98 patients replied via email and were sent consent forms and kits for returning saliva to Mayo Clinic. The study was approved by Mayo Clinic IRB. The cohort was screened by targeted next generation sequencing with a panel consisting of 160 known and candidate monogenic urinary stone disease (MUSD) genes. Clinical information from participants was collected.

Results: 96 individuals from 87 families were screened. The participants were 94% women, average age 49 y. We identified 9 pedigrees with single pathogenic/likely pathogenic (P/LP) variants in genes associated with monoallelic disease: *ATP6V0A4, CASR, PKHD1(2), SLC2A9, SLC34A1(2), SLC34A3(2)*. An additional 5 pedigrees were heterozygous for P/LP variants in 4 genes associated with biallelic MUSD and 24 pedigrees were heterozygous for variants of unknown significance (VUS) in 16 MUSD genes. Only 1 individual carried the *GDNF* promoter variant, that we classified as a VUS given its normal population frequency.

Conclusions: We did not identify one known or candidate MUSD gene to explain a significant proportion of the screened MSK cases (including *GDNF*), but 10.3% had a P/LP variant in a monoallelic MUSD gene, many associated with nephrocalcinosis, that may explain or partially explain the MSK phenotype. The finding of P/LP variants in recessive MUSD genes and many other MUSD gene VUS suggest that MSK individuals may be enriched for risk factor variants. MSK is a complex disease with multiple genetic and environmental inputs. This study supports genetic screening of patients with a clinical MSK diagnosis to identify monogenic causes of nephrocalcinosis.

Funding: NIDDK Support

FR-PO229

Long-Term Efficacy and Safety of Lumasiran in Patients with Primary Hyperoxaluria Type 1: Final Analysis of the ILLUMINATE-A Trial

Jeffrey Saland,[1] John C. Lieske,[2] Richard G. Willey,[3] Yaacov Frishberg,[4] Martin Coenen,[5] Julien Hogan,[6] Cristin Kaspar,[3] Sally Hulton.[7] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Mayo Clinic, Rochester, MN; [3]Alnylam Pharmaceuticals, Cambridge, MA; [4]Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel; [5]Institute of Clinical Chemistry and Clinical Pharmacology, Bonn, Germany; [6]Pediatric Nephrology Department, Hopital Robert-Debré, APHP, Paris, France; [7]Department of Nephrology, Birmingham Women's and Children's Hospital, Bermingham, United Kingdom.*

Background: Primary hyperoxaluria type 1 (PH1) is characterized by hepatic oxalate overproduction, kidney stones, and progressive kidney disease. Lumasiran is approved to treat PH1 in pediatric and adult patients (pts). Here we report final, 60-month (M) data from ILLUMINATE-A (NCT03681184).

Methods: ILLUMINATE-A is a study in pts age ≥6 y with PH1 and eGFR ≥30 mL/min/1.73m^2. A 6M double-blind, placebo-controlled primary analysis period was followed by an extension period of up to 54M in which all pts received lumasiran.

Results: Of 39 pts enrolled, 25/26 (lumasiran/lumasiran group) and 13/13 (placebo/lumasiran group) completed the study. Mean 24-h urinary oxalate (UOx) reductions at end of study (EOS) relative to baseline (BL) were 54% (lumasiran/lumasiran; 60M post–lumasiran initiation) and 56% (placebo/lumasiran; 54M post–lumasiran initiation). For each time point in the extension period, ≥50% of pts in each group achieved 24-h UOx excretion ≤1.5 × upper limit of normal (0.514 mmol/24h/1.73m^2): 50%–88% (lumasiran/lumasiran) and 54%–92% (placebo/lumasiran). Mean reductions in plasma oxalate from BL to EOS were 37% and 50% in the lumasiran/lumasiran and placebo/lumasiran groups, respectively. During the first 6M of lumasiran treatment, plasma glycolate increased (mean change from BL, 119% [lumasiran/lumasiran] and 154% [placebo/lumasiran]), then plateaued and remained stable. From BL through EOS, eGFR remained stable (mean [SEM] change from BL, −2.892 [2.747] and −12.860 [3.894] mL/min/1.73m^2 in the lumasiran/lumasiran and placebo/lumasiran groups, respectively). Kidney stone event (KSE) rates were low (0.47/person-year [PY] and 0.54/PY in the lumasiran/lumasiran and placebo/lumasiran groups, respectively, overall during lumasiran treatment; 0.09/PY and 0/PY, respectively, during the final 6M of the study). Medullary nephrocalcinosis (NC) grade improved at EOS in 16/20 pts with NC. The most common lumasiran-related adverse events were mild injection-site reactions (36% of pts).

Conclusions: Long-term lumasiran treatment (54–60M) in pts with PH1 led to sustained UOx reduction, with an acceptable safety profile and encouraging clinical outcomes data (low rates of eGFR decline, minimal KSEs, and improved medullary NC).

Funding: Commercial Support - Alnylam Pharmaceuticals

FR-PO230

Characteristics of Patients with Enteric Hyperoxaluria

Trisha D. Laxamana, Frank Modersitzki, Miri Cazes, Bronya L. Sandorffy, David S. Goldfarb, Lama Nazzal. *New York University, New York, NY.*

Background: Enteric hyperoxaluria (EH) is a condition characterized by oxalate (Ox) overabsorption in the digestive tract leading to increased renal excretion. It predisposes patients to recurrent kidney stones, nephrocalcinosis, & progressive kidney impairment w/ severe cases requiring renal replacement therapy. Management remains a challenge due to heterogeneity of underlying etiologies, lack of standard laboratory cut-offs for the development of its consequences, & individual treatment responses.

Methods: We conducted a retrospective cohort study of 40 patients enrolled in the EH Registry at NYU Langone Health w/ an aim to contribute to the understanding of EH. Through comprehensive chart review, the study explores demographic characteristics including age, gender (male (M) vs. female (F)), EH etiology, eGFR & interventions including calcium (Ca) supplement & potassium (K) citrate. A cross-section analysis of 24-hour urinary collections was conducted (Table 1).

Results: The cohort comprised 40 patients w/ EH (50% M, 50% F) w/ a mean age of 59 (58 M, 61 F). Etiologies were Crohn's disease (40%), Roux-en-Y gastric bypass (12.5%), pancreatic insufficiency (25%), and short bowel syndrome (22.5%). Patients had eGFR >60 ml/min (70%), 45-59 (10%), 30-44 (10%), 15-29 (5%), <15 (2.5%), & unknown (2.5%). For intervention, 32.5% were on K citrate, 57.5% w/ history of K citrate use, and 22.5% were on Ca supplements. Urine collections showed significant risk for recurrent CaOx stones w/ high Ox & CaOx supersaturation (SS).

Conclusions: This cohort includes patients w/ mild to moderate CKD. Crohn's disease was the most common etiology. Significant gender differences were observed in urinary profiles in EH patients, w/ M showing higher Ox & SS CaOx despite higher volumes & citrate. Supplementation w/ citrate & Ca are used by a significant portion of this cohort but did not alleviate significant risk of stone recurrence or progressive CKD.

Table 1. 24-hour Urinary Profile

	M (n=20) (mean/SD)	F (n=20) (mean/SD)
Volume (L/d)*	2.46(0.96)	1.75(0.92)
SS CaOx (L/d)	13.67(76.70)	12.51(42.95)
Ox (mg/d)	74.96(64.62)	59.26(36.64)
Ca (mg/d)*	137.08(118.28)	80.90(58.06)
Citrate (mg/d)*	426.74(274.99)	288.84(284.23)
pH	6.38(5.55)	6.21(0.78)
Sodium (mmol/d)	187.29(70.88)	125.10(74.02)

*p<0.01

FR-PO231

Enteric Hyperoxaluria: A 13-Year Retrospective Analysis of Urine Metabolic Risk Factors and Kidney Stone Events across Different Etiologies

Ryan Tatton,[1] Stephen R. O'Neill,[1] Deondre Jordan,[2] Lisa E. Vaughan,[2] John C. Lieske,[2] Mira T. Keddis.[1] *[1]Mayo Clinic, Phoenix, AZ; [2]Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Enteric Hyperoxaluria (EH) increases the risk for calcium oxalate nephrolithiasis. This retrospective observational study compared baseline patient characteristics and subsequent nephrolithiasis rates by enteric etiology among EH patients.

Methods: Patients with a measured urine oxalate>40 mg/24hr between Jan1,2010, and Oct31,2023 with an enteric pathology consistent with EH and eGFR >30ml/min at the time of EH diagnosis were included. A stone event was defined as surgical management of kidney stones, stone composition analysis, or emergency department visit with a nephrolithiasis diagnosis. Patient characteristics and nephrolithiasis parameters were evaluated.

Results: Of 715 patients meeting inclusion criteria, the most common EH etiology was malabsorptive bariatric surgery(63%). Characteristics varied significantly by EH cause: non-bariatric surgically associated malabsorption(SAM) patients exhibited the greatest hyperoxaluria, profound hypocitraturia, and lowest eGFR, while Celiac patients had greater hypercalciuria and highest calcium oxalate supersaturation (**Table 1**). Over an average follow-up of 5.3(±3.9) years, the overall median (IQR) stone event rate was 0.6(0,1.54) per year. Exocrine pancreatic insufficiency, SAM, and Celiac groups had the highest stone burden (1.06,0.94, and 0.86 events per year, respectively).

Conclusions: This large EH cohort with comprehensive urine metabolic data reveals significant heterogeneity by enteric etiology. Malabsorptive bariatric surgery was the most common EH cause but had the lowest nephrolithiasis event rate. Other etiologies were less common but had more severe disease with higher stone events and different urine risk profiles, leading to higher overall SS. This study highlights the significant stone burden EH patients face (approximately 1 stone per year) and the need for a robust EH patient registry to define natural history, appropriate endpoints, and targets for tailored treatment across the heterogenous EH population.

Table 1. Patient characteristics and stone events by enteric diagnosis.

	Enteric Diagnosis Group						
Patient Characteristics at time of EH diagnosis	Crohn's (N=80)	Ulcerative Colitis (N=45)	EPI (N=78)	Celiac (N=18)	SAM (N=42)	Bariatric (N=454)	P-value
Age (years), mean (SD)	54 (15)	59 (15)	62 (12)	48 (14)	62 (10)	57 (11)	<0.001
Male Sex, n (%)	61 (76.3%)	33 (73.3%)	49 (64.5%)	10 (55.6%)	19 (45.2%)	123 (27.1%)	<0.001
Race, n (%)							0.93
Non-White	4 (5.0%)	1 (2.2%)	1 (1.3%)	1 (5.6%)	2 (4.8%)	22 (4.8%)	
Other	1 (1.3%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (2.4%)	5 (1.1%)	
White	75 (93.8%)	44 (97.8%)	74 (97.4%)	17 (94.4%)	39 (92.9%)	427 (94.1%)	
Ethnicity, n (%)							0.21
Choose Not to Disclose	2 (2.5%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	2 (4.8%)	4 (0.9%)	
Hispanic/Latino	0 (0.0%)	1 (2.2%)	3 (3.9%)	1 (5.6%)	0 (0.0%)	7 (1.5%)	
Not Hispanic/Latino	78 (97.5%)	43 (95.6%)	75 (96.1%)	17 (94.4%)	40 (95.2%)	443 (97.6%)	
BMI (kg/m2), mean (SD)	28.1 (6.1)	28.8 (7.6)	28.8 (6.7)	29.3 (5.8)	24.2 (6.9)	33.9 (9.0)	<0.001
eGFR* (mL/min/1.73m2), mean (SD)	79 (25)	81 (19)	78 (23)	77 (18)	67 (22)	80 (21)	0.003
Urine Oxalate (mg/24hr), median (IQR)	52.7 (44.5, 64.3)	49.3 (43.0, 58.1)	54.6 (45.8, 72.2)	46.4 (46.7, 68.0)	62.1 (49.3, 91.5)	57.2 (47.5, 73.3)	<0.001
Urine Calcium (mg/24hr), median (IQR)	148 (52, 215)	120 (67, 204)	142 (74, 211)	191 (125, 280)	62 (33, 114)	97 (58, 174)	<0.001
Urine Citrate (mg/24hr), median (IQR)	806 (118, 460)	368 (291, 842)	388 (153, 800)	678 (389, 842)	140 (57, 210)	349 (131, 642)	<0.001
Urine pH, median (IQR)	5.77 (5.50, 6.20)	6.00 (5.70, 6.50)	5.64 (5.20, 6.18)	6.50 (6.00, 6.80)	5.65 (5.40, 5.90)	5.90 (5.50, 6.20)	<0.001
Calcium Oxalate SS (Delta G), median (IQR)	2.15 (1.70, 2.47)	1.84 (1.25, 2.29)	2.05 (1.48, 2.58)	2.19 (1.98, 2.49)	1.67 (1.31, 1.97)	1.98 (1.48, 2.29)	0.16
Nephrolithiasis characteristics							
History of stones at EH diagnosis, n(%)	74 (91.5%)	42 (93.3%)	68 (88.3%)	14 (77.8%)	30 (71.4%)	354 (78.0%)	0.005
Stone event rate after EH diagnosis†, median (IQR)	0.74 (0.13, 1.82)	0.83 (0.08, 1.77)	1.06 (0.35, 1.85)	0.86 (0.16, 2.94)	0.94 (0.18, 2.05)	0.43 (0.00, 1.34)	0.002

Abbreviations: EPI, Exocrine Pancreatic Insufficiency; SAM, Surgically Associated Malabsorption.
*eGFR was calculated using 2021 CKD-EPI race-free equation.
†Stone event rate was calculated by dividing the total number of stones occurring after EH diagnosis and prior to last follow-up by number of years between EH diagnosis and last follow-up

FR-PO232

Enteric Hyperoxaluria Mouse Model: Malabsorption and Gut Permeability

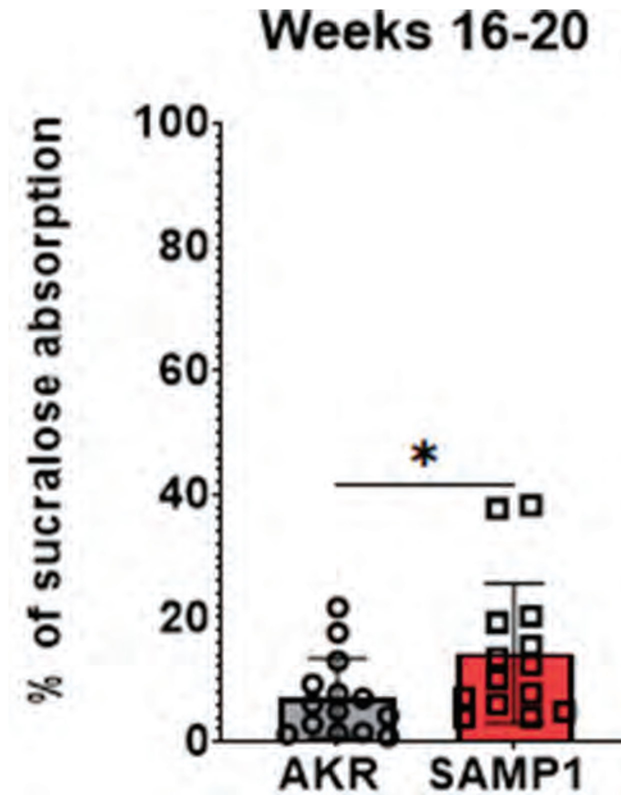
Karim Jaber,[1] Nadim Zaidan,[2] Kyle Merritts,[1] Xiaozhong Xiong,[1] Lama Nazzal.[1] *[1]NYU Langone Health, New York, NY; [2]Staten Island University Hospital, Staten Island, NY.*

Background: Enteric hyperoxaluria (EH) arises from enhanced oxalate (Ox) absorption in the gastrointestinal (GI) tract, often seen in patients with inflammatory bowel diseases. Several mechanisms could contribute to this, including elevated Ox bioavailability, decreased fat absorption, and altered GI permeability. The SAMP1/YitFc (SAMP1) mouse model exhibits spontaneous ileal inflammation resembling Crohn's disease. We hypothesize that SAMP1 mice exhibit increased gut permeability and develop an EH phenotype.

Methods: To assess intestinal permeability, we performed gavage of 10 AKR and 10 SAMP1 mice (1:1 F:M) with sucralose and C-13 Ox at weeks 16, 20, and 26 of life. We collected 24-hour urine post-gavage and measured sucralose via Hydrophilic Interaction Liquid Chromatography (HILIC). To evaluate the impact of ileitis and dietary fat, SAMP1 and AKR mice (n=10/group) were initially fed normal chow before transitioning to a low-fat diet, then a very high-fat diet. Ox was then introduced with incremental decrease in dietary fat. Urine (U) and plasma (P) samples were collected for Ox and creatinine measurements, and fecal samples were collected for Ox and lipidomics analysis to investigate fat malabsorption.

Results: SAMP1 mice had higher % of sucralose absorption, suggesting increased intestinal permeability in IBD mice. Increased dietary fat did not induce increase in UOx. However, dietary oxalate addition to fat led to an increase in UOx, POx and fecal oxalate. Fecal lipidomics indicated increased lipids, particularly fatty acids, in SAMP1 mice confirming fat malabsorption.

Conclusions: SAMP1 mice develop an EH phenotype characterized by increased fat malabsorption, leading to elevated dietary Ox bioavailability. These mice had increased gut permeability, likely promoting passive oxalate absorption across the intestinal membrane.



FR-PO233

Understanding Gastrointestinal Oxalate Metabolism in Kidney Stone Disease: A Stable Isotope Study

Lisa Deesker,[1] Sander F. Garrelfs,[1] Dewi van Harskamp,[2] Tim de Meij,[1] Michiel J. Oosterveld,[1] Jaap Groothoff.[1] *[1]Emma Kinderziekenhuis Amsterdam UMC, Amsterdam, Netherlands; [2]Stable Isotope Research Laboratory, Amsterdam University Medical Centers, Amsterdam, Netherlands.*

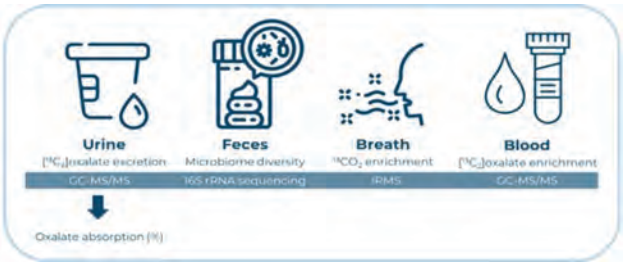
Background: Intestinal oxalate metabolism plays a significant role in calcium oxalate (CaOx) kidney stone disease. However, the gastrointestinal oxalate metabolism remains insufficiently understood, leading to dietary restrictions for patients based on limited evidence. With this study, we aim to obtain more insight into the gastrointestinal absorption and breakdown of oxalate. Measurement of oxalate absorption will be combined with assessment of the gut microbiome, which has been found to correlate with CaOx stone disease and could be one of the key influences on the gastrointestinal bio-availability of oxalate.

Methods: In this cross-sectional case-control study, we aim to study the influence of dietary oxalate on urinary oxalate levels by quantifying the intestinal oxalate absorption in patients with primary or secondary hyperoxaluria and non-hyperoxaluric CaOx stone formers vs. healthy controls, using an oral stable isotope method described by Von Unruh et al. (1998). After ingesting an oral dose of ^{13}C-oxalate, ^{13}C-oxalate enrichments will be measured in plasma and urine samples using GC-MS/MS. In breath samples, $^{13}CO_2$ will be analyzed as an indirect measure of intraluminal oxalate degradation. Intestinal oxalate absorption will be calculated and correlated with microbiome diversity and abundance of oxalate-degrading bacteria measured in fecal samples by 16S rRNA sequencing (F1).

Results: The study is currently ongoing. Preliminary data (in healthy controls, n=4) show that plasma oxalate enrichments peaked between 1-3 hours after tracer ingestion and that 75-89% of ^{13}C-oxalate is excreted via the urine within 6 hours. Similarly, $^{13}CO_2$ enrichments in breath samples (n=2) peaked between 1-3 hours, indicating intestinal oxalate degradation. ^{13}C-oxalate absorption/degradation rates and microbiome correlations will be presented at the congress based on the final results (n≈45).

Conclusions: This study will be the first to combine oxalate absorption, degradation, and intestinal microbiome analysis. This provides unique insights into gastrointestinal oxalate metabolism, the role of the microbiome, and potential new therapeutic targets for different subgroups of CaOx stone formers.

Funding: Private Foundation Support



FR-PO234

Discovery of Small Molecule Drugs with Therapeutic Potential for Hyperoxalemia, Hyperoxaluria, and Related Kidney Stones

Hatim A. Hassan,[1] Marina Subramaniam,[1] Sara F. Dunne.[2] *[1]Mayo Foundation for Medical Education and Research, Rochester, MN; [2]Northwestern University, Evanston, IL.*

Background: Kidney stones (KS) are very common, excruciating, and account for >1.3M ER visits. ~80% of KS are composed of calcium oxalate and very small increases in urine oxalate significantly enhance the stone risk. Oxalate also potentially contributes to CKD and its progression, emphasizing the urgent need for plasma and urinary oxalate lowering therapies, which can be achieved by enhancing enteric oxalate secretion. We previously identified *Oxalobacter*-derived peptides stimulating oxalate transport by human intestinal Caco2-BBE (C2) cells via the oxalate transporters SLC26A6 [A6] & SLC26A2 [A2] and PKA activation. A main limitation of therapeutic peptides is their short half-life due to degradation by proteolytic enzymes. Many attempts to optimize our peptides decreased their functions by 45-100%. Small molecule (SM) therapeutics are superior to peptide-based drugs given their overall favorable drug profile.

Methods: To develop a cell-based high throughput screening (HTS) assay to identify SM activators for A6 and/or A2, Fischer rat thyroid (FRT) cells were engineered to stably co-express human A6 or A2 and a Cl-sensitive yellow fluorescent protein (YFP).

Results: A suitable HTS assay was successfully developed, in which extracellular addition of oxalate (Ox)-containing buffer drives A6/A2-mediated Cl/Ox exchange, leading to increased (dequenched) YFP fluorescence measured by a high content imager. The assay conditions were validated using the anion exchange inhibitors niflumic acid and DIDS, which inhibited the oxalate exchange. Addition of Ox did not change YFP fluorescence in control FRT cells (has YFP but no A6/A2). FDA-approved library was screened, and 24 drugs (22 in human clinical use; including 4 tyrosine kinase inhibitors and 7 drugs interacting with GPCRs) were identified as likely true positive hits, many of which serve as antagonists for pathways that we previously showed to inhibit A6-mediated intestinal oxalate transport. Interestingly, 22 drugs significantly stimulated (~17-107%) apical oxalate transport in C2 cells, with one drug had no effect and another significantly inhibited (~20.5%) oxalate transport.

Conclusions: Several SM drugs were discovered, which greatly stimulated oxalate transport by C2 cells and have significant potential to serve as novel therapeutics for hyperoxalemia, hyperoxaluria, and related KS.

Funding: NIDDK Support, Other NIH Support - Internal startup fund support by Mayo Clinic

FR-PO235

High-Oxalate Diets Increase Urinary Oxalate Excretion and Nanocrystalluria in Healthy Adults and Calcium Oxalate Kidney Stone Formers

Tanecia Mitchell, Parveen Kumar, Shali Zhang, Mary A. Doamekpor, Vivek Verma, Vinoy Thomas, Dean G. Assimos. Mitchell Laboratory. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Kidney stones (KS) affect approximately 10% of the United States population. The majority of KS are comprised of calcium oxalate (CaOx). Urinary oxalate is derived from dietary sources as well as endogenously synthesized. It may exist in soluble or crystalline forms in urine. We recently developed a novel method to detect and quantify nanocrystals in urine. We previously reported that a single dietary oxalate load augments urinary oxalate output and nanocrystalluria in healthy adults within 5 hours. The aim of this study was to determine whether increasing dietary oxalate augments urinary oxalate excretion and nanocrystalluria in CaOx KS formers (CaOx KSF) and healthy adults.

Methods: Sixteen healthy adults without a history of KS and 6 CaOx KSF adults were randomly assigned to consume one of two controlled diets: (50 mg oxalate and 800 mg of calcium/day) or (250 mg oxalate and 800 mg of calcium/day) for 4 days. After a 10-day washout period, they consumed the other diet for 4 days. Urine was collected on the last day of both dietary regimens. Urinary oxalate excretion and the number of nanocrystals were characterized using ion-chromatography-mass spectrometry and nanoparticle tracking analysis, respectively. Microscopy and spectroscopy were used to evaluate morphology and chemical crystal composition.

Results: Both cohorts had increased urinary oxalate excretion while consuming the higher oxalate containing diets compared to the lower oxalate containing diets (Healthy adults – low 6.23 ± 0.80 vs high 13.46 ± 1.46 mg oxalate/g Cr, p<0.007; CaOx KSF – low 7.81 ± 0.59 vs high 13.67 ± 2.03 mg oxalate/g Cr, p<0.069). In addition, nanocrystalluria was significantly elevated (Healthy adults – low 1.39E+08 ± 2.65E+07 vs high 3.00E+08 ± 4.02E+07 particles/mL, p=0.008; CaOx KSF – low 1.91E+08 ± 3.98E+07 vs high 3.90E+08 ± 7.00E+07, p=0.049). Microscopy revealed that the nanocrystals had CaOx morphology, and spectroscopy confirmed that they were composed of CaOx.

Conclusions: These findings suggest that intake of meals containing moderate/large amounts of oxalate augments urinary oxalate excretion and promotes nanocrystalluria, which is more profound in CaOx KSF. Such responses may play a role in KS formation and could be a potential marker for KS risk.

Funding: NIDDK Support

FR-PO236

Comparison of Thiazide vs. Alkali Citrate for Kidney Stone Recurrence among Individuals with Hypocitraturia and High Urine pH

Ryan Hsi,[1] Mary K. Oerline,[4] Joseph J. Crivelli,[2] Sara L. Best,[5] John R. Asplin,[5] Vahakn Shahinian,[4] John M. Hollingsworth.[3] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of Alabama, Birmingham, AL; [3]NorthShore University HealthSystem, Evanston, IL; [4]University of Michigan, Ann Arbor, MI; [5]Laboratory Corporation of America Holdings, Burlington, NC.*

Background: The comparative effectiveness of thiazide versus alkali citrate for the prevention of kidney stone recurrence is unknown among individuals with low urinary citrate and high urine pH. We sought to compare symptomatic stone recurrence among individuals with low urinary citrate and high urine pH prescribed thiazides versus alkali citrate.

Methods: Among Medicare beneficiaries with a 24-hour urine collection obtained between 2010 and 2019, we identified individuals with hypocitraturia (≤300 mg/day for males and ≤350 mg/day for females) and high urine pH (>6.3) who had not received thiazides or alkali citrate in the 6 months prior to the collection. Then, we identified a subset who subsequently received a prescription fill for a thiazide or alkali citrate, but not both, within 6 months after the urine collection. We used the Kaplan-Meier method and multivariable Cox modeling, adjusting for demographic and baseline 24-hour urine parameters to compare the incidence of a symptomatic stone event (i.e., an emergency department visit, hospitalization, or surgery for kidney stones) by 3 years after initiating medical therapy.

Results: Among 1270 individuals (mean age 62.8 years and 68% female), we identified 107 and 1163 people receiving thiazides and alkali citrate, respectively. Comparing those prescribed thiazides versus alkali citrate, we found baseline differences in mean 24-hour urinary citrate (195 mg vs 171 mg, p=0.01) and calcium (209 mg vs 151 mg, p<0.001), but not urine pH (6.7 for both groups). The unadjusted cumulative incidence of a symptomatic stone event was 23.8% for the thiazide group and 33.6% for the alkali citrate group at 3 years (p<0.05). Compared to alkali citrate, thiazide use was associated with a significantly lower hazard of a symptomatic stone event (HR=0.645, 95% CI 0.429-0.970, p=0.04). A sensitivity analysis matching thiazide to alkali citrate users 1:1 by baseline calcium and citrate (n=200) showed similar results (HR=0.445, 95% CI 0.257-0.770, p<0.01).

Conclusions: Compared to alkali citrate, thiazides were associated with a reduction in symptomatic stone events among individuals with hypocitraturia and high urine pH. These data suggest that a prospective trial is warranted to compare their effectiveness.

Funding: NIDDK Support

FR-PO237

Recurrent Kidney Stones and Normocalcemic Hyperparathyroidism: A Report of Two Cases

Matthew C. Breeggemann, Stephen L. Gluck. *University of California San Francisco, San Francisco, CA.*

Introduction: Normocalcemic hyperparathyroidism is a risk factor for the development of kidney stones and can be challenging to identify. We report two patients with recurrent nephrolithiasis who were diagnosed with normocalcemic primary hyperparathyroidism.

Case Description: Patient 1: A 73 year old man with recurrent calcium oxalate nephrolithiasis presents to a nephrology based kidney stone prevention clinic. He has spontaneously passed one kidney stone and required one stone removal procedure. His most recent kidney ultrasound is negative for renal calculi. His 24 hour urine chemistry results are notable for a urine calcium level of 369 mg (< 250 mg/d). He is found to have a PTH of 79 ng/L (18-90 ng/L) and a serum calcium of 10.1 mg/dL (8.6-10.2 mg/dL). A parathyroid ultrasound and nuclear medicine scan are consistent with a parathyroid adenoma for which he undergoes a parathyroidectomy procedure. Subsequent lab testing demonstrates resolution of hypercalciuria (67 mg/d) and reduction in both the PTH (30 ng/L) and serum calcium levels (9.3 ng/dL). Patient 2: A 65 year old man with recurrent calcium nephrolithiasis presents to a nephrology based kidney stone prevention clinic. He has spontaneously passed one kidney stone and required four stone removal procedures. His most recent kidney ultrasound is notable for multiple bilateral non-obstructing calculi. His 24 hour urine chemistry results are notable for a urine calcium level of 562 mg. He is found to have a PTH of 125 ng/L and a serum calcium of 9.7 mg/dL. A parathyroid ultrasound and nuclear medicine scan are consistent with a parathyroid adenoma for which he undergoes a parathyroidectomy procedure. Subsequent lab testing demonstrates resolution of hypercalciuria and reduction in both the PTH and serum calcium levels.

Discussion: Primary hyperparathyroidism is commonly diagnosed following biochemical work up for patients found to have hypercalcemia and is a risk factor for the development of hypercalciuria and calcium based kidney stones. More rarely, patients with primary hyperparathyroidism will be diagnosed after presenting with normal serum calcium and variable PTH levels. Establishing a diagnosis of normocalcemic hyperparathyroidism is more challenging and warrants consideration in patients with unexplained hypercalciuria along with PTH levels elevated out of portion to serum calcium levels.

FR-PO238

Cholecystectomy Association with Kidney Stone Occurrence

Nadim Zaidan,[1,2] Hachem Araji,[1,2] Toni Habib,[1,2] Khalil El Gharib,[1,2] George C. Bonifant,[1,2] Elie El-Charabaty,[1,2] Suzanne E. El Sayegh.[1,2]
[1]Staten Island University Hospital, Staten Island, NY; [2]Northwell Health, New Hyde Park, NY.

Background: Patients with steatorrhea are at increased risk of calculi formation. For instance, malabsorptive bariatric surgery leads to steatorrhea and calcium chelation, which contributes to higher oxalate bioavailability and enteric hyperoxaluria. A disruption of the biliary acid cycle has been described after cholecystectomy which could lead to altered lipid digestion and subsequently increased oxalate reabsorption. We hypothesize that this potential post-surgical bile acid malabsorption could be associated with the occurrence of nephrolithiasis.

Methods: We used the National Inpatient Database (NIS), between 2016 and 2020, to identify patients with diagnoses of urinary tract calculus (CCSR: GEN005) and cholecystectomy (CCSR: HEP006) through the appropriate ICD-10 codes. Only adult patients (>18 years) with identifiable body mass indices (BMI) levels were included in the study. Binary logistic regression was performed to assess whether cholecystectomy was independently associated with nephrolithiasis, while adjusting for basic demographic covariates and known risk factors for kidney stone formations. All statistical analyses were performed using the SAS software.

Results: A total of 5 646 289 patients were included in the final cohort, 1.56% of which had undergone cholecystectomy. 56 234 patients had a diagnosis of kidney or urinary tract calculus, with a mean age of 60.39 years and a female predominance (53.60%). Cholecystectomy was found to be independently associated with the occurrence of calculi (Chi-Square = 51.96; p-value < 0.0001). After adjusting for demographic covariates (age, sex, race, geographic location, payer type, income level) and medical comorbidities (diabetes mellitus, gout, alcohol use, tobacco use, BMI), we found an odds ratio of 1.223 [1.151 – 1.299] of urinary tract calculi in patients that underwent this surgery compared with patients that still had their gallbladder, which indicates an 18.23% percentage increase in risk.

Conclusions: The association between cholecystectomy and urinary tract calculus and the percentage increase in risk in patients that underwent the surgery highlights the underappreciated impact of bile acid physiology on lipid digestion and its potential link with kidney stone disease. Further analysis involving prospective cohorts will be necessary to confirm and better elucidate this association.

FR-PO239

Net Gastrointestinal Alkali Absorption and Risk of Bone Disease

Calyani Ganesan,[1] Gary C. Curhan,[2] Pietro Manuel Ferraro,[3] Julie M. Paik.[2]
[1]Stanford University School of Medicine, Stanford, CA; [2]Brigham and Women's Hospital, Boston, MA; [3]Universita degli Studi di Verona, Verona, Italy.

Background: Studies suggest that the modern Western diet provides a net acid load to the body and may negatively impact bone health. The role of dietary alkali in neutralizing this acid load and mitigating acid-related injury to bone remains unknown. The objective of this study was to investigate the association between gastrointestinal alkali absorption and bone disease.

Methods: We analyzed the association between net gastrointestinal alkali absorption (NGIA) and incident bone disease using three large cohorts - the Health Professionals Follow-up Study, Nurses' Health Study I and Nurses' Health Study II. We estimated NGIA according to the Oh equation using 24-hour urine measurements. The primary composite outcome of bone disease included osteopenia, osteoporosis and fracture (hip, vertebral and wrist). We performed Cox proportional hazards regression to identify the incident risk of bone disease by level of NGIA. We adjusted for factors that impact bone health such as age, sex, body mass index, and smoking status.

Results: We included data from 4,592 participants (1,023 men and 3,569 women). A total of 1,226 bone disease cases were confirmed. The incidence rate of bone disease was 1,922 per 100,000 person-years. The mean (SD) NGIA for quintile 1 was 4 (9.4), for quintile 2 was 19.6 (5.1), for quintile 3 was 29.8 (5.2), for quintile 4 was 41 (6.6) and for quintile 5 was 64.1 (15.9). When compared with the lowest quintile of NGIA, the adjusted HRs of bone disease were 1.12 (95% CI 0.90, 1.35) for quintile 2 of NGIA, 1.07 (0.88, 1.29) for quintile 3, 1.10 (0.91, 1.33) for quintile 4 and 1.27 (1.06, 1.53) for quintile 5 (p-trend=0.20). Results did not materially differ by sex. Factors associated with an increased risk of bone disease included body mass index < 21 kg/m^2 (HR 1.7; 95% CI 1.38, 20.8) and current smoking status (HR 1.50; 95% CI 1.17, 1.93).

Conclusions: When compared with the lowest levels of NGIA, there was no significant association between moderate levels of NGIA and the risk of bone disease; however there was a significant association between the highest levels of NGIA and the risk of bone disease. The heterogeneity in the strength of the association between moderate to high levels of NGIA and bone disease suggests that dietary alkali likely has a modest effect on bone health when compared to other risk factors such as low body mass index and smoking status.

Funding: NIDDK Support

FR-PO240

Association of Serum Vitamin D Levels with Cardiovascular and All-Cause Mortality among Kidney Stone Formers: The National Health and Nutrition Examination Survey, 1988-1994 and 2007-2018

Eduardo Cadore Guzzo, Christina A. Raker, Jie Tang. *Brown University, Providence, RI.*

Background: The associations between serum 25-hydroxy-vitamin D (25D) levels and mortality outcomes in individuals with kidney stone disease (KSD) remain unclear.

Methods: We assessed the relationship between 25D levels and mortality among a sample of US adults (age ≥20 years), using the National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 2011-2018, and its Linked Mortality File (through 2019). KSD was defined as a self-report of any previous episode of kidney stone. Cox proportional hazard regression analyses were used to estimate the risks of all-cause and cardiovascular disease (CVD) mortality.

Results: We included 42,207 participants in the analysis; among them, 3,378 had KSD. Stone formers (SF) tended to be male, white, and older, had a higher BMI, and were more likely to have hypertension, diabetes, and CVD. However, the estimated GFR was similar between SF and non-SF. Among SF, the mean serum 25D was 69.1 ng/ml, there were 749 all-cause deaths and 209 CVD deaths with a median follow-up of 7.8 years, whereas among non-SF, the mean serum 25D was 66.6 ng/ml, and there were 7,761 all-cause deaths and 2,231 CVD deaths with a median follow up of 10.3 years. In both unadjusted and adjusted analyses, unlike non-SF where higher serum 25D was associated with a lower risk for death and CVD death, higher serum 25D was associated with a lower risk for CVD death but not all-cause death in SF [Table].

Conclusions: Among SF, higher serum 25D was associated with a reduced risk for CVD death but not all-cause death. Future prospective studies are needed to clarify the effect of 25D on survival among SF.

Funding: Private Foundation Support

Hazard ratios for 25D* and mortality by KSD

	Stone Formers				Non-Stone Formers			
	CVD Mortality		All-cause Mortality		CVD Mortality		All-cause Mortality	
Model	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted	0.92	0.84-0.99	0.98	0.93-1.03	0.92	0.88-0.95	0.93	0.91-0.95
Adjusted	0.89	0.82-0.97	0.97	0.92-1.01	0.94	0.91-0.97	0.95	0.93-0.97

*Per 10 nmol/L. **Age, sex, race/ethnicity, education, health insurance, BMI, hypertension, diabetes, CVD, smoking, alcohol intake, thiazide use, leisure physical activity intensity; dietary intake of total fluid, sodium, potassium, magnesium; serum total cholesterol, HDL, eGFR.

FR-PO241

Association of Rotating Night-Shift Work with Kidney Stone Risk in the Nurses' Health Studies

Joseph J. Crivelli,[1] Kyle Wood,[1] Eva S. Schernhammer,[2,3] Gary C. Curhan.[2] *[1]The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; [2]Brigham and Women's Hospital, Boston, MA; [3]Harvard T H Chan School of Public Health, Boston, MA.*

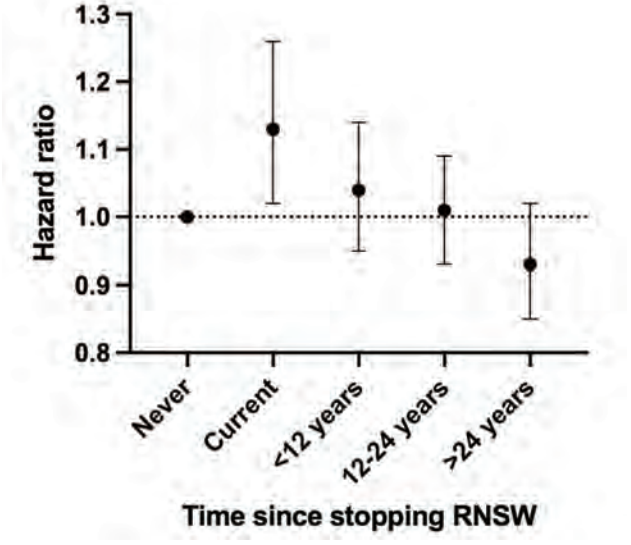
Background: Night shift work is associated with adverse health outcomes including cancer and cardiovascular disease. The extent to which sleep behavior influences kidney stone risk is unknown. We examined the association of rotating night shift work (RNSW), a state of chronically disrupted circadian biology, with incident kidney stone risk in the Nurses' Health Studies (NHS).

Methods: Female participants of NHS I and II with no history of kidney stone disease at baseline (1988-1989) were included in this analysis. Lifetime duration (in years) of RNSW (≥3 night shifts per month plus day and evening shifts) was determined at baseline in NHS I and II and updated every 2-4 years in NHS II. We used multivariable adjusted Cox models to estimate the risk of incident kidney stone disease as a function of RNSW.

Results: A total of 63,493 participants of NHS I and 91,497 participants of NHS II met study criteria. During 24 years of follow-up in NHS I and 32 years of follow-up in NHS II, there were 1,874 and 4,550 incident kidney stones. There was no statistically significant association between duration of RNSW and incident kidney stones in NHS I and II. However, in NHS II, compared to women who have not worked RNS, those with current RNSW had statistically significantly higher kidney stone risk (hazard ratio, 1.13 [95% confidence interval, 1.02-1.26]), with risk decreasing as time since stopping RNSW increased (Figure).

Conclusions: Among female registered nurses, current RNSW was associated with increased kidney stone risk, with waning risk after cessation; however, a consistent dose-response relationship between duration of RNSW and kidney stone risk was not observed.

Funding: NIDDK Support, Other NIH Support - NHS I and II infrastructure grants: UM1CA186107 and U01CA176726., Government Support - Non-U.S.



Hazard ratios of incident kidney stone disease among participants of NHS II stratified by time since stopping rotating night shift work (RNSW). No history of RNSW is the reference group.

FR-PO242

Changes in Diet among Adult Kidney Stone Formers in the United States: The National Health and Nutrition Examination Survey, 1988-2018

Jie Tang, Christina A. Raker. *Brown University Warren Alpert Medical School, Providence, RI.*

Background: Kidney stone disease (KSD) is highly influenced by dietary factors. Here we aim to examine the changes in dietary pattern of adult stone formers (SF) in the United States from 1988 to 2018.

Methods: We examined the dietary data of prevalent SF among a nationally representative sample of US adults (age ≥20 years) using the National Health and Nutrition Examination Survey (NHANES) III and 2007-2018. Weighted multiple linear regression analyses were used to examine the trend.

Results: The study was divided into four time periods, 1988-1994, 2007-2010, 2011-2014 and 2015-2018. Number of SF (males/females) were 450/311, 591/420, 459/427, 573/451 respectively. The KSD prevalence rate increased from 5.5% in 1988-1994 to 10.8% in 2015-2018, with a male-to-female ratio slightly decreased from 1.38 to 1.32. Changes in dietary pattern were shown in the table.

Conclusions: There was a significant increase in polyunsaturated fat, calcium, and fluid intake over time. But dietary potassium intake was reduced. Overall, there were no changes in dietary calories, protein, carbohydrate, fiber, saturated fat, and sodium. The rising KSD prevalence in US is unlikely driven by dietary changes alone.

Funding: Private Foundation Support

Table. Changes in dietary pattern among SF in US adults: NHANES 1988 - 2018

	Population	1988-1994	2007-2010	2011-2014	2015-2018	P value
Total calorie (kcal)	Male	2,395	2,454	2,268	2,426	0.12
	Female	1,664	1,738	1,861	1,806	0.05
	Combined	2,087	2,145	2,066	2,158	0.45
Protein (g)	Male	91	94	87	95	0.14
	Female	63	63	70	67	0.06
	Combined	79.3	80.7	78.4	82.8	0.54
Carbohydrate (g)	Male	298	298	276	280	0.16
	Female	212.9	219.9	227.2	214.7	0.46
	Combined	262	264.3	251.7	251.5	0.36
Total fat (g)	Male	90	95	88	99	0.06
	Female	63	66	73	73	0.02
	Combined	78.4	82.3	80.7	87.8	0.03
Polyunsaturated fat (g)	Male	18.1	19.7	20.2	23.2	0.001
	Female	13.4	15.2	17.3	16.8	<0.001
	Combined	16.1	17.7	18.8	20.4	<0.001
Fiber (g)	Male	17.8	18.7	17.3	18.4	0.60
	Female	15.1	14.1	15.5	14.7	0.31
	Combined	16.7	16.7	16.4	16.8	0.94
Sodium (mg)	Male	3,946	4,184	3,751	4,066	0.14
	Female	2,663	2,850	3,003	2,992	0.11
	Combined	3,405	3,609	3,381	3,603	0.14
Potassium (mg)	Male	3,193	3,074	2,794	2,915	0.007
	Female	2,588	2,296	2,335	2,263	0.09
	Combined	2,938	2,738	2,567	2,634	<0.001
Calcium (mg)	Male	870.7	985.9	962.3	1,043.7	0.02
	Female	695.9	818.4	885.3	838	<0.001
	Combined	797.0	913.6	924.1	955.0	<0.001
Fluid (ml)	Male	2,333	4,216	3,874	4,646	<0.001
	Female	1,793	3,625	3,913	4,151	<0.001
	Combined	2,105	3,961	3,893	4,433	<0.001

Changes in dietary pattern among SF in US adults: NHANES 1988 - 2018

FR-PO243

Trend Analysis of Kidney Stone-Related Mortality, 1999-2020

Luqman Munir,[1] Ahmed J. Chaudhary,[2] Mohammad Ammar ur Rahman,[1] Amna Khalid,[1] Azka Ijaz.[1] *[1]King Edward Medical University, Lahore, Pakistan; [2]Detroit Medical Center, Detroit, MI.*

Background: Kidney stones (KS) are hard deposits that can form inside the kidney or the urethra, obliterating the flow of urine and causing sharp pain. It might consist of calcium oxalate, uric acid and struvite. The stones may pass in urine painlessly, if hydrated enough or may require procedure like lithotripsy for treatment. This study explores the trend of deaths in the US from 1999 to 2020 in relation to kidney stones using age adjusted mortality rate (AAMR) to identify disparities among specific epidemiological groups (age, gender, race, urban/rural).

Methods: Our research involved analysis of death certificates between 1999 to 2000 obtained from the Centers for Disease Control and Prevention Wide Ranging Online Data for Epidemiologic Research (CDC Wonder) database related to AAMR per 100,000 people. And annual percentage change (APC) with 95% confidence interval were determined. Joinpoint regression Program was used to conduct test for parallelism and to determine variations among key demographic groups. (age, gender, race, urban/rural).

Results: A total of 18,539 deaths were recorded in relation to kidney stones from 1999 to 2020 in the US. The AAMR trend is increasing as it was 2.269 in 1999 and 3.554 in 2020. The recorded APC from 1999 to 2014 was 0.4719 and from 2014 to 2020 was 6.1495. There were higher mortality rates in Whites, males, those aged >85 years,

and those residing in rural and western areas. Tests for parallelism revealed disparate trends across Male and Female (p=0.002222), Black and White races (p=0.004222), South and West (p=0.004889), Northeast and South (p=0.002444), Midwest and northeast (p=0.043111) and urban vs. rural demographics(p=0.012000).

Conclusions: An upward trajectory has been seen in kidney stones related deaths from 1999 to 2020. This accentuates the need for further research in kidney health to minimize such rates in upcoming years.

FR-PO244

Combined Occurrence of Cardiovascular and Bone Events in Individuals with Kidney Stone Disease

Pietro Manuel Ferraro,[1] Eric N. Taylor,[2] Gary C. Curhan.[3] *[1]Universita degli Studi di Verona, Verona, Italy; [2]Maine Medical Partners, Portland, ME; [3]Brigham and Women's Hospital, Boston, MA.*

Background: Kidney stone disease (KSD) has been linked to increased risk of adverse cardiovascular (CV) and bone events. This has led to the hypothesis that a shared pathogenic pathway may underlie these events. However, it is unclear whether adverse CV and bone events commonly occur in the same individual. We examined the patterns of occurrence of CV and bone events in individuals with a history of KSD and analyzed their characteristics.

Methods: We analyzed data from three large prospective cohorts, the Health Professionals Follow-up Study (HPFS, men) and the Nurses' Health Study (NHS, women) I and II. Individuals with a self-reported diagnosis of KSD during follow-up and no previous CV or bone events at the time of KSD diagnosis were included in the study and followed until the combination of a CV event (fatal or non-fatal myocardial infarction, need for coronary revascularization) and a bone event (fracture, osteoporosis); individuals who developed cancer or were lost to follow-up were censored. Characteristics of stone formers who experienced only one event (CV or bone), both events, or none were compared with the appropriate statistical tests.

Results: Our study included data from 15,041 individuals with KSD. In HPFS, 28.7% of the participants experienced at least one event: 17.4% a CV event, 8.4% a bone event and 2.8% both events. In NHS I, 46.9% of the participants experienced at least one event: 7.4% a CV event, 33.2% a bone event and 6.3% both events. In NHS II, 27.8% of the participants experienced at least one event: 2.2% a CV event, 24.5% a bone event and 1.1% both events. Baseline characteristics according to the type of event experienced are reported in Table 1: across cohorts, age, BMI, use of thiazides, use of calcium and vitamin D supplements, prevalence of hypertension and diabetes tended to differ between groups.

Conclusions: Cardiovascular and bone events are common in KSD; however, their simultaneous occurrence in the same individual is uncommon, suggesting that risk factors might not be shared between cardiovascular and bone events.

Funding: NIDDK Support

	HPFS				
	No events (n = 2,893)	CV events only (n = 708)	Bone events only (n = 343)	CV and Bone events (n = 115)	p-value
Age (years)	62.5	60.3	61.3	60.0	<0.001
BMI (kg/m²)	26.5	26.9	25.8	26.0	<0.001
Use of thiazides (%)	7.1	9.6	3.8	5.2	0.12
Use of calcium supplements (%)	20.1	21.5	22.2	15.9	0.50
Use of vitamin D supplements (%)	11.9	5.8	6.0	1.0	<0.001
Hypertension (%)	41.8	44.4	30.3	46.1	<0.001
Diabetes (%)	8.5	10.6	5.5	7.8	0.05
	NHS I				
	No events (n = 2,450)	CV events only (n = 341)	Bone events only (n = 1,529)	CV and Bone events (n = 291)	p-value
Age (years)	62.0	59.0	57.6	58.0	<0.001
BMI (kg/m²)	26.1	26.3	26.5	27.5	<0.001
Use of thiazides (%)	12.5	15.0	9.9	17.5	<0.001
Use of calcium supplements (%)	43.9	34.5	38.0	32.4	<0.001
Use of vitamin D supplements (%)	21.7	6.6	10.4	9.3	<0.001
Hypertension (%)	52.3	62.8	37.6	52.2	<0.001
Diabetes (%)	13.8	24.9	8.0	15.1	<0.001
	NHS II				
	No events (n = 4,603)	CV events only (n = 138)	Bone events only (n = 1,560)	CV and Bone events (n = 70)	p-value
Age (years)	48.8	48.8	46.3	45.7	<0.001
BMI (kg/m²)	29.4	32.1	27.1	29.9	<0.001
Use of thiazides (%)	6.3	11.6	5.3	12.9	0.003
Use of calcium supplements (%)	32.8	33.6	34.6	34.4	0.66
Use of vitamin D supplements (%)	20.7	18.8	12.7	8.5	<0.001
Hypertension (%)	33.8	48.6	26.1	48.6	<0.001
Diabetes (%)	9.9	29.0	6.9	22.9	<0.001

FR-PO245

Correlation of Global Climate Change and Kidney Stone Awareness: A Temporal Trends Analysis, 2004-2023

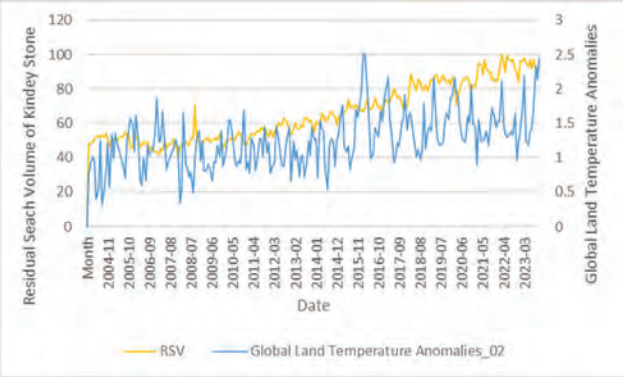
Noppawit Aiumtrakul,[1] Methavee Poochanasri,[2] Chutawat Kookanok,[2] Charat Thongprayoon,[3] Supawadee Suppadungsuk,[3,4] Pajaree Krisanapan,[3,5] Wisit Cheungpasitporn.[3] *[1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; [2]Department of Medicine, Phramongkutklao College of Medicine, Bangkok, Thailand; [3]Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN; [4]Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand; [5]Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand.*

Background: Kidney stones become more prevalent and create impacts on global health. Stone formation is a multifactorial process influenced by dietary, genetic, lifestyle and geographical factors. This study aims to investigate relationships between kidney stone awareness on Google search trends and global temperature over the past 20 years.

Methods: The study utilized Google Trends to quantify awareness of kidney stones, measured by relative search volume (RSV). Pearson's correlation and linear regression model were employed to evaluate the association between the RSV of kidney stones and average global land temperature each month from 2004 to 2023.

Results: The scatter plot showed a clear positive correlation between land temperature and the RSV of kidney stones, indicating increased searches as temperature rises. Despite some data dispersion, the linear regression line's imperfect fit highlighted the relationship's complexity. The modest R-squared value at 0.227 suggested temperature explains only a small portion of search volume variance, hinting at additional influencing factors. The predicting equation for kidney stone search volume by land temperature is Y=39.87+ 20.65*X. In regression analysis, for every unit increase in land temperature, RSV increases by 20.65 ($p < 0.01$). For every standard deviation increase in land temperature, RSV increases by 0.477 ($p < 0.01$).

Conclusions: The correlation between kidney stone RSV and global temperature underscores climate change impact on public health information-seeking behavior. While temperature is influential, other factors also found affect search volume, highlighting the necessity for comprehensive research. Further exploration of these factors is vital for effective public health interventions and management strategies.



FR-PO246

Facility-Level Variation in Nephrology Care among Veterans after Urinary Stone Events

Kaleb Thomas,[1] Calyani Ganesan,[1] Sai Liu,[1] Maria E. Montez-Rath,[1] Simon John Christoph Soerensen,[1] John Leppert,[1,2] Alan C. Pao.[1,2] *[1]Stanford Medicine, Stanford, CA; [2]VA Palo Alto Health Care System, Palo Alto, CA.*

Background: Nephrologists are uniquely qualified to manage recurrent urinary stone disease. The objective of this study was to determine the frequency of nephrology visits after a urinary stone event, a key window of opportunity to assess stone risk.

Methods: We used nationwide data from the United States Veterans Health Administration to identify patients who had an incident stone event between 2016 and 2018. We defined a stone event as having an (index) inpatient or outpatient stone diagnosis code followed by an additional stone diagnosis or procedure code within 6 months of the index diagnosis. We examined the proportion of patients who visited a nephrology clinic within 6 months of a stone event.

Results: We identified 45,133 Veterans who had an incident urinary stone event. Within six months of the stone event, only 5.6% of patients visited nephrology if they did not have a prior nephrology visit; whereas 70% of patients visited nephrology if they had a prior nephrology before the stone event. Veterans who had a lower eGFR were more likely to see a nephrologist after a stone event (for patients who visited nephrology previously OR 2.28, 95% 2.01-2.58; for patients who had not visited nephrology previously OR 5.19, 95% 4.69-5.74). The median odds ratio for a nephrology follow-up visit was 1.51 for patients who had a past nephrology visit, whereas the median odds ratio was higher for patients who did not have a past nephrology visit (1.74). Figure 1 shows the proportion of patients who saw a nephrologist after their stone event across 104 sites.

Conclusions: Nephrologists are infrequently and variably involved in the care of patients with urinary stone disease, suggesting potential for quality improvement.

Funding: Veterans Affairs Support

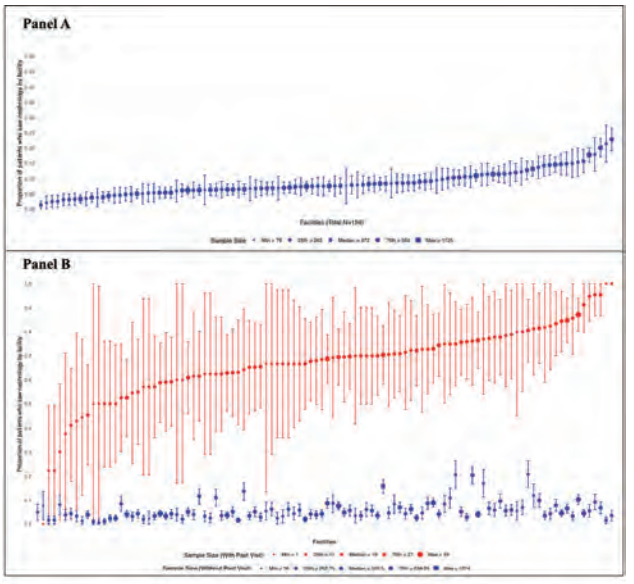


Figure 1. Proportion of patients who saw a nephrologist by VHA facility. Proportion of patients in the total cohort who received a nephrology follow-up visit within 6 months of a stone event ranked by VHA facility **(Panel A.)** Proportion of patients who received a nephrology visit within 6 months of a stone event with a prior nephrology visit (red) and without a prior nephrology visit (blue) **(Panel B.)**

FR-PO247

Acute Kidney Disease (AKD) following Ureteroscopy and Laser Lithotripsy: The Latest Frontier for Nephrologists

Francesco Trevisani,[1] Luigi Candela,[1] Eugenio Ventimiglia,[1] Alessia d'Arma,[1] Christian Corsini,[1] Daniele Robesti,[1] Olivier Traxer,[2] Francesco Montorsi,[1] Andrea Salonia,[1] Luca Villa.[1] *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Tenon hospital, Parigi, France.*

Background: Ureteroscopy (URS) with laser lithotripsy is the gold-standard for treating ureteral and kidney stones up to 2 cm, but complications can occur in up to 25% of cases. AKI post-URS is underestimated due to exclusive urological management. AKD, a transient kidney function alteration lasting less than 90 days, is under-researched despite its high CKD risk. This study aims to evaluate the occurrence and evolution of AKD in stone patients treated with URS.

Methods: A consecutive cohort of 284 patients treated with URS for urinary stones in a tertiary institution was considered. According to KDIGO 2023, AKD was defined as postoperative acute kidney injury (AKI) occurrence, estimated glomerular filtration rate (eGFR) decrease ^{3}35%, or serum creatinine (SCr) increase ^{3}50%. AKI was defined as SCr increase ^{3}0.3 mg/dL or ^{3}50%. AKD evolution was evaluated 60 days post-URS. Univariable (UVA) and multivariable (MVA) logistic regression analyses tested the association of patients' characteristics and perioperative data with the occurrence of AKD.

Results: Descriptive statistic is shown in table 1. Overall, postoperative AKD occurred in 32 (11.3%) patients. Recovery from AKD was found in 26 (82%) patients and persistent AKD occurred in 6 (18%) patients. At UVA, age at surgery (p=0.05), baseline SCr (p=0.02), baseline CKD category (p=0.006), Charlson comorbidity index (p=0.01), operative time (p=0.04) and postoperative complications (<0.001) were associated with AKD (table 2). At MVA, CKD category (OR 2.99, 95% CI= 1.4-6.3; p=0.004), operative time (OR 1.01, 95% CI=1.001-1.018; p=0.023) and postoperative complications (OR 3.5, 95% CI=1.46-8.49; p=0.005) were independent predictors of AKD. (table 3)

Conclusions: AKD is a frequent insidious complication in patients treated with URS. Therefore, a tailored nephrological assessment should be mandatory.

Table 1. Descriptive characteristics of the whole cohort of 284 patients.

Variables	
Age at surgery (years)	
Median (IQR)	58 (48-67)
Sex	
M n (%)	193 (68%)
F n (%)	91 (32%)
BMI (kg/m²)	
Median (IQR)	25 (23-27)
CCI score, n (%)	
0	80 (28%)
≥1	204 (72%)
Baseline SCr level (mg/dL)	
Median (IQR)	1 (0.85-1.2)
CKD category, n (%)	
I	111 (39%)
II	114 (40%)
IIIA	33 (11.5%)
IIIB	16 (5.5%)
IV	10 (3.5%)
Metformin n (%)	14 (5%)
Sartan and/or ACE-i assumption n (%)	57 (20%)

Keys: IQR= interquartile range; BMI= body mass index; CCI= Charlson comorbidity index, SCr= serum creatinine, CKD= chronic kidney disease; ACI-i= angiotensin converting enzyme inhibitors

Table 2. Univariable logistic regression analyses predicting postoperative AKD

Covariates	OR	95% C.I.	p
Age at surgery	1.04	1.01-1.08	0.05
CCI	1.4	1.16-1.64	0.01
Baseline sCr	2.9	1.46-5.8	0.02
CKD category > I	3.9	1.4-10.4	0.006
Operative time (min)	1.01	1.003-1.02	0.04
Complications Clavien ≥2	4.5	1.99-10.2	<0.001

Table 3 Multivariable logistic regression analyses predicting postoperative AKD.

Covariates	OR	95% C.I.	p
Age at surgery	1.02	0.97-1.07	0.38
CCI	1.16	0.97-1.01	0.3
Baseline sCr	1.7	0.75-3.7	0.21
CKD category > I	2.99	1.4-6.3	**0.004**
Operative time (min)	1.01	1.001-1.018	**0.023**
Complications Clavien ≥2	3.5	1.46-8.49	**0.005**

FR-PO248

Risk Factors for Postevaluation Symptomatic Kidney Stones in Donor Candidates: A 17-Year Follow-Up Study

Mira T. Keddis,[1] Jaxon Quillen,[1] Nan Zhang,[1] Andrew D. Rule.[2] *[1]Mayo Clinic, Scottsdale, AZ; [2]Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: We aimed to identify characteristics of kidney donor candidates who develop symptomatic kidney stone events after donor evaluation and assess whether donor status influences the risk of developing a symptomatic stone event.

Methods: A survey was conducted in 2022-2023 among 412 adults with a self-reported history or CT imaging evidence of nephrolithiasis at the time of their kidney donor evaluation at Mayo Clinic between 2000 and 2011. The survey inquired about post-evaluation symptomatic kidney stone events (renal colic pain or gross hematuria), complications, and management. Analyses were performed to assess stone characteristics and risk factors between donor candidates who experienced a symptomatic stone event versus those who did not.

Results: Of the 147 respondents (36% response rate), 94 donated, and 53 did not, with 25 non-donors attributed to kidney stone disease. After a median follow-up of 17 years, 26 respondents (18%) experienced a symptomatic stone event, with 13% being donors and 26% non-donors. Characteristics of donor candidates who experienced a symptomatic stone event post-evaluation are shown in Table 1. Non-donation was a risk factor for a symptomatic stone event in the unadjusted model (OR=2.44, p=0.041). Multivariate analysis indicated younger age (OR=1.05, p=0.031) and the presence of ≥2 kidney stones on imaging (OR=3.09, p=0.02) were associated with symptomatic stone events, while donor status was not (OR=1.49, p=0.41).

Conclusions: Kidney donor candidates who experience symptomatic kidney stones after evaluation tend to be younger, have a higher stone burden on imaging, require more surgical and medical management for stone disease, and were less likely to donate. Our findings suggest that our current donor evaluation process is generally effective in excluding younger stone formers with signficant stone burden on imaging and that these are the key factors to consider in stone formers undergoing donor evaluation.

Table 1. Comparison of demographics, stone characteristics, risk factors, and management among stone formers with versus without a symptomatic kidney stone event post evaluation.

Characteristics	Summary, mean (SD), number (%), or median (Q1-Q3)		
Symptomatic kidney stone event after donor evaluation	Yes N=26	No N=121	P value
Donated	12 (46.2)	82 (67.8)	0.037
Demographics			
Age, years	41.1 (12.1)	47.8 (10.9)	0.006
Sex, female	14 (53.8)	73 (60.3)	0.542
Stone risk factors			
Body mass index >30kg/m2	5 (19.2)	33 (27.3)	0.468
Family history of kidney stones	0 (0.0)	9 (7.4)	0.151
Prior symptomatic kidney stone	4 (15.4)	22 (18.2)	0.735
Number of prior symptomatic kidney stones ≥2	1 (3.8)	9 (7.4)	1.00
Hypertension	4 (15.4)	21 (17.4)	0.808
Diabetes	0 (0.0)	0 (0.0)	1.00
Urinary tract infections (>5)	3 (11.5)	10 (8.3)	0.594
Gout	0 (0)	1 (0.8)	0.642
Chronic diarrhea	0 (0)	0 (0)	1.00
Office systolic blood pressure, mmHg	122 (111-132)	118 (110-131)	0.060
Office diastolic blood pressure, mHg	73 (71-81))	75 (66-81)	0.508
Medullary sponge kidney on imaging	14 (11.6)	3 (11.5)	0.996
Stone characteristics			
Stones present on imaging 0 1 ≥2	 0 (0.0) 10 (38.5) 16 (61.5)	 15 (12.4) 74 (61.2) 32 (26.4)	0.001
Bilateral stones	12 (46.2)	17 (14.0)	<0.001
Diameter of largest stone, mm	2.7 (2.1)	1.9 (1.4)	0.082
Diameter of largest kidney stone ≥3mm	13 (50)	32 (26.4)	0.018
Stone management			
Recommended to drink extra water	21 (80.8)	4 (100)	1.00
Receive medications to reduce kidney stone risk	6 (23.1)	1 (0.8)	<0.001
Stone removed or broken by surgery or procedure (this or last stone episode)	16 (61.5)	0 (0.0)	<0.001
Stone complication			
Kidney stone caused kidney damage	0 (0.0)	0 (0.0)	
Diagnosis of chronic kidney disease	2 (9.5)	2 (9.5)	0.678

FR-PO249

Mineral Bone Disorders after Preemptive Kidney Transplantation

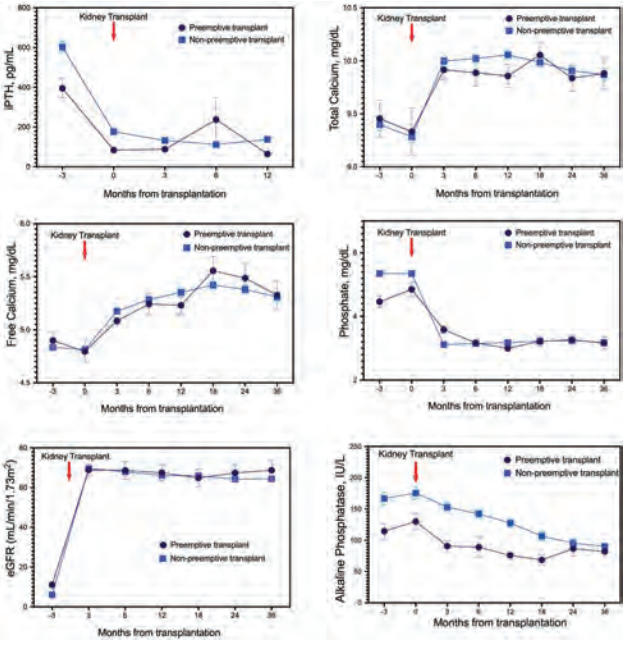
Denisse N. Tinajero Sánchez, Carlos A. Castro Almanza, Nathan Berman, Vianca A. Canaviri, Gabriel Cojuc, Lluvia A. Marino-Vazquez, Luis E. Morales-Buenrostro, Juan Carlos Ramirez-Sandoval. *Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: Mineral bone disorders are common after kidney transplantation. Preemptive kidney transplantation (PKT) may reduce these risks. We aimed to assess the long-term effects of PKT on mineral metabolism outcomes

Methods: Retrospective cohort study with a median follow-up time of 4 years (range 1-9). We compared kidney transplant recipients (KTRs) who underwent PKT (n=26) with KTRs who received hemodialysis before transplantation (n=359). The outcomes included iPTH, free calcium, phosphate, and eGFR trajectories, as well as the presence of post-transplant persistent hyperparathyroidism (iPTH > upper reference level), persistent hypercalcemia (free Ca >5.2 mg/dL) and graft dysfunction (<30 mL/min/1.73m2). Asymptomatic mild hypercalcemia was monitored unless complications developed

Results: Pre-transplant iPTH levels were similar between the PKT and non-PKT groups (median 479 [238-828] Vs 392 [145-603]; p=0.064). There were no differences in the trajectory of biochemical parameters between groups after transplantation. Similarly, when comparing PKT and non-PKT KTRs, we observed no differences in persistent hyperparathyroidism (39% Vs. 45%, P=0.54), persistent hypercalcemia (73% Vs. 62%, p=0.17), and graft dysfunction (4% Vs. 6%, p=0.58). In both groups, PTH levels below 300 were a protective factor against the development of post-transplant hyperparathyroidism or hypercalcemia

Conclusions: PKT in KTRs without controlled hyperparathyroidism did not decrease the risk of hyperparathyroidism or persistent hypercalcemia after transplantation. Medical treatment of mineral bone disorders, with a target iPTH below 300, likely decreases the risk of adverse outcomes in KTRs, including individuals undergoing PKT



FR-PO250

Bone Phenotype and Fracture Risk in Patients with Type 2 Diabetes at the Time of Kidney Transplantation

Sabina C. Hauge,[1] Hanne S. Joergensen,[5,4] Kathleen Claes,[2,3] Patrick D'Haese,[6] Anja Verhulst,[6] Etienne Cavalier,[7] Ditte Hansen,[1,8] Pieter Evenepoel.[2,3]
[1]Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark; [2]Katholieke Universiteit Leuven, Leuven, Belgium; [3]University Hospital Leuven, Leuven, Belgium; [4]Aarhus University, Aarhus, Denmark; [5]Aalborg University Hospital, Aalborg, Denmark; [6]University of Antwerp, Antwerpen, Belgium; [7]University of Liege, Liege, Belgium; [8]University of Copenhagen, Copenhagen, Denmark.

Background: Type 2 diabetes mellitus (T2DM) associates with an increased fracture risk in patients with and without chronic kidney disease (CKD), but underlying mechanisms remain poorly understood. This study investigates the mineral and bone phenotype as well as the fracture risk in patients with T2DM and CKD grade 5-5D (CKDG5-5D).

Methods: Parameters of mineral metabolism (fibroblast growth factor 23 (FGF23), sclerostin) and bone turnover (bone alkaline phosphatase (BALP), pro-collagen type I N-terminal propeptide (intact PINP), tartrate-resistant acid phosphatase 5b (TRAP5b)), bone mineral density (BMD, n=555), and trabecular bone score (TBS, n=198) were assessed in 647 patients (T2DM, n=102) at time of kidney transplantation. Bone histomorphometry was available for 188 patients. Patients with type 1 diabetes were excluded. Fragility fractures were retrieved from medical records.

Results: T2DM associated with higher Z-scores at the lumbar spine (-0.066 vs. -0.760, p<0.001) and femoral neck (-0.679 vs. -0.961, p=0.041), but lower TBS (1.223 vs. 1.294, p=0.010). Intact PINP (68.4 vs. 82.0 ng/mL, p=0.033) and FGF23 (1516 vs. 2449 pg/mL, p=0.027) were lower, while sclerostin (2.1 vs. 1.8 ng/mL, p=0.042) was higher in T2DM vs non-T2DM. Bone histomorphometry revealed no differences in bone microarchitecture, turnover or mineralization. During a median follow-up of 10 years 17% with T2DM and 13% non-T2DM sustained a fragility fracture (p=0.343). In cox regression analysis T2DM did not associate with increased fracture risk of fragility fracture (HR: 1.25; CI 0.71-2.18, p=0.437) after adjusting for age, sex, and BMI.

Conclusions: T2DM associated with a distinct bone phenotype characterized by suppressed bone turnover, higher BMD at trabecular sites, and higher circulating sclerostin levels, but T2DM did not associate with an increased fracture risk.

Funding: Private Foundation Support

FR-PO251

Dual-Energy CT Bone Findings in Kidney Transplant Recipients with Uncontrolled Gout

Bradley A. Marder,[1] Nicola Dalbeth,[2] Abdul A. Abdellatif,[3,4] John K. Botson,[6] Ada Kumar,[1] Lissa Padnick-Silver,[1] Zana Vranic,[1] Fabio Becce.[5] *[1]Amgen, Inc., Thousand Oaks, CA; [2]Department of Medicine, University of Auckland, Auckland, New Zealand; [3]Baylor College of Medicine, Nephrology, Houston, TX; [4]CLS Health, Houston, TX; [5]Department of Diagnostic and Interventional Radiology, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; [6]Orthopedic Physicians Alaska, Anchorage, AK.*

Background: CKD pts are at risk for metabolic bone disease including osteopenia and deposition disease. Monosodium urate crystal (MSU) deposits in gout also cause bone erosions/joint damage. The PROTECT study examined pegloticase safety/efficacy in immunosuppressed kidney transplant recipients (KTRs) with uncontrolled gout; a subset underwent dual-energy CT (DECT). Here we report baseline bone-related findings.

Methods: Pts (eGFR≥15,>1yr post-transplant) with baseline DECT were included. Standard protocols were used to acquire images (bilateral hands/wrists, feet/ankles, and/or knees); default post-processing for MSU detection. A central reader interpreted images (typical DECT artifacts removed) and calculated erosion scores (additive% of pre-specified bones [OMERACT RAMRIS scoring[1]]).

Results: 18regions of 8pts included (all male, 52.3±11.2yrs, time since transplant:18.7±6.9yrs, eGFR:45.6±12.4; SU:10.4±2.1mg/dL, 5.3±4.6 flares/6mo). DECT showed multiple bone abnormalities in all pts, including erosions and osteopenia/osteomalacia (trabecular bone loss, cortical thinning, and/or bone resorption). Erosions were common in feet/ankles and hands/wrists (both 7/8[88%]) and most severe in feet/ankles (≥10% eroded: 3/8[38%], ≥40% eroded: 2/8[25%]) and were adjacent to MSU deposits, non-MSU mineralized matrix, and/or not adjacent to any deposits (**Figure**).

Conclusions: These images provide new insight on bone/soft tissue abnormalities in KTRs with uncontrolled gout. Though not an intended PROTECT outcome, DECT showed overall poor bone health. Given additional erosive bone/joint damage MSU deposits can cause, findings suggest effective gout management as an opportunity to improve an aspect of bone health in KTRs with gout. **Reference** 1. Dalbeth N et al. *Rheumatology* 2011;50:410-6

Funding: Commercial Support - Horizon Therapeutics (now Amgen, Inc.)

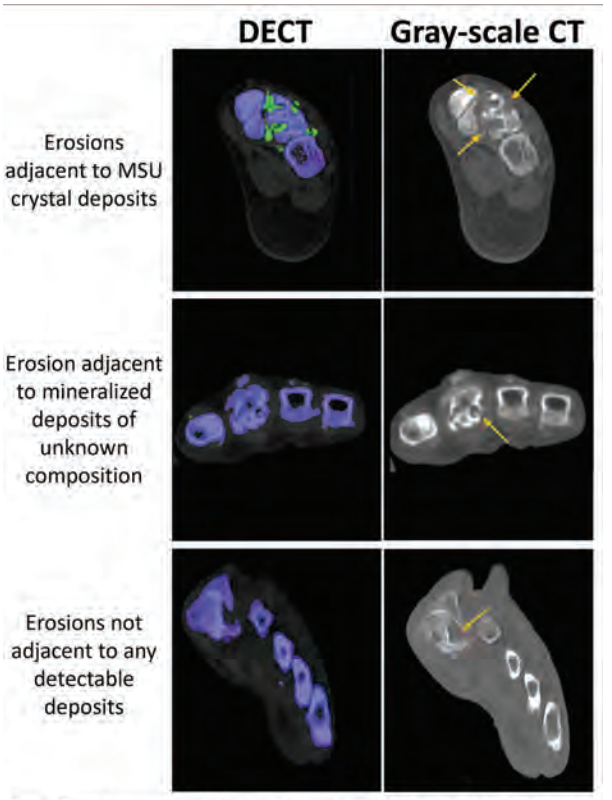


Figure. Renal transplant recipients with uncontrolled gout had notable evidence of bone abnormalities including osteopenia/osteomalacia and bone erosions (arrows). **Top:** Long axis CT image of the foot demonstrated multiple erosions at the bases of the 3rd and 4th metatarsals. DECT imaging revealed MSU crystal deposits (green) adjacent to erosions. **Middle:** Axial CT image of the hand demonstrated mineralized matrix of unknown etiology (white) surrounding the head of the third, fourth, and fifth metacarpal bones with a bone erosion of the 2nd metacarpal head. No definitive MSU color-coded deposits were present on DECT. **Bottom:** Long axis CT image of the foot demonstrated erosions of the 1st metatarsal head. There was no adjacent MSU deposition on DECT or mineralized matrix adjacent to the lateral erosion; possible mineralized matrix/calcium crystal deposits adjacent to the medial erosion with no adjacent MSU deposition on DECT.

FR-PO252

Comparison of Parathyroidectomy vs. Cinacalcet in Treatment of Hyperparathyroidism after Kidney Transplant: A Meta-Analysis

Raphael H. Palma,[1,2] Eduardo L. Rech,[2] Juliana A. Andrade,[1,2] Gisele Meinerz,[1,2] Elizete Keitel.[1,2] *[1]Universidade Federal de Ciencias da Saude de Porto Alegre, Porto Alegre, Brazil; [2]Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil.*

Background: Hyperparathyroidism after kidney transplant (PT-HPT) is a common condition and up to 50% of patients have persistent elevated parathyroid hormone (PTH) levels after 1 year after transplant. The persistent PT-HPT has been associated with higher risk of bone fractures, increased mortality, and decreased allograft survival; therefore, the management of this pathology has varied between transplant centers. Due to the controversies of evidence, we performed a meta-analysis comparing cinacalcet with surgical treatment in PT-HPT.

Methods: We systematically searched PubMed, Scopus, and Cochrane Central Register using terms: ("Kidney Transplantation"[Mesh]OR"Kidney transplantation" OR "Kidney transplant") AND ("Cinacalcet"[Mesh] OR Cinacalcet OR Calcimimetic OR Calcimimetics) AND ("Parathyroidectomy"[Mesh] OR Parathyroidectomy OR surgery). This review was registered in PROSPERO. RevMan Web was used for statistical analysis. Pooled treatment effects for binary endpoints were compared using risk ratio (RR) with 95% confidence interval (CI) and continuous outcome were compared through mean difference. Heterogeneity was examined with Cochran Q test and I 2 statistics. A random effect model was used for outcomes. Risk of bias and quality assessment of individual studies were analyzed with the Cochrane Collaboration's tool.

Results: From 682 screened studies eleven were included, nine retrospective studies and 2 randomized trials. Mean follow-up ranged from 90 days to 2.500 days. Normal calcium serum levels were more frequent in the surgery group (94.1%) than cinacalcet group (71%) and the difference was statistically significant between groups (OR 1.33;

95% CI 1.20-1.48; p < 0.00001, I^2=0%). The incidence of normalized PTH levels was significantly higher in the surgery group (52.5% vs 22.3%, OR 3.18; 95% CI 1.15 - 8.81, p = 0.03, I^2 = 90%). Graft failure was significant lower in parathyroidectomy group (2.1% vs 2.6%, OR 0.45; 95% CI 0.26-0.77, p= 0.004, I^2= 0%). There was no significant difference in mortality between surgery (1%) and cinacalcet group (0.9%), OR 0.61, 95% CI 0.26 - 1.43, p= 0.26, I^2= 0%).

Conclusions: Parathyroidectomy is more effective in controlling calcium and PTH levels in patients with PT-HPT and reduces risk of graft failure but without impact in mortality.

FR-PO253

Impact of DNA Methylation Variation on Risk of Kidney Failure in Type 1 Diabetes Is Mediated through Increased Levels of Circulating Proteins

Eiichiro Satake,[1,2] Zhuo Chen,[3] Sok Cin Tye,[1,2] Zaipul Md Dom,[1,2] Marcus G. Pezzolesi,[4] Rama Natarajan,[3] Andrzej S. Krolewski.[1,2] *[1]Joslin Diabetes Center, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]City of Hope Beckman Research Institute, Duarte, CA; [4]University of Utah Health, Salt Lake City, UT.*

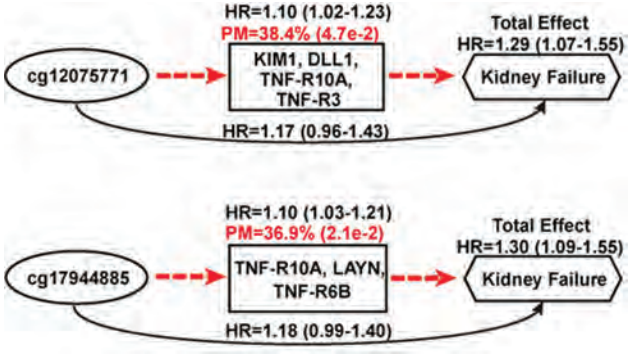
Background: In our recent study (*Chen Z, et al. ASN Kidney Week 2023*), we identified 17 whole blood DNA methylation (DNAmet) sites associated with risk of progression to kidney failure (KF) in type 1 diabetes (T1D) patients. Our prior study (*Md Dom Z I, et al. ASN Kidney Week 2022*) found multiple circulating proteins associated with progression to KF in diabetes. The current study aims to explore the possibility that the effect of DNAmet variation at KF-associated sites on risk of KF is mediated through elevated levels of KF-associated proteins.

Methods: We evaluated data from 264 T1D patients with diabetic kidney disease from the Joslin Kidney Study. The analysis focused on 17 KF-associated DNAmet sites in whole blood DNA and 21 circulating proteins associated with KF progression. Using the SAS MEDIATE Macro, we conducted mediation analyses within a Cox model framework, with the DNAmet as exposures, circulating proteins as mediators, and progression to KF as the outcome.

Results: Out of the 17 DNAmet sites investigated, variations at 5 were significantly associated with variation of at least one of the 21 KF-associated proteins. Among them, three DNAmet sites demonstrated an effect on risk of KF mediated through a single protein, while the remaining two DNAmet sites mediated effects on risk of KF through multiple proteins, cumulatively accounting for over 30% of the total effect on KF progression when combining the proteins as multiple mediators (Figure).

Conclusions: Our findings provide evidence for the first time that the impact of DNAmet variations at certain KF-associated DNAmet sites on risk of kidney failure is partially mediated by variation of plasma levels of multiple KF-associated circulating proteins. These findings may not only propose a novel predictive model for KF risk in patients with diabetes but may also help elucidate the molecular pathways involved in the KF progression in diabetes.

Funding: NIDDK Support, Private Foundation Support



FR-PO254

Sources and Carriers of Circulating MicroRNAs Associated with ESKD in Diabetes

Eiichiro Satake,[1,2] Bozena Krolewski,[1,2] Zaipul Md Dom,[1,2] Maryalice Hartley,[3] Jill Willency,[3] Monika A. Niewczas,[1,2] Jonathan M. Wilson,[3] Kevin L. Duffin,[3] Andrzej S. Krolewski.[1,2] *[1]Joslin Diabetes Center, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Eli Lilly and Company, Indianapolis, IN.*

Background: Our previous study identified 17 (8 risk and 9 protective) circulating miRNAs associated with end-stage kidney disease (ESKD) in diabetes (*Satake et al, JASN 2021*). The current study investigated tissues/sources and carriers of these miRNAs.

Methods: We measured 2,083 human mature miRNAs in plasma and urine obtained from patients enrolled in the Joslin Kidney Study using the HTG EdgeSeq platform, which requires a small sample volume (15 µl) and does not require RNA extraction. Seventeen miRNAs associated with ESKD from these studies were quantified in blood exosomes, urine, lysates, and supernatants of HUVECs (human umbilical vein endothelial cells), RPTECs (renal proximal tubular epithelial cells), and fibroblasts to identify potential sources of miRNA expression and secretion. Plasma from patients was fractionated by FPLC and by size exclusion spin filters to help identify miRNA carriers in blood.

Results: Out of 17 ESKD miRNAs, none were derived from platelets. Risk miRNAs were predominantly found in plasma rather than cell components, while protective miRNAs were more abundant in cellular components. Several risk miRNAs were more abundant in urine than in plasma; most protective ones were abundant in plasma and almost absent in urine. In vitro experiments showed that risk miRNAs were more abundant in supernatants than in cell lysates in HUVECs and RPTECs, but not in fibroblasts. Regarding carriers, most ESKD miRNAs had significantly higher levels in plasma than in exosomes. Size exclusion chromatography identified that ESKD miRNAs were more abundant in the plasma free fraction that included smaller proteins than in lipoprotein particle fractions.

Conclusions: Our findings suggest that endothelial and proximal tubular cells could be a significant source of circulating ESKD miRNAs, and most of these miRNAs were bound to non-exosomal carriers that included proteins smaller than HDL cholesterol. It is important to understand the regulation of circulating ESKD miRNAs secretion, trafficking, and function to advance our understanding of the mechanisms of the progression of diabetic kidney disease to ESKD, so new therapeutic strategies can be developed.

Funding: NIDDK Support

FR-PO255

Spatially Resolved Transcriptomic Profiling of Diabetic Kidney Disease with Stepwise Analysis by Clinical Severity

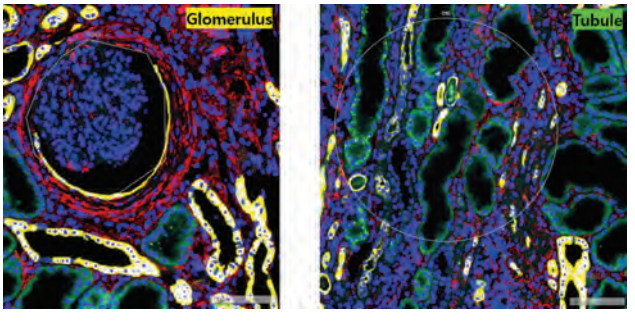
Jae-ik Oh,[2,1] Hyunah Ku,[1] Sehoon Park,[2] Dong Ki Kim.[1] *[1]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease worldwide. Using spatial transcriptomics, we investigated glomerular and tubulointerstitial gene expression profiles in DKD to uncover novel insights for potential biomarkers.

Methods: Spatial transcriptomic profiling using GeoMx was performed on FFPE kidney biopsy specimens from 26 DKD patients and 10 control samples collected from donor kidney biopsy. We configured 73 glomerular and 77 tubulointerstitial ROIs from DKD samples. We compared the gene expression levels of DKD samples with the controls using DESeq2, and performed linear regression analysis for DKD samples categorized as follows, proceeding in the order: 1) random UPCr < 3g/g & eGFR≥60, 2) UPCr≥3 & eGFR≥60, 3) UPCr≥3 & eGFR<60. Gene ontology (GO) annotation was performed using EnrichR and ToppGene, and DEG interactions were mapped with STRING.

Results: The STAT family, VCAM1, TGFB family, and VEGF family, all well known to be associated with DKD, appeared as significant DEGs and showed a significant trend in linear regression analysis (p-value < 0.05). In the tubulointerstitium, 1519 genes showed a negative correlation with worsening proteinuria and eGFR, including metallothionein gene family members (MT1F, MT1H, MT1X) known to mediate SFN renal protection fromd diabetes. G protein-coupled receptor activity and voltage-gated channel activity were among the top enriched GO terms. In the glomeruli, 153 genes showed a positive correlation with worsening proteinuria and eGFR, including SREBF1 and PARL, which are associated with mitophagy regulation. This suggests that a PARL inhibitor may help prevent DKD progression by promoting efficient removal of damaged mitochondria from hyperglycemic conditions. Ribosomal subunits and collagen-containing extracellular matrix were among the top enriched GO terms.

Conclusions: Our study identifies potential therapeutic targets for DKD, supported by consistent trends observed in linear regression analysis. Especially, our findings suggest the potential clinical significance of targeting PARL in DKD.



FR-PO256

Cell States and Niches in Diabetic Kidneys Identified by Spatial Mapping of Targeted Gene Panel at Single-Cell Resolution

Su Woong Jung, Ju young Moon, Sangho Lee, Tae Hoon Lee, Yang Gyun Kim, Hyun Ji Lim, Young yoon Moon, Yoosun Joo. *Kyung Hee University, Seoul, Republic of Korea*.

Background: Technical advance in single-cell genomics ushers into deeper understanding of kidney disease. As kidney is an elaborately organized structure, single-cell research at spatial context in this organ is highly required but few of researches have been tried. Here, we investigated spatial organization of various types of cells in diabetic kidney disease using Xenium In Situ.

Methods: Using Xenium In Situ, we generated single-cell spatial datasets for 475 targeted genes from 4 formalin-fixed, paraffin-embedded human kidney tissues obtained by renal biopsy, which were pathologically diagnosed as advanced stage of diabetic kidney disease.

Results: We created an atlas composed of 168,904 cells and identified major cell types in the kidneys by supervised annotation of marker gene expressions, such as WT1 for podocyte, AQP1 for proximal tubular cells and descending limb of Loop of Henle, CXCL12 for fibroblast, and PTPRC for immune cells. Most of proliferating cells belonged to B cells and macrophages were classified into LYVE^{high}, CCL2^{high}, LGMN^{high}, and others. We defined 12 spatial cellular niches, some of which corresponded to nephron and collecting duct comparment and injury-associated specific cell-enriched comparments such as myofibroblast, B cells, T cells, and plasma cells. These pathologic niches were in close promixity each other, of which forms tertiary lymphoid tissues in which plasma cell niches were surrounded outwardly by B cell and fibroblast niches.

Conclusions: Targeted spatial datesets defines normal and pathologic cellular niches in diabetic kidneys, the latter of which are thought to be the hub for disease propagation.

Funding: Private Foundation Support

FR-PO257

Liquid Chromatography Tandem Mass Spectrometry Analysis of Lipidomic Differences between Renal Cortex and Medulla in db/db Mice

Hyun Ji Lim,[1] Tae Hoon Lee,[2] Young yoon Moon,[2] Yoosun Joo,[2] Su Woong Jung,[2] Yang Gyun Kim,[2] Sangho Lee,[2] Ju young Moon.[2] *[1]Kyung Hee University, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea*.

Background: Lipids play crucial roles in various biological processes and are involved in the development and progression of many diseases, including diabetes. The lipid compositions in the renal cortex and medulla are different, each performing distinct functions in maintaining body homeostasis. Increased accumulation of lipid droplets and alterations in lipid metabolism have been reported, suggesting potential implications for understanding pathological mechanisms associated with diabetes.

Methods: To further explore lipidomic variations across kidney compartments, we employed tandem mass spectrometry and MALDI-Imaging mass spectrometry. We utilized db/db mice, a widely used model for examining diabetic nephropathy, and lipid extractions were performed on the cortex and medulla for LC-MS/MS while for IMS assessment, we prepared FFPE kidney tissue slides using the whole kidney.

Results: As a result, we identified a total of 390 lipids in medulla and 396 lipids in the cortex. The lipid profile differed between the renal cortex and medulla. In the medulla, ceramide-1-phosphate showed significant changes, while in the cortex, ceramide and phosphatidic acid were notably altered. When comparing the MALDI imaging results with the LC-MS/MS results, PC 34:4 and PC 34:3 increased in the medulla, while PC 32:0 increased in the cortex. Furthermore, the levels of PA 36:0 decreased in the cortex, while TG 46:0 and PE 40:3 decreased in the medulla. Pathway enrichment analysis using relational database of metabolomics pathways (RaMP) revealed distinct biological pathway alterations between renal cortex and medulla. Notably, signaling pathways such as insulin signaling exhibited showed significant changes in the medulla, whereas inflammation and immune-related pathways were altered in the cortex.

Conclusions: Our comprehensive examination of lipid composition revealed distinct differences in lipid metabolism between the kidney cortex and medulla. This study could help in identifying pathogenic alterations in the kidney, shedding light on the mechanisms underlying lipid dysmetabolism and diabetic kidney disease.

FR-PO258

Calciprotein Particles Appear to Be Uniquely Present in Diabetic Kidneys

John P. Shapiro,[1] Angela R. Blissett,[1] Leon J. Schurgers,[2] Anjali A. Satoskar,[1] Brad H. Rovin.[1] *[1]The Ohio State University, Columbus, OH; [2]Universiteit Maastricht, Maastricht, Netherlands.*

Background: Diabetes mellitus is commonly associated with diabetic kidney disease (DKD) that can progress to chronic kidney disease and end stage kidney disease. Mass spectrometry (MS) proteome analysis was performed on kidney biopsies obtained from the Kidney Precision Medicine Project (KPMP). Potential biomarkers and molecular mediators of DKD were explored.

Methods: KPMP obtained frozen kidney biopsy sections with DKD (n=11) and AKI (n=4) and normal controls from OSU biorepository (n=4) were analyzed using laser capture microdissection in combination with mass spectrometry. Spectral count global normalization was performed and the proteome of DKD was compared to AKI and controls. Immunofluorescence (IF) microscopy was performed on a cohort of OSU DKD and normal biopsies to confirm mass spectrometry findings.

Results: Analysis of MS data identified secreted phosphoprotein 24 (SPP24), Matrix gla protein (MGP), fetuin-A (AHSG) and serum amyloid P-component (APCS) as uniquely overexpressed in the glomeruli of DKD patients. All 4 proteins demonstrated IF co-localization within the mesangium and interstitial vasculature showing punctate and diffuse staining. These 4 proteins are known to bind to calciprotein particles (CPPs) which are protein decorated cores of calcium/phosphate. Using a monoclonal antibody specific to uncarboxylated MGP (ucMGP), a version of MGP associated with vascular calcification, we demonstrated similar IF staining pattern as the other proteins. Examination of electron micrographs from patients with kidney disease indicates the characteristic presence of electron dense particles only in the expanded mesangium of DKD patients. We believe the IF staining observed in the mesangium and interstitial vasculature and the electron dense particles observed ultrastructurally in DKD glomeruli are correlated and consist of SPP24, ucMGP, APCS and ASHG decorated CPPs.

Conclusions: SPP24, ucMGP, APCS and AHSG decorated CPPS are present in the mesangium and vasculature of DKD patients. Further studies are required to examine the effects of the CPPs and associated proteins in the glomeruli and vasculature of diabetic patients but they could be responsible for induction of endothelial and vascular smooth muscle inflammation and calcification.

Funding: Other NIH Support - kidney precision medicine project

FR-PO259

Understanding the Protective Role of Podocyte-Specific ApoJ in Diabetic Kidney Disease

Nehaben A. Gujarati, Malaika Zaidi, Emily Htam, Sandeep K. Mallipattu. *Stony Brook University Renaissance School of Medicine, Stony Brook, NY.*

Background: Mechanisms that confer resistance to progression of diabetic kidney disease (DKD) are unclear. While podocyte loss occurs early in DKD, proximal tubule (PT) injury ultimately determines DKD progression. ApoJ/Clusterin, a secreted molecular chaperone, is increased in human and mouse models of diabetic kidney disease (DKD). However, the role of ApoJ in mediating the progression of DKD remains understudied. Here, we investigate the mechanism by which podocyte-specific ApoJ preconditions the proximal tubule to attenuate the progression of DKD.

Methods: Human podocytes with ApoJ overexpression were generated using lentiviral method and the podocyte secretome was collected. Uninephrectomy + streptozotocin was used as a diabetic mouse model with the respective control mice. Pharmacological inhibition of CaMK1d, using STO-609, was conducted in primary PT cells and diabetic mice. Oxygen consumption rate (OCR) was measured using a seahorse analyzer. PAS, H&E, picrosirus red, immunofluorescence staining, qPCR and western blot were performed.

Results: Primary PT cells treated with the secretome from podocytes overexpressing ApoJ demonstrated an increase in OCR and pDrp1 levels with a decrease in mitochondrial fragmentation under high glucose (HG) conditions compared to control conditions. Inhibition of Lrp2/megalin using cilastatin mitigated this increase in OCR, suggesting that podocyte-specific ApoJ binds to Lrp2. ApoJ also colocalizes with Lrp2 by immunostaining in the apical surface of the proximal tubule in diabetic mice. IP for calmodulin demonstrated that ApoJ interacts with CaMK1d. *Camk1d-/-* as well as treatment with STO-609 reduced pDrp1 levels, OCR, and CaMK1d kinase activity with an increase in mitochondrial fragmentation and cell injury in primary PT cells. Similarly, STO-609-treated diabetic mice exacerbated PT injury as compared to VEH-treated diabetic mice.

Conclusions: These data suggest that under diabetic conditions, the podocyte-specific ApoJ preconditions the PT against injury by undergoing PT uptake via Lrp2, leading to CaMK1d-mediated restoration of mitochondrial function to prevent DKD progression.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO260

STING-Dependent Podocyte Injury Is Associated with Impaired Mitophagy in Diabetic Kidney Disease (DKD)

Veronika Semenova. *University of Miami Miller School of Medicine, Miami, FL.*

Background: Inflammation plays a significant role in the pathogenesis of diabetic kidney disease (DKD), the most prevalent cause of end stage kidney disease in the USA. We have demonstrated increased glomerular and podocyte expression of the stimulator of interferon genes (STING) pathway in DKD, suggesting that modulated innate immune responses may contribute to glomerular injury. Release of mitochondrial DNA (mtDNA) into the cytoplasm leads to STING activation but the exact mechanism is unknown. Cytosolic mtDNA leakage in DKD is associated with loss of mitochondrial transcription factor A (TFAM) and altered PTEN-induced putative kinase 1 (PINK1)-mediated mitophagy. We hypothesize that TFAM deficiency causes mtDNA escape and STING-mediated podocyte injury via defective PINK1-mediated mitophagy.

Methods: In vitro, human podocytes with knockdown of STING (shSTING), TFAM (shTFAM) and scrambled control (shCTRL) were used to evaluate mitophagy and cytosolic mtDNA. STING and PINK1 expression in shTFAM was assessed by Western blot. In vivo, 16-week-old control (db/+) and diabetic (db/db) mice were used to evaluate TFAM and PINK1 expression by Western blot, mitochondrial morphology by TEM and renal cortical cytosolic mtDNA content by qRT-PCR. Control and STING knockout (STING KO) mice were treated with mtDNA (5mg/kg, 24h) and mice with podocyte specific Tfam deletion (pTFAMfl/fl) were injected with streptozotocin (STZ, 40 mg/kg) to induce diabetes followed by urinary albumin-to-creatinine ratio (ACR), histological and serum analyses. Two-tailed t-test or One-Way ANOVA followed by Tukey's post-test were used to detect statistical changes.

Results: Increased levels of renal cytosolic mtDNA in db/db mice were associated with decreased glomerular TFAM expression and increased PINK1 expression. shTFAM podocytes had increased PINK1 expression and less efficient mitophagosome formation. STING deficiency protected from mtDNA-induced injury in vitro and in vivo. While pTFAMfl/fl mice had no baseline renal injury, STZ treatment resulted in worse renal injury in pTFAMfl/fl mice compared to wildtype.

Conclusions: Our data suggest that podocyte STING activation is driven by TFAM deficiency-mediated mitophagy in association with increased PINK1. Targeting the TFAM/PINK1/STING pathway may lead to new treatment options for DKD.

FR-PO261

Aberrant N-glycation of Complement Factor H Contributes to Alternative Pathway Activation and Disease Progression in Diabetic Kidney Disease

Ying Zhang, Guolan Xing. *The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.*

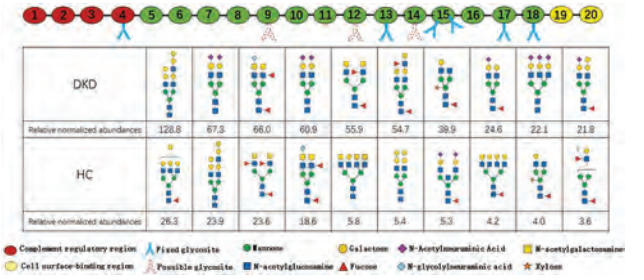
Background: An increasing body of evidence points to an essential role for the activation of complement alternative pathway (AP) in the pathogenesis of diabetic kidney disease (DKD). However, the precise mechanisms of AP activation in DKD are still poorly defined. Complement factor H (CFH), the key regulator of the AP, exerts its decay acceleration activity and cofactor activity to tightly control AP activation. Of note, CFH is a glycoprotein containing 9 N-glycosites, where N-glycation probably affects its 3D structure and function.

Methods: Site-specific N-glycation profile of CFH, including glycosite occupancies, glycan compositions, structural types, and branching patterns, were analyzed using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS). MS data were processed using Byonic software for glycopeptide identification. Subsequently, the AP activity and decay acceleration activity of CFH were measured by ELISA, and the cofactor activity of CFH was evaluated by SDS-PAGE.

Results: Among the 9 N-glycosites, 3 sites (Asn529, Asn718, and Asn822) were unoccupied in controls but occupied in DKD patients. The remaining 6 sites showed consistent N-glycation, with 4 of them exhibiting a higher occupancy rate in DKD. A total of 147 N-glycan compositions were identified in CFH of DKD patients, far exceeding the 25 N-glycans found in controls. CFH from DKD patients revealed increased relative normalized abundances of N-glycans compared to controls. Sialylation was a common branching pattern of CFH, with higher levels observed in DKD. Both the decay acceleration activity and cofactor activity of CFH were reduced, while levels of AP activity were elevated in DKD patients. The amounts of N-glycans in CFH was positively correlated to proteinuria and negatively correlated to eGFR.

Conclusions: Advanced N-glycation of CFH reduced its regulatory capacities, leading to complement AP activation. Aberrantly N-glycated CFH was demonstrated in DKD patients and associated with the activity and severity of renal injury.

Funding: Government Support - Non-U.S.



N-glycation profile of CFH from DKD patients and healthy controls

FR-PO262

Leucine Predicts Progression of Diabetic Kidney Disease and Mediates Metabolic Remodeling in Kidney Tubular Cells of Diabetic Models

Caifeng Shi, Songyan Qin, Aiqin He, Xiaomei Wu, Yemeng Wan, Yu Xiao, Dandan Liu, Lei Jiang, Chunsun Dai, Yang Zhou. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease and end-stage renal failure; however, the dominant mechanisms remain obscure and few biomarkers are available. We recently performed a targeted metabolomics study to identify leucine as a novel metabolite biomarker of DKD. Here, we evaluated whether leucine could play a role in progression of kidney disease in patients with diabetes.

Methods: Urine from participants with diabetes from two independent cohorts determined whether urinary leucine-to-creatinine ratio (ULeuCR) could be a mechanistic biomarker for progression of DKD as demonstrated by composite kidney outcomes, including rapid decline in kidney function, end-stage renal failure, and death from a renal cause. Whether defective leucine degradation causes DKD was assessed by metabolic flux assay and metabolomics analysis in kidney tubular epithelial cells and diabetic mice models.

Results: Composite kidney outcomes were associated with the higher ULeuCR quantile in both discovery cohort (HR 4.55, 95% CI 1.40-14.78) and validation cohort (HR 2.93, 95% CI 1.44-5.97). Kidney function decline was associated with the higher ULeuCR quantile in both female (HR 3.78, 95% CI 1.31-10.95) and male (HR 3.35, 95% CI 1.64-6.82) patients with diabetes. Metabolites and enzymes measurement suggested defective leucine degradation in kidney tubular epithelial cells during the progression of DKD. Genetic or pharmacological improvement of leucine degradation by repressing branched-chain ketoacid dehydrogenase kinase (BCKDK) relieved glucose-induced metabolic remodeling in tubular cells and mitigated DKD in diabetic mice models. Hypoxia inducible factor 1α promoted BCKDK expression. In vitro experiment indicated that leucine stimulated metabolic remodeling in tubular cells via mTOR signaling pathway. Restriction of dietary leucine content was found to dramatically reduce albuminuria, kidney hypertrophy and lipid accumulation in diabetic mice models.

Conclusions: We reveal defective leucine degradation in kidney tubules from diabetic subjects and propose leucine as a causative factor in DKD, which warrants further exploration as therapeutic targets.

Funding: Government Support - Non-U.S.

FR-PO263

Mitochondria-Associated Endoplasmic Reticulum Membranes Activating Mitochondrial Apoptosis through Rtn4b/P53/Ei24 Pathway in Podocytes under High-Glucose Condition

Shanzhi Yang, Xiaoyan Bai, Peimin Liu. *Guangdong Provincial People's Hospital, Guangzhou, China.*

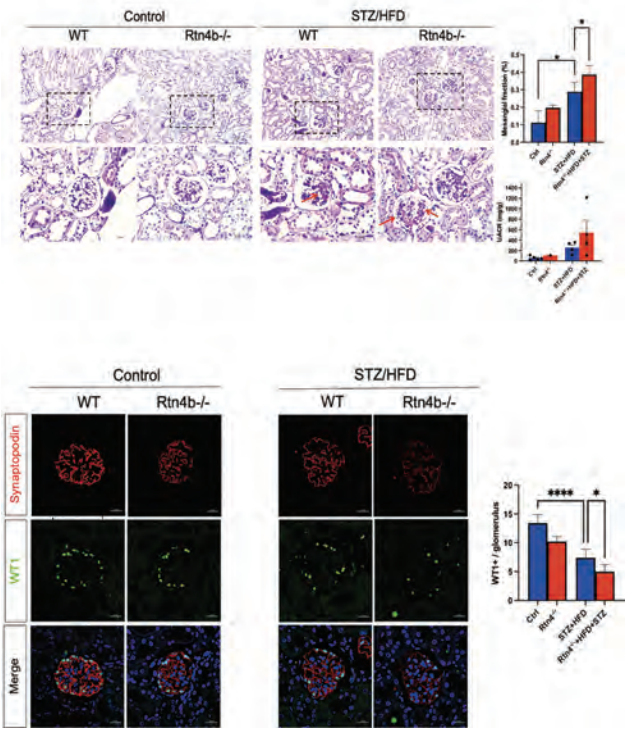
Background: Diabetic nephropathy (DKD) is a global health problem with complex pathogenesis and limited treatment options. The mitochondria-associated endoplasmic reticulum membrane (MAM) is essential for maintaining the normal function of both organelles. In our previous studies, we found the expression level of reticulon 4B (Rtn4b) in renal biopsy tissues of patients with DKD was significantly decreased.

Methods: Here, we explore the underlying role and mechanism in deletion of RTN4B induces podocyte injury.

Results: Results showed as the DKD progresses, the expression level of Rtn4b was gradually decreased in renal biopsy tissues (Fig 1). Altered expression was also observed in type 2 diabetes mice. As with the extension of time of high-glucose exposure, the expression level of Rtn4b in podocytes was gradually decreased. Inhibition of the expression of Rtn4b significantly down-regulated podocyte marker protein synaptopodin, nephrin and podocin.(Fig 2) In *vivo*, global knockout (KO) of Rtn4b deterioated renal function and pathology as presented by aggravated albuminuria, expanded glomerular mesangium and worsened podocyte injury in diabetic mice model (Fig 3). Mechanistically, p53 signaling pathway was among the top 10 enriched items, and mitoptosis related

marker Ei24 ranked the highest score in the differential analysis in HG-cultured podocytes transfected with Rtn4b siRNA (Fig. 4). silencing Rtn4b promoted P53 activation via Ei24 mediated mitochondrial apoptotic pathway (Fig. 5).

Conclusions: Altogether, these results suggest that Rtn4b protects podocytes from diabetic injuries by preventing ER-Mitochondrial crosstalk from mitoptosis and targeting Rtn4b may be a potential therapeutic approach in DN.



FR-PO264

Single-Cell Spatial Metabolomics Reveal That Methylthioadenosine Phosphorylase (MTAP)-Derived Adenine Production Regulates Tubular Mitochondrial Bioenergetics in Type 1 Diabetes (T1D)

Soumya Maity,[1] Ian M. Tamayo,[1] Guanshi Zhang,[1] Alaa Kroma,[1] Hak Joo Lee,[1] Laura Pyle,[2] Ye Ji Choi,[2] Petter Bjornstad,[2] Kumar Sharma.[1]
[1]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [2]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO.

Background: Type 1 diabetic patients (T1D) have an estimated 50% risk of developing diabetic kidney disease (DKD) over time. Mitochondrial dysfunction is associated with DKD progression. Our prior study identified endogenous adenine accumulation as a causative factor for DKD and methylthioadenosine phosphorylase (MTAP) as a major adenine-producing enzyme in Type 2 diabetes. In this study, we employed matrix-assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI) to determine the cell-type-specific MTAP-derived adenine effect on mitochondrial bioenergetics.

Methods: Kidney biopsies from young T1D patients (n=17; 24.4±2.6 year) and healthy controls (HC) (n=7; 23.7±4.05 year) were subjected to MSI to estimate the adenine abundance *in situ*. Human proximal tubular (HK2) cells and rat podocytes were co-cultured in normal glucose (5.5mM) containing media on the ITO-coated slide. The cell monolayer was fixed with 4% formalin followed by MSI with 10 µm spatial resolution to evaluate cell-type specific adenine production. The pre-MALDI autofluorescence (AF) image was overlaid with the MALDI ion image to determine the metabolomic signature of a single cell. Western blot and mitochondrial oxygen consumption rate (OCR) were performed in MTAP knockdown mouse proximal tubular (MCT) cells to investigate the role of MTAP in adenine-induced renal pathology and mitochondrial bioenergetics.

Results: MSI data revealed that adenine is significantly accumulated in T1D kidneys compared to HC. Single-cell spatial metabolomics revealed substantially higher adenine production in HK2 cells compared to podocytes. Moreover, 24h 25 mM glucose (HG) treatment showed adenine overproduction in HK2 cells compared to normal glucose. MTAP protein level was significantly increased with HG, suggesting MTAP-derived adenine overproduction in diabetic conditions. Knockdown of MTAP with siRNA enhanced OCR and inhibited HG-induced fibronectin expression in MCT cells, indicating intracellular adenine abundance regulates mitochondrial bioenergetics and DKD pathology in proximal tubules.

Conclusions: Our findings demonstrate that MTAP-derived adenine overproduction may be associated with tubular mitochondrial dysfunction in diabetes, and high kidney adenine may be an early driver of kidney disease in T1D.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO265

Prevention of Diabetic Nephropathy with Mesenchymal Stromal Cells in Cardiac Surgery Patients and in Nonobese Diabetic (NOD) Mice and Diabetic Dogs with "Neo-Islets," Three-Dimensional Organoids of Mesenchymal Stem Cells (MSCs), and Pancreatic Islet Cells

Christof Westenfelder,[1,2] Anna Gooch.[2] *[1]University of Utah Health, Salt Lake City, UT; [2]SymbioCellTech, LLC, Salt Lake City, UT.*

Background: The most common cause of dialysis requiring ESKD is DNP. Prevention of this serious complication is urgently needed. We addressed this need by utilizing the potent capacity of MSCs to prevent AKI and 2° CKD and to provide immune isolation in Neo-Islet (NI) treated autoimmune T1DM. In a Clinical Trial (NCT00733876) in cardiac surgery patients, at high risk for post-op AKI, we compared the renoprotective efficacy of allogeneic MSCs in diabetic to that in non-diabetic subjects. In 2 preclinical studies we investigated whether the therapy of auto-immune T1DM in NOD mice and dogs (INAD012-776) with allogeneic NIs would prevent DNP.

Methods: Clinical Trial: 16 adult patients, 7 diabetic, undergoing on-pump cardiac surgery (CABG ± valve) and being at high risk for post-op AKI were infused via the suprarenal aorta with allogeneic MSCs. Vital signs, renal function and glycemic control were monitored for 10 yrs and compared to those of well-matched historical controls (n=105). Therapy (i.p.) of diabetic NOD mice and dogs with allogeneic NIs: the response of diabetic NOD mice (n=7) vs. controls (n=7) was monitored x 12 wks and in diabetic dogs (n=9) x 3 yrs. Immune responses and mouse renal pathologies were examined.

Results: Clinical Trial: none of the MSC treated diabetic and non-diabetic patients developed post-op AKI or progressed over 10 years to DNP/ESKD. No mortality and no allo-immune response. In contrast, a significant percentage of historical controls developed post-op AKI, progressed to ESKD and suffered mortalitiy. Response of diabetic NOD mice and dogs to NIs: All NOD mice became euglycemic, none developed DNP, while diabetic controls did. Daily insulin needs of TIDM dogs were durably (3 yrs) reduced by 50% ($p< 0.01$), body weights were stable, blood glucose and HbA1C levels and albuminuria were normalized, renal and liver functions, lipid profiles and CBCs remained normal, and no immune responses to NIs or AEs/SAEs were observed.

Conclusions: These studies demonstrate that these biotherapies prevented the development of DNP and ESKD, and this without the need for anti-rejection drugs. The FDA approved the conduct of our IND-enabling study needed for the planned Phase I/II Clinical Trial in which the therapeutic efficacy of human NIs will be tested in T1DM subjects.

Funding: Commercial Support - SymbioCellTech

FR-PO266

LncRNA evf-2 Exacerbates Podocyte Injury in Diabetic Nephropathy by Inducing Cell-Cycle Reentry and Inflammation through Distinct Mechanisms Triggered by Heterogeneous Nuclear Ribonucleoprotein U (hnRNPU)

Jia Guo, Chaojie Zhang, Zhangsuo Liu. *The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.*

Background: Albuminuria is a hallmark of diabetic nephropathy (DN), heralding the onset of progressive renal dysfunction. Podocyte injury stands as a primary contributor to proteinuria in DN. Our previous study revealed a significant upregulation of lncRNA EVF-2 in podocytes of DN patients, correlating with cell cycle re-entry and inflammation. Notably, the potential contribution of evf-2 to the pathogenesis and progression of kidney diseases, particularly DN, remains largely unexplored.

Methods: We used specific knockout or knockdown of lncRNA evf-2 in diabetic mice or cultured podocytes to confirm the effects of evf-2 in DN. RNA sequencing of evf-2-overexpressing podocytes was used to find out the molecular pathways. Chromatin Isolation by RNA purification-mass spectrometry (ChIRP-MS) was performed to find out the binding proteins of evf-2.

Results: Specific knockout or knockdown of lncRNA evf-2 in diabetic mice or cultured podocytes alleviated podocyte injury driven by cell cycle re-entry and inflammation. RNA sequencing of evf-2-overexpressing podocytes unveiled a predominant enrichment of upregulated mRNAs in cell cycle and inflammation pathways, with alternative splicing events occurring in cell cycle-related mRNAs Ccnb1 and Tacc3 but not in upregulated inflammatory factors. Chromatin isolation by RNA purification- mass spectrometry (ChIRP-MS) analysis highlighted the involvement of ribonucleoprotein complex and mRNA processing-related proteins, with hnRNPU emerging as the primary binding partner of evf-2 in spliceosomes. Partial restoration of the upregulation of the cell cycle and inflammation-related mRNA expression induced by evf-2 overexpression occurred upon hnRNPU-specific knockdown, accompanied by changes in splice variants of Ccnb1 and Tacc3 mRNAs (Ccnb1-202/201 and Tacc3-207/206).

Conclusions: Our study elucidates the interaction between lncRNA evf-2 and hnRNPU, culminating in the upregulation of cell cycle-related genes and inflammatory factors through diverse pathways, potentially involving transcriptional activation, RNA stability modulation, alternative splicing or translational regulation. These findings introduce a novel molecular target and signaling pathway for the treatment of DN.

Funding: Government Support - Non-U.S.

FR-PO267

Cell Type- and Diabetic Kidney Disease-Specific Expression of Long Noncoding RNAs in Human Kidneys

Juliette A. de Klerk,[1,2] Roderick Slieker,[2] Haojia Wu,[3] Yoshiharu Muto,[3] Floris Herrewijnen,[2] Leen M. 't Hart,[2] Rudmer J. Postma,[1] Loïs van der Pluijm,[1] Janneke H. Peerlings,[2] Hans J. Baelde,[4] Tessa Gerrits,[4] Anton J. Van Zonneveld,[1] Benjamin D. Humphreys,[3] Roel Bijkerk.[1]
[1]Department of Internal Medicine, Division of Nephrology, Leiden University Medical Center, Leiden, Netherlands; [2]Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, Netherlands; [3]Department of Medicine, Division of Nephrology, Washington University School of Medicine, Saint Louis, MO; [4]Department of Pathology, Leiden University Medical Center, Leiden, Netherlands.

Background: Long non-coding RNAs (lncRNAs) play diverse roles within cells, often show cell type-specific expression and impact kidney function. Despite the emergence of single-cell RNA sequencing studies to understand cell specificity, past studies focus solely on the protein coding genome. We hypothesize that lncRNAs, due to their cell type-specific nature, have crucial functions within specific renal cells. Our study aims to characterize and explore the roles of lncRNAs in different cell types in human kidneys and their relationship with diabetic kidney disease (DKD).

Methods: To focus specifically on the non-coding region of the genome We reprocessed single-cell RNA sequencing data from kidney samples that were obtained from six control patients, and seven patients with diabetic kidney disease. We characterized lncRNAs in individual cells and identified cell type-specific lncRNAs as well as lncRNAs which were differentially expressed in DKD. RNAscope was used to validate identified lncRNA expression in the kidney.

Results: Among the 10,342 lncRNAs present in the single-cell RNA-seq dataset (constituting 37.5% of the total transcripts in the scRNA-seq), 349 exhibit cell type-specific expression across 15 different cell types in the human kidney, with 104 showing significant associations with DKD. We set up gene regulatory networks to explore functional roles of differentially expressed lncRNAs in the different cell types. We identified *TARID*, a podocyte-specific lncRNA, to be upregulated in DKD, and to strongly correlate with genes involved in podocyte morphology abnormalities (such as abnormal podocyte foot processes), nephrotic syndrome, and albuminuria, while podocyte-specific expression of *TARID* was validated using RNAscope.

Conclusions: Our study provides a valuable resource for lncRNA expression across cell types in the human kidney and as illustrated by the identification of the podocyte specific lncRNA *TARID*, highlights the potential importance of cell type-specific lncRNAs in diabetic kidney disease.

FR-PO268

Targeting Dynein Activator, Dctn1, Ameliorates Podocytopathy in Streptozotocin (STZ)-Induced Diabetic Mice

Jillian Williquett, Chantal Allamargot, Emily J. Steinbach, Hua Sun.
University of Iowa Health Care, Iowa City, IA.

Background: Diabetic nephropathy (DN) is a severe complication of diabetes that contributes to 30-50% of patients developing end stage kidney disease. In our recent work, we showed an upregulation of dynein genes in diabetes. We have since demonstrated that diabetes suppresses AMP-activated protein kinase (AMPK), which activates specificity protein 1 (SP1)-mediated transcription of these dynein genes. Increased dynactin 1 (Dctn1), a dynein subunit that activates the motor protein, promotes trafficking of nephrin to lysosomes for degradation. The upregulation of Dctn1 correlates with a poor renal outcome in human DN, but its exact role in DN pathogenesis has not been defined. We hypothesize that inactivation of dynein via prevention of Dctn1 upregulation can rescue the disruptions to nephrin trafficking that lead to DN.

Methods: We generated a conditional transgenic mouse line with tamoxifen-inducible podocyte-specific knockdown of Dctn1 in C57BL/6 mice by crossing tamoxifen-inducible NPHS2-icre mice with Dctn1$^{loxp/}$ mice. Diabetes was induced by intraperitoneal (IP) injection of Streptozotocin (STZ) in Cre positive wt/wt and wt/loxp mice. Two weeks later, both the diabetic and nondiabetic mice received IP injections of tamoxifen. Co-staining of Cre recombinase and WT1 was performed to confirm a successful flox of Dctn1 in podocytes. The proteinuria of the mice, histology and ultrastructure of the mouse kidney were compared among diabetic and nondiabetic mice with or without podocyte-specific knockdown of Dctn1.

Results: Mice with STZ-induced diabetes showed features of DN, including proteinuria, glomerulosclerosis, and podocytopathy characterized by reduced nephrin protein with upregulated Dctn1. While Dctn1$^{icre, +/-}$ mice did not undergo spontaneous podocytopathy, they showed rescued disruptions to nephrin and podocytes in diabetic mice, as well as the subsequent development of proteinuria and glomerulosclerosis. The knockdown and normalized expression of Dctn1 in diabetic mouse podocytes prevented the loss of nephrin protein and preserved the foot processes and slit diaphragm structure of podocytes.

Conclusions: Inactivation of dynein via prevention of Dctn1 upregulation protects STZ-mice from developing DN. By elucidating the protective effect of targeting dynein in diabetes-induced mistrafficking of nephrin, we provided a new therapeutic strategy for DN.

Funding: Other NIH Support - NIH 1R01DK136563 (PI: H. Sun); 5K12HD027748 (PI: Bassuk), Private Foundation Support

FR-PO269

VAPB Regulates Fatty Acid Oxidation via Maintaining the Integrity of Mitochondria-Associated Endoplasmic Reticulum Membranes in Diabetic Kidney Disease (DKD)

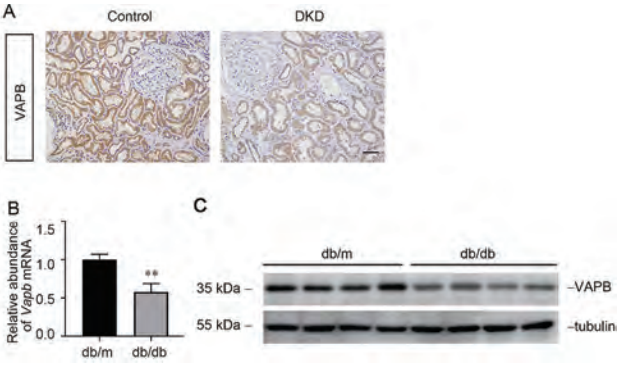
Ting Cai, Xiaobin Liu, Liang Wang. *The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi, China.*

Background: Defective fatty acid oxidation (FAO) in renal tubular epithelial cells plays an important role in the progression of diabetic kidney disease (DKD). Contact between lipid droplets and mitochondria facilitates mitochondrial FAO. We performed transcriptome-wide association studies (TWAS) and identified vesicle-associated membrane protein-associated protein B (VAPB),an ER-anchored protein that mediates tethering between ER and mitochondria, as a potential causative gene for DKD. In this project, we aim to investigate whether VAPB affects FAO in DKD and to elucidate the underlying mechanism.

Methods: VAPB adenovirus or negative control was delivered to the kidneys of male db/db mice and littermate db/m mice at 12 weeks of age by intra-parenchymal injection, and kidneys were harvested 4 weeks after injection. Primary renal tubular cells were transfected with VAPB adenovirus or negative control and then exposed to the high glucose (30mM) treatment for the indicated time.

Results: VAPB expression was found to be decreased in renal tubules of patients with DKD and db/db mice. Inducing overexpression of VAPB attenuated tubular injury and lipid droplet accumulation, and restored expression level of FAO-related enzymes (PPAR-α,ACADL) both in vivo and in vitro. Mechanistically, analysis of VAPB binding partners and membrane contact sites revealed that mitoguardin2 (MIGA2), a mitochondria outer membrane protein and lipid droplet binding protein, may interact with VAPB to maintain the integrity of mitochondria-associated endoplasmic reticulum membranes (MAMs). We found that high glucose reduces the binding of VAPB to MIGA2, disrupts the integrity of MAMs, and increases the distance between lipid droplets and mitochondria in vitro.

Conclusions: We proposed that VAPB may regulate fatty acid oxidation in renal tubules in DKD by maintaining the integrity of MAMs through interaction with MIGA2, which promotes contact between lipid droplets and mitochondria.



FR-PO270

Novel Variant of ARHGEF18 Increases Susceptibility to Adriamycin-Induced Podocyte Injury

Nanditha Anandakrishnan, Jonathan C. Haydak, Anika Hudson, Maria Paola Santini, John C. He, Girish N. Nadkarni, Evren U. Azeloglu. *Icahn School of Medicine at Mount Sinai Department of Medicine, New York, NY.*

Background: Diabetic kidney disease (DKD) is a leading cause of end-stage kidney disease (ESKD) however, therapies have been limited due to disease heterogeneity. Using deep learning we recently identified a novel nonsynonymous disease-causing variant within the Rho GTPase regulatory gene *ARHGEF18* associated with higher risk of ESKD. Overexpression of ARHGEF18 in human podocytes led to impairments in focal adhesion

architecture, cytoskeletal dynamics, cellular motility, and RhoA/Rac1 activation. Here, we further validate the pathophysiology observed *in vitro* using a transgenic mouse model.

Methods: Publicly available KPMP snRNA-seq data was analyzed using Seurat. We created a transgenic mouse line using CRISPR-Cas9 knock-in system to introduce a global G>A point mutation on the mouse *Arhgef18* gene (A1268T), replicating the human rs117824875 variant. We performed retroorbital Adriamycin (ADR) injections in male mice aged 11-13 weeks at 15 mg/kg and urine was collected at baseline and after 1 week to measure the urinary albumin-creatinine ratio (UACR).

Results: We previously showed that rs117824875 led to a pathological accumulation of ARHGEF18 in immortalized podocytes due to increased protein stability, suggesting that increased levels of ARHGEF18 are detrimental to podocytes. Podocyte snRNA-seq data from the KPMP database showed an increased expression of ARHGEF18 in DKD as well as CKD patients (**Figure 1A**). In our transgenic mouse model, we observed a significant increase in UACR in the A1268T mice compared to the WT at one-week after ADR injections (**Figure 1B**). PAS staining and transmission electron microscopy showed increased glomerular area and podocyte foot process effacement, respectively in the A1268T mutant mice compared to the WT (**Figure 1C-D**).

Conclusions: Our data shows that A1268T transgenic mouse model showed increased susceptibility to ADR induced kidney injury. Targeted degradation strategies could be developed as a therapeutic option for management of DKD and CKD.

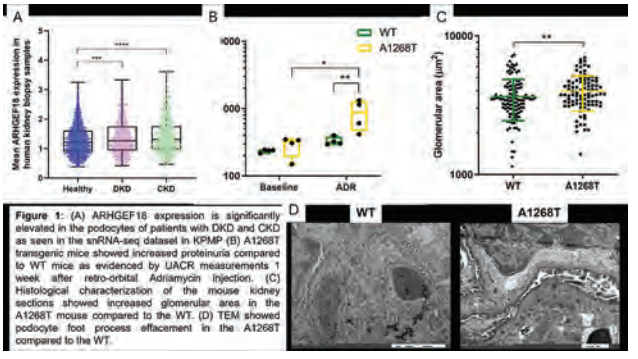


Figure 1: (A) ARHGEF18 expression is significantly elevated in the podocytes of patients with DKD and CKD as seen in the snRNA-seq dataset in KPMP (B) A1268T transgenic mice showed increased proteinuria compared to WT mice as evidenced by UACR measurements 1 week after retro-orbital Adriamycin injection. (C) Histological characterization of the mouse kidney sections showed increased glomerular area in the A1268T mouse compared to the WT. (D) TEM showed podocyte foot process effacement in the A1268T compared to the WT.

FR-PO271

Dehydrolithocholic Acid Mitigates Diabetic Kidney Disease by Activating TGR5 and FXR

Hua Zhou. *The Third affiliated Hospital of Soochow University, Changzhou, China.*

Background: Diabetic kidney disease (DKD) is a significant contributor to chronic kidney disease, with metabolic factors playing a crucial role in its development. Our study aimed to investigate the impact of bile acid (BA) metabolism on DKD progression and to explore the mechanisms through which BA metabolism influences DKD.

Methods: Plasma BA levels in healthy control (HC), type 2 diabetes mellitus (T2DM), and DKD groups were measured using ultrahigh-performance liquid chromatography tandem-mass spectrometry (UPLC-MS/MS). Following the identification of potential biomarkers in the clinical study, further in vivo validation was performed. Dehydrolithocholic acid (DHLCA) intervention was administered to DKD mice, and samples of blood, urine, feces, and kidney tissues were collected at 20 weeks of age. Kidney injury was assessed using HE, PAS, and Masson staining. The expression of Takeda G protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR) in kidney tissues was analyzed using immunohistochemistry, immunofluorescence, real-time quantitative polymerase chain reaction (RT-qPCR), and western blot (WB). Gut microbiota (GM) metagenomic analysis and targeted BA metabolomics were conducted on fecal samples to assess changes in GM composition and BA levels following DHLCA intervention.

Results: Variations in BA levels were noted among HC, T2DM, and DKD groups. The DHLCA levels in the DKD with macroalbuminuria group were significantly lower compared to the T2DM group, and univariate correlation analysis revealed that DHLCA had the strongest correlation with the urine albumin-to-creatinine ratio (UACR) ($r = –0.329$, $P = 0.001$). In the DKD+DHLCA group, UACR, fasting blood glucose (FBG), liver function, and total BA (TBA) levels were significantly reduced compared to the DKD group alone. Kidney tissue pathology showed that DHLCA intervention mitigated renal tubular injury in DKD. Compared to the DKD group, the expression of TGR5 and FXR in kidney tissues was restored following DHLCA intervention. Metagenomic analysis revealed a significant alteration in GM composition in mice post-DHLCA intervention, marked by an increased presence of *Firmicutes*, particularly *Lachnospiraceae bacterium*.

Conclusions: BA metabolism is altered with the progression of DKD. DHLCA may enhance DKD renal tubular recovery by activating TGR5 and FXR. DHLCA could serve as a potential biomarker for DKD diagnosis and treatment.

Funding: Government Support - Non-U.S.

FR-PO272

Loss of Diabetic Nephropathy Phenotype and Higher Esm-1 Map to Germline Mutation in Splicing Factor Sfswap in Inbred Mice

Keshav Narang,[1] Haochen Guan,[1,2] Xiao Ran Luo,[1,3] Randeep S. Nandal,[1] Demetri Maxim,[1,4] Xiaoyi Zheng,[1,5] Vivek Bhalla.[1] *[1]Stanford University School of Medicine, Stanford, CA; [2]Anhui Provincial Hospital, Hefei, China; [3]Duke-NUS Medical School, Singapore, Singapore; [4]Nephrogen Inc., New York, NY; [5]BriaCell Therapeutics, Philadelphia, PA.*

Background: Only a subset of diabetic DBA/2 DN-susceptible mice develop albuminuria and glomerular leukocyte infiltration. Plasma levels of endothelial cell-specific molecule-1, Esm-1, an anti-inflammatory, secreted proteoglycan inversely correlate with albuminuria in mice and humans. Moreover, over-expression of Esm-1 in diabetic DN-susceptible mice prevents albuminuria and podocyte injury independent of blood glucose. Given an inverse correlation of Esm-1 and features of DN that we observed across generations of inbred mice, we explored the genetic regulation of plasma Esm-1 and susceptibility to DN.

Methods: Genomic DNA was extracted from frozen kidney tissue of N=4 mice / generation from before and after a loss of the DN phenotype and rise in plasma Esm-1. Next-generation sequencing (NGS) of 2x150 bp PCR-free paired-end libraries was performed on a NovaSeq 6000 S4 sequencer to a coverage depth of 30x. NGS data were analyzed using the Genome Analysis Toolkit pipeline for variant calling. Restriction fragment length Polymorphism with StuI and Sanger sequencing at a candidate variant locus were used to validate NGS data in N=21 non-diabetic mice across five generations.

Results: We identified a missense variant (nt 1407 CàA, Asn469Lys (N469K) in the Splicing Factor, Arginine/Serine-Rich 8 (Srsf8, Sfswap) gene. Analysis of this variant indicated a significant association of high plasma Esm-1 with presence of the homozygous variant compared to wild-type mice (4.54±0.45 vs. 1.25 ±0.26 ng/mL, $p<0.0001$). We found low (< 3 ng/mL) plasma Esm-1 in 10 out of 11 wild-type but only 2 out of 10 heterozygous or homozygous mutant mice. Heterozygote variant mice had an intermediate phenotype, indicating a gene dosage effect. Asn-469 is located in a binding domain indispensable for binding of Sfswap to similar splicing factors and is evolutionarily conserved. Further experiments to edit this variant in mouse endothelial cells and to quantify secreted Esm-1 are forthcoming.

Conclusions: Our findings reveal that the Sfswap mutant genotype is highly correlated with plasma Esm-1 levels in DN-susceptible mice. In addition to elucidating genetic drift within the DBA/2 mouse colony, these results may provide novel insights into the genetic regulation of Esm-1 and opposing roles of Sfswap and Esm-1 in protection from DN.

Funding: NIDDK Support

FR-PO273

Set7 Methyltransferase and Phenotypic Switch in Diabetic Glomerular Endothelial Cells

Sam El-Osta.[1,2] *[1]Baker Heart and Diabetes Institute, Melbourne, VIC, Australia; [2]Monash University Faculty of Medicine Nursing and Health Sciences, Melbourne, VIC, Australia.*

Background: Hyperglycemia influences the development of glomerular endothelial cell damage, and nowhere is this more evident than in the progression of diabetic kidney disease (DKD). While the Set7 lysine methyltransferase is a known hyperglycemic sensor, its role in endothelial cell function in the context of DKD remains poorly understood.

Methods: Single-cell transcriptomics was used to investigate Set7 regulation in a mouse model of DKD, followed by validation of findings using pharmacological and short hairpin RNA inhibition inhibition of Set7.

Results: Set7 knockout (Set7KO) improved glomerular structure and albuminuria in a mouse model of diabetes. Analysis of single-cell RNA-sequencing data showed dynamic transcriptional changes in diabetic renal cells. Set7KO controls phenotype switching of glomerular endothelial cell populations by transcriptional regulation of the insulin growth factor binding protein 5 (IGFBP5). Chromatin immunoprecipitation assays confirmed that the expression of the *IGFBP5* gene was associated with mono- and dimethylation of histone H3 lysine 4 (H3K4me1/2). This generalizability was investigated in human kidney and circulating hyperglycemic cells exposed to TGFβ1. We showed that the highly selective Set7 inhibitor (R)-PFI-2 hydrochloride attenuated indices associated with renal cell damage and mesenchymal transition, specifically (*1*) reactive oxygen species production, (*2*) *IGFBP5* gene regulation, and (*3*) expression of mesenchymal markers. Furthermore, renal benefit observed in Set7KO diabetic mice closely corresponded in human glomerular endothelial cells with (R)-PFI-2 hydrochloride inhibition or Set7 short hairpin RNA silencing.

Conclusions: Set7 regulates the phenotypic endothelial–mesenchymal transition switch and suggests that targeting the lysine methyltransferase could protect glomerular cell injury in DKD.

FR-PO274

Branched-Chain Amino Acids Drive Mesangial Expansion in Diabetic Kidney Disease

Junichiro Hagita,[1,2] Tomohito Doke,[1] Toshiki Tsuboi,[4,1] Shoma Tsubota,[3] Sawako Kato,[1] Yasuhiko Ito,[2] Takuji Ishimoto,[2] Shoichi Maruyama.[1]
[1]Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Nagoya, Japan; [2]Aichi Ika Daigaku Daigakuin Igaku Kenkyuka Igakubu, Nagakute, Japan; [3]Nagoya Daigaku Igakubu Seikagaku, Nagoya, Japan; [4]Shiritsu Yokkaichi Byoin, Yokkaichi, Japan.

Background: The elevation of serum branched-chain amino acids (BCAAs) in diabetic patients has been observed for more than half a century, and it is reported to be associated with obesity and insulin resistance. We previously reported the unbiased metabolomics study identified significantly elevated levels of BCAAs in the kidneys and serum of db/db mice compared to db/m mice. Furthermore, these increases were reduced with SGLT2 inhibitor, Tofogliflozin. However, the contribution of BCAA to the development or progression of DKD has not been elucidated. This study is aimed to identify the effect of modulating BCAA catabolism on DKD.

Methods: The db/db and db/m mice were given 3,6-dichlorobenzo(b) thiophene-2-carboxylic acid (BT-2) (40mg/kg/day), a small molecule allosteric inhibitor of branched-chain α-keto acid dehydrogenase kinase (BDK) for 12 weeks. As an experimental model for BCAA overload, db/db and db/m mice were given a BCAA enrichment mixture (BCAAem) dissolved water for 8 weeks. The blood glucose levels, body weight, and food intake were regularly examined. Urinary albumin, serum leucine levels, and urinary thiobarbituric acid reactive substances (TBARS) were measured. PAS, PAM, and collagen IV staining were performed on FFPE sections.

Results: Body weight, blood glucose levels, albuminuria, and urinary TBARS levels were not significantly reduced in db/db mice treated with BT2 compared to db/db mice. However, serum leucine level, mesangial expansion, and collagen IV accumulation in the glomeruli were reduced in db/db mice treated with BT2. In contrast, the level of albuminuria and serum leucine were significantly increased in db/db mice treated with BCAAem with no change of urinary TBARS levels. Moreover, mesangial expansion in the glomeruli deteriorated in db/db mice treated with BCAAem.

Conclusions: Mesangial expansion induced by diabetes improved with the accompanying decrease in serum leucine concentration due to BT2 treatment. BCAA enrichment diet in diabetes deteriorates albuminuria and mesangial expansion. These findings suggest that circulating BCAA levels modify DKD progression. Intervention in BCAA metabolism may potentially prevent the progression of DKD.

Funding: Commercial Support - Kowa Company, Ltd.

FR-PO275

SGLT2-Independent Effects of Canagliflozin on NHE3 and Mitochondrial Complex I Activity Inhibit Proximal Tubule Fluid Transport and Albumin Uptake

Wafaa N. Albalawy,[1,2] Elynna B. Youm,[1,2] Katherine E. Shipman,[1] Kimberly R. Long,[1] Youssef Rbaibi,[1] Michael J. Jurczak,[1] Ossama B. Kashlan,[1] Ora A. Weisz.[1] *[1]University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]University of Pittsburgh School of Public Health, Pittsburgh, PA.*

Background: Beyond glycemic control, SGLT2 inhibitors have protective effects on cardiorenal function. Renoprotection has been suggested to involve inhibition of NHE3 leading to reduced ATP-dependent tubular workload and mitochondrial oxygen consumption. NHE3 activity is also important for regulation of endosomal pH, but the effects of SGLT2i on endocytosis are unknown

Methods: We used a highly differentiated cell culture model of proximal tubule (PT) cells to determine the direct effects of SGLT2i on Na+-dependent fluid transport and endocytic uptake in this nephron segment. BCECF-AM were used to measure intracellular pH. The effect of gliflozins on albumin uptake and on fluid transport was quantified in opossum kidney (OK) PT cells; cana vs the NHE3 inhibitor S3226 effect on early endosome pH in OK cells was measured using fluorescence ratio imaging. Effects of gliflozins on AMPK pathway were determined by immunoblotting. 10 week-old male C57BL/6 mice were given cana or empa by oral gavage daily following vehicle gavage. Urine was collected via metabolic cages at baseline and after 24h and 48h. Creatinine and albumin were measured by ELISA

Results: Canagliflozin but not empagliflozin reduced fluid transport across cell monolayers and dramatically inhibited endocytic uptake of albumin. These effects were independent of glucose and occurred at clinically relevant concentrations of drug. Cana acutely inhibited surface NHE3 activity, consistent with a direct effect, but did not affect endosomal pH or NHE3 phosphorylation. In addition, canagliflozin rapidly and selectively inhibited mitochondrial complex I activity. Inhibition of mitochondrial complex I by metformin recapitulated the effects of cana on endocytosis and fluid transport, whereas modulation of downstream effectors AMPK and mTOR did not. Mice given a single dose of cana excreted twice as much urine over 24 h compared with empa-treated mice despite similar water intake

Conclusions: We conclude that cana selectively suppresses Na^+-dependent fluid transport and albumin uptake in PT cells via direct inhibition of NHE3 and of mitochondrial function upstream of the AMPK/mTOR axis. These additional targets of cana contribute significantly to reduced PT Na^+-dependent fluid transport in vivo

Funding: Government Support - Non-U.S.

FR-PO276

SGLT2 Inhibition Alters Methionine Metabolism in Diabetic Kidney Disease

Hiroshi Maekawa, Yalu Zhou, Yuki Aoi, Margaret E. Fain, Navdeep S. Chandel, Susan E. Quaggin. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: SGLT2 inhibition protects the kidney although underlying mechanisms are incompletely known. We hypothesized that cell-specific metabolic pathways activated by SGLT2 inhibition in diabetic kidney disease (DKD) underlie benefits.

Methods: Kidneys harvested from 10-week-old male Sglt2 mutant (MT) and wildtype (WT) mice, fed with normal or high fat diet (HFD, 60% calories from fat) for eight or eighteen weeks, were analyzed. Single cell RNA sequence (scRNA seq) was performed on libraries prepared from whole kidneys. Metabolomic analysis of renal cortex was conducted by Metabolon, Inc. Methionine Adenosyltransferase 2A inhibitor (MAT2Ai, 10 mg/kg BW), an inhibitor of the methionine cycle, was injected into intraperitoneal cavity of WT/MT mice with prior exposure to HFD for eight weeks. Bulk RNA seq and Cleavage under targets and release using nuclease were performed on libraries prepared from renal cortex.

Results: HFD-induced obesity was similar in both MT and WT while compensatory hyperphagia was observed in MT. Glucose intolerance occurred in mice fed HFD (WT>MT). Molecular and functional markers of kidney injury including serum creatinine, KIM-1, number of apoptotic cells and albuminuria were higher in WT-HFD. Analysis of scRNA seq showed emergence of a new class of proximal tubular cells (PTC-H), predominantly found in WT-HFD. PTC-H showed increased expression of genes related to epithelial–mesenchymal transition, apoptosis and inflammation. Analysis of metabolomics uncovered differences in WT-HFD vs MT-HFD; metabolites of methionine cycle including SAM were preferentially increased in MT-HFD. MAT2Ai abrogated renal protection with downregulation of NFκB-target genes in MT. Trimethylation of lysine 27 on histone H3 (H3K27me3), a marker of inactive regions of the genome, within genes related to inflammatory signaling were increased in MT-HFD. Especially, H3K27me3 at the promoters of NFκB-target genes, *Fos*, *Jun*, and *Junb* was enhanced in MT-HFD. H3K27me3 was mostly unchanged at the regions with broad peaks, where this mark is already present in WT. A deposition of the H3K27me3 at the SAM-regulated genes in MT-HFD was decreased by MAT2Ai.

Conclusions: SGLT2 inhibition prevents the emergence of a new class of PTC with inflammatory phenotype via region-specific enhancement of repressive histone methylation through methionine metabolic modulation in DKD.

Funding: Commercial Support - Takeda Science Foundation

FR-PO277

TOMM7 Alleviates Diabetic Kidney Disease by Regulating PINK1/Parkin-Mediated Mitophagy via Intracellular Redistribution of PLA2G6

Yihui Wang.[1,2] *[1]Peking University, Beijing, China; [2]Peking University First Hospital, Beijing, China.*

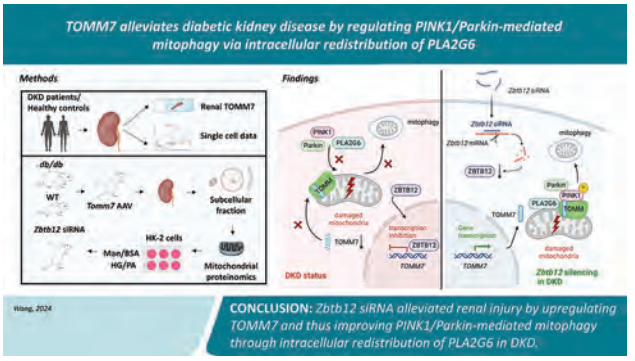
Background: Accumulating evidence showed that renal tubular injury is crucial for the development of diabetic kidney disease (DKD), and mitophagy is a pivotal event to maintain mitochondrial homeostasis especially in renal tubular cells, which are rich in mitochondria. However, the underlying mechanisms of mitophagy regulation remain largely unknown. This study aims to investigate the role of translocase of outer mitochondrial membrane subunit 7 (TOMM7), a critical regulator of mitophagy, in the pathogenesis of DKD.

Methods: TOMM7 expression was determined in the kidney sections of DKD patients. Subcellular fractions of mice kidney were isolated, and mitochondrial proteomics was used to explore the underlying mechanism, which was further validated in HK-2 cells.

Results: Here, we found that the expression of TOMM7 was significantly downregulated in renal specimens of DKD patients and *db/db* mice as well as high glucose/palmitic acid (HG/PA) treated HK-2 cells accompanied by impaired PINK1/Parkin-mediated mitophagy. TOMM7 overexpression in *db/db* mice significantly alleviated renal injury and restored PINK1/Parkin-mediated mitophagy. Mechanistically, TOMM7 regulated PINK1/Parkin recruitment through modulating intracellular redistribution of PLA2G6 between nucleus and mitochondria in renal tubular cells. Moreover, we identified zinc finger and BTB domain containing 12 (ZBTB12) as a transcription repressor of *TOMM7* and developed renal tubular cells targeted small interfering RNA (siRNA) to achieve specific upregulation of TOMM7 in the kidney. In addition, treatment with *Zbtb12* siRNA could relieve tubular injury and improve mitophagy by increasing TOMM7 expression in *db/db* mice.

Conclusions: In conclusion, this study highlighted that TOMM7 improved PINK1/Parkin-mediated mitophagy through intracellular redistribution of PLA2G6 in renal tubular cells in DKD models, and *Zbtb12* siRNA could be a potential treatment strategy targeting renal tubular cells for DKD.

Funding: Government Support - Non-U.S.



Graphical Abstract

FR-PO278

Long-Term Proteomic Changes from Human Urinary Extracellular Vesicles in Diabetic Patients after Administrating SGLT2 Inhibitors

Chih-Chien Sung, Min-Hsiu Chen, Yi-chun Tsai, Shih-Hua P. Lin. *Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.*

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors exert their effect by selectively blocking the SGLT2 transporters in the renal proximal tubules and provide nephroprotective effects. However, the long-term effects of SGLT2 inhibitors on human renal proteins and transporters remain unclear.

Methods: We collected urine from eighteen patients with type 2 diabetes treated with SGLT2 inhibitors before SGLT2 inhibitors and at 3, 6, 9 months after SGLT2 inhibitors. Urinary extracellular vesicles (uEVs) were isolated by ultracentrifuge. We carried out large-scale LC-MS/MS-based quantitative proteomics from purified uEVslabeled by tandem mass tags (TMT).

Results: Characterization of uEVs was confirmed by nanoparticle tracking analysis, transmission electron microscopy, and immunoblotting. Totally, 1108 quantifiable proteins were identified from uEVs. Functional enrichment analysis from upregulated proteins involved in “inhibition of epithelial cell proliferation” and “cell adhesion remodeling”. Downregulated proteins mainly affected cell membrane such as PODXL, ATP1B1, and AQP1. In addition, we identified the co-expressed differentially expressed proteins (DEPs) including upregulated proteins (GPR110, CHMPA4, APPL2, TPPP3) and downregulated proteins (IGHG1, PODXL, SLC4A4, COBLL1) at different time points. After clustering of DEPs from uEVs based on nephron segments, SGLT2 inhibitors recovered the changed renal tubular proteins identified in diabetic patients compared to healthy controls. Among renal solute carrier groups (SLCs), SGLT2 inhibitors mainly affected the SLCs in proximal tubules (SLC5A1, SLC5A2, and SLC4A4) but not the distal tubules (SLC12A1 and SLC12A3). Moreover, proteomic analysis of uEVs in db/db mice administered with SGLT2 inhibitors also showed the changed proteins in terms of “Focal adhesion” and “Slit diaphragm”.

Conclusions: SGLT2 inhibitors affected renal proteins involving changes of membrane proteins and cellular differentiation in diabetic patients. The effects of SGLT2 inhibitors on solute carrier group (SLCs) mainly focused on proximal tubules. This uEVs proteomic study could help us know how long-term effects of SGLT2 inhibitors on human kidney.

Funding: Government Support - Non-U.S.

FR-PO279

Circulating YRNAs and Their Fragments Associate with Diabetic Kidney Disease and Endothelial Cell Function

Qiao Zhao, Rudmer J. Postma, Jacques Duijs, Juliette A. de Klerk, Joris I. Rotmans, Anton J. Van Zonneveld, Roel Bijkerk. *Leids Universitair Medisch Centrum, Leiden, Netherlands.*

Background: Diabetic kidney disease (DKD) occur commonly in patients with diabetes. Early detection of DKD may guide therapeutic strategies, so it is important to discover new biomarkers and therapeutic targets. Non-coding RNAs have been recognized as potential biomarkers or therapeutic targets in many diseases. yRNAs (RNYs), a class of non-coding RNAs, are highly conserved and can be processed into small fragments. Interestingly, yRNAs and their fragments are highly abundant in circulation. Here, we aim to investigate whether yRNAs and their fragments may serve as biomarkers for DKD and investigate their potential causal role.

Methods: RNA was extracted from serum of patients with diabetes (DM, n=12), DKD (n=18) and healthy controls (HC, n=12), as well as from extracellular vesicles (EVs) isolated from these sera. qRT-PCR was used to measure expression levels of yRNAs and their fragments. Also yRNA subtypes ratios were determined, as it was previously shown that unique quantitative ratios of yRNA subtypes may reflect injury status. Human umbilical vein endothelial cells (HUVEC) and Human Dermal Microvascular Endothelial Cells (HDMEC) were used for *in vitro* studies. siRNA-mediated knockdown was performed to inhibit RNY1 expression. Barrier formation and function of endothelial cells were measured via the Electric Cell-substrate Impedance Sensing (ECIS) method.

Results: The ratios of full length RNY4/RNY3 and RNY4/RNY1 increased in serum of patients with DKD, while the ratio of circulating RNY3/RNY1 and RNY4/RNY1 fragments decreased in DKD as compared to HC. We observed that circulating yRNAs are mostly present in EVs. Interestingly, for each type of yRNA, the ratio of fragment to full length yRNA expression increased in the serum of patients with DM but decreased in the DKD group suggesting a general effect on fragmentation. In addition, in vitro studies demonstrate that, upon stimulation with TGF-β and TNF-α, yRNA expression decreased in endothelial cells. Furthermore, RNY1 inhibition impeded the barrier function of endothelial cells that could be mainly attributed to the loss of cell-cell contacts and membrane capacitance.

Conclusions: Our findings suggest that yRNAs are potential biomarkers for DKD, while yRNAs may also be directly involved in vascular injury through regulating EC barrier function.

Funding: Government Support - Non-U.S.

FR-PO280

Impact of the Nonsteroidal Mineralocorticoid Receptor Blocker Esaxerenone on Glomerular Hemodynamics in Diabetic Kidney Disease

Rie Tatsugawa, Kengo Kidokoro, Seiji Kishi, Hajime Nagasu, Tamaki Sasaki, Naoki Kashihara. *Kawasaki Ika Daigaku, Kurashiki, Japan.*

Background: The FIDELIO-DKD trial showed finerenone, a non-steroidal selective mineralocorticoid receptor blocker (MRB), reduced kidney failure and disease progression in diabetic kidney disease (DKD). Esaxerenone, another non-steroidal MRB, decreased albuminuria in hypertensive patients with type 2 diabetes in the ESAX-DN study. However, the mechanisms behind these effects remain unclear. A decrease in eGFR is observed from the early phase of MRB treatment, and eGFR increases again upon discontinuation. This suggests that MR activity functionally regulates GFR and is likely involved in the pathogenesis of glomerular hyperfiltration in DKD. We hypothesize that MR activation induces glomerular hyperfiltration in DKD by diminishing tubuloglomerular feedback (TGF) through a NO-mediated mechanism in macula densa (MD). We examined the suppressive effects of MRB on glomerular hyperfiltration and elucidated its underlying mechanisms.

Methods: Male Sprague-Dawley (SD) ratswere administered aldosterone (1.0 μg/h via osmotic pumps) and esaxerenone orally (3 mg/kg/day). After three days, single nephron GFR (SNGFR), afferent/efferent arteriolar diameters, and glomerular volume were measured using a multiphoton microscope. The effects of esaxerenone on glomerular hemodynamics were also assessed in male db/db mice (type 2 diabetes) and control db/+m mice, both fed a high-salt diet (3% NaCl) and treated with esaxerenone (3 mg/kg/day). SNGFR and arteriolar diameters were measured in vivo. An adenosine A1 receptor (A1aR) antagonist (1 mg/kg) was used to explore TGF mechanisms.

Results: Aldosterone increased afferent arteriolar diameter and SNGFR in SD rats, indicating glomerular hyperfiltration. Esaxerenone mitigated these changes, confirming the role of MR activation in GFR regulation. Db/db mice exhibited higher urinary albumin levels and SNGFR compared to control. Esaxerenone reduced albumin levels and glomerular hyperfiltration. Combining esaxerenone with the A1aR antagonist diminished the inhibitory effect of esaxerenone on glomerular hyperfiltration.

Conclusions: In DKD, MR activation is implicated in glomerular hyperfiltration, likely through a mechanism mediated by TGF. The impact of MR activation in maculodensin on TGF is currently under investigation.

Funding: Commercial Support - Daiichi Sankyo Company

FR-PO281

Liraglutide-Mediated Renoprotection in Type 1 Diabetes: Modulating M1/M2 Macrophage Balance via NOX/TRP Cross-Talk

Natalie Youssef, Mohamad Noureldein, Sarah Almoussawi, Tala R. Kaddoura, Fuad N. Ziyadeh, Assaad Antoine Eid. Eid’s Lab. *American University of Beirut, Beirut, Lebanon.*

Background: Diabetic Kidney Disease (DKD) poses a substantial health burden for patients with diabetes. While studies have demonstrated the renoprotective effects of the GLP-1RA liraglutide in type 2 diabetes (T2D), its impact in type 1 diabetes (T1D) remains less explored. Although some studies suggest renoprotection in T1D, the underlying mechanism remains elusive across both T1D and T2D. Recent evidence highlights the

role of macrophages in the initiation and progression of DKD, where macrophages tend to polarize to an M1 pro-inflammatory instead of an M2 anti-inflammatory phenotype. Besides, extensive data showed that ROS overproduction and calcium signaling dysregulation play a crucial role in DKD progression. Therefore, this study investigates the reno-protective mechanism of liraglutide in T1D and elucidates its effect on restoring macrophage polarization balance by modulating NOX-TRP crosstalk.

Methods: C57/BL6J mice were divided into 3 groups: control group, STZ-induced insulin deficient model mimicking T1D, and a T1D group treated with 0.3mg/kg s.c. injections of liraglutide twice daily. After 13 weeks of treatment, the kidneys were isolated for analysis.

Results: Despite hyperglycemia, liraglutide treatment significantly reduced kidney hypertrophy and improved renal function. Histopathological data confirmed reduced glomerular hypertrophy, glomerulosclerotic index, and collagen deposition. Additionally, fibronectin, Col4, WT1, nephrin, and podocin levels normalized. While liraglutide didn't decrease macrophage infiltration, it did reduce inflammatory cytokine expression and specific M1 macrophage markers. Conversely, anti-inflammatory cytokines increased, along with markers of M2 macrophages. Liraglutide also attenuated ROS overproduction by reducing NADPH oxidase activity. However, further analysis revealed differential modulation of the different NOX isoforms. This finding underscores the pivotal role played by NOX in kidney function and macrophage responses. Besides, liraglutide restored normal TRPM2 and TRPC6 expression and increased TRPM7 expression.

Conclusions: This is the first study to show a reno-protective effect of liraglutide in T1DM manifested by a shift in macrophage polarization from M1 inflammatory to M2 anti-inflammatory phenotype by modulating NOX-TRP crosstalk.

FR-PO282

Protective Role of ST2 Signaling in Diabetic Nephropathy

Vikram Sabapathy, Sai K. Gajula, Saanvi Acharya, Bushra Mehkri, Rahul Sharma. *University of Virginia School of Medicine, Charlottesville, VA.*

Background: Diabetic nephropathy (DN) contributes to morbidity in Diabetes patients (DM), for whom glycemic control remains the primary treatment. The IL-1 superfamily member IL1RL1 (ST2), is activated by its ligand IL-33 was identified in type 2 immune response Recent data suggests loss of IL-33 or its receptor ST2 resulted in increased susceptibility to Type-2 diabetes, increased adiposity, and worsened metabolic profile. Studies from our lab have shown that a novel hybrid cytokine IL233, bearing activity of IL-2 and IL-33, enhances T-regulatory cells (Tregs) and attenuated the loss of kidney function in diabetic Ob/Ob mice, as shown by proteinuria, urinary albumin creatinine ratio (ACR). Histopathology of kidney showed lower inflammation with attenuation of glomerular hypertrophy and mesangial expansion in IL233 treated mice. However, there is lack of knowledge for the role of ST2 signaling in DN.

Methods: We investigated the difference between wild type (WT) and ST2KO mice for susceptibility to DM and DN. We also generated mice with ST2 deletion in Tregs cells (*Il1rl1*$^{fl/fl}$*Foxp3*$^{YFP\text{-}Cre}$) to understand the role of ST2 expressing Tregs in DN. Mice were subjected to multiple low dose streptozotocin (STZ). The structure and function of pancreas and kidney were probed using flow cytometry, histology, immunohistochemistry, ELISA, quantitative PCR as well as enzymatic and biochemical analysis.

Results: Histological analysis of the pancreatic tissue through hematoxylin and eosin staining indicated ST2KO mice had a lower number of islets with smaller islet diameters. Single cell RNA sequencing unraveled unique cell states in knockout islets compared to the WT counterparts. Both immunostaining and transcriptomic analysis indicated lower insulin levels in ST2KO islets compared to WT islets. *In vivo* studies using low dose STZ suggested ST2 deficient mice were more susceptible to diabetes compared to WT mice. In addition, Urinary ACR assay indicated both the global as well as Treg specific loss of ST2 worsened the susceptibility and severity of DN. Flow cytometry data showed increased inflammatory milieu in the pancreas and the kidneys of mice lacking ST2 expression globally or in Tregs.

Conclusions: Results from our studies demonstrate a prominent role of ST2 in islet function, maintain immune homeostasis and protection from DN in a Treg-dependent manner.

Funding: NIDDK Support, Private Foundation Support

FR-PO283

GDF-15 Is a Novel Therapeutic Target for Diabetes-Induced Kidney and Cardiac Injuries in Preclinical Models of Type 2 Diabetes (T2D)

Amani W. Slika, Dalal M. Jomaa, Rita Yehya, Sahar Alkhansa, Sarah Almoussawi, Assaad Antoine Eid. *American University of Beirut, Beirut, Lebanon.*

Background: Diabetic kidney disease (DKD) and diabetic cardiomyopathy (DCM) are severe complications of diabetes, with poorly understood underlying mechanisms. GDF-15, a cytokine belonging to the transforming growth factor-β family, has been recently proposed as a novel biomarker for diabetic complications. Several clinical studies have shown that elevated GDF-15 expression is associated with the development of DKD and DCM. However, the pre-clinical role of GDF-15 as a risk predictor requires further investigation. We have previously shown NETosis, a specialized form of neutrophil-specific cell death, to be involved in the pathogenesis of diabetes. In this study, we examine the role of GDF-15 and its effect on NETs formaion in the development of renal and cardiac injuries associated with type 2 diabetes (T2D).

Methods: Male C57BL/6J mice were used. T2D was induced using a high-fat diet/STZ protocol (DiaComp). Two sets of experiments were conducted. In the first series, mice were categorized into: control mice, GDF-15 antibody (AV-380)-treated control mice (at 7.5mg/kg or 20mg/kg), T2D-induced mice, and AV-380-treated T2D mice (at 7.5mg/kg or 20mg/kg). Short-term treatment was administered for 8 weeks. The second series of experiments included control mice, T2D mice, and AV-380-treated T2D mice (at 7.5mg/kg or 20mg/kg) with long-term treatment administered for 15 weeks. Functional, histopathological, and molecular studies were performed.

Results: Our data show that inhibiting GDF-15 restores renal and cardiac homeostasis in T2D mice. Both short and long term treatments reduced proteinuria, glomerulosclerosis, collagen deposition in the kidneys and heart, as well as improved cardiac ejection fraction in AV-380 treated diabetic mice. The expression levels of prominent inflammatory markers were decreased. Furthermore, increased expression of the cardiac hypertrophic proteins and the reduced expression of cardioprotective markers associated with diabetes were restored following AV-380 treatment. Additionally, GDF-15 inhibition reduced the expression of NETosis markers.

Conclusions: The findings of this study suggest that GDF-15 is a therapeutic target in diabetes-induced cardiac and kidney injuries.

FR-PO284

Renal Cell Type-Associated Therapeutic Effects of Semaglutide in a Mouse Model of Hypertension-Accelerated Diabetic Kidney Disease

Adam B. Marstrand-Jørgensen,[1,2] Louise Dalbøge,[1] Henrik H. Hansen,[1] Ida Rune,[1] Michael Christensen.[1] [1]*Gubra A/S, Hørsholm, Denmark;* [2]*Kobenhavns Universitet, Kobenhavn, Denmark.*

Background: Obesity, hyperglycemia and hypertension are critical risk factors for development of diabetic kidney disease (DKD). While emerging evidence suggests that glucagon-like peptide-1 receptor (GLP-1R) agonists improve cardiovascular and renal outcomes in type 2 diabetes patients, their mode of action is presently unclear. Using paired bulk and single-nucleus RNA sequencing (RNAseq), we profiled renal transcriptome signatures of the long-acting GLP-1R agonist semaglutide alone and in combination with antihypertensive standard-of-care (ACE inhibitor, lisinopril) in a model of hypertension-accelerated, advanced DKD facilitated by adeno-associated virus-mediated renin overexpression (ReninAAV) in uninephrectomized (UNx) female *db/db* mice.

Methods: Seven weeks after ReninAAV administration and six weeks post-UNx, *db/db* UNx-ReninAAV mice were administered (q.d.) vehicle, semaglutide (30 nmol/kg, s.c.) or semaglutide (30 nmol/kg, s.c.) + lisinopril (30 mg/kg, p.o.) for 11 weeks. Endpoints included blood pressure, urine biochemistry, kidney histopathology as well as paired bulk and single-nucleus RNA seq. Cell type deconvolution was performed by referencing expression of treatment-affected genes across all major kidney cell types using single nuclei RNAseq.

Results: Semaglutide robustly reduced hyperglycemia, hypertension, albuminuria and glomerulosclerosis severity. Co-administration of lisinopril further ameliorated hypertension and glomerulosclerosis. Renal gene expression changes after semaglutide mono- and combination treatment were primarily associated with the immune system and extracellular matrix organization. Semaglutide promoted discrete renal gene expression changes in *db/db* UNx-ReninAAV mice with notable suppression of macrophage-associated genes. Combined semaglutide and lisinopril administration resulted in more widespread transcriptome changes in several renal cell types, including macrophages, mesangial cells, podocytes and proximal tubule cells.

Conclusions: Semaglutide improves disease hallmarks in the db/db UNx-ReninAAV mouse model of advanced DKD and suppresses gene expression markers of ECM remodeling and immune system activation. Outcomes were further improved by combined antihypertensive standard-of-care.

Funding: Commercial Support - Gubra A/S

FR-PO285

Single-Cell Sequencing Detects Enrichment of ESKD Biomarkers in Injured Proximal Tubule

Parker C. Wilson,[1] Katsuhito Ihara,[2,3] Eiichiro Satake,[2,3] Benjamin D. Humphreys,[4] Andrzej S. Krolewski.[2,3] [1]*University of Pennsylvania Department of Pathology and Laboratory Medicine, Philadelphia, PA;* [2]*Joslin Diabetes Center, Boston, MA;* [3]*Harvard Medical School, Boston, MA;* [4]*Division of Nephrology, Department of Medicine, Washington University in St. Louis, St Louis, MO.*

Background: Diabetic kidney disease (DKD) leads to rapid decline in some patients, but there are no biomarkers to identify these individuals. Proteomics profiles hundreds to thousands of candidate biomarkers, but little is known about how DKD affects these

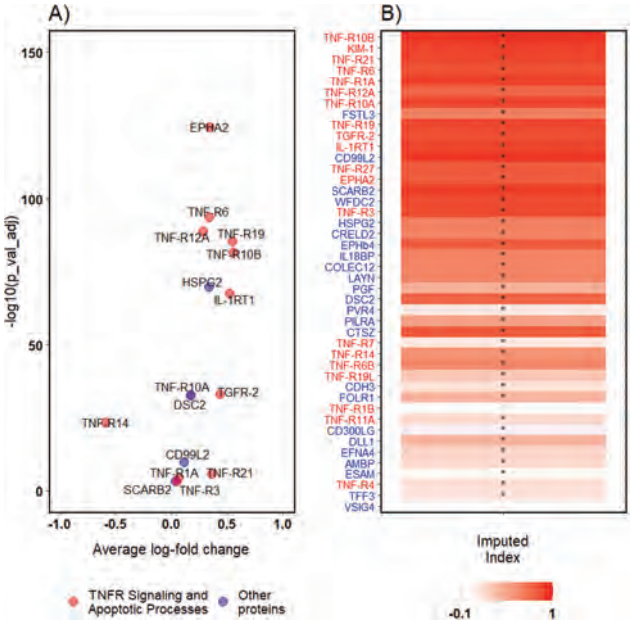
proteins or the cell types they originate from. Here, we identify circulating proteins that predict progression to ESKD using high-throughput proteomics (see Ihara K et al. Kidney Week 2024). We integrate these data with a single-cell atlas from patients with DKD to determine which cell types express these proteins.

Methods: We measured plasma concentration of 455 proteins among 405 individuals with diabetes using the OLINK platform. Elevated concentration of 46 proteins at baseline associated with progression to ESKD after 7-15 years. Single nucleus RNA sequencing (snRNA-seq) from patients with DKD (Wilson et al. 2022) was evaluated for cell-specific expression of biomarkers using Seurat. We focused on injured proximal tubule cells that variably express *HAVCR1* and *VCAM1* because the abundance of this cell type has been associated with kidney function decline.

Results: snRNA-seq showed that 14 of 46 circulating proteins predictive of ESKD were overexpressed in injured proximal tubule cells, including 11 genes encoding apoptosis and TNF-related receptor proteins (Figure A). Cell-specific expression of these biomarkers was correlated with aggregate expression of 205 apoptosis pathway genes. Imputation was performed to mitigate the sparsity of snRNA-seq, which increased the correlation between circulating biomarker expression and apoptosis pathway genes (Figure B).

Conclusions: We hypothesize that injured proximal tubule cells are a significant source of circulating biomarkers that predict progression to ESKD in individuals with diabetes.

Funding: NIDDK Support



FR-PO286

Single-Cell Profiling of Peripheral Blood Mononuclear Cell Identifies Immune Populations Associated with Progression of Diabetic Kidney Disease

Jia Fu,[1] Zeguo Sun,[1] Huei Hsun Wen,[1] Dongyuan Chang,[1,2] Gohar Mosoyan,[1] Kyung Lee,[1] Steven G. Coca,[1] Girish N. Nadkarni,[1] John C. He.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Peking University First Hospital, Beijing, China.*

Background: Emerging evidence has highlighted the pivotal role of inflammation in the development and progression of DKD. Notably, TNF receptors have demonstrated notable associations with eGFR decline in both early and advanced DKD. However, to date, there has not been a comprehensive characterization of circulating immune cell phenotypes in DKD and their relationship with disease progression at the single-cell level.

Methods: In this study, we performed single-cell RNA sequencing of PBMCs from 12 patients, stratified based on high and low serum TNFR levels. Our aim was to discern immune cell subpopulations and their transcriptomic signatures associated with the DKD progression.

Results: By assessing the eGFR slope, serum levels of TNFR-1 and TNFR-2, we have discerned 12 patients demonstrating varying degrees of underlying DKD. Our scRNAseq analysis profiled 109,955 PBMCs, revealing TNFR1 and TNFR2 genes predominantly expressed on CD14 and CD16 monocytes. Circulating TNFR-1 levels correlated positively with monocyte population and negatively with T cells and dendritic cells, while TNFR-2 levels correlated negatively with dendritic cells and CD8 T cell proportion. Increased CD14 and CD16 monocytes and decreased plasmacytoid dendritic cells (pDCs) and CD4 T cells were observed to correlate with DKD progression. Profound alterations in circulatory immune cell signatures were noted, with more upregulated differential expressed genes (DEGs) in slowly progressed DKD and subsequent downregulated in advanced stages. These DEGs primarily involved in cytokine expression, immune-related pathways, apoptotic signaling, and response to IFN, suggesting potential immunomodulatory roles of elevated circulating TNFR in DKD activation. Additionally, important co-expressed genes with TNFR1 and TNFR2 implicated processes such as osteoclast differentiation, cytokine interaction, endocytosis, and MAPK pathways.

Conclusions: Our study utilized single-cell RNA sequencing of PBMCs to comprehensively profile immune cell dynamics in patients stratified by serum TNFR levels, revealing their intricate interplay in the progression of DKD. These findings provide valuable insights into potential immunomodulatory targets for therapeutic intervention in DKD.

Funding: NIDDK Support

FR-PO287

Acute Inflammation Enhances SGLT2-Positive Myeloid Population in Bone Marrow

Ariana G. Alcantar,[1] Alexis P. Jimenez Uribe,[1] Yanxia Cao,[1] Ryan Spear,[1] Steve Mangos,[1] Jochen Reiser,[2] Eunsil Hahm.[1] Hahm Lab. *[1]Rush University Medical Center, Chicago, IL; [2]The University of Texas Medical Branch at Galveston Development Office, Galveston, TX.*

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have exhibited benefits beyond controlling blood sugar levels, including improving cardiac function. Since SGLT2 expression predominantly occurs in kidney proximal tubule cells, understanding SGLT2 expression and its pathophysiological functions outside the kidney remains limited. This study aims to investigate the expression of SGLT2 in immune cells and its implications.

Methods: Leukocytes were isolated from peripheral blood and bone marrow (BM) of *BALB/c* and *C57BL/6* mice under normal conditions and after lipopolysaccharide (LPS)-induced systemic inflammation. CD34+ human hematopoietic cells (HSCs) from healthy donors and the human myelocyte cell line (HL-60) were cultured to study for in vitro myelopoiesis. Staining for SGLT2 and cell markers was performed using multicolor flow cytometry.

Results: Under normal conditions, approximately 1.5% of mouse BM contains an SGLT2+ population that expresses myeloid markers (Ly6C and Ly6G) but not lymphoid markers (CD3 and CD19). Interestingly, this SGLT2+ population increases after LPS challenge in bone marrow, not in peripheral blood. Further characterization shows that these cells display an immature phenotype (Sca-1+), arise from the myeloid lineage (CD11b+), and are monocytic in nature (CD14+). Consistent with our *in vivo* results, in vitro myelopoiesis assays demonstrated that inflammatory signals (TNFa or LPS) increase the SGLT2+ myeloid cells during cell differentiation.

Conclusions: This study reveals that SGLT2 expression is not limited to the kidney. In both mouse and human immune systems, we identified a myeloid population of SGLT2+ cells in the bone marrow that increases under inflammatory conditions. While further investigation is necessary to understand the role of SGLT2 in BM myeloid cells during inflammation, our results imply a novel role for SGLT2 in immune cells. This points to potential clinical implications of SGLT2 inhibitors on immune regulation.

Funding: NIDDK Support

FR-PO288

A Novel Function of FOXO4 and mTORC2 for Regulation of Kidney Gluconeogenesis

John E. Demko, Bidisha Saha, Enzo Takagi, Robert Weber, David Pearce. *University of California San Francisco, San Francisco, CA.*

Background: The proximal tubule of the kidney and the liver are the only organs capable of gluconeogenesis (GNG). Insulin signaling through mTORC2 and Akt2 regulates GNG in the liver, and our recent work confirmed that mTORC2 coordinates regulation of GNG and glucose transport in the kidney. FOXO1 is a well-established transcription factor for GNG in the liver. However, the major gluconeogenic transcription factor in the kidney has not been identified. We initially assumed it was FOXO1, but western blot anomalies suggested a FOXO family member with different molecular weight.

Methods: Rictor deletion causes selective disruption of the mTORC2 complex. Male and female mice with inducible tubule-specific Rictor knockout (TRKO) were made with the Pax8-rtTA TetOCre Rictorflox/flox system. Mice were fasted then refed to induce insulin signaling prior to sacrifice and tissue collection. Whole kidney phosphoprotein abundance was normalized to respective total protein abundance by western blotting.

Results: Our prior work has shown that TRKO mice have situational hyperglycemia due to increased GNG and overexpression of gluconeogenic enzymes. In the current study, we found no difference in phosphorylation of FOXO1 between TRKO and WT mice after refeeding (6.77±0.81 vs 8.25±0.82AU; not significant [ns] by t-test; n=10 per group) or fasting (5.29±1.39 vs 7.19±2.00AU; ns; n=6 per group). However, there was a dramatic reduction in phosphorylation of FOXO4 in TRKO compared to WT mice after

both refeeding (0.068± 0.017 vs 12.44±2.35AU; p<0.001) and fasting (0.40± 0.12 vs 15.31±31AU; p<0.01). Phosphorylation of Akt2 at S473, the target of mTORC2, was reduced in TRKO compared to WT mice after refeeding (4.91± 0.25 vs 6.40± 0.53AU; p<0.05) and fasting (2.98±0.28 vs 10.86±1.47AU; p<0.001). Reduced phosphorylation of FOXO4 and Akt2 followed the same pattern.

Conclusions: These data suggest that FOXO4, rather than FOXO1, is the mTORC2-dependent transcription factor that regulates GNG in the kidney. Akt2 is activated by mTORC2, and Akt2 is likely to directly phosphorylate FOXO4 and FOXO1 given their sequence homology. We propose that FOXO4 plays plays a unique role in the kidney compared to the liver because GNG and glucose transport occur in the same cells of the proximal tubule. Additional experiments are required to confirm and further explore the role of FOXO4 in renal glucose homeostasis.

Funding: NIDDK Support, Private Foundation Support

FR-PO289

IL-32 Is a Lipid Droplet-Associated Mediator of Tubular Injury in Diabetic Kidney Disease

Hyunjae Chung,[1] Sarthak Sinha,[1] Mona L. Chappellaz,[2] Arthur Lau,[2] Waleed Rahmani,[1] Sisay G. Belay,[2] Asha K. Swamy,[2] Kevin R. Chapman,[1] Graciela Andonegui,[2] Hallgrimur Benediktsson,[1] Peter K. Stys,[1] Daniel A. Muruve,[1] Justin Chun.[1] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]University of Calgary, Calgary, AB, Canada.*

Background: Diabetic kidney disease (DKD) is the leading cause of kidney failure worldwide. The mechanisms contributing to DKD progression remains poorly characterized. In biopsies of human DKD, lipid droplets (LD) accumulate primarily in tubules with advanced stages of DKD. The contribution of lipid dysregulation is not well understood for DKD. Here we use human kidney biopsies and DKD patient-derived kidney organoids to investigate how LDs contribute to the pathogenesis of DKD.

Methods: Human kidney biopsies of the DKD as classified by the Renal Pathology Society classification of DKD were stained using Nile Red and analyzed to LD distribution and numbers. To model DKD, induced pluripotent stem cells (iPSC) were reprogrammed from healthy controls and DKD patients and differentiated to kidney organoids. Kidney organoids were treated with diabetic conditions in the absence of the SGLT2 inhibitor canagliflozin and analyzed by single cell RNA sequencing, in vitro assays, digital spatial imaging (CosMx), molecular spatial imaging (GeoMx) and live kidney organoid imaging.

Results: High glucose uptake promoted prominent LD formation in proximal tubular cells (PTC) of human kidney organoids derived from the iPSC of DKD patients. Single cell RNA sequencing of kidney organoids identified *IL32*, a gene encoding a pro-inflammatory cytokine induced by high glucose and downregulated by the SGLT2 inhibitor canagliflozin. Analysis of human DKD biopsies by Nanostring's digital spatial transcriptomics and molecular spatial imaging confirmed enrichment of *IL32* mRNA in injured proximal tubules. In human DKD organoids, IL-32 localized to tubular LD and its upregulation led to mitochondrial reactive oxygen species generation, mitochondrial fragmentation and tubular basement membrane thickening, attenuated by *IL32* knockdown. Overexpression of the beta and gamma isoforms of IL-32 in primary human proximal tubular epithelial cells induced mitochondrial fragmentation, ROS, and caspase-3 and GSDME-mediated cell death.

Conclusions: These findings identify IL-32 as a potential mediator linking metabolic dysfunction to chronic inflammation in DKD. IL-32 is a potentially targetable LD-associated cytokine that can be used to delay the progression of DKD.

Funding: Government Support - Non-U.S.

FR-PO290

Restoration of Branched-Chain Amino Acid Catabolism Improves Kidney Function in Preclinical CKD Models

Rachel Roth Flach, Eliza Bollinger, George E. Williams, Mary Piper, Kimberly L. Steen, Kelly T. Neale, Xian Chen, Mackenzie E. Marshall, Srinath Jagarlapudi, Ying Zhang, Elaine Kuang, Daniel Callahan, John Stansfield, Natalie A. Daurio, Justin Crane, Dinesh K. Hirenallur-Shanthappa, John D. Groarke, Bei B. Zhang. *Pfizer Inc, New York, NY.*

Background: Patients with metabolic syndrome and heart failure (HF) often have accompanying kidney dysfunction, which was recently defined as cardiovascular-kidney-metabolic (CKM) syndrome. Prior metabolomics profiling of metabolic syndrome patients identified a plasma branched chain amino acid (BCAA) signature, and BCAAs are elevated in HF patient myocardium. The rate limiting step of BCAA catabolism is decarboxylation by branched chain ketoacid dehydrogenase enzyme (BCKDH), which is negatively regulated by BCKDH kinase (BCKDK or BDK), and BDK inhibitors improve metabolism and heart failure preclinically. BDK inhibitors such as BT2 have been used preclinically and have demonstrated improvements in cardiometabolic outcomes, but the role of BDK inhibition in renal dysfunction has not been evaluated.

Methods: The BDK inhibitor BT2 was used in the ZSF1 (cross between Zucker diabetic ZDF rat and spontaneously hypertensive SHHF rat) rat model and SDT (spontaneously diabetic torii) rat model with uninephrectomy to test the impact of BDK inhibition on CKM parameters including urine output, albuminuria, GFR, and histology.

Results: BCAA catabolic impairment is associated with and may be causal to CKM, as treatment with the BDK inhibitor BT2 improved urine protein content, glomerular filtration rate, kidney hypertrophy, and kidney pathology in CKM models. Coadministration of BT2 and empagliflozin restored renal function and gene expression signatures towards that of healthy rats.

Conclusions: These data suggest that BDK inhibition could represent a therapeutic avenue for CKM.

Funding: Commercial Support - Pfizer Inc

FR-PO291

Associations between Renin-Angiotensin System and Abnormal Renal Energy Metabolism in a Mouse Model of Diabetic Kidney Disease

Kengo Azushima,[1] Shinya Taguchi,[1] Ryutaro Morita,[1] Kenta Nomura,[1] Kentaro Kawasoe,[1,2] Hiromichi Wakui,[1] Kouichi Tamura.[1] *[1]Yokohama City University Graduate School of Medicine, Yokohama, Japan; [2]Tokyo Women's Medical University, Tokyo, Japan.*

Background: Renin-angiotensin system (RAS) has been a hallmark of the pathogenesis of diabetic kidney disease (DKD), but its underlying mechanisms remain unclear. Recently, abnormal renal energy metabolism has been reported as a novel pathogenesis of DKD. To investigate the association between the RAS and renal energy metabolism, we generated a mouse model of DKD characterized by systemic RAS activation.

Methods: We generated a mouse model of DKD with underlying activation of the RAS by systemic deficiency of angiotensin II (Ang II) type 1 receptor (AT1R)-associated protein (ATRAP), an endogenous suppressor of AT1R signaling, in combination with Ang II stimulation on streptozotocin (STZ)-induced type I diabetes. DKD and non-diabetic control (Ctrl) mice were euthanized to evaluate renal injuries after measurements of urinary albumin excretion (UAE). Renal energy metabolism was estimated by real-time quantitative PCR and western blotting analyses.

Results: A combination of ATRAP deletion with Ang II stimulation in STZ-infused C57BL/6 mice resulted in advanced DKD which had features of human DKD, including overt albuminuria (UAE, Ctrl vs DKD: 10.6±2.0 vs 852.0±195.6 μg/day, p<0.001), glomerular hypertrophy, podocyte loss, mesangial expansion, renal interstitial fibrosis, and functional insufficiency, concomitant with increased angiotensinogen and AT1R expression in the kidneys. Compared to the Ctrl mice, mRNA expression of PGC-1α, a key regulator of mitochondrial metabolism, was significantly increased in DKD mice. In addition, western blotting analysis showed that protein levels of phosphorylated AMPK in DKD mice were significantly decreased, indicating a substantial abnormality of renal energy metabolism in the mouse model of DKD.

Conclusions: Systemic RAS activation induced by the combination of ATRAP deletion with Ang II stimulation accelerated the development of DKD in STZ-induced type I diabetes. In their kidneys, local RAS activity was upregulated along with a perturbation of mitochondrial energy metabolism. Taken together, our findings suggest substantial associations between the RAS and abnormal renal energy metabolism, which might be involved in the underlying mechanisms contributing to the development of DKD.

Funding: Government Support - Non-U.S.

FR-PO292

Tubular Injury-Derived Exosome Interve Podocyte Cytoskeleton Rearrangement in Diabetic Mice

Rui Zhang,[1,2] Rui Yan.[1] *[1]Department of Nephrology, Affiliated Hospital of Guizhou Medical University, Guiyang, China; [2]Department of Pathophysiology, Guizhou Medical University, Guiyang, China.*

Background: Renal tubular epithelial cells are the major source of exosomes in the kidney, carrying biological payload of proteins and nucleic acids to facilitate cellular communication. Here, we aimed to investigate the effect of renal tubule-derived exosomes on podocyte skeletal rearrangement in diabetic mice.

Methods: The mice renal tubular epithelial cells (mRETC), from which exosomes were purified and intravenously injected into wt mice, were cultured under normal glucose as control and high glucose combined with palmitic acid (HG+PA). MicroRNA (miRNAs) sequencing was performed to conduct whole-genome analysis of exosome miRNA by Illumina Hiseq2500. *db/m* mice and *db/db* mice were intravenously injected adeno-associated virus (AAV) vecor knockdown of miR-20a-5p and miRNA mimics overexpression (OE) of miR-20a-5p respectively. The expressions of nephrin, CD2AP, myosin X were detected by real-time PCR or westernblot. F-actin were detected by confocal microscopy. *In vitro* studies were performed in human podocyte cell tranfected with miRNA mimics overexpression of miR-20a-5p, podocyte cell were cultured with normal glucose, high glucose combined with palmitic acid.

Results: In WT mice with HG+PA exosome, renal histology showed podocyte foot process effacement by transmission electron microscope, nephrin, CD2AP, myosin X

were significantly decreased compared with control mice. MiR-20a-5p was identified as one of the most regulated miRNAs in the exosomes from injure human kidney-2 (HK-2). The *db/m* mice treated with miR-20a-5p-OE exist more severely podocyte foot process effacement. In *db/db* mice treated with miR-20a-5p-AAV shRNA, renal histology showed foot process effacement decreased, expression level of nephrin, CD2AP, myosin X were significantly increased compared with *db/db* mice. *In vitro* the dual-luciferase reporter assay verified the binding of miR-20a-5p to *MYH10* promoters, mutant *MYH10* gene had downregulated nephrin, CD2AP expression and exhibited F-actin as polymerized state.

Conclusions: In diabetic mice, the expression of miR-20a-5p in exosomes from renal tubular epithelial cells is elevated. This miR-20a-5p mediates cytoskeletal rearrangement in podocytes by inhibiting myosin X, leading to foot process effacement. Consequently, targeting exosomes could represent a novel therapeutic approach for treating

FR-PO293

Loss of Globotriaosylceramide Protects against Diabetic Kidney Disease

Suresh K Ramakrishnan,[1] Shruti Naik,[1] Indira Dibra,[1] Verena Rickert-Zacharias,[1] Roger Sandhoff,[3] Hermann-Josef Groene,[2] Matias Simons.[1] *[1]UniversitatsKlinikum Heidelberg, Heidelberg, Germany; [2]Philipps-Universitat Marburg, Marburg, Germany; [3]Deutsches Krebsforschungszentrum, Heidelberg, Germany*.

Background: Globotriaosylceramide (Gb3) is a glycosphingolipid that is formed by the addition of a galactose molecule to lactosylceramide by Gb3 synthase (Gb3S). In acute kidney injury models, Gb3 knockout has shown a protective effect on proximal tubular cells (PTCs). This can be attributed to loss of Gb3 contributing to reduced uptake of potentially damaging excess filtrates, such as albumin, lipids and toxins by PTCs. Here, we aimed to study the therapeutic potential of Gb3 inhibition in a mouse model for diabetic kidney disease (DKD).

Methods: 8 week-old Gb3S wildtype (WT) and knockout (KO) mice were injected with streptozotocin (STZ-50mg/ml) consecutively for 5 days. A high fat diet enriched with saturated fatty acids (SFA) was given from 11 weeks until 24 weeks of age. These STZ-SFA mice were described by us to exhibit DKD features (Perez-Marti et al, 2022). Transdermal GFR, urinary parameters, kidney injury and fibrosis markers (qPCR) were measured at the end point of the experiments. Histopathological analysis of kidney sections was performed. Oil red O-staining was used to check for lipid droplets. Western blotting was performed to quantify kidney and lipid markers protein expression.*Drosophila* nephrocytes were used to study lipid droplets upon knockdown of α4GT1, fly ortholog of Gb3S, using UAS-GAL4 system. Bodipy (493/503) staining was used to visualize lipid droplets (Confocal microscopy).

Results: Compared to STZ-SFA WT mice the STZ-SFA KO mice have normal GFR. Also, they display significantly decreased expression of kidney injury and fibrosis markers as well as lower albuminuria and glucosuria. Interestingly, we observed depletion of lipid droplet accumulation in the S2 and S3 proximal tubular segments of STZ-SFA KO mice compared to STZ-SFA WT mice. Protein expression of Perilipin-2 which coats lipid droplets was downregulated in the STZ-SFA KO kidney samples compared to STZ-SFA WT samples. Furthermore, α4GT1 knockdown nephrocytes lacked lipid droplets, suggesting a cell-autonomous effect of Gb3S deficiency on lipid droplets.

Conclusions: Our data suggest that loss of Gb3 is beneficial in alleviating kidney damage in the STZ-SFA mouse model. We speculate that decreased lipid uptake and lower lipid droplet accumulation in the proximal tubules may be one of the possible reasons for the beneficial effects.

FR-PO294

Esm-1 Prevents Glycocalyx Depletion in Glomerular Endothelial Cells in Diabetic Nephropathy

Haochen Guan,[1,2] Alexandre Gaudet,[1,3] Xiaoyi Zheng,[1,4] Vivek Bhalla.[1] *[1]Stanford University School of Medicine, Stanford, CA; [2]University of Science and Technology of China, Hefei, China; [3]Universite de Lille, Lille, France; [4]BriaCell Therapeutics, Philadelphia, PA.*

Background: Glomerular endothelial cell (GEnC) injury is one of the early characteristic signs of diabetic nephropathy (DN). Thus, markers or mediators of GEnC injury may be important to predict or prevent kidney disease, respectively. The GEnC glycocalyx forms the first part of the glomerular filtration barrier and its damage is a key initiator of albuminuria. Endothelial cell-specific molecule-1, Esm-1, is an anti-inflammatory, secreted proteoglycan. Plasma Esm-1 deficiency inversely correlates with markers of DN in humans and mice, and over-expression of Esm-1 in diabetic mice attenuates albuminuria and podocyte injury. However, it is still unclear whether and how Esm-1 modulates GEnC function in DN.

Methods: DN-susceptible DBA/2 mice were subjected to intraperitoneal injections of streptozotocin and fed a high-fat diet, and randomly assigned to receive hydrodynamic injection to overexpress Esm-1. Glycocalyx abundance was quantitated by WGA lectin staining. *In vitro*, human, conditionally immortalized GEnCs were maintained in the presence of glucose, insulin, TNF-α, and IL-6 to mimic a diabetic milieu. We also utilized glomerular RNAseq to characterize effects of Esm-1 expression on GEnC-expressed genes from DN-susceptible mice.

Results: Glycocalyx abundance was reduced following exposure to diabetic conditions both *in vivo* and *in vitro*. Systemic Esm-1 overexpression limited the reduction in WGA lectin glycocalyx staining in DN-susceptible mice (mean fluorescence intensity of Control *vs*. DM *vs*. DM+Esm-1, 101.9±3.643 *vs.* 61.47±2.786 *vs.*101.1±3.814; p<0.0001). Additional studies of GEnC phenotypes *in vitro* are ongoing. In 234 of 300 endothelial-enriched genes, we observe inverse correlations between glomerular Esm-1 mRNA expression and albuminuria (κ=0.53; p=2.29*10-29). For 206 of these 234 correlation genes, systemic over-expression of Esm-1 reverses the expression profile (κ=0.25; p=3.4*10-6), with 'vascular development' and 'blood vessel morphogenesis' being the dominant ontologies among reversible genes.

Conclusions: Our findings indicate that Esm-1 exerts a protective effect against DM-induced GEnC glycocalyx depletion. These data provide a more detailed explanation for potential mechanisms of protection from diabetes-induced albuminuria through significant changes in gene expression across GEnC.

FR-PO295

Mechanism of Disease Progression by Renin Overexpression in the db/db-UNx Model: A Proteomic Analysis

Srinath Jagarlapudi, Rose A. Keenan, Sabra D. Al-Harthy, Simone Romoli, Charles Halsey, Jeffrey A. Culver, Jeffrey Morin, Dinesh K. Hirenallur-Shanthappa, Denis Feliers. *Pfizer, Cambridge, MA, Cambridge, MA*.

Background: The db/db-UNx-renin model has gained in popularity, showing both increased albuminuria and reduced glomerular filtration rate (GFR). Our aim was to characterize the renal injury of db/db-UNx-renin mice using proteomics and to understand the role of renin overexpression in disease progression.

Methods: Four weeks-old db/db mice were subjected to uninephrectomy, two weeks later received an intravenous injection of an AAV containing either an empty vector or the human renin gene and the experiment was terminated at 16 weeks of age. Albuminuria was measured every two weeks, renal oxygen content and renal volume and transcutaneous GFR were determined at the end of the experiment. The remaining kidney was harvested, and proteomics analysis performed on the cortical fraction.

Results: Compared to db/m mice, GFR and renal oxygenation were increased in db/db-UNx mice, indicating a state of hyperfiltration. Renin overexpression caused a significant reduction in GFR in these mice. In db/db-UNx mice, albuminuria progressed throughout the experiment, while in db/db-UNx-renin mice, albuminuria peaked 2 weeks after AAV-renin injection and remained high. Renal hypertrophy was evident in db/db-UNx mice while cardiac hypertrophy was only observed in db/db-UNx-renin mice. Proteomics analysis of renal cortex showed that pathways associated with protein synthesis, energy metabolism, transport activity, mitochondria and respiration, adipogenesis and glycolysis and gluconeogenesis and amino acid metabolism were activated in db/db-UNx mice, suggesting a metabolic adaptation to the hyperfiltration seen in these mice. Renin overexpression, on the other hand, activated pathways associated with renal injury, extracellular matrix remodeling, inflammation, complement activation, macrophage activation, secretion of pro-angiogenic and pro-proliferative factors, and clot formation.

Conclusions: This study sheds light on the mechanism of kidney injury during diabetes and distinguishes two phases of the disease. In the hyperfiltrating phase, the renal tubules adapt by increasing their transport activity and energy production, while activation of complement, inflammation and coagulation pathways seem to play a role in the disease progression phase caused by renin overexpression.

FR-PO296

Single-Nucleus RNA Sequencing Reveals Sex-Specific Renoprotective Mechanisms in Diabetic Kidney Disease

Shuya Liu,[1,2] Tianran Zhang,[1,5] Shun Lu,[1,2] Martin Strauch,[4] Michaël Goedertier,[3] Ivan Costa,[3] Peter Boor,[4] Stefan Bonn,[5] Tobias B. Huber.[1,2] *[1]III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Hamburg Center for Kidney Health (HCKH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Institute for Computational Genomics, RWTH Aachen University Clinic, Aachen, Germany; [4]Institute of Pathology, RWTH Aachen University Clinic, Aachen, Germany; [5]Institute of Medical Systems Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*.

Background: Diabetic kidney disease (DKD) is a major complication of diabetes and the leading cause of end-stage renal disease worldwide. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) and angiotensin receptor blockers (ARB) have shown promise in preventing DKD progression, but their molecular mechanisms remain to be elucidated.

Methods: We treated DKD mice (BTBR *ob/ob*) with SGLT2i, ARB or their combination for 12 weeks. Healthy BTBR wild-type and vehicle-treated BTBR *ob/ob* mice served as controls. Notably, only female DKD mice showed significantly reduced albuminuria across all treatments. To explore the mechanisms, single-nucleus RNA sequencing (snRNA-seq) was performed on kidneys from female mice in each group (n=2/group).

Results: A total of 98,684 single nuclei were identified, which were characterized into 22 clusters and classified into 12 meta-cell types. Differential gene expression analysis was performed to define treatment responsive and non-responsive genes in each meta-cell type. Proximal tubule epithelial cells showed the most significant treatment response, whereas glomerular cell types showed limited responses. CellChat was used to identify renoprotective intercellular communication networks. Pattern recognition showed that proximal tubule epithelial and glomerular cells emerged as key signaling sources, suggesting their crucial role. The limited glomerular response suggests that current therapies may not fully address the disease in these cells. To identify potential therapeutic targets, Drug2Cell was used to predict glomerular cell-specific drug targets for each treatment, highlighting critical signaling pathways and offering insights for future drug development.

Conclusions: This study presents a comprehensive snRNA-seq analysis of female DKD mice treated with SGLT2i and ARB, revealing differential treatment responses by cell type. Intercellular communication networks highlight the importance of glomerular targeting and the discovery of novel drug targets for improved glomerular protection. Future work will integrate the framework for large-scale histomorphometry (FLASH) to correlate morphological lesions with the snRNA-seq data, aiming to provide a more comprehensive picture of DKD treatment at both transcriptomic and morphological levels.

Funding: Government Support - Non-U.S.

FR-PO297

Association of the Polymorphisms of the Angiotensin-Converting Enzyme and FRMD3 Genes in the Development of Diabetic Kidney Disease

Juan D. Diaz Garcia,[1] Enrique F. Morales Lopez,[2] Irving G. Ramirez.[1]
[1]Hospital Clinic de Barcelona, Barcelona, Spain; [2]Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico.

Background: Individual genetic biomarkers, called single nucleotide polymorphisms (SNPs), have been proposed that could represent potential non-invasive markers for the early diagnosis of diabetic kidney disease (DKD), in addition to their association with a characteristic phenotype. Aim: To determine the association of polymorphisms of the Angiotensin Converting Enzyme and FRMD3 genes with the risk of developing ERD in patients with type 2 diabetes.

Methods: Case-control study, comparative, observational, ambispective and cross-sectional, in which men and women, over 18 years of age with T2D with and without ERD and healthy patients, who underwent DNA extraction, participated. genomic and subsequent genotyping, and detection of SNPs by mass spectrometry.

Results: A total of 400 patients participated, 199 men and 201 women, within which they were divided into three groups: 100 patients with type 2 diabetes and ERD confirmed by renal biopsy, 100 patients with type 2 diabetes without ERD and 200 healthy controls. A total of 3 polymorphisms of the ACE and FRMD3 genes were studied. Among the polymorphisms analyzed in the logistic regression, rs179975 CA (OR, 6.2; 95% CI: 1.15-7.48, p=0.03), rs1888747 GA (OR, 6.6; 95% CI: 4.60-8.45, p=0.002) and rs10868025 resulted. CG (OR, 4.1; 95% CI: 2.40-5.60, p=0.002) Table 1.

Conclusions: Our study demonstrated the association of well-established genetic variants of the ACE and FRMD3 gene polymorphisms with the presence of ERD, showing that these SNPs, specifically rs179975 CA, rs1888747 GA and rs10868025 GC, may represent important genetic markers in the development of ERD and could be a predisposing factor due to the high frequency and strength of association that were observed in our studied population, this being the first study in Latin America.

FR-PO298

Scalable Micro-Kidneys for Unbiased Phenotypic Drug Discovery and Target Identification in Diabetic Nephropathy and Inherited Kidney Diseases

Fred Etoc. *RUMI Scientific, New York, NY.*

Background: A key bottleneck in the discovery of therapeutics in nephrology is the lack of physiological models that are compatible with drug discovery at a high-throughput scale for target identification. Currently, available in vitro models consist of impressive reconstitution of kidney tissues that are impractical for screening: 3D mini-kidneys, or micro-physiological systems that are all too large, too variable or too complex to be employed at scale within drug screens. At the other end, 2D cell models are very scalable but lack structural organization. RUMI has uniquely developed a platform that bridge this gap by allowing scalable screening and target ID in fully scalable and standardized complex micro-kidneys. We are leveraging this tool for in-house drug discovery, building a pipeline centered around high unmet needs areas such as DKD and inherited kidney diseases.

Methods: The key component of our platform is a micropatterning technology that allows for the arrayed generation of nearly identical self-organizing human micro-kidney tissues, which are derived from human embryonic stem cells. One multi-well plate can easily generate more than 5'000 replicates, and >100 plates can be generated at once. These large data sets of micro-kidneys images, in disease and control conditions, then enable the use of AI/deep learning to quantify subtle yet robust disease features within micro-kidney structures, as well as the potential for drugs to reverse the disease state to normal, paving the way towards discovery of new therapeutic candidates. Moreover, it has the potential to be coupled with CRISPR-KO genetic "suppressor screens", which are the gold standard for target identification which today and cannot be performed with alternative technologies.

Results: We will present our micro-kidney's characterization, and demonstrate how this system can be leveraged to model multifactorial aspects of the diabetic injury related to DKD. We will show that a key hallmark of kidney injury, KIM1, can be alleviated by knocking out of SLC5A2, demonstrating the validity of our platform in reproducing established clinical results. Moreover, we will discuss our preliminary results for phenotypic discovery of inherited kidney diseases such as Alport Syndrome and Polycystic Kidney Disease.

Funding: Private Foundation Support

FR-PO299

Study on the Pathogenic Role of CDA1 in Diabetic Kidney Disease (DKD) in Diabetic Akita Mice

Minling Huang, Jiali Tang, Tieqiao Wu, Mark E. Cooper, Zhonglin Chai.
Monash University Faculty of Medicine Nursing and Health Sciences, Melbourne, VIC, Australia.

Background: CDA1 has been demonstrated to enhance TGF-β signaling and plays a pathogenic role in experimental diabetic kidney disease (DKD) in STZ-diabetic ApoE knockout mice. The role of CDA1 in other animal models with diabetes induced by different mechanisms is unknown and the mechanisms underlying CDA1's actions have not been fully elucidated. In this study, the pathophysiologic role of CDA1 was investigated in the Akita mouse model of DKD, an insulin-deficient animal model, with RNA-seq analysis performed to explore potential molecular mechanisms.

Methods: Metabolic and relevant renal parameters, such as glomerulosclerosis injury (GSI) index, urine albumin-to-creatinine ratio (ACR), renal mRNA and protein levels of profibrotic and proinflammatory genes, were examined in non-diabetic WT and diabetic Akita mice at the age of 16 weeks in the presence (CDA1 WT) or absence (CDA1 KO) of a functional CDA1 gene. RNA sequencing (RNA-seq) was performed using total RNA isolated from the kidney tissues of these mice (n=6/group).

Results: Akita mice exhibited increased kidney injury, evidenced by elevated GSI (1.4-fold) and ACR (4-fold), as well as increased expression of both profibrotic and proinflammatory markers (2-fold). Importantly, deletion of CDA1 markedly attenuates these changes in Akita mice, leading to a notable 26.7% decrease in ACR and normalization of GSI, fibronectin gene expression, as well as protein expression levels of Collagen III and α-SMA to levels similar to non-diabetic controls. RNA-seq analysis revealed that CDA1 deletion modulates multiple signaling pathways closely associated with fibrosis, inflammation and cell cycle regulation, including the cytokine-cytokine receptor interaction pathway, complement and coagulation cascades, AGE-RAGE, TNF, chemokine, and relaxin signaling pathways. Notably, the expression levels of the p21 (Cdkn1a), a gene crucial in regulating cellular senescence, and senescence-associated secretory phenotype (SASP) expression, including TNF-α and MCP-1, were elevated in Akita mice, these parameters attenuated in Akita mice with CDA1 deletion.

Conclusions: Targeting CDA1 effectively attenuated diabetes associated renal injury, as a result of reduction in the cellular senescence leading to attenuation of the profibrotic and proinflammatory pathways.

Funding: Government Support - Non-U.S.

FR-PO300

Identification and Validation of Pivotal Genes Driving Diabetic Kidney Disease Progression through Weighted Gene Co-Expression Network Analysis

Siyang Ye, Manhuai Zhang, Meng Zhang, Dingding Wang, Jinjin Fan, Bin Li, Yi Zhou, Wei Chen. *The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Currently, the core factors governing the progression of diabetic kidney disease (DKD) remain elusive. Our study aims to explore the progression-related genes of DKD through comprehensive bioinformatics analysis and *in vivo* validation, thus providing novel therapeutic targets for retarding DKD progression.

Methods: Differentially expressed genes (DEGs) within kidney from early and advanced DKD samples were detected using GSE142025 dataset. Besides, the weighted gene co-expression network analysis (WGCNA) and protein-protein interaction (PPI) network were conducted, followed by key module analysis and recognition of pivotal genes driving DKD progression. Furthermore, enrichment analysis was used to determine the biological features of pivotal genes associated with DKD progression, and correlation analysis was utilized to explore the potential link between pivotal genes and altered immune status within DKD tissues. Finally, certain pivotal genes were validated by Western blot and immunohistochemistry (IHC) in diabetic mice kidney.

Results: A total of 44 DEGs were identified between early and advanced DKD specimens. Using WGCNA, the turquoise module was deemed as the DKD progression-related module. A total of 18 genes related to DKD progression were obtained by intersection analysis between the upregulated DEGs and the turquoise module. Enrichment analysis indicated that the above 18 genes were primarily involved in necroptosis and other immune inflammatory responses. Moreover, four genes (*STAT1, MYC, NLRP3,* and *TNFAIP3*) were recognized as pivotal genes implicated in DKD progression by PPI analysis. Correlation analysis showed that the above pivotal genes were mainly positively correlated with the infiltration of T cells. More importantly, Western blot and IHC analysis revealed that the protein levels of these pivotal genes were significantly increased in the kidneys of advanced DKD mice compared to those in the early DKD group.

Conclusions: Our findings suggest that necroptosis, as well as immune and inflammatory responses, are crucial biological events driving DKD progression. Of note, *STAT1, MYC, NLRP3,* and *TNFAIP3* were identified as pivotal genes promoting the progression of DKD. Consequently, targeting necroptosis and the above pivotal genes might represent a promising therapeutic strategy for delaying DKD progression.

Funding: Government Support - Non-U.S.

FR-PO301

WWP2-Induced Pericytes to Myofibroblast Transition Contributes to the Progression of Fibrosis in CKD in Diabetes

Paola Pontrelli,[1] Francesca Conserva,[1] Antonella Cicirelli,[1] Maria Venneri,[1] Rossana Franzin,[1] Alessandra Stasi,[1] Giorgia Sclavo,[1] Elena Squiccimarro,[1] Anna Gallone,[1] Francesco Pesce,[2] Marco Fiorentino,[1] Loreto Gesualdo.[1] *[1]University of Bari Aldo Moro, Bari, BA, Italy; [2]Universita Cattolica del Sacro Cuore Facolta di Medicina e Chirurgia, Roma, Italy.*

Background: CKD in diabetes presents different histological phenotypes commonly classified as diabetic Nephropathy (DN), non-diabetic renal disease (NDRD) and mixed forms (DN+NDRD) and only true DN is characterized by activation of the lysine63 (K63-Ub) ubiquitination pathway involved in the progression of renal fibrosis. WWP2 is an E3 ligase enzyme that modulates myofibroblast activation in cardiac fibrosis and metabolic reprogramming in CKD. The aim of the study was to evaluate the role of WWP2 in renal fibrosis in diabetes and its involvement in K63-Ub.

Methods: The expression of WWP2, K-63Ub, a-sma, PDGFBR, vimentin, NG2 was evaluated by immunohistochemistry, immunofluorescence, qPCR, western blotting and/or flow cytometry in: i) renal biopsies of patients with DN (n=11), nephroangiosclerosis or other renal damage in diabetic patients (NDRD) (n=8) and mixed forms DN+NDRD (n=3); ii) DBA/2J mice treated with streptozotocin in the presence or absence of a specific K63Ub inhibitor (NSC697923); iii) HK2 tubular cells, EAHY926 endothelial cells and pericytes.

Results: WWP2 was expressed at tubular, glomerular and vascular levels in both DN and DN+NDRD compared to NDRD ($p<0.05$ and $p<0.01$ respectively). Increased expression of WWP2 in DN was associated with the accumulation of K63Ub proteins in the tubular and vascular compartment, particularly in pericytes. In diabetic DBA/2J mice, K63Ub inhibition with NSC697923 significantly reduced WWP2 expression in the kidney ($p < 0.05$). Also in vitro, in HK2 cells, NSC697923 significantly reduced hyperglycemia-induced WWP2 and a-sma expression ($p < 0.01$). In pericytes, hyperglycemia induced the expression of WWP2 (RR>3), a-sma (RR>4), PDGFBR (RR>4), vimentin (RR>2) and reduced NG2 (RR>2) suggesting the transition from pericytes to myofibroblasts, and this effect was blocked by NSC697923 ($p<0.05$).

Conclusions: These findings suggest that WWP2 is involved in the K63-Ub pathway and promotes fibrosis progression in DN patients through pericytes to myofibroblasts transition. WWP2 could therefore represent a novel target in preventing the progression of renal damage in patients with DN.

FR-PO302

Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Activates Hedgehog Interacting Protein (Hhip)-Mediated Renal Tubular Cell Senescence in Diabetic Akita Mice

Min-Chun Liao,[1] Xin-Ping Zhao,[1] Shuiling Zhao,[1] Ke Su,[1] Shiao-Ying Chang,[1] Yuchao Pang,[1] Kana Miyata,[2] Junzheng Peng,[1] Julie R. Ingelfinger,[3] John S. Chan,[1] Shao-Ling Zhang.[1] *[1]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Saint Louis University, St Louis, MO; [3]Harvard Medical School, Boston, MA.*

Background: We recently reported that hedgehog interacting protein (Hhip) activates sodium-glucose cotransporter 2 (Sglt2) expression and promotes tubular senescence in murine diabetic kidney disease (DKD) (*Diabetologia 2023*). However, the underlying mechanism(s) are poorly understood. Nuclear factor erythroid 2–related factor 2 (Nrf2) plays a key role in Sglt2 inhibition-reduced tubular cell senescence in DKD (PMID: 34318973); here, we aimed to elucidate the underlying mechanism of Hhip and Nrf2 interaction on tubular senescence in DKD *in vivo* and *in vitro*.

Methods: Male Akita, Akita/Nrf2$^{-/-}$ and Akita/Nrf2$^{-/-}$ mice with renal proximal tubular cell (RPTC)-specific Nrf2 transgene (Akita/Nrf2$^{-/-}$/Nrf2^{RPTC}-Tg), and their respective control mice (non-Akita or Nrf2$^{-/-}$) were studied. Primary RPTCs and human immortalized HK-2 cells were the *in vitro* model used.

Results: Compared to respective controls at the age of 20 weeks, Akita mice displayed typical DKD characteristics (increased urinary albumin/creatinine ratio and glomerular filtration rate) and renal dysmorphology (renal hypertrophy, glomerulosclerosis and tubulopathy); those changes were attenuated in Akita/Nrf2$^{-/-}$ mice. As compared with Akita, Akita/Nrf2$^{-/-}$ mice had less renal tubular Hhip gene expression and decreased tubular senescence as assessed by β-galactosidase activity and p16-, p21-, and p53- immunostaining. However, these protective features were markedly lost in Akita/Nrf2$^{-/-}$/Nrf2^{RPTC}-Tg kidneys. *In vitro*, Nrf2 activators (oltipraz or CDDO-Me) significantly stimulated Hhip gene expression (promotor activity, Hhip mRNA and protein expression), while also promoted cellular senescence. Those effects were more pronounced under high glucose milieu. In contrast, HK-2 cells with Nrf2 knockout largely prevented the above phenotypes.

Conclusions: Nrf2 activates Hhip gene expression in RPTCs. In diabetes, activation of both Nrf2 and Hhip works in concert to accelerate tubular senescence in DKD.

Funding: Government Support - Non-U.S.

FR-PO303

Clearance of P16-Positive Senescent Cells Delays Diabetic Kidney Disease (DKD) by Normalizing Glycolysis and Mitochondrial Metabolic Disorder

Xiao Lu,[1] Jiao Wu,[1] Ewud Agborbesong,[1] Xiaogang Li.[1,2] *[1]Mayo Clinic Department of Internal Medicine, Rochester, MN; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Diabetic kidney disease (DKD) is one of the complications of diabetes, which is characterized by kidney damage and abnormal renal energy metabolism. Studies have shown that senescence is associated with the course of DKD. Recently, attention has focused on the effect of purging p16-positive senescent cells in transgenic mice on the increase of mean lifespan. However, whether and how p16 positive senescent cells promote the progression of DKD remain unknown.

Methods: To evaluate the role and mechanisms of p16 positive senescent cells in DKD progression, we established type 1 diabetes model (DM) through injection of streptozotocin in INK-ATTAC transgenic mice, which allowed a removal of p16Ink4a-positive cells upon administration of a drug, AP20187. We treated human renal tubular epithelial cells (HK2) cultured with different concentration of glucose. We also isolated the primary tubular epithelial cells from vehicle and AP treated DM INK-ATTAC mouse kidneys.

Results: We found that the expression of p16 was increased in renal tubular cells in the kidneys of DM mice and DKD patients as well as in HK2 cells cultured in high glucose media, which promoted senescence and elevated senescence-associated secretory phenotypes (SASPs), including TNF-α, IL-6 and IL-1β, in those kidneys and cells as examined with SA-β-gal staining and qRT-PCR analysis. Importantly, we found that clearance of p16-positive cells 1) delayed the progression of DKD as seen by the decrease of serum creatinine and urine microalbumin in DM INK-ATTAC mouse treated with AP20187, 2) alleviated kidney injury in diabetic mice through Rb-CDK4 pathway and the decrease of SASPs, and 3) restored ATP content, decreased the expression of the key glycolytic enzymes, and improved the metabolic reprogramming in DM INK-ATTAC mouse kidneys. In addition, clearance of p16-positive cells normalized the expression of the genes involved in mitochondrial metabolism through AMPK and mTOR pathway, suggesting that p16 positive senescent cells also played an important role in renal mitochondrial metabolic disorder in DKD.

Conclusions: Our study indicates that p16 positive senescent cells plays an important role in the progression of DKD, and their clearance delays the progression of DKD through normalizing glycolysis and mitochondrial metabolic disorder, which is a novel therapeutic target for DKD.

FR-PO304

Cytochrome P450 Is a Metabolic Regulator of Diabetic Kidney Disease (DKD) Progression

Batoul Dia,[1] Sarah Almoussawi,[1] Sarah Hamade,[1] Sam El-Osta,[2] Assaad Antoine Eid.[1] *[1]American University of Beirut, Beirut, Lebanon; [2]Baker Heart and Diabetes Institute, Melbourne, VIC, Australia.*

Background: Cytochrome P450 (CYP) epoxygenases metabolize arachidonic acid (AA) into 20-HETE (20-Hydroxyeicosatetraenoic acid) and EETs (Epoxyeicosatrienoic acids). Our group has demonstrated the involvement of CYPs and their metabolites in the pathogenesis of diabetic kidney disease (DKD) by activating reactive oxygen species (ROS) production. Polymorphisms of CYP genes can alter the expression of these enzymes, influencing DKD prognosis. We hypothesize that alterations in 20-HETE and EET levels contribute to ROS elevation via an SGLT2/mTOR-dependent mechanism in diabetes. Additionally, we have assessed the genetic contribution in the AA-metabolizing CYPs associated with the progression of DKD

Methods: We enrolled healthy volunteers (n=15) and patients with type 2 diabetes (T2DM) with (n=30) or without (n=70) DKD. We measured 20-HETE and EET levels in

urine and plasma samples by Enzyme Linked Immunosorbent Assay. We also assessed CYP expression in kidney biopsies. SNPs for the CYP4A11, CYP4F8, and CYP2B6 genes were detected using TaqMan PCR assays on DNA extracted from blood samples. To study the preclinical significance, molecular and histological analyses were performed using a T2DM mouse model treated with the pharmacological inhibitors of 20-HETE (HET0016), sEH (AUDA), SGLT2 (Dapagliflozin), and mTOR (Rapamycin, JR-AB2-011 and PP242). In vitro validation studies were performed using human podocyte and proximal tubular epithelial cells

Results: Patients with DKD had elevated 20-HETE levels compared to T2DM patients without DKD, who had higher levels than healthy volunteers. This increase was associated with higher expression of CYP4A11 and CYP4F8 in kidney biopsies. EET levels were lower in DKD patients compared to T2DM patients without DKD, correlating with decreased CYP2B6 expression in kidney biopsies. We identified novel SNPs for CYP2B6 and CYP4A11 in patient groups, suggesting an increased risk with the mutant alleles for diabetes and DKD. Regulation of 20-HETE and EET levels were associated with renal injury mediated by the SGLT2/mTOR/NOX4 axis. This was confirmed in the T2DM mouse mode and validated in the human renal cells

Conclusions: This study provides a framework into novel CYP450 pathways involved in diabetes-induced renal injury. We also describe the potential prognostic and diagnostic biomarkers related to CYP associated pathways in the progression DKD

FR-PO305

Role of Gut Microbiota in the Development of Diabetic Kidney Disease

Sarah Almoussawi,[1,2] Leonard Lawandos,[1] Sarah Hamade,[1] Taghreed Shouman,[1] Sahar Alkhansa,[1] Batoul Dia,[1] Mohamad Noureldein,[1] Assaad Antoine Eid.[1]
[1]American University of Beirut, Beirut, Lebanon; [2]Universite de Limoges, Limoges, France.

Background: The role of microbiota in Diabetes Mellitus (DM) and its complications has garnered significant attention recently. Our research highlighted that DM is associated with intestinal dysbiosis, characterized by decreased *Bacteroidetes* to *Firmicutes ratio*, the two main bacterial species constituting more than 90% of intestinal microorganisms. Interestingly, fecal microbial transplantation (FMT), i.e. the administration of fecal matter from a healthy donor into a recipient's gastrointestinal tract, is emerging as a promising treatment approach for several diseases. Remarkably, reports established the capability of FMT to restore a healthy gut microbiome and alleviate symptoms of these diseases. Herein, we hypothesize that modifying gut microbiota by FMT might affect the pathogenesis and progression of diabetic kidney diseases (DKD) and serve as an effective treatment approach

Methods: FVB/NJ and non-obese type 2 diabetic MKR transgenic mice were used. Mice were divided into three groups: sham, group treated with FMT from healthy mice donors, and group treated with FMT from MKR diabetic donors. Treatment was administered by oral gavage twice weekly for 8 weeks after depleting their gut microbiota using an antibiotic cocktail. Urine and kidneys were collected for functional, histological, and molecular analyses

Results: Our study show a decline in kidney function, as evidenced by increased albuminuria (UAE) and urine albumin-creatinine ratio (UACR) in the FVB group treated with MKR FMT. Histological changes were also observed, along with elevated reactive oxygen species (ROS) production and inflammation, underscoring the presence of dysbiosis in renal deterioration. These findings closely mirrored the results observed in the MKR group, where elevated albuminuria levels and UACR were accompanied by increased sclerosis and collagen deposition, and paralleled by increased NOX induced ROS production and inflammation. Intriguingly, these adverse effects were reversed in the MKR group treated with FVB FMT. This reversal was associated with reduced ROS production, decreased expression of NADPH oxidase (NOX), and dampened inflammation. Notably, the expression of inflammatory cytokines was significantly lower in this group

Conclusions: This study presents novel findings on the impact of microbiota in diabetes-induced renal injury

FR-PO306

PPP2R2B Variant Reduces Protein Phosphatase 2A (PP2A) Complexity and Worsens Diabetic Kidney Disease (DKD) Progression

Zhengying Fang, Zeguo Sun, Kyung Lee, Ruijie Liu, John C. He.
Icahn School of Medicine at Mount Sinai, New York, NY.

Background: We have previously shown that protein phosphatase 2A (PP2A), a major Ser/Thr phosphatase in the kidney, is involved in regulation of podocyte function in diabetic kidney disease. Podocyte-specific knockout of PP2A catalytic unit leads to more severe podocyte injury and progression of DKD. Here, we report the identification of variants in the *PPP2R2B* gene, encoding the podocyte-specific regulatory subunit of PP2A, in DKD patients with ESKD.

Methods: We carried out clinical studies and genetic analyses, including genome-wide linkage analysis and whole-exome sequencing to identify candidate variants. Transgenic mice models were generated to validate the phenotype of the candidate variant. Functional studies on the disease-associated variant were performed in transgenic mice glomeruli and cultured cells.

Results: Several variants of *PPP2R2B* gene were found to be associated with renal outcome in DKD patients. To help elucidate the underlying mechanism, we generated a knock-in mice model with one of the clinical worst outcome-related *PPP2R2B* missense variants (p.T222M). We induced diabetes in these knock-in mice and their littermate controls. We found that mice carried *Ppp2r2b* p.T222M developed worse DKD phenotype such as proteinuria, glomerular hypertrophy, and mesangial expansion, as compared to littermate controls. Crucially, *Ppp2r2b* p.T222M results in impaired glomerular PP2A activity as measured by PP2A activity assay and phosphorylation of its substrate NF-kB. However, the protein expression level of glomerular Ppp2r2b was not affected by the variant. In addition, using in vitro studies, we showed that *PPP2R2B* p.T222M variant reduced PP2A complexity, thus altering cellular PP2A activity and downstream phosphorylation of NF-kB.

Conclusions: Our findings confirmed that mice carrying *Ppp2r2b* p.T222M variant developed more severe renal phenotype. We also demonstrated that *PPP2R2B* p.T222M variant led to impaired glomerular PP2A activity by reducing the complexity of the PP2A holoenzyme, without affecting the protein expression levels. Our study help us better understand the role of PP2A complex in the pathogenesis of human DKD and might provide new insights into therapeutic targets for DKD.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO307

Inhibition of p53 Ameliorates Adenine-Induced Kidney Injury in Mice

Hak Joo Lee,[1,2] Guanshi Zhang,[1,2] Richard Montellano,[1,2] Ian M. Tamayo,[1] Esmeralda Trevino,[1] Jean C. Bopassa,[1] David G. Md,[1] Kumar Sharma.[1,2]
Center for Precision Medicine. *[1]University of Texas Health San Antonio, San Antonio, TX; [2]Audie L. Murphy Memorial Veterans' Hospital, STVHCS, San Antonio, TX.*

Background: Diabetes is associated with premature senescence and an increase in apoptosis in the kidney of patients with diabetes in association with upregulation of p53. In addition, inhibition of production of the endogenous nephrotoxic metabolite adenine ameliorated diabetes-induced kidney injury in mice with type 2 diabetes and adenine has been found to stimulate the senescence associated secretory phenotype (SASP) including p21 mRNA expression in the kidney of WT mice. We therefore hypothesized that deletion of p53 ameliorates adenine-induced kidney injury by inhibiting p21-apoptosis pathway in mice.

Methods: We randomized 8-10 weeks age of p53KO and WT male mice. Mice received 0.2 % adenine-containing diet or normal chow for 4 weeks (n=5-12 per group).

Results: Adenine decreased body weight, blood glucose level, and kidney, liver, and heart weight to tibia length ratio in WT and p53KO mice. p53KO significantly reduced adenine-induced albuminuria, kidney fibronectin accumulation and plasma blood urea nitrogen increment in mice. However p53KO did not affect adenine-increased kidney injury molecules-1 level in the kidney. Adenine increased mRNA expression of SASP in the kidney of both WT and p53KO mice. p53KO significantly decreased adenine induced IL-6 and partially reduced other SASP components (p16, TGFβ1, and IL-1β). p53KO inhibited adenine-induced p21 mRNA expression and degradation of Bcl2.

Conclusions: Our data suggest that the adenine-p53-apoptosis pathway contributes to kidney injury in mice. Adenine-p53 axis could be used for a therapeutic target of diabetes kidney disease and other kidney diseases characterized by adenine excess production.

FR-PO308

Spatial Metabolomics via Matrix-Assisted Laser Desorption Ionization Mass Spectrometry Imaging (MALDI-MSI) Identifies Bioenergetic and Tricarboxylic Acid (TCA) Cycle Metabolites as Pharmacodynamic Biomarkers of Losartan for Diabetic Kidney Disease

Leila Hejazi,[1] Shoba Sharma,[1] Aaron Ruiz,[1] Ian M. Tamayo,[2] Soumya Maity,[2] Guanshi Zhang,[2] Fabio C. Tucci,[3] Kumar Sharma.[2] *[1]SygnaMap, San Antonio, TX; [2]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [3]Epigen Biosciences Inc, San Diego, CA.*

Background: Spatial metabolomics is a powerful platform for drug development for identifying pharmacodynamic biomarkers and mechanism of action (MoA) of therapeutics. Herein, we used an advanced MALDI-MSI platform to identify metabolites regulated by a specific treatment losartan (an angiotensin II receptor blocker used for clinical diabetic kidney disease).

Methods: Fresh frozen kidney tissues were obtained from vehicle-treated and losartan-treated Zucker diabetic fatty (ZDF)-rats (5/group). After sectioning and DAN matrix application, MALDI-MSI was performed using a ThermoFisher Orbitrap QE-Exactive-HFX coupled with a Spectroglyph MALDI/ESI source. All imaging data was uploaded to METASPACE for metabolite annotations using HMDB. Autofluorescence- and histochemical-images were used to identify kidney margins and to correlate different kidney tissue features to the MSI data using MSI-DeepPath and obtain pixel-level annotated metabolites.

Results: Using METASPACE, an average of 300 endogenous metabolites were annotated in each kidney tissue section. To compare levels of metabolites across tissue sections and animal groups, intensity data extracted from METASPACE were co-registered to corresponding tissue sections, normalized and quantified using the MSI-DeepPath platform. Statistically significant results ($p < 0.02$) showed that the most highly up-regulated metabolites in response to losartan treatment were uridine 5'-diphosphate (UDP), orotidylic acid (OMP), and adenosine diphosphate (ADP). The most significantly down-regulated metabolites ($p < 0.005$) were malic acid and fumaric acid, key intermediates in the TCA cycle pathway.

Conclusions: Losartan can reduce levels of fumarate, a potential fibrogenic metabolite in the diabetic kidney, confirming a prior report that losartan can lower urine fumarate. Additionally, losartan increased levels of nucleotides such as UDP, ADP, and OMP, which may significantly impact energy levels and overall metabolic state of a cell. MSI-DeepPath identified losartan's novel effects on fumarate and bioenergetic metabolites, thereby demonstrating the power of quantitative spatial metabolomics for pharmacodynamic biomarkers/MoA.

Funding: NIDDK Support

FR-PO309

Investigating the Therapeutic Potential of Mannose in Diabetic Nephropathy: Targeting Epithelial-Mesenchymal Transition

Sharui Ma,[1] Liumei Song,[2] Xiangchun Liu.[3] *[1]Shaanxi Provincial People's Hospital, Xi'an, China; [2]Xi'an Jiaotong University, Xi'an, China; [3]The Second Hospital of Shandong University, Jinan, China.*

Background: Diabetic nephropathy progression often involves epithelial-mesenchymal transition (EMT) of proximal tubular epithelial cells, driven in part by the activation of transforming growth factor-beta (TGF-β) signaling in response to high glucose levels. Mannose, a hexose sugar, has shown promise in mitigating type 2 diabetes progression by suppressing TGF-β activity and enhancing regulatory T (Treg) cell function.

Methods: Human renal proximal tubular epithelial cells (HRPTECs) were cultured and subjected to control conditions, high glucose exposure, or high glucose combined with mannose treatment. Cell migration was assessed using wound scratch assays, and the expression of EMT-related proteins (E-cadherin, N-cadherin, and Vimentin) was analyzed via Western blotting. Further experiments investigated the regulatory effect of mannose on TGF-β through Western blotting, quantitative real-time polymerase chain reaction (qRT-PCR), and co-immunoprecipitation assays. Rescue experiments involved the overexpression of TGF-β followed by assessment of EMT reversal.

Results: High glucose exposure significantly promoted EMT in HRPTECs, whereas mannose treatment effectively reversed this progression. Mannose also attenuated the upregulation of EMT-related proteins induced by high glucose. Mechanistically, mannose was found to reduce TGF-β protein levels through increased ubiquitination and subsequent degradation, without affecting mRNA levels. Notably, overexpression of TGF-β counteracted the mesenchymal-epithelial transition (MET) induced by mannose, confirming the inhibitory effect of mannose on EMT via TGF-β regulation.

Conclusions: Our findings demonstrate that mannose inhibits high-glucose-induced EMT in HRPTECs by promoting the degradation of TGF-β. This suggests the therapeutic potential of mannose, a simple sugar, in the treatment of diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-PO310

Photobiomodulation in Kidney Function in Rats with Diabetic Kidney Disease

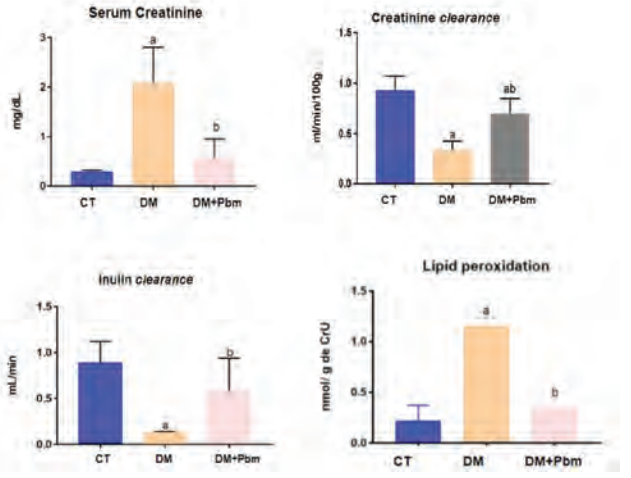
Jessica P. García,[1] Eloiza O. Silva,[1,2] Guilherme H. Ferreira Vieira,[1] Carla D. Victoria,[1] Maikol L. Gonçalves,[1] Alessandra Oliveira Maia,[1] Juliana V. Silva,[1] Mykelly G. Alves,[1] Camila Lima,[1] Luciana Soares C. Santos,[1,2] Mirian Watanabe,[3] Maria De Fatima Vattimo.[1] Group of Studies on Acute Kidney Injury. *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Faculty of Medical Sciences of Santa Casa de Sao Paulo, Sao Paulo, Brazil; [3]United Metropolitan Colleges University Center, Sao Paulo, Brazil.*

Background: Diabetic kidney disease (DKD) is a serious microangiopathic complication of diabetes mellitus (DM). Photobiomodulation therapy (Pbm) is a non-pharmacological therapy based on the red spectral range. Studies with a CKD model in rats showed positive results in CKD after the application of Pbm, such as reduced blood pressure, increased glomerular filtration rate and decreased tubulointerstitial fibrosis. The aim of this study is to evaluate the impact of Pbm on the function of rats with DRD.

Methods: Wistar rats weighing 280-300 g randomized as follows: Citrate (CT): animals that received streptozotocin vehicle (citrate; iv, caudal, single dose); Diabetes Mellitus (DM): animals that received streptozotocin (STZ, 60mg/kg; iv; single dose); Diabetes Mellitus + Low-intensity laser (DM+Pbm): DM animals, in the third, were irradiated with a low-intensity infrared laser (wavelength 808nm, power 100mW, energy 3 Joule, a point on the right flank on the left, 3 times a week, 6 weeks). Renal function (serum creatinine-CrS; creatinine clearance; inulin clearance-Clin) and oxidative profile (urinary peroxides, lipid peroxidation) were evaluated.

Results: The DM group reduced renal function when evaluating serum creatinine, creatinine clearance and inulin, while the DM+Pbm group increased these parameters, attenuating the deterioration of renal function and improving the oxidative profile. The group subjected to photobiomodulation showed a reduction in oxidative stress compared to the DM group.

Conclusions: The results confirmed that photobiomodulation attenuates the reduction in renal function induced by diabetic kidney disease.



FR-PO311

Long-Term Impact of PM2.5 Exposure on Diabetic Kidney Disease Patients Considering Time-Dependent Medication Adjustment

Soie Kwon,[1] Jung Pyo Lee.[2] *[1]Chung Ang University Hospital, Seoul, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea.*

Background: Ambient air pollutants adversely affect renal function and increase type-2 diabetes incidence. However, the impact of air pollution on diabetic kidney disease (DKD) patients remains underexplored, with limited consideration of medication-related effects. We assessed the influence of air pollutants on DKD patients while meticulously adjusting for medication usage.

Methods: We retrospectively enrolled DKD patients. Primary and secondary outcomes included end-stage kidney disease (ESKD) and a composite (ESKD, mortality). Nationwide forecasted ultrahigh-resolution air-pollutant data ($PM_{2.5}$, PM_{10}, NO_2, CO) were obtained from AiMS-CREATE. Monthly updated ambient air pollutants and medication prescription information were considered time-varying variables in multivariable time-dependent Cox analyses.

Results: Patients (n=9,482) were followed for a median of 9 (ESKD) and 11 (composite outcome) years; 20.6% progressed to ESKD, and 46.7% experienced composite outcomes. The DKD-stage patient distribution was 12.5% (stage 1-2), 35.8% (stage 3), and 51.6% (stage 4-5). Initial RAS blocker use increased from 37.4% to 58.5% during Year 1 then gradually declined. During follow-up, all four air pollutant concentrations significantly decreased, with CO exhibiting the most pronounced decline. $PM_{2.5}$ was significantly associated with greater ESKD progression (aHR=1.19, 95% CI=1.020–1.396) and composite outcome (aHR=1.17, 95% CI=1.055–1.299) risk. Unexpectedly, PM_{10} increases were associated with decreased ESKD progression and composite outcome risk, potentially influenced more by social factors (e.g., air pollution alerts).

Conclusions: In this study, there was evidence of $PM_{2.5}$ exposure-related adverse effects on ESKD progression in DKD even after comprehensive medication usage adjustment.

Association between end-stage kidney disease progression or composite outcome and air pollutant exposure.

Air pollutant (unit)	ESKD			Composite outcome		
	HR	95% CI	p value	HR	95% CI	p value
NO2 (10ppb)	1.09	0.967–1.224	0.162	1.00	0.926–1.088	0.924
CO (10ppb)	1.00	0.989–1.015	0.813	1.00	0.991–1.009	0.973
PM10 (10ug/m3)	0.91	0.853–0.963	0.002	0.92	0.886–0.965	<0.001
PM2.5 (10ug/m3)	1.19	1.020–1.396	0.027	1.17	1.055–1.299	0.003

Air pollutants were considered time-dependent covariates. All analyses were adjusted for time-fixed covariates and time-dependent confounders (antidiabetic drug usage and renin-angiotensin blocker usage).

FR-PO312

Modeling Cardiorenal Protection with SGLT2 Inhibition in Type 1 Diabetes: An Analysis of DEPICT-1 and -2

Massimo Nardone,[1] Luxcia Kugathasan,[1] Vikas Sridhar,[1] Pritha Dutta,[3] David Campbell,[2] Anita T. Layton,[3] Bruce A. Perkins,[4] Sean Barbour,[5] Tony K. Lam,[6] Adeera Levin,[5] Leif Erik Lovblom,[1] Istvan Mucsi,[1] Remi Rabasa-Lhoret,[7] Valeria E. Rac,[6] Peter A. Senior,[8] Ronald J. Sigal,[2] Aleksandra Stanimirovic,[6] Alessandro Doria,[9] David Cherney.[1] *[1]Toronto General Research Institute, Toronto, ON, Canada; [2]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [3]University of Waterloo, Waterloo, ON, Canada; [4]Sinai Health, Toronto, ON, Canada; [5]The University of British Columbia, Vancouver, BC, Canada; [6]University of Toronto, Toronto, ON, Canada; [7]Universite de Montreal, Montreal, QC, Canada; [8]University of Alberta, Edmonton, AB, Canada; [9]Harvard Medical School, Boston, MA.*

Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors improve glycemic control and lower insulin requirements in type 1 (T1D) and type 2 diabetes (T2D). While SGLT2 inhibitors lower cardiovascular disease (CVD) and end-stage kidney disease (ESKD) risk in T2D, dedicated cardiorenal outcome trials have not been performed in T1D. Using validated risk prediction models, the current analysis evaluated the effect of SGLT2 inhibition on estimated CVD and ESKD risk in a T1D cohort.

Methods: Demographics, medical history, biomarkers, and blood pressure were extracted from 1,473 participants with T1D enrolled in the DEPICT-1 and -2 trials. Data at baseline, week -24, -52, and -56 (4 weeks off-treatment) were used to estimate 10-year CVD and 5-year ESKD risk using the Steno T1 Risk Engine (SRE) and the Scottish Diabetes Research Network (SDRN) risk prediction models. Risk reduction was determined based on the percent change in risk from baseline between participants receiving dapagliflozin (pooled 5 and 10mg) vs. placebo, and evaluated statistically using a two-factor repeated measures ANOVA.

Results: The relative 10-year estimated CVD risk was significantly lower following 52 weeks of dapagliflozin treatment (SRE: -5.8% [-8.4, -3.3%] & SDRN: -11.9% [-16.1, -7.8%]; ; P<0.01). The 5-year ESKD risk was also significantly lower following 52 weeks of dapagliflozin treatment (SRE: -8.4% [-12.4, -4.4%]; P<0.01). The greatest improvement in ESKD risk was observed at week 56 (-12.8% [-16.6, -9.0%]; P<0.01), in conjunction with an expected rise in eGFR post drug cessation.

Conclusions: Dapagliflozin improves estimated CVD and ESKD risk in T1D participants, emphasizing the need for cardiorenal outcome trials in people living with T1D. By avoiding the acute, reversible GFR “dip” with SGLT2 inhibition, estimation of ESKD risk using models that incorporate GFR may be best performed when drug is discontinued.

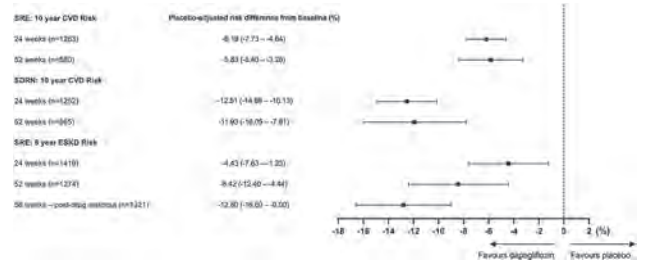


Figure 1.

FR-PO313

Simulated Effect of Dapagliflozin on Reducing Incidence of Albuminuria and CKD Using the Urinary Proteomics Classifier CKD273 in Normoalbuminuric Type 2 Diabetes

Viktor Rotbain Curovic,[1] Frederik Persson,[1] Tine Hansen,[1] Peter Rossing.[1,2] The PRIORITY Study Group. *[1]Steno Diabetes Center Copenhagen, Herlev, Denmark; [2]Kobenhavns Universitet Det Sundhedsvidenskabelige Fakultet, Kobenhavn, Denmark.*

Background: Higher urinary proteomic classifier CKD273 levels are associated with higher albuminuria and chronic kidney disease (CKD) grade 3 risk, in type 2 diabetes (T2D). Treatment with dapagliflozin have shown to significantly lower CKD273 levels. We have investigated if the magnitude of CKD273 reduction, seen after treatment with dapagliflozin, is associated with a lower risk of developing albuminuria and CKD grade 3 in normoalbuminuric T2D.

Methods: Post-hoc simulation of the observational PRIORITY (NCT02040441) study originally designed to assess CKD273 as a predictor of albuminuria. People with T2D and normal albuminuria and eGFR were included. CKD273 levels at baseline were releveled according to the CKD273 reduction seen after dapagliflozin treatment in the DapKid (NCT03509454) study (-0.221 arb. units). Endpoints were development of persistent urinary albumin creatinine ratio >30 mg/g and development of CKD grade 3 (eGFR <60 ml/min/1.73m^2). Cox proportional hazard models were fitted per -0.221 difference in baseline CKD273 level. Models were adjusted for sex, baseline age, diabetes duration, HbA_{1c}, systolic blood pressure, and eGFR.

Results: In total, 1589 were included, 995 (63%) were men, and followed for a median (IQR) of 2.4 (2.0, 3.0) years. Baseline mean (SD) age was 61.9 (8.3) years, diabetes duration was 11.8 (7.8) years, HbA_{1c} was 7.4 (1.1) %, and eGFR was 87 (16) ml/min/1.73m^2. Crude Cox analyses showed a 24% lower risk of albuminuria per 0.221 lower CKD273 levels at baseline (HR (95% CI): 0.76 (0.70, 0.83), p<0.001) and remained significant after adjustment (0.87 (0.80, 0.95), p=0.002). Similar results were seen with development of CKD grade 3, with 27% lower risk in crude models (0.73 (0.70, 0.84), p<0.001), confirmed in adjusted (0.84 (0.76, 0.92), p<0.001).

Conclusions: Across 2.4 years, in a population with T2D and no albuminuria, a 0.221 lower level of CKD273 was associated with a 24% lower risk of developing albuminuria and 27% lower risk of developing CKD grade 3. Associations remained significant after adjustment for relevant risk factors. Our results suggest that a reduction in CKD273 on par with that seen after treatment with dapagliflozin may lower renal events already in normoalbuminuric type 2 diabetes.

FR-PO314

Development and Validation of a Model to Predict a Positive CKD Screening among Patients with Type 2 Diabetes

Gregorio T. Obrador,[1] Ana Freyria,[1] Alma Sotelo,[3] Alejandro Chevaile,[2] Rafael Valdez-Ortiz,[4] Nikita Karuzin,[1] Eduardo Brenner Muslera,[1] Nadia Olvera.[5] *[1]Universidad Panamericana School of Medicine, Ciudad de México, Mexico; [2]Universidad Autonoma de San Luis Potosi, San Luis Potosi, Mexico; [3]Universidad Panamericana School of Nursing, Ciudad de México, Mexico; [4]Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico; [5]Universidad Panamericana, Ciudad de Mexico, Mexico.*

Background: Cost barriers limit chronic kidney disease (CKD) screening in low- and middle-income countries. This study aims to provide a formula for identifying patients with type 2 diabetes mellitus (T2DM) who will be screened positive for CKD to optimize available resources.

Methods: The development cohort consisted of adult patients with T2DM who participated in a CKD screening program in three Mexican states. Demographic and clinical data were collected. Standardized serum creatinine was measured, and the glomerular filtration rate was estimated with the 2021 CKD-EPI equation. The albumin/creatinine ratio was assessed using Siemens’ *Clinitek Status*. Univariate and multivariate logistic regression models were developed, and odds ratios with 95% confidence intervals, receiver operator characteristic curves (ROC), and area under the curve (AUC) were calculated. The validation cohort consisted of adult patients with T2DM who were screened for CKD in three clinics of Mexico City’s Secretariat of Health. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are reported in each cohort.

Results: Overall, 602 patients with T2DM underwent screening in the development cohort. The mean age was 57 years, and 73% were female. The multivariate model included the following variables (ORs): age (1.02), female gender (0.82), fasting glucose (1.0008), years with T2DM (1.01), and family income (0.99). AUC from the ROC was 71.8% (Fig. 1). After setting the threshold to 0.2 to reduce false negatives, the sensitivity was 80.7%, specificity 46.3%, PPV 15.2%, and NPV 95.2%. The validation cohort consisted of 449 patients with T2DM. The mean age was 60 years, and 66% were female. With the same threshold of 0.2, sensitivity reached 80.0%, specificity 38.5%, PPV 4%, and NPV 98.3%.

Conclusions: The formula’s accuracy, high NPV, and easy availability of the included variables make it a valuable tool, mainly when CKD screening resources for patients with T2DM are limited.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.

FR-PO315

Longitudinal Risk Assessment by kidneyintelX.dkdTM to Guide Adaptive Clinical Trials

Steven G. Coca,[1] Sharon Stapleton,[2] Girish N. Nadkarni,[1] Fergus Fleming,[2] Hiddo J. Heerspink.[3] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Renalytix plc, London, United Kingdom; [3]Rijksuniversiteit Groningen, Groningen, Netherlands.*

Background: Albuminuria has been used as a biomarker to guide adaptive clinical trials in Diabetic Kidney Disease. Intra-individual coefficient of variation of albuminuria within an individual is high and 2024 KDIGO CKD guidelines state that increases in UACR less than a doubling, or reductions in albuminuria smaller than 50% are consistent with random fluctuations. The FDA De-novo marketing authozied kidneyintelX.dkd test incorporates biomarkers and clinical variables and categorizes patients at low, moderate, or high risk for progression of Diabetic Kidney Disease. Time-updated changes in future risk per kidneyintelX.dkd may help delineate response to DKD therapy, particularly in those with UACR changes in the ambiguous zone (i.e., -49% to +99%).

Methods: We measured tumor necrosis factor receptor 1 (TNFR-1), tumor necrosis factor receptor 2 (sTNFR-2), and kidney injury molecule (KIM-1) on banked plasma from CANVAS trial participants with baseline DKD (eGFR <60 ml/min/1.73 m^2 or UACR ≥30 mg/mg). We determined the kidneyintelX.dkd risk level at baseline and year 1 and assessed how changes in kidneyintelX.dkd were associated with subsequent DKD progression (composite outcome of ≥40% sustained decline in eGFR, or kidney failure) in those with ambiguous changes in UACR in the same period.

Results: 933 participants with prevalent DKD had baseline and year 1 plasma samples, a median eGFR of 66 ml/min and median UACR of 55 mg/g. Post year 1, 78 (8.4%) participants experienced the outcome over the following median of 4.9 years. Of these, 31% experienced a 50% reduction and 13% experienced more than a doubling of uACR at year 1. In the ambiguous population (56%), 40% initially scored kidneyintelX. dkd moderate or high risk. Of these, at year 1, 27% moved to low risk with event rate was 3.3% (ref), 58% stayed at or moved to moderate risk with event rate 3.3-fold higher at 11%. In those that remained or moved to high risk (14%), the event rate was over 14-fold higher at 45%.

Conclusions: Re-assessment of risk via kidneyintelX.dkd at 1 year in those with ambiguous change in albuminuria robustly stratified patients for future progression of DKD. Adaptive clinical trials can consider kidneyintelX.dkd risk levels over time as a criterion to tailor interventions, particularly for those with moderate or high risk of progression after randomization.

Funding: Commercial Support - Renalytix

FR-PO316

Health Care Costs and Utilisation for Diabetes Mellitus among Hospitalised Patients in Ireland: The National Kidney Disease Surveillance System

Leonard Browne,[1] Meera Tandan,[1] Austin G. Stack.[1,2] National Kidney Disease Surveillance System and Quality Assurance Programme.
[1]University of Limerick, Limerick, Ireland; [2]University Hospital Limerick, Dooradoyle, Ireland.

Background: A better understanding of the frequency, length of stay, and costs of inpatient hospitalisation for diabetes mellitus (DM) is crucial for effective national healthcare planning and resource allocation. We explored the rates of diabetes-related hospitalisations and associated healthcare costs in Ireland.

Methods: We utilised data from the National Hospital In-Patient Enquiry (HIPE) database in 2022, which captured all hospitalisations to public hospitals in Ireland. We included all ICD-10 hospital admissions with a principal or additional diagnosis of diabetes (E10, E11, E13, E14, O24). Age-standardised rates (ASR), length of stay, and costs were computed and compared across demographic characteristics, Charlson comorbidity score (0, 1-2, and ≥3), and 8 health regions. Rates were standardised to the European Standard Population from 2012, and rate ratios (RR) were determined and compared.

Results: In 2022, 8.6% of all hospitalisations in Ireland (146,362/1,711,564) recorded diabetes as a principal or additional diagnosis, costing €601 million. Diabetes as principal diagnosis accounted for 10,511 hospitalisations with the following breakdown: type 2 diabetes (58.5%), type 1 diabetes (28.4%) gestational diabetes (12.7%), and other or unspecified diabetes (0.2%). Average LOS was 4.9 days and increased significantly rising Charlson Comorbidity score (range 3.9 to 9.2 days). Hospital admissions, LOS, and costs increased significantly with increasing comorbidity burden. The most frequent complications were kidney, eye, and circulatory complications. Age standardised rates were higher in men than women (4,071 vs 2,844 per 100, 000 population) and men experienced significantly higher rates than women for kidney (x 1.9 times), eye (x1.8 times), circulatory (x3.6 times), and neurological complications (x1.9 times). Hospitalisation rates varied significantly by region: lowest in the Southwest RR 0.8 (0.8-0.8) and highest in the Midland region RR 1.8 (1.7-1.8) (P<0.01) compared to the national average (RR 1.00).

Conclusions: Diabetes mellitus contributes substantially to healthcare utilisation and costs in Ireland driven by complications related to kidney disease, eye disease and circulatory disease. Demographic and regional disparities exist and highlight the need for strategic healthcare planning and early preventive care.

FR-PO317

Effect of Sotagliflozin on eGFR Slope by Baseline Kidney Function and Glycemic Control

Vikas Sridhar,[1] Deepak L. Bhatt,[4] Ayodele Odutayo,[1] Michael Szarek,[5] Michael J. Davies,[2] Phillip Banks,[2] Bertram Pitt,[3] Philippe Gabriel Steg,[6] David Cherney.[1] *[1]University of Toronto, Toronto, ON, Canada; [2]Lexicon Pharmaceuticals Inc, The Woodlands, TX; [3]University of Michigan, Ann Arbor, MI; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]SUNY Downstate Health Sciences University, New York City, NY; [6]Universite Paris Cite, Paris, France.*

Background: In a secondary analysis of the SCORED trial using the complete laboratory dataset, sotagliflozin (SOTA), a dual SGLT1 & 2 inhibitor, reduced the risk of kidney and cardiorenal composite endpoints in patients with type 2 diabetes (T2D) and diabetic kidney disease (DKD). This *post hoc* analysis of SCORED evaluated the effect of SOTA versus placebo on eGFR slope and the impact of baseline kidney function and glycemia.

Methods: We derived the acute eGFR slope (from baseline to week 4), chronic slope (week 4 to month 12) and total slope using a spline mixed effects repeated measures model on the entire cohort and in the following baseline subgroups – eGFR <30, 30 to <45, ≥45 ml/min/1.73m^2; A1, A2 and A3 albuminuria; glycated hemoglobin A1C <8%, ≥8 to <9%, ≥9%.

Results: Within the entire cohort of 10,574 participants, a placebo-adjusted acute decline in eGFR of -2.59 ml/min/1.73m^2/year (95% CI -2.88, -2.30; p<0.0001) was observed. The chronic slope, measured after this acute decline, was 1.99 ml/min/1.73m^2/ year in favor of SOTA (95% CI 1.63, 2.34; p<0.0001). The total placebo-adjusted slope was -0.08 ml/min/1.73m^2/year (95% CI -0.43, 0.27; p=0.67). The magnitude of the acute decline attenuated across progressively lower eGFR subgroups (P-interaction =0.017). Effects on chronic slope were consistent across baseline eGFR and A1C subgroups (P-interaction=0.48 and 0.22). Compared to placebo, SOTA had a greater benefit on chronic slope with increasing baseline albuminuria (P-interaction=0.023)

Conclusions: In participants with DKD, treatment with SOTA conferred kidney protection across a spectrum of baseline kidney function and glycemic control. The magnitude of kidney protection was larger with increasing albuminuria.

Funding: Commercial Support - Lexicon Pharmaceuticals

Table 1. eGFR slope in overall cohort and by baseline subgroups.

Overall cohort

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-2.49 (0.11)	0.10 (0.11)	-2.59 (-2.88, -2.30)	<0.0001
Chronic	-0.07 (0.13)	-2.06 (0.13)	1.99 (1.63, 2.34)	<0.0001
Total	-1.93 (0.13)	-1.86 (0.13)	-0.08 (-0.43, 0.27)	0.67

eGFR category subgroups

a. eGFR <30

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	0.20 (0.31)	1.60 (0.32)	-1.40 (-2.26, -0.53)	0.0015
Chronic	0.06 (0.04)	-0.16 (0.05)	0.22 (0.10, 0.34)	0.0005
Total	0.07 (0.04)	-0.05 (0.04)	0.12 (0, 0.23)	0.051

b. eGFR 30 to <45

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-1.55 (0.14)	1.11 (0.14)	-2.66 (-3.06, -2.26)	<0.0001
Chronic	0.02 (0.02)	-0.16 (0.02)	0.18 (0.13, 0.22)	<0.0001
Total	-0.08 (0.02)	-0.08 (0.02)	0 (-0.04, 0.04)	0.94

c. eGFR ≥45

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-3.82 (0.17)	-1.04 (0.16)	-2.78 (-3.24, -2.32)	<0.0001
Chronic	-0.04 (0.02)	-0.19 (0.02)	0.15 (0.11, 0.19)	<0.0001
Total	-0.27 (0.02)	-0.24 (0.02)	0.03 (-0.08, 0.01)	0.12

Albuminuria category subgroups

a. Normoalbuminuria (A1)

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-1.86 (0.19)	0.87 (0.19)	-2.72 (-3.25, -2.20)	<0.0001
Chronic	0.05 (0.02)	-0.07 (0.02)	0.12 (0.08, 0.17)	<0.0001
Total	-0.07 (0.02)	-0.01 (0.02)	-0.05 (-0.10, 0)	0.032

b. Microalbuminuria (A2)

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-2.74 (0.18)	0.31 (0.18)	-3.06 (-3.54, -2.56)	<0.0001
Chronic	0.06 (0.02)	-0.11 (0.02)	0.16 (0.11, 0.21)	<0.0001
Total	-0.12 (0.02)	-0.08 (0.02)	-0.04 (-0.08, 0.01)	0.13

c. Macroalbuminuria (A3)

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-2.91 (0.18)	-0.98 (0.18)	-1.93 (-2.43, -1.44)	<0.0001
Chronic	-0.16 (0.02)	-0.38 (0.02)	0.23 (0.17, 0.28)	<0.0001
Total	-0.33 (0.02)	-0.42 (0.02)	0.09 (0.04, 0.15)	0.0007

Glycated hemoglobin category subgroups

a. A1C <8%

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-2.53 (0.17)	0.12 (0.16)	-2.65 (-3.11, -2.20)	<0.0001
Chronic	0.01 (0.02)	-0.15(0.02)	0.16 (0.11, 0.21)	<0.0001
Total	-0.15 (0.02)	-0.14 (0.02)	-0.02 (-0.06, 0.03)	0.46

b. A1C ≥8 to <9%

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-2.76 (0.19)	-0.02 (0.19)	-2.74 (-3.27, -2.21)	<0.0001
Chronic	0.02 (0.02)	-0.18 (0.02)	0.20 (0.15, 0.26)	<0.0001
Total	-0.15 (0.02)	-0.17 (0.02)	0.02 (-0.03, 0.07)	0.43

c. A1C ≥9%

Slope	SOTA: mean (SE)	PBO: mean (SE)	Absolute Difference (95% CI)	p-value
Acute	-2.20 (0.19)	0.19 (0.19)	-2.39 (-2.93, -1.85)	<0.0001
Chronic	-0.05 (0.02)	-0.19 (0.02)	0.14 (0.08, 0.20)	<0.0001
Total	-0.18 (0.02)	-0.16 (0.02)	-0.02 (-0.07, 0.04)	0.54

SOTA - sotagliflozin, PBO - placebo, SE – standard error, CI – confidence interval, A1c - Glycated hemoglobin

FR-PO318

Effects of Canagliflozin on Albuminuria and eGFR Decline Using an Individual Preintervention eGFR Slope

Satoshi Miyamoto,[1] Hiddo J. Heerspink,[2] Dick de Zeeuw,[2] Kota Sakamoto,[1] Michihiro Yoshida,[1] Hiromi Kuramoto,[1] Kenichi Shikata.[1] *[1]Okayama University Hospital, Okayama, Japan; [2]University Medical Center Groningen, Groningen, Netherlands.*

Background: Demonstrating drug efficacy in slowing kidney disease progression requires large clinical trials when targeting participants with early stage of chronic kidney disease (CKD). To assess the effect of canagliflozin on kidney function in patients with type 2 diabetes (T2D) and microalbuminuria, we used a novel trial design using the individual's change in the rate of estimated glomerular filtration rate (eGFR) decline before (preintervention slope) and during treatment (chronic slope).

Methods: We conducted a randomized, parallel-group, open-labeled trial (CANPIONE study) at 21 sites in Japan. We randomly assigned (1:1) participants with T2D, urinary albumin-to-creatinine ratio (UACR) of 50 to <300 mg/g, and an eGFR of ≥45 mL/min/1.73m^2 to receive 52 weeks of canagliflozin or guideline-recommended treatment except for SGLT2 inhibitors (control). The first and second primary outcomes were the geometric mean percentage change from baseline in UACR and the change in eGFR slope (chronic−preintervention), respectively. The study is registered with the Japan Registry of Clinical Trials (jRCTs061180047).

Results: Of 98 randomized participants, 96 received at least one study treatment. The least-squares mean change from baseline in log-transformed geometric mean UACR was greater in the canagliflozin group than the control group (between-group difference, −30.8% (95%CI −42.6 to −16.8); p=0.0002). The change in eGFR slope (chronic−preintervention) was 1.4 (95%CI −0.6 to 3.3) and −3.1 (95% CI −5.1 to −1.0) mL/min/1.73m^2 per year in the canagliflozin and control groups, respectively, resulting in a between-group difference (canagliflozin−control) of 4.4 mL/min/1.73m^2 per year (95%CI 1.6 to 7.3, p=0.0022). The effect of canagliflozin in slowing the rate of eGFR decline was more pronounced in participants with steeper preintervention slope than that in slow progressors (5.6 vs. 3.1 mL/min/1.73m^2 per year).

Conclusions: Canagliflozin reduced albuminuria and the patient-specific eGFR trajectory in patients with T2D and microalbuminuria. The results from the CANPIONE study suggest that the within-individual change in eGFR slope may be a novel approach to identify participants with faster preintervention eGFR decline and to determine the kidney protective potential of new therapies in early stage of CKD.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

FR-PO319

SGLT2 Inhibitors Are Associated with Lower Risk of CKD Progression in Type 2 Diabetes (T2D) than Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs): An Emulated Clinical Trial

Sydney E. Hartsell,[1,2] Amara Sarwal,[1,2] Ravinder Singh,[1,2] Mckenna R. Nevers,[1,2] Jincheng Shen,[1,2] Guo Wei,[1,2] Robert E. Boucher,[1] Tom Greene,[1] Stavros Drakos,[1,2] Srinivasan Beddhu.[1,2] *[1]The University of Utah School of Medicine, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

Background: There is a paucity of data on head-to-head comparisons between GLP1-RA and SGLT2i on the risk of CKD progression in T2D.

Methods: We used an active comparator, new user design to compare insulin glargine (IG), GLP1-RA and SGLT2i among veterans with T2D and CKD (eGFR <60) on metformin who initiated one of these drugs between 01/01/18 and 12/31/21 (N=26,624). Generalized propensity score based inverse probability weighting (IPW) was used to minimize confounding in comparisons across the three drug classes. Outcomes were CKD progression (50% eGFR drop or eGFR <15 sustained over 2 consecutive labs), all-cause mortality (ACM) and renal/ACM composite, followed through 3/31/23. We will add ESRD data with follow-up until 12/21 via USRDS linkage when available July 2024. IPW Cox regression models related study drug class to kidney and mortality outcomes, additionally adjusted for demographics, comorbidities, diabetes severity, and baseline labs and medications.

Results: Prior to weighting, 9,829, 3,799 and 12,996 veterans initiated IG, GLP1-RA and SGLT2i respectively with baseline eGFRs of 48.7(9.0), 48.8(8.0) and 51.1(6.7) ml/min/1.73m^2, mostly in Stage 3A (73.3%, 72,6% and 83.3% respectively). Few had albuminuria >300mg/g (7.7%, 7.7% and 8.2% at baseline) but most did not have urine albumin lab data available within 365 days prior to study drug initiation date (41-46% missing across all groups). Pairwise comparisons of unweighted and weighted event rates and hazard ratios are shown in the table. Compared to those on GLP1-RA, veterans with T2D and CKD on SGLT2i had a 39% lower hazard of 50% decrease in eGFR or progression to CKD Stage V (HR 0.61, 95%CI 0.49-0.75) and a 22% lower hazard of renal/ACM (HR 0.88, 95%CI 0.79-0.98). IG was associated with a higher risk of CKD progression compared to SGLT2i or GLP1-RA.

Conclusions: These data from a large national cohort of veterans with T2D and CKD suggest that SGLT2i may have a renoprotective advantage over GLP1-RA.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support

Outcome	Treatment (Group 1 vs. Group 2)	Group 1 Event Rate, per 100 person-years		Group 2 Event Rate, per 100 person years		Adjusted HRs (95% CI)
		Unweighted	Weighted	Unweighted	Weighted	
CKD Progression (≥50% drop in eGFR or eGFR <15)	IG vs. GLP1-RA	2.13 (572/26867)	1.96	1.65 (169/10268)	1.64	1.25 (1.04, 1.52)
	IG vs. SGLT2i	2.13 (572/26867)	1.96	1.08 (311/29234)	1.19	2.06 (1.74, 2.44)
	SGLT2i vs. GLP1-RA	1.08 (311/29234)	1.19	1.65 (169/10268)	1.64	0.61 (0.49, 0.75)
Mortality-CKD Progression Composite (≥50% drop in eGFR or eGFR <15 or death)	IG vs. GLP1-RA	9.35 (2511/26867)	8.58	5.92 (608/10268)	6.16	1.40 (1.27, 1.54)
	IG vs. SGLT2i	9.35 (2511/26867)	8.58	4.96 (1449/29234)	5.49	1.61 (1.49, 1.74)
	SGLT2i vs. GLP1-RA	4.96 (1449/29234)	5.49	5.92 (608/10268)	6.16	0.88 (0.79, 0.98)
All-Cause Mortality	IG vs. GLP1-RA	7.61 (2178/28618)	6.97	4.61 (497/10781)	4.88	1.41 (1.27, 1.57)
	IG vs. SGLT2i	7.61 (2178/28618)	6.97	4.23 (1268/29944)	4.68	1.43 (1.31, 1.56)
	SGLT2i vs. GLP1-RA	4.23 (1268/29944)	4.68	4.61 (497/10781)	4.88	1.00 (0.89, 1.13)

Table

FR-PO320

Risk-Based Implementation of SGLT2 Inhibitors: Insights from the CANVAS Program and CREDENCE Trial

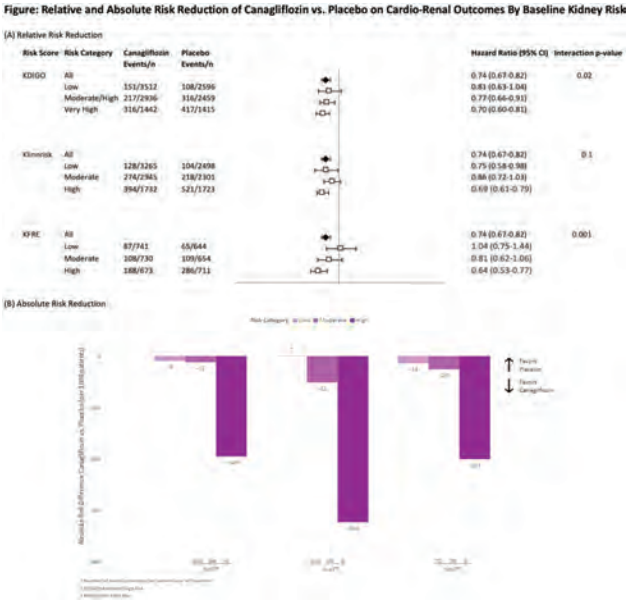
Emily K. Yeung,[1] Thomas W. Ferguson,[2,3] Navdeep Tangri,[2,3] Muthiah Vaduganathan,[4] Clare G. Arnott,[5,6] Min Jun,[5] Sradha S. Kotwal,[5,7] Meg Jardine,[8,9] Vlado Perkovic,[5,10] Hiddo J. Heerspink,[5,11] Brendon L. Neuen.[5,12] *[1]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]University of Manitoba Faculty of Health Sciences, Winnipeg, MB, Canada; [3]Seven Oaks General Hospital, Winnipeg, MB, Canada; [4]Washington DC VA Medical Center, Washington, DC; [5]The George Institute for Global Health, Sydney, NSW, Australia; [6]Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [7]Prince of Wales Hospital and Community Health Services, Randwick, NSW, Australia; [8]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [9]Concord Repatriation General Hospital, Concord, NSW, Australia; [10]University of New South Wales, Sydney, NSW, Australia; [11]Rijksuniversiteit Groningen, Groningen, Netherlands; [12]Royal North Shore Hospital, St Leonards, NSW, Australia.*

Background: The Kidney Disease Improving Global Outcomes (KDIGO) 2024 guideline for the evaluation and management of chronic kidney disease (CKD) recommends using a validated risk score to estimate absolute risk of kidney failure (1A recommendation). Given that those at highest risk of CKD progression are also at highest risk for cardiovascular outcomes, we sought to determine if a risk-based approach would identify those who benefit most from a cardio-kidney perspective with SGLT2 inhibition.

Methods: In this post-hoc individual participant data analysis of the CANVAS program and CREDENCE trial, we categorized participants according to risk of CKD progression using the KDIGO classification of CKD, Klinrisk algorithm, and the Kidney Failure Risk Equation (restricted to participants with eGFR <60 mL/min1/1.73m2). Effects of canagliflozin on a cardio-kidney composite outcome of 40% decline in eGFR, kidney failure or death due to cardiovascular or kidney disease were analyzed using Cox and Poisson regression models.

Results: Across higher kidney risk categories, participants were more likely to have lower eGFR, higher urine albumin:creatinine ratio, higher systolic blood pressure, and longer duration of diabetes (all p<0.0001). Overall, canagliflozin reduced the relative risk of the cardio-kidney composite outcome by 26% (HR 0.74, 95% CI 0.67-0.82). The relative benefits of canagliflozin were at least as large across higher kidney risk categories (Figure; Panel A). Absolute risk reductions were largest in participants at highest baseline risk (Figure; Panel B).

Conclusions: The use of validated kidney risk scores can accurately identify those who benefit most from SGLT2 inhibition with canagliflozin.



FR-PO321

Assessing Heterogeneity of Treatment Effects from Canagliflozin (CANA) on Kidney Outcomes Using the Joslin Kidney Panel: Insights from the CREDENCE Trial

Sok Cin Tye,[1,2] Zaipul Md Dom,[1,2] Eiichiro Satake,[1,2] Michael K. Hansen,[3] Matthew D. Breyer,[3] Andrzej S. Krolewski.[1,2] *[1]Joslin Diabetes Center, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Janssen Research & Development, LLC, Springhouse, PA.*

Background: SGLT2 inhibitors reduce kidney outcomes among patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). The Joslin Kidney Panel of 21 proteins (JKP) predicts end-stage kidney disease (ESKD) in patients with diabetes.[1] This study aims to develop a JKP-based risk model and assess heterogeneity of treatment effects (HTE) in patients with T2D and CKD.

Methods: Post-hoc analysis of the CREDENCE trial, including 1374 participants with CKD stage 3. Baseline JKP protein levels measured via Olink® platform. The kidney outcome studied was first occurrence of estimated glomerular filtration rate (eGFR) decline by 50% or ESKD. A Cox proportional hazard model was used to first derive a clinical markers model with four predictors from the Kidney Failure Risk Equation. Next, JKP was integrated and final model selected using a stepwise Akaike's Information Criterion. Participants classified into risk quartiles (Q1-Q4), with event rates, relative risks, and cumulative incidence (CI) differences estimated.

Results: During 2.6 years follow-up, 155 (placebo) and 82 (CANA) kidney events recorded. The final model, comprising age, sex, eGFR, urinary-albumin-creatinine-ratio, and six JKP proteins, yielded a C index of 0.82 (95% CI 0.77 to 0.87). Estimated median baseline risk was 20.9% (IQR 8.6%-47.0), demonstrating considerable variation among individual patients. Notably, ~50% of patients (N=688) in this study with a lower predicted risk (Q1,Q2) did not benefit from CANA. However, those in the higher risk quartiles showed a substantial relative treatment benefit with hazard ratios (HR) of 0.35 (95% CI 0.19 to 0.66) and HR 0.42 (95% CI 0.30 to 0.59) in Q3 and Q4 respectively. They also had greatest absolute benefit of CANA, shown by a notable CI rate difference. **(Table 1)**

Conclusions: Integrating the JKP into the risk stratification model improves the prediction of kidney outcomes among patients with T2D and CKD. HTE was observed among CANA-treated patients, with those at higher baseline risk benefiting the most

Funding: NIDDK Support, Other NIH Support - Hearst foundation

Table 1: Kidney outcome risk and treatment effects of canagliflozin vs. placebo in CREDENCE subpopulation (N=1374), categorized by risk quartiles.

Predicted risk quartiles	Placebo (N=679) Cumulative risk, % (Events, N)	Canagliflozin (N=695) Cumulative risk, % (Events, N)	Risk difference % (95% CI)	Hazard ratios (95% CI)
Q1	5.87 (7)	3.39 (6)	2.48(1.55-3.41)	0.80(0.27-2.39)
Q2	14.66 (17)	9.96 (12)	4.70(2.97-6.43)	0.69(0.33-1.45)
Q3	30.73 (36)	12.53 (14)	18.20(16.41-20.00)	0.35(0.19-0.66)
Q4	74.64 (95)	41.40 (50)	33.24(31.46-35.02)	0.42(0.30-0.59)
Total	31.53 (155)	16.18(82)	15.35 (11.95-18.75)	0.48 (0.37-0.63)

FR-PO322

Dosing, Treatment Pattern, and Safety of Finerenone Use in Routine Care: An Interim Analysis of the Prospective, Real-World, and Observational FINE-REAL Study

Christoph Wanner,[1] David C. Wheeler,[2] Kevin M. Pantalone,[3] Lixin Guo,[11] Nihar Desai,[4] Ricardo Correa-Rotter,[5] Sankar D. Navaneethan,[6] Susanne B. Nicholas,[7] Samuel T. Fatoba,[8] Andrea Horvat-Broecker,[9] Martin Merz.[10] *[1]Hospital Würzburg, Würzburg, Germany; [2]University College London, London, United Kingdom; [3]Cleveland Clinic, Cleveland, OH; [4]Yale University School of Medicine, New Haven, CT; [5]Instituto Nacional de Ciencias Médicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [6]Baylor College of Medicine, Houston, TX; [7]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [8]Bayer US LLC, Whippany, NJ; [9]Bayer AG, Wuppertal, Germany; [10]Bayer AG, Berlin, Germany; [11]Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China.*

Background: FINE-REAL (NCT05348733) is evaluating the use of finerenone in patients (pts) with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2D) in routine clinical practice. This interim analysis describes the dosing, treatment pattern, and safety of finerenone.

Methods: Global, prospective, single-arm, non-interventional study of pts aged ≥18 years with CKD and T2D treated with finerenone.

Results: Of the 1826 pts in this analysis, 1179 (65%) were male and 1682 (92%) were aged ≥50 years. Median follow-up time (IQR) was 269 (150–363) days. At baseline, UACR was available for 1081 (59%) pts, with a median (IQR) UACR of 300 (89–809) mg/g. Mean (SD) eGFR was 54 (24) mL/min/1.73 m^2 (n=1331). At baseline, ACEi/ARBs, SGLT2i, or GLP-1 RA were used by 1298 (71%), 946 (52%), and 522 (29%) pts, respectively. At initiation, 1475 (81%) pts received 10 mg finerenone and 349 (19%) pts received 20 mg finerenone. At 12 months, 372 (25%) pts starting with 10 mg were up-titrated at least once, while 27 (8%) pts starting with 20 mg were down-titrated at least once. At 12 months, 70% of pts with no UACR available (n=253) received 10 mg finerenone; 29% received 20 mg. Of those with UACR available at 12 months, pts with UACR <30 mg/g (n=22) were less likely to receive 20 mg vs 10 mg finerenone (18% vs 82%) than those with UACR 30–300 mg/g (n=83; 37% vs 62%) or >300 mg/g (n=121; 41% vs 59%). Hyperkalemia events were observed in 140 (8%) pts. Treatment-emergent adverse events (AEs) and serious AEs were observed in 574 (31%) and 153 (8%) pts, respectively.

Conclusions: By UACR, the FINE-REAL study population has milder renal impairment than in other pivotal analyses such as FIDELIO DKD. Comedication of finerenone with ACEi/ARBs, SGLT2i, or GLP-1 RA is more optimized in the FINE-REAL study population than is typically observed in real-world practice. Pts with higher UACR received higher finerenone doses, and pts with no UACR available at baseline received lower doses. Safety was consistent with the known safety profile of the drug.

Funding: Commercial Support - Bayer AG

FR-PO323

Utilization of the Nonsteroidal Mineralocorticoid Receptor Antagonist (MRA) Finerenone with or without Previous Steroidal MRA

Zihe Zheng,[1] Samuel T. Fatoba,[1] Matthew Novin,[1] German Guerrero,[1] Yunxun Wang,[1] Youssef M. Farag,[1] Connor W. Mckee,[2] Wei Huang,[2] Hongping Tian,[2] Rakesh Singh,[1] Yuxian Du,[1] Jon W. Mares,[1] Marco Lavagnino,[1] Drew Rockett,[1] Karthik Sankaralingam.[1] *[1]Bayer US LLC, Whippany, NJ; [2]Cobbs Creek Healthcare LLC, Newtown Square, PA.*

Background: Finerenone is an FDA-approved non-steroidal MRA indicated for reducing cardiovascular risk and slowing CKD progression in patients with CKD and T2D. Treatment inertia with nsMRA may stem from prior use of traditional steroidal MRAs (sMRA) that are known to be associated with increased hyperkalemia. To begin addressing this practice uncertainty, we described the key characteristics of finerenone users in real-world, with and without known prior sMRA use. We expect nsMRA use among eligible prior sMRA users.

Methods: We conducted retrospective study of finerenone users from July 2021 to December 2023 using the IQVIA Longitudinal Access and Adjudication Data. Adult patients with ≥ 12 months of continuous activity prior to their first filled finerenone claim date (index) were included. Patients with claims for both finerenone and sMRA on the same day were excluded. We described baseline demographics, comorbidities, and comedications of finerenone users by prior sMRA use status.

Results: The largest claim-based finerenone user cohort of 107,143 patients were included, among them 8,025 (7.5%) and 3,315 (3.15%) were prescribed sMRA within the past year and over a year, respectively, prior to initiating finerenone. The mean age was 67 with female percentage at 45-47% across subgroups. Those with prior sMRA prescription exhibited a 23-27% higher prevalence of HF and a 26-30% higher loop diuretic use. Comedication percentage for SGLT2i (47-51%) and GLP1RA (35-37%) remained consistent, regardless of prior sMRA use.

Conclusions: Our study shows that almost 11% of current finerenone users had prior or recent prescription of traditional sMRA. These patients exhibited different comorbidities and comedication profiles from those without prior sMRA prescription at the time of finerenone initiation. Future research should investigate the CV, kidney, and safety outcomes of finerenone users who recently used sMRA to inform clinical practice.

Funding: Commercial Support - Bayer US LLC

Table. Demographics, comorbidities and comedication of finerenone users by prior sMRA status

	Without prior sMRA use (n= 95,803)	Recent sMRA use (≤365 days) (n= 8,025)	Remote sMRA use (>365 days) (n= 3,315)
Age, yr (± SD)	67.0 (± 11.6)	66.8 (± 11.6)	67.3 (± 11.3)
Female, %	40,260 (45)	3,442 (46)	1,479 (47)
Hypertension, %	75,323 (79)	6,559 (82)	2,817 (85)
Heart Failure, %	15,573 (16)	3,096 (39)	1,415 (43)
ACEi, %	34,188 (36)	2,231 (28)	857 (26)
ARB, %	39,864 (42)	3,778 (47)	1,513 (46)
CCB, %	47,072 (49)	4,299 (54)	1,831 (55)
Diuretic, %	39,986 (42)	5,342 (67)	2,020 (61)
Loop, %	22,088 (23)	4,278 (53)	1,617 (49)
Thiazide, %	22,671 (24)	2,116 (26)	750 (23)
K-sparring, %	135 (<1)	51 (1)	23 (1)
Insulin, %	37,773 (39)	3,479 (43)	1,469 (44)
Metformin, %	46,403 (48)	3,369 (42)	1,169 (35)
GLP1-RA, %	33,829 (35)	2,823 (35)	1,224 (37)
SGLT2i, %	44,938 (47)	4,075 (51)	1,678 (51)

FR-PO324

Utilization of Guideline-Directed Medical Therapies in Finerenone Users

Zihe Zheng,[1] Samuel T. Fatoba,[1] Matthew Novin,[1] German Guerrero,[1] Yunxun Wang,[1] Youssef M. Farag,[1] Connor W. Mckee,[2] Hongping Tian,[2] Rakesh Singh,[1] Yuxian Du,[1] Jon W. Mares,[1] Drew Rockett,[1] Karthik Sankaralingam,[1] Wei Huang,[2] Marco Lavagnino.[1] *[1]Bayer US, LLC, Whippany, NJ; [2]Cobbs Creek Healthcare LLC, Newtown Square, PA.*

Background: Non-steroidal MRA finerenone reduces CV risk and slows CKD progression in patients with CKD and T2D. Clinical guidelines recommend finerenone for patients with UACR > 30mg/g despite maximum tolerated RAS inhibitor (ACEi/ARB). However, it is reported that 30-50% of patients with CKD and T2D do not receive ACEi/ARBs, and about 30% of those discontinue within 6 months, contributing to the inertia for new disease-modifying therapies. To address this inertia, we assess the key characteristics of finerenone users in real-world setting with and without concomitant ACEi/ARB.

Methods: We conducted a retrospective study of finerenone users from July 2021 to December 2023 using the IQVIA Longitudinal Access and Adjudication Data. Adult patients with ≥ 12 months of continuous activity prior to their first filled finerenone claim date (index) were included. Patient demographics, comorbidities, and comedications stratified by ACEi/ARB status were described.

Results: The largest finerenone user cohort of 107,323 patients were included, among them 49,864 (46.5%) initiated finerenone in the absence of concomitant ACEi/ARB therapy. Patient age, gender, and key comorbidities were largely comparable, except for that finerenone users without ACEi/ARB had slightly higher prevalence of HF (22%) compared to those with ACEi/ARB (16%). Comedications use were 3-10% less common in the finerenone user without ACEi/ARB group, including SGLT2is and GLP1RAs. Interestingly, 5,077 (4.7%) finerenone users initiated SGLT2i after starting finerenone.

Conclusions: Our study shows that 46.5% patients initiated finerenone without concomitant ACEi/ARB. Finerenone use in the absence of ACEi/ARBs is common in routine clinical practice, suggesting that despite guideline recommendations, therapies are used in a variety of sequences and combinations to accommodate patient profiles. Future study should examine CV, kidney, and safety outcomes of finerenone users with and without ACEi/ARB.

Funding: Commercial Support - Bayer US LLC

Table. Demographics, comorbidities and comedication of finerenone initiators by ACEi/ARB status

	With ACEi/ARB (n= 57,459)	Without ACEi/ARB (n= 49,864)
Age, yr (± SD)	66.8 (± 11.7)	67.2 (± 11.5)
Female, %	24,299 (45)	20,963 (45)
Comorbidities, n (%)	-	-
Hypertension	45,252 (79)	39,601 (79)
Heart Failure	9,320 (16)	10,823 (22)
Retinopathy	2,522 (4)	2,227 (4)
Comedications, n (%)	-	-
Diuretic	28,941 (50)	21,842 (44)
Insulin	23,987 (42)	18,817 (38)
Metformin	30,117 (52)	20,897 (42)
GLP1-RA	21,189 (37)	16,754 (34)
SGLT2i	28,941 (50)	21,842 (44)

FR-PO325

Reduction in Urinary Albumin-to-Creatinine Ratio (UACR) in People with CKD and Type 2 Diabetes Initiating Finerenone: A Comedication Subgroup Analysis from the FOUNTAIN Platform

Csaba P. Kovesdy,[1] J. Bradley Layton,[4] Bishnu B. Thapa,[2] Gary C. Curhan,[2] Luis M. Rangel,[2] Alfredo E. Farjat,[3] Fangfang Liu,[3] Catherine B. Johannes,[5] David Vizcaya,[3] Nikolaus G. Oberprieler.[3] *[1]Division of Nephrology, University of Tennessee, Memphis, TN; [2]OM1, Inc., Boston, MA; [3]Bayer AG, Berlin, Germany; [4]RTI Health Solutions Research Triangle Park, Research Triangle Park, NC; [5]RTI Health Solutions Waltham, Waltham, MA.*

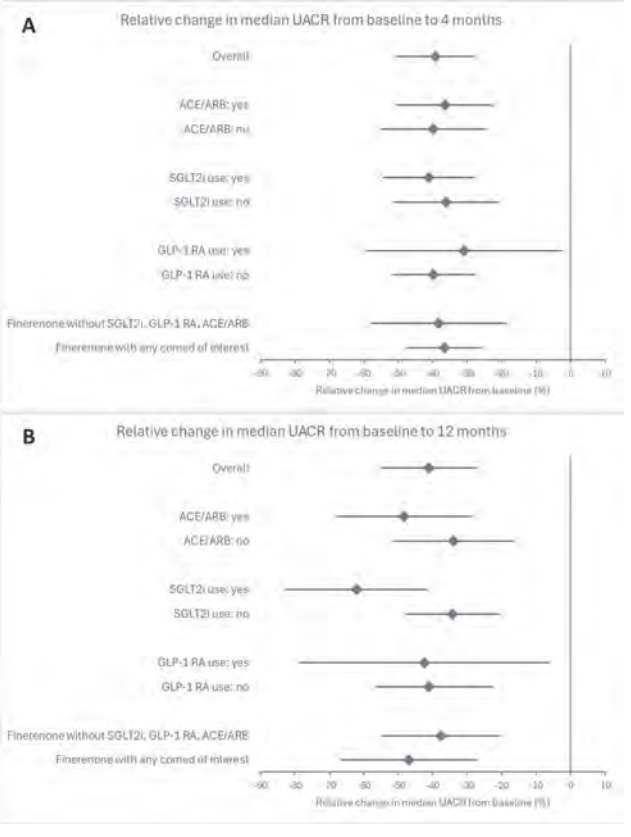
Background: Evidence from clinical trials demonstrates that finerenone reduces UACR and the risk of adverse cardiovascular and renal outcomes among people with CKD and T2D. Here we aim to describe the change in UACR across subgroups of users of other medications in people initiating finerenone in clinical practice in the United States.

Methods: This cohort study included people with prior diagnoses of CKD and T2D initiating finerenone between July 2021 and August 2023. Data were obtained from US electronic health records and insurance claims (OM1 Real-World Data Cloud™). Median UACR was determined at baseline, 4 and 12 months, and we described relative changes from baseline to 4 and 12 months, respectively, with 95% confidence intervals.

Results: Amongst 15,948 new users of finerenone, co-exposure to comedications was frequent: RASi, (49.4%), SGLT2i, (38.0%), GLP-1 RA, (25.6%). UACR measurements were available for 2,137 (13.4%) people at baseline, with a median UACR (Q1, Q3) of 211 mg/g (56, 750). From baseline the median UACR of the overall population decreased by 39.3% (50.8%-27.8%) and 41.2% (55.1%-27.3%) at 4 and 12 months, respectively. The observed reduction of median UACR from baseline to 4 and 12 months for comedication subgroups are depicted in the figure.

Conclusions: This analysis from the FOUNTAIN platform suggests that median UACR level decreases approximately 40% within 4 months after initiating finerenone in routine clinical practice and that this effect is sustained over 12 months. This reduction appears to be consistent irrespective of co-exposure to RASi, SGLT2i, or GLP-1 RA.

Funding: Commercial Support - Bayer AG



FR-PO326

Reduction in Urinary Albumin-to-Creatinine Ratio (UACR) in People with CKD and Type 2 Diabetes Initiating Finerenone: A CKD Stage Subgroup Analysis from the FOUNTAIN Platform

Csaba P. Kovesdy,[1] J. Bradley Layton,[4] Bishnu B. Thapa,[2] Luis M. Rangel,[2] Gary C. Curhan,[2] Alfredo E. Farjat,[3] Fangfang Liu,[3] Catherine B. Johannes,[5] David Vizcaya,[3] Nikolaus G. Oberprieler.[3] *[1]Division of Nephrology, University of Tennessee, Memphis, TN; [2]OM1, Inc., Boston, MA; [3]Bayer AG, Berlin, Germany; [4]RTI Health Solutions Research Triangle Park, Research Triangle Park, NC; [5]RTI Health Solutions Waltham, Waltham, MA.*

Background: Evidence from clinical trials shows that finerenone reduces UACR and the risk of adverse cardiovascular and renal outcomes among people with CKD and T2D. We aim to describe the change in UACR across subgroups of CKD and albuminuria stages in people initiating finerenone in clinical practice in the US.

Methods: This cohort study included people with prior diagnoses of CKD and T2D initiating finerenone between July 2021 and August of 2023. Data were obtained from US electronic health records and insurance claims (OM1 Real-World Data Cloud™). Median UACR was determined at baseline, 4 and 12 months, and we described relative changes from baseline to 4 and 12 months, respectively, with 95% CIs.

Results: Amongst 15,948 new users of finerenone, 3,604 (22.6%) had both a routine UACR and eGFR measurement in the 365 days before initiating finerenone. The proportion of people in the respective CKD stages and albuminuria categories is shown in Figure 1. For the UACR change analysis, routine UACR measurements were available for 2,137 (13.4%) people at baseline, with a median UACR (Q1, Q3) of 211 mg/g (56, 750). From baseline, UACR of the overall population decreased by 39.3% (50.8%-27.8%) and 41.2% (55.1%-27.3%) at 4 and 12 months, respectively. The observed reduction of UACR from baseline to 4 and 12 months by eGFR and albuminuria are depicted in the figure 2.

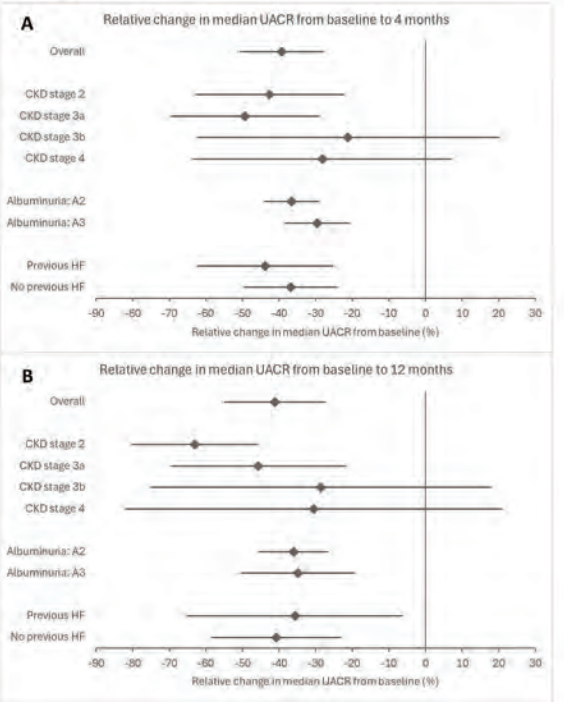
Conclusions: These results suggest that in clinical practice finerenone is used irrespective of CKD stage and albuminuria category. UACR decreases within 4 months after initiating finerenone and this effect is sustained over 12 months. UACR reduction appears to be consistent, albeit with some variation across CKD stages.

Funding: Commercial Support - Bayer AG

Figure 1: Proportion of people initiating finerenone across respective CKD stages and albuminuria categories

		A1 <30	A2 30-<300	A3 ≥300	Total
G1	≥ 90	90 (0.78%)	188 (5.22%)	166 (4.61%)	382 (10.60%)
G2	60-89	111 (3.08%)	393 (10.90%)	336 (9.32%)	840 (23.31%)
G3a	45-59	296 (8.21%)	392 (10.88%)	359 (9.96%)	1,047 (29.05%)
G3b	30-44	213 (5.91%)	353 (9.79%)	454 (12.60%)	1,020 (28.30%)
G4	15-29	46 (1.28%)	90 (2.50%)	179 (4.97%)	315 (8.74%)
	Total	694 (19.26%)	1,416 (39.29%)	1,494 (41.45%)	3,604 (100.00%)

Figure 2: Relative change in median UACR from baseline
A: Relative change from baseline to 4 months. **B**: Relative change from baseline to 12 months.



FR-PO327

Analysis of the Kidney-Brain Axis via the Fractional Amplitude of Low-Frequency Fluctuation in Patients with Diabetic Nephropathy

Jinlei Lv.[1,2] *[1]Renal Division, The First Affiliated Hospital of NanChang University, NanChang, China; [2]Institute of Molecular Immunology for Kidney Disease of NanChang University, NanChang, China.*

Background: Central neuropathies caused by diabetic nephropathy (DN) may share similar characteristics. The fractional amplitude of low-frequency fluctuation (fALFF) technique was applied to detect resting brain function alterations in patients with diabetic nephropathy, and their relationships with Brain clinical manifestations and the kidneys and are discussed. This study aimed to analyze the changes in brain function of patients with DN based on the kidney–brain axis.

Methods: We recruited patients with DN and healthy controls (n=23 per group). All participants underwent brain resting-state functional magnetic resonance imaging examination, and the fractional amplitude of low-frequency fluctuation (fALFF) values were calculated. The sensitivity, specificity, and Youden index were used to assess the authenticity of the diagnosis by constructing receiver operating characteristic curves. We analyzed the correlation between mean fALFF values and DN data using Pearson's correlation.

Results: Compared with control subjects, patients with DN had lower fALFF values in the right cingulum anterior segment (RCA) and left cingulum middle segment(LCM), and increased fALFF values in the right cingulum middle segment(RCM). Furthermore, the mean fALFF values in the RCA correlated with the estimated glomerular filtration rate in DN patients.

Conclusions: There were significant changes in brain function in DN patients compared to the control group. Changes in the central nervous system in patients with DN were mainly due to the dual negative effects of kidney function and diabetes mellitus. We found significant differences in fALFF values in the default mode network and visual cortex-related areas, which may be highly valuable for understanding the kidney–brain axis mechanisms of DN, as well as the associations between diabetic microvascular complications. .

Funding: Government Support - Non-U.S.

FR-PO328

Medication Adherence to SGLT2 Inhibitors vs. Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists: A Meta-Analysis

Whitney Sussman, Erin R. Weeda, Conner E. Johnson. *University of South Carolina School of Medicine Greenville Campus, Greenville, SC.*

Background: Glycemic control with antihyperglycemics in individuals with diabetes has long been associated with reductions in the incidence of chronic kidney disease (CKD). Recent evidence has also demonstrated that sodium-glucose cotransporter-2 inhibitors (SGLT2Is) slow the progression of CKD. However, optimal medication adherence with antihyperglycemics is needed to achieve outcomes. We sought to perform a meta-analysis to compare medication adherence to SGLT2Is versus glucagon-like peptide-1 receptor agonists (GLP-1RAs).

Methods: A systematic search of Medline and Embase was conducted through October 2023. To meet inclusion criteria, articles had to be published in the full text form and directly compare medication adherence to SGLT2Is versus GLP-1RAs. Only studies evaluating real-world data and utilizing proportion of days covered (PDC) to measure adherence were included. Non-adherence, defined as the proportion of patients with a PDC<80%, was the primary outcome for this study. A subgroup analysis evaluating results among studies conducted in the US was performed.

Results: We identified 8 studies evaluating 205,103 patients for inclusion. Most studies derived data from the US (n= 5 studies). The proportion of patients with non-adherence (i.e., a PDC<80%) ranged from 27%-62% among those taking SGLT2Is and 26%-80% among those taking GLP1-RAs across included studies. Upon meta-analysis, SGLT2I use was associated with a numerically lower risk of non-adherence compared to GLP-1RA use but no statistical difference was observed (relative risk [RR] = 0.86; 95% confidence interval [CI] 0.72-1.02). In the analysis including only US studies, SGLT2I use was associated with a 23% lower risk of non-adherence compared to GLP-1RA use (RR = 0.77; 95% CI 0.72-0.82).

Conclusions: In this meta-analysis of 8 studies that included ~200,000 patients, SGLT2I use was associated with numerically higher medication adherence vs. GLP-1RA use; however, this difference was not statistically significant in the overall analysis. SGLT2I use was associated with significantly higher adherence when the analysis was limited to US studies. Adherence may differ across antihyperglycemic regimens and thus impact outcomes achieved with these regimens.

FR-PO329

Transitioning Adults with CKD and Type 2 Diabetes from a Dipeptidyl-Peptidase 4 Inhibitor to a SGLT2 Inhibitor: A Population Health Initiative

Stephanie M. Toth-Manikowski,[1,2] Abigail Forte,[1] Richmond Kwawu,[1] Morgan E. Urdaneta,[1] Howard Shaps.[1] *[1]Healthmap Solutions, Tampa, FL; [2]Alivio Medical Center, Chicago, IL.*

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2Is) are first-line therapy in adults with chronic kidney disease (CKD) and type 2 diabetes (T2DM). Compared to dipeptidyl peptidase-4 inhibitors (DPP-4Is), SGLT2Is superiorly slow CKD progression and may be cost neutral, depending on the payor or pharmacy benefit manager. This initiative evaluated the effect of using a population-level approach and provider outreach to improve SGLT2I prescribing patterns among diabetic adults with CKD already taking a DDP-4I.

Methods: Healthmap Solutions, a kidney population health company, used payor claims to identify adults with a "SGLT2I opportunity," defined as having Stage 3 or 4 CKD, T2DM, and a prescription fill for a DPP-4I but not a SGLT2I. Healthmap communicated this information to primary providers of these individuals. Outreach was deemed successful if individuals with a SGLT2I opportunity were reviewed with the provider or staff via 1) an in-person visit or 2) email/fax communication, per provider request. During a 3-month follow-up period, pharmacy claims were reviewed to identify the proportion of individuals with a new SGLT2I prescription fill. A proportional t-test was used to determine significant change.

Results: Of an initial pool of 53,255 adults, we identified 364 eligible for the initiative (**Figure**). Successful outreach occurred with providers of 273 (75%) individuals of which 12 (4%) started a SGLTI in the follow-up period. Mean time to initiation was 10 days after outreach. Among individuals whose providers were not successfully reached (n=91; 25%), SGLT2I was initiated in 1 (1%) individual (z-score 1.47; p=0.07). Member characteristics by outreach were similar (**Table**).

Conclusions: A population-level approach can be used to identify individuals with T2DM and CKD who may benefit from SGLT2I initiation. More studies are needed to understand how best to engage providers in optimizing pharmaceutical management of CKD in this population.

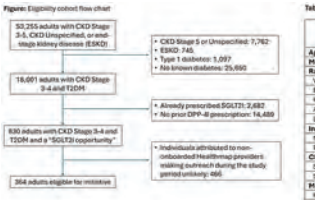


Figure: Eligibility cohort flow chart

Table: Characteristics of individuals with a SGLT2i opportunity, by provider outreach

	Successful Provider Outreach (n=273)	Unsuccessful Provider Outreach (n=91)
Age, years	76	80
Male sex, n (%)	124 (45)	35 (38)
Race, n (%)		
White	230 (84)	76 (84)
Black	4 (1)	3 (3)
Hispanic	2 (<1)	0 (0)
Asian Pacific Islander	1 (<1)	0 (0)
Unknown	36 (13)	12 (13)
Insurance type, n (%)		
Medicare	256 (99)	85 (93)
Private	15 (5)	6 (7)
CKD Stage, n (%)		
Stage 3	222 (81)	70 (77)
Stage 4	51 (19)	21 (23)
Medical Comorbidities, n (%)		
Hypertension	251 (92)	80 (88)
Ischemic heart disease	48 (17)	34 (37)
Heart failure	68 (25)	22 (24)
Stroke	9 (9)	3 (3)

FR-PO330

Diabetes Mellitus Duration and Glycemic Control as Predictors of Diabetic Kidney Disease Progression: Evidence from 2019-2021 Korean National Health and Nutrition Examination Survey

Chang Seong Kim,[1,2] Sang Heon Suh,[1,2] Hong Sang Choi,[1,2] Eun Hui Bae,[1,2] Seong Kwon Ma,[1,2] Soo Wan Kim.[1,2] *[1]Chonnam National University Medical School, Gwangju, Republic of Korea; [2]Chonnam National University Hospital, Gwangju, Republic of Korea.*

Background: The natural progression of diabetic kidney disease (DKD) is characterized by persistent proteinuria followed by a declining glomerular filtration rate (GFR). However, limited epidemiological data exist regarding the duration of diabetes mellitus (DM) and the severity of hyperglycemia with the progression of chronic kidney disease. We investigated the relationship between DM duration and glycemic control and DKD in South Korea by using data from the 2019-2021 Korea National Health and Nutrition Examination Surveys (KNHANES).

Methods: Among the 18,511 participants aged ≥20 years who completed the KNHANES, we analyzed 2,303 patients with DM in this study. DKD was defined as an estimated GFR (eGFR) below 60 ml/min per 1.73 m^2 or urinary albumin-to-creatinine ratio (UACR) of ≥30 mg/g. DM duration and severity were classified into six categories: new onset, <5, 5-10, 10-15, 15-20, and ≥20 years; and hemoglobin A1C (HbA1c) <6.5, 6.5-7, 7-8, 8-9, 9-10 and ≥10 %.

Results: The estimated prevalence of DKD among patients with DM aged ≥20 years was 26.7%. As DM duration and severity increased, UACR also increased gradually in a dose-dependently. The risk of DKD was significantly increased after 10 to 15 years of DM duration or with an HbA1c of 8 to 9% or higher compared to patients with newly diagnosed DM or those with HgA1c <6.5%. Albuminuria (UACR ≥30 mg/g) developed with a shorter duration of DM and at lower HbA1c levels than eGFR decline (<60 ml/min per 1.73 m^2). In multivariable logistic regression models, compared with newly diagnosed patients and those with HgA1c <6.5%, the adjusted odds ratios for DKD were 3.77 (95% CI, 2.60–5.45) and 4.91 (95% CI, 2.80–8.63) in patients with DM duration ≥20 years and HbA1c ≥10%, respectively.

Conclusions: The overall prevalence of DKD among Korean adults is estimated to be three in ten patients with diabetes. Albuminuria was observed in early stages or in less severe hyperglycemic states. We should focus on surveilling kidney function in patients with a long duration of diabetes mellitus or uncontrolled hyperglycemia to prevent the progression of DKD.

FR-PO331

Exploring Patient and Physician Perspectives on the Use of SGLT2 Inhibitors for Adjunct-to-Insulin Treatment in Patients Living with Type 1 Diabetes

Vikas Sridhar,[1,2] Pamela L. Leblanc,[7] Chloe Parezanovic,[7] David Campbell,[7] Bruce A. Perkins,[8,2] Peter A. Senior,[5] Ronald J. Sigal,[7,9] Anita T. Layton,[3] Sean Barbour,[4] Adeera Levin,[4] Tony K. Lam,[1,2] Istvan Mucsi,[1,2] Remi Rabasa-Lhoret,[6] Leif Erik Lovblom,[1] Aleksandra Stanimirovic,[1,2] Valeria E. Rac,[10] David Cherney.[1,2] *[1]University Health Network, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]University of Waterloo, Waterloo, ON, Canada; [4]The University of British Columbia, Vancouver, BC, Canada; [5]University of Alberta, Edmonton, AB, Canada; [6]Universite de Montreal, Montreal, QC, Canada; [7]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [8]Sinai Health, Toronto, ON, Canada; [9]University of Calgary Department of Cardiac Sciences, Calgary, AB, Canada; [10]University of Toronto Dalla Lana School of Public Health, Toronto, ON, Canada.*

Background: Sodium-glucose co-transporter inhibitors (SGLTi) have proven cardiorenal benefits in type 2 diabetes and are promising as adjunct-to-insulin therapy in patients with type 1 diabetes (T1D). However, their regulatory approvals and clinical use in T1D have been limited owing to the augmented risk of diabetic ketoacidosis (DKA). Patient and physician input is critical in understanding how and when the risk-benefit ratio with these therapies is perceived to be favorable for users. This study aimed to explore how risks and benefits of SGLTi are considered by patients with T1D and physicians who treat the condition, particularly in the context of diabetic kidney disease (DKD).

Methods: We used a qualitative descriptive study design, in which we conducted semi-structured interviews with T1D patients (with and without DKD) and physicians who treat this population. Participants were sampled from multiple Canadian sites via online recruitment. Transcripts were analysed inductively using conventional qualitative content analysis to identify themes.

Results: We interviewed 22 patients with long-standing T1D including those with DKD, whose duration of living with diabetes ranged from 8-62 years. We also interviewed 7 physicians, including endocrinologists and nephrologists with a range of 4-20+ years in practice. Our analysis revealed four major themes: i) Strong motivation towards innovative treatments that can improve glycemia and yield cardiorenal benefits; ii) The need for a personalized approach when considering SGLTi initiation – as it was considered to be "not for everyone"; iii) Mitigating risk of DKA through proactive patient and prescriber-oriented strategies; and iv) Concern over absence of empirical evidence and regulatory approvals for this indication.

Conclusions: While there is great interest and motivation toward the use of SGLTi among patients with T1D (both with and without DKD), and the physicians who treat them, there is also clear understanding by all, of the need for personalization of therapy and support for robust evidence to inform care.

Funding: Government Support - Non-U.S.

FR-PO332

The SGLT2 Inhibitor Visual Tour: Bringing Visuals to Increase Prescribing for CKD Plus Type 2 Diabetes Mellitus (T2DM)

Sruthi Sundaram, Siddartha Bhandary, Sana Waheed, Sarah A. Johnson.
Emory University Woodruff Health Sciences Center, Atlanta, GA.

Background: Chronic kidney disease (CKD) is growing in prevalence in the US, and the importance of controlling proteinuria in patients with CKD due to diabetes cannot be overstated. Multiple studies have shown that sodium glucose cotransporter 2 inhibitors (SGLT2i) reduce proteinuria and slow progression of proteinuric CKD. Here, we present a visual aid system that helped increase physician prescribing of SGLT2i to those with clinical indications.

Methods: This quality improvement initiative was conducted in an urban CKD specialty clinic in Atlanta, Georgia. Baseline data over the span of 6 weeks was collected to determine the utilization of SGLT2i in patients who met criteria, which included all patients with type 2 diabetes mellitus (T2DM) who had GFR ≥ 20 mL/min/1.73m^2 - ≤ 75 mL/min/1.73m^2 and urine microalbumin: creatinine ratio ≥ 200 mg/g. Then, a visual aid reminder for physicians that included a large informational poster listing the above criteria was posted in the main physician workroom, and an educational session on indications for prescribing SGLT2i was conducted for providers. Two weeks of post-intervention data was collected to assess utilization of SGLT2i.

Results: There were 360 patient encounters conducted by 16 physicians that were reviewed in the pre-intervention phase. Out of these, 111 patients met the criteria for prescribing SGLT2i, of which 63% were prescribed or already taking an SGLT2i. Common reasons for deferring SGLT2i were the history of UTI or yeast infections. In the post-intervention phase, 83 encounters were reviewed, of which 41 patients met indications for SGLT2i and 73% of those were prescribed an SGLT2i.

Conclusions: Despite numerous studies showing the efficacy of SGLT2i in reducing proteinuria, more than one third of the patients in our CKD clinic were not on one despite meeting the indications. This highlights the importance of both provider education and an augmenting visual aid system to positively impact prescribing practices for SGLT2i among eligible CKD patients. These interventions demonstrated preliminary efficacy in our clinic. Continual reinforcement and patient-directed educational resources may also further the efficacy of these measures. Additional interventions might be necessary to achieve enhancements in adhering to guidelines for prescribing and optimizing care for this vulnerable patient group.

FR-PO333

Use of SGLT2 Inhibitors and Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists in Australian Primary Care Patients with Type 2 Diabetes Mellitus (T2DM) Stratified by CKD Status

Hannah Wallace,[1,2] James Wick,[3] Daniel B. Ketema,[1] Brendon L. Neuen,[1] Meg Jardine,[5] Jialing Lin,[4] Craig L. Nelson,[2] Sallie Pearson,[4] David Peiris,[1] Mark Woodward,[1] Paul E. Ronksley,[3] Martin P. Gallagher,[1,4] Sradha S. Kotwal,[1] Min Jun.[1,4] CKD-CARE. *[1]The George Institute for Global Health, Sydney, NSW, Australia; [2]The University of Melbourne, Melbourne, VIC, Australia; [3]University of Calgary, Calgary, AB, Canada; [4]University of New South Wales, Sydney, NSW, Australia; [5]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia.*

Background: SGLT2i and GLP1-RA reduce the risk of kidney failure and cardiovascular events in patients with T2DM and CKD. We aim to understand their use in Australian primary care patients with T2DM by CKD status.

Methods: We identified adults (≥18 years) with T2DM who attended 1 of 392 general practices participating in a national quality improvement program (MedicineInsight) and had ≥1 eGFR measure between 2011-2019. CKD was defined according to KHA-CARI/KDIGO guidelines. Outcomes assessed were ≥1 prescription for SGLT2i (if eGFR ≥20ml/min/1.73m^2) or GLP1-RA (if eGFR ≥15ml/min/1.73m^2) during 2020-2021, by CKD status. Two secondary analyses were conducted; SGLT2i use in patients with CKD with UACR ≥22.6mg/mmol, and GLP1-RA use in those meeting CKD outcome trial enrolment criteria (NCT03819153; see figure for eGFR/UACR definitions).

Results: 114,499 adults with T2DM were included (113,563 and 113,940 with eGFR ≥20 and ≥15mL/min/1.73m^2, respectively), with a median age of 68, of whom 45% were female, and 32% had CKD. SGLT2i were prescribed 13% in patients without CKD, 14% with CKD and 17% with CKD and UACR ≥22.6mg/mmol (p values vs. no CKD: <0.05). GLP1-RA were prescribed in 8% of patients without CKD, 10% with CKD and 11% meeting CKD outcome trial inclusion criteria (p values vs. no CKD: <0.05).

Conclusions: In this large, contemporary primary care cohort of patients with T2DM, SGLT2i and GLP1-RA prescription rates were higher in CKD than those without, but relatively low across both groups. Implementation strategies to improve medication uptake, with a focus on those who are likely to derive greatest benefit are needed.

Funding: Commercial Support - The Renal Division of The George Institute for Global Health has received sponsorship funding provided by Boehringer Ingelheim and Eli Lilly Alliance and is supported by the University of New South Wales Scientia Program. The design, analysis, interpretation or writing of this work was performed independent of all funding bodies.

Figure 1A: SGLT2 inhibitor prescritpion

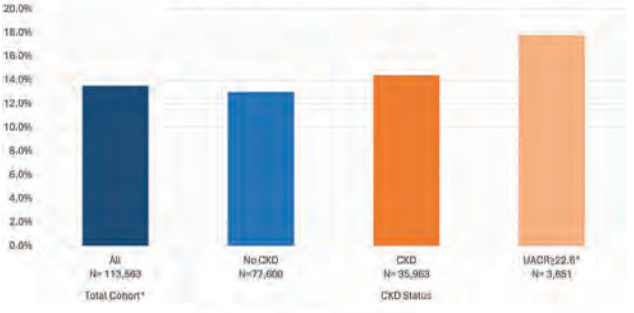
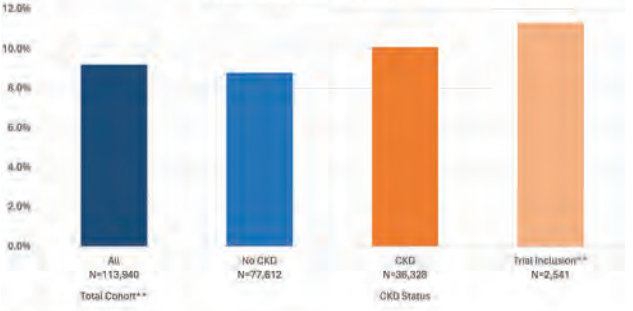


Figure 1B: GLP1-RA prescription



CKD=chronic kidney disease
*Total Cohort SGLT2i Outcome if eGFR ≥ 20ml/min/1.73m^2
**Total Cohort GLP1-RA Outcome if eGFR ≥ 15ml/min/1.73m^2
^UACR≥22.6 = CKD with UACR ≥22.6mg/mmol
^^Trial Inclusion = CKD cohort with eGFR ≥50-<75ml/min/1.73m^2 & UACR >33.9 - <565mg/mmol OR GFR ≥25-<50 ml/min/1.73m^2 & UACR ≥11.3 - <565mg/mmol

FR-PO334

Proteinuria Burden and Clinical Outcomes in Patients with Diabetes: A Nationwide Cohort Study

Junseok Jeon, Kyungho Lee, Jung eun Lee, Wooseong Huh, Hye Ryoun Jang.
Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

Background: Proteinuria is a well-known risk factor for ESKD, cardiovascular disease (CVD), and all-cause mortality in patients with diabetes mellitus (DM). However, clinical implications of fluctuating proteinuria are poorly understood. We aimed to investigate the association between proteinuria burden outcomes using the Korean National Health Insurance Service data.

Methods: This retrospective cohort study included all patients with DM who participated in national health screening between 2015 and 2016 and three health screenings before. Proteinuria burden was defined as the cumulative number of positive dipstick urine protein at each health screening. Outcomes are end-stage kidney disease (ESKD), cardiovascular disease (CVD), and all-cause mortality. Hazard ratio (HR) with 95% confidence interval (CI) were analyzed using Cox proportional hazards regression analysis.

Results: Among total 1,262,194 patients, 1,089,833 (86.3%), 118,835 (9.4%), 31,468 (2.5%), 14,827 (1.2%), and 7,231 (0.6%) had proteinuria burden 0, 1, 2, 3, and 4, respectively. There were dose-dependent association between the proteinuria burden and risk of ESKD, CVD, and all-cause mortality (Compared to proteinuria burden 0, adjusted HR [95% CI] for proteinuria burden 1, 2, 3, and 4, respectively: for ESKD, 3.723 [3.421–3.051], 9.565 [8.810–10.384], 15.079 [13.879–16.383], and 20.009 [13.238–21.845]; for CVD, 1.257 [1.214–1.301], 1.578 [1.491–1.671], 1.969 [1.832–2.117], and 2.221 [2.023–2.437]; for all-cause mortality: 1.364 [1.320–1.410], 1.653 [1.565–1.745], 2.069 [1.932–2.216], and 2.206 [2.016–2.414]). Early positive proteinuria was worse outcomes than late positive proteinuria within same proteinuria burden.

Conclusions: Our study demonstrated that proteinuria burden was dose-dependently associated with ESKD, CVD, and all-cause mortality in patients with DM. Patients with DM who have even a single positive dipstick test require active management.

FR-PO335

Influence of Sex and Other Risk Factors, Including Kidney Function, on Myocardial Microvascular Function in Individuals with Type 2 Diabetes Free of Overt Cardiovascular Disease: The DiaHeart Study

Anne-Cathrine Skriver-Møller,[1] Philip Hasbak,[3] Ida Kirstine B. Rasmussen,[1] Martin B. Blond,[1] Victor Wasehuus,[1] Mats H. Lassen,[2] Morten Lindhardt,[4] Allan Kofoed-Enevoldsen,[6] Urd Lynge Kielgast,[5] Emilie Zobel,[1] Lene Holmvang,[3] Peter Rossing,[1] Tor Biering-Sørensen,[1] Rasmus S. Ripa,[3] Andreas Kjaer,[3] Tine Hansen.[1] *[1]Steno Diabetes Center Copenhagen, Herlev, Denmark; [2]Gentofte Hospital, Hellerup, Denmark; [3]Rigshospitalet, Kobenhavn, Denmark; [4]Zealand University Hospital Holbaek, Holbaek, Denmark; [5]Sjaellands Universitetshospital Koge, Koge, Denmark; [6]Nykobing F Sygehus, Nykobing, Denmark.*

Background: Type 2 diabetes (T2D) is a stronger risk factor for cardiovascular disease (CVD) in women than in men and increased with progressive CKD. This might in part be due to women being more susceptible to developing myocardial microvascular dysfunction when compared with men with a similar risk profile. The myocardial flow reserve (MFR) represents the function of the epicardial arteries and the microvasculature and can be measured with a cardiac (Rb^{82})-PET/CT. We investigated the presence of sex dependent differential effects of CV risk factors, including kidney function, on MFR in people with T2D, free of overt CVD.

Methods: Cross-sectional analysis of a prospective study including 901 T2D individuals. All underwent a cardiac ^{82}Rb-PET/CT for estimation of MFR. Associations between MFR and other risk factors were assessed using linear regression. Differential effects of risk factors by sex were assessed by including an interaction term between one risk factor and sex at a time.

Results: Mean (SD) age was 65 (9) years and 266 (30%) were women. Mean eGFR was 82.1 (21.8) ml/min/1.73^2 and median (IQR) UACR 7.7 (4.9-19.9) mg/g. MFR was lower in women than in men (2.44 (0.61) vs. 2.59 (0.77), p=0.003). MFR was lower with increasing degree of albuminuria; 2.61 (0.73) for normal, 2.35 (0.67) for moderately and 2.11 (0.72) for severely increased albuminuria, p<0.001. In a model including age, sex, diabetes duration, BMI, smoking, systolic blood pressure, logUACR, eGFR, HbA1c, and LDL-cholesterol MFR was negatively associated with female sex β -0.19 (95%CI -0.29 to -0.09, p<0.001), age -0.19 (-0.25 to -0.13, p<0.001), and logUACR -0.09 (-0.13 to -0.05, p<0.001). There were no statistically significant interactions with sex for any of the risk factors.

Conclusions: In individuals with T2D free of overt CVD, MFR was lower in women than in men and lower with higher level of albuminuria. Despite lower MFR in women, we found no indications of sex dependent differential effects of any risk factors including UACR and eGFR on MFR.

Funding: Commercial Support - Novo Nordisk Foundation

FR-PO336

Referral to Nephrologists Mitigates the Progression of Kidney Dysfunction in Patients with Type 2 Diabetes: A Causal Inference Study

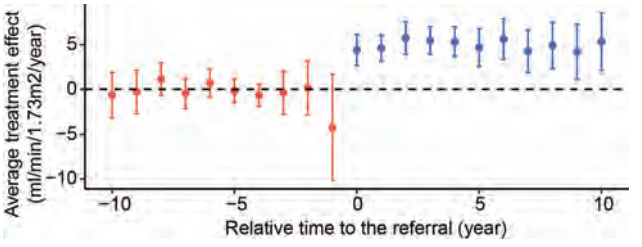
Donghwan Yun, Dong Ki Kim, Yon Su Kim, Seung Seok Han. *Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: Chronic kidney disease is a major complication of type 2 diabetes, necessitating effective management to mitigate kidney progression. This study evaluates the effect of referrals from endocrinologists to nephrologists on kidney function in diabetic patients through causal inference analysis.

Methods: This study included patients with type 2 diabetes who initially visited the diabetes clinic between July 2004 and November 2023. Patients were either referred to a nephrology clinic or continued under the care of endocrinologists. The slope of eGFR per year was calculated based on the annual median difference in yearly eGFRs, and cases were censored when the values dropped below 10ml/min/1.73m^2. We applied a difference-in-differences model to this time-series dataset with an inverse propensity weighting estimator to evaluate the effect of referral to nephrologists.

Results: Among 30,160 patients who visited the diabetes clinic, 3,885 patients (13%) were referred to nephrologists (referral group), while others continued under the care of endocrinologists alone (no referral group). The referral group, compared to the no referral group, had low baseline eGFR (73 [IQR, 59–87] vs 88 [76–98] ml/min/1.73m^2) and high uACR (38 [12–199] vs 14 [8–39] mg/g). The averaged treatment effect of referral to nephrologists displayed an improvement in the eGFR slope, with an increase of 5.8 (95% CI, 4.8–6.8) ml/min/1.73m^2/year. The referral group exhibited higher usage of antihypertensive agents and hypoglycemic agents other than metformin (e.g., DPP-4i and SGLT2i) than the no referral group. Kidney biopsies were more frequently performed in the referral group than in the no referral group (3.8% vs 0.05%), and 50% of patients who received biopsies were diagnosed with other diseases, with or without diabetic nephropathy.

Conclusions: Referral to nephrologists reduces the progression of kidney dysfunction in patients with type 2 diabetes, supporting the need for appropriate referral to nephrologists in type 2 diabetic patients.



The event study plot of the nephrology referral on average treatment effect.

FR-PO337

Improving Conformity to Diabetic Kidney Disease Clinical Guidelines

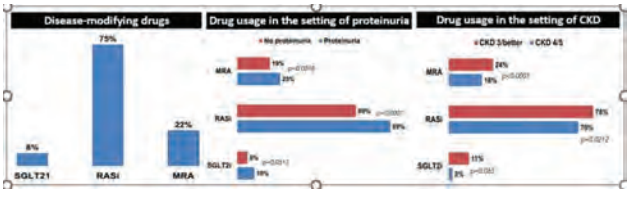
Nicole Piero,[1] Prakash S. Gudsoorkar,[1] Karthikeyan Meganathan,[1] Paul Lewis,[1] Charuhas V. Thakar.[2] *[1]University of Cincinnati, Cincinnati, OH; [2]Queen's University Belfast, Belfast, United Kingdom.*

Background: In the US, 31.5 million adults have chronic kidney disease (CKD), primarily due to type 2 diabetes (DM). KDIGO updated the clinical practice guidelines (CPG) for DM and CKD management, using research on sodium glucose cotransport 2 inhibitor (SGLT2i), glucagon like peptide1 receptor agonist (GLP1RA), and mineralocorticoid receptor antagonist (MRA), with angiotensin converting enzyme inhibitors and angiotensin receptor blocker (RASi).

Methods: We present a two-phase project. Phase 1, an observational cohort on adults with type 2 DM and CKD stages 1-5, excluding those with a prior solid organ transplant or dialysis, at a tertiary academic center renal clinic in 2019. It assessed CKD stage, proteinuria, and conformity to RASi, SGLT2i, and MRA treatments. Chi-square was used to compare groups. Phase 2 analyzed data from Aug to Oct 2022 of renal fellow clinics, using the same criteria as Phase 1. An educational session was conducted on the CPG with an algorithm for optimal prescribing CPG recommended medications. Effectiveness was assessed using pre and post questionnaires assessing knowledge of CPG and Likert scale ratings (1-5) to evaluate prescribing intent.

Results: Phase 1 (fig) identified 1330 adults with CKD and DM seen in a nephrology clinic: 75% were on RASi [89% with proteinuria, 69% without (p<0.0001)], 8% on SGLT2i [10% with proteinuria, 6% without (p=0.018)], and 22% on MRA [25% with proteinuria, 19% without (p=0.0515)]. Medication usage was lower in CKD 4/5 compared to stages 1-3 [SGLT2i 2% vs 11% (p<0.0001); RASi 70% vs 78% (p=0.0212); MRA 18% vs 24% (p=0.065)]. In Phase 2 baseline and prescription characteristics in fellow clinics was similar to phase 1. Phase 2 found that post-education answers on knowledge questions improved from 2 to 3/5. Likert scale (rating 1-5) for self-rated knowledge increased from 3.4 to 4.4. Intent to prescribe ratings rose for SGLT2i from 3.6 to 4.4, GLP1RA from 2.4 to 3.9. Confidence in the impact on guideline adherence improved from 3.6 to 4.2.

Conclusions: Our study demonstrated an implementation gap and an intervention to address it. Continued monitoring and larger scale implementation can improve conformity and patient outcomes.



FR-PO338

Primary Cause of Kidney Failure in 40 Countries in Apollo Dial DB

Yue Jiao,[1] Melanie Wolf,[2] Kaitlyn R. Croft,[2] Paola Carioni,[3] Mitesh Soni,[1] Anke Winter,[2] Luca Neri,[3] Sheetal Chaudhuri,[1] Kanti Singh,[1] Milind Nikam,[4] Stefano Stuard,[2] Adrian M. Guinsburg,[5] Dinesh K. Chatoth,[1] Jeffrey L. Hymes,[1] Kirill Koulechov,[2] Len A. Usvyat,[1] John W. Larkin,[1] Franklin W. Maddux.[6] *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care, Bad Homburg, Germany; [3]Fresenius Medical Care, Crema, Italy; [4]Fresenius Medical Care, Singapore, Singapore; [5]Fresenius Medical Care, Buenos Aires, Argentina; [6]Fresenius Medical Care AG, Bad Homburg, Germany*.

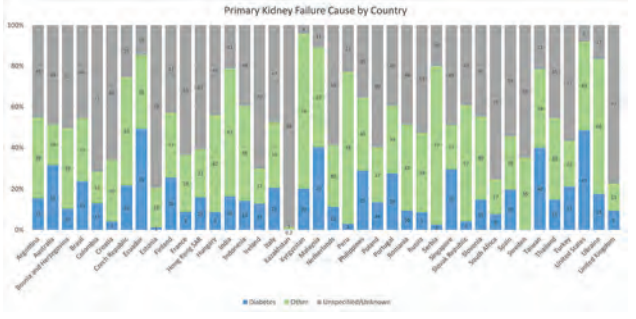
Background: Diabetes is a main cause of kidney failure, but the variability in rates of disease etiology is unknown. We used a global dialysis database, Apollo Dial DB, to assess the primary cause of kidney failure in 40 countries.

Methods: Apollo Dial DB is an anonymized database constructed from real-world data at a kidney care network (Fresenius Medical Care, Bad Homburg, DE). Longitudinal data is captured on an observation-level (each treatment, lab, value). First version has >360 variables (demographics, dialysis, labs, medications, surveys, & outcomes) from 01Jan2018-31Mar2021. Data anonymization was performed in alignment with recommendations from a re-identification risk determination (Privacy Analytics, Ontario, CA). We analyzed the primary cause of kidney failure defined as due to diabetes, other causes, or unspecified/unknown causes.

Results: In 543,169 adults (age ≥18 years) treated by dialysis, 455,769 (80.6%) had a known primary kidney failure cause. Globally, kidney failure due to diabetes was 39.8%, other causes were 40.8%, and unspecified/unknown cause was 19.4%). Cause of primary kidney failure varied dramatically by country ranging for: diabetes from <1% to 49%, other causes from 1% to 77%, and unspecified/unknown cause from 4% to 98% (**Figure 1**).

Conclusions: Leading primary cause of kidney failure is diabetes in four countries, other causes in 13 countries, and unspecified/unknown in 23 countries. Diabetic nephropathy is meaningful in select countries, but considering a global landscape, needs to be determined. The importance of other causes of kidney disease, such as hypertensive and glomerular disorders (including those in diabetes), need to be considered at a local level. The cause of kidney failure appears undetermined in many parts of the world. Findings bring to light the potential role of underdiagnosis, as well as diseases of unknown origin.

Funding: Commercial Support - Fresenius Medical Care



FR-PO339

Regional Differences in Kidney Replacement Therapy in Diabetic Kidney Disease: Apollo Dial DB

Yue Jiao,[1] Melanie Wolf,[2] Kaitlyn R. Croft,[2] Paola Carioni,[3] Mitesh Soni,[1] Anke Winter,[2] Luca Neri,[3] Sheetal Chaudhuri,[1] Kanti Singh,[1] Milind Nikam,[5] Stefano Stuard,[2] Adrian M. Guinsburg,[4] Dinesh K. Chatoth,[1] Jeffrey L. Hymes,[1] Kirill Koulechov,[2] Len A. Usvyat,[1] John W. Larkin,[1] Franklin W. Maddux.[6] *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care, Bad Homburg, Germany; [3]Fresenius Medical Care, Crema, Italy; [4]Fresenius Medical Care, Buenos Aires, Argentina; [5]Fresenius Medical Care, Singapore, Singapore; [6]Fresenius Medical Care AG, Bad Homburg, Germany*.

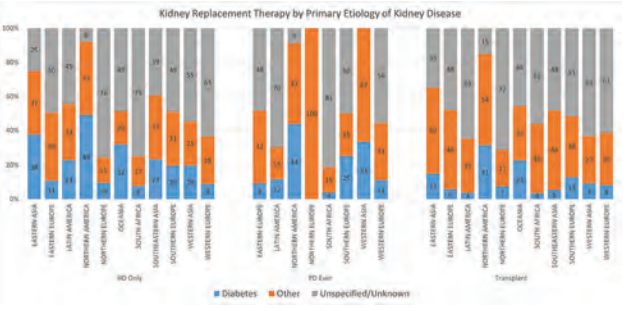
Background: It is unknown if kidney replacement therapy (KRT) types vary in diabetic kidney disease (DKD). We assessed KRT patterns by primary kidney failure etiology in a global database (Apollo Dial DB) representing care in six continents.

Methods: Apollo Dial DB contains longitudinal observation-level data (each treatment, lab, value) from 40 countries in a kidney care network (Fresenius Medical Care, Bad Homburg, DE). Data anonymization was performed in alignment with recommendations from a re-identification risk determination (Privacy Analytics, Ontario, CA). Dataset has >360 variables (demographics, dialysis, diagnoses, labs, medications, surveys, & outcomes) from 01Jan2018-31Mar2021. Analysis assessed KRT rates after dialysis initiation stratified by region. Modality was defined as use of hemodialysis (HD) only, peritoneal dialysis (PD) ever, or transplant.

Results: Among 543,169 adults (age ≥18 years) in 40 countries, 455,769 had a known kidney failure etiology (diabetes=39.8%, other=40.8%, unspecified=19.4%). Overall, 84.8% used HD only, 11.0% used PD, and 4.1% received a transplant for KRT after dialysis initiation. KRT used in DKD showed 40.7% used HD only, 39.1% used PD, and 21.9% received a transplant. PD and transplant rates differed across regions, with lower PD and transplant rates in DKD (**Figure 1**). Regional differences in unspecified etiology were also present.

Conclusions: KRT patterns in DKD may differ from other etiologies. Worldwide, transplant occurred half as often in DKD; greater regional variations existed. Regionally, PD was less frequently used in DKD, specifically in Northern and Latin America, South Africa, and Eastern Europe. Kidney failure etiology is largely unspecified in select regions. Opportunities may exist in expanding KRT options in DKD.

Funding: Commercial Support - Fresenius Medical Care



FR-PO340

Supporting Self-Management of Kidney Health in Diabetic Patients via a Novel Digital Health Intervention: Protocol for a Prospective Interventional Study

Jingyi Wu,[1] Hong'an Pan,[1] Qing Li,[1] Jinwei Wang,[2] Pengfei Li,[1,4] Luxia Zhang.[3,2] *[1]Advanced Institute of Information Technology, Peking University, Hangzhou, China; [2]Renal Division, Department of Medicine, Peking University First Hospital; Peking University Institute of Nephrology, Beijing, China; [3]National Institute of Health Data Science, Peking University, Beijing, China; [4]Institute of Medical Technology, Peking University, Beijing, China*.

Background: Diabetes has become the leading cause of chronic kidney disease in China. Preventing and managing diabetic kidney disease (DKD) is crucial for diabetics, but it often goes undetected due to a lack of early symptoms and low awareness. Urine albumin-to-creatinine ratio (UACR) is an effective early indicator of kidney damage, and we have developed a digital intervention, the UACR home-testing kit (UTK), for self-monitoring of kidney health based on computer-vision algorithms. UTK has been validated to be highly accurate and sensitive in albuminuria screening, and can be a promising new strategy for cost-effective management of kidney health. We proposed a prospective interventional study to evaluate the efficacy of the UTK-based digital intervention in diabetics.

Methods: This study has been conducted since August, 2023 and will recruit over 2,000 diabetics from Yinzhou district, Ningbo city in China for the intervention group. The sample size is calculated based on the assumed odds ratio of 1.3 for the treatment rate of DKD for a matched case-control design. The intervention group will receive a routine UACR home-monitoring using UTK for one year at a recommended frequency by KDIGO, and will complete baseline and final questionnaires and estimated glomerular filtration rate (eGFR) examinations. The control group will be extracted from all 90,940 adult diabetics recorded in Yinzhou Regional Health Information System with repeated eGFR measurements during the study period. The primary outcome is the treatment rate of DKD, and the secondary outcome is DKD progression measured as the incidence rate of a 10% eGFR decline after one-year follow up.

Results: The study is ongoing and has enrolled 4,554 eligible diabetic patients (mean age 68.5±9.2 years, 42.4% males) for the intervention group, with a median follow-up duration of 5.8 (4.0-7.1) months. The baseline eGFR was 86.2±23.1 mL/min per 1.73m^2, and among 445 participants with eGFR < 60 mL/min per 1.73m^2, only 17 (3.8%) of them have received treatment of DKD.

Conclusions: This study will provide quantitative evidence for promising benefits of this user-friendly and cost-effective digital intervention for diabetics self-managing kidney health, which could potentially alleviate the heavy burden on healthcare systems for kidney disease in China.

Funding: Government Support - Non-U.S.

FR-PO341

Intraindividual Difference between Creatinine- and Cystatin C-Based GFR and Association with Cardiovascular Events

Maria Tydén,[1] Gorav Batra,[1,2] Bengt C. Fellstrom,[1] Claes O. Held,[1,2] Johan Lindbäck,[2] Inga Soveri,[1] Ralph A. Stewart,[3] Maria K. Svensson,[1,2] Harvey D. White,[3] Lars Wallentin.[1,2] *[1]Uppsala Universitet Institutionen for Medicinska Vetenskape, Uppsala, Sweden; [2]Uppsala Clinical Research Center, Uppsala, Sweden; [3]Green Lane Cardiovascular Service, Auckland City Hospital and Auckland University, Auckland, New Zealand.*

Background: Association between $eGFR_{ratio}$ ($eGFR_{cys}$/$eGFR_{cr}$) and outcomes, was studied in patients with chronic coronary syndrome.

Methods: A post-hoc analysis of 14,513 patients from the STABILITY trial investigated the association between baseline $eGFR_{ratio}$ and major adverse cardiac events (MACE) and death using Cox-regression. Analyses were adjusted for $eGFR_{cr}$, $eGFR_{cys}$, or both. Discriminative ability was assessed using the C-index, and the incremental value was measured using the fraction of new information (FNI). 2021 CKD-EPI eGFR equations were applied.

Results: The mean age was 65 years, 82% were male. Mean $eGFR_{cys}$ was 77 (61-94) and $eGFR_{cr}$ 79 (65-91) mL/min/1.73 m^2. During median follow-up of 3.7 years, there were 1449 MACE and 1063 deaths. Table 1 presents a comparison of $eGFR_{ratio}$ of 0.7 with 1.0. After adjustment for $eGFR_{cys}$, the $eGFR_{ratio}$ contributed marginally when assessed by FNI. Figure 1 illustrates the adjusted one-year-risk for MACE and death as a function of $eGFR_{ratio}$ for different eGFR levels, indicating a weaker association with the ratio when adjusted for $eGFR_{cys}$.

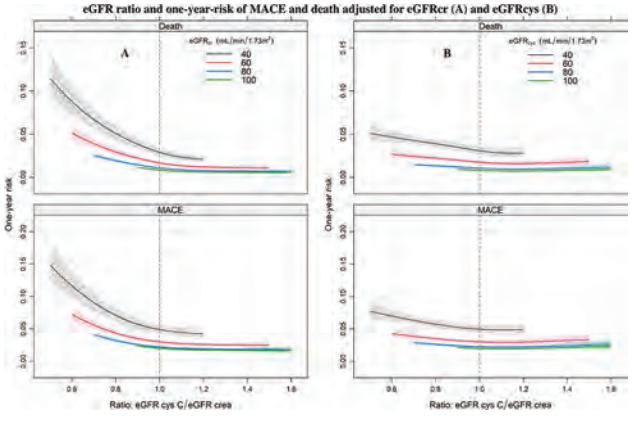
Conclusions: In patients with chronic coronary syndrome, lower $eGFR_{ratio}$ is associated with higher risk of adverse outcomes. After adjustment for $eGFR_{cys}$ the added value of $eGFR_{ratio}$ is limited.

Funding: Commercial Support - GlaxoSmithKline

eGFRratio and outcomes

Outcome	HR [95% CI]	P	C-index	FNI
MACE				
Unadjusted	1.99 [1.80-2.21]	<0.001	0.59	
Adjusted for eGFRcr	1.89 [1.70-2.10]	<0.001	0.62	0.54
Adjusted for eGFRcys	1.29 [1.13-1.46]	0.002	0.61	0.05
Adjusted for eGFRcr+ eGFRcys	1.09 [0.58-2.04]	0.030	0.62	0.03
Death				
Unadjusted	2.52 [2.25-2.84]	<0.001	0.63	
Adjusted for eGFRcr	2.35 [2.08-2.64]	<0.001	0.67	0.57
Adjusted for eGFRcys	1.39 [1.20-1.61]	<0.001	0.67	0.05
Adjusted for eGFRcr + eGFRcys	1.52 [0.75-3.10]	0.090	0.67	0.01

eGFR ratio and one-year-risk of MACE and death adjusted for eGFRcr (A) and eGFRcys (B)



FR-PO342

The Difference between Cystatin C- and Creatinine-Based Estimated Glomerular Filtration Rate and Risk of Peripheral Artery Disease

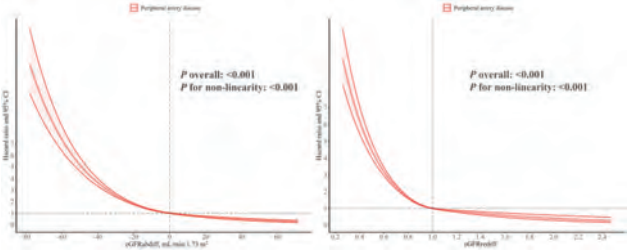
Daijun He,[1] Chenglong Li,[2] Bixia Gao,[1] Chao Yang,[1] Jinwei Wang,[1] Ming-Hui Zhao,[1] Luxia Zhang.[1,2] *[1]Peking University First Hospital Department of Nephrology, Beijing, China; [2]Peking University Health Science Center, Beijing, China.*

Background: The difference between cystatin C-based and creatinine-based estimated glomerular filtration rate (eGFRdiff) has been suggested to reflect factors that are associated with cardiovascular and microvascular risk, independent of kidney function. However, the association between eGFRdiff and risk of peripheral artery disease (PAD) has not been extensively evaluated.

Methods: This prospective cohort study included 466,245 participants with concurrent measured serum creatinine and cystatin C and free of PAD at baseline (2006 to 2010) from the UK Biobank. eGFRdiff was calculated using both absolute difference (eGFRabdiff) and the ratio (eGFRrediff) between cystatin C- and creatinine-based eGFR. Incidence of PAD was ascertained using electronic health records. Cox proportional hazards regression models were used to evaluate the associations of eGFRdiff with PAD. The relative importance of eGFRdiff in predicting PAD was evaluated. We also calculated the area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) to examine the additive value of eGFRdiff in predicting PAD.

Results: During a median follow-up of 13.8 years, PAD developed in 7,210 participants. Each standard deviation increment of eGFRabdiff was associated with a 33% lower risk of PAD. For each 10% increment in eGFRrediff, the hazard ratio (95% confidence interval) was 0.78 (0.77, 0.80) for PAD. eGFRrediff and eGFRabdiff ranked 6th and 11th in the relative importance of PAD prediction, surpassing eGFRcr and some traditional risk factors. Adding eGFRabdiff or eGFRrediff into the established model could improve the performance of PAD prediction (ΔAUC 0.013, NRI 0.325, IDI 0.003 for adding eGFRabdiff; ΔAUC 0.012, NRI 0.287, IDI 0.003 for adding eGFRrediff).

Conclusions: eGFRdiff was associated with risk of incident PAD and had additional value in predicting PAD. These findings may have implications for the management of patients at risk of incident PAD.



Restricted cubic spline models assessing exposure-response associations between eGFRdiff with PAD.

FR-PO343

Advanced CKD and Vascular Disease: Characterization of Cardiovascular Phenotype

Agustin Noboa, Matías Pécora, Cecilia Baccino, Oscar A. Noboa, Jose Boggia. *Universidad de la Republica Uruguay, Montevideo, Uruguay.*

Background: Cardiovascular disease is the leading cause of morbidity and mortality in patients with advanced chronic kidney disease (ACKD). In individuals with chronic kidney disease (CKD), the number of cardiovascular events and mortality increases as glomerular filtration decreases. Non-invasive techniques such as carotid intima-media thickness determination, could allow early detection of vascular damage. Objectives: Determine and compare phenotypes of vascular damage in patients with ACKD and undergoing renal replacement therapy (RRT) with dialysis techniques.

Methods: Cross-sectional study of individuals with ACKD and those undergoing RRT. Patients were recruited from the ACKD outpatient clinic, as well as those undergoing hemodialysis and peritoneal dialysis. Carotid intima-media thickness (IMT) and the presence of atherosclerotic plaques were evaluated.

Results: 37 individuals were evaluated with ultrasound, and 56.7% had carotid atherosclerotic plaques. Age greater or equal to 65 years and being a former smoker were associated ($p < 0.005$) with the presence of atherosclerotic plaques. When compared with population studies of healthy individuals, our cohort had increased IMT in 45.9% or 37.8% of cases, according to Spanish and Argentinean studies, respectively. 75% showed some alteration, either increased IMT or atherosclerotic plaques. No significant differences were found between individuals with ACKD without RRT and those with ACKD on RRT.

Conclusions: Most of patients with ACKD, regardless of the initiation of RRT, present objectively measurable vascular damage. Age equal to or greater than 65 and being a former smoker were associated with the presence of carotid atherosclerotic plaques. In a high percentage of patients, significant vascular damage precedes the initiation of RRT, which should reinforce the prevention of vascular damage in earlier stages of CKD.

Funding: Government Support - Non-U.S.

FR-PO344

Risk Factors for Total Stroke in Patients with CKD: The Chronic Renal Insufficiency Cohort Study

Jing Chen,[1] Myra A. Kleinpeter,[1] Alex R. Zhang,[2] Cong Zhao,[1] Siyi Geng,[1] Flor Alvarado,[1] Arnold B. Alper,[1] Rhea Bhargava,[1] Ivo Lukitsch,[3] Allison N. Marshall,[1] L. Lee Hamm,[1] Jiang He.[1] *[1]Tulane University, New Orleans, LA; [2]Boston University, Boston, MA; [3]Ochsner Health, New Orleans, LA.*

Background: The incidence of stroke is much higher in CKD patients than in the general population. In addition, CKD is associated with a worse outcome after stroke. We studied the risk factors for stroke in a cohort of CKD patients.

Methods: 3,547 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study were included in this analysis after excluding 392 participants with stroke at the baseline visit. Stroke events were reported by participants and adjudicated by 2 vascular neurologists. Cox proportional hazards models with backward selection were used to investigate the association of risk factors with incident stroke. All risk factors, including traditional cardiovascular risk factors, eGFR, urine albumin, inflammatory biomarkers, mineral bone disorder biomarkers, fibrotic biomarkers, and NT-proBNP, were included in the model.

Results: The average baseline age was 57.3 years and 54.7% were women. Over a mean follow-up time of 10.7 years, 167 incident stroke events occurred. The age-adjusted incidence of total stroke was 4.4 per 1,000 person-years: 4.9 per 1,000 person-years in men, and 3.9 per 1,000 person-years in women. The significant multivariable-adjusted hazard ratios (HR) and 95% CI for stroke associated with various risk factors are presented in the **Table**.

Conclusions: This study indicates that age, black race, smoking, albuminuria, and mineral bone disorder are independently associated with an increased risk of stroke. Future studies are warranted to assess the benefits of specific interventions to reduce the risk of stroke in individuals with CKD.

Funding: NIDDK Support, Other NIH Support - Tulane COBRE for Clinical and Translational Research in Cardiometabolic Diseases P20 GM109036

Significant Multivariable-Adjusted Hazard Ratios of Stroke Associated with the Risk Factors

	Multivariable-adjusted	
Variables	Hazard ratio (95% CI)	P-value
Age (per 1SD, 11 years)	1.49 (1.19, 1.87)	0.001
Race Non-Hispanic White vs. Non-Hispanic Black	0.62 (0.40, 0.95)	0.04
Other vs. Non-Hispanic Black	0.58 (0.32, 1.06)	
Current Smoking	1.97 (1.22, 3.19)	0.005
Log (uACR) (per 1SD, 2.31, ug/mg)	1.48 (1.19, 1.84)	0.0004
Alkaline phosphatase (per 1SD, 34.84, u/L)	1.22 (1.05, 1.41)	0.01
Log fibroblast growth factor 23 (per 1SD, 0.75, RU/mL)	1.29 (1.06, 1.56)	0.01

FR-PO345

Glomerular Filtration Rate by Differing Measures and Prediction Utility of Peripheral Artery Disease

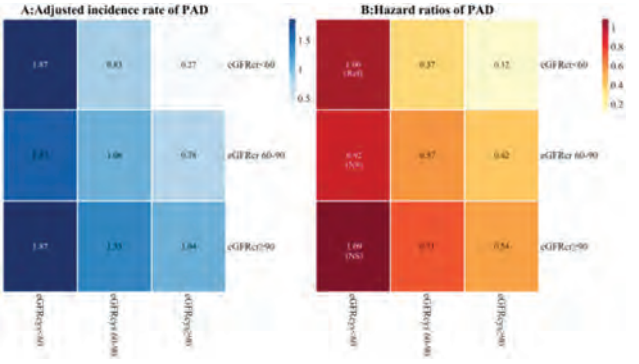
Chenglong Li,[1] Daijun He,[2] Bixia Gao,[2] Chao Yang,[2] Jinwei Wang,[2] Ming-Hui Zhao,[2] Luxia Zhang.[2,1] *[1]Peking University Health Science Center, Beijing, China; [2]Peking University First Hospital Department of Nephrology, Beijing, China.*

Background: The utility of creatinine-based estimate glomerular filtration rate (eGFRcr) for predicting peripheral artery disease (PAD) has been evaluated. However, some guides recommended incorporating cystatin C, either alone or in combination with creatinine, into eGFR formulae, which perform better than eGFRcr in estimating GFR and in predicting the risk of cardiovascular disease and mortality. Therefore, we aimed to determine whether incorporating cystatin C into eGFR formulae would improve risk stratification and prediction for PAD.

Methods: We included 466,245 participants free of PAD at baseline (2006 to 2010) from the UK Biobank. The 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation and 2021 race-free CKD-EPI equations were used to calculate eGFRcys, eGFRcr, and eGFRcr-cys, respectively. Incidence of PAD was ascertained using electronic health records. Cox proportional hazards regression models were used to evaluate the associations of eGFRs with PAD. The relative importance of differentiating eGFRs in predicting PAD was evaluated. We also calculated net reclassification improvement and integrated discrimination improvement to examine the additive value of eGFRs in predicting PAD.

Results: During a median follow-up of 13.8 years, a total of 7,210 PAD cases were recorded. eGFRcys was most evidently associated with PAD and the most important predictor for PAD. Regardless of the eGFRcr, the adjusted incidence rate (aIR) and the hazard ratios (HRs) of PAD were low when eGFRcys≥60 mL/min/1.73 m^2. Conversely, with eGFRcys<60 mL/min/1.73 m^2, the aIR and the HRs of PAD have no difference between eGFRcr groups. eGFRcys presented the most significantly additive value in predicting PAD, while no significant utility was identified for eGFRcr.

Conclusions: eGFRcys appears to be more sensitive and specific for PAD risk. These findings underscore the importance of incorporating cystatin C into eGFR formulae to improve risk stratification and prediction for PAD.



FR-PO346

Serum C-reactive Protein and Risk of Major Kidney Outcomes in Adults with Atherosclerotic Cardiovascular Disease Managed in Routine Care

Katherine R. Tuttle,[6] Faizan Mazhar,[1] Edouard Fu,[1,2] Anne-Laure Faucon,[1,3] Paul Hjemdahl,[1] Jimmi Mathisen,[4] Iram Faqir Muhammad,[4] Oscar Plunde,[4] Vlado Perkovic,[5] Juan J. Carrero.[1,7] *[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands; [3]Department of Clinical Epidemiology, Paris-Saclay University, Paris, France; [4]Novo Nordisk A/S, Søborg, Denmark; [5]University of New South Wales, Sydney, NSW, Australia; [6]School of Medicine, University of Washington and Providence Inland Northwest Health, Spokane, WA; [7]Danderyd Hospital, Danderyd, Sweden.*

Background: Inflammasome pathway activation is involved in atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD), but it is unclear if systemic inflammation, measured by serum C-reactive protein (CRP), predicts major kidney outcomes in patients with ASCVD.

Methods: This was an observational study of adults with ASCVD undergoing routine CRP testing in Stockholm, Sweden. Baseline CRP was defined as the mean of serum CRP test levels over a 3-month window, excluding tests associated with illness or medications. Baseline CRP was analyzed via cause-specific Cox regression for subsequent risk of acute kidney injury (AKI; diagnosis code or KDIGO criteria) or CKD progression (>30% eGFR decline or kidney failure).

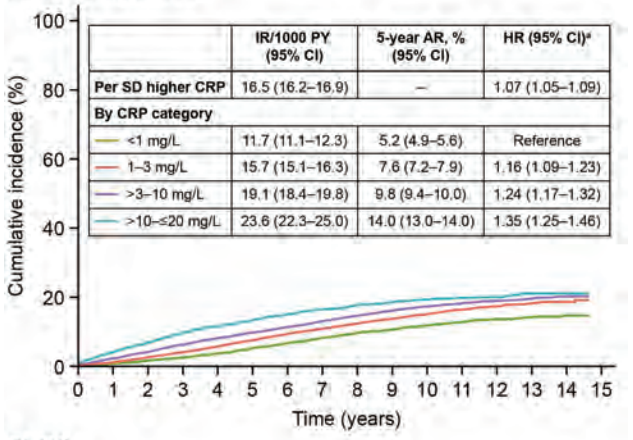
Results: A total of 83,928 adults with ASCVD were included (54% men, mean age 71 years, 59% with CRP ≥2 mg/L). A progressive increase in CRP levels was observed across lower eGFR categories. Over median follow-up of 6.4 years (IQR 3.1–9.8), 8371 CKD progression events, 10,757 AKI events, and 24,954 deaths were recorded. Compared with CRP <1 mg/L, higher CRP levels were associated with increased risks of CKD progression and AKI (Figure). Associations were consistent across subgroups defined by age, albuminuria, selected comorbidities, and use of lipid-lowering therapy. Results were robust when excluding extreme CRP values or early events, and did not appear to be explained by differences in eGFR testing rates.

Conclusions: In a population of adults with ASCVD, systemic inflammation was associated with higher risk of major kidney outcomes.

Funding: Commercial Support - This study was funded by Novo Nordisk A/S.

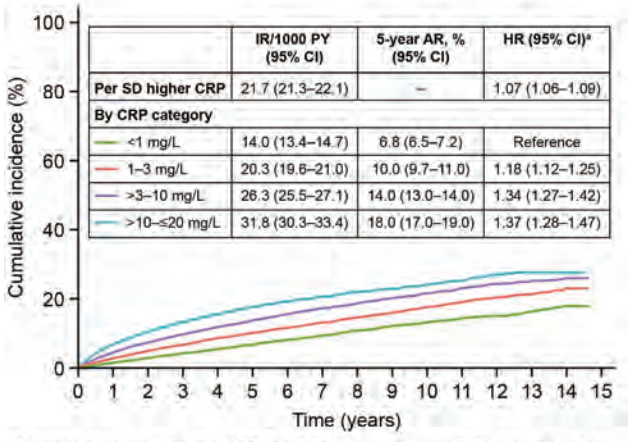
Figure. Cumulative incidence, incidence rates, absolute risks, and hazard ratios for CKD progression (A) and AKI (B), by baseline CRP category

A) CKD progression



	IR/1000 PY (95% CI)	5-year AR, % (95% CI)	HR (95% CI)[a]
Per SD higher CRP	16.5 (16.2–16.9)	–	1.07 (1.05–1.09)
By CRP category			
<1 mg/L	11.7 (11.1–12.3)	5.2 (4.9–5.6)	Reference
1–3 mg/L	15.7 (15.1–16.3)	7.6 (7.2–7.9)	1.16 (1.09–1.23)
>3–10 mg/L	19.1 (18.4–19.8)	9.8 (9.4–10.0)	1.24 (1.17–1.32)
>10–≤20 mg/L	23.6 (22.3–25.0)	14.0 (13.0–14.0)	1.35 (1.25–1.46)

B) AKI



	IR/1000 PY (95% CI)	5-year AR, % (95% CI)	HR (95% CI)[a]
Per SD higher CRP	21.7 (21.3–22.1)	–	1.07 (1.06–1.09)
By CRP category			
<1 mg/L	14.0 (13.4–14.7)	6.8 (6.5–7.2)	Reference
1–3 mg/L	20.3 (19.6–21.0)	10.0 (9.7–11.0)	1.18 (1.12–1.25)
>3–10 mg/L	26.3 (25.5–27.1)	14.0 (13.0–14.0)	1.34 (1.27–1.42)
>10–≤20 mg/L	31.8 (30.3–33.4)	18.0 (17.0–19.0)	1.37 (1.28–1.47)

[a]Adjusted for age, sex, time since ASCVD, eGFR, albuminuria, comorbidities (angina, atrial fibrillation, cancer, COPD, diabetes, heart failure, hypertension, MI, peripheral vascular disease, rheumatoid diseases, and stroke/TIA), procedures (coronary artery bypass grafting and percutaneous coronary intervention), and ongoing medications (ACEi/ARBs, MRAs, β-blockers, SGLT-2is, diuretics, calcium channel blockers, digoxin, lipid-lowering treatments, antiplatelets, NSAIDs).
ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; AR, absolute risk; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PY, person years; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TIA, transient ischemic attack.

FR-PO347

10-Year Cardiovascular Risk Score for Coronary Artery Calcification Progression Depending on Prevalent Coronary Artery Calcification in East Asian Patients with CKD: Findings from KNOW-CKD

Byounghwi Ko, Jong Hyun Jhee, Dong Hoon Kang, Daseul Huh, Ga Young Heo, Cheol Ho Park, Hyung Woo Kim, Jung Tak Park, Seung Hyeok Han, Shin-Wook Kang, Tae-Hyun Yoo. *Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.*

Background: Chronic kidney disease (CKD) is a well-known risk factor for atherosclerotic cardiovascular disease (ASCVD). However, no established prediction model exists for the progression of coronary artery calcification (CAC) in CKD patients. We investigated the association between CAC progression and 10-year ASCVD risk prediction models in CKD patients, particularly in relation to baseline CAC.

Methods: From a nationwide, prospective cohort of Korean patients with CKD, 1,177 were available for CAC progression data analysis. Of these, 809 patients, who were without prevalent ASCVD and eligible for the Pooled Cohort Equation, were included in the study. The main predictor was the 10-year cardiovascular risk score from the Pooled Cohort Equation. Prevalent CAC was defined using computed tomography, with an Agatston score greater than zero. CAC progression was defined as an increase in Agatston score of more than 15% per year at the 4-year follow-up in patients with baseline CAC, while any increase in CAC was defined as progression for those without baseline CAC. For both groups, coronary stenting during the 4-year follow-up period was considered as CAC progression.

Results: Prevalent CAC was observed in 394 (48.7%) patients. CAC progression was observed in 104 (25.1%) patients without baseline CAC, and 259 (65.7%) in those with baseline CAC. Compared with 1st quartile, the odds ratios (95% confidence intervals) for CAC progression of 2nd, 3rd, and 4th quartiles were 2.25 (1.48-3.44), 3.29 (2.16-5.01), and 4.27 (2.80-6.52) in unadjusted model, respectively. However, this graded association was disappeared in those with baseline CAC. A consistent association was observed in complete case analysis and different cutoffs for CAC progression (>30%/yr).

Conclusions: A higher score on the 10-year risk prediction model is associated with CAC progression in CKD patients without baseline CAC, whereas this association is less pronounced in those with prevalent CAC.

Funding: Government Support - Non-U.S.

FR-PO348

Trends in the Burden of Ischemic Heart Disease among Patients with CKD in Alberta

Matthew Cooper,[1] Feng Ye,[3] Anukul Ghimire,[2] Gavin Oudit,[3] Aminu K. Bello.[3] *[1]University of Toronto, Toronto, ON, Canada; [2]University of Calgary, Calgary, AB, Canada; [3]University of Alberta, Edmonton, AB, Canada.*

Background: Ischemic heart disease (IHD) is a leading cause of mortality in patients with chronic kidney disease (CKD). The last decades have witnessed significant improvements in both IHD and CKD care. Information on the burden of IHD in the Canadian CKD population is limited.

Methods: Using the Alberta Kidney Disease Network database, we created a cohort with CKD (aged 18 years and above) who received a diagnosis of IHD between 2003 and 2019. CKD was defined based on standard methods. Case definitions for IHD, STEMI, and NSTEMI were determined using ICD-10 codes and obtained from hospital discharge records, physician billing claims, and ambulatory care classification system (ACCS) files. The date of diagnosis of IHD was the date of inpatient hospital separation or the physician visit, whichever came first. Univariate least squares regression analysis and the negative binomial model were used to evaluate the trend in the adjusted prevalence and incident rates for the conditions of interest. The rates were standardized by age group and sex based on the 2011 Canadian population. STATA v18 was used in the analysis and $p < 0.05$ as the threshold for statistical significance.

Results: The age and sex standardized prevalence of IHD increased across all stages of kidney function. Compared to patients with an eGFR ≥ 60 ml/min, the rate of change in the prevalence of IHD was higher in patients with an eGFR 45-59 ml/min, with an annual rate of change of 0.86 (95% CI: 0.66 - 1.05; test for interaction $p < 0.001$). The incidence of STEMI decreased across all eGFRs from 2003 to 2019 except for patients with an eGFR 45-59 ml/min/1.73m2 (incidence risk ratio (IRR) of 0.93 (CI 95% 0.87, 1.00). The incidence of NSTEMI decreased across all eGFRs from 2003 to 2019 except for patients with an eGFR <15 ml/min/1.73m2 (IRR: 0.96; CI 95%: 0.91, 1.02).

Conclusions: Between 2003 and 2019, the prevalence of IHD increased across all stages of CKD, and there was a concomitant decreasing trend in the incidence of the acute forms of IHD (STEMI and NSTEMI). This may reflect increasing longevity of patients with IHD and CKD in Alberta between 2003 and 2019, due to improvements in their care. Future studies should evaluate the quality of care received by patients with IHD and CKD and relationships to adverse clinical outcomes including hospitalizations, recurrent events and mortality.

Funding: Private Foundation Support

FR-PO349

Accuracy of Identification of Cardiovascular Events with International Classification of Diseases (ICD) Diagnosis Codes vs. Physician Adjudication in CKD and ESKD

Anna M. Zemke, Leila R. Zelnick, Ian De Boer, Nisha Bansal. *University of Washington, Seattle, WA.*

Background: Cardiovascular disease (CVD) in chronic kidney disease (CKD) is an important end-point for research studies. Adjudication by a central committee is considered the most rigorous approach of ascertaining CVD outcomes, but it is resource intensive. We aimed to compare the accuracy of unadjudicated ICD codes vs. physician adjudication for hospitalizations for heart failure (HF), stroke, atrial fibrillation (AF), and myocardial infarction (MI) in those with CKD and ESKD.

Methods: Using the Chronic Renal Insufficiency Cohort (CRIC), we evaluated 31,521 hospitalization events. We determined the positive predictive value (PPV), negative predictive value, sensitivity and specificity of primary code position as well as when using all diagnosis codes from the hospitalization. We calculated hazard ratios for the CVD outcomes determined by each type of ascertainment (ICD-10 codes vs. physician adjudicated) for known CVD risk factors.

Results: In those with CKD, comparing primary ICD diagnosis codes with the adjudicated outcomes, we found the PPV to be 82.5% for HF, 80.8% for ischemic stroke, and 87.6% for AF (Table 1). The PPVs were generally similar for participants who were and those who were not on dialysis. MI events by ICD code had much lower PPV rates, 38.4% in non-dialysis dependent CKD, 47.3% in dialysis dependent, and 62.5% in transplant participants. HR of outcomes for those with CVD risk factors diabetes, body mass index, hypertension, age, and eGFR were similar whether ascertained through ICD codes or physician adjudication.

Conclusions: When using ICD codes to determine CVD outcomes in CKD, PPV was near 80% for HF, AF, and ischemic stroke, and was similar amongst those with ESKD. These data may inform the approach to CVD outcome ascertainment in future studies of kidney disease patients.

Table 1. Accuracy of ICD-10 Code Based versus Physician Adjudicated CVD Outcomes in CKD

Event Type	PPV	NPV	Sensitivity	Specificity
CHF				
All Events	80.9%	94.1%	39.7%	99.0%
Non-ESRD events	82.5%	93.9%	42.0%	99.0%
Dialysis events	75.4%	94.2%	33.2%	99.0%
Transplant events	88.9%	98.9%	53.3%	99.8%
CVA				
All Events	83.3%	99.2%	34.6%	99.9%
Non-ESRD events	80.8%	99.0%	33.8%	99.9%
Dialysis events	93.8%	99.5%	39.0%	100.0%
Transplant events	NA	99.7%	0%	100%
MI				
All Events	41.2%	98.6%	45.2%	98.4%
Non-ESRD events	38.4%	98.5%	42.6%	98.2%
Dialysis events	47.3%	98.8%	50.9%	98.6%
Transplant events	62.5%	99.5%	62.5%	99.5%
AF				
All Events	88.8%	92.7%	12.5%	99.9%
Non-ESRD events	87.6%	92.5%	12.2%	99.8%
Dialysis events	90.8%	92.9%	13.0%	99.9%
Transplant events	100%	97.5%	23.8%	100%

FR-PO350

Application of the AHA/ACC/HFSA Heart Failure Staging Guidelines in CKD

Anna M. Zemke,[1] Leila R. Zelnick,[1] Joachim H. Ix,[2] Alan S. Go,[3] Edward D. Siew,[4] Nisha Bansal.[1] *[1]University of Washington, Seattle, WA; [2]University of California San Diego, La Jolla, CA; [3]The Permanente Medical Group Inc, Oakland, CA; [4]Vanderbilt University Medical Center, Nashville, TN.*

Background: The 2013 American Heart Association (AHA)/ American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) Guidelines for the Management of Heart Failure (HF) proposed a staging system to diagnose HF and its severity, ranging from A to D. In 2022, these guidelines were updated to include the use of cardiac biomarkers. The effect of this HF staging system in CKD is not well established.

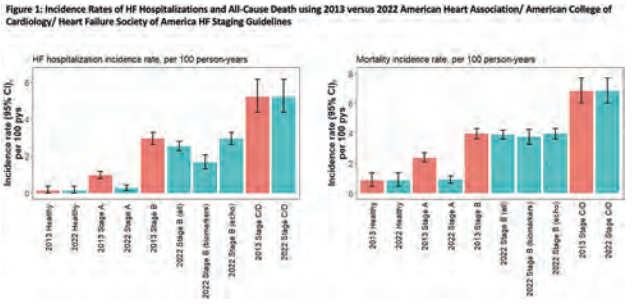
Methods: 2415 participants from the Chronic Renal Insufficiency Cohort were classified into HF stages using 2013 and 2022 guidelines. Echocardiographic changes and cardiac biomarkers (troponin T ≥10 ng/L in females, ≥15 ng/L in males or pro-brain natriuretic peptide ≥125 pg/mL) were utilized in staging. Incidence rates and 95% CIs for HF hospitalizations and all-cause death during follow-up were calculated.

Results: Only 4.8% of CKD participants were classified as "healthy" using either staging guideline. The inclusion of cardiac biomarkers in the 2022 guideline reclassified 55% (n=469) of 2013 guideline Stage A participants to Stage B. Participants with lower eGFRs were more likely to be reclassified (Table 1). Using 2022 guidelines, the incidence of HF hospitalization in Stage B differed when based on biomarkers (1.7 per 100 person-yrs, 95% CI 1.3-2.1) compared to echocardiographic abnormalities (2.9 per 100 person-yrs, 95% CI 2.6- 3.3) whereas death rates were similar between these groups (Figure 1).

Conclusions: Among large CKD cohort, only 20% of participants met the criteria for "healthy" or "at risk" for HF. There was high reclassification of CKD participants into more advanced HF stages with the addition of cardiac biomarkers. Differing HF hospitalization incidence rates between those classified based on biomarkers alone compared to echocardiographic abnormalities suggest reclassification may not reflect true HF status. CKD-specific thresholds for cardiac biomarkers may be useful to improve accuracy of HF staging in CKD.

Table 1: Reclassification Between 2013 and 2022 American Heart Association/ American College of Cardiology/Heart Failure Society of America HF Staging Guidelines by eGFR Category.

eGFR, mL/min/1.73m²	2013 Stage A	2022 Stage A	2013 Stage B	2022 Stage B			% of Stage A using 2013 Criteria that moved to Stage B using the 2022 Criteria
				All (N= 1505)	B_Biomarkers (n=469)	B_Echocardiogram (N=651)	
≥60	262 (31%)	372 (46%)	215 (31%)	305 (20%)	95 (20%)	215 (21%)	80/262 =34.4%
45-59	236 (28%)	516 (31%)	268 (29%)	388 (26%)	120 (26%)	268 (26%)	120/236= 50.8%
30-44	256 (30%)	76 (20%)	297 (29%)	477 (32%)	180 (38%)	297 (29%)	180/256 = 70.3%
15-29	86 (10%)	12 (1%)	234 (23%)	308 (21%)	74 (16%)	234 (23%)	74/86 = 86.0%
<15	6 (1%)	1 (0%)	17 (2%)	22 (1%)	5 (1%)	17 (2%)	5/6 = 83.3%



FR-PO351

CVD Risk Estimates for the US CKD Population with the American Heart Association PREVENT Equation

Carl P. Walther, Lucile Parker Gregg, Sankar D. Navaneethan. *Baylor College of Medicine, Houston, TX.*

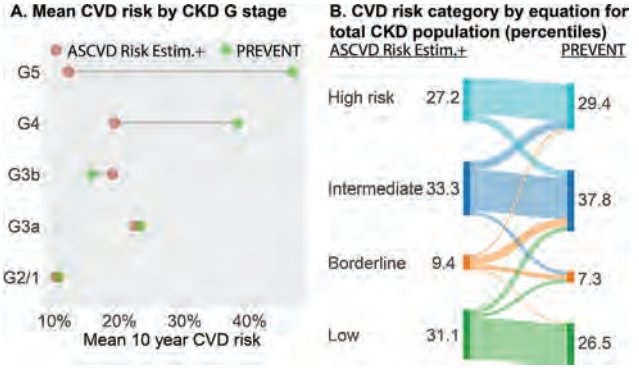
Background: Cardiovascular disease (CVD) risk equations can be useful for assessing and mitigating risk in people with CKD. The 2023 AHA PREVENT equations are the first major equations to incorporate the kidney metrics eGFR and UACR. We studied change in 10-year CVD risk prediction estimates in the US CKD population comparing the PREVENT equation to the previous major equation (ASCVD Risk Estim. Plus 2018).

Methods: We calculated US CKD population estimates of 10-year CVD risk using the most recent data (2017-2020) from NHANES, a probability sampled study of the US community population. CVD risk was calculated using the PREVENT equation (with eGFR and UACR) and the prior major equation (ASCVD Risk Estim. Plus) for the relevant CKD population (age 30-79 years without clinical CVD). CKD was identified using eGFR-Cr and UACR and categorized by G stage. Appropriate survey methods were used to obtain cross-sectional population estimates.

Results: We estimated 21.5 (95%CI 18.6-24.4) million individuals with CKD age 30-79 years without known CVD. Mean±SD age was 58±15 years and 58% were female. CKD stage distribution was: G1/2 A2/3 65%, G3a 26%, 5.8% G3b, 1.8% G4, and 1.2% G5. Median (IQR) 10-year risk in the CKD population using PREVENT is 13% (4.6-21%), substantially higher than the estimates using the prior equation: 9.2% (2.8-22%). More severe CKD stages had larger increase in risk with the new equation (Panel A). Using 10-year CVD risk thresholds (low<5%, borderline 5-7.4%, intermediate 7.5-19.9%, high ≥20%), 30% (6.5 million individuals) changed risk threshold group, with 25% moving to a higher risk category and 5.7% to a lower risk category (Panel B).

Conclusions: Nearly 1 in 3 individuals with CKD in the US are estimated to have substantial change in predicted CVD risk with the PREVENT equation incorporating eGFR and UACR, with most moving to a higher risk category. This highlights the public health importance of kidney measurements for risk prognostication and mitigation.

Funding: NIDDK Support



FR-PO352

Mild Thiazide-Induced Hyponatremia in Hypertensive Patients Is Associated with Increased Mortality Risk

Steven Achinger,[1,2] Juan Carlos Ayus,[3] Ambuj Kumar,[1] Athanasios Tsalatsanis.[1] *[1]University of South Florida Morsani College of Medicine, Tampa, FL; [2]Watson Clinic LLP, Lakeland, FL; [3]University of California Irvine, Irvine, CA.*

Background: There are over 42 million patients with hypertension taking thiazides in the United States. The goal of this study was to determine if outpatients who start a thiazide diuretic and develop hyponatremia are at increased risk of mortality compared with those who do not develop hyponatremia after starting a thiazide.

Methods: We performed a propensity score matched, retrospective cohort study where all patients aged 40 to 90 years between January 1st, 2010 and December 31st, 2021 with essential hypertension and started on a thiazide diuretic were included. The patients with a a serum sodium ≤ 135 mmol/L after initiation of thiazide formed the hyponatremia group and patients with a serum sodium 136-144 mmol/L after initiation of thiazide formed the control group. Data were obtained from the TriNetX research network comprising de-identified electronic medical records of approximately 93 million patients from 76 healthcare organizations worldwide. The primary outcome was one year mortality. The difference in mortality across compared groups was assessed using the log rank test and summarized as hazard ratio along with 95% confidence intervals (CI).

Results: Overall, 256,523 patients met inclusion criteria and after propensity score matching 22,052 patients remained in the hyponatremia and control groups **(Table 1)**. Patients in the hyponatremia cohort had a significantly higher hazard of mortality than patients in control, HR 1.955 (95% CI:1.716, 2.277, p<0.001) **(Figure 1)**.

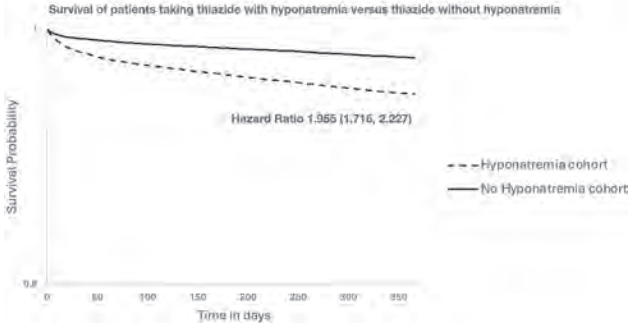
Conclusions: Patients who develop hyponatremia (serum sodium ≤ 135 mmol/L) following initiation of a thiazide diuretic have a higher risk of mortality compared with those who do not develop hyponatremia following initiation of a thiazide diuretic.

Table 1

Hyponatremic (N =22,052) and Control (N =22,052) cohort characteristics after propensity score matching

			Mean ± SD	N (% of Cohort)	P-Value	Std diff.
Demographics						
	Hyponatremic	Age at Index	62.9 +/- 13.2	22,052 (100)	0.329	0.009
	Control		62.8 +/- 12.7	22,052 (100)		
	Hyponatremic	Black or African American		3,186 (14.4)	0.552	0.006
	Control			3,230 (14.6)		
	Hyponatremic	White		15,153 (68.7)	0.512	0.006
	Control			15,089 (68.4)		
	Hyponatremic	Female		11,778 (53.4)	0.504	0.005
	Control			11,848 (53.7)		
	Hyponatremic	Male		9,505 (43.1)	0.430	0.008
	Control			9,423 (42.7)		
	Hyponatremic	Hispanic or Latino		1,184 (5.4)	0.933	0.001
	Control			1,188 (5.4)		
	Hyponatremic	Not Hispanic or Latino		15,243 (69.1)	0.877	0.001
	Control			15,228 (69.1)		
	Hyponatremic	Asian		640 (2.9)	0.133	0.014
	Control			694 (3.1)		
Comorbidity status						
	Hyponatremic	Essential (primary) hypertension		22,052 (100)	—	—
	Control			22,052 (100)		
	Hyponatremic	Ischemic heart disease		3,235 (14.7)	0.968	<0.001
	Control			3,232 (14.7)		
	Hyponatremic	Diabetes mellitus		7,081 (32.1)	0.959	<0.001
	Control			7,076 (32.1)		
	Hyponatremic	Hyperlipidemia		12,824 (58.2)	0.306	0.010
	Control			12,930 (58.6)		
Medications						
	Hyponatremic	Thiazides/ related diuretics		27,283 (100)	—	—
	Control			27,283 (100)		
	Hyponatremic	Loop diuretics		2,356 (10.7)	0.975	<0.001
	Control			2,358 (10.7)		
	Hyponatremic	Potassium sparing/ combination diuretics		2,090 (9.5%)	0.833	0.002
	Control			2,103 (9.5%)		
	Hyponatremic	Antidepressants		5,702 (25.9)	0.579	0.005
	Control			5,651 (25.6)		
	Hyponatremic	Anticonvulsants		3,641 (16.5)	0.838	0.002
	Control			3,657 (16.6)		

Figure 1



FR-PO353

Consequences of Not Maximizing Renin-Angiotensin System Inhibition Due to Hyperkalemia

Cecelia L. Hickey,[1] John M. Dopp,[1] Jodi Meyer,[3] Laura J. Maursetter.[2,3]
[1]University of Wisconsin-Madison School of Pharmacy, Madison, WI; [2]University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI; [3]William S. Middleton VA Hospital, Madison, WI.

Background: Until March, 2024, potassium binders within the Veterans Health Administration were non-formulary with criteria for use that limited prescribing to persistent moderate-severe hyperkalemia (at least two K values ≥ 5.5 mEq/L). Thus, patients with mild hyperkalemia were at risk of repeated hyperkalemia and dose-reductions or discontinuation of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB). We sought to determine if patients with persistent mild hyperkalemia experienced subsequent hyperkalemia and if ACE-I/ARB use was affected in adult Veteran's Affairs (VA) patients with difficult-to-control hypertension and chronic kidney disease (CKD).

Methods: Retrospective chart review was performed for patients in a VA renal hypertension clinic who had at least two potassium values ≥ 5.1 but less than 5.5 mEq/L (mild hyperkalemia) documented in the VA electronic health record. Serum creatinine, proteinuria, and ACE-I/ARB use were recorded from the medical record at the time of the second potassium value between 5.1 and 5.49 mEq/L and at the patient's most recent follow-up visit. Longitudinal hyperkalemia events (K ≥ 5.1 mEq/L) were recorded for all patients.

Results: In patients with persistent mild hyperkalemia (n=54), serum creatinine increased from 2.15±0.1 to 3.01±0.28 mg/dL (mean±SEM) and 2 (1-3) (median and interquartile range) hyperkalemia episodes occurred in the time between their second high K value and their most recent follow-up (median 5 years). At time of their second high K value, 89% of patients were taking an ACE-I/ARB. At the most recent follow-up, 48% of patients taking ACE-I/ARB had their ACE-I/ARB dose reduced or discontinued. In addition, urinary protein to creatinine ratio increased by 546±474 mg/g.

Conclusions: Adult VA patients with CKD, hypertension, and mild hyperkalemia are at risk of subsequent hyperkalemia episodes, worsening of kidney function, and worsening proteinuria. Importantly, approximately half of patients with mild hyperkalemia had de-escalation of renoprotective medications. With the removal of VA formulary restrictions for potassium binders, patients with mild hyperkalemia should be candidates for initiation of potassium binder therapy and optimization of ACE-I/ARB therapy to delay progression of kidney disease.

FR-PO354

Volume Status by Bioimpedance and Blood Pressure in CKD

Katherine S. Ravi,[1,2] Enass Sayed,[1,2] Brendon L. Neuen,[4] Glenn M. Chertow,[3] Finnian R. McCausland.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Stanford University School of Medicine, Stanford, CA; [4]The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia.*

Background: Hypertension is common among patients with chronic kidney disease (CKD) and is a risk factor for cardiovascular events and mortality. Though hypervolemia is thought to be a major contributor to hypertension, the association of objective biomarkers of volume status with blood pressure (BP) among patients with CKD is not well described.

Methods: Using data from the Chronic Renal Insufficiency Cohort (CRIC; n=5,384), we fit unadjusted and adjusted linear regression models and restricted cubic splines to examine the association of vector length (a bioimpedance proxy of volume status) with systolic and diastolic BP (SBP and DBP). We also assessed how the change in vector length over two years was associated with changes in SBP and DBP. Models adjusted for demographics, clinical history, BP medications, and laboratory covariates including log transformed 24-hour urine protein and urine sodium excretion.

Results: Mean age of participants was 59 ±11 years; 44% were female; 43% were Black; and mean SBP and eGFR were 129 ±21 mmHg and 48 ±16 mL/min/1.73m^2, respectively. The adjusted association of vector length with SBP was non-linear (Figure 1). The lowest quartile of vector length (a proxy for relative hypervolemia) was associated with a 3.0 mmHg (95%CI 0.9, 5.1) higher SBP, compared with the third quartile. Similarly, over two years, the lowest quartile of change in vector length (a proxy for more severe hypervolemia) was associated with the largest increase in SBP (3.8 mmHg; 95%CI 1.1, 6.4), compared with the third quartile. No association of vector length with DBP was observed.

Conclusions: Shorter vector length, a bioimpedance proxy of hypervolemia, is independently associated with higher SBP. Whether bioimpedance-guided volume management could improve BP control among patients with CKD requires further exploration.

Funding: NIDDK Support

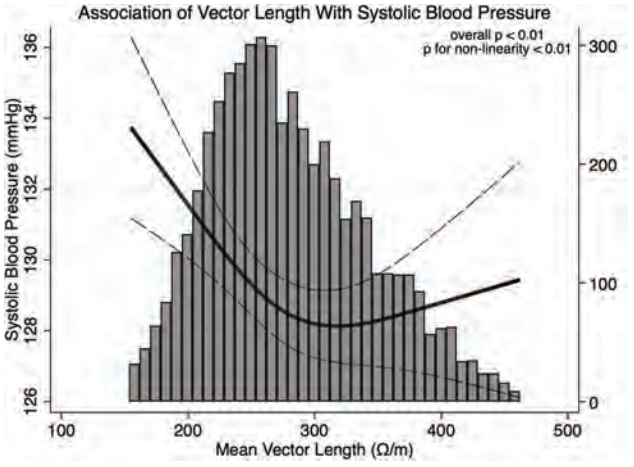
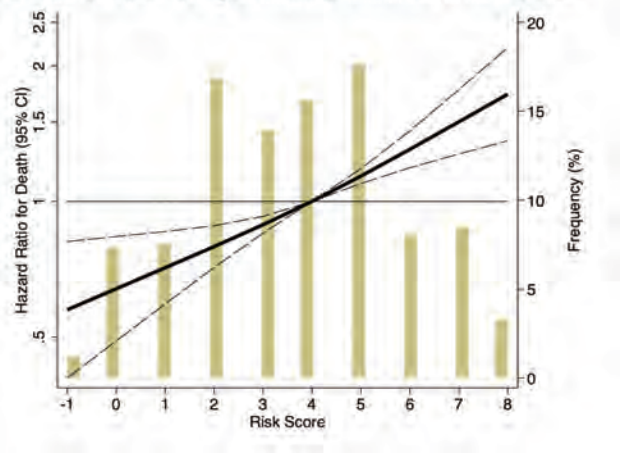


Figure 1. Restricted cubic spline showing adjusted association of ATTR-CM risk score with death. Histogram shows the distribution of the risk score.



FR-PO355

Association of an ATTR Cardiomyopathy Risk Score with Cardiac and Kidney Outcomes among Patients with CKD: Insights from CRIC

Catarina Vale,[1,4] Muthiah Vaduganathan,[2,3] Brendon L. Neuen,[5,6] João Sérgio Neves,[1,4] Finnian R. McCausland.[2,3] *[1]Universidade do Porto Faculdade de Medicina, Porto, Portugal; [2]Brigham and Women's Hospital, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Hospital de Sao Joao, Porto, Portugal; [5]University of New South Wales, Sydney, NSW, Australia; [6]Royal North Shore Hospital, St Leonards, NSW, Australia.*

Background: Transthyretin amyloid cardiomyopathy (ATTR-CM) is thought to be an underdiagnosed cause of heart failure, especially in HF with preserved ejection fraction (HFpEF). A clinical risk-score to predict ATTR-CM has been validated in HFpEF, but its utility among patients with CKD is unclear.

Methods: We applied a 6-variable risk score (age, sex, hypertension, ejection fraction, relative wall thickness, posterior wall thickness; range -1 to +10) to participants of CRIC with available 1-year echocardiographic data (n=2,718) and calculated the prevalence of a high-risk score (≥6 points). Using Cox regression models, landmarked at 1-year, we explored the adjusted association of a high vs. low-risk score with atrial fibrillation (AF), HF, stroke, myocardial infarction (MI), a kidney composite (kidney failure, ≥50% decline in eGFR, eGFR≤15 mL/min/1.73m^2), and all-cause death.

Results: The median score was 4 [2, 5]; 539 (20%) had a high-risk score for ATTR-CM, which was associated with a higher adjusted risk of AF (hazard ratio [HR] 1.87, 95% confidence interval [CI] 1.48, 2.35), HF (HR 1.63, 95%CI 1.27, 2.08), MI (HR 1.82, 95%CI 1.33, 2.49) and all-cause mortality (HR 1.60, 95%CI 1.37, 1.87). There was a trend towards a higher risk of stroke with high (vs low) risk score (HR 1.47, 95%CI 0.94, 2.29) but no association with kidney composite (HR 1.01, 95%CI 0.82, 1.23). Using a restricted cubic spline, a monotonic association of higher risk score with death was evident (Figure 1).

Conclusions: 1 in 5 individuals in CRIC appear to have a high predicted risk for ATTR-CM. A high-risk score was prognostic for adverse cardiac outcomes and death, but not for a kidney composite outcome. Future studies to examine the true prevalence and to determine the optimal screening pathways for ATTR-CM among patients with CKD are warranted.

Funding: NIDDK Support

FR-PO356

Cystatin C-based eGFR Predicts Patient-Reported Outcomes in Heart Failure

Blake N. Lackey,[1] Bethany A. Roehm,[1] Justin Grodin,[1] Susan Hedayati.[2] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]Stony Brook University Hospital, Stony Brook, NY.*

Background: Lower eGFR is linked to worse outcomes in people with heart failure (HF) with reduced (HFrEF) and preserved (HFpEF) ejection fractions. Data on patient-reported outcomes (PROs) in HF and eGFR using Cr (GFRcr) are conflicted and scarce using cystatin C (GFRCys).

Methods: We tested the association between baseline eGFR and the Kansas City Cardiomyopathy Questionnaire (KCCQ), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and 6 min walk test (6MWT) at baseline and 6 mo in 769 participants of EXACT-HF (n=253), RELAX (n=216), and FIGHT (n=300) trials. eGFR measures used were GFRcr, GFRcys, a weighted average of both (GFRcr-cys), and GFRcys/GFRcr<0.7, a predictor of mortality in HFrEF and CKD. Linear regression was used, adjusting for age, sex, diabetes, BMI, NYHA class, NT-proBNP, and treatment arm.

Results: Mean (SD) age was 63 (13). 28% were female, 59% had NYHA class 3-4 symptoms, 72% HFrEF, and 20% GFRcys/GFRcr <0.7. Mean GFRcr was 58 (23), GFRcys 54 (25), and GFRcr-cys 57 (24) ml/min/1.73m2. All GFR measures were associated with 6MWT at baseline. Only Cys-derived measures associated with 6MWT at 6 mo in multivariable analyses. GFRcys/GFRcr <0.7 predicted a drop in 6MWT distance by nearly 35 m at 6 mo. All cys-based eGFR associated with KCCQ at 6 mo but not with MLHFQ in multivariable analyses (Table).

Conclusions: GFR estimates using cystatin C but not Cr predicted worse performance on 6MWT and KCCQ in people in HF. No GFR measures predicted MLHFQ score, indicative of MLHFQ's known lower sensitivity to change. These findings offer new insights on the adverse effects of declining kidney function on HF symptoms. More research is needed on the validity of GFRcys as a measure of frailty in HF.

6 mo	6MWT[1] (HFrEF, HFpEF)		KCCQ[2] (HFrEF)		MLHFQ[2] (HFpEF)	
Multivariable	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
GFRcys/GFRcr <0.7	**-34.9 (-59.4, -10.4)**	**0.005**	**-7.8 (-13.9, -1.7)**	**0.01**	2.3 (-2.9, 7.6)	0.38
GFRcr[3]	4.5 (-0.2, 9.2)	0.06	0.9 (-0.2, 0.2)	0.11	0.3 (-0.9, 1.5)	0.62
GFRcys[3]	**8.7 (4.1, 13.4)**	**<0.001**	**1.9 (0.9, 2.9)**	**<0.001**	0.4 (-0.9, 1.7)	0.56
GFRcr-cys[3]	**7.7 (3.0, 12.5)**	**0.001**	**1.7 (0.6, 2.8)**	**<0.003**	0.4 (-0.8, 1.6)	0.55

[1]Meters, [2]Points, [3]Per 10 ml/min/1.73m^2 increase in eGFR

FR-PO357

Heart Failure with Preserved Ejection Fraction (HFpEF), Heart Failure with Reduced Ejection Fraction (HFrEF), and the Risk of ESKD in Type 2 Diabetes (T2D)

David Kim,[1] Amara Sarwal,[1,2] Guo Wei,[1,2] Robert E. Boucher,[1,2] Ravinder Singh,[1,2] Sydney E. Hartsell,[1,2] Stavros Drakos,[1,2] Srinivasan Beddhu.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

Background: We examined the hypothesis that kidney blood flow is more compromised in HFrEF compared to HFpEF and, as a result, there is a higher risk of ESKD in HFrEF compared to HFpEF in T2D.

Methods: Using the VA informatics and Computing Infrastructure (VINCI), in a cohort of 2.79 million veterans with a diagnosis of T2D from 1/1/2010 to 12/31/2018, we identified a cohort of 316,762 veterans with first time incident HF hospitalizations. Using a validated algorithm and natural language processing, ejection faction (EF) data was obtained. HF was classified as HFpEF (EF >50), HFrEF (EF <40), HFmrEF (EF 40 to 50) and no EF (no data). Index date was HF hospitalization date. Follow-up was until 12/31/2021. ESKD data was obtained by linkage to US Renal Data System data. In multivariate Cox regression models, we related HF subtypes to the risk of ESKD.

Results: Mean age 72 ± 11 years, 98% male, 17% Black, Mean eGFR 64 ± 29. There were 15,126 ESKD events/1,222,038 years of follow-up. HFrEF had the lowest incidence and HFpEF the highest incidence of ESKD (Figure). These associations were attenuated in multivariate cox regression models (Table).

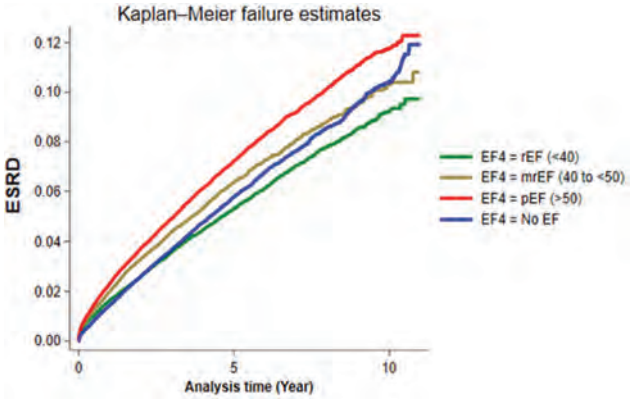
Conclusions: The risk of developing ESKD is higher in the HFpEF compared to HFrEF but adjusting for baseline covariates attenuated this association. Thus, both HFpEF and HFrEF have similar risk for ESKD.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support

HR (95% CI) for ESKD

	HFrEF (<40)	HFmrEF (40 to <50)	HFpEF (>50)	No EF
Model 1	Reference	1.26 (1.20, 1.33)	1.48 (1.41, 1.54)	1.20 (1.15, 1.26)
Model 2	Reference	1.02 (0.97, 1.08)	1.02 (0.97, 1.06)	1.06 (1.01, 1.11)

Model 1 - demographics, CHF diagnosis setting.
Model 2 - Model 1 + comorbidities, SBP, DBP, BMI, CKD, diabetes meds, BP meds, HbA1c



FR-PO358

Association of Kidney Function and Volume Overload with Incident Pulmonary Hypertension in the Chronic Renal Insufficiency Cohort (CRIC) Study

Marcelle Tuttle,[1,2] Hocine Tighiouart,[1,2] Tatsufumi Oka,[3] Wendy I. McCallum,[1] Nicholas S. Hill,[1] Steven Kawut,[4] Mark J. Sarnak.[1] *[1]Tufts Medical Center, Boston, MA; [2]Tufts Clinical and Translational Science Institute, Boston, MA; [3]Osaka Daigaku, Suita, Japan; [4]University of Pennsylvania, Philadelphia, PA.*

Background: Pulmonary hypertension (PH) is common in patients with chronic kidney disease (CKD), but very few studies have examined risk factors for its development. Tricuspid regurgitation velocity (TRV) measured on echocardiogram (TTE) estimates the pressure difference between the right ventricle and the right atrium and correlates with pulmonary artery systolic pressure.

Methods: We included patients without prevalent PH with 2 or more TRV measurements in the CRIC Study. PH was defined as a TRV >= 2.8 m/s. Incident PH was defined as PH on the final TTE. Estimated glomerular filtration rate (eGFR), 24-hour urine albumin, and brain natriuretic peptide (BNP) were considered as the main independent variables. eGFR was calculated using the CKD-EPI 2021 equation. Multivariable logistic regression adjusting for demographics, comorbid conditions, and medications was used to evaluate the relation of kidney function and BNP to incident PH. In further exploratory models, eGFR models additionally adjusted for BNP and vice versa.

Results: The study sample included 848 subjects. At baseline mean eGFR was 45.3 ml/min/1.73m^2 (SD 14.7), median 24-hour urine albumin was 24.8 mg (IQR 7.3, 142.8), and median BNP was 36.6 pg/ml (IQR 15.8, 64.4). 103 (10.4%) subjects developed PH over a mean (SD) of 3.8 (1.3 years). Lower baseline eGFR was associated with higher odds of developing PH, but the effect was slightly attenuated after adjustment for BNP (Table). BNP was associated with higher odds of incident PH regardless of adjustment. There was no association between albuminuria and incident PH.

Conclusions: Higher baseline BNP and lower eGFR are associated with incident PH in CKD. Volume appears to be a key risk factor for the development of PH in patients with CKD.

Funding: Other NIH Support - The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, Award Number T32TR004418. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH., Private Foundation Support

Table. Odds ratios of the association of baseline eGFR, 24-hour urine albumin and BNP with incident PH

Exposure	OR (95% CI)	P-value
eGFR	**per 10 ml/min/1.73m^2 lower**	
Unadjusted	1.39 (1.19, 1.63)	<0.001
Model 1[a]	1.23 (1.05, 1.47)	0.02
Model 2[a,c]	1.19 (0.99, 1.43)	0.06
24-hour urine albumin	**per doubling**	
Unadjusted	1.07 (0.97, 1.19)	0.18
Adjusted[a,c]	0.98 (0.87, 1.11)	0.78
BNP	**per doubling**	
Unadjusted	1.61 (1.33, 1.95)	<0.001
Model 1[a]	1.46 (1.18, 1.81)	<0.001
Model 2 [a,c]	1.43 (1.15, 1.77)	<0.01

[a]Adjusted for age, sex, race/ethnicity, heart failure, diabetes, chronic obstructive pulmonary disease, systolic blood pressure, body mass index, ejection fraction, baseline TRV, receipt of angiotensin converting enzyme inhibitors, angiotensin receptor blockers or diuretics
[b]Adjusted for BNP
[c]Adjusted for eGFR
Data provided by the NIDDK Central Repository, a program of the National Institute of Diabetes and Digestive and Kidney Diseases.

FR-PO359

Percutaneous Coronary Intervention with a Drug-Eluting Stent Is Associated with Better Survival than Coronary Artery Bypass Grafting in Patients on Peritoneal Dialysis in Taiwan

Szu-Yu Pan,[1] Naichi Teng,[2] Likwang Chen.[2] *[1]National Taiwan University Hospital, Taipei, Taiwan; [2]National Health Research Institutes, Zhunan, Taiwan.*

Background: The optimal revascularization strategy for coronary artery disease in patients under peritoneal dialysis (PD) is unclear. Recently, we reported that percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) is associated with better survival than coronary artery bypass grafting (CABG) in patients under either hemodialysis or PD. We aim to perform a dedicated subgroup analysis to study the comparative effectiveness in patients under PD.

Methods: This retrospective population-based cohort study included PD patients hospitalized for either CABG or PCI with a DES between January 1, 2009, and December 31, 2015, identified in the Taiwan National Health Insurance Research Database. Inverse probability of treatment weighting was used to balance the baseline characteristics. Multivariable logistic regression models and Cox proportional hazard models were used to examine the risks of in-hospital mortality and long-term survival, respectively.

Results: From the 4,165 dialysis patients in our cohort, we selected 333 PD patients receiving either CABG (86 patients) or PCI with a DES (247 patients) for analysis. Compared with patients receiving PCI with a DES, the risk of in-hospital mortality was significantly higher in patients receiving CABG [adjusted odds ratio, 5.70; 95% confidence interval (CI) 1.42-22.83; P = 0.014]. The overall mortality was also significantly higher in patients receiving CABG [adjusted hazard ratio, 1.53; 95% CI 1.13-2.08; P = 0.006]. The long-term mortality hazard associated with CABG remained consistent in several sensitivity analyses (Figure 1).

Conclusions: CABG was associated with both higher in-hospital and long-term mortality than PCI with a DES in our national cohort of Taiwan PD patients.

Funding: Government Support - Non-U.S.

Figure 1. Sensitivity analysis for the overall mortality

	HR	95% CI	P value
Original model	1.53	1.13-2.08	0.006
Additional models			
Cox models censoring at different time			
1-year mortality	1.27	0.69-2.35	0.45
2-year mortality	1.59	1.05-2.43	0.03
3-year mortality	1.39	0.93-2.07	0.11
4-year mortality	1.74	1.27-2.37	0.001
5-year mortality	1.65	1.21-2.25	0.001
Survival 90 days after the index revascularization			
Observation since 90 days after the index date	1.74	1.24-2.46	0.002
Two-slope model[a]	1.76	1.26-2.47	0.001
Composite outcome measures			
Death, ACS, or repeat revascularization	0.89	0.66-1.20	0.44
Death or ACS	1.17	0.87-1.56	0.30
Death or repeat revascularization	0.92	0.70-1.22	0.56

[a]The adjusted HR in the second slope (90 days after the index revascularization) was shown.
Abbreviation: ACS, acute coronary syndrome; HR, hazard ratio

FR-PO360

Circulating Mycobiota and Mortality among Patients Undergoing Hemodialysis

Keiichi Sumida,[1] Yamini Mallisetty,[1] Chi-Yang Chiu,[1] Zhongji Han,[1] Cheng Chen,[2] Maki Sumida,[1] Amandeep Bajwa,[1] Jesse C. Seegmiller,[3] Amy B. Karger,[3] Susmita Datta,[4] Michael A. Langston,[2] Csaba P. Kovesdy,[1,5] Joseph F. Pierre.[6] *[1]The University of Tennessee Health Science Center, Memphis, TN; [2]University of Tennessee Knoxville, Knoxville, TN; [3]University of Minnesota, Minneapolis, MN; [4]University of Florida, Gainesville, FL; [5]VA Memphis Medical Center, Memphis, TN; [6]University of Wisconsin Madison, Madison, WI.*

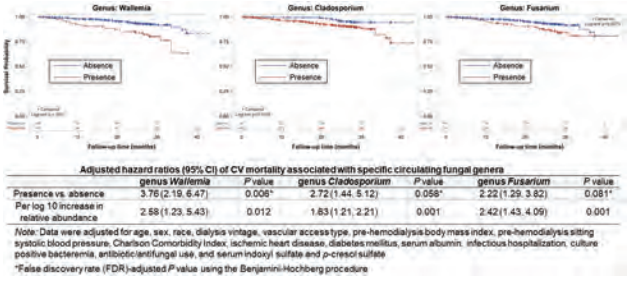
Background: Alterations of the circulating microbiota have recently been implicated in the pathogenesis of cardiometabolic disease. However, the evidence is based primarily on bacterial DNA signatures, and the characteristics and roles of DNA signatures of circulating fungi or 'circulating mycobiota (c-Myco)' remain unknown.

Methods: In a nationwide prospective cohort of 960 patients undergoing hemodialysis (HD), we characterized the signatures of c-Myco (i.e., quantity, α diversity, and composition) in baseline serum samples by means of Internal Transcribed Spacer (ITS) ribosomal DNA (rDNA) sequencing and examined their associations with all-cause and cardiovascular (CV) mortality using the Kaplan-Meier method and multivariable Cox models.

Results: Overall, the mean age was 60 years; 57% of patients had diabetes; and a median HD vintage was 3.1 years. No one used antifungals at baseline. After stringent quality controls, ITS rDNA was detected in 79.8% of patients. Taxonomic analysis demonstrated a total of 397 fungal taxa, including 7 phyla, 149 families, and 241 genera, most of which were rare and observed in <1% of patients at a mean relative abundance (RA) <0.1%. During a median follow-up of 2.2 years, 205 and 75 patients experienced all-cause and CV death, respectively. c-Myco signatures were not associated with all-cause mortality; but higher circulating fungal α diversity (adjusted HR [95% CI], 1.64 [1.14-2.39] per 1 unit increase) and the presence of specific fungal genera (3.76 [2.19, 6.47], 2.72 [1.44, 5.12], and 2.22 [1.29, 3.82] for *Wallemia*, *Cladosporium*, and *Fusarium*, respectively, P_{FDR} <0.1; Figure) were each significantly associated with higher CV mortality. For all three genera, their higher RA was also associated with higher CV mortality (Figure).

Conclusions: c-Myco signatures are independently associated with CV mortality in HD patients. Further studies are needed to determine the reasons for c-Myco detection and the mechanisms underlying the observed association.

Funding: NIDDK Support



Adjusted hazard ratios (95% CI) of CV mortality associated with specific circulating fungal genera

	genus *Wallemia*	*P* value	genus *Cladosporium*	*P* value	genus *Fusarium*	*P* value
Presence vs. absence	3.76 (2.19, 6.47)	0.006*	2.72 (1.44, 5.12)	0.058*	2.22 (1.29, 3.82)	0.081*
Per log 10 increase in relative abundance	2.58 (1.23, 5.43)	0.012	1.83 (1.21, 2.21)	0.001	2.42 (1.43, 4.09)	0.001

Note: Data were adjusted for age, sex, race, dialysis vintage, vascular access type, pre-hemodialysis body mass index, pre-hemodialysis sitting systolic blood pressure, Charlson Comorbidity Index, ischemic heart disease, diabetes mellitus, serum albumin, infectious hospitalization, culture positive bacteremia, antibiotic/antifungal use, and serum indoxyl sulfate and *p*-cresol sulfate
*False discovery rate (FDR)-adjusted *P* value using the Benjamini-Hochberg procedure

FR-PO361

Clinical Characteristics of Undiagnosed Coronary Artery Disease (uCAD) in Individuals Initiating Hemodialysis

Hirohito Sugawara,[1] Kiryu Yoshida,[1] Yoshinori Saito,[1] Masanori Kato,[1] Masahiro Yamamoto,[1] Hidetoshi Ito,[1] Suguru Shimazu,[1] Masahiko Ochiai,[1] Hiroaki Ogata.[1,2] *[1]Showa Daigaku Yokohama-shi Hokubu Byoin, Yokohama, Japan; [2]Showa Daigaku, Shinagawa-ku, Japan.*

Background: Although CAD is prevalent in individuals with CKD, it is difficult to evaluate coronary lesion by coronary angiography (CAG) and coronary computed tomography (CCT) in advanced CKD not on HD because of high risk of contrast nephropathy. We examine the prevalence of uCAD and its clinical characteristics in individuals initiating HD.

Methods: We conducted a cross-sectional study of individuals newly starting HD between January 2002 and December 2023 at our hospital. CAD was screened by CCT immediately after starting HD, and then CAD was confirmed by CCT/CAG. The individuals with history of CAD were excluded. After exclusions, the remaining 272 participants were enrolled in the present study.

Results: A total of 272 participants (mean age, 69 years; female 30%; diabetes, 57%). Coronary lesions were detected in 128 participants (47%). The distribution of stenotic lesions was LAD 73%, LCX 44%, and RCA 49%, respectively. Coronary artery calcification (total Agatston score) was significantly observed in participants with CAD as compared with those without CAD (1290 ± 1652 vs. 390 ± 655; P<0.001). Dyslipidemia, diabetes, and past cerebrovascular disease were more prevalent in participants with CAD. Antiplatelet agents including aspirin and statins were frequently prescribed in participants with CAD. T wave inversion in the ECG were more frequently found in participants with CAD. No significant differences were observed in echocardiographic parameters between participants with and those without CAD. The multiple regression analysis indicated that the history of smoking and the levels of albumin (the odds ratio (OR): 0.53 (95% confidence interval [95% CI], 0.31 to 0.91)) and HDL-C (OR: 0.97 (95% CI, 0.95 to 0.99)) was independently and significantly associated with the formation of CAD.

Conclusions: uCAD were found in approximately half of individuals newly starting HD. Coronary lesions were frequently found in LAD artery. HDL-C and albumin were associated with uCAD.

FR-PO362

Prevalence and Risk Factors of Altered Control of BP during the Night in a Large Hemodialysis Population Evaluated by 48-Hour Ambulatory BP Monitoring

Francesca Mallamaci,[1] Claudia Torino,[2] Pantelis Sarafidis,[3] Robert Ekart,[4] Olga Balafa,[5] Antonio M. Del Giudice,[6] Filippo Aucella,[6] Massimo Morosetti,[7] Rocco Tripepi,[2] Carmela Marino,[2] Giovanni Tripepi,[2] Carmine Zoccali.[8] *[1]GOM Bianchi Melacrino Morelli, Nephrology Unit, Reggio Calabria, Italy; [2]IFC-CNR, Reggio Calabria, Italy; [3]Aristotle University, Thessaloniki, Thessaloniki, Greece; [4]University Clinical Centre Maribor, Maribor, Slovenia; [5]University Hospital of Ioannina, Ioannina, Greece; [6]Nephrology Unit "Casa Sollievo della Sofferenza" San Giovanni Rotondo, San Giovanni Rotondo, Italy; [7]Nephrology Unit, ASL Roma 3, Roma, Italy; [8]Renal Research Institute, New York, NY.*

Background: Altered BP control during the night is recognized as a powerful risk factor for death and CV events in the hemodialysis (HD) population. However, these alterations have been described in relatively small studies and the epidemiology and risk factors for subtypes non-dipping and nocturnal hypertension are still poorly characterized in the current literature. We investigated the problem in the large EURECA-m Registry, the sole adopting 48h ABPM recording in the HD population.

Methods: We included in this analysis 534 HD patients, from 7 centers, led by members of the EURECA-m working group, in 3 European countries. 48h ABPM was measured by using well validated instruments (AAMI/ESH/ISO). As recommended by the ESH guidelines, recordings were made at 15- minute intervals during the day and 30 minutes during the night. Hypertension was defined as 48h blood pressure (BP)>130/80,

nocturnal hypertension as a nighttime BP>120/70 mmHg, non-dipping as a night/day systolic BP fall <10% and reverse dipping as a night/day ratio>1.

Results: Among 534 HD patients, 317 were hypertensive and. 217 normotensive. 274 patients were non-dippers (51%), 32% were reverse dippers, and 381 (71%) had nocturnal hypertension. Of note, forty-one per cent of non-dippers, 37% of reverse dippers and 19% of patients with nocturnal hypertension were normotensives. As expected, the majority of reverse dippers (87%) had frank nocturnal hypertension. In a combined analysis of non-dippers and reverse dippers, as compared to dippers, these patients more frequently exhibited atrial fibrillation and had lower Heart Rate both pre-dialysis (72± 11 vs 77±13 bpm, P=0.004) and post-dialysis (74± 13 vs 78±14 bpm, P=0.03) and lower serum albumin (3.9±0.4 vs 4.0±0.3 g/dL, P=0.02) but did not differ for age and gender.

Conclusions: In a large cohort of HD patients investigated by the state-of-the-art technique, 48hABPM alterations in the nocturnal BP profile were almost universal, and nocturnal hypertension was the more prevalent alteration, followed by non-dipping and reverse dipping. These alterations were independent of age and gender. Long-term, granular follow-up analyses are warranted to identify the prognostic value of these alterations.

FR-PO363

Isolated Diastolic Hypertension in Patients on Hemodialysis

Francesca Mallamaci,[1] Claudia Torino,[2] Pantelis Sarafidis,[3] Robert Ekart,[4] Olga Balafa,[5] Antonio M. Del Giudice,[6] Filippo Aucella,[6] Massimo Morosetti,[8] Rocco Tripepi,[2] Carmela Marino,[2] Giovanni Tripepi,[2] Carmine Zoccali.[7]
[1]CNR-IFC & Nephrology and Renal Transplantation Unit, Reggio Calabria, Italy; [2]IFC-CNR, Reggio Calabria, Italy; [3]Aristotle University, Thessaloniki, Italy, Greece; [4]University Clinical Centre Maribor, Maribor, Slovenia; [5]University Hospital of Ioannina, Ioannina, Greece; [6]Nephrology Unit "Casa Sollievo della Sofferenza" San Giovanni Rotondo, San Giovanni Rotondo, Italy; [7]Renal Research Institute, New York, NY; [8]Nephrology Unit, ASL Roma 3, Roma, Italy.

Background: Isolated diastolic hypertension (IDH) is relatively rare in the general population (prevalence about 6.5%, Front Cardiovasc Med. 2021;8:810105) and of uncertain etiologic implications. The prevalence of this alteration in the hemodialysis (HD) population and the etiologic implications of IDH have not been studied.

Methods: We investigated the prevalence and the risk for all-cause death and cardiovascular events of isolated diastolic hypertension in a population of 534 HD patients enrolled in 7 centres in 3 European countries (the EURECA-m working group). BP was measured by a golden standard method in this population (48h ABPM) using well-validated instruments (AAMI/ESH/ISO). Along with recommendations by the European Society of Hypertension guidelines, recordings were made at 15-minute intervals during the day and 30 minutes at night. According to a consensus document by the EURECAm working group (NDT. 2019;34:1542-1548), isolated diastolic hypertension was defined as 48h diastolic BP > 80 mmHg with a systolic BP <130.

Results: Among 534 HD patients, thirty-one (5.8%) had isolated diastolic HTN, which is very close to the prevalence estimated in the general population (6.5%). During a mean follow-up of 2.6 years, 138 patients died, 188 had at least one CV event, and 249 experienced the combined event. In univariate analyses, diastolic hypertension was associated with death (HR 0.21; 95% CI: 0.05-0.86, P=0.03) and the combined outcome of death and CV events (HR 0.42, 95% CI: 0.20-0.88, P=0.02). However, these associations were no longer significant after adjustment for age and sex (all P≥0.45). Additional sensitivity analyses substantially confirmed these findings. No effect modification by age or gender was observed in these associations.

Conclusions: In a large cohort of HD patients studied by state-of-the-art 48-hour BP monitoring, the prevalence of isolated diastolic hypertension in HD patients (5.8%) is close to that registered in the general population (6.5%). This alteration predicts the risk for clinical outcomes in unadjusted analyses but not after adjustment for age and sex. Isolated diastolic hypertension is as rare as it is in the general population and unlikely to contribute to the high risk of adverse clinical outcomes in the dialysis population.

FR-PO364

Automated Blood Pressure Monitoring Patterns in Peritoneal Dialysis Modalities: Report from a Nephrology Reference Center in Mexico

Rodrigo Quintero Solis, Javier A. Vega Cardona, Edna T. Mendoza Villalobos, Mario A. Ruiz Gonzalez, Felipe De Jesus De La Torre Alvarez, Mireya González Franco, Michelle M. Cedillo, Miriam G. Nava-Vargas, Juan Carlos Anaya, Francisco Robles Garcia, Miguel Angel Franco Barrera, Hugo Sergio Breien Alcaraz, Sidney Torres. *Hospital Regional ISSSTE Valentin Gomez Farias, Zapopan, Mexico.*

Background: Arterial hypertension is a condition that affects most patients with chronic kidney disease and is a modifiable parameter to improve cardiovascular outcomes. Automated Blood Pressure Monitoring is considered the gold standard for surveillance. Various methods of BP measurement have been compared, including office-based measurements and self-monitoring. An analysis by Vaios demonstrated correlation between those compared to ABPM. ABPM classifies BP patterns over 24 hours, specifically during the night when it physiologically decreases, termed as Dipper. If this does not occur, it is considered non-dipper, a condition where BP figures increase, classified as Reverse Dipper, which increases CV risk. There are few studies that relates BP patterns to Renal Replacement Therapy. In a study of 38 patients, failed to demonstrate that the modality of Peritoneal Dialysis modifies BP patterns.

Methods: This is a retrospective, single-center study from 2014 to 2019, involving 150 patients who underwent ABPM for the first time. 64% were male, with a mean age of 49 years. 66% were on APD and 34% on CAPD. 42% were using diuretics, 73% iRAS, 41% calcium channel blockers, 28% a-blockers, and 21% b-blockers.

Results: The study found mean BP of 104 +/- 16 mmHg, daytime mean 105 +/- 16 mmHg, and nighttime mean 102 +/- 19 mmHg. In CAPD, 14% showed Dipper pattern, 36% reverse Dipper; in APD, 21% Dipper, 19% reverse Dipper. Non-parametric distribution confirmed via KS test ($p<0.001$). Significant difference in Dipper distributions by dialysis therapy (Mann-Whitney U test: U=2061.000, Z=-2.005, p=0.045). Significant relationship shown via Pearson's $\chi 2$ ($\chi 2=5.023$, df=3, p=0.170) and linear-by-linear association ($\chi 2=4.260$, df=1, p=0.039). Negative correlation observed through Kendall's Tau-b ($\tau=-0.155$, p=0.045) and Spearman's Rho ($\rho=-0.164$, p=0.045). CAPD had more reverse Dipper compared to APD.

Conclusions: Patients managed with CAPD had a statistically significant higher incidence of reverse Dipper pattern compared to those managed with APD.

FR-PO365

Sex Differences in Re-admissions following Cardiovascular Events in Patients with Kidney Failure

Silvi Shah, Karthikeyan Meganathan. *University of Cincinnati, Cincinnati, OH.*

Background: Hospitalization for cardiovascular disease (CVD) is common in patients with kidney failure. Little is known about sex differences in readmissions following cardiovascular events in patients on dialysis.

Methods: We evaluated 73,210 patients who initiated maintenance dialysis between 7/1/2013 and 6/30/2018 using the United States Renal Data System with linked Medicare claims for all cardiovascular (CV) hospitalizations. Rates of all-cause and CV related readmissions in the ensuing 30 days and 90 days were calculated. Adjusted time-to-event models were used to examine the association of sex with the outcome of 30 day and 90 day all-cause readmissions, CV readmissions, and all-cause death.

Results: Among 140,171 identified CV hospitalizations, the mean age at the time of index CV hospitalization was 70±11 years, and 46.1% of index CV hospitalizations were for women. 34.9% and 57.6% of CV hospitalizations resulted in readmission within 30 and 90 days, respectively; less than one-third of readmissions were CV related (16.1%, 30 days; 29.7%, 90 days). Women had a 6% higher risk of 30 day readmission for any hospitalization (HR, 1.06; 95% CI, 1.11-1.14) and a 14% higher risk of 90-day readmission for any hospitalization (HR, 1.14; 95% CI, 1.11-1.16) after an index CV hospitalization than men. While there was no difference in the risk of 30 readmission for CV hospitalization between men and women, women had a slightly higher risk of 4% for 90 readmission for CV hospitalization (HR, 1.04; 95% CI, 1.01-1.06) after an index CV hospitalization. After an index CV hospitalization, women had a lower risk of 30 day all-cause death (HR, 0.87; 95% CI, 0.84-0.91) and a lower risk of 90 day all-cause death, as compared to men (OR, 0.89; 95% CI, 0.86-0.92).

Conclusions: Among patients undergoing dialysis, women have a higher risk of readmission at 30 days and 90 days for any hospitalization and a higher risk of 90 day readmission for CV hospitalization following an index CV hospitalization than men. Further studies are needed to understand better the factors associated with sex differences in CV outcomes in patients with kidney failure.

Funding: Other NIH Support - 1K23HL151816-01A1 from NHLBI

FR-PO366

Diastolic Dysfunction Parameters in Patients with Intradialytic Hypertension

Thuylinh M. Nguyen, Andrew Horvit, Peter N. Van Buren. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Hypertension and heart failure (HF) are common in hemodialysis (HD) patients, and intradialytic hypertension (IH) further increases mortality risk. We characterized differences in cardiac structure and function in patients with and without IH with a focus on the ratio of mitral inflow velocity (E) to mitral annular early diastolic velocity (e').

Methods: We conducted a retrospective study of Dallas VA HD patients with available transthoracic echocardiograms (TTE). We calculated intradialytic blood pressure slope (IBPS) for each of 3 treatments before and after the TTE using all intradialytic measurements and defined IH as mean IBPS >0. We compared average E/e' in patients with and without IH using Mann Whitney U (raw data) and unpaired t test (log transformed data). We used logistic regression with average E/e' >14 as the primary outcome and IH as the primary predictor

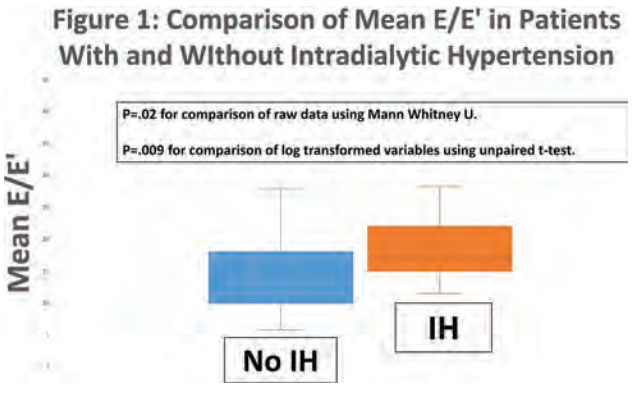
Results: Average E/e' was 17.1 (15-22) in the IH group (n=19) vs. 14.3 (10-18) in the non-IH group (n=37; p=.02). E/A was 1.18 (0.6) in IH vs. 0.95 (0.3) in non-IH (p=.06). IH patients had lower ejection fraction (EF) (p=.04) but higher left ventricular mass index (LVMI) (p=.007). While controlling for age, diabetes, race, and EF, IH predicted E/e' >14 (OR 7.1 [1.6-44]); but this was blunted when controlling for LVMI (OR 3.1 [0.5-31)].

Conclusions: Diastolic dysfunction is common in HD patients and is more severe in IH. LVMI may mediate higher E/e' in IH patients. TTE should be obtained in IH patients to better understand structural and functional abnormalities that may increase CV risk

Funding: NIDDK Support, Veterans Affairs Support

Patient Characteristics

	No IH (N=37)	IH (N=19)	P- Value
Age (years)	65.4 (9.4)	68.1 (9.8)	0.3
Diabetes	29 (78%)	10 (53%)	0.07
Mean IBPS	-3.48 (-6.1,-0.87)	+1.11 (0.5-2.1)	<0.0001
EF (Non-Teicholz) %	55.6 (9.9)	48.1 (17)	0.04
Systolic Dysfunction	7 (19%)	9 (47%)	0.03
Diastolic Dysfunction	25 (89%)	16 (100%)	0.03
LVMI (N= 44;g/m^2)	108 (37)	142 (40)	0.007
E/A (n=53)	0.95 (0.3)	1.18 (0.6)	0.06
Average E/e	14.3 (9.9-18)	17.1 (15-22)	0.02



FR-PO367

Temporal Changes in Cardiac Conduction Disorders in Patients with ESKD on Long-Term Hemodialysis

Taniya Thomas,[1] Thermutis Djanie,[1] Omar Daghstani,[2] Krishnakumar D. Hongalgi,[2] Mikhail Torosoff.[2] *[1]Albany Medical College, Albany, NY; [2]Albany Medical Center, Albany, NY.*

Background: Cardiac amyloidosis is a known complication of end stage kidney disease (ESKD) which manifests with conduction abnormalities, including atrioventricular (AV) blocks, and requires atrial and/or ventricular pacing. The prevalence and temporal changes in conduction disorders in ESKD patients has not been well investigated.

Methods: We conducted a retrospective, IRB approved study of 166 consecutive ESKD patients who underwent arteriovenous (AV) fistula placement between 2006-2023. Electrocardiographic features historically associated with cardiac amyloidosis, including AV blocks and paced rhythms, were examined on pre- and post-AV fistula placement electrocardiograms (ECG).

Results: Mean age was 59.7 +/- 14.7 years old, 41.0% were females, with body mass index (BMI) of 28.1 +/- 6.6, and histories of hypertension in 92.8%, coronary artery disease (CAD) in 48.2%, atrial fibrillation/flutter in 34.4%, diabetes mellitus in 60.8%, chronic obstructive pulmonary disease in 29.5%, coronary artery bypass grafting in 15.7%, and congestive heart failure in 51.2% of patients. The mean duration of hemodialysis (HD) was 57 +/- 50 months. The mean interval between ECG evaluations was 35+/- 28 months. At baseline, 13.9% of patients were noted to have AV blocks or require atrial or ventricular pacing. Advanced age (p=0.03), histories of CAD (p=0.03), and atrial fibrillation/flutter (p=0.02) were strongly associated with conduction abnormalities. Prevalence of AV blocks and the need for pacing significantly increased on the follow-up evaluation, affecting 17.5% of the study cohort (p<0.0001). However, at this point, traditional risk factors for conduction abnormalities were not associated with the need for pacing.

Conclusions: The prevalence of AV blocks and paced rhythms increase overtime in patients with ESKD on long-term HD. These abnormalities are initially more common in ESKD patients with traditional risk factors for cardiac conduction disorders. However, there appears to be no association between traditional risk factors and the prevalence of AV blocks and paced rhythms in ESKD patients on long-term HD post-AV fistula placement. Therefore, routine monitoring for conduction delays is imperative in all ESKD patients on HD.

FR-PO368

Cardiovascular Morbidity Patterns in Patients on Dialysis Globally in Apollo Dial DB

Belen Alejos,[1] Kaitlyn R. Croft,[1] Yue Jiao,[2] Melanie Wolf,[1] Paola Carioni,[3] Mitesh Soni,[2] Anke Winter,[1] Luca Neri,[3] Sheetal Chaudhuri,[2] Kanti Singh,[2] Stefano Stuard,[3] Milind Nikam,[4] Adrian M. Guinsburg,[5] Dinesh K. Chatoth,[2] Jeffrey L. Hymes,[2] Kirill Koulechov,[1] Len A. Usvyat,[2] John W. Larkin,[2] Franklin W. Maddux.[6] *[1]Fresenius Medical Care, Bad Homburg, Germany; [2]Fresenius Medical Care, Waltham, MA; [3]Fresenius Medical Care, Crema, Italy; [4]Fresenius Medical Care, Singapore, Singapore; [5]Fresenius Medical Care, Buenos Aires, Argentina; [6]Fresenius Medical Care AG, Bad Homburg, Germany.*

Background: Cardiovascular diseases (CVDs) affect most people with kidney failure but are undefined globally. We aimed to analyze CVD prevalence among dialysis patients treated in 40 countries across six continents, as represented in the first version of a global dialysis database (Apollo Dial DB).

Methods: Apollo Dial DB includes adult dialysis patient data from a global kidney network during Jan 2018-Mar 2021 (Fresenius Medical Care, Bad Homburg, DE). Data anonymization was performed in alignment with recommendations from a re-identification risk determination (Privacy Analytics, Ontario, CA). This analysis assessed CVD comorbidities based on ICD-10 codes.

Results: Among 543,169 patients included, 79% reported ≥1 CVD condition. The prevalence of CVD conditions showed some differences by age and sex (**Figure 1**). Hypertension was the most common, affecting 73.6% of patients. Atherosclerotic heart disease affected 19.0%, increasing with age (9.9% in 18-44 years to 24.1% in ≥75) and more common in males (20.3%) than females (17.2%). Congestive heart failure affected 17.5%, also increasing with age. Other conditions included peripheral vascular disease (11.5%), cardiomyopathy (7.3%), and cardiac dysrhythmias (7.1%), all more prevalent in older age groups and slightly higher in males.

Conclusions: Hypertension is the most common CVD comorbidity among dialysis patients globally, followed by atherosclerotic heart disease and congestive heart failure. The prevalence of these conditions increases with age and is slightly higher in males. Future analyses are needed to explore differences by world region, which could inform region-specific management strategies.

Funding: Commercial Support - Fresenius Medical Care

		Age (years)				Sex	
	Overall	18-44	45-64	65-74	>=75	Male	Female
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hypertension	399695 (73.6)	64872 (72.6)	165041 (73.7)	97026 (73.3)	72756 (74.7)	232634 (73.6)	167060 (73.5)
Atherosclerotic Heart Disease	103209 (19.0)	8840 (9.9)	40688 (18.2)	30219 (22.8)	23462 (24.1)	64107 (20.3)	39102 (17.2)
Congestive Heart Failure	95032 (17.5)	12238 (13.7)	38709 (17.3)	24932 (18.8)	19153 (19.7)	54956 (17.4)	40076 (17.6)
Peripheral Vascular or Arterial Dis	62361 (11.5)	6083 (6.8)	25937 (11.6)	17844 (13.5)	12497 (12.8)	38098 (12.1)	24263 (10.7)
Cardiomyopathy	39391 (7.3)	5274 (5.9)	16067 (7.2)	10368 (7.8)	7682 (7.9)	24773 (7.8)	14618 (6.4)
Cardiac Dysrhythmias	38832 (7.1)	3117 (3.5)	12844 (5.7)	11660 (8.8)	11211 (11.5)	23268 (7.4)	15564 (6.9)
Myocardial Infarction (Incl Cardiac Arrest)	24147 (4.4)	1669 (1.9)	9646 (4.3)	7444 (5.6)	5388 (5.5)	15570 (4.9)	8577 (3.8)
Cerebrovascular Disease	18888 (3.5)	1728 (1.9)	8019 (3.6)	5341 (4.0)	3800 (3.9)	10087 (3.2)	8891 (3.9)
Valvular heart disease	13919 (2.6)	1691 (1.9)	4523 (2.0)	3806 (2.9)	3899 (4.0)	7541 (2.4)	6378 (2.8)

Figure 1: Distribution of cardiovascular diseases by age group and gender

FR-PO369

Diagnosis of CKD in Patients with Hypertension in German Primary Care: The InspeCKD Study

Christoph Wanner,[1] Frederik M. Mader,[2,3] Thomas Frese,[4] Philipp Stahl,[5] Christoph Weber,[6] Ulrich Opfermann,[7] Fabian Burckhardt,[8] Felix Scherg,[8] Frank Radowsky,[9] Elke Schaeffner.[10] *[1]Department for Clinical Studies and Epidemiology, Comprehensive Heart Failure Center, University Clinic Würzburg, Würzburg, Germany; [2]Joint Practice Nittendorf, Nittendorf, Germany; [3]IU International University GmbH, Erfurt, Germany; [4]Institute of General Medicine, Interdisciplinary Center for Health Sciences, Martin Luther University Halle-Wittenberg, Halle, Germany; [5]Joint Family Practice Meinecke and Stahl, Burg, Germany; [6]Practice Rheinlanddamm, Dortmund, Germany; [7]SYMEDICUM MVZ GmbH, Berlin, Germany; [8]BioPharmaceuticals Medical, AstraZeneca, Hamburg, Germany; [9]Family Practice Radowsky, Leipzig, Germany; [10]Institute of Public Health, Charité - University Medicine Berlin, Berlin, Germany.*

Background: Hypertension (HT) is a known risk factor for chronic kidney disease (CKD) and a strong determinant of kidney and cardiovascular (CV) outcomes. Early diagnosis and therapy of CKD with organ protective treatments reduce the risks of kidney failure and CV complications. Therefore, assessment of kidney function by assessing eGFR and UACR in all patients with HT is recommended by the ESH 2023 and KDIGO 2024 guidelines. To date, there is limited data on the frequency of screening, diagnosis,

and guideline-directed medical therapy of CKD in HT patients in general practitioner (GP) practices. The InspeCKD study was designed to fill this gap.

Methods: 1,244 GPs provided fully anonymized individual data sets for analysis. According to the KDIGO screening recommendation, adult patients with HT, diabetes and/or CV diseases with at least one year of observation period were included in the analysis. In this pre-specified sub-analysis, only HT patients were evaluated.

Results: A total of 448,837 patients were included in the study, of whom 75.8% had HT (53.6% female; median age 66 years). Serum creatinine (SCr) to estimate eGFR (CKD EPI) was measured at least once in 43.4% of HT patients during the mean observation period of 1.7 years. Urine dipstick testing for albuminuria was performed at least once in 6.4% of HT patients and UACR was measured at least once in 0.3% of HT patients. 25.8% of HT patients had at least two SCr or UACR measurements at least three months apart to diagnose CKD. Among HT patients with laboratory confirmed CKD according to KDIGO (2x eGFR <60ml/min/1.73m^2 or 2x UACR >30mg/g in ≥3 months), 86.6% were not diagnosed with CKD. Guideline-directed medical therapy for CKD, defined as combination therapy with RASi and SGLT2i, was administered in 8.2% of HT patients diagnosed with CKD.

Conclusions: The analysis demonstrates the inadequacy of laboratory diagnostics in the early detection of CKD in HT patients at risk for CKD, including those with type 2 diabetes. It also reveals substantial gaps in diagnosis and treatment initiation in a country with full healthcare coverage. It is therefore important to raise awareness among GPs for the early detection and treatment of CKD in HT patients.

Funding: Commercial Support - AstraZeneca, Germany

FR-PO370

AKI as a Key Predictor of Cardiovascular Events in Patients with CKD: The CKD-REIN Study

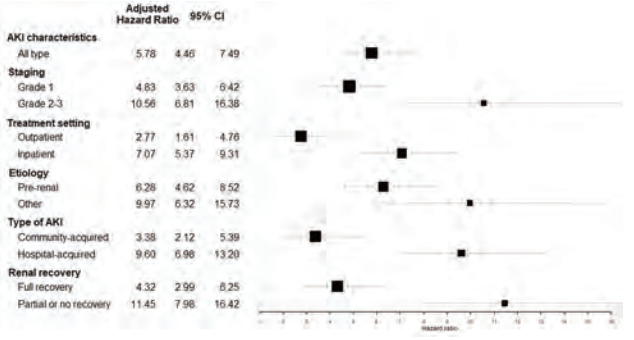
Aghiles Hamroun,[1,2] Estelle Aymes,[1,2] Luc Frimat,[3] Maurice Laville,[4] Celine Lange,[5] Sophie Liabeuf,[6] Ziad Massy,[7] Benedicte Stengel,[8] Natalia Alencar de Pinho,[8] Nans Florens.[9] *[1]Centre Hospitalier Universitaire de Lille, Lille, France; [2]Institut Pasteur de Lille, Lille, France; [3]Centre Hospitalier Regional Universitaire de Nancy, Nancy, France; [4]Universite de Lyon, Lyon, France; [5]Agence de la biomedecine, La Plaine Saint-Denis, France; [6]Centre Hospitalier Universitaire Amiens-Picardie, Amiens, France; [7]AURA Paris, Paris, France; [8]Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; [9]Les Hopitaux Universitaires de Strasbourg, Strasbourg, France.*

Background: Chronic kidney disease (CKD) is a well-established risk factor for cardiovascular events, but less is known about the specific contribution of acute-on-chronic kidney disease events. This study aims to analyze the relationship between incident acute kidney injury (AKI) episodes and subsequent Major Adverse Cardiovascular Events (MACE) in a population of CKD patients.

Methods: From 2013 to 2016, the CKD-REIN prospective cohort enrolled 3033 adults with CKD stages 2-5 from 40 outpatient nephrology clinics in France. During a 5-year follow-up, all AKI episodes were validated by an expert committee according to the KDIGO-AKI definition. Cardiovascular events were classified using clinical trial Cardiovascular and Stroke Endpoint Definitions and cardiovascular deaths adjudicated by expert. The association of incident AKI with subsequent MACE risk was analyzed using a multivariable Cox model, treating AKI as a time-dependent variable and stratifyied by AKI characteristics.

Results: Overall, 530 patients experienced at least one incident AKI episode during follow-up. After adjustment for multiple confounders, we observed a substantial increased hazard of MACE associated with AKI (HR = 5.78 [4.46; 7.49], $p < 0.001$), and this association remained significant for each MACE component. A dose-response relationship was observed, with higher risks in more severe AKI cases and among hospitalized versus non-hospitalized patients (Figure 1). This association was also confirmed across all subgroups, without any interaction with age, sex, CKD stage, nor major comorbidities (diabetes, history of AKI, or cardiovascular events), as well as in the sensitivity analyses.

Conclusions: Our study highlights a strong dose-response relationship between incident AKI and the risk of subsequent MACE in CKD patients. Our findings align with existing pathophysiological evidence, reinforcing the potential causal link between AKI and subsequent cardiovascular remodeling.



FR-PO371

Sex-Specific Relationships between Estimated Potassium Intake and Cardiovascular Outcomes in Patients with CKD: The Fukuoka Kidney Disease Registry Study

Tatsuya Suenaga,[1] Shigeru Tanaka,[1] Hiromasa Kitamura,[2] Kazuhiko Tsuruya,[3] Takanari Kitazono,[1] Toshiaki Nakano.[1] *[1]Department of Medicine and Clinical Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan; [2]Department of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Department of Nephrology, Nara Medical University, Kashihara, Japan.*

Background: Lower potassium intake is associated with an increased risk of cardiovascular disease (CVD) in the general population, and a sex-specific relationship has also been demonstrated. On the other hand, the relationship between potassium intake and CVD risks and its sex-specificity in patients with chronic kidney disease (CKD) has not been adequately investigated. This study aims to investigate the relationship between potassium intake and CVD risk, in addition to examining its sex-specificity in patients with CKD.

Methods: A total of 4,314 Japanese non-dialysis CKD patients aged 18 years or older in the Fukuoka Kidney disease Registry (FKR) Study were prospectively followed for 5 years. Patients were divided into sex-specific quartiles according to estimated potassium intake assessed by the Tanaka formula from spot urine samples. The primary outcome was occurrence of CVD events, defined as a composite of acute myocardial infarction, stable or unstable angina, ischemic or hemorrhagic stroke, peripheral arterial disease, hospitalization for heart failure, and cardiovascular mortality. We estimated the relationship between estimated potassium intake and CVD events using Cox proportional hazards models adjusted for factors related to potential confounding, risk of CVD, and potassium homeostasis.

Results: A total of 431 patients developed the primary outcome during follow-up periods. Patients in quartile 1 (Q1) of the total population had a significantly higher hazard ratio (HR) for CVD events than those in Q4 in the multivariable-adjusted Cox proportional hazards models (fully multivariable-adjusted HR [95% confidence interval {CI}], 1.48 [1.03–2.14]). In addition, there was a significant interaction between estimated potassium intake and CVD events by sex (p for interaction <0.01), and in women, patients in Q1 had an even significantly higher HR for CVD events than those in Q4 (multivariable-adjusted HR [95% CI]: men, 1.,2 [0.66–1.60]; women, 3.32 [1.62–6.81]).

Conclusions: Lower estimated potassium intake in patients with CKD was associated with an increased risk for CVD, and the relationship was significant only in women and not in men.

FR-PO372

Trends in Cardiovascular Mortality among Patients with CKD

Loai Dweik,[1] Ansaam Daoud,[2] Natthavat Tanphaichitr.[1] *[1]Cleveland Clinic Akron General, Akron, OH; [2]University Hospitals, Cleveland, OH.*

Background: Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD). Impaired kidney function accelerates CVD due to factors like hypertension, fluid overload, dyslipidemia, and disturbances in mineral metabolism. Studies investigating trends in cardiovascular mortality among patients with CKD are lacking. We aim to observe the trends in proportionate cardiovascular mortality (PCM) in the last two decades in U.S.

Methods: This retrospective cohort study analyzed data from the Multiple Cause of Death files maintained by the National Center for Health Statistics. The dataset includes death certificates for U.S. residents, specifying the one primary cause of death as determined by the treating physician, up to twenty contributory causes, and demographic details. We explored the trend in PCM, which is the ratio of cardiovascular deaths (primary cause of death coded as I00-I99 in the International Classification of Diseases, version 10 [ICD-10]) to total deaths, in patients diagnosed with CKD (identified by ICD-10 code N18)

from 1999 to 2020. We used Pearson's correlation coefficient for trend analysis and the Chi-square test for comparative assessments.

Results: 1,938,505 deaths occurred in patients with CKD over the study period, with an age adjusted mortality rate of 26.3 per 100,000 people. Overall, 605,384 died of CVD causes (31%). The mean age of CVD mortality was 78 years. PCM decreased from 39% to 24% from 1999 to 2020 (r -0.9326, p<0.0001). PCM was higher in men (32% vs 30%, p<0.0001). Asian or Pacific Islanders exhibited the highest proportionate cardiovascular mortality at 33%, followed by Whites at 32%, African Americans at 28%, and American Indians or Alaska Natives at 24% (p 0.00). The most common cause of cardiovascular deaths was ischemic heart disease at 59%, hypertension 10%, cardiomyopathy 5%, valvular disease 4%, arrhythmia 4% and 20% other causes.

Conclusions: In conclusion, the past two decades have witnessed a significant decline in the proportion of deaths attributed to CVD causes among patients with CKD. Our analysis suggests improved management strategies and potentially highlights the effectiveness of preventative measures in CKD. Further research is needed to elucidate the specific factors contributing to this positive shift in this high-risk population.

FR-PO373

Trend Analysis of Hypertensive Kidney Disease-Related Mortality, 1999-2020

Mohammad Gul Yousaf Khan,[2] Hammad H. Khan,[1] Mohammad Ammar ur Rahman,[1] Luqman Munir,[1] Amna Khalid,[1] Ali Akram Qureshi,[1] Iqra Shahid,[1] Ahsan Zil-E-Ali,[2] Umar Farooq,[2] Fatima H. Abid.[1] NEURALKEy.
[1]King Edward Medical University, Lahore, Pakistan; [2]Penn State College of Medicine, Hershey, PA.

Background: Hypertensive kidney disease is associated with significant mortality because of the associated end-organ damage. This study seeks to evaluate the trend disparities in mortality related to hypertensive kidney disease among various demographic and geographical variables.

Methods: Our research involved a comprehensive analysis of the CDC Wonder database, specifically focusing on hypertensive kidney disease-related age-adjusted mortality rate (AMR) per 1,000,000 people. We conducted a test of Parallelism and calculated Annual Percent Changes (APC) with 95% Confidence Intervals using Joinpoint Regression Analysis. The test of parallelism was deemed significant for unparallel results with a p-value < 0.05.

Results: Overall AMR for hypertensive kidney disease did not significantly change from 1999 to 2020. However, AMR declined from 1999 to 2012 (APC -3.83), followed by a significant increase till 2020 (APC 5.70). All age groups from 25-85+ experienced a significant increase in AMR, with the 85+ having the greatest APC (14.4). There was a significant increase in AMR across all four census regions, with greatest increase in C2: Midwest (APC 11.2). The regions did not differ significantly from one another. Both urban and rural populations saw a significant increase in AMR, with rural population having a significantly greater APC (11.4). The female population experienced a significant decline in AMR, with a significantly negative AAPC of -1.30. The AAPC did not differ significantly between the two genders. The parallelism test was significant for comparison of genders, census regions and urban/rural populations. The Asian or Pacific Islander population experienced a decline in AMR (APC -2.80), with Black population experiencing a significant decrease from 1999-2018 (APC -3.61), followed by a substantial and significant increase till 2020 (APC 24.4).

Conclusions: Hypertensive kidney disease-related mortality has experienced little change in the United States. Certain demographic groups such as the rural population, females, and recently, the Black population experience disparities which require further investigations and directed solutions for these groups.

FR-PO374

Sex Differences in the Association of Cardiovascular Risk Factors with Post-traumatic Stress Disorder (PTSD) among Veterans with CKD

Helena Zhang,[1] David J. Ramsey,[1,4] Sankar D. Navaneethan,[1,2] Joseph Chilcot,[3] Lucile Parker Gregg.[1,4] *[1]Baylor College of Medicine, Houston, TX; [2]Michael E DeBakey VA Medical Center, Houston, TX; [3]King's College London, London, United Kingdom; [4]VA Center for Innovations in Quality Effectiveness and Safety, Houston, TX.*

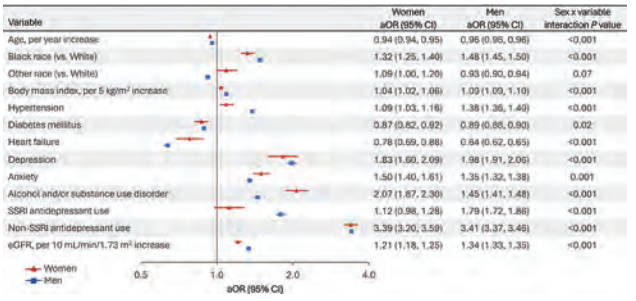
Background: Post-traumatic stress disorder (PTSD) is common among veterans and is associated with chronic kidney disease (CKD) progression and cardiovascular (CV) risk. It is unknown if sex modifies associations of CV risk factors with PTSD in veterans with CKD, who have a unique CV risk profile.

Methods: Using data from the VA Corporate Data Warehouse from 1/1/2009 to 12/31/2020, we conducted a retrospective cohort study of U.S. veterans with incident CKD stages 3-5 (defined as two eGFR values <60 mL/min/1.73 m^2 measured ≥90 days apart with no intervening values ≥60) with and without a diagnosis of PTSD. The index date was the date of the second qualifying eGFR. PTSD was defined by diagnosis codes in ≥2 clinical encounters within 1 year prior to the index date. Multivariable logistic regression assessed associations of demographics, comorbidities, medications, and laboratory values with PTSD, with multiplicative interaction terms to assess if sex modifies these associations.

Results: Of 1,443,878 veterans with CKD, 143,473 (9.9%) had a diagnosis of PTSD. Compared to those without PTSD, those with PTSD were younger (mean [SD] 65 [9] vs 73 [10], standardized mean difference [SMD] .78), more likely to be female (7% vs 3%, SMD .16) and Black (29% vs 16%, SMD .08), and more likely to have CKD stage 3 (97% vs 93%, SMD .15), hypertension (81% vs 70%, SMD .25), atherosclerotic CV disease (23% vs 18%, SMD .13), and depression (43% vs 13%, SMD .70). PTSD was associated with younger age, Black race, hypertension, higher body mass index, depression, anxiety, alcohol or substance use disorder, antidepressant use, and higher eGFR, with significant sex interactions for each. PTSD was more strongly associated with Black race, hypertension, depression, antidepressant use, and eGFR among men, and with anxiety and substance use disorder among women (**Figure**).

Conclusions: PTSD is differentially associated with CV risk factors among men and women veterans with CKD. Studies to improve CV outcomes in patients with PTSD and CKD should stratify by sex.

Funding: Veterans Affairs Support



CV risk factors and PTSD

FR-PO375

Global and Regional Disease Burden of Hypertensive CKD, 1980-2021: An Analysis of GBD Study 2021

Badar U Din Shah,[1] Muhammad Talha Shaukat,[2] Wania Rehman,[2] Aqeeb Ur Rehman,[3] Aleenah Mohsin,[4] Shahzaib Ahmad,[5] John W. O'Bell.[4]
[1]Geisinger Health, Danville, PA; [2]King Edward Medical University, Lahore, Pakistan; [3]The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; [4]Brown University, Providence, RI; [5]Baptist Health South Florida Inc, Coral Gables, FL.

Background: The incidence of hypertensive Chronic Kidney Disease(CKD) has steadily risen over time. The trends of standardized mortality and morbidity of hypertensive CKD are, however, understudied. By analysing trends from 1980-2021, this study provides insight into the longitudinally evolving pattern of hypertensive CKD associated mortality and morbidity.

Methods: Data were extracted from the Global Burden of Diseases (GBD) study, encompassing age-standardized mortality rates (ASMR), Years of Lost Life (YLL), and Disability-Adjusted Life Years (DALYs). The dataset was stratified by continent, with Africa divided into Northern, Southern, Eastern, Western, and Central. Data was further stratified by World Bank income levels and Joinpoint regression determined average annual percentage change (AAPC).

Results: Globally, the Age Standardized Death Rates (ASDR) for hypertensive CKD had an overall incline from 1980-2021. In 1980, ASDR was 4.57 (95% UI:3.8–5.5), which increased to 5.53 (AAPC:0.486; 95% CI:0.415, 0.557) in 2021. Globally, the DALYs were 107.7 (95% UI:91.26-126.9) per 100,000 people in 1990, and climbed to 128.4 (AAPC: 0.566; 95% CI:0.485-0.684) in 2021. From 1990 to 2021, the YLL showed a uniform spike with an AAPC of 0.287 (95% CI:0.19–0.37). In geographical analysis, all continents except Asia had an overall increase in ASDRs, with the highest ASDRs in Africa, and the most prominent spike in America. From 1980-2021, America had AAPC of 1.32 (95% CI:1.15-1.50), Africa had 0.403 (95% CI:0.34-0.46), Europe had 0.54 (95% CI:0.20-0.89) while Asia had -0.19 (95% CI:-0.29- -0.08). Central and Western Africa had the highest ASDRs as compared to other regions of the continent. Upon subanalysis of America, Mississippi and Louisiana had the most prominent incline in ASDRs. According to the World Bank income levels, low and middle income countries(LMICs) also conformed to the global trend and had an increasing death rates trends.

Conclusions: This study reveals a global rise in ASDR for hypertension-related CKD. Moreover, DALYs and age-standardized YLL have also increased, underscoring the need for targeted interventions as well as preventive measures. LMICs also show escalating death rates, emphasizing the need for proactive measures to address this growing health crisis there.

FR-PO376

Incident Hypertension in Young Adults with a Modest eGFR Reduction

Sumaiya Ahmed,[1] Junayd Hussain,[1] Ayub Akbari,[1] Pietro Ravani,[2] Gregory L. Hundemer,[1] Tim Ramsay,[1] Ann Bugeja,[1] Greg A. Knoll,[1] Manish M. Sood.[1] *[1]Ottawa Hospital, Ottawa, ON, Canada; [2]Alberta Health Services, Edmonton, AB, Canada.*

Background: Hypertension (HTN) is a common, modifiable risk factors for cardiovascular (CV) disease with a rising occurrence in young adults (18-39). Advanced chronic kidney disease is well established as a risk factor for HTN, however, uncertainty remains regarding the relationship between modest eGFR declines (between 60 to 100 ml/min) and HTN.

Methods: A retrospective cohort study of 8.7 million individuals (3.6 million aged 18-39 years) using linked provincial healthcare datasets from Ontario, Canada from January 2008 to March 2021. Cox models were conducted to examine the association of categorized eGFR (50-120 mL/min/1.73m^2) and incident HTN, stratified by age (18-39, 40-49, 50-65 years).

Results: Among our cohort (8.7 million individuals, mean age 41.3, mean eGFR 104.2, median follow-up 9.2 years), a step wise increase in blood pressure was observed elevations in blood pressure observed as early as eGFR<90 in young adults (eg. at eGFR 70-80, ages 18-30: 10.5 events per 1000 person-years(p-y), HR 1.31 (1.27-1.40); ages 40-49: 20.4/1000p-y, HR 1.07 (1.05-1.09); ages 50-65: 31.9/1000p-y, HR 1.03 (1.02-1.04) (figure 1). In addition, HTN was detected in patients with mild to negligeable albuminuria with increasing incidence as GFR declined. Among young adults who developed HTN, CV events were higher, and this increased with modest eGFR reductions.

Conclusions: *HTN* in young adults is associated with modest reductions in eGFR (<70-80) and a higher risk of CV consequences warranting early identification, monitoring, and management.

FR-PO377

Influences of Blood Pressure-Lowering Agents on Frailty Progression in Patients with Type 2 Diabetes: A Longitudinal Cohort Study

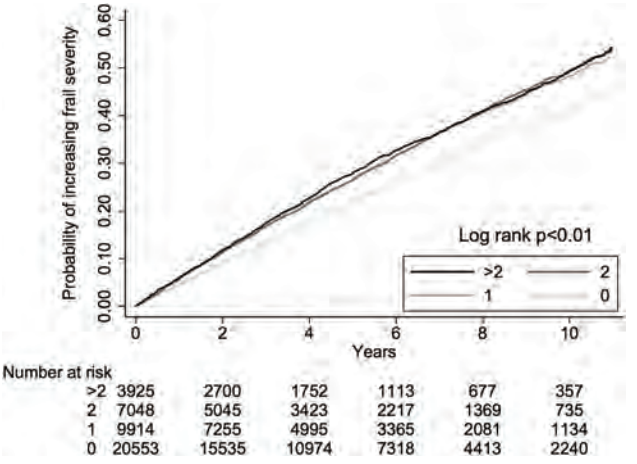
Chia-Ter Chao,[1,2] Jui Wang.[3,1] Cohort of Geriatric Nephrology in NTUH (COGENT Study Group). *[1]National Taiwan University Hospital, Taipei, Taiwan; [2]Min Sheng General Hospital, Taoyuan, Taiwan; [3]National Taiwan University College of Public Health, Taipei, Taiwan.*

Background: Patients with diabetes mellitus (DM) face an elevated risk of developing frailty characterized by increased vulnerability to adverse stimuli. Although the likelihood of frailty development in this population has been explored, few studies investigate the risk factors associated with frailty progression. We examined the influence of different types of blood pressure (BP)-lowering agents on the risk of exacerbating frailty in patients with DM.

Methods: We identified adult patients with type 2 DM from the integrated medical database of National Taiwan University Hospital and its affiliated branches. Clinical variables were recorded and monitored to assess the primary outcome: worsening of frailty. Cox proportional hazards analysis was employed to determine the risk of frailty progression associated with specific classes of BP-lowering agents, adjusting for multiple confounders.

Results: A total of 41,440 patients (mean 64.1 years; 46.3% females) were included, with 27.4% experiencing worsening frailty during 4.09 years of follow-up. The use of at least 1 anti-hypertensive class significant increased the risk of frailty progression (Figure). Cox regression analysis, accounting for potential confounders, revealed that users of diuretics had a significantly higher risk of frailty progression (hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.06-1.18), as did α-blocker users (HR 1.14, 95% CI 1.06-1.23). Conversely, β-blocker users exhibited a significantly reduced risk (HR 0.93, 95% CI 0.88-0.98). Moreover, longer durations and higher dosages of β-blocker use decreased the risk of frailty progression, while diuretics use demonstrated the opposite trend.

Conclusions: Our findings suggest that the choice of BP-lowering agents may significantly impact the risk of frailty progression in patients with DM. Clinicians should carefully consider the potential benefits and risks associated with specific classes of BP-lowering agents when managing hypertensive patients with DM, particularly in relation to frailty-related outcomes.



FR-PO378

Trend Analysis of Hypertensive Heart and Kidney Disease-Related Mortality, 1999-2020

Mohammad Ammar ur Rahman,[1] Ahmed J. Chaudhary,[2] Luqman Munir,[1] Amna Khalid,[1] Muhammad Khan Buhadur Ali,[1] Saleha Azeem.[1] NEURALKEy. *[1]King Edward Medical University, Lahore, Pakistan; [2]Detroit Medical Center, Detroit, MI.*

Background: Hypertensive heart and renal disease is a significant complication of chronic hypertension. Hypertensive heart disease manifests as left ventricular hypertrophy, heart failure, and coronary artery disease, while hypertensive renal disease involves renal parenchymal damage and glomerular injury, leading to progressive kidney dysfunction. In this study, we investigated the increasing mortality rates associated with hypertensive heart and renal disease in the United States from 1999 to 2020. We utilized age-adjusted mortality rates (AAMR) to identify disparities across various epidemiological groups.

Methods: Death certificates from the CDC WONDER (Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research) database were examined spanning the years 1999 to 2020. Analyses included determining age-adjusted mortality rates (AAMR) per 100,000 individuals and calculating the annual percent change (APC) with 95% confidence intervals. Trends among demographic groups, including race, gender, age, and urban/rural classification, were assessed using the Joinpoint Regression Program.

Results: 142,363 mortalities due to Spinal Injuries were reported between 1999 and 2020. Overall AAMR showed an upward trend although inconsistently with an AAPC score of 5.225. From 1999 to 2007, the AAMR showed a decline from 1999 to 2001, with an APC of -19.16 then it showed a steady rise from 2001 to 2014, with an APC of 3.71 and finally it showed a rapid rise from 2014 to 2020 with an APC of 18.56. The AAMR itself rose from 16.405 in 1999 to 48.521 in 2020. The populations with the highest mortality rates were in African Americans and males. The geographical hotspots for mortality were urban and Southern region. Tests for parallelism revealed disparate trends across African Americans and Whites (p=0.00022), Northeastern and Southern regions (p=0.00022) and Large fringe metro and Medium Metro (p=0.00022).

Conclusions: The mortality due to the hypertensive heart and renal disease has been rising since 1999 which is very concerning. Furthermore, the disparity among the demographic variables requires more investigation, and the planning of targeted interventions.

FR-PO379

Exploring High Prevalence and Comorbidities of Autonomous Cortisol Secretion in Primary Aldosteronism: A Cohort Study and Systematic Review

Chun-Fu Lai,[1] Chieh Huang,[2] Li-Yang Chang,[2] Vincent Wu.[1] Taiwan Primary Aldosteronism Investigators (TAIPAI) Study Group. *[1]National Taiwan University Hospital, Taipei, Taiwan; [2]National Taiwan University College of Medicine, Taipei, Taiwan.*

Background: Emerging evidence has suggested a significant prevalence of autonomous cortisol secretion (ACS) among patients diagnosed with primary aldosteronism (PA). Recognizing PA with concurrent ACS is challenging and often complicates patient management.

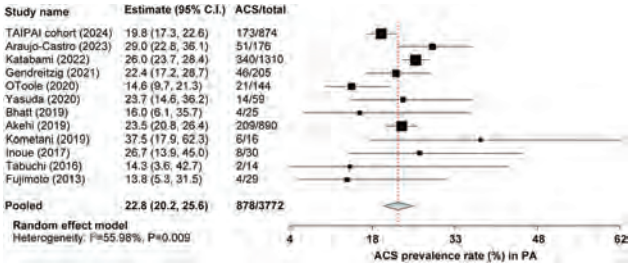
Methods: In the prospectively enrolled Taiwan Primary Aldosteronism Investigators (TAIPAI) cohort, we conducted an evaluation to ascertain the prevalence, characteristics, and comorbidities associated with ACS among 874 patients diagnosed with PA between February 2018 and February 2024. Additionally, we undertook a systematic review and

meta-analysis (CRD42023486755), encompassing publications with comprehensive data up to February 1, 2024, to integrate our findings with global studies for comparative analysis.

Results: Within the TAIPAI cohort (mean age 55.1 ± 11.9 years; female, 52%), a notable proportion (19.8%) of PA patients exhibited ACS. Those with ACS tended to be older (59.4 ± 11.8, *P*< 0.001), have higher aldosterone levels (44.3 ± 31, *P*= 0.003), lower baseline estimated glomerular filtration rates (87.1 ± 29.6, *P*< 0.001), higher glycohemoglobin levels (6.2 ± 1, *P*= 0.019), a greater incidence of adrenal tumors (55.5%, *P*< 0.001) as detected by computed tomography, and larger adrenal tumor sizes(1.86 ± 0.76, *P*< 0.001). The pooled prevalence of ACS among PA patients in the TAIPAI cohort and 11 global studies was 22.8% (95% CI: 20.2, 25.6). [Figure] Significantly, ACS correlated with chronic kidney disease [pooled odds ratio (OR)= 2.09; 95% CI: 1.62, 2.7], diabetes mellitus (pooled OR= 1.63; 95% CI: 1.2, 2.2), and cardiovascular disease (pooled OR=1.63; 95% CI: 1.2, 2.2) among PA patients.

Conclusions: ACS prevalence in PA patients is high, exceeding 20%. There are strong associations between ACS and clinical features of advanced age, impaired kidney function, diabetes, cardiovascular disease, and larger adrenal tumors. These findings underscore the need for vigilant monitoring and prompt detection of ACS in PA patients with these comorbidities.

Funding: Government Support - Non-U.S.



Forest Plot of ACS Prevalence in PA Patients.

FR-PO380

Prognostic Value of Triglyceride Glucose (TyG) Index in a Population with CKD

Jeong-Yeun Lee, Jin Sug Kim, Hyun Kyu Kim, Dae Kyu Kim, Soo-Young Yoon, Kyunghwan Jeong, Hyeon Seok Hwang. *Kyung Hee University Medical Center, Dongdaemun-gu, Seoul, Republic of Korea.*

Background: The triglyceride glucose (TyG) index has been proposed as a reliable marker of insulin resistance and an independent predictor of cardiovascular (CV) event. However, its prognostic value in chronic kidney disease (CKD) remains unclear. This study aims to assess predictive value of the TyG index for clinical outcomes in CKD population.

Methods: This study was conducted using the Korean National Health Insurance Service database. 91,070 individuals with CKD who underwent a national health examination between 2012 and 2015 were enrolled. The study population was divided into four groups based on the quartile of TyG index levels. The primary outcome was a CV event, including myocardial infarction and stroke, and the secondary outcomes were progression to end-stage kidney disease (ESKD) and all-cause mortality.

Results: During a median follow-up time of 80.4 months, CV event, progression to ESKD, and all-cause mortality occurred in 11,676 (12.8%), 3,776 (4.1%) and 13,481 (14.8%) cases, respectively. The cumulative event rate of cardiovascular events, progression to ESKD, and all-cause mortality was the highest among population with TyG quartile 4 (all P < 0.001). In multivariate Cox-regression analysis, a higher TyG index was associated with an increased risk of CV event. Compared with participants in the lowest quartile of TyG index, hazard ratios (HR) and 95% confidence intervals (CI) for CV event were 1.063 (1.008-1.121), 1.104 (1.047-1.165), 1.290 (1.222-1.363) for those in second, third, and fourth quartile of TyG index. The risk of progression to ESKD was also increased as TyG quartile increased [adjusted HR (95% CI) 1.143 (1.027-1.271), 1.282 (1.143-1.437), and 1.826 (1.635-2.039)] for population with TyG quartile 2, 3, and 4, respectively]. However, there was no significant association with an increase in the risk of all-cause mortality.

Conclusions: The TyG index serves as a valuable predictor of CV event, progression to ESKD and all-cause mortality in CKD population.

FR-PO381

Prevalence of Cardiovascular Kidney Metabolic Syndrome among US Hispanic/Latino Participants in the Hispanic Community Health Study/ Study of Latinos, 2008-2011

Amit K. Chakrabarti,[1] Pooja Kondeti,[1] Robert A. Mesa,[1] Yelena Drexler,[1] Julien Tremblay,[1] Linda C. Gallo,[6] James P. Lash,[2] Sylvia E. Rosas,[3] Nora Franceschini,[7] Daniele Massera,[5] Claudia Martinez,[1] Martha L. Daviglus,[2] Matthew Allison,[4] Tali Elfassy.[1] *[1]University of Miami Miller School of Medicine, Miami, FL; [2]University of Illinois Chicago, Chicago, IL; [3]Joslin Diabetes Center, Boston, MA; [4]University of California San Diego Department of Medicine, La Jolla, CA; [5]NYU Langone Health, New York, NY; [6]San Diego State University, San Diego, CA; [7]The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

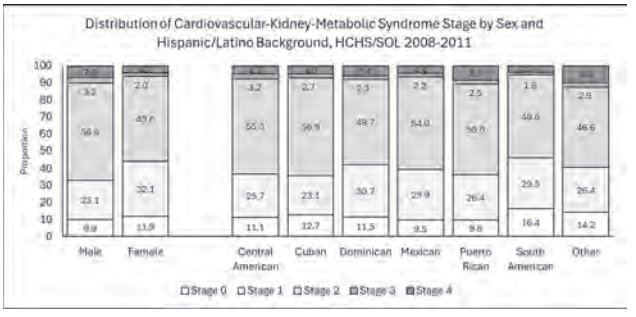
Background: Cardiovascular-Kidney-Metabolic (CKM) syndrome is a staging system that describes the clustering of risk factors and clinical progression of disease at the intersection of metabolic disorders, chronic kidney disease (CKD), and cardiovascular disease (CVD). We described the distribution of CKM stage among diverse US Hispanic/Latino adults.

Methods: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a population-based cohort of Hispanics/Latino adults aged 18-74 years from four US communities. During a comprehensive in person examination (2008-2011), information was collected on: body mass index, waist circumference, glucose tolerance, lipids, blood pressure, metabolic syndrome, CKD, 10-year CVD risk (to define sub-clinical CVD), and self-reported CVD. Participants were classified into four stages of CKM based on American Heart Association definitions: Stage 0 (no risk factors), Stage 1 (excess/ dysfunctional adipose tissue), Stage 2 (metabolic risk factors and CKD), Stage 3 (subclinical CVD in CKM syndrome), and Stage 4 (clinical CVD in CKM syndrome). We estimated the age-standardized prevalence of CKM stage by sex and Hispanic/Latino background. All analyses accounted for the HCHS/SOL complex survey design.

Results: Among the 15,832 participants with complete information, mean age was 41.1 years and 52.3% were female. Overall, 10.9% (SE: 0.4) of participants were in CKM stage 0, 27.7% (SE: 0.6) were in stage 1, 53.4% (SE: 0.6) were in stage 2, 2.5% (SE: 0.2) were in stage 3, and 5.5% (SE: 0.3) were in stage 4. CKM stage differed by sex and Hispanic/Latino background group (Figure, chi-square p values <0.05).

Conclusions: Among diverse US Hispanics/Latinos adults, an absence of CKM risk factors was only observed in roughly one in ten adults, while roughly eight in ten adults had evidence of some cardiometabolic dysfunction.

Funding: NIDDK Support



FR-PO382

Mortality Risks of Cardiovascular-Kidney-Metabolic Syndrome Components Based on a Large Asian Cohort of More than a Half Million Participants

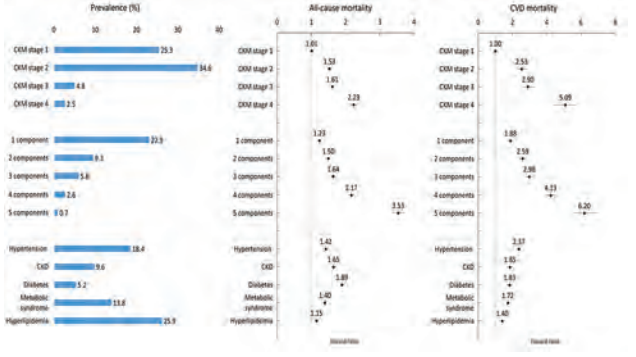
Min Kuang Tsai,[1] Chi Pang Wen,[2] Mei-Yi Wu.[1] *[1]Taipei Medical University Shuang Ho Hospital Ministry of Health and Welfare, New Taipei City, Taiwan; [2]National Health Research Institutes Institute of Population Health Sciences, Zhunan, Taiwan.*

Background: The American Heart Association (AHA) has recently issued guidelines addressing the "Cardiovascular-Kidney-Metabolic (CKM) Syndrome" to mitigate cardiovascular diseases. This interdisciplinary concept of health medicine emphasizes the impact of multiple disease interactions rather than individual disease factors. This study aims to evaluate CKM prevalence and its associated components mortality risks in a substantial Asian cohort.

Methods: The investigation focused on a cohort of 515,602 participants aged 20 years and above enrolled in a health screening program in Taiwan spanning from 1996 to 2017. The study assessed all-cause, cardiovascular disease (CVD) and cause-specific mortality related to CKM stages and its components—hypertension, diabetes, chronic kidney disease, metabolic syndrome, and hyperlipidemia. Multivariate Cox proportional hazards models were employed to calculate hazard ratios (HRs). We use Chiang's life table method to present the years of life lost for each CKM components.

Results: Among this cohort, 67.2% had CKM, with prevalence rates of 25.3%, 34.6%, 4.8%, and 2.5% in Stages 1, 2, 3, and 4, respectively. Among those aged 60 and above, nearly 90% had CKM. CKM was associated with a higher risk of all-cause mortality (HR: 1.37, 95% CI: 1.31-1.43), and CVD mortality (HR: 2.12, 95% CI: 1.89-2.39). Each additional component of CKM was associated with a 23% increase in the risk of death (HR: 1.23, 95% CI: 1.22-1.24) and a 38% increase in the risk of CVD mortality (HR: 1.38, 95% CI: 1.36-1.40) compared to participants without any CKM components. With each additional component, the average life expectancy decreases by 3 years.

Conclusions: The prevalence rates of CKM and its components vary, contributing to distinct risks of mortality. A clustering phenomenon exists among different components, where an increased number of components corresponds to a higher risk of all-cause, CVD mortality and end-stage kidney disease incidence.



FR-PO383

Association between Cardiovascular-Kidney Metabolic (CKM) and Mortality in a Middle- and Older-Aged Asian Population

Charumathi Sabanayagam,[1,3] Pavitra Thyagarajan,[1] Hongwei Ji,[4] Cynthia C. Lim,[2] Tien Yin Wong,[1] Ching-Yu Cheng.[1,3] *[1]Singapore Eye Research Institute, Singapore, Singapore; [2]Singapore General Hospital, Singapore, Singapore; [3]Duke-NUS Medical School, Singapore, Singapore; [4]Tsinghua University, Beijing, China.*

Background: Cardiovascular-kidney metabolic (CKM) Syndrome is recognized by the American Heart Association (AHA) to encompass the interplay among metabolic risk factors, chronic kidney disease (CKD), and cardiovascular disease (CVD). We examined the association between CKM syndrome and all-cause mortality in an Asian population.

Methods: Data for this study was derived from a sample of Chinese, Malay and Indian participants aged 40-80 years (n=6957, men=51.7%) who attended the baseline visit (2004-2011) of the Singapore Epidemiology of Eye Diseases (SEED) study, a population-based cohort study in Singapore. The primary outcome was all-cause mortality obtained by linkage to death registry until 2021. CKM stages (0-4) were defined according to the AHA criteria. As there were few participants in stage 3 (n=31), we combined stages 3 and 4 for analysis. Associations between CKM stages and mortality were assessed using Cox-proportional hazards regression models adjusted for age, sex, and ethnicity, both in the overall population and stratified by sex.

Results: During follow-up (median, 11.8 years), 882 participants died. Most participants were categorized under stage 2 CKM, with prevalence across stages are as follows: 3.2% (stage 0), 7.2% (stage 1), 83.3% (stage 2), and 6.3% (stage 3-4). All-cause mortality was 12.7% (9.3% in women vs. 15.9% in men). CKM stage-specific mortality rates in the overall population were 4.0%, 4.4%, 11.6% and 40.2%. Women had significantly lower mortality than men in all stages ($p<0.05$). In multivariable analysis, compared to stage 0, stage 3-4 CKM showed significant association with all-cause mortality with hazard ratio (HR) (95% confidence interval) of 2.74 (1.39 - 5.38). Sex-specific analysis revealed significant association in stage 3-4 in men only, 2.86 (1.25 - 6.51).

Conclusions: Our findings showed that higher stages of CKM were associated with increased mortality among middle-aged and older Asian adults, particularly in men. Understanding these associations aids in risk stratification and targeted interventions for improved cardiovascular and kidney health outcomes.

FR-PO384

Real-World Analysis of SGLT2 Inhibitors to Prevent Cardiovascular and Kidney Outcomes in Patients with CKD: A Population-Based Cohort Study

Luis Toro, Josefa Valderrama, Diego Polanco. NephroChile Initiative. *Universidad de Chile Facultad de Medicina, Santiago, Chile.*

Background: Randomized clinical trials have shown significant benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in chronic kidney disease (CKD). However, there is little data of real-world effects in this population. The objective of this study was to evaluate the effect in preventing clinical outcomes of SGLT2i in CKD patients, in a real-world population-based cohort.

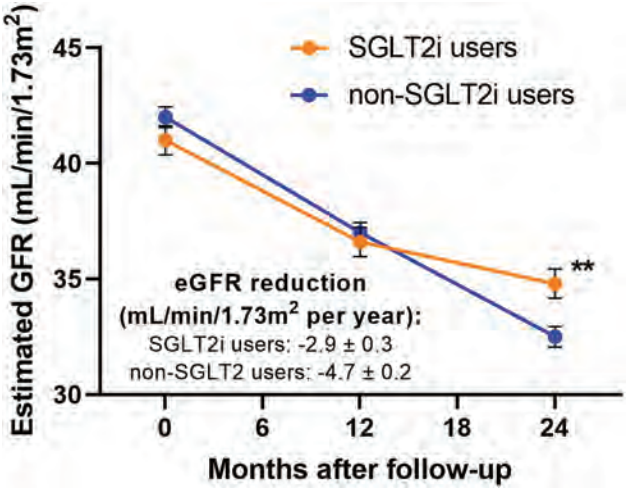
Methods: Observational cohort study of patients > 18 years with CKD (eGFR 20-45 mL/min/1.7m2 or eGFR 45-90 mL/min/1.7m2 with uACR > 200 mg/g) with RAAS blockage, between January 2021 and April 2024. We included patients with and without type 2 diabetes. We performed propensity score matching at a 1:2 ratio. Clinical outcomes were progression of CKD or death from CV causes, reduction of eGFR, development of ESRD, and death from any cause.

Results: We analyzed 3,036 patients, 1,012 SGLT2i users, and 2,024 non-SGLT2 users. Age: 64.5 ± 11.7 years. Female: 1,254 (41.3%). Diabetes: 1,621 (53.3%). eGFR > 45 mL/min/1.7m2: 1,134 (37.3%). eGFR 30-45 mL/min/1.7m2: 1,621 (53.3%). eGFR < 30 mL/min/1.7m2: 281 (9,2%). No baseline differences were present after propensity score matching. Median follow-up: 2.8 years. Patients with SGLT2i had a lower reduction of eGFR than those without SGLT2i (-2.90 ± 0.32 vs. -4.75 ± 0.21 mL/min/1.7m2 per year; p<0.001. Figure 1). Patients with SGLT2i had a lower rate of progression of CKD or death from CV causes (13.9% vs. 19.2%, p<0.001). Multivariate analysis indicated that SGLT2i use was independently associated with reduced adverse clinical outcomes (hazard ratio: 0.71 [0.56-0.88], p<0.001).

Conclusions: Our results indicate that SGLT2 inhibitors have renal and cardiovascular protective effects in real-world conditions. These results support the implementation of current guidelines in clinical practice to improve clinical outcomes in CKD patients.

Study supported by FONDECYT Regular 1221571.

Funding: Government Support - Non-U.S.



FR-PO385

Risk of Target-Organ Damage in Pediatric Patients with CKD and Ambulatory Hypertension: A Systematic Review and Meta-Analysis

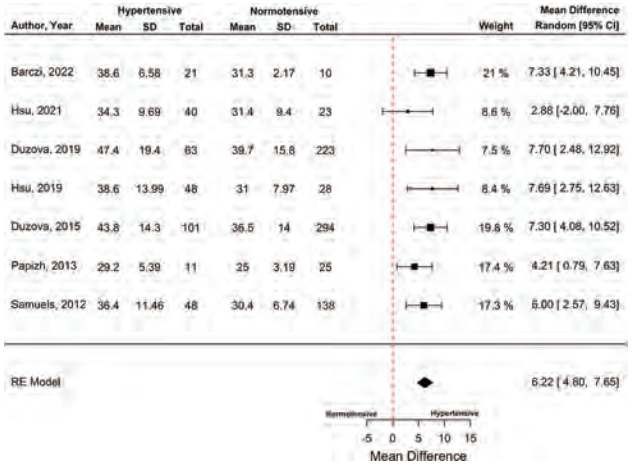
Andrew Yu,[1] Jason Chung,[2] Cal Robinson,[5] Janis M. Dionne,[4] Rulan S. Parekh,[6] Andrew M. South,[7] Mark Mitsnefes,[8] Damien G. Noone,[5] Rahul Chanchlani.[3] *[1]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; [2]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [3]McMaster Children's Hospital, Hamilton, ON, Canada; [4]BC Children's Hospital, Vancouver, BC, Canada; [5]The Hospital for Sick Children, Toronto, ON, Canada; [6]Women's College Hospital, Toronto, ON, Canada; [7]Wake Forest University School of Medicine, Winston-Salem, NC; [8]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

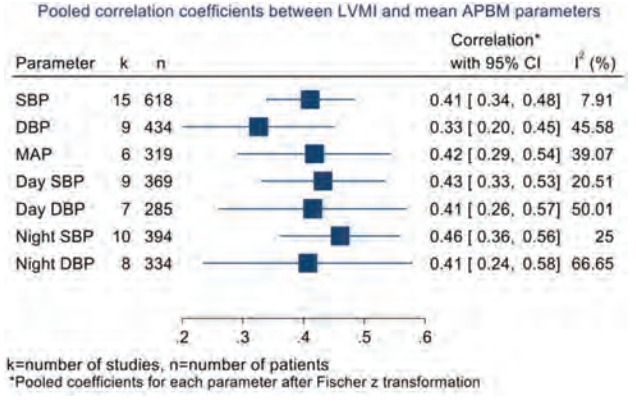
Background: The objective of this systematic review is to determine the association of ambulatory hypertension and various ambulatory blood pressure monitoring (ABPM) parameters with left ventricular mass index (LVMI) in youth with CKD.

Methods: A systematic literature search on nine databases included English publications from 1974-2022. LVMI was indexed to subject height and body surface area ($g/m^{2.7}$). Correlation coefficients were transformed and pooled using a random effects model. All stages of CKD were included for this review. Normative values of ABPM were derived from the German Working Group on Pediatric Hypertension.

Results: Of 1,128 screened studies, 16 studies and 2,254 children and adolescents were included. LVMI was elevated in the CKD hypertensive group compared to the CKD normotensive group (mean difference: 6.22 $g/m^{2.7}$, 95% CI: 4.80-7.65). Youth with hypertension were at 3.34 (95% CI: 2.38-4.68) higher odds of left ventricular hypertrophy compared to normotensive children.

Conclusions: Pediatric CKD patients with ambulatory hypertension especially during nighttime were more likely to have higher LVMI and left ventricular hypertrophy. Adequate blood pressure control among children with CKD may be crucial to avoid the risk of target organ damage and future cardiovascular disease.





FR-PO386

Health Care Resource Utilization and Costs Associated with Childhood Hypertension: A Population-Based Cohort Study

Cal Robinson,[1] Junayd Hussain,[2] Tammy M. Brady,[3] Janis M. Dionne,[4] Sabine Karam,[5] Ashlene M. McKay,[1] Rulan S. Parekh,[6] Rukshana Shroff,[7] Carol Vincent,[8] Rahul Chanchlani.[9] *[1]The Hospital for Sick Children Division of Nephrology, Toronto, ON, Canada; [2]McMaster University Michael G DeGroote School of Medicine, Hamilton, ON, Canada; [3]Johns Hopkins Children's Center, Baltimore, MD; [4]BC Children's Hospital, Vancouver, BC, Canada; [5]University of Minnesota Twin Cities, Minneapolis, MN; [6]Women's College Hospital, Toronto, ON, Canada; [7]University College London, London, United Kingdom; [8]Brenner Children's Hospital and Health Services, Winston-Salem, NC; [9]McMaster Children's Hospital, Hamilton, ON, Canada.*

Background: Pediatric hypertension has risen significantly in recent decades and has been linked to long-term cardiovascular and kidney-related morbidity. However, healthcare resource utilization and costs associated with pediatric hypertension are unclear. This study aims to compare healthcare resource use and costs between children with and without hypertension.

Methods: Population-based retrospective cohort study of children aged 3-18 years diagnosed with hypertension from 1996 to 2021 in Ontario, Canada, using validated case definitions in health administrative databases. Each case was propensity score-matched with five controls without hypertension. Children were followed until death, provincial emigration, or March 31, 2022. Our primary outcome was rates of healthcare system utilization, including hospitalizations, emergency department(ED), and outpatient physician visits, analyzed by negative binomial regression. Secondary outcomes were total healthcare system costs and specialist physician follow-up.

Results: We matched 25,605 children diagnosed with hypertension to 128,025 non-hypertensive controls. Baseline covariates were balanced after propensity score matching. Median age was 15 years[IQR 11-17], 49% were female, and prior comorbidities were uncommon(1% congenital heart disease, 1.7% malignancy, 0.4% diabetes). During median 12.9-year[IQR 6.8-19.9] follow-up, hypertensive children were more likely to be hospitalized(rate ratio [RR] 2.13, 95%CI 2.03-2.22, incidence rate [IR] 105.5 vs 62.8 events per 1000 person-years). Hypertensive children were also more likely to have an ED visit(RR 1.08, 95%CI 1.05-1.11) and outpatient visit(RR 1.33, 95%CI 1.31-1.34). Within 1 year of hypertension diagnosis, 40% of children saw a pediatrician, 24% saw a cardiologist, and 5% saw a nephrologist. Hypertension was associated with substantially higher total healthcare costs throughout follow-up(median $1375 vs. $384 per person-year).

Conclusions: Healthcare utilization and costs were significantly higher among children and adolescents diagnosed with hypertension than matched non-hypertensive children. These results provide a basis for future cost-effectiveness studies of strategies to prevent childhood hypertension occurrence and late complications.

FR-PO387

Racial and Ethnic Disparities in Hypertension Severity and Target Organ Injury at Baseline in Youth Referred for Hypertension Disorders

Elizabeth A. Onugha,[1,2] Ashna Pudupakkam,[1,2] Sahar Siddiqui,[1,2] Andrew M. South,[3] Fallon Campbell,[2,1] Carol Vincent,[3] Giya Harry.[3] *[1]Baylor College of Medicine, Houston, TX; [2]Texas Children's Hospital, Houston, TX; [3]Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC.*

Background: Hypertension (HTN) in youth tracks into adulthood and is associated with subclinical cardiovascular disease. Target organ injury (TOI) is identified in up to 30% of children at HTN diagnosis and is associated with HTN severity. Although racial and ethnic disparities in HTN risk are well established, there is limited data on disparities in the association of HTN severity with TOI in children. We set out to describe racial/ethnic differences in the association between HTN severity and TOI at baseline in youth referred for HTN disorders.

Methods: Retrospective cross-sectional analysis of baseline data from the Study of the Epidemiology of Pediatric Hypertension (SUPERHERO), a multisite Registry of youth referred to subspecialty care for HTN disorders using EHR data. Inclusion criteria were an initial subspecialty clinic visit for HTN disorders identified by ICD-10 codes from 1/1/2016–12/31/2023 and age <19 years. Exclusion criteria were youth on dialysis, kidney transplantation, or pregnancy by ICD-10 codes, as well as missing data. The exposure was stage 1 vs. stage 2HTN based on age, sex, and height-based U.S. guidelines. The outcome was TOI by ICD-10 codes. We conceptualized race/ethnicity as a social construct and defined it as an effect modifier; in this analysis. We estimated the associations with unadjusted generalized linear models with an interaction term and stratified models.

Results: Of the 5,562 participants, mean age was 13.3 years (SD 4.1), 38% were male, 58% were White, 22% were African Americans and 19% were Hispanic/Latino. 39% had stage 2 HTN and 5% had evidence of TOI. The overall TOI risk was 1.3 (95% CL 1.0–1.6). Stratification showed this risk was significant in Black/African American (RR 1.7, 95% CL 1.0–2.7) and Hispanic/Latino participants (RR 1.9, 95% CL 1.1–3.2), but there was no evidence of effect modification by race or ethnicity.

Conclusions: We did not find racial disparities in TOI risk based on HTN severity in our large and diverse multisite cohort of youth referred for hypertension disorders. Future studies will evaluate the impact of BP control on racial disparities in TOI risk.

FR-PO388

Multiple Office Blood Pressure Measurement (mOBPM): A Practical Application for Hypertension Diagnosis in Children

Letizia Dato,[1] Maria Cristina Mancuso,[2] Laura Viola,[3] Giacomo Tamburini,[2] Daniele Rossetti,[2] Andrea Gualtieri,[4] Gianluigi Ardissino.[2] *[1]Università del Piemonte Orientale, Division of Pediatrics, Department of Health Sciences, Novara, Italy; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Nephrology, Dialysis and Transplantation Unit, Milan, Italy; [3]Ospedale di Stato, ISS San Marino, Pediatric Unit, San Marino, San Marino; [4]ISS San Marino, Health Authority, San Marino, San Marino.*

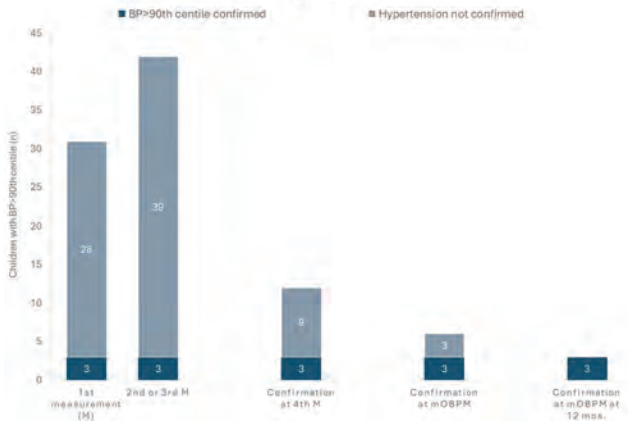
Background: In children office blood pressure (BP) measurement (M) may be unreliable. Multiple office BPM (mOBPM) is the standard practice for hypertension diagnosis in children at our Centre. It consists in taking 10 serial readings at 3-minute intervals by mean of a validated automated oscillometric device, discarding outlier values (<5th and >95th centile), calculating the coefficient of variation (CV) and the mean of the remaining systolic (S) and diastolic (D) BP values through a software. In a previous study, we reported that the first 3 readings are significantly higher than the mOBPM mean, whereas, starting from the 4th one, we found no significant difference. The mOBPM identified a smaller number of subjects with abnormal BP values. This study aimed to test mOBPM as a simple yet effective approach to screen children for hypertension.

Methods: We determined the number of school children with BP>90th centile considering the first 3 readings and the mean of the 2nd and 3rd. Among these, we identified children with pathological BP at 4th M and, subsequently, at mOBPM. Hence, we compared this result with the number of truly hypertensive children confirmed at the mOBPM repeated at 12 months.

Results: One hundred and seventy-five children (93 females, 53%) with a mean age of 8.6±0.3 and a mean BMI of 17.5±2.9 (BMI>20, n=34) were enrolled. Thirteen children were excluded for a CV>15% in SBP or DBP. Figure 1 shows the results. The mean of the 2nd and 3rd M identified 14 children with BP>90th centile, but the 4th showed a further reduction of the number of falsely hypertensive subjects and remains a more practical approach. None of the children with a normal BP value at 4th reading showed a pathological mOBPM result.

Conclusions: Although guidelines recommend 3 readings, our findings suggest that, if the first 3 readings indicate elevated BP values, measuring a 4th value can unmask falsely hypertensive subjects. If the 4th reading is abnormal, we recommend to obtain a complete mOBPM to identify truly hypertensive children.

Figure 1



FR-PO389

Association of Neutrophil-to-Lymphocyte Ratio with Atherosclerotic Cardiovascular Disease and Kidney Outcomes in CKD

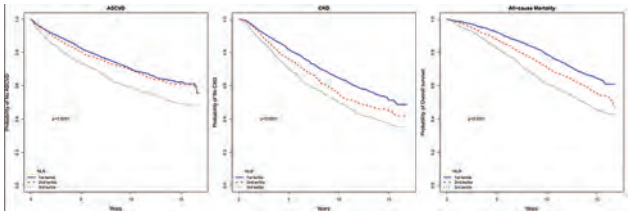
Gauranga Mahalwar,[1] Zhengyi Chen,[2] Edward J. Horwitz,[3] Jonathan J. Taliercio,[1] Mahboob Rahman,[2] Mirela A. Dobre,[2] Andrei Brateanu.[1]
[1]Cleveland Clinic, Cleveland, OH; [2]University Hospitals, Cleveland, OH; [3]MetroHealth Medical Center, Cleveland, OH.

Background: CKD is a highly inflammatory state that results in accelerated atherosclerotic cardiovascular disease (ASCVD). The neutrophil-to-lymphocyte ratio (NLR) is a known inflammatory biomarker related to ASCVD in the general population but is less studied in CKD. We aimed to assess the association between NLR and clinical events in CKD.

Methods: Serum NLR was measured at baseline in 5089 participants with CKD, enrolled in Chronic Renal Insufficiency Cohort (CRIC) study. The primary outcome was a composite incident ASCVD (myocardial infarction, stroke, peripheral arterial disease, and CVD mortality). Secondary outcomes were CKD progression (incident ESKD [either initiation of dialysis or kidney transplantation] or 50% eGFR decline), and all-cause mortality. Cox proportional hazards models were built to investigate the association between NLR tertiles and the time to occurrence of clinical outcomes.

Results: The mean age (SD) was 59.3 (10.8) years and 56% were female. Participants in the highest tertile of NLR were more likely to have diabetes, higher blood pressure, lower eGFR and higher proteinuria levels. Kaplan-Meier curves demonstrated a statistically significant association between higher NLR tertile and clinical outcomes (Figure). In models adjusted for demographics, co-morbidities, medications, eGFR, proteinuria and C-reactive protein, compared to lowest tertile, participants in the highest NLR tertile were more likely to have incident ASCVD (HR 1.27 (1.1, 1.48), p=0.002), CKD progression (HR 1.25 (1.09, 1.44), p=0.002) and all-cause mortality (HR 1.29 (1.12, 1.47), p<0.001).

Conclusions: In a cohort of participants with CKD, elevated NLR levels were associated with a higher risk of ASCVD, progression of CKD and mortality independent of the conventional risk factors. Further research is needed to test whether incorporating NLR into existing risk prediction models would improve their accuracy and facilitate interventions in susceptible CKD patients.



Incidence of the primary ASCVD outcome, kidney events and all-cause mortality by baseline NLR

FR-PO390

Exploring Social Determinants of Hypertension (HTN)

Deepali K. Ernest,[1] Jayna M. Dave,[2] Elizabeth A. Onugha.[2,3] *[1]University of Houston, Houston, TX; [2]Baylor College of Medicine, Houston, TX; [3]Texas Children's Hospital, Houston, TX.*

Background: Many social determinants of health (SDoH) are associated with HTN in adults, but little is known about their contribution to adolescent HTN. We examined the independent and joint effect of common SDoH on HTN among adolescents.

Methods: National Health and Nutrition Examination Survey (2013-2020) data for adolescents 13-18 years were cross-sectionally analyzed. HTN was defined as systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥80mmHg. SDoH included food security, healthcare access, and economic status. SDoH were scored (0=favorable condition, 1=unfavorable condition) and summed to create a joint-impact score (0-9) divided into tertiles. Weighted logistic regression models determined the independent and joint impact of SDoH on HTN risk. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were reported.

Results: Overall 2,623 adolescents were included (mean age=15.4 years, 50% female, and 58.2% White). 2.9% had HTN, 33% had obesity (BMI>95th percentile), 21% were food insecure, 41% received SNAP benefits, 8% had no health insurance, 12% had no routine place for healthcare, and 47% had family poverty index (FPI) ≤1.85. Receiving SNAP benefits was significantly associated with higher odds of HTN (p<0.05). After adjustment for obesity and race/ethnicity, being non-Hispanic Black, receiving SNAP benefits, not having a routine healthcare site, no insurance, foreign-born, English speaking and FPI≤1.85 had increased odds of hypertension. Every 1 unit increase in SDoH score was associated with 11% higher odds of HTN [aOR=1.11; 95% CI: 0.94, 1.32]. Adolescents with SDoH scores in tertile 2 had significantly higher odds of HTN [aOR=2.53; 95% CI: 1.09,5.88; p=0.03] vs. those in tertile 1.

Conclusions: Our findings suggest that SDoH related to food security & assistance, and healthcare access are associated with higher odds of HTN among adolescents and SDoH can cumulatively contribute to the likelihood of HTN in this population.

Table. Comparison of adjusted and unadjusted effects of individual SDoH on hypertension among adolescents (N=2,623)

Characteristics	Odds Ratios (95% CI) Unadjusted	Adjusted ᵃ
Food Security & Assistance		
Food insecurity (Yes vs. No)	0.94 (0.50,1.77)	0.75 (0.42,1.34)
Emergency food provisions (Yes vs. No)	1.07 (0.52,2.20)	0.93 (0.45,1.88)
SNAP Benefits and food stamps (Yes vs. No)	1.83 (1.04,3.2)*	1.58 (0.90,2.77)
Healthcare Access & Utilization		
Routine Healthcare Site (No vs. Yes)	1.87 (0.68,5.08)	1.94 (0.70,5.37)
Current Health Insurance (No vs. Yes)	1.07 (0.45,2.55)	1.00 (0.40,2.48)
Health Insurance past year (No vs. Yes)	1.91 (0.39,9.32)	1.78 (0.31,10.34)
Culture		
Country of Birth (Foreign vs. U.S)	1.14 (0.47,2.75)	1.60 (0.59,4.34)
Family Language (Spanish vs. English)	1.20 (0.52,2.79)	1.21 (0.47,3.08)
Socio-Economic Status		
Family Poverty Index (≤1.85 vs. >1.85)	1.22 (0.63,2.35)	1.04 (0.55,1.96)
SDoH Score		
Tertile 2 vs 1	2.72 (1.31,5.65)*	2.53 (1.09,5.88)*
Tertile 3 vs 1	2.12 (0.93,4.84)	1.91 (0.81,4.50)

* Significant at α=0.05 (p<0.05)
ᵃ adjusted for weight categories and race/ethnicity

FR-PO391

Long-Term Exposure to Nitrogen Dioxide on Cardiovascular Event Risks in Patients with CKD Using Machine Learning-Based Ultra High-Resolution Air Pollution Forecasts

Seung hyun Han,[1] Boram Weon,[1] Ara Ko,[2] Jeonghwan Lee,[1] Dong Ki Kim,[2] Yon Su Kim,[2] Chun Soo Lim,[1] Jung Pyo Lee.[1] *[1]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: Preliminary studies have suggested that nitrogen dioxide (NO_2) is linked to increased cardiovascular risks, yet its impact on individuals with chronic kidney disease (CKD) is not well-documented. This study aims to assess the effect of long-term NO_2 exposure on the risk of major adverse cardiovascular events (MACE) in CKD patients.

Methods: A retrospective cohort study was conducted on CKD patients from two major medical centers in seoul, who visited between 2001 and 2016. Participants without prior cardiovascular diseases history were included, with follow-up until February 2023. Machine learning-based forecasts were used to predict NO_2 exposure levels. The association between NO_2 exposure and MACE (acute myocardial infarction, ischemic stroke, cardiovascular death, or revascularization) was analyzed using a time-varying Cox proportional hazards model.

Results: A total of 39,022 CKD patients were included, and 3,446 of them experienced MACE. After adjusting for multivariable covariates, CKD patients showed a significant increased risk of MACE with each 10 ppb increase in NO_2 concentrations (HR, 1.005; 95% CI, 1.002-1.008). Each MACE component analysis, except for cardiovascular death, showed significant results. In subgroup analyses based on kidney function, non-dialysis CKD patients exhibited a significant increased in MACE incidence risk (HR, 1.006; 95% CI, 1.002-1.010), particularly those with an estimated glomerular filtration rate between 15 and 30 mL/min/1.73m^2 (HR, 1.033, 95% CI, 1.020-1.045).

Conclusions: Chronic NO_2 exposure significantly correlates with an elevated risk of cardiovascular events in CKD patients. This underscores the importance of addressing air pollution as a factor in managing cardiovascular risk among CKD patients, especially for those with CKD stage 4.

Association of NO2 Exposure with MACE and MACE components in CKD patients

	Univariate Model		Multivariate Model	
	HR (95% CI)	p-value	HR (95% CI	p-value
MACE, total	1.01 (1.007,1.013)	< 0.001	1.005 (1.002,1.008)	0.002
Each MACE component				
CV death	1.008(0.999,1.018)	0.086	1.008(0.998,1.018)	0.115
AMI	1.015(1.007,1.024)	< 0.001	1.010(1.002,1.019)	0.021
Coronary revascularization	1.007(1.001,1.013)	0.022	1.006(1.000,1.012)	0.041
Ischemic stroke	1.011(1.007,1.015)	< 0.001	1.005(1.001,1.009)	0.012

FR-PO392

Association of Prevalent Kidney Stone Disease with All-Cause and Cardiovascular Disease Mortality among US Adults

Sandipan Shringi,[1,2] Christina A. Raker,[3] Jie Tang.[1,2] *[1]Rhode Island Hospital, Providence, RI; [2]Brown University Warren Alpert Medical School, Providence, RI; [3]Lifespan Biostatistics, Epidemiology, Research Design, and Informatics Core, Providence, RI.*

Background: Kidney stone (KS) disease is associated with multiple cardiovascular disease (CVD) risk factors. We have reported survival among stone formers from US adults from 1988-1994. We now report all-cause and CVD mortality in prevalent KS disease defined as self-report of any previous episode of KS using updated dataset of US adults from 2007-2018.

Methods: We examined the relationship between KS disease and risk of death among a nationally representative sample of US adults (age ≥20 years) using the National Health and Nutrition Examination Survey (NHANES) 2007-2018 and its linked mortality file. Cox proportional hazard regression analyses were used to estimate the risks of all-cause and CVD death.

Results: 27,959 participants were eligible for the final analysis including 2,689 prevalent KS formers. Stone formers tended to be non-Hispanic, white males, had a higher BMI, and more likely to have hypertension, diabetes, and CVD. There was a total of 2,445 all-cause deaths and 601 CVD deaths. Unadjusted analysis showed that stone formers had a higher risk of death from all-causes (HR 1.63, 95% CI: 1.38-1.93, p<0.001) but not CVD (HR 1.28, 95% CI: 0.94-1.75, p=0.12). However, after multivariate adjustment, stone formers no longer had an increased risk of death from all-causes compared to non-stone formers (HR 0.93, 95% CI: 0.80-1.09, p=0.38). Furthermore, risk of death from CVD after multivariate adjustment was lower in stone formers (HR 0.65, 95% CI: 0.47-0.91, p=0.01). [Table] In comparison, in NHANES III (1988-1994), there was a total of 6,069 all-cause deaths and 1,839 CVD deaths. Unadjusted analysis showed that stone formers had a higher all-cause and CVD mortality, however, there was no independent association of KS disease with all-cause or CVD mortality after multivariate adjustment.

Conclusions: Unlike NHANES III, NHANES 2007-2018 shows that prevalent KS disease is independently associated with lower CVD mortality but not all-cause mortality. Further studies are needed to confirm this finding.

Table: Hazard ratios for all-cause and CVD deaths in stone formers

	NHANES 2007-2018				NHANES 1988-1994			
	All-cause		CVD		All-cause		CVD	
Regression Model	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted	1.63	1.38-1.93	1.28	0.94-1.75	1.79	1.57-2.04	1.94	1.51-2.49
Model 1	1.03	0.89-1.19	0.77	0.56-1.04	1.07	0.95-1.20	1.09	0.87-1.35
Model 2	0.94	0.80-1.09	0.66	0.47-0.92	0.95	0.84-1.09	0.92	0.74-1.15
Model 3	0.93	0.80-1.09	0.65	0.47-0.91	0.95	0.84-1.09	0.93	0.75-1.15

Model 1: Adjusted for age, gender, race, education, insurance.
Model 2: Adjusted for Body mass index, Hypertension, Diabetes, CVD, smoking, alcohol intake, thiazide use, physical activity, eGFR-MDRD, total cholesterol, HDL in addition to model 1.
Model 3: Adjusted for fluid, sodium, potassium, magnesium intake, serum 25(OH) vitamin D in addition to model 2.

Hazard ratios for all-cause and CVD deaths in stone formers

FR-PO393

Kidney Failure Etiology and Modality Worldwide: Apollo Dial DB

Yue Jiao,[1] Melanie Wolf,[2] Kaitlyn R. Croft,[2] Paola Carioni,[3] Mitesh Soni,[1] Anke Winter,[2] Luca Neri,[3] Sheetal Chaudhuri,[1] Kanti Singh,[1] Milind Nikam,[4] Stefano Stuard,[2] Adrian M. Guinsburg,[5] Dinesh K. Chatoth,[1] Jeffrey L. Hymes,[1] Kirill Koulechov,[2] Len A. Usvyat,[1] John W. Larkin,[1] Franklin W. Maddux.[6] *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care, Bad Homburg, Germany; [3]Fresenius Medical Care, Crema, Italy; [4]Fresenius Medical Care, Singapore, Singapore; [5]Fresenius Medical Care, Buenos Aires, Argentina; [6]Fresenius Medical Care AG, Bad Homburg, Germany.*

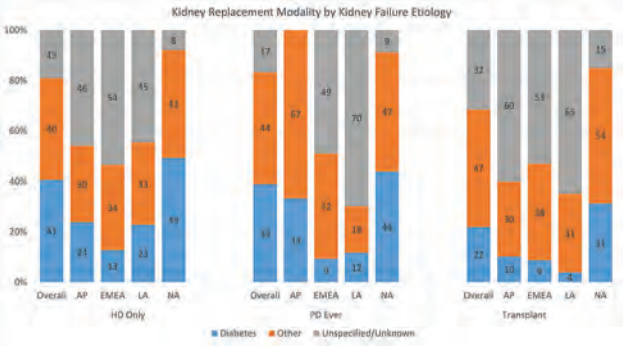
Background: We used a global database representing kidney care across six continents, Apollo Dial DB, to evaluate modality use by kidney failure etiology.

Methods: Apollo Dial DB captures observation-level data (each treatment, lab, value) from 40 countries in a kidney care network (Fresenius Medical Care, Bad Homburg, DE). Data anonymization was performed in alignment with recommendations from a re-identification risk determination (Privacy Analytics, Ontario, CA). The data has >360 variables (demographics, dialysis, diagnoses, labs, medications, surveys, & outcomes) from 01Jan2018-31Mar2021. Kidney failure etiology considered diabetes, other, or unspecified causes. Modality rates after primary dialysis initiation were assessed by etiology group overall, and by world region. Modality use considered hemodialysis (HD) only, peritoneal dialysis (PD) ever, or transplant.

Results: Of 543,169 adults with kidney failure worldwide, 455,769 (80.6%) had a known etiology (diabetes=39.8%, other causes=40.8%, unspecified=19.4%). Overall, 84.8% used HD, 11.0% used PD, and 4.1% used a transplant after dialysis initiation. Modality use by etiology was consistent worldwide for HD and PD, yet kidney failure due to diabetes was associated with lower transplant rates (**Figure 1**). Regional differences were observed, with lower PD and transplant rates for kidney failure due to diabetes in some regions. Further, large regional differences in unspecified kidney failure etiology were present.

Conclusions: Kidney failure etiology appears to influence modality use. About 40% of people with kidney failure due to diabetes use HD and PD, yet transplant rates are >50% lower. Regional variations exist and kidney failure due to diabetes is also associated with lower PD rates in select regions. Unspecified kidney failure etiology varied by region and further analyses are needed.

Funding: Commercial Support - Fresenius Medical Care



FR-PO394

Etiology of Kidney Failure across the World in MONitoring Dialysis Outcomes (MONDO) Dataset

Vladimir Rigodon,[1,2] Yue Jiao,[2] Murilo H. Guedes,[1] Sophanny Tiv,[3] Vincent Peters,[12,7] Melanie Wolf,[4] Kaitlyn R. Croft,[4] Paola Carioni,[5] Anke Winter,[4] Luca Neri,[5] Sheetal Chaudhuri,[2] Milind Nikam,[11] Edwin B. Toffelmire,[6] Constantijn Konings,[7] Stefano Stuard,[5] Rasha H. Hussein,[10] Adrian M. Guinsburg,[9] Roberto Pecoits-Filho,[1] Thyago P. Moraes,[1] Jochen G. Raimann,[8] Xiaoling Ye,[8] John W. Larkin,[2] Peter Kotanko.[8] MONDO Investigators. *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Fresenius Medical Care, Waltham, MA; [3]University of Calgary, Calgary, AB, Canada; [4]Fresenius Medical Care, Bad Homburg, Germany; [5]Fresenius Medical Care, Crema, Italy; [6]Queen's University, Kingston, ON, Canada; [7]Tilburg University, Tilburg, Netherlands; [8]Renal Research Institute, New York, NY; [9]Fresenius Medical Care, Buenos Aires, Argentina; [10]University of Khartoum, Khartoum, Sudan; [11]Fresenius Medical Care, Singapore, Singapore; [12]Catharina Ziekenhuis, Eindhoven, Netherlands.*

Background: **MONDO** initiative is an academic-industry partnership where providers contribute anonymized data to a shared research dataset. We characterized etiology of kidney failure (KF) from the **MONDO 2019** cohort from 41 countries over 20 years.

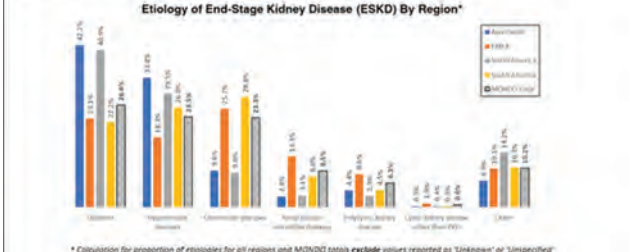
Methods: Nine institutions contributed longitudinal data to **MONDO 2019** (Jan2000-Dec2019). Data anonymization was performed in alignment with recommendations from a re-identification risk determination (Privacy Analytics, Ontario, CA).

Results: MONDO 2019 represents 289,531 patients, of which 170,910 (59.0%) had a known etiology for KF (**Figure 1**). Worldwide, diabetes (DM) was the leading cause of KF (15.8%), followed by hypertensive diseases (HTD, 14.0%) and glomerular diseases (GD,13.9%). Although DM was the leading cause of KF in North America (NA, 35.1%) and Asia-Pacific (AP, 24.2%), GD was the most common cause of KF in Europe-Middle East-Africa (EMEA, 14.9%) and South America (SA, 16.5%). DM was the second leading cause of KF in EMEA (13.4%) and the third leading cause of KF in SA (12.7%). Other regional differences were observed and included HTD being a more common cause of KF in NA (25.3%) and AP (19.4%) than in SA (14.9%) and EMEA (10.6%).

Conclusions: MONDO 2019 dataset shows that the etiology of KF may vary among world regions and warrants further confirmatory investigations, particularly for glomerular disorders associated with DM. These observations are consistent with findings from registries in US and Europe (Stel VS, et al., NDT 2024).

Funding: Commercial Support - Fresenius Medical Care

Figure 1: ESKD Etiologies By Region



* Calculation for proportion of etiologies for all regions and MONDO totals **exclude** values reported as 'Unknown' or 'Unspecified'

	REGION**				
Etiology of Kidney Failure	Asia-Pacific	EMEA	North America	South America	MONDO Total
Unspecified/Unknown	14424 (42.6%)	59627 (42.1%)	2662 (14.2%)	41908 (42.7%)	118621 (40.5%)
Diabetes	8210 (24.2%)	18984 (13.4%)	6583 (35.1%)	12462 (12.7%)	46239 (15.8%)
Hypertensive diseases	6573 (19.4%)	14988 (10.6%)	4747 (25.3%)	14611 (14.9%)	40919 (14%)
Glomerular diseases	1861 (5.5%)	21097 (14.9%)	1444 (7.7%)	16183 (16.5%)	40585 (13.9%)
Other	1339 (4%)	8280 (5.8%)	2279 (12.2%)	5812 (5.9%)	17713 (6.1%)
Renal tubulo-interstitial diseases	551 (1.6%)	10913 (7.7%)	497 (2.7%)	4489 (4.6%)	16450 (5.6%)
Polycystic kidney disease	849 (2.5%)	7062 (5%)	465 (2.5%)	2544 (2.6%)	10920 (3.7%)
Cystic kidney disease other than PKD	55 (0.2%)	796 (0.6%)	84 (0.3%)	169 (0.2%)	1084 (0.4%)
Kidney Failure from All Causes	**33862**	**141750**	**18741**	**98178**	**292531**

** Calculation for proportion of etiologies for all regions and MONDO totals **include** values reported as 'Unknown' or 'Unspecified'.

FR-PO395

Distinguishing among Causes of Death in Patients with Kidney Failure on Hemodialysis

Michelle Tran,[1] Chun Xu,[2] Jonathan A. Wilson,[2] Patti Ephraim,[3] Tariq Shafi,[4] Daniel E. Weiner,[5] Julia J. Scialla,[1,6] Benjamin A. Goldstein.[2] *[1]UVA Health, Charlottesville, VA; [2]Duke University, Durham, NC; [3]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY; [4]Houston Methodist Hospital, Houston, TX; [5]Tufts Medical Center, Boston, MA; [6]University of Virginia Department of Public Health Sciences, Charlottesville, VA.*

Background: Patients treated with maintenance hemodialysis (HD) are at high risk of death from various causes. While predicting all-cause mortality has been shown to be feasible, predicting cause-specific mortality risk could promote personalized treatment. We assessed whether clinical markers can differentiate among distinct causes of death.

Methods: We used electronic health record data from a not-for-profit dialysis provider linked to United States Renal Data System (USRDS) Files for a cohort of adults treated with maintenance in-center HD who died between 2003-2016. We classified USRDS-reported causes of death into five categories: sudden cardiac death (SCD), non-SCD cardiovascular death, infection, other, and unknown. A subcohort was linked to National Death Index (NDI) with similar categories defined. We used gradient boosting trees to discriminate among causes with demographics, vital signs, laboratory measures, health service utilization and comorbidity claims from 30 days prior to death. We created nested case-control populations for each cause of death and used ridge logistic regression to assess clinical factors that associate with distinct causes.

Results: Classification models for USRDS and NDI outcomes had area under the receiver operating curves (AUROCs) between 0.59-0.70 suggesting minimal ability to distinguish among causes of death. In case-control ridge regression models, coefficients were similar across models for distinct causes of death. Correlation of the coefficients across models was very high (Figure) suggesting that most clinical risk factors are shared and do not distinguish among causes.

Conclusions: Using patient-level clinical data from the 30 days prior to death, we were not able to distinguish among causes of death in maintenance HD patients, suggesting that different causes of death in kidney failure either share similar risk factors or that stated causes of death in USRDS or NDI forms are imprecise.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR002553

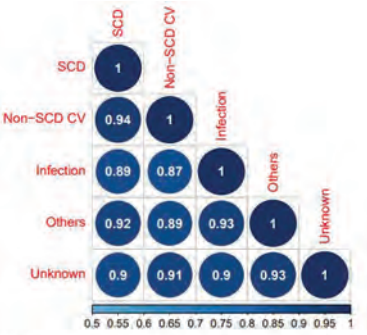


Figure 1. Correlation Plot for Ridge Coefficients for USRDS Cause of Death Using Nested Case-Control Binary Outcome Models Demonstrating High Correlation Across All Models (NDI not pictured)

FR-PO396

Sex- and Cause-Specific Mortality among US Adults Receiving Maintenance Dialysis: A National Cohort Study

Jessica L. Harding,[1] Nanzha Abi,[2] Rachel E. Patzer,[3,4] Ana P. Rossi,[5] Stephen O. Pastan.[1] *[1]Emory University School of Medicine, Atlanta, GA; [2]Emory University Rollins School of Public Health, Atlanta, GA; [3]Indiana University School of Medicine, Indianapolis, IN; [4]Regenstrief Institute Inc, Indianapolis, IN; [5]Piedmont Transplant Center, Atlanta, GA.*

Background: We examined sex differences in cause-specific mortality among incident dialysis patients overall and by age and race.

Methods: We identified adults aged ≥18 years initiating dialysis between 2000 and 2020 from the United States Renal Data System (n=2.16 million; 43.3% women). Cause-specific mortality (cardiovascular (CVD), withdrawal, infection, cancer, and all other causes) was defined from the Centers for Medicare and Medicaid Death Notification Form. All individuals were followed from dialysis start date until date of death, 10-years, or end of follow-up (December 31, 2021), whichever occurred first. Multivariable Cox proportional hazards models assessed the association between sex and cause-specific mortality overall and stratified by age and race.

Results: Overall, 67.9% and 70.7% of men and women died with median survival times of 2.69 and 2.72 years, respectively. CVD was the leading cause of death (38.6% women; 40.2% men), followed by withdrawal (11.1% women; 9.6% men) and infections (9.8% women; 8.6% men). Overall, women had a 9% and 4% increased risk for infection, withdrawal, and other-related mortality compared with men, **Figure**. Conversely, women had a 7% and 10% lower likelihood of CVD and cancer-related mortality, respectively, as compared with men. Younger women (vs. men) aged 18-44 years had higher mortality across all specific causes, while older women (vs. men) aged >75 years had lower risks. Black women (vs. men) had higher mortality across all specific causes, but for all other races, sex differences were similar to the overall population.

Conclusions: Adopting a sex-specific approach that additionally incorporates the intersectionality of age and race is crucial to effectively manage complications and mitigate mortality risk among US dialysis patients.

Figure Association Between Sex and Cause-Specific Mortality Among Adults Initiating Maintenance Dialysis Between 2000 and 2020, with Follow-Up Until December 2021

	Hazard Ratio (95%CI) comparing women to men (reference)															
	CVD		Infection		Withdrawal		Cancer		Other		Unknown		All-cause			
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI		
Total Population																
Crude (women vs. men)	0.88	0.88,0.89	1.16	1.17,1.15	1.16	1.15,1.18	0.83	0.82,0.85	1.05	1.05,1.05	1.04	1.04,1.05	1.03	1.03,1.04		
Adjusted[1] (women vs. men)	0.93	0.92,0.94	1.09	1.08,1.11	1.15	1.14,1.17	0.90	0.87,0.92	1.04	1.02,1.06	0.98	0.97,0.99	0.99	0.98,0.99		
Age[1]																
18-44	1.09	1.05,1.11	1.29	1.19,1.37	1.38	1.26,1.51	1.21	1.01,1.45	1.11	1.04,1.19	1.05	1.03,1.10	1.11	1.09,1.13		
45-64	0.99	0.98,1.00	1.16	1.13,1.20	1.25	1.21,1.32	1.00	0.95,1.05	1.06	1.03,1.10	1.02	0.99,1.01	1.03	1.03,1.04		
65-75	0.91	0.89,0.92	1.12	1.09,1.15	1.18	1.15,1.21	0.88	0.84,0.92	1.04	1.01,1.07	0.95	0.94,0.96	0.98	0.97,0.98		
>75	0.86	0.84,0.87	0.96	0.93,0.98	1.05	1.04,1.08	0.75	0.72,0.79	0.99	0.96,1.02	0.95	0.94,0.97	0.93	0.93,0.94		
P value for interaction	<0.001		<0.001		<0.001		<0.01		<0.05		<0.05		<0.001			
Race[1]																
Non-Hispanic White	0.88	0.87,0.88	1.08	1.06,1.11	1.15	1.13,1.16	0.87	0.84,0.90	1.05	1.02,1.07	0.97	0.96,0.98	0.97	0.97,0.98		
Non-Hispanic Black	1.03	1.01,1.04	1.14	1.10,1.18	1.14	1.11,1.18	0.96	0.93,1.03	1.07	1.03,1.10	1.01	0.99,1.03	1.04	1.03,1.05		
Hispanic	0.96	0.96,1.00	1.07	1.03,1.11	1.16	1.11,1.21	0.87	0.80,0.95	0.98	0.94,1.03	0.93	0.91,0.95	0.99	0.97,1.00		
Other	0.90	0.87,0.93	0.98	0.92,1.05	1.17	1.10,1.25	0.79	0.69,0.90	0.98	0.91,1.05	0.94	0.90,0.97	0.94	0.92,0.96		
P value for interaction	<0.001		<0.05		<0.05		<0.05		<0.05		<0.01		<0.05			

Abbreviations: CVD, cardiovascular diseases; HR, hazard ratios; CI, confidence interval.
[1]Multivariable adjustment for initial dialysis modality, vascular access type, insurance status, body-mass index, smoking status, comorbidities, primary cause of kidney failure and neighborhood-level socioeconomic factors (% Black, % high school educated, % poverty)

FR-PO397

Association of Risk of Death and Hemoglobin (hgb) Variability in Anemia Management of Patients on Hemodialysis

Ariella E. Mermelstein,[3] Tomislav Kovacevic,[1] Yuedong Wang,[2] Doris H. Fuertinger,[4] Jeffrey L. Hymes,[4] Jochen G. Raimann,[3] Peter Kotanko.[3,5] *[1]Vifor Fresenius Medical Care Renal Pharma Ltd, St Gallen, Switzerland; [2]University of California Santa Barbara, Santa Barbara, CA; [3]Renal Research Institute, New York, NY; [4]Fresenius Medical Care Holdings Inc, Waltham, MA; [5]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The current target hgb range for US HD patients treated with erythropoietin-stimulating agents (ESAs) for anemia, is between 10 and 11 g/dL. Earlier retrospective studies show lower mortality rates when hgb was within a range of 10.2 to 12.4 g/dL. This wider range was more favorable independent of hgb variability over

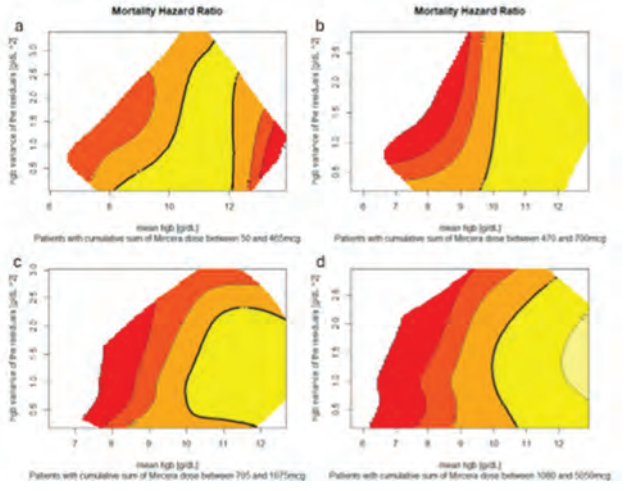
time. For the current analysis we studied hgb variability in different strata of cumulatively administered long-acting ESA (Mircera).

Methods: We defined the baseline period as 6 months from the first ESA dose which had to be administered within 90 days of HD initiation. We calculated patient-specific mean baseline hgb. We fit a linear regression model to calculate the variance of the residuals. We stratified the patient cohort as per the cumulative sum of administered baseline ESA doses (50 to 465, 466 to 700, 701 to 1075, and 1076 to 5050 mcg) and built 4 Cox proportional hazard models of mortality risk over the 18-month follow-up period. Models were adjusted for age, sex, race, diabetes, serum albumin, and phosphorus.

Results: We studied 62,181 HD patients (63.4 years, 57.2% male, 38.8% diabetic, mean baseline hgb 10.42 ± 0.72 g/dL). While a wider and higher range of hgb seems to confer a survival advantage, differences in the patterns in the association between risk of death and hgb are seen at different levels of administered ESA, suggesting variability to increase the risk of death with higher cumulatively administered ESA doses.

Conclusions: Current US guidelines indicate hgb target range of 10 to 11 g/dL when treated with ESAs. Our retrospective research identified a wider and higher hgb range to be associated with lower mortality rates independent of variability. Based on the bivariate investigation, increased variability seems to confer a more accentuated risk increase at higher cumulative ESA doses. In-depth investigation in the underlying pathophysiological dynamics of hgb variability is imperative.

Funding: Commercial Support - Vifor Fresenius Medical Care Pharma Ltd



FR-PO398

Hemoglobin (hgb) Target Range Associated with All-Cause Repeated Hospitalization in Patients on Hemodialysis Treated with Mircera

Ariella E. Mermelstein,[1] Tomislav Kovacevic,[2] Jeffrey L. Hymes,[5] Yuedong Wang,[3] Jochen G. Raimann,[1] Peter Kotanko.[1,4] *[1]Renal Research Institute, New York, NY; [2]Vifor Fresenius Medical Care Renal Pharma Ltd, St Gallen, Switzerland; [3]University of California Santa Barbara, Santa Barbara, CA; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]Fresenius Medical Care Holdings Inc, Waltham, MA.*

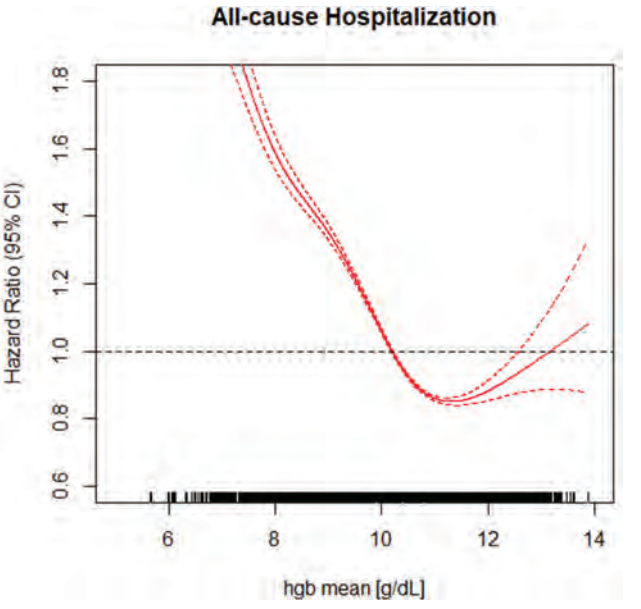
Background: A hgb of 10 to 11 g/dL is recommended for anemia HD patients treated with erythropoietin stimulating agents (ESAs) in the US. However, some recent retrospective analyses have shown lower hospitalization and death rates with higher hgb values than target. We previously studied the mortality risk and found the better range of hgb to be between 10.2 and 12.4 g/dL (Raimann, ASN 2023). We repeated our analyses to determine the risk of repeated hospitalizations for all causes.

Methods: Incident HD patients starting Mircera within 90 days of HD initiation were included. In patients with at least 5 hgb measurements during the 6 month baseline period after first dose of ESA, we quantified the mean hgb. We created a proportional hazard model for repeated hospitalizations in the following 18 months. The hazard ratio was plotted as a univariate spline function versus mean baseline hgb. Model was adjusted for age, sex, race, diabetes, serum albumin, and phosphate.

Results: We studied 62,181 HD patients (63.4 years, 57.2% male, 38.8% diabetic). The mean baseline hgb was 10.42 ± 0.72 g/dL). The hgb range associated with a significantly lower hazard ratio for all-cause hospitalization was 10.1 to 12.2 g/dL.

Conclusions: Current US guidelines call for a hgb target range of 10 to 11 g/dL. In our observational research, we identified a wider and higher hgb range to be associated with lower all-cause hospitalization. Limitations of retrospective research apply. Adequately powered and designed experimental studies are needed.

Funding: Commercial Support - Vifor Fresenius Medical Care Pharma Ltd



Hazard ratio of all-cause repeated hospitalizations and mean baseline hemoglobin quantified with a Cox Proportional Hazards model for repeated events. Adjusted for age, sex, race, diabetes, albumin, and phosphate.

FR-PO399

Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score Predicts the Clinical Prognosis of Patients with ESKD on Hemodialysis

Jin Sug Kim,[1] Jeong-Yeun Lee,[1] Hyun Kyu Kim,[1] Dae Kyu Kim,[1] Soo-Young Yoon,[1] Kyunghwan Jeong,[1] Hyeon Seok Hwang,[1] Yang Gyun Kim.[2] K-cohort Study Group. *[1]Kyung Hee University Medical Center, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea.*

Background: Recently, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score has emerged as a promising index for indicating nutritional status and systemic inflammation. Previous studies have reported its prognostic value in predicting clinical outcomes in various disease conditions. However, only a few studies have analyzed the HALP score in patients with end-stage kidney disease (ESKD) undergoing hemodialysis (HD).

Methods: This study is based on the K-cohort database, a prospective and multi-dialysis center cohort study. Of the 763 incident HD patients enrolled between 2016 and 2022, 543 with available HALP score calculation were included. Patients were divided into two groups (lower and higher HALP score groups) based on the median HALP score. We investigated the predictive value of the HALP score for the occurrence of cardiovascular events and all-cause mortality.

Results: The median HALP score in the study population was 30.7 (interquartile range 22.5-41.3). During a mean follow-up of 42-month, 89 (16.2%) patients experienced cardiovascular events, and 108 (19.7%) all-cause mortality were observed. Patients with a lower HALP score had a significantly higher incidence of cardiovascular events and all-cause mortality compared to patients with a higher HALP score. Multivariable Cox regression analysis revealed that patients with a higher HALP score had a lower risk of cardiovascular events (hazard ratio [HR] 0.540, 95% confidence interval [CI] 0.329-0.888, p = 0.015) and all-cause mortality (HR 0.558, 95% CI 0.363-0.858, p = 0.008) than patients with a lower HALP score.

Conclusions: We have shown that the HALP score is independently associated with cardiovascular events and all-cause mortality in patients with ESKD undergoing HD. The HALP score, which is easily obtained based on some indicators routinely collected during the treatment, may be a useful predictor of cardiovascular events and all-cause mortality in patients with ESKD undergoing HD.

FR-PO400

Impact of Erythropoietin Administration during Hospitalization on Postdischarge Hemoglobin among Patients on Hemodialysis

Mohammed A. Miqdad, Zainulabdeen S. Al-saedi, Lina Alatta, Sheng F. Kuo, Bruce S. Spinowitz. *New York Presbyterian Queens, Flushing, NY.*

Background: Hemoglobin(Hgb) concentration often decreases post hospital discharge among ESKD resulting from underlying cause of hospitalization, absence of erythropoietin (ESA) administration during hospitalization or inadequate dose of

ESA. There is no standardized guideline for management of anemia in such patients. The management may include conservative monitoring, continuation of ESA, or blood transfusion. To achieve quality care and exact cost efficiency, we planned to give all hospitalized ESKD patients 10,000 units per week subcutanoeous. This dose was intended to maintain a level of ESA to prevent apoptosis and maintain Hgb. An analysis of the outcome follows.

Methods: We undertook a retrospective review of the medical records of hemodialysis patients from a single satellite facility admitted to NYP Queens from January to December, 2023. The following data was extracted: Serum Hgb at time of admission, duration of hospital stay, units of blood transfusion, ESA administration during hospitalization, and post discharge hemoglobin upon return to the dialysis facility. The outcome analyzed was post discharge Hgb stability, defined as maintenance of baseline Hgb or increased Hgb concentration. Fisher exact test was utilized for statistical analysis. The Impact on hemoglobin blood transfusion and length of hospital stay were similarly evaluated. All data was gathered and analyzed in an anonymous fashion

Results: 78 patients met the inclusion criteria and have all the required laboratory parameters for review. 36 of these patients received ESA while 42, for unknown reasons, did not receive any ESA dose. This later group, effectively, served as an internal control. The data is displayed below as 2 x 2 tables with calculated P values.

Conclusions: There was no benefit of ESA administration to patients with ESKD during hospitalization, irrespective of length of stay. We speculate that administration of ESA for short-term hospitalization may not be required, resulting in significant cost savings with no negative clinical impact. Further randomized, blinded, multi-dosing ESA trial for patients with ESKD during acute hospitalization may affirm our finding.

	Hgb Stbl	Hgb Dec
ESA +	25	11
ESA -	23	19

All patients (P =NS)

	Hgb Stbl	Hgb Dec
ESA +	20	7
ESA -	21	19

≤10days (P =NS)

	Hgb Stbl	Hgb Dec
ESA +	20	10
ESA -	23	20

All patient/No blood (P = NS)

	Hgb Stbl	Hgb Dec
ESA +	11	7
ESA -	21	18

≤10days/No blood (P = NS)

FR-PO401

Increased Mortality Risk Is Associated with Abnormal Iron Status in Japanese Patients on Hemodialysis: A Nationwide Cohort Study

Hiroki Nishiwaki,[1] Takahiro Imaizumi,[3] Takeshi Hasegawa,[4,2] Takaaki Kosugi,[5] Yukio Maruyama,[6] Kazuhiko Tsuruya,[5] Yasuhiko Ito,[7] Hirokazu Honda,[4] Takahiro Kuragano.[8] *[1]Showa University Fujigaoka Hospital, Yokohama, Japan; [2]Fukushima Kenritsu Ika Daigaku, Fukushima, Japan; [3]Nagoya University, Nagoya, Japan; [4]Showa University, Yokohama, Japan; [5]Nara Medical University, Kashihara, Japan; [6]Jikei University School of Medicine, Minato, Japan; [7]Aichi Medical University, Nagakute, Japan; [8]Hyogo Medical University, Nishinomiya, Japan.*

Background: There have been numerous studies on the characteristics of iron parameters in patients with end-stage kidney disease undergoing hemodialysis (HD), yet it remains unclear whether the interrelationships among these indicators are associated with increased mortality. We investigated the association between the interrelationships of these parameters and 1-year mortality.

Methods: The data utilized in this study were acquired from the Japanese Renal Data Registry (JRDR) database spanning the years 2019 to 2020. This study included patients who were alive and undergoing HD or hemofiltration three times a week without concurrent peritoneal dialysis therapy at the end of 2019. The exposures of interest were ferritin, transferrin saturation (TSAT), iron (Fe), and total iron binding capacity (TIBC). The outcome measure for this study was one-year all-cause mortality. The association between the combination of ferritin and TSAT, and the combination of TIBC and Fe, with mortality at one year was evaluated using contour plots of multivariate Cox proportional hazards models adjusted for the following variables including demographics, cardiovascular disease, laboratory data including C-reactive protein, and medications.

Results: The contour plot for the combination of ferritin and TSAT (Fig1) showed that the hazard ratio (HR) for mortality did not change significantly regardless of the ferritin value in the low TSAT group, but in the high TSAT group, higher ferritin was associated with death; in the combination of Fe and TIBC (Fig2), the HR for mortality was higher in the low Fe group at higher values of TIBC. This relationship disappeared when Fe was above the reference level.

Conclusions: The combination of ferritin and TSAT has been used in a similar approach in pre-dialysis CKD patients in previous studies (Cho 2019 and Guedes 2021), but the results are very different. The reasons for this difference lie in the disparity in populations and the addition of inflammatory markers as adjustment factors.

Figure1

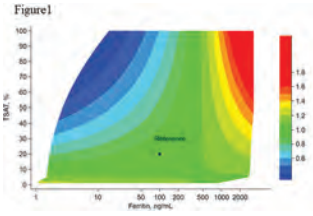
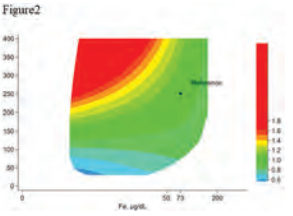


Figure2



FR-PO402

To Be or Not to Be: Elevated Troponin and the Role of Secondary Prevention of Atherosclerotic Cardiovascular Disease in ESKD

Laverne Yip, Ammar A. Vohra, Chee Yao Lim, Kenneth Johan, May Hnin Pwint Soe, Mirtha C. Almanzar, Jorge Gutierrez, Pinal Patel, Juan Martinez Ortega, Rajiv Hans S. Menghrajani, Jiwon Park, Chidinma B. Chijioke, Vidya Menon. *Lincoln Medical Center, Bronx, NY.*

Background: Understanding the association between End-Stage Renal Disease (ESRD) and elevated troponin (cTn) is essential for assessing cardiovascular mortality as well as risk stratification and treatment. Our study aims to analyze mortality rates among ESRD patients with elevated cTn as well as explore the effect of aspirin, beta-blockers and statins on mortality outcomes.

Methods: This single-center observational retrospective study included ESRD patients admitted with elevated cTn from April 2020 to April 2022. Patients with a single cTn measurement on admission, a repeat cTn less than 6 hours from the initial, and admitted for cardiac arrest were excluded from the study. The SONG-HD modified criteria were used to classify the patients into type 1 MI (acute coronary syndrome), type 2 MI (demand ischemia), and chronic cTn elevation groups, and mortality among these was analyzed. Mortality outcomes in patients on aspirin, statin, and beta-blockers were assessed.

Results: 300 patients were included with a mean age of 62±13 years. 60% were male. 48% were Hispanic, 36% Black and 16% were other racial groups. There were no significant differences in mortality rates at admission across Type 1 MI, Type 2 MI, and chronic elevation (p=0.788), and at one year (p=0.699). Aspirin was associated with a significant reduction in mortality at admission (p=0.047) but not at one year (p=0.155). Beta-blockers and statins individually were associated with a significant reduction in mortality both at admission (p=0.001, p=0.005 respectively) and at one year (p=0.049, p=0.024 respectively). When adjusted for age, sex and race, statins were associated with lower mortality odds (OR=0.52, p=0.033) while older age was associated with higher odds (OR=1.024, p= 0.043).

Conclusions: MI subtypes and chronic cTn elevation have comparable mortality. Thus it is vital that diagnostic and therapeutic measures are implemented in all ESRD patients with elevated cTn to improve outcomes. Since ESRD is a low-grade inflammatory state with enhanced risk for atherosclerotic cardiovascular disease, statins, and beta-blockers could benefit ESRD patients. Recent studies have suggested this effect however, more research is needed.

FR-PO403

How Often Do Patients on Haemodialysis Have a Change of Heart? Variability of Troponin I Levels in Patients on Haemodialysis over 1 Year

Ivan Durlen, Petar Babic, Ivana Bedalov Crnkovic. *Dubrava University Hospital, Zagreb, Croatia.*

Background: Patients on chronic haemodialysis (HD) have remarkably higher risk for major adverse cardiovascular events. Haemodynamic and volume changes inbetween dialysis sessions lead to constant cardiac burdain and strain which could increase cardiac troponin levels without signs and symptoms of an acute coronary syndrome (ACS). This makes it more difficult to diagnose acute disorders. Primary goal was to evaluate the basal troponin values of HD patients on their first weekly treatment (the highest volume overload) and observe its oscillations over one year. Our previous trial showed the weekly coefficient of variability (CV) of 20% for troponin in HD patients.

Methods: Data of 55 patients (18 female, 37 male) undergoing chronic HD programme at Dubrava University Hospital were collected after aquiring informed consent. Troponin levels were measured 4 times during the period of one year (every 3 months) while collecting regular monthly tests, using Beckman Coulter High-Sensitivity Troponin I (hs-cTnI) assay - before the first session that week. The upper reference limit (URI) for hs-cTnI is <14.9 ng/L for female patients and <19.8 ng/L for male patients.

Results: The mean hs-cTnI were 30,1 ng/L, 28,0 ng/L, 29,1 ng/L and 33,3 ng/L with mean value of every measurement 29,9 ng/L. The mean values were higher in male patients (33,4 ng/L) than in female patients (22,7 ng/L), but twice more male patients had troponin values in the refference interval, 57% opposed to just 28% in female patients. However, more male patients had troponin values higher than 50 ng/L (6 males, 1 female). Comparing patients on HD and haemodiafiltration (HDF) the average troponine value was two times lower in HD patients (21,9 ng/L) than in HDF patients (43,2 ng/L). The

coefficient of variation was measured for each patient and the mean CV for hs-cTnI values was 31% (3% - 91%) with significant difference between female (26%) and male (34%) patients, and between HD (29%) and HDF (34%) patients.

Conclusions: Our results show that hs-cTnI values were elevated in 53% of patients on chronic HD without signs of ACS. During one year hs-cTnI values had variability of 31%. The variability was lower in female patients (26%) and in patients on HD (29%). Patient's hs-cTnI mean value could be taken as a personal basal value for comparison when diagnosing ACS.

Funding: Government Support - Non-U.S.

FR-PO404

Predictors of New-Onset Atrial Fibrillation in Patients with ESKD: A Multicenter, Retrospective, Observational Cohort Study

Jonathan Mina, Fadi Haddadin, Shaza Almardini, Khalil El Gharib, Suzanne E. El Sayegh. Staten Island Team. *Staten Island University Hospital, Staten Island, NY.*

Background: According to the CDC, A.Fib is the most prevalent heart arrhythmia, cited in 183,321 US deaths in 2019, with 26,535 directly attributed. ESRD is a leading cause of US mortality, impacting 37 million adults. Previous studies link CKD with increased A.fib risk, possibly due to shared risk factors. Our study examines predictive factors for new onset A.fib in ESRD patients at Northwell Health System.

Methods: 6,814 cases of ESRD patients were identified from February 2018 to December 2020. Patients with a prior history of A.Fib were excluded. Patients with missing or extreme BMI data and missing tobacco use data were excluded. Sample size was 5,326. 1,564 diagnosed with ESRD experienced new-onset A.Fib (cases) while 3,762 had no history of A.Fib (controls). Predictors studied were CAD, BMI, Sex, Race, Ethnicity, HTN, Diabetes (DM), and Smoking Status.

Results: Out of the 5,326 ESRD patients, 1,564 (29.4%) were cases, and 3,762 (70.6%) were controls. Increasing age (OR 1.038/yr, p<0.0001), obesity (OR 1.225, p=0.0135), and CAD (OR 1.682, 95%, p<0.0001) were linked to higher odds of A.Fib. African American and other racial patients had decreased odds compared to Whites (OR 0.581 and OR 0.772, respectively). HTN, sex, DM, and smoking did not significantly associate with A.Fib risk.

Conclusions: Age, obesity, and CAD were risk factors for new onset Afib in ESRD, while African American and other racial patients had lower odds compared to Whites. HTN, sex, DM, and smoking showed no significant associations. Further research should delve into underlying mechanisms, explore interventions for A.Fib risk in vulnerable populations, and assess demographic factors' impact on outcomes.

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits		p-value
Age	1.039	1.032	1.045	<0.0001
Sex (Female vs Male)	0.964	0.844	1.101	0.5896
Race Category (African Amer/Black vs White)	0.578	0.494	0.676	<0.0001
Race Category (Asian vs White)	0.795	0.629	1.005	0.0552
Race Category (Multiracial vs White)	0.763	0.598	0.974	0.0301
Ethnic Status (Hispanic/Latino vs Not Hispanic or Latino)	1.058	0.802	1.396	0.6894
BMI (Obese "BMI>30" vs Healthy weight "BMI 20-25")	1.208	1.026	1.422	0.0230
BMI (Overweight "BMI 25-30" vs Healthy weight)	0.955	0.816	1.118	0.5675
BMI (Underweight "BMI<20" vs Healthy weight)	0.879	0.600	1.288	0.5095
DM (Yes vs No)	0.963	0.843	1.100	0.5747
HTN (Yes vs No)	1.120	0.990	1.280	0.060
CAD (Yes vs No)	1.678	1.466	1.920	<0.001
Tobacco Use (Yes vs No)	0.888	0.771	1.022	0.0981

Table: Odds ratio of the different predictors of New-onset Atrial Fibrillation in ESRD patients

FR-PO405

Prevalence and Predictors of Bleeding Events in Patients with ESKD Who Have Autosomal Dominant Polycystic Kidney Disease: A National Database Analysis

Jonathan Mina, Chapman Wei, Fares Saliba, Fadi Haddadin, Ahmad Mustafa, Khalil El Gharib, Suzanne E. El Sayegh. *Staten Island University Hospital, Staten Island, NY.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic disorder characterized by the growth of numerous cysts in the kidneys, often leading to kidney failure and necessitating dialysis. A critical yet underexplored complication in ADPKD patients undergoing dialysis is the incidence and severity of bleeding. This research aims to systematically investigate the prevalence and risk factors of bleeding in ESKD patients with ADPKD.

Methods: ADPKD patients with End Stage Kidney Disease (ESKD) were extracted from the National Inpatient Sample (NIS) database (2016-2018). Demographics, medication history, and comorbidities were extracted from the database using ICD-10 codes. The following bleeding events were analyzed: All Bleeding events, Gastrointestinal (GI) bleeding, Hematuria, Hemorrhagic strokes, Respiratory bleeding, and Other hemorrhages. Patient variables were analyzed using Chi-Square analysis, T-test, and binary logistic regression analysis. P-value < 0.05 was considered significant.

Results: Of the 4255 ADPKD patients with ESKD, there were 185 patients with bleeding events. The most common bleeding event was GI bleed (51.9%), followed by hematuria (36.2%), and hemorrhagic strokes (8.6%). Patients that had bleeding were more likely to be older the 65 years old, have chronic heart failure and have coagulable disorders. After binary logistic regression, the factors that predict bleeding events are chronic heart failure (OR: 1.5 [1.1-2.2]; p=0.02), and obesity (OR:1.6 [1.04-2.32], p=0.03).

Conclusions: In conclusion, 5% of ESKD patients with ADPKD, have a bleeding event. The predictors of bleeding are chronic heart failure and obesity. Larger prospective studies should be performed to corroborate with our findings.

	All Bleeding Events (N=185)	No Bleeding Events (N=4070)	p-value
Age (>65 years old)	63 (34.1)	1103 (27.1)	**0.034***
Sex (Female)	80 (43.2)	1836 (45.1)	0.618
Race			0.245
White	102 (58.6)	2425 (61.5)	
Black	39 (22.4)	726 (18.4)	
Others	43 (29.0)	815 (20.0)	
Cancer	209 (5.1)	11 (5.9)	0.626
Chronic Heart Failure	49 (26.5)	707 (17.4)	**0.002***
Anemia	119 (64.3)	2628 (64.6)	0.946
Dyslipidemia	1176 (28.9)	48 (25.9)	0.386
Coronary Artery Disease	51 (27.6)	930 (22.9)	0.136
Diabetes	48 (25.9)	882 (21.7)	0.169
Obesity	34 (18.4)	560 (13.8)	0.076
Hypertension	19 (10.3)	459 (11.3)	0.671
Coagulable disorders	39 (21.1)	600 (14.7)	**0.018***
Chronic liver disease	17 (9.2)	446 (11.0)	0.450
Oral anticoagulation medications	23 (12.4)	371 (9.1)	0.152

Title: Factors Predicting Bleeding Events in ESKD Patients with ADPKD

FR-PO406

Comparative Outcomes and Risk Analysis of Stroke Incidence in Adult Patients on Dialysis

Sanat Subhash, Haziq H. Rabbani, Rupesh Raina. *Department of Nephrology, Akron Nephrology Associates/Cleveland Clinic Akron General Medical Center, Akron, OH.*

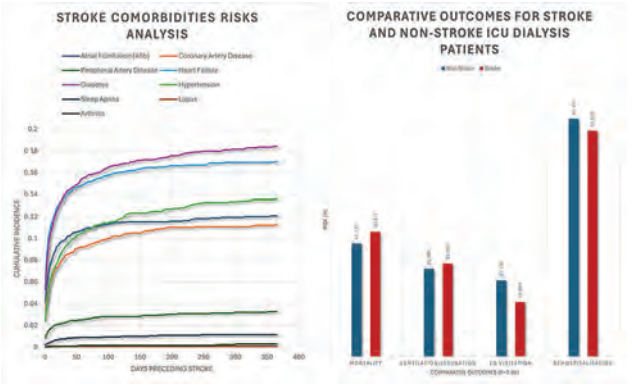
Background: Kidney failure requiring dialysis and its associated costs create substantial burdens on healthcare systems. This study leverages electronic healthcare data to analyze comorbid stroke incidence in ICU dialysis patients over time, characterize stroke epidemiology, and compare outcomes between ICU dialysis stroke patients and non-stroke ICU dialysis patients.

Methods: Using ICD-10 and CPT code queries, adult (18-90 years) ICU patients on dialysis from March 2004 to March 2024 were categorized into three cohorts: (1) non-stroke patients (n=120,414), (2) stroke patients (n=5,750), and (3) ICU dialysis patients (n=128,564). These cohorts were filtered by exclusion factors (kidney transplant status and history of stroke). Cohorts 1 and 2 were propensity-matched for severity of illness (use of vasopressors or ventilation), demographics, diagnoses, medications, and lab values (n=5,698) and used for the comparative outcomes analysis. Cohort 2 pre-matching was also used for the risks analysis, and cohort 3 was used for the incidence and prevalence analysis.

Results: The identified comorbidities for stroke were diabetes (18.42% of patients), heart failure (17.01%), hypertension (13.62%), atrial fibrillation (12.07%), coronary artery disease (11.27%), peripheral artery disease (3.27%), sleep apnea (1.16%), arthritis (0.29%), and lupus (0.08%). ICU dialysis stroke patients had significant increases (p<0.05) in rates of mortality (+4.30%) and ventilation/intubation (+1.98%), while non-stroke

patients had significant increases (p<0.05) in ED visitation (+7.95%) and rehospitalization (+4.42%). ICU readmission rates showed no significant difference (p=0.07). Women and older adults reported higher stroke risk, but there were no significant disparities across racial and ethnic groups.

Conclusions: Stroke has a significant, adverse impact on ICU dialysis patients. Preventative strategies targeting stroke comorbidities are crucial to enhancing patient well-being and mitigating stroke burden.



FR-PO407

Cardiac Arrhythmia and Hypoglycemia in Patients Receiving Hemodialysis with and without Diabetes (the CADDY study): A Danish Multicenter Cohort Study

Dea H. Kofod,[1] Søren Zöga Diederichsen,[1] Tobias Bomholt,[1] Mads Ørbæk Andersen,[1] Ebba Mannheimer,[1] Marianne Rix,[1] Ylian S. Liem,[1] Kristine Lindhard,[2] Henrik P. Hansen,[2] Casper Rydahl,[2] Morten Lindhardt,[3] Kristine D. Schandorff,[4] Julie M. Brøsen,[4] Theis Lange,[6] Kirsten Noergaard,[5] Thomas P. Almdal,[1] Jesper Hastrup H. Svendsen,[1] Bo Feldt-Rasmussen,[1] Mads Hornum.[1]
[1]Rigshospitalet, Kobenhavn, Denmark; [2]Herlev Hospital, Herlev, Denmark; [3]Holbaek Sygehus, Holbaek, Denmark; [4]Nordsjaellands Hospital, Hillerod, Denmark; [5]Steno Diabetes Center Copenhagen, Herlev, Denmark; [6]Kobenhavns Universitet, Kobenhavn, Denmark.

Background: Patients in hemodialysis (HD) are at increased risk of arrhythmias, and dysregulated blood plasma is proposed as a possible risk factor.

Methods: In an 18-month observational cohort study, 70 patients in maintenance HD treatment (35 with diabetes) were monitored with implantable loop recorders and continuous glucose monitoring (CGM). The primary endpoint was the presence of clinically significant arrhythmias (CSA): a combined endpoint of significant bradyarrhythmia, ventricular tachycardia, or ventricular fibrillation. Logistic regressions adjusted for age and sex were used to examine risk factors of CSA.

Results: A total of 1347 CSA were detected in 23 (33%) patients. Table 1 shows CSA and CGM data. Number of hypoglycemic events, time below range, or time above range were not associated with increased odds for CSA (P>0.05), neither in the overall group nor in the diabetes or no-diabetes groups separately.

Conclusions: Patients in HD have a high risk of CSA, but we found no association between CSA and hypoglycemia or time below or above range.

Funding: Commercial Support - Dexcom, Medtronic, Private Foundation Support

Arrhythmias and continuous glucose monitoring data

	All (n=70)	Diabetes (n=35)	No diabetes (n=35)
Patients with at least one CSA event	23 (33)	12 (34)	11 (31)
Number of CSA events	1347	146	1201
Number of CSA events per patient with CSA	7.0 (2.0-37.5)	6.5 (3.5-8.3)	27.0 (1.5-97.0)
CSA subtypes			
Patients with at least one bradyarrhythmia event	18 (26)	8 (23)	10 (29)
Number of bradyarrhythmia events	1335	135	1200
Patients with at least one ventricular tachycardia event	5 (7)	4 (11)	1 (3)
Number of ventricular tachycardia events	12	11	1
Number of ventricular fibrillation events	0	0	0
Continuous glucose monitoring			
Mean sensor glucose (mmol/L)		11.0 (2.6)	6.7 (0.6)
% time above range > 10.0 mmol/L		53.2 (35.1-68.1)	2.4 (0.9-5.8)
% time in range 3.9-10.0 mmol/L		44.6 (31.7-64.3)	93.3 (93.2-97.6)
% time below range < 3.9 mmol/L		0.5 (0.0-1.1)	0.6 (0.0-1.2)
Number of hypoglycemic events		325	539
Patients with at least one hypoglycemic event		27 (77)	32 (91)

Data are presented as mean ± SD, median (interquartile range), or n (%). CSA = clinically significant arrhythmias.

FR-PO408

Predialysis Causal Blood Glucose Level and Mortality in Diabetic Patients on Hemodialysis: A Nationwide Cohort Study from Japan

Shun Manabe,[1] Momoko Seki,[1] Yusuke Ushio,[1] Yuki Kawaguchi,[1,3] Hiroshi Kataoka,[1] Masanori Abe,[2,3] Norio Hanafusa,[1,3] Junichi Hoshino.[1,3] Committee for Renal Data Registry, Japanese Society for Dialysis Therapy.
[1]Tokyo Women's Medical University, Shinjuku-ku, Japan; [2]Nihon University School of Medicine, Itabashi-ku, Japan; [3]Committee for Renal Data Registry, Japanese Society for Dialysis Therapy, Bunkyo-ku, Japan.

Background: Blood glucose level (BGL) is the simplest indicator for glycemic control in diabetic patients; however, it remains unclear which predialysis causal BGL is associated with the lowest mortality in diabetic hemodialysis (HD) patients. We examined the association between predialysis causal BGL and mortality in a cohort from the Japanese Society for Dialysis Therapy.

Methods: We examined maintenance HD patients with diabetes in December 2018, and followed for 3 years. Patients with insufficient dialysis, those with organ transplantation, those with BGL greater than 401 mg/dL, and those with incomplete records for Hb, Alb, or glycemic control were excluded from the analysis. A total of 104,846 patients (29% female; mean age 68.5±11.5; mean dialysis vintage 5.8±5.0 years) were analyzed. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for 3-year mortality after adjusting for 20 potential confounders, including age, sex, dialysis vintage, dialysis modality, vascular complications, smoking, type of diabetes, BMI, use of antihypertensive agents, use of hypoglycemic agents, facility type, Kt/V, nPCR, Hb, Alb, CRP, HDL colesterol, Ca, iP, and PTH. Subgroup analyses were performed in patients with serum Alb <3.5 g/dL and those with malnutritional status by the criteria of Global Leadership Initiative on Malnutrition (GLIM).

Results: We found an U-shaped association between 3-year adjusted mortality and predialysis causal BGLs of ≥141-160 mg/dL [HR 1.10 (1.03-1.17)] and ≥161-180 mg/dL [HR 1.14 (1.06-1.21)], respectively, with the lowest mortality at BGLs of 101-120 mg/dL. Similar U-shaped associations were observed in the sensitivity analyses for patients with malnutritional status, though this trend flattened in these patients. In addition, the adjusted HRs were significantly higher at BGLs of 161-180 mg/dL in patients with low serum Alb (<3.5 mg/dL) [HR 1.11 (1.02-1.22)], and in those with GLIM criteria [HR 1.17 (1.03-1.32)].

Conclusions: Predialysis causal BGL was significantly associated with 3-year mortality in diabetic HD patients. In patients with malnutritional status, such as those with serum Alb < 3.5 mg/dL or those with GLIM criteria, a BGL cutoff of 161-180 mg/dL may represent a promising target for glycemic control in these patients.

FR-PO409

Association of Serum Procalcitonin with All-Cause and Cardiovascular Mortality in Patients with ESKD

Kishan Sinojia,[1] Yamini Mallisetty,[1] Zhongji Han,[1] Chi-Yang Chiu,[1] Jesse C. Seegmiller,[2] Amy B. Karger,[2] Csaba P. Kovesdy,[1] Keiichi Sumida.[1,3]
[1]The University of Tennessee Health Science Center, Memphis, TN; [2]University of Minnesota, Minneapolis, MN; [3]VA Memphis Medical Center, Memphis, TN.

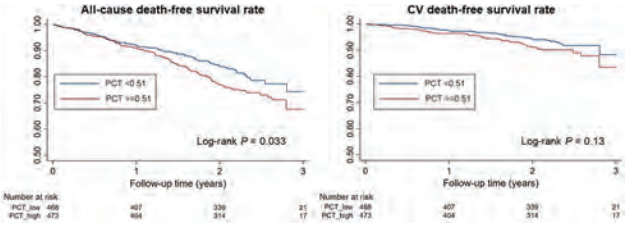
Background: Serum procalcitonin (sPCT) is a diagnostic marker of active bacterial infection. Other conditions may also induce sPCT such as proinflammatory cytokines and non-infectious inflammatory conditions. Elevated sPCT has been associated with poor clinical outcomes like cardiovascular disease (CVD) in various patient populations and even in healthy individuals. However, little is known about sPCT associations with all-cause and CV mortality in patients with end-stage kidney disease (ESKD).

Methods: In a nationwide prospective cohort of 941 patients receiving maintenance hemodialysis from 2011-2013, we examined the association of baseline sPCT with all-cause and CV mortality, using the Kaplan-Meier method and Cox proportional hazards models with adjustment for age, sex, dialysis vintage, vascular access type, BMI, systolic blood pressure, Charlson Comorbidity Index, ischemic heart disease, diabetes mellitus, serum albumin, hemoglobin, white blood cell count, infectious hospitalization, culture-positive bacteremia, and antibiotic or antifungal use. Since a sPCT does not have a universal cut-off interval accepted in dialysis patients, sPCT was treated as a median-stratified binary variable (≥ vs. <0.51 ng/mL).

Results: Overall, patients were 60±13 years old; 53% were male; 40% were African American; and 57% were diabetic. The mean dialysis vintage was 4.3±3.8 years. No patient had clinical evidence of infection at baseline. During a median follow-up of 2.2 years, 204 and 74 patients experienced all-cause and CV death, respectively. The all-cause and CV death rates were higher in those with higher sPCT (log-rank P = 0.033 and 0.13, respectively; Figure). The adjusted hazard ratios [95% CI] of all-cause and CV mortality associated with higher sPCT were 1.48 [1.11-1.98] and 1.67 [1.03-2.69], respectively.

Conclusions: Higher sPCT was significantly associated with higher risk of all-cause and CV mortality in patients with ESKD. sPCT may be a useful biomarker for the risk of premature death even in those without overt infection.

Funding: NIDDK Support



FR-PO410

Associations between Femoral Neck Bone Mineral Density, Kt/Vurea, and Mortality in Patients on Hemodialysis

Sonoo Mizuiri,[1] Yoshiko Nishizawa,[1] Toshiki Doi,[1,2] Aiko Okubo,[1,2] Kenichi Morii,[1,2] Kazuomi Yamashita,[1] Kenichiro Shigemoto,[1] Tomio Mikami,[1] Takao Masaki.[2] *[1]Iryo Hojin Ichiyokai Harada Byoin, Hiroshima, Japan; [2]Hiroshima Daigaku, Higashihiroshima, Japan.*

Background: Several studies have reported the relationships between bone mineral density (BMD), clinical data, and mortality in patients on hemodialysis (HD). However, the relationship between BMD and dialysis efficiency is unclear, and it is unknown which site has a BMD most strongly associated with mortality.

Methods: The cohort comprised 291 patients on maintenance HD. We evaluated the BMD parameters and influence of the BMD at different sites on mortality. BMD, body composition, and clinical data were obtained at baseline and followed up for 3 years. BMD was measured at femoral neck, distal mid-third radius, and lumbar spine using dual energy X-ray absorptiometry. BMD was expressed as percentage of the young adult mean and used to define osteoporosis (BMD<70%), osteopenia (70%≤BMD<80%), and normal BMD (BMD≥80%). Multiple regression analysis for BMD and Kaplan-Meier survival and Cox-Hazard analyses were performed.

Results: The mean age was 65±12 years, 67% were men, the dialysis duration was 73 (36–141) months, and diabetes prevalence was 42.6%. The femoral neck, radius, and lumbar spine were osteoporosis in 118 (40.6%), 90 (30.9%), and 31 (10.7%) patients, respectively, and were osteopenia in 74 (25.4%), 43 (14.8%), and 26 (8.9%) patients, respectively. Compared with the normal BMD group, patients with osteoporosis or osteopenia at all three sites had a significantly higher age, tartrate-resistant acid phosphatase 5b concentration, and Kt/Vurea, but a significantly lower geriatric nutritional risk index, body mass index, and lean tissue index (P<0.05). Kt/Vurea was a significant predictor of the BMD at the femoral neck (β -0.16), radius (β -0.17), and lumbar spine (β -0.23) after adjusting for age, sex, dialysis duration, and diabetes (P<0.05). The 3-year survival rates were 76%, 89%, and 91%, respectively, in patients with osteoporosis, osteopenia, and normal BMD in the femoral neck (P<0.05); but did not differ according to the BMD of the radius and lumbar spine. The femoral neck BMD was a significant predictor of 3-year all-cause mortality, while the radius and lumbar spine BMDs were not.

Conclusions: In patients on maintenance HD, the femoral neck BMD was a significant predictor of 3-year all-cause mortality. The results also suggested an association between BMD and Kt/Vurea.

Funding: Private Foundation Support

FR-PO411

Association of Serum Nickel Concentrations with Clinical Characteristics in Patients with ESKD Undergoing Hemodialysis

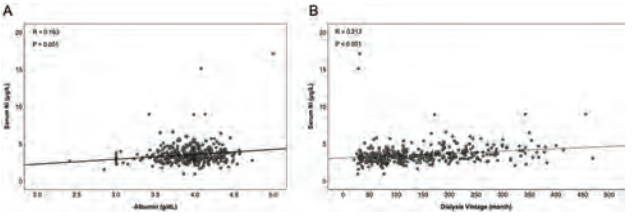
Wen-Yu Ho, Ching-Wei Hsu, Tzung-Hai Yen. Clinical Poison Center, Chang Gung Memorial Hospital. *Department of Nephrology, Chang Gung Memorial Hospital, Taoyuan City, Taiwan.*

Background: Limited studies have investigated serum nickel concentrations in patients with end-stage renal disease (ESRD) undergoing hemodialysis, and the association of serum nickel concentration with dialysis-related profiles is unknown.

Methods: The investigators conducted a prospective cohort study at a tertiary medical center in Taiwan. 409 patients with ESRD undergoing permanent hemodialysis were enrolled. Serum nickel concentrations, hematological and biochemical laboratory data, dialysis-related data, and patient demographics were obtained at baseline. The patients were stratified into 4 quartiles according to serum nickel concentrations. All-cause mortality was recorded after an 18-month follow-up period.

Results: Ninety-eight percent of the patients had elevated serum nickel concentrations compared to the reference value (2 μg/L). There was a significant trend among the four groups, where a greater quartile of serum nickel concentration had higher levels of hemoglobin, albumin, high-density lipoprotein (HDL), and lower levels of white blood cell (WBC), uric acid, triglyceride, and log high-sensitivity C-reactive protein (hs-CRP). Furthermore, a greater quartile of serum nickel had a longer dialysis vintage, higher Kt/V, and higher urea removal rate (URR). Multivariate analysis revealed that albumin level and dialysis vintage were independent factors associated with serum nickel concentration. A positive correlation was observed between albumin level and dialysis vintage with serum nickel concentration (R = 0.163, P = 0.001; R = 0.212, P < 0.001, respectively). There was no statistically significant difference in the all-cause mortality rate across the quartiles.

Conclusions: The majority of ESRD patients undergoing hemodialysis had elevated serum nickel concentrations above the reference level. Longer dialysis vintage and higher albumin level were associated with higher serum nickel concentrations. No association was observed between serum nickel concentration and the all-cause mortality rate.



(A) Correlation between serum nickel and albumin. (B) Correlation between serum nickel and dialysis vintage.

FR-PO412

Multiple Air Pollutant Exposure Is Associated with Higher Risk of All-Cause Mortality in Patients on Dialysis: A French Registry-Based Nationwide Study

Aghiles Hamroun,[1,2] Michaël Génin,[1] François Glowacki,[1] Cécile Couchoud,[3] Florent Occelli.[1] *[1]Centre Hospitalier Universitaire de Lille, Lille, France; [2]Institut Pasteur de Lille, Lille, France; [3]Agence de la biomedecine, La Plaine Saint-Denis, France.*

Background: Little is known about the effect of combined exposure to different air pollutants on mortality in dialysis patients. This study aims to investigate the association of multiple exposure to air pollutants with all-cause and cause-specific death in dialysis patients.

Methods: This registry-based nationwide cohort study included 90,373 adult kidney failure patients initiating maintenance dialysis between 2012 and 2020 identified from the French REIN registry. Estimated mean annual municipality-levels of $PM_{2.5}$, PM_{10} and NO_2 between 2009 and 2020 were combined in different composite air pollution scores to estimate each participant's exposure at the residential place one to three years before dialysis initiation. Adjusted cause-specific Cox proportional hazard models were used to estimate hazard ratios per interquartile range (IQR) greater air pollution score. Effect measure modification was assessed for age, sex, dialysis modality, and baseline comorbidities.

Results: Higher levels of the main air pollution score were associated with a greater rate of all-cause deaths (HR, 1.074 [95% CI, 1.053-1.095] per IQR increase), regardless of the exposure lag. This association was also confirmed in cause-specific analyses, most markedly for infectious mortality (HR, 1.559 [95% CI, 1.365-1.781]). Sensitivity analyses with alternative composite air pollution scores showed consistent findings. Subgroup analyses revealed a significantly stronger association among women and less comorbid patients (Figure 1).

Conclusions: Long-term multiple air pollutant exposure is associated with all-cause and cause-specific mortality among patients receiving maintenance dialysis, suggesting that air pollution may be a significant contributor in the increasing trend of CKD-attributable mortality worldwide.

Funding: Private Foundation Support

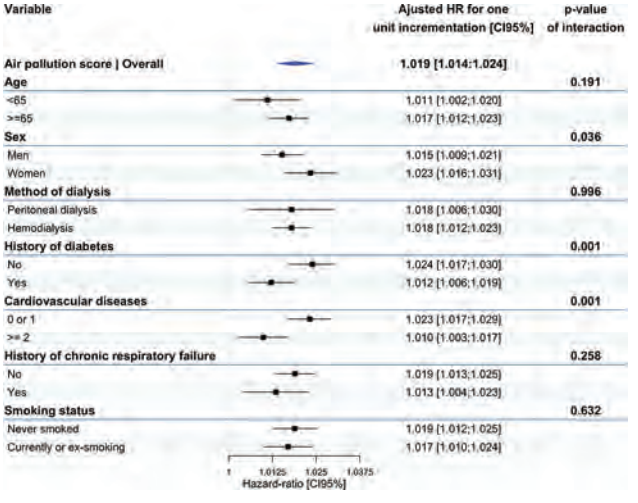


Figure 1. Association between air pollution PCA score and all-cause mortality according to different subgroups.

FR-PO413

Prescription Patterns of Proton-Pump Inhibitors and Antiplatelet Therapy as Risk Factors for Gastrointestinal Bleeding in Patients on Hemodialysis

Michael Che,[1] Sumaiya Ahmed,[1] Ryan J. Chan,[2] Ayub Akbari,[1] Deborah Lynn Zimmerman.[1] *[1]University of Ottawa, Faculty of Medicine, Division of Nephrology, Ottawa, ON, Canada; [2]University of Toronto, Department of Medicine, Division of Nephrology, Toronto, ON, Canada.*

Background: There is an increased risk of gastrointestinal bleeding (GI) in patients with end stage kidney disease (ESKD) for reasons including uremic platelet dysfunction, co-morbid illness, and use of antiplatelet agents. Proton pump inhibitors (PPI) reduce GI bleeding and are recommended for high-risk patients such as those prescribed dual antiplatelet therapy (DAPT). Whether inappropriate prescription of DAPT and/or lack of appropriate use of PPIs contribute to gastrointestinal bleeding risk in hemodialysis patients is not currently known. Thus, the objective of our project was to determine whether patients with ESKD are appropriately prescribed DAPT and PPI therapy.

Methods: A chart review was performed at a satellite hemodialysis unit of The Ottawa Hospital in Ontario, Canada in July 2023. Patients' medical history and use of antiplatelets, PPIs, anticoagulants, non-steroidal anti-inflammatories (NSAIDs), and corticosteroids were identified. Patients' indications for PPI and DAPT were elucidated. Subsequently, a note was added to the electronic medical record and communicated to the patients' primary nephrologist stating if a patient was taking DAPT/PPI and whether these medications were indicated. Adjustments to medications could be made thereafter if needed.

Results: Of 88 hemodialysis patients, 44 were on antiplatelet therapy (4 on DAPT), 1 on NSAID, 12 on corticosteroids, 7 on anticoagulants, 2 on histamine H2-receptor antagonists, and 39 on PPIs. Fourteen percent of PPI users had absolute indication for therapy. One patient in whom PPI therapy was indicated was not prescribed one. Three of 4 DAPT users met current indications for therapy; 1 had a prior indication for DAPT and after review with their primary nephrology team, the patient was reduced to single antiplatelet therapy.

Conclusions: Only one patient in our study had an absolute indication for PPI but had not been prescribed one, and one patient prescribed DAPT no longer met criteria for continued use. Overall, prescribing patterns of DAPT and PPI are unlikely to be a major contributor to the increased risk of gastrointestinal bleeding in patients on hemodialysis at our center. Nevertheless, review of medications and medical history may improve outcomes in patients who have been inappropriately prescribed these therapies.

FR-PO414

Prediction of Gastrointestinal Bleeding Hospitalization Risk in Hemodialysis: Machine Learning vs. Logistic Regression

Suman K. Lama,[1] John W. Larkin,[1] Sheetal Chaudhuri,[1] Yue Jiao,[1] Anke Winter,[2] Manuela Stauss-Grabo,[2] Len A. Usvyat,[1] Jeffrey L. Hymes,[1] Franklin W. Maddux,[3] David C. Wheeler,[4] Peter Stenvinkel,[5] Jürgen Floege.[6] On behalf of the INSPIRE Core Group. *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care Germany, Bad Homburg, Germany; [3]Fresenius Medical Care AG, Bad Homburg, Germany; [4]University College London, London, United Kingdom; [5]Karolinska Universitetsjukhuset Huddinge Njurmedicinska kliniken, Stockholm, Sweden; [6]Rheinisch-Westfalische Technische Hochschule Aachen, Aachen, Germany.*

Background: Gastrointestinal bleeding (GIB) is the most common bleeding event in dialysis. INSPIRE group aimed to see if machine learning (ML) models (XGBoost and logistic regression) can identify GIB related hospitalization risk in hemodialysis (HD) patients.

Methods: We used data from adult dialysis patients treated for ≥30 days at a kidney care network (Jan2018-Mar2021). GIB hospitalization was defined based on ICD diagnosis codes recorded as primary, secondary, or tertiary discharge reason. Two distinct models were created using XGBoost and logistic regression on same dataset. Performance was evaluated using area under receiver operating curve (AUROC), accuracy, sensitivity and specificity. Data was randomly divided into 60% training, 20% test and 20% validation datasets. We used unseen patients and data in test data to evaluate the performance of the model.

Results: Incidence rate of 180-day GIB hospitalization was 1.12% in our test data. AUROC was 0.74 for XGBoost and 0.68 for logistic regression. XGBoost achieved a specificity of 0.68 and a sensitivity of 0.65, while logistic regression demonstrated a specificity of 0.57 and a sensitivity of 0.69. Both models identified age, distribution in anemia/iron indices, recent all-cause hospitalization and bone mineral metabolism markers as strong predictor.

Conclusions: ML modeling has potential to detect of GIB hospitalization risk in hemodialysis patients. XGBoost model outperforms logistic regression, yet both performed well. The link between bone mineral metabolism markers and GI bleeding was not anticipated and merits further investigation. Additional validation may be required to ensure model reliability before implementation in a clinical setting.

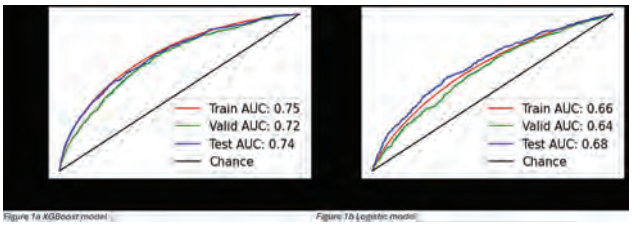


Figure 1 AUROC of GI Bleed model with XGBoost and Logistic Regression model

FR-PO415

Preoperative Kt/Vurea and Postoperative Outcomes in Patients on Maintenance Hemodialysis

Vikram Fielding-Singh,[1] Glenn M. Chertow,[1] Eugene Lin.[2] *[1]Stanford University School of Medicine, Stanford, CA; [2]University of Southern California, Los Angeles, CA.*

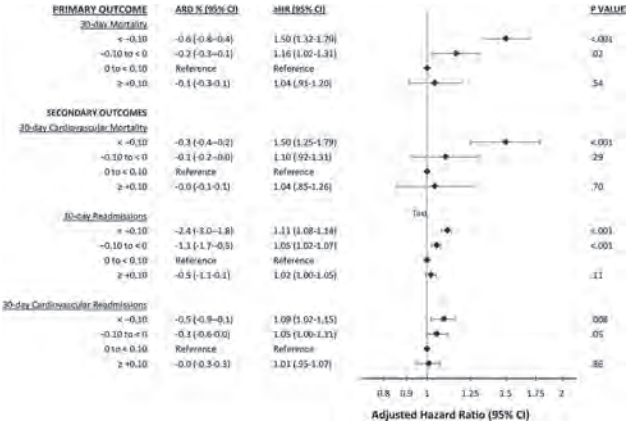
Background: Little is known about whether the hemodialysis prescription prior to surgery affects outcomes. This study investigated the association between changes in preoperative hemodialysis dosing and postoperative outcomes.

Methods: We identified adult patients receiving thrice weekly maintenance hemodialysis who underwent surgical procedures from 2011-2020 in the USRDS. The primary exposure was the difference between the Kt/V_{urea} of the last hemodialysis session prior to the procedure and the patient's average Kt/V_{urea} over the previous 6 months (i.e., whether the preoperative session was lower, the same, or higher than usual). All models included the mean and standard deviation of Kt/V_{urea} values for the 6 months preceding the surgical procedure, in addition to demographic and procedural characteristics. To estimate the association between preoperative deviation in Kt/V_{urea} and postoperative outcomes, we fit multivariable Cox proportional hazards models. A 2-sided $p<0.05$ was considered statistically significant.

Results: Of 151,240 procedures, 31,825 (21.0%) of procedures had a preoperative decrease in Kt/V_{urea} of 0.10 or more, 43,790 (29.0%) had a preoperative decrease in Kt/V_{urea} of less than 0.10, 45,058 (29.8%) had a preoperative increase in Kt/V_{urea} of 0 to <0.10, and 30,567 (20.2%) had a preoperative increase in Kt/V_{urea} of 0.10 or more. In adjusted analysis, compared to patients with a preoperative increase in Kt/V of 0 to <0.10, risk of 30-day mortality was 1.50 (95% CI, 1.32, 1.70) times higher with a preoperative Kt/V decrease of more than 0.10 and was 1.16 (95% CI, 1.02,1.31) times higher with a preoperative Kt/V decrease of less than 0.10.

Conclusions: Among Medicare beneficiaries receiving maintenance hemodialysis, preoperative decreases in Kt/V_{urea} were significantly associated with postoperative mortality.

Funding: Private Foundation Support



Association Between Change in Preoperative Kt/V From 6-Month Baseline Kt/V and Perioperative Outcomes

FR-PO416

Impact of Lupus on Mortality and Causes of Death in Patients on Dialysis: Okinawa Dialysis Study (OKIDS) Registry

Nanako Oshiro,[1] Kentaro Kohagura,[1] Kenya Kusunose,[2] Kunitoshi Iseki.[3]
[1]Dialysis Unit, University of the Ryukyus Hospital, Nishihara-cho, Japan; [2]Department of Cardiovascular Medicine, Nephrology and Neurology, Graduate School of Medicine, University of the Rykyus, Nishihara-cho, Japan; [3]Nakamura Clinic, Urasoe-city, Japan.

Background: Lupus nephritis is one of the most serious complications of systemic lupus erythematosus (SLE), resulting in end-stage kidney disease (ESKD). Despite the introduction of immunosuppressive drugs in the 1990s, a certain number of patients with SLE still develop ESKD. It is known that after dialysis is initiated, SLE patients experience decreased disease activity and can discontinue steroids and immunosuppressive drugs at reduced doses (burn-out). However, it has been reported that hemodialysis patients with SLE have a lower life expectancy than non-SLE patients, although little is known about the causes of death. Our goal was to assess the relative risk of mortality and its causes associated with SLE among dialysis patients in Japan.

Methods: This retrospective longitudinal cohort study using the Okinawa Dialysis Study (OKIDS) registry included all chronic dialysis patients treated in Okinawa, Japan. Kaplan-Meier survival analyses were performed. The study included dialysis patients treated between 1 June 1971 and 31 December 2000, covering the entire OKIDS registry collection period. Patients were censored at death, renal transplantation, or when moving out of Okinawa. Cox proportional hazard models were used to assess whether SLE as a cause of ESKD was associated with an increased risk of death.

Results: A total of 5,246 patients (2,981 male and 2,265 female) were included in this study. There were 111 patients with ESKD secondary to SLE, 87 of whom were female. The patients with ESKD secondary to SLE had a more than 2-fold increased risk of death compared with other patients with ESKD (hazard ratio [HR]: 2.55, 95% confidence interval [CI]: 1.81-3.47, P< 0.0001), after adjusting for age, era at initiation of dialysis, and gender. When the cause of mortality was analyzed, the risk of cardiovascular death (HR: 1.94, 95% CI: 1.13-3.33, P=0.0158) and death due to infection (HR: 4.12, 95% CI: 2.40-7.37, P< 0.0001) were significantly high in SLE patients.

Conclusions: Our study has revealed the heightened mortality risk among dialysis patients secondary to SLE. While dialysis patients with SLE tend to be relatively young, we need to recognize that they constitute a high-risk group for mortality, emphasizing the importance of careful management of their treatment.

FR-PO417

Decreased Risk of Dialysis-Related Amyloidosis in the 2010s: Results from Japanese Nationwide Surveys in 2010 and 2017

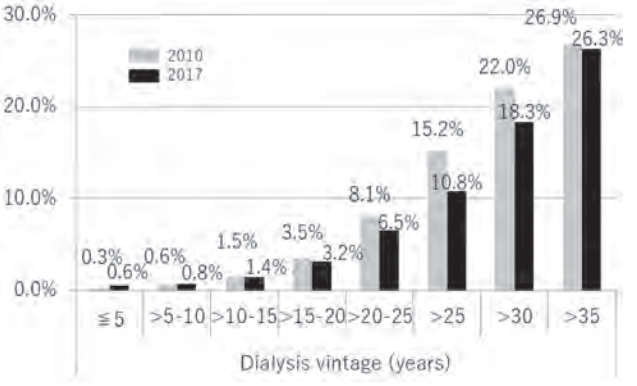
Junichi Hoshino,[1] Yusuke Ushio,[1] Yuki Kawaguchi,[1] Shun Manabe,[1] Hiroshi Kataoka,[1] Suguru Yamamoto,[2] Masanori Abe,[3] Norio Hanafusa.[1] The Committee of Renal Data Registry, the Japanese Society for Dialysis Therapy. *[1]Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan; [2]Niigata Daigaku, Niigata, Japan; [3]Nihon Daigaku, Chiyoda-ku, Japan.*

Background: Incidences and risk factors of dialysis-related amyloidosis may be changed with improvement of dialysis technologies. In this study, we aimed to clarify recent incidences of operation of carpal tunnel syndrome (CTS) by using two large-scale data.

Methods: We used the Japan Renal Data Registries for 2010 and 2017 to compare the crude risk of CTS during the following year, excluding patients with a history of CTS, those who received temporary dialysis or transplantation, and those whose data were incomplete or outliners. The crude risks of new CTS among every 5 years of dialysis vintage up to 35 years or more in the 2010 and 2017 cohorts were analyzed.

Results: A total of 167,793 patients in the 2010 cohort (female, 37%; mean age, 67.4±12.5 years; and mean dialysis vintage, 7.2±6.5 years) and 164,102 patients in the 2017 cohort (female, 35%; mean age, 69.6±12.4 years; and mean dialysis vintage, 7.6±7.0 years) were analyzed. Of the 2010 patients, 1.31% experienced first-time CTS compared with 1.53% of the 2017 cohort. In the 2017 cohort, the crude risks among dialysis vintage 15-20, 20-25, 25-30, 30-35, and over 35 years were 3.2 (95%CI, 2.9-3.5), 6.5 (5.9-7.2), 10.8 (9.7-11.9), 18.3 (16.3-20.5), and 26.3 (23.2-29.6)%, respectively. Those risks were reduced up to 30% from the same dialysis vintage in the 2010 cohort, though the difference was very small in patients with vintage over 35 years.

Conclusions: We previously reported the incidence of first-time onset of CTS was significantly reduced from 1998 to 2010, especially for patients with longer dialysis vintage. The incidence of CTS was also reduced from 2010 to 2017 among the same vintage group, though the degree of reduction was smaller than the previous decade and not observed in patients with dialysis vintage over 35 years.



FR-PO418

Outcomes of Patients with Nonkidney Medical Therapies Dialyzed at Chronic Hemodialysis Centers

Michael A. Kraus, Carol Lee, Amanda Stennett, Lisa E. Koenig, Rheannon Smith, Linda Ficociello, Dinesh K. Chatoth, Jeffrey L. Hymes. *Fresenius Medical Care, Waltham, MA.*

Background: Patients (pts) with non-renal medical therapies (NRMT) such as wearable defibrillators, tracheostomies, continuous cardiac infusions, or left ventricular assist devices (LVAD) may face challenges when seeking dialysis outside of a nursing facility with in-house dialysis or a hospital setting. Fresenius Kidney Care has established policies and a developed process in which requests for dialysis are reviewed by a team of nurses and physicians with collaboration of the dialysis facility. The current analysis aims to determine outcomes of these pts in a chronic hemodialysis unit.

Methods: As part of a quality initiative, we retrospectively assessed time before discharge (due to any reason including renal recovery, transplant, and death) by period (1, 3, 6, and 12 months) for all pts starting treatment 1/22-12/23. At each comparison, only those pts who were eligible for that length of follow-up are included. For the overall analysis, each person is included only once. In the NRMT analysis, a person with multiple NRMT would appear in multiple columns. A group with <5 people (artificial total heart) was not included in the NRMT analysis.

Results: Time on dialysis (no discharge), overall and by NRMT grouping, is shown in table 1. Overall, 87%, 72%, 58%, and 45% of pts were dialyzed at least 1, 3, 6, and 12 months, respectively. There were 0.50 deaths/patient year (py), 0.14 renal recoveries/py, and 0.01 transplants/py. 22% were dialysis dependent AKI and 78% ESKD. Pts with WD were the largest NRMT group, and they had 45% of pts on dialysis at 12 months. In this subgroup, there were 0.48 deaths/patient year (py), 0.13 renal recoveries/py, and 0.01 transplants/py.

Conclusions: Our results show that appropriate pts with destination therapies, NRMT, can be safely cared for at the destination of their choice and do not require life-long institution. Survival, renal recovery and even transplant can be obtained with the assistance of dialysis provided in-center.

Funding: Commercial Support - Fresenius Medical Care

Patients	Overall (one per person)	Non-renal medical therapy			
		wearable defibrillators	continuous cardiac infusion	LVAD	tracheostomy
Patients accepted	942	730	40	64	138
Patients not discharged within 1 months	820 (87%)	637 (87%)	36 (90%)	55 (86%)	107 (77%)
Patients with case start date at least 3 months ago	918	720	39	60	126
Patients not discharged within 3 months	659 (72%)	512 (71%)	27 (69%)	40 (67%)	85 (66%)
Patients with case start date at least 6 months ago	814	641	36	48	109
Patients not discharged within 6 months	476 (58%)	385 (60%)	17 (47%)	18 (38%)	56 (51%)
Patients with case start date at least 12 months	568	463	27	26	61
Patients not discharged within 12 months	256 (45%)	210 (45%)	10 (37%)	8 (31%)	27 (44%)

FR-PO419

A Novel Individualized Patient Performance Scoring System to Predict Hard Outcomes in Patients on Hemodialysis

Carla Santos,[1,2] Carlos Lucas,[1] Eliana Silva,[1] Mathias Haarhaus,[1] Fernando Jose Gordinho R. Macario.[1] *[1]Diaverum AB, Malmo, Sweden; [2]UnIC@RISE, Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal.*

Background: Patients in hemodialysis (HD) face high mortality and hospitalization. This study introduces an individual patient performance score (IPPS) as a novel tool for predicting outcomes in HD.

Methods: Multicenter, retrospective study in 19 countries. Between January and June 2023, patients were categorized into 2 groups based on: 1) survival status; 2) presence of a hospitalization event. IPPS were recorded from 24 months until of the index date. Prediction models were developed incorporating IPPS values, demographic data and quality of life SF-36 survey results of 2021 and 2022. Model discrimination was evaluated by the area under the curve (AUC) and 95% confidence intervals (CI). IPPS were developed as a combined score of 8 major key areas: Vascular Access (20 points): type of VA, episodes of thrombosis and infection; HD adequacy (20): eKt/V, blood flow and treatment time; Anemia (20): hemoglobin, transferrin saturation, ferritin; Arterial hypertension (10); Mineral Bone disease, MBD (15): iPTH, phosphorus and calcium; Fluid status (5): percentage of fluid gain; Nutrition (5): albumin and phosphorus and Others (5): influenzae vaccination, transplantation status and previous hospitalization. The final score is obtained by the weighted sum of positive and negative factors, ranging from 0 to 100 and with a higher score representing a better medical performance.

Results: 41,125 patients were included, with significant differences in mean IPPS observed between the surviving and deceased groups up to 24 months prior to death and the hospitalized and non-hospitalized groups up to 12 months of the event. This difference was observed in all IPPS areas, with the exception of MBD for death. Multiple logistic regression showed a 4% independent reduction in the odds of death and a 3% independent reduction in the odds of hospitalization with the increase of 1 point in global IPPS ($p<0.01$). Predictive model demonstrated a very good discrimination for mortality (AUC of 0.76 [0.75; 0.78]) and a good discrimination for hospitalization (AUC of 0.70 [0.69; 0.71]).

Conclusions: IPPS showed a strong correlation with patient survival and hospitalization. The incorporation of IPPS into HD patient care evaluation emerges as an effective strategy for improving critical outcomes, such as mortality and hospitalization.

FR-PO420

External Validation of Models to Predict Risk of Major Cardiovascular Events and Death for People with Kidney Failure Having Noncardiac Surgery

Gurpreet S. Pabla,[1] Tyrone Harrison,[2] Navdeep Tangri,[3,4] Reid Whitlock,[4] Thomas W. Ferguson.[4] *[1]University of Manitoba Faculty of Health Sciences, Winnipeg, MB, Canada; [2]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [3]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [4]Seven Oaks General Hospital, Winnipeg, MB, Canada.*

Background: Patients with kidney failure undergoing non-cardiac surgery have a significantly higher risk of adverse cardiovascular events and mortality compared to people with normal kidney function. Existing tools for perioperative risk stratification are not valid for patients with kidney failure. Recently, three risk prediction models were developed from a population-based cohort of people with kidney failure in Alberta, Canada. We externally validated the established Alberta models for major cardiovascular events and mortality in patients with kidney failure within 30 days of non-cardiac surgery in Manitoba, Canada.

Methods: Data was sourced from the Manitoba Centre for Health Policy. The cohort included adults (≥ 18 years) with pre-existing kidney failure (estimated glomerular filtration rate < 15 mL/min/1.73m^2 or on maintenance dialysis) undergoing non-cardiac surgery procedures between April 1, 2007, and December 31, 2019. The primary outcome of this study was a composite of acute myocardial infarction, cardiac arrest, ventricular arrhythmia, and all-cause mortality. The models performance was evaluated using C-statistics, Brier scores, and calibration on Manitoba data using two approaches: 1. Model deployment: Used coefficients from the Alberta models to predict outcomes on Manitoba data. 2. Model refitting: Re-estimated model coefficients using logistic regression on Manitoba data while maintaining the same variables as the Alberta models.

Results: We identified 12,082 surgeries and 569 outcomes (5%). All three models performed well with both approaches, with C-statistics ranging from 0.82 for model 1 to 0.87 for model 3 in the first approach. The calibration slopes for models 1, 2, and 3 were 1.3, 1.4, and 1.2, respectively. Once refit, discrimination remained strong with C-statistics ranging from 0.83 (model 1) to 0.86 (model 3). Calibration slopes were 1 across all the models. Brier scores were consistently low at 0.04 for all the models in both approaches.

Conclusions: Our external validation study confirms the original Alberta models' robustness in a geographically distinct Canadian population. Future research should test the impact of these models in clinical care.

Funding: Government Support - Non-U.S.

FR-PO421

Dialysis after Graft Loss: Preliminary Findings of a Large Multinational Database

Oshini Shivakumar,[1] Xiaoling Ye,[2] John W. Larkin,[3] Peter Kotanko,[2] Benjamin E. Hippen,[3] Adrian M. Guinsburg,[4] Jochen G. Raimann,[2] Damien Ashby,[5] Frederick W. Tam,[5] Hutan Ashrafian.[1] *[1]Imperial College London Institute of Global Health Innovation, London, United Kingdom; [2]Renal Research Institute, New York, NY; [3]Fresenius Medical Care Holdings Inc, Waltham, MA; [4]Fresenius Medical Care Argentina SA, Buenos Aires, Argentina; [5]Imperial College Healthcare NHS Trust, London, United Kingdom.*

Background: Dialysis after graft loss(DAGL) make a significant proportion of new dialysis starters; historically reported to have increased mortality compared to transplant-naive(T-N) starters(**Figure1**). This study examines the mortality risk of DAGL compared to T-Ndialysis starters, to ascertain if the former warrant dedicated care.

Methods: A retrospective observational study. All adult patients who started haemodialysis in Fresenius Medical Care from 1stJanuary 2018 to 31stMarch 2021 were identified in the Apollo DialDB dataset. DAGL identified using ICD10 codes 'Kidney transplant failure','Unspecified complication of kidney transplant' and 'Other complication of kidney transplant'. The T-N control group had never received a kidney transplant and had not received immunosuppressants in the first six months of dialysis start.

Results: A total of 360,469 haemodialysis patients from 40countries included in the analysis. 10,010 patients on DAGL, and 350,459 in T-N control group. In univariate analysis, DAGL patients were significantly younger in all age categories and had a higher proportion of male sex. Serum creatinine, ferritin, phosphate and neutrophil-to-lymphocyte ratio were higher in the DAGL group. Haemoglobin was lower in the DAGL group(**Table 1**). In the Cox proportional model adjusted for age, gender, and laboratory markers, patients with DAGL had an equivalent survival probability compared to T-N dialysis starters(HR:0.93,95%CI:0.86,1.02)(**Table 2**).

Conclusions: This preliminary analysis is in line with recent publications of a more equivalent survival in the two groups. Our results are congruous with younger patients receiving kidney transplant early in their renal replacement therapy journey. We posit that DAGL patients may start dialysis at a lower level of renal function, and higher levels of inflammation. We aim to adjust for confounding factors, to present further refined mortality risk comparison by Autumn2024.

Table 1. Summary of patient characteristics in the study group and control group.

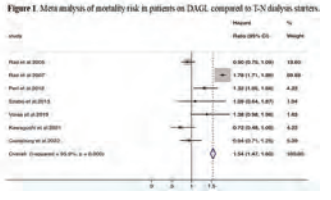
	Transplant naïve (T-N) dialysis starters N = 350,459	*Dialysis after Graft Loss (DAGL)* N = 10,010	*P-value*
Age [years]			
18-44	5,6507 (16%)	3,805 (38%)	<0.0001
45-64	143,221 (41%)	4,488 (45%)	<0.0001
65-74	85,312 (24%)	1,372 (14%)	<0.0001
>=75	65,419 (19%)	345 (3%)	<0.0001
Male [%]	204,615 (58%)	5,984 (60%)	0.0222
Serum Albumin [g/dL]	3.5 (0.5)	3.5 (0.4)	<0.0001
Serum Creatinine [mg/dL]	6.2 (2.6)	7.0 (2.9)	<0.0001
Ferritin [ng/mL]	580 (568)	720 (550)	0.0435
Hgb [g/dL]	10.2 (1.2)	10.0 (1.1)	<0.0001
Serum phosphate [mg/dL]	5.0 (1.3)	5.1 (1.3)	0.0073
NLR	5.5 (23.0)	6.5 (13.4)	<0.0001
MLR	0.5 (1.6)	0.5 (0.4)	<0.0001

Hgb = Haemoglobin, NLR = Neutrophil-to-lymphocyte ratio, MLR = Monocyte-to-lymphocyte ratio.

Table 2. Hazard ratio for all-cause mortality in Cox proportional hazards model.

	HR	*95% CI*	*P-value*
DAGL	0.93	(0.86, 1.02)	0.1287
Age (45-64 vs 18-44)	1.54	(1.46, 1.62)	<0.0001
Age (65-74 vs 18-44)	2.18	(2.07, 2.30)	<0.0001
Age (>= 75 vs 18-44)	2.89	(2.74, 3.05)	<0.0001
Male vs female	1.2	(1.18, 1.23)	<0.0001
Serum Albumin [g/dL]	0.44	(0.43, 0.45)	<0.0001
Serum Creatinine [mg/dL]	1	(1.00, 1.00)	0.0126
Ferritin [ng/mL]	0.74	(0.73, 075)	<0.0001
Hgb [g/dL]	0.92	(0.91, 0.92)	<0.0001
Serum phosphate [mg/dL]	1.05	(1.04, 1.06)	<0.0001
MLR	1.02	(1.01, 1.02)	<0.0001

Figure 1. Meta analysis of mortality risk in patients on DAGL compared to T-N dialysis starters.



FR-PO422

Is the Rate of Resolution of Bacteraemia in Patients Dialysing with Lines Dependent on the Type of Organism Isolated?

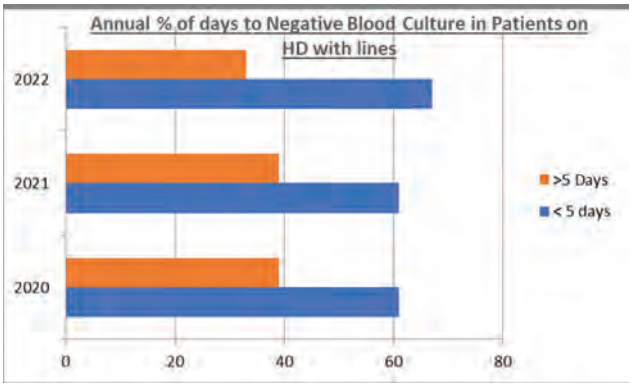
David Makanjuola, Olusegun O. Olalowo, Jahanzaib Chatha, Takudzwa J. Dhlandhlara, Christy R. Ratnakumar. *Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.*

Background: Infection is a common cause of morbidity and mortality in patients on haemodialysis (HD). The majority of bacteraemias are related to the vascular access, with a greater incidence in patients dialysing through lines. We looked at our dialysis cohort to see whether the rate of resolution of the bacteraemia in patients dialysing with lines was dependent on the type of organism isolated.

Methods: Retrospective review of patients on HD who had bacteraemias between 2020 to 2022. Data collected included blood culture results, time to negativity, and organisms isolated. Patients were split into: group A (GA) – those where cultures became negative within 5 days, and group B (GB), those with negative cultures after > 5 days.

Results: Complete data were available in 111 episodes of bacteraemia in 84 patients. 45 were male. Time to negative blood culture was 1 to 26 days. GA had 69 patients with negative cultures within 5 days, and GB, 41 with negative cultures >5 days. In GA, 48 (69%) were Gram positive organisms, 46 (95.8%), were staphylococci, of which 60% were coagulase negative, and 20 (29%) were Gram negative. In GB, 24 (58.5%) were Gram positive organisms, all were staphylococci, of which 67% were coagulase negative, and 17 (41%) were Gram negative. The percentage of patients in both groups was similar over the 3 years (figure 1).

Conclusions: We did not find a significant difference in the types of organisms causing the bacteraemia and the time to resolution, but there was a suggestion that patients with Gram negative bacteraemias may take a bit longer to resolve.



FR-PO423

Bloodstream Infection Standardized Infection Ratios among ESKD Networks

Leticia A. Lamping,[1,2] Jose E. Navarrete,[1,6] Bria M. Jarrell,[1,3] Tamara L. Hoxworth,[1,2] John Keenan,[1,4] Kira Barbre,[1,4] Lu Meng,[1] Stephanie Clark,[5] Delia Houseal,[5] Shannon Novosad,[1] Jonathan Edwards,[1] Andrea L. Benin,[1] Jeneita Bell.[1] *[1]Centers for Disease Control and Prevention, Atlanta, GA; [2]Chenega Corp, Anchorage, AK; [3]Leidos Inc, Reston, VA; [4]Goldbelt Inc, Juneau, AK; [5]Centers for Medicare and Medicaid Services, Baltimore, MD; [6]Emory University, Atlanta, GA.*

Background: Individuals receiving hemodialysis are at increased risk for bloodstream infections (BSIs), and risk varies by vascular access type and sociodemographic characteristics. The Centers for Medicare and Medicaid Services' End Stage Renal Disease Quality Incentive Program (ESRD QIP) tracks the quality of dialysis care, including bloodstream infections. The ESRD Network Program is the administrative governing body for the ESRD QIP. There are 18 geographically defined ESRD Programs that serve the US and its territories to improve cost-effectiveness, ensure and improve quality of care for dialysis patients, encourage kidney transplantation and home dialysis, and assist patients to return to work. We compared BSI standardized infection ratios (SIRs) across the 18 ESRD network regions between 2018 and 2022.

Methods: This study included data reported to the CDC's National Healthcare Safety Network (NHSN) by outpatient dialysis facilities from 2018-2022. SIRs were calculated as the number of observed infections over the number of predicted infections based on 2014 national aggregate data. A SIR of <1 indicated that fewer BSIs occurred than expected. Pooled SIRs were calculated for each region for each year. The 18 ESRD regions were anonymized using alphabetic codes assigned based on highest to lowest 2018 SIR. The Goodman Kruskal Gamma statistic was used to examine whether the rank order of BSI SIRs among 18 ESRD regions varied significantly between 2018 and 2022.

Results: A total of 6,516 and 6,709 outpatient hemodialysis facilities reported data for 2018 and 2022, respectively. The overall pooled BSI SIR was 0.724 (95% CI 0.715-0.734) in 2018 and 0.367 (95% CI 0.361-0.373) in 2022. Compared to 2018, all ESRD regions had significantly lower SIRs in 2022 ($p<0.05$). The Goodman Kruskal Gamma statistic was 0.3, indicating substantial shifts in regions' SIR rankings between 2018 and 2022. Rankings improved by 6 or more for ESRD networks K, O, and Q in the South, and Network P in the Midwest.

Conclusions: BSI SIRs improved from 2018 to 2022 and the rank order of BSI SIRs by region changed significantly over this time. Further investigation of changes in sociodemographics and facility-level characteristics by ESRD region is warranted.

FR-PO424

Anticoagulation in Dialysis Vascular Access

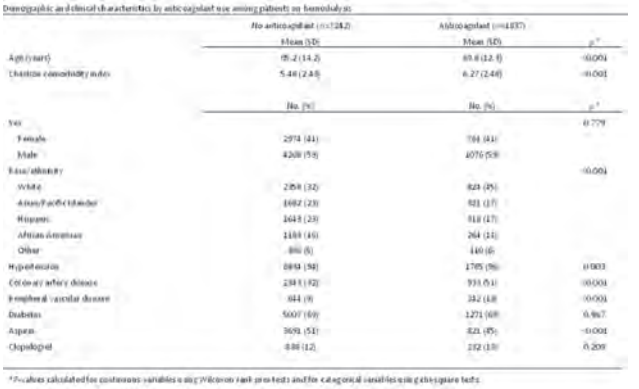
Tariq A. Shaheed, Douglas A. Stram, Aida Shirazi, Sumie Iwasaki, Cynthia Chalk, Sijie Zheng. The KP NCAL CODEX Study Group. *Kaiser Permanente, Oakland, CA.*

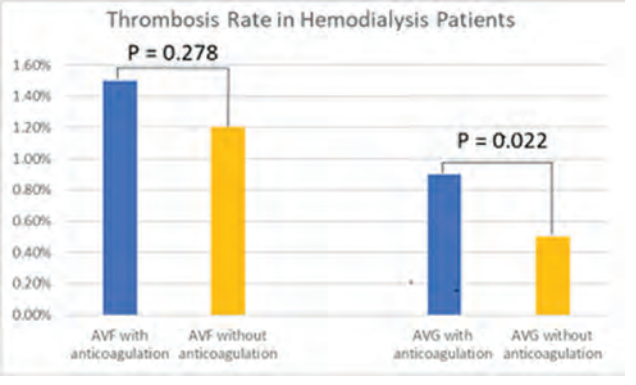
Background: Hemodialysis (HD) patients with dialysis access, arteriovenous fistula (AVF) or arteriovenous graft (AVG), are often placed on anticoagulation to for prevention of future thrombosis. We conducted a retrospective study comparing AVF/AVG thrombosis rates in HD patients with and without anticoagulation within an integrated healthcare network.

Methods: Kaiser Permanente Northern California is an integrated health care system taking care of 4.6 million members. We identified patients on dialysis between Jan 1, 2013, to Dec 31, 2021, who were placed on anticoagulation vs. not. Dialysis initiation date is used as index date. Anticoagulation was started after index date. We compared the AVF and AVG thrombosis rate within one year after the dialysis initiation date.

Results: We identified 9079 patients on hemodialysis in the study period, among them, 7242 did not use anticoagulation and 1837 did. The baseline demographics and comorbidities Indicating an older anticoagulation cohort, has higher Charlson comorbidity Index, HTN, PVD and less use of ASA (table). After one year, the rate of both fistula thrombosis is similar. The graft thrombosis is higher in the anticoagulant patients than non-anticoagulant patients (figure).

Conclusions: In this retrospective study, hemodialysis patients on anticoagulation did not have lower rate of AVF/AVG thrombosis. Baseline patient characteristics might explain this difference. Randomized prospective studies are needed to compare the effect of anti-coagulation in dialysis vascular access patency.





FR-PO425

Efficacy of Patiromer in Management of Long-Weekend Hyperkalemia in Patients on Intermittent Hemodialysis: A Tertiary Centre Experience from Saudi Arabia

Bilal Mohsin, Wael T. Habhab. *King Faisal Specialist Hospital and Research Centre - Jeddah, Jeddah, Saudi Arabia.*

Background: Hyperkalemia is a known complication that is associated with cardiovascular arhythmias and all cause mortality. This complication is frequently encountered in patients with ESKD including those on Intermittent Hemodailysis (IHD) 3 times per week. It is frequently encountered pre dialysis on saturday and sunday in patients on intermittent hemodailysis and is associated with higher incidence of sudden cardiac death specifically after a long weekend without hemodialysis. In our study we tried to identify the incidence of pre dialysis hyperkalemia and efficacy of Patiromer in its management.

Methods: This prospective study was done in Renal dialysis unit of King Faisal Specialist Hospital and Research Centre Jeddah (KFSHRCJ) between 01 January 2024 to 31 March 2024. We screened 161 adult patients on Intermittent hemodailysis by extracting labs pre dialysis after the long weekend i.e. on saturday and sunday. We defined hyperkalemia as serum K more than 5.3 mmol/L. Patiromer was prescribed to patients with serum K more than 5.3 mmol/l over the long weekend and repeat K samples were taken pre dialysis on week 1,2,4,8,12 on saturday and sunday. The changes in serum K levels were recorded as average and percentage and studied according to clinical and demographic characteristics of the patients.

Results: Out of 161 patients, 58 were found to be having pre dialysis hyperkalemia out of who 36 had serum K between 5.3 to 5.9mmol/l; 11 had serum K between 6 to 6.5 mmol/L and 5 had serum K more than 6.5 mmol/L. Patients with age less than 40 years (n=29) had hyperkalemia more than patients above 40 years (n=23). Patiromer was intiated for these patients with a mean reduction of serum K by 0.8-2.6 mmol/l with averge reduction of 1.5 mmol/L and this reduction was persistently observed at a followup at 2,4,8 and 12 weeks. 3 patients dropped out due to lack of compliance, 2 dropped out due to hospitalization and 1 patient refused to continue followup for 12 weeks

Conclusions: Patiormer is an effective tool in the treatment of Predialysis hyeprkalemia and has sustained effect. It can be used with an acceptable tolerance and efficacy specifically during the long weekend in patients on intermittent hemodialysis

FR-PO426

Tenapanor, a Novel Phosphorus Absorption Inhibitor, Softens Stool Properties and Enables Good Phosphorus Management

Kenichi Morii,[1,2] Toshiki Doi,[1,2] Aiko Okubo,[1] Yoshiko Nishizawa,[1] Kazuomi Yamashita,[1] Sonoo Mizuiri,[1] Takao Masaki.[2] *[1]Iryo Hojin Ichiyokai Harada Byoin, Hiroshima, Japan; [2]Hiroshima Daigaku, Hiroshima, Japan.*

Background: Tenapanor is a novel drug that reduces phosphorus absorption from the intestinal tract by inhibiting Na^+/H^+ exchanger isoform 3 (NHE3) in intestinal epithelial cells, thereby decreasing phosphorus permeability in the intercellular space. It is also used as a treatment for constipation-type irritable bowel syndrome (IBS-C) in the United States and Canada. Recently, tenapanor has become available as a hyperphosphatemic treatment for chronic kidney disease patients on dialysis. In this study, we investigated the effects of tenapanor on defecation status and serum phosphorus levels.

Methods: An observational study was conducted on 14 dialysis patients (12 hemodialysis patients, 1 peritoneal dialysis patient, and 1 peritoneal dialysis + hemodialysis hybrid patient) who started tenapanor at our affiliated institutions. A questionnaire was administered to assess the Bristol Stool Form Scale (BSFS: O'Donnell LJ, et al., BMJ 1990) and the number of defecations per week to evaluate the defecation status. Changes in defecation status and serum phosphorus levels after 8 weeks of tenapanor administration were examined.

Results: Four of the 14 patients discontinued medication due to diarrhea, one patient died due to cardiovascular events, and one patient was excluded due to withdrawal of consent. Data from eight individuals were analyzed. A significant difference was found in BSFS between 0 weeks and 8 weeks after starting tenapanor, 3.1 at 0 weeks, and 4.8 at 8 weeks ($P<0.01$). There was no significant difference in the number of defecations per week. Serum phosphorus levels were generally controlled within management goals.

Conclusions: Tenapanor can soften stool properties and control serum phosphorus levels well, although diarrhea has been observed as a side effect.

FR-PO427

Decline in Opioid Prescriptions in US Dialysis and Kidney Transplant Patients, 2011-2020

Paul L. Kimmel,[1] Chyng-Wen Fwu,[2] Thomas D. Nolin,[3] Ivonne H. Schulman,[1] Shannon S. Givens-Bradley,[1] Kenneth J. Wilkins,[1] Susan R. Mendley,[1] Debbie Gipson,[1] Raquel C. Greer,[1] Jenna M. Norton,[1] Kevin L. Chan,[1] Paul Eggers.[1] *[1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [2]Social and Scientific Systems, Inc., a DLH Holdings Corp (DLH) company, Silver Spring, MD; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: Pain is important for ESKD patients, but opioid medication (OM) prescriptions are associated with morbidity and mortality. The CDC issued OM prescription guidelines in 2016 and 2022, associated with dramatically decreased prescription rates in the U.S. population. It is critical to know if nationwide ESRD OM prescription rates have decreased.

Methods: We analyzed the USRDS database from 2011-2020 to describe trends in the proportion of ESRD dialysis and kidney transplant patients who received one or more, or chronic OM prescriptions, examined factors associated with chronic OM prescriptions, and evaluated associations of all-cause death with short-term or chronic OM prescriptions.

Results: From 2011-2022, the study population ranged between 202,000 and 240,000 patients. Dialysis patients decreased over the study from 80.4 to 76.8%. The percent of ESRD patients who received at least one or more, or who had received chronic OM prescriptions decreased steadily, from 60.4% to 42.1%, and from 22.6% to 13.0% (Table), respectively (both P for trend <0.001). The greatest reductions in prescription rates were for hydrocodone and oxycodone. Similar decreases existed for dialysis and kidney transplant patients. Women, the poor and those in rural settings were more likely to receive chronic OM prescriptions. Prescription rates were highest in White patients and those 45-64 years old. Short-term and chronic OM prescriptions were associated with increased mortality in both dialysis and kidney transplant patients.

Conclusions: ESRD patients' OM prescription rates decreased between 2011 and 2020. Determining the risks and benefits of decreasing OM prescription doses in individual ESRD patients will require clinical judgment and shared decision-making between patients and providers to improve treatment of pain and outcomes.

Funding: NIDDK Support

Table. The percent of patients with chronic opioid prescriptions (≥90 days of prescriptions per year) in the population with full-year Parts A, B and D enrollment, USRDS 2011-2020

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	P for trend*
ANY OPIOIDS, %	22.6	22.9	22.6	20.5	20.5	19.9	18.7	16.5	14.4	13.0	<0.001
HYDROCODONE, %	11.8	11.8	11.3	9.8	8.7	8.2	7.4	6.4	5.5	4.8	<0.001
OXYCODONE, %	5.7	5.9	5.9	5.8	6.3	6.3	6.0	5.4	4.8	4.4	0.05
TRAMADOL, %	3.4	3.8	4.0	3.6	3.8	3.8	3.5	3.3	2.8	2.5	0.02
CODEINE, %	0.7	0.6	0.6	0.5	0.7	0.7	0.6	0.6	0.5	0.5	N.S.
MORPHINE, %	0.7	0.7	0.6	0.6	0.6	0.6	0.5	0.5	0.4	0.3	<0.001
HYDROMORPHONE, %	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.4	0.4	<0.001
BUPRENORPHINE, %	0.04	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.3	<0.001
FENTANYL, %	1.2	1.2	1.2	1.1	1.1	1.0	0.8	0.7	0.5	0.4	<0.001

*: P value was derived from simple linear regression for each specific opioid prescription

FR-PO428

Profiles of Home Medication Use in Patients on Dialysis Globally

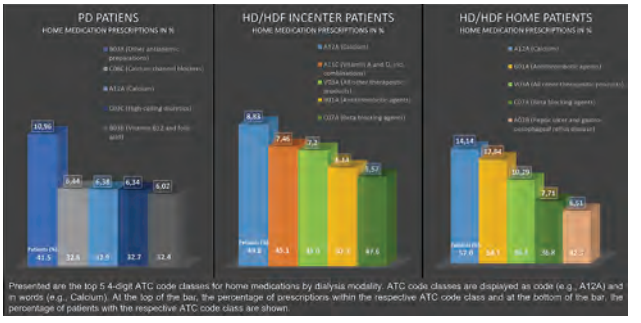
Astrid Feuersenger,[1] Luisa Roth,[1] Melanie Wolf,[1] Otto Arkossy,[1] John W. Larkin,[3] Jan Walter,[2] Hans-Juergen Arens.[1] Global Medical Office. *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care Holdings Inc, Waltham, MA; [3]Fresenius Medical Care Holdings Inc, Waltham, MA.*

Background: Global patterns of medication use in dialysis are undefined. This project aims to provide a real-world view of home medication use in dialysis using a global dialysis dataset from 40 countries called Apollo Dial DB. The most common prescribed medications administered at home by patients were compared by modality.

Methods: Apollo Dial DB includes adult dialysis patient data from a global kidney network during Jan 2018-Mar 2021 (Fresenius Medical Care, Bad Homburg, DE). Data anonymization was performed in alignment with recommendations from a re-identification risk determination (Privacy Analytics, Ontario, CA). Home medications were analyzed based on top (most common) five pharmacological classes defined by first 4-digits of ATC code; classes were stratified by modality.

Results: In Apollo Dial DB 109,888 in-center hemodialysis (HD) patients had 1,459,954 ATC code medication entries (13.3 drugs/patient), 6,466 peritoneal dialysis (PD) patients had 35,873 ATC codes (5.5 drugs/patient), and 1,899 home HD patients 10,228 ATC codes (5.4 drugs/patient). Top pharmacological classes included phosphate binders and antihypertensives for all modalities, yet differences existed by modality (**Figure 1**).

Conclusions: Home medication use appears 2-fold higher for in-center HD versus PD and home HD. Most common medications included calcium phosphate binders, 50% of in-center, 57% of home HD, and 33% of PD patients. Beta-blockers were commonly used for hypertension management in HD (48% in-center, 37% home patients), while calcium channel blockers were most used in PD (33%). Antithrombotics were more prevalent in HD (48% in-center, 54% home patients) and gastroesophageal medications in home HD patients (33%). Antiemetics and diuretics were more prevalent in PD patients (42% and 33%). Insights provide benchmarks for the community. Further research is needed accounting for duration of use and considering real-world application of various drugs (e.g., GLP1 drugs, HIF-PH inhibitors).



Presented are the top 5 4-digit ATC code classes for home medications by dialysis modality. ATC code classes are displayed as code (e.g., A12A) and in words (e.g., Calcium). At the top of the bar, the percentage of prescriptions within the respective ATC code class and at the bottom of the bar, the percentage of patients with the respective ATC code class are shown.

FR-PO429

Hospitalizations Increase Medication Complexity in Patients on Long-Term Hemodialysis

Sharmilee Vuyyuru, Andrew I. Chin. *University of California Davis, Sacramento, CA.*

Background: End stage kidney disease (ESKD) patients are medically complex with significant polypharmacy. Medication regimen complexity index (MRCI) is a validated, non-disease-specific tool that considers medication form, frequency, and special instructions. MRCI has not been well studied in this population. We compared pre and post hospitalization MRCI in hemodialysis (HD) patients.

Methods: This retrospective study included 60 adult patients on HD admitted to a large academic medical center. Data collection included: age; dialysis vintage; hospital length of stay (LOS); admission diagnosis; number of prescriptions and MRCI before hospitalization and at discharge (excluding medications administered at the dialysis clinic). Paired t-test was used to analyze the number of prescriptions and MRCI, comparing pre and post hospitalization. We also examined age, vintage, and LOS for association with MRCI.

Results: Mean age was 63.0 ± 12.7 years, median vintage 5 years (interquartile range 2 to 7), and median LOS 10 days (interquartile range 3 to 19). MRCI was significantly higher post-hospitalization than pre-hospitalization (mean 52.7 versus 48.7; p=0.008). Total medication complexity was driven by both an increase in the number of prescriptions as well as an increase in average prescription complexity (see Table 1). We found no association between pre-hospital MRCI with age, vintage, or LOS.

Conclusions: In ESKD patients on HD, there is a significant increase in MRCI post-hospitalization that is driven by an increase in number of medications as well as average medication complexity. Whether higher MRCI in this population is associated with more adverse outcomes, such as mortality or increased hospital readmissions, remains unanswered.

	Pre-Hosp	Post-Hosp	p-value
MRCI	48.7 ± 19.8	52.7 ± 18.0	0.008
Number of prescriptions	15.8 ± 5.7	16.6 ± 5.3	0.02
Mean MRCI per prescription	3.06 ± 0.44	3.17 ± 0.42	0.03

Table 1: Pre and post hospitalization MRCI and prescription analysis

FR-PO430

Effectiveness of a Multidisciplinary Team Delivered Deprescribing Intervention for Patients with CKD in Qatar: A Preliminary Analysis

Amani Zidan,[1] Abdullah I. Hamad,[2] Hassan A. Al-Malki,[2] Mohamad M. Alkadi,[2] Mohamed A. Elesnawi,[2] Rania A. Ibrahim,[2] Daoud Al-Badriyeh,[1] Muhammad A. Hadi,[1] Ahmed Awaisu.[1] *[1]Qatar University, Doha, Qatar; [2]Hamad Medical Corporation, Doha, Qatar.*

Background: Patients with chronic kidney disease (CKD), especially those receiving hemodialysis (HD), often experience negative consequences related to inappropriate polypharmacy. These can be averted by deprescribing. We aimed to design and assess the impact of a multidisciplinary team-delivered deprescribing intervention for patients receiving hemodialysis in Qatar.

Methods: This study is a randomized, parallel-group, controlled trial (RCT). Adults receiving chronic HD at Qatar's largest ambulatory dialysis center who can communicate in English or Arabic are included. Participants are randomized into the control (usual ambulatory care) or intervention (standardized deprescribing) groups. Intervention patients receive a structured deprescribing intervention using a developed evidence-based guideline. Outcome measures are collected at baseline and six months for all study participants. The primary outcome is the percentage of patients with ≥ 1 potentially inappropriate medication (PIM). The secondary outcomes include pill burden and self-reported adherence (assessed by Adherence to Refills and Medications Scale). A total of 424 patients is needed to reduce the percentage of patients with ≥ 1 PIM by 50%, with an expected attrition rate of 50%.

Results: The study has been ongoing since 19 February 2024. Thirty-seven patients with an average (SD) age of 52.8 (14.6) have been recruited. At baseline, a mean of 1.7 (1.3) PIMs was identified. 83.7% of the patients had at least one PIM prescribed (78.9% control and 88.8% intervention). On average, the participants were taking 132.3 pills per week (131.7 in control and 132.3 in intervention). ARMS mean score was 17.03 (6.12) (control 16.33 (5.16), Intervention 17.76 (7.08)). Twenty-four deprescribing plans have been suggested for 15 patients in the intervention group. Among these, 16 were successfully implemented, 4 were rejected by the physicians, 2 were refused by the patient, and 2 were stopped due to recurrent symptoms.

Conclusions: Our structured deprescribing intervention is promising to improve dialysis patients' health outcomes. With the potential to reduce inappropriate polypharmacy and pill burden, we anticipate a positive impact on patient well-being.

Funding: Government Support - Non-U.S.

FR-PO431

Evaluation of a Novel Pharmacist-Nephrologist Collaborative Care Service for Patients on Hemodialysis in Singapore

Pu En Ow Yong. *Changi General Hospital, Singapore, Singapore.*

Background: The introduction of Collaborative Prescribing by pharmacists has improved the holistic team-based patient care. The standard care (SC) for stable hemodialysis (HD) patients involves a hospital nephrologist's consult in 9-month intervals, with community dialysis team titrating medications every 1-2 monthly. With complex medication regimens and multiple care teams involved, HD patients often face complex and potentially confusing medication regimens. Since medication management is the main activity during nephrologist's consult, we aim to right-site their care with the novel collaborative care (CC) service between nephrologists and pharmacists. In this CC model, stable HD patients are reviewed by a renal pharmacist 6 months after his nephrologist consult. Pharmacist independently conducts a medication review according to patient's clinical status and their HD centre's records. Pharmacists optimise, and prescribe their medications and vaccinations based on the collaborative prescribing framework. This study aims to evaluate safety of the new CC model, with the mean ED visits and all-cause unplanned admissions as the primary outcome.

Methods: A retrospective study of 104 patients in the CC model and 342 patients in SC model in January 2021 – June 2022 was conducted. The patients are matched by the nearest propensity scores, modeled using a multivariate logistic regression adjusted with baseline variables. The number of all-cause unplanned admission and ED visits were compared using a difference-in-difference approach and a negative-binomial mixed effect model.

Results: Mean unplanned admissions was 0.673 and 0.760 for the SC and CC group respectively (p=0.597) with an incidence rate ratio (IRR) of 0.98 (95% CI: 0.58-1.65) for the CC group. The mean ED visits was 0.192 and 0.183 for the SC and CC group respectively (p=0.890) with an IRR for the CC group of 0.73 (95% CI: 0.14-3.81). The differences were not statistically significant. Among patients who require pneumococcal and/or influenza vaccinations, patients in the CC group achieved a higher vaccination rate (pneumococcal: 24.3% vs 3.8%. influenza: 13.5% vs 0.0%).

Conclusions: The study findings support the safety of this novel CC service in ensuring the timely and holistic clinical review of stable HD patients. This new CC service was effectively implemented with no differences in primary safety outcome measures.

FR-PO432

Association between Primary Care Services and All-Cause Mortality among US Patients on In-Center Hemodialysis

Dustin Le,[1] Rohanit Singh,[2] Raquel C. Greer,[1] Morgan Grams,[3] Bernard G. Jaar.[1] *[1]Johns Hopkins Medicine, Baltimore, MD; [2]Yale University School of Medicine, New Haven, CT; [3]New York University Grossman School of Medicine, New York, NY.*

Background: The association between primary care evaluation among individuals requiring maintenance in-center hemodialysis (HD) and all-cause mortality is unclear.

Methods: Using the US Renal Data System (USRDS) and Medicare Parts A, B, and D claims data from 2012 to 2020, we estimated the risk of all-cause mortality, cause-specific mortality, and index hospitalization between those with and without PCP services among incident individuals with pre-existing Medicare coverage who survived the first 90 days on HD. Receipt of PCP services was defined as ≥1 outpatient visits between dialysis initiation and study start (90 days after dialysis initiation) to Family Medicine, Internal Medicine, General Medicine, or Geriatrics. We used inverse probability of treatment weights (IPTW) to achieve exchangeability between those with and without primary care evaluation, and we used Cox-proportional hazards models to estimate the IPTW-hazard ratios (HRs).

Results: We identified 58,011 and 56,653 individuals with and without PCP services in the first 90 days of HD. After IPTW, the average age was 71 years old, 53% were White, and 73% had diabetes. There were 58,982 deaths during a median (interquartile interval) follow-up of 1.78 (0.69 – 3.36) years. The median survival for those with PCP services was 3.2 years vs 3.0 years (a difference of 3.4 months). The IPTW-HR for all-cause mortality was 0.91 (95% CI: 0.89 – 0.92), and there were similar reductions in CV death (0.94 [0.91 – 0.96]), infectious death (0.87 [0.81 – 0.94]), and index hospitalization (0.98 [0.97 – 1.00], p-value = 0.03). There was no difference in first ED visit (1.00 [0.99 – 1.01]). Subgroup analyses such as age, race, Part D subsidy status, and PCP evaluation 3 months prior to dialysis initiation were generally consistent.

Conclusions: Among US Medicare beneficiaries, primary care evaluation within 90 days of in-center HD initiation was associated with lower all-cause mortality and hospitalization.

Funding: Other NIH Support - T32HL007024

FR-PO433

Sex and Age Differences in Hemodialysis Mortality among US Medicare Beneficiaries

Dustin Le,[1] Grant T. Kirby,[1] Morgan Grams,[2] Nityasree Srialluri.[1]
[1]Johns Hopkins Medicine, Baltimore, MD; [2]New York University Grossman School of Medicine, New York, NY.

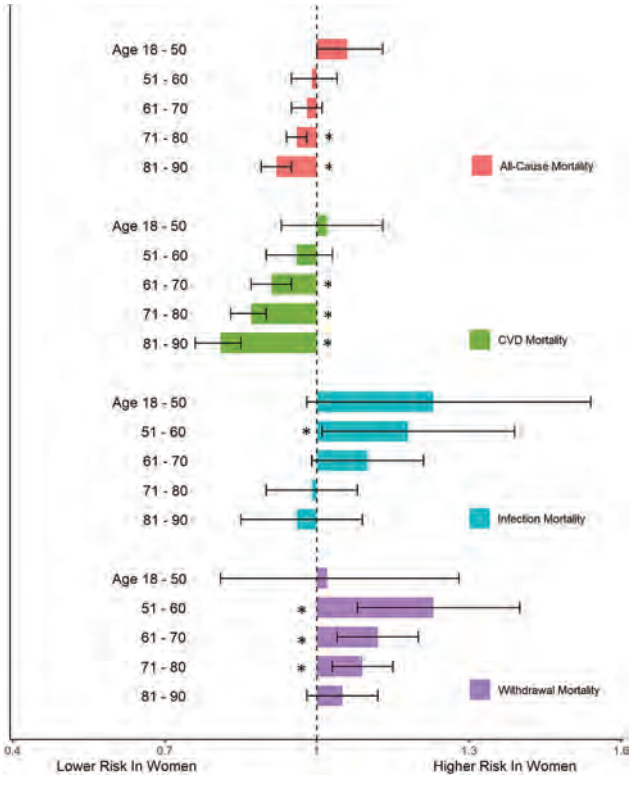
Background: Recent literature has challenged the observation that women (vs men) have a modest survival advantage on hemodialysis. We aimed to investigate if age of dialysis initiation contributes to sex differences in mortality outcomes among US Medicare beneficiaries.

Methods: Using the US Renal Data System (USRDS) and Medicare A, B and D claims from 2011-2020 we assessed all-cause and cause-specific mortality (cardiovascular [CVD], infection, and withdrawal), comparing females to males who survived 90 days on in-center hemodialysis. Participants were stratified by age (18 – 50, 51- 60, 61 – 70, and 81 – 90) and analyzed using competing risk models to account for the competing risk of kidney transplantation. We estimated competing risk regression hazard ratios (HRs) in the overall population and then within each age stratum, adjusting for baseline demographics, comorbidities, and medication use.

Results: Among 85,453 women and 93,205 men who initiated and survived 90 days of in-center hemodialysis, women had a survival advantage (HR: 0.96, 95% CI: 0.95 – 0.98) driven by lower CVD mortality (HR: 0.88, 95% CI: 0.86 – 0.91). Women had similar infection-related mortality (HR: 1.04, 95% CI: 0.99 – 1.10) and higher withdrawal-attributed mortality (HR: 1.08, 95% CI: 1.04 – 1.12). Women 18 – 50 did not have a survival advantage for all-cause (HR 1.06, 95% CI: 1.00 – 1.13, p-value: 0.06) or CVD mortality (HR 1.02, 95% CI: 0.93 – 1.13), while women aged 51-60 had higher infection-related mortality (HR: 1.18, 95% CI: 1.01 – 1.39), **Figure 1**. Withdrawal mortality by age strata was consistent with the overall population estimate.

Conclusions: Among US Medicare beneficiaries, the association between sex and mortality varied based on the age at time of dialysis initiation.

Funding: Other NIH Support - T32HL007024



* P-value < 0.05

FR-PO434

Commercial Health Insurance and Quality of Care in US Dialysis Facilities

Kevin F. Erickson,[1] Anshul Bhatnagar,[1] Daniel E. Weiner,[2] Allison C. Reaves.[3]
[1]Baylor College of Medicine, Houston, TX; [2]Tufts University School of Medicine, Boston, MA; [3]Tufts Medical Center, Boston, MA.

Background: Commercial health insurance typically reimburses at a higher rate for dialysis than Medicare. A recent ruling by the US Supreme Court could result in many commercially insured patients who receive dialysis forgoing their commercial health insurance and shifting to Medicare as the primary payer. We examined whether differences in commercial payers as a proportion of a facility's overall payer mix is associated with the quality of care at dialysis facilities.

Methods: We used publicly available data from US Dialysis Facility Reports and the Dialysis Facility Compare websites in 2019 to identify patients receiving dialysis in the United States. In multivariable linear regression models, we examined the association between the percentage of incident dialysis patients with commercial insurance and seven key dialysis facility quality metrics included in dialysis facility STAR ratings.

Results: Among 5,753 US dialysis facilities, on average 12.0% of incident dialysis patients had commercial insurance. Each 10% absolute increase in percentage of dialysis patients in a facility with commercial insurance was associated with an adjusted 6.7% (95% Confidence Interval (CI) 5.5-7.9%) lower standardized mortality ratio, 2.7% (1.9-3.4%) lower standardized hospitalization ratio, and absolute decreases of 4.0% (2.0-6.0%) in the standardized transfusion ratio, 0.2% (0.1-0.2%) in patient months without adequate dialysis, and 0.7% (0.5-1.0%) in months with a long-term catheter. Higher commercial insurance rates were associated with an increase of 0.8% (0.5-1.1%) in the standardized arteriovenous fistula rate and a 0.05 (0.01-0.10) point higher Consumer Assessment of Healthcare Providers and Systems patient experience score.

Conclusions: These findings suggest that shifting coverage from commercial health insurance to Medicare could adversely impact quality of care at dialysis facilities.

FR-PO435

Representativeness of Populations Recruited in Randomized Controlled Trials of Hemodiafiltration vs. Hemodialysis: A Systematic Analysis in Comparison with Representative Registry Data

Tom Yuen,[1] Ngoc Pham,[2] Kakiu Ho,[1] Manuela Stauss-Grabo,[2] Giovanni Strippoli,[4,5] Krister Cromm.[2,3] CONVINCE Scientific Committee and CONVINCE Investigators. *[1]Fresenius Medical Care Asia Pacific Ltd, Hong Kong, Hong Kong; [2]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [3]Charite Universitatsmedizin Berlin, Berlin, Germany; [4]Universita degli Studi di Bari Aldo Moro, Bari, Italy; [5]University of Sydney, School of Public Health, Sydney, NSW, Australia.*

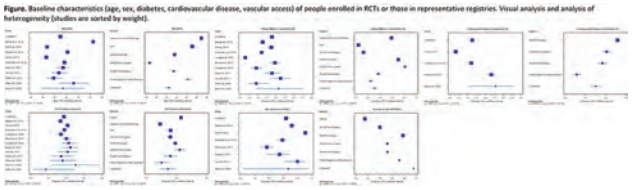
Background: The external validity of randomized controlled trials (RCTs) depends on the comparability of involved populations to the ones in "real life", whose data are usually reported in registries. Following the recent publication of the CONVINCE trial, we compared patient baseline characteristics in all existing RCTs of hemodiafiltration (HDF) vs hemodialysis (HD) and with data of key renal registries from Europe, Australasia and America. Our aim was to ascertain existing heterogeneity and whether the coverage in RCTs was representative of prevalent registry populations.

Methods: We performed a systematic search for RCTs of HDF vs HD using Cochrane methodology (1966 to current). We also searched for annual reports of representative registries (2020-2023). For both RCTs and registries we extracted data on patient characteristics (age, sex, diabetes, cardiovascular disease, vascular access). We compared data between RCTs and registries using visual analysis, descriptive statistics and heterogeneity statistics (I^2).

Results: Thirteen RCTs including CONVINCE and 8 registries were identified. There was substantial heterogeneity for all characteristics within RCTs, substantiating that a large and broadly representative array of people are enrolled in existing RCTs of HDF vs HD. These were in line with registry populations for age, proportion of diabetic patients and sex (p=not significant) but not for cardiovascular disease and proportion having a fistula for vascular access (p<0.05).

Conclusions: There was significant heterogeneity in the patient characteristics of existing RCTs of HD vs HDF. Overall, the data are representative of populations reported in registries of different geographies. While individual trials may appear as outliers compared to the prevalent registry population, the totality of evidence covers a broad spectrum of the end stage kidney disease population receiving renal replacement therapy either as HD or HDF. The similarity between characteristics of patients in RCTs and registries supports that existing RCTs adequately represent the real-life population.

Funding: Government Support - Non-U.S.



FR-PO436

Parkinson Disease and ESKD: Understanding Phenotypic Characteristics and Their Impact on Survival

Cydney E. Parmar,[1,2] Grant D. Scheiffele,[2] Nandita Senthil,[1,2] Jonathan Fischer,[1] Aparna Wagle Shukla,[1] Ashutosh M. Shukla.[1,2] *[1]University of Florida, Gainesville, FL; [2]VA North Florida South Georgia Veterans Health System, Gainesville, FL.*

Background: Similar to end-stage kidney disease (ESKD), Parkinson's disease is a major chronic disease affecting older individuals with a negative impact on the quality of life and survival. While there is an emerging literature on the brain-kidney axis, the clinical phenotype of patients with Parkinson's disease initiating dialysis and their overall survival prospects have never been investigated.

Methods: We identified all incident ESKD patients initiating dialysis between 2009 and 2019 from the United States Renal Database System. Of these, we isolated Parkinson's disease patients using ICD 9 and -10 codes. We used a random forest method to generate propensity scores and created a 1:5-matched non-Parkinson's Disease control cohort. We used the Cox proportional hazards model to conduct a survival analysis.

Results: Of the 1,271,443 eligible patients during the study period, 5,462 had Parkinson's disease at incident ESKD. These patients were significantly older (76.1±8.7 vs. 63.6±14.8 years), had higher functional limitations (43.4% vs. 17.4%), and had a burden of comorbidities such as heart failure (38.6% vs. 29.8%), atherosclerotic disease (37.8% vs. 27.5%), depression (37.0% vs. 11.8%), and had a lower incident of home dialysis use (4.5% vs. 9.5%). Median survival was significantly lower in Parkinson's disease cohort (527 days, IQR: 170 - 1153), compared to the propensity-matched non-Parkinson's disease control cohort (562 days, IQR: 166-1227) with an adjusted hazard ratio for death of 1.15 (1.11 - 1.18). Asian race (0.67, 0.62 - 0.72) and females (0.93, 0.90 – 0.93), and use of peritoneal dialysis (0.86, 0.81 – 0.91) were associated with improved survivals, whereas heart failure (1.26, 1.22 – 1.29), obstructive pulmonary disease (1.23, 1.19 – 1.27), and functional disability (1.44, 1.40 – 1.47) were associated with poorer survivals.

Conclusions: Incident ESKD patients with a preexisting diagnosis of Parkinson's disease are older, have higher comorbidity burden and functional limitations, and have worse survival. More pragmatic analyses accounting for quality of life are needed to understand better the benefits and risks of Parkinson's disease patients initiating dialysis.

Funding: Veterans Affairs Support

FR-PO437

Informal Caregiver Burden in Dialysis Care and How It Relates to Patients' Health-Related Quality of Life and Symptoms

Esmee Driehuis,[1,2] Roemer J. Janse,[3] Anneke Roeterdink,[1,2] Wanda Konijn,[4] Thomas S. van Lieshout,[2,7] Theodôr J. Vogels,[5] Namiko A. Goto,[6] Marjolein Broese van Groenou,[8] Friedo W. Dekker,[3] Brigit C. van Jaarsveld,[2] Alferso C. Abrahams.[1] DOMESTICO Study Group. *[1]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [2]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands; [3]Leids Universitair Medisch Centrum, Leiden, Netherlands; [4]Dutch Kidney Patients Association, Bussum, Netherlands; [5]Maxima Medisch Centrum, Veldhoven, Netherlands; [6]Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, Netherlands; [7]Noordwest Ziekenhuisgroep, Alkmaar, Netherlands; [8]Vrije Universiteit Amsterdam, Amsterdam, Netherlands.*

Background: Starting dialysis has a major impact on both patients' and their informal caregivers' lives. Dialysis patients often experience impaired health-related quality of life (HRQoL) and high symptom burden, relying heavily on their informal caregivers. However, providing informal care for someone undergoing dialysis may lead to significant burden and decreased HRQoL for caregivers themselves, potentially also influencing patients' well-being. Despite the crucial role of informal caregivers, there is a lack of research on this topic. Therefore, we aimed to 1) describe informal caregivers' experienced burden and HRQoL and 2) investigate how these are related to dialysis patients' HRQoL and symptoms.

Methods: We conducted a cross-sectional study at dialysis initiation with 202 adult informal caregiver-dialysis patient dyads. Caregiver burden was measured with the Self-Perceived Pressure from Informal Care (SPPIC) questionnaire, HRQoL with the 12-item Short Form Health Survey (SF-12), and symptom number and burden with the Dialysis Symptom Index (DSI). Data were analysed using linear and logistic ordinal regression.

Results: Around 35% of caregivers experienced moderate to high burden. Patients' lower mental HRQoL (adjusted odds ratio [aOR]=0.95, 95% confidence interval [CI] 0.92; 0.99), higher symptom number (aOR=1.07, 95% CI 1.02; 1.12), and higher symptom burden (aOR=1.03, 95% CI 1.01; 1.04) were associated with greater odds of higher caregiver burden. Patients' lower mental HRQoL (β=0.30, 95% CI 0.15; 0.46), higher symptom number (β=-0.55, 95% CI -0.78; -0.31), and higher symptom burden (β=-0.17, 95% CI -0.25; -0.10) were also associated with a lower mental HRQoL in caregivers.

Conclusions: We show that a third of caregivers feel moderate to high burden and that caregiver burden is associated with patients' mental HRQoL and symptoms. These findings highlight the importance of considering and supporting patients and their informal caregivers together in dialysis care, as the kidney disease and its treatment impact many aspects of both their lives.

FR-PO438

Identifying Symptom Clusters and Associated Social Determinants of Health in Patients with ESKD and Chronic Pain: A Secondary Analysis of the HOPE Trial

Jennifer L. Steel,[1] Mark Lockwood,[2] Carrie E. Brintz,[3] Kerri L. Cavanaugh,[3] Martin Cheatle,[4] Daniel Cukor,[5] Laura M. Dember,[4] Ardith Z. Doorenbos,[2] Heather B. Howell,[10] Francis J. Keefe,[6] Paul L. Kimmel,[7] Jane Liebschutz,[1] Daniel W. Mcneil,[8] Mark L. Unruh,[9] Jonathan G. Yabes,[1] Jesse Y. Hsu,[4] Manisha Jhamb.[1] HOPE Consortium. *[1]University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]University of Illinois Chicago, Chicago, IL; [3]Vanderbilt University Medical Center, Nashville, TN; [4]University of Pennsylvania, Philadelphia, PA; [5]New York University Grossman School of Medicine, New York, NY; [6]Duke University, Durham, NC; [7]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [8]University of Florida, Gainesville, FL; [9]University of New Mexico School of Medicine, Albuquerque, NM; [10]Yale University, New Haven, CT.*

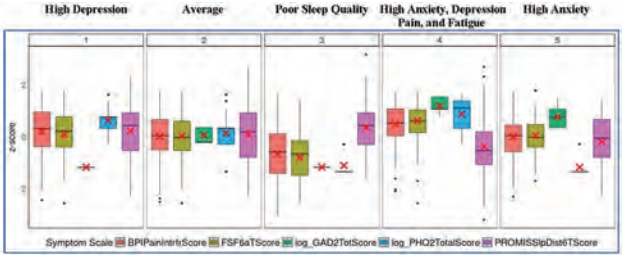
Background: Identifying symptom clusters and associated social determinants of health (SDOH) among people with chronic pain and ESKD may facilitate more effective treatment of symptoms

Methods: The HOPE Consortium Trial to Reduce Pain and Opioid Use in Hemodialysis, designed to address chronic pain in adults receiving maintenance HD, enrolled 643 patients with moderate to severe chronic pain. We used latent profile analysis to identify patterns of an *a priori* symptom cluster (pain, fatigue, anxiety, depression and sleep disturbances) with baseline measures of the Brief Pain Inventory, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, the PROMIS Fatigue and Sleep subscales. We used multinomial logistic regression to assess associations between symptom clusters and SDOH (obtained by self-report and geocoding).

Results: Five symptom cluster phenotypes were characterized based on fit statistics, interpretability, and between-class heterogeneity. There was significant variability in perceived discrimination across the symptom clusters ($p<0.01$). Living in a racially segregated neighborhood was associated with a symptom cluster with high depressive symptoms, relative to "average" symptom cluster (Adjusted OR=1.03, p=0.02). There were no significant associations of symptom clusters with education level, household income, area deprivation index, rural/urban community, walkability index or Gini index of income inequality.

Conclusions: The symptom clusters identified are potentially important to clinicians and researchers for addressing symptom burden. System and individual level SDOH may be important factors to include when developing interventions focused on reducing symptom burden in those with ESKD and chronic pain.

Funding: NIDDK Support



Symptom cluster domains in patients with ESKD and chronic pain

FR-PO439

Emergency-Only Dialysis and the Impact of Transition to Scheduled Dialysis on Survival of Patients with ESKD

Jared G. Imber,[1] Donald A. Molony,[1] Mohammad H. Rahbar,[2] Manouchehr Hessabi,[2] Akram Yazdani,[2] Amirali Tahanan,[2] Rekha K. Trivedi,[3] Jade M. Teakell.[1] *[1]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX; [2]The University of Texas Health Science Center at Houston, Houston, TX; [3]Harris Health System, Houston, TX.*

Background: Patients with end-stage kidney disease (ESKD) without access to scheduled dialysis present to emergency departments (ED) when their clinical status deteriorates to the extent that they require hemodialysis (HD) emergently to evade death. We hypothesize that the patients who receive emergency-only HD (EOHD) and are subsequently transitioned to scheduled HD or peritoneal dialysis (PD) will have increased overall survival compared to those patients who continued to receive EOHD.

Methods: We interrogated the electronic medical record of the Harris Health System (Houston, TX) to evaluate health outcomes for all adult patients with ESKD requiring dialysis (identified using ICD-10 codes) from 2017 to 2021. We compared overall survival in an EOHD cohort between patients who were transitioned to scheduled dialysis (HD or PD) and those who continued EOHD.

Results: We evaluated the outcomes for 914 adults diagnosed with ESKD without eligibility for or access to a conventional funding source for outpatient dialysis. Of the identified patients, 516 received EOHD, and 398 transitioned to scheduled dialysis (382 HD, 16 PD). Patients receiving EOHD demonstrated an adjusted hazard ratio of 4.553 (95% CI 2.20-9.34) when followed for ≤1 year, 2.222 (95% CI 1.07-4.60) when followed for 1-3 years (total), and 0.2199 (95% CI 0.08-0.61) when followed 3-5 years (total) (Table 1).

Conclusions: The cohort of patients with ESKD who transitioned from EOHD to scheduled dialysis treatments benefited from improved overall survival compared to the patients who continued to receive EOHD, except for those with a follow-up period of 3-5 years. The observed relative improvement in survival outcomes in the EOHD group with greater than 3 years of follow-up is likely due to a survivor effect. These findings provide further evidence that transitioning patients from emergency-only HD to scheduled dialysis as the standard of care will result in better outcomes in this marginalized group of ESKD patients.

Funding: Other NIH Support - CTSA - National Center for Advancing Translational Sciences

Table 1. Mortality and approximated Hazard ratios for patients treated with emergency-only hemodialysis and transitioned to scheduled dialysis for ≤ 1 year, 1-3 years, and 3-5 years of follow-up

Follow-up period	No of patients	Mean Age	Number of deaths	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
≤ 1 year (Total)	**119**	**53.03**	**50**		
Emergency only	55	55.17	36	5.835 (2.93 -11.62)	4.533 (2.20 - 9.34)
Transitioned to scheduled	64	51.19	14		
1-3 years (Total)	**294**	**51.03**	**35**		
Emergency only	104	53.10	23	3.258 (1.619- 6.557)	2.222 (1.07 - 4.60)
Transitioned to scheduled	190	49.90	12		
3-5 years (Total)	**494**	**50.44**	**26**		
Emergency only	355	50.67	8	0.2109 (0.076- 0.58)	0.2199 (0.08 - 0.61)
Transitioned to scheduled	139	49.86	18		

Note: In this study, the date of death is missing for 7 deceased patients (2 in emergency and 5 in transitioned), so we removed them from the final analysis.
* Adjusted for covariates (age, self-reported sex, and the length of stay in the hospital (days)).

FR-PO440

Comparative Safety and Effectiveness of Heparin vs. Direct Oral Anticoagulants in Patients with Cirrhosis and ESKD

Abhi Lohana,[1] Usman Akbar,[1] Fnu Muhibullah,[1] Nouman Shafique,[3] Syed Adil Mir Shah,[2] Neeharika Muddana.[1] *[1]Camden Clark Medical Center, Parkersburg, WV; [2]Dow Medical College, Karachi, Pakistan; [3]Nishtar Medical College and Hospital, Multan, Pakistan.*

Background: Anticoagulation therapy in patients with cirrhosis and end-stage renal disease (ESRD) presents unique challenges due to the increased risk of both thromboembolic and bleeding events. This study aims to compare the clinical outcomes of patients treated with Heparin versus direct oral anticoagulants (DOACs) in this high-risk patients. Understanding the safety and effectiveness of these treatments in cirrhosis with ESRD is crucial for optimizing patient care and minimizing adverse events.

Methods: We utilized the US collaborative network platform to perform a comparative outcomes analysis on two cohorts: 7333 patients treated with Heparin and 7323 patients treated with DOACs. Propensity score matching was used to balance the cohorts based on demographic and clinical characteristics. Outcomes measured included mortality, stroke, deep vein thrombosis/pulmonary embolism (DVT/PE), acute myocardial infarction (AMI), and major bleeding after 1 year, with risk differences and p-values calculated to assess statistical significance.

Results: The analysis revealed that the Heparin cohort had a significantly higher risk of mortality (risk difference 0.035, p-value 0.000) and major bleeding (risk difference 0.021, p-value 0.005) compared to the DOACs cohort. Conversely, the DOACs cohort exhibited a higher risk of DVT/PE (risk difference -0.025, p-value 0.000). No significant differences were observed between the cohorts for stroke (risk difference -0.001, p-value 0.801) and AMI (risk difference 0.006, p-value 0.204).

Conclusions: This comparative analysis highlights that Heparin is associated with higher risks of mortality and major bleeding, whereas DOACs are associated with a higher risk of DVT/PE. These findings suggest that DOACs may be a safer alternative to Heparin for certain outcomes, although individual patient factors and clinical judgement should guide treatment decisions. Further research is needed to confirm these findings and optimize anticoagulation therapy.

Outcome	Patients with Outcome (Heparin)	Total Patients (Heparin)	Patients with Outcome (DOACs)	Total Patients (DOACs)	Risk Difference	P Value
Mortality	1532	7333	1270	7323	0.035	0.000
Stroke	255	6917	245	6500	-0.001	0.801
DVT/PE	300	7045	420	6223	-0.025	0.000
AMI	534	6531	437	5782	0.006	0.204
Major Bleeding	863	5002	747	4930	0.021	0.0

1-year outcomes of patients being treated with heparin and Direct oral anticoagulants (DOACs) in patients with ESRD and cirrhosis.

FR-PO441

Comparison of Clinical Outcomes between High-Start and Low-Start Dialysate Fill Volume among Patients with CKD on Peritoneal Dialysis at the National Kidney and Transplant Institute: A Randomized Controlled Trial

Rhaffy B. Rapacon. *National Kidney and Transplant Institute, Quezon City, Philippines.*

Background: There is a lack of consensus among nephrologists on the optimal peritoneal dialysis(PD) choice of starting on low fill or high fill volume due to data gaps.

Methods: This randomized controlled trial included 50 CKD patients at National Kidney Transplant Institute from December 2023 to March 2024. Patients were randomly allocated into two groups to receive either high-start or low-start dialysate fill volume. Endpoints of the study are adverse events and changes from baseline of PD parameters at day 14 of the treatment period.

Results: A significant difference in the pre-and post-treatment in terms of improved eGFR in the low-start group (4.3±2.5 vs 6.9±4.0; D =2.63; p<0.001); increased serum albumin in the high-start group (3.2±0.5 vs 3.5±0.4; D =0.30, p=0.025); and decreased BUN in both high-start (106.2±42.8 vs 53.1±21.3; D =53.09; p<0.001) and low-start group (106.1±36.7 vs 50.8±19.6; D =53.09; p<0.001). In terms of adverse events, bleeding was significantly associated with low-start fill volume (p=0.037). However, groups did not vary significantly in terms of pericatheter leak (RR=1.67; p=0.440); abdominal pain (RR=1.27, p=0.659); swelling (RR=1, p=1); catheter migration (p=0.018); obstruction (RR=0.75, p=0.683); peritonitis (p=0.312) and other complications (RR=1.5, p=0.637).

Conclusions: High-start fill volume resulted in significantly improved post-treatment serum albumin and BUN levels. It was well tolerated and associated with significantly lower bleeding rates compared to low-start fill volume.

Complications of high-start and low-start fill volume among peritoneal dialysis patients (Primary Outcome)

Variables		Low-Start Group		High-Start Group		Risk Ratio (95% CI)	p-value
		f	%	f	%		
Pericatheter leak	Y	3	12	5	20	1.67 (0.45 – 6.24)	0.440
	N	22	88	20	80		
Abdominal pain (6 up)	Y	15	60	19	76	1.27 (0.86 – 1.87)	0.659
	N	10	40	6	24		
Hernia	Y	0	0	0	0	N/A	N/A
	N	25	100	25	100		
Bleeding	Y	4	16	0	0	N/A	0.037
	N	21	84	25	100		
Swelling around exit site	Y	1	4	1	4	1.00 N/A	1.000
	N	24	96	24	96		
Catheter migration	Y	5	20	0	0	N/A	0.018
	N	20	80	25	100		
Catheter obstruction	Y	4	16	3	12	0.75 (0.19 – 3.01)	0.683
	N	21	84	22	88		
Peritonitis	Y	1	4	0	0	N/A	0.312
	N	24	96	25	100		
Other signs and symptoms	Y	2	8	3	12	1.50 (0.27 – 8.22)	0.637
	N	23	92	22	88		

Comparison of pre-treatment and post-treatment across groups according to PD parameters

PD Parameters		Pre-Treatment		Post-Treatment		Mean Difference	p-value
		x̄	SD	x̄	SD		
Estimated glomerular filtration rate (eGFR)	High-Start	4.8	3.0	10.6	14.4	5.86	0.054
	Low-Start	4.3	2.5	6.9	4.0	2.63	0.000*
Serum Albumin	High-Start	3.2	0.5	3.5	0.4	0.30	0.025*
	Low-Start	3.3	0.7	3.4	0.7	0.11	0.343
BUN (Blood Urea Nitrogen)	High-Start	106.2	42.8	53.1	21.3	(53.09)	0.000*
	Low-Start	106.1	36.7	50.8	19.6	(55.30)	0.000*
Dry weight	High-Start	62.6	10.0	63.1	9.8	0.48	0.691
	Low-Start	55.8	8.9	54.1	9.3	(1.73)	0.154

FR-PO442

High Variability of Serum Albumin Is Associated with Increased Risk of All-Cause Mortality in Patients on Peritoneal Dialysis

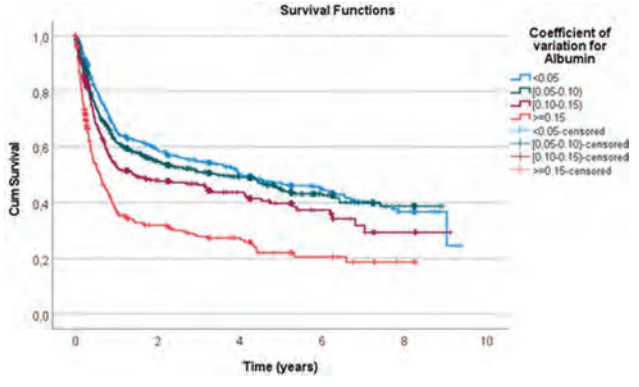
Hanri Afghahi,[1] Salmir Nasic,[1] Björn Peters,[1] Anna Wärme,[1] Helena Rydell,[3] Maria K. Svensson.[2] *[1]Skaraborgs Sjukhus Skovde, Skovde, Sweden; [2]Uppsala Universitet, Uppsala, Sweden; [3]Karolinska Institutet, Stockholm, Sweden.*

Background: Studies that evaluated trends in serum albumin and the association between variability of serum albumin and risk of all-cause mortality with peritoneal dialysis (PD) are limited. **Aim :** The association between variability of serum albumin and the risk of all-cause mortality in patients on maintenance PD.

Methods: 2567 patients with end-stage kidney disease (ESKD) on maintenance PD treatment were followed for mean 3.9±3.5 years by data from the Swedish Renal Register (SRR),. The variability of serum albumin was defined as the coefficient of variation (CV) and the ratio between the standard deviation (SD) and mean value, (SD/mean). The patients were divided in four groups depending on variability of serum albumin. The relationships between serum albumin variability and all-cause mortality were examined by univariable and multivariable Cox regression models and hazard ratios (HR) with 95% confidence intervals (CI) which was adjusted for demographics, laboratory findings, and comorbidities as well as mean value of serum albumin during the study. Lowest serum albumin variability (CV<0.05) was used as reference group for calculation of HR.

Results: During the study period 1144 (45%) deaths occurred. The highest risk of mortality was observed in patients with highest serum albumin variability (CV>0.15) and 59% (237/399) died. Lowest serum albumin variability (CV<0.05) had the best survival and in this group only 42% (303/718) died. In the multivariate analyses, the two groups with the highest serum albumin variability (0.10<CV≤0.15 and CV>0.15) had a significantly increased risk of mortality (HR 1.20, 95% CI 1.002-1.44, p-value=0.048 and HR 1.55, 95% CI 1.27-1.87, p-value<0.001), compared to reference group.

Conclusions: In patients with ESKD and PD high serum albumin variability is associated with increased risk of mortality independent of serum albumin level. Serum albumin variability may be an important risk factor for all-cause mortality in these patients.



FR-PO443

Strict Blood Pressure Control Is Associated with Better Survival in Korean Patients on Hemodialysis, but Not in Patients on Peritoneal Dialysis

Joo Kyung Lee, Min Jee Jo, Gang Jee Ko. *Korea University, Seongbuk-gu, Republic of Korea.*

Background: Adequate blood pressure (BP) control is considered one of main treatment strategies in dialysis patients. However, the goal and ideal range of BP have not been defined exactly among dialysis patients. We aimed to investigate proper management for BP control associated with better survival in dialysis patients.

Methods: Based on the data of health screening results from 2002 to 2018 in the database of the Korean National Health Insurance System (NHIS), we examined the association of BP control with all-cause and cardiovascular mortality among hemodialysis (HD) and peritoneal dialysis (PD) patients using Cox-regression analysis.

Results: A total of 46,649 patients (39,472 HD and 6,177 PD) were enrolled for the analysis. The mean systolic blood pressure (SBP) was 134.4mmHg and 133.8mmHg in HD and PD patients, respectively. A comparable proportion of HD and PD patients was distributed in each SBP category. In this analysis, the reference SBP group was set as 120-140mmHg. In the HD group, the all-cause mortality increased as SBP was managed higher than 140. The mortality risk was also greater when SBP was lower than 120. As well in PD patients, the all-cause mortality risk increased when SBPs were managed below 120mmHg; however, higher systolic BPs in PD patients were not significantly associated with higher mortality. Managing systolic BP above 160mmHg in HD patients showed greater cardiovascular mortality whereas, higher blood pressure was not evidently associated with cardiovascular mortality in PD patients.

Conclusions: Blood pressure should be managed strictly as systolic blood pressure lower than 120mmHg or greater than 140mmHg is associated with higher mortality in Korean hemodialysis patients. Additional research is needed concerning peritoneal dialysis patients, as the impact of the ideal systolic blood pressure target differs from that observed in hemodialysis patients.

Systolic BP (mmHg)	Hemodialysis		Peritoneal Dialysis	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
All-cause mortality				
<120	1.05(0.997-1.111)	0.0647	1.19(1.033-1.364)	0.0158
120-<140	1		1	
140-<160	1.11(1.06-1.165)	<.0001	1.04(0.91-1.183)	0.5832
160-<180	1.24(1.158-1.316)	<.0001	1.12(0.938-1.339)	0.2101
≥180	1.32(1.183-1.47)	<.0001	1.45(1.078-1.957)	0.0143
Cardiovascular mortality				
<120	1.07(0.946-1.207)	0.2877	1.01(0.732-1.404)	0.9349
120-<140	1		1	
140-<160	1.08(0.967-1.201)	0.1766	1.06(0.791-1.419)	0.7003
160-<180	1.40(1.21-1.599)	<.0001	0.98(0.641-1.491)	0.9175
≥180	1.46(1.152-1.848)	0.0017	1.09(0.503-2.321)	0.8437

Table 1. All-cause and Cardiovascular Mortality in PD and HD Patients

FR-PO444

Impact of Obesity on Peritoneal Dialysis Outcomes: A Nationwide Inpatient Sample Analysis

Supawadee Suppadungsuk,[1,2] Charat Thongprayoon,[1] Wisit Kaewput,[3] Supawit Tangpanithandee,[2] Paul W. Davis,[1] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Chakri Naruebodin Medical Institute, Bang Phli, Thailand; [3]Phramongkutklao College of Medicine, Bangkok, Thailand.*

Background: Obesity can pose a significant challenge for performing peritoneal dialysis (PD) in end-stage kidney disease (ESKD) patients. This study aimed to assess the impact of obesity on in-hospital treatments, outcomes, and resource utilization in hospitalized ESKD patients receiving PD.

Methods: This study was conducted using the National Inpatient Sample to identify hospitalized ESKD patients receiving PD from the years 2003 to 2018. The in-hospital treatments, outcomes, and resource utilization were compared between obese and non-obese patients, adjusting for age, sex, race, year of hospitalization, and comorbidities.

Results: A total of 100,523 hospitalized ESKD patients receiving PD were included in the analysis. Of these, 9,890 (9.8%) had an obesity diagnosis. In the adjusted analysis, obese patients had a higher need for procedures for PD catheter adjustment or removal (OR 1.29; 95% CI 1.16-1.43), hemodialysis (OR 1.28; 95% CI 1.19-1.38), and mechanical ventilation (OR 1.29; 95% CI 1.16-1.44), compared to non-obese patients. Obesity was significantly associated with higher risk of PD peritonitis (OR 1.12; 95% CI 1.06-1.19) and fluid overload (OR 1.34; 95% CI 1.23-1.45) but lower in-hospital mortality (OR 0.84; 95% CI 0.73-0.96). No significant differences were observed in the length of hospital stay or hospitalization costs between the two groups.

Conclusions: Among hospitalized ESKD patients receiving PD, obesity was associated with higher PD-related complications but lower mortality. This suggests that while obesity may complicate the management of hospitalized ESKD patients on PD, it does not necessarily translate to increased mortality or healthcare expenses.

	Univariable analysis	p-value	Multivariable analysis	p-value
PD catheter adjustment	1.24 (1.12-1.37)	<0.001	1.29 (1.16-1.43)	<0.001
Hemodialysis	1.17 (1.09-1.25)	<0.001	1.28 (1.19-1.38)	<0.001
Mechanical ventilator	1.23 (1.11-1.36)	<0.001	1.29 (1.16-1.44)	<0.001
PD peritonitis	1.14 (1.08-1.21)	<0.001	1.12 (1.06-1.19)	<0.001
PD mechanical complication	1.00 (0.84-1.18)	0.985	0.94 (0.80-1.12)	0.52
Hyperkalemia	1.19 (1.11-1.27)	<0.001	1.06 (0.99-1.14)	0.10
Metabolic acidosis	1.24 (1.15-1.33)	<0.001	1.07 (0.99-1.16)	0.07
Volume overload	1.53 (1.41-1.65)	<0.001	1.34 (1.23-1.45)	<0.001
Sepsis	1.14 (1.08-1.22)	<0.001	1.06 (1.00-1.13)	0.06
Ventricular arrhythmia/cardiac arrest	1.07 (0.92-1.25)	0.354	0.99 (0.85-1.16)	0.94
In hospital mortality	0.67 (0.58-0.76)	<0.001	0.84 (0.73-0.96)	0.01
Length of hospital stay (days)	-0.14 (-0.31, 0.02)	0.08	0.11 (-0.06, 0.29)	0.20

FR-PO445

Comparative Outcomes of Peritoneal Dialysis across Different Hospital Settings: An Analysis of Urban Teaching, Urban Nonteaching, and Rural Hospitals

Supawadee Suppadungsuk,[1,2] Charat Thongprayoon,[1] Wisit Kaewput,[3] Paul W. Davis,[1] Supawit Tangpanithandee,[2] Wisit Cheungpasitporn.[1]
[1]Mayo Clinic Minnesota, Rochester, MN; [2]Chakri Naruebodin Medical Institute, Bang Phli, Thailand; [3]Phramongkutklao Hospital, Bangkok, Thailand.

Background: Patients with end-stage kidney disease (ESKD) receiving peritoneal dialysis (PD) are treated in a variety of hospital settings, including urban teaching, urban non-teaching, and rural hospitals. Understanding the differences in clinical characteristics, treatments, outcomes, and resource utilization specific to these hospital types is crucial for optimizing patient care.

Methods: This study utilized the National Inpatient Sample to identify hospitalized ESKD patients receiving PD in the United States from 2003 to 2018, The in-hospital treatments, outcomes, and resource utilization were compared across urban teaching, urban nonteaching, and rural hospitals.

Results: The study included 99,528 hospitalized ESKD patients receiving PD. Notable differences were observed across hospital types. The mean age was 57.2±16.1 years overall, with rural hospitals having older patients (59.5±16.1 years). The study population was 49.8% male. Racial distribution varied significantly, with rural hospitals having a higher proportion of White patients (70.4%). Charlson comorbidity scores were similar across all hospitals, with a median score of 4 (IQR 3-5). Hospitalization year, primary payer, and patient income levels varied significantly. Rural hospitals had shorter hospital stays (4 vs. 5 days) and lower costs ($19,534.5 vs. $31,583.5). Urban nonteaching and rural hospitals had slightly lower odds for PD catheter adjustments and lower odds of mechanical ventilation and palliative care. However, they had higher odds of peritonitis. Adjusted mortality odds were lower in rural hospitals (OR 0.72, 95% CI 0.59-0.87).

Conclusions: Significant differences in clinical characteristics, treatments, outcomes, and resource utilization were observed among hospitalized ESKD patients receiving PD across urban teaching, urban nonteaching, and rural hospitals. These findings emphasize the need for tailored approaches to optimize patient care based on the specific characteristics and needs of each hospital setting.

FR-PO446

Combination of Left Ventricular Ejection Fraction and End-Diastolic Diameter and Outcomes in Patients on Peritoneal Dialysis: A Multicenter Retrospective Study

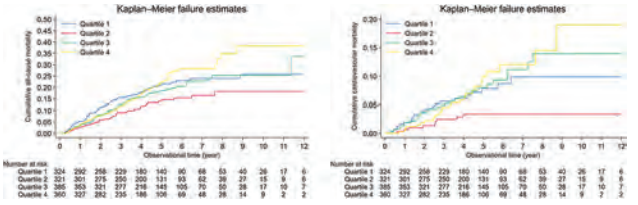
Jiayin You, Xianfeng Wu, Niansong Wang. *Shanghai 6th Peoples Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China.*

Background: End-stage renal disease (ESRD) is often complicated by left ventricular dysfunction, which is associated with a poor prognosis. This study aims to investigate the association between baseline left ventricular ejection fraction (LVEF) plus left ventricular end-diastolic diameter (LVEDD) with outcomes in peritoneal dialysis (PD) patients.

Methods: In this multicenter retrospective study, 1511 incident Chinese patients on PD between January 1, 2005 and December 31, 2021 were enrolled. Restricted cubic splines (RCS) were used to explore the non-linear associations between LVEF+LVEDD and the risk of mortality. Parametric models for interval-censored survival-time data (stintreg) were used to examine the association between LVEF+LVEDD quartiles and the outcomes.

Results: During 6451.11 person-years of follow-up [median 4.81 (IQR 3.61-6.81) years], 247 (17.8%) patients died, including 88 cardiovascular deaths. RCS showed a U-shaped association between LVEF+LVEDD and the risks of all-cause and CV mortality. According to the quartiles, the optimal range of LVEF+LVEDD associated with the lowest risk of all-cause and CV mortality was 103 to 107, which was set as the reference range. Both higher (≥115) and lower (<103) levels of LVEF+LVEDD were associated with increased risks of all-cause mortality (hazard ratio [HR] 2.20, 95% confidence interval [CI] 1.58-3.07; HR 1.68, 95% CI 1.19-2.36) and cardiovascular mortality (HR 2.51, 95% CI 1.33-4.75; HR 1.86, 95% CI 0.96-3.61).

Conclusions: Low and high levels of baseline LVEF+LVEDD were associated with increased risks of all-cause and cardiovascular mortality in PD patients.



FR-PO447

Efficacy and Survival of Patients with Heart Failure on Peritoneal Dialysis as an Ultrafiltration Option: A 10-Year Experience Based on the Catalan Renal Registry

Sara Nunez-Delgado,[1] María Azancot,[1] Juan C. León-Román,[1] Natalia Ramos,[1] Ana Sanchez Escuredo,[2] Maria Jose Soler.[1] *[1]Nephrology Department. Hospital Universitari Vall d'Hebron, Barcelona, Spain; [2]Nephrology Department. Hospital Sant Joan Despí - Consorci Sanitari Integral, Sant Joan Despí (Barcelona), Spain.*

Background: In heart failure (HF) disease, approximately 20% of patients will develop diuretic resistance over time. Peritoneal dialysis (PD) could be a therapeutic option, although its long-term outcomes were not reported. Our objective was to analyze the long-term outcomes of PD patients with HF indication (PD-HF).

Methods: Retrospective study of the Catalan Renal Registry of PD-HF patients between 2013-2022. Baseline clinical characteristics and follow-up until December/2022 was described.

Results: Of the 1874 patients starting PD, 198 (10.6 %) were PD-HF, median eGFR at start was 22.6 (IQR 14.8-32.8)ml/min1.73m^2 and 73.7% have an eGFR above 15 ml/min1.73m^2. The rest of the baseline characteristics are described in **table 1a**. Previous history of ischemic heart disease, arrhythmia or cardiac surgery was recorded, 39% of patients had ≥2 of these pathologies. HF etiology was described in 52.7%, being ischemic heart disease the most prevalent cause (44.4%). Echocardiographic records were available in 19.6% of patients (**table 1b).** Median survival was 20 months (IQR 16-24) (**figure 1**). In the cox multivariate analysis, age >75 years (HR 1.68 [95%CI 1.09-2.60]), frailty (HR 22.64 [95%CI 6.95-73.77]), and past cardiac surgery (HR 1.61 [95%CI 1.08-2.38]) were associated with poor survival (**table 1c**). 67 patients survived over 24 months. In the logistic regression analysis, age >75 years (OR 4.56 [95%CI 1,60-13,04]) and lower education level (OR 2,41 [95%CI 1,10-5,28]) were associated with higher mortality at 24 months (**table 1d**).

Conclusions: PD-HF is an appropriate option in patients with heart failure in non-advanced stages. Older age, frailty and lower education levels worsens the prognosis of PD-HF patients.

Table 1a. Baseline characteristics (n = 198)		
Sex (male): n (%)		145 (73.2)
Age: years ± SD		70.7 ± 9.3
Age (years): n (%)	< 65	41 (20.7)
	65-74	82 (40.9)
	≥75	76 (38.4)
Functional status: n (%)	Independent	30 (15.3)
	Partially frail	148 (80.4)
	Completely frail	6 (3.3)
Education level: n (%)	No education/primary level	106 (58.2)
	Secondary or above level	76 (41.8)
Familiar structure: n (%)	Lives alone	13 (7.1)
	Lives accompanied	169 (91.9)
	Lives in a nursing home	2 (1.1)
Previous follow-up time by Nephrology: months (IQR)		7.5 (2-25)
eGFR at start (CKD-EPI): ml/min·1.73m^2 (IQR)		22.6 (14.8 – 32.8)
eGFR at start (CKD-EPI. ml/min·1.73m^2): n (%)	< 15	46 (25)
	15-30	79 (42.9)
	>30	59 (32.1)
BMI (kg/m^2): n (%)	<20	8 (4.4)
	20-25	136 (73.9)
	>25	40 (21.7)
Diabetes: n (%)		107 (56.6)
Cerebrovascular disease: n (%)		26 (14)
Peripheral vascular disease: n (%)		70 (37.6)
COPD: n (%)		61(32.6)
EAA usage: n (%)		64 (35.6)
Cardiac disease: n (%)	Ischemic disease	117 (62.6)
	Arrythmia	119 (64.3)
	Cardiac surgery	87 (46.5)
Initial PD modality: n (%)	CAPD	187 (94.4)
	APD	11 (5.6)

Table 1b. Cardiac disease parameters		
Etiology of HF: n (%)	Ischemic	43 (23.4)
	Valvular	19 (10.3)
	Hypertensive	5 (2.7)
	Mixed	9 (4.9)
	Others	21 (11.4)
	Unknown	87 (47.3)
LVEF: n (%)	Preserved	7 (3.8)
	Reduced	29 (15.8)
	Unknown	148 (80.4)

Table 1c. Multivariate analysis of overall survival (Cox regression)		
	p	HR (CI 95%)
Sex: male	0.591	1.13 (0.72 - 1.77)
Age: >75 years	0.019	1.68 (1.09 - 2.60)
Functional status: partially frail	0.018	2.32 (1.16 - 4.64)
Functional status: completely frail	<0.001	22.64 (6.95 - 73.77)
Cardiac disease: past cardiac surgery	0.018	1.61 (1.08 - 2.38)

Table 2d: Multivariate analysis for death at 24 months (Logistic regression)		
	p	OR (CI 95%)
Sex: male	0.629	1.24 (0.52 - 2.92)
Age: >75 years	0.005	4.56 (1.60 - 13.04)
Education level: no education/primary studies	0.027	2.41 (1.10 - 5.28)
Functional status: partially frail	0.103	2.89 (0.81 - 10.34)

APD: automated peritoneal dialysis; BMI: Body Mass Index; CAPD: continuous ambulatory peritoneal dialysis; COPD: chronic obstructive pulmonary disease; EAA: erythropoiesis stimulating agents; eGFR: estimated glomerular filtration rate; HF: heart failure; LVEF: left ventricular ejection fraction; PD: peritoneal dialysis.

FR-PO448

Examining the Relationship between Hygiene Practices and Clinical Outcomes in Patients on Peritoneal Dialysis: Insights from the Thailand PDOPPS Initiative

Phatcharida Klinphayom,[1] Jeerath Phannajit,[1] Piyarat Rojsanga,[1] Somchai Eiam-Ong,[1] Kriang Tungsanga,[1] Jeffrey Perl,[3] David W. Johnson,[2] Roberto Pecoits-Filho,[4] Talerngsak Kanjanabuch.[1] *[1]King Chulalongkorn Memorial Hospital Department of Internal Medicine, Bangkok, Thailand; [2]Princess Alexandra Hospital, Woolloongabba, QLD, Australia; [3]St Michael's Hospital, Toronto, ON, Canada; [4]Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: Peritonitis is a leading cause of hemodialysis (HD) transfer and mortality. We investigated the association between hygiene behavior and clinical outcomes in patients on PD.

Methods: Personal hygiene was assessed in patients across 22 facilities in Thailand Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) during 2016-2021. Hygiene behavior was assessed using a short-form hygiene behavioral questionnaire comprising 8 domains (physical hygiene, prevention of contamination, and PD procedure/protocol) with a yes/no answer format. Poor hygiene behavior was defined as a cumulative score of ≥3. Cox proportional hazards model regression and Poisson regression incidence rate ratio (IRR) were employed to estimate associations between hygiene behavior and clinical outcomes, including mortality, HD transfer, and peritonitis.

Results: Of 1566 randomly selected patients on PD from 22 facilities, 669 consented and reported their hygiene behavior. Poor hygiene behavior was prevalent in the PD population (6%), especially in patients with diabetes and caregiver dependence. Poorer self-reported hygiene behavior at baseline was significantly associated with a higher rate of peritonitis and a shorter time to HD transfer but not death. This association persisted after adjusting for age, gender, PD vintage, comorbidities, shared frailty by study sites, and serum albumin.

Conclusions: Personal hygiene behavior was independently associated with higher risk of peritonitis and shorter time to HD transfer, but not death. The findings could potentially pave the way for evaluating hygiene standards using this tool, which could aid in identifying patients at a heightened risk (risk stratification) and determining those who would benefit from preventive measures.

FR-PO449

Higher Peritoneal Dialysis (PD) Facility Census Is Associated with Better PD-Specific Outcomes

Christopher D. Knapp,[1,2] Kirsten L. Johansen,[3,2] Shuling Li.[3] *[1]Hennepin Healthcare System Inc, Minneapolis, MN; [2]University of Minnesota Twin Cities, Minneapolis, MN; [3]Hennepin Healthcare Research Institute Chronic Disease Research Group, Minneapolis, MN.*

Background: Patients who receive PD care at facilities with more PD patients have lower rates of conversion to in-center hemodialysis (ICHD). It is not clear if a higher PD facility census is associated with differences in other outcomes.

Methods: We used the US Renal Data System to identify a cohort of incident PD patients from 2014-2018. Patients were categorized into 3 groups according to the year-end PD census at their initial PD facility: <11, 11-25 and >25 patients. All patients were followed up to one year for mortality and conversion to ICHD. A sub-cohort with Medicare fee-for-service coverage at PD initiation was followed for outcomes of hospitalization for peritonitis or cardiovascular disease (CVD). We used Cox models to estimate the hazards ratios (HR) for mortality, peritonitis, and CVD hospitalization and Fine-Gray competing risk models for conversion to in-center HD. Hazards for each outcome for the PD-census groups were compared.

Results: Of 58,219 PD patients, 15% were managed in a facility with a census of <11 patients, with 32% and 53% in facilities with PD censuses of 11-25 and >25, respectively. Patients in the <11 census group were more likely to be White and to live in non-urban areas. Unadjusted hazards for each outcome were higher for patients managed in lower census facilities (Table). After adjustment, the hazards of conversion to ICHD and peritonitis hospitalization were 6% and 11% higher, respectively (HR 1.06, 95% CI 1.01-1.11 for conversion, HR 1.11, 95% CI 1.01-1.22 for peritonitis) for patients in the 11-25 census group, but they had a 7% lower hazard of mortality compared with the >25 group (HR 0.93, 95% CI 0.87-0.99). Patients in the <11 group had a 20% higher hazard of conversion to ICHD compared with patients in the >25 group (HR 1.20, 95% CI 1.13-1.28).

Conclusions: A high facility PD census was associated with better PD-specific outcomes like peritonitis and conversion to ICHD but not with lower mortality.

Funding: NIDDK Support

Outcomes	PD Facility census ref= >25 PD patients	Unadjusted HR (95% CI) ref= >25 PD patients	Adjusted HR (95% CI) ref= >25 PD patients
All Cause Death	<11 patients	1.09 (1.00-1.18)	0.96 (0.88-1.05)
	11-25 patients	1.01 (0.95-1.08)	0.93 (0.97-0.99)
Conversion to ICHD	<11 patients	1.14 (1.07-1.21)	1.20 (1.13-1.28)
	11-25 patients	1.04 (1.00-1.09)	1.06 (1.01-1.11)
First hospitalization with peritonitis	<11 patients	1.04 (0.92-1.18)	1.08 (0.95-1.23)
	11-25 patients	1.09 (1.00-1.20)	1.11 (1.01-1.22)
First hospitalization for CVD	<11 patients	1.14 (1.04-1.24)	1.06 (0.97-1.17)
	11-25 patients	1.03 (0.96-1.11)	0.99 (0.92-1.06)

FR-PO450

Health Services Accessibility and Clinical Outcomes in Peritoneal Dialysis: Findings from the PDTAP Study

Qinghua Wang, Jie Dong. *Peking University First Hospital Department of Nephrology Renal Division, Beijing, China.*

Background: The association between health services accessibility and clinical outcomes has been revealed in patients with chronic kidney disease, but showing inconsistent findings. The study aimed to explore the association of key factors reflecting four dimensions of health services accessibility and clinical outcomes in peritoneal dialysis (PD) patients.

Methods: This is an affiliated study from the Peritoneal Dialysis Telemedicine-assisted Platform (PDTAP) dataset. Healthcare resource accessibility was evaluated by factors for four dimensions, such as hospital type and regional economic level for healthcare resource accessibility, education level and residence for socio-environmental accessibility, medical insurance and annual income for affordability, and travel distance and travel time for spatial accessibility. The primary outcome was all-cause mortality. The secondary outcomes included transfer to hemodialysis and first-episode PD-related peritonitis.

Results: A total of 7416 PD patients were enrolled between June 2016 and April 2019, with the median of 29.0 (14.3, 45.0) months for follow-up. By multivariable Cox regression analyzes, university-affiliated hospitals (HR 0.881, [0.780-0.996], $p < 0.001$), low regional economic level (HR 1.189 [1.035, 1.366], $p = 0.014$), and low annual income (HR 1.210 [1.023, 1.431], $p = 0.026$) were independently associated with all-cause mortality. The low level of regional economy and annual income played a stronger role in predicting all-cause mortality in university-affiliated hospitals as shown in analyzes for interactive effects. After propensity-score matching, university-affiliated hospitals were still associated with all-cause mortality (HR 0.817, [0.701-0.953], $p = 0.010$) and transfer to hemodialysis (HR 1.265 [1.065-1.502], $p = 0.007$) but not associated with first-episode peritonitis.

Conclusions: This study indicated real-world evidences for health services accessibility and clinical outcomes among patients on PD through a nation-level prospective cohort. Health policymakers and physicians in China should explore strategies to promote the equity in health services accessibility for the improvement of clinical outcomes in the PD population.

Funding: Government Support - Non-U.S.

FR-PO451

Hybrid Dialysis Outcomes in Qatar: 3-Year Experience

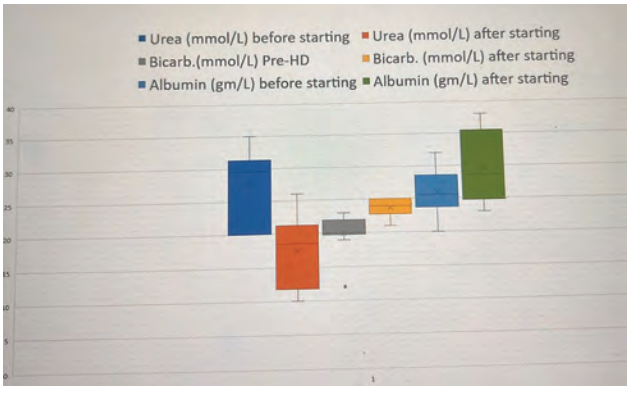
Mohammed E. Hussain, Mohamad M. Alkadi, Hanaa Ahmed, Nahid I. Ali, Merlina Vergel, Linu chacko Chacko, Ahlam B. Ali, Abdullah I. Hamad, Hassan A. Al-Malki. *Hamad Medical Corporation, Doha, Qatar.*

Background: Hybrid Dialysis is a combined dialysis modality using both Hemodialysis and Peritoneal dialysis.

Methods: PD patients with either low solute clearance or inadequate UF despite using the maximum applicable PD regimen were identified. We enrolled twenty-three patients (May 2021-April 2024). All of them were kept on once-weekly HD plus the current PD regimen 6 days per week. We evaluated volume status clinically. Pre-HD urea, potassium, phosphorus, and bicarbonate as indicators of solute clearance, and Albumin level as an indicator of nutritional state. In addition to dialysis catheter-related complications, patient satisfaction and finally checking outcomes.

Results: A significant improvement in volume status was associated with a reduction in mean Systolic Blood Pressure (174 ± 32 Vs 135± 15 mmHg, p < 0.0001). All solute clearance indicators showed significant improvement. Reduction in mean urea by 36.7% *p*-value < 0.001, mean potassium by 23.52% *p*-value <0.0001, and mean phosphorus reduction of 26.5 % *p*-value <0.01. The rise in mean bicarbonate was by 15.6 % *p*-value < 0.001. Improvement of mean serum albumin *p*-value <0.05 was observed. Patient satisfaction index was improved. Five patients (21.7%) shifted to Hemodialysis, Five Patients (21.7%), returned to Peritoneal dialysis, three patients (13%) underwent a kidney transplant, two patient leave the country and eight patients (34.8 %) still doing Hybrid dialysis some of them started more than 25 months, average staying was 16 months.

Conclusions: Hybrid dialysis is a reasonable dialysis model for patients with frequent volume overload, low solute clearance, or both on PD with significant improvement in volume status, Solute clearance, nutritional status, and patient satisfaction. Hybrid dialysis can be used for more than 24 months. Some patients can return to full PD most of them were started due to volume overload. A larger number of patients and is required to generalize the findings of these observations.



FR-PO452

Mortality and Hospitalization and Associated Factors in Assisted Home Hemodialysis Patients in the State of Qatar: A Retrospective Study

Abdullah I. Hamad,[1] Amani Zidan,[2] Mohamed Y. Abdelhai,[1] Mostafa Elshirbeny,[1] Tarek A. Ghonimi,[1] Hamza Ilyes Hassaine,[1] Mossab Filali,[1] Fadwa S. Al-Ali,[1] Mohamad M. Alkadi,[1] Hassan A. Al-Malki.[1]
[1]Hamad Medical Corporation, Doha, Qatar; [2]Qatar University, Doha, Qatar.

Background: Dialysis carries a high burden on patients with end stage kidney disease. It is usually associated with multiple co-morbidities that worsen patients' quality of life and outcome. We established an innovative assisted home hemodialysis (AHHD) program in Qatar in July 2021 for elderly patient who are dependent on ambulance transportation (bed bound or wheelchair). We are presenting data on mortality and hospitalization and associated risk factors in the AHHD program in Qatar.

Methods: We did a retrospective study from July 1st, 2021, to December 31st, 2023. All patients enrolled in our AHHD in Qatar were included. Data were extracted from our national electronic medical record. It included demographics, co-morbidities, laboratory tests, and clinical outcome data. The study was approved by Hamad Medical Corporation IRB.

Results: We included all 120 patients enrolled in AHHD program. Median age was 72.5 and 47.5% were males. The median (IQR) vintage HD was 41 (51) months (among which 13 (10) months of AHHD vintage). 51.7% of the patients used an ambulance with stretcher while 48.3% wheelchair. 87.5% had diabetes, 95% with hypertension, 25% with heart failure, 25% with cerebrovascular accidents, 38.3% with coronary artery disease, and 29.2% with arrhythmias. During the study period, 54.2% were hospitalized at least once. Logistic regression was performed to ascertain the effects of age, gender, AHHD vintage, mobility, and dialysis adequacy on the likelihood of mortality. The regression model was statistically significant, $\chi 2(5) = 28.564$, $p < .0005$. AHHD vintage was the only significant factor and associated with a decreased likelihood of mortality. For each one-month increase in AHHD vintage, the odds of mortality will decrease by 11.4% (CI: 0.801-0.969). For hospitalization, only AHHD vintage was statistically significant risk factor on logitic regression. For each one-month increase in AHHD vintage, the odds of hospitalizations will decrease by 6.9% (CI: 0.877-0.989).

Conclusions: Our study revealed an expected high mortality rate in AHHD program designed for elderly ambulance requiring patients with multiple co-morbidities. Vintage time on AHHD improved survival decreased hospitalization.

FR-PO453

Complexity of In-Hospital Admission Course in Patients on Kidney Replacement Therapy: A Comparative Analysis between Home Hemodialysis and In-Centre Hemodialysis: Experience from Saudi Arabia

Bilal Mohsin, Wael T. Habhab. *King Faisal Specialist Hospital and Research Centre - Jeddah, Jeddah, Saudi Arabia.*

Background: In patients with ESKD, in-center hemodialysis (IHD) and Home Hemodialysis (HHD) are two of the available modalities for Kidney Replacement Therapy (KRT). Patients receiving dialysis, whether in-center or at home, are at a high risk of hospitalization. We wanted to study the in-hospital course in patients undergoing these dialysis modalities.

Methods: This retrospective chart review included 42 adult patients (≥18 years) with ESKD who have completed one year of KRT, either IHD (n=21) or HHD(n=21) at King Faisal Specialist Hospital and Research Centre Jeddah (KFSHRCJ) between 01 August 2022 to 31 July 2023. We studied in-hospital admission encounters in both dialysis modalities in regards to frequency of admission, Inhospital consultations, Estimated length of stay(ELOS), all cause mortality and readmission within 30 days of discharge.

Results: We had a demographically comparable patient population in both groups. There were 59 admission encounters in IHD population as compared to 29 encounters in HHD. For IHD admissions, the number of subspecialities consulted was 2.37 per admission encounter with **total number of consultations (n=140).** In HHD admissions, the number of subspecialities consulted were 2.1 per admission with total **number of consultation (n=61).** The ELOS (Estimated Length of Stay) for IHD patients was 3.7 days per encounter with total hospital days (n=218) in a year follow up as compared to 4.1 days per encounter in HHD patients with total hospital days (n=118). There was **higher readmission rate in IHD** with same or different etiology within 30 days of discharge(n=12) as compared to HHD (n=4). The all cause mortality of patients who completed one year on KRT was 11 in IHD group as compared to 4 in HHD group. The leading cause of mortality was cardiovascular disease in IHD and infections in HHD group.

Conclusions: HHD was associated with lower events of hospitalization, less inhospital consultation burden, less cumulative ELOS, lower all cause mortality and lower rate of readmission as compared to IHD. These findings are limited by small sample size, single centre retrospective followup of one year. We need multicentre study with large sample size over longer duration of time to study the significance of outcomes in our study.

FR-PO454

Peritoneal Dialysis among Patients Initiated on Dialysis at a County Hospital: How to Do Better

Syed Afzal, Neha Siddiqui, Sarwar Khan, Helena Zhang, Hania Kassem. *Baylor College of Medicine, Houston, TX.*

Background: More than 37 million Americans are living with kidney disease. Approximately 800,000 have chronic kidney failure needing dialysis or kidney transplantation. Several studies have demonstrated the cost-effectiveness of peritoneal dialysis (PD) compared to in-center hemodialysis. Despite multiple interventions increasing awareness and incentives for stakeholders, the overall prevalence of patients on PD in the United States remains at less than 12% of total dialysis patients. Our project aimed to increase the rate of PD initiation among patients starting long-term dialysis at Ben Taub, a 402-bed county hospital in Texas, by 50% from baseline.

Methods: An anonymous survey was conducted to assess current understanding of PD among nephrology faculty and trainees at Ben Taub Hospital. The intervention consisted of 1) establishing a screening algorithm to define the eligibility and exclusion criteria for selecting appropriate PD candidates 2) establishing a protocol streamlining the referral process and expediting placement of a PD catheter prior to discharge, and 3) providing an educational session to nephrology faculty and trainees to teach the newly developed algorithm and protocol, bridge knowledge gaps, and address perceived barriers to PD initiation. A chart review study was conducted to collect data on the rates of PD candidacy screening and PD initiation pre- and post-intervention.

Results: In the three months prior to the intervention, a total of 29 ESKD patients were initiated on dialysis. Of those 29 patients, only 8 (27.5%) were screened for PD candidacy and 1 (3.5%) was initiated on PD. At 6 months post-intervention, a total of 78 patients were initiated on dialysis. The percentage of patients initiated on PD increased to 19% (15 of 78 total patients) which reflects nearly a 5-fold increase from baseline. Additionally, the rate of screening improved to 75.6% (59 of 78 total patients).

Conclusions: The results of this study show that simple interventions consisting of providing clinical education on PD to nephrology trainees and faculty and streamlining the referral and initiation process can increase the proportion of ESKD patients screened for PD candidacy and successfully initiated on PD in a county hospital setting.

FR-PO455

Peritoneal Dialysis Is Associated with Lower Mortality and Morbidity Compared with Hemodialysis in Patients Undergoing Cardiovascular Surgery: A Retrospective Cohort Study

Ankur Shah,[1] Osama El Shamy,[2] Jeffrey Perl,[3] Christina A. Raker,[4] Susie L. Hu.[1] *[1]Brown University Warren Alpert Medical School, Providence, RI; [2]The George Washington University, Washington, DC; [3]St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; [4]Rhode Island Hospital, Providence, RI.*

Background: Patients receiving maintenance dialysis face high mortality and complication rates following cardiovascular (CV) surgery. With the growing utilization of peritoneal dialysis (PD), it is important to understand the impact of modality on outcomes following CV surgery.

Methods: This retrospective cohort study used the National Inpatient Sample (2016-2020) to compare outcomes of PD and HD patients undergoing CV surgery. The primary outcome was in-hospital mortality, and secondary outcomes included prolonged ventilation, length of stay, and cost. The primary analysis used multivariable logistic regression to evaluate the association between dialysis modality and in-hospital mortality, adjusting for demographics, comorbid conditions, and hospital factors as potential confounders. Survey-specific analytic procedures incorporated discharge weights, sampling units, and sampling strata to generate nationally representative estimates for all analyses.

Results: A total of 30,155 patients were included in the study, with 28,015 (92.9%) receiving HD) and 2,140 (7.1%) receiving PD. Patients in the PD group experienced better outcomes compared to those in the HD group across all measured variables (table 4). The unadjusted mortality rate was lower in the PD group (4.4% vs 7.8%, OR 0.55, 95% CI 0.35-0.88), and this difference remained significant after adjustment (OR 0.61, 95% CI 0.38-0.97). Similarly, the incidence of prolonged ventilation was lower in the PD group (4.7% vs 9.7%, OR 0.45, 95% CI 0.29-0.71; aOR 0.51, 95% CI 0.32-0.81). The average length of stay was shorter in the PD group (13.6 vs 17.1 days, unadjusted IRR 0.79, 95% CI 0.74-0.85; adjusted IRR 0.85, 95% CI 0.80-0.91). Lastly, total charges were significantly lower in the PD group (mean $307,072 vs $407,556, unadjusted MD -$100,484, 95% CI -$124,773 to -$76,195; adjusted MD -$87,172, 95% CI -$113,523 to -$60,820). Among PD patients, post-operative transition to HD was associated with worse outcomes.

Conclusions: Maintaining PD during the perioperative period may confer benefits over HD, including lower healthcare costs and improved patient outcomes. Careful consideration of dialysis modality in the management of CV surgery patients is needed to optimize clinical outcomes and reduce healthcare costs.

FR-PO456

Associations with Peritoneal Dialysis Treatment Failure in Young Adults: A Mixed-Methods Study

Hannah C. Lyons, Alexander J. Hamilton, Fergus Caskey, Yoav Ben-Shlomo, Lucy E. Selman. *University of Bristol, Bristol, United Kingdom.*

Background: Studies have observed fewer young adults use peritoneal dialysis (PD) compared to haemodialysis (HD). PD is associated with preservation of residual renal function and may provide more flexibility for patients. We sought to understand treatment transitions and patient experiences.

Methods: A sequential explanatory mixed methods study was undertaken. Quantitative analysis utilized data from the Surveying People Experiencing young Adult Kidney failure study, which included individual treatment timelines from 1987 to 2015. Cox proportional hazards analysis examined psychosocial associations with PD failure (defined as a switch to haemodialysis). Semi-structured qualitative telephone interviews were conducted with a purposive sample of young individuals. Transcripts were analysed thematically.

Results: The cohort comprised 470 participants (50% male, 85% Caucasian, mean age of 16 years). Twenty-five percent experienced PD more than once. PD survival rates at 1 and 5 years were 71% and 37% respectively. Risk associations for PD failure included young adulthood (15-19 years hazard ratio (HR) 2.41, 95% confidence intervals (CI) 1.35, 4.28; 20-24 years HR 3.39, CI 1.97, 5.83; 25-30 years HR 3.14, CI 1.65, 6.00; p<0.005, compared to 10-14 years) and primary renal disease (systemic diseases HR 1.97, CI 1.12, 3.46, p=0.02, compared with tubulointerstitial diseases). Leading causes of PD failure were infection (50%), compliance issues (21%), and mechanical problems (18%). Thirteen participants aged 14-29 during PD treatment were interviewed. They had received PD during 2013-2015, but most had received renal transplants by the interview date in 2020 so they explored their experience retrospectively. Major themes included compromised autonomy, life impact and support structures; resilience was reported by PD survivors.

Conclusions: Young adulthood emerges as a high-risk period for returning to haemodialysis both from transplant failure and PD failure. Our study suggests the need for enhanced preparation including detailed information on dialysis modalities including considerations for university life, workplace environments and sexual relationships.

Funding: Government Support - Non-U.S.

FR-PO457

Exploring Peritoneal Dialysis Exits from a Canadian Cohort

Jennifer M. MacRae,[1] Tessa A. Woodside,[1] Bushra Muzammal,[1] Terry J. Smith,[3] Susan A. Jones,[3] Nikhil A. Shah.[2] *[1]University of Calgary, Calgary, AB, Canada; [2]University of Alberta, Edmonton, AB, Canada; [3]Alberta Health Services, Calgary, AB, Canada.*

Background: Growth in a peritoneal dialysis (PD) program is challenging to achieve. In order to increase the number of people receiving PD, the total number of people exiting should be less than the number of new starts. We sought to better understand the PD exits in our program in order to develop interventions to reduce the attrition from PD.

Methods: A 14 month retrospective review of the Alberta Kidney Care (AKC) PD program (comprised of a northern (AKCN, 317 pts) and a southern (AKCS, 298 pts) program with a focus on the reasons why people exited PD from November 1, 2022 until Dec 31, 2023. Differences between programs and between sexes were explored using descriptive statistics and Chi Square where appropriate. The primary outcome was the reason for exit from PD.

Results: During the study period 615 people received PD; 230 patients exited PD during this time frame. There were no differences in demographics between the 2 programs with the overall mean age of 61 ±16.3 years, comorbidities of DM 43% (123), CVD 91% (210) and heart failure 27% (63) and mean time on PD of 2.2 ± 1.9 years. Overall, 37% (230/615) exited PD, 45% (103) transferred to facility-based hemodialysis (HD), 21.3% (49) were transplanted, 19.1% (44) died and 11% (26) withdrew from dialysis. Patients who transferred to HD received PD for a similar amount of time (2.13 ±2.00) as compared to those who were transplanted (2.01± 1.92) or died (2.53 ± 1.88 years). The main reasons for transfer to HD included medical 43% (44), peritonitis 32% (33), and hernia/leaks 24% (24). Despite similar PD peritonitis rates, AKCN had more exit site (8.6% vs 1%) and tunnel (17.1% vs 3%) infections than AKCS. Catheter complications occurred more frequently in AKCS with more leaks (21% vs 8.6%) and catheter associated pain (10% vs 2.9%) in AKCS vs AKCN respectively.

Conclusions: There was a high turnover of people on PD with the majority transferring to HD for reasons of PD related infections and medical etiology. Strategies to reduce PD related infections will be helpful to reduce PD losses in our program. Further research into the differences in catheter complications and PD infections between the two programs is needed.

FR-PO458

Association of Serum Intact Parathyroid Hormone Levels with Sarcopenia in Patients Undergoing Peritoneal Dialysis

Yu Chi Chang,[1] Yu-Hsien Lai,[1,2] Bang-Gee Hsu.[1,2] *[1]Division of Nephrology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan.*

Background: Sarcopenia is highly prevalent in patients undergoing peritoneal dialysis (PD), contributing to adverse clinical outcomes. Animal models suggest that parathyroid hormone (PTH) induces muscle wasting through adipose tissue browning. However, the relationship between PTH dysregulation and sarcopenia in the PD population remains unclear. Thus, we aimed to explore the association between serum intact PTH levels and sarcopenia in PD patients.

Methods: We conducted a cross-sectional analysis using data from the Tzu-Chi PD cohort, comprising 186 PD patients with a mean age of 57.5 ± 14.1 years. Basic information, comorbidities, serum intact PTH levels, and other biochemical data were retrieved. Atherosclerotic cardiovascular disease (ASCVD) includes any history of coronary artery disease, myocardial infarction, peripheral arterial disease, and stroke. All patients were evaluated for appendicular skeletal muscle mass (ASM) using the Body Composition Monitor (BCM), handgrip strength, and 6-meter usual gait speed. Sarcopenia was defined based on the consensus of the Asian Working Group for Sarcopenia 2019. Relative over-hydration (OH) was also assessed using BCM.

Results: The overall prevalence of sarcopenia was 38.2%. Across three groups of PTH levels (< 150 pg/mL, 150-300 pg/mL, and > 300 pg/mL), the prevalence rates were 29.7%, 36.4%, and 46.2%, respectively (p for trend = 0.044). In the unadjusted model, age, ASCVD, subjective global assessment score, body mass index, relative OH, serum phosphorus, and log-transformed intact PTH levels were significantly associated with sarcopenia. After full adjustment for all above factors, age (OR = 1.04, 95% CI = 1.01–1.08), ASCVD (OR = 4.21, 95% CI = 1.37–12.96), BMI (OR = 0.51, 95% CI = 0.41–0.63), relative OH (OR = 1.04, 95% CI = 1.00–1.07), log-transformed intact PTH levels (OR = 3.41, 95% CI = 1.45–8.04) were independently associated with sarcopenia among PD patients.

Conclusions: Among PD patients, elevated serum intact PTH levels are independently associated with sarcopenia. Further longitudinal studies are warranted to confirm their causal relationship.

FR-PO459

Relationship between Exercise and the Occurrence of Abdominal Wall Complications among Patients on Peritoneal Dialysis

Li Xinqiu, Jie Dong. *Peking University First Hospital Department of Nephrology, Beijing, China.*

Background: Concerns about the development of abdominal wall complications are one of reasons for physical inactivity among peritoneal dialysis patients, but there was no direct evidence to confirm the relationship between exercise and abdominal wall complications. In the general population, the relationship between exercise and abdominal wall complications such as hernias remains controversial. This study aims to explore the relationship between exercise and abdominal pressure complications in peritoneal dialysis population.

Methods: A retrospective data analysis of a prospective cohort. Incident and prevalent PD patients between January 2016 and April 2019 were recruited. Abdominal wall complications related to increased intra-abdominal pressure, including hernia, hydrothorax, etc. were recorded during follow-up. Exercise characteristics were collected by outpatient questionnaire, including exercise or not, type of sports, exercise duration and exercise intensity. Competing risk model were used to assess the predictive power of exercise data in the occurrence of abdominal wall complications. The subgroups analysis according to age, gender, diabetes, BMI and eIPP were also performed.

Results: During the median follow-up of 46.0 months among the 475 PD patients, 33 (6.9%) patients developed abdominal wall complications. Totally 377(79.4%) patients had regular exercise. Walking was the major exercise form among 99.5% participants. Only 2 patients combined aerobic and impedance exercise. The median exercise duration per week was 210.0 (140.0, 350.0) minutes. About 52% patients having exercise intensity below fairly light. None of exercise characteristics including exercise or not, exercise duration per week, exercise intensity was found to be associated with abdominal wall complications in univariate or multivariate competing risk analysis. Similarly, no significant prognostic value was found in any subgroup analyses. The number of patients involved in impedance exercise was too small to do further analyse.

Conclusions: This study confirmed for the first time that aerobic exercise in appropriate duration and intensity didn't increase the risk of abdominal wall complications in peritoneal dialysis patients. Further research on resistance exercise and high-intensity exercise need to be further explored in the PD population.

FR-PO460

Summary of Complications in Maintenance Hemodialysis Using Tunneled Cuffed Catheters (TCC) in Our Hospital

Kazue Matsuoka, Kiyoshi Ikeda. *Ikeda Vascular Access Dialysis and Internal Medicine Clinic, Fukuoka, Japan.*

Background: With increasingly older populations, the number of patients using TCC in the long-term is on rising, in contrast to its use as an interim, or bridge, technique in the recent past. We suggest TCC as a vascular access (VA) equivalent to arteriovenous fistula (AVF) and arteriovenous graft (AVG) not only for in-center dialysis (ICHD) but also for patients who are considering home hemodialysis (HHD). In this study, we examined whether TCC can be used as safely as ICHD in HHD, where self-management is more important.

Methods: Patients who underwent maintenance dialysis for at least three months using TCC at our hospital from September 2010 to the end of February 2024 were included in the study. Exit/tunnel infection and bloodstream infection events were extracted retrospectively from the medical records, respectively. The evaluation period was from the date of TCC insertion, and the infection rate was calculated as the number of infections/ total number of dialysis days × 1000. The patency rate was evaluated from the date of insertion to the date of first removal due to complications, excluding bridge use cases.

Results: Among the study participants, 20 were treated with ICHD (TCC inserted age: 61.4 ± 15.2; man:woman ratio: 9:11; insertion period: mean 7.4 years; original disease: diabetes mellitus (DM); non-DM: 11:9) and 11 with HHD (TCC inserted age: 56.5 ± 11.3; man:woman ratio: 8:3; inserted period: mean 4.4 years; original disease: DM; non-DM: 4:7). The exit site/tunnel infection rate in TCC-ICHD was 1.27/1000 dialysis days and the bloodstream infection rate was 1.11/1000 dialysis days. Similarly, for TCC-HHD, the exit site/tunnel infection rate was 0.53/1000 dialysis days and the bloodstream infection rate was 0.91/1000 dialysis days, which were lower than those for TCC-ICHD, although not significantly different. Coagulase-negative *Staphylococci* and *Staphylococcus aureus* accounted for 70-80% of the bacteria detected in the blood cultures for both TCC-ICHD and TCC-HHD. The time to the onset of bloodstream infection was longer for TCC-HHD, averaging 0.5 years for TCC-ICHD and 2.3 years for TCC-HHD, suggesting that a long-term strategy for infection prevention was needed. Catheter patency rates did not differ between TCC-ICHD and TCC-HHD.

Conclusions: TCC represents a safe and effective option as a VA in HHD.

FR-PO461

Effects of Temporary Hemodialysis before Insertion of a Peritoneal Dialysis Catheter

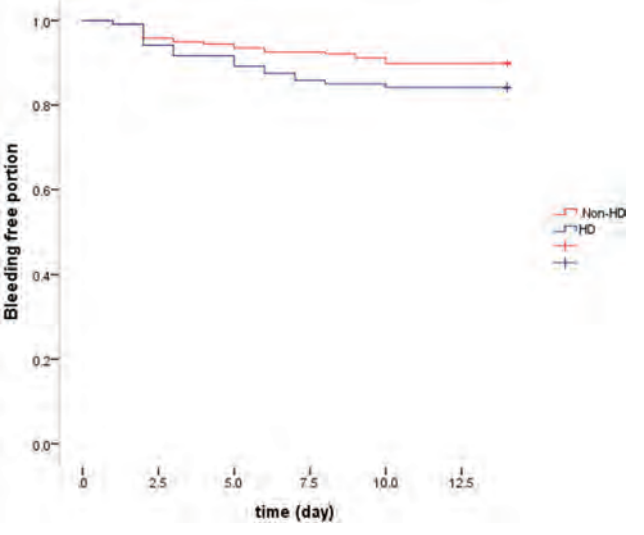
A Young Kim, Seok hui Kang, Ji Hyun Park. *Yeungnam University Medical Center, Daegu, Republic of Korea.*

Background: There is insufficient data on the effects of temporary hemodialysis, such as reducing uremic bleeding side effects when inserting a peritoneal dialysis catheter. We analyzed the effects of pre-emptive hemodialysis before insertion of a peritoneal dialysis catheter.

Methods: We retrospectively analyzed medical records. Patients were divided into two groups: those who underwent temporary hemodialysis before insertion of the peritoneal dialysis catheter and those who did not. Logistic regression and cox regression analysis were used to analyze risk factors affecting bleeding and catheter survival. Statistical significance was set $P < 0.05$.

Results: Of the 336 patients, 120 patients underwent temporary hemodialysis before peritoneal dialysis catheter insertion and 216 patients did not receive hemodialysis. Bleeding complications occurred in 43 (12.8%) of 336 patients. In Logistic regression analysis, there were no risk factors that showed a significant correlation with bleeding in the univariate analysis. In the multivariate analysis, there was a significant correlation between hemodialysis and bleeding (OR=2.2, 95% CI [1.09-4.43], P= 0.001). Hemoglobin and creatinine also showed a significant correlation with bleeding (P=0.027, P=0.017 respectively). The one-year catheter survival rate was 92.3%. Cox regression analysis was performed to analyze risk factors related to catheter survival. In both univariate and multivariate analysis, only infection showed a significant correlation with catheter survival (P= 0,002).

Conclusions: Temporary hemodialysis did not reduce the side effects of bleeding when inserting a peritoneal dialysis catheter. As renal function declines, the risk of uremic bleeding increases. If renal replacement therapy is necessary, it should be performed as soon as possible.



FR-PO462

Association of eGFR at Peritoneal Dialysis (PD) Catheter Insertion with PD-Related Complications

Arti Dhoot,[1,2] Alix Clarke,[3] Robert R. Quinn,[3] Matthew J. Oliver.[1,2] North American PD Catheter Registry. *[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [3]University of Calgary Cumming School of Medicine, Calgary, AB, Canada.*

Background: Guidelines now reflect a shift towards an intent to defer dialysis strategy, irrespective of modality. In peritoneal dialysis (PD), this may increase the risk of early complications. The objective of this study was to determine if early PD-related complications were associated with eGFR prior to PD catheter insertion.

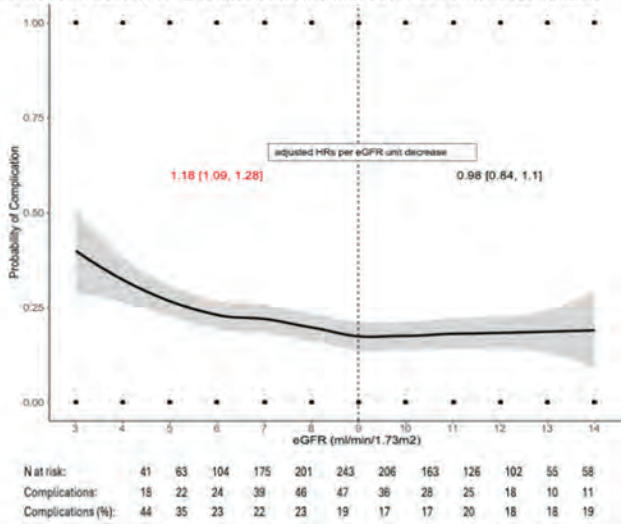
Methods: We conducted a retrospective study using the North American PD catheter registry across 23 sites. Patients undergoing PD catheter insertions were initially grouped by pre-dialysis eGFR ≤ 9 ml/min and ≥10 ml/min. The eGFR was then analyzed as a continuous variable. The primary outcome was the occurrence of PD related complications within 90 days of insertion. Adjusted risk between eGFR and outcomes was calculated using cause-specific Cox models.

Results: Of 1,537 patients with first PD catheter insertions, 1033 (67%) had a pre-dialysis eGFR < 9 versus 504 (33%) with ≥ 10. Patients with eGFR ≤ 9 were more likely to be younger (median age 60 vs.63), female (44 vs 32%) and have fewer comorbidities.

There was no significant difference in PD related complications between the eGFR ≤ 9 and eGFR ≥ 10 groups (aHR 1.12 [0.86, 1.45]). However, in the lower GFR group, which represented two-thirds of the population, there was an increased risk for every 1ml/min eGFR decline below 9ml/min (aHR 1.18 [1.09, 1.28]) (Figure 1). The most common PD-related complications included; flow restriction (7%), leak (3%) and pain (3%).

Conclusions: PD-related complications were similar when comparing an insertion eGFR of ≤9 to ≥10 ml/min. However, when assessing eGFR as a continuum, there was an increased risk of complications by 18% for each 1ml/min drop in GFR below 9ml/min suggesting intent to defer start targets should account for modality.

Figure 1. Probability of PD related outcome with eGFR as a continuous variable



FR-PO463

Novel Use of Intraperitoneal Acyclovir for Herpes Simplex Virus 2-Related Viral Peritonitis: A Case Report

Arti Dhoot,[1,2] Gemini Tanna,[1,2] Bourne L. Auguste.[1,2] *[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada.*

Introduction: Viral etiologies for peritonitis can be misclassified as culture negative peritonitis due to poor accessibility of viral testing in the effluent fluid. Inaccurate diagnosis and subsequent ineffective treatment can lead to unnecessary catheter removal for presumed refractory peritonitis. We present the only reported case of herpes simplex virus-2 (HSV-2) related PD peritonitis that was successfully treated with intraperitoneal (IP) acyclovir.

Case Description: A 73-year old female on continuous cyclic peritoneal dialysis with a past medical history relevant for HSV-2 genital lesions presented with a cloudy effluent, elevated effluent WBC count with lymphocytic predominance and a recent HSV-2 flare. Initially thought to be culture negative peritonitis but no reduction was seen in cell count on empiric IP cefazolin and ceftazidime. Effluent was sent for viral culture on day 8 and discovered to be positive for HSV-2 via PCR on day 12. Oral acyclovir was used initially but then converted to intraperitoneal route to minimize adverse events. IP acyclovir was reconstituted in a 2.5% Dianeal bag and administered for 14 days based on pharmacokinetic data to achieve serum levels similar to intravenous administration. Patient's cell counts improved and repeat effluent testing was negative for HSV-2 on day 27. Patient had no symptoms of neurotoxicity.

Discussion: Culture negative peritonitis can account for up to 20% of peritonitis cases however the effluent is largely just tested for bacterial and fungal presence. Clinicians should be aware to the possibility of viral peritonitis in patients with refractory culture negative peritonitis, especially if risk factors such as a history of HSV infection are present. Early recognition and timely initiation of antivirals may prevent inadvertent catheter removal for presumed refractory peritonitis and help retain patients on PD. Most importantly, utilizing IP route of administration for acyclovir may lead to lower drug related toxicity whilst achieving therapeutic serum concentrations and allow for ongoing outpatient management of home dialysis patients on PD.

Table 1. Timeline of events - including cell count and differential.

	Day 1	Day 3	Day 4	Day 5	Day 8	Day 11	Day 12	Day 13	Day 15	Day 19	Day 20
WBC (X10E6/l)	700	580	414	400	1200	563	403	300	123	61	20
Neutrophil	3%	27%	8%	14%	30%	25%	8%	8%	<1%	No Differential	
Lymphocyte	31%	33%	38%	45%	33%	37%	55%	43%	58%		
Macrophages	60%	38%	42%	29%	28%	27%	30%	39%	38%		
Eosinophils	5%	2%	11%	10%	9%	6%	7%	8%	<1%		
Culture	Culture negative No acid fast bacilli				PCR: HSV-2 Positive (Reported on Day 12)						
Treatment	IP Cefazolin & IP Ceftazidime						Antibiotics stopped PO acyclovir	IP Acyclovir 200-300mg in Dianeal solution			

FR-PO464

Comparison of Peritoneal Dialysis Catheter (PDC) Placement Outcomes via Image-Guided Percutaneous (IGP) Technique vs. Laparoscopic Surgical (ALS) Technique

Ali Poyan-Mehr, Alvina Sundang, Todd Drasin, Neelam M. Bhalla, Sijie Zheng, Leonid Pravoverov. *The Permanente Medical Group Inc, Oakland, CA.*

Background: The IGP technique presents several potential opportunities when placing PDCs. Some cited factors include avoiding general anesthesia, better availability of IR suites, and being less resource-intensive than OR suites. As part of the Kaiser Permanente Northern California (KPNC) quality assurance effort, we have monitored patient and procedure characteristics and compared PDC outcomes by IGP vs. ALS.

Methods: In this retrospective study, we analyzed the outcomes of patients undergoing PDC placement in KPNC from 1/1/18 to 12/31/22. Patients were identified based on procedure codes and ESKD diagnoses. Baseline and outcome variables were extracted electronically.

Results: 3,062 patients underwent PDC placement, and 27% were placed via the IGP technique. As shown in Table 1, patients in the IGP had statistically significantly lower BMI, eGFR, and albumin levels at PDC placement but a significantly higher number of patients with heart failure. A greater proportion of patients in the IGP group had their procedure done while inpatient for other indications. The average length of stay for patients admitted post-procedure was shorter in the IGP group. The 90-day and 180-day catheter intervention rates were lower in the IGP group (not accounting for confounders). There was no statistical difference between the two groups' 30-day readmission and mortality rates.

Conclusions: Expanding utilization of home dialysis is one of the pillars of value-based care in nephrology. This QA study illustrates that IGP can be a safe and effective approach to lowering the barriers to peritoneal dialysis adoption by expanding access to care while maintaining desirable patient outcomes and utilizing fewer healthcare resources.

Funding: Clinical Revenue Support

Patient Characteristics	Total (n=3062)	IGP (n=835)	ALS (n=2227)	p-value
Age, yr, mean (SD)	60 (15)	60 (15)	60 (15)	0.41
Female sex, n (%)	1209 (39)	291 (35)	918 (41)	0.001
Race and Ethnicity				
African American, n (%)	425 (14)	139 (17)	286 (13)	0.008
American Indians or Alaska Natives, n (%)	10 (0.3)	4 (0.5)	6 (0.3)	0.47
Asian or Pacific Islander, n (%)	1033 (34)	312 (37)	721 (32)	0.01
Hispanic, n (%)	653 (21)	155 (19)	498 (22)	0.02
White, n (%)	899 (29)	203 (24)	696 (31)	0.0002
Other/Unknown, n (%)	24 (0.8)	8 (1)	16 (0.7)	0.48
BMI, kg m^2, median (IQR)	28.1 (24.3-32.7)	26.9 (24.1-30.7)	28.4 (24.5-33.6)	<0.0001
eGFR, ml min^{-1}, median (IQR)	10 (7.6-12.6)	9.6 (7.3-12.3)	10.2 (7.8-12.7)	0.001
Hemoglobin, mean (SD)	10.1 (1.8)	9.9 (1.7)	10.2 (1.6)	0.0002
Serum albumin, mean (SD)	3.6 (0.8)	3.5 (0.6)	3.6 (0.6)	0.002
Comorbidities, n (%)				
COPD	263 (8.6)	83 (9.9)	180 (8.1)	0.11
Diabetes	2196 (71.7)	594 (71.1)	1602 (71.9)	0.68
Glomerulonephritis	129 (4.2)	33 (4)	96 (4.3)	0.76
Heart failure	1011 (33)	304 (36.4)	707 (31.8)	0.01
Hypertension	999 (32.6)	248 (29.7)	751 (33.7)	0.03
Polycystic kidney disease	73 (2.4)	13 (1.6)	60 (2.7)	0.08
Procedure Characteristics				
In-patient, n (%)	688 (22.5)	252 (30.2)	436 (19.6)	<0.0001
Out-patient, n (%)	2374 (77.5)	583 (69.8)	1791 (80.4)	<0.0001
Patient Outcomes				
Same-day discharge, n (%)*	2246 (94.6)	542 (93)	1704 (95.1)	0.05
Post procedure length of stay, days, mean (SD)†	2.7 (2.7)	1.8 (0.7)	3.1 (3.1)	0.01
90-day catheter-related interventions, n (%)	64 (2.1)	8 (1)	56 (2.5)	0.006
180-day catheter-relatad interventions, n (%)	99 (3.2)	11(1.3)	88 (4)	0.0001
30-day readmission, n (%)	326 (10.6)	90 (10.9)	236 (10.6)	0.89
30-day mortality, n (%)	14 (0.5)	7 (0.8)	7 (0.3)	0.07

Table 1. Baseline characteristics and key clinical outcomes. *excluding patients already hospitalized for other indications prior to the procedure (out-patient only), † Out-patients who were admitted post procedure. Mean, SD, and t-test were used for continues variable with a normal distribution. Median, IQR, and Mann-Whitney test were used for continues variables without normal distribution. Fisher's exact test used for categorial variables.

Baseline characteristics and key outcomes.

FR-PO465

Partial Replantation Method for Managing Peritoneal Dialysis Catheter Damage and Infections

Seyoung Ryou,[1] Hyung Duk Kim,[2] Yaeni Kim.[1] *[1]The Catholic University of Korea Seoul St Mary's Hospital, Seocho-gu, Seoul, Republic of Korea; [2]The Catholic University of Korea Eunpyeong St Mary's Hospital, Eunpyeong-gu, Seoul, Republic of Korea.*

Background: The revised 2023 guidelines from the International Society for Peritoneal Dialysis (ISPD) emphasize salvage methods for treating refractory exit site infections (ESI) and tunnel infections (TI), preserving the existing catheter by manipulating only the outer cuff above the peritoneum, there by avoiding hemodialysis transfer. Here, we investigated the efficacy of the partial replantation technique.

Methods: In this retrospective study from January 2021 to December 2023 at a single center, we compared 9 patients undergoing salvage methods with 58 patients receiving de novo catheter insertion. Our evaluation included ESI, TI, peritonitis, and catheter dysfunction. The salvage technique involved distal cutting of the infected or mechanically impaired catheter and connecting a new one using a connector comprising a PD adaptor and transfer set [Figure1].

Results: During the study period, nine patients (four males, mean age 56 years) with an average PD duration of 66 months underwent the salvage technique. Post-replantation outcomes included, one ESI case (11.1%), one TI case (11.1%), three peritonitis cases (33.3%), and two catheter removals (22.2%). No procedural complications or catheter

dysfunctions were observed. The control group experienced similar rates of ESI (10.3%), TI (1.7%), peritonitis (19.0%), catheter removal (12.1%), and catheter dysfunction (1.7%). Kaplan-Meier analysis demonstrated no significant differences in outcomes between the two groups (ESI; p=0.31, TI; p=0.094, peritonitis; p=0.84, catheter dysfunction; p=0.69, catheter removal; p=0.39) [Figure2].

Conclusions: This study confirms non-inferiority and effectiveness of the salvage technique compared to de novo for managing ESI, TI and mechanical impairment of the catheter.

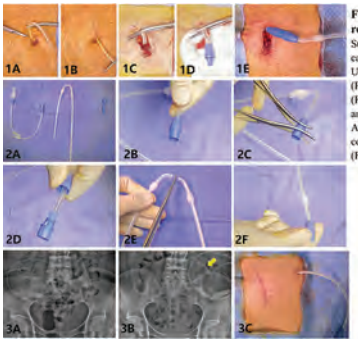


Figure 1. Surgical procedure illustrating the partial replantation technique,
Surgical steps are as follows: Make an incision at the PD catheter exit and cut the proximal part of the catheter (Fig.1B-C). Use Tenckhoff catheter, transfer set, and PD catheter adaptor (Fig.2A). Disassemble the connector with Kelly forceps (Fig.2B-D), cut the new catheter between cuffs (Fig.2E), and connect it at the proximal end (Fig.2F). Attach Luer lock adaptor to old catheter end (Fig.1D), connect to new catheter (Fig.1E), and create a new tunnel (Fig.3C).

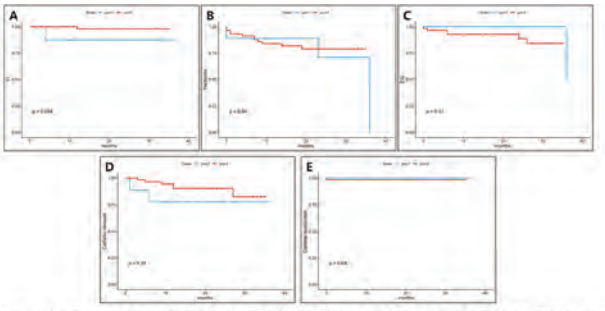


Figure 2. Kaplan-Meier analysis comparing clinical outcomes between partial replantation and de novo catheter insertion of catheters. (A) TI(tunnel infection), p: 0.094, (B) Peritonitis, p: 0.84, (C) ESI(exit-site infection), p: 0.31, (D) Catheter removal, p: 0.39, (E) Catheter dysfunction, p: 0.69, Grp1: catheter replantation, Grp2: de novo catheter insertion

FR-PO466

Tissue Plasminogen Activator (tPA) Use for Peritoneal Dialysis Catheter Dysfunction

Caroline M. Hsu,[1] Harold Manley,[2] Antonia Harford,[2] Austin Gibson,[2] Nien Chen Li,[2] Scot E. Born,[2] Monica Shieu,[2] Daniel E. Weiner,[1] Dana Miskulin,[1] Klemens B. Meyer,[1] Doug Johnson,[2] Eduardo K. Lacson.[2,1] *[1]Tufts Medical Center, Boston, MA; [2]Dialysis Clinic Inc, Nashville, TN.*

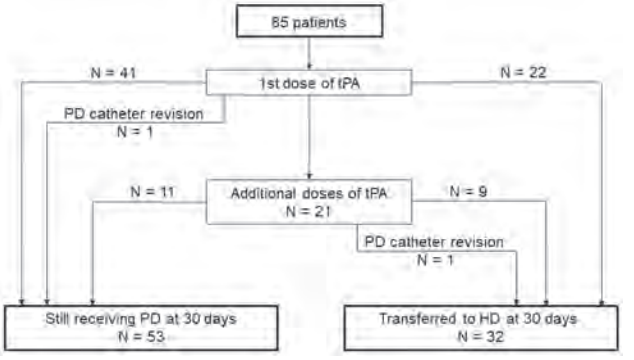
Background: Peritoneal dialysis (PD) catheter dysfunction accounts for 10-14% of PD to hemodialysis (HD) transfers. Tissue plasminogen activator (tPA) is sometimes used for PD catheter dysfunction, but reports of its effectiveness vary.

Methods: This retrospective study included all instances of tPA used for poor flow or catheter dysfunction in PD patients from January 1, 2020 to December 31, 2023, excluding tPA use for peritonitis. Data collected from the electronic health record included the number and timing of tPA doses and whether the patient subsequently continued PD therapy, underwent PD catheter revision, or transferred to HD within 30 days of the initial tPA treatment. Manual chart review collected additional detail on reasons for tPA use.

Results: Among 5297 patients receiving PD at DCI during the study period, tPA was administered 114 times for poor flow or catheter dysfunction in 85 patients (catheter vintage median 11 months [IQR 2, 22]). Per manual chart review, 48 instances were for both poor inflow and poor outflow, 52 instances were for poor outflow only, and the indication for tPA could not be determined in 14 instances. Among 64 patients who received a single dose of tPA, 41 continued PD, 22 transferred to HD without further intervention, and one continued PD after catheter revision (Figure). Among 21 patients who received two or more tPA doses, 11 continued PD and 10 transferred to HD, with one transferring to HD after PD catheter revision. Primary reasons for transfer to HD included PD catheter failure (N = 14), intra-abdominal pathology (5), peritonitis (4), ultrafiltration failure (4), inadequate clearance (1), and not documented (4).

Conclusions: Among 85 patients who received 114 tPA treatments, 53 patients (46%) continued PD. More granular data on patient selection, catheter position, and potential causes of catheter failure will inform optimal use of tPA for PD catheter dysfunction.

Funding: Other NIH Support - NCATS grant 1K12TR004384



FR-PO467

Assessment of Glycemic Profiles Using Continuous Glucose Monitoring in Patients with ESKD Treated with Automated Peritoneal Dialysis

Thatsaphan Srithongkul, Methawoot Khemmongkon, Suchai Sritippayawan, Sukit Raksasuk. *Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.*

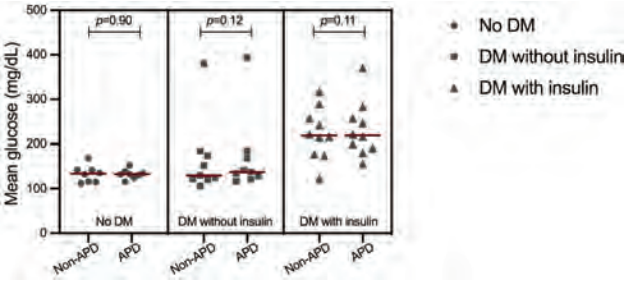
Background: The patients using automated peritoneal dialysis (APD) faced unphysiological glucose loading during nighttime, which caused difficulty in glycemic control. Data on glucose dynamics in patients using APD was still limited. This study aimed to evaluate 24-hour glycemic profiles in APD patients by continuous glucose monitoring (CGM)

Methods: In this cross-sectional study, 30 APD patients were enrolled, including 10 diabetes (DM) with insulin used, 10 DM without insulin used, and 10 non-DM. All participants underwent seven days of CGM. The primary outcome was the glycemic profiles demonstrated by mean and under the curve (AUC) of interstitial glucose concentrations and the mean amplitude of glycemic excursions (MAGE). Data analysis encompassed the whole 7-day period and compared daytime and nighttime

Results: There were no significant differences in the mean glucose, AUC, and MAGE between the APD and non-APD periods in all groups. The mean difference in glucose during daytime and nighttime was comparable between DM with insulin and non-DM group (p= 0.364). During the APD period, the mean glucose, MAGE, and AUC were significantly higher in DM patients with insulin compared to non-DM patients ($p \leq 0.05$). Dialysate glucose exposure did not influence the disparity in mean glucose concentration and AUC during the APD period in both DM (p=0.508) and non-DM groups (p =1.00). From multivariate analysis, only DM with insulin-used status was associated with mean glucose concentration (coefficient 97.84, p =0.03), while membrane transport status and glucose concentration in dialysate showed no association

Conclusions: ESKD patients using APD demonstrated comparable glycemic profiles during the APD and non-APD period with unphysiological non-glucose dipping during nighttime among all DM statuses

Funding: Government Support - Non-U.S.



Mean glucose during APD and non-APD periods in each group

FR-PO468

Glycemia Assessed by Continuous Glucose Monitoring among Patients on Dialysis

Laura Mayeda,[1,2] Leila R. Zelnick,[1] Subbulaxmi Trikudanathan,[1] Irl B. Hirsch,[1] Nathaniel Ashford,[1] Yoshio N. Hall,[1] Ian De Boer.[1] *[1]University of Washington, Seattle, WA; [2]Northwest Kidney Centers, Seattle, WA.*

Background: In kidney failure, patients are at risk for hypo- and hyperglycemia due to impaired insulin sensitivity, insulin secretion, and kidney gluconeogenesis. Little is known about glycemia patterns in dialysis patients and HbA1c is biased in kidney failure and does not reflect fluctuations in blood glucose.

Methods: The Blood Sugar Sensing On Maintenance Dialysis (BLOSSOM) study is a prospective community-based cohort of people treated with dialysis, with or without diabetes mellitus (DM), designed to assess the prevalence, causes, and consequences of dysglycemia using continuous glucose monitoring (CGM). Participant wore a Dexcom G6Pro CGM for 10 days. This interim analysis of the first 373 BLOSSOM participants.

Results: Participants had a mean (SD) age of 61 (14) years. We enrolled 231 participants with DM (including 81 HD patients no longer treated with glucose-lowering drugs) and 142 without DM. Mean CGM blood glucose was high and time in range (TIR) was low (below 70% clinical target in diabetes) for participants with DM, regardless of dialysis modality (Table). PD participants without DM also had low TIR (Table). Hyperglycemia increased throughout the day and was the highest in participants with treated DM on PD (Figure). Hypoglycemia was common for HD patients with or without DM (Table).

Conclusions: In this community-based sample of maintenance dialysis patients, uncontrolled hyperglycemia was highly prevalent, especially among participants with DM and PD participants without DM, and hypoglycemia was frequent.

Funding: NIDDK Support

	Overall (N=373)	HD – No DM (N=118)	HD - Treated DM (N=134)	HD - Untreated DM (N=81)	PD – No DM (N=17)	PD - DM (N=23)
Blood glucose (mg/dL), mean (SD)	170 (63)	121 (16)	211 (62)	163 (56)	142 (19)	223 (62)
Time in range*, % (SD)	60 (29)	78 (15)	44 (28)	69 (27)	54 (27)	38 (27)
Hypoglycemia (<70 mg/dL), number of events (% of participants with one event)	599 (35%)	330 (46%)	187 (29%)	104 (31%)	11 (18%)	17 (35%)

*In range is 70-140 mg/dL for participants without DM, and 70-180 mg/dL for participants with DM.
Diabetes mellitus (DM)

Table. Glycemia metrics assessed using continuous glucose monitoring, by dialysis modality and diabetes status

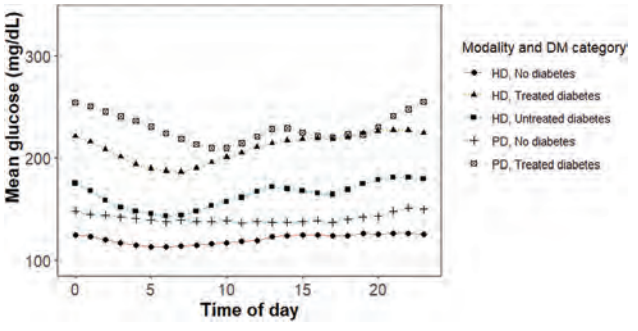


Figure. Continuous glucose monitoring data by dialysis modality and diabetes status

FR-PO469

Understanding the Impact of the Kidney Care Choices (KCC) Model on Utilization and Cost of Care

Darin F. Ullman,[1] Brighita M. Negrusa,[2] Richard A. Hirth,[2] Claudia Dahlerus,[2] Sarah E. Lewis,[3] Kelsey R. Bacon,[1] Annalise Maillet,[1] Vahakn Shahinian,[2] Jonathan H. Segal,[2] Jennifer Wiens.[1] *[1]The Lewin Group, Falls Church, VA; [2]University of Michigan, Ann Arbor, MI; [3]Center for Medicare and Medicaid Innovation, Baltimore, MD.*

Background: The Kidney Care Choices (KCC) Model implements provider incentives designed to delay the onset of end-stage renal disease, better prepare patients for dialysis, coordinate care across settings, and increase kidney transplantation. Nephrology practices could join the Kidney Care First (KCF) model option or could combine with transplant providers and other partners such as dialysis facilities to form a Kidney Contracting Entity (KCE) and join the Comprehensive Kidney Care Contracting (CKCC) model option. This study evaluated how this voluntary model affects Medicare payments and utilization, particularly for modalities of dialysis care.

Methods: Using a difference-in-differences (DiD) approach, we estimated the effect of the KCC Model on outcomes relative to a comparison group from before the model (2017–2019) to the Model's first performance year (PY) (2022). For both model options, the comparison group selection process focused on nephrology practices, with separate comparison groups created for CKCC and KCF model options. We evaluated changes in utilization, Total Medicare Parts A & B payments, and service-specific payments. The sample consisted of 293,491 KCC patients (KCF=23,580; CKCC=269,911) and 138,264 comparison patients (KCF comparison=17,997; CKCC comparison=120,267) across the entire study period. KCC Participants (25 KCFs and 53 KCEs) represented 2,856 nephrology professionals and KCE partnerships included 2,217 dialysis facilities and 133 transplant providers.

Results: In KCF, home dialysis (peritoneal dialysis or home hemodialysis) rose by 2.1 percentage points (pp) ($p<0.05$), or 2% in relative terms. In CKCC, peritoneal dialysis increased by 0.74 pp ($p<0.10$), or 8%. CKCC had an increase in home dialysis training (0.15 pp [$p<0.01$], or 32%). Kidney transplant active waitlisting increased by 1.8 pp ($p<0.01$), or 15%, for CKCC. General utilization measures, such as hospitalizations and emergency department use, were unaffected. KCF home dialysis payments increased by $45 per patient per month ($p<0.01$).

Conclusions: Overall, the KCC Model showed some promising effects in its first year, including increased home dialysis use and active transplant waitlisting.

Funding: Other U.S. Government Support

FR-PO470

Impact of a New Payment Model on Optimal ESKD Starts

Claudia Dahlerus,[1] Darin F. Ullman,[2] Richard A. Hirth,[1] Brighita M. Negrusa,[2] Sarah E. Lewis,[3] Jonathan H. Segal,[1] Vahakn Shahinian,[1] Tammie A. Nahra,[1] Joseph Gunden,[1] Jennifer Wiens.[2] Kidney Epidemiology and Cost Center. *[1]University of Michigan, Ann Arbor, MI; [2]The Lewin Group, Falls Church, VA; [3]Center for Medicare and Medicaid Innovation, Baltimore, MD.*

Background: CMS' Kidney Care Choices (KCC) Model aims to delay ESKD^ onset, better prepare patients for chronic dialysis, and increase kidney transplantation. A nephrology practice can participate under the Kidney Care First (KCF) model option, or, nephrology professionals/practices can partner with transplant providers and other optional partners to form a Kidney Contracting Entity under the Comprehensive Kidney Care Contracting (CKCC) model option. One KCC quality metric is the percentage of patients who have an "optimal ESKD start." Credit is given for any of the following outcomes: ESKD patients that start on home dialysis; start in-center hemodialysis with a fistula or graft vs. a catheter; or receive a preemptive kidney transplant. We examined the impact of the KCC Model on optimal ESKD starts.

Methods: We used a propensity score matched comparison group and difference-in-differences (DiD) methods to assess trends pre (2017-2019) and post model implementation (2022), adjusted for patient, practice, and market differences. We used CMS claims and the CMS 2728 Form to identify optimal starts for patients aligned to KCF and CKCC participants relative to practice level matched comparison groups. The sample consisted of eligible FFS Medicare beneficiaries with Stage 4 or 5 CKD or ESKD aligned to the KCF and CKCC model options and matched comparison groups during the study period. There were 22,131 KCC and 15,087 comparison patients across the entire study period. Ninety-one percent of patients were aligned to the CKCC option.

Results: While the proportion of patients who had an Optimal ESKD Start increased over time for both KCC and comparison groups, the KCC Model increased Optimal ESKD Starts 6.9 percentage points ($p<0.05$, 16% of baseline mean) above the baseline trend for beneficiaries aligned to the CKCC option. This impact was driven by increases in home dialysis starts and starting in-center HD with an AV fistula or AV graft. Improvement was not significantly better in the KCF option relative to its comparison group.

Conclusions: Results suggest nephrologists may be able to modify processes of care to improve planned starts for new ESKD patients. ^For the purposes of this abstract, ESKD and ESRD can be used interchangeably. CMS uses ESRD in the KCC Model to be concordant with the ESRD Medicare benefit.

Funding: Other U.S. Government Support

FR-PO471

Quantifying the Waste Associated with Icodextrin in Patients Undergoing Continuous Cycling Peritoneal Dialysis

Anukul Ghimire,[1] David Ward,[1] Elena Qirjazi,[1] Nikhil A. Shah,[2] George Vitale.[1] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada.*

Background: Effective healthcare waste (HCW) management and HCW reduction are important considerations for medical programs. Dialysis is associated with significant hazardous and non hazardous HCW. Icodextrin is commonly used in patients undergoing continuous cycling peritoneal dialysis (CCPD). In Canada, Icodextrin for CCPD is only available as 2.5 L, single-use bags. Patient's often have Icodextrin fill volumes < 2L, with the remainder of the volume being discarded as non-hazardous HCW. We sought to quantify the volume of discarded Icodextrin solution in the CCPD population of the Alberta Kidney Care South (AKC-S) program.

Methods: A cross sectional audit was performed of the AKC-S program including all patients utilizing CCPD in 2022. Data included Icodextrin dwell volume, patient demographics, and estimated costs associated with Icodextrin use in 2021. Descriptive statistics were used to report the data.

Results: Among 205 patients in the AKC-S program on CCPD, the mean age and PD vintage (± standard error of mean) was 62.7 ± 0.9 years and 27.5 ± 2.1 months respectively. The average Icodextrin dwell volume was 1200 mL. 87% of the patients using Icodextrin were using dwell volumes up to 1500 mL. Our patient population tended to be similar in weight compared to those in previous studies evaluating Icodextrin for the long dwell. In 2021, Icodextrin for CCPD cost AKC-S $1.27 million (CAD).

Conclusions: Among patients in the AKC-S program, there is a notable difference in the average fill volume (1200 mL) and available bags of Icodextrin (2.5L) available. This suggests that a large portion of purchased Icodextrin is being discarded as non-hazardous HCW. This practice pattern may also be reflected in other home dialysis programs and further work is needed to (1) understand the large-scale costs and environmental impact associated with Icodextrin waste, (2) develop effective methods to manage HCW in dialysis programs, and (3) implement quality improvement initiatives to reduce HCW associated with peritoneal dialysis.

FR-PO472

Peritoneal Dialysis in Patients with Crohn Disease: Absolute Contraindication or Grey Area with Pink and Purple Polka Dots?

Shannon Ejiofor, Twinkle Patel, Mowaffaq R. Said, Manar Shmais, Kana Miyata. *Saint Louis University School of Medicine, St Louis, MO.*

Introduction: Most end-stage kidney disease (ESKD) patients with inflammatory bowel disease (IBD) undergo hemodialysis (HD) because IBD has traditionally been considered a clinical contraindication to peritoneal dialysis (PD). Literature regarding PD use in IBD patients is scarce. We present two cases where PD was initiated in patients with Crohn's Disease (CD).

Case Description: Case 1: A 46-year-old man with a history of stricturing ileocolonic CD for 20 years developed ESKD from monoclonal gammopathy of renal significance and acute interstitial nephritis possibly related to Vedolizumab. His CD was in clinical remission with Risankizumab at the initiation of PD. He had surgical history of cholecystectomy and bilateral inguinal repair. PD catheter was placed percutaneously with fluoroscopic guidance by Interventional Nephrology. He was started on continuous cycler peritoneal dialysis, which was later transitioned to once-a-day exchange of Icodextrin. He received a kidney transplant 7 month after the initiation of PD. He did not develop any episodes of PD peritonitis during the period. Case 2: A 27-year-old man with a history of CD for 7 years became ESKD from IgA nephropathy. He had non-stricturing non-penetrating ileal CD, previously treated with Azathioprine, Adalimumab, Ustekinumab, and Vedolizumab without persistent response. He was on Risankizumab at the initiation of PD and he was in endoscopic remission based on a normal ileocolonoscopy. He did not have previous abdominal surgeries. A PD catheter was placed under fluoroscopy. However, he immediately experienced outflow failure. A laparoscopic revision of PD catheter was performed with fibrin sheath dissection and partial omentectomy, during which some adhesions from the omentum to the pelvic wall were found. Because he continued to have PD catheter malfunctioning, the catheter was removed, and he was transitioned to HD. He continued HD until he received a kidney transplant 7 months later.

Discussion: We present one successful and one unsuccessful case of PD use in CD. Our cases demonstrate that it may be possible in IBD patients under the proper conditions, with clear remission and a clear plan for prompt transplantation if they are considered candidates. Further research is needed to define the detailed indications and contraindications of PD in patients with IBD.

FR-PO473

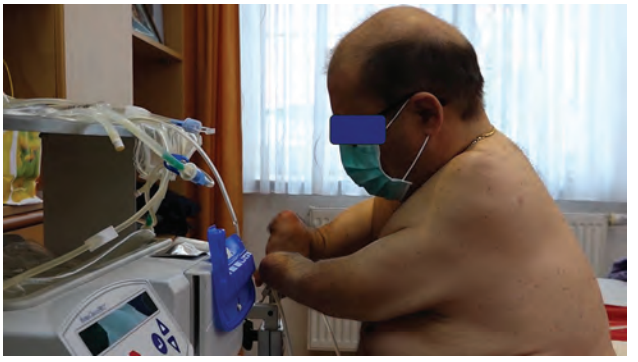
Mission P(D)-possible: Enabling Peritoneal Dialysis in Situations Formerly Thought to Be Impossible, Eight Inspiring Cases

Kijanosh Lehmann, Jan T. Kielstein, Amelie Gienapp, Manuela Lindgren, Reinhard K. Wanninger, Gabriele C. Eden. Kielstein Lab. *Stadtisches Klinikum Braunschweig gGmbH, Braunschweig, Germany.*

Introduction: Tom Cruise currently tries for the seventh time to do the impossible in "Dead Reckoning". We try to do the same in PD, an underutilized form of kidney replacement therapy (KRT). In this abstract we present an inspiring collection of 8 individual cases, in which, despite co-diseases currently thought to be contraindications for PD, this treatment modality could successfully implemented.

Case Description: In 2023, 81 PD catheters were implanted at our center, cahnging the view on "contraindications" to PD. PD despite major abdominal surgery including subtotal colectomy and hemicolectomy as well as comtinuation of PD despite colostomy are reported. Further, a patient with ADPKD and liver cysts who undergoes PD with adequate dialysis effectiveness for almost 5 years, despite rejecting unilateral nephrectomy challanged our view about contriaindications for PD. Moreover, Calciphylaxis (CUA) often considered a contraindication for continuing PD, can successfully be managed with intensified PD and administration of sodium thiosulfate. Frequently anuria is viewed as a contraindication to PD, a view we do not share in general. In cases intellectual disability, hemodialysis is often preferred, however, there are cases in which PD can be carried out successfully such as in trisomy 21. Missing arms are a drastic obstacle to carrying out PD. This hurdle could also be solved through technical assistance and interprofessional collaboration, as was the case with our patient with amelia due to thalidomide embryopathy (Figure 1).

Discussion: It will not be before 2025 that Tom Cruise will accomplish a mission impossible again. Meanwhile interprofessional teams worldwide will do the impossible many times by enabling PD in those patients who have chosen this form of KRT, focussing on patient-centered outcomes.



Patient with Contergan induced dysmelia connecting himself to a PD cycler (consent on file).

FR-PO474

Embedded Peritoneal Dialysis Catheter: When Things Go Wrong

Madhab Ray, Niti Madan, Shubha Ananthakrishnan. *University of California Davis, Davis, CA.*

Introduction: Embedment of peritoneal dialysis catheter is sometimes used when a patient with ESRD does not need dialysis immediately, but it may be necessary in the months to come. The procedure of embedment is relatively safe and short, gives time to develop a scar around the catheter and, reduces chance of infection and leak. The catheter becomes readily available for use upon externalization of the tip. Various complications including malfunction and infection are seen when an embedded catheter is externalized. However, some embedded catheters are never externalized and thus the procedure becomes a futile exercise. Infection in an unused embedded catheter is rare. We report a case of infection in an embedded PD catheter which was never externalized or used.

Case Description: A 61yr old female with HIV (CD4 928, viral load undetectable, on ABC/3TC/DTG), positive HBV core antibody, hypertension, hyperlipidemia and CKD G5 A3 (due to NSAIDS, hypertension and side effect of HIV medications with secondary FSGS) got an embedded PD catheter placed. Nine months later the patient presented with abdominal pain. She was found to have cellulitis of the abdominal wall adjacent to embedded catheter and the culture of the purulent fluid from incision and drainage along with her blood culture showed MRSA infection. The patient was treated with appropriate course of antibiotics and her catheter was surgically removed without any further complication. She never required dialysis and got living donor kidney transplant 10 months after removal of the PD catheter.

Discussion: Embedment of a PD catheter in patients with ESRD under consideration of peritoneal dialysis has gained popularity. It helps in increasing the acceptance rate of peritoneal dialysis as the modality of choice. It offers readiness and gives opportunity for scarring of the surgical site providing a seal around the catheter and reducing the possibility of infection and leak. However, different studies question the overall benefit of such a procedure for the risk of nonfunction of the exteriorized catheter, infection, catheter being never used because of a transplant or change of dialysis modality to hemodialysis. These different possibilities need to be considered before planning to embed a catheter. The risk of infection increases with the duration of embedment and more so in the immunocompromised patient. Proper case selection is crucial to minimize such risk.

FR-PO475

Effect of Dupilumab in Treating Refractory Allergic Dermatitis to Peritoneal Dialysis Catheter: A Case Report

Jun Takeoka,[1] Naohiro Toda,[1] Ryo Sato,[1] Kyoka Fujita,[1] Satoshi Kurahashi,[1] Hisako Hirashima,[1] Eri Muso,[1] Toshiyuki Komiya,[2] Akira Ishii.[1] *[1]Kansai Denryoku Byoin, Osaka, Japan; [2]Otsu Sekijuji Byoin Toshoshitsu, Otsu, Japan.*

Introduction: Eosinophilia during induction of peritoneal dialysis (PD) is frequently caused by icodextrin, but allergic reactions to PD catheters has been rarely reported. We report a case of refractory systemic contact dermatitis associated with a PD catheter that was successfully treated with dupilumab, avoiding catheter removal.

Case Description: A 62-year-old man underwent PD catheter implantation by Moncrief-Popovich technique due to progression of diabetic kidney disease five months before admission. One month later, he developed generalized pruritus and his eosinophils were elevated to 2500/μL. Topical steroids and antihistamines were started, but itching did not get better and eosinophil count remained high. One month before admission, he started PD. The itching became unbearably intense, and the patient was hospitalized because of erythema and desquamation on whole body. Eosinophilic peritonitis and reactivation of human herpes virus 6 (HHV6) were not observed. He was started on PSL (10mg daily), but his eosinophil count remained around 2000/μL and his skin rash did not improve. Drug-induced lymphocyte stimulation test (DLST) was negative for several

drug and positive for PD catheter. Systemic contact dermatitis caused by the PD catheter was diagnosed from the DLST result. After the PSL dose was increased to 40 mg daily for refractory systemic contact dermatitis with liver damage, the eosinophil count and skin rash improved. Administration of dupilumab allowed PSL withdrawal and maintained skin status and eosinophil count.

Discussion: As the patient had type 2 diabetes mellitus, long-term oral administration of PSL should be avoided from the viewpoint of glucose tolerance and susceptibility to infection. Dupilumab is an IL4/IL13 receptor monoclonal antibody and is used for refractory atopic dermatitis, but there are no reports of dupilumab use for allergic dermatitis caused by PD catheters. In this case, the use of dupilumab allowed PD continuation without eosinophil elevation or flare-ups of skin rash even after gradual PSL reduction.

FR-PO476

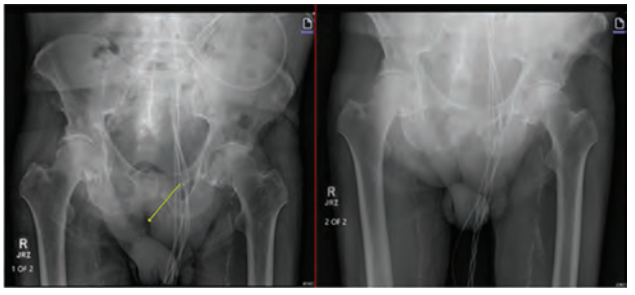
Peritoneal Dialysis Catheter Migration into an Inguinal Hernia

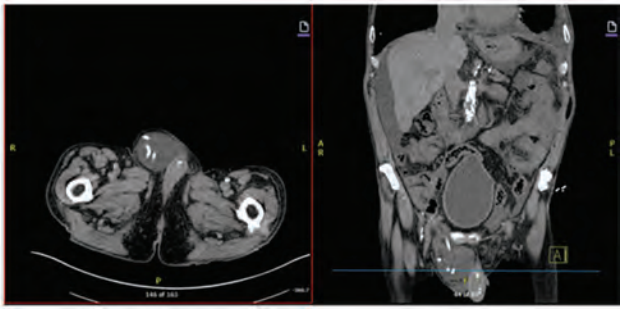
Manuel A. Santos Carrasquillo, Scott D. Cohen, Rute C. Paixao. *Cleveland Clinic Florida, Weston, FL.*

Introduction: Peritoneal Dialysis (PD) is associated with improved patient quality of life compared to hemodialysis. There are important infectious and non-infectious complications of PD that must be recognized to facilitate successful therapy. We present a case of an End Stage Renal Disease (ESRD) patient on Continuous Cyclic Peritoneal Dialysis (CCPD) therapy who presented with catheter malfunction secondary to outflow obstruction.

Case Description: 77-year-old male with a history of ESRD on CCPD and bilateral inguinal hernias presented to the ED with PD catheter drainage problems for 2 days. He underwent a physical exam, a pelvis x-ray (Fig.1) and a CT Abdomen and Pelvis showing a migration of the catheter from the posterior left hemipelvis through his right inguinal hernia into the scrotum (Fig 2). Surgery was consulted and the patient underwent laparoscopy repositioning of the PD catheter and laparoscopic bilateral inguinal hernia repair with mesh (extraperitoneal approach). PD was held after surgery and restarted 48 hrs later with low fill volumes. The patient has continued PD without additional complications to date.

Discussion: It is important to recognize noninfectious complications of PD, including causes of poor catheter drainage. Inguinal hernias are common noninfectious complications in PD (reported in 4–14% of patients). There are several case reports on patients with decreased PD catheter drainage where the catheter was found to have migrated through the inguinal hernia sac. Surgery, ultimately, allowed these patients to continue with PD. Prompt identification and repair of inguinal hernias can facilitate continued PD and prevent catheter drainage issues. Careful physical examination and correction of inguinal hernias are important for PD patients.





FR-PO477

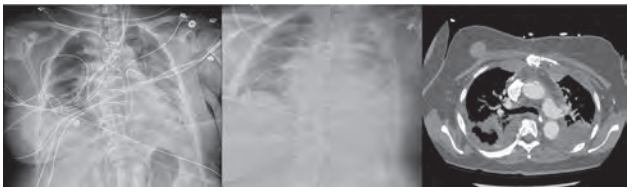
Pleuroperitoneal Diaphragmatic Communication: A Rare Complication in Patients on Peritoneal Dialysis after Cardiac Surgery

Samira M. Samant, Camilo Cortesi. *Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA.*

Introduction: Pleuroperitoneal diaphragmatic communication (PPDC) is an extremely rare but serious complication of peritoneal dialysis (PD). Elevated intra-abdominal pressure creates a fistula between the pleural and peritoneal spaces, allowing peritoneal fluid migration and causing effusions or hydrothorax. While approximately 25% of patients are asymptomatic, presentations include dyspnea or, in extreme cases, lung collapse. To our knowledge, this is the first case of PPDC described in the literature post-cardiac surgery.

Case Description: A 57-year-old female with end-stage renal disease due to focal segmental glomerulosclerosis, recently started on PD and undergoing transplant evaluation, presented with NSTEMI and multivessel coronary artery disease. Post-coronary artery bypass grafting (CABG), she received continuous renal replacement therapy. After her bilateral surgical chest tubes were removed, she resumed PD when off vasopressors three days later. The next day, a routine chest X-ray revealed new bibasilar opacities, and chest CT showed large bilateral pleural effusions. Given her significant negative fluid balance, these large effusions in the absence of hypoxemia were concerning for a pleuroperitoneal leak due to recent chest tubes. Pleural fluid glucose was elevated compared to serum levels. A right chest tube was placed, and she transitioned to hemodialysis with improvement.

Discussion: PPDC, although exceedingly rare, should be considered in PD patients with pleural effusions, particularly if volume negative and postsurgical. PPDC usually arises from increased intra-abdominal pressure due to large-volume PD solution instillation, coughing, straining, or trauma, allowing peritoneal fluid to traverse the diaphragm. In postsurgical patients, recent chest tubes or diaphragmatic instrumentation may be the cause. Elevated pleural fluid glucose indicates peritoneal dialysate presence; MRI or scintigraphy can confirm a fistula. Management includes a PD holiday, pleural cavity tetracycline instillation, surgical patch grafting of the diaphragm, or talc pleurodesis.



CXR with BL chest tubes (left), CXR after chest tube removal with new effusion (middle), CT chest with BL effusions

FR-PO478

The Fastest Way to a Person's Heart: A Case of Peritoneal-Pericardial Leak after Pericardiocentesis in a Patient on Peritoneal Dialysis

Neha Siddiqui, Wolfgang C. Winkelmayer, Hania Kassem. *Baylor College of Medicine, Houston, TX.*

Introduction: While peritoneal dialysis (PD) is a cost effective dialysis modality, it is associated with infectious and non-infectious complications including PD fluid leaks. Leakage of dialysate into the pericardium is an uncommon yet potentially life-threatening complication of PD. To our knowledge, there are very few cases of peritoneal-pericardial leaks reported in the literature.

Case Description: A 55-year-old Hispanic female with a past medical history of CKD stage V secondary to DM and HTN (biopsy proven), presented to the emergency department with shortness of breath and was found to have a pericardial effusion with early tamponade physiology. Patient underwent successful pericardiocentesis via a sub-xyphoid approach with removal of 500cc of serous fluid and was discharged on diuretics. She was readmitted shortly afterwards for shortness of breath, was found to have worsening pleural effusions requiring chest tubes placement, and was initiated on PD urgently during that admission. Patient was admitted again a few days later with similar complaints and was found to have another pericardial effusion. PD was continued during that admission with no improvement in breathing despite multiple changes in the prescription. CXR showed complete opacification of the right lung. Therefore, a CT peritoneography was obtained to rule out pleuroperitoneal communication but showed instead direct communication between the peritoneal dialysate and a large pericardial effusion. Decision was made to discontinue PD and to initiate hemodialysis resulting in improvement in symptoms.

Discussion: Similarly to previous reports, the peritoneal-pericardial communication in this patient likely resulted from pericardiocentesis. The procedure has been reported to cause communications between the pericardium and the pleural and peritoneal space. However, communication with the peritoneum is unlikely to be recognized or be clinically significant except in PD patients due to the possibility of peritoneal fluid leaking into the

pericardium. This represents a rare yet critical complication of PD, posing a significant threat to life. Physicians should be mindful of peritoneopericardial fistulas as a possible complication in PD patients who undergo pericardiocentesis since a timely diagnosis is crucial to promptly discontinue PD and mitigate further risks.

FR-PO479

Peritonitis and Hemoperitoneum in Peritoneal Dialysis: A Rare Traumatic Complication

Michael Liben, Aashvi R. Dalal, Timothy S. Pak, Yuanpu Zheng. *NewYork-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY.*

Introduction: The most common complications of peritoneal dialysis (PD) catheters include infections and mechanical catheter dysfunction. Perioperative complications of catheter insertion include intraabdominal organ perforation and bleeding, while delayed complications include impaired dialysate flow, pericatheter leakage, and superficial cuff extrusion. Here, we present an interesting case of an acutely ill PD patient with multiple PD complications.

Case Description: A 44 year old man with End Stage Renal Disease (ESRD) on PD presented to the hospital with septic encephalopathy, inability to complete cycler PD for three days, and bloody PD effluent. Preceding the admission, he had a three month history of PD peritonitis treated by his outpatient nephrologist with intraperitoneal (IP) Vancomycin. After hospitalization, he was given broad spectrum intravenous (IV) and IP antibiotics for culture confirmed and recurrent Staphylococcus epidermidis peritonitis. Cycler PD was not reattempted, and the patient was given manual PD with 2.5 liters every six hours including IP cefazolin and heparin as well as hemodialysis (HD). He had continued grossly bloody PD effluent with red blood cell counts of 650,000/uL on admission decreasing only to 320,000/uL after one week, necessitating transfusions of ten units of packed red blood cells over this period.

Discussion: Initial and repeat computed tomography of the abdomen and pelvis demonstrated displaced PD catheter tip terminating in the right abdomen, as well as an expanding intraabdominal fluid collection without active IV contrast extravasation. Surgery performed an exploratory laparoscopy with extensive lysis of adhesions, converted to open laparotomy, and the PD catheter course was tracked entering the lower abdomen directly into the urinary bladder. Cystotomy finally revealed that the source of bleeding was within the bladder itself, and the remaining hematoma was evacuated. The PD catheter was completely removed, and Urology was consulted intraoperatively for bladder repair/closure. The patient later remarked that 3 days prior to admission, he fell onto a truck dolly causing blunt force trauma to his abdomen, followed immediately by PD cycler low flow errors and blood in the PD effluent. He remained anuric throughout the hospitalization and eventually clinically recovered. He was discharged in good condition to continue on HD.

FR-PO480

Peritoneal Dialysis-Associated Peritonitis with Kytococcus schroeteri

Akash Hazari, Alexandra Rosario Aulet, Anupkumar Shetty. *Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Peritonitis is a known complication of PD and common organisms include gram-positive cocci such as *Staphylococcus epidermidis, Staphylococcus aureus and enteric Gram negative bacilli.* We present a case of peritonitis in a PD patient with a rare gram-positive organism, *Kytococcus schroeteri.*

Case Description: 50-year-old male with ESRD due to diabetes mellitus and hypertension on peritoneal dialysis was noted to have signs and symptoms of peritonitis and peritoneal effluent culture grew *Kytococcus schroeteri.* Initial fluid was milky with PD fluid WBC count was 16686 predominantly(80%) neutrophils and it came down to 81 on day 6, <50 on day 11, 65 on day 15 and 99 on day 21 after starting intraperitoneal vancomycin. He received intraperitoneal gentamicin during the first 5 days. Rifampin had to be stopped due to allergic reaction to it. Intraperitoneal tPA was given to break the fibrin in the peritoneum and 2 additional weeks of intraperitoneal vancomycin was given with improvement in the PD WBC count to <10 and effluent culture remained negative. Staining and culture for acid fast bacilli and fungal cultures were negative. Proper hygiene and techniques were reinforced.

Discussion: Kytococcus organisms are rare causes of bacteremia in the immunosuppressed and device related infection. This is the first case of PD related peritonitis caused by *K. schroeteri* based on our literature search even though there is one published case report of PD peritonitis from *Kytococcus sedentarius. K. schroeteri* is resistant to penicillin, cephalosporin, erythromycin and clindamycin and sensitive to vancomycin, rifampin, daptomycin and linezolid. Generally dual therapy is needed and rifampin is an important component associated with successful outcome. Since Kytococcus is a skin organism, root cause analysis should include assessment of dialysis technique to prevent future episodes. ISPD has no specific suggestions on treatment of Kytococcus peritonitis, but 3-4 weeks of treatment with two antibiotics seems reasonable along with fungal prophylaxis.

FR-PO481

Mycobacterium abscessus Peritonitis: An Uncommon Yet Significant Cause of Peritoneal Dialysis-Associated Peritonitis

Devin M. Boe, Chanwoo Nam, Keiko I. Greenberg, Negiin Pourafshar. *MedStar Georgetown University Hospital, Washington, DC.*

Introduction: Peritoneal dialysis (PD) is generally safe and well tolerated, but peritonitis is a common complication. Mycobacterium (M) species associated peritonitis in PD patients is uncommon with complex treatment.

Case Description: We report the case of a 79-year-old female with end-stage renal disease (ESRD) due to diabetic nephropathy on PD, breast cancer in remission, initially presented to our institution with abdominal pain and cloudy effluent. CT scan of her abdomen did not show any abnormalities; Initial analysis of PD fluid was negative, with no organism grown. Empirical PD peritonitis treatment with intra-peritoneal antibiotics did not improve her symptoms. Later, culture of PD fluid showed growth of acid-fast bacilli. She required intravenous antibiotics, PD catheter removal and a switch to hemodialysis. Cultures of the PD fluid later grew M abscessus, and the antibiotic regimen was changed appropriately to therapy with intravenous (IV) micafungin, linezolid, Eravacycline, azithromycin, imipenem, and amikacin, leading to clinical improvement. Auditory function was monitored by audiogram every two weeks due to potential ototoxicity of amikacin. Repeat imaging later revealed that the infection had caused a 2 cm abdominal wall abscess, necessitating a longer course of antimicrobials. She remained stable and was discharged on Eravacycline, Linezolid and Amikacin.

Discussion: Mycobacterium abscessus-associated peritonitis in PD patients is an uncommon occurrence. Clinicians should maintain awareness of this possibility when patients fail to show clinical improvement despite treatment with standard broad-spectrum antibiotics, particularly in cases where PD fluid initially deemed to be culture negative. The complex treatment experienced by our patient underscores the importance of remaining vigilant against opportunistic infections, even among immunocompetent individuals without apparent risk factors. To effectively manage such cases, it is imperative to send PD fluid samples for acid-fast bacillus testing. If Mycobacterium species are detected, further analysis using genome-wide sequencing is recommended to confirm the specific strain of Mycobacterium involved. Prompt removal of the catheter along with peritoneal washout is crucial for achieving clinical improvement and preventing further complications.

FR-PO482

Peritoneal Dialysis-Related Peritonitis from Nontuberculous Mycobacterium abscessus: A Rare Complication

Stephanie D. Ice, Ojaswi S. Tomar. *West Virginia University School of Medicine, Morgantown, WV.*

Introduction: Nontuberculous Mycobacterium (NTM) accounts for 3% of Peritoneal dialysis (PD)-related peritonitis, mostly from M. *Fortuitum.* PD-related peritonitis caused by M. *abscessus* is exceedingly rare. Only 38 cases are reported in the literature since 1998 including just 3 previous cases from the USA. Mean interval between diagnosis and treatment initiation is 4 weeks as culture and antibiotic susceptibility results take weeks. Treatment is challenging and prognosis is poor with 25% mortality rate. Diagnosis requires a high index of suspicion. PD fluid should be stained for acid-fast bacilli. Here we report a case of *M. abscessus* causing PD-related peritonitis in a lung transplant recipient.

Case Description: 69 year-old male with 10-year history of lung transplant presented with 4 days of abdominal pain, cloudy effluent and nausea. Admission labs showed CRP 72 mg/L (<10 mg/L), lactic acid of 3.16 mmol/L (<2 mmol/L), WBC count 9000/microL (4000-11000/microL). PD fluid studies showed 828 cells/mm3 with 94% neutrophils consistent with peritonitis. Broad-spectrum antibiotics were started. PD fluid culture grew gram-positive rods on day 8 and acid-fast bacilli on day 9. MTB complex PCR was negative. On day 13, he developed septic shock. PD fluid culture on day 17 grew M. abscessus. PD catheter was removed, and he was transferred to hemodialysis on day 18. He was discharged at 5 weeks on hemodialysis. He received 1 month of azithromycin, 1 month of linezolid, 6 months of intravenous cefoxitin and oral Omadacycline. He succumbed to lung infections 8 months later.

Discussion: Gram-positive or gram-negative bacteria are most common causes of PD-related peritonitis. NTM-related infections are on the rise, but M. abscessus causing PD-related peritonitis is exceedingly rare. It is often mistaken for Corynebacterium species or diphtheroid on gram stain. Immunocompromised and solid organ transplant recipients are at increased risk, hence a high index of suspicion is required. PD fluid must be examined promptly for acid-fast bacilli using Zeihl-Nelson stain. Eradication is difficult and requires several months of antibiotics, longer in immunocompromised patients. Encapsulating peritoneal sclerosis is a serious complication. ISPD guidelines suggest removing the PD catheter. Prognosis with M. *abscessus* is poorer than with other NTM infections.

FR-PO483

A Case of Rare Polymicrobial Quadruple Zoonotic Peritonitis in a Patient on Continuous Cycling Peritoneal Dialysis (CCPD)

Ao Wang,[1,2] Gilana Gomberg,[2] Shuchita Sharma,[2] Jaime Uribarri.[2]
[1]SUNY Downstate Health Sciences University, New York City, NY; [2]Mount Sinai Health System, New York, NY.

Introduction: Polymicrobial peritonitis is associated with higher hospitalization, catheter removal, permanent HD transfer and death than monomicrobial peritonitis. Zoonotic peritonitis is rare with a reported prevalence of only 0.54% of all peritonitis episodes [1]. We present a case of polymicrobial peritonitis caused by four zoonotic organisms including Neisseria Shayeganii, to our knowledge, this is the first case ever reported of PD-peritonitis associated with Neisseria Shayeganii.

Case Description: A 57-year-old male with ESRD on CCPD for 4 years presented to our PD clinic with mild abdominal pain and cloudy peritoneal effluent. Past medical history was relevant for kidney disease due to MGN status post cyclophosphamide and steroids and prostate cancer status post-prostatectomy. Social history was relevant for owning a cat and a dog. Physical exam was remarkable only for tachycardia and hypotension. Peritoneal effluent analysis showed 774 WBC/uL with 69% neutrophils and culture was sent. He was empirically treated with IP vancomycin and gentamicin for peritonitis. His abdominal pain resolved, peritoneal effluent became clear and showed down trending WBC from 774/uL to 25/uL with 58% neutrophil with no growth on cultures after 3 days. One week later, he again presented with abdominal pain and tenderness with nausea, vomiting and diarrhea and found to be tachycardic and hypotensive. He was admitted to the hospital for sepsis. PD effluent analysis showed 26,460 WBC/uL with 78% neutrophils and gram-negative bacilli and gram-positive rods on gram stain. PD culture from first clinic visit had very slow growth and eventually turned out to be positive for Neisseria shayeganii, Paenibacillus glucanolyticuls/lantus, Cutibacterium(propionibacterium) acnes and Capnocytophaga species. He received IP vancomycin, oral ciprofloxacin, fluconazole and later switched to IV piperacillin-tazobactam for 7 days. His symptoms improved and he was discharged with amoxicillin and clavulanate for 3 weeks. However, he continued to have elevated WBC with predominantly neutrophils in PD effluent. Decision was made to remove PD catheter and transfer to HD.

Discussion: We presented an uncommon case of PD related peritonitis with polymicrobial rare zoonotic organisms. We believe this case can help enhance clinician awareness and understanding of Neisseria Shayeganii and other zoonotic-related peritonitis.

FR-PO484

B Cereus! A Case of Peritonitis

Hamza Arif,[1] Ibraheem Murtaza,[2] Hassaan Iftikhar,[1] Maryam Saleem.[1]
[1]Ohio Valley Nephrology Associates, Owensboro, KY; [2]University of Kentucky, Lexington, KY.

Introduction: Peritonitis is a commonly encountered complication of peritoneal dialysis (PD), often associated with poor dialysis hygiene and constipation. Most common etiologies include Gram-negative rods and Gram-positive cocci, particularly *Staphylococcus aureus*. *Bacillus cereus* has been rarely identified as a causative organism of peritonitis.

Case Description: A 59-year-old gentleman with end stage kidney disease on continuous ambulatory peritoneal dialysis (CAPD) for 3 years presented to the dialysis clinic with abdominal pain and cloudy effluent. He had prior episodes of recurrent peritonitis from coagulase-negative Staphylococci (CONS) requring removal of the PD catheter but was restarted on CAPD 3 months after and did not have any peritonitis episode for 2 years. Initial cell count revealed absolute nucleated cell count of 491 and he was empirically started on intraperitoneal (IP) vancomycin and ceftazidime as well as fluconazole for fungal prophylaxis. Gram stain results 2 days later showed gram positive bacilli. After 4 days, PD cultures revealed *Bacillus* species (not anthracis). Sample was sent for further testing and finally identified *Bacillus cereus* with sensitivity to vancomycin 13 days after initial culture date. The patient initially received a 2-week course of IP vancomycin which was extended to 4 weeks given concern for the formation of spores with *Bacillus cereus*. His symptoms initially resolved, but 2 weeks after finishing the antibitics course, he reported abdominal pain again. PD cultures again revealed *Bacillus cereus* and he was initiated on another 3-week course of IP vancomycin.

Discussion: *Bacillus cereus* are gram-positive, aerobic, spore-forming, rod-shaped bacteria. They are usually described in cases related to food poisoning. Literature review indicates rare reports involving peritonitis from this organism. Prior descriptions of peritonitis with *Bacillus cereus* included relapsing, recurrent peritonitis eventually requiring removal of the PD catheter. The patient's history of recurrent peritonitis due to CONS which required removal of the CAPD catheter two years earlier, along with this new *Bacillus cereus* peritonitis, indicate the importance of maintaining hygiene with each treatment and retraining in patients with peritonitis.

FR-PO485

Raising a Brown Flag: An Unusual Presentation of Aspergillus Peritonitis

Maryn Gardner, Megha Salani. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Fungal peritonitis is a rare complication of peritoneal dialysis (PD), but one with high rates of mortality and technique failure. Candida species represent most causative organisms of fungal peritonitis while infection with Aspergillus is less common but associated with higher mortality. We present a rare case of asymptomatic Aspergillus peritonitis identified due to discoloration in the PD catheter transfer set.

Case Description: A 71-year-old male with a history of liver transplant, diabetes, and end-stage kidney disease due to calcineurin inhibitor toxicity presented for his routine PD clinic visit. An area of brown discoloration was seen in the proximal portion of his catheter transfer set (see Picture 1). He noted the color change over 3 days prior without associated abdominal pain or fever. The transfer set was exchanged and sent to anatomical pathology to evaluate the cause of the brown discoloration. PD fluid was sent for cell count and culture. White cell count was elevated: 432 cell/mcL with 54% neutrophils and 11% eosinophils. Intraperitoneal vancomycin and ceftazidime were started for empiric peritonitis treatment. Last peritonitis episode was 7 months before and he had no recent antibiotic exposure. The pathologist's evaluation of the transfer set revealed septate, acute angle branching hyphal elements consistent with mold. The patient was admitted to the hospital, treated with oral voriconzole, and underwent urgent PD catheter removal with transition to hemodialysis. Peritoneal catheter tip culture was positive for Aspergillus species.

Discussion: Aspergillus peritonitis is a rare complication of PD. Even in the absence of classic peritonitis symptoms, brown discoloration in the PD catheter warrants evaluation for potential fungal infection. Early recognition and intervention, with prompt PD catheter removal, are crucial due to associated high mortality and morbidity.

Picture 1: Bisected transfer set with brown discoloration

FR-PO486

Fungal Peritoneal Dialysis (PD) Peritonitis Managed with Simultaneous PD Catheter Removal and New PD Catheter Insertion

Raeesa Soomar, Vesh Srivatana. *Weill Cornell Medicine, New York, NY.*

Introduction: Guidelines for management of fungal PD peritonitis include PD catheter removal and switch to hemodialysis. Here we present a case where we removed the old PD catheter removal and placed a new PD catheter due to patient's wish to avoid hemodialysis

Case Description: This case is of a 46 year old female with a history of ESRD secondary to IgA nephropathy on peritoneal dialysis (PD) and failed renal transplant, as well as a history of Staph A (penicillin resistant) peritonitis who initially presented to outpatient clinic with cloudly PD effluent and abdominal pain. PD fluid cultures and cell count was obtained after which she was started on empiric IP antimicrobials. Her culture returned positive for yeast, after which she was recommended for hospital admission. In the hospital, she was started on IV micafungin and IP fluconazole, and continued on empiric IP antibiotics. She was recommended by her nephrologist for PD catheter removal and switch to HD, however the patient did not want to do HD even if it resulted in worsening clinical progression or death. Therefore after many discussions, she was planned for and underwent PD catheter removal and placement of new PD catheter. She was continued on IV micafungin and IP fluconazole, while IP antibiotics switched to IV antibiotics. PD fluid cell count and cultures were taken daily. Nucleated cell count peaked at 1650, then decreased to 1 throughout hospital course and with antimicrobials.

Her fungal culture grew aureobasidium pullulans. With input from infectious disease team, her micafungin was changed to IV amphotericin B. She was then started on urgent start PD protocol in the hospital. Subsequent cultures also grew psuedomonas putida and fluorenscens (both sensitive to ceftazidime and levaquin). She was discharged with tunneled PICC line for IV amphotericin for 4 week course. She was continued on IP ceftazidime and oral levofloxacin for 3 weeks after negative fluid cultures.

Discussion: This case is unique in management, as our patient was firmly against starting hemodialysis, even after lengthy discussions involving risk of treatment failure and death. Therefore, to keep the patient's wishes to continue with PD and avoid HD, we had to alter the management plan. In this case, we were able successfully treat fungal peritonitis and do urgent start PD with removal of the old PD catheter and placement new PD catheter.

FR-PO487

Amlodipine-Induced Chylous Ascites in a Patient on Peritoneal Dialysis

Oliver P. Yockey,[1] Katherine W. Kwon,[2] Zachary K. Heeringa.[3] *[1]Corewell Health Southwest Michigan, Saint Joseph, MI; [2]Lake Michigan Nephrology, Saint Joseph, MI; [3]Michigan State University College of Osteopathic Medicine, East Lansing, MI.*

Introduction: Chylous ascites (CA) is the appearance of milky, lipid rich peritoneal fluid, often associated with portal hypertension, lymphatic obstruction, congenital abnormalities, infections, or post-operative complications. Previous studies have proposed that a triglyceride content of >187mg/dL confers a 95% specificity. CA has been associated with use of medications, including dihydropyridine (DHP) calcium channel blockers (CCBs). In this case we discuss the presentation of a peritoneal dialysis (PD) patient with amlodipine induced CA that resolved expeditiously on discontinuation of CCB.

Case Description: A 66-year-old man with history of end stage kidney disease secondary to uncontrolled hypertension presented to the hospital with milky, white PD fluid after request by his dialysis team. He was admitted three weeks prior for bacterial peritonitis and was completing a course of intraperitoneal ceftriaxone and vancomycin. CT abdomen and pelvis imaging at the first admission was negative for masses or abscesses. The etiology of his peritonitis was thought to be related to severe constipation with bacterial translocation, however, cultures remained negative. On this admission he was asymptomatic and vitals were unremarkable. Physical exam revealed a distended abdomen without tenderness; the PD site was without erythema or drainage. PD fluid showed 68 nucleated-cells/μL. Fungal culture, AFB culture and smear were negative. The PD fluid triglyceride level was 322mg/dL, consistent with CA. Antibiotics were continued. Review of the literature revealed case reports of other DHP CCB's causing CA; therefore, amlodipine was suspected and discontinued in hospital. He was discharged the next day. On a follow up two days later, his PD fluid was noted to be entirely clear, without a milky appearance.

Discussion: Previous research has established other DHP CCB's in the formation of CA in PD patients. However, despite widespread use of amlodipine as an anti-hypertensive, it accounts for one documented case of CCB-induced CA. Our case further implicates amlodipine as a rare etiology of CA. Furthermore, cessation of amlodipine led to rapid resolution, similar to other documented CCB-induced CA. This is the first report we have identified where CA developed months following CCB initiation; it is imperative that a careful review of medications be performed in patients with CA of unknown etiology.

FR-PO488

Long-Term Prophylactic Intraperitoneal Antibiotics in Outpatient Peritoneal Dialysis Patients: A Case Series

Derrick Soong,[1] Wasim El Nekidy.[2] *[1]Windsor Regional Hospital, Windsor, ON, Canada; [2]Cleveland Clinic, Abu Dhabi, United Arab Emirates.*

Introduction: Bacterial peritonitis is a potentially fatal complication for peritoneal dialysis patients. Despite following ISPD guidelines, patients in remote areas are at higher risk of developing peritonitis due to decreased direct access to experienced nursing staff. Those patients in remote areas also are less likely to relocate closer to a hemodialysis center if perionteal dialysis cannot be continued. One approach to prevent peritonitis in these patients with frequent peritonitis is to use prophylactic intraperitoneal antibiotics. However, extended use antibiotic prophylaxis to prevent bacterial peritonitis in peritoneal dialysis patients is not well characterized in the literature. The risk of developing multi-drug resistant organisms limits its widespread use.

Case Description: In this case series, we investigated the safety and efficacy of prophylactic intraperitoneal antibiotics in 3 peritoneal patients with a history of relapsing Staphylococcal peritonitis infections unwilling to transition to hemodialysis.

Discussion: Each patient had an exit site infection causing multiple relapsing peritonitis infections whereby each patient refused PD catheter removal during a peritonitis exacerbation, limiting the nephrologist to antibiotic therapy. As a last resort, all three patients received intraperitoneal and an oral antibiotic to double-cover the identifed pathogen. In all three cases, no opportunistic infections were reported in the observation period despite absence of fungal peritonitis prophylaxis. Patients did not report any side-effects after starting prophylactic antibiotics. Dialysis adequacy did not appear to be affected by prophylactic antibiotics in the observation period. Two of the cases passed away due to failure to thrive or to complications after foot amputation. No cloudy effluent or signs of peritonitis was observed near time of death. After this relatively successful case series of prophylactic antibiotics in this small subset of peritoneal dialysis patients, randomized prospective studies should be conducted to assess the feasibility of this novel approach to sustain peritoneal dialysis longevity.

Patient Demographics / Infection Information

Patient	PD Duration	Exit Site Organism / Treatment	Peritonitis History / Treatment	Prophylaxis Regimen
Caucasian male (1938-2020), BMI 30	Dec 2017-Jan 2020	Jan 2018 (MSSA) - IP cefazolin 2g daily x2 weeks Mar 2018 (MSSA) - PO cephalexin 500 mg BID x10 days	Aug 2018 - MSSA - IP vancomycin 2g q4days x3 weeks Sept 2018 - MSSA - IP vancomycin 2g q3days x3 weeks Nov 2018 - MSSA - IP cefazolin 2g daily x3 weeks May 2019 - MSSA - IP cefazolin 2g daily x3 weeks then IP cefazolin 2g daily + PO rifampin 600 mg daily x2 weeks	IP cefazolin 1g - Mon/Wed/Fri (July 2019-Jan 2020)
Caucasian male (1942-2021), BMI 26	Feb 2018-Apr 2021	Mar 2019 (MRSA) - PO SMP/TMX DS daily x10 days	Sept 2018 - MRSA - IP vancomycin 2g q4days x3 weeks Nov 2018 - MRSA - IP vancomycin 2g q4days x3 weeks Jan 2019 - MRSA - IP vancomycin 2g q4days + PO rifampin 600 mg daily x3 weeks	IP vancomycin 2g every Friday (Feb 2019-Apr 2021)
Caucasian male (1947-present), BMI 31	Nov 2019-present	July 2020 (coagulase-negative Staphylococcus) - PO cephalexin 500 mg BID x7 days	Apr 2020 - coagulase negative Staph* - IP vancomycin 2g q4days x2 weeks Oct 2020 - coagulase negative Staph* - IP vancomycin 2g q4days x2 weeks Nov 2020 - coagulase negative Staph* - IP vancomycin 2g q4days + rifampin 600 mg daily x4 weeks Dec 2020 - coagulase negative Staph* - IP vancomycin 2g q4days + clindamycin 300 mg daily x4 weeks	IP vancomycin 2g weekly (Dec 2020 - present)

FR-PO489

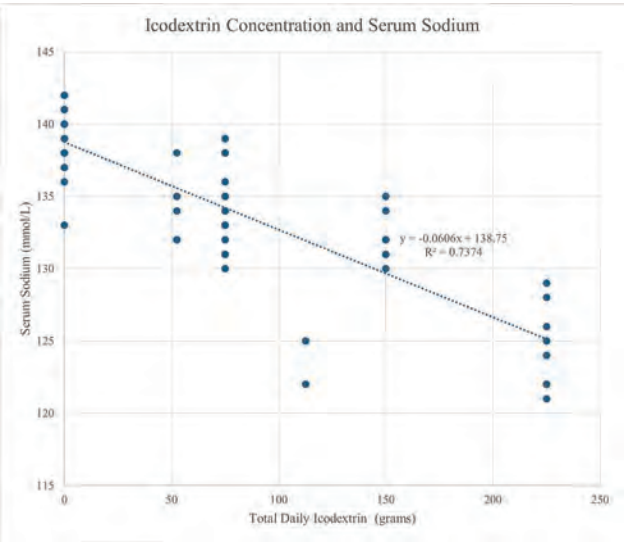
Icodextrin (ICO) Lowers Serum Sodium (Na) in Dose-Dependent Fashion

Sophia Sugar, Marko A. Karakadze, Isaac Teitelbaum. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Introduction: ICO is widely used in peritoneal dialysis (PD). Hyperosmolar hyponatremia (hypoNa) has been reported as an adverse event of ICO but it is unknown whether there is a dose effect relationship between the two. We present a case demonstrating this relationship.

Case Description: A 34.5 Kg woman with ESKD began PD with a single daily dwell of 1L of ICO. Her serum Na (mmol/L) fell from 138.9 ± 2.2 (SD) to 133.6 ± 2.1. She developed a pericardial effusion prompting a change in prescription (Rx) to 4 exchanges of 1.5L, 1.5% dextrose; Na rose to 138. Her effusion improved, and Rx was switched back to 2 cycles of 1.5L of ICO. 11 days later Na was 122. Measured serum osmolality (osm) was 302 with calculated osm 264 and a gap of 38. Whole blood Na matched serum Na. She was intravascularly contracted and given boluses of NS and the same PD Rx was continued. She had a mild increase in Na (≤ 129) but never achieved normonatremia. One month later she was still hypoNa at 121. The Rx was decreased to 1 cycle of 1.5L ICO and Na improved to 125. Her Rx was switched to 3 cycles of 1.5% dextrose with no ICO, and Na improved to 135, during which measured serum osm was 299 and calculated osm of 291 with a gap of 8. She maintained normonatremia (139.2 ± 1.5) for the subsequent 2 years – all while her Rx was dextrose based. Years later a single 2L ICO dwell was started, and she developed hypoNa (131). ICO was stopped, and Na normalized.

Discussion: HypoNa is a risk factor for ESKD patients that leads to increased morbidity and mortality. ICO can cause increases in serum osm and hypoNa, the degree of which, we've shown, is related to the dose of ICO used. The concentration of ICO [ICO] is 75g/L (7.5%). We plotted the Na vs [ICO] and show a strong correlation (R^2 >0.7). For patients considering stopping ICO due to hypoNa it may be reasonable to lower the dose instead.



Serum Na vs. total daily ICO in grams

FR-PO490

Icodextrin Toxicity in a Patient with ESKD Secondary to Multiple Myeloma

Daniel Rospert,[1] Sreedhar A. Mandayam,[2] Justin Bull,[2] Biruh Workeneh.[2]
[1]The University of Texas Health Science Center at Houston, Houston, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX.

Introduction: Icodextrin is a peritoneal dialysis solution often used in diabetic patients with difficult to control type 2 diabetes. It is reported to be safer than dextrose containing PD solutions, due to less absorption than dextrose. There are reported adverse effects, the most common being skin rashes and rare cases of other adverse effects. We present a case of icodextrin toxicity in a patient with ESRD secondary to light chain deposition disease from multiple myeloma.

Case Description: 76 year old man with ESRD on peritoneal dialysis was sent for inpatient admission for hyponatremia. ESRD was secondary to light chain deposition disease related to multiple myeloma. Once declared ESRD, he opted for peritoneal dialysis with icodextrin due to difficult to control type 2 diabetes. On initial evaluation he had Na 122, calculated serum Osm 287 in the setting of azotemia and measured Osm 336 with resultant Osm gap of 49. An alcohol panel was negative and immunoglobulin levels were normal. He had elevated liver enzymes with AST 419, ALT 400, and Alk Phos 144 with a negative viral hepatitis evaluation. The constellation of metabolic abnormalities were concerning for icodextrin toxicity. He was transitioned to a mixed bag with 2.5% dextrose dialysate. His hyponatremia resolved over the course of 2 days, with improvement in liver enzymes as well resulting in diagnosis of icodextrin toxicity in the setting of multiple myeloma.

Discussion: Per manufacturer, less than 5% of patients using icodextrin dialysate develop any of hyponatremia, AST, ALT, or alkaline phosphatase. The patient reported had all four. There have been case series of patients who developed a hyperosmolar, hyponatremia as described in the patient presented. There have also been reports of hepatotoxicity related to icodextrin. To our knowledge, there has not been a reported case of icodextrin toxicity resulting in the combination of hyponatremia and transaminitis in a patient with multiple myeloma. It is unclear whether this patient's diagnosis of multiple myeloma made him more susceptible to icodextrin toxicity, however, this case the importance of frequent metabolic evaluation in patients on icodextrin dialysate. More research is needed to determine if patients with multiple myeloma may be more susceptible to icodextrin toxicity.

FR-PO491

Cola-Colored Peritoneal Dialysate in a Patient with Impella Device-Associated Hemolysis

William Qin, Chitra R. Reddy. *Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA.*

Introduction: In PD patients, Cola-colored effluent is a rare and ominous complication, which is usually associated with rhabdomyolysis or hemorrhagic pancreatitis, noted prior cases were fatal. The mechanism by which this occurs is thought to be as a result of breakdown of heme from hemoglobin and myoglobin, subsequent reaction of hemin with albumin to form methemalbumin. This case presents a novel occurrence, as hemolytic anemia from Impella placement resulted in cola-colored dialysate.

Case Description: 48-year-old male with ESRD on PD, CAD s/p multiple PCI and recent DES placement, and HFrEF, who was found to have NSTEMI. He underwent cardiac catheterization with findings of diffuse mvCAD. He developed worsening cardiogenic shock, was transitioned to CRRT – an axillary Impella device was placed on hospital day 12. He was noted to have pink CRRT effluent suggestive of hemolysis, suspected to be due to malposition of the Impella device. The Impella was repositioned with ultrasound guidance. The patient had unconjugated bilirubinemia to 17.0 mg/dL, serum LDH 5866 U/L, and lactic acidosis. PD fluid was drawn to rule out infection, and noted to be dark brown in coloration. The fluid resulted with negative gram stain and culture, however total bilirubin of the fluid was 6.2 mg/dL, LDH was 1626 U/L. Patient had clear peritoneal dialysate until this point.

Discussion: This case of dark PD fluid discoloration was not associated with any of the previously documented risk factors, and is instead associated with hemolysis from impella placement, which is a novel occurrence. The presence of dark discoloration or bilirubin in the dialysate should prompt rule-out of intra-peritoneal sources of heme or bile, and is considered an ominous clinical sign. All documented cases have been fatal, and this patient also expired from complications of refractory shock.

FR-PO492

An Unprecedented Case of Autologous Stem-Cell Transplant in a Patient with Multiple Myeloma with ESKD on Peritoneal Dialysis

Hanna Larson, Danish Waqar, Julia Schneider. *Loyola University Medical Center, Maywood, IL.*

Introduction: Since 2011, when bundled payments changed to equal pay for peritoneal dialysis (PD) and hemodialysis (HD), home PD rates have nearly doubled. Rise in PD utilization has had no significant effect on patient mortality or morbidity. Still little is known about how PD impacts other care aspects, such as stem cell transplant. Autologous stem cell transplants (AutoSCT) in dialysis dependent patients are rare. Given the lack of studies with PD in SCT, patients are often advised to temporarily switch to HD with a central venous catheter (CVC) peri-transplant to avoid peritonitis risks. However, this recommendation is unsubstantiated and may increase serious infection risks like bacteremia. Literature search yields only one other reported case of AutoSCT in a PD patient in Spain. We present a successful AutoSCT in a PD patient without major dialysis-related issues in the US.

Case Description: A 68-year-old man with advancing kidney disease started PD. One month later, he was diagnosed with IgG-Kappa Multiple Myeloma (MM) based on an elevated protein gap and anemia refractory to epoetin. Bone marrow biopsy confirmed Stage III MM. After 5 chemotherapy cycles with a combination of daratumumab, lenalidomide, and dexamethasone, he was admitted for Melphalan AutoSCT. He received standard antibacterial, antifungal, and antiviral prophylaxis with Levaquin, Fluconazole, and Acyclovir. Routine PD exit site care per ISPD guidelines was maintained. Adequate ultrafiltration and clearance were achieved throughout the hospital course. Complications included pancytopenia, hematuria, hemorrhoidal bleeding, mucositis, atrial fibrillation and COVID-19. Despite neutropenia, no PD-related infections occurred. He was discharged on day 13 post-AutoSCT and completed outpatient chemotherapy. MM remains in remission on PD 2 years post-AutoSCT.

Discussion: To our knowledge this is the first successful reported case of AutoSCT in a PD patient without major dialysis-related complications in the US. With routine exit site care and SCT antimicrobials, PD appears safe for those undergoing AutoSCT obliviating the need for CVC insertion. A paradigm shift is needed for PD due to the increasing interest in home dialysis and patient preferences for renal replacement therapy. Further studies are needed to understand the risks and outcomes of patients on HD vs. PD receiving AutoSCT.

FR-PO493

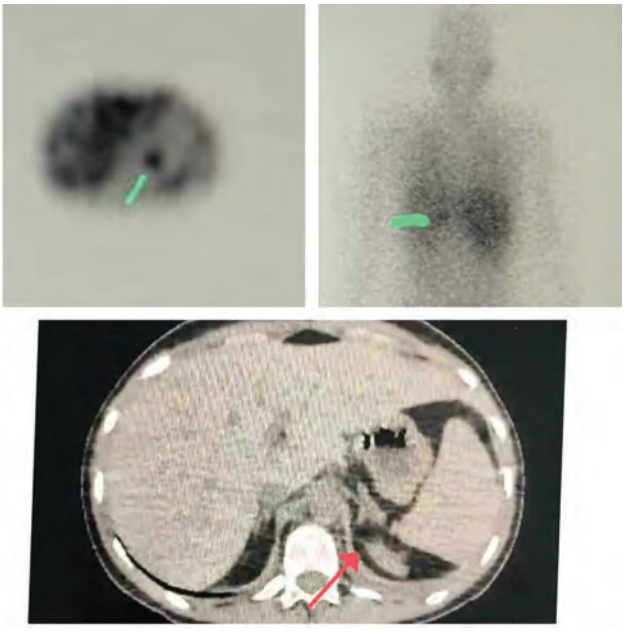
Peritoneal Dialysis Uncovers an Unusual Medical Condition

Emad A. Odeh,[1,2] Jehad Yousef.[1] [1]*Al-Basheer hospital, Amman, Jordan;* [2]*Mutah University, Mutah, Jordan.*

Introduction: PD is used to treat individuals with end-stage kidney disease(ESKD), by introducing dialysate into the peritoneal cavity using the peritoneum as a filter to remove an excess fluids and waste products from the body We present a case of a patient who started on PD, which later uncovered an unusual disease

Case Description: A17-year-old female was diagnosed at the age of 16 with ESKD of unknown etiology, investigations revealed only positive ANA, kidney biopsy not done. At that time she underwent urgent hemodialysis(HD), found to have hypertension which was controlled with amlodipin5mg/day, and discharged on PD After APD initiation she started suffering from reccurent episodes of abdominal pain, headach, and BP-elevation during PD-treatment. These symptoms persist despite several changes in PD settings. Later she presented with cough, hemoptysis, severe HTN and found to have acute pulmonary hemorrhage confirmed by imaging and bronchoscopy. Treated as vasculitis with PLEX and steroid. One month after discharge she again suffered from the same symptoms during PD, followed by a second attack of pulmonary hemorrhage associated with resistant HTN, panic attack and headach that prompted us to exclude secondary HTN. Renal doppler study was normal. Aldosterone renin ratio and serum cortisone were normal. At that time she was anuric so 24hrs urine collection for metanephrine not done. Adrenal MRI without contrast was not informative. MIBIG scan done and confirmed left adrenal pheochromocytoma The patient shifted permanently to HD,BP controlled with doxazocine, lecardipine. Carvidolol was added3weeks later.plan for left adrenalectomy

Discussion: ***Take-home messages:*** several well-known causes of PD failure exist, but occasionally you may encounter an uncommon cause Dialysate instillation during PD can increase intra-abdminal pressure and may lead to catecholamine release from a masked adrenal tumour



FR-PO494

Vasovagal Syncope during Peritoneal Dialysis

Claudia Waters, Neepa Shah, Siddhartha Kattamanchi, Rebecca Blonsky. *Marshfield Clinic Health System, Marshfield, WI.*

Introduction: Vasovagal syncope can be difficult to predict for patients encountering new medical environments. Physicians must identify patients in which vasovagal syncope can interfere with their ability to reliably and safely participate in their care.

Case Description: A 65-year-old man with medical history significant for newly diagnosed ESRD due to IgA nephropathy who was recently started on peritoneal dialysis (PD) presented following a syncopal episode. The patient elected to start with in-center PD prior to dialyzing in his home. With his first ever fill he felt nauseated, but following this he tolerated treatments without symptoms. During his second week of treatment, he experienced a syncopal episode at the completion of his initial fill. His preceding symptoms included lightheadedness, nausea, tunnel vision, and dry heaving. He spontaneously awoke and completed the dwell under supervision of the nursing staff. He remained hemodynamically stable, however, was admitted for further evaluation. Laboratory workup was non-revealing, findings as per table one. Echocardiogram showed mild aortic stenosis which was stable from previous examination. Given the typical vasovagal-like prodrome coupled with an unremarkable cardiac workup, the patient was diagnosed with vasovagal syncope. His beta blocker was discontinued and inpatient PD was tolerated without recurrence of symptoms.

Discussion: Vasovagal syncope is an uncommon complication during early days of PD and usually happens during infusion of the PD fluid. In such scenarios alternate causes of syncope needs to be ruled out. When the cause is thought to be secondary to vasovagal syncope from PD infusion, then the rate of infusion must be lowered and attempted in a hospital setting to see if patient can tolerate this modality. Additionally, vagomimetic agents such as beta blockers should be lowered or stopped. With these interventions our patient was able to successfully remain on PD.

FR-PO495

Broadening Access to Home Hemodialysis with VersiHD GuideMe Software

Kristen R. Lile, Anitha Vijayan. *Intermountain Healthcare, Salt Lake City, UT.*

Introduction: Home hemodialysis (HHD) allows independence for patients with end stage kidney disease (ESKD) & is associated with improved patient satisfaction & clinical outcomes. In addition to bettering quality of life, HHD can improve blood pressure & fluid control. Despite proven benefits, the use of HHD remains limited due to the complexity of HHD training & concern for adverse events. The VersiHD GuideMe software aims to make HHD available to more patients by simplifying HHD.

Case Description: Training for HHD takes 8-12 weeks, leading to significant time commitment for patients & care partners. We followed a patient training for HHD using the VersiHd GuideMe software. This software is available with the NxStage system & provides step-by-step instructions through a simplefied interface to improve ease & speed of learning for patients. Our patient suffered from chronic fluid overload & recurrent hospitalization while undergoing traditional, thrice weekly hemodialysis through an

arteriovenous fistula. Using the VersiHD GuideMe software, the patient & their care partner were able to safely complete HHD training over a span of 3 weeks dating from 2/22/24-3/14/24. As of this writing, the patient has had no adverse events associated with HHD or new hospitalizations. This patient has had improved debilitation & is now undergoing transplant evaluation.

Discussion: Despite improved clinical outcomes with HHD, utilization in practice has remained limited in part due to the technical complexity of treatment. Training for HHD can be a time-consuming process, with training taking 8-12 weeks. Using the VersiHD GuideMe software, our patient was able to complete HHD training in 3 weeks, resulting in an improvement in cardiovascular outcomes that were not achievable with traditional dialysis. The VersiHD GuideMe software provides a user-friendly, succinct method for training patients on HHD therapy, opening the door to more ESKD patients who can benefit from this therapy.

Figure 1: Time in weeks for HHD training, study patient

FR-PO496

A Novel Hybrid Technique for Peritoneal Dialysis Catheter Insertion

Szu-Yuan Li, Ming-Tsun Tsai, Chih-Ching Lin. *Taipei Veterans General Hospital, Taipei, Taiwan.*

Background: Peritoneal Dialysis (PD) is an essential treatment for end-stage kidney disease (ESKD). Existing methods for PD catheter insertion have various limitations. This study introduces a novel hybrid method that combines laparoscopic and Seldinger techniques for PD catheter insertion.

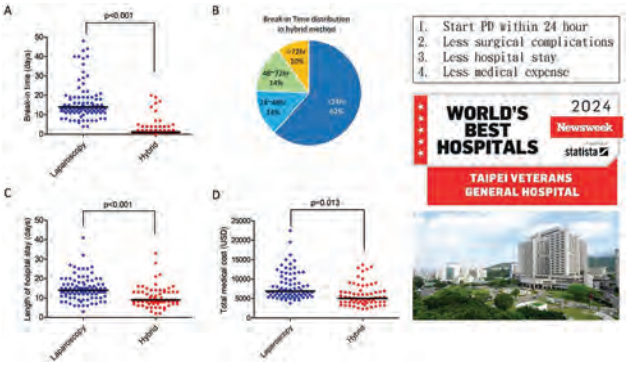
Methods: This retrospective study analyzed 320 patients undergoing their first PD catheter insertion, 23% of whom had a history of abdominal surgery. The cohort had two groups of patients: 170 patients received the traditional laparoscopic method, while 150 underwent the new hybrid method. Surgical outcomes, early and late complication rates, hospital stay duration, and medical expenses were compared between the two groups.

Results: No significant differences were observed in baseline demographics and comorbidities between the groups. The hybrid method had in a significantly shorter break-in period (within 24 hours) and eliminated the need for temporary hemodialysis. Patients in the hybrid group had shorter hospital stays (1 week less) and lower medical expenses (saving $3000 USD) compared to those in the laparoscopic group (all $p<0.05$). The incidence of early complications was lower in the hybrid group, while late complication rates were comparable between the groups.

Conclusions: The hybrid method is a safe and effective alternative for PD catheter insertion, especially for patients with previous abdominal surgeries or at risk of abdominal adhesions. It enables urgent-start PD, reduces hospital stays, and lowers medical costs, supporting its adoption as the new standard of care for ESKD patients requiring PD catheter insertion.

Summary of different PD catheter implantation techniques

	Open surgery	Laparoscope	Seldinger technique	Novel Hybrid method
Operator	Surgeon/Physician	Surgeon	Physician	Surgeon
Anthesis	General anthesis	General Anthesis	Local Anthesis	General Anthesis
Tissue manipulation	More	More	Minimal	Minimal
Direct Visualization	No	Yes	No	Yes
Break-in time	14 days	14 days	1 day	1 day
Suitable for patients with previous abdominal surgery	No	Yes	No	Yes



FR-PO497

Uremic Serum Results in an Activation and Phenotypic Switch of Pig Venous and Arterial Smooth Muscle Cells (SMCs)

Huanjuan Su,[1] Eyla C. Arteaga,[1] Christine Wai,[1] Unimunkh Uriyanghai,[1] Vinay A. Sudarsanam,[1] Samuel Haddad,[1] Edward M. Bahnson,[2] Prabir Roy-Chaudhury,[1] Gang Xi.[1] *[1]The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC; [2]The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: ESKD patients suffer from both an aggressive vascular access stenosis in the venous segment of AVFs and AVGs and widespread peripheral arterial disease (PAD). Both disease states respond poorly to conventional endovascular and surgical interventions. Despite the magnitude of the clinical problem, the exact pathogenetic role of the uremic state in both these conditions remains unclear.

Methods: Uremic serum was obtained from our previously described pig model of uremia (documented creatinine of >8mg/dL for over 3 weeks). Control serum was obtained from an age matched non-uremic pig. The MTT assay was used to assess cell proliferation and a cell-scratch assay was utilized to assess cell migration. Western blot expression was used to assess markers of cellular proliferation (PCNA and p53), phenotypic switch (myocardin and calponin), extracellular matrix (ECM) production (vitronectin and fibronectin) and calcification (Runx2).

Results: The MTT assay demonstrated that 30% uremic serum was able to stimulate the proliferation of both arterial (1.25±0.14 fold increase) and venous (1.17±0.13 fold increase) SMCs. Uremic serum also consistently enhanced PCNA and p53 expression in both cell types. The production of ECM proteins such as vitronectin and fibronectin was also increased when cells were exposed to uremic serum (ApSMC > VpSMC). SMC migration showed that uremic serum increased the migration of ApSMC (1.21±0.14 fold increase) and VpSMC (1.23±0.12 fold increase). Uremia also induced a phenotypic switch in both cell types (greater in ApSMC), with a suppression of myocardin and calponin expression (indicating a switch to a more activated, dedifferentiated and synthetic phenotype). Uremic serum also significantly stimulated cellular calcification (Runx2) particularly in ApSMC.

Conclusions: Uremia results in phenotypic switch of both venous and arterial SMCs *in vitro* with an increase in proliferation and migration, ECM production and expression of cell calcification markers. These changes were often exaggerated in ApSMCs as compared to VpSMCs. Our findings suggest that uremia per se could play an important role in both the aggressive arteriovenous stenosis and PAD in hemodialysis patients.

Funding: NIDDK Support

FR-PO498

Uremia, Angioplasty Injury, and Vessel Type (Artery vs. Vein) Activate Differential Gene Expression and Pathway Profiles

Unimunkh Uriyanghai, Christine Wai, Huanjuan Su, Eyla C. Arteaga, Vinay A. Sudarsanam, Samuel Haddad, Edward M. Bahnson, Prabir Roy-Chaudhury, Gang Xi. *The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC.*

Background: Patients with CKD and ESKD suffer from aggressive dialysis vascular access stenosis within the venous segment of AVFs and AVGs. They also suffer from a huge burden of vascular disease, which responds poorly to interventions such as angioplasty. Despite the huge morbidity, mortality, and economic costs associated with both dialysis vascular access dysfunction and peripheral vascular disease in CKD and ESKD patients, the pathogenetic pathways responsible for this remain unclear.

Methods: Pigs were made uremic by performing a right sided nephrectomy followed by a selective ligation of the branches of the left renal artery. After 2 weeks of uremic condition, we performed an angioplasty of the femoral artery and vein on one side, with the contralateral side serving as a control. Animals were sacrificed two weeks post angioplasty, and arterial and venous samples from the femoral artery and vein on both

sides were collected for RNA extraction and bulk RNA sequencing. An identical set of experiments was performed on a non-uremic pig.

Results: Differential expression gene analysis revealed that uremia up-regulated 21 genes in the control artery but only 7 genes in the control vein. In contrast, 177 genes were up-regulated in injured vein but only 1 gene was up-regulated in injury artery. In addition, the injury up-regulated 510 genes in normal vein but only 56 genes in normal artery. Additional pathway enrichment studies revealed differentially enriched pathways in different groups. For example, olfactory receptor activity, positive regulation of immune system process and interferon gamma response were the 3 maximally enriched pathways in uremic control artery whereas neuropeptide receptor activity, neuropeptide signaling pathway and molecular transducer activity were the 3 maximally enriched pathways in uremic control vein.

Conclusions: Our results suggest that all three variables, uremia, angioplasty injury, and vessel type contribute to the differential gene expression and pathway analyses. Our data suggests that the optimal therapy to reduce restenosis following angioplasty of the venous segment of an AVF in an ESKD may be very different from that needed to reduce restenosis following arterial angioplasty injury in a CKD/ESKD patient.

FR-PO499

Differential Gene Expression and Signal Pathways Activation Lead to Differences in Cell Proliferation and Migration of Venous and Arterial Pig Smooth Muscle Cells

Eyla C. Arteaga, Huanjuan Su, Christine Wai, Unimunkh Uriyanghai, Vinay A. Sudarsanam, Samuel Haddad, Prabir Roy-Chaudhury, Gang Xi.
The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC.

Background: Arteriovenous fistulae (AVF) are the preferred mode of dialysis vascular access but have a maturation failure rate of over 50% due to a venous segment stenosis, which is characterized by smooth muscle cells (SMCs) proliferation and migration, resulting in neointimal hyperplasia. Despite the clinical significance of venous segment AVF stenosis, the exact gene expression profile and activation pathways responsible for venous SMC proliferation and migration remain unclear.

Methods: Pig arterial SMCs (ApSMCs) and venous SMCs (VpSMC) were cultured in DMEM containing 10% FBS and 1% P/S. Total RNA was isolated for bulk RNA sequencing. Cell lysates were collected for analyzing protein expression levels. MTT assays were used to measure cell proliferation, and cell scratch assays were used to assess cell migration ability.

Results: Bulk RNA sequencing results indicated that 265 genes were expressed highly in VpSMCs, while another 301 genes were highly expressed in ApSMCs. PCA and signal pathway analyses demonstrated clear differences in gene expression and pathway activation between VpSMCs and ApSMCs. For instance, cell migration, cell junction and cell communication pathways were activated in VpSMCs while collagen-containing extracellular matrix and extracellular matrix pathways were activated in ApSMCs. Importantly, different sets of genes were utilized even within the same activated pathways. Western blot results demonstrated that FAK protein levels were increased in VpSMCs while Paxillin and Vinculin levels were similar in both cell types. ECM proteins, such as fibronectin and vitronectin proteins were produced more by VpSMCs. Importantly, VpSMCs proliferated faster than ApSMCs (1.80±0.21 vs 1.56±0.19 fold after 48hr in growth media). However, their response to PDGF in serum free media was similar (1.53±0.16 vs 1.49±0.17 fold after 48hr). Migration assays revealed that VpSMCs had a faster migration as compared to ApSMCs in growth media and serum-free media.

Conclusions: Differential gene expression and pathway activation in VpSMCs and ApSMCs.are likely responsible for their differences in cell proliferation and migration, suggesting a much needed precision medicine approach to AVF maturation failure.

Funding: NIDDK Support

FR-PO500

Impact of CKD on Arteriovenous Fistula Remodeling: Studies in a Murine Model of Autosomal Dominant Polycystic Kidney Disease

Suzanne Laboyrie, Dorien J. Peters, Roel Bijkerk, Juliette A. de Klerk, Margreet R. de Vries, Joris I. Rotmans. *Leids Universitair Medisch Centrum, Leiden, Netherlands.*

Background: The arteriovenous fistula (AVF) is the gold standard for hemodialysis vascular access, although inadequate vascular remodelling and intimal hyperplasia pose a major limitation. We utilised an autosomal dominant polycystic kidney disease (ADPKD) model, the most common hereditary cause of chronic kidney disease (CKD), to study the effect of CKD on AVFs. We hypothesized that CKD accelerates AVF failure.

Methods: Jugular-carotid AVFs were created in adult B6Ola*Pkd1*$^{nl/nl}$ (ADPKD) mice and B6Ola*Pkd1*$^{+/+}$ litter mates. AVFs were harvested seven days post-surgery for bulk mRNA sequencing or three weeks post-surgery for histological analysis. We performed weekly AVF flow measurements using doppler ultrasound and assessed kidney morphology and function by histology and blood urea analysis. Blood pressure was measured using a tail cuff, before and six days after AVF-surgery. Longitudinal flow data was analysed using Mixed-effects model, histological data using the Mann-Whitney U test.

Results: *Pkd1*$^{nl/nl}$ mice developed cystic kidneys and elevated blood urea levels (8.7 ± 2.8 mmol/L versus 24.0 ± 3.8 mmol/L) and higher mean arterial blood pressure (92 versus 113). AVF flow in *Pkd1*$^{nl/nl}$ mice was consistently higher post-AVF creation (1.9-fold difference, p<0.001), with a 50% reduction in intimal hyperplasia and 30% increase in luminal AVF volume. RNA sequencing showed altered regulation of extracellular matrix in the venous ADPKD AVF, with reduced collagen deposition in the venous outflow tract.

Conclusions: *Pkd1*$^{nl/nl}$ mice are a suitable model to study AVF remodeling in a CKD setting, resulting in enhanced luminal volume and higher AVF flow when compared to normotensive mice with healthy renal function.

FR-PO501

Senescence in the Arteriovenous Fistula (AVF): Early Development and the Prosenescent Effects of Heme Treatment In Vivo and In Vitro

Raman D. Singh, Anthony J. Croatt, Allan W. Ackerman, Karl A. Nath.
Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN.

Background: Our prior studies demonstrated a senescent phenotype in the rat AVF at 1 and 2 weeks after creation, as measured by elevated p16 and p21 mRNA levels, increased senescence-associated-β-galactosidase (SA-β-Gal) activity, and a prominent senescence associated secretory phenotype (SASP). We also showed that chronic treatment with hemin reduced AVF flow, the latter hypothesized to be a pro-senescent effect of this treatment. We now examine whether senescence occurs at an earlier timepoint in the AVF, and if heme treatment induces markers of senescence in the vasculature of rats with AVFs, and in human umbilical vein endothelial cells (HUVECs).

Methods: Subtotal nephrectomy was performed in rats after which an AVF was created by anastomosing the femoral artery and vein. At 3 days after AVF creation, AVF veins were assessed for expression of cell cycle inhibitors (p16 and p21 mRNA), and SASP factor expression. In additional studies, the effects of heme (hemin) treatment were assessed in the aortas of rats with AVFs and in HUVECs using established measurements.

Results: 3 days after AVF creation, p16 and p21 mRNA levels were markedly elevated in AVF veins compared with sham veins and was accompanied by the appearance of a robust SASP (SASP factors such as TNF-a, IL-6, CCL2, IL-1β, CINC-1, and PAI-1 mRNA were all induced). Three-week heme treatment in rats with AVFs induced SASP factor mRNA expression (TNF-a, IL-6, CCL2, IL-1b, SDF-1, TF, CCL5) in the aorta. In HUVECs, 16-hour heme treatment increased p16 protein expression, decreased lamin-B1 protein expression, and significantly increased SA-β-Gal activity and SASP factor mRNA expression - all effects consistent with a senescent phenotype.

Conclusions: We demonstrate that the rat AVF in the presence of CKD exhibits a senescent phenotype as early as 3 days after AVF creation. We also identify heme as a novel inducer of senescence in vitro and in vivo. Intravascular hemorrhage is known to be a driver of atherosclerosis, putatively through the effects of free heme. Neoangiogenesis is also known to occur in both rodent and human AVFs, and this may predispose to intramural hemorrhage. We speculate that, in this manner, heme may contribute to a senescence phenotype in the AVF and, in turn, neointimal hyperplasia and AVF dysfunction.

Funding: NIDDK Support

FR-PO502

Single-Nucleus Transcriptomics Reveal Cell Type-Specific Diversification in Left Ventricle in Mice Undergoing Arteriovenous Fistula Creation with Cardiac-Specific Overexpression of PDE5A

Paul C. Collie, Nguyen T. Nguyen, Tatyana Isayeva Waldrop, Travis Ptacek, Kevin A. Ingle, Lingyun Wang, Timmy C. Lee. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: PDE5A, an enzyme that hydrolyses cyclic guanosine phosphate (cGMP), has been implicated in various cardiovascular conditions. We have observed an increase in protein levels of cardiac PDE5A following arteriovenous fistula (AVF) creation in left ventricle (LV) (Fig.1-A). AVF creation has been associated with increased cardiac output and dilation of LV leading to adverse cardiac remodeling (Fig.1-B). We performed single nuclei RNA-seq to understand the cellular transcriptional profiles and pathway changes after AVF creation and the role of PDE5A in LV remodeling.

Methods: AVF's were created in cardiomyocyte-specific overexpression PDE5A transgenic mice (homozygous, HO) and littermate controls (WT). LVs were collected at day 7. Single nuclei RNA-seq was performed to identify gene signatures in WT (n=5), WT-AVF (n=4), HO (n=5), and HO-AVF (n=4) groups. Integration of Single Nuclei data (10X Chromium) was done using Seurat v.4 package.

Results: We observed 19 different clusters, including 9 subtypes of cardiomyocytes (CM). Two CM clusters were not present in AVF group (Fig.1-C). There was a significant increase in endothelial cell count following AVF creation ($p=3.2e^{-3}$). Notable gene expression changes include a downregulation in genes related to oxidative phosphorylation and ATP production ($p=3.2e^{-18}$), an upregulation in genes linked to cardiomyocyte death and oxidative stress pathways ($p=5.65e^{-310}$), downregulation in genes essential for sarcomere assembly and myofibrillogenesis ($p=1.22e^{-190}$), and downregulation in genes essential for autophagy ($p=1.153e^{-38}$), cytokines and inflammatory response ($p=1.16e^{-99}$).

Conclusions: Our snRNA-seq data indicates that AVF creation and PDE5A expression in cardiomyocytes contribute to cardiac impairment pathways and adverse remodeling.

Funding: NIDDK Support

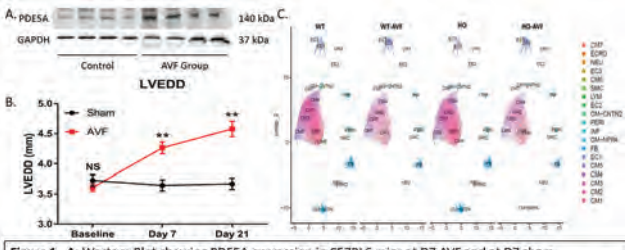


Figure 1. A: Western Blot showing PDE5A expression in C57BL6 mice at D7 AVF and at D7 sham. **B:** Graph showing greater Left Ventricle End Diastolic Diameter (LVEDD) C57BL6 mice following AVF creation compared to sham group. **C:** UMAP LV cardiac cellular composition of HO, HO-AVF, WT, and WT-AVF groups (CM= Cardiomyocytes; EC=Endothelial cells; FB=Fibroblasts; INF=Inflammatory cells; MPH=Macrophages; PERI=Pericytes; SMC=Smooth Muscle Cells).

FR-PO503

SGLT2 Inhibitor Ameliorates Smooth-Muscle Cell Proliferation via Endothelial Microparticles Stimulated by Indoxyl Sulfate

Shina Lee, Seung-Jung Kim. *Ewha Womens University Mokdong Hospital, Seoul, Republic of Korea.*

Background: Endothelial microparticles (EMPs) are closely associated with vascular dysfunction. Recent research has revealed a link between SGLT2 inhibition and improved endothelial functions. We investigated the effects of SGLT2 inhibitors (SGLT2i) on EMP generation from indoxyl sulfate-stimulated endothelial cells and their impact on smooth muscle cell (SMC) proliferation.

Methods: We measured CD31+CD42-EMP counts by flow cytometry in supernatants of human umbilical vein endothelial cells (HUVECs) incubated with indoxyl sulfate. We examined the EMP responses to SGLT2i by incubating EMPs from indoxyl sulfate-stimulated HUVECs with or without SGLT2i.

Results: 1. Indoxyl sulfate induced EMP release in HUVECs. 2. SGLT2i inhibited EMP generation induced by indoxyl sulfate. 3. The EMPs induced by indoxyl sulfate stimulated smooth muscle cell proliferation, and this effect was reversed by treatment with SGLT2i.

Conclusions: SGLT2 inhibitor ameliorates smooth muscle cell proliferation via endothelial microparticles stimulated by indoxyl sulfate. SGLT2i could be a treatment option for neointimal hyperplasia in vascular access stenosis.

FR-PO504

Retrograde Flow in Rat Arteriovenous Fistula

Hannah M. Northrup,[1] Timmy C. Lee,[2,3] Yan-Ting E. Shiu.[1,4] *[1]University of Utah, Salt Lake City, UT; [2]University of Alabama at Birmingham, Birmingham, AL; [3]Birmingham VA, Birmingham, AL; [4]Salt Lake City VA, Salt Lake City, UT.*

Background: The arteriovenous fistula (AVF) is the preferred vascular access for patients on maintenance hemodialysis but has high maturation failure rates, due to insufficient increases in lumen diameter and flow of the venous limb. There is a paucity of studies investigating the role of the AVF's distal artery in maturation failure. Retrograde flow in the AVF's distal artery is sometimes seen in patients and is associated with conditions such as steal syndrome. However retrograde flow has been rarely studied in context of AVF remodeling. Both computational fluid dynamics (CFD) and animal models have become a popular research tool to analyze the hemodynamics of the AVF. We have reported that rat femoral AVFs have anastomosis angles and disturbed flow similar to those in human forearm AVFs. Here we present a novel CFD study analyzing retrograde flow in rats with AVF.

Methods: 15 Sprague Dawley rats (12-16 week old males) underwent femoral artery (side) to femoral vein (end) AVF creation. 7 or 21 days after AVF creation rats underwent magnetic resonance imaging (MRI). MRI-based CFD was used to analyze the presence of retrograde flow in the distal artery 5 mm away from the anastomosis, and venous diameter and flow rate 5 mm away from the anastomosis. Spearman correlations were calculated to analyze association.

Results: 14 out of 15 rats exhibited retrograde flow in the distal artery during the cardiac cycle. 2 rats had retrograde flow throughout 5-20% of the cardiac cycle. 7 rats exhibited retrograde flow over 70% of the cardiac cycle and 5 experienced 100% retrograde flow. Correlation between % retrograde flow and venous diameter was -0.140 with a p value of 0.614. Correlation between % retrograde flow and venous flow rate was 0.198 with a p value of 0.477.

Conclusions: Retrograde flow in the distal artery is present and prevalent in rat femoral AVF. Consequently, rat models may be a translational model for studying steal syndrome. There were no statistically significant associations between retrograde flow in the distal artery and AVF venous diameter and flow in rat models. Studies in human and other animal models of AVFs are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

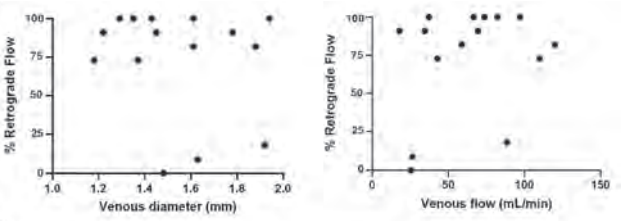


Figure 1: Percent retrograde flow vs. venous diameter (left) or venous flow (right) measured at 5 mm from the anastomosis.

FR-PO505

The Role of SFRP2 in Vascular Remodeling of Arteriovenous Fistula (AVF) Maturation

Chung-te Liu.[1,2] *[1]Division of Nephrology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [2]Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.*

Background: The glycoprotein SFRP2 is known to activate Wnt/β-catenin signaling and myofibroblast transition in myocardial fibrosis. Previous studies have indicated that myofibroblast proliferation is present in the vascular thickening of arteriovenous fistula (AVF). Thus, it's hypothesized that SFRP2 may promote AVF maturation.

Methods: In the prospective observational study, native veins (NV) harvested during AVF creation surgeries were examined to determine the correlation between preoperative SFRP2 expression and AVF maturation. In addition, SFRP2 expression was compared between mature and immature AVF. In mouse experiment, SFRP2 will be administered intravenously to find its effect on vascular wall remodeling.

Results: We had obtained 69 specimens of NV during the surgery of AVF creation, which contains 22 mature AVF and 47 nonmature AVF at 2 months. The results showed a trend of higher SFRP2 expression in NV that matured. (Figure 1A-C). Additionally, we collected 7 mature AVF from thrombectomy and 2 nonmature AVF in revision surgery. A trend of higher SFRP2 expression in mature AVF was found. (Figure 1D-F). The above results have not achieved statistical significance. The animal experiment showed that SFRP2 treatment induced vascular wall thickening, increased expression of αSMA and nuclear colocalization of β-catenin similar to that in AVF. (Figure 2).

Conclusions: Our preliminary data showed that SFRP2 may induce vascular wall remodeling associated with AVF maturation in human. Nonetheless, its exact role needs confirmation in further investigation.

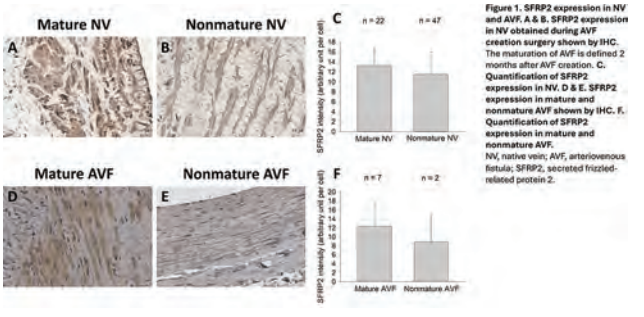


Figure 1. SFRP2 expression in NV and AVF. A & B. SFRP2 expression in NV obtained during AVF creation surgery shown by IHC. The maturation of AVF is defined 2 months after AVF creation. C. Quantification of SFRP2 expression in NV. D & E. SFRP2 expression in mature and nonmature AVF shown by IHC. F. Quantification of SFRP2 expression in mature and nonmature AVF.
NV, native vein; AVF, arteriovenous fistula; SFRP2, secreted frizzled-related protein 2.

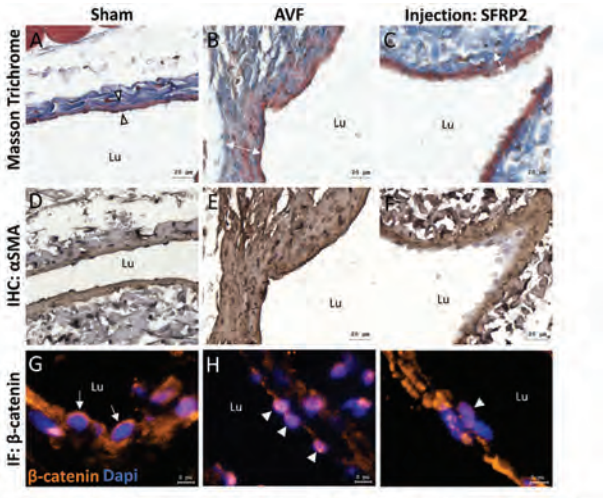


Figure 2. SFRP2 treatment induces vascular wall thickening and Wnt/β-catenin signaling activation in vivo. A-C. Section of native mouse IVC, AVF, and IVC treated with SFRP2 stained by Masson trichrome method, respectively. **D-F.** Section of native mouse IVC, AVF, and IVC treated with SFRP2 stained by IHC against α-SMA, respectively. **G-I.** IF showing the nuclear colocalization of β-catenin of native mouse IVC, AVF, and IVC treated with SFRP2, respectively.
White double arrow, the thickening of mouse AVF or IVC; Hollow arrow head, normal thickness of IVC; White arrow head, nuclear colocalization of β-catenin; IVC, inferior vena cava; AVF, arteriovenous fistula; IF, immunofluorescence stain; α-SMA, smooth muscle α actin; SFRP2, secreted frizzled related protein 2.

FR-PO506

Layer-Specific Transcriptomics Changes from Native to Arteriovenous Fistula Vein in Patients on Dialysis

Yong He, Qiongyao Hu, Guoshuai Cai, Scott A. Berceli. *University of Florida, Gainesville, FL.*

Background: The molecular mechanism of hemodialysis arteriovenous fistula (AVF) vein remodeling may be specific to its layers (intima, media, and adventitia) but is poorly understood. To address this gap, we studied layer-specific transcriptomics in veins of two-stage AVF creation.

Methods: Vein samples were collected during the initial creation of brachial artery-basilic vein AVF (1st stage) or the 2nd stage vein transposition surgery 6 weeks later. Veins were sectioned in OCT and tissues from each layer were separately collected by laser microdissection. Following Takara's SMARTer Stranded Total RNA-Seq Pico Input protocol, libraries were constructed and sequenced in NovaSeq. The sequencing reads were processed by fastp, aligned to genome GENCODE 45 by STAR and gene-level counts were estimated by RSEM. Layer-specific differentially expressed genes between 1st and 2nd stage were detected by edgeR and further identified the enriched pathways using Qiagen IPA.

Results: 47 (24 1st stage) veins were collected from 27 patients. 13,522 protein-coding genes that had a raw count of at least 10 in more than 70% of samples were included in analysis. Compared to 1st stage, the 2nd-stage samples showed disproportional upregulation of gene expression with at least 2-fold changes and FDR<0.05 in all layers of intima (511/831), media (260/296), and adventitia (385/535). Among the 3 layers, Intima had the largest number of differentially expressed genes, followed by adventitia and media. Pathway analysis showed that all layers had activated extracellular matrix organization, collagen biosynthesis and modifying enzymes, and assembly of collagen fibrils and other multimeric structures. Cell migration, growth, and proliferation were inferred to be increased while apoptosis was inferred to be decreased in all layers. Angiotensinogen (AGT), TGFB1, TNF, and IL1B were the common key upstream regulators in all three layers. Interestingly, intima shows the least degree of activation of extracellular matrix and p38 MAPK pathway and no increase of cell viability, as compared to the other two layers.

Conclusions: Similarity and difference of transcriptome changes were found in the 3 layers of the vein following AVF creation. This study provides new data of layer-specific mechanism underlying AVF adaptation that can be used to develop layer-specific therapies to improve AVF remodeling.

Funding: NIDDK Support

FR-PO507

Single-Cell Determinants of Hemodialysis Fistula Failure

Laisel Martinez,[1] Marwan Tabbara,[1] Filipe F. Stoyell-Conti,[1] Miguel G. Rojas,[1] Simone Pereira-Simon,[1] Roberto I. Vazquez-Padron.[1,2] *[1]University of Miami Miller School of Medicine, Miami, FL; [2]VA Miami Healthcare System, Miami, FL.*

Background: Approximately half of newly created AVFs fail to mature without intervention. Despite this glaring statistic, all efforts to improve maturation have been unsuccessful due to our limited understanding of the venous adaptive response to arterial circulation. Our work presents a comprehensive cellular atlas of veins in ESKD patients before and after anastomosis, with a focus on molecular processes associated with failure.

Methods: We performed single-cell transcriptomic analyses on 70,281 cells obtained from 20 subjects on three different occasions: before anastomosis (n=6), one week after (n=2), and during transposition or revision of second-stage fistulas (n=6 matured, n=6 failed). Unsupervised clustering and gene expression analyses revealed the transcriptomic signature of AVF failure.

Results: The most abundant cells in pre-access veins and AVFs were endothelial cells (EC), fibroblasts, monocyte/macrophages, and NK/T cells. Gene expression profiles uncovered >1,000 differentially expressed genes (DEG) between pre-access veins and early AVFs in most cell clusters. Inflammation, not proliferation, dominated the initial transformation of vascular cells after anastomosis, a phenotype that prevailed in AVFs with unsuccessful maturation. Infiltrated monocytes were the primary source of wall cytokines dominating vascular remodeling. Immunofluorescence further confirmed the higher abundance of macrophages in failed vs. mature AVFs. Sub-clustering analyses discovered two new types of postoperative ECs, expressing hemostasis/shear stress factors or extracellular matrix genes, and a new population of fibroblasts characterized by upregulation of chemokine genes. The number of DEGs between mature and failed AVFs per cluster was less than one-tenth the one observed in the former comparison indicating that most transcriptional changes occur in the first week of remodeling. Upregulation of *COL8A1* in ECs and myofibroblasts was associated with failure, identifying the cell sources for this previously validated failure-associated risk factor.

Conclusions: We uncovered the early and late adaptive response of the human vein after anastomosis at the single-cell resolution. We highlight the essential roles of postoperative EC populations, fibroblasts, and macrophages in orchestrating the reparative response of the vein to secure hemostasis and maturation.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support, Private Foundation Support

FR-PO508

Informing Choices about Arteriovenous Fistula Creation: Insights from a Prospective Cohort Study

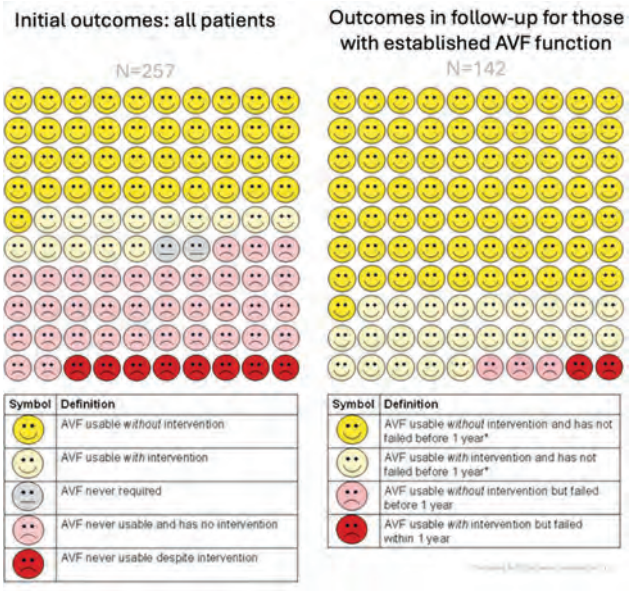
Anukul Ghimire,[1] Anita Lloyd,[3] Susan Szigety,[3] Jose Luis Merino,[2] Robert R. Quinn,[1] Marcello Tonelli.[1] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]Hospital Universitario del Henares, Coslada, Spain; [3]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada.*

Background: Selection of a dialysis access type should incorporate patients' circumstances and preferences, termed the "Kidney Failure Life Plan". Data on long-term outcomes for arteriovenous fistulas (AVF) can guide decisions surrounding the Plan. We did this study to inform patients' choices about AVF creation, accounting for the risk of primary non-function and the presence of competing risks.

Methods: Prospective observational study of 257 adults with newly created AVF in Alberta, Canada. Participants were followed for 15 years or until the first outcome of death, outmigration, modality switch, or AVF failure/abandonment/ligation/removal. The primary outcome was primary function. Secondary outcomes included loss of primary patency and loss of secondary patency, assessed using Fine-Grey subdistribution hazard models to account for competing risks.

Results: Of 257 participants, 63.0% were male with mean age 62.3y, 54.9% had a radiocephalic AVF, and median follow up was 18.5 months. 50 AVF could not be assessed for primary function, with death being the most common reason. Of the remaining 207 AVF, 105 had primary function, and function was eventually established in 37/102 with primary non-function. In the 142 AVF with established function, loss of primary patency at 1, 3, and 5 years was 36.6%, 65.5% and 66.2% respectively. Similar values for loss of secondary patency were 0.7%, 11.3% and 16.2%. Overall, of 257 participants undergoing AVF creation, only 55% ultimately used that AVF for hemodialysis. These data were used to create the icon array (Figure) which is the basis for a decision aid.

Conclusions: This study highlights patient-important outcomes that may inform patients' Kidney Failure Life Plans and choices about AVF creation. Future studies will validate and refine decision aids with input from patients.



FR-PO509

A Data-Driven, Evidence-Based, Patient-Centered Optimal Initiation Time for Dialysis Treatment

Eva Lee.[1,2] The Kaiser Nephrology Team. *[1]The Data and Analytics Innovation Institute, Atlanta, GA; [2]AccuHealth Technologies, Atlanta, GA.*

Background: When to start dialysis is an important decision for end-stage CKD care. The difficulty in determining a common gold standard lies partly in the high heterogeneity among patients and available treatment conditions, and in random factors in disease progression / treatment process. This work optimizes pre-dialysis care timing.

Methods: A novel interpretable machine learning model ingests EMR / unstructured data to classify treatment effects and disease prognosis wrt each disease staging and timeline. Our ML model can classify disease-action into the same outcome groups under different conditions/features (hence multiple pathways). A ML-knowledge treatment timing model is developed to determine an outcome-driven GFR threshold for creating access of various types that maximizes the goodness of patient's health conditions. Patient preference is incorporated.

Results: 11,913 CKD patients with 213,344 GFR s from 2011-2018 were extracted. Among those with initiated dialysis, 67% initiated HD, 32% PD, and 1% CVC. Current 'sub/optimal' initiation shows diverse variance. AI/ML uncovers critical features that affect outcome; and GFR-windows for dialysis initiation and begin dialysis that render good outcome. Table 1 shows 2 interpretable optimal timing and dialysis start time, w.r.t. patient preferences. Only 2-12% of current practice falls within these optimal initiation time. Simulating the 2 policies for 2 years on 1000 patients shows reduction of 16.4%-35% avoidable deaths and 8%-19% increase in utility reward. A new CPG for Phase I implementation was established.

Conclusions: This work has critical health practice implications. We establish *the optimal initiative timing model for late-stage CKD management*. The novel ML-decision system includes distinct analytic advances as it leverages hidden knowledge within EMR to enable evidence-based patient-centered policy making. The results show that current practice is far from optimal and can be improved considerably. Clinical trial has to be conducted to gauge potential outcome improvemet.

Funding: Other U.S. Government Support

Two optimal timing policies returned from our model (simplified for brevity).

	Policy 1	Policy 1	Policy 2	Policy 2
Type	Optimal Initiation time (pre-dialysis care)	Begin dialysis	Optimal Initiation time (pre-dialysis care)	Begin dialysis
HP	GFR < 20	GFR < 12	GFR < 24	GRF < 15
PD	GFR < 18	GFR < 10	GFR< 21	GFR < 12
Suboptimal	With uremia	GFR < 10	With uremia	GFR < 12
Suboptimal	Without uremia	GFR < 7	Without uremia	GFR < 9

FR-PO510

A Feasibility Study Investigating the Role of Kidney Failure Risk Equation in Optimizing the Timing of Vascular Access Creation

Mohammad Atiquzzaman,[1] Bingyue Zhu,[2] Lee Er,[2] Alexandra Romann,[2] Ognjenka Djurdjev,[2] Adeera Levin.[1] *[1]The University of British Columbia, Vancouver, BC, Canada; [2]BC Provincial Renal Agency, Vancouver, BC, Canada.*

Background: KFRE 2-year risk threshold of >40% along with existing eGFR based referral for vascular access (VA) creation may improve VA resource utilization. We investigated if KFRE score can play a role in optimizing the timing of VA creation.

Methods: We analyzed a cohort of 2,581 patients with CKD who had an eGFR of <20 ml/min/1.73m2 and chose hemodialysis (HD) as their preferred mode of dialysis. We created the cohort using data from PROMIS, a population-level registry database for patients with CKD in BC, Canada. Modality selection date was index date. In step 1, we explored the association between KRFE-2 threshold and timing of HD initiation among patients who reached kidney failure and initiated HD within 24 months from the index date in two ways: First, we categorized the patients based on time to HD initiation into 0-3, 3-6, 6-9, 9-12 and 12-24 months, and investigated the corresponding distribution of KFRE-2 scores at index. Second, we categorized the patients based on index KFRE-2 score into <40%, 40-<50%, 50-<60%, 60-<70%, 70-<80% and >80% and investigated the distribution of time to HD initiation. In step 2, we explored the positive predictive value (PPV) of initiating HD within 6 and 24 months using the aforementioned KFRE-2 thresholds among the entire cohort.

Results: Study cohort included 2581 patients, median age 71 years, and 40% female. Of the 1,562 patients who initiated HD within 2 years, a total of 733 (47%) patients initiated HD within 6 months and the median index KFRE-2 was ≥69% (Table 1A). On the other hand, 207 (13%) patients had an index KFRE-2 of 60 - <70% and the median time to initiate HD was 6.4 months (Table 1B). PPV gradually increased with increasing KFRE-2 threshold for both HD initiation within 6 and 24 months (Fig 1).

Conclusions: KFRE-2 score has the potential to guide the timing of VA creation. Future research using sophisticated methodology is required to identify an optimal KFRE-2 score for fistula/graft creation.

Table 1A: KFRE-2 threshold by time to initiate HD

Time to initiate HD from modality selection date	n (%) (Total N = 1,562)	Median (IQR) KFRE-2 score on index date
0 - <90 days	419 (27%)	73.8 (50.5, 90.6)
90 - <180 days	314 (20%)	68.8 (50.6, 80.8)
180 – <270 days	241 (15%)	61.3 (46.0, 75.2)
270 – <365 days	202 (13%)	54.7 (38.9, 71.7)
365 days – 2 years	386 (25%)	46.8 (31.6, 60.7)

Table 1B: Time to initiate HD by KFRE-2

KFRE-2 score on index date	n (%) Total N = 1,562	Median (IQR) time to initiate HD
<40%	366 (23%)	290.0 (117.0, 475.0)
40% – <50%	196 (13%)	296.5 (161.0, 466.5)
50% – <60%	216 (14%)	260.5 (118.5, 407.0)
60% – <70%	207 (13%)	195.0 (114.0, 339.0)
70% – <80%	223 (14%)	179.0 (94.0, 286.0)
≥ 80%	354 (23%)	82.5 (31.0, 175.0)

Figure 1: positive predictive value of HD initiation by KFRE-2 threshold

KFRE-2 score on index date	Initiated HD within 2 years from index date, n (%)			Initiated HD within 6 months from index date, n (%)		
	Yes	No	Total	Yes	No	Total
<40%	366 (36%)	663 (64%)	1029	126 (12%)	903 (88%)	1029
40-<50%	196 (66%)	103 (34%)	299	54 (18%)	245 (82%)	299
50-<60%	216 (67%)	104 (33%)	320	78 (24%)	252 (76%)	320
60-<70%	207 (76%)	67 (24%)	274	97 (35%)	177 (65%)	274
≥70%	577 (88%)	82 (12%)	659	384 (58%)	275 (42%)	659
Total	1562	1019	2581	739	1842	2581

FR-PO511

Abstract Withdrawn

FR-PO512

Incidence and Determinants of Primary Arteriovenous Access Failure in Dialysis Patients: A Qatar-Based Retrospective Analysis

Tarek A. Ghonimi,[1] Abdullah I. Hamad,[1] Musab Elgaali,[1] Mohamed Y. Ali,[1] Mohamed T. Abdellatif,[2] Anees J. Alomari,[1] Athar I. Ibrahim,[1] Rania A. Ibrahim,[1] Hassan A. Al-Malki.[1] *[1]Hamad Medical Corporation, Doha, Qatar; [2]Misr University for Science and Technology, 6th of October City, Egypt.*

Background: The demand for hemodialysis (HD) among patients with end-stage kidney disease (ESKD) is increasing globally. A well-functioning Arterio-vascular access (AV) is crucial for effective HD therapy. This study aimed to determine the incidence and risk factors associated with primary AV access failure in HD patients.

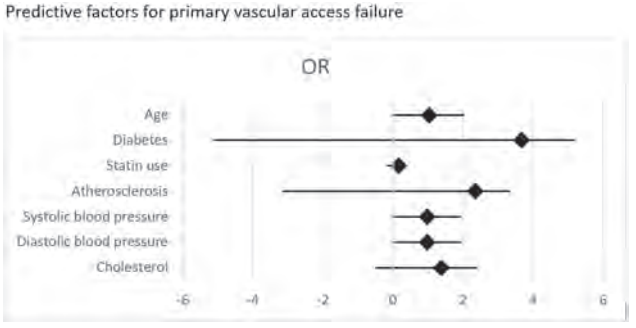
Methods: This retrospective study included HD patients who underwent AV access creation between 01/01/2021 and 31/12/2023 in Qatar's dialysis centers. Data were obtained from electronic health records, including demographics, medical comorbidities, VA types, time to maturation, and incident of primary AV access failure.

Results: A total of 242 AV accsess creations were included. The incidence of primary AV Access failure was 28%. It was highly significant in patients with Left radio cephalic arterio-veinous fistula (in 32.3%). Significant associations were found between primary AV access failure and older age ($p < 0.001$), diabetes ($p = 0.027$), atherosclerosis ($p = 0.019$) and lower systolic and diastolic blood pressure ($P < 0.016$ and < 0.0001

respectively). However, statin use showed significant reduction in primary AV access failure (p = 0.001). Multivariate analysis identified older age, diabetes, atherosclerosis and lower systolic BP as significant risk factors for AV access failure, while statin use was associated with a reduced risk (odds ratio 0.167, 95% CI 0.080-0.347, p < 0.0001).

Conclusions: Primary VA failure in HD patients is notable, with older age, diabetes, and atherosclerosis as significant risk factors. Interestingly, statin use is linked to lower risk of primary AV access failure, emphasizing the need for early risk factor identification and management to improve AV access outcomes in HD patients.

Funding: Private Foundation Support



FR-PO513

"Optimal" vs. "Suboptimal" Haemodialysis Start with a Line

Michael Corr,[1] Agnes Masengu,[2] Jennifer B. Hanko.[2] *[1]Queen's University Belfast, Belfast, United Kingdom; [2]Belfast City Hospital, Belfast, United Kingdom.*

Background: Monitoring whether patients commence haemodialysis with a central venous catheter (CVC), or an arteriovenous fistula (AVF) is commonly used to audit the quality of a vascular access service. However, this crude metric of measurement can miss the increasing nuance and complexity of vascular access planning. At times, commencement of haemodialysis with a CVC may be the most appropriate access choice for an individual patient or be due to unpredictable events rather than representing a failure in access service delivery. We aimed to understand whether commencing haemodialysis with a CVC represented an 'optimal' or 'suboptimal' outcome and how this could influence assessment of a vascular access service.

Methods: From a prospective clinical database, patients known to nephrology >90 days before initiating haemodialysis as first ever renal replacement therapy (2011-2020) from a single centre were included. Descriptive statistical analyses were completed using SPSS Statistics.

Results: 158/254 patients started haemodialysis with a CVC, 96 with an arteriovenous fistula. For 91 patients the CVC was deemed 'optimal' care- due to unpredictable deterioration in renal function (n=41) and inadequate veins for AVF creation (n=24). For 67 patients the CVC was 'suboptimal'- no/late referral to access assessment (n=25) and delays in the AVF creation pathway (n=13). Two-year mortality was 53% 'optimal' CVC, 37% 'suboptimal' CVC and 30% AVF start. There was no difference in mean survival between AVF and 'suboptimal' groups (2.53 vs. 2.21 years p= 0.31). There was a survival difference between AVF versus CVC (2.53 vs 1.97 years p=0.002) and 'suboptimal' versus 'optimal' CVC cohorts (2.21 vs 1.40 years p=0.16).

Conclusions: Understanding whether CVC is 'optimal' or 'suboptimal' allows more nuanced analysis of service provision. High mortality in the 'optimal' group suggests a frailer cohort where CVC is potentially best care. Meanwhile, appreciating many 'optimal' CVC patients had unsuitable veins for AVF creation prompted review of our vein preservation strategy. Finally, studying 'suboptimal' CVC starts helps identify practice and system issues preventing 'optimal' care.

FR-PO514

Multidisciplinary Vascular Access Team Impact on the Number of Arteriovenous Fistulae and 12-Month Mortality

Rafael Figueiredo, Miguel L. Relvas de Carvalho, Hugo Diniz, Luis Coentrao. *Centro Hospitalar Universitario de Sao Joao, Porto, Portugal.*

Background: Autologous arteriovenous fistulae (AVF) are the vascular access (VA) of choice for most haemodialysis (HD) patients. The creation of multidisciplinary VA teams (mVAT) improves access-related outcomes, and thus overall survival. This study evaluates our center's mVAT impact on matured AVFs and 12-month mortality.

Methods: A retrospective case-control analysis was performed, comparing our center's incident HD patients from years 2019 and 2022. A mVAT was created in 2021. Patient data was collected from their electronic health record, namely demographic variables, comorbidities, prior nephrology (NA) and vascular access appointments (VAA), access typology at the beginning of HD and the number of unprogrammed initiations. The primary outcome was the number of functioning AVFs in incident and 12-month prevalent HD patients. Secondarily, 12-month mortality was assessed, and its clinical predictors were derived from a combined-year Cox proportional hazard regression model.

Results: 169 and 184 incident HD patients were included from 2022 and 2019, respectively. There were no significant differences between years regarding demographic variables, comorbidities, prior NA/ VAA/ VA construction, and the number of unprogrammed initiations. More incidents started HD with an AVF in 2022 (50.9% vs 37.5%, p= .011), independently of demographic variables and comorbidities. The number of functioning AVFs in 12-month HD prevalents was also greater (85.2% vs 76.6%, p = .041). The 12-month cumulative mortality was 11.2% and 14.7% in 2022 and 2019, respectively (Log Rank X2(1) = 0.881; p= .348), with no significant differences regarding the categorized cause of death between years. In our combined-cohort Cox proportional hazard regression model (X2 (11) = 180.266; p < .001), age (HR 1.05, p= .009) and initiation with a CVC (HR 10.01, p< .001) were predictors of 12-month mortality; and VA construction (HR 0.09, p < .001) and the number of days with a CVC (HR 0.988, p < .001) were negative predictors. No comorbidity obtained statistical significance after adjustment.

Conclusions: Our mVAT impacted both the number of functioning AVFs in incident and 12-month prevalent HD patients. We did not detect a significant mortality difference between years. HD initiation with a CVC appears to be the strongest 12-month mortality predictor.

FR-PO515

Patient and Provider Perspectives Surrounding Arteriovenous Fistulas vs. Grafts: A Qualitative Substudy of the AV Access Trial

Dipal M. Patel,[1] Katherine E. White,[1] Allison Chandler,[3] Ashley E. Strahley,[3] Deidra C. Crews,[1,2] Mariana Murea.[3] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [3]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: People with kidney failure on hemodialysis (HD) require sustainable vascular access. While the "Fistula First" initiative recommended arteriovenous fistulas (AVF) as the optimal access for all people on HD, AV grafts (AVG) may have similar outcomes in select populations such as older adults who more commonly experience AVF maturation failure. The AV Access trial is a randomized controlled trial studying outcomes of adults > 60 years old with ≥ 1 major comorbidity, on chronic HD with a tunneled catheter, who are then randomized to receive an AVF or AVG. Patient recruitment for this trial has been slower than anticipated. We sought to explore perspectives of relevant stakeholders surrounding the perceived optimal access for HD, and to assess the implications of these perspectives on trials of AV access.

Methods: We planned focus groups with site investigators and individual semi-structured interviews with nephrology providers, vascular access surgery providers, and older adults on HD who were approached for enrollment in the AV Access trial. Thematic analysis was used to analyze data.

Results: Two focus groups (n= 4 nephrology and 4 vascular access surgery site investigators), and 31 semi-structured interviews (n=10 nephrology providers, 9 vascular access surgery providers, and 12 eligible patients) were conducted. We identified three common themes of participant perspectives (**Table**).

Conclusions: Prioritizing AVF placement in all patients on HD is pervasive. Educational initiatives aimed at increasing patient and provider knowledge of potential equipoise between AVF and AVG in select populations, as well as patient-centered practices, may enable patient enrollment in trials studying dialysis vascular access.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging

Themes	Exemplary quotations
Biases stemming from the "Fistula First" initiative are pervasive	"Sometimes in academia, we feel, as specialists, that the information that we have and that we're premising our research on, is common knowledge…We have to explain the controversy and then the premise of our study, and then go on to explain the methodology in our outcome. I think in this situation, it's just unappreciated. Not only how much—how effective 'fistula first' has been, how limited the knowledge is around the existing controversy, but also the impact of the economics that are driving dialysis centers and the nephrologists that manage them to continue to chase the quality performance metrics that underlie reimbursement." (*Vascular surgery site investigator*) "…over the last 20 years, the medical community has really emphasized that the fistula or their own vein is better. The study is now trying to prove that that may not always be the case, but they're going against a big tsunami of 20 years of information that was given to us…" (*Vascular surgery site provider*)
Buy-in from providers surrounding equipoise between AVF and AVG in select populations is key for enrollment	"We sat down, as a group of surgeons, and basically said, "If you want to be a part of this study, you have to be willing to randomize any patient that meets criteria that passes screening. Even if they've got a big cephalic vein, you can't turn them down." We've made a concerted effort to get buy-in amongst the entire surgery group, that they're willing to enroll any patient that meets criteria that passes screening. That seems to have helped us a lot. I think all the group of surgeons now feel like they have buy-in. I think that's—ultimately, I feel like we are the gatekeepers for the trial. I don't think it's the nephrologists. I think it's the surgeons, because we're the ones that sit down and have more conversations about dialysis access with these people than anybody else." (*Vascular surgery site investigator*)
Patient-centered practices and accommodations could facilitate patient participation in research surrounding vascular access	"I don't even know what's gonna happen. I talked to the doctor about it, and I don't know that—I kinda got chased out of the room before I really got explained what was gonna happen anyway. I asked him, "Do you have a—show me a picture of what's gonna happen to my arm or whatever," That kinda got swept under the carpet…." (*Patient approached for trial enrollment*) "I think it's more, to me, the patients are not worried about compensation, but time commitment, right? Up front, if you tell them a clear idea of what is involved, it is probably easier. These are the number of visits. This is what we will do. I think they will have a clear understanding and then can make a decision." (*Nephrology site investigator*)

Themes and exemplary quotations.

FR-PO516

Assessing Permanent Dialysis Access in Underserved Patients with Advanced Kidney Disease in Austin, Texas

Nidharshan S. Anandasivam, Tessa K. Novick, Raymonda El Khoury, Michelle L. Lubetzky, Paul C. Nader. *The University of Texas at Austin Dell Medical School, Austin, TX*.

Background: Arteriovenous fistulas (AVFs) have several advantages over central venous catheters (CVCs), primarily lower complication rates and more reliable blood flow rates. However, many underserved patients with advanced kidney disease start dialysis with CVCs.

Methods: In this retrospective study, we reviewed the medical records of underserved patients receiving emergency-only hemodialysis (EoHD) at an academic medical center (January 2022-March 2023), and of non-dialysis dependent patients with estimated glomerular filtration rate (eGFR)<20 ml/min/1.73m^2 at two community nephrology clinics (January 2021-December 2023) in Austin, Texas. We assessed the prevalence of each access type. Utilizing questionnaire interviews with health care providers and staff, we discussed barriers to arranging permanent dialysis access and recommendations for intervention.

Results: Among 38 patients receiving EoHD, 29 (76%) had an AVF or arteriovenous graft (AVG) whereas 9 (24%) had a CVC. Average time from first hemodialysis to AVF/AVG creation was 104 days. Among 301 patients receiving care at community nephrology clinics, 71 (24%) had eGFR<20 ml/min/1.73m^2. Of these 71: 19 (27%) had AVF/AVG, 8 (11%) had been referred to Vascular Surgery but did not have AVF/AVG, 15 (21%) had not been referred to Vascular Surgery, and 29 (41%) did not have any recent clinic notes as they may have transitioned their routine nephrology care to a dialysis center. Noted barriers included: primary language other than English, uncertainty of the patient regarding commitment to being treated with dialysis, need for additional patient education about dialysis, and failure to attend scheduled Vascular Surgery appointments. Recommended interventions included: creating culturally sensitive educational materials, and workflow diagrams for providers/staff for referral to Vascular Surgery.

Conclusions: Optimizing permanent vascular access among underserved patients with advanced kidney disease is challenging due to numerous barriers.

FR-PO517

Presurgery Plasma Metabolites Are Associated with Arteriovenous Fistula Maturation Outcomes

Xin Wang,[1] Syed S. Zaidi,[5] Cindy Chan,[4] Yan Yi Cheung,[2] Nadja Grobe,[1] Peter Kotanko,[1,3] Sandip Mitra,[5] Milind Nikam.[2] *[1]Renal Research Institute, New York, NY; [2]Global Medical Office, Fresenius Medical Care, Singapore, Singapore; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Fresenius Medical Care Asia Pacific Ltd, Hong Kong, Hong Kong; [5]Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, United Kingdom.*

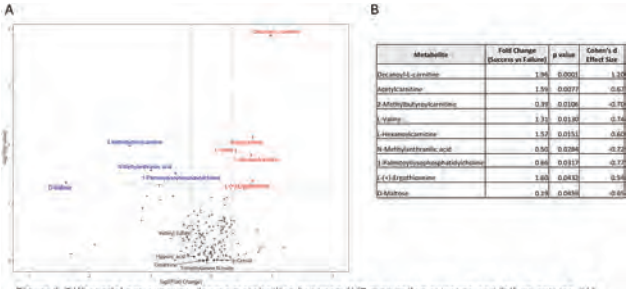
Background: Arteriovenous fistulas (AVFs) are the preferred vascular access for most hemodialysis (HD) patients. Previously, we showed that plasma metabolome clusters prior to AVF surgery associate with AVF maturation outcomes. Here we aim to further annotate pre-surgery plasma metabolites as potential biomarkers of AVF maturation outcomes.

Methods: Successful AVF maturation was defined as either adequate HD or a combination of ultrasound features (vein size > 4 mm with AVF flow ≥ 500 ml/min) and clinical assessment. Pre-surgery plasma samples from the day of AVF creation surgery were analyzed by liquid chromatography-mass spectrometry. Metabolites were identified by matching to in-house and METLIN libraries.

Results: The study cohort included 28 patients with successful AVF maturation and 16 with AVF failure. We annotated 147 metabolites in the pre-surgery plasma samples. In patients with successful AVF maturation, 5 were significantly up-regulated and 4 were down-regulated (**Fig. 1**). The metabolites are linked to the metabolism of lipids, amino acids, or starch. Four of the 9 metabolites are acylcarnitines, which are responsible for transporting fatty acids into the mitochondria for β-oxidation, suggesting a role of energy metabolism in AVF maturation. AVF maturation outcomes did not correlate with age, sex, diabetes, and cardiovascular disease.

Conclusions: Nine pre-surgery plasma metabolites were differentially regulated between patients with successful or failed AVF maturation. If validated by further targeted analysis and corroborated in larger cohorts, these potential biomarkers could inform precision vascular access planning.

Funding: Commercial Support - Renal Research Institute, Fresenius Medical Care, Government Support - Non-U.S.



Metabolite	Fold Change (Success vs Failure)	p value	Cohen's d Effect Size
Decanoylcarnitine	1.94	0.0001	1.30
Acetylcarnitine	1.59	0.0077	0.83
2-Methylbutyroylcarnitine	0.39	0.0106	-0.70
L-Valine	1.33	0.0130	0.74
L-Hexanoylcarnitine	1.52	0.0151	0.80
N-Methylanthranilic acid	0.50	0.0286	-0.72
1-Palmitoylglycerophosphatidylcholine	0.66	0.0317	-0.77
L-(+)-Ergothioneine	1.60	0.0432	0.94
D-Maltose	0.39	0.0456	-0.85

Figure 1. Differential pre-surgery plasma metabolites between AVF maturation success and failure groups. (A) Volcano plot displaying up-regulated (in red) and down-regulated (in blue) metabolites in AVF maturation versus failure group with p-value <0.05 (the horizontal dashed line) and fold change <0.75 or >1.25 (left or right vertical dashed lines). Metabolites outside of the cutoffs are depicted in gray, including five uremic retention solutes (shown in black). **(B)** Statistic analysis of plasma levels of 9 differential metabolites indicated in (A).

FR-PO518

Sacubitril/Valsartan Can Improve Vascular Access Flow in Patients on Hemodialysis with Heart Failure with Reduced Ejection Fraction

Chih-Ching Lin.[1,2] *[1]Taipei Veterans General Hospital, Taipei, Taiwan; [2]National Yang Ming Chiao Tung University, Taipei, Taiwan.*

Background: Sacubitril/valsartan improves heart function in maintenance hemodialysis (HD) patients with heart failure with reduced ejection fraction<40% (HFrEF); however, the effect of sacubitril/valsartan on access flow (Qa) of vascular access in this population is unclear. Therefore, we conducted this study to evaluate this effect.

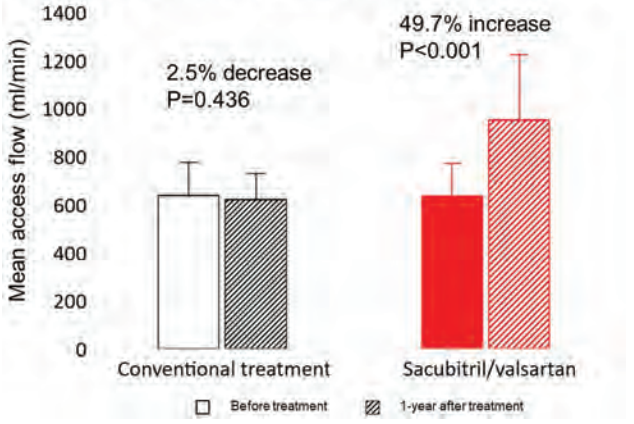
Methods: We retrospectively screened the HD patients in two hospitals. Patients with HFrEF receiving echocardiography and Qa measurement twice at 1 year apart were enrolled and divided into sacubitril/valsartan group and conventional treatment group. We compared the change of Qa(ΔQa) and echocardiographic parameters after 1-year treatment. Correlations between ΔQa and echocardiographic parameters were examined. Multiple linear regression analysis was applied to predict ΔQa.

Results: Thirty-three HD patients with HFrEF were analyzed. Sixteen patients received sacubitril/valsartan treatment; their mean Qa increased significantly from 633.8 to 948.8 mL/min (P<0.001). There was no significant change of Qa for the conventional treatment group (from 637.7 to 621.8 mL/min, P=0.436). The change of left ventricular ejection fraction (ΔLVEF) significantly differed between the two groups. The ΔQa had significant correlation with ΔLVEF(rs = 0.929, p<0.001) and with the change of interventricular septum thickness in diastole (ΔIVSd, rs = -0.736, p=0.001) in sacubitril/

valsartan group. The ΔQa was predicted as -44.034+15.868*ΔLVEF-25.072*ΔIVSd+145.964* (sacubitril/valsartan use or not), with $R^2 = 0.909$ and adjusted $R^2 = 0.899$.

Conclusions: Sacubitril/Valsartan improves Qa ~150 ml/min in HD patients with HFrEF. In addition, ΔQa was ~15ml/min for each % increase of LVEF.

Figure 1. The mean of access flow(Qa) before and after 1-year of conventional treatment or of sacubitril/valsartan.



FR-PO519

Use of Early Ultrasound Scan to Predict Arteriovenous Fistula Maturation

Syed S. Zaidi,[1,2] Cindy Chan,[3] Xin Wang,[6] Yan Yi Cheung,[4] Nadja Grobe,[6] Peter Kotanko,[6,5] Sandip Mitra,[1,7] Milind Nikam.[4] *[1]Manchester University NHS Foundation Trust, Manchester, United Kingdom; [2]The University of Manchester, Manchester, United Kingdom; [3]Fresenius Medical Care Asia Pacific Ltd, Hong Kong, Hong Kong; [4]Clinical Affairs, Global Medical Office, Fresenius Medical Care, Singapore, Singapore; [5]Icahn School of Medicine at Mount Sinai, New York, NY; [6]Renal Research Institute, New York, NY; [7]Manchester Academy of Health Sciences, Manchester University Hospitals, Manchester, United Kingdom.*

Background: The Manchester Vascular Access study (MANVAS) was a prospective observational study which investigated arteriovenous fistula (AVF) maturation. We interrogated the MANVAS data to evaluate whether early doppler ultrasound (DUS) scan could predict AVF maturation.

Methods: Patients undergoing upper limb AVF creation surgery were recruited. In addition to pre-operative vascular mapping, recruited patients had protocolised post-surgery AVF scans, done at weeks 2, 6, 12 after surgery, to assess anatomical and rheological parameters such as blood flow rate and velocities in the index AVF, and the feeding artery. The primary outcome was AVF maturation, which was defined either, as successful haemodialysis using the AVF or a combination of DUS features (vein size > 4 mm with AVF flow ≥ 500 ml/min) and clinical assessment. In this sub-group analysis (where DUS data was available, n=57), we used week 2 post-surgery DUS scan to identify predictors of AVF maturation. We used logistic regression models to explore differences between matured and non-matured groups.

Results: We found that minimal AVF diameter (D-Min), arterial peak systolic velocity (PSV) and end diastolic velocity (EDV), and AVF blood flows (Qa) were significantly higher in matured group compared to non-matured group (Table 1). Of note, the average Qa was almost 2-fold in the group which subsequently had mature AVFs vs the non matured group. After adjusting for age, sex, comorbidities and AVF type, PSV and Qa remained statistically significant.

Conclusions: Vascular flow attributes measured using DUS performed as early as 2 weeks post AVF creation can predict fistula maturation. If validated in a larger cohort, these findings could impact current clinical pathways considering early AVF maturation assessment and intervention.

Funding: Commercial Support - Fresenius Medical Care

Logistic Regression Analysis of Week 2 US Scans (n = 57)

US Parameters	Non matured	Matured	p-Value*
D-Min (cm)	0.31±0.08	0.41±0.12	0.0739
PSV (cm/sec)	111.3±52.1	189.0±70.7	0.0234
EDV (cm/sec)	47.0±18.9	98.3±41.6	0.0560
Averaged AVF blood flow (cc/min)	264.7±152.2	494.4±305.7	0.0481
Brachial Artery (cc/min)	378.7±267.6	569.9±399.3	0.0526

*Adjusted for age, sex, race, DM, CVD, and AVF location (i.e. brachial or radial)

FR-PO520

Comparative Evaluation of UAB and NKF-KDOQI Criteria for Predicting Unassisted Arteriovenous Fistula Maturation Using Postoperative Ultrasound Measurements

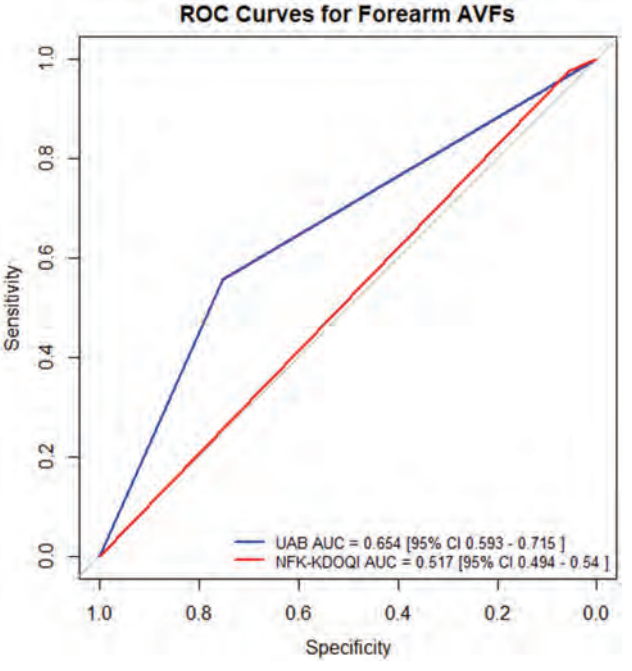
Seung Yun Chae, Yaeni Kim, Hoon suk Park. *The Catholic University of Korea Seoul St Mary's Hospital, Seoul, Seocho-gu, Republic of Korea.*

Background: This study aimed to compare the predictive performance of the University of Alabama at Birmingham (UAB) criteria with the NKF-KDOQI guidelines in forecasting unassisted arteriovenous fistula (AVF) maturation. Additionally, we sought to evaluate how the predictive accuracy of these criteria varies between upper arm AVFs and forearm AVFs.

Methods: We retrospectively analyzed the age, gender, BMI, and comorbidities of chronic kidney disease patients who underwent AVF creation and were monitored from January 2017 to March 2021 at a single medical center. Additionally, we assessed the types of AVFs, the success rate of the first cannulation, and postoperative AVF ultrasound measurements.

Results: Among the 560 patients analyzed, 68.6% experienced unassisted AVF maturation. Specifically, upper arm AVFs had a higher unassisted maturation rate (70.2%) compared to forearm AVFs (66.8%). The NKF-KDOQI guidelines had a higher positive predictive value for overall unassisted AVF maturation (0.85) than the UAB criteria (0.77), while UAB showed a better negative predictive value (0.57). Receiver Operating Characteristic Curve analysis revealed that UAB (AUC = 0.643, 95% CI 0.602–0.684) outperformed NKF-KDOQI (AUC = 0.56, 95% CI 0.532–0.589) in predicting overall AVF maturation. For forearm AVFs, UAB (AUC = 0.654, 95% CI 0.593–0.715) also demonstrated superior predictive ability compared to NKF-KDOQI (AUC = 0.517, 95% CI 0.494–0.540), which was close to random chance.

Conclusions: In conclusion, the UAB criteria proved superior in predicting the overall unassisted maturation of AVFs compared to the NKF-KDOQI guidelines. This was especially evident for forearm AVFs, where the predictive ability of the NKF-KDOQI criteria for unassisted maturation was nearly random.



ROC curve : Forearm AVF

FR-PO521

Efficacy and Safety of Apixaban for Prevention of Recurrent Thrombosis after Thrombectomy of Hemodialysis Vascular Access: A Randomized Controlled Trial

Chih-Cheng Wu. *National Taiwan University Hospital, Hsin-Chu Branch, Hsinchu City, Taiwan.*

Background: Dialysis vascular access thrombosis poses a substantial challenge for individuals undergoing hemodialysis. The efficacy and safety of apixaban, a direct oral Xa inhibitor, in preventing recurrent access thrombosis have yet to be explored.

Methods: This was a multi-center randomized control studyregistered at ClinicalTrials. Gov (NCT04489849). The study enrolled hemodialysis patients who underwent successful endovascular thrombectomy within 48 hours. Participants

were assigned to standard care or standard care plus apixaban, 2.5mg twice daily for three months. The trial design involved open-label administration, with independent adjudication of endpoints. The primary efficacy endpoint was recurrent access thrombosis within 3 months after thrombectomy.

Results: A total of 186 patients were enrolled; 93 patients randomized to the apixaban group and 93 to the control group, with well-balanced baseline characteristics. The apixaban group demonstrated a lower rate of access thrombosis at 3 months than the control group (24.0% vs. 40.8%; hazard ratio, 0.52 [HR]; 95% confidence interval [CI], 0.31-0.88, p=0.01), along with a better primary patency failure rate at 3 months (32.2% vs. 49.5%, HR, 0.57, 95% CI 0.36-0.91, P=0.02). Safety outcomes showed comparable death rates and major bleeding incidents but higher incidence of minor bleeding in the apixaban group (22.6% vs. 7.5%, p=0.01). The effect of apixaban did not show interaction in subgroups of different access types, antiplatelet usage, or history of thrombosis.

Conclusions: Apixaban effectively reduces the risk of recurrent thrombosis in hemodialysis vascular access. Despite a minor increase in bleeding adverse effects, the net clinical benefit supports the use of apixaban in this context.

Funding: Government Support - Non-U.S.

Efficacy outcomes

Outcomes	Hazard Ratio	95% CI(LB)	95% CI(UB)	P value
Access thrombosis at 3 mo	0.52	0.31	0.88	0.01
Primary patency failure at 3 mo	0.57	0.36	0.91	0.02
Secondary patency failure at 3 mo	2.55	0.49	13.1	0.26
Access thrombosis at 6 mo	0.63	0.41	0.98	0.04
Primary patency failure at 6 mo	0.65	0.44	0.96	0.03
Secondary patency failure at 6 mo	1.70	0.41	7.12	0.47

FR-PO522

Far Infrared Radiation Does Not Improve Time to Cannulation in Newly Placed Arteriovenous Fistulas in Patients on Hemodialysis

Kristine Lindhard,[1] Henrik P. Hansen,[1] Kirstine M. Gliese,[5] Emilie K. Hansen,[1] Kristine Hommel,[2] Boye Jensen,[3] Ylian S. Liem,[4] Brian L. Pedersen,[4] Mahshid Pourarsalan,[6] Marianne Rix,[4] James Heaf,[5] Ditte Hansen.[1]
[1]Herlev Hospital, Herlev, Denmark; [2]Holbaek Sygehus, Holbaek, Denmark; [3]Syddansk Universitet, Odense, Denmark; [4]Rigshospitalet, Kobenhavn, Denmark; [5]Sjaellands Universitetshospital Roskilde, Roskilde, Denmark; [6]Nordsjaellands Hospital, Hillerod, Denmark.

Background: There is a need to improve arteriovenous fistula (AVF) maturation and decrease the number of central venous catheter days in patients on hemodialysis (HD). Far infrared radiation (FIR) is a treatment modality, which may improve AVF maturation and patency. The present trial examined FIR's effect on AVF maturation

Methods: A randomized, controlled, open-label clinical trial was performed. Patients were randomized to receive FIR treatment (FIR) or no FIR (control). After AVF placement, the FIR group received FIR on their AVF for 40 minutes at every HD treatment for one year. The primary outcome was the difference in time to cannulation, defined as the number of days from AVF placement to the first HD treatment with two functioning dialysis needles in the AVF. The difference was explored in a Kaplan-Meier analysis censored for thrombosed AVFs, death, loss to follow-up, and change of renal replacement therapy. Hazard ratios (HR) were determined by Cox regression analyses and adjusted for age, sex, diabetes, cardiovascular disease, albumin, type of AVF, size of AVF in mm at placement, and peroperativ flow.

Results: In total, 91 patients were randomized to FIR (n=46) or control (n=45). There were no differences in baseline characteristics between groups. No significant difference in time to cannulation with median days of 68 days [52;109.5] in the FIR group and 68 days [56.5;85] in the control group (p=0.8) was seen. The HR for chance of cannulation was 0.71; (95% confidence interval (CI), 0.43-1.18, p=0.19) in the FIR group compared to the control group. HR after adjustment for clinical variables was 0.68 (95% CI 0.40-1.15, p=0.12) in the FIR group compared to the control group. The number of thrombosed AVFs before cannulation was 9 in the FIR group and 4 in the control group (p=0.23)

Conclusions: FIR does not improve time to cannulation in newly placed AVFs in patients on hemodialysis. However, the influence of FIR on clinical maturation, the long-term risk of thrombosis, and the number of interventions in the AVFs are yet to be explored.

Funding: Private Foundation Support

FR-PO523

Arteriovenous Fistula Failure Prediction Using Single Treatment Information

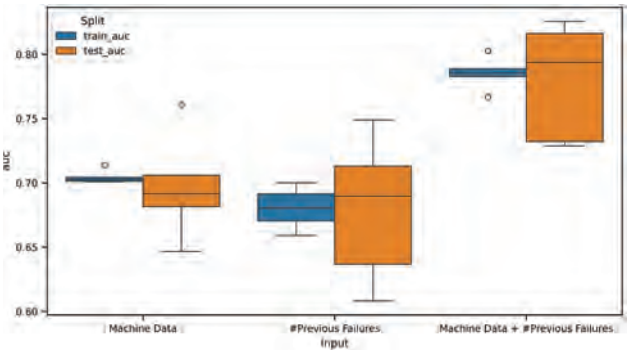
Alessandro Bregoli,[1] Francesco Bellocchio,[2] Andreas Maierhofer,[3] Jeffrey L. Hymes,[4] Len A. Usvyat,[4] Luca Neri,[2] Fabio Stella.[1] *[1]Universita degli Studi di Milano-Bicocca, Milano, Italy; [2]Fresenius Medical Care Italia SpA, Palazzo Pignano, Italy; [3]Fresenius Medical Care AG, Bad Homburg, Germany; [4]Fresenius Medical Care Holdings Inc, Waltham, MA.*

Background: Predicting the natural course of AVF complications with technical surveillance has been an elusive task. We developed a machine learning algorithm assessing the risk of failure of AVF using information collected by the dialysis machine in a single treatment.

Methods: We included all patients undergoing hemodialysis with AVF from the clinics belonging to Nephrocare France between 2021 and 2022. We extracted data from the European Clinical Database (EuCliD), and we combine it with the data sampled every minute from the sensors of the dialysis machine. We developed a model combining a continuous time naive Bayes and a logistic regression to access the risk of failure of a fistula within a month using as input variables the number of previous failures and the machine data of a single dialysis session such as: venous pressure, arterial pressure, blood flow and clearance.

Results: We included 171,969 hemodialysis sessions performed with an AVF over 1,845 French patients in the period from June 1, 2021, to May 31, 2022. During this period, 164 AVF failures were observed among 90 distinct patients. We evaluated the performances of the classifiers calculating the Area Under the Curve (AUC) over a 5-fold cross validation. Figure 1 shows that the classifier combining machine data and number of previous failures achieves the best performance. This result's statistical significance was accessed with a Wilcoxon signed-rank test ($p<0.1$).

Conclusions: Considering the performances obtained, the simplicity of the model and the prevalent use of machine data, this might suggest that it would be possible to install such a model directly on dialysis machines to have a timely assessment of the risk of failure at each treatment without performing any specific time-consuming test.



Performance obtained in cross validation by the 3 classifiers

FR-PO524

Software-Based Surveillance Supplementing Clinical Monitoring for Hemodialysis Vascular Access

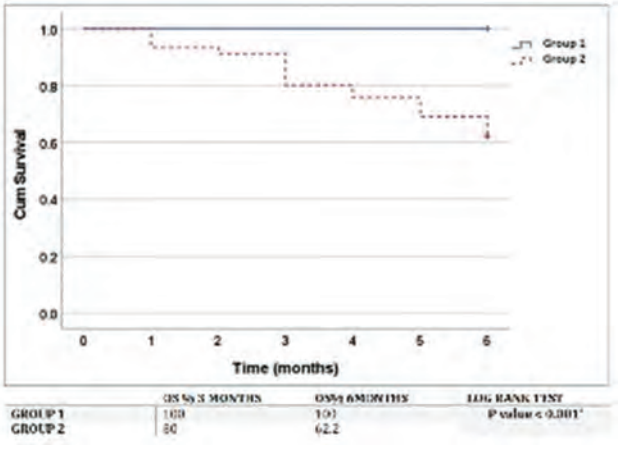
Dimitrios J. Poulikakos,[1,2] Rosemary L. Donne,[1,2] David M. Lewis,[1] Maharajan Raman,[1] Zulfikar A. Pondor,[1] Paul S. Hinchliffe,[1] Jan Cowperthwaite,[1] Jazzle Lim,[1] Paula J. Gleave,[1] Jonathan Allsopp,[1] Marinela L. Resiga,[1] Alshymaa R. Eltahan.[3,1] *[1]Northern Care Alliance NHS Foundation Trust Salford Care Organisation, Salford, United Kingdom; [2]Manchester Metropolitan University, Manchester, United Kingdom; [3]Helwan University, Helwan, Egypt.*

Background: Efficient arteriovenous access (VA) surveillance is vital for early identification of dysfunctional access, allowing timely intervention to prevent thrombosis. This study compares the efficacy of adding remote software surveillance to standard clinical care across our units.

Methods: We conducted a 12-month prospective study on maintenance hemodialysis (HD) patients, using Vasc-Alert software for clinical decision-making in 2 satellite HD units (Group 1), while providing standard care in 3 other HD units (Group 2). Patients with high Vasc-Alert access risk scores (≥7) received clinical assessments and were referred for fistulogram based on Kidney Disease Outcome Quality Initiative (KDOQI) criteria. We collected data on referrals for fistulograms, preemptive stenosis corrections, avoidable thrombosis (defined as thrombosis occurring while waiting for elective stenosis correction), and VA-related costs. We also measured the post-intervention primary patency rate.

Results: In Group 1, there were 23 (28.1%) preemptive stenosis corrections and 6 (7.3%) thrombosis episodes, while Group 2 had 40 (19.5%) corrections and 21 (10.2%) episodes (p = 0.155 and 0.587, respectively). Avoidable thrombosis occurred in 83% of Group 1 compared to 19% in Group 2 (p = 0.004). The median time from fistulogram request to thrombosed VA was 26 days. Group 1 showed better post-intervention primary patency rates (p < 0.001). The average VA-related cost per patient was £1600 for Group 1 and £1868 for Group 2.

Conclusions: Supplementing clinical surveillance with Vasc-Alert technology was associated with improved early detection of high-risk VA and higher primary patency rates, Improving elective interventional radiology (IR) capacity for timely intervention is crucial to materialize the benefits of enhanced surveillance.



FR-PO525

Investigation of the Effect of Variations in the Puncture Site of the Arteriovenous Fistula on Access Blood Flow Measurement by Ultrasound Dilution Method

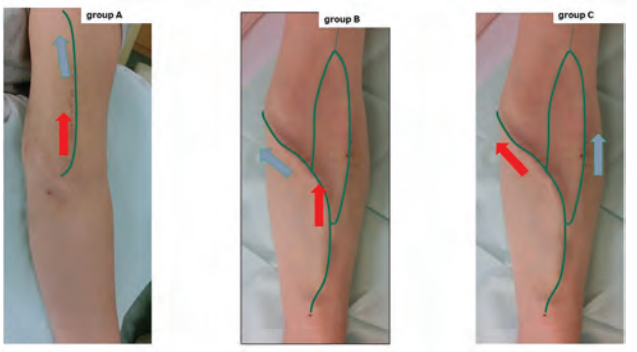
Toshihide Naganuma, Kentaro Shin, Tomoaki Iwai, Yoshiaki Takemoto, Junji Uchida. *Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan.*

Background: In assessing vascular access (VA) function, access blood flow (Qa) using the UDM method is more common. However, because of the wide variety of vascular branches in arteriovenous fistula (AVF), Qa measurement may be difficult depending on the puncture position, considering the measurement principle of the ultrasound dilution method (UDM). In this study, we investigated the effect of puncture variation on Qa measurement in AVF. The results were also compared with Qa by ultrasonic Doppler method (Qa (DU)).

Methods: The 337 dialysis patients with AVF were divided into 3 groups (Figure1) (Group A:117 patients without a vascular branch between A and V at the puncture site, Group B:112 patients with a vascular branch, and Group C:98 patients with a separate vessel). Qa was measured during dialysis using HD03 dialysis monitor. Qa (DU) was also measured in the brachial artery by the ultrasonic Doppler method. This study protocol was conducted in accordance with the Principle of the Declaration of Helsinki, and was approved by the Ethics Committee of Osaka Metropolitan University (approval No.2021-243).

Results: As a result, Qa measurement errors in group A were 28/117 (23.9%), in group B 39/122 (32.0%), and in group C 96/98 (98.0%). Qa (DU) was measurable in all groups in this case. Moreover, group A showed a significant positive correlation between Qa and Qa (DU) (R=0.712, P<0.0001), group B showed a significant positive correlation between Qa and Qa (DU) (R=0.565, P<0.0001), and group C showed no correlation between Qa and Qa (DU) due to many measurement errors of Qa.

Conclusions: Based on these results, we believe that the choice of puncture position is important for Qa measurement by UDM, and that if recirculation is not observed or if a vascular bifurcation is present, the puncture position is not suitable for Qa measurement. On the other hand, Qa(DU) could be measured in all cases, which may be a better method of measuring access flow in AVF.



FR-PO526

Probability of Heart Failure with Preserved Ejection Fraction and Outcomes after Arteriovenous Fistula Creation

Karina S. Kanamori,[1] Darah Dilmaghani,[2] Barry A. Borlaug,[1] Vesna D. Garovic,[2] Karl A. Nath,[2] Yogesh N. Reddy.[1] *[1]Mayo Clinic, Department of Cardiovascular Medicine, Rochester, MN, Rochester, MN; [2]Mayo Clinic Department of Internal Medicine, Rochester, MN.*

Background: End stage renal disease (ESRD) patients develop symptomatic fluid retention related to renal failure with difficulty to differentiate from heart failure (HF). Therefore, clinical implications of co-existing myocardial dysfunction related to HF with preserved ejection fraction (HFpEF) on outcomes in ESRD following arteriovenous fistula creation (AVF) remain unknown.

Methods: Patients undergoing AVF from 2000 to 2015 who had echocardiography (echo) before AVF were retrospectively reviewed. HF with reduced ejection fraction (HFrEF) was defined by baseline EF<50%. Among those with EF≥50%, baseline probability of HFpEF was determined using a validated HFpEF score algorithm. Patients at risk for HFpEF were stratified as low(<25%), intermediate(25-75%) and high(>75%) probability. Baseline cardiac structure and function by echo and outcomes of mortality, HF hospitalization, and AVF maturation rate were compared across HFpEF probability groups.

Results: There were 366 patients(213 men) who underwent AVF and had echo before the procedure. Most patients(79%) had EF≥50% at the time of AVF, while 21% had HFrEF. Of those with EF≥50%, 131(45%) had high, 120(41%) had intermediate and 39(13%) had low probability for HFpEF. Higher HFpEF probability grouping was associated with higher echo estimated filling pressures as assessed by E/e'(13.4±5.1, 16.6±7.3, 19.0±8.7, p=0.0008), larger LA volume index(33.3±12.2. 37.3±11.7, 43.0±15.3, p=0.0006), higher right atrial pressure(5.9±2.3, 7.3±3.9, 8.8±4.2, p=0.0003), higher pulmonary artery systolic pressure(33.8±10.7, 40.1±13.7, 45.3±13.8, p=0.0003) and increased LV mass(200±79, 225±76, 246±86, p=0.01). AVF maturation rates were not different across HFpEF probability groups(31,33,35% p=0.56). Increasing HFpEF probability was associated with worse survival(HR per decile of HFpEF probability 1.11 [95%CI 1.06-1.17], p<0.0001) and increased risk of death or HF hospitalization(HR per decile of HFpEF probability 1.12 [95%CI 1.07-1.18], p<0.0001).

Conclusions: Increasing probability of HFpEF in patients with ESRD undergoing AVF is associated with worse cardiac remodeling and increased risk of death and HF hospitalization on maintenance hemodialysis. Whether treatment targeting the myocardial HFpEF component in patients with ESRD is beneficial requires further study.

Funding: Other NIH Support - NIH T32 HL007111

FR-PO527

A Change of Heart: Effect of High-Flow Arteriovenous Fistulas on Cardiovascular Outcomes, a Systematic Review and Synthesis without Meta-Analysis (SWiM)

Nasir A. Shah,[1,2] Morgan E. Hind,[3] Zoltan Endre,[2,1] Blake Cochran,[4] Tracie Barber,[5] Jonathan H. Erlich.[1,2] *[1]University of New South Wales School of Clinical Medicine, Sydney, NSW, Australia; [2]Prince of Wales Hospital and Community Health Services, Randwick, NSW, Australia; [3]The University of Notre Dame Australia School of Medicine, Fremantle, WA, Australia; [4]University of New South Wales School of Biomedical Sciences, Sydney, NSW, Australia; [5]University of New South Wales School of Mechanical and Manufacturing Engineering, Sydney, NSW, Australia.*

Background: Heart failure is a common cardiovascular condition in patients on haemodialysis. Case reports and a selection of studies have found associations between arteriovenous fistula (AVF) flow and heart failure, but the exact relationship remains unclear. The aim of this study was to describe the relationship between AVF flow and cardiac outcomes.

Methods: A comprehensive search of the PubMed, EMBASE, and Cochrane databases was used to identify observational studies and randomized controlled trials reporting clinical, echocardiographic, or biomarker effects of AVF flow on cardiac outcomes. Study heterogeneity made meta-analysis not feasible. Synthesis without meta-analysis (SWiM) was performed using vote counting of direction of effect as the primary outcome.

Results: The initial search strategy retrieved 3622 studies. After screening, 100 studies were analysed including a total of 8414 patients. A positive direction of effect was observed with cardiac output (29/34 studies), BNP (13/18 studies), ANP (2/3 studies), left ventricular hypertrophy and left ventricular mass (10/15 studies), left ventricular mass index (11/19 studies), left atrial volume index (10/12 studies) and incident heart failure or heart failure symptoms (21/25 studies). A neutral direction of effect was observed with ejection fraction (29/41 studies), E/A ratio (13/13 studies), E/E' ratio (8/11 studies), tricuspid annular plane systolic excursion (6/9 studies), and measures of pulmonary hypertension (13/26 studies). A negative direction of effect was observed for all-cause mortality (3/7 studies).

Conclusions: This systematic review and synthesis without meta-analysis showed a positive direction of effect between AVF flow and several cardiovascular outcomes, but an inverse relationship between AVF flow and mortality. The methodological heterogeneity of studies highlights the need for well-designed prospective research with standardised definitions of high flow AVFs and measures for reporting of cardiovascular outcomes.

FR-PO528

Arteriovenous Fistula-Associated Ascites

Michael D. Kolman, Lincoln J. Kavinsky, William L. Whittier, Roger A. Rodby. *Rush University Medical Center, Chicago, IL.*

Introduction: Dialysis-associated ascites (DAA) is a diagnosis of exclusion in End-Stage Kidney Disease (ESKD). The prognosis is grim and typically obviates kidney transplantation. We present a case of refractory ascites in a hemodialysis (HD) patient initially diagnosed as DAA, later determined to be cardiac ascites from arteriovenous fistula (AVF) related high-output heart failure (HOHF). The ascites resolved and the HOHF improved with AVF ligation and the patient was subsequently able to receive a kidney transplant.

Case Description: A 43 year-old woman with ESKD on HD via a mildly aneurysmal AVF developed ascites with a serum albumin ascitic gradient (SAAG) < 1.1 g/dL. After comprehensive workup for ascites, she was diagnosed with DAA. Later she was found to have an ejection fraction (EF) of 25% and due to this plus her ascites, she was deemed to not be a kidney transplant candidate. Doppler studies of the AVF showed elevated peak systolic velocities and subsequent right heart catheterization (RHC) revealed a high cardiac index (CI) that normalized upon AVF occlusion (see Table). After AVF ligation and tunneled dialysis catheter placement for HD, her EF improved to 45% and ascites resolved in 3 months. She became eligible for and received a kidney transplant 9 months later.

Discussion: DAA is a diagnosis of exclusion and has a mortality rate of 45% within 15 months of diagnosis. While a kidney transplant is the definitive treatment, our patient was unsuitable due to her reduced EF and ascites. Flow studies of her AVF were elevated and subsequent RHC revealed an abnormally high CI that normalized with AVF occlusion. An AVF alters peripheral circulation hemodynamics, reducing resistance and increasing cardiac output. Excessive blood influx can raise central venous pressure and left ventricular end-diastolic pressure, resulting in HOHF and cardiogenic ascites. With AVF ligation, her EF improved to 45%, ascites resolved, and she recieved a kidney transplant. This case emphasizes the need to consider AVF related HOHF as a reversible cause of ascites in the patient with ESKD, especially if the AVF is aneurysmal.

Cardiac output (CO) and Index (CI) before and after AVF occlusion with a BP cuff

Condition	CO	CI (nl 2.6-4.2)
Baseline	6.7L/min	4.5L/min
Cuff Inflated	4.1L/min	2.7L/min
Cuff Deflated	6.7L/min	4.4L/min

FR-PO529

Chylothorax and Chylopericardium in a Patient on Dialysis

Chelsea Gertze, C. E. Cervantes, Mohamad A. Hanouneh. *The Johns Hopkins University School of Medicine, Baltimore, MD.*

Introduction: Chylous effusions, a rare complication in hemodialysis patients, was observed in a patient with central venous stenosis (CVS) following arteriovenous fistula (AVF) creation.

Case Description: A 24-year-old man with acute kidney injury on CKD stage IV underwent hemodialysis via right intrajugular venous catheter. After creating a left arm AVF, he developed dyspnea and left arm swelling. CT chest showed bilateral pleural and pericardial effusions with milky fluid extracted from a right chest tube and pericardial drain with triglycerides levels of 1,008 mg/dL and 1,349 mg/dL respectively, indicating Chylothorax and Chylopericardium (Fig 1). Dynamic MR lymphangiography and 3-D MR angiography revealed bifid thoracic duct with dilation and lymphatic leakage around the diaphragmatic hiatus and right lower thorax (Fig 2A). Stenosis was noted in the right brachiocephalic vein and superior vena cava (SVC) with occlusion in the left brachiocephalic and left subclavian veins (Fig 2B). He recovered to CKD stage IV after 6 months of dialysis. He underwent AVF ligation, dialysis catheter removal, and venoplasty of SVC, left subclavian, brachiocephalic veins, followed by kissing stents through SVC and brachiocephalic veins (Fig 2C). Despite these interventions, stenosis reccurred. Consequently, ligation of the right thoracic duct and embolization of the left one resolved the effusions.

Discussion: CVS involves narrowing of central veins, commonly seen in dialysis patients. AVF creation can exacerbate symptoms by raising venous pressure. Rarely, CVS leads to Chylous effusions due to increased pressure in the thoracic duct causing leakage. In our patient, chylous effusions resulted from aggravated CVS, worsened by the dialysis catheter and elevated venous pressure after AVF creation.

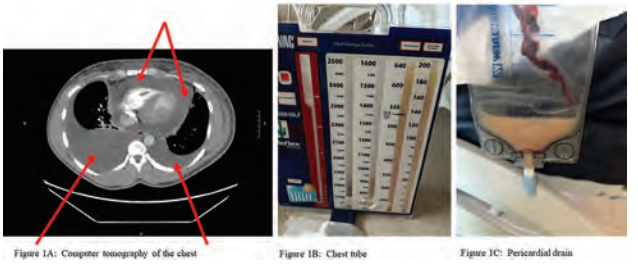


Figure 1A: Computer tomography of the chest Figure 1B: Chest tube Figure 1C: Pericardial drain

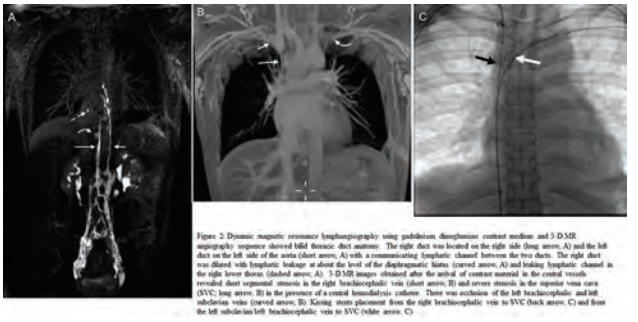


Figure 2: Dynamic magnetic resonance lymphangiography using gadolinium dimeglumine contrast medium and 3-D MR angiography sequence showed bifid thoracic duct anatomy. The right duct was located on the right side (long arrow; A) and the left duct on the left side of the aorta (short arrow; A) with a communicating lymphatic channel between the two ducts. The right duct was dilated with lymphatic leakage at about the level of the diaphragmatic hiatus (curved arrow; A) and leaking lymphatic channel in the right lower thorax (dashed arrow; A). 3-D MR images obtained after the arrival of contrast material in the central vessels revealed short segmental stenosis in the right brachiocephalic vein (short arrow; B) and severe stenosis in the superior vena cava (SVC; long arrow; B) in the presence of a central hemodialysis catheter. There was occlusion of the left brachiocephalic and left subclavian veins (curved arrow; B). Kissing stents placement from the right brachiocephalic vein to SVC (back arrow; C) and from the left subclavian/left brachiocephalic vein to SVC (white arrow; C)

FR-PO530

Closure of an Endovascular Arteriovenous Fistula Initially Created for Dialysis Access by Placement of Radial Artery Covered Stent

Hector Quintero Alvarez,[1] Carlos Claudio-Rodriguez,[2] Julio A. Peguero,[2] Cesar F. Hernandez-Arroyo.[1,2] *[1]Universidad Central Del Caribe, Bayamon, Puerto Rico; [2]Azura Vascular Care, Juana Diaz, PR.*

Introduction: Endovascular arteriovenous fistula (eAVF) creation offers a minimally invasive technique for creating arteriovenous fistulas for hemodialysis. The Ellipsys® System has demonstrated safety and effectiveness in creating eAVFs. However, questions remain regarding the optimal approach for reversing eAVFs when necessary. We present the first documented closure of a radial artery to perforator vein eAVF using a proximal radial artery covered stent.

Case Description: 50-year-old man with end-stage renal disease on hemodialysis sought closure of his eAVF due to chronic left upper arm swelling attributed to total occlusion of left innominate vein. Ultrasound confirmed patency and flow of the radial and ulnar arteries. The radial artery was cannulated, patient heparinization, and a catheter and guidewire were advanced into the brachial artery for direct arteriogram to identify the anatomy and arterial anastomosis. A Gore Viabhan endoprosthesis was deployed under fluoroscopic guidance, angioplasty done to anchor stent, and finally a direct brachial artery arteriogram confirmed occlusion of eAVF anastomosis.

Discussion: As proceduralists gain more experience, they become increasingly adept at maintaining this new type of access. Our aim is to provide insights into the potential closure of eAVFs and remain optimistic about the improved quality of care and reduced overall health complications this innovative technology offers.

Figure 1: Vascular anatomy of endovascular fistula

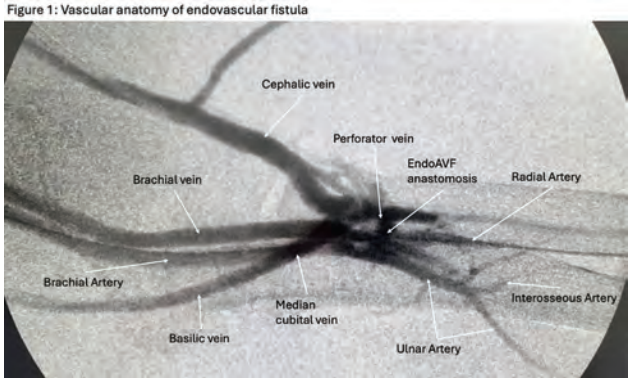
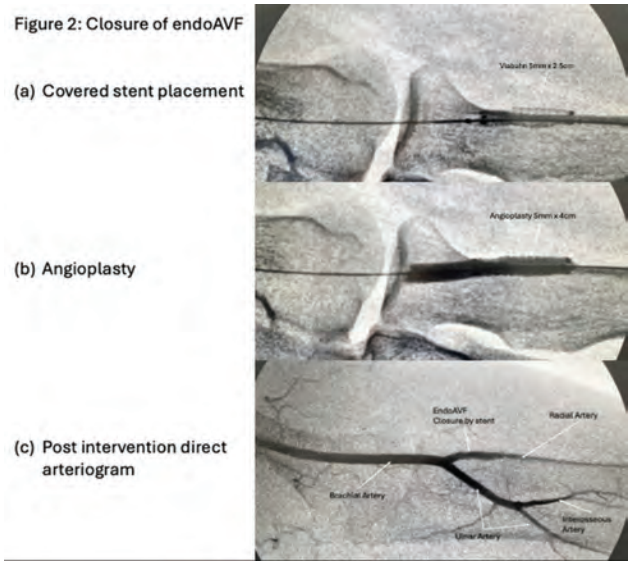


Figure 2: Closure of endoAVF



FR-PO531

The KIDNEY-CAP: A Novel Device in the Management of Bleeding in Intermittent Hemodialysis Patients

Adam Forster,[1,2] Faisal Rehman,[1,2] Benjamin K. Thomson.[3] KIDNEY-CAP.
[1]Western University Schulich School of Medicine & Dentistry, London, ON, Canada; [2]London Health Sciences Centre, London, ON, Canada; [3]Johns Hopkins University, Baltimore, MD.

Background: Out of hospital arteriovenous graft (AVG) and arteriovenous fistula (AVF) bleeding occurs in 1-3/1000 hemodialysis patients per year. It is associated with hospitalization, hemorrhagic shock, and death. Presently there are no approved out of hospital devices available to aid patients if they develop an out of hospital bleed. The KIDNEY-CAP is a 3D printed cap that has been developed for patient use in this scenario. This study assessed attitudes towards vascular access, transplantation, and home dialysis in nephrology health care workers (NHCs) such as nephrologists, nephrology nurse practitioners, and body access coordinators, as well as ESKD patients on hemodialysis (ESKD-D) and how the KIDNEY-CAP influences these impressions.

Methods: Survey 1 studied KIDNEY-CAP introduction into the CKD/ESKD patient experience, and how it would impact NHC recommendations for kidney care. Parameters such as recommendation for transplantation, vascular access modality, and home dialysis opportunities were explored. In survey 2, in-center ESKD-D patients were evaluated for how the KIDNEY-CAP might modify decisions regarding their end stage kidney disease care. When survey respondents already had an AVG/AVF, their level of concern regarding AVG/AVF bleeding was quantified, while evaluating for common bleeding risk factors.

Results: In survey 1, 41% of respondents indicated that they were more likely to recommend home dialysis and vascular access with AVG/AVF if a KIDNEY-CAP was available. Providers were more likely to recommend these options in patients not yet on dialysis. In survey 2, 66% of patients indicated at least slight concern about bleeding from their access site. 66% also felt they would benefit from having a device to help control bleeding outside the dialysis unit. 27.8% indicated that they would be more likely to select AVG/AVF as their vascular access of choice if they had a KIDNEY-CAP. There was no difference in feelings toward home dialysis or transplantation.

Conclusions: We demonstrate that the KIDNEY-CAP is a device of interest for providers in determining vascular access for patients approaching dialysis. There may also be benefit to patient comfort with vascular access should the KIDNEY-CAP be available. Further exploration in the predialysis patient population is warranted, as is prospective study on the KIDNEY-CAP's adoption.

FR-PO532

Comparative Analysis of Anti-phospholipid-Antibody Positivity and Confirmation as Potential Risk Factors for Arteriovenous Fistula Thrombosis in Patients on Hemodialysis

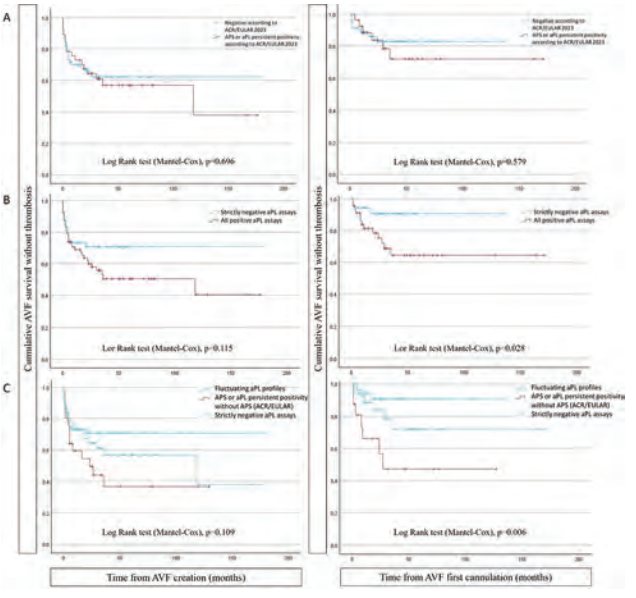
Maxime Taghavi,[1,2] Lucas Jacobs,[1,2] Frederic Collart,[1,2] Joelle L. Nortier.[1,2]
[1]UVC Brugmann - Site Victor Horta, Brussels, Belgium; [2]Universite Libre de Bruxelles, Bruxelles, Belgium.

Background: The classification criteria (CC) for antiphospholipid syndrome require antiphospholipid antibody (aPL) persistent positivy (aPL PP)(i.e. confirmation assay at 12 weeks). aPL PP frequent in hemodialysis (HD) (prevalence up to 56%) and seems to be associated with native arteriovenous fistula (AVF) thrombosis, but studies have a heterogeneous aPL positivity definition. This study aims compare real-life situation of aPL positivity in terms of AVF thrombosis.

Methods: We retrospectively identified 127 HD patients with native AVF. We performed Kaplan-Meier analyses and compared AVF thrombosis prevalence during the follow-up. We evaluated different subgroups of patients representative of real-world practice: Analysis 1 according to CC; Analysis 2 comparing all patients with at least one positive aPL assay to strictly negative patients and analysis 3 comparing 'aPL PP according to CC' and 'patients with one aPL positive assay' and 'strictly negative patients'.

Results: aPL PP represented 30% of the cohort, only 8% of the patients were aPL+ once (without confirmation) and 16% were aPL+ with a negative control. The prevalence of AVF thrombosis was significantly higher in analysis 2 and tended to signification in analysis 3. Kaplan-Meier analysis showed significant shorter access survival without thrombosis from AVF first cannulation in analyses 2 and 3 (Mean time to first event (months ± SD) was 115.8 ± 12.7 *vs* 124.0 ± 6.6 in analysis 2 and 124.0 ± 6.6 *vs* 128.6 ± 15.1 in analysis 3 (Figure 1)).

Conclusions: The present in-depth comparative analysis of different aPL profiles encountered in real life situations, shows an significant associated with AVF thrombosis. Detection of aPL positivity could be a useful tool for the clinicians in assessing AVF thrombosis risk.



FR-PO533

Drug-Eluting Stents in Treating Arteriovenous Graft Thrombosis: A Pilot Study

Ivana Boktor,[1] Ahmed E. Ali,[2] Alian Albalas,[3] Ammar Almehmi.[3] *[1]George Walton Comprehensive High School, Marietta, GA; [2]Mayo Foundation for Medical Education and Research, Rochester, MN; [3]The University of Alabama at Birmingham, Birmingham, AL.*

Background: Thrombosis of the arteriovenous graft (AVG) related to venous anastomosis stenosis is associated with poor access survival in dialysis population. The use of standard and drug-coated balloons and covered stents is associated with poor primary access patency. On the hand, drug-eluting stents (DES) have been used successfully in coronary and peripheral interventions with low reintervention rates.

Hence, this study sought to explore the effect of DES in treating AVG thrombosis and subsequent overall access patency.

Methods: This is a retrospective study that included a total of 9 patients receiving dialysis via AVGs who presented with thrombosis and underwent DES deployment during the thrombectomy procedure. Patient demographics and post-intervention follow-up data were extracted from the vascular database. Primary endpoints included graft primary patency, procedural success, and complication rates.

Results: The cohort included 4 men and 5 women with a median age of 55 years (ranging from 22 to 81 years). Common comorbidities included hypertension 100% (9/9), diabetes mellitus 67% (6/9), and hyperlipidemia 44% (4/9). The main indication for DES deployment was recurrent thrombosis of an existing AVG. After the procedure, all the patients were prescribed dual antiplatelet therapy for one month. All stents were deployed successfully and no immediate complications were encountered. The target lesion for DES placement was the venous-graft anastomosis. The median follow-up period was 421 days (IQR: 78). Results showed a significant improvement in graft patency rates, with a target lesion primary patency rate of 55.5%. During the follow-up, 5 patients required no interventions, the other 4 patients continued to suffer from access thrombosis requiring a new dialysis access placement.

Conclusions: The findings of this case series underscore the potential role of DES in managing AVG thrombosis related to venous anastomosis stenosis. Moreover, while this study is hypothesis-generating in nature, it invites further investigation to understand the complex pathophysiology of dialysis access lesions.

65-year-old female presented with clotted arteriovenous graft (AVG) due to venous anastomosis (VA) lesion treated with Percutaneous transluminal angioplasty (PTA) and Eluvia stent with no intervention needed in the follow-up period.

FR-PO534

A Novel Use of JETi Thrombectomy Device Mediates Embolic Complication during Graft Thrombectomy

Luis G. Osorio, Kevin T. Onofrey, Loay Kabbani, Lalathaksha Murthy Kumbar. *Henry Ford Hospital, Detroit, MI.*

Introduction: We present a case detailing the use of a novel thrombectomy device to treat acute upper limb ischemia as a complication of percutaneous arteriovenous graft (AVG) thrombectomy. The JETi Hydrodynamic thrombectomy System (Abbot Vascular, Abbot Park, IL) is a mechanical thrombectomy device indicated for peripheral vasculature which has demonstrated efficacy in acute venous thromboembolism[1] and acute arterial limb ischemia (ALI)[2].

Case Description: A 59-year-old female presented with a clotted AVG of 6-day duration. Mechanical rheolytic thromboaspiration using the Angiojet Thrombectomy system (Boston Scientific, Marlborough, MA) was performed followed by angioplasty of venous stenosis. Stenosis at arterial anastomosis was also identified and angioplastied. Completion angiogram showed patent AVG with no residual stenosis. Completion arteriogram also revealed an embolus in the distal brachial artery with no flow distal to the occlusion. Angioplasty and Angiojet thrombectomy interventions proved unsuccessful. Subsequently, the JETi thrombectomy system was employed, leading to the successful retrieval of the clot and restoration of blood flow into the forearm.

Discussion: While arterial embolism during percutaneous thrombectomy of dialysis access is a recognized complication, it is uncommon.[3] The JETi thrombectomy system integrates clot fragmentation and catheter aspiration.[1] Traditionally used for deep venous thrombosis and ALI, this case exemplifies a unique utilization of the of the JETi system in managing a complication from AVG thrombectomy where more traditional methods failed. The JETi thrombectomy system presents a promising alternative for addressing embolic complications resulting from percutaneous AVG thrombectomies and warrants consideration as a primary treatment modality. However, further studies investigating AVG thrombectomies are imperative to ascertain its suitability as a standard of care.

FR-PO535

Trends in Epidemiologic Characteristics and Clinical Patterns of Vascular Access of Incident Hemodialysis Patients: Nationwide Cohort Study (2006-2019) in Korea

Kyoung Sook Park. *National Health Insurance Service Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea.*

Background: The number of patients with end-stage kidney disease (ESKD) undergoing hemodialysis (HD) was rapidly growing in Korea. Although there was a Korean Renal Dialysis System (KORDS) registry for analyzing HD practice patterns in Korea, the registration rate (63.8% in 2022) wasn't sufficient to represent real-world aspects. Thus, we analyzed HD patients' clinical practice patterns in Korea using National Health Insurance System (NHIS) data.

Methods: Subjects were extracted from NHIS data, comprising patients with code V001 for financial support in rare incurable patients (i.e., ESKD) and code O70102 for HD from 2006 to 2019. We examined epidemiological characteristics and practice patterns of vascular access in initiated HD patients. We defined the central venous catheter (CVC) user to the presence of O7012, CVC-related code for the charge of the Health Insurance Service Procedure 6 months before encoding the HD-related code, and the arteriovenous (AV) access user to the presence of AVF-related codes (O2083, O2056, O2081, O2082, O2083, and O2059) 6 months before encoding the HD-related code.

Results: Patients initiating HD surged from 4,927 in 2006 to 14,049 in 2019. The proportion of those aged 70-79 and above 80 rose from 10% and 1% in 2006 to 25% and 18% in 2019, respectively. CVC usage increased from 43% in 2006 to 54% in 2019, while AV access rose from 15% to 28%. Especially in the 60-79 age group, AV access users increased significantly (from 5% in 2006 to 15% in 2019). The mean duration after AV access creation before usage increased (from 2.3 months in 2006 to 3.6 months in 2019).

Conclusions: The trends in epidemiologic characteristics showed similarities compared to the KORDS registry. However, clinical patterns of vascular access in HD initiation differed. Our report might help represent real-world aspects in ESKD patients who have started HD.

FR-PO536

Bedside Ultrasound (US)-Guided Nonfluoroscopic Insertion of Right-Sided Tunneled Dialysis Catheter: Largest Experience from a Single Center

Sejal Khandelwal,[1] Audrey Tassillo,[2] Mukesh Khandelwal.[2] *[1]Western University Schulich School of Medicine & Dentistry, London, ON, Canada; [2]Niagara Health System, St. Catharines, ON, Canada.*

Background: Tunneled dialysis cuffed catheters (TDCs) are often used for initial access in crash start and other hemodialysis (HD) patients due to lack of arteriovenous fistulae. While the NKF-KDIGO guidelines recommends fluoroscopic-guided TDC insertion by interventional radiology (IR) as the standard of care, there is a growing body of evidence supporting the safety, efficacy, and promptness of bedside ultrasound (US)-guided nonfluoroscopic TDC insertion. This study aims to evaluate the feasibility and safety of bedside US-guided TDC insertion by a nephrologist.

Methods: A comprehensive retrospective chart review of patients who underwent bedside TDC insertion at Niagara Health from 2011-2024 was conducted. Patients were identified from office electronic medical records (EMR) using the provincial billing code for TDC insertion. Inclusion criteria comprised a patent right internal jugular (RIJ) vein, INR<1.5, absence of anticoagulation at the time of insertion, and the ability to assume a supine or at least 30° upright position. Exclusion criteria encompassed patients with right-sided pacemakers or AICDs, severe coagulopathy, active sepsis, an occluded RIJ vein, or known superior vena cava stenosis.

Results: A total of 901 catheters were inserted in 867 patients by one nephrologist. Four patients were unsuccessful due to guidewire negotiation issues and necessitated IR intervention. Catheter tip position was confirmed by nephrologist and chest x-ray. Catheter tip was in the right ventricle in two cases, and one patient had azygos vein placement. In one patient with a right-sided pacemaker, left-sided TDC was attempted, but catheter tip ended in right IJV and required repositioning by IR. Complications include occasional premature ventricular contractions, one hyperkalemia-induced cardiac arrest with successful resuscitation, catheter kinking in 2 cases, and minor bleeding in 12 cases. Additionally, two cases with very high BMI (> 700 lbs) that were deemed unsuitable by IR underwent successful bedside insertion. Furthermore, another case with a right-sided pacemaker had successful insertion of a right TDC, after cardiology approval.

Conclusions: US-guided bedside TDC insertion by nephrologists is highly successful and safe, offering a viable alternative to fluoroscopic-guided insertion.

FR-PO537

Implantation of Hemodialysis Catheter in the Iliac Vein vs. Placement in Femoral Vein with Ultrasound Guidance

José J. Gutiérrez Hernandez, Brenda Aguilar, Hugo B. Espinoza, Francisco J. Padilla Gomez, Carolina Covarrubias Castellon, David A. Juárez, Rosa M. Resendez Gonzalez, Christian Ali R. Esquinca, Brenda G. Rosales Torres, Cristian J. Ramos Mares, Javier Soto-Vargas, Paulina De Niz Hernández, Renato Parra Michel, Juan O. Romero Tafoya, Jose A. Barbarin Sosa, Diana M. Reyes Martinez. *Instituto Mexicano del Seguro Social, Guadalajara, Mexico.*

Background: We compare the results of implantation of hemodialysis catheter in the iliac vein versus placement in femoral vein both guided with ultrasound, analyzing complications, technique and survival

Methods: All patients required chronic hemodialysis and to who were determined not to place a catheter in the internal jugular vein, femoral with history of multiple vascular access, AV fistula or grafts where it was essential to obtain an alternative vascular access. When the procedure for the insertion for the iliac vascular access was realized was

always with US guidance. The results were compared with patients who underwent the implantation of a tunneled vascular access in the femoral region

Results: The insertion of catheters were realized by the nephrologists experts in vascular access from the HGR 46 of the IMSS in Guadalajara, Jalisco, Mexico, between 2021-2024. A total of 12 iliac catheters were implanted all with US guidance. The iliac catheter group had the same amount of punctures as the femoral catheter group, arterial punctures were rare in both techniques. No differences were observed in complications related to the procedures.

Conclusions: Implantation of iliac catheters in patients with impossibility for conventional site insertion is a safe procedure and feasible in patients with vascular exhaustion. The rate of complications and survival was not inferior to the femoral catheter group. It is necessary to know the inguinal region anatomy as well as the correct selection of patients.

	Femoral catheter (n=15)	Iliac catheter (n=12)
Age (years)	48 ± 11	37± 14
Previous catheters (mean)	7.6	13.8
Successful insertion	15	12
Chronic kidney disease	15	15

	Femoral catheter (n=15)	Iliac catheter (n=12)
Successful insertion	15	12
Punctures (mean)	1.21	1.19
Artery Punctures	2	1
Average time of use (months)	11.6	6.8
Removal causes		
Transfer to peritoneal dialysis	0	0
Renal transplantation	1	0
Catheter thrombosis	1	1
Catheter related infection	1	1
Arterio-venous fistula	3	2
Accidental removal	0	0
Death	2	2
Malposition	0	0
Soft tissue hematoma	1	1
Nerve injury	0	0
Abdominal piercing	0	0
Major bleeding	1	0

FR-PO538

Long-Term Outcomes after Percutaneous Transluminal Angioplasty for Hemodialysis Catheter Placement

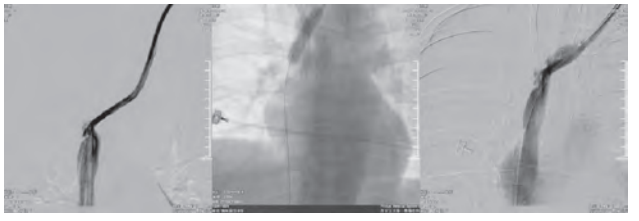
Kehui Shi. *Department of Critical Care Nephrology and Blood Purification, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China*.

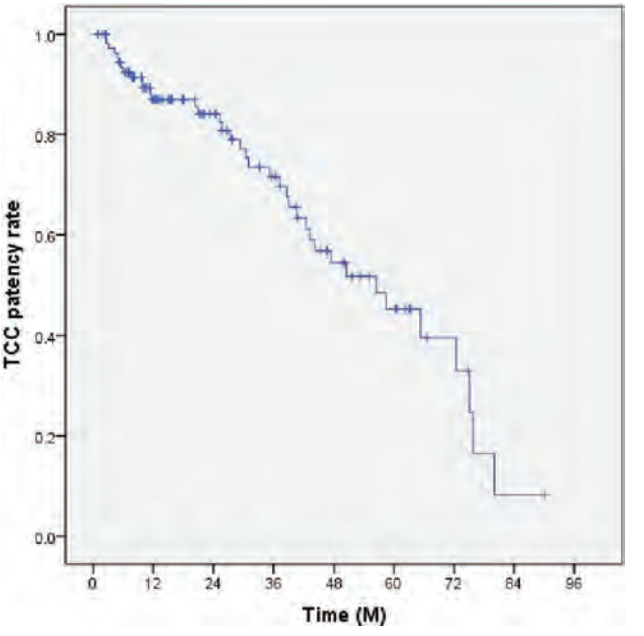
Background: Percutaneous transluminal angioplasty (PTA) is the treatment of central vein stenosis or occlusion, it has been applied during hemodialysis catheter placement. However, data came from case reports or small series, and the long-term outcome has rarely been reported. This retrospective study aims to observe the application of PTA for hemodialysis catheter placement and the Long-term outcomes after surgery.

Methods: Retrospective analysis of patients who underwent digital subtraction angiography (DSA) guided tunneled cuffed catheter (TCC) placement surgery from March 1, 2015 to August 31, 2023. When there was central vein stenosis (CVS) or occlusion, or fibrin sheath, PTA was performed to dilate the central vein or disrupt the fibrin sheath (Figure 1). Then, a new catheter was inserted. The Kaplan-Meier method was used to investigate the survival rates of the catheters.

Results: A total of 149 TCCs were placed in 125 patients, of which 106 cases were underwent PTA. There were 98 cases (66%) of fibrin sheath formation, 76 cases (51%) of CVS, 20 cases (13%) of central vein occlusion, and 6 cases (4%) of central vein thrombosis. The technical success was 98.7% (147 of 149), and the clinical success with resumption of at least one session of normal dialysis occurred in 145 cases (97.3%). The median follow-up was 21.9 months (range, 1–90 months). The survival rates of the catheters at 12, 24, 36, and 60 months were 87%, 84%, 72%, and 46%, respectively. (Figure 2)

Conclusions: PTA is safe and effective for hemodialysis catheter placement when there was CVS or central vein occlusion or fibrin sheath formation.





FR-PO539

Persistence of Left Superior Vena Cava Anomalies: From Shrewd Suspicion to Accurate Diagnosis

Pedro G. Pascoal, Juliana Hickmann de Moura, Luiggy J. Vaca Demera, Vanderlei C. Bertuol, Ariana Custodio Vieira, Arthur G. Manfro, Gusthavo Mandelli, Gustavo G. Thomé. *Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil*.

Introduction: Persistent left superior vena cava (PLSVC) is an important anatomical variation that challenges hemodialysis (HD) vascular access placement and may lead to adverse outcomes. We present three cases of PLSVC, including one leading to an inaccurate thoracotomy.

Case Description: Case 1: A 17-year-old kidney recipient with graft failure returning to HD had a non-tunneled catheter (NTC) inserted in his left internal jugular vein (LIJV). Computed tomography (CT) revealed unusual left mediastinum anatomy, suggesting a perforation of the catheter through the left atrium, which led to urgent thoracotomy. The procedure revealed a PLSVC with a lateral course to the aorta, without atrial perforation. The anomalous vein encircled the left atrium and drained into the inferior cavoatrial junction, where the catheter tip resided. Case 2: A 46-year-old woman admitted for HD underwent a catheter insertion through the right internal jugular vein. Fluoroscopy revealed guidewire path through the brachiocephalic vein to the LSVC. It was then opted to cannulate the LIJV, with the catheter going through the LSVC to the right atrium. CT confirmed an isolated persistent left superior vena cava (IPLSVC). Case 3: A 60-year-old woman with a corrected atrial septal defect was admitted to the intensive care unit due to sepsis-associated kidney injury requiring dialysis. After a NTC was inserted via the LIJV, CT demonstrated a PLSVC with the catheter tip in the right atrium. The catheter functioned properly.

Discussion: PLSVC occurs in 0.3-0.5% of healthy individuals and 1.3-11% of those with congenital heart diseases (CHD). Embryologically, it arises due to persistence of the left common cardinal vein. IPLSVC is rarer, manifesting in 0.09%-0.13% of patients with CHD. Often asymptomatic, PLSVC can lead to complications during HD vascular access placement or misinterpretation of exams. These cases highlight the importance of awareness of this anatomical variation.

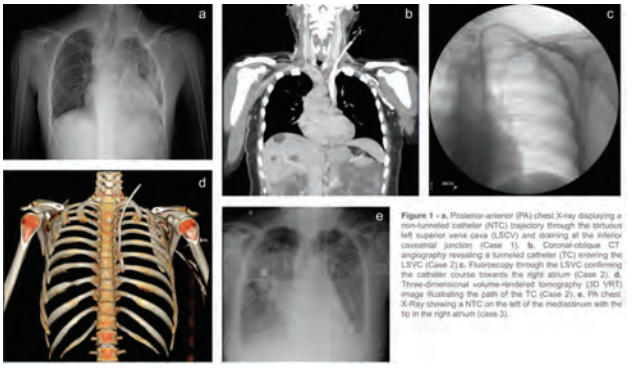


Figure 1 - a. Posterior-anterior (PA) chest X-ray displaying a non-tunneled catheter (NTC) trajectory through the tortuous left superior vena cava (LSCV) and draining at the inferior cavoatrial junction (Case 1). **b.** Coronal-oblique CT angiography revealing a tunneled catheter (TC) entering the LSVC (Case 2).**c.** Fluoroscopy through the LSVC confirming the catheter course towards the right atrium (Case 2). **d.** Three-dimensional volume-rendered tomography (3D VRT) image illustrating the path of the TC (Case 2). **e.** PA chest X-Ray showing a NTC on the left of the mediastinum with the tip in the right atrium (case 3).

FR-PO540

Rare Complication of Hemodialysis Catheter Insertion: Tissue Dilator Embolism

Jasper Sim,[1] Sajan Das,[2] Sonali Gupta.[1,2] *[1]Albert Einstein College of Medicine, Bronx, NY; [2]Montefiore Medical Center, New York, NY.*

Introduction: Central line catheterization is one of the most common invasive procedures performed. Of the potential complications, mechanical complications are often overlooked given the assumption of device integrity. While catheter fragmentation has been previously reported in literature, there has only been one reported case of a tissue dilator fracture and embolism during femoral catheterization. In this case report, we describe a tissue dilator fracture and embolism during left internal jugular vein catheterization.

Case Description: A 55-year-old male with non-ischemic cardiomyopathy and prior LVAD placement was admitted with biventricular heart failure and underwent RVAD. Hospital course was complicated by persistent cardiogenic shock, hypoxic respiratory failure, volume overload and acute respiratory distress syndrome. It was decided to begin slow continuous ultrafiltration to manage his volume status. During an attempt to obtain vascular access, the tissue dilator tip fractured and migrated to the right pulmonary artery. Interventional radiology attempted retrieval of the foreign body but was unable to retrieve it after multiple snare attempts. Procedure was complicated by hemorrhage requiring embolization of the right pulmonary artery branch. Over the next few days, the patient remained hemodynamically unstable, and the family eventually decided to withdraw care.

Discussion: Our case highlights how a simple, routine procedure can be associated with grave complications. There are occasional reports of vascular catheter tips or guidewire fragmentation, but dilator tip fragmentation is rare. It is important to note the expiration date and integrity of instruments and devices, such as the guidewire, catheter, and dilator, before use. It is also crucial to ensure all devices used for a vascular procedure contain a radiopaque marker for rapid identification in the case of fragmentation. As retained foreign bodies increase the risk for sepsis, hemorrhage, embolism, cardiac arrythmia and mortality, retrieval should be done promptly after discovery. In this case, the foreign body failed to be recovered despite minimally invasive methods.

FR-PO541

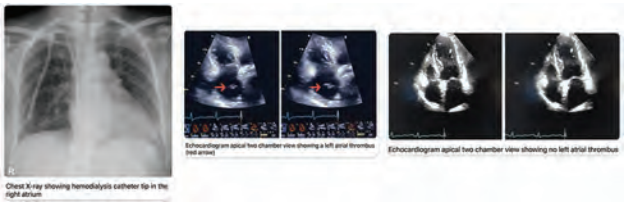
Catheter Tip Thrombus: A Rare but Serious Complication

Mendell Ray T. Sinda, Grecia Darunday, Ruben A. Maguad, Eratosthenes S. Polito. *Perpetual Succour Hospital, Cebu City, Philippines.*

Introduction: The hemodialysis catheter serves as a crucial instrument in renal replacement therapy. While it can be life-saving, its insertion is not without risks. Despite being rarely reported, catheter tip thrombosis lacks a standardized approach due to its infrequency.

Case Description: We present a case involving a 62-year-old woman with diabetes and hypertension, along with a history of ischemic stroke and one year of dialysis. Initially, she had a temporary hemodialysis catheter placed in the right internal jugular vein due to a non-maturing arteriovenous fistula (AVF) on her left arm. However, she experienced intermittent palpitations and chest discomfort exacerbated by certain movements, eating, and dialysis sessions. Cardiac arrhythmias (supraventricular tachycardia and rapid atrial fibrillation) were documented, necessitating pharmacological cardioversion. A chest X-ray revealed the catheter tip was erroneously positioned in the right atrium, likely contributing to the arrhythmias. Though repositioning was planned, echocardiography revealed a 1.1 cm x 0.4 cm thrombus attached to the catheter tip in the right atrium, increasing the risk of embolization during manipulation. Hence, a conservative approach was adopted, initiating intravenous anticoagulation and dual antiplatelet therapy (clopidogrel and aspirin). Symptoms gradually improved over six days of treatment, with a subsequent echo scan showing thrombus resolution. Anticoagulation was ceased, and the patient was discharged on antiplatelet therapy, now undergoing dialysis without symptoms.

Discussion: Catheter tip thrombosis in hemodialysis patients represents a rare yet grave complication associated with considerable morbidity. Its diagnosis requires a high index of suspicion since it can mimic an acute coronary syndrome, particularly in patients predisposed to cardiac events. In hemodynamically stable individuals, considering anticoagulation and antiplatelet therapy as treatment options may prove beneficial.



FR-PO542

Tunneled Catheter-Associated Quadruple Valve Endocarditis

Heather Rowe, Zeyad J. Rifai, Nirali B. Ramani. *Southern Illinois University School of Medicine, Springfield, IL.*

Introduction: The Advancing American Kidney Health (AAKH) initiative was launched in 2019 to establish a new framework for kidney care in the United States (US). Unfortunately, the complexities of addressing health equity were left out of the initiative.

Case Description: A 45-year-old African American man experiencing homelessness with untreated schizophrenia, nicotine dependence, and uncontrolled hypertension complicated by End-Stage Renal Disease (ESRD) via tunneled catheter presented to the hospital with fever, rigors, malaise, dyspnea, chest pain, and pain over his tunneled catheter site since catheter exchange 3 weeks ago. His last dialysis session was two days prior. The patient has a history of missed dialysis sessions likely due to his untreated schizophrenia and lack of transportation. Blood cultures showed Methicillin Sensitive Staphylococcus Aureus with echocardiogram revealing vegetations on the pulmonic valve, new mitral and tricuspid valve flail chords, and new severe aortic insufficiency compared to echocardiogram from 2 weeks prior. The patient underwent catheter exchange after a line holiday and negative repeat blood cultures, and was prescribed an intradialytic regimen of cefazolin.

Discussion: This unfortunate case of quadruple valve endocarditis is a sobering reminder of the moral obligation of healthcare professionals to care for all individuals, particularly the most vulnerable. Patients with schizophrenia have an increased prevalence of diabetes, hypertension, and cardiovascular disease which are all risk factors for kidney disease. Nephrologists must work closely with psychiatrists, dialysis nurses, and other healthcare providers to create a comprehensive care plan that addresses both the psychiatric and medical needs of the patient. Comanagement with a psychiatrist may implement and support behavioral strategies to improve adherence to dialysis to avoid catastrophic outcomes. Raising awareness in the Nephrology community is a step toward compassionate, inclusive care for our most vulnerable patients.

FR-PO543

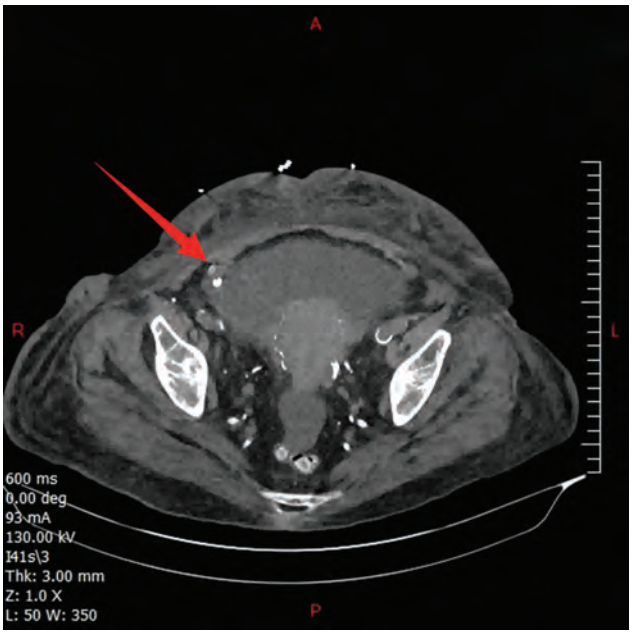
Beyond Appearances: A Case Report of Mistaken Identity in Dialysis Access

Ephrem D. Demie,[1] Shahin C. Owji,[2] Mohammad Shafiq,[2] Srikanth K. Raayasa.[2] HCA Nephrology Team. *[1]HCA Healthcare Inc, Nashville, TN; [2]HCA Healthcare Graduate Medical Education, Brentwood, TN.*

Introduction: In this case report, we present a remarkable case involving a patient with a transhepatic hemodialysis (HD) catheter. The transhepatic hemodialysis catheter involves placing a catheter through the right or middle hepatic veins when other options have been exhausted. The catheter became dislodged into the peritoneal cavity and was subsequently mistaken for a peritoneal dialysis catheter.

Case Description: A 34-year-old female with a history of lupus, hypertension, and end-stage renal disease on hemodialysis presented to the ER with concerns about a malfunctioning hemodialysis catheter for a week. During her ER visit, an initial x-ray revealed a percutaneous catheter in the right abdomen. A CT scan of the abdomen and pelvis showed a dislodged transhepatic hemodialysis catheter, misinterpreted as a peritoneal dialysis catheter, leading to a delay in treating the potential causes of the patient's symptoms. Both the ER physician and the hospitalist failed to promptly diagnose the issue, resulting in the patient not receiving timely appropriate surgical intervention and renal replacement treatment.

Discussion: Catheters utilized for hemodialysis access, such as transhepatic access, exhibit varying radiographic appearances, yet share common features of large bore catheters with a double lumen. A properly positioned transhepatic hemodialysis catheter traverses subcutaneously through the liver parenchyma, hepatic vein, and inferior vena cava before terminating within the right atrium. However, transhepatic catheters are susceptible to migration, often evidenced by imaging depicting the catheter tip retrogressing into the hepatic vein or descending into the peritoneal cavity. This can lead to delays in diagnosis and management, as was evident in this case.



CT scan showing the Transhepatic HD catheter

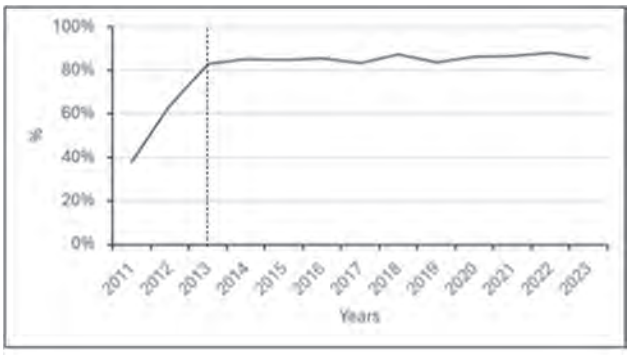
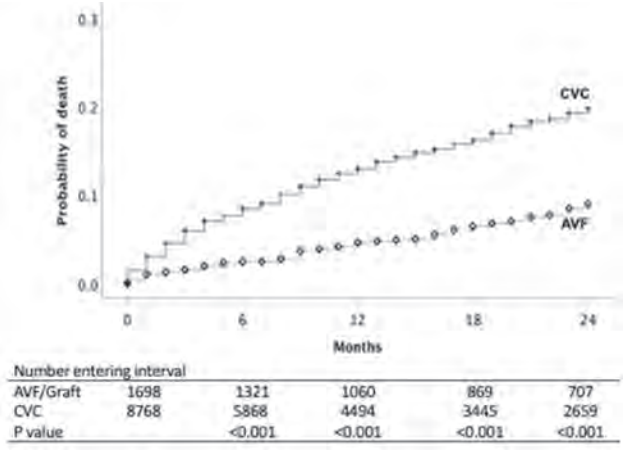


Fig 1. Time trend of CVC use in Brazil



Number entering interval					
AVF/Graft	1698	1321	1060	869	707
CVC	8768	5868	4494	3445	2659
P value		<0.001	<0.001	<0.001	<0.001

Fig 2. KM curves

FR-PO544

Use of Central Venous Catheter (CVC) as Vascular Access at Hemodialysis Entry in Brazil: Impact on 2-Year Mortality

Guilherme Schittine Bezerra Lomba,[1] Angelica P. Da Silva,[1] Fabiana B. Nerbass,[3] Helbert N. Lima,[4] Ricardo Sesso,[2] Jocemir R. Lugon.[1] *[1]Universidade Federal Fluminense Hospital Universitario Antonio Pedro, Niteroi, Brazil; [2]Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil; [3]Pró-Rim Foundation, Joinville, Brazil; [4]Universidade da Regiao de Joinville, Joinville, Brazil.*

Background: The recommended access for starting HD is arteriovenous fistula (AVF), but CVC is frequently used. Its use has been associated with higher mortality worldwide, but Brazilian data on this is scarce. Using data from the Brazilian Dialysis Registry, we aimed to evaluate the time trend of CVC use at the start of HD and assess its impact on all-cause mortality over 2 years.

Methods: This was a national registry-based retrospective cohort study with data of ≥18-year incident HD patients from Jan-2011 to Dec-2023. The variable of primary interest was the initial vascular access: CVC or AVF/graft. The main outcome was all-cause 2-year mortality. For analyses, we used the Kaplan-Meier method and Cox proportional hazards regression.

Results: We studied 10,466 patients. The mean age was 58±16 years; 60% were male, and 33% had diabetes. CVC use at HD entry increased in the last 10 years (Fig. 1). Two-year survival curves are in Fig. 2. In a univariate Cox regression model, the HR of CVC use was 2.56 (95%CI 2.10-3.14); after adjustment for age, sex, BMI, diabetes, hypertension, Hep B and C, HIV, albumin, and Hb, it was 1.92 (95%CI 1.30-2.83). Other independent variables associated with mortality were: age (HR 1.04; 95%CI 1.03-1.05), BMI (HR 0.97; 95%CI 0.95-0.99), albumin (g/L) (HR 0.91; 95%CI 0.89-0.93), and Hb (g/L) (HR 0.96; 95%CI 0.95-0.97).

Conclusions: CVC use was associated with a 2-fold increase in the risk of 2-year mortality. The upward trend in CVC use in Brazil is worrying and calls for changes in medical care aimed at the early implementation of permanent vascular access for HD start.

FR-PO545

Access-Related Infections in Icelandic Patients on Hemodialysis

Lára B. Birgisdóttir,[1] Olafur S. Indridason,[2] Runolfur Palsson,[2,1] Asta D. Jonasdottir.[2,1] *[1]Haskoli Islands, Reykjavik, Iceland; [2]Landspitali, Reykjavik, Iceland.*

Background: Hemodialysis (HD) requires a well-functioning access to the vascular system, preferably an arteriovenous (AV) fistula or graft. Many patients initiate maintenance HD using a central venous catheter (CVC) which is prone to complications, including bacteremia. The aim of the study was to examine the frequency of CVC use for HD access in Iceland, and the incidence of catheter-related complications.

Methods: This was a retrospective study that included all patients aged >18 years who started HD for end-stage kidney disease in Iceland in 2017-2022. Demographic and clinical information, including the type of vascular access and access related complications was obtained from electronic medical records. Access-related bacteremia was defined as positive blood culture from a peripheral vein or the dialysis circuit and absence of other cause of the infection. The incidence of infections was calculated per patient-year for each access type.

Results: Among 164 patients who initiated HD during the study period, 79 (42.8%) started with a tunneled CVC as vascular access, 35 (21.3%) a non-tunneled CVC, 47 (28.7%) an AV fistula and 3 (1.8%) with an AV graft. A tunneled or non-tunneled CVC was used by 127 (77.4%) patients at some point. The use of tunneled CVCs increased during the study period, with 23 catheters placed in 18 individuals in 2017, while 38 were placed in 32 individuals in 2022. The use of non-tunneled CVCs decreased markedly, as13 such catheters were placed in 12 individuals in 2017, but only a single non-tunneled CVC in 2022. Cumulative patient-years with each access type was 98.2 for tunneled CVCs, 2.9 for non-tunneled CVCs, 198 for AV fistulas and 20.1 for AV grafts. The incidence of access-related bacteremia was 0.28 per patient-year (0.77 per 1000 CVC days) for tunneled CVCs, 1.37 per patient-year (3.8 per 1000 CVC days) for non-tunneled CVCs, 0.025 per patient-year for AV fistula, no bacteremia was observed in patients with AV grafts. The most common infectious agent was Staphylococcus aureus, causing 14 (37.8%) bacteremia episodes, followed by coagulase-negative staphylococci causing 10 (27%) episodes.

Conclusions: The use of CVCs is high in Iceland compared to other countries in Europe. However, the decreasing proportion of non-tunneled catheters is exemplary and likely explains the low incidence of bacteremia in patients with CVCs.

FR-PO546

Vascular Access-Related Hospitalizations in Hemodialysis

Leonella Luzardo,[1,2] Maria A. Zinoveev,[1] María Laura Ceretta,[1] Alejandro Ferreiro,[1,2] Maria C. Gonzalez-Bedat.[1] *[1]Uruguayan Dialysis Registry, Montevideo, Uruguay; [2]Nephrology Center, Hospital de Clínicas, Montevideo, Uruguay.*

Background: Arteriovenous fistulas (AVF) are recommended for patients on HD due to their benefits over catheters(CAT), that are associated with higher morbidity. The aim of this research is to analyze vascular access–related hospitalizations.

Methods: We analyzed the HD cohort of patients on HD during 2022 in Uruguay. Data was extracted from the Uruguayan Dialysis Registry. Vascular access were divided into catheters (CAT) or arteriovenous grafts or fistulas(AV). Vascular access–related hospitalizations were classified into infectious or non-infectious and 4 categories were established: CAT-inf, CAT-non inf, AV-inf, AV-non inf. Those complications that did not require hospital admission were not included. We calculated the rate of admissions/1,000 HD sessions.

Results: A total of 3,472 patients (60.1% M; 66.2% diabetes) were included, 62.9 years (SD ± 16.2). 390,920 chronic HD sessions were performed, on 64.4% of them the vascular access was an AV graft or fistula. We analyzed 716 vascular access – related admissions (589 patients) and 69.7% of them were nonrelated to infection. The rate of admissions related to AVFs was 2,18/1000 HD session (95% CI: 2,00–2,36) and the rate of admissions related to CAT was 1,21/1000 HD session (95% CI:1,04–1,41). Hospitalizations due to an AV-non inf complication were the most frequent with a rate of 1,82/1000 HD session (table1). Patients who required admission had similar age (63.0vs62.7 years; *p*=ns) but had more diabetes (70.5% vs 60.4%; *p*=0.02).

Conclusions: Unexpectedly, mechanical complications of AVFs were responsible for most admissions. This is probably multifactorial and is related to the comorbidities of the population and a decrease in infectious complications of catheters due to their improvement. An analysis of the trend over the last years would be of interest for a better understanding of the complications associated with vascular access.

Table 1. Vascular access-related morbidity rate.

AV-INF	0.36
AV-non INF	1.82
CAT-INF	0.91
CAT-non INF	0.30

Admissions /1,000 HD sessions. AV-inf: arteriovenous graft or fistula infections; AV-non inf: arteriovenous graft or fistula non infection; CAT-inf: catheter related infections; CAT-non inf: catheter related non infection.

FR-PO547

Hospital Admissions for Bloodstream Infections Acquired during Outpatient Hemodialysis through a Central Venous Catheter (HD-CVC): Patient Population and Selected Outcomes

Jared L. Crandon,[1] Sharada Weir,[2] Mary P. Michaud,[1] Peter Sullivan,[1] Liz Hurlburt.[1] *[1]CorMedix Inc., Berkley Heights, NJ; [2]Health economist in private practice, Austin, TX.*

Background: HD-CVC patients are at an increased risk for catheter related bloodstream infections. The purpose of this study was to characterize the demographics, clinical baseline characteristics, and selected outcomes for HD-CVC patients who were hospitalized for treatment of bloodstream infections (BSIs).

Methods: All admissions of adult HD-CVC patients in the Premier Healthcare Database with discharge dates during 2020-2022 were retrospectively evaluated. The first hospital admission in which each patient presented with a BSI was included in the final analysis. BSIs were identified by ICD-10 codes and blood culture collection dates. A BSI was deemed present-on-admission (BSI-POA) if the blood culture date was <3 calendar days after admission. Descriptive analyses included baseline demographics, clinical characteristics, and outcomes. Hospital costs were estimated based on patient level data reported from each hospital.

Results: Admissions were identified for 91,448 unique patients; 25% (N=22,902) presented with a BSI. Patients were 58.2% white, 27.1% black, and 56.6% male. Most (59.3%) were aged ≥60 years and more than three-quarters resided in census tracts above the median ranking on CDC's Social Vulnerability Index, with 47.0% in the most vulnerable quartile of neighborhoods nationwide. Patients had many comorbidities at baseline with 87.8% having ≥3 Charlson comorbid conditions and 42.6% with ≥6. Median length-of-stay was 16 days, with 53.8% of admissions including time in the ICU (median: 8d). 26.8% of patients were readmitted within 90 days, 46.3% were BSI-related. All-cause, in-hospital mortality was 10.3%, with a further 4.7% expiring within 90d of discharge. The median total admission cost was $157K. Of which, a median cost of $65K was allocated to ICU care.

Conclusions: We described the characteristics of HD-CVC patients who presented to hospitals with BSIs. These data highlight the complexity and social vulnerability of these patients and the extensive healthcare utilization resultant from these infections. Moreover, care of these patients was associated with considerable healthcare costs and 1-in-10 patients died whilst inpatient. Future studies should characterize risk factors and evaluate potential prevention strategies for this high-risk population.

Funding: Commercial Support - CorMedix Inc.

FR-PO548

Efficacy of Using Chlorhexidine Impregnated Foam Dressing (BIOPATCH) among Patients on Haemodialysis with Tunneled Haemodialysis Catheters

Nasreen Samad, Dharshi Hewa Wellalage, Jerilyn Lalu, Santhi Selvakumar. *Barts Health NHS Trust, London, United Kingdom.*

Background: Tunneled haemodialysis catheter related blood stream infections (CRBSI) lead to increased morbidity and mortality, including hospital admissions and antibiotic resistance with increased health care costs. Therefore, proper tunneled haemodialysis line exit site care and dressings are a vital step in preventing the above mentioned consequences. With this background an audit was performed to confirm the efficacy of (BIOPATCH) in reducing the exit site infections in haemodialysis patients in single dialysis unit.

Methods: All patients with Tunneled haemodialysis catheters in Queens Hospital Haemodialysis unit, Romford, UK were included in the audit. Patients were verbally consented for dressing change and exit sites swabs. Audit and re-audit cycles spanned over a total period of 15 months. All exit site routine swab positivity data was collected over this period. From January 1, 2023 to May 30, 2023 sterile transparent dressing without BIOPATCH was used. From May 31, 2023 to October 30, 2023 all the patients were offered chlorhexidine impregnated foam dressing (BIOPATCH) as a standard practice. The first audit cycle was completed and haemodialysis staff was informed about the findings of the audit with emphasis on adherence to strict aseptic protocols and completion of IPC chart (Infection Prevention and Control Chart) for each haemodialysis session. Thereafter a re-audit was carried out from November 1, 2023 to March 30, 2024.

Results: Total number of patients were 52. 13 patients had positive exit site swabs from January to May 2023 where only the transparent dressing was used without BIOPATCH. From May to October 2023 when BIOPATCH was initially used, 20 exit site positive swabs were found. During reaudit from November 1, 2023 to March 30, 2024, BIOPATCH use with increased compliance with aseptic protocols resulted in reduction of positive swabs to 9.

Conclusions: BIOPATCH dressing with adherence to aseptic practice led to the lowest number of patients (9) with tunneled line exit site positive swabs. However, using BIOPATCH without meticulous adherence to infection control protocol did not improve exit site swab positivity rate. The use of chlorhexidine impregnated foam dressing (BIOPATCH) along with the strict aseptic protocols is superior in reducing the exit site swab positivity rates.

Funding: NIDDK Support

FR-PO549

Maintaining Zero Central Line-Associated Bloodstream Infections in Dialysis Catheters

Marlyn A. Batan, Bernadette Garcia, John Varilla, Maria Monique M. Granados. LHH Dialysis. *Lenox Hill Hospital, New York, NY.*

Background: The Dialysis team at Lenox Hill Hospital gives high priority to preventing central line-associated bloodstream infections (CLABSI) related to hemodialysis (HD) central line catheters. In 2014, two incidences of HD CLABSIs were reported. The Dialysis team, Quality Management Department, and Infection Control held root cause analysis meetings for these cases. As a result, there was a re-evaluation of dressing kits and in-services for nursing teams were conducted on dressing changes and catheter monitoring. This resulted in a decrease of HD CLABSIs to 1 in 2015 & 2016, 0 in 2017 and 1 in 2018. The team was determined to reach 0 HD CLABSIs. In 2019, 2 new processes were added to achieve 0. Since then, there have been 0 HD CLABSIs

Methods: 2 monitoring processes were created and added to the dialysis workflow. First, a daily central venous catheter (CVC) monitoring tool was created to assess and document the state a HD catheter is in. Monitoring is done daily and performed for all HD patients in the hospital regardless of the frequency of dialysis sessions. The tool includes fields for demographics, CVC type, location, date of insertion, if the dressing is intact, if the patient is allergic to chlorhexidine, and the plan of care for the site. Next, an access tracking tool to trace any access issues, the licensed provider who inserted the line or is taking care of the patient, the plan of care for the access, and communication with any long-term care facility, was created.

Results: After adding the two monitoring workflows there have been 0 HD CLABSIs to date, despite having an increased amount of dialysis treatments done through a CVC. In 2019, 1367 out of 2892 total dialysis sessions were of patients with a HD CVC (47.27%). In 2023, 1405 out of 2415 had a HD CVC (58.18%). This suggests that despite the increase in volume of treatments with dialysis catheters, the monitoring workflows may have contributed to the prevention of HD CLABSIs.

Conclusions: These processes may have contributed to maintaining 0 HD CLABSIs. Additional opportunities found including a deeper dive into catheter maintenance and line caregiver knowledge for home dialysis or long-term care bound patients. Recent findings show that patients discharged with home dialysis were frequently readmitted with infected dialysis catheters. These findings call for additional data analysis.

FR-PO550

Hemodialysis Catheter and Infections from a National US Cohort, 2018-2023

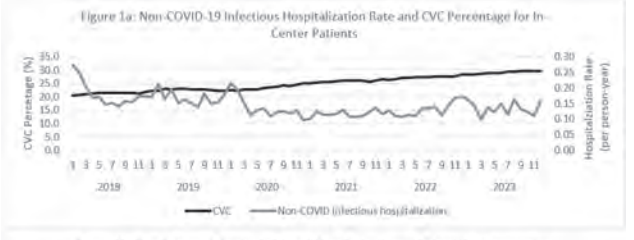
Monica Shieu,[1] Nien Chen Li,[1] Harold Manley,[1] Antonia Harford,[1] Caroline M. Hsu,[2] Daniel E. Weiner,[2] Dana Miskulin,[2] Doug Johnson,[1] Eduardo K. Lacson.[1,2] *[1]Dialysis Clinic Inc, Nashville, TN; [2]Tufts Medical Center, Boston, MA.*

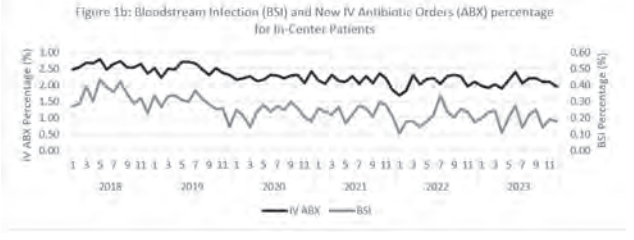
Background: Multiple factors have impacted arteriovenous hemodialysis (HD) vascular access creation and central venous catheter (CVC) usage throughout the pandemic. We describe longitudinal trends in CVC use, bloodstream infections (BSI), new IV antibiotics orders (ABX), and non-COVID-19 infection-related hospitalizations (INFH) from a national US dialysis provider.

Methods: Among adult maintenance HD patients treated at Dialysis Clinic, Inc. from 2018-2023, monthly percentages of patients with CVC, BSI, and ABX were calculated. INFH was defined by length of stay of at least 2 nights. For patients with a CVC, the mean time to first fistula/graft surgery was ascertained.

Results: Among 36,849 maintenance HD patients, there was a 44.4% increase in CVC use during the study period. There was a 40.7% decrease in INFH (Fig. 1a), 33.3% decrease in BSI, and 21.4% decrease in ABX (Fig. 1b). Among incident HD patients, CVC was the sole access present at initiation in 59% of patients in 2018, 62% in 2019, 67% in 2020, 69% in 2021, 72% in 2022, and 70% in 2023. Among initial access surgeries within the first year of a CVC, mean time to fistula/graft surgery was 97 days in 2018, 106 days in 2019, 107 days in 2020, 117 days in 2021, 121 days in 2022, and 124 days in 2023.

Conclusions: From 2018-2023, CVC use increased with more patients initiating HD with CVC alone and waiting longer for fistula/graft surgeries. Despite this, percentages of infections and ABX declined, suggesting maintenance of care process integrity within dialysis facilities, particularly infection precautions and prevention procedures during the pandemic. To minimize morbidity from CVC-related infections, the nephrology community should maintain these infection control practices and additionally work with regulators, payers, surgeons, and hospitals to reduce CVC use to pre-pandemic levels.





FR-PO551

mTORC1-Mediated Megalin Phosphorylation Acts as a Switch between Endocytosis and Cell Proliferation

Eileen Dahlke, Madlen Kunke, Hannah Knöfler, Yuanhao Shen, Yaman Anan, Franziska Theilig. *CAU Kiel Institute of Anatomy, Kiel, Germany*.

Background: The importance of proper renal proximal tubular (PT) function is displayed by its loss of function in Fanconi syndrome which can be induced by mTORC1 inhibition. Protein endocytosis is one of the main PT function and involves the scavanger receptor megalin (LRP2) to internalize a variety of proteins from the ultrafiltrate. mTORC1 induces PT endocytosis and we discovered a specific mTORC1 phosphorylation site on megalin S4577 which function we aimed to identify.

Methods: Transient transfection of megalin mini-construct 2 (MMR2) with mutations in S4577 (MMR S->A mimics permanent non-phosphorylated state, MMR2 S->D mimics permanent phosphorylated state) in MDCK2 or EBNA/HEK cells, followed by functional endocytosis assays, immunocytological stainings and super resolution STED microscopy, western blotting, surface expression analysis, and co-immunoprecipitations were performed.

Results: Megalin phosphorylation by mTORC1 in S4577 was confirmed. MMR2 S4577 phosphorylation showed no impact on MMR2 surface expression level, but demonstrated a reduced endocytosis rate for albumin. The subcellular distribution of mutants showed minor alterations in co-localization with clathrin vesicles and early endosomes and no difference in co-localization with Rab35-positive vesicles. Surprisingly, S4577 phosphorylation leads to stronger binding affinity of MMR2 to the endocytosis adaptor protein ARH. In culture conditions, MMR2 was occassionally observed to be colocalized with alpha-tubulin in mitotic spindles and S4577 phosphorylation reduced cell proliferation rate.

Conclusions: mTORC1 mediated phosphorylation of megalin C-terminus at S4577 lowers endocytosis rate to allow increased cell proliferation and may therefore be encountered as cellular switch between endocytotic function and cell proliferation.

FR-PO552

Gout Risk Variant ABCG2 Q141K Alters Renal Amino Acid Metabolism and Alpha-Ketoglutarate

Owen M. Woodward,[1,2] Yong Li,[2] Victoria L. Halperin Kuhns,[1] Ava M. Zapf,[1] Anna Kottgen.[2] *[1]University of Maryland School of Medicine, Baltimore, MD; [2]Albert-Ludwigs-Universitat Freiburg Medizinische Fakultat, Freiburg, Germany*.

Background: ABCG2 is an epithelial and proximal tubule efflux transporter. A common missense variant, Q141K, increases hyperuricemia and gout risk. GWAS studies identified associations of *ABCG2* SNPs and HbA1c levels, BMI, LDL, creatinine, and C-reactive protein, suggesting a metabolic role for ABCG2. The relationship between ABCG2, renal function, urate and metabolic disease remains unclear.

Methods: We conducted a metabolomic study on paired plasma and urine samples of 1033 carriers and 3879 non-carriers of *Q141K ABCG2* participating in the GCKD study. To dissect causal mechanisms for observed differences, *i.e. ABCG2* dysfunction versus hyperuricemia, similar paired metabolomics as well as whole-kidney RNA-seq data were generated from two hyperuricemia mouse models: the orthologous *Q140K Abcg2*, and an inducible uricase knockout, *Uox-iKO*.

Results: Enriched pathways based on altered metabolites identified in both human and mouse *ABCG2* variants were highly correlated (plasma r=0.83; $p=2.4x10^{-54}$, urine r=0.7; $p=8.47x10^{-32}$), supporting the use of the *Q140K Abcg2* model to study mechanisms in humans. In urine, the strongest enrichment of metabolites comparing *Q141K* carriers and non-carriers was observed for urate and related pathways, including organic nitrogen compounds. The most significant non-urate containing pathways were carboxylic acids (*FDR-p*=$3.02x10^{-9}$) and organic acid derivates (*FDR-p*=$2.87x10^{-6}$). To discern a role for ABCG2 in renal function, we focused on metabolites in these pathways that were only altered in urine of human *Q141K ABCG2* carriers, and found lower polyamine, urea cycle metabolites and alpha-ketoglutarate (AKG; all $p<0.05$). The *Q140K Abcg2* mice also displayed lower urinary polyamine metabolites and AKG. Kidney RNA-seq found significantly altered key genes of the polyamine and urea cycle in *Q140K Abcg2* mice: *Agr2* and *Cpt1* and AKG transporter *SLC13A3*. In contrast, *Uox iKO* mice showed higher urinary polyamide, urea cycle metabolites and AKG along with altered expression of the AKG receptor *Oxgr1* and the HCO3-/Cl- exchanger *Slc26a4* (pendrin). Physiological data suggested increased urinary AKG altered plasma HCO3- in the *Uox iKO* mice, consistent with OXGR1 activation of pendrin.

Conclusions: Combination of orthologous human and mouse metabolomic data suggests a role for ABCG2 in regulating proximal tubule amino acid metabolism and AKG.

Funding: NIDDK Support, Government Support - Non-U.S.

FR-PO553

KCNJ16-Depleted Kidney Organoids Recapitulate Tubulopathy and Lipid Recovery with Statin Treatment

Anne Metje van Genderen,[1] Elena Sendino Garví,[1] Gijs J. van Slobbe,[1] Jeroen H. De Baaij,[2] Joost Hoenderop,[2] Manoe J. Janssen,[1] Rosalinde Masereeuw.[1] *[1]Universiteit Utrecht Utrechts Instituut voor Farmaceutische Wetenschappen, Utrecht, Netherlands; [2]Radboud Universitair Medisch Centrum, Nijmegen, Netherlands*.

Background: The *KCNJ16* gene has recently been associated with a kidney tubulopathy phenotype, including disturbed acid-base homeostasis, hypokalemia and altered renal salt transport as main disease features. *KCNJ16* encodes for Kir5.1, which together with Kir4.1 constitutes a potassium channel located in the basolateral membrane of the tubular kidney cells. Despite previous *in vitro* and rodent models provided with mechanistical links between Kir5.1 and the recently described disease phenotype, the pathophysiological mechanisms of the disease are still poorly understood. In this project, we aimed to generate a characterize a novel advanced kidney organoid model that better recapitulates the disease phenotype to further investigate the pathophysiological mechanisms underlying the disease.

Methods: For this we used CRISPR-Cas9 to generate heterozygous and a compound heterozygous *KCNJ16* mutant cell lines from healthy human induced pluripotent stem cells (iPSC). Both the healthy (*KCNJ16*^{WT}) and mutated (*KCNJ16*$^{+/-}$ and *KCNJ16*$^{-/-}$ iPSC lines were differentiated into kidney organoids using a 25-day differentiation protocol and maturation in an air-liquid interface environment.

Results: After successful depletion of Kir5.1, *KCNJ16*-depleted kidney organoids showed transcriptomic impairment of key electrolyte and water-balance transporters such as AQP1, NBC1, SNAT-3 and PEPCK. We also observed cysts formation ($p<0.01$) and staining with the bodipy probe and collagen-I revealed lipid droplet accumulation ($p<0.001$) and fibrosis ($p<0.01$). Following these results, we performed a large scale and a glutamine tracer flux metabolomics analysis and found that KCNJ16-/- depleted organoids display TCA cycle and lipid metabolism impairments when compared to *KCNJ16*^{WT} ($p<0.01$-0.0001), particularly at glutamine and citrate levels. By testing different drug compounds on the kidney organoids, we discovered that treatment with statins reversed the lipid droplet accumulation ($p<0.01$-0.0001) and collagen I deposition ($p<0.01$) in *KCNJ16*$^{-/-}$ kidney organoids.

Conclusions: In conclusion, mature kidney organoids represent a relevant *in vitro* model for investigating Kir5.1 function, providing novel molecular targets for this genetic tubulopathy and identifying statins as a potential therapeutic strategy.

Funding: Government Support - Non-U.S.

FR-PO554

Additive Diuretic Action of SGLT2 Inhibitor and Loop Diuretic Combination Avoids Body Fluid Loss by Promoting Vasopressin-Independent Compensatory Fluid Intake

Takahiro Masuda,[1] Masahide Yoshida,[1] Tatsushi Onaka,[1] Volker Vallon,[2] Daisuke Nagata.[1] *[1]Jichi Medical University, Shimotsuke, Japan; [2]University of California San Diego, La Jolla, CA.*

Background: We have shown that SGLT2 inhibitors maintain euvolemic fluid status by stimulating antidiuretic hormone (vasopressin: AVP) secretion and fluid intake in response to diuresis, whereas loop diuretics reduce AVP secretion and cause net body fluid loss (Physiol Rep 2020, AJP Renal 2022). In addition, we recently reported that the combination of SGLT2 inhibitor and loop diuretic maintains body fluid balance in chronic kidney disease patients (Front Med 2023), but the mechanism remains unclear.

Methods: Non-diabetic Sprague-Dawley rats were divided into 4 groups: 1) Vehicle (Veh), 2) SGLT2 inhibitor ipragliflozin 5 mg/kg (Ipra), 3) loop diuretic furosemide 50 mg/kg (Furo), and 4) ipragliflozin and furosemide combination (Ipra+Furo) with free access to fluid and normal rodent chow. Drugs were suspended in 0.5% methylcellulose and given by gavage, and rats were kept in metabolic cages for 2 days. * $p<0.05$ vs. Veh; $^{\#}$ vs. Ipra; $^{+}$ vs. Furo.

Results: Urine volume on day 2 increased equally in Ipra and Furo and was highest in Ipra+Furo (Veh 8±9, Ipra 120±21*, Furo 102±26*, Ipra+Furo 287±112* %). The change in fluid intake was highest in Ipra+Furo, with a smaller increase in Furo (-4±5, 21±5, 11±8, 50±6^{+} %). Urinary AVP (0.24±0.04, 0.38±0.06, 0.10±0.03$^{\#}$, 0.06±0.01$^{\#}$ ng/day/100g bw) and solute-free water reabsorption (13.3±1.5, 23.5±1.6, 11.1±1.4$^{\#}$, 16.6±1.2$^{\#}$ mL/day/100g bw) were elevated by Ipra but decreased by Furo and Ipra+Furo combination vs. Ipra. The changes in fluid balance (fluid intake-urine volume) (1±8, -8±5, -32±9*, 6±6^{+} %) and plasma volume calculated by the Strauss formula (16±6, 18±4, -8±4$^{\#}$, 14±5^{+} %) were negative in Furo but positive in Ipra+Furo. The changes in serum Na^{+} (-1.3±0.5, 0.1±0.5, -1.1±0.5, -2.0±0.7$^{\#}$ %) and Cl^{-} (0.8±0.7, 1.5±0.6, -3.3±1.2*$^{\#}$, -3.1±0.9*$^{\#}$ %) concentrations were significantly lower in Ipra+Furo vs. Ipra. Serum osmolality was similar among the 4 groups.

Conclusions: Combination of SGLT2 inhibitor and loop diuretic avoided body fluid loss by promoting compensatory fluid intake despite suppressed AVP tone and absence of serum Na^{+} and osmolality increase. These results may indicate a novel non-osmoregulatory thirst mechanism induced by the combination of SGLT2 inhibitors and loop diuretics.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO555

Modeling Kidney Proximal Tubular Crystallopathy In Vitro

Rosalinde Masereeuw, Mara Vonk, Chaja Klein, Manoe J. Janssen, Devon Barnes. *Universiteit Utrecht, Utrecht, Netherlands.*

Background: Kidney crystallopathy can be characterized by the presence of crystals within renal tubules, leading to obstruction, cytotoxic effects, and inflammatory responses. Here, a novel proximal tubule cell model was developed to investigate the mechanisms underlying toxicant-induced crystal formation and renal inflammation.

Methods: Conditionally immortalized proximal tubule epithelial cells (ciPTECs) were used to investigate the role of uric acid, a known crystal-forming metabolite, and the influence of pH on crystal formation. A series of *in vitro* assays were used to assess cytotoxicity, oxidative stress, mitochondrial function, inflammation as well as the expression of NLRP3 inflammasome related markers on the protein level.

Results: Exposing ciPTECs to uric acid decreased cell viability, which was more pronounced under reduced pH conditions with a significant reduction starting at 200 μg/ml at pH 5.5 *vs* 800 μg/ml at pH 7.4. Various shapes of uric acid crystals were formed (Figure 1). Reactive oxygen species production was increased at 200 μg/ml at all pH levels tested (*viz.* 5.5, 6.0 and 7.4). Furthermore, uric acid induced the expression of the inflammasome-related markers caspase-1, ASC, TNFα at the mRNA level, and IL-1β at the protein level. In line with cell viability, these effects were most pronounced with higher uric acid concentrations and at lower pH levels.

Conclusions: A novel model was established simulating kidney crystallopathy and its impact on inflammasome components, caspase activity, cytokine production, and the NF-κβ pathway. This model will be used to study crystallopathy in more detail to provide an adverse outcome pathway for crystal-forming nephrotoxicants. *This project received funding from the European Union's Horizon 2020 research and innovation programme (GA No 963845, ONTOX).*

Funding: Government Support - Non-U.S.

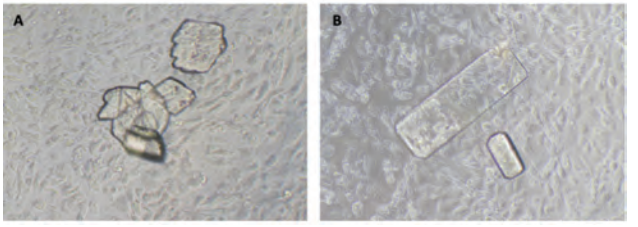


Figure 1. Uric acid crystals formed after 72h incubation with A) 800 μg/ml at pH 5.5 and B) 600 μg/ml at pH 5. 10x magnification.

FR-PO556

Differentiated Cell Types in the Kidney's Thick Ascending Limb: Functional Insights on TAL α and TAL β

Jessica P. Bahena-López,[1] Jonathan W. Nelson,[2] Xiao-Tong Su,[1] Hasan Demirci,[3] Joshua N. Curry,[1] Markus Bleich,[4] Sebastian Bachmann,[3] David H. Ellison.[1] *[1]Oregon Health & Science University, Portland, OR; [2]University of Southern California, Los Angeles, CA; [3]Charite Universitatsmedizin Berlin, Berlin, Germany; [4]Christian-Albrechts-Universitat zu Kiel Islamwissenschaft, Kiel, Germany.*

Background: The Thick Ascending Limb (TAL) plays a key role in reabsorbing NaCl and Ca^{++} and Mg^{++}, driven ultimately by NKCC2. Spanning from the outer medulla to the cortex, the TAL has traditionally been viewed as a single functional cell type, but recent transcriptomic findings indicate the existence of two TAL cell clusters, with high Claudin 10 and Claudin 16 expression (PMID 28028216). Beyond mosaic expression of claudins, however, the specifc functions of these two cell types are unknown. Here, to better understand the heterogeneity within the TAL population, we enriched for TAL nuclei and performed single-nucleus transcriptomics.

Methods: Kidneys from male NKCC2-Cre-INTACT (Isolation of Nuclei TAgged in specific Cell Types, which fluorescently labels nuclei) mice were harvested for single-nucleus RNA-seq to create an enriched TAL dataset. Data were compared with re-analyzed datasets from mouse (PMID 31689386), rat (PMID 37023747), and human (PMID 37468583). IHC of kidney from the same species was performed.

Results: Enriched TAL sn-RNA sequencing identified two cell clusters: TAL α and TAL β. Differential Gene Expression analysis showed distinct gene profiles. TAL α cells express *Cldn10* and factors regulating sodium transport, including *Wnk4*, *Stk39*, and *Avpr2*, and display arachidonic acid signaling genes like *Ptger3*. TAL β express *Cldn16* and genes related to calcium homeostasis, such a *Casr*, *Pth1r* and *Vdr*, as well as higher levels of *Kcnj10* and *Wnk1*. TAL clustering also shows segregation following a gradient-like pattern across kidney zones, revealing TAL subtypes or states unique to each zone. This transcriptional heterogeneity was similar among mouse, rat, and human. Immunofluorescence confirmed two cell types. In the cortex and OSOM, Kir4.1 was coexpressed with CaSR and Claudin-16 (TAL β), while apical ROMK was observed in TAL α cells, expressing Claudin-10. In the ISOM, Kir4.1 and ROMK maintained their exclusive patterns, with Claudin-10 present in both cell types.

Conclusions: Combined morphological and transcriptomic analyses identified two distinct TAL cell types, each linked to specific transport pathways, presenting a novel model of interconnected ion transport in the TAL.

Funding: NIDDK Support

FR-PO557

Heterogeneity in the Renal Thick Ascending Limb Cell Composition: Insights from Ultrastructure, Immunohistochemistry, and Single-Cell Transcriptomics

Hasan Demirci,[1] Jessica P. Bahena-López,[2] Jonathan W. Nelson,[3] Xiao-Tong Su,[2] David H. Ellison,[2] Sebastian Bachmann.[1] *[1]Charité-Universitätsmedizin Berlin, Department of Anatomy, Berlin, Germany; [2]Oregon Health & Science University, School of Medicine, Division of Hypertension and Nephrology, Portland, OR; [3]University of Southern California, Department of Medicine, Los Angeles, CA.*

Background: The thick ascending limb (TAL) provides the driving force for the renal concentrating mechanism through its capacity to dilute the urine via the "single effect" of reabsorbing NaCl. It also transports divalent cations like $Ca2^+$ and $Mg2^+$. A single, terminally differentiated cell type with zone-related specificities has so far been defined to line TAL, but recent transcriptomic findings report distinct TAL cell clusters with mosaic expression pattern, illustrated by differential expression of ion transporters and junctional components. Here we couple structure and immunohistochemistry with single-cell (sc) RNA sequencing technology to define unique cell features across kidney zones and local mosaicism.

Methods: Rat, mouse, and human kidney samples were used to examine the morphology of medullary (mTAL) and cortical (cTAL) TAL epithelia. Immunohistochemistry was used to assess the expression of ROMK, NKCC2, pNKCC2, Kir4.1, CaSR, Cldn10 and Cldn16 in TAL. Additionally, scRNA-seq datasets (PMID: 31689386) from mouse kidney were leveraged to define transcriptomic signatures of TAL.

Results: NKCC2 was expressed throughout TAL and macula densa. Mosaic expression of ROMK in TAL showed 46 ± 7% ROMK-negative cells in mTAL, decreasing with cTAL. ROMK-negative cells inversely displayed p-NKCC2 signal chiefly in mTAL, suggesting mosaic NaCl transport activity. Cldn10 and ROMK were colocalized in mTAL and cTAL. CaSR and Kir4.1 were mutually exclusive to ROMK, and a subset of CaSR/Kir4.1 cells expressed Cldn 16 in outer stripe and cTAL cells; here, Cldn 16 dominated over Cldn 10 in mosaic junctional belt conformation. Macula densa expressed exclusively Cldn 10. ScRNA-seq analysis defined Cldn 10 and Cldn 16 as distinct cell clusters, with Cldn 10 coexpressing Stk39, Ptger3, and Cryab, and Cldn16 cells coexpressing Kir4.1, CaSR, Wnk1, and Pth1r.

Conclusions: TAL cells exhibit marked heterogeneity in transporter and tight junction protein expression, correlated with distinct cell clusters from scRNA seq. Modeling TAL function with two distinct cell types, one providing transepithelial voltage generation, the other paracellular divalent cation transport suggests separate functions within TAL cells serving renal concentrating ability and ion transport homeostasis.

FR-PO558

Lack of Role of NHE4 in Renal Ammonia Metabolism

Hyun-Wook Lee,[1] Autumn N. Harris,[1] Kelly A. Hyndman,[2] I. D. Weiner.[1,3] *[1]University of Florida, Gainesville, FL; [2]The University of Alabama at Birmingham, Birmingham, AL; [3]Gainesville VAMC, Gainesville, FL.*

Background: Renal ammonia absorption by the thick ascending limb of Henle's loop (TAL) is a critical step in renal ammonia handling and excretion. The Na^+/H^+ exchanger, isoform 4 (NHE4) has been proposed to have a critical role in TAL ammonia reabsorption by acting as a basolateral Na^+/NH_4^+ exchanger mediating basolateral NH_4^+ exit. This study's purpose was to determine whether NHE4 gene deletion alters renal ammonia metabolism.

Methods: We backcrossed homozygous NHE4 KO mice (Jax Labs, MMRRC stock #34266) with 129S6/SvEv mice (Taconic Biosciences, 129VE), which matches the ES cell used to generate NHE4 KO mice, to obtain heterozygous NHE4 KO mice. We then bred heterozygous dams and sires. All studies compared homozygous deletion ~4-month-old mice with wild-type (WT) littermates. Both male and female mice were studied.

Results: Under basal conditions, serum Na^+, K^+, and HCO_3^- did not differ between WT and KO mice. KO mice had a urine pH that was significantly more acidic than WT mice and also exhibited significantly increased urinary ammonia, titratable acid, and net acid excretion. Immunoblot analysis showed that NHE4 KO increased the expression of phosphoenolpyruvate carboxykinase (PEPCK), a critical ammonia-generating enzyme. It decreased the expression of glutamine synthetase (GS), a critical ammonia-recycling enzyme in cortical proximal tubule segments. After acid-loading for seven days, neither urine pH and ammonia excretion changes nor serum Na^+, K^+, and HCO_3^- differed significantly between WT and NHE4 KO mice. Thus, NHE4 deletion-induced increases in ammonia excretion involve increased PEPCK expression and decreased GS expression, and its deletion does not alter the response to acid-loading. Because of this lack of effect of NHE4 KO to inhibit ammonia metabolism, we examined its expression using KO mice as a negative control. Both immunoblot analysis and immunohistochemistry showed no detectable NHE4 expression. snRNA-seq analysis of WT mouse kidney showed no significant NHE4 expression in TAL1 or TAL2 cells or cortical TAL.

Conclusions: We conclude that: 1) NHE4 is neither expressed in the TAL nor does it contribute to renal ammonia metabolism; and (2) extrarenal roles of NHE4 may induce mild metabolic acidosis upon its deletion that leads to a compensatory stimulation of ammonia metabolism.

Funding: NIDDK Support

FR-PO559

A Novel State-of-the-Art Intravital Microscopy Technique to Track Magnesium in Living Kidneys

Pieter A. Leermakers,[1] Georgina Gyarmati,[2] Janos Peti-Peterdi,[2] Veronika Shchepetkina,[3] Daniela Buccella,[3] Joost Hoenderop,[1] Jeroen H. De Baaij.[1] Dept of Medical BioSciences. *[1]Radboud Universitair Medisch Centrum, Nijmegen, Netherlands; [2]University of Southern California, Los Angeles, CA; [3]New York University, New York, NY.*

Background: Magnesium is an essential mineral for human physiology. Therefore, the serum magnesium concentration is tightly controlled by the kidney. It is currently not possible to measure real-time renal magnesium reabsorption in living organisms. To study the regulation of magnesium reabsorption in the kidney, we aim to perform multi-photon microscopy using a novel ratio-metric magnesium-reporter (MagZet1).

Methods: Mice were anesthetized, received a cannula, and were surgically prepared for kidney imaging. Subsequently, the superficial kidney cortex was continuously imaged with multiphoton microscopy for ratio-metric emission of magnesium-bound and magnesium-free MagZet1, and Albumin-AF594 as a contrast agent. During imaging, injections of Albumin-AF594 and MagZet1 were followed by bolus injections of $MgSO_4$, CaGluconate, or saline.

Results: *in vitro*, MagZet1 ratio-metric emission can be used to discriminate <0.2mM changes in $[Mg^{2+}]$ in plasma filtrate. *In vivo*, i.v. injection of MagZet1 results in free renal filtration, and MagZet1 can be detected in plasma and tubular segments in the kidney of live animals. The maximal imaging depth of MagZet1 is less than 100 μm, so only superficial proximal and distal tubules can be imaged with this technique. Injection of $MgSO_4$ results in an increased MagZet1 fluorescence emission ratio in all visible tubular segments, while injection of saline or CaGluconate did not change the MagZet1 fluorescence emission ratio.

Conclusions: MagZet1 is a magnesium dye that is discriminative of small changes in $[Mg^{2+}]$ in physiological conditions. MagZet1 can be detected in live animals *in vivo* using multi-photon microscopy for at least two hours after injection. In future experiments, we aim to screen the effects of genetic models and candidate drugs on renal magnesium reabsorption.

Funding: Government Support - Non-U.S.

FR-PO560

Genomic Organization and Regulation of Gene Expression in the Distal Convoluted Tubule

Jeroen H. De Baaij, Eveline Kahlman, Lotte Tholen, Sara B. van Katwijk, Femke Latta, Joost Hoenderop. *Radboud Universitair Medisch Centrum, Nijmegen, Netherlands.*

Background: The distal convoluted tubule regulates blood pressure, K^+ balance and Mg^{2+} homeostasis. The complex regulation of DCT-specific ion channels, metabolic activity and hormonal signaling pathways depends on DNA accessibility, polymerase binding and transcription factor activity. Here, we aimed to determine DCT-specific transcriptional regulation by integration of RNA-seq, ATAC-seq, chromosome confirmation capture and histone-modification ChIP-seq datasets.

Methods: We generated a comprehensive atlas of transcriptional regulation in a mouse DCT cell line by generating and integrating chromatin accessibility (ATAC-seq), gene expression (RNA-seq) and histone mark ChIP-seq datasets (H3K4me3, H3K27ac). Moreover, we generated a chromosome conformation capture (Hi-C) map to unravel 3D genomic interactions.

Results: ATAC sequencing demonstrated 14,231 open chromatin regions in the mouse DCT cells. Fifty percent of these regions contained promoter elements and twenty percent active enhancer regions, characterized by H3K4me3 and H3K27ac respectively. GO-term analysis of these regulatory regions demonstrated enrichment of epithelial pathways, such as cilia development, cell junctions and cytoskeleton organization. Hi-C uncovered the basis of 3D genome characteristics in the DCT. As example of how our map of DCT genome organization can be used, we studied the importance of long-range chromatin interactions in transcriptional regulation mediated by transcription factor HNF1β. Our analysis revealed that promoter bound HNF1β primarily controls the expression of genes with general cell functions, such as mRNA processing and protein transport. In contrast, HNF1β binding to enhancer regions at large distance of the promoter was associated with expression of HNF1β-specific processes, such as kidney and urogenital development.

Conclusions: In conclusion, we describe the first comprehensive map of genome organization in a DCT cell line and demonstrate that the 3D architecture of the genome controls specificity of HNF1β-mediated gene transcription.

FR-PO561

Lipopolysaccharide-Responsive Beige-Like Anchor Protein Is Essential for Sodium and Water Homeostasis

Yu Hara, Fumiaki Ando, Hideki Yanagawa, Kanako Nagaoka, Tamami Fujiki, Hiroaki Kikuchi, Shintaro Mandai, Yutaro Mori, Takayasu Mori, Koichiro Susa, Eisei Sohara, Shinichi Uchida. *Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan.*

Background: Lipopolysaccharide-responsive beige-like anchor protein (LRBA) is essential for aquaporin-2 (AQP2) phosphorylation, and its absence results in the polyuric phenotype in mice. Most of the biallelic pathogenic mutations in the *LRBA* gene cause instability of the protein, resulting in LRBA deficiency. LRBA deficiency is a rare disease characterized by immune dysregulation and chronic diarrhea; however, the polyuric phenotype of LRBA deficiency has not been reported.

Methods: We established an international observational registry including 38 patients with LRBA deficiency. The physiological role of LRBA in sodium homeostasis was examined using *Lrba*$^{-/-}$ mice.

Results: The urine specific gravity of LRBA deficiency patients (median, 1.008, n=17) was similar to *Lrba* $^{-/-}$ mice, and urine was dilute in spite of diarrhea-induced dehydration. Low urinary concentrating ability usually induces hypernatremia due to free-water diuresis. However, the serum sodium level of LRBA deficiency patients was low (median, 135 mEq/L, n=38). Therefore, we next investigated renal sodium homeostasis using *Lrba* knockout mice. Low-sodium diet (LSD) decreased serum sodium and chloride concentration in *Lrba* $^{-/-}$ mice (WT vs. *Lrba* $^{-/-}$: Na 146.5 vs. 143.6 mEq/L, Cl 110.1 vs. 105.9 mEq/L). Thiazide diuretics which are inhibitors of sodium-chloride cotransporter (NCC) did not increase FENa in *Lrba* $^{-/-}$ mice fed with LSD. Due to the impairment of NCC activity, blood pressure was low in *Lrba* $^{-/-}$ mice and unresponsive to thiazide treatment. WNK-SPAK-NCC signaling is a main trigger to promote sodium reabsorption from urine via NCC. LRBA was colocalized with SPAK at intercellular vesicles in the distal convoluted tubules. In *Lrba* $^{-/-}$ mice, the protein expression level of SPAK was decreased and that of WNK was compensatorily increased. LRBA directly bound to SPAK and inhibited its lysosomal degradation.

Conclusions: We demonstrated that LRBA is essential for the activation of both NCC and AQP2, thereby ensuring sodium and water homeostasis in renal tubules. LRBA deficiency causes a loss of sodium and water into the urine, as well as diarrhea, which may be a strong risk factor for prerenal kidney failure due to dehydration. Careful attention to the sodium and water balance in patients with LRBA deficiency is required to prevent severe dehydration.

Funding: Government Support - Non-U.S.

FR-PO562

Heterotypic Site-Specific Interactions between WNK4, TSC22D2, and NRBP1 Promote Kinase Activity and Co-localization in WNK Bodies

German R. Magaña,[1,2] Hector Carbajal-Contreras,[1,2] Norma H. Vázquez,[1] Gerardo Gamba,[1,2] Maria Castañeda-Bueno.[1] Unidad de Fisiología Molecular. [1]*Universidad Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico;* [2]*Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: The WNK4 kinase regulates the activity of the thiazide-sensitive Na:Cl cotransporter, NCC, through the activation of the kinases SPAK/OSR1. Disregulation of this pathway is associated with altered sodium and potassium homeostasis. Recently, we found that WNK kinases associate in vivo with the pseudokinase NRBP1 and with proteins of the TSC22D family. These proteins co-localize with the kinase WNK4, KS-WNK1, and SPAK in biomolecular condensates called "WNK-bodies" that are observed in distal convoluted tubule (DCT) cells. The SPAK-WNK interaction is well characterized and involves RFXV motifs present in WNK kinases and a Conserved C-Terminal (CCT) domain present in SPAK. So how is WNK4 interacting with NRBP1 and TSC22Ds? Long TSC22D proteins have a conserved RFXV motif, NRBP1 has a conserved CCT domain, and WNK kinases have two CCT domains in addition to the RFXV motifs. In this work, our objective was to study the effect of these proteins in the WNK4-SPAK pathway and to investigate their interaction mechanisms.

Methods: HEK293 cells were transiently transfected with NRBP1, TSC22D1.1,TSC22D2, WNK4 and SPAK. Western blots of cell lysates and immunoprecipitated proteins and immunofluorescent stainings were performed.

Results: We observed that mutations in the CCT domain of WNK4 dramatically decreased WNK4's activity, TSC22D2 binding, and colocalization of WNK4 with TSC22Ds in condensates. Interestingly, SPAK co-expression allowed for TSC22D2 recruitment into condensates formed with the WNK4-CCT mutant. The loss of both, the CCT domains and the RFXV motif in WNK4 produced an inactive WNK4 that was not activated by NRBP1/TSC22D2, and that was not able to co-localize in TSC22D condensates in the presence of SPAK.

Conclusions: In conclusion, our data show that TSC22D1.1, TSC22D2, and NRBP1 are novel components of WNK-bodies in vivo in the DCT. NRBP1 and long TSC22D isoforms positively modulate WNK activity. Heterotypic interactions established by the CCT domains and the RFXV motif of WNK kinases permit co-localization of WNKs with TSC22D proteins and NRBP1 in condensates and promote activation of the kinase. Redundancy in interactions between these proteins can preserve the activity of the pathway when one interacting motif or domain is affected.

Funding: Government Support - Non-U.S.

FR-PO563

CRISPR/Cas9 Screening Identifies Key Transcription Factors Regulating Aqp2 Gene Transcription

Lihe Chen, Adrian R. Murillo-de-Ozores, Euijung Park, Shuo-Ming Ou, Mark A. Knepper. *National Institutes of Health, Bethesda, MD.*

Background: Aqp2, responsible for water reabsorption in kidney collecting duct cells, plays a crucial role in water balance. Prior translational studies demonstrated that dysregulation of *Aqp2* transcription plays a central role in a variety of water balance disorders, yet the underlying regulation of *Aqp2* transcription remains unclear.

Methods: We engineered an mpkCCD cell line to express GFP under the control of the *Aqp2* promoter and also stably express Cas9 and designed a lentiviral sgRNA library targeting over 1500 transcription factors (TFs) in the mouse genome. We then conducted CRISPR/Cas9 screens to identify TFs involved in regulation of *Aqp2* transcription.

Results: We demonstrated that the GFP provided a quantitative readout of Aqp2 and was sensitive to the stimulation of dDAVP and consequently could be used for the TF screen based on flow sorting. Two independent screens using the sgRNA TF library were carried out and the cells were sorted based on the GFP expression levels. The enrichment of sgRNA sequences was analyzed by *MAGeCK*. We hypothesize that sgRNAs targeting positive regulators of *Aqp2* would be enriched in GFP^{negative}/GFP^{low} relative to GFP^{high}, while those sgRNAs targeting negative regulators would show enrichment in GFP^{high} relative to GFP^{negative}/GFP^{low}. The screens identify several known positive regulators for *Aqp2* including *Gata3*, *Nfat5*, *Hnf1b*, *Grhl2*, *Nr3c1*, and *Pax8*. In addition, the analyses identify some novel positive regulators, among these are transcription factors that form DNA-binding heterodimers, transcription factors that are associated with histone modifications and chromatin remodelers, and several zinc finger TFs. For each of these candidates, cell lines with loss-of-function mutations were generated. Among the cell lines lacking the positive regulators, *Gata3*KO, *Nfat5*KO, *Hnf1b*KO, and *Nr3c1*KO cell lines showed no increase in the abundance of Aqp2 protein with dDAVP in contrast to control cell lines that showed large increases. Subsequent RNA-seq confirmed modulation of *Aqp2* transcripts upon knockout of the candidate transcription factors. Further ATAC-seq analyses identified critical DNA elements involved in *Aqp2* transcription.

Conclusions: CRISPR/Cas9 identifies both positive and negative regulators for *Aqp2* transcription, significantly expanding our understanding of *Aqp2* gene regulation.

FR-PO564

Kidney Tubuloid Model to Study Aquaporin 2-Mediated Water Transport in the Collecting Duct

Joost Hoenderop,[1] Emre Dilmen,[1] Charlotte Olde Hanhof,[1] Femke Latta,[1] Marianne C. Verhaar,[2] Idil Orhon,[1] Jeroen H. De Baaij,[1] Jitske Jansen.[3] [1]*Radboud Universitair Medisch Centrum, Nijmegen, Netherlands;* [2]*University Medical Center Utrecht, Utrecht, Netherlands;* [3]*Universitatsklinikum Aachen, Aachen, Germany.*

Background: The last segment of the kidney tubules is the collecting duct (CD), where finetuning of sodium and water reabsorption occurs. A dysfunction of this process can lead to nephrogenic diabetes insipidus (NDI) that causes the inability to concentrate urine which can lead to severe dehydration. NDI is caused by dysfunction of the water channel aquaporin 2 (AQP2) or the vasopressin 2 receptor (V2R) in the CD. Despite promising results of pre-clinical experiments, clinical trials often fail due to ineffectiveness or side-effects. Tubuloids are kidney organoid models that are derived from adult stem cells with the promise to study kidney (patho) physiology with increased translational value compared to conventional in vitro research models. By utilizing these tubuloid models, our lab previously demonstrated functional CD-specific sodium regulation. In this study, we show that tubuloids are capable of physiological CD-specific water transport regulation by AQP2 and V2R.

Methods: Tubuloids derived from human kidney tissue were grown were exposed to differentiation medium and differential expression was studies by single cell RNA-seq. The differentially expressed genes were studied by gene ontology analysis. The CD marker and water transporter AQP2 expression and localization was characterized by western blot and immunocytochemistry. Functional water transport assay was performed by measuring swelling over time.

Results: Tubuloids can be differentiated towards the distal tubules, including CD as shown by single cell sequencing. Further experiments revealed that the endogenously expressed AQP2 can be regulated by forskolin and desmopressin shown by significantly increased expression of AQP2 protein. In addition, the translocation towards the apical membrane of AQP2 where it increases water permeability was observed. Finally, we performed 3D swelling assays which confirmed that CD tubuloids are indeed capable of increased water transport and thereby respond to stimuli by swelling.

Conclusions: Human kidney tubuloids endogenously express relevant markers for CD-specific water transport, and AQP2 signaling regulated by physiological stimuli which is measurable in 3D functional assays. These results further confirm that kidney tubuloid models hold great promise to study kidney (patho) physiology, including NDI.

FR-PO565

Single-Cell CRISPR Screening Is a Powerful Tool for Gene Regulatory Network Studies in Kidney Collecting Ducts

Shuang Cao,[1,2] Karen I. López-Cayuqueo,[1] Kai M. Schmidt-Ott.[1,2]
[1]Medizinische Hochschule Hannover, Hannover, Germany; [2]Charite Universitatsmedizin Berlin, Berlin, Germany.

Background: The renal collecting duct plays a crucial role in maintaining the body's fluid and electrolyte balance, which is essential for overall physiological homeostasis. However, the molecular mechanisms governing the functions of the medullary collecting duct remain insufficiently understood. Recent advancements in single-cell genomics and CRISPR-based genetic tools have opened new avenues for dissecting the complex regulatory networks. By identifying and characterizing the molecular regulators of the renal collecting ducts, we can gain deeper insights into their physiological mechanisms and potentially uncover novel understandings of collecting duct disorders.

Methods: 1. SCENIC analysis: We used established snRNA-seq data from mouse kidneys and applied SCENIC methods to construct cell type-specific regulatory networks, and identified regulons based on gene co-expression and binding motifs. 2. Identification of transcription factors: From the constructed networks, we identified 24 specific transcription factors associated with collecting duct principal cells that exhibited significant gene regulatory network activities. 3. CRISPR-based single cell screen: To investigate the biological functions of these 24 TFs, we performed a CRISPR-based single cell screen experiment in an in vitro mIMCD3 cell model, perturbing TF expression and assessing the resulting transcriptomic phenotypes to understand their impact on gene expression profiles.

Results: The single-cell CRISPR screen effectively reproduced the transcriptional regulatory influence of the established transcription factor Grhl2 on downstream target genes, including Cldn4. The perturbation of the transcriptome profile of this transcription factor, which served as a central quality control parameter for the entire screen experiment, demonstrated the reliability of the study conducted. Among 24 candidates, we identified the transcription factor Ilf2 as a novel potential functional regulator of medullary collecting duct cell homeostasis.

Conclusions: Our study highlights the potential of CRISPR single cell screening as a powerful tool for uncovering the functions of novel genes in kidney cells. This approach improves our understanding of the molecular mechanisms involved in collecting duct cell physiology and provides a promising framework for future kidney disease research in nephrology.

FR-PO566

Artificial Intelligence (AI)-Based Prospective Repurposing Studies for the Identification of New Promising Vasopressin V2 Receptor Ligands

Ines Angelini,[1] Daniela Trisciuzzi,[2] Mariangela Centrone,[1] Annarita Di Mise,[1] Marianna Ranieri,[1] Giovanna Valenti,[1] Cosimo D. Altomare,[2] Susanna Cotecchia,[1] Orazio Nicolotti,[2] Grazia Tamma.[1] *[1]Department of Biosciences, Biotechnologies and Environment, University of Bari "Aldo Moro", Bari, Italy; [2]Department of Pharmacy - Pharmaceutical Science, University of Bari Aldo Moro, Bari, Italy.*

Background: The vasopressin V2 receptor (V2R) controls renal water balance. As a G protein-coupled receptor (GPCR), the V2R transduces the vasopressin signals activating the cAMP/PKA pathway. Besides water reabsorption, the activation of V2R is involved in abnormal cell proliferation, cancer, and cyst enlargement in polycystic kidney disease. In this perspective, we performed an inverse screening of a large collection of known drugs to identify novel V2R ligands that might modulate different receptor-mediated effects.

Methods: The inverse screening campaign was run by using PLATO, our homemade target fishing platform. Structure-based studies were also carried out. Renal collecting duct MCD4 cells, stably expressing human V2R and aquaporin-2 (AQP2), were used as an experimental model to test the effects of drugs. Fluorescence Resonance Energy Transfer (FRET), and calcein fluorescence quenching (CFQ) were applied to evaluate changes in intracellular cAMP and DDAVP-induced water flux.

Results: Our prospective repurposing studies identified five promising drugs as potential V2R ligands (perphenazine, cloxacillin, clopidogrel, cabergoline, and F2544). FRET studies were conducted to test whether these compounds affect the DDAVP-induced cAMP responses. Interestingly, only one of them (F2544) at 1nM concentration significantly reduced the DDAVP-dependent cAMP production. Functional CFQ studies revealed that this modulator reduced the DDAVP-induced water reabsorption, with effects comparable to tolvaptan, a well-known V2R antagonist. In this respect, an *in-depth* computational investigation showed a nice overlap of the molecular interaction fields generated from the binding sites of V2R and F2544. Finally, molecular docking simulations returned a promising posing and scoring of F2544 in the V2R binding site.

Conclusions: The present findings identify for the first time new V2R ligands by applying an AI-based approach. Moreover, by combining *in-depth* computational investigations and functional studies F2544 was prioritized for being repurposed for treating diseases associated with abnormal V2R signaling.

Funding: Government Support - Non-U.S.

FR-PO567

CRISPR/Cas9 Screening for Protein Kinases That Regulate Aquaporin-2 Gene Transcription in Collecting Ducts

Euijung Park, Lihe Chen, Mark A. Knepper. *National Heart Lung and Blood Institute, Bethesda, MD.*

Background: Water transport in the collecting duct is controlled in part through regulation of transcription of the gene that codes for aquaporin-2 (AQP2). Animal models of water balance disorders have revealed defective control of AQP2 transcription in both polyuric and water retention disorders. Here, we have used CRISPR screening of the entire kinome in a mouse cortical collecting duct cell line (mpkCCD) to identify protein kinases that regulate AQP2 gene transcription.

Methods: A CRISPR knockout pooled library was utilized, targeting 713 protein kinases with 4 guides (gRNAs) for each gene. These gRNAs were simultaneously transduced into GFP-reporting mpkCCD cells, allowing GFP as a reporter for AQP2 transcription. In the presence of vasopressin analog dDAVP, the gRNA-transduced cells were sorted into four groups (GFP-negative, low, mid, and high) based on GFP intensity. RNA sequencing was then performed to identify the targeted kinases.

Results: Among 713 targets, 29 protein kinases showed significant bias in GFP abundance including 16 positive regulators of AQP2 gene transcription and 13 negative regulators. One positive regulator was PKA catalytic α (Prkaca) that had been previously identified as a positive regulator. Conversely, PKA regulatory subunit (Prkar1a), is known to inhibit PKA catalytic subunit, was identified as a negative regulator. These findings provide positive controls for the methodology. Novel positive regulators include AKT1, PIM3 and the polarity kinase MARK2. Negative regulators include both subunits of the TGF-β receptor (previously implicated in the vasopressin escape phenomenon) and several components of the stress-activated MAP kinase pathway (Map3k1, Map2k4, and Map2k7).

Conclusions: Whole kinome CRISPR screening identified 29 protein kinases as putative regulators of AQP2 gene transcription. Pending one-by-one systematic validation of roles for each kinase as determinants of AQP2 protein abundance, the data will provide a basis for understanding mechanisms involved in defective transcription of the AQP2 gene in water balance disorders and a valuable information resource guiding future studies of regulation in collecting duct principal cells.

FR-PO568

GPR39 Activation Alters Cytoskeleton Integrity and AQP2 Trafficking in Collecting Duct Cells

Mackenzie Kui,[1] Helle A. Praetorius,[2] Jennifer L. Pluznick.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]Aarhus Universitet, Aarhus, Denmark.*

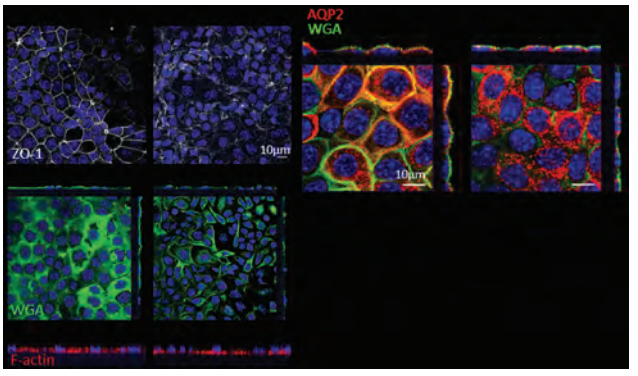
Background: Despite being highly expressed in the kidney, the G-protein coupled receptor, GPR39, has no known role in renal physiology.

Methods: A Gpr39 RNAScope probe was used to localize renal Gpr39. Activation by a GPR39-specific agonist, cpd1324, was used in murine principal kidney cortical collecting duct cells (mpkCCDs); we also utilized GPR39 knockout (KO) cells (made via CRISPR). mpkCCD respond to vasopressin (dDAVP) by expressing and trafficking AQP2 to the apical membrane. Endpoint assays included immunofluorescence (IF), transepithelial resistance (TER), Western Blots (WB) and cAMP assays.

Results: RNAScope for Gpr39 and IF for aquaporin 2 (AQP2) revealed colocalization of Gpr39 transcripts in AQP2-positive cells of the inner medullary and cortical collecting ducts. To study the effect of GPR39 activation, mpkCCD cells were treated with 1μM GPR39 agonist cpd1324 with 10μM cofactor $ZnCl_2$ or $ZnCl_2$ alone. After 4 hours, cpd1324 impaired TER (WT/veh=12.5±0.7, WT/cpd = 0.92±0.35, KO/veh = 7.9±0.2, KO/cpd = 8.9±0.3, n=3 per condition ($k\Omega x cm^2$), disrupted tight junctions (zona occludens-1 (ZO-1), Fig 1A), altered apical membrane morphology (apical marker wheat germ agglutinin (WGA), Fig 1B), targeted F-actin to the basolateral compartment (phalloidin, Fig 1C), and induced AQP2 internalization (Fig 2). After 24 hours of treatment, AQP2 was degraded (by WB), but the cytoskeleton morphology and TER recovered. These effects were not seen in GPR39 KO cells. In cAMP assays, 15-minute dDAVP treatment induced cAMP accumulation from 206.5±0.3 pmol/mL to 213.11±1.3 pmol/mL; however, 4h and 24h pretreatment with cpd1324 only reduced dDAVP-mediated cAMP pools to 211.3±0.6 and 210.0±1.5 pmol/mL, respectively. These data suggest that the effect on AQP2 and the cytoskeleton are only minimally affected by reductions in V2-receptor signaling.

Conclusions: These data suggest that the effect on AQP2 and the cytoskeleton are only minimally affected by reductions in V2-receptor signaling.

Funding: NIDDK Support



FR-PO569

The TRIM28-PARP1-CTNNB1 Complex Is Associated with the Transcriptional Elongation Machinery for Aqp2 Gene Transcription

Hyo-Ju Jang,[1] Euijung Park,[2,4] Hyun Jun Jung,[3] Tae-Hwan Kwon.[1]
[1]Kyungpook National University School of Medicine, Daegu, Republic of Korea; [2]National Heart Lung and Blood Institute, Bethesda, MD; [3]The Johns Hopkins University School of Medicine, Baltimore, MD; [4]National Institutes of Health, Bethesda, MD.

Background: Vasopressin enhances water reabsorption in collecting duct cells by increasing the abundance of Aquaporin-2 (AQP2) through transcriptional and post-translational mechanisms. We recently discovered that a complex comprising CTNNB1 and PARP1 acts as a transcriptional regulator of Aqp2 gene transcription in response to vasopressin. In this study, we introduce a Bromodomain protein, Tripartite motif-containing 28 (TRIM28; also known as KAP1), into the transcriptional machinery that controls RNA polymerase II (RNA Pol II) transcription elongation in the AQP2 regulation.

Methods: For in vitro experiments, we used the mouse collecting duct cell line mpkCCDc14, grown on semipermeable filters and treated with dDAVP for 24 h to induce AQP2 expression. We applied siRNA-mediated knockdown of Ctnnb1 or Trim28 using a reverse transfection strategy. RNA sequencing (RNA-Seq) was then conducted on mpkCCD cells with Ctnnb1 knockdown. We employed immunolabeling and immunoblotting to verify TRIM28 protein expression in kidney tissues and immunoprecipitated proteins.

Results: RNA-Seq demonstrated that dDAVP significantly induces Aqp2 expression, which is reduced after Ctnnb1 knockdown. Bioinformatic analysis identified transcriptional regulators related to the promoters of genes differentially expressed after dDAVP treatment or Ctnnb1 knockdown, and highlighted the role of these regulators in RNA Pol II modulation. Bioinformatics and immunoprecipitation assays identified several Bromodomain proteins, including TRIM28, as interacting partners of CTNNB1 and PARP1 associated with RNA Pol II elongation. Immunohistochemistry demonstrated the nuclear presence of TRIM28 in mouse kidney collecting duct cells. Importantly, siRNA-mediated knockdown of Trim28 in mpkCCDc14 cells significantly reduced the dDAVP-induced Aqp2 gene expression, observable at both mRNA and protein levels after 6 and 24 h of treatment. An immunoprecipitation assay further confirmed a direct interaction between TRIM28 and RNA Pol II.

Conclusions: This study reveals TRIM28 as a crucial element of the transcriptional machinery that regulates RNA Pol II activity in the transcription of the Aqp2 gene. These findings provide insights into the transcriptional regulation of Aqp2, highlighting the role of the TRIM28-containing regulatory complex in controlling RNA Pol II function.

Funding: Government Support - Non-U.S.

FR-PO570

Development of Direct AQP2 Water Channel Inhibitors

Chisato Takahashi,[1] Shinya Harada,[1] Shotarou Michizoe,[1] Makoto Abe,[1] Yumi Noda,[2] Sei Sasaki,[2] Tatemitsu Rai.[1] *[1]Dokkyo Ika Daigaku, Shimotsuga-gun, Japan; [2]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan.*

Background: The regulation of urinary output is essential for the maintenance of body fluid homeostasis. Loss-of-function mutations of aquaporin-2 (AQP2) water channel cause renal diabetes insipidus and severe dehydration. In contrast, gain of function of AQP2 is implicated in the pathogenesis of congestive heart failure, liver cirrhosis, and SIADH. Inhibitors of AQP2 are expected to be potent pure water diuretics with few side effects, but their development has not been successful so far.

Methods: The objective of this study is to establish a drug screening system for the development of direct inhibitors of AQP2. 1. mpkCCDcl4 cells, which are immortalized cultured cells derived from renal collecting duct epithelial cells of SV40 large T cell antigen transgenic mouse, were utilized. The expression of AQP2 in mpkCCDcl4 cells and its cellular localization upon vasopressin stimulation were confirmed by Western blotting and fluorescent immunostaining. 2. mpkCCDcl4 cells were seeded on semipermeable filters (96-well polycarbonate Transwell plate, 0.4-μm pore size) to form an epithelial cell layer. Sucrose was added to the basolateral side to apply high osmotic pressure (Δ 850 mOsm). Water permeability was evaluated by the decrease in volume of the apical compartment. 3. Small molecule compounds in the compound library were applied to the apical compartment of this system to screen for the water permeability inhibitory effect of each compound. DMSO was applied as a negative control.

Results: 1. mpkCCDcl4 cells expressed AQP2, which showed polarized trafficking to the apical plasma membrane in response to vasopressin stimulation. 2. In mpkCCDcl4 cells cultured in a 96-well Transwell plate, the volume of fluid transported from the apical to the basolateral side were 27.2±1.6% of the initial volume (mean±SD, n=8) in the presence of osmotic gradient. Osmotic water flux across the grown cells was inhibited by 0.3 mM $HgCl_2$. 3. Among the 156 compounds applied for initial screening, 13 compounds exerted inhibitory effect on osmotic water flux by under -2SD of the negative control.

Conclusions: An effective screening system was established to evaluate the water permeability of AQP2 using cultured cells. Initial screening of small-molecule compounds revealed several compounds with possible water permeability inhibitory effects.

FR-PO571

Can Acetylation of Lysine 282 of Aquaporin 3 Improve Urinary Concentration in Mice with Lithium-Induced Nephrogenic Diabetes Insipidus?

Nha V. Huynh, Cassidy Rehage, Phi-Hung Nguyen, Kelly A. Hyndman.
The University of Alabama at Birmingham Division of Nephrology, Birmingham, AL.

Background: The principal cell basolateral water channel AQP3 is decreased in lithium-induced nephrogenic diabetes insipidus (NDI) and AQP3-null mice have an NDI phenotype with polyuria. We previously identified a novel AQP3 post-translational modification, acetylation of lysine 282 (K282), which we found to affect protein membrane localization. We hypothesized that lysine acetylation of AQP3 may improve the polyuria in NDI.

Methods: Mice with homozygous mutations of AQP3 K282R (deacetylated mimetic, R) or K282Q (acetylated mimetic, Q) were compared to wild type K282 (WT) mice. Male and female 11–16-week-old mice were fed a lithium-containing diet or control diet (40 mmol LiCl or NaCl/kg dry food) for 14 days (n = 5-6/group). 24 h food and water intake, urine flow, and plasma osmolality at day 14 were measured.

Results: On the control diet, food intake (WT 6.8±0.3, Q 6.3± 0.7, R 6.2±0.8 g/day, p=0.9), water intake (WT 3.6±0.3, Q 3.4±0.3, R 4.0±0.2, p=0.9), and urine flow (WT 1.4±0.4, Q 1.3±0.3, R 1.3±0.3 ml/day, p = 0.9) were similar among the male mice. The control diet females also had similar food intake (WT 6.4±0.4, Q 6.2±0.3, R 6.2±0.7 g/day, p = 0.38), water intake (WT 3.2±0.3, Q 3.4±0.2, R 3.9±0.4, p=0.9), and urine flow (WT 0.2±0.1, Q 0.5±0.1, R 0.5 ±0.2 ml/day, p=0.9). As expected, the lithium-diet fed mice developed polyuria/polydipsia. In male mice, food intake was lower in the WT (5.5±0.3 g/day) than Q and R (7.4±0.6 and 7.0±0.4 g/day, p = 0.02); however, R mutant mice had greater urine flow (12.8 ± 1.2 ml/day) than WT (4.8±0.5 ml/day) and Q mice (7.9±1.8 ml/day, p=0.0004). The females ate similar amounts of lithium diet (WT 6.4±0.3, Q 6.4±0.5, R 5.4±0.5 g/day, p=0.99) but urine flow was enhanced in Q (9.8±1.4 ml/day) and R (8.5±1.3 ml/day) mice compared to WT (4.8±0.5 ml/day, p=0.02). Water intake was significantly increased in all lithium-fed mice regardless of genotype (p<0.001). There were no significant effects of treatment or genotype on plasma osmolality among the groups.

Conclusions: Contrary to our hypothesis, AQP3 acetylation- and deacetylation-mimetics had worsened polyuria in lithium-induced NDI, suggesting that K282 is an important regulatory site for AQP3 function perhaps independent of acetylation status.

Funding: NIDDK Support

FR-PO572

Downregulation of the Vasopressin-AQP2 Pathway Explains Secondary Nephrogenic Diabetes Insipidus Associated with Cystinosis: In Vivo and In Vitro Evidence

Angela Ferrulli,[1,2] Rik Gijsbers,[2] Annarita Di Mise,[1] Arend Bokenkamp,[4] Sara Cairoli,[5] Grazia Tamma,[1] Lambertus P. Van den Heuvel,[2,3] Elena Levtchenko,[4] Giovanna Valenti.[1] *[1]Universita degli Studi di Bari Aldo Moro, Bari, Italy; [2]Katholieke Universiteit Leuven, Leuven, Belgium; [3]Radboud Universiteit, Nijmegen, Netherlands; [4]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [5]Ospedale Pediatrico Bambino Gesu, Roma, Italy.*

Background: Cystinosis, an autosomal recessive lysosomal storage disease, is caused by mutations in the *CTNS* gene, encoding cystinosin, leading to the accumulation of cystine. Kidneys are the first and most affected organs, with severe tubular dysfunction and glomerular damage. Secondary Nephrogenic Diabetes Insipidus (NDI) has been reported in cystinosis. The lack of a collecting duct *in vitro* model for cystinosis has however limited the research on the mechanisms involved in the impairment of urine concentrating ability. In this study, we established the first mouse collecting duct *in vitro*

model knocked out for *CTNS* using the CRISPR/Cas9 technology. In parallel, the renal response to vasopressin was tested in four cystinosis patients.

Methods: By employing virus-like particles carrying CRISPR/Cas9 technology, *CTNS* was efficiently knocked out in MCD4 cells, a mouse renal collecting duct cell line stably expressing the human AQP2 and the vasopressin receptor 2 (V2R). Sanger sequencing, qPCR and mass spectrometry were performed to validate the editing efficiency and assess cystine accumulation. Urinary AQP2 excretion in cystinosis patients was evaluated by ELISA.

Results: The CTNS KO cell line showed a strong reduction of AQP2 expression. In CTNS KO cells, exposure to desmopressin did not increase osmotic water permeability, likely due to reduced AQP2 expression. Interestingly, inhibition of the autophagic pathway by chloroquine treatment resulted in a significant increase in AQP2 expression, indicating that the observed AQP2 reduction in CTNS KO cells is mediated by enhanced autophagic degradation. In cystinosis patients, AQP2 excretion, a biomarker for collecting duct responsiveness to vasopressin, did not significantly increase after desmopressin administration and urine osmolarity remained below 800 mOsm/L.

Conclusions: In conclusion, we established the first collecting duct *in vitro* model for the study of secondary NDI associated with cystinosis, demonstrating that vasopressin resistance associated with cystinosis depends on reduced expression of AQP2 due to autophagy-mediated degradation. These data together with the *in vivo* study indicate that secondary NDI in cystinosis is due to a defect in the vasopressin-AQP2 axis.

Funding: Government Support - Non-U.S.

FR-PO573

Elexacaftor/Tezacaftor/Ivacaftor (ETI) Treatment Corrects the Salt-Losing Phenotype in People with Cystic Fibrosis

Jens G. Leipziger,[1] Samuel L. Svendsen,[1] Amalie Q. Rousing,[1] Sascha Bandulik,[2] Richard Warth,[2] Mads V. Sorensen,[1] Majbritt Jeppesen,[3] Peder Berg.[1] *[1]Aarhus Universitet, Aarhus, Denmark; [2]Universitat Regensburg, Regensburg, Germany; [3]Aarhus Universitetshospital, Aarhus, Denmark.*

Background: PwCF have an increased risk for fluid and electrolyte imbalances caused by fluid and salt loss. Congruently, guidelines advocate increased salt intake. In this study, we investigate the effect of ETI treatment on blood pressure and fluid- and electrolyte homeostasis in pwCF.

Methods: We quantified the effect of 6 months ETI treatment in pwCF (n=45) on blood pressure; electrolyte- and acid-base balance; aldosterone levels; and the diuretic response to an oral $NaHCO_3$ loading test. Furthermore, to explore sweat-independent pathophysiological mechanisms contributing to the phenotype of pwCF, we NaCl-depleted CF, pendrin KO, and WT mice for 7 days. Hereafter, the renal adaptation and systemic electrolyte and acid-base homeostasis were assessed.

Results: In pwCF, ETI treatment increased: blood pressure, venous Na^+, and the diuretic response to oral $NaHCO_3$-loading. Congruently, treatment markedly decreased heart rate, aldosterone levels, venous tCO_2 and the proportion of pwCF with low Na^+ levels. In CF mice, NaCl depletion caused lower Na^+, K^+, and Cl^- levels while HCO_3^- and aldosterone levels were increased. Interestingly, CF mice failed to increase renal pendrin protein abundance. During NaCl depletion, pendrin KO mice developed severe hyponatremia, hypochloremia, hypokalemia, metabolic alkalosis, and weight loss.

Conclusions: In pwCF, ETI treatment improves NaCl and fluid conservation. CF mice have an impaired ability to retain salt and fluid when NaCl-depleted, which is explained by insufficient renal pendrin regulation. Hence, part of the treatment effect in pwCF is likely attributed to correction of renal CFTR. Salt repletion appears less necessary in ETI-treated pwCF.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO574

Influence of Murine Background Strain on Renal Water Balance and Urine Concentration

Sarah Christine Whelan, Stephanie Mutchler, Thomas R. Kleyman, Shujie Shi. *University of Pittsburgh, Pittsburgh, PA.*

Background: Kidneys are essential in maintaining body fluid and electrolyte balance. Several mouse strains, specifically C57 and 129, are widely used for studying renal physiology and diseases. Previous observations suggest background strains influence urinary behaviors and diuretic responses in mice; however, a systematic analysis has not yet been performed and the underlying mechanisms for these differences remain unclear.

Methods: The present study aims to examine differences in salt and water handling between the C57 and 129 mouse strains. Adult male mice were housed in metabolic cages for 24-hour urine collection. Weight, water, and food intake were measured daily. At the end of the study, mice were sacrificed for blood and tissue collections.

Results: We show that while C57 mice demonstrate greater 24-hour water consumption and 24-hour urinary output, plasma osmolality and blood chemistry between strains remain comparable. Both strains demonstrate greatest urination during dark periods. Despite having a greater body weight, kidneys were significantly smaller in C57 male mice compared to 129s. Western blot reveals C57 mice have remarkably reduced expression of both the Na-K-Cl cotransporter (NKCC2) and renal outer medullary potassium channel (ROMK), suggesting reduced Na^+ reabsorption in the thick ascending limb of C57 mice. Notably, the expression of the sodium-chloride transporter (NCC) remains consistent between the two strains. Additionally, C57 mice show significantly less expression of several aquaporins (AQPs), specifically AQP1, AQP2, and AQP3; indicating impaired water reabsorption along the nephron. Taken together, our data suggests differences in sodium and water handling, as a consequence of NKCC2 and AQPs expression, contribute to the discrepancies in water balance and urine concentrating abilities seen between C57 and 129 mice. Finally, both uromodulin expression and PKA-phosphorylated substrate abundance were appreciably lower in the C57 strain and as such, may contribute to the decreased expression of AQP2 and NKCC2 by means of the vasopressin-cAMP-PKA pathway.

Conclusions: Our data emphasizes the idea that murine background strains are highly variable and should be considered in designing renal physiology studies.

Funding: NIDDK Support

FR-PO575

Tamoxifen Prevents the Lithium-Induced Increased Cilium Length and Necroptosis Reduction

Mariangela Centrone,[1] Ines Angelini,[1] Mariagrazia D'Agostino,[1] Annarita Di Mise,[1] Barbara Barile,[1] Grazia Paola Nicchia,[1] Stine Julie Tingskov,[2] Rikke Norregaard,[2] Giovanna Valenti,[1] Grazia Tamma.[1] *[1]Department of Biosciences Biotechnologies and Environment, University of Bari Aldo Moro, Bari, Italy; [2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.*

Background: Lithium is often used to treat some mental illnesses including bipolar disease. However, numerous adverse effects have been reported including acquired nephrogenic diabetes insipidus, a disorder characterized by a defective renal concentrating ability that causes a significant water loss. Tamoxifen, an estrogen receptor modulator, mitigates the onset of lithium-induced NDI by regulating the expression and function of AQP2 and AQP3.

Methods: Renal collecting duct MCD4 cells were used as an experimental model. *Ex vivo* and *in vivo* experiments were performed as well. Western Blotting analysis was applied to evaluate the expression and function of proteins involved in controlling cell deaths.

Results: *Ex vivo* and *in vivo* experiments revealed that treatment with Tamoxifen prevented the lithium-induced reduction in necroptosis. Specifically, Western Blotting data showed that lithium administration significantly decreased the expression levels of RIPK3 and MLKL which are key players in controlling necroptosis. Conversely, these effects were prevented by Tamoxifen treatment. *In vitro* experiments confirmed those findings. Also, a decrease in the expression of BID and an increase of beclin, selective markers of apoptosis and autophagy respectively, were found as well. Moreover, lithium exposure increased cell proliferation, the transepithelial electrical resistance (TEER), and the length of the primary cilium as assessed by the super-resolution stimulated emission depletion (STED) microscopy. The lithium responses were prevented by Tamoxifen treatment.

Conclusions: Together, these data revealed for the first time that exposure of renal collecting ducts to lithium resulted in a significant reduction in the expression level of selective markers of necroptosis. In addition, lithium promotes inappropriate cell proliferation possibly associated with increased transepithelial electrical resistance and elongation of the primary cilium. All these effects are prevented by Tamoxifen.

Funding: Government Support - Non-U.S.

FR-PO576

Claudin-3: Physiological Role in Renal Cortical Collecting Duct

Thibaut Charlemagne, Alexandra Chassot, Eric Feraille, Ali Sassi. Eric Feraille's Group. *Department of Cellular Physiology and Metabolism, Faculty of Medicine, Geneva, Switzerland.*

Background: In the kidney, ion and fluid transport across epithelia can occur *via* the transcellular or paracellular pathways. Tight junctions play a key role in mediating paracellular ion reabsorption in the kidney. The renal collecting duct (CD) is the place of fine tuning of Na+ reabsorption and it is mainly regulated by aldosterone. Aldosterone classically regulates Na+ transport through the transcellular pathway. We hypothesized that aldosterone modulates also the paracellular pathway. Paracellular ion permeability is mainly dependent on tight junction permeability. Claudin-3 is one of the main tight junction proteins expressed along the CD.

Methods: We used cultured mouse CD principal cells (mCCD) and mouse models to study the effects of aldosterone on claudin-3. Overexpression and silencing of claudin-3 were used to assess the paracellular permeability of claudin-3. WT and claudin-3 knockout male mice were fed for 7 days with either low (0.01 %), normal (0.18 %) or high sodium (1.25 %) diet. One group of mice fed a low sodium diet received 0.35 mg/100g body wt/day of spironolactone for 7 days.

Results: We showed that aldosterone increased protein levels of claudin-3 in cultured CD principal cells. Overexpression of claudin-3 was associated with a reduction in paracellular permeability to sodium and chloride, whereas silencing of claudin-3 was associated with the opposite effect. We also showed that a low-salt diet, which stimulated aldosterone secretion, was associated with increased claudin-3 abundance in the mouse kidney. Reciprocally, mice treated with spironolactone, a mineralocorticoid receptor antagonist, displayed decreased claudin-3 expression. Importantly, claudin-3 knockout mice displayed increased γ-ENaC and claudin-4 protein abundance under low-salt diet compared to WT mice.

Conclusions: Our results show that aldosterone modulates the expression of claudin-3 and that claudin-3 acts as paracellular NaCl barrier. We also show a specific adaptation of clausin-3 deficient mice to low-salt diet. Claudin-3 may then play an important role in preventing the backflow of reabsorbed NaCl.

FR-PO577

Role of H,K-ATPase 2 in the Response to Mineralocorticoid Excess

Luciana Morla,[1,2] I. Jeanette Lynch,[3] Lydie Cheval,[1,2] Samia Lasaad,[4] Justine Billiet,[1,2] Gilles Crambert,[1,2] Charles S. Wingo.[3,5] Physiologie Rénale et Tubulopathies. *[1]CNRS EMR8228, Paris, France; [2]Centre de Recherche des Cordeliers, UMRS1138, Paris, France; [3]University of Florida, Gainesville, FL; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]North Florida/South Georgia Veterans Health System, Gainesville, FL.*

Background: Aldosterone is a key hormone in blood pressure maintenance. In excess, aldosterone induces an increase in Na retention and blood volume. Natriuretic factors come into play to inhibit renal Na absorption and escape aldosterone effects. We have recently identified a Na secretion pathway (Morla et al 2016) involving the renal H,K-ATPase type 2 (HKA2) and the basolateral, bumetanide sensitive, cotransporter NKCC1, in the collecting duct. Here we ask if HKA2 plays a role in the aldosterone escape.

Methods: We treated wild type (WT) and HKA2KO (KO) mice with a normal salt diet (0.3% NaCl) and deoxycorticosterone pivalate (DOCP), an aldosterone analogue. We performed microperfusion of cortical collecting ducts (CCD) of DOCP treated WT and HKA2KO. We determined Na net fluxes before and after adding bumetanide to the bath. We studied mice in metabolic cages to determine daily Na urine excretion before and after DOCP treatment. During the escape phase: after 2 days of DOCP treatment (D2), we tested the effect of amiloride on urine Na excretion.

Results: DOCP treated WT and KO mice CCDs showed net Na reabsorption flux which declined over time in DOCP WT mice CCDs ($p<0.04$). This decrease was blunted in KO mice CCDs and in WT mice bumetanide-treated CCDs. DOCP induced urine Na retention in both mice groups 24h after DOCP injection. WT mice recovered a normal Na balance on D2 but KO mice excreted much more Na in their urines than WT mice and failed to keep a normal Na balance. Immunoblot analysis of D2 WT and KO mice kidneys showed similar increase of the expression of the NaCl cotransporter NCC. Interestingly, we found a smaller increase of the epithelial Na channel subunit αENaC ($p<0.001$) and a greater decrease of γENaC ($p<0.05$) in DOCP treated KO mice, when compared to DOCP treated WT mice suggesting ENaC could be less active in the KO mice. To confirm our hypothesis, we compared the effect of amiloride in WT and KO mice on D2 and found KO mice excreted less Na after amiloride treatment than WT mice ($p<0.02$).

Conclusions: Our data suggest that during the aldosterone escape, renal H,K-ATPase type 2 Na secretion in the CCD is necessary for Na balance maintenance. To compensate the exagerated Na retention, WT mice secrete Na through HKA2. In HKA2KO mice, ENaC inhibition in he CCD could allow to escape at the price of a greater Na loss.

Funding: Government Support - Non-U.S.

FR-PO578

Renal Kallikrein-1 Contributes to Cleavage of Gamma-Epithelial Sodium Channel (ENaC) in Response to a Short-Term, Low-Sodium, High-Potassium Diet

Joshua N. Curry,[1] Xiao-Tong Su,[1] Yujiro Maeoka,[2] Chao-Ling Yang,[1] Eric J. Delpire,[3] Paul A. Welling,[4] David H. Ellison.[1] *[1]Oregon Health & Science University, Portland, OR; [2]Hiroshima Daigaku Byoin, Hiroshima, Japan; [3]Vanderbilt University Medical Center, Nashville, TN; [4]Johns Hopkins Medicine, Baltimore, MD.*

Background: Tissue kallikrein, encoded in part by *Klk1*, is a serine protease that has been proposed to cleave and activate Na^+ channels (ENaC). In the kidney, kallikrein-1 is found primarily in the aldosterone sensitive distal nephron, and its transcript abundance is markedly reduced by deletion of the mineralocorticoid receptor. While global deletion of kallikrein-1 leads to defective renal K^+ handling and reduced gamma-ENaC cleavage, it is not clear if these findings result from loss of renal kallikrein-1 or from systemic abnormalities observed with global kallikrein-1 loss.

Methods: In order to determine the direct effects of renal kallikrein-1 on ENaC, we generated mice with conditional deletion of kallikrein-1 in the distal nephron: *Klk1*$^{fl/fl}$ Calbindin-Cre (KS-Klk1 KO). Mice were treated with either control (Ctrl, 0.49% NaCl, 1%. KCl) or low Na^+, high K^+ (LNHK, 0.03% NaCl, 5% KCl) diet for 5 days. On Day 4, urine was collected during 24 hours. Urine electrolytes were measured by flame photometry or colorimetric assay, and kallikrein activity was measured using amidolytic assay. Western blotting was used to quantify gamma-ENaC, with or without Peptide -*N*-Glycosidase F (PNGase F).

Results: Deletion of kallikrein-1 was confirmed by western blotting; it resulted in striking, but incomplete, reduction in urinary kallikrein excretion. Serum [K^+] was similar across genotypes on both Ctrl and LNHK diets. Urine [Na^+] and [K^+] excretion rates were also similar between genotypes. Cleaved gamma-ENaC was higher on LNHK than Ctrl diet in both groups, but the ratio of cleaved:uncleaved was not as high in KS-Klk1 KO (WT 3.3+/-0.04 vs KO 2.05+/-0.55). To improve ENaC resolution, we treated kidney samples with PNGase F. Under LNHK conditions the 52 kDa (distally cleaved) gamma-ENaC band was 52% lower in KS-Klk1 KO (WT 100% vs KO 51.5%, $p=0.006$). There was also a trend towards lower phosphorylated-NCC in the KS-Klk1 KO mice on LNHK diet, suggesting a compensatory response.

Conclusions: These results suggest that kidney kallikrein-1 contributes to, but is not the only protease, that cleaves gamma-ENaC at its distal site in response to a short-term low Na^+ and high K^+ diet. Further studies are needed to better understand how renal kallikreins are produced and their role in gamma-ENaC cleavage and ENaC function.

Funding: NIDDK Support, Other NIH Support - 1T32HL166128-01A1

FR-PO579

Kir4.1/Kir5.1 Channel Inhibition Acutely Ameliorates Hyperkalemia in Male Rats with Reduced Kidney Function

Sati A. Alexander,[1] Bianca Tubalinal,[1] Kathleen A. Coleman,[1] Jenny Nguyen,[1] Oleg Palygin,[2] Mykola Mamenko.[1] *[1]Augusta University, Augusta, GA; [2]Medical University of South Carolina, Charleston, SC.*

Background: Patients with advanced chronic kidney disease (CKD) can develop hyperkalemia, a life-threatening condition causing cardiac arrhythmia, paralysis, and death. Basic science lacks a suitable animal model that accurately reflects hyperkalemic states observed in patients with CKD, and there is an unmet need for novel pharmacological approaches managing hyperkalemia in CKD, as current interventions are fraught with adverse effects. Inhibition of the renal basolateral K^+ channels, like Kir4.1 and Kir4.1/5.1, does not rely on glomerular filtration and is an attractive target to treat hyperkalemia in patients with advanced CKD. Genetic deletion of either Kir4.1 or Kir5.1 protein leads to hypokalemia and salt wasting. Here, we test the hypothesis that pharmacological blockade of these channels provides an effective treatment against hyperkalemia.

Methods: First, we established a rat model of chronic hyperkalemia. To do this, ten 35-week-old Sprague-Dawley rats of both sexes underwent 5/6-nephrectomy moderately elevating serum K^+ levels to 5.3±0.3 mEq/L in males and 5.0±0.5 mEq/L in females. Nephrectomized rats were placed on a 10% KCl diet for 7 days to achieve persistent hyperkalemia with serum K^+ significantly increased to 6.9±1.1 mEq/L in males and 6.7±0.9 mEq/L in females. To assess the effect of Kir4.1 and Kir4.1/5.1 Kir channel inhibition on circulating potassium, a commercially available antagonist, VU0134992, was administered by oral gavage (100mg/kg) and serum K^+ concentration was measured at 4 and 24 hours after the treatment.

Results: In males, serum K^+ concentration was significantly reduced to 6.0±0.6 mEq/L and 5.8±0.8 mEq/L at 4 and 24 hours after VU administration, respectively. In females administered with VU serum K^+ remained comparable to pre-treatment levels at 6.5±0.6 mEq/L and 7.4±1.2 mEq/L at 4 and 24 hours after the intervention.

Conclusions: Our study establishes 5/6 nephrectomized rats on a 10% KCl diet as a model of chronic hyperkalemia. Inhibition of Kir4.1 and Kir4.1/5.1 Kir channels acutely reduces serum K^+ levels in hyperkalemic male rats with reduced renal function, but not in females.

Funding: NIDDK Support

FR-PO580

Sex- and Cell-Specific Changes in BKα Protein Expression in the Aldosterone-Sensitive Distal Nephron (ASDN) in Response to Dietary K+

Samia Lasaad, Lisa M. Satlin, Rolando Carrisoza-Gaytan. *Icahn School of Medicine at Mount Sinai Department of Pediatrics, New York, NY.*

Background: Within the cortical collecting duct (CCD) of the ASDN, BK channels are essential for renal adaptation to a high K^+ diet (HKD) and mediate flow-induced K^+ secretion. We have previously reported that dietary K^+ loading for 10 d leads to an increase in whole-cell BKα protein expression in female rabbits and channel activity in male mice (Carrisoza-Gaytan et al. 2017, 2020). In whole kidney immunoblots, expression of BKα in females exceeds that in males (Yu et al. 2017). The purpose of this study was to examine the sex- and cell-specific responses to dietary K^+ over an 11 d period on BKα protein expression and subcellular distribution in mouse CCD.

Methods: 8-wk-old male (M) and female (F) C57BL/6 mice maintained on a control diet (2.4% K^+), were randomly switched to a low K^+ diet (LKD, 0.0%) or HKD (10%) for up to 11 d, before study at 0, 3, 5, 7, 9, and 11 d (3-4 mice/sex per day). Kidney cryosections were obtained and processed for BKα and AQP2 coimmunostaining to

identify CCD AQP2+ principal cells (PCs) and AQP2- intercalated cells (ICs) by confocal microscopy. Whole-cell BKα protein abundance and distribution were quantified in PCs and ICs and normalized to values obtained on day 0.

Results: BKα abundance was greater in F vs. M at day 0 in PCs and ICs (2.29±0.46 and 1.57±0.26, respectively, p≤0.005). With HKD, BKα abundance increased by 3 d in PCs and ICs in M (1.41±0.32 and 1.37±0.19, p≤0.001 vs. 0 d) and F (1.17±0.20 and 1.21±0.16, p≤0.05 vs. 0 d), followed by a sustained elevation after 7 d in M only (1.59±0.28 and 1.89±0.20, p≤0.001 vs. 0 d). A LKD led to a reduction in apical and sub-apical expression of BKα in ICs of M (0.53±0.09, p≤0.0001 vs. 0 d), but not F, by 7 d. Basolateral BKα expression increased in M ICs by 7 d (1.87±0.41, p≤0.0001 vs. 0 d), with no changes in F.

Conclusions: This study highlights sex- and cell-specific differences in BKα abundance and distribution in the mouse CCD in response to dietary K^+. Future efforts will be directed at unraveling the underlying sex-specific regulatory mechanisms.

Funding: NIDDK Support, Private Foundation Support

FR-PO581

Compensatory Upregulation of Renal H+/K+- ATPase Function in Pendrin-Null Mice Serving K+ Preservation

Niklas Ayasse,[1,2] Peder Berg,[2] Mads V. Sorensen,[2] Jens G. Leipziger.[2]
[1]Universitatsklinikum Mannheim, Mannheim, Germany; [2]Aarhus Universitet Institut for Biomedicin, Aarhus, Denmark.

Background: The renal Cl^-/HCO_3^- exchanger pendrin (SLC26A4) contributes to the maintenance of acid/base and intravascular volume homeostasis. Several studies have also suggested a possible role of pendrin in K^+homeostasis. The aim of this study was to identify possible compensatory K^+ retaining mechanisms in pendrin null mice. Since K^+ deficiency potently stimulates the activation of renal H^+/K^+-ATPases (HKA), we hypothesized that functional HKA activity is increased in pendrin null mice, thus allowing the preservation of K^+homeostasis. We recently suggested that benzamil can block the renal HKAs and thus may serve to functionally test its activity in vivo.

Methods: The acute effect of benzamil on urinary pH was investigated in bladder-catheterized pendrin$^{+/+}$ and pendrin$^{-/-}$mice. The magnitude of benzamil-induced urinary alkalization was used as a surrogate for the functional activity of the renal HKA. The effect was investigated under control and low K^+ diet conditions to increase HKA activity.

Results: Under control diet conditions, baseline urinary pH was lower in pendrin$^{-/-}$ mice as compared to pendrin$^{+/+}$mice. This may be caused by reduced pendrin-dependent HCO_3^- secretion or activation of an unknown tubular H^+ secretory mechanism or both. Interestingly, the magnitude of benzamil-induced urinary alkalization was greater in the pendrin$^{-/-}$ mice. Under low K^+ diet conditions, baseline urinary pH was not different between the pendrin$^{+/+}$ and the pendrin$^{-/-}$ group. Benzamil-induced urinary alkalization was larger in WTs during K^+-depletion, but not different between K^+ depleted $^{+/+}$ and $^{-/-}$ mice.

Conclusions: We propose that benzamil may function to indicate the HKA activity. Its greater effect in pendrin$^{-/-}$ mice under control diet indicates an increased baseline activity of the renal HKAs, likely caused by hypokalemia in these mice. The marked augmentation of benzamil-induced urine alkalization during low K+ conditions was confirmed in this study. The absence of dietary potassium depletion-induced increase of HKA activity in pendrin $^{-/-}$ mice could indicate a ceiling effect of the activated renal HKA. We suggest that renal HKA might indeed contribute to K^+ preservation in the absence of pendrin. This might indicate a hierarchical relationship where the need to preserve K^+ occurs at the expense of H^+ loss despite higher plasma HCO_3^- levels.

FR-PO582

Kidney Medullary Range NaCl Modulates CD8+ T Cell Survival and Function and Associates with Their Accumulation in Kidney Allografts

Peyman Falahat,[1] Adrian Goldspink,[1] Jessica Schmitz,[2] Jan H. Braesen,[2] Niklas Klümper,[1] Marieta I. Toma,[1] Sibylle Von Vietinghoff.[1]
[1]Universitatsklinikum Bonn, Bonn, Germany; [2]Medizinische Hochschule Hannover, Hannover, Germany.

Background: Recent research revealed a significant impact of electrolytes, namely NaCl, on immune responses. The role of the chief renal mobile osmolytes NaCl and urea for $CD8^+$ T cell function and accumulation in the kidney has not been systematically explored.

Methods: Human primary kidney and blood $CD8^+$ T cell survival and function was studied in elevated NaCl and urea concentrations. Renal T cell and antigen presenting cell densities were quantified in cortex and medulla of allograft biopsies in relation to diuretic therapy in a group of 66 consecutive biopsies obtained in a surveillance program 92.9±2.6 days after transplantation graded according to the Banff classification.

Results: An elevated NaCl but not urea concentration decreased human primary blood $CD8^+$ T cell and effector marker $KLRG1^+$ cell numbers. Urea inhibited $CD8^+$ T cell proliferation. NaCl, but not urea, increased apoptotic $CD8^+$ T cell death. In human kidneys in vivo, in tissues obtained during loop diuretic therapy that depletes the concentration gradient, cytotoxic $CD8^+$ T cells were significantly more abundant. This observation also was maintained if only tissues without histological rejection were included to the analysis. Ex-vivo primary renal cortical, but not medullary T cell survival and response was impaired by environmental NaCl.

Conclusions: Our data introduce a role of kidney medullary range NaCl and urea concentrations for $CD8^+$ T cell proliferation, survival and response. This is amenable to therapeutic interventions, which remain to be studied prospectively.

Funding: Government Support - Non-U.S.

FR-PO583

Lymphatic Endothelial Cell Permeability Is Regulated by Sodium and Nkcc1

Jianyong Zhong, Haichun Yang, Valentina Kon, Elaine L. Shelton. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Interstitial sodium (Na+) accumulation is a halmark of proteinuric kidney disease. Lymphatic endothelial cells (LECs) play an integral role in regulating interstitial fluid uptake and transport. Interstitial fluid drains into lymphatic capillaries composed of permeable LECs with button-like cell junctions. These capillaries transition into contractile collecting vessels lined with relatively impermeable LECs with continuous zipper-like junctions, which facilitate the transport of fluid without leakage. We have previously shown that increased Na+ diminished the pumping capacity of renal lymphatic collecting vessels and reduced the activity of the Na-K-2Cl cotransporter, Nkcc1. In addition, furosemide, a Nkcc1 inhibitor, blunted lymphatic vessel pumping dynamics. Of note, ethacrynic acid, another Nkcc1 inhibitor, had no effect on vessel contractility. In this study we evaluated the effects of increased Na+ and Nkcc1 inhibition on LEC barrier formation and integrity.

Methods: Mouse LECs were cultured in normal or high Na+ conditions with or without bumetanide, a Nkcc1 inhibitor. Bulk RNA sequencing and qRT-PCR identified differentially expressed genes. LECs were also used in Trans-Epithelial Electrical Resistance (TEER) assays to measure changes in monolayer formation and barrier integrity.

Results: RNA sequencing revealed high Na+ upregulated 456 genes and downregulated 499 genes. Addition of bumetanide reversed these effects for 136 genes and augmented these effects for 2 genes. TEER assays found LECs exposed to high Na+ could establish a monolayer, but that monolayer was more permeable when compared to cells cultured in normal Na+ conditions. qRT-PCR showed tight and adherens junction genes were decreased in high Na+ conditions. Monolayer integrity further decreased with addition of bumetanide, but not ethacrynic acid.

Conclusions: These results demonstrate that Na+ avid states promote LEC permeability and that bumetanide-induced inhibition of Nkcc1 can further augment this effect. While increasing permeability in lymphatic capillary LECs may be conducive for draining excess interstitial fluid, altering the permeability of LECs in collecting vessels may cause leakage and be detrimental to fluid clearance. In addition, ethacrynic acid may be superior to other loop diuretics due to the lack of off target effects on lymphatic vessel contractility and permeability.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO584

Urine Proteomics Captures Unique Spatial Transcriptomic Signatures of ADPKD in a Mouse Model

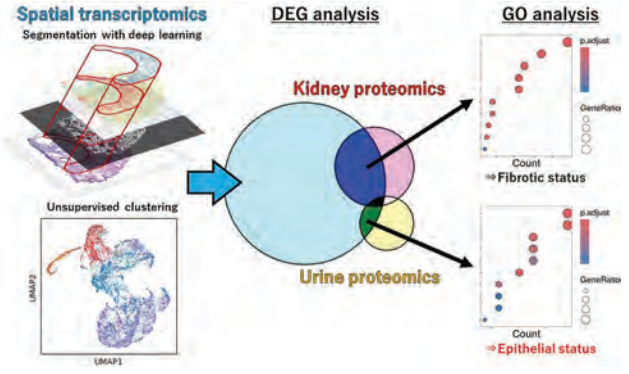
Kazuhiro Morishita, Yoshifumi Uesumi, Kohji Nagano, Naoshi Horiba, Yasuhiro Ichida. *Chugai Pharmaceutical Co. Ltd., Yokohama, Japan.*

Background: ADPKD is the most prevalent inherited kidney disease. Although the impairment of primary cilia is thought to be the cause of cyst formation, an insufficient understanding of the molecular mechanism has impeded the discovery of biomarkers reflecting PKD-specific pathology. Here, we performed multi-omics analysis to discover potential biomarkers for PKD.

Methods: Spatial transcriptomics, kidney proteomics, and urine proteomics were conducted on normal and PKD model mice. For spatial transcriptomics, we applied unsupervised clustering, spatial segmentation by deep learning, and differentially expressing gene (DEG) analysis. Kidney and urine proteomics were subjected to DEG and gene ontology (GO) analysis.

Results: Spatial transcriptomics revealed that the extent of transcriptomic change from normal mice to PKD mice varies depending on the kidney region, with the cortex along with the OSOM showing the most prominent changes. By stratifying the transcriptome with spatial information, we performed DEG analysis on the peri-cystic areas of each kidney region. Then, we investigated which DEG features could be captured with kidney or urine proteomics, but we found that there was little overlap between DEGs in kidney and urine proteomics. This suggests that these two types of proteomics capture different aspects of kidney pathology in PKD. In GO analysis, the common DEGs between kidney proteome and spatial transcriptome were associated with fibrosis, implying that kidney biopsy is likely to detect fibrotic status, a general signature of kidney inflammation. In contrast, the common DEGs between urine proteome and spatial transcriptome were associated with epithelium, suggesting that urine proteomics can effectively capture abnormalities in the tubular epithelium of PKD.

Conclusions: Our study highlights the potential of urine proteomics in terms of not only its low invasiveness but also its effectiveness in detecting epithelial changes, which could lead to the identification of novel biomarkers reflecting the unique pathology of ADPKD.



FR-PO585

In Vivo Analysis of Polycystin-1: Heterotrimeric G-protein Binding by NanoBiT

Brenda S. Magenheimer, Robin L. Maser. *The University of Kansas Medical Center, Kansas City, KS.*

Background: Polycystin-1 (PC1) is an atypical GPCR reminiscent of the Adhesion GPCR family. Both families undergo *cis*-autocatalyzed cleavage to form extracellular N-terminal and membrane-embedded C-terminal (CTF) fragments with an N-terminal CTF stalk acting as a tethered agonist. PC1-G protein regulation is central to cystogenesis, but little is known regarding mechanisms. Previous studies used truncated PC1 C-tail constructs and *in vitro* methods to show PC1-G protein binding, with little reported for full-length PC1. We are developing in vivo assays to assess PC1-G protein binding/activation. In this initial analysis, we determined the relative G protein binding preference of PC1 CTF and mutants using Nanoluciferase Binary Technology (NanoBiT) technology that relies on reconstitution of Nanoluc subunits, Large BiT (LgB) with Small BiT (SmB), to form an active enzyme with very bright luminescence.

Methods: Gα-LgB expression clones and HEK293-ΔG7 cells (KO of s,s-L, q,11,12,13, z) were provided by Drs. J. Hansen and A. Inoue. The Native Product (NP) version of SmB was fused to the C-terminus of CTF, 'stalkless' ΔstCTF and ADPKD mutants, R4136G and L4137P in the G protein activation motif. HEK293T or ΔG7 cells transfected with CTF-NP and Gα-LgB clones were assessed for Nanoluc complementation with a cell-permeable substrate. Controls included FRB-LgB+FKBP-SmB (positive), and empty vector+Gα-LgB or CTF-NP+FRB-LgB (negative). Luminescence was monitored for 40 min after substrate addition. Relative levels of CTF and Gα-LgB proteins were determined by Western blot and area under the curve was normalized to protein expression levels.

Results: NP did not affect expression or signaling of CTF proteins. CTF had a relative binding preference: Gi > Gq > Gs families in both cell lines. In ΔG7 cells, preferential binding by CTF for Gq > G11 and by ΔstCTF for Gq > Gs was lost. Analyses with a subset of Gα-LgB constructs (s, q, i1) in ΔG7 cells showed reduced binding of Gq relative to Gs for both R4136G and L4137P.

Conclusions: PC1 CTF-G protein binding is promiscuous *in vivo* and is influenced by the stalk and mutations within the G protein activation motif. Preliminary studies hint that PC1-mediated G protein regulation is complex and may be biased by multiple factors. Future experiments will examine binding in ΔG7 cells with pertussis toxin treatment, longer PC1 expression constructs, and additional mutants.

Funding: NIDDK Support

FR-PO586

Modeling the Impact of Polycystic Kidney Disease Genetic Modifiers Using Kidney Organoids Generated from Autologous Induced Pluripotent Stem Cells

Sara Knezevic,[1,2] Jessie Davis,[2] Elhussein A. Elhassan,[3,1] Michelle Clince,[3] Katherine A. Benson,[1] Peter J. Conlon,[3] John Crean.[2] *[1]Royal College of Surgeons in Ireland Faculty of Medicine and Health Sciences, Dublin, Ireland; [2]University College Dublin, Dublin, Ireland; [3]Beaumont Hospital, Dublin, Ireland.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease caused by pathogenic variants in *PKD1* or *PKD2*. Preliminary evidence for an effect of genetic modifiers (non-pathogenic variants which modify patient phenotype) on disease severity has been reported. Kidney organoids (KO) grown from patient-derived induced pluripotent stem cells (iPSCs) can be used to inform on the variability in disease severity between family members and offer a deeper understanding of ADPKD pathogenesis. Here, iPSCs were generated from an affected individual with ADPKD.

Methods: Patient was recruited from the inherited kidney disease clinic at Beaumont Hospital (Ireland) based on their genetic risk profile. A urine sample was collected and Urinary Epithelial Cells (URECs) were isolated and cultured. URECs were reprogrammed to iPSCs (UiPSC) and validated. KOs were generated from both patient and healthy control UiPSCs and characterised by RT-qPCR and immunocytochemistry. KOs from both patient and healthy control were treated with forskolin to induce cystogenesis and assessed for tubular swelling by brightfield microscopy.

Results: The index patient, a 77-year-old female, was diagnosed with hypertension, a family history of ADPKD and reduced eGFR (35 mL/min) at the last follow-up. Imaging revealed enlarged cystic kidneys and liver cysts indicative of ADPKD. Exome sequencing revealed *PKD1* complex variants, a diagnostic variant [c.7300C>T:p.R2434W] and two genetic modifiers [c.C2755T:p.R919W and c.C8293T:p.R2765C]. URECs were successfully isolated from the patient and reprogrammed into UiPSCs. KOs generated from healthy control expressed markers of mature proximal tubule, podocyte, endothelia and stroma. Patient KOs developed cysts alone or with forskolin injury. Tubular abnormalities were evident by Day 9 and more pronounced by Day 13. Healthy control KOs formed cysts only upon forskolin treatment.

Conclusions: Autologous UiPSCs can be used to generate KOs which mimic pathogenic cystogenesis, both spontaneously and post-acute injury. Further comparative studies will examine the mechanisms through which genetic modifiers confer risk and contribute to the severity of the disease, informing future therapeutic approaches to the management of ADPKD.

FR-PO587

Generation of Kidney Organoids Model of Nephronophthisis from Human Induced Pluripotent Stem Cells (iPSCs)

Takefumi Suzuki, Koichiro Susa, Hiroaki Kikuchi, Tomoki Yanagi, Yuta Nakano, Yu Hara, Tamami Fujiki, Fumiaki Ando, Shintaro Mandai, Yutaro Mori, Takayasu Mori, Shinichi Uchida, Eisei Sohara. *Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences Department of Nephrology, Bunkyo-ku, Japan.*

Background: Nephronophthisis (NPH) is an inherited kidney disease characterized by progressive tubulointerstitial fibrosis. NPH is clinically important as the most common cause of end-stage kidney disease in the juvenile period; however, no reliable animal model faithfully mimicking the pathology of human NPH is available. Consequently, the molecular mechanism of NPH caused by *NPHP1* deficiency, the most common form of NPH, has not yet been elucidated. Therefore, new models to recapitulate the pathology of NPH are required. In this study, we used human induced pluripotent stem cells (iPSCs) to generate a 3D kidney organoid model of fibrosis that provides insight into the pathogenesis of NPH.

Methods: Wild-type iPSCs and *NPHP1*$^{-/-}$ iPSCs derived from the same cell line were induced to differentiate into 3D kidney organoids, and the phenotypes associated with *NPHP1* deficiency were analyzed. First, we compared the morphology of both wild-type and *NPHP1*$^{-/-}$ organoids by immunofluorescence. Next, we induced fibrosis by treatment of IL-1β and evaluated the difference in the severity of fibrosis between the two groups.

Results: We successfully generated kidney organoids from both wild-type and NPHP1$^{-/-}$ iPSCs. In the absence of any stimulation, no difference in morphology, including nephron-like structure or fibrotic status, was observed between the two groups. This is consistent with the clinical course of human NPH caused by *NPHP1* deficiency, in which renal dysfunction does not appear during the postnatal period. On the other hand, fibrosis was induced at a significantly lower dose of IL-1β in *NPHP1*$^{-/-}$ organoids compared to wild-type organoids. This suggests that the *NPHP1*-deficient kidney is more sensitive to fibrotic stimuli than the wild-type kidney, which may explain why *NPHP1*-deficient NPH patients reach end-stage kidney disease earlier.

Conclusions: We generated *NPHP1*-deficient 3D kidney organoids; the first system capable of reproducing NPH pathology using human cells. This is an important pathological model for investigating the pathogenesis of NPH and developing therapeutic strategies.

Funding: Government Support - Non-U.S.

FR-PO588

Analysis of Pkd1 Gene Function in a Three-Dimensional Tubulogenesis Assay

Lukas Westermann,[1] Kilian Rhein,[1] Johannes Jahn,[2] Felix Schöler,[1] Matthias Niedermoser,[1] Elena Seidl,[1] Niklas Moser,[1] Shanli Seyed Tarrah,[1,3] Lea Reimund,[1] Tilman Busch,[1] Bjoern Neubauer,[1] Yong Li,[4] Anna Kottgen,[4,3] Michael Kottgen.[1,3] *[1]Renal Division, Department of Medicine, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [2]Department of Radiology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [3]CIBSS - Centre for Integrative Biological Signalling Studies, Freiburg, Germany; [4]Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany*.

Background: Autosomal-dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease. The majority of ADPKD patients (85%) harbors mutations in *Pkd1* encoding for Polycystin-1 (PC1). PC1 function is still insufficiently understood. The establishment of a robust cellular readout for PC1 function mimicking impaired tubular morphogenesis observed in ADPKD could help to overcome these roadblocks.

Methods: Wildtype mIMCD-3 cells were seeded in a Matrigel-collagen-scaffold in the presence of hepatocyte growth factor in 96-well plates. Within 7 days, cells organized into complex tubular or spheroid structures. Structures were imaged with a confocal microscope. Data analysis was performed by training of a neural network (U-Net), followed by automated segmentation for 3D structure detection that enabled unbiased quantification and classification. Analysis of genotype-dependent morphological alterations and longitudinal transcriptomic profiling of 3D structures aimed at the identification of functional interaction partners of PC1.

Results: Automated segmentation revealed a significant reduction of mean tubules per well in *Pkd1* knockout (KO) vs isogenic control cells (71 vs 214 tubules, respectively; $p<0.0001$) as well as a significant reduction in mean tubule area (1335 vs 2811 μm^2, respectively; $p<0.0001$). This phenotype was highly robust and confirmed in multiple *Pkd1* KO and inducible *Pkd1* knockdown (KD) cells. Longitudinal differential gene expression analysis of genotype-dependent tubulogenesis identified potential signaling effectors of *Pkd1*. Transcriptomic analysis comparing early stages of tubulogenesis in wildtype and isogenic *Pkd1* KO cells revealed 118 differentially expressed genes (53 genes up-, 65 downregulated) with stringent cut-off-criteria (adjusted $p<0.01$, $\log_2$ fold change ≤-1 and ≥1). We are currently investigating whether KD of the most significantly downregulated transcripts (*GC, Scd1, C3, Chst15 and Tns1*) phenocopies PC1 loss in the 3D tubulogenesis assay.

Conclusions: We demonstrate the establishment of a robust 3D tubulogenesis assay that allows for monitoring of PC1 function with an automated image analysis platform. This cell-based assay for PC1 function enables high-throughput screening for mechanistic studies and drug discovery.

Funding: Government Support - Non-U.S.

FR-PO589

Chemical Modulation of the Ire1α-Xbp1 Pathway Reduces Cyst Size in ADPKD Mouse and Human Three-Dimensional Spheroids

Fatema Hasan,[1] Rishi Bhardwaj,[1] Michael Rehman,[1] Yiqiang Cai,[1] Ke Dong,[1] Adrian Cordido,[1] Carlotta Pioppini,[2] Duygu Elif Yilmaz,[2] Xin Tian,[1] Stefan Somlo,[1] Matteus Krappitz,[2] Sorin V. Fedeles.[1] *[1]Yale University School of Medicine, New Haven, CT; [2]Charite Universitatsmedizin Berlin, Berlin, Germany*.

Background: The Ire1α -XBP1 pathway is the most conserved UPR branch from yeast to mammals. Genetic inactivation of XBP1 leads to a significant improvement in disease severity in neonatal and adult *Pkd1*-dependent ADPKD mouse models through a pro-apoptotic mechanism driven by Ire1α kinase domain. The endoribonuclease domain of Ire1α splices an intron from the XBP1 mRNA leading to the formation of active XBP1 which acts as a transcription factor to mitigate ER stress. Here we set forth to test whether chemical inhibition of the Ire1α endoribonuclease domain through toyocamycin (previously tested in a Phase 1 study with a favorable safety profile) can alleviate cyst growth in 3D spheroid cyst models derived from ADPKD human and mouse kidney tubule cells.

Methods: Human (*PKD1*: 10594C>T (Gln3 532*)) and mouse wild-type or *Pkd1* deficient cells were grown in matrigel. At Day 1, cells were administered either ddAVP (human cells) or forskolin (mouse cells) to promote cyst growth. Following that, cells were treated with various concentrations of toyocamycin over several days followed by fixation and image processing. We calculated lumen and spheroid area (um^2) in addition to measuring cell viability via CellTiterGlo.

Results: Mouse cells (in the presence or absence of the adenylate cyclase activator, forskolin) displayed a clear genotype/phenotype correlation with the *Pkd1*-KO cells forming abundant spheroids with large lumen sizes as compared with their WT counterparts which did not exhibit almost any lumen formation. In the presence of toyocamycin (up to 500nM), we found an almost complete normalization of the lumen/spheroid area ratio compared with the untreated cells. When the human spheroids were treated with toyocamycin (from 30nM to 1uM), the spheroid area was reduced to baseline levels at all concentrations tested. This was accompanied by an increase in cell death as well as decrease in ATP levels.

Conclusions: Our results describe a relevant 3D spheroid model system in mouse and human ADPKD tubule cells that was employed to test the effect of the Ire1α-XBP1 endoribonuclease inhibitor, toyocamycin, on spheroid formation/growth. We found a very potent effect of toyocamycin on spheroid and lumen size which warrants further *in vivo* investigations.

Funding: Other U.S. Government Support

FR-PO590

Glis3 Is a Modifier of Cyst Progression in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Zemeng Wei, Xin Tian, Michael Rehman, Ke Dong, Yiqiang Cai, Adrian Cordido, Stefan Somlo. *Yale University Department of Internal Medicine, New Haven, CT*.

Background: ADPKD is caused by mutations affecting polycystin-1 (PC1) or -2 (PC2). The existence of a 'cilia-dependent cyst activation' (CDCA) pathway has been identified by demonstrating that structurally intact primary cilia are crucial for cyst growth following loss of polycystins. We used translating ribosome affinity purification (TRAP)-RNAseq on precystic mouse kidney cyst cells to determine the translatome that meet the criteria for CDCA and identified Glis2 as an early effector of polycystin signaling. Here, we investigate the potential role of Glis3 which, while not transcriptionally altered, encodes a cilia-localized transcription factor belonging to the same family of proteins as Glis2.

Methods: We used Glis3-EGFP and live cell imaging to study the subcellular localization of Glis3 under ciliated conditions and in the presence or absence of *Pkd1*. We generated *Glis3^{fl}* conditional allele and crossed it with *Pkd1$^{fl/fl}$; Pax8^{rtTA}; TetO^{cre}*mice to investigate the potential genetic interaction in early (postnatal day 14, P14) and adult (14 weeks) ADPKD models.

Results: Live cell confocal imaging of wild type or Pkd1 knockout mIMCD3 cells stably expressing Glis3-EGFP and the Nphp3$^{1-200}$-mApple cilia marker shows that Glis3 is localized in both the nucleus and primary cilium, and its localization does not change upon inactivation of PC1. In the P14 early onset ADPKD model, compared to *Pkd1*-only knockouts, *Glis3;Pkd1*double knockouts have increased kidney-to-body weight ratio, cystic index, and blood urea nitrogen level, indicating a significantly worsening polycystic phenotype. Histological analysis of Glis3-only knockouts shows very occasional and sporadic tubule dilation at P14, which does not affect renal function. Immunofluorescence shows intact cilia in all four genotypes. Consistent with the early model, adult inactivation of both *Glis3;Pkd1* also exacerbates cyst progression. Glis3-only knockouts evaluated at 14-, 18- and 24-weeks are all normal. Transcriptional targets of Glis3 are under investigation through multiple approaches (RNAseq, Cut&Run, and ATACseq).

Conclusions: As a primary cilium localized transcription factor, Glis3 is genetically interacting with Pkd1. Loss of Glis3 exacerbates cystic progression in both early and adult onset ADPKD mouse model.

Funding: NIDDK Support

FR-PO591

Structural Analysis of the Extracellular Portion of Polycystin-1

Sabrina Baldauf,[1] Matthew Gaines,[2] Michael Pilsl,[1] M. Gregor Madej,[1] Olga Maier,[1] Reinhard Rachel,[1] Christine M. Ziegler,[1] Bertram Daum,[2] Ralph Witzgall.[1] *[1]University of Regensburg, Regensburg, Germany; [2]University of Exeter, Exeter, United Kingdom*.

Background: *PKD1* and *PKD2* code for polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Mutations in both of these genes lead to autosomal dominant polycystic kidney disease, yet the precise mechanism of cyst formation is still not completely understood. To learn more about its biological function, we have begun with the structural analysis of the extracellular NH_2-terminus of PC1 that is cleaved through cis-autoproteolysis.

Methods: HeLa cells were stably transfected with an expression plasmid encoding the StrepII-tagged extracellular NH_2-terminus of PC1 (amino acids 1-3074). For recombinant protein purification, the cell culture supernatant was loaded onto Streptactin affinity columns. Fractions of interest were concentrated for further purification by gel filtration, finally the recombinant protein was subjected to mass spectrometry, polyacrylamide gel electrophoresis combined with silver staining, and negative staining with subsequent electron microscopy. The fraction with the highest purity and concentration was plunge frozen for cryo-EM and the micrographs processed with cryoSPARC. Further characterization included deglycosylation, mass photometry and CD spectroscopy. Natural PC1 was purified from urine by sucrose density gradient ultracentrifugation. Fractions containing PC1 were identified by Western blotting and again further purified

by gel filtration. Finally, PC1 was frozen for cryo-EM, and single-particle analysis was performed with Relion and cryoSPARC.

Results: The recombinant extracellular NH_2-terminus of PC1 exists as highly glycosylated monomers. PC1 particles are filamentous and consist mostly of β-sheets as secondary structure elements. In contrast, natural PC1 purified from urine forms a very peculiar structure which can be found in different species. This peculiar structure is also present in recombinant PC1 samples although at a much lower frequency.

Conclusions: The structural characterization of the NH_2-terminus of PC1 opens new opportunities for a better understanding of its biological functions. The COOH-terminus of PC1 requires PC2 for transport, therefore the lower frequency of the peculiar PC1 structure observed in recombinant PC1 may be explained by the absence of PC2 in HeLa cells.

Funding: Government Support - Non-U.S.

FR-PO592

Guanine Quadruplex DNA in Human PKD1 Reveals a Mechanism for Second-Hit Mutagenesis in ADPKD

Erik D. Larson, Agata M. Parsons, Gerrit J. Bouma, Greg Vanden Heuvel. *Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, MI.*

Background: Somatic inactivation of the *PKD1* gene causes the cystogenesis characteristic of ADPKD, however the mechanisms of mutagenesis are unresolved. *PKD1* is prone to mutation in humans, but not in mice. Both genes share similar functions, but mice do not faithfully recapitulate ADPKD. A notable difference between the genes is that human *PKD1* is repetitive in sequence, with the potential to form four-stranded guanine-quadruplex (G4) DNAs. G4 DNA structures naturally occur in the genome and have regulatory roles, but if left unresolved they inhibit polymerases and cause DNA breaks and mutagenesis.

Methods: We asked if human or mouse PKD1 form G4 DNA structures in human HEK293T or mouse mIMCD3 cells using chromatin immunoprecipitation and immunofluorescence microscopy with antibodies specific for G4 DNA. DNA break formation at the PKD1 locus was measured by chromatin immunoprecipitation with an antibody specfiic to a chromatin marker for DNA breaks, gammaH2AX.

Results: We found abundant G4 sequences in human, but not mouse, *PKD1*. Immunoprecipitations with a G4-specific antibody enriched for G4-forming regions of human *PKD1* and we observed nuclear G4 DNAs by immunofluorescence microscopy in ADPKD tissue. Antibodies to G4 also colocalizes with the *PKD1* locus, which was identified using a tagged version of dCAS9 targeted to the 3′ end of the gene. Repeat regions in *PKD1* form alternative DNA structures in vitro and stabilization of G4 DNA by culturing HEK cells with the G4 ligand Phen-DC3 resulted in phosphorylation of histone H2AX (gammaH2AX) at *PKD1*. Mouse *Pkd1* did not form G4 DNA or G4-induced DNA breaks.

Conclusions: Our results connect G4 formation with promoting the precursor DNA lesions in human *PKD1* that inactivate the gene, which provokes a pathway of cystogenesis in ADPKD individuals. This reveals a mechanism for second hit mutagenesis of human PKD1 where unresolved G4 DNAs increase the risk of DNA damage, which then leads to loss of heterozygosity and disruption of polycystin-1 activity.

Funding: NIDDK Support, Private Foundation Support

FR-PO593

mRNA Translation Reprogramming in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Charlotte Leemans,[1,2] Najla El Hachem,[2] Jean-Paul Decuypere,[3] Djalila Mekahli,[3] Francois Jouret,[1,2] Pierre Close.[2] Laboratory of Cancer Signaling, Laboratory of Translational Research in Nephrology. *[1]Centre Hospitalier Universitaire de Liege, Liege, Belgium; [2]Universite de Liege, Liege, Belgium; [3]Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven Campus Gasthuisberg, Leuven, Belgium.*

Background: Global regulation of mRNA translation has emerged as a central mechanism driving cellular adaptation in various diseases. tRNA modifications play a specific role in promoting the reprogramming of mRNA translation. We aim to better understand the importance of mRNA translation reprogramming in the development of cysts in ADPKD.

Methods: Murine inner medullary collecting duct (IMCD) cells knocked out for *Pkd1* by CRISPR-Cas9 were grown *in vitro*. A range of different techniques were used to characterize mRNA translation regulation in these cells. First, we compared the proteome of control or *Pkd1* KO cells by label-free quantitative proteomics. In parallel, we assessed mRNA translation regulation by polysome profiling and OP-Puro incorporation. Finally, we purified tRNAs from cells and we performed a systematic analysis of most of the described tRNA modifications by LC-MS/MS analysis.

Results: We generated lists of proteins that are up- and down-regulated upon loss of *Pkd1* in IMCD cells. We focused on proteins whose expression is upregulated in *Pkd1* KO as compared to controls. Performing Gene Set Enrichment Analyses, we uncovered a series of specific cellular and molecular pathways that are significantly upregulated in *Pkd1* KO cells. We found that "tRNA modification" was enriched in cells KO for *Pkd1*: a series of enzymes, such as Dus3l or Pus10, associated with tRNA modification were specifically upregulated. We plotted enzymes known to regulate tRNA modification and compared their expression in control *versus Pkd1* KO cells. These data were corroborated with a systematic analysis of tRNA modifications. Interestingly, this approach highlighted reproducible changes in specific tRNA modifications between control and *Pkd1* KO cells. Differences in abundance of each tRNA modification were plotted and correlated with catalyzing enzyme expression.

Conclusions: Our data indicate that differences in tRNA modification pattern are observed between control and *Pkd1* KO IMCD cells and could define specific tRNA modification pathways as a new vulnerability targets in cyst formation in ADPKD.

Funding: Government Support - Non-U.S.

FR-PO594

Cleavage of N-terminus of Polycystin-1 Increases Calcium Permeability of Polycystin-1/Polycystin-2 Receptor Channel Complexes

Runping Wang, Danish Idrees, Mohammad Amir, Biswajit Padhy, Jian Xie, Chou-Long Huang. Huang Lab in Dept of Internal Medicine, University of Iowa. *University of Iowa Health Care, Iowa City, IA.*

Background: Mutations on *PKD1* and *PKD2* encoding PC1 and PC2, respectively, cause autosomal-dominant polycystic kidney disease. It is postulated that PC1 and PC2 form receptor channel complexes. PC1 undergoes N-terminal autocleavage to expose a hidden "stalk" region hypothesized acting as "tethered agonist". Current studies of PC2 channel focus on patch-clamp recording on the primary cilium and gain-of-function (GOF) PC2 in *Xenopus* oocytes. Difficulty to record functional wildtype (WT) PC2 limits the progress on receptor-channel complex hypothesis.

Methods: Xenopus oocytes expressing PC2 ± PC1 or PC1 deletion mutants were recorded by two-electrode voltage-clamp.

Results: Longer expression of WT PC2 in oocytes produced functional channels with similar order of cation selectivity as in primary cilia. PC1 and PC2 formed complexes with unique biophysical properties but same order of cation selectivity as PC2 homomers. Biophysical properties of PC1 and GOF PC2 differ from WT PC1/PC2 heteromers. Deleting PC1 N-terminus to expose the stalk increased calcium permeability of PC1/PC2 heteromers that required the presence of stalk region and intracellular C-terminus. Extracellular application of synthetic stalk peptide increased calcium permeation on stalkless PC1/PC2. Pull-down assays showed Wnt9B interacted with the leucine-rich repeat (LRR) at the N-terminus of PC1. Application of Wnt9B increased calcium permeability of PC1/PC2, but not heteromers containing cleavage resistant mutant PC1. Preincubation with LRR fusion protein prevented the effect of Wnt9B from increasing calcium permeability of the PC1/PC2 complexes.

Conclusions: *Xenopus* oocytes is a good experimental system for studying wildtype polycystin function. PC1 and PC2 form heteromeric receptor-channel complexes that differ from complexes formed by PC1 and GOF-PC2. Wnt9B interacts with LRR in PC1 N-terminus to expose stalk domain of PC1 and activates heteromeric channel including increased calcium permeability. Future studies will include structure-function of the complexes, identification of additional ligands, and further elucidation of regulatory mechanism. Our study provides proof-of-principle for new therapeutic strategies for *PKD1* N-terminal mutations by direct targeting downstream regions such as TOP domain.

Funding: NIDDK Support

FR-PO595

Functional Studies of Polycystin-1 Using a Novel Pkd1-HaloTag Mouse

Adrian Cordido,[1,2] Ke Dong,[1,2] Yiqiang Cai,[1,2] Xin Tian,[1,2] Zemeng Wei,[1,2] Michael Rehman,[1,2] Stefan Somlo.[1,2] *[1]Yale University, New Haven, CT; [2]Yale University School of Medicine, New Haven, CT.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disease caused primarily by mutations in genes encoding Polycystin-1 (PC1) and Polycystin-2 (PC2). The physiological function of polycystins and the process through which their dysfunction leads to cystogenesis remains unclear. The localized expression of PCs, particularly PC1, in kidney and other tissues has been challenging to detect. HaloTag is a versatile protein labeling system which allows antibody independent covalent ligand-based labeling of the targeted protein and can improve the sensitivity and intensity of the protein localization signals. We applied this system to PC1 in vivo.

Methods: Based in our preliminary data in transfected cells showing that PC1-HaloTag expression can be detected by HaloTag ligand labeling in western blotting and live cell immunofluorescence, we produced a Pkd1-knockin mouse with a C-terminal fusion of 3XHA-HaloTag with PC1 ($PC1^{Halo}$). We characterized the viability and kidney phenotype of the mice and the maturation and expression of $PC1^{Halo}$ by western blotting and confocal immunofluorescence microscopy.

Results: *$Pkd1^{Halo/Halo}$* mice are born in normal Mendelian ratios and have normal renal and liver phenotypes at 6 months age indicating that $PC1^{Halo}$ is fully functional in vivo. Adult induced *$Pkd1^{fl/Halo}$; $Pax8^{rtTA}$; TetO-Cre* mice are also normal. We detected normal

maturation of PC1^{Halo} by western blot of multiple tissue lysates and primary kidney cell cultures from *Pkd1$^{Halo/Halo}$* mice. We detected endogenous PC1^{Halo} in cilia of primary kidney cell culture from *Pkd1$^{Halo/Halo}$* mice by confocal imaging following HaloTag ligand labeling in live cells as well as fixed cells.

Conclusions: PC1 C-terminal fusion with HaloTag produces a fully functional PC1^{Halo} in vivo. Endogenous PC1^{Halo} can be detected in tissue lysates and can be imaged in primary kidney cell cultures. PC1^{Halo} will be a useful tool for exploring native PC1 in vitro and in vivo.

FR-PO596

Adult-Onset Conditional Deletion of Pkd1 and Tulp3 in Mice Exert Different Effects on Kidney Cyst Formation and Mitochondria Phenotypes

Biswajit Padhy, Jian Xie, Danish Idrees, Chou-Long Huang. *University of Iowa Carver College of Medicine, Iowa City, IA.*

Background: Mutations on *PKD1* and *PKD2* coding for PC1 and PC2 cause ADPKD. PC1 and PC2 are widely expressed in multiple subcellular locations. Tulp3 (Tubby-like protein-3) is an adaptor protein that traffics membrane proteins including PC1 and PC2 into cilia. A previous study reported that mice with adult-onset deletion of Tulp3 develop mild cysts at 42 weeks old, much delayed than mice with deletion of Pkd1 or Pkd2. Metabolic reprogramming is an important modifier of ADPKD cystogenesis. The cause of mitochondrial dysfunction in ADPKD remains elusive. Here, we performed side-by-side comparison on kidney cyst and mitochondria phenotypes in mice with adult-onset deletion of Pkd1 & Tulp3 gene, respectively.

Methods: Mice 4- to 6-week-old carrying Pax8-LC1 allele and homozygous Pkd1-floxed allele or Tulp3-floxed allele were treated with doxycycline for 10 days. Kidneys were harvested from mice 16-20 weeks after Doxy induction for analysis of cyst formation and ciliary expression of PC's by H&E-stained histology and immunofluorescent staining, for mitochondria morphology by TEM, and for mito DNA mass and regulator gene expression by RT- PCR.

Results: In mice 14 weeks after Pkd1 deletion vs control, kidneys showed markedly increased cyst index. TEM showed altered mitochondria morphology including decreased mitochondria area, perimeter, cristae number and density, and increased roundness. About 60% mitochondria surface was in contact with ER forming mitochondria-associated ER membranes (MAMs). The distance between ER-mitochondria contact was increased and the length of contact was decreased in Pkd1-cKO. These changes began in precystic stages (4 weeks after Doxy). In contrast, Tulp3-deleted kidneys had relatively normal mitochondria morphology and no cysts. PC1 and PC2 were absent in cilia, but present in extra-ciliary locations of Tulp3-deleted mice. Mitochondria master regulators PGC1α and PPARα, and DNA mass were reduced in Pkd1-deleted kidneys but unchanged in Tulp3-deleted.

Conclusions: Loss of PC1 and PC2 in primary cilia of Tulp3-deleted mice is not sufficient for kidney cyst formation and mitochondria morphological changes as in Pkd1-deleted mice. Extraciliary polycystins are also important. Alternatively, other factors lost in Tulp3-deleted mice may protect against cystogenesis.

Funding: NIDDK Support

FR-PO597

Defining Precystic vs. Cystic Alterations in Pkd1 Renal Mutants

Daniel Spies,[1,2] Sara Clerici,[1] Marco Chiaravalli,[1] Gangqi Wang,[3] Laura Cassina,[1] Ton J. Rabelink,[3] Alessandra Boletta.[1] Unit of Cystic Kidneys Disorders - Alessandra Boletta Lab. *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Universita Vita Salute San Raffaele, Milano, Italy; [3]Leids Universitair Medisch Centrum, Leiden, Netherlands.*

Background: ADPKD is among the most prevalent monogenic diseases. Multiple relevant orthologous animal models were generated over the years and helped defining mechanism of disease progression and identifying therapies able to retard end-stage-kidney-disease. We have previously reported that PKD tissue is characterized by a profound metabolic reprogramming. However, the initial stages of renal cystogenesis and whether metabolic re-programming is an early or late event in disease evolution is unknown. Identification of the cellular alterations occurring at the onset of cystogenesis would provide important information on mechanism of disease. Here we present a strategy aimed at identifying the earliest events occurring immediately after inactivation of the Pkd1 gene

Methods: Inducible Cre lines were used to inactivate the *Pdkd1* gene at different time-points. Characterization was done by IHC and IF analysis. For spatial metabolomic tracing 350μm thick kidney sections were incubated with either 13C labeled Glucose, Glutamine or Linoeleate before being sectioned into 10μm thick slices and subjected to MALDI-MS followed by multiplexed IF staining

Results: We developed a tamoxifen-inducible *Pkd1* mouse model carrying a fluorescent switch cassette (mT/mG) that allows identification of cells in which the Cre recombinase has been activated to study the initiating events in cystogenesis. Induction by 3 low dose injections of Tamoxifen resulted in cyst formation within two weeks. 5 days after the last injection we identified renal tubules completely green, but not cystic, while 8 days post injection green cells started to form cysts. mKspCrePkd1fl/fl;mT/mG kidneys were collected at 5 or 8 days post inactivation, and subjected either to spatial metabolic tracing by incubation with 13C labeled Glucose, Glutamine or Linoeleate followed by MALDI- MS, or subjected to scRNAseq. Data are being analyzed and the preliminary results will be presented

Conclusions: We have generated and characterized an inducible *Pkd1* mouse model that enables the study of two time windows: cells are *Pkd1* mutated but not yet cystic and cells are inactivated and cystic, in both cases carrying a GFP cassette for tracking. Our combined analysis of scRNAseq and spatial metabolic tracing will provide the first glimpse on changes of likely causative and consequential events in cyst initiation

Funding: Private Foundation Support

FR-PO598

Methylation-Controlled J Protein as a Target to Alleviate Kidney Fibrosis and Cyst Growth

Marie-Louise T. Monaghan, Isabel A. Layne, Jelena Klawitter, Evgenia Dobrinskikh, Alyx E. Gray, Raphael A. Nemenoff, Michel Chonchol, Seth B. Furgeson, Katharina Hopp. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Kidney mitochondrial function is abnormal in autosomal dominant polycystic kidney disease (ADPKD) with reduced aerobic glycolysis/oxidative phosphorylation (OXPHOS). Methylation-controlled J protein (MCJ) is the only endogenous inhibitor of electron transport chain (ETC) Complex I. Loss of MCJ enhances Complex I activity, increasing OXPHOS/ATP generation, without increasing reactive oxygen species (ROS). In liver injury models, MCJ genetic or siRNA-based (siMCJ) depletion lessens liver pathology by improving OXPHOS.

Methods: We mined published/in house single nucleus/cell (sn/sc) RNAseq data of human and murine normal and ADPKD kidney samples to assess MCJ expression and mitochondrial gene set enrichment (GSE). In mice (WT/*Pkd1*$^{RC/RC}$), we assessed kidney purine metabolites via LC-MS/MS. Using unilateral ureteral obstruction (UUO) and *Pkd1*$^{RC/RC}$ mice on the MCJ$^{-/-}$ background, we assessed MCJ's role in mediating kidney fibrosis and kidney cyst growth. Fluorescence Lifetime Imaging Microscopy (FLIM, quantification of free NADH) and Electron Paramagnetic Resonance Spectroscopy (EPRS) were used to assess kidney OXPHOS and ROS levels. IV injection of naked siMCJ to WT mice was tested as a therapeutic strategy.

Results: Analysis of sn/sc RNAseq revealed global MCJ expression in kidney epithelia, with a significant increase in human ADPKD samples. GSE analyses identified OXPHOS, ATP production, and ETC as the most differentially regulated pathways in WT vs *Pkd1*$^{RC/RC}$ collecting ducts. LC-MS/MS revealed reduced energy charge (1.28-fold) and ATP/ADP ratio in *Pkd1*$^{RC/RC}$ vs WT kidneys (1.34-fold). MCJ$^{-/-}$ vs MCJ$^{+/+}$ mice had reduced kidney fibrosis 2wks post UUO (10.2% vs 14.5% fibrosis, $p<0.001$). 3mo old *Pkd1*$^{RC/RC}$;MCJ$^{-/-}$ vs *Pkd1*$^{RC/RC}$;MCJ$^{+/+}$ mice had reduced kidney/body weight (0.77-fold, $p<0.001$) and computed cyst volume (1.55-fold, $p<0.05$). FLIM showed increased OXPHOS in *Pkd1*$^{RC/RC}$;MCJ$^{-/-}$ vs *Pkd1*$^{RC/RC}$;MCJ$^{+/+}$ mice, but without increasing kidney ROS levels (EPRS). Lastly, IV injected siMCJ resulted in significantly reduced kidney MCJ levels.

Conclusions: These findings suggest that targeting MCJ corrects abnormal kidney mitochondrial function and altered metabolic pathways that contribute to kidney fibrosis and cyst growth.

Funding: NIDDK Support

FR-PO599

Three-Dimensional Imaging and Genetic Characterisation of a Rat Model of Polycystic Kidney Disease

Maria K. Ougaard, Frederikke E. Sembach, Michael Christensen. *Gubra, Hørsholm, Denmark.*

Background: Polycystic kidney disease (PKD) is a congenital fibrocystic disorder for which there is no curative treatment. Consequently, PKD is classified as a medical condition with high unmet therapeutic need. Animal models with improved clinical translatability can optimally inform about potential efficacy of novel drug candidates for PKD. The polycystic kidney (PCK) rat is an established genetic model of PKD with natural history and renal histologic abnormalities that resemble the human disease. Gubra has established a PCK rat breeding program to enable fast turnaround time of preclinical drug discovery studies for PKD. In this study, we have characterised disease progression in the PCK rat to aid in designing future pharmacological intervention studies.

Methods: Male PCK (PCK/CrljCrl-Pkhd1pck/Crl) and control (CRL:CD(SD)) rats were randomised into groups based on body weight at the age of 10 weeks. At the age of 17 and 25 weeks, rats underwent urine collection for quantification of albuminuria, and plasma sampling for analysis of urea and creatinine levels. At termination, kidneys were collected for RNAseq and imaging where 3D and total kidney volume, cyst number and volume were analysed using quantitative 3D light sheet imaging.

Results: Compared to age-matched controls, PCK rats displayed marked albuminuria at 25 weeks of age. Plasma urea was progressively increased at both 17 and 25 weeks, while plasma creatinine was only increased at week 25. 3D light sheet imaging enabled whole-kidney counting of cysts and quantification of cyst volume (control: 11 mm^3 vs 25 wks.: 414 mm^3) as well as the total kidney volume. The PCK rats displayed differentiated expressed genes associated with angiogenesis, cellular stress, extracellular matrix remodelling, and inflammation.

Conclusions: The PCK rat displays hallmarks of PKD, characterized by age-dependent progressive increase in biomarkers and regulation of genes associated with kidney injury, kidney hypertrophy and cyst formation. Quantitative whole-kidney 3D light sheet imaging is highly instrumental for detailed assessment of progressive kidney disease in the PCK rat. Accordingly, these imaging modalities are instrumental as key endpoints for assessment of potential therapeutic effects of preclinical drug candidates in the PCK rat model.

Funding: Veterans Affairs Support, Commercial Support - Gubra

FR-PO600

Studying Macrophage Phenotype and Function in Slowly Progressing Models of PKD

Fariha Nusrat, Sarah J. Miller, Marybeth Humphrey, Kurt Zimmerman.
The University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background: Macrophages have been associated with the progression of polycystic kidney disease (PKD) for several decades. While data suggest that macrophages promote cyst progression through the production of pro-inflammatory cytokines, the majority of data supporting this paradigm were collected using rapidly progressing mouse models of disease. The phenotype and function of macrophages in slowly progressing forms of the disease remain poorly understood.

Methods: To understand how the rate of PKD progression impacts macrophage phenotype and function, we generated a comprehensive single-cell RNA sequencing (scRNAseq) atlas of kidney resident macrophages (KRM) isolated from slowly and rapidly progressing models of PKD as well as non-cystic controls.

Results: Using single-cell RNA sequencing (scRNAseq), our lab identified a subset of kidney resident macrophages (KRM), termed *Trem2*+ cyst associated macrophages (CAM), that were highly enriched in slowly progressing mouse models when compared to rapidly progressing models and non-cystic controls. *Trem2*+ CAM had an enrichment of genes associated with phagocytosis and the lysosome. Functional analyses indicate that *Trem2*+ CAM also had enriched lysosomal activity compared to total KRM and were located adjacent to apoptotic cystic epithelium, suggesting these cells may be restricting PKD progression through phagocytosis and lysosomal degradation of the apoptotic cystic epithelium (efferocytosis). To test this hypothesis, we crossed two PKD mouse models (*Ift88* and *Pkd1*$^{RC/RC}$) to the *Trem2*-/- background. Analysis of preliminary data indicate that loss of *Trem2* significantly worsened cystic disease as measured by 2KW/BW and BUN. Further, loss of *Trem2* resulted in increased apoptotic cystic epithelium.

Conclusions: Collectively, our data suggest that *Trem2*+ CAM restrict cyst progression through phagocytosis and lysosomal degradation of the apoptotic cystic epithelium.

Funding: NIDDK Support, Private Foundation Support

FR-PO601

Cell State Transition Associated with Cyst Development in Autosomal Dominant Polycystic Kidney Disease

Hyun Jun Jung,[1] Patricia Outeda,[2] Owen M. Woodward,[2] Terry J. Watnick,[2] Paul A. Welling.[1] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]University of Maryland School of Medicine, Baltimore, MD.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD), caused by genetic mutations in the Polycystin genes (Pkd1 and Pkd2), is the most common form of polycystic kidney disease, characterized by the development of cysts in the kidneys. Mechanisms underlying the initiation of cystogenesis are poorly understood, but developmental stage plays an important role. In mouse models, cyst formation is greatly accelerated when Pkd1/2 genes are knocked out before postnatal day 13 (P13), leading severe cyst development within weeks, compared to months when Pkd1/2 knockout is induced after P13. Here, we investigated the molecular signature of cell state transitions around P13 underlying the dynamic changes in the initiation of cyst development.

Methods: To identify transcriptomic signatures and their changes associated with cell state transitions around P13, single nucleus RNA sequencing (snRNA-Seq) was performed on whole kidneys obtained from mice with an intact Pkd2 gene (Pkd2$^{fl/fl}$; Pax8-rtTA; TetO-Cre-) at P13 and P15. Nuclei (n=2 per group, 54,324 nuclei) isolated from whole kidneys were analyzed using 10x Chromium and NovaSeq6000 (50,000 read pairs per nucleus). Data were processed and analyzed using CellRanger and Seurat.

Results: snRNA-Seq identified kidney cell populations according to known kidney cell types. At both P13 and P15, a cell proliferation signature was observed in subpopulations of proximal tubule, loop of Henle, and distal tubule cells. Differential gene expression analysis (P13 vs P15) identified 142 genes commonly changed in proliferative tubular cells and revealed that these genes were enriched in calcium signaling. Further analysis of proliferative tubular cell subclusters identified 6 common genes (A330015K06Rik, Dapk2, Exoc3l2, Gli2, Greb1, and Slc14a2) and revealed that the cell proliferation signature was less prominent at P15 compared to P13. Additionally, 48 genes encoding secretory proteins exhibited cell type-selective changes within proliferative cell subpopulations.

Conclusions: We identified a transcriptomic signature of a proliferative cell state and their changes between P13 and P15. This study offers a valuable resource for understanding cell state transitions in proliferative epithelial cells, potentially implicated in the development of cystogenesis in ADPKD.

Funding: NIDDK Support

FR-PO602

Investigating the Biogenesis and Degradation of Polycystin 2 Missense Mutants

Christopher J. Guerriero, Marcelo D. Carattino, Jeffrey L. Brodsky.
University of Pittsburgh, Pittsburgh, PA.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a prevalent inherited disorder and cause of end-stage renal disease. ADPKD arises from mutations in *PKD1* and *PKD2*, which encode polycystin 1 (PC1) and polycystin 2 (PC2). These mutations lead to aberrant signaling, cell proliferation, and fluid secretion. Given its size, complexity, and primary localization to the endoplasmic reticulum (ER), we hypothesize that PC2 missense mutants may misfold and be degraded by the ER-associated degradation (ERAD) pathway.

Methods: Disease-causing PC2 variants that were computationally predicted to be folding defective were expressed in *S. cerevisiae* and HEK293 cells to evaluate their stability and function. Stability and poly-ubiquitination levels were measured in the presence or absence of a proteasome inhibitor (MG132). TEVC studies in *Xenopus* oocytes and cell surface biotinylation revealed PC2 activity and cell surface residence. We tested the ability of PC2 missense variants to rescue growth in yeast lacking two plasma membrane potassium transporters and determined response to cold temperature correction and chemical chaperones.

Results: Select PC2 missense mutants exhibited more poly-ubiquitination and were degraded faster than wild-type PC2 in both yeast and HEK293 cells. Treatment with MG132 increased poly-ubiquitinated protein levels, suggesting proteasomal turnover of these mutants. The yeast growth assay reports on protein folding, assembly, trafficking, and activity; some mutants failed to rescue yeast growth, while others exhibited normal growth. Incubation at lower temperatures improved growth of select mutants, perhaps indicating a potential for pharmacological rescue. Some yeast growth defects were recapitulated in oocytes, validating our yeast model system. Finally, surface biotinylation of PC2 variants in HEK293 cells showed reduced amounts of unstable PC2 missense variants at the cell surface, which may contribute to the ADPKD phenotype.

Conclusions: While some PC2 alleles are stable yet dysfunctional, suggesting trafficking defects or impaired ion transport as the source of dysfunction, we find that select PC2 missense mutants are targeted for the ERAD pathway. Protein folding modulators are a rapidly expanding therapeutic strategy for ERAD-related diseases, and based on our data some PC2 mutants would be amenable to pharmacological correction.

Funding: NIDDK Support, Other NIH Support - NIGMS

FR-PO603

Studying the Involvement of the Complement Receptor C5ar1 in Polycystic Kidney Disease

Audrey M. Cordova,[1] Aaron Pan,[1] Bibi Maryam,[1] Katharina Hopp,[2] Kurt Zimmerman.[1] *[1]The University of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Polycystic Kidney Disease (PKD) is caused by mutations in cilia-related genes and results in fluid-filled cysts throughout the kidney. Previous data indicates that immune cells, in particular macrophages, are important in regulating the progression of cystic disease. To understand possible functions of macrophages in cystic kidney disease, our lab performed single cell RNA sequencing (scRNAseq) on macrophages isolated from control and cystic mice. scRNAseq data indicate that kidney resident macrophages isolated from cystic mice have increased expression of the complement 5a receptor 1 (*C5ar1*) gene. C5ar1 is a G-protein coupled receptor that binds to the anaphylatoxin C5a that promotes inflammation and macrophage recruitment.

Methods: To test the importance of *C5ar1* in cyst progression, we crossed *C5ar1* deficient mice onto two different cystic backgrounds (*Pkd1*$^{RC/RC}$ and Cagg Cre^{ERT2} *Ift88*$^{fl/fl}$) and analyzed PKD severity and immune cell numbers using flow cytometry.

Results: Preliminary analysis of *Pkd1*$^{RC/RC}$ *C5ar1*-/- mice at three months of age indicate no effect on PKD phenotype compared to controls. In contrast, loss of *C5ar1* significantly worsened the PKD phenotype in *Pkd1*$^{RC/RC}$ mice compared to controls at 1 year of age. Likewise, loss of *C5ar1* in adult induced *Ift88* mice resulted in worsened PKD phenotype when analyzed 6-7 months post induction (~9 months of age). Analysis

of flow cytometry data in 1 year old *Pkd1*$^{RC/RC}$ and 9 month old *Ift88* mice revealed that loss of *C5ar1* resulted in significantly more Ly6c^{lo} monocytes, CD4+ T cells, and CD8+ T cells compared to controls. Surprisingly, loss of *C5ar1* resulted in significantly fewer *Mrc1+/Trem2+* KRM in *Pkd1*$^{RC/RC}$ mice but significantly more *Mrc1+/Trem2+* KRM in *Ift88* mice.

Conclusions: Collectively, our data suggest that *C5ar1* restricts PKD progression, possibly through modulation of adaptive immune cell accumulation.

Funding: NIDDK Support, Private Foundation Support

FR-PO604

Polycystins Regulate Ezrin Function and Cleavage to Control Renal Cell and Tubular Morphology

Ava M. Zapf, Eryn E. Dixon, Denis Basquin, Terry J. Watnick, Owen M. Woodward. *University of Maryland School of Medicine, Baltimore, MD.*

Background: Renal cyst formation in ADPKD requires altered cell and tubular morphology. Previously, we used inducible inactivation of *Pkd2* in a 3D-tubuloid model to measure acute changes in tubuloid shape after *Pkd2* loss and observed alterations in tubule morphology before changes in overall volume, arguing that morphological changes are among the first consequences of polycystin loss. We hypothesized a direct role for the polycystin complex in regulating the apical cytoskeleton protein, ezrin (EZR), to control cell and tubular morphology.

Methods: We used clonal cell lines derived from the kidneys of *Pkd1 or Pkd2* Pax8rtTA TetOCre mice crossed with the SV40 immorto-mouse: *Pkd1-iKO* (#313) and *Pkd2-iKO* (#125). *Pkd1/2* can be efficiently deleted with addition of Doxycyline (DOX) to the cell media.

Results: We observed a strong correlation between the loss of *Pkd1/2* and increased apical cell area, as defined by ZO1, in 2D *Pkd1/2-iKO* cells. The acute loss of *Pkd1/2* also resulted in decreased ezrin abundance and altered localization. Although *Pkd1/2* deletion resulted in decreased ezrin we found upregulation of *Ezr* mRNA in both the DOX treated *Pkd2-iKO* cells and in human ADPKD cystic tissue, leading us to hypothesize that PC1/2 regulates ezrin protein more directly. Immunoprecipitation experiments of HEK293 cells transfected with ezrin, Myc-PC2 or Flag-PC1 showed both PC1 and PC2 successfully pulled down ezrin sugesting a protein interaction. Interestingly, the pull down efficiency was greater with the full length PC1 than the CTF-PC1 fragment. To confirm an endogenous interaction between ezrin and PC1 we isolated primary renal epithelial cells from a transgenic *Pkd1-HA* mouse and found again HA-PC1 successfully pulled down ezrin. Mechanistically, ezrin activity is regulated by cystine proteases calpain 1 and 2. We observed a substantial increase in the N-terminal 55KDa ezrin cleavage product after acute *Pkd2* loss in the DOX treated *Pkd2-iKO* cells as well in human APDKD cystic tissue. Chemical inhibition of either calpain 1 or calpain 2 led to increased ezrin cleavage in control cells mimicking *Pkd2* loss. However, inhibition of both calpain 1 and 2 reduced ezrin cleavage in DOX treated *Pkd2-iKO* cells to levels comparable to control cells.

Conclusions: The polycystin proteins regulate ezrin function and cleavage to control renal cell and tubular morphology.

Funding: NIDDK Support

FR-PO605

Tubule-Specific Deletion of Adamts1 Slows Cyst Expansion in Polycystic Kidney Disease

Vijayakumar R. Kakade, Zafer Akman, Manga Motrapu, Lloyd G. Cantley. *Yale University, New Haven, CT.*

Background: Autosomal dominant polycystic kidney disease is caused by mutations in either the PKD1 or PKD2 genes leading to cyst growth. We have shown that with loss of Pkd1 the tubules can enlarge without an increase in tubular cell numbers, suggesting that tubular basement membrane (TBM) remodeling is important for cystic dilation. Bulk RNAseq and qPCR analysis of metalloproteinases showed that A Disintegrin and Metalloproteinase with Thrombospondin Motif 1 (Adamts1) expressed by proximal tubule is the most significantly upregulated metalloproteinase following loss of Pkd1 expression. We now show that Adamts1 promotes cyst growth following Pkd1 loss.

Methods: Mice were developed with inducible tubule-specific knockout of Pkd1 alone (Pkd^{TKO}) or both Pkd1 and Adamts1 (P/A^{TKO}) using doxycycline induction at age 4-6 weeks. Uninduced (UI) mice were used as controls.

Results: At 12 weeks age, P/A^{TKO} mice showed less kidney enlargement than Pkd^{TKO} mice (KW/BW ratio 0.009±0.003 vs 0.017±0.01 respectively, p<0.05) and a lower cyst index (29.1±7.2 vs 44.2±6.1 respectively, p<0.01) (Fig 1). Western blot showed a 2.5-fold increase in the 70kDa V1 neoepitope of the Adamts1 cleavage substrate versican that was prevented in P/A^{TKO} kidneys, with IF localizing the cleaved versican to the TBM in Pkd^{TKO} kidneys (Fig 2). The 70kDa cleaved versican, named versikine, has been shown to activate macrophage. Our data confirm that the decreased versikine levels in P/A^{TKO} kidneys correlate with a significant reduction in peritubular macrophage accumulation compared to Pkd^{TKO} kidneys.

Conclusions: Adamts1 is upregulated with the loss of Pkd1 expression, resulting in versican cleavage in the TBM with enhanced cyst formation and accelerated loss of kidney function.

Funding: Other U.S. Government Support

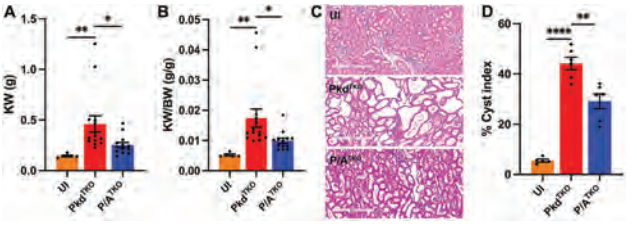


Fig 1. Deletion of Adamts1 slows cyst growth. (A) Kidney weight; (B) kidney weight to body weight ratio; (C) H&E images and (F) Cyst index.

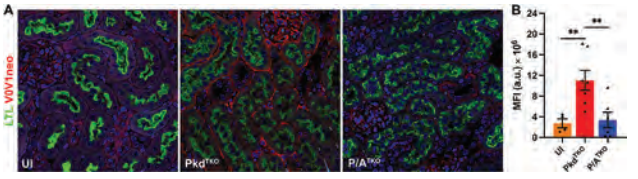


Fig 2. Adamts1 cleaved versican in the TBM. (A) IF staining for V0V1 neoepitope. (B) Mean fluorescence intensity.

FR-PO606

Role of Valosin-Containing Protein (VCP) in Ciliary Morphology and ADPKD: Exploring VCP as a Novel Genetic Interactor in Disease Progression

Carlotta Pioppini,[1] Rishi Bhardwaj,[2] Sorin V. Fedeles,[2] Duygu Elif Yilmaz,[1] Matteus Krappitz.[1] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Yale University, New Haven, CT.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder characterized by the progressive development of fluid-filled cysts in the kidneys, leading to organ enlargement and functional impairment. The main causative genes encode for the ciliary proteins PC1 and PC2, which position ADPKD amidst the spectrum of ciliopathies. Within PKD1-deficient cells, the accumulation of misfolded PC1 and PC2 proteins triggers the unfolded protein response (UPR). In this study, we investigated the genetic relationship between an associated interactor of the UPR, Valosin-containing protein (VCP), and PC1 dependent cystogenesis. Finally, we elucidate VCP's dual engagement as a ciliary protein, as well as its regulatory role in cilia morphology.

Methods: IMCD3^{wt} and IMCD3$^{Pkd1-/-}$ were treated with both pharmacological inhibitor of VCP or anti-VCP siRNA for 24 hours. Gene and protein expressions were detected respectively via qRT-PCR and western blotting. CelltiterGlo viability assay was used for cell viability analysis. Primary cilia were isolated from Pkd1$^{V5/+}$ cells and cilia localization of VCP was detected via confocal microscopy.

Results: VCP was identified as a ciliary protein in renal epithelial cells. By inhibiting VCP using pharmacological agents and siRNA-mediated genetic suppression, ciliary length was decreased for both treatments. Importantly, inhibition of VCP selectively decreased the viability of Pkd1 deficient cells by upregulating ER-dependent apoptotic pathways. This selective response highlights a novel therapeutic approach for targeting cells responsible for cyst development in ADPKD. The findings suggest that VCP is involved in ciliary dynamics but also in cellular survival mechanisms underpinning cystogenesis.

Conclusions: This study confirms the critical involvement of VCP in regulating ciliary morphology and suggesting its potential as a therapeutic target in ADPKD. By proving that VCP inhibition selectively reduced the viability of Pkd1 deficient cells while increasing ER-dependent apoptosis, our research implicates VCP as a novel viability factor of cyst lining cells. These novel insights open new perspectives for the development of targeted therapies aimed at modulating ciliary morphology and inducing apoptosis in cyst-forming cells.

Funding: Government Support - Non-U.S.

FR-PO607

Mitochondria-Targeted Antioxidant Therapy Ameliorates Arterial Dysfunction in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease

Nidhi Dwivedi, Brittany A. Stone, Zachary S. Clayton, Michel Chonchol, Berenice Y. Gitomer, Katharina Hopp, Vienna E. Brunt. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Cardiovascular diseases (CVD) are the leading cause of death in adults with ADPKD in part due to arterial dysfunction, e.g. endothelial dysfunction and aortic stiffening. ADPKD-associated arterial dysfunction appears to be mediated by impaired nitric oxide (NO) bioavailability secondary to excess mitochondria-derived reactive oxygen species. We tested efficacy of oral supplementation with mitochondrial antioxidant MitoQ (MQ) for improving arterial function in an orthologous mouse model of ADPKD.

Methods: Male/female C57Bl/6J *Pkd1*$^{RC/RC}$ mice were supplemented with 250 μM MQ in drinking water from 4-10 mo of age (i.e. mild to severe kidney disease) vs control water (n=5-8/group/sex). At intervention end, we assessed *in vivo* aortic stiffness as aortic pulse wave velocity (PWV) and endothelial function as endothelium-dependent dilation (EDD) to acetylcholine in isolated carotid arteries. Aorta rings were collected to assess aortic elastic modulus (EM), a measure of stiffness that isolates structural factors, and for histology. Key assessments were also made in wildtype (WT) mice (n=9/sex). Data are mean±SD. Stats are 1-way ANOVA with Tukey's post-hoc.

Results: Control *Pkd1*$^{RC/RC}$ (CONT) mice had impaired carotid artery EDD (peak EDD: 79±11 vs WT: 95±3 %, P<0.001) that was ameliorated by MQ (91±6%, P<0.01) via enhanced NO bioavailability (Δpeak EDD ± the NO synthase inhibitor L-NAME, CONT: 32±21 vs MQ: 48±10 %, P=0.03). There were no sex differences for endothelial function. Aortic PWV was higher in CONT *Pkd1*$^{RC/RC}$ vs WT mice (males: 447±36 vs 346±29 cm/s; females: 426±17 vs 369±26 cm/s; both P<0.01). MQ attenuated *in vivo* aortic stiffening in male (400±15 cm/s, P=0.02) but not female (427±39 cm/s, P>0.99) mice, and also lowered aortic *ex vivo* stiffness in male mice only (EM, CONT: 6437±1477 vs MQ: 4691±1790, P=0.08). However, aortic medial collagen content (Masson-trichrome, CONT: 25±12 vs MQ: 17±12%; P=0.05) was lower with MQ in both sexes, suggesting reduced fibrosis.

Conclusions: MQ supplementation in an orthologous model of ADPKD improves conduit artery endothelial function and arterial stiffness, although there may be some sex differences in efficacy. MQ represents a promising strategy for treating arterial dysfunction, and thereby reducing CVD risk, in ADPKD.

FR-PO608

IP1 Deletion Rescues Kidney Cyst Formation in Pkd1 KO Mouse Models

Ario Mohammadi,[1] Davoud Ghazanfari,[1,2] Armaghan Ayub,[1] Erica Zhou,[1] Jing Zhou.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: ADPKD (Autosomal Dominant Polycystic Kidney Disease) is a genetic disorder characterized by the development of multiple cysts in the kidneys. The disease is caused by mutations in *PKD1* and *PKD2*, encoding PC1 and PC2 respectively. To date, PC1 and PC2 have been implicated in modulating a number of cellular events such as Ca^{2+} signaling, mTOR, cyclic AMP, Wnt, PCP, and STAT3 pathways. Currently, there is limited knowledge regarding the mechanism(s) by which the *PKD1/2* mutations dysregulate these signaling pathways. Our research group and others have reported that simultaneous loss of genes including *ift88*, *Wdr19*, and *CRTC2*, in *Pkd1* KO mice models rescues cystogenesis and disease progression demonstrating potential therapeutic targets to attenuate ADPKD. It has been reported that IP1 forms a complex with PC1 and regulates multiple biological functions critical in ADPKD. Thus, IP1 is a potential therapeutic target for ADPKD.

Methods: Mice homozygous with an inducible mutation in *Pkd1* or *Pkd1IP1* genes were generated by intraperitoneal injection of tamoxifen at 3 weeks postnatal. Mice were dissected after 10 weeks. Kidney/BodyWeight (K/BW) ratios were calculated to analyze phenotype changes in the *Pkd1* KO and *Pkd1IP1* DKO mice. Various techniques such as immunohistochemistry, immunostaining, and western blotting were utilized for analysis and validation.

Results: To see if *IP1* deletion rescues *Pkd1* KO-induced cystogenesis, the *Pkd1* KO and *Pkd1IP1* DKO mice were dissected and kidneys were harvested at 10 weeks PI. The (K/BW) were significantly increased in the *Pkd1* KO mice and significantly reduced in the *Pkd1IP1* DKO. Histology analysis confirmed cyst formation in the *Pkd1* KO mice and that *IP1* deletion reduced cystogenesis. Immunostaining analysis revealed that cilia were significantly shortened in the DKO mice compared to the *Pkd1* KO mice. The western blotting analysis revealed that integrin α6 expression and Wnt and mTOR signaling pathways are dysregulated in the *Pkd1* KO mice, which was significantly reduced in the DKO mice. Further analysis is being conducted to gain more insight into the mechanism by which *IP1* deletion rescues ADPKD.

Conclusions: IP1 is a novel therapeutic target to rescue ADPKD. In vivo analysis revealed that *IP1* deletion rescues *Pkd1* KO-induced cytogenesis and shorten elongated cilia and corrected Wnt and mTOR signaling pathways in *Pkd1* KO mouse model.

Funding: NIDDK Support, Private Foundation Support

FR-PO609

Segment-Specific Cyst Index (SSCI): A Quantitative Analysis of Segment-Specific Responses during Cystogenesis

Zafer Akman, Vijayakumar R. Kakade, Lloyd G. Cantley. *Yale University School of Medicine, New Haven, CT.*

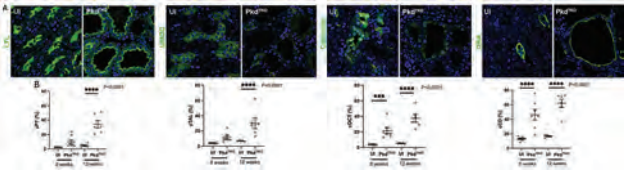
Background: Polycystic kidney disease (PKD) is a genetic disease in which loss of polycystin-1 or 2 causes tubular segments to undergo proliferation and dilation leading to progressive renal dysfunction. We developed SSCI to better quantify segment-specific responses during cystogenesis

Methods: Immunofluorescence microscopy using *Lotus tetragonolobus lectin* to identify proximal tubule (PT); uromodulin for thick ascending limb (TAL); calbindin for distal convoluted tubule (DCT); and *Dolichos biflorus agglutinin* for collecting duct (CD) was performed on cortex images from *Pkd1*$^{fl/fl}$*;Pax8-rtTA;TetO-Cre* mice (treated ± doxycycline from 4-6 weeks) at 8 and 12 weeks. Lumen and tubular area quantification for each cortical tubule segment was determined by manual masking in 5-7 randomly assigned boxes. The SSCI was expressed as ratio of lumen to tubular area percentage.

Results: Uninduced (UI) control kidneys showed a slight increase in SSCI from 8 to 12 weeks in all segments likely related to growth-induced GFR increases. Pkd1 tubule knock-out (Pkd^{TKO}) led to progressive dilation of all segments. Consistent with previous observations, CD exhibited the greatest SSCI (46% at 8 weeks and 62% at 12 weeks), with PT, TAL, and DCT showing less lumen dilation (10%, 11%, and 21% at 8 weeks, and 34%, 30%, and 37% at 12 weeks, respectively). Because CD had a significantly higher baseline SSCI in UI kidneys than all other segments, the fold-increase in SSCI following Pkd1 loss was the least in CD compared to the other 3 segments (3.7-fold for CD vs 7.4-fold for PT; 4.4-fold for TAL; and 7.3-fold for DCT).

Conclusions: SSCI reveals that Pkd1 loss caused expansion of all segments at 8 and 12 weeks, with the greatest lumen area found in CD. However, CD exhibited the least fold increase in SSCI following loss of Pkd1, suggesting that the CD, despite being the most cystic, may respond less to the loss of Pkd1 than other segments

Funding: Other U.S. Government Support



8-week images of (A) LTL for cPT, UMOD for cTAL; calbindin for cDCT and DBA for cCD (B) SSCI for each segment; dots signify the mean value calculated from one kidney *P<0.05, **P<0.01, ***P<0.001 and ****P<0.0001

FR-PO610

Labeling of Denatured Collagen in ADPKD and Comparison to Fibrotic Area

Caroline R. Sussman, Heather L. Holmes, Mohamed A. Addani, Seth M. Entriken, Damon A. Montgomery, Angel M. Obiorah, Vibhuti Amin, Kevin L. Webb, Deema Anaam, Diana Alzamareh, Slobodan Macura, Vicente E. Torres, Timothy L. Kline, Michael F. Romero, Peter C. Harris. *Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the fourth most common cause of kidney failure, and manifests through the proliferation of countless kidney cysts. Mounting research suggests the extracellular matrix (ECM) is integral to disease progression. Collagen, the predominant protein within the ECM, is encoded by 44 genes, forming intricate supramolecular structures that constitute 28 distinct collagen types. Methods used in ADPKD for tracking total collagen histologically are primarily trichrome or Picrosirius red (PSR) staining to determine percent fibrotic area. Besides fibrosis, destruction of collagen assemblies is a hallmark of tissue injury and disease. We examined here if denatured collagen is a more sensitive disease indicator than fibrotic area.

Methods: *Pkd2*^{hi4166} zebrafish were used with heterozygous adults compared to sibling WT. *Pkd1*$^{RC/RC}$ mice were used in C57BL/6J and compared to wildtype (Jackson Laboratory). Collagen hybridizing peptide (CHP, 3Helix) was used for fluorescence labeling of denatured collagen. CHP labeling was compared to fibrotic area determined from PSR staining. PSR staining, CHP labeling, and tissue area were calculated using ImageJ. Data are shown as mean ± SEM, p-values by t-test or ANOVA.

Results: CHP labeling surrounded 47.9% ± 14.5 of tubules in *pkd2*$^{+/-}$ zebrafish (n=8 fish), while no labeling was seen in WT (n=10; p=0.002). Labeling occurred around both proximal tubules/collecting ducts (LTL+; 41.7% ± 25.0, n=4) and distal tubules (DBA+; 54.0% ± 18.2, n=4). Labeling in mouse was not clearly associated with individual tubules and was present in normal and cystic regions. Quantification of fluorescence-tagged CHP in entire kidney sections showed more labeling in *Pkd1*$^{RC/RC}$ mice (581 au ± 68.3; n=6 mice) vs WT (341 au ± 14.4; n=6; p=0.006).

Conclusions: Denatured collagen labeling by CHP showed more consistent differences than fibrotic area by PSR. Additionally denatured collagen was detected distant from cysts in *Pkd1*$^{RC/RC}$ mice and in *pkd2*$^{+/-}$ zebrafish which lack cysts. These data suggest measuring denatured collagen may allow more reliable and sensitive detection of collagen changes in ADPKD than fibrotic area.

Funding: NIDDK Support

FR-PO611

Role of Ankyrin Repeat and Single KH Domain 1 in Autosomal Dominant Polycystic Kidney Disease Pathogenesis and CyclinD1/CDK4-Induced Proliferation

Maria-Eirini Terzenidou,[1,2] Fiona Macleod,[1,2] Maria Fragiadaki.[1]
[1]Queen Mary University of London Faculty of Medicine and Dentistry, London, United Kingdom; [2]The University of Sheffield Faculty of Medicine Dentistry and Health, Sheffield, United Kingdom.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of renal failure worldwide. It is a multisystem and progressive disease presenting with renal cyst formation, kidney enlargement, and extrarenal organ involvement. ADPKD involves mutations in *PKD1*, which encodes for polycystin-1 (PC1), and accounts for 85% of ADPKD cases, and *PKD2*, which encodes for polycystin-2 (PC2), and contributes to 15% of cases. PC1 and PC2 play a crucial role in controlling cell proliferation, while mutations in these proteins lead to uncontrolled proliferation, is a driver of ADPKD. The only clinically approved medicine for ADPKD, Tolvaptan, has limited use due to its high cost and adverse effects, e.g. liver failure. It is crucial to develop new therapeutic approaches. Ankyrin Repeat and single KH Domain 1 (ANKHD1) is a cancer-associated protein, which drives uncontrolled cellular proliferation and growth and has never been studied in ADPKD previously. We report that ANKHD1 drives excessive proliferation in mouse and human models of ADPKD.

Methods: We used immunostaining and advanced microscopy along with Western blotting. We performed our experiments in mouse models of ADPKD and patient-derived cell lines.

Results: In this study, we find that ANKHD1 protein levels are elevated in human and murine models of ADPKD and localise in cyst-lining cells. ANKHD1 knockdown in human ADPKD-derived epithelial cells or knockout of ANKHD1 in mouse tissues results in reduced proliferation, slower cystic growth in vitro and smaller kidneys in vivo; critically leading to improved renal function. To gain mechanistic insight we coupled RNA-seq with RNA immunoprecipitation (RIP)-seq, revealing that ANKHD1 controls the CDK4/cyclin D1 axis by binding to CDK4 mRNA. ANKHD1 mediates enhancement of CyclinD1/CDK4 activity via increased retinoblastoma phosphorylation (pRB). This is a p19-dependent and p53/p21-independent mechanism.

Conclusions: Taken together, we find a novel key role for ANKHD1 in ADPKD as a regulator of Cyclin D1/CDK4 cell cycle activity and proliferation, which in the context of ADPKD contributes to disease progression.

Funding: Government Support - Non-U.S.

FR-PO612

Activation of Toll-Like Receptor 2 Stimulated NF-κB-Mediated Inflammatory Responses and ERK-Mediated Cell Proliferation in ADPKD

Yang Zhang,[1,2] Matthew V. Plansinis,[1] Sophia Y. Peake,[1] Elisabeth G. Weber,[1] Gail Reif,[3] Darren P. Wallace,[3] Yan Zhang.[1,3] *[1]Michigan Technological University, Houghton, MI; [2]Nanchang University, Nanchang, China; [3]The University of Kansas Medical Center, Kansas City, KS.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive formation of numerous fluid-filled cysts. Aberrant innate immune responses play pivotal roles in driving cyst growth and disease progression; however, the precise molecular mechanisms remain poorly understood. Toll-like receptors (TLRs) are the key components of the innate immunity. Upon ligand binding, TLRs recruit MyD88, an adaptor protein, leading to the activation of transforming growth factor-β-activated kinase 1 (TAK1). TAK1 in turn activates ERK and NF-κB, key factors regulating disease progression in ADPKD. Currently, the effect of TLR activation has not been studied in ADPKD.

Methods: We measured the expression levels of TLR2, TLR4, MyD88, IκBα, and NF-κB p65 in human ADPKD kidneys and normal human kidneys (NHK) by qPCR) and immunoblot. NF-κB p65 nuclear localization was assessed using immunohistochemistry (IHC). To determine the effects of TLR2 and TLR4 activation, cultured ADPKD and NHK cells were treated with Pam3CSK4, a synthetic TLR2 agonist, or ultra-pure LPS-EK, a specific TLR4 agonist, and NF-κB signaling pathways, phosphorylated ERK (P-ERK), and cell proliferation were assessed.

Results: mRNA levels of TLR2, TLR4, MyD88, and NF-κB were significantly elevated in human ADPKD kidneys compared to NHK. IHC analysis revealed increased nuclear localization of NF-κB p65 in human ADPKD kidneys, along with reduced IκBα protein, demonstrating that the TLRs/NF-κB is upregulated in human ADPKD kidneys. Cellular experiment showed that treatment with Pam3CSK4 for increased the phosphorylation of IκBα (P-IκBα) and decreased total IκBα in ADPKD cells. Pam3CSK4 remarkably increased nuclear levels of NF-κB p65 and consequently increased the mRNA of IL-1β, TNF-α, and MCP-1, key factors creating a pro-inflammatory microenvironment in ADPKD kidneys. Moreover, we found that Pam3CSK4 increased P-ERK/ERK and cell proliferation in ADPKD cells but not in NHK cells. LPS-EK had limited effects on NF-κB and ERK in ADPKD and NHK cells.

Conclusions: Activation of TLR2 stimulated NF-κB-mediated expression of inflammatory cytokine and chemokines and ERK-mediated proliferation in ADPKD cells, providing insight into the molecular mechanisms by which innate immunity promotes disease progression.

Funding: NIDDK Support, Private Foundation Support

FR-PO613

Activation of Apelin Receptor Inhibits Cystogenesis in a Mouse Model of Polycystic Kidney Disease

Duuamene Nyimanu, Stephen C. Parnell, Christine V. Behm, Darren P. Wallace, Alan S. Yu. *The University of Kansas Medical Center, Kansas City, KS.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder characterized by increased cAMP signaling, cell proliferation, and fluid accumulation within the cysts. Tolvaptan is approved for ADPKD treatment, but its use is limited by various adverse effects, leaving an unmet clinical need for safe and effective therapy. The apelin receptor is a Gαi-coupled receptor which binds two endogenous ligands, apelin and Elabela/Toddler, to promote vasodilation, hypotension, and a decrease in cardiac hypertrophy. ADPKD patients have reduced circulating apelin which is associated with tubular damage, disease progression, and poor survival. We hypothesized that low apelin signaling in ADPKD contributes to cystogenesis and that exogenous apelin may ameliorate disease.

Methods: Male and female *Pkd1*$^{RC/RC}$; *Pkd2*$^{+/-}$ (PKD) mice were given 2 mg/kg body weight (BW) [Pyr^{1}]apelin-13, the small molecule apelin receptor agonist azelaprag (2 mg/kg), the vasopressin receptor antagonist mozavaptan (0.1% in food), or vehicle control by daily intraperitoneal injection for 27 days. Tail-cuff plethysmography was obtained, animals were euthanized, and the kidneys and heart were harvested. Kidney weight (%KW/BW) and heart weight (HW/BW), a measure of hypertrophy, were assessed. Blood urea nitrogen, an indicator of renal function, was determined by ELISA. Human ADPKD cells were cultured to form *in vitro* cysts in a 3D collagen matrix and treated with apelin receptor agonists for 7 days, and then cyst number and cystic area were analyzed.

Results: Exogenous [Pyr^{1}]apelin-13 significantly reduced %KW/BW (2.36±0.14 vs 1.70±0.04, p<0.0001) similar to mozavaptan (2.36±0.14 vs 1.75±0.06, p<0.0001), when compared to vehicle. Azelaprag, had a mild but significant reduction on %KW/BW (2.36±0.14 vs 1.93±0.06, p<0.01). Both [Pyr^{1}]apelin-13 and mozavaptan significantly reduced BUN in these animals. Cystic animals did not show any evidence for cardiac hypertrophy (HW/BW) and their blood pressure remained unaffected. Preliminary data from APDKD cells grown in 3D cell culture suggest inhibition of cyst formation by both apelin and azelaprag.

Conclusions: Targeting apelin receptor signaling may be a novel therapeutic strategy for treating ADPKD. Future experiments will explore the molecular mechanisms mediating the effects of apelin on cystogenesis.

Funding: Private Foundation Support

FR-PO614

Studying the Mechanism of Kidney Resident Macrophage Niche Filling after Temporary Depletion

Alex Yashchenko,[1,2] Kurt Zimmerman.[1,2] *[1]The University of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]The University of Oklahoma Department of Medicine, Oklahoma City, OK.*

Background: ADPKD is characterized by large, bilateral fluid-filled cysts scattered throughout the kidney. Our lab and others have previously shown that kidney resident macrophages (KRM) promote cyst progression in mouse models of ADPKD and are histologically cyst-associated. Continuous pharmacological depletion of KRM reduces cystic index and slows disease progression in mice; however, long term depletion of KRM using this approach is not feasible as the depletion is non-specific, affecting resident macrophage populations in multiple tissues. Therefore, we switched our focus to temporary KRM depletion in order to 1) study the mechanism of KRM niche filling, and 2) identify and test factors responsible for engraftment of KRM precursors (monocytes) into an opened KRM niche.

Methods: To study the mechanism of KRM niche filling, we used liposomal clodronate to deplete the KRM niche in *Ms4a3*^{Cre}-*Rosa26*^{TdTomato} and *Ms4a3*^{Cre}-*Rosa26*^{TdTomato}-*Pkd1*$^{RC/RC}$ mice. We analyzed the kinetics (i.e. timing) of KRM niche filling, degree of monocyte input into the KRM niche, and intracellular Ki67 staining by flow cytometry. Disease progression was analyzed by H&E staining.

Results: Analysis of preliminary data indicate that the KRM niche in both *Ms4a3^{Cre}-Rosa26^{TdTomato}* and *Ms4a3^{Cre}-Rosa26^{TdTomato}-Pkd1$^{RC/RC}$* mice is repopulated ~12 weeks after depletion due to the recruitment, engraftment, and differentiation of bone marrow-derived monocytes and through self-replication of the remaining kidney resident macrophages. Using single cell RNA sequencing, we identified *Cx3cr1* as a gene that was possibly required for the differentiation of monocytes into KRM during post-embryonic niche filling periods. To test the importance of *Cx3cr1* expression in monocytes during niche filling, we crossed *Lyz2^{Cre}* mice to *Cx3cr1$^{f/f}$* mice. Analysis of preliminary data from *Lyz2^{Cre}-Cx3cr1$^{f/f}$* mice show that CX3CR1 protein expression is significantly reduced in monocytes and KRM compared to controls although KRM was not impacted. Ongoing studies will address the role of monocyte-specific *Cx3cr1* in niche filling after depletion in healthy and *Pkd1$^{RC/RC}$* mice.

Conclusions: Our data suggest that the open KRM niche is replenished through both monocyte recruitment and engraftment as well as self-proliferation of the remaining KRM. Ongoing studies are addressing the importance of monocyte-specific *Cx3cr1* in the process of niche filling.

Funding: NIDDK Support, Private Foundation Support

FR-PO615

LSD1 Nuclear Condensation Promotes Cyst Growth in Polycystic Kidney Disease

Xiaoyan Li,[1,2] Xia Zhou,[1] Shasha Cheng,[1,2] Xiaogang Li.[1,2] *[1]Mayo Clinic Department of Internal Medicine, Rochester, MN; [2]Mayo Clinic Department of Biochemistry and Molecular Biology, Rochester, MN.*

Background: Epigenetic regulation has been a focus of scientific investigation in ADPKD. We have investigated the role of lysine demethylase LSD1 in ADPKD and show that LSD1 is upregulated in *Pkd1* mutant cells and tissues, and inhibition of LSD1 with its inhibitor delays cyst growth in *Pkd1* mutant mice. LSD1 contains two intrinsic disordered regions (IDRs), which are frequently found in phase-separated components, suggesting that LSD1 may form liquid-liquid phase separation (LLPS) to promote target gene transcription in *Pkd1* mutant cells and kidneys.

Methods: We confirm the formation of LSD1-LLPS by 1) immunofluorescence (IF) staining in *Pkd1* mutant cells and kidneys, and 2) by generating LSD1 truncated constructs with one or two IDRs. We identify 1) co-factors of LSD1 in LLPS by immunoprecipitation and mass spectrometry (MS) analysis, and 2) LSD1 target genes by ChIP-seq and RNA-Seq analysis.

Results: We found that upregulated LSD1 formed LLPS droplets in *Pkd1* mutant kidneys, which was rare in *Pkd1* wild type kidneys. GFP-tagged LSD1 with IDR1 or both IDR1 and IDR2 formed LLPS in HEK293T cells, similar as did by full length LSD1. The DNA binding domain (DBD) was necessary for its formation, supporting by that the LSD1-IDR1-DBD (IDR1 and SWIRM) but not LSD1-IDR1 alone formed nuclear puncta in cells. LSD1 target genes identified in ChIP-seq analysis are associated with immune response, DNA, lipid and amino acid metabolic signaling pathways. We identified that CREB might be a potential co-factor of LSD1 in LLPS and CREB also bound to the promoter of LSD1 to regulate its transcription. Treatment with PKA activator FSK increased the nuclear level of LSD1 and its formation of LLPS, whereas treatment with PKA inhibitor H89 decreased the expression of LSD1 and the formation of LLPS in cells. In addition, treatment with FSK and 1,6-hexanediol (1,6-HD, a molecule known to disrupt phase separation), increased the nuclear levels of LSD1, but suppressed the formation of LSD1-CREB contained LLPS, decreased LSD1 mediated demethylation of H3K4 and H3K9, suggesting that LSD1 might promote cyst progression through LSD1-CREB LLPS mediated regulation of gene transcription.

Conclusions: In this study, we identify that LSD1 forms LLPS and CREB is co-factor in this process and confirm that the formation of LSD1-CREB mediated phase separation regulates LSD1 target gene transcription to promote cyst growth in ADPKD.

Funding: NIDDK Support

FR-PO616

Lipid Metabolism Reprogramming in ADPKD

Davide Stefanoni,[1] Sara Clerici,[1] Daniel Spies,[1,3] Angelo D'Alessandro,[2] Alessandra Boletta.[1,3] *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]University of Colorado Anschutz Medical Campus, Aurora, CO; [3]Universita Vita Salute San Raffaele, Milano, Italy.*

Background: ADPKD, caused by either loss of PKD1 or PKD2, is characterized by metabolic changes such as increased glycolysis, glutaminolysis, and fatty acid synthesis (FAS). Recently, our group assessed the critical role of asparagine synthase (ASNS) to fuel the TCA cycle through glutamine. We reported that antisense oligonucleotides (ASO) therapy against *Asns* results in reduced disease progression. We also showed that central carbon metabolism alterations are improved upon silencing of *Asns*. Moreover, we previously stated an upregulation of reductive carboxylation in PKD, which generates great levels of citrate broken into acetyl-CoA required to fuel FAS. Here, we asked to which extent lipids are altered in PKD kidneys and whether they can be rescued by inhibition of *Asns*.

Methods: To assess the impact of *Asns* knockdown on FAS we performed untargeted lipidomics analysis by mass spectrometry (LC-MS) using kidney tissue samples of a *TamCre;Pkd1$^{\Delta C/flox}$* mouse model in which tamoxifen was injected at P45 and mice followed up for 160 days, and treated with either scramble or *Asns*-ASO.

Results: Lipidomics profiling identified over 900 lipids, with many altered in PKD murine tissues. Specifically, KO samples exhibited 347 significant lipid changes to untreated controls. Among those only 120 lipids preserved significance following *Asns*-ASO treatment, whereas the majority were rescued. In line with this, PCA analysis revealed a clear separation between controls and KO, which *Asns*-ASO treatment largely rescued. A disease-characteristic signature emerged in KO samples as exhibited by lipid class composition analysis, which shows steryl esters, and fatty acids (FA) as the most upregulated, whereas triglycerides (TG) as the most down-regulated lipids. Volcano plot and enrichment analyses of the lipid classes confirmed these data. Of note, changes in TG were significantly rescued upon *Asns* silencing, while sterols and FA only partially, revealing a connection between ASNS and lipid dysregulation in ADPKD.

Conclusions: We previously identified *Asns* as a key player in multiple metabolic pathways in PKD including FAS. Our data show that along with central carbon metabolism, major changes in lipid composition can be observed in PKD kidneys. Unexpectedly our data seem to suggest a potential mechanistic link between ASNS and FAS and confirm the therapeutic significance of targeting *Asns* in ADPKD.

FR-PO617

Role of Pannexin-1/P2X7 Interaction in Kidney Cyst Development

Veniamin Ivanov,[1] Sergey N. Arkhipov,[1,2] Tengis S. Pavlov.[1,2] *[1]Henry Ford Health System, Detroit, MI; [2]Wayne State University, Detroit, MI.*

Background: Active extracellular ATP release is conducted by ion channel pannexin-1 (Panx1), expressed in the kidney and previously has been shown to be upregulated in both autosomal dominant and recessive polycystic kidney disease (ADPKD, ARPKD) cystic epithelium and coupled with upregulation of P2X7. Mechanism of regulation of Panx1 channel has not well characterized. We hypothesized that activation of purinergic signaling is a major factor of cystogenesis and regulation of this signaling involves an interaction with P2X7.

Methods: We used a model of cystogenesis to test if purinergic signaling affects growth of cysts formed by mpkCCDcl4 cells in Matrigel in a presence of Forskolin with further evaluation of protein and mRNA expression. To test the regulation of purinergic signaling and interaction of Panx1 and P2X7, patch-clamp experiments in transfected or co-transfected CHO cells and co-immunoprecipitation has been performed.

Results: Stimulation of P2X receptors of mpkCCDcl4 cysts with α, βMe-ATP, an ATP analog drug, stimulates cyst growth (mean cyst size; vehicle 2903 um^2 vs 4343 um^2 treated<0.001) and Panx1 protein expression ($p<0.05$) with no effect on mRNA level. Co-immunoprecipitation experiments in $mpkCCD_{cl4}$ cells revealed that P2X7 receptors bind panx1. Treatment of CHO-K1 cells, co-transfected with PANX1 and P2X7 cDNA plasmids, with αβ-MeATP significantly and reversibly stimulated the activity of Panx1 channels. mRNA level of expression of Panx1 and P2X7 in kidney of Pkd1$^{RC/RC}$ mice was increased compared to the normal mice (Panx1 6.79-fold, $p<0.05$; P2X7 3.52-fold, $p<0.05$).

Conclusions: Stimulation of P2X7 receptor promote cystogenesis in vitro with subsequent increase of Panx1 protein expression. Activity of Panx1 channel is increased in a similar manner. Giving previously investigated data on Panx1 and P2X7 expression in cystic models, we assume that this mechanism contributes to the ATP release into the cystic space and act as a major factor in cystogenesis.

Funding: NIDDK Support

FR-PO618

Specific Population of Urinary Extracellular Vesicles Distinguishes Pediatric Patients with ADPKD from Controls

Christian Hanna, Ryan Helland, Hana Yang, Zejfa Haskic, Luke C. Radel, David Soma, Fouad T. Chebib, Peter C. Harris, John C. Lieske, Muthuvel Jayachandran. *Mayo Clinic Minnesota, Rochester, MN.*

Background: There is an urgent need for specific cellular and molecular biomarkers to predict ADPKD progression in children. Emerging studies show that renal cell-derived urinary extracellular vesicles (EVs) are stable biomarkers of kidney pathophysiology. Animal studies suggested that certain EVs promote cyst growth. However, the excretion of EVs from specific renal tubular segments and interstitial pro-and anti-inflammatory immune cells in children with ADPKD is unknown. Thus, we quantified urinary excretion of EVs from renal tubular and interstitial immune cells in children with and without ADPKD using an established and published method of digital flow cytometer.

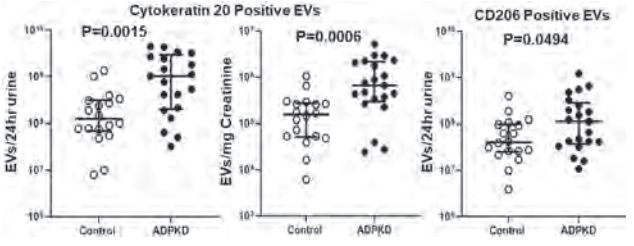
Methods: We collected 24-hour urine from children (9-18 years old; median 14) with genetically defined ADPKD (n=21; 12F/9M) and age-/sex-matched controls (n=18; 7F/11M). Data are presented as median (25th, 75th percentile) and analyzed by the Mann-Whitney test to identify significant ($P<0.05$) differences between groups.

Results: Excretion of EVs from papillary epithelium (cytokeratin 20 (CK20) positive/24hr urine or mg creatinine) was significantly greater in ADPKD patients

compared to controls (Fig.1). Excretion of EVs from M2 macrophages (Mϕ's; anti-inflammatory; CD206 positive/24hr urine) was significantly increased in ADPKD patients (Fig.1). Excretion of urinary EVs from the proximal tubule, thin and thick limb, distal and collecting tubules, monocytes, M1-Mϕ's, other M2-Mϕ's markers, T-cells, B-cells, NK-cells, and plasma cells did not different between groups. There was a trend toward increased excretion of phosphatidylserine and CD63-positive urinary EVs in ADPKD patients. Number of CK20 positive EVs correlated (Pearson (r) =0.57; P=0.032) with height-adjusted total kidney volume (ml/m) in ADPKD patients.

Conclusions: These results suggest that pediatric ADPKD patients have increased excretion of CK20-carrying urinary EVs, as well as EVs derived from M2-Mϕ's. The potential role and pathophysiological significance of these urinary EV biomarkers requires further study.

Funding: NIDDK Support, Other NIH Support - Zell Family Foundation



FR-PO619

The Cystogenic Effects of Ouabain in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Require Cell Caveolae

Jordan Trant, Jeff P. Mcdermott, Gladis S. De Blanco, Gustavo Blanco. *University of Kansas Medical Center Department of Cell Biology and Physiology, Kansas City, KS.*

Background: We have previously shown that the hormone ouabain is a circulating factor which can accelerate the progression of autosomal dominant polycystic kidney disease (ADPKD). At physiologic concentrations, ouabain increases cyst area and fibrosis in kidneys from ADPKD but not wildtype mice. These effects are mediated through ouabain binding to its specific receptor, Na,K-ATPase (NKA). In ADPKD, a fraction of the NKA has an abnormally high affinity for ouabain, leading to an over-activation of the NKA signal transduction cascade. Previous studies in cell lines suggest that ouabain's effects are mediated by the NKA located in the cell caveolae. Here, we determined the role of caveolae in NKA-mediated and ouabain-induced effects in ADPKD using a new mouse model in which caveolar formation is disrupted on the background of ADPKD (*Pkd1*$^{RC/RC}$*Cav1*$^{-/-}$).

Methods: Mice homozygous for the knockout of caveolin-1 (Cav1), a main structural component of caveolae, were crossed with *Pkd1*$^{RC/RC}$ mice to obtain the *Pkd1*$^{RC/RC}$*Cav1*$^{-/-}$ model where caveolae no longer form in the kidney. Ouabain (0.3 mg/kg) or saline was injected intraperitoneally to *Pkd1*$^{RC/RC}$ or *Pkd1*$^{RC/RC}$*Cav1*$^{-/-}$ mice daily for 5 months. Kidneys from these mice were analyzed for cyst area, kidney weight to body weight ratio (%KW/BW) and fibrosis. Cell proliferation (using Ki67 as a marker) and the activation of downstream members of ouabain-NKA signaling (ERK and Akt) were measured.

Results: The ablation of Cav1 and disruption of caveolae in the kidney was confirmed in *Pkd1*$^{RC/RC}$*Cav1*$^{-/-}$ mice by immunoblot and electron microscopy. Loss of caveolae abolished the high ouabain affinity component of NKA seen in *Pkd1*$^{RC/RC}$ mice, with all NKA having the same ouabain affinity as wildtype mice. After 5 months of ouabain administration, *Pkd1*$^{RC/RC}$*Cav1*$^{-/-}$ kidneys did not show the ouabain-induced increase in cyst number or fibrosis seen in *Pkd1*$^{RC/RC}$ mice. In addition, the ouabain-induced phosphorylation of ERK and AKT and the increase in cell proliferation in *Pkd1*$^{RC/RC}$ kidneys was blunted in the *Pkd1*$^{RC/RC}$*Cav1*$^{-/-}$ mice.

Conclusions: Our results show that disruption of caveolae through deletion of caveolin-1 abolishes the abnormal high ouabain affinity fraction of NKA and the cystic effects of ouabain in ADPKD mice, providing *in vivo* evidence for the need of cell caveolae in the signaling function of NKA.

Funding: NIDDK Support

FR-PO620

Hyper-O-GlcNAcylation of AMP-Activated Protein Kinase (AMPK) and Acetylated α-Tubulin in ADPKD Pathogenesis

Matthew A. Kavanaugh, Stephen C. Parnell, Chad Slawson, Darren P. Wallace, Pamela V. Tran. *The University of Kansas Medical Center, Kansas City, KS.*

Background: Altered cell metabolism is an important component of autosomal dominant polycystic kidney disease (ADPKD) pathogenesis, but drivers of these alterations are not understood. The addition of O-linked β-N-acetylglucosamine (O-GlcNAc) onto protein substrates by O-GlcNAc transferase (OGT) integrates multiple metabolic signals that are dysregulated in ADPKD. We have reported that protein O-GlcNAcylation is increased in kidneys of ADPKD patients and mouse models, and that genetic downregulation of O-GlcNAcylation markedly attenuates disease severity and extends mouse survival. To determine the underlying pathogenic mechanisms, we sought to identify proteins that are hyper-O-GlcNAcylated in ADPKD.

Methods: We generated juvenile and adult *Pkd1* conditional knockout (cko) and *Pkd1;Ogt* double knockout (dko) mice using the HoxB7-Cre and the doxycycline-inducible Pax8rtTA;LC1-Cre recombinases (induced from 4-6 weeks of age). Juvenile and adult mouse kidneys were analyzed on postnatal day (P)14 and at 4 months of age, respectively. Hyper-O-GlcNAcylated proteins were identified via immunoprecipitation and Western blot, after which sites were mapped via mass spectrometry with generation and analysis of relevant point mutants to follow.

Results: In juvenile mice, *Ogt* deletion in *Pkd1* cko mice reduced renal cystogenesis and kidney weight:body weight ratios (KW/BW); restrained renal cilia lengths; reduced inflammation and fibrosis; increased activation of the energy sensor AMPK; and improved kidney function. Further, while *Pkd1* cko mice die between P14-P20, *Pkd1;Ogt* dko mice survive beyond one year. In adult mice, deletion of *Ogt* in *Pkd1* cko mice reduced renal cystogenesis and KW/BW. In P14 kidney extracts, hyper-O-GlcNAcylation of metabolic regulator, AMPKα1/α2, as well as of acetylated α-tubulin, which comprises the ciliary axoneme, was observed. In AMPKα1, Ser184 was identified as an O-GlcNAc site, adjacent to the activating phosphorylation site.

Conclusions: In PKD, protein O-GlcNAcylation, including of AMPK and acetylated α-tubulin, is increased, and deletion or inhibition of OGT reduces cyst growth and disease severity, demonstrating that O-GlcNAcylation is an important driver of PKD progression. We propose that targeting O-GlcNAcylation may have therapeutic potential in ADPKD.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO621

Exploring the Role of Interferon-Gamma in Injury-Accelerated Cystic Kidney Disease

Morgan E. Smith,[1] Katharina Hopp,[2] Kurt Zimmerman.[1] [1]*The University of Oklahoma Health Sciences Center, Oklahoma City, OK;* [2]*University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Acute kidney injury (AKI) accelerates cystogenesis in mouse models of polycystic kidney disease (PKD); however, the mechanism underlying this acceleration remains unclear. Previous data from our lab indicate that genetic deletion of adaptive immune cells (T and B cells) rescues injury accelerated PKD. Additionally, single cell RNA sequencing data suggest that the cytokine interferon gamma (IFNγ), which is produced by CD4+ and CD8+ T cells, is responsible for driving the injury accelerated phenotype. Based on these data, we hypothesize that IFNγ is a significant contributor to injury accelerated PKD.

Methods: To test if IFNγ is essential for injury accelerated cystic disease, we crossed mice lacking IFNγ *(Ifng*$^{-/-}$*)* with our murine model of cystic kidney disease (Cagg Cre^{ERT2} *Ift88*$^{f/f}$). At 8-10 weeks of age, mice were induced with tamoxifen followed by intraperitoneal injection of folic acid (FA) at 11-12 weeks of age to induce kidney injury. Sodium bicarbonate solution was used as a vehicle control. Kidneys were collected 56 days post-injury and the PKD phenotype was measured by quantifying cystic index and cyst number.

Results: Analysis of preliminary data indicate that loss of IFNγ significantly reduced the severity of PKD as measured by 2KW/BW, cystic index, cystic number, and cyst size compared to controls. Likewise, loss of IFNγ was associated with reduced kidney fibrosis and improved kidney function. Analysis of immune cell numbers via flow cytometry indicate that loss of IFNγ significantly reduced the number of neutrophils and kidney resident macrophages (KRM) compared to controls. To test if CD4+ or CD8+ T cell-derived IFNγ was responsible for the observed phenotypic rescue in IFNγ deficient mice, we crossed mice deficient in CD4+ or CD8+ T cells to our mouse model of cystic kidney disease. Analysis of preliminary data indicate that loss of CD4+ T cells, but not CD8+ T cells, was associated with improved phenotypic outcome following FA induced injury. Loss of CD4+ T cells, but not CD8+ T cells, also reduced the number of KRM and neutrophils following FA induced injury.

Conclusions: Collectively, our data suggest that CD4+ T cell-derived IFNγ drives injury accelerated cystic kidney disease.

Funding: NIDDK Support

FR-PO622

Deletion of the Homeobox Gene Cux1 Decreases Ciliogenesis in a Mouse Model of Polycystic Kidney Disease

Greg Vanden Heuvel,[1] Zhi Nee Wee,[1,2] Kristi L. Bailey.[1] [1]*Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, MI;* [2]*Charles River Laboratories International Inc, Mattawan, MI.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common inherited disorders affecting the kidney. Renal cyst development in ADPKD results from mutations in the PKD1 or PKD2 genes, which encode the proteins polycystin1 (PC1) and polycystin2 (PC2). PC1 and PC2 proteins are localized to primary

cilia where they are proposed to form a receptor channel complex that detects flow transmitting a calcium-mediated signal. Primary cilia are critical to the pathogenesis of ADPKD, which is one of many ciliopathies that exhibit renal cystic disease. Cux1 is a cell cycle dependent transcriptional repressor that regulates the cyclin kinase inhibitor p27. Cux1 is highly and ectopically expressed in mice carrying a collecting duct (CD) specific mutation of Pkd1 (Pkd1 knockout) and in human ADPKD cells. Mice carrying mutations in both Cux1 and Pkd1 have reduced cystic disease and an increased life span.

Methods: To begin to determine whether Cux1 regulates ciliogenesis we evaluated cilia morphology and the expression of the ciliary proteins OFD1, Ptch1, and Ift122 in kidneys isolated from Pkd1 knockout and Pkd1/Cux1 double knock out mice. Cilia morphology was assessed by immunofluorescence labeling of alpha- tubulin, a major component of cilia, and the collecting duct marker dolichos biflorus agglutinin (DBA) to identify cells in which Pkd1 was deleted.

Results: Cilia in Pkd1/Cux1 double knockout kidneys were significantly shorter than cilia in the Pkd1 knockout kidneys alone, consistent with previous studies showing that decreased cilia length corresponds to decreased cystic disease. In addition, expression of OFD1, an inhibitor of cilia formation was significantly increased in Pkd1/Cux1 double knockout kidneys compared to Pkd1 knockout kidneys alone.

Conclusions: Taken together, our results suggest a novel role for Cux1 in regulating ciliogenesis in polycystic kidney disease.

FR-PO623

NOTCH2 Mutations Associated with Alagille Syndrome Result in Longer Primary Cilia and Inactivation of Ift88 in Mice with Notch Signaling-Deficient Kidneys Partly Rescues Kidney Abnormalities

Matthew Mckillop,[1] Jennifer DeRiso,[1] Ayesha Anwer,[1] Kameswaran Surendran.[1,2] Surendran Lab. *[1]Sanford Research, Sioux Falls, SD; [2]University of South Dakota Sanford School of Medicine, Sioux Falls, SD.*

Background: Alagille Syndrome (ALGS) is an autosomal dominant congenital disorder linked to mutations in *NOTCH2*, which codes for a receptor in the Notch signaling pathway. ALGS has a variable penetrance of kidney disease with a variety of kidney abnormalities including hypoplastic and multi-cystic kidneys. Notch signaling deficiency in nascent nephrons in mice results in small multi-cystic kidneys and epithelial cells with long primary cilia. It is unknown if *NOTCH2* mutations associated with kidney disease in ALGS also result in longer cilia. Also unknown is if the long cilia mediate cyst formation in the kidney and decline in renal function in mice with Notch-signaling deficient kidneys.

Methods: We analyzed kidney structure and function in mice with inactivation of one allele of *Notch1* and two alleles of *Notch2* along with varying number of *Intraflagellar transport protein 88* (*Ift88*) alleles in developing mouse nephrons. We modeled ALGS associated *NOTCH2 R2003X* (*N2R2003X*) and *NOTCH2 Exon33 splice acceptor* (*N2Ex33sp*) mutations in Madin-Darby Canine Kidney (MDCK) and performed RNA-sequencing to identify differentially expressed genes. We also determined proteins that are proximal to Notch2 versus N2Ex33sp mutant in MDCK cells.

Results: Cystic kidney phenotype and decline in renal function in mice with *Notch1* & *2* deficient kidneys were rescued when *Ift88* is in the heterozygous state. MDCK cells with *N2R2003X* and *N2Ex33sp* mutations have longer cilia while inactivating both alleles of *Notch2* by introducing a stop codon into exon5 in MDCK (*N2-/-*) does not increase cilia length. Many primary cilia related genes are differentially expressed in *N2Ex33sp* and not in *N2-/-* cells compared with wild type cells. Many cilium assembly proteins are proximal to wild type Notch2 and not N2Ex33sp mutant.

Conclusions: ALGS associated N2+/R2003X and N2+/Ex33sp mutations, which result in truncated Notch2 proteins, likely function in a dominant manner and the long cilia phenotype is not just due to loss of Notch2. While many cilia related genes are differentially expressed in N2+/Ex33sp cells, and N2Ex33sp mutant protein has reduced proximity to cilium assembly proteins, partial inactivation of *Ift88* suppresses Notch-deficiency dependent kidney disease.

Funding: NIDDK Support

FR-PO624

Axoneme Hypoglutamylation in Primary Cilia Promotes Cystogenesis in ADPKD

Kai He, Xiaobo Sun, Jinghua Hu. *Mayo Clinic Minnesota, Rochester, MN.*

Background: ADPKD is primarily caused by mutations in the *PKD1* and *PKD2* genes, which encode the proteins PC1 and PC2, respectively. PC1 and PC2 are hypothesized to form a receptor-channel complex on primary cilia membrane, which is crucial for maintaining the normal function and structure of renal tubules. PC1 and PC2 reciprocally regulate each other's ciliary localization by unclear mechanism. Loss of PC1 and PC2 in cilia significantly contribute to the progression of PKD. Therefore, increasing the levels of PC1/2 within cilia emerges as a potential therapeutic strategy for PKD. However, feasible methods or molecular targets to increase ciliary levels of PC1 and PC2 in the context of PKD are currently lacking. Polyglutamylation (PG) is a prominent post-translational modification of tubulin that occurs on the primary cilia axoneme. The established correlation between axoneme hypoglutamylation (reduced glutamylation) and human ciliopathies, which often present with cystic kidney phenotypes, suggests a plausible link between impaired axoneme PG and PKD pathogenesis. Our prior research has revealed that axoneme is crucial for ciliary localization of PC2. In this study, we foucs on the role of axoneme hypoglutamylation in renal cystogenesis in ADPKD.

Methods: 1. 3D sephroid culture. 2. Immunofluoresent. 3. siRNA/shRNA-based knockdown. 4. Lentivirus-based overexpression.

Results: Loss of PC1 leads to marked axoneme hypoglutamylation in PKD1 mutant renal epithelial cells. Remarkably, genetically or pharmacologically reducing axoneme PG significantly promotes 3D cystogenesis, while increasing axoneme PG suppresses it in PKD1 mutant renal tubular epithelial cells. Furthermore, reducing axoneme PG decreases, while increasing axoneme PG enhances the ciliary levels of PC2. These data suggest that PC1 regulates the ciliary localization of PC2 through modulating axoneme PG, and that axoneme hypoglutamylation significantly contributes to PKD progression. Our ongoing work focuses on investigating the role of axoneme hypoglutamylation in *in vivo* cystogenesis and testing whether increasing axoneme PG could attenuate PKD progression in $Pkd1^{RC/RC}$ mice.

Conclusions: 1. PKD1 deletion leads to axoneme hypoglutamylation in renal epithelial cells. 2. Reducing axoneme PG aggrevates, while increasing axoneme PG suppresses cystogenesis in 3D culture. 3. Axoneme hypoglutamylation contributes to PC1-deficicency induced ciliary loss of PC2.

Funding: NIDDK Support, Private Foundation Support

FR-PO625

Loss of ARL13B's Guanine Nucleotide Exchange Factor Activity for ARL3 in Cilia Suppresses Cystogenesis in Adult Mouse Models of Polycystic Kidney Disease

Robert E. Van Sciver,[1] Avery Forster,[1,2] Tamara Caspary.[1] *[1]Emory University School of Medicine, Atlanta, GA; [2]Boston University College of Arts & Sciences, Boston, MA.*

Background: Polycystic kidney disease (PKD) is largely driven by mutations in *PKD1* or *PKD2*, which encode for ciliary polycystin proteins. Mouse models predict the presence of a cilia-dependent cyst activating (CDCA) pathway that functions in cilia to drive PKD cystogenesis. This CDCA pathway is normally inhibited by the polycystin proteins, yet the identity of this pro-cystic pathway remains unknown. ARL13B is an atypical ciliary GTPase which also possesses guanine nucleotide exchange factor (GEF) activity for another ARL family GTPase, ARL3. Recent work revealed a central role of ARL13B's cilia localization in cystogenesis, yet its role in the CDCA pathway is unknown.

Methods: To directly test ARL13B's role in the CDCA pathway, we engineered two distinct *Arl13b* mutant alleles at the endogenous locus in mice: (1) $Arl13b^{V358A}$, which mutates a single amino acid in ARL13B's cilia-localization motif; and (2) $Arl13b^{R79Q}$, which prevents its GEF activity for ARL3. $ARL13B^{V358A}$ retains all known ARL13B biochemical functions, is stably expressed yet is undetectable in cilia. $ARL13B^{R79Q}$ localizes to cilia, retains its GTPase activity, yet cannot activate ARL3. Combining these alleles with the kidney-specific loss *Pkd1* allowed us to directly test ARL13B's ciliary and enzymatic roles in kidney cystogenesis *in vivo*.

Results: At 18-weeks, control mouse kidneys had a kidney weight to body weight ratio (KW:BW) of 1.39±0.04. In adult induction models, loss of *Pkd1* alone led to severe cystic kidneys with KW:BW of 11.98±0.99. Ciliary exclusion of ARL13B (V358A), total loss of its GEF activity for ARL3 (R79Q), or loss of its GEF activity, specifically in cilia (V358A/R79Q) suppressed the cystic phenotype caused by loss of *Pkd1* alone with KW:BW of 2.47±0.36 and 4.09±0.78, 3.75±0.70, respectively.

Conclusions: In PKD mouse models, loss of ARL13B from cilia, its GEF activity for ARL3 everywhere, or its GEF activity specifically in cilia suppressed the severe cystic kidney phenotype caused by loss of *Pkd1* alone. These results suggest that the ARL13B–ARL3 axis are major components of the CDCA pathway. Our findings indicate that ARL13B activates a pro-cystogenic pathway via its GEF activity for ARL3 in cilia, providing a mechanism that could be targeted therapeutically.

Funding: NIDDK Support, Other NIH Support - NIGMS

FR-PO626

Tryptophan Metabolism as a Link between Cilia and Mitochondria in Renal Tubule Cells

Brennan Winkler,[1] Xiaofeng Zuo,[1] Peifeng Deng,[1] Wayne R. Fitzgibbon,[1] Joshua H. Lipschutz.[1,2] *[1]Medical University of South Carolina, Charleston, SC; [2]Ralph H Johnson VA Health Care System, Charleston, SC.*

Background: Primary cilia and mitochondria are centrally involved in ADPKD. We showed that the exocyst trafficking complex is necessary for ciliogenesis, knockdown (KD) of the central exocyst component Exoc5 resulted in absent cilia with increased susceptibility to H_2O_2, overexpression (OE) of Exoc5 increased cilia length with protection from H_2O_2, and renal tubule-specific knockout (KO) of Exoc5 in mice led to PKD. Intraflagellar transport protein 88 (Ift88) is also necessary for ciliogenesis.

Methods: We performed Seahorse assays, staining for reactive oxygen species (ROS), transmission electron microscopy (TEM), and a metabolomics screen in Exoc5 OE, Exoc5 KD, Exoc5 ciliary targeting sequence point mutant (cts-mut), and control Madin-Darby canine kidney tubule (MDCK) cells, and murine Ift88 KO and rescue cells. We also crossed Exoc5$^{fl/fl}$ and Ift88$^{fl/fl}$ mice with mice expressing CreERT2 driven by the proximal tubule-specific sodium-dependent inorganic phosphate transporter and performed bilateral ischemia reperfusion (I/R).

Results: There was decreased mitochondrial respiration, increased ROS, and abnormal mitochondria in Exoc5 KD, Exoc5 cts-mut cells, and Ift88 KO cells compared to control MDCK and Ift88 rescue cells, with opposite effects seen in Exoc5 OE cells. In our metabolomics screen tryptophan levels were increased 113- and 58-fold, respectively, in Exoc5 cts-mut and Exoc5 KD compared to control cells. Concomitantly, kynurenine which is directly downstream of tryptophan was decreased in these cells. Similar results were seen in the Ift88 KO compared to rescue cells. In Exoc5 OE cells tryptophan was decreased and kynurenine was increased. Metabolism of tryptophan to kynurenine occurs via indoleamine 2, 3-dioxygenases (*IDO1 and IDO2*) and changes in mRNA levels by RT-qPCR were consistent with the metabolomics data. Proximal tubule-specific Exoc5 and Ift88 KO mice lacked cilia, had decreased levels of mitochondrial ATP synthase, increased tryptophan, and aggravated renal injury following I/R injury compared to control mice (p=0.005 for Exoc5, p=0.04 for Ift88).

Conclusions: Tryptophan metabolism may be the "cilia-dependent cyst activating" mechanism with cilia loss resulting in a metabolic derangement that prevents cell proliferation and cyst formation. We also show that loss of cilia primes renal tubule cells for injury.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO627

Defining the Interaction Network of the CPLANE Complex Reveals Cilia and Actin Regulatory Components

Rita K. Kalot,[1,2] Sima Babayeva,[1] Elena Torban.[1,2] *[1]McGill University Health Centre, Montreal, QC, Canada; [2]McGill University, Montreal, QC, Canada.*

Background: Almost all vertebrate cells have a single primary cilium that protrudes to the extracellular space and acts as a signalling nexus. Defects in primary cilia cause a set of diseases termed ciliopathies that affect multiple organs including the kidneys. Mutations in ciliogenesis and planar cell polarity (CPLANE) genes *FUZZY, INTURNED and WDPCP* lead to human ciliopathies. Although the homologs of CPLANE proteins in *Drosophila Melanogaster* regulate the planar cell polarity and actin polymerization, their functions in ciliation and the etiology of ciliopathies remain elusive. We hypothesize that CPLANE proteins regulate ciliary and actin-regulating proteins to control primary cilia formation.

Methods: Co-immunoprecipitation assay was used to validate the interactions between IQGAP1 and CPLANE proteins. IQGAP1 knockdown was achieved by siRNA transfection in hTERT-RPE-1 cells. Ciliation and YAP localization were assessed by immunofluorescence using anti-ARL13b and anti-YAP antibody, respectively. BioID baits were genrated by gateway cloning and transfected in FlpIn TREX293 cells. Pulldown coupled to mass spectrometry was used to identify CPLANE interactors. Protein identification and analysis of interactions were done in Prohits, and SAINT.

Results: Using a preliminary Bio-ID we identified IQGAP-1(an actin-regulating protein) as a novel interactor of Fuzzy. We established that IQGAP1 interacts with all CPLANE proteins and showed that the knockdown of IQGAP1 reduces ciliation and cilia length in htERT-RPE-1 cells. Since IQGAP1 does not localize to the ciliary basal body, we propose an indirect link where IQGAP1 regulates cilia length by modulating YAP1 downstream ciliary transcriptional targets. To better understand the roles of CPLANE in ciliogenesis, we generated CPLANE BioID baits and conducted an interaction study. Coupling BioID with MS and bioinformatics we identify multiple CPLANE interactors that further link actin regulation to primary cilia functions.

Conclusions: This study unravels a link between the CPLANE complex and actin regulators. Identifying CPLANE-specific proximity interactors helps discover novel molecular components regulating ciliation, particularly through the regulation of actin dynamics. This bridges the gap between actin regulatory pathways and ciliation and proposes potenitial actin-targeting therapeutics as treatment for ciliopathies.

Funding: Government Support - Non-U.S.

FR-PO628

A High-Content Screening Approach to Unveil the Molecular Mechanism of the Ciliary Response to Glutamine

Francesco Consolato, Maria Elena Steidl, Laura Cassina, Alessandra Boletta. *IRCCS Ospedale San Raffaele, Milano, Italy.*

Background: Polycystic Kidney Disease (PKD) is the most common ciliopathy, caused by malfunctioning primary cilia. Primary cilia are microtubule-based organelles at the cell surface that integrate metabolic and signaling cues, though their exact sensory function is unclear. We recently demonstrated that primary cilia sense nutrient availability and adjust the cellular metabolic response. Glutamine deprivation causes cilia elongation, while its supplementation induces shortening due to TCA cycle anaplerosis. We identified asparagine synthetase (ASNS) as a key enzyme; its silencing reduces both anaplerosis and cilia shortening. We aim to identify the full pathway driving this cilia response, believing it will be crucial in PKD.

Methods: mIMCD3 stable transfectants with Arl13b-GFP were generated, subcloned, and used to set up an automated quantification of ciliary length in response to glutamine using the ImageXpress Micro Confocal Imaging System by Molecular Devices, scalable to 384 wells. Cells were transfected with key siRNAs for setup studies, and 48 hours later, were analyzed by western blotting or for cilia length. For each well, 16 fields were acquired, measuring over 1,000 cilia per condition, with post-image analysis performed using MetaXpress Custom Modules software.

Results: To clarify the molecular mechanism behind ciliary dynamics under stress conditions, we developed a high-content screening method to automatically measure cilia length in response to various stimuli and optimized conditions for silencing known pathway components. According to literature, silencing *Ift88*, *Arl13b*, *Ccdc41*, and *Prpf8* induced ciliary shortening, while silencing *Asns*, *Vdac1*, *Kif2a*, and *Cep170* led to elongation. The system is now operational. We plan to use a whole genome siRNA library to identify pathway components that drive elongation without glutamine and promote shortening with glutamine replenishment.

Conclusions: Understanding primary cilia's role in regulating cellular metabolism is crucial for insights into their functions in health and disease. Dysfunction of primary cilia leads to various ciliopathies, including kidney disorders like PKD. Our data support using a high-content screening platform to identify novel components of the pathway responsible for the ciliary response to glutamine.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO629

Klc3 Regulates Ciliary Trafficking and Cyst Formation in Kidney Epithelial Cells

Yejin Ahn, Gyuyeong Rah, Je Yeong Ko, Jaehee Jun, Chaewon Oh, Songyo Ma, Jong Hoon Park. *Sookmyung Women's University, Yongsan-gu, Seoul, Republic of Korea.*

Background: Primary cilia are microtubule-based organelles that extends from the cell membrane and function as biosensor to regulate intracellular signaling pathways. As primary cilia cannot synthesis proteins by themselves, trafficking of ciliary protein via the process of intraflagellar transport (IFT) is crucial for cilia maintenance and function.

Methods: Immunocytochemistry and co-IP were used to examine the effect of kinesin light chain-3 (Klc3) in ciliary trafficking. By modulating Klc3 expression levels, we evaluated the effect of Klc3 in ciliary trafficking and *in vitro* cyst formation.

Results: We identified Klc3 as ciliary trafficking regulator of kidney epithelial cells. Klc3 localized to adjacent to basal body of cilia and regulated ciliary IFT recruitments by interacting with IFT-B core-2 complex via its tetratricopeptide-repeat (TPR) domains. Also, Klc3 overexpression increased *in vitro* cyst formation of kidney epithelial cells, whereas suppression of Klc3 relieved *in vitro* cyst enlargement induced by *Pkd1* or *Pkd2* deficiency. In support our findings, ciliopathy models such as human ADPKD and animal PKD models with ciliary IFT accumulations had an increased Klc3 expression.

Conclusions: We provide conclusive evidences of KLC3 roles for regulating ciliary IFT recruitment and cyst formation in kidney epithelial cells.

Funding: Government Support - Non-U.S.

FR-PO630

ANKHD1 Has a Cytoprotective Role in Stressed Kidney Cells

Jordan Mullenger,[1,2] Martin Zeidler,[1] Maria Fragiadaki.[2,1] *[1]The University of Sheffield, Sheffield, United Kingdom; [2]Queen Mary University of London, London, United Kingdom.*

Background: ANKHD1 is a ubiquitously expressed RNA binding protein composed of ankyrin repeat domains for protein binding and a KH domain for nucleic acid binding. ANKHD1 is overexpressed in renal cancer, driving proliferation and growth. Clinically, increased expression of ANKHD1 is associated with increased metastasis and larger tumours, resulting in poorer patient prognosis. Our lab has predicted a similar function for ANKHD1 in autosomal dominant polycystic kidney disease (ADPKD). ADPKD is the most common genetic form of renal failure and is characterised by excessive proliferation resembling early tumorigenesis. The signalling pathways activated in the proliferation of cancer cells and ADPKD closely resemble one another.

Methods: Immunohistochemistry of ANKHD1 was performed in kidney sections to examine protein localisation. Recombinant ANKHD1 was produced in HEK293T cells and elevated expression was validated using western blot and RT-qPCR. The resultant protein was purified via immunoprecipitation (IP), and its interacting partners were identified via mass spectrometry (MS). Bioinformatics analysis was performed on the experimentally validated ANKHD1 interactome from BioGrid, and analysis of function was performed using online platforms. Cells were exposed to cellular stress by growth in serum-free media for 24hrs, and viability was assessed via MTT assay.

Results: In ADPKD kidneys, ANKHD1 is localised to the cyst lining epithelial cells. Recombinant constructs of human ANKHD1 and its protein interactors were expressed and purified via IP; MS identified 267 interacting proteins. Combining our MS results with published protein-interaction databases revealed 17 overlapping ANKHD1-interacting proteins, 10 of which are involved in cellular responses to stress. Hence, we decided to test the putative role of ANKHD1 in protecting from stress. Serum starvation caused a 23% reduction in cell viability, while overexpression of ANKHD1 rescued this phenotype in a proliferation and apoptosis-independent manner. Serum-starved cells showed increased stress granules, which was suppressed by ANKHD1 overexpression. A physical interaction between ANKHD1 and HSPA8, a heat-shock chaperone involved in protein folding, was also demonstrated.

Conclusions: ANKHD1 interacts with proteins involved in the cellular stress response, and has a proposed novel role as a cytoprotective molecule during cellular stress.

FR-PO631

Influence of PKD1-Mediated Apoptosis on Proliferation and Autophagy in Human Embryonic Kidney Cells

Ebtehal Ahmed, Maria Fragiadaki. Fragiadaki Group. *William Harvey Research Institute, Centre for Translational Medicine and Therapeutics (TMT), Lifelong Health Theme, Queen Mary University of London, London, United Kingdom.*

Background: Polycystic Kidney Disease (PKD) is the most common genetic cause of chronic kidney disease, affecting millions globally. The condition is characterized by kidney cysts, excessive proliferation, apoptosis, and fibrosis. PKD arises from a mutation in the PKD1 gene, encoding polycystin-1 (PC1), a transmembrane protein. Loss of PC1 is linked to centrosome amplification, genomic instability, and excessive proliferation, but the underlying mechanisms are unclear. This study examines the consequences of PC1 loss, focusing on apoptosis and its effects on proliferation and autophagy. It also investigates the potential therapeutic impact of apoptosis-inhibitory small molecules (Z-DEVD-FMK and Z-VAD-FMK) on reversing the condition in PKD1-silenced Human Embryonic Kidney Cells (HEK293T).

Methods: We silenced PKD1 and verified knockdown by sequencing. Cell viability was measured by MTT assay. Apoptosis, proliferation, and autophagy were examined by immunostaining and western blot. Apoptosis inhibitors were used to rescue PKD1-silenced cells. Lastly, we generated spheroids for the control and PKD1 silenced cells embedded in Matrigel, collagen, and ECM hydrogel to assess the effect of PKD1 deletion and apoptosis inhibition in three-dimensional cultures.

Results: PKD1 loss significantly reduced cell viability to 56.8% (p=0.0394), indicating its importance in metabolic activity. This was not due to changes in proliferation but rather due to a significant induction of apoptosis (p=0.0131) comparable to the potent apoptosis-inducer staurosporine. PKD1 silencing also reduced autophagy, decreasing LC3B expression to 2.781% (p=0.0058) of controls (10.77%). The caspase-3 inhibitor (Z-DEVD-FMK) and pan-caspase inhibitor (Z-VAD-FMK) both reduced caspase-3 expression, but the latter was more effective at reducing cleaved PARP (p=0.0257). These results highlight PKD1's critical role in regulating apoptosis and autophagy.

Conclusions: We uncover PKD1's critical role in controlling apoptosis and offer a potential therapeutic avenue to mitigate disease progression.

FR-PO632

Regulated Cell Death in the Pathogenesis of Cystic Kidney Diseases

Emilia Kieckhöfer,[1,2] Lena K. Ebert,[1,2] Thomas Benzing,[1,2] Bernhard Schermer.[1,2] Nephrolab Cologne. *[1]Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; [2]CECAD, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany.*

Background: Hereditary cystic kidney diseases, such as autosomal dominant/recessive polycystic kidney disease (ADPKD/ARPKD) or nephronophthisis (NPH) are caused by mutations in genes encoding proteins essential for the structure and function of primary cilia. Cilia are sensory organelles that project from the surface of tubular epithelial cells into the lumen, functioning like diminutive cellular antennae. In many cystic kidney diseases, a significant loss of tubular epithelial cells occurs. Consequently, we investigated the extent to which pathways of regulated cell death (RCD) are interconnected with cilia and play a role in cystic kidney pathologies.

Methods: We studied pathways of regulated cell death (including apoptosis, necroptosis, and pyroptosis) in cultured renal epithelial cells with and without primary cilia, and in *Kif3a*-deficient mouse kidneys. Additionally, we deleted *Ripk3* and *GsdmD* in the JCK mouse model of cystic kidney disease and performed renal phenotyping. To gain mechanistic insights, we conducted proteomics and single-nucleus RNA sequencing (snRNA-Seq) analyses.

Results: Loss of cilia in murine kidney epithelial cells led to an increased expression of the key kinase RIPK3 *in vitro* and *in vivo*, enhancing the susceptibility of tubular epithelial cells to necroptotic cell death. Notably, RIPK3 deletion in JCK mice resulted in a significant improvement in renal histology and function. Deleting Gasdermin D (GSDMD), an effector of pyroptosis, had a similar effect in this mouse model. Single-nucleus RNA sequencing (snRNA-Seq) analyses provided insight into the mechanisms underlying cyst formation and the beneficial effects of RIPK3 and GSDMD deletion on various cell populations, offering potential new intervention points.

Conclusions: Taken together, our data highlights the significance of RCD in the development of cystic kidney diseases and ciliopathies, suggesting a potential role of RCD as a target for future therapeutic strategies.

FR-PO633

Autophagy Knockout Results in ERK Activation, Increased Proliferation, and Apoptosis of Cyst-Lining Epithelial Cells and Worse Polycystic Kidney Disease

Daniel Atwood, Zhibin He, Makoto Miyazaki, Katharina Hopp, Charles L. Edelstein. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Studies remain contradictory and the mechanistic role of autophagy in cyst growth. Autophagy has not been detailed in rodent and cell models translational to the human disease.

Methods: Mice were treated with chloroquine at a dose of 60mg/kg from 50-120 days. An array of mTOR and autophagy proteins was measured in the kidney by immunoblot analysis. Apoptosis and proliferation were measured by TUNEL and PCNA IHC respectively. Cells were treated with 25 or 50uM tat-beclin1 peptide for 4 or 24hrs

Results: Suppressed autophagic flux (lack of increase in LC3-II in kidney 2 hrs after IP bafilomycin injection) was observed in 150 d old, but not 70 or 120 d old Pkd1RC/RC kidneys. Pharmacological inhibition of autophagy with chloroquine from an early age suppressed autophagic flux in Pkd1RC/RC kidneys, but had no effect on PKD severity. Knockout of autophagy (ATG7) in kidney tubule specific Pkd1 knockout mice, a rapid model of cyst growth, had no effect on cyst growth or kidney function. Knockout of ATG7 in Pkd1RC/RC mice, a slower and more clinically-relevant model of PKD, resulted in activation of p-ERK, a surge of apoptosis and proliferation of cyst lining epithelial cells and severely worse PKD (See Table). In human PKD 9-12 cells, autophagy induction with Tat-beclin 1 peptide resulted in increased conversion of LC3-I to LC3-II, decreased p-ERK and decreased proliferation and apoptosis (See table).

Conclusions: In vivo, autophagy knockout activates p-ERK resulting in a surge of proliferation and apoptosis in cyst lining epithelial cells and worse PKD. In vitro, autophagy induction resulted in decreased p-ERK decreased proliferation and apoptosis. In conclusion, there is an abnormal autophagy, ERK, proliferation/apoptosis axis in cells lining the cyst in ADPKD. Cre-lox technology was used to create ATG7, RC/RC double knockout mice

Funding: Veterans Affairs Support

In Vivo	Pkd1RC/RC	Pkd1RC/RC ATG7-/-	In Vitro	VEH	Tat-Beclin1 25uM
2K/BW (%)	2.1	3.6#	PCNA/β-actin	1.2	1.0*
Cyst Index (%)	9	26***	MTT OD(390)	0.4	0.2#
Cyst #	160	491***	AnnexinV (% gated)	23	3.5#
PCNA+ per cyst	5	22***	LC3-I/LC3-II (RDU)	0.4	1.0***
TUNEL+ per cyst	1.1	30.1**	pN-ERK (RDU)	2.3	1.1**
LC3-I/LC3-II (RDU)	0.9	4**			
pN-ERK (RDU)	0.9	1.4*			

*P<0.01,**P<0.01, ***P<0.001, #P>0.0001. RDU=relative densitometry units on immunoblot

FR-PO634

Pkd1 Mutation Modulates Cognitive Function via N-methyl-D-aspartate Receptor-Mediated Synaptic Transmission and Autophagy

Zeba Firdaus,[1,2] Lu Li,[1,2] Xinyue Mao,[1,2] Xia Zhou,[1,2] Xiaogang Li.[1,2] *[1]Mayo Clinic Department of Internal Medicine, Rochester, MN; [2]Mayo Clinic Department of Biochemistry and Molecular Biology, Rochester, MN.*

Background: ADPKD is a prevalent, life-threatening monogenic disorder linked to *PKD* gene mutations. However, whether this mutation affects brain function is unknown. In this study, we investigate whether *PKD1* mutation activates N-methyl D aspartate receptors (NMDAR), dominant calcium channels, and impairs autophagy in brain to disrupt synaptic transmission and contribute to cognitive dysfunction.

Methods: We performed behavioral experiment (Y-maze test) to evaluate the anxiety in wild type (WT) and $Pkd1^{RC/RC}$ mice. To understand the underlying molecular mechanisms, we isolated cerebral cortex (CC) and hippocampus (HP) from WT and $Pkd1^{RC/RC}$ brain and did Western blot and qRT-PCR analysis. We also checked the effect of senolytic treatment on brain in $Pkd1^{RC/RC}$ mice. Lastly, we did the co-IP to check the interaction between GluN2a and carboxy-terminal end of PC1 using N2a cells.

Results: We observed increased anxiety-like behavior in $Pkd1^{RC/RC}$ mice compared to WT controls. The expression of NMDAR subunit GluN2A, synaptic protein PSD-95, and neurotrophic factor BDNF was increased in the CC and HP of $Pkd1^{RC/RC}$ mice compared to WT control, suggesting an increase of synaptic signaling, whereas the expression of RE-1 silencing transcription factor (REST), responsible for repression of synaptic

proteins, was downregulated in *Pkd1*$^{RC/RC}$ brains. In addition, impaired autophagy, as characterized by the increase of p62 and pTFEB and the decrease of Atg7, beclin1, and LC3 in *Pkd1*$^{RC/RC}$ mice brains compared to WT controls. Treatment with senolytic combination of Dasatinib and Quercetin (DQ), improved anxiety-like behavior in *Pkd1*$^{RC/RC}$ mice and restored the expression of above autophagy markers. Treatment with DQ also normalized the expression of synaptic proteins as seen by a decrease of the upregulated GluN2A, PSD-95, and BDNF, and an increase of the downregulated REST. Moreover, the carboxy-terminal of PC1 interacts with GluN2A, indicating that PC1 may suppress this NMDAR subunit in wild-type brains through this interaction.

Conclusions: This study finds that *Pkd1* mutation alters NMDAR and REST expression, along with impaired autophagy, leading to increased synaptic protein availability at synapses, thereby amplifying synaptic transmission and causing excitability. Consequently, *Pkd1* mutation induces anxiety in an ADPKD animal model, resulting in mild cognitive dysfunction.

FR-PO635

Neuroinflammation in Polycystic Kidney Disease

Jelena Klawitter, Garrett B. Wheeler, Katharina Hopp, Jost Klawitter, Uwe Christians. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: The incidence of intracranial aneurysms (IA) in patients with autosomal dominant polycystic kidney disease (ADPKD) is three- to four-times higher than that in the general population. Inflammation plays a key role in the development of IA and their rupture. Systemic inflammation and associated metabolic changes in the kidney are well described in ADPKD. However, the presented results describe, for the first time, the inflammation-related alterations and metabolic derangements in the brains of animals with PKD.

Methods: Brains (cortex and hippocampus) were collected from 6-mo old WT and *Pkd1*$^{RC/RC}$ (orthologous ADPKD model) mice. Proteome Profiler Mouse cytokine arrays, in conjunction with Western blot and confocal microcopy analyses, were used to assess the degree of neuroinflammation. Mass spectrometry-based metabolomics was used to assess the metabolic changes and the levels of oxidative stress.

Results: Accumulation of multiple proinflammatory proteins including several interleukins, C-reactive protein, RANTES, and Vascular Cell Adhesion Protein 1 (VCAM1) was observed in brains of both sexes *of Pkd1*$^{RC/RC}$ mice. This was accompanied by astrocyte (GFAP^{+}) and microglia (Iba1^{+}) activation. Protective cytokines such as Chemerin were downregulated in brains of *Pkd1*$^{RC/RC}$ mice. Metabolically, *Pkd1*$^{RC/RC}$ mice presented with decreased brain levels of multiple energy-supplying amino acids (ARG, LEU, ASP). TRP metabolism via kynurenine pathway was increased resulting in lower TRP availability and serotonin production. We also observed an accumulation of several uremic toxins (indoxyl- and p-cresyl sulfate) and oxidative stress markers in PKD mice. The accumulation of these uremic toxins has been shown to directly associate with increased blood-brain barrier (BBB) permeability. Together with kynurenines, they bind to aryl hydrocarbon receptor (AhR), that regulates vascular homeostasis and integrity, and whose expression we confirmed to be higher in *Pkd1*$^{RC/RC}$ brains.

Conclusions: We show that neuroinflammation is present in the brains of *Pkd1*$^{RC/RC}$ mice. Genetic polycystin deficiency and increased systemic inflammation lead to a disruption of BBB resulting in an accumulation of uremic toxins, increased oxidative stress and derangements in cellular metabolism. Increased expression of VCAM1 and AhR could further contribute to the vessel modulation and IA pathology.

FR-PO636

Genome-Wide Association Study of GFR Slope Decline in a Diverse Cohort from the Million Veteran Program

Adriana Hung,[1,2] Jefferson L. Triozzi,[1,2] Cassianne Robinson-Cohen,[1,2] Hua-Chang Chen,[1] Zhihong Yu,[1] Otis D. Wilson,[1,2] Guanchao Wang,[1] Talat Alp Ikizler,[1,2] Ryan Hsi,[1] Lee Wheless,[1,2] Edward D. Siew,[1,2] Ran Tao.[1] Million Veteran Program. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]VA Tennessee Valley Healthcare System, Nashville, TN.*

Background: Rapid chronic kidney disease (CKD) progression is associated with poor outcomes and interventions to slow progression are scarce. Only a few genetic loci have been associated with kidney function decline, as assessed by eGFR slope over time. We here perform the largest and most diverse investigation of genetic determinants of eGFR slope to date.

Methods: We performed a genome-wide association study (GWAS) of eGFR decline among 541,845 individuals enrolled in the Million Veteran Program. Our primary outcome was the annualized relative slope defined as longitudinal change in outpatient eGFR (% change per year), adjusted for age, sex, and 10 principal components of ancestry. Analyses were stratified by genetic ancestry and diabetes and inverse variance-weighted fixed-effect meta-analyses were carried out using and METAL.

Results: The strongest trans-ancestry association in patients with diabetes was in *PDILT*/*UMOD* (rs77924615; p=3x10^{-42}). Other significant associations in patients with diabetes included *SLC47A1* (rs2247436 p = 1x10^{-15}), *BICC1* (rs10763564 p=3x10^{-9}), *NDST4* (rs144322816 p=5x10^{-8}). In non-diabetic individuals, associations were noted at *PDILT* (rs77924615; p= 1x10^{-45}), *BICC1* (rs1649081; p=2x10^{-10}), *AZIN2* (rs116832156; p=6x10^{-10}), *TRIM62* (rs116120304; 1x10^{-9}), *PRKGA2* (rs10265221; p=2x10-9), *WDR72* (rs689751; p=2x10^{-9}); *TPPP* (rs4990988; 1x10^{-8}), *RORA-AS1* (rs919582144; p=4x10^{-8}). In the overall meta-analysis, associations included *SLC47A1* (rs2440155; p=3x10^{-11}), *PDILT/UMOD* (rs77924615; p=3x10^{-82}), *WDR72* (rs6416452;p=1x10^{-13}), *BICC1* (rs34275789; p=3x10^{-17}), *PRKGA2* (rs10265221; p=1x10^{-13}), *RORA-AS1* (rs919582144; p=4x10^{-8}), *APOE* (rs429358, p=3x10^{-8}), *PLCH1* (rs3851357; p=1x10^{-8}), *GP2* (rs62032857;7x10^{-9}) and several intergenic loci with GWAS significance near *LINC02694*, *PRDM8*, *OR52E1*, *NIRP.*

Conclusions: Sixteen loci (three novel) were associated with longitudinal changes with GWAS significance and multiple with nominal association. *SLC47A1*, *BICC1* and *APOE* are being study as potential targets. Meta-analysis with 125,000 participants in BioVU is underway. This work will provide the basis for the construction of a diverse CKD polygenic risk score and will allow for exploration of druggable targets using actionable proteins.

Funding: Veterans Affairs Support

FR-PO637

Genetic GLP1R Gene Expression and Kidney Disease Progression: A Mechanistic Proteome-Wide Analysis in the Million Veteran Program

Jefferson L. Triozzi, Zhihong Yu, Otis D. Wilson, Elvis A. Akwo, Cassianne Robinson-Cohen, Talat Alp Ikizler, Ran Tao, Adriana Hung. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Glucagon-like peptide-1 receptor agonists (GLP1RA) may have nephroprotective properties beyond weight loss and glycemic control. We assessed the effect of genetically proxied GLP1RA on kidney disease progression, while accounting for its effects on obesity and diabetes as well the plasma proteome.

Methods: We assembled a national retrospective cohort of Veterans from the Million Veteran Program between 2011 and 2021. A Cox proportional hazards survival analysis assessed the association between genetically proxied GLP1RA and kidney disease progression. A proteome-wide mendelian randomization analysis examined the effect of genetically proxied GLP1RA on changes in plasma protein levels to provide mechanistic insights. The exposure was a genetic risk score for systemic *GLP1R* gene expression that was calculated for each study participant based on genetic variants associated with *GLP1R* mRNA levels within the Genotype-Tissue Expression project. The primary composite outcome was the incident 40% decline of estimated glomerular filtration rate or end-stage kidney disease. The proteome-wide analysis included up to 4907 aptamer-based plasma proteins measured by SomaScan.

Results: Among 353153 individuals, 16327 (4.6%) experienced kidney disease progression during a median (IQR) follow-up of 5.1 (3.1;7.2) years. Overall, higher genetic *GLP1R* gene expression was associated with a lower risk of kidney disease progression in the unadjusted (HR = 0.956, 95% CI [0.921 – 0.993], *p*-value = 0.022) and fully adjusted models accounting for baseline characteristics, body mass index, and the presence or absence of diabetes (HR = 0.961, 95% CI [0.925 – 0.999], *p*-value = 0.042). The results were similar in analyses stratified by diabetes or obesity status. Higher genetic *GLP1R* gene expression was associated with lower body mass index (*p*-value = 0.0087), fasting glucose (*p*-value = 0.040), and changes in metabolic plasma proteins including the downregulation of leptin (*p*-value = 0.0046).

Conclusions: Higher genetic *GLP1R* gene expression was associated with a lower risk of kidney disease progression, even after accounting for its effects on body weight and glycemic control, supporting the role of pleiotropic nephroprotective mechanisms.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO638

Canonical Correlation Analysis Identifies Single Nucleotide Polymorphisms and Gene Expression Associated with CKD Subtypes

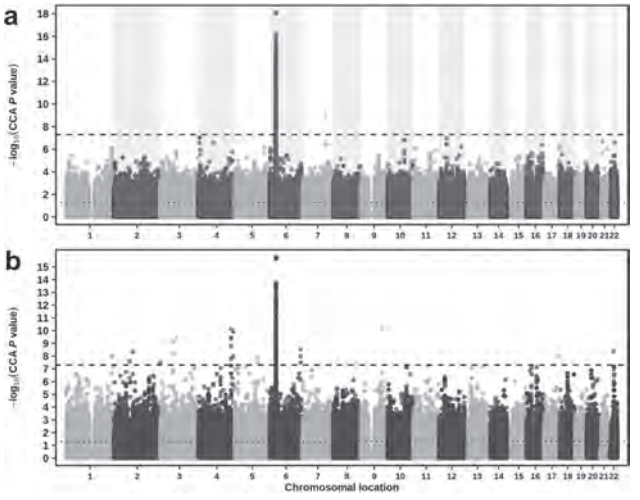
Amy J. Osborne,[1] Samantha J. Hayward,[1] Liz Colby,[1] Philip A. Kalra,[2] Olivier Radresa,[3] Philipp Skroblin,[3] Maarten W. Taal,[4] Gavin I. Welsh,[1] Moin A. Saleem,[1] Ian C. Campbell.[1] Bristol Renal. *[1]University of Bristol, Bristol, United Kingdom; [2]Northern Care Alliance NHS Foundation Trust Salford Care Organisation, Salford, United Kingdom; [3]Evotec International GmbH, Gottingen, Germany; [4]University of Nottingham, Nottingham, United Kingdom.*

Background: Genetic risk variants have been associated with chronic kidney diseases (CKD) by univariate statistical methods. Multivariate statistics such as canonical correlation analysis (CCA) have not been investigated for CKD sub-types and may provide additional insights.

Methods: We applied CCA to our NURTuRE-CKD and Salford Kidney Study (SKS) CKD single nucleotide polymorphism (SNP) datasets. We assessed expression quantitative trait loci (eQTL) colocalisation, SNP differential gene expression and allele frequency.

Results: We identified 943 replicated SNPs in the human leukocyte antigen (*HLA*) region that showed significant correlation with membranous nephropathy (MN) compared to other CKD. Most SNPs were not previously reported. The 5 lead SNPs (previously unreported) were significantly more common in both MN and diabetic nephropathy Type 1 (T1D) compared to healthy controls and showed strong eQTL colocalisation with 17 genes. Of these, five genes in blood or monocytes (*ATF6B, HLA-DQA1, HLA-DQB1, NOTCH4, RNF5*) showed differential gene expression between MN and either healthy individuals or IgA nephropathy across 11 published Gene Expression Omnibus datasets, suggesting MN-specific expression. Differential gene expression analyses suggested that the five lead SNPs affected *C4B, HLA-DQB1* and *RNF5P1* expression in CKD.

Conclusions: In summary, we found previously unreported, replicated SNPs associated with MN and T1D, likely involved in altering *HLA-DQB1* gene expression.



Single nucleotide polymorphisms for membranous nephropathy by canonical correlation analysis. Results for (a) NURTuRE-chronic kidney disease and (b) Salford Kidney Study. Each point is a SNP with chromosome and co-ordinates (x-axis) and -log10 CCA *P*-value (y-axis). The dashed line is Bonferroni-corrected 0.05 *P*-value.

FR-PO639

UMOD p.Thr62Pro Pathogenicity Is Modified by Polygenic CKD Risk

Alexander R. Chang,[1] Ian Dinsmore,[1] Bryn S. Moore,[1] Anthony J. Bleyer,[2] Tooraj Mirshahi.[1] *[1]Geisinger Health, Danville, PA; [2]Wake Forest University School of Medicine, Winston-Salem, NC.*

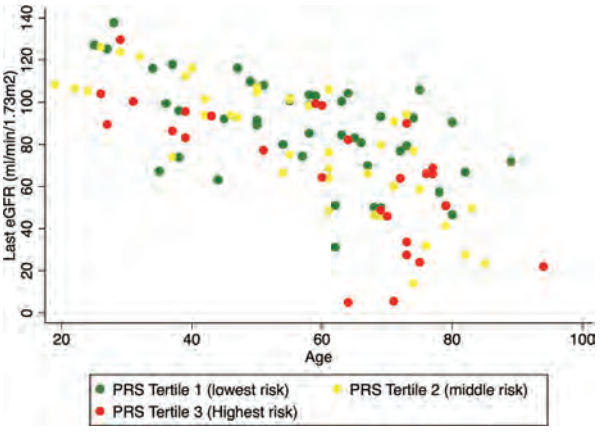
Background: UMOD p.Thr62Pro has been reported as having intermediate penetrance for chronic kidney disease (CKD) with end-stage kidney disease (ESKD) occurring at a median of ~70 years of age. Since p.Thr62Pro results in an intermediate intracellular trafficking defect, we hypothesized that age and CKD polygenic risk would modify the association of Thr62Pro with estimated glomerular filtration rate (eGFR).

Methods: Using data from Geisinger MyCode/DiscovEHR, a health system-based cohort with exome sequencing and electronic health record data, we created a polygenic risk score (PRS) using summary statistics from the UK Biobank for individuals of European ancestry. Heterozygotes with UMOD p.Thr62Pro were compared to those without UMOD rare variants using linear regression for continuous outcomes and Firth logistic regression for categorical outcomes, adjusted for age, sex, and race. Primary outcome was most recent eGFR. Secondary outcomes included eGFR<60, eGFR <30, gout, and ESKD. We tested for an interaction by age ≥ or < 60 years, and conducted subgroup analyses by age group.

Results: UMOD p.Thr62Pro heterozygotes (median age 61, interquartile interval 46-72) had increased risk of ESKD (OR 2.91, 95% CI: 1.23, 6.91; p=0.02), eGFR <30 (OR 2.21, 95% CI: 1.15, 4.25; p=0.02), eGFR <60 (OR 1.64, 95% CI: 1.02, 2.64), but not gout (OR 0.48, 95% CI: 0.14, 1.71). The association of UMOD p.Thr62Pro with eGFR was stronger in adults ≥60 vs. <60 years of age (p=0.04 for interaction term) with lower eGFR for heterozygotes ≥60 years of age (-7.29 ml/min/1.73m^2, 95% CI: -2.60, -1.98) and a smaller effect for those <60 years of age (3.79, 95% CI: -1.21, 8.79; p=0.1). CKD PRS was associated with lower eGFR in UMOD p.Thr62Pro (per SD: -7.28 ml/min/1.73m2, 95% CI: -11.40, -3.16).

Conclusions: Adults with the intermediate-penetrance UMOD p.Thr62Pro variant experience increased risk of eGFR decline after 60 years of age, and risk is modified by CKD PRS.

Funding: NIDDK Support



FR-PO640

Individuals Heterozygous for SLC34A3 Predicted Pathogenic Variants Are at Increased Risk of Nephrolithiasis

Alexander R. Chang,[1] Bryn S. Moore,[1] Jonathan Z. Luo,[1] Ion D. Bucaloiu,[1] Andrea G. Cogal,[2] Shannon K. McDonnell,[2] Jacob A. Frank,[2] Steven J. Scheinman,[1] Jun Ma,[2] Peter C. Harris,[2] John C. Lieske.[2] *[1]Geisinger Health, Danville, PA; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Prior studies have suggested that individuals heterozygous for *SLC34A3* pathogenic variants are at risk for nephrolithiasis, but this association has not been examined comprehensively.

Methods: We used data from Geisinger MyCode/DiscovEHR (n=174,172) and the Mayo Clinic Biobank (MCBB) (n=43,743), health system-based cohorts with exome sequencing and electronic health records. An electronic phenotyping algorithm for nephrolithiasis was developed and validated in the 2 cohorts. Gene burden tests were completed using several masks based on pathogenicity predictions from LOFTEE, REVEL, and AlphaMissense (AM). We considered a Bonferroni-corrected p value <0.00714 significant. Variant-specific analyses were done using Firth logistic regression models. Analyses were adjusted for age, sex, and genetic ancestry.

Results: Prevalence of predicted pathogenic *SLC34A3* variants ranged from 0.00095 (LOFTEE) to 0.0037 (LOFTEE or AM or REVEL). Predicted pathogenic variants in *SLC34A3* using 4 of the 7 masks were associated with nephrolithiasis in MyCode (Table). Replication analyses in MCBB showed a modest association signal. In MyCode, several variants were associated with nephrolithiasis [Ser192Leu (OR 1.73; p=0.005) and Ser138Phe (OR 2.06; p=0.006)], or of borderline significance [Met403Arg (OR 2.36; p=0.1), Thr202Ile (OR 2.43; p=0.1), Met145Ile (OR 3.78; p=0.1), Gly518Arg (OR 4.13; p=0.05)]. Ser138Leu was the strongest association seen in MCBB (OR 4.65; p=0.001).

Conclusions: One in 270 individuals were carriers of *SLC34A3* predicted pathogenic variants, which were associated with increased risk of nephrolithiasis. Future studies are needed to understand the impact of *SLC34A3* on kidney stone severity, recurrence risk, and whether personalized treatment of these individuals can reduce nephrolithiasis burden.

Funding: NIDDK Support

Gene Burden test for SLC34A3 and nephrolithiasis

	Geisinger ACAT0 p-value	Mayo ACAT0 p-value
LOFTEE	0.061	0.016
REVEL	0.030	0.073
Alpha Missense (AM)	1.31E-07	0.060
REVEL or AM	2.51E-07	0.045
LOFTEE or AM	3.29E-08	0.027
LOFTEE or REVEL	0.013	0.004
LOFTEE or AM or REVEL	6.03E-08	0.012

FR-PO641

Predicted Pathogenic Missense Variants in CLDN10 Are Associated with CKD

Alexander R. Chang,[1] Bryn S. Moore,[1] Jonathan Z. Luo,[1] Andrew J. Mallett,[2] Erik Biros,[2] Tooraj Mirshahi,[1] John A. Sayer.[3] *[1]Geisinger Health, Danville, PA; [2]James Cook University, Townsville, QLD, Australia; [3]Newcastle University, Newcastle upon Tyne, United Kingdom.*

Background: *CLDN10* encodes the tight junction protein claudin-10. and has been linked to a non-Bartter, non-Gitelman autosomal recessive salt-losing tubulopathy. Recently, heterozygous protein truncating variants (PTVs) in *CLDN10* have been associated with higher cystatin C, creatinine, urea, and uric acid levels. In this study we

examined whether predicted pathogenic missense variants were associated with estimated glomerular filtration rate (eGFR) and other renal phenotypes.

Methods: We used data from the MyCode/DiscovEHR study, a health system-based cohort (n=174172) in central and northeast PA and the UK Biobank study (n=394,841). In the MyCode cohort, predicted pathogenic missense variants were determined using Alpha Missense, a deep learning-based prediction tool. In UK Biobank, missense variants/low confidence (LC) loss of function variants were grouped together (www.genebass.org). Renal phenotypes available in UK Biobank included plasma cystatin C, creatinine urea, urate. For MyCode, renal phenotypes examined included creatinine-based estimated glomerular filtration rate (eGFR), eGFR <60, eGFR<30, dipstick proteinuria, and gout. Age and sex-adjusted gene burden analyses for *CLDN10* predicted pathogenic missense variants were examined using linear regression for eGFR and Firth logistic regression for categorical variables.

Results: In MyCode, there were 118 individuals heterozygous for 37 predicted pathogenic *CLDN10* missense variants. Individuals heterozygous for predicted pathogenic *CLDN10* missense variants had lower eGFR (-7.30 ml/min/1.73m^2, 95% CI: -10.96, -3.64; p=9.2E-5), and higher risk of eGFR <60 (OR 2.80, 95% CI: 1.75, 4.47; p=1.6E=-05). Associations were not significant for gout (OR 1.90, 95% CI: 0.93, 3.93; p=0.08), eGFR <30 (OR 1.27, 95% CI: 0.56, 2.87; p=0.6), or dipstick proteinuria (OR 1.28, 95% CI: 0.79, 2.07; p=0.3). In UK Biobank rare missense/LC *CLDN10* variants were associated with cystatin C (p-value SKATO =8.66E-19), urea (p=1.88E-7), urate (p=6.25E-8), and creatinine (p=1.76E-7).

Conclusions: Predicted pathogenic missense variants in *CLDN10* were associated with reduced eGFR and eGFR<60.

Funding: NIDDK Support

FR-PO642

Association of Heterozygous CLDN10 Protein-Truncating Variants with CKD, Proteinuria, and Gout: Insights from the Geisinger MyCode/ DiscovEHR Study

Mohammad H. Al Khateeb, Bryn S. Moore, Ion D. Bucaloiu, Tooraj Mirshahi, Alexander R. Chang. *Geisinger Medical Center, Danville, PA.*

Background: The CLDN10 gene encoding the tight junction protein Claudin-10, is crucial for paracellular ion transport in the kidney's thick ascending limb. Previous studies have implicated CLDN10 in a Hypokalemic-Alkalotic Salt-Losing Tubulopathy, an autosomal recessive tight junction disease, characterized by reduced renal calcium and magnesium excretion. Heterozygous protein truncating variants (PTVs) in CLDN10 have been associated with increased markers of renal function, such as cystatin C, urea, urate, and creatinine. We analyzed data from the Geisinger MyCode/DiscovEHR study to expand our understanding of the renal phenotypes in individuals heterozygous for PTV's in CLDN10.

Methods: We identified individuals heterozygous for CLDN10 PTVs using data from Geisinger MyCode/DiscovEHR, an unselected health system-based cohort (n=174172) in central and northeast Pennsylvania with available exome sequencing and electronic health record data. We used linear regression, adjusted for age, sex, and genetic ancestry, to determine whether CLDN10 PTV heterozygosity was associated with lower estimated glomerular filtration rate (eGFR). Using Firth logistic regression, we also estimated risk for dipstick proteinuria, gout, hypokalemia, and hypocalcemia. Electronic medical records were examined to provide additional context on phenotypic features of CLDN10 heterozygotes.

Results: Among 42 individuals who were heterozygous for CLDN10 PTVs (mean age: 53.5 ± 6.3 years; 16 males, 26 females), 19 had hypertension, 14 had diabetes mellitus, 10 had chronic kidney disease, 15 had 1+ or greater persistent proteinuria, 4 had gout, 3 had nephrolithiasis, 1 patient had end-stage kidney disease at age 70 years attributed to diabetes; no patients had overt hypokalemia, hypercalcemia or hypermagnesemia. Compared to non-carriers, CLDN10 PTV heterozygotes had lower eGFR (-14.8, 95% CI: -26.13, -3.55; p=0.01), and were at higher risk of eGFR<60 (OR 4.16, 95% CI: 1.91, 9.04; p<0.001), 1+ persistent proteinuria (OR 2.83, 95% CI: 1.47-5.46, p=0.002, and 2+ persistent proteinuria (OR 3.13, 95% CI: 1.49, 6.60; p=0.003), and gout (OR 8.37, 95% CI: 1.81, 38.72; p=0.007).

Conclusions: *CLDN10* PTV heterozygotes are at increased risk of CKD as well as mild to moderate proteinuria and gout.

Funding: Private Foundation Support

FR-PO643

Phenome-Wide Association Study of APOL1 Risk Genotypes in the Mass General Brigham Biobank Using Data-Driven Disease Association Clustering

David R. Vanderwall,[1,2] Michelle Mcnulty,[2] Janewit Wongboonsin,[2] Matt G. Sampson.[2,3] Sampson Lab for Kidney Genomics. *[1]Harvard Medical School, Department of Cell Biology, Boston, MA; [2]Boston Children's Hospital, Division of Nephrology, Boston, MA; [3]Harvard Medical School, Boston, MA.*

Background: To identify clinical associations with APOL1 risk genotypes using genotype and ICD-10 diagnostic codes of 53,395 participants in the Mass General Brigham Biobank (MGBB).

Methods: The 53,395 participants in MGBB with exome sequencing data were queried for the presence of at least one *APOL1* kidney risk variant (rs73885319 and rs60910145, ["G1"] or rs71785313 ["G2"]). Presence of the G0 reference allele was noted. Individuals were classified as "Low-Risk (LR)" (G0/G1 or G0/G2) or "High-Risk (HR)" (G1/G1, G2/G2, or G1/G2). Demographic data and ICD-10 codes for each patient were extracted. A pairwise incidence matrix of all ICD-10 codes from qualifying participants was generated. The value at each matrix position reflects the number of patients in which both ICD-10 codes were mutually identified. Incidence data was subsequently clustered by Weighted Gene Correlation Network Analysis to produce clusters of broadly correlated ICD-10 codes, and further sub-clustered to produce small disease modules with at least 5 highly related ICD-10 codes. Disease module significance between the HR and LR cohorts was evaluated using Chi-Square test.

Results: 1,949 participants had at least one G1 or G2 variant, including 349 HR and 1,600 LR. The HR cohort was significantly enriched for CKD, Nephrotic Syndrome, and ESRD ($p < 0.0001$), but did not differ in T2D ($p = 0.821$). Discrete analysis of individual ICD-10 codes identified 55 codes enriched among the HR cohort; the most significant ICD-10 code was "Nephrotic Syndrome and FSGS" (OR= 15.4, [14.6 – 16.2]). Our network approach produced 251 disease modules of co-occurring ICD-10 codes; 31 disease modules were differentially enriched. A majority of these disease modules were specific for renal pathology. The most significant disease module included ICD-10 codes for "Hypertension Secondary to Renal Disorders," "Stage 5 CKD," and "Secondary Hyperparathyroidism of Renal Origin." 32.3% of significant modules mapped to non-kidney diseases, raising hypotheses of other consequences of HR variants on human health.

Conclusions: Disease network clustering across a large, densely phenotyped cohort offers an opportunity for discovery of potentially significant clinical associations of HR genotypes that would otherwise not be identified.

FR-PO644

Kidney Outcomes in APOL1 High-Risk and Mendelian Variant in Patients with Adult Nephrotic Syndrome in Mass General Brigham Biobank

Janewit Wongboonsin,[1,2] Anya Greenberg,[3] Michelle Mcnulty,[3] Ana C. Onuchic-Whitford,[2,3] Dongwon Lee,[3] Sagar U. Nigwekar,[5] Matt G. Sampson.[3,4] *[1]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [2]Brigham and Women's Hospital, Boston, MA; [3]Boston Children's Hospital, Boston, MA; [4]Broad Institute, Cambridge, MA; [5]Massachusetts General Hospital, Boston, MA.*

Background: Published studies demonstrating the value of genetic stratification in nephrotic syndrome (NS) have often focused on children or research cohorts with specific characteristics. The prevalence and clinical correlates of known genetic forms of NS in adults are less well understood but may have important implications. The EHR-linked Biobank provides a unique opportunity to identify patients with NS for subsequent genomic discovery

Methods: Patients with NS were identified via ICD-10 diagnosis codes, reviews of renal pathology, and manual chart review. Exome data of NS patients were analyzed using VarSeq, with variants assessment using published guidelines. 192 genes associated with proteinuric kidney disease were evaluated. Clinical data were extracted from the Research Patient Data Registry. Adjudication of End-Stage Kidney Disease (ESKD) status was combined with data from the United States Renal Data System. ESKD status was evaluated by both logistic regression and time-to-event survival analysis. Longitudinal trends in laboratory data were analyzed using a linear mixed model

Results: 693 patients had NS, 358 of these have exome data. Diagnoses included FSGS (299 cases), MCD (29 cases), and MN (45 cases), with some patients having multiple diagnoses. 37 patients (11%) had pathogenic Mendelian variants (MV) considered causative of disease and 25 (7%) carried high-risk APOL1 genotype (APOL1-HR). 213 (59%) progressed to ESKD. Upon adjusting for age, sex, race, presence of hypertension, and diabetes mellitus, patients with MV had a 3.0 (1.3–7.3) increased odds for developing ESKD. Those with APOL1-HR had an OR of 7.6 (1.5–37.8). There was a higher hazards for ESKD in both genetic groups: 1.7 (1.2–2.6) for MV and 3.1 (1.8–5.3) for APOL1-HR. Genetic variants were significantly associated with increased monthly creatinine elevation compared to patients without variants (MV: 0.02 ml/min/month; APOL1-HR: 0.04 ml/min/month)

Conclusions: The Biobank presents an opportunity for assessment of genetic variant impact in rare kidney diseases like NS. In this population cohort of adults, both MV and APOL1-HR have a negative impact on kidney health. These findings emphasize the critical role of genetic characterization in predicting renal prognosis among nephrotic syndrome patients

Funding: Private Foundation Support

FR-PO645

Challenges and Results of ClinGen Gene-Disease Clinical Validity Curation for Complement-Mediated Kidney Disease

Janewit Wongboonsin,[1,2] Ryan F. Webb,[3] Pamela A. Robertson,[3] Alicia B. Byrne,[3] Yasar Caliskan,[4] Anuja Java,[5] David Kavanagh.[6,7] ClinGen Complement-Mediated Kidney Diseases Gene Curation Expert Panel. *[1]Brigham and Women's Hospital, Boston, MA; [2]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [3]Broad Institute, Cambridge, MA; [4]Saint Louis University, St Louis, MO; [5]Washington University in St Louis, St Louis, MO; [6]National Renal Complement Therapeutics Center, Newcastle, United Kingdom; [7]Newcastle University, Newcastle upon Tyne, United Kingdom*.

Background: ClinGen is a National Institutes of Health-funded central resource to systematically evaluate the clinical validity of gene-disease relationships (GDRs) and assess variant pathogenicity. The ClinGen Kidney Disease Clinical Domain Working Group (CDWG) was established in 2019 to focus on monogenic kidney diseases. In 2022, the Complement-Mediated Kidney Disease Gene Curation Expert Panel (CMKD-GCEP) began its work by focusing on atypical hemolytic uremic syndrome (aHUS), and C3 glomerulopathy (C3G). GDR evaluation is crucial for clinical testing as it provides the foundational evidence necessary for variant interpretation

Methods: ClinGen's evidence-based semi-quantitative gene curation framework has been implemented across GCEPs. This framework encompasses genetic and experimental evidence. Genetic evidence includes case-level data, family segregation, and case-control data, while experimental evidence comprises data from functional assays and related models. The final clinical validity of the GDR is categorized into levels ranging from Refuted to Definitive. Curations undergo review by the GCEP, with feedback from complementologists incorporated to refine curation practices

Results: To date, CMKD-GCEP has evaluated 7 genes associated with aHUS and C3G. Well-known genes such as *C3, CFH, CFI,* and *CFB* were prioritized for curation and achieved Definitive GDR classifications for aHUS. *THBD* was refuted. We encountered a challenge in curating CFH-related proteins as the framework was tailored for small nucleotide variants (SNVs). *CFHR1* was the first gene curated with a limited number of SNV cases, resulting in insufficient evidence. Given the number of cases with structural variants (SV), the GCEP modified the framework to incorporate genetic evidence from SVs, thereby elevating the strength from Limited to Moderate. As only genes with at least Moderate evidence can be considered for clinical genetic testing, neglecting SVs would weaken evidence strength, hindering further genomic discoveries in complementopathy.

Conclusions: The CMKD-GCEP was established to offer high-quality GDR evidence to the public. With combined input from renal complementologists and ClinGen framework experts, the curation framework can be adapted to accommodate challenging kidney-affecting genes, such as *CFHR1*

FR-PO646

Genome-Wide Association Studies of Pediatric Nephrotic Syndrome Identify Variants Associated with Corticosteroid Response

Tiffany Tu,[1] Alejandro Ochoa,[1] Amika Sood,[3] Ciburn Chan,[1] Eileen T. Chambers,[1] Annette M. Jackson,[1] Adebowale A. Adeyemo,[2] Rasheed A. Gbadegesin.[1] *[1]Duke University, Durham, NC; [2]National Institutes of Health, Bethesda, MD; [3]University of Georgia, Athens, GA*.

Background: Nephrotic syndrome (NS) is one of the most common glomerular diseases seen in children. It is classified based on response to corticosteroid therapy as either steroid-sensitive nephrotic syndrome (SSNS), or steroid-resistant nephrotic syndrome (SRNS). The genetic architecture and the molecular mechanisms of NS are poorly understood, and there are currently no reliable predictors of therapeutic response. To improve our understanding of the genetic basis of NS and define predictors of therapy response, we carried out genome-wide analyses of previously unstudied multi-ancestry cohorts of children with NS.

Methods: We did genome-wide association studies (GWAS) in 994 children with NS and 3,558 ancestry matched controls using a logistic mixed-effects model as implemented in the *SAIGE* software package. Replication analysis was done on 1,483 children with NS in two additional independent cohorts. We imputed classical HLA alleles for allelic and haplotype association testing.

Results: Our GWAS showed that common genetic variants in the chromosome 6 major histocompatibility complex (MHC) region (in *HLA-DQB1, HLA-DRB1, HLA-DQA1*) are robustly associated with SSNS, but not SRNS. The top variant for SSNS is rs17843604 (OR 2.57, 95% CI 2.25-2.94). In addition, we identified a chromosome 16 locus with leading variant rs12925642 (OR 0.67, 95% CI 0.59-0.77) in *CLEC16A* as a major second genetic hit for SSNS outside of chromosome 6. Two other secondary genome-wide significant loci for NS were found on chromosomes 5 and 10. A haplotype defined by alleles at three *HLA* classical loci *HLA-DQA1*02:01~DQB1*02:02~DRB1*07:01* confers almost 4 times the risk of developing SSNS (OR 3.8, 95% CI 3.3-4.4). A GWAS using SRNS as cases and SSNS patients as controls identified a genome-wide significant *HLA-DQB1* locus (lead SNP rs9274639, OR 0.38 [95% CI 0.27-0.52]) that explains the differences in steroid responsiveness.

Conclusions: Our findings of genome-wide HLA class II variants and a robust genome-wide significant HLA haplotype of large effect across multiple ancestries indicate that SSNS, but not SRNS, is a predominantly immune-mediated disorder. The findings of additional secondary loci add to the slowly growing list of non-HLA risk loci and to our knowledge of NS mechanisms.

Funding: NIDDK Support, Other NIH Support - NIAID

FR-PO647

Genetic Causal Relationship and Risk Factors Associated with Type 2 Diabetes and CKD

Weicong Zeng, Qiongqiong Yang. *Sun Yat-Sen Memorial Hospital, Guangzhou, China*.

Background: T2D is the most important risk factor of CKD.T2D-related CKD has family heritability and is heterogeneous. Compared with European and others, T2D patients in Asian are more likely to develop CKD and ESRD. But there is a lack of researchs about the genetic susceptibility of T2D-CKD in different ethnic groups and whether T2D-related genetic factors cause CKD.

Methods: We used East Asian-based GWAS of T2D and CKD from BBJ and European-based GWAS of T2D from DIAGRAM and CKD from UKB to explore the genetic causal relationship and risk genes associated with T2D-CKD in different ethnic groups. We performed: (1)LDSC to estimate the genetic correlation;(2)7 Mendelian randomization(MR) or MR-equivalent methods to infer the putative causality;(3) MAGMA and SMR to identify and verify new risk genes;(4)STRING and Reactome to predict the Protein-Protein Interaction and common biological pathways.

Results: In both East Asian and European, we all observed significant positive genetic correlation between T2D and CKD(EAS:rg=74.91%; EUR:rg=42.93%). MR also both showed causal effect of T2D on CKD. In East Asian, the OR of IVW is $1.30(P=5.84\times10^{-10})$. In European, the OR is $1.17(P=1.60\times10^{-10})$. In contrast, no evidence supports a causal effect of CKD on T2D. Between two populations, Z test showed no significant difference in genetic correlation ($P=1.74\times10^{-1}$). But in MR analysis, the IVW showed that the causality value in East Asian was significantly higher than that in European ($P=4.03\times10^{-2}$). In East Asian, MAGMA and SMR identified 3 new risk genes whose expression levels were likely involved in the putative causality of T2D on CKD. In European, 27 new risk genes were identified. STRING showed that *ZSCAN21* in East Asian was structurally similar to *ZNF195* in European, and they had gene co-expression and protein interaction. Reactome Pathways showed that they have some common biological pathways.*ARC* in East Asian and *MPP3* in European also had similar findings.

Conclusions: In both East Asian and European, we all found the genetic causal effect of T2D on CKD, and the risk of CKD in T2D patients in Asian is higher.3 and 27 new risk genes associated with T2D-CKD were respectively identified in East Asian and European. We found some Protein-Protein Interactions and common biological pathways around some of them. These findings posed new paths on guiding the prevention and early-stage diagnosis of CKD in T2D patients.

FR-PO648

Multiancestry Genome-Wide Association Meta-Analyses of Kidney Function Traits: The CKDGen Consortium R5 Project

Sahar Ghasemi,[1] Eva König,[2] Mathias Gorski,[3] Pascal Schlosser,[1] Matthias Wuttke.[1] CKDGen Consortium. *[1]Institute of Genetic Epidemiology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany; [2]Institute for Biomedicine, Eurac Research, Bolzano, Italy; [3]Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany*.

Background: Advancing Chronic Kidney Disease (CKD) genetics research involves aggregating genome-wide association studies (GWAS) from multiple ancestries on several kidney function phenotypes including estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). Multi-lateral collaborations and rigorous, centralized data quality control (QC) are crucial to obtain reliable results.

Methods: We used our newly developed "metaGWASmanager" package for streamlined high-quality QC workflow. Studies imputed genotypes using state-of-the-art reference panels including low-frequency variants (SNPs/InDels), and implemented the same distributed set of scripts for standardized phenotyping and GWAS (regenie). Following ancestry alignment based on principal component analysis of allele frequencies, GWAS were combined in a hierarchical fixed-effects meta-analysis (METAL): within-ancestry meta-analysis (Step1) followed by between-ancestry meta-analyses (Step2)., GWAS were combined in a trans-ethnic meta-regression analysis (MrMega).

Results: In an ongoing effort, we already aggregated >1,500 GWAS from >100 studies, with improved representation of global diversity: 60% European (EUR), 20% East Asian (EAS), 12% African (AFR), 4% Hispanic/Latino (HIS), 3% South Asian (SAS), and 1% Middle Eastern (MID) ancestries. Employed imputation panels include 69% TopMed, 20% 1000Genomes, and 9% Haplotype Reference Consortium. Preliminary meta-analysis (METAL-Step2) verified known positive controls like *UMOD* (rs13329952, p=2.1e-269, n=2,264,920) and *CUBN* (rs1801239, p=6.0e-130, n=625,976) for eGFR and UACR, respectively. Both METAL and MrMega showed *UMOD* being heterogeneous across ancestries, while *CUBN* was homogeneous (**Table**).

Conclusions: By leveraging the large sample size, multi-ancestry representation through >100 studies, and the assessment of non-SNP genetic variations, the CKDGen Round 5 promises to substantially enhance our understanding of the genetic basis of CKD.

Funding: Government Support - Non-U.S.

Variant		METAL-Step1						METAL-Step2	MrMega	
Gene, Phenotype		AFR	HIS	EUR	EAS	SAS	MID	Multi-ancestry	Multi-ancestry	
rs13329952	Het I^2	0	0	70.9	0	0	0	95.9	p-anc-het	7.5e-20
UMOD, eGFR	*N*(studies)	18	7	83	30	6	1	145	*N*(studies)	148
rs1801239	Het I^2	6.7	0	29.5	NA	13.7	0	0	p-anc-het	0.34
CUBN, UACR	*N*(studies)	6	2	35	0	2	1	46	*N*(studies)	51

Hierarchical meta-analysis and trans-ethnic meta-regression results for *UMOD* and *CUBN*

FR-PO649

Insights into Kidney Protein Handling through a Genome-Wide Association Study (GWAS) of the Urine Proteome

Stefan Haug, Oleg Borisov, Yong Li, Anna Kottgen. *Institute of Genetic Epidemiology - University of Freiburg, Freiburg, Germany.*

Background: Urine contains small amounts of protein under physiological conditions. Levels of urine proteins are determined by filtration from plasma, exosomes and membrane patches of kidney and urothelial cells, and active tubular secretion and reabsorption. Genetic screens of the urine proteome and comparisons to similar plasma studies may offer insights into renal protein handling, particularly in kidney tubules.

Methods: We performed genome-wide association studies with 2886 proteins quantified by the antibody-based Olink Explore 3072 platform from urine samples of 1246 German Chronic Kidney Disease study participants with eGFR>45 and ≤60 mL/min/1.73m^2 and UACR<300 mg/g. In a discovery-replication design, we studied relations of protein levels and 6 million common genetic variants, adjusted for urine dilution and potential confounders. Significantly associated ($p<1.7x10^{-11}$) variants were assigned to protein quantitative trait loci (pQTLs). To examine significant urine pQTLs in detail, we performed finemapping and identified independent credible sets (CS) of variants most likely to cause association signals in each locus, comparisons to pQTLs from corresponding plasma proteome screens (UK Biobank), and genetic colocalization analyses.

Results: We identified 173 pQTLs, arising from 127 distinct genetic regions and 170 unique proteins. The 173 pQTLs contained 153 *cis* associations, with the index variant in close proximity to the protein's cognate gene, supporting the precision and validity of urine proteomics. Median protein variance explained by pQTLs was 10.3%, with a maximum of 67.2% for variant chr8:142681841:T:TG and prostate stem cell antigen levels (*PSCA* locus, GWAS p-value $1.2x10^{-451}$). Finemapping revealed 254 independent CS (1-8 CS per region). Colocalization with plasma pQTLs detected shared signals, reflecting genetic fingerprints on the systemic proteome recovered from urine. Urine-specific associations were found for at least 15 proteins including mucin-13, where a regulatory variant altering transcription factor binding in an enhancer region determined urine levels of this epithelial barrier protein.

Conclusions: Genetic screens of the urine proteome can reveal mechanisms involved in human renal protein handling. Our ongoing investigations include connections of pQTLs to the transcriptome, the urine and plasma metabolome, and clinical traits and diseases.

Funding: Government Support - Non-U.S.

FR-PO650

Causal Association between Plasma Oxalate and Kidney Disease: Mendelian Randomization Analysis

Jade E. Bowers,[1,2] Jefferson L. Triozzi,[1,2] Piera A. Sosa,[1,2] Zhihong Yu,[1] Otis D. Wilson,[1,2] Guanchao Wang,[1,2] Ryan Hsi,[1,2] Christianne Roumie,[1,2] Adriana Hung.[1,2] Million Veteran Program. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]VA Tennessee Valley Healthcare System, Nashville, TN.*

Background: Elevated urinary oxalate contributes to tubulointerstitial fibrosis and kidney disease progression. Plasma oxalate, however, is elevated in patients with kidney disease due to reduced filtration raising the question of whether plasma oxalate is a consequence of kidney disease or a causal factor in its development. This study investigated the potentially causal association between plasma oxalate and kidney disease.

Methods: We performed a mendelian randomization experiment to assess the effect of genetically determined plasma oxalate levels on kidney outcomes within the Million Veteran Program (MVP). The exposure was derived from a genome-wide association study (GWAS) of plasma metabolite levels measured using the Metabolon platform among European ancestry individuals (N = 6,136). The MVP outcomes were derived from GWASs of eGFR (N = 397,650), chronic kidney disease (CKD), and end stage renal disease (ESRD), with an additional urine protein-to-creatinine ratio outcome from the CKDGen Consortium. The mendelian randomization experiment was conducted utilizing the inverse variance weighted (IVW) analyses. Sensitivity analyses were performed in subgroups with or without diabetes mellitus (DM).

Results: In the mendelian randomization IVW analysis, higher genetically determined plasma oxalate levels were associated with increased risk of CKD (OR 1.12, 95% CI [1.03, 1.21], p-value = 0.007). In the sensitivity analyses, the non-DM patients did not show a significant effect but the DM patients showed a significant effect for all outcomes: eGFR (p-value = 0.01), CKD (p-value 0.04), and ESRD (p-value = 0.01). These genetic associations did not show evidence of heterogeneity or directional pleiotropy, supporting a potentially causal relationship.

Conclusions: Our genetic association study supports the hypothesis that increased plasma oxalate levels may increase the risk of kidney disease, especially among patients with DM. Further investigation of the mechanisms underlying this association including but not limited to genetic and dietary contributions.

Funding: Veterans Affairs Support

FR-PO651

Building a Biobank for Genetic Studies on Primary and Recurrent Focal Segmental Glomerulosclerosis

Elena Martinelli,[1,2] Tze Yin Lim,[1] Juntao Ke,[1] Ibrahim Batal,[1] Krzysztof Kiryluk,[1] Matt G. Sampson,[3] Moin A. Saleem,[4] Martin Pollak,[5] Friedhelm Hildebrandt,[3] Ali G. Gharavi,[1] Rasheed A. Gbadegesin,[6] Sumit Mohan,[1] Simone Sanna-Cherchi.[1] *[1]Columbia University, Division of Nephrology, New York, NY; [2]Universita degli Studi di Parma, Parma, Italy; [3]Division of Nephrology, Boston Children Hospital, Boston, MA; [4]Division of Pediatric Nephrology, University of Bristol, Bristol, United Kingdom; [5]Division of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; [6]Division of Pediatric Nephrology, Duke University, Durham, NC.*

Background: Primary and Recurrent focal segmental glomerulosclerosis (pFSGS/rFSGS) carry high burden of morbidity and graft loss after kidney transplant. Genetic studies are mostly directed to non-immune forms of FSGS leaving the complex genetic etiology of p/rFSGS unresolved. A hurdle in designing adequate genetic studies is the lack of large multiethnic cohorts. We propose a multicenter strategy to collect genetic data across lifespan and ancestries to perform genetic studies for unraveling targets amenable for drug development.

Methods: We ascertained 13,000 cases with nephrotic syndrome (NS)/FSGS from national and international centers across ages, response to immunosuppression and ancestries. DNA is available for all cases and genetic data have been generated in 60% of them. To identify p/rFSGS case we are conducting a sequential filtering by removal of cases with Mendelian/APOL1-FSGS, followed by chart review to remove secondary forms (prematurity, obesity, structural kidney anomalies, and other factors). Cases are further stratified in two tiers: 1) ESKD who have experienced post-transplant recurrence (rFSGS); 2) cases not transplanted but with predictors indicating high probability of rFSGS (full NS with >80% foot process effacement at EM, initial response to steroids with evolution to resistance, initial biopsy showing MCD and subsequent biopsy consistent with FSGS).

Results: A pilot analysis on 1,127 cases from 6 cohorts removed 202 cases with Mendelian/APOL1 FSGS (18%) and 121 cases with secondary FSGS, resulting in a group of 804 cases enriched for pFSGS. Database and chart review identified 52 individuals with rFSGS (Tier1): 63.3% pediatric (35/52), 65.4% male (34/52); across different genetic ancestries: European 55.1%, Admixed 12.2%, Latinx 10.2%, African 18.4%, Asian 4.1%. Tier2 analysis is ongoing.

Conclusions: Based on estimates from our pilot analysis we will identify at least 8,000 individuals with pFSGS for genome-wide association studies (GWAS) and exome-based rare variant burden analyses. We will then validate results on the Tier1 (estimated N>500) and Tier2 (N>2,000) subgroups individually or in aggregate. These datasets will power adequate genetic discovery studies for rare forms of FSGS.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO652

Importance of Copy Number Variant Analysis in Patients with Monogenic Kidney Diseases: Insights from 8 Years of Experience in an Expert Centre's Genome Diagnostic Laboratory

Albertien M. van Eerde, Laura R. Claus, Robert F. Ernst, Martin Elferink, Hanneke W. van Deutekom, Bert Van der Zwaag. *Universitair Medisch Centrum Utrecht Genetica, Utrecht, Netherlands*.

Background: Genetic testing can reveal monogenic causes of kidney diseases, offering diagnostic, therapeutic, and prognostic benefits. While single nucleotide variants (SNVs) and copy number variants (CNVs) can result in kidney disease, CNV analysis is not always included in genetic testing. With read depth-based tools for CNV detection (e.g. ExomeDepth) emerging, massively parallel sequencing can detect both SNVs and CNVs. This makes CNV detection more efficient as it does not require a separate test (e.g. SNP-array, MLPA).

Methods: We investigated the diagnostic value of CNV analysis in 2,432 kidney disease patients genetically tested at the University Medical Centre Utrecht between 2014 and May 2022. We combined previous diagnostic testing results, encompassing SNVs and CNVs, with newly acquired results based on retrospective CNV analysis. The reported yield considers both ACMG variant classification and whether the genotype actually results in disease.

Results: We report a diagnostic yield of at least 23% for our complete diagnostic cohort. The total diagnostic yield based solely on CNVs was 2.4%. The overall contribution of CNV analysis, defined as the proportion of positive genetic tests requiring CNV analysis, was 10.5% and varied among different disease subcategories, with the highest impact seen in congenital anomalies of the kidney and urinary tract and chronic kidney disease at a young age. We highlight the efficiency of exome-based CNV calling, which reduces the need for additional diagnostic tests. Furthermore, a complex structural variant, likely a *COL4A4* founder variant, was identified. Additional findings unrelated to kidney diseases were reported in a small percentage of cases. This study also offers a comprehensive overview of our expert centre's diagnostic results over the past eight years covering both SNVs and CNVs.

Conclusions: In summary, this study demonstrates the substantial diagnostic value of CNV analysis, providing insights into its contribution to the diagnostic yield and advocating for its routine inclusion in genetic testing of kidney disease patients.

FR-PO653

Results of Genetic Testing with a 385-Gene Panel in African American Patients with Kidney Diseases

Anthony J. Bleyer,[1,2] Keisha L. Gibson,[4] Jessica Chaperon,[3] Jennifer Deyo,[3] Margaret Westemeyer,[3] Nour Baddar,[3] Michelle Bloom,[3] Sumit Punj,[3] Hannah C. Ainsworth,[1] Stanislav Kmoch,[1,2] Barry I. Freedman.[1] *[1]Wake Forest University School of Medicine, Winston-Salem, NC; [2]Univerzita Karlova, Praha, Czechia; [3]Natera, Inc., Austin, TX; [4]The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC*.

Background: While genetic factors like apolipoprotein 1 (*APOL1*) high-risk genotypes (HRG) account for much of the excess risk of end-stage kidney disease in African American (AA) patients, no broad studies of other monogenic kidney diseases in AA patients have been performed. Here we not only assessed the prevalence of *APOL1* HRGs, but also tested for other genetic causes of kidney disease and the combined prevalence of *APOL1* HRGs with these other genetic factors in a large cohort of AAs with kidney disease.

Methods: A retrospective analysis was performed on samples from a large cohort of self-reported AA patients who underwent testing with a 385 gene panel associated with common and rare genetic kidney diseases (the Renasight™ test).

Results: Of 8696 AA patients with kidney disease included in this study, positive genetic results were identified in 36.5% (3175/8696), of whom 62.5% (1985/3175) had a sole *APOL1* HRG finding with no other positive genetic findings. Among the remaining 1190 patients, positive results spanned 119 genes including *PKD1/2* (11.3%, n=359), *COL4A3/4/5* (9.2%, n=293), *HBB* (beta hemoglobinopathies/thalassemia) (2.6%, n=84), and 113 other genes (15.3%, n=487). The frequency of *APOL1* HRGs in patients with other genetic findings were: *PKD1/2* (12.3%; 44/359), *COL4A3/4/5* (24.9%; 73/293), *HBB* (22.6%;19/84), and other genetic diagnoses (21.8%;106/487). Compared with the reported frequency of *APOL1* HRG in the general AA population (13.0%), in our cohort, *APOL1* HRGs were present at a significantly higher frequency among AA patients with *COL4A3/4/5*, *HBB*, other genetic diagnoses ($P < 0.05$), but not with *PKD1/2*.

Conclusions: This study demonstrates that genetic factors beyond *APOL1* HRGs are prevalent among AA patients with kidney disease. The broad range of genetic etiologies identified in this study demonstrates the need for comprehensive genetic testing in AA patients with kidney disease. Further research around the clinical characteristics of patients with *APOL1* HRGs and a second positive finding will be needed to understand how kidney disease is driven by these genetic findings.

FR-PO654

Exome Sequencing Reveals a Monogenic Cause of Kidney Disease in 34% of Pediatric Patients at a Single Saudi Arabian Center

Katharina Lemberg,[1] Mohamed A. Shalaby,[2] Shirlee Shril,[1] Florian Buerger,[1,3] Ronen Schneider,[1] Kirollos Yousef,[1] Nils D. Mertens,[1] Bshara Mansour,[1] Caroline M. Kolvenbach,[1] Lea M. Merz,[1,4] Ken Saida,[1] Konstantin Deutsch,[1] Selina Hölzel,[1] Seyoung Yu,[1] Izzeldin Elmubarak,[1] Alina Braun,[1] Gijs A. Franken,[1] Sherif M. El Desoky,[2] Jameela A. Kari,[2] Friedhelm Hildebrandt.[1] Hildebrandt Lab. *[1]Boston Children's Hospital, Boston, MA; [2]King Abdulaziz University, Jeddah, Saudi Arabia; [3]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [4]Universitatsklinikum Leipzig, Leipzig, Germany*.

Background: In pediatric patients, the most frequent causes for end stage kidney disease (ESKD) are congenital anomalies of the kidney and urinary tract (CAKUT), followed by glomerulonephritis, steroid-resistant nephrotic syndrome (SRNS), renal ciliopathies and nephrolithiasis/nephrocalcinosis. A significant fraction of these disease entities is due to monogenic causes, ranging from ~10% in CAKUT to about ~55% in renal ciliopathies. Exome sequencing (ES) has revealed numerous disease-causing genes and pathogenic variants in these genes. Nevertheless, continuous efforts are crucial to expand the knowledge on these variants to establish unequivocal diagnoses. In this study, we report ES data from a single Saudi-Arabian center with an underrepresented population. Through this study, we aim to explore potential founder effects and determine specific genotype-phenotype correlations based on clinical diagnoses and genetic ancestry.

Methods: We consolidated 377 families with either SRNS, CAKUT, NPHP and stone disease / tubulopathy. In these families, we performed ES and analyzed the obtained data for variants in established disease genes for the respective diseases. These families were recruited between 2007 – 2023 at King Abdul Aziz University in Jeddah, Saudi Arabia.

Results: In this highly homozygous cohort (homozygosity by descent: 116 Mb (mean), 91 Mb (median)) 163/377 (43%) patients had SRNS, 155/377 (41%) had CAKUT, 36/377 (9.5%) had renal ciliopathies and 23/377 (6%) had stone disease / tubulopathies. Pathogenic variants were identified in 36% of families with SRNS, 18% of families with CAKUT, 75% of families with NPHP, and 61% of families with stone disease.

Conclusions: We identified a genetic cause of kidney disease in 33.6% of patients from a single Saudi-Arabian center. Elucidating prevalent disease genes and disease variants in a defined region and genetic ancestry group can provide important insights into variant pathogenicity assessment, disease management, and prognosis.

Funding: Government Support - Non-U.S.

FR-PO655

Genetic Testing in Biopsy-Confirmed Kidney Disease

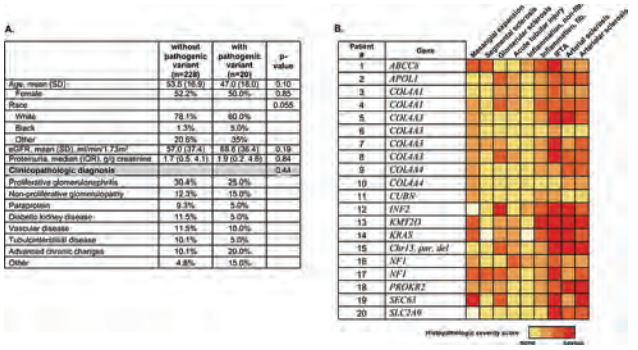
Insa M. Schmidt,[1] Ashish Verma,[1] Sophie E. Claudel,[1] Ragnar Palsson,[4] Anand Srivastava,[3] Isaac E. Stillman,[2] Sushrut S. Waikar.[1] *[1]Boston Medical Center, Boston, MA; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]University of Illinois Chicago, Chicago, IL; [4]Massachusetts General Hospital, Boston, MA*.

Background: Chronic kidney disease (CKD) is a major public health burden, with monogenic causes identified in approximately 10% of adult patients. Broad gene panels offer promising diagnostic avenues but the correlation between specific gene variants and distinct histologic patterns of injury has not been systematically explored in cohorts with biopsy-confirmed CKD.

Methods: We conducted genetic testing using a commercially available 385-gene kidney disease panel on 248 individuals who had biopsy-confirmed kidney disease and available DNA samples with pathologist-adjudicated semi-quantitative assessments of histopathology. Both pathogenic and likely pathogenic variants in autosomal dominant, X-linked, and autosomal recessive genes were reported.

Results: Positive genetic findings, specifically pathogenic variants, were identified in 8.1% (20/248) of cases. Mean baseline eGFR was 69±36 and 57±37 ml/min/1.73m^2 and median proteinuria [IQR] was 1.9 [0.2–4.6] and 1.7 [0.5–4.1] g/g creatinine in individuals with and without a positive genetic finding (p=0.19 and p=0.84, respectively). The most common primary clinicopathologic diagnosis of those with a positive genetic finding were proliferative glomerulonephritis (25.0%) and advanced chronic changes (20%) (**Figure 1A**). Positive results occurred most frequently in the *COL4A3* (19%), *COL4A1* (9.5%), *COL4A4* (9.5%), *CUBN* (9.5%), and *NF1* (9.5%) genes. Two variants in the same gene (*CUBN*) were identified in one case. **Figure 1B** illustrates the patterns of histopathologic changes observed in individuals with positive genetic findings. Pathogenic variants in genes such as *INF2*, *KMT2D*, and *KRAS* showed a trend towards severe patterns of injury, including high scores in interstitial fibrosis and tubular atrophy, glomerulosclerosis, and arterial and arteriolar sclerosis.

Conclusions: Integrating genetic data with detailed tissue-level changes may inform future research aimed at elucidating the genotype-phenotype relationships in CKD. This approach may help to identify potential areas for targeted interventions, ultimately aiming to improve patient outcomes by tailoring treatments to specific genetic and histologic profiles.



A.

	without pathogenic variant (n=228)	with pathogenic variant (n=20)	p-value
Age, mean (SD)	53.8 (16.9)	47.0 (14.0)	0.10
Female	52.2%	50.0%	0.85
Race			0.055
White	78.1%	90.0%	
Black	1.3%	5.0%	
Other	20.6%	35%	
eGFR, mean (SD), ml/min/1.73m²	57.0 (27.4)	68.6 (36.4)	0.19
Proteinuria, median (IQR), g/g creatinine	1.7 (0.5, 4.1)	3.9 (0.2, 4.8)	0.84
Clinicopathologic diagnosis			0.44
Proliferative glomerulonephritis	30.4%	25.0%	
Non-proliferative glomerulopathy	12.3%	15.0%	
Paraprotein	9.3%	5.0%	
Diabetic kidney disease	11.5%	5.0%	
Vascular disease	11.5%	10.0%	
Tubulointerstitial disease	10.1%	5.0%	
Advanced chronic changes	10.1%	20.0%	
Other	4.8%	15.0%	

B.

Figure 1. A. Baseline characteristics of Boston Kidney Biopsy Cohort (BKBC) participants with and without positive genetic findings. **B.** Shown are the histopathologic patterns of injury in patients with a pathogenic variant (n=20). The color intensity from yellow to red represents the histopathologic severity score, ranging from none to mild, moderate, and severe. eGFR, estimated glomerular filtration rate; non-fib., non-fibrosed interstitium; fib., fibrosed interstitium; IFTA, interstitial fibrosis and tubular atrophy

FR-PO656

Genotype-Phenotype Correlations in Combined Kidney Histopathology and Genetic Testing on a 385-Gene Kidney Disease Panel

Cristian Riella,[1] Dan Colombo,[1] Helmut G. Rennke,[2] Isaac E. Stillman,[1] Astrid Weins,[2] Seymour Rosen,[1] Yael K. Heher,[1] Giada Bianchi,[2] Anthony J. Bleyer,[3] Stanislav Kmoch,[4] Weining Lu,[5] Peter G. Czarnecki.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Wake Forest University School of Medicine, Winston-Salem, NC; [4]Univerzita Karlova, Praha, Czechia; [5]Boston University, Boston, MA.*

Background: The magnitude of causative and contributory genetic mechanisms in adult chronic kidney disease is unknown. We aimed to investigate genotype data from large kidney disease gene panel tests in the context of histopathologic findings and identify the diagnostic strengths of both methods alone and in combination. We further sought to find correlations between genetic variants and histologic and ultrastructural phenotypes.

Methods: We analyzed genetic test results, clinical parameters of kidney disease and renal histopathology findings in 115 patients from two major academic medical centers in Boston.

Results: In 37.4% of cases, kidney disease was sufficiently diagnosed by pathology, in 34.8% of cases a precision diagnosis was made by combined pathology and genetic testing, and in 33.0% of cases, pathology only delivered a less specific pattern diagnosis. Genetic testing alone led to a final diagnosis in 29.6% of cases, and it was particularly powerful in cohorts with positive family history of CKD and in the absence of diabetes, glomerulonephritis or immune deposition disease. We discovered a surprisingly high amount of TBMN-Alport-spectrum disease with no detectable collagen gene mutations (63.3%). We also demonstrate that the magnitude of age-independent global glomerulosclerosis strongly correlates with the presence of genetic variants in ADTKD-, CAKUT- and podocyte genes. In the course of our analysis, we identified variants of uncertain significance in at least 10 kidney disease genes that are potentially pathogenic.

Conclusions: Our study highlights the specific strengths of combined histopathology and genetic testing in the precision diagnosis of renal parenchymal disease, suggesting genetic causation in patients with positive family histories, absence of diabetes, glomerulonephritis and immune deposition disease. We demonstrate the genetic complexity of TBMN-Alport-spectrum disease that is far beyond collagen-IVα mutation, and we find supporting evidence for the hypothesis that age-independent global glomerulosclerosis is driven by genetic factors.

Funding: NIDDK Support, Private Foundation Support

FR-PO657

Utility of Genetic Testing in Patients with CKD of Uncertain Etiology: Results from an Underserved, Predominantly African American, Urban Population

Nahida Baigam, Tammy N. Do, Annalisa B. Perez, Siddhartha D. Bajracharya, Rajesh Mohandas. *LSU Health New Orleans, New Orleans, LA.*

Background: Genetic testing is being increasingly used in the diagnosis of patients with Chronic Kidney Disease(CKD) of uncertain etiology. Most centers limit the use to young patients with unexplained CKD or those with a strong family history of kidney disease. The utility of genetic testing might vary depending on the genetic composition of the population studied. We report our experience with genetic testing in a large, urban, predominantly African American population, associated with an academic practice in New Orleans

Methods: DNA from a cheek swab of 65 patients with CKD of uncertain etiology was evaluated for 385 gene panels (the RenasightTM test).

Results: The mean age of the patient population was 55 +/- 13 years. Of those most were males 78 %, and African American 71 %. Overall, 34 % had a known pathogenic mutation while 66 % had negative tests. The mean age in the positive and negative test groups was 52.58 and 56.86 years, respectively. Many patients who did not have a pathogenic mutation had carrier status for APOLA1 or COL4.

Conclusions: CKD-focused genetic panels have significantly enhanced clinical diagnoses. In our patient population, which was not restricted by age or a positive family history, 1/3 patients had a definitive diagnosis for their CKD because of genetic testing. These findings advocate for the broader implementation of genetic test panels in the clinical care of CKD patients with unknown etiology.

FR-PO658

The RenaCARE Study: Updating Genetic Testing Results in Response to New Gene-Disease Association and Variant Upgrade

Margaret Westemeyer, Sangeeta Bhorade, Hossein Tabriziani, Dinah Clark. *Natera Inc, Austin, TX.*

Background: Genetic testing enables physicians to identify underlying molecular diagnoses and tailor treatment to optimize patient care. For chronic kidney disease (CKD), positive genetic results have been shown to impact patient management in up to 89% of cases. Genetic test results may change over time due to variant reclassification or new gene-disease associations. In such cases the testing laboratory may issue an updated report to notify physicians of new findings.

Methods: The Renasight Clinical Application, Review, and Evaluation (RenaCARE) study was conducted to evaluate the diagnostic and clinical utility of genetic test results in patients with CKD. 1624 patients (median: 55 years; range 18-96) were enrolled. Genetic testing was performed using a CKD-focused 385-gene panel (the Renasight™ test, Natera, Inc) on patient samples. Genetic testing results were compared at one year post-test with those at the original report date to determine the number and nature of cases with updated genetic test results. (e.g. establishment of new gene-disease associations, or upgrade of variant/s classified as a variant of uncertain significance (VUS) to likely pathogenic/ pathogenic variant.

Results: 338 study patients originally had positive results in 54 genes. 18 additional cases (n=356) had a new positive result at one year; these involved five genes: *COL4A3* (n=1), *IFT140* (n=9), *PKD1* (n=6), *PKD2* (n=1), and *RRM2B* (n=1). Variants in *IFT140* were previously only associated with an autosomal recessive ciliopathy; new evidence associating single IFT140 loss of function variants with ADPKD resulted in a result change from "carrier" to "positive" for all 9 patients. For the other 9 patients, incorporation of new data resulted in upgrades from VUS to pathogenic or likely pathogenic classification. These findings represent a 1.1% increase in positive rate and comprise 5.1% of positive study results at one year.

Conclusions: This study demonstrated how new evidence in gene-disease association and variant classification can impact patients who underwent genetic testing with a broad CKD-focused panel beyond their initial result. These findings are representative of the evolving findings in CKD genetic testing and can increase the diagnostic/clinical utility of the test.

FR-PO659

Fabry Disease Genetic Diagnosis in a Large CKD Population Tested with a Broad Kidney Gene Panel

Margaret Westemeyer,[1] Jennifer Deyo,[1] David G. Warnock,[2] Eric L. Wallace.[2] *[1]Natera, Inc., Austin, TX; [2]University of Alabama at Birmingham, Birmingham, AL.*

Background: Fabry disease (FD) is a genetic disorder caused by variants in *GLA* that encode lysosomal enzyme α-galactosidase A and leads to progressive damage in various organs especially kidneys, heart, and brain, due to glycosphingolipid accumulation. Due to X-linked inheritance, FD is generally more severe in males. Females with FD exhibit heterogeneous presentation, are underdiagnosed and are expected to inherit the disease twice as often. Patients may undergo a diagnostic odyssey, with an estimate of at least 15 years between FD onset and diagnosis. Early diagnosis is key to preventing severe complications through initiation of multiple available FD treatments. We assessed the real-world prevalence and characteristics of FD detected by genetic testing in individuals with kidney disease.

Methods: Cases with a pathogenic (P) or likely pathogenic (LP) variant in *GLA* were identified in a large database of individuals that underwent genetic testing with a 385 renal gene panel (the Renasight™ test, Natera, Inc.). Available clinical and demographic data including age, ethnicity, sex, and ICD-10 codes, were collected.

Results: Out of 67,437 cases, 111 (M:50; F:61) had a positive *GLA* finding, an overall prevalence of 1:608 (0.16%). The mean age of *GLA*-positive patients at the time of testing was 43.6y (M:44.4y; F:43.0y) and 47.8% were Caucasian. Of all *GLA*-positive cases, 47.7% had a clinical FD diagnosis, representing 58.0% and 39.3% of male and female patients, respectively. 9.9% (11/111) of *GLA*-positive cases had a second positive genetic

finding, two of which had an a priori FD diagnosis. 72.7% (8/11) of cases with a second positive finding were female.

Conclusions: This study showed that broad genetic testing identified FD in kidney disease patients without a clinical diagnosis. The prevalence of FD among individuals with CKD, identified via genetic testing is significantly higher than the general population (1:40,000). The low proportion of female patients reporting FD suggests that diagnosis is less likely to be suspected in female patients with kidney disease. Furthermore, the high prevalence of dual positive findings in this cohort underscores the importance of testing with a broad genetic panel. Diagnosis of FD through genetic testing can inform the use of tailored therapeutics and diagnostic decisions.

FR-PO660

Importance of 3-Year-Old Urinalysis in Diagnosing Alport Syndrome

Hideaki Kitakado, Yuka Kimura, Yuta Inoki, Yu Tanaka, Chika Ueda, Nana Sakakibara, China Nagano, Tomoko Horinouchi, Tomohiko Yamamura, Shingo Ishimori, Kandai Nozu. *Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan.*

Background: Alport syndrome (AS) is an inherited kidney disease caused by pathogenic variants in COL4A3, COL4A4, and COL4A5, which encode the α3, α4, and α5 chains of type IV collagen. The prevalence is estimated at 1 in 5000 individuals, with autosomal dominant (ADAS), autosomal recessive (ARAS), and X-linked (XLAS) forms. Symptoms typically begin with hematuria in the early stages, progressing to increased proteinuria and eventual kidney failure. Renin-Angiotensin-Aldosterone System inhibitors can delay at which kidney failure occurs, underscoring the importance of early diagnosis and intervention, especially in patients with proteinuria. In Japan, a mass urinalysis is available for all 3-year-old children and annually for all elementary to high school students, and the 3-year-olds urinalysis has been shown to be potentially useful in the early detection of AS.

Methods: We examined diagnostic events in 337 cases of AS diagnosed by genetic testing from August 2015 to September 2023, with patients aged 18 years or younger.

Results: Among the 337 cases, 175 were males (52%), and the median age was 6 years. The most common event for detecting urinary abnormalities was the 3-year-old urine test, accounting for 102 cases (30%). Other events included the incidental detection of urinary abnormalities during the examination of other diseases (77 cases, 23%), episodes of macroscopic hematuria (76 cases, 23%), school urine tests (18 cases, 5%), and nursery urine tests (18 cases, 5%). Among the 102 cases identified by the 3-year-old urine test, the breakdown of each genetic form was XLAS males (29%), XLAS females (44%), ADAS (20%), and ARAS (7%). Of these, 42 cases showed both hematuria and proteinuria, with XLAS males accounting for 15 out of 30 cases (50%), XLAS females for 15 out of 45 cases (33%), ADAS for 6 out of 20 cases (30%), and ARAS for 6 out of 7 cases (86%).

Conclusions: The 3-year-old urine test is the most common diagnostic event for AS, encompassing all genetic forms. The proportion of cases with proteinuria is higher in ARAS and XLAS males, but it is present in all genetic forms. In over 40% of cases, urinary protein is already observed, enabling early intervention. It is important that the benefits of the 3-year-old urine test for the early detection of AS.

FR-PO661

Familial Variability of Disease Progression in Autosomal Dominant Alport Syndrome: Results from SHRAS

Xuantong Dai, Ningning Hu, Gengru Jiang, Fujun F. Lin. *Renal Division, Department of Internal Medicine, Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.*

Background: Autosomal dominant Alport syndrome (ADAS), caused by heterozygous *COL4A3* or *COL4A4* pathogenic variants, is characterized by a large variability of disease progression. This study aims to evaluate the intrafamilial variability of disease progression and the relevant predictors in Chinese ADAS patients from the Shanghai Registry of Alport syndrome (SHRAS).

Methods: SHRAS, part of the Shanghai Registry of Genetic Kidney Disease, performed collection of clinical, and genetic data of ADAS patients referred from 14 leading tertiary hospitals across China since 2006. In kindreds with ≥ 2 affected individuals, discordant disease progression were evaluated in 2 categories: age at onset of proteinuria and stage 3 chronic kidney disease (CKD). Marked intrafamilial variability was defined as the onset age across 2 categories differed ≥ 20 years in at least 2 patients in one kindred, or in kindred with both pediatric and adult patients, proteinuria or stage 3 CKD developed in at least 1 pediatric patient while the phenotype of adult patient was isolated hematuria.

Results: Among 73 kindreds of 311 ADAS patients (118 pediatric and 193 adult patients), 31 kindreds (42.47%) of 72 patients (21 pediatric and 51 adult patients) were deemed as discordant disease progression. Intrafamilial variability was not associated with family size nor genotype (Table 1). Multivariate mixed-effects model revealed concomitant kidney disease and disease onset age as risk factors of variability (Figure 1).

Conclusions: In ADAS cohort of SHRAS, marked intrafamilial variability of disease progression was observed. Our findings didn't reveal a significant genotype influence on intrafamilial variability, which necessitates a more thorough identification of relevant clinical and genotypic factors.

Table 1. Characteristics of ADAS kindreds with intrafamilial variability of disease progression

Variables	Intrafamilial variability	Concordant families	P-value
Numbers of kindreds (numbers of patients)	31 (72)	42 (96)	–
2 members per kindred, N (%)	24 (77.4)	32 (76.2)	0.902
> 2 members per kindred, N (%)	7 (22.6)	10 (23.8)	
Patients with proteinuria, N (%)	54 (75.0)	34 (35.4)	<0.001
Onset age of proteinuria	27.5 ± 19.0	35.3 ± 14.0	0.031
Patients reaching stage 3 CKD, N (%)	7 (9.7)	7 (7.3)	0.573
Onset age of stage 3 CKD	36.7 ± 13.7	55.7 ± 13.1	0.026
COL4A3/A4-truncating variants, N (%)	7 (22.6)	10 (23.8)	0.902
COL4A3/A4-nontruncating variants, N (%)	24 (77.4)	32 (76.2)	

Figure 1. Cox proportional hazard model for intrafamilial variability of ADAS disease progression

Variables	Univariate analysis	P-value	Multivariate analysis	P-value
	HR (95% CI)		HR (95% CI)	
Onset age of disease (yrs)	0.93 (0.91, 0.95)	<0.001	0.93 (0.91, 0.95)	<0.001
Male	1.05 (0.68, 1.62)	0.821		
Hypertension	0.94 (0.55, 1.60)	0.822		
COL4A3/A4-truncating variants	1.27 (0.78, 2.09)	0.339		
Concomitant kidney disease	2.17 (0.998, 4.73)	0.051	3.17 (1.43, 7.03)	0.005

FR-PO662

The ClinGen Alport Syndrome Variant Curation Expert Panel: Guiding Variant Classification in COL4A3, COL4A4, and COL4A5

Alicia B. Byrne,[1] Janewit Wongboonsin,[2] Mary-Beth Roberts,[3] Judith A. Savige,[4] Rachel Lennon.[5] ClinGen Alport Syndrome Variant Curation Expert Panel. *[1]Broad Institute, Cambridge, MA; [2]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [3]Cleveland Clinic, Cleveland, OH; [4]University of Melbourne, Melbourne, VIC, Australia; [5]The University of Manchester, Manchester, United Kingdom.*

Background: The ClinGen Alport Syndrome (AS) Variant Curation Expert Panel (VCEP) was established in 2023 with the purview to define variant classification criteria tailored for the genes *COL4A3*, *COL4A4*, and *COL4A5* in the context of AS and its associated phenotypes. These refined criteria will then be used to determine expert classifications of variant pathogenicity and interpretations of relevance to disease causality. ClinGen VCEPs across other disease areas have demonstrated that this process enhances the accuracy and consistency of variant classification, and can decrease the number of variants that are of uncertain significance.

Methods: Using the 2015 ACMG/AMP Sequence Variant Classification framework as the basis, the AS VCEP is systematically reviewing the 26 defined lines of evidence to determine ways in which they can be refined to be more specific to the known biology of collagen genes and the known characteristics of AS presentations.

Results: The lines of evidence considered in variant classification fall into two main categories: human observational data and predictive and functional data. In refining the use of human observational data-related evidence, the AS VCEP have defined the phenotypes that must be present for an individual to be considered a 'case'; a concept integral to the application of multiple of these evidence types, and established thresholds to determine whether a variant's frequency in the population is consistent with disease causality. In reviewing predictive lines of evidence, the AS VCEP is paying particular attention to glycine variants affecting the Gly-X-Y repeat in the triple helical domain, developing guidance for how to appropriately weight the known damaging impact of this established, dominant negative disease mechanism in comparison to other variant types. Finally, recommendations are also being developed to guide calibrated integration of evidence provided by functional assays.

Conclusions: The work of the AS VCEP in developing tailored criteria for the classification of variants in *COL4A3*, *COL4A4*, and *COL4A5* will provide a harmonized framework that maximizes the utility of available evidence, leading to improved accuracy in variant classification and interpretation, in turn, improving clinical care for individuals with variants in these genes.

Funding: Other NIH Support - NHGRI U24 HG006834

FR-PO663

Increased Odds of Nephrotic Syndrome and ESKD in Fin-Major Heterozygotes

Adrian O. Banerji,[1] Aarno Palotie,[2,3] Matt G. Sampson.[1,4] FinnGen.
[1]Boston Children's Hospital, Boston, MA; [2]Helsingin yliopisto, Helsinki, Finland; [3]Massachusetts General Hospital, Boston, MA; [4]Harvard Medical School, Boston, MA.

Background: *NPHS1* loss of function (LOF) variants are known to cause congenital nephrotic syndrome (NS) with recessive inheritance. Fin-Major was the first described *NPHS1* LOF variant. The clinical impact of Fin-Major in the heterozygous state is incompletely understood. We assessed the prevalence of nephrotic syndrome and end stage kidney disease (ESKD) for Fin-Major heterozygotes in the FinnGen study, in which 10% of the Finnish population (n=520,212) is enrolled.

Methods: The FinnGen database was used to identify individuals heterozygous for Fin-Major, and those without identified *NPHS1* variants. Patients homozygous for Fin-Major or with at least one other *NPHS1* variant were excluded, thereby excluding known compound heterozygotes. Individuals without identified *NPHS1* variants were used as controls. Individuals with NS or ESKD (chronic dialysis or kidney transplant) were identified by ICD-10 code. As these are chronic conditions, only individuals with repeated codes for each condition were included for further analysis.

Results: Among all FinnGen participants, 8,944 individuals were heterozygous for Fin-Major, 859 had NS, and 3,536 had ESKD. Individuals heterozygous for Fin-Major had 2 times increased odds to have nephrotic syndrome and 1.5 times increased odds to have ESKD compared to those without Fin-Major (P<0.001). After exclusion of Fin-Major heterozygotes with congenital NS (n=8), Fin-Major heterozygous individuals had 1.4 times increased odds to have nephrotic syndrome and 1.3 times increased odds to have ESKD (p=0.1, p=0.01).

Conclusions: Individuals heterozygous for the Fin-Major variant have increased risk for nephrotic syndrome and ESKD. This persists even after exclusion of individuals with congenital nephrotic syndrome. Further work, including exome sequencing of *NPHS1*, is needed to identify if this risk is due to unrecognized compound heterozygosity or if *NPHS1* haplo-insufficiency is a contributor to kidney disease risk.

Funding: NIDDK Support

FR-PO664

A Novel Pattern of Mutations in Northern Indian Children with Steroid-Resistant Nephrotic Syndrome

Narayan Prasad, Brijesh Yadav, Jeyakumar Meyyappan. *Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.*

Background: Steroid Resistant Nephrotic Syndrome(SRNS) in children poses treatment challenges, and many had genetic mutations. Data on genetics is scarce.

Methods: A prospective study(Oct2018–April2023) enrolled children with SRNS who consented to DNA isolation and next-generation sequencing to explore genetic variants and their clinical outcomes. Clinical, histological and genetic data were recorded.

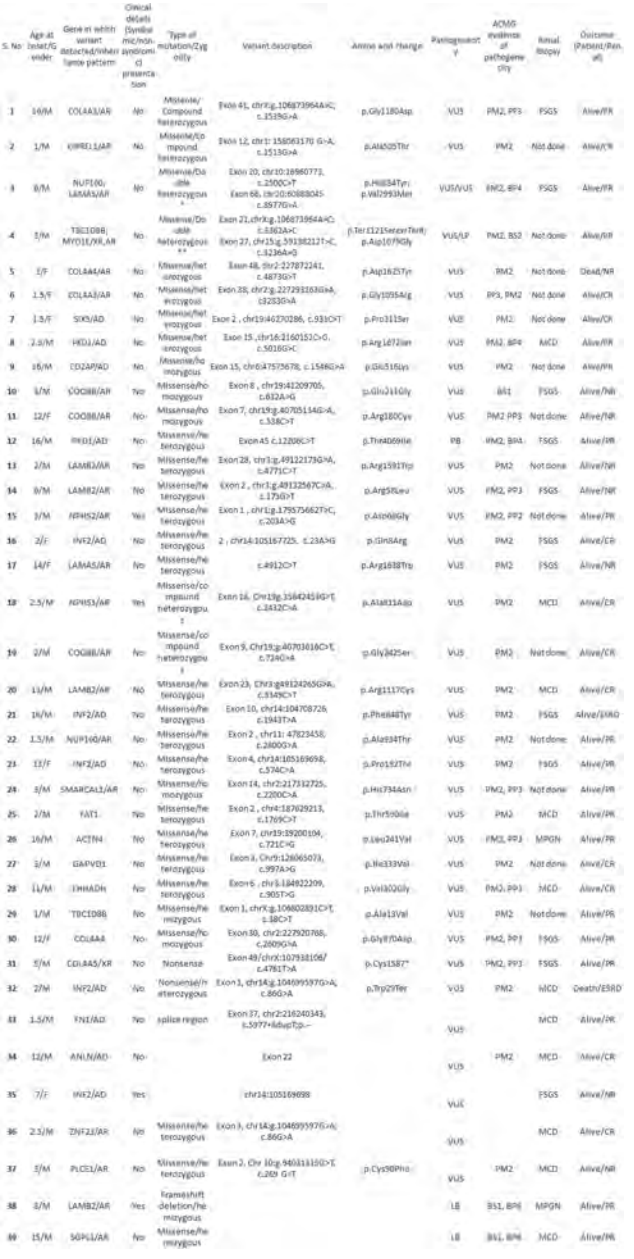
Results: Out of 680 NS patients, 121(17.8%) had SRNS and 96consented to genetic analysis. Of them 69(71.9%) were early SRNS and 27(28.1%) late nonreponder. 63(65.7%) had reportable genetic variants and genetic variant Pathogenic or likely Pathogeneic is shown in Image1, and genetic variant Variant of Unknown Significance or likely benign in Image 2. COL4A genes mutation was seen in 20(31.7%) patients. Renal biopsy showed FSGS in 31/42(74%) with variants. Complete(11%) and Partial remission(23.9%) with CNI was observed.

Conclusions: 65.7% SRNS patients had genetic variants, and COL4A variants were responsible for 31.7 %. CNI reponse was also observed.

Funding: Government Support - Non-U.S.

S. No	Age at onset/Gender	Gene in which variant detected/inheritance pattern	Clinical details (Syndromic/ non-syndromic) presentation	Type of mutation/Zygosity	Variant description	Amino acid change	Pathogenesity	ACMG evidence of pathogenecity	Renal Biopsy	Outcome (Patient/Renal)
	9/M	BBS12/AR	Bardet Biedl Syndrome	Missense/Homozygous	chr4:123663297G>A	p.Gly84Arg	LP	PM3, PP3	Not done	Alive/PR
	17/F	LMX1B/AD	Nail Patella Syndrome	Missense/Compound heterozygous	chr9:129455566, c.705G>C	p.Leu226Arg ; p.Lys235Asn	LP	PP3, PM2		Alive/PR
	6/M	COL4A4/AR	No	Frameshift/ Heterozygous	Exon 30/chr2:227920745	p.Pro878fs	LP	PVS1, PM		Alive/PR
	16/M	COL4A3/AD	Yes	Splice site/heterozygous	spicesite_3:c.547-1delG		LP	PVS1, PM	FSGS	Alive/PR
	17/M	COL4A5/XR	Yes	Nonsense/Hemizygous	Exon 1,chrX:g.108440189C>T, c.64C>T	p.Gln22Ter	LP	PVS1, PM	Not done	Alive/NR
	17/M	COL4A5/XR	Yes	Frameshift deletion/Hemizygous	Exon 36,chrX:107869489, c.3158delC	p.Pro1053LeufsTer99	LP	PVS1, PM		Alive/PR
	13/M	COL4A5/XR	No	Missense/Hemizygous	Exon 29, chrX:g.108606874G>A, c.2377G>A	p.Gly793Arg	LP	PP3, PM2	FSGS	Alive/PR
	6/M	COL4A5/XR	No	Missense/Hemizygous	Exon 40, ChrX:g.108667183G>C c.3604G>C	p.Gly1202Arg	LP	PP3, PM2	FSGS	Alive/ESRD
	6/F	COL4A4/AR	No	Missense/Homozygous	Exon 45, Chr2:g.227012226C>T c.4288G>A	p.Gly1430Arg	LP	PP3, PM2	FSGS	Alive/ESRD
	9/M	NPHS2	No	Missense/Heterozygous	Exon 7, chr1:g.179552604C>T c.872G>A	p.Arg291Gln	LP	PM2, PM5	FSGS	Alive/CR
	17/M	COL4A4	Yes	Missense/so mpound heterozygous	Exon 39, chr2:227896932 c.3638G>A;	p.Gly1213Glu;	LP	PP3, PM2	Not done	Alive/PR
	17/M	PAX2/AD	No	Missense/Heterozygous	Exon 3, chr10: 102510464; c.226G>A	p.Gly76Ser	P	PS4, PP1	MCD	Alive/PR
	17/F	LMX1B	No	Missense/Heterozygous	Exon 4, chr9:129455525, c.668G>A	p.Arg223Gln	P	PS3, PP3	FSGS	Alive/PR
	17/M	COL4A5/XR	Yes	Splice site/Hemizygous	Exon 24, chrX:107840799		P	PVS1, PM	Not done	Alive/ESRD
	4/M	COQ2	No	Frameshift/ Heterozygous	Exon 1, chr4:84206019 , c.48dupC	p.Ala17fs	P	PS4, PVS	Not done	Alive/CR
	16/M	COL4A5	Yes	Stop gain/ Homozygous	Exon 51, chr2:228175548, c.4812C>A	p.Cys1604	P	PM3, PVS	Not done	Alive/ESRD
	17/M	COL4A5	Yes	Stop gain/ Homozygous	Exon 51, chr2:228175548, c.4812C>A	p.Cys1604	P	PM3, PVS	Not done	Alive/ESRD (RTR)
	2/F	NPHS1/AR	No	Missense/Double heterozygous	Exon 9, chr19:36339610, c.1099C>T	p.Arg367Cys	P	PM3, PS3	Not done	Alive/CR
	16/M	LMX1B/AD	Yes	Missense/heterozygous	Exon 8 , chr9:129458594, c.1085A>G	p.Asp362Gly	LP	PM2, PP3	FSGS	Alive/ESRD
	8/M	COL4A5/XR	Yes	Frameshift deletion/ Hemizygous			P		MCD	Alive/PR
	16/M	COL4A5/XR	Yes	Frameshift deletion/ Hemizygous			P		FSGS	Alive/ESRD
	12/M	COL4A5/XR	Yes	Frameshift deletion/ Hemizygous			P		FSGS	Alive/CR
	1.5/F	COL4A5/XR	No	Missense/hemizygous	Exon 38, ChrX:g.108457182G>C, c.3604G>C		LP		MCD	Alive/PR

Genetic profile of patients with genetic variant classified as Pathogenic(P) or likely Pathogeneic (LP)



S. No	Age at Initial/G vider.	Gene in which variant detected/Inheri tance pattern	Clinical details (familial mic/non-syndromic) presentation	Type of mutation/Zygosity	Variant description	Amino acid change	Pathogenicity	ACMG evidence of pathogenicity	Renal Biopsy	Outcome (Patient/Renal)
1	16/M	COL4A3/AR	No	Missense/ Compound heterozygous	Exon 41, chr3:g.106873964A>C, c.1519G>A	p.Gly1180Asp	VUS	PM2, PP3	FSGS	Alive/FR
2	1/M	KIRREL1/AR	No	Missense/Compound heterozygous	Exon 12, chr1: 158656170 G>A, c.1513G>A	p.Ala505Thr	VUS	PM2	Not done	Alive/CR
3	8/M	NUP160, LAMA5/AR	No	Missense/Double heterozygous	Exon 20, chr10:18960773, c.2500C>T Exon 68, chr20:60888045-c.8977G>A	p.His834Tyr; p.Val2993Met	VUS/VUS	PM2, BP4	FSGS	Alive/FR
4	3/M	TBC1D8B, MYO1E/XR,AR	No	Missense/Double heterozygous**	Exon 21,chr8:g.106873964A>C, c.3362A>C Exon 27, chr15:g.59338212?>C, c.3236A>G	p.Ter1121SerextTer8; p.Asp1079Gly	VUS/LP	PM2, BS2	Not done	Alive/FR
5	1/F	COL4A4/AR	No	Missense/heterozygous	Exon 48, Str2: 227872241, c.4873G>T	p.Asp1625Tyr	VUS	PM2	Not done	Dead/NR
6	1.5/F	COL4A3/AR	No	Missense/heterozygous	Exon 33, chr2:g.227293163G>A, c.2233G>A	p.Gly1059Arg	VUS	PP3, PM2	Not done	Alive/CR
7	1.5/F	SOX5/AD	No	Missense/heterozygous	Exon 2 , chr19:46270286, c.931C>T	p.Pro311Ser	VUS	PM2	Not done	Alive/CR
8	2.5/M	PKD1/AD	No	Missense/heterozygous	Exon 15 ,chr16:2160152>G, c.5018G>C	p.Arg1672Ser	VUS	PM2, BP4	MCD	Alive/FR
9	16/M	COL2A1/AD	No	Missense/homozygous	Exon 15, chr6:47575678, c.1546G>A	p.Gly516Lys	VUS	PM2	Not done	Alive/FR
10	3/M	COQ8B/AR	No	Missense/homozygous	Exon 8 , chr19:41209705, c.812A>G	p.Glu271Gly	VUS	BS1	FSGS	Alive/NR
11	12/F	COQ8B/AR	No	Missense/homozygous	Exon 7, chr19:g.40705154G>A, c.538C>T	p.Arg180Cys	VUS	PM2 PP3	Not done	Alive/NR
12	16/M	PKD1/AD	No	Missense/heterozygous	Exon 45 c.12208C>T	p.Thr4069Ile	PB	PM2, BP4	FSGS	Alive/FR
13	2/M	LAMB3/AR	No	Missense/heterozygous	Exon 28, chr1:g.49122173G>A, c.4771C>T	p.Arg1591Trp	VUS	PM2	Not done	Alive/NR
14	8/M	LAMB2/AR	No	Missense/heterozygous	Exon 2 , chr1:g.49132567C>A, c.175G>T	p.Arg59Leu	VUS	PM2, PP3	FSGS	Alive/NR
15	3/M	NPHS2/AR	Yes	Missense/heterozygous	Exon 1 , chr1:g.179575662T>C, c.203A>G	p.Asn68Gly	VUS	PM2, PP2	Not done	Alive/FR
16	2/F	INF2/AD	No	Missense/heterozygous	2 , chr14:105167725, c.23A>G	p.Gln8Arg	VUS	PM2	FSGS	Alive/CR
17	14/F	LAMA5/AR	No	Missense/heterozygous	c.4912C>T	p.Arg1638Trp	VUS	PM2	FSGS	Alive/NR
18	2.5/M	NPHS1/AR	Yes	Missense/compound heterozygous	Exon 16, Chr19g.35642458G>T, c.2432C>A	p.Ala811Asp	VUS	PM2	MCD	Alive/CR
19	2/M	COQ8B/AR	No	Missense/compound heterozygous	Exon 9, Chr19:g.40701616C>T, c.724G>A	p.Gly242Ser	VUS	PM2	Not done	Alive/CR
20	11/M	LAMB2/AR	No	Missense/heterozygous	Exon 23, Chr3:g.49124265G>A, c.3343C>T	p.Arg1117Cys	VUS	PM2	MCD	Alive/CR
21	16/M	INF2/AD	No	Missense/heterozygous	Exon 10, chr14:104708726, c.1943T>A	p.Phe648Tyr	VUS	PM2	FSGS	Alive/ESRD
22	1.5/M	NUP160/AR	No	Missense/heterozygous	Exon 2 , chr11: 47823458, c.286G>A	p.Ala34Thr	VUS	PM2	Not done	Alive/FR
23	13/F	INF2/AD	No	Missense/heterozygous	Exon 4, chr14:105169698, c.574C>A	p.Pro192Thr	VUS	PM2	FSGS	Alive/FR
24	3/M	SMARCAL1/AR	No	Missense/homozygous	Exon 14, chr2:2173132725, c.2200C>A	p.His734Asn	VUS	PM2, PP3	Not done	Alive/FR
25	2/M	FAT1	No	Missense/heterozygous	Exon 2 , chr4:187629213, c.1769C>T	p.Thr590Ile	VUS	PM2	MCD	Alive/FR
26	16/M	ACTN4	No	Missense/heterozygous	Exon 7, chr19:19200104, c.721C>G	p.Leu241Val	VUS	PM2, PP3	MPGN	Alive/FR
27	3/M	GAPVD1	No	Missense/heterozygous	Exon 3, Chr9:12656073, c.997A>G	p.Ile333Val	VUS	PM2	Not done	Alive/CR
28	11/M	LMNA/DH	No	Missense/heterozygous	Exon 5 , chr1:156822209, c.905T>G	p.Val302Gly	VUS	PM2, PP3	MCD	Alive/CR
29	1/M	TBC1D8B	No	Missense/Heterozygous	Exon 1, chrX:g.106802891C>T, c.38C>T	p.Ala13Val	VUS	PM2	Not done	Alive/FR
30	12/F	COL4A4	No	Missense/homozygous	Exon 30, chr2:227920768, c.2609G>A	p.Gly870Asp	VUS	PM2, PP3	FSGS	Alive/FR
31	5/M	COL4A5/XR	No	Nonsense	Exon 49/chrX:107931066/ c.4781T>A	p.Cys1587*	VUS	PM2, PP3	FSGS	Alive/FR
32	2/M	INF2/AD	No	Nonsense/heterozygous	Exon 1, chr14:g.104699597G>A, c.86G>A	p.Trp29Ter	VUS	PM2	MCD	Death/ESRD
33	1.5/M	FN1/AD	No	splice region	Exon 37, chr2:216240343, c.5977+1dupT;p.--		VUS		MCD	Alive/FR
34	12/M	ANLN/AD	No		Exon 22		VUS	PM2	MCD	Alive/CR
35	7/F	INF2/AD	Yes		chr14:105169698		VUS		FSGS	Alive/NR
36	2.5/M	ZNF21/AR	No	Missense/heterozygous	Exon 3, chr1&g.104699597G>A, c.86G>A		VUS		MCD	Alive/CR
37	5/M	PLCE1/AR	No	Missense/heterozygous	Exon 2, Chr 10:g.96011610G>T, c.269 G>T	p.Cys90Phe	VUS	PM2	MCD	Alive/NR
38	8/M	LAMB2/AR	Yes	Frameshift deletion/heterozygous			LB	BS1, BP4	MPGN	Alive/FR
39	15/M	SGPL1/AR	No	Missense/heterozygous			LB	BS1, BP4	MCD	Alive/NR

Genetic profile of patients with genetic variant classified as Variant of Unknown Significance (VUS) or likely benign (LB)

FR-PO665

Population Frequency of Genetic Causes of Autosomal Dominant FSGS

Mary Huang, Judith A. Savige. *The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, Melbourne, VIC, Australia.*

Background: Patients with autosomal dominant (AD) Focal and Segmental Glomerulosclerosis (FSGS) often have pathogenic variants in the Alport genes (*COL4A3, 4),* or in *ACTN4, INF2, PAX2, TRPC6* or *WT1*. This study determined how often 'predicted pathogenic' variants in the commonest genes affected in AD FSGS were found undiagnosed in the normal population.

Methods: Genes were downloaded from gnomAD v2.1 and annotated in ANNOVAR. Structural and null variants were 'predicted pathogenic' and missense variants assessed for predicted pathogenicity based on rarity, computational scores, and whether they affected a conserved amino acid. As an example, our approach for predicting pathogenic missense variants in *INF2* had a sensitivity of 95% and specificity of 95% when compared with 20 benign and 20 pathogenic variants reported in LOVD. The population frequencies for the genes were then compared with variants classified Pathogenic or Likely pathogenic in ClinVar. (ClinVar variant assessments are likely to be accurate but lists may be incomplete.)

Results: Predicted pathogenic variants (null, structural and missense changes) in *COL4A3* and *COL4A4* affected about one in 113 individuals. Predicted pathogenic variants in the other genes for AD FSGS affected one in 186 individuals. The number of people with a variant in an AD FSGS gene classified Pathogenic or Likely Pathogenic in Clin Var was much less, corresponding to one in 4711 of the population.

Conclusions: Predicted pathogenic variants in *COL4A3* and *COL4A4* together are more common than other genes associated with AD FSGS. The true population frequency is likely to be greater than that calculated from variants reported Pathogenic or Likely pathogenic in ClinVar and may be closer to our assessment. However the penetrance of these predicted pathogenic variants for AD FSGS is not known.

Number of people with predicted pathogenic variant in AD FSGS genes

	Total of COL4A3, 4	ACTN4	INF2	PAX2	TRPC6	WT1	Total of other genes
Null and structural variants	350 (one in 323)	22	24	28	65	109	248 (one in 436)
Missense variants – our assessment	649 (one in 174)	87	106	48	97	21	359 (one in 301)
Total with our assessment	999 (one in 113)	109	130	76	162	130	607 (one in 186)
ClinVar	824 (one in 137)	2	3	13	2	3	23 (one in 4711)

FR-PO666

Population Frequency of Common Genetic Causes of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

Mary Huang,[1] Judith A. Savige.[2] *[1]The University of Melbourne, Melbourne Medical School, Melbourne, VIC, Australia; [2]The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, Melbourne, VIC, Australia.*

Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) is the leading cause of kidney failure in children. Imaging suggests that CAKUT affects one in 200 newborns and genetic causes are estimated in 20% of these or one in 1000. Six genes are commonly affected and, while more than 250 have been reported, most are only found in individual families. This study determined a more accurate population frequency for genetic causes of CAKUT from the number of predicted pathogenic variants in the commonest CAKUT genes and from pathogenic variants found in variant databases.

Methods: *HNF1B, SALL1, EYA1, PBX1, GATA3, PAX2* variants were downloaded from gnomAD v.2.1, and annotated in ANNOVAR. Structural and null variants were considered pathogenic and missense variants were assessed for pathogenicity based on their rarity, scores in PP2, SIFT and MT, and whether they affected a residue conserved in vertebrates. This approach for predicted pathogenic missense variants in *HNF1B* had a sensitivity of 80% and specificity of 63%. The population frequencies for the 6 genes were then compared with those in the control gnomAD subset, and with the variants classified as pathogenic in ClinVar, LOVD or HGMD.

Results: Overall, predicted pathogenic variants in the 6 CAKUT genes affected one in 230 of the gnomAD population and one in 270 controls. The population frequency of structural and null variants alone was one in 1642. Predicted pathogenic variants causing CAKUT were least common in Ashkenazi people (one in 864) and Finns (one in 837). The population frequencies for all pathogenic variants were one in 1263 for ClinVar, one in 437 for LOVD, one in 40 for HGMD.

Conclusions: Genetic forms of CAKUT resulting from predicted pathogenic variants in the most frequently affected genes are found more often than previously suspected and may represent the major cause of CAKUT rather than environmental factors.

FR-PO667

Genetic Landscape of Glomerular Diseases and FSGS among More than 50,000 People Genetically Tested for CKD

Michelle Bloom, Dinah Clark, Robert T. Burns, Elizabeth Garrity, Sumit Punj, Stephen Andrews. *Natera Inc, Austin, TX.*

Background: Focal segmental glomerulosclerosis (FSGS) is a histologic feature that is characteristic of a variety of glomerular diseases (GD). Etiologies of FSGS can be genetic, environmental, or idiopathic. Genetic testing can directly identify the cause of disease; without it, the various forms can be indistinguishable. A recent study demonstrated the utility of genetic investigation to identify an underlying cause of FSGS, especially important given the heterogeneity and that most genetic subtypes are not responsive to steroid therapies. Here we investigate the landscape and contribution of FSGS-related genes in GD in a large cohort.

Methods: A retrospective analysis of results from patients tested with a renal gene panel (the Rensight™ test) May 2020 - July 2023 identified cases that: a) indicated a GD and/or an ICD-10 code in the N00-N08 range on the requisition form and/or b) had positive findings (1 pathogenic (P) or likely pathogenic (LP) variant in a gene associated with autosomal dominant or X-linked disease, or 2 P/LP variants or risk alleles in an autosomal recessive gene) in one of 35 FSGS-related genes. The proportion of P/LP variants in each gene and odds ratios of variants in the GD and non-GD groups were assessed.

Results: Across 57205 individuals, 15490 had a positive test result, of which 49.9% (7737) were in one or more FSGS-related genes. Of the 35 FSGS-related genes queried, positive results were identified in 26. While *APOL1* and *COL4A3/4/5* were the most prevalent findings, 10.5% (810/7737) of positive cases had findings in the remaining 22 genes. Six FSGS-related genes (*WT1, LMX1B, INF2, TRPC6, NPHS1, APOL1*) were strongly associated with GD phenotypes (odds ratios 1.86 - 10.26; $p < 0.016$).

Conclusions: Identification of causative variants spanning 26 genes in this cohort illustrates the genetic heterogeneity of FSGS. Notably, several of the FSGS-related genes with the highest prevalence of positive findings were not among those with the strongest associations with GD phenotype. This suggests that patients with these variants may have clinical presentations that are mild and/or precede GD. As FSGS is a histologic indication of later stage disease, longitudinal clinical information would provide insight into the prognosis of individuals with variants in these genes.

FR-PO668

Diagnostic Yield and Clinical Utility of Genomic Testing in Patients with Suspected Genetic Kidney Disease: Singapore's First-Year Experience

Ru Sin Lim,[1] Regina S. Lim,[1] Ziyin Wang,[1] Yaochun Zhang,[2,3] Si Ting Lim,[2,3] Mya Than,[2,3] Jun Li Ng,[2,3] Kay Yuan Chong,[5] Jing Yi Ho,[4] Esther Huimin Leow,[4] Yong Hong Ng,[4] Jason Choo Chon Jun,[5] Gek Cher Chan,[2,3] Yi Da,[3] Ruochen Du,[2] Kar Hui Ng.[2,3] Renal Alliance for Precision Diagnosis in Singapore (RAPIDS). *[1]Tan Tock Seng Hospital, Singapore, Singapore; [2]National University of Singapore Yong Loo Lin School of Medicine, Singapore, Singapore; [3]National University Health System, Singapore, Singapore; [4]KK Women's and Children's Hospital, Singapore, Singapore; [5]Singapore General Hospital, Singapore, Singapore.*

Background: The genetic diagnostic yield for monogenic kidney disease is 25-30% in children and 10-30% in adults. Recognizing genetic kidney disease (GKD) as a cause of chronic kidney disease (CKD) has clinical implications. We aim to evaluate the diagnostic yield and clinical utility of genomic testing in suspected GKD patients.

Methods: We included patients with primary glomerular diseases with suspected genetic etiology or CKD of unknown etiology. Proband samples underwent clinical-grade targeted panel testing of 84 glomerular genes or whole exome sequencing (WES). This study was conducted at four tertiary hospitals in Singapore from March 2023 to January 2024.

Results: We recruited 147 probands: 102 (69.4%) adults and 45 (30.6%) children, with 61 (41.5%) females. The mean recruitment age was 33.1 ± 18.4 years and the mean disease onset age was 24.5 ± 17.4 years. They comprised of 118 (80.2%) Chinese, 12 (8.2%) Malays and 10 (6.8%) Indians. The genetic diagnostic rate was 34/147 (23.1%): 12/45 (26.7%) in children and 22/102 (21.6%) in adults involving ten distinct disorders, of which Alport syndrome accounts for 76%. 4 probands (2.7%) had suspicious variants of uncertain significance. Female gender (OR 6.7; p=0.001), extrarenal malformations (OR 3.5; p=0.039), and Alport features on kidney biopsy (OR 17.7; p=0.029) predict a GKD diagnosis. Of those with GKD diagnosis who had post-genetic counselling (n=26), genomic testing had significant clinical impact in 20/26 (77%), entailing providing appropriate treatment in 13/26 (50%), avoiding kidney biopsy in 5/26 (19.2%), initiating extra-renal surveillance in 10/26 (38.5%), confirming the genetic diagnosis, offering closure and prognostication in 16/26 (61.5%), guiding reproductive decisions in 9/26 (34.6%), offering cascade family testing in 14/26 (53.8%), and aiding in selecting suitable living kidney donor while predicting post-transplant recurrence in 4/26 (15.4%).

Conclusions: Our study shows that genomic testing has a high diagnostic yield, impacting patient management for both positive and negative findings. This supports integrating genomic testing into standard kidney disease care and underscores its clinical utility in suspected GKD.

Funding: Government Support - Non-U.S.

FR-PO669

Trio Exome Sequencing Implicates Wnt Signaling in the Pathogenesis of Bladder-Exstrophy-Epispadias Complex

Leah Bolsius, Katelyn N. Ralston, Lily Hiltebeitel, Joseph G. Borer, Richard S. Lee, Friedhelm Hildebrandt, Ted Lee, Nina Mann. *Boston Children's Hospital, Boston, MA.*

Background: Bladder-exstrophy-epispadias complex (BEEC) describes a spectrum of lower abdominal and genitourinary midline malformations, including epispadias, bladder exstrophy, and cloacal exstrophy. Although the cause of BEEC is uncertain, increased concordance rates among monozygotic (62%) vs. dizygotic twins (11%) and previously identified BEEC candidate genes suggest a hereditary component. This study aims to uncover novel genetic causes of BEEC through exome analysis.

Methods: We performed exome sequencing for 38 BEEC case-parent trios and 57 singlet probands who received care at a single institution between 09/2022 and 04/2024. For analysis, we employed a candidate gene approach utilizing a list of 130 genes curated from previously published BEEC genomic studies and mouse models. Unbiased exome analysis was also conducted to identify novel BEEC candidate genes.

Results: We identified a *de novo* pathogenic variant in *PORCN* (c.1186C>T; p.Arg396*) in one proband with bladder exstrophy and focal dermal hypoplasia (FDH). *PORCN* is required for Wnt protein secretion, and variants have previously been described in patients with both bladder exstrophy and FDH. In addition, we detected 2 potentially deleterious heterozygous variants in Wnt pathway genes among 2 singlet probands: *WNT5A* (c.1033G>C; p.Asp345His) and *WNT8B* (c.185G>A; p.Arg62His). Both variants have deleterious *in silico* prediction scores and show a strong conservation. Interestingly, *WNT5A* knockout mice display severe defects in urethral tube formation. Through unbiased trio analysis, we also identified 2 novel candidate genes in 2 probands: *TAF5L* (c.1328C>T, p.Thr443Met) and *EVX1* (c.832C>A, p.Pro278Thr). Both variants arose *de novo*, have deleterious *in silico* prediction scores, are strongly conserved, and are absent from large population databases. *EVX1* is a transcription factor involved in cloacal membrane development and acts downstream of *WNT3A*.

Conclusions: Through exome analysis, we identified a pathogenic *PORCN* variant in one proband with bladder exstrophy and FDH, along with 3 potentially deleterious variants in Wnt pathway genes among 3 probands with BEEC. This further supports a role of Wnt signaling in disease pathogenesis.

Funding: NIDDK Support

FR-PO670

Systematic Screening of ADTKD-MUC1 27dupC Variant through Exome Sequencing

Laurent Mesnard,[1,2] Ilias Bensouna,[1,2] Thomas Robert,[4] Laure Raymond,[3] Marine Serveaux Dancer.[3] *[1]Sorbonne Universite, Paris, France; [2]INSERM, Paris, France; [3]Eurofins Biomnis Lyon, Lyon, France; [4]Assistance Publique Hopitaux de Marseille, Marseille, France.*

Background: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is associated with pathological variants in the MUC1 gene. Traditional next-generation sequencing (NGS) methods struggle with the variable number tandem repeat (VNTR) region in MUC1, where the pathogenic "27DupC" variant is found in over 80% of cases. We propose a novel pipeline using a k-mer approach to detect variants in this challenging region, optimized for exome sequencing, which typically cannot identify these variations due to the VNTR.

Methods: wo tools were employed: Shark®, which targets the MUC1 region and reduces data processing time, and VNtyper®, which uses the k-mer approach for variant calling. The SharkVNTyper pipeline was first evaluated in 26 positive and 52 negative control samples. Next, retrospective analysis was conducted on 3512 patients with chronic kidney disease (CKD) and exome sequencing, and prospective analysis started in November 2023 on 825 patients. Snapshot PCR, specifically targeting 27dupC, was used to confirm positive SharkVNTyper results.

Results: SharkVNTyper identified the 27dupC variant in 25 out of 26 positive controls (96.2%) and found no variants in the 52 negative controls. Among the 4337 patients in the combined retrospective and prospective cohorts, SharkVNTyper detected a frameshift variant in 36 patients previously lacking a molecular diagnosis. Snapshot PCR confirmed the presence of 27dupC in 30 of these cases, leading to unexpected diagnoses of ADTKD-MUC1 for these patients. Patients with typical ADTKD with non-27DupC variants are under scrutiny for similar bioinformatic development.

Conclusions: Utilizing bioinformatics tools based on the k-mer method allows for effective analysis of the MUC1 VNTR. This approach facilitates the diagnosis of ADTKD-MUC1 from exome sequencing data in CKD patients, specifically identifying the critical 27dupC variant for systematic screening from the exome output.

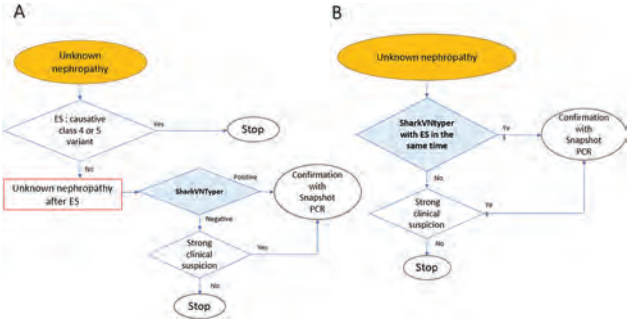


Chart 1: Proposed diagnostic framework for 27dupC detection responsible for ADTKD-*MUC1 with ES*

FR-PO671

Autosomal Dominant Tubulointerstitial Kidney Diseases

Telma Pais, Sofia C. Jorge, Marcia I. Rodrigues, José Agapito Fonseca, Iolanda Godinho, Cristina Outerelo, Estela Nogueira, Jose A. Lopes. *Unidade Local de Saude Santa Maria, Lisboa, Portugal*.

Background: Autosomal dominant tubulointerstitial kidney diseases (ADTKD) are characterized by chronic interstitial nephritis and mutations in *UMOD, MUC1, REN*, and *HNF1B* genes have been implicated. Advances in molecular diagnostics have improved the diagnosis of ADTKD. We aimed to characterize the patients evaluated for ADTKD at the Nephrogenetics Clinic of our tertiary care hospital.

Methods: Adult patients with chronic kidney disease (CKD) of unknown etiology and findings suggestive of chronic interstitial nephritis were investigated for ADTKD. Genetic study was performed stepwise: 1) Next-Generation Sequencing (NGS) analysis for *UMOD, REN, HNF1B* and *SEC61A1* genes; 2) if negative NGS, search for cytosine insertion in the variable-number tandem repeat sequence in the *MUC1* gene; 3) if negative, search for *HNF1B* deletion. Patients with undefined phenotype were analyzed using broader gene panels for CKD in young patients (173 genes), and those with cystic phenotype with a cystic disease panel (72 genes). Negative results are under review.

Results: We studied 37 families (33 with suspected ADTKD; 2 cystic; 2 with undefined phenotype) and confirmed an ATDKD genetic diagnosis in 15 families (40.5%), identifying 38 patients (pts). Genetic study revealed: pathogenic *MUC1* variants in 4 families (18 pts); *UMOD* variants in 4 families (11 pts); heterozygous *HNF1B* variants in 5 families (7 pts). In one family (5 pts) with initially negative results, further testing included whole exome sequencing (WES), and histochemical investigation of fsMUC1, the latter being positive. Reviewing negative results we found: pathogenic *COL4A3* variant in 1 family (2 pts); pathogenic homozygous *SDCCAG8* variant in 1 family (2 pts); likely pathogenic *PAX2* variant in 1 family (3 pts); likely pathogenic *PKD1* variant in 1 family (3 pts).

Conclusions: We established a genetic diagnosis of ADTKD in 40.5% of the families studied and confirmed a genetic diagnosis of CKD in 54%. The most prevalent genes implicated were *MUC1* and *UMOD*, similar to other ADTKD cohorts. Re-analysis using larger gene panels, WES, and collaboration with reference laboratories increased our diagnostic yield. Using larger gene panels initially, along with specific methods like snapshot for *MUC1*, could improve future investigations.

FR-PO672

Assessment of Combined α-Galactosidase (α-GAL) Enzyme Activity and Lyso-GL3 for Fabry Disease Screening in Women

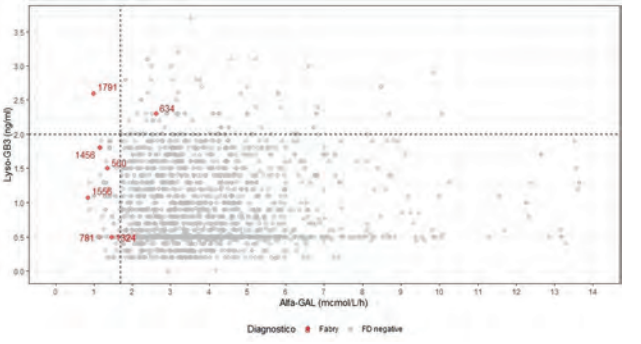
Cassiano Augusto B. Silva,[1] Fellype Barreto,[2] Osvaldo M. Vieira Neto,[3] Leandro J. Lucca,[3] Fernando A. Vieira,[4] Ana Paula Gueiros,[5] Marta V. Boger,[6] Artur Q. Silva,[7] Felipe Leite Guedes,[7] Karla Cristina P. Israel,[8] Gina Moreno Gordon,[9] Valeria Veloso,[10] Gabriela Sevignani,[11] Carolina Barretto,[12] Roberta C. Pascotto,[13] Gelzie S. Ennes,[14] Eduarda M. Souza,[15] Márcia G. Ribeiro,[16] Luis Gustavo Modelli de Andrade.[1] *[1]Universidade Estadual Paulista Julio de Mesquita Filho, Botucatu, Brazil; [2]Universidade Federal do Parana, Curitiba, Brazil; [3]Universidade de Sao Paulo Faculdade de Medicina de Ribeirao Preto, Ribeirao Preto, Brazil; [4]Clirenal, Caratinga, Brazil; [5]Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil; [6]Metta Saúde Clínica do Rim, Foz do Iguaçu, Brazil; [7]Universidade Federal do Rio Grande do Norte, Natal, Brazil; [8]Universidade Federal do Amazonas, Manaus, Brazil; [9]Grupo Instituto do Rim do Paraná, Curitiba, Aruba; [10]Universidade Federal de Goias, Goiania, Brazil; [11]Fundação Pro-Rim, Joinville, Brazil; [12]Santa Casa de Misericórdia de Itabuna, Itabuna, Brazil; [13]Santa Casa de Maringa, Maringa, Brazil; [14]Centro de Nefrologia de Nova Friburgo, Nova Friburgo, Brazil; [15]Universidade de Sao Paulo, Sao Paulo, Brazil; [16]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*.

Background: The spectrum of clinical presentation of Fabry disease (FD) in women is broad and challenging. The aim is to evaluate the effectiveness of an alternative screening method for FD in women.

Methods: A collaborative multicenter cross-sectional study to evaluate the sensitivity and specificity of the combination of two tests (α-GAL enzyme activity and lyso-GL3) for the diagnosis of FD in women. We included women with CKD stages 3 to 5, receiving conservative treatment or on dialysis programs.

Results: We evaluated 1,874 patients. Isolated decreased α-GAL activity was found in 64 patients, while isolated increased lyso-GL3 levels were found in 67 patients, with one patient presenting alterations in both tests. All cases with low α-GAL activity and/or increased lyso-GL3 levels underwent genetic analysis for FD variants (132 patients). Low α-GAL activity had higher sensitivity and specificity to detect FD compared to the other measures (elevated lyso-GL3 alone or both altered). The negative predictive value (NPV) of α-GAL activity was 99%, and the positive predictive value (PPV) was 9.2%. For lyso-GL3 assay, the specificity was 99.7% and the PPV was 2.9%, therefore considered inferior to α-GAL assay. Both assays altered, had higher PPV (100%) and higher NPV (99.7%) considered the best method. We found 7 cases of GLA gene variants, resulting in an prevalence of 0.37% for FD in this sample female population.

Conclusions: This study contributes to the diagnostic value of this biomarkers in the context of FD in women with CKD. The combination of these biomarkers was an effective approach for the diagnosis, with high PPV and NPV.



The relationship between α-GAL and lyso-GL3 levels and the presence of Fabry disease.

FR-PO673

Screening for Fabry Disease in Haemodialysis Population (SoFAH) Study

Khai Ping Ng,[1] Manjinder K. Sandhu,[2] Tarekegn Geberhiwot,[2] Indranil Dasgupta.[2] *[1]University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom; [2]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom*.

Background: Fabry disease is an X-linked inherited lysosomal storage disorder with an estimated prevalence amongst end-stage kidney disease (ESRD) population of 0.3% in men and 0.1% in women. Due to its non-specific manifestations, Fabry disease especially the later-onset variant, is often under-diagnosed. We aimed to estimate its prevalence in a large haemodialysis (HD) population in the UK.

Methods: SoFAH is a cross-sectional, multi-centre screening study. All adult HD patients at 8 renal units in the Midlands, UK were invited to the study. All male participants are tested using dried blood spot alfa-galactosidase enzyme and Lyso-Gb3 assay. If either the enzyme (≤2.8 μmol/L/H) or Lyso-Gb3 (≥ 3.5 ng/mL) level was abnormal, genetic testing for GLA mutation was performed. All females had alfa-galactosidase enzyme, Lyso-GB3 and genetic tests. We also performed symptoms' survey. The study was approved by the UK Health Research Authority.

Results: Of the 2,452 HD patients, 1323 consented to the study. Their mean age was 68 (SD 15) year-old, 67% male, 64% white ethnicity, dialysis vintage of 2.6 (IQR 8.1) months and 32% had renal biopsy. Diabetic nephropathy (28%) was the most common cause of ESRD. 21% had no known cause of ESRD and 9% had hypertensive/ischaemic nephropathy. Majority had cardiovascular disease (85%), including 10% with heart failure. 27% self-reported burning pain in extremities, 25% heat intolerance, 25% gastrointestinal symptoms without a cause, 22% family history of renal disease and 41% family history of heart disease or stroke. Overall, 216 (16%, 156 male) had low enzyme level but all had normal Lyso-Gb3 level. Only 3 (0.2%) had abnormal Lyso-Gb3 but all had normal enzyme level. One female participant with normal enzyme and Lyso-Gb3 levels but GLA variant, heterozygous c.937G>T (p.(Asp313Tyr), which was deemed to be non-pathogenic variant.

Conclusions: Despite implementing stringent screening in both male and female to avoid false negative, we did not identify any new cases of Fabry disease in 1,323 HD patients. This finding suggested lower prevalence of Fabry disease than previously reported but might also be influenced by our cohort's demography and older age. Symptoms commonly associated with Fabry disease were non-specific and self-reported in almost a quarter of the participants.

Funding: Commercial Support - Sanofi-Genzyme

FR-PO674

A Real-World Study on the Clinical Characteristics and Treatments of Complement-Mediated Kidney Diseases in China

Sheng Nie,[1] Qing Zou,[1] Shiyu Zhou,[1] Fei Gao,[2] Tianwei Zhang.[2] *[1]Division of Nephrology, National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Beijing Novartis Pharma. Co. Ltd, Shanghai, China.*

Background: Complement-mediated kidney diseases (CMKDs) are partly caused by overactivation of the alternative complement pathway, including C3 glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), Immunoglobulin A nephropathy (IgAN), membranous nephropathy (MN), lupus nephritis (LN), among others. Despite their significant impact, studies on epidemiology and treatment patterns of CMKD in China are relatively scarce.

Methods: This is a retrospective, observational study using a nationwide real-world medical database in China (CRDS). Patients with CMKD were diagnosed at 24 regional central hospitals between 31 December 1998 until May 08, 2023. Descriptive analysis was performed on demographics, clinical characteristics and treatment approaches.

Results: A total of 57086 CMKD patients were included in the study, including 102, 843, 27456, 10988, and 17697 patients with C3G, aHUS, IgAN, MN and LN, respectively, with an average age of 46.8 years and 39.1% being males. 22.3% of CMKD patients had an eGFR<60ml/min/1.73m^2, 47.8% had low serum complement C3, and 18.5% had low serum C4. Among 11715 patients with kidney biopsy report, 69.1% was positive in C3 immunofluorescent staining and 17.5% was positive in C1q immunofluorescent staining (Table 1). Among all CMKD patients, 35.4% received corticosteroids, followed by Renin-angiotensin system inhibitor (28.6%) and non-steroid immunosuppressants (22.2%) (Table 2), and the treatment pattern was significantly different among subtypes of CMKD.

Conclusions: The clinical characteristics and treatment of CMKDs varied among subtypes. The overall treatment proportion at baseline was low. This may suggest that the current treatment strategies for CMKDmay be insufficient, and treatment programs need further improvement.

Funding: Commercial Support - Beijing Novartis Pharma. Co. Ltd

Table 1.Partial demographics and clinical characteristics by specific CMKD subtypes

	Total (N=57086)	C3G (N=102)	aHUS (N=843)	IgAN (N=27456)	MN (N=10988)	LN (N=17697)
Demographics						
Age, mean (SD)	46.8 (15.99)	28.0 (20.61)	33.8 (23.57)	38.5 (15.36)	49.5 (13.44)	35.3 (13.01)
Male, n(%)	22302 (29.1)	53(52.0)	418(49.6)	12999(47.3)	6553(59.6)	2209(12.5)
Clinical Characteristics						
eGFR(<60mL/min/1.73m^2)(n,%)	6838 (22.3)	26 (32.5)	192 (44.2)	3391 (27.3)	1124 (14.6)	2064 (22.6)
Serum C3 (g/L) (n,%)						
Low level (<0.9)	11152(47.8)	57(69.5)	163(47.0)	2911(32.6)	1340(22.6)	6681(53.1)
Normal level (≥0.9 &≤1.8)	12063(51.7)	25(30.5)	184(53.0)	5997(67.0)	4521(76.2)	1346(10.7)
High level (>1.8)	126(0.5)	0(0.0)	0(0.0)	37(0.4)	74(1.2)	15(0.1)
Serum C4 (g/L)						
Low level (<0.1)	4301 (18.5)	54 (6.2)	28(8.1)	83 (0.9)	78 (1.3)	4107 (33.1)
Normal level (≥0.1 & ≤0.4)	17322(74.2)	73 (90.1)	299(86.4)	8962(94.0)	5183(87.5)	3813(47.9)
High level (>0.4)	1241 (5.3)	3(3.7)	19(5.5)	448 (5.0)	661 (11.2)	110 (1.4)
Presence of immunofluorescent staining (kidney biopsy)						
N	11715	43	33	6609	3926	1104
C3, n (%)	8096 (69.1)	37(86.0)	7(21.2)	4767(72.1)	3216(81.9)	2476(85.1)
C1q, n (%)	2047 (17.5)	5(11.6)	2(6.1)	221(3.3)	3209(81.7)	1044(268)

Abbreviations: eGFR, estimated glomerular filtration rate.

Table 2. CMKD-related partial treatments by specific CMKD subtypes at baseline

CMKD-related treatments, n(%)	Total (N=57086)	C3G (N=102)	aHUS (N=843)	IgAN (N=27456)	MN (N=10988)	LN (N=17697)
Renin-angiotensin system inhibitor	14412(28.6)	34 (35.8)	157(21.0)	6577(29.0)	4652(47.1)	2992(19.6)
Angiotensin converting-enzyme inhibitor	5538 (11.0)	20 (21.1)	116(15.5)	2441 (10.8)	1414 (14.3)	1547 (10.1)
Angiotensin II receptor blocker	10210(20.3)	16 (16.8)	56 (7.5)	4732 (19.4)	3678 (37.3)	1728 (11.3)
Corticosteroid	17799(35.4)	33 (34.7)	424 (56.6)	4808 (19.8)	3924 (39.7)	8610 (56.3)
Non-steroid immunosuppressants	11163(22.2)	19 (20.0)	120 (16.0)	1680 (6.9)	2207 (22.4)	7136 (46.7)
Hydroxychloroquine	5551 (11.0)	0 (0.0)	13 (1.7)	92 (0.4)	68 (0.7)	5378 (35.2)
Statin	7885 (15.7)	11 (11.6)	66 (8.8)	2503 (10.3)	4163 (42.2)	1142 (7.5)
Diuretics	9646 (19.2)	22 (23.2)	286 (38.2)	1998 (8.2)	3475 (35.2)	3865 (25.3)
Calcium channel blockers	8413 (16.7)	17 (17.9)	199 (26.6)	3316 (13.6)	2317 (23.5)	2564 (16.8)
Plasma therapy	6019 (12.0)	16 (16.8)	275 (36.7)	1878 (7.7)	1599 (16.2)	2252 (14.7)

FR-PO675

Rare Diseases: Significance of Molecular Genetic Analyses in Finding a Diagnosis

Annette D. Wagner,[1] Sena Hoffer,[1] Christian Beger,[1] Christian Kempf,[2] Friedmar R. Kreuz,[2] Saskia Biskup,[2] Heinz Gabriel.[2] *[1]Medizinische Hochschule Hannover, Hannover, Germany; [2]Center for Human Genetics, Tübingen, Germany.*

Background: Diagnosing rare diseases remains a challenge despite improved diagnostic methods. In the past, it often took patients years to receive a final diagnosis. We aim to show that genetic testing should be used as one of the first steps in the diagnostic process of patients with rare diseases. Whereas in the past only single-gene diagnostics were available, today a large number of genes can be sequenced in parallel using next-generation sequencing.

Methods: In the outpatient clinic for rare inflammatory diseases 85 patients with unclear diagnoses have undergone molecular genetic analyses over the last years. Most diagnoses could be made by whole exome sequencing (WES). This involves sequencing of the coding regions of all human genes. Using bioinformatic methods, the genes that can be associated with the symptoms are “filtered out” from the data set. This has the great advantage that the selection of genes can be kept up-to-date and flexible.

Results: In the case of atypical courses or non-response to treatment, genetic tests were arranged, which led to the correct diagnosis in a total of 85 patients. In addition to a larger group of 25 patients with periodic fever syndromes, neurological disorders could be identified in 14 patients. Among this group 8 patients were diagnosed with tuberous sclerosis. 12 Patients were affected by a disorder of the skeletal system (mostly hypophosphatasia). In 7 patients a muscle disease was found. The other patients were classified as follows: kidney disease (6x), hereditary cancer syndromes (6x), immunological disorder (5x), metabolic disorder (2x), hepatic disorder (1x), ophthalmological disorder (1x), heart defect (1x), connective tissue disorder (1x) and 3 patients with other conditions.

Conclusions: The recent changes in the field of genetics have an impact on our work in outpatient clinics for rare diseases. The diagnostic direction from “phenotype to genotype” has therefore often been reversed to “genotype to phenotype”. Frequently, several single-gene analyses were carried out in succession until the causative pathogenic variant could be identified. In our clinic, diagnoses could mostly be made by WES. Thanks to the close co-operation between our outpatient clinic and a genetic diagnostics laboratory, a final diagnosis can be made in many cases within a few weeks.

Funding: Private Foundation Support

FR-PO676

Pathogenic Mutations in Ras-MAPK Pathway Genes in Patients with Lupus Nephritis

Changming Zhang,[1] Xiaoman Jing,[2] Yangyang Zhang,[1] Ying Jin,[1] Zhihong Liu.[1] *[1]National Clinical Research Center for Kidney Diseases, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China; [2]Southeast University School of Medicine, Nanjing, China.*

Background: Pathogenic mutations in genes encoding components of Ras-MAPK pathway cause RASopathy, which include several clinically overlapping disorders, such as Noonan syndrome, Costello syndrome and neurofibromatosis. Here we describe five unrelated patients with lupus nephritis (LN) carrying mutations in components of Ras-MAPK pathway.

Methods: Causative mutations in the five LN patients were identified by whole-exome/genome sequencing and validated by Sanger sequencing.

Results: Five pathogenic mutations was identified in four Ras-MAPK genes, including NRAS:c.G38A: p.G13D; ARAF:c.C1435T: p.R479C; KRAS:c.T341C: p.V114A; PTPN11:c.G455A: p.R152H; NRAS:c.G34A: p.G12S. Three of them have been identified as pathogenic in individuals with Noonan syndrome and/or lupus. Two novel variants (R479C in ARAF and V114A in KRAS) are classified as likely pathogenic according to American College of Medical Genetics and Genomics criteria. The patients commonly manifested in early childhood and adolescence (range: 7-42 years of age). Kidney injury was the main feature, presenting with nephrotic syndrome (2/5), proteinuria and hematuria (2/5). Acute kidney injury and rapidly progressive nephritic syndrome was noted in one patient each. Other clinical features included mucocutaneous lesions (5/5), cardiac involvement (4/5, such as myocardial hypertrophy, pulmonary hypertension, enlargement of left atrium and ventricular), and arthralgia (3/5). Laboratory abnormalities included hypocomplementemia (5/5), presence of antiphospholipid (4/5), decreased Treg cells (3/3 patients tested), pancytopenia (3/5, one consistent with Evans syndrome), and persistent monocytosis (two with NRAS mutations). Histopathological findings included LN-V in two, LN-IV+V and LN-III+V in one patient each. All patients received methylprednisolone pulse therapy, followed by prednisone combined with cyclophosphamide or mycophenolate mofetil or tacrolimus. The patient with NRAS p.G12S mutation also received Rituximab therapy. Most patients responded well, with the exception of the patient with NRAS p.G13D mutation who died.

Conclusions: Kidney involvement may be the main feature of the clinical spectrum of RASopathy. Genetic screening should be considered for early-onset LN patients.

Funding: Government Support - Non-U.S.

FR-PO677

Genetic Analysis of Familial Mediterranean Fever in an ESKD Cohort

Ahmed Al-Sheyyab,[1] Rania A. Wahdan,[2] Anas Bani Hani,[1] Mohammad H. Al-thnaibat,[1] Salem Yasin,[1] Lubna H. Tahtamouni.[1] *[1]The Hashemite University, Zarqa, Jordan; [2]Ministry of Health, The Hashemite Kingdom of Jordan, Amman, Jordan.*

Background: Familial Meditiranean Fever (FMF) is an autoinflammatory genetic disorder that results from a mutation in MEFV gene. FMF increases the risk of secondary amyloidosis (i.e., renal amyloidosis). Limited FMF research have studied populations with the ultimate hard outcome of renal amyloidosis, or End-Stage-Renal-Disease

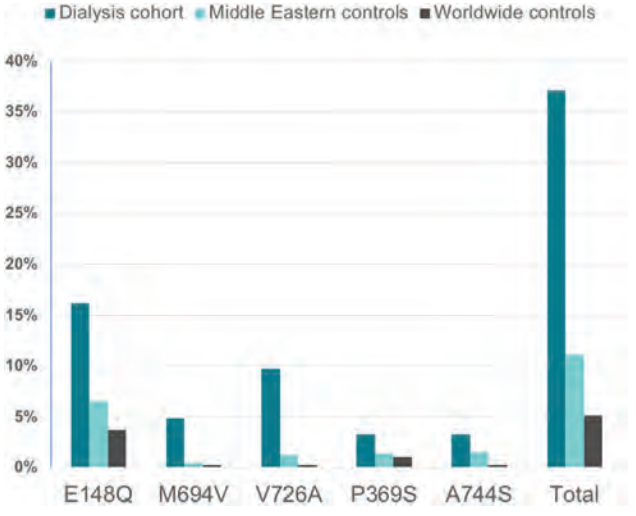
patients (ESRD). Our study aimed to assess the frequency rate of FMF gene variants in an ESRD cohort and correlate it with the general population.

Methods: The study was a prospective study of hemodialysis a jordanian cohort. Enrolled patients underwent laboratory screening for FMF by conducting Polymerase Chain Reaction and reverse hybridization. Patients with a positive FMF genetic screening were offered colonoscopy with multiple rectal biopsies. Amyloid staining were used to assess for pathological evidence of amyloidosis. Genetic data for control subjects where obtained from GnomAD v4.0.0 database, those with Middle Eastern Ancestry were segregated and used as our control group.

Results: Our study demonstrated that our studied ESRD patients, when compared with healthy controls, carry a higher allele frequency rate of all FMF variants (30% Vs 11.1%). For patients with a positive FMF gene, two patients demonstrated symptoms of FMF. The remaining asymptomatic patients, one out of 5 patients who consented for colonscopy, had confirmed pathological evidence of amyloidoisis.

Conclusions: Among our Jordanian cohort, patients with ESRD carry higher allele frequency of FMF variants than healthy controls.

	Dialysis cohort n (%), n = 79	Middle Eastern controls n (%), n = 6,602	
E148Q:	10 (16.13)	393 (6.5)	p <. 012
M694V:	3 (4.84)	28 (0.46)	p <.001
V726A:	6 (9.68)	75 (1.24)	p <.001
P369S:	2 (3.23)	85 (1.4)	–
A744S:	2 (3.23)	91 (1.5)	–
Total FMF variant:	24 (30)	672 (11.1)	Chi2 = 34.1363 p p <.001



FR-PO678

Exome Sequencing in Patients with Loin Pain Hematuria Syndrome

Bhanu Prasad,[1] Aditi Sharma,[2] Aarti Garg,[2] Clara Schott,[3] Dervla M. Connaughton,[3] Matthew B. Lanktree.[4] *[1]Regina General Hospital, Regina, SK, Canada; [2]University of Regina, Regina, SK, Canada; [3]Western University Schulich School of Medicine & Dentistry, London, ON, Canada; [4]McMaster University Faculty of Health Sciences, Hamilton, ON, Canada.*

Background: Loin pain hematuria syndrome (LPHS) is a rare clinical syndrome with a reported prevalence of ~1 in 10,000 characterized by severe pain localized to the kidney, and gross or microscopic hematuria. Because of an inadequate understanding of the pathophysiology of the disease, the goal of management has been limited to symptomatic pain management. We used whole exome sequencing to investigate the genetic factors affecting the glomerular filtration barrier, contributing to hematuria in patients with LPHS. We describe herein their phenotypes and variant spectra.

Methods: In this single-center study, 17 consecutive patients with LPHS underwent whole exome sequencing (WES) from Jan 2022 to Jan 2023. A bioinformatically created hematuria gene panel (n = 143) was evaluated. American College of Medical Genetics and Genomics (ACMG) guidelines were followed for interpreting the identified variants.

Results: Among the 17 patients, 13 exhibited overt hematuria, while 4 had microscopic hematuria. 9/17 (53%) patients had a preceding history of kidney stones, but none had an obstructing stone on imaging at the time. Analysis of pedigree charts revealed that 8/17 (43%) patients had a family history of kidney stones, and 3/17 (18%) had a family history of hematuria. None of the 17 patients had a family history of LPHS. A total of 35 variants were identified in 25 of 143 hematuria gene panel genes in 14 patients. 29 of the 35 were variants of uncertain significance. We detected 3 pathogenic or likely pathogenic mutations, including two heterozygous missense variants and a frameshift deletion in COL4A3/4 genes.

Conclusions: In 17 patients with LPHS, 35 variants of uncertain significance were identified among 25 genes reported to impact the glomerular basement membrane and cause hematuria. Determining the causality of these variants is challenging.

FR-PO679

Founder Effect for the APOE Tokyo-Maebashi Variant in the Northern Chinese Population

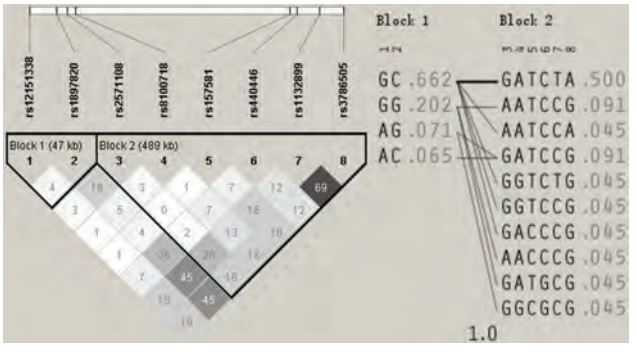
Mengshi Li, Ruilian You, Zhiying Liu, Yang Li, Xu-jie Zhou, Hong Zhang. *Peking University First Hospital, Beijing, China.*

Background: Lipoprotein glomerulopathy (LPG) is a rare hereditary kidney disorder characterized by lipoprotein thrombi in glomeruli, often linked to APOE gene mutations. Predominantly found in China and Japan, LPG remains understudied. Notable regional APOE mutations include APOE Kyoto (p.R43C) in West China and APOE-Sendai (p.R163P) in eastern Japan. This study investigates the genetic causes of LPG in northern Han Chinese and explores genotype-phenotype correlations.

Methods: Patients suspected or diagnosed with LPG were recruited at a nephrology center in Northern China from 2000 to 2023. Inclusion criteria: (1) Renal biopsy showing Oil Red O-positive lipid thrombi in glomeruli; (2) Known pathogenic APOE mutations via genetic testing. Exclusion criteria: Incomplete genetic testing post-biopsy or unavailable DNA samples. Whole exome sequencing (WES) was used to identify mutations, with clinical data collected at enrollment.

Results: The study included 28 LPG patients from 24 families, with an average age of 34.2 years (range 17-54). The male-to-female ratio was 19:9. The mean proteinuria level was 4.94 g/24h, the mean eGFR was 78.3 mL/min/1.73 m2, and hyperlipidemia was observed in all cases. Three variants were identified in 25 cases: 15 had APOE Tokyo-Maebashi (p.L162_K164del), 8 had APOE Kyoto (p.C43R), and 2 had APOE Chengdu (p.L173P). APOE Tokyo-Maebashi was most frequent, mainly in Hebei Province. Haplotype analysis suggested a founder effect for APOE Tokyo-Maebashi. Genotype-phenotype analysis showed a trend towards higher eGFR and lower urinary total protein (UTP) and urinary red blood cells (URBC) in APOE Tokyo-Maebashi carriers, though differences were not statistically significant.

Conclusions: WES is instrumental in identifying molecular pathogenic variants in LPG patients and genetic hotspot mutations in specific populations. Despite high phenotypic variability in APOE-associated LPG, the APOE Tokyo-Maebashi variant is the most common mutation in Northern China, presenting with relatively milder clinical manifestations.



FR-PO680

Establishment of a High-Throughput Screening System for Membrane Expression of Mutant Nephrin

Haruki Tsuhako, Mary Ann Suico, Tsuyoshi Shuto, Hirofumi Kai. *Kumamoto Daigaku, Kumamoto, Japan.*

Background: Congenital Nephrotic syndrome of the Finnish type (CNF) is caused by a mutation in the *NPHS1* gene that hinders the cell surface expression of nephrin and disrupts slit membrane formation. In this study, we constructed a novel evaluation system to search for compounds promoting the expression of nephrin on the cell membrane.

Methods: To detect the membrane-expressed nephrin, we used the HiBiT nanoluciferase system by tagging Nephrin wild-type (wt) and mutants (mt) with HiBiT. For high throughput screening (HTS), we generated stable expression cell lines of HiBiT- wt and mutant nephrin (HiBiT-Neph) using the Flp-In™ System. Phosphorylated-Nephrin, which indicates the ability to be translocated to the surface, was also assessed by immunoblotting.

Results: In contrast to wt HiBiT-Neph, most mutants did not produce luminescence and were not phosphorylated. Furthermore, among the mutants, we confirmed that the reduction of HiBiT activity in the S366R and E725D stable mutant cells met the HTS criteria. Using E725D stable cells, we screened several chemical chaperones and a natural products compound library. Chemical chaperone β-alanine, a CFTR corrector (Corr-4a), and 78 compounds from the library increased the HiBiT-Neph E725D. Cytotoxicity

assays and further validation by immunoblotting of phosphorylated nephrin trimmed the candidate compounds to ten. Focusing on these compounds, we revealed their effects on post-translational modifications and degradation rates of Nephrin to promote the expression of nephrin mutants on the membrane.

Conclusions: The HTS evaluation system identified compounds that increased mutant nephrin phosphorylation and cell surface expression and showed that this evaluation system is useful as a drug discovery platform for CNF. Moreover, the identified compounds help to elucidate the mechanisms of mutant nephrin cell regulation.

FR-PO681

Prematurity Reprograms Nephron Progenitor Cells, Impairing Nephrogenesis and Kidney Health

Athar Amleh,[1] Mehran Piran,[2] Julie L. Moreau,[2] Morris Nechama,[1] Alexander N. Combes,[2] Oded Volovelsky.[1] *[1]Hadassah University Medical Center, Jerusalem, Israel; [2]Monash University, Melbourne, VIC, Australia.*

Background: Premature birth is linked to reduced nephron number and an increased risk of chronic kidney disease. Despite insight from surgical models, the molecular mechanisms by which preterm birth affects nephron formation remain incompletely understood. We aimed to study the changes in nephrogenesis after preterm birth.

Methods: We used a mouse model of induced preterm birth at gestational day 18 using mifepristone, a progesterone antagonist. Nephrons were counted using acid maceration. Kidney function was evaluated via serum sampling and 24-hour urine collection in metabolic cages. Immunofluorescence was used to assess the duration of nephrogenesis (SIX2), nephron progenitor cell (NPC) apoptosis (CASP3), and proliferation (Ki67, BrdU). NPCs were sorted using Six2-GFP and profiled using RNA-sequencing and RT-PCR.

Results: At postnatal day 30, preterm offspring exhibited significantly decreased kidney/body weight ratio and 30% less nephrons alongside elevated serum urea and 24-hour urine albumin levels compared to term counterparts. Notably, the duration of nephrogenesis was extended by one day in preterm kidneys. In preterm kidneys, proliferation was increased in Six2+ NPCs at post-consumption (PC) day 20.5, with no change in apoptosis. Gene expression profiling of NPCs revealed dysregulated Wnt signaling, cell proliferation, hypoxic response, and differentiation signatures in preterm kidneys but not term controls. Preterm NPCs had decreased *Six2* but increased *Lhx1*, *Jag1*, and *Bmp2* expression. Altogether, these results indicate that preterm birth reduces nephron number by altering NPC differentiation and proliferation state.

Conclusions: Preterm birth reduces nephron endowment by altering NPC self-renewal and differentiation dynamics. Therapeutic attempts to boost nephrogenesis after preterm birth may protect against adult kidney morbidity.

FR-PO682

Role of Angiotensinogen in Children with a History of Preterm Birth and Nephron Hypertrophy

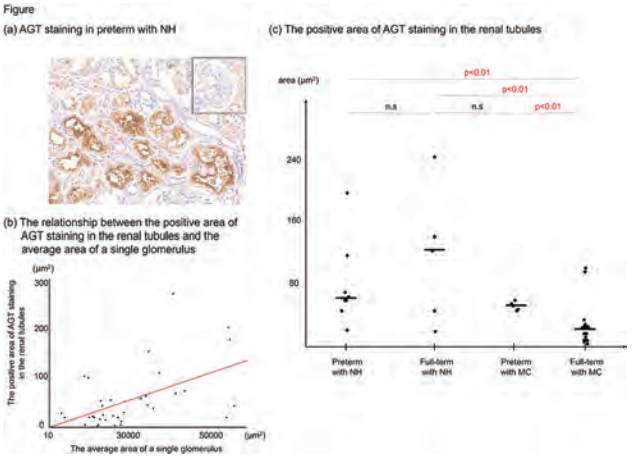
Shingo Ishimori,[1,2] Yuka Kimura,[1] Hideaki Kitakado,[1] Chika Ueda,[1] Yuta Inoki,[1] Yu Tanaka,[1] Junya Fujimura,[3] Tomoko Horinouchi,[1] Tomohiko Yamamura,[1] Nana Sakakibara,[1] China Nagano,[1] Kandai Nozu.[1] *[1]Kobe University Graduate School of Medicine, Kobe, Japan; [2]Takatsuki General Hospital, Takatsuki, Japan; [3]Kakogawa Chuo Shimin Byoin, Kakogawa, Japan.*

Background: A history of preterm birth and low birth weight (preterm) is a risk factor for chronic kidney disease, which is primarily characterized by tubulointerstitial damage resulting from a decrease in nephron number and compensatory nephron hypertrophy (NH). While the renin–angiotensin system (RAS) plays a crucial role in renal development, no pathological studies have examined the association between RAS and tubulointerstitial lesions in children with a history of preterm birth.

Methods: We performed immunohistochemical staining of renal biopsy specimens collected from 2000 to 2023. Patients were eligible if they had pathological minimal change (MC) or NH without other types of nephritis, and if the indication for renal biopsy was asymptomatic proteinuria, nephrotic syndrome, or decreased renal function. Immunohistochemical staining of angiotensinogen (AGT) was used as a marker of intrarenal RAS, and angiotensin II was used as a marker of systemic RAS.

Results: We enrolled 36 children with a median age at the renal biopsy of 13.4 years. AGT staining was negative in the glomeruli of children with NH but positive in the renal tubules (Fig. a). The positive area of AGT staining in the renal tubules was significantly correlated with an increase in the average area of a single glomerulus ($p<0.01$, Fig. b). The positive area of AGT staining in the renal tubules of preterm children with NH (n=8), full-term children with NH (n=5), and preterm children with MC (n=5) was significantly more extensive than that in full-term children with MC (n=18) (65.8, 153.2, and 53.0 μm^2 vs 19.4 μm^2, all $p<0.01$; Fig. c). Angiotensin II staining was weakly positive in the renal tubules across all four groups, with no significant difference between the groups.

Conclusions: AGT may play a major role as an indicator of intrarenal RAS in preterm children even before the onset of NH.



FR-PO683

Dysregulation of Podocyte Clock-Controlled Autophagy in a Neonatal Hyperoxia Model

Joanne Duara,[1,2] Rachel Njeim,[2,3] Jeffrey D. Pressly,[2,3] Pingping Chen,[1] Sandra M. Merscher,[2,3] Alessia Fornoni.[2,3] *[1]University of Miami Batchelor Children's Research Institute, Miami, FL; [2]Peggy and Harold Katz Family Drug Discovery Center, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL; [3]Katz Family Division of Nephrology and Hypertension, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL.*

Background: Premature birth and low birthweight, prevalent in around 11% of pregnancies and disproportionately affecting Black Americans, amplify the long-term risk of chronic kidney disease (CKD). Neonatal hyperoxia leads to impaired development of the renal tubules, renal corpuscle enlargement, tubular necrosis, interstitial inflammation, and fibrosis. Furthermore, global kidney health is a mounting concern with CKD affecting both children and adults. Emerging evidence links Chaperone-Mediated Autophagy (CMA) to the degradation of oxidized proteins within cells, a process intensified during oxidative stress through mechanisms involving substrate protein modifications and transcriptional up-regulation of the Lysosome-associated membrane glycoprotein 2 (LAMP2A) at the lysosome. We hypothesize that in neonate, hyperoxia-induced oxidative stress triggers adaptive increases in CMA, which although protective initially, may lead to impaired CMA activity over time due to persistent oxidative conditions.

Methods: Sprague Dawley rat pups were reared in hyperoxic (HYP) with FiO2 of 0.85 or normoxic (RA) conditions until 10 days of life. Urine was sent for Urine Protein and Creatinine levels. Western blot and immunofluorescence were performed on kidney cortices. Immortalized human podocytes were cultured and exposed to hyperoxia or normoxia for 48 hours. Bulk RNA Sequencing analysis was conducted on rat kidney cortices and human podocytes.

Results: Urinalysis of hyperoxia-exposed rats revealed worsened proteinuria (Urine protein 132 mg/dl vs 20 mg/dl) and higher Urine protein/Creatinine ratio (14.2 vs 4.2). Western blot analysis of protein lysates from rat kidney cortices reveals a reduction in p62 expression in HYP rats with an increase in LC3 II/I ratio in HYP rats when compared to RA animals indicating an activation of autophagy. RNA sequencing results reveal decreased podocyte expression of circadian clock -controlled autophagy markers in bone metabolism including BHLHE41, CHRD, MAP1LC3A and TGFB1.

Conclusions: Taken together, these results indicate a role for altered circadian clock-mediated autophagy in hyperoxia-exposed podocytes affecting renal function.

Funding: Other NIH Support - CTSI K12

FR-PO684

A Missense Mutation in Exon 10 of WT1 Might Lead to Focal Segmental Glomerulosclerosis Due to Its Mislocalization and Downstream Dysregulation

Toru Kanamori,[1] Tomohiro Udagawa,[2] Mika Okutsu,[1] Takayasu Mori,[2] Eisei Sohara,[2] Shinichi Uchida.[2] *[1]Tokyo Ika Shika Daigaku Daigakin Ishigaku Sogo Kenkyuka, Bunkyo-ku, Japan; [2]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan.*

Background: Wilms' tumor suppressor gene 1 (WT1) is associated with the development of the urogenital system and regulates genes involved in sex differentiation. While mutation of exon 8 or 9, and intron 9 of WT1 are known as a cause of focal segmental glomerulosclerosis (FSGS) and sexual disorders, the pathological role of the mutation in exon 10 is largely unknown in FSGS. We found a missense Arg495Gly in a Japanese boy with FSGS connecting to the end stage kidney disease. His renal podocytes histopathology showed that WT1 is localized in not only the cytoplasm but also the

nucleus. Additionally, his kidney sample's expressions of NPHS1 were patchy pattern rather than normal smooth and linear pattern.

Methods: To analyze the pathogenic mechanism of the mutation in FSGS, we evaluated WT1 localization in cultured HEK293T cell transfected with expression constructs encoding the wildtype or $WT1^{R495Q}$ protein by immunofluorescence staining and western blotting with nuclear/cytoplasm fractionations. Then, to examine the effect of $WT1^{R495Q}$ on the regulation of key podocyte genes, we quantitatively assessed mRNA expression levels isolated from wild type or mutation-expressing cells by qPCR.

Results: The WT1 localization was different between cells transfected WT1wildtype/$WT1^{R495Q}$ under phosphorylation-accelerated conditions induced by Forskolin. $WT1^{R495Q}$ is not affected by Forskolin stimulation, while WT1wildtype affected by Forskolin stimulation and expression of WT1 in the nuclear is decreased and in the cytoplasm is increased. Compared to wild types, the expression of the NPHS1 gene is decreased in the cells transfected with $WT1^{R495Q}$. When wild type and mutant WT1 were co-transfected with the same dose, the expression of NPHS1 was the same as when only the mutant was transfected and its expression was reduced in a mutant dose-dependent manner.

Conclusions: We demonstrated $WT1^{R495Q}$ mutation could affect on WT1 protein localization and dysregulates NPHS1 expression in podocytes. This type of WT1 mutation on exon10 could be loss of function mutation and have a dominant negative effect on expression of podocyte genes. These may have influence podocyte recovery systems using phosphorylation which is essential for regulation of podocyte-specific protein.

FR-PO685

Recessive Variants in the Intergenic NOS1AP-C1orf226 Locus Cause Monogenic Kidney Disease

Florian Buerger,[1,2] Victoria C. Gauntner,[1] Vineeta Sharma,[1] Sergio Guerrero Castillo,[2] Liang Sun,[1] Alexis C. Gomez,[1,3] Michelle Mcnulty,[1,4] Matt G. Sampson,[1,4] Mohamed Al-hamed,[5] James P. Fawcett,[6] Friedhelm Hildebrandt,[1] Amar J. Majmundar.[1] *[1]Boston Children's Hospital, Boston, MA; [2]University Children's Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Brigham and Women's Hospital, Boston, MA; [4]Broad Institute, Cambridge, MA; [5]King Fahad Medical City, Riyadh, Saudi Arabia; [6]Dalhousie University, Halifax, NS, Canada*.

Background: An accurate expression landscape of disease genes is crucial to enable precise genetic diagnoses. Canonical NOS1AP, encoding nitric oxide synthase 1 (NOS1) adaptor protein, is known to regulate hippocampal neuronal functions through C-terminal interactions with the enzyme NOS1 (Jaffrey *Neuron* 1998; Zhu *Nat Med* 2014). We previously discovered that N-terminal variants in *NOS1AP* cause monogenic nephrotic syndrome (NS) in humans and mice (Majmundar *Sci Adv* 2021). However, the role of the NOS1AP C-terminus in NS pathogenesis was unclear.

Methods: Transcriptomics and proteomics data of human and murine kidney samples were evaluated. Exome sequencing was performed in human NS subjects. Mouse models altering the *Nos1ap* locus were evaluated for features of NS.

Results: We, here, detected intergenic splice products of *NOS1AP/Nos1ap* and the neighboring open reading frame *C1orf226/Gm7694* as the predominant isoform in both human and mouse kidney tissue in contrast to brain tissue. In this isoform, the canonical C-terminal NOS1-binding domain is replaced by C1orf226 or Gm7694, respectively. In line with our previously published Nos1ap-deficient mice, exclusive disruption of the intergenic product in $Gm7694^{-/-}$ mice similarly resulted in NS features including albuminuria, podocyte foot process effacement, and glomerular basement membrane thickening. We, next, evaluated whether recessive variants exclusively impacting the intergenic splice form can be detected in NS patients. For this, we reanalyzed NS exome sequencing data and thereby identified a likely pathogenic *NOS1AP-C1orf226* essential splice site variant (c.1258+1G>C) in a patient with congenital NS. Of note, this variant was initially misclassified as benign due to annotation based on the canonical transcript (c.1259G>C, p.G420A).

Conclusions: Mendelian variants impacting an intergenic product in the *NOS1AP-C1orf226* locus cause NS, suggesting that, unlike in the brain, NOS1AP functions in the kidney through NOS1-independent mechanisms. Moreover, this highlights the importance of understanding tissue-specific splicing to facilitate discovery and clinical diagnosis of Mendelian disorders.

Funding: NIDDK Support, Private Foundation Support

FR-PO686

Role of Eicosanoids in Hyperfiltration-Mediated Injury: Insights from Human Participants and a Mouse Model

Tarak Srivastava,[1] Ginger L. Milne,[3] Mukut Sharma.[2] *[1]Children's Mercy Kansas City, Kansas City, MO; [2]Kansas City VA Medical Center, Kansas City, MO; [3]Vanderbilt University, Nashville, TN*.

Background: The mechanism of hyperfiltration-mediated kidney injury in children with a solitary functioning kidney (SFK) is not known. Changes in vasoactive metabolites including Prostaglandin E_2 (PGE_2) modulate glomerular hemodynamics. We demonstrated upregulation of the cyclooxygenase-2-PGE_2-Prostanoid receptor EP2 (COX2-PGE_2-EP2) pathway in unilateral nephrectomy (UNX) mouse model of hyperfiltration-mediated kidney injury and its attenuation using EP2 and EP4 agonists and antagonists. Following these results, we hypothesize altered urinary eicosanoid profile in children with SFK and altered expression of eicosanoid metabolizing enzymes and receptors in UNX mice.

Methods: Children with SFK (n=57, 37 boys) and healthy children with monosymptomatic enuresis (N=72, 49 boys) were included. Data on age, gender, height, weight, blood pressure (BP) and a urine sample were collected during the clinic visit. Urinary metabolites of various eicosanoids were measured using liquid chromatography-tandem mass spectrometry (Eicosanoid Core Laboratory, University of Nashville TN). The Wilcoxon test was used for non-parametric analysis of human data. sv129 mice (4 weeks old) were used for Sham or UNX surgery and observed for 6 months. Mouse kidney cortical tissue was used for transcriptomic and proteomic analysis at the University of Missouri Core Facilities, Columbia MO, followed by bioinformatic analysis.

Results: Healthy children and children with SFK did not differ significantly in age, Z-scores for height, weight, and BP. However, urinary PGE_2 (p=0.013), TxB_2 (p=0.024), 11,12-DHET (p=0.003), and 14,15-DHET (p=0.011) were elevated in children with SFK compared to healthy children. No significant differences were found for other eicosanoids. Transcriptomic and proteomic analyses of mouse kidney tissue showed that the expression of proteins related to PGE_2 and TxB_2 metabolism and activity, as well as cytochrome P450 enzymes, were significantly altered in the UNX group. Expression of Cbr1, Ptgr2, Akr1c14, Cyp2d12, and Cyp2j5 showed changes at both the gene and protein expression level ($p<0.05$).

Conclusions: Present data from children with SFK and UNX mouse model corroborate previous findings and suggest the importance of eicosanoids and related enzymes and receptor proteins in hyperfiltration-mediated kidney injury in SFK.

Funding: NIDDK Support

FR-PO687

MAGED2 Enhances Sodium Chloride Cotransporter (NCC) Expression at the Plasma Membrane by Inhibiting Its Ubiquitination and Lysosomal Degradation under Hypoxia

Aline N. Radi, Sadiq Nasrah, Michelle Auer, Stefanie Weber, Elie Seaayfan, Martin Kömhoff. *Department of Pediatrics, Philipps-University Marburg, Marburg, Germany*.

Background: Transient antenatal Bartter's syndrome (tBS) is characterized by massive polyhydramnios, impaired expression of the cAMP-sensitive renal salt-transporters NKCC2 and NCC, marked perinatal mortality and preterm birth followed by spontaneous recovery from polyuria in survivors. tBS is caused by mutations in the gene encoding MAGED2, which inhibits endocytosis of Gαs under hypoxia, a prerequisite for generation of cAMP by membrane-bound adenylate cyclase (mAC). As spontaneous recovery from renal salt wasting overlaps with developmental increase of renal oxygenation, lack of MAGED2 dependent cAMP generation under hypoxia explains, at least in part, the severe but transient renal salt loss in tBS patients. The present study aims to elucidate how MAGED2 controls NCC-trafficking.

Methods: Cell-surface biotinylation, endocytosis, exocytosis and activity of NCC were analyzed in HEK293 and HeLa cells under hypoxia with or without MAGED2-depletion (siMAGED2). Results were assessed using western blotting, immunocytochemistry and CoroNa Green, a sodium ion indicator.

Results: In renal cells exposed to hypoxia, siMAGED2 significantly reduced the expression of total and plasma membrane-bound NCC as well as its activity. Conversely, MAGED2 overexpression promoted expression of both total and plasma membrane-bound NCC, whereas Gαs depletion led to the opposite. Interestingly, forskolin abrogated the effect of siMAGED2 on NCC expression and localization at the plasma-membrane, the latter of which was recapitulated by immunocytochemistry in HeLa cells. Of note, MAGED2 overexpression did not rescue NCC expression in Gαs-depleted cells, confirming functioning of Gαs downstream of MAGED2. Reduced expression of NCC at the cell surface resulted from decreased NCC exocytosis and enhanced endocytosis in MAGED2-depleted cells. Additionally, siMAGED2 enhanced NCC lysosomal degradation by increasing its ubiquitination.

Conclusions: In conclusion, our study demonstrates the crucial role of MAGED2 under hypoxic conditions in regulating NCC lysosomal degradation and its trafficking to the plasma membrane. This sheds light on the underlying mechanisms of tBS and offers potential avenues for therapeutic intervention by targeting MAGED2-mediated pathways.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO688

Severe Kidney Dysplastic Phenotypes Caused by WT1 Exon 9 Missense Variants

Huong Quynh Tran Thuy,[1] Tuyen T. Nguyen,[2,3] Kenji Fukui,[4] China Nagano,[5] Kandai Nozu,[5] Riku Hamada,[6] Hiroyasu Tsukaguchi.[1,7] *[1]Kansai Medical University, Second Department of Internal Medicine, Hirakata, Japan; [2]Kansai Medical University, Department of Genome Editing, Hirakata, Japan; [3]Children's Hospital 1- Ho Chi Minh City, Neonatology 2, Metabolic and Genetic Department, Ho Chi Minh, Viet Nam; [4]Osaka Medical and Pharmaceutical University, Faculty of Medicine, Department of Biochemistry, Takatsuki, Japan; [5]Kobe University Graduate School of Medicine, Department of Pediatrics, Kobe, Japan; [6]Tokyo Metropolitan Childrens Medical Center, Department of Nephrology, Fuchu, Japan; [7]Kansai Medical University Hospital, Clinical Genetics Center, Hirakata, Japan.*

Introduction: Mutations of the Wilms tumor suppressor-1 gene (*WT1*) are typically linked to a triad of glomerulopathy, defective genital development, and Wilms' tumor. The hallmark clinical phenotype Denys-Drash Syndrome (DDS, OMIM194080) is caused by Exon 9 missense variants. p.Arg467Trp is the most commonly reported and accounts for approximately 50% of DDS.

Case Description: We recently found the *WT1* p.Arg467Gln variants in five neonates with early onset ESRD (3 males, 2 females). Most cases developed ESRD within the first month of their life (median 8 days, range one day to 90 days). Three of them underwent bilateral nephrectomy remain healthy after kidney transplantation. Two (cases 1 and 2) show hyperechoic, normal or smaller kidneys on ultrasonography. Renal histology (case 3) revealed severe mesangial sclerosis with tubular dysgenesis and some overgrowth of stromal elements. Two males showed external genital abnormality (cryptorchidism, hypospadias, etc). One child (case 2) had lung hypoplasia (Potter syndrome). All were sporadic with the exception of case 1 affecting the two siblings. The pathogenic p.Arg467Gln variant, which substitutes the most frequent, hot-spot Arg467 residue in the 3rd zinc finger and typically causes Denys-Drash syndrome. Structural modeling predicted that an Arg-to-Trp substitution confers obvious structural hinderance for the 3rd Zinc finger to bind the DNA, consistent with the inability to transactivate the luciferase functional assay. On the other hand, an Arg-to-Gln substitution modestly altered the hydrogen bonding for the DNA binding. Reviews of previous clinical reports showed that p.Arg467Gln leads to earlier onset NS and faster progression to ESRD compared to the p.Arg467Trp (p.Arg467Gln *n*=6, onset 0.04±0.02 year, ESRD 0.17±0.07 year, *vs* p.Arg467Trp *n*=40, onset 1.4±0.2 year, ESRD 2.29±0.4 year).

Discussion: We found that *WT1* p.Arg467Gln tend to cause severe kidney dysplastic phenotype compared to the classic DDS variant p.Arg467Trp. Further study is necessary to see whether p.Arg467Gln have functionally more deteriorating effects on transcription predisposing to severe nephron dysplasia than does p.Arg467Trp or other second genetic factors contribute to modify the severe nephron developmental defects.

FR-PO689

Structured Application of Nephrogenetics in a Pediatric Kidney Clinic Is Clinically Impactful and Challenging

Jordy Salcedo-Giraldo, Krista R. Wink, Andrew Freiman, Lisa M. Guay-Woodford, Louise C. Pyle, Ashima Gulati. *Children's National Hospital, Washington, DC.*

Background: As clinical genetic testing becomes more accessible, their use as a diagnostic tool for kidney disease is becoming more common. While the utility of genetic testing has been described in adult nephrology clinics, its application and impact in pediatric kidney clinics is less clear.

Methods: We retrospectively reviewed 10-years of clinical and genetic data on patients presenting to our pediatric kidney genetics program. The data analyzed includes genetic variants classified as pathogenic (P) or likely pathogenic (LP) by the ACMG criteria and their impact on clinical care. Details on genetic testing strategies and variants of uncertain significance (VUS) were collected.

Results: Among 331 patients, with a mean age of 8.6 ± 6.7 years, N=166 (50%) received clinical genetic testing. Of these, 106/166 had informative genetic test results: 75% of which had a P or LP variant explaining their condition, while 25% had a P/LP variant non-explanatory for the kidney disease condition. Top genes with P/LP variants were *PKD1* (N=16), *PKHD1* (N=12, 11 were biallelic), *TSC2* (N=11), *HNF1B* (N=9), *AVPR2* (N=4). A carrier state unrelated to the kidney condition was reported in 28/166 patients, most commonly in *APOL1* (N=9) and *NPHS2* (N=4). A VUS was reported in 77/166 patients, with 49% of these having a VUS in ≥ 5 genes, most frequently in *PKHD1* (N=15) and *PKD1* (N=13). Testing strategies included a broad gene panel (>50 genes; N=40/166), limited gene panel (≤ 50 genes; N=49/166), exome sequencing (N=11/166), chromosomal microarray, (N=4/166) or combinations (N=13/166). Clinical impact measured for patients with P/LP variants included reclassification of diagnosis (38/106), disease-modifying therapy initiation (37/106), and avoidance of unnecessary procedures (22/106) and medications (44/106). Genetic results assisted in transplant evaluation (4/166), extra-renal screening (70/106), and reproductive counseling (42/106).

Conclusions: In a select cohort of children referred to a kidney genetics program, genetic testing was used in 50% of cases and is clinically impactful in patients with a P/LP variant explaining the disease condition. Genetic variants not directly related to the disease condition are frequent and pose a challenge for interpretation and counseling.

FR-PO690

Single-Center Experience in Establishing a Pediatric Kidney Genetics Clinic

Bree E. Martin, Friedhelm Hildebrandt, Nina Mann, Amar J. Majmundar. *Boston Children's Hospital, Boston, MA.*

Background: Genetic testing is recommended by KDIGO to establish a cause of chronic kidney disease. However, providing this service requires expertise in kidney genetics and genetic counseling and organizational support for navigating insurance approval. Here we describe our experience in establishing a pediatric kidney genetics clinic (KGC) at a single center.

Methods: We performed a retrospective chart review of patients referred over 18 months (11/22-4/24) to the Boston Children's Hospital KGC (Boston, MA, USA) led by two pediatric nephrologists and a certified genetic counselor with expertise in genetic kidney disease. We analyzed clinical and laboratory characteristics, genetic testing results, and clinical utility.

Results: 86 patients were referred to the KGC. 53 (61%) were referred for genetic testing after evaluation and pre-test counseling. 46/53 (87%) patients had renal disease while 7/53 (13%) were asymptomatic individuals referred based on a family history of kidney disease. Glomerular and cystic kidney diseases were the most frequent clinical diagnoses (16/53 and 15/53, respectively). We performed genetic testing in 32/53 (60%) patients while 11 families declined testing after counseling. Kidney phenotype-specific (16) or broad kidney disease panels (11) were most frequently ordered. 20/32 (62%) had a pathogenic/likely pathogenic variant identified. The remaining 33 patients seen in the KGC were referred for counseling for prior testing performed by the primary nephrologist or other subspecialty (26/33 and 4/33, respectively) or for CLIA-confirmation of research results (3/33). Of all testing conducted by our clinic, the majority were through a traditional insurance approval process (22/36 tests) while 14/36 were company-based. All variants (including those of uncertain significance) were manually adjudicated by the KGC team, and KGC reanalysis of uncertain variants led to genetic diagnoses in 3 cases. Ultimately, 50/86 (58%) patients seen in our KGC had a genetic diagnosis in one of 29 genes. Alport Syndrome (*COL4A3*/4/5) was the most frequent genetic diagnosis (11/50 patients). Overall, genetic testing impacted clinical management in 41/65 cases (63%).

Conclusions: A dedicated KGC provides utility in providing genetic counseling and expertise in kidney genetic disease as well as streamlining insurance approval.

FR-PO691

Artificial Intelligence for Total Kidney Volume Measurements in Pediatric ADPKD: Comparison of Three-Dimensional Ultrasonography with Magnetic Resonance Imaging

Adriana Gregory, Ryan Helland, Kate Knoll, Kendra Petersen, Hana Yang, Fouad T. Chebib, Maria V. Irazabal, Peter C. Harris, Timothy L. Kline, Christian Hanna. *Mayo Clinic Minnesota, Rochester, MN.*

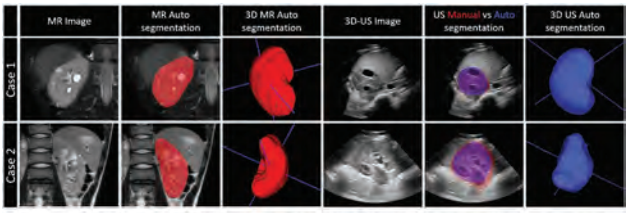
Background: Identifying biomarkers to predict ADPKD progression in children is imperative. Total kidney volume (TKV), utilized in adults, holds promise as a biomarker for children as well. MRI, the standard method for measuring TKV, is often impractical for children. Recently, 3D ultrasound (US) has emerged as a low-cost, accessible alternative. This study aims to use 3D US and Artificial Intelligence (AI) deep learning techniques to measure TKV in pediatric ADPKD patients accurately. We will validate 3D US measurements by comparing them to AI MR-based TKV measurements.

Methods: Using a Philips EPIQ scanner with a panoramic 3D X6-1 matrix array probe and MR scanners with 3T and 1.5T magnetic field strength, we acquired volumetric 3D-US images and MR images to segment the kidney automatically. A deep convolutional network was trained on retrospective 3D US images (n=130) of ADPKD adult subjects using a C5-1 probe and evaluated on prospectively acquired 3D US volumes (n=22). Training employed 5-fold cross-validation with images stratified by patient and kidney volume into training and validation (80/20) cohorts. We compared AI 3D US-based and MR-based TKV measurements using linear regression and Bland–Altman plots.

Results: We analyzed 11 patients with genetically defined ADPKD carrying either *PKD1* or *PKD2* pathogenic variants. A significant correlation was observed between the reference standard total kidney volume (TKV) measured by MRI and both manual and automated 3D ultrasound (US) volumes (r=0.95, P<0.001 and r=0.86, P=0.001, respectively). The US volumes were lower compared to MR volumes, with a bias of -20.5% and -43.3% for the manual and automated measurements, respectively. **Figure 1** illustrates two representative cases from the study.

Conclusions: Volumetric TKV measurements in pediatric ADPKD are feasible through 3D US images. Enhanced model training, incorporating pediatric data utilizing the X6-1 probe, is anticipated to enhance segmentation performance.

Funding: NIDDK Support



Example cases of volumetric kidney segmentation performed on MR and 3D US imaging. Case 1, a 14-year-old female's right kidney, showed volumes of 180ml on MR, 134ml on manually segmented US, and 131ml predicted by automated US. In Case 2, a 13-year-old male's left kidney had volumes of 223ml on MR, 192ml on manually segmented US, and 148ml predicted by automated US.

FR-PO692

Clinical Features of Cystinosis and Practice Patterns: A Report of the NAPRTCS Cystinosis Registry

Jodi M. Smith,[1] Sara A. Boynton,[2] Paul C. Grimm,[3] Larry A. Greenbaum,[4] Alicia Neu,[2] Bradley A. Warady.[5] *[1]Seattle Children's Hospital, Seattle, WA; [2]Johns Hopkins University, Baltimore, MD; [3]Stanford University, Stanford, CA; [4]Emory University, Atlanta, GA; [5]Children's Mercy Kansas City, Kansas City, MO.*

Background: The NAPRTCS Cystinosis Registry is a prospective cohort study of children & young adults with cystinosis whose objective is to describe clinical features of cystinosis and practice patterns of providers.

Methods: Children & young adults (< 25 yrs) with cystinosis at any NAPRTCS center are eligible. At enrollment, demographic & clinical data from time of initial presentation with cystinosis, time of enrollment, and every 6 months.

Results: Data were collected from 30 centers on 104 subjects diagnosed from 12/1999 to 8/2023 (Table 1). The most commonly reported medications at diagnosis included cystine lowering medications (81.8%), cysteamine eye drops (34.3%), and phosphorus and potassium supplementation (43.4%, 42.4%). During longitudinal follow-up more than 90% of patients remained on cysteamine oral therapy. The type varied over time with an increase in Procysbi use following FDA approval in 2013. Median creatinine at registry enrollment was 0.73 mg/dL (eGFR 69.0 ml/min/1.73m2) and 0.94 mg/dL (58.3 ml/min/1.73m2) at 36 months post enrollment. Almost half of patients (48.9%) had a g-tube at registry entry. Over 90% of patients were at grade level with 34.8% receiving special services. The majority of patients reported 1 to 2 nephrology visits in the past 6 months. The most common subspecialty visits were ophthalmology (28.4%), endocrinology (24.2%) and GI (17.9%).

Conclusions: Children with cystinosis present early in life with majority of patients diagnosed under 2 years of age. Patients typically present with 6 months of symptoms before a diagnosis is made with failure to thrive present in more than 50%. Children and young adults with cystinosis have complex care needs which are often met through non-local, multispecialty care providers.

Table 1. Demographics of the Cystinosis Registry

	n=104
Age at diagnosis	**16.5 months (12, 33)**
Age at registry entry	**9 years (6, 14)**
Time since dx	**6 years (3, 11)**
Male	**55 (52.9%)**
Race	
White	81 (77.9%)
Black	4 (3.8%)
Asian	2 (1.9%)
Multi-racial	9 (8.7%)
Not reported or Unknown	8 (7.7%)
Ethnicity	
Hispanic or Latino	7 (7.7%)
Not Hispanic or Latino	72 (79.1%)
Not reported or Unknown	12 (13.2%)
Insurance	
Private	47 (45.2%)
Medicaid	27 (26.0%)
Distance from center (n=62)	
<20 miles	23 (20.8%)
20-50 miles	19 (18.3%)
>50 miles	30 (28.8%)
Median duration of symptoms prior to	**6.0 months (2.0, 10.0)**
Findings at presentation	
Failure to thrive	54 (54.5%)
Vomiting	39 (39.4%)
Corneal crystals	32 (32.3%)
Dehydration	31 (31.3%)
Other	28 (28.3%)
Labs at diagnosis	
WBC cystine level by assay	
Granulocyte (n=35)	5.06 nmol/mg protein (2.7, 9.0)
Leukocyte (n=22)	2.99 nmol/mg protein (2.1, 4.4)
Genetic analysis	26 (26.3%)

FR-PO693

Thiamine beyond Beriberi

Sandra Iragorri, Brett Boyer, Aditi Tiwari. *Oregon Health & Science University, Portland, OR.*

Introduction: In resource-abundant settings thiamine deficiency is usually limited to those on daily diuretics, alcohol use disorder, very restrictive diets, and post gastric bypass. Children are rarely affected. We present two cases highlighting other at-risk populations with unusual manifestations and potential dire consequences if unrecognized and untreated.

Case Description: Case 1 is a 13-year-old with relapsed ALL post CAR Tcell therapy admitted after 4 weeks of poor dietary intake due to typhlitis and C diff infection, who suddenly developed a severe unexplained lactic acidosis. Recognizing the Warburg effect as the source of the lactic acidosis, lead to thiamine supplementation. Within three hours the lactate dropped from 19 to 3 mmol/L, TCO2 increased from 14 to 26 mmol/L, and the serum pH was 7.46. Unfortunately, a few weeks later the patient died of complications of ALL Case 2 is a 9-year-old with long-standing self-injurious behavior, vomiting, and restricted oral intake, who presented with altered mental status, hypertonia, hyperreflexia, and seizures, leading to intubation and anticonvulsant therapy. Initial laboratories showed AKI and serum sodium of 197 mmol/L. The FeNa of 0.13% and the urine osmolality of 1005 mOsm/kg support the diagnosis of functional AKI. The water deficit was estimated at 7 liters. The admit CK was 777 U/L but despite an initial downtrend, from day 4 onwards (when the serum Na was down by only 37 mmol/L) it steadily rose by 10.000 units/day, peaking at 136,900 U/L on day 9, and steadily dropping thereafter. Thiamine supplementation was started on day 6 following a brain MRI which showed diffusion restriction consistent with either extra pontine myelinolysis or Wernicke's encephalopathy. Clinically the patient improved with inpatient rehab, but to communicate verbally they required an AAC.

Discussion: The Warburg effect refers to a situation where thiamine deficiency prevents pyruvate entry into the oxidative phosphorylation cycle, staying in the cytosol where it is fermented to lactate. The second case underscores how thiamine deficiency impairs the generation of ATP, which in the myocyte is essential for muscle relaxation. An active calcium ATPase, returns calcium from the sarcoplasm to the sarcoplasmic reticulum, leading to relaxation. When contraction persists, rhabdomyolysis ensues. These cases remind us of the diverse and essential biochemical functions of thiamine manifesting as clinical conundrums.

FR-PO694

Defining the Urine Proteome in Boys with Posterior Urethral Valves

Xin Wang,[1,2] Liwen Zhang,[3] Brian Becknell,[1,2] Daryl J. Mcleod.[1,2]
[1]Kidney and Urinary Tract Center, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Nationwide Children's Hospital, Columbus, OH; [3]The Ohio State University Wexner Medical Center, Columbus, OH.

Background: Posterior urethral valves (PUV) occur in 1 in 4000 live male births and are a leading cause of pediatric end-stage kidney disease (ESKD). Among patients with PUV, estimated glomerular filtration rate (eGFR) often remains unchanged until late in the disease process due to adequate renal reserve, limiting proactive intervention opportunities. Distinguishing changes in eGFR due to the natural progression of disease vs. modifiable factors is also challenging. Therefore, measures of chronic kidney disease (CKD) progression that are both timely and specific to PUV are critically needed.

Methods: Boys with PUV (cases) and age- and sex-matched healthy children (controls) were recruited from our multispecialty uronephrology clinic and general pediatric clinics, respectively. Urine was obtained through clean catch, catheterization, or urine bag. Urinary proteins from 20 cases and 20 controls were detected using LC/MS/MS. Differential expression analysis identified proteins that varied between cases and controls, and between cases with normal vs. low eGFR. Functional enrichment analysis was profiled to detect specific biological functions. Correlation analyses examined relationships between these proteins and clinical factors, such as eGFR, creatinine, age, and weight.

Results: We identified conserved urine proteins and biological pathways that are dysregulated in cases compared to controls, along with differences in the urinary proteome between cases with normal versus reduced eGFR. Unique subgroups among cases emerged, each characterized by distinctive urine protein profiles and pathways. Cases with low eGFR accumulate angiogenesis-associated proteins, such as AGT, VCAM1, and CDH5, while exhibiting reduced levels of IGFBP7 and L1CAM. Correlation analyses between eGFR and urinary proteins revealed 31 proteins highly correlated in cases, helping to trace the development of obstruction nephropathy.

Conclusions: These results enhance our understanding of kidney injury in PUV and identify potential urine biomarkers for further investigation. The discovery of these markers and pathways could aid in early diagnosis of obstructive nephropathy, providing healthcare providers with tools for proactive intervention and more precise therapeutic strategies.

Funding: NIDDK Support

FR-PO695

MIP Assay-Based Targeted Gene Resequencing Identifies 22 Novel and Extremely Rare Variants in Known and Putative New Candidate Genes in Lower Urinary Tract Obstruction

Markus H. Zeilmann,[1] Arif Ekici,[11] Clara Vidic,[9] Wolfgang Krebs,[10] Marcin Zaniew,[12] Agnieszka Szmigielska,[4] Monika Miklaszewska,[5] Maria Szczepanska,[6,7] Katarzyna Taranta-Janusz,[8] Przemyslaw Sikora,[13] Katarzyna Zachwieja,[5] Friedhelm Hildebrandt,[3] Alina Hilger.[1,2] CaRE for LUTO.
[1]Department of Pediatrics and Adolescent Medicine, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany; [2]Research Center On Rare Kidney Diseases (RECORD), University Hospital Erlangen, Erlangen, Germany; [3]Division of Pediatric Nephrology, Boston Children's Hospital, Boston, MA; [4]Department of Pediatrics and Nephrology, Warsaw Medical University, Warsaw, Poland; [5]Department of Pediatric Nephrology and Hypertension, Cracow Medical College of the Jagiellonian University, Cracow, Poland; [6]Department of Pediatrics, Silesian Medical University, Faculty of Medical Sciences in Zabrze, Zabrze, Poland; [7]Department of Pediatrics, Silesian Medical University in Katowice, Katowice, Poland; [8]Department of Pediatrics and Nephrology, Medical University of Bialystok, Bialystok, Poland; [9]Department of Human Genetics, Rheinische Friedrich-Wilhelms-Universitat Bonn, Erlangen, Germany; [10]IT Unit, Nuremberg Institute of Technology, Nuremburg, Germany; [11]Department of Human Genetics, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany; [12]Department of Pediatrics, University of Zielona Góra, Zielona Góra, Poland; [13]Department of Pediatric Nephrology, Medical University of Lublin, Lublin, Poland.

Background: Lower urinary tract obstruction (LUTO) is the main cause of kidney failure in childhood. In about 60% LUTO occurs as posterior urethral valves (PUV). To date, little is known about the genetic causes of LUTO. Hence, we aimed to decipher the contribution of the known and previously identified candidate genes to the development of LUTO in our cohort of 500 individuals.

Methods: Therefore, 17 candidate genes were evaluated, using single-molecule molecular inversion probe (MIP) assay. After NextGen sequencing, data was filtered using a stringent algorithm including the quality of the reads, population frequency, and pathogenicity in prediction programs as the CADD-phred score to determine novel and extremely rare variants. The filtered variants were subjected to Sanger sequencing for validation and familial segregation if available.

Results: In total 22 different variants were identified in 20 patients in 11 of the re-sequenced genes (figure 1). Four genes were previously described as possible LUTO disease genes, 4 genes were found to reside in close proximity to regions identified in previous LUTO genome-wide association studies (GWAS) and 3 genes are newly identified candidate genes by our group. All variants matched the known or assumed inheritance patterns for the respective genes.

Conclusions: We suggest that the identified potentially disease-causing variants provide evidence that the underlying genes may be involved in the development of LUTO. Nevertheless, possibly disease-causing variants could only be identified in just 1,8% of all investigated LUTO individuals showing that LUTO is very heterogeneous. Still, the identification of new candidate genes, followed by warranted functional studies on these genes, will lead to a deeper understanding of the development of LUTO.

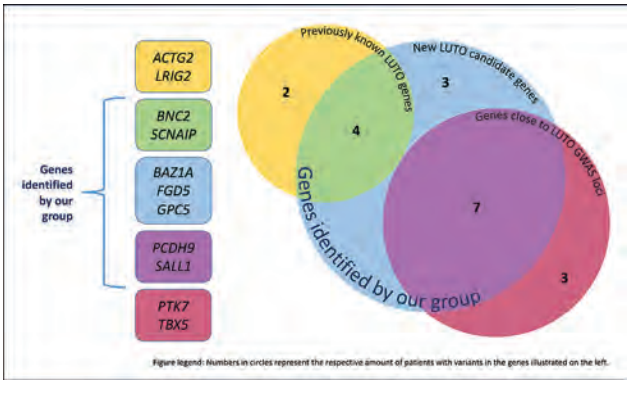


Fig. 1

FR-PO696

Ribonuclease Inhibitor Regulates Host Antimicrobial Activity toward Uropathogenic Escherichia coli

Yusuf Ali,[1,2] Hanna H. Cortado,[1,2] Birong Li,[1,2] Brian Becknell.[1,2] [1]*Kidney and Urinary Tract Center, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH;* [2]*Nationwide Children's Hospital, Columbus, OH.*

Background: Members of the Ribonuclease A Superfamily exert bactericidal activity toward uropathogenic *Escherichia coli* (UPEC) and their activity is regulated by an endogenously expressed high affinity binding partner, Ribonuclease inhibitor (RI). Here, we tested the hypothesis that RI serves a critical role in regulating the antimicrobial activity of RNase 3.

Methods: UPEC colony forming units (CFU) were enumerated to assess the antimicrobial activity of recombinant RNase 3 protein in the presence and absence of RI. We tested the interaction, colocalization and UPEC mediated regulation of RNase 3 by RI in human MOLM-13 cells, monocytes, and neutrophils by co-immunoprecipitation (Co-IP), Western blotting and immunofluorescence (IF). Binding of RNase 3 with RI was studied by native gel electrophoresis and visualized by silver staining. Using Cre/LoxP recombination, we deleted RI in murine phagocytes. We transurethrally inoculated control and RI conditional knockout mice with UPEC and enumerated bacterial burden in urinary tract tissues.

Results: RNase 3 exhibited potent antimicrobial activity towards UPEC, which was suppressed by the addition of RI. RI and RNase 3 colocalize and form a complex in monocytes and neutrophils that dissociates with UPEC treatment. Recombinant RNase 3 and RI proteins associate directly in cell-free conditions, and this is disrupted by pre-incubation with H_2O_2, suggesting a redox dependent interaction. Phagocyte-specific RI conditional knockout mice exhibited augmented UPEC clearance during experimental UTI, consistent with a model in which RI limits antimicrobial RNase activity.

Conclusions: RI forms a reversible complex with RNase 3 to limit its antimicrobial activity toward UPEC. UPEC infection dissociates this complex – possibly as a consequence of oxidation - resulting in augmented RNase 3 activity and UPEC clearance. Studies in RI knockout mice substantiate its role as a negative regulator of phagocyte antimicrobial activity *in vivo*.

FR-PO697

Single-Center Case Series of Congenital Anomalies of the Kidney and Urinary Tract and Hepatoblastoma

Rebecca Farr,[1] Julie Bonn,[1,2] Mohamad Eyad Khorki,[1] Stuart Goldstein,[1,2] Alexander Bondoc,[1,2] Greg Tiao,[1,2] Katherine Somers,[1,2] James I. Geller,[1,2] Meredith P. Schuh.[1,2] [1]*Cincinnati Children's Hospital Medical Center, Cincinnati, OH;* [2]*University of Cincinnati College of Medicine, Cincinnati, OH.*

Introduction: Hepatoblastoma (HB) is the most common pediatric primary liver malignancy. Several congenital anomalies and syndromes are associated with an increased incidence of HB and have recommended HB screening guidelines. While multiple case reports describe HB in children with congenital anomalies of the kidney and urinary tract (CAKUT), true incidence is unknown and screening guidelines do not exist. We report a case series of eight patients with bilateral CAKUT and HB.

Case Description: All patients were male, preterm (gestational age 24-34 weeks), and diagnosed with HB between 5 months and 2 years from 2008-2022. Seven patients initiated dialysis (median start 54 days of life). Five were found to have HB incidentally on imaging obtained for surgical planning, two had imaging due to abdominal pain/distension and vomiting, and one had imaging as part of an evaluation for hypercalcemia. Four patients achieved successful remission with a combination of chemotherapy and surgical resection, while four patients were offered liver transplant due to the extent of their disease after chemotherapy. In this small cohort, neither the age at diagnosis, length of time on dialysis prior to diagnosis, nor alpha fetal protein (AFP) concentration at diagnosis (26-545,797ng/mL) was associated with the extent of disease or outcome (Table 1).

Discussion: This case series highlights bilateral CAKUT and HB at our center and represents 3.5% of bilateral CAKUT seen within the study period. Importantly, most were diagnosed with HB incidentally, and half needed liver transplantation due to the extent of their disease. We suggest a proactive screening protocol in patients with bilateral CAKUT has potential to identify HB at an earlier stage, thus possibly negating the need for liver transplantation. Further multicenter studies are needed to define the true incidence of HB in bilateral CAKUT and identify specific patient factors, such as genetic predisposition, to inform screening protocols.

Pt #	Sex	Race	GA at Birth (weeks)	Birth Weight (g)	BCAKUT diagnosis	Age at initiation of KRT (days)	Age at HB Dx (months)	Time from KRT start to HB Dx (months)	Clinical Presentation at diagnosis	AFP at diagnosis (ng/mL)	PRETEXT	Surgical Therapy	Long term Outcome
1	M	White	33	2530	PUV, kidney dysplasia	130	24	2	Incidental imaging (CT angiography) obtained for kidney transplant evaluation	180,153	II	Resection	Transitioned care
2	M	Unknown	33	Unknown	PUV, kidney dysplasia	7	29	28.8	Incidental imaging (abdominal ultrasound) obtained prior to bladder augmentation surgery	889	III	Offered (unknown liver/kidney)	Family pursued listing at different institution.
3	M	White	34	2045	ARPKD	99	5	6	Found on imaging (abdominal ultrasound) obtained for abdominal pain and vomiting	121	III	Failed resection, liver/kidney transplant	Transplanted 6 years ago, no recurrent disease.
4	M	White	24	460	Bilateral dysplastic cystic kidneys	N/A	12	N/A	Found on imaging (kidney ultrasound) obtained for hypercalcemia workup	545,797	IV	Liver/kidney transplant	Deceased 5 days after transplant.
5	M	Black	33	3445	Bladder outlet obstruction	54	22	20.2	Incidental imaging (abdominal ultrasound) obtained for kidney transplant evaluation	8,536	I	Resection	Off therapy for 21 months no recurrent disease.
6	M	White	34	2830	Multicystic dysplastic kidneys	29	5	3	Incidental imaging (CT venogram) obtained for dialysis catheter placement	9,702	IV	Liver/kidney transplant	Transplanted 5 years ago, no recurrent disease.
7	M	Middle Eastern	32	Unknown	Presumed PUV, kidney dysplasia	100	26	3	Found on imaging (abdominal ultrasound) obtained for abdominal distension and vomiting	26	II	Resection	Lost to follow up 7 years ago. Has been off therapy 3.5 years with no recurrent disease.
8	M	White	33	Unknown	Bilateral [illegible] PUV	2	2	4.9	Found incidentally on routine imaging (kidney ultrasound)	2,226	II	Resection	Deceased: [illegible] failure after 2nd chemo cycle (cancer free at time).

Table 1. GA = gestational age, BCAKUT = bilateral congenital anomalies of the kidney and urinary tract, KRT = kidney replacement therapy, AFP = Alpha-fetoprotein, PRETEXT = pre-treatment extent of disease staging system, Dx = diagnosis.

FR-PO698

Regulation of Urinary Tract Infection (UTI) Susceptibility by Stat3-Driven DMBT1 Expression

Sudipti Gupta, Shradha Rajak, Brian Becknell, John D. Spencer, Christina B. Ching. *Nationwide Children's Hospital, Columbus, OH.*

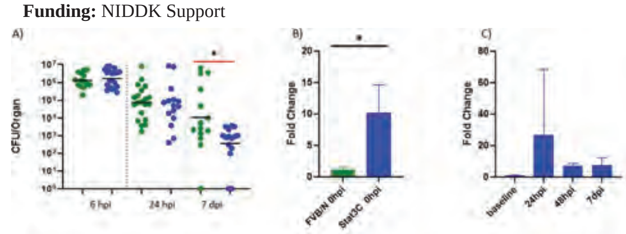
Background: Innate immune effectors like antimicrobial peptides exist to reduce UTI susceptibility in humans. We focus on studying the regulation of innate immune mechanisms by transcription factor, Stat3, to limit UTI susceptibility. Deleted in Malignant Brain Tumors-1 (DMBT1) protein is an antimicrobial peptide with antibacterial properties likely due to its function as a pattern recognition receptor. A clinical study shows lower DNA copy number of *DMBT1* leads to increase the odds of recurrent UTI. While DMBT1 has been demonstrated to be regulated by Stat3 in models of Crohn's disease, it has not been associated with Stat3 expression in models of UTI. We hypothesized that Stat3 manipulation in UTI would impact DMBT1 expression.

Methods: 6-8 weeks old female FVB/N wild type (WT) and constitutively active Stat3 (Stat3C) mice underwent experimental UTI. Urine and bladder tissue was collected up to 7 days post infection (dpi). Dilution plating was performed to quantify bladder and urine bacterial burden. Qiagen RT^2 profiler PCR mouse antimicrobial array was performed on bladders followed by confirmatory qRT-PCR. Results were evaluated by unpaired t-test or Mann-Whitney U test when appropriate, with $p<0.05$ being significant.

Results: Stat3C mice demonstrated reduced urine and then bladder burden by 7 dpi (p=0.0123). Evaluation of antibacterial responses on PCR array between the Stat3C and WT mice demonstrated significant differences in DMBT1 at baseline, peaking at 24hpi, and then persisting at 7dpi (p<0.01). Upon confirmatory qRT-PCR, DMBT1 was significantly elevated at baseline and 24hpi between Stat3C and WT mice (p<0.008). DMBT1 induction in infected Stat3C mice peaked at 24hpi with a 46-fold increase over baseline. This induction persisted even at 7dpi (8 fold over baseline).

Conclusions: Urothelial Stat3 overexpression results in baseline up-regulation of DMBT1 gene expression with a further increase during infection, particularly peaking at 24hpi. This is the first evidence of DMBT1 expression being regulated by Stat3 during UTI.

Funding: NIDDK Support



A) Stat3C mice have significantly decreased bladder burden in a delayed manner after UTI (7dpi)
B) Significantly higher induction of certain DMBT1 at baseline Stat3C mice on qRT-PCR
C) Time course DMBT1 fold induction following eUTI

FR-PO699

Phagocyte-Derived Ribonuclease 3 Promotes Bacterial Clearance during Urinary Tract Infection

Hanna H. Cortado,[1,2] Macie M. Kercsmar,[1,2] Birong Li,[1,2] Sudipti Gupta,[1,2] Christina B. Ching,[1,2] Ashley R. Jackson,[1,2] Juan de Dios Ruiz-Rosado,[1,2] Brian Becknell.[1,2] *[1]Nationwide Children's Hospital, Columbus, OH; [2]Kidney and Urinary Tract Center, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH.*

Background: Urinary tract infections (UTI) are common, serious bacterial infections in children, most often caused by uropathogenic *Escherichia coli* (UPEC), and can lead to urosepsis, acute kidney injury, and renal scarring. Identifying mechanisms of host defense against UTI is crucial in the development of innovative and effective strategies to mitigate these sequelae. The production of antimicrobial peptides (AMPs) is an important component of the innate host immune response against uropathogens. Our group is focused on identifying AMPs within the RNase A superfamily that play a role in controlling UTI. Here, we determine the contribution of human RNase3 to host UTI defense *in vivo* and its impact on phagocyte antimicrobial activities.

Methods: Urine RNase3 levels were measured by ELISA in girls with UTI and compared to unaffected controls. Humanized *RNASE3* transgenic mice underwent transurethral inoculation of UPEC, and bacterial colony forming units (CFU) were enumerated in urinary tract organs. We utilized immunofluorescence microscopy and intracellular flow cytometry to identify cellular sources of RNase3. The bactericidal activity of RNase3 toward UPEC was investigated using recombinant RNase3 and *RNASE3* transgenic phagocytes.

Results: RNase3 amino-terminal peptide exhibited dose dependent antimicrobial activity towards UPEC. RNase3 levels were elevated in urine from pediatric patients with UTI compared to healthy controls. Studies in *RNASE3* transgenic mice and human tissues evince that RNase3 is expressed by neutrophils, monocytes and macrophages that infiltrate the infected kidney and bladder following UPEC exposure. *RNASE3* transgenic mice are protected from ascending UPEC infection, and *RNASE3* transgenic phagocytes are more adept at UPEC killing compared to non-transgenic controls.

Conclusions: Our data establish that RNase3 is an antimicrobial peptide induced during human UTI with potent bactericidal activity toward UPEC. Functionally, evidence in *RNASE3* transgenic mice and phagocytes demonstrates that RNase3 effectively limits disseminated UPEC infection.

FR-PO700

Impact of MicroRNA Depletion on Maintenance of Adult Bladder Urothelium

Macie M. Kercsmar,[1,2] Hanna H. Cortado,[1,2] Kelly Grounds,[1,2] Ashley R. Jackson,[1,2] Brian Becknell.[1,2] *[1]Kidney and Urinary Tract Center, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Nationwide Children's Hospital, Columbus, OH.*

Background: MicroRNA (miRNA) serve essential roles in epithelial cell development, maintenance, and response to injury through the regulation of mRNA and protein expression, however their functions in urothelium remains unknown. To address this knowledge gap, we engineered mice with temporally-restricted, urothelium specific inactivation of Dicer, an exonuclease required for miRNA biogenesis.

Methods: We generated tamoxifen-inducible urothelial Dicer conditional knockout mice by intercrossing *Dicer*$^{fl/fl}$ and *Upk2*CreERT$_2$ or *Shh*CreERT$_2$ animals. A tdTomato (tdT) fluorescent protein was expressed in a Cre/LoxP dependent manner to identify cells in which *Dicer* inactivation had occurred. Urothelial lineage markers were evaluated by immunofluorescence microscopy, Western blotting, and QRT-PCR.

Results: Bladders from control animals showed the expected urothelial morphology with three distinct layers: Krt5+;Krt14+ basal (B) cells, Krt5+;Upk+ intermediate (I) cells, and Upk+;FABP4+ superficial (S) cells. In contrast, adult bladders with *Upk2*CreERT$_2$-specific *Dicer* inactivation displayed rounded and exfoliated S cells with discontinuous Fabp4 expression. This coincided with increased Krt5 and Krt14 protein expression, whereas *Krt5* and *Krt14* mRNA levels were unaffected. In contrast, *Shh*CreERT$_2$-specific *Dicer* knockout mice displayed immature B cells and abundant I cells, whereas S cells maintained FABP expression but exhibited a round and more columnar morphology.

Conclusions: Dicer serves essential roles in urothelial structural integrity by promoting the maintenance of superficial, intermediate, and basal cells. This justifies further studies to identify specific miRNA responsible for this role.

FR-PO701

MicroRNA 146a Is a Negative Regulator of the Host Innate Immune Response to Urinary Tract Infection

Birong Li,[1,2] Macie M. Kercsmar,[1,2] Hanna H. Cortado,[1,2] Brian Becknell.[1,2] *[1]Kidney and Urinary Tract Center, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Nationwide Children's Hospital, Columbus, OH.*

Background: Urinary tract infections (UTIs) rank among the most common bacterial infections in children and adults. The innate immune response is essential for pathogen detection and eradication during UTI, but excessive inflammation can lead to renal injury and scarring. MicroRNA (miR) are small, non-coding RNA with key roles in regulating renal inflammation and tissue remodeling, but their expression and function in UTI are unknown. We investigated miR dynamics and the specific role of miR146a in the setting of experimental cystitis.

Methods: Female C57BL/6J mice underwent transurethral inoculation with uropathogenic *Escherichia coli* (UPEC). Bladders were harvested 7 days post infection for miR and total RNA sequencing. Transcriptome analysis was performed using GO and Ingenuity. Differential miR expression was validated by QRT-PCR during experimental cystitis. *miR146a* deficient and control mice were challenged with experimental UTI to investigate differences in susceptibility.

Results: UPEC infection led to dynamic changes in the bladder miRome, and miR146a was identified as the miR with the greatest fold-change. QRT-PCR validated induction of miR146a, and analysis of the predicted targets of miR-146a suggest its regulatory role in reducing inflammation. Mice with global *miR146a* deficiency were more susceptible to experimental UTI.

Conclusions: MiR146a is a negative regulator of the host innate immune response during UTI. Further studies are justified to identify the direct targets of miR146a and the therapeutic impact of miR146a mimetics during UTI.

FR-PO702

Predictive Value of Initial Diagnostic Imaging for Congenital Ureteropelvic Junction Obstruction Requiring Pyeloplasty

Adaobi Solarin,[1,2] Shivam Joshi,[3] Sudipti Gupta,[1,2] Christina B. Ching,[1,2] Brian Becknell.[1,2] *[1]Kidney and Urinary Tract Center, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Nationwide Children's Hospital, Columbus, OH; [3]The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Hydronephrosis is one of the most common findings on prenatal ultrasound. While prenatal hydronephrosis resolves in most instances, 6% of cases represent ureteropelvic junction obstruction (UPJO) that will require pyeloplasty, and differentiating between obstructive and non-obstructive hydronephrosis remains an unmet challenge. Usually, a combination of factors such as the Society of Fetal Urology (SFU) grade, drainage pattern, and differential renal function (DRF) on diuretic renogram are used in assessing the severity of hydronephrosis. We sought to identify predictive features on initial postnatal imaging for pyeloplasty among children with suspected UPJO.

Methods: We conducted a prospective, single-center study of children with prenatal hydronephrosis, postnatal imaging suggestive of isolated UPJO without other congenital anomalies, and two years of follow-up. Demographic, clinical and radiologic data from initial postnatal imaging were retrieved. Chi-squared test or Fisher's exact test was used to examine associations between categorical variables and surgical intervention, and Wilcoxon rank sum test identified the differences in the distribution of continuous variables across surgical interventions. A logistic regression model was utilized to identify potential predictors of surgical intervention.

Results: There were 98 cases of UPJO, of whom 49 (50%) underwent pyeloplasty. The median age at initial imaging was 4.4 months, 77 (79%) were male and 81 (84%) Caucasian. The initial SFU grade and gravity assisted drainage (GAD) on radionuclide imaging were associated with pyeloplasty. Logistic regression analysis indicated that age (p=0.0090), GAD (p=0.0009), and DRF (p=0.0422) are significant predictors of pyeloplasty. The model explained 45% of the variance in the outcome and correctly classified 83% (AUC=0.83) of cases undergoing pyeloplasty.

Conclusions: The initial diagnostic imaging has shown an excellent performance in predicting surgical intervention with age, DRF and GAD as significant predictors. Ongoing studies seek to extend these observations in an independent patient cohort and superimpose candidate urinary biomarkers to further discriminate UPJO from non-obstructive hydronephrosis at the time of initial postnatal imaging.

Funding: NIDDK Support

FR-PO703

Long-Term Kidney Outcomes in Pediatric Renal Vein Thrombosis

Mayra A. Oseguera,[1] Myda Khalid,[2] Bryce A. Kerlin.[3,1] *[1]Nationwide Children's Hospital, Columbus, OH; [2]Indiana University School of Medicine, Indianapolis, IN; [3]Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH.*

Background: Pediatric renal vein thrombosis (RVT) may increase the long-term risk for adverse renal outcomes. Most literature focuses on neonatal RVT, with low emphasis on long-term renal outcomes. There is sparse data on renal outcomes following RVT in older children. The goal of this project is to determine long-term renal outcomes of RVT across the pediatric age spectrum.

Methods: The PHIS (Pediatric Health Information System) database was used to identify patients from birth to 21 years of age with a diagnosis of RVT. We looked for the occurrence and persistence of hypertension, proteinuria, and eGFR reduction. Secondary outcomes analyzed were end stage renal disease and mortality.

Results: We identified 516 children with a diagnosis of RV in the PHIS database (Table 1). 51.9% were male. The mean age for RVT diagnosis was 2.6 years, the most common age at diagnosis was in the neonates. Children as old as 17 years of age were also identified. 20% of the affected individuals had residual CKD. Residual HTN occurred in 30.6% of the patients. (Table 1).

Conclusions: Pediatric RVT is a risk factor for the development of CKD and hypertension regardless of age at RVT diagnosis. Survivors of pediatric RVT should be routinely screened for evolving CKD and/or hypertension. We plan a deeper analysis of these data to determine if anticoagulant therapy alters long-term renal outcomes following pediatric RVT.

Characteristic	N (%)
Unique patients	516
Male sex	268 (51.9)
Age at RVT, years	2.6 (0.01–11.1)
Renal complex chronic condition flag (before or after RVT)	319 (61.8)
Mortality	66 (12.8)
Renal Outcomes	190 (36.8)
AKI	106 (20.5)
CKD	103 (20.0)
Kidney failure	3 (0.6)
Atrophy of kidney	13 (2.5)
Small kidney	5 (1.0)
Infarction of the kidney	21 (4.1)
Dialysis dependent	26 (5.0)
HTN	158 (30.6)
Proteinuria	15 (2.9)

Table 1

FR-PO704

Kidney Function and Isolated Kidney Transplant Outcomes in Primary Hyperoxaluria Type 1 Treated with Long-Term Lumasiran

Michael J. Somers,[1] Arnaud Devresse,[2] Richard G. Willey,[3] Michael D. Murphy,[3] Anne-Laure A. Sellier-Leclerc,[4] Cristin Kaspar,[3] Justine Bacchetta.[5] *[1]Division of Pediatric Nephrology, Boston Children's Hospital, Boston, MA; [2]Department of Nephrology, Cliniques Universitaires, Brussels, Belgium; [3]Alnylam Pharmaceuticals, Cambridge, MA; [4]Division of Pediatric Nephrology-Rheumatology, Hôpital Femme-Mère-Enfant, Lyon, France; [5]Lyon Est Medical School, Hospices Civils de Lyon, Lyon, France.*

Background: Primary hyperoxaluria type 1 (PH1), a rare autosomal recessive disorder associated with hepatic oxalate overproduction, leads to progressive kidney damage. Prior to availability of the RNA interference therapeutic lumasiran, reported graft survival rates after isolated kidney transplantation (iKT) in PH1 patients (pts) were poor: 54% at 3 months (M) and 46% at 1 year (y). Phase 2 (NCT03350451) and 3 Phase 3 trials (ILLUMINATE-A, NCT03681184; ILLUMINATE-B, NCT03905694; and ILLUMINATE-C, NCT04152200) have shown sustained urinary oxalate and plasma oxalate (POx) reduction and acceptable safety with lumasiran across a wide range of ages and baseline (BL) kidney function. Long-term follow-up allows evaluation of native kidney survival and iKT outcomes in lumasiran-treated pts.

Methods: Descriptive kidney function data from lumasiran clinical trials and post-transplant outcomes in pts following iKT were compiled.

Results: Mean annual rates of eGFR change (mL/min/1.73m^2/y) were –0.6 over 48 M in the Phase 2 trial (N=20), –1.2 over 48 M in ILLUMINATE-A (N=35), and –0.8 over 30 M of follow-up in ILLUMINATE-B (N=15). The range of BL eGFR values was 32–174 mL/min/1.73m^2 in these 3 trials. ILLUMINATE-C enrolled PH1 pts with advanced kidney disease; pts were assigned to Cohort A (not on hemodialysis [HD]) or Cohort B (on HD). Three pts in Cohort A, who had the lowest BL eGFR (8.6–16.5 mL/min/1.73m^2), required HD before the M36 data cutoff; the other 2 remaining Cohort A pts (BL eGFR 24.0, 34.1 mL/min/1.73m^2) had annual rates of eGFR decline of –2.3 and –0.9 mL/min/1.73m^2/y, respectively, over 36 M. Five Cohort B pts underwent iKT as of M36. All 5 had POx reduction from BL prior to transplantation, and further reduction post-transplant indicating improved POx clearance with functioning kidney grafts. No patients experienced oxalate nephropathy post-transplantation. All 5 remained HD-free and continued lumasiran treatment post-transplant as of M36.

Conclusions: Lumasiran treatment for PH1 resulted in minimal annual eGFR decline over 30 to 60 M in pts with BL CKD stages 1–4, and effectively lowered POx to allow for iKT, rather than liver-kidney transplantation, in some pts with end-stage kidney disease.

Funding: Commercial Support - Alnylam Pharmaceuticals

FR-PO705

Analysis of Underlying Diseases Associated with Kidney Stones in Korean Children and Adolescents

Heeyeon Cho, Jinwoon Joung. *Samsung Medical Center, Gangnam-gu, Seoul, Republic of Korea.*

Background: Recently, the prevalence of kidney stones occurring in children and adolescents is increasing worldwide. The renal stones may appear as the clinical manifestations of underlying diseases or as a complication of the treatment. Therefore, this study aimed to analyze the underlying diseases including genetic causes and assess clinical outcomes of Korean children with nephrolithiasis.

Methods: From January 2022 to December 2023, we retrospectively analyzed demographic data for patients aged 0 to 18 who were newly diagnosed with kidney stones using ultrasonography who visited Samsung Medical Center. Medical records including sex, gestational age, underlying disease, medication history, genetic analysis, and ultrasonography were retrospectively reviewed. The authors reviewed whether there was the underlying diseases or interventions related to kidney stones, and if such an underlying disease was not confirmed at the time of diagnosis, a genetic test such as whole exome sequencing was performed to distinguish hereditary kidney disease.

Results: A total of 102 patients were diagnosed with kidney stones, and the male to female ratio was 1.04. The average age at diagnosis was 76 months. The underlying diseases were prematurity (45.0 %), tubulopathy after chemotherapy in pediatric patients with malignancy (13.8 %), hereditary disease confirmed through genetic testing (13.8%), and congenital anomalies of the kidney and urinary tract (CAKUT) with hydronephrosis or cyst (12.7%). In addition, underlying diseases such as congenital heart disease requiring diuretic treatment (5.9%), epilepsy taking anti-seizure medication that cause stones (3.9%), and inflammatory bowel disease (2.9%) were found. There were two cases in which these underlying diseases were not found. There were 2 cases that required urological surgery, and 1 case had renal function decline of chronic kidney disease stage 3.

Conclusions: This study suggests that kidney stone may appear in association with various underlying diseases and be a clinical clue of hereditary disease. Therefore, the screening for stone in patients with relevant underlying disease or the active evaluation of the genetic cause should be considered. The prognosis for surgery or decline in renal function is relatively favorable.

FR-PO706

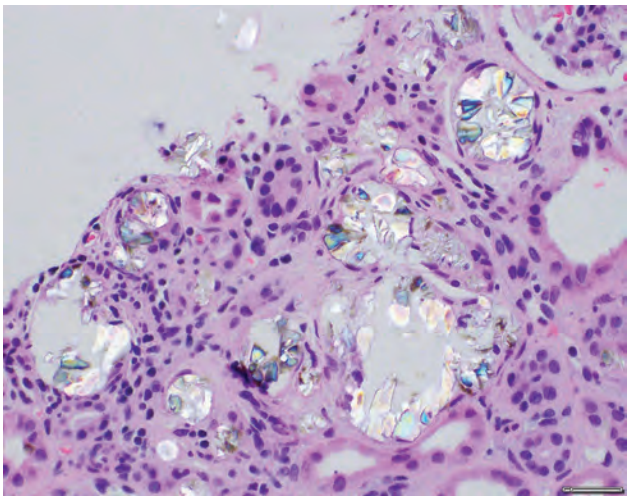
Little Stones, Big Trouble: Nutritional Oxalosis in a Child

Vivian Shi, Xixi Zhao. *Stanford University, Stanford, CA.*

Introduction: Oxalate nephropathy is a rare condition that results in acute kidney injury and chronic kidney disease. Although primary hyperoxaluria (PH) accounts for the majority of cases of oxalate nephropathy in pediatrics, our case highlights the importance in considering secondary causes. We present a case of a 9-year-old girl with kidney injury requiring dialysis due to nutritional oxalosis.

Case Description: A 9-year-old female with a history of failure to thrive presented with bilateral leg pain. Physical exam revealed extreme cachexia. Admission labs were notable for Na 101, K 6.6, BUN 157, and creatinine 8.56 (previous baseline 0.38 obtained 16 months prior), which prompted emergent hemodialysis (HD). Kidney biopsy showed diffuse oxalate crystals and severe interstitial fibrosis with tubular atrophy. Systemic oxalosis workup was negative. Genetic testing for PH was negative. A review of patient's diet prior to illness revealed large consumption of many high oxalate containing foods, including nuts, spinach, chocolates, as well as daily vitamin C supplements. Elevated plasma oxalate levels normalized with maintenance HD and diet control. She continued on HD until kidney transplantation.

Discussion: The patient presented at a young age with sudden end stage kidney disease due to oxalate nephropathy. Differentiating PH from secondary hyperoxaluria is crucial in determining the treatment of choice. PH is a rare inborn error of glyoxylate metabolism that results in hepatic overproduction of oxalate, leading to increased urinary excretion and kidney disease. Secondary hyperoxaluria can result from increased dietary intake or enteric hyperoxaluria. This case highlights the need for genetic testing and considering secondary causes of hyperoxaluria in pediatrics. The case also emphasizes the need for regular monitoring of nutritional sources in pediatric patients with failure to thrive, since their diet may be high in a single nutritional compound such as oxalate.



Oxalate crystals

FR-PO707

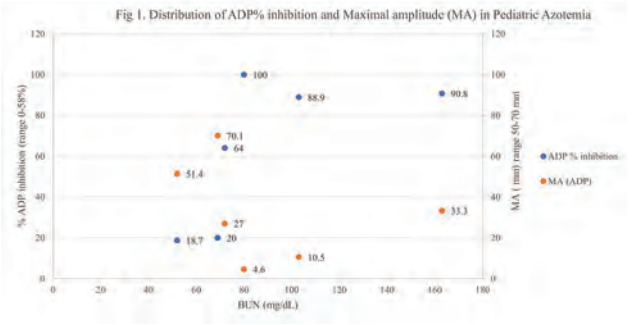
A Case Series of Thromboelastography (TEG) to Describe Patterns of Uremic Thrombocytopathy in Pediatric Kidney Dysfunction

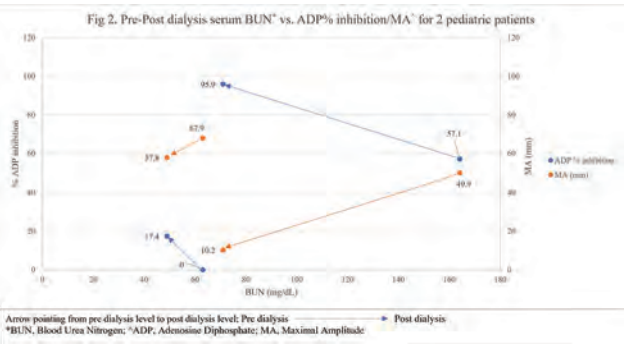
Shrea Goswami, Evan A. Rajadhyaksha, Andrew L. Schwaderer, Michelle C. Starr. TEG Team. *Riley Hospital for Children at Indiana University Health, Indianapolis, IN.*

Introduction: Renal azotemia can contribute to platelet dysfunction and subsequent bleeding risk. Thromboelastography (TEG) is commonly used to evaluate bleeding risk in patients with liver pathology and trauma, however, TEGs role in kidney dysfunction is unclear. We report TEG results in a case series of children with kidney dysfunction and describe TEG changes after dialysis.

Case Description: TEGs were collected from 8 patients (10 TEG samples). Ages ranged from 15 days to 18 years old, 3 had AKI and 5 had ESKD. All had urea (BUN) ≥50 mg/dL at first TEG sample. We found no significant relationship between BUN and markers of platelet inhibition (adenosine diphosphate, ADP% inhibition) nor clotting strength (maximum amplitude, MA) **(Fig 1)**. In 2 patients with pre/post hemodialysis (HD) TEGs, we saw an increase in inhibition and decrease in clot strength after dialysis **(Fig 2)**. This paradoxical increase in clot inhibition and decrease in clot strength is of unclear etiology but may represent correction of a previously hypercoagulable state.

Discussion: The absence of an identifiable relationship between urea and ADP% inhibition/MA in this case series may be secondary to the heterogeneity of the cohort (age, underlying disease process, azotemia duration). The paradox of increased clot inhibition and decreased clot strength with urea reduction may relate to decreased fibrinogen/vonWillebrand factor due to dialysis. Our case series is in accord with existing literature, which suggests TEG may have limited use in diagnosing uremic platelet dysfunction. Future longitudinal studies may clarify the utility of TEG to create hemostatic profiles for patients with kidney dysfunction.





FR-PO708

Automated Learning and Early Recognition Technology for Neonatal AKI (ALERT-NAKI)

Tahagod Mohamed,[1,3] Jonathan L. Slaughter,[1,3] Sven Bambach,[1] Jacqueline K. Magers,[1] Laura Rust,[1,3] Shama Patel,[1,3] Steve Rust,[1] John D. Spencer,[1,3] Francis P. Wilson.[2] *[1]Nationwide Children's Hospital, Columbus, OH; [2]Yale University, New Haven, CT; [3]The Ohio State University College of Medicine, Columbus, OH.*

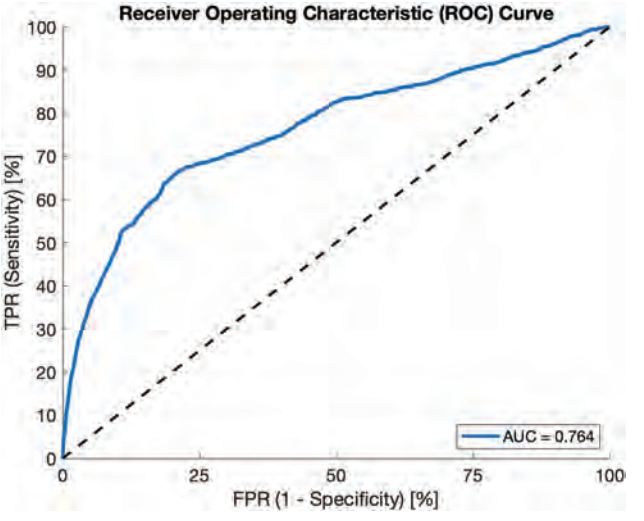
Background: Neonatal acute kidney injury (AKI) is underrecognized despite its high prevalence and known adverse effects on short- and long-term outcomes. Evidence-based tools for providers to predict and recognize neonatal AKI risk are limited. Under recognition of neonatal AKI prohibits providers from timely interventions on modifiable AKI risk factors. We hypothesized that neonatal AKI occurrence can be predicted by utilizing existing EHR data and machine learning algorithms.

Methods: Using retrospective EHR data from 5400 infants admitted in 2017-2021 to our level IV NICU for >183,000 patient days, we trained a machine learning model to predict neonatal AKI occurrence. Data were collected after local IRB approval. Known neonatal AKI risk factors were identified from existing literature. Neonatal AKI was defined by changes in serum creatinine (sCr) and urine output (UOP) according to the neonatal modification of KDIGO criteria. We used least absolute shrinkage and selection operator (LASSO) algorithm to identify reliable neonatal AKI predictors and to develop a predictive model. The area under the curve (AUC) was utilized to evaluate model performance

Results: When provided with 34 known neonatal AKI risk factors, LASSO chose 8 reliable predictors including fluid balance status, hypotension requiring vasopressors, invasive ventilation, FiO2%, congenital anomalies of the kidneys and urinary tract, sepsis, sCr monitoring and value changes. The model predicts significant changes in sCr and UOP during the next 48 hours with an AUC of 0.76, **Figure 1**.

Conclusions: Neonatal AKI can be reliably predicted by utilizing machine learning algorithms and available EHR data. This is the first step to empower providers with evidence-based tools to improve neonatal AKI prediction and recognition and to allow time for intervention on modifiable risk factors before kidney injury occurs.

Funding: Private Foundation Support



FR-PO709

Impact of Tobacco Smoke on Pediatric Kidney Function: Evidence from Urine Cotinine Levels

Jeong Yeon Kim. *Chungnam National University, Daejeon, Republic of Korea.*

Background: Tobacco smoking is a well-established risk factor for the development of chronic kidney disease (CKD) in adults. Additionally, exposure to tobacco smoke impacts pediatric kidney function and the progression of CKD. Urine cotinine (uCot), a metabolite of nicotine, serves as a biomarker for tobacco smoke exposure and is a more reliable indicator of CKD risk compared to self-reported smoking. This study evaluated the association between uCot levels and pediatric kidney function.

Methods: Data were extracted from the Korea National Health and Nutrition Examination Survey (KNHANES) conducted between 2019 and 2021. A total of 195 children aged 10–18 years were included in the analysis. The estimated glomerular filtration rate (eGFR) was calculated using the bedside Schwartz equation. Demographic and clinical characteristics of the study population were reported as weighted values. Weighted regression analysis was used to analyze the association between uCot levels and kidney function.

Results: Of the 195 children, 68.2% were male, with a mean age of 15.3±0.2 years. The mean eGFR was 99.4±1.8 ml/min/1.73m², and the mean urine albumin-to-creatinine ratio (uACR) was 7.1±0.5 mg/g. The mean uCot level was 327.0±50.5 ng/mL, and the mean uCot-to-creatinine ratio (uCCR) was 173.2±27.1 ng/mg. Among the children, 28.6% were exposed to secondhand smoke from parents, and 37.6% were smokers. Smoking was positively associated with uCot levels ($p<0.0001$) and uCCR ($p<0.0001$). However, parental secondhand smoke exposure did not show a significant association with uCot levels or uCCR. Both uCot levels ($R^2=0.07$, regression coefficient estimate=-0.009, $p<0.0001$) and uCCR ($R^2=0.04$, regression coefficient estimate=-0.01, $p=0.0123$) were negatively associated with eGFR. While smoking showed a significant negative association with eGFR ($R^2=0.02$, regression coefficient estimate=-9.5, $p<0.001$), parental secondhand smoke exposure did not exhibit a clinically significant association with eGFR. Neither uCot nor uCCR showed significant associations with uACR.

Conclusions: In conclusion, tobacco smoking negatively impacts kidney function in the pediatric population and can be monitored using uCot levels or uCCR. In this study, parental secondhand smoke exposure did not affect the kidney function of healthy children. Therefore, uCot levels in children could help identify those at high risk for developing CKD.

FR-PO710

AKI in Patients with Multisystem Inflammatory Syndrome in Children

Jennifer K. Nhan, Marva M. Moxey-Mims, Sun-Young Ahn. *Children's National Hospital, Washington, DC.*

Background: Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious condition associated with COVID-19 with over 9300 cases between May 2020 and January 2023 reported in the US. There are limited published studies on the effects of MIS-C on kidney function in the pediatric population. Etiologies of acute kidney injury (AKI) proposed were cardiac dysfunction, hyperinflammatory state and exposure to nephrotoxins for COVID-19 treatment. However, more large-scale studies are needed to further elucidate the clinical characteristics of kidney injury in children with MIS-C.

Methods: We performed a retrospective study of patients between the ages of 0-21 years diagnosed with MIS-C, who were hospitalized at Children's National Hospital between March 2020 and January 2023. To assess kidney injury, we evaluated serum chemistry, inflammatory markers and urine laboratory values. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to identify 29 patients with AKI and 104 patients without AKI.

Results: Among patients with AKI, 79.3% were male and 20.7% were female. Patients with AKI had significantly higher peak CRP levels than non-AKI patients (22.23 vs 16.26 mg/dl, $p<0.001$). Serum cytokine levels, including TNF-α, IL-1, IL-6, IL-8, and IL-12, were not significantly different between the 2 groups. Patients with AKI had significantly lower levels of albumin at nadir and discharge. A higher proportion of patients with AKI compared to those without AKI were exposed to inotropes (27.6 vs 11.5%,$p=0.04$), vasopressors (79.3 vs 43.3%,$p=0.001$) and mechanical ventilation (24.1 vs 3.8%,$p=0.002$). Urine protein to creatine ratios were similar between AKI and non-AKI patients. Patients with AKI were more likely to have received steroids (55.2 vs 24%,$p=0.003$) and/or anakinra (93.1 vs 59.6%,$p<0.001$), than those without AKI.

Conclusions: The degree of elevation in CRP reflects the hyperinflammatory state in MIS-C patients, which corresponded with AKI development. MIS-C patients who required ventilatory and cardiac support had higher rates of AKI. Receiving steroids and/or anakinra reflects the severity of illness in patients with AKI. This is the largest single center study, to our knowledge, of features and risk factors for AKI in children with MIS-C.

FR-PO711

Predicting Mortality Risk in Neonatal Patients with AKI with an Artificial Neural Network Algorithm

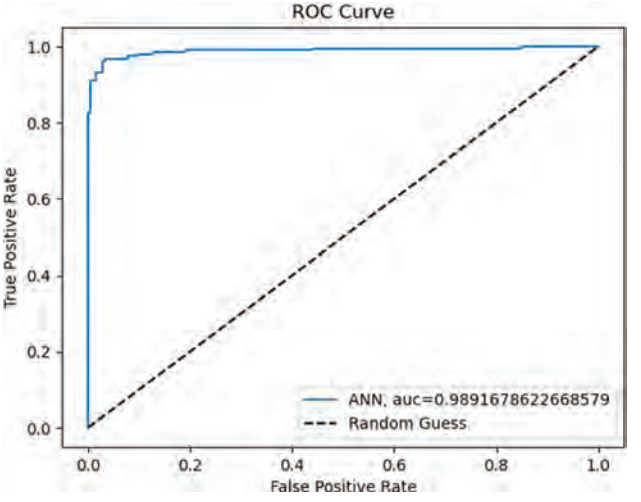
Aadi H. Pandya, Arnav Vyas, Maximilian Dawson, Sidharth K. Sethi, Kianoush Kashani, Rupesh Raina. *Akron Nephrology Associates/Cleveland Clinic Akron General Medical Center, Akron, OH.*

Background: Acute Kidney Injury (AKI) presents a substantial burden in healthcare, especially in the neonatal intensive care unit. Physiological variability and limited biomarkers complicate care for neonatal patients, and artificial intelligence shows promise for clinical implications in neonatal AKI.

Methods: Five deep learning models were tested with two independent neonatal patient datasets sourced from eleven healthcare centers. Data preprocessing techniques were enforced to amalgamate these datasets, followed by SMOTE to augment the imbalanced deceased patient class. The data was subsequently split into training and testing cohorts. Initial modeling was conducted with 36 training features, after which feature reduction techniques, including Recursive Feature Elimination, were utilized to isolate the top ten most influential features, creating parsimonious models.

Results: From both datasets, 1,362 patients with a median age of 14.10 hours were included in this study. The chosen algorithm was a custom-constructed Keras sequential artificial neural network (ANN) architecture with excelling validation-cohort metrics: AU-ROC = 0.9859; AU-PRC = 0.9919; accuracy = 0.9731; sensitivity = 0.9657; specificity = 0.9805. Given ten patient parameters for a neonate patient at risk of AKI, the model calculates a mortality risk level, which can be further utilized to dictate the potential intensification of patient treatment procedures. The robustness and generalizability of the ANN-based model were confirmed through K-fold cross-validation studies.

Conclusions: This study implements an ANN algorithm to predict mortality risk for neonates susceptible to AKI based on ten input parameters. Utilizing this healthcare-based deep learning model provides insight to aid physicians in patient management.



FR-PO712

Perceptions and Practice Surrounding Pediatric CRRT Liberation

Evan A. Rajadhyaksha,[1] Dana Y. Fuhrman,[4] David T. Selewski,[3] Shina Menon,[2] Katja M. Gist,[5] Michelle C. Starr.[1] *[1]Riley Hospital for Children at Indiana University Health, Indianapolis, IN; [2]Seattle Children's Hospital, Seattle, WA; [3]Medical University of South Carolina, Charleston, SC; [4]UPMC, Pittsburgh, PA; [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

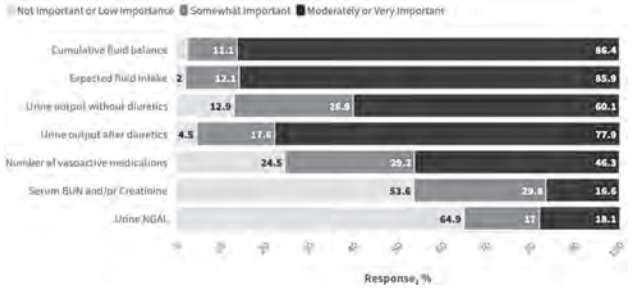
Background: Recent work by WE-ROCK reports a lower likelihood of Continuous Renal Replacement Therapy (CRRT) liberation with longer duration of therapy or low urine output. However, approaches to CRRT liberation and factors influencing decision-making remain inadequately studied.

Methods: A survey was distributed internationally through WE-ROCK to characterize perceptions and practice surrounding CRRT liberation in pediatric patients.

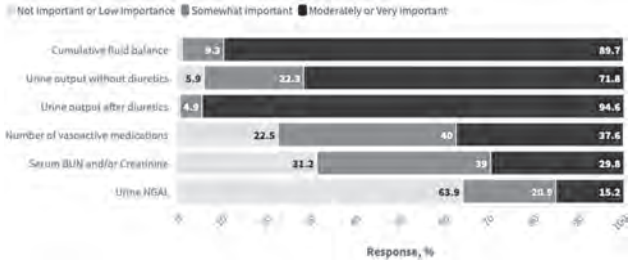
Results: Of 206 respondents, 37% were nephrologists and 63% were intensivists. Fourteen countries were represented (85% USA). Few (4%) reported an institutional standardized approach to CRRT liberation, though 28% had a personal approach. Reported approaches most often (59%) included loop and thiazide diuretics, given at median 4h after stopping CRRT (IQR 2-6h). Cumulative fluid balance and expected fluid intake were rated the most important factors in determining readiness to attempt liberation **(Figure 1A)**, followed by urine output in response to diuretics. Cumulative fluid balance and urine output in response to diuretics were considered most important in determining CRRT liberation success **(Figure 1B)**. Nephrologists were more likely than intensivists to rate native urine output (73% vs. 48%, $p=0.01$) and number of vasoactive medications (62%

vs. 38%, *p*=0.04) as important determinants of readiness to attempt CRRT liberation, and they placed higher importance on spontaneous urine output (85% vs 65%, *p*=0.03) for determining successful liberation.

Conclusions: These findings provide a first look at current CRRT liberation practices in pediatrics. Variation in approach to CRRT liberation and differences in stakeholders' perceptions of factor importance highlight the need for further research and standardization.



Factors in Determining Readiness to Liberate from CRRT



Factors in Determining CRRT Liberation Success

FR-PO713

Rasburicase for Treatment of Hyperuricemia-Related Neonatal AKI

Evan A. Rajadhyaksha, Michelle C. Starr. *Riley Hospital for Children at Indiana University Health, Indianapolis, IN.*

Introduction: Up to 10% of neonates with Trisomy 21 (T21) will develop Transient Myeloproliferative Disorder (TMD). Though tumor lysis syndrome (TLS) has been described with treatment of TMD, acute kidney injury (AKI) from hyperuricemia without TLS in this population has not been reported. We describe the case of a preterm neonate with T21, TMD-spectrum leukocytosis, and hyperuricemia-related AKI who was treated with recombinant uricase.

Case Description: A 31 weeks' gestation, low-birth weight neonate was born with T21 and severe leukocytosis (56,000 k/cumm) with blasts, along the spectrum of TMD. Hyperuricemia (8.6 mg/dL) followed, and with elevated lactate dehydrogenase (1516 U/L) was presumptively secondary to high cell turnover. Within the first 3 days of life, he developed stage 3 AKI, with rising urea (BUN) and creatinine (Cr) and decreased urine output, for which the nephrology team was consulted. Suspecting his rapidly progressive AKI may be secondary to hyperuricemia-related injury, and with the goal of avoiding renal replacement therapy (RRT) given the considerable risk associated with initiating RRT in an infant this size (1750 g), a single dose of rasburicase (0.2 mg/kg) was administered to treat the hyperuricemia. Following administration, BUN and Cr dropped precipitously (Figure 1), urine output increased by 67%, and he avoided RRT.

Discussion: Given his T21 and TMD, this neonate was at increased risk for hyperuricemia, and his response to rasburicase suggests that he suffered from hyperuricemia-related AKI. Uric acid mediates AKI through both reduction in renal blood flow and proximal tubule (PT) toxicity, and he may have been particularly susceptible to this PT toxicity given his prematurity. This case demonstrates that hyperuricemia should be considered in the differential for AKI in neonates with T21 and TMD-spectrum disease, and that recombinant uricase is an effective treatment that may help to preserve kidney function and avoid RRT.

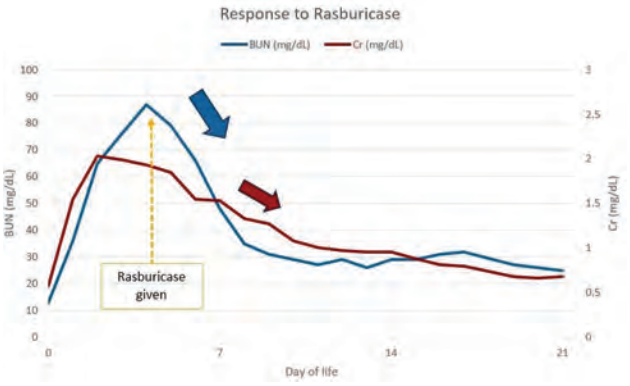


Figure 1. Trend in kidney function tests (BUN and Cr) following rasburicase on day of life 4.

FR-PO714

Advantages of Acute Peritoneal Dialysis in Children: Lessons from a Large Escherichia coli O157:H7 Outbreak in Calgary

Naji Al Dhawi,[1,2] Susan M. Samuel,[1,2] Lorraine A. Hamiwka,[1,2] Andrew W. Wade,[1,2] Alyssa J. Archibald,[1,2] Silviu Grisaru.[1,2] *[1]Alberta Children's Hospital, Calgary, AB, Canada; [2]University of Calgary, Calgary, AB, Canada.*

Introduction: Technical innovations in extracorporeal kidney replacement equipment have significantly expanded the availability of these modalities for children and small infants with oligo-anuric acute kidney injury (AKI), rapidly replacing the traditional preference for acute peritoneal dialysis (APD) in this age group. In September 2023, an unprecedented outbreak of O157:H7 Shiga toxin-producing E. coli (STEC), predominantly affecting daycare children aged 2 to 4 years, occurred in Calgary, AB, Canada. Infections were acquired from contaminated food item provided by a central kitchen to multiple daycares. This report aims to highlight the advantages of APD during this outbreak.

Case Description: 356 children tested positive for Shiga toxin 1 and 2, having been infected with an E. coli O157:H7 pathogen. Approximately 250 exhibited symptoms of gastroenteritis, and 27 children developed hemolytic uremic syndrome (STEC-HUS), characterized by anemia, thrombocytopenia, and acute kidney injury. A consistent management approach to oligo-anuria associated with (STEC-HUS) was applied. Transfusions of packed red cells were performed as necessary; however, platelet transfusions were avoided, and antibiotics were reserved for prophylactic prevention of peritonitis and management of other confirmed infections. Within 4 days (September 4 – 8), seven swan neck PD catheters were inserted by two pediatric urologists in children who developed oligo-anuria secondary to STEC-HUS. Continuous PD was performed in 8 children on pediatric wards for an average of 10.3 ± 2.4 days. Two children experienced serious extrarenal complications, but there were no fatalities, and all affected children recovered normal estimated glomerular filtration rates by three months post-infection.

Discussion: In children, APD remains an effective form of acute kidney replacement therapy (KRT), that is accessible outside intensive care units. Since this is an important advantage in an outbreak scenario, pediatric centers should maintain skills and capacity necessary to initiate APD in large numbers of children. In addition, outcomes of childhood oligo-anuric STEC-HUS may be influenced by the choice of acute KRT modality, a hypothesis that needs to be explored in prospective clinical trials.

FR-PO715

Urinary Neutrophil Gelatinase-Associated Lipocalin in Preterm Neonates

Nicole Asdell,[1] Tahagod Mohamed,[1] Shivam Joshi,[2] Elizabeth Bonachea,[1] Jonathan L. Slaughter.[1] *[1]Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University, Columbus, OH.*

Background: Acute kidney injury (AKI) is common in hospitalized preterm neonates. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) is a promising noninvasive biomarker for detection of AKI. However, normal values of uNGAL in preterm neonates without AKI are poorly characterized limiting its' clinical utility in this population.

Methods: Neonates born < 32 weeks GA admitted to our level IV NICU who didn't have AKI, UTI, NEC, or sepsis were included. Urine was collected in the first postnatal week (n=100) and patients were categorized to 3 GA groups (23-25, 26-28, 29-31 weeks). uNGAL and urine creatinine (uCr) concentrations were evaluated using immunoturbidimetry and an enzymatic assay respectively. The Chi-squared test was used to examine the association between categorical variables and GA groups, while the Kruskal-Wallis rank sum test and ANOVA were used to identify differences in the distribution of continuous variables across GA groups. Pearson's correlation assessed

the relationship between GA and uNGAL and GA and the uNGAL/uCr ratio. Statistical significance was determined at an alpha level of 0.05.

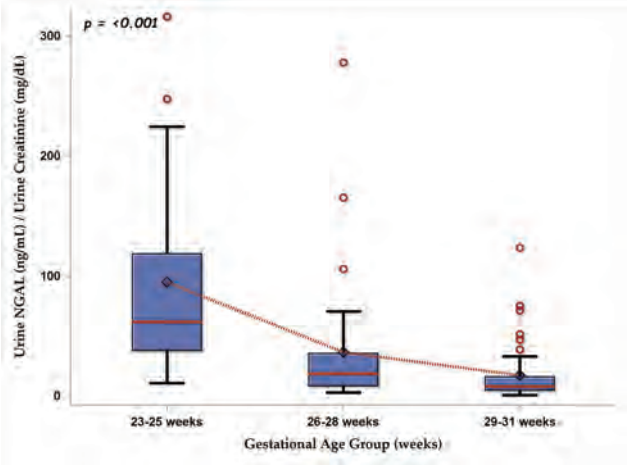
Results: The median uNGAL for infants born 23-25, 26-28, and 29-31 weeks were 653, 205, and 78 ng/dL respectively. Similarly, the uNGAL/uCr ratios at these GA were 62,19, and 7.9 ng/dL respectfully. Baseline concentrations of both uNGAL (R=-0.606, p<0.001) and uNGAL/uCr (R=-0503, p= <0.0001) decreased as GA increased.

Conclusions: Baseline urinary NGAL levels were shown to be elevated in preterm neonates. NGAL is present in the urine as early as 23 weeks gestation and its' concentration decreases with increasing gestational age.

Funding: Private Foundation Support

uNGAL by GA

Variable		N	Overall N=100	23-25 weeks N=23	26-28 weeks N=36	29-31 weeks N=41	P-Value	Metrics
Sex	F M	100	40 (40%) 60 (60%)	8 (34.78%) 15 (65.22%)	13 (36.11%) 23 (63.89%)	19 (46.34%) 22 (56.66%)	0.556	N (%) N (%)
Urine Creatinine		100	10.65 (6.9,15.8)	7.1 (4.6,10.9)	11.5 (6.85,16.05)	11.6 (9,16.1)	0.038	Median (Q1, Q3)
Urine NGAL		100	178 (73,428.5)	653 (210,1034)	205 (93,323)	78 (42,252)	<.001	Median (Q1,Q3)
BW (g)		100	1129.88 (341.60)	729.26 (126.07)	1058.61 (203.69)	1417.20 (249.58)	<.001	Mean (SD)
Urine NGAL/Urine Creatinine		100	17.49 (6.36,50.58)	61.52 (37.10,118.93)	18.51 (7.67,35.94)	7.86 (4.00,16.39)	<.001	Median (Q1, Q3)



FR-PO716

Plasma Renin as a Biomarker for AKI and Mortality in Neonates Undergoing Mechanical Circulatory Support

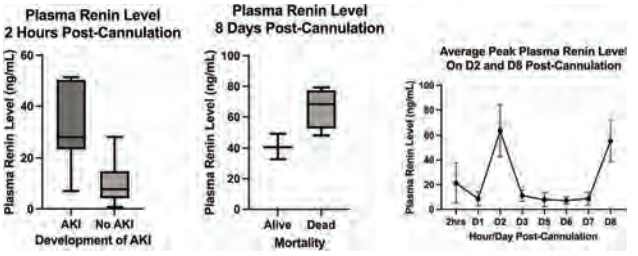
Michael F. Young, Esther Y. Pascal, Vidhi Tyagi, John D. Spencer, Andrew R. Yates, Tahagod Mohamed. *Nationwide Children's Hospital, Columbus, OH.*

Background: Extracorporeal membrane oxygenation (ECMO) is a life-saving intervention for neonates with severe cardiorespiratory failure. Acute kidney injury (AKI) is associated with mortality in children receiving ECMO. Renin is essential for homeostasis and has been studied as a novel biomarker for predicting AKI and mortality in critically ill adults. Its role as biomarker for AKI and mortality in neonates requiring ECMO support is unknown. We hypothesized that neonates who develop AKI have higher plasma renin levels following ECMO initiation.

Methods: Single center study evaluating term neonates admitted to the ICU at Nationwide Children's Hospital requiring ECMO support between 3/2015 and 12/2018. Baseline renal function was normal in all neonates prior to initiating ECMO. Plasma renin levels were collected daily beginning 2 hours through day 8 after cannulation and analyzed using ELISA. Diagnosis of AKI was based on KDIGO.

Results: Cohort included 12 term neonates with 13 ECMO initiations. The most common comorbidities were congenital diaphragmatic hernia (58%, N = 7) and congenital heart disease (42%, N = 5). Most patients were initially placed on venous-arterial (VA) ECMO (85%, N = 11). Mortality rate was 67% (N = 8). Plasma renin levels were highest on days 2 and 8 post-cannulation, regardless of circuit type. On average, day 2 levels were 7-fold higher and day 8 levels were 6-fold higher than day 1 levels. There was no significant difference between peak plasma renin levels on days 2 and 8 (p = 0.38). Higher levels of plasma renin 2 hours and 8 days after cannulation were associated with development of AKI (p = 0.015) and mortality (p = 0.036), respectively.

Conclusions: Elevated plasma renin 2 hours after cannulation and day 8 post-cannulation was associated with AKI and mortality, respectively suggesting that plasma renin can be used as a prognostic biomarker in neonates receiving ECMO. Further studies should evaluate the renin-angiotensin-aldosterone system as a potentially modifiable target in preventing AKI and mortality in patients receiving ECMO.



FR-PO717

Quantification of Uremic Toxins in Pediatric CKD: A Potential Biomarker and Mechanistic Driver of Cardiorenal Syndrome

Heshini Dalpathadu,[1] Andrew W. Wade.[2,1] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]Alberta Children's Hospital Research Institute, Calgary, AB, Canada.*

Background: Cardiovascular disease is the leading cause of morbidity and mortality among pediatric chronic kidney disease (CKD) patients. This pathological interaction between the heart and kidneys, known as cardiorenal syndrome (CRS), may be caused by the accumulation of uremic toxins. Compared to adults, CRS is understudied in pediatric patients, and consequently, their composition and levels of uremic toxins are not well established. Currently, there are no definitive clinical guidelines for treating cardiovascular complications in pediatric CKD patients. Furthermore, findings from adults cannot be extrapolated to children due to the presence of preexisting cardiac (and chronic) disease in this population.

Methods: To address this gap in knowledge of CRS in children, we collected blood samples longitudinally from pediatric patients (mean age 8.3±4.9 years; 58.3% males and 41.7% females). These included 3 CKD patients with cardiac dysfunction, 3 CKD patients with resolved cardiac dysfunction, and 6 control patients who had CKD without cardiac dysfunction. Cardiac dysfunction was defined as cardiac ejection fraction <50%.

Results: In children with CKD and no cardiac dysfunction (n=13), concentrations of indoxyl sulfate (IS) and fibroblast growth factor-23 (FGF23) were 355.1±147.9 ng/mL and 54.1±45.5 ng/mL, which are 24-fold lower and 42-fold higher, respectively than levels seen in adults. Levels of p-cresyl sulfate (4.0±1.3 ng/mL) and trimethylamine N-oxide (34.1±11.5 ng/mL) (n=28) were not significantly different from adults. In patients with CKD and ongoing cardiac dysfunction (n=3), IS and FGF23 concentrations increased to 3,245.3±431 ng/mL and 2,206.7±974.9 ng/mL, respectively. The levels of IS and FGF23 normalized in children whose cardiac dysfunction resolved (n=5). We further investigated these findings using an *in vitro* model. Human induced pluripotent stem cells were differentiated to beating cardiomyocytes and exposed to IS (4000-8000 ng/mL). Following exposure, initial results show that the beating rate decreased from 52±15 to 26±7 beats per minute.

Conclusions: Our results highlight important pediatric differences in the serum concentrations of IS and FGF23. Our in vitro model recapitulates the effects of uremic toxins on cardiac function and provides insight into the mechanism of cardiorenal syndrome.

FR-PO718

Clinical and Genetic Differences between Congenital and Infantile Nephrotic Syndrome

Yuta Inoki, Tomoko Horinouchi, Yuka Kimura, Yuta Ichikawa, Yu Tanaka, Chika Ueda, Hideaki Kitakado, Atsushi Kondo, Nana Sakakibara, Tomohiko Yamamura, Shingo Ishimori, China Nagano, Kandai Nozu. *Department of Pediatrics, Kobe University Graduate School of Medicine, Hyogo, Japan.*

Background: More than half of the patients with congenital nephrotic syndrome (CNS) or infantile nephrotic syndrome (INS) are known to have a monogenic etiology. However, the difference in clinical course, disease-causing gene, and genotype-phenotype correlation between genetic CNS and INS remains unknown.

Methods: Patients diagnosed with nephrotic syndrome within the first year of life and referred to our hospital for genetic analysis were enrolled. In patients with identified causative genes, characteristics and their renal outcome were compared between CNS and INS patients.

Results: Among 74 patients enrolled, disease-causing genetic variants were detected in 52 patients. The median age at development of end-stage kidney disease (ESKD) in the CNS and INS groups was 13.2 and 20.0 months old, respectively ($P = 0.13$). Compared to the CNS patients with *NPHS1* variants, the age at development of ESKD was significantly earlier in CNS patients with the other variants (1.0 vs. 31.0 months old; $P < 0.001$). In patients with pathogenic variants other than *NPHS1*, there was significant difference in the age at development of ESKD between CNS and INS patients (1.0 vs. 17.0 months old; $P < 0.001$). All INS patients with *NPHS1* variants had no truncating variants. Patients with no truncating variant did not develop ESKD during follow-up, and the age at ESKD

in patients with no truncating variant was significantly later than in those with biallelic or monoallelic truncating variants (- vs 31.0 months old; $P = 0.025$). In addition, among patients with *WT1* pathogenic variants, those with severe variants, exon 8 or 9 missense variants in DNA-binding regions, developed ESKD significantly earlier than those without severe variant (1.5 vs. 15.0 months old; $P = 0.0058$). All of the CNS patients and 37.5% (3/8) of the INS patients had severe variants.

Conclusions: Our findings suggest that whether CNS onset or INS onset could influence renal prognosis in patients with genetic nephrotic syndrome who are less than 1 year old. Moreover, among patients with pathogenic variant in the same gene, INS patients can be more likely to have a mild genotype and good renal prognosis.

FR-PO719

A Novel Multimethylation Site Assay to Predict Steroid-Resistance in Initial Treatment of Nephrotic Syndrome

Wang Yinfeng,[1,2] Junzhen Zhu,[2] Tingya Jiang.[2] *[1]Jiangsu University, Zhenjiang, China; [2]AlloDx Biotech, Shanghai, China.*

Background: Approximately 20% of nephrotic syndrome (NS) patients exhibit steroids-resistant nephrotic syndrome (SRNS). If SRNS can be identified prior to the initial treatment, potential adverse effects associated with subsequent steroid use can be reduced by employing alternative immunosuppressive agents. Current research shows that about 30% of SRNS are caused by genetic mutations associated with podocytes. However, the causes of the other of 70% SRNS cases are unknown. In this study, we confirmed the correlation of gene methylation changes with SRNS and established an REscore to predict SRNS by detecting the multi-CpG sites of specific gene

Methods: Frozen peripheral blood mononuclear cell (PBMC) samples from 25 non-genetic NS patients (12 SRNS and 13 non-SRNS) were retrospectively enrolled in this study. Systematic investigation into the DNA methylation in the promoter regions of three genes: NLRP3,NR3C1 and CASP1. Multiplexed target bisulfite sequencing (Target-BS) and a risk prediction model (Random Forest, RF) were established to distinguish SRNS and non-SRNS with 15 patients for training and 10 patients for validating

Results: We investigated 37 CpG sites covered in total,and finally found out that 7 sites showed significant differences between the SRNS and non-SRNS group ($p < 0.05$). The 7 sites were analyzsed using RF model to obtain a resistance score (REscore) for predicting the response to steroid in NS. The results of the ROC analysis showed an AUC of 0.98,sensitivity of 90%,specificity of 100%,with a cutoff value REscore is 0.74,positive predictive value (PPV) was 100%,and the negative predictive value (NPV) was 93.3% in the training set. In the validation set,the RF model achieved an AUC of 0.92,sensitivity of 83.3%,specificity of 100%,PPV of 100%, and NPV of 80%

Conclusions: In conclusion, this study identified significant changes methylation markers in the NLRP3,NR3C1 and CASP1 genes in patients with SRNS. Furthermore,the RF model was used to create the REscore, which can effectively predict the risk of SRNS. It is need more samples and more pathological type of nephropathy to verify the conclusion of this study in future

FR-PO720

Comparative Effectiveness of Cyclophosphamide and Calcineurin Inhibitors in Childhood Nephrotic Syndrome

Cal Robinson,[1,2] Josefina A. Brooke,[1] Rahul Chanchlani,[3] Brian H. Cuthbertson,[4] Vaneet Dhillon,[1] Eddy Fan,[2] Christoph Licht,[1] Ashlene M. McKay,[1] Damien G. Noone,[1] Rachel J. Pearl,[1] Seetha Radhakrishnan,[1] Veronique Rowley,[1] Chia Wei Teoh,[1] Jovanka Vasilevska-Ristovska,[1] Rulan S. Parekh.[5] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]McMaster Children's Hospital, Hamilton, ON, Canada; [4]Sunnybrook Research Institute, Toronto, ON, Canada; [5]Women's College Hospital, Toronto, ON, Canada.*

Background: Nephrotic syndrome is a common pediatric kidney disease with high morbidity. Cyclophosphamide and calcineurin inhibitors are the most used second-line medications, but their comparative effectiveness is unknown.

Methods: Using target trial methods, we emulated a pragmatic, open-label clinical trial using Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics study data. We included children (1-18yr) diagnosed with nephrotic syndrome from 1996-2019 in Toronto, Canada that initiated cyclophosphamide or calcineurin inhibitors. Randomization was emulated by propensity score overlap weighting. The primary outcome was time-to-relapse, analyzed by weighted Cox proportional hazards models.

Results: Of 578 children, 252 started cyclophosphamide and 131 calcineurin inhibitors. Baseline characteristics were balanced after propensity score weighting. During median 5.5-year (IQR 2.5-9.2) follow-up, there was no difference in relapses after calcineurin inhibitor vs. cyclophosphamide (HR 1.25, 95%CI 0.84-1.87). There were also no differences in relapses by 1, 2, or 5-years, hypertension, or chronic kidney disease. Calcineurin inhibitor use was associated with hospitalization (HR 1.83, 95%CI 1.14-2.92) and intravenous albumin use (HR 2.81, 95%CI 1.65-4.81).

Conclusions: There was no difference in risk of relapse after cyclophosphamide vs. calcineurin inhibitor treatment in childhood nephrotic syndrome. Cyclophosphamide treatment is shorter in duration and more accessible in low-to-middle income countries.

Funding: Government Support - Non-U.S.

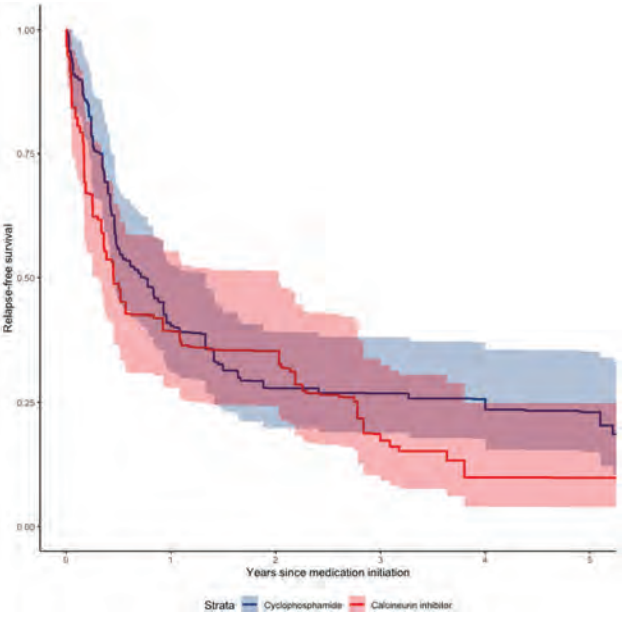


Figure. Weighted relapse-free survival after cyclophosphamide vs. calcineurin inhibitor initiation

FR-PO721

An Increase in TCR/BCR Repertoire Clonality by Prednisolone Therapy and Recovery of the Diversity by Rituximab in Childhood Idiopathic Nephrotic Syndrome

Tomoko Horinouchi,[1] Yuka Kimura,[1] Yuta Inoki,[1] Yuta Ichikawa,[1] Yu Tanaka,[1] Hideaki Kitakado,[1] Chika Ueda,[1] Nana Sakakibara,[1] China Nagano,[1] Tomohiko Yamamura,[1] Junya Fujimura,[2] Naohiro Kamiyoshi,[3] Shingo Ishimori,[1,4] Hiroshi Kaito,[5] Yuko Shima,[6] Yukio Nakamura,[7] Asako Sakai,[8] Izumi Okugaito,[8] Kandai Nozu,[1] Kazumoto Iijima.[9,10] *[1]Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan; [2]Department of Pediatrics, Kakogawa Central City Hospital, Kakogawa, Japan; [3]Department of Pediatrics, Japanese Red Cross Society Himeji Hospital, Himeji, Japan; [4]Department of Pediatrics, Takatsuki General Hospital, Takatsuki, Japan; [5]Department of Nephrology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan; [6]Department of Pediatrics, Wakayama Medical University, Wakaya, Japan; [7]Repertoire Genesis Inc., Ibaraki, Japan; [8]Zenyaku Kogyo Co., Ltd., Tokyo, Japan; [9]Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan; [10]Department of Advanced Pediatric Medicine, Kobe University Graduate School of Medicine, Kobe, Japan.*

Background: In diseases related to autoimmunity, it is known that the T-cell receptors (TCR) / B-cell receptors (BCR) repertoire along with lymphocyte subpopulations exhibits various characteristics, but there is no data available for idiopathic nephrotic syndrome (NS) in children.

Methods: We conducted TCR / BCR repertoire analysis on peripheral blood mononuclear cells using high-throughput sequence method on 45 pediatric nephrotic syndrome patients and 11 non-nephrotic individuals with abnormal urinalysis as controls, totaling 96 samples (control n=11; initial-onset NS n=70; complicated NS with rituximab (Rtx) treatment n=15).

Results: There was no significant difference in the diversity of TCR/BCR repertoires between the control group (n=11) and the initial-onset pretreatment NS group (n=36). When comparing pairs before and after prednisolone (PSL) therapy (n=34), the diversity of TCR/BCR repertoire was decreased; Shannon index (e.g. TRA 6.99 (SD 0.99) vs 6.05 (SD 1.17) $p<0.0001$, IgM 7.79 (SD 0.85) vs 7.52 (SD 0.91) $p<0.03$). In patients with pre-Rtx treatment complicated NS (n=9), the diversity of TCR/BCR repertoire was decreased significantly compared to patients with initial-onset NS; Shannon index (e.g. TRA 6.97 (SD 0.97) vs 5.32 (SD 1.15) $p<0.0003$, IgM 7.78 (SD 0.86) vs 6.69 (SD 0.83) $p<0.003$). After Rtx treatment, when B cells recovered, recovery of the diversity was also observed (n=6).

Conclusions: While no changes were observed in initial-onset NS, PSL treatment led to an increase in specific clones. A decrease of diversity in TCR/BCR repertoires was seen in complicated NS requiring Rtx, while diversity recovered after rituximab administration, likely promoting restoration of immune tolerance.

Funding: Commercial Support - Zenyaku kogyo

FR-PO722

Risk Factors for Rituximab Dependency in Pediatric and Young-Adult Patients with Refractory Nephrotic Syndrome

Nao Uchida. *Tohoku University Hospital Department of Pediatrics, Sendai, Japan.*

Background: Rituximab (RTX) has been shown to be effective for childhood-onset refractory nephrotic syndrome and is being administered worldwide. While steroid discontinuation is possible in many patients after RTX, a certain number of patients cannot be weaned from RTX administration due to relapses of nephrotic syndrome after B cell recovery.

Methods: this is a single-center, retrospective study. Twenty-five patients with refractory nephrotic syndrome who received RTX at our department from January 2011 to November 2021 were recruited in this study. They were divided into two groups; a group that could not be weaned from RTX administration (group A) and a group that could be controlled without RTX for more than two years (group B).

Results: There were 10 patients in group A (male:female = 7:3) and 15 patients in group B (male:female = 7:8). The patients in group A had a significantly higher age at first RTX administration than the patients in group B (12±4.0; 7.8±3.7 years, $p<0.05$), and a longer period from the onset of nephrotic syndrome to RTX administration (8.1±4.0; 4.1± 3.2, year, $p<0.05$). The IgG level at the first administration was significantly higher in group A (708.8±220.0; 467.2±263.6, mg/dL, $p<0.05$), perhaps due to the older age of the patients, but the IgG levels at the final examination were not significantly different between the two groups (649.5±244.7; 723.8±337.2, mg/dL, $p=0.59$). There was no significant difference in age at onset between the two groups (3.9±1.7; 3.7±3.3 years, $p=0.82$).

Conclusions: The rate of RTX dependence was as high as 40% in our hospital. The age at the first RTX administration was higher in the dependent group (group A), suggesting a relationship between the immunological developmental process and the efficacy and sensitivity of RTX. Because side effects of long-term use of RTX have not been fully understood, we should be cautious in maintaining therapy with RTX. Limitations were; 1) the number of patients who were analyzed in this study was small; 2) the preference of RTX was affected by other factors due to the fact that RTX has few side effects regarding blood pressure, blood glucose level or physical appearance, with the exception of infusion reactions and various kinds of immunological deficits.

Funding: Government Support - Non-U.S.

FR-PO723

Urinary Lipid Biomarkers Predict Progression in Focal Segmental Glomerulosclerosis

Jacob A. Humphrey,[1] Aaron M. Armando,[2] Oswald Quehenberger,[2] Jonathan P. Troost,[3] Elif Erkan.[1] *[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]University of California San Diego, La Jolla, CA; [3]University of Michigan, Ann Arbor, MI.*

Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common glomerular cause of pediatric end stage kidney disease. We propose that patients with FSGS display a unique milieu of urinary and serum free fatty acid (FFA) and phospholipid (PL) profiles that can serve as biomarkers for prediction of diagnosis and prognosis in FSGS.

Methods: Urine and serum samples were obtained from 30 patients with FSGS and MCD as an ancillary study to Nephrotic Syndrome Study Network (NEPTUNE) cohort. Healthy controls were obtained from Discovery biobank, Cincinnati Children's Hospital. We included patients aged 2-21 years with biopsy proven FSGS or MCD, urine protein to creatinine ratio (UPCR) of >1 and eGFR >60mL/min/1.73m^2. We excluded patients with DM, systemic disease, organ/bone marrow transplantation, or known genetic cause of FSGS. Targeted lipidomic analysis was performed by mass spectrometry to measure PL and FFA in samples. Disease progression was defined as a 20% decrease in eGFR. Logistic regression models with unadjusted/adjusted models for age, race and proteinuria were utilized to determine ROC curves and AUC.

Results: Mean follow up was 48 months (IQR 30-56 months). Serum arachidic acid ($p = 0.02$) and very long chain fatty acid (VLCFA) cerotic acid ($p = 0.02$) were elevated in FSGS patients. Urinary omega-3 FA, eicosapentaenoic acid (AUC 0.86, $p = 0.0007$) and omega-6 FA, arachidonic acid (AA) (AUC 0.76, $p=0.002$) and AA by products polyunsaturated adrenic acid (AUC 0.9, $p = 0.01$), docosapentaenoic acid (n3 and n6, AUC 0.93 and 0.84, $p = 0.003$ and 0.01, respectively) and PL metabolite lysophosphatidylcholine (LPC)(AUC 0.8, $p = 0.004$) predicted FSGS progression by univariate analysis in adjusted and unadjusted models.

Conclusions: Lipidomic analysis of serum and urine samples provided key information in pathophysiology of FSGS and identified potential biomarkers. Elevated serum levels of VLCFA in patients with FSGS suggest peroxisomal dysfunction and defective fatty acid β oxidation. Elevated urine AA and its metabolites in association with membrane PL and LPC serve as potential biomarkers for progression in FSGS. We postulate that increased activity of proinflammatory AA and LPC driven by phospholipase A2 contributes to progression in FSGS.

Funding: Other NIH Support - National Center for Advancing Translational Sciences (NCATS)

FR-PO724

Corticosteroids Augment Cyclosporine Nephrotoxicity in Pediatric Nephrotic Syndrome: Potential Role of CD163+ M2-type Macrophage

Yuji Matsumoto, Tomomi Kondo, Takuma Ando, Naonori Kumagai, Yohei Ikezumi. *Fujita Health University School of Medicine Department of Pediatrics, Toyoake, Japan.*

Background: Cyclosporin A (CsA) is an effective steroid-sparing agent for patients with steroid-dependent nephrotic syndrome (SDNS), however, it can cause chronic interstitial damage. We previously reported that alternativley-activated (M2) macrophages (MQ) are intimately involved in interstitial fibrosis pathogenesis in chronic progressive kidney disease. In this study, we investigated the possible involvement of M2 MQ in CsA nephrotoxicity in SDNS.

Methods: A total of 33 children diagnosed with SDNS who were treated with CsA for more than 2 years were investigated. Thirteen biopsy specimens from age-matched SDNS children who had not received CsA treatment were used as the control. Renal fibrosis was assessed by Masson chrome staining of biopsy sections. Sections were also stained for α-smooth muscle actin (α-SMA), type I collagen, CD68 (total MQ) and CD163 (M2 marker). Urine levels of CCL2 were measured by ELISA. Cultured human monocyte-derived MQ were stimulated with dexamethasone (Dex) for 48hr and RNA levels compared to control cells.

Results: The CsA-treated group showed a significant increase in interstitial fibrosis (10.8 vs 6.7%, $P<0.001$) with accumulation of interstitial CD163$^+$CD68$^+$ MQ (10.8 vs 7.9/HPF, $P<0.001$) compared with SDNS control patients. There was a significant correlation between the degree of interstitial fibrosis and the number of interstitial CD163$^+$ cells ($p<0.001$), and between interstitial fibrosis and the dose of steroid used during CsA treatment ($p<0.001$), while no correlation was found between the dose of steroid used before CsA treatment and histological changes. Stimulation of MQ with Dex induced up-regulation of CD163 and cytokines and growth factors associated with inflammation and fibrosis (*CCL2*, *NOS1*, *NOS2*, *FGF-8*, *FGF-21* and *CTGF*). Immunostaining revealed significant expression of CTGF and CCL2 in biopsies from CsA group which co-localized with CD163$^+$MQ. In addition, the urine CCL2/creatinine ratio was increased 4-fold in CsA group vs control group (940.0 vs 204.1, $P=0.012$)

Conclusions: Our findings suggest that CD163$^+$ M2-type MQ may participate in the development of interstitial fibrosis induced by CsA. Steroid treatment during CsA treatment might contribute to augment CsA nephrotoxicity through the production of pro-fibrotic and pro-inflammatory factors.

Funding: Government Support - Non-U.S.

FR-PO725

Macrophage Activation Syndrome in an Adolescent Male with Dialysis-Dependent Kidney Failure and Systemic Lupus Erythematosus Flares

Subashini Azhagappa, Syeda Asfia Hussain, Asma B. Shaoba, Oluwatoyin F. Bamgbola. SUNY Downstate Pediatric Nephrology. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: MAS is a life-threatening dysregulation of the immune system that progresses to multisystem organ failure. It occurs typically in systemic juvenile idiopathic arthritis (sJIA) & rarely in SLE. We describe a unique instance in an adolescent male with SLE who developed MAS.

Case Description: This case is of a 17-year-old African American male with family history of severe SLE, diagnosed at age 12. He developed class IV lupus nephritis, deep vein thrombosis, & pulmonary embolism 2 years later. He failed therapy with Mycophenolate mofetil, Cyclophosphamide, Rituximab and Belimumab & was dialysis dependent in less than 1 year of kidney disease. Before the current illness, he had recurrent hypotension, pancytopenia, low complement, & high serological markers for 10 months. At presentation, he had fever, emesis, diarrhea & fluid-resistant hypotension. He recieved empiric antibiotics & pulse steroids, however, he developed respiratory failure, tonic-clonic seizure, hyperglycemia, and pancreatitis. Lab values were consistent with MAS (Fig 1), including HScore >250, signifying a >99% probability of MAS. MRI showed a chronic atrophic cerebral cortex. Infectious workup was negative. He responded to infusions of Anakinra.

Discussion: Severe SLE was complicated by MAS in our patient which is rare. Recurrent hypotension before MAS, suspicious of cytokine storm, has not been described. Rapid involvement of the liver, pancreas, central nervous system and acute increase in ferritin lead to a diagnosis. Frequent relapses, chronic cytopenia, intense immunosuppression, & intractable hypotension may precede MAS as seen in our case. Early treatment may reverse clinical deterioration, improving survival.

Fig 1: Laboratory data of a 17-year-old dialysis-dependent male with severe SLE that complicated by MAS compared to diagnostic criteria.

Laboratory Parameters	Measured value	Diagnostic Criteria
Hemoglobin (g/L)	9.5	≤9.0
White blood cell count (K/uL)	0.66	≤4.0
Platelet count (K/uL)	40	≤150
S. ferritin (ng/mL)	> 40,000	>500
S. fibrinogen (mg/dL)	105	≤150
S.triglycerides (mg/dL)	>1000	>178
Aspartate Aminotransferase (U/L)	506	>40
LDH (units/L)	363	>567
Clinical Criteria: Fever (>38°C) Hepatomegaly (≥3 cm below the costal margin) Splenomegaly (≥3 cm below the costal margin) Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding) Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)		

FR-PO726

Area Deprivation and Mineral Metabolism in Pediatric CKD

Marciana Laster,[1,2] Bradley A. Warady,[3,5] Susan L. Furth.[4] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Riley Hospital for Children at Indiana University Health, Indianapolis, IN; [3]University of Missouri-Kansas City School of Medicine, Kansas City, MO; [4]The Children's Hospital of Philadelphia, Philadelphia, PA; [5]Children's Mercy Kansas City, Kansas City, MO.*

Background: CKD-MBD is a comorbidity of CKD that leads to poor growth, fractures and cardiovascular death. Levels of PTH and vitamin D differ by racial-ethnic group. Given that race is a social construct that coincides with a disproportionate burden of poverty within minorities, a complete understanding of racial differences must consider socioeconomic status (SES). The objective of this study is to define the relationship between SES and MBD markers including phosphate, calcium, intact parathyroid hormone (PTH), and 25-hydroxyvitamin D (25OHD).

Methods: In 540 participants from the CKID cohort, we assessed the relationship between area deprivation index (ADI), median household income (MHI) and longitudinal CKD-MBD biomarkers using linear mixed effects models with backward selection (p value <0.1). Biologically relevant variables including age, sex, and medication use were maintained in all models. Categories of deprivation (high vs. low) were defined according to previous standards as a value >=113.45.

Results: 11.8% of participants lived in areas of high deprivation. Race differed between high and low deprivation cohorts (Table 1). In linear mixed effects models (Table 2), increasing deprivation was associated with lower 25OHD and increasing MHI with higher 25OHD. Stratification by Black and non-Black race demonstrated a persistent relationship but of greater magnitude in Black race. Of the other markers, only intact PTH demonstrated a trend with increasing MHI which predicted decreased PTH (Table 2).

Conclusions: Vitamin D status as reflected by 25OHD is related to area-level social metrics including ADI and median neighborhood income. Persistence upon racial stratification helps to untangle the structural contributors to vitamin D status. Further studies are needed to understand the specific contributors to this finding.

Funding: NIDDK Support

Table 1: Cohort Characteristics

	High Deprivation	Low Deprivation	p value
n	64	476	
Age	11.8 (4)	11.2 (4.4)	0.3
Sex			0.06
Male	32(50)	296 (62.2)	
Female	32 (50)	180 (37.8)	
Race			<0.0001
White	15 (23.4)	279 (58.6)	
Black	32 (50)	97 (20.4)	
Hispanic	17 (26.6)	66 (13.9)	
Asian	0	9 (1.9)	
Other	0	25 (5.3)	
Diagnosis			0.5
Glomerular	19 (29.7)	121 (25.5)	
Non-glomerular	45 (70.3)	354 (74.4)	
CKD Stage			0.7
1	3(4.7)	14 (2.9)	
2	16 (25)	118 (24.8)	
3	34 (53.1)	286 (60.1)	
4	10 (15.6)	55 (11.6)	
5	1 (1.6)	3 (0.6)	
Active Vitamin D			0.2
Yes	13 (20.3)	132 (27.7)	
No	51 (79.7)	344 (72.3)	
Nutritional Vitamin D			
Yes	7 (10.9)	48 (10.1)	0.8
No	57 (89.1)	428 (89.9)	
Phos z score	-0.3 (1.5)	-0.2 (1.5)	1
Calcium	9.5 (0.5)	9.5 (0.6)	0.4
IPTH	61.8 (58.6)	58.5 (61.7)	0.9
Vitamin D 25	24.5 (13)	28.4 (11.4)	0.004

Table 2: Linear Mixed Effects Models

Population	Outcome	Exposure	Beta (SE)	p value
Entire Cohort	25-OHD	ADI (worsening deprivation)	-0.07 (0.02)	0.003
Entire Cohort	25-OHD	MHI (improving MHI)	7.7 (2.11)	0.0003
Black	25-OHD	ADI	-0.2 (0.07)	0.02
Non-Black	25-OHD	ADI	-0.06 (0.02)	0.02
Entire Cohort	IPTH	MHI	-0.15 (0.08)	0.07

Backward Selection models (p<0.1) for 25OHD: age, sex, diagnosis, race, vitamin D use, CKD duration and stage selected out

FR-PO727

Bridging the Gap: Assessing Nephrology Transition Practices in Pediatric and Adult Care Settings

Andrew Vissing,[1,2] Priya S. Verghese,[2] Angelina M. Dixon,[3] Cybele Ghossein.[1] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [3]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: The transition from pediatric to adult care can be challenging for young adults living with kidney disease. The International Society of Nephrology has recommended establishing a transition process for this vulnerable population; however, the prevalence of transition clinics or standardized transition processes (established approaches for transitioning patients at an institution) is currently unknown. Our study surveyed pediatric and adult nephrology programs nationwide to explore the current state of transition practices.

Methods: Four different surveys were created to assess transition practices in adult and pediatric general nephrology and transplant nephrology care. Surveys were distributed via email to the leadership of academic general and transplant nephrology programs. Listservs and online forums were also used for survey distribution.

Results: The overall response rate for all four surveys was 38.5%. The percentage of programs that had transition clinics or an established process for transitioning care for young adult patients are shown in Table 1. Amongst adult and pediatric centers that indicated partnerships in transitions of care, a large discrepancy existed in how transitions were performed. Between affiliated adult and pediatric programs, 54.8% of general nephrology programs and 46.7% of transplant programs were misaligned in their reported transition of care procedures.

Conclusions: By examining the presence of transition clinics and processes, we reveal the lack of standardized transition planning for young adults with kidney disease. Furthermore, our study highlights the lack of coordination between affiliated adult and pediatric centers in implementing transition plans for this at-risk demographic. Future studies will aim at examining the benefits and obstacles of established transition clinics and processes.

Presence of Transition Clinics and Processes at Nephrology Programs

Programs	Programs with a Transition Clinic	Programs with a Transition Process	Programs without a Transition Clinic or Process
Adult General Nephrology (n=71)	13 (18.3%)	24 (33.8%)	34 (47.9%)
Adult Transplant Nephrology (n=37)	11 (29.7%)	15 (40.5%)	11 (29.7%)
Pediatric General Nephrology (n=49)	8 (16.3%)	28 (57.1%)	13 (26.5%)
Pediatric Transplant Nephrology (n=31)	6 (19.4%)	22 (71.0%)	3 (9.7%)

FR-PO728

Obstacles in Establishing Transition Clinics in Pediatric and Adult Medical Centers

Andrew Vissing,[1,2] Priya S. Verghese,[2] Angelina M. Dixon,[3] Cybele Ghossein.[1]
[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [3]University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: In 2011, the International Society of Nephrology published a consensus statement regarding the importance of a transition process from pediatric to adult care for young adults with kidney disease, ideally facilitated through transition clinics. Despite this recommendation, institutions continue to struggle with the transfer and transition of care for this group. Here we report on potential barriers to implementing this recommendation.

Methods: Four different surveys were created to assess transition practices in adult and pediatric general nephrology and transplant nephrology care. Surveys were distributed via email to the leadership of academic general and transplant nephrology programs. Respondents without a transition clinic were asked to identify the primary obstacles to establishing such a clinic. The identified obstacles were classified into one or more of the following categories: logistics, resources, provider-related, patient-related, or absence of need/obstacles. Fisher's exact test was used ($P < 0.05$) to compare frequencies of obstacles between the adult and pediatric programs.

Results: There were a total of 119 comments. The most frequently mentioned barrier for adult programs was resources (53%) and for pediatric programs was provider-related (52.8%). Patient-related obstacles were statistically less cited in adult programs compared to pediatric programs (1.5% vs 15.1%, $P = 0.01$). Adult programs were more likely to mention no perceived need/obstacles compared to pediatric programs (16.7% vs 3.8%, $P = 0.04$). There was no statistical difference in how frequently other obstacles were mentioned between the two groups.

Conclusions: Despite guidelines recommending pediatric to adult transition programs for young adults, transition clinics remain uncommon in nephrology transitions of care. Resource availability as well as provider-related obstacles, are the main perceived barriers by both pediatric and adult programs. Future work will involve understanding and overcoming these barriers.

Obstacles for Establishing a Transition Clinic

Obstacles	Adult Programs (n=66)	Pediatric Programs (n=53)	p-value
Logistics	17 (25.8%)	19 (35.8%)	0.32
Resources	35 (53.1%)	24 (45.3%)	0.46
Provider-related	29 (43.9%)	28 (52.8%)	0.36
Patient-related	1 (1.5%)	8 (15.1%)	0.01
No Perceived Need or Obstacles	11 (16.7%)	2 (3.8%)	0.04

FR-PO729

Molecular Regulation of Podocyte Development by Transcription Factor 21

Vidhi Dalal,[1,2] Yalu Zhou,[2] Dilip K. Deb,[2] Hiroshi Maekawa,[2] Margaret E. Fain,[2] Anthony Chang,[3] Eunah Chung,[2] Joo-Seop Park,[2] Susan E. Quaggin.[2]
[1]Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [2]Northwestern University Feinberg School of Medicine, Chicago, IL; [3]University of Chicago Pritzker School of Medicine, Chicago, IL.

Background: Transcription factor 21 (Tcf21) is expressed in developing podocytes from the S-shaped body onwards. Our laboratory previously showed that deletion of *Tcf21* from podocyte precursors at the S-shaped stage of glomerular development in mice resulted in abnormal podocyte morphology, impaired glomerular basement membrane (GBM) formation, and defects in foot process formation, underscoring a vital role for *Tcf21* in normal podocyte development and function. However, the molecular mechanism(s) by which *Tcf21* regulates podocyte development are not well-understood. To address this gap in knowledge, we performed single cell RNA sequencing (scRNAseq) of kidneys from mice with *Tcf21* deletion.

Methods: *Tcf21* was deleted from podocyte precursors at the S-shaped stage of glomerular development using Cre recombinase driven by the *Pax8* promoter. 2 mutant mice and 2 littermate controls were euthanized at 2 weeks of age, and their kidneys were subjected to single cell digestion. 20,000 cells were captured from each of the 4 samples for scRNAseq. Library preparation was completed, and the samples are awaiting sequencing.

Results: Mutant mice had substantial proteinuria (100-500 mg/dL versus negative to trace urine protein for littermate controls). On histology, proximal tubular protein reabsorption droplets were noted in kidneys of both mutant mice, and glomerular crescent formation was noted in the kidney of one mutant mouse. Kidneys from control mice appeared normal. The mutant mice did not have significant glomerulosclerosis, suggesting that podocyte injury was still in its early stages. ScRNAseq will be used to determine changes in expression of podocyte structural genes, GBM genes, and transcription factors after *Tcf21* deletion. The CellChat package in R will be used to identify changes in how mutant podocytes interact with surrounding glomerular cells.

Conclusions: *Tcf21* deletion from podocyte precursors caused proteinuria and severe defects in podocyte development. ScRNAseq is a first step to unravel the molecular mechanism(s) by which *Tcf21* regulates podocyte structure and the interaction of podocytes with other glomerular cells. Ultimately, understanding the mechanisms that are required for normal podocyte structure and function will also help us understand how podocytes become dysregulated in disease states.

Funding: NIDDK Support

FR-PO730

Effects of Sex and Kidney Mass on Podocyte Density in Rats

Patrick S. Means,[1] Blakeley D. Griffin,[1] Suzanna Camp,[1] Jacqueline M. Chivers,[1] Christian C. Story,[1] Purva R. Chopde,[4] Geoffrey A. Williamson,[4] Karen A. Griffin,[2,3] Aaron J. Polichnowski.[1]
[1]East Tennessee State University James H Quillen College of Medicine, Johnson City, TN; [2]Loyola University Chicago Stritch School of Medicine, Chicago, IL; [3]Edward Hines Junior VA Hospital, Hines, IL; [4]Illinois Institute of Technology, Chicago, IL.

Background: Chronic kidney disease (CKD) progresses faster in males; however, the underlying mechanisms are not well understood. We investigated sex differences in podocyte density in rats with intact kidneys and uninephrectomy (UNX) to understand its potential role in the sex disparity in CKD progression.

Methods: Sprague-Dawley rats (10-13-week-old) underwent UNX (n=8/sex) or sham UNX (n=8/sex). Six weeks later, kidneys were perfusion-fixed and podocytes were detected using Wilms' Tumor 1 1° Ab, Cy-3 2° Ab, and DAPI. Podocyte density was assessed in 20 glomeruli/left kidney/rat in a blinded fashion according to Venkatareddy et al. (PMID 24357669). Data were compared using a 2-way ANOVA with Sidak post hoc analysis and linear regression. Data are mean±SE, and P<0.05 was considered statistically significant.

Results: As shown in Table 1, body weight, kidney weight, and glomerular tuft volume were greater (P<0.05) in male vs. female rats within both intact and UNX groups. Within both sexes, kidney weight and glomerular tuft volume, but not body weight, were greater (P<0.05) in UNX vs. intact groups. No significant differences in the total number of podocytes per glomerular tuft were observed between sexes or between intact and UNX groups. On average, podocyte density was ~10% lower in males vs. females and ~17% lower in UNX vs. intact groups. As shown in Figure 1, a robust correlation (P<0.05) was observed between podocyte density and glomerular tuft volume, but not the total number of podocytes per glomerular tuft.

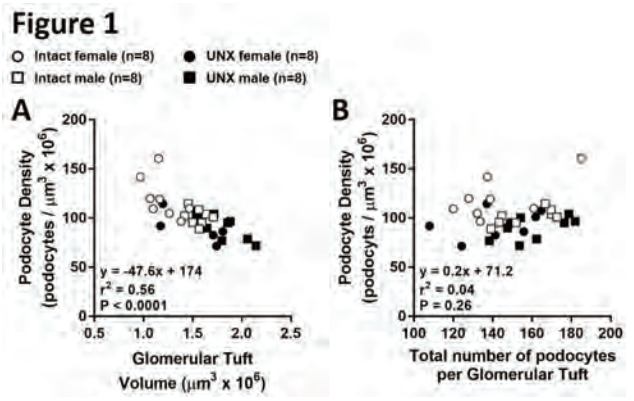
Conclusions: Sex differences in podocyte density are largely dependent on sex differences in kidney size and glomerular tuft volume, which may contribute to the sex disparity in the rate of CKD progression.

Funding: Other NIH Support - NHLBI

Table 1

Group	Body Weight (grams)	Kidney Weight (grams)	Glomerular Tuft Volume ($\mu m^3 \times 10^6$)	Total Number of Podocytes per Glomerular Tuft	Podocyte Density (podocytes / 10^6 μm^3)
Intact					
Female (n=8)	321 ± 13	1.4 ± 0.1	1.2 ± 0.1	142 ± 7	120 ± 8
Male (n=8)	503 ± 18[#]	2.3 ± 0.1[#]	1.6 ± 0.1[#]	157 ± 5	101 ± 3[#]
UNX					
Female (n=8)	324 ± 12	2.3 ± 0.1*	1.5 ± 0.1*	143 ± 7	94 ± 5*
Male (n=8)	525 ± 9[#]	3.6 ± 0.1*[#]	1.8 ± 0.1*[#]	162 ± 6	89 ± 4

Data are mean ± standard error. [#] P<0.05 vs. respective female group; * P<0.05 vs. respective intact group. UNX = uninephrectomy.



FR-PO731

Protective Role of Active Vitamin D in Transforming Growth Factor (TGF)-β1-Associated Podocyte Injury through Inhibition of p21 Upregulation

Takehiko Wada,[1] Kaichiro Sawada,[2] Hirotaka Komaba,[2] Masafumi Fukagawa.[2]
[1]Toranomon Hospital, Tokyo, Japan; [2]Tokai University School of Medicine, Isehara, Japan.

Background: Podocyte cell death is closely associated with proteinuria-related kidney diseases and the progression of glomerulosclerosis. Transforming growth factor-β1 (TGF-β1) has long been recognized as a key player in the pathogenesis of diabetic kidney disease (DKD). Our previous studies have demonstrated that the cell cycle regulatory protein p21 is involved in this process. However, therapeutic approaches to inhibit this pathway have not been developed.

Methods: To confirm the albuminuria-suppressing effects of active vitamin D, we utilized a streptozotocin-induced diabetic mouse model. These mice were administered paricalcitol, an active form of vitamin D, thrice weekly to observe its effects. *In vitro* experiments using temperature-sensitive mouse podocytes were conducted to assess TGF-β1-induced cell motility and determine cell cycle regulatory molecule expression. We also investigated the change of these expressions in the presence of active vitamin D. Additionally, we evaluated changes in the expression of vitamin D receptors to examine alterations in signaling pathways in the presence of active vitamin D.

Results: Administration of paricalcitol significantly suppressed albuminuria in the DKD model mice. In cultured podocytes, the increased cell motility induced by TGF-β1 in the scratch assay was inhibited in the presence of paricalcitol. Under these conditions, examination of the expression of cell cycle regulatory proteins revealed that TGF-β1 stimulation led to an increased expression of p21, which was suppressed when paricalcitol was present. Additionally, paricalcitol was found to enhance the mRNA expression of the vitamin D receptor, suggesting a potential positive feedback mechanism in vitamin D signaling in podocytes.

Conclusions: Active vitamin D exerts a protective effect against TGF-β1-induced podocyte injury in DKD, potentially through the suppression of p21 induction.

Funding: Government Support - Non-U.S.

FR-PO732

Loss of Vasorin (VASN) Promotes Podocyte Cell-Cycle Reentry and Dedifferentiation: A Novel FSGS Mechanism and Disease Modifier?

Pierre-Louis Tharaux,[1,2] Julien Dang,[1] Nassim Mahtal,[1] Anis Chaba,[1] Alexandre Karras,[1,3] Nicole Endlich,[4,5] Olivia Lenoir.[1,2] *[1]Paris Centre de Recherche Cardiovasculaire, Paris, France; [2]Universite Paris Cite UFR de Medecine, Paris, France; [3]Hopital Europeen Georges Pompidou, Paris, France; [4]Universitatsmedizin Greifswald, Greifswald, Germany; [5]NIPOKA GmbH, Greifswald, Germany.*

Background: Podocyte loss of quiescence contributes to focal segmental glomerulosclerosis (FSGS) and crescentic glomerulonephritis (CGN). Here, we characterized the role of Vasorin (VASN), a protein highly expressed in mature podocytes.

Methods: We combined laser capture microdissection with RNA sequencing of human glomeruli, RNAscope-based *in situ* hybridization, immunostaining, and mouse models with selective targeting of the *Vasn* gene in podocytes and cultures of human podocytes.

Results: VASN mRNA is strongly expressed in healthy human and mouse glomeruli with a podocyte-specific pattern. Both global and podocyte-specific, constitutive or inducible gene deletion of *Vasn* in mice induced nephrotic syndrome and kidney failure after day 14, with podocyte dedifferentiation and loss and severe FSGS, indicating a fundamental role of VASN in podocyte homeostasis. Furthermore, we measured markedly decreased VASN expression in podocytes of patients with FSGS and ANCA-associated CGN but not with Minimal Change Disease and Membranous Nephropathy. We then wondered whether VASN abundance could be a disease modifier. Mice with podocyte-specific heterozygous deletion of *Vasn* displayed accentuated podocyte loss, albuminuria, and kidney failure when challenged with diabetes or CGN experimental models. Human podocytes transduced with lentiviral VASN-targeting shRNA (shVASN) displayed increased focal adhesion dynamics, enhanced migratory capacity, and epithelial-mesenchymal transition (EMT). shVASN podocytes had a higher proliferative capacity and increased cell-cycle reentry. Accordingly, shVASN podocytes and isolated mouse VASN-deficient glomeruli displayed up-regulation of genes involved in cell metabolism, adhesion, and EMT and down-regulation of genes involved in the S to G2/M phase transition. We confirmed that VASN deficiency increased podocyte proliferation *in vivo* and urinary shedding.

Conclusions: These findings indicatte the role of VASN as an essential master protein that maintains podocyte quiescence and homeostasis during health and kidney diseases. VASN controls mechanisms driving podocyte cell-cycle reentry and detachment, promoting extracapillary diseases. VASN expression level may also discriminate various glomerular diseases trajectories.

FR-PO733

The Role of Combinatorial Inflammatory and Senescence-Associated Secretory Phenotype (SASP) Signaling Pathways in Podocyte Aging

Jana Sharara,[1] Jeffrey W. Pippin,[2] Alexander A. Zarouk,[1] Uyen Tran,[1] Stuart J. Shankland,[2] Oliver Wessely.[1] *[1]Cleveland Clinic, Cleveland, OH; [2]University of Washington, Seattle, WA.*

Background: Podocytes play a pivotal role in maintaining the integrity and function of the glomerular filtration barrier. In the aged kidney, podocytes undergo shortened lifespan and reduced health-span, characterized by altered morphology, decreased cellular proliferation, and impaired function. This age-associated podocyte senescence could contribute to the decline in renal function observed in elderly individuals and increase susceptibility to various renal pathologies. Previous findings show that multiple inflammatory and senescence-associated secretory phenotype (SASP) pathways are upregulated in aged and injured podocytes. We hypothesize that these pathways contribute to decline in podocyte function via autocrine and paracrine signaling.

Methods: To investigate the numerous inflammatory and SASP pathways upregulated in podocyte aging/injury, a classic one-factor-at-a-time approach which tests each pathway individually is impractical and also does not consider synergistic interactions. To holistically address the complexity of the aging and injury secretome, our study implements a Design-of-Experiment (DoE) approach. In this approach, all inflammatory and SASP pathways are altered simultaneously through computer-generated experiments to obtain optimal results and quality. This allows us to directly identify which specific combination of inflammatory cytokines and SASP proteins secreted from aged/injured podocytes are causally involved in altered podocyte function.

Results: We performed DoE approaches in well-characterized young and aged primary mouse podocytes. We interrogated 13 different antagonists to various inflammatory and SASP pathways and studied two outcomes, apoptosis and senescence. The DOE identified pathways with the most robust pro- and anti-aging and injury responses. These specific combinations were then characterized and analyzed, using a more traditional approach by assessing the inflammatory/aging phenotype with mRNAseq, qPCR, and immunohistochemistry.

Conclusions: The DoE approach provides a comprehensive understanding of the interplay between inflammatory and SASP pathways in podocyte aging and disease. It offers potential targets for therapeutic intervention that may lead to the development of novel treatments to preserve kidney function in the elderly.

Funding: NIDDK Support, Other NIH Support - R01AG079935-01A1

FR-PO734

Podocyte Cell Cycle in Aging

Laura Perin,[1,2] Xiaogang Hou,[1] Valentina Villani,[1] Charmi Dedhia,[1] Paola Aguiari,[1] Roger E. De Filippo,[1,2] Kevin V. Lemley.[1,2] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]University of Southern California, Los Angeles, CA.*

Background: Glomerulosclerosis is a prominent pathologic change of aging kidneys associated with hypertrophy and loss of podocytes. Podocytes are quiescent cells, but under a pathological state, they re-enter the cell cycle which promotes their loss when they cross the G1/S checkpoint. Here we study how the podocyte cell cycle phases change during aging in male vs female mice.

Methods: We established a FUCCI mouse (fluorescent ubiquitination-based cell cycle indicator) with fluorescent reporters exclusively in podocytes (Pod/FUCCI) to study cell cycle dynamics during aging in male and female mice. We analyzed n=8 males and n=12 females at 2-4m; n=17 males and n=15 females at 1 year, and n=29 males and n=24 females at 2 years of age. Podocytes were isolated by flow cytometry based on their cell cycle phase and podocyte loss was quantified by WT1 staining for all the time points. RNA seq was performed to study transcriptomics changes in podocytes at different cell cycle phases (G0 vs G1) at different ages.

Results: Podocyte number per glomerulus decreased during aging and podocyte loss was accompanied by an increase in glomerular size (hypertrophy) both in males and females. Flow cytometry results showed that in males, 92% of the podocytes at 4m were in G0 compared to 83% at 1 year and 81% at 2 years, while podocytes in the G1 phase increased from 4% at 4m to 12% and 17% at 1 year and 2 years, respectively. In female mice, 90% of podocytes were in G0 at 4m compared to 91% at 1 year and 79% at 2 years, 8% of the podocytes were in G0 at 4m compared to 3.5% and 17% at 1 year and 2 years, respectively. Sequencing results indicate that important molecular singling regulate the entrance in G1 phase, especially at later ages and that these signalings are different between males and females, highlighting the importance of sex differences related to the regulation of podocyte cell cycle phases.

Conclusions: Our data confirm, for the first time, that changes in podocyte cell cycle during aging differ between males and females, especially in relation to the G1 phase. Understanding the mechanisms that regulate cell cycle progression will help to identify new pathways that can be targeted to prevent podocyte loss and kidney disease accounting for sex differences.

Funding: Private Foundation Support

FR-PO735

Extracellular Vesicle and Modulation of miR-93 in Kidney Diseases

Laura Perin,[1,2] Charmi Dedhia,[1] Valentina Villani,[1] Xiaogang Hou,[1] Paolo Neviani,[1] Geremy Clair,[3] Velia Alcala,[1] Paola Aguiari,[1] Giuseppe Orlando,[4] Roger E. De Filippo,[1,2] Stefano Da Sacco,[1,2] Benedetta Bussolati,[5] Sargis Sedrakyan.[1,2] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]University of Southern California, Los Angeles, CA; [3]Pacific Northwest National Laboratory, Richland, WA; [4]Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC; [5]University of Torino, Torino, Italy.*

Background: Modulation of miRNA expression in glomerular cells is associated with renal disease. MiR-93, a potent regulator of glomerular damage, is downregulated in glomeruli of mice with Alport syndrome (AS, a renal disease characterized by a mutation in *col4a5* gene) and in glomeruli of AS patients. Here, we investigated the role of extracellular vesicles (EVs) from human amniotic fluid stem cells (hAFSC) in disease-modifying activity in vitro and in vivo by regulation of miR-93 and its targets.

Methods: AS and WT glomeruli were characterized by bulk RNA-seq. hEVs, isolated by ultracentrifugation, were characterized by Exoview, TEM, super resolution microscopy, miRNA-seq, and proteomics. Expression of miR-93 was silenced in hEVs using a specific miR-93 antigomiR (KD-hEVs). Transfer and modulation of miR-93 (and its targets) in human glomerular cells was evaluated in vitro. hEV disease-modifying activity was evaluated by bulk RNA-seq in vitro, in AS mice by biodistribution, renal function, survival, and by spatial transcriptomics (ST) using the Visium 10X Genomics. Data were confirmed in AS patient biopsy using CosMX SMI (Nanostring).

Results: Glomerular endothelial cells are responsible for downregulation of miR-93 along disease progression. RNA-seq revealed alteration of miR-93 targets in AS glomeruli. Cell damage decreased expression of miR-93 and its targets, which were prevented by normal hEVs and not by KD-hEVs. hEV proteomics and miR-seq identified specific cargo and pathways central to disease progression. When injected in AS mice, hEVs localized in the kidney, ameliorated proteinuria, and prolonged lifespan compared to KD-hEVs. ST data showed that hEV injection upregulated important pathways responsible for glomerular regeneration, slowing down AS progression. Analysis of CosMX SMI also showed alteration of miR-93 targets in human AS patients.

Conclusions: hEVs modulated pathways that are central to glomerular homeostasis and improved kidney function by miR-93 transfer. These data suggest hEVs and modulation of miR-93 signaling might be important in translational settings.

Funding: NIDDK Support

FR-PO736

Senescent Podocytes in Human Obesity Release Urinary Extracellular Vesicles (uEVs)

Mina H. Al Saeedi, Xiang yang Zhu, Aleksandar Denic, Andrew D. Rule, Li Xing, Lei Zhang, Hui Tang, Kyra L. Jordan, Amir Lerman, Mary E. Fidler, Aleksandra Kukla, Lilach O. Lerman. Nephrology and Hypertension. *Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Obesity induces cellular senescence, which is implicated in renal disease progression. Senescent cells are characterized by the expression of senescence markers like P19, a cyclin-dependent kinase inhibitor, and possibly pro-inflammatory monocyte chemoattractant protein (MCP)-1. However, whether podocytes marked by podocalyxin (Podxl)+ undergo senescence in obesity is unclear. We hypothesized that patients with obesity show elevated levels of P19+/Podxl+/MCP1+ uEVs suggestive of podocyte senescence

Methods: Blood and urine samples were collected from 21 obese (OB) and 10 lean subjects for uEVs quantification (NanoSight) and characterization (Flow Cytometry) for P19, Podoxl, and MCP1 expression (Fig1). Their fraction out of total uEVs was correlated with body mass index (BMI), urinary protein, kidney injury molecule (KIM)-1, and insulin levels

Results: OB subjects had elevated BMI but preserved renal function (Table). The total uEV number was similar in OB and lean, but the fractions of P19+/Podxl+ and P19+/Podoxl+/MCP1+ uEVs were higher in OB and directly correlated with BMI. P19+/Podoxl+/MCP1+ uEVs also correlated with urine protein, KIM1, and insulin levels (Fig2)

Conclusions: Senescent podocytes in obese subjects with preserved renal function shed uEVs in proportion to obesity severity. The uEVs fraction shed by a subset of inflamed (MCP1+) senescent podocytes further correlates with renal injury markers. These may serve as early markers of glomerular senescence and guide the management of patients with obesity

Funding: NIDDK Support, Other NIH Support - DK120292 (NIDDK) and HL158691 (National Heart, Lung, and Blood Institute)

Table. Demographics

Parameter	Lean	OB
Age, Yrs.	47±15	48±12
Sex, M/F	3/7	7/14
BMI, Kg/m^2	25±1	44±6*
Serum Creatinine, mg/dl	0.9(0.7,1.2)	0.8(0.6,1.4)
eGFR, ml/min/1.73m^2	90±10	96±17
Urine Protein, mg/mmol	32(2,57)	66(3,189)

Mean ± SD or median (min, max) *P<0.05 vs. Lean

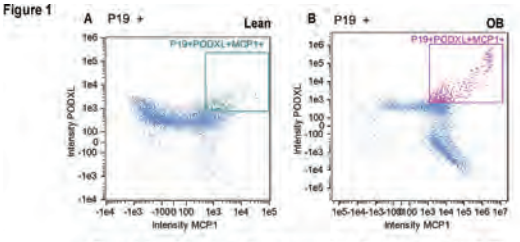


Figure 1. Flow Cytometry scatterplot images of tag-it-violet lean **(A)** and OB **(B)** (P19+/Podxl+/MCP-1+)% uEVS.

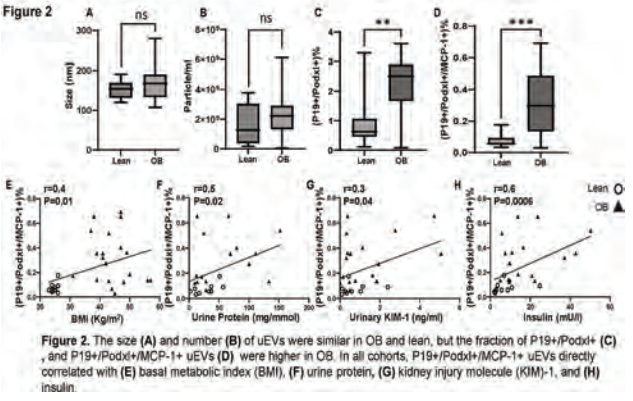


Figure 2. The size **(A)** and number **(B)** of uEVs were similar in OB and lean, but the fraction of P19+/Podxl+ **(C)** , and P19+/Podxl+/MCP-1+ uEVs **(D)** were higher in OB. In all cohorts, P19+/Podxl+/MCP-1+ uEVs directly correlated with **(E)** basal metabolic index (BMI), **(F)** urine protein, **(G)** kidney injury molecule (KIM)-1, and **(H)** insulin.

FR-PO737

Role of Cargo Receptor Surf4 in Podocyte Proteostasis

Andrey V. Cybulsky, Joan Papillon, Christian-Landry Konde Bilogui. *McGill University, Montreal, QC, Canada.*

Background: Protein misfolding in the endoplasmic reticulum (ER) of podocytes/glomerular epithelial cells (GECs) induces ER stress, and contributes to the pathogenesis of glomerular diseases. The unfolded protein response (UPR) and autophagy may be activated to sustain proteostasis. In GECs during ER stress, the COPII vesicle component Sec23B localizes in autophagosomes along with collagen IV-α5 (COL4A5). Thus, the secretory pathway is redirected to ERphagy (ER-specific autophagy), with COL4A5 being a potential ERphagy substrate. In GECs, ERphagy was facilitated by the activation of the UPR transducer IRE1α. Discovery proteomics in GECs exposed to ER stress showed that IRE1α facilitated expression of Surf4, an ER-COPII vesicle cargo receptor. The present study examines whether Surf4 may redirect misfolded proteins for autophagosomal degradation.

Methods: We studied IRE1α-replete (control) GECs in culture and GECs with genetic knockout (KO) of IRE1α. Immunofluorescence microscopy was used to quantify autophagosome number/area by setting a suitable particle size/threshold.

Results: Basal Surf4 expression was greater in control compared to IRE1α KO GECs. During ER stress induced with tunicamycin (TM), there was activation of the UPR, although Surf4 did not increase above basal levels. TM increased LC3-II and Surf4 particle areas, as well as colocalization of LC3 and Surf4; increases were smaller in KO GECs compared to control. Thus, during ER stress, a subset of Surf4 localizes in autophagosomes. TM increased COL4A5 particle area and colocalization of Surf4 with

COL4A5 in control and KO GECs, implying that during ER stress, some of the COL4A5 localizes in autophagosomes. The GEC toxin adriamycin (ADR) induced autophagy (LC3-II), but not the UPR. Unlike TM, ADR did not promote localization of Surf4 or COL4A5 in autophagosomes. However, both TM and ADR could enhance colocalization of LC3-II and Hsp60 (a mitochondrial protein), consistent with mitophagy. Analysis of a human glomerular gene expression dataset showed increased Surf4 and UPR gene expression in membranous nephropathy and focal segmental glomerulosclerosis compared to healthy controls.

Conclusions: During ER stress, Surf4 is redirected from the secretory pathway to autophagosomes. Surf4 may help deliver misfolded ER cargo such as COL4A5 for degradation. This represents a novel role for Surf4 in sustaining proteostasis.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO738

Synergistic Effects of Endoplasmic Reticulum-Associated Degradation and Autophagy in Podocyte Function

Xiaoqiong Wei, Ling Qi. *University of Virginia, Charlottesville, VA.*

Background: Podocytes are specialized epithelial cells, key to the kidney glomerular filtration barrier, through which the blood is filtered by forming interdigitating foot processes with neighboring podocytes. The slit diaphragm is a specialized cell junction composed of multiple proteins including nephrin to connect foot processes. Impaired biosynthesis of these proteins leads to foot process effacement and renal failure. Endoplasmic reticulum (ER)-associated degradation (ERAD) and autophagy are two major protein quality-control machineries to maintain protein homeostasis. However, the crosstalk between these two quality-control systems has not yet been investigated in the podocyte function.

Methods: The podocyte-specific Sel1L and Atg7 double knock-out mice (DKO) were generated. Mouse body weight and survival curves were recorded. Urine samples from mice at 1, 3, and 5 weeks of age were collected to assess the abundance of albumin. Kidneys from wild-type (WT), Sel1L knock-out, Atg7 knock-out and DKO mice were collected for histology examination by H&E staining, ultrastructure observation via scanning electron microscopy (SEM) and transmission electron microscopy (TEM), as well as determination of abundance and cellular location by immunofluorescence staining and western blot.

Results: DKO mice exhibited severe early onset renal failure at 3 weeks of age and premature death as early as 6 weeks of age, while Sel1L knock-out mice died with a median life span of ~14 weeks. Atg7 knock-out mice were normal like WT mice until 1 year of age. At 3 weeks of age, large protein casts were only observed in the renal tubules of DKO mice. SEM and TEM revealed that DKO mice developed effaced foot process much earlier than Sel1L knock-out mice. Mechanismlly, nephrin, an ERAD substrate, accumulated in the ER of Sel1L-deficient podocytes. In the absence of ERAD, ATG7 deficiency increased nephrin accumulation in the ER, further impairing its trafficking to the cell membrane.

Conclusions: ERAD and autophagy synergistically regulate podocyte function. Deficiencies in ERAD and autophagy lead to podocyte foot process effacement and subsequent renal failure by affecting nephrin maturation and cell membrane trafficking.

Funding: NIDDK Support

FR-PO739

Mechanisms and Implications of Podocyte Autophagy in Alport Syndrome

Rachel Njeim, Maria Ficarella, Antonio M. Fontanella, Haley Gye, Jin Ju Kim, Alla Mitrofanova, Hassan Ali, Sandra M. Merscher, Alessia Fornoni. *University of Miami Miller School of Medicine, Miami, FL.*

Background: Alport syndrome (AS) is a hereditary disease affecting the glomerular basement membrane, leading to renal fibrosis and end stage renal disease. We have previously shown that the accumulation of lipid droplets (LD) in podocytes contributes to the pathogenesis of proteinuric kidney diseases, including AS. Chaperone-mediated autophagy (CMA) is a selective lysosomal pathway for the degradation of cytosolic proteins. Recent studies suggest that CMA also plays a crucial role in LD breakdown, a process termed chaperone-mediated lipophagy (CML). We hypothesized that dysregulated autophagy in AS exacerbates LD accumulation in podocytes, thus driving disease progression.

Methods: Publicly available CKD and AS patient RNASeq datasets (NephroSeq, GSE134011) were used to analyze differential gene expression of various autophagy markers. Autophagy genes were determined by QRT-PCR and Western blot analysis of proteins isolated from kidney cortices and immortalized podocytes derived from wildtype (WT) and Col4a3 knockout (AS) mice. To investigate lipophagy, podocytes were treated with Lalistat, a lysosomal acid lipase inhibitor, and LD accumulation was assessed. Unbiased phenotypic profiling (Cell Painting) will be employed to further investigate the role of autophagy in WT and AS podocytes treated with autophagy inducers.

Results: Transcriptomic analysis showed altered expression of various autophagy genes. LD accumulation was significantly increased in AS compared to WT podocytes. PLIN2 protein expression was significantly increased in LD isolated from AS compared to WT podocytes. mRNA and protein expression of the rate-limiting enzyme of CMA, LAMP2A, was significantly increased in AS podocytes and in kidney cortices of AS mice, suggesting activation of CML. LC3II/I and GATE16 expression were significantly increased and p62 significantly decreased in AS, further supporting activation of autophagy in AS. Treatment of AS podocytes with Lalistat further increased LD accumulation in AS podocytes, indicating that lipophagic flux is efficient in AS podocytes and that the observed LD accumulation may be attributed to lysosomal LD accumulation.

Conclusions: Taken together, our findings suggest that autophagy and CML are functional in AS but are not sufficient to reduce LD accumulation and prevent podocyte lipotoxicity.

Funding: NIDDK Support

FR-PO740

Extracellular Vesicles Rebalance Glomerular Endothelial Lipid Metabolism in CKD

Sargis Sedrakyan,[1,2] Hasmik Soloyan,[1] Geremy Clair,[3] Janielle M. Cuala,[2] Hripsime Chomoyan,[1] Qi Zhang,[1] Matthew E. Thornton,[2] Senta K. Georgia,[1,2] Paolo Cravedi,[4] Andrea Angeletti,[5] Roger E. De Filippo,[1,2] Stefano Da Sacco,[1,2] Laura Perin.[1,2] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]University of Southern California Keck School of Medicine, Los Angeles, CA; [3]Pacific Northwest National Laboratory, Richland, WA; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]Istituto Giannina Gaslini, Genova, Italy.*

Background: Chronic kidney disease (CKD) affects more than 10% of the population worldwide, and our understanding of the mechanisms in many forms of CKD are poorly understood. Alport syndrome (AS), is a form of CKD caused by mutations in the collagen IVα3, α4, or α5 gene. Even though injury to glomerular endothelial cells (GEC) in AS is well established, the role of GEC in Alport progression has not been elucidated. Here, we describe the role of mitochondria and lipid metabolism in GEC injury in an animal model of AS, and the potential of using amniotic fluid stem cell (AFSC) derived extracellular vesicles, (EVs) as a rescue strategy to restore glomerular homeostasis.

Methods: The phasor approach to fluorescent lifetime imaging microscopy (FLIM) and flow cytometry was applied to evaluate the mitochondria and metabolic changes in GEC in AS vs WT mice. GEC isolated by FACS from Tek-tdT reporter AS and WT mice were compared by bulk RNA-seq, lipidomic and flow cytometric analysis. In vitro, silencing experiments on primary human primary GEC were performed to study the role of fatty acid synthase (FASN) in mitochondrial dysfunction and GEC damage. FASN-carrying AFSC-EVs and control EVs were applied both *in vitro* and *in vivo* to restore lipid homeostasis in GEC.

Results: FLIM studies showed strong correlation between the metabolic state of GEC and the age and severity of disease in AS mice. RNA-seq analysis revealed changes in the pathways associated with lipid metabolism and mitochondria function. Mitochondrial dysfunction was confirmed using flow cytometric analysis of the MitoTracker signal in tdTomato expressing GEC. Lipidome analysis revealed high abundance of triglycerides in AS GEC. We confirmed accumulation of lipid droplets in the glomeruli of AS mice and in FASN KO human primary GEC, *in vitro*. These results suggest potential mitochondrial dysfunction in GEC. AFSC derived EV treatment restored lipid homeostasis in GEC, both in vitro and in vivo.

Conclusions: We report for the first-time mitochondrial dysfunction in Alport GEC, and the ability of AFSC-derived EVs to rescue this phenotype. Better understanding of the metabolic changes in AS GEC could lead to the development of targeted new therapies also for other forms of CKD.

Funding: NIDDK Support, Private Foundation Support

FR-PO741

APOM Deficiency Affects Kidney Function in an Experimental Mouse Model of Alport Syndrome

Judith T. Molina David, Matthew Tolerico, Jin Ju Kim, Antonio M. Fontanella, Arianna Carrazco, Sandra M. Merscher, Alessia Fornoni. Katz Family Div of Nephrology and Hypertension/Peggy and Harold Katz Family Drug Discovery Center. *University of Miami Miller School of Medicine, Miami, FL.*

Background: We have previously reported that glomerular APOM deficiency correlates with eGFR in patients with glomerular diseases enrolled in the Nephrotic Syndrome Study Network (NEPTUNE). However, little is known about the significance of APOM deficiency in kidney disease development and progression. With this study, we investigate if APOM deficiency occurs in Alport Syndrome (AS) and how ApoM deficiency may contribute to disease progression. We first analyzed glomerular APOM expression in a mouse model of progressive renal disease associated with AS (Col4a3 KO mice) and in podocytes isolated from Col4a3 KO mice. We found reduced mRNA and protein expression of APOM in glomeruli and podocytes isolated from Col4a3 KO mice.

Methods: To investigate if APOM replenishment would improve renal function in this mouse model, we injected Col4a3 KO mice with human recombinant APOM

(rhAPOM). Three groups of mice were studied, n=6 mice per group: (1) Col4a3 +/+ (WT) + vehicle, (2) Col4a3 -/- (KO) + vehicle, and (3) Col4a3 -/- (KO) + rhAPOM. rhAPOM was administered by weekly ip injection starting at 4 w of age and until sacrifice at 8 w of age. APOM protein levels in podocytes were measured by Western blot analysis. Serum and urine samples were used to determine blood urea nitrogen (BUN), creatinine, and urinary albumin/creatinine ratios (ACR). Triglyceride content (TG) was assayed using a colorimetric kit and lipid droplets (LD) content was using the OPERA screening system. Histological analysis was performed by Periodic Acid Schiff (PAS), renal fibrosis was evaluated by Picro Sirius Red (PSR), renal lipid content was determined by Oil Red O (ORO) and WT1 to detect podocytes number.

Results: Glomerular APOM mRNA and protein expression were markedly reduced in Col4a3 KO mice when compared to WT mice. Treatment of Col4a3 KO podocytes with rhAPOM reduce TG levels and LD content and treatment of Col4a3 KO mice with rhAPOM normalized renal APOM levels and resulted in a significant reduction of serum BUN and creatinine levels, a reduced ACR.

Conclusions: rhAPOM treatment protected from the development of glomerulosclerosis and kidney fibrosis.

FR-PO742

Impact of Glomerular Basement Membrane Stiffness on Podocyte Metabolism in Alport Syndrome

Jin Ju Kim,[1,2] Maria Ficarella,[1,2] Judith T. Molina David,[1,2] Flavia Fontanesi,[3] Sandra M. Merscher,[1,2] Jeffrey H. Miner,[4] Alessia Fornoni.[1,2] *[1]University of Miami Katz Family Division of Nephrology and Hypertension, Miami, FL; [2]Peggy and Harold Katz Drug Discovery Center, University of Miami, Miller School of Medicine, Miami, FL; [3]University of Miami Miller School of Medicine Department of Biochemistry, Miami, FL; [4]Washington University School of Medicine, Division of Nephrology, St. Louis, MO.*

Background: Cells utilize mechanotransduction to sense mechanical cues, which regulate behaviors like proliferation and apoptosis. These pathways are linked to metabolic processes, with ECM stiffness influencing cellular metabolism and cytoskeletal integrity. Stiff ECM promotes glycolysis, while soft ECM suppresses it, affecting glucose utilization. Key pathways involve phosphofructokinase 1(PFK1) in glycolysis and tripartite motif-containing protein 21(TRIM21) in protein degradation, with TRIM21 activity inhibited by actin-mediated sequestration. In Alport Syndrome(AS), mutations in type IV collagen genes lead to a softer, more degradable glomerular basement membrane(GBM) composed of α112 chains of collagen IV. This study investigates the impact of GBM stiffness on podocyte metabolism and structure, focusing on stressfiber formation and mitochondrial function.

Methods: Immortalized AS and WT podocytes were created by breeding Col4a3KO mice with H-2kb-tsA58 transgenic mice, then cultured on soft(1.5 kPa) and stiff(10-12 kPa) gelatin hydrogel matrices. Mitochondrial respiration was measured using a high-resolution respirometer. CPT1A, PFK1, and TRIM21 expression were assessed via western blot. Mitochondrial function was evaluated through ATP production and mitochondrial membrane potential(MMP) assays. Stress fiberformation and TRIM21 colocalization were analyzed using immunofluorescence microscopy.

Results: Fatty acid oxidation(FAO) was significantly increased in AS podocytes compared to WT podocytes($P<0.05$), with higher CPT1 expression in AS podocytes. Actin cytoskeleton rearrangement was observed in WT podocytes on soft matrices compared to stiff matrices. Mitochondrial function was impaired in AS podocytes, as indicated by reduced ATP production($P<0.05$) and decreased MMP($P<0.01$). Decreased PFK1 and increased TRIM21 activity were observed in podocytes on soft matrices, suggesting suppressed glycolysis and enhanced protein degradation and stress response.

Conclusions: Changes in GBM stiffness in AS mice may lead to a metabolic shift in podocytes from glycolysis to fatty acid oxidation, reduced stress fibers, and impaired mitochondrial function. These findings underscore the importance of ECM stiffness and related mechanotransduction pathways in developing treatments for AS and potentially other glomerular diseases.

Funding: NIDDK Support

FR-PO743

Identification of Novel Therapeutic Targets for Alport Syndrome Using Near Super-Resolution Imaging of Podocytes

Kaye E. Brathwaite, Queen Polin, Pongpratch Puapatanakul, Chengqing Qu, Hani Suleiman, Jeffrey H. Miner. *Washington University in St Louis, St Louis, MO.*

Background: Alport Syndrome is a rare disease currently without a cure. It is characterized by hematuria and proteinuria and eventual ESKD. Obtaining a deeper understanding of the alterations to the cytoskeletal architecture of podocytes from their interactions with the abnormal glomerular basement membrane (GBM) in Alport syndrome is one promising approach to identify novel therapeutic targets. Sarcomere-like structures (SLSs), are intertwining actin and myosin that form in areas of podocytes where foot processes become effaced. We hypothesize that SLSs are different in frequency in Alport mouse podocytes compared to COL4A3 rescued mouse podocytes.

Methods: We performed magnified analysis of proteome (MAP) expansion microscopy of kidneys from wild type, Alport and rescued mice. Col4a3-/- Alport mice are rescued using a doxycycline-inducible Col4a3 transgene in podocytes, which normalizes the GBM and extends the time to ESKD. Doxycycline was started at 2 or 6 weeks of age and mice sacrificed 6 weeks later. Incubating paraffin embedded tissue in a high concentration of acrylamide, we expanded mouse kidney tissue near 4 times its original size. Antibody staining with synaptopodin and myosin was performed on expanded kidney sections. Airyscan confocal microscopy was used to image SLSs and images were analyzed using the ImageJ software.

Results: Airyscan was used to demonstrate sarcomere-like structures (SLSs) in our mouse models. The percentage of the capillary wall covered with SLS was determined using the ImageJ software to identify alternating synaptopodin and myosin. Sarcomere-like structures were significantly less in mice rescued at 2 weeks compared to Alport mice. SLS were also less in mice induced at 2 weeks compared to those at 6 weeks of life. SLS were more organized throughout glomerular capillary loops in rescued mouse podocytes compared to Alport mouse podocytes.

Conclusions: SLS are significantly reduced in podocyte foot processes in Alport mice successfully rescued at 2 weeks of life compared to those induced at 6 weeks of life. Utilizing restoration of the GBM in the inducible rescue mice to study its impact on podocyte cytoskeletal architecture, could provide the key to understanding mechanisms at play in maintenance of foot processes and the glomerular filtration barrier in Alport syndrome.

Funding: Other NIH Support - NICHD

FR-PO744

Genetic NRF2 Activation Worsens Kidney Injury in an Alport Syndrome Mouse Model

Desmond Ng,[1,2] Hannah L. Hartman,[1] Hsuan Yeh,[1] Josie Gilbert,[1] Joy A. Stewart,[1] Corry D. Bondi,[1] Jeffrey H. Miner,[4] Roderick J. Tan.[1,3] *[1]University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Carnegie Mellon University, Pittsburgh, PA; [3]US Department of Veterans Affairs, Washington, DC; [4]Washington University in St Louis School of Medicine, St Louis, MO.*

Background: Alport syndrome (AS) is caused by mutations in type IV collagen, resulting in abnormal glomerular basement membrane, proteinuria, and progressive kidney disease. The KEAP1/NRF2 pathway mitigates cellular damage through upregulation of antioxidant and detoxifying genes. KEAP1 is an endogenous inhibitor of NRF2. Bardoxolone methyl (CDDO-Me) induces NRF2 through disruption of the KEAP1-NRF2 interaction and was tested as a treatment for AS in human clinical trials. While CDDO-Me increased estimated glomerular filtration rate (GFR), it was unclear if CDDO-Me meaningfully altered disease progression. In addition, CDDO-Me exposure was associated with paradoxical worsening of proteinuria. To determine the effects of NRF2 activation in AS, we examined how genetic reduction in *Keap1* expression (hypomorphism) affected AS in a mouse model. We hypothesized that higher NRF2 activity would worsen proteinuria and overall kidney injury in AS.

Methods: AS mice possessing a deletion mutation in *Col4a3* were bred with *Keap1* hypomorphic (HM) mice to generate double mutant *Col4a3*$^{-/-}$ *Keap1*$^{HM/HM}$ progeny. Proteinuria was measured over the course of 30 weeks using an albumin ELISA. GFR was measured through the transdermal measurement of FITC-sinistrin clearance. We performed histology and qPCR for renal injury biomarkers to assess overall injury. We used electron microscopy to examine podocyte foot process effacement and basement membrane ultrastructure.

Results: Consistent with their lower expression of *Keap1*, the double mutant mice exhibited higher expression of *Nrf2* target genes compared to single mutant *Col4a3*$^{-/-}$ mice. The double mutants exhibited significantly more proteinuria throughout the time course and a lower GFR compared to mice with only the *Col4a3*$^{-/-}$ mutation. Double mutants also exhibited more interstitial fibrosis and increased biomarkers of glomerular injury, tubular injury, and inflammation. Electron microscopy revealed extensive foot process effacement and basement membrane thickening that did not differ between groups.

Conclusions: Our findings demonstrate that excessive NRF2 activity worsens AS kidney injury in mice. These findings suggest that NRF2 has deleterious actions in AS and that NRF2 inducers such as CDDO-Me should be avoided in the treatment of this disease.

Funding: NIDDK Support, Veterans Affairs Support, Other U.S. Government Support

FR-PO745

Dysregulated Glomerular S1P Metabolism Contributes to Glomerular Injury

Antonio M. Fontanella, Matthew Tolerico, Judith T. Molina David, Rachel Njeim, Arianna Carrazco, Haley Gye, George W. Burke, Alla Mitrofanova, Sandra M. Merscher, Alessia Fornoni. *University of Miami Miller School of Medicine, Miami, FL.*

Background: Genetic defects in sphingosine-1-phosphate (S1P) lyase (SGPL1) are associated with steroid-resistant nephrotic syndrome (NS), suggesting a causative role of S1P and aberrant sphingolipid (SL) metabolism in glomerular injury. S1P is a sphingolipid which, in the absence of its carrier, Apolipoprotein M (APOM), causes pro-apoptotic signaling. We demonstrated that altered glomerular APOM and SL related gene expression in patients with glomerular disease correlates with poor renal outcome. Alport Syndrome (AS) is an inherited glomerular disease (GD), most frequently caused by Col4a3 gene mutations, where lipid accumulation is thought to play a role in its pathogenesis. This study aims at investigating the role of APOM deficiency and S1P signaling in renal injury using Alport Syndrome as a model of APOM deficient glomerular disease.

Methods: Publicly available glomerular expression data of SL related genes in glomeruli of CKD patients and in wildtype (WT) and Col4a3 knockout (Col4a3 KO) mice were analyzed. The SL content in renal cortices of the mice was also assessed. Mice were treated with 0.1uM S1P and urine ACR and renal histology were analyzed. Immortalized murine control (IMWT) and Col4a3 KO (IMAL) podocytes, and APOM knockdown (siAPOM) or scramble control (SC) human podocytes were treated with S1P or an Sgpl1 inhibitor. SL related gene expression was analyzed by qRT-PCR and Western blot. Apoptosis was assessed.

Results: Multiple SL related genes, including APOM, showed similar differential expression in glomeruli of patients with NS, in glomeruli of Col4a3 KO mice and in IMAS. Renal cortical S1P content was significantly increased Col4a3 KO and S1P treatment of Col4a3 KO mice, of IMAL and siAPOM podocytes, but not of controls, resulted in increased ACR and apoptosis, respectively.

Conclusions: Our data suggest that aberrant SL metabolism may contribute to glomerular injury. The observation that Col4a3 KO, IMAL and siAPOM but not controls were susceptible to S1P-mediated injury suggests a role for APOM deficiency in this process. Targeting pathways involved in the APOM/S1P signaling axis may represent novel treatment options for patients with glomerular diseases.

Funding: NIDDK Support

FR-PO746

Protective Effect of GIT2 against Podocyte Injury in Mice

Jun Matsuda,[1] Naoyuki Shimada,[1] Kana Asano-Matsuda,[1] Maho Tokuchi,[1] Agnieszka Masztalerz,[2] Serge Lemay,[2] Tomoko Takano,[2] Yoshitaka Isaka.[1] *[1]Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Japan; [2]Division of Nephrology, McGill University Health Centre, Montreal, QC, Canada.*

Background: Podocytes have an intricate structure featured by numerous actin-based projections called foot processes (FP). Rho GTPases, including Rac1, play important roles in actin cytoskeletal remodeling required for cell morphology and adhesion. We previously showed that Rac1 activation in podocytes causes FP effacement and proteinuria, but the upstream regulatory mechanism directing Rac1 is largely unknown. Recently, we identified focal adhesion protein GIT2 as one of the Rac1-interacting proteins in immortalized human podocytes, and showed that GIT2 knockdown elicited Rac1 activation.

Methods: The protein and mRNA expression of GIT2 in mice kidney were studied by immunoblotting and *in situ* hybridization, respectively. *Git2*-floxed mice were established using CLICK (CRISPR with long single-stranded DNA inducing conditional knockout alleles). They were then crossed with NPHS2-Cre mice to generate podocyte-specific *Git2* knockout (KO) mice. KO mice and age-matched controls were subjected to the minimal change disease model by lipopolysaccharide (LPS) or the salt-sensitive hypertension model by uninephrectomy (UNx) with deoxycorticosterone acetate (DOCA)/salt.

Results: GIT2 was relatively enriched in glomeruli including podocytes in the kidney. In KO mice, glomerular expression of GIT2 protein was significantly reduced compared with controls. When challenged with LPS, KO mice showed sustained high levels of proteinuria, resulting in a significantly higher urine albumin to creatinine ratio (ACR) at 48hours compared with controls. When treated with UNx-DOCA/salt, systolic blood pressure was increased similarly at day14 in both KO and control mice. While UNx-DOCA/salt induced a significant increase of ACR in both mouse groups, KO mice tended to have more severe proteinuria. Rac1 inhibitor NSC23766 significantly decreased ACR in UNx-DOCA/salt-treated KO mice. Serum UN was significantly increased in UNx-DOCA/salt-treated KO mice compared with controls. In both LPS and UNx-DOCA/salt models, FP effacement was exacerbated in KO mice compared with controls.

Conclusions: In the current study, we demonstrated that GIT2 protects podocytes and glomerular function against injury. GIT2 may become a new therapeutic target on the Rac1 pathway in podocytopathy.

FR-PO747

GIT2 Maintains Podocyte Architecture through Suppressing Rac1 Activity and Focal Adhesion Turnover

Naoyuki Shimada,[1] Jun Matsuda,[3] Maho Tokuchi,[1] Kana Asano-Matsuda,[1] Tomoko Takano,[2] Yoshitaka Isaka.[1] *[1]Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Japan; [2]Division of Nephrology, McGill University Health Centre, Montreal, QC, Canada; [3]Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Japan.*

Background: Podocyte foot processes are supported by the actin cytoskeleton which is precisely organized by Rho GTPases including Rac1. Overactivation of Rac1 in podocytes causes structural changes in foot processes and proteinuria. To elucidate the regulatory mechanism of Rac1, we performed proximity-based ligation assay and identified GIT2 as a Rac1-interacting protein in immortalized human podocytes (HP).

Methods: Subcellular localization of endogenous GIT2 in HP was examined by immunocytochemistry. HP with GIT2 knockdown (KD), GIT2 overexpression (OE) and control (CTRL) cells were established using lentiviral transduction. Rac1 activity was assessed by pull-down assay. Cell areas were quantified in fixed cells stained by phalloidin. Focal adhesion dynamics were analyzed using time-lapse fluorescence microscopy in cells transfected with mRFP-paxillin. Subcellular localization of the tyrosine phosphatase, PTP1B, was monitored using time-lapse fluorescence microscopy.

Results: GIT2 localized with paxillin in focal adhesions. GTP-bound (active) Rac1 levels were significantly higher in GIT2 KD HP than in CTRL. GIT2 KD elicited cell spreading with marked lamellipodial protrusions, which was significantly attenuated by the Rac1 inhibitor NSC23766. GIT2 KD HP had smaller focal adhesions than CTRL. Focal adhesion disassembly rate was significantly higher in GIT2 KD HP, resulting in shorter focal adhesion lifetime. Among the major focal adhesion proteins, tyrosine phosphorylation of p130Cas protein was most prominently increased in GIT2 KD HP, as compared with CTRL. PTP1B localization to focal adhesions was impaired in GIT2 KD HP. The phenotypes observed in GIT2 KD HP shown above were reversed by GIT2 OE.

Conclusions: We demonstrated that GIT2 suppresses Rac1 activity in focal adhesions and contributes to maintaining podocyte morphology and function. Furthermore, we showed that GIT2 facilitates translocation of the PTP1B to focal adhesions where it dephosphorylates p130Cas, thereby suppressing local Rac1 activity.

FR-PO748

Loss of FAM114A1 Attenuates Glomerular Injury by Preserving the Podocyte Cytoskeleton

Norifumi Hayashi,[1,2] Hitoshi Yokoyama,[1] Kengo Furuichi,[1] Laurence H. Beck.[2] *[1]Kanazawa Ika Daigaku, Kahoku-gun, Japan; [2]Boston University, Boston, MA.*

Background: Transcriptomic analysis of microdissected human glomeruli has suggested novel molecular signatures associated with MN by revealing several genes differentially upregulated in MN compared to other glomerular diseases. We focused on a novel protein, Family with sequence similarity 114 member A1 (FAM114A1) that was identified as the top classifier gene in the dataset.

Methods: To detect exact localization of FAM114A1 in glomeruli, we applied immunofluorescence (IF) staining with normal human kidney specimens. Staining area was compared to determine if the expression of FAM114A1 increased at the protein level in human MN and rat passive Heymann nephritis (PHN). We knocked down *FAM114A1* in cultured podocytes by siRNA transfection and conducted functional assays. We investigated protein structure of FAM114A1 in silico. To detect interacting proteins, affinity pulldown assay was performed using FAM114A1-3XFLAG protein and human glomerular extract. To determine the role of FAM114A1 in vivo, we analyzed *Fam114a1* conventional knockout mice and conducted lipopolysaccharide (LPS) -induced albuminuria tests.

Results: IF studies showed the expression of FAM114A1 in the kidney was podocyte-specific and FAM114A1 mainly localized to podocyte primary and foot processes. The expression of FAM114A1 was increased in the human MN and rat PHN model. In cultured podocytes, FAM114A1 was colocalized with F-actin and adhesion molecules. Silencing *FAM114A1* affected podocyte cytoskeletal development and podocyte cell migration. Affinity pulldown screening revealed that FAM114A1 interacts with several cytoskeleton-associated proteins. Mice lacking *Fam114a1* displayed no overt proteinuria and histopathological abnormalities in glomeruli. However, the genetic loss of *Fam114a1* attenuated albuminuria induced by LPS injury.

Conclusions: These findings suggest that glomerular injury can increase FAM114A1 expression which might promote podocyte cytoskeletal disruption. Loss of FAM114A1 could protect against glomerular injury by maintaining podocyte foot process structure.

Funding: NIDDK Support

FR-PO749

Characterization of Rho-Family of Small GTPases Interactome in Podocytes

Sajida Ibrahim, Zachary Nurcombe, Lamine Aoudjit, Jun Matsuda, Thomas M. Kitzler, Tomoko Takano. Takano Lab. *Research Institute of the McGill University Health Centre, Montreal, QC, Canada.*

Background: Podocyte injury is the major cause of proteinuria, a hallmark of kidney diseases and an important risk factor for progression to kidney failure. Rho GTPases play critical roles in podocyte cytoskeleton regulation and their alteration leads to foot process effacement. However, their regulatory mechanisms and signaling networks are largely unknown. Here, we investigated the interactomes of RhoA, Rac1, and Cdc42 in podocytes.

Methods: We defined Rho GTPases interactomes in human podocytes (HP) using the proximity-dependent biotinylation assay (BioID). We generated RhoA guanine nucleotide exchange factors (GEFs) KO lines by CRISPR/Cas9 and KIAA1522 KD zebrafish by morpholinos. We used CRISPR/Cas9 to generate systemic Arhgef6 KO mice then adriamycin and LPS injections to induce FSGS phenotype.

Results: Network analysis revealed that ~50% of the interactions are unique to podocytes while enrichment analyses highlighted biological processes related to cell adhesion and cell shape organization. BioID revealed a large panel of potential effectors, including the uncharacterized protein KIAA1522. We found that KIAA1522 translocates to filopodia in response to Cdc42 activation. KIAA1522 KD in Zebrafish induced pericardial effusion, similar to Nephrin KD. BioID also identified 20 GEFs, eleven of which interacted with RhoA. Analyses of public scRNAseq datasets showed that RhoA regulators are highly enriched in primary human podocytes. KO of the majority of identified RhoA-GEFs reduced podocyte migration, cell size and basal RhoA activity, with ARHGEF12 KO having the highest impact on RhoA activity. In addition, BioID detected ARHGEF6 as a Rac1-specific GEF. Interrogation of public transcriptomic datasets showed that Arhgef6 expression is low in healthy kidneys and increases in glomeruli with FSGS. uACR analysis showed that Arhgef6 KO mice are protected against proteinuria 5 weeks post-ADR and 24h post-LPS injections. KO mice were also resistant to ADR-induced weight restriction.

Conclusions: We dissected for the first time the upstream regulators and downstream effectors of Rho GTPases in podocytes. We identified KIAA1522 as a novel Cdc42 effector. We identified RhoA as a predominant Rho GTPase in podocytes and uncovered its key regulators. Our findings suggest that increased ARHGEF6 expression might be implicated in FSGS progression.

Funding: Government Support - Non-U.S.

FR-PO750

Molecular Mapping of Injury-Induced Contractile Actomyosin Phenotypes in Podocytes Using Expansion Microscopy

Pongpratch Puapatanakul,[1,2] Dema Yaseen Alsabbagh,[1] Ewa Langner,[1] Moe Mahjoub,[1] Jeffrey H. Miner,[1] Guy M. Genin,[3] Hani Suleiman.[1]
[1]*Washington University in St Louis School of Medicine, St Louis, MO;* [2]*Chulalongkorn University, Bangkok, Thailand;* [3]*Washington University in St Louis, St Louis, MO.*

Background: The reorganization of actin cytoskeletons into sarcomere-like structures (SLSs), characterized by the periodic intertwining of synaptopodin and myosin IIA, has been previously observed in injured podocytes both in vivo and in vitro.

Methods: To further investigate SLSs in three dimensions at super-resolution, we employed Ultrastructure Expansion Microscopy (U-ExM) on kidney tissues. Deparaffinized 5-µm kidney sections from wild-type mice and mice with nephrotic syndrome (Cd2ap-/-, adriamycin nephropathy) were anchored and embedded in acrylamide-rich hydrogels, denatured at 95C, expanded isotropically in water, and immunolabeled with relevant antibodies. The expanded samples were then imaged in z-stacks using an Airyscan confocal microscope.

Results: U-ExM enabled en-face visualization of individual foot process boundaries by staining for nephrin, a major slit diaphragm protein. In healthy podocytes, actin and the actin-binding protein synaptopodin appeared in longitudinal bundles in foot processes, while myosin IIA was present in cell bodies and major processes, but absent from foot processes. In both injury models, there was a significant increase in foot process width, indicating foot process effacement. Within the widened foot processes, actin cables were disrupted and reorganized into antiparallel bands, alternating with myosin IIA that relocated from the major processes, forming SLSs (Fig.1A). Tropomyosin 1/2 and Caldesmon, important components of actomyosin bundles in smooth muscle and non-muscle cells, were found only in mesangial cells in healthy controls, but were present in the effaced foot processes as part of SLSs, in locations corresponding to myosin IIA and actin, respectively (Fig.1B-C).

Conclusions: Injured podocytes establish SLSs with a molecular composition similar to muscle sarcomeres, suggesting this contractile machinery is an adaptive response against detachment, opening avenues for future therapeutic interventions aimed at preventing podocyte loss and progression to kidney failure.

Funding: NIDDK Support, Other NIH Support - R01 Grant, Private Foundation Support

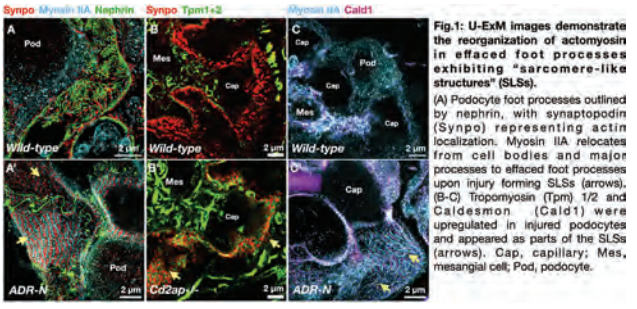


Fig.1: U-ExM images demonstrate the reorganization of actomyosin in effaced foot processes exhibiting "sarcomere-like structures" (SLSs).
(A) Podocyte foot processes outlined by nephrin, with synaptopodin (Synpo) representing actin localization. Myosin IIA relocates from cell bodies and major processes to effaced foot processes upon injury forming SLSs (arrows). (B-C) Tropomyosin (Tpm) 1/2 and Caldesmon (Cald1) were upregulated in injured podocytes and appeared as parts of the SLSs (arrows). Cap, capillary; Mes, mesangial cell; Pod, podocyte.

FR-PO751

The Actin Cytoskeleton of Injured Podocytes Transforms from a Disorganized Meshwork into Organized Contractile Sarcomere-Like Structures

Pongpratch Puapatanakul,[1,2] Ewa Langner,[1] Chengqing Qu,[3] Shumeng Jiang,[3] Moe Mahjoub,[1] Guy M. Genin,[3] Jeffrey H. Miner,[1] Hani Suleiman.[1]
[1]*Washington University in St Louis School of Medicine, St Louis, MO;* [2]*Chulalongkorn University, Bangkok, Thailand;* [3]*Washington University in St Louis, St Louis, MO.*

Background: Podocytes develop synaptopodin (Synpo)-myosin IIA (MyoIIA)-positive sarcomere-like structures (SLSs) in proteinuric kidney diseases. SLSs are mechanosensitive and may prevent detachment and contribute to recovery. To better understand SLSs biology, we investigated their development in vivo at different stages of injury.

Methods: The Adriamycin nephropathy mouse model was used to portray ongoing podocyte injury. Kidneys were collected at 3, 5, 7, 9, and 14 days post-Adriamycin injection. We combined Ultrastructural Expansion Microscopy and high-resolution confocal imaging to visualize podocyte foot processes (FPs) and SLSs. The extent of SLSs was evaluated by the percentage of SLS area per total FP area.

Results: Albuminuria was evident as early as day 2 and became pronounced by days 5-7. By light microscopy, glomeruli appeared normal on day 5, but segmental sclerosis was observed on days 9 and 14. SLSs were observed focally and segmentally starting from day 3. SLS area percentage increased over time, reaching nearly 100% by day 9. A progression of three Synpo and MyoIIA patterns in SLSs was observed (Fig.1A-C). Pattern 1: Synpo occupying most of the FP space with a few areas infiltrated by MyoIIA. Pattern 2: Alternating, disorganized Synpo-MyoIIA, with Synpo-positive bundles retained at the FP periphery. Pattern 3: Periodic, well-organized Synpo-MyoIIA striations, perpendicular to the original longitudinal axis, with peripheral Synpo bundles gone. Pattern 1 was dominant on day 3, while Pattern 3 represented over 80% of SLSs from day 7 onward. Pattern 2 became dominant on day 5, then yielded to Pattern 3 (Fig.1D).

Conclusions: Correlation between SLS patterns and timing after injury suggests that SLSs undergo stages of development from less organized actomyosin to well-organized sarcomeric patterns that exert longitudinal contractile forces. Further clinical correlation of SLS patterns may aid in predicting the fate of podocytes and disease prognosis.

Funding: NIDDK Support, Other NIH Support - R01 Grant, Private Foundation Support

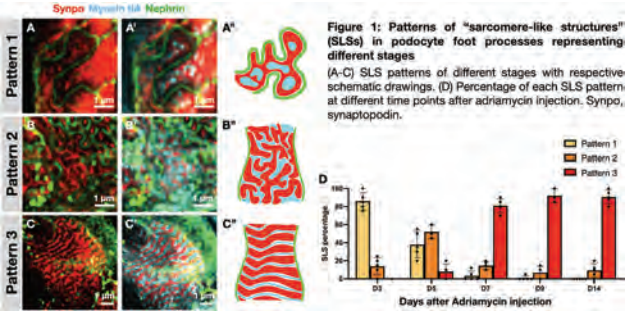


Figure 1: Patterns of "sarcomere-like structures" (SLSs) in podocyte foot processes representing different stages
(A-C) SLS patterns of different stages with respective schematic drawings. (D) Percentage of each SLS pattern at different time points after adriamycin injection. Synpo, synaptopodin.

FR-PO752

N-ethylmaleimide Sensitive Factor (NSF) Is Essential for Maintaining Podocyte Focal Adhesion

Atsuhiro Imai, Kazunori Inoue, Hiroki Okushima, Ayumi Matsumoto, Isao Matsui, Yoshitaka Isaka. *Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Japan*.

Background: Focal adhesion proteins in podocytes are critical for attaching to the glomerular basement membrane. Reduction in these proteins causes podocyturia, frequently observed in focal segmental glomerulosclerosis patients. We aimed to explore the regulation of focal adhesion molecules in podocytes.

Methods: We used a mouse model in which the Talin1 gene (*Tln1*) can be specifically knocked out in podocytes by administering doxycycline (Dox). These mice, referred to as *Tln1* cKO mice, develop progressive proteinuria and eventually experience renal failure (*J Clin Invest.* 2019 1;129(3):1295-13). We focused on the early phase of podocyte injury by examining *Tln1* cKO mice 10 days after Dox treatment (*Tln1* cKO 10d), as they showed proteinuria without elevated serum creatinine at this stage. We performed single-cell RNA sequencing (scRNAseq) on kidney samples from *Tln1* cKO 10d mice and analyzed the differentially expressed genes (DEGs). Based on the DEG analysis results, we generated another mouse model with podocyte-specific knockout of the *Nsf* gene (*Nsf* cKO mice). Using primary cultured podocytes from these *Nsf* cKO mice, we investigated the role of NSF in focal adhesion.

Results: *Nsf* was significantly down-regulated in *Tln1* cKO 10d mice podocytes. Notably, *Nsf* cKO mice developed proteinuria as early as 2 weeks of age and succumbed to end-stage kidney disease by 9 weeks. *Nsf* cKO podocytes showed a marked reduction in cell spreading, decreased mature Integrin α3β1, and increased immature Integrin α3. Immunofluorescence staining indicated expansion of the ER and ER-Golgi intermediate compartment (ERGIC) area in *Nsf* cKO podocytes. Additionally, COP2 and COP2 associated SNARE protein increased in *Nsf* cKO podocytes. These findings suggested that the deletion of *Nsf* in podocytes leads to a disruption in ER-to-Golgi transport, thereby impairing the trafficking of focal adhesion proteins such as Integrin α3.

Conclusions: NSF plays a crucial role in maintaining podocyte focal adhesions by regulating ER-to-Golgi transport and the trafficking of proteins such as Integrin α3β1. This study provides new insights into the molecular mechanisms of podocyte injury and kidney disease progression.

FR-PO753

Mathematical Modeling of Podocyte Adhesion Highlights the Role of Cell Contractility and Fluid Shear Stress on Kidney Function

Shumeng Jiang,[1] Pongpratch Puapatanakul,[2] Chengqing Qu,[1] Ewa Langner,[2] Moe Mahjoub,[2] Jeffrey H. Miner,[2] Guy M. Genin,[1] Hani Suleiman.[2,3]
[1]Washington University in St Louis, St Louis, MO; [2]Washington University in St Louis School of Medicine, St Louis, MO; [3]The University of Texas Southwestern Medical Center, Dallas, TX.

Background: Diseases of the kidney's glomerular filtration barrier can lead to podocyte detachment, which impairs filtration and ultimately leads to end-stage kidney disease. However, the mechanisms responsible for securing podocyte attachment to the glomerular basement membrane (GBM), as well as how these malfunctions in pathological conditions, are not fully understood.

Methods: In order to predict the stability of podocyte attachment, we developed a mathematical model of the actin cytoskeleton in podocyte foot processes and their connections to the GBM. This model considers forces from filtration shear and cell contraction, and their impact on the stability of integrin bonds that connect foot processes to the GBM.

Results: Our modeling reveals that specific integrin patterning in the foot processes and a balance between extrinsic and intrinsic stresses play a crucial role in maintaining stable attachment of podocytes. These findings were further supported by a new mouse model with controllable glomerular filtration rate (GFR) and cell contractility. The use of expansion microscopy (ExM) and super-resolution imaging confirmed the predicted integrin patterns, while assessments of kidney injury validated our predictions regarding the stability of podocyte attachment under varying environmental forces.

Conclusions: Our simulations and mouse model verifications emphasize the significance of mechanical stresses, specifically cell contractility and fluid shear stress, in maintaining glomerular filtration function. This insight presents new therapeutic opportunities for chronic kidney diseases by manipulating these mechanical cues.

Funding: NIDDK Support

FR-PO754

Mechanism of TPPP3-Affecting Podocyte Cytoskeleton Stability by Regulating the Acetylation Level of α-Tubulin

Qilin Chen,[1,2] Li Qiu.[1,2] *[1]Children's Hospital of Chongqing Medical University National Clinical Research Center for Child Health and Disorders, Chongqing, China; [2]Children's Hospital of Chongqing Medical University Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China*.

Background: Podocytes exhibit a unique cytoskeleton architecture, which is closely related to their function in maintaining the kidney filtration barrier. As the core structure of the skeleton network, microtubules (MTs) play a key role in supporting and maintaining the skeleton network, but there is a lack of understanding of podocyte MTs.

Methods: Single cell transcriptome sequencing and spatial transcriptome sequencing were performed on children 's kidneys. Immunofluorescence (IFA), immunohistochemical (IHC) and western blot (WB) were used to determine the expression of TPPP3, α-tubulin, acetylated tubulin (Ace-tubulin), actin microfilaments. *TPPP3*-siRNA was used to knock down podocytes, and WB was used to verify the knock-out results.

Results: Single-cell combined spatial transcriptome sequencing of children's kidneys revealed that human podocytes significantly expressed tubulin-related molecule TPPP3. The results of IHC, IFA and WB confirmed that TPPP3 was specifically expressed in the nucleus and cytoplasm of human glomerular podocytes. Surprisingly, TPPP3 was not expressed in kidneys and podocytes of mice and rats. The expression of TPPP3 was significantly increased in HPC differentiation stage compared with HPC in proliferative stage without podocyte molecular characteristics. When TPPP3 was knocked down by siRNA, the results of cell fluorescence and WB showed that the Ace-tubulin was significantly decreased, and the filamentous structure of Ace-tubulin and α-tubulin was broken, the continuity was destroyed. It is worth noting that knockdown of TPPP3 in HPCs directly leads to decreased actin (F-actin) and structural disorder. Furthermore, using drug intervention, increasing the level of microtubule acetylation can partially restore the microtubule structure damage caused by knockdown of TPPP3. In addition, the results of IFA and IHC confirmed that the expression of TPPP3 in glomeruli of MCD and FSGS patients was decreased. The in vitro podocyte injury model suggested that the expression of slit membrane protein Podocin and TPPP3 was decreased.

Conclusions: Human podocytes specifically expressed microtubule-associated protein TPPP3, which maid be involved in regulating the level of acetylated tubulin and affecting the cytoskeleton such as actin microfilaments in podocytes

FR-PO755

Identification of Crb2 Partner Proteins in Podocytes Using BioID

Soichiro Suzuki, Sajida Ibrahim, Lamine Aoudjit, Simon Leclerc, Serge Lemay, Tomoko Takano. *Research Institute of the McGill University Health Centre, Montreal, QC, Canada*.

Background: Crb2 is an essential protein expressed at the slit diaphragm of podocytes and its mutations cause hereditary nephrotic syndrome. We also reported that anti-Crb2 antibodies may be causal in idiopathic nephrotic syndrome. However, how Crb2 functions in podocytes is not fully understood. To obtain insight into the signaling pathways of Crb2, we conducted proximity-dependent biotinylation and proteomics (BioID).

Methods: BioID is based on the fusion of a promiscuous *E.coli* biotin ligase (BirA) to a target protein, Crb2. Intracellular domain of human Crb2 (1223-1285aa) was subcloned downstream of the extracellular/transmembrane domain of IL2R, conjugated with BirA, and expressed in human podocytes. As a control, human podocytes expressing GFP-BirA were used. Biotinylated proteins were captured and analyzed by mass spectrometry. Results (n=3) were analyzed using Scaffold 5.

Results: Protein identification by BioID revealed 328 proteins exhibiting significant interaction with Crb2 (compared with GFP-control, $p<0.05$). Identified proteins were analyzed by enrichment analysis using Reactome pathways and gene ontology annotations. The results showed that Crb2 partner proteins are predominantly involved in Rho, Rac and Cdc42 GTPase signaling pathways, covering 20 out of the 25 most significantly enriched Reactome pathways. Furthermore, Crb2 interactors significantly contribute to actin cytoskeleton organization (GO ID 30036, adjusted p-Value 4.70E-08) and cell adhesion (GO ID 7155, adjusted p-Value 1.91E-06). Of interest, ARHGEF26, an upstream activator of Rho family proteins, was identified as one of the Crb2 interactors. We confirmed the interaction by co-immunoprecipitation and immunostaining showed ARHGEF26 and Crb2 colocalization in both immortalized human podocytes and mouse glomeruli. Analysis of public scRNAseq datasets showed that ARHGEF26 expression in the kidney is highly specific to podocytes. CRISPR/Cas9 KO of ARHGEF26 in podocytes reduced RhoA and Rac1 activation as well as cell projection formation in response to EGF.

Conclusions: Crb2 plays a crucial role as a cytoskeletal regulatory protein in podocytes, and alterations in Crb2 signaling will likely lead to cytoskeletal changes and subsequent podocyte injury. We are investigating the identified proteins to elucidate their roles in Crb2 signaling, with the goal to identify novel therapeutic targets.

FR-PO756

Molecular Architecture of the Kidney Slit Diaphragm Revealed by Cryo-electron Tomography

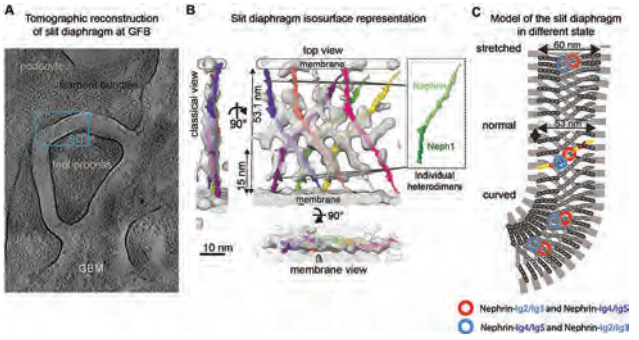
Alexandra N. Birtasu,[1] Konstantin Wieland,[1] Florian Grahammer,[2] Achilleas Frangakis.[1] *[1]Goethe-Universitat Frankfurt am Main, Frankfurt am Main, Germany; [2]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: In this contribution, we will present the molecular architecture of the slit diaphragm (SD), the primary cell-cell junction between podocytes, as imaged by cryo-electron tomography (cryoET) at nanometer resolution. The molecular components of the SD are known from comprehensive mass spectrometry and other studies. Here, we put this information into the context of our cryoET images and depict the SD as an elaborate network of criss-crossing molecules resembling a molecular sieve.

Methods: We isolated mouse glomeruli using the sieving method and vitrified them by high-pressure freezing. Next, we used cryo-focused ion beam milling for specimen thinning, and cryo-electron tomography to visualize the vitreous lamellae obtained from the frozen glomeruli.

Results: Our images show that the SD resembles a fishnet pattern. Fitting of the molecular components provides detailed insights into its structural organization. We construct a blueprint of the SD, describing the complex interaction pattern with multiple contact sites between the molecules Nephrin and Neph1

Conclusions: The SD is a quasi-crystalline, sheet-like molecular polymer that provides the necessary stability and flexibility to compensate for mechanical forces occurring within glomeruli. This advances the understanding of SD biology and holds promise for future studies on structural changes of the SD.



FR-PO757

Deciphering the Role of Slit-Diaphragm Interactors in Podocyte Integrity and Glomerular Diseases

Badr Khbouz, Bernhard Dumoulin, Hui Wu, Tobias B. Huber, Florian Grahammer. *Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: Renal filtration is determined by the slit-diaphragm (SD), a cell-cell junction between the foot processes of renal podocytes. Through an unbiased screening approach, we have identified several interaction partners of the SD core proteins Nephrin, Neph1 and Podocin. Here, we investigate the role of two of them: the natriuretic peptide receptor 3 (NPR3), a member of the ANP Receptors, and MER Proto-Oncogene, Tyrosine Kinase (MERTK), a member of the TAM receptor tyrosine kinases.

Methods: Podocyte specific knockout C57BL/6 mice (*NPR3*$^{-/-}$) and (*MERTK*$^{-/-}$) were used. *NPR3*$^{-/-}$ and *WT* mice (n=54) were exposed (or not) to unilateral nephrectomy followed by Deoxycorticosterone acetate (DOCA) high salt hypertension model. After weekly measurements of blood pressure (BP) and albuminuria (6 weeks), the kidneys and blood were harvested for functional and tissue assessment. Next *NPR3*$^{-/-}$ and *WT* mice (n=20) were subjected to the Adriamycin nephropathy model, 10 days' post treatment, urine, blood and kidney were collected for analysis. Lastly, *MERTK*$^{-/-}$ and *WT* mice (n=26) were exposed to nephrotoxic serum induced nephritis (NTN) model, with the assessment of albuminuria and glomerular damage 4 and 8 days' post-treatment.

Results: Following DOCA administration, the systolic BP, kidney weight, glomerular tuft volume, and albuminuria were increased in treated animals compared to controls ($p<0,01$), *NPR3*$^{-/-}$ mice showed intermedium profile between *WT* and *controls*. Adriamycin treatment induced a mild albuminuria in *WT*, unlike *NPR3*$^{-/-}$ mice ($p<0,05$). Blood Urea Nitrogen (BUN) was not different. Following NTN treatment, albuminuria levels and glomerular damage were increased in both genotypes, yet this phenotype was significantly more severe in *MERTK*$^{-/-}$ mice compared to *WT* animals.

Conclusions: Given that both NPR3 and MERTK are involved in cellular signaling, these results suggest a potential role of these interactors in the dynamic adaptation of podocyte and/or SD function. The molecular mechanisms behind these dynamic changes are currently being deciphered.

Funding: Government Support - Non-U.S.

FR-PO758

Fluid Flow Shear Stress-Induced Podocyte Glycosylation Changes: Implications for Glomerular Function

Tarak Srivastava,[1] Jan Novak,[3] Stacy D. Hall,[3] Colin Reily,[3] Mukut Sharma.[2] *[1]Children's Mercy Kansas City, Kansas City, MO; [2]Kansas City VA Medical Center, Kansas City, MO; [3]The University of Alabama at Birmingham Department of Cell Developmental and Integrative Biology, Birmingham, AL.*

Background: We have demonstrated that hyperfiltration-induced increase in fluid flow shear stress (FFSS) causes podocyte injury and loss of glomerular function following unilateral nephrectomy (UNx) in rodent models. To explain how glycosaminoglycans (GAGs) on cell surfaces respond to FFSS, Tarbell (J Intern Med. 2006:339) introduced the 'wind in the trees' model. Here, GAGs, akin to branches of proteoglycans in the glycocalyx, detect fluid flow (wind) and convey the force to the membrane/actin cytoskeleton network (ground) through the core protein (tree trunk). To address the chain of events and mechanism of FFSS-induced podocyte injury, we hypothesize that increased FFSS affects the membrane glycoproteins with extensive network of glycans exposed to the environment.

Methods: Differentiated immortalized murine podocytes were treated with FFSS (2 dynes/cm^2) for 2 h (37°C, 5% CO_2) and studied at the end of FFSS treatment, and 2 h and 24 h post-FFSS were termed End-FFSS, Post-2h, Post-24h and Control (untreated). Western blot analysis of podocyte glycoproteins was performed using lectins specific for high-mannose glycans (GNL), *N*-glycans with 3 and 4 antennas (PHA), alpha2,3-linked sialic acid (MAA), alpha2,6-linked sialic acid (SNA), and core 1 *O*-glycans (jacalin). RT-qPCR using Qiagen PCR arrays was performed to determine changes in gene expression of selected glycosylation enzymes.

Results: Lectins GNL, PHA, and SNA reacted with more glycoproteins of a wide range of molecular mass compared to MAA and jacalin. Podocytes at End-FFSS and Post-2h showed increased alpha2,6- and alpha2,3-linked sialic acid and more tri- and tetra-antennary *N*-glycans compared to Control. Post-24h samples showed results comparable to Control. Gene expression of specific glycosyltransferases, such as sialyltransferases and GlcNAc-transferases was upregulated at End-FFSS or Post-2h compared to Control and reverted to Control levels.

Conclusions: Brief FFSS caused immediate changes in podocyte glycosylation including *N*-glycosylation consistent with increased branching and sialylation. These transient but substantial changes were paralleled by changes in the expression of specific glycosylation enzymes. Persistent hyperfiltration-induced increase in FFSS may result in lasting changes in glycan metabolism and thus alter the membrane interface leading to functional changes.

Funding: NIDDK Support

FR-PO759

Change of Podocyte-Glomerular Basement Membrane Interaction in Glomerular Disease or Under Fluid Shear Stress

Minseob Eom,[1] Ji-Hee Kim,[2] Bao T. Dang,[1] Jae Won Yang,[1] Seung-Kuy Cha,[1] Jae seok Kim.[1] *[1]Yonsei University Wonju College of Medicine, Wonju, Gangwon-do, Republic of Korea; [2]Soonchunhyang University, Asan, Chungcheongnam-do, Republic of Korea.*

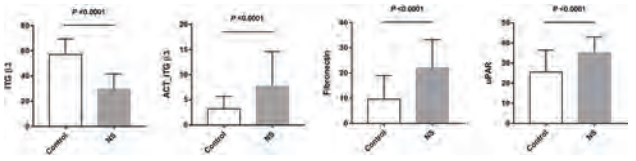
Background: The interaction between podocyte and glomerular basement membrane (GBM) determines podocyte stability. We hypothesized that the interaction between podocyte and GBM changed in response to adverse conditions, such as glomerular disease or fluid shear stress (FSS). Here, we aimed to explore the podoctye-GBM interaction in glomerular disease or under FSS through investigating changes of integrin (ITG) αVβ3, fibronectin, and uPAR.

Methods: We performed immunohistochemical staining for ITG β3, fibronectin, and uPAR in human kidney tissues obtained from patients with trauma (control) and nephrotic syndrome (NS). Furthermore, we exposed conditionally immortalized human podocyte cells to 200 rpm of FSS and observed changes in the expression of ITG β3, fibronectin, and uPAR. Lastly, we evaluated cell viability depending on the condition of dish coating.

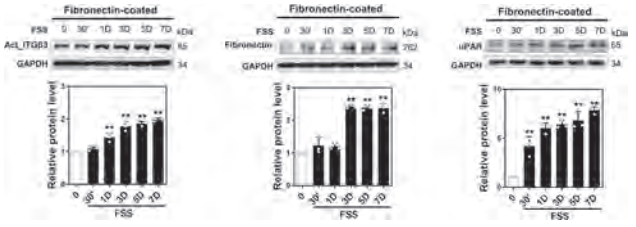
Results: The results showed that ITG β3 expression was lower in the NS group, while the expressions of activated ITG β3, fibronectin, and uPAR were higher compared to the control (Figure 1). Furthermore, FSS increased the expressions of activated ITG β3, fibronectin, and uPAR (Figure 2). Dish coating with collagen or fibronectin improved cell viability compared to a non-coated dish under FSS.

Conclusions: ITG αVβ3 is activated in glomerular diseases or under FSS. The activation of ITG αVβ3 is associated with increased fibronectin and uPAR. The improvement of cell viability in a coated dish suggests that the interaction between extracellular matrix and activated ITG αVβ3 contributes to increasing podocyte stability.

Funding: Government Support - Non-U.S.



Expressions of ITG b3, activated ITG b3, fibronectin, and uPAR between control and nephrotic syndrome groups.



Changes of activated ITG b3, fibronectin, and uPAR under fluid shear stress.

FR-PO760

Diabetes and SGLT2 Inhibitor Treatment Alter Podocyte Glycocalyx

Alejandra Becerra Calderon, Hasen Alkoraishi, Audrey Izuhara, Sachin K. Deepak, Greta H. Trogen, Janos Peti-Peterdi, Georgina Gyarmati. *University of Southern California, Los Angeles, CA.*

Background: The glycocalyx between the podocyte foot processes and the glomerular basement membrane (GBM) has been difficult to study in vivo, therefore its function remains elusive. Recently we developed and initially characterized the Pod-Sdc1-GFP mouse model with podocyte specific genetic labeling to study the physiological role of podocyte glycocalyx. Here we aimed to visually demonstrate the alterations in podocyte glycocalyx in diabetes with and without SGLT2i treatment in vivo.

Methods: New genetic mouse models were generated by the knock-in of pCAG-Lox-STOP-Lox-EGFP-Sdc1 to generate animals with Cre-dependent expression of a syndecan-1 (Sdc1) fusion protein with N-terminal, extracellular GFP. Sdc1-GFP^{flox} animals were crossed with Podocin-Cre mice for the specific genetic labeling of the glycocalyx in podocytes. Intravital multiphoton microscopy (MPM) was used to measure changes in the depth of glycocalyx and corresponding changes in GFB function in vivo over time in streptozotocin induced diabetic kidney disease with or without SGLT2i empagliflozin treatment. Alexa-594 conjugated wheat germ agglutinin (WGA) lectin was used to label the glycosaminoglycan (GAG) component of the glycocalyx, and Alexa-680 conjugated albumin was used to visualize GFB permeability.

Results: Co-localization of genetic GFP and Alexa-594 WGA confirmed podocyte glycocalyx labeling. MMP9 injection significantly reduced podocyte glycocalyx thickness and resulted in glomerular albumin leakage confirming podocyte glycocalyx functionality. In vivo MPM imaging in diabetic mice revealed a significant decrease in glycocalyx thickness on both the apical and the basal surface (0.76+/-0.01 um) compared to control (1.03+/-0.02 um) and increased GFB permeability. SGLT2i treatment restored podocyte glycocalyx thickness (0.9+/-0.01 um) and reduced albumin leakage in diabetic mice but not in healthy control animals (1.01+/-0.01 um).

Conclusions: In conclusion, the specialized podocyte glycocalyx at the GBM may function as an important new layer of the GFB, may play an important role in the disruption of GFB functions in diabetic kidney disease, and may be involved in the pleiotropic renoprotective effects of SGLT2i treatment.

Funding: NIDDK Support, Private Foundation Support

FR-PO761

Endosomal Recycling and Proteasomal Degradation of R168H Variant Podocin Contributes to Nephrotic Syndrome Pathophysiology

Aude Dorison,[1,2] Inês P. Santos,[3] Irene Ghobrial,[1,2] Rachel Lam,[1,2] Katrin Stuber,[4] Jillian C. Danne,[5] Michael M. See,[1,2] Georg Ramm,[5] Fernando J. Rossello,[1,2] Mirana Ramialison,[1,2] Kristina B. Emdal,[4] Melissa H. Little.[1,2] *[1]Murdoch Children's Research Institute, Parkville, VIC, Australia; [2]Novo Nordisk Foundation Center for Stem Cell Medicine - reNEW Melbourne, Melbourne, VIC, Australia; [3]Novo Nordisk Foundation Center for Stem Cell Medicine - reNEW Copenhagen, Copenhagen, Denmark; [4]NNF Center for Protein Research, University of Copenhagen, Copenhagen, Denmark; [5]Monash University, Melbourne, VIC, Australia.*

Background: Nephrotic syndrome (NS) arising from *NPHS2* variants is most common in children over 3 months of age. Using stem-cell derived kidney organoid podocytes, we previously reported distinct mistrafficking of specific missense *NPHS2* variants, with a distinct Golgi accumulation of the p.R168H variant podocin. While a novel mislocalisation for this variant, the pathophysiology of this mistrafficking remained unclear.

Methods: Induced human pluripotent stem cells generated from a homozygous (HOM) *NPHS2* p.R168H patient, healthy heterozygous (HET) parent and healthy wild type (WT) individual were differentiated into kidney organoids. Organoid glomeruli isolated from each genotype were analysed by transcriptomics and proteomics followed by gene set enrichment analyses. Immunostaining and immunogold electron microscopy (EM) were performed to validate omics data and study PODOCIN subcellular localisation in podocytes.

Results: Glomerular proteomics revealed significant differences in protein prevalence and ubiquitination between HOM and healthy podocytes. Reduced diglycine-modified lysine residues suggested preferential inhibition of YAP1 ubiquitination in HOM podocytes. This was supported by a trend of increased nuclear translocation for this transcription coregulator. A combined analysis of proteomics and transcriptomics revealed reduced ER-to-Golgi trafficking (decreased KDELR1/2, SURF4 and PDCD6) but increased recycling endosome activity (elevated RAB25) in HOM podocytes, suggesting a return from the membrane to the Golgi of the variant protein. This was confirmed using immunogold EM which detected p.R168H at the membrane, in multivesicular bodies, endosomes and Golgi while the WT protein was mainly located at the membrane. Finally, while lysosomal trafficking was reduced, p.R168H protein levels were elevated upon treatment with a proteasomal inhibitor, Bortezomib.

Conclusions: Our data indicate that p.R168H variant podocin can reach the slit-diaphragm but is then recycled back to the Golgi and/or targeted for degradation by the proteasome. This variant-specific pathophysiology will assist in the design of treatments for this form of genetic NS.

Funding: Government Support - Non-U.S.

FR-PO762

Podocytes Derived from Patients with Proteinuria Associated with Truncating Mutation in CLCN5 Display Increased Apoptosis and Defective Endocytosis

Brandon M. Lane,[1,2] Megan Chryst-Stangl,[1,2] Sue Zhang,[1] Guanghong Wu,[1,2] Rasheed A. Gbadegesin.[1,2] *[1]Duke University, Durham, NC; [2]Duke Molecular Physiology Institute, Durham, NC.*

Background: Pathogenic mutations in the gene encoding Chloride Voltage gated channel 5 (CLCN5) are generally associated with Dent Disease, a tubular disorder characterized by nephrolithiasis. However, a few *CLCN5* variants have also been reported to cause nephrotic syndrome (NS) phenotypes. We previously identified a novel segregating hemizygote truncating mutation (c. 1199del, p.Gly400ValfsTer29) in *CLCN5* in a family with four affected boys with NS phenotypes and biopsy proven focal segmental glomerulosclerosis (FSGS). *CLCN5* encodes a member of the chloride ion channels and ion transporters that regulate endosomal acidification and receptor-mediated endocytosis in tubules but is also expressed in the podocyte. However, it is unknown if pathogenic mutations that produce NS phenotypes can affect podocyte homeostasis.

Methods: To determine if pathogenic mutations in CLCN5 can alter podocyte homeostasis, we examined endocytosis and apoptosis phenotypes in iPSC-derived podocytes from patients with *CLCN5* mutations and their unaffected family members. We also examined the effect of CLCN5 gene deficiency in multiple immortalized podocyte cell lines by using lentiviral based gene knockdown. Automated live-cell imaging of internalized fluorescent pHrodo labeled dextran molecules was used quantify the endocytosis of small molecules. Live-cell imaging of fluorescent reporters of caspase 3 activity as well as propidium iodide were used to measure podocyte viability when podocytes were exposed to serum starvation.

Results: Podocytes derived from the affected family members with the truncating *CLCN5* variant displayed decreased endocytosis of fluorescent dextran molecules and increased apoptosis compared to podocytes from unaffected family members ($p<0.001$ for both assays). Immortalized podocytes with *CLCN5* gene deficiency displayed similar phenotypes.

Conclusions: Pathogenic variants in *CLCN5* capable of inducing NS phenotypes cause decreased podocyte endocytosis. These reductions in endocytosis likely contribute to the reduced viability associated with deficiencies in *CLCN5*. Further investigation is required to determine if additional processes contribute to the increased apoptosis in *CLCN5* deficient podocytes.

Funding: Private Foundation Support

FR-PO763

Synaptobrevin, a Major Protein of v-SNARE, Participates in Maintenance of Foot Processes of Podocytes: Downregulation of Synaptobrevin Is an Initiation Event Leading to Podocyte Injury in Minimal Change Nephrotic Syndrome (MCNS) Model

Takashi Nagai, Mutsumi Kayaba, Ying Zhang, Guoqing Chang, Yoshiyasu Fukusumi, Hiroshi Kawachi. *Department of Cell Biology, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: Podocytes contain synaptic-like vesicle that contributes to maintaining specialized podocyte morphology and function. We reported synaptic vesicle protein 2B (SV2B) is expressed on the vesicle and plays a critical role in podocytes. However, the molecular basis and the function of the vesicle are not well understood. Synaptobrevin is a v-SNARE expressed on the synaptic vesicle and plays a central role in docking to plasma membrane. In this study we investigated the association with SV2B, expression and localization, and physiological and pathological roles of synaptobrevin in podocytes.

Methods: Association with SV2B was analyzed with SV2B-deleted podocytes. The expression in normal and injured podocyte was analyzed. The function was elucidated with cultured podocyte treated with siRNA for synaptobrevin.

Results: The expression of synaptobrevin was lowered in SV2B knockdown cultured podocyte (24.7±6.4%, $p< 0.05$). Synaptobrevin was restrictedly expressed in podocyte in glomeruli. In both rat and human kidney sections synaptobrevin was detected as a dot-like pattern along capillary loop. Major parts of synaptobrevin were co-stained with synaptopodin, a marker of foot processes. mRNA expression of synaptobrevin was decreased already at 1h in PAN nephropathy, a mimic of MCNS (37.9±16.4 % to normal) and the synaptobrevin staining became discontinuous on day 10, when proteinuria peaked and foot processes effacement was broadly detected (score: 2.23 ±0.03 vs. normal; 3.74±0.06, $p<0.05$). The expression of synaptobrevin in cultured podocytes increased with differentiating (2.88 times higher). If synaptobrevin was deleted, podocyte changed to round shape and the rate of podocytes possessing processes was lowered (19.3±4.7% vs. 34.0±2.6%, $p<0.01$), and mRNA expressions of slit diaphragm molecules were lowered (nephrin, 50.9±1.9%; CD2AP, 47.3±3.2%, $p<0.05$).

Conclusions: Synaptobrevin participates in maintenance of foot processes of podocytes in cooperation with SV2B. Downregulation of synaptobrevin is involved in effacement of foot process and consequent downregulation of slit diaphragm molecules, which leading to proteinuria. Synaptobrevin can be an early marker and a therapeutic target of podocyte dysfunction.

Funding: Government Support - Non-U.S.

FR-PO764

Identification of RNASE1 as a Novel Contributor to Cytoskeleton Remodeling in Podocytes

Patricia Bolanos-Palmieri,[1] René Krüger,[1] Evren U. Azeloglu,[2] Mario Schiffer.[1] *[1]Universitatsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: A dynamic cytoskeleton is critical to the health and function of the podocytes as it provides structural and signalling support to the cell. We have previously shown that recovering the cytoskeleton can be a viable strategy to treat podocyte dysfunction. In this project, we used a unique human peptide library to identify native bioactive peptides with the capacity to modify the podocyte cell structure and cytoskeleton.

Methods: To test the fractions derived from the hemofiltrate peptide library, protein kinase C epsilon knockout mouse podocytes (PKCε KO) were used as a model for cytoskeletal dysfunction. After iterative tests in cell culture, the bioactive fraction was selected and the candidate peptide (CP) was identified by mass spectrometry. We used a purified recombinant version of the CP to test its effect on PKCε KO cells and on dasatinib treated human podocytes. Morphological changes were quantified by imaging components of the cytoskeleton. Possible mechanistic targets were analyzed by western blot and transcriptomics.

Results: Using PKCε KO podocytes we systematically tested the hemofiltrate and were able to identify one fraction capable of influencing cell morphology. Further analysis showed that RNASE1 could be a mediator of the observed structural changes. To explore this, additional tests were performed using recombinant RNASE1 which showed that exposing the PKCε KO podocytes to RNASE1 lead to an increase in cell spreading and number of focal adhesions resulting in improved cell attachment and cell morphology that more closely resemble that of wild type podocytes. This result was further confirmed using other injury models like human podocytes exposed to dasatinib. Preliminary data looking into the mechanisms involved in cytoskeleton rearrangement in response to RNASE1 suggest that there may be differential tyrosine kinase signalling in podocytes treated with RNASE1. Additionally, RNA sequencing identified 18 differentially regulated genes as candidates for further analysis.

Conclusions: This systematic approach led to the identification of a novel candidate protein able to positively alter podocyte morphology. By modifying the structural changes that result from injury, RNASE1 could provide new insights into the molecular mechanisms that result in podocyte dysfunction and proteinuria as well as open new avenues for treatment.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO765

Forces of Filtrate Flow on Podocyte Foot Processes Studied by Three-Dimensional and Two-Dimensional Computational Fluid Dynamics

Alexander Fuhrmann,[1] Balazs Pritz,[1] Karlhans Endlich,[2] Wilhelm Kriz.[3] *[1]Karlsruher Institut fur Technologie, Karlsruhe, Germany; [2]Universitatsmedizin Greifswald, Greifswald, Germany; [3]Universitat Heidelberg, Heidelberg, Germany.*

Background: The glomerular filtration barrier is exposed to forces arising from filtration pressure and filtrate flow. Filtrate flow acts on podocyte cell bodies in Bowman's space and on foot processes (FPs) lining the filtration slit. Besides a previous estimate of 8 Pa (Endlich & Endlich, *Semin. Nephrol.* 2012), the magnitude of shear stress to FPs remains unknown.

Methods: We used numerical flow simulations to study forces arising from glomerular filtration. Simulations were run with a 3D model of a filtration unit and the filtration parameters of the rat kidney. The filtration unit consisted of fenestrated endothelium, the GBM, and two opposing halves of FPs bridged by the slit diaphragm (SD). The GBM was modeled as a porous medium, the SD as a zipper structure (Rodewald & Karnovsky, *J. Cell Biol.* 1974).

Results: Filtrate flow exerted a mean wall shear stress (WSS) of 39 Pa with a maximum of 152 Pa on the plasma membrane of FPs and up to 250 Pa on the SD zipper structure. After crossing the GBM and converging into the filtration slit, filtrate flow is markedly accelerated. Thus, the filtration slit acts like a nozzle explaining the high shear stress on FPs. SD accounted for 25% of the hydrodynamic resistance of the glomerular filtration barrier. Based on the results of the 3D model, we developed a 2D model with 20-fold reduced computing time to perform extensive parameter variations. In the 2D model, GBM and SD were both represented as porous media with independent viscous resistances. When SD resistance was increased (and GBM resistance was lowered in such a way to keep filtrate flow velocity constant) WSS increased noticeably. Reducing the filtration slit width by 25% from 40 to 30 nm almost doubled WSS, demonstrating the non-linearity of the nozzle effect. On the other hand, increasing filtrate flow velocity by 50 and 100% increased WSS by 47 and 94%, respectively, in a practically linear way. Changes in net filtration pressure did not affect WSS, as long as filtrate flow velocity was kept constant.

Conclusions: Our data demonstrate that FPs are likely to experience high levels of wall shear stress in the filtration slit that markedly exceed levels of endothelial wall shear stress. Two factors were identified to account for the high shear stress: the nozzle geometry of the filtration slit and the hydrodynamic resistance of the slit diaphragm.

Funding: Government Support - Non-U.S.

FR-PO766

Synaptopodin-Enhanced Podocytes Perpendicular Force Resistance In Vivo and In Vitro

Chengqing Qu,[1] Shumeng Jiang,[1] Jeffrey H. Miner,[2] Guy M. Genin,[1] Hani Suleiman.[2] *[1]Washington University in St Louis, St Louis, MO; [2]Washington University in St Louis School of Medicine, St Louis, MO.*

Background: Focal adhesions are able to resist shear forces in almost all types of cells. However, kidney podocytes face a unique challenge as they must also withstand stress that is perpendicular to their basement membrane. We hypothesis that synaptopodin, a specialized actin-binding protein that is highly expressed in podocytes, acts as a linker to facilitate the resistance of focal adhesions to these perpendicular forces.

Methods: We developed an in vitro system to study the impact of perpendicular forces on cells cultured on hydrogels with defined stiffness and coated with Laminin a5b2g1. By applying centrifugal forces, this setup was able to mimic the perpendicular forces experienced by podocytes in their natural glomerular microenvironment. We used primary podocytes taken from both wild-type control (WT) mice as well as mice lacking synaptopodin (Synpo KO). We compared these cells to osteosarcoma cells (U2OS cells), a bone cancer cell that also highly express synaptopodin. We assessed the cellular responses to the centrifugal forces using morphological analysis as well as immunostaining for integrins, synaptopodin, a-actinin-4, myosin IIA and actin. We also used AAV8-TBG-Ren1 virus to increase the blood pressure in vivo and further increased the detaching force on the podocytes from the basement membrane.

Results: The WT primary podocytes spread and form a continuous skirt of integrins at their periphery. The continuous integrin is colocalized with synaptopodin and maintains the sarcomere like structure (SLS) at the periphery. However, Synpo KO primary podocytes do not exhibit this continuous integrin b1 pattern at the cell periphery. Instead, Synpo KO cells show a diffuse pattern and are likely to detach. After the injection of AAV8-TBG-Ren1virus in WT and Synpo KO mice, we observed the severe proteinuria with Albumin/Creatinine ratio (ACR) measurement.

Conclusions: We discovered a mechanical role for synaptopodin in podocytes. When centrifugal force is applied, WT primary podocytes can withstand these perpendicular forces by significantly rearranging their focal adhesions. A deficiency in synaptopodin weakens the podocytes' ability to respond to these forces and is linked to increased detachment. This function of synaptopodin may play a crucial role in podocyte adhesion to the basement membrane during their responses to elevated stresses and injury.

FR-PO767

Investigation of Alternative Splicing in Mechanically Stretched Podocytes as a Model for Glomerular Hypertension

Nicole Endlich,[1,2] Felix Kliewe,[1] Francescapaola Mattias,[1] Elke Hammer,[6] Olga Tsoy,[3] Alexander Gress,[4] Stefan Simm,[5] Jan Baumbach,[3] Uwe Völker,[6] Karlhans Endlich.[1] Endlich Lab. *[1]Department of Anatomy and Cell Biology, University Medicine Greifswald, Greifswald, Germany; [2]NIPOKA GmbH, Greifswald, Germany; [3]Institute for Computational Systems Biology, University of Hamburg, Hamburg, Germany; [4]Department of Drug Bioinformatics, Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Helmholtz Centre for Infection Research (HZI), Saarbrücken, Germany; [5]Institute of Bioinformatics, University Medicine Greifswald, Greifswald, Germany; [6]Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany*.

Background: Alterations in pre-mRNA splicing play an important role in disease pathophysiology. However, the role of alternative splicing (AS) in hypertensive nephropathy (HN) has not been investigated. The purpose of the Sys_CARE (Systems Medicine Investigation of AS in Cardiac and Renal Diseases) project was to identify AS events that play a role in the development and progression of HN.

Methods: Cultured mouse podocytes were exposed to mechanical stretch for 3 days under low and high stretch conditions using the *Stretchy* apparatus (NIPOKA GmbH, Greifswald). Subsequently, mRNAs and proteins were analyzed by RNA-Seq and LC-MS/MS. Splicing and transcript expressions were studied with bioinformatical tools.

Results: Transcriptome analyses of mechanically stretched podocytes by RNA-seq showed that mechanical stress leads to a high number of differentially expressed genes compared to unstretched podocytes. GO analysis revealed that a higher number of actin-binding genes were down- and mRNA processing genes were up-regulated. To identify alternative splicing (AS) events, different AS tools were used. We found a wide variety of splice events. The most frequent event was exon skipping, followed by intron retention. We found 290 alternatively spliced genes after mechanical stretch, which were detected with three different splice analysis tools (rMATS, leafcutter, Whippet). Out of these candidates, the IsoformSwitchAnalyzeR identified 17 genes exhibiting significant isoform switches. To prioritize the candidates, we performed a screening that included only those genes that were identified by proteomic analysis, are expressed in podocytes *in vivo* or showed an altered expression patterns in glomerular disease. This screening led to the two candidates Shroom3, an actin-binding protein, which is crucial for podocyte morphology and function and Myosin light chain 6 (Myl6), a component of the myosin motor protein complex.

Conclusions: Mechanical stretch of cultured mouse podocytes, which is an excellent model to simulate hypertensive nephropathy, leads to alterations in isoform expression due to alternative splicing. These changes in the expression of isoforms, such as Shroom 3 and Myl6, have the potential to play a key role in the pathophysiology of hypertension-induced nephropathy.

FR-PO768

Liquid-Liquid Phase Separation of Lmx1b Contributes to Its Gene-Regulatory Effects, Including Noncanonical Wnt Signaling in Podocytes

He Chen,[1,2] Richard A. Tillmann,[1,2] Antonios Papadakis,[2] Eva Wiesner,[1,2] Andreas Beyer,[2] Thomas Benzing,[1,2] Martin Kann.[1,2] Nephrolab. *[1]Universitatsklinikum Koln, Koln, Germany; [2]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany*.

Background: Lmx1b is a transcription factor (TF) that is essential for podocyte maintenance. However, the function and mechanism of action of Lmx1b in podocytes remain poorly understood. Liquid-liquid phase separation (LLPS) has gained attention as a key mechanism for regulating transcription via the formation of nuclear transcriptional condensates, which is mediated by multivalent interaction between TFs, coactivators and general transcriptional machinery. Here, we investigate if Lmx1b undergoes LLPS as a biophysical mechanism of action and elucidate gene-regulatory effects of Lmx1b loss of function in podocytes *in vivo*.

Methods: Tamoxifen inducible conditional podocyte-specific Lmx1b knockout mice (Lmx1b-ipko) and cell lines were used as model systems. LLPS was investigated using recombinant proteins *in vitro* as well as in cell culture by overexpression. Lmx1b-ipko mice were phenotyped by STED microscopy. The gene-regulatory effects of Lmx1b *in vivo* were assessed in a time-series approach by glomerular Multiome (snRNAseq & snATACseq). The effect of Wnt ligands on the level of calcium and the actin cytoskeleton in podocytes was investigated *ex vivo* using acute kidney slices from transgenic mice expressing fluorescent actin reporter and calcium sensor.

Results: Tamoxifen induction in Lmx1b-ipko mice resulted in a progressive, time-dependent FSGS phenotype. Here, Lmx1b staining in podocyte nuclei showed speckled pattern in STED, suggesting nuclear condensation formation *in vivo*. Recombinant Lmx1b can undergo LLPS *in vitro*. Live cell imaging of eGFP.Lmx1b demonstrated that an intrinsic disordered region in Lmx1b is essential for driving LLPS in cells. Transcriptional effects of Lmx1b revealed by Multiome analysis indicated a progressive dysregulation of the non-canonical Wnt signaling pathway, in particular an upregulation of Wnt5b. In an *ex vivo* podocyte reporter system, the stimulation of glomeruli using Wnt5b resulted in increased calcium signals and altered actin cytoskeleton indicative of podocyte damage.

Conclusions: We determined that LLPS of Lmx1b is a key mechanism of its gene-regulatory action. Lmx1b-dependent gene regulation can be linked to non-canonical Wnt signaling in podocytes as novel downstream effects for mediating podocyte damage.

Funding: Government Support - Non-U.S.

FR-PO769

Influence of Mitochondrial Signals on Metabolic Signaling Pathways in Podocytes

Katrin Reitmeier,[1,2] Johanna Odenthal,[1,2] Bernhard Schermer,[1,2] Thomas Benzing,[1,2] Paul T. Brinkkoetter.[1,2] Nephrolab Cologne. *[1]University of Cologne Center for Molecular Medicine Cologne, Cologne, Germany; [2]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany*.

Background: Mitochondrial signals are of interest in podocyte research due to the identification of single gene mutations associated with glomerular diseases, including a cluster of genes linked to mitochondrial dysfunction. We recently identified a link between structurally impaired mitochondria due to the loss of PHB2, a protein essential for the fusion of mitochondria, and hyperactivation of the Insulin signaling cascade in *Phb2* deficient podocytes. The mouse model revealed that hyperactive Insulin signaling causes a severe glomerular phenotype and premature death of the animals. This phenotype was ameliorated by blocking of insulin receptor signaling via double knockout of the Insulin and IGF-1 receptor (Ising et al. 2015).

Methods: We use *Drosophila melanogaster* nephrocytes to examine the signaling mechanism from dysfunctional mitochondria to the Insulin receptor. These podocyte-equivalent cells exhibit functional and structural similarities with mammalian podocytes, making them an established model for podocyte research. We employ nephrocyte-specific RNAi-mediated knockdown and simultaneous overexpression of target genes. The effects are assessed by performing fluorescent tracer uptake assay and immunofluorescence staining to evaluate nephrocyte filter function and morphology.

Results: We successfully replicated the phenotype observed in the PHB2 knockout mouse model in nephrocytes. Phb2 depletion led to a functional and morphological phenotype, and insulin signaling hyperactivation. We were able to interfere with and rescue this phenotype by overexpressing a functionally disabled insulin receptor variant. Notably, elevated ROS levels were observed upon Phb2 knockdown, even when insulin signaling was blocked. We hypothesized that ROS transduce a signal from dysfunctional mitochondria to the insulin receptor. To test this, we overexpressed SOD1 in the Phb2 knockdown background, which depleted ROS levels and significantly rescued the Phb2 phenotype.

Conclusions: Our results demonstrate that nephrocytes are a suitable model to study the link between dysfunctional mitochondria and insulin signaling hyperactivation. We propose a signaling mechanism where mitochondrial dysfunction elevates mitochondrial ROS levels, sensitizing podocytes to insulin signaling by targeting the insulin receptor and initiating receptor autophosphorylation.

Funding: Government Support - Non-U.S.

FR-PO770

Elovl7 Enhances Podocyte Ferroptosis in Glomerulopathy by Participating in Polyunsaturated Fatty Acid Elongation

Minchao Kang,[1] Linnan Bai,[1] Qiu-yu Li,[3] Yi Wang,[2] Junnan Wu.[1] *[1]Zhejiang University School of Medicine Sir Run Run Shaw Hospital, Hangzhou, China; [2]The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [3]Zhejiang University School of Medicine Children's Hospital, Hangzhou, China*.

Background: Podocytes are terminally differentiated visceral epithelial cells that form a crucial part of the glomerular filtration barrier. Podocytopathy is becoming increasingly prevalent worldwide. However, the mechanisms underlying podocyte injury remain unclear. Numerous studies have attributed podocyte loss in glomerular diseases to apoptosis, and research on podocyte-targeting therapies has emerged. This study aims to elucidate the specific mechanisms of injury and the ultimate mode of death of podocytes.

Methods: We performed single-nucleus RNA sequencing (snRNA-seq) on kidney tissues from various glomerular diseases, including adriamycin-induced nephropathy (AN), chronic kidney disease (CKD), minimal change disease (MCD), and obesity-related glomerulopathy (ORG). Cell death pathway scoring on podocytes identified the predominant form of podocyte death. Gene enrichment analyses along with pseudo-time analysis revealed multiple lipid metabolism pathways associated with podocyte

injury. Targeted lipidomics on adriamycin-stimulated Mpc5 cells (Mouse Podocyte Clone-5) and metabolic pathway scoring pinpointed changes in phospholipid types and lipid metabolism pathways. Conditional knockout mice and intracellular knockdown experiments were conducted to validate the impact of key gene in the lipid metabolism pathway we screened.

Results: Cell death pathway scoring on podocytes demonstrated elevated ferroptosis scores in nephropathies with severe podocyte injury, such as AN and CKD. Additionally, Injured podocytes had higher levels of phospholipids with long-chain unsaturated fatty acid side chains, which are sensitive to ferroptosis, compared to the control group. Metabolic pathway scoring revealed dysregulation of Elovl7-involved fatty acid elongation in the podocytes of the AN group. Podocyte-specific Elovl7 knockout in mice and Elovl7 knockdown in Mpc5 cells abolished the elevated levels of phospholipids with long-chain polyunsaturated fatty acids and lipid peroxides.

Conclusions: In summary, we found substantial podocyte loss and annotated a subset of injured podocytes in snRNA-seq data from podocytopathies. This may be due to the increased synthesis of long-chain polyunsaturated fatty acids mediated by Elovl7, which eventually leads to the accumulation of intracellular lipid peroxidation and ferroptosis.

Funding: Government Support - Non-U.S.

FR-PO771

SMPDL3b Overexpression Is Associated with STING Activation in Podocytes in CKD

Alla Mitrofanova, Antonio M. Fontanella, Veronika Semenova, Rachel Njeim, Judith T. Molina David, George W. Burke, Sandra M. Merscher, Alessia Fornoni. *University of Miami Miller School of Medicine, Miami, FL.*

Background: Chronic kidney disease (CKD) is a global health challenge marked by rising incidence, prevalence, and poorly understood pathogenesis. Our prior work suggests that sphingolipids, especially sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b), regulate podocyte function and survival. Sphingolipids also modulate inflammation, a key driver of CKD progression. Our recent findings link STING activation to podocyte foot process disruption, proteinuria, and CKD progression. Here, we aim to explore if increased SMPDL3b expression leads to podocyte injury through chronic STING activation.

Methods: Illumina sequencing RNA data analysis, qRT-PCR and Western blot analysis were used to characterize the immortalized control (CTRL) or overexpression (SMP OE) human podocytes. Cells were treated with c-diAMP (10μM), a STING specific agonist, for 24h. 8-week-old mice with podocyte specific Smpdl3b deficiency ($pSMP^{fl/fl}$) or overexpression ($pSMP^{Tg}$) were used to evaluate glomerular STING activation. $pSMP^{fl/fl}$ and $pSMP^{Tg}$ mice were intraperitoneally injected with a single dose of c-diAMP, 50mg/kg or 5% DMSO and sacrificed 72h after injection, followed by urinary albumin-to-creatinine ratio (ACR), histological and serum analyses. Two-tailed t-test or One-Way ANOVA followed by Tukey's post-test were used to detect statistical changes.

Results: We observed significant changes in the expression of genes related to cytosolic DNA sensing pathways in SMP OE podocytes. Both *in vitro* and *in vivo* experiments revealed elevated levels of STING phosphorylation (pSTING). Treatment with c-diAMP increased pSTING levels in control podocytes but not in SMP OE podocytes. While baseline proteinuria was absent in both $pSMP^{fl/fl}$ and $pSMP^{Tg}$ mice, administration of c-diAMP led to a notable increase in ACR specifically in $pSMP^{Tg}$ mice. No significant changes in body weight or levels of serum BUN and creatinine in either $pSMP^{fl/fl}$ or $pSMP^{Tg}$ mice following c-diAMP treatment. TEM analysis revealed FPE in control and $pSMP^{Tg}$ mice treated with c-diAMP, but not in $pSMP^{fl/fl}$ mice.

Conclusions: Our data indicate that SMPDL3b overexpression is associated with STING activation in podocytes *in vitro* and STING-dependent proteinuria *in vivo*.

Funding: Private Foundation Support

FR-PO772

Elevated Expression of Isthmin-1 Impairs Glomeruli Filtration Leading to Proteinuria in CKD

Ge Gao,[1,2] Zhongjun Zhou.[2] [1]*Guangdong Provincial People's Hospital, Guangzhou, China;* [2]*The University of Hong Kong Li Ka Shing Faculty of Medicine, Hong Kong, Hong Kong.*

Background: The incidence of chronic kidney disease (CKD) accounts for 10 to 13% in adults and is usually accompanied by cardiovascular diseases, exhibiting high morbidity and mortality. We observed upregulated Isthmin-1 (Ism1) in nephropathy models and aging kidneys. Ism1 transgenic (*Ism1 Tg*) mice exhibited focal segmental glomerular sclerosis (FSGS) and impaired cytoskeleton in podocytes and proteinuria, as shown by podocyte foot process effacement. In contrast, loss of Ism1 can protect mice from undergoing Adriamycin-induced FSGS and cytoskeleton injury in podocytes. However, the mechanism remains unresolved.

Methods: As a secreted protein, Ism1 functions through interacting with receptor to activate or inhibit the downstream signaling. Since ligand-receptor interaction is normally transient and weak, we took advantage of HRP-induced proximity labelling in kidney tissues to search for the potential receptor of Ism1 in glomeruli.

Results: Based on our unbiased screening of receptors with consideration to kidney phenotypes in genetically modified mice, we identified a specific Integrin as a potential receptor of Ism1 in the adult kidney. The interaction between Ism1 and this Integrin was validated in 293T cells. In addition, Ism1 triggered the activation of specific Integrin signaling, leading to the impairment of the podocyte cytoskeleton. We therefore propose that elevated Ism1 results in podocyte cytoskeleton injury by activating Integrin signaling.

Conclusions: Our findings highlight the critical role of Ism1 in the pathogenesis of kidney diseases and provide a novel target for alleviating podocyte injury and CKD.

Funding: Private Foundation Support

FR-PO773

TAZ Shows Limited Ability to Substitute for YAP in Preserving Podocytes, Demonstrating Distinct Roles of the Transcriptional Regulators at the Kidney Filtration Barrier

Lioba Ester,[1,2] Eva Wiesner,[1,2] He Chen,[1,2] Paul Diefenhardt,[1,2] Paul T. Brinkkoetter,[1,2] Thomas Benzing,[1,2] Martin Kann,[1,2] Bernhard Schermer,[1,2] Inês Cabrita.[1,2] [1]*Universitatsklinikum Koln, Koln, Germany;* [2]*Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany.*

Background: Podocytes must effectively adapt to considerable mechanical forces at the filtration barrier throughout an organism's lifespan. However, the precise molecular mechanisms governing podocyte adaptation to such mechanical stressors remain elusive. YAP and TAZ, two paralogous transcriptional regulators, have emerged as pivotal mechanotransducers capable of sensing and transducing mechanical stimuli to regulate transcriptional activity.

Methods: We employed conditional deletion targeting Yap (YAP^{pKO}), Taz (TAZ^{pKO}), or both (YAP^{pKO}/TAZ^{pKO}) specifically in podocytes to delineate the distinct and shared roles of YAP and TAZ in podocyte homeostasis. Utilizing single-nucleus RNA sequencing (snRNA-Seq) analysis of isolated glomeruli, we elucidated overlapping and unique transcriptional responsibilities of these regulators.

Results: Conditional deletion of Yap in podocytes resulted in foot processes effacement and progressive renal failure, whereas Taz deletion did not cause disease. Notably, simultaneous deletion of Yap and Taz led to a neonatal lethal phenotype. Intriguingly, even mice lacking three out of the four Yap and Taz alleles proved non-viable, revealing a compensatory capacity shared between these two regulators. Our snRNA-Seq analysis unveiled an AP-1-dominated stress response as one of the compensatory mechanisms, evident in a subcluster of both YAP- and TAZ-deficient podocytes. Furthermore, dysregulation of Rho-GTPase activity, contributing to actin cytoskeleton de-arrangement, emerged as a primary driver of injury in YAP^{pKO} podocytes. Lastly, the loss of ERBB4 expression in YAP^{pKO}, but not in TAZ^{pKO}, delineated a key distinction between the two regulators, emphasizing a YAP-specific role in regulating ERBB4 signaling to sustain podocyte survival.

Conclusions: Our study comprehensively dissects the distinct and overlapping functions of YAP and TAZ in podocyte homeostasis. Through snRNA-Seq analysis, we identified several pivotal molecular mechanisms, some of which are shared by both regulators while others are dependent solely on YAP. Notably, while YAP can adequately compensate for loss of TAZ, TAZ lacks the capacity to effectively substitute for YAP, resulting in podocyte injury in the absence of YAP.

FR-PO774

Functional Role of the Mechanosensitive Channel Piezo for Nephrocyte Biology

Karl K. Alornyo,[1] Paris Hazelton-Cavill,[1] Kristina Schulz,[1] Ilka Edenhofer,[1] Maja Lindenmeyer,[1] Christian Lohr,[2] Tobias B. Huber,[1] Barry Denholm,[3] Sybille Koehler.[1] [1]*Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany;* [2]*Universitat Hamburg Fakultat fur Mathematik Informatik und Naturwissenschaften, Hamburg, Germany;* [3]*Biomedical Sciences, University of Edinburgh, Edinburgh, United Kingdom.*

Background: Due to their position on glomerular capillaries, podocytes are continuously counteracting biomechanical filtration forces. Most therapeutic interventions known to generally slow or prevent the progression of chronic kidney disease appear to lower the biomechanical forces on podocytes, highlighting the critical need to better understand podocyte mechano-signalling pathways.

Methods: Here we investigated the hypothesis that the mechanotransducer Piezo is involved in a mechanosensation pathway in *Drosophila* nephrocytes, the podocyte homologue in the fly.

Results: Our data show Piezo is expressed in nephrocytes where it localises to the nephrocyte diaphragm. Loss of function analysis in Piezo depleted nephrocytes revealed a morphological and functional phenotype. Further, we show that elevated Piezo expression levels resulted in Rho1 hyperactivity and accumulation of actin stress fibres, culminating in a severe nephrocyte phenotype, suggesting that pathway hyperactivity is detrimental as well. Interestingly, expression of Piezo, which lacks mechanosensitive channel activity, did not result in a severe nephrocyte phenotype and activation of Rho1, suggesting the observed changes in Piezo wildtype overexpressing cells are caused by

the mechanosensitive channel activity. Further, pharmacological activation of Piezo with Yoda1 caused a significant increase of intracellular Ca^{++} upon exposure to mechanical force in nephrocytes, as well as filtration disturbances and Rho1 activation. Moreover, blocking Piezo activity using the tarantula toxin GsMTx4 reversed filtration disturbances, Rho1 hyperactivation as well as actin stress fibre accumulation in nephrocytes overexpressing Piezo.

Conclusions: Taken together, these data show that Piezo plays an important role in nephrocyte mechanotransduction and mediates downstream signalling such as Rho1 activation and actin stress fibre formation.

FR-PO775

Topology and Structure of Membrane-Inserted APOL1

John C. Edwards, Jonathan M. Bruno. *Saint Louis University School of Medicine, St Louis, MO.*

Background: ApoL1 is an amphipathic protein that enters membranes at low pH and after titration to neutral pH, functions as a non-selective cation channel. Prior studies provide a model of membrane topology of active channel (Schaub et al., JBC (2021) 297: 101009): two loops span the membrane between positions 177 and 228 and positions 257 and 356, generating two segments exposed to the trans compartment. The segment from 335 to 356 forms a homodimer with the same segment of another molecule, forming the ion pore. A leucine zipper structure in the C-terminus is implicated in stabilizing the homo-dimer. We sought gain a fuller understanding of the sequences and environmental determinants that allow ApoL1 to form a functional pore.

Methods: Using purified recombinant ApoL1 constructs and pre-formed phospholipid membranes: 1. Accessibility of 26 single cysteine substitution mutants for modification from the cis and trans compartment was determined under a variety of conditions 2. Proximity of individual cysteines in membrane-inserted protein complexes was determined with crosslinking reagents 3. Effect of elimination of charged amino acids in the first transmembrane loop on membrane topology, activity, and pH sensitivity of membrane association was assessed 4. Effect of disruption of putative leucine zipper motif on dimerization, topology and activity was determined

Results: Cysteine accessibility confirms the topology model and demonstrates an additional trans-accessible segment in protein associated under optimal Cl permeability conditions. Crosslinking membrane-inserted cysteine-labelled protein identifies multiple sites of proximity between the dimers in addition to the pore-forming transmembrane segment. Elimination of the three glutamates in the first transmembrane loop alters the pH sensitivity of membrane association, but also eliminates activity and does not allow stable formation of the first transmembrane loop. Disruption of the leucine zipper motif eliminates activity, crosslinking at the pore segment, and stable formation of the first transmembrane loop.

Conclusions: The data provide new constraints on any model of membrane inserted ApoL1 structure. Most importantly, the leu zipper data indicates a direct interaction between the C-terminal segment and the first transmembrane loop, suggesting a structural basis for the effects of the C-terminally located disease-associated sequence variants that activate the channel.

Funding: NIDDK Support

FR-PO776

Hypoxia-Induced Peroxisomal Stress Mediates Cytotoxicity of APOL1 Variants

Ji Young Kim, Isaac Z. Karel, Pei-Hui Lin, Navjot Pabla, Sethu M. Madhavan. *The Ohio State University, Columbus, OH.*

Background: *APOL1* variants (*G1* and *G2*) are critical drivers of CKD in individuals of African ancestry. Not all individuals with *APOL1* kidney risk variants (KRVs) develop kidney disease, consistent with the need for a “second hit” like interferon or hypoxia to initiate disease. The mechanisms that cause CKD under the influence of these triggers remain uncertain. This study aims to identify “second hit” trigger genes and pathways in order to develop therapeutic approaches to modify their function.

Methods: A genome-wide siRNA and CRISPR screen on ~20,000 genes (3 targets/gene) was conducted in HEK293 cells expressing APOL1-G0, G1, and G2 under hypoxia ($1\%O_2$) using cytotoxicity as the readout, which identified peroxisomal genes. Individual targets were validated by siRNA knockdown. APOL1 localization to peroxisomes was analyzed using proximity biotinylation, peroxisome isolation and STORM imaging, and peroxisomal stress was measured by catalase activity in HEK293 cells and human podocytes. Candidate drug screening was performed in HEK293 cells. Peroxisomal localization of APOL1 in healthy human kidneys and FSGS was examined by PEX14 immunohistology. Glomerular peroxisomal protein expression (healthy kidneys n=4, FSGS n=12) was analyzed by mass spectrometry.

Results: Hypoxia increased APOL1-G1 and G2 cytotoxicity in HEK293 cells and human podocytes. siRNA and CRISPR screens revealed that knockdown of genes involved in peroxisome biogenesis or *Peroxins* (*PEX3, PEX5, PEX11, PEX13, PEX16, PEX19, FIS1)* intensified APOL1 KRV-induced cytotoxicity under hypoxia. STORM imaging and fractionation studies showed translocation of APOL1s to peroxisomes under hypoxia. A C-terminal peroxisomal targeting signal facilitated this translocation, leading to increased catalase activity by APOL1 KRVs, indicating peroxisomal stress. Enhancing peroxisomal function genetically (PEX overexpression) or pharmacologically (PPAR-α agonists) alleviated hypoxia-induced APOL1 KRV cytotoxicity. APOL1 co-localized with peroxisomes in podocytes of healthy human kidneys, while Peroxin expression in glomeruli was reduced in FSGS.

Conclusions: Peroxisomal genes are novel genetic modifiers of APOL1 nephropathy, protective against podocyte dysfunction caused by APOL1 KRVs under hypoxic conditions. Augmenting peroxisomal function represents a potential therapeutic strategy to ameliorate CKD associated with APOL1 KRVs.

Funding: NIDDK Support

FR-PO777

Lysosomal Cathepsin B Assists to Withstand Mechanical Stress in Podocytes

Franziska Theilig,[1] Magdalena Westermann,[1] Felix Kliewe,[2] Makhabbat Saudenova,[1] Alexander Siebertz,[1] Fatih Demir,[3] Markus M. Rinschen,[3] Nicole Endlich,[2] Eileen Dahlke.[1] *[1]CAU Kiel Institute of Anatomy, Kiel, Germany; [2]University Greifswald Institute of Anatomy and Cell Biology, Greifswald, Germany; [3]Aarhus University Department of Biomedicine, Aarhus, Denmark.*

Background: During filtration podocytes are exposed to mechanical stress and have to buttress the glomerular filter against the filtration pressure. Especially, glomerular hypertension is thought to damage podocytes with concomitant foot process effacement and urinary podocyte loss. Lysosomes are important regulators of cellular physiology and act on cell stress with a lysosomal stress response. Aim of this study was to identify the role of lysosomes and the lysosomal hydrolase cathepsin B (CTSB) in mechanical stress of podocytes.

Methods: Immortalized mouse podocytes and primary podocytes isolated from CTSB -/- and respective control mice were exposed to mechanical stress and examined by immunocytochemistry (ICC) and western blot (WB) analysis. In addition, immortalized mouse podocytes were treated with the CTSB inhibitor CA074Me and morphological alterations were determined. Isolated glomeruli of CTSB -/- and respective control mice were used for proteomic and N-terminomic analysis.

Results: Immortalized podocytes underwent mechanical stress demonstrated an increased expression of lysosomes, lysosomal hydrolases (CTSB, CTSL) and an augmented autophagy (p62, LC3). Inhibiting CTSB in podocytes with mechanical stress revealed lower stress resistance characterized by increased detachment rate and alterations in the number and length of cell processes. N-terminomic analysis of glomeruli from CTSB -/- and control mice showed significant less proteolytic processing of intermediate filaments, actin binding and associated proteins and focal adhesion proteins. WB and ICC analysis of identified proteolytic processed protein confirmed cleavage and demonstrated an altered expression level.

Conclusions: Our data show that mechanical stress in podocytes leads to a lysosomal stress response to increase the expression level of CTSB to induce processing of cytoskeletal associated proteins and adhesion proteins to cope with and withstand higher levels of mechanical stress.

Funding: Government Support - Non-U.S.

FR-PO778

Cathepsin B Alleviates the Development of Focal Segmental Glomerulosclerosis

Franziska Theilig,[1] Mairon Trujillo Miranda,[1] Jessica Promnitz,[1] Makhabbat Saudenova,[1] Magdalena Westermann,[1] Geraldine Mollet,[4] Theresa Riebeling,[3] Stefan Krautwald,[3] Fatih Demir,[2] Markus M. Rinschen,[2] Eileen Dahlke.[1] *[1]CAU Kiel Institute of Anatomy, Kiel, Germany; [2]Aarhus University Department of Biomedicine, Aarhus, Denmark; [3]University Clinic Schleswig-Holstein, Department of Nephrology, Kiel, Germany; [4]Université Paris Cité, Laboratory of Hereditary Kidney Diseases, Inserm UMR1163, Imagine Institute, Paris, France.*

Background: Focal segmental Glomerulosclerosis (FSGS) is one of the most typical histopathological causes of glomerulopathy affecting primarily the podocyte. Lysosomes are responsible for the degradation of molecules via hydrolytic enzymes, such as cathepsin B (CatB) and may serve as a platform mediating cellular signaling in podocytes. Additionally, podocyte stress is associated with lysosome dysfunction. In this study we aim to explore the role of CatB in the progression of podocyte dysfunction to FSGS.

Methods: Podocyte-specific NPHS2 deleted mouse model ($Pod^{Cre}NPHS2^{flox}$) leading to FSGS development were used and cross-bred for additional podocyte-specific or complete CatB deletion. Renal function parameter analysis, histolmorphological analysis, transmission electron microscopy (TEM) imaging and immunohistochemistry (IHC) were performed after 3 weeks of induction. Isolated glomeruli from the mouse models were analyzed by proteomic/N-terminomic analysis.

Results: Renal function parameter demonstrated higher BUN, plasma creatinine levels and proteinuria in Pod^{Cre}NPHS2^{flox} compared to Pod^{Cre}NPHS2^{flox} with CatB deletion and to control. Morphological analysis revealed higher glomerular and tubulointerstitial damage score in PodCreNPHS2flox compared to Pod^{Cre}NPHS2^{flox} with CatB deletion and to control. IHC revealed an increased expression of TFEB, LAMP1 and galectin 3 in Pod^{Cre}NPHS2^{flox} which was attenuated by additional CatB deletion. TEM analysis demonstrated a significant increase in mitochondrial and podocyte injury in Pod^{Cre}NPHS2^{flox} compared to control and mice with additional CatB deletion which corroborates with higher processing of various mitochondrial proteins identified by N-terminomic analysis. Inflammasome activation was strongly induced in Pod^{Cre}NPHS2^{flox} compared to control and tom mice with additional CatB deletion.

Conclusions: CatB deletion prevents the development of FSGS, keeping the Pod^{Cre}NPHS2^{flox} mouse model to a minimal change disease. In FSGS progression, CatB induces inflammasome activation and spreading and mitochondria dysfunction, showing that CatB may be an option to target FSGS treatment.

Funding: Government Support - Non-U.S.

FR-PO779

Angiotensin II Increases Nephrin Endocytosis via AT1-Receptor ERK 1/2 Activation

Eva Koenigshausen, Ulf Zierhut, Martin Rütze, Lars C. Rump, Lorenz Sellin. *Heinrich-Heine-Universitat Dusseldorf, Dusseldorf, Germany.*

Background: Albuminuria is characterized by a disruption of the glomerular filtration barrier, which is composed of the fenestrated endothelium, the glomerular basement membrane, and the slit diaphragm. Nephrin is a major component of the slit diaphragm. Apart from hemodynamic effects, Angiotensin II (Ang II) enhances albuminuria by β-Arrestin2 dependent nephrin endocytosis.

Methods: 1. Isolated mouse glomeruli were stimulated with Ang II and co-immunopreciptiation of nephrin with β-Arrestin 2 performed. 2. Differentiated murine podocytes were stimulated with Ang II and biotinylation assay with immunoprecipitated nephrin performed. 3. HEK293T cells were pretreated with AT1-receptor blockers candesartan and irbesartan before treatment with Ang II. 4. An AT1-receptor mutant, defective of EGFR transactivation and β-Arrestin 2 recruitment, was used as well as mutant β-Asrrestin2 K11/K12R. Different ERK 1/2 inhibitors were tested. Immunofluorescence imaging was performed in Cos7 cells.

Results: Ang II increases nephrin-β-Arrestin2 binding in murine glomeruli and endocytosis in murine podocytes. Blocking the AT1 receptor with candesartan and irbesartan reduces the Ang II-mediated nephrin-β-Arrestin2 interaction. The inhibition of MAPK ERK 1/2 blocks Ang II-enhanced nephrin-β-Arrestin2 binding. ERK 1/2 signaling, which follows AT1 receptor activation, is mediated by G-protein signaling, EGFR transactivation, and β-Arrestin2 recruitment. A mutant AT1 receptor defective in EGFR transactivation and β-Arrestin2 recruitment reduces the Ang II-mediated increase in nephrin β-Arrestin2 binding. The mutation of β-Arrestin2^{K11,K12}, critical for AT1 receptor binding, completely abrogates the interaction with nephrin, independent of Ang II stimulation. β-Arrestin2^{K11R,K12R} does not influence nephrin cell surface expression.

Conclusions: The data presented here deepen our molecular understanding of a blood-pressure-independent molecular mechanism of AT-1 receptor blockers (ARBs) in reducing albuminuria by nephrin endocytosis. MAP kinase signalling events play a relevant role in Ang II mediated nephrin endocytosis.

FR-PO780

Genotype-Phenotype Correlations in Congenital Nephrotic Syndrome Associated with Nephrin Gene C-terminal Mutations

Ewelina Hejenkowska, Agnieszka Swiatecka-Urban. *University of Virginia, Charlottesville, VA.*

Background: Nephrin is a transmembrane protein forming homo- and hetero-dimeric interactions critical to the function of the glomerular slit diaphragm (SD). Homozygous nephrin gene mutations lead to congenital nephrotic syndrome (CNS). Loss of the last 132 aa at the nephrin C-terminal tail (p.R1109X) leads to more severe symptoms than the absence of the last 81 aa (p.R1160X), but the mechanism is not understood. The R1109X nephrin is thought to lack SD localization, while the R1160X mutant retains the SD localization. Studies were performed to test the hypothesis that the sequence between aa 1109 and 1160 in the nephrin C-terminal tail is critical for its plasma membrane (PM) localization.

Methods: Immortalized human podocytes were transfected with wild-type (WT) nephrin, R1109X, or R1160X. The nephrin PM localization at steady state was examined by cell surface biotinylation and western blotting. The nephrin PM stability was examined over time in the presence of cycloheximide to inhibit new protein translation.

Results: Similar to nephrin R1160X, the R1109X mutant was expressed at the PM, and both had lower PM abundance at steady state, compared to WT nephrin. Nephrin R1160X was more stable at the PM, compared to WT nephrin while the PM stability of nephrin R1109X was similar to WT. The total cellular stability of nephrin mutants was similar to WT nephrin.

Conclusions: Unlike the previous report, we demonstrate that nephrin R1109X traffics to the PM in human podocytes, and thus, the C-terminal sequence between aa 1109 and 1160 is not essential to PM localization. The decreased PM abundance and similar PM and total cellular stability suggest that the R1109X truncation decreases nephrin biosynthetic processing but does not alter its PM dynamics or degradation. The decreased abundance and increased stability of nephrin R1160X at PM suggest that R1160X truncation impairs biosynthetic processing and PM dynamics. Our data provide novel insights into the role of the nephrin cytoplasmic tail domain. Ongoing studies focus on examining protein-protein interactions affected by the nephrin truncations to understand their genotype-phenotype correlations in CNS further.

Funding: Other NIH Support - National Institutes of Health grant R01-144539, Private Foundation Support

FR-PO781

Podocyte EGR1 Expression in Patients with Primary Focal Segmental Glomerulosclerosis and Minimal Change Disease

Masahiro Okabe,[1] Kentaro Koike,[1] Nobuo Tsuboi,[1] Taiji Matsusaka,[2] Takashi Yokoo.[1] [1]*Jikei University School of Medicine, Tokyo, Japan;* [2]*Tokai University School of Medicine, Ieshara, Japan.*

Background: We have reported that early growth response 1 (EGR1) expresses in injured podocytes from early stage in an inducible podocyte-injury mouse model, NEP25. We also found that the percentage of EGR1-positive podocytes (%EGR1pod) is associated with podocyte injury in patients with glomerular diseases. Primary focal segmental glomerulosclerosis (pFSGS) and minimal change disease (MCD) both present nephrotic syndrome but have very different prognoses, suggesting a potential difference in the degree of podocyte injury between these two conditions. In this study, we aim to examine the difference in podocyte EGR1 expression between patients with pFSGS and MCD.

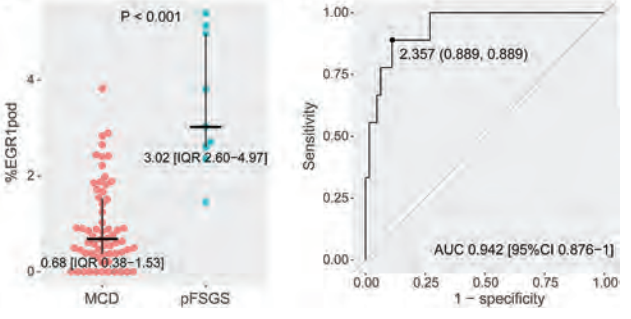
Methods: Adult patients with biopsy-proven pFSGS or MCD who presented acute-onset nephrotic syndrome were enrolled from Jikei University Hospital, Japan, and Jikei University Daisan Hospital, Japan, between 2001 and 2020. Patients over 70 years of age and patients with serum creatinine levels greater than 1.5 mg/dL were excluded. The %EGR1pod was determined through immunohistochemistry and was compared between the pFSGS and MCD groups.

Results: Patients with pFSGS (n = 9) were significantly older than those with MCD (n = 63) (median, 51 [Interquartile range (IQR), 50–58] vs 39 [29–48] years, P = 0.003), but there was no significant difference in sex, urinary protein level, serum albumin level, or serum creatinine level. The %EGR1pod was significantly higher in the pFSGS group than the MCD group (3.02 [2.60–4.97]% vs 0.68 [0.38–1.53]%, P < 0.001) (Figure 1A). Receiver operating curve (ROC) analysis revealed an area under the curve (AUC) of 0.945 [95% confidence interval, 0.876–1] for distinguishing between pFSGS and MCD patients (Figure 1B).

Conclusions: Stronger podocyte injury was observed in patients with pFSGS than in those with MCD, which may impact kidney prognosis. The %EGR1pod may be a useful marker for differentiating pFSGS from MCD.

Funding: Government Support - Non-U.S.

Figure 1



FR-PO782

Relative Roles of CCL5 on Podocytes and Macrophages in Glomerular Injury

Issei Okunaga, Ika N. Kadariswantiningsih, Maulana A. Empitu, Kaho Yamasaki, Masashi Aizawa, Katsuhiko Asanuma. *Chiba Daigaku, Chiba, Japan*.

Background: We had previously reported that Notch2 activation reduces podocyte damage, and now we have identified and analyzed C-C motif chemokine ligand 5 (CCL5) as the downstream molecule. CCL5 is a secreted protein that acts on macrophages (Mϕ), T cells, and epithelial cells, but its role in glomerular injury is controversial. An earlier study has shown that a functional CCL5 antagonist attenuates glomerulonephritis, while another study reported that it exacerbates glomerular damage in glomerular disease models. Using *in vitro* and *in vivo* studies, we delved into the role of CCL5 in podocytes and bone marrow-derived cells.

Methods: We performed immunostaining of human kidney samples to investigate the expression of CCL5 in glomerular disease. Cultured CCL5 knockout (KO) podocytes and CCL5 KO mice were created. Cultured WT podocytes and CCL5 KO podocytes were treated with adriamycin (ADR), and then the apoptosis rate was evaluated. WT and CCL5 KO mice were injected with ADR to induce nephropathy, and then we investigated the kidney pathology. We performed bone marrow transplantation in WT and CCL5 KO mice to study the CCL5 function in podocytes or bone marrow-derived cells.

Results: We found that CCL5 expression in glomeruli was upregulated in patients with glomerular disease and in ADR-induced nephropathy mice. ADR-induced injury in cultured WT podocytes was ameliorated by exogenous CCL5 administration and exacerbated by CCL5 deficiency. These *in vitro* studies suggested that CCL5 has a protective role in injured podocytes. Next, to check the role of CCL5 *in vivo*, ADR nephropathy mice were used. Unexpectedly, ADR-induced nephropathy was ameliorated in CCL5 KO mice. To elucidate the discrepancy, we transplanted the bone marrow of CCL5 KO mice to ADR-induced nephropathy WT mice. The transplantation of CCL5 KO bone marrow ameliorated the ADR-induced nephropathy in the WT mice.

Conclusions: CCL5 exacerbates ADR nephropathy via bone marrow-derived cells but plays a protective role in podocytes. The results suggest that CCL5 has ambivalent cellular effects in glomerular diseases.

FR-PO783

Unveiling Functional Renin-Angiotensin System-Related Signaling in Parietal Epithelial Cells

Mykhailo Fedoriuk,[1] Mariia Stefanenko,[1] Justin P. Van Beusecum,[2,1] Daria Ilatovskaya,[3] Oleg Palygin.[1] *[1]Medical University of South Carolina, Charleston, SC; [2]Ralph H. Johnson VA Medical Center, Charleston, SC; [3]Augusta University, Augusta, GA.*

Background: The Bowman's capsule envelops the kidney's glomerular tuft, comprised of a single layer of parietal epithelial cells (PECs) that form a vital barrier between the urinary space and the renal interstitium. When PECs undergo pathophysiological activation, they transition from their usual quiescent state to one characterized by proliferation and migration towards the glomerular tuft, causing glomerular injury. Numerous proteinuric kidney diseases are linked to PEC activation, yet the precise mechanisms governing functional receptor signaling in these cells remain poorly understood. This study aims to explore the presence of components of the renin-angiotensin system (RAS) and the corresponding intracellular mechanisms within PECs.

Methods: The vibrodissociation technique was utilized to obtain freshly isolated Bowman's capsules with PECs from discarded adult male human transplant tissues and 12-week-old Wistar male and female rats. Live confocal microscopy detected changes in intracellular Ca^{2+} concentrations (Fluo8) and nitric oxide (NO; DAF-FM) response to acute Ang II applications. Scanning electron microscopy (SEM) was used to examine the PECs structure.

Results: In SEM, we confirmed the intact nature of the isolated PECs of the Bowman capsule. The acute administration of Ang II peptide elicited rapid NO production in cells isolated from both males and females, while no significant intracellular Ca^{2+} influx in response to Ang II. To identify the functional receptor responsible for Ang II signaling in PECs, we preincubated cells with AT1R or AT2R blockers (Losartan and PD123319, respectively). Our findings demonstrated that Ang II facilitates NO production via AT2R activation, which held true in both sexes. Importantly, in separate experiments, we confirmed the similarity of these signaling mechanisms between the rat and human species.

Conclusions: Our research offers insight into Ang II-mediated signaling within PECs. For the first time, we present evidence establishing a direct link between Ang II and redox homeostasis in PECs. Further exploration utilizing this newly developed approach will be crucial for understanding the involvement of PECs in glomerular function and devising potential treatments targeting the hyperplasia of activated PECs and associated chronic kidney pathologies.

Funding: NIDDK Support, Other NIH Support - R01 DK126720, R01 DK129227, VA CDA-2 1IK2BX005605-01, Veterans Affairs Support

FR-PO784

Parietal Epithelial Cell (PEC)-Specific Knockout of Integrin-αv Attenuates PEC Activation and Proliferation in Proliferative Glomerulopathy

Deepa Sathee, Anirudh Krishnan, Yiqing Guo, Robert Bronstein, Sandeep K. Mallipattu. *Stony Brook University Renaissance School of Medicine, Stony Brook, NY*.

Background: Parietal epithelial cell (PEC) activation and proliferation contributes to crescent formation, leading to glomerulosclerosis and eventual loss of kidney function in proliferative glomerulopathies. Our previous single nucleus RNA-seq in mice with proliferative glomerulopathy demonstrated an enrichment in Integrin avb6 signaling in activated PECs. Here, we investigate the role of Itgav in PEC activation and proliferation in models of proliferative glomerulopathy.

Methods: Mouse PECs with Itgav knockdown (*Itgav-/-*) were generated by lentiviral method. RTPCR was employed for determining PEC activation markers. Scratch assay was performed to assess the migration pattern. PEC-specific inducible *Itgav-/-* mice were generated using the "tet-on" system. NTS (Nephrotoxic serum) was used as a model of proliferative glomerulopathy. Albuminuria, histopathological assessment for crescent formation, PEC markers and fibrotic markers were measured.

Results: *Itgav-/-* PECs showed a reduction in activated PEC markers (CD44, CD74, CCND1, DOCK10, FOSL2, CLDN1) as compared to control cells. In addition, *Itgav-/-* PECs exhibited changes in morphology, less proliferation (MTT, cell count) and migration as compared to control cells. PECs treated with monoclonal-ab against avb6 also attenuated PEC activation and proliferation. NTS-treated *Itgav-/-* mice showed a decrease in albuminuria at day 7 post-NTS as compared to NTS-treated WT mice, with a decrease in activated PECs (reduced CD44 expression) and fibrotic markers (α-SMA, picrosirius red).

Conclusions: These data suggest that loss of Itgav in PECs attenuates PEC activation, cell migration, crescent formation and eventual fibrosis in models of proliferative glomerulopathy.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO785

Murine Model of Glomerular Thrombotic Microangiopathy Results in Glomerular Endothelial-to-Mesenchymal Transition

Patrick Droste,[1,2] Sonja Djudjaj,[1] Barbara M. Klinkhammer,[1] Eva M. Buhl,[1] Elisabeth Kemter,[3] Peter Boor.[1,2] Laboratory of Nephropathology. *[1]Institute of Pathology, University Hospital RWTH Aachen, Aachen, Germany; [2]Department of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; [3]Institute of Molecular Animal Breeding and Biotechnology, Gene Center and Department of Veterinary Sciences, Ludwig-Maximilians-Universität München, München, Germany*.

Background: Thrombotic microangiopathies (TMAs) are rare diseases with a poor prognosis and a multifaceted manifestation pattern. The pathological processes in the glomerulus during TMA are incompletely understood, also because very few animal models are available. Here, we characterized a murine model with glomerular-limited endothelial cell injury with thrombi.

Methods: Eight-week-old healthy wild-type littermate mice were compared with mutated diseased mice (generated by random mutagenesis). Perfused kidneys were investigated with histological, immunohistochemical, and immunofluorescence stainings combined with RNA *in situ* hybridization by quantitative optical sectioning and image analysis. Transmission electron microscopy was used to study ultrastructural alterations. Renal functional, hemolysis, and complement system parameters were assessed in serum and urine.

Results: The mice developed a spontaneous phenotype with diffuse and global signs of glomerular TMA resulting in impaired kidney function, decreased body weight, and lifespan. The glomeruli were enlarged and showed thrombi, double contours of the glomerular basement membrane (GBM) with cell interposition, and endothelial cell swelling. Mesenchymal markers were expressed in a unique circular pattern around the capillaries in the glomerulus colocalized with the double contour of the GBM. The glomerular endothelial cells lost part of their characteristic endothelial markers, displayed *de novo* expression of mesenchymal markers, and showed ultrastructural features of mesenchymal cells, suggesting an endothelial-to-mesenchymal transition. The progressive course of the disease was further documented by the development of interstitial fibrosis and inflammatory cell infiltrations in the kidney cortex. No signs of hemolysis or serological evidence of complement activation were detected, suggesting a glomerular-limited disease.

Conclusions: The present mouse model showed typical signs of endothelial injury and glomerular remodeling found in TMA, revealing a novel pathological process of chronic glomerular injury in TMA via glomerular endothelial-to-mesenchymal transition.

Funding: Government Support - Non-U.S.

FR-PO786

Glomerular Endothelial Plasmalemma Vesicle-Associated Protein (PLVAP) Is Re-expressed in Thrombotic Microangiopathy and Associated with Endothelial Cell Dedifferentiation and Increased Permeability

Chelsea C. Estrada,[1,2] Craig Wilson,[2,1] Sumaya Ahmed,[2] Nehaben A. Gujarati,[2] Sandeep K. Mallipattu.[2,1] *[1]Northport VA Medical Center, Northport, NY; [2]Stony Brook University, Stony Brook, NY.*

Background: GEnC injury is a common feature across the wide spectrum of glomerular diseases and is the inciting event that drives downstream glomerular changes and eventual chronic kidney disease in both Diabetic Kidney Disease (DKD) and Thrombotic Microangiopathy (TMA). We recently reported the development of subacute TMA and GEnC injury in mice with the combined double knockout of endothelial *Klf4* and *Nos3* (DKO), compared with wild type mice (*Klf4*$^{fl/fl}$) or single endothelial knockout of either *Klf4* (*Klf4*$^{\Delta EC}$) or eNOS (*Nos3*$^{-/-}$), however the mechanism(s) of GEnCs response to injury are poorly understood.

Methods: Single-cell RNAseq libraries were generated from frozen kidney cortex from 12-wk old male mice in each group (*Klf4*$^{fl/fl}$, *Nos3*$^{-/-}$, *Klf4*$^{\Delta EC}$, DKO), which were analyzed in R using Seurat. The differentially expressed genes (DEG) were further examined with ClusterProfiler. Immunofluorescence (IF) for PLVAP was performed in the four groups. Immortalized murine GEnCs with stable *Plvap* overexpression were generated with lentiviral delivery and gene expression was measured with rt-PCR. Proliferation was measured with the MTS assay and monolayer permeability was measured with a transwell system.

Results: Using SnRNAseq, pathway analysis of the upregulated DEGs of the endothelial cluster revealed perturbation in pathways involved in angiogenesis, permeability, focal adhesion and cytoskeletal organization in DKO mice. We identified *Plasmalemmal Vesicle like-protein (Plvap*), a component of fenestral diaphragms and previously shown to be re-expressed in injured GEnCs in DKD, as upregulated specifically in the GEnC cluster in TMA, which was confirmed using IF. Overexpression of *Plvap* (*Plvap-ORF*) in immortalized GEnCs resulted in increased proliferation at 37 degrees compared with control cells (*EV*), as well as loss of the mature differentiation marker *Ehd3*. GEnC monolayers with *Plvap-ORF* had increased permeability compared with *EV* cells, as well as increased expression of *Cav-1* and *Vcam1*, both associated with EC permeability.

Conclusions: *Plvap* is upregulated in injured GEnCs in TMA and is associated with increased permeability and endothelial cell dedifferentiation. Whether this is a driver versus response to GEnC injury is yet to be determined and the focus of future studies.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO787

Shiga Toxin Downregulates the uPAR/uPA Fibrinolytic Pathway in Human Umbilical Vein Endothelial Cells and on Glomeruli of a Murine Model of Enterohemorrhagic Hemolytic Uremic Syndrome

Celestina Mazzotta,[1,2] Julie R. Ingelfinger,[1,2] Julia Davies,[1] Gregory L. Stahl,[2,3] Eric F. Grabowski.[1,2] *[1]Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Brigham and Women's Hospital, Boston, MA.*

Background: Coagulation and fibrinolysis ensures balanced hemostasis through the coordinate interaction of pro-coagulant/fibrinolytic factors and the activation of the complement systems. Enterohemorrhagic hemolytic uremic syndrome (eHUS), caused by Shiga toxin results in a prothrombotic microenvironment in the kidney, especially in the glomeruli, with platelet and fibrin deposition and activation of the lectin pathway of complement. We used human umbilical vein endothelial cell (HUVECs) and kidneys of our murine model of eHUS (MBL$^{+/+}$2mbl1$^{-/-}$mbl2$^{-/-}$) to study the expression of the fibrinolytic pathway: urokinase-type Plasminogen Activator (uPA) and urokinase Plasminogen Activator Receptor (uPAR).

Methods: Using immunofluorescence (IF) and western blot, uPA and uPAR were evaluated in HUVECs treated with TNF-α, Stx-1 or both, *vs.* control. Expression of uPA and uPAR was studied with IF in kidneys of mice treated with Stx-2, +/- anti-MBL2 antibody (3F8), anti-factor XIa antibody (3G3), or both, *vs.* untreated mice. In kidneys of our mouse model, colocalization of uPAR/PAI-1 and uPA/PAI-1 (Plasminogen Activator Inhibitor-1) was evaluated.

Results: Stx-1, TNF-α or both significantly reduced uPA and uPAR expression in HUVECs. The glomeruli of mice treated with Stx-2 showed decreased levels of uPA and uPAR *vs* mice treated with Stx-2 +3F8, or +3G3, or both. Endothelial cells in mouse glomeruli treated with Stx-2 expressed low levels of uPA and uPAR *vs.* untreated mice and *vs.* Stx-2+3F8, or +3G3 or both. The levels of PAI-1 in kidneys increased in mice treated with Stx-2 *vs.* Stx-2+3F8 or +3G3, or both. PAI-1/uPAR and PAI-1/uPA colocalization significantly increased in glomeruli of mice treated with Stx-2 compared to Stx-2+3F8 or +3G3, or both.

Conclusions: In the presence of Stx-1, TNF-α, or both, uPA and uPAR expression declined in HUVECs. The glomeruli of mice treated with Stx-2 showed reduced levels of uPA and uPAR which are restored with 3F8, 3G3 or both. Our findings provide evidence that the fibrinolytic pathway mediated by uPA/uPAR is affected in the presence of Stx, suggesting that the higher deposition of fibrin and the thrombotic events in the kidney might be generated by dysregulated fibrinolysis modulated by uPA/uPAR.

Funding: NIDDK Support

FR-PO788

Effects of Nanoplastic Particles on the Kidney

Melina Yarbakht,[1] Michelle Hinrichs,[1] Marie Hecker,[1] Mustafa Kocademir,[3] Zeynab Mirzaei,[2] Mario Schiffer,[1] Janina Müller-Deile.[1] *[1]Universitatsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; [2]Innovative Institute for Nanotechnology and Correlative Microscopy e.v. INAM, Forcheim, Germany; [3]Fraunhofer-Institut fur Keramische Technologien und Systeme IKTS - Standort Forchheim, Forchheim, Germany.*

Background: Nanoplastic particles as a new type of emerging pollutant have become a huge scientific concern. Due to the common existence of plastic particles, they have a potential effect on human health. However, it is not known if these particles can reach the kidney or have disease causing potential.

Methods: Fluorescence-labelled carboxylated polystyrene nanoplastic particles with a size of 0.05 µm were used to scan their potential effect on kidney cells. Cultured immortalized human podocytes and human glomerular endothelial cells as well as zebrafish larvae were exposed to the particles. Quantitative PCR, cell viability tests and phalloidin staining were performed after particle exposure. 3D construction models visualized the location of particles. Furthermore, tracking of particle uptake in both cultured glomerular cells and zebrafish was done by immunofluorescent microscopy and Raman spectroscopy.

Results: Both, podocytes and glomerular endothelial cells were able to take up polystyrene nanoplastic particles although expression of cell specific markers did not seem to be affected. However, morphology and cytoskeleton of cells were altered due to the particle showing their general effect on glomerular cells. Nanoplastic particles were incorporated in the zebrafish larvae through the digestive system and they could also be detected in the glomerular region of larvae. Electron microscopy revealed the ultrastructural localization of the particles. In zebrafish with glomerular damage nanoparticle were more likely to pass the glomerular basement membrane to reach the podocytes.

Conclusions: Polystyrene nanoplastic particles can be incorporated via the digestive system, reach the kidney and be taken up by glomerular cells which is facilitated in glomerular diseased state with impaired glomerular filtration barrier.

Funding: Government Support - Non-U.S.

FR-PO789

Atopic Dermatitis-Like Chronic Inflammation May Be Associated with Kidney Inflammation

Arisa Ikeda, Ge Peng, Wanchen Zhao, Alafate Abudouwanli, Shigaku Ikeda, Francois Niyonsaba, Yusuke Suzuki. *Juntendo Daigaku Igakubu Daigakuin Igaku Kenkyuka, Bunkyo-ku, Japan.*

Background: Cross-sectional and case control studies recently indicated the association between renal abnormalities and atopic dermatitis (AD). AD causes not only skin lesions, but also the dysregulation of a wide range of cytokines in the serum. S100A8/9 is one of the calcium binding proteins belonging to the S100 family, derived from neutrophils and macrophages, and also involved in chronic inflammatory diseases such as AD. However, the underlying mechanism of S100A8/9 for a potential link between kidney diseases and AD remains unknown.

Methods: To evaluate the status of kidney functions of patients with AD, we analyzed the serum and urine samples of US adults from the National Health and Nutrition Examination Survey (NHANES). In addition, a chronic AD-like mouse model was induced by repeatedly applying 2,4-dinitrochlorobenzene on the ears and back. The renal function was evaluated by urine and serum examinations, histological staining and electron microscopy imaging of kidneys. The expression of glomerular filtration barrier proteins was evaluated by immunoblotting and immunofluorescence staining. Furthermore, real-time PCR and ELISA assays were performed both in vivo and in vitro to analyze kidney inflammation.

Results: Analysis of NHANES data confirmed the upregulation of urine protein creatinine ratio and downregulation of estimate GFR in patients with AD compared to the healthy subjects. In addition, AD-like mice showed higher albuminuria and serum creatinine than control mice. Moreover, these mice had an increase in glomerular cell infiltration, including neutrophils and macrophages, and foot process effacement of podocytes, indicating dysfunction of glomerular filtration by AD-like inflammation. Kidneys from AD mice showed downregulated expression of glomerular filtration barrier proteins. Concurrently, S100A8/9 was found to be elevated in the serum and renal cortex of these mice. Expression of S100A8/9 in the renal cortex correlated with the status of albuminuria and AD-like inflammation.

Conclusions: Our findings suggest that dysfunctional glomerular filtration and reduced kidney function in AD-like mice might be correlated with the increased levels of S100A8/9 derived from neutrophils and macrophages.

FR-PO790

Bone Marrow Inflammation and Alteration Fuel CKD Progression

Ryan Spear,[1] Alexis P. Jimenez Uribe,[1] Yanxia Cao,[1] Steve Mangos,[1] Flavio Vincenti,[2] Jochen Reiser,[3] Eunsil Hahm.[1] *[1]Rush University, Chicago, IL; [2]University of California San Francisco, San Francisco, CA; [3]The University of Texas Medical Branch at Galveston, Galveston, TX.*

Background: Altered hematopoiesis in the bone marrow (BM) is commonly found in various conditions associated with CKD, including infection, chronic inflammation, diabetes, CVD, cancer, and aging. Our group recently identified BM-derived immature myeloid cells as key contributors to glomerular dysfunction in mice. Despite its potential importance in CKD development, the role of the central immune system, specifically the BM, has not been thoroughly interrogated in humans. Here, for the first time, we examine human BM in CKD and uncover how altered BM myelopoiesis contributes to the progression of CKD.

Methods: BM samples from CKD patients (4 primary and 5 secondary FSGS, 1 non-FSGS) and healthy donors (7) were analyzed. In vitro myelopoiesis was complete using human hematopoietic stem cells. Cellular and molecular characteristics were assessed with flow cytometry, ELISA, scRNA-, RNA- and ATAC-seq. Functional studies included high-throughput IF assays on cultured podocytes and filtration function assays in a transgenic zebrafish model.

Results: CKD patients exhibited significantly elevated levels of TNFα and suPAR, with a myeloid-biased hematopoiesis and increased inflammatory monocytes expressing uPAR. scRNA-seq revealed increased monocyte activation via upregulated genes associated with proinflammatory cytokine and signaling pathways. Consistently, in vitro myelopoiesis demonstrated that TNFα skews hematopoietic differentiation towards activated monocytic lineage cells. These TNFa-driven monocytic subsets exhibited increased uPAR expression, suPAR secretion, and altered transcriptomic, epigenetic, and motif binding profiles. These profiles showed enhanced expression and chromatin accessibility to genes similar to those in patients' BM. Significant cytoskeletal rearrangement was observed in cultured podocytes treated TNFa-induced myeloid cell secreted factors (TIMCSFs) or FSGS patient serum but not by TNFa alone. Similarly, TIMCSFs led to filtration dysfunction in a transgenic zebrafish model.

Conclusions: This study reveals the functional connection between BM myelopoiesis and CKD in humans. Our findings suggest that TNFα, driven by chronic inflammation, plays a key role in altering BM myeloid cells, thereby contributing to glomerular dysfunction in CKD patients. These findings highlight the BM-kidney axis as a potential novel therapeutic target for CKD.

Funding: NIDDK Support

FR-PO791

Increased Type 2 Innate Lymphoid Cells (ILC2s) in Patients with Idiopathic Nephrotic Syndrome (INS)

Chang-Yien Chan,[1,2] Liangjian Lu,[2] Sharon Teo,[2] Kar Hui Ng,[1,2] Hui Kim Yap.[1,2] *[1]National University of Singapore, Singapore, Singapore; [2]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, Singapore.*

Background: Th2 cytokine producing ILC2s have been implicated in steroid-dependent and resistant allergic asthma. We have previously reported elevated Th2 cytokine production in steroid-dependent nephrotic syndrome (SDNS). This study therefore aimed to characterize ILC2s in INS patients in relapse.

Methods: 14 patients with childhood-onset INS (relapse and remission) and 7 age-matched healthy controls were recruited. ILC subsets were analysed using flow cytometry. ILC2s were cultured with IL-33, IL-25, TSLP (10ng/ml) and IL-2 (20ng/ml) for 72h and culture supernatants were harvested for cytokine quantification. To investigate the response of ILC2s to steroids, cells were incubated with or without Dexamethasone (DEX) (0.1μmol/ml). Statistical analysis was done using Mann-Whitney U tests, Wilcoxon signed-rank test for paired samples and ANOVA with repeated measures.

Results: Relapse INS patients had higher proportion of ILC2s compared to controls (19.0±2.2% vs 9.6±2.3%, p=0.01). Paired analysis in INS patients showed significant decrease in ILC2s during remission compared to relapse (p=0.01). Additionally, cytokine profiles in relapse INS patients showed significantly increased Th2 cytokines IL-5 and IL-13, and Th2-related cytokines IL-9, IL-10 and Eotaxin (Table 1). ILC2s in relapse INS patients also had significantly higher levels of IL-12, IFNγ, RANTES and VEGF. Incubation with DEX increased ILC2s by 5.8±1.1% (p<0.001), which was similar in both patients and controls (p=0.83 for interaction).

Conclusions: ILC2s were significantly elevated in relapse INS patients. This was associated with classic Th2 signature following culture in cytokine conditioned medium, which was not suppressible by DEX.

Funding: Government Support - Non-U.S.

Table 1: Cytokine profile in healthy controls and INS patients in relapse

Cytokines (pg/ml)	Controls	INS Relapse	p-value
Th2-related			
IL-5	34.7±8.2	73.2±14.2	0.04
IL-9	72.6±16.1	150.6±15.7	0.007
IL-10	3.0±0.6	7.6±2.4	0.005
IL-13	39.9±15.3	162.4±57.9	0.04
Eotaxin	2.2±0.4	3.8±0.6	0.04
Th1-related			
IL-12	5.6±0.8	13.1±2.8	0.02
IFNγ	294.2±196.9	2763.7±1234.8	0.04
Chemokines			
RANTES	1067.4±839.1	1768.1±834.2	0.02
Angiogenic factor			
VEGF	137.8±13.5	181.0±11.6	0.04

Data were expressed as mean ± standard error of the mean (SEM)

FR-PO792

Selective B Cell Expansion Occurs in a Subset of Patients with Idiopathic Nephrotic Syndrome and Is Associated with Rituximab Response

Chang-Yien Chan,[1,2] Chenshi Lin,[1] Jian-Zhou Cui,[1] Jinmiao Chen,[3] Hui Kim Yap,[1,2] Liangjian Lu.[2] *[1]National University of Singapore, Singapore, Singapore; [2]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, Singapore; [3]Agency for Science Technology and Research, Singapore, Singapore.*

Background: Rituximab response in idiopathic nephrotic syndrome (INS) is highly heterogenous. This may be because only a sub-group of patients have B-cell driven disease, while others have T-cell driven disease. We aimed to investigate the extent of B-cell dysregulation in INS, and correlate this with Rituximab response.

Methods: 11 patients with relapsed steroid-sensitive INS were recruited together with 16 healthy controls, and B-cell subsets enumerated by flow cytometry. Single-cell RNA sequencing (scRNA-seq) was used to further characterize baseline B-cells in 4 patients with bifurcated Rituximab response (2 early relapse by 7 months, 2 sustained remission).

Results: INS patients had elevated CD27-IgD+ naïve B-cells (14±1.8% lymphocytes vs 8.1±0.7%, p=0.002) as well as elevated CD27+IgD- switched memory B-cells (2.8±0.7% vs 1.6±0.2%, p=0.05). K-means clustering of the cohort into 2 groups using these 2 parameters resulted in 7 patients clustering with all controls, and the remaining 4 patients with marked naïve and switched memory B-cell expansion forming a separate cluster (p=0.019). Detailed B-cell subclustering utilizing scRNA-seq revealed sustained Rituximab response was associated with expansion of an atypical B-cell cluster (2.4±1.9 vs 0.2±0.09% B-cells) that was IgD+CD27+/-CD24+CD38- and expressed PAX5 and elevated IL15. Furthermore, differentially expressed genes in B-cells showed that poor Rituximab response was strongly associated with upregulated "positive regulation of T-cell activation" (p<0.00002) and "Th17 cell differentiation" (p<0.0001), suggesting a primarily T-cell driven disease in these patients.

Conclusions: INS patients who demonstrate a good response to Rituximab likely have B-cell driven disease characterized by expansion of specific B-cell subsets.

FR-PO793

T Cell Hyporesponsiveness in Focal Segmental Glomerulosclerosis Responsive to Rituximab Is Associated with B Cell Activation and Production of Podocyte Damaging Factors

Liangjian Lu,[1] Chang-Yien Chan,[2,1] Sharon Teo,[1] Kar Hui Ng,[2,1] Hui Kim Yap.[2,1] *[1]National University Health System, Singapore, Singapore; [2]National University of Singapore, Singapore, Singapore.*

Background: The mechanistic basis of Rituximab response in idiopathic nephrotic syndrome (INS) remains uncertain. We previously showed that Rituximab-response in childhood-onset focal segmental glomerulosclerosis (FSGS) was associated with T-cell hypo-responsiveness. We aimed to investigate if dysregulated B-cell activity was associated with T-cell hypo-responsiveness prior to Rituximab.

Methods: 37 patients with childhood-onset FSGS were recruited. Rituximab was administered for clinical indications, with response defined as the ability to wean off steroids and calcineurin inhibitors by 3 months after Rituximab while remaining in complete remission. T-cell hypo-responsiveness was determined by stimulated INFγ production <2.5%. B-cell activation was measured by flow cytometry of activation markers and multiplexed cytokine analysis without further stimulation. Podocytes were incubated with B-cell conditioned media, and stained for F-actin with phalloidin. Staining was scored from 0-3, with higher scores reflecting greater abnormality, i.e. more cortical F-actin and less stress fibres. Comparison between groups was performed using t-test, Wilcoxon rank-sum test or Fisher's exact test.

Results: Baseline T-cell hypo-responsiveness was associated with Rituximab response (65% vs 29%, p=0.049). Comparing T-cell hypo-responsive and normo-responsive patients, total CD19+ B-cells were unchanged (p=0.6), but CD19+ CD80+ B-cells were increased (16% (IQR 11-26) vs 5% (IQR 5-9), p=0.006). There was a striking upregulation in resting B-cell cytokine production in patients with T-cell hypo-responsiveness, including INFγ (p= 0.005), IP10 (p=0.014) and TNFα (p=0.022). Podocytes incubated with B-cell conditioned medium from T-cell hypo-responsive patients demonstrated increased F-actin score (2.05±0.11 vs 1.36±0.15, p=0.02), but not when B-cells from T-cell normo-responsive patients were used (p=0.14). Repeat analysis 6 months post-Rituximab revealed no differences in B-cell cytokine production.

Conclusions: The association between Rituximab response and T-cell hypo-responsiveness likely reflects underlying B-cell activation, with B-cell mediated production of podocyte damaging factors. T-cell hypo-responsiveness may be an epiphenomenon reflecting T-cell exhaustion from chronic B-cell stimulation.

Funding: Government Support - Non-U.S.

FR-PO794

B Cells Are Essential for Proteinuria Induction in a Mouse Model of Autoimmune Idiopathic Nephrotic Syndrome

Simon Leclerc,[1,2] Lamine Aoudjit,[1,2] Tomoko Takano.[1,2] *[1]Research Institute of the McGill University Health Centre, Montreal, QC, Canada; [2]McGill University Faculty of Medicine and Health Sciences, Montreal, QC, Canada.*

Background: The idiopathic nephrotic syndrome (INS) is defined by heavy proteinuria, hypoalbuminemia, and edema. This occurs when the kidney's specialized epithelial cell, the podocyte, is injured by mechanisms that are still unknown. The recent discovery of autoantibodies targeting podocyte proteins like nephrin and Crb2 in human patients hints at the role of B cells and autoantibodies in INS, but their exact role is still unclear. Our objective is to establish if B cells are essential for the induction of proteinuria in a mouse model of autoimmune INS.

Methods: As previously published (Hada et al., J Am Soc Nephrol, 2022), 19 C3H/HeN mice were immunized three times at 2-wks intervals with recombinant Crb2, a transmembrane protein expressed at the podocyte slit diaphragm. One week after the first immunization, 10 mice received anti-CD20 (MB-11, BioXCell) to deplete B cells and 9 an isotype control. Serum and urine were tested for anti-Crb2 antibody and albuminuria, respectively. Inguinal lymph nodes and spleens were immunophenotyped at 6 wks.

Results: Mice that received anti-CD20 ('treated') showed a 95% decrease in circulating CD19+ B cells at 2 and 4 wks. At 6 wks, no treated mice (0/10) developed INS compared to 88% (8/9) of the mice receiving the isotype control ('control'). Anti-Crb2 antibody titers were lower in treated mice (1591±759 *vs.* 7207±3985 µg/mL, $p<0.003$). In the inguinal lymph nodes of treated mice, a respective 50% and 80% decrease in the number of CD4+ and CD19+ cells ($p<0.001$) were observed compared to controls. This was driven by a 75% decrease in switched memory B cells (CD19+ IgD- IgM- IgG+; $p<0.005$). The germinal centers in the inguinal lymph nodes of treated mice were reduced in size ($p<0.007$) and showed a reduced number of IgG+ positive B cells ($p<0.003$).

Conclusions: These results suggest that autoantibody-producing B cells are essential for proteinuria induction in this mouse model of autoimmune INS. Moreover, their role may not be limited to autoantibody production, as their crosstalk with T cells is likely significant. A better understanding of these mechanisms is crucial to develop targeted treatments for patients with autoimmune INS.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO795

Desialylated IgM by Idiopathic Nephrotic Syndrome Subjects Induce Proteinuria and Podocyte Injury

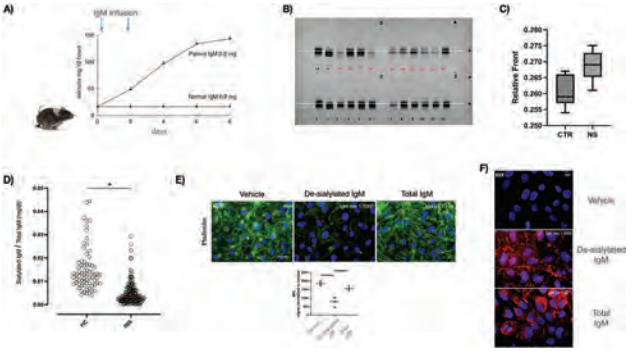
Xhuliana Kajana,[1] Sonia Spinelli,[1] Gianluca Caridi,[1] Gian Marco Ghiggeri,[1] Maurizio Bruschi,[1] Paolo Cravedi,[2] Andrea Angeletti.[1] *[1]Istituto Giannina Gaslini, Genova, Italy; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: IgM deposition is a common finding in the glomeruli of patients with idiopathic nephrotic syndrome (INS) and represents a risk factor for poor treatment response and disease progression. However, the pathological role of IgM in INS is controversial. Sialylation is a post-translational modification that significantly affects IgM function, but its role in the pathogenesis of INS is unknown.

Methods: IgM derived from patients with INS and controls (HC) were injected in 8 Sprague-Dawley rats. Sialylation induces an anionic charge to proteins, therefore, we tested the charge of IgM derived by 12INS and 12HC, as an indirect sign of sialylation, measuring IgM migration through an electrophoretic assay. To test a larger cohort (220 INS and 75 HC), we developed an ELISA and we measured the sialylation of IgM through incubation with biotinylated *Sambucus nigra* agglutinin. Immortalized human podocytes were exposed to total and desialylated IgM (obtained through desialylation of total IgM).

Results: IgM from INS induced higher levels of proteinuria compared to IgM from HC in rats. (**Fig1A**). IgM purified from patients with INS (red) had a significative higher cationic charge than IgM from controls (black) (**Fig1B**), as summarised in **Fig1C**. In a larger cohort, the ratio between the sialylation of IgM and total IgM was significantly lower in INS than HC (**Fig1D**). Co-incubation with desialylated IgM, but not total IgM altered the cytoskeletal protein phalloidinin of human podocytes, as evidenced in **Fig1E**. Intact IgM is internalized, while desialylated IgM remains on the podocyte surface (**Fig1F**), suggesting a different interaction of these types of IgM with podocytes.

Conclusions: IgM sialylation in INS is lower than HC and de-sialylated IgM induces *in vivo* proteinuria and *in vitro* podocyte damage. We recently demonstrated a causal link between IgM and disease relapse in a clinical study of patients with INS (DOI: 10.1016/j.ekir.2024.04.006). Overall, these data support that sialylation of IgM may play a pathogenic role in INS.



FR-PO796

Anti-nephrin Autoantibodies Cause Minimal Change Disease

Felicitas E. Hengel, Silke Dehde, Oliver Kretz, Tobias B. Huber, Nicola M. Tomas. *Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: Circulating autoantibodies against the podocyte slit diaphragm protein nephrin have recently been identified in patients with podocytopathies. However, whether these autoantibodies cause the observed minimal change disease phenotype with nephrotic syndrome is unknown.

Methods: Using immunoprecipitation and subsequent Western blotting, we screened patient-derived anti-nephrin autoantibodies for reactivity with glomerular extracts from multiple species. Anti-nephrin autoantibody containing patient IgG (further referred to as anti-nephrin IgG) or control human IgG was then transferred to animals that were identified to react with anti-nephrin IgG. Upon IgG transfer, animals were monitored for proteinuria, serum anti-nephrin IgG, and morphological lesions.

Results: The passive transfer of human anti-nephrin IgG resulted in substantial proteinuria and detectable anti-nephrin IgG in animal serum samples. Anti-nephrin IgG further induced podocyte foot process effacement in the absence of electron-dense deposits in electron microscopy, while Periodic-Acid-Schiff staining revealed no histological changes. Immunofluorescence analyses showed sparse positivity for human IgG at the glomerular filtration barrier, while it was absent in animals that received control IgG.

Conclusions: Our study demonstrates for the first time the direct pathogenicity of patient-derived anti-nephrin autoantibodies in the development of a podocytopathy with minimal change lesions. Further studies are necessary to better understand the molecular mechanisms of anti-nephrin autoantibody action on podocytes.

Funding: Government Support - Non-U.S.

FR-PO797

A Novel Subtype of Minimal Change Disease

Unnati Bhatia,[1] Ritu Calla,[2] Nishant Aggarwal,[1] Abhishek Swami.[1] *[1]Corewell Health Beaumont Hospital, Royal Oak, MI; [2]St Bernards Medical Center, Jonesboro, AR.*

Introduction: Minimal change disease (MCD) is a podocytopathy which causes failure of the glomerular filtration barrier by loss of slit diaphragm architecture. Etiology is unclear. It is characterized by normal light microscopy and negative immunofluorescence(IF) with diffuse foot process effacements noted on electron microscopy(EM) however punctate IgG staining on biopsy may indicate a novel autoimmune mechanism.

Case Description: A 59 yo Caucasian male with history of CKD 3b(baseline S.Cr 1.8-2), cerebral palsy complicated by chronic urinary retention with supra-pubic catheter, HTN presented with worsening B/L lower extremity edema and weight gain. The physical exam showed anasarca. Labs showed S.Cr 2.77, serum albumin 1.5 g/dl, urine albumin creatinine ratio 11,905 mg/g, dyslipidemia. UA showed 4+ proteinuria, >20 RBCs, >20 hyaline casts. Further workup for nephrotic syndrome including PLA2R antibody, HIV, hepatitis, syphilis, SPEP/UPEP, free light chains, complement levels, ANA, ANCA, cryoglobulins was negative. Kidney biopsy was consistent with MCD, mild acute tubular injury and interstitial fibrosis, moderate thickening of arteries and tubular atrophy. IF showed positive granular staining for IgG in Bowman's space and GBM. EM showed

diffuse effacement of foot processes and was unremarkable for immune complex deposits or fibrillary materials. Oral prednisone was started with plan for slow taper. Edema improved with diuretic therapy.

Discussion: MCD is characterized by diffuse effacement of podocyte foot processes on EM, absence of dense deposits or immune complexes and unremarkable LM. This case is unique with positive findings on IF showing positive granular staining for IgG in Bowman's space and GBM. Underlying molecular mechanisms are debatable, however efficacy of B-cell targeted therapies in steroid dependent and relapsing cases suggests autoantibody etiology. Anti-nephrin autoantibodies have been associated with massive proteinuria in animal models and as alloantibodies in post transplant children with congenital nephrin deficiency. A recent study (Watts et al.) hypothesized punctate IgG staining may represent in situ binding of nephrin autoantibodies resulting in redistribution of nephrin and disruption of intercellular junctions between podocytes. Further research is needed to establish prognostic significance of this subclassification of MCD and the role for targeted treatment.

FR-PO798

Investigation of NOD-Like Receptor Thermal Protein Domain Associated Protein 3 Inflammasome/Pyroptosis Stimulation through the CD36 Activation in Adults with Minimal Change Disease

Yuki Kajio, Taihei Suzuki, Kazuki Kobayashi, Hirokazu Honda. *Showa University School of Medicine, Tokyo, Japan.*

Background: Minimal change disease (MCD) basically occurs in childhood. Although MCD well reacts to the steroid therapy, adult onset MCD have frequent recurrency and need prolonged immunosuppressive therapy, compared to childhood MCD. Accordingly, the investigation for the pathogenesis of adult MCD has been required. MCD is usually accompanied with severe dyslipidemia. Oxidized low-density lipoprotein (ox-LDL) is known to work as a damage-associated molecular patterns through CD36, and trigger NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome and programmed cell death called pyroptosis. The relationship between the pathogenesis of MCD and NLRP3 inflammasome/ pyroptosis has not been understood fully. In this study, we assessed the factors which are regarding to NLRP3 inflammasome/ pyroptosis cascade in the patients diagnosed as MCD in our university hospital.

Methods: We performed histological and clinical assessment using kidney sections and urine samples taken from the MCD patinets (N=56), compared to the kidney doners (N=15) and health volunteers (N=15). Secondary MCD, the patients with any clinical data defect, and the patients without urine sample at the timing of renal biopsy (RBx) were excluded.

Results: Total 26 MCD patients were finally enrolled in this study. The number of the podocytes was lower in MCD than that of the control. Urinary ox-LDL levels were higher in MCD, compared to the control. Analysis of immunofluorescent staining revealed that NLRP3 and CD36 were activated in MCD podocytes. Urinary interleukin (IL)-18 levels increased in the MCD patients. Steroid therapy applied before RBx contributed to maintaining the number of podocytes in glomeruli and reduce urinary ox-LDL and IL-18 levels.

Conclusions: In this study, NLRP3 inflammasome cascade seemed to be activated *via* upregulation of CD36 in podocytes and the elevation of urinary ox-LDL. The elevation of urinary IL-18 levels could suggest that pyroptosis might occur in MCD, further studies are required to detect certain pyroptosis in podocytes.

FR-PO799

Role of LDL-Scavenger Receptor CD36-Positive Macrophages in Refractory Nephrotic Syndrome with Hyperlipidemia under High-Dosage Steroid Treatment

Yohei Ikezumi,[1] Tomomi Kondo,[1] Takuma Ando,[1] Yuji Matsumoto,[1] David J. Nikolic-Paterson,[2] Naonori Kumagai.[1] *[1]Fujita Health University School of Medicine Department of Pediatrics, Toyoake, Japan; [2]Monash University Department of Medicine, Clayton, VIC, Australia.*

Background: Most cases of pediatric nephrotic syndrome (NS) are steroid-sensitive (SSNS); however, about 10% of cases are steroid-resistant (SRNS), and some patients develop SRNS during treatment. We have previously reported that chronic lesions, including matrix expansion and fibrosis, seen during steroid therapy are associated with increasing numbers of macrophages (MQ). This study examined expression of the LDL-scavenger receptor (CD36) in MQ in pediatric SRNS.

Methods: Renal biopsies and clinicopathological findings from 25 children with SSNS and 18 children with SRNS were compared. The number of glomerular $CD36^+CD68^+$ MQ was assessed by immunofluorescence staining. Urine levels of CCL2 were measured by ELISA. Cultured human monocyte-derived MQ were stimulated with dexamethasone (Dex) and/or oxidized LDL (oxLDL) for 48hr and RNA levels compared to control cells.

Results: Children with SRNS has significantly lower serum albumin levels, higher serum levels of total cholesterol and LDL cholesterol, higher proteinuria and were on higher doses of Prednisolone at time of biopsy (all $P<0.01$ vs SSNS). Combined stimulation of cultured MQ with Dex plus ox-LDL induced up-regulation of mRNA levels of *CD36*, cytokines and growth factors associated with inflammation and fibrosis (*CCL2, IL25, NOS2, FGF1, FGF2, CTGF*), and extracellular matrix proteins (*COL1A2, COL4A1, COL4A2, COL13A1*). Immunostaining showed a 3-fold increase in the number of glomerular $CD36^+CD68^+$ MQ in SRNS vs SSNS (2.3 vs 0.8, $P<0.001$), and revealed expression of FGF1, AGT and CCL2 in biopsies from SRNS patients which co-localized with glomerular $CD36^+CD68^+$ MQ. In addition, the urine CCL2/creatinine ratio was increased 5-fold in SRNS vs SSNS patients (986.2 vs 200.8, $P=0.012$).

Conclusions: The significant hyperlipidemia seen in steroid-treated pediatric SRNS was associated with a substantial increase in the number of glomerular $CD36^+CD68^+$ MQ. In vitro studies support a direct link between steroids and ox-LDL in stimulating MQ expression of CD36 and of the genes involved in both inflammation and fibrosis. Thus, cholesterol processing $CD36^+CD68^+$ MQ may contribute to resistance to treatment in SRNS through the production of pro-fibrotic and pro-inflammatory factors.

Funding: Government Support - Non-U.S.

FR-PO800

Podocyte Exopher Formation as a Novel Pathomechanism in Membranous Nephropathy

Catherine Meyer-Schwesinger,[1] Karen Lahme,[1] Wiebke Sachs,[1] Sarah Froembling,[1] Kristin Surmann,[2] Roland Thuenauer,[3] Stephanie Zielinski,[1] Johannes Brand,[1] Stephan Michalik,[2] Marina Zimmermann,[4] Thorsten Wiech,[5] Tobias N. Meyer,[7] Lars Fester.[6] *[1]Institute of Cellular and Integrative Physiology, Center for Experimental Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany; [3]Technology Platform Microscopy and Image Analysis (TP MIA), Leibniz Institute of Virology, Hamburg, Germany; [4]Institute of Medical Systems Biology, Center for Biomedical AI, Center for Molecular Neurobiology, Hamburg, Germany; [5]Institute of Pathology, Nephropathology Section, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [6]Institute of Neuroanatomy, Medical Faculty, University of Bonn, Bonn, Germany; [7]Nephrology, Asklepios Klinikum Barmbek, Hamburg, Germany.*

Background: Membranous nephropathy (MN) is caused by autoantibody binding to podocyte foot process antigens such as THSD7A and PLA_2R1. The mechanisms of the glomerular antigen/autoantibody deposition and clearance are unknown.

Methods: We explore the origin and significance of glomerular accumulations in (1) diagnostic and follow-up biospecimens from $THSD7A^+$ and PLA_2R1^+-MN patients compared to nephrotic non-MN patients, and (2) in experimental models of $THSD7A^+$-MN.

Results: We discovered podocyte exophers as correlates of histological antigen/autoantibody aggregates found in the glomerular urinary space of MN patients. Exopher vesicle formation represents a novel form of toxic protein aggregate removal in *Caenorhabditis elegans* neurons. In MN patients, podocytes released exophers to the urine. Enrichment of exophers from MN patient urines established them as a glomerular exit route for antigens and bound autoantibody. Exophers also carried disease-associated proteins such as complement and provided a molecular imprint of podocyte injury pathways. In experimental $THSD7A^+$-MN, exophers were formed from podocyte processes and cell body. Their formation involved the translocation of antigen/autoantibody from the subepithelial to the urinary side of podocyte plasma membranes. Urinary exopher-release correlated with lower albuminuria and lower glomerular antigen/autoantibody burden. In MN patients the prospective monitoring of urinary exopher abundance and of exopher-bound autoantibodies was additive in the assessment of immunologic MN activity.

Conclusions: Exopher-formation and release is a novel pathomechanism in MN to remove antigen/autoantibody aggregates from the podocyte. Tracking exopher-release will add a non-invasive diagnostic tool with prognostic potential to clinical diagnostics and follow-up of MN patients.

FR-PO801

Serial Changes of Molecular Expression of Slit Diaphragm Proteins in Post-transplant FSGS Recurrence Associated with Anti-nephrin Antibodies

Yoko Shirai,[1] Kenichiro Miura,[1] Sekiko Taneda,[1] Kazuho Honda,[2] Kenji Tanabe,[1] Motoshi Hattori.[1] *[1]Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan; [2]Showa Daigaku, Shinagawa-ku, Japan.*

Background: Recently, we reported very early pathological changes in podocytes in patients with post-transplant recurrence of focal segmental glomerulosclerosis (rFSGS) associated with circulating anti-nephrin antibodies (abs), suggesting that anti-nephrin abs are a possible candidate for circulating factors involved in the pathogenesis of rFSGS (Hattori et al, Am J Transplant, 2022; Shirai et al, Kidney Int, 2024). Here, we analyzed serial changes of molecular expression of slit diaphragm proteins in post-transplant FSGS recurrence associated with anti-nephrin abs, using serial graft biopsies.

Methods: We analyzed four kidney transplant recipients with childhood-onset primary FSGS who had positive circulating anti-nephrin abds and underwent serial graft biopsies including 1 hour graft biopsy (1hGBx). All patients underwent whole exome sequencing and no pathogenic variants in FSGS-related genes were identified. Dual immunofluorescence staining images of IgG and nephrin, CD2-associated protein (CD2AP), and podocin were obtained using the structured illumination microscopy.

Results: In all 4 rFSGS patients, 1hGBx showed punctate IgG deposition co-localizing with nephrin that had altered distributions from foot process to podocyte intracellular area. CD2AP was diffusely expressed in podocyte cell bodies before re-perfusion, and 1hGBx showed granular aggregation of CD2AP. In graft biopsies during recurrence (rGBx) obtained at median POD 38 (IQR, 18, 55), the expression of nephrin and CD2AP was decreased in all patients. In contrast, foot process expression of podocin was neither decreased nor altered in 1hGBx and rGBx specimens of three patients. In the remaining one patient, who did not respond to treatment and rapidly progressed to graft loss, expression of podocin was neither decreased nor altered in 1hGBx, but was decreased without altered localization in rGBx.

Conclusions: Nephrin showed altered distributions from foot process to podocyte intracellular area, and CD2AP showed decreased expression and granular aggregation at very early phase of exposure to anti-nephrin abs. In contrast, podocin localization was not altered even after progression of FSGS recurrence. These findings may contribute to better understanding the mechanism of podocyte injury associated with anti-nephrin abds.

Funding: Government Support - Non-U.S.

FR-PO802

Target Protein of Passive Heymann Nephritis and Its Role in the Mechanism of Proteinuria in Membranous Nephropathy (MN)

Renan G. Diniz,[1,2] Ashok K. Singh.[2] *[1]University of Illinois Chicago, Chicago, IL; [2]Hektoen Institute LLC, Chicago, IL.*

Background: PHN is an established rat model of human MN. However, the target protein of PHN on the glomerulus is unknown and so is also the mechanism of proteinuria in PHN. Because of the striking similarity of the staining patterns of PHN and podocalyxin (PDX) we hypothesize that the target protein of the PHN antibody could likely be PDX. We examined this hypothesis by quantifying PDX in PHN rats at the time of proteinuria.

Methods: Rats were divided into one control (Cont) and six experimental (EX) groups. EX received 1 mL iv anti-gp600 antiserum to induce PHN while\ Cont received 1 mL of iv saline. PHN was confirmed by a strong glomerular capillary wall staining as seen by indirect immunofluorescence (IF). Rats were maintained by ad libitum access to food and water. Proteinuria was assessed at the end of each week until 6 weeks. At 6 weeks rats were euthanized and kidney was fixed with 10% buffered formalin. PDX was stained by IF and quantified using the Image J software. Data were statistically analyzed and compared using student t test and ANOVA.

Results: Proteinuria was significantly elevated progressively from 1-6 weeks in EX (208mg/24h at 6 weeks). PDX staining in EX was significantly reduced by 25% at 6 weeks compared to Cont (36.6 ± 1.9 vs 48.4 ± 2.6 intensity units/glomerulus; p< 0,05) (Figure 1 below)

Conclusions: In conclusion, reduction of PDX in PHN suggests that the target of PHN antibody, and by analogy in MN, appears to be PDX, a podocytic protein that is known to be coupled with the actin cytoskeleton of the cell and therefore important in maintaining the foot process structure of the podocytes. We speculate that the reduction of PDX could be the mechanism of proteinuria in MN as its loss must disrupt the foot process architecture of the podocytes leading to the breakdown of the glomerular filtration.

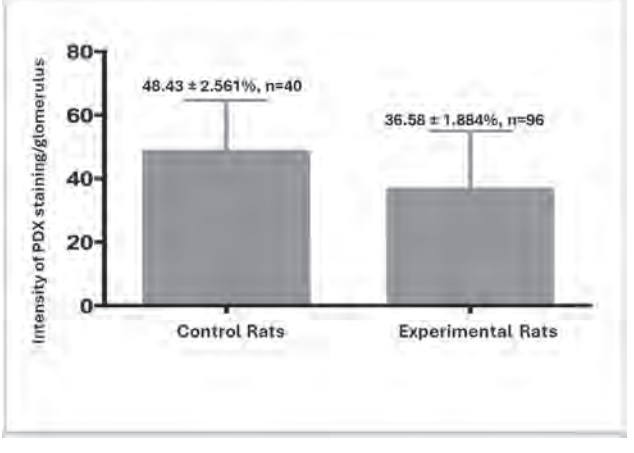


Figure 1: PDX staining in Cont and EX: intensity units/glomerulus

FR-PO803

Deciphering Antigen-Specific Glomerular Injury Mechanisms in Membranous Nephropathy via Single-Cell RNA Sequencing (scRNA-seq) and a Glomerulus-on-a-Chip Model

Stefano Da Sacco,[1] Laura Perin,[1] Qi Zhang,[1] Jack F. Wetzels,[3] Roger E. De Filippo,[1] Paolo Cravedi.[2] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Radboud Universiteit, Nijmegen, Netherlands.*

Background: Primary membranous nephropathy (MN) is a prevalent cause of adult nephrotic syndrome, caused by anti-podocyte antibodies targeting proteins like PLA2R1 and THSD7A in the glomerular subepithelial space. This study explores the effects of these antibodies on glomerular cells using single-cell transcriptomics within a human glomerulus-on-a-chip (GOAC) model.

Methods: Human primary podocytes and glomerular endothelial cells were cultured within GOACs and subjected to sera containing anti-PLA2R or anti-THSD7A antibodies for a duration of 72 hours. Sera from healthy donors served as controls. Albumin permeability assays confirmed cellular injury, and single-cell RNA sequencing (scRNA-seq) was performed at a depth of 80,000 reads per cell, with subsequent detailed transcriptomic evaluations, followed by comprehensive transcriptomic analysis.

Results: Anti-PLA2R and anti-THSD7A exposure induced albumin leakage in GOACs, signaling injury. scRNA-seq revealed a pronounced activation of the complement pathway. For example, in podocytes, antigen-specific injury-related pathways such as EIF2 and mTOR signaling, and PTEN in glomerular endothelial cells, exhibited differential responses to anti-PLA2R sera, as opposed to anti-THSD7A or healthy sera, suggesting that concurrent early injury mechanisms drive podocyte dysregulation together with the complement cascade.

Conclusions: The study validates the application of scRNA-seq for the analysis of human cells in GOACs exposed to MN patient-derived sera. This methodological synergy offers insights into the pathogenic mechanisms at play in MN, providing a foundation for the identification of new therapeutic avenues for glomerular disorders.

Funding: NIDDK Support, Private Foundation Support

FR-PO804

Differential Expression of Renal and Hepatic PCSK9 during Development of Hypercholesterolemia in the Passive Heymann Nephritis Rat Model of Nephrotic Syndrome

Eduardo Molina-Jijon,[1] Camille E. Mace,[1] Carmen Avila-Casado,[2] Lionel C. Clement.[1] *[1]Rush University Medical Center, Chicago, IL; [2]University of Toronto, Toronto, ON, Canada.*

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in the regulation of LDL-c levels in the liver. In the kidney, PCSK9 is expressed in the cortical collecting duct (CCD) where it plays a role of chaperone protein for the epithelial sodium channel. We showed increased PCSK9 expression in kidney biopsies of patients with primary glomerular disease and its implication in the initiation of development of hypercholesterolemia in the Buffalo-Mna rat (model of focal and segmental glomerulosclerosis) and the Rrm2b$^{-/-}$ mouse (model of collapsing glomerulopathy) (Molina-Jijon et al, 2020) following proteinuria. We then studied the expression of PCSK9 in the PHN rat (model of Membranous Nephropathy (MN)).

Methods: Male Sprague-Dawley rats were injected twice with sheep serum (Controls, 750 µl/rat on Day 0 and Day 1) or sheep anti-Fx1A antibody (PHN, 750 µl/rat on Day 0 and Day 1). Rats were euthanized on Days 3, 7, 10 and 17 after first injection. Proteinuria, PCSK9 and total cholesterol serum levels were assessed. PCSK9 gene and protein expression in liver and kidney were studied by Real Time PCR, Western blot, and confocal microscopy. Human patient kidney sections were stained with PCSK9 and AQP2 antibodies to study PCSK9 protein expression and localization.

Results: Control rats do not develop proteinuria neither hypercholesterolemia nor have high levels of serum PCSK9. PHN rats develop proteinuria from day 3 (4.26 ± 0.98 mg/18h, P<0.01; 198.73 ± 21.22 mg/18h at day 17, P<0.001), high serum PCSK9 levels from day 7 (60.427 ± 73.33 ng/ml, P<0.05; 1,404.96 ± 280.29 ng/ml at day 17, P<0.001), and hypercholesterolemia from day 7 (184.49 ± 7.98 mg/dL, P<0.001; 352.58 ± 29.16 mg/dL at day 17, P<0.001). PCSK9 protein and gene expression increased in the kidney but not in the liver at the same time points studied.

Conclusions: As PHN rats develop NS, PCSK9 protein level increases in the kidney, but not in the liver. CCD-PCSK9 may play a role in the initiation of hypercholesterolemia in MN-related NS. CCD-PCSK9 could become a new therapeutic target to prevent development of hypercholesterolemia in NS patients in which prolonged hypercholesterolemia may worsen kidney disease and increase risk of cardiovascular disease.

Funding: NIDDK Support

FR-PO805

Kidney NELL1 Expression Peaks during Onset of Autoimmunity in Genetically Predisposed SKG Mice

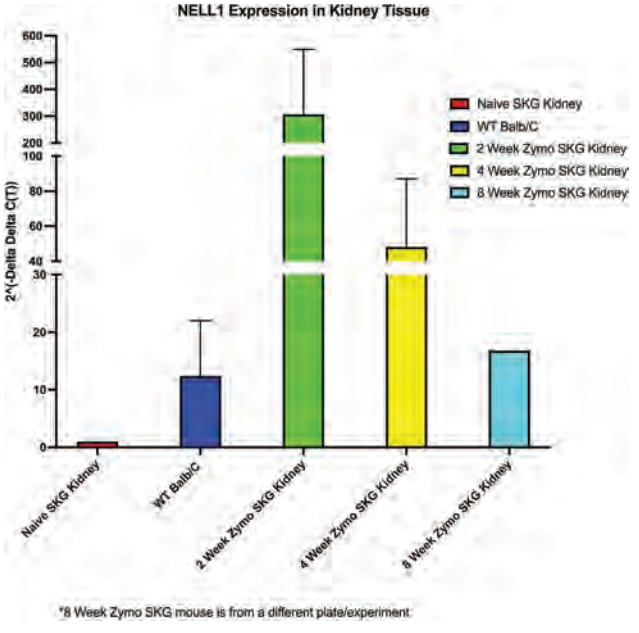
Lisa T. Kumasaka,[1] Amy L. Seufert,[2,3] Rupali S. Avasare,[2] Emily E. Vance,[2,3] Ruth J. Napier.[2,3] *[1]Oregon Health & Science University School of Medicine, Portland, OR; [2]Oregon Health & Science University, Portland, OR; [3]Portland VA Medical Center, Portland, OR.*

Background: Inflammation is a key process in disease, including autoimmune disorders and cancer. Neural Epidermal Growth Factor-Like 1 (NELL1) is a multifunctional protein involved in various cellular processes, including development and tissue repair. Understanding the relationship between inflammation and NELL1 expression can provide insights into inflammatory mechanisms underlying tissue-specific pathologies, including the autoimmune kidney disease, NELL1-Membranous Nephropathy (MN).

Methods: SKG mice were given one intraperitoneal injection of zymosan to induce T cell-mediated inflammation, followed by weekly clinical scoring for joint swelling, redness, or deformities (Rosenzweig et al., 2023). Mice were euthanized at 2, 4, and 8 weeks post-zymosan, kidneys and brains were harvested and stored in RNAlater. Tissues were homogenized, RNA isolated, and expression of Nell1 was measured via qRT-PCR.

Results: Inflammatory conditions due to zymosan induced autoimmune arthritis coincided with higher NELL1 expression levels in the kidney tissue of SKG mice compared to naïve SKG mice that did not receive the zymosan injection. NELL1 expression peaked at the 2-week post zymosan injection and showed a progressive decline at the 4-week and 8-week time points. While NELL1 expression does coincide with arthritic inflammation in this model, it is important to note that NELL1 does not peak when severity of autoimmune arthritis peaks.

Conclusions: Our research shows NELL1 mRNA expression is enhanced in zymosan induced autoimmune arthritic mice kidneys compared to naïve controls. Interestingly, NELL1 expression is elevated prior to peak arthritis. Our work provides foundational knowledge for the development of a mouse model to study mechanisms of kidney inflammation that drive the development of NELL1 MN.



FR-PO806

SARS-CoV-2 Protein Deposition Enhances Renal Complement Activation and Aggravates Kidney Injury in Membranous Nephropathy after COVID-19

Hong Cheng,[1] Guo-qin Wang,[1] Lei Yang,[1] Xiao-yi Xu,[1] Weiyi Guo,[1] Li-jun Sun,[1] Yan-yan Wang,[1] Wenrong Cheng,[1] Nan Ye,[1] Lingqiang Kong,[1] Xiaoyi Zhao.[2] *[1]Beijing Anzhen Hospital Affiliated to Capital Medical University, Chaoyang-qu, China; [2]Affiliated Hospital of Chifeng University, Neimenggu, China.*

Background: COVID-19 has been reported to be associated with the occurrence and recurrence of membranous nephropathy (MN). The clinicopathological characteristics and complement system activation of MN after COVID-19 are unclear.

Methods: A total of 38 patients with biopsy-proven MN who developed new onset proteinuria after COVID-19 were enrolled in this study. One hundred patients with primary MN diagnosed before COVID-19 pandemic as control. Renal immunohistochemical staining for SARS-CoV-2 nucleocapsid protein was performed in 38 patients with MN after COVID-19. Serum membrane attack complex (MAC) was detected by enzyme-linked immunosorbent assay. Glomerular staining for the complement proteins in different pathways were detected by immunohistochemical.

Results: Thirteen of 38 patients had positive staining for SARS-CoV-2 nucleocapsid protein. Compared with control-patients, the clinical manifestations were more severe in patients after COVID-19. Patients with positive SARS-CoV-2 staining had a higher proportion of nephrotic syndrome, lower level of serum albumin, and greater severity of renal interstitial fibrosis than those of patients with negative SARS-CoV-2 staining. Serum MAC level and renal MAC staining intensity of MN after COVID-19 were significantly higher than those of control-patients. MAC expression in MN patients with positive SARS-CoV-2 staining was stronger than that in both control-patients and MN after COVID-19 with negative SARS-CoV-2 staining. Meanwhile, the expression trend of factor H was consistent with that of MAC.

Conclusions: Excessive activation of the complement system aggravated symptoms in MN after COVID-19. The complement alternative pathway might be involved in renal injury. Therapeutic strategy targeting the complement system may need to be considered.

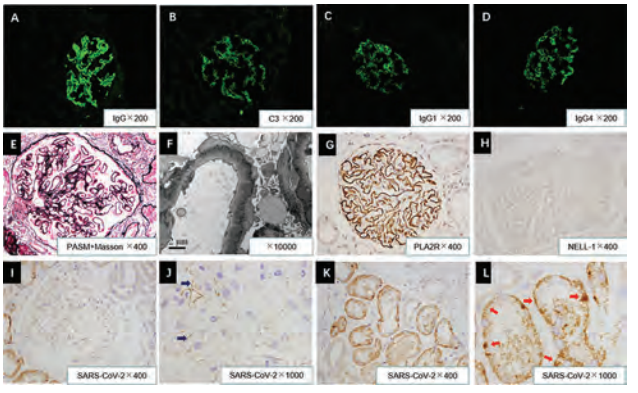


Figure. The renal pathologic images of a patient with PLA2R-positive MN patient after COVID-19 who also is positive for SARS -COV-2 staining.

FR-PO807

ACE in Neutrophils Ameliorates Glomerular Damage in Immune Complex-Mediated Crescentic Glomerulonephritis via Complement C3 and C and N Domains of ACE

Suguru Saito,[1] Zakir Khan,[1] Ellen A. Bernstein,[1] Yoshihiko Kanno,[2] Kenneth E. Bernstein,[1] Michifumi Yamashita.[1] *[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]Tokyo Medical University, Tokyo, Japan.*

Background: Angiotensin-converting enzyme (ACE) is composed of catalytically active C and N domains, and widely known to regulate blood pressure as a major component of the renin-angiotensin system. We recently reported that glomerular injury of immune-complex (IC) mediated crescentic glomerulonephritis (GN) was attenuated in the mice overexpressing ACE specifically in neutrophils (NeuACE mice). Mechanistically, the renoprotective role was mediated by complement C3b-complement receptors 1/2 (CR1/2): C3b-CR1/2 axis. NeuACE mice showed increased level of serum C3b. NeuACE neutrophils exhibited enhanced IC uptake with elevated surface expressions of CR1/2 and FcγRs. Here, we further investigate the precise mechanism of the neutrophilic ACE-mediated renoprotective effects in GN.

Methods: Nephrotoxic serum nephritis (NTN) was induced in the mice with four different conditions, and analyzed in renal function and histology: 1) Neutrophils were depleted in WT and NeuACE mice by administering anti-neutrophil Ab. 2) ACE-overexpressed neutrophils were adoptively transferred into WT mice. 3) ACE C-domain KO (Tg-CKO) mice, ACE N-domain KO (Tg-NKO) mice, and WT-ACE transgenic (Tg-ACE) mice were also examined. 4) Lastly, NeuACE mice that lack complement C3 (NeuACE-C3KO) and C3KO mice were compared.

Results: 1) WT mice without neutrophils showed amerioliated glomerular injury in proteinuria and histology, while NeuACE mice lacking neurophils lost the renoprotective effect. In WT mice, neutorphils are needed for glomerular injury; in NeuACE mice, neutrophils are required for the renoprotection. 2) WT mice with ACE-overexpressing neutrophils exhibited less severe glomerular injury. 3) Tg-CKO or Tg-NKO showed partially lost the renoprotective role compared with Tg-ACE mice, likely both C and N domains are needed for full renoprotection. 4) Furthermore, NeuACE-C3KO mice did not show the renoprotective effects of overexpressed ACE in neurophils anymore, compared with C3KO mice. Complement C3 is essential for the renoprotective role of overexpressed ACE in neutrophils in NeuACE mice.

Conclusions: The renoprotective effects of overexpressed ACE in NeuACE mice in IC-mediated GN require specifically neutrophils, both C and N domains of ACE, and complement C3.

FR-PO808

The Role of von Willebrand Factor (vWF) in the Pathogenesis of C3 Glomerulopathy (C3G)

Zixin Hua. *Peking University First Hospital, Beijing, China.*

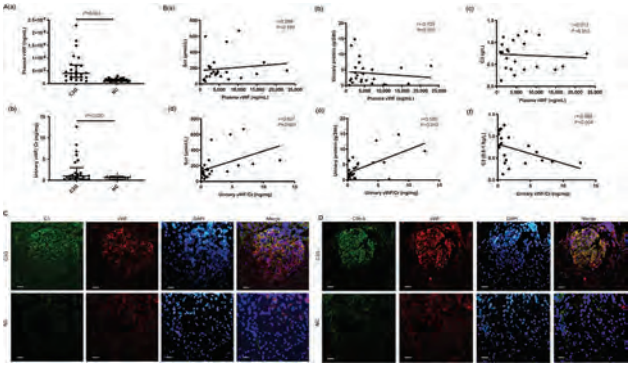
Background: C3G is caused by dysregulation of complement activation. Our previous study found that C3G patients showed rare variants in vWF. However, role of vWF in C3G's pathogenesis remains unclear.

Methods: The levels of vWF in plasma, urine and kidney specimens of C3G patients were detected and their associations with clinicopathological data were analyzed. A *VWF*-knockout C3G ($FH^{m/m}P^{-/-}VWF^{m/m}$) mice was generated using the CRISPR/Cas9 system to examine the cellular and molecular mechanisms.

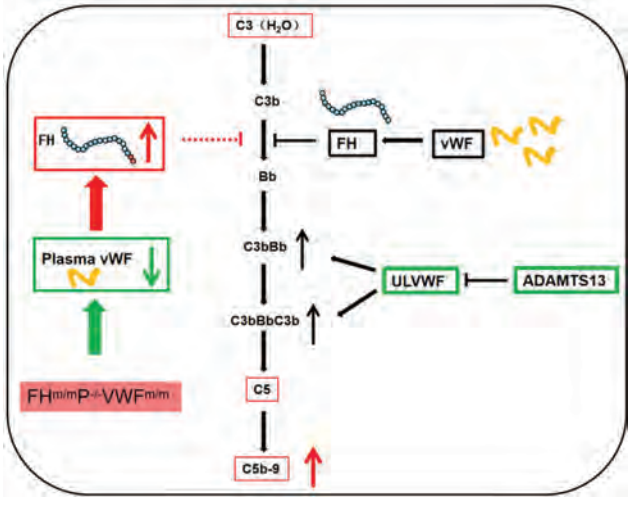
Results: The urinary level of vWF/Cr in C3G patients was associated with level of serum creatinine (r=0.627, *P*<0.001), proteinuria (r=0.505, *P*=0.010), serum C3 (r=-0.582, *P*=0.004), and was a risk factor for worse prognosis (HR 1.294, 95% CI 1.050-1.595, *P*=0.015). VWF was co-localized with C3 and C5b-9 in kidneys. Compared with $FH^{m/m}P^{-/-}$ mice, $FH^{m/m}P^{-/-}VWF^{m/m}$ mice showed significantly higher levels of serum creatinine (140.70±61.87vs31.39±12.28μmol/L,*P*<0.001),proteinuria(3.50±2.25vs0.86±0.11g/mol, *P*<0.001), more severe renal pathological manifestations, more renal C3 and C5b-9 deposition, and worse prognosis (*P*=0.001). *VWF* gene deficiency was associated with complement factor H (FH) overexpression in $FH^{m/m}P^{-/-}VWF^{m/m}$ mice.

Conclusions: The levels of vWF were associated with disease severity and poor prognosis of C3G patients. *VWF* gene deficiency led to the aggravation of kidney damage and FH overexpression in C3G mouse model, which indicated that vWF might play a protective role in the pathogenesis of C3G.

Funding: Government Support - Non-U.S.



Associations of vWF levels with histopathological data in C3G patients



Mechanism of aberrant complement activation in *VWF* knockout C3G mice

FR-PO809

Complement C3 Contributes to the Pathogenicity of Galactose-Deficient IgA1-Containing Immune Complexes in IgA Nephropathy

Stacy D. Hall,[1] Graham Gurganus,[1] Zhi qiang Huang,[1] Barbora Knoppova,[1] Shihong Qiu,[1] Rodney G. King,[1] Shigeaki Nakazawa,[1,3] Nicolas Maillard,[2] Zina Moldoveanu,[1] Dana V. Rizk,[1] Bruce A. Julian,[1] Matthew B. Renfrow,[1] Todd J. Green,[1] Jan Novak.[1] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Hospital and University Jean Monnet of Saint-Etienne, Saint-Etienne, France; [3]Osaka Daigaku Daigakuin Igakukei Kenkyuka Igakubu Igaku Senko, Suita, Japan.*

Background: IgA nephropathy (IgAN) is an autoimmune kidney disease wherein circulating immune complexes (IC) contain IgA1 with some *O*-glycans deficient in galactose (galactose-deficient IgA1; Gd-IgA1) bound by IgG autoantibodies specific for Gd-IgA1. Additional serum components, such as complement proteins, can be also associated with these IC. Some of these Gd-IgA1-containing IC deposit in the glomeruli and induce kidney injury. In this study, we assessed the role of complement C3 in the pathogenicity of Gd-IgA1-IgG IC.

Methods: IC from native or IgA1-depleted sera of patients with IgAN were isolated by size-exclusion chromatography. Engineered IC were formed using recombinant polymeric Gd-IgA1 and recombinant IgG autoantibodies specific for Gd-IgA1 in C3-depleted or C3-repleted serum and isolated by size-exclusion chromatography. Biological activity of the isolated IC or engineered IC was determined based on their capacity to induce cellular proliferation of cultured primary human mesangial cells. IgA, Gd-IgA1, and IgA-IgG and IgA-C3 complexes were determined by ELISA. SDS-PAGE immunoblotting under non-reducing conditions was used to determine covalent association of C3 with IgA or IgG. Reducing conditions were used to determine C3 processing, i.e., presence of alpha-chain or its fragments indicative of C3, C3b, and iC3b, respectively.

Results: IC >700 kDa from IgAN sera increased cellular proliferation of quiescent mesangial cells by 2-4-fold. These IC contained IgA, IgG, and C3; C3 was covalently associated with IgA and IgG. C3 molecular forms included C3, C3b, and iC3b. Removal of IgA1 from sera removed these stimulatory IC; the resultant preparations were devoid of IgA, IgG, and C3. To confirm the role of C3, we used engineered IC formed in C3-depleted or repleted serum. C3 was required for formation of large-molecular-mass engineered IC that stimulated mesangial cells to proliferate. Moreover, IgA and IgG formed covalent complexes with C3 in C3-repleted serum; these engineered IC contained C3, C3b, and iC3b.

Conclusions: In summary, C3 has a central role in the formation of Gd-IgA1-containing IC with a nephritogenic capacity for IgAN.

Funding: NIDDK Support, Other NIH Support - NIAID, Private Foundation Support

FR-PO810

Engineering of CX3CR1-Expressing Induced Regulatory T-Like Cells (iTregs) to Treat Acute Glomerulonephritis

David L. Puetz,[1,2] Jasper F. Nies,[2,1] Claudio Sierra Gonzalez,[2,1] Bastian Trinsch,[2,1] Paul T. Brinkkoetter,[2,1] Bernhard Schermer,[2,3] Thomas Benzing,[2,1] Paul Diefenhardt,[2,1] Sebastian Braehler.[2,1] *[1]University of Cologne Center for Molecular Medicine Cologne, Cologne, Germany; [2]Universitatsklinikum Koln, Koln, Germany; [3]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany.*

Background: T cell based strategies emerge as a targeted treatment option for autoimmune diseases including glomerulonephritis. T regulatory cells (Tregs) are uniquely equipped to dampen inflammation and thus prevent excessive tissue damage. To harness their full potential, however, they have to be directed to the site of inflammation. The chemokine receptor CX3CR1 detects CX3CL1, which has been shown to be selectively expressed in kidneys during GN. This study aims to engineer CX3CR1 expressing Tregs by retroviral transduction of Foxp3 and Cx3cr1 and assess their suppressive – and ultimately - therapeutic potential in GN.

Methods: A retroviral vector was generated containing the coding sequences of Foxp3 and Cx3cr1 linked by a P2A site. Subsequently, primary naïve murine T cells were transduced *in vitro*. The generated T cells (termed *induced Treg like cells; iTregs*) were examined with regards to known Treg markers using flow cytometry. In addition, their suppressive function was assessed *in vitro* by T cell proliferation assay and ELISA.

Results: Viral transduction of primary mouse T cells resulted in the generation of iTregs expressing FOXP3 as well as CX3CR1 with a high transduction efficiency. Interestingly, these cells expressed the Treg markers CD25, CTLA-4, PD-1, GITR, ICOS and Helios to a similar degree as naturally occurring Tregs. Confirming their regulatory nature, proliferation of T effector cells was suppressed by these iTregs *in vitro*. In addition, they produced copious amounts of the anti-inflammatory cytokine IL-10, suggesting immunosuppressive functionality.

Conclusions: Retrovirally engineered CX3CR1+ iTregs have suppressive functions *in vitro* and obtain a Treg like phenotype. Future studies will assess their behaviour and migratory preferences *in vivo*. Ultimately, their therapeutic potential will be tested in a murine model of acute glomerulonephritis.

FR-PO811

Deciphering Complement Activation Mechanisms in Childhood IgA Nephropathy

Srishti Sahu,[1,2] Natalie Patey,[1,2] Arnaud Bonnefoy,[1,2] Stephan Troyanov,[3,2] Anne-Laure Lapeyraque,[1,2] Cambier Alexandra.[1,2] Cambier's Laboratory.
[1]Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada; [2]Universite de Montreal Faculte de Medecine, Montreal, QC, Canada; [3]Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada.

Background: The complement pathway plays a crucial role in the development of IgA nephropathy (IgAN), as evidenced by the association of complement C3 with IgA deposits. However, the specific mechanisms that trigger complement pathway activation remain poorly understood. Recent research has implicated soluble CD89 (sCD89) in kidney inflammation among childhood IgAN (cIgAN) patients. Thus, this study seeks to understand how sCD89 activates collectin 11—a crucial initiator of the lectin pathway—ultimately resulting in the formation of C5b-9 and subsequent kidney inflammation.

Methods: A prospective cohort of cIgAN patients was enrolled in the study (n=52). The levels of soluble C5b-9 (sC5b-9) and collectin-11 (C-11) were determined in both the urine and plasma of these patients using ELISA. These levels were correlated with biological, histological and clinical data. Kidney biopsies were assessed for inflammation and C5b-9 deposition. Next, we evaluated the expression and secretion of C-11 in human mesangial cells (HMCs) using RT-PCR and ELISA respectively. HMCs were stimulated with cIgAN plasma or recombinant sCD89 (rsCD89). Additionally, to detect the presence of C-11 within circulating immune complexes (CICs) we used sCD89 immunoprecipitation.

Results: Our research findings demonstrate several significant associations in cIgAN patients. sC5b-9 correlates with lower eGFR and increased proteinuria. Elevated levels of sC5b-9 were also linked to cellular inflammation, glomerulosclerosis and fibrotic crescents. Notably, we found that plasma sC5b-9 is linked to endocapillary deposition of C5b-9 in kidney glomeruli. Furthermore, C-11 levels are elevated in cIgAN patients compared to healthy controls. There exists a positive correlation between plasma C5b-9 and C-11 levels. Our *in vitro* results indicate that C-11 is expressed and secreted by the HMCs, with its upregulation upon stimulation by cIgAN plasma and rsCD89. Interestingly, we also observe the presence of C-11 within the CICs.

Conclusions: Our study indicates that both sC5b-9 and C-11 are associated with disease severity in cIgAN. They show promise as prognostic markers for cIgAN, potentially obviating the need for invasive kidney biopsy procedures. Additionally, the interplay between C-11 and sCD89 may provide insights into the underlying mechanisms of complement pathway activation in cIgAN.

FR-PO812

In Vivo Evidence of Complement Requirement for Mesangioproliferative Activity of Immune Complexes Containing Galactose-Deficient IgA1 in IgA Nephropathy

Zina Moldoveanu, Stacy D. Hall, Graham Gurganus, Lea Novak, Zhi qiang Huang, Shihong Qiu, Todd J. Green, Jan Novak. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Patients with IgA nephropathy (IgAN) have distinctive immune complexes (IC) in the circulation containing IgA1 with some *O*-glycans deficient in galactose (Gd-IgA1) bound by IgG autoantibodies (AuAb) specific for Gd-IgA1. Additional serum proteins, such as complement components, often associate with these IC. Some of these Gd-IgA1-containing IC deposit in the glomeruli and induce kidney injury. Here we have tested the role of complement C3 in the pathogenicity of these IC by using our passive mouse model of IgAN in which the intravenous (i.v.) injection of pre-formed complexes containing human Gd-IgA1 and IgG AuAb induce mesangioproliferative glomerular injury.

Methods: We used engineered IC (EIC) formed *in vitro* from recombinant human polymeric Gd-IgA1 and recombinant human IgG AuAb. The amount of Gd-IgA1, IgG, and IgG-IgA IC were determined by ELISA. Serum complement C3 was depleted by intraperitoneal (i.p.) injection of cobra venom factor (CVF). We have optimized the CVF dose and established the conditions in which C3 was <99% depleted from the circulation 1 day after CVF injection, and this depletion was maintained for at least 5 days. C3 was analyzed by SDS-PAGE and immunoblotting. One day after CVF injection that depleted C3, EIC were administered i.v. on three consecutive days to a group of nude mice and to another group without CVF treatment. A control group of mice received only CVF, and other control mice did not receive either EIC or CVF. The pathologic glomerular changes were evaluated by quantitative morphometry using H&E-stained sections of kidneys harvested one day after the last EIC dose. At least 25 glomeruli were analyzed for each mouse.

Results: The results showed that EIC administration increased glomerular cellularity compared to control (P=0.0001) and that CVF blocked that effect (P=0.021). CVF alone did not alter glomerular cellularity. Our data indicate that CVF-mediated C3 depletion prevented mesangioproliferative changes induced by EIC *in vivo*.

Conclusions: These results provide experimental evidence *in vivo* that complement C3 is required for the pathogenic activity of Gd-IgA1-containing IC in IgAN, confirming our *in vitro* findings with cultured human mesangial cells.

Funding: NIDDK Support, Private Foundation Support

FR-PO813

Transferrin Receptor 1 Mediates Lysosomal Accumulation of Galactose-Deficient IgA1 in Mesangial Cells, Contributing to IgA Nephropathy

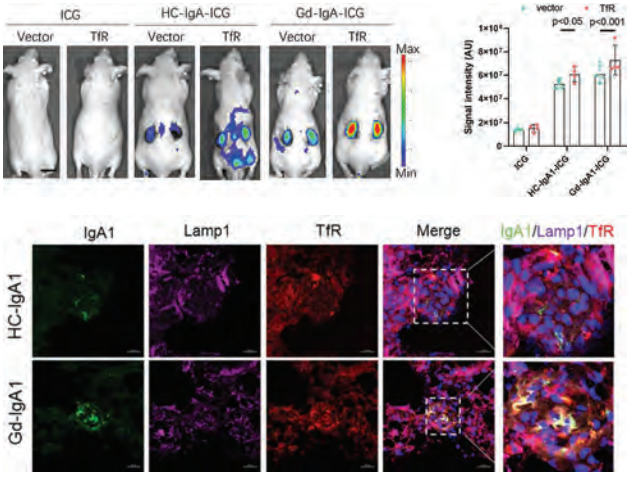
Mengting Fang, Meijun Si, Xueqing Yu. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: The deposition of Gd-IgA1 in the mesangium is a pathological characteristic of IgA nephropathy (IgAN), but the mechanism remains unclear.

Methods: We used CRISPR/Cas9 to screen for potential membrane proteins mediating the binding of mesangial cells to Gd-IgA1 and identified transferrin receptor 1 (TfR1) as one of the candidates. *In vitro*, we overexpressed and knocked down TfR in mesangial cells and explored its influence on Gd-IgA1 binding with mesangial cells. *In vivo*, we overexpressed TfR in BALB/c nude mice via AAV9, injected with ICG, HC-IgA1-ICG, and Gd-IgA1-ICG (i.v.), and then monitored the deposition intensity of IgA1 in kidneys by intravital fluorescent imaging. We also validated our finding on renal tissues from patients with IgAN. TfR expression and localization were detected.

Results: We observed that Gd-IgA1 showed significantly reduced binding to mesangial cells in the TfR knockdown group compared to controls. Conversely, Gd-IgA1 demonstrated significantly increased binding to mesangial cells in the TfR overexpression group compared to controls. We demonstrated that Gd-IgA1 deposition in kidneys was significantly enhanced in TfR overexpression mice, and Gd-IgA1 was found co-localized with TfR and the lysosomal marker lamp1 in renal. To validate our finding, we performed immunohistochemical staining and revealed that TfR expression was significantly increased in glomeruli of patients with IgAN compared to para-cancercontrols, and TfR was found co-localized with IgA. Transmission electron microscopy (TEM) and immunoelectron microscopy (IEM) revealed the presence of IgA1 protein accumulation in the lysosomes of mesangial cells in patients with IgAN.

Conclusions: Our research elucidates that TfR in mesangial cells promotes the binding and endocytosis of Gd-IgA1, leading to intracellular aggregation in lysosomes and have potential novel strategies for IgAN therapy.



FR-PO814

CD89 Triggers APRIL Activation in Pediatric IgA Nephropathy

Cambier Alexandra,[1] Lison Lachize Neanne,[1,2] Natalie Patey,[1] Renato C. Monteiro,[4] Olivia Boyer,[3] Julien Hogan.[5] Cambier's Laboratory.
[1]Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada; [2]Universite de Montreal Faculte de Medecine, Montreal, QC, Canada; [3]Hopital Universitaire Necker-Enfants Malades, Paris, France; [4]Centre de Recherche sur l'Inflammation, Paris, France; [5]Emory University, Atlanta, GA.

Background: IgAN, characterized by renal deposition of IgA, involves a multi-hit development with formation of circulating immune complexes (CICs) containing Gd-IgA1 and sCD89, contributing to renal inflammation. A Proliferation-Inducing Ligand (APRIL) is implicated in the immune response. The aim of this study is to investigate APRIL implication, especially in children with IgAN (cIgAN), who often exhibit more inflammation than adults.

Methods: First, we evaluated APRIL levels in human mesangial cells (HMC) after stimulation with recombinant sCD89 (rsCD89) or plasma from cIgAN patients. Subsequently, we conducted a comprehensive international cross-sectional study

involving 86 cIgAN patients and 48 control recruited from France and Canada. Our investigation included quantification of APRIL plasma levels and CICs, which were then compared with biological, clinical, and histological characteristics of the disease. Additionally, we performed immunohistochemistry analysis on kidney biopsies from cIgAN patients to visualize APRIL staining patterns.

Results: We demonstrated first that stimulations with cIgAN plasma and rsCD89 induced inflammation in HMC, leading to increased APRIL mRNA and protein production. We observed elevated levels of Gd-IgA1, sCD89-IgA1, sCD89 and soluble APRIL in the plasma of cIgAN patients compared to control subjects. Moreover, we found evidence suggesting that APRIL may be trapped within CICs, colocalizing with IgA in same-size complexes in Western blot experiments. Plus, IgA-APRIL and CD89-APRIL complexes were detected in cIgAN samples using ELISA and immunoprecipitation techniques. Levels of CICs correlated with plasma APRIL levels, and presence of IgA-APRIL and CD89-APRIL in CICs was linked to a worst initial clinical presentation, prognosis with kidney failure and relapses with persistent proteinuria. Staining of cIgAN biopsies revealed the presence of APRIL deposits within the glomerulus in the mesangium and near the Bowman capsule.

Conclusions: Our research highlights the role of APRIL in the pathways of cIgAN, with sCD89 as a potential trigger of APRIL activation in HMCs. APRIL holds promise as a valuable biomarker, offering a non-invasive means to detect forms of cIgAN with the worst progression, thereby potentially reducing reliance on biopsy. APRIL inhibition as therapeutic strategy presents an exciting opportunity for cIgAN treatment.

FR-PO815

Mechanism of Intestinal IgA Class Switching Regulated by TRIM21 through Downregulation of AID (Activation-Induced Cytidine Deaminase) in IgA Nephropathy

Qian Chen, Ming Xia, Hong Liu. *The Second Xiangya Hospital of Central South University Department of Nephrology, Changsha, China.*

Background: IgA nephropathy (IgAN) is the most common primary glomerular disease and the leading cause of end-stage renal disease (ESRD). At present, the 'multi-hit hypothesis' is a generally recognized pathogenesis of IgAN. However, the mechanism that initially triggers abnormal IgA synthesis has not been fully elucidated, specific treatment options are still lacking. Studies have shown that aberrant class switching of IgA antibodies in B cells within intestinal peyer patches plays a central role in generating pathogenic IgA. TRIM21 (Ro52/SS-A1) is an E3 ubiquitin ligase that participates in cellular immune response and antibody production. This study aims to elucidate the underlying mechanism of TRIM21 in regulating intestinal IgA class switching.

Methods: IgA deposition in the Intestinal tract was detected by immunofluorescence. The expression level of AID in peyer patches was detected by immunohistochemical staining and Western Blot. The mRNA levels of IgA transcripts in peyer patches were detected by RT-qPCR. To investigate the mechanism of TRIM21 influencing the down-regulation of IgA-switching enzyme AID by inhibiting NF-κB pathway. The interaction of TRIM21 with IκBα was analyzed by CO-IP. The change of protein ubiquitination was analyzed by Western Blot.

Results: Upon knocking out TRIM21, there was an increase in AID expression and IgA class switch. Additionally, the NF-κB pathway was activated, leading to increased AID expression in B cell lines Following the administration of an NF-κB pathway inhibitor, the AID expression in TRIM21 knockdown cells was restricted, and there were alterations in the overall protein ubiquitination levels. TRIM21 was identified to interact with IκBα, an inhibitory protein of NF-κB.

Conclusions: The findings of this study reveal that TRIM21 acts as a negative regulator of AID expression, and IgA class switching. Through ubiquitination of IκBα, TRIM21 exerts a negative effect on the NF-κB pathway, thereby upregulating AID expression. Our study provides a promising aspect of TRIM21 in IgAN through the NF-κB signaling pathway. Our study reveals the role of TRIM21 in immune response and the development of IgAN.

Funding: Other NIH Support - This work was supported by the National Natural Science Foundation of China (82270752)

FR-PO816

KLF4 Promotes Gd-IgA1 Synthesis in B Cells of IgA Nephropathy

Yangang Gan, Qiongqiong Yang, Li Hao, Jiajia Li, Wenchao Li, Hao Yu, Weicong Zeng. *Sun Yat-Sen Memorial Hospital, Guangzhou, China.*

Background: B cells are thought to perform a crucial function in IgA nephropathy (IgAN) pathogenesis by generating abnormal IgA1 and antibodies. Nonetheless, the machinery behind the aberrant gene expression of B cells in IgAN patients remains ambiguous.

Methods: This study has revealed an extensive range of differences in chromatin accessibility within the B cells of IgAN via ATAC-seq evaluation of active DNA regulatory components.

Results: B cells of IgAN were noted to display enhanced chromatin accessibility in genes affiliated with transcription regulation. Moreover, KLF4 was also recognized as a crucial transcription factor supporting the generation of IgA1 and galactose-deficient IgA1 (Gd-IgA1). In vitro, the knockdown of KLF4 suppressed the production of Gd-IgA1 in IgA-secreting cell lines. The study further showed that KLF4 could regulate the expression of genes related to the intestinal immune network for IgA production through RNA-seq. Combining ChIP-seq and RNA-seq, it was found that KLF4 can bind to the IL-6 promoter and regulate its expression. Mechanistically, a luciferase reporter assay verified that KLF4 directly binds to the cis-regulatory element of IL-6 and promotes its expression. KLF4 knockdown has been demonstrated to mitigate renal lesions and mesangial hypercellularity in IgAN mice.

Conclusions: Findings from this study reveal a mechanism mediated by chromatin underlying the differential responses of B cells in IgAN and identify KLF4 as a potential therapeutic target of IgAN.

Funding: Government Support - Non-U.S.

FR-PO817

Clinical Evidence That Defines IgAN as a Tissue-Specific Autoimmune Glomerulonephritis

Yoshihito Nihei,[1] Ayako Koizumi,[1] Jonathan Barratt,[2] Hitoshi Suzuki,[1,3] Yusuke Suzuki.[1] *[1]Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan; [2]Leicester General Hospital, Leicester, United Kingdom; [3]Department of Nephrology, Juntendo University Urayasu Hospital, Chiba, Japan.*

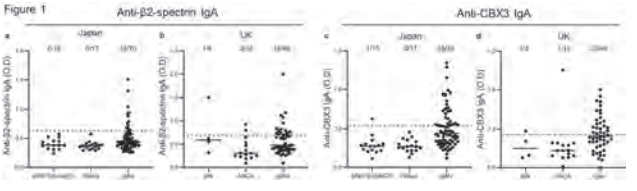
Background: IgA nephropathy (IgAN) is thought to be mediated by immune complexes containing galactose-deficient IgA (Gd-IgA1) and antigen specificity of glomerular IgA has not been emphasized in the pathogenesis of IgAN. However, we recently reported that IgA-type autoantibodies against mesangial cells (anti-β2-spectrin and anti-CBX3 IgA) were detected in the sera of IgAN model mice (**Sci. Adv. 2023. Life Sci. Alliance 2024**). Here, we aimed to show clinical evidence of these IgA autoantibodies in human IgAN.

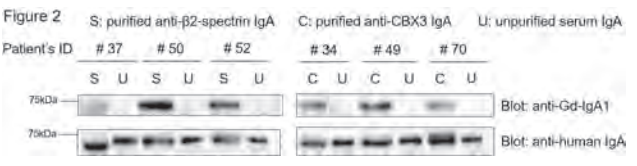
Methods: Patients with biopsy-proven IgAN (n=119) and the other kidney disease (DC: disease control, n=51) were recruited from Juntendo University Hospital in Japan (70 IgAN and 32 DC patients) or Leicester General Hospital in the UK (49 IgAN and 19 DC patients). Serum anti-β2-spectrin and anti-CBX3 IgA were measured by ELISA. Glycosylation of purified anti-β2-spectrin and anti-CBX3 IgA were analyzed by western blot (WB) using anti-Gd-IgA1 antibody.

Results: Anti-β2-spectrin and anti-CBX3 IgA were more frequently detected in patients with IgAN than DC in both Japan and the UK cohort (**Figure 1**). Overall, 30 of 119 IgAN and 3 of 51 DC patients were positive for anti-β2-spectrin IgA (sensitivity, 25.2%; specificity, 94.1%), while 48 of 119 IgAN and 3 of 51 DC patients were positive for anti-CBX3 IgA (sensitivity, 40.3%; specificity, 94.1%). Sixteen IgAN patients were positive for both anti-β2-spectrin and anti-CBX3 IgA. WB analysis revealed that the purified serum anti-β2-spectrin and anti-CBX3 IgA from IgAN patients were enriched for Gd-IgA1 than the total serum IgA (**Figure 2**).

Conclusions: The anti-β2-spectrin and anti-CBX3 IgA are detected in IgAN patients with high specificity. Furthermore, these IgA-type autoantibodies have the property of galactose deficiency, namely, anti-mesangium Gd-IgA1 are present in circulation of IgAN patients. Thus, we provide clinical evidence that anti-mesangium IgA is involved in the pathogenesis of human IgAN and defines IgAN as a tissue-specific autoimmune glomerulonephritis.

Funding: Government Support - Non-U.S.





FR-PO818

A Human Origin Anti-GdIgA1 Antibody and Its Implications in IgA Nephropathy

Haipei Tang, Huikun Zeng, Zhenhai Zhang, Xueqing Yu. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: IgA nephropathy (IgAN) is a common kidney disease where IgA deposits in the mesangial region, leading to mesangial cell proliferation. The underlying mechanism of IgAN remains unclear. The 'four-hit' hypothesis proposes that immune

complexes formed by Galactose-deficient IgA1 (GdIgA1) and anti-GdIgA1 are crucial in the disease. However, the reasons for the deposition of these immunoglobulins in the mesangial region and their role in the disease process are not yet understood.

Methods: The study collected GdIgA1 binding B cells from peripheral blood and sequenced through scBCR-Seq. A set of candidate antibodies was then synthesized and screened. Among these candidates, P4 showed high affinity for GdIgA1. The study investigated the binding affinity between mature and naïve P4 by reverting sequences to germline. Furthermore, P4, HAA, and KM55 were used to compare the GdIgA1 levels in IgAN patients and healthy controls. Finally, preliminary in vitro experiments were conducted to explore the role of P4 in the pathogenesis of IgAN.

Results: High-affinity anti-GdIgA1 antibody (P4) was obtained in peripheral blood B cells (PBMCs), encoded by IGHV3-64D|IGHJ4, IGKV1-39|IGKJ2 and IGHA2, with a KD value of 1.508×10^{-8}(M) to GdIgA1. Heavy chain dictated the binding to GdIgA1, while the light chain affected the affinity slightly. Most importantly, P4 in naïve state did not bind to GdIgA1 which indicate it was elicited by antigens other than GdIgA1. P4 exhibited comparable ability in measuring serum GdIgA1 levels with KM55 and HAA. A larger validation set conducted by third-party laboratory confirmed the potential of P4 in clinical usage. In vitro experiments revealed that co-stimulation of mesangial cells with P4 and GdIgA1 upregulates the Wnt pathway and potentially cause the proliferation of the mesangial cell while neither P4 nor GdIgA1 alone had this effect.

Conclusions: In summary, the discovery of a high-affinity anti-GdIgA1 antibody, P4, holds promise for effectively measuring GdIgA1 levels. The study's findings suggest that high-affinity anti-GdIgA1 auto-antibodies may be induced by antigens mimicking the hinge region of GdIgA1. Moreover, the upregulation of the Wnt pathway by co-stimulation of P4 and GdIgA1 highlights the critical role of P4. Further exploration of the molecular and cellular mechanisms of IgAN may offer valuable insights.

Funding: Government Support - Non-U.S.

FR-PO819

Cell-Surface Glycosylation Identifies Subpopulations of B Cells in IgA Nephropathy with Distinct Signaling Corresponding to the Production of the Main Autoantigen, Galactose-Deficient IgA1

Taylor Person,[1] Dana V. Rizk,[2] Jan Novak,[1] Colin Reily.[2,1] *[1]Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL; [2]Department of Medicine, Nephrology Division, University of Alabama at Birmingham, Birmingham, AL.*

Background: Patients with IgA nephropathy (IgAN) have elevated levels of circulating autoantigen, galactose-deficient IgA1 (Gd-IgA1), that is recognized by IgG autoantibodies. Some of the resultant immune complexes deposit in the glomeruli and induce kidney injury. Based on the polymeric form of Gd-IgA1 in the circulating immune complexes and synpharyngitic hematuria at disease onset/activity, we hypothesize that only a subpopulation(s) of IgA1-secreting cells is responsible for Gd-IgA1 production, and that abnormal cellular responses further enhance Gd-IgA1 levels in circulation. However, as the autoantigen is released from B cells, identification of those subpopulations is difficult. Here we report that distinct cell-surface glycosylation and cellular responses to CpG-ODN (oligodeoxynucleotides) stimulation, are associated with Gd-IgA1 production and distinct intracellular signaling.

Methods: Immortalized IgA1-producing cells derived from peripheral blood of IgAN patients and healthy controls were stimulated with CpG-ODN (2 ug/mL) for 30 min and then stained with HPA and PNA to detect cell-surface GalNAc and GalNAc-Gal glycoconjugates and anti-IgA antibody to identify IgA-positive cells. Intracellular signaling was assessed using fluorochrome-conjugated antibodies specific for pSTAT1, pSTAT3, pSTAT5, pSTAT6, p38-MAPK, pERK1/2, p65-NF-kB, with flow cytometry readout using a BD FACSymphony with spectral compensation. Cells were incubated for 48 h for analyses of IgA and Gd-IgA1 in cell-culture supernatants by ELISA.

Results: CpG stimulation decreased the number of HPA^+/PNA^+ cells ($p<0.05$) as well as the amount (detected as median fluorescence index; MFI) ($p<0.05$). Cells with high HPA vs. low HPA differed in baseline and CpG-induced pSTAT3 ($p<0.02$), pSTAT5 ($p<0.01$), and pMEK1/2 ($p<0.01$). Cells with high HPA^+/PNA^+ showed significant correlation between Gd-IgA1 production and p38-MAPK ($p<0.01$), pSTAT3 ($p<0.01$), and p65 NF-kB ($p=0.05$) after CpG stimulation.

Conclusions: Differential cell-surface glycosylation identified differential cellular signaling, both baseline and CpG-induced, that correlated with Gd-IgA1 production. Further characterization of these cell subpopulations will provide insight into mechanisms involved in IgAN pathobiology.

Funding: NIDDK Support

FR-PO820

Loss of GalNAc-T14 Links O-glycosylation Defects to Alterations in B Cell Homing in IgA Nephropathy

Nicholas J. Steers,[1] Sindhuri Prakash-Polet,[1] Isabel Robbins,[1] Jenna Simpson,[1] Sharvari Pathak,[1] Kelsey O. Stevens,[1] Simone Sanna-Cherchi,[1] Vivette D. D'Agati,[1] Jan Novak,[2] Ali G. Gharavi.[1] *[1]Columbia University Irving Medical Center, New York, NY; [2]University of Alabama at Birmingham, Birmingham, AL.*

Background: Defects in *O*-glycosylation of IgA1 are a characteristic finding in IgA nephropathy (IgAN). It is not known if aberrant *O*-glycosylation can impact IgA homeostasis, such as B-cell residence, homing, and migration. Up to 20 different *N*-ace tylgalactosaminyltransferases (GalNAc-Ts) can initiate *O*-glycosylation of proteins in humans.

Methods: We studied the circulating IgA, and the mucosal and non-mucosal tissue resident B-cells in *Galnt14-/-* and WT mice using ELISA and flow cytometry.

Results: *GALNT14* is expressed in human and murine lymphoid tissues, specifically within germinal centers, the major site for B-cell maturation, antibody class switching, and proliferation. We have identified a heterozygous predicted loss-of-function (LOF) variant in *GALNT14* in a family with IgAN. *Galnt14*-null mice had elevated serum IgA levels compared to WT mice (0.88±0.2 mg/ml and 0.37±0.1 mg/ml, respectively, $P<0.01$), and the *Galnt14*-null mice developed glomerular IgA deposition with aging and after induction of sterile colitis. *Galnt14*-null mice also displayed an attenuated mucin layer in the colon and redistribution of IgA-producing cells from mucosal to systemic sites. A significant decrease in the percentage of IgA+ B-cells was observed in the Peyer's patches of *Galnt14-/-* mice compared to WT mice (20.2±3.7% and 24.4±3.8%, respectively, $P<0.01$), and an increase in the percentage of IgA+ B-cells was observed in non-mucosal tissues of *Galnt14-/-* mice compared to WT mice (spleen: 4.2±0.9% and 3.0±0.7%, respectively, $P<0.01$; PMBC: 3.9±0.7% and 2.6±0.4%, respectively, $P < 0.01$). The increased IgA in the circulation in *Galnt14-/-* mice correlated with the increased IgA+ B-cells in the circulation ($P<0.01$) and the reduced IgA+ B-cells in the Peyer's patches ($P<0.01$). Analysis of the germinal center B-cells in *Galnt14-/-* mice demonstrated a reduction on the *O*-glycosylation of cell-surface molecules. Finally, adoptive-transfer experiments indicated impaired homing of spleen-derived *Galnt14*-deficient B-cells, resulting in increased retention in peripheral blood.

Conclusions: These findings suggest that abnormalities in *O*-glycosylation alter mucosal immunity and B-cell homing, pointing to an expanded role of aberrant *O*-glycosylation in the pathogenesis of IgAN.

Funding: NIDDK Support

FR-PO821

Distinct O-glycoforms Profiles in the Hinge Region of Immunoglobulin A1 in Patients with IgA Nephropathy and IgA Type Multiple Myeloma

Xinfang Xie,[1] Wanhong Lu,[1] Yong Zhang.[2] *[1]The Frist Affiliated Hospital of Xi'an Jiaotong University, Beijing, China; [2]West China Hospital, Sichuan University, Chengdu, China.*

Background: Galactose-deficient IgA1 (GdIgA1) is critical in the formation of circulating IgA polymer and poly-IgA immunodeposits in IgA nephropathy (IgAN). However, very rare patients with IgA type multiple myeloma(IgAMM) complicated by IgAN, although IgAMM patients had signigicantly high IgA1 and limited data also showed higher GdIgA1 composition in purified IgA1 from IgAMM patients. In this study we aimed to investigate the GdIgA1 levels, polyIgA1 levles and IgA1 O-glycoforms profiles in the hinge region (HR) of IgA1 from patients with the two diseases respectively.

Methods: 25 patients with IgA type multiple myeloma and 66 patients with IgAN were included in the study. Plasma IgA, GdIgA1, CD89 captured polyIgA1 and IgA-IgG complex were detected by ELISA. Total IgA1 was purified from the plasma of the participants. The variation in O-glycoforms in HR of purified plasma IgA1 was evaluated by using mass spectrometry of EThcD-sceHCD MS/MS fragmentation mode.

Results: IgAMM patients included were older than IgAN patients (68.6±10 vs. 32±8 ys). Compared with IgAN patients, IgAMM patients had significantly higher levels of IgA1 (39.7±26.1 vs. 3.1±1.1 mg/ml, $p<0.05$), GdIgA1 (28.8±7.1 vs. 4.9±0.3 ug/ml, $p<0.01$) and CD89 captured polyIgA1(13.6±3.1 vs. 3.8±0.4 ug/ml, $p<0.01$). While GdIgA1/IgA levels were much higher in IgAN, and IgAN patients had higher IgA-IgG complexes. EThcD-sceHCD MS/MS showed the number of Nacetylgalactosamine (GalNAc) bound to one HR was higher in IgAN patients. The proportions of GalNAc4 (defined as O-glycans bound to one HR at 4 sites) and GalNAc5 were highest in all patients. The proportions of 3-5 galactose/HR were higher and 4 galactose/HR were with the highest proportions in both diseases (61.8%±11.1% vs. 52.8%±4.4% $p<0.05$, IgAMM vs. IgAN). Galactose deficiency profile per HR were investigated, we found deficiency of 1-2 galactose/HR were most common, and significant higher percentages of total galactose deficiency/HR were detected in IgAN than IgAMM group (87.7%±1.9% vs. 34.9%±6.1% $p<0.01$). PCA analysis indicated that the O-glycoforms profiles of IgA1 differed greatly between the two diseases.

Conclusions: Distinct IgA1 O-glycoforms profiles in HR were showed in IgAN and IgAMM. Our data also supported higher levels of GdIgA1/IgA1 and IgA-IgG complexes play crucial roles in the pathogeneisis of IgAN.

FR-PO822

Identification of the Localization of the Pathogenic IgA Autoantibodies on Mesangial Cells in IgA Nephropathy

Kazuaki Mori,[1] Yoshihito Nihei,[1] Hitoshi Suzuki,[1,2] Yusuke Suzuki.[1]
Dept of Nephrology, Juntendo University Faculty of Medicine. *[1]Department of Nephrology, Juntendo University Faculty of Medicine, Bunkyo, Japan; [2]Department of Nephrology, Juntendo University Urayasu Hospital, Urayasu, Japan.*

Background: IgA nephropathy (IgAN) has been considered as an immune complex-mediated disease, and its possible existence of autoantigens has not been clarified. Recently, we discovered IgA autoantibodies specific to mesangial cells (MCs) in the sera of its patients. We identified two autoantigens targeted by these IgA (β2-spectrin and CBX3), both of which are originally known for their intracellular existence. Although *in vivo* studies with monoclonal antibodies against the autoantigens revealed their selective expressions on MC surfaces, their mechanisms have not been elucidated. To investigate them, we aimed to establish methods to visualize the MC-surface expression of these autoantigens *in vitro*.

Methods: For immunofluorescence microscopy (IFM), human primary MCs (HMCs) were cultured on cover glasses for 24 hours. The HMCs were fixed with methanol for intracellular protein staining or 4% paraformaldehyde (4%PFA) for cell-surface protein staining and stained with anti-β2 spectrin or CBX3 antibody and with DAPI. For immune electron microscopy (IEM), 24h-cultured HMCs were fixed with 4%PFA and stained with anti-β2 spectrin or CBX3 antibody and then with colloidal gold. To perform transmission electron microscopy, these cells were fixed with 2.5% glutaraldehyde in 0.1M phosphate buffer and then with 2% OsO_4 in the same buffer followed by dehydration with a graded series of ethanol and embedded in Epok-812. Ultrathin sections were removed, and uranyl acetate and lead citrate were applied.

Results: By IFM analyses after application of methanol on the HMCs, we detected the intracellular expression of β2 spectrin and CBX3. And then by IFM analyses after application of 4%PFA on the HMCs, cell-surface β2 spectrin and CBX3 were detected. To elucidate their locations either on the cell surfaces or inside of the cells, we utilized IEM and clearly visualized their cell-surface locations with continuous cell membranes.

Conclusions: We identified the localization of β2 spectrin and CBX3 on the surfaces of HMCs by both IFM and IEM. We will utilize these methods to investigate the mechanisms of the MC-surface expression of each of these autoantigens and their relations with clinical features of IgAN.

FR-PO823

Fc Receptor TRIM21 Degrades Mesangial Intracellular IgA and Inhibits Cell Proliferation in IgA Nephropathy

Haiyang Liu,[1,2] Hong Liu.[1] The Second Xiangya Hospital of Central South University. *[1]The Second Xiangya Hospital of Central South University Department of Nephrology, Changsha, China; [2]The Second Xiangya Hospital of Central South University Department of Geriatrics, Changsha, China.*

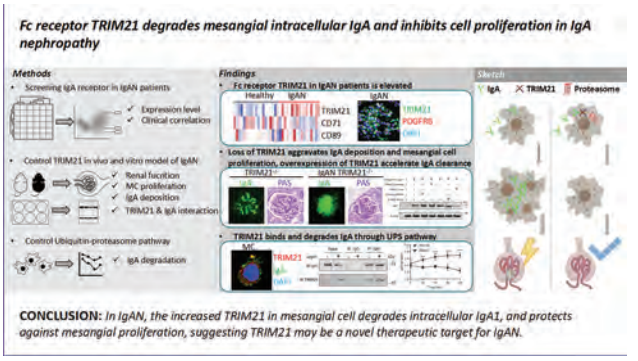
Background: IgA nephropathy (IgAN) characterized by abnormal deposition of IgA in the mesangial area in renal biopsy. Mesangial cells have the function of transferring IgA into cells' cytoplasm. Tripartite motif containing-21 (TRIM21) is a cytosolic ubiquitin ligase and antibody receptor, studies showed that IgA neutralizes adenovirus infection in an intracellular TRIM21- dependent manner.

Methods: 1. Screening IgA receptor in IgAN patients The expression level of IgA receptor genes in the glomerulus in IgAN was screened using datasets GSE93798 in the Gene Expression Omnibus (GEO). The protein expression were confirmed by staining utilized in the renal biopsy samples. 2. Knock out or over-expression TRIM21 in vivo and vitro model of IgAN The vivo mice IgAN model was made by oral mucosal immunization. The vitro model was made by aggregated IgA1 (aIgA1) added to human mesangial cells (HMCs). 3. Inhibit ubiquitin-proteasome pathway in vitro IgAN model MG132 or a corresponding amount of DMSO was added to the medium for different time intervals before the vitro experiment.

Results: 1. TRIM21 is upregulated and expressed in the mesangial cells of IgAN. 2. The upregulation of TRIM21 in the glomeruli of IgAN patients is associated with higher serum creatinine levels. 3. The upregulation of TRIM21 in the glomeruli was co-localizes with IgA. 4. Loss of TRIM21 in IgAN mice induces massive IgA deposition in the mesangial region. 5. Inhibiting TRIM21 in IgAN causes serious mesangial cell proliferation both In Vivo and In Vitro. 6. IgA enters the mesangial cells and is degraded through the ubiquitin-proteasome pathway. 7. TRIM21 regulates IgA degradation in mesangial cells via the ubiquitin-proteasome pathway.

Conclusions: This study illustrates that the increased TRIM21 in the glomeruli of IgAN could degrade the IgA in mesangial cells and inhibit cells proliferation, the mechanism involves the protease ubiquitination pathway. These results suggest TRIM21 may be a novel therapeutic target for degrading IgA in mesangial cells of IgAN.

Funding: Government Support - Non-U.S.



FR-PO824

Cell Type Specificity of FcγRIIB Involving NLRP3 Inflammasome and Dectin-2 in a Mouse Model of IgA Nephropathy

Shuk-Man Ka,[1] Ann Chen.[2,3] *[1]Department of Medicine, National Defense Medical Center, Taipei, Taiwan; [2]Department of Pathology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan; [3]Taiwan Autoantibody Biobank Initiative, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan.*

Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis and represents a leading cause of end-stage renal disease. Ample evidence confirms the deposition of IgA and IgG and the filtration of mononuclear leukocytes in renal biopsy specimens from IgAN patients. Previously, we established an experimental IgAN model in B cell-deficient mice, which implicated interactions between Fcγ receptors (FcγRs) in the pathogenesis of IgAN. Although it is generally accepted that FcγRIIB plays a regulatory role in humoral responses, it remains unknown whether this function and the cell type-specificity of FcγRIIB are reno-protective in IgAN.

Methods: We observed a dramatic increase in albuminuria, renal function impairment, and renal injury in FcγRIIB knockout mice with induced IgAN. Utilizing a mouse model of IgAN and three different types of FcγRIIB-deficient mice, including CEBP/α Cre (myeloid cells), CD11c Cre (dendritic cells) and CD19 Cre (B cells) in floxed FcγRIIB mice, as well as several specific cell models.

Results: We demonstrated that macrophage- and dendritic cell-specific FcγRIIB deficiency blunted the activation of the NLRP3 inflammasome and inhibited the development of IgAN. Moreover, activation of the inflammasome was induced by IgA immune complexes dependent on TLR4/MyD88 signaling, associated with crosstalk between TLR4 and Dectin-2.

Conclusions: These results suggested that activation of FcγRIIB and its downstream signaling pathways could moderate progression of IgAN involving the suppression of the NLRP3 inflammasome. A cell type-specific targeting FcγRIIB may help in establishing a therapeutic strategy for this renal disease.

Funding: Government Support - Non-U.S.

FR-PO825

Establishment of Human IgG Autoantibodies Derived from Patients with Lupus Nephritis and Deposition of Resultant Human IgG-Containing Immune Complexes in the Kidney and Skin of Mice

Shuk-Man Ka,[1,3] Ann Chen.[2] *[1]Department of Medicine, National Defense Medical Center, Taipei, Taiwan; [2]Department of Pathology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan; [3]Taiwan Autoantibody Biobank Initiative, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan.*

Background: In Taiwan, lupus nephritis (LN) has a trend of 4.3–13.4% rate of progression to end-stage renal disease (ESRD). Treatment for LN mainly relies on glucocorticoids and other immunosuppressants, but targeting more specific pathogenic molecules from the upstream pathways involved in the development and progression of the disease, e.g., etiological autoantibodies (autoAbs), is crucial and remains a unmet medical need.

Methods: We have recently established a human hybridoma platform to generate two human IgG against dsDNA autoantibodies (autoAbs) using peripheral blood mononuclear cells (PBMCs) from LN patients (LiuK-NDMC-01 and LiuK-NDMC-02) to which we performed sequencing and tests for capacity of inducing inflammatory responses and deposition of immune complexes (ICs) in the kidney and skin of ASID mice that mimics the human disease.

Results: By injecting intravenously a single dose of the LiuK-NDMC-01 autoAb against dsDNA and human dsDNA extracted from a human THP-1 monocyte cell line, renal deposition of the human IgG-containing ICs in ASID mice was induced. Immunofluorescence examination showed deposition of human IgG and C3 diffusely in the kidney and IgG in the skin. This effect was also confirmed by a Western blot analysis using renal proteins extracted from the ASID mice. Moreover, increased NLRP3 inflammasome-mediated IL-1β secretion was observed in human macrophages that were primed with the ICs containing the LiuK-NDMC-01 autoAb and dsDNA compared with saline-control counterparts.

Conclusions: Collectively, two new human IgG autoantibodies were established using PBMCs from LN patients. One of these human IgG autoAb was further validated for deposition of the IgG-containing ICs in both the kidney and skin, mimicking LN patients. The ICs was shown to induce inflammatory reaction as demonstrated by resultant activation of NLRP3 inflammasome and subsequent IL-1β secretion in human macrophages.

Funding: Government Support - Non-U.S.

FR-PO826

Serum Levels of APRIL Correlate with Proteinuria in IgA Vasculitis: Findings from the GIGA-Kids Study

Josep Miquel Blasco Pelicano,[1,2] Cecilia C. Berrouet,[3] Lee G. Andrews,[4] Asher D. Schachter,[4] Aftab S. Chishti,[5] Margaret C. Hastings,[6] Joseph T. Flynn,[7] William E. Smoyer,[8] Raoul D. Nelson,[9] Krzysztof Kiryluk.[3] The GIGA-kids Study. *[1]Columbia University Irving Medical Center, New York, NY; [2]Hospital Clinic de Barcelona, Barcelona, Spain; [3]Columbia University, New York, NY; [4]Visterra Inc, Waltham, MA; [5]University of Kentucky, Lexington, KY; [6]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [7]Seattle Children's Hospital, Seattle, WA; [8]Nationwide Children's Hospital, Columbus, OH; [9]University of Utah Health, Salt Lake City, UT.*

Background: IgA vasculitis (IgAV) is the most common systemic vasculitis in children and is characterized by variable kidney involvement. As in IgA nephropathy (IgAN), IgAV nephritis (IgAVN) is associated with increased levels of galactose deficient IgA1 (Gd-IgA1) and anti-glycan antibodies. While elevated levels of APRIL correlate with IgAN progression, the role of APRIL in IgAVN is unclear.

Methods: The GIGA-kids (Genomics of IgA-related disorders in kids) study aims to recruit 1,000 pediatric cases of IgAN and IgAV for genetic and biomarker studies. Here, we analyzed biomarkers for the first 495 GIGA-kids participants, including 54 with IgAV, 260 with IgAVN, 169 with IgAN, and 12 healthy pediatric controls. Serum levels of APRIL, Gd-IgA1, and anti-glycan-antibodies were measured in all 495 participants and correlated with disease status and severity.

Results: Among all biomarkers tested, serum levels of Gd-IgA1 were significantly elevated in IgAN and IgAVN cases compared to healthy controls (p=0.013, and p=0.0079, respectively). Neither Gd-IgA1 nor anti-glycan antibody levels correlated with proteinuria among IgAN or IgAVN cases. In contrast, APRIL levels were significantly associated with higher proteinuria in IgAVN before and after adjustment for age, sex, race/ethnicity and immunosuppression (p=0.0033 and p=0.0064, respectively). This association was not statistically significant in the IgAN cohort, which was potentially due to a smaller sample size and lower acuity of IgAN vs IgAVN.

Conclusions: Serum APRIL levels were positively correlated with proteinuria, and Gd-IgA1 levels were elevated in pediatric IgAVN, supporting the involvement of APRIL in the pathogenesis of nephritis. Therapeutic strategies targeting APRIL in IgAN may also benefit patients with IgAVN.

Funding: Other NIH Support - Pediatric Nephrology Research Consortium, Commercial Support - Visterra, Private Foundation Support

IgAVN (n=260)

	Proteinuria							
	Unadjusted				Adjusted			
	Estimate	Sd. error	t	p	Estimate	Sd. error	t	p
APRIL	1.595e-04	5.341e-05	2.987	0.0033**	1.518e-04	5.481e-05	2.770	0.00636**
GdIgA1	3.397e-06	2.247e-05	0.151	0.88	4.450e-06	2.288e-05	0.195	0.8460
Anti-glycan Antibodies	-0.6685	0.3625	-1.844	0.0672.	-0.4699248	0.3874968	-1.213	0.227

FR-PO827

Upregulation of Type I Interferon Pathway in Microscopic Polyangiitis

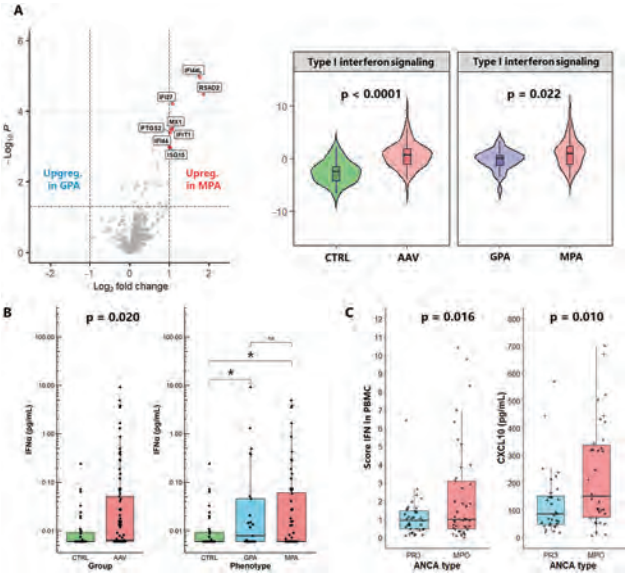
Benoit Brilland,[1] Andrea Boizard-Moracchini,[2] Nathalie Merillon,[1] Giorgina B. Piccoli,[3] Patrick Blanco,[2] Jean Francois Augusto.[1] Maine-Anjou Registry Research Group. *[1]CHU Angers, Angers, France; [2]Centre Hospitalier Universitaire de Bordeaux Groupe hospitalier Pellegrin, Bordeaux, France; [3]Centre Hospitalier du Mans, Le Mans, France.*

Background: The two main types of ANCA-associated vasculitis (AAV), microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), share common characteristics but also differ on many aspects (epidemiological, genetic, clinical, outcomes). To identify more specific targetable pathways, we compared the kidney transcriptome of MPA vs. GPA patients with AAV-glomerulonephritis (AAV-GN) and further characterized pathways of interest.

Methods: Immune gene transcript analysis (n = 750) was performed on RNA extracted from 97 adult AAV-GN kidney biopsies from the French Maine-Anjou Registry using NanoString technology (33 GPA, 64 MPA). Significant transcripts were examined to identify immune pathways of interest. We assessed IFNα levels with an ultrasensitive method. We also used a publicly available dataset to explore these identified pathways.

Results: Eight genes were found differentially expressed, all being upregulated in MPA (logFC > 1, q-value < 0.05). Seven belonged to the type I interferon (IFN-I) signaling pathway (**Figure 1A**). Nearly 20% of AAV-GN patients displayed elevated IFNα levels (**Figure 1B**, p = 0.02), which correlated with IFN-I activation in kidneys. Analyzing unpublished publicly available data, we identified a significantly more pronounced IFN-I related signature (expression of interferon regulated genes in PBMC and levels of CXCL10 in serum) in MPO-AAV vs PR3-AAV (**Figure 1C**).

Conclusions: We identified a type I interferon signature in AAV-GN, both in kidneys and in blood, especially in patients with MPA (or MPO-AAV) in comparison to GPA (or PR3-AAV). This is in line with previous evidence suggesting a role for IFN-I in AAV and especially in MPO-AAV. This signature may help gain a deeper understanding of the AAV-GN pathogenesis and provide insights for developing new therapeutic options.



FR-PO828

Siglec-9 and Its Ligand in ANCA-Associated Vasculitis

Dana Kidder,[1] Catriona Walls,[2] Jon Yoldi,[2] Simon C. Satchell,[3] Cosimo De Bari.[2] *[1]NHS Grampian, Aberdeen, United Kingdom; [2]University of Aberdeen, Aberdeen, United Kingdom; [3]University of Bristol Bristol Renal, Bristol, United Kingdom.*

Background: Sialic acid-binding Ig-like lectin 9 (Siglec-9) is expressed on leukocytes. The expression and role of siglec-9 and its ligand in the context of ANCA-associated vasculitis (AAV) is unknown.

Methods: Leukocytes and serum were isolated from venous blood and siglec-9 expression analysed by flow cytometry/ELISA. Leukocytes were stimulated with MPO/PR3 to assess Siglec-9 shedding. An Fc protein was used to identify ligands under inflammatory conditions (TNF-α/C5a) on conditionally immortalised glomerular endothelial cells (ciGEnC) or AAV renal sections. BulkRNA sequencing will hilight biological relevance of ligand interactions.

Results: Neutrophils and intermediate monocytes from MPO-AAV patients had reduced Siglec-9 expression versus PR3-AAV. Stimulation of neutrophils with MPO, not PR3, induced a shedding phenotype (Fig. 1). Analysis of serum showed decreased Siglec-9 in MPO-AAV compared to PR3-AAV. A positive correlation of serum Siglec-9

was detected with disease activity and MPO-ANCA titre. Siglec-9 ligand was identified on glomerular endothelial cells from kidney biopsies of AAV patients and two distinct patterns of expression on ciGEnC, which was altered under inflammatory conditions.

Conclusions: Cellular and serum Siglec-9 expression differs in MPO and PR3-AAV and may be influenced by ANCA serotype. Positive Siglec-9 ligand expression on ciGEnC suggests a direct interaction between Siglec-9 on leukocytes and glomerular endothelium. Our data suggest a possible role for Siglec-9/ligand interactions in the context of AAV - but further study is required to assess the biological relevance of these findings.

Funding: Clinical Revenue Support

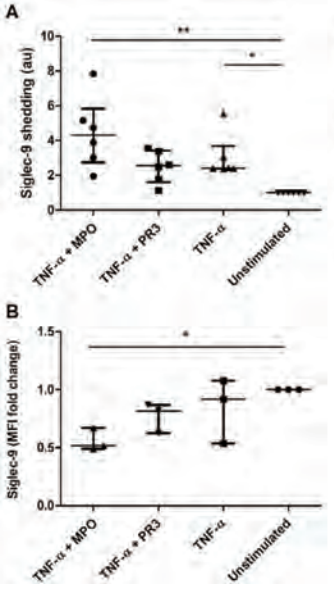


Figure 1 – MPO-ANCA induces Siglec-9 shedding. Neutrophils were stimulated with TNF-α, MPO-ANCA or PR3-ANCA. A) Shedding was increased with MPO-ANCA stimulation (n = 6). B) Cellular expression was decreased with MPO-ANCA stimulation (n = 3). Data shown is median ± IQR. * P < 0.05; ** P < 0.01

FR-PO829

Elderly Patients' Prognostic Disadvantage Might Be Substantiated by Distinct Tubulointerstitial Lesions in Newly Diagnosed ANCA-Associated Renal Vasculitis

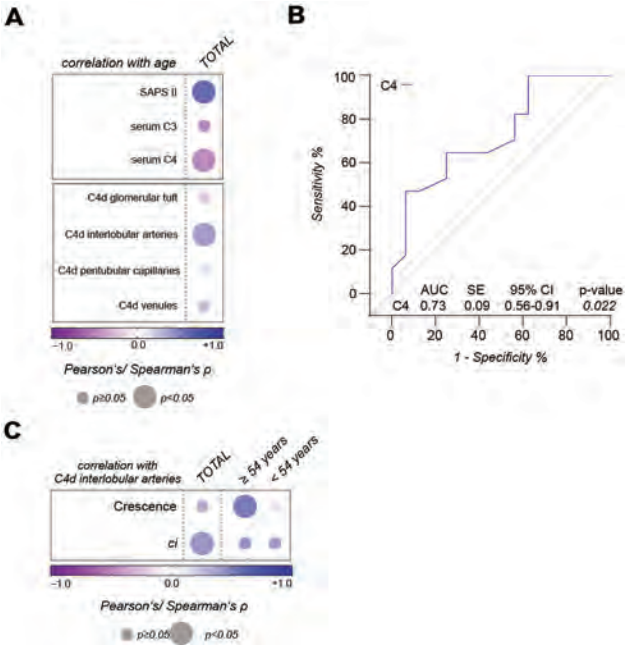
Eva Baier, Bjoern Tampe. *Universitatsmedizin Gottingen Klinik fur Nephrologie und Rheumatologie, Gottingen, Germany.*

Background: Although advanced age negatively predicts renal survival in antineutrophil cytoplasmic antibody (ANCA-) associated renal vasculitis (AArV), histopathological lesions substantiating this prognostic disadvantage remain elusive. Thus, we aimed to identify histopathological correlates in relation to patient's age in newly diagnosed AArV.

Methods: A total of n=45 biopsy-affirmed AArV cases were enrolled in a single-center retrospective cohort study. Receiver operating characteristics (ROC) curve analyses enabled group dichotomization. Age subgroups were compared concerning clinicolaboratory and histopathological parameters. Correlative analyses were performed regarding tubulointerstitial lesions and complement deposition in distinct renal compartments.

Results: Serum C4 levels inversely correlated with patient's age (β=-0.32, *p=0.009*). Maximized Youden index of ROC curve analyses for serum C4 levels (AUC 0.7, *p=0.044*) provided an age cut-off of 54 years enabling group dichotomization. Significantly more interstitial fibrosis (ci, *p=0.0415*), interstitial inflammation (i-IFTA, *p=0.0062*) and tubulitis (t-IFTA, *p=0.0069*) in areas of scarred cortex (IFTA) was observed in the elderly's subgroup. C4d-deposited interlobular arteries prevailed more often in the elderly (*p=0.0031)* and were associated with interstitial fibrosis *(*β=0.31, *p=0.038*) and crescent formations (β=0.44, *p=0.009*).

Conclusions: We here show that age-dependency of renal survival in AArV might be substantiated by specific histopathological lesions characterized by interstitial fibrosis and complement deposition in the tubulointerstitial compartment of the elderly. A latent complement-driven interstitial fibrogenesis might constitute to a vulnerability of the elderly to be severely affected by an acute flare of AArV.



FR-PO830

Patient-Derived Cell Line as an In Vitro Model System for Autoantigen-Specific B Cells in Myeloperoxidase-ANCA

Young-Hyun Moon,[1] Dhruti P. Chen,[1] Justin J. Taylor,[2] Ronald Falk,[1] Donna O. Bunch.[1] *[1]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; [2]University of Virginia School of Medicine, Charlottesville, VA.*

Background: Autoantigen-specific B cells are important in ANCA vasculitis but are rare and hard to study. Existing myeloperoxidase (MPO)-ANCA vasculitis mouse models have been insightful although limited by their non-human nature, time intensiveness and cost. We hypothesized that a patient-derived B cell line could be modulated to differentiate into antibody-producing cells and establish an in vitro model system to inform specific targeting of human B cells.

Methods: We created Epstein-Barr virus immortalized B cell lines with PBMCs from patients with ANCA vasculitis (23 MPO, 23 PR3). Two lines were cultured in "B cell media" (IMDM, penicillin-streptomycin, 10% FBS, GlutaMax, β-ME, CD40L, CpG) with or without MPO autoantigen and IL-21. Autoantibody production was tracked longitudinally by testing supernatants for anti-MPO IgG by ELISA. Cells were stained with allophycocyanin (APC)-tagged MPO-tetramers, positively selected for APC, and analyzed by flow cytometry.

Results: Immortalized cells maintained expression of B cell markers (CD19, CD22) and 4% MPO-specificity. Cells cultured with MPO and IL-21 had more CD27high/CD22low B cells, consistent with plasmablast differentiation, in both parent (9%) and antigen-specific populations (15%) compared to cells cultured without MPO or IL-21 (5 and 10% respectively) (**Fig 1a**). This cell line produced ANCAs; cells cultured with MPO and IL-21 produced more autoantibody than cells grown without (**Fig 1b**). Cells cultured to 92 days maximally had 29% MPO-specificity.

Conclusions: We developed immortalized patient-derived B cell lines that maintain antigen-specificity in culture, with targetable B cell markers, and inducible autoantibody production. This system could be used to test B cell-depleting and autoantigen-specific therapies. In summary, an immortalized patient-derived cell line offers a viable model system of autoantigen-specific B cells in ANCA vasculitis.

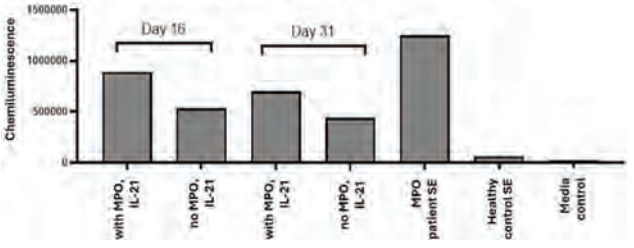
Funding: NIDDK Support

Figure 1a. Immunophenotyping by flow cytometry

	Parent population		Tetramer-specific population	
Selected phenotype	w/ MPO, IL-21	w/o MPO, IL-21	w/ MPO, IL-21	w/o MPO, IL-21
% CD22 positive	59	74	56	68
% CD27high_CD22low (plasmablasts)	9	5	15	10

*Gated on live cells > CD19 positive cells

Figure 1b. Immortalized cells produce MPO-ANCA



FR-PO831

Hydralazine-Associated Anti-neutrophilic Cytoplasmic Antibody (ANCA)-Associated Vasculitis: A Model of Drug-Associated Autoimmunity

Gang Xi,[1] Olivier Lardinois,[2] Peiqi Hu,[1] Elizabeth A. McInnis,[1] John S. Poulton,[1] Meghan E. Free,[1] Dhruti P. Chen,[1] Evan Zeitler,[1] Eve Wu,[1] Vimal K. Derebail,[1] J. Charles Jennette,[1] Ronald Falk.[1] *[1]The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC; [2]Mass Spectrometry Research and Support Group, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC.*

Background: Drug-associated autoimmunity is a recognized phenomenon, but underlying mechanisms are not completely elucidated. We previously demonstrated that hydralazine adduct formation on myeloperoxidase (MPO) resulted in production of anti-hydrazone MPO antibodies, which contributed to development of hydralazine associated ANCA vasculitis. Here, we examine additional disease-associated drugs *in vitro* and further explored the *in vivo* effects of modified MPO using mouse models.

Methods: Aminoguanidine (AG)- or propylthiouracil (PTU)-modified myoglobin (Mb) were analyzed with reverse phase HPLC and electrospray mass spectrometry. Levamisole- or AG-modified MPO were used to investigate the mechanism by which drugs could modify MPO. Unmodified and modified mouse recombinant MPO (rmMPO) were injected into wild type C57BL/6 mouse or MPO null mice. Mouse T cells were isolated for ELISpot assays 4 weeks after immunization. Splenocytes from immunized mice were isolated and injected into Rag2 $^{-/-}$ mice to study the pathogenic activity of modified MPO. After 2 weeks, mice were sacrificed. Serum IgG and IgM were measured with ELISA and kidneys were collected for histology.

Results: Mass spectrometry data showed that, like hydralazine, the amine group of AG bound to a carbonyl group of Mb. PTU bound to Mb via sulfenic/sulfinic/sulfonic derivatives to generate a PTU adduct. AG was able to competitively block hydrazone adduct formation on MPO. Levamisole, like PTU, bound to MPO with sulfenic derivatives and was unable to prevent hydrazone formation on MPO. ELISpot data revealed that hydralazine-modified rmMPO only stimulated IL-17a production while unmodified rmMPO stimulated both IFNγ and IL-17a production. Anti-rmMPO or anti-hydralazine modified MPO IgG were detected, but IgM was undetectable in both settings. Splenocytes from MPO$^{-/-}$ mice immunized with hydralazine modified rmMPO caused glomerulonephritis when injected into Rag2$^{-/-}$ mice.

Conclusions: Our current study suggest that different drugs may bind to MPO via different mechanisms but can still induce ANCA by similarly forming an adduct on MPO. Animal models clearly demonstrate hydralazine-modified MPO stimulates T-cell activation and pathogenic IgG that induces ANCA glomerulonephritis in mice.

Funding: NIDDK Support

FR-PO832

Perlecan Is a Novel Target of Autoantibodies in Anti-glomerular Basement Membrane Disease

Huang Kuang, Zhao Cui, Ming-Hui Zhao. *Peking University First Hospital Department of Nephrology, Beijing, China.*

Background: Anti-glomerular basement membrane (anti-GBM) disease is an autoimmune kidney disease in which autoantibodies are directed against GBM components. Type IV collagen and laminin α5β2γ1 (LM521) within GBM are two major target antigens in anti-GBM disease. Perlecan is a type of heparan sulfate proteoglycan, ubiquitously expressed in basement membranes, and a target of antibodies implicated in allograft rejection. The present study aimed to investigate whether perlecan could be recognized by anti-GBM antibodies, and further analyzed the properties and clinical associations of anti-perlecan antibodies.

Methods: A total of 108 patients diagnosed with anti-GBM disease between January 2000 to December 2018 were included in the study. Additionally, one hundred patients with various active glomerular diseases were utilized as disease controls, along with 20 health controls. IgG antibodies against perlecan were detected by enzyme-linked immunosorbent assay and immunoblot.

Results: Circulating IgG antibodies against perlecan were detected in 18.5% (10/108) of the anti-GBM patients, but not in healthy controls or any other disease controls. Anti-perlecan IgG antibodies were predominantly of IgG3 subclass. Patients with anti-perlecan autoantibodies had a higher prevalence of lung hemorrhage than those without (55.0% vs 26.1%, $P = 0.012$). A "triple-positive" subgroup in anti-GBM disease was identified, who had circulating autoantibodies simultaneously against type IV collagen, laminin 521, and perlecan. This subgroup had the highest prevalence of lung hemorrhage (66.7%, 10/15) and incidence of end-stage kidney disease events (93.3%, 14/15), indicating a more aggressive immune-mediated tissue injury among these patients.

Conclusions: Perlecan was identified as another novel target in anti-GBM disease and expanded the repertoire of target antigens of anti-GBM antibodies. The discovery of autoantibodies against perlecan identified a triple-positive subgroup with more severe clinical phenotype among patients with anti-GBM disease. The pathogenic role of autoimmunity against perlecan and the pathophysiology of the co-presence of three autoantibodies merit further investigation in future.

FR-PO833

HSP27 Promotes Activation of Parietal Epithelial Cells and Crescent Formation in Crescentic Glomerulonephritis

Lisa Melis,[1,2] Hamza Sakhi,[6] Morgan Gallazzini,[4] Léonie Pate,[1] Carmen Garrido,[7] Vincent Audard,[5] Khalil El Karoui.[1,3] *[1]Inserm U1155, Paris, France; [2]Sorbonne Universite, Paris, France; [3]Hopital Tenon, Paris, France; [4]Institut Necker-Enfants Malades, Paris, France; [5]Hopital Henri Mondor, Creteil, France; [6]Institut Mondor de Recherche Biomedicale, Creteil, France; [7]INSERM U1231, Dijon, France.*

Background: Crescentic glomerulonephritis (CrGN) is the most severe form of kidney disease. CrGN is characterized by a pathological accumulation of parietal epithelial cells (PEC) forming the cellular "crescent" in the urinary space leading to end stage renal disease in 30-50% of cases. While current treatments consist of immunosuppressive therapies, none of them directly targets molecular pathways associated with crescent formation and PEC activation. Heat Shock Protein 27 (HSP27) is a stress-induced chaperone protein largely known for its anti-apoptotic and pro-proliferative effect in cancer. Here, we aim to investigate whether HSP27 is involved in PEC activation and crescent formation.

Methods: To explore the role of HSP27, we used a nephrotoxic serum (NTS)–induced crescentic glomerulonephritis preclinical model and biopsies from patients diagnosed with CrGN. In vitro, we used primary cell cultures of PEC, either with or without HSP27 knockdown, to examine migration, proliferation, and the expression of activation markers (CD44, EGF receptor activation).

Results: HSP27 is largely overexpressed in PEC within glomerular crescents in both patients with CrGN and in kidneys from NTS-treated mice. Targeting of HSP27 with the antisense oligonucleotide (OGX-427) results in reduced development of crescents in the NTS model. In vitro, pharmacologic or genetic silencing of HSP27 in PEC induces a reduction in cellular migration and activation (measured by CD44 expression). These data suggest that HSP27 could promote crescents formation by promoting PEC activation and proliferation. To better understand, we explored the EGFr pathway known to be involved in glomerular epithelial cells activation. Silencing of HSP27 leads to a reduction in the activation of the EGF receptor, explaining at least part of the impact in PEC activation.

Conclusions: Taken together, our data highlight a role for HSP27 in the development of crescent lesions and pave the way for innovative therapeutic approaches for CrGN patients.

Funding: Government Support - Non-U.S.

FR-PO834

FRA-2 (Fosl2) Epigenomic and Splicing Dynamics in Crescentic Glomerulopathies

Robert Bronstein,[1] Nehaben A. Gujarati,[1] David J. Salant,[2] Sandeep K. Mallipattu.[1] *[1]Stony Brook University, Stony Brook, NY; [2]Boston University, Boston, MA.*

Background: Proliferative glomerulopathies are end-stage kidney diseases. Their complex etiology is apparent in disorders like diabetes, sickle cell disease and HIV. There are no curative therapies, therefore a more mechanistic view of disease features is needed. A patho-proliferative cell in the kidney glomerulus is the parietal epithelial cell (PEC) lining the inner wall of Bowman's capsule, and growing evidence shows it contributes to disease progression - forming crescentic lesions in diseases such as focal segmental

glomerulosclerosis. Our two mouse models of proliferative glomerulopathy (nephrotoxic serum nephritis and podocyte-specific *Klf4* knock-down) identify transcription FRA-2 as crucial to disease progression.

Methods: 10X Multiomic datasets were generated from nephrotoxic serum (NTS – Days 0,7 & 14) and podocyte-specific *Klf4* deletion models of proliferative glomerulopathy. Seurat (RNA) and ArchR (ATAC) were the primary R tools used in bioinformatic analysis, with: CellChat, Monocle3 & clusterProfiler. FRA-2 immunoprecipitation and mass spectrometry (RIME) was performed in a PEC cell line, as were *Fosl2* knock-down experiments.

Results: Analysis of multiomic features after glomerular injury identified *Fosl2* and its motif as enriched in PECs (**Fig. 1A)**. Ligand-receptor interactions in NTS dataset pointed to PEC-specific *Spp1/Cd44* interactions as conserved molecular features in these disease models (**Fig. 1B)**. RIME analysis of *Fosl2* interactors showed enrichment in splicing factors, in agreement with Fosl2+/Cd44+ sub-clusters 1&2 (**Fig. 1C)**. Knock-down of *Fosl2* in an immortalized PEC cell line resulted in a reduction in *Cd44* isoforms V7-V9 (**Fig. 1D)**. Gene-Splice Junction (SJ) relationships in the temporal and pseudo-time transition between PECs and Myofibroblasts point to isoform switching of key fibrosis genes (**Fig. 1E)**.

Conclusions: These data suggest that FRA-2 (*Fosl2*) is a regulatory TF in proliferative glomerulopathies across the crescentic to fibrotic boundary (Day 7 to 14) - through the modification of alternative splicing dynamics.

Funding: NIDDK Support, Veterans Affairs Support

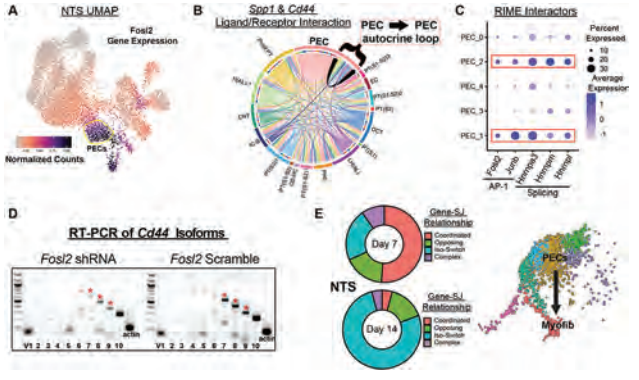


Fig. 1

FR-PO835

Hypoxia-Inducible Factor (HIF) Activation in Podocytes Exacerbates Crescentic Glomerulonephritis

Yu Kurata,[1] Tetsuhiro Tanaka,[2] Mai Sugahara,[1] Imari Mimura,[1] Masaomi Nangaku.[1] *[1]Tokyo Daigaku Daigakuin Igakukei Kenkyuka Naikagaku Senko Jinzo Naibunpi Naika, Bunkyo-ku, Japan; [2]Tohoku Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Sendai, Japan.*

Background: Hypoxia-inducible factor (HIF) is a transcription factor that mediates cellular responses to hypoxia. Although various studies have explored the effects of HIF activation in renal diseases, the role of HIF in podocytes remains unclear. We established podocyte-specific HIF-prolyl hydroxylase (PH) 1/2/3 conditional knockout mice, in which HIF was specifically activated in podocytes. To examine the role of HIF activation in podocytes during glomerular injury, we subjected these mice to crescentic glomerulonephritis induced by nephrotoxic serum (NTS).

Methods: We crossed Podocin-Cre mice with HIF-PH1/2/3 triple-floxed mice to generate podocyte-specific HIF-PH1/2/3 conditional knockout (KO) mice. Cre-negative littermates were used as controls (WT mice). Crescentic glomerulonephritis was induced by the intravenous administration of NTS (1.2 μL/g). NTS was produced by immunizing sheep with isolated rat glomeruli.

Results: First, we confirmed podocyte-specific HIF-1 activation in KO mice by immunohistochemical staining. There were no significant differences in the histological findings of the kidney, kidney function, and urinary albumin levels between WT and KO mice. Next, we induced nephrotoxic serum nephritis (NTN). On day 7, KO mice exhibited significantly higher urinary albumin levels th WT mice. Histological analysis revealed exacerbated glomerular crescent formation and tuft necrosis in KO mice. The number of Ki-67-positive parietal epithelial cells (PECs) and CD44-positive glomeruli significantly increased in KO mice. Glomerular deposition of sheep IgG and mouse IgG was similar in WT and KO mice. To further investigate the underlying mechanism, we conducted bulk RNA-seq of the isolated glomeruli. Comparison of WT and KO mice subjected to NTN identified a total of 167 differentially expressed genes (DEGs). Enrichment analysis revealed that the DEGs were significantly enriched in leukocyte chemotaxis, DNA-templated DNA replication, positive regulation of cell death, regulation of leukocyte activation, and positive regulation of cell migration.

Conclusions: HIF activation in podocytes worsened glomerular injury in a crescentic glomerulonephritis model. Aggravated inflammatory responses and excessive PEC activation may exacerbate glomerular injury.

Funding: Government Support - Non-U.S.

FR-PO836

A Case of Collapsing FSGS: Lupus Podocytopathy or APOL1-Mediated Kidney Disease?

Kavita Mistry,[1] Isaac E. Stillman,[2] Stewart H. Lecker.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: High risk APOL1 alleles are a key driver of proteinuric kidney disease in the Black population. Although the combined allele frequency among African Americans is 34%, only a minority of individuals with two APOL1 risk alleles go on to develop kidney disease, suggesting the need for a second hit.

Case Description: A 59-year-old African American woman with a history of undifferentiated connective tissue disease and monoclonal gammopathy of unknown significance (MGUS) presented with 6 weeks of fevers of unknown origin, fatigue and malaise. Vital signs were normal and physical exam revealed axillary lymphadenopathy. Creatinine was 0.7 mg/dL with albumin of 3.0 g/dL and 2.8 g/g proteinuria. SPEP and UPEP revealed monoclonal IgG kappa light chain estimated at 84 mg/day in urine. Bone marrow biopsy revealed 9% plasma cells consistent with MGUS. Infectious diseases workup was negative apart from positive CMV IgM. Nephrology and rheumatology were consulted and recommended workup as follows: ANA positive 1:1280, dsDNA positive 1:1280, C3 slightly low at 84 mg/dL, C4 normal, anti-PLA2R IgG negative, HIV and hepatitis B/C serologies negative, and positive antibodies for RNP, anti-Sm, SS-A and SS-B. The patient was started on prednisone 60 mg/day for presumed lupus nephritis. A renal biopsy was performed and revealed collapsing focal segmental glomerulosclerosis (cFSGS) with negative immunofluorescence. Electron microscopy revealed extensive foot process effacement with no subendothelial deposits and rare subepithelial deposits, consistent with lupus podocytopathy. The patient was discharged on ARB and SGLT2 inhibitor and proteinuria improved to 0.3 g/g. Steroids were tapered off and mycophenolate was initiated. APOL1 genotyping returned as high risk G2/G2. Mycophenolate was tapered off due to gastrointestinal side effects with no rebound increase in proteinuria, suggesting that this patient's cFSGS was driven by APOL1-mediated kidney disease triggered by CMV infection rather than by lupus podocytopathy.

Discussion: This report adds to a growing literature of cases that describe cFSGS in patients with high risk APOL1 alleles after viral infection. The biological basis for the development of cFSGS in patients with APOL1 high risk genotype, lupus and viral infection remains to be elucidated, although can be presumed to result from parallel, additive and/or synergistic processes.

FR-PO837

Effaced but Not Erased: A Case of Consecutive Recurrences of Lupus Podocytopathy in Kidney Transplants

Renuka Tolani, Nibras Fakhri, Luan D. Truong, Angelina Edwards, Sadhna Dhingra. *Houston Methodist, Houston, TX.*

Introduction: Lupus podocytopathy is considered a distinct subtype of lupus nephritis. Histologically it can present as minimal change disease (MCD) and/or Focal segmental glomerulosclerosis (FSGS). We present a case of lupus podocytopathy in a 29 year old woman that relapsed in 2 consecutive transplants.

Case Description: At first presentation patient had serology positive for lupus, urine protein/creatinine ratio (UPCR) of 10, native kidney biopsy showed lupus podocytopathy with minimal change features. After living unrelated kidney transplant, there was delayed graft function and dialysis was initiated. Induction immunosuppression was changed from Simulect to thymoglobulin, and belatacept, mycophenolate and prednisone were chosen for calcineurin-inhibitor avoidance. Patient noted to have malar rash, serology positive for antinuclear anitbodies 1:320, and double stranded DNA. Wedge allograft biopsy 3 days post-transplant showed recurrent Lupus podocytopathy. Patient was treated with Cytoxan, plasmapheresis, plaquenil and steroids; discharged off dialysis. Patient was then readmitted 2 weeks later for acute renal injury; restarted on dialysis. 24 hour urine collection showed 25 grams protein. Repeat allograft biopsy showed collapsing variant of FSGS. Patient was treated with plasmapheresis and immunosuppression with no response, progressed to graft failure with dialysis dependence Patient received a second living unrelated kidney transplant 3 years later with Thymoglobulin induction. As a means to reduce the risk of recurrence, patient received pre and post-transplant plasmapheresis and 4 doses of rituximab. She was discharged with creatinine 1 mg/dL but nephrotic proteinuria present with UPCR 6. A protocol biopsy showed recurrent podocytopathy/ focal segmental glomerulosclerosis. Patient was maintained on plasmapheresis, with stable allograft function.

Discussion: Lupus podocytopathy is not a benign lesion. It requires vigilance for specific diagnosis and aggressive immunosuppression for treatment. Classically patients with FSGS subtype are less likely to respond to treatment, particularly with the collapsing variant. Even those with MCD features, may have relapsing events.

FR-PO838

Neutrophils Generate Higher Levels of Reactive Oxygen Species after Stimulation by Inactive vs. Active Lupus Nephritis Serum

Rebecca Lightman, Nicholas A. Shoctor, Makayla Brady, Shweta Tandon, David W. Powell, Dawn J. Caster. *University of Louisville School of Medicine, Louisville, KY.*

Background: There is increasing evidence for the role of neutrophils in lupus nephritis (LN) pathogenesis. Release of reactive oxygen species (ROS) by neutrophils may be a source of glomerular damage in LN. Our previous work investigating LN neutrophil ROS generation suggested the possibility of endogenous neutrophil activators in LN serum. To further this investigation, we aimed to identify differences in healthy donor neutrophil activation in response to different LN serum treatments based on active versus inactive disease.

Methods: Neutrophils were isolated from whole blood of 6 healthy donors. Cell treatment groups included untreated, 10% pooled active LN serum, 10% pooled inactive LN serum, or 10% pooled healthy donor platelet poor plasma (PPP). Active disease was defined as urine-protein-to-creatinine ratio greater than 500. Active and inactive LN serum samples were paired from 3 LN patients on different dates. ROS generation was measured using superoxide assay.

Results: Results were calculated using Dunn's multiple comparisons test. Statistics were performed with GraphPad Prism 10.2.1. Neutrophil stimulation with healthy donor PPP, active LN serum, and inactive LN serum resulted in more ROS generation than in the untreated condition ($p=0.009$, $p<0.0001$, $p<0.0001$). Healthy donor PPP resulted in less ROS generation than either active or inactive LN serum ($p=0.0009$, $p<0.0001$). Treatment with inactive LN serum caused the highest level of ROS generation, more than the active LN serum treatment ($p<0.0001$).

Conclusions: Serum from inactive LN stimulated neutrophils to produce the most ROS despite lower clinical disease activity than active LN. These results may be attributable to differences in serum contents related to disease status. These data warrant further investigation to characterize serum contents for active and inactive LN. Greater sample size and a bigger patient pool may further our understanding of these differences. Improving understanding of serum characteristics by disease status may have implications for experimental designs in LN research, for elucidating patterns of remission and relapse in LN, and for future clinical LN management.

Funding: NIDDK Support

FR-PO839

Immunologic Changes over Time in Repeat Kidney Biopsies from the AURORA Studies of Voclosporin in Lupus Nephritis

Samir V. Parikh,[1] Maddalena Bolognesi,[2] Ivana Grbesa,[3] Brad H. Rovin,[1] Giorgio Cattoretti,[2] Vincenzo L'Imperio,[2] Arnon Arazi,[4] Lucy S. Hodge,[5] Ernie Yap.[5] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]Universita degli Studi di Milano-Bicocca, Milano, Italy; [3]Qiagen Digital Insights, Sibenik, Croatia; [4]The Broad Institute, Cambridge, MA; [5]Aurinia Pharmaceuticals Inc, Edmonton, AB, Canada.*

Background: The AURORA 1 and 2 studies investigated the use of voclosporin (VCS) plus standard-of-care (SOC) for the treatment of lupus nephritis (LN). All patients underwent a kidney biopsy for enrollment (Bx1), and a subset of patients elected to undergo a second biopsy (Bx2) to assess how histology of the kidney changes in response to treatment. Here we have used multiplex immunofluorescence (mIF) to investigate changes in the immunologic landscape of the kidney in response to immunosuppression using these paired biopsies.

Methods: Formalin-fixed paraffin-embedded tissue sections were stained with MILAN technology with a 10-marker panel. Sequential acquisitions for each biopsy were registered, and autofluorescence subtracted. Dedicated ImageJ-based pipelines were used to measure total biopsy areas and immunopositive markers and/or to count cells and related positivity for markers of interest.

Results: A total of 27 paired samples were available for mIF (17 and 10 from VCS- and SOC-treated patients, respectively). CD34 and Ki67 were significantly overexpressed in Bx2 compared to Bx1 (Table 1). Within each treatment group, there was a trend toward upregulation of CD34; the differences were not statistically significant (adjusted p-values of 0.07 [VCS] and 0.12 [SOC], respectively).

Conclusions: CD34 and Ki67, which have been implicated in tissue regeneration and healing in glomerulonephritides, showed significantly higher expression in repeat biopsies of patients with LN treated with immunosuppression during the AURORA trials. The lack of difference within each treatment group may indicate a lack of concordance between clinical response and immunological landscape but may also be reflective of the small sample size. The potential utility of CD34 and Ki67 as biomarkers of response requires further investigation.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

Table 1. 10-marker multiplex immunofluorescence panel

Antigen	Fold-change Bx2 vs Bx1*	p-value
CD3	1.0988	0.8839
CD20	1.3569	0.7998
CD68	-1.1467	0.9147
CD163	1.0304	0.7333
CD74	1.4481	0.2475
gH2ax	1.3074	0.3403
KI67	1.4852	0.0227
Mx1	1.2295	0.3157
CD248	1.3638	0.0702
CD34	1.3370	0.0037

*VCS and SOC treatment groups combined
Multiplex immunofluorescence results were analyzed in QIAGEN OmicSoft Studio (v12.6.3.5). Normality of the variables was tested by the Shapiro-Wilk normality test. For comparisons of groups, statistical significance was estimated by the Wilcoxon rank-sum test. Bx, biopsy.

FR-PO840

Role of Hexokinase 2-Mediated Enolase 1 Translocation in Podocyte Injury

Zilv Luo. *The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

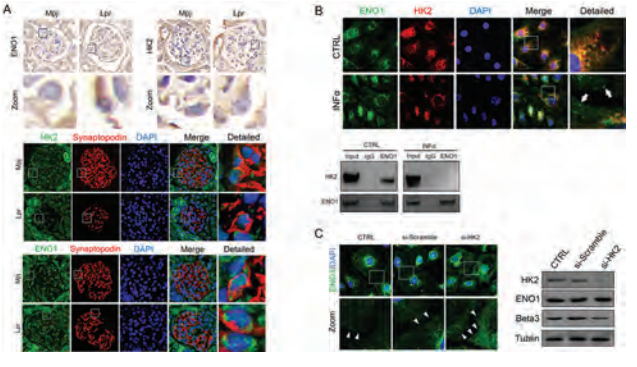
Background: Lupus nephritis (LN) is one of the most common and serious complications of systemic lupus erythematosus. Podocyte injury is associated with proteinuria and renal impairment in LN, and podocyte is dependent on glycolysis. However, the relationship between glycolysis and LN remains unclear. Hexokinase 2 (HK2) and enolase 1 (ENO1) are the glycolytic enzymes in cytoplasm. In physiological conditions, different glycolytic enzymes can form complexes, which contribute to their intracellular localization. In pathological conditions, the intracellular localization of glycolytic enzymes would be altered. Notably, cell membrane-localized ENO1 has the activity of plasminogen binding receptor, and is associated with cell adhesion and integrin beta3 activation.

Methods: In lupus mice and interferon α-stimulated cultured podocytes, immunohistochemical and immunofluorescent staining were performed to examined the expression patterns of ENO1 and HK2, and the binding of HK2 and ENO1 by Co-IP. After interfering with siHK2 in cultured podocytes, the intracellular localization of ENO1 and integrin expression were detected.

Results: WB and IF showed the downregulation of HK2 and the upregulation of ENO1 in lupus mice and interferon α-stimulated cultured podocytes. In addition, interferon α increase the ENO1 localization on podocyte membrane compared with control group. siHK2 increased the ENO1 localization at the cell membrane surface, accompanied by downregulation of integrins. (Figure)

Conclusions: HK2 binds to ENO1 and restricts ENO1 in podocytes. In LN conditions, the dissociation of ENO1 and HK2 leads to an increased localization of ENO1 at the cell membrane, which lead to LN podocyte injury by affecting podocyte adhesion and influencing integrin beta3 expression.

Funding: Government Support - Non-U.S.



A. The expression patterns of ENO1 and HK2 in mice, Synaptopodin is podocyte mark. B. The expression patterns and the binding of ENO1 and HK2 in cultured podocytes, ENO1 at the podocyte membrane identified by white arrows. C. The expression patterns and the location of ENO1 in cultured podocytes, ENO1 at the podocyte membrane identified by white triangle.

FR-PO841

EPHB2 Mediates Inflammation in Podocytes of Lupus Nephritis

Huajing Peng, Zilv Luo, Wei Chen. *The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Podocyte injury in lupus nephritis (LN) is a critical contributor to the substantial proteinuria observed in LN patients. However, the potential for a unique inflammatory pattern of podocyte injury specific to lupus nephritis remains to be elucidated. The erythropoietin-producing hepatocellular receptor (Eph) family, the largest

group of receptor tyrosine kinases, have been implicated in a wide range of diseases. Elevated expression of EPHB2 has been observed in the kidneys of models with IgA nephropathy (IgAN) and ischemia-reperfusion (IR) injury. However, the specific role of EPHB2 in the context of podocyte injury in lupus nephritis remains unknown.

Methods: To investigate the underlying mechanisms, we developed a nephrotoxic nephritis (NTN) mouse model of lupus and an IFNα-stimulated podocyte injury model. We observed changes in proteinuria and renal pathology in the mice. The expression of inflammatory proteins like MMP7, VCAM-1 and the activity of the NFκB pathway were assessed using Western blotting, and immunofluorescence. Additionally, we utilized adenoviral vectors to interference with EPHB2 expression in vivo and in vitro. Similar methods were employed to detect and compare the expression of inflammatory molecules before and after EPHB2 interference.

Results: In vivo experiments revealed that NTN lupus mice exhibited significantly increased proteinuria and severe glomerulosclerosis. In vitro, IFNα stimulation led to cytoskeletal protein disruption in podocytes. Elevated expression of MMP7 and VCAM1, as well as increased activity of the NFκB pathway, were observed in the renal cortex of NTN lupus mice and in IFNα-stimulated podocytes. Interference with EPHB2 expression in the kidney resulted in a significant reduction in proteinuria and alleviation of glomerulosclerosis in NTN lupus mice. Additionally, the expression of MMP7 and VCAM1, as well as the activity of the NFκB pathway, were significantly reduced in both the renal cortex and IFNα-stimulated podocytes after EPHB2 expression was inhibited.

Conclusions: High expression of EPHB2 in podocytes is implicated in the activation of renal inflammation in LN. Interfering with EPHB2 expression in vivo and in vitro have been shown to alleviation podocyte inflammation and improve renal outcomes by inhibiting the NFκB pathway. Intervention targeting EPHB2 represents an effective strategy for controlling inflammation activation in LN podocytes.

FR-PO842

Roxadustat Regulates the NKA/Src/HIF-1/ROS Signaling Pathway to Improve Kidney Outcomes in Mice with Lupus

Changxuan Liu, Danni Shao. *The Central Hospital of Wuhan, Wuhan, China.*

Background: Sustained release of ROS can aggravate podocyte injury in lupus nephritis. NKA(Na-K-APTase)is widely distributed in renal tissues and releases a large number of ROS after activation, which promotes the apoptosis of renal tubular epithelial cells/podocytes. Roxastat, as an inhibitor of HIF-1, can inhibit the release of ROS. We speculate that Roxastat may disrupt the positive feedback loop of ROS release by stabilizing HIF-1 protein and blocking the damage of tubular epithelial cells/podocytes, thereby protecting kidney tissue and delaying the progression of disease.

Methods: Mice were divided into the following groups: 1. Control group; 2. 2. MRL/LPR model group (lupus group); 3. Roxastat intervention group(Roxa group); Biochemical indexes: urine protein, Scr, BUN; The WB method was used to detect NKA, p-Src, HIF in mouse kidney tissue. Annexin V/PI flow cytometry was used to detect apoptotic cells. The ROS content in mouse kidney tissue was detected by flow cytometry with DCFH-DA probe method. MCP-1 and NGAL were detected by ELISA.

Results: 1. Proteinuria in MRL/LPR group was significantly up-regulated compared with control group (499.36±77.67vs45.68±23.66mg/L, $p < 0.001$), and down-regulated in Roxa group (499.36±77.67vs277.44±45.67 mg/L, $P < 0.001$). $p < 0.001$); 2. Scr in MRL/LPR group was increased (314.18±23.67vs106.63±15.67umol/L, $p < 0.05$), but decreased in Roxa group (243.54±17.33vs314.18±23.67umol/L, $p < 0.05$); 3. MCP-1 in MRL/LPR group was significantly up-regulated (437.84±50.5vs119.90±28.9pg/ml, $p < 0.001$)., but decreased in Roxa group(321.38±13.5vs437.84±50.5pg/ml, $p < 0.001$). 4. Annexin V/PI showed up-regulated in MRL/LPR group (30.05%±2.05%vs0.21%±0.02%); decreased in Roxa group (16.23%±2.23%vs 30.5% ±2.05%). 5. The ROS release was detected by DCFH-DA : which was up-regulated in MRL/LPR group (39.88%±2.88%vs3.28%±0.28%); lower in Roxa group (26.54%±2.54%vs39.88%±2.88%).

Conclusions: Roxastat may reduce the release of ROS by NKA/Src/HIF-1, thereby improving the injury of tubule/podocyte, reducing the excretion of proteinuria, and delaying the progression of lupus nephritis.

Funding: Government Support - Non-U.S.

FR-PO843

A Novel Lectin-Glycan Axis in Lupus Nephritis

Rohit Upadhyay,[1] Hao Li,[2] George C. Tsokos,[2] Rhea Bhargava.[1] *[1]Tulane University School of Medicine, New Orleans, LA; [2]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematosus (SLE) that can lead to end-stage kidney disease and increased mortality. We have previously demonstrated that immunoglobulin (IgG) in LN patients is aberrantly glycosylated and can lead to podocyte injury. Specifically, fucose on IgG can be pathogenic to podocytes while galactose can be protective. CLEC7A (C-type lectin domain containing 7A or Dectin1) is a transmembrane lectin receptor which functions as a pattern-recognition receptor and is the only known mammalian receptor to recognize fucose on IgG. Here, we evaluated the role of this lectin-glycan axis in podocyte injury in LN.

Methods: Human podocytes were exposed to serum/ IgG from healthy subjects, SLE, LN and LN-remission patients. Curdlan (ligand for CLEC7A) was used to activate inflammatory response and CLEC7A signaling. Flow-cytometry assisted calcium flux, immunocytochemistry, qPCR, western blotting, wound healing assay, phalloidin staining and silencing of CLEC7A were utilized to delineate CLEC7A signaling in human podocytes. Frozen kidney biopsies from individuals with LN and controls were stained with CLEC7A and SYK.

Results: Podocytes exposed to serum or IgG from LN patients, overexpressed CLEC7A and inflammatory pathway genes. Curdlan and LN-derived IgG (LN-IgG) altered podocyte cytoskeleton and motility along with decreasing nephrin expression. IgG bound to CLEC7A in podocytes while deglycosylation of LN-IgG disrupted CLEC7A binding and normalized podocyte cytoskeleton, motility and nephrin expression. In addition, curdlan and LN-IgG increased Ca flux compared to deglycosylated LN-IgG. More importantly, we found that curdlan and LN-IgG activated spleen tyrosine kinase (Syk) in human podocytes and its pharmacological inhibition effectively prevented LN-IgG induced podocyte injury. Translationally immunofluorescence staining of kidney biopsy tissue revealed increased podocyte CLEC7A and Syk expression in LN. Furthermore, de-glycosylation of LN-IgG and silencing CLEC7A protected podocytes from injury in LN.

Conclusions: To our knowledge this is the first study to demonstrate the role of lectins recognizing specific carbohydrates in podocyte injury and LN. Our data provides a novel mechanistic insight and reveals several novel therapeutic targets for LN.

Funding: Other NIH Support - NIAID

FR-PO844

Global Lactylome Reveals Lactylation-Dependent Mechanisms Underlying Th17 Differentiation in Lupus Nephritis

Mingyang Zhang. *Army Medical University, ChongQing, China.*

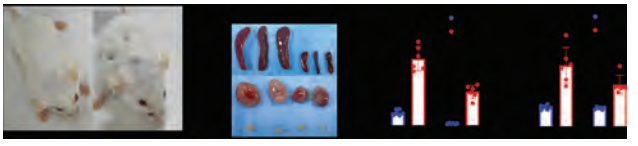
Background: The dysregulation of $CD4^+$T cell differentiation is closely related to the occurrence and development of lupus nephritis, Metabolic reprogramming from oxidative phosphorylation to glycolysis and accumulation of lactate are involved in this process. lactate-derived lactylation regulated the aberrant activation and differentiation of T cells. However, the underlying mechanisms remain unclear.

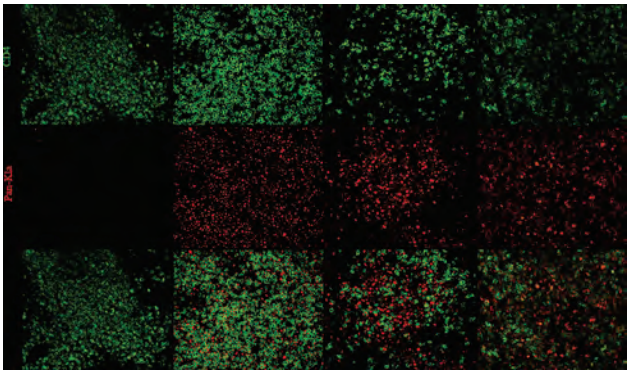
Methods: Western blot and immunofluorescence were used to show the changes of lactylation level of $CD4^+$T cells in MRL/Lpr mice at different stages of disease. The impact of reducing and increasing lactylation by intraperitoneal administered of the pyruvate dehydrogenase kinase dichloroacetate (DCA) and rotenone, aiming to assess their disease progression of lupus nephritis (LN). Global lactylome reveals important differential lactylation modification sites, and ChIP-seq was used to analyze the key downstream genes regulated by lactylation modification sites, thus influencing the differentiation process of $CD4^+$ T cells.

Results: we find that lactate-derived lactylation regulated $CD4^+$T cell differentiation. Lactylation levels in $CD4^+$T cells increased with the progression of lupus nephritis (LN). Inhibition of lactylation suppressed TH17 differentiation and attenuated LN inflammation. The global lactylome revealed the landscape of lactylated sites and proteins in the $CD4^+$T cells of normal and MRL/Lpr mice. Specifically, hyperlactylation of Ikzf1 at Lys^{373} promoted Th17 differentiation by directly modulating the expression of Th17-related genes. However, Delactylation of Ikzf1 at Lys^{373} impaired TH17 differentiation.

Conclusions: Ikzf1 Lactylation is involved in the pathogenesis of lupus nephritis by specifically promoting Th17 differentiation,It may become a potential therapeutic target for delaying the progression of lupus nephritis.

Funding: Clinical Revenue Support





FR-PO845

Elucidating Lupus Nephritis (LN) Pathogenesis by Evaluating the Intersection between Glycomics and Metabolism

Rhea Bhargava,[1] Rohit Upadhyay,[1] Jing Chen,[1] Prasad V. Katakam,[1] George C. Tsokos.[2] *[1]Tulane University, New Orleans, LA; [2]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Lupus nephritis (LN) is the most devastating complication of systemic lupus erythematosus (SLE). Patients with LN have higher mortality than SLE patients without LN. The ability to accurately identify SLE patients destined to develop LN could shift the current management to prevention. Podocyte injury is an early event in LN and occurs by exposure to aberrantly glycosylated IgG. Here, we demonstrate that in LN, aberrantly glycosylated IgG can reprogram podocyte metabolism leading to podocyte injury.

Methods: Human podocytes were exposed to IgG with and without treatment with PNGase from healthy subjects, SLE, LN and LN-remission patients. ATP rate, glycolytic rate assay and untargeted metabolomics were performed. Podocyte injury was evaluated by scratch assay, phalloidin staining and nephrin expression. Urine podocytes were isolated and targets were validated by droplet digital PCR in urine and urine cells.

Results: Glycolysis was the primary process for energy production in podocytes. Podocytes exposed to LN IgG had a lower rate of glycolysis compared to deglycosylated and healthy IgG. Untargeted intracellular metabolomics revealed 332 metabolites across the 9 samples. A total of 56 metabolites were significantly different between cells treated with LN vs deglycosylated LN IgG. Metabolite set enrichment analysis (MSEA) was carried out in reference to the database of pathway-associated metabolite sets (SMPDB). Glycolysis was the most enriched pathway with 5 hit compounds (pyruvic acid, phosphoenolpyruvic acid, 2-phosoglycerate, 3 phosphoglycerate, fructose 1,6 biphosphate) that were differentially regulated. The fold enrichment for the pathway was 8.4. These metabolites were validated in urine/urine cells isolated from 15 SLE patients with and without LN. Urine pyruvate and PKM levels in cells were found to differentiate active LN from controls.

Conclusions: To our knowledge this is the first study to demonstrate a link between glycoproteins regulating cell metabolism. These data plausibly suggest that LN-derived IgG leads to significant podocyte injury by reducing their ability to compensate for the increased energy supply required for repair and maintenance of their shape and structure, leaving them vulnerable to any stress and possibly accelerating LN.

Funding: Other NIH Support - K99AI162843, Government Support - Non-U.S.

FR-PO846

Significant Correlation of Antibody Repertoire Perturbations to Clinical Manifestations in Lupus Nephritis

Huikun Zeng, Haipei Tang, Zhenhai Zhang, Xueqing Yu. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: Lupus nephritis (LN), characterized by immune complex formation through autoantibodies recognizing multiple autoantigens and kidney deposition, is a major cause of morbidity and mortality that affects up to 60% of the SLE population during disease. However, detailed antibody repertoire profiling of all 5 isotypes and 9 subtypes remains unclear. Moreover, whether and the extent to which antibody repertoire features associate with important clinical manifestations of LN is unclear.

Methods: PBMC samples for 58 LN patients and 58 healthy controls were collected. Using a highly accurate repertoire sequencing strategy developed in our lab, we acquired antibody repertoires of all nine subtypes with single experiment. The base errors and amplification bias intrinsic to antibody repertoire sequencing were further corrected using the bioinformatics pipeline of DUMPArts. The isotype specific repertoire features were then compared between patients and healthy controls.

Results: Preferential up- and down-regulation of various IGHV genes in IgM, IgD, IgG, and IgA and subtypes of IgG and IgA indicate the perturbation of antibody repertoire for both naïve and activated B cells. The CDR3s of LN patients were significantly shorter than those in healthy controls in almost all isotypes. The SHMs were lower in repertoires of activated isotypes for LN patients while the SHMs in IgD repertoire were significantly higher, which suggests IgD+ B cells may be important for the disease severity. Evidenced clonal expansion in IgM and IgD compared to the activated isotypes (IgG, IgA, IgE). Combined repertoire-based features and support vector machine (SVM) model could distinguish LN patients from healthy donors with high accuracy.

Conclusions: Our results demonstrated multi-faceted nonunanimous perturbations of the antibody repertoire. The findings of significant changes in naïve repertoire compartment, especially changes in IgD. Repertoire features might serve as a biomarker for disease severity.

Funding: Government Support - Non-U.S.

FR-PO847

Na+-K+-ATPase Enables Pathological B Cell Survival and Leads to Glomerular Basement Membrane (GBM) Thickening in Lupus Nephritis

Tayyaba Ishaq, Irene Chernova. *Yale University School of Medicine, New Haven, CT.*

Background: The kidney in lupus nephritis (LN) is characterized by a significant immune cell infiltrate and glomerular pathology. How lymphocytes lead to the characteristic damage of glomerular structures in LN is poorly understood. We recently published that intrarenal B lymphocytes upregulate Na^+-K^+-ATPase (NKA) in LN and that pharmacologic or genetic blockade of NKA results in fewer intrarenal B cells and reduced albuminuria, dependent on the genotype of the immune cell and not the host. As changes in kidney B cells were the only notable difference between control and NKA-inhibited mice, we hypothesize that kidney B cells affect glomerular basement membrane (GBM) structure and that mice with fewer kidney B cells would have preserved GBM and improved albuminuria.

Methods: We compared lupus-prone MRL^{lpr} and MRL^{lpr}.*Fxyd2*$^{-/-}$ mice—which lack a gamma NKA subunit and have fewer intrarenal B cells—to define glomerular pathology. Podocyte and GBM pathology were investigated using immunofluorescence (IF), electron microscopy (EM) and real-time PCR.

Results: We found that MRL^{lpr} mice have proteinuria and thickened GBM on EM as compared to non-lupus B6 mice (277nm and 162nm, respectively, $p<0.0001$). Both proteinuria and GBM thickness were significantly improved in MRL^{lpr}.*Fxyd2*$^{-/-}$ mice as compared to MRL^{lpr} controls (200nm and 277nm, respectively, $p<0.0001$). We found immune complex deposits in both genotypes, with no notable differences on EM. IF showed homogeneously thickened collagen IV staining in MRL^{lpr} as compared to MRL^{lpr}.*Fxyd2*$^{-/-}$ mice ($p<0.0001$) while whole-kidney gene expression studies confirmed that the increased expression of glomerular collagen IV genes in MRL^{lpr} was reduced in the MRL^{lpr}.*Fxyd2*$^{-/-}$ mice. We are currently investigating collagen IV expression in contributing cell types (i.e. podocytes and endothelial cells) as well as looking at metalloproteinases to see if collagen breakdown is affected. Additionally, we are characterizing lupus kidney cytokine profiles to test the hypothesis that B cell-derived cytokines are promoting abnormal collagen deposition in LN.

Conclusions: We show that lupus-prone MRL^{lpr} mice have a significantly thickened GBM when compared to non-lupus and MRL^{lpr}.*Fxyd2*$^{-/-}$ animals, likely due to abnormal collagen IV deposition. We are currently investigating whether these findings are due to differences in intrarenal B cell numbers and cytokine levels.

Funding: NIDDK Support, Private Foundation Support

FR-PO848

NLRP3 Inflammasome Gene Expression Profile and Treatment Response in Lupus Nephritis: A Prospective Cohort Study

Camila B. Oliveira, Gisele Vajgel, Denise M. Costa, Paula S. Sandrin-Garcia. PatGen. *Universidade Federal de Pernambuco, Recife, Brazil.*

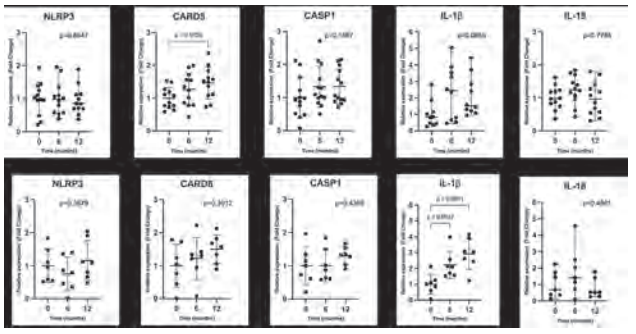
Background: Lupus nephritis (LN) is a severe complication of SLE characterized by inflammation and immune complex deposition in the kidneys, leading to progressive renal damage and impaired function. The inflammasome plays a crucial role in the innate immune response, has been implicated in the pathogenesis of LN. The aim of this study was to evaluate de gene expression profile of inflammasome NLRP3 in LN patients according to treatment response.

Methods: A prospective cohort study of adult patients with biopsy-proven active LN (class III, IV, and/or V). Clinical, laboratory, and histopathological data were collected at baseline (T0), 6 months (T6), and 12 months (T12) of immunosuppressive treatment. Gene expression of NLRP3, CARD8, CASP1, IL-1B, and IL-18 in peripheral blood mononuclear cells was analyzed using RT-qPCR. Treatment response was classified as primary efficacy renal response (PERR) or non-primary efficacy renal response (no-PERR).

Results: Twenty patients with active LN were included in the study. The mean age was 31.9 ± 8.3 years, with 19 females and 1 male. Laboratory evaluation showed median sCr 0.8 (0.7-1.3), median eGFR 103 (54-119), median 24-hour urine protein 3.3 (1.7-4.9). The mean SLEDAI score was 14.6 ± 4.4 and 95% of patients had complement C3 consumption (mean C3 57.2 ± 22.6 mg/dl). Among the 20 patients, 65% achieved PERR after 12 months of therapy. Gene expression analysis revealed that IL-1B expression was significantly higher in the no-PERR group after 12 months. Other inflammasome genes did not show significant changes between the groups.

Conclusions: The differential expression of NLRP3 inflammasome components, especially IL-1B, highlights its potential role as a biomarker for predicting treatment response in LN patients.

Funding: Private Foundation Support



Gene expression of inflammasome NLRP3 in patients with active LN divided by treatment response: primary efficacy renal response (PERR) and with no-PERR. At baseline (T0), 6 months (T6) and 12 months (T12). PERR, primary efficacy renal response

FR-PO849

Concomitant Sparsentan (SPAR) and SGLT2 Inhibitors in Adults with IgA Nephropathy in the Ongoing Phase 2 SPARTACUS Trial

Isabelle Ayoub,[1] Sydney Tang,[2] Laura Kooienga,[3] Priscila Preciado,[4] David S. Lee,[4] Stephanie Moody,[4] Brad H. Rovin.[1] *[1]Division of Nephrology, Ohio State University Wexner Medical Center, Columbus, OH; [2]Division of Nephrology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [3]Colorado Kidney Care, Denver, CO; [4]Travere Therapeutics, Inc., San Diego, CA.*

Background: SPAR is a nonimmunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA) approved in the US and EU for adults with IgAN. In patients (pts) with IgAN, SPAR showed sustained proteinuria reduction and preservation of kidney function in the phase 3 PROTECT trial. In a subgroup analysis from DAPA-CKD and EMPA-KIDNEY, SGLT2is reduced the risk of progression to kidney failure in pts with IgAN. The combination of SPAR and an SGLT2i may therefore provide therapeutic benefits with potentially additive kidney protection. The ongoing phase 2 SPARTACUS trial will evaluate the efficacy and safety of SPAR added to an SGLT2i in adults with IgAN.

Methods: SPARTACUS is a 28-wk, open-label, multicenter study of the efficacy and safety of SPAR added to a stable SGLT2i in pts with IgAN at high risk of disease progression. Pts had biopsy-proven IgAN, urine albumin-to-creatinine ratio (UACR) of ≥0.3 g/g, and an estimated glomerular filtration rate (eGFR) of ≥25 mL/min/1.73 m^2 despite a stable SGLT2i and maximized renin-angiotensin-system inhibition for ≥12 wk. Endpoints include change from baseline in UACR at wk 24 (primary); achievement of UACR of <0.2 g/g or 30% or 50% reduction in UACR at wk 24 (secondary); change from baseline in UACR, urine protein-to-creatinine ratio, eGFR, and blood pressure at each visit (secondary); and adverse events. We describe pts in a prespecified interim analysis 24 wk after ≈20 pts were enrolled.

Results: Pt demographics and baseline characteristics are reported in the **Table**.

Conclusions: Enrollment in SPARTACUS will allow for assessment of the efficacy and safety of SPAR added to a stable SGLT2i in pts with IgAN. The presentation will include data from the interim analysis.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table. Patient Demographics and Baseline Characteristics of SPARTACUS

	All patients (N=20)
Age at informed consent, mean (SD), y	52.9 (14.97)
Time from initial kidney biopsy to informed consent, mean (SD), y	7.0 (6.03)
Sex, n (%)	
Male	13 (65)
Female	7 (35)
Race, n (%)	
Asian	9 (45)
White	11 (55)
Weight, mean (SD), kg	90.94 (22.780)
Body mass index, mean (SD), kg/m^2	31.42 (5.623)
Blood pressure, mean (SD), mm Hg	
Systolic	129.8 (12.49)
Diastolic	78.8 (10.89)
UPCR, median (IQR), g/g	1.446 (1.063-2.400)
UACR, median (IQR), g/g	0.845 (0.524-1.260)
eGFR, mean (SD), mL/min/1.73 m^2	54.8 (20.60)
Blood glucose, mean (SD), mmol/L	6.09 (1.504)
Hematuria, n (%)	10 (50)

eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

FR-PO850

Cardiorenal Outcomes in Patients with IgAN: The FinnGen Study

Tomas J. Visser,[1] Laura Pyle,[2] Phoom Narongkiatikhun,[8] Ye Ji Choi,[10] David Cherney,[4] Rodosthenis S. Rodosthenous,[9] Krzysztof Kiryluk,[5] Petter Bjornstad,[3] Teemu Niiranen,[6] Patrik Finne,[7] Daniel Gordin.[7,11] FinnGen. *[1]Helsingin Yliopisto Laaketieteellinen Tiedekunta, Helsinki, Finland; [2]University of Colorado Anschutz Medical Campus, Aurora, CO; [3]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [4]Toronto General Hospital, Toronto, ON, Canada; [5]Columbia University, New York, NY; [6]Turun Yliopisto Laaketieteellinen Tiedekunta, Turku, Finland; [7]Helsingin Seudun Yliopistollinen Keskussairaala, Helsinki, Finland; [8]Chiang Mai University, Chiang Mai, Thailand; [9]Helsingin Yliopisto Suomen Molekyylilaaketieteen Instituutti, Helsinki, Finland; [10]University of Colorado Anschutz Medical Campus, Aurora, CO; [11]Minerva Foundation Institute for Medical Research, Helsinki, Finland.*

Background: Long-term cardiorenal outcomes of Immunoglobulin A Nephropathy (IgAN) are incompletely understood. We assessed kidney function and cardiorenal events in patients with IgAN in the FinnGen study, which covers approximately 10% of the Finnish population (N=520210).

Methods: Patients with IgAN were identified using Finnish ICD10 diagnosis codes. The outcomes of interest were annual estimated glomerular filtration rate (eGFR) decline, start of kidney replacement therapy (KRT), and major adverse cardiovascular events (MACE). Out of 889 patients with IgAN, 265 were selected based on available data for eGFR. We compared outcomes in patients with IgAN (cases) vs. those with diabetes (controls), being the most common group requiring KRT in Finland. Cases (n=265) and controls (n=1060) were matched by eGFR, age, sex, and birth year (ratio 1:4). Multivariable-adjusted Cox regression and mixed-effects models were used to compare the groups.

Results: Annual eGFR decline was more rapid in patients with IgAN (-2.26; 95% Confidence Interval [95% CI] -2.33, -2.18 ml/min/1.73 m^2 per year) compared to those with diabetes (-1.28; 95% CI -1.43, -1.12 ml/min/1.73 m^2 per year). The cumulative incidence of KRT and MACE in patiens with IgAN and diabetes is shown in Figure 1. The risk for KRT was higher in individuals with IgAN compared to those with diabetes (Hazard Ratio [HR] 4.63; 95% CI 3.49, 6.16). However, the risk for MACE was lower in patients with IgAN (HR 0.61; 95% CI 0.47, 0.88) compared to patients with diabetes.

Conclusions: In this large register study, we demonstrated that patients with IgAN had a faster decline in eGFR and greater risk for KRT compared to patients with diabetes. In contrast, risk for MACE was lower in IgAN compared to diabetes in long-term follow-up.

Funding: Private Foundation Support

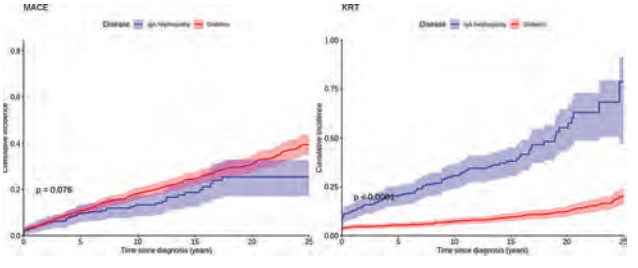


Figure 1: Cumulative incidence of major adverse cardiovascular events (MACE) and kidney replacement therapy (KRT) from diagnosis in patients with IgA nephropathy and diabetes.

FR-PO851

Concomitant Sparsentan (SPAR) and SGLT2 Inhibitors in Patients with IgA Nephropathy in the PROTECT Open-Label Extension (OLE)

Laura Kooienga,[1] Robert Malecki,[2] Priscila Preciado,[3] Heeral Nandola,[3] Alex Mercer.[4] On behalf of the DUPRO Steering Committee and PROTECT Investigators. *[1]Colorado Kidney Care, Denver, CO; [2]Nephrology Department of MSS in Warsaw, Warsaw, Poland; [3]Travere Therapeutics, Inc., San Diego, CA; [4]JAMCO Pharma Consulting, Stockholm, Sweden.*

Background: SPAR, a nonimmunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA), demonstrated superior efficacy for proteinuria reduction and better preservation of kidney function vs irbesartan in pts with IgAN in the PROTECT trial. SPAR combined with an SGLT2i may offer additive kidney protection. We report data from pts who were prescribed an SGLT2i added to ongoing SPAR treatment in the PROTECT OLE.

Methods: Pts who completed the PROTECT double-blind period and met eligibility criteria were enrolled in the PROTECT OLE. All pts received SPAR (target dose, 400 mg/d). Concomitant SGLT2i treatment could be initiated at any time during the OLE at investigator discretion. Pts were excluded from this analysis if they participated in the

randomized controlled OLE SGLT2i substudy. Body weight, systolic and diastolic blood pressure, and urine protein-to-creatinine ratio (UPCR; based on 24-h urine sample) were evaluated at baseline (defined as the OLE visit closest to SGLT2i start) and at weeks 12, 24, 36, and 48 after baseline. Treatment-emergent adverse events (TEAEs) were examined.

Results: At data cutoff, 62 pts (mean [SD] age, 46 [11.3] y; female, n=16 [26%]) had received SPAR and add-on SGLT2i in the OLE. Median (IQR) time from OLE start to SGLT2i start was 273 (148.0-429.0) days. Summary data for body weight, blood pressure, and proteinuria over the 48 weeks are presented in the **Table.** Body weight and blood pressure remained relatively stable. Forty-one (66%) pts had TEAEs; the most common were COVID-19, hyperkalemia, hypertension, and hypotension.

Conclusions: These data show that an SGLT2i added to a stable dose of SPAR is generally well tolerated and may lead to further reductions in proteinuria. The safety and efficacy of sparsentan with or without concomitant SGLT2i treatment are also being investigated in a separate randomized substudy within the PROTECT OLE.

Funding: Commercial Support - Travere Therapeutics, Inc.

Summary Data for Clinical Variables at Each Time Point During the PROTECT OLE for Pts Who Received SGLT2i Added to SPAR

	Pre-SGLT2i treatment baseline*	Week 12 (n=49)	Week 24 (n=42)	Week 36 (n=34)	Week 48 (n=26)
Body weight, mean (SD), kg	88.9 (29.37)†	87.9 (29.93)	84.1 (21.46)	84.4 (22.61)	88.2 (37.97)
Systolic blood pressure, mean (SD), mm Hg	127.3 (12.04)‡	124.7 (13.10)	123.6 (15.46)	125.8 (13.03)	120.5 (15.55)
Diastolic blood pressure, mean (SD), mm Hg	81.6 (9.23)‡	80.6 (8.33)	79.5 (9.15)	80.7 (8.56)	77.3 (9.98)
UPCR, median (IQR), g/g	1.35 (0.82-2.48)§	1.16 (0.62-2.05)‖	1.51 (0.55-2.45)¶	1.08 (0.66-2.80)#	1.17 (0.61-2.82)**

OLE, open-label extension; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
*Baseline was defined as the OLE visit closest to the start of SGLT2i medication. †n=39. ‡n=60. §n=62. ‖n=41. ¶n=35. #n=31. **n=25.

FR-PO852

First Real-World Evidence of Sparsentan Efficacy in Patients with IgA Nephropathy Treated with SGLT2 Inhibitors

Moritz Schanz, Severin Schricker, Andrea Schwab, Joerg Latus. *Robert-Bosch-Krankenhaus GmbH, Stuttgart, Germany*.

Background: Following the publication of the PROTECT trial, sparsentan, a dual-acting antagonist for both the angiotensin II receptor type 1 and the endothelin receptor type A, has emerged as a promising therapeutic agent for the treatment of IgA nephropathy and is currently under review for approval in Europe. However, real-world evidence, particularly on the additive antiproteinuric effect under SGLT2 inhibitors, which were an exclusion criterion in the double-blind period of the PROTECT trial, is lacking.

Methods: We started treating n=7 patients with sparsentan with IgA nephropathy from December 2023 through the Managed Access Program prior to official launch. Patients were stable under maximum tolerated RAAS and SGLT2 inhibitor therapy with an eGFR >30 ml/min/1.73 m2 and a urine protein-creatinine ratio (UPCR) >0.75 g/gCreatinine. All patients provided their informed written consent. Statistical analysis was conducted using the Wilcoxon matched-pairs signed rank test.

Results: Of the seven patients, the median (IQR) baseline eGFR (CKD-EPI) was 35 mL/min/1.73 m² (29-69) and the median (IQR) baseline UPCR was 1.79 g/g (0.94-3.84). The median blood pressure before initiating sparsentan was 130/80 mmHg. After initiating sparsentan, the UPCR significantly decreased (p=0.016) to a median of 0.86 g/g (IQR: 0.63-2.12) in the 2-week follow-up and further significantly declined (p=0.031) to a median of 0.67 g/g (0.43-1.07) after 6 weeks, corresponding to a relative reduction of proteinuria greater than 60%. A similar significant reduction was observed for the urine albumin-creatinine ratio (UACR). No serious adverse events were reported.

Conclusions: In a real-world setting, sparsentan demonstrates a significant effect on proteinuria and albuminuria as early as 2 weeks after initiation, resulting in a relative reduction of UPCR greater than 60% after 6 weeks, even in patients already being treated with SGLT2 inhibitors and steroids.

FR-PO853

Safety and Efficacy of Iptacopan in Patients with IgA Nephropathy with Baseline eGFR 20 to <30 mL/min: Phase 3 APPLAUSE-IgAN Subcohort Results

Dana V. Rizk,[1] Dmitrij Kollins,[2] Olympia Papachristofi,[2] Thomas Hach,[2] Severina Jacinto-Sanders,[2] Tobias Merkel,[2] Robert L. Schmouder,[3] Kenneth M. Kulmatycki,[4] Ronny W. Renfurm,[2] Vlado Perkovic.[5]
[1]University of Alabama at Birmingham, Birmingham, AL; [2]Novartis Pharma AG, Basel, Switzerland; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [4]Novartis Institutes for Biomedical Research, Cambridge, MA; [5]University of New South Wales, Sydney, NSW, Australia.

Background: Treatment of patients (pts) with advanced IgAN and estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m² is limited to supportive care. Iptacopan specifically binds Factor B and inhibits the alternative complement pathway (AP), which is involved in IgAN pathogenesis. We present results from the APPLAUSE-IgAN subcohort with baseline eGFR 20-<30 mL/min/1.73 m².

Methods: APPLAUSE-IgAN (NCT04578834), a Phase 3, randomized, double-blind, placebo (pbo)-controlled trial, enrolled adults with biopsy-confirmed IgAN with proteinuria ≥1 g/g despite stable supportive therapy. Pts were randomized 1:1 to iptacopan 200 mg or pbo twice daily for 24 months while remaining on supportive therapy. Safety, efficacy, and pharmacokinetics (PK) of the low baseline eGFR subcohort were descriptively assessed at Month (M) 9 at time of interim analysis (IA).

Results: The analysis included 27 pts (13 iptacopan, 14 pbo) randomized to the low eGFR cohort at time of IA. Baseline demographic and disease characteristics were similar for iptacopan vs pbo: median (IQR) 24h urine protein-creatinine ratio (UPCR) 2.1 (1.7-2.5) vs 1.8 (1.4-2.4) g/g; mean (SD) eGFR 24.7 (2.8) vs 25.8 (2.9) mL/min/1.73m². All pts received maximally approved/tolerated RASi doses. Serious adverse events (AEs) occurred in 2 pts in each arm and AEs leading to treatment discontinuation in 1 pt in each arm. The most frequent AE was COVID-19 (23.1% iptacopan, 35.7% pbo). Proteinuria (24h-UPCR and 24h urine albumin-creatinine ratio) decreased from baseline to M9 in the iptacopan arm but increased in the pbo arm (**Table**). At M9, the relative reduction in median 24h-UPCR was 34.5% for iptacopan vs pbo, consistent with the primary analysis. PK data will be presented.

Conclusions: In pts with baseline eGFR 20-<30 mL/min/1.73m², iptacopan was well tolerated with a favorable safety profile, and decreased proteinuria vs pbo (34.5% at M9). Iptacopan may therefore represent a potential treatment option for pts with low eGFR.

Funding: Commercial Support - Novartis Pharma AG

Table. Descriptive statistics of proteinuria outcomes in the low eGFR population

Proteinuria measure	Unit	Iptacopan (n=11)*		Placebo (n=10)*	
		Baseline	Month 9	Baseline	Month 9
24h-UPCR (g/g)	Median (IQR)	2.07 (1.68, 2.54)	1.49 (1.16, 2.24)	1.78 (1.40, 2.17)	2.06 (1.39, 3.38)
	Median (IQR) % reduction	-	28 (-3, 35)	-	-10 (-56, 19)
24h-UACR (g/g)	Median (IQR)	1.66 (1.26, 2.08)	1.17 (0.90, 1.80)	1.57 (1.09, 1.80)	1.71 (1.05, 2.50)
	Median (IQR) % reduction	-	27 (-3, 45)	-	-8 (-46, 26)

*Patients with available measurements at baseline and Month 9. 24h-UACR, urine albumin–creatinine ratio from 24h collection; 24h-UPCR, urine protein–creatinine ratio from 24h collection; IQR, interquartile range.

FR-PO854

Results from Longer Follow-Up with Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in IgA Nephropathy (RUBY-3 Study)

Arvind Madan,[1] Rajesh Yalavarthy,[2] Dong Ki Kim,[3] Ju young Moon,[4] Inwhee Park,[5] Sreedhar A. Mandayam,[6] Frank B. Cortazar,[7] Sung Gyun Kim,[8] Rupert H. Davies,[9] Amanda M. Enstrom,[9] Heather Thomas,[9] Jiahua Li,[9] Stanford L. Peng,[9] James A. Tumlin.[10,11]
[1]Central Florida Kidney Specialists, Orlando, FL; [2]Western Nephrology, Arvada, CO; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [5]Ajou University School of Medicine, Suwon-si, Republic of Korea; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]New York Nephrology Vasculitis and Glomerular Center, Albany, NY; [8]Hallym University Sacred Heart Hospital, Anyang-si, Republic of Korea; [9]Alpine Immune Sciences, Inc., Seattle, WA; [10]NephroNet Clinical Trials Consortium, Atlanta, GA; [11]Emory University School of Medicine, Atlanta, GA.

Background: BAFF and/or APRIL inhibition has shown promise in IgAN, lupus, LN, and pMN, with the potential to exert a disease-modifying effect. Povetacicept (ALPN-303) is an Fc fusion protein of a variant TACI domain engineered for more potent dual BAFF/APRIL inhibition vs WT TACI or anti-BAFF/-APRIL Abs. In healthy volunteers, povetacicept mediated on-target reductions in Ab-secreting cells and levels of Ig, including the IgAN-specific biomarker Gd-IgA1. Earlier results from the ongoing RUBY-3 study of povetacicept (NCT05732402) showed good tolerability and promising improvements in IgAN disease activity, including UPCR reductions and stable renal function, accompanied by Gd-IgA1 reductions (Tumlin J, et al. Poster MON-304 presented at WCN 2024).

Methods: RUBY-3 is an open-label, multiple ascending dose, ph 1b/2a study of povetacicept 80 or 240 mg SC Q4W for 24 wk, followed by a 28-wk extension; participants (pts) meeting prespecified criteria at 48 wk may enter an optional 52-wk extension. Eligible pts are aged ≥18 y with IgAN, pMN, LN, or ANCA-associated vasculitis (biopsy-confirmed diagnosis required for IgAN, pMN, and LN). Pts must be on maximally tolerated ACEi/ARB therapy, with well-controlled BP, and disease-specific immunosuppressive therapy where applicable. Primary objective: safety; secondary objectives: PK, PD, immunogenicity, biomarkers, efficacy.

Results: As of 1 Mar 2024, 41 pts with IgAN have enrolled, with 12 and 29, respectively, at the povetacicept dose levels of 80 and 240 mg SC Q4W. Povetacicept was well tolerated at both dose levels. At 9 mo (n=6), a 64% reduction in UPCR and 69% reduction in Gd-IgA1 were achieved with povetacicept 80 mg; 67% of pts achieved remission, all pts with hematuria at BL had hematuria resolution, and stable renal function was observed. At the time of presentation, ≥20 pts are expected to have completed 36 wk across both dose levels and updated findings will be reported.

Conclusions: Experience with povetacicept to date strongly supports its further development in glomerulonephritis and particularly in IgAN, for which a pivotal trial (RAINIER) is in preparation and planned for initiation later this year.

Funding: Commercial Support - Alpine Immune Sciences, Inc.

FR-PO855

AFFINITY Study: 1-Year Results of Atrasentan in IgA Nephropathy

Jonathan Barratt,[1] Sung Gyun Kim,[2] Lesley A. Inker,[3] David K. Packham,[4] Dwarakanathan Ranganathan,[5] Michelle N. Rheault,[6] Mark Vishnepolsky,[7] Yasmin G. Brahmbhatt,[8] Yi Wang,[9] Valeria Beckett,[8] Seung Hyeok Han.[10]
[1]University of Leicester, Leicester, United Kingdom; [2]Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea; [3]Tufts Medical Center, Boston, MA; [4]Melbourne Renal Research Group, Reservoir, VIC, Australia; [5]Royal Brisbane and Women's Hospital, Herston, QLD, Australia; [6]University of Minnesota Twin Cities Division of Pediatric Nephrology, Minneapolis, MN; [7]Kidney Specialists of Southern Nevada, Las Vegas, NV; [8]Chinook Therapeutics Inc, A Novartis Company, Seattle, WA; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [10]Severance Hospital, Seodaemun-gu, Seoul, Republic of Korea.

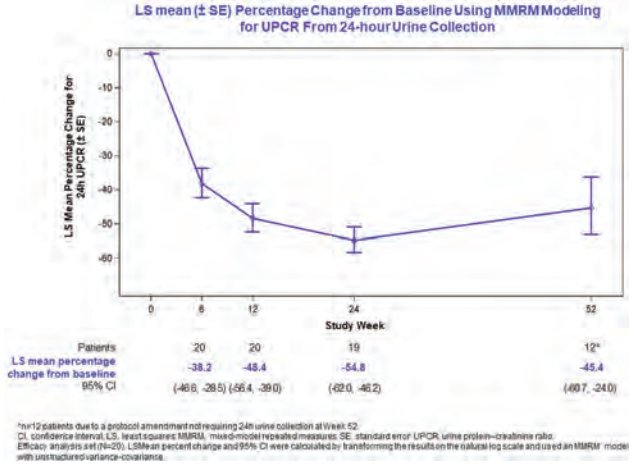
Background: Endothelin A (ET_A) receptor activation drives kidney dysregulation in glomerular diseases (GD). Atrasentan, a potent, selective ET_A receptor antagonist, has been shown to reduce proteinuria and may preserve kidney function in patients (pts) with IgAN and other GD. AFFINITY is a Phase 2, open-label basket study evaluating the efficacy and safety of atrasentan in pts with GD. We present results from the IgAN cohort through 1 year (52 wks) of treatment.

Methods: The IgAN cohort included adults with biopsy-proven IgAN; eGFR ≥30 mL/min/1.73m^2, UPCR ≥0.5 g/g and <1.0 g/g (first morning void), and on max. tolerated/stable RASi for ≥12 wks. Pts took 0.75 mg oral atrasentan daily for 52 wks. The primary endpoint was change in 24h UPCR from baseline (BL) to Wk 12.

Results: The IgAN cohort enrolled 20 pts (median age 44.5 y, 50% women, 45% White, 45% Asian); 19 pts completed 52 wks of treatment. BL median 24h total urine protein was 1.2 g/d, 24h UPCR was 0.8 g/g, eGFR was 46 mL/min/1.73m^2, and systolic/diastolic blood pressure (BP) was 128/82 mmHg. Reduction in 24h UPCR was evident by Wk 6 (LS mean % change from BL -38.2% [95% CI: -46.6, -28.5]), and sustained through Wk 12 (-48.4% [-56.4, -39.0]) to Wk 52 (-45.4% [-60.7, -24.0]; Fig). Atrasentan was well tolerated with no treatment-related serious adverse events (AEs) or deaths. AEs were seen in 18 pts; one pt discontinued treatment at Wk 13 due to an AE of headache considered treatment related. There was no evidence of significant fluid retention (no clinically meaningful mean changes from BL in body weight, brain natriuretic peptide, or BP).

Conclusions: Atrasentan, in addition to standard of care, was well tolerated and resulted in a clinically meaningful, stable reduction in proteinuria over 1 year of treatment, supporting its therapeutic potential in IgAN. The ongoing global Phase 3 ALIGN study (NCT04573478) is evaluating the effect of atrasentan on proteinuria and kidney function in pts with IgAN.

Funding: Commercial Support - Chinook Therapeutics Inc, A Novartis Company



FR-PO856

A Phase 1/2 Trial of Zigakibart in IgA Nephropathy

Jonathan Barratt,[1] Biruh Workeneh,[2] Sung Gyun Kim,[3] Eun Young Lee,[4] Chun Lam,[5] Erin L. Filbert,[6] Bess Sorensen,[6] Yuanbo Song,[5] Zeeshan Khawaja,[6] Laura Kooienga.[7]
[1]University of Leicester, Leicester, United Kingdom; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea; [4]Soonchunhyang University Cheonan Hospital, Cheonan, Republic of Korea; [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [6]Chinook Therapeutics Inc, A Novartis Company, Seattle, WA; [7]Colorado Kidney Care, Denver, CO.

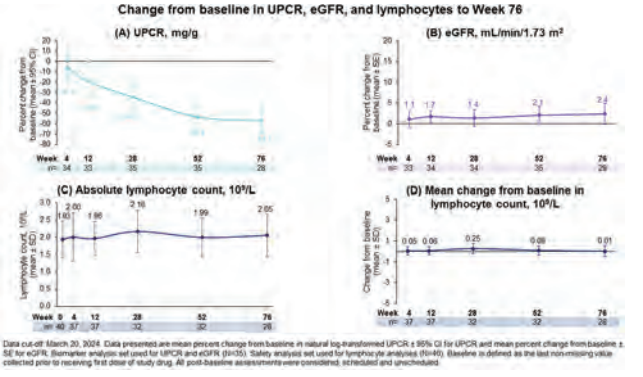
Background: IgAN is the leading cause of primary glomerulonephritis with limited treatment options. Zigakibart is a novel investigational, humanized monoclonal antibody that blocks A PRoliferation-Inducing Ligand (APRIL), a cytokine elevated in patients with IgAN, which promotes pathogenic galactose-deficient IgA1 production, leading to inflammation and kidney injury.

Methods: ADU-CL-19 is an ongoing Phase 1/2 trial (NCT03945318) of zigakibart. Part 3 enrolled patients ≥18 years with biopsy-proven IgAN, total urine protein ≥0.5 g/24h or UPCR ≥0.5 g/g, eGFR ≥30 mL/min per 1.73 m^2, and on stable/optimized dose of RASi for ≥3 months prior to screening (or RASi intolerant). Patients received zigakibart 450 mg Q2W IV, transitioning to 600 mg Q2W SC at ≥24 weeks (Cohort 1) or 600 mg Q2W SC (Cohort 2) for up to 124 weeks. Key objectives include safety, tolerability, immunogenicity, pharmacodynamic effects, and preliminary effects on proteinuria and eGFR.

Results: Overall, 40 patients were enrolled (n=10 [Cohort 1], n=30 [Cohort 2]); median age 38.5 years; 70% male; 60% White and 33% Asian. Zigakibart was well-tolerated with no adverse events (AEs) leading to study drug discontinuation or deaths. AEs were observed in 34 (85%) patients, most commonly infections (78%) of Grade 1 or 2 in severity; one patient experienced Grade 3 infections. One patient experienced infections deemed treatment related. IgA and IgM levels were reduced by 71% and 79% from baseline, respectively, through Week 76, while reduction in IgG was mild to modest (35%). At Week 76, proteinuria, measured as UPCR from a 24h collection, was reduced by 57% from baseline, and eGFR remained stable (Fig. 1A, 1B). Circulating lymphocyte counts remained stable through the study (Fig. 1C, 1D).

Conclusions: Zigakibart was well tolerated and led to sustained, clinically meaningful reductions in proteinuria and eGFR stabilization in patients. The global Phase 3 BEYOND study (NCT05852938) is also evaluating the efficacy and safety of zigakibart in adults with IgAN.

Funding: Commercial Support - Chinook Therapeutics Inc, A Novartis Company



FR-PO857

Safety, Tolerability, and Efficacy of Mezagitamab (TAK-079) as Add-On to Standard of Care Therapy in Individuals with Primary IgA Nephropathy: Interim Results from an Open-Label Phase 1b Study

Jonathan Barratt,[1] Yusuke Suzuki,[2] Van Anh Nguyen,[3] Iwona Dobler,[3] Cheryl Li,[3] MK Farmer.[3]
[1]Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; [2]Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan; [3]Takeda Development Center Americas Inc, Cambridge, MA.

Background: IgA nephropathy (IgAN) is the most prevalent form of primary glomerulonephritis worldwide and is associated with a poor prognosis including progression to end-stage kidney disease or death in some cases. Therapeutic options for IgAN are limited. Mezagitamab, a fully human anti-CD38 IgG1 monoclonal antibody, depletes plasma cells, plasmablasts, and natural killer cells expressing CD38. Mezagitamab depletes cells that produce galactose-deficient IgA1 (Gd-IgA1) and autoantibodies, which results in decreased immune complex formation, potentially reducing proteinuria/promoting stabilization of kidney function over time.

Methods: This open-label, single-arm, phase 1b, multicenter study (NCT05174221), evaluated mezagitamab as an add-on to standard of care therapy (ACEi, ARB) in IgAN. Eligible participants had biopsy-proven disease/proteinuria by urine protein to creatinine ratio (UPCR) ≥1 mg/mg or urine protein excretion (UPE) ≥1 g/24 hours, despite optimized renin-angiotensin-aldosterone system therapy. Participants received subcutaneous mezagitamab 600 mg once weekly for 8 weeks, then 600 mg every 2 weeks for 16 weeks (16 total doses). Primary endpoint was percentage of participants with treatment emergent adverse events (TEAEs). Secondary and exploratory endpoints included serum IgA and Gd-IgA1 levels, percentage change from baseline in UPCR, and change from baseline in eGFR. Results are from a prespecified interim analysis.

Results: Seventeen participants enrolled (mean age 40.8 years, 53% female, 71% Asian). No serious TEAEs, discontinuations due to TEAEs, grade ≥3 infectious TEAEs, or opportunistic infections were reported. Most common TEAEs were upper respiratory tract infection (35.3%), pyrexia (23.5%), and oropharyngeal pain (23.5%). There were rapid and sustained reductions from baseline levels in serum IgA (nadir −70.1%) and Gd-IgA1 (nadir −62.2%). At Week 36, a 54.9% mean reduction in proteinuria (UPCR) was observed. Renal function (eGFR) remained stable though Week 36.

Conclusions: Mezagitamab was generally well tolerated as an add-on to standard of care therapy. Rapid and sustained reductions in UPCR, serum IgA, and Gd-IgA1 levels were seen with stable eGFR.

Funding: Commercial Support - Takeda Pharmaceutical Company Limited

FR-PO858

Concordance of Proteinuria Thresholds between Chinese and UK Cohorts with IgA Nephropathy

Jonathan Barratt,[1,2] David Pitcher,[6] Ceri Hirst,[3] Daniel P. Gale.[4,5] *[1]University of Leicester, Leicester, United Kingdom; [2]Leicester General Hospital, Leicester, United Kingdom; [3]Novartis Pharmaceuticals UK Ltd, London, United Kingdom; [4]Royal Free Hospital, London, United Kingdom; [5]University College London, London, United Kingdom; [6]UK Kidney Association, Bristol, United Kingdom.*

Background: IgA nephropathy (IgAN) is a heterogenous disease with various clinical manifestations, including proteinuria. Proteinuria is a surrogate endpoint for predicting long-term outcomes in IgAN, with KDIGO guidelines identifying proteinuria <1 g/day as a therapeutic target. However, a recent study in China suggests a lower threshold of <0.3 g/day (approximately 26 mg/mmol), with patients below this level having a reduced risk of reaching 50% estimated glomerular filtration rate (eGFR) reduction or end-stage kidney disease (Tang et al. 2024; https://doi.org/10.1053/j.ajkd.2023.12.016). Here, we used the UK RaDaR registry, one of the largest and most comprehensive population-based datasets for patients with IgAN, to evaluate and compare the population differences of IgAN patients in the RaDaR UK and Chinese cohorts. Additionally, we evaluated the concordance of proteinuria findings between these two populations.

Methods: We analyzed a population of 3493 adults with biopsy proven IgAN enrolled on the RaDaR registry up to September 2022 and compared population characteristics and proteinuria findings to the Chinese cohort.

Results: Compared to the Chinese cohort, patients on the UK registry were more likely to be male (70.5% vs 51.4%) and were on average older (42.8 ± 14.4 years vs 36.5 ± 12.0 years). RaDaR patients had a higher stage of chronic kidney disease (69.2% Stage 3+ vs 30.8%), and eGFR was lower (47.8 ± 31.0 vs 78.43 ± 30.45 mL/min/1.73 m^2). During follow-up, 2040 (58%) of UK registry patients progressed to kidney failure with a median survival time of 8 (7.5-8.7) years. Survival time was directly correlated with proteinuria, with a notably lower median survival time in patients with proteinuria ≥100 mg/mmol (HR 3.072 (95% CI 2.32-4.06). The median survival for patients with proteinuria <50, 50-99, 100-199, 200-299 and >300 mg/mmol was 10.4 (7.3-NE), 9.7 (7.6-NE), 5.8 (4.3-7.7), 3.3 (2.1-4.8) and 1.4 (0.9-1.9) years, respectively.

Conclusions: While there are population differences between patients with IgAN across cohorts, patients with specific characteristics have a consistently poorer prognosis. Proteinuria levels indicate that risk of kidney failure persists even in patients below the recommended threshold. Therefore, a lower threshold for treatment goals warrants consideration.

Funding: Commercial Support - Novartis Pharma AG, Basel, Switzerland

FR-PO859

Impact of Nefecon on Complement Pathways in IgA Nephropathy: An Analysis of Lectin, Alternative, and Terminal Pathways

Nadia Nawaz, Roisin C. Thomas, Jonathan Barratt. *University of Leicester College of Life Sciences, Leicester, United Kingdom.*

Background: Complement system activation is increasingly recognized as a critical factor mediating glomerular damage in immunoglobulin A (IgA) nephropathy (IgAN), and can be a predictor of poor outcomes. Nefecon, a targeted-release formulation of budesonide for the treatment of IgAN, targets the gut-associated lymphoid tissue of the distal ileum. In the Phase 3 NefIgArd trial, 9 months of Nefecon 16 mg/day treatment significantly reduced proteinuria and slowed kidney function decline compared with placebo. In the Phase 2b NEFIGAN trial, biomarker analyses supported a role for Nefecon in modulating complement activation in IgAN. In this analysis, we investigated the effects of Nefecon on complement pathways in the NefIgArd trial.

Methods: Patients with IgAN received Nefecon 16 mg/day or placebo for 9 months on top of supportive care, followed by a 15-month observational period off study drug. Commercially available enzyme-linked immunosorbent assays were used to measure serum levels of mannan-binding lectin serine protease 2 (MASP2; lectin pathway), Factor B (alternative pathway) and complement 5 (C5; terminal pathway) at 3, 6, 9, 12, and 18 months (Nefecon group, n=110; placebo group, n=113). Unpaired t-tests were used to compare groups at each timepoint (significance threshold of $p<0.05$).

Results: Nefecon 16 mg/day treatment for 9 months resulted in a significant and sustained reduction in serum levels of factor B (3 months, $p<0.0001$; 6 months, $p<0.0001$; 9 months $p<0.0001$; 18 months $p=0.04$) vs placebo. By contrast, Nefecon treatment did not change serum levels of MASP2 or C5 at any timepoint.

Conclusions: The effect of Nefecon on complement pathways was analysed by examining representative proteins of the lectin, alternative, and terminal pathways. Nefecon specifically and significantly reduced serum levels of the alternative pathway protein, Factor B. This effect is likely to impact positively on reducing glomerular inflammation and provides additional support for the kidney-protective action of Nefecon in IgAN. This effect was specific for Factor B, as no significant effect was observed on critical lectin and terminal pathway proteins. We are currently investigating the mechanisms responsible for this specific modulation of the alternative pathway, which may obviate the need for additional complement inhibition for the treatment of IgAN.

Funding: Commercial Support - Calliditas Therapeutics AB

FR-PO860

Studying IgA Nephropathy at a Population Level over a 21-Year Period

Sinead Stoneman,[1] Jialin Han,[1] Jonathan Barratt,[2] Mohammad Atiquzzaman,[1] Sean Barbour.[1,3] *[1]Division of Nephrology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada; [2]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [3]BC Provincial Renal Agency, Vancouver, BC, Canada.*

Background: Individuals with IgA nephropathy [IgAN] risk progression to end-stage kidney disease [ESKD] and death. Studies in IgAN to date have been mostly single- or multi-center research cohorts with inclusion criteria and selection bias that limits generalizability. Herein we report the methodology used to study outcomes of adult IgAN at the population level in a large Canadian province.

Methods: This is a population-level cohort study of adults ≥18 years with IgAN using the British Columbia [BC] Glomerulonephritis [GN] Registry. All kidney biopsies are processed by nephropathologists in a single center. Any biopsy with GN is automatically registered in the BC GN Registry, which links with healthcare administrative databases to capture comorbidities, laboratory data, treatment and outcomes.

Results: The BC GN Registry successfully captured 1382 individuals with primary IgAN over 21 years from 2000 to 2020. At the time of biopsy, median age was 44.3 years, eGFR was 54.1 ml/min/1.73m^2, and proteinuria was 1.4 g/day (Table 1); 92.4% and 88.1% of patients had available eGFR and proteinuria. During follow-up, there were 19 (IQR 9, 38) and 12 (IQR 4, 25) eGFR and proteinuria measurements per patient, which were measured every 1.2 (IQR 0.4, 3.0) and 2.8 months (IQR 1.1, 4.8) respectively. The 20-year risk of ESKD was 49.4% and of death was 15.6% (Figure 1).

Conclusions: We demonstrate the feasibility of using a provincial biopsy registry linked with administrative databases to study IgAN at the population-level in a large multi-ethnic Canadian province. The structure of the BC GN Registry captures all patients in BC with IgAN without selecting bias. Future steps will be to study treatment patterns, clinical outcomes, and healthcare utilization.

Funding: Commercial Support - Novartis AG

Table 1: Baseline Characteristics	Overall
Total number (N)	1382
Age at biopsy (years; median, IQR)	44.3 (34.3, 56.3)
Male sex (%)	821 (59.4%)
eGFR at biopsy (ml/min/1.73m², median, IQR)	54.1 (31.7, 80.1)
<30 (N/%)	293 (21.2%)
Proteinuria at biopsy (g/day, median, IQR)	1.4 (0.7,2.6)
Duration of follow-up (years, median, IQR)	7.6 (3.0,13.8)
Comorbidities (N/%)	
DM	210 (15.2%)
Dyslipidemia	404 (29.2%)
Hypertension	994 (69.7%)
Smoking	82 (5.7%)
CV disease	234 (16.9%)

Table 1

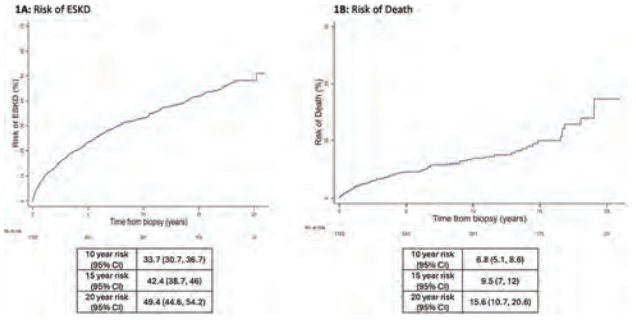


Figure 1

FR-PO861

Baseline Characteristics and Associations of Using SGLT2 Inhibitors in IgA Nephropathy in China: Results from the CPO-IGAN

Chaosheng Chen,[1] Ji Zhang,[1] Gengru Jiang,[2] Rong Wang,[6] Chuanyan Zhao,[3] Qinkai Chen,[11] Min Chen,[10] Hen Xue,[5] Niansong Wang,[4] Qiuling Fan,[12] Guoping Qiu,[7] Hongbo Ma,[8] Lixia Yu.[9] *[1]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [2]Shanghai Jiaotong University School of Medicine Xinhua Hospital, Shanghai, China; [3]Northern Jiangsu People's Hospital, Yangzhou City, China; [4]Shanghai 6th Peoples Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China; [5]Ya'an People's Hospital, Ya'an, China; [6]Shandong Provincial Hospital, Jinan, China; [7]Jiujiang First People's Hospital, Jiujiang, China; [8]Zibo Central Hospital, Zibo, China; [9]Kunshan First People's Hospital, Kunshan, China; [10]Chengdu First People's Hospital, Chengdu, China; [11]First Affiliated Hospital of Nanchang University, Nanchang, China; [12]Shanghai General Hospital, Shanghai, China.*

Background: IgA nephropathy (IgAN) is most common primary glomerular disease in China. The 2024 KDIGO CKD guideline recommends Sodium-glucose co-transporter 2 inhibitors (SGLT2i) as first-line treatment for CKD. SGLT2i use in Chinese IgAN patients is understudied. The Clinical Practice Optimization Initiative for Chinese Patients with IgA Nephropathy (CPO-IGAN) is the first nationwide project with the aim of optimizing clinical practices in IgAN across China.

Methods: As of March, 2024 we recruited 2783 IgAN patients from 33 hospitals across 12 provinces. And for the SGLT2i sub-group, we have extracted and analyzed the data pertaining to IgAN patients administered with SGLT2i.

Results: In total, 2264 Primary IgAN patients were included, 100 of whom had initiated SGLT2i therapy at the baseline: The median age was 42 years, 46% were females and the median (IQR) of eGFR was 88.29 mL/min/1.73 m2 and 24-hour urinary protein was 1269 mg/day (Table 1). The non-SGLT2i group and SGLT2i group, mainly differing in age, the initial treatment post-diagnosis and comorbidity(Table 1). More than half of patients using SGLT2i were concentrated in 2023(51%). A logistic regression analysis indicated that the clinician's selection of SGLT2i was correlated with comorbidity of Type 2 diabetes (OR = 11.82, P < 0.001) (Table 1). Post-follow-up effects of SGLT2i is undergoing.

Conclusions: This study indicates that SGLT2i were used in IgAN patients in China. The association of SGLT2i using with diabetic status suggests that nephrologist may consider SGLT2i more as a diabetes medication than as a treatment for CKD. The critical need for enhancing clinician awareness and education about SGLT2i's benefits for IgAN patients.

Funding: Clinical Revenue Support

Baseline characteristics

Characteristics	Non-SGLT2i group	SGLT2i group	p value
Cases	2,164	100	
Age, years (Median [IQR])	38.00 [29.00, 49.00]	42.00 [35.00, 52.25]	0.002
<25, n (%)	213 (9.9)	6 (6.0)	0.004
25–<35, n (%)	665 (30.8)	17 (17.0)	
35–<45, n (%)	536 (24.8)	36 (36.0)	
≥45, n (%)	747 (34.6)	41 (41.0)	
Sex, n (%)			
Female	1092 (50.5)	46 (46.0)	0.591
Male	1072 (49.5)	54 (54.0)	
Nationality, n (%)			
Han nationality	2107 (97.4)	98 (98.0)	0.24
Others	20 (0.9)	2 (2.0)	
Unknow	37 (1.7)	0 (0.0)	
eGFR, mL/min/1.73m2 (Median [IQR])	87.73 [61.12, 110.98]	88.29 [66.46, 103.32]	0.76
The 24-hour urine protein, mg/day, Mean (SD)	1247.00 [650.00, 2380.00]	1269.00 [700.00, 2810.00]	0.502
UACR, mg/g (Median [IQR])	898.80 [370.12, 1905.09]	1085.03 [393.80, 1807.10]	0.653
Systolic Blood Pressure, mmHg, Mean (SD)	130.43 (34.89)	133.99 (17.74)	0.319
Diastolic Blood Pressure, mmHg, Mean (SD)	82.90 (25.51)	84.69 (12.74)	0.493
Serum uric acid level, μmol/L (Median [IQR])	375.00 [304.00, 448.10]	354.50 [293.25, 464.75]	0.693
Serum potassium, mmol/L (Median [IQR])	4.02 [3.80, 4.27]	3.96 [3.70, 4.26]	0.169
Oxford histologic score, n(%)			
M			0.156
0	766 (35.4)	28 (28.0)	
1	1395 (64.6)	72 (72.00)	
E			0.637
0	1344 (62.1)	65 (65.0)	
1	819 (37.9)	35 (35.00)	
S			0.060
0	501(23.3)	32 (32.0)	
1	1650 (76.7)	68 (68.00)	
T			0.262
0	1320 (61.0)	67 (67.0)	
1	617 (28.5)	21 (21.0)	
2	227 (10.5)	12 (12.0)	
C			0.596
0	1500 (69.8)	66 (66.0)	
1	592 (27.5)	32 (32.0)	
2	57 (2.7)	2 (2.0)	
The initial treatment post-diagnosis , n(%)			
RAASi	1314 (60.7)	75 (75.0)	0.006
Glucocorticoids	818 (37.8)	40 (40.0)	0.735
Immunosuppressive medications	388 (17.9)	25 (25.0)	0.097
Chinese patent medicine	264 (12.2)	26 (26.0)	<0.001
Hydroxychloroquine	827 (38.2)	28 (28.0)	0.051
Comorbidity, n (%)			
Type 2 diabetes	55 (2.5)	26 (26.0)	<0.001
Hypertension	951 (43.9)	53 (53.0)	0.093
Cardiovascular diseases	31 (1.4)	2 (2.0)	0.971
Infectious Diseases	142 (6.6)	7 (7.0)	1

Results of logistic regression analysis

Variable	OR	95% CI	p-value
Age			
<25 (reference)			
25–<35	1.02	[0.39, 3.18]	0.967
35–<45	2.43	[0.99, 7.30]	0.075
≥45	1.54	[0.61, 4.73]	0.399
Male sex	1.11	[0.71, 1.72]	0.648
BMI, kg/m^2	1.01	[0.99, 1.01]	0.31
eGFR, mL/min/1.73m^2	1	[1.00, 1.01]	0.308
The 24-hour urine protein	1	[1.00, 1.00]	0.275
Diabetes, yes	11.82	[6.58, 21.01]	<0.001
Hypertension, yes	0.85	[0.54, 1.34]	0.496

FR-PO862

Disease Burden of IgA Nephropathy (IgAN): A Linguistic Analysis of Global Social Media Conversations over Time: A Comparison of Results, 2019-2023

Dorothee Oberdhan,[1] Sarah N. Ali,[1] Erin Morea,[2] Akansha Batra,[2] Jennifer Dandy.[2] *[1]Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, NJ; [2]Real Chemistry International LLC, New York, NY.*

Background: The treatment landscape for Immunoglobulin A Nephropathy (IgAN) has evolved with the approval of several new therapies for patients requiring a comparative evaluation of a prior and updated ethnographic study to understand changes in patient experiences of disease manifestations, disease impact, and treatment of IgAN as described by patients, caregivers, and healthcare providers (HCPs).

Methods: We compare results from two social listening studies using the same methodology to capture global, public, social media (i.e., X, Reddit, etc.) posts from Period 1: 5/1/2019 – 5/30/2021 and Period 2: 12/1/2022 – 12/31/2023, using technologies such as web crawlers and data partnerships. Sociolinguists analyzed the posts in the native language using qualitative and quantitative methods.

Results: Overall, total social media posts describing the disease experience of individual patients with IgAN from Period 1 to Period 2 increased (1,024 to 1,165) and was comprised of identifiable patients (902, 1,105), caregivers (102, 39), and HCPs (20, 21) respectively. Posts increased from Japan (+106), the United Kingdom (+40), South Korea (+32), Germany (+37), and Canada (+19) and decreased from the United States (-59) and France (-39). Posts about symptoms were similar (229 to 248); treatments increased (627 to 723) and impact decreased (400 to 233). Post characteristics over time are detailed in Table 1 below.

Conclusions: This comparative analysis of real-world social media posts assessed discussion trends of patients with IgAN to better understand their experiences. Social media conversations increased over time and their global distribution, patient characteristics, and content changed. This analysis demonstrates that patient experiences of IgAN are not static; regular updates to detect changes in patient experiences of disease manifestations, disease impact, and treatment of IgAN can help inform future research studies.

Funding: Commercial Support - Otsuka Pharmaceutical Development and Commercialization, Inc.

Table 1: Post Characteristics Over Time from Period 1 to Period 2

Post Characteristic*		Period 1 (%)	Period 2 (%)
Status	Seeking Diagnosis	16	8
	Newly Diagnosed	23	12
	In Treatment	32	77
	Kidney Failure	29	3
Symptoms	Hematuria	34	35
	Proteinuria	42	33
	Fatigue	12	8
	Pain	5	12
	High Blood Pressure	16	7
Impact	Emotional	30	57
	Physical	17	22
	Treatment Burden	24	3
	Caregiver/Relationship	17	2

*Single post could mention more than one characteristic

FR-PO863

Disease Burden of IgA Nephropathy: An Updated Linguistic Analysis of Global Social Media Conversations

Dorothee Oberdhan,[1] Sarah N. Ali,[1] Erin Morea,[2] Akansha Batra,[2] Jennifer Dandy.[2] *[1]Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, NJ; [2]Real Chemistry International LLC, New York, NY.*

Background: New therapies have been approved to treat Immunoglobulin A Nephropathy (IgAN) and a refresh of a prior ethnographic study is needed to understand patient experiences of disease manifestations, disease impact and treatment of IgAN as described by patients, caregivers and healthcare providers (HCPs).

Methods: A social listening methodology captured public social media (e.g., X, Reddit) posts from 12/1/2022-12/31/2023 globally, using technologies such as web crawlers and data partnerships. Sociolinguists analyzed the posts in the native language using qualitative and quantitative methods.

Results: A total of 1,165 posts described the experience of individuals with IgAN from 1,105 identifiable patients, 39 caregivers and 21 HCPs. Countries with the most posts were Japan (66%), the United States (13%), the United Kingdom (7%) and South Korea (4%). In the analysis, a single post could report multiple patient experience characteristics. Disease manifestations were reported in 248 posts (21%); the top described were hematuria (35%), proteinuria (33%) and pain (12%). Treatments were reported in 723 posts (62%); the top described were steroids (62%) and lifestyle management (16%). Impact of disease was reported in 233 posts (20%). Top impacts described were Emotional (e.g., disease progression anxiety, depressive thoughts about their disease and fear about their chronic illness with "no cure") (57%), Physical (e.g., "extreme" fatigue/pain and impact on mobility/sleep) (22%) and Work/School (e.g., ability to function, stigma/pressures to contribute with a chronic illness, concern of symptoms/diagnosis and impact on military status (7%). Approved IgAN therapies were only mentioned in US posts (12%).

Conclusions: This updated analysis of real-world social media posts assessed discussion trends of patient experiences with IgAN and suggested that IgAN's effect on patients may arise more from disease manifestations and treatments. Although patients described heightened anxiety over their kidney function levels, and patients and caregivers highlighted the desire for advanced treatments that protect kidney function, surprisingly, newly approved therapies for IgAN were rarely mentioned. With the advent of newer therapies, this update demonstrates the importance of capturing IgAN patient experiences to inform research.

Funding: Commercial Support - Otsuka Pharmaceutical Development and Commercialization, Inc.

FR-PO864

Dapagliflozin Alters Extracellular Vesicle MicroRNAs in Patients with IgA Nephropathy

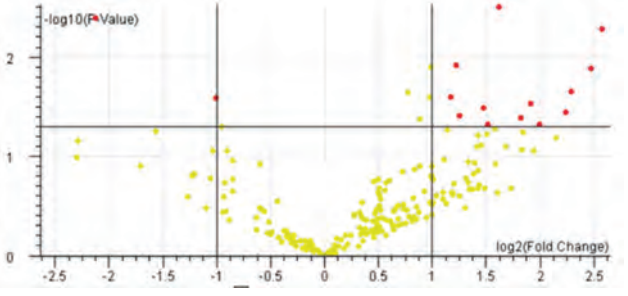
Kootae Park, Soon hyo Kwon. *Soonchunhyang University Hospital, Seoul, Republic of Korea.*

Background: Extracellular vesicle (EV) containing microRNAs (miRNAs) play a crucial role in regulating gene expression in a variety of tissue and contribute to the pathophysiology of various renal disease. Sodium glucose co transporter 2 inhibitors (SGLT2i) has improved renal outcomes in IgA nephropathy (IgAN). This study aims to explore how dapagliflozin affect EVs-miRNAs in IgAN patients.

Methods: We prospectively enrolled 26 biopsy-proven IgAN patients who had not previously been treated with SGLT2i. The participants were received dapagliflozin (10 mg/day). Serum samples were collected both before treatment and after 6 months of dapagliflozin therapy. Using RNA sequencing, we assessed the serum EV-miRNAs profile of all participants.

Results: The cohort predominantly consisted of male (n=15, 64%) with a mean age was 48.6 ± 12.2 years. Dapagliflozin reduced estimated GFR over the study period (73.9 ± 23.7 vs 69.8 ± 21.5 mL/min, p = 0.012). RNA sequencing revealed differential expression of 21 miRNAs in before and after dapagliflozin. Biological pathway analysis of these miRNA indicated that they are likely involved in proteoglycan in cancer and Hippo signaling pathway (Figure 1).

Conclusions: Dapagliflozin alters the EVs-miRNAs expression profile in IgAN patients. These miRNAs may be promising candidates for the predicting prognosis and treatment of IgAN.



FR-PO865

Efficacy and Safety of Telitacicept in IgA Nephropathy: A Real-World Study

Lingqiu Dong, Wei Qin. *West China Hospital of Sichuan University, Chengdu, China.*

Background: IgA nephropathy (IgAN) is the most common primary glomerular disease in the world. Telitacicept is a humanized fusion protein composed of a transmembrane activator and calcium-modulating cyclophilin ligand interactor receptor and human IgG. This study was designed to evaluate the efficacy and safety of telitacicept in patients with IgAN.

Methods: Biopsy-proven IgAN patients with 24-hour proteinuria greater than 0.5 g/day who received telitacicept 240 mg once a week were recruited in this study and 1:1 matched with patients received supportive treatment only or immunosuppressive treatment by propensity score matching. The primary outcome was the change from baseline in 24-hour proteinuria over the 3-month follow-up.

Results: Twenty-one patients in each group were enrolled. The mean eGFR was 80.1 ml/min/1.73m^2, and the median 24-hour urine protein was 1.48 g/day. At the end of the 3-month follow-up, telitacicept reduced median proteinuria by 0.72 g/d (54.6%) from baseline, compared with a reduction of 0.18 g/d (20%) in the supportive treatment group ($P < 0.001$), and 1.12 g/d (72.1%) in the immunosuppressive treatment group ($P = 0.814$). Preserved eGFR levels were observed in the telitacicept group (1.9 ml/min/1.73 m2

[4.3%]), while the eGFR level declined in the supportive treatment group (- 2.9 ml/min/1.73 m^2 [- 5.8%]) and immunosuppression group (- 6.1 ml/min/1.73 m^2 [- 8.4%]). No serious adverse events were observed in the telitacicept treatment group. Injection site reactions were more prevalent in the telitacicept group, meanwhile immunosuppression group had more respiratory tract infections.

Conclusions: Telitacicept can reduce proteinuria in patients with IgAN and showed a favourable safety profile.

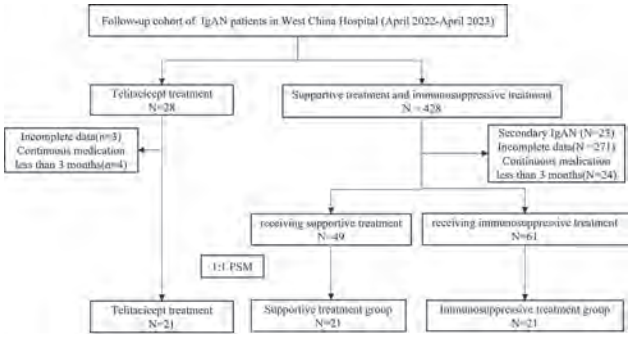


Figure 1. Participant recruitment and exclusion flowchart.

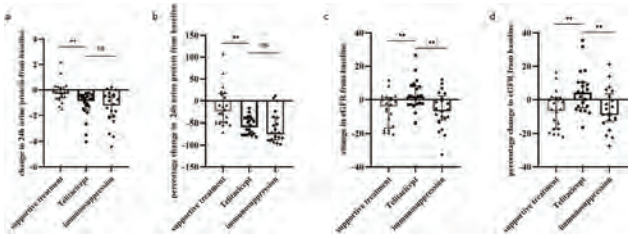


Figure 2. Changes in proteinuria and eGFR levels from baseline.

FR-PO866

Results from a Real-World Case Series of Patients with IgAN Who Received at Least 9 Months of Tarpeyo

Christopher Ngai,[1] Giancarlo Pesce,[2] Sarah Zaidi,[2] Nadia Petiot,[2] Ramin Tolouian,[1] Terri Madison.[1] *[1]Calliditas Therapeutics AB, New York, NY; [2]Certara Inc, Princeton, NJ.*

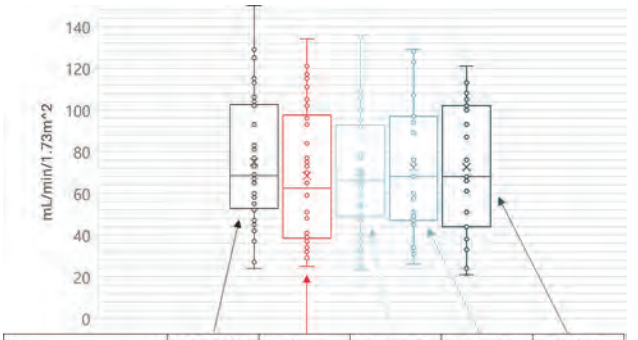
Background: Tarpeyo, a targeted-release formulation of budesonide, is currently the only FDA-approved treatment for IgA nephropathy (IgAN) to significantly reduce the loss of kidney function. This research evaluated safety and effectiveness outcomes in a cohort of Asian-American patients who received ≥ 9 months of Tarpeyo in a real-world setting.

Methods: Patients with IgAN who received Tarpeyo for ≥9 consecutive months at the Chinatown Kidney Care (CKC) practice (NY, USA) before Nov 30 2023 (data abstraction cutoff) were included in this retrospective analysis. Data were abstracted from patient-level electronic medical records.

Results: For the 30 patients meeting eligibility criteria, the mean age was 46 years, 57% were male, and 100% were Asian-American. Patients received Tarpeyo for an average 11.7 months and were followed-up for an average 14.6 months since Tarpeyo initiation. On average, eGFR was 68.4 mL/min/1.73m^2 at Tarpeyo initiation, which was 6.7 mL/min/1.73m^2 lower than when first seen at CKC (annual decrease until Tarpeyo initiation: 0.6 mL/min/1.73m^2). After Tarpeyo initiation, eGFR increased by average 3.6 mL/min/1.73m^2 in 9 months [Figure]. Overall, adverse events (AEs) were observed in 2 patients; both were mild and resolved. In one patient the AE resulted in a dose reduction. Preliminary results for a subgroup of patients treated for > 9 months (n=23, mean Tarpeyo treatment duration=12.5 months) showed continued preservation of kidney function without an increase in incidence of serious AEs.

Conclusions: Results from this case series demonstrated that real-world use of Tarpeyo was well-tolerated and can reduce loss of kidney function in patients who receive ≥9 months of treatment.

Funding: Commercial Support - Calliditas Therapeutics AB



	First eGFR measurement at CKC	Tarpeyo initiation (index)	+3 months after index	+6 months after index	+9 months after index
No. patients with data	30	30	28	23	19
Mean (SD)	75.1 (31.4)	68.4 (32.5)	70.0 (29.7)	72.5 (31.7)	72.6 (31.5)
Median [IQR]	68.5 [53.0;102.0]	62.5 [39.0;96.0]	66.0 [49.5 92.5]	68.0 [47.0;97.0]	68.0 [44.0;102.0]
Mean change vs index (SD)*	6.7 (12.3)	-	1.1 (11.2)	3.2 (7.6)	3.6 (10.6)

*only patients with measurements at both time points

Fig. eGFR distribution in IgAN patients before and after Tarpeyo initiation

FR-PO867

Patient-Reported Outcomes (PROs) Use in IgA Nephropathy (IgAN)

Michelle M. Richardson,[1,2] Sarah N. Ali,[1] Hema K. Gandhi,[1] Dorothee Oberdhan.[1] *[1]Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, NJ; [2]Tufts University School of Medicine, Boston, MA.*

Background: Immunoglobulin A Nephropathy (IgAN) is a progressive disease with high patient-reported burden and disease-related impact. New therapies could alter the course of disease, presenting the need for appropriate measurement of patient-reported outcomes (PROs). PRO requirements include content validity, acceptable measurement properties, information on meaningfulness and most importantly, must be fit for context of use (e.g., screening, diagnosis, likelihood of being impacted by treatment). With the advent of newer therapies, assessing PROs used in IgAN clinical trials is needed to evaluate their applicability for regulatory use.

Methods: We conducted a targeted MEDLINE search for PROs used in IgAN clinical trials from 2021-2024 to update a 2021 systematic review, compiled the PROs used and evaluated individual instrument characteristics: context of use, purpose and meaningful change over time.

Results: 464 articles were identified, 11 remained after title and abstract review and 3 underwent full text review and were included. Of the 7 clinical trials (6 from the previous search, 1 newly identified), 1 was an interventional trial of the effects of exercise on depression symptoms, 1 was an observational longitudinal study, 2 were cross-sectional studies, and 3 were studies of PRO development work. Two studies enrolled only patients with IgAN, the others enrolled <10 IgAN patients each. 19 different PROs were used throughout the included studies: only 1 was specific to kidney disease (Peds QL ESRD module), 5 were generic measures, 14 were disease- or symptom-specific measures (e.g., depression, anxiety, mobility) 11 were for use in adults and 8 in pediatrics. No PRO met context of use or responsiveness criteria.

Conclusions: This review evaluated 19 PROs used in IgAN clinical trials. The only interventional longitudinal trial that was identified tested a life-style intervention and did not report responsiveness. One PRO was kidney-disease specific but was only used in pediatric patients. Currently, published studies of PROs in IgAN clinical trials do not provide sufficient information to support regulatory use and additional evidence is needed. In future research, selecting a high-quality PRO that is integrated with other clinical trial outcomes and most effective for regulatory use requires attention to context of use, purpose and meaningful change.

Funding: Commercial Support - Otsuka Pharmaceutical Development and Commercialization, Inc.

FR-PO868

Patient-Reported Outcomes in the PROTECT Clinical Trial Comparing Sparsentan with Irbesartan for IgA Nephropathy

Shikha Wadhwani,[1] Mark E. Bensink,[2] John D. Peipert,[1] Isabelle Ayoub,[3] Priscila Preciado,[2] Diana Garbinsky,[4] Lee Bennett,[4] Wu Gong,[2] Jula K. Inrig,[2] Radko Komers.[2] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Travere Therapeutics Inc, San Diego, CA; [3]The Ohio State University Wexner Medical Center, Columbus, OH; [4]RTI Health Solutions Research Triangle Park, Research Triangle Park, NC.*

Background: In the phase 3, double-blind PROTECT trial (NCT03762850), sparsentan (SPAR), a dual endothelin and angiotensin II receptor antagonist (DEARA), showed efficacy in reducing proteinuria and preserving renal function compared with a maximally tolerated dose of irbesartan (IRB) in patients with immunoglobulin A nephropathy (IgAN). Safety profiles for the two treatments were similar. This analysis aimed to evaluate the effect of SPAR compared with IRB on patient-reported outcomes (PROs) in patients with IgAN enrolled in PROTECT.

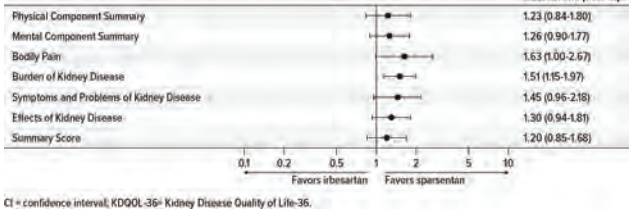
Methods: Adult patients were randomized to receive SPAR or IRB for 110 weeks. The Kidney Disease Quality of Life–36 (KDQOL-36) PRO measure was administered at baseline and at weeks 24, 48, 70, 94, and 110. Changes from baseline in Physical Component Summary, Mental Component Summary, Bodily Pain, and kidney-targeted subscale scores were analyzed using least-squares means from mixed models for repeated measures. A score change of 5 was considered clinically meaningful. Time-to-event endpoints, including first improvement, were analyzed using Cox models.

Results: Baseline KDQOL-36 scores were similar for patients randomized to SPAR and IRB. In general, least-squares mean changes from baseline indicated an improvement in Burden of Kidney Disease (BKD) score (week 110 difference [SPAR – IRB], 5.1; 95% confidence interval [CI], 0.45-9.67; $P < 0.05$]), while other scores were stable through week 110. Hazard ratios for time to first improvement in BKD score (1.51; 95% CI, 1.15-1.97) favored SPAR (Figure A).

Conclusions: For patients with IgAN, analysis of PROs from the PROTECT trial suggests that patients receiving SPAR have less burden of kidney disease over time and a general trend toward improved health-related quality of life compared with those receiving a maximally tolerated dose of IRB.

Funding: Commercial Support - Travere Therapeutics

Figure A. Hazard Ratio Forest Plot for Time to First Improvement in KDQOL-36 Scores



CI = confidence interval; KDQOL-36= Kidney Disease Quality of Life-36.

FR-PO869

Complement and B Cell Modifying Pipeline to Address Unmet Needs in IgA Nephropathy (IgAN)

Justin Snyder, Meghan Weiss. *Spherix Global Insights, Exton, PA.*

Background: Therapeutic developments for IgA nephropathy (IgAN) are at the forefront of innovation, supported by the accelerated approval of two recently apprproducts and a robust pipeline with various mechanisms of action. In upcoming years, new products will likely be available that will further help physicians address IgAN at the pathogenic level.

Methods: Data from 454 audited patient charts were collected in partnership with 142 US nephrologists in January 2024 and in partnership with an additional 105 US nephrologists in February 2024 via online surveys.

Results: With the approvals of delayed-release oral budesonide and sparsentan in IgAN, most nephrologists (80%) indicate that they feel better equipped to treat their IgAN patients. Currently, 72% and 66% of nephrologists are using budesonide or sparsentan, respectively, positioned as third-line or later treatments after RAASi and SGLT2 inhibitors. However, nearly half (46%) remain unconvinced that they can achieve the desired proteinuria goals with only the existing therapies. It is theorized that the Peyer's patches are the main source of the galactose-deficient (Gd) IgA1 antibodies that cause damage and inflammation to the kidneys, yetand almost one-half (4357%) of nephrologists are unconvinced that targeting the Peyer's patch is an important goal in treatment. However, 68% of nephrologists agree that IgAN is a B-cell mediated disease, where the root cause of Gd-IgA1 production comes from overstimulated B-cells and plasma cells. Additionally, 76% believe that the complement system plays an active role in the pathogenicity of IgAN. There are several IgAN pipeline agents that potentially target B-cell and plasma factors. Two products that are in Phase 3 trials include iptacopan, which is a complement factor B inhibitor, and atacicept, which is a B lymphocyte stimulator (BlyS) inhibitor and a proliferation-inducing ligand (APRIL) inhibitor that targets B cells and plasma cells. If approved, nephrologists indicate that they would be at least somewhat likely to prescribe iptacopan or atacicept to approximately one-third of the IgAN patients included in the study.

Conclusions: Nephrologists continue to see an unmet need in the IgAN space, leaving room for new market entrants to effectively treat the root cause of the disease and further enable physicians to individualize treatments.

FR-PO870

Exploring the Impact of Loin Pain in IgA Nephropathy: A United Kingdom-Wide Mixed-Methods Qualitative Study and Pilot Survey

Kristina L. Newman,[1,2] Jonathan Barratt,[1,3] Justyna Szklarzewicz,[1,3] Lydia E. Roberts,[1] Roisin C. Thomas,[1] Alice C. Smith,[1] Zoe E. Plummer,[5] Susan Pywell,[5] Sherry Masoud,[5,6] Daniel P. Gale,[4] David Pitcher,[5] Haresh Selvaskandan.[1,3] Mayer IgAN Group and RaDaR. *[1]University of Leicester, Leicester, United Kingdom; [2]Nottingham Trent University, Nottingham, United Kingdom; [3]Leicester General Hospital, Leicester, United Kingdom; [4]Royal Free London NHS Foundation Trust, London, United Kingdom; [5]UK Kidney Association, Bristol, United Kingdom; [6]University College London, London, United Kingdom.*

Background: Loin pain (LP) is a commonly reported symptom by patients with IgA nephropathy (IgAN). Currently there is little known about the frequency of LP, the impact of LP on quality of life or appropriate strategies to manage LP in IgAN.

Methods: An online pilot survey was developed with input from IgAN patients and the National Registry of Rare Kidney Diseases (RaDaR). The survey recorded demographic, kidney disease, and LP parameters, alongside The Kidney Symptom Score, Short-Form McGill Pain Questionnaire-2, Pain Self-Efficacy Questionnaire, and Brief Illness Perception Questionnaire. A separate semi-structured interview study with patients, carers and healthcare professionals (HCPs) explored experiences of loin pain through thematic analysis.

Results: 366 patient responses were analysed. 261 (71.1%) experienced LP; 28% currently, 33% in the last month, and 39.1% in the past. 70.7% experienced LP at least monthly. 80.5% reported LP as always the same, with 'aching' being the most common descriptor used. LP was associated with a poorer self-perception of mental and physical health, and strongly associated with the presence of systemic symptoms including itching, anorexia, and loss of libido. Only 41.6% could manage their LP with analgesics. 44.7% spoke to HCPs about LP, but 61.7% did not find this helpful. LP affected mobility in 43.9%. 48 interviews were conducted; 21 patients, 14 carers, and 13 HCPs (27% male, 73% female, 70% White British, age range 23-75 years). Five themes were developed in the thematic coding process; 1) 'Achy pain' in the 'kidney area'; 2) Managing LP with limited options; 3) LP as a warning: anxiety of declining kidney function; 4) Impact to daily life dependent on severity; 5) Differing opinions between patients and healthcare professionals.

Conclusions: Loin pain is a common symptom in patients with IgAN, affecting the majority of respondents. It has a negative impact on quality of life and self-perception of physical and mental health. Despite this, options to manage LP in IgAN remain limited, with HCPs having little knowledge or insight into optimal management strategies. Further work is being undertaken to explore these themes in other kidney diseases.

Funding: Commercial Support - Omeros

FR-PO871

Conceptual Model of the Patient Experience of IgAN: A Qualitative Literature Review and Model Update

Sarah Knight,[1] Greg Davis,[1] Tamara Al-zubeidi,[1] Sasikiran Nunna,[2] Hema K. Gandhi,[2] Sarah N. Ali,[2] Michelle M. Richardson,[2,3] Dorothee Oberdhan.[2] *[1]Clarivate Analytics UK Limited, London, United Kingdom; [2]Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, NJ; [3]Tufts University School of Medicine, Boston, MA.*

Background: A robust conceptual model (CM) is an essential foundation to inform clinical outcome assessments (COAs) for patient-centered trials in immunoglobulin A nephropathy (IgAN). This study updated a previous CM of adult and pediatric patient experiences of IgAN including disease manifestations, treatment side-effects and impact on functioning and well-being.

Methods: A targeted review of "A Summary of Survey Results and Call to Action from the IgA Nephropathy Foundation", a 2021 IgAN Disease Burden Global Analysis (internal report) and an updated qualitative literature search was conducted to identify patient-reported concepts to update a previous CM. Semantic, qualitative and directed content analysis techniques, aided by ATLAS.tiv9, were used. Relevant concepts were coded and cross-checked against the previous CM and newly identified codes were flagged and evaluated for inclusion into the update. The domains were refined by grouping related concepts, where applicable.

Results: In addition to the two reports, three new studies were identified from the literature review, one of which was the development paper for the previous CM. A comparison of the previous and updated CM is detailed in Table 1. Data sources did not reveal the most salient/bothersome experiences, and a large portion of the new concepts were not reported by age groups.

Conclusions: This updated CM identified new symptoms and impacts of IgAN in adult and pediatric patients that can be used to inform the selection, development and/or amendment of COAs for future IgAN clinical trials. Patient and clinician input is needed to differentiate symptoms and impacts by age groups and to clarify relationships between concepts and domains.

Funding: Commercial Support - Otsuka Pharmaceutical Development and Commercialization, Inc

Table 1: Comparison of existing to updated CM

Domains	Previous CM	Updated CM
Disease manifestations	Swelling/puffiness (edema); pain/aches/discomfort; fatigue; weight gain; sleep problems; urinary problems; gastrointestinal problems	Edema locations; hematuria and proteinuria; swollen tonsils and respiratory problems; kidney discomfort and back/flank pain; disrupted sleep; vitamin D deficiency and frequent infections
Impact	Emotional/psychological wellbeing; physical functioning/activities of daily living; social functioning; work/school and relationships	Feeling unequipped to manage disease alone; school attendance; family and friend relationships; diagnosis delay; misdiagnosis or lack of clinician familiarity with IgAN, dietary restrictions, dialysis restrictions and length, shock and regret at prolonged diagnosis

FR-PO872

Implications of Proteinuria Remission on Estimated Glomerular Filtration Rate (eGFR) Trajectory in Patients with IgA Nephropathy in the PROTECT Trial

Hiddo J. Heerspink,[1,2] Vladimir Tesar,[3] Radko Komers,[4] Bruce M. Hendry,[4] Priscila Preciado,[4] Edward Murphy,[4] Brad H. Rovin.[5] On behalf of the DUPRO Steering Committee and PROTECT Investigators. *[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, Groningen, Netherlands; [2]The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia; [3]Department of Nephrology, General University Hospital, Charles University, Prague, Czechia; [4]Travere Therapeutics, Inc., San Diego, CA; [5]Division of Nephrology, Ohio State University Wexner Medical Center, Columbus, OH.*

Background: In PROTECT, sparsentan (SPAR) reduced proteinuria and increased the proportion of pts achieving complete proteinuria remission (CR; urine protein excretion [UPE] <0.3 g/d) (31%) vs irbesartan (IRB) (11%). Lower proteinuria and CR are associated with slower kidney function decline in IgAN. To explore this relationship in PROTECT, we determined eGFR trajectories in pts whose proteinuria fell to low levels.

Methods: PROTECT is a randomized, double-blind trial of efficacy and safety of SPAR vs active-control IRB in adults with IgAN at risk of progression to kidney failure despite maximum RASi. In this analysis, 404 randomized pts were pooled and grouped by achievement of CR or UPE <0.5 g/d at any time over 110 wk. Outcomes were absolute (abs) change from baseline (BL) in eGFR at wk 110 and chronic (wk 6 to 110) and total (d 1 to wk 110) eGFR slopes (adjusted for BL UPE).

Results: While BL age, sex, and race were similar in pts achieving low UPE vs those who did not, BL UPE was lower and eGFR higher in the low proteinuria pts (**Table**). The abs decline in eGFR and the loss of eGFR over time were substantially lower in pts with CR or UPE <0.5 g/d vs those who did not achieve these targets.

Conclusions: In IgAN, achievement of low proteinuria is strongly predictive of better long-term kidney function. eGFR preservation was more evident in pts who achieved low proteinuria vs those who did not; notably, in pts who achieved CR, the mean rate of kidney function decline (eGFR chronic slope) was <1.0 mL/min/1.73 m^2/y. As SPAR-treated pts achieved proteinuria remission more frequently vs IRB in PROTECT, this analysis further supports the benefit of SPAR for long-term preservation of kidney function.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table. Baseline Characteristics and eGFR Outcomes by Proteinuria Remission Status*,†

	CR (UPE <0.3 g/d) achieved at any time		UPE <0.5 g/d achieved at any time	
	Yes (n=65)	No (n=319)	Yes (n=151)	No (n=253)
Baseline characteristics				
Age; mean (SD), y	44.3 (13.76)	46.5 (12.04)	45.1 (13.17)	46.5 (11.98)
Sex, male, n (%)	54 (64)	228 (71)	99 (66)	183 (72)
Race, White, n (%)	53 (82)	249 (80)	97 (64)	175 (69)
BL eGFR, mean (SD), mL/min/1.73 m^2	65.1 (26.46)	54.8 (22.76)	60.3 (24.98)	54.9 (23.08)
BL UPCR, median (IQR), g/g	0.92 (0.66-1.17)	1.34 (0.91-1.88)	1.01 (0.67-1.47)	1.36 (0.94-1.92)
BL UPE, median (IQR), g/d	1.27 (0.97-1.86)	2.01 (1.40-2.95)	1.43 (1.03-2.24)	2.03 (1.44-3.01)
Treatment assignment, n (%)				
SPAR	52 (72.9)	140 (43.9)	103 (68.2)	99 (39.1)
IRB	23 (27.1)	179 (56.1)	48 (31.8)	154 (60.9)
Change from BL in eGFR week 110 (LS mean), mL/min/1.73 m^2 (95% CI)	−4.0 (−5.40 to −1.69)	−8.6 (−9.90 to −7.34)	−4.2 (−5.99 to −2.53)	−9.9 (−11.37 to −8.49)
Difference (95% CI; *P* value)	4.6 (1.88-7.27; =.0005)		5.7 (3.38-7.92; <.0001)	
eGFR chronic slope, mL/min/1.73 m^2/year (95% CI; *P* value)	−0.4 (−1.35 to 0.60)	−4.2 (−4.74 to −3.67)	−1.1 (−1.64 to −0.40)	−4.8 (−5.46 to −4.26)
Difference (95% CI; *P* value)	3.8 (2.71-4.84; <.0001)		3.7 (2.80-4.67; <.0001)	
eGFR total slope, mL/min/1.73 m^2/year (95% CI; *P* value)‡	−1.0 (−1.98 to −0.04)	−4.3 (−4.83 to −3.78)	−1.6 (−2.32 to −0.90)	−4.9 (−5.47 to −4.30)
Difference (95% CI; *P* value)	3.3 (2.20-4.39; <.0001)		3.3 (2.35-4.26; <.0001)	

BL, baseline; CR, complete remission; eGFR, estimated glomerular filtration rate; IRB, irbesartan; LS, least squares; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.
* Based on on-treatment data.
† eGFR slopes were assessed using linear mixed effects model and adjusted for baseline log transformed proteinuria.
‡ Baseline (day 1) eGFR is included as a response variable and covariate.

FR-PO873

Single-Cell Transcriptomics Tracking the Evolution of Cell and Gene Expression in Blood and Urine Cells of a Patient with IgA Nephropathy before, during, and after Therapy

Francesco P. Schena,[1] Monica Limardo,[3] Deborah D'Aliberti,[2] Silvia Spinelli,[2] Rocco Piazza,[2] Vincenzo L'Imperio,[2] Sharon N. Cox.[1] *[1]Universita degli Studi di Bari Aldo Moro, Bari, Italy; [2]Universita degli Studi di Milano-Bicocca, Milano, Italy; [3]ASST-Lecco, Lecco, Italy.*

Background: Longitudinal studies on IgAN patients with active renal lesions at an early stage of the disease using parallel single-cell transcriptomics (scRNA) during therapeutic intervention have never been conducted. Our objective was to investigate transcriptomic variations at a single-cell level in PBMCs and urinary cells before, during, and after therapy.

Methods: The IgAN patient with active renal lesions (E1,C1) was followed up for one year after undergoing 4 months of pulse and oral corticosteroids and supportive therapy. PBMCs and urinary cells were collected at baseline, during therapy (at the 2nd and 4th month), and after 4 months. Cells were processed using a Chromium 10x platform. Libraries were obtained with a Single Cell 3′ Kit followed by sequencing on a Novaseq 6000. Data analysis included read processing with Cell Ranger v. 7.1.0 and Seurat v. 5.0. Unique Molecular Identifiers were regressed out, followed by PCA for dimensionality reduction. UMAP was applied for further reduction and cluster identification using FindNeighbors and FindClusters algorithms. SingleR was used for cell type identification, followed by manual curation. Differentially expressed genes were obtained comparing scRNA profile obtained from 2 healthy control donors using Wilcoxon nonparametric tests.

Results: Laboratory data revealed stable eGFR and progressive reduction of proteinuria (from 1.5 g to 0.2 g/day) after 1 year. scRNA data analysis showed significant transcriptional changes in IgAN, particularly affecting genes associated with B and T cell receptors, as well as the complement cascade. An inversion of the CD4/CD8 ratio and increase in the monocytic fraction were found. Specific changes in gene expression and cell type composition were noted upon treatment and ongoing analysis is evaluating the effect of corticosteroids on urinary cells.

Conclusions: Transcriptional and cell type composition changes were found in PBMCs at a single cell resolution in IgAN, particularly demonstrating specific alterations during corticosteroid therapy.

Funding: Government Support - Non-U.S.

FR-PO874

Investigating Circulating Inflammatory Proteins in IgA Nephropathy: Implications for Disease Progression

Hiroki Kobayashi, Masanori Abe. *Division of Nephrology, Hypertension, and Endocrinology, Nihon University School of Medicine, Tokyo, Japan.*

Background: Immunoglobulin A nephropathy (IgAN), the most common primary glomerulonephritis globally, involves complex inflammatory processes contributing to kidney damage. This study aims to elucidate the relationship between circulating inflammatory proteins and the kidney disease progression of IgAN, and comparing the circulating level of proteins with other autoimmune nephritis.

Methods: This cohort study included 134 Japanese patients with biopsy-proven IgAN, alongside groups with membranous nephritis (MN, n=24), minimal change disease (MCD, n=23), and lupus nephritis (LN, n=23), collected from Nihon University School of Medicine Itabashi Hospital, Tokyo, between 2009-2018. Serum samples were analyzed pre-biopsy for 10 inflammatory proteins (TNF-R1, TNF-R2, LTBR, TNF-R4, TNF-R6B, CD27, TNF-R10A, RELT, EDA2R, and IL-1RT1) that we previously identified as important biomarker for future progression to ESKD in diabetic kidney disease. Kidney function was assessed using eGFR and proteinuria levels, with histological evaluation based on the MEST score.

Results: TNF-R1 and TNF-R2 showed significant increases in all patient groups compared to healthy controls, with statistical significance. For LTBR, TNF-R4, TNF-R6B, TNF-R10A, RELT, and EDA2R, the levels increased with advancing stages in the IgAN group; however, no increase was observed at the normoalbumiuric stage. Additionally, while levels rose in both the MN and Lupus groups, no increase was observed in the MCD group. On the other hand, for CD27, a significant elevation was noted as early as the normoalbumiuric stage compared to healthy controls. Multivariate logistic analysis identified CD27 as an independent predictor of tubular atrophy/interstitial fibrosis in IgAN. Furthermore, TNF-R1, TNF-R2, LTBR, CD27, and EDA2R were significantly associated with the risk of progression to the composite outcome (CKD stage 3, 30% eGFR decline, and ESKD by Cox regression analysis, emphasizing their potential as biomarkers for IgAN progression.

Conclusions: Elevated levels of specific TNFR family proteins and CD27 are strongly associated with IgAN progression, underscoring their utility in predicting kidney function decline. Future studies should focus on these biomarkers for early intervention strategies.

Funding: Private Foundation Support

FR-PO875

Unsupervised Learning with Network Biomarkers for Risk Stratification in IgA Nephropathy and Its Clinical Implications

Jiaxing Tan. *West China Hospital of Sichuan University, Chengdu, China.*

Background: This study integrated network biomarkers with unsupervised learning clustering (KMN) to refine risk stratification in IgA nephropathy (IgAN) and explore its clinical value, addressing the limitations of existing models that heavily rely on renal indicators and lack therapeutic guidance.

Methods: Involving a multicenter prospective cohort, we analyzed 1,460 patients and validated the approach externally with 200 additional patients. Deeper metabolic and microbiomic insights were gained from two distinct cohorts: 63 patients underwent ultra-performance liquid chromatography-mass spectrometry (UPLC-MS), while another 45 underwent fecal 16s RNA sequencing.

Results: Our study utilized hierarchical and k-means clustering methods, integrating renal, extrarenal, and network biomarkers to analyze a cohort with an average follow-up of 58.8 months. This approach identified four distinct patient clusters, with severity and prognosis worsening from Cluster 1 to Cluster 4. The k-means network biomarker (KMN) method emerged as the most effective, achieving an Area Under the Curve (AUC) of 0.77, significantly outperforming the International IgAN Prediction Tool (IIgAN-PT) and RF-RG schemes, which recorded AUCs of 0.72 and 0.69, respectively. Longitudinal analysis over three years highlighted significant differences across clusters in urinary protein and serum creatinine levels—Cluster 1 exhibited stable kidney function while Cluster 4 showed rapid progression towards renal failure. The KMN stratification facilitated personalized treatment, advocating for ACEI/ARBs for lower-risk groups and immunosuppressive therapy for higher-risk groups. It also revealed potential links between IgAN progression and alterations in serum metabolites and gut microbiota. These findings suggest a correlation, though further research is required to establish causality and deepen our understanding of IgAN's underlying mechanisms.

Conclusions: The effectiveness and applicability of the KMN scheme indicate its substantial potential for clinical application in IgAN management.

FR-PO876

Validation of the Klinrisk Kidney Disease Progression Model in Individuals with IgA Nephropathy

Bryce Barr,[1] Ryan J. Bamforth,[2] Thomas W. Ferguson,[2] Oksana Harasemiw,[2] Ian W. Gibson,[1] Olivier Tremblay-Savard,[1] Navdeep Tangri.[1,2] *[1]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [2]Seven Oaks General Hospital, Winnipeg, MB, Canada.*

Background: IgA nephropathy is the most common primary glomerulonephritis worldwide, and leads to kidney failure in a significant proportion of those affected. Recent clinical trials have relied on persistence of proteinuria >1 g/day as the best predictor of poor long-term kidney outcomes, and other tools rely on detailed clinopathologic data which may not be readily available. We sought to validate the Klinrisk prediction model in a population-based cohort of all individuals aged 18 years and older with IgA nephropathy in the Canadian province of Manitoba from 2002 to 2019, inclusive.

Methods: Participants were identified from the Manitoba Glomerular Diseases Registry. Klinrisk is a machine learning model constructed using random forests that uses routinely collected laboratory data to predict the risk of a composite of 40% decline in eGFR or kidney failure, defined as receipt of dialysis for at least 3 months or kidney transplantation. Discrimination was assessed using area under the receiver operating characteristic curves (AUC). Calibration was assessed using Brier scores, and calibration plots to compare predicted with observed risk.

Results: A total of 230 individuals with biopsy-proven IgA nephropathy were included in the analysis. Median age at biopsy was 41.5 years, median eGFR was 51.5 mL/min/1.73m^2, and median ACR was 158 mg/mmol. At 2 and 5 years, 73 and 89 individuals reached the primary outcome, respectively. Model discrimination was good, with an AUC of 0.878 (95% CI 0.830, 0.925) at 2 years and 0.827 (95% CI 0.760, 0.894) at 5 years. Calibration was appropriate, with Brier scores of 0.142 and 0.167 at 2 and 5 years. Visual inspection of the calibration plots showed under-prediction at higher levels of observed risk.

Conclusions: The results demonstrate the utility of the Klinrisk model in predicting kidney failure among individuals with IgA nephropathy. Our results are limited by a small sample size and require confirmation in a separate cohort. If confirmed, Klinrisk could be implemented in a clinical setting to predict individual kidney failure risk to aid treatment decisions, or in a research setting to identify high-risk individuals for participation in clinical trials using routinely available data.

FR-PO877

Analysis of Time to Referral and Kidney Biopsy in IgA Nephropathy in Five European Countries

Philipp Csomor,[1] Meghan Weiss,[2] Justin Snyder,[2] Lucy Santos.[1] *[1]Vifor Pharma Management AG, Glattbrugg, Switzerland; [2]Spherix Global Insights, Exton, PA.*

Background: IgAN is the most common form of primary glomerulonephritis globally, yet time to referral and kidney biopsy is often protracted. This study investigated real-world management of IgAN patients from referral to biopsy in five European countries using a physician questionnaire and patient chart review.

Methods: From 21 Dec 2023 to 31 Jan 2024, physicians from France, Germany, Italy, Spain and the UK completed a questionnaire on IgAN management and a patient chart audit. Physicians were required to have ≥50 CKD stage 1–4 patients, including ≥4 non-dialysis IgAN patients. Patient chart inclusion criteria included ≥13 years of age; non-dialysis IgAN; estimated glomerular filtration rate ≥15 mL/min/1.73 m^2.

Results: 272 physicians completed the questionnaire and chart audits on 514 IgAN patients. 71% of patients were referred to their current physician by a primary care physician and 6% by another nephrologist, of which 24% of these patients were referred for specialised care. For 94% of patients, urine lab and/or blood work results triggered referral. 62% of nephrologists advocate CKD stage 1/2 as the ideal time for referral to specialised care, yet 28% of patients were perceived by their physician as being referred late or extremely late. In the UK, France and Germany, ≥60% of patients were referred to a nephrologist pre-diagnosis, compared with ≤55% in Spain and Italy. 72% of nephrologists agreed that all suspected glomerular disease patients should undergo a biopsy, and few reported having difficulties in ordering or having a biopsy performed; however, 9% of patients are presumed to have IgAN without a confirmatory biopsy. On average, patients had a kidney biopsy 4.1 months after they were referred. For patients biopsied after 6 months or more, reasons for delay included the physician's perception that the patient was not in good enough health for the procedure and that a biopsy was not deemed clinically relevant at the time.

Conclusions: Many physicians perceive that IgAN patients are referred to them late or extremely late. Furthermore, not all suspected IgAN cases receive a timely confirmatory biopsy. This study highlights the need for earlier referrals of IgAN patients and emphasises the need for timely kidney biopsies to confirm diagnosis.

Funding: Commercial Support - CSL Vifor

FR-PO878

Follow-Up Kidney Biopsy Might Be a Mandatory Procedure after Treatment in IgA Nephropathy

Byoung-Soo Cho,[1] Won-Hee Cho.[2] *[1]Dr.Cho's Kidney Clinic, Seoul, Republic of Korea; [2]Sahm-Yook General Hospital, Seoul, Republic of Korea.*

Background: IgA nephropathy is one of the most common chronic glomerulonephritis and 30-45% fall into CKD over a period of 20 to 25 years. Lots of therapeutic regimens have been tried such as ARB, ACEi, omega-3, corticosteroids, endothelin inhibitors, Nefecon, complement inhibitors[K1], finerenone, methylprednisolone pulse, SGLT2 inhibitor etc, however need a longterm follow up studies to confirm the efficacy. Disappearance of proteinuria has long been regarded as surrogate marker of treatment effect, however we have reported that disappearance of proteinuria could not be a surrogate marker after treatment (2022 ASN) At this time we compare the pathological changes who showed clinically improved by methylprednisolone pulse therapy in IgAN.

Methods: During last 10 years our clinic performed 1,982 cases of renal biopsy were done, of which 619 cases (31.2%) were IgAN. We performed follow up renal biopsies in 160 cases (25.8%), who showed clinical improvement include normalized urinalysis findings. Follow up renal biopsy findings were divided into 3 groups : group A: improved renal pathology, group B: no significant pathological changes and group C: aggravated pathological finding One cycle of MP pulse therapy consists of MP (20-30mg/kg, max 1gm/day) IV for 3 consecutive days. Depends on the severity, we performed 3-17 cycles every 2 weeks

Results: Male to female ratio were 81:79, Mean ages were 33 years old. Of the 169 follow up cases 83 (51.9%) showed improved pathologically (Group A) such as disappearance of electron dense deposits, restoration of foot processes, decreased mesangial proliferation, 63 cases (39.3%) showed no significant changes (Group B) and 14 cases (8.8%) showed aggravated pathological changes such as increased glomerulosclerosis, tubular atrophy and interstitial fibrosis

Conclusions: Among the 160 cases of clinically improved cases, only 83 (51.9 %) were pathologically improved, Normalized urinary findings could not be a prognostic marker of improved pathology and so group B & C patients need a careful follow up Follow up renal biopsy might be a mandatory procedure to define the efficacy of treatment in IgA nephropathy

FR-PO879

A 10-Year Analysis of IgAN Management in China: Results from the CPO-IGAN Study

Fujun F. Lin,[1] Gengru Jiang,[1] Rong Wang,[2] Chaosheng Chen,[3] Qinkai Chen,[18] Wenge Li,[4] Chang Ying Xing,[17] Niansong Wang,[5] Hongli Jiang,[16] Zhenhua Yang,[6] Yonggui Wu,[7] Ping Fu,[8] Hong Liu,[9] Qiuling Fan,[10] Hen Xue,[11] Guangyu Bi,[12] Qinghong Zhang,[13] Xinjian Li,[14] Siyi He,[15] Bingbing Zhu.[15]
[1]Renal Division, Department of Internal Medicine, Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Shandong Provincial Hospital, Jinan, China; [3]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [4]China-Japan Friendship Hospital, Beijing, China; [5]Shanghai 6th Peoples Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China; [6]The First Affiliated Hospital of Guangxi Medical University, Nanning, China; [7]The First Affiliated Hospital of Anhui Medical University, Hefei, China; [8]West China Hospital of Sichuan University, Chengdu, China; [9]The Second Xiangya Hospital of Central South University, Changsha, China; [10]First People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai, China; [11]Ya'an People's Hospital, Ya'an, China; [12]Northern Jiangsu People's Hospital, Yangzhou, China; [13]Taihe Hospital, Shiyan, China; [14]Affiliated Hospital of Jining Medical University, Jining, China; [15]Tianjin Happy Life Technology Co. Ltd, Shanghai, China; [16]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [17]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [18]First Affiliated Hospital of Nanchang University, Nanchang, China.

Background: Nationwide data on the treatment of IgA nephropathy (IgAN) in Chinese patients remains unclear. Clinical Practice Optimization Initiative for Chinese Patients with IgA Nephropathy (CPO-IGAN), the first nationwide project to optimize IgAN clinical practices in China, conducted a 10-year nationwide analysis to assess adherence to evidence-based guidelines.

Methods: This retrospective study recruited biopsy-proven IgAN patients across China from January 2015,age ≥18 years with at least one follow-up after treatment initiation. Demographic factors, comorbidities, laboratory results, renal histology reports and therapeutic regimens were collected from clinical information systems.

Results: By April 2024, 2229 IgAN patients from 33 tertiary hospitals in 12 Chinese provinces had been recruited. Table 1 summarizes the clinical characteristics at the time of renal biopsy.74.3% and 5.4% of patients received RASi and SGLT2i as supportive treatment respectively. As shown in Table 2, SGLT2i use increased after the 2021 publication of the DAPA-CKD IgAN subgroup results.46.0% and 6.2% of patients recevied corticosteroids and MMF, and Figure 1 shows the characteristics of these patients. MMF use increased following the KDIGO 2021 guideline recommending it for Chinese IgAN patients.

Conclusions: Optimized treatment of IgAN in China, including the addition of SGLT2i as the new standard of care needs to be implemented. Accordingly,CPO-IGAN will conduct nationwide training to raise awareness among Chinese nephrologists. Given the high use of corticosteroids and MMF in Chinese IgAN patients, disease progression and long-term prognosis will be analyzed through further longitudinal studies by CPO-IGAN.

Table 1 Characteristics of Patients at the Time of Initial Renal Biopsy (N=2,229)

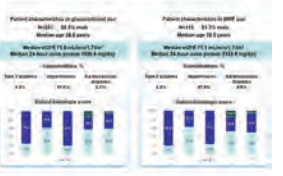
Characteristics	Description
Age, years	
Median (IQR)	38.0 (30.0, 49.0)
<25, n (%)	267 (12.0)
25–<35, n (%)	680 (30.5)
35–<45, n (%)	559 (25.1)
≥45, n (%)	723 (32.4)
Sex, n (%)	
Female	1121 (50.3)
Male	1108 (49.7)
eGFR, mL/min/1.73m², Median (IQR)	84.9 (58.8, 107.3)
The 24-hour urine protein, mg/day, Median (IQR)	1250.0 (660.0, 2364.5)
Serum uric acid level, μmol/L, Median (IQR)	374.0 (303.0, 450.0)
Serum albumin level, g/L, Median (IQR)	37.9 (34.3, 41.5)
The initial treatment post-diagnosis, n (%)	
Renin-angiotensin-system inhibitor (RASi)	1373 (74.3)
Sodium-glucose co-transporter 2 inhibitor (SGLT2i)	100 (5.4)
Corticosteroids	851 (46.0)
Mycophenolate mofetil (MMF)	115 (6.2)
Hydroxychloroquine	290 (15.7)
Comorbidities, n (%)	
Type 2 diabetes	79 (3.5)
Hypertension	990 (44.4)
Cardiovascular diseases	33 (1.5)
Infectious Diseases	147 (6.6)
Oxford histologic score, n(%)	
M	
0	781 (35.0)
1	1448 (65.0)
E	
0	1388 (62.3)
1	841 (37.7)
S	
0	531 (23.8)
1	1698 (76.2)
T	
0	1370 (61.5)
1	625 (28.0)
2	234 (10.5)
C	
0	1549 (69.5)
1	621 (27.9)
2	59 (2.6)

Table 2 Proportion of Initial Medication Type Post-Renal Biopsy Before and After KDIGO 2021 Guideline for Glomerular Diseases

Years	2015-2020	2021-2024	2015-2024
N	1173	1056	2229
RASi (%)	73.5	75.2	74.3
SGLT2i* (%)	1	10	5.4
Corticosteroids (%)	45.8	46.3	46
MMF (%)	3.7	8.8	6.2
Hydroxychloroquine (%)	6.3	25.4	15.7

* The usage of SGLT2i started in 2019, and from 2019 to 2024, the annual usage rate of SGLT2i was 1.0%, 4.3%, 1.9%, 8.4%, 10.0%, and 28.6%.

Figure 1 Clinical Characteristics of IgA Nephropathy Patients Treated with Corticosteroids and Mycophenolate Mofetil



FR-PO880

IgA Nephropathy and Impact of Proteinuria Level and CKD Stage on Health Care Resource Utilization in Germany

Thilo Schaufler,[1] Antonio Ramirez de Arellano,[1] Sonali Dasgupta.[2] *[1]CSL Vifor, Glattbrugg, Switzerland; [2]IQVIA Inc, Wayne, PA.*

Background: Proteinuria ≥1.0 g/day is a risk factor for immunoglobulin A nephropathy (IgAN) progression. This study describes the impact of proteinuria level and chronic kidney disease (CKD) stage on healthcare resource utilization (HRU) and costs among patients with IgAN in Germany.

Methods: Eligible patients had ≥1 ICD-9 583.9, ICD-10 N02.8, or ICD-10 N02.9 code between 2015 and 2022. CKD stage was defined by ICD-10 N18 code and estimated glomerular filtration rate. Patients were divided into two subgroups based on proteinuria: <1 g/day and ≥1 g/day. Average HRU costs for in-patient and out-patient visits were calculated based on German Diagnosis-Related Groups Statistic 2022 and published literature. Owing to data unavailability in the German database, emergency visit counts were extrapolated using German base rates updated with costing ratios and patient count ratios from the UK and Spain.

Results: We identified 1,600 patients with IgAN (mean age 58 years, 67% male). For all visit types combined, the mean total cost per patient was >14-fold higher for CKD stage 5 than stage 1 (€57,977 vs €4,046). Mean total cost per patient was >2.5-fold higher with proteinuria ≥1 g/day than with <1 g/day (€5,530 vs €2,154) (Figure 1). Out-patient visits were low compared with other markets and likely underreported. For in-patient and out-patient visits, HRU increased with advancing CKD and higher proteinuria level (Figure 2).

Conclusions: In patients with IgAN in Germany, advanced CKD stage and elevated proteinuria were associated with higher HRU and costs. Treatments that reduce proteinuria can slow disease progression and prevent rapid kidney function decline while potentially reducing IgAN-related HRU and associated costs.

Funding: Commercial Support - CSL Vifor

Figure 1. Mean total cost per patient for all visit types, breakdown by chronic kidney disease stage and proteinuria level

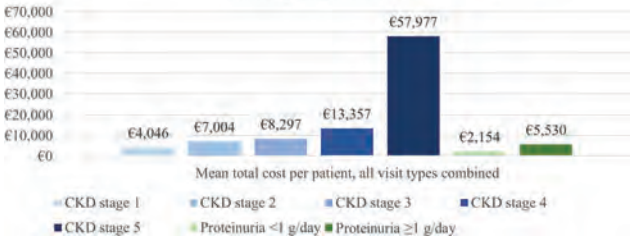
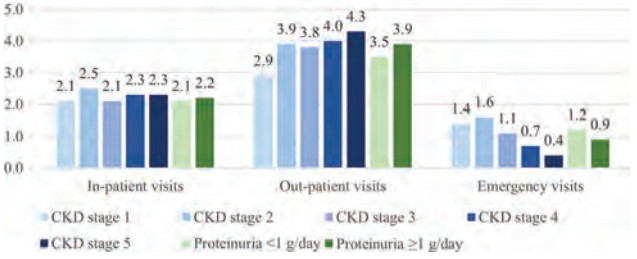


Figure 2. Average number of visits per patient per year, breakdown by chronic kidney disease stage and proteinuria level



FR-PO881

Impact of Proteinuria Level and CKD Stage on Health Care Resource Utilization among Adults with IgA Nephropathy in Spain

Thilo Schaufler,[1] Antonio Ramirez de Arellano,[1] Sonali Dasgupta.[2] *[1]CSL Vifor, Glattbrugg, Switzerland; [2]IQVIA Inc, Wayne, PA.*

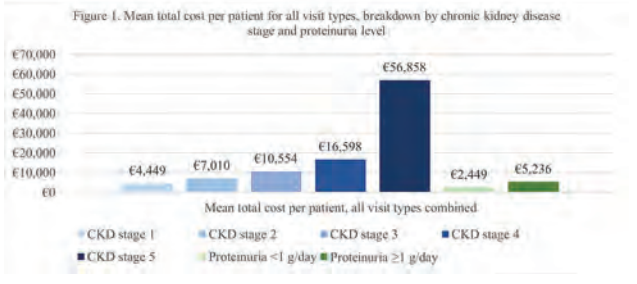
Background: Patients with immunoglobulin A nephropathy (IgAN) and proteinuria ≥1.0 g/day are at increased risk of disease progression. This study assessed the impact of chronic kidney disease (CKD) stage and proteinuria level on healthcare resource utilization (HRU) and costs among patients with IgAN in Spain.

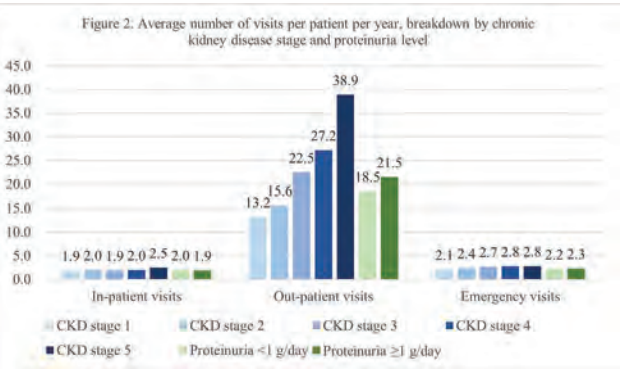
Methods: Patients who were included had ≥1 ICD-9 583.9, ICD-10 N02.8, or ICD-10 N02.9 code recorded between 2015 and 2022. CKD stage was defined by ICD-10 N18 code and estimated glomerular filtration rate. Patients were divided into two subgroups based on proteinuria: <1 g/day and ≥1 g/day. Average HRU costs for in-patient, out-patient and emergency visits were calculated using Official Journal of the Catalan government prices for 2020 and published literature.

Results: 1,080 patients with IgAN (mean age 53 years, 66% male) were identified. The mean total cost per patient with CKD stage 5 was >12-fold higher than for stage 1 (€56,858 vs €4,449). Mean total cost per patient was >2-fold higher with proteinuria ≥1 g/day than with <1 g/day (€5,236 vs €2,449) (Figure 1). Average number of visits per year increased with advancing CKD stage for all visit types, and with higher proteinuria level for out-patient and emergency visits (Figure 2).

Conclusions: In Spanish patients with IgAN, advanced CKD stage and elevated proteinuria were associated with higher HRU and costs across visit types. Interventions to lower proteinuria may help prevent rapid kidney function decline and reduce IgAN-related HRU and costs.

Funding: Commercial Support - CSL Vifor





FR-PO882

Combination of Acanthocyturia and Elevated Serum IgA Level for the Diagnosis of IgA Nephropathy

Ayaa M. Zarm, Ana I. Stark, Rosemary Kovacic, Swetha Rani Kanduri, Juan Carlos Q. Velez. Ochsner Group. *Ochsner Medical Center, New Orleans, LA.*

Background: Serum IgA level (sIgA) has been assessed as a clinical test for the diagnosis of IgA nephropathy (IgAN). Its performance has been modest with sensitivity (SENS) and specificity (SPEC) around 65%. However, studies had tested its performance independently of urinary findings. We hypothesized that idenitfication of acanthocyturia by microscopic examination of the urinary sediment (uSEDI) may increase the pre-test probability of IgAN and, therefore, the diagnostic yield of sIgA may improve when utilized in cases where acanthocyturia is present.

Methods: We prospectively collected data of patients seen in nephrology consultation who had a urine specimen subjected to uSEDI as part of the clinical evaluation over a 5-yr period. Within this cohort, we identified cases in which: 1) urinary acanthocytes were identified by uSEDI; 2) a kidney biopsy was perfomed; and 3) sIgA was obtained as part of the diagnostic work up. Normal range of sIga for our hospital laboratory is 40-350 mg/dL. We assessed the diagnostic performance of sIgA.

Results: Among 801 patients assessed by uSEDI, 240 (30%) underwent kidney biopsy. Urinary acanthocytes were identified in 96 (40%), and 49 (51%) had sIgA measured. Mean age was 53 years, 45% women, 71% white and 27% black. Median serum creatinine was 2.2 (0.6-19.2) mg/dL. Diagnosis was IgAN in 22 (24%), pauci immune glomerulonephritis (GN) in 18 (20%), lupus GN in 8 (9%), other proliferative or infection-related GN (IRGN) in 9 (10%), and thin basement membrane nephropathy in 5 (5%). One case was IgA-dominant IRGN. Median sIgA was higher in IgAN or IgA-dominant IRGN than in others (360 vs 253 mg/dL, p=0.012). Using the laboratory normal range, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of elevated sIgA for identifying IgAN (or IgA-dominant IRGN) were 53%, 68%, 42% and 77%. The AUROC for sIgA for IgAN diagnosis was 0.74 (95% CI 0.59-0.88, p=0.013). The optimal cuttoff was 327 mg/dL. Notably, all IgAN cases were ≥ 230 mg/dL.

Conclusions: sIgA performs modestly as a diagnostic test for IgAN. Adjusting the cutoff to a level within normal range increases the NPV. We suggest that in patients with acanthocyturia, sIgA may be part of the serological work up.

FR-PO883

IgA Nephropathy: A Timeline from Hematuria/Proteinuria to Nephrology Referral and Kidney Biopsy

Zain AlShanableh, Syeda B. Ahmad. *UPMC, Pittsburgh, PA.*

Background: IgA nephropathy (IgAN) is the most common cause of glomerulonephritis with hematuria being its hallmark finding. This study is aimed to look at the time between the development of hematuria and/or proteinuria and nephrology referral as well as time to biopsy.

Methods: We did a retrospective analysis of patients seen at UPMC seen by UPP nephrology who underwent a kidney biopsy from 1/1/20 to 3/13/24. The onset of hematuria and/or proteinuria was noted and compared to when the nephrology referral was made. The time in days between the first nephrology appointment and renal biopsy was also noted. Exclusion criteria were patients with secondary causes of IgA or those not seen by UPP nephrology.

Results: Preliminary data analysis revealed a total of 15 patients that were included. There were 8 men, 7 women, average age 43, 3 Asians and 12 Caucasians/White. Time between onset of hematuria/proteinuria to nephrology referrals ranged from 0 to 3633 days with a mean of 747 days. Whereas time between first nephrology encounter and biopsy ranged from 2 to 815 days with a mean of 149 days.

Conclusions: Recent data from UK registry indicates that patients with IgA nephrology and proteinuria have worse outcomes. With several novel treatments emerging for IgA Nephropathy, early referral and diagnosis is crucial to prevent progression to ESRD.

Age	Sex	Race	BMI	Baseline eGFR (mg/dL)	Proteinuria (g/g at time of biopsy)	Hematuria/proteinuria to referral (days)	Renal appt. to biopsy (days)	Cr (mg/dl) at biopsy	BP (mmHg)	Oxford class.	RAAS / SGLT2 inhibition	Immunosuppression
43	M	White	36	1.5	25	1	44	1.7	136/91	M1S1E0T0-C0	ACE/ARB	None
56	M	White	35	1	0.62	101	194	1.1	120/82	M1E0S0T0-C0	Both	None
32	M	White	32	1.5	0.8	7	815	1.8	142/95	M1E0S1T1-C0	ACE/ARB	None
31	F	White	19	1	2.7	18	22	1.2	136/89	M1E0S1T0-C0	Both	None
35	F	White	27	1.2	0.49	1	34	1.4	136/87	M1S1E0T0-C1	ACE/ARB	Steroids
43	M	White	28	1	0.1	1331	147	0.9	95/61	M1E0S0T0-C0	None	None
40	F	White	31	0.8	4.2	220	2	0.7	139/90	M0S0E0T0-C1	ACE/ARB	None
48	M	White	28	1	0.166	0	14	2.2	115/77	M0E0S0T0-C0	None	Steroids
69	M	White	27	0.7	6.43	2	77	0.7	168/94	M0E0S0T1-C0	ACE/ARB	None
40	M	White	32	1.1	1.97	302	12	2.3	140/103	M1E1S2T1-C1	Both	None
46	M	White	45	1.3	0.4	1001	532	1.6	133/77	M0E0S0T1-C0	ACE/ARB	MMF
46	F	Asian	20	0.7	0.082	3633	61	0.6	131/81	M1E0S0T0-C0	None	None
59	F	White	30	0.7	0.7	2678	57	0.9	129/80	M1E0S0T0-C0	ACE/ARB	None
29	F	Asian	23	1	2.3	131	85	1.1	126/98	M1E0S1T1-C1	ACE/ARB	Tarpeyo
33	F	Asian	33	0.7	0.35	1783	134	0.7	114/63	M1E1S1T0-C0	None	None

FR-PO884

Exploring Kidney Function Decline and Proteinuria in IgA Nephropathy: Insights from a Single-Center Study

Joana P. Dias,[1] Vitória V. Paes de Faria,[1] Maria B. Bessa,[1] Rute Carmo,[1] Clara Almeida,[1] Ana Marta Gomes.[1,2] *[1]Unidade Local de Saude de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; [2]Universidade do Porto Unidade Multidisciplinar de Investigacao Biomedica, Porto, Portugal.*

Background: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis and a major cause of CKD worldwide. Reduction in proteinuria is a surrogate end point for IgAN. We aimed to assess demographic, clinical, histologic and analytic characteristics of our population and determine if there was any association with renal function decline.

Methods: Disease progression was classified as the need for dialysis initiation or doubling of creatinine by the end of follow-up. Patients with secondary IgA were excluded. Data were analyzed using parametric and non-parametric tests.

Results: Data on 26 patients were included. Results are shown in image 1. Progressors exhibited significantly lower hemoglobin, albumin and eGFR at diagnosis, and higher mean proteinuria during follow-up. At the last visit, they continued to show significantly lower hemoglobin and eGFR, and higher proteinuria. Non-progressors had higher usage of ACEi and iSGLT2. The linear regression revealed a significant association between mean proteinuria and eGFR (r = -,673, p<0,001).

Conclusions: In our study, progressors had significantly lower renal function at baseline, which could have limited the extent of our intervention. The lower levels of hemoglobin and albumin in progressors align with the expected findings given their reduced eGFR. Additionally, our study shows that progressors experienced higher proteinuria during follow-up, emphasizing the association between poorer kidney function, higher proteinuria and disease progression. Our findings underscore the significance of proteinuria as a predictor of renal function decline in IgAN, aligning with existing literature. Given the retrospective nature of our study and its inherent limitations, such as small sample size and lack of comprehensive exploration of biomarkers, determining the ideal threshold for proteinuria reduction was beyond the scope of this investigation.

	Progressors (n=12)	Non-progressors (n=14)	P value
Male sex	6 (50%)	8 (57,1%)	0,716
Age (years)	48,75±16,1	40,86±8,84	0,193
Follow-up (months)	50,2±48,4	61,2±50,9	0,667
Values at diagnosis			
Hypertension	11 (91,7%)	14 (100%)	0,462
Hemoglobin (g/dL)	11,19±1,84	13,12±1,87	0,014
Albumin (g/dL)	3,5±0,65	4,07±0,47	0,044
eGFR (ml/min/1,73m2)	35,59±23,98	67,97±31,13	0,007
Proteinuria (g/g)	3,27±3,37	1,41±0,77	0,244
IgA	374,56±115,32	385±120,43	0,815
C3	110,91±10,37	130,07±20,68	0,061
C4	32,27±10,37	30,15±10,34	0,704
During follow up			
ACEi (n,%)	8 (66,7%)	14 (100%)	0,033
iSGLT2 (n,%)	1 (8,3%)	8 (57,1%)	0,014
Immunosuppression (n,%)	4 (33,3%)	7 (50%)	0,391
Mean proteinuria (g/g)	1,99±0,95	0,78±0,46	0,003
Mean eGFR	62,5±25,56	15,73±11,8	< 0,001
Values at last visit			
Hemoglobin (g/dL)	10,5±1,51	14,34±1,95	0,001
Albumin (g/dL)	4,04±0,43	4,35±0,33	0,072
eGFR (ml/min/1,73m2)	10,21±7,74	57,62±21,21	< 0,001
Proteinuria (g/g)	2,32±1,8	0,77±0,59	0,02

FR-PO885

Nonalbumin Protein-to-Creatinine Ratio in IgA Nephropathy: Clinical and Pathological Correlations

Go Kanzaki, Kotaro Shimoyama, Hideaki Kuno, Saeko Hatanaka, Hirokazu Marumoto, Takaya Sasaki, Kotaro Haruhara, Kentaro Koike, Hiroyuki Ueda, Nobuo Tsuboi, Takashi Yokoo. *Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan.*

Background: Although albuminuria is beneficial for the early detection of kidney disease, it is insufficient for the characterization of tubular and hyperfiltration proteinuria. This study evaluated the non-albumin protein-to-creatinine ratio (NAPCR) in patients with IgA nephropathy, from both clinical and pathological perspectives.

Methods: This study included 59 patients diagnosed with IgA nephropathy via kidney biopsy at our hospital between June 2022 and November 2023. NAPCR (g/gCr) was determined by subtracting urinary albumin (ACR) from urinary protein (PCR). The clinical grade (C-grade) of IgA nephropathy at the time of biopsy was assessed according to the criteria of the Japanese Society of Nephrology (JSN) criteria. Histological severity was classified based on the JSN histological grading criteria or the Oxford classification. Risk stratification for dialysis was determined by combining clinical and histological grades (H-grade) according to the JSN and categorized into low, medium, high, or super-high risk of progression to end-stage kidney disease (ESKD).

Results: he average age of the patients was 48 years (31 males, 53.4%). The mean estimated glomerular filtration rate (eGFR) was 56.3 ml/min/1.73m^2. The average PCR was 0.51 g/gCr, and the ACR was 0.35 g/gCr. Higher NAPCR values correlated with increased clinical and histological severity (Table), whereas PCR did not correlate with histological severity.

Conclusions: NAPCR was significantly associated with clinical and histological severity of IgA nephropathy.

Table. NAPCR and Clinical Pathological Categories

	ALL	NAPCR Grade1	NAPCR Grade2	NAPCR Grade3	p-value
Glomerulosclerosis/global sclerosis (%)	16.2 [0.7-33.9]	8.00 [0.00-15.8]	27.1 [6.79-43.8]	21.7 [0-55-33.3]	0.028
Glomerular tuft segmental sclerosis (%)	0.00 [0.00-6.25]	0.00 [0.00-5.26]	0.00 [0.00-4.20]	8.70 [0.00-23.0]	0.013
Glomerular tuft crescent(%)	0.00 [0.00-0.03]	0.00 [0.00-0.03]	0.00 [0.00-0.03]	0.00 [0.00-0.03]	0.859
Interstitial fibrosis/tubular atrophy(%)	20.0 [10.0-40.0]	10.0 [10.0-20.0]	30.0 [10.0-40.0]	30.0 [20.0-50.0]	0.015
Sclerosis of glomeruli(%)	30.0 [20.0-40.0]	20.0 [20.0-30.0]	30.0 [20.0-30.0]	40.0 [20.0-70.0]	p<0.001
arteriolosclerosis	30(67.2)	14(57.9)	16(72.0)	13(68.4)	0.519
M1, n (%)	6(10.3)	3(15.8)	2(9.09)	1 (5.3)	0.564
E1, n (%)	12(20.7)	4(21.1)	1 (3.0)	7(36.8)	0.009
S1, n (%)	28(48.3)	9(51.6)	9(45.0)	13(68.4)	0.071
T1≤1, n (%)	26(44.8)	4(21.1)	11(55.0)	11(57.9)	0.026
C1≤2, n (%)	19(27.6)	4(21.1)	7(33.0)	5(20.4)	0.309
C-grade I, n (%)	34(58.6)	19(100)	14(70.0)	1(5.3)	p<0.001
C-grade II, n (%)	9(15.5)	0(0.0)	3(15.0)	6(31.6)	
C-grade III, n (%)	15(25.9)	0(0.0)	3(15.0)	12(63.2)	
H-grade I, n (%)	30(51.7)	16(84.2)	8(40.0)	6(31.6)	0.011
H-grade II, n (%)	16(31.1)	2(10.5)	8(40.0)	6(42.1)	
H-grade III, n (%)	5(8.6)	1(5.3)	3(15.0)	1 (5.3)	
H-grade IV, n (%)	5(8.6)	0(0.0)	1(5.0)	4(21.1)	
H-Grade A, n (%)	18(31.0)	5(23.8)	3(30.0)	6(33.3)	0.092
H-Grade C, n (%)	40(69.0)	16(84.2)	7(70.0)	15(78.9)	0.010
Low, n (%)	21 (36.2)	13(70.0)	6(30.0)	0(0.0)	p<0.001
Medium, n (%)	16(27.6)	2(10.5)	7(35.0)	7(36.8)	
High, n (%)	19(31.0)	2(10.5)	7(35.0)	9(47.4)	
Super-High, n (%)	3(5.2)	0(0.0)	0(0.0)	3(15.8)	

FR-PO886

Revisiting Gross Hematuria in IgA Nephropathy in the COVID-19 Era

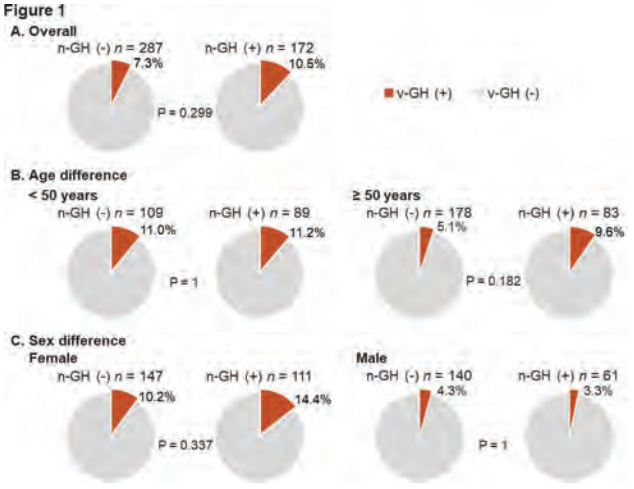
Masahiro Okabe, Nobuo Tsuboi, Saeko Hatanaka, Kotaro Haruhara, Shinya Yokote, Takaya Sasaki, Hiroyuki Ueda, Takashi Yokoo. *Jikei University School of Medicine, Tokyo, Japan.*

Background: Sudden gross hematuria is occasionally observed in patients with IgA nephropathy (IgAN) after COVID-19 mRNA vaccination (v-GH), which is similar to that after acute mucosal infection as part of the natural history of IgAN (n-GH). V-GH and n-GH may share a clinical background or immune mechanism, although the relationship between the development of v-GH and n-GH is not yet clear. Therefore, we aimed to determine the effect of n-GH on the development of v-GH in patients with IgAN.

Methods: Adult patients with IgAN who received COVID-19 mRNA vaccinations were enrolled from four hospitals in Japan. The incidence of v-GH in patients with n-GH was compared with that in patients without n-GH.

Results: Among 459 participants, 287 (63%) did not have a history of n-GH, while 172 (37%) did. Of the patients without n-GH and with n-GH, 21 (7.3%) and 18 (10.5%), respectively, had v-GH, with no statistically significant difference between the groups (Figure 1A). Subgroup analyses demonstrated that this relationship was not changed by age and sex (Figure 1B and 1C). Multivariable analysis including previously reported related factors such as age, sex, and the presence of microscopic hematuria showed no significant association of n-GH with the development of v-GH (Odds ratio 0.89 [95% confidence interval 0.43–1.83]).

Conclusions: Despite some possible similarities in pathogenesis, we failed to demonstrate a clear relationship between v-GH and n-GH, suggesting the involvement of factors specific to each condition. To better understand the pathogenesis of IgAN, further studies are warranted to elucidate the various immunological activation pathways that are commonly or differentially involved in the development of gross hematuria due to infection or vaccination.



FR-PO887

Successful Use of Rituximab in Patients with IgA Nephropathy and Podocytopathy: A Case Series

Mingfang Sun, Dai H. Zi. *Daping Hospital & Research Institute of Surgery, Army Medical University, ChongQing, China.*

Background: IgA nephropathy (IgAN) with podocytopathy is a rare pathological type of glomerular disease. The use of rituximab (RTX) in the treatment of glomerular diseases has increased in recent decades, but the efficacy of rituximab in the treatment of IgAN with podocytopathy has rarely been reported.

Methods: A single-center retrospective study of IgAN patients with podocytopathy who were treated with RTX as second-line therapy was conducted at our center from 2019 to 2022. The aim of this study was to investigate the efficacy and safety of RTX in IgAN patients with podocytopathy.

Results: Seven out of eight patients met the criteria for complete remission following RTX therapy. Only one patient had adverse events (infectious diarrhea and pulmonary infection). Seven patients had complete remission at the time of the last follow-up, and 1 patient experienced relapse six months after RTX therapy. The maximum relapse time after RTX therapy was 20 months, while the maximum relapse-free time before RTX therapy was only 6 months. The number of relapses before RTX therapy (per year) was 1-4; however, seven patients did not relapse and maintained remission at the last follow-up despite steroid withdrawal after RTX therapy.

Conclusions: Overall, RTX effectively reduced proteinuria, increased the maximum relapse-free time and reduced the number of relapses per year and helped patients stop steroid use as soon as possible. RTX also helped most patients achieve clinical remission. RTX appears to be an effective and safe alternative for IgAN patients with podocytopathy with steroid dependance or frequent relapse.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

FR-PO888

Transcriptome Profiles of IgA Nephropathy after COVID-19 mRNA Vaccination

Satoru Sanada, Kanji Chida, Mitsuhiro Sato. *Japan Community Health Care Organization Sendai Hospital, Sendai, Japan.*

Background: The onset of IgA nephropathy has not been fully understood, however, tonsillitis is known to associate with gross hematuria and disease progression. In the previous several years, we have experienced COVID-19 vaccines which have triggered IgA nephropathy with gross hematuria.

Methods: We assessed the clinical features of 13 patients with vaccine-associated IgA nephropathy. Then we measured RNA expressions of peripheral blood mononuclear cells in patients with tonsillitis-associated (n=3) and vaccine-associated IgA nephropathy (n=3). Differential expression analysis and enrichment analysis were performed.

Results: Most of gross hematuria in vaccine-associated IgA nephropathy occurred within one day after vaccinations and all cases of hematuria appeared after the second and subsequent shot. RNA sequencing identified 76 differentially expressed genes (DEGs) between tonsillitis-associated and vaccine-associated IgA nephropathy, which were enriched in gene ontology terms “MHC protein complex” and “MHC class I protein complex”. DEGs upregulated in tonsillitis-associated IgA nephropathy were related to regulation of T cell activation via T cell receptor contact with antigen bound to MHC molecule on antigen presenting cell. However, the upregulated gene set of vaccine-associated IgA nephropathy was related to positive regulation of T cell activation.

Conclusions: The antigen presenting process could be different between tonsillitis-associated and vaccine-associated IgA nephropathy which may be crucial for their pathogenesis. Immune reaction of antigen presenting cells to extracellular vesicles containing mRNA vaccine could be a key to understand vaccine-associated IgA nephropathy.

FR-PO889

Characterization of Patients with Active Glomerular Inflammation in IgAN: Data from the Adelphi DSP

Briana C. Ndife,[1] Carolina A. Aldworth,[1] Jonathan de Courcy,[2] Emma Chatterton,[2] Jade Garratt-Wheeldon,[2] Richard A. Lafayette.[3] *[1]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [2]Adelphi Group Ltd, Bollington, United Kingdom; [3]Stanford University Department of Medicine, Stanford, CA.*

Background: Immunoglobulin A nephropathy (IgAN), the most common primary glomerulonephritis, is characterized by the deposition of immune complexes in the glomerular mesangium and a multitude of inflammatory responses. Active glomerular inflammation in IgAN is poorly defined. We describe active glomerular inflammation in a real-world, multi-country setting, using MEST-C scores and hematuria.

Methods: Data were drawn from the Adelphi Real World IgAN Disease Specific Programme™, a cross-sectional survey of IgAN-treating physicians, including retrospective data, in China, France, Germany, Italy, Japan, Spain, UK, and the USA, from June–October 2021. Physicians reported data on patient (pt) demographics, MEST-C scores, and clinical characteristics. Analyses were descriptive. Active glomerular inflammation was defined using MEST-C scores at diagnosis of M1, E1, or C1/2 and/or hematuria persisting from diagnosis to survey. Declining eGFR (≥40% reduction from diagnosis to survey) and proteinuria ≥1g/day at survey, despite treatment with supportive care (ACEi, ARB, or SGLT2i), were assessed within the population.

Results: Nephrologists (n=271) completed records for pts who had received supportive care for ≥3 consecutive months during their treatment history (n=1254). Mean (SD) pt age was 43 (14) years, 60% were men, and median (IQR) time since IgAN diagnosis was 2 (1–5) years (n=1201). M1, E1, or C1/2 was reported for 59% (n=741) of pts. Within this population, mean (SD) age was 42 (14), 61% were men, and median (IQR) time since diagnosis was 2 (1–4) years. Proteinuria ≥1g/day despite treatment was noted in 32% (n=239) and declining eGFR in 4% (n=29). 30% had persistent hematuria (n=223). M1, E1, or C1/2 and/or persistent hematuria were reported for 67% (n=837) of pts. Within this population, mean (SD) age was 42 (14), 61% were men and median (IQR) time since diagnosis was 2 (1–4) years. Proteinuria ≥1g/day despite treatment was noted in 31% (n=263), and declining eGFR in 4% (n=31).

Conclusions: IgAN pts with active glomerular inflammation can be identified from pt charts within this dataset, and many pts had multiple indicators of active glomerular inflammation. Further research is needed to improve the treatment and management of IgAN pts and further validate the active glomerular inflammatory phenotype.

Funding: Commercial Support - Novartis Pharmaceutical Corporation

FR-PO890

Visualization of Remission Status in IgA Nephropathy Using the Multistate Model

Keiichi Matsuzaki,[1] Hitoshi Suzuki,[2] Takashi Sozu,[3] Keita Hirano,[4] Takashi Yasuda,[5] Takashi Yokoo,[4] Yusuke Suzuki.[6] *[1]Department of Public Health, Kitasato University School of Medicine, Sagamihara, Japan; [2]Department of Nephrology, Juntendo University Urayasu Hospital, Urayasu, Japan; [3]Department of Information and Computer Technology, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan; [4]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [5]Akihabaraizumi Clinic, Tokyo, Japan; [6]Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.*

Background: Transition of urinary abnormalities during the clinical course of IgA nephropathy (IgAN) is associated with renal prognosis. We had proposed new criteria for clinical remission in patients with IgA nephropathy (Clin Exp Nephrol, 2014), and reported the association for renal prognosis (Clin Exp Nephrol, 2021). Multi-state model enables the visual interpretation of the transition to each state over time from the multistate transition probability diagram. The aim of study is to estimate the transition probabilities of remission status both hematuria and proteinuria.

Methods: We extracted the 904 Japanese adults patients with biopsy-proven IgAN (male 50.1%, median age 35.0) from the multicenter cohort study which was previously reported (JAMA Netw Open. 2019). Baseline characteristics were evaluated at biopsy, and clinical data including serum creatinine, urinary findings, treatment options were collected at every visit. Multistate-model during 5 years after biopsy was defined using the proposed remission criteria, for patients with hematuria or patients with proteinuria, respectively. Stacked prediction probabilities of remission was calculated at 5 years after renal biopsy.

Results: 824 patients were included in the analysis for patients with hematuria, and 748 patients were included in the analysis for patients with proteinuria. Tonsillectomy was performed for 198 patients with hematuria, and for 179 patients with proteinuria. While the entire cohorts, the stacked prediction probabilities for remission of hematuria was 0.32 and of proteinuria was 0.30. Figure shows that the stacked transition probabilities of remission status by urinary abnormalities and tonsillectomy. In both criteria of hematuria and proteinuria, tonsillectomy derived higher probabilities in remission than without tonsillectomy (hematuria: 0.50 vs 0.26, proteinuria: 0.42 vs 0.26).

Conclusions: In present study, we proposed visualization of the remission status. Tonsillectomy leads to higher remission rate both hematuria and proteinuria.

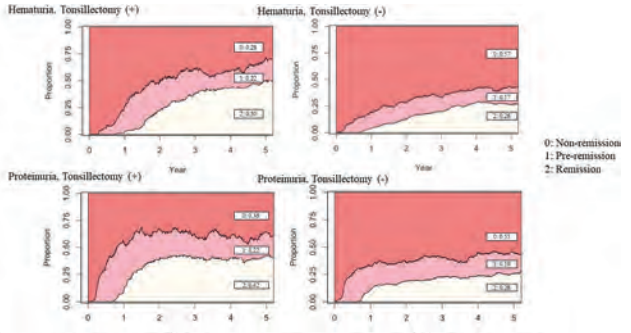


Figure: Stacked prediction probabilities of remission status by urinary abnormalities and with/without tonsillectomy

FR-PO891

Dasatinib Blocks Mesangial Cell Activation by IgA1-Containing Immune Complexes in IgA Nephropathy In Vitro and In Vivo

Zhi qiang Huang, Stacy D. Hall, Joshua C. Anderson, Zina Moldoveanu, Lea Novak, Shihong Qiu, Todd J. Green, Bruce A. Julian, Christopher D. Willey, Jan Novak. *University of Alabama at Birmingham, Birmingham, AL.*

Background: IgA nephropathy (IgAN) is caused by deposition of circulating immune complexes (IC) consisting of galactose-deficient IgA1 (Gd-IgA1) and anti-Gd-IgA1 autoantibodies. These IC activate mesangial cells (MC) and induce kidney injury but the mechanisms of these effects are unknown. We have identified signaling pathways induced in MC by Gd-IgA1-containing IC and targeted them using dasatinib, a broad-spectrum kinase inhibitor.

Methods: IC from sera of patients with IgAN (native IC) or engineered IC formed *in vitro* from polymeric Gd-IgA1 and recombinant IgG autoantibodies in human serum were isolated by size-exclusion chromatography. IC-depleted samples served as controls. In cultured primary human MC, biological activities of native IC or engineered IC were assessed for their capacity to induce cellular proliferation and activate protein-tyrosine kinases, without or with dasatinib in the culture medium. In our passive mouse model of IgAN, nude mice received an intravenous dose of engineered IC (every other day x 3 doses) without or with dasatinib (30 mg/kg/d by gavage; n=5 in each group). Control mice did not receive any IC. Glomerular cellularity was evaluated by quantitative morphometry.

Results: Compared to control samples, native and engineered IC increased proliferation of MC in culture by 4.0±2.2-fold and 2.9±0.7-fold, respectively. Kinomic profiling identified multiple activated signaling pathways. These pathways overlapped and encompassed 20 up-regulated kinases, including signaling pathways involving Src-family kinases and protein-tyrosine kinases in the EGF, VEGF, and PDGF pathways. Several up-regulated kinases, including Syk, Tec, Axl, and Eph, are involved in cellular proliferation or trans-activation of other kinases. Dasatinib inhibited upregulation of these kinases and cellular proliferation. In the mouse model of IgAN, engineered IC increased glomerular cellularity (P<0.0001 vs. control mice); dasatinib prevented these changes (P<0.0001 *vs.* mice given only engineered IC).

Conclusions: Gd-IgA1-containing ICs activated multiple signaling pathways in MC in culture and stimulated cellular proliferation *in vitro* and *in vivo*. Dasatinib blocked these effects, suggesting its potential utility for IgAN treatment.

Funding: NIDDK Support, Private Foundation Support

FR-PO892

Histopathological Outcomes and Clinical Correlates of IgA Nephropathy: A 10-Year Single-Center Study of 68 Biopsy-Confirmed Cases in Saudi Arabia

Sultan Al Dalbhi, Asma M. Alotaibi. *Prince Sultan Military Medical City, Riyadh, Saudi Arabia.*

Background: IgA Nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, and often leads to cause of end-stage renal disease (ESRD), This study analyzes trends in biopsy-confirmed IgA Nephropathy (IgAN) over a ten-year period and evaluates correlations between clinical/laboratory parameters and histopathological features to identify factors influencing disease progression and patient prognosis.

Methods: A retrospective observational study of 68 biopsy confirmed IgAN cases from 2013 to 2022 was conducted. Correlations between clinical/laboratory parameters and histopathological features were examined using statistical methods, including trend and correlation analysis.

Results: The incidence rate of IgAN showed variability over the years. Significant correlations were found between age, serum creatinine, eGFR, and histopathological features. Age positively correlated with mesangial hypercellularity (p=0.22) and interstitial fibrosis (p=0.12), while serum creatinine positively correlated with mesangial hypercellularity (p=0.04), tubular atrophy (p=0.09), and interstitial fibrosis (p=0.01). eGFR negatively correlated with these features (all p<0.05). The comparison between non-COVID-19 (2013-2019) and COVID-19 (2020-2022) periods showed no significant difference in incidence rates (p=0.158).

Conclusions: This study emphasizes the importance of tailored treatment strategies for IgAN and underscores the need for further research into factors influencing disease progression. The positive correlations between age, serum creatinine, and histopathological severity highlight the need for comprehensive patient monitoring.

Table 1: Annual Incidence Rate of IgA Nephropathy

Year	IgAN Cases	Total Biopsies	Incidence Rate (%)
2013	7	70	10.0
2014	9	80	11.25
2015	8	55	14.55
2016	10	60	16.67
2017	5	95	5.26
2018	7	85	8.24
2019	8	90	8.89
2020	4	50	8.00
2021	6	75	8.00
2022	3	60	5.00

Table 4: Correlation Matrix of Laboratory Parameters and Histopathological Features with p-values

Laboratory Parameter	Mesangial Hypercellularity	Endocapillary Hypercellularity	Segmental Sclerosis	Tubular Atrophy	Interstitial Fibrosis
Serum Creatinine	0.25 (p=0.04)	-0.15 (p=0.22)	0.18 (p=0.13)	0.20 (p=0.09)	0.30 (p=0.01)
eGFR	-0.30 (p=0.01)	0.20 (p=0.09)	-0.22 (p=0.06)	-0.25 (p=0.04)	-0.35 (p=0.00)
Proteinuria	0.15 (p=0.21)	0.10 (p=0.38)	0.12 (p=0.31)	0.18 (p=0.13)	0.22 (p=0.06)
Hemoglobin	-0.10 (p=0.38)	0.08 (p=0.48)	-0.05 (p=0.66)	-0.12 (p=0.31)	-0.15 (p=0.21)

FR-PO893

Comparative Efficacy and Safety of New Therapies for IgA Nephropathy: A Systematic Review and Network Meta-Analysis

Larissa A. Lucena,[1] Deivyd V. Cavalcante,[5] Larissa C. Hespanhol,[2] Caroline C. Balieiro,[3] Pedro Romeiro,[6] Paulo d. Castro,[7] Ocilio d. Ribeiro Gonçalves,[8] Rafael A. Rego,[1] Antonio L. Arruda de Oliveira,[1] Rafael Costa Borges,[1] Luis Claudio Santos Pinto,[4] Rodrigo A. de Oliveira.[1] *[1]Universidade Federal do Rio Grande do Norte, Natal, Brazil; [2]Universidade Federal de Campina Grande, Cajazeiras, Brazil; [3]Universidade do Estado do Amazonas, Manaus, Brazil; [4]Centro Universitario da Amazonia, Belem, Brazil; [5]Universidade Federal do Maranhao, Sao Luis, Brazil; [6]Centro Universitario de Maceio, Maceio, Brazil; [7]Universidade de Sao Paulo, Sao Paulo, Brazil; [8]Universidade Federal do Piaui, Teresina, Brazil.*

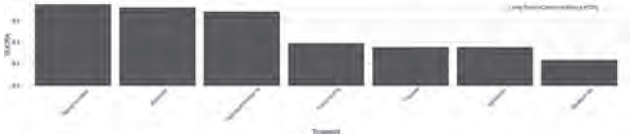
Background: Immunoglobulin A nephropathy (IgAN) can lead to progressive renal dysfunction. This network meta-analysis evaluated novel therapies targeting IgAN's mechanisms, comparing their efficacy and safety to standard care, aiming to optimize clinical management based on current evidence.

Methods: We evaluated 11 randomized controlled trials involving 861 IgAN patients published in the past 10 years. A Bayesian network meta-analysis compared the efficacy of various treatments against placebo, using mean differences and SUCRA values. We searched PubMed, Embase, and Cochrane Central databases to identify studies evaluating primary outcomes: Urine Protein/Creatinine Ratio (UPCR) and estimated Glomerular Filtration Rate (eGFR) change over time.

Results: Mycophenolate (0.754), Atacicept (0.724), and Hydroxychloroquine (0.686) ranked highest in SUCRA values for UPCR reduction. Mycophenolate significantly reduced proteinuria with a mean difference of –0.59 (95% CrI: –1.7, 0.55). Atacicept and Hydroxychloroquine had mean differences of –0.50 (95% CrI: –1.4, 0.38) and –0.46 (95% CrI: –1.6, 0.62). Iptacopan and Budesonide showed limited efficacy, with mean differences of 0.046 (95% CrI: –1.1, 1.2) and 0.17 (95% CrI: –0.60, 0.93). For eGFR preservation, Telitacicept (0.739) (MD 8.1; 95% CrI –6.6, 22.0) and Mycophenolate (0.724) (MD 8.1; 95% CrI –7.3, 23.0) ranked highest, followed by Budesonide (0.712)

(MD 6.5; 95% CrI −1.1, 15.0) and Atacicept (0.550) (MD 4.0; 95% CrI −7.0, 17.0). Hydroxychloroquine (0.436) (MD 2.4; 95% CrI −11.0, 16.0), Iptacopan (0.415) (MD 2.0; 95% CrI −12.0, 16.0), Placebo (0.250), and Fluticasone (0.175) (MD −2.8; 95% CrI −17.0, 11.0) demonstrated lower efficacy in preserving kidney function.

Conclusions: This systematic review and network meta-analysis indicate Mycophenolate and Telitacicept are most effective in reducing UPCR and improving eGFR, suggesting these as preferable treatments for IgAN patients.



FR-PO894

Specificity of Nefecon in Targeting Pathogenic IgA in IgA Nephropathy While Preserving Systemic Humoral Immunity

Roisin C. Thomas, Nadia Nawaz, Jonathan Barratt. *University of Leicester College of Life Sciences, Leicester, United Kingdom*.

Background: Nefecon, an FDA- and EMA-approved targeted-release formulation of budesonide, is recognized for its efficacy in treating immunoglobulin (Ig) A nephropathy (IgAN) by specifically targeting the gut-associated lymphoid tissue (GALT). In the Phase 2b NEFIGAN trial, Nefecon 16 mg/day significantly reduced levels of pathogenic galactose-deficient IgA1 (Gd-IgA1) and IgA-containing immune complexes (IgA-IC) vs placebo, but not IgA1, total IgA, or total IgG. Subsequently, an interim analysis of the larger Phase 3 NefIgArd trial confirmed that Gd-IgA1 ($p<0.0001$) and IgA-IC ($p=0.0169$) were significantly reduced by 9 months of Nefecon 16 mg/day treatment vs placebo. The trial also showed significant proteinuria reduction and kidney function benefit over 2 years with Nefecon vs placebo. Here, we assess the effect of Nefecon on total serum Ig levels in NefIgArd.

Methods: In NefIgArd, patients with IgAN received Nefecon 16 mg/day or placebo for 9 months on top of supportive care, followed by a 15-month observational period off study drug. Enzyme-linked immunosorbent assays (ELISAs) were used to measure serum levels of IgA1, total IgA, and anti-tetanus toxoid antibodies (Nefecon group, n=110; placebo group, n=113), as well as serum levels of total IgG (Nefecon, n=32; placebo, n=38 [at 9 months]). An in-house ELISA was used to measure serum anti-tetanus toxoid Igs; commercial ELISAs were otherwise used. Serum Ig levels were compared between groups at baseline, 3, 6, 9, 12, and 18 months, using unpaired t-tests (significance level $p<0.05$).

Results: There was no significant change from baseline in anti-tetanus toxoid Igs, total IgA, or total IgG levels following Nefecon 16 mg/day treatment for 9 months. There was a slight reduction from baseline in IgA1 at 3 months with Nefecon ($p=0.02$), with no reductions at any other timepoint.

Conclusions: The ability of Nefecon to specifically modulate pathogenic Gd-IgA1 production in the GALT, while leaving systemic IgA responses and total IgA and IgG levels unchanged, supports its use as a generally well tolerated, targeted, locally-acting treatment option for IgAN. Unlike other B cell–directed therapies currently in development for IgAN, Nefecon does not impair systemic humoral immunity and, therefore, offers a therapeutic advantage by selectively reducing pathogenic Gd-IgA1 while preserving overall serum Ig levels.

Funding: Commercial Support - Calliditas Therapeutics AB

FR-PO895

The Role of Complement and JAK/STAT Pathway in IgA Nephropathy

Mateus J. Luvizotto, Precil D. Neves, Luis Yu, Lectícia Jorge, Cristiane B. Dias, Viktoria Woronik. *Universidade de Sao Paulo, Sao Paulo, Brazil*.

Background: IgA nephropathy is the most frequent primary glomerulopathy worldwide and an important cause of End-Stage Renal Disease. The pathophysiology of the disease is not very well established and complement-activation pathways is involved in IgAN. JAK/STAT signaling pathway may play an important role in the pathogenesis of the disease.

Methods: A retrospective analysis was performed on all IgAN patients diagnosed by kidney biopsy between 2002 and 2016. Clinical and laboratory data were collected at baseline and at the end of follow up. Kidney tissue sections were stained with antibodies specific for CD68 and for components of JAK-STAT pathway, including JAK2, JAK3, p-STAT and STAT3. As controls 6 renal tumor border tissues were used. CD68 positive cells were quantified in glomeruli and tubulointerstitium and correlated with MEST score.

Results: Clinical features are summarized in Table 1. Mean follow-up time in the study population was 102 months. More than half of patients achieved remission and 31.1% achieved the primary outcome primary outcome that was defined as ESRD or doubling of baseline creatinine. Staining for JAK3 was observed observed in the renal tubule and glomeruli. Staining for JAK3 was enhanced in patients with IgAN compared to controls. Interstitial CD68-positive cells showed correlation with initial and final eGFR, proteinuria and intersticial fibrosis. Logistic regression analysis showed that CD68-positive cells were significantly associated with progression to ESRD and hematuria.

Conclusions: The role of complement and JAK/STAT pathway in IgAN may provide potential targets and rationale for development of targeting therapy of the disease.

Clinical and laboratory data at the time of biopsy and at the end of follow-up

n	63
Age (years)	33.00 [24.50-46.00]
Woman (n,%)	35 (55.6)
Not White (n,%)	17 (27.0)
Creatinine mg/dL	1.39 [0.94-2.21]
eGFR CKD-EPI (ml/min/1.73 m2)	58.00 [31.00-95.00]
Proteinuria g/day	1.60 [1.11-3.06]
Hematuria (n,%)	54 (85.7)
Follow up (months)	102.00 [34.00-144.50]
Delta eGFR/year	-1.19 [-3.95-(-0.19)]
Remission (n,%)	31 (54.4)
Creatinine duplication or ESRD (n,%)	19 (31.1)

FR-PO896

Urine Complement Activation Products in IgA Nephropathy

Xiaolan Zhang,[1] Li Zhang,[2] Anjali A. Satoskar,[1] Daniel J. Birmingham,[1] Brad H. Rovin.[1] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]The First Hospital of Jilin University, Changchun, China*.

Background: Complement activation appears to play an important mechanistic role in kidney injury in IgA Nephropathy (IgAN). In most patients with IgAN overt systemic complement consumption is not observed as measured by levels of serum complement components C3 and C4. To evaluate the possibility that complement activation occurs primarily within the kidney in IgAN we tested patient urine samples for the presence of complement activation products (CAPs), and correlated levels with the Oxford MEST-C score to determine the relationship of CAPs with kidney injury.

Methods: Serum and spot urine samples were collected from 80 IgAN patients at the time of diagnostic kidney biopsy and 29 healthy volunteers. Biopsies were classified by the Oxford MEST-C score. The CAPs assessed were fragment Ba that is generated during activation of the alternative pathway (AP), C5a, and the terminal pathway membrane attack complex C5b-9. These were measured by ELISA (C5a and C5b-9) or EIA (Ba). ANOVA, nonparametric Wilcoxon test, and multiple linear regressions were done using JMP17 pro for data analysis.

Results: Ba, C5a and C5b-9 did not correlate with serum C3 or C4 levels. Ba, C5a, and C5b-9 were 98, 44, and 2600-fold higher, respectively in the urine of IgAN patients than healthy individuals ($p<0.0001$ for all). C5a measured in IgAN patient serum collected at the same time as urine (n=40) showed no relationship with urine C5a. Although urine C5a and urine C5b-9 did not correlate with any MEST-C component, the level of urine Ba increased 1.6 and 6.4-fold in patients with T1 and T2 Oxford MEST-C lesions, compared to patients with T0 lesions ($p=0.0005$). Similarly, compared to patients with S0 lesions, Ba was 4.6-fold higher in patients with S1 lesions ($p=0.0004$). Interestingly Ba did not correlate with M, E, or C lesions. Ba increased with decreasing eGFR ($R^2=0.35$, $p<0.0001$).

Conclusions: CAPs are found in the urine of patients with IgAN. The lack of association of simultaneously collected urine and serum C5a, and the large molecular mass of C5b-9 suggest CAPs appearing in the urine of IgAN patients are due to intra-renal complement activation. Unexpectedly, CAPs did not correlate with the inflammatory components of MEST-C score. Ba, a marker of AP activation, did however associate with chronic damage in IgAN, perhaps suggesting a role for the AP in mediating kidney fibrosis.

Funding: Clinical Revenue Support

FR-PO897

Serum GDF15 Could Predict Cardiorenal Prognosis in Patients with IgA Nephropathy

Hong Cheng, Ziwei Wei, Weiyi Guo, Xiao-yi Xu, Guo-qin Wang, Li-jun Sun, Hong-rui Dong, Lingqiang Kong. *Beijing Anzhen Hospital Affiliated to Capital Medical University, Beijing, China*.

Background: To investigate the correlation between serum GDF15 and the clinical and pathological characteristics of patients with immunoglobulin A nephropathy (IgAN) and further explore its relationship with the cardiac and renal prognosis of IgAN patients.

Methods: This study enrolled 104 patients who were diagnosed with primary IgAN at our center from January 2018 to December 2022 and were regularly followed up for at least one year. Serum GDF15 was measured, and the correlation between serum GDF15 and the clinical and pathological characteristics of patients with IgAN at the time of renal biopsy was analyzed. Furthermore, the relationship was analyzed between the serum GDF15 and the cardiac and renal prognosis of patients with IgAN.

Results: We found that serum GDF15 levels were positively correlated with 24h urinary protein quantification ($r=0.405$, $P<0.001$), negatively correlated with eGFR ($r= -0.606$, $P<0.001$), and were higher in patients correlated with tubular atrophy or

interstitial fibrosis, crescent-shaped lesions, and intrarenal arteriolar lesions. The median GDF15 825.60 pg/ml was used as the cut-off value to divide IgAN patients into a high-level GDF15 group (Group High, n= 52) and a low-level GDF15 group (Group Low, n=52). Compared to Group Low, IgAN patients in Group High presented with had a higher proportion of diabetes mellitus (P=0.002) and basic cardiovascular disease (P=0.005), had higher levels of systolic blood pressure (P=0.019023), BMI (P=0.031), initial urinary proteins (P<0.001), blood creatinine (P<0.001), blood total cholesterol (P=0.045), complement C4 (P=0.008), and left ventricular mass index (P=0.008), while having lower levels of blood albumin (P=0.002) and eGFR (P<0.001). Moreover, the cardiac and renal prognosis was significantly worse in patients of Group High (P=0.002).

Conclusions: High serum GDF15 levels correlated with disease severity in IgAN, and high serum GDF15 levels may suggest a poorer cardiorenal prognosis in IgAN patients.

FR-PO898

Comparative Proteomic Analysis of Laser Microdissected Glomeruli and Tubules in IgA Nephropathy

Kazuo Takahashi,[1,2] Yudai Tsuji,[1] Sei Saitoh,[3] Yukako Ohyama,[1,2] Masaya Hirayama,[1,4] Naotake Tsuboi.[2] *[1]Department of Biomedical Molecular Sciences, Fujita Health University School of Medicine, Toyoake, Japan; [2]Department of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan; [3]Department of Disease Systems Analysis Medicine, School of Medical Sciences, Fujita Health University, Toyoake, Japan; [4]Department of Morphology and Diagnostic Pathology, School of Medical Sciences, Fujita Health University, Toyoake, Japan.*

Background: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide, and 30–40% of cases progress to end-stage kidney disease. Although the glomerular mesangium is the leading site of IgA deposition in IgAN, tubulointerstitial lesions vary among patients. A new workflow for laser capture microdissection coupled with mass spectrometry (MS) was developed. Using this workflow for glomeruli and tubules, we attempted to detect molecules associated with the pathogenesis and disease progression in IgAN.

Methods: Using the treatment protocol for IgAN at the Fujita Health University Hospital, patients with IgAN were divided into immunosuppressive (tonsillectomy and steroid pulse therapy, n=19) and conservative (n=14) therapy groups. Glomerular and tubular cross-sections were microdissected from stored formalin-fixed paraffin-embedded kidney biopsy tissues and control kidney tissues (n=10) purchased from OriGene Technologies. Samples were analyzed using liquid chromatography-mass spectrometry, and the relative amounts of glomerular and tubular proteins were compared between the groups.

Results: Glomerular proteomic analysis quantified 1807 proteins, of which 85 had significantly different abundances in patients with IgAN than in controls. Comparing the different treatment groups of patients with IgAN, 78 proteins showed significantly different abundances. These proteins are mainly a part of the complement system and are a group of extracellular matrix proteins. Tubular proteomic analysis quantified 2354 proteins, of which 73 were significantly differentially expressed between patients with IgAN and controls. When comparing the different IgAN treatment groups, 75 proteins showed significantly different abundances. These proteins include extracellular matrix and epithelial-mesenchymal transition proteins.

Conclusions: Using LMD-coupled MS, we demonstrated that the complement system in the glomerular lesion and the epithelial-mesenchymal transition system in the tubular interstitial lesion differed between different treatment groups. Investigating the relationship between these molecules and kidney prognosis is crucial for discovering new biomarkers to determine kidney prognosis.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO899

Efficacy and Safety of Dapagliflozin in the Treatment of Adult Primary IgA Nephropathy: A Single-Center, Prospective, Open, Randomized Controlled Study

Xiao Fei, Wang Ling, Dai H. Zi. *Department of Rheumatology and Clinical Immunology, Daping Hospital, Army Medical University (Third Military Medical University), Chongqing, China.*

Background: Despite optimized renin-angiotensin-aldosterone system (RAAS) inhibition, 20 % ~ 40 % of immunoglobulin A nephropathy (IgAN) patients will progress to end-stage renal disease within 10 ~ 20 years after diagnosis. We evaluated the efficacy and safety of dapagliflozin, when added to the treatment regimen of patients with IgAN.

Methods: Participants had IgAN proven by kidney biopsy(proteinuria with protein excretion of 0.3-3.5 g/d, serum albumin > 30g/L and estimated glomerular filtration rate(eGFR)) > 30 mL/min/1.73 m^2) and were receiving optimized RAAS inhibitor therapy. Patients were randomly assigned 1:1 to receive daily oral dapagliflozin or not for 6 months. The primary outcome was percentage change in 24-hour urine protein excretion(24HUPE), first-morning urine albumin-creatinine ratio (UACR) between baseline and 6 months.

Results: 60 participants (mean eGFR, 83.17 mL/min/1.73 m2; median 24HUPE 0.77 g/d; median UACR 636mg/g.Cr) were recruited and randomly assigned to receive dapagliflozin(n = 30) or not (n = 30). Percentage change in 24HUPE at 6 months was significantly different between the dapagliflozin group and the control group (45.8% [inter quartile range (IQR), 65.2%, 4.2%] vs 10.1% [IQR, –46.1%, 53.1%]; P < 0.05, respectively). At 6 months, median 24HUPE level was significantly lower in the dapagliflozin group than control group (0.35 [IQR, 0.18, 0.75] g/d vs 0.62 [IQR, 0.37, 1.21] g/d; P < 0.05, respectively). The change trend of UACR was the same as that of 24HUPE. No serious adverse events were recorded during the study in either study group.

Conclusions: Dapagliflozin in addition to optimized RAAS inhibition significantly reduced proteinuria in patients with IgAN over 6 months without evidence of adverse events. These findings require confirmation in larger treatment trials.

Funding: Government Support - Non-U.S.

FR-PO900

Analysis of Clinical Risk Factors of Prognosis in IgA Nephropathy Based on Machine-Learning Approaches

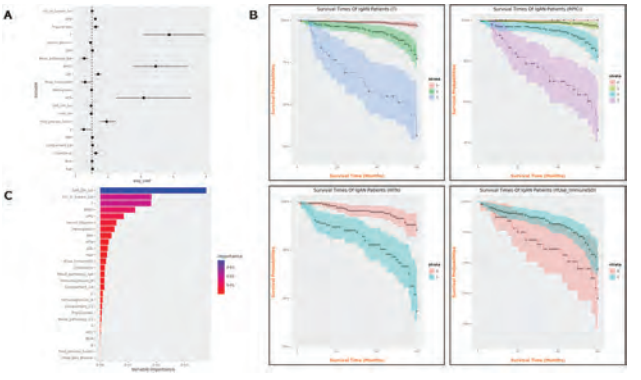
Qin Zhu. *Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, China.*

Background: Immunoglobulin A nephropathy (IgAN) is one of the leading causes of end-stage kidney disease (ESKD). Many studies have shown the significance of pathological manifestations in predicting the outcome of patients with IgAN. Evaluating prognosis by using baseline clinical characteristics is beneficial for both clinicians and patients.

Methods: A dataset of 892 patients with IgAN is used to develop prediction model for estimating the prognosis of patients with IgAN based on the cox regression and random forest algorithm. The 5-year ESKD prediction models using clinical variables were developed to evaluate the probability of ESKD or doubled serum creatinine(Scr). Cross-validation were implemented to mitigate bias, while the area under the receiver operating characteristic curve (AUROC) was used for model evaluations.

Results: For the 5-year ESKD prediction model, the base model achieved an AUROC of 0.86 (95% CI: 0.75–0.97). Six clinical factors exhibited statistical significance ($p < 0.05$) in predicting IgAN prognosis: BMI (HR: 1.025, 95% CI: 1.003-1.047, p = 2.25×10–2), cholesterol (HR: 1.24, 95% CI: 1.097-1.398, p = 5.42×10–4), and T in Oxford classification (HR: 2.747, 95% CI: 1.573-4.797, p = 3.79×10–4) were identified as risk factors, while estimated glomerular filtration rate (eGFR) (HR: 0.964, 95% CI: 0.947-0.982, p = 1.16×10–4), use of immunosuppressive drugs (HR: 0.498, 95% CI: 0.264-0.941, p = 3.19×10–2), and renal pathology IgA (HR: 0.603, 95% CI: 0.386-0.940, p = 2.57×10–2) exhibited a protective effect against ESKD or doubled Scr.

Conclusions: A prediction model incorporating clinical characteristics was constructed to estimate prognosis in patients with IgAN. The findings suggest that BMI, cholesterol, and T score in Oxford classification increase the risk of ESKD or doubled Scr, while higher eGFR, immunosuppressive drug use, and renal pathology IgA confer a protective effect. Further validation through randomized controlled trials is warranted to corroborate these findings.



FR-PO901

Serum MCP-1 and TGF-β as Biomarkers of Immunosuppressive Treatment Effectiveness in IgA Nephropathy

Junseok Jeon,[1] Younmin Yoon,[2] Kyungho Lee,[1] Jung eun Lee,[1] Wooseong Huh,[1] Hye Ryoun Jang.[1] *[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Chosun University Hospital, Chosun University School of Medicine, Gwang-ju, Republic of Korea.*

Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis, and a significant proportion of patients progress to end-stage kidney disease. Predicting patient prognosis and response to immunosuppressive therapy is crucial for proper management. We aimed to investigate the clinical factors and biomarker for response to immunosuppressive therapy in patient with IgAN

Methods: This retrospective study included adult patients who were diagnosed with biopsy-proven IgAN between 2010 and 2020. Study variables included clinical and pathological variables and biomarkers, including serum and urine MCP-1, RANTES, TGF-beta, and VEGF, and tissue CD45+ cells. Outcome was the good prognosis defined as urine protein to creatinine ratio (uPCR) ≥ 50% reduction or < 0.5 mg/mg and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m2 or decrease < 5 mL/min/1.73 m^2 at one year from the kidney biopsy.

Results: Mean age, eGFR, and uPCR were 44.3 ± 12.7 and 42.0 ± 13.3 years; 56.9 ± 29.4 and 68.6 ± 30.7 mL/min/1.73 m^2; 2.1 ± 1.6 and 1.6 ± 1.6 mg/mg in the control and gool prognosis groups, respectively. A good prognosis at one year is a good reflection of long-term renal outcomes. High body mass index, no hypertension, high eGFR, low uPCR, low histologic grade, and immunosuppressive therapy were predictors of good prognosis. After adjusting with clinical and pathological variables, lower serum MCP-1 and higher serum TGF-β were associated with good prognosis in patients with immunosuppressive therapy, but not with conservative therapy. The proportion of CD4+ cells were not associated with prognosis in patients with immunosuppressive therapy.

Conclusions: Immunosuppressive therapy was associated with good prognosis in patients with IgAN, although there may be selection bias. Serum MCP-1 and TGF-β have the potential to be biomarkers for the effectiveness of immunosuppressive therapy in patients with IgAN.

Funding: Government Support - Non-U.S.

FR-PO902

Novel Serodiagnostic Biomarkers for IgA Nephropathy Using Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) Mass Spectrometry Glycoprofiling of IgA1

Shigeaki Nakazawa,[1] Jan Novak,[2] Norio Nonomura,[1] Yoichi Kakuta.[1]
[1]Osaka Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Suita, Japan; [2]The University of Alabama at Birmingham, Birmingham, AL.

Background: IgA nephropathy (IgAN) is one of the most common primary glomerulonephritides worldwide, with many patients progressing to kidney failure. IgAN is characterized by IgA1 glomerular immunodeposits enriched for galactose-deficient IgA1 glycoforms (Gd-IgA1). Human IgA1 hinge region contains 3-6 clustered *O*-glycans, and patients with IgAN have elevated serum levels of Gd-IgA1. Gd-IgA1 glycoforms have *N*-acetylgalactosamine (GalNAc) residues exposed and available for binding by a GalNAc-specific lectin (e.g., from *Helix pomatia*; HPA). These Gd-IgA1 glycoforms can be also recognized by autoantibodies specific for Gd-IgA1, resulting in the formation of nephritogenic immune complexes. Previously, we comprehensively analyzed IgA1 *O*-glycan profiles using MALDI-TOF mass spectrometry (MS). We determined that IgAN patients have elevated serum levels of Gd-IgA1 and that these glycoforms have reduced number of Gal residues. In this study, we assessed whether the IgA1 *O*-glycan profiling can provide diagnostic-level data for IgAN.

Methods: Kidney-transplant recipients who underwent transplantation at Osaka University Transplant Group from 2013 to 2024 were recruited, with kidney donors serving as controls. The volunteers were divided into two cohorts: a discovery cohort (n=85) and a validation cohort (n=46). Serum IgA was isolated, digested with trypsin, and the released IgA1 hinge-region glycopeptides were isolated and analyzed by MALDI-TOF MS on a BRUKER Ultraflex instrument. An IgAN-MS index was calculated using multiple regression analysis based on the relative representation of specific glycoforms of IgA1 hinge-region glycopeptides. A cut-off value was determined by ROC curve analysis in the discovery cohort, and the diagnostic ability was tested in the validation cohort.

Results: In the discovery cohort, setting a cut-off value of 0.38 yielded a high diagnostic performance with an AUC of 0.89. This diagnostic performance was confirmed using the validation cohort, with a sensitivity of 72% and specificity of 68%.

Conclusions: In summary, analysis of IgA1 *O*-glycoforms by MALDI-TOF MS represents a novel, noninvasive biomarker for IgAN that can provide another level of information in addition to kidney-biopsy evaluation.

FR-PO903

Urinary Proteomics Identify Biomarkers for Predicting Complete Remission of Proteinuria in Pediatric IgA Nephropathy

Jianmei Zhou, Xuhui Zhong, Jie Ding. *Peking University First Hospital, Beijing, China.*

Background: This study aimed to identify urinary biomarkers for predicting complete remission (CR) of proteinuria in pediatric IgAN.

Methods: We enrolled pediatric patients with biopsy-proven IgAN from the Registry of IgA Nephropathy in Chinese Children (RACC, NCT03015974). Patients were divided into CR (defined as 24-hour urinary protein ≤200 mg/d or protein:creatinine ratio ≤200 mg/g) group and non-complete remission (NCR) group, according to whether they achieved CR within 6 months after the baseline. We profiled the proteome of baseline urine samples with data-independent acquisition mass spectrometry. Based on three machine-learning algorithms (including least absolute shrinkage and selection operator, random forest, and support vector machine), the biomarkers with the best ability to distinguish between CR group and NCR group were selected. The added value of these biomarkers on the clinical-pathological parameters were evaluated. The enrichment analysis for differentially expressed proteins were used to analyze the biological process associated with CR of proteinuria.

Results: A total of 48 children were enrolled, including 34 children in the CR group and 14 children in the NCR group. The urine proteomics quantified a total of 1,721 proteins in baseline urine samples. The following four urinary biomarkers with the best predictive performance were identified: complement component C8 alpha chain, pigment epithelium-derived factor, tyrosine-protein kinase Yes and ribonuclease P protein subunit p38. Compared with clinical-pathological parameters alone, the addition of the new biomarkers on the clinical-pathological parameters significantly increased the predictive accuracy for CR of proteinuria (AUC from 0.819 to 0.969, P<0.001). The differentially expressed proteins between the two groups were mainly enriched in the complement coagulation pathway, regulation of actin cytoskeleton, regulation of apoptosis, and etc.

Conclusions: The addition of the new urinary biomarkers identified by urine proteomics on the traditional clinical-pathological parameters could significantly improve the model fit for predicting CR of proteinuria in pediatric IgAN, thus helping achieve accurate prediction. Proteinuria remission might be associated with complement and coagulation pathway, regulation of actin cytoskeleton, regulation of apoptosis, and etc.

FR-PO904

IgA Nephropathy (IgAN) in Pediatric Patients: A Kidney Health Initiative (KHI) Artificial Intelligence (AI)-Assisted Literature Review

David T. Selewski,[1] Eleanor M. Kerr,[8] Cecile Fajardo,[10] Barbara S. Gillespie,[13] Sai Prasad N. Iyer,[9] Myda Khalid,[3] Radko Komers,[4] Koichi Nakanishi,[5] Raoul D. Nelson,[6] Jun Oh,[7] Lokesh N. Shah,[10] Nicholas J. Webb,[12] Xuhui Zhong,[11] Howard Trachtman.[2] KHI Pediatric IgA Nephropathy Work Group.
[1]Medical University of South Carolina, Charleston, SC; [2]University of Michigan, Ann Arbor, MI; [3]Indiana University, Bloomington, IN; [4]Travere Therapeutics Inc, San Diego, CA; [5]University of the Ryukyus, Nishihara, Japan; [6]University of Utah Health, Salt Lake City, UT; [7]Universitat Hamburg, Hamburg, Germany; [8]Ripple Effect, Rockville, MD; [9]SeaStar Medical, Denver, CO; [10]Otsuka America Inc, San Francisco, CA; [11]Peking University, Beijing, China; [12]GSK plc, Brentford, United Kingdom; [13]University of North Carolina, Chapel Hill, NC.

Background: With proteinuria as an accepted reasonably likely surrogate endpoint in IgAN, availability of accelerated approval of new therapies has resulted in a surge of randomized clinical trials (RCT) for adults. There is a need to characterize the disease in pediatric patients and define a regulatory pathway for approval of new therapies in this age group. The KHI convened a work group to address this knowledge gap and conducted an AI-supported literature review of pediatric IgAN to determine similarities and differences in children and adolescents vs adults.

Methods: Published literature through 2023 was compiled using DistillerSR software and reviewed manually in a 2-step process by title, abstract, and full text if needed. Articles that combined adult and pediatric patients without the ability to analyze pediatric patients separately, that did not report IgAN as a separate entity, had a sample size less than 10, case reports, reviews, duplicate reports, and articles that focused on IgA vasculitis were excluded. Relevant content was extracted using Elicit, an artificial intelligence tool, validated, and reviewed by the work group.

Results: 84 articles were included after preliminary review and classified into the following subgroups: Natural History/Epidemiology (n=41), Clinical Trials (n=10) and Biomarkers (n=33). Prompts were engineered for use in the AI extraction tool, allowing for systematic extraction of study characteristics, e.g., study design, trial region, sample size, patient characteristics, and outcome measures. Analysis of the papers is underway and is anticipated to be completed by August 2024.

Conclusions: AI-supported methods provide a novel strategy for future extensive literature reviews. They can identify in-scope articles, extract and expedite the review of large amounts of relevant data, and foster wider application in clinical research. The KHI-sponsored project will identify areas of similarity and difference regarding the clinical course, response to therapy, and clinically relevant endpoints in pediatric vs adults with IgAN to guide extrapolation of data from adults with IgAN to affected children and facilitate the performance of RCT in the pediatric age range.

FR-PO905

Profiles of IgA Deposition and Patterns in Kidney Diseases

Jiarong Song,[1,2] Xuejing Zhu,[1,2] Shuguang Yuan,[1] Hong Liu,[1,2] Yifu Li.[2,3]
[1]The Second Xiangya Hospital of Central South University Department of Nephrology, Changsha, China; [2]Institute of Nephrology, Central South University, Changsha, China; [3]The Second Xiangya Hospital of Central South University Center for Medical Research, Changsha, China.

Background: IgA is the most abundant type of antibodies in human body. It involved in the susceptibility of mucosal pathogens in celiac disease, inflammatory bowel diseases and certain kidney diseases. Kidney biopsy with dominant or co-dominant mesangial IgA

staining is required for diagnosis of IgA nephropathy (IgAN). However, there are IgA depositions or not in other kidney diseases or its pattern was not fully understood.

Methods: This retrospective study reviewed the renal biopsy records between August 2011 and November 2022 from a single medical center in Changsha, China. Relevant clinical and histological records were documented for standard diagnosis. Grouping the IgA deposit patterns as "Mesangial area only", "Glomerular capillary loops only" and "co-staining" were based on immunofluorescence staining records, which summarized the IgA deposition and pattern profiles in kidney diseases.

Results: Totally 12,205 cases of renal biopsy were performed in the period. Finally 12,102 cases were enrolled for analysis after removal of the cases with incompleted data. 7,040 of 12,102 cases (58.17%) had IgA positive staining. Among them, 4,034 cases (57.30%) were diagnosed as IgAN. The most common IgA staining positive diseae is IgAN (100%), IgA vasculitis nephritis (95%), Lupus nephritis (75%), and HBV-associated nephropathy (60%), see detail in Table 1. The IgA deposition pattern differnece had been noted in major IgA associated disease (Table 2).

Conclusions: Mesangial IgA deposition is a histopathologic hallmark of IgAN, however, IgA deposits in kidney is also common in some IgA associated diseases such as IgAVN, LN and HBVAN. Whether deposition intensity and patterns of IgA is associated with hetergenous clinical phenotypes needs further investigation.

Table 2. IgA deposition patterns in major IgA associated kidney diseases

Pattern	IgAN	IgAVN	LN	HBVAN
Mesangial area only	3389(84.01%)	346(77.93%)	81(13.48%)	182(53.37%)
Glomerular capillary loops only	0	7(1.58%)	220(36.61%)	75(21.99%)
co-staining	645(15.99%)	91(20.50%)	300(49.92%)	84(24.63%)

Table 1 IgA deposition rates in different kidney diseases

Diseases	IgA deposits	Total cases	Positive rate
IgA nephropathy(IgAN)	4034	4034	1.00
IgA vasculitis nephritis(IgAVN)	444	466	0.95
Lupus nephritis(LN)	601	804	0.75
HBV-associated nephropathy (HBVAN)	341	572	0.60
Endocapillary proliferative glomerulonephritis (EPGN)	36	80	0.45
Membranous nephropathy(MN)	571	1761	0.32
Membranoproliferative glomerulonephritis(MPGN)	52	165	0.32
Diabetic kidney disease	140	467	0.30
Renal amyloidosis	57	224	0.25
IgM nephropathy(IgMN)	14	56	0.25
Anca associated vasculitis(AAV)	14	58	0.24
Minimal change disease (MCD)	221	917	0.24
Focal segmental glomerulosclerosis (FSGS)	262	1437	0.18
Monoclonal immunoglobulin deposition disease (MIDD)	10	200	0.05

FR-PO906

Sparsentan (SPAR) in Combination with SGLT2 Inhibitors (SGLT2i) in Patients with IgA Nephropathy (IgAN): A Case Series

Prasanth Ravipati,[1] Gates Colbert,[2] Sarah J. Evans,[3] Agness Pelts Block,[4] Christopher Gisler,[4] Renuka Sothinathan.[5] *[1]University of Nebraska Medical Center, Omaha, NE; [2]Texas A&M College of Medicine, Dallas, TX; [3]DuBois Nephrology Associates, DuBois, PA; [4]Travere Therapeutics, Inc., San Diego, CA; [5]Virginia Nephrology Group, Arlington, VA.*

Introduction: SPAR is a nonimmunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA) that is approved in the US and EU for adults with IgAN at risk of rapid disease progression. Previously reported evidence from a small number of pts with IgAN in the PROTECT open-label extension study support an additive benefit in proteinuria reduction with an SGLT2i added to SPAR, but evidence on the combination treatment in the real-world setting is limited. Here we report a series of 4 pts with IgAN receiving SPAR in combination with an SGLT2i.

Case Description: Four pts with biopsy-proven IgAN (aged 29-62 y) received SPAR (400 mg/d; dose increased from 200 mg/d after 2 weeks [or at closest follow-up visit]) in combination with the SGLT2i dapagliflozin. Individual case details are summarized in the **Table.** Three pts received prior steroid/immunosuppressive treatment (tx; alone or in combination with a renin-angiotensin system inhibitor [RASi]); 1 pt received a prior RASi (losartan) alone. Duration of follow-up on SPAR tx ranged from 3 to 7 mo, with all pts still receiving SPAR + SGLT2i combination tx at last follow-up. A decrease in proteinuria (urine protein-to-creatinine ratio [UPCR]) was seen in all pts regardless of eGFR at initiation. One pt achieved complete remission of proteinuria (UPCR <0.3 g/g) after 3 mo of SPAR + SGLT2i tx. In all pts, proteinuria improved to a greater extent with SPAR + SGLT2i than it had from diagnosis to the end of previous treatment. All pts had hematuria at SPAR initiation; it resolved in 1 pt after 8 mo on SPAR + SGLT2i. Blood pressure was generally stable with the combination tx. SPAR + SGLT2i tx was generally well tolerated, with no liver function test elevations.

Discussion: This case series supports the safety and efficacy of SPAR in combination with the SGLT2i dapagliflozin in pts with IgAN; improvements were observed in proteinuria regardless of eGFR or UPCR at SPAR initiation. Cases also highlight an additive benefit of SPAR, with greater proteinuria improvements achieved with SPAR + SGLT2i than previous treatment.

Table. Case Summaries

Age, y	Sex	Race	Time since IgAN diagnosis	Other treatment history*	SGLT2i duration	Duration of follow-up on SPAR, mo	UPCR at diagnosis, g/g	UPCR at SPAR initiation,† g/g	UPCR at follow-up, g/g	eGFR at SPAR initiation,† mL/min/1.73 m²	eGFR at follow-up, mL/min/1.73 m²
62	Female	White	4 mo	Prednisone RASi	3 mo	3	1.6	1.9	0.4	102	102
29	Female	White	13 mo	Prednisone Rituximab	3 mo	3	1.1	3.48	0.16	48	56
53	Male	White	11 y	Losartan	2 y	5	3.8	2.43	1.5	20	21
44	Female	White	4 y	Prednisone Cyclophosphamide Mycophenolate mofetil	2 mo‡	7	5.1	2.2	1.1	60	58

eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RASi, renin-angiotensin system inhibitor; SPAR, sparsentan; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
*Treatment(s) discontinued. †Values at initiation derived from visit at which SPAR was initiated or most recent visit prior to initiation. ‡Total duration of interrupted treatment.

FR-PO907

Sparsentan (SPAR) in Patients with Prior or Concurrent Immunosuppressive Treatment (IST) for IgA Nephropathy (IgAN): A Case Series

Luis E. Velez,[1] Reva Siva,[2] Agness Pelts Block,[3] Christopher Gisler,[3] Pablo Garcia.[4] *[1]South Texas Renal Care Group, San Antonio, TX; [2]Virginia Nephrology Group, Arlington, VA; [3]Travere Therapeutics, Inc., San Diego, CA; [4]University of New Mexico School of Medicine, Division of Nephrology, Albuquerque, NM.*

Introduction: SPAR is a nonimmunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA) approved in the US and EU for the treatment of adults with IgAN. Little is known about the effects of SPAR in patients receiving IST for IgAN. We report a series of 5 cases involving patients with IgAN who received SPAR after previous IST or initiated SPAR in addition to ongoing IST.

Case Description: Five patients with biopsy-proven IgAN (ages 21-71 y) initiated SPAR (400 mg/d; dose increased after 2 weeks at 200 mg/d) after discontinuing IST (n=3; IST discontinued due to insufficient response or completion of treatment course) or in addition to ongoing IST (n=2). Individual case details are summarized in the **Table**. Duration of follow-up on SPAR ranged from approximately 4 to 6 mo; all patients were receiving ongoing SPAR treatment at last follow-up. A decrease in proteinuria (urine protein-to-creatinine ratio [UPCR]) was seen in all patients after SPAR treatment, regardless of estimated glomerular filtration rate (eGFR) or UPCR at initiation, with 2 achieving complete remission (UPCR <0.3 g/g). Overall, there were no major fluctuations in blood pressure or eGFR decline at follow-up, with an improvement in eGFR seen in 1 patient. Of 4 patients with hematuria at SPAR initiation, hematuria improved in 1 patient and resolved in 2 patients. SPAR was generally well tolerated by these patients. In 1 patient, SPAR treatment was briefly interrupted due to elevated liver function tests but was resumed (initially at 200 then 400 mg/d) without further issue.

Discussion: These cases support the safety and efficacy of SPAR in patients with previous or ongoing IST. Improvements in proteinuria were observed regardless of eGFR or UPCR at SPAR initiation, including in patients in whom target proteinuria was not achieved with IST alone.

Table. Case Summaries

Age, y	Sex	Race or ethnicity	Time since IgAN diagnosis	Other treatment history (duration)	Steroid/IST (duration)	Duration of follow-up on SPAR (mo)*	UPCR at SPAR initiation,† g/g	UPCR at Follow-up, g/g	eGFR at SPAR initiation,† mL/min/1.73 m²	eGFR at follow-up, mL/min/1.73 m²
44	Female	White	18 mo	SGLT2i (5 mo; discontinued‡) ACEi (9 mo; discontinued‡)	[illegible] (9 mo; discontinued‡)	6	0.98	0.24	[illegible]	94
58	Male	White	8 mo	ACEi (NS; discontinued‡)	Budesonide (9 mo; ongoing)	4	2.6	0.6	35	36
71	Female	Hispanic	4.5 y	ARB (NS; discontinued‡)	Budesonide (8 mo; ongoing); Tacrolimus + Mycophenolate (NS; ongoing)	5	2.98	1.25	65	[illegible]
51	Male	White	11 y	ACEi (NS; discontinued‡)	Prednisone (9 mo; discontinued)	5	3.2	1.75	24	25
21	Male	Asian	3 y	ACEi (23 mo; discontinued‡)	Cyclophosphamide (6 mo; discontinued); Prednisone (6 mo; discontinued)	6	0.74	0.25	127	121

[illegible]

FR-PO908

Is Age Just a Number? A Comparative Analysis of Glomerular Disease across Ages from the CureGN Network

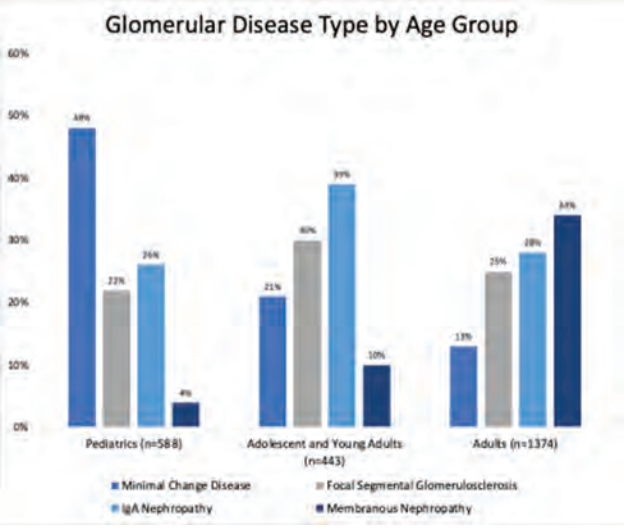
Andrew Vissing,[1,2] Shikha Wadhwani,[1] Abigail R. Smith,[1] Jerome C. Lane,[2] Cybele Ghossein,[1] Jill Krissberg.[2] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL.*

Background: Currently, there is limited research that investigates the characteristics and outcomes of adolescents and young adults (AYA) living with glomerular disease (GD). Our study seeks to understand how this group fares compared to younger and older patients.

Methods: Cure Glomerulonephropathy (CureGN) network is a multicenter prospective cohort study of children and adults with biopsy-proven GD diagnosed by biopsy within 5 years prior to enrollment. For our study, patients were categorized into the following groups: pediatric (≤13 years of age), AYA (14 to 25 years of age), and adult (≥26 years of age). Demographics and baseline disease characteristics were collected at enrollment and compared across age groups.

Results: The study included 2,405 patients (588 pediatric, 443 AYA and 1,374 adult). The prevalence of GD varied by age with minimal change disease being the most common in pediatrics (47.6%), IgA nephropathy in AYA (39.1%), and membranous nephropathy in adults (33.8%). More pediatric patients had active disease at enrollment (77.2% vs 68.9% in AYA and 69.4% in adults) but were also more likely to have reached complete remission at some point prior to enrollment (49.7% vs 32.1% in AYA and 22.3% in adults). Adults exhibited the lowest eGFR at enrollment (68.7 ml/min/1.73m^2 vs 86.0 ml/min/1.73m^2 in AYA and 104.6 ml/min/1.73m^2 in pediatrics).

Conclusions: This study highlights that AYA with GD have unique clinical characteristics when compared to either pediatric or adult populations. Recognizing this can help guide treatment and management strategies. Ongoing analysis for this project will explore whether AYA with GD have renal outcomes that differ compared to their younger and older counterparts.



FR-PO909

Sex Differences in Glomerular Diseases and Their Long-Term Outcomes

Aglaia Chalkia, Emelina Stambolliu, Margarita Bora, Elpiniki Stathopoulou, Athanasios Papras, Dimitrios I. Petras. *Hippokration General Hospital, Athens, Greece.*

Background: Sex differences in kidney diseases have received limited attention. Research in this area is crucial for developing targeted prevention and intervention strategies that address the unique needs and risk factors of diverse populations.

Methods: Retrospective, single-centre study at a reference centre for glomerular diseases. We evaluated the prevalence of glomerular diseases among males and females in terms of clinical characteristics and long-term outcomes. Logistic regression analysis and time-to-event analyses were employed.

Results: 232 patients were included; 63% male and 37% female. The most common glomerular disease in males was IgA nephropathy (29%), while females most frequently presented with ANCA-associated glomerulonephritis (19%) and FSGS (19%). Notably, IgG4-related nephritis and membranoproliferative glomerulonephritis were observed only in males. At diagnosis, hypertension was more prevalent in males (71% vs 56%, p=0.035). There were no significant differences in the severity of kidney disease between sexes with the total cohort having a median (interquartile range) eGFR of 51 (25-85) ml/min/1.73m^2 and proteinuria 3 (1-6) gr/24h]. During the first year, females had a higher likelihood of infections compared to males (adjusted odds ratio OR 3.0 [95% CI 1.31-7.3], p=0.01), after adjusting for the type of immunosuppressive treatment. Renal recovery at 1st year was similar between the sexes, with males and females showing comparable eGFR increases [8±19 vs 11±21 ml/min/1.73m^2, p=0.50] and decreases in proteinuria [57% (0-90) vs 55% (0-83), p=0.35]. Over a median follow-up of 2 years (0.5-4), the 5-year overall survival rate was 90% with no significant difference between males and females (log-rank, p=0.181). In the total cohort, the 5-year renal survival rate was 86%. However, in the subgroup of patients with baseline eGFR<30ml/min/1.73m^2, males tended to have worst renal survival (log-rank, p=0.087).

Conclusions: This study highlights sex differences in glomerular diseases, particularly in infection rates and hypertension prevalence. Despite these differences, long-term survival rates were similar between sexes. However, males with severe kidney disease at baseline showed a trend towards worse renal survival.

FR-PO910

Incident Diabetes in Glomerular Diseases

Samuel Haddad,[1] Calvin Andrews,[5] Margaret Helmuth,[4] Abigail R. Smith,[3] Cynthia C. Nast,[2] Amy K. Mottl.[1] *[1]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Cedars-Sinai Medical Center, Los Angeles, CA; [3]Northwestern University, Evanston, IL; [4]University of Michigan, Ann Arbor, MI; [5]Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: Glomerular diseases (GDs) can result in significant kidney morbidity. Comorbid diabetes (DM) can occur following GD onset and may exacerbate the rate of decline in eGFR. We examined risk factors for incident DM, and the association of incident DM with major adverse kidney events (MAKE).

Methods: Adults with MCD, FSGS, MN, or IgAN enrolled in the prospective CureGN observational cohort study were included. Multivariable Cox regression models of time from biopsy to incident diabetes and MAKE (40% decline in eGFR or ESKD) were fitted. The base model associated age at biopsy, sex, racial/ethnic minority, family history of DM, and BMI with incident DM risk. Additional models sequentially tested GD diagnosis (IgAN, FSGS, MCD, MN), smoking, baseline eGFR, and time-dependent steroid or CNI use. Associations between time-dependent diabetes incidence and MAKE were adjusted for base model covariates.

Results: Of 1,729 adults enrolled in CureGN, 142 developed incident DM (Table); median (IQR) time from biopsy to DM was 23 (5-58) months. Older age, higher BMI, and smoking history were associated with higher risk of incident DM; no associations between steroid and CNI use and risk of incident DM in GD were detected (Figure). No association between incident DM after GD diagnosis was detected for MAKE (HR=0.99; 95% CI: 0.66-1.50).

Conclusions: Long-term risks of incident DM in GD remain to be determined.

Funding: NIDDK Support

Table 1. Sociodemographic and clinical characteristics of adult participants in the CureGN cohort, stratified by incident diabetes.

	Incident diabetes N=142	Without diabetes N=1587
Diabetes type		
Type 1	2 (1%)	--
Type 2	128 (90%)	
Unknown	9 (6%)	
Medication induced diabetes	69 (49%)	--
Time from biopsy to DM diagnosis (mos), median (IQR)	23 (5, 58)	--
Diabetes Treatment		
Diet control	64 (45%)	--
Insulin use	27 (19%)	
Other	69 (49%)	
Age at biopsy (years), median (IQR)	53 (43, 60)	44 (32, 57)
Age at enrollment (years), median (IQR)	55 (46, 63)	46 (34, 56)
Female	52 (37%)	710 (45%)
Minority Race	52 (37%)	479 (30%)
Hispanic/Latino Ethnicity	19 (13%)	207 (13%)
Glomerular disease		
MCD	16 (11%)	215 (14%)
FSGS	38 (27%)	405 (26%)
MN	55 (39%)	497 (31%)
IgAN	33 (23%)	470 (30%)
Follow-up time from biopsy (years), median (IQR)	6 (3.4, 7.6)	5.1 (1.9, 7.1)
BMI at enrollment, adults only, median (IQR)	31.6 (26.8, 36.9)	28 (24.4, 33)
Current or Ever Smoking status at enrollment	82	603
Major adverse kidney event	47 (33%)	391 (25%)
Family history of diabetes	66 (46%)	530 (33%)
Immunosuppression use	105 (74%)	1103 (70%)
Steroids	86 (61%)	917 (58%)
ACTH	5 (4%)	33 (2%)
Tacrolimus	18 (13%)	275 (17%)
Number of IV steroid pulses, median (IQR)	0 (0, 0)	0 (0, 6)
Cumulative exposure to IV steroids (mos), median (IQR)	15 (11%)	255 (16%)
Cumulative exposure to any steroids (mos), median (IQR)	6 (2, 14)	9 (5, 18)

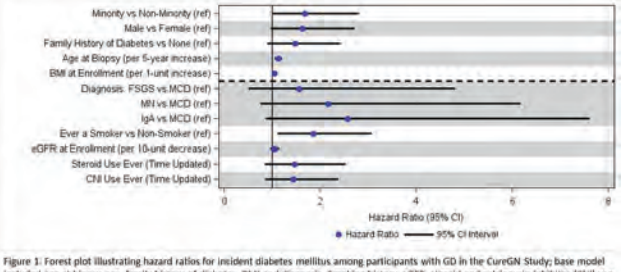


Figure 1: Forest plot illustrating hazard ratios for incident diabetes mellitus among participants with GD in the CureGN Study; base model included age at biopsy, sex, family history of diabetes, BMI and diagnosis. Smoking history, eGFR, steroid and calcineurin inhibitor (CNI) use were added to the base model sequentially.

FR-PO911

Pregnancy Outcomes in Patients with Primary Glomerular Diseases and the Impact on Kidney Outcomes

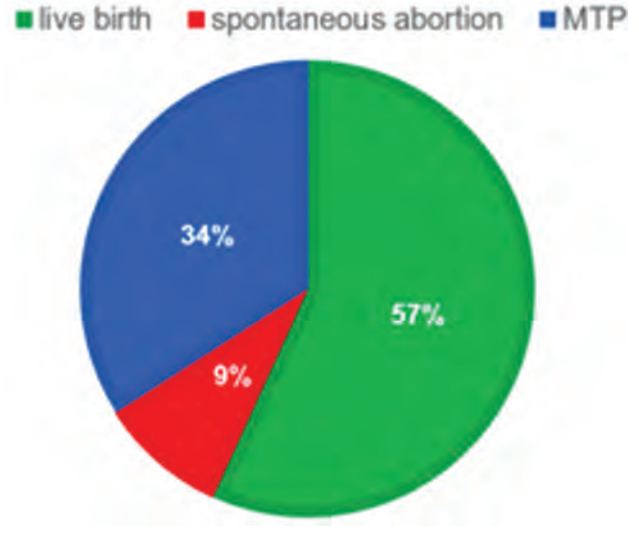
Jaideep Menda, Snikitha Tummala, Arunkumar Subbiah, Sandeep Mahajan, Dipankar M. Bhowmik, Soumita Bagchi. *All India Institute of Medical Sciences, New Delhi, India.*

Background: Primary glomerular diseases frequently affect women in childbearing age. There is a dearth of information about the impact of pregnancy on the outcome in such diseases. This retrospective cohort study examines pregnancy outcomes in women with biopsy-proven primary glomerular disease and the impact on renal survival.

Methods: We assessed the medical records of women in child bearing age (18-45 years) diagnosed with biopsy proven primary glomerular disease (IgAN, FSGS, MGN, MCD) from 2012- 2022 at a single centre AIIMS New Delhi. Patients with end stage kidney disease (ESKD) at the time of biopsy and/or at time of conception and those who had undergone kidney transplantation were excluded. Pregnancy and Kidney outcomes were recorded. Relapse was defined as increase in proteinuria to >3.5g/day (>1g/day for IgAN) and renal disease progression as >40% sustained decline in eGFR and/or ESKD.

Results: Of 238 women assessed, 81 were lost to follow up and 125 did not conceive after biopsy. 44 pregnancies were documented in 32 women (IgAN n=21, FSGS n=6, MGN n=10, MCD n=7). The median age of conception was 28.5 (25.2-33.0) years and the median time from biopsy to conception was 3 (2-5.8) years. 15 pregnancies (34%) were medically terminated, 4 (9%) resulted in spontaneous abortions, and 25 (57%) culminated in live births. 12 of 44 (27%) pregnancies occurred while the patient was on ACEi/ARBs of which 7 pregnancies resulted in live births. 12 out of 25 live births were premature and IUGR below 10th percentile affected 15 pregnancies. Preeclampsia affected 6 pregnancies. From a renal perspective, 9 women had active disease at the time of conception. 7 (33%) women had a relapse of kidney disease during pregnancy and 2 (9.5%) women relapsed immediate postpartum. 8 of these 10 women received steroids during pregnancy. In 6 women, there was renal disease progression, of which 1 developed ESKD.

Conclusions: Pregnancy is associated with adverse maternal and fetal outcomes in women with primary glomerular diseases.



Distribution of pregnancy outcomes

	All (n= 25)	IgA (n=11)	FSGS (n=2)	MGN (n=6)	MCD (n=6)
Pregnancy outcomes					
Preeclampsia	6	4	2	0	0
Number of LSCS deliveries	18	8	2	5	3
Number of Pre term deliveries	12	8	1	3	0
Number of IUGR	15	8	0	5	2
Renal Outcomes					
Relapse during pregnancy	7	5	0	1	1
Relapse immediate postpartum	2	2	0	0	0
Developed nephrotic range proteinuria	4	2	1	1	0
Renal disease progression	6	4	1	1	0

FR-PO912

Comprehensive Druggable Genome-Wide Mendelian Randomization Reveals Therapeutic Targets for Kidney Diseases

Zhihang Su, Rui Xue, Qijun Wan. *Shenzhen Second People's Hospital, Shenzhen, China.*

Background: Kidney diseases, including membranous nephropathy (MN), IgA nephropathy (IgAN), and chronic kidney disease (CKD), present global health challenges due to their prevalence and severe outcomes. Mendelian randomization (MR) has been used extensively to repurpose drugs and identify novel targets. Thus, our study aims to identify therapeutic targets for kidney diseases, analyze their mechanisms, and assess potential side effects.

Methods: Integrated with currently available druggable genes, Summary-data-based Mendelian Randomization (SMR) analysis was conducted to estimate the causal effects of blood expression quantitative trait loci (eQTLs) on kidney diseases. To validate the identified genes, a replication study was performed using distinct blood eQTL and disease genome-wide association study (GWAS) data sources. eQTL data was obtained from eQTLGen and GTEx v8.0, with sample sizes of 31,684 and 15,201, respectively. The data on kidney diseases was sourced from the Kiryluk Lab, CKDgen, and the Finngen consortium, with sample sizes ranging from 7,979 to 412,181. The study population consists of European individuals. Subsequently, two-sample MR and colocalization analysis were employed for further validation. Finally, the potential side effects of the identified key genes in treating kidney diseases were assessed using phenome-wide MR and mediation MR.

Results: After correcting for the false discovery rate, a total of 20, 23, and 6 unique potential genes were found to have causal relationships with MN, IgAN, and CKD, respectively. Among them, MN showed validated associations with one gene (HCG18), IgAN demonstrated associations with four genes (AFF3, CYP21A2, DPH3, HLA-DRB5), and chronic kidney disease (CKD) displayed an association with one gene (HLA-DQB1-AS1). Several of these key genes are druggable genes. Further phenome-wide MR analysis revealed that certain genes may be associated with diabetes and fat metabolism, suggesting that these factors could potentially serve as mediators.

Conclusions: This study presents genetic evidence that supports the potential therapeutic benefits of targeting these key genes for treating kidney diseases. This is significant for prioritizing drug development efforts for kidney disease treatments.

FR-PO913

Immunosuppressive Therapy (IST)-Related Adverse Events in Patients with Glomerular Disorders (GDs)

Andrea Lim,[1] Belia O. Roybal,[3] Mimi J. Yao,[1,2] Aida Shirazi,[1] Jessica B. Lapasia,[1] Ali Poyan-Mehr.[1] *[1]Kaiser Permanente San Francisco Medical Center, San Francisco, CA; [2]University of California San Diego, La Jolla, CA; [3]Kaiser Permanente Division of Research, Oakland, CA.*

Background: Treatment-emergent adverse events (TAE) in GD patients include infection (IF) and gastrointestinal bleed (GI). Unfortunately, data about TAE prevalence in GD patients receiving IST is scant, and effectiveness of prophylaxis is unknown.

Methods: In this retrospective study, we identified 806 patients with a biopsy-proven GD diagnosis between 1/1/2010 and 10/31/2022 who were treated with IST. We evaluated TAE prevalence within an 18-month follow-up period from time of treatment initiation. We also evaluated risk-modifying factors with baseline clinical characteristics.

Results: The proportion of those with IF- or GI-TAE was highest in vasculitis-related GD (37.4% and 30.1%, respectively) compared to other GD diagnosis categories. Further, IF and GI-TAEs were more prevalent in patients treated with glucocorticoids than other IST (66.4% and 72.6%, respectively). Significant differences in baseline characteristics exist between those with and without TAEs.

Conclusions: Our preliminary results find that IF- and GI-TAEs appear to be more prevalent in those treated with glucocorticoids and those with vasculitis-related GD. A multi-regression analysis is being conducted to identify factors that can identify those at high risk for TAEs.

Funding: Clinical Revenue Support

Table 1A. Patients diagnosed with glomerular disease receiving immunosuppressive therapy were stratified as those with at least one infectious complication versus those without any infectious complication during the follow-up period. UPCR: Urine protein to creatinine ratio. BMI: Body mass index. MGRS: Monoclonal gammopathy of renal significance. *Values at time of diagnosis. P values were computed using a parametric test (t test), a non-parametric test (Wilcoxon rank test), Kruskal Wallis for group differences, and Chi-square and Fisher's exact test for categorical variables.

Baseline Characteristics – Infectious Complication

	Overall	IF	No IF	P-Value
Total, n (%)	806 (100)	131 (16.2)	675 (83.7)	
Age*, years, median (IQR)	52 (36-67)	63 (43-73)	50 (35-66)	<0.001
Female, n (%)	442 (54.8)	72 (55.0)	370 (54.8)	0.96
Race				0.11
White, n (%)	263 (32.6)	52 (39.7)	207 (31.1)	
Black, n (%)	60 (7.4)	12 (9.2)	48 (7.1)	
Hispanic, n (%)	182 (22.9)	28 (21.4)	154 (23.2)	
Asian/Pacific Islander, n (%)	231 (29.0)	32 (24.4)	199 (29.9)	
Unknown/Other, n (%)	44 (5.5)	3 (2.3)	41 (6.2)	
BMI*, mean (SD)	29.3 (7.0)	30.0 (7.0)	29.1 (7.0)	0.20
Creatinine* (mg/dL), mean (SD)	2.0 (1.5)	2.7 (1.8)	1.9 (1.4)	<0.001
UPCR* (g/g), mean (SD)	6.2 (6.4)	5.4 (4.8)	6.3 (6.7)	0.07
Serum albumin* (mg/dL), mean (SD)	2.9 (0.8)	3.0 (0.8)	2.9 (0.8)	0.28
Comorbidities				
Coronary artery disease, n (%)	21 (2.6)	5 (3.8)	16 (2.4)	0.36
Heart failure, n (%)	58 (7.3)	18 (13.7)	40 (6.0)	<0.01
Hypertension, n (%)	441 (55.4)	97 (74.0)	344 (51.7)	<0.001
Diabetes mellitus type 2, n (%)	126 (15.8)	27 (20.6)	99 (14.9)	0.10
Underlying glomerular disease				<0.001
FSGS, n (%)	107 (13.4)	16 (12.2)	91 (13.7)	
IgA nephropathy, n (%)	147 (18.5)	17 (13.0)	130 (19.5)	
Lupus nephritis, n (%)	127 (16.0)	24 (18.3)	103 (15.5)	
MGRS, n (%)	9 (1.1)	3 (2.3)	6 (0.9)	
Membranous nephropathy, n (%)	79 (9.9)	7 (5.3)	72 (10.8)	
Minimal change disease, n (%)	92 (11.6)	6 (4.6)	86 (12.9)	
Vasculitis, n (%)	183 (23.0)	49 (37.4)	134 (20.2)	
Other	51 (6.4)	8 (6.1)	43 (6.5)	
Treatment characteristics, n (%)				0.29
Glucocorticoid, n (%)	570 (71.6)	87 (66.4)	483 (72.6)	
Calcineurin inhibitor, n (%)	31 (3.8)	4 (3.1)	27 (3.1)	
Mycophenolate, n (%)	85 (10.7)	12 (9.2)	73 (11)	
Rituximab, n (%)	78 (9.8)	15 (14.3)	59 (8.9)	
Cyclophosphamide (oral), n (%)	28 (3.5)	7 (5.3)	21 (3.2)	
Cyclophosphamide (IV), n (%)	17 (2.1)	4 (3.1)	13 (2.0)	

Table 2B. Patients diagnosed with glomerular disease receiving immunosuppressive therapy were stratified as those with at least one gastrointestinal complication (gastrointestinal ulcers or bleed) versus those without any such complication during the follow-up period. UPCR: Urine protein to creatinine ratio. GI: gastrointestinal complication. BMI: Body mass index. MGRS: Monoclonal gammopathy of renal significance. *Values at time of diagnosis. P values were computed using a parametric test (t test), a non-parametric test (Wilcoxon rank test), Kruskal Wallis for group differences, and Chi-square and Fisher's exact test for categorical variables.

Baseline Characteristics – Gastrointestinal Complication

	Overall	GI	No GI	P-Value
Total, n (%)	806 (100)	74 (9.2)	732 (90.8)	
Age*, years, median (IQR)	52 (36-67)	67 (46-73)	51 (36-66)	<0.001
Female, n (%)	438 (55.0)	30 (41.1)	408 (56.4)	<0.05
Race				0.57
White, n (%)	259 (32.5)	27 (37.0)	232 (32.1)	
Black, n (%)	80 (10.1)	7 (9.6)	73 (10.1)	
Hispanic, n (%)	182 (22.9)	20 (27.4)	162 (22.4)	
Asian/PI, n (%)	231 (29.0)	16 (21.9)	215 (29.7)	
Unk/Other, n (%)	44 (5.5)	3 (4.1)	41 (5.7)	
BMI*, mean (SD	29.3 (7.0)	30.1 (6.4)	29.2 (7.0)	0.25
Creatinine* (mg/dL), mean (SD)	2.0 (1.5)	3.1 (2.2)	1.9 (1.4)	<0.001
UPCR* (g/g), mean (SD)	6.2 (6.4)	6.5 (5.3)	6.2 (6.5)	0.58
Serum albumin* (mg/dL), mean (SD)	2.9 (0.8)	2.9 (0.8)	2.9 (0.8)	1.00
Comorbidities				
Coronary artery disease, n (%)	21 (2.6)	6 (8.2)	15 (2.1)	<0.01
Heart failure, n (%)	58 (7.3)	16 (21.9)	42 (5.8)	<0.001
Hypertension, n (%)	441 (55.4)	61 (83.6)	380 (52.6)	<0.001
Diabetes mellitus type 2, n (%)	126 (15.8)	13 (17.8)	113 (15.6)	0.63
History of peptic ulcer disease, n (%)	7 (0.9)	5 (6.8)	2 (0.3)	<0.001
History of gastrointestinal bleed, n (%)	23 (2.9)	11 (15.1)	12 (1.7)	<0.001
Underlying glomerular disease				<0.01
FSGS, n (%)	107 (13.4)	11 (15.1)	96 (13.3)	
IgA nephropathy, n (%)	147 (18.5)	8 (11.0)	139 (19.2)	
Lupus nephritis, n (%)	127 (16.0)	11 (15.1)	116 (16.0)	
MGRS, n (%)	9 (1.1)	2 (2.7)	7 (1.0)	
Membranous nephropathy, n (%)	79 (9.9)	9 (12.3)	70 (9.7)	
Minimal change disease, n (%)	92 (11.6)	2 (2.7)	90 (12.4)	
Vasculitis, n (%)	183 (23.0)	22 (30.1)	161 (22.3)	
Treatment characteristics				0.94
Glucocorticoid, n (%)	570 (71.6)	53 (72.6)	517 (71.5)	
Calcineurin inhibitor, n (%)	31 (3.8)	2 (2.7)	29 (4)	
Mycophenolate, n (%)	85 (10.7)	6 (8.2)	79 (10.9)	
Rituximab, n (%)	78 (9.8)	9 (12.3)	69 (9.5)	
Cyclophosphamide (oral), n (%)	28 (3.5)	3 (4.1)	25 (3.5)	
Cyclophosphamide (IV), n (%)	17 (2.1)	1 (1.4)	16 (2.2)	

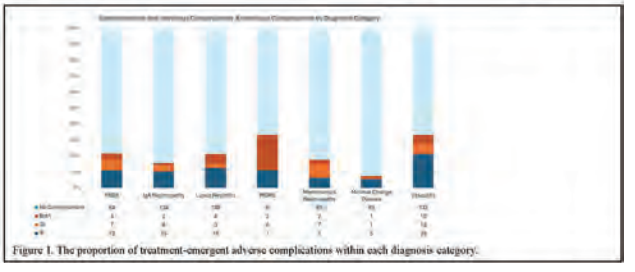


Figure 1. The proportion of treatment-emergent adverse complications within each diagnosis category.

FR-PO914

Immunosuppressant Use in Infective Endocarditis-Associated Glomerulonephritis: A Systematic Review

Mostafa G. Aly,[1,2] Reem Sayad,[3] Leenah N. Sherif,[5] Muhammed Edib Mokresh,[4] Mohamed Mohamed Shawqi,[6] Yasmine A. Mohammed,[3] Eslam A. Hawash,[7] Ahmed M. Ali,[3] Ahmed Saad Elsaeidy.[7] *[1]Nephrology Unit, Internal Medicine Department, Assiut University, Assiut, Egypt; [2]Nephrology Department, Sana-Klinik Hof, Hof, Germany; [3]Assiut University Faculty of Medicine, Assiut, Egypt; [4]Hamidiye International School of Medicine, University of Health Sciences, Istanbul, Turkey; [5]Emergency Department, Faculty of Medicine, Menoufia University, Menoufia, Egypt; [6]Emergency Medicine Department, Faculty of Medicine, Benha University, Benha, Egypt; [7]Benha University Faculty of Medicine, Benha, Egypt.*

Background: Patients with infective endocarditis (IE) can develop various renal diseases, including infection-related glomerulonephritis (GN). Antibiotics are essential for eradicating the infection. However, the prognosis for renal function remains poor. The use of immunosuppressants in IE-associated GN is still debated. This systematic review examines the role of immunosuppressants in managing these cases.

Methods: A comprehensive search was performed across four databases: PubMed, Scopus, MedLine, and Web of Science up to April 2024. We included studies that investigated patients with any type of GN due to IE who were treated with immunosuppressants. Data extraction was conducted using a standardized sheet, and study quality was assessed using the JBI critical appraisal tool.

Results: The review incorporated 55 studies encompassing 84 cases, 65 of whom were male. The median age was 46.5 years. Predisposing factors and cardiac and renal manifestations are detailed in Figure 1. Immunosuppressants used included steroids (oral and/or IV), cyclophosphamide, rituximab, azathioprine, mycophenolate mofetil, and hydroxychloroquine. Thirty cases required dialysis. Following immunosuppressive

therapy, 69 cases improved, 10 worsened, and 5 showed no improvement in renal function. There were 10 fatalities, with 4 cases due to sepsis, 3 due to congestive heart failure, 1 due to cardiac arrhythmia, 1 due to renal failure, and 1 due to an unreported cause. Additional treatments included plasma exchange, with 9 cases receiving plasmapheresis/plasma exchange. Of these, 8 patients showed marked renal function improvement, and 1 patient showed partial improvement. Three patients also received IVIG.

Conclusions: Immunosuppressive therapy led to renal function improvement in the majority of cases, suggesting its potential benefit in managing IE-related GN. However, variability in response and significant mortality highlight the need for individualized treatment strategies and further research to optimize management. **Legend** Figure 1: PRISMA Flowchart for the selection of studies and an algorithm summarizing the included cases.

FR-PO915

Long-Term Risk of ESKD in Postinfectious Glomerulonephritis

Rune Bjoerneklett, Lars S. Bostad, Thomas Knoop, Leif H. Bostad.
Department of Clinical Medicine, University of Bergen, Bergen, Norway.

Background: Kidney biopsy is usually not required for the diagnosis of post-infectious glomerulonephritis (PIN). When kidney biopsies are nevertheless performed for example in patients with PIN and severe or atypical clinical presentations, the light microscopic picture is characteristic in the form of endocapillary glomerulonephritis. The immunological picture is however less specific for PIN as in many cases this is dominated by complement factor C3 deposits. In such cases, PIN can theoretically be confused with complement 3 nephropathy (C3N) based on the immunological findings. While PIN is considered a self-limiting condition with a good prognosis, C3N, often has a progressive course leading to end-stage kidney disease (ESKD) in a significant proportion of patients. To what extent confusion of PIN versus C3N has occurred in clinical practice in Norway is unknown. As such prognostic data is limited we have analyzed the very long-term risk of ESKD in patients with biopsy-verified PIN registered in the Norwegian Kidney Biopsy Registry (NKBR) in the period 1991-2012.

Methods: Cases of biopsy-verified PIN 1991-2012 including demographic, clinical, laboratory, and histological variables at the time of diagnosis were retrieved from the NNBR. The cohort was linked with the Norwegian Kidney Registry for identification of patients with ESKD by May 1, 2024.

Results: We identified 82 patients with PIN. Men; 45 (55%), age; 35 years (SD 22), systolic BP; 140 mmHg (SD 24), diastolic BP; 80 (SD 14), hypertension 42 (51%), eGFR 58 ml/min/1.73m2 (SD 37), eGFR<15; 12 (15%), eGFR 15-29; 8 (10%) and eGFR 30-59; 26 (32%), serum albumin; 31 gram/liter (SD 6), proteinuria; 3.8 gram/24 hours (SD 4.2), nephrotic syndrome; 20 (24%), crescents; 26 (32%), >50% tubulointerstitial fibrosis; 17 (21%) and isolated C3 positivity 29 (35%). During an average observation time of 21 years, there were no patients who progressed to ESKD.

Conclusions: Despite many cases with severe kidney affection at the time of diagnosis, no patients with PIN progressed to ESKD during a very long follow-up time. A C3N resembling immunological image is not associated with the risk of ESKD in patients with PIN.

Funding: Commercial Support - Novartis

FR-PO916

Corticosteroids after Hemodialysis May Improve Kidney Function in Infection-Related Glomerulonephritis

Evani Patel, Kwon Soo Kim, Andrew Murphy. *Penn Medicine, Philadelphia, PA.*

Introduction: Staphylococcus-associated Glomerulonephritis (SAGN) is an uncommon renal phenomenon following staphylococcal bacteremia, where management involves intravenous antibiotics. We report a case of severe, persistent SAGN requiring hemodialysis, with improvement through glucocorticoids, thus, paving a path for the reassessment of guidelines for SAGN after the use of antibiotics.

Case Description: A 74-year-old male with a history of end-stage renal disease, kidney transplant and now on tacrolimus, nephrectomy for oncocytoma presented with a right foot digit gangrene and septic shock. Workup was remarkable for a urinalysis consistent with a UTI, and blood cultures showing methicillin-susceptible staphylococcal aureus. His course was further complicated by endocarditis, worsening creatinine from baseline, and volume expansion refractory to diuretics requiring hemodialysis. Following 4 sessions, his creatinine continued to rise. Due to a broad set of differentials including transplant rejection, thrombotic microangiopathy and tacrolimus toxicity, a renal biopsy was performed. At this time, he had a negative ANCA-level and hypocomplementemia with C3, most consistent with IRGN which was later confirmed by biopsy. Given the severity of his AKI requiring HD, a decision was made to treat with a course of 500mg IV methylprednisolone followed by 5mg Prednisone daily, after which his creatinine down-trended and he did not require further dialysis.

Discussion: Infection-related glomerulonephritis (IRGN), more specifically SAGN, involves the deposition of preformed immune complexes during, or a few days following concurrent infection. It is presumed that treatment with antibiotics will reduce antigen production, and therefore, decrease kidney inflammation. Previous studies show that treatment with corticosteroids is ill-advised as it poses a risk of recurrent sepsis and increases mortality. Our case highlights three pearls: the uniqueness of a severe acute kidney injury requiring hemodialysis, the importance of a kidney biopsy for an unclear etiology, and the initiation of high-dose corticosteroids in an immunocompromised individual for uncontrolled glomerulonephritis. This case brings to light the need to constantly evaluate the driving process of SAGN, whether it is inflammation or infection, to determine if an immunosuppressive approach should be taken.

FR-PO917

Efficacy of Pneumocystis jirovecii Pneumonia Prophylaxis in Preventing Infections among Patients with Kidney Disease Receiving Rituximab Therapy

Jing Miao, Pajaree Krisanapan, Maria Jose Vargas-Brochero, Charat Thongprayoon, Lisa E. Vaughan, Fernando C. Fervenza, Ladan Zand. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Pneumocystis jirovecii pneumonia (PJP) prophylaxis is frequently used in kidney disease patients during rituximab (RTX) therapy. However, the effectiveness of PJP prophylaxis in this context is uncertain.

Methods: This retrospective study included adult patients with AAV, LN, MN, primary podocytopathy who began RTX therapy between 2012 and 2022. The association between treatment group (with vs. without PJP prophylaxis at RTX initiation) and the risk of incident infection post-treatment was analyzed using Cox proportional regression model. Patients were censored at death, transplantation, loss to follow-up, or one year post-treatment initiation, whichever came first.

Results: A total of 441 patients met inclusion criteria. At the time of first dose of RTX, 316 (72%) were on PJP prophylaxis, and 125 (28%) were on RTX alone (Fig.). AAV patients were more likely to receive PJP prophylaxis with RTX, whereas MN patients were more likely to receive RTX alone (*P<0.001*). Overall, no significant difference in infection risk was found between the groups (HR [95% CI], 0.92 [0.57, 1.47], *P=0.71*). Adjusting for kidney disease type, PJP prophylaxis was linked to a lower infection risk, though not statistically significant (HR, 0.67 [0.39, 1.15], *P=0.15*). Stratified by kidney disease type, PJP prophylaxis was associated with a lower infection risk in both AAV patients (HR 0.74 [0.34, 1.65], *P=0.46*) and non-AAV patients (HR 0.61 [0.28, 1.33], *P=0.21*), but not statistically significant.

Conclusions: The study found no significant protective effect of PJP prophylaxis on incident infections in kidney disease patients receiving RTX treatment. However, a reduced risk was noted when adjusting for disease types and in AAV patients. Further research is needed to evaluate these findings.

Table. Characteristics and incident infections in patients at first initiation of RTX therapy, overall and by treatment group

	Total (n=441)	RTX only (n=125)	PJP + RTX (n=316)	P value
Age (years)	61.8 ± 15.7	60.7 ± 15.3	62.3 ± 15.9	0.21
Male Gender, n (%)	256 (58.0%)	78 (62.4%)	178 (56.3%)	0.24
White race, n (%)	406 (92.9%)	115 (92.0%)	291 (93.3%)	0.84
BMI (kg/m²)	28.8 (24.6, 32.7)	28.7 (24.5, 32.7)	28.8 (24.7, 33.1)	0.71
Kidney Disease Type, n (%)				**<0.001**
AAV	255 (57.8%)	25 (20.0%)	**230 (72.8%)**	
LN (III, IV, V)	13 (0.73%)	8 (6.4%)	5 (1.5%)	
MN	152 (34.5%)	**85 (68.0%)**	67 (21.2%)	
MCD	11 (2.5%)	2 (1.6%)	9 (2.8%)	
Primary FSGS	10 (2.3%)	5 (4.0%)	5 (1.6%)	
Comorbidities, n (%)				
DM	74 (16.8%)	26 (20.8%)	48 (15.2%)	0.16
HTN	276 (62.6%)	82 (65.6%)	194 (61.4%)	0.41
Cardiovascular disease	79 (17.9%)	22 (17.6%)	57 (18.0%)	0.91
Pulmonary disease	79 (17.9%)	22 (17.6%)	57 (18.0%)	0.91
Laboratory				
SCr (mg/dL)	1.68 (1.15, 2.90)	1.30 (1.09, 1.90)	1.98 (1.20, 3.23)	**<0.001**
eGFR (ml/min/1.73m²)	46.6 ± 31.3	58.2 ± 29.4	42 ± 30.9	**<0.001**
Albumin (g/dL)	3.30 (2.70, 3.90)	3.40 (2.60, 4.00)	3.30 (2.70, 3.80)	0.43
24h proteinuria (g/24h)	2.24 (0.72, 6.00)	4.23 (1.79, 8.50)	1.40 (0.59, 4.30)	**<0.001**
CRP (mg/L)	11.9 (2.9, 81.5)	2.9 (2.9, 4.8)	26.5 (5.0, 97.6)	**<0.001**
ESR (mm/hr)	43 (21, 75)	30 (12, 59)	48 (26, 80)	**0.002**
WBC (x10⁹/L)	8.3 (6.1, 12.0)	6.7 (5.5, 8.3)	9.3 (6.6, 13.4)	**<0.001**
Neutrophils (x10⁹/L)	5.20 (3.55, 9.30)	4.02 (3.01, 5.30)	6.42 (4.16, 11.07)	**<0.001**
Lymphocytes (x10⁹/L)	1.44 (0.97, 2.01)	1.71 (1.21, 2.10)	1.33 (0.88, 1.90)	**0.002**

FR-PO918

Estimating Causal Effects of Glucocorticoid Use on Infection Rates in Glomerular Diseases Using a Novel Marginal Structural Proportional Rates Model

Jarcy Zee,[1,2] Qian Liu,[2] Dorey A. Glenn,[3] Michelle Denburg,[2,1] Douglas E. Schaubel.[1] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]The Children's Hospital of Philadelphia, Philadelphia, PA; [3]The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC.*

Background: Estimation of time-varying glucocorticoid treatment effects on infections have been limited to risks of first infection events, thus ignoring recurrent infections. Given the common recurrences of infections in patients with glomerular disease, and the need to account for time-dependent confounders, novel statistical methods are required to estimate causal treatment effects on recurrent outcomes.

Methods: We developed a marginal structural proportional rates model (MSPRM) to estimate the causal effect of a time-varying treatment on recurrent outcomes in the presence of time-dependent confounding. We derived estimation and inference procedures and conducted simulations to demonstrate model performance. We used the MSPRM to estimate the effect of time-varying glucocorticoid use on recurrent infection-related acute care events (hospitalizations or ER visits) accounting for proteinuria and serum albumin over time in the Cure Glomerulonephropathy (CureGN) study. Baseline confounders included age, sex, race, Hispanic ethnicity, glomerular disease type, eGFR, comorbidities, tobacco use, and time from biopsy to CureGN enrollment.

Results: Out of N=2496 CureGN study participants, N=405 had at least one infection, with a total of 590 infections. The MSPRM estimated that glucocorticoid use increased rates of infection by 1.70 (95% CI 1.32-2.18) times compared to no use (Figure). Based on simulations, the MSPRM has little bias compared to standard proportional rates models, which suffer from confounding and/or overadjustment bias.

Conclusions: The MSPRM can estimate causal time-varying treatment effects on recurrent time-to-event outcomes using weights to balance time-dependent confounders. Including recurrent events can better capture disease burden and morbidity compared to only considering the first event, and our proposed model provides a semi-parametric method to analyze these longer-term outcomes.

Funding: Private Foundation Support

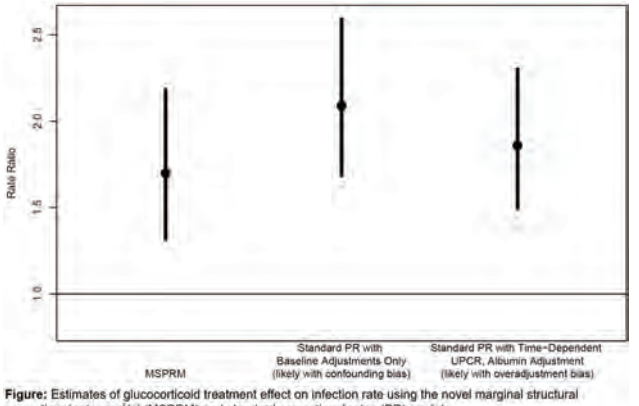


Figure: Estimates of glucocorticoid treatment effect on infection rate using the novel marginal structural proportional rates model (MSPRM) and standard proportional rates (PR) models.

FR-PO919

A Needs Assessment of HIV Providers in the Evaluation of Kidney Function in People Living with HIV

Rachel Shulman, William R. Short, Amanda L. Binkley, Amanda K. Leonberg-Yoo. *University of Pennsylvania, Philadelphia, PA.*

Background: Kidney disease is common in people living with HIV (PLHIV). Unique factors in HIV, including sarcopenia and certain antiretroviral drugs, can make creatinine unreliable. HIV providers are often the primary healthcare resource for PLHIV and the recognition of kidney disease lies in their hands.

Methods: We conducted a pilot survey of HIV providers in the University of Pennsylvania Health System. Questions focused on (1) current clinical practices for kidney function assessment, (2) identifying knowledge and attitudes for best clinical practices for kidney function assessment, and (3) identifying care gaps in the management of PLHIV.

Results: A total of 22 providers responded to the survey, including 16 physicians, 2 infectious disease pharmacists, 1 advanced practitioner. For routine care of PLHIV, most providers assess kidney function with a serum creatinine and urinalysis (95% and 68%, respectively). For PLHIV with an elevated creatinine, 95% of providers (n=21) would obtain a repeat creatinine. Only 23% (n=5) would obtain a cystatin C. To determine drug dosing, 32% of providers (n=7) use an estimated GFR (eGFR) equation, 9% (n=2) use Cockcroft Gault creatinine clearance, and 14% (n=3) use serum creatinine. Nearly half of providers (n=10, 45%) responded "I am not sure". Only 18% of providers (n=4) felt comfortable with the use of cystatin C. There was variable practice in nephrology referral, with 41% of providers (n=9) referring at an eGFR<60mL/min/1.73m^2 and 21% (n=5) at 45mL/min/1.73m^2. Only 21% (n=5) waited until the KDIGO guideline of 30mL/min/1.73m^2.

Conclusions: In this pilot survey, HIV providers reported high uncertainty regarding kidney function measurement and the identification of kidney disease. HIV providers may benefit from targeted education to reduce medication errors related to drug dosing as well as appropriate nephrology referrals.

Funding: NIDDK Support

Survey Question	Answer	N (%)
Knowledge & Current Practice What test(s) do you order to assess kidney function in a **typical patient with HIV?**	[ ] Serum Creatinine	21 (95)
	[ ] Cystatin C	3 (14)
	[ ] Urinalysis	15 (68)
	[ ] Renal ultrasound	2 (9)
	[ ] Urine protein or albumin measurement	12 (54)
Knowledge & Current Practice What test(s) do you order to assess kidney function in a patient with HIV and **an elevated creatinine?**	[ ] Repeat serum Creatinine	21 (95)
	[ ] Cystatin C	5 (23)
	[ ] Urinalysis	17 (77)
	[ ] Renal ultrasound	8 (36)
	[ ] Urine protein or albumin measurement	15 (68)
Knowledge & Current Practice For persons with impaired kidney function and living with HIV, **how do you determine dosing** of anti-retroviral therapy or other medications?	[ ] Cockcroft-Gault creatinine clearance	2 (9)
	[ ] Estimated GFR	7 (32)
	[ ] Serum creatinine	3 (14)
	[ ] I consult with another specialist	0 (0)
	[ ] I consult with a pharmacist	0 (0)
	[ ] I am not sure	10 (45)
Knowledge & Attitudes **How familiar** are you with serum cystatin C as a measure of kidney function?	[ ] Never heard of it.	0 (0)
	[ ] I have heard of it, but I don't know its use.	5 (22)
	[ ] I have heard of it and know its uses, but it is not a part of my clinical practice.	11 (50)
	[ ] I occasionally order it but don't know how to interpret it.	3 (14)
	[ ] It is a part of my routine clinical practice.	4 (18)
Knowledge & Attitudes **When do you refer** a patient to nephrology?	[ ] Elevated creatinine	11 (50)
	[ ] eGFR less than 60	9 (41)
	[ ] eGFR less than 45	5 (22)
	[ ] eGFR less than 30	5 (22)
	[ ] eGFR less than 20	0 (0)
	[ ] Proteinuria	17 (77)
	[ ] Hematuria	7 (32)
	[ ] Nephrolithiasis	4 (18)
	[ ] Hypertension	4 (18)
	[ ] Electrolytes	7 (32)

FR-PO920

The Spectrum of Biopsy-Proven Kidney Disease in People Living with HIV in Tertiary-Care Centers in Mexico City

Adrián Esteban Caballero-Islas,[1] Carlos Ascencion Lopez,[1] Lillana Pacchiano,[1] Arnulfo Mendoza,[1] Jose A. Leon Ortiz,[1] Marcos G. Nava,[1] Enzo C. Vasquez Jiménez,[2] Gustavo A. Casas-Aparicio.[1] *[1]Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico; [2]Hospital Juarez de Mexico, Mexico City, Mexico.*

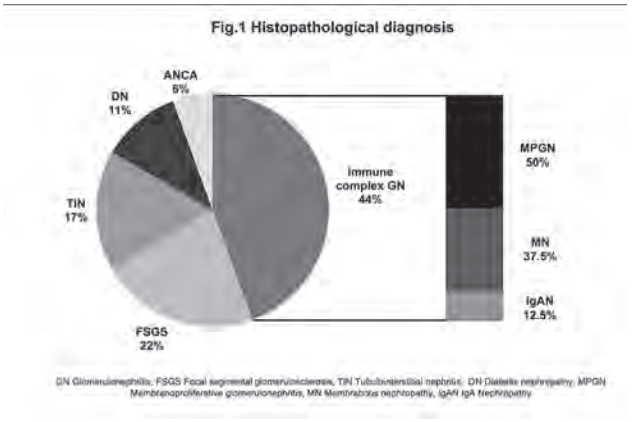
Background: People living with HIV are prone to kidney disease as a result of multiple mechanisms; those directly related to the virus, drug effects, and related infections. Kidney biopsy allows a more accurate approach to kidney disease in this setting.

Methods: A retrospective study that included all HIV-positive patients with a clinical indication for a kidney biopsy was performed between January 2018 and May 2024 at 3 centers in Mexico City. Data was collected at the time of the biopsy

Results: Eighteen kidney biopsies were included. The mean age was of 44.7 years and the median time from diagnosis to biopsy was 92 months(4.5-128). The most common indication was nephrotic syndrome(61%). Glomerular lesions were the most frequent finding(83%) and immune complex-mediated glomerular disease the most prevalent lesion. Among diabetic patients, 60% presented lesions not related to diabetes.

Conclusions: In our study, immune complex-mediated glomerular disease was the most common diagnosis. In individuals with diabetes, 60% had a kidney disease not related to diabetes, emphasizing the importance of performing biopsies to improve outcomes.

Age, yrs(mean±SD)	44.7±13.6
Male,n(%)	16(89)
Serum creatinine,mg/dL(median, IQR)	1.76(1.18-2.34)
eGFR, mL/min/1.73 m2	44.9(34.1-71)
Serum albumin,g/dL	2.21(0.97-4.01)
Proteinuria, g/d or g/g	3.9(2.1-7.6)
CD4 count, cells/mL	315(116-653)
Diabetes,n (%)	5(28)
Hypertension	7(39)
Hepatitis B	2(11)
Hepatitis C	2(11)
On Antiretroviral therapy	17(94)
CD4 count > 200 cells/mL	11(61)
Viral load < 40 copies	11(61)



FR-PO921

Development of Machine Learning-Based Biopsy Algorithm for Kidney: Multicenter-Based Model Development and Validation Study in South Korea

Hae-Ryong Yun, Hyung Woo Kim, Jung Tak Park, Seung Hyeok Han, Shin-Wook Kang, Tae-Hyun Yoo. *Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.*

Background: Kidney biopsy has become an essential procedure for microscopic assessment of kidney disease. However, the decision of kidney biopsy can be inconsistent due to the complexity of interpreting patient data and varying clinician expertise. Therefore, based on three nephrologists' decisions, we developed three machine-learning (ML) algorithms, integrating them into a biopsy recommendation algorithm for kidney.

Methods: First, using 8,228 patients with proteinuria, hematuria, and/or unexplained kidney function abnormalities who visited outpatient clinics between 2010 and 2018, we trained a deep-learning algorithm to mimic nephrologists' decisions for kidney biopsy. Subsequently, we tested the performance of the biopsy algorithm on 760 patients who underwent kidney biopsy between 2020 and 2023 in Severance Hospital. The XGBoost was employed to develop the algorithm and the confusion matrix was used to evaluate the performance of the algorithm.

Results: Among the 8,228 patients, the number of cases in which nephrologists decided to conduct kidney biopsy was 1,290 (15.6%), 1,261 (15.3%), and 1,106 (13.4%), respectively. The area under the receiver operating characteristic curve (AUROC) for each ML-algorithm was 99.6%, 99.8%, and 97.0%, respectively. These results suggest that each algorithm closely emulates the decisions of corresponding nephrologists in determining the need for kidney biopsy, demonstrating proficiency in accurately replicating clinical decisions. The integrated final kidney biopsy algorithm, combining the three algorithms, achieved an AUROC of 99.5%. Finally, we applied the algorithm to the patients who underwent kidney biopsy. Among the 760 patients, 659 (86.7%) received a diagnosis of glomerular, tubule-interstitial, or inherited diseases. The AUROC for the algorithm was 86.2%. In addition, the positive predictive value of the algorithm was 100.0 %.

Conclusions: We developed an ML-algorithm to emulate nephrologists' decisions on kidney biopsy. We expected that this algorithm could support clinicians in strengthening the decision-making process and simplifying patient management workflows for kidney biopsy in primary care.

FR-PO922

Kidney Biopsy Practice Varies in the United States and Internationally

Michael Toal,[1,2] Christopher Hill,[2] Michael P. Quinn,[1] Ciaran O'Neill,[1] Alexander P. Maxwell.[1] *[1]Queen's University Belfast Faculty of Medicine Health and Life Sciences, Belfast, United Kingdom; [2]Belfast City Hospital, Belfast, United Kingdom.*

Background: There is substantial variation in kidney biopsy practices between countries, however the reasons for this are unclear due to limited research.

Methods: A case-vignette questionnaire was developed. A biopsy propensity score (0-44) was generated from responses to indications and contraindications, which categorised respondents into one of five categories for instant feedback. Dissemination occurred by email, social media and the National Kidney Foundation.

Results: 1181 nephrologists/fellows from 83 countries participated, making this the largest international study of kidney biopsy practice. The mean score was 24.2 (higher score=increased propensity). The US was the largest national group with 293 participants from 43 states. US mean=24.6. A biopsy was most likely for nephrotic and nephritic syndromes and least likely in the setting of reduced kidney size. An adjusted multiple linear regression model demonstrated significantly higher scores for males, younger participants and those who performed biopsy more frequently (p=0.01). A previous severe complication (requiring intervention/death) did not affect propensity (p=0.76). In countries with over 20 participants, the mean score ranged from 22.1 (Nigeria) to 26.9 (Mexico) (p<0.001). There were significant differences between the 18 US states with 5 or more participants (p=0.003) and mean score ranged from 20.3 (WI) to 29.2 (NJ & VA) (Fig.1). Increased propensity was demonstrated in states with higher nephrologist density and lower deprivation levels (p=0.002).

Conclusions: International and US kidney biopsy practice is highly variable. Ease of access to biopsy may influence propensity. State-level disparities could be affected by socioeconomic factors and nephrologist availability. The significant variations in kidney biopsy practice warrants further examination, given its potential implications for timely care and resource use.

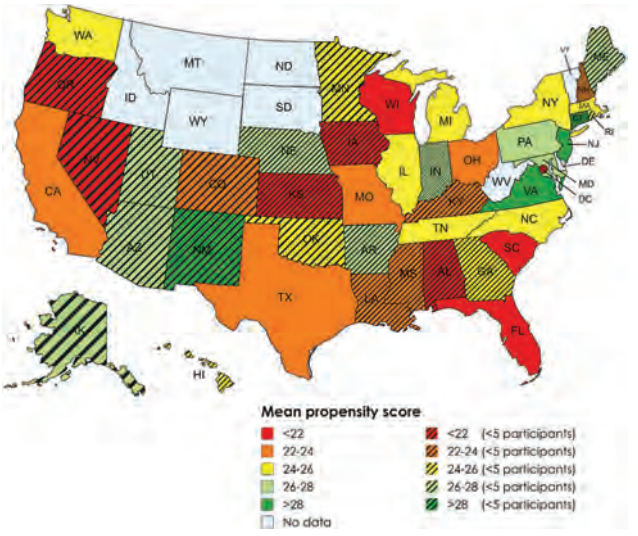


Fig. 1 Propensity score by US state

FR-PO923

Paradox of Precision: More Parameters, Fewer Complications in Kidney Biopsy Outcomes

Joao M. E Lima Souza, Marclebio M. Dourado, Maria Z. Nogueira de Azevedo, Ana Paula Gueiros, Thiago Vinícius P. Paiva, Breno M. Sá, Tiago M. Freitas. *Universidade Federal de Pernambuco, Recife, Brazil.*

Background: Kidney biopsy is definitive for diagnosis of various glomerular diseases. Although minimal, this procedure is not done without risks. There is still no consensus regarding on best pre-biopsy protocol

Methods: Retrospective analysis of all post-renal biopsy complications in a single center after a change to a more restrictive protocol, starting in November 2018 until December 2022. All biopsied patients met the pre-established parameters showed in table 01. If any parameter was out of range, a specific intervention was performed (transfusion, antihypertensive, dialysis). Complication rate was also analyzed within after the procedure: fall in hemoglobin levels, blood transfusion, need for hemodynamic intervention, refractory pain, nephrectomy, and death.

Results: A total of 370 patients were included in the study, the majority being female [243 patients (65.6%)], and 88.9% of the biopsies performed on native kidneys. The age range varied from 4 to 76 years, with the majority between 14 and 53 years (81.6%). Regarding pre-biopsy parameters, the average hemoglobin was 11.3g/dL; platelets, 251,000/mm3; INR 1.09; systolic pressure 126mmHg and diastolic 79mmHg. In terms of glomerular filtration rate (GFR) and BUN, about 23.6% of patients had a GFR below 30mL/min, with BUN > 65, requiring pre-biopsy dialysis. Following this protocol, major complications occurred in only 4.86% of patients (10 patients with macroscopic hematuria, 6 patients requiring blood transfusion, 2 with intense pain). There were no instances requiring hemodynamic intervention, nephrectomy, or resulting in mortality. There was no association of complications with age, biopsy indication, or final diagnosis.

Conclusions: A comprehensive renal biopsy protocol with well-defined parameters proved to be effective and feasible, with minimal complication rates.

Parameters	Value	Necessary intervention if required
hemoglobin (g/dL)	≥ 9.0	Transfusion
plaquetas (mm3)	> 100.000	Transfusion
International Normalized Ratio (INR)	< 1,4	Transfusion
Systolic blood pressure (mmHg)	< 140	antihypertensive medication 1 hour prior
Diastolic blood pressure (mmHg)	< 90	antihypertensive medication 1 hour prior
Blood urea nitrogen (BUN)	< 65	Dialysis

FR-PO924

Kidney Biopsy Quality Improvement Study

Niveditha Girimaji Satishchandra, Duncan B. Johnstone, Reem Mustafa.
The University of Kansas Medical Center, Kansas City, KS.

Background: Kidney biopsy is essential for definitive diagnosis of kidney disease. Recent data indicate an increasing biopsy miss rate and inadequacy. Most retrospective analyses report kidney biopsy major complications in 1-2% of patients, and inadequate tissue for diagnosis in 14%. The study aimed to review the adequacy and complications of kidney biopsy.

Methods: A retrospective single-center quality improvement study of patients who underwent renal biopsies between January-2020 and December-2023. Univariate and binomial logistic regression was used to predict adequacy and complications.

Results: Study included 181 patients, 72(39.8%) were male. Mean age and BMI was 52.9±17.3 years and 29.5±7.8 kg/m^2. Mean baseline serum creatnine and hemoglobin(Hb) was 2.36±1.75 mg/dL and 11.25±2.4 g/dL.28.8% patients had stage 2 or 3 AKI. Mean eGFR in CKD stages <3 was 32.18 ± 15.94 ml/min.5.5% were on active anticoagulation.18 Gauge needle was used in all biopsies. 126(69.6%) biopsies were determined to be adequate(defined >= 10 glomeruli on LM, 1 glomerulus on IF and EM). Sex, age, BMI, length of kidney, and creatinine did not predict the likelihood of adequate sample. Total number of major complications was 11(6.1%) with 4(2.2%) requiring embolization or angiography, 5(2.7%) requiring transfusions <7 days, and 2(1.1%) requiring both. Among age, sex, creatinine, platelet, INR, number of passes, total core length, active anticoagulation, AKI, baseline Hb, pre-biopsy SBP and DBP, and radiologist, total core length predicted major complications on univariate analysis(p=0.04) and just missed significance on logistic regression(p=0.06).

Conclusions: One-third of kidney biopsies were inadequate with rare but considerable major complications. No specific predictors linked current biopsy protocols to adequacy. Total core length correlated to major complications. A shallower, wider biopsy with 16G needle would strike a balance between adequacy and minimizing complication. This study is limited by small sample size.

Binomial linear regression for adequacy of sample

Variable		Adequate Sample ª	Sample not Adequate ª	p value
		n = 126	n = 55	
Sex	Female	77 (61.2%)	32 (58.1%)	0.69
Age (Years)		51.4 ± 18.3	56.4 ± 14.4	0.07
BMI (kg/m^2)		29.4 ± 8.04	30.0 ±7.2	0.41
Kidney Length (Cm)		10.9 ± 1.3	11.2 ± 1.6	0.33
Creatinine(mg/dl)		2.2 ± 1.6	2.8 ± 1.9	0.08

Univariate analysis for major complications

Variable		Major Complication ª	No complication ª	p value
		n = 11	n = 170	
Sex	Female	5(45.45%)	104(61.17)	0.31
Age (Years)		51.8 ± 12.1	53.0 ± 17.6	0.832
Number of Passes		3.1 ± 0.3	3.3 ± 0.9	0.364
SBP before biopsy(mmhg)		125.1 ± 16.6	128.7 ± 16.4	0.49
Hemoglobin(g/dl)		10.22 ± 2.1	11.3 ± 2.4	0.14
Platelet * 10^3		197.7 ± 100.1	266.1 ± 115.6	0.07
Creatinine(mg/dl)		2.9 ± 2.3	2.3 ± 1.7	0.30
Active Anticoagulation	Yes	2(18.18%)	8(5.06%)	0.12
Total Core Length(cm)		3.3 ± 0.9	2.7 ± 0.8	0.04

FR-PO925

Importance of Integrating Clinical, Serological, Morphological, and Genetic Data to Optimize Care and Prognostication for Patients with Glomerular Diseases

Thien Kim N. Co,[1] Cynthia C. Nast,[2] Tiane Dai,[1] Ryan Peretz,[1] Sharon G. Adler.[1] *[1]Harbor-UCLA Medical Center, Torrance, CA; [2]Cedars-Sinai Medical Center, Los Angeles, CA.*

Introduction: KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Disease states that kidney biopsy is not needed to confirm the diagnosis for patients with nephrotic range proteinuria and a positive anti-PLA2R antibody test, especially if kidney function is normal or if there are contraindications. Our case highlights the importance of integrating clinical information, kidney biopsy findings, serologies, and genetics in patients whose clinical course do not progress as expected.

Case Description: A 63-year-old male with diabetes mellitus type 2 (DM), hypertension and hyperlipidemia was referred for nephrotic range proteinuria (4,311 mcg/mg). Serological evaluation was negative except for positive anti-PLA2R antibody with negative urine/serum protein electrophoresis, Hepatitis B, Hepatitis C, HIV, and RPR. Kidney size was normal. Urine sediment was inactive. Kidney biopsy showed membranous nephropathy (PLA2R positive), focal and segmental glomerulosclerosis with glomerulomegaly, features suggestive of renal vein thrombosis, and mild to moderate arterio- and arteriolosclerosis. Imaging ruled out venous thrombosis. He was treated with Rituximab and steroids, attaining complete serological remission with negative anti-PLA2R antibody after 9 months. However, 12 months after serologic remission, he had persistent proteinuria of ~2-3g, suggesting a secondary process. Given the FSGS with glomerulomegaly, genetic testing was performed (Natera Renasight) which identified a heterozygous likely pathogenic variant in the gene COL4A3 mutation; pathogenic variants in COL4A3 are associated with Alport Syndrome with either autosomal dominant or recessive inheritance patterns. Audiological evaluation revealed reduced hearing. Ophthalmological evaluation is pending.

Discussion: If a kidney biopsy was not pursued, the persistent proteinuria might have been attributed to secondary FSGS or DM. However, the biopsy findings led to genetic testing, which revealed concern for concomitant Alport syndrome. This case underscores the importance of integrating clinical, serological, histological, and genetic information to evaluate an unexpected clinical course. With these advances, we aim to tailor medical therapy and genetic counseling to address each patient's unique clinical picture.

FR-PO926

Tangential Approach: An Innovative Technique in Ultrasound-Guided Native Kidney Biopsy (KB)

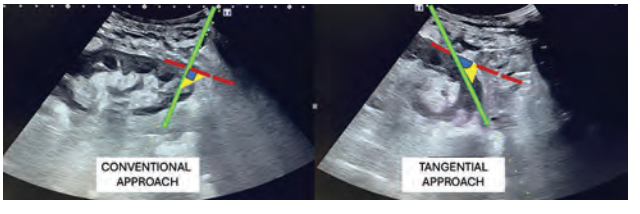
Haridian Sosa Barrios,[1,2] Cristina Riaza Ortiz,[1] María del Pilar Morán Magro,[1] Victor Burguera,[1] Irene Minguez,[1] Jorge Sánchez,[1] Milagros Fernandez-Lucas,[1,2] Maite Rivera Gorrin.[1,2] *[1]Hospital Universitario Ramon y Cajal, Madrid, Spain; [2]Universidad de Alcala Facultad de Medicina y Ciencias de la Salud, Alcala de Henares, Spain.*

Background: KB is the gold standard to diagnose renal pathology, but not without complications. In the conventional approach (CA) the needle enters the kidney at 60-90 degrees. The tangential approach (TA) is proposed as an alternative since it minimizes crossing the renal sinus (angle less than 60 degrees) and vessels of larger caliber (Figure 1). Objective: to demonstrate the non-inferiority of TA in native KB versus CA in terms of diagnostic yield and complications.

Methods: Retrospective single center study (May 2022-March 2024). Demographic data, KB and complications comparing CA vs TA were collected. The physician performing the KB chose one approach or the other according to the patient's anatomical characteristics and personal preferences.

Results: A total of 102 patients were biopsied, 65 (63.7%) male, mean age 54.18±17.3 years, 51% hypertensive. Twenty-two patients were anticoagulated/anti-aggregated and 24 required intravenous desmopressin preKB. Lower pole was biopsied in all cases, 86.3% left kidneys and only in one case both were biopsied. The mean number of passes was 2.5 (N.S.), with a mean yield of 2 cylinders. Cost-effectiveness of BR: Both the percentage of valid samples for diagnosis and the percentage of cortical obtained was statistically superior for AT, not so for the mean number of glomeruli obtained 18±11 vs 19±9 (p=0.647). Complications There were no statistically significant differences regarding major or minor complications. - Major: One patient required embolization and transfusion of blood products (CA). - Minor: We found statistically significant difference in the rate of asymptomatic arterio-venous fistulae (p=0.003), but not in minor hematoma or hematuria.

Conclusions: Native KB by TA is a novel technique. In our study, TA showed higher diagnostic yield without increasing complications, probably because large vessels are avoided during the procedure. We propose this alternative approach in selected cases, but larger prospective studies are needed.



FR-PO927

Glomerular Diameter Is Associated with Reduction in Urinary Protein during Treatment with Dapagliflozin, a SGLT2 Inhibitor, in Patients with CKD

Hiroaki Komatsu, Arata Osanami, Keitaro Nishizawa, Masato Furuhashi.
Sapporo Ika Daigaku, Sapporo, Japan.

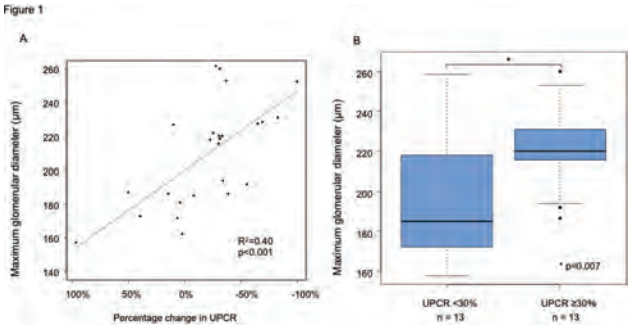
Background: Several clinical trials have shown that sodium-glucose cotransporter 2 (SGLT2) inhibitors have protective effects against chronic kidney disease (CKD) complicated with or not complicated with type 2 diabetes mellitus (DM). Since one of the renoprotective mechanisms by SGLT2 inhibitors is supposed to reduce glomerular hyperfiltration, we hypothesized that glomerular diameter, which can represent abnormal glomerular hemodynamics, is associated with reduction in urinary protein after the initiation of treatment with SGLT2 inhibitors.

Methods: This study was a retrospective multicentered study using 26 adult patients with CKD (mean age: 50±14 years) who underwent kidney biopsy and were then treated with dapagliflozin, an SGLT2 inhibitor, during the period between April 2019 to March 2024 in Sapporo Medical University Hospital and Steel Memorial Muroran Hospital. The association of glomerular diameter with changes in urinary protein before and 4-8 weeks after the initiation of treatment with dapagliflozin were investigated.

Results: Levels of median estimated glomerular filtration rate and urinary protein at baseline were 53 [interquartile range: 32.3-69.9] mL/min/1.73m^2 and 1.5 [0.69-2.84] g/gCre, respectively. Prevalences of DM and use of renin-angiotensin-system blockers were 15% and 88.4%, respectively. Maximum glomerular diameter was significantly and positively correlated with change (before – after) in urinary protein-to-creatinine ratio (UPCR) (R^2=0.40; p<0.001; Figure 1A). Maximum glomerular diameter was significantly larger in patients who achieved ≥30% reduction in UPCR after the initiation of treatment with dapagliflozin than in patients who achieved <30% reduction in UPCR (220 [215, 231] vs. 185 [172-218], p=0.007; Figure 1B).

Conclusions: Glomerular diameter is associated with reduction in urinary protein after the initiation of treatment with dapagliflozin in patients with CKD.

Figure 1



FR-PO928

Association of Serum Uric Acid with Podocyte Injury and Kidney Histopathologic Lesions

Sophia H. Rosan,[1] Ashish Verma,[1] Sophie E. Claudel,[1] Ragnar Palsson,[5] Anand Srivastava,[2] Tobias B. Huber,[3] Isaac E. Stillman,[4] Joel M. Henderson,[1] Sushrut S. Waikar,[1] Insa M. Schmidt.[1] *[1]Boston Medical Center, Boston, MA; [2]University of Illinois Chicago, Chicago, IL; [3]Universitat Hamburg Medizinische Fakultat, Hamburg, Germany; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]Massachusetts General Hospital, Boston, MA.*

Background: Hyperuricemia may impair podocyte function by promoting oxidative stress and inflammatory responses, but these effects have not been comprehensively studied in patients with chronic kidney disease (CKD). This study explores the association between serum uric acid (SUA) levels, histopathologic lesions, and podocyte injury evidenced by foot process effacement (FPE) in patients with biopsy-confirmed kidney disease.

Methods: We measured SUA levels in 519 individuals enrolled into the Boston Kidney Biopsy Cohort, a cohort of individuals with biopsy-confirmed semi-quantitative assessment of histopathology. We assessed the correlation between SUA, estimated glomerular filtration rate (eGFR), and proteinuria using Spearman correlation coefficients. Multivariable linear regression models tested the associations of SUA levels with histopathologic lesion severity and FPE.

Results: The mean SUA level was 8.3±2.6 mg/dL, the mean eGFR was 57±36 ml/min/1.73m^2, and the median proteinuria [IQR] was 3.0 [0.4–4.0] g/g creatinine. SUA levels correlated negatively with eGFR and positively with proteinuria (r = -0.28, p<0.001 and r = 0.18, p<0.001, respectively) (**Figure 1a**). After multivariable adjustment for age, sex, race, and eGFR, more severe segmental sclerosis was associated with higher SUA levels (β= 0.64, p=0.020) (**Figure 1b**). More severe FPE was also associated with higher SUA levels. This relationship remained consistent in multivariable models after adjustment for demographics, eGFR, and proteinuria (β = 0.52, p = 0.048) (**Figure 1c**).

Conclusions: This study demonstrates an association between hyperuricemia and podocyte injury. Further research is needed to determine whether urate-lowering therapy could help reduce podocyte injury and potentially delay the onset of CKD.

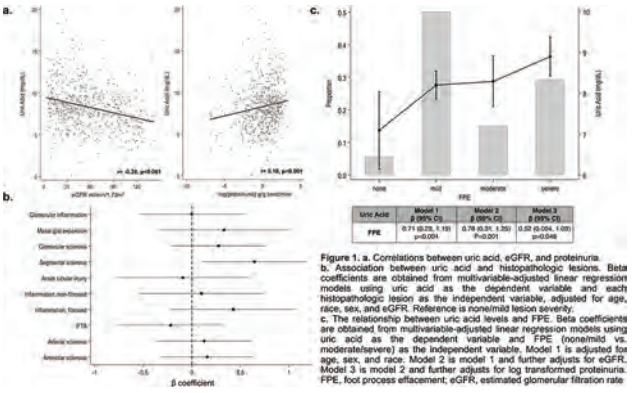


Figure 1. a. Correlations between uric acid, eGFR, and proteinuria. b. Association between uric acid and histopathologic lesions. Beta coefficients are obtained from multivariable-adjusted linear regression models using uric acid as the dependent variable and each histopathologic lesion as the independent variable, adjusted for age, race, sex, and eGFR. Reference is none/mild lesion severity. c. The relationship between uric acid levels and FPE. Beta coefficients are obtained from multivariable-adjusted linear regression models using uric acid as the dependent variable and FPE (none/mild vs. moderate/severe) as the independent variable. Model 1 is adjusted for age, sex, and race. Model 2 is model 1 and further adjusts for eGFR. Model 3 is model 2 and further adjusts for log transformed proteinuria. FPE, foot process effacement; eGFR, estimated glomerular filtration rate

FR-PO929

Association of Podocyte Injury with Kidney Histopathologic Lesions and Disease Progression

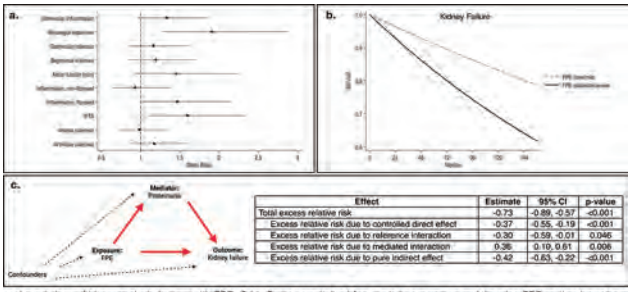
Marius Wittig,[1] Ashish Verma,[5] Andrea Bellavia,[7] Sophia H. Rosan,[5] Sophie E. Claudel,[5] Aditya L. Surapaneni,[6] Ragnar Palsson,[2] Anand Srivastava,[3] Isaac E. Stillman,[4] Morgan Grams,[6] Eugene P. Rhee,[2] Tobias B. Huber,[1] Joel M. Henderson,[5] Sushrut S. Waikar,[5] Insa M. Schmidt.[5] *[1]Universitat Hamburg Medizinische Fakultat, Hamburg, Germany; [2]Massachusetts General Hospital, Boston, MA; [3]University of Illinois Chicago, Chicago, IL; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]Boston Medical Center, Boston, MA; [6]NYU Langone Health, New York, NY; [7]Harvard Medical School, Boston, MA.*

Background: Foot process effacement (FPE), a marker of podocyte injury observable via electron microscopy (EM), is critically involved in the pathophysiology of proteinuria and kidney disease progression in glomerular diseases. The association of FPE with histopathologic lesions and adverse clinical outcomes across a range of kidney diseases has not yet been explored.

Methods: We developed a semi-quantitative scoring system to assess FPE severity using EM reports from 813 participants in the Boston Kidney Biopsy Cohort (BKBC), a prospective cohort of individuals with biopsy-confirmed kidney disease and pathologist-adjudicated assessment of histopathology. Logistic regression models assessed the relationship between FPE severity and histopathologic lesions. Accelerated failure time models examined the relationship between FPE and progression to kidney failure. Lastly, we employed mediation analyses to decompose the effect of FPE severity on kidney failure, exploring the role of proteinuria as a mediator in this pathway.

Results: Mean eGFR was 58.4 ±35.6 ml/min/1.73m^2 and median proteinuria (IQR) was 1.6 [0.4–4.0] g/g creatinine. Six % had no FPE, 50% had mild FPE, 15% had moderate FPE, and 29% had severe FPE. After multivariable adjustment, more severe mesangial expansion (OR 1.91, 95% CI 1.26 to 2.88, p=0.002) and more severe interstitial fibrosis/tubular atrophy (OR 1.60, 95% CI 1.09 to 2.33, p=0.015) were significantly associated with more severe FPE (**Figure 1a**). In the fully adjusted model, moderate or severe FPE was associated with a 2-fold higher hazard of progression to kidney failure compared to none or mild FPE (HR=2.01 (95% CI 1.41, 2.87), (**Figure 1b**). Mediation analysis showed that FPE affected kidney failure survival times through both direct effects (-0.37) and indirect effects via proteinuria (-0.42), both p<0.01 (**Figure 1c**).

Conclusions: FPE is linked to glomerular and tubulointerstitial patterns of injury and may serve as a prognostic tool for assessing the risk of disease progression across a range of kidney diseases. Further research on the mechanistic links between FPE severity and adverse kidney outcomes is needed to evaluate targeting podocyte integrity in therapeutic strategies.



a. Associations of histopathologic lesions with FPE. Odds Ratios are derived from logistic regression models using FPE as the dependent and each histopathologic lesion as the independent variable. Models are adjusted for age, race, sex, and eGFR. b. Adjusted survival curves show the association between FPE and time-to-kidney failure (defined as the need for kidney replacement therapy). Results are obtained from accelerated failure time exponential models. Models are stratified by site and adjusted for age, sex, race, log(proteinuria), primary clinicopathologic diagnosis, and eGFR. c. Decomposition of the relationship between FPE, proteinuria, and kidney failure using mediation analysis. IFTA, interstitial fibrosis/ tubular atrophy; FPE, foot process effacement

FR-PO930

Targeting Podocyte Calcium Influx with TRPC6 Inhibitor BI 764198: Implications for Glomerular Filtration Barrier Protection

Stefano Da Sacco,[1] Qi Zhang,[1] Steven S. Pullen,[2] Laura Perin.[1]
[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]Boehringer Ingheleim Pharmaceuticals, Ridgefield, CT.

Background: The glomerular filtration barrier (GFB) is essential for blood homeostasis, with podocyte function being vital for GFB integrity. Damage to podocytes leads to foot process effacement, apoptosis, and compromised glomerular permselectivity. Activation of the TRPC6 channel-mediated calcium influx in podocytes induces actin cytoskeleton rearrangement, leading to impaired filtration barrier function. This study evaluates the efficacy of TRPC6 inhibitor BI 764198 in mitigating TRPC6-mediated podocyte effects and elucidates its action mechanism.

Methods: Primary human podocytes and glomerular endothelial cells (GECs) were cultured in high glucose and exposed to angiotensin II, with or without TRPC6 inhibitor BI 764198. Cellular responses were gauged using immunofluorescence and qPCR. Calcium influx was monitored with Fura Red and Fluo-4 dyes. The inhibitor's protective effect on the GFB was also tested using a glomerulus-on-a-chip model and single cell-RNAseq and proteomics analyses were performed on collected cells and filtrate.

Results: High glucose upregulated TRPC6 expression in podocytes but not in GECs, thus highlighting the specificity of the TRPC6 activity in podocytes. Angiotensin II induced a significant calcium influx in podocytes, which BI 764198 effectively inhibited. GECs showed no calcium response to angiotensin. BI 764198 successfully reduced albumin leakage in the glomerulus-on-a-chip, indicating barrier protection. Preliminary scRNAseq and proteomics data support BI 764198's role in preventing TRPC6-mediated podocyte injury.

Conclusions: The findings provide in vitro validation of the therapeutic potential of the selective TRPC6 inhibitor BI 764198, shedding light on its protective mechanism of action.

Funding: Commercial Support - Boehringer Ingelheim

FR-PO931

STING Pathway Activation Is Associated with Poor Prognosis in Acute Tubulointerstitial Nephritis

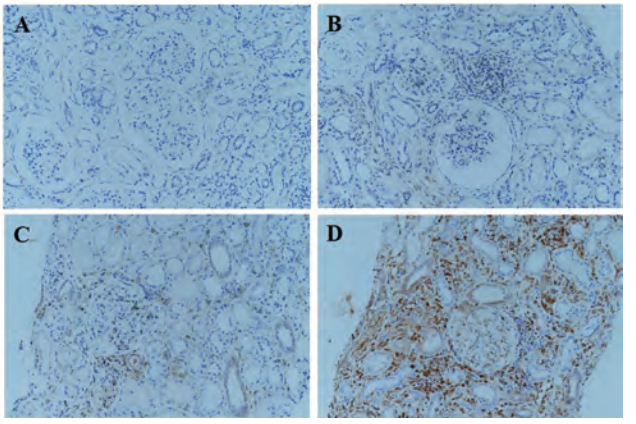
Byung chul Yu, Soo Jeong Choi, Moo Yong Park, Jin kuk Kim.
Soonchunhyang University Hospital Bucheon, Bucheon, Gyeonggi-do, Republic of Korea.

Background: We hypothesized that acute tubulointerstitial nephritis (ATIN) pathogenesis may be associated with mitochondrial injury and that the degree of mitochondrial injury at the time of diagnosis may serve as a valuable prognostic marker.

Methods: We prospectively enrolled 41 patients with ATIN. We analyzed the signal intensity of immunohistochemical (IHC) staining of the stimulator of interferon genes (STING) in kidney tissues at diagnosis as a proxy of mitochondrial injury in patients with ATIN. We evaluated clinical outcomes including achievement of complete remission (CR), defined as a doubling of estimated glomerular filtration rate (eGFR) compared with baseline values or eGFR≥ 60 mL/min/1.73m^2 at 1 year after diagnosis.

Results: A single pathologist categorized the signal intensity of the IHC staining from negative to 3+ (Figure 1). Patients were divided into the low- (n = 22) and high- (n = 19) intensity groups, with a cut-off of 2+. The mean baseline eGFR did not differ between low- and high-intensity group (24 ± 16 vs. 21 ± 14 mL/min/1.73m^2, p = 0.541). The mean eGFR at 1 year after diagnosis were higher in the low- than in the high-intensity group (56 ± 25 vs. 39 ± 22 mL/min/1.73m^2, p = 0.032). More patients achieved CR in the low- than in the high-intensity group (81.8 vs. 47.4%, p = 0.020). Low-intensity group was associated with CR (hazard ratio, 4.61; 95% confidence interval, 1.62 to 9.76, after adjustment for confounding factors including etiology, underlying pathological lesions, and presence of immunosuppressant administration).

Conclusions: More severe mitochondrial injury, indicated by a high for STING IHC signal intensity at diagnosis, could be used as a prognostic marker to predict a poor prognosis in ATIN.



Representative images of immunohistochemistric staining for STING on kidney tissue obtained from patients with acute tubulointerstitial nephritis. Patients were classified into negative (A), 1+ (B), 2+ (C), and 3+ (D) according to the IHC signal intensity.

FR-PO932

Discovery of a Small Molecule with an Inhibitory Role for RAB11 with Validation in Nephrocytes

Camille Lempicki,[1] Julian Milosavljevic,[1] Christian Laggner,[2] Konrad Lang,[1] Tobias F. Hermle.[1] *[1]Renal Division, Department of Medicine, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany; [2]Atomwise Inc, San Francisco, CA.*

Background: DNA variants in *TBC1D8B* have been discovered as a monogenic cause of nephrotic syndrome. TBC1D8B dysfunction has been linked to disinhibition of RAB11. No specific small molecule inhibitor for RAB11 has been described so far but might offer potential therapeutic value.

Methods: To identify candidate compounds, the proprietary AtomNet platform was utilized for deep learning-based computational screening. For experimental confirmation, we employed an *in vitro* platform reflecting RAB11 activity through the exocytosis of GFP. We further examined autophagy, which independently relies on RAB11. Toxicity was assessed by Annexin V/propidium iodide exposure and flow cytometry in cultured podocytes. Toxicity in vivo was studied by exposure of *Drosophila* larvae. In podocyte-like *Drosophila* nephrocytes, we further explored the impact of feeding the compound on subcellular localization of endogenous Rab11 and endocytic nephrocyte function.

Results: From 94 candidate molecules identified *in silico*, we confirmed nine compounds through a decrease of secretory GFP in the cellular supernatant, which suggests efficient inhibition of RAB11. We then validated three compounds by measuring a decrease in autophagic flux suggesting inhibition on another cellular function dependent on RAB11. All three inhibitors showed druglike properties. Flow cytometry after Annexin V/propidium iodide exposure indicated absence of toxicity for these chemicals. The survival rate of *Drosophila* larvae fed with the inhibitors was unaffected compared to the control, similarly suggesting low toxicity *in vivo*. *Drosophila* larvae exposed to compound with highest oral bioavailability showed subcellular dispersal of endogenous Rab11 and a decrease in RAB11-dependent nephrocyte function.

Conclusions: We identified three small molecules exhibiting inhibitory function for Rab11. This discovery may open avenues for treating RAB11-associated nephrotic syndrome and other RAB11-associated disorders.

Funding: Commercial Support - Atomwise Inc., Government Support - Non-U.S.

FR-PO933

Computationally Derived Characterization of Tubular Changes in Relation to the Development of Interstitial Fibrosis

Fan Fan,[1] Qian Liu,[2] Jarcy Zee,[3,2] Takaya Ozeki,[8] Dawit S. Demeke,[4] Bangchen Wang,[5] Jackson Jacobs,[6] Manav P. Shah,[6] Alton B. Farris,[7] Laura H. Mariani,[8] Kyle J. Lafata,[9] Yijiang Chen,[10] Lawrence B. Holzman,[11] Jeffrey B. Hodgin,[4] Anant Madabhushi,[6,12] Laura Barisoni,[5,13] Andrew Janowczyk.[6,14] *[1]Emory University, Atlanta, GA; [2]The Children's Hospital of Philadelphia Research Institute, Philadelphia, PA; [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [4]University of Michigan Department of Pathology, Ann Arbor, MI; [5]Duke University Department of Pathology, Durham, NC; [6]Emory University School of Medicine, Atlanta, GA; [7]Emory University Department of Pathology and Laboratory Medicine, Atlanta, GA; [8]University of Michigan Department of Internal Medicine, Ann Arbor, MI; [9]Duke University Department of Radiation Oncology, Durham, NC; [10]Stanford University Department of Radiation Oncology, Stanford, CA; [11]University of Pennsylvania Department of Medicine, Philadelphia, PA; [12]Atlanta Veterans Administration Medical Center, Atlanta, GA; [13]Duke University Department of Medicine, Durham, NC; [14]Department of Oncology, Division of Precision Oncology, University Hospital of Geneva, Geneva, Swaziland.*

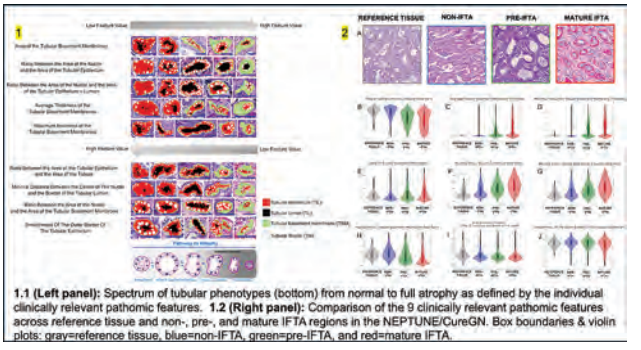
Background: The development of interstitial fibrosis & tubular atrophy (IFTA) is a progressive process. Visually it is challenging to quantify the spectrum of tubular changes from normal to atrophy and their spatial relationship with degree of interstitial fibrosis. This study utilizes computational image analysis to uncover tubular pathomic signatures that reflect the spectrum of tubular changes and their relationship with the microenvironment.

Methods: Cortex, pre-, mature-, and non-IFTA sub-regions were manually segmented in n=254 NEPTUNE/CureGN PAS-stained whole slide images (WSIs, n=135 FSGS,119 MCD/MCD-like). We developed and applied segmentation algorithms for tubular epithelium, lumen, nuclei, and basement membranes (288,172 tubules and 323,6081 nuclei) on 13 nephrectomies (reference tissue) and the NEPTUNE/CureGN dataset. 9 out of the 99 extracted, hand-crafted tubule-level features were previously shown to be associated with clinical outcomes and mapped to WSIs to identify the spectrum of tubular pathomic signatures across non-, pre-, and mature- IFTA regions.

Results: A progressive simplification of the tubular epithelium, thickening/area of the tubular basement membranes, and decreased nuclear distance to lumen from normal to full tubular atrophy was witnessed as one transitions between less to more diseased regions (Figure 1.1). The trajectory of tubular changes corresponds to the development of interstitial scarring (Figure 1.2).

Conclusions: Clinically relevant computationally derived tubular characteristics quantify the tubular changes across the spectrum of IFTA development, providing insights into tubule-level heterogeneity and atrophy pathway. This level of detail and quantification is not possible with human assessment alone and opens new opportunities for disease trajectory and biomarker studies.

Funding: NIDDK Support, Other NIH Support - 1) the National Institute of Health (NIH) under the following awards: i) by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under the award number 2R01DK118431-04; ii) the National Cancer Institute (NCI) under award numbers R01LM013864, R01CA249992-01A1, R01CA202752-01A1, R01CA208236-01A1, R01CA216579-01A1, R01CA220581-01A1, R01CA257612-01A1, 1U01CA239055-01, 1U01CA248226-01, 1U54CA254566-01, and 1U01DK133090; iii) the National Heart, Lung and Blood Institute under award numbers 1R01HL15127701A1, R01HL15807101A1; iv) the National Institute of Biomedical Imaging and Bioengineering under award number 1R43EB028736-01; and v) the National Center for Research Resources under award number 1 C06 RR12463-01, 2) VA Merit Review Award IBX004121A from the United States Department of Veterans Affairs Biomedical Laboratory Research and Development Service. 3) the Office of the Assistant Secretary of Defense for Health Affairs, through i) the Breast Cancer Research Program (W81XWH-19-1-0668), ii) the Prostate Cancer Research Program (W81XWH-15-1-0558, W81XWH-20-1-0851), iii) the Lung Cancer Research Program (W81XWH-18-1-0440, W81XWH-20-1-0595), iv) the Peer Reviewed Cancer Research Program (W81XWH-18-1-0404, W81XWH-21-1-0345). 4) the Kidney Precision Medicine Project (KPMP) Glue Grant and sponsored research agreements from Bristol Myers-Squibb, Boehringer-Ingelheim, and Astrazeneca. 4) The Nephrotic Syndrome Study Network (NEPTUNE) is part of the Rare Diseases Clinical Research Network (RDCRN), which is funded by the National Institutes of Health (NIH) and led by the National Center for Advancing Translational Sciences (NCATS) through its Division of Rare Diseases Research Innovation (DRDRI). NEPTUNE is funded under grant number U54DK083912 as a collaboration between NCATS and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Additional funding and/or programmatic support is provided by the University of Michigan, NephCure Kidney International, Alport Syndrome Foundation, and the Halpin Foundation. RDCRN consortia are supported by the RDCRN Data Management and Coordinating Center (DMCC), funded by NCATS and the National Institute of Neurological Disorders and Stroke (NINDS) under U2CTR002818. 5) Additional support was also provided by NephCure and the Henry E. Haller, Jr. Foundation. 6) Funding for the CureGN consortium is provided by U24DK100845 (formerly UM1DK100845), U01DK100846 (formerly UM1DK100846), U01DK100876 (formerly UM1DK100876), U01DK100866 (formerly UM1DK100866), and U01DK100867 (formerly UM1DK100867) from the NIDDK/NIH. Patient recruitment is supported by NephCure. Dates of funding for first phase of CureGN was 9/16/2013-5/31/2019., Veterans Affairs Support, Other U.S. Government Support, Private Foundation Support



1.1 (Left panel): Spectrum of tubular phenotypes (bottom) from normal to full atrophy as defined by the individual clinically relevant pathomic features. **1.2 (Right panel):** Comparison of the 9 clinically relevant pathomic features across reference tissue and non-, pre-, and mature IFTA regions in the NEPTUNE/CureGN. Box boundaries & violin plots: gray=reference tissue, blue=non-IFTA, green=pre-IFTA, and red=mature IFTA.

FR-PO934

Podocyte-Derived Vesicles as Urinary Markers of Kidney Function

Luisa Schnobrich,[1] Klaus J. Stark,[2] Hayo Castrop.[1] *[1]Universitat Regensburg Fakultat fur Biologie und Vorklinische Medizin, Regensburg, Germany; [2]Universitat Regensburg Fakultat fur Medizin, Regensburg, Germany.*

Background: Changes in the integrity of the glomerular filtration barrier (GFB) cause the endocytosis of albumin by podocytes from the subpodocyte space, as shown by intravital imaging in rats. Albumin-containing podocyte-derived vesicles are subsequently released into the urinary space and can be recovered from the urine. These vesicles are characterized by the presence of podocalyxin. Based on these results we hypothesized that urinary vesicular albumin (vACR) and vesicular podocalyxin (vPCR) may serve as early biomarkers of changes of the integrity of the GFB in humans.

Methods: Urinary vesicles were isolated by ultracentrifugation from spot urine samples collected from participants of a prospective study, a cohort of mobile elderly subjects (aged 70 years +). Urine samples were collected and an array of clinical parameters was determined at baseline (BL: n = 626), after 3 years (follow-up 1: n = 626) and after 7 years (follow-up 2: n = 197). Vesicular albumin and podocalyxin concentrations were measured using commercially available ELISA kits and results were normalized to urinary creatinine concentration. Using SPSS 28.0.0.0 the association between vesicular parameters and clinical parameters (eGFRCys, urinary albumin/creatinine ratio (uACR), and alpha-1-microglobulin/creatinine ratio (a1M/Cr)) were determined.

Results: A negative association between eGFRCys and vACR was observed for all time points ($p<.001$). Annual changes in eGFRCys were not predicted by vesicular variables. Linear regression analysis between vACR or vPCR and uACR or a1M/Cr, both adjusted for age, sex and eGFRCys, showed a positive association between the variables at all timepoints ($p<.05$). Thus, elevated vACR and vPCR were accompanied by increased uACR and a1M/Cr concentrations. Increased vACR and vPCR concentrations at baseline were associated with a reduced increase of uACR over time, suggesting that the formation of podocyte-derived vesicles reduces the progression of albuminuria by some protective effect on the filtration barrier ($p<.01$).

Conclusions: In summary, increased vACR is associated with decreased GFR, and both vACR and vPCR are associated with the degree of albuminuria and tubular dysfunction. Our data suggests that both vACR and vPCR may serve as new biomarkers of kidney function and may predict the development of albuminuria over time.

Funding: Government Support - Non-U.S.

FR-PO935

Dysmorphic vs. Isomorphic Microhematuria in the Diagnostic Approach of Glomerular Diseases

Jorge A. Sanchez, Sheila Bermejo Garcia, Hector L. Bedoya, Marina López-Martínez, Gerson B. Redondo, Jorge I. Zamora Carrillo, Marc Patricio-Liébana, Natalia Ramos, Irene Agraz Pamplona, Maria Jose Soler. *Hospital Universitari Vall d'Hebron, Barcelona, Spain.*

Background: Dysmorphic microhematuria has been related to glomerulonephritis(GN). This technique has a high specificity with variable sensitivity. The objective of study was to evaluate patients with GN and to study the prevalence of dysmorphic and isomorphic microhematuria and to evaluate factors associated with dysmorphia.

Methods: Retrospective study of patients with GN associated with microhematuria in our hospital from 2013 to 2024. Clinical and analytical characteristics of the patients were analyzed comparing patients who presented or not dysmorphic red blood cells (dRBCs).

Results: 119 patients diagnosed with GN were included:68 men(57.1%), mean age 51.6(±19) years, 55.5%(n=66) hypertension. At the time of the kidney biopsy, creatinine 1.8[0.9-3.6]mg/dl, eGFR 44[15-81] mL/min/m^2 and albumin/creatinine ratio 650[281-1634]mg/gr. The more frequent indication of kidney biopsy was proteinuria and microhematuria(n=52, 43.7%). IgA nephropathy(n=34, 28.6%) was GN with more prevalence. 105 patients(88.2%) had microhematuria, of which 51(48.6%) had dRBCs. Patients with cryoglobulinemia, anti-GBM and IgA Nephropathy, a higher percentage of dRBCs was detected(80%, 57% and 51.6%, respectively p=0.013). A higher prevalence of dRBCs in acute kidney injury, proteinuria and microhematuria as indication of kidney biopsy (p=0.046). Furthermore, patients with hypertension(p=0.013) and men(p=0.038) presented more prevalence of dRBCs. However, patients who did not present dRBCs had a higher ischemic heart disease(p=0.019), antiplatelet agents(p=0.016), protein/creatinine ratio(p=0.043) and positive urine culture(p= 0.046). In the logistic regression analysis, low protein/creatinine ratio(1.03-9.09 OR:3.06, p=0.044) was the only variable associated with the presence of dysmorphia. A ROC curve was obtained with an AUC of 0.72(0.619-0.822 p<0.001). The sensitivity was 31.9% and specificity 91.5%.

Conclusions: Patients with GN and microhematuria, dysmorphia was detected in approximately half of patients. The absence of hypertension, ischemic heart disease, antiplatelet agents, negative urine culture and lower level of proteinuria were related to the presence of dysmorphia, with a sensitivity 31.9% and a specificity 91.5%.

FR-PO936

Urinary White Blood Cell Casts Suggest Presence of Crescentic Lesions in Acute Glomerulonephritis

Muner Mohamed,[1,2] Khalid M. Mohammed,[3] Dustin R. Chalmers,[4] Vipin Varghese,[5] Swetha Rani Kanduri,[1,2] Juan Carlos Q. Velez.[1,2] Ochsner Group. *[1]Ochsner Health, New Orleans, LA; [2]The University of Queensland, Brisbane, QLD, Australia; [3]Tanta University, Tanta, Egypt; [4]Louisiana State University, Baton Rouge, LA; [5]University of Michigan, Ann Arbor, MI.*

Background: Unlike standard dogma of their association with acute interstitial nephritis, urinary white blood cell casts (uWBCC) are more commonly detected in cases of acute glomerulonephritis (GN). However, granular aspects of this association have not been explored. We hypothesized that uWBCC may correlate with specific morphological histopathological findings in GN.

Methods: We prospectively collected data of patients seen in nephrology consultation who had a urine specimen subjected to microscopic examination of the urinary sediment (uSEDI) as part of the clinical evaluation. Within this cohort, we identified cases in which a kidney biopsy was performed and a diagnosis of GN was made. We assessed the performance of uWBCC in predicting specific lesions in GN: cresentic/necrotizing (Cresc/Necr) lesions, endocapillary proliferation (EC) or intersitial inflammatory inflitrate (III).

Results: Among 801 patients assessed by uSEDI over a 5-year period, 107 (15%) had biopsy-proven GN. Within that group, 24 (22%) had uWBCC. Mean age was 54 years, 51% women, 50% white and 38% black. Median serum creatinine at diagnosis was 3.6 (0.7-15.6) mg/dL. Biopsy diagnosis was pauci immune GN in 6 (25%), IgA nephropathy in 6 (25%), lupus GN in 3 (13%) and other proliferative or infection-related GN in 9 (37%). The sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) of uWBCC for identifying Cresc/Necr lesions were 34%, 90%, 71% and 28%, respectively, whereas the SENS, SPEC, PPV and NPV of uWBCC for identifying EC were 28%, 80%. 38% and 27%. Also, the SENS, SPEC, PPV and NPV of uWBCC for III were 75%, 48%, 38% and 96%. Notably, 6 out of 9 GN cases with uWBCC and III also had Cresc/Necr lesions.

Conclusions: Identification of uWBCC by uSEDI in patients GN is fairly specific to predict Cresc/Necr lesions. This observation suggests that WBCs contained in casts likely originate from circulating cells that travel from the glomerular capillary lumen into the Bowman space through glomerular basement membrane (GBM) breaks. In addtion, absence of uWBCC is highly predictive of absence of III. These findings offer diagnostic/therapeutic insight for the clinician in anticipation of a kidney biopsy.

FR-PO937

Value of Diffusion Kurtosis Imaging in Assessing IgG4 Kidney Disease: A Feasibility Study

Fei Teng, Xiaoxiao Zhang, Gu-Mu-Yang Zhang, Xuemei Li, Hao Sun, Ke Zheng. *Peking Union Medical College Hospital, Beijing, China.*

Background: Immunoglobulin G4 (IgG4)-related kidney disease (IgG4-RKD) is pathologically featured by interstitial IgG4+ plasma cell infiltration and interstitial fibrosis, and often leads to chronic kidney dysfunction. Our study aims to explore the use of invasive diffusion kurtosis imaging (DKI) in assessing IgG4-RKD and to evaluate the potential of DKI-based quantitative parameters in the clinical assessment of IgG4-RKD.

Methods: A prospective study was conducted on 23 IgG4-RKD patients who underwent bilateral renal MRI with T1WI, T2WI, and DKI sequences. Two radiologists evaluated the MR images and determined the distribution pattern and signal intensity of the renal lesions. The mean kurtosis (MK), mean diffusivity (MD), and apparent diffusion coefficient (ADC) of the renal parenchyma, cortex, and medulla were measured. Correlation analysis with clinical indicators such as creatinine, estimated glomerular filtration rate (eGFR), IgG4, IgG, complement, and erythrocyte sedimentation rate (ESR) was performed, and interclass correlation coefficient (ICC) was used to evaluate consistency of measurement.

Results: IgG4-RKD showed bilateral (90.91%), multiple (95.24%) and wedge- or round-shaped renal parenchymal lesions (90.91%) with iso-signal on T1WI (80.96%), low signal on T2WI (85.71%) and high-signal on DKI (95.24%). MK, MD, and ADC did not differ between the left and right kidneys. There were no significant differences in MK and ADC in the renal parenchyma, renal cortex, and renal medulla, but MD was higher in the renal cortex. There was a strong negative correlation between eGFR and renal cortical MK (r = 0.66, p = 0.002), as well as a weak positive correlation between serum IgG4/IgG and parenchymal ADC (r=0.37, p=0.038). The C4 was positively correlated with MD-P (r=0.51, p=0.118), and ESR was positively correlated with renal parenchymal MK (r=0.58, p=0.005). The agreement of DKI parameters was moderate to good, except for bilateral renal medullary MD.

Conclusions: DKI images can be used to assess IgG4-RKD renal imaging alterations, and the quantitative parameter MK obtained on the basis of DKI correlates with serum creatinine, eGFR and IgG4/IgG ratio. DKI images have the potential to assess IgG4-RKD clinical condition.

FR-PO938

Variations in Creatinine Generation among Patients with Glomerular Diseases

Shalini S. Ramachandra,[1] Melody Chiang,[2] Michael Arbit,[2] Dorey A. Glenn,[3] Laura H. Mariani,[2] Jarcy Zee.[1,4] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of Michigan Department of Internal Medicine, Ann Arbor, MI; [3]The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC; [4]The Children's Hospital of Philadelphia Research Institute, Philadelphia, PA.*

Background: Estimation of glomerular filtration rate (eGFR) assumes that creatinine generation (CrG) is relatively stable, but the relationship between CrG variability and glomerular disease activity is unknown.

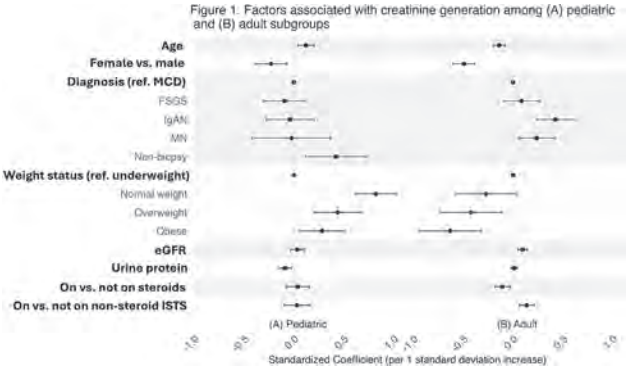
Methods: CrG was calculated using 24-hour timed urine collections from children and adults with MCD, FSGS, MN, IgAN, or non-biopsied pediatric nephrotic syndrome enrolled in the NEPTUNE and CureGN cohort studies. Intraclass correlation coefficients (ICC) were used to estimate CrG variability within individuals over time. Multivariable linear mixed models were used to identify: (1) factors associated with CrG and (2) the impact of change in CrG (ΔCrG) on changes in serum creatinine (ΔSCr), adjusting for simulated true GFR.

Results: A sample of 4626 CrG measurements were analyzed from 1081 study participants (26.7%<18 years). A moderate correlation between intra-individual measurements overall (ICC = 0.517, 95% CI: 0.482, 0.548), and a weak correlation among non-biopsied pediatric participants (ICC = 0.241 (95% CI: 0.000, 0.558) were observed. Among all pediatric participants, factors significantly associated with CrG included age, sex, weight status, and urine protein [Figure 1A]. Among adults, age, sex, disease diagnosis, weight status, eGFR, steroid use, and non-steroid immunosuppressant (IST) use were significantly associated with CrG [Figure 1B]. After adjustment for simulated true GFR (based on ρ=0.512 correlation with ΔCrG and ρ=-0.835 correlation with ΔSCr) and other covariates, every 10 mg/kg/day increase in ΔCrG was associated with a 0.48 mg/dL increase in ΔSCr (p < 0.001).

Conclusions: Creatinine generation was highly dynamic within individuals over time and varied with glomerular disease activity and treatments. The impact of changes in creatinine generation on estimation of kidney functions is potentially large. Accounting for these changes and/or routine use of other markers to measure kidney function may be beneficial for patients with glomerular disease.

Funding: NIDDK Support

Figure 1. Factors associated with creatinine generation among (A) pediatric and (B) adult subgroups



FR-PO939

Air Quality and Kidney Health: Assessing the Effects of PM10, PM2.5, CO, and NO2 on Kidney Function in Primary Glomerulonephritis

Jinyeong Yi,[1] Yun Jung Oh,[2] Julee You,[3] Jiwon Ryu.[3] *[1]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [2]H Plus Yangii Hospital, Seoul, Republic of Korea; [3]Seoul National University Bundang Hospital, Seongnam, Republic of Korea.*

Background: Although extensive research has established associations between exposure to air pollution and chronic disease, such as cardiovascular disease and diabetes, the nuanced impact on specific kidney pathologies like primary glomerulonephritis (GN)—an immunological kidney disorder—remains underexplored. Given the increasing burden of GN and the notable gap in research on its relation to air quality, our study focuses on exploring the long-term effects air pollutants on renal function in patients with primary GN.

Methods: This retrospective cohort study analyzed 1,394 primary GN patients diagnosed at Seoul National University Bundang Hospital and Seoul National University Hospital. We used time-varying Cox regression and linear mixed models (LMM) to determine the impact of yearly average air pollution levels on renal function deterioration and change in estimated glomerular filtration rate (eGFR). Renal function deterioration (RFD) is defined as a sustained eGFR less than 60 mL/min per 1.73 m^2.

Results: Over a mean follow-up of 5.1 years, 350 patients developed RFD. Notably, increased interquartile range (IQR) levels of air pollutants—PM_{10} (particles ≤10 micrometers, HR 1.383, 95% CI 1.194–1.601), $PM_{2.5}$ (particles ≤2.5 micrometers, HR 1.341, 95% CI 1.15–1.564), CO (carbon monoxide, HR 1.254, 95% CI 1.092–1.441), and NO_2 (nitrogen dioxide, HR 1.174, 95% CI 1.017–1.356)—were significantly linked to higher RFD risk, after adjusting for demographic and health factors. Additionally, exposure to PM_{10} and $PM_{2.5}$ was associated with decreased eGFR.

Conclusions: This study demonstrates a significant relationship between exposure to air pollution and renal function in primary GN, highlighting the importance of environmental factors in immune-mediated kidney disease.

FR-PO940

Demographics and Trends of Tubulointerstitial Nephritis-Related Mortality in the United States, 1999-2020

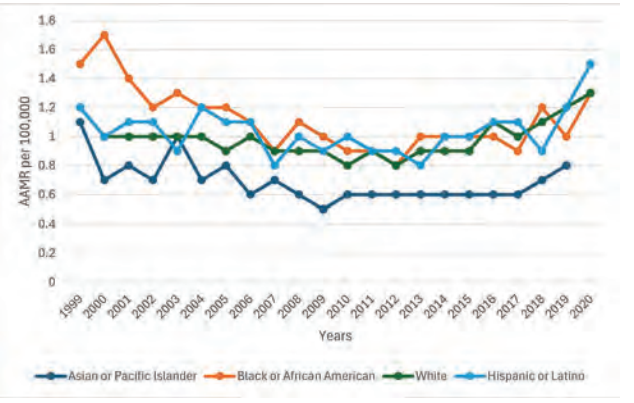
Badar U Din Shah,[1] Wania Rehman,[2] Muhammad Talha Shaukat,[2] Malik S. Hayat,[2] Muhammad Mukarram Shoaib,[2] Aqeeb Ur Rehman,[3] Aleenah Mohsin,[4] John W. O'Bell.[4] *[1]Geisinger Health, Danville, PA; [2]King Edward Medical University, Lahore, Pakistan; [3]The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; [4]Brown University, Providence, RI.*

Background: The incidence of tubulointerstitial nephritis as a cause for mortality is on the rise in the US. In this study, we aim to investigate the patterns of mortality associated with it spanning from 1999 to 2020 in the United States.

Methods: Data was extracted from the CDC WONDER database from 1999 to 2020. Age-adjusted mortality rate (AAMR) per 100,000 individuals and annual percent changes (APC) with 95% Confidence Intervals (CI) were calculated using Joinpoint regression for different epidemiological cohorts stratified by gender, race, and locale (metropolitan vs. non-metropolitan).

Results: From 1999 to 2020, a total of 37,611 deaths were reported due to tubulointerstitial nephritis. The overall AAMR showed a gradual decline from 1999 to 2012 followed by a progressively increasing trend from 2012-2020, with an APC of -2.1853 and 5.0345 respectively. The analysis revealed significant disparities in mortality rates among different demographic groups and geographical regions. The mortality rates were found to be higher in female patients (AAPC: 0.3% (95% CI -0.74 to 1.35)), Latino/Hispanic patients (AAPC: 1.5% (95 % CI 0.87 to 3.97)) and residents of metropolitan areas (AAPC: 1.22% (95% CI -1.75 to 4.28)).

Conclusions: Our study revealed an increasing trend of tubulointerstitial nephritis-related mortality from 2012 onwards with demographic and geographical disparities, which underscores the necessity for further research to address these disparities and mitigate the rising mortality associated with tubulointerstitial nephritis.



Trends of mortality due to tubulointerstitial nephritis across different races in the United States;1999-2020

FR-PO941

Demographics and Trends of Mortality Due to Nephritic Syndrome in the United States, 1999-2020

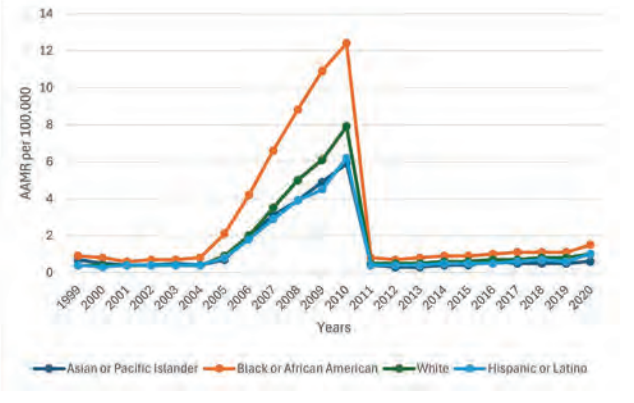
Badar U Din Shah,[1] Muhammad Talha Shaukat,[2] Wania Rehman,[2] Malik S. Hayat,[2] Fatima Shahid,[2] Aqeeb Ur Rehman,[3] Aleenah Mohsin.[4] *[1]Geisinger Health, Danville, PA; [2]King Edward Medical University, Lahore, Pakistan; [3]The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; [4]Brown University, Providence, RI.*

Background: The mortality rate associated with nephritic syndrome in the US is on the rise. We analyze mortality trends from 1999 to 2020 using age-adjusted mortality rates (AAMR) to identify disparities among different demographic groups.

Methods: Data was extracted from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research (CDC WONDER) database from 1999 to 2020. Age-adjusted mortality rate (AAMR) per 100,000 individuals and annual percent changes (APC) with 95% Confidence Intervals (CI) were calculated using Joinpoint regression analysis for different epidemiological cohorts stratified by gender, race, and locale.

Results: From 1999-2020, 120103 nephritic syndrome-related deaths were documented. APC of 89.21 from 2003-2007, 26.75 from 2007-2010, and 14.2 from 2013-2020 indicate an increasing trend in AAMR from 1999-2020. However, there was a notable drop in nephritis associated mortality between 2010 and 2013 (APC= -62.73). Certain groups experienced consistently higher death rates, including African Americans (average annual percentage change (AAPC):2.72, 95% CI:-3.8 to 9.7), males (AAPC:4.04, 95% CI:-0.9 to9.2), individuals aged 85 and older. The Midwest region had the highest mortality rates (AAMR:1.8), followed by the South and West (AAMR:1.7) and the Northeast (AAMR 1.3). Specific states with high mortality rates included Tennessee, South Carolina, Minnesota, Wisconsin and Oregon. There was no significant difference in mortality rates between metropolitan (AAPC:3.62) and non-metropolitan areas (AAPC: 3.90).

Conclusions: The rise in nephritic syndrome-related mortality from 1999 to 2020 is concerning and underscores the need for focused research and targeted interventions. Continued efforts are essential to ensure equitable access to effective treatments and improve patient outcomes across all affected demographic groups.



Mortality trends of nephritic syndrome across different races

FR-PO942

Trend Analysis of Renal Tubulointerstitial Disease-Related Mortality, 1999-2020

Mohammad Ammar ur Rahman,[1] Ahmed J. Chaudhary,[2] Eisha Moazzam,[1] Luqman Munir,[1] Amna Khalid,[1] Haram Aftab,[1] Azka Ijaz.[1] NEURALKEy. *[1]King Edward Medical University, Lahore, Pakistan; [2]Detroit Medical Center, Detroit, MI.*

Background: Renal tubulointerstitial disease is a term which encompasses primary injury of renal structures resulting in inflammation of kidney and the surrounding tissues (interstitial tissues), hence it is also referred to as tubulointerstitial nephritis. It can a result of a hypersensitivity reaction to certain medications, exposure to heavy metals and infections. For treatment, removing the causative agent is preferred followed by corticosteroid therapy. The aim of this study was to analyze the trend of deaths as a result of renal tubulo-interstitial disease in the US from 1999 to 2020 using age-adjusted mortality rate (AAMR) and to identify variations among key demographic variables.

Methods: We obtained death certificates from 1999 to 2020 from the website of Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER). AAMR per 1,000,000 people and annual percent change (APC) with 95% confidence interval were determined. Joinpoint Regression Program was used to determine trends among demographics groups (gender, age, race, urban/rural).

Results: In total, 7,341 deaths due to renal tubulointerstitial diseases were recorded. The age-adjusted mortality rate (AAMR) surged from 15.228 in 1999 to 17.962 in 2020. The annual percentage change (APC) in AAMR indicated following trends: from 1999 to 2011, the APC was -2.1150, demonstrating a decline; from 2011 to 2018, the APC rose to 3.8974; and from 2018 to 2020, the APC showed a noticeable peak at 9.5021. On analysis, higher mortality rates were recorded among Black individuals, those living in rural areas, the residents of western region, males, and individuals aged 85 years and older.

Conclusions: The mortality rate due to renal tubulointerstitial diseases has experienced a concerning rise in the last two decades. Persistent disparities among the demographic variables highlight the need for further investigation and intervention.

FR-PO943

Changes in the Spectrum of Kidney Diseases: A 14-Year Kidney Biopsy Study from a Single Center

Zishan Lin, Shidong Xie, Wenfeng Wang, Tao Hong, Jianxin Wan, Yanfang Xu. *The First Affiliated Hospital of Fujian Medical University, Fuzhou, China.*

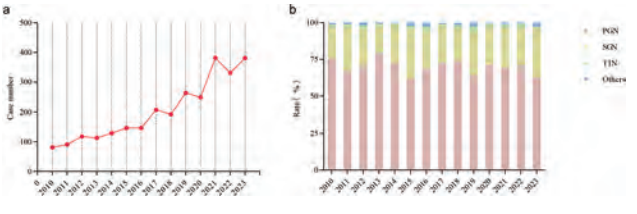
Background: CKD is a critical global public health concern. Early detection and treatment are crucial in preventing progression. Renal biopsy remains a cornerstone in diagnosing various kidney diseases. Recent decades have seen shifts in the disease spectrum, driven by factors like hepatitis B, diabetes, and aging. The study aims to investigate the changing spectrum of kidney diseases for disease prevention and public health interventions.

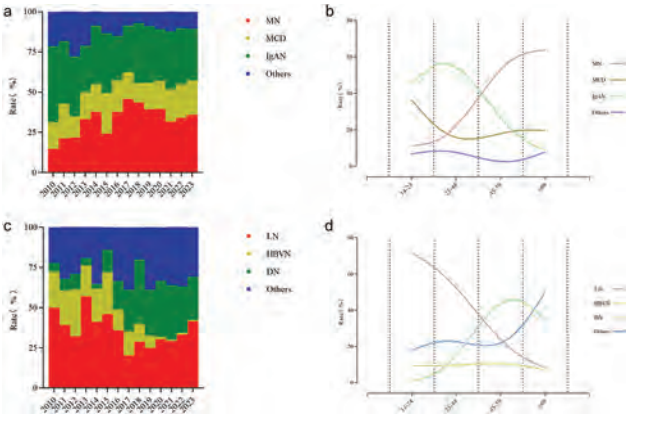
Methods: Patients (≥14 years of age) who underwent renal biopsy at the First Affiliated Hospital of Fujian Medical University from January 2010 to December 2023 were included in the study. Clinicopathological data was collected.

Results: This study involved 2832 patients. Annual renal biopsy numbers rose from 81 in 2010 to 381 in 2023 (Fig 1A). Primary glomerulonephritis (GN) was the leading cause of kidney diseases (Fig 1B). Patients aged ≥60 years grew from 9.3% in 2020 to 23.2% in 2023, showing a demographic shift towards an older population. MN, IgAN, and MCD were the most common primary GN subtypes, representing 34.9%, 34.5%, and 18.5% of cases, respectively (Fig 2A). From 2010 to 2023, MN cases increased from 14.8% to 36.0%. MN predominantly occurred in the elderly, with rising prevalence with age (Fig 2B). LN, DN, and HBVN were the top secondary GN causes, accounting for 34.3%, 24.8%, and 9.0% of cases, respectively (Fig 2C). DN notably rose from 5.6% in 2010 to 40.0% in 2018. HBVN incidence consistently declined. LN primarily affected younger patients, while DN was more prevalent in older individuals, peaking at 43.8% in the 45-59 age group (Fig 2D).

Conclusions: The spectrum of kidney disease has changed within the last 14 years. The relative frequency of MN and DN increased significantly, while that of HBVN decreased significantly.

Funding: Government Support - Non-U.S.





FR-PO944

Geospatial Mapping to Identify Primary Glomerulonephritis Hot Spots in Saskatchewan

Bhanu Prasad,[1] Aditi Sharma,[2] Aarti Garg,[2] Abdul Raouf,[5] Matthew Patterson,[4] Pouneh P. Dokouhaki.[3] *[1]Regina General Hospital, Regina, SK, Canada; [2]University of Regina, Regina, SK, Canada; [3]The University of British Columbia, Vancouver, BC, Canada; [4]University of Saskatchewan, Saskatoon, SK, Canada; [5]Saskatchewan Polytechnic - Regina Campus, Regina, SK, Canada.*

Background: Saskatchewan (SK), a province rich in oil, minerals, and agriculture, with 1.2M population, is principally served by its two urban renal centers in Regina and Saskatoon. There is a lack of comprehensive data on the association of GN subtypes with rural-urban divide, and geographic hotspots like mines and refineries. Utilizing the kidney biopsy, our objective was to identify clusters of GN subtypes, calculate yearly incidence rates, urban/rural comparisons, and distance and travel time to access care.

Methods: A centralized provincial kidney pathology database was used to capture all incident cases of biopsy-proven GN in the adult population from 2002 - 2018. Only patients with primary GN were included (n=1372). Demographic attributes, 3-digit postal codes, lab parameters, definitive GN diagnosis, the date of biopsy, dialysis start, and death were collected and analyzed. To analyze the variation of GN across different regions in SK we used SaTScan v10.1.3 software. The population data from Census 2016 was used as a reference, and age and sex were taken as covariates.

Results: GN incidence increased from 4.6 to 13.6 per 100,000 persons from 2002 to 2018 ($p<0.001$). GN incidence was higher in rural areas than in urban areas ($p<0.001$). Significantly higher dialysis progression rates were seen for rural and remote areas ($p<0.01$). We identified a geospatial cluster of 345.7 km^2 for lupus nephropathy (Figure 1(f)), with an incident rate ratio of 1.73, a relative risk of 2.7, and a Log likelihood ratio of 13.87. No significant clusters were identified for any other subtypes of GN.

Conclusions: We identified a geographic cluster for lupus nephropathy, encompassing both urban and rural areas. While there was a higher incidence of MN and AGBM in rural areas, we did not identify any geographic clusters for the same. Addressing and understanding the multifaceted factors driving these disparities are essential steps towards easing the burden of GN on impacted communities.

Figure 1: Lupus Cluster in the entire province (highlighted in red). The inset on the left represents regions that are part of the lupus cluster in Saskatoon.

FR-PO945

Incidence of Glomerulonephritis and Clinical Outcomes of Kidney Biopsy Patients at the National and Transplant Kidney Institute, 2016-2022

Melanie T. Estolas. *National Kidney and Transplant Institute, Quezon City, Philippines.*

Background: Glomerulonephritis remains a predominant cause of end stage kidney disease and is potentially reversible but entails a kidney biopsy for definitive diagnosis, management decisions and prognostication. There is limited data on incidence of glomerular diseases in the Philippines, and a national kidney biopsy registry is lacking for the years 2016 and onwards.

Methods: A total of 2249 patients who had native kidney biopsy at NKTI from 2016-2022 were identified and a retrospective review of their chart records, laboratory results and kidney biopsy findings was done, with a follow up for at least 12 months.

Results: The median age for kidney biopsy was 34 years with a higher female prevalence (56.16%). Primary glomerulonephritis comprised 74.17% of cases and secondary GN for 23.5%. IgA nephropathy at 45.86% and FSGS at 19.78 were the most common for primary GN. For secondary GN, Lupus nephritis was the most prevalent at 56.7%. IgAN had the highest incidence of complete and partial remission. Progression to ESRD requiring dialysis was almost similar for IgAN and FSGS.

Conclusions: IgA nephropathy is still the most prevalent type of primary glomerulonephritis in this single center study, while Lupus nephritis is the most common secondary GN. A significant overall improvement in kidney function and proteinuria was noted on follow up.

FR-PO946

Enhancing Patient Comprehension of Glomerular Disease Terminology: Role of Artificial Intelligence (AI) in Simplifying Medical Communication

Yasir Abdelgadir, Charat Thongprayoon, Iasmina Craici, Wisit Cheungpasitporn, Jing Miao. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Glomerular disease is complex and difficult for patients to understand due to its involvement in various areas such as renal anatomy, pathophysiology, immunology, genetics, and diverse treatment strategies. This study employed the AI language model ChatGPT to simplify glomerular disease terms, proposing a new way to improve patient comprehension of this condition.

Methods: Seventy-three terms related to glomerular disease were analyzed using GPT-4 through two inquiries: one for easy-to-understanding and another for patients with an education level of 8th grade or lower. GPT-4's accuracy was scored from 1 (incorrect) to 5 (correct and comprehensive), and readability was assessed using the Consensus Reading Grade (CRG) Level, incorporating the Flesch-Kincaid Grade (FKG) and SMOG indices. Paired t-test compared the accuracy and readability of both inquiries.

Results: GPT-4's easy-to-understanding explanations of glomerular disease terms averaged a 12th-grade readability level (12.5 by CRG and 12 by FKG), reflecting the topic's complexity (Fig.). When inquired for patients with 8th grade or lower, readability improved, averaging 9.7 by CRG and 8.7 by FKG, with the SMOG index indicating a further reduction from 10.2 to 7.2. However, the accuracy in GPT-4's explanations for patients at or below the 8th-grade level was significantly lower than that for easy-to-understanding explanations (*p=0.01*).

Conclusions: While GPT-4 effectively simplified information about glomerular diseases, it compromised its accuracy in the process. Although ChatGPT has the potential to contribute to enhancing patient understanding of glomerular disease, it is crucial to closely examine and work on improving its accuracy when generating simplified explanations with human nephrologist to ensure that the information provided is not only easy to understand but also medically accurate and appropriate for patient education.

Fig. Accuracy and Readability of GPT-4's Explanations of Glomerular Disease Terms in Different Inquiries

	GPT-4's explanations for easy-to-understanding	GPT-4's explanations for patients at or below 8th grade	P value
Accuracy [a]	4.44 ± 0.51	4.26 ± 0.35	0.01[c]
CRG level [b]	12.52 ± 1.20	9.69 ± 0.78	<0.0001 [c]
FKG level	12 ± 1.46	8.72 ± 0.85	<0.0001 [c]
SMOG Index	10.17 ± 1.15	7.24 ± 0.85	<0.0001 [c]

[a] Accuracy, scaled from 1 to 5: 1=Completely incorrect, 2=Mostly incorrect, 3=Partly correct and partly incorrect, 4=Correct but not comprehensive, and 5=Correct and comprehensive. The accuracy is assessed independently by two nephrologists and the average score is used for each explanation.

[b] Consensus Reading Grade (CRG) Level is calculated through a free online Readability Scoring System (https://readabilityformulas.com/readability-scoring-system.php) based on 7 readability metrics: the Automated Readability Index, Gunning Fog Index, Flesch-Kincaid Grade (FKG) Level, Coleman-Liau Index, Simple Measure of Gobbledygook (SMOG) Index, Linsear Write Formula, and the FORCAST Readability Formula. When writing content for the general public, aim for a reading level equivalent to around 8th grade. ***The FKG test is used extensively in the field of education. SMOG index is also widely used, but particularly for checking health messages.***

[c] A paired two-sided t test.

FR-PO947

Hypercalcemia in IgG4-Related Tubulointerstitial Nephritis: An Unusual Presentation

Ravi K. Singh. *Jaypee Hospital, Noida, Noida, India.*

Introduction: Tubulointerstitial nephritis IgG4 type (TIN-IgG4) is a rare autoimmune kidney condition characterized by IgG4-positive plasma cell infiltrates, leading to renal interstitium inflammation and fibrosis. Associated with IgG4-related disease affecting various organs, diagnosis involves elevated IgG4 levels, with hypercalcemia hinting at parathyroid involvement. This case presents TIN-IgG4 with hypercalcemia without parathyroid abnormalities, detailing clinical presentation, diagnostic workup, and treatment strategies.

Case Description: A 30-year-old female (a known case of cholelithiasis and hypothyroidism) presented with malaise, vomiting, abdomen pain and dizziness for 3-5 days. Investigations showed hypercalcemia, 24-hour urinary calcium of 288 mg/dL, creatinine of 770 mg/day and protein of 301 mg/dL (Table). Ultrasound showed signs of medullary nephrocalcinosis. There was no evidence of parathyroid adenoma. Renal biopsy confirmed the diagnosis of TIN-IgG4 based on histopathological findings of interstitial fibrosis, tubular atrophy, and abundant IgG4-positive plasma cell infiltration. Serological testing for free light chains (Kappa and Lambda), renal ultrasound and CT, and histopathological examination of renal tissue were obtained. Serum IgG4 level was elevated and imaging findings supported TIN-IgG4 diagnosis. Denosumab, steroids along with her routine thyroid medications were initiated. Long-term management involves regular monitoring of renal function, disease activity, and avoiding potential complications such as renal failure or systemic involvement.

Discussion: Early recognition and intervention in TIN-IgG4, including thorough evaluations for hypercalcemia, are crucial for favorable outcomes and preventing disease progression.

Laboratory values on admission

Laboratory Tests	Values	Urine report/24 hrs	Values
Serum urea	72 mg/dL	Calcium	288 mg
Serum creatinine	3.04 mg/dL	Creatinine	770 mg
PTH	7 pg/mL	Protein	301 mg
Kappa free light chain	56.70 mg/L	–	–
Lambda free light chain	29.20 mg/L	–	–
1,25 dihydroxyvitamin D3	13.7 pg/mL	–	–
Total IgG	15.90 g/L	–	–

IgG, immunoglobulin G; P-ANCA, perinuclear antineutrophil cytoplasmic antibodies; PHT, parathyroid hormone.

FR-PO948

A Case of Lupus-Negative Full-House Staining on Kidney Biopsy, Causing Nephrotic Syndrome during Pregnancy

Prathap Simhadri,[1,2] Renish Contractor,[1] Michael R. Filoramo,[1] Prabhat Singh,[3] Deepak Chandramohan.[4] *[1]Florida State University Daytona Beach Regional Medical School Campus, Daytona Beach, FL; [2]AdventHealth East Florida, Daytona Beach, FL; [3]Christus Spohn Health System, Corpus Christi, TX; [4]The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease and is recognized by a constellation of clinical, laboratory, and histopathological findings. Lupus nephropathy is a common manifestation of SLE, with immune-mediated inflammatory damage to the glomerulus leading to end-stage renal disease. The literature has described a small subset of patients demonstrating renal limited "lupus-like nephropathy", defined by pathological biopsy findings typical of lupus nephropathy without systemic manifestations or laboratory biomarkers of the disease. A full-house stain, identified by positive immunofluorescence staining of all three isotypes of immunoglobulins, is a pathological finding highly associated with SLE. This pathological pattern has been associated with renal-limited lupus-like nephropathy. However, few studies have identified full-house renal-limited "lupus-like nephropathy" in pregnancy.

Case Description: A 24-year-old G1P0 woman at 14 weeks gestation was referred to nephrology for further evaluation of proteinuria. At 16 weeks gestation, 24-hour urine revealed 14 g of proteinuria and a serum albumin level of 1.52 mg/dL. The patient was ANA positive and had elevated C1q antibody titer but negative for other SLE autoantibodies, including anti-Sm, anti-dsDNA, normal C3, and C4 complements. Biopsy revealed membranous nephropathy with positive staining for IgG, IgA, IgM, C3, C1Q, and Lp-PLA2, consistent with full-house immunoglobulin staining. She was started on 500 mg pulse dose methylprednisolone for 3 days, which was gradually tapered to 5 mg daily, and cyclosporine 75 mg BID. Successfully induced at 36 weeks, she delivered a baby with 50% percentile birth weight. Six-month follow-up revealed 1g protein on 24-hour urine collection and normal C3/C4 levels. She continues exhibiting no signs of SLE, and the C1q antibody titer improved.

Discussion: A 24-year-old pregnant female presented with pathological evidence of full-house renal limited "lupus-like nephropathy" without clinical or laboratory evidence consistent with SLE. This case adds to the limited literature describing this condition and more evidence is essential to guide proper treatment and management.

FR-PO949

Spontaneous Remission of Minimal Change Disease during Pregnancy

Henry Yip, Claire Kim, Hira Tahir, Navdeep Kaur. *Stony Brook University Hospital, Stony Brook, NY.*

Introduction: Minimal change disease (MCD) is a pediatric predominant glomerulonephropathy which can cause nephrotic syndrome (NS). Current societal guidelines for the management MCD in adults is based on observational data from the pediatric population, creating limitations in management. In this case we present a case of new onset MCD in a pregnant adult.

Case Description: A 34 year old female with no past medical history who is one month pregnant presents for evaluation of new onset edema. Initial testing found urine protein:creatinine ratio (UPCr) 4.5, urine microalbumin creatinine ratio (UMACR) 2.9, serum albumin of 2.9g/dL. Serum creatinine was 0.49 mg/dl. Further serologic and infectious workup was negative; genetic testing was performed and was inconclusive. A 24-hour urine collection showed 6 grams of protein. A biopsy was performed, with no findings on light microscopy and podocyte effacement on electron microscopy. Maternal fetal medicine (MFM) started her on aspirin and enoxaparin for venous thrombosis (VTE) prophylaxis. Repeat UPCr had decreased to < 3 by her 18th gestational week and a joint decision was made to defer treatment with monitoring given improvement in proteinuria. Patient delivered on time without any complications. UPCr continued to trend down and at her one month postpartum visit, urinalysis showed no protein in urine.

Discussion: Nephrotic syndrome occurs in 0.012% of all pregnancies, and specifically minimal change disease predominantly occurs in children making the presence of new onset MCD during pregnancy uncommon. Adults also tend to have a higher incidence of relapse and take longer to achieve remission. Our electron microscopy showed 40-50% podocyte effacement which could suggest secondary MCD however her history and genetic testing were negative. Although multiple therapeutic options for MCD exist, management in the adult and pregnant populations are not well defined. There have been reports of spontaneous remission of MCD however this appears to be rare and not well described. In our case at her two month postpartum follow up, she has stayed in remission since gestational week 18 without treatment, and highlights the lack of research regarding MCD management in adults, as well any additional accommodations for the pregnant population.

FR-PO950

Minimal Change Disease (MCD) and Human Chorionic Gonadotropin (hCG)-Mediated Thyrotoxicosis during Pregnancy

Laura Aponte Becerra, Gilbert W. Moeckel, Maryam Gondal. *Yale University, New Haven, CT.*

Introduction: Thyroid hormones influence cardiac output and RAAS activity with effects in GFR. Proteinuria has been associated with hypothyroidism but rarely with hyperthyroidism or Graves' disease in non-pregnant adults. This is a case of AKI with severe proteinuria due to MCD in a woman presenting with hyperemesis gravidarum and gestational thyrotoxicosis.

Case Description: A 19-year-old woman at 14 weeks of gestation presented with 4 weeks of hyperemesis accompanied by myalgias, fainting, and muscle weakness. Patient was normotensive, with dry skin and without peripheral edema. Labs showed AKI with creatinine (Cr) of 3.09mg/dL from a normal baseline, BUN of 123mg/dL, hypokalemia, hypophosphatemia, elevated CK of 663 U/L, transaminitis with direct bilirubinemia of 2.4 mg/dL and hypoalbuminemia of 3.0g/dL. TSH was undetectably at <0.005uIU/mL low with elevated free T4 at 4.07ng/dL and normal T3, antithyroid antibodies were negative. Diagnosis of HCG-mediated thyrotoxicosis was made. Urine studies showed total protein-to-Cr ratio of 10.3mg/mg and an albumin-to-Cr ratio of 5.7mg/mg. Kidney biopsy showed diffuse and severe acute tubular injury with myoglobin cast nephropathy. Electron microscopy showed global effacement of foot processes, vacuolization and microvillus transformation of podocytes and the absence of immune deposits. Patient received intravenous fluids, electrolyte replacement and symptomatic treatment of thyrotoxicosis with Propranolol. Emesis improved and she was able to tolerate an oral diet. At 17 weeks of gestation, creatinine had returned to baseline with mild proteinuria and no albuminuria. TSH and free T4 normalized.

Discussion: MCD is rare in pregnancy, the etiology is unclear and management includes initiation of immunosuppression. High HCG levels during the first trimester of pregnancy can trigger thyrotoxicosis given structural homology with TSH and hyperemesis. In this case, we observed normalization of albuminuria and thyroid hormone levels as HCG levels dropped with pregnancy progression. We hypothesize that hyperfiltration from pregnancy and increased cardiac output due to increased thyroid activity could have played a role in proteinuria leading to podocyte effacement. Whether immune or inflammatory mechanisms are involved in the interaction between thyroid and kidney disease during pregnancy is unknown.

FR-PO951

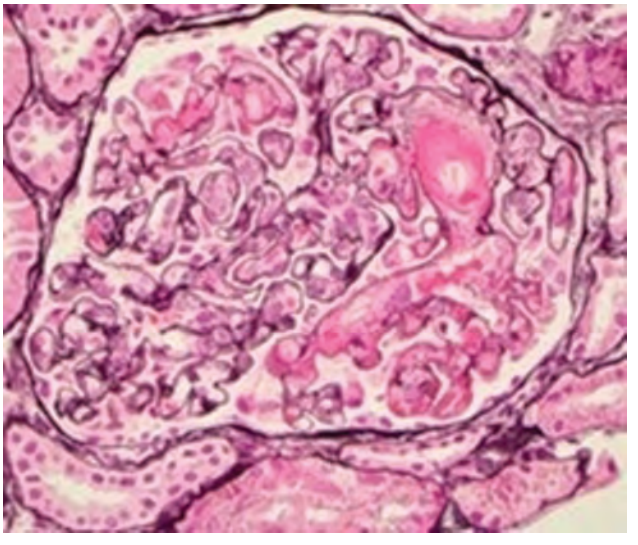
Not All Proteinuria in Pregnancy Is Preeclampsia

Iqra Naeem,[1] Ahmad Basharat,[1] Rebecca Blonsky,[1] Weixiong Zhong.[2] Marshfield Clinic and Health System, Dept of Internal Medicine and Dept of Nephrology; University of Wisconsin Madison, Dept of Pathology. *[1]Marshfield Clinic Health System, Marshfield, WI; [2]University of Wisconsin-Madison, Madison, WI.*

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare disease caused by dysregulation of the alternative complement cascade leading to uncontrolled terminal complement activation causing a systemic thrombotic microangiopathy (TMA). Nephrotic syndrome is a rare presentation of aHUS. We present a case of a pregnant patient presenting with nephrotic syndrome as the sole manifestation of renal limited aHUS.

Case Description: 27-year-old female with history inclusive of prematurity presented at 19 weeks gestation with new onset severe hypertension and anasarca. Patient was found to have 4.268 g/24hr of proteinuria. She was started on steroids while serologic workup for nephrotic syndrome was completed. Her hypertension was treated with diuretics and calcium channel blocker. The patient did not respond to steroids and serologic work up was non-revealing including CBC and LFTs. Patient had pregnancy complication with severe fetal growth restriction and near reversal of placental flows. Kidney biopsy showed findings consistent with acute on chronic TMA as shown in figure. Serologic workup for aHUS demonstrated elevated levels of complement factor Bb. Other potential causes for TMA were negative as was genetic testing. Unfortunately, she lost her pregnancy at 21 weeks gestation, and we changed her antihypertensives to ACE-I. The proteinuria peaked at 9.87 g/g and following addition of ACE-I improved to 1.333 g/g. Eculizumab was the started following appropriate vaccination with remission allowing for decreasing doses of ACE-I.

Discussion: Pregnancy-triggered aHUS can occur during pregnancy and up to 60 days postpartum and accounts for 7% of all aHUS cases. Typically, aHUS present as a systemic TMA with extrarenal manifestations. Isolated nephrotic syndrome is rare, particularly in adults, making this case unique. Eculizumab remains the mainstay of treatment with better outcomes when initiated early in the disease course.



FR-PO952

Long-Term Resolution of HIV-Associated Nephropathy (HIVAN) after Treatment with Highly Active Antiretroviral Therapy (HAART)

Mohamed T. Elkhodary,[1] Barry M. Wall.[2,1] *[1]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [2]Veterans Affairs Medical Center, Memphis, TN.*

Introduction: HIVAN is strongly associated with APOL1 homozygosity. There is usually a second hit, HIV infection being the prototype, which facilitates or precipitates the onset of collapsing focal segmental glomerulosclerosis (FSGS). Removal of this second hit could potentially allow renal recovery. We describe a patient who developed nephrotic range proteinuria and renal failure secondary to HIVAN, necessitating hemodialysis, who recovered renal function following HAART and has had long-term preservation of renal function with no opportunistic infections.

Case Description: 47-year-old African American male with bipolar disorder and CKD 3a presented in 2010 with fever, diaphoresis, and a gluteal abscess. Serum creatinine was markedly elevated, 8.0 mg/dl. Urinalysis was positive for +2 proteinuria, but negative for RBCs, WBCs, or cellular casts. UPCR was 7.75 mg/g. On imaging, kidneys were enlarged with increased echogenicity. Serological investigations were negative and

complement levels were normal. Tests for RPR and hepatitis C were negative. HBsAg was positive. HIV-1 / 2 western blot returned positive with reduced CD4 count, 52 cells/μL, and HIV viral load of 246,940 copies/ml. He required hemodialysis support. Renal biopsy demonstated collapsing FSGS. HAART was initiated with continued outpatient hemodialysis. CD4 count improved and HIV viral load markedly decreased within 5 months of starting HAART. Renal function gradually improved and hemodialysis was discontinued. Proteinuria markedly improved, and he has maintained a stable serum creatinine (2.1 mg/dl) for 14 years while continuing antiviral treatment with nondetectable HIV viral load, CD4 count remaining >250 cells/μL and no opportunistic infections.

Discussion: HIVAN is driven by direct infection of kidney epithelial cells with HIV and subsequent HIV gene expression, particularly in patients of African ancestry with APOL1 homozygosity. Histologically, HIVAN results in a collapsing form of FSGS with tubular dilation and interstitial inflammation. HIVAN typically presents with rapid decline in kidney function with nephrotic range proteinuria. The risk increases if the patient has CD4 < 200 cells/μL, and /or high viral load. Early initiation of HAART can be associated with improvement in CD4 counts and HIV viral load, and can lead to subsequent long term improvement in GFR and proteinuria.

FR-PO953

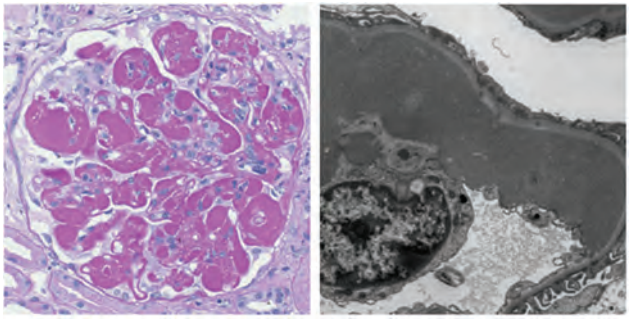
Lymphoplasmacytic Lymphoma with Extensive Subendothelial Deposits Resembling Wire Loop Lesions: A Case Report

Shinichiro Ogawa, Hidekazu Ikeuchi, Masato Kinoshita, Junya Suwa, Hiroko Hamatani, Yoriaki Kaneko, Keiju Hiromura. *Gunma Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Maebashi, Japan.*

Introduction: Lymphoplasmacytic lymphoma (LPL) is an indolent B-cell non-Hodgkin lymphoma that primarily involves lymphocytes differentiating into plasma cells producing IgM-type immunoglobulins. It can occasionally present with renal impairment. Here, we report a rare case of LPL with renal lesions resembling wire loop lesions of lupus nephritis.

Case Description: A 65-year-old male presented with leg edema and proteinuria. A renal biopsy revealed numerous glomeruli with wire loop-like lesions (Left Figure). IF staining showed deposits of IgG, IgA, IgM, C3, and C1q in the mesangial and subendothelial regions, with positive κ light chain. Congo-red staining was negative. Electron microscopy identified extensive subendothelial deposits (Right Figure). Tests for antinuclear and anti-DNA antibodies were negative, with no extrarenal manifestations of systemic lupus erythematosus. Immunoelectrophoresis detected an IgM-κ type M protein in the serum, and cryoglobulins were negative. A bone marrow biopsy confirmed LPL. Upon presentation, the laboratory results were as follows: serum creatinine (S-Cr) 1.49 mg/dL, urine protein/creatinine ratio 1.54 g/gCr, and CH50 <14.0 U/mL. The patient was started on DRC therapy (dexamethasone, rituximab, and cyclophosphamide), resulting in a decreasing trend in IgM to 128 mg/dL, proteinuria to 0.37 g/gCr, and S-Cr to 1.41 mg/dL at 6 months.

Discussion: Renal complications of LPL include hyperviscosity syndrome, amyloidosis, and cryoglobulinemia. This case featured widespread subendothelial deposits, resembling lupus nephritis wire loop lesions. To our knowledge, such lesions have not been previously reported in LPL. Chemotherapy led to reductions in IgM levels, proteinuria, and improved renal function, indicating monoclonal IgM's role in forming these lesions.



FR-PO954

A Viral Conundrum: Hepatitis D and Immune-Complex Glomerulonephritis

Sneha M. Vaddadi, Nasim Wiegley, Shubha Ananthakrishnan, Niti Madan. *UC Davis Health, Sacramento, CA.*

Introduction: Viral-associated glomerulonephritis (GN) is a well-recognized phenomenon, notably seen with hepatitis B (HBV), hepatitis C and HIV. These viral infections can lead to diverse histologic glomerular lesions, including immune-complex GN. There is little literature on Hepatitis D (HDV) associated GN. It is considered a hybrid virus as it uses HBV's surface antigen (HBsAg) as its envelope protein for replication. We present a case of nephrotic syndrome, with biopsy-proven immune-complex GN with active HDV infection.

Case Description: 42-year-old South Asian woman G8P7 at 14w gestation with past medical history of chronic HBV, HDV, and latent TB presented with acute kidney injury (creatinine 1.3 mg/dL, baseline 0.92 mg/dL) and new nephrotic syndrome with urine protein-to-creatinine ratio 3.5 g/g and albumin 2.8 g/dL. Initial kidney biopsy deferred due to pregnancy. Course was complicated by severe pre-eclampsia requiring emergent C-section, and postpartum kidney biopsy with evidence of immune-complex GN with segmental sclerosis. HDV viral load was elevated to 270k, HBV viral load negative, and autoimmune serologies were negative. Glomerular disease was determined to be due to chronic Hepatitis B and coinfection with active Hepatitis D.

Discussion: There are few reports establishing a correlation between hepatitis D and immune-complex GN. In this patient with chronic HBV and HDV co-infection, there was high suspicion of the hepatitis D being the causative pathogen given the elevated viral load. Immunosuppressive therapy was deferred for the patient's GN, and HDV treatment was initiated with an experimental regimen (Bulevirtide and Tenofovir), with improvement of the viral load and proteinuria from peak 5.7 g/g to 1.2 g/g. This case demonstrates a potential novel association between hepatitis D and immune-complex GN, responsive to Hep D targeted anti-viral therapy.

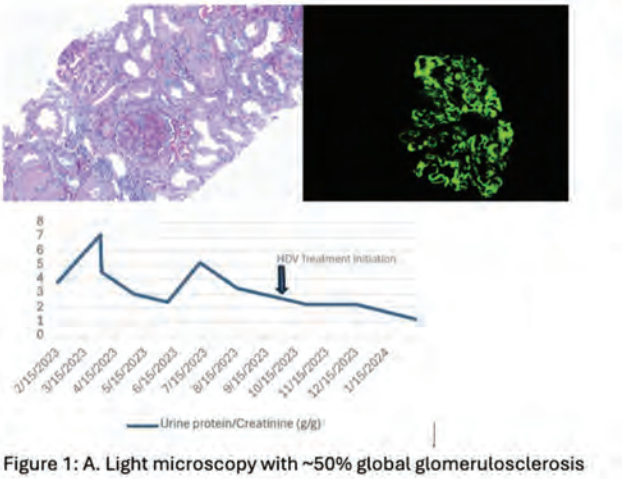


Figure 1: A. Light microscopy with ~50% global glomerulosclerosis with several segmentally sclerotic glomeruli.
B. Full-house positivity on immunofluorescence.
C. Urine protein/Creatinine over time, with initiation of HDV treatment.

FR-PO955

THSD7A-Associated Membranous Nephropathy Involves Both Complement-Mediated and Autonomous Podocyte Injury

Jing Liu, Yan Ge, William T. Gunning, Lance D. Dworkin, Rujun Gong. *The University of Toledo Medical Center, Toledo, OH.*

Background: As a distinctive subtype in the serology-based classification of membranous nephropathy (MN), thrombospondin type 1 domain containing 7A (THSD7A)-associated MN has attracted increasing interest, because THSD7A is also expressed in preclinical species, facilitating the study of its role in MN. This study aimed to establish models of THSD7A-associated MN by using a commercial antibody. Potential pathomechanisms and therapeutic efficacy of repository corticotropin injection (RCI; Purified Cortrophin® Gel, ANI Pharmaceuticals, Inc.) were tested in this model.

Methods: Primary mouse podocytes were cultured in complete medium supplemented with fetal bovine serum containing complements or preheated to inactivate heat-labile complements, followed by exposure to a commercial rabbit anti-THSD7A antibody. *In vivo*, mice were injected with the anti-THSD7A antibody and treated with RCI or vehicle. To deplete complement, some mice were treated with cobra venom factor (CVF).

Results: Mice developed massive proteinuria upon anti-THSD7A antibody insult, concomitant with histologic lesions of glomerular injury, including epimembranous or intramembranous electron-dense deposits in glomeruli as well as variable podocyte foot process effacement on electron microscopy, reminiscent of glomerular ultrastructural changes in human MN. Complement depletion with CVF only partially attenuated proteinuria and glomerular injury in this model, suggesting that complement-independent pathomechanisms also contribute. Consistently, in cultured primary podocytes, exposure to the anti-THSD7A antibody caused evident podocytopathic changes, such as disruption of the actin cytoskeleton integrity, podocyte hypermobility, oxidative stress and apoptosis. These signs of podocyte injury were preserved, although to a lesser extent, after complement inactivation, denoting an autonomous podocytopathic activity of this antibody. As an FDA-approved treatment option for primary nephrotic glomerulopathies including MN, RCI appeared to be beneficial in this model and significantly attenuated proteinuria and glomerular injury.

Conclusions: Both complement-dependent and autonomous podocytopathy are involved in the mouse model of THSD7A-associated MN, which could be attenuated by RCI. This model, based on the use of a commercial anti-THSD7A antibody, could be an important tool for MN research.

Funding: Commercial Support - ANI Pharmaceuticals, Inc

FR-PO956

Integrating Histopathology-Based Analysis with Spatial Transcriptomics of Human Kidneys: Towards Precision Pathology

Pierre Isnard, Dian Li, Qiao Xuanyuan, Haojia Wu, Benjamin D. Humphreys. *Washington University in St Louis, St Louis, MO.*

Background: During spatial transcriptomic (ST) data analysis, computationally-annotated clusters are often superimposed on a histological image without any consideration of the tissue morphology by standard light microscopic pathologic evaluation, thereby ignoring important information that can help interpretation of the ST data

Methods: We conduct a histopathological-based analysis (by a practicing renal pathologist) of spatial transcriptomics (10X genomics, Visium) on 4 human kidney samples with CKD corresponding as closely as possible to how a kidney biopsy is interpreted in clinical practice

Results: We first validated the relevance of this pathological-based clustering by showing that the DEGs and cell composition of each cluster were those expected in relation to the structure analyzed. By examining each sector independently, we showed in particular that ST data can be used to confirm the diagnosis of different structures (TLS, tumor). We also showed how this strategy could be used to: identify potential diagnostic biomarkers, determine cell composition, or study molecular pathways specific to a lesion. We performed a comparative molecular analysis of healthy and pathological glomerular and tubular segments. We could identify several known cellular and molecular mechanisms behind kidney lesions in CKD and were able to identify potential candidate genes in glomeruli (FXYD5, CXCL12) and tubules (TMSB4X, NQO1, MGST1, SQSTM1) possibly involved in disease progression or acting as defense mechanisms. Finally, we show that this pathological-based clustering could be transferred to study other human kidney ST Visium data (nephrectomy sample or needle kidney biopsies). This last result implies that our pathological clustering is potentially not restricted to the analysis of a single slide, and could be projected coherently onto another slide, paving the way for the constitution of spatial molecular banks of lesions and structure as slide analysis progresses

Conclusions: In conclusion, we show the feasibility of a morphological-based approach to interpreting ST data, helping to improve our understanding of kidney lesions in CKD, at both cellular and molecular levels. This work introduces a method to combine traditional histopathology with ST data to pave the way for the future of molecular microscopy and precision pathology

Funding: Private Foundation Support

FR-PO957

Computational Characterization of Arteries/Arterioles in FSGS/Minimal Change Disease

Jin Zhou,[1] Dawit S. Demeke,[2] Xiang Li,[1] Timothy A. Dinh,[2] Christopher L. O'Connor,[2] Qian Liu,[5] Jarcy Zee,[7,5] Yijiang Chen,[3] Andrew Janowczyk,[4,6] Lawrence B. Holzman,[8] Laura H. Mariani,[2] Markus Bitzer,[2] Laura Barisoni,[1] Jeffrey B. Hodgin,[2] Kyle J. Lafata.[1] *[1]Duke University, Durham, NC; [2]University of Michigan, Ann Arbor, MI; [3]Stanford University, Stanford, CA; [4]Emory University, Atlanta, GA; [5]The Children's Hospital of Philadelphia, Philadelphia, PA; [6]Hopitaux Universitaires Geneve, Geneve, Switzerland; [7]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [8]University of Pennsylvania, Philadelphia, PA.*

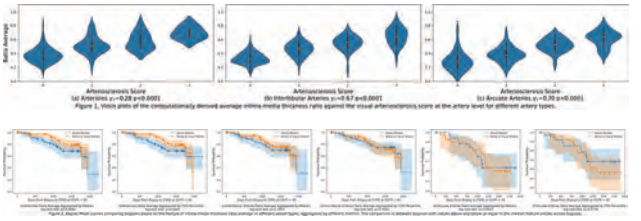
Background: The clinically used semi-qualitative scoring of arteriosclerosis is poorly standardized and reproducible. We developed a computational pipeline to precisely and reproducibly characterize the morphology of arteries/arterioles using digital kidney biopsies.

Methods: One trichrome-stained whole slide image (WSI) from N=229 NEPTUNE/CureGN participants with focal segmental glomerulosclerosis (N=128) or minimal change disease (N=101) was used. We developed, applied, and quality controlled deep learning models for segmentation of muscular vessels and intra-vascular compartments (lumen, intima, media). Each vessel was classified into (i) arcuate and (ii) interlobular artery, (iii) 2 muscle layers arteriole, and (iv) 1 muscle layer arteriole and venule. (i), (ii), and (iii) were visually scored for arteriosclerosis (0-3). Intra-arterial thickness was measured using radial sampling and ray casting, with average intima-media thickness ratio computed for each artery/arteriole for correlation with visual scores. These features were summarized for each WSI using aggregation metrics (median, 75th percentiles) for association with disease progression (40% eGFR decline or renal failure).

Results: N=1509 arterioles, 695 interlobular and 131 arcuate arteries were segmented. There was a statistically significant correlation between arteriosclerosis scores and intima-media thickness ratio average (Spearman ρ=0.28, $p<0.0001$ for arterioles; ρ=0.67, $p<0.0001$ for interlobular arteries; ρ=0.70, $p<0.0001$ for arcuate arteries). Arteriole features aggregated at median and 75th percentiles associated with disease progression (log-rank $p<0.1$). No association was identified in arcuate and interlobular artery features (log-rank $p>0.1$).

Conclusions: We developed a novel approach to automatically segment arteries/arterioles sub-compartments and to computationally characterize morphologic features of arteriosclerosis. This technique demonstrated potential as a promising reproducible tool to aid pathologists' clinical assessment.

Funding: NIDDK Support, Private Foundation Support



FR-PO958

Phospholipase A2 Receptor (PLA2R)-Positive Membranous Nephropathy by Laser Microdissection and Mass Spectrometry in Patients with Negative Routine Immunofluorescence Microscopy for PLA2R on Kidney Biopsy

Ilario Russo,[1,2] Ladan Zand,[1] Fernando C. Fervenza,[1] Benjamin J. Madden,[4] Sanjeev Sethi.[3] *[1]Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN; [2]Universita degli Studi di Bari Aldo Moro Dipartimento di Medicina di Precisione e Rigenerativa e Area Jonica, Bari, Italy; [3]Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester, MN; [4]Mayo Clinic Minnesota, Rochester, MN.*

Background: The discovery of novel antigens in membranous nephropathy (MN) was done using laser microdissection followed by mass spectrometry (LMD/MS). Direct immunofluorescence microscopy (IF) for PLA2R was used to classify MN into PLA2R-positive MN and PLA2R-negative MN. PLA2R-negative MN cases were then used to detect novel antigens.

Methods: 250 cases of PLA2R-negative MN were studied in the discovery cohort. All 250 cases had bright granular staining for IgG and were negative for PLA2R along the glomerular basement membrane by IF. The glomeruli were microdissected and the peptides were separated with a high-performance liquid chromatography (HPLC) system coupled to a Mass Spectrometer. Protein quantification was obtained via spectral counting.

Results: 10 out of 250 (4%) patients with negative IF studies for PLA2R were positive for PLA2R on LMD/MS. Baseline PLA2R counts are typically in the range of 0-5 in PLA2R negative cases. The total spectral count (TSC) in the PLA2R positive by LMD/MS ranged from 13 to 75 (avg 39.5, ± 20.56) in the 10 cases. Only 3 cases showed moderate TSC of 13, 15 and 18, whereas the remaining cases shows high TSC ranging from 28 to 75. Of the available data in 7 patients, 2 had positive serum anti-PLA2R antibodies. The baseline clinical and demographic characteristics are shown in Table 1.

Conclusions: LMD/MS is a new methodology to detect the antigens in MN. 4% of PLA2R-negative MN by IF were positive for PLA2R by LMD/MS. LMD/MS appears to be more sensitive in detecting PLA2R than conventional IF.

Patient Number	Spectral Count	Age	Gender	Anti-PLA2R	uProt (g/24h)	eGFR (ml/min/1.73m2)	serum Albumin (g/dl)
1	40	26	M	Negative	2.5	120	4.2
2	72	49	M	Negative	N/A	77.66	1.1
3	15	83	M	N/A	N/A (3+)	69.44	2.2
4	42	65	M	Negative	15	73.17	N/A
5	75	47	M	Negative	6	92	1.5
6	13	25	F	Negative	N/A (3+)	123	0.9
7	28	69	F	Positive	14.3	47	N/A
8	48	65	F	N/A	0.5	95.91	4.3
9	18	69	M	Positive	5.8	81.43	2.5
10	44	58	M	N/A	N/A (3+)	73.61	1.9

Table 1.

FR-PO959

Fewer Podocytes Associate with Progressive CKD Independent of Glomerular Volume and Nephrosclerosis or Clinical Characteristics

Aleksandar Denic,[1] Mahesh Kumar,[1] Fnu Aperna,[1] Afsana Ansari Shaik,[1] Aidan F. Mullan,[1] Mariam P. Alexander,[1] Jeffrey B. Hodgin,[2] Andrew D. Rule.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]University of Michigan, Ann Arbor, MI.*

Background: Per podometric hypothesis, podocyte loss leads to glomerulosclerosis and proteinuria, eventually leading to chronic kidney disease (CKD). Podometrics include the podocyte density, volume, and number per glomerulus. Prior studies investigated podometrics in kidney donors, autopsy kidneys or patients with specific kidney diseases such as IgA nephropathy. The goal of this study is to investigate associations between podometrics and progressive CKD in patients with radical nephrectomy.

Methods: We evaluated the WT1 (stains podocyte nuclei) and Glepp1 (stains podocyte cytoplasm) wedge sections of renal parenchyma from radical nephrectomies due to kidney tumor performed between 2000 and 2021. QuPath software was used to quantify number of WT-1 positive cells and Glepp-1 positive area within a glomerular tuft. Progressive CKD was defined as dialysis, kidney transplantation, sustained eGFR <10 ml/min per 1.73m^2 or sustained 30% eGFR decline from the post-nephrectomy eGFR during follow-up to March 2024. Each case of progressive CKD was age-sex-matched to 1 control without progressive CKD. Logistic regression models assessed the risk of progressive CKD with podometric measures adjusting for glomerular volume, nephrosclerosis and clinical characteristics (age, sex, body mass index, diabetes, hypertension, baseline eGFR, and 24 hour urine protein).

Results: There were 35 cases and 35 controls. Compared to cases, controls had higher podocyte density (207 vs. 158 per 10^6 μm^3, p=0.004), higher podocyte number per glomerulus (503 vs. 422, p=0.01), but smaller total podocyte cell volume (3,286 vs. 3,868 μm^3, p=0.047). Lower podocyte density and larger podocyte cell volume associated with hypertension. Lower podocyte density and lower podocyte number per glomerulus associated with progressive CKD (**Table**).

Conclusions: Fewer podocytes in glomeruli are strongly associated with progressive CKD independent of established clinical and histological prognostic factors for CKD.

Funding: NIDDK Support

Per SD	Unadjusted		Adjusted for glomerular volume and nephrosclerosis		Adjusted for clinical characteristics	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Podocyte density, per μm3	0.46 (0.25-0.78)	0.007	0.33 (0.11-0.81)	0.03	0.38 (0.18-0.74)	0.007
Podocyte number per glomerulus	0.49 (0.25-0.84)	0.02	0.48 (0.23-0.87)	0.03	0.40 (0.19-0.74)	0.007
Podocyte volume	1.71 (1.02-3.23)	0.06	1.75 (0.72-5.15)	0.24	1.70 (0.87-3.75)	0.15

FR-PO960

Pathologic Spectrum of Kidney Disease Associated with Snake Bites

Anila A. Kurien, Jansi Prema K.S, Malathi Cv. *Renopath Center for Renal and Urological Pathology Pvt Ltd, Chennai, India.*

Background: Snake bites are a rare cause of acute renal failure, of which the underlying pathology is poorly understood. We present a series of 216 patients from India who developed kidney failure in temporal association with snake bites to demonstrate the spectrum of histopathologic findings in this setting

Methods: Patients with history of snake bite who underwent kidney biopsy from 2013-2024 were identified from the kidney pathology archives of the Renopath Center for Renal and Urologic Pathology in Chennai, India. Demographics, laboratory values and pathologic data were reviewed

Results: A total of 216 patients who underwent a kidney biopsy with history of recent snake bite were identified. Biopsies were received from 52 centers throughout India. There were 123 males(56.9%) and 93 females(43.1%), mean age was 44.7±14.3 years. All but one patient presented with acute kidney injury with a mean serum creatinine of 6.9±3.2 mg/dL. Of 216 biopsies, 211 were adequate for diagnosis. Biopsy diagnoses from this cohort of patients included acute tubular injury(ATI, n=64), acute interstitial nephritis(AIN,n=58), acute tubular injury combined with acute interstitial nephritis (ATI/AIN,n=28), renal cortical necrosis alone(n=11), thrombotic microangiopathy(TMA,n=48), mesangioproliferative glomerulonephritis(n=1), and IgA nephropathy with acute interstitial nephritis(n=1). Pigmented casts, seen in the setting of intravascular hemolysis or rhabdomyolysis, were present in 32 cases of ATI(50% of those with ATI), 9 ATI/AIN cases(32%), and 3 patients with TMA(6%). Immunohistochemical stain confirmed hemoglobin pigment in 18 and myoglobin pigment in 11 cases. Two patients with ATI had both hemoglobin and myoglobin casts. Concurrent cortical necrosis was present in 23 patients with TMA(48%). Nearly all cases were without chronic changes on biopsy. Mean global glomerulosclerosis was 7.0%. The majority of patients lacked interstitial fibrosis and tubular atrophy(no IF/TA,92.8%). Arteriosclerosis was seen in 18.1% biopsies

Conclusions: The major histopathologic diagnoses in patients with acute renal failure with a recent history of snake bite, in descending order are ATI(30.3%), AIN(27.5%), TMA(22.7%), ATI/AIN(13.3%), and renal cortical necrosis(5.2%). Hemoglobin and myoglobin casts were commonly seen in ATI and AIN cases, suggesting hemolysis and/or rhabdomyolysis as etiologic drivers of disease

FR-PO961

Clinicopathologic Findings in Kidney Biopsies from Patients with Pancreatitis

Anila A. Kurien,[1] Jansi Prema K.S,[1] Malathi Cv,[1] Tiffany Caza.[2] *[1]Renopath Center for Renal and Urological Pathology Pvt Ltd, Chennai, India; [2]Arkana Laboratories, Little Rock, AR.*

Background: Patients developing acute kidney injury (AKI) in the setting of pancreatitis rarely undergo kidney biopsy, however, histopathologic findings vary and biopsies can inform proper diagnosis and treatment. We present a series of 62 patients with acute or chronic pancreatitis who underwent kidney biopsy to demonstrate the spectrum of pathologic diagnoses in this setting.

Methods: Patients with a clinical history of pancreatitis were identified from renal pathology archives at the Renopath Center for Renal and Urological Pathology in Chennai, India. Clinical data, laboratory values, and histopathology were reviewed

Results: A total of 62 patients with pancreatitis who underwent a native kidney biopsy were identified. The mean age of patients was 35 ± 13 years. There was male predominance (85.5%). Twelve patients had a history of diabetes (19%) and 28 had hypertension (45%). All patients presented with AKI or rapidly progressive renal failure with a mean creatinine of 2.5 ± 2.3 mg/dL. Of the 62 patients, 54 had acute pancreatitis (87%) and 8 had chronic calcific pancreatitis (13%). Six patients had recurrent pancreatitis (10%). Fifteen patients had ≥ 1 diagnosis (24.2%). These included 16 separate entities. Diagnoses included, in descending order, thrombotic microangiopathy (TMA, n=21), acute tubular injury (ATI, n=19), ATI with pigmented casts (n=8), diabetic glomerulopathy (n=6), acute interstitial nephritis (n=4), renal cortical necrosis (n=4), chronic tubulointerstitial nephritis (CTIN, n=3), crescentic glomerulonephritis (n=2), proliferative glomerulonephritis (n=2), renal papillary necrosis (n=1), nephrocalcinosis (n=1), minimal change disease (n=1), IgA nephropathy (n=1), arterionephrosclerosis (n=1), collapsing glomerulopathy (n=1), and extramedullary hematopoiesis (n=1). For patients with TMA, 10 had concurrent cortical necrosis (47.6%). Of patients with ATI with pigmented casts, 3 had myoglobin-positivity (consistent with rhabdomyolysis), and 1 was both myoglobin and hemoglobin positive. Of patients with CTIN, one was IgG4-related disease. Of crescentic glomerulonephritis cases, one was pauci-immune and one was anti-GBM disease

Conclusions: Patients presenting with renal failure in the setting of pancreatitis had a wide array of diagnoses, supporting use of biopsy in management of these critically ill patients.

FR-PO962

Temporal and Demographic Trends in Medical Kidney Disease Epidemiology in the Southwestern United States, 1993-2022

Akira Takahashi,[1] Daisuke Kiyozawa,[1] Takamasa Miyauchi,[1] Yi Mi Kevin Ren,[1] Toshiki Doi,[2] Hae Yoon Grace Choung,[1] Mercury Y. Lin,[1] Jean Hou,[1] Takao Masaki,[2] Yoshinao Oda,[3] Mark Haas,[1] Cynthia C. Nast,[1] Michifumi Yamashita.[1] *[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]Hiroshima University Hospital, Hiroshima, Japan; [3]Kyushu University, Fukuoka, Japan.*

Background: Epidemiological study identifies the prevalence of disease, and could provide the important information to shine new light on the pathogenesis and a basis for further hypothesis-driven research**.** In the United States, there is only a single large-scale epidemiological study for glomerular diseases from the Southeast. Here, we describe 30-year temporal and demographic trends in biopsy-proven, not only glomerular but also non-glomerular diseases in the Southwestern United States.

Methods: We selected native kidney biopsy cases classified into one of 35 widely recognized and common renal disease categories, referred to the Division of Renal Pathology at Cedars-Sinai Medical Center between 1993 and 2022. Biopsy era (1993-2002, 2003-2012, and 2013-2022) and demographics (age, sex, and race) were our primary and secondary predictors, respectively, and the relative frequency of each glomerular/non-glomerular disease subtype was our primary outcome.

Results: 57,613 patients were identified, with a mean age 51.0 (±19.2) years, 52.2% men, 53.8% White, 19.5% Latino, 11.0% Black, 10.2% Asian, and 5.5% other race. Glomerular disease frequency was always higher than non-glomerular disease frequency. Among the glomerular diseases, the frequency of diabetic glomerulosclerosis was constantly and rapidly increasing (9.3%, 15.6%, and 23.8%, each 10 years), while those of other common glomerular disease subtypes were decreasing except for ANCA/pauci-immune glomerulonephritis. Among the non-glomerular diseases, acute tubular necrosis was increasing in the frequency. These temporal trends were largely preserved in all studied demographic subgroups (sex, race, age), although there were several cross-sectional differences of glomerular disease frequencies within each demographic subgroup.

Conclusions: We provided the largest and latest epidemiological data about native kidney biopsy, which may provide valuable insights for nephrologists and pathologists to characterize various kidney diseases and its outcomes in the future, as well as to predict the relative likelihood of a disease diagnosis in a daily medical practice.

FR-PO963

Long Noncoding RNA Associated with Exacerbation of IgA Nephropathy by Exposure to Fine Particulate Matter

Daun Song, Ji won Lee, Se-Hee Yoon, Sung-Ro Yun, Won Min Hwang, Yohan Park. Div of Nephrology, Dept of Internal Medicine. *Konyang University Hospital, Daejeon, Republic of Korea*.

Background: The pathophysiology of IgA nephropathy has been extensively elucidated. However, little is known about long non-coding RNAs (lncRNAs) associated with exacerbation of IgA nephropathy. Fine particulate matter is a significant emerging environmental issue, yet its impact on the exacerbation of IgA nephropathy has not been studied. This study aims to investigate the exacerbation of IgA nephropathy by exposure to fine particulate matter and to explore the associated lncRNAs in a spontaneous IgA nephropathy animal model.

Methods: This study used high serum IgA (HIGA) mice as disease group and BALB/c mice as control group, with a total of twelve 8-week-old mice divided into fine particulate matter exposure groups (HIGA-E:3, BALB/c-E:3) and non-exposure groups (HIGA-NE:3, BALB/c-NE:3). Fine particulate matter exposure was conducted using a sealed cage system, with exposure for 1 hour at a time, 5 times a week, for 12 weeks. The mice were sacrificed at 24 weeks of age. B-cells were separated from the spleen using magnetic-activated cell sorting. RNA isolation was performed from the extracted live B-cells, and total RNA sequencing was conducted.

Results: Regardless of exposure, the HIGA groups had significantly higher serum IgA levels compared to the BALB/c groups. IgA lectin binding assays showed higher levels of glycosylated IgA in the HIGA-NE than in the HIGA-E group, suggesting higher levels of pathologic IgA in the HIGA-E group. Increased expressions of toll-like receptor (TLR)-9 were observed in the lungs of BALB/c-E and HIGA-E groups, with significantly elevated serum APRIL and BAFF levels in the HIGA-E group. Kidney pathology results showed the strongest mesangial IgA deposit and the highest renal injury score in the HIGA-E, followed by the HIGA-NE group (7.7±0.6 vs. 5.3±0.6, P=0.043). Splenic B-cell RNA sequencing revealed more than a two-fold decrease in the expression of specific lncRNAs (Gm54045, Chaserr, LOC115487771, 2310058N22Rik) in the HIGA-E compared to the HIGA-NE group.

Conclusions: Fine particulate matter increases lung TLR-9 expression, leading to elevated BAFF, APRIL, and pathologic IgA levels, and exacerbates IgA nephropathy in the HIGA mice. This exacerbation is associated with a decrease in specific lncRNAs in splenic B-cells, suggesting these lncRNAs may serve as potential therapeutic or diagnostic targets.

FR-PO964

Clinicopathologic Features of Karyomegalic Tubulointerstitial Nephritis

Tiffany Caza,[1] Christopher P. Larsen,[1] Anila A. Kurien.[2] *[1]Arkana Laboratories, Little Rock, AR; [2]Renopath Center for Renal and Urological Pathology Pvt Ltd, Chennai, India*.

Background: Karyomegalic interstitial nephritis (KTIN) is a very rare genetic tubulointerstitial kidney disease caused by mutations in the FAN1 gene. Less than 100 cases have been reported to date, the majority in case reports or small case series. Here, we examine a series of 16 patients of KTIN to further characterize clinical and pathologic features of the disease.

Methods: Patients with a diagnosis of KTIN were identified from renal pathology archives at Arkana Laboratories (USA) and the Renopath Center for Renal and Urological Pathology (India). Clinical data, laboratory values, and histopathology were reviewed.

Results: Sixteen patients with KTIN who underwent kidney biopsy were identified, including eight from the United States and eight from India. These included 15 patients whom had a native biopsy and one with an allograft biopsy (transplant from a sibling). There was male predominance (87.5%) with a mean age of 42 ±12 years. Five patients had a history of hypertension (31.3%) and six had diabetes mellitus (37.5%). None had a history of malignancy. Three patients had a positive family history of kidney disease. All presented with chronic kidney disease, with a mean serum creatinine of 2.9 ± 1.0 mg/dL. Nine had proteinuria of 1+ or greater, three were nephrotic range. Kidney biopsies from all patients demonstrated acute tubular injury with markedly enlarged nuclei. There was chronic injury present in the majority of cases, with a mean global glomerulosclerosis of 31.6 ± 22.4%. There was interstitial inflammation and tubulitis seen in 12 patients, six which had only mild inflammation (10-25% cortex). Interstitial inflammation was lymphoplasmacytic in 11 and one was neutrophil-rich. All cases were negative for SV40 and CMV, ruling out viral cytopathic effects. Eight had a second kidney biopsy diagnosis, including 2 with IgA nephropathy, 2 with minimal change disease, 1 with thin glomerular basement membranes, 1 with focal segmental glomerulosclerosis, 1 with chronic active pyelitis, and 1 with T cell mediated rejection.

Conclusions: KTIN patients were predominantly males presenting in middle age with chronic kidney disease and proteinuria. The majority of patients had no greater than mild interstitial inflammation, of which is lymphoplasmacytic in character. A concurrent second kidney biopsy diagnosis was present in one-half of patients.

FR-PO965

Spectrum of Kidney Pathology in Patients with Syphilis

Tiffany Caza, Christopher P. Larsen. *Arkana Laboratories, Little Rock, AR*.

Background: Syphilis has been associated with multiple kidney diseases, primarily studied within small series. A large cohort of patients with active syphilis who underwent kidney biopsy were examined to evaluate the histopathologic spectrum and clinicopathologic features of disease.

Methods: Patients with syphilis who underwent a native kidney biopsy were identified from the renal pathology archives at Arkana Laboratories from 2006-2024. Patients were identified through a listed clinical history of syphilis in the medical record and/or positive laboratory testing for RPR or anti-treponemal antibodies. Patients with a remote or treated syphilitic infection were excluded.

Results: A total of 111 patients with syphilis who underwent kidney biopsy were identified. The mean age was 42.0 ±14.5 years and there was male predominance (86.5%). The majority of patients presented with acute kidney injury with a mean serum creatinine of 4.4 ± 3.8 mg/dL. Co-infections were common, with HIV in 53 (47.7%), HBV in 9 (8.1%), and HCV in 9 (8.1%). The most common disease states, in descending order, included membranous nephropathy (MN) (n=29), HIV-associated diseases (n=21), acute interstitial nephritis (AIN, n=11), acute tubular injury (n=11), infection-associated glomerulonephritis (n=9), and IgA nephropathy (n=8). The remaining patients had various diagnoses unlikely to be associated with syphilitic infection, such as diabetic glomerulosclerosis (n=12) and arterionephrosclerosis (n=7), among others. Of 29 patients with MN (26.1%), 2 were PLA2R+, 2 were EXT+, and the remaining were PLA2R negative of unknown type. Staining for multiple immune reactants was common in MN cases with IgA staining in 24.1%, IgM in 34.5%, C3 in 89.7%, C1q in 44.8%, and 10.3% were 'full-house'. Of 21 patients with HIV-associated pathology (18.9%), 17 had collapsing glomerulopathy (HIVAN) and 7 had mesangial immune complex deposition (HIVICK). Of 11 patients with AIN, 5 were plasma cell rich, 1 was neutrophil rich, and the remaining had mixed infiltrates. Three of 8 patients with IgA nephropathy were secondary to liver disease related to viral hepatitis.

Conclusions: The most common kidney biopsy diagnosis seen in patients with syphilis was membranous glomerulopathy. Disease associated with co-infections, particularly HIV and viral hepatitis, were also common in this setting.

FR-PO966

IgM-Positive Plasma Cells in Lip Biopsy Specimens from Patients with Tubulointerstitial Nephritis with IgM-Positive Plasma Cells (IgMPC-TIN)

Naoki Takahashi,[1] Toshio Imafuku,[5] Takahisa Kawaguchi,[2] Akira Iguchi,[3] Yawara Yamashita,[4] Kenji Kasuno,[1] Masayuki Iwano,[1] Tadashi Toyama.[1] *[1]Fukui Daigaku, Fukui, Japan; [2]Kawasaki Shiritsu Kawasaki Byoin, Kawasaki, Japan; [3]Nagaoka Sekijuji Byoin, Nagaoka, Japan; [4]Kagoshima Daigaku, Kagoshima, Japan; [5]Shonan Clinic, Kamakura, Japan*.

Background: In 2017, we introduced the concept of tubulointerstitial nephritis with IgM-positive plasma cells (IgMPC-TIN), in which many IgM-positive plasma cells infiltrate the renal interstitium. Although IgMPC-TIN may be part of a systemic disease, few reports have evaluated IgMPC infiltration in organs other than the kidney and liver in patients with IgMPC-TIN. In this study, we investigate whether many IgMPC infiltrates are also present in lip biopsy specimens of patients diagnosed with IgMPC-TIN on renal biopsy.

Methods: We collected lip biopsy specimens from a total of 18 patients from our hospital and collaborating centers nationwide: 8 patients (IgMPC-TIN group) (7 with Sjögren syndrome) diagnosed with IgMPC-TIN by renal biopsy and 10 patients (non-IgMPC-TIN group) with other diseases (3 with IgG4-related disease, 4 with Sjögren syndrome and 3 with SLE). We used an immunoenzymatic method to do double staining with IgM and CD138 and then counted PC and IgMPC and calculated the percentage of IgMPCs among all PCs in each group. We calculate the cut-off values, sensitivity, and specificity using ROC analysis (SigmaPlot 15.0).

Results: In lip biopsy, the average number of plasma cells (PCs) in the three fields of view was not significantly different (94 vs. 90/high-power field (HPF), P=0.895). The IgMPC-TIN group had a significantly higher average number of infiltrated IgMPCs in the three fields of view (44 vs. 9/HPF, P<0.001), the maximum number of IgMPCs (59 vs. 11/HPF, P<0.001), and a significantly higher percentage of IgMPCs among all PCs (46% vs. 10%, P<0.001). The cut-off values (sensitivity and specificity, respectively) by ROC analysis were the percentage of IgMPCs among all PCs 17.2% (100% and 90%), the average number of IgMPCs 18.8/HPF (87.5% and 90%) and the maximum number of IgMPCs 23.5/HPF (87.5% and 90%). In renal and lip biopsies, there was no significant correlation between the percentage of IgMPCs among all PCs, the average number of IgMPCs in the three fields of view, and the maximum number of IgMPCs.

Conclusions: The IgMPC-TIN group had more IgMPCs in lip biopsies than the non-IgMPC-TIN group. The percentage of IgMPCs among all PCs was most useful in determining IgMPC-associated salivary gland findings. IgMPC-TIN may be a renal manifestation of a systemic disease with IgMPC infiltration.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO967

A Rare Case of Leukocyte Chemotactic Factor 2 (ALECT2)-Associated Amyloidosis and Membranoproliferative Glomerulonephritis (MPGN) Associated with Cryoglobulinemia

Stefani M. Thompson, Lalathaksha Murthy Kumbar. *Henry Ford Health System, Detroit, MI.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) associated with cryoglobulinemia is an uncommon renal condition, often secondary to infectious or autoimmune etiologies. Hepatitis B infection less frequently manifests as cryoglobulinemia compared to hepatitis C. Concurrently, Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is an exceedingly rare form of amyloidosis, characterized by the deposition of leukocyte chemotactic factor 2 protein in the kidneys, with a higher prevalence among individuals of Mexican descent. The simultaneous presence of MPGN from cryoglobulinemia and ALECT2 in a single kidney biopsy represents a rare diagnostic finding. Here, we present a unique case of a patient with hepatitis B induced MPGN associated cryoglobulinemia and concurrent ALECT2.

Case Description: We present the case of a 68-year-old male with a medical history notable for hypertension, lower extremity rash with biopsy consistent with leukocytoclastic vasculitis, and post herpetic neuralgia who presented with chest pain and dyspnea attributed to a pericardial effusion and found to have acute kidney injury. Urinalysis revealed hematuria and proteinuria while urine microscopy demonstrated 3-4 dysmorphic red blood cells per high-powered field. Serological investigations revealed positive antinuclear antibodies, positive rheumatoid factor, trace cryoglobulin, and decreased C3 and C4 levels. Steroids were started for a suspected flare of overlap syndrome. Kidney biopsy histopathology revealed features consistent with MPGN Type II cryoglobulinemia and immunohistochemical staining confirmed ALECT2 presence within the amorphous deposits, positive for amyloidosis. The coexistence of MPGN and ALECT2 in the context of cryoglobulinemia secondary to hepatitis B infection was noted as exceedingly rare. The patient was started on Entecavir for hepatitis B treatment.

Discussion: This case shows the diagnostic challenges posed by MPGN in the backdrop of active hepatitis B infection and cryoglobulinemia. The additional discovery of ALECT2 raises questions regarding its clinical implications and significance. Further research and case reports are imperative to unravel potential relationships and underlying mechanisms associated with ALECT2 and cryoglobulinemia.

FR-PO968

10 Years of C3 Glomerulopathy in the Netherlands: A Large Cohort of a Rare Kidney Disease

Rick H. Overwijk,[1] Fiona R. Kolbinger,[2] Mark Eijgelsheim,[1] Andreas Kronbichler,[3] Ingeborg M. Bajema.[1] *[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]Purdue University, West Lafayette, IN; [3]Medical University Innsbruck, Innsbruck, Austria.*

Background: C3 glomerulopathy (C3G) is a rare but devastating disease affecting both children and adults. It frequently leads to end stage kidney disease within ten years after diagnosis and no specific treatment exists. C3G is used as a collective term for dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) and is thought to sometimes occur in post-infectious settings (C3-PIGN). Currently little is known about the occurrence and distribution throughout the population. In this study we analyzed a large cohort of C3G patients in the Netherlands regarding disease distribution in relation to geographical factors and histopathological findings.

Methods: A search in the Dutch national pathology database (PALGA) was performed. All patients diagnosed with C3G from January 2014 until December 2023 were identified by two independent observers. Cross tabulations were used to determine the correlation of disease subtypes and glomerular patterns, and their geographical distribution. Non-parametric analysis was used to evaluate the age distribution at diagnosis.

Results: The selection resulted in a cohort of 280 patients consisting of: C3GN (101), DDD (39), unspecified C3G (106), C3-PIGN (29) and other (5). The median age of diagnosis was 19 for DDD and 58 for C3GN, showing that age distribution depends on C3G subtype ($p<0.001$). C3G subtypes were also associated with glomerulonephritis patterns ($p<0.001$), with DDD and C3G associated with mesangiocapillary pattern and C3-PIGN with endocapillary or exudative pattern.

Conclusions: This large cohort is a stepping stone for better characterizing contributing factors in the etiology of C3G and can potentially demystify this rare and devastating disease.

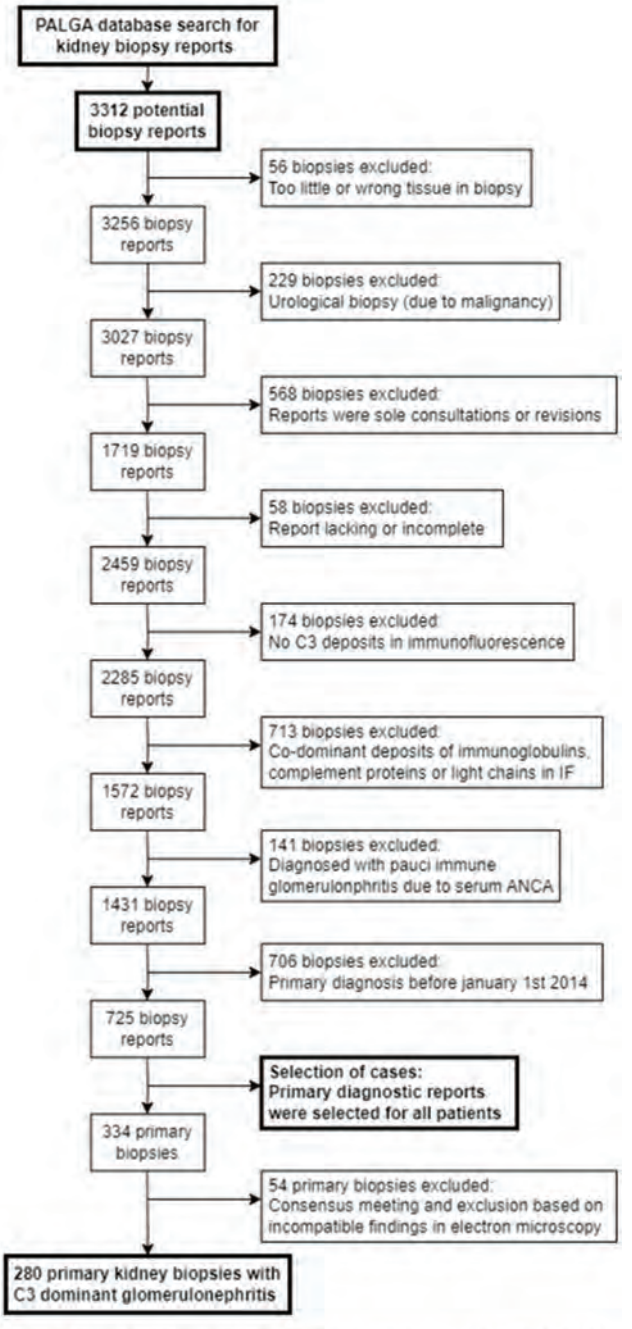


Figure 1: Flowchart of case selection showing excluded cases and applied criteria.

FR-PO969

Glomerular Intracytoplasmic Vacuolization in a Patient Receiving Polyethylene Glycol Biopharmaceutical

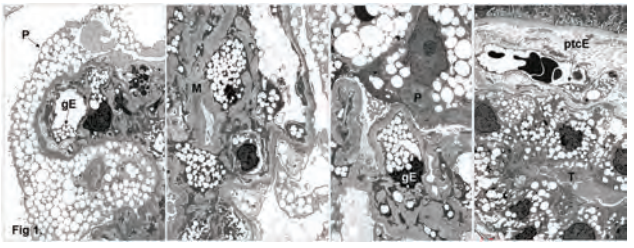
Shamila Mauiyyedi,[1] Amit Lahoti,[2] Amanda Tchakarov.[1] *[1]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX; [2]The University of Texas MD Anderson Cancer Center Division of Cancer Medicine, Houston, TX.*

Introduction: Conjugation of biologics to HMW polyethylene glycol (PEG) enhances drug delivery/efficacy by extending half-life. Clearance of PEG causes cellular vacuolization by light microscopy in liver, spleen, brain and kidney in animal models. No human study, electron microscopy, or impact on cell function are reported. We report the first case of marked glomerular cytoplasmic vacuolization in a patient who received PEGylated nucleoside analog.

Case Description: A 67 year old male received PEGylated nucleoside analog for metastatic gastric carcinoma. Within 4 weeks of the drug being stopped due to disease progression, the patient developed 7 g/day proteinuria, cough, dyspnea, and edema. Studies

showed a normal C3, C4 and negative ANCAs. Renal biopsy revealed focal segmental glomerulosclerosis with enlarged, reactive, vacuolated podocytes along with acute tubular epithelial injury with areas of tubular epithelial vacuolization. Immunofluorescence was negative. Electron microscopy (Fig. 1) revealed extensive intracytoplasmic vacuolization in glomerular podocytes (P), endothelium (gE), mesangial cells (M), tubular epithelial cells (T) and peritubular capillary endothelium (ptcE). Vacuoles were membrane bound, colorless and variably sized 0.3-6.5 μm. Some vacuoles contained granular material but majority were empty. No zebra bodies were seen. Podocytes had the most prominent vacuoles plus extensive foot process effacement.

Discussion: We report the first case of marked intracytoplasmic vacuolization related to PEG in renal glomerular, endothelial and tubular cells. Animal studies suggest vacuolization may be an adaptive response to clear PEG rather than a toxic effect. However, we hypothesize that PEG vacuoles can alter cell function with pathological changes and adverse clinical outcome, such as the podocytopathy seen in this case. Further clinical studies are needed to understand the safety of PEGylated therapies.



FR-PO970

Clinical, Histopathologic, and Molecular Characterization of Allograft Mesangial Glomerulopathy

Kelly D. Smith, Yuan Huang, Christopher D. Blosser, Nicolae Leca, Behzad Najafian, Shreeram Akilesh. *University of Washington, Seattle, WA.*

Background: Donor-derived cell-free DNA (dd-cfDNA) is a non-invasive biomarker used to detect allograft rejection. In the absence of other signs of graft dysfunction elevated levels of dd-cfDNA can prompt allograft biopsy. We describe three donor specific antibody (DSA)-negative, dd-cfDNA positive patients with an allograft mesangial glomerulopathy that is histologically distinct from traditional transplant glomerulitis (Figure 1).

Methods: Kidney allograft biopsies from 2018-2022 that had dd-cfDNA testing were reviewed to identify DSA-negative, dd-cfDNA-positive cases with mesangial proliferative glomerulopathy. Clinical and pathologic data were collected. Biopsy material from mesangial proliferative glomerulopathy cases were analyzed using digital spatial profiling (GeoMx, Nanostring) and compared to DSA-negative, dd-cfDNA positive and without obvious transplant glomerulopathy. Biopsies were hybridized with the Whole Transcriptome Atlas and bound probes were collected, sequenced and quantified from glomerular and tubulointerstitial regions of interest (ROI).

Results: Patients with mesangial glomerulopathy had fluctuating dd-cfDNA levels but maintained stable renal function (follow-up period 5-7 years post-transplant). The biopsies demonstrated a histologically unique form of allograft mesangial glomerulopathy. Analysis of glomerular ROI from control (17), mesangial glomerulopathy (11) and DSA-/cfDNA+ patients without glomerulopathy (37) revealed PD-L1 signaling as the most enriched pathway for differentially expressed genes in allograft mesangial glomerulopathy.

Conclusions: This small cohort of patients with allograft mesangial glomerulopathy exhibited fluctuating levels of dd-cfDNA, but stable allograft function. DSP analysis supports a distinct molecular pathophysiology for allograft mesangial glomerulopathy compared to DSA-/cfDNA+ glomerulitis.

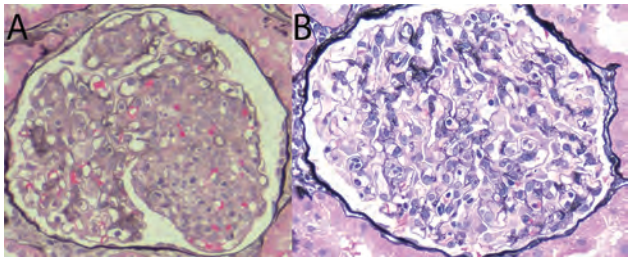


Figure 1. DSP uncovers gene expression differences in allograft mesangial glomerulopathy. A) Glomerulus from a patient with allograft mesangial glomerulopathy. B) Glomerulus from a patient with DSA-/cfDNA+ glomerulitis.

FR-PO971

Erythrocyte Glycocalyx Reports Glomerular Endothelial Glycocalyx Damage in Disease and Predicts Glomerular Albumin Permeability

Matthew J. Butler, Michael Crompton, Raina D. Ramnath, Rebecca R. Foster, Simon C. Satchell. Bristol Renal. *University of Bristol, Bristol, United Kingdom.*

Background: The endothelial glycocalyx (EnGlx) is damaged in acute and chronic kidney diseases contributing to the development albuminuria and vascular damage. However, directly detecting EnGlx loss has proven difficult, limiting research and slowing the development of targeted therapeutics. The red blood cell (RBC) and endothelial glycocalicies contain shared components. Both are exposed to circulating sheddases. We hypothesised therefore that the RBCGlx could provide a surrogate measure of EnGlx damage.

Methods: RBC from male Wistar rats and human trials were labelled with fluorescently tagged Glx-binding lectins and rhodamine 18. Images were obtained using confocal microscopy. Analysis was 'blinded', using machine learning to identify RBC and custom analysis software to measure the distance between Gaussian modelled fluorescence profile peaks to provide a measure of RBCGlx 'depth'.

Results: In rats (control, STZ (diabetic), STZ spironolactone (treated)) we confirmed a linear corelation between RBCGlx and glomerular EnGlx depth(r^2 0.72, $p<0.0001$, n=19). RBCGlx thickness also corelated with cardiac capillary EnGlx thickness measured using electron microscopy (r^2 0.78, p=0.0016, n=8). Serial blood samples confirmed significant RBCGlx damage 4 weeks after STZ, however a significant therapeutic response to spironolactone was detected 2 weeks after treatment. In all groups RBCGlx thickness corelated with ex vivo glomerular albumin permeability (MOA lectin, r^2 0.95, $p<0.0001$, n=9,) suggesting RBCGlx damage can be used to predict glomerular damage. On human kidney biopsies (minimal change nephropathy and thin basement membrane disease) RBCGlx thickness corelated (r^2 0.9226, $p<0.0001$, n=12) with cortical capillary EnGlx thickness. Measuring the RBCGlx in healthy pregnant women (venous blood) we confirmed a corelation with sublingual GlycoCheck™ readings (r^2 0.25, p=0.007, n=27). In patients with COVID-19 we rapidly confirmed significant RBCGlx damage (t-test, p=0.0002, n=26,) supporting published work suggesting EnCGlx damage.

Conclusions: Our test provides a reliable surrogate marker of EnGlx damage in kidney disease and predicts endothelial function. Larger human trials are underway to investigate the full potential of this major discovery in renal and cardiovascular disease monitoring and therapeutics.

Funding: Government Support - Non-U.S.

FR-PO972

Detection of Autotaxin and Lysophosphatidic Acid Receptors in Glomerular Diseases within Glomerulus

Naonori Kumagai, Masaya Hirayama, Takuma Ando, Tomomi Kondo, Yuji Matsumoto, Yohei Ikezumi. *Fujita Ika Daigaku, Toyoake, Japan.*

Background: Lysophosphatidic acid (LPA) is a lysophospholipid that acts as a chemical mediator. It acts through six dedicated receptors, LPA receptor 1-6 (LPAR1-6). LPA is mainly produced by autotaxin (ATX) in blood from lysophospholipids in blood as a substrate. Moreover, LPA is produced by mPA-PLA within cells from phosphatidic acid in the cells as a substrate. be. The Pathophysiological role of the LPA and ATX in glomerular diseases within glomerulus remains unclear.

Methods: Immunostaining for LPAR1-5 and ATX was performed on renal biopsy specimens of pediatric glomerular diseases such as lupus nephritis, membranous nephropathy, idiopathic nephrotic syndrome, IgA nephropathy, and mesangioproliferative glomerulonephritis (MPGN). Moreover, ATX mRNA was detected by in situ hybridization.

Results: LPAR1-5 and ATX were strongly stained in lupus nephritis and membranous nephropathy. They were stained negative to weakly positive in the other glomerular diseases. ATX mRNA was detected in mesangial cells in IgA nephropathy and MPGN, however, was hardly detected in lupus nephritis and membranous nephropathy.

Conclusions: In systemic lupus erythematosus and lupus nephritis, ATX is assumed to be produced in macrophage and released into blood, resulting in elevated concentration in blood and urine. Taken together with the present study, these findings imply that in systemic lupus erythematosus and lupus nephritis ATX in blood is deposited in the glomerulus and LPA is produced in situ. Produced LPA acts in an autocrine and/or paracrine manner through LPA receptors and are involved in pathophysiological role. Conversely, in IgA nephropathy and MPGN, ATX is produced in situ within the glomerulus and is involved in the pathophysiological role. It is needed to elucidate the pathophysiological role of LPA and ATX in each glomerular disease within glomerulus.

Funding: Government Support - Non-U.S.

FR-PO973

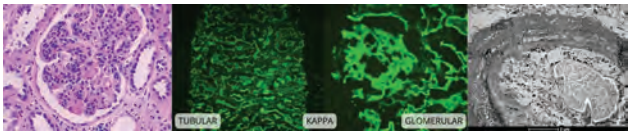
Monoclonal Immunoglobulin Deposition Disease (MIDD) or Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID): Which Diagnosis Fits Better?

Alexandre B. Liborio,[1] Rafaela J. Linhares,[3] Louise Salles,[3] André C. Teixeira,[2] Dulce M. Barrero.[3] *[1]Universidade de Fortaleza, Fortaleza, Brazil; [2]Centro Universitario Christus, Fortaleza, Brazil; [3]Hospital Geral de Fortaleza, Fortaleza, Brazil.*

Introduction: MIDD and PGNMID originate from monoclonal immunoglobulin-glomerular deposits. In MIDD, IF shows κ light chain restriction in up to 90% of cases and tubular basement membrane (TBM) involvement in 100% of cases. In PGNMID, LM shows proliferative or MPGN, and IF, by definition, reveals monotypic deposits restricted to the glomeruli (unlike MIDD), with IgG in 90% of cases. We describe a patient with renal-limited disease presenting a PGNMID-compatible clinical course/light microscopy findings but an IF-based diagnosis of MIDD.

Case Description: 48-year-old male presented with dialysis-requiring renal failure, hematuria (more than 100 RBC/HPF), proteinuria of 4.6g/24h and hypoalbuminemia. Due to clinical suspicion of RPGN, high-dose corticoid therapy was initiated. Renal biopsy (figure) demonstrated hypercellularity due to leukocytes and duplication of the GBM. Red congo negative. IF was positive only for κ light chains (4+/4) in both the GBM and TBM. Electron microscopy did not show glomeruli but non-organized electron-dense deposits in TBM. Renal response ocurred one month after corticoid therapy (sCr:1.56 mg/dL and proteinuria, 177 mg/24h). Corticoid withdrawal was followed by worsening renal function, leading to reintroduction with new response. A κ peak was present in the urine and despite no evidence of multiple myeloma, bortezomib was added.

Discussion: This case has features that prompt us to reconsider the most fitting diagnosis and, in any case, expand our understanding of the spectrum of glomerular involvement by monoclonal deposits. Although the IF findings (κ restriction and deposits in the TBM) and the initial presentation can be compatible with MIDD, the dramatic and rapid glucocorticoid response aligns with the clearance of inflammatory cells, a main feature of PGNMID as the primary pathologic substrate. Patients with MIDD treated with bortezomib had renal remission, but only after several months (PMID: 30578255). Therefore, we suggest that PGNMID is the most appropriate and more informative diagnosis for clinicians' management; alternatively, two concominant diagnosis can be considered



FR-PO974

A Rare Case of Granulomatosis with Polyangiitis Presenting with Esophagitis

Greeshma A. Thomas, Tyler Morgan, Rupinder Kaur, Nabeel Siddiqui, Olawale M. Osunsanya. *Southeast Health, Dothan, AL.*

Introduction: Granulomatosis with polyangiitis (GPA) is a rare autoimmune disorder characterized by necrotizing granulomas, mainly affecting the upper respiratory tract, lungs, and kidneys. The typical presentation of kidney involvement is in the form of RPGN. The exact etiology of GPA remains unknown. Diagnosis should be suspected in any patient with nonspecific constitutional symptoms, clinical evidence of glomerulonephritis with upper or lower respiratory tract involvement, and lab evidence of positive ANCA serology. Here, we present a case of a patient with a baseline serum creatinine of 1.5 who initially presented with esophagitis and was ultimately found to have GPA.

Case Description: 76 y/o Caucasian female with PMH of hyperlipidemia, anemia, and GERD who initially presented to outside facility due to weakness and diarrhea. Found to be COVID-19 positive and anemic, with Hb 7.6 and a Hct 23. She underwent EGD and colonoscopy, which revealed esophagitis, esophageal candidiasis, and gastritis. She was discharged after receiving conservative management. She presented again to the same facility 2 weeks later with acute hypoxic respiratory failure. Labs revealed Hb of 5.6 and Cr of 10.40. After initial stabilization, she was transferred to our facility for higher care. Labs revealed Hb 8.2, Na 131, K 5.8, S. Cr 10.58, GFR 3.6. Urinalysis- 2+ protein, 3+ blood, leuk esterase, and many bacteria. ANA, C3, C4, PR3-ANCA, and GBM Ab negative. Protein electrophoresis revealed an M spike. Her C-ANCA titer was found to be greater than 1:640. A kidney biopsy showed necrotizing and crescentic glomerulonephritis with mild interstitial fibrosis and tubular atrophy, consistent with GPA. She was initially started on SLED followed by HD with steroids and Rituximab.

Discussion: Due to the wide variety of possible associated clinical manifestations, initial diagnosis of GPA can be difficult. In the case presented in this paper, the patient initially presented to an outside hospital with esophagitis. She did not undergo further workup for her symptoms and presentation until she re-presented with AKI and respiratory distress. At that time, GPA rose on the differential and was confirmed via kidney biopsy. This case showcases a rare presentation of GPA with esophagitis, which we hope to highlight to improve physician awareness.

FR-PO975

Quantification of Urine Podocytes (Podo) Using Imagining Flow Cytometry (IFC)

Alireza Ayoubi, Abbal Koirala, Jonathan R. Fromm, Behzad Najafian. *University of Washington System, Seattle, WA.*

Background: Podo injury and loss contribute to the progression of most kidney diseases causing ESRD. Quantification of Podo in the urine is a noninvasive approach for early detection of glomerular injuries and monitoring kidney disease progression. Current approaches for urine Podo quantification are time-consuming and difficult to standardize. We aimed to develop a standardized, faster approach using IFC

Methods: Laboratory standards for positive and negative controls were developed using human Podo (markers: podocalyxin, GLEPP1), urothelial (marker: UPK3) and proximal tubular (marker: LRP2) cell lines. Validation process included sensitivity, specificity, linearity and lower limit of quantification. Limited urine samples from patients were examined. IFC was done using Mark-II Imagestrem. Data was analyzed using IDEAS software.

Results: IFC reliably separated Podo from urothelial and proximal tubular cells. There was close to perfect correlation between podocalyxin and GLEPP1 signals. Analysis of triplicate samples at 5 dilutions demonstrated linearity down to a lower limit of quantification of 500 Podo/75 uL of analyte. IFC of spot urine samples from 5 random patients with membranous nephropathy, pauci-immune glomerulonephritis, diffuse lupus nephritis, IgA nephropathy and Fabry disease quantified a range of 4-146 Podo/ml urine with a detection sensitivity of 0.07% of total events captured.

Conclusions: We have developed laboratory standards for the quantification of urine Podo and have validated IFC protocols. In contrast to conventional flow cytometry, IFC is capable of detecting rare cells and can be a powerful tool to quantify urine Podo loss. Further work is needed to explore podocyturia variability in healthy and disease conditions.

Funding: NIDDK Support, Commercial Support - Sanofi

FR-PO976

NIH Activity and Chronicity Indices in Lupus Nephritis: A Critical Analysis

Valentina Querin,[1] Fiammetta Ravaglia,[2] Augusto Vaglio,[1,3] Ingeborg M. Bajema.[4] *[1]Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Florence, Florence, Italy; [2]Nephrology and Dialysis Unit, Santo Stefano Hospital, Prato, Italy; [3]Nephrology and Dialysis Unit, Meyer Children's University Hospital - IRCCS, Florence, Italy; [4]Universitair Medisch Centrum Groningen Pathologie en Medische Biologie, Groningen, Netherlands.*

Background: Inclusion of NIH activity and chronicity indices (AI & CI) in the ISN/RPS classification of lupus nephritis (LN) aims to provide a more precise characterization of the amount of active/chronic lesions next to the lupus class. AI is based on 6 lesions (range 0-24) and CI on 4 lesions (range 0-12). We here report how the AI and CI values vary in a large multicenter cohort; which lesions in particular determine the index; and what their relation is to lupus class.

Methods: We collected 86 LN kidney biopsies from 2 international centers, excluding those with <10 scorable glomeruli or with a concomitant glomerular disease. We calculated the NIH AI and CI according to the 2018 ISN/RPS classification revision. We used Pearson's coefficient to explore correlations and One-way ANOVA to analyze AI and CI distribution in the classes.

Results: More than 90% of the biopsies showed an AI <10 (4.5±3.7) and a CI <8 (2.6±2.7). Class IV (±V) had the highest AI, classes I/II had an AI of 0. Endocapillary hypercellularity was the most common active lesion (table), showing the strongest correlation with neutrophils ($r=0.71$, $p<0.001$). Cellular crescents correlated with fibrinoid necrosis and interstitial inflammation ($r=0.317$, $p=003$; $r=0.415$, $p<0.001$). There were no differences over classes in CI distribution. Interstitial fibrosis, tubular atrophy and glomerulosclerosis were related to each other ($p<0.001$) but not to fibrous crescents.

Conclusions: In this cohort, AI and CI scores were medium-low and rarely reached the highest values. Endocapillary hypercellularity was the most common lesion driving AI score. It is crucial to reassess if the lesions included in AI and CI reflect the actual activity and chronicity of LN. Investigating potential modifications of the indices may lead to a more balanced and accurate scoring system.

Variables	Patients (n=86)
Age in years at kidney biopsy, mean (SD)	31.6 (17.5)
> 18 years, n (%)	58 (67.4)
Female gender, n (%)	61 (70.9)
Histological class, n (%)	
I	1 (1.2)
II	4 (4.7)
III	24 (27.9)
IV	39 (45.3)
V	10 (11.6)
III+V	3 (3.5)
IV+V	5 (5.8)
NIH AI, mean (SD)	4.5 (3.7)
Endocapillary hypercellularity, n (%)	65 (75.6)
Neutrophils/karyorrhexis, n (%)	51 (59.3)
Fibrinoid necrosis, n (%)	12 (14)
Hyaline deposits, n (%)	26 (30.2)
Cellular/fibrocellular crescents, n (%)	30 (34.9)
Interstitial inflammation, n (%)	27 (31.4)
NIH CI, mean (SD)	2.6 (2.7)
Total glomerulosclerosis score, n (%)	47 (54.7)
Fibrous crescents, n (%)	12 (14)
Tubular atrophy, n (%)	41 (47.7)
Interstitial fibrosis, n (%)	44 (51.2)

Table. Demographic and histologic characteristics of the LN cohort

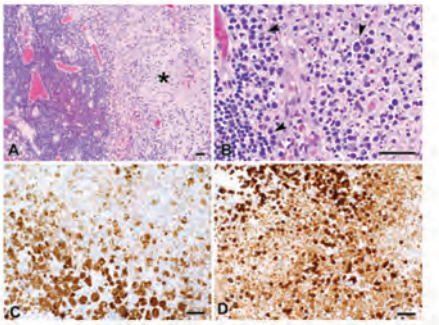


Figure 1: The excisional lymph node biopsy showed areas of necrosis alternating with preserved nodal architecture (Fig. 1A). Tissue at the edges of the lesions contained numerous plasma cells (Fig. 1B) and CD68-positive macrophages (Fig. 1C), but neutrophil infiltration was minimal. Lesional and perilesional tissue contained abundant CD3-positive T-cells (Fig. 1D).

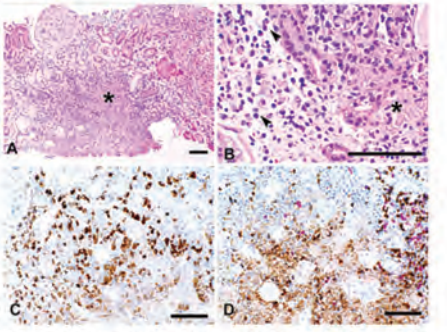


Figure 2: The percutaneous renal biopsy contained an area of dense interstitial inflammation and necrosis with features similar to those seen in the lymph node (Fig. 2A and 2B). As with the lymph node biopsy, CD68-positive macrophages were numerous (Fig. 2C), and the areas of necrosis and surrounding tissue contained abundant CD3-positive T-cells (Fig. 2D). No hematoxylin bodies were seen in either biopsy.

FR-PO977

Renal Necrotizing Histiocytic Lesions in a Patient with Systemic Lupus Erythematosus (SLE)

Rasha Raslan, Maria Fernanda Ortiz Kaemena, Anand S. Lagoo, David N. Howell. *Duke University Health System, Durham, NC.*

Introduction: Patients with SLE can develop lupus lymphadenitis (LL) with necrotizing lesions in lymph nodes and is difficult to distinguish from Kikuchi-Fujimoto Disease (KFD). There have been no cases depicting histological evidence of necrotizing lymphadenitis in the kidney

Case Description: A 35 year old female with SLE presented with fevers & cervical lymphadenopathy. Extensive workup for infections was negative. A lymph node and native kidney biopsy were performed (figures 1 & 2). These showed a necrotizing inflammatory process with CD8 + T cells, plasma cells and macrophages

Discussion: KFD & LL have both distinct and overlapping features. On histology, KFD is characterized by patchy areas of necrosis with abundant karyorrhectic nuclear debris. Neutrophils & eosinophils are typically absent. Immunohistochemical testing often shows CD3 & CD8 T cells. Presence of neutrophils, hematoxylin bodies, & abundant plasma cells is more consistent with LL. C4d staining (more common in LL) may be useful in distinguishing the two. There are reports of AKI in patients with KFD, however, direct involvement of renal parenchyma by necrotizing inflammation recapitulating lymphadenitis is not documented. One explanation is an over-active immune response that leads to localized inflammation in nearby tissues. KFD is typically limited to lymph nodes, so how it spreads to distant organs is less clear. Possible explanations include migration of inflammatory cells from elsewhere, or de novo inflammatory process that initiated in the kidney. It is unclear why this necrosis predominantly involves histiocytes and not neutrophils. Our case highlights another entity that can be encountered in a patient with SLE & the need for renal biopsies when a diagnosis is not clear. Obtaining an adequate sample is important to not miss other pathological processes

FR-PO978

Hydroxychloroquine (HCQ)-Associated Zebra and Myeloid Bodies in Patients with Systemic Lupus Erythematosus (SLE)

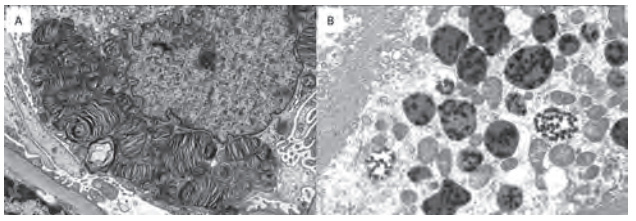
Shun Manabe,[1] Momoko Seki,[1] Yusuke Ushio,[1] Yuki Kawaguchi,[1] Shizuka Kobayashi,[1] Shiho Makabe,[1] Naoko Ito,[1] Hiroshi Kataoka,[1] Sekiko Taneda,[1] Kazuho Honda,[2] Junichi Hoshino.[1] *[1]Tokyo Women's Medical University, Shinjuku-ku, Japan; [2]Showa University, Shinagawa-ku, Japan.*

Background: Zebra and myeloid bodies are characteristic findings in Fabry disease. However, the presence of lamellar bodies (LBs) in HCQ-treated patients (HCQ+) occasionally poses a diagnostic challenge in differentiating Fabry disease. Here we aimed to elucidate the histological features of kidney biopsy associated with HCQ treatment.

Methods: We analyzed SLE patients who underwent kidney biopsy from 2019 to 2024. Electron microscopic (EM) images were evaluated for the maximum number of LBs within involved cells, presence of curvilinear bodies, and intracellular vesicles with osmiophilic granules. We evaluated four Fabry disease cases similarly.

Results: A total of 37 SLE patients, including 17 HCQ+, underwent kidney biopsy. No case was clinically suggestive for Fabry disease. EM images were taken from 23 patients (Female 20, mean age; 43.5±12.5), including 12 HCQ+. LBs were observed in all 12 HCQ+ (Figure A) and in three (27.2%) cases without HCQ treatment (HCQ-). The maximum number of LBs ranged from one to 49, median (IQR); 2.5 (1-4), in HCQ+, and one, one, and 4 in HCQ-. Of 4 HCQ+ with a single LB, 2 had initiated HCQ less than 10 days prior. A HCQ- with 4 LBs were treated with sertraline; a medicine can be associated with LB. Among Fabry disease patients, the number ranged from 59 to 141 (median, 79.0). Curvilinear bodies were observed in three HCQ+ only. Intracellular vesicles with osmiophilic granules within proximal tubular cells (Figure B) were observed in 7 out of 10 (70%) HCQ+ with images of proximal tubules, and none of (0%) HCQ-. One case underwent globotriaosylceramide 3 staining with a positive result. Three HCQ+, with 4, 5, and 49 LBs, including a case with urinary mulberry cells, underwent genetic testing for α-galactosidase A with normal results.

Conclusions: The appearance of LBs might be a universal phenomenon associated with HCQ treatment, though the number of LBs was apparently smaller than in Fabry disease. The number of LBs and presence of intracellular vesicles with osmiophilic granules might help differentiate HCQ-associated LBs from Fabry disease.



FR-PO979

A Diagnostic Challenge of AL Amyloidosis in a Patient with Positive Immunohistochemistry for AA Amyloidosis Later Confirmed to be AL Amyloidosis by Mass Spectrometry

Saad A. Alshihri, Gabriel B. Lerner. *Yale University School of Medicine, New Haven, CT.*

Introduction: We present a case of a 64-year-old male with progressive orthostatic hypotension and multi-organ dysfunction ultimately diagnosed with AL amyloidosis following renal biopsy and mass spectrometry analysis. The case underscores the diagnostic challenge posed by atypical presentations of amyloidosis and highlights the importance of kidney biopsy in diabetic patients with proteinuria that does not fit the typical presentation. It also emphasizes the utility of mass spectrometry in indentifying the amyloid subtype.

Case Description: This is a 64-year-old Hispanic male with a history of type 2 diabetes, hypertension, hyperlipidemia, and cerebrovascular accident who had a 3-year history of dizziness and orthostatic hypotension progressing to syncopal attacks, unintentional weight loss, paresthesia of the lower extremity and generalized weakness. Despite extensive evaluations, including neurologic and malignancy workups, the underlying cause remained elusive. Nephrology consultation was sought due to significant proteinuria with UPCR of 19 g/g. Renal biopsy revealed Congo red-positive amyloid deposits with positive immunohistochemistry for AA amyloidosis, but there was lambda restricted staining on IF with no kappa staining suggested a possible AL amyloidosis. Serum and urine electrophoresis along with serum IFE were negative for abnormal bands, urine IFE showed discrete monoclonal bands. Subsequent mass spectrometry analysis identified AL amyloidosis, and bone marrow biopsy with approximately 15% lambda light chain restricted plasma cells prompting initiation of CyborD chemotherapy. However, advanced multi-organ involvement, including cardiac and gastrointestinal manifestations, led to a palliative care approach.

Discussion: This case highlights the importance of considering amyloidosis in the differential diagnosis of patients with orthostatic hypotension. Kidney biopsy is a valuable tool for establishing the diagnosis, with mass spectrometry emerging as a novel modality for accurate subtyping. Early recognition of AL amyloidosis is crucial for timely intervention and prevention of further amyloid deposition, as prognosis is poor in advanced disease stages with multi-organ involvement.

FR-PO980

Percutaneous Kidney Biopsy of Native Kidneys in Adults: A Single-Center, 40-Year Experience

Stephen M. Korbet, William L. Whittier. *Rush University Medical Center, Chicago, IL.*

Background: Percutaneous renal biopsy (PRB) of native kidneys is an essential tool in the diagnosis and management of renal disease. We report one of the largest single center experiences on the success and safety of the procedure.

Methods: From 6/1983 to 12/2022, 1384 adults underwent PRB using real-time ultrasound guidance using predominantly automated 14- (n 839) or 16- (n 312) gauge needles. An attending nephrologist or a fellow (85% of biopsies) under the supervision of an attending nephrologist performed all biopsies. Following the procedure, patients were observed for 24 hours. A complication was defined by the need for an intervention, such as a transfusion of blood products or invasive radiologic or surgical procedure, or those resulting in the need for readmission or death. Data was collected prospectively in 1153 (83%) biopsies. Statistical analysis was performed using the Mann-Whitney test and Wilcoxon matched pairs test for continuous data or the Fisher's exact test for categorical data. Data are reported as mean ± standard deviation (SD) and a p-value of < 0.05 was considered significant.

Results: Pts were 46±17 yo, 38% were male, 38% white and 43% AA. The serum creatinine (SCr) was 2.3±2.4 with 47% >1.5 mg/dl. The pre-PRB hemoglobin (Hgb) was 11.7±2.2 and the post-PRB Hgb was 10.7±2.1 g/dl (delta 0.97 g/dl, P <0.0001). Adequate tissue for diagnosis was obtained in 99% of biopsies. The total glomeruli (light + immunofluorescence microscopy) per biopsy was 30±14 with 77% having ≥20 glomeruli. Significantly more glomeruli were obtained using the 14 vs 16-gauge automated needle (32±14 vs 27±11, P <0.0001) with 81 vs 74% having ≥20 glomeruli (P 0.01). Complications occurred in 7.0% of biopsies with transfusions required in 5.6% of biopsies. There was 1 (0.09%) death from post-PRB bleeding. There was no difference in complication rate (7.0 vs 8.0%, P 0.6) or transfusion requirement (5.6 vs 5.8%, P 0.9) for PRB with a 14- vs 16- gauge needle. Complications post-PRB were identified in ≤8 hrs in 73%, ≤12 hrs in 84% and ≤24 hrs in 90% of pts with 10% of complications occurring >24 hrs post-PRB.

Conclusions: PRB of native kidneys using real-time ultrasound with an automated needle remains a successful and safe procedure. We find that the use of a 14-gauge automated needle not only provides a larger biopsy sample but is as safe as a 16-gauge automated needle.

FR-PO981

Clinicopathological Features and Prognostic Outcomes of Adenovirus Nephritis: A Systematic Review of 51 Cases

Khanh Duy Doan,[1] Clarissa A. Cassol.[2] [1]*Temple University, Philadelphia, PA;* [2]*Arkana Laboratories, Little Rock, AR.*

Background: Adenovirus nephritis is a rare condition primarily associated with kidney allografts, presenting significant diagnostic and management challenges.

Methods: A systematic review was conducted on published data concerning adenovirus nephritis.

Results: 36 studies comprising 51 cases (47 allograft kidneys, 4 native kidneys) were included. Median age is 45 years and males are predominant. 72.3% occurred within the first year post-transplantation. Presentations included fever (72.5%), gross hematuria (52.9%), dysuria (39.2%), and graft pain (17.6%). Kidney biopsy patterns was shown in table 1. Adenovirus immunohistochemistry demonstrated high sensitivity (94.1%), while electron microscopy identified viral particles in 45% of cases. Immunosuppressive treatment reduction occurred in most patients (95.7%), with only 36.2% receiving antiviral therapy. Allograft failure was rare (4.4%), despite aggressive presentation, with 84.4% of patients experiencing creatinine normalization post-treatment.

Conclusions: Adenovirus immunohistochemistry showed high sensitivity, albeit limited availability. Despite its aggressive presentation, adenovirus nephritis infrequently results in graft failure.

Kidney biopsy results

	Cases (51)	Percentage (%)
Tubulointerstitial inflammation	47	92.2
Granuloma	30	58.8
Viro-pathic changes	28	54.9
Interstitial necrotizing	22	43.1
Interstitial hemorrhage	13	25.5

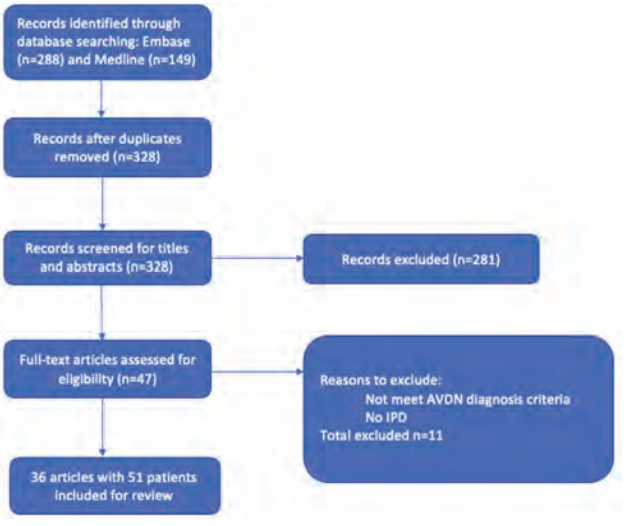


Figure 1. Study flowchart

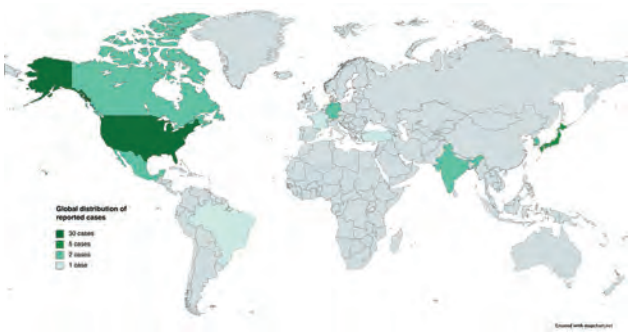


Figure 2. Global distribution of cases

FR-PO982

Discovering the Etiology of a Rare Diagnosis of Anti-brush Border Antibody (ABBA) Disease

Jessenia A. Contreras, Sumie Iwasaki. *Kaiser Permanente Northern California Region, San Francisco, CA.*

Introduction: Anti-low density lipoprotein receptor related protein 2 (Anti-LRP2) nephropathy (a.k.a. anti-brush border antibody (ABBA) disease) is a rare entity with only around 67 cases confirmed by LRP2 immunostaining and indirect immunofluorescence. It is common in white men around the age of 70s, and there is often an association with autoimmune diseases, paraneoplastic syndromes, or monoclonal gammopathy. LRP2 is found in multiple organs, but within the kidneys, LRP2 is expressed only in proximal tubular (PT) brush borders. The disease causes acute tubular injury (ATI) via immunoglobulin G (IgG) immune complex deposits along the PT basement membrane and circulating autoantibodies to the PT brush border protein LRP2. We report a case of ABBA and the process of evaluating the etiology.

Case Description: A 74-year-old man with history of dextrocardia s/p heart transplant, osteopenia, and CKD stage IV presented with back pain and weakness, with hypercalcemia [13 mg/dL], anemia, and acute on CKD. PET scan was negative. Calcium supplements were discontinued on admission, and he was treated with IV fluids with some improvement in hypercalcemia but not in renal function. Hypercalcemia workup revealed suppressed PTH, elevated vitamin D 25- OH and ACE levels, small M-protein spike on SPEP and IgG kappa on serum immunofixation; PTHrP, Vitamin D 1,25- OH2, TSH, ANCA, ANA panel, and kappa/lambda light chain ratio were normal. He had a recent history of Epstein- Bar Viremia but no signs of PTLD. Imagings were unremarkable. Renal biopsy showed ATI with tubular membrane disease deposits consistent with ABBA. Confirmatory testing for anti-LRP2 was sent to Arkana. The patient had worsening renal function and started on dialysis.

Discussion: This rare case of ABBA assesses potential etiologies. There could be an association between ABBA and heart transplant but there were no indications to check DSAs. Regarding his hypercalcemia, LRP2 is also located in the parathyroid gland, and unclear whether the autoantibodies affected the calcium sensing receptor. We are continuing to rule out other possibilities prior to initiating treatment, but most patients with ABBA do not respond to immunosuppressants and have poor prognosis.

FR-PO983

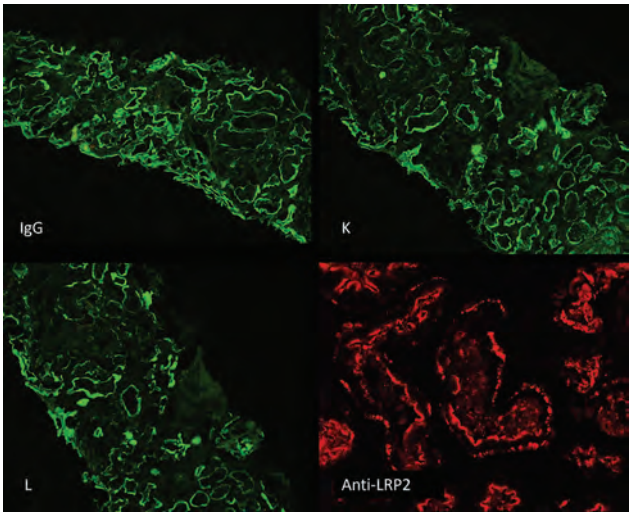
Kidney Dysfunction in Hematologic Malignancy Unveiling Anti-brush Border Antibody Disease

Paul W. Davis,[1] Alessia Buglioni,[1] Christopher P. Larsen,[2] Wisit Cheungpasitporn,[1] Silvia Titan.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Arkana Laboratories, Little Rock, AR.*

Introduction: Anti-brush border antibody disease (ABBA) is a rare disorder where antibodies target the low-density lipoprotein receptor-related protein 2 (LRP2 or megalin). Despite its rarity, ABBA warrants consideration in the differential of renal injury of unknown etiology or when IgG deposits in the TBM are seen. We present a case of ABBA with malignancy discussing diagnosis and treatment.

Case Description: The patient, a 56 year-old-male with a PMHx of HTN, DM, stroke, and PE (on apixaban) presented with worsening renal function. Two years ago with normal sCr and Hgb levels, he had knee replacement complicated by infections, treated with long term antibiotics. Anemia persisted, prompting a bone marrow biopsy revealing LGLL, treated with cyclophosphamide. Exam: normal BP, pallor and BLE edema. Labs: Hgb 9.1 g/dL, Cr: 1.9 mg/dL, eGFRcr 42 mL/min/BSA, cysC 2.1 mg/L, eGFRcys 29 mL/min/BSA and eGFRcrcys 34mL/min/BSA, glucose 156 mg/dL, urine: UACR 82 mg/g, UPCR 0.56 mg/mg, RBP 97905 mcg/24 hours, and negative for RBCs or Hgb; small serum monoclonal IgG kappa, positive ANA Hep-2 substrate 1:160, anti-DS DNA 145 IU/mL, positive lupus anticoagulant. Renal ultrasound: bilateral mild cortical thinning. Kidney biopsy findings were consistent with ABBA disease. Treatment: Prednisone and mycophenolate. Cr remains stable, Hgb is improved.

Discussion: This case emphasizes considering ABBA in the differential of AKI or CKD of unknown causes. It may occur alone or with systemic diseases, notably hematological malignancies and auto-immune conditions. Diagnosis relies on biopsy showing IgG TBM deposits, with positive IF staining for LRP2 within TBM or serologic confirmation of anti-LRP2 antibodies by indirect IF on normal kidney. High CKD progression risk stresses the need for researching biomarkers and treatment options.



Proximal TBM granular staining positive for IgG, kappa, lambda, and anti-LRP2

FR-PO984

Diagnostic Utility of Urinary Sediments in Light-Chain Proximal Tubulopathy (LCPT): Report of Three Cases

Anna Nakai, Shun Manabe, Momoko Seki, Yusuke Ushio, Hiroshi Kataoka, Junichi Hoshino. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Introduction: LCPT is characterized by crystals within proximal tubular epithelial cells and is typically associated with Fanconi syndrome. However, in cases without Fanconi syndrome, diagnosing LCPT is challenging. Microscopic analysis of urinary sediments may be valuable for LCPT, as cells and casts might contain light chain-derived crystals. Although their diagnostic value remains underreported, we present three cases of LCPT without Fanconi syndrome, where urinary sediments with crystals were crucial in understanding their condition.

Case Description: A 54-year-old female with macroglossia, carpal tunnel syndrome, subcutaneous nodules, and IgA-κ type M protein was diagnosed with AL amyloidosis. Urine protein was 5.3 g/gCr, and serum creatinine (sCr) was 1.09 mg/dL. However, urinary sediments revealed crystals within tubular epithelial cells, inconsistent with amyloidosis. Kidney biopsy was negative for amyloid deposition, and LCPT was diagnosed. A 55-year-old male with psoriasis and hypertension experienced a gradual decline in renal function. sCr level was 1.92 mg/dL. Urinary sediments revealed crystals within tubular epithelial cells and casts. Light chain staining of the sediments was positive for kappa light chain only. IgG-κ type M protein was identified, and kidney biopsy demonstrated LCPT with significant tubular casts containing crystals. A 66-year-old female presented with fever, edema, and impaired renal function. sCr level was 2.41 mg/dL. IgG-κ type M protein was detected. Urinary sediments were suspicious for crystals within tubular epithelial cells and macrophages. Immunostaining and electron microscopic analysis of cell blocks confirmed crystals in both cell types. Kidney biopsy disclosed LCPT and crystals within interstitial macrophages. Moreover, a biopsy of a subcutaneous soft mass detected histiocytes containing crystals. These findings led to a diagnosis of Crystal-Storing Histiocytosis.

Discussion: Direct observation of tubular epithelial cells and casts in urine supported the diagnosis of LCPT. Immunostaining and electron microscopic analysis were informative for identifying the origin of crystals, the type of light chain, and the cell type containing crystals, deepening the understanding of the patient's condition without invasive kidney biopsy. Further consideration is required.

FR-PO985

IgG Kappa Monoclonal Gammopathy of Renal Significance (MGRS) Manifesting as Noncrystalline Light-Chain Proximal Tubulopathy (LCPT) with Fibrils

Alcino Gama, Veronica Zamora-Olivencia, Carla L. Ellis. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Introduction: LCPT is a rare manifestation of paraproteinemia (5% of MGRS cases). It can present with crystalline or non-crystalline deposition in the tubular epithelium and is more commonly associated with kappa light chain (KLC) predominance. Clinically, it presents with a variable degree of CKD, proteinuria, and/or Fanconi syndrome.

Case Description: A 53 y/o male with IgG kappa MGUS (serum IgG 1.6 mg/dL, free KLC 13.5 mg/dL, kappa/lambda (K/L) 14.3, bone marrow with 7% plasma cells and no anemia, hypercalcemia, or bone lesions) was referred to nephrology due to eGFR of 68 mL/min. Clinical exam was unremarkable. Urinalysis showed trace blood and non-nephrotic proteinuria: 0.9 g/24h with a 0.3 g M-spike on UPEP. There was no Fanconi syndrome. All other serologies were negative. A renal biopsy was performed. Light microscopy showed diffuse, acute tubular injury with epithelial cell swelling, ballooning type vacuolization and granular cytoplasmic inclusions (Fig 1A). No definitive crystalloid structures, tubular necrosis, or tubulitis were identified. Frozen immunofluorescence (F-IF) showed a slight kappa predominance in tubular cell droplets compared to lambda (Fig 1B-C). Immunohistochemical (IHC) staining showed markedly increased staining with Kappa relative to Lambda in tubular epithelial cells (Fig 2A-B). Congo red was negative. EM showed fibrillar inclusions arranged in parallel arrays, ~10.2 nm (Fig 2C). The patient has been treated with daratumumab and bortezomib for six months with no evidence of disease progression and has sutained stable levels of KLC (5.8 mg/dL), with K/L 14.5.

Discussion: This case represents a rarely reported variant of non-crystalline LCPT with fibrils and without significant renal dysfunction. KLC monoclonality was more evident in IHC than in F-IF staining. While paraffin IF (P-IF) is the standard for a diagnosis of LCPT, this case represents a variable technique that can be helpful in settings with limited access to P-IF technology.

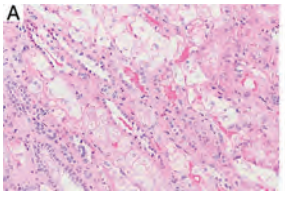


Figure 1. A: Diffuse acute tubular injury with ballooning type vacuolization and granular cytoplasmic inclusions (H&E, 400x). B/C: F-IF for for Kappa (B, 400x) slightly increased in tubular epithelial cells compared to Lambda (C, 400x).

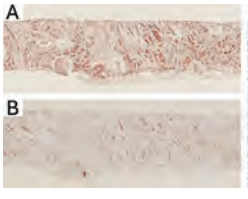


Figure 2. A/B: IHC for Kappa (A, 40x) markedly positive in tubular epithelial cells compared to Lambda (B, 40x). C: EM highlighting fibrillar inclusions arranged in parallel arrays, measuring in average 10.2 nm.

FR-PO986

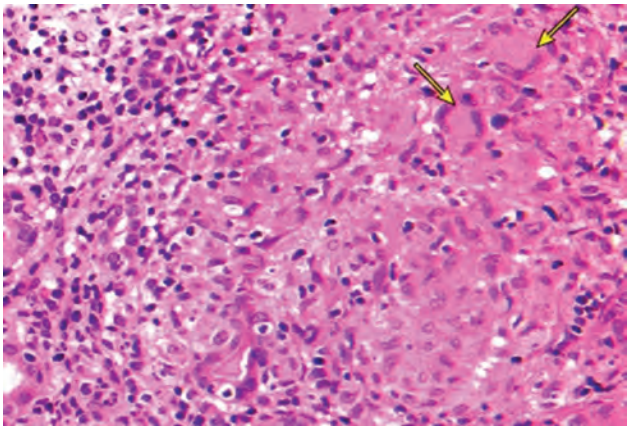
A Rare Case of Renally Limited Sarcoidosis

Fatima Raza, Arda Akoluk. *The University of Texas at Tyler, Tyler, TX.*

Introduction: The most common manifestations of sarcoidosis involve the lung. The prevalence of renal involvement in sarcoidosis is variable, with some studies reporting approximately 6% of sarcoidosis case presenting with renal manifestations. However, the majority of these cases present with concurrent extrarenal manifestations. We present a case of sarcoidosis diagnosed with manifestation limited to the kidneys and the workup it entailed.

Case Description: The patient is a 68 yo male with chronic low back pain, atrial fibrillation, CAD who presented to ED for evaluation of diarrhea. He was found to have renal insufficiency on that admission which was thought to be secondary to dehydration. In December 2020 he presented again with renal insufficiency and hypercalcemia. He underwent workup including kidney biopsy in January of the which showed noncaseating granulomatous interstitial nephritis. Autoimmune workup was negative, inflammatory markers unremarkable, BUN 54, Cr 3.67. Chest x ray was normal. He was initiated on dialysis. Patient's review of systems was negative except for fatigue and chronic bilateral knee pain. Initially, kidney biopsy was thought to be drug induced noncaseating granulomatous interstitial nephritis from chronic NSAID use as patient did not have chronic hypercalcemia and pathology was not typical for renal sarcoidosis. Subsequently, patient was found to be recurrently hypercalcemic with elevated PTH RP, high ACE. He was treated in the acute setting with pamidronate infusion and prednisone daily He was found to have no other organ involvement of his sarcoidosis. He was subsequently evaluated for renal transplant.

Discussion: Renally limited sarcoidosis is a rare presenstation and renal biopsy is essential for diagnosis. Typical findings on renal biopsy are noncaseating granulomas and giant cell formation, but athology findings on renal biopsy may vary and a broad differential should be considered. Workup should include chest radiograph and PFTs. Treatment typically consists of prednisone and if needed, supportive care with dialysis.



FR-PO987

Histopathologic and Clinical Characteristics of Nephropathies in Burmese Refugees

Hannah S. Hyaduck,[1,2] Irene Nunuk,[1] Shunhua Guo,[1,2] Carrie L. Phillips,[1,2] Michael T. Eadon,[1] Jessica L. Hata.[1,2] *[1]Indiana University Health Inc, Indianapolis, IN; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: Understanding the spectrum of nephropathies among cultural minorities may be beneficial for nephrologists and pathologists serving multicultural communities. Myanmar (formerly Burma) has been challenged by natural disasters, civil war, poverty, oppression, and human rights violations, displacing many Burmese people to the United States. This population continues to experience limited access to healthcare and poor health outcomes.

Methods: We identified 50 kidney core biopsies from 48 Burmese patients from 2006-2024. The biopsies were examined by light (LM), immunofluorescence (IF), and electron (EM) microscopy using conventional methods. Biopsies were scored by LM using the Oxford Criteria. Podocyte foot process effacement was assessed by EM.

Results: 20 patients were male and 28 were female with a mean age of 32.5 years (range 11-53 years). 34 (71%) had IgA nephropathy (IgAN), 10 (21%) had Lupus nephritis (LN), and 4 (8%) had minimal change disease, amyloidosis, thrombotic microangiopathy, or acute tubular necrosis. Most patients with IgAN presented with hematuria and proteinuria. The average urine protein-creatinine ratio was 3.8 grams with a median creatinine of 0.92 mg/dL. 35% had hypertension with rare other comorbidities; the average body mass index was 24.4 kg/m^2. Additional findings in IgA patients included increased rates of segmental sclerosis (S1, 71%) and mesangial hypercellularity (M1, 71%), endocapillary hypercellularity and crescent formation (E1 16% and C1 19%, respectively), and no cases with >25% crescents. Tubulointerstitial fibrosis was mild overall (68% T0, 19% T1). Podocyte injury was prominent with 41% of cases showing >50% foot process effacement and 26% with glomerular collapsing features, tubular microcystic change, and/or increased tubular protein resorption droplets. Moderate and severe arterial and arteriolosclerosis were present at 43% and 44%, with 35% showing moderate to severe hyalinosis.

Conclusions: Burmese patients with IgAN had greater than expected rates of segmental sclerosis, podocyte injury, proteinuria, and vascular disease, raising the possibility of an underlying genetic predisposition to podocyte and endothelial injury. Advancing our understanding of the nephropathy spectrum in Burmese immigrant patients may lead to improved strategies for disease prevention and management.

FR-PO988

Clinicopathologic Features of CKD Kidney Precision Medicine Project (KPMP) Participants

Ramya Narasimhan,[1] M. Luiza A. Caramori,[4] Sushrut S. Waikar,[1] Laura H. Mariani,[3] Glenda V. Roberts,[5] Joel M. Henderson,[1] Sylvia E. Rosas.[2] Kidney Precision Medicine Project (KPMP). *[1]Boston Medical Center, Boston, MA; [2]Joslin Diabetes Center, Boston, MA; [3]University of Michigan, Ann Arbor, MI; [4]Cleveland Clinic, Cleveland, OH; [5]Kidney Research Institute, University of Washington, Seattle, WA.*

Background: Patients with CKD have significant heterogeneity in the patterns of kidney (Kd) lesions. Herein, we analyzed research KPMP Kd biopsies (Bx) to determine if clinical features were associated with histopathologic patterns in CKD ppts with diabetic (DN) or vascular (VN) nephropathy.

Methods: Ppts recruited from 15 US centers underwent comprehensive clinical evaluation and research KdBx. Histopathology was assessed by two renal pathologists on whole slide images and consensus score assigned for morphologic features. Clinicopathologic diagnoses (Dx) were adjudicated by a committee of consortium members in 154 CKD Bx, and ppts assigned a primary Dx of DN, VN, "other", or "could not determine."

Results: 42% of Bx had DN and 32% had VN as primary Dx. Age was 58±12 vs. 63±11 yrs (*p=0.02), and* 32% vs. 10% were of Hispanic ethnicity *(p=0.01)* in the DN and VN cohort, respectively. UACR (median; 95%CI) was higher (*p<0.005)* in DN [1176 (833-2393)] vs. VN [191 (39-579) mg/g] ppts. There were no differences between DN and VN ppts in the proportion of females (45 vs.40%) and African Americans (32 vs.35%), or in BMI (32±7 vs. 30±6 Kg/m^2) and eGFR (55±22 vs. 47±18 mL/min/1.73 m^2). The presence and/or severity of global and segmental glomerulosclerosis, podocytopathy, interstitial fibrosis/tubular atrophy, and interstitial eosinophils were not different between groups, while arteriolar hyalinosis was more frequent in DN ppts (Table). Acute tubular injury was seen in the majority of DN and VN Bxs.

Conclusions: Protocol research KdBx are feasible and safe in CKD. Relative to KPMP CKD entry criteria, most ppts exhibited features of DN or VN and varying extent of chronic histopathologic changes. Unanticipated acute histopathologic changes including acute tubular injury were also commonly observed. Work is underway to further examine relationships between clinical features, histopathologic and -omics findings in KPMP ppts.

Funding: NIDDK Support

Histopathologic Features	DN (n=65) %	VN (n=48) %	*p-value*
Interstitial fibrosis, moderate to severe	53.9	39.6	0.18
Tubular atrophy, moderate to severe	56.9	41.7	0.12
Tubular casts	36.9	52.1	0.12
Interstitial eosinophils	18.5	6.3	0.09
Arteriolar hyalinosis	95.4	79.2	0.01
Arteriosclerosis, severe	32.3	45.9	0.21

DN=diabetic nephropathy; VN=vascular nephropathy

FR-PO989

30 Years of Kidney Biopsy Data in Western Mexico

Maria de la Luz Alcantar Vallin, Marisol Lopez, Jorge L. Padilla Armas, Susana M. Sainz Del Real, Jonathan Chavez, Estefania Villalvazo Maciel, Andres Aranda, Martha K. Franco Garcia, Carlos E. Orozco, Fernando Cruz Aragon, Guillermo Navarro Blackaller, Ramon Medina. *Hospital Civil de Guadalajara Unidad Hospitalaria Fray Antonio Alcalde, Guadalajara, Mexico.*

Background: A kidney biopsy provides the best opportunity to establish the etiology of the Chronic Kidney Disease (CKD), thereby improving management and predicting prognosis.

Methods: A retrospective study was conducted that included adult patients who underwent renal biopsy between 1990 and 2019, performed by nephrologists in 4 centers in western Mexico and analyzed by 2 nephropathologists.

Results: In the 30 years of study, 1933 kidney biopsies were studied, FSGS was the most frequent finding in 28%, followed by Lupus Nephritis. Table 1. We found predominance of lupus nephritis in women and IgAN in men.

Conclusions: In Western Mexico, FSGS is the most frequent histological findings. In the last two decades, we observed a increase in lupus nephritis, pauci-immune glomerulonephritis and tubulopathies, which could be related to changes in causal factors. In the last decade we also observed a greater number of kidney graft biopsies, compatible with the increase in the number of kidney transplants performed. We consider that the proportion of the chronic kidney disease burden constituted by glomerulonephritis would be illuminated by dissecting it through a comprehensive epidemiological approach.

Histopathologic Diagnoses

	1990-2000	2001-2010	2011-2019
MCD	1 (0.9)	6 (1.9)	49 (4.1)
FSGS	28 (25.5)	139 (44.8)	406 (34)
MN	9 (8.2)	42 (13.5)	84 (7)
IgA/HSP	1 (0.9)	16 (5.2)	104 (8.7)
MPGN/C3GP	13 (11.8)	25 (8.1)	35 (2.9)
Amyloid	3 (2.7)	4 (1.3)	34 (2.8)
Diabetic GS	9 (8.2)	42 (13.5)	84 (7)
LN	6 (5.5)	38 (12.3)	181 (15.2)
Pauci-immune GN	2(1.8)	3 (1)	68 (5.7)
TMA	0	1 (0.3)	9 (0.8)
DDD	0	0	1 (0.1)
C1q N	0	1 (0.3)	6 (0.5)
Nodular GS	0	2 (0.6)	6 (0.5)
Proliferative Mesangial GN (NOS)	42 (38.2)	18 (5.8)	2 (0.2)
Post infections GN	1 (0.9)	2 (0.6)	7 (0.6)
Tubulointerstitial	2 (1.8)	4 (1.3)	71 (5.9)
ATN	0	2 (0.6)	66 (5.5)
Deposition	0	0	6 (0.5)
Inespecific	0	0	5 (0.5)

FR-PO990

Quantification of Urine Podocytes (Podo) and Their Globotriaosylceramide (GL3) Content Using Imaging Flow Cytometry

Alireza Ayoubi, M. Brendan Shannon, Behzad Najafian. *University of Washington, Seattle, WA.*

Background: Fabry disease (FD) is a lysosomal storage disease caused by a deficiency of α-galactosidase A (α-Gal-A) leading to intracellular GL3 (main α-Gal-A substrate) leading to critical end-organ damage. Podo injury and loss play key roles in FD nephropathy pathogenesis. We aimed to develop a non-invasive assay for quantification of urine Podo and intracellular GL3 content.

Methods: A CRISPR/Cas9 GLA knock-out (KO) conditionally immortalized human Podo cell line and its wild type (WT) counterpart were used as laboratory controls. Urothelial and proximal tubular cell lines were used as negative controls. IFC protocols for Podo and GL3 quantification were validated. 37 ml random urine sample from a male patient with FD who had been on enzyme replacement therapy (ERT) for over 20 years was analyzed using IFC.

Results: IFC reliably separated Podo from urothelial and proximal tubular cells in our laboratory controls based on GLEPP1 expression. In addition, IFC reliably detected intracellular GL3 with a granular pattern based on CD77 staining intensity. The GLA-KO Podo showed 2.4 fold greater GL3 signal compared to the WT Podo. 41% of GL3 signal in GLA-KO Podo was colocalized with LAMP1, consistent with both intra- and extra-lysosomal GL3 accumulation. IFC of the urine sample from the FD patient showed 124 Podo (~3 Podo/ml urine) as a distinct population with variable intracellular GL3, likely reflecting an ERT effect (Figure).

Conclusions: IFC is a powerful tool for the quantification of rare cells in the urine, such as Podo. In FD patients, quantifying urine Podo and their GL3 content may serve as potentially useful non-invasive biomarkers of kidney involvement and evaluation of treatment effect.

Funding: NIDDK Support, Commercial Support - Sanofi

FR-PO991

Deep Phenotyping of Urinary Cells with Cytometry by Time of Flight Reveals CD8+CD38+ T Cells as a Biomarker to Detect T Cell-Mediated Rejection

Nina Goerlich,[1,2] Diana Metzke,[2] Emil Grothgar,[2] Leonie F. Wagner,[2] Mira Choi,[2] Lennard Ostendorf,[2] Pouneh Mirkheshti,[2] Jan Klocke,[2] Fabian Halleck,[2] Klemens Budde,[2] Paolo Cravedi,[1] Miguel Fribourg,[1] Kerstin U. Amann,[3] Sabine Baumgart,[4] Philipp Enghard.[2] Translational Transplant Research Center. *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Charite Universitatsmedizin Berlin, Berlin, Germany; [3]Universitatsklinikum Erlangen, Erlangen, Germany; [4]Universitatsklinikum Jena, Jena, Germany.*

Background: Non-invasive monitoring and early detection of rejection are of high priority in kidney transplantation. Previously, we established urine flow cytometry (FC) as tool for non-invasive rejection detection. We hypothesized that an even deeper phenotyping of urinary cells improves the diagnostic yield of urinary T cells. Therefore, we established Cytometry by time of flight (CyTOF) analysis of urine cells to derive an improved biomarker for the detection of rejection in kidney transplant recipients (KTR). Our findings were subsequently validated in a FC-based validation cohort.

Methods: A total of 140 urine samples from KTR were analyzed from patients undergoing indication transplant biopsy. We developed a method for preserving urinary cells, enabling analysis using FC and CyTOF. Our antibody panel comprised 41 targets on kidney infiltrating immune cells and graft parenchymal cells. During data analysis,

cells were clustered according to differential protein expression patterns and cluster identities were manually curated. Proportional patterns of different cell types per sample were correlated with pathological diagnoses indicated by reports of biopsies. CD8+CD38+HLA-DR+ T cells were identified as a potential biomarker for T cell-mediated rejection (TCMR) with CyTOF, which was confirmed in a validation cohort using FC.

Results: By utilizing CyTOF combined with a clustering approach, we identified CD8+CD38+HLA-DR+ T cells as a potential biomarker for TCMR. We translated our finding to FC and validated urinary CD8+CD38+, CD8+HLA-DR+, and CD8+CD38+HLA-DR+ T cells as a biomarker for TCMR in a validation cohort of 83 KTR. CD8+CD38+ T cells showed the best performance in identifying TCMR, showing an even higher AUC in this validation cohort (AUC 0.898) than our prior published urinary biomarkers to detect TCMR.

Conclusions: Urinary cell signature analysis by CyTOF is feasible and enables identifying potential new biomarkers in kidney transplantation. KTR with TCMR showed increased urinary CD8+ CD38+ T cells, which could be validated in a separate cohort by FC. We plan to test the capability of urinary CD8+CD38+ T cells to detect TCMR in a prospective trial.

Funding: Government Support - Non-U.S.

FR-PO992

Investigating Hepatocyte Nuclear Factor 4 Alpha as a Central Regulator of Kidney Graft Repair

Slaghaniya Neupane,[1] Stefan Petrovic,[2] Aninda D. Saha,[5] Maya A. Allen,[1] Nadia Sachewsky,[2] Rohan John,[2] Markus Selzner,[2] Lisa Robinson,[4] Sergi Clotet Freixas,[3] Ana Konvalinka.[1,2] *[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]University Health Network, Toronto, ON, Canada; [3]McMaster University, Hamilton, ON, Canada; [4]Sick Kids Foundation, Toronto, ON, Canada; [5]Stanford Medicine, Stanford, CA.*

Background: Kidney transplantation is the optimal treatment for end-stage kidney disease. However, ischemia-reperfusion injury (IRI) harms all transplanted kidneys, limiting their short- and long-term survival. Previously, we determined that superior kidney function/structure after IRI is associated with preserved expression of mitochondrial proteins during normothermic *ex vivo* kidney perfusion (NEVKP). We identified a potential transcriptional regulator of these mitochondrial proteins, hepatocyte nuclear factor 4a (HNF4A), which may present a novel target for kidney repair. Our goal is to determine whether a novel HNF4A agonist, N-trans caffeoyltyramine (NCT), protects kidneys from IRI. We will evaluate the effectiveness of NCT treatment *in vitro* studying male and female primary proximal tubular cells (PTECs), and *in vivo* studying male and female mice.

Methods: First, we inhibited HNF4A in primary male and female PTECs, using a pharmacologic or genetic approach. We then assessed gene expression, cell death and mitochondrial function. Next, we treated PTECs with NCT/vehicle and examined cell death and expression of HNF4A target genes. Lastly, male and female mice were subjected to bilateral IRI, and kidney function and structure were assessed on post-operative day 2 and 14.

Results: HNF4A inhibition *in vitro* increased PTEC death and decreased mitochondrial function, while NCT increased the expression of *HNF4A* and mitochondrial genes, suggesting that NCT may be protective. We developed a sex-specific model of bilateral IRI and demonstrated that warm ischemia (27-minutes in males, 40-minutes in females) impairs kidney function on post-operative day 2, indicated by elevated serum creatinine and tubular injury. Mice also developed tubulointerstitial fibrosis on post-operative day 14.

Conclusions: Based on the preliminary results, HNF4A is important for the metabolic function and viability of PTECs. We will next administer NCT to mice prior to IRI and examine whether HNF4A agonist preserves mitochondria and improves kidney function and structure.

FR-PO993

MIF-CD74 Pathway and Its Effect on Effector T Cell Exhaustion in Alloimmunity

Nour K. Younis,[1] Nadim Al Rahy,[1] Zhabiz Solhjou,[1] Abdullah B. El Kurdi,[2] Hengcheng Zhang,[1] Soltan Al Chaar,[1] Houda Djebli,[1] Andrew P. Badaoui,[1] John Y. Choi,[1] Marta Piecychna,[3] Edward H. Doherty,[3] Richard Bucala,[3] Jamil R. Azzi.[1] *[1]Brigham and Women's Hospital, Boston, MA; [2]American University of Beirut, Beirut, Lebanon; [3]Yale University, New Haven, CT.*

Background: Our recent clinical study has shown a significant upregulation of CD74, the cognate receptor for the cytokine MIF, in the urinary exosomal mRNAs of kidney transplant recipients during rejection, highlighting this pathway's role in alloimmunity.

Methods: WT, CD74-/-, and RAG-/- B6 ($H2^b$) mice were transplanted with fully mismatched BALB/c ($H2^d$) hearts. Single-cell RNA sequencing and immunophenotyping were conducted on allografts, draining lymph nodes(dLNs), and spleens. Additionally, various studies were performed to evaluate the effect of MIF-CD74 on T cells

Results: Fully mismatched heart transplants survived indefinitely in CD74-/- hosts. Despite that, CD74-/- recipients had significantly higher % of CD8 and CD8 effector T cells in their dLNs and spleens. Also, CD74-/- T cells exhibited a more exhausted phenotype, with higher expression of LAG3 and PD1, lower CD127, and less release of Granzyme B compared to WT cells. Moreover, flow-sorted CD74-/- CD8 effector T cells exhibited lower memory response to donor antigens in vitro. CD74-/- CD4 effector T cells displayed a similar exhaustion phenotype as CD8 effector T cells. Additionally, compared to WT cells, both CD74-/- CD4 and CD8 T cells were less capable of proliferating in vitro when stimulated non-specifically, and less capable of inducing rejection in a RAG-/- heart transplant model. Our single-cell data on allograft-infiltrating T cells supported these findings. WT CD4 and CD8 effector T cells were less clonally diverse than CD74-/- cells, indicating that WT effector T cells are more antigen-specific and capable of allograft rejection. Moreover, exhaustion gene signature and pathways were significantly upregulated in CD74-/- effector T cells, while activation gene signature and pathways such as allograft rejection, IFN-g signaling, and complement were downregulated. This impairment of effector T cells in CD74-/- recipients was accompanied by superior regulatory T cell function, as we previously described.

Conclusions: CD74 deletion impairs effector T cell proliferation and activation while enhancing regulatory T cell function. The MIF-CD74 pathway exerts a differential effect on effector T cells vs regulatory T cells, potentially explaining its role in allograft rejection.

FR-PO994

Structural Identification of Immunodominant Human Leukocyte Antigen (HLA) Epitopes Targeted by HLA-Specific Antibodies in Kidney Allograft Recipients

Aaron Lucander, John Killian, Rodney G. King, Todd J. Green, Frances E. Lund. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Donor-specific antibody (DSA) targeting Human Leukocyte Antigen (HLA) mismatches causes kidney allograft damage and loss. Currently, there are no reliable methods to predict which HLA epitopes will be recognized by alloreactive B cells and antibodies (Abs), thus limiting optimal matching of kidney transplant (KT) donors and recipients. The purpose of this study was to define structural determinants of HLA immunogenicity by identifying HLA epitopes recognized by DSA.

Methods: B cells reactive with donor HLA-A*01:01 (A1) were isolated from blood and allograft of a KT recipient, then B cell receptors (BCR) from these allospecific B cells were cloned and expressed as monoclonal antibodies (mAbs, n=50). Coupling BCR-repertoire sequencing of B cells from peripheral blood and allograft with serum immunoglobulin proteomics, clonally-expanded lineages of A1-specific B cells were identified and linked to DSA in circulation. Three mAbs (E07, L02, M07), each representing distinct immunodominant clonal lineages, were complexed with A1 and the HLA epitopes recognized by these mAbs were determined by either X-Ray Crystallography or Cryo-Electron Microscopy. Epitopic overlap with other A1-reactive mAbs (n=47) and polyclonal DSA in the serum of other A1-mismatched KT recipients (n=11) was assessed by cross inhibition studies and A1 single amino acid point mutants.

Results: The E07, L02, and M07 epitopes are distinct and collectively encompass most solvent-accessible mismatched residues (15/20, 75.0%) on the membrane-distal face of A1. All other A1-specific mAbs (n=47) recognize HLA epitopes that overlap with those of E07, L02, or M07 and mAbs with shared epitopes exhibit common binding to specific mismatched HLA residues. Other KT recipients (n=11) who received a mismatched A1 allograft produced Abs that recognized the same immunodominant A1 epitopes and targeted the same mismatched residues irrespective of their self HLA alleles.

Conclusions: In our cohort of KT recipients, DSA preferentially targeted mismatched residues exposed on the membrane-distal face of HLA, recognizing a limited number of immunodominant epitopes. These results indicate that mismatched residues in HLA are differentially recognized by the immune system suggesting that some HLA residue mismatches may be more likely to elicit DSA responses than others.

Funding: Other NIH Support - NIAID U19 AI142737, NIAID T32 AI007051

FR-PO995

Urinary Single-Cell RNA Sequencing of Kidney Allograft Recipients Detects Podocyte Epithelial-to-Mesenchymal Transition in Kidney Transplant Recipients

Thangamani Muthukumar,[1] Aziz Belkadi,[2] Carol Y. Li,[1] Gaurav Thareja,[2] Darshana M. Dadhania,[1] Manikkam Suthanthiran.[1] *[1]Weill Cornell Medicine, New York, NY; [2]Weill Cornell Medicine-Qatar, Doha, Qatar.*

Background: Podocytes undergo epithelial-to-mesenchymal transition (EMT) under states of cellular stress. We did urinary scRNA-Seq of kidney transplant recipients and detected the presence of podocyte EMT.

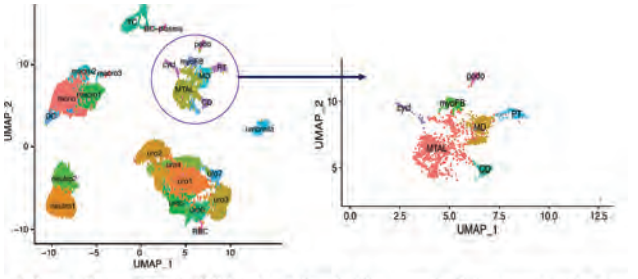
Methods: We obtained urine samples from 12 kidney transplant recipients (7 biopsy-matched urine samples [3 ABMR, 1 TCMR, and 3 no-rejection] and 5 stable patients without biopsy). We processed them fresh for scRNA-Seq on a 10x Chromium platform/

Illumina sequencer. We used the Seurat package for computational analysis. We defined cell types based on the expression of established lineage marker genes.

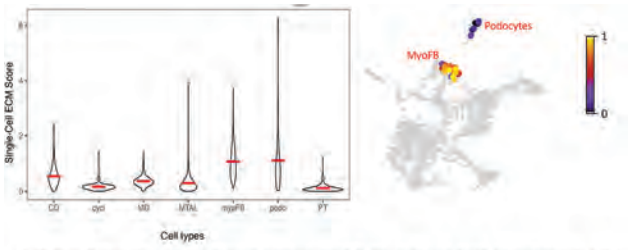
Results: We generated 19404 high-quality single-cell transcriptomes from the urine of 12 kidney transplant recipients (Fig.1). Extracellular matrix (ECM) includes collagens, glycoproteins, and proteoglycans. We applied the single-cell ECM expression score *(Kuppe et al. Nature 2021)* to various kidney parenchymal cells. The podocyte score was highest among the kidney parenchymal cells and was similar to the myofibroblast score (Fig.2 left). To confirm podocytes' EMT, we ordered cells pseudo-temporally using *scVelo* (uses RNA velocity graph to draw descendants/ancestors coming from specified starting cells). Our analyses revealed a potential transition from podocytes (starting cells), but not other cells, to myofibroblasts (terminal states) (Fig.2 right).

Conclusions: By scRNA-Seq of urinary cells, we detected EMT in the podocytes of kidney transplant recipients. The role of the podocyte EMT in kidney allografts has not been well studied. Further characterization of podocyte EMT will help decipher the mechanisms underlying kidney allograft fibrosis.

Funding: Other NIH Support - NIAID



Left panel: Major cell types in 19,404 single cells from the 12 urine samples. Kidney parenchymal cells are shown within the circle.
Right panel: Kidney parenchymal cells



Left pane: Podocytes express ECM genes similar to myoFB. The single-cell ECM expression score is the highest for myofibroblasts and podocytes.
Right panel: Velocity graph showing the pseudotime trajectory. Podocytes were chosen as the root of origin (pseudotime = 0). The orientation of the cell types is the same as shown in the right panel of Fig 1.

FR-PO996

Ex Vivo Allogeneic Expansion of Peripheral Blood Mononuclear Cells (PBMCs) from Stable Kidney Transplant Recipients Differentially Regulates Long Noncoding RNA Expression

Anil K. Chandraker,[1] Brittany L. Schreiber,[2] Sudipta Tripathi.[1] [1]*University of Massachusetts Chan Medical School, Worcester, MA;* [2]*Brigham and Women's Hospital, Boston, MA.*

Background: We have successfully expanded human Antigen Specific T Regulatory cell enriched Lines (ASTRLs) from stable kidney transplant recipients. Characterization of this preclinical heterogenous cell therapy product to gain greater insight and to interpret how this cellular heterogeneity can be leveraged particularly in its clinical therapeutic applications is pertinent. The purpose of this study is to understand the cellular heterogeneity of *ex vivo* expanded ASTRLs using cutting edge single cell RNA sequencing. This will provide information about unexplored/ pathways that play a role in cell-cell interaction in heterogenous cell therapy products.

Methods: Single cell RNA sequencing was performed on frozen samples of pre-expanded PBMCs and a post-expanded ASTRL from 5 stable kidney transplant recipients using the 10X Genomics platform. The gene expression counts and TCR/BCR clonotypes were generated using Cellranger pipelines with the human genome reference (GRCh38). The data were imported and analyzed using Seurat and djvdj in R.

Results: Single cell gene expression profile show ASTRLs are enriched for T and NK cell populations and contain very few B cells and monocytes. UMAP clustering distinguishes the CD4+ T cell compartment in all the five ASTRLs as a distinct T cell subset as expected and very similar to the corresponding PBMC samples. Our data shows a number of long noncoding RNA are differentially expressed both in the CD4 and CD8 compartment of ASTRLs in comparison to the PBMC samples. GATA3-AS1, the lncRNA contiguous to GATA3 and essential for the transcription of IL-5 and IL-13, is upregulated 3-fold in the CD4 compartment of ASTRLs, corroborating our previous observation that ASTRLs exhibit a Th2 type Treg phenotype and produce a significantly high levels of IL-13. LINC00402 known as a regulator of allogeneic response in transplantation is 6-fold downregulated in ASTRLs validating the regulatory nature of ASTRLs, that are donor antigen specific. We also observe multiple lncRNA associated with cholesterol biosynthesis and fatty acid oxidation pathways upregulated >2-fold in ASTRLs in comparison to PBMC.

Conclusions: Examination of the differential expression of lncRNAs in ASTRL shows a bias towards fatty acid metabolism and aTh2 like Treg phenotype.

Funding: Private Foundation Support

FR-PO997

Kidney Transplantation in Mice Leads to Allograft-Restricted Activation and Maintenance of Allospecific Memory T Cells

Bo Wang,[1,2] Laurence Kupferschmid,[1] Frederic Arnold,[1] Xudong Liu,[1] Sagar -,[3] Christoph Schell,[4] Yakup Tanriver.[1,5] [1]*Institute of Microbiology and Hygience, Faculty of Medicine, University of Freiburg, Freiburg, Germany;* [2]*Factuly of Biology, University of Freiburg, Freiburg, Germany;* [3]*Department of Internal Medicine II, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany;* [4]*Institute of Surgical Pathology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany;* [5]*Department of Internal Medicine IV, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany.*

Background: Pre-existing allospecific memory T cells are rapidly activated in response to allografts, expressing functions that mediate graft injury and failure, directly impacting patient survival. However, the early dynamics of their activation, graft infiltration, and effector functions remain largely unclear. Therefore, it is crucial to gain an in-depth understanding of their activation, migration, and effector functions during transplantation, including their ability to recruit other immune cells to drive allograft rejection.

Methods: To address those open questions, we infected recipient mice (wt) with OVA expressing Listeria monocytogenes (*LM-OVA*) to generate allospecific memory against OVA. Four weeks later, we transplanted kidneys from Act-mOVA transgenic mice, which express ovalbumin ubiquitously as an alloantigen. Then, we use fluorochrome-conjugated SIINFEKL: H2-Kb tetramer (SIIN-tet) to follow the dynamics of the endogenous CD8 T cells response against OVA after kidney transplantation. Finally, single cell RNA sequencing was used to obtain a comprehensive understanding of the immune cell landscape within allogenic kidney grafts on day 14.

Results: We show that in contrast to pathogen-activated memory T cells allospecific memory T cells are not activated in secondary lymphoid organs but rather directly in the allograft, where they are a maintained by forming a stem-like population, proliferate and differentiate in response to their cognate antigen. This interaction leads to the recruitment and activation of various immune subsets, ultimately resulting in allograft rejection. In addition, the scRNA-seq data expose a complex composition of myeloid and lymphoid immune cell subsets and pathogenic transcriptional states in the kidney allograft, which is orchestrated by the T cell memory response.

Conclusions: Allospecific memory T cells have a unique response pattern, which will help to devise new strategies to prevent and treat allograft rejection that is mediated by memory T cells

FR-PO998

The Yin and Yang of Acute Rejection in Kidney Allografts

Zahraa Khan,[1,2] Carol Y. Li,[1] Sheavonnie Wright,[1] Alex Devito,[1] Mia Montecillo,[1] Darshana M. Dadhania,[1] Thangamani Muthukumar,[1] Manikkam Suthanthiran.[1] [1]*Weill Cornell Medicine, New York, NY;* [2]*NewYork-Presbyterian Weill Cornell Medical Center, New York, NY.*

Background: Acute rejection undermines the life - prolonging benefit of kidney transplantation. We and others have demonstrated that acute rejection is exemplified by proinflammatory effectors such as cytopathic granzyme B, perforin and pro - inflammatory cytokines such as interferon gamma and interleukin 2. Because preclinical models have elucidated the essential role of negative regulators of immunity such as CTLA4 and PD1 in limiting inflammation, we tested the hypothesis that acute rejection is also associated with the over expression of the prototypic negative regulator CTLA4. We tested our novel postulate by urinary cell mRNA profiling, an accurate reflector of immune events in a rejecting kidney allograft.

Methods: We isolated RNA from biopsy matched urine samples, reverse transcribed to cDNA and measured absolute mRNA levels of CTLA4 using preamplification enhanced real time quantitative PCR assays in 58 biopsy - matched urine samples from 52 recipients with acute T cell mediated rejection and 176 biopsy matched urine samples from 158 recipients with biopsies without rejection features (NR).

Results: The median (IQR) absolute copy number of CTLA4 mRNA in TCMR - biopsy matched 58 urine samples was 720 copies (197 - 2906) per microgram of total RNA compared to 167 copies (12.5 – 448) per microgram of total RNA in NR - biopsy matched 176 urine samples (P - value < 0.0001). Figure 1, the Box and Whisker plots, in addition to showing the distribution of CTLA4 mRNA copy numbers stratified by biopsy diagnosis, show significant overexpression of 18S normalized, log10 transformed CTLA4 mRNA in urine samples matched to TCMR biopsies compared to urine samples matched to NR biopsies (P-value <0.0001). Figure 2, Receiver operating Characteristic Curve analysis showed urinary cell level of CTLA4 discriminates TCMR biopsy matched urine from NR biopsy – matched urine samples and the area under the curve (AUROC) was 0.71 (95% Confidence interval 0.63 – 0.8, P-value < 0.0001) to distinguish TCMR from NR.

Conclusions: Our finding demonstrating over expression of CTLA4 mRNA during an episode of acute T cell mediated rejection has identified a counter regulatory mechanism to limit the proinflammatory forces associated with acute rejection. The finding also advances a mechanistic rationale for the use of CTLA4-Ig for the treatment of acute TCMR.

FR-PO999

Molecular Signatures of Reperfusion in Ischemic Donor Kidneys: Distinguishing Rejection and Nonrejection Risk Genotypes through Single Nuclear RNA Sequencing

Cem Kuscu,[1] Murat Dogan,[1] Canan Kuscu,[1] Henry B. Randall,[2] Krista L. Lentine,[2] John C. Edwards,[2] Ajay Jain,[2] Mustafa Nazzal,[2] Yasar Caliskan.[2]
[1]The University of Tennessee Health Science Center, Memphis, TN; [2]Saint Louis University, St Louis, MO.

Background: *LIMS1* rs893403 homozygous GG genotype in donors is associated with decreased risk of T-cell mediated rejection after kidney transplantation. However, the effects of ischemia and reperfusion injury (IRI) on donor kidney expression profile at single cell level have not been studied in a human kidney model. Using non-utilized human kidneys, we investigated the effects of IRI on the nuclear expression of LIMS1, GCC2, and associated genes in donor kidneys with different genotypes and compared results between ex-vivo normothermic machine perfusion (NMP) model and cold static storage (CS).

Methods: Deceased donor kidneys (n=5) on CS underwent 6-hr NMP (n=5) following CS. Cells at baseline on CS and after 6 hrs of NMP were harvested. Single nucleus transcriptomics of the donor kidneys after 6 hrs of NMP was directly compared with the profile on baseline CS. Specimens sharing the same genotype were subsequently processed together using the droplet-based 10X Genomics approach.

Results: Three kidneys possessed the AG allele (donor rejection risk genotype), while two exhibited the GG allele (donor non-rejection risk genotype) for the *LIMS1* gene (rs893403). The study yielded a collection of over 60,000 cells accompanied by 2 billion reads. 13 unique kidney cell types were identified using Seurat (v7.0). SnRNA-seq analyses showed induction of LIMS1 and GCC2 in tubule cells particularly in ischemic donor kidneys with non-rejection risk genotype (GG) after NMP. LIMS1 and GCC2 expression increase is significant in proximal and distal tubule cells after 6 hrs of NMP in non-rejection risk kidneys (GG) (Fig1a, 1b). Transcriptomic response to NMP is different in kidneys with GG and AG genotypes (Fig 1c).

Conclusions: NMP significantly increased the LIMS1 and GCC2 expression on proximal and distal tubule cells with *LIMS1* rs893403 GG variant but not on the kidney with AG variant. Donor *LIMS1* genotype is important in the transcriptomic response to IRI.

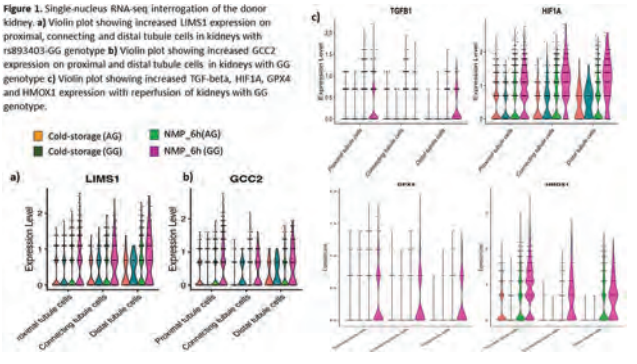


Figure 1. Single-nucleus RNA-seq interrogation of the donor kidney. **a)** Violin plot showing increased LIMS1 expression on proximal, connecting and distal tubule cells in kidneys with rs893403-GG genotype **b)** Violin plot showing increased GCC2 expression on proximal and distal tubule cells in kidneys with GG genotype **c)** Violin plot showing increased TGF-betA, HIF1A, GPX4 and HMOX1 expression with reperfusion of kidneys with GG genotype.

FR-PO1000

Urinary Extracellular Vesicles: Early Indicators of Kidney Allograft Injury after Transplantation

Maja Vodusek,[1,2] Maja Stalekar,[3] Katja Goricar,[2] Marija Holcar,[2] Polona Kogovšek,[3] Metka Lenassi,[2] Miha Arnol.[1] *[1]Department of Nephrology, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [3]Department of Biotechnology and Systems Biology, National Institute of Biology, Ljubljana, Slovenia.*

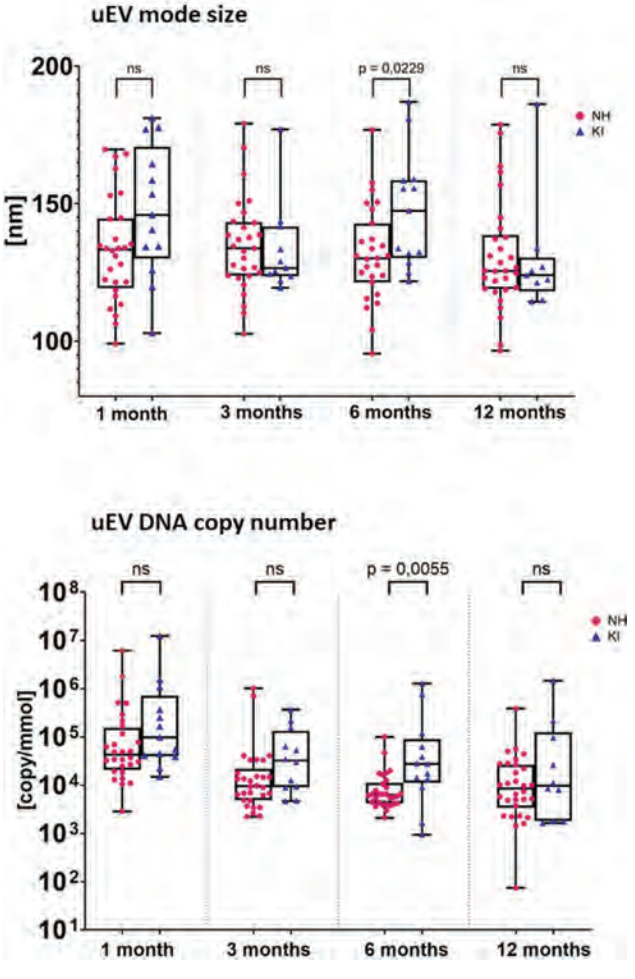
Background: Allograft biopsy is the standard method for assessing the status of transplanted kidneys. Our aim was to determine whether urinary extracellular vesicles (uEVs) and their characteristics can predict kidney injury (KI) one year after transplantation (Tx).

Methods: In a prospective longitudinal study, 49 well-defined adult kidney transplant patients were followed up 1, 3, 6 and 12 months post-Tx. Blood and second morning urine samples were collected at each visit. At the time of surveillance biopsy (Bx) (382 (330-404) days post-Tx), patients were categorized into two groups based on histologic and molecular analysis (MMDx) of allograft tissue: normal histology (NH, n=33, 67%) or KI (rejection and non-rejection; n=16, 33%). uEVs were isolated by size exclusion chromatography and their characteristics were analyzed by nanoparticle tracking analysis, genotyping and digital droplet PCR.

Results: After 6 months, the KI group had higher uEV mode size (P=0.0229) and increased uEV DNA copy number normalized to urine creatinine (P=0.0055; Figure). Using a multivariable model at 6 months, we were able to predict the diagnosis of KI at the time of surveillance biopsy with an area under the curve of 0.88 (95% CI: 0.77 to 0.99), a sensitivity of 0.69 and a specificity of 0.89 (P=0.0001). The negative predictive value was 86% and the positive predictive value was 75%.

Conclusions: Our results emphasize the potential of uEV characteristics for monitoring and early diagnosis of kidney allograft injury, which could reduce the need for invasive biopsy procedures.

Funding: Government Support - Non-U.S.



FR-PO1001

Gut Microbiome Alterations Precede Graft Rejection in Kidney Transplantation Patients

Johannes Holle,[1,2] Rosa P. Reitmeir,[2] Felix Behrens,[1] Daniela Schindler,[3] Markus Gerhard,[3] Jun Oh,[4] Ulrike Löber,[2] Nicola Wilck,[1] Hendrik Bartolomaeus.[1] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Max Delbruck Centrum fur Molekulare Medizin Experimental and Clinical Research Center, Berlin, Germany; [3]Deutsches Zentrum fur Infektionsforschung eV Standort Munchen, Munchen, Germany; [4]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany*.

Background: Kidney transplantation (KT) is the optimal treatment for end-stage kidney disease, with graft survival critically affected by the recipient's immune response. The role of the gut microbiome in modulating this immune response remains underexplored. Our study investigates how microbiome alterations might associate with allograft rejection.

Methods: We analyzed existing biomaterials of a multicenter prospective study involving 217 KT recipients and 28 kidney donors from the German Center for Infection Research. Changes in the gut microbiome were analyzed using 16S rRNA gene amplicon sequencing and functional predictions (PICRUSt2) and quantitative PCRs for the production potential of propionate and butyrate. Propensity score matching was utilized to compare patients who experienced graft rejection with those who did not.

Results: The gut microbiome showed gradual recovery post-KT, marked by an increase of Shannon diversity and SCFA-producing bacterial taxa. However, prior to graft rejection, significant alterations were noted in microbiome composition, characterized by a decrease in microbial diversity and SCFA-producing taxa. Post-rejection analysis revealed normalization of these microbiome features. Functional analysis highlighted a decreased potential for SCFA production in patients prior to rejection. Comparison to published associated microbiome signatures from chronic kidney disease (CKD) patients demonstrated a partial overlap of the microbiome alterations preceding graft rejection with the alterations typically found in CKD.

Conclusions: Our findings suggest that alterations in the gut microbiome composition and function may precede and influence KT rejection, suggesting potential for use as biomarker and early therapeutic microbiome-targeting interventions to improve transplant outcomes.

FR-PO1002

Podocyte Injury in Kidney Allograft with Chronic Antibody-Mediated Rejection: Late Occurrence and Association with Glomerular Basement Membrane Thickening

Dema Yaseen Alsabbagh, Pongpratch Puapatanakul, Jeffrey H. Miner, Sanjay Jain, Tarek Alhamad, Hani Suleiman. *Washington University in St Louis, St Louis, MO*.

Background: The histologic hallmarks of chronic antibody-mediated rejection (CAMR) are evidence of endothelial injury and glomerular basement membrane (GBM) thickening and double contour without immune complex depositions. Our previous data show that endothelial injury is the primary injury that causes initial GBM thickening. However, proteinuria is usually present suggesting podocytes are also injured, but this has not been extensively studied. Recently, we described sarcomere-like structures (SLSs), a feature of injured podocytes and cytoskeletons rearrangement that is found in various glomerular diseases. We aim to assess the prevalence of SLSs in various stages of CAMR.

Methods: We utilized super-resolution imaging of kidney tissues to investigate the association between GBM changes in transplant glomerulopathy and podocyte injury at various stages of CAMR. Paraffin sections from 9 allograft biopsies with CAMR and 7 nephrectomy controls were analyzed. Immunofluorescence staining for synaptopodin and myosin IIA was performed to visualize SLSs, Nephrin and laminin α5, Col4a1a1a2 and Col4a3a4a5 were used to label the slit diaphragms and GBM.

Results: Compared with the control samples, laminin α5 staining shows a significant GBM thickening in CAMR biopsies. In the thickened areas of the GBM, increase in Col4a1a1a2 was observed, especially, on the endothelial side of the GBM with no changes in the Col4a3a4a5. SLSs, defined by presence of alternating synaptopodin and myosin IIA clusters in podocyte foot processes, were observed predominantly in CAMR groups. The extent of SLSs in advanced stages of CAMR (Banff cg2-3) was significantly higher when compared to earlier stages (Banff cg1a-b) and was present in areas with foot process effacement as suggested by low, blunt nephrin density. The chance of SLSs occurrences was significantly higher as GBM thickness increased.

Conclusions: The positive correlation between podocyte injury and the degree of GBM thickening in CAMR where the injury starts primarily from antibody-mediated endothelial damage suggests that alterations in the GBM convey injurious signals to podocytes. This finding provides new insight into the progression of CAMR and, if incorporated into the disease classification, may enhance prognostic evaluation.

FR-PO1003

Epithelial Injury Patterns Induced by Acute T Cell-Mediated Rejection in Kidney Transplants

Lorenz Jahn,[1] Anna M. Pfefferkorn,[2] Janna Leiz,[1] Vera A. Kulow,[3] Svjetlana Lovric,[1] Jessica Schmitz,[6] Jan H. Braesen,[6] Irina Scheffner,[1] Michael Fähling,[3] Felix Aigner,[4] Kai M. Schmidt-Ott,[1] Wilfried Gwinner,[1] Philip F. Halloran,[5,7] Muhammad Imtiaz Ashraf,[2] Christian Hinze.[1] *[1]Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; [2]Department of Surgery, Experimental Surgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany; [3]Institute for Translational Physiology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [4]Department of Surgery, Krankenhaus der Barmherzigen Brüder, Graz, Austria; [5]University of Alberta Alberta Transplant Applied Genomics Centre, Edmonton, AB, Canada; [6]Institute of Pathology, Nephropathology Unit, Hannover Medical School, Hannover, Germany; [7]Department of Medicine, Division of Nephrology and Transplant Immunology, University of Alberta, Edmonton, AB, Canada*.

Background: Acute T-cell mediated rejection (TCMR) remains a major challenge after kidney transplantation, posing risks for the long-term outcome of the transplant. Previous research highlighted the importance of TCMR-induced renal epithelial injury for transplant outcome. Yet, the detailed cellular origin of these injury responses and the associated gene expression profiles remain poorly understood.

Methods: To induce acute rejection, we used two different mouse models (C57BL/6 and BALB/c) for allogeneic kidney transplantation and syngeneic controls. We analyzed the molecular changes in renal gene expression during TCMR by using single nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics on the kidneys 7 days post-transplant. Differentially expressed genes between allogeneic and syngeneic kidneys were analyzed and a published gene set predictive of allograft outcomes was investigated per cell type. All results were compared to our snRNA-seq data from three human TCMR kidney biopsies and three stable allografts.

Results: Mouse kidneys from allogeneic transplantation showed all histological hallmarks of TCMR. SnRNA-seq revealed a strong gene expression response, especially in C57BL/6 kidneys transplanted into BALB/c mice, most pronounced in kidney epithelial cells, particularly in the proximal tubules (PT) and thick ascending limbs (TAL), inducing distinct injury-associated cell states. Spatial transcriptomics identified a heterogeneous spatial distribution of these cell states between cortex and medulla. Published genes indicative of allograft outcome were mostly expressed in injured PT and TAL but showed heterogeneous differential expression in the different injured PT and TAL cell states. Cross-species analysis revealed a substantial overlap of epithelial cell states between mouse and human TCMR.

Conclusions: Our study offers a detailed exploration of cell type-specific gene expression changes during TCMR in humans and mice. The analysis of allograft outcome-associated genes revealed their origin from various injured epithelial cell states. This insight may help identify injured cell states most responsible for reduced graft function, potentially enabling targeted therapeutic interventions.

FR-PO1004

A Mouse Model for "Definitive" Polyomavirus Nephropathy with Lytic Viral Replication

Volker Nickeleit, Dalton R. Butcher, Bawana D. Thompson, Harsharan K. Singh. *The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC*.

Background: A mouse model for polyomavirus nephropathy (PyVN) with lytic viral replication has not been described. Studies of PyVN based on observations in kidney transplants have limitations due to concurrent alloimmune injury. Aim: Characterization of a model of PyVN in native mouse kidneys.

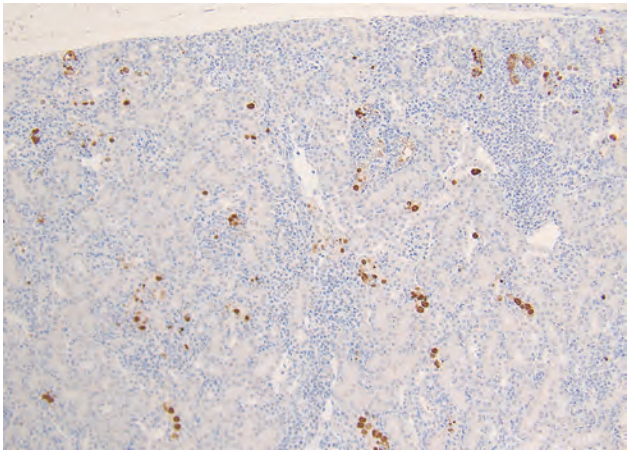
Methods: Black Swiss mice i.p. injected with murine strain A2 PyV (MUPyV; $1x10^7$ PFU) reliably developed PyVN. Animals (n>100) were sacrificed at different intervals (end point 54 weeks). Testing performed: light microscopy (LM), electron microscopy (EM), immunohistochemistry (IHC), plasma anti-MUPyV antibody titers, PCR (kidney, plasma, urine), genetics on MUPyV stability.

Results: PyVN with lytic replication occurred in all animals 2 weeks post infection. It peaked at 2-5 weeks (Fig: IHC for PyV-Capsid Protein-1; viral replication in 6.1% (median) of cortical tubules), subsequently decreased (weeks 6-30) and ultimately cleared by LM/IHC in all animals (weeks 47-54). At the end of follow-up subclinical infections (positivity in kidney/plasma/urine only by PCR; no changes by LM/IHC) were only seen in 15% of mice. Viral progeny were detected in the cytoplasm and nuclei of tubular and some mesenchymal cells by EM. Viral injury dominated in distal tubules and cortical collecting ducts. It was associated with inflammation rich in CD3+and CD4+ cells (75%) with fewer admixed myofibroblasts and F4/80+ histiocytes (20%-40%). Fibrosis did not occurr. During PyVN, MUPyV remained genetically stable. In week 3-5 post infection animals mounted a transient IgM reponse that disappeared during week 6-30 when IgG

titers peaked. At the end of follow-up IgM was no longer detected while IgG titers were low positive in 92% of animals.

Conclusions: Our PyVN mouse model in native kidneys is robust. Morphologic, molecular, genetic, and immunologic changes mimick human disease whereas scarring is absent. The model is well suited for targeted studies/ interventional drug trials.

Funding: Clinical Revenue Support



FR-PO1005

Characterization of the BKPyV-Specific Memory B Cell Response in KTx Recipients and Blood Donors

Patrick Affeldt, Christoph Kreer, Roman-Ulrich Mueller, Gertrud Steger, Florian Klein. *Universitatsklinikum Koln, Koln, Germany.*

Background: While BK-Polyomavirus (BKPyV) infection is asymptomatic in immunocompetent individuals, it causes Polyomavirus-associated Nephropathy (PyVAN) in about 10% of all kidney transplant (KTx) recipients. PyVAN is one of the leading causes of premature graft function loss. Importantly, there is currently no virus-specific therapy available. Since the presence of BKPyV-directed antibodies has been associated with control of BKPyV infections, we set out to analyze the memory B-cell response against BKPyV on a single-cell level and isolate BKPyV neutralizing monoclonal antibodies (mAb).

Methods: Two cohorts of i.) 200 kidney transplant recipients (KTx) and ii.) 100 blood donors (BD) were screened for plasma neutralization against BKPyV genotypes Ib2 and IV using a pseudovirus neutralization assay. Based on plasma neutralizing activity, we selected the top 5 KTx and 5 BD neutralizers and isolated BKPyV-VP1-specific IgG+ memory B cells from peripheral blood mononuclear cells (PBMC) via Fluorescence activated cell sorting (FACS). Naturally paired heavy and light chain sequences were generated by total RNA reverse transcription and a BCR-specific nested PCR following sequence analysis. Clonality was inferred from IgBLAST annotated sequences and at least one antibody from each identified BKPyV-reactive B cell clone was selected for recombinant antibody production. Monoclonal antibodies were eventually evaluated for VP1-binding and neutralization against BKPyV genotypes (I-IV).

Results: Higher neutralization titers and BKPyV cross neutralizing activity against genotypes I-IV was observed in sera from KTX patients compared to the BD group. 1089 BKPyV specific memory B-cells from the top 5 neutralizers from each group were isolated and 768 memory B-cell receptor sequences analyzed. As a first proof of principle, 16 mAbs (5 BD, 11KTx) were produced and screened for neutralizing activity against all genotypes. Of those, mAb COR32_1_C2(KTx) showed a potent cross neutralizing activity (max. IC_{50} <0.03 ug/ml) against all genotypes.

Conclusions: We established a pipeline to isolate BKPyV-Vp1-specific antibodies from human peripheral blood and found BKPyV-neutralizing antibodies in both the BD and the KTX group. Importantly, we identified COR32_1_C2 (KTx) as a promising candidate with highly potent neutralizing activity against all BKPyV genotypes.

FR-PO1006

Arteriolar Molecular Pathways in Children after Kidney Transplantation with Preceding Peritoneal Dialysis

Maria Bartosova,[1] Conghui Zhang,[1] Gesine Messerschmidt,[1] Iva Marinovic,[1] Rebecca Herzog,[2] Betti Schaefer,[1] Ariane Zaloszyc,[4] Jun Oh,[3] Klaus Kratochwill,[2] Claus Peter Schmitt.[1] International Pediatric Peritoneal Biobank. *[1]UniversitatsKlinikum Heidelberg, Heidelberg, Germany; [2]Medizinische Universitat Wien, Wien, Austria; [3]University Hospital Hamburg, Hamburg, Germany; [4]University Hospital Strasbourg, Strasbourg, France.*

Background: Patients on peritoneal dialysis (PD) suffer from accelerated vascular disease. Following kidney transplantation (KTx) vascular disease progresses, underlying molecular pathomechanisms are uncertain.

Methods: Omental arterioles microdissected from age-matched children (median 6,5y) with chronic kidney disease (CKD5), on PD with neutral pH, low-GDP-PD fluids, and from children 4-5 weeks after successful KTx and preceding PD (n=5-8/group) underwent multi-omics followed by gene set enrichment-, gene ontology and protein interaction analysis. Key pathways were validated in independent cohorts by quantitative immunohistochemistry (n=15/group) and *in vitro.*

Results: 5000 most variable arteriolar transcripts (p-value<0.05,|r| >0.5) were grouped into 23 modules, 8 significantly differed between CKD5, PD and KTx, one was PD-specific, seven were KTx-specific. PD-specific module was associated with muscle cell proliferation, detoxification, complement activation, with thrombospondin as hub gene. In independent cohorts, thrombospondin and terminal complement complex were higher in PD children vs. CKD5/KTx. KTx-specific modules related to fatty acid biosynthesis, negative regulation of RNA metabolism, cell cycle arrest, and apoptosis. Key drivers of fibrotic process in PD (TGF-ß/pSMAD2/3) persisted high after KTx, cell cycle arrest marker p16 and apoptosis marker cCasp3 were higher after KTx vs. PD/CKD5. Multi-omics demonstrated upregulation of lipid and fatty acid biosynthesis after KTx, with the hub gene fatty acid synthase (FASN). Intima and media FASN were three-fold higher after KTx vs. PD/CKD5, arteriolar triacylglycerols (TAG) two-fold higher in KTx vs. PD/CKD5. Arteriolar lipidomics revealed long chain TAG in all groups, short chain TAG were increased in KTx arterioles. *In vitro*, methylprednisolone and tacrolimus, but not mycophenolate increased FASN abundance and activity in human arterial endothelial and vascular smooth muscle cells.

Conclusions: Following KTx, PD-induced complement activation is reversed to CKD level, but profibrotic pathway activation persists and cell cycle arrest, apoptosis and fatty acid biosynthesis increase. Methylprednisolone and tacrolimus presumably activate hub gene FASN, and increase vascular short chain triacylglycerol content.

Funding: Government Support - Non-U.S.

FR-PO1007

Plasma-Derived Extracellular Vesicles of Antibody-Mediated Allograft Rejection Kidney Transplant Patients Mediate Reprogramming of Human Podocytes: Role of SGLT2 Inhibitors

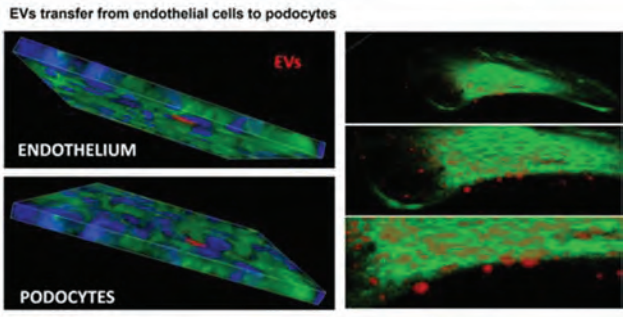
Giuseppe Castellano,[1,2] Silvia Armelloni,[1] Deborah Mattinzoli,[1] Min Li,[1] Masami Ikehata,[1] Valentina Bollati,[1,2] Matteo Abinti,[1] Manuel A. Podestà,[1] Carlo Alfieri.[1,2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Universita degli Studi di Milano, Milano, Italy.*

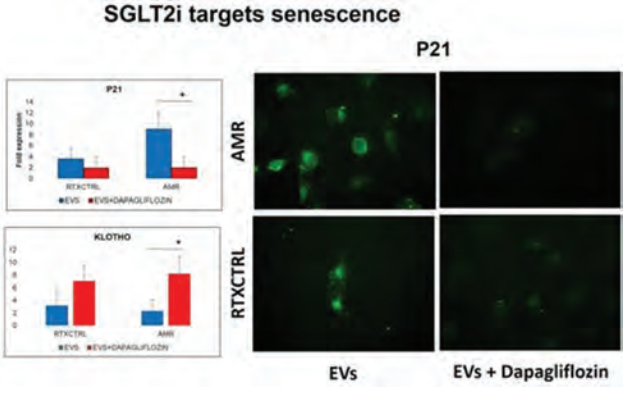
Background: Extracellular vesicles (EVs), cell-derived particles, contribute to kidney diseases. Their role in antibody-mediated allograft rejection (AMR) is unclear. We aim to test their impact on human immortalized podocytes (PODO) and evaluate Dapagliflozin (Dapa) role as a pharmacological approach.

Methods: The study involved 28 Rtx patients (14 with AMR, 14 stable CTRL). PODO were exposed to plasma-EVs for 24h, then 100nM Dapa for 24h. Ultracentrifugation at 110,000g was used, followed by Nanosight counting and flow cytometry per MISEV2018. PKH26-EVs were used to examine PODO incorporation via Z-stack microscopy. RNA and protein were extracted for analysis, and cells were fixed for immunostaining.

Results: PODO incorporated and shared EVs. AMR-EVs increased CD9, a cell activation marker (p=0.028), induced a senescence-associated secretory phenotype in PODO (MCP1 p=0.041, TNFalpha p=0,046), and raised cytoskeletal rearrangement. They also increased the expression of EMT proteins like VIM (p=0.026), senescence P21 (p=0.04), inflammation CD44 (p=0.034), and decreased Klotho (p=0.002) (fig.1). Dapa incubation reduced PODO activation, decreasing P21 expression (p=0.039) and increasing Klotho (p=0.047), thus abrogating inflammaging (fig.2).

Conclusions: Our findings demonstrate that plasma AMR-EVs induce PODO reprogramming processes, comprising senescence, cytoskeleton rearrangement, secretion of inflammatory cytokines, decrease of nephroprotective protein Klotho and senescence increase. Dapa can efficiently counteract this pathogenic process.





FR-PO1008

Delivery of Point-of-Care Adipose-Derived Regenerative Cell Population to Kidneys during Normothermic Machine Perfusion

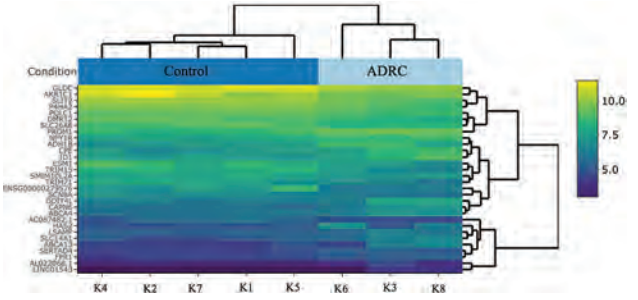
Robert Pearson,[1,2] William G. Norton,[1] Patrick B. Mark,[2] Marc J. Clancy.[1]
[1]Queen Elizabeth University Hospital, Glasgow, United Kingdom;
[2]University of Glasgow, Glasgow, United Kingdom.

Background: Normothermic machine perfusion (NMP) of kidneys provides a period of assessment prior to implantation with the potential benefit of improving organ utilisation. Furthermore, it provides an opportunity to deliver therapeutics without negotiating the systemic circulation. The immunoregulatory properties of adipose-derived regenerative cells (ADRC) have been shown in numerous organ systems, including the kidney, and can be readily extracted from adipose tissue without the need for culture expansion.

Methods: Eight declined human kidneys were randomised to four hours of blood-based NMP with (n=3) or without (n=5) the administration of ADRC. The ADRC population was extracted from 150ml of donor peri-renal adipose tissue using the approved Celution® 800/CRS System and delivered directly via the arterial limb of the perfusion circuit. Samples of urine, perfusate and graft biopsies were taken for subsequent analysis.

Results: ADRC harvest from peri-renal tissue had a cell viability of 78-85% with cell number of between 1.2 and 1.4 million. There were no adverse events, such as glomerular thrombus, with NMP + ADRC. There were no apparent differences between NMP + ADRC and NMP alone with regard to urine output, perfusion parameters or histological grading of acute tubular injury. RNA sequencing demonstrated 24 differentially expressed genes with NMP + ADRC. Gene ontology analysis revealed upregulated biological processes within the ADRC group including nephron tubule epithelial cell differentiation.

Conclusions: ADRC were successfully extracted from donor perirenal tissue and delivered at point-of-care without culture expansion to kidneys during NMP, with no apparent adverse haemodynamic effect nor adverse histological change. Although theoretically desirable differential gene expression was demonstrated, further studies incorporating implantation will be required to assess whether this appoach provides meaningful clinical benefit.



Heatmap of top 24 differentially expressed genes

FR-PO1009

Recurrence of Atypical Hemolytic Uremic Syndrome (HUS) after Kidney Transplantation in Patients with the Complement C3 p.Arg161Trp Variant

Lieke ter Steeg,[1] Romy N. Bouwmeester,[1] Caroline Duineveld,[2] Anne-Els van de Logt,[2] W.A.G. van der Meijden,[2] Lambertus P. Van den Heuvel,[1,3] Kioa L. Wijnsma,[1] Jack F. Wetzels,[2] Nicole Van De Kar.[1] *[1]Radboud University Medical Center, Amalia Children's Hospital, Radboud Institute for Molecular Life Sciences, Department of Pediatric Nephrology, Nijmegen, Netherlands; [2]Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Nephrology, Nijmegen, Netherlands; [3]University Hospitals Leuven, Department of Pediatrics/Pediatric Nephrology, Department of Development and Regeneration, Leuven, Belgium.*

Background: Graft loss due to disease recurrence is a major concern in kidney transplant (KTx) recipients with complement-mediated atypical hemolytic uremic syndrome (CaHUS). Gain-of-function mutations have been identified by KDIGO as a high risk factor for recurrent CaHUS. We describe a large cohort of transplant recipients with the common Dutch variant C3 p.Arg161Trp.

Methods: We retrospectively analyzed the outcome after first KTx in CaHUS patients with this variant. None of the patients received eculizumab prophylaxis, according to the Dutch guideline. Relapses were defined as restart of treatment (eculizumab or plasmapheresis) by treating physician.

Results: This study included 15 CaHUS patients with the C3 p.Arg161Trp variant. Median (range) time between first presentation of CaHUS and KTx was 6 (1-23) years, and median (range) follow up time after KTx was 6 (0-12) years. Treatment for suspected CaHUS recurrence was initiated in 5 (33%) patients. Median (range) time between KTx and recurrence was 10 (4-46) months. A trigger was identified in all patients with recurrence and included rejection (n=3) and infection (n=2). Two relapses, occurring at 4 and 10 months, were characterized by acute kidney disease and systemic thrombotic microangiopathy (TMA). Notably, one relapse, occurring after 4 years, presented only with slow eGFR loss and signs of chronic TMA in kidney biopsy. Laboratory data was missing for two relapses. Recurrence was treated with eculizumab (n=2) or plasmapheresis (n=3). Graft loss occurred in two patients, both treated with plasmapheresis. In patients treated with eculizumab, kidney function improved to baseline or stabilized. One patient experienced two more relapses, after eculizumab discontinuation, in subsequent years without graft loss.

Conclusions: CaHUS patients with the C3 p.Arg161Trp variant show low risk of early recurrence after kidney transplantation. Post-transplant recurrence may present solely with gradual loss of kidney function.

FR-PO1010

Impact of Mannose-Binding Lectin (MBL) on Graft Survival in Transplant Recipients with IgAN

E. D. Stea, Ighli di Bari, Tommaso M. Marvulli, Rossana Franzin, Adele Mitrotti, Simona Simone, Paola Pontrelli, Loreto Gesualdo. *Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), Nephrology and Urology Units, University of Bari Aldo Moro, Bari, Italy.*

Background: The progression of IgAN has been linked to functional defects and serum levels of MBL. Specific SNPs in the promoter and exon1 of the MBL2 gene are associated with these qualitative/quantitative deficiencies. Given that deregulation of the lectin pathway may impact IgAN progression in native kidneys, we evaluated whether MBL2 SNPs and MBL levels affect graft survival in kidney transplant recipients with IgAN.

Methods: We enrolled 60 kidney transplant patients diagnosed with IgAN in the native kidney. The MBL2 variants (promoter: L/H, Y/X, P/Q alleles and exon1: A/O allele) were analyzed by Sanger sequencing.MBL levels were measured using

ELISA kit. Clinical data at baseline and during the follow-up were collected. An eGFR <60mL/min/1.73m2 (CKD-EPI) was considered the primary outcome in univariate and multivariate analyses.

Results: No significant impact of MBL2 genotype and serum levels on demographic features, donor variables, transplant-related variables, recurrence, and DGF was found. However, patients with the "O" allele exhibited higher creatinine values at the time of graft biopsy and lower MBL serum levels (P<0.001). The "L" and "Y" alleles were linked to faster disease progression in native kidneys but not during transplantation. Notably, patients with low MBL levels had worse graft outcome (P = 0.0023) over an average follow-up of 151 months.

Conclusions: Low MBL levels are associated with graft dysfunction in kidney transplant recipients with IgAN. This finding highlights the importance of monitoring MBL levels as a potential marker for graft prognosis in these patients.

Funding: Clinical Revenue Support

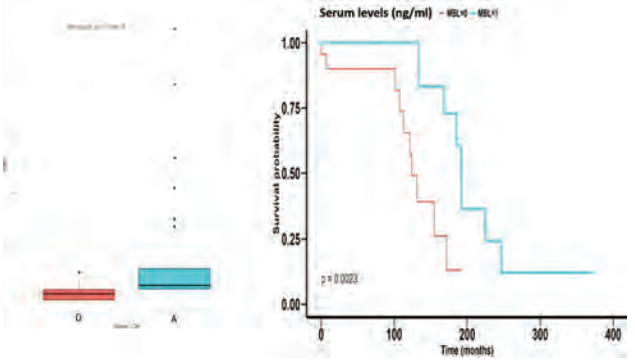


Table 1.

Allele A/O			
Characteristic	**Mut, N = 24[1]**	**Wt, N = 36[1]**	**p-value[2]**
Sieric MBL	122.68 (10.35, 198.20)	279.98 (211.93, 588.91)	**<0.001**
sCr at PRB	2.04 (1.54, 2.84)	1.53 (1.22, 2.11)	0.074
Allele X/Y			
Characteristic	**Mut, N = 18[1]**	**Wt, N = 42[1]**	**p-value[2]**
Time PRB to HD (years)	3.00 (1.00, 7.00)	8.00 (3.00, 16.25)	**0.022**
Allele H/L			
Characteristic	**Mut, N = 46[1]**	**Wt, N = 14[1]**	**p-value[2]**
Time PRB to HD (years)	5.00 (1.25, 10.00)	13.00 (8.00, 19.00)	**0.009**

[1]Median (IQR)

[2]Wilcoxon rank sum test

FR-PO1011

Immune Cells in Compensatory Kidney Hypertrophy after Unilateral Nephrectomy

Qisen Guo, Mahta F. Gooya, Shishir K. Patel, Hyun Jun Jung, Sanjeev Noel, Hamid Rabb. *Johns Hopkins Medicine, Baltimore, MD.*

Background: The mechanisms of compensatory renal hypertrophy (CRH) following unilateral nephrectomy (UNx) are incompletely understood. We hypothesized that immune cells are involved in the compensatory increase in kidney size and function.

Methods: C57BL/6J mice underwent left kidney UNx. GFR was measured by transdermal FITC-sinistrin clearance. Kidney mononuclear cells were harvested from the remnant kidney and immunophenotyped via flow cytometry. Single-cell RNA sequencing (scRNA-seq) was performed on CD45+ cells post-UNx to capture gene expression changes. Adaptive immunity in CRH was evaluated using *Rag1*$^{-/-}$ mice lacking T and B cells.

Results: Kidney to-body weight ratio (KW:BW) for the remnant kidney increased at 24hr (5.5±0.2 mg/g baseline vs 6.7±0.1 mg/g 24hr; *P*<0.001) and 8wk (8.1±0.3 mg/g) while GFR fell at 4hr (47.6±6.5% average WT baseline; *P*<0.001) then rose at 24hr (73.5±4.4% vs 4hr; *P*<0.01) and stabilized throughout the 8wk period. Flow cytometry showed that, compared to baseline (56.7±2.2% CD4; 31.2±1.9% CD8; 11.8±0.8% CD4-CD8-), CD4 T cells increased at 4hr (67.5%; *P*<0.01) and 8wk (65.7±1.3%; *P*<0.05), CD8 T cells decreased at 4hr (15.8±3.5%; *P*<0.001) and 72hr (13.2±1.5%; *P*<0.001), and CD4-CD8- double negative T cells rose at 72hr (31.2±2.7%; *P*<0.001). PD1+CD4 T cells were elevated at 4wk (31.5±2.1%) compared to 1wk (14.8±1.3%; *P*<0.05) and 8wk (16.0±1.7%; *P*<0.05). TIGIT+CD8 T cells rose at 4hr compared to baseline (3.2±1.3% vs 1.0±0.2%; *P*<0.05). scRNA-seq showed changes in B cells (16.7% control, 22.6% 24hr, 16.0% 1wk, 20.5% 4wk), neutrophils (1.5% control, 10.8% 24hr, 5.8% 1wk, 2.6% 4wk), and NK cells (6.5% control, 8.5% 24hr, 12.6% 1wk, 12.9% 4wk). *Rag1*$^{-/-}$ GFR was increased compared to WT at 4hr (68.9±4.4% average *Rag1*$^{-/-}$ baseline; *P*≤0.05), 1wk (90.0±4.3%; *P*<0.01), and 4wk (93.3±3.9%; *P*<0.05). KW:BW at 4wk and 8wk were similar for WT vs *Rag1*$^{-/-}$.

Conclusions: Immune cells in the remnant kidney quantitatively and phenotypically change after UNx, seen in flow cytometry and scRNAseq. T and B cell deficiency led to increased GFR at select time points after UNx. Immune cells may participate in the compensatory GFR increase after UNx with implications for kidney donors, transplant recipients, recovery from AKI, and CKD progression.

Funding: NIDDK Support

FR-PO1012

Deep-Learning Based Pathological Assessment in Frozen Procurement Kidney Wedge Biopsies: An Independent Validation Study

Zhengzi Yi, Weijia Zhang. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: In order to minimize observer variability and avoid inappropriate discard pre-transplant, a deep-learning based pathological assessment pipeline in frozen procurement kidney needle biopsies has been developed and was shown to be able to accurately capture normal/sclerotic glomeruli, arteries/arterial intimal fibrosis regions and tubules. A composite Kidney Donor Quality Score (KDQS) was derived and used in combination with clinical factors to predict graft loss or assist organ utilization. However the performances of pipeline and graft loss model in frequently performed wedge biopsies were not thoroughly investigated.

Methods: We processed an independent cohort of procurement kidney wedge biopsies (n=786) which were mostly transplanted in 2019-2021 and were provided by Gift of Hope OPO center. Clinical data were obtained from OPTN under institutional IRB approval. Glomerulosclerosis grade was the only available pathologists' score and was used to correlate with digital feature Sclerotic Glomeruli%. Performance of pre-trained 1-year graft loss model using KDQS and clinical factors: cold ischemic time (CIT), use of pump and induction therapy was also evaluated.

Results: The digital feature Sclerotic Glomeruli% was strongly correlated with pathologists' glomerulosclerosis grade (R=0.63, *p*=1.8e-62). Sclerotic Glomeruli% (6m: *p*=9.6e-07, 12m: *p*=4.4e-07), Arterial Intimal Fibrosis% (6m: *p*=0.003, 12m: *p*=4.8e-05), and Interstitial Space Abnormality% (6m: *p*=0.003, 12m: *p*=0.016) were all significantly correlated with post-transplant eGFR. The KDQS was significantly associated with graft loss (*p*=5.4e-04, HR=1.39). Both individual and composite digital features were superior to the pathologists' glomerulosclerosis grade in association with graft outcomes. By applying the pre-trained 1-year graft loss model to wedge biopsy cohort using KDQS and clinical factors, we obtained an AUC of 0.67, which surpassed the model performance using clinical factors (AUC=0.53) or KDPI (AUC=0.57) alone. KDQS>=7 identified 5 kidneys could have been discarded within which 1 patient lost graft at day 122, 3 patient had 12m eGFR<=32, the rest patient had moderate eGFR (47) at 6m.

Conclusions: This study further validated the previously trained needle biopsy based method in wedge biopsies, therefore expended the utility of our deep-learning pipeline in clinical practice.

Funding: Private Foundation Support

FR-PO1013

Inflammatory Status in Deceased Kidney Donors Led by Impaired Mitochondrial Metabolism through the HIF1α Hypoxia Pathway

Elena Guillen-Gomez,[1] Jordi Vilardell,[1] Yolanda Arce,[1] Irene Silva,[1] Sonia Fernandez-Veledo,[2] Carme Facundo,[1] Beatriz Bardaji de Quixano,[1] Montserrat M. Diaz Encarnacion.[1] Group of Renal Inflammatory Diseases (GERI). [1]*Fundacio Puigvert, Barcelona, Spain;* [2]*Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain.*

Background: The type of kidney donor determines prognosis of recipient's renal function, being worst in deceased donors' (DD) grafts than in living donors' (LD). This is due to the pre-implantation inflammation status and development of fibrotic processes in DD, related to hypoxia status, where even the cause of death can make a difference. Mitochondrial succinate dehydrogenase (SDH) complex is associated to inflammatory markers and macrophages. Succinate plays a key role in inflammatory processes. HIF-1α is a transcription factor regulated by succinate and hypoxia, setting a link between cellular energy metabolism, oxygen levels and response to stress situations. The aim of this study is to determine whether hypoxia processes through HIF-1α can increase renal succinate and induce infiltration of inflammatory cells in DD.

Methods: Expression of 159 genes was analyzed from pre-implantation kidney biopsies of 47 kidney DD and 19 LD to determine effect of hypoxia on kidney inflammation/fibrosis. Genes with strong positive correlation with HIF1α were grouped in functional clusters. Serum succinate levels were measured in 27 brain-death DD (BD-DD) and 10 healthy volunteers (HV) (comparable to LD). Levels of 18 monocyte/macrophage cytokines stimulating pro-inflammatory (M1) or restorative (M2) macrophages were determined in serum of BD-DD and HV, and the expression of characteristic cell markers in circulating monocytes extracts of these subjects.

Results: DD exhibited higher serum succinate levels while showing lower renal mRNA of SDH subunits ($p<0.001$) vs LD. DD grafts showed significantly increased levels of HIF-1α ($p<0.001$), suggesting enhanced hypoxia status. 24 (out of 159) genes were found only in DD samples, all showing a strong correlation with HIF-1α in DD (Rho > 0.5). Both cytokines involved in monocyte recruitment and adhesion and serum levels of pro-inflammatory IL-6 were higher in BD-DD vs HV. Anti-inflammatory M2 proteins were significantly increased in DD monocyte protein extracts.

Conclusions: Pre-implantation inflammation assessment in DD kidneys and monitoring of circulating monocytes in transplanted patients may contribute to determine renal prognosis and improve transplantation outcome.

Funding: Private Foundation Support

FR-PO1014

Mechanism of Impaired Protein Homeostasis in Kidney Grafts following Cold Storage and Transplant

Seongok Lee, Nirmala Parajuli. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Cold ischemia is an unavoidable event during the cold storage (CS) process of donor kidneys before transplantation. We have previously reported that CS impaired protein homeostasis in transplanted rat kidneys and reduced graft function. However, the mechanisms of how CS contributes to graft damage are largely unknown.

Methods: Isolated donor rat kidneys were stored in a University of Wisconsin (UW) solution at 4°C for 0 or 18 hours, followed by transplantation to recipient rats (CS+Tx). To simulate an in vitro model of CS+Tx, rat or human proximal tubular cells (PTCs) were incubated in UW solution at 4°C for CS, followed by rewarming (RW) with normal media at 37°C (CS+RW).

Results: Two members of 70-KDa heat shock proteins (HSPs) were dysregulated—a robust increase of Hsp72 and a decrease of Hsc70—in kidney grafts after CS+Tx. CS+Tx decreased HSF1, a stress-activated transcription factor that induces HSPs, along with its band shift in western blot, suggesting that the CS injury contributes to a post-translational modification of HSF1 in rat kidneys. To further elucidate the CS-mediated changes of these proteins in PTCs, renal cells were exposed to CS+RW. Consistent with in vivo data, CS alone increased HSF1 in PTCs, and rewarming episode increased Hsp72 and decreased Hsc70 and HSF1 proteins in a time-dependent manner. To assess protein localization during CS+RW, we performed immunocytochemistry (ICC), which revealed a dense staining pattern of HSF1, Hsp72, and Hsc70 proteins after CS+RW. Unlike western blot data, Hsc70 or HSF1 levels remained unchanged after ICC, suggesting that CS+RW induces aggregation of Hsc70 or HSF1 in PTCs. Adding HS-72, a specific inhibitor of Hsp72, to the CS solution partially restored Hsc70 levels, reduced aggregation of Hsp72, increased HSF1 level, and improved cell viability after rewarming in PTCs. Finally, the addition of HS-72 during CS improved graft function after CS+Tx.

Conclusions: These data indicate that the CS-mediated increase of Hsp72 protein is a negative regulator of kidney function. Inhibiting Hsp72 during CS improves PTCs health and graft function and therefore HS-72 could be a potential therapeutic during CS to improve outcomes after kidney transplantation.

Funding: NIDDK Support

FR-PO1015

Cold Storage-Mediated Activation of P38MAPK-MK2 Axis Induces Kidney Injury after Transplantation

Dinesh Bhattarai, Nirmala Parajuli. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Most donor kidneys undergo cold storage (CS) before transplantation (Tx), but this often results in suboptimal outcomes because CS activates cellular pathways that damage kidney tissue. Previously we showed that normal proteasome function is needed to maintain kidney function and CS followed by transplantation (CS+Tx) reduces proteasome function and increases inflammation in rat renal grafts; however, the mechanisms behind the CS-mediated proteaome dysfunction and inflammation remain unclear.

Methods: In vivo rat kidney CS followed by transplantation (CS+Tx) and in vitro rat renal cell CS followed by rewarming (CS+RW) models were used. Proteasome function was assessed using renal cell extract and fluorescent-based peptide substrates. Protein levels were evaluated using renal extracts and western blotting analysis.

Results: CS increased phosphorylation of P38MAPK in rat renal cells in a time-dependent manner, suggesting activation of P38MAPK pathway. Inhibiting P38MAPK with a selective inhibitor, VX-745, during CS followed by rewarming restored the proteasome activity and mitigated cell injury in rat renal cells, suggesting that P38MAPK negatively regulates proteasome function in renal cells during CS+RW. We evaluated MK2, a downstream signaling molecule of P38MAPK activation that promotes inflammation in eukaryotic cells. We observed that CS+RW increased MK2 activation in rat renal cells. Finally, inhibiting P38MAPK with VX-745 during CS reduced activation of MK2 in renal cells following rewarming, suggesting that the p38PMAK could be a critical regulator of CS-mediated inflammation via MK2 pathway.

Conclusions: Our data indicate that the P38MAPK is a contributor of CS-mediated proteasome dysfunction and renal injury. Similarly, P38MAPK-MK2 axis may promote inflammation in renal cells during CS+Tx and this pathway may serve as a new therapeutic target to improve the outcomes of kidney transplantation and potential clinical applications during organ transplant.

Funding: NIDDK Support

FR-PO1016

Cold Storage Exacerbates Complement Pathway Activation in Kidneys following Transplantation

Madison K. Mcgraw, Nirmala Parajuli. *University of Arkansas for Medical Sciences College of Medicine, Little Rock, AR.*

Background: Cold storage (CS) of kidneys is a vital process that enables the transport of kidneys sourced from deceased organ donors to the desired recipient. Our lab previously reported that the complement system (C3 and C5b-9) is activated in kidneys after CS combined with kidney transplantation (CS+Tx). Here, we have chosen to focus on the C5 component upstream of C5b-9, as it is a clinically relevant therapeutic target in organ transplants. It is published that reactive oxygen species (ROS) increases localization of C5aR1, a receptor for the cleaved C5 protein C5a, to mitochondrial membranes contributing to the dysfunction of oxidative phosphorylation. Interrogating oxidative stress caused by Tx and the involvement of the C5a/C5aR1 axis is vital.

Methods: Lewis rat kidneys were removed from the donor rat, flushed, and placed in University of Wisconsin (UW) or CS solution at 4°C. After 18 hours of CS exposure, the left kidney was transplanted into a recipient rat for 1 post-operative day of reperfusion. Autotransplant (transplant with no CS) and Sham surgeries were used as controls. The proteome of rat kidney homogenates was analyzed using tandem mass-tag (TMT) mass spectrometry. C5 and C5aR1 were further characterized via SDS-PAGE western blotting and immunohistochemistry (IHC).

Results: In the TMT dataset, 5,951 individual proteins were identified in all animal groups. Pathway analysis revealed significant complement dysregulation, and 34 complement proteins were differentially abundant in CS+Tx compared to ATx, suggesting that CS intensifies complement activation. The level of C5 protein was increased after CS+Tx in rat kidneys. Intriguingly, C5 was increased in isolated mitochondria fractions, and this increase correlated with mitochondrial injury. C5aR1 predominantly localizes in the renal medulla and distal tubules in Sham and ATx, but displays diffusely positive staining in the cortex after CS+Tx.

Conclusions: We have identified significant dysregulation of the complement pathway during CS+Tx. Increased C5 in the mitochondrial fraction after CS+Tx suggests the involvement of the C5a/C5aR1 axis. Future studies will clarify the role of C5a/C5aR1 in the mitochondria during CS+Tx.

Funding: NIDDK Support, Private Foundation Support

FR-PO1017

Isolation of Extracellular Vesicles and Associated Biomarkers from Organ Preservation Fluid in Kidney Transplantation

Leonie Kubitza,[1] Tobias Tertel,[2] Moritz Kaths,[3] Johannes Jaegers,[1] Bernd Giebel,[2] Lars Pape,[1] Marvin Droste,[4] Anja K. Büscher.[1] *[1]Universitatsklinikum Essen Klinik fur Kinderheilkunde II, Essen, Germany; [2]Universitatsklinikum Essen Institut fur Transfusionsmedizin, Essen, Germany; [3]Universitatsklinikum Essen, Essen, Germany; [4]Universitatsklinikum Dusseldorf, Dusseldorf, Germany.*

Background: Donor kidneys are in short supply and many potentially preventable complications lead to loss of organ function. Biomarkers may help to detect these at an early stage. Analyzing extracellular vesicles (EVs) from organ perfusate could be a non-invasive way to obtain information about the donor organ prior to transplantation. Since there is no standardized method to isolate EVs from organ perfusate yet, we compared several common purification methods. Finally, to the best of our knowledge, we demonstrate the first in-depth proteomic analysis of perfusate-derived EVs.

Methods: Purification of EVs from kidney allograft perfusate was performed by ultrafiltration (UF), precipitation (PEG), size exclusion chromatography (SEC), and ultracentrifugation (UC), respectively, as well as a combination of these. Following purification, EVs were detected by electron microscopy, immunocapturing-based flow cytometry and nanoscale imaging flow cytometry. Particle-to-protein ratios were calculated to determine sample purity. EV protein composition was analyzed by mass spectrometry and bioinformatic analysis of the EV proteome.

Results: Electron micrographs demonstrated the successful purification of EVs. Microbead-based immunoprecipitation indicated the presence of the vesicular tetraspanins CD9, CD63 CD81 and of CD235a and semi-quantitative multiplex analysis the composition of the EV fraction of several subtypes. Imaging Flow Cytometry and nanoparticle tracking revealed that UC purified more EV marker-carrying nanoscale objects and bulk nanoparticles than the combinations UF-SEC and PEG-SEC, however, accepting a lower grade of purity. Impurity induced by hemolysis was associated with an increased ratio of CD63+/CD235a+-EVs. Proteomic analysis revealed that the preparations were highly enriched for vesicular proteins.

Conclusions: For the first time, we tested different EV purification methods for organ preservation fluid. Depending on the aim of research, the applied methods can be used according to their advantages to isolate EVs from organ perfusate. In addition, we have generated a proteome dataset from perfusate-derived EVs that can serve as a reference for further studies, for example in biomarker analyses.

Funding: Private Foundation Support

FR-PO1018

Alginate Microencapsulation Enhances Islet Function by Protecting against IL-1β

Dahlia A. Abdulsattar, Sophia H. Roberts, Shahab Hafezi, John Cashin, Dina Ibrahim, Batool Arif, Maria S. Remedi, Tarek Alhamad, Yiing Lin, Mohamed A. Zayed. Zayed Lab. *Washington University in St Louis School of Medicine, St Louis, MO.*

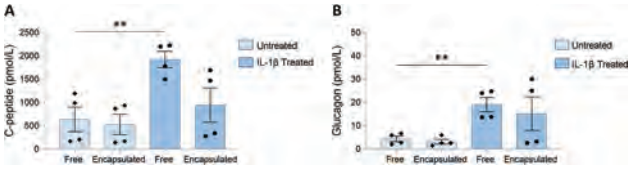
Background: Islet transplantation is a potential therapeutic avenue for type 1 diabetes mellitus. However, the lack of an effective vehicle for transplantation poses a challenge in sustaining long-term islet viability and shielding from immune rejection *in vivo*. Alginate encapsulation can be a promising strategy to optimize the microenvironment of transplanted cells. The most utilized form is sodium alginate for its natural biocompatibility. We hypothesize encapsulation of islets within alginate can enhance their viability and protect against detrimental effects of Interleukin-1 beta (IL-1β), a pro-inflammatory cytokine known to impair islet viability and function.

Methods: Pancreatic islets were purchased from Prodo Laboratories, Inc. (Aliso Viejo, CA). Islets were encapsulated in alginate utilizing a custom 3D-printed droplet generator and cured with barium chloride (10 mM BaCl). Microencapsulated islets were cultured in PRODO media supplemented with IL-1β (50 pmol/L). After 48 hours, viability was assessed utilizing Calcein AM and Ethidium homodimer-1 staining. Furthermore, islet function was evaluated using Glucose Stimulated Insulin Secretion (GSIS). ELISA was used to detect c-peptide production and glucagon release and islet viability was quantified using ImageJ.

Results: Non-encapsulated islets demonstrated a significant increase in c-peptide production in the presence of IL-1β ($p < 0.01$; Figure 1A). On the other hand, microencapsulated islets demonstrated an increase in c-peptide production. A similar response was observed with glucagon release for non-encapsulated ($p < 0.01$; Figure 1B) and microencapsulated islets treated with IL-1β. There was no significant change in viability for encapsulated and non-encapsulated islets exposed to IL-1β.

Conclusions: Encapsulation of pancreatic islets appears to protect islets from pro-inflammatory stress, thereby preserving their functionality. This microencapsulation holds potential for enhancing islet transplantation and longevity of islets *in vivo*. While encapsulated islets exhibit comparable viability to non-encapsulated islets, their function is improved when treated with IL-1 β.

Funding: Private Foundation Support



FR-PO1019

Association of Long-Term Exposure to Air Pollution with Population-Level Rates of Incident ESKD in the United States

Kirsten L. Johansen,[1,2] Jiannong Liu,[1] Paul E. Drawz,[2] James B. Wetmore,[1] David T. Gilbertson,[1] Nicholas S. Roetker,[1] Eric D. Weinhandl,[3,1] Jesse D. Berman.[4] *[1]Hennepin Healthcare Research Institute Chronic Disease Research Group, Minneapolis, MN; [2]University of Minnesota Twin Cities, Minneapolis, MN; [3]Davita Clinical Research, Minneapolis, MN; [4]University of Minnesota Twin Cities School of Public Health, Minneapolis, MN.*

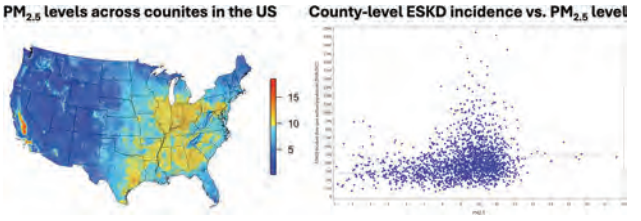
Background: Patient-level analyses suggest that long-term exposure to air pollution is associated with higher risk of incident end-stage kidney disease (ESKD). We sought to examine the extent to which geographic variations in the rate of incident end-stage kidney disease (ESKD) are correlated with long-term exposure to air pollution.

Methods: We used air pollution models from NASA's Socioeconomic Data and Applications Center to estimate long-term exposure to fine particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) at the county level. We calculated the 10-year average $PM_{2.5}$ concentration from 2007-2016 and assigned each county the value derived from the county's population-weighted centroid based on the 2010 US Census. We used data from the US Renal Data System to calculate county-level rates of incident ESKD in 2018-2022 based on population estimates from the 2020 Census. We mapped $PM_{2.5}$ concentration and examined the association between $PM_{2.5}$ concentration and the subsequent incidence of ESKD among counties with ≥15,000 residents (excluding 3.4% of the population residing in counties too small to generate stable ESKD incidence).

Results: There was wide variation in exposure to $PM_{2.5}$ with large areas in the Midwest and Southeast having levels ≥10 μg/m^3 (left panel of Fig). There was also considerable variation in incident ESKD rates, from 64 to 16,789 per million population. $PM_{2.5}$ concentration was significantly correlated with incident ESKD rate (Spearman correlation =0.26; right panel of Fig).

Conclusions: Long-term exposure to air pollution was associated with rates of incident ESKD at the population level. Further analysis is needed to examine whether this association may partially explain racial/ethnic and socioeconomic disparities in rates of incident ESKD.

Funding: NIDDK Support



FR-PO1020

Relationship between Exposure to the Natural Environment and Psychological Well-Being in People Living with CKD

Gurneet K. Sohansoha, Eleanor M. Taylor, Courtney J. Lightfoot, Ella C. Ford, Roseanne E. Billany, Noelle Robertson, Alice C. Smith. *University of Leicester, Leicester, United Kingdom.*

Background: The natural world is beneficial to human health and wellbeing. People with CKD often experience psychological distress which can result in poor health outcomes. We explored the association between exposure to the natural environment and psychological wellbeing in CKD.

Methods: 319 participants across CKD stages (188 non-dialysis, 70 kidney transplant recipients, 40 haemodialysis and 21 peritoneal dialysis) from 9 UK NHS hospitals completed an online survey comprising the Distress, Anxiety, Stress Scale (DASS-21), 12-Item Short Form Health Survey (SF-12) and bespoke questions relating to access to and time spent in the natural environment. Data were analysed using frequency analysis, multiple linear regression, and logistic regression.

Results: Access to and time spent in the natural environment was similar for the different CKD groups. In the summer, 45% of participants spent more than an hour a day, at least five days a week, in the natural environment, whilst in the winter, this was only 19% of participants. Increased exposure to the natural environment was significantly associated with lower levels of depression (p<0.001), anxiety (P=0.002), and stress (p=0.029), and higher levels of mental health-related quality of life (HRQoL) (P<0.001). Participants reporting greater exposure to the natural environment were less likely to report experiencing stress (OR: 11.118, P=0.002) or depression (OR: 4.109, P<0.001).

Conclusions: Greater exposure to the natural environment is associated with better psychological wellbeing and mental HRQoL in people with CKD, suggesting the value of the natural world. Healthcare professionals should support people with CKD to access and engage with the natural environment. This data could inform the development of nature-based interventions for people with CKD to improve HRQoL.

FR-PO1021

Developing City-Level Nephrology Indicators Using Open Data

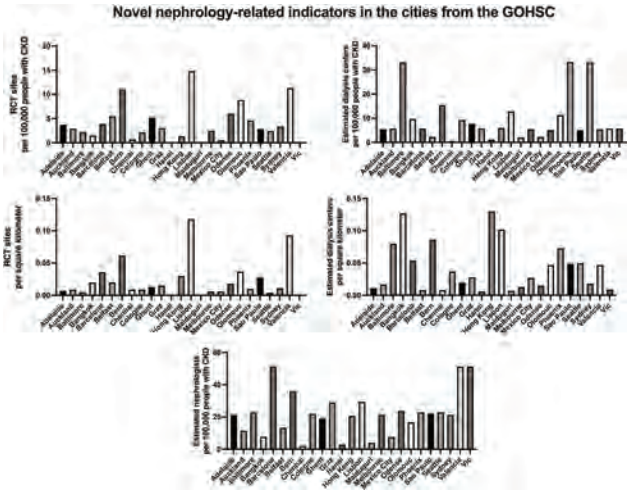
Gabriel Cojuc,[1,2] Alan Braverman-Poyastro,[4] Alejandra De Las Fuentes,[5] Andrea Mizrahi Drijanski,[4] Briana Rodriguez-Paniagua,[3] Alberto Nordmann-Gomes,[1] Alberto Moscona-Nissan,[3] Alberto Guijosa,[3] Vianca A. Canaviri,[6] Denisse N. Tinajero Sánchez,[1] Bhavna Chopra,[2] Ricardo Correa-Rotter,[1] Juan Carlos Ramirez-Sandoval.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]Universidad Panamericana, Ciudad de Mexico, Mexico; [4]Red de Universidades Anahuac, Naucalpan de Juarez, Mexico; [5]Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico; [6]Hospital Obrero No 1, La Paz, Bolivia, Plurinational State of.*

Background: Sustainable Development Goal 11—sustainable cities and communities— holds the potential to improve kidney health by enhancing access to CKD care. Most nephrology indicators overlook local heterogeneity. We aimed to develop novel city-level nephrology indicators.

Methods: We obtained data from open sources (Global Burden of Disease, WHO, ISN-GKHA, Global Observatory of Healthy and Sustainable Cities [GOHSC]) and from our systematic review of pharmacologic CKD randomized controlled trials (RCTs). We selected 214 RCTs with GOHSC participant cities. We calculated the following indicators: CKD-prevalence-adjusted (per 100,000 with CKD) RCT sites [95% CI], nephrologists, and dialysis centers; RCT sites and dialysis centers per km^2, RCTs/nephrologist, and CKD stage 5 RCTs per dialysis center.

Results: Among GOHSC, Lisbon had the highest number of CKD-prevalence-adjusted RCT sites (14.8 [13.7-16.1]), and Mexico City had the lowest (0.5 [0.5-0.6]). Spanish cities had the highest prevalence-adjusted nephrologists, and United States cities had the highest prevalence-adjusted dialysis centers (51.3 [47.7-55.4] and 33.21 [31.2-35.6], respectively), while Chennai had the lowest (2.1 [2.0-2.3] and 0.6 [0.6-0.6], respectively). Lisbon had the most RCT sites/km^2 (0.1), Seattle had the fewest (0.004). Hong Kong had the highest dialysis centers/km^2 (0.1), and Hanoi had the lowest (0.006). Odense had the highest RCTs/nephrologist (2.8) and stage 5 CKD RCTs per dialysis center (8.3), and Cologne and Baltimore had the lowest (0.1 and 0.03, respectively).

Conclusions: City-level, standardized nephrology indicators should be developed for policymaking and benchmarking. We provided an initial comprehensive model for further global elaboration.



FR-PO1022

Barriers to Participation in CKD Clinical Trials: A 25-City Analysis

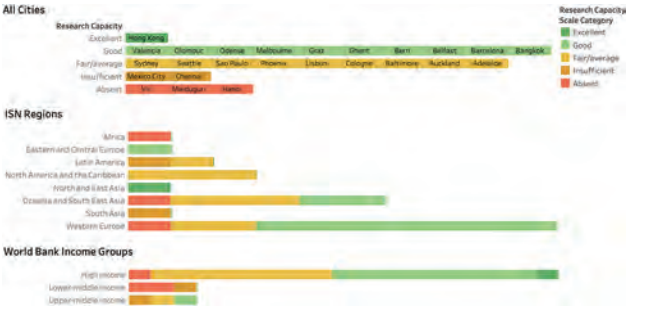
Gabriel Cojuc,[1,2] Alan Braverman-Poyastro,[4] Alejandra De Las Fuentes,[5] Briana Rodriguez-Paniagua,[3] Andrea Mizrahi Drijanski,[4] Alberto Nordmann-Gomes,[1,3] Alberto Moscona-Nissan,[3] Alberto Guijosa,[3] Denisse N. Tinajero Sánchez,[1] Vianca A. Canaviri,[1,6] Bhavna Chopra,[2] Ricardo Correa-Rotter,[1] Juan Carlos Ramirez-Sandoval.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]Universidad Panamericana, Ciudad de Mexico, Mexico; [4]Red de Universidades Anahuac, Naucalpan de Juarez, Mexico; [5]Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico; [6]Hospital Obrero No 1, La Paz, Bolivia, Plurinational State of.*

Background: Access to healthcare among those with limited resources, alongside several other factors, may influence participation in randomized controlled trials (RCTs). We aimed to identify barriers to CKD RCT participation in the cities from the Global Observatory of Healthy and Sustainable Cities (GOHSC).

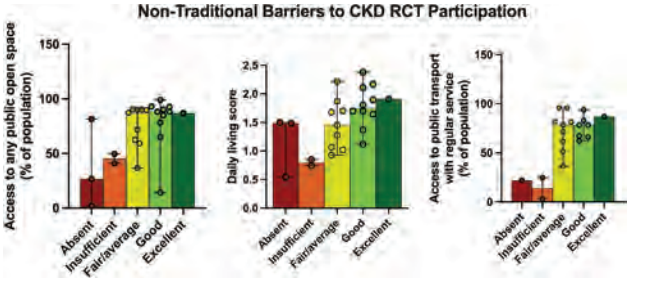
Methods: Cross-sectional study of 214 pharmacologic CKD RCTs published between 2003-2023 and including participants from 146 GOHSC research sites. We obtained indicators from WHO, GOHSC, ISN-GKHA, and GBD. We developed a three-point *CKD research capacity scale* with six variables (population-weighted RCTs, sites/km^2, funding, site span, facility type, RCTs/site). We classified *research capacity* as absent (0-1 points), insufficient (2-4), fair (6-7), good (7-8), or excellent (9-10) and compared financial, urban, and healthcare variables across categories.

Results: Odense had the highest population-weighted RCTs (7.01 RCTs/100,000 population), and Mexico City had the lowest (0.06). Compared with cities with absent or insufficient *research capacity*, those with good or excellent *research capacity,* had higher health expenditures, more nephrologists, public CKD care coverage, and dialysis centers. We identified non-traditional barriers to CKD RCT participation. Daily living score, access to public transport, open space, and a fresh food market were higher in cities with better *research capacity.*

Conclusions: Urban, financial, and healthcare barriers may affect RCT participation in the GOHSC. International initiatives should address local disparities in CKD research capacity.



Research capacity scale results



FR-PO1023

Does Clinical Utility of the Kidney Failure Risk Equation in Routine Clinical Practice Vary by Socioeconomic Status?

Heather Walker,[1] Shabana Khan,[1] Bhautesh D. Jani,[1] Katie I. Gallacher,[1] Patrick B. Mark,[1,2] Michael K. Sullivan.[1,2] *[1]University of Glasgow College of Medical Veterinary and Life Sciences, Glasgow, United Kingdom; [2]Queen Elizabeth University Hospital, Glasgow, United Kingdom.*

Background: Risk prediction models such as the kidney failure risk equation (KFRE) have been recommended to identify patients at heightened risk of kidney failure requiring treatment (KFRT). Incorporating KFRE into clinical practice may be limited by rates of albuminuria testing. We used routine healthcare data to ascertain albuminuria testing rates in CKD by sub-groups including socio-economic deprivation, age or sex.

Methods: We used routine healthcare data for all adults in NHS Greater Glasgow, UK (population approximately 1.5mill). Two cohorts and analyses were performed. Analysis 1 cohort: CKD G3-5 (eGFR<60mL/min/1.73m^2 for >90 days without KFRT). Analysis 2 cohort: as per cohort 1 with albuminuria values within 6 months of meeting CKD diagnostic criteria. Analysis 1 used logistic regression models to quantify associations between predictor variables and albuminuria testing. Analysis 2 assessed the predictive performance of KFRE.

Results: Cohort 1 included 10,874 adults. Albuminuria testing was missing in 55.5% of people. Individuals most likely to have albuminuria testing were those aged 40-50 years (adjusted odds ratio (aOR) 1.83 (95% confidence interval (CI) 1.15-2.91), p=0.01) and those living in the least socioeconomically deprived areas (aOR 1.11 (95% CI 1.00-1.23), p=0.01). Individuals least likely to have albuminuria testing were females (aOR 0.86 (95% CI 0.79-0.93), p<0.001), those with hypertension (aOR 0.69 (95% CI 0.63-0.77), p<0.001) and those without a diagnosis of diabetes (aOR 0.43 (95% CI 0.39-0.47), p<0.001). Cohort 2 included 4,902 adults, median eGFR 51.5 ml/min/1.73m^2. The highest albuminuria and KFRE risk values were identified in males, those aged 40-50 years old, people with a diagnosis of diabetes and individuals living in the most socio-economically deprived areas. KFRE model performance at five years was good but with over prediction at higher KFRE predicted risk groups (AUC 0.82).

Conclusions: KFRE performed well in this large observational population-based study using routinely collected data. KFRE could only be calculated for less than half of adults with CKD due to low rates of albuminuria testing, particularly for females, those without diabetes and those living in the most deprived areas.

Funding: Private Foundation Support

FR-PO1024

Redefining Strategies for Kidney Disease Screening in Low-Resource Settings

Sanjib K. Sharma,[1] Ujwal Gautam,[1] Urza Bhattarai,[1] Pradip Katuwal,[1] Nensi Shah,[1] Srista Manandhar,[1] Sigiriya Aebischer Perone,[2] Kathrine Zimmermann,[2] Olivia Heller,[2] François Chappuis.[2] *[1]BP Koirala Institute of Health Sciences, Dharan, Nepal; [2]Hopitaux Universitaires Geneve, Geneve, Switzerland.*

Background: Equitable access to kidney care remains a major challenge in low- and middle- income countries (LMICs) like Nepal. Kidney, Hypertension, Diabetes, and Cardiovascular diseases (KHDC) program was formed in 2003 as part of an initiative from ISN for detection and management of major Non-Communicable Diseases (NCDs) in LMICs. The program, has since, shifted priorities from population-based mass screening to a targeted hish-risk approach. An integrated modality to improve service delivery on NCDs, including CKD, at primary care facilities was implemented in a municipality of Eastern Nepal. We present here an analysis of secondary data of risk factors among individuals with kidney disease.

Methods: Capacity building on early detection and management of NCDs, including CKD, was provided to 42 non-physician healthcare providers (HCPs). This was followed, between 2019 and 2023, by population-based screening among 14,517 individuals. Individuals were assessed for risk factors and NCDs through self-report forms, BMI, waist hip ratio, blood pressure, dipstick urine test, serum creatinine, fasting blood glucose and HbA1c measurements. Positively screened individuals were managed at primary care facilities. Kidney disease was defined as either or both of proteinuria and raised serum creatinine.

Results: Kidney disease was detected among 3.1% (n=454) with 88.3% of them having no prior history. 2.6% (n=375) and 1.2% (n=168) had proteinuria and elevated serum creatinine, respectively. Males were more likely [OR: 1.69 (95% CI: 1.38 – 2.06)] to exhibit kidney disease. Hypertension [OR: 2.51 (95% CI: 2.05 – 3.07)] and raised fasting glucose [OR: 2.81 (95% CI: 2.26 – 3.49)] were associated with occurrence of kidney disease. 132 cases required referral for further evaluation and kidney biopsy.

Conclusions: Population based screening strategies employed for early detection of kidney disease highlighted a significant disease burden. While integrating CKD screening as a part of regular NCD care is plausible, further exploration of the risk factors' distribution within the population can be crucial in directing the screening efforts to the high-risk groups. Competency based trainings can be an effective means to mobilize available resources through task sharing as outlined by the KHDC experience.

Funding: Government Support - Non-U.S.

FR-PO1025

Social Risk Factors Associated with Disparate Posthospitalization Care among AKI Survivors

Tomonori Takeuchi,[1,2] Seda Babroudi,[3] Lama Ghazi,[1] Orlando M. Gutierrez,[1] Javier A. Neyra.[1] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan; [3]Tufts Medical Center, Boston, MA.*

Background: The 2012 Kidney Disease Improving Global Outcomes (KDIGO) acute kidney injury (AKI) practice guideline recommends kidney function to be reassessed within 3 months of AKI occurrence. The purpose of this study was to evaluate the association of social risk factors with receipt of post-hospitalization AKI care within 3 months among KDIGO stage 2 and 3 AKI survivors of intensive care unit (ICU) hospitalization.

Methods: Using data from a single academic center in the Southwestern United States, we retrospectively evaluated the association of insurance status, Area Deprivation Index (ADI), and Rural Urban Commuting Area (RUCA) code with receipt of post-AKI care. Patients aged ≥18 years hospitalized in the ICU with KDIGO stage 2 or 3 AKI between 10/2014 and 9/2017 who survived 90 days post-hospital discharge and did not require dialysis were included. Receipt of post-AKI care was defined as occurrence of a clinic visit and serum creatinine measurement within 90 days of hospital discharge. Multivariable logistic regression was performed, adjusting for patient demographics, comorbidities, and AKI severity.

Results: Of 1491 critically-ill AKI survivors, mean (SD) age was 55.8 (17.1), 40.2% were Black, 9.7% were uninsured, 30.2% lived in a neighborhood with the highest disadvantage, and 6.8% lived in a rural neighborhood. Only 536 (35.9%) patients received post-AKI care within 3 months. Uninsured status (aOR 0.44 [95% CI, 0.27, 0.68]) and living in a neighborhood of socioeconomic deprivation (highest tertile of ADI, aOR 0.72 [95% CI, 0.58, 0.89]) were significantly associated with decreased odds of receiving post-AKI care after adjustment (Table 1).

Conclusions: Only one-third of critically-ill KDIGO stage 2 or 3 AKI survivors had an outpatient visit and a serum creatinine measurement within 3 months of hospital discharge. Uninsured status and high neighborhood area deprivation significantly and negatively associated with follow-up, suggesting presence of socioeconomic disparities in post-AKI care.

Funding: Other NIH Support - National Center for Advancing Translational Sciences, National Institutes of Health, Award Number TL1TR002546

Table 1. Association of social risk factors with receipt of post-hospitalization AKI care

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Insurance		
Insured	*ref*	*ref*
Uninsured	0.36 (0.23, 0.55)	0.44 (0.27, 0.68)
Area Deprivation Index		
Lowest risk	*ref*	*ref*
Moderate risk	0.84 (0.70, 1.00)	0.83 (0.69, 1.00)
Highest risk	0.78 (0.65, 0.93)	0.72 (0.58, 0.89)
Rural Urban Commuting Area		
Urban dwelling	*ref*	*ref*
Rural dwelling	1.03 (0.67, 1.56)	1.01 (0.65, 1.55)

Adjusted for age, sex, race, body mass index, diabetes mellitus, hypertension, cardiovascular disease, Charlson Comorbidity Index, baseline serum creatinine, maximum serum creatinine during hospitalization, and serum creatinine at time of discharge

FR-PO1026

Medicaid and Dual Eligibility Are Negatively Associated with Kidney Function Recovery in Patients with AKI Receiving Outpatient Dialysis

Seda Babroudi,[1] Hocine Tighiouart,[2,1] Daniel E. Weiner,[1] Javier A. Neyra,[3] Ronald Sanders,[4] Harold Manley,[4] Eduardo K. Lacson,[4,1] David A. Drew.[1] *[1]Tufts Medical Center, Boston, MA; [2]Tufts Medical Center Institute for Clinical Research and Health Policy Studies, Boston, MA; [3]UAB Hospital, Birmingham, AL; [4]Dialysis Clinic Inc, Nashville, TN.*

Background: Access and quality of social risk data in patients with acute kidney injury receiving outpatient dialysis (AKI-D) are severely limited. However, Medicare-Medicaid dual eligibility status is an indicator of social risk and has been previously associated with worse dialysis outcomes among maintenance hemodialysis patients. We sought to explore the relationship of insurance status at baseline with kidney function recovery among patients with AKI-D.

Methods: Using a multi-center retrospective cohort design, we evaluated the association of insurance status at baseline with kidney function recovery to dialysis independence among patients with AKI-D who initiated hemodialysis between 2017 and 2021 at a medium-sized dialysis provider. We used Cox proportional hazard models adjusting for demographics, comorbidities, hemodialysis characteristics previously associated with recovery, and other social risk factors (modified area deprivation index, rurality of primary residence).

Results: Among 2,544 patients with AKI-D across 238 dialysis facilities, mean (SD) age was 65 (14) years, 58% were men, and 19% were Black. The most common primary insurer was Medicare/Medicare Advantage/Veterans Affairs (47%), with 17% dual eligible, and 12% insured with Medicaid. 857 (34%) patients recovered kidney function with a median (IQR) follow-up time of 103 (28, 180) days from first outpatient hemodialysis session. Medicaid and dual eligibility negatively associated with kidney function recovery when compared to Medicare/Medicare Advantage/Veteran Affairs as the primary insurer, even after multivariable adjustment (aHR 0.54, 95% CI 0.34, 0.84; aHR 0.67, 95% CI 0.47, 0.95, respectively) (Table 1).

Conclusions: Medicaid and dual eligible status negatively associated with kidney function recovery among patients with AKI-D, suggesting a role for upstream socioeconomic factors associated with insurance coverage to be used in future research exploring health disparities and shaping health policy in this population.

Funding: Other NIH Support - National Center for Advancing Translational Sciences, National Institutes of Health, Award Number TL1TR002546

Table 1. Association of insurance status at baseline with kidney function recovery

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Insurance		
Medicare/MA/VA	*ref*	*ref*
Commercial	1.11 (0.86, 1.42)	0.93 (0.69, 1.24)
Medicaid	0.73 (0.50, 1.08)	0.54 (0.34, 0.84)
Dual Eligible	0.76 (0.55, 1.05)	0.67 (0.47, 0.95)

Adjusted for age, sex, body mass index, diabetes mellitus, hypertension, cardiovascular disease, congestive heart failure, cirrhosis, albumin, hemoglobin, interdialytic weight gain (proxy for urine output), net ultrafiltration, ultrafiltration rate, modified area deprivation index, and rurality
Abbreviations: MA, Medicare Advantage; VA, Veterans Affairs

FR-PO1027

Out-of-Pocket Expenditures for Patients with CKD in the Medical Expenditure Panel Survey (MEPS)

Abhishek K. Das,[1] Sri Lekha Tummalapalli.[2] [1]*Johns Hopkins University, Baltimore, MD;* [2]*Weill Cornell Medicine, New York, NY.*

Background: Chronic kidney disease (CKD) affects 37 million Americans and nearly half of patients with CKD report experiencing financial hardship from medical bills. Out-of-pocket healthcare costs are a key source of financial strain. An analysis of 2002-2011 data from the Medical Expenditure Panel Survey (MEPS) found that average out-of-pocket costs declined from $1,707/yr to $1,218/yr during the study period. Prescription drugs accounted for $730/yr in costs in 2010/2011. Recent novel therapeutics such as SGLT2 inhibitors may contribute to excess out-of-pocket costs and more contemporary estimates are needed.

Methods: We used data from the Medical Expenditure Panel Survey (MEPS), which is a nationally representative set of extensive surveys of individuals, their medical providers, and employers across the United States. We used the full-year household component consolidated data files from 2018 to 2021 and restricted to individuals with ICD-10 codes for CKD (N18). We examined mean out-of-pocket costs per year for inpatient hospital stays, emergency department visits, hospital outpatient visits, office-based visits, and prescription medicines. Sample weights were applied to account for the complex survey design.

Results: Among the 115,114 people surveyed by MEPS from 2018-2021, we restricted to 291 observations from 141 patients with diagnosis codes for CKD. Average out-of-pocket costs were $234.53/yr for inpatient costs, $135.89/yr for emergency department visits, $143.04/yr for hospital outpatient visits, $833.93/yr for office-based visits, and $783.77/yr for prescription medicine costs.

Conclusions: Patients with CKD experienced higher out-of-pocket costs in 2018-2021 compared with prior estimates. Prescription medicine costs accounted for a higher share of out-of-pocket expenditures, which may be attributable to novel therapeutics for CKD. Health policy levers such as the Medicare Part D out-of-pocket spending caps in the Inflation Reduction Act may lessen the financial burden of CKD and its complications.

FR-PO1028

Switching Back to Medicare Fee-for-Service after 1 Year of Medicare Advantage Coverage among Patients with ESKD

Jiannong Liu,[1] James B. Wetmore,[1,2] Haifeng Guo,[1] David T. Gilbertson,[1] Nicholas S. Roetker,[1] Kirsten L. Johansen.[1,2] [1]*Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN;* [2]*University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Medicare beneficiaries with end-stage kidney disease (ESKD) were able to switch from Medicare fee-for-service (MFFS) to Medicare Advantage (MA) starting in 2021. About 11.6% of dialysis patients (pts) and 5.4% of kidney transplant (Tx) pts switched in 2021. This study assessed how many pts switched back to MFFS in 2022, a potential indicator of dissatisfaction with the program.

Methods: We used United States Renal Data System data to identify adult ESKD pts who switched from MFFS to MA in 2021 and survived to 2022. "Switching back" was defined as enrollment in MFFS in January 2022. For comparison, we assessed the rate of switching to MFFS in 2022 among those ESKD pts who were continuously enrolled in MA 2020-2021. Analyses were stratified by ESKD modality.

Results: Among 31,972 pts (27,644 dialysis, 4,328 Tx) who switched from MFFS to MA in 2021, 1.41% of dialysis pts and 1.52% of Tx pts switched back to MFFS in 2022, whereas only 0.50% of dialysis pts and 0.44% of Tx pts switched to MFFS in 2022 among those who were continuously enrolled in MA. Among dialysis pts who switched to MA in 2021, switching back to MFFS was more common among those who were older (2.79% in 75-85 years and 2.92% 85+), Asian (2.50%) or Other race (2.49%), or living in Northeast (2.03%); and less common in younger groups, Black or Hispanic, and Medicare-Medicaid dual enrolled (Table). The pattern was less clear among dialysis pts who were in MA 2020-2021 and among Tx pts.

Conclusions: One year after switching from MMFS to MA in 2021, a small percentage switched back. However, the switch rate was triple that of pts who were originally in MA. Further studies should assess if switching back is related to the quality of services in MA compared with MFFS.

Funding: NIDDK Support

Table. Characteristics of dialysis patients who switched from MFFS to MA in 2021 and who were in MA for both 2020 and 2021 and their percentages of switching to MFFS in 2022

	Dialysis Patients switched to MA from MFFS, 2021		Dialysis Patients in MA, 2020 and 2021	
	N	Percent Switched back to MFFS at Beginning of 2022	N	Percent Switched to MFFS at Beginning of 2022
Total	27644	1.41	89853	0.50
Age Group				
18-44	2741	1.09	3032	0.69
45-55	5499	1.22	6161	0.31
55-64	9211	0.88	14690	0.50
65-74	7278	1.80	32372	0.54
75-84	2435	2.79	26103	0.49
>=85	480	2.92	7495	0.45
Sex				
Female	11499	1.50	40423	0.51
Male	16145	1.35	49430	0.49
Race				
NH-White	7674	1.54	34151	0.57
NH-Black	13587	1.32	30480	0.51
Hispanic	5061	1.19	18640	0.36
Asian	719	2.50	4923	0.47
Other	603	2.49	1659	0.54
MM Dual Eligible				
Yes	14337	1.17	35447	0.55
No	13307	1.68	54406	0.47
Cause of ESKD				
Diabetes	12494	1.39	46331	0.50
Hypertension	9434	1.53	26926	0.46
Glomerulonephritis	2554	1.45	5798	0.47
Other	3162	1.14	10798	0.61
Census Region				
Midwest	3680	1.39	16611	0.52
Northeast	2408	2.03	12468	0.78
South	15936	1.33	32390	0.45
West	5620	1.41	28384	0.42

Abbreviations: MFFS, Medicare fee-for-service; MA: Medicare fee-for-service; ESKD: End-stage kidney disease; NH: Non-Hispanic

FR-PO1029

Likelihood of Switching from Medicare Fee-for-Service Coverage to Medicare Advantage among Patients on Maintenance Dialysis in 2022

Jiannong Liu,[1] Haifeng Guo,[1] James B. Wetmore,[1,2] Nicholas S. Roetker,[1] David T. Gilbertson,[1] Kirsten L. Johansen.[1,2] [1]*Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN;* [2]*University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Medicare beneficiaries with end-stage kidney disease (ESKD) were able to switch from traditional Medicare fee-for-service (MFFS) to Medicare Advantage (MA) during open enrollment periods for the first time in 2021. About 11.6% of MFFS dialysis patients switched to MA in 2021, and switching was more common among patients who were younger, Black or Hispanic, poor or low-income, and living in the South. This study assesses whether patterns in switching were similar in 2022.

Methods: Using the United States Renal Data System data, we examined who switched to MA in January 2022 among adult (age ≥18 years) dialysis patients covered by MFFS as primary payor as of December 2021.

Results: In total, 240,360 patients were included; 6.5% switched from MFFS to MA in 2022. Switching was most common in individuals who were aged 55-64 years (9.0%), Black race (9.4%), Medicare-Medicaid dual enrolled (8.0%), in Medicare Part D (6.8%), or living in the South (8.4%) and least common among those who were aged 85+ (2.6%), Asian (3.7%), non-dually enrolled (5.4%), not in Medicare Part D (5.5%), or living in the Northwest (4.7%) (Table). The adjusted odds ratios for switching and the corresponding 95% confidence intervals are shown in the Table.

Conclusions: A smaller percentage of MFFS patients switched to MA in 2022 than in 2021, although switchers shared similar characteristics in both years. The availability of zero-premium plans and lower out-of-pocket spending limits will continue to incentivize switching to MA. However, whether the pre-authorization requirement and limited provider network will affect the quality of care or the rate of switching back to MFFS needs to be monitored.

Funding: NIDDK Support

Table. Characteristics of patients on dialysis and enrolled in Medicare fee-for-service at the end of 2021 and percentage of patients who switched to Medicare Advantage at the beginning of 2022, by patient characteristic group.

	Enrolled MFFS at End of 2021	Percent Switched to MA at Beginning of 2022	Adjusted Odds Ratio of Switch and 95% CI
N	240,360	6.5	
Age Group			
18-44	25774	6.5	Ref
45-54	33082	8.3	1.72 (1.51, 1.95)
55-64	52852	9.0	2.16 (1.91, 2.43)
65-74	70786	6.0	1.57 (1.39, 1.77)
75-84	44348	4.1	1.13 (0.96, 1.33)
>=85	13518	2.6	0.74 (0.43, 1.27)
Sex			
Female	99816	6.5	1.02 (0.95, 1.09)
Male	140544	6.5	Ref
Race			
NH-White	107201	4.9	Ref
NH-Black	75326	9.4	1.84 (1.69, 2.00)
Hispanic	36716	6.4	1.37 (1.24, 1.52)
Asian	12647	3.7	0.90 (0.76, 1.08)
Other	8470	5.3	1.32 (1.05, 1.68)
MM Dual Enrollment			
Yes	100903	8.0	1.18 (1.09, 1.28)
No	139457	5.4	Ref
Part D Enrollment			
Yes	177941	6.8	1.58 (1.44, 1.73)
No	62419	5.5	Ref
Cause of ESKD			
Diabetes	105915	6.7	Ref
Hypertension	73042	6.9	1.00 (0.91, 1.09)
Glomerulonephritis	23583	5.7	0.89 (0.81, 0.99)
Other	37820	5.4	0.85 (0.78, 0.94)
Census Region			
Midwest	44916	5.9	
Northeast	36192	4.7	0.77 (0.69, 0.87)
South	97389	8.4	1.12 (1.02, 1.22)
West	61863	5.0	0.76 (0.68, 0.85)

Abbreviations: ESKD, End-stage kidney disease; MFFS, Medicare fee-for-service; MA, Medicare Advantage; NH, Non-Hispanic; MM, Medicare-Medicaid

FR-PO1030

Associations of Income Variability and Incident ESKD in Diabetes: A Population-Based Cohort Study

Min Woo Kang, Sehoon Park, Dong Ki Kim, Yong Chul Kim, Kook-Hwan Oh, Jinsun Lee. *Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.*

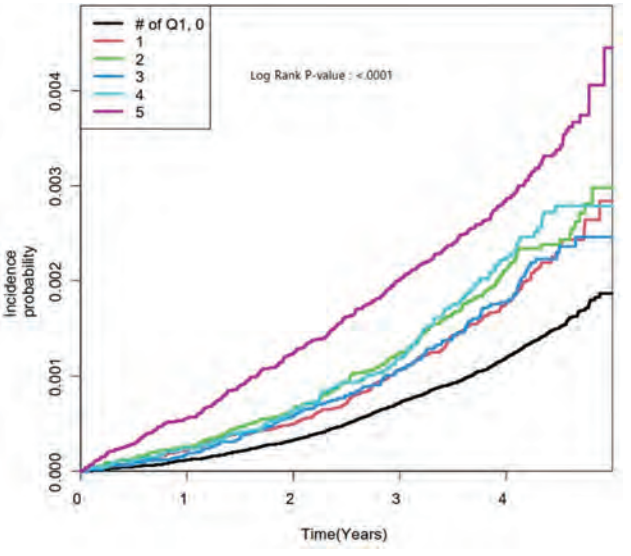
Background: Studies analyzing the association between income variability and incident end-stage kidney disease(ESKD) among individuals with type 2 diabetes(T2D) are limited.

Methods: Based on data from the Korean National Health Insurance Service, 1,481,371 adults aged 30-64 with no history of kidney disease were identified among individuals with T2D who underwent health checkups from 2015 to 2016. Annual income levels from the preceding 4 years to the baseline year were categorized into four quartiles. Income parameters were analyzed in three aspects: (1) cumulative number of years belonging to a specific income status quartile, (2) income volatility, and (3) changes in income status between the initial and end points during the observation. The primary outcome was defined as the first occurrence of incident ESKD, followed up until December 31, 2020. Cox proportional hazard models were used to estimate hazard ratios(HRs) and 95% confidence intervals(CIs).

Results: Persistent low income status over 5 years was associated with an increased risk of ESKD (HR 5years vs. 0years: 1.54, 95% CI 1.33-1.78; Ptrend<0.0001). High income volatility was associated with an increased risk of ESKD (HR highest vs. lowest quartile: 1.43, 95% CI 1.27-1.60; Ptrend<0.001). Irrespective of initial income status, individuals whose income status declined during the 5 years of observation, comparing between the initial and end points, had an increased risk of ESKD. The increase in ESKD risk was most pronounced among those whose income status declined steeply from the highest to the lowest quartile (HR steepest decline vs. unchanged: 1.58, 95% CI 1.19-2.09; Ptrend=0.0025).

Conclusions: Among adults aged 30–64 with T2D, individuals with more persistent low income status, higher income volatility, and steeper income decline had a significantly increased risk of ESKD.

Funding: Government Support - Non-U.S.



FR-PO1031

Impact of Population Health Management to Modify Disparate Use of SGLT2 Inhibitors/Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs)

Linda-Marie U. Lavenburg,[1,2] Zhuoheng Han,[1] Mitra Mosslemi,[1] Alaa A. Alghwiri,[1] Thomas D. Nolin,[1,2] Melanie R. Weltman,[1,2] Jonathan G. Yabes,[1] Manisha Jhamb.[1,2] *[1]University of Pittsburgh, Pittsburgh, PA; [2]UPMC, Pittsburgh, PA.*

Background: Negative social determinants of health (SDOH) are associated with more CKD incidence and progression, partly due to suboptimal management. Sex and age differences in CKD management also exist. We studied whether population health management (PHM) modified the association of demographic differences and SDOH factors with initiation of SGLT2i or GLP1RA.

Methods: In this exploratory analysis of the Kidney Coordinated HeAlth Management Partnership (KCHAMP) trial which cluster randomized 101 primary care offices to control arm vs PHM intervention (nephology e-consult, CKD education, and pharmacist medication review). Enrolled patients with type 2 diabetes, not on baseline SGLT2i/GLP1RA were included. Associations between SGLT2i/GLP1RA initiation with a priori factors were examined in the control arm using Poisson regression with random practice intercept, adjusted for age, gender, race, BMI, Charlson Comorbidity Index, follow-up time as the offset. Effect modification by KCHAMP was assessed using interaction terms. Significance level 0.2 was used.

Results: Cohort had 891 patients (402 KCHAMP; 489 Control); 55% female; 11% black race/other; 89% white race; with mean±SD age 73±9yrs; BMI 33±7kg/m^2; HbA1c 7.3±1.5%; and 18% were rural living. In the control arm, gender (IRR [95%CI] 1.07 [0.99-1.17]), and HbA1c (1.05 [1.02-1.10]) were significantly associated with SGLT2i/GLP1RA initiation. KCHAMP had a marginally significant interaction effect with BMI (1.06 [1.00-1.12]; p = 0.20).

Conclusions: We found disparities in SGLT2i/GLP1RA use due to age and gender. But, SDOH factors were not associated with drug use. The association between some factors (age, gender, BMI, HBA1c) with the initiation of drugs slightly differed between control and KCHAMP. We were under-powered to detect interaction effects of K-CHAMP, yet a marginally significant intervention interaction effect with BMI, suggests that KCHAMP may increase SGLT2i/GLP1RA use in those with higher BMI.

Funding: NIDDK Support, Private Foundation Support

Table 1: Adjusted Analysis

Variable	Control Incidence Rate Ratio [95% CI]	P-value	KCHAMP Incidence Rate Ratio [95% CI]	P-value	Interaction P-value
Age	0.97 [0.93, 1.01]	0.21	0.92 [0.87, 0.98]	0.009	0.50
Gender	1.07 [0.99, 1.17]	0.10	1.02 [0.90, 1.15]	0.77	0.27
Race	1.03 [0.91, 1.16]	0.63	1.07 [0.89, 1.30]	0.47	0.89
BMI	1.00 [0.96, 1.04]	0.96	1.06 [1.00, 1.12]	0.049	0.20
HbA1c	1.05 [1.02, 1.10]	0.005	1.06 [1.01, 1.12]	0.02	0.42
CCI	1.02 [0.98, 1.06]	0.32	1.00 [0.94, 1.06]	0.97	0.45
CKD Stage	0.97 [0.89, 1.05]	0.47	0.90 [0.80, 1.02]	0.10	0.63
Income	1.01 [0.97, 1.05]	0.80	1.00 [0.94, 1.07]	0.90	0.91
Distance to Clinic	1.03 [0.98, 1.07]	0.22	1.02 [0.96, 1.08]	0.51	0.60
ADI	0.99 [0.95, 1.03]	0.54	1.00 [0.94, 1.06]	0.89	0.71
Percent Vacant Land	0.98 [0.94, 1.03]	0.48	1.02 [0.96, 1.07]	0.57	0.36
RUCA	1.00 [0.89, 1.11]	0.95	0.99 [0.86, 1.13]	0.84	0.95
Gini Index	1.00 [0.96, 1.04]	0.90	0.99 [0.93, 1.04]	0.62	0.83
Insurance					
Medicaid	1.05 [0.96, 1.14]	0.27	1.02 [0.90, 1.15]	0.75	0.50
Medicare	1.12 [0.91, 1.37]	0.29	1.21 [0.85, 1.72]	0.85	0.91
Others	1.12 [0.87, 1.43]	0.39	1.08 [0.71, 1.64]	0.71	0.67

CCI- Charlson Comorbidity Index; ADI- Area Deprivation Index; RUCA- Rural-Urban Commuting Area codes

FR-PO1032

Community Health Center Penetration and Kidney Outcomes among Nonelderly Adults with Incident ESKD

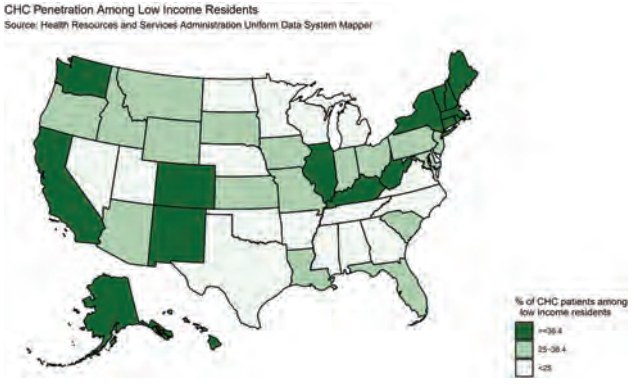
Yoshio N. Hall,[1,2] Wyatt P. Bensken,[4] Suzanne E. Morrissey,[4] Indhira De la Cruz Alcantara,[5] Mark L. Unruh,[3] David K. Prince.[2] *[1]VA Puget Sound Health Care System Seattle Division, Seattle, WA; [2]University of Washington, Seattle, WA; [3]University of New Mexico School of Medicine, Albuquerque, NM; [4]Oregon Community Health Information Network, Portland, OR; [5]Sea Mar Community Health Centers, Seattle, WA.*

Background: In the US, populations who experience kidney health disparities often rely on Community Health Centers (CHCs) for affordable ambulatory care.

Methods: We conducted a retrospective cohort study to examine whether CHC penetration of the state-level low-income population was associated with prevalent kidney disease risk factors, ESKD incidence, process measures reflective of pre-ESKD care quality, and 1-year ESKD survival and kidney transplantation. We studied 318,809 nonelderly adults aged 18-64 years who initiated treatment for ESKD in the US during 2016-2020 and the population characteristics of all 1,370 HRSA CHCs and 51 states for the same time period.

Results: CHC penetration among low-income residents (percentage of low-income residents who were CHC patients in each state) was highest among states in the northeast and lowest among states in the south (mean 35.5% [SD, 19.2%]). The prevalence of diabetes, high blood pressure and obesity were respectively lower in states with high versus low CHC penetration. There were no significant differences in age- and sex-standardized ESKD incidence according to CHC penetration. In individual-level analyses, higher CHC penetration was significantly associated with a higher likelihood of prolonged nephrology care (adjusted OR: 1.04 [95%CI: 1.03-1.05]), arteriovenous fistula or graft usage at hemodialysis initiation (1.11 [1.09-1.12]), home dialysis usage (1.04 [1.02-1.05]), and 1-year kidney transplant (1.09 [1.05-1.12]) and ESKD survival (1.06 [1.04-1.07]). CHC penetration was not associated with the likelihood of pre-emptive kidney transplant (1.00 [0.96-1.04]).

Conclusions: Higher CHC penetration of low-income populations was associated with a lower prevalence of kidney disease risk factors, and better preparedness for, and higher survival after, ESKD onset. These findings warrant additional study into the role and impact of Community Health Centers in addressing longstanding disparities in kidney health.



FR-PO1033

Pilot Data from a Community Health Worker Intervention for Patients on Hemodialysis

Tessa K. Novick,[1] David A. Giraldo,[1] Michelle M. Osuna-Diaz,[1] Elizabeth Jacobs,[1] Deidra C. Crews.[2] *[1]The University of Texas at Austin Dell Medical School, Austin, TX; [2]Johns Hopkins Medicine, Baltimore, MD.*

Background: Health-related social needs, such as housing and food insecurity, are common among hemodialysis patients. Social needs are associated with worse outcomes and pose barriers to care. Community-health worker (CHW) interventions have been successful at addressing social needs in other populations.

Methods: We piloted a single-arm, two-month CHW intervention for in-center hemodialysis patients who were eligible for Medicaid at three dialysis facilities in Austin, Texas. Objectives were to determine (1) the feasibility and acceptability of using a CHW to improve community resource navigation to social needs assistance, and (2) how measures of treatment attendance, patient reported stress, and mental health and clinical parameters performed in this population.

Results: Of the 17 enrolled participants to date, mean (SD) age was 56 (9) years, 67% were male, 50% identified as Black, 50% as Hispanic, 100% reported annual income <$25,000, and health related social needs were high (70%, 65%, 47%, and 24% reported housing, food, transportation and utility needs, respectively). Baseline hemodialysis treatment attendance, mental health, and clinical parameters were poor (Figure). All eligible patients approached agreed to participate, however CHW case load and burden of participants'social needs necessitated slowing the pace of enrollment.

Conclusions: Social needs were prominent among hemodialysis patients with low socioeconomic status and were associated with mental health concerns and emotional distress, supporting the importance of developing interventions to address them.

Funding: NIDDK Support

Table. Baseline Participant Characteristics

Characteristic	N = 17
Clinical factors	
Central venous catheter, n (%)	8 (47)
Days hospitalized in past 6-months, mean (SD); range	7 (11); 0-40
Number of treatments terminated early in past 30-days, mean (SD); range	3 (2); 0-7
Missed sessions in past 30-days, mean (SD), range	1 (1); 0-4
Waitlisted for kidney transplant, n (%)	0 (0)
Laboratory findings	
spKt/V mean (SD); range	1.6 (0.4); 1.1-2.3
Albumin g/dL, mean (SD); range	4.0 (0.4); 3.1-4.3
PTH pg/mL, mean (SD); range	915 (810); 172-3493
Potassium meq/L, mean (SD); range	5.1 (0.6); 4.2-6.1
Phosphorus mg/dL, mean (SD); range	6.4 (1.4); 3.4-9.2
Hemoglobin g/dL, mean (SD); range	10.8 (1.7); 7.8-13.7
Mental health	
Generalized Anxiety Disorder 7-item moderate or severe, n (%)	8 (50)
Post-traumatic Stress Disorder positive screen, n (%)	9 (53)
Patient Health Questionnaire positive screen, n (%)	9 (53)
Perceived Stress, moderate or high, n (%)	13 (76)

FR-PO1034

Why Am I on Dialysis? Exploring the Gap between Patient Perspectives and Clinical Diagnosis of Kidney Disease in California's Central Valley

Marimar Contreras Nieves,[1] Angelina J. Powers,[1] Stefan A. Jaskulak-Gonzalez,[1] Esteban Banda,[1] Xue Yu,[1] Manjula Kurella Tamura,[1,2] Shuchi Anand.[1] *[1]Stanford University, Stanford, CA; [2]VA Palo Alto Health Care System, Palo Alto, CA.*

Background: In the agricultural hub of California's Central Valley, where the incidence of end-stage kidney disease (ESKD) is amongst the highest in the nation, investigating the discrepancies between patients' understanding of their kidney disease and their clinical diagnoses holds critical importance, given potential communication barriers including due to language differences, and varying health literacy levels.

Methods: We interviewed 163 patients (range 18-60 year-old) undergoing hemodialysis in Soledad, Salinas, and Fresno, California. We compared the agreement between patients' reported diagnosis with those documented by clinicians in the CMS 2728. Chi-squared and Mann-Whitney U tests were performed to assess whether the agreement differed by age, gender, and educational background. Educational background was categorized as follows: absence of formal schooling, completion of less than 9th grade, completion of 9th to 11th grade, graduation from high school or obtaining a GED (General Educational Development) equivalent, partial completion of college or attainment of an Associate's degree (AA), and attainment of a college degree or higher.

Results: The survey response rate among those eligible and approached was 80%. The median age of respondents was 49 years (25th, 75th percentile 40, 55 years), 68% were men, and 79% were Hispanic. Patient agreement with clinician documented causes was highest for diabetes (71%) and lowest for hypertension (31%) (Table 1). Agreement rates did not differ by age, gender, or education level.

Conclusions: There was poor concordance between the cause of ESKD documented in clinical records and patients' understanding, particularly for those with a clinical diagnosis of hypertensive kidney failure or unknown. The findings could indicate both communication gaps, but also inaccuracies in the CMS 2728 categories or the clinician's diagnosis.

Funding: NIDDK Support

Table 1: Cause of ESKD and Agreement Between Patients' and Clinicians' Diagnosis

Clinician designated cause of ESKD	N (%)	Agreement with patient perceived cause (%)
Diabetes	79 (48)	71
Hypertension	26 (16)	31
Glomerular Disease	11 (7)	64
Unknown	33 (20)	36

FR-PO1035

Crash Dialysis Starts in Northern Alberta: Demographics, Outcomes, and Uptake of Home Therapies

Bernadine Jugdutt, Feng Ye, Aminu K. Bello, Nikhil A. Shah. *University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada.*

Background: "Crash" dialysis starts (i.e. emergency hemodialysis initiation) remain a frequent occurrence, despite guidelines for early referral. They are associated with higher healthcare costs and worse patient outcomes. Better understanding of the crash lander population is key to targeting interventions to reduce crash starts and improve outcomes.

Methods: We performed a retrospective chart review of patient initiating hemodialysis (HD) in northern Alberta from 2008-2019. Patients with prior renal replacement therapy or short-term HD were excluded. Patients were categorized into planned HD starts (>3 months Nephrology exposure) and unplanned (<3 months), with subdivisions for late exposure (2 weeks - 3 months) and no exposure (<2 weeks). Demographics, uptake of home therapies, and short-term outcomes were compared between groups using Kruskal-Wallis for continuous variables and χ^2 for categorical; $p<0.05$ indicated significance.

Results: 2,685 adult patients were included; of those, 28.1% had an unplanned HD start, and 19.7% started HD with no prior exposure to Nephrology. Crash dialysis patients were more likely to live rurally (17.2% vs 13.7%, p=0.022), and reported fewer instances of comorbid conditions including diabetes, hypertension, cardiovascular disease, and stroke. While percentage conversion to home therapies and listing for renal transplant was similar between groups, there was a higher prevalence of conversion to peritoneal dialysis specifically in the unplanned group at 1 year (9.4% vs 6.4%, p=0.007) and at the end of the study (13.0% vs 8.6%, p<0.001), and a lower prevalence of conversion to home hemodialysis as compared to the planned group. Unplanned HD starts had longer initial hospitalizations, earlier re-hospitalizations, and longer waits to achieve permanent access.

Conclusions: Despite optimal referral guidelines, crash dialysis starts remain a significant problem in Alberta and demonstrate worse short-term outcomes than their planned HD counterparts, emphasizing the need for further quality improvement work in this area.

Short-term outcomes for unplanned vs planned hemodialysis (HD) patients

	Unplanned	Planned	p-value
Mean length of hospital admission for HD initiation (days)	33.9	31.7	0.032
Length of time (days) to obtain permanent access	9.7	3.0	<0.001
Mean time (months) to next all-cause hospitalization	10.9	12.6	<0.001
Conversion to fistula access, N (%)	281 (37.3%)	1,199 (62.2%)	<0.001

FR-PO1036

Comparison of Clinical and Sociodemographic Characteristics of Hemodialysis Modalities

Belen Alejos,[1] Kaitlyn R. Croft,[1] Anke Winter,[1] Adrian M. Guinsburg,[2] Jeffrey L. Hymes,[3] John W. Larkin,[3] Len A. Usvyat,[3] Martin E. Guinsburg,[2] Franklin W. Maddux.[4] *[1]Fresenius Medical Care, Bad Homburg, Germany; [2]Fresenius Medical Care, Buenos Aires, Argentina; [3]Fresenius Medical Care, Waltham, MA; [4]Fresenius Medical Care AG, Bad Homburg, Germany.*

Background: Hemodiafiltration (HDF) is a well-established kidney replacement therapy. However, the selection of the dialysis modality is normally made according to individual characteristics. We aimed to compare clinical and sociodemographic characteristics (with special interest in mineral bone disease (MBD) markers) according to hemodialysis modality among patients treated in 4 countries in Latin America in the first version of the global database (Apollo Dial DB).

Methods: Apollo Dial DB includes adult dialysis patient data from a global kidney network during Jan 2018-Mar 2021 (Fresenius Medical Care, Bad Homburg, DE). Data anonymization was performed in alignment with recommendations from a re-identification risk determination (Privacy Analytics, Ontario, CA). We included patients with HD or HDF for >90 days, with >90% of their assigned treatment for 12 weeks.

Results: A total of 20,350 patients were analyzed, 17,916 (88%) patients on HD, 2,434 (12%) on HDF. Figure shows differences in sociodemographic and clinical characteristics of the patient groups. Patients in HDF group were younger, had higher vintage, lower prevalence of preexisting CVD and diabetes, higher prevalence of fistula as vascular access, larger use of Vitamin D analogs, phosphate binders and calcimimetics. OCM Kt/V and blood flow were higher among HDF compared to HD. Slightly higher target achievement were observed for calcium and phosphate parameters on HDF group.

Conclusions: Prescription of HDF as kidney replacement therapy is not solely determined by specific guidelines but significantly influenced by various patients' characteristics that may lead to selection bias when analyzing the treatment effect. Hyperphosphatemia is particularly an indication for HDF in most LatAm countries, therefore future research is needed to evaluate how HDF affects MBD markers independently of other patient's factors.

Funding: Commercial Support - Fresenius Medical Care

Figure: Differences in patients characteristics according to hemodialysis modality

	HD (n=17916)	HDF (n=2434)	P-value
Age (years), mean (SD)	55.7 (16.4)	53.1 (16.7)	<0.001
Female gender, n (%)	10487 (58.5)	1634 (67.1)	<0.001
Preexisting diabetes, n (%)	7034 (39.3)	723 (29.7)	<0.001
Preexisting CVD diseases, n (%)	1872 (10.5)	211 (8.7)	0.007
Fistula Vascular access, n (%)	12208 (68.2)	2020 (83.0)	<0.001
Vintage (days), mean (SD)	798 (176; 1909.5)	1308 (371; 2533)	<0.001
Dialysis frequency (day/week), mean (SD)	3.00 (0.08)	3.01 (0.12)	0.031
Duration of session (min), median (IQR)	240 (240; 250)	240 (240; 250)	<0.001
Blood flow (ml/min), median (IQR)	358 (322; 388)	414 (401; 431)	<0.001
OCM Kt/V, mean (SD)	1.60 (0.30)	1.76 (0.35)	<0.001
Use of phosphate binders, n (%)	9722 (54.3)	1502 (61.7)	<0.001
Vitamin D analogs, n (%)	7020 (39.2)	1149 (47.2)	<0.001
Calcimimetics, n (%)	613 (3.4)	221 (9.1)	<0.001
Calcium corrected (mg/dl), mean (SD)	8.81 (0.70)	8.88 (0.73)	<0.001
Target 8.4-10.2, n (%)	11861 (73.7)	1682 (75.5)	0.072
Phosphate (mg/dl), mean (SD)	4.58 (1.39)	4.46 (1.36)	<0.001
Target (if P binder <5.5, if no P binder 2.5-5.5) n (%)	13139 (73.7)	1869 (76.9)	<0.001
iPTH corrected (pg/ml), mean (SD)	429.67 (408.48)	470.45 (439.98)	<0.001
Target 130-585, n (%)	8525 (57.4)	1335 (56.1)	0.256

FR-PO1037

Social Risk Factors and Quality of Life in Patients on Hemodialysis

Hailey Yetman,[1] Huei Hsun Wen,[1] Lin-Chun Wang,[2] Zijun Dong,[2] Lela Tisdale,[2] Yvette Foby,[2] Mariam M. Olagoke,[2] Stephan Thijssen,[2] Peter Kotanko,[2,1] Girish N. Nadkarni,[1] Lili Chan.[3] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Renal Research Institute, New York, NY; [3]Icahn School of Medicine at Mount Sinai Department of Medicine, New York, NY.*

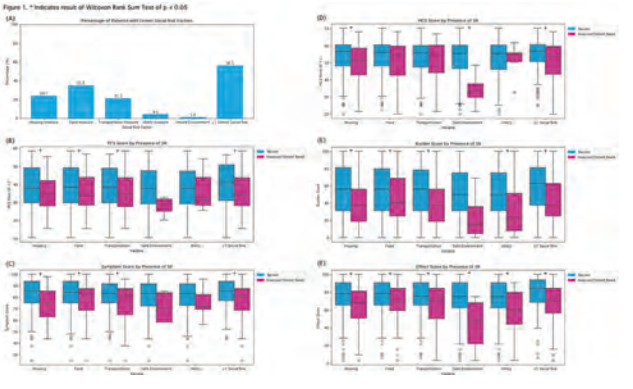
Background: Hemodialysis (HD) patients often have lower quality of life (QoL) than non-HD patients. While social risk (SR) factors are linked to poor health and low QoL, their association with QoL in HD patients remains unstudied.

Methods: We surveyed HD patients at five dialysis units using the Kidney Disease Quality of Life (KDQOL) and the AHC Health-Related Social Needs Screening Tool (AHC-HRSN), evaluating their access to housing, food, transportation, utilities, and safety. We calculated physical component score (PCS), mental component score (MCS), burden score, symptoms of kidney disease score, and effect of kidney disease score using the KDQOL. Lower scores indicate an increased negative impact of kidney disease. The relationship between unmet SR and each of the sub-scores was investigated using the two-tailed Wilcoxon Rank Sum test.

Results: We studied 324 patients; high burdens of unmet SR were observed (Fig. 1A). Lower PCS and lower symptom scores were significantly associated with having at least one unmet SR factor, specifically in housing, food, and transportation insecurity (Fig. 1B, C). Lower MCS was significantly linked to having at least one unmet SR factor, including housing insecurity and unsafe environments (Fig. 1D). Lower burden score was significantly related to experiencing at least one unmet SR factor, including housing, food, transportation, and utilities insecurity (Fig. 1E). Lower effect score was significantly linked to having any unmet SR (Fig. 1F).

Conclusions: Unmet SR factors are common and associated with lower QoL in HD patients. Improved screening and attempts to address unmet SR may improve QoL in HD patients.

Funding: NIDDK Support



FR-PO1038

Dialysis Disparities: A Systematic Review of Homelessness and ESKD Care Challenges

Phong T. Nguyen,[1] Prakrati C. Acharya,[2] Charat Thongprayoon,[3] Sadhana Gonuguntla,[2] Jennifer Zhang,[2] Supawadee Suppadungsuk,[3] Pajaree Krisanapan,[3] Jing Miao,[3] Adeel Ahmad,[2] Wisit Cheungpasitporn.[3] *[1]William Beaumont Army Medical Center, El Paso, TX; [2]Texas Tech University Health Sciences Center El Paso, El Paso, TX; [3]Mayo Clinic Minnesota, Rochester, MN.*

Background: Patients with end-stage kidney disease (ESKD) who are homeless face challenges including medication storage, transportation, adherence to restrictions, dialysis treatments and exacerbating health issues

Methods: We conducted systematic reviews in OVID Medline, Embase, and Cochrane databases up to March 2024 to examine demographic data, substance use, dialysis access, mental health, healthcare utilization, and transplantation outcomes for homeless ESKD patients. Data categories included demographics such as age, ethnicity, and urban vs. rural living; types of dialysis access; psychiatric conditions; and outcomes, including survival rates, hospital visits, and transplantation suitability. The protocol was registered in PROSPERO CRD42024509023.

Results: 6 studies were identified involving 986 homeless ESKD individuals. The prevalence of homelessness among ESKD patients varied from 0.35% to 32.6%, with varying sample sizes in these studies. 4 studies with a total of 58003 ESRD patients, had 900 homeless patients, thus with a prevalence of 1.5%. The largest study involved veterans, demonstrating that approximately 3% had both ESKD and homelessness. Black patients were particularly affected with over half of the patients being Black in all studies. ESKD patients who were burdened by homelessness were associated with a high risk of 90-day hospital readmission (OR 2.92, 95% CI: 1.02, 13.16, p= 0.05). Patients with unstable housing had a higher risk of death compared with patients with stable housing in one study (adjusted hazard ratio [AHR], 1.20 [95% CI: 1.04-1.37]), with Kaplan-Meier analysis demonstrating 1-year and 4-year survival rates of 94.4% and 80.6%, respectively. Homelessness is an independent risk factor for ESKD, with incidence rates of ESKD significantly higher than stable housing peers (10.9 vs. 7.4 per 1000 person-years) in one study. These patients also faced mental health and substance abuse disorders.

Conclusions: Homelessness significantly impedes the management of ESKD. The data highlight the critical need for integrated healthcare services, including stable housing and mental health support. Future research should focus on comprehensive data collection to better address the barriers faced by homeless ESKD patients in getting necessary treatments

FR-PO1039

Trainee Awareness of Transplant Barriers for Undocumented Immigrants

Katherine M. Rizzolo,[1,2] Santhoshi R. Bavi,[1,2] Kurtis A. Pivert,[4] Lilia Cervantes.[3] *[1]Boston Medical Center, Boston, MA; [2]Boston University, Boston, MA; [3]University of Colorado Anschutz Medical Campus, Aurora, CO; [4]American Society of Nephrology, Washington, DC.*

Background: Undocumented immigrants face no regulatory barriers to receive a transplant based on immigration status; the primary barrier is lack of affordable insurance. Our objective was to evaluate nephrology trainee knowledge of eligibility and barriers to kidney transplants for undocumented immigrants and understand their referral practices for this population.

Methods: We analyzed deidentified responses from 450 fellows completing our 8-question instrument in ASN's 2023 survey of US nephrology fellows. Data were summarized as mean ± SD (continuous variables) or counts/percentages/frequency distributions (categorical).

Results: Results are summarized in Table 1.55.5% of participants identified as male, with a mean age of 33.9 years (SD 4.2 years), 88.8% were in adult programs. 54.8% reported treating undocumented immigrants in their nephrology clinic, yet the minority of respondents correctly identified that undocumented people are eligible for living donor (39.1%) and deceased donor transplantation (31.7%). 44.6% were unsure of what insurance was available to undocumented people. The highest rated barriers to transplant were lack of insurance (56.8%) and financial support (52.6%).

Conclusions: This research demonstrates a gap in nephrology trainee knowledge of undocumented immigrants' eligibility and barriers to kidney transplantation. As nephrology trainees often work in health safety net settings where undocumented people seek care, building clinician awareness and knowledge is critical for health equity in transplant care for undocumented individuals. This work may inform future initiatives to include the care of immigrant populations in nephrology trainee education and strengthen health equity efforts.

Funding: NIDDK Support

Table: Participant Characteristics and Responses	
Participant Characteristics	
Gender	**N° (%)**
Male	250 (55.5%)
Female	190 (42.2%)
Not answered	10 (2.2%)
Age	**Years**
Mean ± SD	33.9 ± 4.2
Nephrology Fellowship Completed	**Years**
Mean ± SD	1.6 ± 0.5
Type of fellowship training	**N° (%)**
Adult Nephrology	400 (88.8%)
Pediatric Nephrology	41 (9.1%)
Adult/Pediatric Nephrology	9 (2%)
Location of fellowship training	**N° (%)**
Mid-Atlantic	101 (22.4%)
South Atlantic	73 (16.2%)
East North Central	62 (13.7%)
Pacific	58 (12.8%)
West South Central	39 (8.6%)
New England	37 (8.2%)
West North Central	30 (6.6%)
East South Central	20 (4.4%)
Not answered	12 (2.6%)
Medical training outside the US	**N° (%)**
International medical graduates (IMGs)	266 (59.1%)
Exposure to undocumented immigrants and practice patterns	
Percent of undocumented immigrants in outpatient nephrology clinic	**N° (%)**

FR-PO1040

Barriers to Kidney Transplantation in the Largest Safety Net Hospital in New York: A Quality Improvement Project

Adrianne F. Basa,[1,2] Nicole Ali,[1] Robin G. Layman,[1] Nina J. Caplin.[1,2] *[1]NYU Langone Health, New York, NY; [2]New York City Health and Hospitals Bellevue, New York, NY.*

Background: Kidney transplant (KT) is the preferred treatment for patients with ESKD because of increased survival and improved quality of life. However, there is a lower rate of transplant among underserved patients. Bellevue Hospital Center (BHC) is a safety net hospital and serves primarily a disadvantaged population. It was observed that a minority of BHC patients receiving dialysis or CKD5 had been referred for transplant evaluation. The goal of this QI project is to assess if a new approach to systematic and coordinated referral would help rectify the disparity in this population and identify the obstacles BHC patients experience.

Methods: The renal staff identified admitted patients who might qualify for transplantation. The patients' names were sent to the NYU transplant coordinator. We interviewed patients to discuss obstacles to scheduling appointments, completing screening, and receiving a transplant. A chart review correlated referral patterns with dialysis unit (DU) CMS ratings, location and patients' home address. We conducted a zoom lecture for interested patients to reinforce the benefits of KT.

Results: From March 2023 to September 2023, 38 patients were referred for KT evaluation. 53% scheduled an appointment with a transplant center. 47% were interviewed. INTERVIEWED PATIENTS 55% of patients live in Brooklyn, 27% in Manhattan, 16% in the Bronx, and 5% in Queens. 58% of the DU are located in a zip code with median household income of less than $60,000. The average CMS rating of the dialysis units is 3.5. 72% had called and received an appointment within a month. 3 completed evaluation and one was transplanted; 61% are still undergoing evaluation. Reasons patients had for not calling: uncertain how to proceed, forgot to call or forgot about the referral. 44% wanted to join a virtual class to learn about KT. 2 patients attended the virtual class.

Conclusions: There is a disparity in the rates of referral to transplant centers among underserved patients. To address this disparity at BHC, we created a coordinated referral system with our affiliated transplant center. We also identified some barriers that impede the completion of this cumbersome process. Facilitating the process of kidney transplant evaluation and providing more support would benefit our underserved population and enable more access to this superior treatment option.

FR-PO1041

Socioeconomic Factors Affect Access to Kidney Transplant in the Ohio River Valley

Catherine E. Kelty,[1] Adam S. Wilk,[1] Oluwafisayo O. Adebiyi,[1] Asif A. Sharfuddin,[1] Jonathan A. Fridell,[1] Syed J. Sher,[1] Anne M. Huml,[2] Stephen O. Pastan,[3] Sharon M. Moe,[1] Rachel E. Patzer.[4,1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Cleveland Clinic, Cleveland, OH; [3]Emory University, Atlanta, GA; [4]Regenstrief Institute Inc, Indianapolis, IN.*

Background: Kidney transplant (KTx) improves patient survival and quality of life compared to dialysis, though many inequities exist due to social factors critical for fostering KTx access. To improve equity in KTx in the Ohio River Valley (IN, KY, OH), we must first understand the social drivers of health affecting access in our region.

Methods: Adult patients with incident end stage kidney disease residing in IN, KY, or OH at dialysis start among n=680 dialysis facilities from January 2016-June 2020 (followed through June 2021) were assessed. U.S. Renal Data System data were linked to referral and evaluation data from n=4 KTx centers contributing to the Early Steps to Transplant Access Registry and ZIP code-level characteristics from the 2021 American Community Survey. Associations were assessed between social and clinical variables and key outcomes: 1) evaluation start within 6 months of referral among referred patients, 2) waitlisting within 6 months of evaluation start among all evaluated, and 3) days between these events. Associations were examined—overall and in patient samples stratified by ZIP code-level median household income tertiles—by multivariable logistic regression and log rank test.

Results: Of n=8824 referred patients, 3265 (37%) started evaluation within 6 months and 981 (11%) were waitlisted within 6 months. More patients starting evaluation within 6 months were from high-income areas (39%) vs. middle (29%) and low (32%) ($p<0.001$). Overall, access to KTx was poorer for low-income (vs. high-income), as well as for Medicaid-insured (vs. commercial), Black (vs. non-Hispanic White), and female (vs. male) patients. Inequities were broadly consistent across income groups. For example, Medicaid-insured patients had a longer median time from evaluation start to waitlisting (197 days) vs. commercial insurance (121 days) in low-income areas ($p=0.004$); this disparity was 189 vs. 115 days for high-income ($p=0.047$).

Conclusions: Patients with Medicaid or living in low-income ZIP codes in the Ohio River Valley had reduced access to prewaitlisting KTx services relative to patients with commercial insurance or in high-income areas. This suggests that interventions to improve equity in KTx access should target patients in low-income areas and those without private insurance.

Funding: Other NIH Support - T32 grant Kirschstein-NRSA DK120524; R01 grant (National Institute of Diabetes and Digestive and Kidney Diseases R01DK122701)

FR-PO1042

Nonadherence and Patient Empowerment on the Path to Kidney Transplant

Jennifer L. Mcdonnell, Ellen Idler, Monique Hennink, Adam S. Wilk. *Emory University, Atlanta, GA.*

Background: Compared to dialysis, kidney transplant conveys quality of life and survival benefits, yet only 15% of incident patients are waitlisted or receive a kidney transplant within 1 year of dialysis start. KDIGO guidelines recommend that patients with past non-adherence be considered for kidney transplant, but many kidney care professionals (KCPs) consider transplant to be contraindicated for these patients, potentially contributing to low waitlisting rates among eligible patients. Patients' understanding of non-adherence and its perceived impact on their access to kidney transplant is not well understood.

Methods: We conducted 20 in-depth interviews during 2024 with hemodialysis patients in the US. A semi-structured interview guide was used to explore what non-adherence means to patients in the context of kidney transplant. We purposively recruited patients by age, race, SES, gender, and transplant status to achieve a diverse sample. Interviews were conducted via phone and Zoom and were recorded and transcribed verbatim. We used MAXQDA software to manage data. A grounded theory approach was used to collect and analyze data.

Results: Preliminary results indicate that patients experience tension between being empowered to understand and manage their care and meeting their KCPs' expectations for adherence. Patients described non-adherence as ambiguously defined by KCPs, encompassing a range of behaviors from occasionally missing dialysis treatments to being considered a "difficult patient". Some patients described being labeled "non-compliant" by KCPs when attempting to advocate for their care (e.g., asking questions about recommended testing or expressing concerns about the iatrogenic or social consequences of treatment), resulting in their KCPs denying them referral or waitlisting. Women and Black patients, more often than men and white patients, reported that their efforts to actively engage in their health care were perceived as insubordinate ("If somebody doesn't like what you're saying, they can label you as non-compliant. It's such a scary term for patients.")

Conclusions: Patients consider non-adherence an ambiguously defined and "scary" label that can interfere with their access to kidney transplant. Evidence-based protocols for assessing adherence are needed to reduce potential bias in eligibility decisions when KCPs perceive patients as "non-compliant".

FR-PO1043

It Takes a Village: Barriers to Optimal Pediatric ESKD Care

Judith S. VanSickle, Darcy K. Weidemann, Bradley A. Warady. *Children's Mercy Kansas City, Kansas City, MO.*

Background: Kidney transplantation (KT) is the preferred method of treatment for children with end stage kidney disease (ESKD). Pre-emptive KT (PKT) is associated with improved patient and graft survival. The effect of social isolation due to insufficient family support (IFS) or underlying psychosocial conditions have not been evaluated as a potential additional influential factor in the pediatric ESKD population.

Methods: Single-center, retrospective chart review of 177 children who received ESKD care (dialysis only (D), dialysis followed by KT (D-KT), and PKT only) in our center from 2010 to 2020. Based on patient addresses, neighborhood disadvantage was categorized using the Child Opportunity Index (COI). Pediatric pre-KT psychology evaluations of all patients referred for KT during the study period were reviewed to identify additional barriers to PKT based on 4 standardized questions: AK=adequate knowledge about transplant, AT=ability to adhere to the treatment based on previous history, Psych= relevant mental health issues likely impacting on transplant success in the parents or in the child and evidence of IFS. Groups were compared based on race (R), modalities, and COI groups. Differences in characteristics between groups were determined by the chi-square test. Multinomial logistic regression analysis was conducted to identify the most significant factors influencing receipt of PKT.

Results: PKT was more likely among white children ($p=0.037$) but was not associated with COI ($p=0.095$). Only IFS and Psych in child correlated with a decreased likelihood of PKT;. Subjects were more likely to remain on D if they had IFS ($p<0.001$) or had a Psych in child ($p= 0.002$). IFS was more likely among non-white ($p=0.003$), and families who lived in low COI areas ($p<0.001$). However, Psych in child did not correlate with R ($p=0.54$) or COI (0.67). Multinomial logistic regression was conducted using 4 variables (COI, R, Psych in child and IFS) to evaluate the likelihood of receiving a PKT: with only having no psychiatric illness in the child (LR=8.69, $p=0.013$, OR:0.15 95% CI: 0.032-0.698) and sufficient family support (LR=16.965, $p<0.001$, OR: 5.98, 95% 0.728-49.17) were significant contributing factors to receive a PKT.

Conclusions: Psychosocial issues appear to play a significant role in access to transplant care, with social support from family being a significant predictor for PKT.

Funding: Clinical Revenue Support

FR-PO1044

Examining Insurance-Related Disparities in Kidney Transplantation Access and Outcomes: A Systematic Review and Bibliometric Analysis

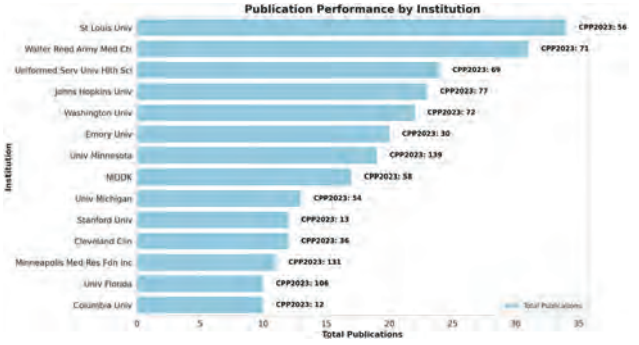
Oscar A. Garcia Valencia,[1] Supawadee Suppadungsuk,[1] Charat Thongprayoon,[1] Caroline Jadlowiec,[2] Napat Leeaphorn,[3] Pooja Budhiraja,[2] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic Arizona, Scottsdale, AZ; [3]Mayo Clinic in Florida, Jacksonville, FL.*

Background: Equitable access to kidney transplantation is vital for patients with end-stage kidney disease, however insurance and social determinants significantly affect access and outcomes. This study examines disparities in waitlisting, access, and post-transplant outcomes based on insurance types, focusing on promoting diversity and equity in kidney health.

Methods: This systematic review and bibliometric analysis from MEDLINE, EMBASE, and Cochrane Database searches up to November 2023, assessed the impact of insurance types on kidney transplantation disparities. The systematic review followed PRISMA guidelines, and the bibliometric analysis examined research trends, leading institutions, and citation impact.

Results: St. Louis University and Walter Reed Army Medical Center lead in publications and citation impact. A systematic review of 15 U.S. studies (2008-2023) revealed disparities in waitlisting and outcomes linked to insurance. Medicare beneficiaries have better survival rates. African Americans on Medicaid are less likely to be added to the waitlist. Public insurance holders have fewer preemptive transplants, heightened mortality and allograft failure rates. Alarmingly, over a quarter of transplant ethics consultations highlight insurance limitations affecting treatment. Those holding dual (private/public) insurance exhibit higher rates of medication nonadherence. Medicare's coverage expansion to include immunosuppressive drugs might help mitigate these disparities.

Conclusions: Our systematic review and bibliometric analysis reveal disparities in kidney transplant outcomes influenced by insurance and social factors. Public insurance holders, especially Medicare or Medicaid beneficiaries, face significant obstacles in transplant access and increased post-transplant risks. Addressing these disparities in kidney transplantation and recognizing the contributions of leading research institutions and investigators is crucial.



FR-PO1045

Amplifying Patient Voices: Artificial Intelligence (AI)-Driven Insights from Kidney Health Discussions on Reddit

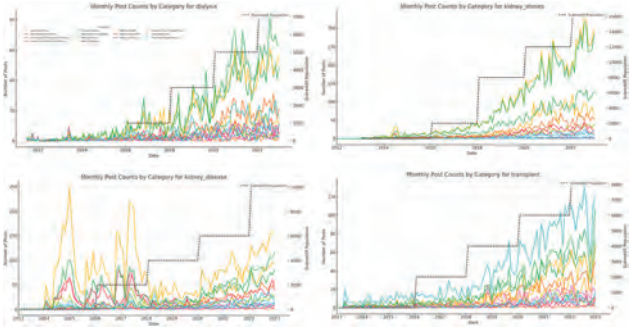
Rajesh Anumolu,[1,2] Aaron Delory,[3] Anil K. Chandraker.[1,2] *[1]University of Massachusetts Chan Medical School, Worcester, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]IO Design Team LLC, Danvers, MA.*

Background: Advancements in technology and social media have revolutionized discussions on medical conditions, surpassing traditional data collection methods in scope and speed. With over 850 million monthly users, platforms like Reddit provide a vast source of user-generated content. By utilizing large language models (LLMs), these discussions can be systematically analyzed to assess community sentiments, track conversations, identify trends, and address unmet needs. This approach offers valuable insights for o guide research, inform product development, and enhance patient support strategies.

Methods: The study analyzed 39,637 posts from subreddits related to kidney health, including /r/dialysis, /r/kidneydisease, /r/kidneystones, and /r/transplant. LLMs were used to categorize and evaluate the content, specifically leveraging OpenAI's Chat GPT-4 to identify trends and insights within each subreddit.

Results: By 2022, kidney-related subreddits saw significant growth: Dialysis (7,000), Kidney Disease (10,000), Kidney Stones (16,000), and Transplant (8,000) subscribers. Discussions often focused on medical queries, treatment experiences, and financial concerns, highlighting the need for advice and support. Spikes in activity correlate with policy changes, economic factors, or medical research, with advocacy events driving periodic increases. Steady population growth and increased post volume indicate active participation. Understanding these trends and the sentiment helps better address community needs.

Conclusions: These insights help healthcare professionals, researchers, and pharmaceutical companies support patient communities, inform product development, and enhance care strategies. LLMs provide real-time insights into patients' states, helping identify issues and adjust care. They study patient experiences, public health trends, side effects, satisfaction, and unmet needs. LLMs highlight health disparities, guiding interventions and inclusive policies. Analyzing social media data with LLMs helps stakeholders understand patient trends, improving outcomes and support strategies.



FR-PO1046

Peer-to-Peer Patient Partner Recruitment: Enhancing Peer Engagement for Successful Patient Partner Recruitment in a National Kidney Health Research Network

Melanie D. Talson,[1,2] Claudia Wilde,[1,2] Charles L. Cook,[2] Kelly Loverock.[2] Can-SOLVE CKD Network. *[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]Can-SOLVE CKD Network, Vancouver, BC, Canada.*

Background: Patient partnership in kidney health research is recognized as an equitable approach to improving patient outcomes. *Patient Partners/People with Lived Experience* (PWLE) are co-researchers with lived experience of illness as patients or caregivers. Methods to recruit PWLE are poorly understood and not widely reported on. Together with two PWLE as co-researchers, we present successful PWLE recruitment strategies within the national Can-SOLVE CKD research network, funded in part by the Canadian Institutes of Health Research's Strategy for Patient-Oriented Research whose focus is on transforming kidney research through meaningful patient engagement. We present the results of the co-development of practical PWLE recruitment methods and tools, including a peer-to-peer recruitment strategy.

Methods: We conducted an environmental scan of existing research in academic publications; gathered data from the network's nine project reports and reviews, from the network website that connects researchers with PWLE; and, finally we conducted a survey and roundtable discussions with two network patient advisory councils to identify the most effective recruitment methods and strategies. Data were consolidated and analyzed thematically to identify successes and challenges to inform the development of a PWLE recruitment toolkit.

Results: A common challenge among researchers is the recruitment of PWLE; especially for recruiting ethnically- and gender-diverse participants. Effective PWLE recruitment strategies are categorized thematically along socio-spatial distances, including: (1) macro-level; (2) meso-level; and (3) micro-level and temporally according to illness/treatment stabilization. Peer engagement in the form of peer-to-peer recruitment is the most common route to patient partnership; however, a multi-faceted approach is the most effective way to reach the most diverse participants.

Conclusions: Recruiting PWLE as partners in research in the kidney health research context may present some challenges, especially for harder-to-reach participants; however, by targeting various levels of reach, considering timing of recruitment and promoting peer-to-peer recruitment will enable a strategy for success.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO1047

Can-SOLVE CKD: Capturing Our IDEA Journey as a Patient-Oriented Kidney Research Network

Keila L. Turino Miranda,[1] Jocelyn M. Jones,[2] Heather Harris,[2] James W. Scholey,[4,2] Melanie D. Talson,[2] Michelle Hampson,[2] Charles L. Cook,[2] Julie Wysocki,[6,7] Taylor Hainstock,[5] Selina Allu.[2,3] *[1]McGill University, Montreal, QC, Canada; [2]Can-SOLVE CKD, Vancouver, BC, Canada; [3]University of Calgary, Calgary, AB, Canada; [4]University of Toronto, Toronto, ON, Canada; [5]BC Support Unit - Island Health, Victoria, BC, Canada; [6]Kidney Foundation of Canada, Montreal, QC, Canada; [7]KRESCENT, Montreal, QC, Canada.*

Background: Despite increasing recognition that Inclusion, Diversity, Equity, and Accessibility (IDEA) principles are essential to research, how to meaningfully quantify and apply these principles at a network level is unclear. Here, we outline a holistic approach taken by our patient-oriented kidney research network, Can-SOLVE CKD.

Methods: A multidisciplinary team, composed of patient partners, researchers, clinicians, and network partners, co-developed a series of 7 brainstorming workshops (3 groups; 19 patient partners, 17 researchers/clinicians, 13 staff from July 2023 to January 2024) to identify the network's existing IDEA strengths and key priorities. A thematic analysis identified themes to inform the network's IDEA mobilization plan.

Results: Four themes were identified: (1) Strength in existing network culture through Indigenous input and patient-oriented approach, establishing culturally safe spaces and ensuring systematic support and safety in communication; (2) Barriers in equitable participation due to a fragmented understanding of opportunities and accommodation limitations; (3) Ensuring permanence within the broader health context via maintenance concerns, awareness of network initiatives and promoting kidney health equity; and, (4) Outreach at the public, network and team levels focused on overcoming recruitment barriers and enhancing impact. This reveals an opportunity to tailor implementation strategies based on the scale of change within the network, ensuring that IDEA interventions are appropriately calibrated to the magnitude of the mobilization plan.

Conclusions: Meaningful assessment and application of IDEA principles requires the involvement of people with diverse lived experiences. We describe a collaborative, holistic approach our patient-oriented kidney research network has taken to identify core strengths and guide our IDEA strategy moving forward.

Funding: Government Support - Non-U.S.

FR-PO1048

Effects of Orally Ingested Microplastics on the Structure and Function of the Kidneys

Hannah Triebel, Frank Schweda, Hayo Castrop. *University of Regensburg, Institute of Physiology, Regensburg, Germany.*

Background: Plastics are chemically inert and durable materials with long-term deposition in the environment. Little is known about the functional consequences of oral microplastic (MP) ingestion. Most MP particles in the environment consist of fibers and irregular fragments. The size, shape, and composition of the MP particles presumably determine the degree of MP toxicity. Thus, fibers are generally more critical than aspherical fragments, and fragments are more problematic than spherical particles. In the present study we assessed the distribution of MP particles in the organism and the consequences of MP deposition in the kidney. We hypothesized that sharp and aspheric particles, mimicking the real-world situation of MP in the environment, are more deleterious compared with spherical particles.

Methods: Aspheric and spheric MP of different polymers were synthetized, and fluorescence labeled (polystyrene, polypropylene, polyethylene terephthalate, 1-50 µm). The deposition of the labeled particles was determined in mice after oral gavage (2.5 mg/d, 5 or 10 consecutive days, 30 mice (n=6 each)). 3-D histological assessment was performed by fluorescence confocal microscopy of thick tissue sections. In addition, the quantitative organ distribution was determined in vivo using MP with embedded upconverting nanoparticles ($NaYF_4$:Yb,Tm).

Results: We found a considerable enrichment of MP particles in the kidney. Furthermore, MP particles were present in renal blood vessels including glomerular capillaries. Large MP particles (> 5 µm) were also found in the lumen of some tubules of the renal cortex and were accompanied by an influx of immune cells, suggesting a pro-inflammatory effect of MP particles. Experiments using the isolated perfused kidney model showed the increased tubular uptake of labeled albumin in nephrons in which particles were located, suggesting a loss of the integrity of the filtration barrier with subsequent passage of particles from glomerular capillaries into the tubular system.

Conclusions: In summary, ingested MP particles with properties similar to those found in the environment, compromise the structural and functional integrity of the kidney and may trigger local inflammatory responses leading to kidney injury.

Funding: Government Support - Non-U.S.

FR-PO1049

Effects of Type of Protein Intake on Risk of Kidney Disease Progression among Patients with Nondialysis-Dependent CKD: A Systematic Review

Michelle M. Wong,[1] Dani Renouf,[2] Megan Borkum,[1] Emily Lauren L. Simms,[1] Nicole Huang,[3] Adeera Levin.[1] *[1]University of British Columbia, Vancouver, BC, Canada; [2]St. Paul's Hospital, Vancouver, BC, Canada; [3]Fraser Health Authority, Surrey, BC, Canada.*

Background: While diets restricted in protein quantity are recommended by kidney nutrition guidelines, the effect of the type of protein on CKD progression is not known. Thus, we performed a systematic review to assess the effects of plant-based diets on CKD progression.

Methods: We searched MEDLINE, EMBASE, Cumulative Index of Nursing and Allied Health Literature, Education Resources Information Center, Cochrane Central Register of Controlled Trials, Web of Science from January 1990-November 28, 2022. We included RCTs and observational studies with prospectively-collected data assessing type of protein in patients with non-dialysis CKD. The primary outcome was progression to kidney failure. Secondary outcomes included change in eGFR, albuminuria, all-cause mortality, quality of life. Two authors independently screened titles/abstracts, reviewed full text articles, and extracted data. Meta-analysis was not possible due to variability in outcome reporting and sparse data. Risk of bias was assessed using the Nutrition Quality Evaluation Strengthening Tools.

Results: Eight studies assessing type of protein or dietary patterns emphasizing plant-based food were included. There were 3 RCTs (N=179 patients), which assessed soy protein (2 studies) and Mediterranean diet (1 study) *vs.* control diets. There were 5 cohort studies (N=4221) assessing plant-based protein intake (3 studies), Mediterranean diet score (1 study), and DASH diet score (1 study). While RCTs demonstrated inconsistency in eGFR outcome, cohort studies demonstrated that higher plant-based protein intake and higher DASH/Mediterranean diet scores were associated with lower risks of end-stage kidney disease and mortality (Figure). Risk of bias was high in RCTs due to selection bias.

Conclusions: Our systematic review of type of protein on CKD progression demonstrated reduced risk of CKD progression in cohort studies, but RCT evidence was limited.

Figure. Summary of Findings

Outcome	Type of Study	Intervention/ exposure of interest and comparator	Range of Effects	# of studies by result	# of participants (# of studies)	Certainty of Evidence
Kidney Failure (ESKD)	RCT Cohort	N/A High vs. low DASH diet score	N/A Adjusted HR 0.38 (95% CI 0.26-0.53) to 0.83 (95% CI 0.69-0.99)	0 2 studies favored high DASH diet score	0 3513 (2)	N/A Moderate
Change in eGFR	RCT	Soy protein diet; Mediterranean diet vs. control diet	% change: -5.9% plant-based diet vs. +11.3% control diet (p=0.048) Mean difference: 0.15 to 0.60 ml/min/1.73 m^2 (95% CI -1.21-2.41)	1 study favored soy protein diet 2 studies: no statistically significant difference	179 (3)	Low
	Cohort	Plant protein as a continuous measure	Adjusted change in eGFR: 0.17 (95% CI -0.03 - 0.38) to 1.60 (-19.7 - 22.3) ml/min/1.73 m^2 for each 10 g/day of plant protein	1 study favored higher plant-based protein intake 1 study: no statistically significant difference	858 (2)	Moderate
Mortality	Cohort	High vs. low DASH diet score; High vs. low plant protein intake to total protein ratio	Adjusted HR 0.67 (95% CI 0.46-0.96) to 1.07 (95% 0.84-1.35)	2 studies favored of high DASH diet score or high plant protein diet 1 study: no statistically significant difference	4578 (3)	Moderate

FR-PO1050

Beverage Patterns and Risk of CKD Progression in the Diet, CKD, and Apolipoprotein L1 (DCA) Study

Tolulope V. Adebile,[1] Runqi Zhao,[1] Theophilus I. Umeizudike,[7] Bolanle A. Omotoso,[2] Nanna R. Ripiye,[3] Yemi R. Raji,[4] Ernestina Eduful,[12] Rasheed A. Gbadegesin,[5] Edward P. Kwakyi,[6] Manmak Mamven,[3] Adaobi Solarin,[7] Ifeoma I. Ulasi,[8] Dwomoa Adu,[6] Akinlolu Ojo,[9] Sushrut S. Waikar,[1] Rulan S. Parekh,[10] Diane C. Mitchell,[11] Titilayo O. Ilori.[1] *[1]Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [2]Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Nigeria; [3]University of Abuja Teaching Hospital, Gwagwalada, Nigeria; [4]University of Ibadan and University College Hospital, Ibadan, Nigeria; [5]Duke University Medical Center, Durham, NC; [6]Department of Medicine and Therapeutics, University of Ghana Medical School, Accra, Ghana; [7]Lagos State University College of Medicine, Ojo, Nigeria; [8]College of Medicine, University of Nigeria, Nsukka, Nigeria; [9]The University of Kansas School of Medicine, Kansas City, KS; [10]Department of Medicine, Women's College Hospital, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada; [11]Texas A&M AgriLife Research, College Station, TX; [12]The Bank Hospital, Accra, Ghana.*

Background: A few studies have established a relationship between beverage patterns and CKD progression, with sugar-sweetened beverages increasing the risk of CKD. We aim to identify beverage consumption patterns of well-phenotyped West Africans with CKD and examine their association with CKD progression.

Methods: We conducted a prospective analysis from the DCA cohort (n=748) to investigate diet-gene interactions in APOL1. We included data from a subset of

participants with complete information on beverage intake from the 24-hour dietary recalls. CKD progression was defined as ≥40% decline from baseline eGFR at enrollment to DCA (2021-2023) and initiation of dialysis. Beverage consumption patterns were identified through principal component (PC) analysis, and their associations with CKD progression were analyzed using multivariate Cox proportional hazard models.

Results: There were 52 cases of CKD progression over a median follow-up period of 31 (IQR: 33.41,25.17) months. We identified four beverage patterns (Table), of which Low Sugar-Sweetened Beverages Plus Alcohol Beverage Pattern demonstrated a significantly lower risk of CKD progression [tertile 2 vs 1 HR: 0.42, 95% CI: 0.19,0.93].

Conclusions: The Low Sugar-Sweetened Beverages Plus Alcohol Beverage Pattern was associated with lower risk of CKD progression, indicating that moderate adherence to this pattern is linked to a reduced risk of CKD progression. The study is the first to establish the beverage patterns of well-phenotyped West African CKD patients and their association with CKD progression. Future investigations should conduct long-term prospective studies to validate and further explore the observed association.

Funding: NIDDK Support, Commercial Support - Department of Medicine, Boston Medical Center.

Table: Association of Beverage Consumption Patterns* in the Diet, CKD, and APOL1 study with CKD Progression (n =304)

	Tertile of Beverage Patterns'			Continuous	P-value
	Tertile 1	Tertile 2	Tertile 3		
Alcoholic Beverage Pattern (PC1)					
Model 1	1 (ref)	1.64 (0.75, 3.59)	2.16 (0.10, 4.65)	1.10 (0.80, 1.52)	0.55
Model 2	1 (ref)	1.67 (0.74, 3.74)	2.01 (0.84, 4.80)	1.07 (0.79, 1.46)	0.65
Dairy and Tea Beverage Pattern (PC2)					
Model 1	1 (ref)	0.53 (0.23, 1.21)	0.89 (0.44, 1.79)	0.95 (0.72, 1.26)	0.74
Model 2	1 (ref)	0.53 (0.22, 1.27)	1.04 (0.50, 2.17)	0.96 (0.71, 1.30)	0.79
Low Sugar-Sweetened Beverages Plus Alcohol Beverage Pattern (PC3)					
Model 1	1 (ref)	0.58 (0.31, 1.10)	1.01 (0.47, 2.17)	1.05 (0.80, 1.36)	0.74
Model 2	1 (ref)	**0.42 (0.19, 0.93)**	0.64 (0.27, 1.48)	1.03 (0.77, 1.36)	0.86
Medium Sugar-Sweetened Beverage Pattern (PC4)					
Model 1	1 (ref)	0.80 (0.45, 1.43)	0.59 (0.20, 1.74)	0.84 (0.58, 1.23)	0.38
Model 2	1 (ref)	0.93 (0.50, 1.75)	0.37 (0.10, 1.41)	0.81 (0.53, 1.23)	0.32

** Each beverage consumption pattern was defined by the correlation of the PCs with the beverage consumed (±0.20).*

' The participants received a score for each pattern based on their consumption and the PC scores were divided into three equal groups to facilitate comparisons. Tertile 3 represents the highest adherence to a specific beverage pattern, tertile 2 moderate, and tertile 1 the lowest.

Model 1: adjusted. for age, sex, and Pid site.

Model 2: adjusted for Hypertension, age, Sex, Education, Income, Smoking, Diabetes, proteinuria, baseline eGFR, BMI, Total Energy (per 1,000 KCAL), and Pid site.

The proportional assumption was tested, with no violations observed.

FR-PO1051

Kidney Function and Ultra-processed Food Intake among Older Puerto Rican Adults Living in Boston

Kristin Leonberg,[1] Kaylea D. Flanagan,[2] Katherine L. Tucker,[2] Tammy Scott,[1] Manish Maski,[3] Elena N. Naumova.[1] *[1]Tufts University Friedman School of Nutrition Science and Policy, Boston, MA; [2]University of Massachusetts Lowell, Lowell, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Ultra-processed food (UPF) intake has been associated with higher chronic kidney disease (CKD) risk and disease progression. These foods are ready-to-eat industrial formulations offering convenience and lower cost, but lower nutritional value. Trends in increased consumption have been reported among the general United States (US) population across the lifecycle and among population subgroups. Previous reports indicate that, in the US Hispanic population, 63% of energy intake is from UPF. However, these studies do not provide specific information on the Puerto Rican (PR) subpopulation, as the composition of the Hispanic race/ethnic groups remain unclear. We, therefore, aimed to describe kidney function and UPF intake and their trends among older adults enrolled in the Boston Puerto Rican Health Study (BPRHS).

Methods: The BPRHS is a longitudinal cohort of older PR adults in the Boston area, established in 2004. We estimated kidney function (eGFR) using the 2021 CKD_{epi} equation (without race) at baseline, and ~2 and ~6-year follow-ups. We estimated the percentage of energy intake (Pkcal) from UPF using dietary data collected with a food frequency questionnaire, and identified UPF based on the Nova processed food classification system at baseline and ~2-y follow-up.

Results: At baseline, 1371 (71% female) adults with mean (SD) age 57.1 (7.6) y had eGFR and Pkcal-UPF data available. Mean (SD) eGFR was 91 (±18.0) mL/min/1.73m^2. Mean (SD) Pkcal-UPF was 27% (±12%) and did not differ between males and females (P = 0.43). A total of 1145 (71% female) adults had eGFR and Pkcal-UPF data available at the ~2-year follow-up. Mean eGFR decreased by 3% (87.9 mL/min/1.73m^2) after ~2-y and Pkcal-UPF remained similar, representing 26% (±12%) dietary intake.

Conclusions: Among participants enrolled in BPRHS, the Pkcal-UPF was relatively low, relative to reports from other populations. Further evaluation is needed to assess the temporal association between Pkcal-UPF and eGFR decline in this population.

FR-PO1052

Association between Healthy Dietary Patterns and CKD: Findings from the Korean National Health and Nutrition Examination Survey (KNHANES), 2019-2021

Minsang Kim,[1] Kyungdo Han,[2] Sehoon Park,[1] Jin hyuk Paek,[3] Woo Yeong Park,[3] Kyubok Jin,[3] Seungyeup Han,[3] Dong Ki Kim,[1] Yaerim Kim.[3] *[1]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [2]Soongsil University, Dongjak-gu, Seoul, Republic of Korea; [3]Keimyung University School of Medicine, Daegu, Republic of Korea.*

Background: A healthy dietary pattern is linked to a lower risk of developing chronic kidney disease (CKD) and its progression. Considering the different dietary pattern by country, we aim to evaluate the impact of dietary pattern on the risk of incident CKD using the Korean Healthy Eating Index (KHEI), a tool designed to assess diet quality in Koreans.

Methods: In this cross-sectional study, we included participants ≥19 years-old in the eighth Korean national health and nutrition examination survey conducted from 2019 to 2021. The KHEI consists of 3 categories and 14 components (eight for adequacy, three for moderation, three for balance), with a higher KHEI indicating healthier eating habits. CKD was defined as an estimated glomerular filtration rate <60 mL/min/1.73m^2 or urine albumin-creatinine ratio ≥30 mg/g. The risk of CKD was evaluated according to the quartiles of the KHEI using logistic regression analysis, adjusted for various clinicodemographic characteristics.

Results: In total, 12,454 participants were included in this study. Those in the higher quartile of the KHEI were older, had lower proportions of men, current smoker, and heavy alcohol drinker. Although there were higher proportion of CKD or lower eGFR in the highest quartile of KHEI, adjusted mean of KHEI was lower in participants with CKD. Among the subcategories of KHEI, there was no difference in moderation or energy balance, but the score of most components in adequacy category were higher in participants with CKD (Figure 1). Participants in the highest quartile of KHEI had a significantly lower risk of CKD (adjusted odds ratio, 0.75 [0.60–0.95]) compared to those in the lowest quartile (Table 1).

Conclusions: The dietary pattern representing KHEI is associated with various characteristics including comorbidities. A greater KHEI decreased risk of incident CKD, and healthy eating pattern would be suggested especially in participants with a risk of CKD.

FR-PO1053

Effects of Sulforaphane Supplementation on Gut Microbiota in Nondialysis-Dependent Patients with CKD

Denise Mafra,[1,2] Marcia M. Ribeiro,[2] Isadora Britto,[2] Bruna R. de Paiva,[1] Ludmila F. Cardozo,[1] Pedro Ivo N. de Almeida,[3] Henrique F. Santos.[1] *[1]Universidade Federal Fluminense, Niteroi, Brazil; [2]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [3]Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil.*

Background: Gut dysbiosis is associated with systemic inflammation and the accumulation of uremic toxins. Sulforaphane isothiocyanate (SFN) is a bioactive compound derived from cruciferous vegetables that may mitigate gut dysbiosis. SFN has anti-inflammatory and antioxidant properties, improving permeability and intestinal function and impacting dysbiosis. This study aimed to explore the effects of SFN supplementation on gut microbiota in patients with CKD.

Methods: This study was a placebo-controlled longitudinal study. The patients were randomly assigned to either the intervention group, which received 400 ug/day of SFN, or the placebo group, which received corn starch for 30 days. We assessed the fecal microbiome using high-throughput sequencing of 16S rRNA gene amplicons on the Illumina MiSeq platform. The data was processed using the QIIME 2 software package. We calculated the alpha diversity using RStudio and the phyloseq library. We used a network of nodes and edges to represent the genus-level taxa and the correlations between them. We analyzed the co-occurrence patterns using the SparCC algorithm and the SpiecEasi library in R. The PageRank algorithm was used to identify the core members of each microbiome. We performed Kruskal-Wallis and PERMANOVA tests to analyze differences between profiles.

Results: 16 patients participated (12 women, age 61.4 ± 11.6 years, BMI 30.1 ± 7.0 kg/m^2, and glomerular filtration of 37.4 ± 12.9 mL/min). We constructed gender co-occurrence networks for SFN and placebo groups. After the intervention, the frequency of genera Bacteroidetes, Firmicutes, and Proteobacteria was reduced (Fig 1).

Conclusions: The intervention simplified the co-occurrence network of microbial generation in the gut of non-dialysis CKD patients. Expressing the ability of SFN to modify the diversity of the gut microbiota.

Funding: Government Support - Non-U.S.

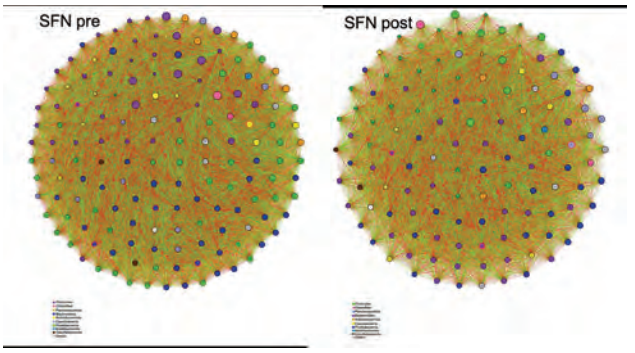


Fig 1. Co-occurrence measures in patients who received SFN

FR-PO1054

Effects of Propolis Supplementation on the Gut Microbiota in Patients Undergoing Hemodialysis: A Randomized Controlled Clinical Trial

Denise Mafra,[1,2] Larissa d. Fonseca,[1] Marcia M. Ribeiro,[2] Júnia Schultz,[3] Andresa Berretta,[4] Marcelo Ribeiro-Alves,[5] Alexandre Rosado.[3] *[1]Universidade Federal Fluminense, Niteroi, Brazil; [2]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [3]King Abdullah University of Science and Technology, Thuwal, Saudi Arabia; [4]Apis flora, Ribeirão Preto, Brazil; [5]Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil.*

Background: Several studies have shown that propolis (resin made by bees) could modulate gut microbiota *in vitro* and animal models. However, no study has been conducted on patients with chronic kidney disease (CKD) undergoing hemodialysis (HD). This study aimed to evaluate the effects of propolis supplementation on the gut microbiota of CKD patients undergoing HD.

Methods: This is a longitudinal, double-blind, placebo-controlled trial with 42 patients randomized into two groups: one group received propolis (4 capsules of 100 mg/day containing concentrated and standardized dry EPP-AF® green propolis extract), and the other group received a placebo (4 capsules of 100 mg/day containing microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide) for two months. Gut microbiota composition was assessed by extracting fecal DNA, PCR amplification of the V4 region of the 16S rRNA gene, and short-read sequencing on the Illumina NovaSeq PE250 platform.

Results: Forty-one patients completed the study, with twenty in the placebo group [45.5 ± 14 years, seven men and 13 women, BMI 24.8± 6.8 kg/m^2, time on HD 44.5 ± 46.5 months, Kt/V 1.7 ± 0.58] and twenty-one in the propolis group [45 ± 12 years, eight men and 13 women, BMI 22.8 ± 3.7 kg/m^2, time on HD 68 ± 60 months, Kt/V 1.66 ± 0.44]. The obtained data revealed that propolis supplementation increased the gut microbiota's evenness and richness (observed) (**Fig. 1**).

Conclusions: Short-term supplementation with EPP-AF® propolis dry extract seems to increase the alpha diversity of gut microbiota in patients with CKD on HD.

Funding: Government Support - Non-U.S.

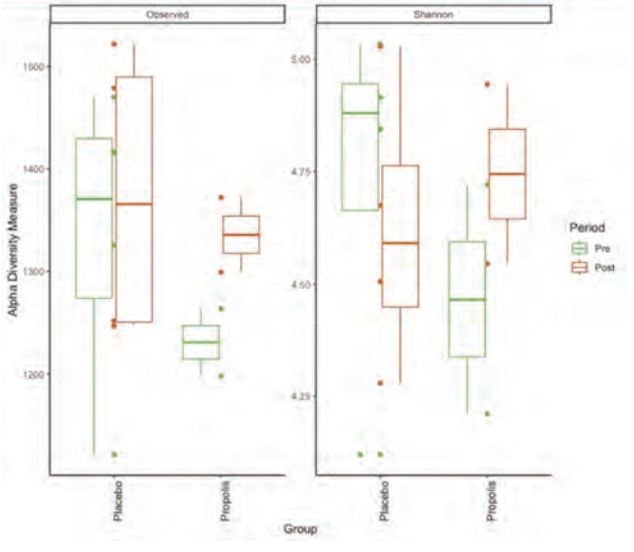


Fig 1. Alpha-diversity of CKD (HD) patients' gut microbiota on propolis and placebo supplementation. (A) Observed zOTUs (richness) and (B) Shannon index (diversity).

FR-PO1055

Impact of Fermentable and Viscous Dietary Fiber on Gut-Derived Uremic Toxins in Rats with Progressive CKD

Annabel Biruete,[1,2] Kalisha O'Neill,[2] Kathleen M. Hill Gallant,[4,2] Henriette de Loor,[3] Pieter Evenepoel,[3] Neal X. Chen,[2] Sharon M. Moe.[2] *[1]Purdue University, West Lafayette, IN; [2]Indiana University School of Medicine, Indianapolis, IN; [3]Katholieke Universiteit Leuven, Leuven, Belgium; [4]University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Dietary fiber has been shown to lower gut-derived uremic toxins. However, this effect may depend on the fiber's physicochemical properties. Our goal was to examine the dietary fiber impact based on their fermentability (i.e., metabolized by the gut microbiota) and viscosity (i.e., gel-forming capacity) properties on circulating and urinary microbially-derived uremic toxins in a rat model of progressive CKD.

Methods: 22-wk-old Cy/+ male rats (~50% kidney function of normal; CKD hereafter) were randomly assigned to one of four treatments (all 10% w/w; **Table 1**). Treatments lasted 10 wk and rats were euthanized at 32-33 wk of age (kidney failure; ~15% of normal). During the last week of the study, rats were placed in metabolic cages for 3 days for urine collection. Serum and urine creatinine (Cr) were analyzed using colorimetric assays; indoxyl sulfate, P-cresyl sulfate, and phenyl sulfate were quantified in urine (normalized to Cr) and serum by ultra-performance liquid chromatography-tandem mass spectrometry. One-way ANOVA was used to test the effect of dietary fiber types on outcomes with post-hoc comparisons vs. cellulose.

Results: At 32-33 wk, serum indoxyl sulfate was not different between treatments, but urinary indoxyl sulfate was 2-3 times higher with pectin compared to cellulose ($p=0.008$). Serum P-cresyl sulfate was lower in the inulin and psyllium groups compared to cellulose ($p<0.0001$), but urinary P-cresyl sulfate was 7-17 times higher in pectin compared to cellulose ($p<0.0001$). Serum phenyl sulfate was lower in the psyllium and pectin groups compared to cellulose ($p<0.0006$), but urinary phenyl sulfate was lower in all groups compared with cellulose ($p<0.009$). Of note, serum and urine phenyl sulfate concentrations were near zero in the psyllium-treated rats.

Conclusions: Aromatic amino acid-derived uremic toxins were differentially impacted by dietary fiber types in rats with progressive CKD. This suggests that fiber's fermentability and viscosity properties are important to consider in future trials.

Funding: Other NIH Support - KL2/K12 awards: KL2TR002530, UL1TR002529, K12TR004415/TR/NCATS

Table 1. Treatment groups

Treatment	Fermentable	Viscous
Cellulose	No	No
Inulin	Yes	No
Psyllium	No	Yes
Pectin	Yes	Yes

FR-PO1056

Investigating the Correlation between Serum Cholinesterase Levels and Kidney Function

Chenyu Lei, Xinyi Fu, Wenjing Cai, Qingying Shi, Anning Xu, Linlin Yuan, Xinling Liang, Zhiming Ye, Zhilian Li. *Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangdong, China.*

Background: Serum cholinesterase is a commonly used biomarker for organophosphate poisoning and liver function assessment. However, the relationship between serum cholinesterase levels and renal function, as defined by estimated Glomerular Filtration Rate (eGFR), remains poorly understood. This retrospective study aimed to explore the correlation between these two biomarkers in a large patient cohort.

Methods: We retrospectively analyzed data from 488,118 patients aged 18 years or older with renal and liver function data from Guangdong Provincial People's Hospital from January 2019 to October 2023. Patients with abnormal liver function tests were excluded. Patients were stratified into five groups based on estimated glomerular filtration rate (eGFR) according to KDIGO CKD staging guidelines. Serum cholinesterase levels were compared across these groups using the Kruskal-Wallis test. Statistical analyses were performed using SPSS version 22.0.

Results: The median serum cholinesterase in the study population was 7837.00 U/L (IQR: 6693.00 - 9018.00 U/L). A significant inverse correlation was observed between serum cholinesterase levels and eGFR ($p < 0.01$). Median serum cholinesterase levels decreased progressively with declining eGFR, as shown below: eGFR ≥ 90 mL/min/1.73 m^2: 7917.0 (6789.0, 9097.0) U/L eGFR 60-89 mL/min/1.73 m^2: 7888.0(6768.0,9035.0)U/L eGFR 30-59 mL/min/1.73 m^2:7251.0(6097.0,8451.0)U/L eGFR 15-29 mL/min/1.73 m^2: 6201.0(4982.5,7468.5)U/L eGFR < 15 mL/min/1.73 m^2: 5907.0(4861.0,6980.0) U/L Pairwise comparisons between each eGFR group also revealed statistically significant differences ($p < 0.01$).

Conclusions: Our findings demonstrate a clear association between serum cholinesterase levels and renal function decline. As eGFR decreases, serum cholinesterase levels significantly decrease, suggesting a potential role for serum cholinesterase as a marker of renal dysfunction progression. Further research is warranted to explore the clinical implications of this association.

FR-PO1057

Association between Dietary Fiber Intake and Uremic Pruritus in Patients with CKD

Yihuan Cai, Qianqian Han, Fengchu Qing, Qiongqiong Yang. *Sun Yat-Sen Memorial Hospital, Guangzhou, China.*

Background: Uremic pruritus is one of the common symptoms of chronic kidney disease (CKD). Previous studies suggest that mild-inflammation may be one of the causes. The role of dietary fiber in reducing inflammatory factors has become increasingly recognized. It is not clear whether the level of intake of dietary fiber is related to the itchiness in CKD patients.

Methods: This was a cross-sectional study that included patients with CKD stages 1-5 and excluded those who used hormones and immunosuppressants within 3 months and suffered from other skin diseases. The level of itchiness was assessed by visual analog scale (VAS). Patients were classified as pruritus group(VAS >0) and non-pruritus group(VAS = 0). Dietary fiber intake was recorded using a 3-day dietary survey method. The differences in intake of total dietary fiber, vegetable dietary fiber, and cereal dietary fiber were compared between different groups.

Results: A total of 151 patients were included in this study, with a median age of 49.00 (37.00, 58.00) years and a median eGFR of 28.07 (8.27, 77.00) ml/min/1.73m^2. A total of 42 (27.81%) patients had pruritus, the mean itch VAS score was 5.28±0.35. Compared to patients without pruritus, CKD patients with pruritus were older [53.50(45.75, 61.00) years *vs* 47.00(34.00 56.00) years, *P*=0.003], lower glomerular filtration rate [9.87 (5.23, 37.35) ml/min/1.73m^2 *vs* 36.15 (12.04, 83.98) ml/min/1.73m^2, *P* <0.001], blood potassium [4.37(3.89,4.82) mmol/L *vs* 4.07(3.70,4.43) mmol/L, *P* =0.018], and had higher eosinophil levels [0.22(0.13,0.40) x 10^9/L *vs* 0.16(0.08,0.26) x 10^9/L, *P*=0.007]. For dietary fiber intake, pruritic patients consumed less vegetable dietary fiber than non-pruritic patients [3.55(2.20,5.03) g/day *vs* 4.40 (2.55,6.40) g/day, *P*=0.011], but there was no difference in terms of grain dietary fiber [2.55(1.78,3.33) g/day *vs* 2.30(1.50. 3.20) g/day, *P*=0.419]. In unadjusted logistic regression, lower vegetable dietary fiber was associated with a higher risk of itching (OR:0.819, 95% CI: 0.695-0.965, *P*=0.017). However, after adjusting for age, serum creatinine, and blood potassium, vegetable dietary fiber was not associated with the risk of itching (*P*=0.059).

Conclusions: Patients with pruritus in CKD consumed less vegetable dietary fiber than those without pruritus. Low levels of vegetable dietary fiber intake may be associated with uremic pruritus.

FR-PO1058

Dietary Fiber Intake and Mental Health in a Multicenter Prospective Hemodialysis Cohort

Yoko Narasaki,[1] Amy S. You,[1] Silvina Torres Rivera,[1] Danh V. Nguyen,[2] Kamyar Kalantar-Zadeh,[3] Connie Rhee.[1] *[1]University of California Los Angeles, Los Angeles, CA; [2]University of California Irvine, Irvine, CA; [3]Harbor-UCLA Medical Center, Torrance, CA.*

Background: While studies in CKD patients show dietary fiber intake is associated with better health outcomes including lower incidence of CKD, risk of CV events, generation of uremic toxins and inflammatory markers, and less symptom burden (i.e., constipation), little is known about the impact of dietary fiber intake on mental health. We thus sought to examine the relationship of dietary fiber intake with depression in a prospective HD cohort.

Methods: Among 584 HD patients from the multicenter NIH MADRAD cohort recruited across 16 outpatient dialysis clinics, information regarding dietary fiber intake obtained via protocolized Food Frequency Questionnaires (FFQs) and depression severity ascertained by the Beck Depression Inventory-II (BDI-II) administered over 10/2011-9/2022. We examined associations of dietary fiber intake categorized as quartiles with likelihood of having a low (more favorable) BDI-II score (i.e., lowest quartile [Q1]) using multivariable logistic regression models.

Results: The mean±SD of age of the cohort was 54±15 years, among whom 55% were male, 33% were of Black race, and 48% were of Hispanic ethnicity. In unadjusted, case-mix, expanded case-mix, and expanded case-mix+laboratory adjusted analyses, the highest quartile (Q4) of residual dietary fiber intake was associated with higher likelihood of a lower (more favorable) BDI-II score (Ref: Q1, Table 1). In the expanded case-mix+laboratory models, compared to patients with the lowest quartile (Q1) of fiber intake, those with the highest quartile (Q4) of fiber intake had a 2.3 higher likelihood of having a more favorable BDI-II score.

Conclusions: In a well-characterized prospective HD cohort, higher dietary fiber intake was associated with lower likelihood of depression. Further studies are needed to determine the causal mechanisms underlying dietary fiber intake and mental health in this population.

Funding: NIDDK Support

	Residual Dietary Fiber Intake			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Unadjusted model	Reference	1.73 (0.92, 3.26)	**1.97 (1.07, 3.62)**	**2.34 (1.29, 4.27)**
Case-mix model	Reference	1.75 (0.93, 3.31)	**2.05 (1.10, 3.84)**	**2.41 (1.29, 4.50)**
Expanded case-mix model	Reference	1.69 (0.88, 3.25)	**1.99 (1.05, 3.78)**	**2.42 (1.27, 4.60)**
Expanded case-mix + laboratory	Reference	1.64 (0.85, 3.18)	**1.97 (1.03, 3.76)**	**2.31 (1.20, 4.43)**

FR-PO1059

Effects of Intradialytic Parenteral Nutrition on Blood Glucose in Patients on Maintenance Hemodialysis: A Multicenter, Randomized, Open-Label Study

Miyuki Tani,[1] Michihiro Hosojima,[2] Hideyuki Kabasawa,[2] Eiichiro Kanda,[3] Miho Nagai,[4] Toshiko Murayama,[5] Satoru Kamoshita,[1] Akiyoshi Kuroda,[6] Yoshihiko Kanno.[4] *[1]Medical Affairs Department, Research and Development Center, Otsuka Pharmaceutical Factory, Inc., Tokyo, Japan; [2]Department of Clinical Nutrition Science, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [3]Department of Health Data Science, Kawasaki Medical School, Okayama, Japan; [4]Department of Nephrology, Tokyo Medical University, Tokyo, Japan; [5]Department of Health and Nutrition, Faculty of Human Life Studies, University of Niigata Prefecture, Niigata, Japan; [6]Research and Development Center, Otsuka Pharmaceutical Factory, Inc., Tokyo, Japan.*

Background: The intradialytic parenteral nutrition (IDPN) is reported to improve the nutritional status in the dialysis patients. However, effects of IDPN on the blood glucose (BG) are not enough studied while intra-dialysis unconscious hypoglycemia is the issue if the patients are malnourished.

Methods: Study patients were 27 maintenance hemodialysis patients. The investigational (IE) group received the IDPN with ENEFLUID® (550mL; energy, 310kcal; glucose, 37.5g; amino acids, 15g; lipid, 10g) 3 times a week for 12 weeks (wks); control (CT) group did not. The interstitial fluid glucose concentration was monitored every 15 minutes 2 wks after study initiation and before study completion. Outcomes: frequencies and durations of hypoglycemia (BG<70mg/dL) and hyperglycemia (BG>180mg/dL) per 24 hours, area over the curve for glucose<70mg/dL (AOC) per 24 hours, area under the curve for glucose>180mg/dL (AUC) per 24 hours, and Time in Range (BG, 70-180mg/dL). The Mann-Whitney U test was used for the intergroup comparisons.

Results: Mean age was 70.6 and mean body mass index was 19.9 for the study patients. Patients used for the statistical analysis were 14 in the IE group and 13 in the CT group; however, 2 of the IE group withdrew and could not receive the BG monitoring 2 wks before study completion. The median [interquartile range (IQR)] frequency of hypoglycemia during dialysis for 2 wks were smaller in the IE group than in the CT group resulting in a significant difference between 2 groups: 2 wks after study initiation, 0.0 (0.0-2.0) in the IE group and 6.9 (0.0-56.7) in the CT group; P=0.01; 2 wks before study completion, 0.0 (0.0-7.6) in the IE group and 12.0 (0.0-30.3) in the CT group; P=0.04. Similar results were obtained for the duration of hypoglycemia and AOC. No intergroup difference was observed for the frequency and duration of hyperglycemia and AUC. The median (IQR) Time in Range during dialysis for 2 wks after the study initiation was 100 (98-100)% in the IE group and 86 (41-99)% in the CT group (P=0.005), showing that higher proportion of the IE group patients achieved the target BG.

Conclusions: The IDPN with ENEFLUID® in the maintenance hemodialysis patients may suppress the hypoglycemia while not increasing the hyperglycemia.

Funding: Commercial Support - Otsuka Pharmaceutical factory Inc.

FR-PO1060

Efficacy and Safety of Intradialytic Parenteral Nutrition Using ENEFLUID in Malnourished Patients Receiving Maintenance Hemodialysis: A Multicenter, Randomized, Open-Label Study

Hideyuki Kabasawa,[1] Michihiro Hosojima,[1] Eiichiro Kanda,[2] Miho Nagai,[3] Toshiko Murayama,[4] Miyuki Tani,[5] Satoru Kamoshita,[5] Akiyoshi Kuroda,[6] Yoshihiko Kanno.[3] *[1]Department of Clinical Nutrition Science, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Department of Health Data Science, Kawasaki Medical School, Okayama, Japan; [3]Department of Nephrology, Tokyo Medical University, Tokyo, Japan; [4]Department of Health and Nutrition, Faculty of Human Life Studies, University of Niigata Prefecture, Niigata, Japan; [5]Medical Affairs Department, Research and Development Center, Otsuka Pharmaceutical Factory, Inc., Tokyo, Japan; [6]Research and Development Center, Otsuka Pharmaceutical Factory, Inc., Tokyo, Japan.*

Background: The objective of this study was to investigate the efficacy and safety of intradialytic parenteral nutrition (IDPN) using ENEFLUID® (310 kcal, 550 mL) in mild-moderate malnutrition patients receiving maintenance hemodialysis.

Methods: A total of 40 adult patients with a Nutritional Risk Index-Japanese Hemodialysis (NRI-JH) score of 5-10 were enrolled in this multicenter, randomized, open-label study. Patients in the intervention group received IDPN using ENEFLUID® via the dialysis circuit 3 times a week for 12 weeks; those in the control group did not. The primary endpoint was change in serum transthyretin (TTR). The secondary endpoints were changes in nutritional laboratory tests, nutritional parameters, food intake.

Results: For both groups, mean age (72.1±11.4 years) and BMI (20.3±3.0), and median NRI-JH score [7.0 (interquartile range, 6 – 8)], did not differ. One patient withdrew before intervention, leaving 20 intervention and 19 control patients. Mean (95% confidence interval) change in serum TTR (mg/dL) at 12 weeks did not differ between groups: Intervention, 1.0 (-1.1 – 3.2); Control, -0.3 (-2.4 – 1.9); Intragroup difference, 1.3 (-1.7 – 4.3); P = 0.41. The values reflecting protein intake at 12 weeks compared to those on the study initiation day increased in the intervention group [the changes of blood urea nitrogen, 9.4 (2.6 – 16.2) mg/dL; P = 0.007, and normalized protein catabolic rate, 0.10 (0.02 – 0.18) g/kg/day; P = 0.02]. Mean food protein intake (g/kg/day) at 12 weeks increased in the intervention group and decreased in the control group, and differed between groups: Intervention, 0.12 (-0.03 – 0.28); Control, -0.18 (-0.43 – 0.08); Inter-group difference, 0.30 (0.00 – 0.60); P = 0.050. No adverse events occurred.

Conclusions: In patients with mild to moderate malnutrition receiving ENEFLUID® for 12 weeks as IDPN, serum TTR was not improved, decreases in protein intake was mitigated, no adverse events occurred (Trial registration: jRCTs031220296).

Funding: Commercial Support - Otsuka Pharmaceutical Factory, Inc.

FR-PO1061

Comparison of Nutritional Outcomes between Different Techniques of Intradialytic Amino Acid Infusion in Patients on Hemodialysis: A Randomized Controlled Trial

Sophon Dumrongsukit, Yingyos Avihingsanon, Somchai Eiam-Ong, Piyawan Kittiskulnam. *King Chulalongkorn Memorial Hospital Department of Internal Medicine, Bangkok, Thailand.*

Background: Amino acid (AA) loss during catabolic process of dialysis deteriorates protein-energy status of hemodialysis (HD) patients. Therefore, AA replacement is crucial. This study aimed to compare intradialytic amino acid (IDAA) infusion between loading and continuous intradialytic infusion technique, which could provide better AA retention indicated by serum albumin levels.

Methods: This randomized controlled trial (TCTR 20230401003) involved high flux membrane HD patients with a serum albumin level between 3.5 and 3.9 g/dL. Those were randomly assigned in a 1:1 ratio to loading group that started with 50% glucose 100 ml infused for 20 minutes, followed by AA 200 ml infused for 20 minutes at the last hour of the session, or continuous group that administered 50% glucose 100 ml after starting HD followed by AA 200 ml until the end of HD, with a total duration of approximately 3.5 hours. The primary outcome was the difference of albumin levels after 3 months of IDAA supplementation between the two techniques.

Results: A total of 48 HD patients completed the study (n=24 per group). The mean age was 68.9±12.8 years with average MIS of 6.4±2.8 points. Baseline characteristics were not different between groups. Despite comparable energy and protein intake, serum albumin levels were significantly increased in continuous group after 3 months of IDAA (from 3.75±0.14 to 3.94±0.22 g/dL, $p<0.01$) whereas it was still unchanged in the loading group (from 3.76±0.11 to 3.88±0.36 g/dL, $p=0.21$). The average total AA losses in dialysate were not significantly different between the continuous and loading groups (6.7±1.4 VS 7.8±3.7 g/session, respectively, p=0.17). Both plasma essential (p=0.59) and non-essential AA levels (p=0.66) between groups were also similar at the end of study. Muscle mass, strength, and gait speed did not differ between both groups (all p>0.05). Neither volume overload nor hyperglycemia requiring additional insulin therapy was found throughout the study.

Conclusions: IDAA supplementation using continuous infusion during dialysis session appears to be superior to a loading technique in terms of an improvement in serum albumin levels, a survival surrogate among HD patients. The impact of IDAA on clinical outcomes may require larger scale with longer period of study.

Funding: Private Foundation Support

FR-PO1062

Declining Serum Albumin in the Shadow of Stable Body Mass Index: A Mortality Indicator in Predialysis CKD

Menaka Sarav,[1] Prabin Shrestha,[2] Adnan Naseer,[2] Fridtjof Thomas,[2] Keiichi Sumida,[2] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[2] *[1]Yale University School of Medicine, New Haven, CT; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [3]University of California Los Angeles, Los Angeles, CA.*

Background: Patients with CKD often experience alterations in body composition and nutritional status as their kidney function declines. Body Mass Index (BMI) has been used as a nutritional marker but may not reflect these changes accurately due to concomitant muscle wasting and fluid retention. The role of alternative nutritional measures such as serum albumin in patients with CKD and stable BMI is unclear.

Methods: We analyzed data from a nationwide cohort of 20,164 US Veterans with stable BMI and multiple serum albumin levels who transitioned to kidney replacement therapy from October 2007 through March 2015. We calculated slopes of serum albumin using mixed effects models for three years preceding dialysis. We examined the association of albumin slope with post-dialysis mortality using Cox models adjusted for demographic characteristics, comorbidities, and baseline eGFR and serum albumin.

Results: The cohort had a mean age of 64 years, with 96% male and 30% African American participants. Despite maintaining stable BMI, 81% of patients displayed a decline in serum albumin levels in the pre-dialysis period (median slope: -0.09 g/dl/year, 25th and 75th percentile: -0.17, -0.02). A steeper decline in serum albumin over time was associated with significantly higher post-dialysis mortality (multivariable-adjusted hazard ratio associated with -1 g/dl/year decline in serum albumin: 1.86, 95% confidence interval: 1.65-2.10, p<0.001).

Conclusions: A significant proportion of patients with advanced CKD display a clinically relevant decline in serum albumin despite maintaining a stable BMI. Our study highlights the inadequacy of stable BMI as a marker of nutritional adequacy in advanced CKD, emphasizing the need for comprehensive nutritional assessments in CKD management.

Funding: NIDDK Support

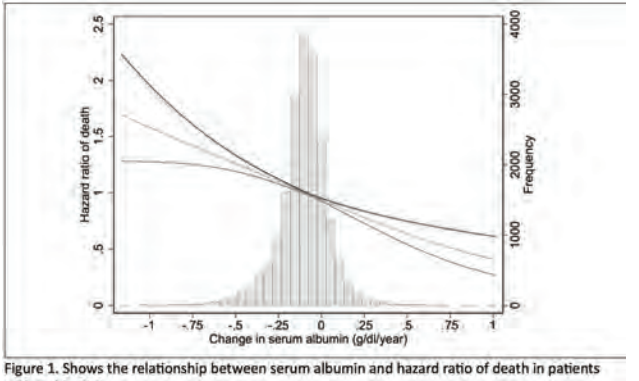


Figure 1. Shows the relationship between serum albumin and hazard ratio of death in patients with stable BMI.

Figure 1. Shows the relationship between serum albumin and hazard rate of death in patients with stable BMI.

FR-PO1063

A Journey through Low-Energy Diets in Adults with Kidney Disease: Insights from the Slow-CKD Feasibility Study

Marguerite M. Conley,[1,2] Nicole J. Scholes-Robertson,[6] Soraya L. Cunningham,[1] Kirsten S. Hepburn,[4,3] Hannah L. Mayr,[1,3] David W. Mudge,[5,3] Justin J. Holland,[2] David W. Johnson,[5,3] Andrea K. Viecelli,[5,3] Helen L. MacLaughlin.[2,4]
[1]Department of Nutrition and Dietetics, Princess Alexandra Hospital, Brisbane, QLD, Australia; [2]Queensland University of Technology Faculty of Health, Kelvin Grove, QLD, Australia; [3]The University of Queensland, Brisbane, QLD, Australia; [4]Kidney Health Service Metro North Hospital and Health Service, Brisbane, QLD, Australia; [5]Department of Kidney and Transplant Services, Brisbane, QLD, Australia; [6]School of Public Health, the University of Sydney, Sydney, NSW, Australia.

Background: Low energy diets (LEDs) (800-1000 kcal/day) are a proven approach in diabetes management to achieve 10 to 15kg weight loss and diabetes remission. LEDs are an emerging strategy for obesity management in CKD. Understanding consumer experiences of LED programs is critical to help explore feasibility, acceptability and future development and translation. The aim of this study is to describe participants' experiences of, and satisfaction with being involved in a LED weight loss randomized controlled trial (RCT).

Methods: Participants living with stages 1-3 CKD and BMI >30kg/m^2 from the SLOW-CKD feasibility RCT participated in semi-structured interviews. Interviews were audio-recorded, transcribed verbatim and analyzed using thematic analysis. The questions explored participants' experiences and perceptions of following a 3-month LED followed by a 3-month weight maintenance program, or receiving usual care (UC) weight loss support, and participating in a RCT.

Results: Twenty-five adults (14 intervention, 11 UC) were interviewed. Six themes emerged reflecting the lifelong mental and physical struggle of living with obesity; varied motivation to join the study; the importance of health professional and peer support, flexible study appointments and LED approach; and benefits beyond weight loss. After overcoming initial challenges, intervention participants adapted to the LED and were pleased with their commitment and success, many noting improvements in eating habits, diet quality, physical function, and sleep. Several UC participants expressed disappointment and a sense of missed opportunity.

Conclusions: Our findings recognize the uphill battle faced by adults living with CKD and excess weight. Various internal and external factors influenced their decision to start and continue their weight loss journey. LED programs are acceptable if individualised and backed by trusted healthcare professionals. Our findings support LED use in clinical practice and further research on effectiveness on slowing CKD progression. Future trials should include innovative ways to strike balance between scientific rigour and minimising randomisation disappointment.

Funding: Private Foundation Support

FR-PO1064

Effects of a Low-Protein Diet in Patients with CKD Taking Renin-Angiotensin System Inhibitors: A Post Hoc Subanalysis of the RICE Study

Michihiro Hosojima,[1] Hideyuki Kabasawa,[1] Mai Tanaka,[1] Akihiko Saito,[2] Ichiei Narita.[3] *[1]Department of Clinical Nutrition Science, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Department of Applied Molecular Medicine, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [3]Division of Clinical Nephrology and Rheumatology, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*.

Background: Globally, evidence for dietary therapy in patients with chronic kidney disease (CKD) is lacking, and there is an urgent need to accrue such evidence. Previously, we conducted the "Randomized Crossover Trial of Therapeutic Specialized Foods (Low-Protein Rice) for Patients with Chronic Kidney Disease (RICE Study) (Clinical Trial registration number: UMIN000015630)" and demonstrated that the use of low-protein rice (LPR) improves adherence to recommended protein-restricted diets and leads to a reduction in urinary protein in CKD patients. However, some opinions suggest that most reports supporting a low-protein diet (LPD) were conducted before the widespread use of renin-angiotensin system (RAS) inhibitors. Hence, it is crucial to investigate the impact of LPDs on CKD patients who are on RAS inhibitors.

Methods: The RICE study included 104 patients with CKD (Stages G3aA2 to G4) who were randomly assigned to receive nutritional counseling every four weeks alone (control group) or in addition to LPR (LPR group) for 24 weeks. The primary outcome was estimated dietary protein intake determined using the Maroni formula. The secondary outcomes included creatinine clearance (CCr) and urinary protein on the basis of 24-hour urine collection. In this sub-analysis, we targeted only patients taking RAS inhibitors (42 in each group) and conducted similar evaluations.

Results: Protein intake decreased from 1.00 g to 0.90 g/kg ideal body weight (IBW)/day in the control group and from 1.01 g to 0.77 g/kg IBW/day in the LPR group. Adjusted protein intake at baseline showed a decrease of 0.14 g/kg IBW/day (95% CI, 0.0003 to 0.27 g/kg IBW/day) in the LPR group compared to the control group at 24 weeks (P = 0.049). Similarly, urinary protein levels decreased significantly by 0.45 g/day (95% CI, 0.15 to 0.74 g/day) in the LPR group compared to the control group at 24 weeks (P = 0.003). There was no significant difference in CCr between the two groups at 24 weeks.

Conclusions: The LPD using LPR is effective in achieving protein restriction and may contribute to the reduction of urinary protein levels, even in patients with CKD taking RAS inhibitors. Further detailed verification, including prospective studies, is required in the future.

FR-PO1065

Association of Macronutrients with CKD Progression in West Africans

Edward P. Kwakyi,[1] Runqi Zhao,[2] Yemi R. Raji,[3] Manmak Mamven,[4] Tolulope V. Adebile,[2] Adaobi Solarin,[5] Nanna R. Ripiye,[4] Theophilus I. Umeizudike,[5] Ifeoma I. Ulasi,[6] Dwomoa Adu,[1] Rasheed A. Gbadegesin,[7] Rulan S. Parekh,[8] Akinlolu Ojo,[9] Diane C. Mitchell,[10] Sushrut S. Waikar,[2] Titilayo O. Ilori.[2] *[1]University of Ghana Medical School, Accra, Ghana; [2]Boston Medical Center, Boston, MA; [3]University of Ibadan and University College Hospital, Ibadan, Nigeria; [4]University of Abuja, Abuja, Nigeria; [5]Lagos State University Teaching Hospital, Lagos, Nigeria; [6]University of Nigeria, Nsukka, Nigeria; [7]Duke University School of Medicine, Durham, NC; [8]Women's College Hospital, Toronto, ON, Canada; [9]Kansas State University, Manhattan, KS; [10]Texas A&M University System, College Station, TX*.

Background: Dietary modifications slow chronic kidney disease (CKD) progression. However, the association of macronutrients with CKD progression is not well understood.

Methods: We obtained 24h dietary recall data from participants in the Diet, Apolipoprotein L1 and CKD (DCA) study. We determined macronutrient consumption (g/day) for protein, carbohydrates, polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs) and saturated fats; and expressed consumption in quartiles. Our outcome was the total eGFR slope over 3 years. We used a mixed effect linear regression model with the clinical center as a random effect to evaluate the association of macronutrient consumption with total eGFR slope. The results were expressed as beta coefficients with 95% confidence intervals.

Results: We analyzed data from 510 participants: mean age 49 (SD=18) years, 53% male, and mean eGFR was 71ml/min/1.73m^2 (SD=39). In the adjusted models compared to the lowest quartiles of consumption (Q1), Q4 of carbohydrate consumption and PUFAs consumption were associated with a positive eGFR slope change; and saturated fats (Q4 vsQ1) was associated with eGFR slope decline. The p for trend was significant moving from lower to higher polyunsaturated fatty acid consumption (Table 1).

Conclusions: To our knowledge, this is the first study showing the association of macronutrients with CKD progression in a well-phenotyped West African CKD population. Our observations of a positive association between saturated fat consumption and CKD progression and a protective effect of PUFAs are consistent with previous publications. Carbohydrate consumption results were likely due to the higher quality carbohydrates consumed in West Africa.

Funding: NIDDK Support

Table 1. Association of Macronutrient Consumption (g/day) with eGFR Slope (ml/min/1.73m2/year) in a West African Cohort of CKD patients.

Macronutrient (g/day)	Estimated Beta Coefficient (95% CI)				P-Trend
	Q1	Q2	Q3	Q4	
Protein					
Model1	Ref	-0.28 (-0.98, 0.43)	-0.37 (-1.09, 0.35)	-0.26 (-0.98, 0.47)	0.47
Model2	Ref	-0.12 (-0.83, 0.64)	-0.09 (-0.87, 0.76)	0.22 (-0.71, 1.23)	0.66
Carbohydrate					
Model1	Ref	0.06 (-0.65, 0.75)	0 (-0.73, 0.7)	0.08 (-0.7, 0.83)	0.89
Model2	Ref	0.39 (-0.36, 1.12)	0.56 (-0.29, 1.37)	**1.14 (0.01, 2.24)**	0.06
Fat					
Model1	Ref	0.2 (-0.5, 0.9)	-0.12 (-0.88, 0.58)	0.04 (-0.81, 0.8)	0.88
Model2	Ref	0.38 (-0.35, 1.09)	0.25 (-0.62, 1.02)	0.71 (-0.41, 1.69)	0.24
PUFAs					
Model1	Ref	0.56 (-0.14, 1.25)	-0.17 (-0.91, 0.52)	0.51 (-0.25, 1.22)	0.51
Model2	Ref	**0.79 (0.07, 1.5)**	0.19 (-0.59, 0.93)	**1.08 (0.2, 1.93)**	0.06
MUFAs					
Model1	Ref	-0.1 (-0.82, 0.6)	-0.03 (-0.76, 0.67)	-0.34 (-1.18, 0.42)	0.46
Model2	Ref	0.02 (-0.73, 0.73)	0.2 (-0.63, 0.96)	0.08 (-0.98, 1.02)	0.79
Saturated fats					
Model1	Ref	0.06 (-0.66, 0.74)	-0.35 (-1.08, 0.32)	**-0.91 (-1.68, -0.27)**	0.01
Model2	Ref	0.07 (-0.66, 0.75)	-0.32 (-1.13, 0.38)	**-0.87 (-1.82, -0.11)**	0.05

Model 1: Adjusted for Age, Sex, Education, Income, Smoking, Alcohol, Diabetes, SBP, BMI, Baseline eGFR, Baseline Urine Protein, Antihypertensive Medications with clinical sites as random effect
Model 2: Additionally adjusted for daily kcal intake CKD: Chronic Kidney Disease
eGFR: estimated Glomerular Filtration Rate, MUFAs: Monounsaturated fatty acids, PUFAs: Polyunsaturated fatty acids

FR-PO1066

A Center for Nutrition Care to Provide Renal Nutrition Therapy to Patients with CKD

Abril G. Espinoza,[1] Julia Nava,[2] Nadia I. Aldana Solis,[2] Araceli Aguilar Gamiño,[2] Sara De La Rosa Diez,[2] Adriana Salinas Rico,[1] Joel D. Kopple.[3] CEAN. *[1]Fresenius Kabi Mexico SA de CV, Tijuana, Mexico; [2]Fresenius Kabi Mexico SA de CV, Ciudad de Mexico, Mexico; [3]The Lundquist Institute, Torrance, CA.*

Background: It is often time-consuming and difficult to both explain the importance of dietary therapy to CKD patients and locate expert renal dietitians. This may discourage physicians and patients from seeking nutritional therapy. This paper describes a novel program that provides nutritional care to people with chronic kidney disease (CKD)

Methods: This is an observational study of the structure and function of CEAN (Centro de Atencion Nutricional – Center for Nutritional Care) Centers in metropolitan areas in Mexico that provide nutritional care to patients with CKD. Data on nutritional outcomes to treatment were obtained retrospectively from the clinic electronic records

Results: The centers consist of several connected offices and are staffed by licensed dietitians who have undergone training in renal nutrition and are experienced in treating patients with CKD. Any licensed physician in Mexico can refer patients to these centers for nutritional assessment and counseling. Patients are followed in the CEAN Center at varying intervals; almost 50% of the patients make four or more follow-up visits to the Center. A comparison of several nutritional measures obtained at the patient's initial baseline visit and at their tenth visit indicate that patients have reduced their dietary protein intake with no reduction in serum albumin or handgrip strength. Body mass index, which averaged in the overweight range, decreased slightly.

Conclusions: The CEAN Centers in Mexico provide an unusual opportunity to provide sophisticated nutritional assessment, dietary therapy and nutritional follow-up for patients with CKD. Preliminary data suggest good nutritional responses to treatment in these centers. Clinical trials are needed to examine more definitively whether these centers improve nutritional and clinical outcomes in patients with CKD

FR-PO1067

Associations of Kidney Dietary Adherence with Kidney Function among Veterans with Diabetic Kidney Disease

Luis M. Perez,[1] Otis D. Wilson,[2,3] Jefferson L. Triozzi,[2,3] Christine D. Jones,[1,4] Adriana Hung,[2,3] Talat Alp Ikizler,[2,3] Yan Sun,[5,6] Sridharan Raghavan.[1,4] Million Veteran Program. *[1]Veterans Affairs, Aurora, CO; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Veterans Affairs, Nashville, TN; [4]University of Colorado Anschutz Medical Campus, Aurora, CO; [5]Emory University, Atlanta, GA; [6]Veterans Affairs, Atlanta, GA.*

Background: Dietary management of chronic kidney disease (CKD) is a key component of improving clinical outcomes, quality of life, and potentially delaying or preventing the progression of kidney disease. Despite debate regarding CKD dietary guidelines, Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations for dietary management and CKD medically tailored meal (MTM) standards provide a foundational basis for nutritional interventions. The aim of this study was to evaluate the relationship between dietary patterns and diabetic CKD progression among Veterans in the VA Million Veteran Program (MVP).

Methods: We studied 11,477 Veteran MVP participants with diabetic CKD with nutrition and health data available. We developed a CKD diet score reflecting patient adherence to eight nutrient recommendations (0-2 points each; total of 16 points) based on KDOQI and MTM standards. We calculated potential renal acid load (PRAL in mEq/d) as a second dietary predictor variable. We used generalized linear models to estimate the association of the CKD diet score with co-primary study outcomes, estimated glomerular filtration (eGFR) at 0- and 12-months and 12-month progression to end-stage kidney disease (ESKD; eGFR <15 mL/min/1.73m^2). Models were incrementally adjusted for age, body mass index (BMI), race/ethnicity, smoking, medications, baseline eGFR, hemoglobin a1c, blood pressure, and cardiovascular disease.

Results: Participant demographics were mean (± standard deviation) age 71 ± 9 years, BMI 32.5 ± 6.5 kg/m^2, 97.2% male, and baseline eGFR 40.4 ± 18.1 mL/min/1.73m^2. Higher CKD diet scores, β 0.360 (95% confidence interval 0.091 to 0.629, p=0.01), and lower PRAL values, β -0.077 (-0.098 to -0.056, p<0.01), were associated with higher baseline (0-month) kidney function in fully adjusted models. However, CKD diet scores and PRAL were not associated with 12-month eGFR change or ESKD progression (both p>0.05) in any models.

Conclusions: In adults with diabetic CKD, kidney dietary adherence and lower PRAL were associated with higher kidney function at baseline, but not eGFR change or reduced ESKD progression over a one-year period. Further research is needed to understand and isolate the mid- to long-term impacts of diet for kidney disease progression.

Funding: Veterans Affairs Support

FR-PO1068

Association of Appetite, Oral Frailty, and Oral Health-Related Self-Efficacy with Kidney Replacement Therapy

Shiho Kosaka,[1] Yuki Ohara,[4] Masaaki Yanishi,[3] Tsuguru Hatta,[5] Masami Hamada.[2] *[1]Toho Daigaku, Ota-ku, Japan; [2]Josai Kokusai Daigaku, Togane, Japan; [3]Kansai Ika Daigaku, Hirakata, Japan; [4]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan; [5]Hatta Naika Clinic, Kyoto, Japan.*

Background: Patients with hemodialysis (HD) have a high risk of xerostomia and periodontal disease and an increased likelihood of developing gingival hyperplasia after kidney transplantation (KTX) owing to their use of immunosuppressive drugs. However, we are not aware of published studies on the association of oral frailty status and appetite with kidney replacement therapy. To examine the association between appetite, oral frailty, and oral health-related self-efficacy (OSE) in patients with HD and KTX recipients.

Methods: The following were investigated in patients with HD and KTX recipients by using a questionnaire: demographics (age, sex, height, weight, blood test results, blood pressure, and number of teeth), appetite (CNAQ-J), oral frailty (Oral Frailty Checklist), and OSE (OSE Scale). We statistically analyzed participants after allocating them to two groups: low and high risk for oral frailty. We used χ-squared tests for categorical variables, t-tests for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, and multiple and logistic regression analysis to examine related factors. This study was approved by the Ethics Committee.

Results: Sixty-one patients with HD and 42 KTX recipients were included in this study. Appetite (HD, 28.9±47.4 vs. KTX, 30.5±3.2; p=0.021) and oral frailty (HD, 3.5±5.7 vs. KTX, 2.39±2.0; p=0.022) scores were both significantly better in KTX recipients, but no significant differences were observed in OSE between the groups. Multivariate analysis revealed that the incidence of oral frailty was 73% lower among KTX recipients (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.11 to 0.62) than that among patients undergoing HD, but the incidence was not significantly different when adjusted for age and sex (adjusted OR, 0.53; 95% CI, 0.18 to 1.52).

Conclusions: In this study, appetite was better and oral frailty was lower among KTX recipients than those among patients with HD. However, whether kidney transplantation has a positive impact on oral frailty and appetite compared to dialysis is difficult to determine, because KTX recipients were significantly younger, and multivariate analysis revealed no significant differences. Longitudinal studies with age- and sex-matching should be performed to determine whether such associations exist.

Funding: Government Support - Non-U.S.

FR-PO1069

Monitoring of Dietary Sodium Intake by Salt-Meter Decreases Serum Sodium and Blood Pressure in Patients on Hemodialysis

Wilaiporn Akkabut, Surasak Kantachuvesiri. Ramathibodi Hospital. *Mahidol University Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand.*

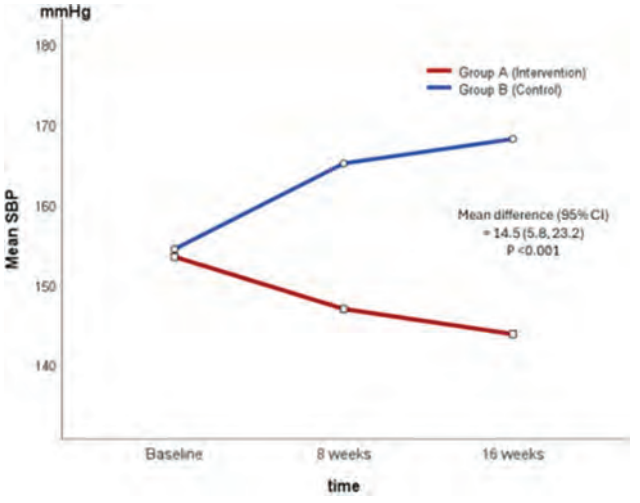
Background: Excessive sodium intake increases the extracellular fluid volume and osmolarity in hemodialysis patients. This study aimed to investigate the efficacy of self-monitoring of sodium intake by using salt meter and nutrition education in HD patients.

Methods: A quasi-experimental study was conducted at Ramathibodi Hospital in Bangkok, Thailand, during July 2023 to February 2024. Hemodialysis patients were randomized to receive intensive dietary education in combination with dietary diary and salt meter for 8 weeks (group A) or standard dietary education alone (group B). Body composition and sodium-related outcomes were measured at baseline, 8 and 16 weeks after recruitment.

Results: 46 patients were enrolled, 21 in group A and 25 in group B. The mean age was 64.8 years, and 52.2% were males. Mean baseline interdialytic weight gain (IDWG) was 3.6 kg, mean SBP and DBP were 153.9 and 74.8 mmHg, respectively. Mean IDWG in group A were stable from baseline to 16 weeks whereas mean IDWG in group B increased from baseline by 0.9 and 1.2 kg at 8 and 16 weeks, respectively (p<0.05). At 16 weeks, mean SBP of participants in group A decreased by 9.7 mmHg from baseline (p<0.05). Group B's mean SBP increased by 10.7 mmHg at 8 weeks and 13.7 mmHg at 16 weeks (p<0.05). The trends were similar for DBP. Serum sodium levels in group A decreased from baseline by 1.8 mmol/L at 8 weeks (p<0.01). Interestingly, at 16 weeks, participants in group A had significantly less %BF and more %FFM compared to baseline.

Conclusions: The use of salt meter and intensive dietary education for self-monitoring sodium intake for 8 weeks was more effective in controlling blood pressure than standard education alone. Decreased serum sodium levels while applying the intervention demonstrated adherence to less salt intake. A salt meter and dietary diary should be considered to control sodium consumption in hemodialysis patients.

Funding: Other NIH Support - Ramathibodi Hospital



FR-PO1070

Effects of High-Dietary Salt on Immune Cells and Microbiome: Results from a Randomized Clinical Trial

Harithaa Anandakumar, Hendrik Bartolomaeus, Sofia K. Forslund, Nicola Wilck. *Charite Universitatsmedizin Berlin, Berlin, Germany.*

Background: High dietary salt intake ranks among the most prominent risk factors and has been tied to hypertension and mortality. The mechanisms responsible are incompletely understood and have been extended to inflammatory and microbiome-associated processes. Building on preliminary data, the present study investigates whether a moderate increase in salt intake in healthy subjects primes host physiology to a more transiently unstable state, potentially leading to changes in the microbiome-immune axis.

Methods: We conducted a prospective, randomized, double-blinded trial to evaluate the effect of high dietary salt in healthy participants (NCT03024567), where the intervention group (n = 19) was given 6g of salt (NaCl) in addition to their daily normal salt intake, essentially doubling the recommended salt intake against a placebo group (n=19) for 14 days. Clinical parameters, stool and PBMC were collected at baseline and day 14. Shotgun metagenomic sequencing, metabolomics (stool and serum), and single-cell sequencing (CITEseq) of whole PBMCs and CD4+ sorted T cells was performed.

Results: The results confirm previous findings showing an increase in the dissimilarity of the microbiome composition under a high salt diet. Differential abundance of the microbiome's functional space, as quantified by functional gut-specific modules, picked up a salt-specific module (M00494, NatK-NatR (sodium extrusion) two-component regulatory system) in the salt group. Furthermore, among all immune cell subsets, we detected 500 common differently expressed genes (DEGs) solely in the salt group. Most of which belonged to to mitochondrial respiration and energy metabolism. Interestingly, we found appr. 8000 DEG in naïve T helper cells and 4000 DEGs in naïve cytotoxic T cells. Commonly, we detected a gene set enrichment for mitochondrial respiration in naïve T cell populations (CD4, CD8), functionally validated by Real Time Cell Metabolic Analysis (Seahorse).

Conclusions: Our study is among the first to utilize different omics techniques to identify high-salt-induced changes in the microbiome and immunome in healthy individuals that may be relevant to the development of pathological conditions in the long term.

FR-PO1071

Levels of the Endogenous Nephrotoxin Adenine in Healthy Humans and Effects of Diet

Subrata Debnath, Yan Du, Christiane L. Meireles, Shane Matta, Richard Montellano, Afaf Saliba, Carlos Lorenzo, Kumar Sharma. *The University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: Recent publications indicate that endogenous adenine is likely in the causative pathway for kidney disease in humans and urine adenine/creatinine ratio (UAdCR) is a mechanistic biomarker for ESKD in prospective studies of patients with DKD. However, adenine level in urine of healthy individuals has not been well studied. It is also not known if adenine levels vary according to age, gender, and body mass index (BMI). To shed light on these we conducted two separate studies.

Methods: In one study (Healthy Study), we determined adenine concentrations using validated HPLC-MS/MS analysis in random urine samples collected from apparently healthy individuals (n=122, age 18-89 yrs) without diabetes and hypertension and with eGFR >90 mL/min/1.73m^2. We also performed a post-hoc analysis of the KETO Study (NCT05071287) data that randomized 60 individuals (age 25-82 yrs) with eGFR of >60 mL/min/1.73m^2 to either low-fat or keto diet for 6 months with primary outcome of weight change.

Results: In the Healthy Study, mean±SD urine adenine/creatinine ratio (μM/mM) in females (n=60; 0.052 ± 0.065) was significantly higher compared to males (n=62; 0.010 ± 0.012, P = 0.0016). Similar significant difference was noted in the KETO Study. Urine adenine level did not correlate with age in either study. In the KETO Study, BMI declined in both males and females at 3-Mon and 6-Mon compared to Baseline values (P for all <0.01) but did not correlate with UAdCR. Compared to Baseline, UAdCR level declined significantly only in females at 6-Mon (0.06 ± 0.01 vs 0.03 ± 0.05, P=0.04). There was no correlation of eGFR or UACR with the UAdCR.

Conclusions: Reduction in urine adenine/creatinine ratio observed in females was similar with both type of diets, suggesting that weight reduction by diet may be reno-protective. Further work is warranted to explore mechanistic pathway for higher urine adenine/creatinine ratio in females and clinical implications of these novel findings.

FR-PO1072

You Are What You Eat: Should It Be All Meat?

Hannah E. Wilson, Sharon M. Moe. *Indiana University School of Medicine, Indianapolis, IN.*

Introduction: Fad diets have exploded in popularity with the advent of social media. Support for one such diet, the carnivore diet, stems solely from historical and anecdotal evidence. The effect of the carnivore diet on kidney stones is of interest as its effect has not been described, and higher animal protein diets are counter to current management guidelines.

Case Description: A 73 y/o man with a history of kidney stone disease, gout, and hypertension presented to nephrology for follow up. Kidney stones were first seen incidentally on X-Ray at age 45 followed by first stone passage at age 55 and 9 lithotripsies. He was referred to stone clinic in 2012 for 90% CaOx/10% CaP stones and started HCTZ and a low sodium, low protein diet. He subsequently was increased to 25 mg chlorthalidone in 2018 due to continued stone growth, after which he no longer formed more stones. 6 months before his nephrology appointment in 2023, the patient had 2 gout attacks 2 weeks apart. His PCP advised him to view a popular physician-made YouTube video on the carnivore diet as a treatment for gout. Following advice from his PCP, the patient modified his diet to include 90% meat with rare fruit and vegetable consumption. Table 1 shows 24-hr urine studies done six months before and six months after the change to the carnivore diet.

Discussion: Urine studies demonstrate a doubling of uric acid and uric acid supersaturation despite similar volumes, increasing risk for uric acid and calcium oxalate stones. Urine studies also demonstrate an increase in urine calcium, likely due to increased sodium intake or increased acid load from high purine consumption. Citrate decreased as expected, likely due to acid load and reduced fruit/vegetable. The increase in oxalate confirms disputed study findings that urinary oxalate excretion increases in high animal protein diets. One rationale is that lower dairy intake may have increased intestinal oxalate absorption due to reduced calcium to bind oxalate. Our patient demonstrates an increased risk of stone formation after adoption of the carnivore diet. This presents a need for high-quality evidence to examine fad diets and necessitates informing patients of the potential harms of pursuing health information on social media.

	Vol	SS CaOx	Ca	Ox	Cit	SS CaP	pH	SS UA	UA
Before Carnivore Diet:	2.95	3.47	181	47	303	0.25	5.631	1.14	0.883
After Carnivore Diet:	2.99	2.71	129	35	342	0.17	5.602	0.54	0.395
Reference Range:	0.5-4	6-10	<250	20-40	>450	0.5-2	5.8-6.2	0-1	<0.8

FR-PO1073

Detailed History Unravels the Mystery: An Unusual Case of Almond Breeze Hypercalcemia

Johnathon Phillips,[1] Swetha Rani Kanduri,[1] Juan Carlos Q. Velez,[1,2] Karthik Kovvuru.[1,2] *[1]Ochsner Health, New Orleans, LA; [2]UQ-Ochsner Clinical School, New Orleans, LA.*

Introduction: Serological tests play a vital role in teasing out the etiology of hypercalcemia. However, obtaining a thorough history is required to unravel a mystery. Herein, we report an unusual case of a patient with chronic kidney disease (CKD) presenting with hypercalcemia and acute kidney injury (AKI) due to consumption of excess almond breeze milk.

Case Description: A 66-year-old male with uncontrolled type 2 diabetes mellitus and hypertension was admitted to the hospital due to severe hypercalcemia [serum calcium (sCa) 15.4 mg/L] and acute on chronic kidney injury (serum creatinine 3.7 mg/dL, baseline of 1.5-1.8 mg/dL). Upon admission, he was drowsy but arousable. According to his wife, he was not in his usual state of health for over a week. Denied intake of over-the-counter medications, vitamin supplements. Additional laboratory data included blood urea nitrogen (BUN) 51 mg/dL, bicarbonate 23 mmol/L, albumin 3.8 g/dL, ionized calcium 1.5 mmol/L. Serological work up revealed suppressed parathyroid hormone (PTH) of 14.5 pg/mL, normal PTH-related peptide of 1.0 pmol/L, vitamin D 29 nm/L, 1,25-dihydroxy vitamin D 10 pg/mL, and a serum protein electrophoresis negative for monoclonal bands. Renal ultrasound unremarkable. Upon further inquiry, wife reported habitual drinking of a gallon of milk every day for years and a recent switch to sugar-free

almond breeze milk 3 weeks prior to index hospital admission, in an attempt to control his blood glucose levels. Upon review of the product label of almond breeze milk, 1 cup contains 450 mg of calcium which corresponds to 7 g of calcium/gallon of almond breeze, which is 50% more calcium than regular milk. The patient was treated with IV normal saline and calcitonin. sCa improved to 10.2 mg/dL and patient was discharged home and instructed to avoid almond breeze milk. sCa remained within normal limits at a follow-up clinic visit.

Discussion: With increasing availability of highly fortified drinks and supplements, patients with CKD are at risk of ingesting higher than recommended dosages potentially leading to ill effects. In addition to obtaining a thorough history, advising patients with CKD to pay attention to product labels and discuss them with physicians is highly encouraged.

FR-PO1074

Changes in Vitamin and Mineral Intake after a Whole-Food, Plant-Based Nutrition Education Program in Hypertensive Patients with CKD

Scott E. Liebman,[1] Janany J. Sabescumar,[1] Rebeca D. Monk,[2,1] Shamsul Hasan,[3] Anne Zhang,[1] Susan Friedman,[1] Thomas M. Campbell,[1] Ted D. Barnett,[4] Erin K. Campbell,[1] Nellie Wixom.[1] *[1]University of Rochester Medical Center, Rochester, NY; [2]Highland Hospital, Rochester, NY; [3]UPMC, Pittsburgh, PA; [4]Rochester Lifestyle Medicine, Rochester, NY.*

Background: Evidence suggests adoption of a predominately whole food plant-based diet (WFPBD) may be beneficial in both hypertension and CKD. Our pilot trial previously showed that individuals with CKD 3 or 4 who attend an education program emphasizing the benefits of a WFPBD achieved a statistically significant decrease in weight, BMI, total, LDL, and HDL cholesterol levels and trended towards improvement in systolic blood pressure without a statistically significant increase in serum potassium. Here we report the changes in intake of vitamins and minerals during the intervention.

Methods: 40 subjects with CKD 3 or 4, with hypertension but without proteinuria or hyperkalemia, were randomized to attend the education program (known as Jumpstart [JS]) or not. JS is a 15 day educational program designed to foster lifestyle changes including adoption of a WFPBD via a combination of lectures, support systems and food demonstrations. Individuals had food diaries done pre and post JS (or equivalent times for controls). We compared dietary intake of vitamins and minerals both within and between groups at the end of the trial.

Results: Compared to baseline, the intervention group showed significant increases in intake of vitamins A, C, and K, folate, magnesium, manganese, copper and oxalate, and significant decreases in the intake of vitamins B-12, D, and E, niacin. zinc, and selenium. Compared to the control group, the intervention group had significant increases in intake of vitamins A, C, and K, thiamine, folate, magnesium, manganese, and oxalate by the end of the trial. Significant decreases were seen in intake of vitamins B-12, D, and E, pantothenic acid, zinc and selenium. The intervention group also significantly reduced their added sugar consumption, glycemic index, and glycemic load compared to both baseline and with the control group at the end of the trial. Iron intake in the intervention group was not statistically different compared to either baseline values, or controls at the end of the trial.

Conclusions: Subjects with CKD 3 and 4 attending a 15-day education program emphasizing a WFPBD had significant changes in vitamin and mineral intake. Further studies are needed to determine the significance of these changes.

Funding: Clinical Revenue Support

FR-PO1075

Dietary Intake of ESTEEM (Exercise Study Testing Enhanced Energetics of Muscle Mitochondria in CKD) Participants

Olivia A. Moss, Tae Youn Kim, Baback Roshanravan. *UC Davis Health, Sacramento, CA.*

Background: Diet intake in people with CKD impacts metabolic acidosis and may have downstream effects on physical performance. Potential renal acid load (PRAL) is the acid or base forming potential from food, with greater acid production from protein foods, grains and diary and alkali production from fruits and vegetables. Protein amount and source are of interest for physical performance and plays a role in metabolic acidosis. The following is an analysis of dietary intake in people with CKD enrolled in a randomized exercise control trial.

Methods: Participants were randomized to receive supervised exercise for 12 weeks or to participate in a control group consisting of education on healthy lifestyle. All participants were provided a brochure containing diet recommendations by the NKDEP. No other dietary information was provided to participants. Three 24-hour diet recalls were performed pre and post invention using ASA24 software. Physical performance was measured via 6-minute walk test (6MW). Healthy Eating Index 2020 (HEI), PRAL, and protein intake were calculated. Differences between treatment groups and amongst intervention group were determined, and linear mixed effects models were performed on dietary intake variables and performance on 6MW.

Results: The average age of participants (n=30) was 64 years old, 60% were male, 46.6% had diabetes, and the mean eGFR was 34 mL/min. There were no significant differences in PRAL, HEI score, or protein intake between groups pre and post intervention. HEI and PRAL did not significantly affect changes in 6MW, however protein intake was inversely associated with 6MW in all participants (-60.50, 95%CI: -111.95 – -9.04, p= 0.021) as well as among exercisers (-64.59, 95%CI: -124.36 – -4.82, p=0.034).

Conclusions: PRAL and HEI did not affect 6MW performance. Average protein intake was adherent to KIDGO guidelines (0.6-0.8 g/kg). Further investigation is needed to determine if increased protein intake beyond recommended guidelines in CKD adversely impacts exercise adaptation.

Funding: NIDDK Support, Clinical Revenue Support

	Control (n=9)		Intervention (n=21)	
	Baseline	Post	Baseline	Post
Protein (g/kg)	0.77 (0.21)	0.76 (0.26)	0.68 (0.24)	0.68 (0.29)
HEI	58.7 (10.6)	59.7 (12.3)	57.1 (13.5)	55.7 (8.2)
PRAL (mEq/day)	3.4 (15.3)	0.3 (11.2)	9.7 (15.1)	14.3 (15.4)
6MW (meters)	483 (77)	465 (62)	454 (92)	482 (75)

Values mean (SD)

FR-PO1076

Novel Model of Kidney-Cardiovascular-Metabolic Injuries by Unilateral Nephrectomy and an Extreme Western Diet: Beneficial Effects by a Natural Food Additive (FLX)

Bengt C. Fellstrom,[1] Lucas Carvalho,[2] Maria Tydén,[1] Matheus Monteiro,[2] Daniel C. Andersson,[2] Tomas A. Schiffer,[2] Mattias Carlstrom.[2] *[1]Dept Medical Sciences, Nephrology, Uppsala, Sweden; [2]Dept Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden.*

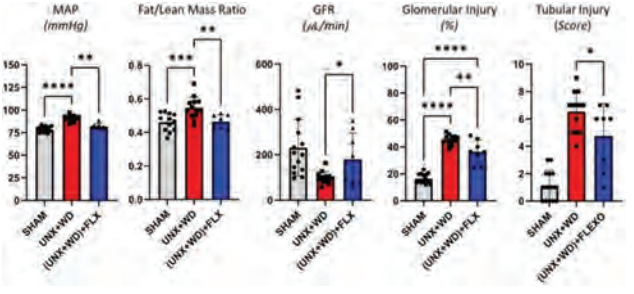
Background: CV complications are severe in renal failure and patients continue to die from CVD. A novel mouse model with progressive renal, CV and metabolic injuries was developed. Beneficial results from preventive treatment with a food additive were found. We aimed to characterize reno-cardio-metabolic dysfunctions, induced by renal failure and Western diet (WD) rich in sugar, fat and salt, and explore preventive effects by a novel food additive.

Methods: C57BL/6J mice (n=18) were subject to unilateral nephrectomy (UNX), fed a WD rich in fat, carbs and salt and followed for 12 weeks compared with SHAM-operated mice on standard chow. A group of UNX+WD mice (n=8) was fed a food additive (FLEXOVITAL [FLX]: extracts of Rhodiola, beetroot, L-arginine and citrulline). Body weight (BW), blood pressure (BP), endothelial-dep. vasorelaxation (myograph), glucose metabolism (IPGTT), body fat-lean mass (DEXA), adipocyte area, renal function (GFR : FITC-inulin), and mitochondrial function (Highresolution respirometry) were measured plus markers of heart injury (TnI), inflammation (IL6) and histology.

Results: In the UNX+WD group, notable increases in BW were observed along with higher fat/lean-mass ratio (17%) and adipocyte area (31%), all of which were mitigated by FLX. Fasting glucose levels were elevated but decreased with FLX. BP was increased (MAP of 78 to 90 mmHg, p<0.001), substantially attenuated by FLX. Endothelial dysfunction in UNX+WD mice was partially preserved with FLX. GFR decreased by 60%, yet a 75% protective effect by FLX. Glomerular and tubular injuries emerged, but less severe in the FLX group. TnI levels increased 2-3-fold but normalized with FLX. Additionally, FLX reduced IL6 levels. Mitochondrial dysfunction in kidneys and hearts improved with FLX.

Conclusions: Cardiovascular, renal and metabolic dysfunction/injuries emerge in this model and significant protection were demonstrated with the food additive FLEXOVITAL

Funding: Commercial Support - BioConcept AB, Stockholm, Sweden, Private Foundation Support, Clinical Revenue Support



FR-PO1077

Altered Gene Expression Profile in the Jejuna and Kidneys of Mice on High-Fructose or High-Fat Diet

Kamyar A. Zahedi,[1,2] Sharon L. Barone,[1,2] Marybeth Brooks,[1,2] Christos Argyropoulos,[1] Manoocher Soleimani.[1,2] Soleimani Lab. *[1]University of New Mexico Health Sciences Center, Albuquerque, NM; [2]Veterans Health Administration, Albuquerque, NM.*

Background: Metabolic syndrome (MetS) is a complex disorder characterized by visceral obesity, hypertension, and insulin resistance. The increased prevalence of MetS correlates with enhanced dietary consumption of refined sugars (i.e. high fructose corn syrup), fat, and salt. To ascertain the molecular pathways critical to the development of MetS (and specifically hypertension), we examined the alterations in the renal and jejunal transcriptomes of mice on high fructose or high fat diet.

Methods: Jejunal and kidney transcriptomes of mice on high fructose or high fat diet for 4 weeks were compared with mice on normal diet. Enrichment analyses were performed to identify the affected biological processes and molecular pathways.

Results: Provision of high fructose or high fat diet led to extensive alterations in gene expression patterns in both jejuna and kidneys. Enrichment analyses identified specific GO-biological process pathways in both groups. Major metabolism-associated pathways specific to carbohydrate and fat metabolism were dominant in jejuna of high fructose and high fat mice, respectively. Similarly, pathways associated with insulin response and reaction to stress were prevalent in both groups. Intriguingly, pathways associated with immune and inflammatory responses (e.g., TNF-a response, cytokine response and production) were detected in both high fructose and high fat groups. The latter pathways were significantly enriched in the jejuna of mice on high fat vs. high fructose diet. Enrichment analysis of kidney RNA-seq data revealed fewer overt derangements in high fat vs. high fructose group, which included significant enrichment in pathways associated with the regulation of inflammatory and stress responses. Comparison of high fat to high fructose enrichment terms in the kidney revealed increased enrichment in alterations associate with salt and sugar absorption, stress, and insulin response pathways.

Conclusions: Our studies demonstrate the induction of gene alterations due to increased consumption fat and fructose. These changes include metabolic alterations as well as derangements in inflammatory and stress responses which can contribute to elevated blood pressure. Increased dietary fat and/or fructose, individually or in tandem, can significantly contribute to the onset of pathologies associated with MetS.

Funding: Other NIH Support - NIH/NHLBIT32HL007736, Veterans Affairs Support, Private Foundation Support

FR-PO1078

PRDM16 Controls Cellular Senescence and Organ Aging by Promoting Oxidative DNA Damage

Qian Yuan, Yuting Zhu, Chun Zhang. *Wuhan Union Hospital, Huazhong University of Science and Technology Tongji Medical College Union Hospital, Wuhan, China.*

Background: With the increasing lifespan, the burden of aging and age-related diseases has emerged as a global public health concern. The accumulation of senescent cells contributes to accelerated body aging through the secretion of senescence-associated phenotypes. Epigenetic modifications, including DNA methylation, histone methylation, and histone acetylation, play crucial roles in promoting cellular senescence. PRDM proteins interact with various epigenetic-modifying enzymes along with transcription factors, to collectively regulate gene expression. However, the precise involvement of PRDM family members in cellular senescence and aging remains elusive.

Methods: We screened PRDM family in multiple organs from mice at young (2 months) and old (24 months) age by qRT-PCR. Bioinformatics analysis and qRT-PCR were utilized to verify the correlation between PRDM16 and age in humans and mice. Natural aging global and renal tubular specific *PRDM16* knockout mice were obtained to observe multiple organ aging, and kidney aging associated diseases with single-cell RNA sequencing. PRDM16 overexpression lentivirus was applied in old mice. RNA-sequencing, ChIP-seq, ChIP, were used to clarify the mechanism of PRDM16 in senescence.

Results: By detecting the expression of PRDM family members, particular attention was given to PRDM16 due to its significantly altered expression between young and old lung and kidney tissues. The levels of PRDM16 in brain hippocampus, kidney, and lung tissues exhibited a negative correlation with age and p21 expression. Notably, global deletion of PRDM16 in mice at only 3 weeks of age resulted in the accumulation of senescent cells in multiple organs. Renal tubular specific *PRDM16* knockout aggravated ischemia reperfusion injury in aging kidney induced by irradiation. Conversely, overexpression of PRDM16 using lentivirus successfully rescued kidney aging in aged mice as well as senescent tubular cells. Mechanistically, deficiency of PRDM16 promoted oxidative DNA damage through disruption of glutathione metabolism. Specifically, downregulation of PRDM16 led to reduced production of reduced glutathione via transcriptional downregulation GSTM1.

Conclusions: PRDM16 deficiency accelerates cellular senescence and multiple organ aging by promoting oxidative DNA damage in a GSTM1-dependent manner.

Funding: Government Support - Non-U.S.

FR-PO1079

Magnesium Deficiency in a Multiethnic Asian Patient Population with CKD

Boon Wee Teo,[1,2] Gek Cher Chan.[2] *[1]National University of Singapore Yong Loo Lin School of Medicine, Singapore, Singapore; [2]National University Hospital, Singapore, Singapore.*

Background: Magnesium homeostasis is primarily regulated by the kidneys. Due to the poor correlation between serum magnesium (mmol/L) and total body magnesium, magnesium deficiency is difficult to diagnose in the chronic kidney disease (CKD) population. We analyzed serum magnesium concentrations, 24-hour urinary magnesium excretion (24UMg, mol), and fractional excretion of magnesium (FEMg) in a multi-ethnic Asian cohort of CKD and healthy participants to determine magnesium deficiency.

Methods: We retrieved data from 232 patients with stable CKD from the Asian Kidney Disease Study, and 103 healthy participants without diabetes, hypertension or urinary abnormalities from the Singapore Kidney Function Study. Participants had 24-hour urine collection followed by blood and spot urine sampling, and measurement of the glomerular filtration rate using Tc99m-DTPA. We analyzed using JMP14 and SPSS with standard statistical tests. Magnesium deficiency is defined as 24UMg <1.9444 and serum magnesium ≦0.75.

Results: There are 19/335 (5.67%) participants with (16/19, 84.21% have diabetes). There are 23/335 (6.87%; 17/23 had CKD) participants with serum magnesium ≦0.75. There is no difference by age (p = 0.244), gender (p =0.162), and ethnicity (p = 0.520). However, participants with serum magnesium ≦0.75 have higher body weight on average 74.74±16.5 kg versus 63.86±11.5 kg, p = 0.009. Serum magnesium is lower in CKD patients (0.86 ± 0.11 vs 0.90 ± 0.68, p <0.001), and positively correlated with declining GFR (p <0.001, r = -0.569). More CKD (89/232, 38.36%) patients compared to healthy individuals (26/103, 25.24%) have 24UMg <1.9444 (p = 0.0196). Older patients are more likely to have 24UMg <1.9444 (p = 0.0253).

Conclusions: A combination of 24-hour urine collection for magnesium and serum magnesium concentrations may identify patients at risk of magnesium deficiency, especially in diabetic and CKD patients.

Funding: Government Support - Non-U.S.

FR-PO1080

Effects of Sodium Zirconium Cyclosilicate on Quality of Life in Patients Undergoing Hemodialysis with Hyperkalemia: Design and Rationale of the Y-QOL Study

Hiromichi Wakui, Daisuke Kanai, Shiori Yoshimura, Masaaki Hanaoka, Hiroshi Mitsuhashi, Tomoyuki Kawano, Mari Katsumata, Satoshi Yamaguchi, Nariaki Ogawa, Masato Ohsawa, Naohito Okami, Shinya Taguchi, Sho Kinguchi, Kengo Azushima, Tadashi Kuji, Kouichi Tamura. *Yokohama Shiritsu Daigaku Igakubu Daigakuin Igaku Kenkyuka, Yokohama, Japan.*

Background: Patients undergoing hemodialysis (HD) experience inadequate control of fluid and electrolyte balance through dialysis alone, requiring stringent dietary restrictions. This negatively impacts the quality of life (QOL), which is markedly lower in chronic kidney disease (CKD) patients on dialysis compared to healthy individuals. Moreover, reduced QOL has been linked to poorer prognosis in patients on maintenance dialysis. Hyperkalemia, a common issue in these patients, significantly correlates with increased mortality and necessitates strict dietary potassium restrictions, further diminishing QOL. Traditional potassium binders, like calcium and sodium polystyrene sulfonate, are limited by frequent dosing requirements and adverse effects. Sodium zirconium cyclosilicate (SZC) presents a promising alternative, offering effective potassium removal from the gut with minimal impact on other electrolytes and reduced dosing frequency. This study evaluates whether SZC treatment improves QOL by easing dietary potassium restrictions in patients undergoing HD.

Methods: The Y-QOL study is an 8-week, multicenter, randomized, parallel-group, open-label trial. It plans to enroll 200 hyperkalemic outpatients (potassium levels 5.5 to 6.4 mEq/L after a 2-day inter-dialytic interval) undergoing regular thrice-weekly HD. Participants will be randomized to either receive daily SZC (starting at 5 g on non-dialysis days, with potential adjustments up to 15 g based on serum potassium levels) plus dietary guidance, or to a control group receiving only dietary guidance aimed at maintaining serum potassium levels between 4.0 and 5.4 mEq/L. The primary endpoint is changes in QDIS-7 scores at Week 8 from baseline in the intervention group and control group, respectively.

Results: The recruitment of the first participants commenced on January 24, 2024. As of May 2024, 28 participants have been enrolled. The study is projected to conclude on March 31, 2026.

Conclusions: The Y-QOL study aims to determine the effectiveness of SZC in improving QOL concerning dietary potassium intake restrictions in patients undergoing hemodialysis with hyperkalemia.

Funding: Commercial Support - AstraZeneka K.K.

FR-PO1081

Association of Renal Artery Calcium Scoring with Decline in eGFR

Nabeel Aslam,[1] Danielle Mason,[2,1] Ibrahim Khambati,[1] Hiroshi D. Hikida,[1] Christopher L. Trautman,[1] Tambi Jarmi.[1] *[1]Mayo Clinic, Jacksonville, FL; [2]Lincoln memorial DeBusk College of Osteopathic Medicine, Harrogate, TN.*

Background: Coronary artery calcium scoring is associated with adverse cardiovascular events and a lower estimated glomerular filtration rate (eGFR). However, limited data exist on the association of renal artery calcium (RAC) scoring with the rate of decline of eGFR.

Methods: We conducted a single center, retrospective study of adult patients followed in a nephrology clinic with available CT imaging of the abdomen. Data collected included demographics, comorbidities, medications, and eGFR at 3-month intervals for 24 months post-CT scan. Aorta and RAC scoring was calculated using a semiautomated software package designed for quantifying coronary artery calcium by the Agaston method.

Results: A total of 274 patients were included in the analysis: median age 67 years, 65% males, and 90% white. Comorbid conditions included diabetes mellitus 31%, hypertension 82%, hyperlipidemia 68%, and pre-existing chronic kidney disease (CKD) 69%. The cohort was divided into groups based on RAC score: RAC = 0; 1-100; >100. RAC >100 was significantly associated with the decline in eGFR from baseline to 24 months as compared to the RAC 0 group (p=0.03). There was no significant association between RAC 1-100 and RAC 0 with the decline in eGFR from baseline to 24 months (p=0.75). There was no association of aorta calcium scoring with a change in eGFR from baseline to 24 months (p=0.23).

Conclusions: In our cohort, RAC score >100 is associated with a decline in eGFR over the 24 months of follow-up. RAC score may provide prognostic information for eGFR decline in patients with risk factors for developing CKD or pre-existing CKD. Further studies are needed to evaluate the utility of RAC scoring in identifying patients at higher risk of eGFR decline.

Funding: Clinical Revenue Support

FR-PO1082

Relationships between Physical Activity, Vessel Health, and Kidney Function in CKD: An Observational Study

Mark Davies,[1] Aamer Sandoo,[2] Abdulfattah Alejmi,[3] Jamie H. Macdonald.[2] *[1]NHS Wales Cardiff and Vale University Health Board, Cardiff, United Kingdom; [2]Institute for Applied Human Physiology, Bangor University, Bangor, United Kingdom; [3]NHS Wales Betsi Cadwaladr University Health Board, Bangor, United Kingdom.*

Background: The aims of this prospective, observational study were to determine if i) physical activity and kidney function were independently associated with markers of vessel health in patients with mild-moderate CKD; and ii) physical activity and vessel health exacerbate kidney function decline.

Methods: People with CKD stages 1 to 4 and healthy controls had baseline measurements of physical activity (by accelerometer), vessel health (micro-vessel and large artery endothelial-dependent (EDD) and independent (EID) dilation, and carotid intima-media thickness (cIMT)) and kidney function (estimated glomerular filtration rate (eGFR)). During a longitudinal follow-up period, the rate of decline in eGFR was measured. Multiple linear regression was used: i) in a cross-sectional analysis, to determine if vessel health, in additional to clinical variables (age, blood pressure, insulin resistance) was associated with physical activity or kidney function; and ii) in a longitudinal analysis, to determine if physical activity and vessel health (specifically, micro-vessel EDD), in additional to clinical variables, exacerbated kidney function decline.

Results: Answering aim i), 71 people with CKD and 12 controls were recruited and provided baseline data. Physical activity was independently associated with both large artery (ß=0.32;p=0.03) and micro-vessel EDD (ß=0.26;p<0.01) and cIMT (ß=-0.2;p=0.01). In contrast, kidney function was only independently associated with cIMT (ß=-0.25;p=0.01). Answering aim ii) 60 people with CKD were followed up for median (IQR) 20 (16 to 29) months. Neither micro-vessel EDD (ß=-0.07;p=0.20) nor physical activity (ß=0.04;p=0.69 independently predicted eGFR decline but exploratory analyses suggested large vessel EDD may predict eGFR decline (ß=0.12;p=0.07).

Conclusions: In the first study to combine objectively measured physical activity, vessel health and kidney function in people living with CKD, physical activity was independently associated with vessel function (micro and large vessel EDD), whilst physical activity and kidney function were independently associated with atherosclerosis (cIMT). These findings have implications for CKD cardiovascular risk management. Future research should confirm whether physical activity, via improvements in vessel health, can attenuate kidney function decline.

Funding: Private Foundation Support

FR-PO1083

The Burden of Ventricular Premature Complexes Is an Independent Risk Factor of the Development of Kidney Failure in Patients with CKD

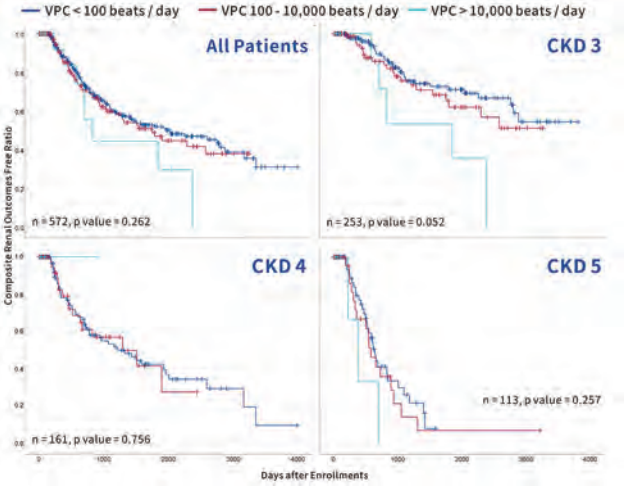
Chih-Hen Yu,[1,2] Chao-Yu Chen,[1,2] Chien-Shien Lee,[1,2] Ting-Chun Huang,[1,2] Po-Tseng Lee,[1,2] Mu-Shiang Huang,[1,2] Ping-Yen Liu,[1,2] An-Bang Wu,[1,2] Chin Chung Tseng,[1,2] Junne-Ming Sung.[1,2] *[1]National Cheng Kung University College of Medicine, Tainan, Taiwan; [2]National Cheng Kung University, Tainan, Taiwan.*

Background: Ventricular premature complexes (VPCs) are strongly linked to heart failure, and a higher VPCs burden independently increases the risk of cardiovascular mortality; however, whether the VPCs lead to renal impairment beyond cardiovascular events remains unknown. The primary objective of the study is to assess whether a high VPCs burden serves as an independent risk factor for the development of kidney failure in CKD patients.

Methods: We conducted a single-center, perspective cohort to clarify the role of VPC burden in composite renal outcome. We follow up the patients with CKD 3b to 5, who's indicated of Holter exam. The composite renal outcome was defined as sustained eGFR decline of at least 40%, sustained GFR<15mL/min/1.73 m^2, maintenance dialysis, or death from kidney failure.

Results: A total of 527 patients was enrolled. The mean follow-up duration was 571 days (Q1:202, Q3:1093). Events shorter than 180 days were excluded. The hazard ratio (HR) for Log VPCs was 1.159 (95%CI, 1.030-1.305, *p*=0.014), adjusted for age (HR 0.986 95%CI, 0.973-0.999, *p*=0.041), diabetes (HR 1.428, 95%CI 1.046-1.950, *p*=0.025), and CKD stages (CKD stage 3: ref, stage 4: HR 2.743 95%CI 1.97-3.945, *p*<0.001, stage 5: HR 5.404 95%CI 3.621-8.063, *p*<0.001). In categories of different VPC burdens, compared to individuals with a VPC burden<100/day, HR of VPC 100-10,000 beats/day and VPC>10,000 beats/day regarding the composite outcome were 1.251(95%CI, 0.868-1.677, *p*=0.353), and 2.42(95%CI, 1.165-5.020, *p* =0.018), respectively.

Conclusions: High burden of VPCs, defined by log VPC, or with cutoff of 100 beats/day and 10,000 beats/day, are independent predictors of composite renal outcome in CKD population.



Kaplan-Meier Analyses for Composite Renal Outcome of VPC Burdens in All Patient and Different CKD Stages

FR-PO1084

N-terminal Pro B-Type Natriuretic Peptide (NT-proBNP), Troponin T, and Incident Heart Failure: The Chronic Kidney Disease Prognosis Consortium

Nisha Bansal, Markus P. Schneider. CKD Prognosis Consortium. *CKD Prognosis Consortium, New York, NY.*

Background: Recently, the American Heart Association PREVENT equation was developed to predict 10-year risk of incident heart failure (HF) in persons without prevalent atherosclerotic cardiovascular disease (ASCVD), incorporating eGFR and albuminuria. We aimed to determine the added value of NTproBNP and troponin T (TnT) as predictors of HF in the ambulatory setting, across a broad range of cohorts and including participants with prevalent ASCVD.

Methods: We performed individual-participant data meta-analysis of 38,274 individuals without a history of HF. Adjusted Cox models were used to quantify the associations of NT-pro-BNP and troponin T with HF after adjusting for variables in the PREVENT model, and to assess whether the associations varied by age and CKD status.

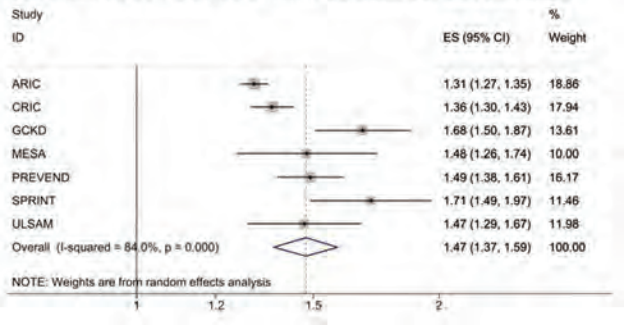
Results: There were 3,990 incident HF events over a mean of 12 years. In meta-analysis, a 2-fold higher NTproBNP was associated with 1.47-fold (95% CI: 1.37-1.59)

higher risk of HF. The association between NTproBNP and HF was stronger in older age but not different by GFR. The increase in C-statistic was 0.029 (0.018, 0.040) over the base model and was greater among older (0.044, 95% CI: 0.030, 0.059) than younger adults (0.024, 95% CI: 0.010, 0.038). For TnT, a 2-fold higher value was associated with 1.45-fold (95% CI: 1.33-1.57) higher risk of HF, but the increase in C-statistic was smaller (0.009, 95% CI: 0.006, 0.012). Adding TnT to a model with NTproBNP resulted in minimal increment in c-statistic (0.002, 95% CI: 0.001, 0.004).

Conclusions: NTproBNP adds robust information to the PREVENT model for discrimination of HF risk, particularly among older adults.

Funding: NIDDK Support, Private Foundation Support

Figure 1: Forest plot of the hazard ratio of NTproBNP and incident heart failure across cohorts.



FR-PO1085

Arterial Stiffness and Cognitive Decline in the Chronic Renal Insufficiency Cohort (CRIC) Study

Renee A. Dreher, Ester Oh, Zhiying You, Michel Chonchol, Kristen L. Nowak. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Kidney function decline is associated with impaired cognitive function, and there is evidence that higher carotid-femoral pulse-wave velocity (PWV), a measure of arterial stiffness, is associated with cognitive impairment in non-chronic kidney disease (CKD) studies. However, it has yet to be investigated if PWV is predictive of incident cognitive impairment in patients with CKD. We hypothesized that higher PWV is associated with a decline in cognitive function over time in adults with CKD who participated in the CRIC study.

Methods: We included 1,864 participants from the observational cohort study, CRIC, with baseline carotid-femoral PWV measurements and no baseline cognitive impairment, defined as Modified Mini-Mental State Examination (MMSE) score >1 SD below the cohort mean at baseline. Cox proportional hazard regression was used to examine the association between PWV and time to cognitive impairment, defined as a decline in MMSE scores of >1.0 SD below the cohort mean (determined from baseline cognitive scores).

Results: Participants were 58±11 years old, 56% (n=1048) were male, baseline estimated glomerular filtration rate (eGFR) was 47±15 ml/min/1.73m^2, baseline carotid-femoral PWV was 10.7±3.7 m/s, and baseline MMSE score was 94.9±4.3. During a follow-up of 9.1±4.6 years, 280 participants (15%) had a clinically significant decline in MMSE score (i.e. incident cognitive impairment). After adjustment for age, sex, race/ethnicity, education, and baseline MMSE there was a significantly greater risk of incident cognitive impairment (Hazard Ratio [HR]: 1.04, 95% CI: 1.00-1.07 per 1 unit increase in PWV). However, this association was attenuated after further adjustment for systolic blood pressure, hypertension, diabetes, cardiovascular disease history, alcohol use, stroke history, smoking status, body-mass index, antihypertensive and anticoagulant usage, eGFR, and 24-hour albuminuria (HR: 1.02 [0.98, 1.06]).

Conclusions: In adults with mild to moderate CKD higher PWV was associated with a greater risk of incident cognitive impairment; however, this association was no longer significant after full adjustment for covariates.

Funding: NIDDK Support

FR-PO1086

Sex Differences in Probable Dementia and Mild Cognitive Impairment in CKD and Non-CKD: The SPRINT MIND Randomized Clinical Trial

Ester Oh, Zhiying You, Vienna E. Brunt, Michel Chonchol, Kristen L. Nowak. *University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO.*

Background: Females have higher risk of cognitive decline as compared to males in the general population. However, little is known whether this sex-specific risk pattern of cognitive decline translates to individuals with chronic kidney disease (CKD). This study examined sex differences in the risk of cognitive decline in older adults with elevated blood pressure and at high risk of cardiovascular events, who participated in the Systolic Blood Pressure Intervention Trial Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study, both with and without CKD.

Methods: A Cox proportional hazard model was used to compare sex differences in the risk of incident cognitive outcomes (probable dementia [PD], mild cognitive impairment [MCI]; and their composite) in males and females matched for propensity scores (based on age, race, education, randomization arm, smoking status, cardiovascular disease history systolic blood pressure, body-mass index, and estimated glomerular filtration rate [eGFR]), separately for those without and with CKD (defined as eGFR 20-59 ml/min/1.73m^2).

Results: Adults without CKD (n=2,506; 50% F; mean±SD age 68±9 y; eGFR 81±16 ml/min/1.73m^2) and with CKD (n=1,362; 50% F; 70±9 y; eGFR 49±10 ml/min/1.73m^2) were included in the study. The median (IQR) follow-up was 4.6 years (3.6-5.9) and 4.1 years (3.3-5.9) for the non-CKD and CKD groups, respectively. In adults without CKD, there were no sex differences in the risk of MCI/PD composite or PD. Males without CKD had higher MCI risk than females (**Figure A**). Males with CKD had higher risk of MCI/PD composite and PD than females (**Figure B**). Additionally, MCI risk in males with CKD tended to be higher than females.

Conclusions: Males with CKD had a higher risk of PD than females; this sex difference in the risk of dementia was not observed in participants without CKD.

Funding: Private Foundation Support

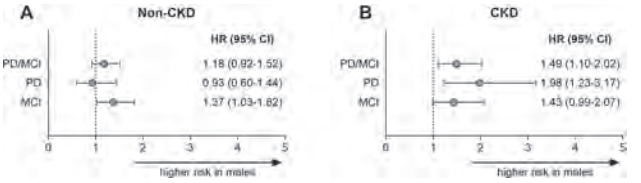


Figure. Sex differences in the risk of PD/MCI composite, PD, and MCI in adults without CKD **(A)** and with CKD **(B)**.

FR-PO1087

Blood Pressure, eGFR, and Kidney Mortality in Mexico: A Prospective Study of 150,000 Adults

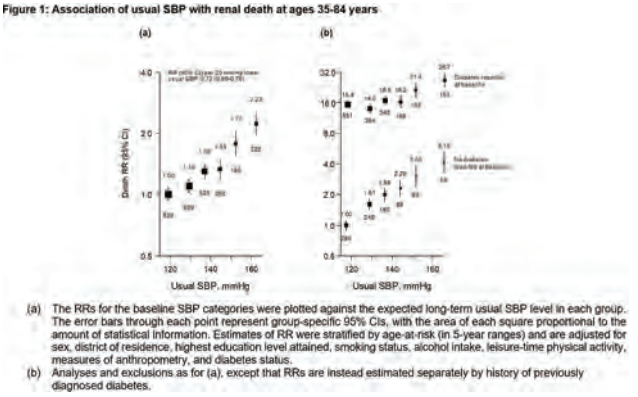
Doreen Zhu,[1] Pablo A. Kuri-Morales,[2] Rachel Wade,[1] Natalie Staplin,[1] Adrian Garcilazo-Avila,[2] Carlos L. Gonzalez-Carballo,[2] Diego J. Aguilar-Ramirez,[1] Fiona Bragg,[1] Louisa G. Friedrichs,[1] William G. Herrington,[1] Lisa E. Holland,[1] Michael R. Hill,[1] Jason M. Torres,[1] Michael P. Turner,[1] Eirini Trichia,[1] Colin Baigent,[1] Richard Peto,[1] Jaime Berumen,[2] Jonathan Emberson,[1] Richard Haynes,[1] Roberto Tapia-Conyer,[2] Jesus A. Alegre-Diaz.[2] Mexico City Prospective Study Group. *[1]University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom; [2]Universidad Nacional Autonoma de Mexico Facultad de Medicina, Ciudad de Mexico, Mexico.*

Background: Chronic kidney disease (CKD) is a leading cause of death and disability in Mexico and blood pressure (BP) may be an important contributor.

Methods: From 1998-2004, 150,000 adults aged ≥35 years from Mexico City were recruited into a blood-based prospective study and followed for cause-specific mortality. A resurvey of 10,000 survivors including urine samples was conducted in 2015-2019. Cox regression related usual BP to risk of death from kidney failure (renal death), excluding those with prior disease (other than diabetes) and adjusted for confounders. Logistic regression related baseline BP to baseline CKD (self-reported and/or eGFR <60 ml/min/1.73m^2) and resurvey BP to resurvey albuminuria (<3, 3-30 and ≥30 mg/mmol).

Results: Systolic BP (SBP) was continuously log-linearly related to renal death risk before age 85 years, with each 20 mmHg lower usual SBP associated with 28% lower risk (RR 0.72, 0.68-0.76) (Fig 1). The association was stronger in those without (RR 0.55, 0.50-0.60) than with diabetes (RR 0.81, 0.76-0.87), but the absolute relevance of SBP to risk was larger in those with diabetes. Overall, the excess renal death risk associated with hypertension (self-reported, treated or measured BP ≥140/90 mmHg) accounted for 27% of all renal deaths. 2% of participants had CKD at baseline and 25% of participants who provided a resurvey urine sample had albuminuria. At baseline, 20 mmHg lower SBP was related to a 31% lower odds of CKD (OR 0.69, 0.66-0.72), while at resurvey 20 mmHg lower SBP was related to a 42% lower odds of albuminuria (OR 0.58, 0.53-0.63).

Conclusions: In this study of Mexican adults, BP was strongly related to the risk of renal death and CKD.



(a) The RRs for the baseline SBP categories were plotted against the expected long-term usual SBP level in each group. The error bars through each point represent group-specific 95% CIs, with the area of each square proportional to the amount of statistical information. Estimates of RR were stratified by age-at-risk (in 5-year ranges) and are adjusted for sex, district of residence, highest education level attained, smoking status, alcohol intake, leisure-time physical activity, measures of anthropometry, and diabetes status.
(b) Analyses and exclusions as for (a), except that RRs are instead estimated separately by history of previously diagnosed diabetes.

FR-PO1088

Ambient Air Pollutant Mixture, Sleep Pattern, and Incident CKD: Results from a Prospective Cohort Study

Feifei Zhang,[1] Chao Yang,[2] Luxia Zhang.[1,2] *[1]Peking University Health Science Center, Beijing, China; [2]Peking University First Hospital Department of Nephrology, Beijing, China.*

Background: The associations of sleep behavior and air pollution with chronic kidney disease (CKD) have been investigated individually, yet the role of their interaction in the incidence of CKD is not well understood.

Methods: This study involved 402,451 participants from the UK Biobank cohort. A composite sleep index was calculated according to five sleep behaviors including sleep duration, chronotype, insomnia symptoms, snoring, and daytime sleepiness. Seven air pollutants, including $PM_{2.5}$, PM_{10}, NO_2, NO_X, SO_2, CO, and benzene, were examined jointly and individually. Cox proportional hazards model was used to calculate associations and to investigate potential modifying effects by assessing the significance of cross-product interaction terms of sleep index and air pollutants.

Results: With a median follow-up duration of 13.6 years, 3.6% of the participants was diagnosed with CKD. Each of the seven air pollutants demonstrated a positive association with the incidence of CKD. Co-exposure to seven air pollutants was associated with an increased risk of CKD incidence (hazard ratio: 1.093, 95% confidence interval: 1.067-1.119, **Figure 1**). There was a significant multiplicative interaction between sleep index and combined air pollutant exposure and the risk of incident CKD (p for interaction: 0.014). Stratified analyses by sleep index showed that the negative effect of air pollution was less pronounced for participants with healthier sleep patterns. Similar interactions existed for individual air pollutants including PM_{10}, NO_2, NO_X, and CO. Subgroup analyses suggested the elderly and females may experience fewer toxic effects from air pollution by adhering to healthy sleep patterns.

Conclusions: Sleep patterns may modify the relationship between air pollution exposure and onset of CKD. Our study highlights the potential of improving sleep as a preventive measure to counteract the detrimental effects of air pollution on incident CKD.

Funding: Government Support - Non-U.S.

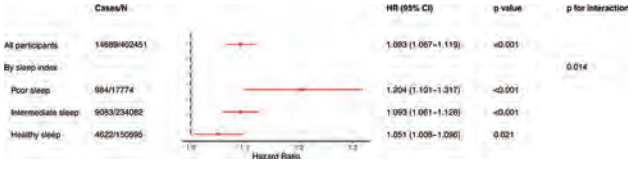


Figure 1. Hazard ratios and 95% CIs for chronic kidney disease associated with joint exposure to seven air pollutants in the total population and subpopulations stratified by sleep index. HR, hazard ratio. CI, confidence interval.

FR-PO1089

Impact of PM2.5 Pollution on Kidney Diseases in São Paulo, Brazil

Iara Da-Silva,[1] Alejandro H. Delgado Peralta,[1] Mario E. Gavidia-Calderón,[1] Edmilson D. De Freitas,[1] Talita R. Sanches,[2] Alessandra Tammaro,[3] Jesper Kers,[3] Maria Andrade,[1] Lucia Andrade.[2] *[1]Department of Atmospheric Sciences, Institute of Astronomy, Geophysics and Atmospheric Sciences, São Paulo, Brazil; [2]Nephrology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil; [3]Amsterdam University Medical Center, Amsterdam, Netherlands.*

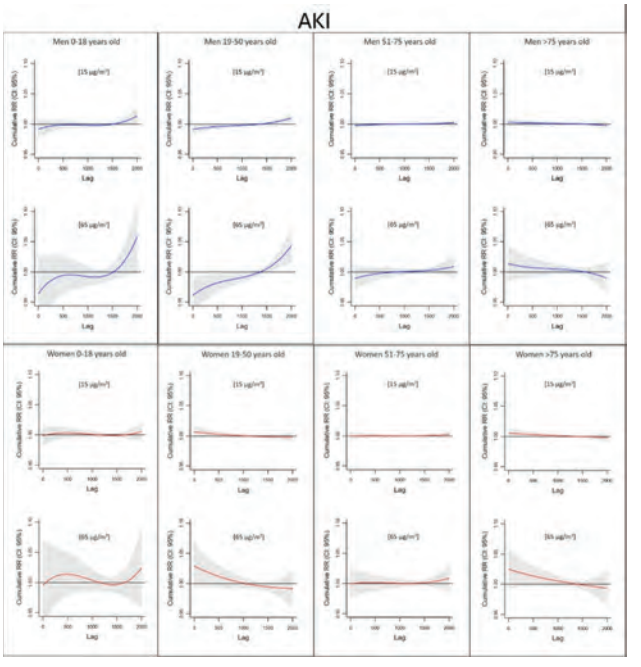
Background: Exposure to $PM_{2.5}$ has been associated with a risk of CKD. We have demonstrated that $PM_{2.5}$ aggravates AKI-induced IRI in mice. We evaluated the impact of $PM_{2.5}$ concentration on the incidence of CKD, AKI and glomerulopathy.

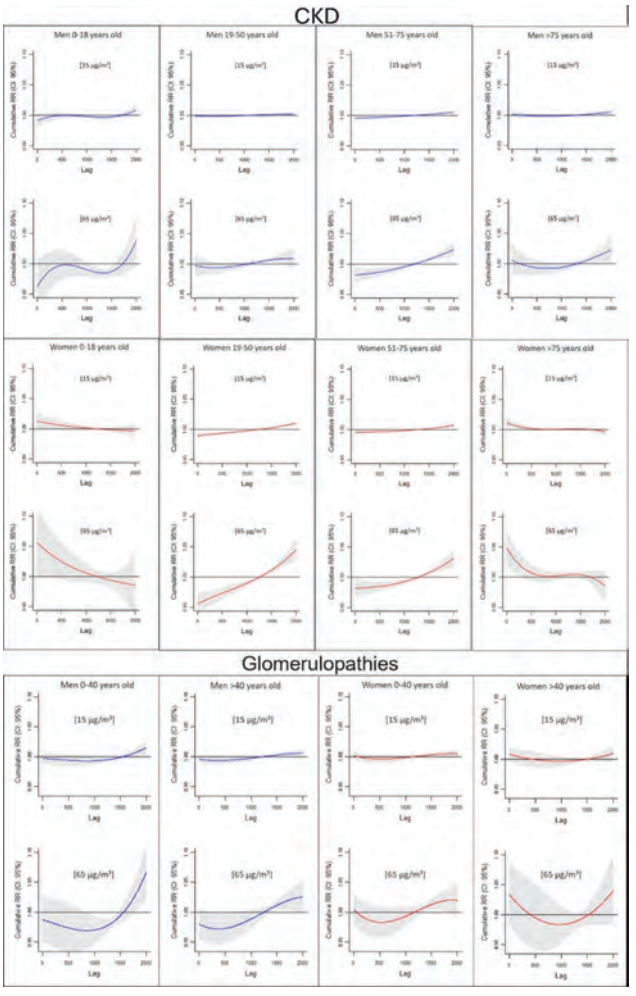
Methods: We analyzed meteorological variables, $PM_{2.5}$ concentrations and hospital admissions in São Paulo City during the 2011–2021 period. Admissions were categorized by age group and sex. We performed regression analysis with a generalized additive model and negative binomial distribution of exponential probability, assessing the cumulative medium-term impact of exposure, and a distributed lag non-linear model, which provides the effects of time lags (up to 2,000 days in our study), for AKI, CKD and glomerulopathy.

Results: Of the 37,170 records analyzed, 55% represented male individuals. Exposure to $PM_{2.5}$ was found to increase CKD risk by 1-4 times (95% CI: 1.009-1.18). Long-term exposure to higher $PM_{2.5}$ concentrations (65 $\mu g/m^3$) increases that risk considerably for men and women aged 19-50 years—RR: 1.01 (95% CI: 1.005-1.015) and RR: 1.013 (95% CI: 1.01-1.018), respectively—the risk being ≤ 2.5 times higher in men aged 51-75 years (RR: 1.025; 95% CI: 1.015-1.032). Between genders and among age groups, the risk of AKI after prolonged exposure to high $PM_{2.5}$ concentrations was highest for men aged 19-50 years (RR: 1.04; 95% CI: 1.012-1.07). The risk of glomerulopathy was highest in the < 40-year age group, especially among men, for whom the RR was 1.02 (95% CI: 1.007-1.025) and 1.07 (95% CI: 1.02-1.11) for concentrations of 15 $\mu g/m^3$ and 65 $\mu g/m^3$, respectively.

Conclusions: Our findings underscore the urgency to develop global strategies for air pollution reduction. (FAPESP, NWO, CAPES)

Funding: Government Support - Non-U.S.





FR-PO1090

Effects of Environmental Factors on the Progression of CKD in Inhabitants of São Paulo, Brazil

Tiana C. Moreira,[1] Alessandra Tammaro,[2] Thais Mauad,[3] Itamar d. Santos,[4] Maria Andrade,[5] Lucia Andrade,[1] Jesper Kers.[2] *[1]Nephrology, University of São Paulo School of Medicine, São Paulo, Brazil; [2]Amsterdam UMC, Amsterdam Cardiovascular Science, University of Amsterdam, Amsterdam, Netherlands; [3]Pathology, University of São Paulo School of Medicine, São Paulo, Brazil; [4]Internal Medicine, University of São Paulo School of Medicine, São Paulo, Brazil; [5]Institute of Astronomy, Geophysics and Atmospheric Sciences, University of São Paulo, São Paulo, Brazil.*

Background: Epidemiological evidence links air pollution to an increased risk of developing chronic diseases. Exposure to air pollution, especially PM_{10} and $PM_{2.5}$, has received special attention due to its potential associations with cardiovascular disease (CVD), diabetes mellitus, lung cancer and chronic obstructive pulmonary disease, but its relationship with CKD is still poorly established. In Brazil, around 11% of the population suffers from CKD. We aim to evaluate the relationship between the progression of CKD and exposure to environmental factors such as air pollution, green areas, built-up areas, traffic density in the City of São Paulo in a wave of the Brazilian Longitudinal Study of Adult Health.

Methods: For each participant, we assessed demographic data, environmental data, and risk factors. Two different indicators of exposure to green spaces were used: number of street trees and land cover. Land cover classification was based on the random forest algorithm using geometrically corrected aerial photography (orthophotos). Pollutant exposure was evaluated indirectly using the distance-weighted traffic density of the participant residence and from using the annual mean concentration of PM_{10} ($\mu g/m^3$) at the monitoring station closest to the participant residence. Linear regression models were used to evaluate the importance of the environment on CKD progression; the dependent variables were GFR (CKD-EPI), albuminuria (mg/g creatinine) and microalbuminuria (mg/dL), whereas the independent variables were demographic data, environmental data and risk factors.

Results: Cardiac risk according to the American Heart Association, obesity and lower educational level were associated with a higher risk of GFR decline. We also found that traffic density was marginally associated with GFR decline ($\beta = 0.004$; CI: 0.008–0.001; $p = 0.098$). In addition to their associations with CVD and obesity, albuminuria and microalbuminuria were found to correlate inversely with the number of trees ($\beta = 0.03$; CI: 0.06–0.00; $p = 0.04$ and $\beta = 0.002$; CI: 0.004–0.001; $p = 0.05$).

Conclusions: To decrease exposure to air pollution and slow the progression of CKD, large-scale street tree planting should be encouraged.

Funding: Government Support - Non-U.S.

FR-PO1091

Correlating Kidney Failure Risk Equation and Kidney Biopsy Chronicity Score as Kidney Failure Predicting Tools

Ana C. Brás, Filipa G. Pereira, Joaquim F. Tinoco, Carolina A. Padrão, Afonso Santos, Patricia S. Carrilho, Rita Theias Manso. *Hospital Professor Doutor Fernando Fonseca EPE, Amadora, Portugal.*

Background: Progression to kidney failure (KF) may be estimated by the Kidney Failure Risk Equation (KFRE), based on age, gender, eGFR and uACR. Kidney biopsy (KB) chronicity score (KBCS), which evaluates the degree of glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis, also predicts progression to KF. We aimed to compare and validate both scores in outcome prediction in a retrospective single-center cohort study.

Methods: Patients who underwent KB from 2017 to 2022 were analyzed. Exclusion criteria were: acute kidney injury, rapidly progressive glomerulonephritis; kidney replacement therapy (KRT) dependence up to 90 days after KB; insufficient histological sample; follow up <2years or death.

Results: From a total of 235 patients, 121 patients were included: 55% (n=68) were male, with a median age of 53 years (IQR 43-65); 78% (n=94) were hypertensive, 63% (n=75) had overweight and 35% (n=42) diabetes. At the time of KB, median eGFR was 43ml/min/1.73m2 (IQR 25-68); median uACR was 2469 mg/g (IQR 964-4490); 74% (n=89) had microscopic hematuria. Median KFRE at 2 years was 2.6% (IQR 0.2-19.3) and at 5 years 9.6% (IQR 0.7-56.5). Median KBCS was 6 (IQR 3-8). At 2 and 5 years of follow-up, 23% (n=28) and 9% (n=11) of patients reached KF, respectively. At 2 and 5 years, KBCS correlated with progression to KF (r=0.543 and r=0.613, p<0.001) as well as KFRE (r=0.553, and r=0.542, p<0.001). Both KBCS and KFRE correlated with each other at 2 and 5 years (r=0.622 and r=0.613, p<0.001). In the subgroup of patients with eGFR>60ml/min/1.73m2 (n=42, 35%) at the time of biopsy, the scores KFRE and KBCS were unable to predict progression to KF (p=0.656 and p=0.084, respectively).

Conclusions: In our cohort, there was a positive correlation between KFRE and KBCS, irrespectively of eGFR. Overall, both KFRE and KBCS were able to estimate progression to KF at 2 and 5 years, showing the usefulness of these tools in clinical practice and in providing timely guidance to patients regarding KRT. In the subgroup of patients with eGFR>60ml/min/1.73m2, however, neither KFRE or KBCS associated with KF, revealing a gap in clinical, laboratory and histological markers that can better define risk progression in this population.

FR-PO1092

Improving the Quality of CKD Care with Risk Prediction and Personalized Recommendations: 1-Year Results from the GEMINI-RAPA Study

Navdeep Tangri,[1,2] Silvia J. Leon Mantilla,[2] Don Watts,[5] Cedric Woo,[5] Samuel T. Fatoba,[3] Pablo E. Pergola.[4] *[1]University of Manitoba Department of Internal Medicine, Winnipeg, MB, Canada; [2]Chronic Disease Innovation Centre, Winnipeg, MB, Canada; [3]Bayer AG, Leverkusen, Germany; [4]Renal Associates PA, San Antonio, TX; [5]Khure Health Inc, Toronto, ON, Canada.*

Background: CKD is associated with cardiovascular disease, progression to kidney failure and early mortality. Clinical guidelines recommend (ACEi, SGLT2i, non-steroidal MRA) to slow CKD progression and prevent heart failure in CKD-T2D patients Unfortunately, most patients are recognized late and use of guideline testing and therapies remain low. We implemented Klinrisk, a highly accurate risk prediction algorithm for CKD progression, with clinical decision support (CDS) to identify patients at risk with the goal of improving quality of CKD care in a large nephrology practice.

Methods: Patients >18 years and not on dialysis were included. Data for estimated glomerular filtration rate, albuminuria, demographics, other laboratory tests and comorbid conditions was extracted from the electronic health record (EHR). Individuals were risk stratified using an externally validated risk prediction equation (Klinrisk[1]), deployed on Khure Health's CDS platform Reports are generated quarterly to inform and educate physicians. One year data on changes in guideline directed care are presented here.

Results: Of 16,099 patients that were risk-stratified, 29% were at high risk of CKD progression. Higher risk individuals were similar in age, but more likely to have diabetes, hypertension and heart failure. At one year, UACR testing increased 3 fold from 12.3 to 38.8 %, and UACR/PCR values were available in 83 % of individuals. Among high risk patients (> 10 % risk of progression over 2 years) there was a 19% increase in prescription of RAASi, 96 % increase in prescription of SGLT2i and an 65 % increase in prescription of ns-MRAs.

Conclusions: Integration of a highly accurate machine model for CKD progression when paired with EHR linked clinical decision support improves guideline-recommended testing and therapy in high -risk patients with CKD. Longer follow up and periodic assessment is planned to observe changes in quality metrics and patient outcomes.

Funding: Commercial Support - Bayer

FR-PO1093

Statewide Impact of CKD Attributable to Dietary Risk Factors in the United States, 1990-2021: Insights from the GBD 2021 Study

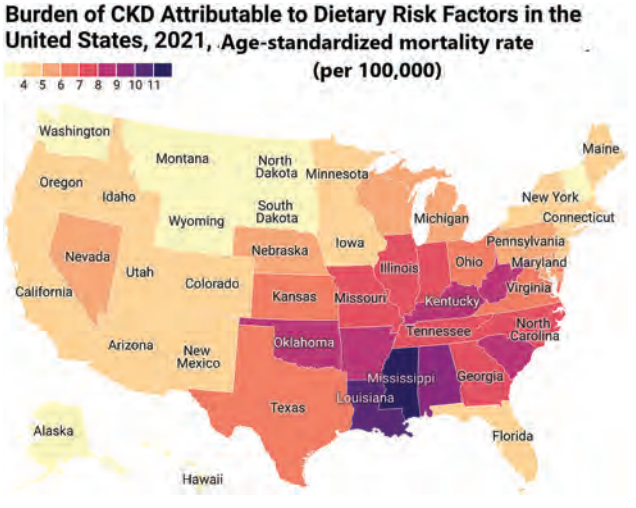
Ashutosh Rangani,[1] Ashwinikumar Shandilya,[4] Mohit Lakkimsetti,[2] Haseeb Madiha,[7] Ram Prasanjith Reddy,[6] Vishrant Amin,[3] Juhi Patel,[3] Hardik Desai,[5] Saif Syed.[8] *[1]Ternopil National Medical University, Ternopil, Ukraine; [2]Mamata Medical College, Khammam, India; [3]Gujarat Medical Education and Research Society Medical College & Hospital Valsad, Valsad, India; [4]Rural Medical College, Pravara Institute of Medical sciences, Ahmednagar, India; [5]Gujarat Adani Institute of Medical Science, Bhuj, India; [6]MediCiti Institute of Medical Sciences, Medchal, India; [7]Jinnah Sindh Medical University, Karachi, Pakistan; [8]Royal College of Surgeons in Ireland, Dublin, Ireland.*

Background: Chronic Kidney Disease (CKD) represents a significant healthcare challenge in the United States, with direct medical costs ranging from $6,592 to $280,727 per person. Among the major modifiable risk factors, dietary habits play a crucial role, yet state-wise comparative assessments remain scarce.

Methods: Using the Global Burden of Disease (GBD) 2021 toolkit, we evaluated the impact of seven dietary risk factors on CKD-related deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) across the US from 1990 to 2021, segmented by age, sex, year, and location.

Results: The study observed the highest total percentage change (TPC) in CKD-related deaths due to high consumption of sugar-sweetened beverages (497%), followed by diets high in processed meat (473%), low in vegetables (386%), high in red meat (352%), low in whole grains (332%), and low in fruits (294%) over the studied period. Oklahoma saw the most significant increase in age-standardized mortality rates by 234%, with Alabama experiencing a 43% rise in YLD rates. The age group 80-84 reported the highest number of deaths at 5,468, followed by the 70-74 age group at 13,847 in 2021. Males experienced a higher burden compared to females over the last three decades.

Conclusions: Dietary risk factors accounted for 26.70% of all CKD-related deaths in 2021. Given these findings, enhancing public awareness through targeted e-health and m-health educational campaigns is critical to mitigate the impact of poor dietary habits on CKD.



FR-PO1094

Global Burden of CKD in Individuals 20 Years and Older in 204 Countries and Territories, 1990-2021

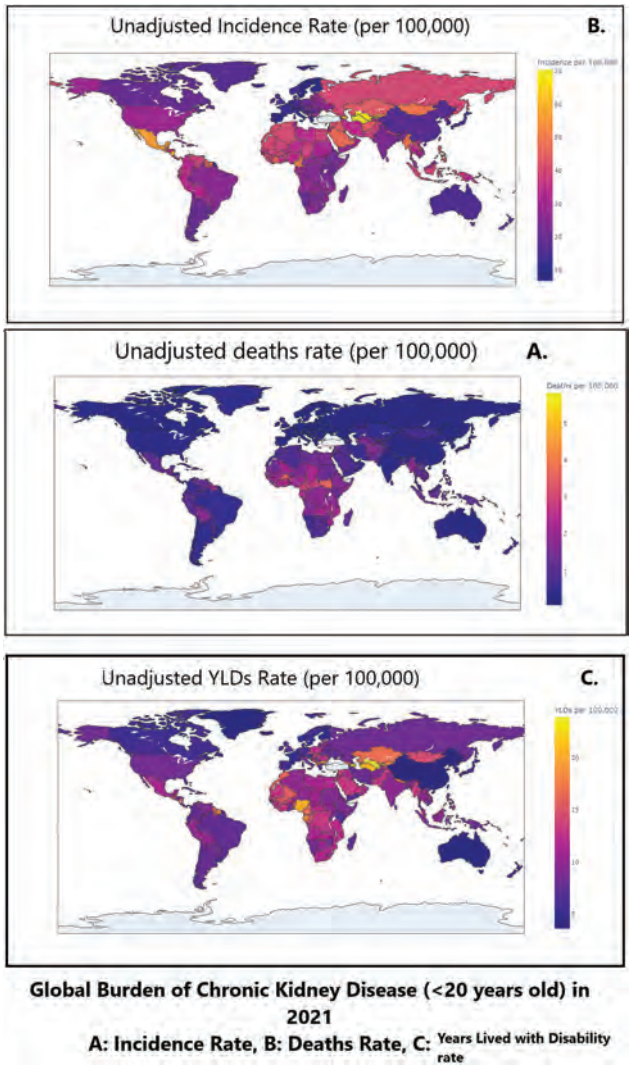
Ishita D. Hirpara,[1] Geethika C. Potluri,[5] Anushka Dekhne,[6] Sashank S. Bollu,[2] Sai Nitya Tejaswi Anne,[2] Asmita Gera,[3] Hardik Desai.[4] *[1]GMERS Medical College Junagadh, Junagadh, India; [2]Gandhi Medical College, Secunderabad-Padmarao Nagar, India; [3]Tianjin Medical University, Tianjin, China; [4]Gujarat Adani Institute of Medical Science, Bhuj, India; [5]Dr YSR University of Health Sciences, Vijaywada, India; [6]American University of Antigua, Coolidge, Antigua and Barbuda.*

Background: The impact of CKD in individuals <20 is profound, affecting their physical health, quality of life, and psychosocial development. The study was aimed at assessing global epidemiological trend of CKD <20 years of age.

Methods: Employing the Global Burden of Disease 2021 framework, we estimated incidence, prevalence, deaths, disability-adjusted life years (DALYs), year lived with disabiliy (YLDs) stratified by age, sex, and year across 204 countries and territories from 1990-2021 for individuals <20 years old.

Results: The total percentage of change (TPC) in prevalence increased by 21% (95%UI: 19-23%), incidence by 20% (14-27%) from 1990-2021. However, there was a decrease in DALYs by 22% and in deaths by 23% over the last three decades. Regionally, the highest TPC in CKD incidence was observed in central Africa by 141%. The Low Sustainable Development Index (SDI) countries exhibited the most significant increases in deaths (32%) and DALYs (33%) from 1990-2021. The unadjusted incidence rate in the 15-19 age group rose by 44%, followed by a 37% increase in 10-14 age group from 1990-2021. Gender disparities were evident in the burden of CKD, with males experiencing a higher overall impact. The TPC in incidence for males increased by 25% compared to 15% for females from 1990-2021.

Conclusions: CKD accounted for 0.43% deaths amongst all casualties in 2021 <20 years old. The study highlights the urgent need for targeted interventions and resources to address the escalating prevalence of CKD in young individuals, particularly in regions with the highest incidence rates and in countries with low SDI countries.



Global Burden of Chronic Kidney Disease (<20 years old) in 2021
A: Incidence Rate, B: Deaths Rate, C: Years Lived with Disability rate

FR-PO1095

Palliative Care and Hospice Utilization in US Veterans Treated with Conservative Management vs. Dialysis

Yoko Narasaki,[1] Connie Rhee,[1] Amy S. You,[1] Man Kit Michael Siu,[1] Csaba P. Kovesdy,[2] Ji Hoon Yoon,[1] Lisa Le,[1] Danh V. Nguyen,[3] Kamyar Kalantar-Zadeh.[4]
[1]University of California Los Angeles, Los Angeles, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]University of California Irvine, Irvine, CA; [4]Harbor-UCLA Medical Center, Torrance, CA.

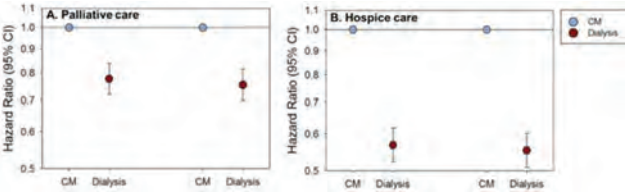
Background: There is growing need for the role of palliative care in the routine nephrology management of the advanced CKD population given the high physical and psychological symptom burden of these patients, particularly among those who are aging and ailing. However, the utilization of palliative and hospice care services among advanced CKD patients in the US has not been well-studied. We thus sought to examine palliative and hospice care utilization among advanced CKD patients treated with conservative management (CM) vs. dialysis in a national cohort of US Veterans.

Methods: Using national Veterans Affairs (VA) data linked with the USRDS and Medicare databases, we examined advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis (defined as non-receipt vs. receipt of dialysis within 2-years of 1st eGFR <25) over 2010-19. We compared time to 1st referral to palliative care (primary outcome) or hospice (secondary outcome) among CM vs. dialysis patients who were matched by propensity score (PS) using a 1:1 ratio with a caliper distance of ≤0.2 to address confounding using Cox models.

Results: Baseline characteristics were well-balanced among 13,020 CM patients PS-matched to 13,020 dialysis patients. In PS-matched analyses, patients treated with dialysis had a lower likelihood of both palliative and hospice care referral compared to those treated with CM: HR (95%CI) 0.78 (0.72-0.84) and 0.57 (0.52-0.62), respectively (Figures 1A &1B). We observed similar findings in analyses doubly-adjusted for PS covariates.

Conclusions: In a national cohort of US Veterans with advanced CKD, those who transitioned to dialysis were less likely to be referred to palliative or hospice care than those treated with CM. Further studies are needed to determine factors contributing to differential palliative/hospice care utilization in advanced CKD patients treated with CM vs. dialysis.

Funding: NIDDK Support



FR-PO1096

Natural Language Processing Artificial Intelligence (AI) Predicts CKD Progression in Medical-Word Virtual Space

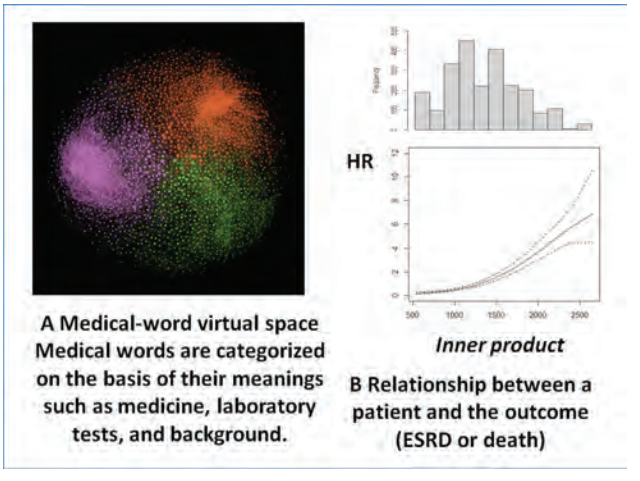
Eiichiro Kanda,[1] Bogdan I. Epureanu,[2] Taiji Adachi,[3] Tamaki Sasaki,[1] Naoki Kashihara.[1] *[1]Kawasaki Ika Daigaku, Kurashiki, Japan; [2]University of Michigan, Ann Arbor, MI; [3]Kyoto Daigaku, Kyoto, Japan.*

Background: Chronic kidney disease (CKD) leads to end-stage renal disease (ESRD) or death. A new surrogate marker reflecting its pathophysiology has been needed for CKD therapy.

Methods: In this study, we developed a virtual space where data in medical words and those of actual CKD patients were unified by natural language processing and category theory.

Results: A virtual space of medical words was constructed from the CKD-related literature (n=165,271) using Word2Vec, in which 106,612 words composed a network. The network satisfied the definition of vector calculations, and retained the meanings of medical words. The data of CKD patients of a cohort study for 3 years (n=26,433) were transformed into the network as medical-word vectors. We let the relationship between vectors of patient data and the outcome (dialysis or death) be a marker (inner product). Then, the inner product accurately predicted the outcomes: C-statistics of 0.911 (95% CI 0.897, 0.924). Cox proportional hazards models showed that the risk of the outcomes in the high-inner-product group was 21.92 (95% CI 14.77, 32.51) times higher than that in the low-inner-product group.

Conclusions: This study showed that CKD patients can be treated as a network of medical words that reflect the pathophysiological condition of CKD and the risks of CKD progression and mortality.



A Medical-word virtual space
Medical words are categorized on the basis of their meanings such as medicine, laboratory tests, and background.

B Relationship between a patient and the outcome (ESRD or death)

FR-PO1097

Evaluating a Computable Phenotype for CKD Detection in Adult Patients Treated in Primary Care

Joseph D. Nguyen, Lalida Kunaprayoon, Benjamin Silverberg, Indika V. Mallawaarachchi, Jennie Z. Ma, Jason A. Lyman, Julia J. Scialla. *University of Virginia, Charlottesville, VA.*

Background: Chronic kidney disease (CKD) affects about 37 million Americans, particularly those with diabetes and hypertension, and is often detected via laboratory studies prior to symptom onset. This project aims to evaluate the accuracy of a computable phenotype to detect adults with CKD stage 3 or higher. The ultimate goal is to improve CKD recognition and evaluation by launching a best practice advisory (BPA) in patients likely to have CKD.

Methods: We developed an algorithm to identify probable cases of CKD in adult patients seen at a primary care clinic at one academic medical center between October 2023 and February 2024. The algorithm identifies patients with estimated glomerular filtration rate (eGFR)<60 ml/min/1.73m2 during the clinic visit, as well as on a prior date (90 to 730 days prior to the index test). If a patient identified by the algorithm is not yet enrolled into the EPIC CKD registry, the BPA alert is activated for probable CKD. If a patient was alerted multiple times, we analyzed the first alert. For patients flagged for probable CKD, we conducted chart review to collect: (1) laboratory parameters for CKD and (2) data relevant to the clinical impression of CKD that may also consider other elements like markers of kidney damage (e.g. albuminuria) or structural kidney disease (e.g. imaging abnormality).

Results: Of 277 probable CKD cases, 155 individuals were alerted. 133 of these individuals met stringent laboratory criteria for CKD stage 3 or higher (e.g. no intervening normal that disagree). 115 met laboratory criteria and were also deemed to have CKD by the clinical impression of the reviewer (74% of total alerted individuals). The remaining 26% either did not fully meet laboratory criteria (n=22) or were deemed to not clearly have CKD clinically (n=18). Most of these cases were due to either borderline eGFR near 60 ml/min/1.73m2, disagreement between different eGFR equations, recovered eGFR, or oscillating eGFR.

Conclusions: Our computable CKD definition demonstrated a relatively high rate of confirmed CKD, but clinician confirmation is advisable to ensure diagnostic accuracy prior to recommending further evaluation or treatment. Future directions include refining the BPA to include other measures of kidney damage in patients with equivocal eGFR.

FR-PO1098

Validation of Machine Learning-Based Screening Tools for Early Detection of CKD in Patients with Type 2 Diabetes (T2D)

Julian Martinez,[1] Alejandra Perez-Rondon,[1] Jose Zea,[1] Isabella Ilano,[1] Natalia Castano-Villegas,[1] Luong Nguyen Cong,[2] Ahmed Hadaoui.[3] *[1]Arkangel AI, Bogota, Colombia; [2]AstraZeneca, Ho Chi Minh, Viet Nam; [3]AstraZeneca, Algiers, Algeria.*

Background: With the increasing burden of CKD among pts with T2D, early detection is critical. Annual screening is challenging, especially in developing nations. We developed 2 minimal resource models to identify pts at high risk of CKD based on estimated glomerular filtration rate (eGFR) alterations. Our study validated the models on iCaReMe global registry T2D pts.

Methods: Arkangel AI™ software was used to develop 2 algorithms. Machine-learning architectures were used for training and ranking the algorithms. An ensemble learning model was built from the 2 algorithms. A combination of predictions from these algorithms decides whether the pt is positive or negative for CKD. These algorithms were applied to an observational iCaReMe database spanning 6 low-middle-income countries to generate an eGFR-based model. Demographic data including age, duration of T2D, sex, body mass index, and systolic and diastolic blood pressure were extracted for pts with T2D. Pts with eGFR <60 mL/min/1.73m^2 were considered positive cases and those with eGFR ≥60 mL/min/1.73m^2 were negative cases. The study determined the accuracy, sensitivity, specificity, positive predictive values, area under the curve (AUC), and F1 scores of the model.

Results: A total of 4342 pts with validated eGFR measurements were included in training the models. The ensemble learning model reported 85.19% (95% confidence interval [CI]: 82.82 to 87.55) sensitivity, 39.97% (95% CI: 38.34 to 41.59) specificity, and 48.96% (95% CI: 47.48 to 50.45) accuracy. Furthermore, the model has shown a positive predictive value of 26.06% (95% CI: 24.44 to 27.68) indicating a moderate proportion of true positive cases with CKD. The F1 score of the model was 39.91%, presenting a good predictive performance. The AUC was 62.58% showing that the model can distinguish between pts with and without CKD.

Conclusions: The model reported a good sensitivity for identifying CKD risk in the diabetic population with minimal pt information. They can help bridge the unmet need for screening for CKD among at-risk populations in resource-limited, real-world settings.

Acknowledgment: Medical writing support - Priyanka Grandhi (Fortrea Scientific Pvt. Ltd)

Funding: Commercial Support - AstraZeneca International

FR-PO1099

Age-Specific Estimated Glomerular Filtration Rate for Mortality Prediction in the Korean Population: A Retrospective Kangbuk Samsung Health Cohort Study

Kyu-Beck Lee, Jihyun Yang, Young Youl Hyun. *Kangbuk Samsung Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: With the advance of the glomerular filtration rate (GFR) formula and the recognition of age-related variations, there is a concern regarding the need to reconsider/adapt a distinct GFR equation for the elderly. We conducted a comparative analysis of the predictive accuracy of CKD-EPI 2009, 2021 (race-free) and the European Kidney Function Consortium (EKFC) equation for mortality prediction across different age groups.

Methods: We analyzed 670,320 participants who underwent a comprehensive health examination, enrolled in Kangbuk Samsung Health Cohort from January 1, 2002 to December 31, 2019 and followed them up for mortality until December 2019. The age group was divided from 18 to 39, 40-64, and over 65 years old (group 1,2,3).

Results: The participants' median follow-up period was 8.8 years, mean age was 39.8 years old (minimum 18, maximum 97), and 53.6% were male. Mean eGFR using 2009 CKD-EPI was 95.1 ml/min/1.73m^2, 100.6 ml/min/1.73m^2 using 2021 CKD-EPI, 94.0 ml/min/1.73m^2 using EKFC. There was no difference between the equations in group 1. Discriminatory power for all-cause mortality prediction was the best when using EKFC in group 2 and group 3. Moreover, the EKFC showed better discriminatory power for CVD mortality in all age groups.

Conclusions: The EKFC equation showed better prediction and explanation in middle age to the elderly.

FR-PO1100

Identification of Rapid Decline of Kidney Function in Older Adults with Different Types of Aging

Mengjing Wang, Jing Chen. *Nephrology, Huashan Hospital, Fudan University, Shanghai, China.*

Background: This study aims to assess the role of glomerular filtration rate (GFR) combined with urine albumin-creatinine ratio (ACR) in predicting rapid kidney function decline (>30% decline in GFR within 2 years) across older adults with three types of aging (healthy aging, aging with comorbidities, aging with nephropathy).

Methods: Categorical analyses were conducted using data from the Rugao Longevity and Aging Study (RLAS) cohort in China (470 older adults with healthy aging and 505 with comorbidities) and healthcare data from Huashan Hospital of Fudan University (315 older adults with nephropathy) between 2011 and 2022. Corrected (age) absolute risk probabilities (aAR) were calculated for different GFR and ACR intervals, stratified by aging category. Finally, the importance of different categories of GFR and ACR in different aging populations for determining rapid decline in kidney function was identified based on random forest (RF) models.

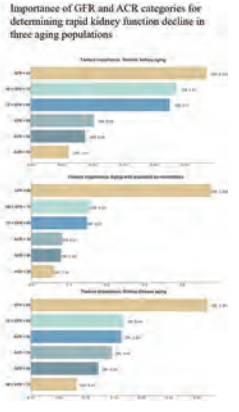
Results: Compared to the healthy group, the risk of rapid decline of kidney function was generally higher in the comorbidity group and highest in the nephropathy group across all GFR combined with ACR categories. The risk thresholds varied among the three populations: for the healthy group, ACR >30 mg/g combined with GFR <75 ml/min/1.73 m2 (moderate risk); for the comorbidity group, ACR >30 mg/g (moderate risk), particularly with GFR <60 ml/min/1.73 m2 (high risk); and for the nephropathy group, at all stages (moderate risk), particularly ACR >30 mg/g combined with GFR <75 ml/min/1.73 m2(high risk). Besides, GFR is of the most importance in distinguishing rapid decline in kidney function, but the discrimination of GFR decreases with the occurrence of comorbidities and kidney diseases, while the discrimination of ACR increases in this two populations.

Conclusions: The thresholds for GFR and ACR to predict rapid decline in kidney function in the elderly population need to be established according to different types of aging.

Funding: Government Support - Non-U.S.

The adjusted absolute risk for GFR and ACR combination in different elderly populations (healthy aging, aging with comorbidities, aging with nephropathy). Colors indicating adjusted absolute risk gradient: green (low risk: 0% - 9.9%), yellow (medium risk : 10% - 19.9%), red (high risk : 20% and above).

Three types	First eGFR and ACR in the baseline	Adjusted absolute risk probability (based on 30% decline in GFR during the 2-year baseline period)			
		GFR > 90	GFR 75 - 90	GFR 60 - 75	GFR < 60
Healthy aging	ACR < 30				
	ACR > 30				
Aging with expected co-morbidities	ACR < 30				
	ACR > 30				
Kidney disease aging	ACR < 30				
	ACR > 30				



FR-PO1101

Impact of Adopting the 2021 CKD-EPI Equation on CKD Detection in a Multiethnic Dutch Population: The HELIUS Study

Brechje Huisman, Taryn G. Vosters, Bert-Jan Van den Born, Irene van Valkengoed, Liffert Vogt. *Amsterdam UMC Locatie AMC, Amsterdam, Netherlands.*

Background: Until recently, the standard method of estimating GFR for the diagnosis of CKD included an ethnicity coefficient for those of African descent. There has been debate whether or not to exclude the coefficient from the CKD-EPI equation, which resulted in the 2021 CKD-EPI equation. We explored the impact of adopting this formula on eGFR and CKD detection in a multi-ethnic Dutch population.

Methods: We analyzed data of 21,617 participants (mean age 44yr, 42% male) of the multi-ethnic HELIUS cohort study (Amsterdam, the Netherlands). Three groups were distinguished: African Surinamese (4,151), Ghanaian (2,339) and Non-corrected (15,127; i.e., those who required no correction for ethnicity. eGFR was calculated using the uncorrected and corrected 2009 and 2021 CKD-EPI equation. CKD prevalence (i.e., eGFR (<60mL/min/1.73m^2) and/or ACR (≥3mg/mmol) was calculated. CKD case detection for all three equations were compared in high risk groups (i.e., diabetes mellitus, hypertension or cardiovascular disease). C-statistics for CKD probability were compared. Inter-rater reliability was measured via Cohen's kappa and consistency calculation.

Results: Compared to the Non-corrected group (mean eGFR 102 mL/min/1.73m^2), age- and sex-adjusted differences (p<0.001) in the mean eGFR(SE) were 4.6±0.2 vs -8.9± 0.2mL/min/1.73m^2 in the African Surinamese and 3.2±0.3 vs -10.4±0.3mL/min/1.73m^2 in the Ghanaian participants for the 2009 and 2021 CKD-EPI equation, respectively. CKD prevalences were similar for both equations overall and in subgroups (e.g., 10.9 vs 11.6% (p=0.33) among African Surinamese). CKD case detection did not differ between equations. The C-index for CKD probabilities was not influenced by the equation. The internal consistency in detecting CKD of the 2009 and 2021 equation was high (Figure 1).

Conclusions: In our cohort, adoption of the 2021 CKD-EPI equation leads to lower eGFR in African Surinamese and Ghanaian participants, but similar overall estimates of CKD prevalence. Our study indicates that discontinuation of the ethnicity-coefficient may have very little impact on CKD detection in a multi-ethnic Dutch population.

Figure 1. Internal consistency between CKD-EPI 2009 and 2021 in detecting CKD (y/n) per group

Consistency (%)	Non-corrected group CKD 2009			African Surinamese CKD 2009			Ghanaian CKD 2009		
	99.7%	y	n	99.3%	y	N	98.9%	y	n
CKD 2021	y	1526	0		452	28		267	28
	n	39	13462		0	3691		0	2023

FR-PO1102

Insufficient Referral and Monitoring of CKD in Germany: A Nationwide, Retrospective Cohort Study

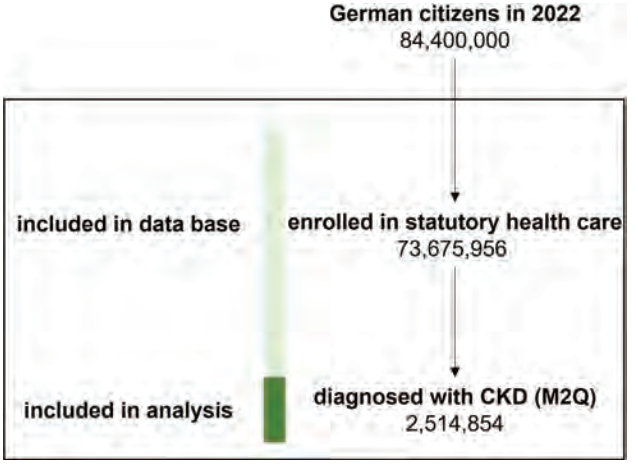
Friedrich A. von Samson-Himmelstjerna,[1] Edgar Steiger,[2] Benedikt Kolbrink,[1] Roland Schmitt,[1] Kevin Schulte.[1] *[1]University Hospital Schleswig-Holstein, Campus Kiel, Department of Nephrology and Hypertension, Kiel, Germany; [2]Central Research Institute of Ambulatory Health Care in Germany, Berlin, Germany.*

Background: Chronic kidney disease (CKD) is one of the most significant drivers of the global disease burden and an increasing public health issue. Adequate referral of high-risk patients to nephrologists is associated with improved management of CKD. Whether this is accomplished in Germany, a country with very high health care expenditure, is unknown.

Methods: We retrospectively analyzed outpatient claims data of 73,675,956 Germans who were covered by statutory health care in 2022.

Results: We identified 2,514,854 patients with prevalent CKD, 207,015 of which had CKD stage 4. Merely 134,132 (64.8%) patients with diagnosed CKD stage 4 received specialist care by a nephrologist in 2022. Failure to refer was associated with insufficient monitoring rates of kidney function and proteinuria. In a mixed logistic regression model, referral to nephrologists was less likely for women (odds ratio [OR] 0.72, 95% confidence interval [CI] 0.71-0.74), for higher age (OR per year 0.97, CI 0.96-0.97) and for nursing home inhabitants (OR 0.62, CI 0.60-0.64). These findings remained steady despite multi-variable adjustment for individual morbidity, population density, urbanization, and nephrologist density.

Conclusions: Our findings suggest serious short comings of the German health care system with inability to provide adequate referral to nephrology services for patients with late-stage CKD, particularly disadvantaging women, the elderly, and nursing home inhabitants. Change of public health policy is needed for better prevention of kidney failure as well as to reduce the CKD-associated burden of disease.



All statutory health care recipients with a diagnosis of CKD in the year 2022 were included. Only reconfirmed cases were included, meaning that a diagnosis of CKD was claimed in at least 1 additional quarter within 1 year after the initial diagnosis (M2Q).

FR-PO1103

Enhancing Access to Nephrology Care: Development of a Telenephrology Dashboard via Human-Centered Design

Melissa L. Swee,[1,2] Diana I. Jalal,[1,2] M. Lee Sanders,[1,2] Mary V. Sarrazin,[1,2] Angie R. Thumann,[1] Kantima Phisitkul,[1] Masaaki Yamada,[1,2] Heather Reisinger,[2,1] Bradley S. Dixon.[1] *[1]VA Iowa City Healthcare System, Iowa City, IA; [2]University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Chronic kidney disease (CKD) is common and associated with high rates of morbidity and mortality. Despite evidence that early referral to nephrology improves outcomes, it is estimated that less than half of patients with CKD see a nephrologist. We aimed to improve access to nephrology care by developing a user-friendly Telenephrology dashboard for the 40,000 Veterans receiving care through the Iowa City Veterans Affairs Health Care System.

Methods: The development process adhered to the human-centered design framework, encompassing five phases: (1) Empathize, (2) Define, (3) Ideate, (4) Prototype, and (5) Test. We interviewed patients' and providers' regarding perceptions of structural barriers and facilitators for the Telenephrology program, using the Consolidated Framework for Implementation Research (CFIR) as a guide. Data from these interviews were analyzed using directed content analysis. Then, a rapid ideation workshop was convened to generate creative solutions that balance technical requirements with the needs of clinicians and patients.

Results: The iterative design process identified three critical needs: (1) clarity in visualizing data, (2) accuracy of information, and (3) balancing standardization with individualization. The final Telenephrology Dashboard developed through the rapid ideation workshop included: (1) a graph of kidney function over time, (2) tables synthesizing lab data, (3) options to drill down events to specific times, (4) customization of views, and (5) integration of kidney disease progression models. Since the inception of the Telenephrology program in 2018, clinic productivity has increased and wait times have decreased. Key facilitators identified in interviews included increased access to specialist care and convenience for providers and Veterans. Perceived barriers included: concerns of decreased autonomy and increased workload for primary care providers, added complexity, and lack of sustainability.

Conclusions: Telenephrology increases nephrology access and convenience. Nevertheless, future challenges include concerns around primary care autonomy, workload, and system complexity. Ongoing research is needed to validate the impact of Telenephrology on patient outcomes and physician satisfaction and effectiveness.

Funding: NIDDK Support, Private Foundation Support

FR-PO1104

Integrating Clinical Decision Support Tools in CKD Management

Heather Thiessen Philbrook,[1] Dipal M. Patel,[1] Jack Bitzel,[1] Steven Menez,[1] C. E. Cervantes,[1] Bernard G. Jaar,[1] Morgan Grams,[2] Chirag R. Parikh.[1] *[1]Johns Hopkins Medicine, Baltimore, MD; [2]NYU Langone Health, New York, NY.*

Background: Integrating clinical decision support (CDS) tools into nephrology outpatient clinics provides an opportunity to improve patient care by leveraging existing data in electronic medical records (EMR).

Methods: In January 2022, three CDS tools were deployed for use in Johns Hopkins nephrology clinics. A viewer within the EMR system displays Kidney Failure Risk Equation (KFRE) scores, risk of cardiovascular disease and longitudinal graphical

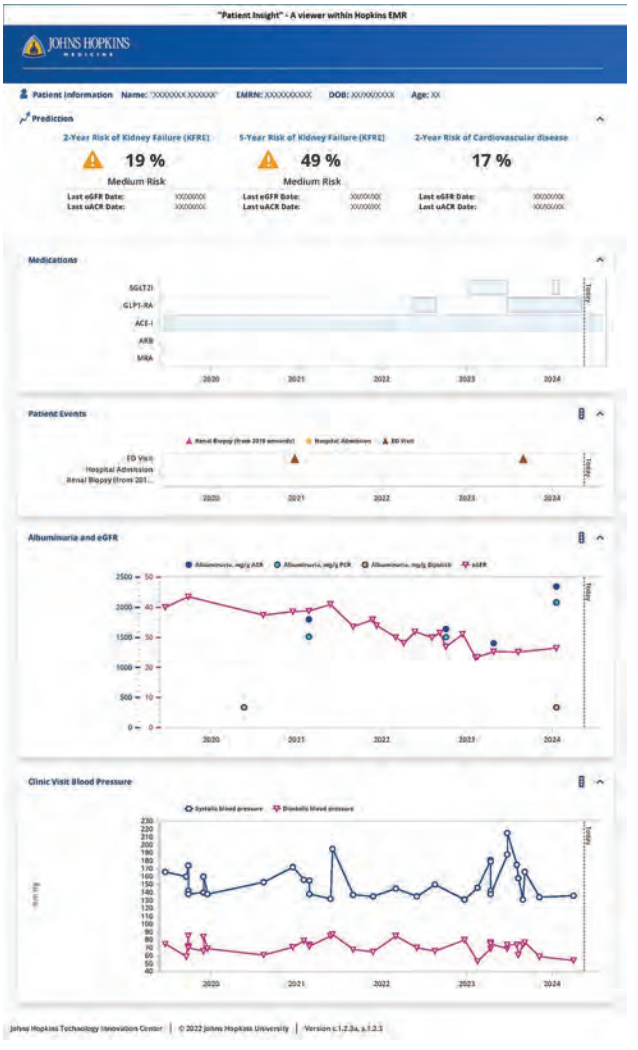
visualizations including prescription status for the top 5 KDIGO-recommended proteinuria-reducing therapies, and laboratory measurements (Figure). Nephrologists can also view the 2-year KFRE on the EMR dashboard and utilize a dotphrase in clinic notes. We examined trends in clinical care practices before (2020-2021) and after (2022-2023) implementation of these CDS tools for patients with advanced kidney disease, and within a subgroup of diabetic patients.

Results: Practice patterns improved with a reduction in the percentage of patients without recent albuminuria measurements (Table). Prescription rates of evidence-based therapies to reduce proteinuria and protect kidney function increased over time.

Conclusions: CDS tools can highlight guideline-based recommendations for clinical care and provide an opportunity to evaluate their impact in real-world clinical settings. More analyses are needed to define mechanisms by which CDS tools impact clinical practices.

Funding: Clinical Revenue Support

		All Patients		Patients with Diabetes	
		Before (n=2037)	After (n=2223)	Before (n=1084)	After (n=1126)
Patient Care	# nephrology encounters, median (25th pct, 75th pct)	3 (2,5)	3 (2,5)	3 (2,5)	3 (2,5)
	# eGFR measurements, median (25th pct, 75th pct)	7 (4,13)	8 (4,13)	7 (4,13)	8 (5,13)
	Missing urine albumin to creatinine, urine protein to creatinine, or urine protein dipstick measurement, %	12%	10%	11%	9%
Prescription	Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), %	66%	70%	73%	76%
	Glucagon-like peptide-1 receptor agonist (GLP1), %	10%	15%	19%	27%
	Sodium/glucose cotransporter-2 inhibitors (SGLT2), %	15%	30%	21%	40%
	Mineralocorticoid receptor antagonists (MRS), %	11%	14%	13%	16%



FR-PO1105

CKD Care: Evaluating the Role of Clinical Pharmacists

Masaaki Yamada,[1,2] Qianyi Shi,[1,2] Brian C. Lund,[2] Mary K. Good,[2] Benjamin R. Griffin,[1] Melissa L. Swee,[1,2] Sadaf Akbari,[1] Korey Kennelty,[1] Elissa Z. Faro,[1] Mary V. Sarrazin,[1,2] Diana I. Jalal.[1,2] *[1]University of Iowa Hospitals and Clinics, Iowa City, IA; [2]Iowa City VA Medical Center, Iowa City, IA.*

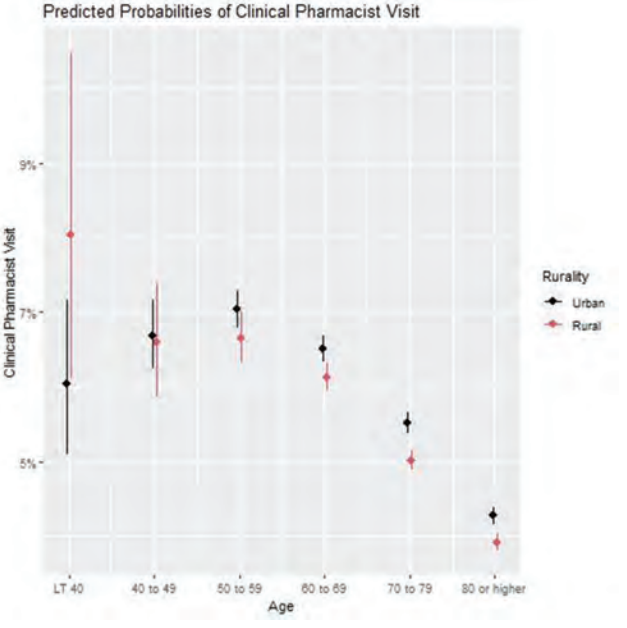
Background: Clinical pharmacists are proven to lower cardiovascular (CV) risks in chronic disease management. Chronic kidney disease (CKD) increases CV events, yet studies on clinical pharmacist-driven CKD care remain scarce. We evaluated the pharmacist utilization in CKD within the Veterans Health Administration–known for its robust clinical pharmacist workforce.

Methods: We conducted a retrospective cohort study of Veterans with CKD. CKD was defined by an estimated glomerular filtration rate (eGFR) <60 mL/min (measured twice, ≥90 days apart) during 2018 to 2019. Pharmacist users were individuals who had at least 1 clinic visit with a clinical pharmacist. Logistic regression analysis was used to identify factors associated with pharmacist use.

Results: Our cohort (732,003 Veterans with CKD) was predominantly White (72%) and male (96%), with mean age=75 years (yrs) and mean eGFR=46 mL/min; 37% lived in rural areas. 22% were identified as pharmacist users. Compared to pharmacist non-users, pharmacist users were younger (70 vs. 75 years), less likely to live in rural areas (35% vs. 37%) and had a higher prevalence of diabetes mellitus (74% vs. 46%). Logistic regression analysis indicated lower pharmacist utilization among Veterans aged ≥70 yrs (odds ratio [OR] 0.82 for age 70-79 yrs and 0.63 for age ≥80 yrs, p <0.01), particularly in rural areas (p for interaction, <0.05) as shown in Figure. Rurality was associated with underutilization of pharmacist-led care (OR, 0.92, p <0.001). Clinical pharmacist utilization did not differ across varied CKD stages (p >0.05).

Conclusions: Approximately 1 in 5 Veterans with CKD utilize clinical pharmacist care. Older age and rural residence significantly associate with underutilization of pharmacists in CKD care.

Funding: Veterans Affairs Support



FR-PO1106

Iohexol Plasma Clearance Measurement Protocol Standardization: A Consensus of the European Kidney Function Consortium

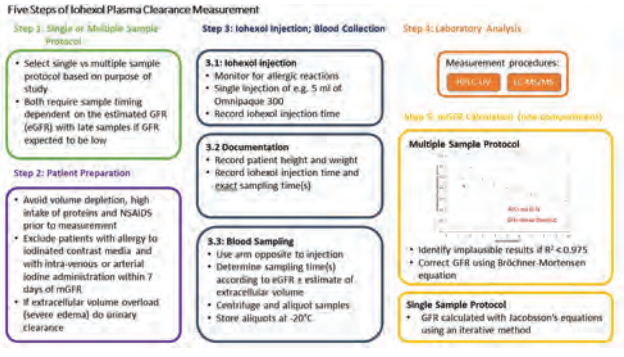
Natalie Ebert,[1] Elke Schaeffner,[1] Tariq Shafi,[3] Bjorn O. Eriksen,[6] Arend Bokenkamp,[8] Marco van Londen,[9] Jesse C. Seegmiller,[10] Runolfur Palsson,[7] Olafur S. Indridason,[7] Pierre Delanaye,[5] Etienne Cavalier,[2] Laurence Dubourg,[11] Christine A. White.[4] European Kidney Function Consortium (EKFC). *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Universite de Liege, Liege, Belgium; [3]Houston Methodist, Houston, TX; [4]Queen's University, Kingston, ON, Canada; [5]CHU de Liege - Hopital du Sart Tilman, Liege, Belgium; [6]UiT Norges Arktiske Universitet, Tromso, Norway; [7]Landspitali, Reykjavik, Iceland; [8]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [9]Rijksuniversiteit Groningen, Groningen, Netherlands; [10]University of Minnesota Twin Cities, Minneapolis, MN; [11]Hospices Civils de Lyon, Lyon, France.*

Background: International consensus and the 2024 KDIGO guidelines supports the development of standardized protocols for measured glomerular filtration rate (mGFR) to facilitate the adoption of mGFR in both clinical and research settings.

Methods: The European Kidney Function Consortium (EKFC) convened an international group of mGFR experts and performed an extensive literature search to inform the development of recommendations for mGFR determination using one-compartment plasma clearance models and iohexol as the exogenous filtration marker. Iohexol was selected as it is non-radiolabeled, safe, inexpensive, widely available, and can be assayed at a central laboratory. Other commonly used non-radio labeled tracers have been (inulin) or are soon to be (iothalamate) discontinued. A plasma clearance model was selected as it does not require timed urine collections. A one-compartment model was preferred to a two-compartment model as it requires fewer samples. The resulting recommendations were based on published evidence complemented by expert opinion.

Results: Recommendations include practical advice for patients and health professionals, preparation, administration and safety aspects of iohexol, laboratory analysis, blood sample collection and sample timing for both multiple and single sample protocols, description of the mGFR mathematical calculations as well as implementation strategies (Figure). The EKFC will provide materials such as patient information sheets, standard operating procedures, a study protocol template, and support for mGFR calculation.

Conclusions: Members of the EKFC have evaluated the evidence and formulated recommendations that include all aspects of iohexol plasma clearance measurement using a one-compartment model. Nephrologist education and widespread dissemination is critical to making mGFR available for patient care and research.



FR-PO1107

Association of Urine-to-Plasma Urea Ratio with the Incidence of Kidney Failure in Patients with CKD

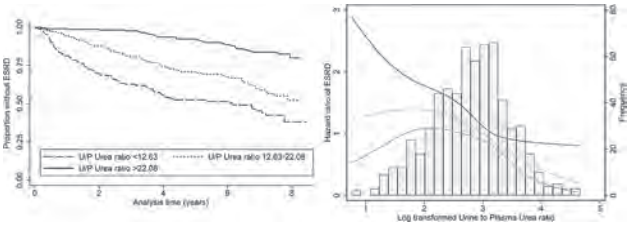
Usha Kumari,[1] Mohamed T. Elkhodary,[1] Keiichi Sumida,[1] Barry M. Wall,[1,2] Csaba P. Kovesdy.[1,2] *[1]The University of Tennessee Health Science Center, Memphis, TN; [2]VA Memphis Healthcare System, Memphis, TN.*

Background: Estimated glomerular filtration rate (eGFR) and proteinuria are traditional markers used to assess the risk of kidney outcomes. Measures of tubular function such as the ratio of urine to plasma urea (U/P urea) can offer additional insight on the kidneys' functional capacity, but its association with long term kidney outcomes is unclear.

Methods: In a retrospective cohort of 638 patients with eGFR <60 ml/min/1.73m^2 from a single institution, we measured U/P urea from single spot urine specimens. We examined the association of U/P urea with end-stage kidney disease (ESKD, defined as the initiation of kidney replacement therapy) using the Kaplan Meier method and multivariable adjusted Cox models with adjustment for demographic characteristics, smoking status, comorbidities, eGFR and proteinuria. U/P urea was analyzed both as a natural log-transformed continuous variable and as a categorical variable divided in tertiles.

Results: The mean±SD age was 67±10 years old, 96% were male, 58% were African-American and the mean±SD eGFR was 21±11 mL/min/1.73 m^2. There were 188 ESKD events (event rate, 65.9/1000PY; 95% CI: 57.1-76.1) over a median follow-up of 4.5 years. Lower U/P urea was associated with higher risk of ESKD in unadjusted (hazard ratio and 95%CI for 1 log-unit lower U/P urea: 2.39 [1.95-2.92], p<0.001) and after multivariable adjustment (1.40 [1.06-1.85], p=0.018, Figure).

Conclusions: Lower U/P urea ratio, a marker of impaired renal concentration ability, is associated with higher risk of ESKD independent of known risk factors such as eGFR and proteinuria. U/P urea obtained from spot urine specimens could provide additional information for risk stratification in patients with chronic kidney disease.



FR-PO1108

Large-Scale Proteomics Improve Prediction of CKD in the General Population without Diabetes

Ziliang Ye, Fan Fan Hou, Xianhui Qin. *Southern Medical University Nanfang Hospital, Guangzhou, China.*

Background: To develop a protein risk score (PRS) for predicting chronic kidney disease (CKD) and compare its predictive capability with a validated clinical risk model (CKD Prediction Consortium [CKD-PC]) and CKD genetic risk score (GRS) in the general population without diabetes.

Methods: The development cohort included 36,307 participants from England area in the UK biobank. Participants in the development cohort were randomly divided into a training set and a testing set in a 7:3 ratio. The validation cohort included 4,813 participants from Scotland and Wales area in the UK biobank.

Results: In the training set, a PRS for CKD risk was constructed using 86 out of 2,911 proteins. In the testing set, the CKD PRS was significantly positively associated with incident CKD (per SD increment, HR, 1.88; 95%CI: 1.67, 2.12). The C-index of the CKD PRS in predicting CKD risk was 0.838 (95%CI: 0.814-0.861), which was significantly better than that of CKD GRS (C-index, 0.749; 95%CI, 0.721-0.777). Adding CKD PRS to CKD-PC risk factors significantly increased the C-index (from 0.825 to 0.853; difference, 0.029; 95%CI, 0.018-0.040), the continuous 10-year net reclassification (0.162; 95%CI, 0.074-0.259) and integrated discrimination index (0.009; 95%CI, 0.001-0.026). The C-index for the alternative CKD PRS, compromising only the top 5 proteins (CD59, COL6A3, HRC, ITGB2, and KIM-1), was 0.810 (95%CI: 0.785-0.836), contributing most of the prediction power of original CKD PRS. These results were verified in the validation cohort.

Conclusions: The CKD PRS was a potent predictor for CKD risk in the general population without diabetes. When incorporated into a validated clinical risk model, the CKD PRS significantly improved CKD risk discrimination and reclassification.

Funding: Government Support - Non-U.S.

Model	C index (95%CI)	C index increase (95%CI)	10-y IDI improvement (95%CI)	10-y Continuous NRI (95% CI)
Testing set in the development cohort				
Age + sex + race + CKD polygenic risk score	0.749(0.721-0.777)			
Age + sex + race + CKD protein risk score	0.838(0.814-0.861)			
CKD-PC risk factors	0.825(0.799-0.850)			
Reference model: CKD-PC risk factors				
CKD-PC risk factors + CKD polygenic risk score	0.825(0.799-0.850)	0.000(-0.001, 0.001)	0.000(-0.000, 0.002)	0.000(0.000, 0.000)
CKD-PC risk factors + CKD protein risk score	0.853(0.830-0.876)	0.029(0.018, 0.040)	0.009(0.001, 0.024)	0.162(0.074, 0.259)
Validation cohort				
Age + sex + race + CKD polygenic risk score	0.745(0.665-0.826)			
Age + sex + race + CKD protein risk score	0.866(0.803-0.929)			
CKD-PC risk factors	0.832(0.774-0.889)			
Reference model: CKD-PC risk factors				
CKD-PC risk factors + CKD polygenic risk score	0.851(0.799-0.902)	0.019(-0.005, 0.049)	0.009(-0.004, 0.096)	0.167(-0.159, 0.385)
CKD-PC risk factors + CKD protein risk score	0.890(0.842-0.938)	0.058(0.025-0.102)	0.073(0.009, 0.204)	0.116(-0.019, 0.350)

Table 1. The chronic kidney disease (CKD) risk prediction performance of protein risk score for CKD risk in the testing set of the development cohort and validation cohort. CKD-PC risk factors represent those variables included in the CKD-PC model, including age, sex, race, eGFR, history of cardiovascular disease, never smoking, hypertension, body mass index, and albuminuria

FR-PO1109

A Phenome-Wide Association Study to Investigate the Role of Carbamylation in CKD: Findings from the Chronic Renal Insufficiency Cohort

Aya Awwad,[1,2] Eugene P. Rhee,[2,1] Pranav S. Garimella,[3] Sagar U. Nigwekar,[2,1] Anders H. Berg,[4] James P. Lash,[5] Mengyao Tang,[2,1] Sahir Kalim.[2,1]
[1]Harvard Medical School, Boston, MA; [2]Massachusetts General Hospital, Boston, MA; [3]University of California San Diego Division of Nephrology-Hypertension, San Diego, CA; [4]Cedars-Sinai Medical Center, Los Angeles, CA; [5]Department of Medicine, University of Illinois at Chicago, Chicago, IL.

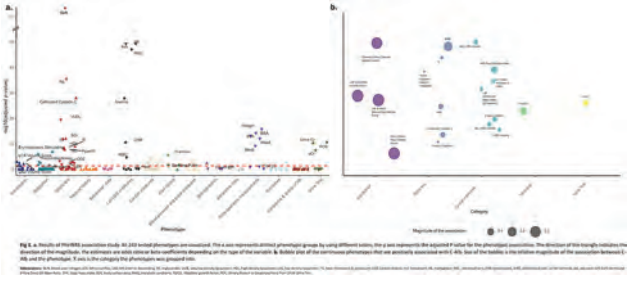
Background: Protein carbamylation, a urea driven post-translational protein modification, increases in patients with CKD and contributes to the excess morbidity and mortality observed in this population. Given urea's, and thus carbamylation's, ubiquitous nature in the body, we hypothesized carbamylation would associate with a broad range of clinical phenotypes.

Methods: We evaluated the cross-sectional association of carbamylation -assessed by carbamylated albumin (C-Alb)- with 243 phenotypic correlates among 3,111 CKD participants in the Chronic Renal Insufficiency Cohort using a phenome-wide association study (PheWAS). Models were adjusted for demographics, eGFR, and proteinuria, and a conservative Bonferroni adjusted threshold for significance was applied. Results prompted a focused post-PheWAS analysis on the association between C-Alb and coronary artery calcification (CAC) measured by Agatston scores.

Results: C-Alb was significantly associated with hematological abnormalities such as anemia diagnosis (OR: 2.04; 95% CI [1.81, 2.3], adj. pvalue=2.17 × 10-28), cardiovascular abnormalities such as increased left ventricular mass (OR: 1.38; 95% CI [1.19, 1.61], adj. pvalue=5.9 × 10-3), and lipid profile among other phenotypes (Fig.1a). C-Alb's positive association with calcification indices was the largest numerically in standardized magnitude among significant phenotypes (Fig.1b). The association with Agatston score remained significant even after adjusting for traditional atherosclerotic risk factors (β 0.77, 95% CI [0.35-1.19], pvalue <0.001).

Conclusions: Our findings showcase the wide systemic correlates of carbamylation in patients with CKD, particularly in the cardiovascular system. Carbamylation emerged as an independent risk factor for CAC, suggesting its potential as a target for therapeutic intervention to mitigate cardiovascular risk in CKD populations.

Funding: NIDDK Support



FR-PO1110

Plasma Transcriptome Profile Associated with CKD Progression

Anvesha Srivastava,[1] Mark Maienschein-Cline,[3] Richard L. Amdur,[2] Ana Pabalan,[1] Vaishali I. Parekh,[1] Dominic S. Raj.[1] *[1]The George Washington University, Washington, DC; [2]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY; [3]University of Illinois System, Urbana, IL.*

Background: Understanding the molecular signals associated with the progression of kidney disease is vital for risk stratification and targeted treatment. Advances in RNA-sequencing technology has enabled us to translate extracellular transcriptome profiles to precision diagnostics.

Methods: We evaluated the plasma mRNA profile of participants exhibiting slow (n=119) and fast (n=119) decline in estimated glomerular filtration rate (eGFR) among the Chronic Renal Insufficiency Cohort (CRIC) in a nested case control study. The two groups were matched for age, sex, race, baseline eGFR, proteinuria and diabetes status. The next generation sequencing data was analyzed edgeR to identify differentially expressed genes (DEGs) and associated pathways. We also compared the top plasma DEGs with gene expression in microdissected human CKD kidney.

Results: We identified fragments from ~28,000 annotated genes, of which 783 transcripts exhibited differential expression between slow and fast CKD progressors. Among 629 protein coding genes, 469 were overexpressed in slow progressors, while 157 showed increased expression in fast progressors. Expression of GLI2, CUX1, NOTCH1 and LRP1 transcripts were amplified in slow progressors. Pathway analysis linked these differentially expressed genes to WNT/β-catenin signaling, IL-12 signaling and production in macrophages, Netrin-1 Signaling and Epithelial-Mesenchymal Transition pathways. Many of the plasma differentially expressed genes were also upregulated in human CKD kidney. A risk score containing transcripts GABA, NEUROG and SHISAL2B was able to predict fast progressors (ROC 0.85 [95% CI= 0.75-0.95]).

Conclusions: Warranting further validation, circulating levels of aberrantly expressed transcripts hold potential to be used as biomarkers for fast CKD progression.

Funding: NIDDK Support

FR-PO1111

Impact of Bariatric Surgery on Kidney Function: A Prospective Analysis of Short-Term Outcomes

Rolando Claure-Del Granado,[1,2] Verónica N. Carlos-Rodríguez,[1,2] Sergio O. Aparicio-Yuja.[1,3] *[1]Universidad Mayor de San Simon, Cochabamba, Bolivia, Plurinational State of; [2]Department of Medicine, Clinica "Los Olivos", Cochabamba, Bolivia, Plurinational State of; [3]Department of Surgery, Clínica Los Olivos, Cochabamba, Bolivia, Plurinational State of.*

Background: Obesity and diabetes mellitus are leading causes of chronic kidney disease. Patients with obesity are more likely to develop chronic kidney disease and end-stage kidney failure. In the long-term, individuals with a body mass index (BMI) greater than 30 kg/m^2 have a significant higher risk of glomerular filtration rate decline. This study investigated the effects of bariatric surgery on estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (ACR) in morbidly obese patients.

Methods: Clinical variables for patients who underwent bariatric surgery were prospectively analyzed over a 12-month follow-up period between January 15, 2021, and August 14, 2023. eGFR (ml/min/1.73m^2) was calculated using the serum creatinine CKD-EPI formula. Urinary ACR was measured during the follow-up. Body mass index (BMI, kg/m^2), percent weight loss (%WL), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded during the follow-up.

Results: Eighty-two patients were included, 48,8% (n=40) underwent bariatric surgery-laparoscopic Roux-en-Y gastric bypass (LRYGB), 39% (n=32) underwent laparoscopic sleeve gastrectomy (LSG; n = 39) and 12,2% (n=10) underwent intestinal bipartition. Baseline characteristics and follow-up parameters are presented in Table 1. The eGFR of both groups increased at the follow-up outpatient visits (months 1, 3 and 12) ($p < 0.001$) as shown in Table 1. The ACR decreased in the first month and twelve months after the bariatric surgery ($p < 0.0001$). The SBP and DBP decreased after bariatric surgery, with no significant difference between the three groups ($p > 0.05$).

Conclusions: Bariatric surgery is associated with improvements in postoperative renal function 1, 3 and 12 months following surgery, with significant reductions in ACR and better blood pressure control.

	Baseline values	1 month	3 months	6 months	12 months
Systolic Blood Pressure (mmHg)	126.5±12.1	119.2±12.1 (p<0.0001)	115.3±7.9 (p<0.0001)		113.6±10.5 (p<0.0001)
Diastolic Blood Pressure (mmHg)	79.6±5.9	74.2±6.3 (p<0.0001)	72.5±6 (p<0.0001)		72.4±6.2 (p<0.0001)
Glucose levels (mg/dL)	96.6±25.8	85.6±11.8 (p<0.0001)	85.1±11.8 (p<0.0001)		81.3±17.4 (p<0.0001)
HbA1c (%)	5.88±1.3			5.03±0.35 (p=0.001)	5.27±0.6 (p<0.0001)
Serum Creatinine (mg/dL)	0.98±0.16	0.94±0.153 (p<0.0001)	0.94±0.284 (p<0.0001)		0.92±0.158 (p<0.0001)
eGFR (ml/m/1.73 m²)	96.8±16.5	97.5±14.5 (p<0.0001)	92.7±20.1 (p<0.0001)		93.8±16.8 (p<0.0001)
Total Cholesterol (mg/dL)	206±50.8			164.3±30.3 (p<0.0001)	170.7±27.5 (p<0.0001)
LDL (mg/dL)	124.5±42			83±32.1 (p<0.0001)	91.7±22.4 (p<0.0001)
HDL (mg/dL)	50.9±10.1			52.6±8.4 (p<0.0001)	51.1±8.1 (p<0.0001)
VLDL (mg/dL)	29.9±12.6			36±20.4 (p<0.001)	20±7.4 (p<0.0001)
Triglycerides (mg/dL)	139.6±76.9			116.2±43.3 (p<0.0001)	99.4±36.3 (p<0.0001)

Table 1. Improvement in different parameters, blood pressure values, and eGFR after bariatric surgery

FR-PO1112

Overweight/Obesity and Pulse Pressure: Kidney Prognosis in Young and Elderly Patients with ADPKD Regarding Attribute-Based Medicine (ABM) Insights

Hiroshi Kataoka, Toshio Mochizuki, Shun Manabe, Yusuke Ushio, Momoko Seki, Ken Tsuchiya, Kosaku Nitta, Junichi Hoshino. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Background: How aging impacts renal prognosis in autosomal dominant polycystic kidney disease (ADPKD) has yet to be fully undertaken. We sought to explore these distinctions in kidney disease progression among young and elderly ADPKD patients, focusing on the influence of overweight/obesity and pulse pressure, related markers of arteriosclerosis.

Methods: We enrolled 553 ADPKD patients who were not undergoing renal replacement therapy, with a median age of 43 years, an estimated glomerular filtration rate of 55.9 mL/min/1.73 m^2, and a total kidney volume of 1335.4 mL. The renal outcome, defined as a 30% reduction in estimated glomerular filtration rate or initiation of renal replacement therapy, was assessed using Cox regression analysis.

Results: The study followed 236 patients over a median period of 9.1 years to assess renal outcomes. Multivariable Cox analyses identified several significant risk factors for kidney disease progression: female sex (HR=1.82), age (HR=0.76 per 10-year increase), eGFR (HR=0.58 per 10 mL/min/1.73 m^2 increase), urinary protein excretion (HR=1.72), and total kidney volume (HR=1.03 per 100 mL increase). Notably, interactions were observed between age (≥50 years) and urinary protein excretion (P=0.0050), higher pulse pressure (≥50 mmHg) (P=0.0386), and overweight (BMI ≥25 kg/m^2)(P=0.0414). Subgroup analysis revealed that total kidney volume (HR=1.03 per 100 mL increase) and overweight/obesity (HR=2.01) were risk factors in patients under 50, while urinary protein (HR=2.55) and pulse pressure ≥50 mmHg (HR=1.74) were significant in patients over 50.

Conclusions: Poor renal prognosis was associated with increased total kidney volume and obesity in younger patients, but increased protein in the urine and increased pulse pressure in older patients. In recent years, treatments and research that are tailored to patient attributes have been proposed, but in the case of ADPKD patients, it is necessary to change treatment policies depending on age attributes.

Funding: Government Support - Non-U.S.

FR-PO1113

Long-Term Dynamic Effect of Body Mass Index on Adverse Cardiovascular Outcomes with the Targeted Maximum Likelihood Estimation Method: Results from the KNOW-CKD Study

Yun Jung Oh,[1] Kook-Hwan Oh,[2] Wookyung Chung,[3] Ji Yong Jung.[3] *[1]H Plus Yangji Hospital, Seoul, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Gachon University Gil Medical Center, Incheon, Republic of Korea.*

Background: Unlike the general population, the obesity paradox, referring to the association of high body mass index (BMI) with better survival, has been observed in patients with chronic kidney disease (CKD). However, the impact of long-term BMI changes in CKD patients on the risk of cardiovascular outcomes considering time varying exposure and confounding, has been rarely studied.

Methods: A total of 1,061 patients enrolled as part of The Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) were analyzed at 3 observational points (baseline, 3-year; early, and 7-year; late) at which BMI was measured. We used longitudinal targeted minimum loss-based estimation (TMLE) and marginal structural models (MSM) to estimate the cumulative incidence of cardiovascular events (CVEs) of dynamic exposure to high BMI (≥23kg/m^2) comparing counterfactuals (BMI <23kg/m^2) adjusted for time varying confounding (systolic blood pressure, estimated glomerular filtration rate) and baseline covariates (age, sex, smoking, diabetes, cardiovascular disease, and proteinuria).

Results: Patients with sustained high BMI throughout 7-year follow-up had significantly reduced risk of CVEs than those with counterfactuals (relative risk [RR], 0.279; 95% confidence interval, 0.143-0.546; P < 0.001). However, the RR were 0.319 (0.001-136.9; P = 0.712) and 0.988 (0.296-3.298; P = 0.985) for early and late change to high BMI comparing sustained low BMI, respectively. In MSM, hazard ratio (HR) of accumulative high BMI frequency were 0.925 (0.663-2.189; P = 0.645) up to 3 years and 0.562 (0.406-0.779; P = 0.001) up to 7 years, respectively.

Conclusions: In CKD patients, higher BMI is associated with better cardiovascular outcome, and the protective effect is observed only in patients who retained high BMI consistently over long-term period.

Funding: Government Support - Non-U.S.

FR-PO1114

Muscle Density Changes in CKD and Clinical Outcomes

Sarah J. Schrauben,[1] Babette Zemel,[3] Jin Long,[4] Francis P. Wilson,[2] Michelle Denburg,[3] Sogol Mostoufi-Moab,[3] Joshua F. Baker.[1] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]Yale University School of Medicine, New Haven, CT; [3]The Children's Hospital of Philadelphia, Philadelphia, PA; [4]Stanford University, Stanford, CA.*

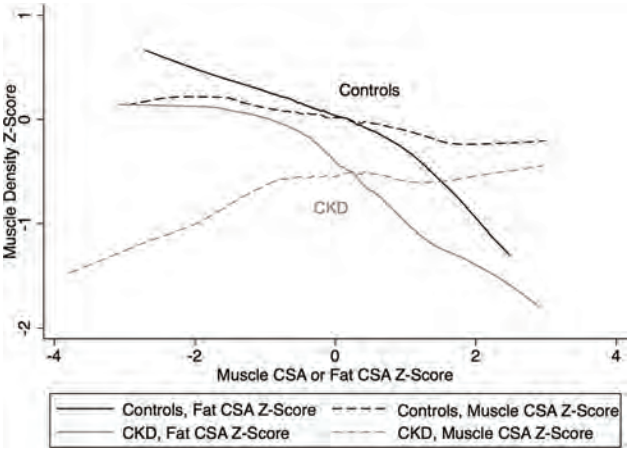
Background: Low muscle density associates with muscle impairment and poor outcomes. We measured muscle density annually over 2 years in CKD participants, compared with controls to determine predictors of muscle density decline, and associations with cardiovascular disease (CVD) and death.

Methods: Adults with CKD were recruited as an ancillary to the CRIC Study. Healthy adults, ages 21-78 years were enrolled as controls. Muscle and fat cross-sectional area (CSA, cm^2) in the calf were obtained by peripheral quantitative CT (pQCT). pQCT muscle density (mg/cm^3) was used as a composite index of intra- and extra-myocellular fat content. pQCT measures were converted to age- and sex-specific Z-Scores based on distributions in controls. Linear regression analyses evaluated group differences and changes in muscle density over time in CKD. Cox proportional hazards models evaluated associations of muscle density with CVD and death over mean 8 years.

Results: Included were 501 controls and 277 with CKD. Muscle density was lower in CKD [β: -0.60, 95% CI: -0.75, -0.45]; difference was attenuated when adjusted for BMI. Deficits were most notable among those with sarcopenia (low muscle CSA) (**Figure**). Diabetes and low calf CSA also predicted greater muscle density 2 yr decline [diabetes β: -0.09, 95% CI: -0.18, -0.01, calf CSA Z-score ≤ -1 β -0.17, 95% CI: -0.30, -0.04]. Lower muscle density was associated with a higher risk of death and CVD, but not independently of age, race, sex, diabetes, smoking, CVD, and eGFR [HR per SD: 1.27 (0.92, 1.72); HR: 1.25 (0.97, 1.61), respectively].

Conclusions: Low muscle density was observed among CKD patients with diabetes, greater adiposity, low calf CSA, low BMI, and more advanced CKD. Greater declines in muscle density were associated with baseline diabetes and low muscle mass. These observations suggest loss of muscle density in CKD occurs in the context of metabolic obesity as well as sarcopenia.

Funding: NIDDK Support



FR-PO1115

Sex Differences in Handgrip Strength in Nondialysis-Dependent CKD

Amy S. Li, Angelina M. Dixon, Zhiying You, Jessica B. Kendrick. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Handgrip strength (HGS) is a simple, reliable measure of skeletal muscle function and a surrogate marker of protein-energy status and functional status in patients with chronic kidney disease (CKD). We assessed HGS using the NIH Toolbox grip strength test in CKD patients.

Methods: We studied 105 individuals (49.5% women) with CKD stage 3b-4 (eGFR 15-44 ml/min/1.73m^2). HGS was measured using the NIH Toolbox grip strength test, a standardized and validated test in the US population, with the Jamar Plus Digital dynamometer.

Results: The mean (SD) age and eGFR were 61 ± 12 years and 34.9 ± 9.8 mL/min/1.73m^2. When compared to the NIH Toolbox reference population, CKD participants scored, on average, below the 50th percentile on HGS in both the dominant and nondominant hand. Women scored in a significantly lower percentile than men, p<0.0001. When adjusted for age, sex, race/ethnicity, and education level, women had a higher dominant mean grip strength score than men but this was not statistically significant. There were no significant differences in HGS between participants with CKD stage 3b or 4.

Conclusions: Participants with CKD have lower HGS when compared to the general population, with women scoring in a significantly lower percentile than men. Women tended to have greater dominant grip strength compared to men, but this was not statistically significant. Further studies are needed to study sex differences in skeletal muscle function in CKD.

Funding: Other NIH Support - NHLBI

	Men Adjusted Score	Men Percentile	Women Adjusted Score	Women Percentile	p-value Adjusted Score	p-value Percentile
Grip Strength (pounds)						
Dominant hand	43.3 ± 13.9	64.2 ± 26.4	47.5 ± 9.5	28.2 ± 18.1	0.08	<0.001
Nondominant hand	43.9 ± 11.8	65.4 ± 24.6	46.1 ± 8.4	25.2 ± 17.5	0.29	<0.001
	CKD stage 3b Adjusted Score	CKD stage 3b Percentile	CKD stage 4 Adjusted Score	CKD stage 4 Percentile	p-value Adjusted Score	p-value Percentile
Grip Strength (pounds)						
Dominant hand	46.5 ± 11.3	49.4 ± 29.5	43.0 ± 13.5	42.1 ± 29.4	0.16	0.23
Nondominant hand	45.5 ± 10.4	47.7 ± 28.8	43.9 ± 10.3	42.9 ± 30.6	0.45	0.44

Mean (SD)
Adjusted score: adjusted for age, sex, race/ethnicity and education level

FR-PO1116

Unveiling the Association between Nonalcoholic Fatty Liver Disease and CKD: Insights from NHANES, 1999-2016

Yaerim Kim,[1] Jin hyuk Paek,[1] Woo Yeong Park,[1] Kyubok Jin,[1] Seungyeup Han,[1] Jung Pyo Lee.[2] *[1]Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea.*

Background: Although non-alcoholic fatty liver disease (NAFLD) increases the risk of kidney dysfunction genetically, the clinical association in different conditions has not been evaluated yet. Herein, we aimed to evaluate the association between NAFLD and chronic kidney disease (CKD) using a fatty liver index (FLI), a useful non-invasive method for assessing the status of NAFLD.

Methods: This study utilized data from the National Health and Nutrition Examination Survey (NHANES) 1999-2016. The participants were categorized into FLI quartiles, with the 1st quartile serving as the reference group. CKD was defined based on the estimated glomerular filtration rates (eGFR) <60 mL/min/1.73 m^2. To evaluate the risk of CKD, we performed multivariate logistic regression model adjusted with age, sex, ethnicity, education, alcohol consumption, smoking status, comorbidities, laboratory parameters, and total calorie intake.

Results: Among 51,688 participants, 9.4% (n=4,843) were defined with CKD. The 4th quartile of FLI significantly increased the risk of CKD with 1.81 times than 1st quartile, and it was maintained after adjustment with such variables (adjusted odds ratio [aOR] 1.35, 95% CI 1.18-1.55). In the subgroup analysis, the significance of FLI was prominent in age ≥60 (aOR 1.38, 95% CI 1.19-1.61). The impact of the highest quartile of FLI was maintained irrespective of sex. In comparing the participants according to the presence of comorbidities, the significance of 4th quartile of FLI was maintained in participants without hypertension (aOR 1.47, 95% CI 1.15-1.87), without diabetes (aOR 1.42, 95% CI 1.21-1.66), or without dyslipidemia (aOR 1.50, 95% CI 1.24-1.82).

Conclusions: NAFLD representing with higher FLI is significantly associated with the risk of incident CKD. The association between FLI and CKD was more prominent in elderly population and without comorbidities such as hypertension, diabetes, or dyslipidemia. FLI could be applied in specific populations as a good predictor of CKD.

FR-PO1117

Gout Prevalence and Management Strategies among Patients with Moderate to Advanced CKD

Deepika Laddu,[1] Dhajanae Sylvertooth,[1] Murilo H. Guedes,[1] Brian Bieber,[1] Roberto Pecoits-Filho,[1] Bradley A. Marder,[2] Brian LaMoreaux,[2] Angelo Karaboyas.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Amgen Inc, Thousand Oaks, CA.*

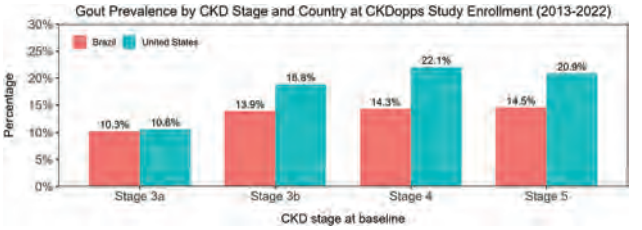
Background: Gout, a hallmark clinical manifestation of hyperuricemia-induced inflammation in joints and soft tissue, frequently coexists with chronic kidney disease (CKD), potentially exacerbating as kidney function declines. Despite its growing global burden, there is limited data on gout monitoring and treatment practices among CKD patients. This multi-country study describes the prevalence, patient characteristics, and medical management of gout in a cohort of non-dialysis patients with moderate to advanced CKD.

Methods: Cross-sectional data from 3,524 non-dialysis stage 3b-5 CKD patients enrolled in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) in Brazil (n=942) and the United States (US; n=2,582) at study enrollment (2013-2022) were analyzed. History of gout (yes/no) was extracted from medical records by study coordinators. Patient characteristics, gout treatment, and uric acid measurement practices were summarized by gout diagnosis and country.

Results: Prevalence of gout was 19% overall – 21% in the US vs. 14% in Brazil – and was higher in stage 4-5 vs. stage 3b CKD in both countries (Figure). Gout patients (versus no gout) were more likely to be male (66% vs. 49%) and have a higher prevalence of cardiovascular comorbidities, despite similar BMI levels across groups. Among gout patients, allopurinol was the most utilized gout treatment in both Brazil (75%) and the US (62%). Colchicine (13%) and Febuxostat (8%) were also used in the US, but rarely in Brazil (<5%). Mean uric acid among gout patients was 7.0 mg/dL in Brazil vs. 6.7 mg/dL in the US; however, only 30% of US gout patients had a uric acid measurement, vs. 70% in Brazil.

Conclusions: Gout affects a substantial proportion of the non-dialysis CKD population, with differing management and monitoring strategies between the US and Brazil. Further examination of the effectiveness of gout diagnosis and treatment practices between countries may provide an important opportunity to improve patient outcomes.

Funding: Commercial Support - Horizon Therapeutics plc (now Amgen, Inc.)



FR-PO1118

Incidence and Risk Factors of Gout in Nondialysis-Dependent Patients with CKD and Asymptomatic Hyperuricemia

Ilia Beberashvili, Elad Nizri, Shai Efrati. *Shamir Medical Center Assaf Harofeh, Tzrifin, Israel.*

Background: The association between asymptomatic hyperuricemia and the development of gout in chronic kidney disease (CKD) patients in stages 3-5 who are not yet on dialysis has not been fully investigated. This study aimed to assess the prevalence of gout in this population and identify risk factors for its development.

Methods: A retrospective analysis of a clinical database of ambulatory CKD patients without dialysis who had asymptomatic hyperuricemia and no prior history of gout was conducted. The study period was from 2010 to the present. Gout diagnoses confirmed during the follow-up period were based on the Rome criteria and were confirmed by the institution's rheumatology clinic.

Results: This study included 771 CKD patients in stages 3-5 without dialysis, with an average age of 72 years, of whom 44% were women. Over a median follow-up period of 47 months, 18% of the patients developed gout. Analysis using a Cox proportional hazards model with backward conditional elimination identified four independent risk factors for gout: age, diuretic use, uric acid levels, and creatinine levels. Cutoff points for continuous variables were determined based on ROC curve analysis, and then these risk factors were combined into a scoring system based on multivariate logistic regression coefficients. This system allowed for the estimation of gout risk and showed a hazard ratio (HR) of 2.25 (95% CI: 1.60-3.16) for CKD patients under 71 years of age who use diuretics regularly, have uric acid levels above 8.3 mg/dL, and creatinine levels below 1.5 mg/dL. This association remained significant even after adjustment for multiple variables, including the Charlson Comorbidity Index and BMI.

Conclusions: Gout prevalence is high among CKD patients with asymptomatic hyperuricemia. Early treatment aimed at lowering blood uric acid levels may be beneficial for high-risk populations. These findings warrant further validation through interventional studies.

FR-PO1119

Association between Alcohol Consumption and the Risk of Incident CKD in Community-Dwelling Older Adults

Ju hwan Oh,[1] In O Sun,[1] Eunjin Bae,[2] Soon hyo Kwon,[3] Byung chul Yu,[4] Jae Won Yang,[5] Won Min Hwang,[6] Yu Ah Hong.[7] *[1]Presbyterian Medical Center, Jeonju, Jeollabuk-do, Republic of Korea; [2]Gyeongsang National University Hospital, Jinju, Republic of Korea; [3]Soonchunhyang University Hospital, Yongsan-gu, Seoul, Republic of Korea; [4]Soonchunhyang University Hospital Bucheon, Bucheon, Gyeonggi-do, Republic of Korea; [5]Wonju Severance Christian Hospital, Wonju, Gangwon-do, Republic of Korea; [6]Konyang University Hospital, Daejeon, Republic of Korea; [7]The Catholic University of Korea Daejeon St Mary's Hospital, Daejeon, Republic of Korea.*

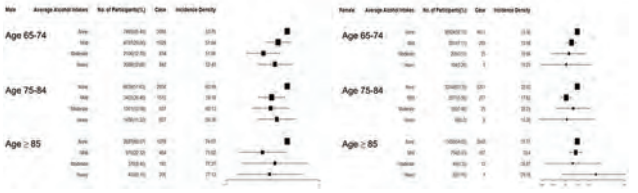
Background: The relationship between alcohol consumption and kidney function decline is not established in older adults. This study aimed to investigate the effects of alcohol consumption on the risk of incident CKD in community-dwelling older adults.

Methods: Adults aged ≥ 65 years with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2 between 2009 and 2010 were recruited and followed through 2018 from a Korean national population-based cohort. Alcohol consumption was categorised into non, mild, moderate, and heavy drinking groups based on self-administered questionnaires. New-onset CKD was defined as an eGFR <60 mL/min/1.73 m2.

Results: Of the total 122,319 subjects, the non, mild, moderate, and heavy drinking groups were 99,091 (81.0%), 14,842 (12.1%), 4,257 (3.5%), and 4,139 (3.4%). During follow-up, 19,796 (20.0%), 4,636 (31.2%), 1,696 (39.8%), and 1,695 (41.0%) developed CKD in the non, mild, moderate, and heavy drinking groups. Univariate Cox regression analyses showed a increased risk of incident CKD in older adults in all drinking groups compared to non-drinkers (all $P < 0.001$). However, hazard ratios for developing CKD were 0.90 (95% CI 0.87–0.94, $P < 0.001$) for mild, 0.89 (95% CI 0.84–0.95, $P < 0.001$) for moderate, and 0.93 (95% CI 0.88–0.99, $P = 0.027$) for heavy drinkers after fully adjusting for confounding variables. This inverse relationship between alcohol consumption and CKD risk was observed in males in all drinking groups, whereas in females it was found in mild drinkers.

Conclusions: In the subgroup analysis, the beneficial effect of alcohol consumption on incident CKD was prominent among moderate drinkers aged 65–75 years, male mild drinkers aged ≥ 75 years, and female mild drinkers aged < 85 years. This study shows that alcohol consumption is inversely associated with the risk of incident CKD in older adults. Further studies are required to elucidate the effects of alcohol on kidney damage in older adults.

Figure 2



FR-PO1120

Association of Depression and eGFR Decline in World Trade Center Responders

Farrukh M. Koraishy,[1] Sean Clouston,[1] Frank D. Mann,[1] Monika Waszczuk,[2] Benjamin J. Luft,[1] Ruqiyya Bano.[1] *[1]Stony Brook University, Stony Brook, NY; [2]Rosalind Franklin University of Medicine and Science, North Chicago, IL.*

Background: Depression is associated with kidney disease, however if this association is independent of a closely associated condition, posttraumatic disorder (PTSD), is not known. To address this question, we studied the World trade Center (WTC) Responders who have a higher incidence of depression and PTSD compared to the general population.

Methods: Serum creatinine measurements were obtained from 9313 WTC Responders from 2015 to 2022. eGFR was calculated using the CKD-EPI 2021 Equation after excluding individuals with end-stage kidney disease. CKD was defined as an eGFR measurement < 60 ml/min/1.73 m2 or by ICD codes, stratified by mild (eGFR > 45) and moderate/severe (eGFR ≤ 45). eGFR decline was characterized as normal (± 1.0 ml/min/1.73 m2 per year) or rapid (≥5 ml/min/1.73 m2 per year). Depression was defined as a score ≥ 10 on the Patient Health Questionnaire (PHQ)-9 questionnaire administered during annual WTC visits. Stepwise logistic regression (LR) was employed to test the associations.

Results: At baseline, 12% had depression and 3% had CKD. Individuals with baseline CKD had a higher baseline PHQ and were more likely to have depression at the end of their follow-up period, seen mostly in those with moderate/severe CKD. After adjustment for relevant covariates, the association between baseline moderate/severe CKD and final depression was highly significant (OR: 3.76, p = 0.001). Assessing only eGFR decline, 11% had rapid eGFR decline and 41% had normal eGFR decline. Individuals with rapid eGFR decline had a higher proportion of depression diagnosis during their follow-up period. After adjustment for relevant covariates, the association between rapid eGFR decline and depression was significant (OR: 1.37, p = 0.001). 4% developed incident CKD during the observation period. PHQ was higher in those with who developed incident CKD during follow up and PTSD was also more prevalent. Evaluating individuals with only depression and no PTSD at baseline, the association of baseline depression with incident CKD was highly significant (OR: 1.935, p = 0.009) after adjustment.

Conclusions: Moderate to severe CKD at baseline is associated with depressive symptoms, but the prospective prediction of incident CKD by depressive symptoms appears to depend on the relative absence of comorbid PTSD.

FR-PO1121

Dietary Sodium and Potassium Intake and Risk of CKD Progression, ESKD, or Death in the Million Veteran Program

Hannah Angle,[1] Andrew Guide,[2,1] Robert Greevy,[2,1] Otis D. Wilson,[2,1] Jefferson L. Triozzi,[1] Talat Alp Ikizler,[1] Andrew S. Terker,[1] Elvis A. Akwo,[1] Adriana Hung.[2,1] Million Veteran Program; KidPhenGen. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Nashville VA, Nashville, TN.*

Background: It is established that high sodium (Na) intake and low potassium (K) intake are associated with lower blood pressure and better cardiovascular outcomes. The associations between Na and K intake and chronic kidney disease (CKD) are less clear. This study assessed the relationship between reported Na and K intake and the risk of CKD progression, while accounting for genetic ancestry and other covariates.

Methods: We built a retrospective cohort (n=256,438) from the Million Veteran Program with baseline eGFR >30 ml/min who completed a nutritional survey. The primary outcome was a composite of 40% eGFR decline, ESRD, or death. Stratified Cox proportional hazard models were used to evaluate the individual associations of dietary Na and K intake with the composite outcome, stratified by genetic ancestry. A subgroup analysis by diabetes (DM) was also performed.

Results: In veterans of African (AFR) n=27,896 and European (EUR) ancestry n=219,795, higher Na intake was associated with increased risk for the primary composite (comparing highest to lowest quintile, AFR: aHR 1.06, 95% CI 1.02-1.10, EUR: aHR 1.02, 95% CI 1.00-1.04). Higher K intake was associated with lower risk (AFR: 0.93, 0.90-0.97, EUR: 0.88, 0.87-0.89). Subgroup analyses showed similar effects in patients without DM (AFR: Na aHR 1.09, 1.03-1.15, K aHR 0.89, 0.84-0.94, EUR: Na aHR 1.04, 1.02-1.06, K aHR 0.85, 0.84-0.87). However, in patients with DM the effects were strongly attenuated (AFR: Na aHR 1.01, 0.95-1.08, K aHR 1.00, 0.95-1.07, EUR: Na aHR 0.98, 0.95-1.01, K aHR 0.92, 0.90-0.95).

Conclusions: A diet low in Na and high in K is protective against CKD, though to varying degrees based on ancestry and DM status. Notably, the protective effect of K disappeared in AFR-DM patients. Future nutritional studies accounting for the impact of eGFR, genetics, and DM status are critical.

Funding: Veterans Affairs Support

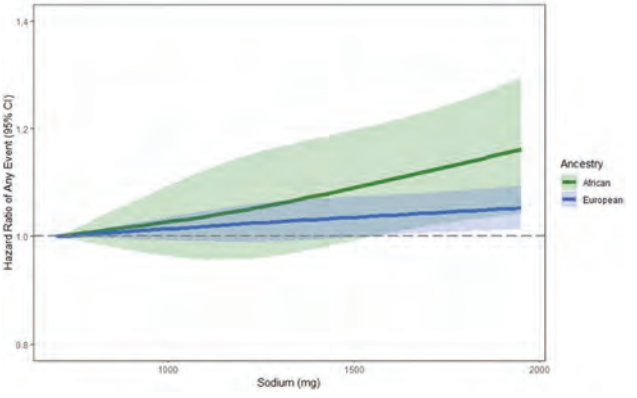


Fig 1: HR for adjusted Na for any event

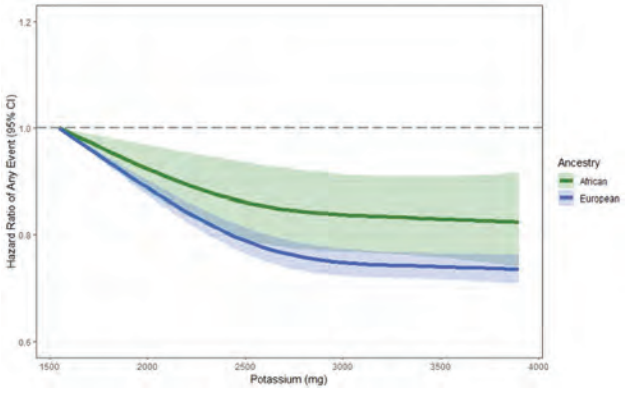


Fig 2: HR for adjusted K for any event

FR-PO1122

Impact of Weekend Catch-Up Sleep on CKD and Albuminuria in Adults: Evidence from NHANES, 2017-2020

Seung hyun Han,[1] Ara Ko,[2] Jeonghwan Lee,[1] Dong Ki Kim,[2] Yon Su Kim,[2] Chun Soo Lim,[1] Jung Pyo Lee.[1] *[1]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: How weekend catch-up sleep (WCS) influences chronic kidney disease (CKD) risk is unknown. We investigated the association between WCS and CKD prevalence in adults.

Methods: In National Health and Nutrition Examination Survey (NHANES, 2017–2020) participants (n=4,961; age≥40 years), we assessed the relationships of WCS (>1-hr increased sleep duration on weekends) with CKD and albuminuria prevalence via multivariate logistic regression analysis adjusted for potential confounders.

Results: WCS participants exhibited notably lower CKD prevalence than non-WCS participants, even after confounding variable adjustment (adjusted odds ratio [OR]=0.67; 95% confidence interval [CI]=0.45-0.99). Specifically, 1-2 hours of WCS was associated with decreased CKD (OR=0.59; 95% CI=0.38-0.91, p=0.03). Furthermore, 1-2 hours of WCS was also significantly associated with lower albuminuria (OR=0.13; 95% CI=0.06-0.30, p<0.001) prevalence among individuals sleeping <6 hours on weekdays.

Conclusions: WCS is significantly associated with lower CKD and albuminuria prevalence, particularly among adults with restricted weekday sleep. These findings suggest potential preventive effects of WCS against kidney disease. Longitudinal studies are needed to confirm these results.

FR-PO1123

Impact of Treating Metabolic Acidosis in CKD: Consideration of Time-Varying Confounding among Treatment, Kidney Function, and Acidosis through G-formula

Soie Kwon,[1] Jung Pyo Lee.[2] *[1]Chung Ang University Hospital, Seoul, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea.*

Background: The debate on whether treating metabolic acidosis decelerates CKD progression persists despite extensive research. Bicarbonate therapy mitigates metabolic acidosis, yet CKD exacerbates it, highlighting the necessity to examine these interactions comprehensively. This study employs G-formula to assess the impact of metabolic acidosis treatment in CKD, considering those intricate interactions.

Methods: A retrospective cohort study was conducted on patients whose eGFR of less than 60 was confirmed at 3-month intervals in two tertiary referral centers. Time-varying Cox analysis and G-formula were used to consider the time-varying effect of metabolic acidosis. In particular, the G-formula was adopted to account for the time-varying confounding between bicarbonate medication, serum total CO2, and creatinine level.

Results: The study included 19,627 participants over a median follow-up of 12 years. 4,127 patients advanced to ESKD and 6,273 patients died. Previous serum TCO2 levels (Coefficient 0.163, 95% CI 0.140–0.186) and bicarbonate treatment (0.898,0.897–0.899) positively influenced the following visit's serum TCO2, whereas previous serum creatinine (-0.398, -0.406– -0.391, <0.001) showed a negative correlation. Time-varying Cox analysis suggested metabolic acidosis treatment heightened risks of ESKD progression (aHR 4.28, 95% CI 3.950–4.637) and mortality (aHR 1.22, 95% CI 1.096–1.353). However, implementing the G-formula revealed treatment significantly reduced ESKD progression (aHR 0.90, 95% CI 0.874–0.927) and mortality rates (aHR 0.94, 95% CI 0.934–0.950). Determining the optimal TCO2 levels for bicarbonate administration, we found that <22 offered the most considerable risk reduction (Table 1).

Conclusions: Properly addressing the time-varying confounding among bicarbonate treatment, metabolic acidosis, and renal function suggests the potential benefit of metabolic acidosis treatment in lowering the rates of ESKD progression and mortality among CKD patients.

Table 1. Impact of metabolic acidosis treatment assessed through G-formula: sensitivity analysis based on initial TCO2 levels

Treatment	ESRD		All-cause mortality	
	Risk ratio	95% CI	Risk ratio	95% CI
Always	0.90	0.874–0.915	0.94	0.934–0.950
TCO2 <18	0.99	0.990–0.993	0.998	0.998–0.998
TCO2 <20	0.98	0.977–0.985	0.994	0.994–0.995
TCO2 <22	0.97	0.959–0.973	0.985	0.985–0.988

Time-fixed covariates: Age, Sex, Comorbidities (diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, stroke, myocardial infarction, cerebral hemorrhage, cerebral infarction), hospital, body mass index, medication usage (metformin, sulfonylurea, dipeptidyl peptidase inhibitor, sodium-glucose cotransporter2 inhibitor, insulin, meglitinide, thiazolidinedione, a-glucosidase inhibitor, angiotensin 2 receptor blockers, angiotensin-converting enzyme inhibitor, calcium channel blocker, diuretics, beta blocker, statin, ezetimibe, fenofibrate, omega-3, aspirin, clopidogrel, and direct oral anticoagulants) and laboratory findings (white blood cell count, hemoglobin, albumin, total cholesterol, glucose, aspartate aminotransferase)
Time-varying covariate: Serum total CO2 and creatinine level

FR-PO1124

Beta-Blocker Prescriptions in Nondialysis-Dependent Patients with CKD: The French CKD-REIN Study

Margaux Costes-Albrespic,[1] Sophie Liabeuf,[2] Solene M. Laville,[2] Oriane Lambert,[1] Ziad Massy,[1,3] Natalia Alencar de Pinho.[1] *[1]Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; [2]Centre Hospitalier Universitaire Amiens-Picardie, Amiens, France; [3]AURA Paris et Service de Néphrologie Hôpital Ambroise-Paré AP–HP, Boulogne-Billancourt, France.*

Background: Beta-blockers (BB) are a heterogeneous drug class often prescribed to patients with moderate to severe CKD. We aimed at describing real-world BB prescription patterns in these patients.

Methods: We analyzed 2,996 patients with CKD stages 2–5 under nephrology care from the CKD-REIN cohort study. BB prescriptions from any medical doctor were collected by clinical research associates based on anatomical therapeutic chemical (ATC) codes, as were patients' demographic, clinical, and laboratory characteristics. Adverse drug reactions occurring during follow-up were adjudicated by a team of pharmacologists.

Results: Compared with patients with no BB prescription (n=1733, 58%), patients on BB (n=1263, 42%) were older (median age 68 vs. 70 years, respectively), had a higher mean systolic BP (143 vs 140 mm Hg), lower mean heart rate (68 vs 74 bpm), and more comorbidities including diabetes (53% vs 36%), coronary disease (CD, 39% vs 14%), heart failure (HF, 21% vs 7%) and atrial fibrillation (AF, 17% vs 8%). Fourteen different BB agents were prescribed, mostly cardioselective (94%), lipophilic (78%), and non-vasodilatory (71%). Bisoprolol (572, 45.3%), nebivolol (296, 23.5%) and atenolol (179, 14.2%) were the most common agents. Bisoprolol was more often prescribed to patients with history of HF, CD or AF than to patients with no CV history (32.5% vs 56.5%). In contrast, nebivolol exhibited a different pattern, with fewer prescriptions in patients with CV history compared to those without (17.6% vs. 30%). Over the 5 years of follow-up, the rate of adverse drugs reactions attributed to BBs was 7.5 per 1000 person-years (PY), notably bradycardia (4.1 per 1000 PY).

Conclusions: In pre-dialysis CKD patients, BB seems to be well-tolerated and commonly prescribed to high risk CV patients, with a preference for prescribing bisoprolol, nebivolol and atenolol.

Funding: Commercial Support - Fresenius Medical Care and GlaxoSmithKline (GSK) since 2012 and Vifor France since 2018, Sanofi-Genzyme from 2012 to 2015, Baxter and Merck Sharp & Dohme-Chibret (MSD France) from 2012 to 2017, Amgen from 2012 to 2020, Lilly France from 2013 to 2018, Otsuka Pharmaceutical from 2015 to 2020, AstraZeneca from 2018 to 2021 and Boehringer Ingelheim France since 2022., Government Support - Non-U.S.

FR-PO1125

Lubiprostone Use and Kidney Outcomes in Patients with CKD and Constipation: A Large, Nationwide, Observational Study of US Veterans

Keiichi Sumida,[1] Yamini Mallisetty,[1] Rida N. Khan,[1] Prabin Shrestha,[1] Fridtjof Thomas,[1] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[1,3] *[1]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [2]Harbor-UCLA Medical Center Department of Internal Medicine, Torrance, CA; [3]VA Memphis Medical Center, Memphis, TN.*

Background: Lubiprostone, a chloride channel activator, has been shown to exert renoprotective effects by improving the gut microbiota in animal studies. Little is known about the association of lubiprostone use with kidney outcomes in patients with CKD.

Methods: In a nationwide cohort of 86,157 US veterans with an eGFR <60 mL/min/1.73m^2 and constipation receiving care from the VA healthcare system over 2004-2019, we examined the association of incident chronic use of lubiprostone (*de-novo* prescription with ≥30-day supply) with subsequent risk of a composite kidney outcome (incident ESKD, incident eGFR <15 mL/min/1.73m^2, or 57% reduction in eGFR), using multivariable Cox models and propensity score (PS)-overlap weighted analysis accounting for sociodemographics, comorbidities, vital signs, eGFR, and relevant medications. Untreated patients were enrolled on a randomly assigned date based on the start dates in the treated group to mitigate differential start of follow-up bias.

Results: Patients were 73±10 years old; 96% were male; 16% were African American; and 86% were diabetic. Their baseline eGFR was 49±9 mL/min/1.73m^2. Among 86,157 patients, 945 (1.1%) started lubiprostone therapy. After multivariable adjustment, incident use (vs. non-use) of lubiprostone was significantly associated with a lower risk of a composite kidney outcome (adjusted HR [95% CI], 0.66 [0.55-0.78]). A similar association was observed in the PS-overlap weighted analysis (0.71 [0.59-0.85]) (Table).

Conclusions: Incident use (vs. non-use) of lubiprostone is independently associated with a lower risk of kidney outcomes in patients with CKD and constipation.

Funding: Veterans Affairs Support

Table. Association of incident use (vs. non-use) of lubiprostone with a composite kidney outcome in patients with CKD and constipation

	Incidence rate per 1000 PY (95% CI)	HR (95% CI)	
		Multivariable adjusted (un-weighed) model	PS-overlap weighted model
No Lubiprostone Treatment	55.1 (54.2-55.9)	1 [reference]	1 [reference]
Lubiprostone Treatment	40.1 (33.2-47.1)	0.66 (0.55-0.78)	0.71 (0.59-0.85)

Note: Data were adjusted for age, sex, race, marital status, smoking status, service connectedness, mean per capita income, diabetes, hypertension, myocardial infarction, ischemic heart disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, peptic ulcer disease, rheumatic disease, chronic lung disease, liver disease, malignancy, depression, dementia, HIV/AIDS, bowel disorders (inflammatory bowel disease, irritable bowel syndrome with diarrhea), body mass index, systolic blood pressure, eGFR, and medication use (statins, calcium channel blockers, proton pump inhibitors, renin-angiotensin-aldosterone system inhibitors, thiazide diuretics, loop diuretics, potassium-sparing diuretics, phosphate binders [lanthanum, sevelamer, and calcium acetate], sodium polystyrene sulfonate, oral irons, NSAIDs, opioid analgesics, and non-lubiprostone laxatives

FR-PO1126

Safety Profile of SGLT2 Inhibitor and Glucagon-Like Peptide 1 Receptor Agonist (GLP-1 RA) Use in Patients with CKD

Iqra Nawaz, Sandeep K. Mallipattu. *Stony Brook University, Stony Brook, NY.*

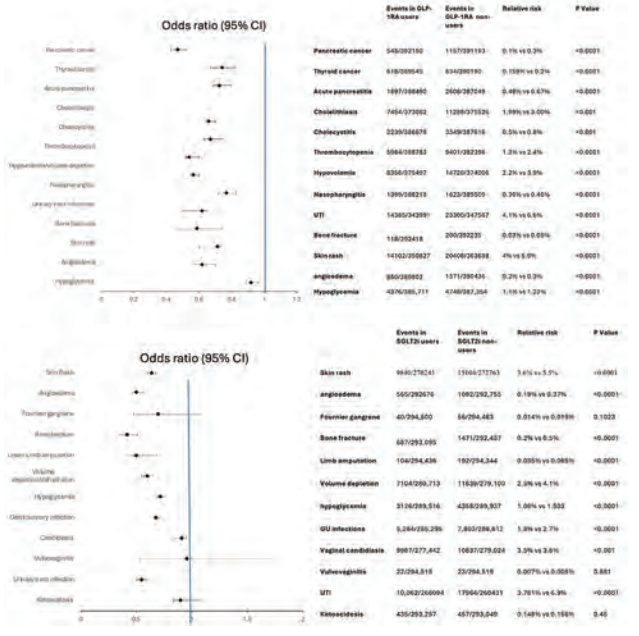
Background: The novel hypoglycemic agents SGLT2i and GLP-1RA have demonstrated combined reno and cardiovascular protective and mortality benefits. Multiple studies have extensively assessed the safety analyses and adverse events

associated with these agents among patients with diabetes and cardiovascular disease. However, there is a paucity of data on the safety analyses of these agents among patients with chronic kidney disease.

Methods: TriNetX database was used to determine patients aged ≥ 18 with CKD (eGFR 30-89) within the USA collaborative network from Jan 1st, 2015, to Dec 31st, 2023. The SGLT2i and GLP-1RA users and nonusers were propensity-scored matched on factors such as Diabetes, HTN, Heart failure, hyperlipidemia, obesity, use of Insulin, sulfonylureas, metformin, ACEi/ARBs, diuretics, and other hypoglycemic agents.

Results: Our results indicate that of 295,798 SGLT2i users and 9885755 non-users, 294567 patients were propensity-scored matched in both groups. The risk of UTI 3.7% (10062) in SGLT2i users, compared to 6.89% (17964) in non-users, genitourinary infections 1.8% (5284) vs. 2.7% (7803), Hypoglycemia 1.08% (3126) vs 1.5% (4358), bone fractures 0.23% (687) vs. 0.5% (1471), limb amputation 0.03% (104) vs 0.06% (192), ketoacidosis 0.14% (435) vs. 0.16 % (457), volume depletion 2.5% (7104) vs. 4% (11639). The risks of Vulvovaginitis are 0.007% (22) vs. 0.008% (23), vaginal candidiasis 3.6% (9978) vs. 3.8% (10837), Fournier gangrene 0.01% (40) vs. 0.019 % (56) were almost similar in both SGLT2I users and nonusers respectively. The results of adverse events comparison of GLP-1RA users with non users is shown in figure 1.

Conclusions: Overall, the results of our study demonstrate that the risks of adverse events in the SGLT2i and GLP-1RA users in patients with chronic kidney disease are relatively lower than in the nonuser groups.



FR-PO1127

Real-World Use of SGLT2 Inhibitors in Patients with CKD with and without Diabetes: A Population-Based Cohort Study

Luis Toro, Josefa Valderrama, Diego Polanco. NephroChile Initiative.
Universidad de Chile Facultad de Medicina, Santiago, Chile.

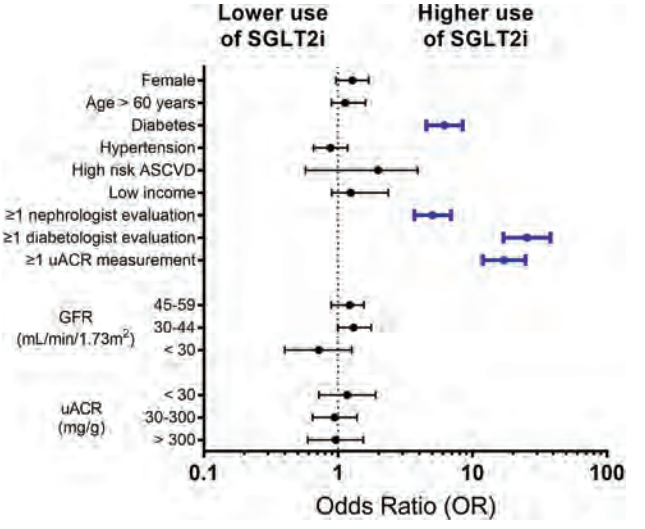
Background: Several studies have revealed cardiovascular and renal benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in chronic kidney disease (CKD). Recent studies indicate that SGLT2i are underutilized in real-world situations. This study aimed to assess the usage rates in primary care practices regarding SGLT2i use among CKD patients.

Methods: Observational study of CKD patients > 18 years (eGFR < 60 mL/min/1.73m2) in medical control in primary care facilities between January 2022 and December 2023. We included both patients with and without type 2 diabetes. We excluded patients with type 1 diabetes, polycystic kidney disease, and an initial eGFR < 20 mL/min/1.73m2. The study assessed the use of SGLT2i and analyzed variations in their usage through multivariate analysis.

Results: 1,062 patients were included in the study. Age: 61.1±8.3 years. Female: 472 (44.4%). Diabetes: 254 (23.9%). CKD G3a: 504 (47.5%), G3b: 478 (45.0%), G4: 80 (7.5%). 690 (64.9%) had at least one urine albumin-to-creatinine ratio (uACR) measurement. Only 254 (23.9%) were using SGLT2i. Predictors of SGLT2i use included the presence of diabetes (OR: 6.1 [4.5-8.4]), at least one consultation with a nephrologist (OR: 5.0 [3.6-6.9]) or diabetologist (OR: 25.4 [16.9-37.8]), and at least one uACR measurement (OR: 17.1 [11.9-24.7]), regardless of the value (Figure 1). No significant differences were found in age, socioeconomic status, healthcare system, or cardiovascular risk factors.

Conclusions: The utilization rates of SGLT2i are notably low among CKD patients. The results suggest that patients managed by physicians who are more knowledgeable about current CKD guidelines are more likely to receive SGLT2i. These findings highlight significant opportunities to improve the use of SGLT2i, particularly in primary care settings, to prevent future adverse clinical outcomes. Study supported by FONDECYT Regular 1221571.

Funding: Government Support - Non-U.S.



FR-PO1128

Budget Impact Analysis for Empagliflozin in Patients with Nondiabetic CKD

Satabdi Chatterjee,[1] Neda Al Rawashdh,[2] Pablo Anaya,[2] Anastasia Uster,[3] Anna R. Aguirre Mazo,[3] Mafalda Ramos,[4] Laetitia Gerlier,[5] Mark Lamotte.[4]
[1]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; [2]IQVIA Inc, Falls Church, VA; [3]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [4]Th(is)2Modeling, Asse, Belgium; [5]IQVIA Belgium, Zaventem, Belgium.

Background: In a wide range of patients with chronic kidney disease (CKD) with and without diabetes enrolled in EMPA-KIDNEY, empagliflozin (EMPA) on top of standard of care (SoC) showed favorable effects on kidney disease progression or cardiovascular death. Our previous research established the cost-effectiveness of adding EMPA to SoC in these patients. This study assessed the budget impact of integrating EMPA into a US commercial payer formulary, and focused on the non-diabetic patients, as they constitute majority of the CKD population.

Methods: In a hypothetical plan covering 1 million lives, data on CKD prevalence, use of angiotensin converting enzyme inhibitors [ACEis] or angiotensin receptor blockers [ARBs] in CKD, and prevalence of diabetes in CKD were used to estimate number of EMPA-eligible patients in non-diabetic CKD. The baseline market utilization was 100% for ACEi/ARB and 0% for dapagliflozin and EMPA. The projected utilization of EMPA and dapagliflozin for years 1-5 were estimated from internal sources (EMPA: 0.17% in year 1 to 19.24% in year 5; dapagliflozin: 2.60% in year 1 to 13.81% in year 5). Drug costs were based on published wholesale acquisition costs; dosing data was obtained from product prescribing information. The annual average costs of treating one patient with EMPA+SoC and comparators were derived from our previous research that included costs of drugs, complications and disease progression management costs. Model results were reported for total budget impact, per member per month (PMPM), and per patient per month (PPPM) costs for each year and cumulatively for years 1-5.

Results: Adding newer therapies such as EMPA to SoC for non-diabetic CKD yielded a net budget impact of -$155,557,417 (-1.83%), -$2.59 in PMPM and -$96.66 PPPM for a commercial payer over five years. This was driven by savings in year 3 and onwards, with $34 million reduction in year 3, $76 million reduction in year 4, and $55 million reduction in year 5, attributable to the reduced expenses for kidney replacement therapies for patients on EMPA compared to SoC alone.

Conclusions: Overall, findings suggest cost savings with adding newer therapies such as EMPA in non-diabetic CKD for commercial payers, and provide evidence on value of EMPA in this high unmet need population.

Funding: Commercial Support - Boehringer Ingelheim Pharmaceuticals

FR-PO1129

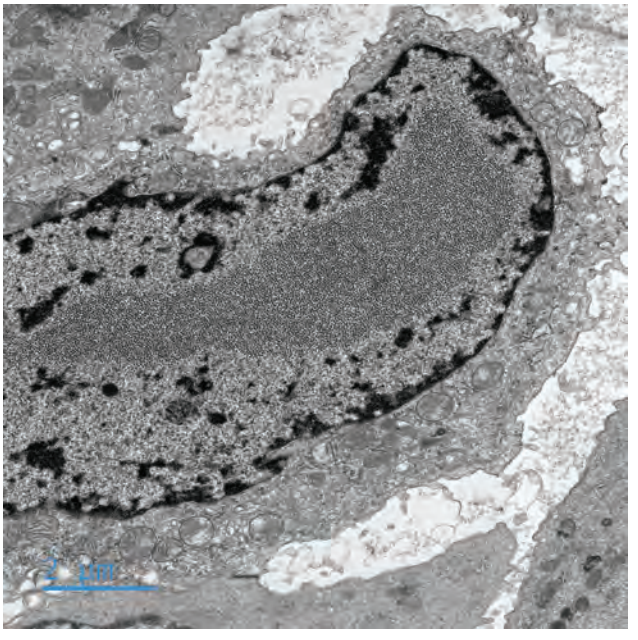
A Rare Cause of Kidney Failure: Native Kidney BK Polyomavirus Nephropathy after Lung Transplant

Taylor R. Moody, Josephine Abraham, Sydney E. Hartsell, Monica P. Revelo Penafiel, Sarah Gilligan. *University of Utah Health, Salt Lake City, UT.*

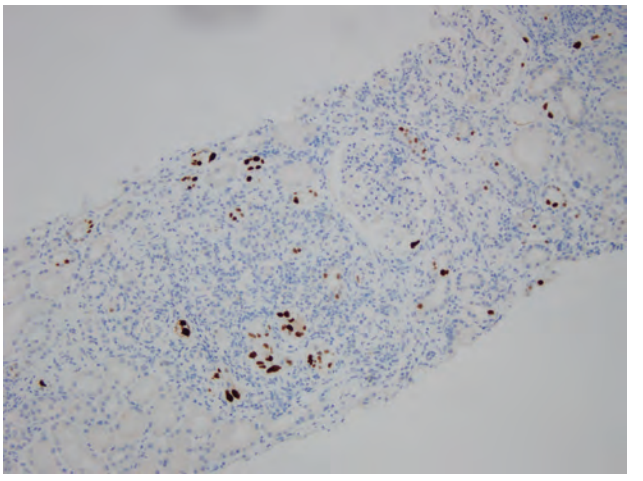
Introduction: BK polyomavirus nephropathy (BKVN) is a common complication of kidney transplantation, affecting 1-10% of renal transplant patients. It is rare in the native kidneys and is most often reported following hematopoietic stem cell transplantation. We present a case of native kidney BKVN leading to end-stage kidney disease (ESKD) in a lung transplant recipient.

Case Description: A 71-year-old woman with history of obliterative bronchiolitis who received a bilateral lung transplant in 2021 (on everolimus, mycophenolate mofetil, and prednisone) with course complicated by ischemic stroke, intermittent hypotension, and frequent urinary tract infections was referred to the renal clinic with progressive renal failure in 2023. At the time of referral her serum creatinine had risen from 1 to 2 mg/dl over 12 months. Workup was remarkable for pyuria with positive urine culture. Kidney ultrasound was without obstruction and serologies were negative. She underwent a kidney biopsy which revealed BK polyomavirus nephropathy with 40% interstitial fibrosis and tubular atrophy. Despite minimizing immunosuppression, her kidney function continued to worsen. She was started on cidofovir and, though her BK serum viral load improved, her renal function deteriorated and she developed ESKD. She is now on peritoneal dialysis undergoing evaluation for kidney transplant.

Discussion: BK nephropathy of the native kidneys in non-kidney solid organ transplant recipients is gaining recognition as an important cause of renal failure and progression to ESKD. Patients with unexplained renal failure after non-renal solid organ transplant may benefit from screening for BK virus to facilitate early diagnosis of BK polyomavirus nephropathy.



Viral inclusions within the tubuler epithelial cells.



Postive SV40 staining of tubular epithelial cells.

FR-PO1130

Insights into Mesoamerican Nephropathy: A Case Report of Environmental and Occupational Influences on CKD

Fnu Shivani,[1] Abhi Lohana,[2] Sejal Neel.[3] *[1]Ascension Saint Joseph - Chicago, Chicago, IL; [2]Camden Clark Medical Center, Parkersburg, WV; [3]Hackensack Meridian Jersey Shore University Medical Center, Neptune, NJ.*

Introduction: In the last 20 years, distinctive forms of chronic kidney disease (CKD) have emerged, unrelated to conventional risk factors like diabetes or hypertension. These diseases, termed as chronic kidney disease of undetermined cause (CKDu), are named after their geographical prevalence, such as Sri Lanka nephropathy or Mesoamerican nephropathy (MeN). Recent studies suggest a combination of environmental and occupational risk factors significantly contribute to the etiology of MeN, including high temperatures, excessive heat stress, agrochemicals, and environmental pollutants.

Case Description: A 40-year-old male from Nicaragua with a past medical history of hypertension presented to the ED with complaints of tingling and numbness in his hands and feet. On arrival, the patient's lab work was remarkable for hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia, hypomagnesemia, elevated creatinine, and BUN. Renal ultrasound showed echogenic kidneys. During the hospital stay, the patient's electrolyte derangements were corrected, but his creatinine consistently stayed around 8.5 mg/dL. The patient's urinalysis was remarkable for nephrotic range proteinuria with normal serum albumin. Extensive workups for renal failure, including autoimmune and infectious markers, were unremarkable. Eventually, a kidney biopsy was done, which showed chronic tubule-interstitial injury being more prominent than glomerular sclerosis, suggesting secondary focal segmental glomerular sclerosis (FSGS), raising suspicion of Mesoamerican nephropathy due to the patient's Nicaraguan origin.

Discussion: Mesoamerican Nephropathy (MeN) is an emerging form of chronic kidney disease prevalent among young males of low socioeconomic status and agricultural workers in hot climates, particularly in Central America. While its exact cause remains unknown, factors such as high temperatures, dehydration, excessive NSAID use, and exposure to pollutants and agrochemicals are associated with MeN development. The chronic tubule-interstitial injury observed in the patient's kidney biopsy aligns with the established understanding of MeN as a condition characterized by tubulointerstitial damage. Studies suggest dehydration-induced acute kidney injury and NSAID overuse contribute to tubulointerstitial nephritis, and disruptions in electrolyte balance worsen MeN progression.

FR-PO1131

Estimating GFR in Young Adults with Cystatin C

Lesley A. Inker. CKD-EPI. *Tufts Medical Center, Boston, MA.*

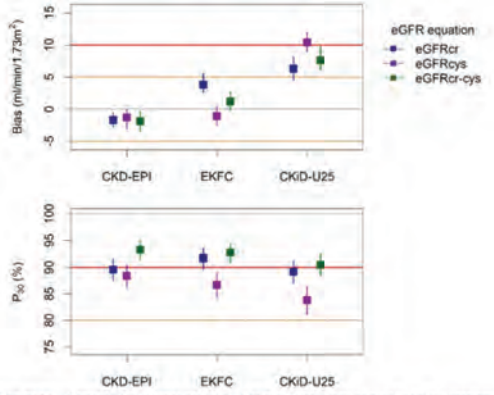
Background: Several research groups have developed eGFR equations for GFR evaluation in young adults. The use of different equations may lead to different eGFR values and uncertainty in GFR-based decision making. We previously showed that creatinine-based eGFR (eGFRcr) using the CKD-EPI 2021 had a small overestimate of measured GFR (mGFR), whereas European Kidney Function Consortium (EKFC) and Children under 25 (CKiD U25) equations had a small to moderate underestimate. We hypothesized that the differences among equation performance were related to populations differences in non-GFR determinants of serum creatinine, such as muscle mass, in the development dataset. Cystatin C is less affected by these non-GFR determinants and therefore cystatin C based eGFR (eGFRcys and eGFRcr-cys) equations may be more similar across populations.

Methods: We compared the CKD-EPI, EKFC and CKiD U25 eGFR equations in young adults (aged 18 to 40 years) in an independent dataset (751 participants from 9 studies). Equation performance compared to measured GFR was assessed as bias (median difference between mGFR and eGFR) and percentage of eGFR within 30% of mGFR (P_{30}).

Results: Mean (SD) age was 31.9 (5.8) years and mGFR was 96.1 (32.2) mL/min/1.73m². There was small bias for the CKD-EPI and EKFC eGFRcys and eGFRcr-cys equations [figure]. In contrast, CKiD-U25 eGFRcys and eGFRcr-cys equations had a moderate underestimation of mGFR. P_{30} was moderate to high for all CKD-EPI, CKiD-U25 and EKFC equations. P_{30} for eGFRcr-cys equations was higher than eGFRcr and eGFRcys for all equations.

Conclusions: Differences in performance between CKiD U25 vs. CKD-EPI and EKFC equations are observed for eGFRcys as well as eGFRcr. This suggests that population differences among the development datasets may vary by factors in addition to muscle mass. Additional research in young adults is needed to understand differences among populations and refine recommendations for use of eGFR equations.

Funding: NIDDK Support



Top panel – Grey line represents zero bias. Estimates between orange lines indicate small bias. Estimates between orange and red lines indicate medium bias. Estimates above red line indicate large bias. Bottom panel – Grey line represents 100% accuracy. P_{30} estimates below orange line indicates low accuracy. Estimates between orange and red lines indicate moderate accuracy. Estimates above red line indicate high accuracy. Equations include CKD-EPI (2021 eGFRcr & eGFRcr-cys, 2012 eGFRcys), EKFC (2021 eGFRcr, 2023 eGFRcys & eGFRcr-cys average) and CKiD U25 (2021 eGFRcr & eGFRcys, eGFRcr-cys average).

FR-PO1132

Association between Median Liver Stiffness and Proteinuria among US Adults: NHANES, 2017-2020

Kamonluk Rodsom,[1] Chutawat Kookanok,[1,2] Sansanee Thotsiri,[3] Methavee Poochanasri,[2] Narathorn Kulthamrongsri,[4] Voramol Rochanaroon,[7] Ariya Mongkolporn,[5] Tulaton Sodsri,[3] Varissara Sinkajarern,[6] Thutpharritchn Phoonakh,[6] Ekamol Tantisattamo.[1] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Phramongkutklao College of Medicine, Bangkok, Thailand; [3]Mahidol University Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand; [4]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [5]Thammasart University Faculty of Science and Technology, Khlong Nueng, Thailand; [6]Vimut Hospital, Bangkok, Thailand; [7]Rayong Hospital, Tha Pradu, Thailand.*

Background: Liver stiffness is linked to CKD and proteinuria. There is limited national-scale evidence on the impact of gender on this relationship. This study explores if gender influences the risk of proteinuria associated with liver stiffness.

Methods: A national study involving 6,525 adults, using NHANES 2017-2020, investigated the relationship between median liver stiffness and ACR. Liver stiffness was categorized into four fibrosis scores with cut-off points at 2-7, 7-11, 11-19, and ≥19 kPa. Three linear regression (LR) models were utilized, considering each gender subgroups [Table 1].

Results: Median liver stiffness was categorized into four fibrosis scores (F1 through F4) among male and female participants. For males, the majority were classified as F1, with 2,620 individuals (84.57%). This was followed by 355 individuals (11.46%) with F2, 99 individuals (3.20%) with F3, and 24 individuals (0.77%) with F4. Similarly, most females were classified as F1, with 3,019 individuals (88.15%). This was followed by 296 individuals (8.64%) with F2, 91 individuals (2.66%) with F3, and 19 individuals (0.55%) with F4. In the final adjusted LR model, the ACR increased significantly for each unit increase in median liver stiffness, by 0.76 (95% CI: 0.13-1.40) in the total group and by 1.74 (95% CI: 0.70-2.79) in female [Table 1].

Conclusions: A significant positive correlation between ACR and median liver stiffness, influenced by gender, was found among US adults. This suggests that monitoring kidney function and proteinuria, especially in women with a history of liver disease, is crucial for the early detection of kidney injury.

	Model 1		Model 2		Model 3	
	β-Coefficients(95% CI)	P-value	β-Coefficients(95% CI)	P-value	β-Coefficients(95% CI)	P-value
Total	1.48 (1.06, 1.91)	<0.001	0.99 (0.36, 1.63)	<0.002	0.76 (0.13, 1.40)	<0.018
Male	1.54 (0.97, 2.11)	<0.001	0.51 (-0.29, 1.31)	0.212	0.28 (-0.52, 1.08)	0.494
Female	1.66 (1.04, 2.29)	<0.001	1.92 (0.87, 2.96)	<0.001	1.74 (0.70, 2.79)	0.001

Fig 1: Table of correlation analysis between Median Liver Stiffness and Albumin Creatinine Ratio (ACR) using three different logistic regression models. The first model included only Median Liver Stiffness, the second model added age, race, smoking, and drinking, and the third model further included dyslipidemia, hypertension, diabetes, coronary artery disease, congestive heart failure, and stroke.

FR-PO1133

Measured GFR Implemented in a US Clinical Practice: Accuracy of eGFR Cannot Be Assumed without Measured GFR

Robert L. Jameson, Jacob Nielsen, Xin Yi, Angelina Edwards, Shane A. Bobart, Tariq Shafi. *Houston Methodist Hospital, Houston, TX.*

Background: In clinical practice, GFR estimated from serum creatinine (eGFR-CR) is often assumed to be accurate for individual patients and eGFR estimated from either serum cystatin C (eGFR-Cys) or both (eGFR-Cr-Cys) is considered the "confirmatory" test. However, without clinical availability of measured GFR (mGFR) these assumptions cannot be verified. We have implemented mGFR (4-hour plasma iohexol clearance; non-radiolabeled) as part of routine clinical care at a large urban academic medical center. The test is orderable in Epic and implemented in our outpatient infusion center. We present case studies to highlight that mGFR is essential for clinical practice and eGFR-Cys is not a universal confirmatory test for GFR.

Methods: We describe three patients that had simultaneous measurement of creatinine, cystatin C, and mGFR by 4-hour plasma iohexol clearance as part of routine clinical care. We defined eGFR to be accurate in assessing mGFR if it was within ± 5 mL/min/1.73m2 of the mGFR.

Results: See Table 1

Conclusions: Availability of mGFR in clinical practice is essential for interpretation of eGFR, when an accurate assessment is needed. Cystatin C eGFR's should not automatically considered to be an mGFR replacement.

Table 1

The clinical and laboratory characteristics of three patients with simultaneous eGFR and mGFR

Characteristic	Patient #1	Patient #2	Patient #3
mGFR indication	Relatively low eGFR in a young male with high muscle mass.	"CKD" in the setting of HIV.	"CKD 3b" in an older female
Age, years	40	45	66
Race/Ethnicity	Black	Asian	Black
Sex	Male	Male	Female
Drugs affecting creatinine secretion	None	Cobicistat (affects tubular creatinine efflux by inhibiting SLC47A1)	None
CVD	No	No	No
Diabetes	No	Yes	No
Hypertension	No	Yes	Yes
Body surface area, m²	2.24	1.61	1.99
BMI, kg/m²	31.2	22.7	31.3
Urine ACR, mg/g	<3	5	<21
Serum Creatinine, mg/dL	1.27	1.72	1.39
Serum Cystatin C, mg/L	0.81	1.1	1.29
Iohexol GFR (4 hr), mL/min/1.73m²	**74**	**77**	**59**
CKD-EPI eGFR mL/min/1.73m²			
Creatinine (Bias*)	**73 (–1)**	49 (-28)	42 (-17)
Creatinine-cystatin C (Bias*)	95 (+21)	62 (-15)	48 (-11)
Cystatin C (Bias*)	111(+37)	**73 (-1)**	50 (-9)
Teaching Points	**eGFR-Cr is accurate**	**eGFR-Cys is accurate, but eGFR-Cr-Cys is inaccurate**	**None of the eGFRs are accurate. CKD stage is incorrectly assumed as "3b"**

* Bias = eGFR – mGFR

FR-PO1134

Performance of eGFR Slope as a Surrogate End Point for Clinical Kidney Events in a Nonglomerular Mechanism of Acute eGFR Change

Alexandra Gallagher,[1,2] Rachel L. O'Connell,[2] George Mangos,[1,4] Brendan Smyth,[1,2] Anthony C. Keech,[5,2] Meg Jardine.[3,2] The FIELD Investigators.
[1]St George Hospital Department of Renal Medicine, Kogarah, NSW, Australia; [2]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [3]Concord Repatriation General Hospital, Concord, NSW, Australia; [4]University of New South Wales School of Clinical Medicine, Sydney, NSW, Australia; [5]Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia.

Background: Glomerular Filtration Rate (GFR) decline is a proposed surrogate kidney endpoint and attractive alternative to the lengthy, expensive, and large sample size requirements to reach "hard" clinical events in trials. Estimated (e)GFR decline has been successfully modelled using eGFR slope, where the correlation between total and chronic eGFR slopes and clinical endpoints was established. To date GFR slope has been tested on agents where acute GFR decline is driven by changes in glomerular haemodynamics. We tested the association of total and chronic eGFR slopes with clinical endpoints for fenofibrate, an agent with an acute eGFR decline mediated by non-glomerular actions.

Methods: The FIELD trial randomised adults to fenofibrate or placebo. Total eGFR slope was calculated using a repeated measures 2-slope linear mixed model for the entire intervention period. Sensitivity analyses were also performed limited to 3 years. Chronic eGFR slope was calculated from month 4. The clinical kidney endpoint was doubling of serum creatinine/eGFR<15ml/min/1.73m^2, renal death or kidney replacement therapy. Frequency of clinical kidney endpoints based on baseline to 8-week washout eGFR was an exploratory subgroup analysis.

Results: 9795 participants were followed for 5 years. A post-washout eGFR was ascertained in 94.3% of the washout sub-study participants. Fenofibrate was associated with a mean acute eGFR decline of -9.05 ml/min/1.73m^2/annum. Fenofibrate slowed rate of chronic eGFR decline by 0.61 ml/min/1.73m^2/annum (95% CI 0.50 to 0.71, P<0.0001), but worsened total eGFR slope (mean diff -1.54, 95% CI -1.65 to -1.44, P<0.0001). Fenofibrate use increased the clinical kidney endpoint 1 (HR 1.48, 95% CI 1.16 to 1.89, P=0.002) (Figure 1). There was no difference for clinical kidney outcomes in washout analyses.

Conclusions: Results generally support use of eGFR slope change as a surrogate for clinical kidney endpoints. Assessment post-wash out should be considered for agents with a large acute eGFR decline.

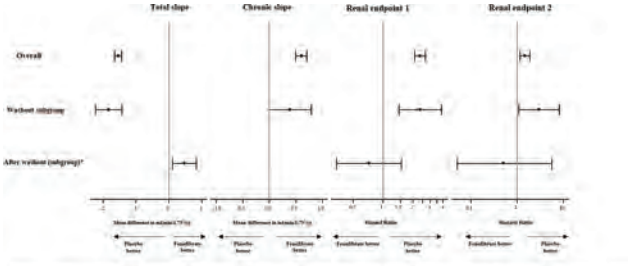


Figure 1: treatment effect on total slope, chronic slope and renal clinical endpoints, overall and in washout subgroup. Renal endpoint 1 is defined as 40% decline in eGFR, eGFR<15, or End Stage Kidney Disease (ESKD). Renal endpoint 2 is defined as doubling of serum creatinine, eGFR<15, or ESKD.
**For washout timepoint treatment effect on total slope is based on a two-sample t-test of each subject's washout-baseline difference over follow-up duration*

FR-PO1135

Assessing Kidney Function Markers and Myocardial Perfusion Imaging with Thallium-201 in Patients with CKD

Wei-Yu Su,[1,2] Yi-Ting Lin,[3,4] Ming-Yen Lin,[1] Mei-Chuan Kuo,[1,4] Yi-Wen Chiu,[1,4] Yi-chun Tsai,[1,4] Jer-Ming Chang,[1,4] Shang-Jyh Hwang,[1,4] Ping-Hsun Wu.[1,4]
[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Department of General Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [4]Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

Background: Chronic kidney disease (CKD) is a substantial public health challenge worldwide, associated with elevated morbidity and mortality rates. Myocardial perfusion imaging (MPI), a non-invasive diagnostic modality, can detect early-stage cardiovascular disease in patient with CKD. This study aimed to investigate the association between renal function and semi-quantitative parameters of Thallium-201 MPI in CKD patients.

Methods: This retrospective study included 1443 CKD patients who underwent Thallium-201 MPI between August 2008 and December 2021. The risk classification proposed by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines is based on estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (UACR). Semi-quantitative parameters were analyzed using AutoQUANT Version 6.5 software.

Results: Multivariable analysis showed that both lower eGFR and higher UACR stage were significantly associated with worse myocardial perfusion parameters, including higher summed motion scores (SMS), summed motion (SM), summed thickening scores (STS), summed thickening (ST), end-diastolic volume (EDV) and end-systolic volume (ESV), and lower left ventricular ejection fraction (LVEF). Higher CKD stage was significantly associated with increased odds of higher summed difference score (SDS), ST, and SM. Higher UACR stage was significantly associated with increased odds of higher ST. Furthermore, KDIGO category classified as very high risk was significantly associated with higher summed stress score, summed stress percentage, summed rest score, summed rest percentage, SDS, summed difference percentage (SD), stress extent of perfusion defects, stress total perfusion deficit (sTPD), resting extent of perfusion defects, resting total perfusion deficit, SMS, SM, STS, ST, EDV, ESV, lower LVEF, and increased odds of higher lung-to-heart ratio, sTPD, SDS, ST, and SM.

Conclusions: The results suggest that worse kidney function is associated with poorer myocardial perfusion and left ventricular function in participants with CKD, which can inform clinical decision-making, risk stratification, and targeted management strategies for CKD patients, ultimately aiming to improve their cardiovascular outcomes and overall prognosis.

FR-PO1136

Application of eGFR Thresholds as End Point Components in a Kidney Hierarchical Composite End Point

Niels Jongs,[1] Samvel B. Gasparyan,[2] Lars Frison,[2] Patrick Schloemer,[3] Meike Daniela Brinker,[4] Jerome A. Rossert,[5] Dustin J. Little,[5] Hiddo J. Heerspink.[1,6]
[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [2]Late Stage Development, Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [3]Pharmaceuticals, Research and Development, Bayer AG, Berlin, Germany; [4]Pharmaceuticals, Research and Development, Bayer AG, Wuppertal, Germany; [5]Late Stage Development, Cardiovascular, Renal and Metabolism (CVRM), Biopharmaceuticals R&D, AstraZeneca, Gaithersburg, MD; [6]The George Institute for Global Health, Sydney, NSW, Australia.

Background: We developed and validated a kidney hierarchical composite endpoint (HCE) combining time-to-event endpoints with the rate of estimated glomerular filtration rate (eGFR) decline (eGFR slope) as a continuous endpoint. An alternative to this continuous endpoint is to apply thresholds on an absolute scale for the pairwise comparisons in the eGFR slope component. We assessed the impact of different thresholds on the treatment effects and statistical power on the kidney HCE analysed using win odds.

Methods: We calculated the win-odds in the DAPA-CKD trial and compared treatment effects for the original HCE versus HCEs with different eGFR thresholds (0.5, 0.75, or 1.0 mL/min/1.73m^2/year eGFR slope difference; **Table**). We estimated the statistical power for these thresholds using a bootstrap sampling procedure and replicated these analyses in the RENAAL, IDNT, ALTITUDE, SONAR, CREDENCE, and FIDELIO-DKD trials.

Results: In DAPA-CKD, the win-odds and statistical power were consistent regardless of which eGFR thresholds were included (**Table**). Results were similar in all the six kidney outcome trials.

Conclusions: Our findings indicate that application of eGFR thresholds in the kidney HCE does not alter treatment effects or compromise statistical power and may facilitate clinical interpretation of trial results.

Funding: Commercial Support - AstraZeneca

Table. Pairwise comparisons per component of the HCE and win-odds

		Dapagliflozin 10 mg	Placebo		Win-odds	Power*
		Wins (%)	Wins (%)	Ties (%)	(95% CI)	%
Kidney HCE eGFR (continuous)	All-cause death	247971 (5.4)	171435 (3.7)	0		
	End-stage kidney disease	124658 (2.7)	85196 (1.8)	0		
	Sustained decline of eGFR >15	83467 (1.8)	61327 (1.3)	0		
	57% eGFR decline from baseline	62964 (1.4)	24776 (0.5)	0		
	50% eGFR decline from baseline	62138 (1.3)	26080 (0.6)	0		
	40% eGFR decline from baseline	160461 (3.5)	118693 (2.6)	0		
	eGFR slope	1975543 (42.7)	1426395 (30.8)	0		
	Total	2717202 (58.7)	1913902 (41.3)	0	1.42 (1.32, 1.52)	97.4
Kidney HCE with eGFR threshold of >0.5 mL/min	eGFR slope	1794224 (38.7)	1252131 (27.0)	355583 (7.7)		
	Total	2535883 (54.8)	1739638 (37.6)	355583 (7.7)	1.42 (1.32, 1.52)	92.4
Kidney HCE with eGFR threshold of >0.75 mL/min	eGFR slope	1702693 (36.8)	1168907 (25.2)	530338 (11.5)		
	Total	2444352 (52.8)	1656414 (35.8)	530338 (11.5)	1.41 (1.32, 1.51)	91.8
Kidney HCE with eGFR threshold of >1.0 mL/min	eGFR slope	1611160 (34.8)	1088509 (23.5)	702269 (15.2)		
	Total	2352819 (50.8)	1576016 (34.0)	702269 (15.2)	1.40 (1.31, 1.50)	92.9

*Statistical power for a simulated trial of 500 participants is shown

FR-PO1137

More Accurate eGFR Creatinine Calculation Formula for Japanese Patients Using Insulin Clearance as a Control

Ryoya Tsunoda, Shuhei Nakajima, Kentaro Nakajima, Tatsuya Shimizu, Toshiaki Usui, Hirayasu Kai, Naoki Morito, Joichi Usui, Kaori Mase, Chie Saito, Kunihiro Yamagata. *Tsukuba Daigaku Igaku Iryokei, Tsukuba, Japan.*

Background: There are several formulas to calculate estimated glomerular filtration rate (eGFR), and some formulas devised overseas have been proposed to correct for Japanese patients, but their accuracy has not been sufficiently verified, and a correction method for Japanese patients suitable for the CKD-EPI formula 2021 is unknown.

Methods: eGFR by Cr was calculated using the MDRD formula (corrected for Japanese), the Japanese formula, the CKD-EPI formula 2009 (corrected for Japanese), and the CKD-EPI formula 2021, respectively, in 404 patients whose Cr and inulin clearance were measured at our hospital between 2009 and 2018 and for whom high quality results were obtained. The correlations and errors with the inulin clearance values (C_{inu}) were compared. We also examined the performance of the correction factor for eGFR using the 2021 version of the CKD-EPI formula.

Results: The median Cinu was 62.8 mL/min and the interquartile range was 51.5. The correlation coefficients between eGFR and Cinu were 0.862 for the MDRD formula, 0.871 for the Japanese formula, 0.877 for the CKD-EPI formula 2009, and 0.875 for the CKD-EPI formula 2021, in decreasing order of root mean square of the difference between Cinu and eGFR. The root mean square of the difference between C_{inu} and eGFR was smaller than that of the CKD-EPI 2009, Japanese, MDRD, and CKD-EPI 2021, when the eGFR of the CKD-EPI 2021 was multiplied by 0.824.

Conclusions: Although the Japanese formula was the most accurate of the known Japanese eGFR calculation methods, the CKD-EPI formula 2021 with a novel correction factor may be more accurate.

FR-PO1138

Comparison of Creatinine-Based Glomerular Filtration Rate Equations for Mortality Prediction in Korean Population: A Retrospective Kangbuk Samsung Health Cohort Study

Daseul Huh, Jihyun Yang, Young Youl Hyun, Kyu-Beck Lee. *Kangbuk Samsung Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: Several creatinine-based equations have been developed for estimating glomerular filtration rate (GFR). However, their relative performance for mortality prediction in Koreans is unclear, thus the creatinine-based equations have been evolving. We aim to compare the CKD-EPI 2009 and 2021 (race-free) equations to the European Kidney Function Consortium (EKFC) equation for mortality prediction in a large Korean cohort.

Methods: We analyzed 670,320 participants who underwent a comprehensive health examination, enrolled in Kangbuk Samsung Health Cohort from January 1, 2002 to December 31, 2019 and followed them up for mortality until December 2019.

Results: The participants' median follow-up period was 8.8 years, mean age was 39.8 years old (minimum 18, maximum 97), and 53.6% were male. Mean eGFR using 2009 CKD-EPI was 95.1 ml/min/1.73m^2, 100.6 ml/min/1.73m^2 using 2021 CKD-EPI, 94.0 ml/min/1.73m^2 using EKFC. The EKFC equation had the highest discriminatory power to predict all-cause mortality (Harrell's C index of EKFC = 0.694 (95% confidence interval 0.687-00.701), 2021 CKD-EPI = 0.665 (95% CI 0.659-0.672), 2009 CKD-EPI = 0.667 (0.636-0.648), p < 0.001) and cardiovascular disease (CVD) mortality (Harrell's C index of EKFC = 0.745 (95% CI 0.728-0.762), 2021 CKD-EPI = 0.716 (95% CI 0.699-0.732), 2009 CKD-EPI = 0.716 (95% CI 0.699-0.732)).

Conclusions: In this large cohort of Koreans, the EKFC equation showed superior discrimination for predicting all-cause and CVD morality versus CKD-EPI equations. These findings support the adoption of the EKFC equation for GFR estimation and mortality risk prediction in this population.

FR-PO1139

Performance of Three Creatinine-Based Equations in Predicting All-Cause Mortality and Cardiovascular Events in a Multiethnic Asian Population: The Singapore Epidemiology of Eye Diseases Study

Zhong Hong Liew,[1] Miao li Chee,[2] Cynthia C. Lim,[1] Ching-Yu Cheng,[2] Charumathi Sabanayagam.[2] *[1]Singapore General Hospital, Singapore, Singapore; [2]Singapore Eye Research Institute, Singapore, Singapore.*

Background: The comparative prediction of novel creatinine-based equations for all-cause mortality and cardiovascular events is not well established. We aimed to compare risk prediction for all-cause mortality and cardiovascular events by estimated glomerular filtration rate (eGFR) using CKD-EPI creatinine equation 2009 (Creat-ASR 2009), CKD-EPI creatinine equation 2021 (Creat-AS 2021) and CKD-EPI creatinine-cystatin equation (Creat-cys 2021) in a multiethnic Asian population.

Methods: In this population-based cohort study, we included Chinese and Indian adults aged 40-80 years who attended baseline visit (2007-2011). Serum cystatin C was measured using particle-enhanced turbidimetric assay. Information on death and cardiovascular events was obtained by data linkage with National Registry of Diseases Office until 31 Mar 2021. Outcomes were all-cause mortality and incident cardiovascular events among those without prior cardiovascular disease. Using Cox proportional hazards model, we conducted multivariate regression analyses to evaluate association of CKD and the outcomes. Net reclassification improvement was performed to compare prediction performance of these 3 equations.

Results: During a mean follow-up of 11.3±2.2 years, all-cause mortality rate was 12.9% (743 of 5738 participants). Using Creat-ASR 2009, Creat-AS 2021, and Creat-cys 2021, mortality rates among those with CKD (eGFR < 60 ml/min/1.73 m^2) were 6.67% vs 5.04% (P <0.001) vs 6.26% (P <0.001), respectively. After excluding those with existing cardiovascular disease, incident cardiovascular event rate was 9.9% (508 of 5120 participants). Reclassification using Creat-AS 2021 compared with Creat-ASR 2009 had poorer prediction performance for all-cause mortality and cardiovascular event (Creat-AS 2021 vs Creat-ASR 2009: NRI= -0.040, p<0.001 and -0.050, p<0.001, respectively). Reclassification using Creat-cys 2021 compared with Creat-ASR 2009 allowed better prediction for all-cause mortality and cardiovascular event (Creat-cys 2021 vs Creat-ASR 2009: NRI = 0.077, p<0.001 and 0.091, p<0.001, respectively).

Conclusions: Creat-cys 2021 was associated with improved risk prediction of all-cause mortality and cardiovascular event, compared with Creat-ASR 2009 and Creat-AS 2021.

FR-PO1140

Systolic Blood Pressure Threshold and Clinical Outcomes in Patients with CKD Stage 4/5

Jiacong Luo,[1] Claire Ryan,[1] Scott Sibbel,[1] Carey Colson,[1] Gilbert Marlowe,[1] Michael H. O'Shea,[2] Francesca Tentori,[1] Steven M. Brunelli.[1] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO.*

Background: KDIGO guidelines suggest a systolic blood pressure (SBP) <120 mmHg for chronic kidney disease (CKD) patients. However, there is a paucity of published evidence directly comparing relevant health outcomes across various SBP targets. We investigated the possible impact of various SBP targets on hospitalizations, mortality, and ESKD transitions among CKD stage 4/5 patients.

Methods: We used the Optum® de-identified Integrated Clinical-Claims Dataset that links administrative claims and clinical data from providers across the continuum of care.[1] We selected patients (n=973) with a first diagnosis of CKD 4/5 following 365+ days insurance coverage, who were prescribed 1+ antihypertensive medication. We excluded patients with SBP <110 mmHg to minimize potential confounding from advanced cardiomyopathy. We used the method of recycled predictions to estimate the effect of time updated SBP aligned to guideline targets (separately for <120 and <140 mmHg) on clinical outcomes accounting for clinical confounders.

Results: SBP <140 mmHg was present during 66% of follow up time. Blood pressures in line with this threshold were not differentially associated with rates of mortality or hospitalization; they were associated with a lower rate of ESKD transition (the anticipated change in transition rate is -2.3 transitions per 100 patient years). SBP <120 mmHg was present during 14% of follow up time. Blood pressures in line with this threshold were not differentially associated with rates of mortality or ESKD transition; they were associated with a higher rate of hospitalization (the anticipated average change in admission rates is +22.4 admissions per 100 patient years).

Conclusions: A SBP target of <120 mmHg in patients with CKD is associated with a higher rate of hospitalization without demonstrable benefits. Conversely, a target of <140 mmHg may reduce ESKD transitions without worsening other outcomes. Current guidelines should be reconsidered.[1] Optum's de-identified Integrated Claims-Clinical dataset (2007-2021)

	Follow-up years	Mortality			Hospitalizations			ESKD Transitions		
		Total Deaths	Deaths per 100 patient years	Anticipated Average Change	Total Admits	Admits per 100 patient years	Anticipated Average Change	Total ESKD Transitions	Transitions per 100 patient years	Anticipated Average Change
≥140 mmHg	577	61	10.6	Ref.	298	51.7	Ref.	60	10.4	Ref.
<140 mmHg	1,154	140	12.3	1.8 (-1.7, 5.3)	600	52.9	0.3 (-6.0, 6.4)	63	5.6	-2.3 (-4.5, -0.3)
≥120 mmHg	647	73	11.3	Ref.	317	49	Ref.	60	9.3	Ref.
<120 mmHg	107	19	17.9	+6.5 (-0.42, 19.3)	82	77	+22.4 (3.2, 45.7)	7	6.6	0.1 (-10.6, 10.1)

Bold indicates statistical significance

FR-PO1141

Systolic Blood Pressure Rhythm Is a Protective Predictor of eGFR in Older Hypertensive Men

Lulu Wang, Han Tian, Lei Jiang. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China*.

Background: It is recognized that blood pressure (BP) follows a circadian rhythm, exhibits two peaks during 24 hours. But it is uncertain whether BP has 12 hours rhythm and the influence of this rhythm.

Methods: A total of 200 older hypertensive males without overt cardiovascular or cerebrovascular diseases were recruited in the longitudinal study. 12 patients had less than 20 ambulatory blood pressure readings during 24 hours. Therefore, a total of 188 patients were included in the analyses. The 12 hours circadian rhythmicity of blood pressure was analyzed by ARSER. Blood pressure with 12h rhythmicity was selected by $P < 0.05$. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. The primary outcome was the change of eGFR.

Results: The average age was 64.9±7.2 years, and the eGFR was 83.5±14.7 mL/min/ 1.73m^2. 17 patients had 12 hours rhythmicity in both Systolic blood pressure (SBP) and diastolic blood pressure (DBP). 128 patients had arrhythmicity in either SBP or DBP. At a mean follow-up period of 3 (2.5–3.7) years, 16 patients died, 33 patients were lost to follow-up. The mean eGFR in baseline and follow-up time was 86.4±14.2 and 81.7±16.1 mL/min/ 1.73m^2 (P=0.010). There was no significant difference in the level of urinary protein and creatinine ratio (7.5(3.8-19.4) vs 8.3(7.0-12.7) mg/g, P=0.059). Compared to participants in rhythmic SBP group, the other group had more eGFR decline(P=0.005). But the change of eGFR was similar between DBP rhythmicity group and arrhythmicity group. We defined eGFR decline as the falling difference over 1/2 SD between follow-up and baseline. The risk of eGFR decline in patients with arrhythmic SBP was third that of rhythmic rhythm SBP group after adjusting for confounding factors including age, smoke, alcohol, DM,BMI and albumin(HR = 3.005(1.122-8.048), P=0.029).

Conclusions: The rhythm of systolic blood pressure is a protective predictor of eGFR in older hypertensive males. We need to focus on the rhythm pattern of BP.

Funding: Government Support - Non-U.S.

FR-PO1142

Time in Target Range of Systolic Blood Pressure and All-Cause Mortality in CKD Population in Korea

Soo-Young Yoon,[1] Dae Kyu Kim,[1] Su Woong Jung,[2] Jin Sug Kim,[1] Ju young Moon,[2] Hyeon Seok Hwang,[1] Kyunghwan Jeong.[1] *[1]Kyung Hee University Hospital, Dongdaemun-gu, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea*.

Background: Time in target range (TTR) of systolic blood pressure (SBP) is the percentage of time that SBP remains within the range of 110–130 mmHg. The TTR metric can be used to express the degree of SBP control over time. The association between SBP-TTR and mortality in patients with chronic kidney disease (CKD) remains unclear, and may depend on the extent of its control. We evaluated the risk of mortality, cardiovascular events, and renal events between SBP-TTR groups in Korea.

Methods: A total of 16,037 patients with CKD who underwent health check-ups at least three times between 2012 and 2015 were recruited from the Korean National Health Insurance Database. The patients were divided into four SBP-TTR categories based on SBP-TTR levels: SBP-TTR 100%, SBP-TTR 51–75%, SBP-TTR 26–50%, and SBP-TTR 0–25%. The primary outcome was the association between SBP-TTR level and mortality by Cox-regression analysis. Secondary outcomes were cardiovascular risk and end-stage kidney disease (ESKD) progression based on SBP-TTR groups.

Results: The median eGFR in the study was 56.08 ml/min per 1.73m^2. The adjusted hazard ratios (HRs) were 1.17 (95% confidence interval [CI], 0.96–1.41), 1.21 (95% CI, 0.998–1.47), and 1.23 (95% CI, 1.02–1.49) for patients with SBP-TTR 51–75%, 26–50%, and 0–25%, respectively. The adjusted HRs for cardiovascular events increased significantly as the SBP-TTR decreased below 50%. For SBP-TTR 26-50%, the adjusted HR was 1.19 (95% CI, 1.01–1.40), and for SBP-TTR 0-25%, the adjusted HR was 1.40 (95% CI, 1.19–1.64). The adjusted HRs for ESKD progression increased gradually: 1.22 (1.01–1.47) for SBP-TTR 51–75%, 1.28 (1.05–1.56) for SBP-TTR 51–75%, and 1.80 (1.50–2.16) for SBP-TTR 0–25%.

Conclusions: Among patients with CKD, those with a low SBP-TTR showed an increased risk of mortality, cardiovascular events, and progression to ESKD.

FR-PO1143

Frequent Premature Atrial Contractions Are Associated with Increased Mortality Risk and Poor Kidney Outcomes in Patients with CKD

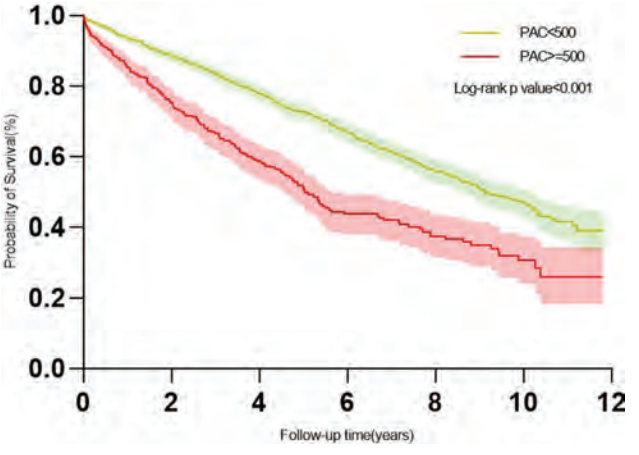
Lu Heng Lu, Ming-Yen Lin, Szu-Chia Chen, Yi-Ting Lin, Yi-chun Tsai, Mei-Chuan Kuo, Yi-Wen Chiu, Jer-Ming Chang, Shang-Jyh Hwang, Ping-Hsun Wu. *Division of Nephrology, Department of Internal Medicine, Kaohsiung, Taiwan*.

Background: Frequent premature atrial contractions (PACs) are associated with atrial fibrillation, cardiovascular events, and death in general population. However, the prognostic significance of PAC burden is not fully elucidated in patients with chronic kidney disease (CKD). This study aims to examine the association between PACs and the risks of all-cause mortality and end-stage kidney disease (ESKD) in non-dialysis CKD patients.

Methods: This retrospective study included 2303 CKD patients receiving 24-hour Holter recording from Kaohsiung Medical University Hospital Health care system between April 2009 and November 2021. Patients were categorized into two groups based on PAC burden, with frequent PACs defined as ≥500 PACs per 24 hours. Cox regression analyses, survival analysis, and subgroup analysis were performed to evaluate the impact of PACs on death and ESKD.

Results: The Kaplan-Meier curve demonstrated a ≥500 PACs group was associated with a higher death risk than < 500 PACs group. In multivariable-adjusted model, frequent PACs were associated with increased all-cause mortality (Hazard Ratio [HR] 1.48, 95% confidence interval [CI] 1.26-1.73, p <0.001) and progression to ESKD (HR 1.37, 95% CI 1.07-1.76, p=0.012). In subgroup analysis, the risk of high PAC burden was consistently higher than in low-burden group across pre-specified subgroups, especially in those with high Kidney Disease Improving Global Outcomes (KDIGO) risk categories.

Conclusions: Frequent PACs were associated with all-cause mortality and poor renal outcomes. Further studies are required to examine the implication of therapeutic strategies in CKD patients with PACs, in order to prevent potential subsequent adverse outcomes.



K-M curve of PACs and survival

FR-PO1144

Prevalence and Burden of CKD-Associated Pruritus in Europe (CENSUS-EU)

James Burton,[1] Amandine Perrin,[2] Despina Ruessmann.[2] *[1]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [2]Vifor Pharma Management AG, Glattbrugg, Switzerland.*

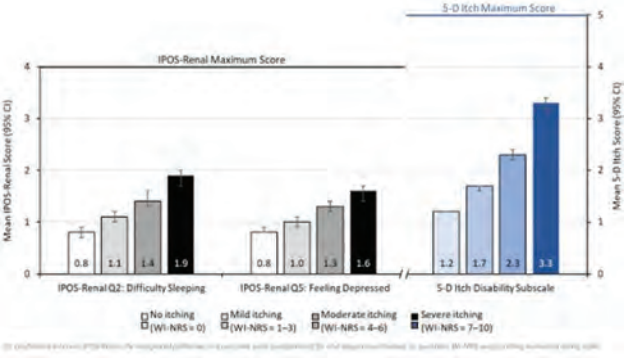
Background: Chronic kidney disease-associated pruritus (CKD-aP) is common and can impair health-related quality of life (HRQoL). Despite this, there has been a lack of clarity on its prevalence and impact.

Methods: CENSUS-EU is a real-world, cross-sectional, multicenter study in Europe, which aimed to assess the prevalence of CKD-aP and its impact on HRQoL in adult patients receiving hemodialysis. Patients completed questionnaires on pruritus presence/severity (the Worst Itching Intensity Numerical Rating Scale), and HRQoL (including the 5-D itch scale and the integrated palliative care outcome scale symptom list for end-stage renal disease). Medical records were used to gather information on dialysis, treatment, and healthcare resource use. Data were analyzed by pruritus severity (no, mild, moderate, and severe).

Results: Data were evaluated for 2,963 patients. Patients had a mean age of 66.2 years and 62.7% were male. Overall, the prevalence of CKD-aP was 53.5%; 22.3% of patients experienced mild, 18.0% moderate, and 13.2% severe pruritus. As pruritus severity increased from no pruritus to severe pruritus, patients reported more difficulty sleeping and feelings of depression. 5-D itch disability subscale scores also increased with pruritus severity (**Figure**). Patients with severe pruritus were hospitalized more often than those with mild or moderate pruritus (2.1 versus 1.8 and 2.0 times/patient/year, respectively). The proportion of patients receiving ≥1 ongoing anti-itch treatment increased with pruritus severity but remained low in all subgroups (18.3%, 25.3%, and 39.9% of patients with mild, moderate, and severe pruritus, respectively).

Conclusions: In this study, a third of patients on hemodialysis experienced moderate or severe pruritus, and HRQoL decreased with pruritus severity.

Funding: Commercial Support - CSL Vifor



FR-PO1145

Quantification of Muscle Wasting in CKD by Texture Analysis on 1H-Magnetic Resonance Images

Lisa Hur,[1] Nicole Latman,[2] Alireza Akbari,[2] Justin R. Dorie,[2] Tanya Tamasi,[2] Christopher W. McIntyre.[2,1] *[1]Western University, London, ON, Canada; [2]London Health Sciences Centre, London, ON, Canada.*

Background: Functionally significant muscle wasting is prevalent in chronic kidney disease (CKD). Currently, muscle quality assessment requires biopsy and microscopy. ^{1}H-Magnetic Resonance Imaging (MRI) is non-invasive and can be used to assess changes in skeletal muscle composition. This study aims to utilize ^{1}H-MRI to establish a quantitative metric for muscle heterogeneity, a potential biomarker of muscle quality and composition in patients with CKD, both requiring hemodialysis (HD) and earlier stages.

Methods: ^{1}H T1-weighted axial images (3 Tesla) of the calf were acquired on 43 CKD, 34 HD, and 8 with cardiorenal syndrome (CR). Gastrocnemius and soleus muscles were delineated and the heterogeneity quantification algorithm was applied. The magnitude of pixel intensity gradation between pixel-pair combinations was computed, resulting in a value, zeta, to represent the mean heterogeneity. A one-way ANOVA was performed for significance in heterogeneity between the three cohorts. Combining all participants (n=85), Pearson correlations was completed for blood markers of kidney function in relation to muscle heterogeneity.

Results: Muscle heterogeneity of HD and CR were comparable but significantly more heterogeneous relative to CKD (Figure 1). Negative correlations were seen with albumin and 1,25 Vitamin D with relation to muscle heterogeneity (Figure 2A, B). A positive association was seen with PTH with respect to muscle heterogeneity (Figure 2C).

Conclusions: Muscle heterogeneity of HD and CR may be indicative of fibrosis and wasting that is more pronounced than progressive CKD not on dialysis. Relationship between blood markers of kidney function and muscle heterogeneity suggest texture analysis to be a useful tool for non-invasive evaluation of kidney disease on skeletal muscle structure and function.

Funding: Government Support - Non-U.S.

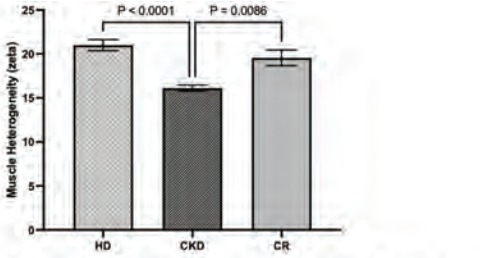


Figure 1. Mean heterogeneity in gastrocnemius and soleus muscles of T1-weighted MR images on hemodialysis (n=34), chronic kidney disease (n=43), and cardiorenal syndrome (n=8) participants. Error bars represent standard error of the mean.

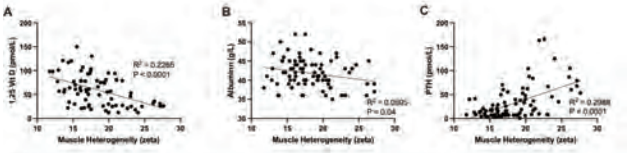


Figure 2. Relationship between muscle heterogeneity of gastrocnemius and soleus muscle as quantified by zeta and blood markers: (**A**) 1,25 Vitamin D (**B**) Albumin (**C**) PTH measured in 85 renal participants (34 hemodialysis, 43 chronic kidney disease, 8 cardiorenal syndrome).

FR-PO1146

Intramuscular Adipose Tissue (IMAT) Accumulation and Muscle Function in Patients with Moderate to Advanced Kidney Disease

Ragibe Gulsah Dilaver,[1] Mert Demirci,[2] Rachelle Crescenzi,[2] Michael Pridmore,[2] Talat Alp Ikizler,[1] Jorge Gamboa.[1] *[1]Vanderbilt University Medical Center, Department of Medicine, Nashville, TN; [2]Vanderbilt University Medical Center Department of Radiology, Nashville, TN.*

Background: Sarcopenia is common in patients undergoing maintenance hemodialysis (MHD) and is associated with poor physical function. Excessive accumulation of intramuscular adipose tissue (IMAT) is associated with poor physical function in patients with obesity, heart failure, and type 2 diabetes. We examined the extent of IMAT accumulation in MHD patients compared to individuals without kidney disease. We further investigated the factors that are associated with IMAT accumulation.

Methods: We cross-sectionally studied 49 participants (23 controls and 26 patients on MHD). IMAT accumulation in the leg muscle groups was measured using magnetic resonance imaging (MRI) by finding the widest part of the calf. Additional analyses were done for body composition, muscle function (hand grip strength), inflammatory biomarkers, and markers of mitochondrial function (mtDNA).

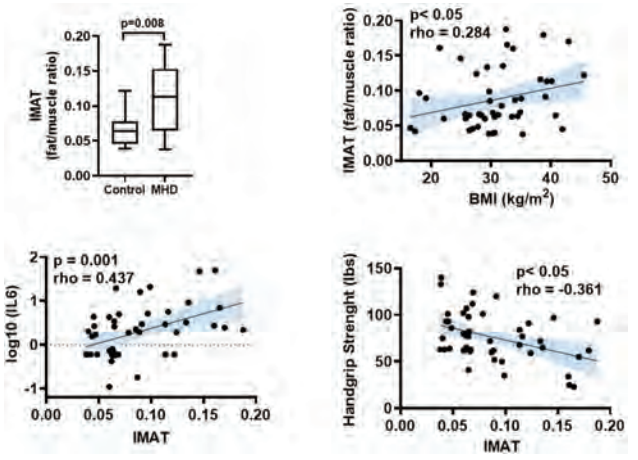
Results: The controls and patients were matched by age (52±13 versus 56±15 years), gender (%83 male versus %86), and BMI (31.9±4.9 vs 29.7±7.7 kg/m^2). IMAT accumulation was significantly higher in the MHD group compared to the controls (IMAT 0.113 (0.065 – 0.143) for MHD vs 0.063 (0.047 – 0.073) for control; p = 0.0008; **Figure 1A)**. IMAT accumulation was positively associated with BMI ($p < 0.05$, Rho = 0.284) **(Figure 1B)**, IL-6 (p = 0.001, Rho = 0.437) **(Figure 1C)**, and negatively associated with the hand grip test ($p < 0.05$, Rho = -0.361) **(Figure 1D)**.

Conclusions: Patients on MHD display a greater accumulation of IMAT compared to matched controls. IMAT accumulation could be mediated by systemic inflammatory response and might be responsible for decreased muscle function and sarcopenia in patients on MHD.

Funding: NIDDK Support, Veterans Affairs Support

Table 1.

Parameter	Total (n = 49)	Control (n = 23)	MHD (n = 26)	p-value
IL-6	1.93 (0.6 – 3.63)	0.72 (0.6 – 2.14)	2.72 (0.72 – 6.97)	p < 0.001
TNF-α	8.36 (5.17 – 17.83)	5.17 (4.19 – 6.28)	17.65 (17.65 – 20.4)	p < 0.001
hs-CRP	4.8 (1.2 – 12.3)	1.8 (0.9 – 4.45)	10.3 (4.22 – 17.12)	p < 0.001
Max Hand Grip (lbs.)	76.7±26.1	91.2±25.1	63.8±19.6	p = 0.001



FR-PO1147

Assessment of Nutritional Status in Nondialysis-Dependent Patients with CKD Using Handgrip Strength

Minsang Kim,[1] Dha Woon Im,[2] Eunjeong Kang,[1] Kook-Hwan Oh.[1] KNOW-CKD (The KoreaN Cohort Study on the Outcome of Chronic Kidney Disease Patients). *[1]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [2]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea.*

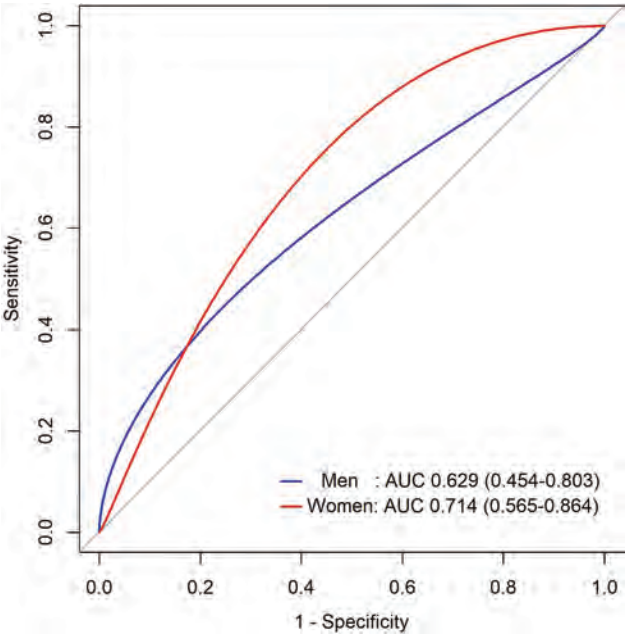
Background: Although handgrip strength (HGS) has been suggested as an indirect assessment of nutritional status in chronic kidney disease (CKD) patients, additional evidences regarding the diagnostic usefulness of HGS for malnutrition in non-dialysis-dependent CKD (NDD-CKD) are warranted.

Methods: A total of 467 patients enrolled in the Phase II KoreaN Cohort Study for Outcome in Patients With CKD who underwent nutritional assessment were included in this study. The exposure was the maximum value of HGS, which was measured twice in each hand. The outcome was a malnutrition status defined as a malnutrition-inflammation score (MIS) of 6 or higher. In this cross-sectional study, the risk of malnutrition was calculated using logistic regression analysis adjusted for age, sex, history of diabetes mellitus (DM), stage of CKD, and income and education status. Predictability of HGS for malnutrition was assessed by area under the curve (AUC) using receiver operating characteristic curve analysis.

Results: Patients with lower HGS, defined as HGS values below sex-specific median values, were older and had a higher proportion of DM. A higher HGS was significantly associated with a lower risk of malnutrition after adjustment (per 1 standard deviation increase, adjusted odds ratio, 0.51 [0.26–0.98]). I]). In the subgroup analyses stratified by age, sex, DM, and CKD stage, these clinical factors did not show significant interaction between HGS and the risk of malnutrition. The tendency of a negative association between HGS and the risk of malnutrition was consistently observed in all subgroups. Furthermore, HGS exhibited fair significance for the prediction of malnutrition in men and women (Figure 1).

Conclusions: HGS is a useful diagnostic indicator of malnutrition in NDD-CKD patients.

Funding: Government Support - Non-U.S.



FR-PO1148

Feasibility of a Home-Based, Video-Supervised 12-Week Exercise Program in Nondialysis-Dependent CKD: The ESTEEM-VIDA Pilot Randomized Clinical Trial

Gwenaelle Begue,[1] Catherine L. Welsh Osuna,[1] Jesse Gipe,[2] Chenoa R. Vargas,[2] Hiba Hamdan,[2] Tae Youn Kim,[2] Thomas Jue,[2] Jorge Gamboa,[3] Baback Roshanravan.[2] *[1]California State University Sacramento, Sacramento, CA; [2]University of California Davis, Davis, CA; [3]Vanderbilt University, Nashville, TN.*

Background: Sarcopenia is prevalent in CKD and is a central component of the frailty phenotype associated with adverse clinical outcomes. Regular exercise improves muscle function and physical capacity in CKD. There is a critical need for practical, safe, interactive, and personalized exercise program targeting improvements in physical functioning in patients living with CKD.

Methods: The ESTEEM-VIDA CKD pilot randomized clinical trial (NCT02923063) tested the feasibility of a home-based, video-supervised, and personalized exercise program in stage 3-5 non-dialysis CKD. Exercise consisted of 30-40min exercise sessions, thrice a week for 12 weeks. Session 1) high-intensity interval training (HIIT) targeted a hard effort with a rate of perceived exertion (RPE) above 14, session 2) strength training, and session 3) powerwalking both targeted a moderate effort with a RPE of 12-14. One week of video-supervised exercise alternated with one week of self-directed exercise. Each one-week video-supervised session was conducted by exercise trainers using a videoconference tool. Self-directed exercise weeks used pre-recorded exercise videos sent via email to participants. Feasibility was measured via adherence to the exercise dose as well as number of adverse effects and dropouts.

Results: Out of 22 participants randomized to exercise (EX), 21 completed the 12-weeks exercise program with 1 loss to follow-up. EX (n=21) had a mean age of 63±10.3 years (47% male, 47% diabetic) with mean eGFR of 35±12 mL/min/1.73 m^2. Adherence was 90.3% with 32 sessions (range: 14-36) completed out of 36 over 12 weeks. Only 2 (9.5%) exercisers reported less than 75% adherence. Exercisers reported average RPE of 14.3±1.3 compared to targeted RPE of above 14 for HIIT session, and RPEs of 13.9±1.8 for strength and powerwalking sessions compared to targeted RPE of 12-14. No adverse effects due to the exercise protocol were reported.

Conclusions: A 12-weeks home-based video-supervised exercise program is feasible and safe in people with moderate-severe non-dialysis CKD. Future studies should consider exercise protocol that are practical offering various exercise modality to increase participants adherence and physical functioning. **Funding:** R01DK129793, R01DK125794, DCI-4112

Funding: NIDDK Support, Private Foundation Support

FR-PO1149

Home-Based Exercise Improves Skeletal Muscle Mitochondrial Energetics in CKD: Results from the ESTEEM-VIDA Pilot Randomized Clinical Trial

Jennifer E. Norman,[1] Gwenaelle Begue,[2,1] Jesse Gipe,[1] Sarah E. Brashear,[1] Armin Ahmadi,[1] Tae Youn Kim,[1] Jorge Gamboa,[3] Baback Roshanravan.[1]
[1]University of California Davis, Davis, CA; [2]California State University Sacramento, Sacramento, CA; [3]Vanderbilt University Medical Center, Nashville, TN.

Background: Impaired muscle mitochondrial function is mechanistically linked to sarcopenia and frailty in chronic kidney disease (CKD). Loss of electrons from the electron transport chain (ETC) lead to increased reactive oxygen species (ROS) production with mitochondrial dysfunction. Exercise interventions may improve mitochondrial functioning and decrease ROS production.

Methods: ESTEEM-VIDA is a 12-week pilot randomized clinical trial (NCT02923063) of a home-based, personalized, and video-supervised exercise intervention (EX), compared to usual care (UC) in persons with stage 3-5 non-dialysis CKD. We assessed changes in *ex vivo* mitochondrial respiration rates (O_2 consumption) and ROS (H_2O_2) production of vastus lateralis muscle biopsy homogenate using high resolution respirometry (Oroboros O2k-Fluo respirometer). We used linear mixed effects models to test changes in mitochondrial respiration rates and ETC efficiency (H_2O_2 production relative to O_2 consumption) after 12 weeks and at baseline between groups and within each group.

Results: Participants randomized to EX (n=21) had a mean eGFR of 35 ± 12 mL/min/1.73m^2 and mean age of 63 ± 10.3 years, as compared to 31.3 ± 13.5 mL/min/1.73m^2 and 68.1 ± 8.7 years in those randomized to UC (n=7). There were significant ($p<0.05$) between group differences in oxidative phosphorylation (OXPHOS) respiration rates in the presence of succinate and pyruvate and after the addition of rotenone (Figure 1). After 12 weeks, the EX group exhibited significant increases in respiration rates, while ETC efficiency improved (decreased H_2O_2/O_2). No changes were seen in the usual care group.

Conclusions: Twelve weeks of home-based exercise can increase skeletal muscle mitochondrial respiration rates, while improving ETC efficiency. This supports the hypothesis that an exercise intervention improves mitochondrial health and efficiency in persons with CKD.

Funding: NIDDK Support, Private Foundation Support

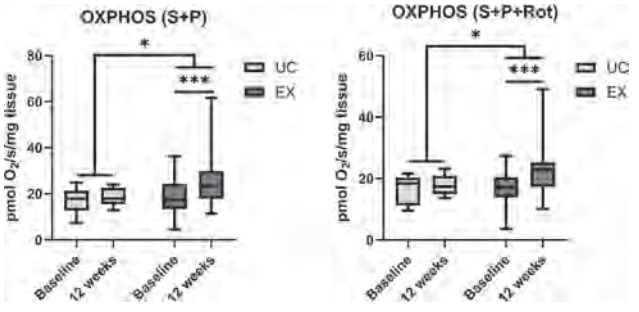


Figure 1. Selected mitochondrial respiration rates.

FR-PO1150

Home-Based Exercise Increases Mitochondrial Respiratory Rates of Quadriceps Muscle Permeabilized Fibers in CKD: Results from the ESTEEM-VIDA Pilot Randomized Clinical Trial

Jennifer E. Norman,[1] Gwenaelle Begue,[3,1] Jesse Gipe,[1] Sarah E. Brashear,[1] Armin Ahmadi,[1] Usman Rehman,[1] Tae Youn Kim,[1] Thomas Jue,[1] Jorge Gamboa,[2] Baback Roshanravan.[1] *[1]University of California Davis, Davis, CA; [2]Vanderbilt University Medical Center, Nashville, TN; [3]California State University Sacramento, Sacramento, CA.*

Background: Impaired mitochondrial function contributes to sarcopenia and frailty in chronic kidney disease (CKD). Exercise interventions may help improve skeletal muscle mitochondrial function, ameliorating sarcopenia and frailty.

Methods: ESTEEM-VIDA is a 12-week pilot randomized clinical trial (NCT02923063) of home-based, personalized, and video-supervised exercise intervention (EX), compared to usual care (UC) in persons with stage 3-5 non-dialysis CKD. We measured *ex vivo* mitochondrial respiration of vastus lateralis permeabilized muscle fibers using high resolution respirometry (Oroboros O2k-Fluo respirometer). Baseline *ex vivo* mitochondrial respiration rates were compared to baseline *in vivo* ^{31}P magnetic resonance spectroscopy (MRS) measurement of skeletal muscle oxidative capacity using Spearman correlations. We used linear mixed effects models to test changes in *ex vivo* mitochondrial respiration rates, comparing 12 week and baseline measurements within each group.

Results: Participants randomized to EX (n=21) had a mean eGFR of 35 ± 12 mL/min/1.73m^2 and mean age of 63 ± 10.3 years, compared to 31.3 ± 13.5 mL/min/1.73m^2 and 68.1 ± 8.7 years in the UC group (n=7). At baseline, maximal OXPHOS and ET capacity rates, with pyruvate, malate, glutamate, and succinate substrates, were positively correlated with MRS measurement of *in vivo* oxidative capacity (R= 0.386, p=0.047 and R=0.435, p=0.023 for maximal OXPHOS and ET capacity, respectively). Sub-saturating and saturating ADP OXPHOS rates with pyruvate and malate as substrates significantly ($p<0.05$) increased after 12 weeks in the EX group (Figure 1). No changes were seen in any of the measured rates after 12 weeks in the UC group.

Conclusions: Twelve weeks of home-based exercise increases pyruvate and malate supported OXPHOS respiration rates in persons with CKD. The mechanisms behind this increase are yet to be determined but may partially proceed through improved pyruvate dehydrogenase functionality.

Funding: NIDDK Support, Private Foundation Support

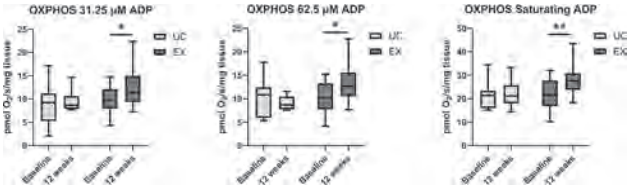


Figure 1. Pyuvate and malate supported OXPHOS.

FR-PO1151

Exercise Alters Peripheral Blood Mononuclear Cell Mitochondrial Respiratory Rates in Persons with CKD: Results from the ESTEEM-VIDA Pilot Randomized Clinical Trial

Jennifer E. Norman,[1] Armin Ahmadi,[1] Erik R. Gertz,[2] Brian J. Bennett,[2,1] Jesse Gipe,[1] Tae Youn Kim,[1] Gwenaelle Begue,[4,1] Jorge Gamboa,[3] Baback Roshanravan.[1] *[1]University of California Davis, Davis, CA; [2]USDA Agricultural Research Service, Davis, CA; [3]Vanderbilt University Medical Center, Nashville, TN; [4]California State University Sacramento, Sacramento, CA.*

Background: Impaired muscle mitochondrial function is mechanistically linked to sarcopenia and frailty in chronic kidney disease (CKD). Exercise interventions may improve mitochondrial function and preserve physical function in this population. Assessment of mitochondrial respiration in peripheral blood mononuclear cells (PBMCs) may provide insight into the effects of exercise on immunometabolism.

Methods: ESTEEM-VIDA is a 12-week pilot randomized clinical trial (NCT02923063) of a home-based, personalized, and video-supervised exercise intervention (EX), compared to usual care (UC), in persons with stage 3-5 non-dialysis CKD. We assessed changes in *ex vivo* mitochondrial respiration in intact (non-permeabilized) PBMCs. High resolution respirometry (Oroboros O2k-Fluo respirometer) was used to assess routine, leak, ATP-linked, electron transport (ET) capacity, and reserve capacity respiration rates. Linear mixed effects models were used to test changes in these mitochondrial respiration rates, comparing 12 week and baseline measurements within each group.

Results: Participants randomized to EX (n=21) had a mean eGFR of 35 ± 12 mL/min/1.73m^2 and mean age of 63 ± 10.3 years, compared to 32.3 ± 12 mL/min/1.73m^2 and 67.1 ± 8.3 years for those randomized to UC (n=9). While no changes occurred in ATP-linked respiration, significant ($p<0.05$) decreases were seen in routine, leak, ET capacity, and reserve capacity respiratory rates in the EX group after the intervention (Figure 1). No changes were observed in any of the measured respiratory rates in the UC group.

Conclusions: In persons with CKD, a home-based exercise intervention reduced all measured PBMC respiratory rates, with the exception of ATP-linked respiration. It could be hypothesized that ATP-linked respiration does not change due to cellular energy requirements being fixed. Further studies are needed to determine if the changes observed are related to improvements in oxidative stress and inflammation with exercise.

Funding: NIDDK Support, Private Foundation Support

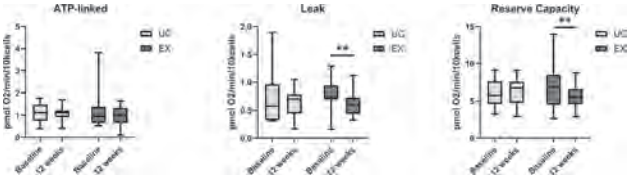


Figure 1: Selected PBMC mitochondiral respiration rates.

FR-PO1152

Skeletal Muscle Structural Adaptation to Exercise Training in CKD

Sarah E. Brashear,[1] Vishal Rao,[1,3] Anas Mohamed Sulthan,[1] Denise J. Chan,[1] Gwenaelle Begue,[2] Jorge Gamboa,[4] Baback Roshanravan,[1] Lucas R. Smith.[1] *[1]University of California Davis, Davis, CA; [2]California State University Sacramento, Sacramento, CA; [3]Charles R Drew University of Medicine and Science, Los Angeles, CA; [4]Vanderbilt University Medical Center, Nashville, TN.*

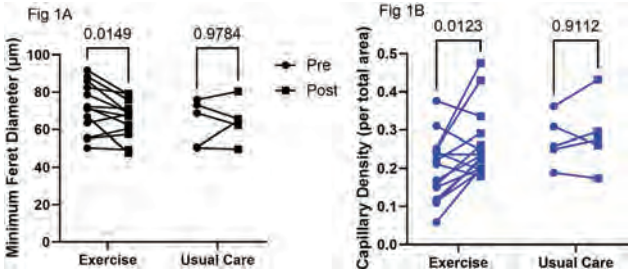
Background: Chronic kidney disease (CKD) is associated with sarcopenia leading to functional impairment. Studies suggest increased muscle fibrosis in CKD with excess extracellular matrix (ECM), particularly collagen. It is not known how exercise in patients with CKD may impact the extent of collagen cross-linking or fibrosis impairing muscle adaptations to exercise.

Methods: We conducted a pilot randomized, controlled trial of 12 weeks home-based, exercise training in CKD. We analyzed vastus lateralis muscle biopsies from patients randomized to exercise (EX, n=19) and usual care (UC, n=6). We tested for collagen content and cross-linked collagen using hydroxyproline assay. Cryosections were stained to study ECM area, satellite cells, vasculature, fibro-adipogenic progenitors (FAPs), and muscle fiber types. We stained for fiber type and vasculature analyzed using semi-automatic muscle analysis using segmentation of histology (SMASH).

Results: The EX group had an mean age of 64 (SD=9.4) years, mean eGFR of 35 (SD=11.69) ml/min/1.73m2 with 52.6% males and 47.4% diabetes compared to 68 (SD=8.85), 35 (SD=6.12), 16.6%, and 66.7% in UC. The amount of collagen and collagen cross-linking were not altered by exercise. No changes in ECM area or collagen packing density were noted with picrosirius red staining in EX vs UC. Minimum feret diameter and percentage of type I (slow twitch) fibers decreased in most patients in the EX group (Fig 1A). Type I and type IIa (fast oxidative) fiber size also significantly decreased, while there was no change in type IIx (fast glycolytic) fiber size. Capillaries (CD31+) increased with exercise in EX vs UC (Fig 1B). There was no change in satellite cells (PAX7+) or FAPs (PDGFRα+) in either the exercise or no exercise groups.

Conclusions: Muscle tissue in CKD patients responded to exercise training, shown by increased capillary density. Exercise induced muscle fiber size and type distribution changes indicate CKD being responsive to an exercise program. This supports exercise as a powerful tool to study muscle plasticity in CKD.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated grant number: DCI-4112



FR-PO1153

Bioimpedance Analysis for the Assessment of Body Composition and Relation with Muscle Strength in Patients with CKD Stage G3 to G5 and Healthy Controls

Elife Ozturk, Amber van Dulmen, Monique Mullens, Jessica Noelmans, Jeroen Kooman, Marc H. Hemmelder. *Maastricht Universitair Medisch Centrum+, Maastricht, Netherlands.*

Background: Bioimpedance analysis (BIA) is an increasingly used method to assess body composition (BC) and the prevalence of sarcopenia in patients with chronic kidney disease (CKD). BIA measurement can be performed at a whole-body level by the Body Composition Monitor (BCM). The InBody S10 Biody Water Analyzer (BWA) enables additional modelling of body segments, extremities and trunk, whereas BCM allows for assessment of overhydration as a separate compartment. This study compares BCM and BWA measurements with respect to assessment of fat free mass (FFM) and its association with handgrip strength (HGS) in patients with CKD stage G3 to G5 and in healthy controls.

Methods: This is a prospective observational study. 50 patients with CKD (23 stage G3 and 27 stage G4-5) and 30 control subjects were included. BC was assessed with the BCM and BWA. HGS was measured to assess muscle strength. BCM and BWA measurements were analyzed with Bland-Altman plots. The relation between BC and HGS in relation to renal function was assessed with multivariable analysis.

Results: FFM of the BCM was 1.4 kg higher than the BWA (95%-CI=0.016 to 2.78, p=0.047, limits of agreement -7.3 to 10.1) for the CKD group and 1.8kg lower for the controls (95%-CI=-3.25 to -0.40, p=0.014, limits of agreement -8.4 to 4.8). Body cell mass (BCMa) of the BCM was 8.1kg lower than the BWA (p=<0.001) for the CKD group and 10.6kg lower for the controls (p=<0.001). HGS was significantly correlated with FFM-BCM (for CKD: B=0.6, 95%-CI=0.4 to 0.9, β=0.59, p=<0.001 and for controls: B=0.7, 95%-CI=0.5 to 0.8, β=0.87, p=<0.001) and with FFM-BWA (for CKD: B=0.8, 95%-CI=0.5 to 1.0, β=0.65, p=<0.001 and for controls: B=0.6, 95%-CI=0.4 to 0.8, β=0.86, p=<0.001).

Conclusions: FFM estimates was significantly different between BCM and BWA for both the CKD group and the healthy controls. The large difference in BCMa might be attributed to differences in expression of BC compartments between the BCM and BWA. Both FFM and BCMa showed high individual variability. FFM assessed by both methods significantly correlated to HGS. Future studies will have to define whether device specific cut-off reference values of BIA estimates are needed to enhance its applicability in clinical care for CKD patients.

FR-PO1154

Inorganic Nitrate for Improving Vascular Endothelial Function in CKD: A Randomized, Placebo-Controlled Clinical Trial

Matthew J. Rossman,[1] Sanna Darvish,[1] Katelyn Ludwig,[1] Akpevweoghene P. Ikoba,[1] Mckinley Coppock,[1] Morgan Berryman-Maciel,[1] Kevin O. Murray,[1] Michel Chonchol,[2] Douglas R. Seals.[1] *[1]University of Colorado Boulder, Boulder, CO; [2]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Cardiovascular disease (CVD) is the leading cause of death in chronic kidney disease (CKD). A key antecedent to CVD in CKD is vascular endothelial dysfunction mediated by declines in nitric oxide (NO) bioavailability due to excess reactive oxygen species (ROS)-related oxidative stress. Here, we tested the safety and efficacy of targeting the nitrate-nitrite-NO pathway with inorganic nitrate for improving endothelial function in indviduals with mild renal dysfunction through moderate CKD.

Methods: Twenty-six older men and women with mild renal dysfunction to stage III CKD (estimated glomerular filtration rate [eGFR; CKD-EPI]: 40-89 mL/min/1.73m^2) underwent 3 months of supplementation with nitrate-rich beetroot juice (BRJ: 70 mL, 6.45 mmol nitrate/day) (n=13, 7 women; age: 65±2 yrs; eGFR: 68±2 mL/min/1.73m^2) or nitrate-depleted BRJ (placebo) (n=15, 8 women; age: 67±2 yrs; eGFR: 78±3 mL/min/1.73m^2) in a randomized, placebo-controlled, parallel-group design clinical trial. Endothelial function assessed by brachial artery flow-mediated dilation (FMD_{BA}) was the primary outcome. To determine mechanisms of action, acetylcholine-stimulated NO production (DAR-4M-AM) and ROS bioactivity (CellROX) were assessed in human aortic endothelial cells (HAECs) exposed to 10% subject serum collected before/after nitrate-rich BRJ or placebo supplementation.

Results: Nitrate-rich BRJ supplementation was safe, well-tolerated and increased FMD_{BA} by 26% (pre: 4.7±0.7%, post: 5.9±0.8%; p=0.03). FMD_{BA} did not change with placebo (pre: 4.6±0.9%, post: 4.5±0.8%; p>0.05). The improvement in FMD_{BA} with nitrate-rich BRJ was negatively associated with baseline eGFR (r=0.41, p=0.02). Diastolic blood pressure was reduced by ~2 mmHg with nitrate-rich BRJ (P<0.05), but other traditional CVD risk factors were unchanged (p>0.05). NO production was 7% higher (p=0.05) and ROS bioactivity was 25% lower (p=0.02) in HAECs exposed to serum collected after vs. before nitrate-rich BRJ; there were no changes with serum obtained pre-post placebo (P>0.05).

Conclusions: Nitrate-rich BRJ holds promise for improving endothelial function in CKD, in part by inducing changes to the circulating milieu that increase NO production and lower oxidative stress in endothelial cells.

Funding: NIDDK Support

FR-PO1155

Sex Hormones and Vascular Endothelial Function in Men and Women with CKD

Ester Oh,[1] Anna Ostrow,[1] Michel Chonchol,[1] Vienna E. Brunt,[1] Kristen L. Nowak,[1] Anna Jovanovich,[2] Jessica B. Kendrick,[1] Kerrie Moreau.[1] *[1]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [2]Bozeman Health, Bozeman, MT.*

Background: Vascular endothelial dysfunction is common in chronic kidney disease (CKD) and independently predicts cardiovascular disease events. In older healthy females and males, lower estrogen and testosterone levels contribute to endothelial dysfunction, leading to higher cardiovascular risk. However, limited studies to date have examined the association of sex hormones with endothelial function in patients with CKD. As such, this study investigated if sex hormones are associated with endothelial function in adults with CKD.

Methods: Circulating levels of total testosterone (TT), free testosterone (FT), FT/TT ratio, estrone (E1), estradiol (E2), E1/E2 ratio, and TT/E2 ratio, were measured in males (age 29-81 years) and females (23-80 years) with stage 3-4 CKD, who participated in one of three completed clinical trials (PMID: 28784657 and 37228030; and NCT02209636 [in press]). The association of each sex hormone with brachial artery flow-mediated dilation (FMD_{BA}; a gold-standard measure of conduit artery endothelial function in humans) was assessed via multivariable linear regression.

Results: A total N=187 males (46% white; mean±SD age 61±11 y; eGFR 37±11 mL/min/1.73m²) and N=104 females (49% white; 61±12 y; eGFR 34±10 mL/min/1.73m²) were included. In males, FT/TT was positively associated with FMD_{BA} in the unadjusted model (β=1.59; 95% confidence interval 0.44–2.74). However, this association was attenuated following adjustment for age (**Figure A**). In females, TT, FT, and E2 tended to be associated with lower FMD_{BA} and E1/E2 with higher FMD_{BA} after adjusting for age (**Figure B**).

Conclusions: Sex hormones were not associated with FMD_{BA} in males and females with CKD. Further mechanistic research is needed to better understand sex differences in cardiovascular risk in patients with CKD.

Funding: Private Foundation Support

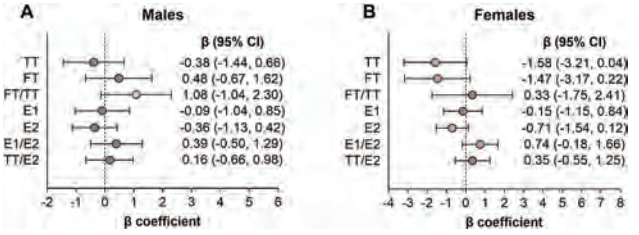


Figure. The association of sex hormones with FMD_{BA} in males **(A)** and females **(B)**, adjusted for age.

FR-PO1156

Phase 3 Clinical Candidate Rilparencel Demonstrates Weak Association with Renal Epithelial Senescence-Associated Secretory Phenotype

Mark A. Rohlfing, Ashley Greenawalt, Brooke Bauer, Andrew T. Bruce, Dominic M. Justewicz. *ProKidney LLC, Morrisville, NC.*

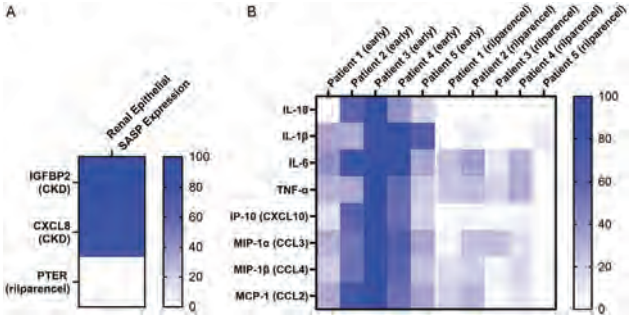
Background: CKD is associated with an enhanced senescence-associated secretory phenotype (SASP) and high inflammation, which can induce senescence. This study evaluated the renal epithelial SASP of rilparencel. Biopsy-derived rilparencel is a first-in-class autologous renal epithelial cell product in Phase 3 clinical trials for patients with T2D and CKD. Data from two Phase 2 clinical trials suggest that cortical administration of rilparencel potentially stabilizes estimated glomerular filtration rate (eGFR).

Methods: rilparencel manufactured from kidney biopsies of each of 5 patients with T2D and CKD (NCT02836574) was submitted for scRNA-seq, and 52 differentially expressed genes (DEGs) were evaluated for this study. Additionally, for each patient, proteins secreted by rilparencel were compared to proteins secreted from a manufacturing precursor to rilparencel (Intelliflex). Fifty-one secreted proteins and 52 DEGs were seeded into the SASP atlas, a proteomic analysis of renal epithelial cells 10 days post-irradiation (PMID:31945054), to determine if any are associated with a renal epithelial SASP. As comparison, IGFBP2 and CXCL8, senescence markers known to be elevated in CKD, were used as positive controls.

Results: Of the secreted proteins and DEGs associated with rilparencel, only PTER (a DEG) was identified as being secreted by renal epithelial cells according to the SASP atlas. The SASP atlas reports that PTER protein expression is approximately 2-fold less than IGFBP2 and CXCL8, which serve as positive SASP controls for comparison (A). Additionally, rilparencel secretes reduced levels of proinflammatory cytokines compared to an earlier stage in the product manufacture (B), which also suggests a reduced senescence phenotype.

Conclusions: Our proprietary manufacturing process generates a renal epithelial cell-based product (rilparencel) from renal cortex tissue with a low SASP, which may in part underlie its therapeutic activity in the clinic.

Funding: Commercial Support - ProKidney LLC



FR-PO1157

Effect of Glymphatic System Function on Cognitive Function in Patients with CKD

Changmin Heo, Yoo jin Lee, Yang Wook Kim, Bongsoo Park, Sihyung Park, Eul Jo Jeong, Jiyae Yi. *Inje University Haeundae Paik Hospital, Busan, Republic of Korea.*

Background: The aim of this study was to investigate the effects of glymphatic system function on cognitive function in patients with chronic kidney disease (CKD).

Methods: We prospectively enrolled the patients with CKD and healthy controls. We divided the patients with CKD into two groups according to their cognitive function. All of them underwent brain magnetic resonance imaging, which included diffusion tensor imaging (DTI). We calculated the diffusion tensor image analysis along the perivascular space index (DTI-ALPS index) based on the DTI which was the marker for glymphatic system function (Fig1). We compared the DTI-ALPS index between the groups.

Results: DTI-ALPS index in patients with CKD was lower than that in healthy controls (1.436 vs. 1.632, p<0.001). In addition, there were significant differences of the DTI-ALPS index between CKD patients with and without CI. DTI-ALPS index in CKD patients with CI was lower than that in those without CI (1.338 vs. 1.494, p=0.031, Fig 2). Furthermore, DTI-ALPS index was negatively correlated with age (r=-0.326, p=0.014) in the patients with CKD.

Conclusions: This study observed that the DTI-ALPS index was lower in patients with CKD, suggesting glymphatic system dysfunction in patients with CKD. Moreover, within the CKD patient group, those with CI had lower DTI-ALPS index compared to those without CI, indicating a potential link between glymphatic system dysfunction and CI. These findings suggest that glymphatic system dysfunction may contribute to CI in patients with CKD.

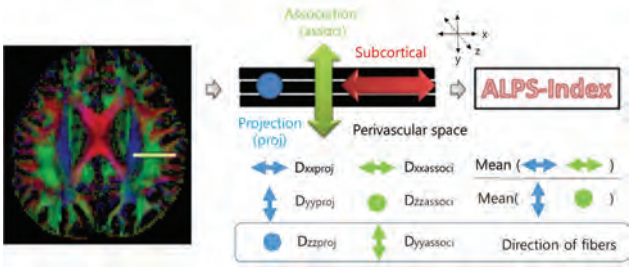


Figure 1. Calculation of the DTI-ALPS index

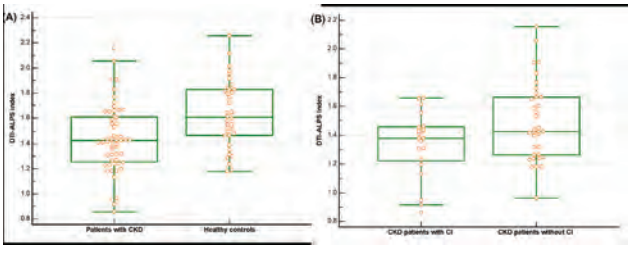


Figure 2. Differences of the DTI-ALPS index between the groups

FR-PO1158

Association between Serum β2-Microglobulin and Executive Function in Patients with Nondialysis-Dependent CKD: The VCOHP Study

Kazuhiko Tsuruya,[1] Hisako Yoshida.[2] [1]*Nara Kenritsu Ika Daigaku, Kashihara, Japan;* [2]*Osaka Koritsu Daigaku, Osaka, Japan.*

Background: Previously, we investigated the association between grey matter (GM) volume ratio (GMR) on brain MRI and the executive function assessed by trail making test (TMT) in 95 patients with non-dialysis chronic kidney disease (ND-CKD). We reported a significant negative correlation between GMR and TMT scores (Tsuruya K, et al. PLoS One 2015;10(12):e0143706). β2-microglobulin (BMG) is a low molecular weight protein composed of 99 amino acids, with a molecular weight of 11,800 and no sugar chains. As the glomerular filtration rate (GFR) decreases, serum BMG levels rise because it is no longer excreted into the urine, thus elevating in cases of kidney dysfunction. Cognitive impairment (CI) and brain atrophy have been reported to progress with declining of GFR. Since BMG levels increase as GFR declines, a possible association between BMG levels and CI has been considered; however, it has not been fully elucidated to date. Therefore, we examined this association in patients with ND-CKD.

Methods: We conducted a cross-sectional study with 95 ND-CKD patients who had no overt CI or history of stroke. The subjects underwent brain MRI scans and completed

TMT part A (TMT-A) and part B (TMT-B). The segmentation algorithm from Statistical Parametric Mapping 8 software was applied to each T1-weighted MRI scan to extract tissue maps corresponding to GM, white matter (WM), and cerebrospinal fluid (CSF). To normalize for head size variability, GMR was calculated as the ratio of GM volume to the total intracranial volume, which is the sum of GM, WM, and CSF volumes.

Results: A linear regression analysis demonstrated significant associations between serum BMG levels and the scores of TMT-A, TMT-B, and ΔTMT (TMT-B – TMT-A) in the univariable analysis. These associations remained robust even after adjusting for confounding factors, including age, sex, body mass index, original kidney disease, history of cardiovascular disease, smoking habits, systolic blood pressure, hemoglobin level, serum levels of albumin, low-density lipoprotein cholesterol, and C-reactive protein, urinary protein-to-creatinine ratio, estimated GFR (eGFR), and GMR.

Conclusions: BMG is an independent factor associated with CI (executive dysfunction) independent of kidney dysfunction and brain atrophy.

FR-PO1159

Kidney Impairment Exacerbates Periventricular White Matter Hyperintensities in Patients with CKD

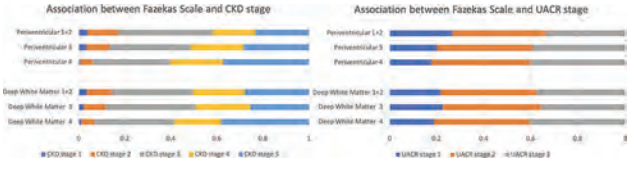
Feng-Ching Shen,[1] Yi-Ting Lin,[3,2] Ming-Yen Lin,[1] Mei-Chuan Kuo,[1,2] Yi-Wen Chiu,[1,2] Jer-Ming Chang,[1,2] Shang-Jyh Hwang,[1,2] Ping-Hsun Wu.[1,2] *[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.*

Background: Cognitive impairment is commonly observed in patients with chronic kidney disease (CKD) and tends to worsen as estimated glomerular filtration rate (eGFR) declines and albuminuria increases. Brain magnetic resonance imaging (MRI) scans are valuable in detecting structural brain lesions. Cerebral white matter hyperintensities (WMHs), indicating small vessel diseases, are associated with cognitive decline. The Fazekas scale quantifies WMHs and highlights parenchymal changes in brain MRI. This study investigated the association between kidney function status (eGFR and albuminuria) and WMHs in CKD.

Methods: A cross-sectional study of 1,738 CKD patients was conducted at Kaohsiung Medical University Hospital, Taiwan. Brain MRI scans were utilized to measure WMHs according to the Fazekas scale, separately assessing periventricular WMHs (PWMHs) and deep WMHs (DWMHs). The eGFR was calculated using the MDRD formula. The urinary albumin to creatinine ratio (UACR) was categorized into three stages with cutoff values at 30 mg/g and 300 mg/g. The prognosis of CKD was accessed based on the 2024 KDIGO guidelines, considering both eGFR and albuminuria. Ordinal regression models with potential confounders adjustment were used for the analysis.

Results: Impaired renal functions are associated with increased severity of PWMHs. An increase in eGFR is linked to a decrease in PWMHs with an odds ratio (OR) of 0.987 (95% confidence interval [CI]: 0.979-0.994, $p < 0.001$). UACR stage 3 shows a significant association with increased PWMHs (OR [95% CI]: 1.645 [1.066-2.540], $p = 0.024$) compared with UACR stage 1. Those catagorized as very high-risk group by KDIGO guidelines are associated with increased PWMHs (OR [95% CI]: 1.832 [1.184-2.840], $p = 0.007$), compared to those with low and moderately increased risk. However, impaired renal functions are not associated with DWMHs.

Conclusions: Our findings highlight the impact of renal impairment on brain damage in CKD patients, as evidenced by the increased severity of PWMHs. DWMH shows no significant association with renal function.



Association between Fazekas Scale with CKD stage and UACR stage

FR-PO1160

Posterior Reversible Encephalopathy Syndrome in CKD: A Comprehensive National Analysis, 2016-2019

Mingyue He, Avrum Gillespie. *Temple University Hospital, Philadelphia, PA.*

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is an acute clinical-radiographic neurological syndrome that is potentially reversible with timely treatment. However, if untreated, it may result in severe complications such as intracerebral hemorrhage (ICH). Patients with kidney disease are at an increased risk of developing PRES. It remains unclear whether this is due to concurrent conditions such as hypertension and autoimmune disorders or if renal dysfunction itself is an independent risk factor. Furthermore, the impact of kidney function on the outcomes of PRES is still uncertain. This study aimed to examine the incidence and outcomes of PRES across various stages of chronic kidney disease (CKD), compared to a kidney disease-free group (NKD).

Methods: We conducted a retrospective analysis using the Nationwide Inpatient Sample (NIS) database to identify adult patients non-electively admitted with PRES from 2016 to 2019, categorizing them into CKD stages 3, 4, 5; end-stage kidney disease (ESKD); NKD; and an Others group.

Results: The study included 12,605 patients, representing 0.014% of all admissions. PRES hospitalizations increased significantly from 2016 to 2019. (trend p=0.012). The cohort had a mean age of 57.5 years, with 71.5% female and 72.5% White. Patients with CKD had higher PRES incidence in a dose-response manner as CKD stages advanced from 3 to ESKD. Key risk factors for PRES included gender, hypertension, metastasis, drug use, history of solid organ transplant, carotid artery stenosis, cerebral atherosclerosis, migraine, SLE, and systemic sclerosis. ESKD patients had significantly higher in-hospital mortality (aOR 4.61, 95% CI 1.84-11.57, p= 0.001). Differences in ICH and stroke rates across CKD stages/ESKD and NKD were not statistically significant.

Conclusions: Our findings provide valuable insights into the impact of CKD on the incidence and outcomes of PRES. Our study establishes an association between CKD and PRES, demonstrating a dose-response relationship. ESKD is an independent risk factor for in-hospital mortality. Given these insights, our study emphasizes the need for heightened awareness and targeted management strategies to improve outcomes for this vulnerable group. It also calls for further research to explore the specific mechanisms linking CKD and PRES.

FR-PO1161

Comparative Effectiveness of Roxadustat vs. Erythropoiesis-Stimulating Agents (ESAs) on Anemia and Kidney Outcomes among Patients with CKD: A Retrospective Cohort Study

Jinwei Wang,[1] Luxia Zhang,[1,2] Ming-Hui Zhao.[1] *[1]Peking University First Hospital, Beijing, China; [2]Peking University Health Science Center, Beijing, China.*

Background: Anemia is a common complication of chronic kidney disease (CKD), causing adverse outcomes. Traditional treatments, including iron and erythropoiesis stimulating agents (ESAs), may arouse drug-related adverse events, while the newly developed hypoxia inducible factor prolyl hydroxylase inhibitor (HIF-PHI) demonstrated both efficacy and safety. However, previous evidence largely comes from clinical trials and mainly focused on patients with kidney failure. The “head-to-head” comparison of the effectiveness in real-world setting among patients with CKD regarding HIF-PHI and ESAs is lacking.

Methods: Patients with CKD receiving either intravenous/subcutaneous ESAs or oral Roxadustat capsules (one type of HIF-PHI) were identified from the electronic health records-based CKD registry in Yinzhou district of Ningbo city in China from December of 2018 to December of 2021. The propensity score-based inverse probability of treatment weighting was used to control confounding. The difference regarding hemoglobin (Hb) change between the treatments was evaluated by linear mixed effect model, while association of the treatments with Hb response (Hb>110 g/L with an absolute increase of Hb ≥10 g/L from a baseline of ≥80 g/L or ≥20 g/L from a baseline of <80 g/L) and composite kidney outcomes (initiation of kidney replacement therapy, doubling of serum creatinine or ≥50% reduction of kidney function) by Cox regression model.

Results: Totally, 473 patients receiving ESAs and 189 receiving Roxadustat were identified, with a median follow-up of 8.4 (interquartile range: 6.5-21.8) and 5.8 (3.3-11.3) months, respectively, for Hb response. The Roxadustat group demonstrated a significantly faster Hb increase rate than ESAs group (9.49 [95% confidence interval: 3.66-15.32] g/L/year versus 1.91 [0.83, 2.99] g/L/year, P=0.01). The Roxadustat group also showed a faster achievement of Hb response (weighted hazard ratio=1.496 [95% confidence interval: 1.121-1.652]) during 52 weeks of follow-up. There were 43 and 192 composite kidney outcomes occurred in the Roxadustat and ESAs group, respectively, corresponding to lower risk of composite kidney outcomes (weighted hazard ratio=0.686 [0.489-0.963]).

Conclusions: This study suggests patients with CKD receiving Roxadustat treatment has faster increase of Hb and lower risk of kidney outcomes than ESAs.

FR-PO1162

A Phase 1b, Double-Blind, Placebo-Controlled Study of DISC-0974, an Anti-hemojuvelin Antibody, in Patients with Nondialysis-Dependent CKD and Anemia

Samir Arora,[1] Pablo E. Pergola,[2] Arnold L. Silva,[3] Geoffrey A. Block,[4] Sima Bhatt,[5] Akshay Buch,[5] Olivia Pelletier,[5] Will Savage.[5] *[1]Centricity Research, Columbus, OH; [2]Renal Associates PA, San Antonio, TX; [3]Boise Kidney & Hypertension Institute, Meridian, IN; [4]Rocky Mountain Kidney Care, Lone Tree, CO; [5]Disc Medicine Inc, Watertown, MA.*

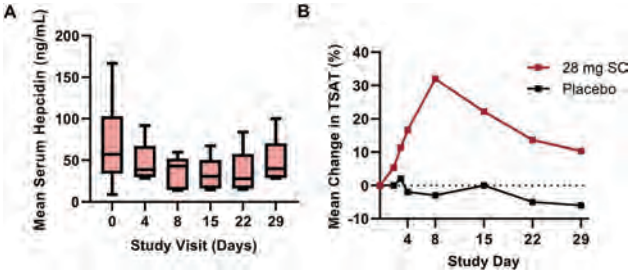
Background: Hepcidin, a key regulator of iron homeostasis, is pathologically elevated in patients with non-dialysis-dependent CKD (NDD-CKD) and contributes to the onset and severity of anemia. DISC-0974 is an investigational, first-in-class, monoclonal

antibody that blocks hemojuvelin (HJV), a co-receptor in the BMP-signaling pathway regulating hepcidin expression. By inhibiting endogenous production of hepcidin and enhancing iron availability, DISC-0974 may provide a novel approach for treatment of anemia.

Methods: DISC-0974-103 is a Phase 1b, double-blind, placebo-controlled, single-ascending dose study (NCT05745883) to assess the safety, PK, and PD of DISC-0974 in patients with NDD-CKD and anemia. On Day 1, participants receive a single dose of DISC-0974 subcutaneously with evaluations through 57 days of follow-up. Dose-escalation is planned across 4 cohorts (n=8), with 3:1 randomization of DISC-0974 (28, 40, 60, and 90 mg) to placebo. Eligible participants include NDD-CKD Stages 2-5, hemoglobin <11 g/dL, serum ferritin ≥75 μg/L, and transferrin saturation (TSAT) ≤35%. Major exclusionary criteria include concomitant treatment with intravenous iron or ESAs.

Results: Initial data in participants (n=8) who received a single dose of 28 mg DISC-0974 showed sustained reductions in serum hepcidin (Figure 1a) with a corresponding doubling of TSAT (Figure 1b) over mean baseline TSAT values of 17%. DISC-0974 was generally well tolerated; 2 subjects treated with DISC-0974 had a TEAE (33%) vs. 2 on placebo (100%); 2 treated subjects had SAEs deemed not related to DISC-0974.

Conclusions: Initial data provide proof-of-concept that DISC-0974 can result in meaningful reductions in hepcidin and improve mobilization of iron. DISC-0974 was generally well tolerated at the evaluated dose level. Additional ascending-dose cohort data will be presented.



a) Serum hepcidin levels and b) change in TSAT over time following single-dose administration of 28 mg DISC-0974 (n=6) or placebo (n=2)

FR-PO1163

Impact of Real-World, Off-Label Dose of Apixaban on Long-Term Clinical Outcomes in Patients with Atrial Fibrillation and CKD

Hark Rim,[1,2] Byeonghwa Bak,[1,2] Ye na Kim,[1,2] Ho Sik Shin,[1,2] Yeonsoon Jung.[1,2] *[1]Kosin University Gospel Hospital, Busan, Republic of Korea; [2]Transplantation Research Institute, Kosin University College of Medicine, Busan, Republic of Korea.*

Background: Apixaban represent one of the cornerstone treatments to prevent cardioembolic events in patients with nonvalvular atrial fibrillation (NVAF). However, the choices of Apixaban dose guided by the decision-making process of the physician, which considers specific according to kidney functions are inconsistent in the real-world practice. The objective of the present study is to evaluate the effects of real-world Off-label dose of Apixaban on long-term clinical outcomes in NVAF patients with chronic kidney disease (CKD)

Methods: Our database of AF patients diagnosed with CKD from 2018 to 2023 was used to obtain laboratory, echocardiography, electrocardiogram (ECG), and clinical outcomes data. Inclusion criteria were all AF patients with CKD using Apixaban. And we compared bleeding, systemic thrombotic events including stroke/systemic embolism and death according to off-label real -world dose of Apixaban.

Results: Among 635 patients with AF and CKD (76.9±10.4 years), 335 (52.8%) patients took off-label underdosed Apixaban. Difference in the baseline characteristics was not observed among patients including CHA2DS2 VASc score and HASBLED score. During the median 18-month follow-up, a lower incidence of bleeding events (P=0.001) was observed in the off-label underdosed Apixaban group compared to those with standard dose or off-label overdosed Apixaban. However, there was no significant difference of systemic thrombotic events including stroke/systemic embolism and death according to off-label real-world dose of Apixaban (off-label underdose vs. standard dose, P=1.000; off-label overdose vs. standard dose, P=1.000; off-label underdose vs. off-label overdose, P=0.609). In multivariate analysis, HASBLED score was independent risk factors for bleeding events (OR 9.650; CI 1.998- 46.622; P=0.005).

Conclusions: Compared with standard or off-label overdose of Apixaban, off-label underdose of Apixaban was associated with a lower risk of bleeding in patients with AF and CKD, with no difference in the risk of stroke/systemic embolism or death, supporting the apixaban dosing tailored to specific clinical features and drug pharmacokinetics of the Asian patients.

FR-PO1164

Plasma Ceramides and CKD Progression in Type 2 Diabetes

Augustine Takyi, Amara Sarwal, Robert E. Boucher, Sydney E. Hartsell, Niharika Katkam, Farahnaz A. Moghaddam, Akhil Ramanujam Chakravartula, Scott Summers, Tom Greene, Marcus G. Pezzolesi, Srinivasan Beddhu. *University of Utah Health, Salt Lake City, UT.*

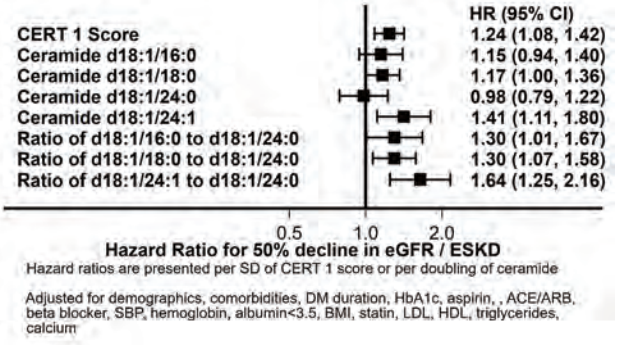
Background: The Cardiovascular Event Risk Test (CERT) 1 score is used in general population to predict atherosclerotic CV events; however, whether altered plasma ceramides (CER) and CERT1 scores predict the progression of CKD is unknown.

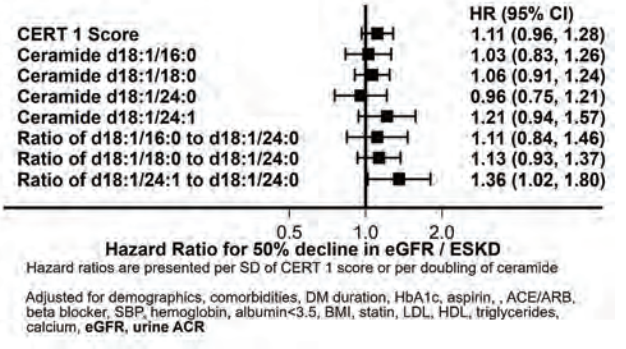
Methods: We measured plasma CER with targeted lipidomics in year 1 visit samples of 1054 Chronic Renal Insufficiency Cohort (CRIC) participants with T2D. Based on plasma CER 16:0, 18:0, 24:1 and their ratios to 24:0, CERT1 scores were calculated (2 points for concentrations/ratios in the 4th quartile and 1 point for concentrations/ratios in the 3rd quartile of reference population). In separate multivariate Cox regression models, we related CERT1 scores (Model 1) and individual CER and their ratios (Model 2) with a composite kidney outcome defined as a 50% decline in eGFR or the onset of ESKD.

Results: Baseline mean age was 61 ± 9 years and eGFR 46 ± 13, respectively. 57% were male, 49% were Black, CERT1 score median (IQR) was 4 (2,7). There were 377 kidney events/6127 years of follow-up. CERT1 score was associated with higher risk of kidney events. In a separate Cox model of its components, CER 18:0, CER 24:1 and the ratios were associated higher risk of kidney events (Figure 1). However, with further adjustment for baseline eGFR and UACR, only CER ratio 24:1/24:0 associated with the kidney outcome (Figure 2).

Conclusions: CER ratio 24:1/24:0 but not CERT1 score predicted CKD progression, independent of baseline eGFR and UACR. Interventions targeting plasma CER, in particular CER ratio 24:1/24:0 might slow CKD progression in T2D.

Funding: NIDDK Support





FR-PO1165

Plasma Ceramides and Risk of Cardiovascular Events in CKD

Farahnaz A. Moghaddam,[1,2] Marcus G. Pezzolesi,[1,2] Amara Sarwal,[1,2] Robert E. Boucher,[1,2] Augustine Takyi,[1,2] Sydney E. Hartsell,[1,2] Akhil Ramanujam Chakravartula,[1,2] Niharika Katkam,[1,2] Guo Wei,[1,2] Jincheng Shen,[1,2] Scott Summers,[1,2] Srinivasan Beddhu.[1,2] *[1]University of Utah Health, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

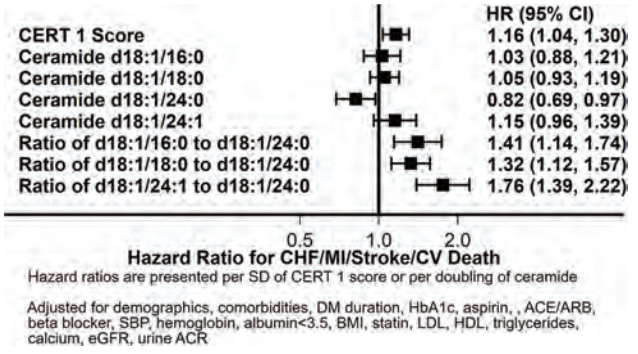
Background: Ceramide (CER) accumulation in tissues is implicated in platelet dysfunction, inflammation, insulin resistance, and atherosclerosis. As altered plasma CER predicts CV events, a Cardiovascular Event Risk Test (CERT)1 score based on plasma CER has been developed in the general population. It is unknown whether plasma CER and CERT1 scores predict CV events in CKD.

Methods: We measured plasma CER with targeted lipidomics in year 1 visit samples of 1054 Chronic Renal Insufficiency Cohort (CRIC) participants with T2D. Based on plasma levels of CER 16:0, 18:0, 24:1 and their ratios to CER 24:0, CERT1 scores were calculated as 2 points for concentrations or ratios in the 4th quartile and 1 point for concentrations or ratios in the 3rd quartile of the reference population. In separate multivariate Cox regression models adjusted for variables listed in Figure, we related individual CER, ratios, and CERT1 scores with a composite of adjudicated MI, HF, stroke or CV death.

Results: The mean age was 61 ± 9 years, 57% were male, 49% were African American, baseline eGFR was 46 ± 13 ml/min/1.73 m^2 and mean CERT1 score was 4.4 ± 3.4. There were 454 CV events/8654 patient years of follow-up. While CER 16:0, 18:0, and 24:1 were not associated with CV events (Figure), CER 24:0 had a lower risk and the ratios of CER 16:0, 18:0, and 24:1 to CER 24:0 were significantly associated with higher CV risk. Each standard deviation increase in CERT1 score (3.4 points) was associated with CV events(HR 1.16, 95% CI 1.04 to 1.30).

Conclusions: CER 24:0 and the ratios of CER 16:0, 18:0, 24:1 to CER 24:0 predict CV events in CKD independent of BMI, serum lipids and statin use. CERT1 score but not all of its components were associated with CV events in CKD suggesting that calibration and discrimination of CERT1 score in CKD could be improved with a CKD specific score.

Funding: NIDDK Support, Other NIH Support - NIA, Veterans Affairs Support



FR-PO1166

Propensity Score Matching in CKD: Evaluating Guca2b as a Biomarker for Diagnosis and Treatment Monitoring

Aaron L. Carrithers,[1] Luke E. Morrison,[1] Ryan Ott,[2] Stephen L. Carrithers.[1]
[1]PrognostX Health, LaGrange, KY; [2]Ethos Biosciences, Newtown Square, PA.

Background: Limitations of early diagnosis of CKD with standard of care have been well documented. Guanylate cyclase activator 2B (Guca2b), a prohormone that delivers the bioactive hormone moiety uroguanylin to its receptors lining the nephron, has recently been shown to significantly increase in the circulation during increased severity of renal impairment and early chronic kidney damage. Guca2b exhibits a dual paracrine-endocrine secretion mechanism, being released into the tubular lumen and arterioles, where protease activation in the glomerulus enables immediate nephroprotective effects on the proximal tubule (PT) by maintaining salt and fluid homeostasis and conserving energetic expenditure. Guca2b mediates natriuresis and kaliuretic actions through cGMP-dependent and -independent pathways. These include downregulation of the PT Na^+-pump, inhibition of Na^+/H^+ exchanger (akin to SGLT2i's) and $Na^+/K^+/2Cl^-$ in the mTAL (site of action for loop diuretics), and distal ClC-K2 chloride channels (mitigating activation by AII and emulating renoprotective properties of ACEI/ARBs).

Methods: To account for potential differential treatment effects on circulating Guca2b levels as an early biomarker for CKD and balance covariates between CKD stages and controls, nearest neighbor propensity score matching with caliper width 0.2x±SD of the logit was conducted on age, race, gender, and eGFR in a 426-patient case-control observational study. Median treatment effect on circulating Guca2b levels (ng/ml) was calculated for cases and controls treated with therapeutic agents that act on tubular salt transport channels.

Results: Mild reductions in Guca2b levels were observed across all treatment groups within the nested G3a/G3b subgroups, yet none were statistically significant: loop diuretics (3.57 vs 3.81; MTE, -0.54; n=18), thiazide diuretics (3.10 vs 3.16; MTE, -0.06; n=18), all diuretics (3.41 vs 4.02; MTE, -0.61; n=28), and ACEI/ARBs (3.06 vs 3.51; MTE, -0.45; n=32). Baseline characteristics and eGFR's were matched in stage A1/A2 CKD patients to healthy controls, demonstrating significantly higher mean Guca2b levels (2.70 vs 1.20, n=43, p<0.05) yet lower than matched G3a/G3b (2.55 vs 3.94, n=37, p<0.05).

Conclusions: This study suggests a multifactorial mechanism of early renal pathogenesis independent of GFR and potential biomarker for early CKD detection.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO1167

Association between Irisin and Cardiovascular Structure and Function in Patients with Advanced CKD

Hannah E. Wilson, Nikita F. Samanani, Gayatri Narayanan, Neal X. Chen, Heather Burney, Sharon M. Moe, Kenneth Lim. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Emerging evidence suggests that irisin, a myokine released from muscle during exercise, could exert cardiovascular (CV) protective effects. Circulating irisin is reduced as CKD progresses, and low irisin has been associated with increased risk of vascular calcification and CV mortality in patients on hemodialysis. However, to-date no studies have comprehensively studied its role in regulating CV structure and function in advanced CKD.

Methods: We performed a cross-sectional analysis of 149 patients from the Cardiopulmonary Exercise Testing in Renal Failure and After Kidney Transplantation (CAPER) cohort. All patients underwent cardiopulmonary exercise testing to assess CV functional capacity, echocardiography, and applanation tonometry. Patients were stratified by sex (M/F) and dialysis status (pre-dialysis (P), dialysis (D)) (n=16 P/F, n=41 D/F, n=23 M/P, n=69 M/D). Wilcoxon rank-sum tests were performed to assess differences in irisin levels. Multiple linear regression models were performed to examine associations between irisin and outcomes. Plasma irisin (ng/mL) was assessed via ELISA (Phoenix Pharmaceuticals, EK-067-29).

Results: The mean age of the dialysis group was higher than the pre-dialysis group among males but not females (M: 50.8±13.9, p=0.0055, vs F: 41.3±13.7 yr, p=0.3). Additionally, there was no difference in BMI among all strata groups (p>0.05). Interestingly, irisin was higher in male dialysis compared to pre-dialysis patients (n=92, 8.8 vs 5.4 ng/mL, p=0.0003) but not in females (n=57, 8.3 vs 8.6 ng/mL, p=0.67). Multiple linear regression demonstrated that plasma irisin was not associated with VO_2Max, left ventricular mass index, pulse pressure or augmentation index after adjusting for age, sex, BMI, dialysis status and phosphate levels. However, irisin concentration was negatively associated with maximum workload after the same adjustment (β=-1.8, p=0.04).

Conclusions: This study suggests that irisin is dysregulated in kidney failure and may target the musculoskeletal system, rather than CV structure in advanced CKD patients. Additionally, the lack of a validated blood irisin assay is a current limitation in clinical studies. Future studies will assess the association of irisin with physical performance and quantitative musculoskeletal metrics (i.e. DXA) in CKD patients.

FR-PO1168

Association of Plasma Uromodulin with Kidney Outcomes in the SPRINT Trial

Jesse C. Ikeme,[1] Rebecca Scherzer,[1] Pranav S. Garimella,[2] Stein I. Hallan,[3] Ronit Katz,[4] Michelle M. Estrella,[1] Joachim H. Ix,[2] Michael Shlipak.[1]
[1]University of California San Francisco, San Francisco, CA; [2]University of California San Diego, La Jolla, CA; [3]Norges Teknisk-Naturvitenskapelige Universitet, Trondheim, Norway; [4]University of Washington, Seattle, WA.

Background: Uromodulin (UMOD) is a kidney tubule biomarker that may help identify persons at greater risk of eGFR decline. We evaluated the associations of plasma UMOD with kidney outcomes in persons with CKD and hypertension.

Methods: This was a secondary analysis of the Systolic Blood Pressure Intervention Trial, in which an intensive SBP target reduced risk of CV events and mortality. Plasma UMOD was measured at baseline in 2,302 participants with eGFR <60 ml/min/1.73m^2. Acute kidney injury (AKI) was determined based on serious adverse event reporting during the trial. Quarterly labs were used to determine 30% and annual % eGFR decline from baseline. Cox proportional hazards (AKI, 30% eGFR decline and ESKD) and linear mixed models (annual % eGFR decline) were adjusted for baseline characteristics, including eGFR and albuminuria.

Results: Plasma UMOD and eGFR had a Spearman correlation of 0.47. In fully adjusted models, each standard deviation higher plasma UMOD was associated with lower risk of 30% eGFR decline and slower annual eGFR decline **(Table)**. There were no independent associations with risk of future AKI or ESKD. The association with lower risk of 30% eGFR decline appeared stronger in those randomized to a usual SBP target (HR 0.73, 95% CI 0.62-0.87) than in those randomized to an intensive SBP target (HR 0.90, 0.79-1.02; p-interaction = 0.03). Associations with other outcomes appeared similar across randomized treatment arms (p-interaction >0.10).

Conclusions: Higher plasma UMOD levels are independently associated with lower risk of 30% eGFR decline and slower decline in eGFR among hypertensive persons with nondiabetic CKD.

Funding: NIDDK Support

Adjusted associations of baseline plasma uromodulin (per SD higher) with kidney outcomes in 2,302 SPRINT participants with CKD

Outcome	n	Hazard Ratio (95% CI)	p
Acute kidney injury	179	0.84 (0.70, 1.01)	0.06
30% eGFR decline	461	0.84 (0.75, 0.94)	0.002
ESKD	72	0.91 (0.70, 1.19)	0.51
		% estimate (95% CI)	p
Annual % eGFR change		+0.58 (+0.22, +0.94)	0.002

Models adjusted for randomized SBP target, age, sex and race; baseline eGFR, log urine albumin, log urine creatinine, smoking, BMI, SBP, anti-hypertensive medications number and class, cardiovascular disease, heart failure, high-density lipoprotein, total cholesterol, and statin use.

FR-PO1169

Association of Kidney Length with Clinical Outcomes among Individuals with CKD

Cassianne Robinson-Cohen, Rashedeh Roshani, Roy Zent, Jennifer E. Below. *Vanderbilt University Medical Center, Nashville, TN.*

Background: The assessment of kidney health is typically limited to estimates of glomerular filtration (eGFR) and glomerular integrity (albuminuria). These are insufficient, given the complexity and heterogeneity of renal pathology, and disease misclassification using these biomarkers is a well-known problem in clinical and research settings. Measuring and evaluating kidney size may provide a complementary understanding of kidney function and structure, particularly among individuals with chronic kidney disease (CKD).

Methods: We studied 3,585 non-dialysis requiring CKD patients from Vanderbilt University Medical Center's electronic health record (EHR) databank, BioVU. We ascertained kidney length using computational free text mining techniques within abdominal MRI radiology report notes. We examined associations of kidney length with time to end-stage kidney disease or death, using Cox proportional hazards regression models stratified by diabetes status. Secondarily, a phenome-wide association study was conducted to explore associations of kidney length with other phenotypes in the EHR.

Results: During a median follow-up of 2.5 years, 138 patients had an incident ESKD event and 643 died (incidence rate for composite endpoint: 6.0 events per 100 person-years). After adjustment, among non-diabetic patients (n=2,515), shorter kidneys were associated with risk of the combined endpoint (hazard ratio (HR), 1.08 (1.02, 1.15) for each cm increment in kidney length, p=0.012). In contrast, kidney length was not associated with risk of ESKD or death among diabetic patients (HR 1.04 (0.92, 1.18)). PheWAS signaled additional associations of kidney length with subclinical and clinical cardiovascular outcomes, acute kidney injury and liver diseases.

Conclusions: Shorter kidney length was associated with an increased risk of ESKD and mortality among CKD patients without diabetes. Efforts to establish the broader clinical significance of kidney size are underway.

FR-PO1170

Advancement in CKD Stages Leads to Increased Levels of Soluble PD-L1 in Serum

Ayaka Hayashi, Izumi Yamamoto, Mayuko Kawabe, Akio Nakashima, Takashi Yokoo, Mitsuyoshi Urashima. *Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan.*

Background: Programmed death-ligand 1 (PD-L1) and its receptor, programmed death-1 (PD-1), play crucial roles in immune tolerance through their interactions. PD-L1, expressed on antigen-presenting cells, cancer cells, placental tissue, vascular endothelial cells, and tubular epithelial cells, suppresses T-cell activation when it binds to PD-1 on T cells. Recent studies indicate that soluble PD-L1 (sPD-L1) also induces immunotolerance, with levels varying in clinical conditions such as cancer and pregnancy. However, data on sPD-L1 levels in chronic kidney disease (CKD), including hemodialysis (HD) patients, are lacking. This study aims to compare serum sPD-L1 levels among individuals without CKD and patients with CKD stages 1 to 5.

Methods: Serum sPD-L1 levels were measured using ELISA in samples from three cohorts (n=2,816): healthy individuals who received the SARS-CoV-2 mRNA vaccine (n=1,781) with or without underlying conditions such as hypertension and diabetes; cancer patients without CKD and with CKD stages 1 to 4 (n=402); and HD patients (n=633).

Results: sPD-L1 levels increased with worsening CKD stages. Median sPD-L1 levels were higher in HD patients compared to those with stage 4 CKD. In a 1:1 matched case-control study of 394 HD patients with age- and sex-matched healthy controls, HD patients exhibited significantly higher median sPD-L1 levels than non-HD individuals (231.7 pg/mL vs. 85.0 pg/mL, p<0.0001). This finding remained consistent after excluding and re-matching patients with hypertension, diabetes, and cancer. Furthermore, longer HD vintage was associated with higher sPD-L1 levels.

Conclusions: Serum sPD-L1 levels increase with CKD progression, reaching the highest levels in HD patients, particularly those with longer treatment duration. Future research will focus on elucidating the mechanisms behind the increase in sPD-L1 levels due to declining renal function and investigating whether elevated sPD-L1 levels heighten the risk of cancer or infections in dialysis patients.

FR-PO1171

Exploring the Effects of Low-Energy Diets on Risk Factors and Markers of Kidney Disease: Findings from the Slowing Kidney Disease with Weight-Loss Feasibility Study

Marguerite M. Conley,[1,2] Kirsten S. Hepburn,[3,4] Hannah L. Mayr,[1,4] David W. Mudge,[5,4] Justin J. Holland,[2] Andrea K. Viecelli,[5,4] David W. Johnson,[5,4] Helen L. MacLaughlin.[6,2] *[1]Department of Nutrition and Dietetics, Princess Alexandra Hospital, Brisbane, QLD, Australia; [2]Queensland University of Technology Faculty of Health, Kelvin Grove, QLD, Australia; [3]Kidney Health Service, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [4]Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia; [5]Department of Kidney and Transplant Services, Princess Alexandra Hospital, Brisbane, QLD, Australia; [6]Dietetics & Food Services, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.*

Background: Whether weight loss can delay or prevent the progression of obesity-associated CKD, and the amount of weight loss that may confer such benefit have not been well-established. This feasibility study explored kidney disease risk factors and markers of kidney function in a six-month randomised controlled trial (RCT).

Methods: Forty-nine adults with stages 1-3b CKD, body mass index (BMI) ≥30kg/m^2, and proteinuria (urinary protein to creatinine ratio (uPCR) >3mg/mmol) were randomised 1:1. The low energy diet (LED) group followed a 3-month LED (800-1000 kcal/day) with dietitian support; followed by a 3-month exercise and nutrition program. Usual care offered standard weight loss support. Changes in CKD risk factors and kidney markers were examined.

Results: Thirty-eight adults (78%) with a median age of 56 years, eGFR 57 mL/min/1.73m^2 and BMI 39kg/m^2 completed the study. At 6 months, significant intervention effects were observed for weight (WT) and waist circumference (WC) but not for uPCR, systolic blood pressure (SBP), diastolic blood pressure (DBP) or estimated glomerular filtration rate (eGFR) measures (Table 1). There was large variability across eGFR measures.

Conclusions: Low energy diets can significantly reduce body weight and waist circumference and may lead to improvements in eGFR, proteinuria and systolic blood pressure. Interpreting estimates of kidney function remains problematic when coupled with changes in body mass. Longer and larger trials exploring the use of LEDs on risk factors and measures of CKD progression are warranted.

Funding: Private Foundation Support

Table 1. Changes in risk factors and markers of kidney function, following six-month weight loss program.

	Change score 0-6 month Median (interquartile range)		
Variable	LED (n=16)	Usual Care (n=22)	p-value
WT (kg)	-9 (-12, -7)	0 (-4, 2)	<.001
WT (%)	-8 (-12, -6)	0 (-3, 2)	<.001
WC (cm)	-10 (-13, -6)	-3 (-5, 2)	.002
SBP (mmHg)	-7 (-13, 1)	-1 (-9, 11)	.300
DBP (mmHg)	-3 (-5, 0)	1 (-3, 5)	.120
uPCR (g/mol)	-7 (-110, 19)	-4 (-44, 34)	.330
eGFR			
CKD-EPI CR^ mL/min/1.73m^2	4 (1,7)	-2 (-6, 4)	.056
CKD-EPI CR^ (BSA) mL/min	4 (2, 6)[a]	-2 (-7, 5)[b]	.187
CKD-EPI C-C# mL/min/1.73m^2	11 (0, 35)[c]	7 (-2, 20)[d]	.245
CKD-EPI C-C# (BSA) mL/min	14 (-1, 44)[e]	8 (-1, 25)[f]	.371

^CKD Epidemiology Collaboration Creatinine equation (2009)
#CKD Epidemiology Collaboration Creatinine-Cystatin C equation (2021)
BSA; un-indexed using actual body surface area at each time point
Excludes eGFR >120ml/min/1.73m^2
[a]n=12; [b]n=20; [c]n = 13; [d]n = 17; [e]n = 12; [f]n = 16

FR-PO1172

Plasma Potassium Negatively Correlates with Sodium-Chloride Cotransporter (NCC) Abundance and Phosphorylation in Urinary Extracellular Vesicles (uEVs) from Patients with CKD

Aihua Wu,[1,3] Paul A. Welling,[2] Andrew S. Terker.[1] Leudcq Network Potassium in Hypertension. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Johns Hopkins Medicine, Baltimore, MD; [3]Princess Alexandra Hospital, Woolloongabba, QLD, Australia.*

Background: Hypertension is a leading cause of CKD. Low potassium diet is often advised in moderate to severe CKD. Emerging data now suggest that higher dietary potassium may be beneficial in these patients, but the underlying mechanism is unclear. Using uEVs we recently demonstrated that dietary potassium interventions can regulate distal sodium and potassium handling via the "renal-K switch" mechanism (the WNKs-SPAK/OSR1-NCC pathway) in both healthy adults and those with primary aldosteronism

(PA). The close relationship between blood pressure and CKD has led to the hypothesis that blood pressure-lowering effects of high potassium intake may also be reno-protective through the same mechanism. This study is to use uEVs to evaluate if plasma potassium negatively correlates with NCC and its phosphorylation in patients with CKD.

Methods: Morning blood and 2nd morning urine were collected on a single occasion between 8-11 am from patients with CKD at all stages. Clinical and biochemical features were assessed by Pathology Queensland. uEVs were obtained by progressive ultracentrifugation and analysed by Western blot. Those taking SGLT2 inhibitors or K binders were excluded

Results: Analysis of 20 participants demonstrates plasma potassium negatively correlates with uEV abundance of NCC (R^2=0.41, P=0.003) and its phosphorylation (R^2=0.22, P=0.04). These correlations persisted even patients with a low level of uEV. (Figure 1).

Conclusions: Plasma potassium measurements showed a strong negative correlation with the abundance of NCC and its phosphorylation state in uEVs from 20 patients with CKD. If the "renal-K switch" mechanism in CKD functions in the same way as has previously been demonstrated in patients without CKD, then increasing dietary potassium may assist in natriuresis, providing a renoprotective effect via reductions in blood pressure.

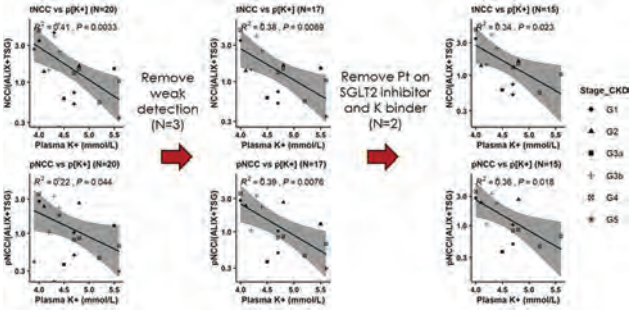


Figure 1. Correlations of plasma K^+ with uEV levels of NCC and pNCC.

FR-PO1173

Assessing the Selectivity of Urinary Proteins Using Albumin as an Alternative to Transferrin

Masayoshi Kukida, Shingo Kinnami, Fumikazu Kondo, Satoru Shichijo, Ken-ichi Miyoshi, Osamu Yamaguchi. *Ehime Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Toon, Japan.*

Background: Since the 1960s, the utility of urinary protein selectivity in diagnosing and predicting the prognosis of glomerular diseases has been reported. Urinary protein selectivity has traditionally been assessed using the Selectivity Index (S.I.), which compares the clearance of high molecular weight protein IgG to that of medium molecular weight protein transferrin. Although albumin is a major medium molecular weight urinary protein, its measurement accuracy was initially low, leading to the use of transferrin in calculating the S.I. However, recent improvements in the measurement accuracy of albumin have been noted. At our institution, serum albumin is measured using the modified bromocresol purple (BCP) method, while urinary albumin is measured using an immunoturbidimetric assay.

Methods: In this study, we analyzed data from 224 patients, comprising both outpatients and inpatients at our institution, whose concentrations of IgG, transferrin, and albumin in serum and urine were measured simultaneously between January 2014 and December 2023.

Results: Firstly, we calculated the S.I. using albumin (S.I. (Alb)) and S.I. using transferrin (S.I. (Tf)) and then analyzed their correlation. The results of linear regression analysis revealed a significant correlation, with S.I. (Alb) = S.I. (Tf) × 1.077 + 0.00295 ($p < 0.0001$, R2 = 0.7077) in patients with trace albuminuria or more, and S.I. (Alb) = S.I. (Tf) × 0.9570 + 0.0360 ($p < 0.0001$, R2 = 0.7516) in those with massive proteinuria equivalent to nephrotic syndrome (3.5g or more). Subsequently, we performed the receiver operating characteristics (ROC) analysis to examine the utility of the S.I. for the diagnosis of minimal change disease, characterized by its high selectivity for urinary protein. According to the ROC analysis, the AUC of S.I. (Tf) was 0.85 (95% CI, 0.74 – 0.95), and the AUC of S.I. (Alb) was 0.85 (95% CI, 0.74 – 0.96).

Conclusions: The findings suggest that the versatile S.I. (Alb) may be as useful as S.I. (Tf) in diagnosing glomerular diseases.

FR-PO1174

Analysis of In-Hospital Mortality Risk Factors and Establishment of a Nomogram Prediction Model for Patients with Stage 5 CKD in the Intensive Care Unit (ICU)

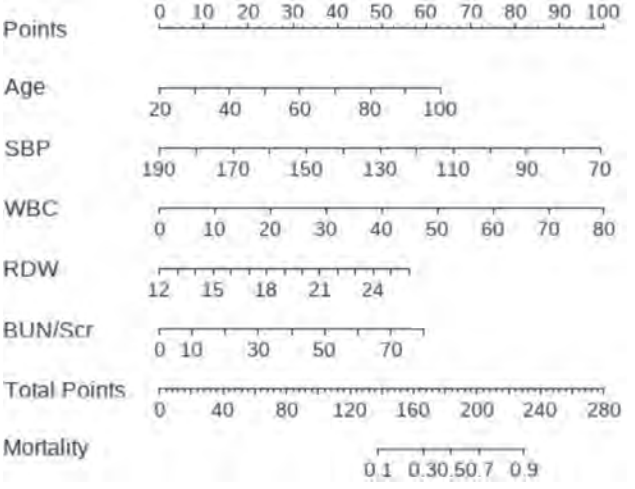
Fanna Liu. *The First Affiliated Hospital of Jinan University, Guangzhou, China.*

Background: Patients with stage 5 chronic kidney disease (CKD5) have a high risk of mortality. ICU patients have lots of abnormal results. Defining the risk factors for in-hospital mortality in ICU CKD5 patients will help doctors pay more attention to the most important factors and intervene in a timely manner. In this study, we analyzed the risk factors related to in-hospital mortality and drew the nomogram to predict in-hospital mortality in CKD5 non-dialysis (CKD 5ND) patients.

Methods: According to the diagnosis code, 495 CKD 5ND patients were selected from the MIMIC-IV database. The differences between the survival group and the death group were analyzed by two independent samples t-test, rank-sum test, or chi-square test. The nomograms to predict the risk of in-hospital mortality in CKD 5ND patients were established respectively. In order to evaluate the nomogram, ROC curve, calibration curve, and DCA curve were used. Boostrap-resampling was used for internal verification. eICU patients were used for external verification. And the predictive performance of the nomogram was compared with commonly scores.

Results: There were 1439 CKD5 patients in the MIMIC-IV database, including 495 non-dialysis patients. There were 425 CKD5 ND patients in the survival group and 70 patients in the death group. Age, SBP, WBC, RDW, and BUN/Scr were the correlation factors for in-hospital mortality in CKD5 ND patients. Internal and external validation showed that the CKD5 ND patients nomogram prediction model had good calibration, clinical benefit, and discrimination (training set AUC=0.832, validation set AUC=0.770). The predictive ability of nomogram was better than the three commonly used scores.

Conclusions: The nomogram prediction model predicting in-hospital mortality of CKD5 ND patients has good discrimination, calibration, and clinical value, which are established by Age, SBP, WBC, RDW, and BUN/Scr.



FR-PO1175

Development of a Comprehensive Human Urine Single-Cell RNA Sequencing (scRNA-seq) Atlas for Enhanced Diagnostic Accuracy of Kidney Diseases

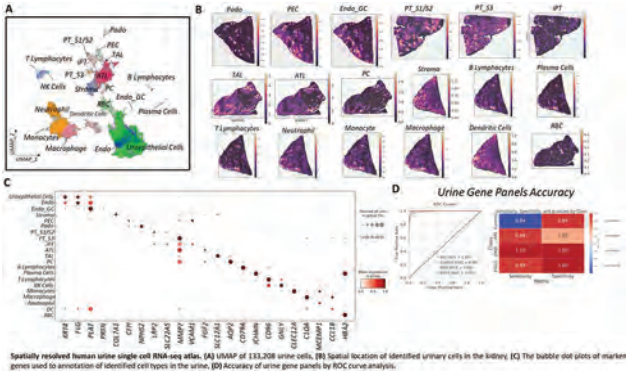
Amin Abedini,[1] Konstantin A. Kloetzer,[2] Katalin Susztak.[3] *[1]University of Maryland Medical Center, Baltimore, MD; [2]Medizinische Universitat Graz, Graz, Austria; [3]University of Pennsylvania, Philadelphia, PA.*

Background: Understanding the cellular composition of human urine is crucial for advancing diagnostic and therapeutic strategies for kidney and urinary tract diseases. Previous studies have provided insights into individual conditions, but a comprehensive, spatially resolved single-cell RNA-sequencing (scRNA-seq) atlas of human urine has been lacking.

Methods: We generated a human urine scRNA-seq atlas by integrating various published datasets. Deep generating modeling (scVI) was used for the data integration. Identified cell types were validated using kidney spatial transcriptomics. Additionally, we utilized the largest human kidney scRNA-seq atlas and MetaNeighbor analysis to further confirm our findings. Differentially expressed genes (DEGs) were identified and used to develop gene panels for the diagnosis of various conditions. We trained a logistic regression model with the gene expression data to evaluate the diagnostic performance of gene panels.

Results: Our integration of 86 samples yielded a comprehensive urine scRNA-seq atlas comprising 133,208 cells from various kidney conditions. This atlas captures a broad spectrum of cell types, including all kidney cell types, immune cells, and uroepithelial cells. The identified cell types were validated using kidney spatial transcriptomics. Importantly, identified cell types were successfully integrated and validated against the largest human kidney scRNA-seq data. The gene panels derived from DEGs demonstrated high sensitivity and specificity in diagnosing different conditions, supported by validation against a large human kidney scRNA-seq atlas.

Conclusions: The establishment of a spatially resolved human urine scRNA-seq atlas marks a significant advance in the non-invasive monitoring and diagnosis of kidney and urinary tract diseases. The validated gene panels offer promising tools for precise condition diagnosis, potentially changing current diagnostic practices and reduce our reliance on kidney biopsy.



Spatially resolved human urine single cell RNA-seq atlas. (A) UMAP of 133,208 urine cells, (B) Spatial location of identified urinary cells in the kidney, (C) The bubble dot plots of marker genes used to annotation of identified cell types in the urine, (D) Accuracy of urine gene panels by ROC curve analysis.

FR-PO1176

Single-Cell and Spatial Transcriptome Profiling Identifies a Tenascin C-Enriched Niche Promoting Kidney Inflammation

Li Li, Jinlin Liao, Yuxi Zhang, Haiyan Fu, Youhua Liu. *Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China*.

Background: Kidney fibrosis is often accompanied by inflammatory cell infiltration and interstitial inflammation. Among all inflammatory cells, macrophage infiltration plays an important role in the occurrence and development of renal fibrosis. However, the mechanism by which macrophages promote renal fibrosis remain to be elucidated. In this study, we demonstrate that tenascin-C-enriched microenvironment promotes the development of renal inflammation and fibrosis by activating macrophages.

Methods: Unilateral ischemic-reperfusion injury (UIRI) and unilateral ureteral obstruction (UUO) were used as models of kidney fibrosis. Single-cell RNA sequencing (scRNA-Seq) and spatial transcriptome (ST) sequencing techniques were used to characterize various cell subpopulations after kidney injury. Decellularized kidney tissue scaffold (dKTS) was prepared. The role of tenascin-C (TNC) in macrophage activation and proliferation was investigated in vitro. TLR4-KO mice and TLR4 inhibitor were used in vivo. A bone marrow chimera model was established by transplanting the bone marrow from TLR4 KO to WT mice.

Results: Single-cell and spatial transcriptome profiles of normal and UIRI kidney showed a significant increase of macrophages in the injured site, which was closely associated with TNC expression. Compared with the TNC-low region, the TNC-high region was associated with an increased infiltration of macrophages and activation of proinflammatory and profibrotic signaling. TNC-enriched dKTS from fibrotic kidney induced macrophage activation and proliferation, characterized by an increased expression of TNF-α, c-Fos, PCNA, c-Myc, TLR4, p-P65 and P65. Furthermore, TNC induced the activation, proliferation, migration and phagocytosis of macrophages via activating TLR4/NF-κB signaling in vitro. Inhibition or knockout of TLR4 and knockdown of TNC alleviated renal inflammation and fibrosis by inhibiting the activation, proliferation and migration of macrophages.

Conclusions: This study showed that TNC-enriched microenvironment promotes the development of renal inflammation and fibrosis by activating macrophages via TLR4/NF-κB signaling. Targeted inhibition of TNC and TLR4 could be novel therapeutic strategies for protecting kidney against inflammation in CKD.

FR-PO1177

RNA Sequencing (RNA-seq)-Based Machine-Learning Models for Kidney Injury Genes in Patients with CKD

Feifei Sun, Jiahui Cai, Yunbo Sun, Qiaoyun Pan, Shasha Zhao, Danshu Wang, Runyan Tan, Feng Yang, Yanling Yan. *Yanshan University, Qinhuangdao, China*.

Background: Chronic kidney diseases (CKD) are prevalent and cause high patient mortality and healthcare costs. However, mechanisms have not been well characterized. We hypothesized that machine learning (ML) would provide new insights into the exploration of RNAseq assessment to identify gene networks driving disease for early diagnosis of CKD.

Methods: We retrieved CKD datasets from the Gene Expression Omnibus (GEO) database. GSE180394 and GSE47184 were randomly split for training and GSE37455 for testing. Differentially expressed genes (DEGs) were screened to differentiate CKD from healthy controls. Weighted Gene Co-expression Network Analysis (WGCNA) further selected Modules and critical genes related to CKD as potential candidates. Characteristic hub genes were identified following being trained independently with ML model algorithms, including Support Vector Machine - Recursive Feature Elimination (SVM-RFE) and Least Absolute Shrinkage and Selection Operator (LASSO). Several ML models were created to predict CKD. The relationship between the potential targets and traditional renal function parameters was also examined.

Results: WGCNA and ML algorithms identified five central Hub genes, namely COL10A1, DUSP1, GADD45A, TSC22D3, and ZFAND5. Those genes could be instrumental in diagnosing CKD through multivariate logistic regression analysis. Four ML models were established, as shown in Figure 1. The model performed robustly evidenced by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve (93.6%, 90.7%, 93.8%, and 95.0%, respectively) in the validation cohort. The Nephroseq database was utilized to reveal a positive correlation between hub-genes GADD45A (R=0.55, p=0.0084) & TSC22D3 (R=0.53, p=0.011) and GFR, as well as a negative correlation between the above two hub-genes and SCr (R=-0.61, p=0.0096; R=-0.87, p=0.011, respectively), ensuring the predicted accuracy for CKD. In addition, immunological infiltration analysis showed that these hub genes affected the recruitment and infiltration levels of immune cells in CKD.

Conclusions: ML approaches endow RNAseq analysis with promising potential for diagnosing renal injuries. Implementation of the ML model can help identify the CKD patients who would benefit from early intervention to delay CKD progression and reduce healthcare costs.

Funding: Government Support - Non-U.S.

FR-PO1178

Causal Effects from Kidney Function to Plasma Proteome: Integrated Observational and Mendelian Randomization Analysis with More than 50,000 UK Biobank Participants

Jeongmin Cho,[1,2] Minsang Kim,[3] Semin Cho,[2] Soojin Lee,[4] Dong Ki Kim,[3] Sehoon Park.[3] *[1]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [2]Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Gyeonggi-do, Republic of Korea; [3]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [4]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea*.

Background: Chronic kidney disease (CKD) causes detrimental systemic consequences leading to substantial morbidity and mortality. However, the causal effect of reduced kidney function on systemic proteomic signatures is incompletely understood. The plasma proteome is a phenotype of dynamic molecular changes within cells and tissues, providing insights into the underlying disease mechanisms and potential drug targets.

Methods: We performed an integrated Mendelian randomization (MR) and observational analysis to identify the causal association between kidney function and plasma protein levels, based on 1,815 plasma protein profiles in 50,407 UK Biobank participants and the CKDGen phase 4 GWAS meta-analysis for the genetic instruments of eGFR.

Results: The MR analysis revealed 383 plasma proteins causally associated with eGFR. Reduced kidney function was found to be causally associated with an increase in the plasma levels of 381 proteins, among which FABP1, TNF, and IGFBP4 were included, while the level of 2 proteins, NPHS1 and SPOCK1, decreased. Apoptosis-related pathway was significantly enriched in the gene-set enrichment analysis. Through the network analysis, TNF was identified as a hub protein with multiple linkages to molecules included in the TNF-signaling pathways, involved in inflammation, fibrosis, and apoptosis. In addition, the eGFR-associated proteins were annotated to molecular function GO term related to insulin-like growth factor binding.

Conclusions: In this proteo-genomic analysis, we identified 383 plasma proteins causally associated with eGFR, highlighting TNF-associated pathways as pathologically relevant processes in kidney disease progression, systemic inflammation, and organ fibrosis, warranting further investigation.

Figure 1

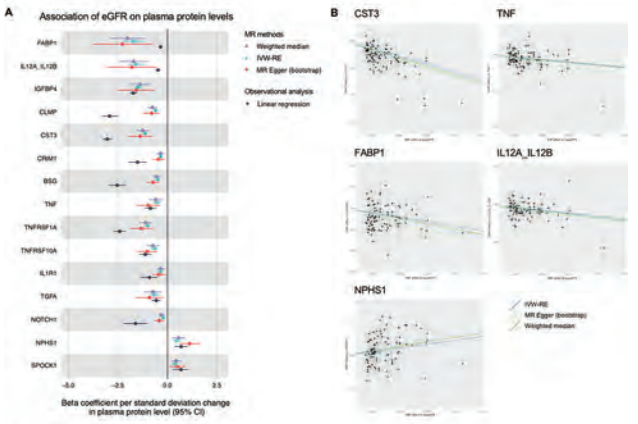
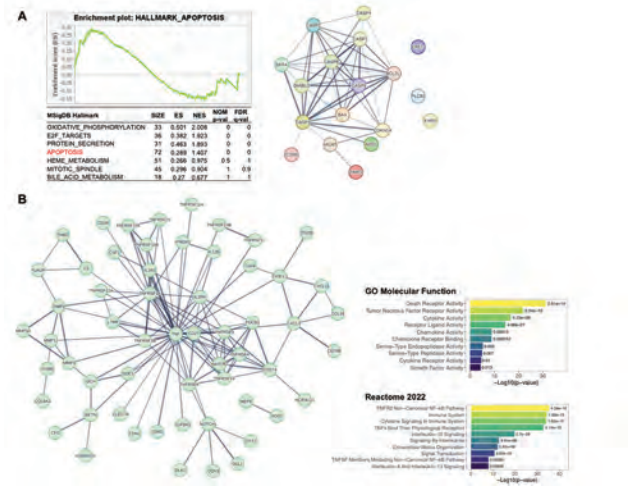


Figure 2



FR-PO1179

Differences in Plasma Proteomic Profiles between Patients with and without Type 2 Diabetes and CKD: New insights from DAPA-CKD

Mark A. De la Rambelje,[1] Niels Jongs,[1] Peter J. Greasley,[2] Rasmus Ågren,[2] Ann Hammarstedt,[2] David Sjostrom,[2] Adriaan A. Voors,[3] Hiddo J. Heerspink.[1] DAPA-CKD Biomarker Committee. *[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]AstraZeneca, Gothenburg, Sweden; [3]Universitair Medisch Centrum Groningen Afdeling Cardiologie, Groningen, Netherlands.*

Background: The pathophysiology of chronic kidney disease (CKD) in patients with and without type 2 diabetes (T2D) may share common and distinct pathways. To better understand potential pathophysiological differences between patients with CKD with or without T2D, we compared circulating protein profiles between these two groups.

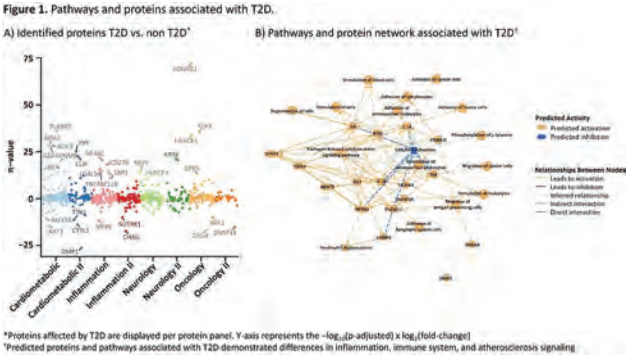
Methods: We used baseline plasma samples and clinical data from 2485 patients with CKD with and without T2D from the phase 3, randomized, placebo-controlled DAPA-CKD trial. We used the Olink® Explore 3072 panel with 2941 unique proteins for obtaining biomarker profiles of patients with CKD. We cross-sectionally compared patients with vs. without T2D. Differentially abundance testing was performed using Wilcoxon rank-sum test. Pathway analysis was performed with ingenuity pathway analysis (IPA).

Results: The 2485 included patients had a similar eGFR, UACR, and diabetes distribution compared with the overall clinical trial population. Patients with T2D compared with those without T2D were older (64.8 vs. 56.8 years), had a higher eGFR (44.4 vs 41.8 mL/min/1.73m^2), and a higher UACR (median 990 vs. 870 mg/g). Patients with T2D compared to those without had higher levels of adhesion G protein-coupled receptor G1, keratin 8, kidney injury marker-1, natriuretic peptide B and interleukin 6 with respectively significant (Bonferroni adjusted p-value < 0.05) fold changes of 2.39, 1.97, 1.74, 1.56, and 1.39. These differentially expressed proteins, along with others, were associated with atherosclerosis signaling and increased inflammation and immune system activity in those with vs without T2D and CKD.

Conclusions: Plasma proteomic profiles of patients with CKD and T2D were revealed to be related to atherosclerosis and increased inflammation and immune system activity compared to CKD patients without T2D. These findings may aid in identifying new treatment targets for patients with diabetic and non-diabetic CKD.

Funding: Commercial Support - AstraZeneca

Figure 1. Pathways and proteins associated with T2D.



*Proteins affected by T2D are displayed per protein panel. Y-axis represents the $-\log_{10}$(p-adjusted) x $\log_2$(fold-change)
†Predicted proteins and pathways associated with T2D demonstrated differences in inflammation, immune system, and atherosclerosis signaling

FR-PO1180

Elucidating Metabolic Microenvironment of Tertiary Lymphoid Structures in the Kidney

Hiroyuki Arai,[1] Yuki Sugiura,[2] Motoko Yanagita.[1,3] *[1]Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu, Kyoto, Japan; [2]Center for Cancer Immunotherapy and Immunobiology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [3]Kyoto Daigaku Hito Seibutsu Koto Kenkyu Kyoten, Kyoto, Japan.*

Background: Tertiary lymphoid structure (TLS) is an ectopic lymphoid structure induced in non-lymphoid organs by chronic inflammation. Functionally, TLSs serve as local sites for adaptive immune responses and are characterized by robust lymphocyte proliferation and cytokine production. During TLS formation, ectopic recruitment of a considerable number of cells to non-lymphoid organs implies a propensity for dramatic metabolic remodeling in both immune and parenchymal cells. However, the mechanism underlying metabolic remodeling required for TLS formation remains to be elucidated.

Methods: Imaging mass spectrometry and metabolomics were used to investigate the metabolic pathways that characterize TLSs. We also performed *in situ* hybridization combined with immunofluorescence and pharmacological inhibition to explore the expression and function of the key molecules that govern the pivotal metabolic pathways of TLSs. Furthermore, we analyzed urine samples from both mice and humans to explore the metabolites that predict the presence of TLSs.

Results: Significant accumulation of glutathione was observed specifically within TLSs and the kidneys with TLSs exhibited higher glutathione concentrations than healthy kidneys. Compared to other organs, the kidney contained more cysteine/cystine, the crucial substrates for glutathione synthesis. TLSs also displayed significant accumulation of 4-HNE and 8-OHdG, prominent markers of oxidative stress. Dendritic cells and fibroblasts within TLSs selectively express xCT, an inducible cystine transporter that governs the rate limiting step of glutathione synthesis. Pharmacological inhibition of xCT prevented TLS formation with enhanced cell death and oxidized lipid accumulation that promotes ferroptosis. Furthermore, urinary metabolite profiles significantly differed depending on the presence of TLSs both in mice and humans. In patients with IgA nephropathy, urinary metabolite profiles effectively detected TLSs in the kidney by multivariate logistic regression analysis.

Conclusions: Glutathione accumulation is a distinctive metabolic signature of TLSs in the kidney. Glutathione synthesis plays a pivotal role in TLS formation, acting as a resilience mechanism to oxidative stress and ferroptosis. Urinary metabolite profiles hold important clinical promise to identify TLSs in the kidney.

Funding: Government Support - Non-U.S.

FR-PO1181

Absence of Lymphoid Cells May Aggravate Macrophage-Mediated Kidney Injury but Improve Repair in Immunodeficient Mouse Model of Adenine-Induced CKD

Federica Petrillo,[1] Shrikant R. Mulay,[1] Kevin Woollard,[1] Lorraine Miller,[1] Tajana Tesan Tomic,[2] Magnus Soderberg,[2] Aurelie Thomas,[1] Pernille B. Laerkegaard Hansen,[2] Matthew S. Dearman,[1] Stephanie Ling.[1] Early CVRM Renal Bioscience, AstraZeneca R&D. *[1]AstraZeneca R&D Cambridge, Cambridge, United Kingdom; [2]AstraZeneca R&D Gothenburg, Molndal, Sweden.*

Background: Myeloid and lymphoid subpopulations have shown to be both protective and mediators of kidney injury. Mechanisms of crosstalk between pro- and anti-inflammatory actions of these effector cells is still unclear.

Methods: NSG mice *(NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ)* are deficient in mature lymphocytes, in natural killer cell cytotoxic activity and in cytokine signalling. In the current study we established a novel NSG mouse model of kidney injury by inducing renal failure through dietary delivery of 0.15% adenine for 7 days, compared to C57BL/6N mice and examined response to recovery by removing adenine diet for 14 days. We used Image Mass Cytometry to label 34 markers of immune cell kidney network and kidney injury pattern in adenine versus controls in NSG mice.

Results: CKD was induced in NSG and C57BL/6N mice by feeding 0.15% adenine diet. NSG-CKD mice showed 12% and 17% weight-loss (WL) after 3 and 6 days, respectively, while C57BL/6N-CKD mice showed 10% WL after 7 days. Blood Urea Nitrogen (BUN) and plasma Creatinine were increased 2-fold in NSG-CKD than C57BL/6N-CKD mice with a considerable amount of urinary excreted kidney injury markers, KIM-1 and NGAL after 4 days of treatment. NSG-CKD mice showed downregulation of epithelial markers (Megalin, SGLT2, GLUT-1, NKCC2, E-Cadherin) and upregulated markers of fibrosis (αSMA, Collagen I, Vimentin) that was not seen in C57BL/6N-CKD mice. Immune profile of NSG-CKD mice revealed increased macrophage-based inflammation with upregulated F4/80, CD45, CD11b, CD206, and loss of innate and adaptive lymphocytes immune response, CD4 and MHCII. This suggests that lack of lymphoid cells in NSG mice leads to a perpetual recruitment of macrophage cells and a worsening damage to the kidney in CKD. Interestingly, unlike C57BL/6N-CKD mice, removing adenine diet after 4 days in NSG-CKD mice completely recovered kidney function (BUN, NGAL, KIM-1) at 14 days. More work is underway to phenotype lymphoid subpopulations which may aggravate injury but boost repair during recovery in adenine-induced CKD.

Conclusions: This data highlights the need to unravel the dichotomy of inflammatory actions of lymphoid subpopulations, as T-regulatory and cytotoxic T-cells in CKD.

FR-PO1182

LYVE1 Ectodomain Shedding Promotes Renal Interstitial Retention of Macrophages Cleared by Lymphatic Vessels and Kidney Fibrosis

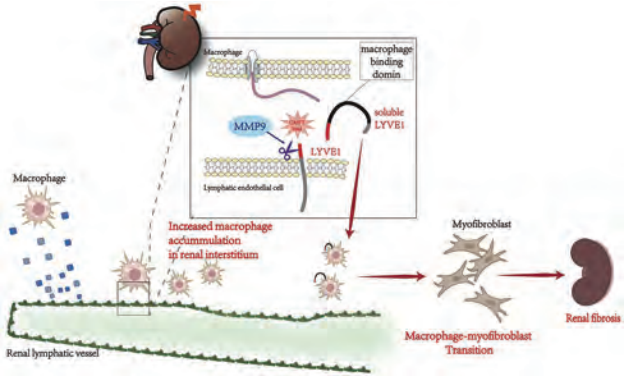
Jing Liu, Chen Yu. *Tongji Hospital Affiliated to Tongji University, Shanghai, China.*

Background: Macrophage accumulation has been associated with the progression of renal fibrosis. However, most previous studies have focused on the recruitment of macrophages while neglecting their efflux. Lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) has a macrophage-binding domain at the extracellular site, which mediates macrophage adhesion and subsequent translocation in lymphatic vessels (LVs). However, it is unknown whether LYVE1 is altered in renal disease and whether it thereby mediates changes in macrophage trafficking.

Methods: Models of ureteral obstruction (UUO), ischemia/reperfusion (I/R), folic acid (FA)-induced renal fibrosis models were created for in vivo experiments and human lymphatic endothelial cell (hLEC) line was used for in vitro experiments.

Results: First, we found that macrophages were significantly recruited and clustered around LVs in the mouse fibrosis models. We further showed that in renal fibrosis models and TGF-β1-cultured hLECs, LYVE1 shed its extracellular domain on LECs and therefore lost its macrophage-binding domain, thus hindering macrophage adhesion to LECs. Meanwhile, LYVE1 shedding fragments were shown to mediate macrophage-to-myofibroblast transition (MMT) to promote fibrosis. Mechanistically, elevated MMP9 mediated LYVE1 ectodomain shedding, resulting in the loss of sites for macrophage binding. The use of chemical shedding inhibitors or MMP9 targeting siRNA attenuated LYVE1 shedding, restored macrophages trafficking and alleviated renal fibrosis.

Conclusions: LYVE1 shedding is tightly associated with progression of renal fibrosis, whereas inhibition of LYVE1 shedding is capable of ameliorating macrophage aggregation and MMT to attenuate disease progression.



Schematic graph

FR-PO1183

Identification the Classification and Heterogeneity of Lymphatic Endothelial Cells, and Their Role in Mice with Kidney Fibrosis via Single-Cell RNA Sequencing Analysis

Zheng Wang, Rui Zeng, Gang Xu, Ying Yao. *Huazhong University of Science and Technology Tongji Medical College Tongji Hospital, Wuhan, China.*

Background: We previously found that knockdown of lymphatic endothelial cells (LECs) delayed the progression of chronic kidney disease. However, due to the relatively low abundance of LECs, little is known about their classification and the heterogeneity in renal inflammation and subsequent fibrosis.

Methods: We established a unilateral ureteral obstruction (UUO) model of mouse and isolated CD31+LYVE-1+ cells using CD31 magnetic bead enrichment and LYVE-1 flow sorting. We employed single-cell RNA sequencing to analyze the heterogeneity of LECs in mice with renal fibrosis. In order to selectively suppress proliferating lymphatic vessels, LYVE-1-TK transgenic mice were constructed.

Results: LECs are classified into three types, including capillary lymphatic endothelial cells (Cap.LECs), pre-collecting lymphatic endothelial cells (Pre-col.LECs) and collecting lymphatic endothelial cells (Col.LECs). Single-cell sequencing analysis showed that Cap.LECs are characterized to participate in cell adhesion, angiogenesis and metal ion transport. Pre-col.LECs are primarily associated with ERK and WNT signaling as well as anion transport. Col.LECs are mainly focused on the regulation of antigen presentation, lipid transport, and immune cell migration. After UUO, all three types of renal LECs shows significant proliferation, and the activity of lymphangiogenesis related transcription factors, proliferation related genes, and lymphangiogenesis related receptors were upregulated. Pseudotime trajectory analysis showed that Pre-col.LECs had strong stem cell characteristics, and both Cap.LECs and Col.LECs were directly derived from the Pre-col.LECs. In the UUO group, the expression of the APP protein, secreted specifically by Pre-col.LECs and Col.LECs, was found to be upregulated. This protein interacts with the CD74 receptor expressed by NK cells and T cells, chemotactically attracting these cells and influencing their function. Knockdown of proliferative lymphatic vessels significantly reduced the number of Pre-col.LECs and Col.LECs in the UUO kidney, resulting in a significant decrease in the populations of T cells and NK T cells, thereby improving the inflammatory microenvironment and fibrosis.

Conclusions: These findings provide a theoretical basis for future interventions targeting lymphangiogenesis in kidney diseases.

FR-PO1184

PCK1 Plays a Central Role in the Control of Metabolic and Mitochondrial Activities in Renal Tubular Cells

Delal Dalga,[1] Thomas Verissimo,[1] Anna Faivre,[1,2] Sophie M. De Seigneux.[1,2] *[1]Universite de Geneve Faculte de Medecine, Geneve, Switzerland; [2]Hopitaux Universitaires Geneve, Geneve, Switzerland.*

Background: During chronic kidney disease (CKD), renal gluconeogenesis is impaired, leading to metabolic dysfunction. Among the enzymes involved in gluconeogenesis, Phosphoenolpyruvate Carboxykinase 1 (PCK1), which facilitates the conversion of oxaloacetate to phosphoenolpyruvate, is rate-limiting. In this study, we hypothesize that the alteration of PCK1 expression in kidney proximal cells contributes to metabolic alterations during CKD and renal dysfunction, through modifications of acid-base balance and cataplerosis.

Methods: Using kidney tubular-specific knockout (KO) and knockin (KI) PCK1 mice models, we assessed the influence of PCK1 expression changes on renal function and kidney metabolism under physiological and pathological conditions. We utilized models of AKI (ischemia) and CKD (proteinuria and platinum toxicity).

Results: Under physiological conditions, PCK1 deletion leads to a loss of renal function and hyperchloremic metabolic acidosis. PCK1 inhibition also induces significant alterations in mitochondrial structure and function, as evidenced by Seahorse analysis and electron microscopy. Additionally, metabolomic analysis revealed that the loss of PCK1 results in decreased cataplerosis, leading to the accumulation of TCA cycle intermediates such as fumarate and malate in the kidney, thereby impeding the TCA cycle. In models of AKI and non-diabetic CKD, PCK1 deletion exacerbated renal dysfunction and mortality. Conversely, in two models of non-diabetic CKD, restoration of PCK1 in kidney tubular cells improved renal function, reduced tubular injury, and slowed fibrosis progression. Similarly, PCK1 restoration mitigated mitochondrial damage by promoting TCA cataplerosis.

Conclusions: PCK1 is essential for maintaining renal tubular acid-base balance, mitochondrial energy production, and TCA cataplerosis. Restoring PCK1 could be a crucial target for preventing mitochondrial dysfunction and the progression of kidney disease during CKD.

FR-PO1185

Knockdown of Translocator Protein (TSPO) Slows AKI to CKD Transition through Regulating Mitochondrial Dysfunction

Yuchen Feng, Wai Han Yiu, Jingyuan Ma, Kar Neng Lai, Sydney Tang. *The University of Hong Kong, Hong Kong, Hong Kong.*

Background: Acute kidney injury (AKI) has been widely recognized as an important risk factor for the occurrence and development of chronic kidney disease (CKD). Emerging studies suggest that mitochondrial dysfunction is a pivotal contributor to the transition from AKI to CKD. Translocator protein (TSPO), located on the outer mitochondrial membrane, is associated with kidney tubular cell death and regeneration in AKI. However, the role of TSPO in AKI to CKD transition remains unknown.

Methods: Kidney tubule-specific TSPO knockout (Tubule-TSPO-/-) mice were created by crossing TSPO floxed (TSPOflox/flox) mice on a C57BL/6J background with tamoxifen inducible Ksp-CreERT2 mice. Unilateral ischemia-reperfusion injury (uIRI) for different timepoints was performed on both Tubule-TSPO-/- and TSPOflox/flox wildtype mice to establish AKI to CKD transition. Kidneys were harvested for histology, inflammation, fibrosis and mitochondrial function measurements.

Results: Both TSPO mRNA and protein levels were increased at day 1 and lasted for at least 14 days after uIRI. Histopathologically, uIRI-induced tubular damage was reversed by knockdown of TSPO at day 7 and day 14. Induction of fibronectin, Col-1, TNF-α, CCL-2 and IL-1β mRNA in the uIRI kidney was reduced in knockout mice compared to control. In 14 day-uIRI mice, immunohistochemical analysis further confirmed significant reduction of Col-1 and Col-3 expression by TSPO depletion. Furthermore, PGC1-α, the master regulator of mitochondrial function, was significantly increased after knockdown of TSPO. Electron microscopy demonstrated a higher number of mitochondria and improved mitochondrial morphology with TSPO depletion. Reduction of mitochondrial DNA copy number by uIRI was also reversed by knockdown of TSPO.

Conclusions: Knockdown of TSPO in tubular cells could alleviate kidney inflammation and fibrosis in murine uIRI models, increase mitochondrial number and restore mitochondrial structure. The results suggested that TSPO could play an important role in regulating mitochondrial function during AKI to CKD transition progress. Funding: Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 09202356); Hong Kong Society of Nephrology Research Grant 2022

FR-PO1186

Metabolic Landscape of Naturally Occurring CKD in Cats: An Integrated Multiomics Study

Qinghong Li,[1] Ornella Cominetti,[3] Eugenia Migliavacca,[3] James Holzwarth,[3] Sonia Karaz,[3] Mathieu Membrez,[3] Charlotte Macron,[3] Marie-Claude Courtet-Compondu,[3] Stacie Summers,[2] Vincenzo Sorrentino,[4] Loïc Dayon.[3] *[1]Nestle Purina PetCare Co, Saint Louis, MO; [2]Oregon State University, Corvallis, OR; [3]Nestle Research, Lausanne, Swaziland; [4]National University of Singapore, Singapore, Singapore.*

Background: Human and feline CKD shares similar pathophysiology, including chronic tubulointerstitial inflammation and fibrosis. The underlying mechanisms for both diseases are incompletely understood. This study outlined our first step towards creating a metabolic atlas of feline CKD.

Methods: Cats diagnosed with CKD were staged according to the International Renal Interest Society guidelines. Targeted and untargeted metabolomics was performed on serum samples. Transcriptomics and proteomics were performed on cortical and medullar tissues from cats euthanized for humane reasons unrelated to the study. Linear model was applied for data analysis with false discovery rate (FDR)<0.05 for differential metabolites and genes, and FDR<0.15 for differential proteins between groups.

Results: Serum concentrations of free fatty acids, 3-hydroxy fatty acids, and acylcarnitines were elevated, while renal RNA and protein expressions of enzymes for fatty acid transport and oxidation were downregulated in CKD cats compared to control cats. Tissue protein expressions of several glycolytic enzymes were increased but decreased for gluconeogenic enzymes in CKD cats. While the levels of oxidized glutathione, glutamine and several Krebs cycle intermediates accumulated in the circulation, tissue RNA and protein expressions of enzymes involved in glutathione biosynthesis, glutaminolysis, Krebs cycle, ketolysis, and NAD+ biosynthesis were reduced in CKD cats compared to control cats. Further, tissue gene expressions of profibrotic (TGFβ1, CTGF, GAL3, α-SMA, FN1, LOX) and proinflammatory (IL11, IL16, TNF) markers, and hypoxia inducible factor HIF1A were upregulated, while gene expressions of anti-fibrotic klotho and hypoxia inhibitors (FIH1, PHD2) were downregulated in CKD cats vs control cats. Finally, targeted metabolomics revealed elevated circulating uremic toxins, including TMAO, indoxyl sulfate, p-cresol sulfate, phenol sulfate, while RNA expressions of renal tubular transporters OAT1, OATP4C1 and ABCC2 were downregulated in cats with CKD.

Conclusions: Our study unveiled extensive abnormalities and readaptations in bioenergetics, impaired redox homeostasis and uremic toxin excretion, and increased inflammation, fibrosis, and hypoxia in cats with CKD.

Funding: Commercial Support - Nestle Purina PetCare Company

FR-PO1187

Plasma Calciprotein Particles and Calcification Propensity in Cats with CKD Stabilized on a Phosphate-Restricted Diet

Pak Kan Tang,[1] Makoto Kuro-o,[2] Miki Tsuchida,[2] Rebecca Geddes,[3] Rosanne E. Jepson,[3] Yu-Mei Chang,[1] Jonathan Elliott.[1] *[1]The Royal Veterinary College Department of Comparative Biomedical Sciences, London, United Kingdom; [2]Jichi Medical University Center for Molecular Medicine, Shimotsuke, Japan; [3]The Royal Veterinary College Department of Clinical Science and Services, Hatfield, United Kingdom.*

Background: Fetuin-A aggregates with calcium and phosphate ions to form calciprotein monomers, preventing precipitation (low-density calciprotein particles [L-CPP]). Consolidation of L-CPP with further protein leads to amorphous CPP which transform spontaneously into pro-inflammatory crystalline CPP over time (high-density CPP [H-CPP]). The transition time (T50) from amorphous to crystalline CPP indicates the calcification propensity. This study evaluated relationships between CPP levels, T50 and CKD-MBD parameters in cats with azotemic CKD.

Methods: Cross-sectional study: Frozen heparinized fasted plasma samples from cats with naturally occurring CKD stabilized on a phosphate-restricted diet (forming ≥50% of diet consumed) were retrospectively identified for CPP and calcification propensity (T50) assessment. Total CPP (T-CPP), L-CPP and H-CPP were measured by an infrared fluorescent bisphosphonate (OsteoSense), in conjunction with gel filtration. Associations between CPP, T50 and CKD-MBD parameters were evaluated by Spearman or Pearson correlations and linear regression models.

Results: 38 euthyroid client-owned cats with International Renal Interest Society (IRIS) stage 2–3 azotemic CKD were enrolled. Moderate negative correlations were found between T-CPP, L-CPP and H-CPP with T50 (**Table 1**). FGF-23 correlated positively with T-CPP, L-CPP (**Table 1**) and total calcium (r=0.41; *P*=0.011), and negatively with T50 (r=-0.44; *P*=0.006) and total magnesium (r=-0.42; *P*=0.011). FGF-23 was a significant predictor of T-CPP and L-CPP.

Conclusions: Plasma FGF-23 was a major determinant of T-CPP and L-CPP in fasted samples obtained from CKD cats stabilized on restricted phosphate diets. Comparable findings were reported in human patients with CKD, suggesting a similar relationship between FGF-23 and CPP in both species. Like humans, cats spontaneously develop CKD and FGF-23 is predictive of progression, therefore, studying cats could provide additional insights into the pathophysiology underlying CPP and CKD progression for humans.

Funding: Commercial Support - Royal Canin SAS

	T-CPP	L-CPP	H-CPP
T50	**r_s = -0.5; p = 0.001**	**r_s = -0.42; p = 0.009**	**r_s = -0.49; p = 0.002**
Total calcium (tCa)	r_s = 0.07; p = 0.67	r_s = 0.09; p = 0.58	r_s = -0.03; p = 0.841
Ionized calcium (iCa)	r_s = -0.04; p = 0.834	r_s = 0.05; p = 0.791	r_s = -0.07; p = 0.699
Phosphate	r_s = 0.15; p = 0.363	r_s = 0.12; p = 0.489	r_s = -0.02; p = 0.9
Calcium-phosphate product (CaPP)	r_s = 0.15; p = 0.374	r_s = 0.11; p = 0.526	r_s = 0.01; p = 0.967
Creatinine	r_s = 0.17; p = 0.318	r_s = 0.21; p = 0.211	r_s = 0.08; p = 0.613
Total magnesium	r_s = -0.01; p = 0.971	r_s = -0.04; p = 0.833	r_s = -0.02; p = 0.901
Fibroblast growth factor-23 (FGF-23)	**r_s = 0.45; p = 0.006**	**r_s = 0.46; p = 0.005**	r_s = 0.16; p = 0.345

Table 1. Spearman (r_s) correlation between the different forms of calciprotein particles (CPP) and T50 and various CKD-MBD parameters in cats with CKD.

FR-PO1188

Sirtuin 3 Promotes Renal Gluconeogenesis in Fibrotic Kidneys

Pinglan Lin, Ming Wu. *Department of Nephrology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China.*

Background: Decreased renal gluconeogenesis is currently identified as a hallmark of chronic kidney disease, which may contribute to renal fibrosis. Sirt3 is a crucial metabolic sensor that regulates ATP generation, mitochondrial adaptive response to stress, and glucose metabolism. Sirt3 is renal protective in fibrotic kidneys, however its underlying mechanisms is not completely known.

Methods: Sirt3 inhibitor (3-TYP) was used to evaluate the effect of Sirt3 on renal fibrosis and renal gluconeogenesis in UUO mice. The effect of Sirt3 on proximal tubular cells was evaluated in *in vitro*, *ex vivo* and *in vivo* models of renal fibrosis. Mechanistically, the effect of Sirt3 on metabolic transcription factors FOXO1 was evaluated. Finally, pharmaceutical activation of Sirt3 by its agonist HKL on renal gluconeogenesis and systemic glucose metabolism was assessed in *in vivo* model.

Results: Decreased sirt3 expression was accompanied by reduced expression of gluconeogenesis rate-limiting enzymes (PCK1, FBP1) in UUO kidneys. Sirt3 is co-localized with PCK1 and FBP1 expression in proximal tubular cells of fibrotic kidneys. Sirt3 adenovirus alleviated renal fibrosis and improved the glucose homeostasis *in vitro*, *ex vivo* and *in vivo* models of renal fibrosis. Furthermore, Sirt3 agonist or overexpressed of sirt3 by adenovirus improved gluconeogenesis through activation of metabolic transcription factor FOXO1 and PGC-1α in *in vitro* and *ex vivo* models. A direct

interaction between FOXO1 and Sirt3 was revealed through co-immunoprecipitation experiment by using primary kidney tubular cells. FOXO1 inhibitor abolished the pro-gluconeogenic effect of Sirt3 agonist in fibrotic renal cells. Pharmaceutical activation of Sirt3 improved renal gluconeogenesis and systemic glucose metabolism in UUO mice.

Conclusions: Sirt 3 promotes renal gluconeogenesis in proximal tubular cells of fibrotic kidneys through direct interaction and up-regulation of FOXO1. Pharmaceutical activation of Sirt3 could be a new strategy to improve glucose metabolism in chronic kidney disease patients.

Funding: Government Support - Non-U.S.

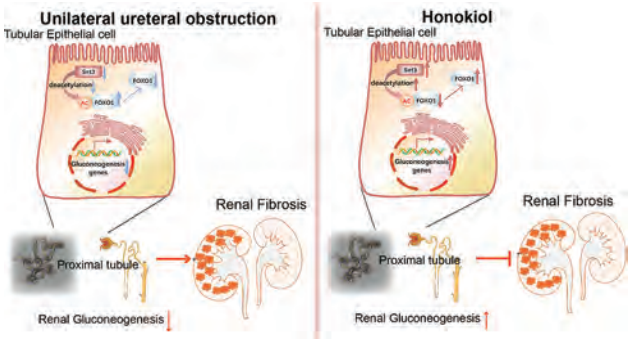


Diagram depicts SIRT3 regulating gluconeogenesis in renal fibrosis

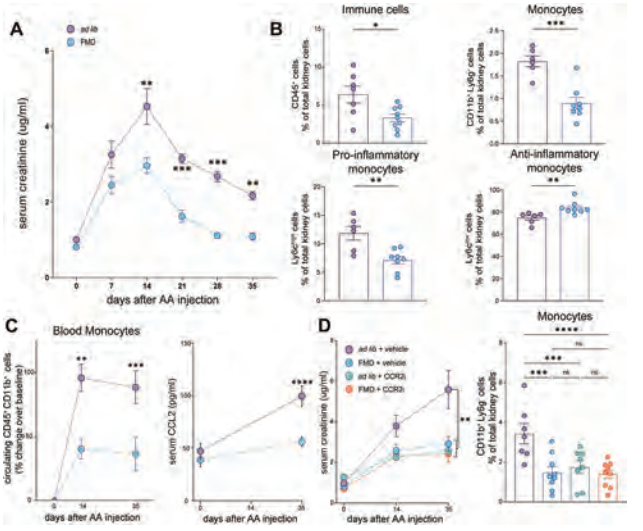


Figure 1: FMD reduces renal damage and kidney monocyte infiltrates inhibiting CCL2/CCR2 axis.

FR-PO1189

Less Is More: Protective Effects of Caloric Restriction on Acute and Chronic Kidney Injury

Paolo Molinari,[1,2] Alberto Verlato,[2] Johan Noble,[2] Sara Alibrandi,[2] Carlo Alfieri,[1] Giuseppe Castellano,[1] Paolo Cravedi.[2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Acute kidney injury (AKI) leads to an high risk of progression to chronic kidney disease (CKD). Monocytes are crucial in renal injury pathogenesis, and caloric restriction appears to inhibit the CCL2/CCR2 axis and monocyte recruitment. Thus, we hypothesized that caloric restriction via a fasting-mimicking diet (FMD) reduces both acute and chronic kidney injury.

Methods: We compared the effects of FMD (5 days of caloric restriction and 2 days of ad libitum (*ad lib*)) vs. *ad lib* diet on the severity of aristolochic acid (AA)-induced AKI and kidney recovery in BALB/c male mice. Samples were collected after 2 days of normal diet in FMD mice.

Results: At 14 (AKI phase) and 35 (CKD phase) days post-injury, serum creatinine levels were significantly lower in mice on FMD **(Figure 1A)**. Importantly, the protective effects of FMD on CKD were present also when FMD was started at the peak of AKI severity (14 days). Overall, kidney infiltrating monocytes were reduced in FMD mice both at 14 and 35 days. Especially during transition from AKI to CKD (35 days), kidney monocyte infiltrates were markedly reduced by FMD, showing a clear shift towards Ly6c^{low} anti-inflammatory monocytes **(Figure 1B)**. FMD markedly inhibited CCL2/CCR2 axis, leading to lower serum CCL2 levels and lower monocyte recruitment throughout kidney damage progression **(Figure 1C)**. In the presence of a selective CCR2 inhibitor, FMD had no additional effects on kidney function, monocyte recruitment and infiltrating kidney monocytes indicating the key involvement of CCL2/CCR2 signaling in FMD's mechanism of action **(Figure 1D)**.

Conclusions: FMD appears to mitigate acute and chronic kidney injury by decreasing CCL2-mediated recruitment of pro-inflammatory monocytes in the kidney.

Funding: NIDDK Support

FR-PO1190

Effects of Bariatric Weight Loss on Inflammatory Protein Signatures and Shear Elastographic Evidence of Kidney Injury in Obesity

Clara L. Ngoh,[1,2] Boon Wee Teo,[1,2] Asim Shabbir,[1,2] Jorming Goh,[2] Horng-Ruey Chua.[1,2] The ELASTO Study Group. *[1]National University Hospital, Singapore, Singapore; [2]National University of Singapore, Singapore, Singapore.*

Background: Bariatric surgery represents a unique human model of accelerated metabolic optimization. Preclinical models have demonstrated improvements in inflammatory correlates of kidney injury after weight loss, although mechanisms in humans are poorly elucidated without kidney biopsies. We detected substantive improvements in estimated glomerular filtration rate (eGFR) in obese patients with CKD, following bariatric surgery. While this suggests attenuated kidney injury with reduced adiposity, creatinine-based eGFR is confounded by lean muscle loss. Novel kidney imaging by shear wave elastography bridges these gaps by quantifying kidney parenchymal stiffness non-invasively.

Methods: We studied 50 CKD patients with obesity planned for bariatric surgery. Shear wave elastography (Axiplorer, Hologic) and inflammatory biomarkers (Olink proteomic assays) were sampled at baseline and 6 months post-surgery. Kidney shear wave scans were performed by 2 independent investigators. The average of 12 measurements was taken.

Results: Absolute GFR demonstrated resolution of hyperfiltration 6 months after bariatric surgery (139 versus 103 ml/min, P =0.005). Despite initial high glomerular filtration rates, baseline kidney stiffness by shear wave elastography pre-surgery was 26.1 ± 6.2 kPa, levels of which based on our previous work, should correlate with CKD stage 3. Kidney stiffness improved 1 year-post surgery to 13.1 ± 6.2 kPa (P =0.008). This correlated with improvements in body mass indices from 40.2 ± 11.2 kg/m^2 (baseline) to 26.8 ± 12.5 kg/m^2 (post-surgery). 276 plasma proteins were sampled. At 1-year post-surgery, 17 protein biomarkers showed decreased expression, in particular CUB-domain containing protein (CDCP1) and Delta/notch-Like EGF repeat (DNER) (All P <0.0001). Conversely, 3 proteins: Fibroblast growth factor-19 (FGF-19), Chemokine ligand-9 (CXCL9), Chemokine ligand-23 (CCL23) showed increased expression (All P <0.05).

Conclusions: By demonstrating kidney stiffness reversal in parallel with reduction in systemic inflammation following bariatric surgery-induced weight loss, this study advocates for intensive weight loss as a means of attenuating CKD progression. Novel serum and elastographic imaging biomarkers hold potential to surpass traditional eGFR in assessment of metabolic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO1191

Alleviating Obesity-Related Kidney Injury with Polyethylene Glycol-Capped Ceria-Zirconia Nanoparticles by Enhancing Autophagy Flux

Eun Kyung Kim, YunSeok Choi, Daun Song, Won Min Hwang, Sung-Ro Yun, Yohan Park, Se-Hee Yoon. Div of Nephrology and Dept of Internal Medicine, Myunggok Medical Research Institute. *Konyang University College of Medicine, Daejeon, Republic of Korea*.

Background: Obesity poses a significant contemporary health challenge, contributing to a range of complications. The underlying mechanisms remain incompletely understood, with obesity often triggering various pathological signals, such as lipotoxicity. Despite the considerable efforts by individuals to lose weight, achieving this goal is challenging. Polyethylene glycol-capped ceria-zirconia nanoparticles (PEG-CZNPs) have garnered attention for their antioxidant properties and their ability to restore autophagy flux. In this study, we investigated the protective effect of PEG-CZNPs against obesity-induced kidney injury.

Methods: An in vitro model of obesity was established using palmitate in HK-2 cells. The change in lipid droplet deposition, reactive oxygen species (ROS), inflammation, and autophagy flux were evaluated using the oil-red O assay, western blotting, polymerase chain reaction, and immunofluorescence assays. An in vivo model of obesity was induced in mice through a high-fat diet. Biochemical analysis, histological stains, and immunohistochemistry were performed on the liver, kidney, and adipose tissue of the obese mice at 12 weeks after initiating the high-fat diet.

Results: PEG-CZNPs successfully reduced lipid droplet deposition in HK-2 cells exposed to palmitate by restoring autophagy flux dysfunction. ROS, inflammation, and fibrotic change caused by palmitate were also improved by PEG-CZNPs treatment. PEG-CZNPs attenuated glucose intolerance and serum cholesterol levels in animal models of obesity. Additionally, PEG-CZNPs notably decreased cellular lipid droplet deposition.

Conclusions: PEG-CZNPs alleviated obesity-induced kidney injury by reducing inflammation and oxidative stress and by decreasing organ lipid deposition through the restoration of autophagy flux function.

Funding: Government Support - Non-U.S.

FR-PO1192

Six Months of High-Fat Diet and Physical Inactivity in Thermoneutrality Are Insufficient to Cause CKD in Mice

Precious C. Opurum, Stephen Decker, Deborah Stuart, Alek D. Peterlin, Venisia L. Paula, Alejandro Sanchez, Nirupama Ramkumar, Katsuhiko Funai. *University of Utah Health, Salt Lake City, UT*.

Background: Chronic kidney disease (CKD) is a progressive disorder marked by a decline in kidney function. The process by which obesity and sedentary behavior contribute to the development of CKD is poorly understood. Studies suggest a decline in mitochondrial function likely contributes to the pathogenesis of CKD, but the detailed mechanisms remain unclear. This knowledge gap is contributed to by a lack of a murine CKD model that does not rely on injury, toxin, or gene deletion to induce reduced kidney function.

Methods: Here, we employed a recently published model of sedentariness developed in our lab, which phenocopies many of the systemic metabolic adaptations that occur in human sedentary behavior. Wildtype C57BL/6J male mice housed under ambient (22°C) or thermoneutral conditions (29°C) were fed standard chow or Western high-fat diet (HFD) with or without small mice cage (SMC) intervention for 6 months.

Results: However, while HFD or SMC tended to increase the glomerular filtration rate (GFR), these interventions were insufficient to cause CKD. Histological and gene expression data suggested a potential early onset of fibrosis programming, but the magnitudes of these changes were minor. High-resolution respirometry and fluorometry experiments showed increases in mitochondrial respiration and ATP synthesis capacities, also likely demonstrating early adaptive responses to heightened kidney burden.

Conclusions: Given the long duration of the intervention, these data reinforce the technical challenge associated with modeling CKD in mice. They also suggest that metabolic pressures caused by obesogenic diet and/or sedentariness may be insufficient to robustly negatively influence kidney function.

Funding: NIDDK Support

FR-PO1193

The Golgi Apparatus-Hosted ATP7A-Fibulin-4 Complex Mediates Activation of LOX to Promote Kidney Fibrosis

Wenqian Zhou, Chen Yu. *Tongji Hospital Affiliated to Tongji University, Shanghai, China*.

Background: Lysyl oxidase (LOX) is a copper-dependent monoamine oxidase whose primary function is the covalent cross-linking of collagen and elastin in extracellular matrix (ECM), however, the regulation of LOX activity in renal fibrosis is not well understood.

Methods: To explore the relationship between cellular copper overload and LOX activity, we employed copper chelator tetrathiomolybdate and implemented specific knockdown of copper transporter1 (CTR1) both in vivo and in vitro. Subsequently, we evaluated LOX activity and activated LOX expression by LOX assay kit and western blot. The specific regulatory mechanism of LOX activity was elucidated by knocking-down expression of ATPase copper transporting alpha (ATP7A) and Fibulin-4 (FBLN4) in vitro or in vivo.

Results: 1) Expression of LOX and extracellular matrix (ECM) cross-linking were markedly increased in fibrotic kidneys of ischemia/reperfusion (IR) induced renal fibrosis model. Treatment with tetrathiomolybdate or the knockdown of CTR1 resulted in a reduction in copper levels, leading to decrease LOX activity and ameliorated renal fibrosis. 2) The upregulation of ATP7A expression increased copper levels in the Golgi apparatus of renal tubular epithelial cells, resulting in enhanced LOX activity and ECM crosslinking, thereby promoting the progression of renal fibrosis. 3) FBLN4 was essential for ATP7A-transfering copper to LOX and formed a ternary complex of ATP7A-FBLN4-LOX in renal tubular epithelial cells.

Conclusions: Our results suggest that the ATP7A-FBLN4 complex facilitates the aberrant accmulation of copper in the Golgi apparatuses, thereby promoting the activation of LOX to catalyze ECM cross-linking and contribute to the progression of renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO1194

Trim21 Alleviates Renal Tubulointerstitial Fibrosis by Mediating Loxl2 Ubiquitination Modification and Degradation

Hanlu Jiang, Chunsun Dai. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China*.

Background: Extracellular matrix (ECM) accumulation is closely associated with renal interstitial fibrosis. However, its mechanisms is largely unknown. Tripartite motif 21 (Trim21), as a member of the TRIM family, has been demonstrated to be an E3 ubiquitin ligase. The involvement of Trim21 in immunity, inflammation, antiviral response and tumorigenesis has been documented. However, whether Trim21 involved the occurrence and development of renal interstitial fibrosis is unclear. This study aimed to investigate the role and mechanism of Trim21 in renal tubulointerstitial fibrosis.

Methods: Renal tubule-specific knockout Trim21 mice were constructed, and unilateral ureteral obstruction (UUO) and ischemic reperfusion injury (IRI) were conducted to induce renal interstitial fibrosis. In vitro Trim21 overexpression plasmid or siRNA were used to disrupt Trim21 expression in cultured primary renal tubular epithelial cells, and then treated with transforming growth factor β1 (TGFβ1) for induce ECM production.

Results: We first found that Trim21 mRNA and protein levels were elevated in kidney of CKD patients and UUO and IRI-induced renal interstitial fibrosis model. Moreover, knockout of Trim21 in tubular cell significantly exacerbated renal interstitial fibrosis induced by UUO and IRI. In primary renal tubular epithelial cells, silencing Trim21 upregulated lysyl oxidase-like protein 2 (Loxl2) and extracellular matrix deposition by inhibiting ubiquitination modification and degradation of Loxl2, while overexpression was the opposite. Immunoprecipitation experiments showed that PRY/SPRY domain of Trim21 interacted with amino-terminal of Loxl2.

Conclusions: In summary, Trim21 directly interacts with Loxl2 through the PRY/SPRY domain, promotes ubiquitination modification and degradation of Loxl2, inhibits extracellular matrix production and attenuates renal fibrosis. Therefore, Trim21 plays an essential role in Loxl2 regulated ECM deposition and may be a viable target for treating chronic kidney diseases.

Funding: Government Support - Non-U.S.

FR-PO1195

Dietary Sodium Modulates mTORC1-Dependent Trained Immunity in Macrophages to Accelerate AKI to CKD Transition

Guochun Chen, Jie Song, Li Zeng. *The Second Xiangya Hospital of Central South University, Changsha, China*.

Background: Chronic Kidney Disease (CKD) constitutes a substantial global health concern, with its etiology closely associated with dietary patterns, particularly elevated salt consumption, and recurrent infections that precipitate the transition from Acute Kidney Injury (AKI) to CKD. However, the mechanistic pathways underpinning this progression have yet to be fully elucidated.

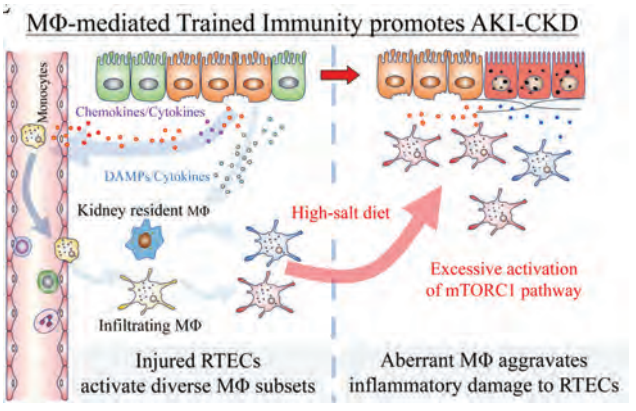
Methods: Flow cytometry,RT PCR,ELISA,Western blot analysis, renal histological analysis, immunofluorescent and immunohistochemical staining were performed to measure the inflammatory response of macrophages in AKI to CKD and how high-salt diet aggravates this response by modulating mTORC1 pathway.

Results: Analysis shows elevated CD45+F4/80+ macrophage infiltration and inflammatory cytokine production under high-salt conditions. Distinct responses were observed between circulating and resident renal macrophages to a high-salt diet, with a notable upsurge in the migration of pro-inflammatory macrophages, driven by CCL2-CCR2 signaling and aberrant mTORC1 pathway activation. Treatment with

rapamycin-liposome effectively reduced this inflammatory cascade by mitigating mTORC1 signaling. Transplantation of monocytes from CKD mice with a high-salt diet significantly exacerbates renal inflammatory damage in the host mice, showing increased migratory tendency and inflammatory activity. The cell co-culture experiment further confirmed that macrophages derived from CKD mice, particularly those under conditions of high salt exposure, significantly induced apoptosis and inflammatory responses in renal tubular cells.

Conclusions: Recurrent exposure to LPS elicits the activation of trained immunity, consequently augmenting inflammatory response of monocytes/macrophages in the involved kidneys. The high-salt diet exacerbates this phenomenon, attributable at least in part to the overactivation of the mTORC1 pathway.

Funding: Government Support - Non-U.S.



FR-PO1196

Lysine-Specific Demethylase 1A Is a Targetable Kidney Disease Causal Gene

Kolligundla L. Prasanna,[1] Dhanunjay Mukhi,[1] Hongbo Liu,[1,2] Katalin Susztak.[1] Katalin Susztak Group. *[1]University of Pennsylvania, Philadelphia, PA; [2]University of Rochester Medical Center, Rochester, NY.*

Background: Large scale chronic kidney disease genome-wide association study (GWAS) identified more than eight hundred genetic risk loci for kidney dysfunction, however, causal genes, cell types, and targetable pathways remain elusive. In our research, we leveraged human kidney expression and methylation quantitative trait loci (eQTL, meQTL), and single cell open chromatin and gene expression information to prioritized KDM1A (Lysine specific demethylase 1A) on chromosome 1 as a likely causal gene. KDM1A controls genes expression by demethylating histone 3 lysine 4 di-or mono methylation residues.

Methods: We generated kidney-specific KDM1A knockout mice by breeding with KDM1A floxed mice with Six2 cre or Ksp cre mice. We analysed these mice at baseline and following kidney injury by cisplatin or unilateral ureteral obstruction. Kidney function was analyzed by measuring serum creatinine, and blood urea nitrogen, and cystatin C levels, and gene expression by real-time PCR and protein levels by western blotting, and immunohistochemistry. In addition, primary tubule cells were employed and treated with TGFβ1 or ORY-1001, an inhibitor of KDM1A, and analyzed fibrosis markers. Chromatin immunoprecipitation sequencing, single nuclear RNA-seq, and ATAC-seq were applied to find the molecular mechanism.

Results: By applying a comprehensive gene prioritization strategy, we identified that genetic variants on chromosome 1 regulate KDM1A gene expression. RNA and protein expression studies revealed that KDM1A levels were higher in kidney disease patients and animal models. Tubule-specific KDM1A knockout mice were healthy at baseline but showed lower kidney injury in models of acute kidney injury by cisplatin, and chronic fibrosis by UUO. In vitro studies with TGFβ1 treatment showed lower fibrosis markers expression in the presence of ORY-1001 or in KDM1A knockout tubule cells. Inhibition of KDM1A with ORY-1001 in mice also showed protection against UUO-induced kidney fibrosis. Our future studies will investigate the mechanistic role of KDM1A in kidney disease development.

Conclusions: Our studies propose that lysine specific demethylase 1A could be a therapeutic option to combat kidney disease.

Funding: NIDDK Support

FR-PO1197

Critical Role of Lysine-Specific Histone Demethylase 1 in Kidney Inflammation and Fibrosis

Baihai Jiao,[1] Hao Du,[1] Melanie Tran,[1] Yanlin Wang.[1,2] *[1]University of Connecticut School of Medicine, Farmington, CT; [2]VA Connecticut Healthcare System, West Haven, CT.*

Background: Chronic kidney disease is characterized by inflammation and fibrosis. Inflammation often triggers fibrosis, and fibrosis is the end result of chronic inflammatory reactions. Kidney inflammation is characterized by inflammatory cell infiltration and activation leading to inflammatory and fibrotic molecule production. However, there is a critical knowledge gap on molecular mechanisms underlying kidney inflammation and fibrosis. In this study, we evaluated the impact of lysine-specific histone demethylase 1 (LSD1) on kidney inflammation and fibrosis.

Methods: To explore the role of LSD1 in kidney inflammation and fibrosis in vivo, we generated mice with tamoxifen inducible deletion of LSD1 using Cre-LoxP strategy. Unilateral ureteral obstruction (UUO) and ischemia-reperfusion injury (IRI) models were used to induce kidney inflammation and fibrosis. Cultured macrophages were used to examine the role of LSD1 in the regulation of macrophage activation in vitro.

Results: LSD1 expression markedly increased in the kidneys following obstructive or ischemic injury. Mice with a tamoxifen-inducible deletion of LSD1 exhibited no significant morphological abnormalities in the kidney. Compared with Cre negative, floxed LSD1 mice, mice with tamoxifen-induced deletion of LSD1 exhibited fewer α-SMA$^+$ myofibroblasts and expressed less α-SMA protein in the kidneys following UUO or IRI. Inducible deletion of LSD1 significantly ameliorated total collagen deposition and ECM protein production in the kidneys in response to UUO or IRI. Real-time RT-PCR showed that the mRNA expression levels of proinflammatory and profibrotic molecules were significantly increased after UUO or IRI, which were significantly reduced in LSD1 deficient mice. Furthermore, the activity of NF-κB signaling was significantly decreased in LSD1-deficient mice following UUO or IRI. In cultured macrophages, inhibition of LSD1 reduced NF-κB signaling activation and proinflammatory and profibrotic molecule expression.

Conclusions: Our study demonstrates that LSD1 is a key regulator of inflammation and renal fibrosis in chronic kidney disease. Targeting LSD1 could provide a novel therapeutic approach to mitigate kidney inflammation and fibrosis and ameliorate the progression of chronic kidney disease.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

FR-PO1198

The Micropeptide LSMEM1 Attenuates Renal Tubulointerstitial Fibrosis by Reducing Lipid Droplet Accumulation

Peimin Liu, Xiaoyan Bai. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: Chronic Kidney Disease (CKD) is a syndrome defined by persistent changes in kidney structure, function, or both, and today the global burden of CKD is increasing. Regardless of the starting injury or disease, the most common pathological manifestation of CKD is some form of renal fibrosis that eventually progresses to end-stage renal disease (ESRD). Micropeptides are commonly defined as polypeptides with arelatively arbitrary length of less than 100–150 amino acids (aa) in length. Evolving evidence suggests that micropeptides regulate a variety of biological processes, and more and more micro-molecule peptides being discovered as technology develops. In recent years a variety of diseases have detected up-regulation of LSMEM1 which is a micropeptide enriched with 133 amino acids.

Methods: Analysis of renal expression levels of LSMEM1 in CKD patients compared to normal controls using the GEO database and nephroseq database. Though the immunohistochemical staining, the level of LSMEM1 was examined in patients with CKD caused by different diseases. In the vivo, We constructed the LSMEM1-knockout mice followed by unilateral ureteral ligation (UUO) surgery and executed the mice 7 days later. In the vitro, lentivirus was used to silence or over-expression LSMEM1 in HK-2 cells under the TGF-β stimulation. Other testing methods include RNA-seq, ELISA, Colorimetric Assay, Western Bloting, Masson staining, Sirius Red Staining and et al.

Results: Compared to normal controls, LSMEM1 expression is upregulated in CKD kidneys. Animal and cellular experiments showed that LSMEM1 expression levels increased with increasing degrees of fibrosis. Animal experiments showed that renal fibrosis was aggravated in UUO mice after LSMEM1 knockdown compared with the SHAM group. Cellular experiments showed that silencing LSMEM1 elevated the level of fibrosis induced by TGF-β in HK-2 cells and, conversely, overexpression reduced. RNA-seq analysis shows lipid metabolism-related pathways are significantly enriched in the kidney of LSMEM1-KO mice. Knockdown of LSMEM1 caused more severe lipid accumulation in mice and cell, conversely, overexpression attenuated.

Conclusions: Current study suggests the micropeptide LSMEM1 could attenuates renal tubulointerstitial fibrosis by reducing lipid droplet accumulation and may be a therapeutic target in CKD.

FR-PO1199

Characterizing Lipid Metabolism in Diseased Kidneys and Understanding the Impact of Blood Contamination

Kimberly L. Steen, Zhongyuan Sun, Srinath Jagarlapudi, Rose A. Keenan, Simone Romoli, Denis Feliers, Justin Crane. Internal Medicine Research Unit. *Pfizer Inc, Cambridge, MA*.

Background: The kidney exhibits a high bioenergetic flux owing to constitutive filtration and absorption. Dysfunction of proximal tubule metabolism, specifically reduced mitochondrial fatty acid oxidation and increased lipid synthesis, are considered key drivers of chronic kidney disease (CKD) and are recapitulated in CKD mouse models. There are numerous ways to characterize these processes, including lipid profiling, enzyme activities and flux tracing of energy substrates. However, the kidney is enriched by blood, which itself contains lipids and may influence the measurement of endogenous lipids or synthesis byproducts.

Methods: We characterized lipid abundance, mitochondrial markers and kidney functional readouts in two renal disease models: 1) AAV-renin, uninephrectomized db/db mice and 2) mice fed a 0.15% adenine diet for 6 weeks. Lipids were measured by HPLC, mtDNA by qPCR, and mitochondrial enzymes by absorbance kinetic assays. To isolate endogenous kidney lipids from the blood, we compared kidneys from C57BL6 mice with and without systemic PBS perfusion prior to collection. We also compared the effects of perfusion on de novo lipogenesis (DNL) by tracing D2O incorporation into tissue palmitate. All procedures performed on animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional Animal Care and Use Committee or through an ethical review process.

Results: In the db/db Unx Renin mice, we found reduced GFR and mitochondrial content and a significant elevation of plasma cholesterol and cholesterol esters relative to controls. However, we observed no impact on kidney cholesterol or triglyceride levels. Similarly, in the adenine model, we found reduced GFR, mitochondrial content, and kidney cholesterol content. There were no effects of perfusion on kidney triglyceride levels or rates of DNL, yet there was higher free cholesterol in perfused vs. non-perfused kidney.

Conclusions: In two renal disease models we found reduced mitochondrial oxidative capacity, but no elevation in kidney lipids. Moreover, the lack of lipid changes in diseased kidney is unlikely to be due to contamination of kidney lipids by the blood, but further studies are warranted.

Funding: Commercial Support - Pfizer, Inc

FR-PO1200

ECT2-PLXNB2 Signaling Inhibits Ribosome Biogenesis Leading to Kidney Fibrosis

Kaixin Song, Hua Su. *Huazhong University of Science and Technology Tongji Medical College First Clinical College Union Hospital Department of Nephrology, Wuhan, China*.

Background: During kidney fibrosis, the G2/M arrest and senescence of Tubular Epithelial Cells (TECs) are key pathogenic events. Ribosome Biogenesis (RiBi) refers to the assembling of ribosome complex, and RNA Pol1 catalyzing rDNA transcription is essential in RiBi. When RiBi is inhibited, ribosomal proteins RPL5 and RPL11 combine with HDM2 to form an Impaired Ribosome Biogenesis Checkpoint (IRBC) complex, which subsequently results in p53 upregulation. Formerly, it is reported RiBi partakes in senescence, however, whether RiBi is involved in kidney fibrosis is uncovered. It is reported that ECT2 plays important roles in G2/M arrest, aging and fibrosis, however whether ECT2 could regulate RiBi is unknown. Currently, we aim to investigate whether and how ECT2 regulate RiBi during renal fibrosis.

Methods: The UUO and in vitro TGF-β stimuli were utilized to setup fibrosis models. CX5461 was administrated to inhibit rDNA transcription. EU staining was used to detect the synthesis of nascent RNA. Cell proliferation and senescence were observed by CCK8 and SA-β-Gal staining respectively. Besides, RT-qPCR, WB, Masson, IF and multiple IF, Flow cytometry, Co-IP and transcriptome sequencing were used in this study.

Results: In vitro and in vivo, multiple IF and EU staining revealed a significant reduction of nascent RNA during fibrosis, and which was reconfirmed by the decline of 47S rRNA level tested via RT-qPCR. Above findings indicated that RiBi was depressed in fibrotic status. Moreover, using CX5461 successfully disrupted RiBi along with kidney fibrosis, G2/M arrest and cell senescence. Interestingly, CX5461 treatment increased the binding of HDM2 to RPL5 and RPL11. Next, we found ECT2 induced RiBi failure, contrarily, blocking ECT2 mitigated the inhibition of RiBi and kidney fibrosis caused by CX5461. Furthermore, transcriptome sequencing indicated that PLXNB2 was one of the down-regulated genes of ECT2. Knocking down PLXNB2 inhibited RiBi and promoted fibrosis, however, this effect could be partially abolished by co-transfection with ECT2 siRNA. These data implied that the elevated ECT2 depressed PLXNB2, and which consequently led to the failure of RiBi and kidney fibrosis.

Conclusions: Collectively, our findings indicated that blocking RiBi initiated G2/M arrest and senescence of TECs as well as kidney fibrosis. ECT2 mediated PLXNB2 decline was a potential mechanism accounting for the impaired RiBi in fibrosis.

FR-PO1201

Rolling-Translation of circVMP1 Promotes Proteinuric Nephropathy by Inhibiting Autophagy in Tubular Epithelial Cells

Peng Wang,[1] Tongtong Ma.[2] *[1]Department of Nephrology, and Guangdong Provincial Key Laboratory of Autophagy and Major Chronic Non-communicable Diseases, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China; [2]The Department of Anesthesiology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China*.

Background: Proteinuria promotes the progression of chronic kidney disease (CKD) to end-stage renal disease by impairing tubular epithelial cells (TECs). Recent studies have found that autophagy and circRNAs play important roles in injured TECs. However, the functions and molecular mechanisms of circRNAs in autophagy and CKD progression is largely unclear. Our previous work revealed a novel mechanism, by which circBNC2 regulated cell cycle progression through encoding a previously unidentified protein, BNC2-681aa. However, whether circRNA mediates autophagy by translation remained to be elucidated.

Methods: High-throughput sequencing was carried out to identify differentially expressed circRNA in albumin-stimulated HK2 cells. The expression level of one candidate circRNA, circVMP1, was analyzed using Northern blot, FISH and real-time PCR. The effects of circVMP1 on autophagy was evaluated using TEM, RFP-GFP-LC3 cells. The encoding capacity of circVMP1 was proved through LC/MS and IRES reporter assay. After the validation of VMP1-143aa with a customized monoclonal antibody, the proteins that interact with VMP1-143aa was identified by LC/MS and Co-IP assays. Tubule-specific circVMP1 knockout mice were generated by crossing circVMP1$^{f/f}$ mice with Ksp-Cre mice.

Results: The expression level of circVMP1 in albumin-stimulated HK2 cells and biopsy samples from CKD patients with proteinuria was elevated. Knocking out circVMP1 in TECs alleviated renal inflammatory injury by promoting TECs autophagy in mouse adriamycin nephropathy model. Mechanistically, circVMP1 was found to inhibited TECs autophagy by translating a novel protein VMP1-143aa to function as a molecular decoy by interacting with BECN1 and TP53INP2, thereby inhibiting the function of VMP1 protein.

Conclusions: Collectively, circVMP1 promotes renal inflammatory injury in proteinuric nephropathy by hindering autophagy flux in a translation-dependent manner. Therefore, targeting circVMP1 or it's translation product, VMP1-143aa, might provide a potential angle for proteinuric nephropathy by restoring TECs autophagy.

Funding: Government Support - Non-U.S.

FR-PO1202

Dysregulated Renal Microcirculation in Human Obesity Detected by Urinary Extracellular Vesicles (uEVs)

Mina H. Al Saeedi, Xiang yang Zhu, Aleksandar Denic, Andrew D. Rule, Hui Tang, Kyra L. Jordan, Amir Lerman, Aleksandra Kukla, Lilach O. Lerman. Nephrology and Hypertension. *Mayo Foundation for Medical Education and Research, Rochester, MN*.

Background: Obesity may dysregulate angiogenesis, and renal inflammation may induce microvascular proliferation. Plasmalemmal vesicle-associated protein (PLVAP) is a peritubular capillaries (PTC) marker, and the notch ligand pathway delta-like ligand-4 (DLL4) is a microvascular metabolic sensor that regulates angiogenesis, but their role in the kidney in obesity is undetermined. We hypothesized that human obesity dysregulates the renal microcirculation, detectable by elevated urinary levels of renal endothelial cell-derived PLVAP+/DLL4+ uEVs

Methods: Blood and urine samples were prospectively collected from obese patients (OB, n=22) and lean kidney donors (n=11). uEVs were quantified and characterized for CD31, PLVAP, CD144, and DLL4 expression and their relationship with body mass index (BMI), insulin, and plasma angiopoietin levels. PTCs were also counted in time-0 biopsies of OB (n=20) and lean (n=17) kidney donors

Results: OB patients had preserved renal function and elevated insulin levels(Table). The total uEV number was similar, but the fraction of CD31-/PLVAP+/CD144-/DLL4+ uEVs was higher in OB and directly correlated with BMI, plasma angiopoietin, and insulin levels (Fig1). Congruently, PTC density and count/tubule were higher in OBs than lean(Fig2)

Conclusions: Obese patients show elevated urinary markers of renal PTC proliferation that correlate with obesity severity. These may aim to support tubular enlargement and indicate the development of early microvascular kidney injury that might be useful in the risk stratification of obese patients

Funding: NIDDK Support, Other NIH Support - DK120292 (NIDDK) and HL158691 (National Heart, Lung, and Blood Institute)

Demographics

Parameter	Lean	OB
Age, Yrs.	47±15	48±12
Sex, M/F	4/7	7/15
BMI, Kg/m^2	25±2	38±11*
Serum Creatinine, mg/dl	0.9±0.2	0.8±0.2
eGFR, ml/min/1.73m^2	90±9	98±18
Insulin, mU/l	5(2,25)	14(3,50)*

mean±SD or median(min,max)*P<0.05 vs.lean

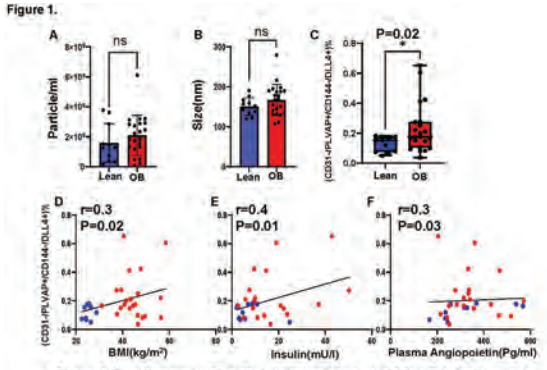


Figure 1. No difference in (NanoSight) size and number of OBs uEVs (red) vs. lean (blue) **(A-B)**, significantly higher fraction (FlowCytometry) of OBs (red) CD31-/PLVAP+/CD144-/DLL4+ **(C)** than lean (blue). In the cohort, BMI **(D)**, insulin **(E)**, and plasma angiopoietin **(F)** correlated directly with the fraction of CD31-/PLVAP+/CD144-/DLL4+.

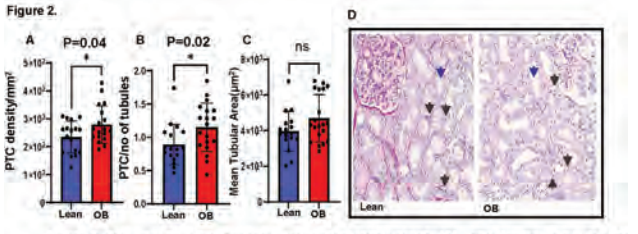


Figure 2. OBs (red) have higher peritubular capillary (PTC) density **(A)**, and PTC/no. of tubules **(B)** than lean (blue), but not mean tubular area **(C)**. Periodic Acid Schiff-stained (PAS) kidney biopsy slides **(D)**, black arrow-PTC, and blue-complete tubule.

FR-PO1203

RNA-Binding Protein Hu Antigen R (HuR) Mediates Kidney Fibrosis in Mice with CKD Induced by Deoxycorticosterone Acetate-Salt and Angiotensin II Infusion

Lili Zhuang, Zhou Wang, Yufeng Huang. *University of Utah Health, Salt Lake City, UT.*

Background: The RNA-binding protein Hu antigen R (HuR) is pivotal in modulating mRNA turnover and translation of genes implicated in immune response and inflammation. Elevated HuR levels have been observed in patients with chronic kidney disease (CKD), yet its specific role in CKD pathogenesis remains elusive. This study aims to investigate the involvement of HuR in progressive renal injury resulting from deoxycorticosterone acetate-salt (DOCA) and angiotensin II (AII) infusion in mice, utilizing the HuR inhibitor KH3.

Methods: Male mice at age of 12 weeks were subjected to DOCA+AII infusion along with 1% NaCl in drinking water. Subsequently, they were treated either with or without the HuR inhibitor, KH3 (administered at 40mg/kg-BW daily via intraperitoneal injection) (DOCA+AII+KH3) for a duration of 3 weeks. Control mice (NC) received saline injections without any infusion.

Results: DOCA+AII infusion significantly increased HuR expression by 2.67 folds in the kidneys, a response effectively mitigated by KH3 treatment. Notably, KH3-treated mice exhibited a partial reduction in blood pressure compared to untreated DOCA+AII mice (SBP, 137.7±7.58 vs. 158.1±3.97 mmHg, P<0.05 vs. DOCA+AII). Additionally, KH3 treatment arrested the progression of albuminuria and led to a significant reduction in impaired renal function, kidney hypertrophy, and glomerular and tubulointerstitial fibrosis by 47.5%, 39.9%, 47.5% and 88.8% respectively (P<0.01), compared to untreated DOCA+AII mice. These improvements were accompanied by ameliorated podocyte injury, evidenced by reduced podocyte foot process effacement; and alleviated tubular injury, indicated by decreased mRNA and protein expression of KIM-1, NGAL and OPN in tubular cells, compared with untreated DOCA+AII mice. Furthermore, KH3 treatment significantly attenuated renal macrophage infiltration and the production of NF-kB-p65, Nox2, TGFß1 and Wisp1, markers of inflammation, oxidative stress and major profibrotic modulators induced by DOCA+AII infusion.

Conclusions: Our findings suggest that HuR is upregulated in DOCA+AII induced kidney injury in mice and contributes to hypertensive, oxidative stress, inflammatory, and fibrotic pathways associated with CKD. Inhibition of HuR holds promise as a potential therapeutic strategy for CKD treatment.

Funding: NIDDK Support

FR-PO1204

Single-Cell Detection of Somatic Copy Number Alterations in Human Kidney by Chromatin Accessibility Profiling

Xinyi E. Chen,[1] Nancy Zhang,[1] Parker C. Wilson.[2] [1]*University of Pennsylvania Wharton School, Philadelphia, PA;* [2]*University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

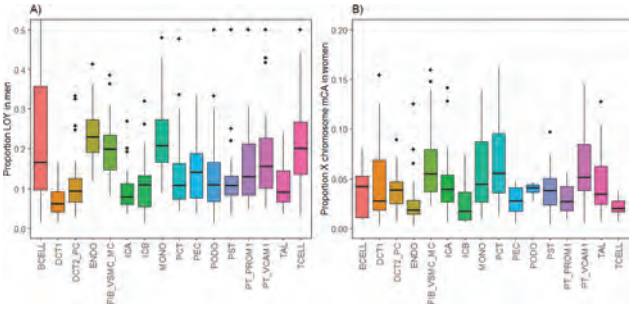
Background: Loss of Y chromosome (LOY) is the most common somatic chromosomal alteration (mCA) in men. Until recently, it was thought that LOY was unique to hematopoietic tissue, but it also occurs in the kidney and is enriched in injured proximal tubule (PT) cells – a cell state defined by a pro-inflammatory signature that predicts kidney function decline (Wilson et al. Genome Biology 2023). We hypothesize LOY is an indicator of genomic instability, however, LOY is not a perfect marker because the majority of injured PT cells do not have LOY and it is unclear if similar mCA occur in female cells.

Methods: We realigned and preprocessed single-cell multiome or single-cell ATAC (snATAC) datasets using SnapATAC2, integrated them with scvi-tools and annotated cell barcodes using established markers. To detect mCA, we modeled ATAC fragment coverage as a proxy of single-cell copy number. For our model, let X_{ci} be the fragment coverage of region i (which can be a chromosome arm) and cell c. We assume a negative-binomial model for the fragment coverage, $X_{ci} \sim NB(\alpha_c \beta_i \gamma_{ci}, \Phi_{ci})$ where α_c is the cell-specific library size, β_i is a region-specific background bias, and Φ_{ci} is a cell- and region-specific dispersion, to be estimated by the observed variance-mean relationship in the data. The parameter γ_{ci}, which captures the cell-specific fold enrichment/depletion of fragment coverage for region i, is an estimate of copy number state.

Results: We analyzed 526,903 kidney cells from 99 male or female donors with or without CKD. Injured PT (PT_VCAM1, PT_PROM1), endothelial cells (ENDO), fibroblasts (FIB_VSMC_MC) and mononuclear cells (MONO) had approximately two-fold higher proportion of LOY than other cell types (Figure 1A). mCA involving the X chromosome were enriched in some of the same cell types in women, but at a lower proportion than LOY (Figure 1B). Both LOY and X chromosome mCA were associated with an increased autosomal mCA burden.

Conclusions: Somatic mCA are enriched in specific kidney cell types and may provide insight into factors that drive CKD progression.

Funding: NIDDK Support



FR-PO1205

Evaluation of Glucocorticoid Metabolism in CKD as a Therapeutic Target against Sarcopenia

Michael S. Sagmeister,[1,2] Ana Crastin,[1] Angela E. Taylor,[1] Simon W. Jones,[1] Lorraine Harper,[1,2] Rowan S. Hardy.[1] [1]*University of Birmingham College of Medical and Dental Sciences, Birmingham, United Kingdom;* [2]*Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom.*

Background: Skeletal muscle loss and weakness, termed sarcopenia, has been linked to dysregulation of glucocorticoid hormones in CKD. Glucocorticoid excess is favoured by loss of the renal enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) type 2 that inactivates cortisol to cortisone. The cortisol-activating counterpart, 11βHSD type 1, which is upregulated in skeletal muscle in response to inflammation, has not yet been investigated in this context. This study tests whether raised glucocorticoid activation by 11βHSD1 in skeletal muscle contributes to sarcopenia in CKD and represents a novel therapeutic target.

Methods: An observational study recruited 17 patients with pre-dialysis CKD (eGFR <30) and 14 healthy volunteers aged 60-80 years. Muscle phenotype was assessed by bio-impedance body composition, grip strength and short physical performance battery. Steroid hormones were measured in early morning serum and 24-hour urine by liquid

chromatography/mass spectrometry. The rate of enzymatic cortisol activation by 11βHSD1 in muscle was determined in vastus lateralis biopsies *ex vivo*. Using the adenine mouse model of renal impairment, an animal experiment examined the therapeutic potential of 11βHSD1 suppression to protect against muscle atrophy.

Results: Serum cortisol is similar in CKD, while serum cortisone is reduced relative to healthy controls ($p<0.0001$). Serum cortisol or 24-hour urinary glucocorticoid excretion are not associated with skeletal muscle mass or strength. In contrast, 11βHSD1 enzymatic activity in skeletal muscle correlates negatively with muscle strength independent of age and gender ($p=0.002$). Despite its association with muscle strength, 11βHSD1 activity is not significantly different between patients with CKD and healthy volunteers. In the mouse model of renal impairment, genetic silencing of 11βHSD1 fails to improve skeletal muscle atrophy.

Conclusions: Low muscle strength correlates with cortisol activation by 11βHSD1 in skeletal muscle. However, renal impairment by itself does not alter 11βHSD1 function in muscle, and 11βHSD1 suppression does not prevent muscle atrophy in a mouse model of CKD. Future studies may explore to what extent glucocorticoids contribute to sarcopenia in human CKD through alternative mechanisms, or whether 11βHSD1 is significant for sarcopenia development in settings unrelated to CKD.

Funding: Government Support - Non-U.S.

FR-PO1206

Role and Mechanism of PCK2 in Regulating Fatty Acid Oxidation during Kidney Interstitial Fibrosis

Wei Xiong, Chun Zhang. *Huazhong University of Science and Technology, Wuhan, China.*

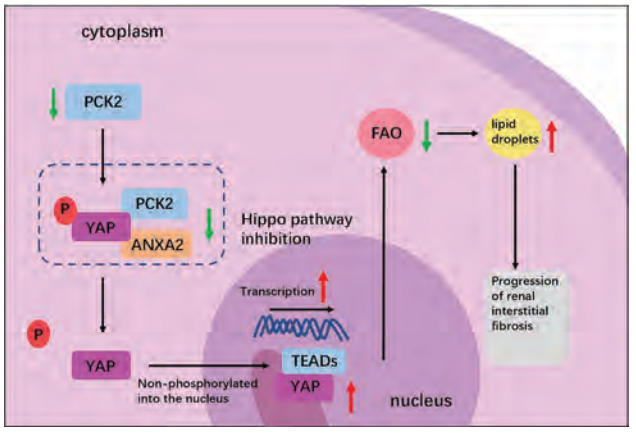
Background: Renal interstitial fibrosis is the final stage of the progression of chronic kidney disease. Currently, the means to restore or prevent the renal fibrosis process are still very limited. Abnormal metabolism is an important concomitant feature of renal fibrosis, in which the sharp reduction of fatty acid oxidation capacity is the key factor of tubulointerstitial energy metabolism failure. Phosphoenolpyruvate carboxyl kinase 2 (PCK2) is a mitochondrial subtype of phosphoenolpyruvate carboxyl kinase (PEPCK), widely involved in cell metabolism and plays an important role in maintaining cell homeostasis. However, the role and mechanism of PCK2 in renal interstitial fibrosis have not yet been revealed.

Methods: Western blot, immunoblot analysis and immunohistochemistry were used to detect the expression of PCK2. PCK2 over expression lentivirus in HK2 cells and proximal tubule-specific transgenic mice were used to upregulate PCK2. EMT related markers, collagen I, fibronectin, and Hippo signal pathway related makers were detected by western blot and immunofluorescence. Lipid metabolism-related product kits such as triglyceride kits, fatty acid kits, fatty acid synthase kits, and cholesterol detection kits were applied to measure the specific content changes of various lipid components.

Results: PCK2 expression is significantly decreased in renal interstitial fibrosis and is highly correlated with the severity of fibrosis. Overexpression of PCK2 can reduce renal interstitial fibrosis. Further research reveals that PCK2 is enriched with multiple lipid metabolism pathways. PCK2 increases the level of renal tubular fatty acid oxidation and activate the Hippo pathway.

Conclusions: PCK2/Hippo axis is involved in the progression of renal interstitial fibrosis by regulating fatty acid oxidation.

Funding: Government Support - Non-U.S.



Schematic diagram

FR-PO1207

Dapagliflozin Ameliorates High-Fat, Diet-Induced, Megalin-Mediated Autolysosomal Disorders in Mouse Proximal Tubules

Kazuya Takemoto, Michihiro Hosojima, Hideyuki Kabasawa, Ichiei Narita, Akihiko Saito. *Niigata University, Niigata City, Japan.*

Background: Megalin is a multi-ligand endocytic receptor located in the apical membrane of proximal tubules (PTs). Our prior study (*JASN* 2016) elucidated that megalin-mediated endocytosis of glomerular-filtered lipotoxic substances drives tubulo-glomerular alterations in mice fed a high-fat diet (HFD). In this model, pathological vacuolation appears particularly in segment 2 (S2) of PTs due to megalin-dependent autolysosomal disorders. Receptor-mediated endocytosis (RME) is the primary pathway for substance uptake in S1 (greater than S2), while fluid-phase endocytosis (FPE) prevails in S2, which is vulnerable to metabolic overload due to its less advanced endolysosomal systems. This investigation aims to explore the impact of dapagliflozin, an SGLT2 inhibitor, on autolysosomal disorders in PTs of HFD-fed mice and its underlying mechanism.

Methods: Nine-week-old male C57BL/6J mice were fed an HFD with oral administration of dapagliflozin (1mg/kg body weight/day) or vehicle for 28 days (n=10 each). Kidney sections underwent PAS staining, and Image-Pro Plus ver. 7.0 evaluated the vacuolar area/cortical tubular area. Urinary C-megalin, a marker for lysosomal overload in PTs (*Diabetes* 2017), was also measured. Renal megalin expression was gauged via immunoblotting, qPCR, and immunohistochemistry. Megalin's endocytic function was assessed by measuring the urinary excretion of α_1-microglobulin, an endocytic ligand of megalin. RME and FPE were scrutinized on kidney sections post intravenous injection of fluorescent lysozyme and dextran, respectively, in 9-week-old male kidney-specific conditional megalin KO mice and littermate controls, and C57BL/6J mice receiving dapagliflozin or vehicle for 5 days.

Results: Dapagliflozin administration significantly reduced the vacuolar area/cortical tubular area and urinary C-megalin excretion in HFD-fed mice. While renal megalin expression remained unaltered, urinary α_1-microglobulin excretion increased with dapagliflozin administration. In megalin KO mice, the uptake of fluorescent lysozyme and dextran in PTs decreased. Similarly, the administration of dapagliflozin to mice diminished the uptake of both tracers in PTs.

Conclusions: Dapagliflozin ameliorates HFD-induced, megalin-mediated autolysosomal disorders particularly in S2 of PTs by suppressing both RME and FPE dependent on megalin.

Funding: Commercial Support - Denka Company Limited, Government Support - Non-U.S.

FR-PO1208

Evaluating the Role of Urinary Volatile Organic Compounds in CKD

Henry Wu,[1,2] Malcolm Possell,[5] Long T. Nguyen,[1,3] Wenbo Peng,[4] Carol A. Pollock,[1,3] Sonia Saad.[1,3] *[1]Kolling Institute of Medical Research, St Leonards, NSW, Australia; [2]University of New South Wales, Sydney, NSW, Australia; [3]Royal North Shore Hospital, St Leonards, NSW, Australia; [4]University of Technology Sydney, Sydney, NSW, Australia; [5]The University of Sydney, Sydney, NSW, Australia.*

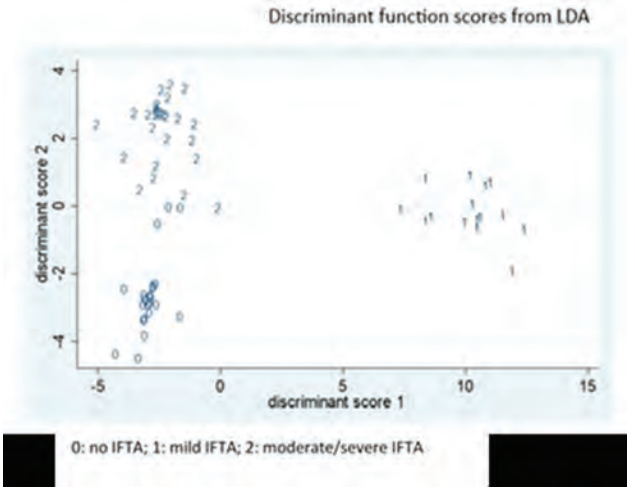
Background: Volatile organic compounds (VOCs) are gaseous products of metabolic processes in organisms which are conventionally released with greater abundance in disease. Whether urinary VOCs are valuable as a non-invasive source in reflecting CKD status is unclear.

Methods: Adults aged 18-75 years with kidney biopsy performed were included. All biopsy samples had an interstitial fibrosis and tubular atrophy (IFTA) grade scored by standardized assessment. Pre-biopsy urine were collected. Urine supernatant was extracted from residue and sampled for stir bar sorptive extraction, followed by gas chromatography–mass spectrometry (GC-MS). Post-processing of GC-MS data involved measuring mass-to-charge ratios and fragment patterns for identification and quantification of individual VOCs. Linear discriminant analysis (LDA) assessed the ability of urinary VOCs in discriminating between no IFTA, ≤25% (mild) IFTA and >25% (moderate/severe) IFTA. Linear regression analysis adjusting for age, sex, eGFR and diabetes mellitus status was conducted to determine significantly upregulated urinary VOCs with IFTA progression.

Results: 64 study participants were included (22 individuals no IFTA, 15 individuals mild IFTA, 27 individuals moderate/severe IFTA). LDA demonstrated individuals with no IFTA, mild, and moderate/severe IFTA could easily be separated by their urinary VOCs profile (see figure). 34 VOCs were identified to be helpful in correctly classifying between the IFTA groups, of which 7 VOCs were significantly upregulated in the mild IFTA compared to the no IFTA group and 3 VOCs were significantly upregulated in the moderate/severe IFTA compared to the mild IFTA group ($p<0.05$). 'Benzaldehyde, 4-methyl' is positively associated with IFTA progression across all stages ($p<0.05$).

Conclusions: We report novel links between urinary VOCs and tubulointerstitial histopathology. Urinary VOCs may have a clinical diagnostic role in CKD going forward.

Funding: Government Support - Non-U.S.



FR-PO1209

Aryl Hydrocarbon Receptor Promotes Kidney Fibrosis via Accelerating Cell Senescence in Tubular Epithelial Cells

Qian Ren, Hui Li, Liang Ma, Ping Fu. *Department of Nephrology, Kidney Research Institute, West China Hospital of Sichuan University, Chengdu, China*.

Background: Chronic kidney disease (CKD) has a high prevalence worldwide and tubulointerstitial fibrosis is considered the final convergent pathway of progressive CKD regardless of etiology. However, mechanisms underlying kidney injury-induced fibrosis largely remain unknown. The aryl hydrocarbon receptor (AhR) is a well-known ligand-activated cytoplasmic transcription factor that contributes to cellular responses against environmental toxins and carcinogens. AhR activity is strongly implicated throughout the course of CKD but its certain role and underlying mechanism remains unknown.

Methods: AhR expression was examined in the kidney specimens of CKD patients as well as in the kidneys of mouse models with experimental kidney fibrosis (unilateral ureteral obstruction [UUO], adenine nephropathy [Aden], and aristolochic acid-induced nephrotoxicity [AA]). The potential role of AhR in renal fibrosis was further validated by AhR conditional knock out in mice or AhR siRNA in TCMK-1 cells. ATAC-seq combined with RNA-seq was employed to explore the underlying mechanisms.

Results: Increased AhR expression was observed in the kidneys of both CKD patients of various etiology and three mouse models with kidney fibrosis. The elevated AhR expression was mainly located within tubualr cells and was associated with the levels of Scr and eGFR in CKD patients. Tubule-specific knock out of AhR in mice alleviated UUO- and Aden-induced renal fibrosis. Mechanistically, in tubular epithelial cells, AhR exerted a profibrotic role via a NF-κB-dependent signaling. AhR promoted the activation of NF-κB by regulating the transcription of IκBα and thus accelerating tubular senescence. Pharmacological inhibition of AhR ameliorated tubular senescence and renal fibrosis in both animal models and TCMK-1 cells.

Conclusions: Tubular AhR plays an important role in kidney fibrosis by suppressing profibrotic NF-κB signaling. Hence, our findings suggest that modulating the activity of tubular AhR may be a new therapeutic option for treating tubulointerstitial fibrosis and subsequent CKD.

Funding: Government Support - Non-U.S.

FR-PO1210

Quinolinic Acid Excess May Promote Kidney Fibrosis

Marie Christelle Saade, Amanda J. Clark, Valerie Etzrodt, Kyle Q. Vu, Samir M. Parikh. Parikh Lab. *The University of Texas Southwestern Medical Center, Dallas, TX*.

Background: Acute kidney injury (AKI) and chronic kidney disease (CKD) are characterized by decreased NAD+ biosynthesis. The de novo NAD+ pathway, one of the three pathways for NAD+ biosynthesis, involves quinolinic acid, a metabolite catalyzed by quinolinate phosphoribosyl transferase (QPRT) and converted into NAD+. Primarily recognized as a neurotoxin acting through the NMDA receptor, little is known about quinolinic acid's kidney effects. We hypothesized that sustained accumulation of quinolinic acid might worsen renal health and favor fibrosis.

Methods: We used 8-week-old wild-type C57BL/6 male mice. Two injury models were employed: an acute injury with cisplatin 25 mg/kg harvested on day 3 and a CKD model with folic acid (FA) 250 mg/kg harvested on day 14. We primarily measured fibrosis and kidney injury markers using qPCR, serum BUN, and creatinine. We compared 8 to 72-week-old wild-type (WT) mice. We generated conditional inducible mice that overexpress QPRT with doxycycline 0.2 mg/mL. FA model WT mice were harvested at 0, 36 hours, day 7, and day 14 for metabolomics analysis. Quinolinic acid 0.5 g/L was administered for 14 days, and for 28 days with the FA model starting at day 14. Cell cultures assessed the profibrotic effect of quinolinic acid (1 μM). Memantine 250 nM was applied to pericytes +/- quinolinic acid.

Results: Our results verified the age-related decline in QPRT and the progressive accumulation of quinolinic acid with CKD development. Renal tubular induction of the QPRT enzyme reduced excess quinolinic acid and protected renal function in mice induced with cisplatin. Excessive quinolinic acid administration achieved serum levels comparable to CKD and was sufficient to worsen baseline renal function. Introducing quinolinic acid in the FA model exacerbated kidney damage. Application of quinolinic acid to various cell types revealed a specific profibrotic response exclusively in pericytes, a population of cells responsible for fibrosis. Memantine, a NMDA receptor antagonist, protected pericytes from the fibrotic effects of quinolinic acid.

Conclusions: Quinolinic acid accumulation may contribute directly to CKD progression. As CKD progresses, the QPRT enzyme expression decreases, and quinolinic acid accumulates. This metabolite may act through NMDA receptors on pericytes to promote a fibrogenic program. Further studies may unveil new ways to target renal fibrosis.

Funding: NIDDK Support, Other NIH Support - 5R01DK095072-10

FR-PO1211

Glutamine Metabolism Inhibition Alleviates Kidney Fibrosis through the Immunometabolic Axis

Huang-Yu Yang,[1,2] Chung Ying Tsai,[1] Kuan-Hsing Chen,[1] Chih-Wei Yang.[1,2] *[1]Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan; [2]Chang Gung University, Taoyuan, Taiwan.*

Background: Chronic kidney disease manifests as a gradual loss of kidney function, which is partly attributed to fibrosis. An inflammatory response is elicited in a unilateral ureteral obstruction (UUO) model and contributes to kidney fibrosis. A glutamine antagonist, 6-diazo-5-oxonorleucine (DON), acts as an immune modulator. However, the role of glutamine metabolism in kidney fibrosis remains unclear.

Methods: Fibrosis induced by UUO is reduced in DON-treated mice than that in untreated mice. Single-cell RNA sequencing is used to characterize the effects of DON on immune and proximal tubule (PT) cells following UUO.

Results: DON induces oxidative stress in T cells infiltrating the kidney and skews the T cells toward regulatory phenotype via HIF-1α-KDM4C-ROS axis. Hypomethylation of the FOXP3 promoter occurred under glutamine deprivation with elevated levels of reactive oxygen species, a result of fatty acid β-oxidation and attenuated intracellular glutathione levels. Moreover, infiltrating macrophages show an Mmp12+ reparative phenotype. Patrolling monocytes decrease upon DON treatment. The percentage of aged neutrophils also increases, showing an apoptotic phenotype. DON alleviates UUO-induced hypoxia and increases oxidative phosphorylation in PT cells. DON-treated kidneys show reduced collagen and CD52 levels and upregulated the macrophage migration inhibitory factor communication pathway.

Conclusions: Hence, the inhibition of the glutamine pathway reduces kidney fibrosis after injury and can be exploited as a therapeutic strategy for chronic kidney fibrosis.

FR-PO1212

Glutamine Reprograms Metabolism in CKD-Induced Pathological Cardiac Remodeling via the GLS1/GLUD1 Axis

Linnan Bai,[1] Yi Wang,[2] Minchao Kang,[1] Qiu-yu Li,[3] Junnan Wu.[1] *[1]Zhejiang University School of Medicine Sir Run Run Shaw Hospital, Hangzhou, China; [2]The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [3]Zhejiang University School of Medicine Children's Hospital, Hangzhou, China*.

Background: CKD-induced cardiac remodeling is characterized by myocardial hypertrophy, however, available therapeutic options are limited. Here, we employed a multi-omics approach to analyze a total of 36 mice hearts to detect cardiac structural changes.

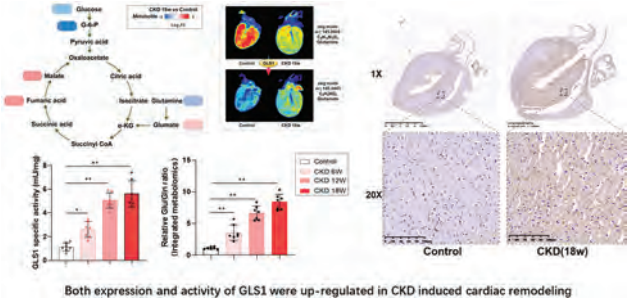
Methods: We performed 5/6 nephrectomy surgery on mice and collected samples at multiple time points during disease progression (6, 12, and 18 weeks post-surgery). Initially, we performed snRNA-seq and a comprehensive metabolomics strategy including in situ metabolomic was conducted to obtain the in situ metabolic profiles. We screened out the most significantly changed metabolic pathway and corresponding rate-limiting enzymes. Using targeted metabolomics and Western blotting, we validated metabolic reprogramming signatures. We further created CKD mice with conditional knockout of the rate-limiting enzyme in cardiomyocytes and monitored the degree of cardiac tissue damage.

Results: Our findings illustrate the time course of changing gene expression patterns for multiple CKD stages. The TCA cycle was defective in the chronic phase but was transiently activated in the very early stages of CKD. The glutaminolysis pathway, however, was persistently activated throughout the time course and reached a peak at

18 weeks post-surgery, especially in left ventricle and interventricular septum region. Our gene-metabolite interaction network showed that glutaminase 1 (GLS1), the rate-limiting enzyme in glutaminolysis, and its target gene glutamate dehydrogenase 1 (GLUD1) were activated and up-regulated in CKD cardiomyocytes. Cardiac-specific deletion of GLS1 was achieved, and this ameliorated cardiac dysfunction and cardiomyocyte hypertrophy in response to CKD. At the mechanistic level, GLS1 controls the epigenetic expression of pro-hypertrophic genes. Moreover, GLS1 and GLUD1 are both transaminases, leading to the accumulation of ammonia in mitochondria.

Conclusions: These findings suggested the GLS1/GLUD1 axis plays an essential role in maintaining a homeostatic metabolic response in cardiomyocytes under CKD.

Funding: Government Support - Non-U.S.



Both expression and activity of GLS1 were up-regulated in CKD induced cardiac remodeling

FR-PO1213

Effects of the Preservative Sodium Benzoate and a High-Fat Diet on Kidneys

Anna Lipinski, Alayna R. Wells, Adam E. Gaweda, Michael Merchant, Loretta L. Jophlin, Michelle T. Barati. *University of Louisville, Louisville, KY.*

Background: Sodium Benzoate (SB) is used as a food preservative and generally recognized as safe by the Food and Drug Administration (FDA). Reports suggest altered kidney function and oxidative stress in kidneys of mice exposed to SB. However, effects of dietary SB exposure on renal structures are unclear. Given the rising prevalence of obesity and increased risk of kidney disease with intake of ultraprocessed foods, effects of SB at dosages relevant to human dietary exposures coupled to a high fat diet, remain to be determined. This study addressed the hypothesis that SB with a high fat diet alters kidney histology and anti-oxidative mechanisms.

Methods: 5-week-old male and female mice were assigned to either control diet (CD; 13% Kcal fat) or high fat diet (HFD; 42% Kcal fat). After 6 weeks, animals continued on their diet and assigned to groups gavaged with distilled water or distilled water containing SB (99mg/kg bw) daily for 28 days. Based on intake, this exposure approximated a highly processed diet where all food contained 0.1% added SB (FDA limit). Kidney sections were PAS-stained for histologic analysis of tubulo-interstitium and glomeruli. Protein abundance of superoxide dismutase (SOD-1), fibronectin, and glutamyl-cysteine synthetase (GCS) analyzed by western blot. Three-way ANOVA used to compare diet and SB effects between female and male. Two-way ANOVA used to compare diet and SB effects within either sex group.

Results: Male mice had higher body weight than female mice in and all groups. Increased body weight from HFD was not altered by SB in male mice. Kidneys of mice in HFD, SB, and HFD+SB groups had focal areas of interstitial cell proliferation and fibrosis. Male mice on HFD had increased tubule vacuolization and a trend for increased glomerular mesangial matrix. Focal tubule injury/necrosis detected in kidneys of mice in HFD+SB groups. Abundance of SOD-1 was unaltered in all diet/treatments, while GCS was lower in kidneys of male mice.

Conclusions: In conclusion, HFD and SB increased kidney tubule-interstitial fibrotic foci and tubule injury, suggesting that long term dietary intake of highly processed foods may cause kidney fibrosis, a hallmark of chronic kidney disease. Additionally, these findings suggest that HFD and SB may reduce protective measures against oxidative stress, a characteristic consistent with kidney disease.

Funding: NIDDK Support

FR-PO1214

Blockade of Tubule-Specific Mitochondrial Calcium Uniporter (MCU) Augments Renal Fatty Acid Oxidation in High-Fat Diet-Induced Obese Mice

Soumya Maity, Pragya Singh, Ian M. Tamayo, Afaf Saliba, Hak Joo Lee, Richard Montellano, Kumar Sharma. *The University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: Impaired fatty acid oxidation (FAO) is a consequence of obesity-induced chronic kidney disease. Proximal tubular cells depend on FAO to fulfill their high energy demand. The mitochondrial Ca^{2+} uniporter (MCU) complex mediates acute mitochondrial Ca^{2+} influx to drive mitochondrial bioenergetics. However, loss of *Mcu* is reported to enhance muscle performance with a preferential shift toward fatty acid metabolism. Here, we examined the role of MCU in renal fatty acid metabolism in a high-fat diet (HFD)-induced obese model.

Methods: 8-12 weeks wildtype (WT) and tubule-specific *Mcu* knock-out (*Mcu*$^{fl/fl}$ X *Pax*8-Cre$^{+/-}$; *Mcu* KO) male mice were fed with HFD for six months. MALDI-MSI followed by untargeted analysis using MetaboAnalyst 6.0 was carried out to evaluate the distribution of lipid species in the kidney cortex. The mitochondrial oxygen consumption rate (OCR) was used as a functional readout of mitochondrial bioenergetics. Histological staining, western blots, and biochemical assays were employed to establish the mechanism.

Results: Loss of MCU did not affect kidney growth and maturation. Histological staining showed a significant decrease in the size and number of lipid droplets in renal tubules of *Mcu* KO compared to WT mice under HFD stress. Lipid droplet-associated protein perilipin 2 was decreased in HFD *Mcu* KO mouse kidneys. MSI data demonstrated that kidneys from HFD group accumulated several lipid species, notably different subtypes of phosphatidylcholine and ceramides, in WT tubules. These lipid species were significantly reduced in *Mcu* KO tubules. Palmitic acid treatment in MCU knockdown human proximal tubular (HK2) cells showed a higher OCR and less lipid accumulation. The upregulation of CPT1 in HFD *Mcu* KO mice's kidneys suggests that MCU loss facilitates FAO in renal tubules. Moreover, increased L-carnitine and phosphorylation of pyruvate dehydrogenase α1 at ser-293 in kidneys of *Mcu* KO mice with regular diet indicate that renal tubules undergo metabolic reprogramming towards favorable FAO in absence of MCU to combat lipid stress.

Conclusions: Loss of MCU promotes fatty acid oxidation in kidney tubules and reduces renal lipid accumulation in high-fat diet stress. These findings open possibilities for treating obesity-induced lipotoxicity in the kidney by tubule-specific MCU inhibition.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO1215

Dysregulated Intestinal Group 3 Innate Lymphoid Cell (ILC3) Fatty Acid Uptake Mediates Susceptibility to Colitis in Kidney Injury

Ziwen Tang, Zhou Liang, Chang-Jian Zhu, Yi Zhou. *The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Renal injury is commonly accompanied by systematic disorder and remote organ dysfunction. Patients with renal injury often display gastrointestinal symptoms and increased risk of colitis. However, the role and underlying mechanisms of intestinal immunity in mediating renal injury-associated colitis susceptibility have not yet been elucidated.

Methods: Mice that have undergone sham surgery or unilateral ureteral obstruction (UUO) were exposed to dextran sodium sulfate (DSS) to induce experimental colitis. To clarify the contribution of group 3 innate lymphoid cells (ILC3s) in renal injury-associated colitis, ILC3s-deficient mice (*Rorc*$^{GFP/GFP}$ mice) or ILC3s-reconstruction mice were exposed to DSS, and then severity of colitis was measured. Single-cell RNA sequencing of intestinal ILC3s was performed to identify their functions and molecular regulatory mechanisms. And flow cytometry was used to detect the corresponding changes in intestinal ILC3s. ILC3s were stained with BODIPY C16 and BODIPY 493/503 to assess their capacity of fatty acid uptake and storage. IL-22 secretion from intestinal ILC3s and the severity of colitis were measured in sham or UUO mice after administration of SSO, a fatty acid uptake inhibitor.

Results: Compared to sham-DSS controls, UUO-DSS mice exhibited exacerbated colitis, faster weight loss, shorter colon length, and higher DAI and histological scores. The exacerbation of colitis also existed in ILC3-complete *Rorc*$^{GFP/+}$-UUO mice, which was abolished in ILC3-deficient *Rorc*$^{GFP/GFP}$ mice. In contrast, colitis in UUO-intestinal-ILC3s-reconstituted mice was more severe than in mice receiving sham-intestinal ILC3s. Further analysis revealed that UUO-ILC3s had significantly reduced IL-22 secretion and markedly upregulated fat digestion and absorption pathways, which was confirmed by higher MFI of BODIPY C16 and BODIPY 493/503 than sham-ILC3s. SSO inhibition of UUO-ILC3s fatty acid uptake restored IL-22 expression and prevented UUO-induced colitis exacerbation.

Conclusions: Our data demonstrate that ILC3s are required and sufficient to mediate the susceptibility to colitis associated with renal injury. Mechanistically, upregulation of fatty acid absorption and storage in UUO-ILC3s leads to impaired IL-22 secretion and loss of intestinal barrier protective function.

Funding: Government Support - Non-U.S.

FR-PO1216

Astragaloside Ameliorates Kidney Fibrosis by Inhibiting the Sonic Hedgehog Signaling Pathway

Long Mei, Weijian Xiong, Fan Li. *Chongqing Traditional Chinese Medicine Hospital, Chongqing, China.*

Background: Sonic hedgehog (SHH) signaling plays a critical role in promoting renal fibrosis.*Astragalosid* (*As-IV*) is the main integrete of the traditional Chinese medicine(TCM) *Astragalus membranaceus*(*Huangqi*). Our preliminary researches indicated that intervention with some TCM formulas containing *Huangqi* led to a

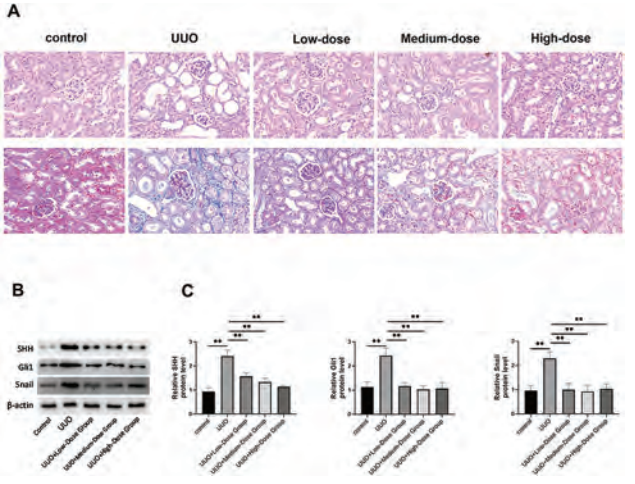
significant amelioration of renal interstitial fibrosis. This study aims to explore the mechanism by which *As-IV* mitigates renal interstitial fibrosis in mice model of unilateral ureteral obstruction(UUO) through the modulation of the SHH signaling pathway.

Methods: Thirty male mice were randomly assigned into five groups: a control group, a UUO model group, and three *As-IV* treatment groups with low, medium, and high doses. Except for the control group, the other four groups underwent ligation of a single ureter to establish an animal model of renal interstitial fibrosis. The *As-IV* groups was administered *As-IV* via daily gavage for 14 days. Then Scr and BUN were measured in all groups. Renal tissue morphology was observed using HE staining, and Masson's trichrome staining was employed to assess the deposition of extracellular matrix(ECM) in the renal tissue. The expression of SHH and its downstream signaling molecules Gli1 and Snail was detected using Western blot analysis.

Results: Compared with the control group, the UUO model group exhibited elevated levels of Scr and BUN, increased expression of ECM, and heightened levels of SHH. The protein expression of Gli1 and Snail were markedly upregulated ($P < 0.05$). In contrast to the UUO model group, *As-IV* groups significantly reduced Scr and BUN levels, diminished ECM deposition, and downregulated the levels of SHH as well as the protein expression levels of Gli1 and Snail(figure 1).

Conclusions: *As-IV* has been shown to improve renal function and inhibit renal interstitial fibrosis in mice model of UUO, with its effects potentially being associated with the blockade of the SHH signaling pathway.

Funding: Government Support - Non-U.S.



FR-PO1217

Omega-3 Fatty Acid Mitigates Mitochondrial Dysfunction and Modifies Renal Myostatin Expression in Adenine-Induced Uremic Rats

Binna Park, Dongeun Yang, Soy Kang, Won Suk An. *Dong-A University, Busan, Republic of Korea.*

Background: Mitochondrial dysfunction and inflammation play a central role in the progression of chronic kidney disease. Myostatin may be related to inflammation but expression of renal myostatin remains unclear. We aimed to investigate whether omega-3 fatty acids (FA) regulate mitochondrial dysfunction in adenine-induced uremic rats. We also tried to elucidate whether omega-3 FA affects renal myostatin expression and renal mitochondrial morphology.

Methods: Male Sprague-Dawley rats were fed diets containing 0.75% adenine and 2.5% protein for three weeks. Rats were randomly divided into four groups that were fed diets containing 2.5% protein and saline with cholecalciferol (3000 IU/kg/week) or omega-3 FA (300 mg/kg/day) with cholecalciferol by gastric gavage for two weeks: normal control, adenine control sacrificed at 3weeks, adenine control sacrificed at 5weeks, and omega-3 FA group sacrificed at 5weeks. The renal expression of myostatin and mitochondrial mediators was examined by western blot analysis. Renal mitochondrial morphology was evaluated using transmission electron microscopy.

Results: Compared to normal, serum creatinine in adenine control was increased and improved in the omega-3 FA group. Compared with normal, PGC-1α, SIRT1/3, and Nrf2 were down-regulated in adenine control. DRP-1 was up-regulated in adenine control and recovered with omega-3 FA supplementation for 2 weeks. PINK1, BNIP3, and NIX were down-regulated in adenine control and recovered in the omega-3 FA group. Compared to normal, renal myostatin expression was continuously downregulated at 3 weeks and 5 weeks and recovered with omega-3 FA. The size and number of tubular mitochondria were decreased at 5 weeks and mitigated with omega-3 FA supplementation for 2 weeks.

Conclusions: Omega-3 FA is beneficial for mitochondrial dysfunction and morphology in uremic rats. Further studies are necessary to find the pathogenic mechanism for decreased renal myostatin expression in uremia.

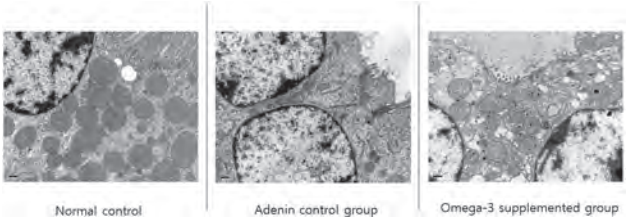


Figure 1. Electron Microscopic Finding of Tubular Mitochondria

FR-PO1218

Urinary Clearances of Indoxyl Sulfate and P-cresol Are Directly Correlated with the Functional Stress Response of the Proximal Tubule

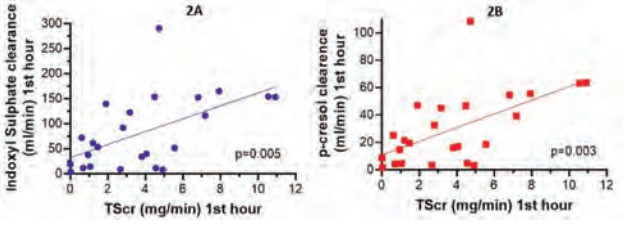
Magdalena Madero,[1] Ana K. Fernandez Yepez,[1] Jesse C. Seegmiller,[3] Guadalupe M. Montesinos Ojeda,[1] Alan J. Guzmán Portillo,[1] Aurora I. Estrada Escamilla,[1] Bernardo Rodriguez-Iturbe.[1,2] *[1]Instituto Nacional de Cardiologia Ignacio Chavez, Ciudad de Mexico, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [3]University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Urinary clearance of cardiotoxic and nephrotoxic indoxyl sulfate (IS) and p-cresol (pC) largely depends on the function of organic anionic (OAT) and cationic (OCT) transporters of the proximal tubule. Therefore, we examined the relationship between the clearance of IS and pC and the functional stress response of OAT and OCT in normal individuals and in patients with reduced glomerular filtration rate (GFR)

Methods: Studies were performed in 24 patients (GFR range 14 -129 ml/min/1.73m^2). Serum and urine IS and pC were determined by mass spectrometry for clearance determinations (UV/P). GFR (iohexol), serum and urinary creatinine (autoanalyzer) and urinary furosemide (HPLC), were assayed to determine the tubular secretion of creatinine (TScr) and furosemide (TSfr), hourly for 4 hours after the oral administration of 5g of creatinine and 1-1.5 mg of furosemide intravenously. This was intended to induce maximal stimulation of OCT and OAT, respectively. Studies were performed with induced water diuresis. Complete bladder emptying was assured via ultrasound evaluation.

Results: TScr and TSfr (mg/min, mean±SD) were higher in the first hour (KDIGO 1: TScr = 4.1±2.44, TSfr =0.4±0.15; KDIGO 2: TScr= 6.8±4.37, TSfr= 0.4±0.29; KDIGO 3: TScr= 3.2±1.88, TSfr= 0.3±0.15; KDIGO 4: TScr= 2.3±2.08, TSfr= 0.2±0.13) and became stable and similar after the second hour. There was no significant correlation between GFR and TScr or TSfr (Figure 1A-1B). The TScr and TSfr of the first hour correlated significantly with the clearances of IS and pC. The significant correlation was observed between stimulated TScr and IS clearance (p=0.005) and pC clearance (p=0.003 (Figure 2A - 2B)

Conclusions: The urinary clearance of IS and pC is associated and directly correlated with the secretory response of the organic transporters of the proximal tubule



FR-PO1219

Type 1 Interferon Signaling Inhibition Blocks Effects of Indoxyl Sulphate Exacerbation of Glomerular Endothelial Cell Injury In Vitro

Asha Seth,[1] Heena S. Stone,[1] Sambit K. Nanda,[2] Catharina Lindholm,[3] Nicola Ferrari,[1] Kevin Woollard.[1] *[1]AstraZeneca PLC, Cambridge, United Kingdom; [2]AstraZeneca US, Gaithersburg, MD; [3]AstraZeneca Swe, Gothenburg, Sweden.*

Background: High levels of uremic toxins, including indoxyl sulphate (IS), are associated with poor outcomes in chronic kidney disease. Previous work by us has shown anifrolumab, a type I IFN receptor mAb approved for the treatment of moderate to severe systemic lupus erythematosus (SLE), reduces the levels of IS in patients with lupus nephritis (LN). To explore the mechanisms through which anifrolumab treatment and IS reduction may provide benefit in kidney disease we examined if IS has direct damaging effects on renal cells and explored whether interferon signalling is mediating these effects.

Methods: We used an in vitro model of human primary glomerular endothelial cells (HGECs) to investigate the effects of IS treatment on the activation of inflammatory signaling and markers of endothelial dysfunction (IL-1A, IL-6, IL-8 VCAM1, ICAM1) and on the induction of an interferon response (IFI27, RASD2). We first challenged the

cells with LPS to prime the cells and mimic the increased vascular permeability that is seen in kidney disease. In further studies cells were treated with anifrolumab or human IgG1 isotype control, prior to the LPS and IS treatment. Cell lysates and supernatants were then collected for RNA and protein analysis respectively.

Results: Treatment of HGECs with IS significantly exacerbated the induction of the inflammatory markers IL-6, IL1A, and CXCL8 and the vascular dysfunction markers VCAM1 and ICAM1 caused by LPS priming. The treatment of the cells with IS alone had no effect on the markers assessed. The expression of type I IFN-responsive IFI27 and RASD2 genes following treatment with LPS was increased and no additional effects were seen when IS was added. The addition of anifrolumab prior to stimulation reduced IS mediated increases in injury and inflammation markers. In addition, anifrolumab prevented the increase in the type I IFN-response genes IFI27 and RASD2 in response to LPS treatment.

Conclusions: This study shows IS has a direct damaging effect on glomerular endothelial cells and this is mediated by type I IFN signalling. This mechanism may in part account for the link observed between increased IS levels and poor prognosis in CKD.

Funding: Commercial Support - AstraZeneca

FR-PO1220

Nr1d1 Deficiency in Renal Proximal Tubular Cells Aggravates Kidney Fibrosis by Increasing Lipid Accumulation

Cheng Jia, Xiaolan Wang, Chun Zhang. *Huazhong University of Science and Technology Tongji Medical College Union Hospital, Wuhan, China.*

Background: Renal functions are closely associated with circadian rhythms. However, the specific role and mechanism of clock genes in kidney pathophysiology remain unclear. Here, we aim to investigate the function of core clock molecular-nuclear receptor subfamily 1, group D member 1 (Nr1d1) in the development of chronic kidney diseases (CKD) and how it works.

Methods: CKD mouse model was established by unilateral ureteral obstruction. Renal proximal tubular cell-specific Nr1d1 knockout mice were generated. The effect of Nr1d1 was further evaluated by injection of the agonist SR9009 in CKD mice. The downstream of Nr1d1 was examined through chromatin immunoprecipitation.

Results: 1. Down-regulation of Nr1d1 exacerbated renal fibrosis in UUO-induced CKD mice. 2. Nr1d1 deficiency increased lipid accumulation in renal proximal tubular cells through targeting nuclear factor interleukin 3-regulated (NFIL3). 3. The Nr1d1 agonist SR9009 alleviated renal fibrosis and lipid deposition in CKD mice.

Conclusions: Our findings suggest that Nr1d1 deficiency aggravates renal fibrosis via targeting Nfil3 to increase lipid accumulation in renal proximal tubular cells in CKD mice.

Funding: Government Support - Non-U.S.

FR-PO1221

PM2.5 Induces Epithelial-to-Mesenchymal Transition by Oxidative Stress in Renal Tubular Kidney Cells

Duk-Hee Kang, Chor ho Jo, Dal-Ah Kim. *Ewha Womans University College of Medicine, Seoul, Republic of Korea.*

Background: The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide. Recently, the exposure to air pollution, especially particulate matter$_{2.5}$ ($PM_{2.5}$) was newly identified to be a potential risk factor for CKD, however there are no studies on whether exposure to $PM_{2.5}$ is a direct cause of CKD ccurrence and exacerbation. Epithelial-to-mesenchymal transition (EMT) of tubular cells is one of the early mechanisms of progression of renal disease. Therefore, the identification of association between fine dust and EMT may allow to reveal the casualty toward CKD.

Methods: Fine dust collected by $PM_{2.5}$ filter (Ulaanbaatar, Mongolia) was dissolved in DMSO by sonication. Renal tubular kidney cells (NRK) were treated with dissolved $PM_{2.5}$ (2 & 5 μL/mL). EMT was evaluated by morphological changes of NRK cells and the expressions of E-cadherin, α-SMA, and vimentin after the stimulation with $PM_{2.5}$ and TGF-β (5 ng/mL) by WB and immunostaining. ROS generation was assessed by DCF-DA and MitoSox staining. RNA-seq analysis (Ebiogen, Korea) was performed to investigate which upregulated/downregulated-genes are associated with $PM_{2.5}$-induced phenotype transition in NRK cells.

Results: $PM_{2.5}$ at the concentrations of 2 and 5 μL/mL did not alter LDH release and cell proliferation up to 48 hours of exposure. $PM_{2.5}$ induced EMT of NRK cells assessed by morphologic changes associated with a decreased E-cadherin expression and de-novo expression of α-SMA and vimentin. $PM_{2.5}$ also increased DCF-DA and Mito-Sox staining. RNA-seq analysis demonstrated the differences in gene expression related to EMT (16.7%), adipokine (15.9%), apoptotic process (13.7%), and oxidative stress (12.8%). Among them, lipocalin 2 (LCN2), Interleukin-11 (IL-11), and hyaluronan synthase 2 (HAS2) expression showed the highest fold difference (2.7-folds, 2.5-folds, and 2.0-folds, respectively) between control and $PM_{2.5}$-treated NRK cells.

Conclusions: This data suggest that exposure to $PM_{2.5}$ induces EMT and oxidative stress in NRK cells, which may be one of the possible mechanisms for the association between fine dust exposure and the development of renal disease.

Funding: Government Support - Non-U.S.

FR-PO1222

A High-Content and High-Throughput Imaging Screen to Identify a Small Molecule Inhibitor for the Lipid Uptake Function of KIM-1

Amrendra K. Ajay,[1,2] Yutaro Mori,[3] Joseph V. Bonventre.[1,2] Bonventre Laboratory. *[1]Brigham and Women's Hospital Department of Medicine, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Rikagaku Kenkyujo, Wako, Japan.*

Background: Kidney Injury Molecule-1 (KIM-1) is a glycosylated protein upregulated following proximal tubular injury in humans and mice. KIM-1 mediates the uptake of oxidized lipids and long-chain fatty acids bound to albumen by the proximal tubule. Overexpression of KIM-1 causes inflammation and fibrosis in mice.

Methods: We developed a cell-based high throughput functional assay for KIM-1-mediated uptake of DiI-labeled ox-LDL and screened 14,414 unique compounds of known bioactive library (FDA approved (Biomol 4, and Selleck) and Non-FDA approved including Cayman, MedChemExpress, and Tocris), using 769-P cells that express high levels of KIM-1. After setting up a score based on each compound's potential to inhibit cellular ox-LDL uptake, we selected 240 potential hits and cherry-picked them from the primary screening. We performed secondary assays to confirm whether TW-37 quenches the fluorophore or cleaves the extracellular domain of KIM-1. Cell-based binding assays, competitive inhibition assays, and Raman spectroscopy were employed to investigate the binding of recombinant human KIM-1 to the compound that showed the highest level of inhibition of ox-LDL uptake, TW-37.

Results: Out of a number of compounds with varying degrees of inhibition, we identified TW-37 as the top hit. TW-37 is known to have Bcl2 inhibitory activity; however, this activity is likely not related to the inhibition of uptake since another specific Bcl-2 inhibitor, ABT-263, did not block ox-LDL uptake. TW-37 is not toxic to epithelial cells at concentrations up to 11 μM. Our results from fluorescence quenching and KIM-1 cleavage assays confirmed that TW-37 does not quench the DiI-fluorophore used for the uptake experiments, nor does it cleave KIM-1. Our *in silico* docking experiments showed a putative TW-37 binding pocket spanning residues from 37 to 52 of human KIM-1. Raman spectroscopy revealed that TW-37 specifically binds in a dose-dependent manner to recombinant human KIM-1 and not to the BSA.

Conclusions: TW-37 inhibits the oxidized lipid uptake after binding to the KIM-1 protein. Thus, TW-37 is a promising therapeutic agent for blocking lipid uptake by KIM-1 in fibrotic kidney disease.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim

SA-PO001

Nephrology Tools: Using Chatbots for Image Interpretation and Answering Questions

Oscar A. Garcia Valencia, Charat Thongprayoon, Pajaree Krisanapan, Supawadee Suppadungsuk, Wisit Cheungpasitporn, Jing Miao. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Effective medical diagnosis and treatment planning rely heavily on clinical imaging. As of September 2023, ChatGPT-4 had broadened its functionality to allow image interpretation, providing comprehensive explanations and problem-solving insights. However, the effectiveness of chatbots in image interpretation remains understudied. We aimed to evaluate the performance of leading chatbots (i.e GPT-4, Bard AI, and Bing Chat), in interpreting nephrology images and addressing related test questions.

Methods: We assessed 57 nephrology test questions with their associated images from the Nephrology Self-Assessment Program and Kidney Self-Assessment Program tests. This group included 19 kidney histopathological images, 28 radiological images, and 10 images from miscellaneous categories. We ommited the image descriptions to focus only on the chatbots' interpretative abilities. Each question was analyzed two times through GPT-4, Bing Chat, and Bard AI. We then calculated and compared the accuracy and concordance rates for both image interpretation and question answering by these AI models.

Results: Regarding image interpretation, GPT-4 showed a 79% total accuracy, outperforming Bard AI's 51% and Bing Chat's 35% ($p<0.001$). All chatbots displayed a similar performance across image types ($p=0.57$, 0.39, and 0.38 for GPT-4, Bard AI and Bing Chat, respectively). On image-related questions, GPT-4, Bard, and Bing Chat yielded comparable results, with total accuracy rates of 60%, 53%, and 61% ($p>0.05$) and concordance rates of 75%, 68%, and 74% ($p>0.05$), respectively. Notably, GPT-4 and Bard AI were likely to provide correct answer when their image interpretation was accurate (correct response 60% vs 37%, $p=0.01$ for GPT-4; 60% vs 27%, $p<0.001$ for Bard AI when image interpretation was correct and incorrect respectively), while Bing Chat's accuracy on answering questions did not differ based on its accuracy of image interpretation (58% vs 51%, $p=0.50$).

Conclusions: These results highlight the challenges in developing AI-driven chatbots for medical image interpretation in nephrology, with GPT-4 showeing remarkable potential. The study provides valuable insights for further refinement of AI models, emphasizing the importance of accuracy, especially in scenarios where medical decisions rely on precise image interpretations.

SA-PO002

The Role of Artificial Intelligence (AI) Chatbots in Educating Patients with CKD on Intermittent Fasting

Joel N. Shah,[1] Adeel Ahmad,[1] Charat Thongprayoon,[2] Wisit Cheungpasitporn,[2] Prakrati C. Acharya.[1] *[1]Texas Tech University Health Sciences Center El Paso, El Paso, TX; [2]Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Intermittent fasting (IF) is a growing nutritional intervention trend that may provide health and weight loss benefits in patients. However, research is limited regarding the effects of IF in CKD patients. AI Chatbots hold enormous potential in patient education regarding various lifestyle modifications. This study aims to provide an analysis of the effectiveness of AI Chatbots on patient education regarding the effects of IF in CKD patients.

Methods: A Nephrologist generated 25 questions related to IF and CKD. Responses were generated from three AI-based Chatbots, Chat GPT 3.5, Chat GPT 4.0, and Claude 3 Sonnet. Responses for each question were generated twice across all three Chatbots with >24 hours between each. Responses were evaluated and compared to the current literature regarding IF and CKD for accuracy.

Results: The 3 AI Chatbots each generated accurate responses though the vocabulary, use of paraphrasing, and formatting differed. Each chatbot's individual responses were roughly similar though some key differences were noted. Chat GPT 4.0 noted "[Patients] should be fully informed about...the lack of extensive research specifically in CKD populations." in response number 2 for a question, an answer absent from the 1st response. Claude 3 Sonnet was noted to have large variations between its responses, including one question in which electrolyte imbalances were categorized in the 1st response but replaced by a discussion of proteinuria in the 2nd. Chat GPT 4.0, Chat GPT 3.5, and Claude 3 Sonnet referenced limited literature or the need for more extensive research in 32%, 42%, and 40% of the responses generated respectively.

Conclusions: AI Chatbots provide a novel way to educate patients with CKD on lifestyle modifications including IF. Chat GPT 3.5, Chat GPT 4.0, and Claude 3 Sonnet provided mostly accurate responses with evidence of active learning between the 2 responses for each. Chat GPT 3.5, despite being the free version of Chat GPT, provided a greater percentage of responses correctly addressing the limited literature or the need for more research regarding IF and CKD. AI Chatbots require additional technological modifications and advancements to improve patient education regarding lifestyle interventions. Additionally, further research is necessary to establish the effects of IF in CKD patients.

SA-PO003

Enhancing Large Language Models (LLM) Performance in Nephrology through Prompt Engineering: A Comparative Analysis of ChatGPT-4 Responses in Answering AKI and Critical Care Nephrology Questions

M. Salman Sheikh, Charat Thongprayoon, Fawad Qureshi, Yasir Abdelgadir, Iasmina Craici, Kianoush Kashani, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Large Language Models (LLMs) have significantly advanced the field of artificial intelligence (AI). The effectiveness of LLMs is substantially influenced by the structure and formulation of input queries, a process known as prompt engineering. Prompt engineering techniques, such as the chain of thought approach, which involves thinking through problems step by step, have shown promising accuracy compared to regular prompts. This study investigates the impact of the chain of thought approach on the accuracy of ChatGPT-4 in addressing acute kidney injury (AKI) and critical care nephrology questions.

Methods: We presented ChatGPT-4 with 101 questions from the Kidney Self-Assessment Program (KSAP) and Nephrology Self-Assessment Program (NephSAP). We employed two prompting methods: one using the original question and the other utilizing the chain of thought approach. The McNemar test was used to assess differences in accuracy, while Cohen's kappa was employed to evaluate agreement between the two prompting methods.

Results: ChatGPT-4 demonstrated an accuracy of 87.1% with chain of thought prompting, outperforming the 81.2% accuracy achieved with regular prompting (P=0.15). The kappa statistic for the responses provided by the two prompts is 0.80. Consistency between the two methods was observed in 84.2% of the questions, with 78.2% being correctly answered by both methods. Chain of thought prompting correctly answered nine questions that were missed under regular prompting. Among the thirteen questions missed under chain of thought prompting, a notable 76.9% were repeated errors from regular prompting. Only three questions incorrectly answered with the chain of thought prompting were correct under regular prompting.

Conclusions: The chain of thought approach improves ChatGPT-4's accuracy in addressing nephrology-related questions compared to regular prompting, although the difference is not statistically significant. These findings emphasize the importance of developing effective prompting strategies to optimize the application of LLMs in clinical decision support. Future research should aim to generalize these findings across different medical specialties to maximize the benefits of LLMs in clinical decision-making.

SA-PO004

Self-Captured Images Recognition by Artificial Intelligence (AI) in Common Nephrology Medications: A Comparative Analysis of ChatGPT-4 and Claude 3 Opus

M. Salman Sheikh, Benjamin Dreesman, Erin F. Barreto, Jing Miao, Charat Thongprayoon, Fawad Qureshi, Iasmina Craici, Kianoush Kashani, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Accurate medication identification is crucial in nephrology, where patients with kidney diseases often require complex regimens. Artificial intelligence (AI) shows the potential to assist medication management, particularly when patients cannot remember medication names or labels are unavailable. Self-captured image recognition by AI could enhance medication safety and reduce errors for these patients by streamlining medication reconciliation, improving adherence, and supporting clinical decision-making. This study evaluates ChatGPT-4 and Claude 3 Opus in identifying common medications in nephrology from self-captured images.

Methods: Twenty-five medications commonly encountered in nephrology were randomly selected and systematically photographed using an iPhone 13 Pro Max, capturing both front and back views. The images were analyzed by ChatGPT-4 and Claude Opus with the inquiry, "What is this medication?" The percentage of correct identifications determined the accuracy of each model, and a two-tailed Fisher's exact test was used to compare the accuracy rates between the two models, with a P-value < 0.05 considered statistically significant.

Results: ChatGPT-4 showed a robust performance, correctly identifying twenty-two out of twenty-five medications, with an accuracy rate of 88%. Errors occurred in identifying hydrochlorothiazide, nifedipine, and spironolactone due to challenging imprints. Conversely, Claude 3 Opus only accurately identified one medication – trazodone. It misidentified the remaining twenty-four medications, achieving a notably lower accuracy rate of 4%, even though it correctly read the imprint of eighteen of these. ChatGPT-4 significantly outperformed Claude 3 Opus ($P<0.001$).

Conclusions: The study highlights the superiority of ChatGPT-4 over Claude 3 Opus in the task of identifying common medications from self-captured pictures. While ChatGPT-4 demonstrated high accuracy, Claude 3 Opus showed significant limitations, underscoring its inadequacy for clinical application in this context. These findings advocate for further development and integration of robust image recognition technology to support accurate medication management in nephrology.

SA-PO005

Data Preprocessing: A Key Factor in Large Language Models' Performance in Critical Care Nephrology

M. Salman Sheikh, Charat Thongprayoon, Fawad Qureshi, Jing Miao, Iasmina Craici, Kianoush Kashani, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: In clinical evaluations, data is often encountered in the form of tables from outside sources. These tables can be processed as images or reformatted into text before being input into multimodal large language models (LLMs). The use of LLMs in medical education and decision-making is gaining traction. However, their accuracy in interpreting complex clinical data, particularly when presented as images rather than reformatted text, remains a concern. This study evaluates the impact of data formatting on the performance of ChatGPT-4 and Claude 3 Opus in answering critical care nephrology questions from the Kidney Self-Assessment Program (KSAP).

Methods: Fifty-six AKI and critical care nephrology questions from KSAP were reviewed, focusing on 46 questions that included tables with pertinent information such as laboratory values and diagnostic results. Initially, tables were inputted in an image-encoded format (screenshots), and the models' responses were recorded. Subsequently, the tables were reformatted into pure-text format, and the models were reassessed using the same questions. McNemar test assessed the statistical significance of the improvement in accuracy, and Cohen's Kappa test evaluated the agreement between pre-formatting and post-formatting answers for each model.

Results: In the initial run with tables in image-encoded format, ChatGPT-4 and Claude 3 Opus achieved accuracies of 50% and 43.5%, respectively. After reformatting from image-encoded format to pure-text based format, ChatGPT-4 and Claude 3 Opus' accuracies improved significantly to 73.9% and 60.87% ($p<0.001$), respectively. The Cohen's Kappa score for the agreement between GPT-4's pre-formatting and post-formatting answers is approximately 0.141, while the Cohen's Kappa score for the agreement between Claude 3 Opus's pre-formatting and post-formatting answers, after aligning the data for the same set of questions, is 0.350.

Conclusions: Data formatting significantly impacts the performance of LLMs in interpreting complex clinical data in critical care nephrology. Reformatting tables from image-encoded to pure-text format significantly improves the accuracy of ChatGPT-4 and Claude 3 Opus in answering KSAP questions. This highlights the importance of data preprocessing in optimizing LLM performance for clinical decision support.

SA-PO006

Integrating Artificial Intelligence (AI) in Nephrology Workflows: Evaluating ChatGPT's Performance in Triaging Patients to Nephrology Subspecialty Clinics

Priscilla Koirala, Charat Thongprayoon, Jing Miao, Oscar A. Garcia Valencia, M. Salman Sheikh, Iasmina Craici, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: The rising prevalence of kidney-related conditions and aging global populations pose challenges for the healthcare sector, particularly nephrology. Efficient patient referral and treatment processes are crucial, and artificial intelligence offers promise in revolutionizing medical triage. This study evaluates ChatGPT's utility in triaging nephrology cases through simulated real-world scenarios, aiming to enhance decision-making efficiency and accuracy in clinical settings.

Methods: Two nephrologists created 100 simulated cases, encompassing a variety of aspects within nephrology and its intersecting subspecialties, to test ChatGPT 4.0. We assessed ChatGPT's performance in two separate evaluation attempts in March and April 2024. The evaluation focused on two main areas: the appropriateness of nephrology consultations and the accuracy in identifying suitable nephrology subspecialties.

Results: ChatGPT demonstrated high overall accuracy (98.5%) in identifying the need for nephrology consultations across two rounds, achieving 99% on the first attempt and 98% on the second. However, some misreferrals occurred to nephrology subspecialty clinics, such as recommending an Electrolyte Disorders clinic instead of Onconephrology for a cancer patient with worsening renal failure. While ChatGPT's suggestions were reasonable and safe, they sometimes lacked the depth needed to fully prioritize the intertwined oncological impacts. The AI's triage suggestions showed a reasonable level of clinical appropriateness by identifying related nephrological issues, even when the optimal subspecialty choice was missed. The output was grounded in logical clinical reasoning but could better integrate multidisciplinary care approaches for complex, intersecting medical conditions.

Conclusions: ChatGPT demonstrated high accuracy in triaging nephrology cases, providing safe and clinically appropriate recommendations. However, the AI could be enhanced to better integrate multidisciplinary care approaches for patients with complex, intersecting medical conditions. This study highlights the potential of AI in improving medical triage efficiency and accuracy while identifying areas for refinement.

SA-PO007

Optimizing Triage of Emergency, Urgent, and Elective Inbox Messages in Nephrology Using Artificial Intelligence (AI)

Justin Pham,[1,2] Charat Thongprayoon,[2] Jing Miao,[2] Iasmina Craici,[2] Wisit Cheungpasitporn.[2] *[1]Mayo Clinic College of Medicine and Science, Rochester, MN; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: In nephrology clinics, the workload burden associated with responding to patient inbox messages is significant. Some cases require emergent attention, such as those with severe electrolyte disorders or significant acute kidney injury. Efficient triage of these messages is crucial for ensuring timely medical attention based on urgency, reducing workload, and ultimately improving patient care. The integration of large language models like ChatGPT-4 into clinical practice has the potential to enhance operational efficiency by automating the triage process. This study aims to evaluate the accuracy of ChatGPT-4 in categorizing patient inbox messages in a nephrology clinic setting.

Methods: Two nephrologists wrote 150 patient inbox messages based on cases encountered in everyday practice at a nephrology outpatient clinic. 50 were written to simulate emergencies, 50 were urgent, and 50 were non-urgent. They were then submitted to ChatGPT-4 for independent triage into the same categories. The process was repeated after two weeks. ChatGPT responses were graded as correct, overestimation (higher priority), or underestimation (lower priority). Cohen's kappa statistic (κ) was calculated to quantify inter-rater and internal agreement.

Results: ChatGPT correctly triaged 140/150 messages (93.3%; κ = 0.9) in each trial, with an intra-rater agreement rate of 92% (κ = 0.88) across trials. It had the highest accuracy for emergent messages, followed by non-urgent, then urgent ones. There were more instances of overestimation than to underestimation. Subcategorical results are included in **table 1**.

Conclusions: ChatGPT-4 demonstrated near-perfect inter-rater agreement with nephrologists and high internal consistency in triaging 150 simulated patient inbox messages based on cases encountered in an outpatient clinic. The study highlights the potential for AI-driven triage systems to enhance operational efficiency and improve care for patients with kidney diseases. More research with larger datasets across medical specialties is needed to validate the generalizability of these findings.

Table 1

		ChatGPT Trial 1			ChatGPT Trial 2		
Category	Number	Correct	Overestimate	Underestimate	Correct	Overestimate	Underestimate
Nonurgent	50	49	1	0	46	4	0
Urgent	50	45	3	2	45	5	0
Emergency	50	46	0	4	49	0	1
All	150	140	4	6	140	9	1

SA-PO008

Artificial Intelligence (AI) and Green Nephrology: Assessing the Commitment of ChatGPT Models to Environmental Sustainability

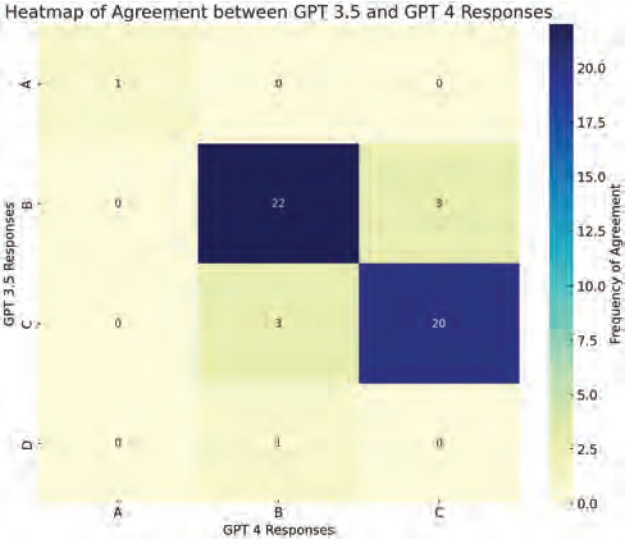
Suryanarayanan Balakrishnan,[1] Charat Thongprayoon,[2] Jing Miao,[2] Iasmina Craici,[1] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic Health System, Mankato, MN.*

Background: With increasing use of AI and large language models in healthcare, including nephrology, there is growing concern about their potential impact on the environment and sustainable medical practices. Green nephrology has been increasingly emphasized in recent years due to climate change and environmental concerns. However, the commitment of AI models to green nephrology remains unclear.

Methods: Between March and May 2024, a set of 50 simulated questions, reviewed by two nephrologists, were created to assess the commitment of ChatGPT 3.5 and 4.0 to green nephrology practices. The questions were scored on a scale of 0 to 3, with 0 indicating no support for green nephrology and 3 indicating strong support. The total scores for GPT 3.5 and GPT 4 were calculated and compared. The Cohen's kappa coefficient was used to measure the agreement between the answers of GPT 3.5 and GPT 4.

Results: The total scores for GPT 3.5 and GPT 4 were 142/150 and 144/150, respectively. Both had the same score on 88% of the questions, with GPT 4 outperforming GPT 3.5 on 8% of the questions. The Cohen's kappa coefficient for the agreement between the answers of GPT 3.5 and GPT 4 was approximately 0.74. Both identified key barriers, such as high energy consumption, waste management challenges and limited awareness. They suggested strategies like implementing energy-efficient technologies, developing recycling programs and integrating sustainability into education and training to address these barriers.

Conclusions: GPT 3.5 and GPT 4 demonstrated commitment to green nephrology practices, providing valuable insights into the barriers to sustainable nephrology and potential solutions. The high agreement between them suggests that AI can be developed to support sustainable medical practices. Further research is needed on AI's environmental impact in healthcare.



SA-PO009

Harnessing Artificial Intelligence (AI): Evaluating Models for Social Discourse Analysis among Patients with Kidney Disease in Online Communities

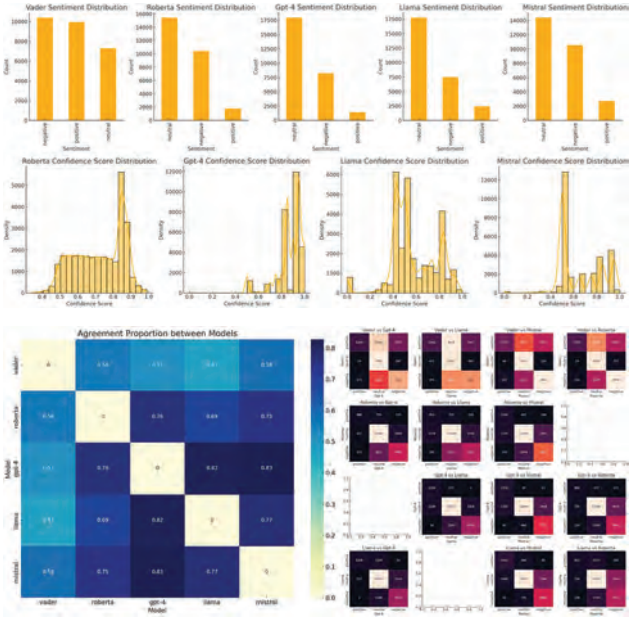
Rajesh Anumolu,[1,2] Aaron Delory,[3] Anil K. Chandraker.[1,2] *[1]University of Massachusetts Chan Medical School, Worcester, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]IO Design Team LLC, Danvers, MA.*

Background: The rapid exchange of information through technology has transformed healthcare communication. Online patient communities generate data too quickly for traditional methods, offering opportunities for sentiment analysis to guide research and inform pharmaceutical development. While many researchers use OpenAI's Chat-GPT, the variability and nuances of different large language models (LLMs) are under-assessed. Understanding these differences is crucial for selecting the appropriate model for specific applications. This study compares four LLMs to evaluate their strengths and weaknesses in sentiment analysis.

Methods: The study analyzed 39,637 Reddit posts and 283,326 comments from 2011 to 2022 across subforums related to dialysis, kidney disease, kidney stones, and transplants. The following LLMs were used: **VADER**: Rule-based model for social media sentiment analysis **RoBERTa**: Transformer-based model optimized for sentiment analysis tasks **Chat-GPT 4o**: Fine-tuned version of OpenAI's GPT-4 **LLaMA 3 8b-instruct and Mistral 283k**: Transformer-based models Each model analyzed the text for sentiment (positive/negative/neutral) and provided confidence scores. The results were compared to assess agreement and model-specific biases.

Results: Visualized results on graphs. Models' Biases: -VADER: Tends to overestimate positive sentiment due to sensitivity to positive keywords. **-RoBERTa**: Classifies more posts as neutral, possibly underrepresenting emotional extremes. **-GPT-4**: Balanced sentiment with a slight positive bias, capturing nuanced positivity. **-LLaMA**: Frequently predicts neutral sentiment, ensuring conservative interpretation. **-Mistral**: Higher count of negative predictions, emphasizing detection of negative expressions.

Conclusions: Recognizing the variability among LLMs is crucial for selecting the right tool, as even this analysis of four models showed different emphases and nuances. In the best of circumstances, these models may provide insights into patient experiences, highlight health disparities, guide equitable interventions, and amplify marginalized voices. However, without proper evaluation, we may miss the mark. Future research should explore diverse datasets to enhance our understanding of these platforms.



SA-PO010

Role of Artificial Intelligence (AI) in Clinical Interpretation of 24-Hour Ambulatory Blood Pressure Monitoring

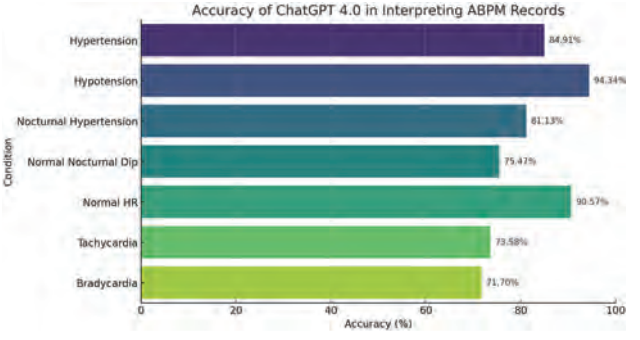
Sreyoshi F. Alam, Maria Lourdes Gonzalez Suarez, Charat Thongprayoon, Jing Miao, M. Salman Sheikh, Oscar A. Garcia Valencia, Gary L. Schwartz, Iasmina Craici, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: The utility of AI in interpreting ambulatory blood pressure monitoring (ABPM) data is increasingly recognized. Evaluating the accuracy of AI models, like ChatGPT 4.0, in clinical settings can inform their integration into healthcare processes. However, limited research has been conducted to validate the performance of such models against expert interpretations in real clinical scenarios.

Methods: This study assessed the performance of ChatGPT 4.0 in interpreting 24-hour ABPM records from 54 cases at Mayo Clinic, Minnesota, in March 2024. The AI's interpretations were compared with results confirmed by two nephrologists, who reached a consensus on the presence or absence of specific conditions based on the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.

Results: ChatGPT 4.0 demonstrated varied accuracy across different conditions: Hypertension (84.91%), Hypotension (94.34%), Nocturnal Hypertension (81.13%), Normal Nocturnal Dip (75.47%), Normal Heart Rate (90.57%), Tachycardia (73.58%), and Bradycardia (71.70%). These outcomes highlight the model's capability to reliably interpret complex clinical data with considerable accuracy. The model's performance in identifying tachycardia and bradycardia, however, was comparatively lower, suggesting room for improvement in these areas.

Conclusions: The findings suggest that ChatGPT 4.0 has the potential to assist in the clinical interpretation of 24-hour ABPM. However, the model's current performance indicates that further improvements in accuracy are necessary before it can be effectively incorporated into clinical practice. Ongoing advancements and training on diverse datasets could enhance the model's diagnostic precision, making AI a promising tool for the routine analysis of ABPM data. While the results are encouraging, further research is needed to refine the model's performance and validate its utility across larger, more diverse patient populations.



SA-PO011

Natural Language Processing for Extracting Kidney Biopsy Pathology Diagnoses: The Houston Methodist Hospital Kidney Biopsy Registry

Shane A. Bobart, Enshuo Hsu, Luan D. Truong, Amy D. Waterman, Stephen L. Jones, Tariq Shafi. *Houston Methodist Hospital, Houston, TX.*

Background: Kidney biopsy reports provide detailed description of kidney pathology, but the diagnosis is not captured as searchable, discrete data in electronic health records (EHR) requiring labor-intensive manual review and abstraction. We sought to use Natural Language Processing (NLP) to extract kidney biopsy pathology diagnoses as an initial step to create an automatically updated Houston Methodist Hospital Kidney Biopsy Registry (HM-KBR).

Methods: We identified 3,087 native kidney biopsies (2,700 patients) from June 2016 to December 2023. We extracted 1000 native kidney biopsy reports in PDF format from the Epic EHR. A domain expert (SAB) manually annotated the primary diagnosis in the 1000 reports and a renal pathologist (LT) validated 20% (n=200). We processed the PDFs into machine-readable free text with SQL server (database management software) and Python (programming language). We split the biopsy reports into a training set (80%) and used the bidirectional encoder representations from transformers (BERT) NLP model to extract primary diagnoses. We evaluated the NLP model performance in a stand-alone test set (20%). The evaluation metrics included precision (false positive rate), recall (false negative rate), F1 score (harmonic mean of precision and recall, ranging 0 to 1, with 1 implying perfect model performance) and AUROC (overall performance, 1.0 is best). Due to the preliminary size of the training set, we limited the diagnosis types to those present in at least 20 reports for the evaluation metrics.

Results: The median age was 57 years, 50% were female, 28% Black and 23% Hispanic. The agreement between the two reviewers in the validation sample was assessed by Cohen's kappa statistic (0.76; excellent). The NLP extracted diagnoses showed an F1 score of 0.66 and AUROC of 0.93 (Table 1).

Conclusions: Our preliminary data shows an accurate and scalable NLP based model to extract the primary diagnosis from free text kidney biopsy pathology reports.

Table 1: Standard Evaluation Metrics of the NLP model

Biopsy Diagnosis	Total (N=1000)	Training set (N=800)	Test set (N=200)	Precision	Recall	F1	AUROC
Diabetic Kidney Disease	235	191	44	0.917	1.000	0.957	0.997
Arterionephrosclerosis	228	171	57	0.830	0.684	0.750	0.921
Focal Segmental Glomerulosclerosis	140	119	21	0.727	0.762	0.744	0.922
Acute Tubular Necrosis	105	81	24	0.783	0.750	0.766	0.919
IgA Nephropathy	102	89	13	0.867	1.000	0.929	1.000
Tubulointerstitial Nephropathy/Fibrosis	95	77	18	0.500	0.167	0.250	0.722
Acute Interstitial Nephritis	93	69	24	0.737	0.583	0.651	0.964
Lupus Nephritis	86	73	13	1.000	0.923	0.960	0.971
Membranous Nephropathy	73	58	15	1.000	1.000	1.000	1.000
Pauci-immune GN/ANCA Vasculitis	40	31	9	0.833	0.556	0.667	0.995
Arteriosclerosis	37	28	9	0.000	0.000	0.000	0.578
Thrombotic Microangiopathy	34	28	6	1.000	0.833	0.909	1.000
Other	30	23	7	0.667	0.286	0.400	0.838
Minimal Change Disease	29	23	6	1.000	1.000	1.000	1.000
Amyloidosis	26	19	7	1.000	1.000	1.000	1.000
Chronic Interstitial Nephritis	26	17	9	0.000	0.000	0.000	0.776
Non-Specific Findings	24	18	6	0.500	0.333	0.400	0.835
Crescentic Glomerulonephritis	22	18	4	0.333	0.250	0.286	0.986
Global Glomerulosclerosis	22	20	2	0.500	0.500	0.500	1.000
Immune Complex Mediated GN	20	13	7	0.750	0.429	0.545	0.990
Average (at least 20 notes)						**0.662**	**0.930**

SA-PO012

Use of Natural Language Processing and Deep Learning to Analyze Kidney Ultrasound Reports and Their Correlation with CKD Diagnosis

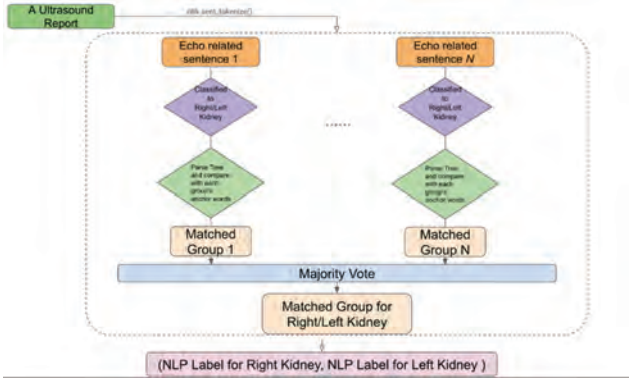
Farrukh M. Koraishy, Chenlu Wang, Ritwik Banerjee, Harry Kuperstein, Hamza Malick, Hira Tahir, Ruqiyya Bano, Priyal Sakhuja, Janos G. Hajagos. *Stony Brook University, Stony Brook, NY.*

Background: Natural language processing (NLP) can analyze unstructured data in imaging reports for clinical correlation, but this has not been reported in the context of kidney ultrasound reports and chronic kidney disease (CKD).

Methods: From the set of 1,068 patient ultrasound reports, NLP models were developed for kidney echogenicity and length. Kidney echogenicity was divided into 'normal', 'echogenic' or 'others' categories using NLP Toolkit to isolate sentences pertinent to echogenicity and Parse Tree Method and BioBERT to determine the word-level and sentence-level echogenicity classification respectively. Embeddings from Language Models was used to extract kidney size data and length classified as 'normal' or 'small' based on percentiles.100 reports were randomly selected for annotation by nephrologists to develop ground-truth ultrasound labels that were initially tested on the model. Subsequently the model was used to analyze the association of kidney ultrasound features with CKD diagnosis using logistic regression (LR) models.

Results: The word-level NLP method (Figure 1) demonstrated higher accuracy and precision for the classification of increased echogenicity compared to the sentence-level method. Subsequently only the word -level NLP model was used for further analyses with clinical correlations. Based on the 10% percentile, kidneys measuring under 8.5 cm in females and under 9.0 cm in males were categorized as "small". On multivariable LR, in addition to traditional factors like age, sex, diabetes, hypertension, heart failure and AKI; the presence of bilaterally echogenic kidneys was a strong predictor of CKD (OR = 5.49 [3.44, 8.75]; p<0.0001). The presence of bilaterally small kidneys was also a significant predictor (OR = 3.77 [1.25, 13.87)]; p=0.046).

Conclusions: Advanced NLP models with detailed text analysis can accurately detect CKD features in kidney ultrasound reports.



SA-PO013

Identifying Peripheral Artery Disease in Persons with and without CKD from Electronic Health Records

Georgia Parsons, Gomathy Parvathinathan, Margaret R. Stedman, Tara I. Chang. *Stanford University School of Medicine, Stanford, CA.*

Background: Peripheral artery disease (PAD) may be more difficult to identify in CKD due to altered pathophysiology. We aimed to develop a model to identify PAD in persons with and without CKD from electronic health records (EHR) to facilitate future studies.

Methods: We used the Stanford Medicine Research Repository (STARR) EHR mapped to the OMOP Common Data Model to identify adults with ≥1 PAD encounter 1/2020 to 9/2022. We randomly selected 993 patients for chart review for ground truth PAD status. Potential variables included PAD billing codes, demographics, comorbidities, diagnostic testing, and specialist visits. We built logistic regression models using age, diabetes and the top 10 percentile of variables selected by random forest. We assessed sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV), and accuracy overall and by CKD status (defined using ≥2 codes/labs). We chose the threshold probability to maximize Youden's index with specificity>sensitivity. We calculated 95% confidence intervals [CI] by bootstrapping 1,000 samples.

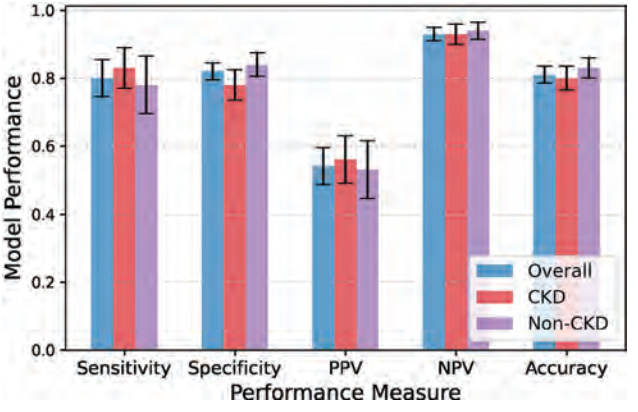
Results: In our cohort (**Table**), 222 (22%) had PAD (130 with CKD, 92 without). Our model had high sensitivity, specificity, NPV and accuracy but low PPV (**Figure**). Results were similar by CKD status.

Conclusions: Our study is among the first to focus on PAD ascertainment in CKD. Using discrete EHR data elements, our model generally performed well regardless of CKD status, but due to the lower prevalence of PAD, the PPV was relatively low. Future approaches will use natural language processing to incorporate clinical notes and diagnostic reports to improve model performance.

Funding: Other NIH Support - NHLBI

	Overall (n = 993)	CKD (n = 498)	Non-CKD (n = 495)
Age, y, mean (SD)	73.6 (12.7)	76.2 (12.3)	70.9 (12.5)
Women	484 (48.7%)	232 (46.6%)	252 (50.9%)
White race	620 (62.4%)	300 (60.2%)	320 (64.6%)
Hispanic ethnicity	115 (11.6%)	55 (11.0%)	60 (12.1%)
Selected Comorbidities			
Hypertension	772 (77.7%)	453 (91.0%)	319 (64.4%)
Diabetes mellitus	445 (44.8%)	273 (54.8%)	172 (34.7%)
Smoker	231 (23.3%)	117 (23.5%)	114 (23.0%)
PAD-related procedure			
Revascularization	72 (7.3%)	40 (8.0%)	32 (6.5%)
Diagnostic imaging	227 (22.9%)	132 (26.5%)	95 (19.2%)
Specialist visit	304 (30.6%)	141 (28.3%)	163 (32.9%)
≥2 PAD-related encounters	669 (67.4%)	350 (70.3%)	319 (64.4%)

Baseline Characteristics



Model Performance

SA-PO014

Validation of an Electronic Phenotyping Algorithm for Nephrolithiasis

Nicholas B. Larson,[1] Shannon K. McDonnell,[1] Jun Ma,[1] Jacob A. Frank,[1] Alexander R. Chang,[2] Ion D. Bucaloiu,[2] Steven J. Scheinman,[2] Peter C. Harris,[1] John C. Lieske.[1] *[1]Mayo Foundation for Medical Education and Research, Rochester, MN; [2]Geisinger Commonwealth School of Medicine, Scranton, PA.*

Background: Computable phenotypes using electronic health record (EHR) data are highly useful for facilitating research for various disease conditions, including history of kidney stones (KS). However, evaluating the performance and limitations of phenotyping algorithms is essential.

Methods: We defined a KS phenotyping algorithm using ICD-9/10 and CPT codes. To assess its performance, we designed a phenotyping validation study using EHR data from Mayo Clinic Biobank (MCBB) participants. Gold standard chart abstraction was performed by two readers blinded to the predicted KS status. A random sample of 150 predicted KS cases and 150 predicted controls were abstracted, with phenotyping performance assessed by sensitivity, specificity, PPV, and NPV, with 95% confidence intervals (CIs), adjusted for verification bias. Inter-reader reliability was assessed on 80 participants evaluated by both readers via Cohen's k. Finally, external validation was performed on a random sample from the Geisinger MyCode/DiscovEHR participants.

Results: Among 46,207 MCBB participants eligible for our study, 3917 (7.9%) were screen positive using the KS algorithm. For the 80 MCBB participants abstracted by both readers, 75/80 (93.8%) matched abstracted KS status (k = 0.88; 95% CI: [0.77,0.98]). Estimated performance measures are reported in Table 1. Overall, we observed very high specificity of 0.992, but sensitivity was moderate at 0.456. These estimates suggest a true MCBB KS prevalence of ~15.6%. Similar performance was observed in the MyCode/DiscovEHR participants.

Conclusions: Our code-based KS electronic phenotyping algorithm demonstrated excellent specificity but moderate sensitivity. Additional sensitivity may be possible through inclusion of natural language processing, similar AI-based clinical note interpretation, and/or inclusion of patient questionnaire data.

Funding: NIDDK Support, Private Foundation Support

Performance Measures

Measure	MCBB: Estimate [95% CI]	MyCode/DiscovEHR: Estimate [95% CI]
PPV	0.913 [0.857, 0.949]	0.923 [0.832, 0.967]
NPV	0.905 [0.848, 0.843]	0.827 [0.767, 0.873]
Sens	0.456 [0.416, 0.496]	0.348 [0.315, 0.381]
Spec	0.992 [0.990, 0.993]	0.991 [0.988, 0.993]

Phenotyping algorithm performance measures and 95% confidence intervals. PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval, Sens = sensitivity, Spec = specificity

SA-PO015

Comparative Accuracy of Self-Reported vs. Electronic Health Record (EHR)-Derived Charlson Comorbidity Index among Veterans with Advanced CKD

Nandita Senthil,[1,2] Grant D. Scheiffele,[2] Cydney E. Parmar,[1,2] Popy Shell,[2] Huanguang Jia,[2] Ashutosh M. Shukla.[1,2] *[1]University of Florida, Gainesville, FL; [2]VA North Florida South Georgia Veterans Health System, Gainesville, FL.*

Background: Inaccurate or missing diagnosis codes limit the prognostic power of EHR-derived comorbidity indices, such as, Charlson Comorbidity Index (EHR-CCI). CCI calculated by patients self-reporting individual comorbidities (SR-CCI) can address these errors but are subject to patient awareness and recollection bias. The relative accuracy of SR-CCI vs. EHR-CCI has not been examined, especially among the US Veterans with CKD.

Methods: Using the baseline data of the ongoing randomized Trial to Evaluate and Assess the impact of Comprehensive pre-kidney failure education on Home dialysis among Veterans (TEACH-VET) on variety of patient outcomes, this study aimed to assess the concordance and accuracy of SR-CCI and EHR-CCI among veterans with advanced CKD. In addition to the detailed data for demographic and socioeconomic variables, all enrollees were self-queried for the individual comorbidities by trained study staff to collect their CCI at the enrollment. SR-CCI was compared against EHR-CCI, extracted from VA database, anchoring for each patient's enrollment date.

Results: Of the 551 Veterans with advanced CKD enrolled in TEACH-VET, 338 participants with complete baseline data, including SR-CCI were included for this analysis. The primary outcome, the aggregate CCI score did not differ significantly between the SR-CCI and EHR-CCI (p=0.1), however, there were significant differences in individual comorbidities composing CCI. Of the 17 comorbidities comprising CCI, 13 (76.5%), notably, CKD-related comorbidities, e.g., moderate to severe CKD and liver disease, diabetes with or without complications, and myocardial infarction, etc., had substantial disagreements (p<0.0001) between the two methods, whereas peripheral vascular disease, mild liver disease, hemiplegia, and AIDS had no significant difference between the two methods. There were no significant differences in the demographic characteristics across the score patterns.

Conclusions: Most comorbidities used for CCI are either over or under accounted for by EHR-CCI, raising concerns for its routine use in clinical and epidemiological research. Future qualitative studies comparing SR-, and EHR-CCI comparison are needed to determine optimal method for reporting CCI and similar comorbidity indices.

Funding: Veterans Affairs Support

SA-PO016

Real-World Data in an Observational Medical Outcomes Partnership/ Common Data Model (OMOP/CDM) Platform: Assessing the Impact of Statins on Reducing the Need for Dialysis of Diabetic Patients Treated with ARBs/ACE Inhibitors

Cesar A. Truyts, Rogerio Passos, Maria T. Abrahao, Uri P. Flato, Amanda G. Rabelo, Mateus d. Freitas, Diogo F. Patrão, Edson Amaro Junior, Adriano José Pereira. *Sociedade Beneficente Israelita Brasileira Albert Einstein, Sao Paulo, Brazil.*

Background: Diabetics are at high risk of developing kidney dysfunction. Angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) are often employed to mitigate the risk of kidney disease progression. Statins also show promise in reducing the risk of chronic kidney disease (CKD) progression. This study examines the impact of statins on reducing the need for dialysis among diabetic patients treated with ACEIs or ARBs, utilizing the OMOP CDM framework within the Hospital Israelita Albert Einstein in São Paulo/Brazil.

Methods: This retrospective, observational cohort study at a single hospital used the OMOP CDM framework to analyze electronic health records of diabetic patients treated with ACEIs/ARBs, from 2017 to 2023. Adult Type 2 Diabetes Mellitus patients receiving ACEIs/ARBs, and possibly statins were included. Statistical analyses using Python involved Chi-square and Mann-Whitney U tests, and multivariate logistic regression, ensuring significance with p-values less than 0.05.

Results: Out of 55,764 diabetic patients using ACEIs or ARBs, 36,378 (65.2%) were taking statins. Statin users were older (median [range], 65 years [53–75] vs. 45 years [35–59]; P < 0.01) and predominantly male (56% vs. 44%; P < 0.001). Logistic regression adjusted for age and sex showed that statin users had a lower dialysis rate (0.20% vs. 2.88%; P < 0.001 - Table 1)

Conclusions: The data suggest that statin therapy was associated with a reduced need for dialysis in high-risk diabetic patients with ACEIs/ARBs. The OMOP CDM framework was an easy way to simplify and accelerate analysis of large amount of data, in an integrated and protected environment, highlighting its value in advanced medical research.

Baseline demographics

Variables	Statin Users (n = 36,378)	Nonstatin users (n = 19,386)	P Value
Age, years median [IQR]	65 [53;75]	45 [35;59]	< 0.01
Sex (Male) n(%)	20,311 (56%)	8,574 (44%)	< 0.001
Dialysis n(%)	73 (0,20%)	559 (2,88%)	< 0.001

SA-PO017

A Randomized Controlled Trial of Video-Assisted Electronic Consent vs. Standard Consent for Percutaneous Kidney Biopsy (eConsent Bx)

Pedro H. Gois,[1,2] Vera Y. Miao,[4] Rebecca Saunderson,[4] Marina Wainstein,[2] Kylie-Ann Mallitt,[6] Shaun P. Chandler,[5] Belinda Elford,[5] Rebecca Hudson,[7] Julia Jefferis,[5] Helen G. Healy,[5,2] Ann Bonner.[3] *[1]John Hunter Hospital, New Lambton Heights, NSW, Australia; [2]The University of Queensland, Brisbane, QLD, Australia; [3]Griffith University Griffith Sciences, Southport, QLD, Australia; [4]Northern Sydney Local Health District, St Leonards, NSW, Australia; [5]Royal Brisbane and Women's Hospital, Herston, QLD, Australia; [6]The University of Sydney, Sydney, NSW, Australia; [7]Fiona Stanley Hospital, Murdoch, WA, Australia.*

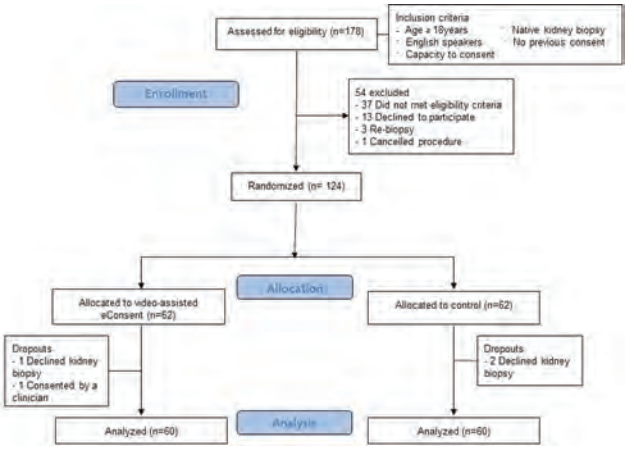
Background: Video-assisted electronic consent (eConsent) enhances understanding, reduces anxiety, and boosts satisfaction in medical procedures. Yet, its impact on percutaneous kidney biopsies (PKB) remains unexplored. We aimed to assess patient-reported benefits of eConsent versus conventional consent for PKB.

Methods: In a single-center, open-label, RCT, consecutive patients undergoing PKB were randomized (1:1) to either video-assisted eConsent (intervention) or conventional consent (control). The intervention group accessed an online platform featuring an 8-minute explanatory animation before providing eConsent, while the control group was consented by clinicians and signed a paper form. The primary outcome was questionnaire-based patient comprehension, with secondary outcomes including patient-reported experience (KidneyPREM), anxiety, and satisfaction with consent.

Results: Median participant age was 52 years (IQR [34-65]), 30.7% had ≤ year 12 education and 69.3% post-secondary qualifications. Baseline characteristics were similar between groups. PKB comprehension was significantly higher in the intervention group compared to control (3 more questions correct/9; p<0.001), regardless of education level. Moreover, the intervention group demonstrated better understanding of critical information related to pre- and post-PKB care and when to seek medical attention for complications. There were no statistically significant differences in KidneyPREM, anxiety, or satisfaction between groups.

Conclusions: Video-assisted eConsent enhances PKB comprehension without affecting KidneyPREM, anxiety or satisfaction. These benefits extend to patients with lower education levels. Its implementation could standardize and streamline consent processes in PKB, with potential application in other nephrology domains.

Funding: Private Foundation Support



SA-PO018

Health 360x Registry (H360xR): Artificial Intelligence (AI)-Enabled Equitable Access to Point-of-Care Decentralized Clinical Trials

Chamberlain I. Obialo,[1,2] Eva Lee,[1] Elizabeth O. Ofili.[2,1] *[1]Accuhealth Technologies Inc, Atlanta, GA; [2]Morehouse School of Medicine, Atlanta, GA.*

Background: The lack of diversity in clinical trial population and non-involvement of community physicians are major barriers to recruitment and retention of representative populations in industry sponsored and National Institute of Health [NIH] research studies.

Methods: AH received an NIH Fast Track Small Business Innovation Research (SBIR) Award to implement a scalable access to point of care decentralized clinical trials (DCT), by systematically addressing gaps in the practice infrastructure of resource limited small-medium practices. The conceptual model is the Practical, Robust Implementation and Sustainability (PRISM) that targets barriers at the patient, provider and practice levels. We developed H360x Clinical Research Platform and Registry as an artificial Intelligence [AI] enabled digital health platform (DHT) that uses machine learning to analyze electronic health records [EHR] and identify suitable clinical trial participants. Primary outcome: Adoption and implementation progress, with performance indicators based on the H360xR protocol; IRB/informed consent; PhenX surveys for social determinants; Recruitment and Retention rates. Method of measurement: surveys; observation; key informant interviews; focus groups.

Results: H360xR includes data from 35 community-based practices, who have conducted 3 NIH and 1 industry sponsored study. Over a 3- year period, H360xR had 7513 participants. Median age 70 yr., 90% black, 7% white, 58% female, 15% rural residents while 51% have annual income <$25,000. H360xR supplements patient clinical and EMR data with surveys and questionnaires on social determinants. Qualitative analysis demonstrated that EMR AI/ML recruitment resource and Training of site teams are dominant themes; 75% references to H360x patient engagement, 85% references to training of site teams and research workflows (p<0.02 compared to baseline). H360x system usability scale was 95%.

Conclusions: H360xR resource support of trusted healthcare providers, who are research naïve, enabled successful participation in NIH and industry sponsored studies. The DCT/DHT model can effectively scale the participation of underserved populations in clinical trials. Ongoing analysis will generate a full representation of multi-dimensional patient characteristics, with human-in-the-loop AI/ML, and adapted to practice workflows.

Funding: Other NIH Support - NIH-NCATS SBIR, Commercial Support - AMGEN

SA-PO019

Point-of-Care Atrial Fibrillation Screening Using Mobile Electrocardiography in a CKD Patient Population

Ajay Mittal, Mansi Patel, Victor A. Savu, Mark S. Segal. *University of Florida, Gainesville, FL.*

Background: Recent metadata analysis suggests chronic kidney disease (CKD) patients have an increased incidence of atrial fibrillation (AF). Mobile electrocardiograms (ECGs) provide a low-cost, scalable technology for simple and efficient AF screening. In this study, we aim to use the KardiaMobile (AliveCor), a single-lead mobileECG, to examine the detection of subclinical AF amongst CKD patients in an outpatient nephrology setting.

Methods: From October 2020 to April 2024, 353 University of Florida Shands Nephrology patients filled out an informed consent form and one-page survey regarding heart and kidney health. A 30-second ECG rhythm strip was obtained by a trained research assistant using the Kardia Mobile ECG. The subsequent ECG reading provided by the device, along with the survey results were: flagged for abnormalities, applied to a CHA2DS2-VASc score to stratify the risk of stroke, and assessed by an electrophysiologist ordering a 12-lead ECG to confirm previously undetected AF in CKD Stage III-IV patients.

Results: The ECG readings determined 281 (79.6%) of patients had a normal single-lead rhythm strip, 72 (20.4%) had an irregular strip with possible arrhythmia indication of which 51 (14.4%) patients were confirmed to have AF. Of the previous undetected AF in CKD patient population the average CHA2DS2-VASc score was 3.2, indicating an elevated risk for stroke and oral anticoagulant therapy being recommended regardless of sex. The sample population was 51.03% female and 48.46% male with 0.51% of patients not answering. The mean age of participants was 65.25 with a standard deviation of 13.69.

Conclusions: The KardiaMobile device allowed for a primary screening tool to be applied in an outpatient clinic setting enabling CKD patients to gain insight about cardiovascular health through a 30-second single lead rhythm strip. Early detection and appropriate medical management of AF reduces risk of stroke, providing the nephrologist valuable information to optimize patient care. Further testing in larger, more diverse patient populations could help establish more direct connections between kidney disease and AF.

SA-PO020

Can Automated Digital Counseling Enhance Mental Health in Patients with Chronic Heart Failure or Kidney Disease? The ODYSSEE-vCHAT Study

Bourne L. Auguste,[1,2] Janice Montbriand,[3] Christopher T. Chan,[3,1] Robert Nolan.[3] ODYSEE-vCHAT Investigators. *[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [3]University Health Network, Toronto, ON, Canada*.

Background: Chronic Kidney Disease (CKD) and Chronic Heart Failure (CHF) significantly impact morbidity, mortality, and quality of life. We evaluated the ODYSSEE-vCHAT automated digital counseling program, including social network support, to enhance mental health and quality of life in patients with CHF and CKD. The primary aim was to assess the effect of ODYSSEE-vCHAT on Mental Component Summary (MCS) of the SF-36 health survey.

Methods: This 11-month, multicenter, open-label trial evaluated adults with CHF (reduced EF) or CKD (2-year KFRE≥ 10%), focusing on self-care skills (medication adherence, exercise, diet, smoke-free living) via a digital platform. The primary outcome was achieving a minimal clinically important difference in MCS (ΔMCS ≥ 3.8 or MCS ≥ 65).

Results: Of 215 enrolled participants, 174 completed the study, with a mean age of 54.4 years; 61% (n=106) had CKD. Significant improvements in MCS scores were noted for both CKD and CHF patients. However, no statistically significant changes were found in KDQOL or MCS scores for CKD patients alone, though small-to-moderate effect sizes were observed: Vitality (0.40, p=0.16), Emotional Well-Being (-0.11, p=0.70), Social Functioning (-0.37, p=0.19), Role Limitations (0.43, p=0.12), aggregate MCS (0.15, p=0.60), and KDQOL Subscale CKD Burden (0.36, p=0.12). These suggest meaningful small-to-moderate improvements (Fig 1). Participants experienced reduced CKD burden and enhanced quality of life.

Conclusions: The ODYSSEE-vCHAT program showed potential in enhancing mental health and quality of life among CKD patients, indicating value in digital health interventions in managing chronic diseases. These findings underscore the need for further trials to establish the efficacy of digital counseling in CKD patient care.

Funding: Other NIH Support - Canadian Institutes of Health Research-MS2 173076 - Type of funding sources: Public grant(s) – National budget only

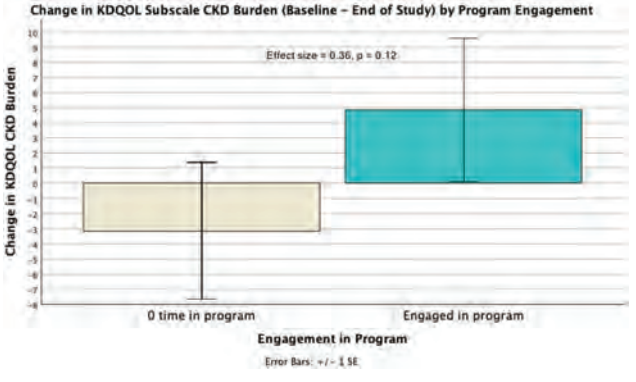


Figure 1. Change in KDQOL-CKD Burden Scale (End of Study – Baseline) by Program Engagement

SA-PO021

Technology in Education of Patients with CKD in Singapore

Ying-ying Seow, Hui Boon Tay, Lee Ying Yeoh. *Sengkang General Hospital, Singapore, Singapore*.

Background: With high penetration of technology and a shrinking workforce in Singapore, healthcare is turning increasingly to the former to improve patients' knowledge and self-management skills. However, for it to be effective, patients need to have adequate health literacy skills. In this study, we aim to evaluate current technology use, electronic health literacy and receptiveness of education via electronics means among our CKD patients.

Methods: This is a cross-sectional survey of 200 CKD patients attending renal clinics at Sengkang General Hospital, Singapore between Feb-Jun 2022. The survey consisted of questions on technology use, the validated eHealth Literacy Scale (eHEALS), and patient preference of modality for CKD education.

Results: We sampled 100 men and 100 women, median age was 56.5y (IQR 44.5-68). 51% of patients was CKD stages 1-3. 22.5% were on dialysis at the time of the study. 38.5% were not aware of their diagnosis of CKD. 37.5% had >10years of formal education. 53% were employed, 61.3% of whom were professionals. The median eHEALS score was 29 (IQR 24-32). 194 (97%) participants had mobile phones, with 158 (79%) using the internet on them. The top modality preferred for CKD education was for in person education by a renal coordinator (66.5%). Overall, 94 (47%) participants were receptive to education by electronic means (website or mobile application), though only 19.5% chose it as their top choice. Older participants were less likely to be receptive to education by electronic means (OR=0.95, CI 0.91-0.98, p=0.003), while those with a higher eHealth literacy were more likely (OR=1.14, CI 1.05-1.23, p=0.001). Education level and internet use on phone were not associated.

Conclusions: Access to technology was high among our Singapore CKD patients but electronic health literacy scores lower than CKD counterparts in the US. Receptiveness to education by electronic means was associated with younger age and higher eHEALS scores. Face-to face education was still much preferred.

Funding: Government Support - Non-U.S.

Regression analysis for receptiveness of education via electronic means

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.95	0.93-0.97	<0.001	0.95	0.93-0.98	0.002
Education	2.15	1.43-3.27	<0.001	1.31	0.70-2.46	0.394
eHEALS score	1.17	1.10-1.25	<0.001	1.14	1.05-1.23	0.001
Internet use on phone	5.80	2.43-13.87	<0.001	1.05	0.30-3.72	0.935

SA-PO022

Bridging the Future: Perspectives of a Multinational Group of Nephrologists on Artificial Intelligence (AI) in CKD Management

Eliana Silva, Carla Santos, Carlos Lucas, Luis Rodrigues, Jesus Garrido, Lidia Santos, Fernando Jose Gordinho R. Macario. *Diaverum AB, Malmo, Sweden*.

Background: Artificial intelligence (AI) techniques, particularly machine learning (ML) and deep learning, have made significant strides in predicting and diagnosing chronic kidney disease. This study aims to explore the perceptions of a multinational group of nephrologists regarding the application of AI in clinical practice. Understanding their views is crucial for the integration of AI in nephrology.

Methods: A prospective, observational study was conducted in March 2024, involving nephrologists from 17 countries across four continents, all affiliated with a large hemodialysis provider. The survey, validated by 6 nephrologists, comprised 8 technical questions using a 5-point Likert scale, with 1 corresponding to "totally disagree" and 5 to "totally agree." Demographic data were also collected. Results presented as mean±standard deviation or proportions, as appropriate. T-test was used for statistical analysis, with a p-value below 0.05 considered statistically significant.

Results: Among the 196 valid responses, 80% of nephrologists recognized the term "AI," and 65% were familiar with "ML." Nephrologists acknowledge the potential of AI in the future but currently rely more on traditional tools to support the clinical decision-making process (3.74±1.14 vs. 3.12±1.07, p<0.05). This reliance on traditional tools is more evident among nephrologists not familiar with the term "ML" (3.90±0.93 vs. 3.09±1.01, p<0.05). When asked about the advantages of AI and ML in supporting clinical decision-making, the highest score was attributed to "simplification of decision algorithms" (3.82±1.10). Interestingly, nephrologists without previous contact with AI-supported decision-making tools considered the role of AI less significant in "assisting in making decisions, allowing concentration on high-value activities", compared to those with previous experience in this area (3.38±1.22 vs. 3.88±0.97, p<0.05).

Conclusions: Enhancing the understanding of AI can facilitate the integration of these technologies into nephrology practice, benefiting patient care. Given the perceived potential of AI in managing different types of CKD patients, efforts to promote AI literacy in the nephrology community may be fundamental for the adoption of these tools in regular clinical practice.

SA-PO023

Clinical and Cost-Effectiveness of a 6-Month Digital Health Intervention to Improve Physical Activity and Mental Health-Related Quality of Life in People with CKD (Kidney BEAM)

Sharlene A. Greenwood,[1,2] Jackie Campbell,[4] Nicola Cooper,[3] Christy G. Walklin,[1] Hannah M. Young,[3] Ellen M. Castle,[6] Roseanne E. Billany,[3] Jamie H. Macdonald.[5] Kidney Beam. *[1]King's College Hospital, London, United Kingdom; [2]King's College London, London, United Kingdom; [3]University of Leicester, Leicester, United Kingdom; [4]University of Northampton, Northampton, United Kingdom; [5]Bangor University, Bangor, United Kingdom; [6]Curtin University, Perth, WA, Australia*.

Background: There is inequity in provision of physical rehabilitation services for people living with chronic kidney disease (CKD). The Kidney BEAM trial evaluated the clinical value and cost effectiveness of a physical activity digital health intervention in CKD. We hypothesised that the Kidney Beam intervention would be a cost-effective solution to improve mental health-related quality of life (HRQOL) for people with CKD.

Methods: In a single-blind, 11 centre, randomised controlled trial, 340 adult participants with CKD were randomly assigned to either the Kidney BEAM physical activity digital health intervention or a waitlist control. This study assesses the difference

in the Kidney Disease Quality of Life Short Form 1.3 Mental Component Summary (KDQoL-SF1.3 MCS) between intervention and control groups at 6 months, and cost-effectiveness of the intervention.

Results: At 6 months there was a significant difference in mean adjusted change in KDQoL MCS score between Kidney BEAM and waitlist control (intention-to-treat adjusted mean: 5.9 {95% confidence interval: 4.4 to 7.5} arbitrary units, p<0.0001), and a significant increment in quality-adjusted life years (QALYs) of 0.027 {95% confidence interval: 0.013 to 0.040} years per participant, resulting in a cost per QALY of £3,446 for the Kidney BEAM intervention, and a 93% and 98% probability of the intervention being cost-effective at a willingness to pay threshold of £20,000 and £30,000 per quality-adjusted life year gained.

Conclusions: The Kidney BEAM physical activity digital health intervention is a clinically valuable and cost-effective means to improve mental health related quality of life in people with CKD.

SA-PO024

Targets for Improvement of Care for Hospitalized Patients with AKI

Dion G. de Martines,[1] Gozewijn D. Laverman,[2] Aaltje Y. Adema,[3] Peter T. Luik,[4] Ernst C. Hagen,[4] Aernoud Fiolet,[1] Christina M. Gant.[1] AKI PATROL Consortium. *[1]Universiteit Utrecht, Utrecht, Netherlands; [2]Ziekenhuisgroep Twente, Almelo, Netherlands; [3]Medisch Centrum Leeuwarden, Leeuwarden, Netherlands; [4]Stichting Meander Medisch Centrum, Amersfoort, Netherlands.*

Background: Acute Kidney Injury (AKI) complicates 20% of hospital admissions and is associated with prolonged hospital stay, increased mortality and end stage renal disease. Timely guideline based management can prevent further deterioration of kidney function and improve AKI-associated outcomes. Prior research has shown low adherence to these recommendations. Large scale data regarding quality of care are currently lacking. To enhance guideline adherence, understanding the quality of care is of the utmost importance to formulate targeted interventions such as e-alerts or tailored management advice for physicians.

Methods: We conducted a retrospective cohort study in three large teaching hospitals in The Netherlands. Hospitalized patients that developed AKI were included over a period of one year, between January 2022 to October 2023. AKI was identified using an algorithm using KDIGO criteria for serum creatinine (>50%/week or >26µmol/l/48h increase compared to baseline). We logged the occurrence of interventions recommended by the guideline.

Results: 2367 episodes of AKI were included. Mean age of patients at AKI was 72 years, 45% were female. AKI was documented in the electronic health record in 70% of cases. Urine tests were performed in 58%, renal imaging conducted in 31%. In 47% of cases, intravenous fluids were started, in 60% nephrotoxic medication was ceased and in 17% a nephrologist was consulted. Anti-hypertensives were ceased in 57%. In 14% of cases patients received iodine contrast during AKI. A follow-up appointment with a nephrologist was made in 10% of patients. Lower adherence rates to KDIGO guideline recommendations were found in surgery wards (such as performing urine diagnostics in 22%, documenting AKI in 65% of cases).

Conclusions: Quality of care for patients with AKI in Dutch hospitals is suboptimal. The most promising targets for improvement of quality of care for patients with AKI are timely recognition of AKI, cessation of antihypertensives and nephrotoxic medication, consultation of a nephrologist, and initiation of fluid therapy. Guideline adherence differed depending on the ward of admission. Tools like an AKI alert may aid in guideline adherence rates.

SA-PO025

Seven-Day AKI Nursing Team Leads to Secondary Care Transformation

Gemma Highway, Riaz V. Bavakunji, Liz Grace. *Walsall Manor Hospital, Walsall, United Kingdom.*

Background: Our district general hospital, reported high mortality rates for AKI admissions of 33.2% vs UK average of 26.61%, with an adjusted standardized mortality ratio 1.09. We noted high incidence of chronic kidney disease at 5.2% (stages G3a-5), in a 36% ethnic minority population. Our median length of stay (LoS) for all Acute Kidney Injury (AKI) stages was 13 days median while UK was 12. Getting It Right First Time report showed over 75% patients are transferred to hub for dialysis later than 24 hours. This delay has led to harm in 100% of patients. We implemented a 3-member, 7-day AKI nursing service and aim to evaluate the new nursing service and its impact.

Methods: We appointed 3-AKI nurses, for a 7-day service in 2022 Prospective data was collected between April 1, 2023, to March 31, 2024. Outcome data was collected on timely intervention, dialysis transfer times, number of ICU days after patient stabilised, LoS data and 90-day major adverse kidney events (MAKE90: death, renal replacement therapy).

Results: The nursing team reviewed 891 patients during the study period. We noted that 78% of patients presented with community-acquired AKI (CA-AKI) and 22% had Hospital-acquired AKI. There were 54% male and 31% of the total have preexisting CKD. The mortality was 50% in G4 and G5 patients. Patients reviewed same day (within 6 hours) were 16% for AKI stage 1 and 72% for AKI stages 2/3 with MAKE 90 outcomes showing 28% mortality and 8.9% required ICU haemofiltration. The mean transfer time for dialysis was 20.19 hours, aligning with GIRFT recommendations. Patients remained in the ICU for an average of 4.92 hours post-stabilization before transfer to the dialysis unit, reducing ICU bed pressure. The mean AKI LoS was decreased to 6.99 days, with a median of 5 days (IQR 2, 9). We conclude this reduction in LoS was due to nursing input as this was the only new intervention implemented.

Conclusions: The 7-day AKI nursing team has significantly improved the timeliness of renal replacement therapy decisions, reduced ICU bed utilization, and streamlined the transfer process to the regional hub. The service introduction estimates a cost-saving, assuming the entire costs associated with a bed day can be removed, the reduction in LoS can contribute £1.8 million in avoided costs. We plan to implement a community PILOT GP AKI stage reporting, with rapid review protocols potentially preventing hospital admissions.

SA-PO026

Low Baseline Creatinine Reduces the Likelihood of Nephrology Consultation in Stage 3 AKI

Casey G. Hardin, Mary V. Sarrazin, Jason Misurac, Diana I. Jalal, Benjamin R. Griffin. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Acute kidney injury (AKI) is common among hospitalized patients and significantly affects clinical outcomes. Previous studies suggest that inpatient nephrology consultation improves outcomes in patients with AKI. We analyzed consult rates for Kidney Disease: Improving Global Outcomes (KDIGO) stage 3 AKI to determine nephrology consult rates and to explore reasons for lack of consultation.

Methods: This single-center, retrospective cohort study included adults admitted in 2019 with in-hospital KDIGO stage 3 AKI. Baseline creatinine was defined as the lowest creatinine within six months of admission. High nephrotoxin exposure was determined based on the current Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) definition as ≥3 nephrotoxins on one day or ≥3 days of intravenous vancomycin or aminoglycoside. Patients were stratified into high and low baseline creatinine, and Chi-squared analysis was used to investigate rates of renal consultation, nephrotoxin exposure, and in-hospital mortality.

Results: Among 634 patients with stage 3 AKI, the nephrology consultation rate was 54%. The most significant factor influencing consult rates was peak creatinine; 81% of patients with peak creatinine greater than the median of 3.25 mg/dL had a nephrology consultation compared to 27% of patients below the median (p<0.001). Similarly, 74% of patients with a baseline creatinine above the median of 0.7 mg/dL had a nephrology consult versus 38% less than the median (p<0.001). Females, elderly, and patients with a history of malignancy were statistically more likely to have baseline creatinine below the median. Neither rates of in-hospital mortality (25% vs. 23%, p=NS) nor high nephrotoxin exposure (32% vs. 35%, p=NS) were different in patients above and below median baseline creatinine.

Conclusions: Rates of renal consultation were low among patients with stage 3 AKI (54%), and this was exacerbated in patients with a baseline creatinine of 0.7 mg/dL or below (38%), who were more likely to be elderly females. There was no significant difference between those above and below median baseline creatinine for in-hospital mortality or nephrotoxin exposure, suggesting that patients with low baseline creatinine and stage 3 AKI are an underrecognized patient subset with equally poor outcomes and equal need for nephrology consultation.

SA-PO027

Nephrology Follow-Up and Mortality of Critically Ill Patients with AKI

Rachel Jeong,[1] Alix Clarke,[1] Pietro Ravani,[1] Robert R. Quinn,[1] Matthew T. James,[1] Sean M. Bagshaw,[2] Henry T. Stelfox,[2] Tyrone Harrison,[1] Neesh I. Pannu,[2] Daniel Niven,[1] Ngan Lam.[1] *[1]University of Calgary, Calgary, AB, Canada; [2]University of Alberta, Edmonton, AB, Canada.*

Background: Acute kidney injury (AKI) is common in the intensive care unit (ICU) and associated with adverse outcomes. We sought to estimate the association between nephrology follow-up within 3 months post-discharge and mortality in survivors of critical illness and moderate-to-severe AKI, compared to family physician-only follow-up.

Methods: In this retrospective cohort study in Alberta, Canada, we identified adult patients admitted to ICU with KDIGO stage 2-3 AKI from 2005-2020 who survived to 3 months post-discharge without kidney replacement therapy or eGFR <15 mL/min/1.73 m^2. Patients with nephrology follow-up were matched 1:1 on their propensity scores for nephrology vs. family physician-only follow-up within 3 months post-discharge. The primary outcome was death from 3 months post-discharge, reported as the cumulative incidence at 12, 24 and 50 months and hazard ratios (HR [95% confidence interval, CI]).

Results: Of 8979 survivors of critical illness and stage 2-3 AKI at 3 months post-discharge, 500 (6%) received nephrology and 7455 (83%) received family physician-only follow-up. Outcome analysis included 437 patient pairs. Risks at 12, 24, and 50 months in patients with nephrology follow-up were 7%, 13%, and 26%, respectively, compared to 14%, 21%, and 36%, in patients with family physician-only follow-up (Figure 1).

Nephrology follow-up was associated with lower mortality risk compared to family physician-only follow-up (HR 0.58 [95% CI: 0.44, 0.77] in the first 35 months and 1.09 [95% CI: 0.83, 1.42] after 35 months).

Conclusions: In survivors of critical illness and stage 2-3 AKI, nephrology follow-up was associated with lower mortality, with potential benefits up to 3 years.

Funding: Private Foundation Support

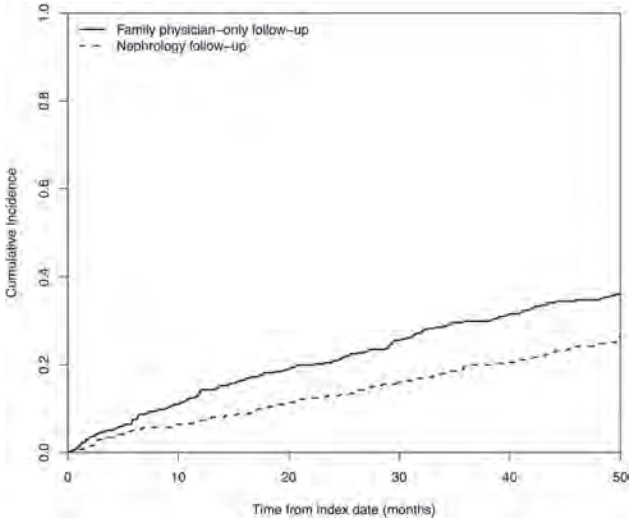


Figure 1. Cumulative incidence of death.

SA-PO028

Nephrology Follow-Up Care Patterns for Survivors of Neonatal Intensive Care Unit AKI

Anna E. Williams,[1] Clarissa J. Diamantidis,[2] Rasheed A. Gbadegesin.[1]
[1]Duke University School of Medicine, Durham, NC; [2]Wake Forest University School of Medicine, Winston-Salem, NC.

Background: Acute kidney injury (AKI) is the sudden loss of kidney function and complicates nearly 25% of neonatal intensive care unit (NICU) hospitalizations. Neonates who survive AKI events are at increased risk of long term adverse outcomes such as the development of chronic kidney disease, however few guidelines exist to promote nephrology follow-up at discharge for this high-risk group. We investigated patterns of neonatal AKI survivor nephrology follow-up to determine patient- and provider-level factors associated with receipt of AKI follow-up at discharge.

Methods: Retrospective review of 100 neonates at a single academic center NICU with diagnosis of AKI during the first month of life identified via ICD-10 diagnostic codes and confirmed by laboratory findings concordant with KDIGO neonatal AKI diagnosis. Data collected included patient-level characteristics—sex, gestational age, AKI stage, and AKI etiology—and provider-level characteristics—discharging provider type. The primary outcome was outpatient nephrology follow-up care as defined by a scheduled follow-up visit at time of discharge. Data were compared by Fisher's exact test.

Results: From January 2017-December 2020, 85 neonates with diagnosis of AKI survived to discharge. The population was male predominant (66%) with a median gestational age of 26 weeks. About three quarters (75%) experienced Stage 2 or Stage 3 AKI. Etiology of AKI was predominantly due to nephrotoxic medication exposure such as indomethacin, gentamicin and vancomycin (82%). Inpatient nephrology involvement in NICU care was limited (10%). Most neonates were discharged home by neonatal nurse practitioners (92%). Few neonates (3%) had scheduled nephrology follow-up care recorded at discharge. AKI stage, AKI etiology or receipt of inpatient nephrology consultation did not correlate with receipt of outpatient nephrology follow-up care at discharge.

Conclusions: Post-AKI nephrology follow-up is lacking in survivors of neonatal AKI regardless of AKI severity or etiology. Though not clinically significant, infrequent pediatric nephrology consultation in the hospital likely influenced lack of outpatient nephrology follow-up. This provides opportunity for provider education and collaboration with pediatric nephrologists to unify follow-up practices and mitigate adverse AKI-related outcomes in this population.

Funding: Private Foundation Support

SA-PO029

Health Care Provider Awareness of AKI in Patients with Advanced CKD Undergoing Surgery: A Descriptive Study of Preoperative Notes

Jonah Buckstein,[1,2] Sarah M. Hammond,[1,2] Tyrone Harrison,[3] Samuel A. Silver.[1,2] *[1]Kingston Health Sciences Centre, Kingston, ON, Canada; [2]Queen's University, Kingston, ON, Canada; [3]University of Calgary, Calgary, AB, Canada.*

Background: Postoperative acute kidney injury (AKI) is a frequent complication of surgery, with an incidence of 18-47%. The KDIGO guidelines offer a bundle of preventative strategies to mitigate AKI risk. Our study examined how often the risk of AKI and elements of the KDIGO bundle were mentioned by healthcare providers in their preoperative notes.

Methods: We retrospectively identified patients ≥ 18 years followed in a tertiary care advanced chronic kidney disease (CKD) clinic who underwent elective surgery with a preoperative anesthesia assessment between January 1, 2017 and December 31, 2022. We extracted data on provider awareness of AKI, inclusion of KDIGO bundle elements in preoperative assessments, and qualitative comments on AKI risk assessment. We analyzed the quantitative data descriptively, stratifying our findings by preoperative healthcare provider awareness of AKI. We used a constant comparison technique and consensus to analyze qualitative comments.

Results: Of 91 patients, the mean age was 76 (±13) years, 75% were male, and 96% had category 4 or 5 CKD. Postoperative AKI and dialysis frequencies were 13% and 1%, respectively. Few anesthesia providers (n=22/91, 24%) mentioned the risk of postoperative AKI. The most commonly documented KDIGO recommendations included holding ACEi/ARB medications (n=15/21, 80%), obtaining a preoperative creatinine measure (n=66/91, 73%), and considering hemodynamic monitoring (n=28/91, 31%). The least mentioned KDIGO recommendations included avoiding radiocontrast media (n=0/91, 0%), controlling hyperglycemia (n=2/91, 2%), and documenting the need for a postoperative creatinine (n=2/91, 2%). There was no difference in the inclusion of KDIGO bundle elements when stratifying preoperative awareness of AKI. In qualitative comments, providers who recognized postoperative AKI risk frequently mentioned the potential for dialysis (n=12/22, 55%), rarely utilized risk scores (n=1/22, 5%), and did not provide any actionable postoperative orders (n=0/22, 0%).

Conclusions: Among patients with advanced CKD, only 24% of anesthesia providers mentioned the risk of AKI in their pre-operative assessments. Opportunities may exist to improve the perioperative care of patients with advanced CKD by increasing awareness of AKI risk and the KDIGO bundle elements.

SA-PO030

Validation of AKI Prediction Model as Clinical Decision Supporting System

Eun Mi You,[1] Jinyeong Yi,[2] Sangyub Han,[3] Sejoong Kim,[1,4] Giae Yun.[4,5]
[1]Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [2]Seoul National University Graduate School of Convergence Science and Technology, Gwanak-gu, Seoul, Republic of Korea; [3]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [4]Seoul National University College of Medicine Department of Internal Medicine, Seoul, Republic of Korea; [5]Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Gyeonggi, Republic of Korea.

Background: Acute kidney injury (AKI) is a critical clinical syndrome requiring immediate intervention. Our previous research developed a 'PRIME solution' AI model for AKI. This study aims to evaluate the usefulness of this AI model in improving the predictive capabilities of AKI prediction.

Methods: We utilized convolutional neural networks with a residual block to predict AKI in hospitalized patients. The training set comprised data from 183,221 patients at Seoul National University Hospital (2013-2017). At Seoul National University Bundang Hospital (2020-2021), we randomly selected 74 patients from departments with high AKI rates, including 15% AKI cases. We assessed the impact of an AI model on clinical decisions by comparing evaluations with and without AI assistance.

Results: Accuracy was highest for physicians, with students and the AI model were similar (physician: 0.797, student: 0.574, AI: 0.568). AI assistance improved recall and F1 scores for all almost individuals (recall: 52.4% to 71.4%, F1: 37.7% to 46.1%). In the AKI predicted group, recall increased while F1 decreased for physicians (recall: 36.4% to 60%, F1: 43.2% to 33.3%) and students (recall: 54.5% to 80%, F1: 44.4% to 36.9%). For the non-AKI predicted group, both saw significant gains in recall and F1 with AI (physicians: recall 16.7% to 87.5%, F1: 18.2% to 66.7%; students: recall 44.4% to 75%, F1: 21.1% to 40%). Review times decreased for all with AI (median: 69.0 to 52.0 seconds, p=0.032), especially in the non-AKI predicted group (68.5 to 46.0 seconds, p<0.001; AKI predicted group 71.0 to 57 seconds, p<0.001).

Conclusions: AI notably improved physician performance, especially in the non-AKI predicted group with significant time savings and higher F1 scores. However, its impact was less marked in the AKI-predicted group. Alongside enhancing AI, studies on its application and target groups are essential.

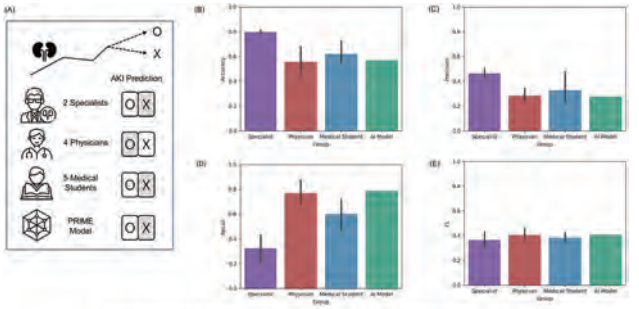


Figure 1. Comparison of Diagnostic Metrics Between Specialist, Physician, Medical students, and the PRIME solution.
(A) Visual Representation of AKI Prediction (B) Accuracy (C) Precision (D) Recall (E) F1 score
The bars represent the average performance of each group, with error bars reflecting the 95% confidence interval (CI).

SA-PO031

Risk vs. Reward: Impact of Kidney Biopsies on the Management of Critically Ill Patients

Adrian Llama, Sagar S. Sadarangani, Dennis G. Moledina, Randy L. Luciano. *Yale University School of Medicine, New Haven, CT.*

Background: Kidney biopsy is the gold standard for diagnosing many renal diseases, providing crucial information that guides treatment decisions and potentially improves patient outcomes. However, these benefits must be balanced against the risks, particularly in critically ill patients, who are at higher risk of complications due to unstable hemodynamics and coagulation abnormalities. Here we examine the safety and benefit of kidney biopsies in critically ill patients compared to others.

Methods: In participants enrolled in the Yale Kidney biobank, we compared the safety and benefit of kidney biopsies between those in the ICU, inpatient wards, and outpatients. The benefit was changes in management, defined as the initiation of steroids, immunosuppressive agents, pheresis, or drug discontinuation post-biopsy. Secondary outcomes included changes in diagnosis, the need for short-term hemodialysis, and chronic hemodialysis dependence. We also assessed safety outcomes using a composite measure of medium/large hematomas, drops in hemoglobin, the need for additional imaging, and interventional radiology procedures.

Results: Of the 748 participants, 30 were in the ICU, 202 were inpatient, and 516 were outpatients (Table). Kidney biopsies in the ICU group had a significant impact on management, with 18/30 (60%) of the biopsy results leading to changes in or avoidance of immunosuppressive therapy relative to what would have been the standard of care based on the pre-biopsy diagnosis. The remaining biopsies either confirmed the pre-biopsy diagnosis or resulted in a change between two non-treatment-requiring processes. Safety events were observed in all groups, with the highest rate in the critically ill.

Conclusions: Kidney biopsies in the critically ill can significantly impact management but may carry a higher risk of safety events. This risk needs to be compared to the potential benefit and should not be a barrier to a biopsy in select patients.

Table. Comparison of kidney biopsy safety and adequacy outcomes amongst biopsies performed in patients in different admission/outpatient settings

Characteristic	Outpatient	Inpatient	ICU	P value
Composite safety outcome	115 (22.3%)	66 (32.7%)	15 (50.0%)	<0.001
Transfusions due to complication, n (%)	5 (1.0%)	11 (5.7%)	1 (3.4%)	0.001
Medium/large hematoma found after biopsy n (%)	11 (2.2%)	10 (5.2%)	3 (10.0%)	0.014
Immediately after biopsy	7 (1.4%)	4 (2.3%)	0	0.569
Within 30 days of biopsy	6 (2.4%)	7 (5.8%)	3 (18.8%)	0.003
Hemoglobin drop	1.10 (0.60, 1.75)	1.20 (0.60, 2)	1.50 (1, 2.80)	0.016
Hb drop ≥1 but <2 g/dl	180 (36.3%)	66 (33.8%)	11 (36.7%)	0.827
Hb drop ≥2 g/dl	103 (20.8%)	51 (26.2%)	12 (40.0%)	0.025
IR intervention	8 (1.6%)	11 (5.6%)	2 (7.1%)	0.007
Additional Imaging, n (%)	53 (10.5%)	53 (27.2%)	13 (43.3%)	<0.001
For drop in Hb	4 (0.8%)	3 (1.5%)	2 (6.7%)	0.017
For flank/back pain	17 (3.4%)	10 (5.1%)	0	0.300
For concern for bleeding	8 (1.6%)	16 (8.2%)	4 (13.3%)	<0.001
For hypotension	2 (0.4%)	3 (1.5%)	1 (3.3%)	0.098
Reason not specified	22 (4.4%)	21 (10.8%)	6 (20.0%)	<0.001

SA-PO032

Low-Sodium Diet and Mortality in Patients with Heart Failure with Worsening Kidney Function during Hospitalization

Minhyung Kim, Seungmin Song, Kyungho Lee, Jung eun Lee, Wooseong Huh, Hye Ryoun Jang, Junseok Jeon. *Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.*

Background: Sodium restriction can help prevent and alleviate congestion in patients with heart failure (HF), but the benefits of sodium restriction are controversial. Patients with worsening renal function (WRF) during treatment of heart failure have worse outcomes and may benefit from more strict volume control. We investigated the prognostic impact of sodium restriction in patients hospitalized with HF focusing on WRF.

Methods: This retrospective cohort study included patients hospitalized for HF from 2000 to 2019. WRF was defined as a decrease in estimated glomerular filtration rate (eGFR) >20% from admission at any point during hospitalization. The difference in weight from admission to discharge was used to estimate the degree of decongestion. Low-sodium diet status was estimated from the diet prescription at the time of discharge. The primary outcome was all-cause mortality.

Results: In a total of 1,079 patients, 566 (52.5%) developed WRF and 325 (30.1%) consumed a low-sodium diet. There was no difference in baseline characteristics between the low-sodium diet and control groups, except for eGFR (low-sodium diet vs control: 58 vs 66 mL/min/1.73 m^2; p=0.001). The proportion of low-sodium diets did not differ between the WRF and no-WRF groups (31% vs 29%; p=0.548). The low-sodium diet group lost more weight than the control group (-2.2 vs -1.9 kg; p=0.015) during hospitalization. During a median follow-up of 33.1 months (IQR 4.7–64.5), 229 (21.2%) patients died. Low-sodium diet was associated with lower mortality in the WRF group (HR 0.563, 95% CI 0.385–0.822, p=0.003), but not in the no-WRF group (HR 0.922, 95% CI 0.563–1.510, p=0.747). Low-sodium diet showed association with lower mortality after multivariable adjustment in the WRF group (adjusted HR 0.668, 95% CI 0.452-0.987, p=0.043).

Conclusions: Low-sodium diet could be beneficial for patient with HF requiring hospitalization, especially with WRF.

SA-PO033

Intravenous Contrast-Induced Nephropathy Risk in Acute Kidney Disease: Nationwide Taiwanese Cohort Study

Li-Chun Lin, Vincent Wu. NSARF (National Taiwan University Hospital Study Group of ARF). *National Taiwan University Hospital, Taipei, Taiwan.*

Background: Current debate surrounds the clinical relevance of nephropathy post-iodinated contrast media (ICM) administration. Limited research exists on the specific impact of intravenous ICM on renal outcomes in acute kidney disease (AKD) patients.

Methods: We conducted a nationwide retrospective cohort study in Taiwan from January 2015 to September 2022, identifying adult patients transitioning from acute dialysis to AKD status. Propensity score weighting and entropy balancing were used to minimize heterogeneity between contrast-enhanced computed tomography (CT) and non-contrast exposure groups. Primary outcome was redialysis, with MAKE as secondary outcomes, defined as redialysis or a ≥50% increase in serum creatinine from baseline AKD value. Follow-up extended up to one year.

Results: A total of 19,505 AKD patients were included (mean age: 68.70 years, male 58.80%). Among them, 14.9% underwent intravenous ICM. Following propensity score weighting and entropy balancing adjustment, the ICM-exposed group did not exhibit a significantly elevated risk of redialysis compared to the non-contrast group (odds ratio (OR) 0.88, 95% confidence interval (CI) 0.74–1.05) and entropy balancing adjustment (OR 0.81, 95% CI 0.69–0.94). Similarly, the risk of MAKE was not significantly different between the ICM and non-contrast groups (propensity score weighting: OR 1.00, 95% CI 0.88–1.12; entropy balancing: OR 0.94, 95% CI 0.84–1.05). Subgroup analysis for patients with an estimated glomerular filtration rate (eGFR) either ≥ 30 or <30 ml/min 1.73 m2 yielded similar results; for the patients with eGFR of ≥ 30 ml/min 1.73 m2, the OR of redialysis and MAKE were 0.93 (95% CI: 0.74-1.16) and 1.04 (95% CI: 0.92-1.18), respectively; for those with eGFR < 30 ml/min 1.73 m2, the OR of redialysis and MAKE were 1.15 (95% CI: 0.96-1.37) and 1.10 (95% CI: 0.95-1.30), respectively.

Conclusions: In patients with AKD, intravenous administration of ICM for contrast-enhanced CT scans did not significantly increase the risk of redialysis or MAKE within one year

SA-PO034

Breaking the Myth: Does Albumin before the Furosemide Test Work?

Nayeli N. López Villa, Ricardo A. Garza Treviño, Juan P. Gomez Villarreal, Mara C. Olivo Gutierrez, Sofia Lopez-Guzman, Lilia M. Rizo Topete. *Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico.*

Background: Acute kidney injury is a common complication in patients in the intensive care unit. It has multiple etiologies and risk factors that lead to adverse clinical outcomes, chronic kidney disease or death. Patients undergoing the furosemide stress

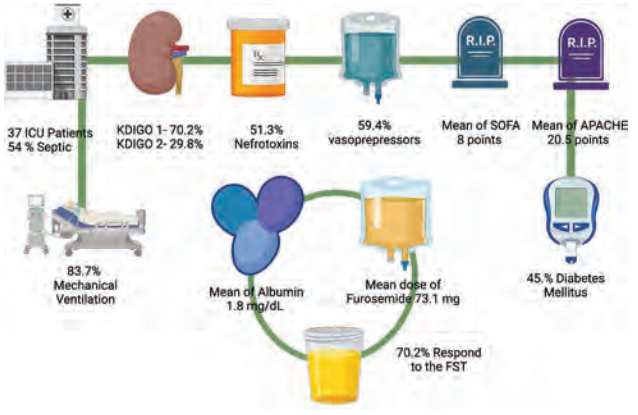
test are classified as responders or non-responders based on whether their urine output is greater than 200 ml or not within 2 hours after the administration of furosemide. We consider that hypoalbuminemia could be an important factor for the diuretic response, as 95% of furosemide binds to plasma proteins. Therefore, we sought to evaluate the effectiveness of the Furosemide Stress Test in patients with hypoalbuminemia.

Methods: This is a prospective quasi-experimental study. Informed consent was obtained, with prior authorization from the ethics committee. Patients were obtained from the intensive care unit of the Dr.José Eleuterio González University Hospital with KDIGO 1 and 2 AKI and serum albumin less than 3 g/dL. A bolus of furosemide was administered at a dose calculated to be 1-1.5 mg/kg in a single dose to patients without a prior diagnosis of kidney disease and without clinical signs of hypovolemia.

Results: A total of 37 patients were enrolled, aged between 19 and 77 years, of which 45% had diabetes mellitus, 40% had hypertension, 51% were on at least one nephrotoxic medication, and 40% had sepsis as the cause of AKI. The mean albumin level was 1.8 g/dL. To evaluate the relationship between albumin levels and the use of furosemide, a correlation analysis was performed between albumin levels and the response to the furosemide stress test, which found no decrease in urinary response in patients with hypoalbuminemia.

Conclusions: According to the population evaluated in our study, we determined that hypoalbuminemia does not decrease the response to the furosemide stress test. Therefore, we conclude that intravenous albumin should not be administered before furosemide.

Funding: Government Support - Non-U.S.



SA-PO035

Hemofiltrate Reinfusion (HFR)-Supra during Sepsis-Associated (SA)-AKI Treats Inflammation and Improves Patient Outcomes

Giuseppe Gernone. *ASL Bari, Bari, Italy.*

Background: Sepsis is life-threatening organ dysfunction caused by dysregulated response to an infection leading to systemic inflammation (SI). AKI is final common pathway of this immune dysregulation. KRT is often required in SA-AKI. HFR-Supra (HFR) trought is adsorbing resin cartridge that remove myoglobin, cytokines and pro-inflammatory mediators, have been used anecdotally. Aim of this study is to test HFR on outcome of SA-AKI in critically ill patients (pts).

Methods: A retrospective observational study evaluated 16 SA-AKI pts. No ESKD pts in chronic dialysis. SA-AKI were treated with daily HFR-S. Given the laboratory operating standards they were assessed: urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), WBC, platelets (PLT), myoglobin, albumin, mean arterial pressure (MAP), need for vasopressor and outcome. The values have been reported as mean±SD or median and interquartile range. AKI was defined according to KDIGO. Statistical analyzes by Wilcoxon Test

Results: Among 16 pts 10 had AKI III stage. Age was 73.1±11.1 y, 90% are hypertensive, some with heart disease, 60% with CKD, 60% obese or with diabetes. All received mechanical ventilation, 80% received amines. They underwent to 5.5±3.4 HFR treatments (range 2-13); Qb= 238±29.6 ml/m', TT 233.2±45.8 m'. UF 477.9±185.5ml/h. HFR show significant abatement of CRP, PCT and myoglobin. Albumin remain stable. The effect on WBC and PLT reflect the trend of sepsis. Cardiovascular instability decreased allowing suspension of vasoactive amines given significant increase in MAP. (Tab. 1) 7 pts did not survive within follow four weeks, 5 pts had renal recovery, 2 pts had chronic dialysis.

Conclusions: HFR represent a new strategy to decrease SI and support renal recovery in SA-AKI pts. The adsorbing resin is able to remove myoglobin, proinflammatory cytokines and many other mediators that improve MAP and reduce critical illness scores. HFR is safe and cheapest for SA-AKI in comparison to the CRRT, Cytosorb and others. Has excellent cost-effectiveness-sustainability ratio regarding treatment times and staff-sparing. Our evidence gradually help to build a new scientific evidence.

Tab. 1- Median and interquartile range (IQR)	*Baseline*	*After*	*p value < 0,05*
CRP mg/L	222.5 (180.5 - 292)	50,1 (26.5-80.9)	*p < 0,01*
PCT ng/ml	23.7 (13.5 - 75)	2.2 (0,9 - 5)	*p < 0,01*
WBC mm³	17.7 (6.2 - 27)	9.6 (7.8 – 17.4)	*p = 0,23*
Myoglobin ug/L	1666 (907.5 – 6749.5)	453 (219.5 - 557)	*p = 0,01*
Albumin g/dl	1.8 (1,7 – 1.9)	2,1 (2.1 - 2,3)	*p = 0,06*
MAP mmHg	70,5 (68,2 - 88,7)	87.8 (78,5 - 96,2)	*p = 0,02*
PLT mm³	198.5 (105,7-262,5)	187 (148-258.5)	*p = 0,43*

SA-PO036

UNI-494 Phase 1 Safety, Tolerability, and Pharmacokinetics

Guru Reddy, Sanjay S. Mourya, Steve Hasal, Shalabh Gupta.
Unicycive Therapeutics Inc, Los Altos, CA.

Background: Currently, there are no effective treatments approved for acute kidney injury (AKI). Inflammation and reactive oxygen species driven mitochondrial permeability transition pore (mPTP) opening causes mitochondrial dysfunction/swelling and cell death. This is implicated in acute diseases originating from ischemia reperfusion injury or delayed graft function (DGF). Furthermore, unresolved inflammation exacerbates sustained mPTP opening, evident in chronic kidney diseases. UNI-494 is a selective mitochondrial ATP-sensitive potassium channel activator that binds to ATP-sensitive potassium channels which reverses mitochondrial dysfunction by closing mPTP. We present results from a study evaluating safety, tolerability, and pharmacokinetics (PK) of UNI-494 capsules administered to healthy subjects.

Methods: This was a single-center, double-blind, placebo-controlled, randomized single ascending dose (SAD) (Part 1) and multiple ascending dose (MAD) (Part 2) study in healthy males and females of non-childbearing potential. Part 1 enrolled up to 40 subjects in 5 cohorts of 8 subjects each (6 active/2 placebo per cohort). There was an interim decision meeting after each dose cohort, to review the safety, tolerability, and PK data up to 48 h post-dose to decide the dose level for the subsequent cohort. Part 2 enrolled up to 20 subjects in 2 cohorts of 10 subjects each (8 active/2 placebo per cohort) dosed for 5 days. The dose level for the Part 2 Cohort 1 was selected based on the safety, tolerability, and PK data from Part 1.

Results: Following single and multiple oral administration of 10, 20, 40, 80, and 160 mg UNI-494 capsules there were no serious or severe adverse events, and no subjects were withdrawn for adverse events. In the SAD cohorts, mean UNI-494 C_{max} was 14.9, 52.8, and 80.3 ng/mL and mean $AUC_{(0\text{-last})}$ was 44.6, 154, and 308 hour*ng/mL for the 40, 80, and 160 mg UNI-494 dose groups, respectively.

Conclusions: Single and multiple doses of UNI-494 capsules were safe and well-tolerated in healthy volunteers. Exposure to UNI-494 increased in a dose-proportional manner. Therapeutic levels of nicorandil in SAD dosing were achieved at 160 mg UNI-494. UNI-494 is a potential candidate for the prevention of DGF and other AKI clinical conditions. Future studies should evaluate this promising treatment in the target population of patients with AKI.

Funding: Commercial Support - Unicycive Therapeutics, Inc.

SA-PO037

Trace Element Intake and Major Adverse Kidney Outcomes in Critically Ill Patients with Severe Sepsis

Tsai-Jung Wang,[1,2] Cheng-Hsu Chen.[1] *[1]Taichung Veterans General Hospital, Taichung, Taiwan; [2]Chung Shan Medical University, Taichung, Taiwan.*

Background: Acute Kidney Injury (AKI) is common in ICU and can lead to poor renal outcomes. The balance of trace elements (e.g., selenium, zinc, and copper) in AKI patients is often disrupted. This study aims to investigate the relationship between trace element intake and renal outcomes in critically ill patients with severe sepsis.

Methods: In this prospective cross-sectional and follow-up study, ICU patients with severe sepsis, older than 20 years, and who stayed in the ICU for >48 hours, excluding those with end-stage renal disease, were included. Major adverse kidney events (MAKE-28) were determined by one or more criteria (e.g., dialysis, sustained Cr doubling from baseline, or death) on the 28th day after ICU admission. The patients' data were collected on the 1st day of ICU admission, and the mean 7-day nutrient intake from both enteral and parenteral nutrition was recorded.

Results: Of 80 patients, the mean age was 69.5 ± 14.2 years and 53 (66.25%) patients developed AKI on ICU admission. During follow-up, 28 (35%) patients experienced MAKE-28. After adjusting for age, gender, and APACHE II score, we found significant associations between nutritional intake and MAKE-28. Specifically, among patients who were admitted with AKI, there were significant correlations between various nutritional intake parameters and MAKE-28, including mean energy intake, mean carbohydrate intake, mean protein intake, and mean selenium/zinc/copper intake. However, for non-AKI patients, nutritional intake was not significantly associated with renal outcomes.

Conclusions: Our findings suggest that nutritional intake, including not only macronutrients but also trace elements plays a critical role in renal outcomes in critically ill patients, particularly those admitted with AKI.

Funding: Government Support - Non-U.S.

Table 1. Adjusted odds ratios of MAKE-28 in critically ill patients stratified by AKI status on ICU admission.

	All patients (n=80)			No AKI on admission (n=27)			AKI on admission (n=53)		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Mean energy intake (kcal/d)	0.997	0.994–0.999	**0.003**	0.997	0.991–1.002	0.200	0.996	0.994–0.999	**0.008**
Mean carbohydrate intake (g/d)	0.967	0.948–0.987	**0.001**	0.962	0.918–1.008	0.104	0.968	0.942–0.995	**0.005**
Mean fat intake (g/d)	0.989	0.932–1.009	0.128	0.958	0.858–1.070	0.446	0.975	0.934–1.018	0.244
Mean protein intake (g/d)	0.930	0.887–0.974	**0.002**	0.933	0.839–1.038	0.206	0.925	0.874–0.978	**0.006**
Mean selenium intake (μg/d)	0.979	0.951–1.027	0.386	0.964	0.894–1.039	0.335	0.939	0.899–0.980	**0.004**
Mean zinc intake (mg/d)	0.783	0.679–0.904	**0.001**	0.847	0.570–1.258	0.411	0.783	0.641–0.907	**0.001**
Mean copper intake (mg/d)	0.075	0.015–0.377	**0.002**	0.185	0.002–1.435	0.472	0.058	0.008–0.412	**0.004**

OR, odds ratio; CI, confidence intervals.
Adjusting for age, gender and Acute Physiology and Chronic Health Evaluation II score at admission.

Table. Adjusted odds ratios of MAKE-28 in critically ill patients stratified by AKI status on ICU admission.

SA-PO038

Hepatorenal Syndrome-AKI Reversal and Liver Transplant Rates in Patients Treated with Terlipressin

Justin M. Belcher,[1] Kevin R. Regner,[2] Ram Subramanian,[3] Muhammad A. Mujtaba,[4] Andrew S. Allegretti,[5] Sanaz Cardoza,[6] Hani Wadei.[7] *[1]Yale University School of Medicine, New Haven, CT; [2]Medical College of Wisconsin, Milwaukee, WI; [3]Emory University, Atlanta, GA; [4]The University of Texas Medical Branch at Galveston, Galveston, TX; [5]Massachusetts General Hospital, Harvard Medical School, Boston, MA; [6]Mallinckrodt LLC, Bridgewater, NJ; [7]Mayo Clinic in Florida, Jacksonville, FL.*

Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) occurs in patients (pts) with advanced cirrhosis and ascites. Liver transplantation (LT) is the definitive treatment for the underlying disease, while pre-LT renal replacement therapy (RRT) is associated with poorer post-LT outcomes. Terlipressin (terli) reverses HRS-AKI, which is associated with a reduced need for RRT and improved LT outcomes. However, there are concerns that HRS-AKI reversal and the consequent decrease in serum creatinine (SCr) may reduce the MELD score and thereby negatively affect LT prioritization. The FDA recommends using terli in pts with SCr <5 mg/dL, ACLF grade 0–2, and MELD score <35 (if transplant listed).

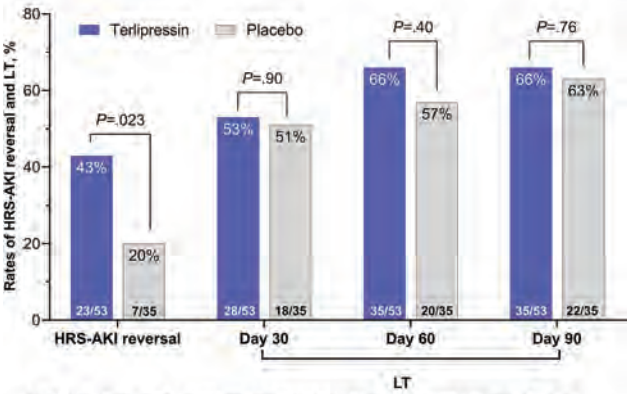
Methods: Pts LT-listed at baseline who met the FDA criteria from 2 Phase III, randomized, placebo (pbo)-controlled studies of terli in pts with HRS-AKI (CONFIRM and REVERSE) were pooled for analysis.

Results: In LT-listed pts (terli: n=53; pbo: n=35), the rate of HRS-AKI reversal was significantly higher in the terli group vs pbo (terli: 43% vs pbo: 20%, *P*=.023) (**Figure**). The RRT rate in the terli group vs pbo was 28% vs 46% (*P*=.094) by Day 30; 32% vs 54% (*P*=.038) by Day 60; and 36% vs 54% (*P*=.087) by Day 90. However, the LT rate was similar in the terli and pbo groups: 53% vs 51% (*P*=.90) by Day 30; 66% vs 57% (*P*=.40) by Day 60; and 66% vs 63% (*P*=.76) by Day 90 (**Figure**).

Conclusions: Terli increased the rate of HRS-AKI reversal and reduced the need for RRT vs pbo. Importantly, the increase in HRS-AKI reversal in the terli group (vs pbo) did not negatively impact the LT rate in pts listed for LT at baseline in the population meeting the FDA criteria for terli treatment.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals

Figure. Rates of HRS-AKI reversal and LT among patients listed for LT at baseline; Subgroup of patients meeting FDA treatment criteria from the pooled ITT population in CONFIRM and REVERSE



HRS-AKI, hepatorenal syndrome-acute kidney injury; ITT, intent-to-treat; LT, liver transplantation.

SA-PO039

Novel Predictors of Hepatorenal Syndrome Response to Terlipressin: Biomarker Analysis from the CONFIRM Trial

Andrew S. Allegretti,[1] Josh Levitsky,[4] Pratima Sharma,[2] Tianqi Ouyang,[1] Scott Silvey,[3] Jasmohan S. Bajaj.[3] *[1]Massachusetts General Hospital, Boston, MA; [2]University of Michigan, Ann Arbor, MI; [3]Virginia Commonwealth University, Richmond, VA; [4]Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Terlipressin is the only FDA approved vasoconstrictor for hepatorenal syndrome (HRS). The CONFIRM study is the largest trial of terlipressin vs. placebo (HRS response as primary outcome). Novel predictors of HRS response are required to enrich patient selection and optimize outcomes.

Methods: Samples at initiation were tested using (a) LC-MS of 1594 plasma/1420 urine metabolites (Metabolon Inc), (b) aptamer-based array of 7289 plasma proteins (SomaScan), and (c) 14 serum/urine ELISA assays. The CONFIRM trial's original definition of HRS response was used (2 creatinine [SCr] <1.5 mg/dL).

Results: 116 patients (79 terlipressin-treated [TT] and 36 placebo-treated [PT]) provided samples. Baseline characteristics, outcomes, and 2:1 TT:PT allocation were preserved from the original 300 patient trial. 36/116 (31.0%) patients achieved HRS reversal. Demographics were similar by HRS response (**Table**). In metabolite analysis, PT had the most significant differences in HRS responders (n=26 plasma, n=50 urine), with fewer in TT (n=1 plasma, n=2 urine), and in all patients (n=3 plasma, n=7 urine). There were no significant aptamers associated with HRS response after false-discovery correction. HRS responders had lower SCr (p = 0.001), cystatin C (p = 0.005), angiopoietin-2 (p = 0.04), and B2 microglobulin (p = 0.006), while osteopontin, VEGF, and NGAL were similar.

Conclusions: SCr, Cystatin C, angiopoietin-2, and B2 microglobulin, were associated with HRS response. Further study of predictors of HRS response may enrich for better candidates for terlipressin.

Funding: Commercial Support - This work was supported by an investigator-initiated research grant from Mallinckrodt Pharmaceuticals.

Demographics and Analytes by HRS Response

	HRS Response (n = 36)	No Response (n = 79)	P value
Age (mean (SD))	53.91 (12.95)	53.94 (11.67)	0.99
Male Sex (%)	25 (69.4)	42 (53.2)	0.15
Alcohol-related cirrhosis (%)	28 (77.8)	50 (63.3)	0.19
Creatinine at enrollment (median [IQR])	2.75 [2.50, 3.30]	3.50 [2.65, 4.10]	0.001
Mean arterial pressure at enrollment (mmHg)	78.67 [72.08, 84.25]	76.67 [68.67, 86.00]	0.477
MELD score at enrollment	31.00 [25.00, 39.25]	33.00 [26.00, 39.00]	0.499
Serum albumin at enrollment (g/dL)	3.60 [3.10, 4.05]	3.70 [3.50, 4.20]	0.083
Serum Cystatin C (g/dL)	3.39 [3.05, 4.21]	4.02 [3.50, 4.88]	0.005
Serum TIMP-1 (ng/mL)	370.1 [294.3, 489.9]	450.3 [323.9, 831.7]	0.082
Serum Angiopoietin-2 (ng/mL)	12.13 [9.52, 19.77]	17.10 [11.59, 25.48]	0.042
Serum Osteopontin (ng/mL)	95.02 [60.38, 143.00]	109.50 [61.49, 232.69]	0.201
Serum B2 microglobulin (mg/L)	6.47 [4.43, 8.60]	8.70 [5.89, 11.26]	0.006
Serum NGAL (ng/mL)	384.67 [273.99, 468.90]	464.89 [335.84, 665.34]	0.083
Urine NGAL (ng/mL) n = 89	64.53 [6.08, 149.07]	92.00 [31.22, 283.21]	0.089

SA-PO040

Comparison of Conventional and High-Dose Continuous Kidney Replacement Therapy in Critically Ill Patients with Septic AKI

Chan-Young Jung,[1] Jiyun Jung,[3] Jeong-Hoon Lim,[4] Jin hyuk Paek,[6] Kipyo Kim,[5] Yong Chul Kim,[2] Jae Yoon Park,[3] Hyosang Kim,[1] Chung Hee Baek.[1] RENERGY. *[1]Asan Medical Center, Seoul, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Dongguk University Ilsan Hospital, Seoul, Gyeonggi-do, Republic of Korea; [4]Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea; [5]Inha University Hospital, Incheon, Republic of Korea; [6]Keimyung University School of Medicine, Daegu, Republic of Korea.*

Background: Although prospective studies have suggested no differences in patient outcomes between high-dose and conventional-dose continuous kidney replacement therapy (CKRT) in critically ill patients undergoing CKRT, real world data are lacking. This study aimed to compare patient outcomes between conventional and high-dose CKRT in critically ill patients with septic acute kidney injury (AKI).

Methods: This multi-center, retrospective, observational cohort study included 1,390 critically ill patients with septic AKI treated with either conventional (<35 mL/kg/h; *n* =552) or high-dose (≥35 mL/kg/h; *n* = 838) CKRT. The primary outcome was 28-day mortality. Secondary outcomes included 90-day mortality, CKRT duration, kidney replacement therapy (KRT) dependence at discharge, and intensive care unit (ICU) and hospital stays.

Results: No significant differences were observed for both 28- (52.2% vs. 52.4%, *P*=0.938) and 90-day (59.8% vs. 61.7%, *P*=0.475) mortality rates among the conventional and high-dose groups. Compared to the conventional-dose group, the adjusted hazard ratios (95% confidence interval [CI]) for 28- and 90-day mortality were 0.91 (95% CI, 0.78-1.06, *P*=0.213) and 0.94(95% CI, 0.81-1.08, *P*=0.383), respectively. The conventional-dose group was associated with both a higher rate of KRT dependence at discharge (17.6% vs. 9.0%, *P* <0.001) and longer length of ICU stay (median 9.5 vs. 7.0 days, *P*=0.010), compared to the high-dose group.

Conclusions: While mortality rates did not significantly differ, when compared to conventional-dose CKRT, high-dose CKRT appeared to have lower rates of KRT dependence at discharge and shorter lengths of ICU stays.

SA-PO041

Bioelectrical Impedance Analysis to Assess Fluid Balance in Children Undergoing Continuous Kidney Replacement Therapy

Shruthi Mohan,[1] Ryan W. Schablein,[1] Kelli A. Krallman,[1] Stuart Goldstein,[1,2] Natalja L. Stanski.[1,2] *[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]University of Cincinnati, Cincinnati, OH.*

Background: Acute kidney injury (AKI) is common in critically ill children and may require continuous renal replacement therapy (CRRT). Accurate fluid balance (FB) assessment during CRRT is important but challenging as traditional methods show limited agreement and variation. BIA has been studied in adults on CRRT, but no data exist in children. We aimed to (1) assess the feasibility of BIA to evaluate FB in pediatric CRRT, and (2) compare it to traditional methods. We hypothesized that bedside and BIA assessments of FB would be discrepant.

Methods: Ongoing single-centered, prospective, observational study of patients 3-25 years (Y) receiving CRRT. We performed BIA (InBody BWA 2.0) at several timepoints (prior to CRRT, Day 2, 4, and 7 *or* prior to CRRT discontinuation) to measure total body water (mTBW). These values were compared to calculated TBW (cTBW) using the Morgenstern equation, weight (kg), cumulative FB (L), and clinician assessment of FB (nephrology/ICU).

Results: Five included patients (60% males, mean age 15.8Y) contributed 11 BIA measurements. Seven (64%) demonstrated >10% difference between mTBW and cTBW, with an absolute mean difference of 17.5% (SD 14.1%). Temporal trends in mTBW, weight and FB for patients with complete data are shown in Figure1. Concordance of FB assessment was 50% or less for all possible combinations of BIA/nephrology/ICU (Table1).

Conclusions: BIA for assessment of FB in critically ill children receiving CRRT is feasible and discrepant with traditional methods, highlighting its possible role in guiding fluid removal on CRRT.

Funding: NIDDK Support

Figure 1: Comparison of changes in mTBW (L), cumulative FB (L) and weight (kg) for individual patients on CRRT. a* = mTBW measured on Day3 due to CRRT discontinuation.

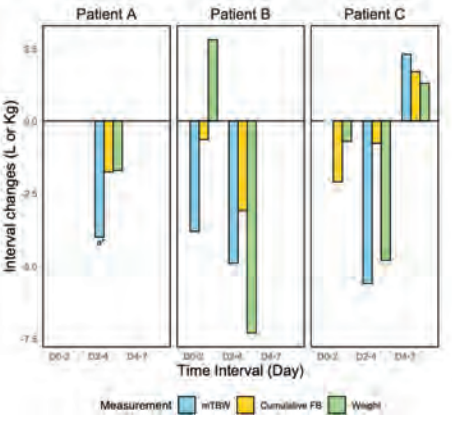


Table 1: Fluid status assessment by BIA and clinical teams.
(E = mTBW data excluded due to measurement error; NR = no response)

Patient ID	CRRT Day	BIA	Nephrology	PICU
A	2	Hypervolemic	Hypervolemic	Hypervolemic
	4	Hypervolemic	Hypervolemic	Euvolemic
B	2	Hypervolemic	Hypervolemic	Hypervolemic
	4	Hypervolemic	Euvolemic	NR
C	2	Hypovolemic	Hypervolemic	Euvolemic
	4	Hypovolemic	Euvolemic	Hypervolemic
	7	Hypovolemic	Hypovolemic	NR
D	2	Euvolemic	Hypervolemic	Hypervolemic
	4	E	Hypervolemic	Euvolemic
	7	E	Euvolemic	Euvolemic
E	2	E	NR	Euvolemic

SA-PO042

Characteristics of Antimicrobial Administration in Patients Receiving CRRT

Danica Quickfall, Jay L. Koyner. *University of Chicago Division of the Biological Sciences, Chicago, IL.*

Background: Antimicrobials are given frequently to patients requiring renal replacement therapy (RRT) in the intensive care unit (ICU). Antibiotic overuse is associated with increasing antimicrobial resistance, which comes with individual, public health, and socioeconomic consequences. While early antimicrobial therapy crucial for surviving sepsis, there are no studies that characterize the incidence of confirmed infection and antimicrobial resistance in patients receiving continuous RRT (CRRT).

Methods: A retrospective chart review identified 954 ICU patients admitted to University of Chicago Medicine between May 2016 and April 2020 who received an antimicrobial of interest and continuous veno-venous hemodialysis (CVVHD). Antimicrobial administration, specimen cultures and sensitivities were recorded. Patients were grouped according to the antimicrobial received, culture type, microbe present and sensitivities.

Results: In 954 patients receiving antimicrobials on CVVHD, vancomycin was the most administered (941, 99%), followed by cefepime (824, 86%). Of the patients receiving antibiotics, 175 (18.3%) had a confirmed infection identified with culture data. A total of 13,960 cultures were sent, with 4022 (28.8%) returned positive. The most common infections were respiratory (36.7%), blood stream (31.3%) and skin and soft tissue infections (12.8%). The most common bacteria were *Pseudomonas aeruginosa* identified in 10.3% of positive cultures (Table 1). In patients with positive cultures 132 (75.4%) died compared to 557 (71.1%) in culture negative patients (p = 0.24).

Conclusions: The incidence of positive cultures in ICU patients receiving CVVHD was low, but when present was most often a respiratory or blood stream infection. Vancomycin is administered in nearly every patient despite the high incidence of vancomycin resistant pathogens. Additionally, positive cultures are not associated with increased mortality.

Antimicrobial	n (% total patients)	Culture	n (% positive cultures)	Pathogen	n (% positive cultures)	Sensitivities	Percentage of Resistant Isolates (%)
Cefepime	824 (86)	Respiratory	1140 (36.7)	Candida sp.	910 (22.6)	Vancomycin resistance	76.6
Meropenem	124 (13)	Blood stream	972 (31.3)	P. aeruginosa	428 (10.6)	Carbapenem resistance	17.8
Piperacillin-Tazobactam	223 (23)	Urine	365 (11.3)	E. coli	193 (4.8)	Cefepime resistance	34.1
Vancomycin	941 (99)	Skin and soft	398 (12.8)	S. aureus	310 (7.6)		

Table 1 – Summary of most administered antibiotics confirmed source of infection and causative pathogens in ICU patients on CVVHD.

SA-PO043

Anticoagulation in Extended Kidney Replacement Therapy (EKRT) for Critically Ill Patients with AKI: Efficacy and Safety of Citrate vs. Saline

Lucas B. Mota,[1] Etienne Macedo,[2] Renato A. Caires,[1] Ligia C. Battaini,[1] Elerson Costalonga,[1] Maristela C. Costa,[1] Emmanuel A. Burdmann,[1] Veronica T. Costa e Silva.[1] *[1]Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; [2]University of California San Diego, La Jolla, CA.*

Background: Regional citrate anticoagulation (RCA) is becoming a popular alternative to heparin for EKRT in acute kidney injury (AKI) patients in the intensive care unit (ICU). Single-pass batch dialysis (SBD) is well suited for EKRT, yet there is limited data with RCA. This study compares efficacy and safety of RCA vs. saline for SBD-EKRT in ICU patients with AKI.

Methods: We conducted a prospective cohort using SBD-EKRT in critically ill adults with AKI from January 2015 through February 2020 at a tertiary university hospital in Brazil. Patients were divided in two groups, RCA and normal saline (NS). RCA used either citrate 4% or acid citrate dextrose (ACD) 2.2%, initial dose of 3 mmol/L. Calcium levels were measured every 2 hours for adjustment. The saline infusion rate (mL/h) matched the blood flow (mL/min). The primary outcome was filter clotting.

Results: The RCA group included 25 patients, and 39 EKRT sessions, while the NS group included 17 patients, and 31 EKRT sessions. All 42 patients were 63y (47-67), 59% male, main AKI cause was sepsis (60%), 20% on vasopressors, and 7% on mechanical ventilation. RCA had longer therapies, lower median blood flow, and higher ultrafiltration (UF) targets, compared to NS. Clotting interruption occurred in 3 (7.9%) RCA sessions and in 5 (16.1%) NS therapies (p=0.28). Hypotension (mean blood pressure <65 mmHg) frequency was similar (p=0.60) in both groups. A good metabolic control was achieved by RCA-SBD, post KRT laboratory disclosed creatinine 2.19 mg/dL (1.6-3.0), urea 55 mg/dL (29-105), potassium 3.9 mEq/L (3.5-4.2), and ionized calcium 4.1 mg/dL (3.9-4.4). During RCA-SPB, frequency of severe hypocalcemia (≤ 4 mg/dL) and bicarbonate ≥ 29 mEq/L were 35% and 8%, respectively.

Conclusions: This is the largest series of ICU patients with AKI with RCA in SBD-EKRT, showing safety and efficacy.

Funding: Government Support - Non-U.S.

Table 1 - KRT data

	CITRATE (N=38)	SALINE (N=31)	p
Blood = dialysate flow, mL/min	180 (180-200)	200 (200-250)	<0.001
Time, min	420 (360-480)	240 (180-330)	<0.001
Ultrafiltration, L	2.0 (1.4-2.5)	1.0 (0-1.7)	<0.001
Filter clotting, n (%)	3 (7.9%)	5 (16.1%)	0.288
Hypotension, n (%)	8 (21.0%)	5 (16.1%)	0.603

Results in number (%), or median (25-75 IQR)

SA-PO044

Extracorporeal Treatment with Hemoperfusion in the Management of Acute Poisoning

Enzo C. Vasquez Jiménez, Mayra Aviles, Octavio R. Garcia-Flores. *Hospital Juarez de Mexico, Mexico City, Mexico.*

Background: Acute poisonings are a major cause of morbidity and mortality in the world, especially in developing countries like Mexico. Hemoperfusion (HP) is a technique for clearing medium and large molecular weight, lipophilic and highly protein-binding molecules, based on the principle of adsorption through a sorbent. It can be used alone or combined with other renal replacement techniques. Hemoperfusion removes toxins from the blood or plasma by attaching to a surface incorporated into a cartridge or resin where the toxin is adsorbed. The advantage of adsorption when compared to diffusion is that it is not limited by the molecular weight or protein binding of the toxin. In this study, we present the experience of using hemoperfusion in acute poisoning by different poisons.

Methods: Eight poisoned patients were treated with Hemoperfusion.

Results: Results are shown in Table 1

Conclusions: Extracorporeal treatment of poisoning is considered in serious situations in which immediate elimination of the poison is indicated. Also in situations where there are no antidotes available or when toxicity is expected to be prolonged despite treatments to eliminate toxins. To make the decision to use ECT, some properties of the venom must be considered: molecular weight, protein binding, volume of distribution, and clearance pathway. Some of the indications where hemoperfusion has been used are in acute poisoning; in poisoning by drugs (valproate, carbamazepine, quetiapine), chemicals (paraquat, organophosphates) or natural toxic products (fungi, snake bite).

Clinical experience in Hemoperfusion Treatment

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Xenobiotic	Paraquat	Quetiapine	Zinc Phosphide	Zinc Phosphide	Zinc Phosphide	Quetiapine	Zinc Phosphide	Viper venom
Exposition	Intentional	Intentional	Intentional	Intentional	Intentional	Intentional	Intentional	Accidental
Basal GFR (ml/min/1,73m2)	126	125	135	90	114	101	107	90
AKI at admission	Yes	No	Yes	No	Yes	Yes	No	Yes
KDIGO stage	1		1		1	1		2
HCO3 (mmol/L	17.6	16.2	8	15.3	13	17	10	15.3
Lactate (mmol/L)	0.9	2.6	10	3.6	7.5	2.5	5.5	3.3
Mechanical Ventilation	No	Yes	No	No	No	Yes	No	No
Time until Hemoperfusion (hours)	38	50	32	12	29	25	31	36
Extracorporeal treatment	HD + HP	HP	HDF + HP	HP	HDF + HP	HDF + HP	HDF + HP	HDF + HP
No of treatments	1	2	2	1	1	3	1	1
Outcome	Survived	Survived	Survived	Dead	Dead	Survived	Survived	Survived

SA-PO045

Safety and Efficiency Evaluation of Carbon Dioxide Removal in Combination with Continuous Veno-Venous Hemodialysis/ Hemodiafiltration Therapy: Baseline Characteristics of the multiECCO2R Study

Anna P. Wammi,[1] Stefan Kluge,[2] Dominik Jarczak,[2] Carsten Willam,[3] Stefan H. Blaas,[4] Bertram Ottillinger,[5] Natalia Korolev,[1] Jennifer Braun,[1] Manuela Stauss-Grabo.[1] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [3]Universitatsklinikum Erlangen, Erlangen, Germany; [4]Klinik Donaustauf, Donaustauf, Germany; [5]Ottillinger Life Sciences, Brunnthal, Germany.*

Background: Extracorporeal carbon dioxide removal ($ECCO_2R$) was introduced to reduce the level of blood CO_2 in patients with acute respiratory distress syndrome (ARDS) and to limit the risk of ventilator-induced lung injury. The use of CO_2 removal gas exchangers could allow non-invasive ventilation techniques or the adoption of protective invasive mechanical ventilation reducing pulmonary stress. The CO_2 blood gas exchanger multiECCO2R with a surface of 1,35 m^2 can be integrated into a CRRT platform downstream of the dialyzer, allowing simultaneous treatment of adult patients with ARDS and acute kidney injury.

Methods: The open, interventional post-market clinical follow-up study plans to enroll 40 patients overall in Germany, it is currently in the recruitment phase. Patients with combined renal failure and hypercapnia due to acute lung failure in COVID-19 and other forms of respiratory insufficiency (e.g. ARDS) are being recruited and will be treated on the multiFiltrate MFT/MFT PRO (Fresenius Medical Care) with the multiECCO$_2$R gas exchanger (EUROSETS) for up to 72 hours.

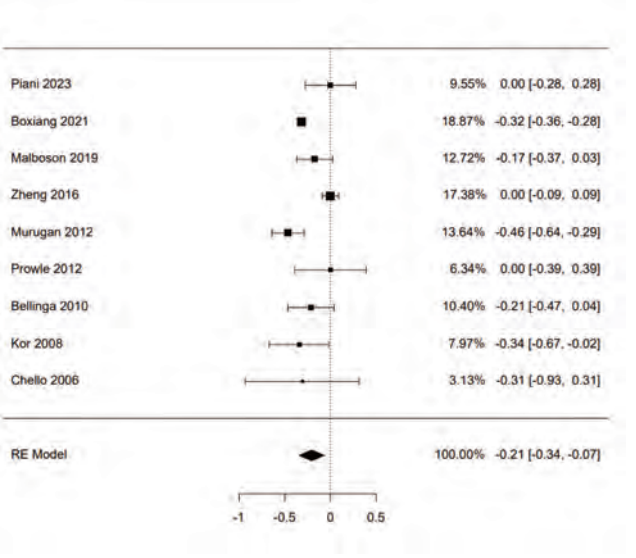
Results: 17 patients (12 males) with a mean age of 66.8±11.3 years and a baseline paCO2 value of 59.2±8.3 mmHg treated with best possible protective ventilation setting have been recruited. The leading cause for renal disease was sepsis (42.1%), and the leading cause for lung disease was pneumonia (50%). All included patients were treated in a CVVHD setting, with a mean blood flow of 186.5±75.3 ml/h and anticoagulation with heparin (47.1%) or citrate (52.9%).

Conclusions: The multiECCO$_2$R study will evaluate safety and efficiency of CO_2 removal in combination with CRRT treatment. Trial results are planned to be reported in 2025.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH

Table 1 Baseline Characteristics collected in the multiECCO$_2$R study

Baseline Characteristic		Overall (N=17) Mean ± SD, n(%)
Age [years]		66.8 ± 11.3
Gender (M/F)		12 (70.6)/ 5 (29.4)
Leading cause(s) of primary renal disease:	*Glomerulonephritis*	1 (5.3)
	Shock	1 (5.3)
	Sepsis	8 (42.1)
	Other	9 (47.4)
	Multiple answers	20 (100)
Leading causes of primary lung disease:	*Covid-19*	1 (4.5)
	Sepsis	3 (13.6)
	Pneumonia	11 (50.0)
	Other	7 (31.8)
	Multiple answers	22 (100)
Body weight [kg]		87.1 ± 19.7
BMI [kg/m²]		29.0 ± 5.8
SOFA score		15.5 ± 3.3
AKI Stage at Baseline, n (%)		Stage 3 (100.0)
Anticoagulation strategies (Citrate/Heparin)		9 (52.9)/ 8 (47.1)
ECCO$_2$R Characteristics		
paCO$_2$ [mmHg]		59.2 ± 8.3
pCO$_2$ pre exchanger [mmHg]		51.3 ± 11.5
pCO$_2$ post exchanger [mmHg]		17.6 ± 17.6
pO$_2$ pre exchanger [mmHg]		46.8 ± 10.6
pO$_2$ post exchanger [mmHg]		319.9 ± 185.1
Tidal volume [mL/kg PBW]		5.1 ± 1.1
Max. inspiratory pressure [mbar]		26.8 ± 4.0
PEEP [mbar]		10.5 ± 3.1
Driving pressure [mbar]		15.8 ± 4.6
Sweep gas flow [L/min]		2.7 ± 1.2
CRRT Characteristics		
Blood flow rate [mL/min]		186.5 ± 75.3
Dialysate flow rate [L/h]		2.32 ± 1.12
CVVHD		17 (100.0)



SA-PO046

Impact of Statins on Mortality and Length of Hospital Stay among Patients with AKI: A Systematic Review and Meta-Analysis

Abdulmueti Alshareef,[1,2] Mutaz Bellah Abudrea,[3] Abdulmohimen A. Elkhadar,[3,2] Ibrahim Ben Shady.[3,2] *[1]Zawia Teaching Hospital, Zawia, Libya; [2]Preventive Medicine Hospital, Tarabulus, Libya; [3]Tripoli Medical Center, Tripoli, Libya.*

Background: Acute kidney injury (AKI) is a frequent complication in critically ill patients, with very high mortality rates. Several studies have suggested that statin therapy, beyond its effects on cholesterol, may have impacts on the course of AKI and its complications. However, we conduct a systematic review and meta-analysis to assess the impact of statin on mortality and the length of hospital stay in hospitalized AKI patients

Methods: We conducted a systematic review and meta-analysis to investigate the impact of Statin on the Length of hospital stay in AKI patients, A literature search was performed using electronic databases and engines including; PubMed, Google Scholar, Scopus, and Web of Science, from inception to May 2024. We included all Original studies that investigate the mortality and length of hospital stay among hospitalized AKI patients.

Results: Nine studies were included in our meta-analysis, the pooled analysis showed a statistically significant reduction in the length of hospital stay for patients using statins compared to those not using statins. The overall standardized mean difference (SMD) was -0.21 (95% CI: -0.32, -0.08), indicating a moderate effect size favoring statin use. In terms of mortality, the pooled analysis of three studies showed a significant reduction of mortality with statin therapy OR (95% CI), 0.728 (0.68, 0.77) ($p < 0.001$)

Conclusions: Our current meta-analysis shows that important beneficial association between statin use and reduction of the overall mortality and reduction of hospital stay length among hospitalized AKI patients, Highlighting the potential benefits of statins beyond their lipid-lowering effects. Even with a limited number of studies that investigate the association, these findings should be further explored in ongoing international, randomized clinical trials.

SA-PO047

Effect of Cessation of Renin-Angiotensin System Inhibitors on Clinical Outcomes in AKI

Amrita Makhijani, Farah Yasmin, Dennis G. Moledina, Yu Yamamoto, Francis P. Wilson. *Yale University School of Medicine, New Haven, CT.*

Background: In the ELAIA-2 trial, we investigated whether an automated clinical decision support system affects discontinuation rates of potentially nephrotoxic medications and improves clinical outcomes in patients with AKI. One of the findings of the ELAIA-2 trial was that the proportion of RAASi prescribed were significantly altered due to the best practice alerts the providers received. We conducted a subgroup analysis to evaluate the differences in clinical outcomes between patients with RAASi inhibitors discontinued vs. cessation and clinical outcomes using an instrumental variable regression. A secondary objective was to evaluate the existence of a causal relationship between ACE/ARB inhibition and clinical outcomes and to evaluate if the effect of the drugs is influenced by potential patient characteristics using an instrumental variable regression.

Methods: All statistical analysis was conducted on STATA (Stata, v.18., College Station, TX).

Results: There was a significantly higher proportion of in-patient mortality, dialysis, AKI progression and composite outcomes at 14-days follow-up in the group that had their ACE/ARB discontinued. However, we observed no causal relationship of cessation of RAASi on clinical outcomes upon instrumental variable regression. This was the case amongst all examined subgroups including congestive heart failure, chronic kidney disease, pulmonary disease, hypertension, depression, malignancy and liver disease (Table 1).

Conclusions: There is minimal causal relationship between RAASi cessation and outcomes among hospitalized patients with AKI.

Table 1: Regression of RAASi on Clinical Outcomes

	Composite Outcome	AKI Progression	Mortality	Dialysis
Unadjusted Cohort	2.49 (1.96-3.16)	2.08 (1.62-2.67)	4.88 (3.24-7.33)	4.34 (2.31-8.16)
Instrumental Variable Regression				
CHF Absent	0.153 (-0.34-0.65)	0.214 (-0.251-0.679)	0.0532 (-0.32-0.43)	0.144 (-0.0115-0.403)
CHF Present	-0.17 (-0.61-0.27)	-0.088 (-0.486-0.309)	-0.042 (-0.36-0.276)	0.037 (-0.0155-0.23)
CKD Absent	0.297 (-0.22-0.82)	0.251 (-0.237-0.738)	0.245 (-0.146-0.636)	0.137 (-0.121-0.395)
HTN Absent	0.469 (-0.454-1.39)	0.398 (-0.458-1.25)	0.323 (-0.378-1.02)	0.38 (-0.206-0.965)
HTN Present	-0.103 (-0.462-0.256)	0.0000958 (-0.33-0.33)	-0.061 (-0.33-0.207)	0.0266 (-0.139-0.192)
Liver Disease Absent	-0.054 (-0.41-0.3)	0.048 (-0.274-0.37)	0.048 (-0.274-0.37)	0.082 (-0.087-0.251)
Liver Disease Present	0.503 (-0.524-1.53)	0.327 (-0.625-1.278)	0.34 (-0.469-1.15)	0.204 (-0.365-0.773)

SA-PO048

SGLT2 Inhibitor Treatment during AKI and Its Association with Major Adverse Kidney Events

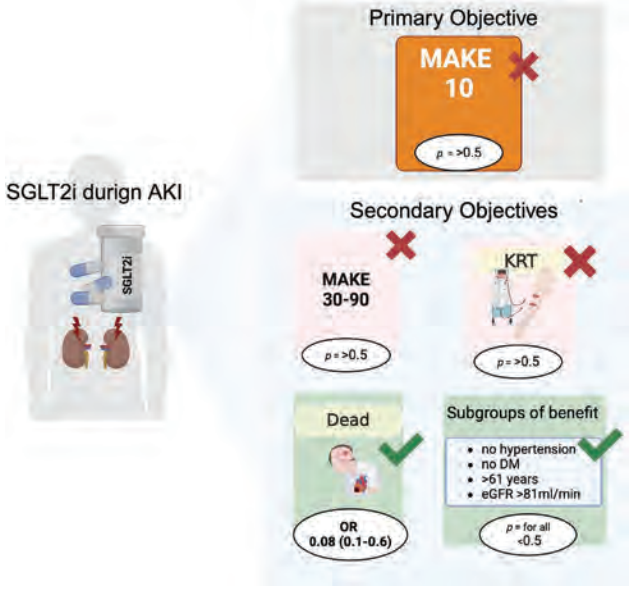
Jonathan Chavez,[1,2] Guillermo Garcia-Garcia,[1] Ramon Medina,[1,2] Francisco O. Ruiz Ochoa,[1] Yulene Navarro Viramontes,[1] Narda C. Ramírez,[1] Jose G. De la Rosa Medina,[1] Ixchel De la Torre De la Vega,[1] Jenifer M. Langarica López,[1] Fernando Cruz Aragon,[1] Guillermo Navarro Blackaller,[1] Maria de la Luz Alcantar Vallin.[1] *[1]Universidad de Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico.*

Background: The association between the administration of sodium–glucose cotransporter 2 inhibitors (SGLT2i) during acute kidney injury (AKI) and the incidence of major adverse kidney events (MAKEs) is not known.

Methods: This retrospective cohort study included patients with AKI and compared outcomes for those who were treated with SGLT2i during hospitalization and those without SGLT2i treatment. The associations of SGLT2i use with MAKEs at 10 and 30-90 days, each individual MAKE component and the prespecified patient subgroups were analyzed.

Results: From 2021 to 2023, 374 patients were included—316 without SGLT2i use and 58 with SGLT2i use. Patients who were treated with SGLT2i were older; had a greater prevalence of diabetes, hypertension, chronic heart failure and chronic kidney disease; required hemodialysis less often; and presented stage 3 AKI less frequently than those who were not treated with SGLT2i. Logistic regression analysis with nearest-neighbor matching revealed that SGLT2i use was not associated with the risk of MAKE10 (OR 1.08 [0.45-2.56]) or with MAKE30-90 (OR 0.76 [0.42-1.36]). For death, the stepwise approach demonstrated that SGLT2i use was associated with a reduced risk (OR 0.08; 0.01-0.64), and no effect was found for kidney replacement therapy (KRT). The subgroups of patients who experienced a reduction in the risk of MAKE in patients with AKI treated with SGLT2i were those older than 61 years, those with an eGFR >81, and those without a history of hypertension or DM ($p \leq 0.05$ for all).

Conclusions: The use of SGLT2i during AKI had no effect on short- or medium-term MAKE, but some subgroups of patients may have experienced benefits from SGLT2i treatment.



SA-PO049

Impact of SGLT2 Inhibitors on the Risk of Postoperative AKI

Seungmin Song,[1] Minhyung Kim,[1] Kyungho Lee,[1,2] Junseok Jeon,[1,2] Hye Ryoun Jang,[1,2] Wooseong Huh,[1,2] Jung eun Lee.[1,2] *[1]Samsung Medical Center, Gangnam-gu, Seoul, Republic of Korea; [2]Sungkyunkwan University School of Medicine, Suwon, Republic of Korea.*

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT-2i), recognized for the cardiovascular and renal benefits, impact intraglomerular pressure through tubuloglomerular feedback restoration, potentially altering the risk of acute kidney injury (AKI). This is supported by increased AKI occurrences in patients receiving Renin-Angiotensin-Aldosterone system inhibitors. We aimed to assess the real-world preventive effects of SGLT-2i on risk of postoperative AKI.

Methods: We conducted a retrospective study on diabetic patients who underwent a major surgery at a tertiary hospital in Korea from 2013 to 2023 (n=5902). We compared patients taking SGLT-2i with those taking dipeptidyl peptidase-4 inhibitors (DPP4i) before surgery to evaluate the development of AKI within seven days after surgery. Due to substantial differences in baseline characteristics between the two groups, we performed 1:3 propensity score matching to adjust for 11 potential confounders.

Results: Before matching, the mean age was 67.4 years, with males comprising 66.5% of the cohort. In the unmatched cohort, the incidence of AKI was 14.4% in the SGLT2i group (n=1006) and 14.9% in the DPP-4i group (n=4896), showing no difference between the two groups. Following matching, the incidence of postoperative AKI was 12.9% in patients with SGLT-2i and 16.0% in those with DPP-4i (p=0.030). This difference persisted even after adjusting for patient and operation-related factors (odds ratio 0.742; 95% confidence interval 0.565-0.968; p=0.029). Moreover, the development of severe AKI, defined as a serum creatinine increase of three times or more, was 0.1% in the SGLT-2i group and 1.0% in the DPP-4i group (p=0.014).

Conclusions: The use of SGLT-2i were independently associated with a lower risk of postoperative AKI than the use of DPP-4i in type 2 diabetes. SGLT-2i could potentially become the first-line medication for preventive use in high-risk groups for postoperative AKI.

A. Any-stage of AKI	OR (95% CI)	p value
Overall	0.779 (0.622-0.968)	0.026
Adjusted for patient related factors	0.783 (0.610-1.000)	0.052
Adjusted for patient & operation related factors	0.742 (0.565-0.968)	0.029
B. Stage 3 AKI		
Overall	0.106 (0.006-0.503)	0.028
Adjusted for patient related factors	0.173 (0.009-0.955)	0.102
Adjusted for patient & operation related factors	0.204 (0.012-1.416)	0.194

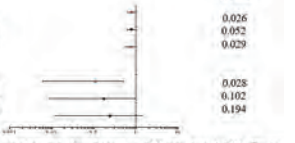


Figure 1. Univariate and multivariate logistic regression model assessing development of postoperative AKI and stage 3 AKI after 1:3 propensity score matching
Analyses were adjusted for patient related factors, including sex, age, body mass index, comorbidities (hypertension, coronary artery disease, and heart failure), medication taking before surgery (Renin-Angiotensin-Aldosterone system inhibitors, diuretics, and nonsteroidal anti-inflammatory drugs), baseline estimated glomerular filtration rate, proteinuria, hyponatremia, hypoalbuminemia, anemia, hemoglobin A1c and operation related factors, including operation time, type of operation (cardiovascular surgery vs. noncardiovascular surgery), use of intraoperative cardiopulmonary bypass, emergent operation and estimated blood loss.

SA-PO050

Bleeding Complications after Native Kidney Biopsy Associated with Aspirin Use

Steven Menez,[1] David Hu,[1] Heather Thiessen Philbrook,[1] Jack Bitzel,[1] Yumeng Wen,[1] Mohamed G. Atta,[1] Nityasree Srialluri,[1] John Sperati,[1] Bernard G. Jaar,[1] Celia P. Corona Villalobos,[1] Kyra A. Shelton,[2] Amrita Makhijani,[2] Dennis G. Moledina,[2] Chirag R. Parikh.[1] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Yale University School of Medicine, New Haven, CT.*

Background: Bleeding complications following native kidney biopsy include a drop in hemoglobin (Hgb) and the need for blood transfusion. Anti-platelet agents such as aspirin are often discontinued for 7 days pre-biopsy, and this washout period can lead to delays in diagnosis and clinical decision-making. We explored the association of aspirin exposure pre-biopsy with post-biopsy bleeding complications.

Methods: Among adult patients receiving native kidney biopsies at the Johns Hopkins Hospital (JHH) between 2019-2022, and at Yale University Hospital between 2015-2018, aspirin exposure was categorized by last documented use pre-biopsy. Outcomes included a Hgb drop within 3 days and packed red blood cell (pRBC) transfusion within 7 days post-biopsy. Logistic regression was used to determine the odds of these complications by aspirin use, adjusting for pre-biopsy Hgb and platelet count. We adjudicated relatedness of pRBC transfusion to kidney biopsy in a subset of patients.

Results: At JHH, last aspirin use within 3 days pre-biopsy was not significantly associated with higher risk of Hgb drop ≥ 1 g/dL (aOR 1.51; 95% CI: 0.90-2.51) compared to patients with no prior aspirin use within a year. The overall incidence rates of pRBC transfusion were 126/711 (18%) and 33/166 (20%) at JHH and Yale respectively. There was no significant increase in the odds of pRBC transfusion by timing of aspirin discontinuation. In a sub-cohort of 166 patients at JHH, after adjudication, only 8 (4.8%) were deemed to be biopsy-related. Similar results were seen at Yale.

Conclusions: Aspirin exposure pre-biopsy was not associated with increased odds of significant bleeding complications, with biopsy-related pRBC transfusion between 5-8%. These risks should be discussed when consenting patients where urgent biopsy diagnosis is necessary for timely therapeutic decision-making.

Table 1. Bleeding complications following percutaneous kidney biopsy

Overall native kidney biopsy cohorts					
Outcome	Aspirin Use Before Biopsy	n (%)		Odds Ratio* (95 % CI)	
		Yale (N=166)	JHH (N=711)	Unadjusted	Adjusted*
Hgb Drop ≥ 2 g/dL within 3 days	No History	9/122 (7%)	25/418 (6%)	reference	
	Within 3 days	2/18 (11%)	9/86 (10%)	1.76 (0.75, 3.78)	1.69 (0.70, 3.76)
	3-6 days	0/9 (0%)	3/95 (3%)	0.49 (0.12, 1.44)	0.44 (0.10, 1.33)
	6-365 days	0/16 (0%)	5/115 (4%)	0.70 (0.23, 1.73)	0.60 (0.29, 2.26)
Hgb Drop ≥ 1 g/dL within 3 days	No History	41/122 (34%)	104/418 (25%)	reference	
	Within 3 days	7/18 (37%)	29/86 (34%)	1.54 (0.92, 2.51)	1.51 (0.90, 2.51)
	3-6 days	2/9 (22%)	27/95 (29%)	1.20 (0.72, 1.95)	1.17 (0.69, 1.94)
	6-365 days	4/16 (25%)	23/115 (21%)	0.78 (0.46, 1.28)	0.90 (0.52, 1.50)
pRBC^ Transfusion within 7 days	No History	20/122 (16%)	70/418 (17%)	reference	
	Within 3 days	5/19 (26%)	14/86 (16%)	0.97 (0.50, 1.76)	1.11 (0.56, 2.13)
	3-6 days	4/9 (44%)	16/95 (17%)	1.61 (0.54, 1.79)	1.16 (0.60, 2.15)
	6-365 days	4/16 (25%)	26/115 (23%)	1.50 (0.89, 2.48)	1.21 (0.69, 2.06)
Adjudication of pRBC transfusion – relatedness to kidney biopsy- sub cohorts					
Patient cohort	Overall pRBC transfusion rate			Adjudicated pRBC transfusion rate	
Yale (n=166)	33 (20%)			13 (7.8%)	
JH sub-cohort (n=168)	28 (17%)			8 (4.8%)	

* for JH cohort alone
† adjusted for pre-biopsy hemoglobin and platelet count
^ pRBC = packed red blood cell

SA-PO051

Grading and Follow-Up of T Lymphocyte-Mediated Acute Interstitial Nephritis following Checkpoint Inhibitor Therapy

Ping L. Zhang, Wei Li, Hassan D. Kanaan. *Corewell Health, Royal Oak, MI.*

Background: Immuno-check point inhibitors (CPI) such as PD-1/PD-L1 inhibitors have been used to treat a variety of metastatic carcinoma with positive effects. However, there are complications such as gastrointestinal symptoms and/or kidney dysfunction. This study was determine what dominant inflamatory cells were involved in the CPI-associated acute interstitial nephritis (AIN) and if the AIN can be gradred using a modified Banff criteria for the cellular rejection of renal transplants.

Methods: Totally 20 renal biopsies from 18 patients were performed to evaluate renal pathology due to acute kidney injury following CPI treatment for various metastatic carcinomas. Infiltrating lymphocytes were stained for CD3 to highlight T lymphocytes and for CD20 to identify B lymphocytes. Then the AIN was graded by modifying the popular Banff criteria for borderline changes and acute cellular rejection (ACR) (see Table below).

Results: The identified cases represented 0.7 % of all our renal biopsies. In 15 biopsies, typical AIN was dominated by CD3-positive T lymphocytes and a small percent of B lymphocytes with minimal eosinophils or plasma cells; there were 1 grade 3 AIN, 4 grade 2 AIN and 10 grade 1 AIN. No vasculitis was seen. Five patients' biopsies without AIN had either chromic thrombotic microangiopathy (TMA, n = 1) or acute tubular injury (ATN, n = 4). Following renal biopsies with a diagnosis of AIN, 10 out of 15 patients (66.7 %) with AIN had clinical improvement with steroid treatment. Four patients were found deceased during the recent follow-up check.

Conclusions: Our study indicate that the nephrotoxicity due to CPI treatment is characterized by T lymphocyte mediated AIN as CPI mainly activates T lymphocytes for attaching tumor cells and incidentally attacking normal targets such as renal tubular epithelium. Therefore, using the popular Banff criteria for borderline changes and ACR can be easily adapted for grading AIN due to CPI (the majority was grade 1 AIN). Most patients had some renal functional recovery in response to steroid treatment.

Funding: Clinical Revenue Support

Table 1. Modified Banff Criteria for Grading Acute Interstitial Nephritis (AIN) Induced by CPI

Morphologic changes	CPI associated AIN	Banff criteria for ACR
Lymphocytic infiltration less than 25% of parenchyma with rare tubulitis	AIN 1	Borderline changes
Lymphocytic infiltration more than 25 % parenchyma with mild tubulitis (>4 lymphocytes per cross tubular section).	AIN 2	Grade 1a
Lymphocytic infiltration more 50% parenchyma with moderate or severe tubulitis (>10 lymphocytes per cross tubular section)	AIN 3	Grade 1b

SA-PO052

AKI after Percutaneous Cryoablation of Kidney Tumors: A Retrospective Cohort Study

Shirley Botros, Aman Pal, Krishnakumar D. Hongalgi, Swati Mehta. *Albany Medical Center, Albany, NY.*

Background: Preservation of renal function is an important consideration in the management of renal tumors as decreased renal function is associated with a higher number of cardiovascular events, length-of-stay and overall mortality. Techniques for localized tumor management consist of radical or partial nephrectomy, and thermal ablation, which is considered the least invasive. To further assess the safety of thermal ablation, we evaluated the incidence of acute kidney injury (AKI) and need for hemodialysis after percutaneous renal cryoablation (PRC).

Methods: This multicentric retrospective study involved two tertiary care centers between 2016 and 2022. Subjects were identified through a filter search of electronic medical records for any patient who underwent PRC for a renal tumor. A total of 311 patients were identified and the following data was collected: demographics, comorbidities, use of anticoagulation, laboratory data, tumor characteristics, and procedural data. AKI was identified by KDIGO definition of an absolute increase in serum creatinine (SCr), at least 0.3 mg/dL within 48 hours or by a 50% increase in SCr from baseline within 7 days. Baseline was defined as the lowest SCr within 1 year or most recent SCr if there was evidence of new baseline. Patients were excluded if there was no SCr recorded within 1 year prior to cryoablation or no SCr was obtained within 7 days post-cryoablation.

Results: Among the cohort of 311 patients, only 44 met the inclusion criteria. 14 patients (32%) developed AKI, and 30 patients (68%) did not have AKI. Additionally, there were no patients who required hemodialysis following PRC. Of the patients that developed AKI at the primary center, all 8 of them had resolution of AKI within one month.

Conclusions: PRC is a relatively safe and effective way to treat renal tumors while preserving kidney function. A major limitation of this study is the small number of patients with labs available pre- and post-cryoablation, which may be attributed to clinical stability of the patient precluding the need to obtain labs. Other limitations include lack of control group, short follow-up interval, and retrospective nature of study. These results are promising and warrant larger, randomized controlled trials to be conducted to validate the safety profile of PRC from a renal perspective.

SA-PO053

A Rare Case of Severe Myositis with Microsporidia Invasion of the Kidneys

Sheeraz G. Abro,[1] Paras A. Abro,[2] Javier A. Neyra,[1] Huma Fatima,[1] Emmy K. Bell.[1] *[1]The University of Alabama at Birmingham Division of Nephrology, Birmingham, AL; [2]Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan.*

Introduction: Anncaliia algerae is an obligate intracellular microsporidian parasite known to cause severe myositis among immunocompromised patients. The majority of reported cases are limited to renal transplant patients. We present a case of native renal parenchymal microorganism invasion in a patient with disseminated microsporidia.

Case Description: A 59-year-old man presented with a six-month history of progressive muscle weakness and pain. His condition deteriorated to the point he could no longer ambulate or care for himself. Medical history included Crohn's disease and arthritis, diagnosed in his early twenties and managed with long-term steroid use. Prior to his current illness, he was receiving methotrexate for 6 months and infliximab for 3 months. He only received 3 doses of infliximab before discontinuation due to presumed anti-TNF-induced myositis. Despite administration of intravenous immunoglobulin and pulse-dose steroids, his condition continued to deteriorate. A muscle biopsy revealed necrotizing myositis. Extensive work-up revealed no autoimmune causes for myositis. Urinalysis showed 3+ blood and 2+ protein, along with RBC casts on microscopy. The urine protein-to-creatinine ratio was 1.9 g/g. Renal biopsy **(Figure 1)** revealed uniform-sized, oval-shaped intratubular microorganisms without inflammation, highly suspicious for microsporidia invasion. A tongue biopsy **(Figure 2)** supported this diagnosis, which was confirmed by cell-free DNA testing identifying Anncaliia algerae. Treatment with albendazole was initiated, and immunosuppressants were tapered off. Due to persistent parasitemia complicated with septic shock and multiorgan failure including acute kidney injury requiring dialysis, fumagillin -a mycotoxin from Aspergillus- was administered. Subsequently, his clinical condition improved significantly, with marked recovery of multiorgan function including kidney function.

Discussion: This complex case underscores the importance of comprehensive investigations to uncover rare infectious etiologies and highlights the challenges of managing disseminated microsporidia.

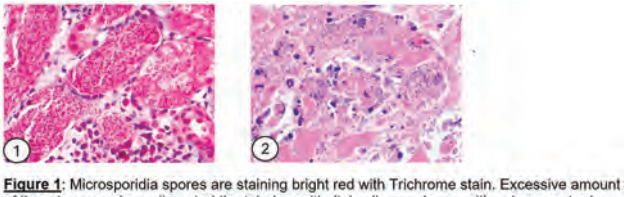


Figure 1: Microsporidia spores are staining bright red with Trichrome stain. Excessive amount of the microorganisms disrupted the tubular epithelial cells membrane with subsequent release of spores into the lumen. Trichrome x 40. **Figure 2:** Tongue biopsy showing microsporidia myositis. Necrotizing myositis with prominent karyorrhexis and spores within the necrotic cytoplasm of the myocytes. Hematoxylin and Eosin, x60.

SA-PO054

Epstein-Barr Virus-Associated Acute Interstitial Nephritis in an Adult Presenting with Chronic Osteomyelitis

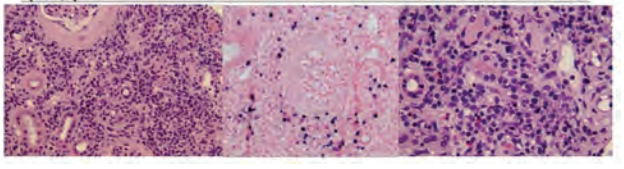
Simran Dhillon,[1,2] Amin Abedini,[2] Songul Onder.[1,2] *[1]University of Maryland School of Medicine, Baltimore, MD; [2]University of Maryland Medical System, Baltimore, MD.*

Introduction: Epstein Barr Virus (EBV) is a rare cause of acute interstitial nephritis (AIN) in adults. It is primarily reported in children and young adults. The use of steroids and duration of the steroid use in viral intertitial nephritis is controvertial.

Case Description: 45 Year old female with chronic osteomyelitis and open wound presented with fever, hypotension, fatigue, flank/abdominal pain and sore throat. Her past medical history was significant for chronic kidney disease stage 3b due to diabetic nephropathy, with baseline serum creatinine at 2.0 mg/dl. Initial labs revealed acute on chronic kidney failure, with serum creatinine at 4.4 mg/dl, cholestatic hepatitis, leukopenia and anemia. She was started on intravenous vancomycin and piperacillin-tazobactam. EBV IgM was positive with elevated viral load. Bilateral flank pain, AKI and cholestatic liver injury worsened despite discontinuing antibiotics. She was started on hemodialysis (HD). Kidney biopsy revealed extensive interstitial inflammatory infiltrates, Epstein-Barr encoding region (EBER) in situ hybridization positive consistent with EBV associated AIN. She was started on Prednisone 60 mg/day and valganciclovir due to worsening symptoms and renal/liver indices. Her symptoms and renal and liver parameters improved to baseline after 10 days course of Prednisone.

Discussion: We here report fast recovery of EBV-associated AIN with short course of prednisone and valganciclovir. Case reports and retrospective cohorts support the use of corticosteroids and antivirals in addition to supportive care in severe complicated EBV-associated AIN. The use of corticosteroid for renal recovery had to be balanced against infectious concerns with osteomyeltis, and thus corticosteroid course was discontinued at ten days after greatly improved renal/liver indices, improved clinical symptoms and liberation from HD. Early recognition and timely initiation of corticosteroid treatment may be crucial for favorable outcomes in EBV-AIN requiring HD.

Labs	Initial	Peak	Post-Treatment
Creatinine (mg/dl)	4.36	7.32	2.4
Bilirubin (mg/dl)	1.0	18.7	1.8
Alkaline phosphatase (units/L)	375	1930	415



Lab results and renal biopsy

SA-PO055

Hemopure Therapy in Postpartum Hemorrhagic Shock: Challenges in Laboratory Interference and Kidney Assessment

Issa R. Haddad, Chintan V. Shah, Sheena Pramod. *Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida College of Medicine, Gainesville, FL.*

Introduction: HBOC-201 (Hemopure) is a second-generation hemoglobin-based oxygen carrier (HBOC) derived from bovine (cow) hemoglobin. It is intended to be used as an alternative when human blood is unavailable or unsuitable, such as in emergencies or when a patient refuses blood transfusion for religious or personal reasons. Challenges arise with its interference in laboratory tests, particularly in assessing renal function.

Case Description: We describe the case of a previously healthy 35-year-old pregnant Jehovah's Witness who presented at 38 weeks gestation with placental abruption necessitating emergent cesarean section, leading to postpartum hemorrhagic shock with acute hemoglobin drop to 2.5 g/dL. Due to religious beliefs, she declined human blood products, prompting her transfer to a tertiary center for participation in a clinical trial of Hemopure therapy. The hospital course was further complicated by peripartum cardiomyopathy, ventilator-dependent respiratory failure, and non-oliguric acute kidney injury with refractory hyperkalemia, necessitating intermittent hemodialysis followed by continuous venovenous hemodiafiltration. However, despite regional anticoagulation, circuit clots resulted in further blood loss. Hemopure administration, erythropoiesis-stimulating agents, and intravenous iron were initiated. Hemopure use was complicated by inaccurate laboratory results, including creatinine, blood urea nitrogen, and potassium, due to interference with ion selective electrode, making the interpretation of laboratory parameters unreliable. Due to lack of accurate laboratory parameters, further decisions for renal replacement therapy remained solely on clinical grounds and indirect parameters (altered mental status, electrocardiogram, etc.). The patient's condition eventually improved, leading to extubation, improvement in kidney function, and rise in hemoglobin up to 10 g/dL, allowing discharge from the hospital.

Discussion: This case highlights the complexity of managing postpartum hemorrhagic shock in Jehovah's Witness patients, necessitating alternative therapies like Hemopure. Its interference with laboratory tests poses significant challenges critical for guiding therapy, especially for nephrologists. Further research is imperative to elucidate Hemopure's impact on metabolic panel accuracy, aiding nephrologists in clinical decision-making.

SA-PO056

What to Do When It RAINs?

Pratap Kumar Upadrista,[1,2] Purva D. Sharma.[1,2] *[1]Northwell Health, New Hyde Park, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, NY.*

Introduction: Recurrent Acute Interstitial Nephritis (RAIN) is a poorly studied condition, associated with adverse kidney outcomes. Treatment options for RAIN are not well established, making management more challenging. Systematic approach for ruling out underlying causes and prompt diagnosis and treatment are of paramount importance to salvage kidneys. However, no precise cause can be identified in many cases. Here, we present a case of idiopathic RAIN that was successfully treated with MMF.

Case Description: A 70 Y/O F with Hx of DM, HTN, HLD came to ED with fever of ~ 2 weeks, low back ache, chills, and malaise. She was on Metformin, Losartan, HCTZ and Omeprazole. Physical examination was unremarkable. On presentation, she had anemia (Hb 9.8 gm/dL), AKI with a Scr of 4.0 mg/dL (baseline Scr 6 weeks ago was 0.9 mg/dl) and BUN of 40mg/dL. UPCR was 0.6 g/g. Blood & urine cultures were negative. Hepatitis B & C serologies were negative and SPEP was normal. A kidney biopsy was suggestive of AIN, presumed to be due to PPI. Omeprazole was stopped and she was started on prednisone 1mg/kg/day (80mg/d), her creatinine started to improve with a nadir of 1.6 mg/dl and prednisone was slowly tapered off over 2 months. Off prednisone, for a month, her creatinine worsened to 2.75 mg/dL. Other causes of AKI were ruled out, and she was restarted on prednisone at 0.75mg/kg/d for AIN recurrence. Creatinine improved to 1.25mg/dL and prednisone tapered off. However, 3 weeks later, she again developed AKI (Scr 1.6mg/dL). Due to 2nd recurrence of AIN, we looked for systemic disorders. IgG, ANA, ENA profile & ANCA were negative. CT chest and abdomen was negative for malignancy. Repeat protein electrophoresis, FLC ratio were normal. PET-CT ruled out any inflammation. She was started on MMF 500mg BID as steroid sparing agent for idiopathic recurrent AIN. Her creatinine stabilized at 1.26 mg/dL and repeat UA was negative for proteinuria and hematuria. She has remained stable for the last 9 months on this regimen.

Discussion: RAIN needs thorough work up. Its management options are not standardized. MMF, Azathioprine, CNI and Rituximab have been tried with some success. Biomarkers to diagnose and prognosticate AIN like CXCL-9, TNF-α, IL-9 are under consideration. We aim to highlight the management of idiopathic RAIN with MMF as steroid sparing agent with good outcome. We need more studies to establish guidelines to effectively manage this entity.

SA-PO057

Tacrolimus as a Treatment of Immunotherapy-Induced Minimal Change Disease

Richard Odle, Hsu pheen Chong, William G. Petchey. *West Suffolk NHS Foundation Trust, Bury Saint Edmunds, United Kingdom.*

Introduction: Immune-related adverse reactions affecting the kidneys are a well-recognised complication of immune-checkpoint inhibitors (ICIs). Causatively suspected with temporarily related acute kidney injuries (AKI), acute interstitial nephritis (AIN) is believed to represent the most common pathology for ICI-induced kidney injury. ESMO guidelines currently recommend consideration of a renal biopsy on a case-by-case basis. However, glomerulonephritis is an increasingly recognised manifestation of ICI-induced kidney injury.

Case Description: We outline the case of a 76 year-old male who developed an AKI one week after receiving combination ipilimumab-nivolumab, with baseline creatinine of 86 umol/L which peaked at 529 umol/L. Urinalysis demonstrated 1+ protein and 3+ blood, and ICI-induced AIN was presumed. He received IV methylprednisolone 1 g x 3 doses, and weaned off steroids completely in Jan 2024 as his renal function returned back to baseline. Within 3 weeks of stopping steroids he then sustained a further AKI, with an albumin: creatinine ratio of 814 mg/mmol – 4 months after last receiving immunotherapy. After a normal ultrasound, renal biopsy confirmed minimal change disease. He was initiated on IV methylprednisolone, followed by a weaning course of prednisolone with tacrolimus 1 mg BD and switch thereafter to tacrolimus monotherapy - his renal recovery has so far been maintained with a normalised urinary ACR and creatinine.

Discussion: This case highlights a case of minimal change disease which was steroid responsive and now remains in remission with a single steroid sparing agent (Tacrolimus). It has been suggested that approximately 8% of immunotherapy- induced AKI have glomerular involvement. Identifying proteinuria early is therefore of vital importance to raise diagnostic suspicion, and to aid with decisions around whether to perform a renal biopsy. Identification of minimal change disease also enables the utilisation of the steroid-sparing agent tacrolimus, which has been suggested to be non-inferior to steroids. This case demonstrates no relapse despite completion of a steroid reducing regime whilst on tacrolimus therapy at time of writing.

SA-PO058

AKI Due to Idiopathic Tubulointerstitial Nephritis with Uveitis Syndrome

Krishna Mohita Kuruvada,[1] Moazam M. Cheema,[1] Lanny T. DiFranza,[2] Maureen Brogan,[1] Deep Sharma,[1] Kettia N. Guillite.[1] *[1]Department of Nephrology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY; [2]Department of Pathology, Montefiore Medical Center/ Albert Einstein College of Medicine, Bronx, NY.*

Introduction: Tubulointerstitial nephritis with uveitis(TINU) syndrome is a rare oculorenal inflammatory disorder. It generally affects younger individuals and is more prevalent in females. Uveitis is often bilateral and develops simultaneously with renal disease. We report a case of TINU syndrome presenting with uveitis.

Case Description: 27-year-old man with a history of GERD presented with left temporal headache and ocular symptoms including pain, foreign body sensation, photophobia, and redness, without preceding ocular trauma. He was taking aspirin for headaches and omeprazole 20mg for gastritis. Physical examination revealed no skin rash or peripheral edema. He was evaluated by ophthalmology and diagnosed with bilateral nongranulomatous anterior uveitis. Laboratory tests showed an elevated creatinine level of 2.76 mg/dl compared to a recent baseline of 1.3 mg/dl. Urinalysis revealed 6-10 WBCs, no RBCs, and a spot UPCR of 433 mg. ESR was elevated to 59mm/hr, and CRP was elevated to 5.1mg/dl. Urine beta 2 microglobulin was elevated to 19.55mg/L. Kidney ultrasound was unremarkable. Our differentials included Sjögren syndrome, SLE, granulomatosis with polyangiitis and infectious causes such as leptospirosis which were excluded based on serologies. Kidney biopsy showed acute and chronic interstitial nephritis with light microscopic findings of neutrophilic, eosinophilic, and lymphocytic tubulitis and a moderate degree of tubular atrophy and interstitial fibrosis. The simultaneous onset of bilateral acute anterior uveitis and biopsy-proven tubulointerstitial nephritis confirmed a diagnosis of TINU syndrome. The patient was started on systemic steroids and eventually kidney function returned to baseline.

Discussion: TINU syndrome is generally considered an autoimmune disease, with medications(such as NSAIDs and antibiotics) and infections acting as acquired risk factors. Serum beta-2 microglobulin is a sensitive biomarker of interstitial nephritis that is helpful in the diagnosis of TINU although a biopsy is confirmatory. Mainstay of treatment involves the use of corticosteroids which reduces oculorenal inflammation in the active phase. Our case highlights the importance of using a high index of suspicion when dealing with a patient with both uveitis and kidney dysfunction as early treatment reduces the risk of progression to CKD.

SA-PO059

Treating TAFRO Syndrome: A Case Study of Castleman Disease Kidney Complications

Jennifer A. Schoonmaker, Paavana Varanasi, Evamaria Anvari. *Mayo Clinic Arizona, Scottsdale, AZ.*

Introduction: TAFRO syndrome, a rare variant of idiopathic multicentric Castleman disease, presents with Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis on bone marrow biopsy, and Organomegaly (TAFRO). This case details successful treatment of a young male with siltuximab, steroids and eculizumab.

Case Description: A previously healthy 19-year-old male presented to an outside hospital with respiratory symptoms. Imaging exposed pleural and pericardial effusions requiring drainage, antibiotics, antifungals, and steroids. At that time, he had Cr 1.3 mg/dL, low-grade proteinuria, and negative serologic workup for glomerulonephritis (GN). He presented 3 weeks later with worsening fatigue, edema, nausea, vomiting and diarrhea with Cr 2.5 mg/dL and thrombocytopenia. Renal function rapidly declined, requiring dialysis. Renal biopsy showed features of thrombotic microangiopathy (TMA). He was transferred for higher level of care. Another extensive GN and infectious workup was negative. Imaging showed lymphadenopathy and splenomegaly. Initial lymph node biopsy was inconclusive. Bone marrow biopsy was negative. Patient continued to deteriorate despite steroids to treat suspected Castleman's disease. A second renal biopsy again showed TMA. Eculizumab was started with improvement in renal function, but not thrombocytopenia. A second lymph node biopsy confirmed a plasma cell variant of Castleman's disease diagnosing TAFRO. He was started on siltuximab and thrombocytopenia improved after 6 doses. Renal function improved, dialysis was weaned off, and eculizumab was stopped after Castleman's disease was controlled.

Discussion: TAFRO syndrome involves systemic inflammation and is a subtype of multicentric Castleman's disease (MCD). Lymph node biopsy findings in MCD are crucial for TAFRO diagnosis. Thrombocytopenia, always found in TAFRO, is not always present in MCD. The renal pathology in TAFRO is unclear, but TAFRO may trigger the complement cascade, leading to TMA. Eculizumab can be stopped once TAFRO is controlled. As in other complement mediated diseases, Eculizumab can also be weaned off once the triggering disease is controlled. Further research is needed to understand renal involvement, optimal treatment, and long-term outcomes in TAFRO.

SA-PO060

AKI in IgG4-Related Retroperitoneal Fibrosis: A Case Report

Saman Rashid,[1] Bharath Duraisamy Swami Kannan,[2] Faizan Babar.[3] *[1]Karachi Medical and Dental College, Karachi, Pakistan; [2]Government Sivagangai Medical College and Hospital, Sivagangai, India; [3]Nephrology Associates of Lexington, Lexington, KY.*

Introduction: IgG4 related disease is a chronic fibro-inflammatory disease with multiorgan involvement. Although a multisystem disease, renal involvement is the most common presentation, exhibiting the features of tubulointerstitial nephritis. The pathological hallmark of the disease is dense lymphoplasmacytic infiltrate with elevated IgG4 positive plasma cells. First line treatment for IgG4-RKD is steroids and any delay in the treatment can lead to irreversible kidney damage, necessitating early diagnosis and prompt treatment.

Case Description: A 35 year old male presented with weight loss, unexplained anemia, and generalized lymphadenopathy. On admission, laboratory investigations revealed :BUN/Cr 72/12 and K+5.9. Urinalysis was unremarkable and Renal Ultrasonogram revealed moderate to severe hydronephrosis bilaterally. CT scan revealed new proliferative abnormal soft tissue in the lower retroperitoneum and bilateral iliac regions, suggesting retroperitoneal fibrosis with bilateral ureteral obstruction which was not present in the previous scans two months prior to presentation. Initial diagnosis of post-renal AKI was managed with nephrostomy tube placement and a single dialysis session. Anemia evaluation showed positive ANA (1:80) and elevated total protein (9.0 mg/dL), IgG (3107 mg/dL) and IgA (492 mg/dL) with no M spike on SPEP. Further IgG subtyping showed mildly elevated IgG4 (101 mg/dL). A diagnosis of idiopathic retroperitoneal fibrosis was made after all other differentials were ruled out.

Discussion: IgG4-RD has a rare incidenceof less than 1 per 100,000 population. Renal damage in IgG4-RD can be attributed to direct parenchymal damage or retroperitoneal fibrosis around the ureters resulting in hydronephrosis and post renal AKI, as seen in our patient. A comparative analysis from past CT scan showed diffuse retroperitoneal fibrosis around the external, common and internal iliac arteries and mesenteric arteries, indicating the severity and rapidly progressive nature of the disease. Following a treatment plan with high dose steroids, there was no significant response as evidenced by a repeat CT scan showing fibrosis in multiple areas throughout the body. As per treatment protocol, the patient was started on four week Rituximab therapy with tapering steroid and weekly Methotrexate. The patient currantly has stable disease based on repeat imaging and levels of inflammatory markers.

SA-PO061

Successful Management of Membranoproliferative Glomerulonephritis with Repository Corticotropin Injection

Muhammad R. Khan, Kelly H. Beers. *Albany Medical Center, Albany, NY.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury subdivided by light microscopy into immune complex/monoclonal immunoglobulin-mediated, complement-mediated, and MPGN without immunoglobulin or complement deposition. Treating underlying causes is ideal, but idiopathic immune complex MPGN is often managed with immunosuppressive medications. Repository corticotropin injection shows promise in hard-to-treat cases, as illustrated in a successful treatment involving significant psychiatric side effects from steroids.

Case Description: A 30-year-old female with MPGN diagnosed at age 16, presented to hospital with lower extremity edema and AKI. Before the presentation she was treated with prednisone 20 mg daily for many years and any attempt to taper prednisone resulted in MPGN flares. She was previously also trialed on mycophenolate with lower dose prednisone, but gastrointestinal side effects led to discontinuation of mycophenolate. She was then treated with repository corticotropin injection with prednisone 5 mg and was stable for two years until she had another flare with urine protein creatinine ratio (UPCR) rising to 3.2 g/g. Increasing prednisone to 50 mg/day temporarily improved UPCR, but severe depression with suicidal ideation prompted cessation of steroids. Subsequently, her renal function declined, with creatinine rising and UPCR reaching 4 g/g. After discontinuing all her medications for six months, severe deterioration ensued, with creatinine at 3.19 and UPCR at 12 g/g. She was admitted to hospital and renal biopsy was done which showed MPGN immune complex. Despite induction therapy with cyclophosphamide and rituximab her UPCR remained at 8.5 g/g after three months. Repository corticotropin injection was initiated at 80 mg biweekly, reducing UPCR to 4.35 g/g in a month and further to 0.75 g/g over three months.

Discussion: Our case of difficult-to-treat idiopathic immune complex MPGN responded only to high steroid doses, which were discontinued due to steroid-induced suicidal ideation. Repository corticotropin injection, which stimulates endogenous steroid production, offered lower steroid exposure and fewer side effects. This may be a good option to avoid systemic side effects of steroids in other hard to treat cases.

SA-PO062

Iptacopan in C5 Blockade for Refractory Atypical Hemolytic Uremic Syndrome

Minh-Ha Tran,[1] Stefan O. Ciurea,[2] Sheetal Desai,[3] Arash Rezazadeh Kalebasty,[4] Matthew D. Nguyen,[5] Vu Q. Nguyen,[5] Samir D. Patel,[5] Umut Selamet,[6] Ramy M. Hanna.[5] *[1]University of California Irvine - Department of Pathology - Division of Transfusion Medicine, Irvine, CA; [2]University of California Irvine - Department of Medicine - Division of Hematology/Oncology-Bone Marrow Transplant Unit, Irvine, CA; [3]University of California Irvine - Department of Medicine - Division of Rheumatology, Irvine, CA; [4]University of California - Irvine - Department of Medicine - Division of Hematology/Oncology, Irvine, CA; [5]University of California Irvine Nephrology Hypertension & Kidney Transplantation, Orange, CA; [6]Harvard - Dana Farber Cancer Institute - Department of Medicine-Division of Oncology, Boston, MA.*

Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is a life-threatening disease related to mutations in the complement system resulting in overactivation and dysregulation of the alternate pathway. Currently, there are only two United States Food and Drug Administration (FDA) approved treatments for aHUS, eculizumab and ravulizumab, which target complement factor 5 (C5) and prevent the formation of C5b-9. Iptacopan (Fabhalta) is a small-molecule inhibitor of complement factor B (FB) that binds to FB and prevents the formation of the alternative pathway (AP) C3-convertase (C3bBb). This limits the cleavage of C3 to the active fragment C3b and can prevent C3b-mediated extravascular hemolysis. We report the first known case of the factor B inhibition with Iptacopan in treatment of aHUS.

Case Description: 21-year-old Pakastani male with heterozygous complement factor related protein 4 mutation and aHUS, had an initial partial response to eculizumab and then complete response to ravulizumab, which resulted in the patient coming off dialysis. Patient had a sudden and unexpected flare 2 years after his initial presentation. The treatment failure was not abated by redosing with ravulizumab, leading to the use of multiple advanced diagnostics (including artificial intelligence algorithms) to look for a possible differential. No malignancy or other aggravating factor was found even after bone marrow biopsy. Recent data on Iptacopan's use in C5 refractory Paroxysmal Nocturnal Hemoglobinuria provided a therapeutic rationale. An application for the compassionate use of Iptacopan was filed and approved by the FDA. Patient's blood counts completely recovered, his microangiopathic hemolytic anemia ceased, his acute kidney injury completely resolved thus permitting discontinuation of renal replacement therapy was discontinued. Human Anti-murine anti-drug antibodies were suspected as the cause of C5-blockade failure but could not be confirmed.

Discussion: To our knowledge this is the first report of using Iptacopan in treatment of aHUS in the United States. Larger clinical trials involving diverse patient populations are needed to validate these initial findings, assess safety, and establish Iptacopan as a potential treatment for the management of aHUS.

SA-PO063

Acute Tubular Necrosis (ATN) after Hemopure in a Patient with Sickle Cell Disease (SCD)

Sabiha M. Khan, Syeda B. Ahmad. *UPMC, Pittsburgh, PA.*

Introduction: Hemopure (HBOC-201) is a bovine hemoglobin-based oxygen carrier (HBOC), classified as a semi-synthetic, cell-free, purified hemoglobin product. It effectively binds and delivers oxygen to tissues, mimicking the function of red blood cells. This is the first case report, to our knowledge, which details the clinical trajectory of a patient who developed ATN after hemopure administration.

Case Description: A 57-year-old female Jehovah's Witness with SCD and vaso-occlusive crisis was intubated for mixed respiratory failure. She had influenza pneumonia and pulmonary edema attributed to high output failure from severe anemia. Her blood pressure (BP) was normal. Her laboratory results showed a hemoglobin (Hgb) of 6.0 g/dL and a creatinine (Cr) of 1.1 mg/dL. Her ferritin was 1365 ng/mL. She was given Epogen 20,000 IU daily and was diuresed with robust urinary response (3L/24hr). Her Cr remained 1.0-1.3 mg/dL over the following days; however, her Hgb decreased 5.3 to 4.9 g/dL, and she was given 2 units (32.5 g/unit) of IV Hemopure. The day after infusion, her Cr increased to 1.8 mg/dL and her systolic BP rose to 200 mmHg. A urine sediment showed muddy brown casts suggestive of ATN. A renal ultrasound with doppler showed no renal papillary necrosis or obstruction. She became progressively volume overloaded and started urgent peritoneal dialysis. Further doses of Hemopure were held, her volume status improved, and she was extubated. One month later, she demonstrated renal recovery to baseline kidney function.

Discussion: Hemopure has been approved for use by the FDA's Expanded Access Program since 2013 for patients with life-threatening anemia who are unable to receive blood transfusions. HBOCs offer several unique advantages such as reduced risk of alloimmunization and infection. They have been hypothesized to reverse the sickling process in SCD. As a bloodless medicine, they can be utilized in patients who decline blood transfusions for religious reasons like Jehovahs' Witness. Hemopure trials in surgical patients resulted in increased mean arterial pressure, serum urea (N_2), bicarbonate, and base extract. Renal side effects include hypertension attributed to heme scavenging of endothelial nitric oxide, and nephrotoxicity possibly from renal oxidative stress and vasoconstriction. This case seeks to contribute to the growing body of literature on the safety and risks associated with HBOCs.

SA-PO064

BRASH Syndrome: Familiar Yet Difficult to Manage, a Case Series

Hong Hieu Truong,[1] Pabitra Adhikari,[1] Laith S. Sorour,[1] Muhammad Albanna,[1] Sopiko Gogia,[1] Le Y Nhi Vo,[2] Valiko Begiashvili.[1] *[1]Ascension Saint Francis, Evanston, IL; [2]University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Viet Nam.*

Introduction: BRASH syndrome is characterized by the combined effects of AV nodal blockers and Renal dysfunction, leading to Hyperkalemia, severe Bradycardia, and Shock. Although the connection between these medications and renal failure has been known for years, managing the syndrome remains challenging.

Case Description: Case 1: A 78-year-old woman with atrial fibrillation and severe mitral valve stenosis (MVS) presented with fatigue. She was taking metoprolol, diltiazem. Upon arrival at the emergency department (ED), her heart rate (HR) of 50 beats per minute (bpm), blood pressure (BP) of 65/30 mmHg, and a potassium (K+) level of 8.3 mEq/L, and creatinine level of 5.17 mg/dl from a baseline of 1.23 mg/dl. She was given norepinephrine, home medications were stopped, and hyperkalemia treatment was initiated, resulting in lowering her K+ level to 4.8 mEq/L and an increase in HR to 77 bpm. Echocardiography later revealed pulmonary hypertension from MVS, which was identified as the underlying cause of her AKI. Kidney function gradually improved with furosemide within the context of cardiorenal syndrome stemming from MVS. Upon discharge, her creatinine level was 1.9 mg/dl **Case 2:** An 84-year-old male with hypertension (HTN), chronic kidney disease (CKD), and benign prostatic hypertrophy (BPH) was on carvedilol. In the ED, his HR was 18 bpm, BP was 92/43 mmHg, K+ level was 8.1 mEq/L, and creatinine was 2.7 mg/dL (baseline 1.96 mg/dL). A bladder scan showed significant urinary retention. Foley catheter placement helped resolve the obstruction. He was also hypothermic, with rectal temperature of 90.9°F, and passive warming methods were employed. He received hyperkalemia treatment without response. Both pacing attempts and atropine administration were unsuccessful. IV dobutamine was also started for hypotension. His HR increased to 40 bpm. Immediate dialysis was performed for life-threatening hyperkalemia, reducing K+ level to 5.2 mEq/L. His HR improved slowly to 50 bpm. Cardiology was consulted and diagnosed BRASH syndrome on top of sick sinus syndrome

Discussion: BRASH syndrome affects patients with various levels of kidney function, from normal eGFR to ESRD on dialysis. It can involve multiple etiologies or just a single cause. Most patients improve with supportive care, but standard hyperkalemia and bradycardia treatment protocols should be followed.

SA-PO065

Atypical Presentation of IgG4-Negative Idiopathic Retroperitoneal Fibrosis

Kyra Colston, Margaret Spolnik. *Indiana University School of Medicine, Indianapolis, IN.*

Introduction: Retroperitoneal fibrosis (RPF) is a rare condition in which fibro-inflammatory tissue surrounds the iliac arteries and abdominal aorta. Ureteral obstruction is common, resulting in acute or chronic renal failure. Most cases are idiopathic and often develop alongside autoimmune conditions or IgG4-related disease. Clinical manifestations include fever, anorexia, and weight loss with back or flank pain.

Case Description: A 53-year-old African American male presented to the emergency room with extreme fatigue, worsening anorexia, and weight loss. Past medical history included hypertension, type 2 diabetes mellitus, obstructive sleep apnea, depression, and medication noncompliance. Physical exam was unremarkable and blood testing revealed serum creatinine of 5.28 (baseline 1.2), eGFR of 12.2 (68.6), and BUN of 35 (17). He denied flank pain, urinary symptoms, and history of kidney disease. Ultrasound showed moderate to severe bilateral hydronephrosis. CT scan of the abdomen and pelvis revealed no stones within the urinary tract but identified a retroperitoneal mass at the level of the aortic bifurcation. Following admission, bilateral upper pole percutaneous nephrostomy tubes and lower pole nephroureteral stents were placed. CT scan of the chest showed no evidence of malignancy. Two weeks later, diuretic renal scintigraphy determined renal function to be 68% (left) and 32% (right). Repeat CT abdomen/pelvis revealed improved hydronephrosis. Biopsy of the retroperitoneal mass showed myofibroblastic proliferation with thick collagen and inflammatory cells but rare IgG4-positive plasma cells. Treatment of idiopathic RPF was initiated with high dose corticosteroids. Serum creatinine has since decreased to 1.89, eGFR increased to 41.9, and BUN decreased to 22.

Discussion: This case illustrates the importance of maintaining a broad differential in the setting of AKI and considering rare causes for hydronephrosis. Idiopathic RPF can have a varied clinical presentation as seen in our patient lacking back or flank pain despite extensive fibrosis causing hydronephrosis. Prompt recognition of idiopathic RPF is vital to early intervention and preservation of renal function.

SA-PO066

Thrombotic Microangiopathy Treated with Eculizumab in a Patient with Known Immune Thrombocytopenic Purpura

Ali R. Koksal, Golnaz Vahdani, Hasan T. Ozpolat, Erika R. Bracamonte, Iyad S. Mansour, Bijin Thajudeen. *Banner - University Medical Center Tucson, Tucson, AZ.*

Introduction: Thrombotic Microangiopathy (TMA) is rare but part of a broad spectrum of syndromes that can cause severe kidney failure. Here, we present a TMA case that was previously followed by hematology with a diagnosis of immune thrombocytopenic purpura (ITP), which was proven by a kidney biopsy despite severe thrombocytopenia.

Case Description: A 64-year-old female with traumatic fever, mitral stenosis post mechanical valve replacement, and thrombocytopenia due to ITP presented to ED with severe headache, dizziness, and double vision for 3 days. Cranial CT scan showed subdural hemorrhages, along with trans tentorial herniation. She underwent successful suboccipital craniotomy and and was transferred to the ICU. Hematology was consulted for worsening thrombocytopenia measuring 49 K, down from 102 K on admission, prompting the initiation of 1 mg/kilogram/day prednisone. The patient experienced episodes of hypotension resulting in acute kidney injury. On admission creatinine was 0.7 mg/dL and increased to 4.8 mg/dL in one week. Urine sediment microscopy showed multiple granular casts WBCs and rare isomorphic RBCs, UACR 78 mg, UPCR 800 mg, and urine NGAL:492. Renal ultrasound showed no signs of obstruction or chronicity. Subsequently, her thrombocytopenia continued to worsen along with increasing creatinine, but on peripheral smear there was no evidence of schistocytes, ADAMTS13 activity was normal, and GN panel was negative. She required intermittent HD for clearance and ultrafiltration. Kidney biopsy was performed due to delayed kidney recovery, and revealed thrombotic microangiopathy with predominant chronic lesions, with patchy moderate interstitial fibrosis 40%. Complement- targeted therapy was started with diagnosis of chronic TMA/ atypical Hemolytic Uremic Syndrome (HUS) vs. renal limited TMA. She received an induction of Eculizumab 900 mg weekly for one month and continued with maintenance thereafter. The patient creatinine improved, and hemodialysis was discontinued. Long-term creatinine was stable at 2.5 mg/dL on third month follow-up visit.

Discussion: Severely progressive AKI with thrombocytopenia can be related to TMA with a component of atypical HUS. Eculizumab is a good option for maintaining immunosuppression when there is a concern of atypical HUS.

SA-PO067

A Unique and Successful Story of Atypical Hemolytic Uremic Syndrome (aHUS)

Beshoy Abdalla, Jia Yi, Nahomie I. Veguilla Rivera, Naveen Punchayil Narayanankutty. University of South Florida, Dept of Nephrology and Hypertension. *University of South Florida, Tampa, FL.*

Introduction: Microangiopathic hemolytic anemia, thrombocytopenia & end organ damage is a clinical scenario that can present in a plethora of similar conditions including TTP, HUS, aHUS & HELLP syndrome. The caveat being that establishing the correct diagnosis & starting treatment early is critical for good outcomes.

Case Description: In this case, a 62-year-old female with a history of HTN & CKD3a with a recent COVID associated hospitalization a few months prior to presentation. The patient presented with progressive fatigue & headaches. She reported an associated unintentional 20 lb weight loss over 2 months & occasional foamy urine. Noted to be hypertensive with elevated Cr 5.4 (baseline of 1.7) & lab evidence of microangiopathic hemolytic anemia. The presence of schistocytes on peripheral smear was inconsistent. The majority of the workup was negative including Coombs, infectious & ADAMTS13 levels. Renal imaging was unremarkable. Patient underwent renal biopsy which revealed 15% globally sclerotic glomeruli w/ acute tubular injury without necrosis, interstitial fibrosis & edema involving 40-50% of cortical parenchyma, focal intimal thickening & hyalinosis. Immunofluorescence was unremarkable. Electron microscopy showed some ischemia with some podocyte foot process effacement. The patient was started alternating days of intermittent hemodialysis & plasmapheresis for 4 doses each without much improvement prior to being transferred for further treatment. Repeat testing showed continued mild hemolysis. After much review of the case & extensive discussions about the risks & possible benefits of using monoclonal C5 inhibitors & the possibility of renal recovery. Treatment of Eculizumab was started in the inpatient setting & discharged to continue treatment in the outpatient setting. On discharge, although the patient had some residual renal function, she was still dependent on hemodialysis. Genetic testing eventually returned with variant of Complement F associated with aHUS.

Discussion: It is improtant to consider the totality of the case, not just limited to age while maintaing a broad differential & evaluate treatment response. In this case, based on the previous findings, presentation after transfer & renal biopsy results, the decision to treat for aHUS was made. Eventually, the patient was taken off dialysis & has continued treatment with Ravulizumab.

SA-PO068

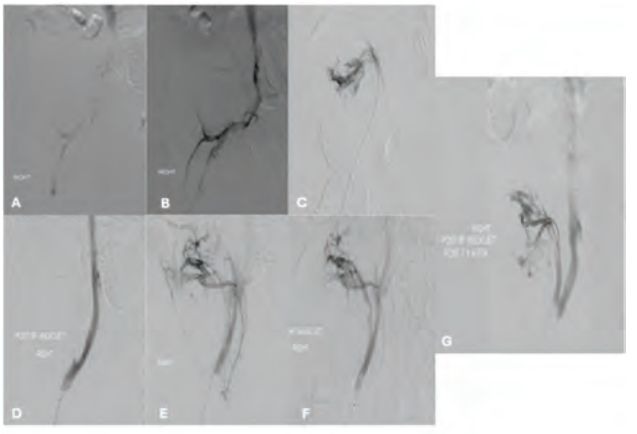
Thrombosis Turnaround: Successful Endovascular Rescue in Common Iliac Vein Thrombosis of Kidney Allograft

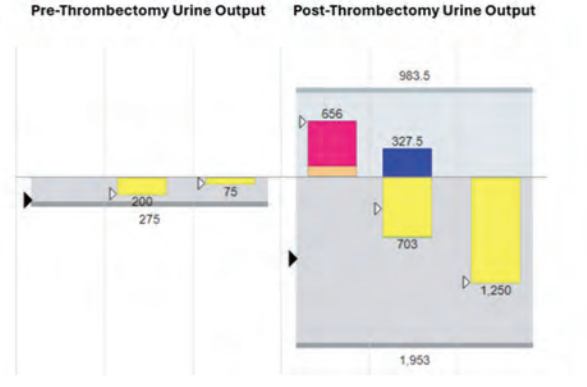
Sabita Budhathoki, Deena Chihade, Kriti Devkota, Michael Lioudis, Ankur Chawla. *SUNY Upstate Medical University, Syracuse, NY.*

Introduction: This is a case of kidney transplant dysfunction due to right common iliac vein (civ) thrombosis that occurred 4 years after kidney transplantation. Late venous thrombotic events in kidney transplant patients are rare compared to early arterial or venous thrombosis or stenosis (1).

Case Description: A 78-year-old male with history of ESKD status post brain death donor kidney transplant on 3/6/2020 came with abdominal pain. He had an acute kidney injury (AKI) with serum creatinine (SCr) 3.66 mg/dL that had increased from his baseline of 0.77 mg/dL. He was hypotensive. Clinical exam was benign. The doppler ultrasound revealed diminished flow within the renal and iliac veins along with heterogenous echogenic material within iliac vein concerning for occlusion. Nephrostomy tube was deferred due to concern of civ thrombosis and started on a heparin drip. Renal angiogram confirmed right civ and external iliac vein thrombosis extended into both the donor renal vein and inferior venacava. He underwent AngioJet Tissue plasminogen activator and right civ thrombectomy. Urine output (UO) improved immediately post op. SCr started decreasing the next day. The patient was discharged 5 days post op.

Discussion: Kidney transplantation is the goal for ESKD patients. Transplanted patients have a better quality of life and improved long term survival. Vascular thrombosis is a rare complication that can result in loss of the allograft. Patients present with AKI and abrupt decrease in UO. There is limited evidence that prophylactic low dose aspirin is beneficial in decreasing the incidence of vascular thrombosis (2). Individuals with high-risk of thrombosis may benefit from anticoagulation (AC) after kidney transplantation (2). Endovascular intervention is the best approach if AC fails (3).





SA-PO069

Regional Citrate Anticoagulation: Going around in Circles!

Sara Jane Chan,[1] Ruzita Ghani,[2] Manish Kaushik.[2] *[1]Ministry of Health Holdings Pte Ltd, Singapore, Singapore; [2]Singapore General Hospital Department of Renal Medicine, Singapore, Singapore*.

Introduction: Regional Citrate Anticoagulation (RCA) is widely used during Continuous Kidney Replacement Therapy (CKRT). Adequacy of RCA and efficacy of RCA-CKRT are monitored by post-filter ionized calcium (iCa) and systemic total calcium (TCa), iCa, metabolic and acid-base parameters, respectively.

Case Description: An elderly lady with end stage kidney disease on peritoneal dialysis and endometrial carcinoma with previous hysterectomy was admitted for septic shock secondary to buccal abscess. She commenced RCA-CKRT as per institutional protocol. Her circuit clotted in 15 minutes due to catheter flow issue. On her second circuit, without catheter port reversal, laboratory tests were significant for extremely low post-filter iCa (<0.10 mmol/L: target 0.25-0.40 mmol/L). Systemic TCa and iCa showed a gradual increase over 12 hours, necessitating a progressive reduction in her systemic intravenous Ca replacement to 25% of initial rate. Also, her metabolic acidosis persisted despite uninterrupted CKRT. Access recirculation was suspected, and confirmed (>85% recirculation) with simultaneous measurements of systemic, access, pre-filter and post-filter: urea, TCa, iCa and bicarbonate. Abdominal CT scan revealed tip of left femoral dialysis catheter in the external iliac vein but no vein thrombus or external catheter compression. A longer catheter was inserted in right femoral vein and RCA-CKRT continued uneventfully. The removed catheter demonstrated luminal blood clots.

Discussion: The observations were explained by access recirculation and consequent high citrate accumulation locally (low post-filter iCa; filter acidosis) but without adequate systemic buffer contribution (systemic acidosis). In patients on RCA-CKRT, unexpected extremely low post-filter iCa or increasing systemic TCa and iCa requiring decreasing intravenous calcium replacement, should raise suspicion of access recirculation. Improper catheter size and tip position increase risk of recirculation, compromising dialysis delivery despite well anticoagulated functioning filter.

All values in mmol/L and IV Ca in mmol/hour	Pre RCA-CKRT	1 hour	3 hour	6 hour	12 hour	18 hour
Systemic						
Urea	6.6	8.0		7.7	7.9	7.8
Total Ca	2.06	2.32		2.49	2.24	2.03
Ionic Ca	1.13	1.20	1.27	1.23	1.03	0.97
Bicarbonate	22.4	20.6		18.8	17.3	18.3
Access Port						
Urea						4.2
Total Ca						1.07
Ionic Ca						0.12
Bicarbonate						13.7
Pre-filter						
Urea						3.7
Total Ca						<1.0
Ionic Ca						<0.10
Bicarbonate						12.3
Post-filter						
Urea						3.3
Total Ca						<1.0
Ionic Ca		<0.10				<0.10
Bicarbonate						12.6
IV Calcium		4.6	3.45	2.3	1.15	1.15

Table: Laboratory parameters and intravenous calcium replacement

SA-PO070

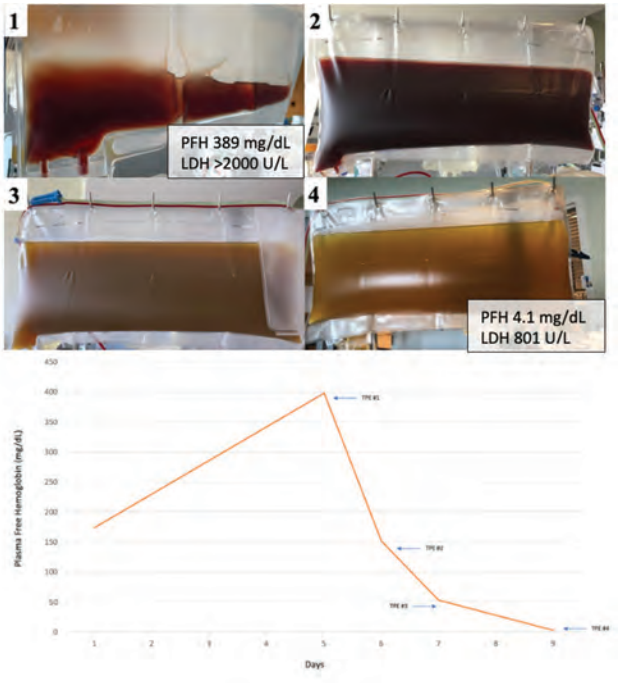
Clearance of Plasma Free Hemoglobin by Therapeutic Plasma Exchange for Mechanical Hemolysis-Related Pigment-Induced AKI

Clarkson Crane,[1] Alexander H. Song,[2] Dinna Cruz.[1] *[1]University of California San Diego, La Jolla, CA; [2]Stanford University School of Medicine, Stanford, CA.*

Introduction: Intravascular hemolysis is a complication of extracorporeal membrane oxygenation (ECMO) and associated with pigment-induced AKI and increased mortality. Elevated plasma-free hemoglobin (PFH) can promote thrombosis in an acquired thrombotic thrombocytopenic purpura (TTP) process by inhibiting von Willebrand factor (VWF) cleavage by ADAMTS13. We report use of therapeutic plasma exchange (TPE) in an attempt to reduce ECMO circuit clotting and promote AKI recovery.

Case Description: A 42-year-old woman admitted for COVID-19 respiratory failure required cannulation to ECMO. She developed thrombocytopenia and microangiopathic hemolytic anemia with LDH >2,500 U/L, elevated total bilirubin, undetectable haptoglobin, and schistocytes, attributed to ECMO-induced hemolysis. PFH was elevated 398.0 mg/dL and it was hypothesized this caused an acquired TTP-like presentation. She subsequently developed anuric AKI attributed to pigment nephropathy. CRRT was initiated and in-line TPE started to remove PFH to stop the cycle of thrombolysis/hemolysis to potentially allow for AKI recovery. Four sessions of TPE were performed with supernatant transitioning from dark red (from PFH) to a lighter color as PFH level decreased to 4.1 mg/dL (Figure 1). LDH decreased and haptoglobin became detectable. Given these, TPE was considered successful. However, before an improvement in urine output could be demonstrated, she developed refractory septic shock and expired.

Discussion: We describe a case where PFH due to ECMO-related hemolysis was successfully removed with TPE, resulting in improved hematologic parameters and the potential for continuation of mechanical circulatory support and recovery of AKI. In similar clinical settings, this therapy has potential to provide clinical benefit and merits ongoing study.



SA-PO071

Hemoperfusion in the Treatment of Doxylamine-Induced Rhabdomyolysis

Vincent Anthony S. Tang, Elizabeth Montemayor. *Division of Adult Nephrology, Department of Medicine, University of the Philippines - Philippine General Hospital, Manila, Philippines*.

Introduction: Rhabdomyolysis is characterized by myocyte necrosis and release of intracellular contents into the circulation. It may manifest as myalgia, acute kidney injury (AKI), electrolyte abnormalities, and arrhythmia. Doxylamine succinate is a 1st generation antihistamine, and an active ingredient in many over-the-counter decongestant products. Doxylamine overdose has been reported to cause severe rhabdomyolysis. Cornerstones of management include prompt recognition, adequate hydration, and close monitoring of electrolytes. Literature on drug intoxication have explored the role of hemoperfusion as an adjunct to facilitate rapid clearance of drugs from the circulation. To date, however, the use of hemoperfusion for doxylamine-induced rhabdomyolysis has not been previously reported.

Case Description: A 23-year old female presented with decreased sensorium, generalized myalgia, and oliguria five hours after consuming 190 tablets of doxylamine succinate. Her past medical, family, and personal-social histories were non-contributory. On admission, her vital signs were normal and the systemic physical exam was unremarkable. She was lethargic, but without any focal neurologic deficits. Initial laboratory tests showed elevated creatine kinase (CK) levels, azotemia, myoglobinuria, hyperkalemia, hyperphosphatemia, and metabolic acidosis. She was managed as a case of severe rhabdomyolysis complicated by AKI secondary to doxylamine intoxication. Despite aggressive volume expansion and supportive therapy, she remained oliguric with intractable hyperkalemia and metabolic acidosis. Hence, she underwent emergency, combined hemoperfusion (HP) and hemodialysis (HD) on the 1st three hospital days. Serial monitoring of urine output, CK, creatinine, and electrolyte levels on succeeding days showed resolution of the rhabdomyolysis. The patient was eventually weaned off HP-HD and discharged improved on the 7th hospital day.

Discussion: Doxylamine overdose is posited to cause rhabdomyolysis through direct myocyte injury. In cases of impaired renal clearance, plasma concentrations of said drug remains elevated for an extended duration, allowing for persistent muscle injury. Due to its lipophilic nature and relatively high molecular weight, systemic clearance of doxylamine in patients with severe AKI can be facilitated by hemoperfusion, leading to faster recovery and shorter length of hospital stay.

SA-PO072

Unraveling a Case of Oxalate Nephropathy: A Complex Presentation

Rafael E. Cardenas, Salil Mangi. *Doctor at Renaissance (DHR), McAllen, TX.*

Introduction: Hyperoxaluria, a rare condition, elevates calcium oxalate levels in the body, leading to deposition in various organs, particularly the kidneys. This can result in progressive renal function decline or kidney failure, known as oxalate nephropathy. Primary hyperoxaluria, a rare inborn error in glyoxylate metabolism, involves excessive oxalate production. Secondary hyperoxaluria is associated with either increased intake of oxalate rich food or increased absorption of oxalate from the gut in patient who have undergone intestinal surgeries, including gastric bypass. We will present a case of AKI associated with oxalate nephropathy in a patient with a history of uric acid stones

Case Description: Patient, a 62-year-old female with longstanding type 2 diabetes mellitus, hypertension, asthma, morbid obesity, and obstructive sleep apnea managed with CPAP at home, has a history of surgical interventions including hysterectomy, cholecystectomy, and gastric bypass surgery in 2015. She experiences intermittent diarrhea managed by gastroenterologists. Previous nephrolithiasis episodes led to extracorporeal shockwave lithotripsy in 2012 and percutaneous nephrolithotomy in 2013 for left staghorn stones. Stone analysis revealed 100% uric acid composition. Multiple other episodes in 2014 were resolved via extracorporeal shockwave lithotripsy and fluoroscopic imaging. She has been followed by a nephrologist for gradual kidney function decline. In 2023, she presented with severe fatigue, weakness, and mild respiratory distress, found to have acute kidney injury (AKI) superimposed on chronic kidney disease. Initial labs showed elevated BUN, creatinine, and proteinuria. Kidney biopsy revealed oxalate nephropathy and diabetic glomerulopathy with interstitial fibrosis. Serum oxalate was markedly elevated at 52. She required hemodialysis and blood transfusions followed by placement of a Permcath for outpatient hemodialysis. The patient was discharged stable to continue care as an outpatient

Discussion: This case sheds light on the persistent challenges of diagnosing and managing oxalate nephropathy in a rapidly progressive kidney failure in a patient with a complex medical history. It important to keep this entity in mind, especially in patients who are likely to develop secondary hyperoxaluria even though they may have had a different category of kidney stones in the past prior to their gastric bypass surgery

SA-PO073

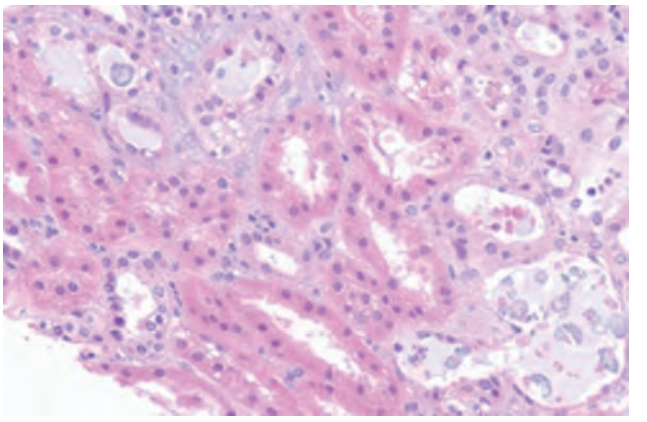
From Marathon to Miracles: Managing Dialysis-Dependent Oxalate Nephropathy with Ethylenediamine Tetra Acetic Acid (EDTA)

Paavana Varanasi, Srekar N. Ravi, Leslie F. Thomas. *Mayo Clinic Arizona, Scottsdale, AZ.*

Introduction: Oxalate nephropathy is a rare cause of kidney injury due to oxalate crystal deposition within tubules, causing direct tubular injury and obstruction. Excessive vitamin C intake can cause secondary hyperoxaluria and acute kidney injury (AKI). Early diagnosis and management are crucial to prevent ESRD, but there is no known cure. We present a case of stage 3 AKI due to biopsy-proven oxalate nephropathy requiring dialysis that was successfully treated.

Case Description: A 31-year-old female without known medical problems presented with intractable nausea, vomiting, back pain, and minimal urine output after running a marathon. One week prior, she took 400-600 mg of ibuprofen daily for migraine headaches and oral vitamin C supplements. Immediately following the race, she received a total of 3.5 L of IV fluids and one IV vitamin C infusion at mobile hydration units. Labs showed Cr 8.42 mg/dL, BUN 64 mg/dL, and CK 2400 U/L. Urinalysis had pyuria without hemoglobinuria. On hospital presentation, she was oliguric (200-300cc/day) and renal function continued to worsen despite aggressive IV fluid resuscitation. Dialysis was started on hospital day 3 and a kidney biopsy revealed acute tubular injury with abundant calcium oxalate deposits consistent with oxalate nephropathy. Given limited interstitial fibrosis and tubular atrophy (10-15%), she was trialed on IV EDTA 250 mg infusion for 3 consecutive days. She had increased urine output with each subsequent dose and return of kidney function with discontinuation of dialysis.

Discussion: This case demonstrates a novel treatment for oxalate nephropathy with IV EDTA infusion. The patient's recovery from dialysis-dependence is rare. 24-hour urine studies before and after EDTA showed increased oxalate, presumably from renal excretion of soluble oxalate after calcium chelation with EDTA in the tubules. This underscores the consideration of oxalate nephropathy in AKI patients with high vitamin C intake and suggests a potential therapy for further study.



SA-PO074

Paradoxical Role of Myeloid Cell PD-L1 Expression in AKI

Oliver B. Pelletier, Franklin J. Herbert, Vikram Sabapathy, Bushra Mehkri, Rahul Sharma. *University of Virginia School of Medicine, Charlottesville, VA.*

Background: Blocking of immune checkpoint molecules Programmed Death-1 (PD-1) and its ligands PD-L1 and PD-L2 have revolutionized cancer therapy via activation of anti-tumor immunity. However, this checkpoint inhibitor therapy also led to increase in immune check-point inhibitor (ICPI)-associated inflammatory diseases including acute kidney injury (AKI) suggesting a protective role of PD-1 and its ligands in AKI. While PD-1 is mainly expressed on T-cells, PD-L1 and PD-L2 are expressed on tumor, stromal, and immune cells including myeloid cells. Treatment of mice with antibodies to PD-1, PD-L1 and PD-L2 worsens ischemia reperfusion injury (IRI). Expression of PD-1 on the T-regulatory cells (Tregs) is important for protection from IRI (ASN Kidney week 2020, PO-0152). However, the role of PD-L1 expression on myeloid cells, as related to AKI remains a knowledge gap.

Methods: To investigate the role of PD-L1 expression on myeloid cells, we generated mice with deletion of PD-L1 in myeloid cells using lysozyme-driven Cre (*LysM-Cre*) to generate *PD-L1$^{fl/fl}$.LysM-Cre* mice. Mice were subjected to unilateral IRI and euthanized on day 14 after nephrectomy of contralateral kidney on day 13 or subjected to Cisplatin-induced renal injury. Blood, spleen and kidneys were analyzed for immunophenotype, and kidneys were analyzed for inflammation and injury by flow cytometry, histopathology and quantitative PCR.

Results: Deletion of PD-L1 in myeloid cells resulted in an overall inflammatory phenotype in mice as represented by lymphadenopathy and splenomegaly with greater accumulation of activated and memory T-cells that produced more proinflammatory cytokines. However, despite the inflammatory conditions, *PD-L1$^{fl/fl}$.LysM-Cre* mice displayed lower levels of injury and kidney dysfunction as compared to PD-L1 sufficient mice with IRI or cisplatin. While the infiltration of neutrophils in the PD-L1 deficient mice was lower, the infiltration of monocytes was significantly higher. Interestingly, the dendritic cells in the spleen and kidneys of PD-L1 deficient mice expressed lower levels of co-stimulatory molecules suggesting of lower activation status.

Conclusions: The data reveals a paradoxical role of PD-L1 expression in myeloid cells in promoting ischemic and cisplatin AKI, such that myeloid-cell specific deletion of PD-L1 was protective in AKI via promoting a tolerogenic milieu.

Funding: NIDDK Support, Private Foundation Support

SA-PO075

Myeloid Cells Alleviate Kidney Fibrosis after Folic Acid-Induced AKI via Vascular Endothelial Growth Factor (VEGF)-A Signaling

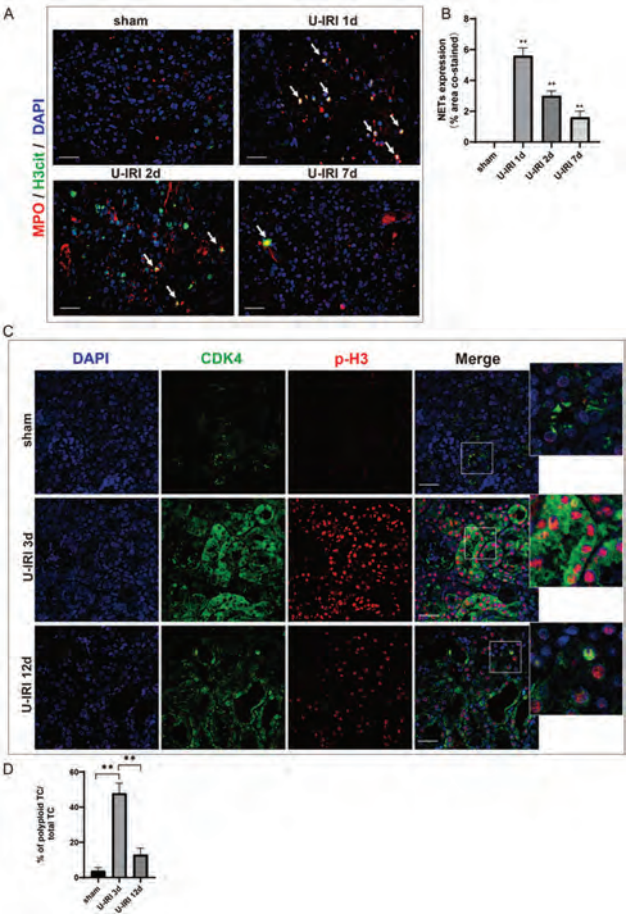
Kazutoshi Ono,[1] Takayuki Isagawa,[1] Daisuke Nagata,[1] Norihiko Takeda.[1,2]
[1]*Jichi Ika Daigaku, Shimotsuke, Japan;* [2]*Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Bunkyo-ku, Japan.*

Background: Tubular epithelial cells (TEC) consume oxygen and nutrients to maintain its physiological function. Peritubular capillaries (PTC) maintain oxygen environment in kidney tissues, and its density is correlated with renal function and its prognosis. In healthy kidney, TEC act as a predominant source of vascular endothelial growth factor-A (VEGF-A) a major angiogenic cytokine which is required for the maintenance of PTC. However, how do angiogenesis and subsequent tissue repair take place in acute kidney injury (AKI) or its transition to chronic kidney disease (CKD) are largely unknown.

Methods: The mouse folic acid acute kidney injury (FA-AKI) model was used as an AKI model. We first performed histological and gene expression analysis of the kidneys of the wild-type mice over time after FA-AKI. Next, we performed single-cell RNA-sequencing (scRNA-seq) on kidneys of the wild-type mice 7 days after FA-AKI to detect VEGF-A-producing cells where TEC decreased.

Results: Histological analysis showed that proximal TEC and PTC gradually decreased until day 14 after FA-AKI. The mRNA expression levels of kidney *Vegfa* and *Megalin* (proximal TEC specific gene) were significantly lower on day 2 compared to baseline. *Megalin* was still lower on days 7 and 14, whereas *Vegfa* increased on days 7 and 14. ScRNA-seq revealed that the major source of *Vegfa* was macrophages (MΦ) among the leukocytes accumulated in the kidney 7 days after FA-AKI. In addition, fluorescence-activated cell sorting showed that F4/80^{lo} MΦ and F4/80^{hi} MΦ subpopulations accumulated biphasically in the kidney after FA-AKI, and F4/80^{lo} MΦ expressed higher levels of *Vegfa* than F4/80^{hi} MΦ. Finally, we generated myeloid cell-specific VEGF-A conditional knockout mice (mVEGFA CKO: *LysM*-Cre *Vegfa*$^{flox/flox}$) and controls (Control: *Vegfa*$^{flox/flox}$). PTC formation and TEC regeneration were significantly suppressed and tissue fibrosis was more pronounced in mVEGF-CKO compared to Control 14 days after FA-AKI.

Conclusions: Our data suggest that kidney macrophages substitute VEGF-A production in AKI where TEC derived VEGF-A secretion is impaired. Kidney macrophages have a potential as a therapeutic target in the management of AKI. Further study regarding how macrophages accumulate and produce VEGF-A in kidney tissues will help us to understand the pathological process of AKI to CKD transition.



Expression of NETs and polyploid tubular cells in IRI model

SA-PO076

Neutrophil Extracellular Traps Promote Polyploidization of Tubular Epithelial Cells after Kidney Injury

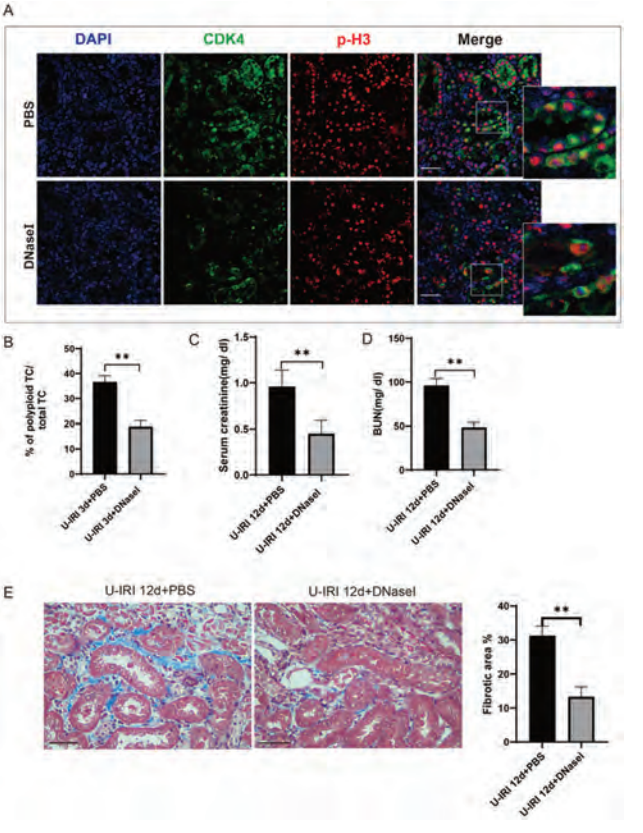
Wenchao Li, Li Hao, Yangang Gan, Jiajia Li, Hao Yu, Qianqian Han, Weicong Zeng, Qiongqiong Yang. *Sun Yat-Sen Memorial Hospital, Guangzhou, China.*

Background: Renal tubular epithelial cells undergo polyploidization after acute kidney injury (AKI), which promotes tubular cell senescence and renal fibrosis, the underlying mechanism remains unclear. Neutrophil extracellular traps (NETs) play a crucial role in tubular injury after AKI, but whether NETs promote tubular cell polyploidization is uncear.

Methods: The expression of NETs and polyploid tubules were analysed in renal ischemia-reperfusion (IRI) model. DNase I was emplayed as inhibitor of NETs, and the effects of tubular cell polyploidization and renal fibrosis was detected.

Results: The expression of NETS and polyploid tubular cells were upregulated after AKI. Clearing NETs decreased the amount of polyploid tubules and ameliorated renal fibrosis.

Conclusions: NETs regulate the transition from AKI to CKD by promoting polyploidization of renal tubular cells.



Removal of NETs decreased polyploid tubular cell formation in IRI model

SA-PO077

AKI Induces Neutrophil Swarms in Lung Alveolar Capillaries That Cause Perfusion Deficits and Hypoxemia

Yohei Komaru,[1] Rupal Ojha,[1] Liang Ning,[1] Anusha Suresh,[1] Carine Lama,[1] Eirini Kefalogianni,[1] Mark J. Miller,[1] Andreas Herrlich.[1,2] *[1]Washington University in St Louis School of Medicine, St Louis, MO; [2]Veterans Administration Health Care System, St. Louis, MO.*

Background: Acute kidney injury (AKI) complicated by respiratory failure is common among critically ill patients and associated with high mortality. We recently showed that circulating osteopontin released from the injured kidney causes remote lung inflammation with hypoxemia (Sci Adv 2022). However, mechanisms that rapidly establish remote lung inflammation after AKI and the underlying cause of hypoxemia remain incompletely understood.

Methods: Single-cell RNA-seq analysis with cell-cell communication analysis was employed to investigate remote lung inflammation 24 hours after bilateral renal ischemia-reperfusion injury (IRI). Intravital imaging of the lung conducted by two-photon microscopy, was performed 1.5-2 hours after IRI, with capillary flow assessment by iv injection of 1-μm beads. Intracellular F-actin in circulating neutrophils was visualized using phalloidin staining. Fibrinogen and CD41 were used as markers for thrombosis in immunofluorescent staining.

Results: AKI induces rapid intravascular "neutrophil train" formation in lung capillaries, a novel form of neutrophil swarming. Neutrophils are rapidly captured in lung capillaries due to AKI-induced actin cytoskeleton rearrangement leading to reduced deformability that impedes neutrophil lung capillary passage. Unlike in direct lung injury where neutrophils extravasate driven by the concerted action of non-classical monocytes and alveolar macrophages, in remote lung inflammation after AKI neutrophils do not extravasate and are retained and assembled into lung capillary neutrophil trains by CXCL2 released by lung classical monocytes; this occurs independent of non-classical monocytes or alveolar macrophages. Lung capillary neutrophil trains significantly impede perfusion and cause thrombosis in a significant part of the lung capillary network.

Conclusions: We thus discovered a novel feature of kidney-lung crosstalk after AKI, capillary perfusion deficits that lead to reduced oxygenation despite proper alveolar function and ventilation, unlike in infectious inflammatory lung processes, such as bacterial pneumonia, where alveolar ventilation is typically compromised by inflammatory exudates. Our findings highlight potential therapeutic targets in post-AKI remote organ inflammation, which cannot be addressed by existing therapies including dialysis.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO078

Single-Cell RNA Sequencing and Spatial Transcriptomics Reveal Unique Subpopulations of Infiltrating Macrophages and Dendritic Cells following AKI

Arin Melkonian, Matthew D. Cheung, Elise Erman, Yanlin Jiang, Anupam Agarwal, James F. George. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Kidney infiltrating macrophages (KIMs) and kidney dendritic cells (KDCs) have been strongly associated with inflammation and fibrosis in acute kidney injury (AKI). Contrary to kidney resident macrophages (KRMs), which are self-renewing and present in the kidney prior to injury, KIMs are bone-marrow derived F4/80^{int}, CD11b^{high} macrophages. Here, we combined single-cell RNA sequencing (scRNAseq) and spatial transcriptomics to elucidate temporal, spatial, and transcriptional characteristics of unique subpopulations of KIMs and KDCs in AKI.

Methods: CD11b^{high} KIMs and KDCs from C57BL/6J mice were sorted using fluorescence activated cell sorting (FACS). We collected macrophages before injury and at days 1, 6, and 28 following 19 minutes of bilateral ischemia reperfusion injury (BIRI). Cells were subjected to scRNAseq using the 10X Genomics Chromium platform. Gene ontology was conducted to elucidate the functional roles of differentially expressed genes. Spatial transcriptomics were evaluated using the 10X Visium Spatial Gene platform. Data from all timepoints were integrated and analyzed using Seurat 5.0.

Results: scRNAseq results revealed 3 unique KIM and 2 KDC subpopulations. All 5 clusters were localized in unique microenvironments in untreated mice, and their locations were dynamically regulated following BIRI. We have shown that a specific KIM cluster, identified by its Arginase 1 expression, infiltrates the kidney medulla at day 1 and migrates to the cortex at day 6 post-injury. We have also identified a macrophage precursor cell population that expresses genes specific to cell proliferation and regeneration (e.g., *Stmn1* and *Top2a*) that are predicted to reside in the medulla in uninjured states. Gene ontology analysis revealed distinctive functional characteristics that set apart each KIM and KDC population.

Conclusions: We have identified distinct subpopulations of KIMs and KDCs within the kidney, each of which infiltrates at different times (i.e., 1 and 6 days) and occupies specific microenvironments after AKI. Because KIMs and KDCs are involved in inflammation and AKI, it is paramount we understand their dynamics—temporally and spatially—to develop macrophage-specific therapeutics aimed towards targeting kidney disease and promoting tissue repair.

Funding: NIDDK Support

SA-PO079

Macrophage Infusion Rescues Cisplatin (CP)-Induced AKI

Xiaojia Guo,[1] Leyuan Xu,[1] Heino Velazquez,[1,2] Tian-Min Chen,[1] Robert L. Safirstein,[1,2] Gary V. Desir.[1,2] *[1]Yale University School of Medicine, New Haven, CT; [2]VA CT Healthcare System, West Haven, CT.*

Background: CP induces AKI, and repeated doses leads to chronic kidney disease (CKD) in humans. Previously, we produced a mouse model using two doses of CP two weeks apart that recapitulates the features of CP-AKI and CP-CKD in humans. Here, we employ 13 different KO mouse models to identify genes that play a critical role in kidney injury.

Methods: Single-cell RNA sequencing (scRNAseq) was performed on kidneys of wild-type (WT) mice 0, 1, 3, and 5 days (D) after 15 mg/Kg CP to identify the transcriptional response changes in major cell types during the induction of injury. These findings were confirmed by immunohistochemistry and quantitative reverse transcription polymerase chain reaction (RTqPCR). The course of AKI and CKD was then followed in KO mice. Bone marrow-derived macrophages (BMDM) were isolated from either WT or KO mice and injected into KO mice treated with cisplatin to identify protective genes.

Results: Plasma creatinine at D0, D1, D3, and D5 was 0.07±0.01, 0.08±0.09, 0.42±0.05, and 0.16±0.09 mg/dL, respectively, n=3, ($p<0.005$ for D3 by one way ANOVA). The % of injured proximal tubule cells (PT) of D0, D1, D3, and D5 were 0.15, 0.44, 4.36, and 2.93 respectively; Neutrophils increased from 0.04% at D0 to 0.89% at D3 and reduced to 0.31% at D5. Macrophage and T cell plateaued at D3. ScRNAseq and whole kidney RTqPCR showed CP increased Cxcl1, p21, Tlr2, Sox9 in injured PT; Apobec1, Tlr4, Tlr2, RIPK3, Ccl2, Ccr2, Cxcl1, p21 in macrophages; and Ppif, Lcn2 in neutrophils and reduced RNLS in whole kidney. Of 13 KOs of these 12 genes plus double KO of Tlr2 and Tlr4, only Apobec1 and RNLS showed profound effects on the course of AKI/CKD as none of the Apobec1 KOs survived the initial dose of CP, and Rnls KOs developed more severe CKD. As Apobec1 and Rnls were expressed by macrophages, we injected undifferentiated WT BMDM in each KO mouse. WT macrophage infusion reduced kidney injury in Apobec1 KO (BUN 53.81±3.52 vs 72.74±1.4 mg/dL, n=4, $p<0.01$) and Rnls KO mice (49.16±4.39 vs 68.57±2.89 mg/dL, n=4, $p<0.01$) as compared to mice infused with KO BMDM and reduced the expression of KIM-1 and Ccl2 in the kidneys of these mice.

Conclusions: Our results indicate that Apobec1 and RNLS are key cargo components within the macrophages and are crucial to the outcome of the injury and suggest that macrophages can be a potent delivery system of these molecules.

Funding: NIDDK Support

SA-PO080

Kidney Macrophage IL-1 Receptor Limits Endoplasmic Reticulum Stress and Nephrotoxic Serum Nephritis

Yanting Chen,[1] Yu Li,[1] Jiafa Ren,[2] Chia-Chun Wu,[3,1] Xiaohan Lu,[1] Steven D. Crowley,[1,4] Jamie R. Privratsky.[1] *[1]Duke University, Durham, NC; [2]Nanjing First Hospital, Nanjing, China; [3]Chi Mei Medical Center, Tainan, Taiwan; [4]Durham VA Health Care System, Durham, NC.*

Background: Acute kidney injury (AKI) often leads to chronic kidney disease. Macrophages play divergent roles in kidney injury and repair. Previously, we demonstrated a protective role of IL-1R1 in CD11c-expressing kidney myeloid cells in early AKI. This study aims to determine the role of IL-1R1 in myeloid cells in chronic kidney injury. We hypothesized that myeloid cell IL-1R1 signaling would limit chronic inflammation after AKI.

Methods: Mice with CD11b-expressing myeloid cells-specific deletion of IL-1R1 (*LysMCre*(+) / *Il1r1fl/fl* - MKO) and littermate wildtype controls (*LysMCre*(-) / *Il1r1fl/fl* - MWT) were subjected to nephrotoxic serum nephritis (NTS) and chronic ischemia/reperfusion (I/R) models. Kidney and glomerular injury were assessed by albuminuria, histologic injury scoring, and kidney injury biomarkers kidney injury molecular (KIM)-1 and neutrophil gelatinase-associated lipocalin (NGAL). Fluorescent cell-sorting and single cell RNA sequencing were used to profile gene expression and identify cell-specific ligand-receptor interactions. Renal HK-2 cells were co-cultured with bone marrow-derived macrophages (BMDM) from MKO and MWT mice.

Results: Compared to MWT mice, MKO mice demonstrated worsened nephritis as indicated by increased albuminuria (mean ± SD: MWT 24,638 ± 4,262 vs MKO 30,826 ± 3,237 μg/mg urinary creatinine, $p=0.02$), elevated KIM-1 mRNA and exacerbated histologic injury scoring. MKO mice also displayed evidence of increased tubular injury following chronic I/R. We found increased endoplasmic reticulum stress

(ER stress)-mediated apoptosis and pro-inflammatory polarization in macrophages from NTS injured MKO kidneys, which was associated with elevated renal expression of type I interferons (IFNs). Nichenet analysis revealed that high mobility group protein B1 (HMGB1) is a prioritized ligand from macrophages that could induce type I IFNs in damaged tubular cells. In co-culture studies, we confirmed the increased ER stress and pro-inflammatory cytokines in MKO macrophages, which led to heightened cellular injury and elevated type I IFNs in HK-2 tubular cells. In turn, anti-IFNR1 therapy ameliorated these detrimental effects in vivo.

Conclusions: IL-1R1 signaling on macrophages constrains ER stress-mediated pro-inflammatory polarization and ameliorates type I IFNs-induced tubular injury and NTS injury.

Funding: NIDDK Support, Other NIH Support - NIGMS

SA-PO081

Major Vault Protein Promotes Kidney Inflammation and Macrophage Recruitment in a Murine Model of AKI

Cheuk Yin Wong, Susan Yung, Tak Mao D. Chan. *The University of Hong Kong Li Ka Shing Faculty of Medicine, Hong Kong, Hong Kong.*

Background: Acute kidney injury (AKI) is characterized by deterioration of kidney function and increased risk of developing chronic kidney disease (CKD). AKI-to-CKD transition following acute injury results from maladaptive repair leading to renal tubular loss, chronic inflammation and kidney fibrosis. We previously demonstrated that major vault protein (MVP) contributed to kidney inflammation and fibrosis in murine models of CKD. This study investigated the role of MVP in AKI and AKI-to-CKD transition.

Methods: MVP expression was assessed using immunocytochemical staining in kidney biopsies from patients with active proliferative lupus nephritis, acute tubular injury, pauci-immune ANCA-associated renal vasculitis or kidney allograft dysfunction. AKI was induced in wild-type (WT) and MVP-knockout (KO) mice by a single dose of folic acid (250 mg/ kg) in 0.3 M sodium bicarbonate administered by intra-peritoneal injection. Mice were sacrificed after 7 days and kidneys harvested for investigation of histopathology and expression of mediators relating to tubular injury and inflammation. Mice administered 0.3 M sodium bicarbonate served as non-AKI Control.

Results: MVP was weakly expressed in normal human kidney specimens, but its expression was markedly increased in proximal renal tubular epithelial cells in kidney biopsies of patients with AKI. In WT AKI mice, MVP gene expression was increased by 5.85±1.22-fold compared to WT non-AKI Control mice ($p<0.0001$), and was accompanied by increased serum urea level, tubular atrophy, macrophage recruitment and increased expression of mediators of tubular injury and inflammation including KIM-1, NGAL, TNF-α, IL-1β, CCL2 and CCL5 *($p<0.01$, for all)*. MVP KO mice subjected to induction of AKI showed less severe kidney histopathological features with reduced macrophage infiltration and serum urea level and decreased expression of mediators of tubular injury and inflammation ($p<0.05$, for all).

Conclusions: Our data suggest that MVP contributes to tubulo-interstitial inflammation and tubular injury in murine folic acid-induced AKI, which may modulate AKI-to-CKD transition.

Funding: Government Support - Non-U.S.

SA-PO082

TREM2 Macrophages Ameliorate the Transition of AKI-CKD via a PI3K/AKT Signaling Pathway

Yiming Zhou,[1] Yating Zhang,[1] Siweier Luo,[1] Yufei Du,[1] Le Wang,[1] Hanzhi Liang.[2] *[1]Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; [2]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China.*

Background: Macrophages have been shown to contribute to renal injury and fibrosis as well as repair. Their multiple phenotypes may explain the diverse functions of macrophages in acute kidney injury (AKI) and subsequent chronic kidney disease (CKD). TREM2 macrophages have recently been shown to play an important role in regulating tissue inflammation and repair. But their role in the AKI-CKD transition remains unclear.

Methods: A unilateral ischemia-reperfusion injury (UIRI) mouse model was used to generate the transition of AKI-CKD. After operation, sham and UIRI mice were sacrificed on day 14. Serum urine, and kidney samples of each mouse were collected. Serum creatinine and urea nitrogen levels were determined by ELISA. Urinal albumin levels were determined by a CBB gel staining method. qPCR and WB were used to determine the expression levels of genes and proteins in kidney samples. H&E, PAS, Masson and Sirus Red staining were used to evaluate the renal histology. Bone marrow-derived macrophages from WT and TREM2 knockout mice were harvested and treated with the hypoxia and reoxygenation (HR) condition. Stable TREM2 overexpression macrophages were used to investigate the renal protective effect in UIRI mice.

Results: In this study, we found that TREM2 macrophages play a strong protective role in the transition from AKI to CKD. The population of TREM2 macrophages was significantly increased in the UIRI-induced AKI-CKD transition mice. Knockout of Trem2 resulted in increased renal inflammation, exacerbated renal injury and fibrosis. In addition, we found that TREM2 expression enhanced macrophage phagocytosis but reduced the expression of pro-inflammatory cytokines, resulting in lower levels of tubular cell apoptosis and fibrosis. RNA-seq analysis revealed that these effects of TREM2 were controlled by PI3K/AKT pathway. Notably, the kidney injury and fibrosis in the UIRI mice was effectively attenuated by cell therapy with TREM2-overexpressing macrophages.

Conclusions: Our study demonstrates that TREM2 macrophages play a protective role in the transition of AKI-CKD and targeting TREM2 may be a therapeutic strategy for this disease.

SA-PO083

Myofibroblast-Macrophage Cross-Talk Supports Proliferative Tubule Repair after Kidney Injury

Bhavya Bharathan, Leyuan Xu, Jiankan Guo, Lloyd G. Cantley. *Yale University School of Medicine, New Haven, CT.*

Background: After ischemia-reperfusion injury (IRI), macrophages expressing arginase 1 (Arg1) exclusively localize to the outer medulla adjacent to injured and dying S3 proximal tubule cells. Genetic deletion of macrophage Arg1 leads to less tubular proliferation and decreased mouse survival after IRI. Arg1 is known to be required for protein translation, and we speculate that upregulation of Arg1 leads to macrophage secretion of unidentified factor(s) that are required for downstream tubular cell proliferation.

Methods: Unilateral IRI with contralateral nephrectomy (IRI/CL-NX) was used to induce ischemic kidney injury in mice. Cultured macrophages were induced to express Arg1 by co-culture with renal tubular cells + GM-CSF. We performed bulk RNA sequencing and quantitative PCR (qPCR) of primary cultured renal cells and single cell RNA sequencing of mouse kidneys 3 days after IRI or sham to identify relevant growth factors and cell types after IRI. PDGFRβ± cells were isolated from injured and control kidneys using Magnetic-Activated Cell Sorting, and RNA was isolated to analyze relevant growth factors by qPCR.

Results: scRNAseq from day 3 injured kidneys demonstrated that Insulin-like Growth Factor-1 (Igf1) is upregulated in myofibroblasts (PDGFRβ+ cells), and Igf1 Receptor (Igf1R) is upregulated on proximal tubule cells. Conditioned medium from Arg1 expressing macrophages induced an 8.95-fold increase in expression of Igf1 in cultured PCRC (containing a mix of ~94% tubular cells and ~5% PDGFRβ+ myofibroblasts). Isolation of PDGFRβ+ cells from the kidney on day 2 after IRI revealed a 14.83±0.14-fold increase in Igf1 in these myofibroblast-enriched cells as compared to PDGFRβ- cells ($p<0.0001$), with a 7.51±0.14 fold increase compared to PDGFRβ+ cells from uninjured kidneys ($p<0.0002$)

Conclusions: Arg1-expressing macrophages secrete a yet unidentified factor(s) that can induce Igf1 expression by primary cultured renal cells, likely myofibroblasts, with concomitant upregulation of Igf1R on tubular cells. We hypothesize that this macrophage-myofibroblast crosstalk underlies Igf1-induced proliferative tubule repair by surviving proximal tubule cells.

Funding: NIDDK Support

SA-PO084

Immunomodulation and T Cell Infiltration in AKI Caused by Ischemia-Reperfusion (IR): Role of Sex Difference and Angiotensin II Type 2 Receptor (AT2R)

Tahmid Faisal,[1] Riyasat Ali,[1,2] Tahir Hussain.[1] *[1]University of Houston, Houston, TX; [2]The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: A greater renoprotection against injury in females compared to males has been suggested. However, the mechanism and factors responsible for this difference are unknown. Recently, we have reported that angiotensin AT2R activation (by its agonist compound C21) attenuates immune cells infiltration in the kidney and increases protective/reparatory regulatory T cells ($CD4^+$-$FoxP3^+$ Treg) accumulation in the IR kidney in male rats. Present study is designed to evaluate sex difference in immune cell infiltration and T cells profiles in the IR kidney and the signaling mechanism by which AT2R promotes Treg modulation.

Methods: Male, female (ovary intact, Ovi) and ovariectomized (Ovx) SD rats were divided into 3 groups- sham, IR, and IR+C21 (daily 0.3 mg/kg, i.p). After 30 mins ischemia and 3 days of reperfusion, kidneys were incised and digested to make kidney cell suspension for flow cytometry of immune cells. To understand the signaling pathway(s) associated with AT2R mediated modulation of CD4 T cells into Treg cells, primary splenic CD4 T cells were cultured, induced Treg formation with pharmacological agents.

Results: Flow cytometry revealed that CD45 cells accumulation was increased in the IR kidney, being 2-fold higher in males than Ovi. The AT2R agonist C21 treatment reduced CD45 in both males and females equally. Preliminary studies show Ovx did not affect CD45 compared with Ovi but attenuated the response of the AT2R activation on CD45 cell reduction. Like CD45, basal CD3 and CD4 were higher in males than in Ovi, but these cells were similar in the IR groups and reduced by C21 treatment. Treg cells were higher in male than Ovi in IR and C21. There is an increasing pattern of AT2+Tregs cells in IR rats of all groups with 50% cells with AT2R expression. Normal blood CD3, CD4, CD4+AT2+T and Tregs cells did not show sex difference. Kidney injury markers

showed less injury in IR Ovi females than males. Ex vivo studies show AT2R activation by C21 in splenic T cells modulation to Tregs is inhibited totally by the PP2A inhibitor okadaic acid and only partially by NO synthase inhibitor L-NAME.

Conclusions: Under AKI, there are fewer immune cells, including T cells accumulation in females compared to males and AT2R function is reduced by Ovx in females, suggesting a sex difference. AT2R modulates Tregs via PP2A pathway.

Funding: Other NIH Support - NIH RO1DK117495 NIH R01DKO61578

SA-PO085

Interferon Regulatory Factor 4 (IRF4)-Dependent Type 2 Conventional Dendritic Cells (cDC2s) Promote Kidney Inflammation and Injury in Ischemia-Reperfusion Injury (IRI)-Induced AKI/AKD

Hao Long,[1,2] Kristina O. Borisova,[1] Hans J. Anders,[1] Julia Lichtnekert.[1]
[1]Division of Nephrology, Department of Medicine IV, University Hospital, Ludwig-Maximilians-University, Munich, Germany; [2]Department of Urology, The Affiliated Hospital of Southwest Medical University, Luzhou, China; Sichuan Clinical Research Center for Nephropathy, Luzhou, China.

Background: Ischemia-reperfusion injury(IRI) is a frequent cause of AKI/AKD. cDCs play pivotal immunoregulatory roles in kidney injury and repair. Previous research had indicated that cDC1s and cDC2s may have opposing roles. We demonstrated a protective function of cDC1s in the IRI-induced AKI/AKD model. In our study, we investigated the functions of cDC2s in AKI/AKD.

Methods: *In vivo*, we did unilateral IRI on IRF4$^{fl/fl}$Clec9a^{cre} and WT mice.IRF4 deletion on DC lineage led to a diminished proportion of the cDC2s. We analyzed kidney function, kidney immune cells, i.e., DC subsets, neutrophil infiltration, T cell differentiation, inflammatory responses. We differentiated *in vitro* bone-marrow-derived DCs from IRF8$^{fl/fl}$Clec9a^{cre} and WT mice using an in-house produced FLT3L supernatant and a recombinant GM-CSF. We compared the phenotype of the generated cells based on the surface markers and essential genes. With different TLR stimulants, we analyzed cytokine secretion, DC activation, migration, and phagocytosis (IHC, IF, ELISA, flow cytometry, transwell migration assay, qPCR).

Results: IRF4 ko mice had a lower proportion of cDC2s in kidney than WT mice. After uIRI, IRF4 ko mice showed reduced renal tubular cell injury, improvement of kidney function and recovery than WT mice. This was associated with increased expression of anti-inflammatory, decreased pro-inflammatory cytokines and acute tubular cell death, reduced recruitment of neutrophils, and differentiation of Th2 and Th17 cells. *In vitro*, WT DCs exhibited a cDC1 phenotype, but IRF8 ko cells resulted in the evolution to cDC2. With LPS and CpG stimulations, these cDC2-like cells displayed elevated activation, phagocytic and migration capabilities. Additionally, they exhibited a higher proinflammatory roles, with increased levels of CXCL2 than WT cells.

Conclusions: Our data demonstrated that IRF4 was essential for the differentiation of kidney cDC2s. The reduction of cDC2s ameliorated kidney inflammation, reduced kidney injury, and promoted kidney recovery. In-vitro IRF4^{high} cDC2-like cells could be generated by IRF8 deletion in DC lineage cells, which led to a shift in cell fate and an increased proinflammatory phenotype. Together, cDC2s had an immunoregulatory role in AKI/AKD and could serve as a potential therapeutic target for improving kidney injury and inflammation.

SA-PO086

Spatial Transcriptomics Enables Generation of a Complement Atlas of Mouse AKI

Vikram Sabapathy,[1] Daniel Chauss,[2] Shuqiu Zheng,[1] Resmi Raju,[3] Jeremie O. Piña,[3] Rahul Sharma,[1] Tilo Freiwald,[4] Behdad Afzali,[2] Didier Portilla.[1]
[1]University of Virginia, Charlottesville, VA; [2]NIH/NIDDK, Bethesda, MD; [3]NICHD/NIH, Bethesda, MD; [4]University Med Ctr, Hamburg, Germany.

Background: Kidney tubulointerstitial fibrosis plays an essential role in progressive kidney disease. Our previous studies suggest that increased expression of intracellular complement (C') components contribute to the pathogenesis of kidney fibrosis. The identity of the C' components that participate in this process and cellular mechanisms involved in their activation remain under-explored. We hypothesized that increased local expression of C' and its receptors directly in kidney tissue is compartmentalized and that local interactions involving this system impact fibrosis.

Methods: We used Spatial Transcriptomics (ST) by 10X Xenium, and formalin-fixed paraffin embedded (FFPE) kidney tissue from mice subjected to IRI and UUO to map all C' components and their receptors (n=100 genes) in tandem with a multi-tissue atlasing panel (n=380 genes). Computational analyses included Seurat, integration by Harmony and clustering by UMAP.

Results: We generated a high-resolution map of C' components and their receptors in control kidneys (Ctrl), UUO and IRI. Key C' components were clearly differentially induced in AKI models compared to Ctrls. These included *C3*, factor B (*CFB*), factor H (*CFH*) and properdin (*CFP*). *C3* and *CFB* were localized to failed to repair (FTR) PTs in AKI. CFH was highly induced in stromal cells, which were more than 3-fold expanded following AKI and UUO. CFP was localized to interstitial immune cells. We noted that infiltrating immune cells coalesced around FTR PTs and expressed the C3AR1 as well as receptors for C5a. The majority of immune cells were macrophages expressing high levels of F480, IL-1b and TNF, suggesting that they were proinflammatory macrophages. RNAscope, RT-PCR and confocal microscopy confirmed the changes seen by ST. The proximity of inflammatory immune cells expressing C3AR1 to PTs expressing their cognate ligand suggests bi-directional signaling between FTR PTs and immune cells. Ongoing work will functionally explore these observations and determine the local roles of CFH and CFP in AKI and fibrosis.

Conclusions: Compartmentalized induction of C' components and receptors occurs following AKI and may modulate inflammation and subsequent fibrosis through interactions with local immune and stromal cells.

Funding: NIDDK Support

SA-PO087

The Human Sepsis Blood Transcriptome Correlates with Molecular Signatures of Murine Sepsis-Associated AKI

Danielle Janosevic, Sean D. Mccabe, Thomas De Luca, Michael T. Eadon, Takashi Hato, Pierre C. Dagher. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Sepsis is a common cause of acute kidney injury for which we lack predictive biomarkers. In murine models of sAKI, renal tissue injury progresses through precise tissue gene expression stages that are mirrored in the blood transcriptome. We hypothesize that blood-based murine sAKI biomarkers can help diagnose and stratify human subjects with sepsis.

Methods: Whole blood RNAseq (25-30 million read depth/sample, mm10 transcriptome) was performed in a murine model of sAKI at 0 and 1,16 hr after endotoxin injection. Counts were TMM normalized and log-transformed (counts-per-million, EdgeR). Human data was derived from GSE 65682 (Scicluna et al., MARS consortium) and "abdominal-sepsis" (sepsis) and "control-GI" (non-sepsis) groups of blood RNA were compared. A within-species analysis was used to calculate gene log fold changes (LFC). Spearman correlations were calculated using a filtered gene set (> +/- 0.25, human, > +/- 1.5, murine samples) to determine sample relatedness.

Results: Murine blood-based sAKI biomarkers were able to discriminate between septic and non-septic patients. Correlations of gene changes between human non-sepsis with murine controls (0 hr) were as high as 0.43 and as high as 0.44 between human sepsis and murine late sAKI samples (16 hr, Figure). Correlated genes upregulated in sepsis were related to immune function (Bcl11b, Hvcn1, Cx3cr1) and metabolism (Pask).

Conclusions: Correlation of blood-based RNA biomarkers between human and murine sepsis data revealed shared alterations in critical processes related to sepsis-immune system regulation and metabolism. Defining such biomarkers may aid in the identification of subjects at risk for sAKI and afford early interventions to attenuate or reverse sAKI.

Funding: NIDDK Support, Private Foundation Support

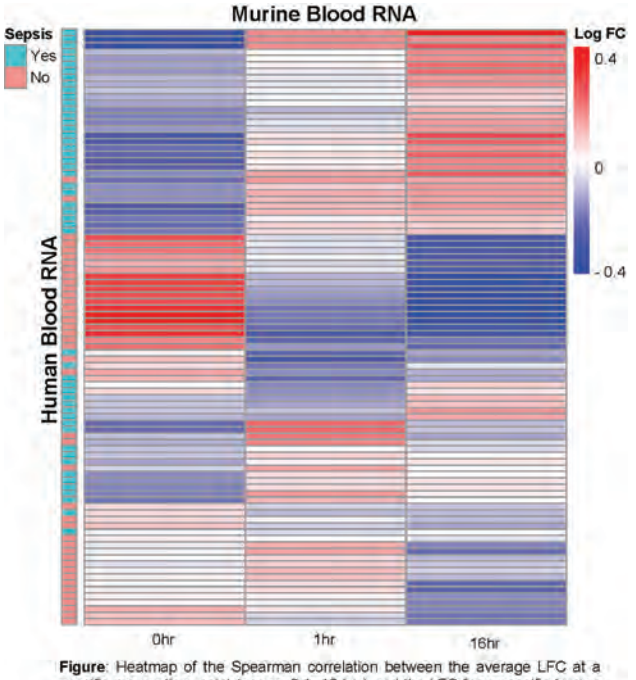


Figure: Heatmap of the Spearman correlation between the average LFC at a specific mouse time point (across 0,1, 16 hrs) and the LFC for a specific human sample (sepsis vs non-sepsis). Only genes with the LFC greater than 0.25 for the human sample and greater than 1.5 for the mouse sample were included.

SA-PO088

Unraveling Autoimmunity and Tissue Residency in a Model of CD8 T Cell-Driven Nephritis

Frederic Arnold,[1,2] Laurence Kupferschmid,[2] Philipp Weissenborn,[2] Sagar -,[4] Manuel Rogg,[3] Christoph Schell,[3] Yakup Tanriver.[1,2] AG Tanriver.
[1]Department of Internal Medicine IV, University Medical Center Freiburg, Freiburg im Breisgau, Germany; [2]Institute for Microbiology and Hygiene, University Medical Center Freiburg, Freiburg im Breisgau, Germany; [3]Institute for Pathology, University Medical Center Freiburg, Freiburg, Germany; [4]Department of Internal Medicine II, University Medical Center Freiburg, Freiburg, Germany.

Background: There is strong evidence, that autoreactive cytotoxic T cells (CTLs) play a crucial role in different forms of autoimmune nephritis (*e.g.*, acute interstitial nephritis or immune checkpoint inhibitor-related nephritis). Yet, mechanisms of differentiation and memory formation of autoreactive CTLs in the kidney are poorly understood. Distinct tissue-resident memory T cells (T_{RM}) providing localized immunity have been identified in the kidney. However, their role in context of renal autoimmunity remains elusive.

Methods: A murine model of CTL-driven nephritis was established to dissect the role of autoreactive CTLs. It is based on NOH mice, that express ovalbumin (OVA) on podocytes. CTL-driven autoreactivity was induced by adoptive transfer of OVA-specific CTLs (OT-1 cells) into NOH hosts and activation through infection with OVA-expressing pathogens. The transcriptome and T cell phenotype was analyzed applying scRNASeq and multi-dimensinal flow cytometry on circulating and renal CTLs. Additional histopathological analysis was performed on kidneys of NOH mice and patients with interstitial nephritis.

Results: Autoreactive CTLs induced a robust renal phenotype in NOH mice. Despite the phenotype, peripheral OT-1 counts declined more rapidly in NOH *vs.* wildtype mice. In line with that, scRNASeq and cytometry analysis of OT-1 cells revealed a distinct peripheral T memory phenotype. It was characterized by higher expression of markers associated with T cell dysfunction (*e.g.*, Tox, Ctla4, Lag3), indicating functional restriction of autoreactive CTLs. While peripheral immunity appeared curtailed, robust accumulation of OT-1 cells was detected in kidneys of NOH mice. Within OT-1 infiltrates a subpopulation of autoreactive renal T_{RM} cells ($CD103^+CD69^+$), most likely required for maintaining the phenotype, could be identified. Histopathological analysis of human samples revealed a comparable T_{RM} subpopulation in interstitial nephritis.

Conclusions: CTLs show a distinct transcriptome and immune phenotype in a model of CTL-driven nephritis. While the systemic immune response is curtailed, CTLs persistently accumulate at the site of autoantigen cross-presentation. Differentiation of T_{RM} cells within infiltrates of mice and nephritis patients indicate a crucial role of renal T_{RM} cells in context of sustained renal autoimmunity.

Funding: Government Support - Non-U.S.

SA-PO089

Tertiary Lymphoid Structures and Late-Stage Lymphangiogenesis at Very-Late Time Points following Ischemic Kidney Injury

Gelare Ghajar-Rahimi,[1] Arin Melkonian,[1] Daria Barwinska,[2] Grace Whipple,[1] Malgorzata Kamocka,[2] Seth Winfree,[3] James F. George,[1] Timmy C. Lee,[1] Tarek M. El-Achkar,[2] Anupam Agarwal.[1] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Indiana University School of Medicine, Indianapolis, IN; [3]University of Nebraska Medical Center, Omaha, NE.*

Background: The role of the lymphatic system in the transition from AKI to CKD is unknown. In several AKI models, kidney lymphatics undergo expansion or lymphangiogenesis (LA), which is considered acutely protective, but long-term changes post-injury have not been assessed. This study aimed to determine if long-term alterations in kidney lymphatics persist and their relationship to inflammation and injury.

Methods: C57BL/6J mice underwent bilateral ischemia-reperfusion injury (BIRI) and were followed for 9 months. Kidney function was assessed using serial glomerular filtration rate (GFR) measurements. The abundance and spatial distribution of LYVE-1+ lymphatic vessels were determined using quantitative three-dimensional tissue cytometry (3DTC). Lymphangiogenesis (LA) was evaluated by quantitative real-time PCR for lymphangiogenic markers. Single-cell and single-nucleus transcriptomic datasets of murine and human endothelial cells were analyzed to identify additional target genes. Sequential immunofluorescence characterized tertiary lymphoid structures in the kidney.

Results: BIRI induced AKI within 24 hours. While GFR recovered, BIRI mice showed progressive histological signs of CKD overtime, including fibrosis and CCR7+ lymphoid aggregates. Sham-operated mice did not display these phenotypes. 3DTC revealed an increase in cortical LYVE-1+ vessels in BIRI compared to sham groups at 3 days and 6 months post-surgery, with no significant difference at intermediate time points. Expression of lymphatic marker gene *Flt4* and *Lyve1* increased acutely, while *Flt4*, *Lyve1*, and *Pdpn* were elevated later. Increased *Ccl21a* expression was detected in kidneys collected 6 months after BIRI. Single-cell/nucleus transcriptomics suggest the source of *Ccl21a* is likely a subpopulation of lymphatic endothelial cells.

Conclusions: Three distinct phases of kidney lymphatic responses occur after BIRI: acute LA, an intermediate regression to a basal phenotype, and late-stage LA coinciding with increased *Ccl21a* expression and tertiary lymphoid tissue formation. Future studies will aim to examine the precise spatial and functional relationship between injury-associated lymphatics, tertiary lymphoid structures and kidney function.

Funding: Veterans Affairs Support

SA-PO090

Single-Cell RNA Sequencing of Kidney-Gut Axis during Microbiome Manipulation of Severe AKI to CKD Progression

Jiahui Yao, Shishir K. Patel, Sanjeev Noel, Patrick Cahan, Hamid Rabb.
Johns Hopkins University, Baltimore, MD.

Background: The gut microbiome modifies experimental acute kidney injury (AKI) outcomes. The antibiotic drug amoxicillin, accelerates kidney repair and decreases fibrosis after severe AKI, likely through CD8 T cells (Kidney International, 2023). The goal of this study was to uncover specific genes and pathways that mediate T cell response to amoxicillin and regulate recovery and repair from severe AKI.

Methods: 8-10 week old male C57BL6 mice underwent unilateral ischemia reperfusion injury (UIRI) to kidney (n=10/group). Mice were given vehicle (1% glucose) or amoxicillin (50 mg/ml) in drinking water starting soon after UIRI and kidney and colon tissues collected after 15 days. Non surgery mice treated with vehicle and amoxicillin were used as controls. CD3+ cells were flow sorted for 10X Chromium 5-prime single cell RNA sequencing (scRNA-seq). Cells were annotated using machine learning classification and manual annotation using established cell markers. Differential gene expression and Gene Set Enrichment Analysis (GSEA) was performed to identify specific genes and pathways that differed between corresponding cell types across conditions.

Results: After quality control, we recovered 22,260 cells from the kidney and 14,669 cells from the colon. Nine cell types were annotated, including Th1, Th2, Th17, regulatory T cells, effector and memory CD8+ cells, and naive CD4+, CD8+, double negative and double positive T cells. Amoxicillin treatment after UIRI increased the proportion of CD8+ T cells and reduced that of CD4+ T cells in kidney, while the colon decreased the fraction of CD8+ T cells. GSEA revealed aldosterone-regulated sodium reabsorption (downregulated Prkcb, Insr, Nedd4l, etc) and JAK-STAT signaling pathway in kidney (downregulated Jak1, Ccnd3, and Socs1, etc), as well as estrogen signaling pathway (downregulation was repaired after Amoxicillin, marked by Jun, Fos, Hsp90aa1, etc) and renin secretion (downregulated Gnai2, Adrb1, Gnas, etc) in the colon.

Conclusions: These scRNA-seq results show shifts in T cell populations in gut-kidney axis during severe AKI and corroborated our prior flow cytometry observations. Our scRNA-seq data and analyses promise to yield novel mechanisms, markers, therapeutic options for severe AKI and gut microbiome-kidney cross talk.

Funding: NIDDK Support

SA-PO091

Pathological Effects of IL-17A on Renal Leukocyte Infiltration in Murine Septic AKI (SAKI)

Yoshitaka Naito, Tomoyuki Fujikura, Akihiko Kato, Hideo Yasuda. *Hamamatsu Ika Daigaku, Hamamatsu, Japan.*

Background: There are no specific treatments for SAKI. Hyperinflammation in kidney leads to renal leukocyte infiltration, which contributes to SAKI. In non-septic AKI, neutrophils and NK cells are first recruited to kidney, followed by inflammatory monocytes. However, the course of renal leukocyte infiltration in SAKI has not been clarified. We have shown that knockout of IL-17A improved survival and SAKI after cecal ligation and puncture (CLP) surgery. We next focused on the downstream of IL-17A. It is well known that IL-17A stimulates non-myeloid cells, such as epithelial cells, to produce chemokines that promotes leukocyte recruitment to inflammatory site. We hypothesized that IL-17A contributes to the pathogenesis of SAKI by promoting leukocyte infiltration into kidney.

Methods: IL-17A knockout (IL-17AKO) or wild type mice (WT) were subjected to CLP to induce polymicrobial sepsis or sham surgery. We assessed leukocyte (neutrophil, macrophage, NK cell, B cell, and T cell) infiltration into kidney by flow cytometry and IL-17A, CXCL-1, and -2 concentration in kidney tissue by ELISA at 3, 6, and 18 h after CLP. We also assessed whether recombinant human IL-17A can promote production of human IL-8, a functional homolog of murine CXCL-1 and -2 and a potent promoter of neutrophil recruitment, in HK-2 (human kidney 2) cells in vitro.

Results: In WT, CLP upregulated neutrophil and B cell infiltration into kidney at 3 h; neutrophil, NK cell, and T cell infiltration at 6 and 18 h after CLP. IL-17AKO attenuated neutrophil and macrophage infiltration at 3 h and neutrophil, macrophage, and NK cell infiltration at 18 h after CLP. CLP upregulated IL-17A, CXCL-1, and -2 production in kidney tissue at 18 h after CLP, which is significantly decreased by IL-17AKO. Recombinant IL-17A promoted human IL-8 production in HK-2 cells.

Conclusions: We have shown that in SAKI, first neutrophils and B cells infiltrated into kidney, followed by NK cells and T cells; IL-17A contributed to neutrophil, NK cell, and macrophage infiltration. IL-17A promoted CXCL-1 and -2 production in kidney. These findings indicates that IL-17A promotes neutrophil infiltration via CXCL-1 and -2 production in kidney after CLP. We are planning further studies to determine how IL-17A promotes NK cell or macrophage infiltration into kidney after CLP.

SA-PO092

Viral Priming Enhances Kidney Injury at Early Time Points in Lipopolysaccharide (LPS)-Induced Sepsis-Associated AKI

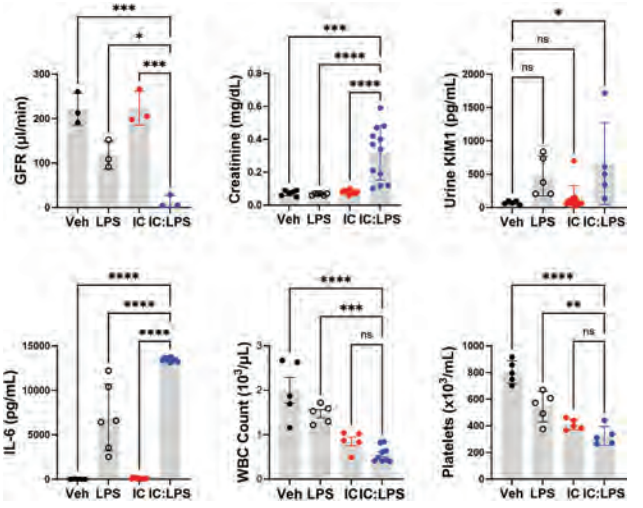
James D. Odum, Giacynta A. Vollmer, Juheb Akhter, Subhashini Bolisetty. *The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.*

Background: Sepsis-associated acute kidney injury (SA-AKI) is a heterogenous syndrome inflicted by the sepsis inflammatory cascade and phenotype-specific mechanisms. Viral priming followed by bacterial sepsis causes exaggerated inflammation and is associated with higher mortality than bacterial sepsis alone. We generated a novel murine SA-AKI model that recapitulates the viral primed bacterial sepsis phenotype using polyinosinic-polycytidylic (poly(IC)) acid, a synthetic viral double-stranded DNA analog, followed by low-dose lipopolysaccharide (LPS).

Methods: Using 8-week-old male C57BL/6J mice, we induced viral priming at 0h via poly(IC) intraperitoneal (IP) injection (10 mg/kg) vs. saline control. At 24h post-poly(IC), we administered low-dose LPS (0.5 mg/kg via) by IP injection vs. PBS control. We measured glomerular filtration rate (GFR) at 28h via FITC-sinistrin and sacrificed mice at 32h for collection of blood and urine. Analysis employed 2-way ANOVA; $p<0.05$ deemed significant.

Results: GFR was significantly reduced by 28h in poly(IC)+LPS (IC:LPS, 12.9± 8.0 uL/min) mice compared to poly(IC)+PBS (IC, 223.3± 7.9 uL/min, $p<0.001$), saline+LPS (LPS, 117.4±31.4 uL/min, $p=0.014$) or control (Veh, 221.3±35.8 ml/min, $p<0.001$) mice. This corresponded to increased serum creatinine in IC:LPS mice at 32h compared to normal creatinine in other cohorts. At 32h, IC:LPS mice had significantly increased IL6 along with leukopenia and thrombocytopenia compared to LPS or Veh mice. Urine kidney injury molecule-1 was elevated in IC:LPS mice, but not in IC mice.

Conclusions: We generated a novel murine model to study mechanisms of viral primed SA-AKI. Poly(IC) alone does not cause kidney injury. Poly(IC)+LPS leads to early and significant kidney injury despite low dose LPS that has modest reduction in GFR with no changes in creatinine. Viral priming imparts a synergistic injurious response and warrants further investigation.



SA-PO093

The Initiating Effect of Acute-Phase Serum Amyloid A (A-SAA) on AKI

Dier Li, Haiyan Fu. *State Key Laboratory of Organ Failure Research, National Clinical Research Center of Kidney Disease, Renal Division, Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: Acute kidney injury (AKI) is a common and rapidly progressing condition lacking effective therapies. Understanding key molecular events during AKI initiation and progression is crucial. This project aims to identify factors that trigger AKI. Integrating biological experiments, bioinformatics, and mathematical modeling, we identified acute-phase serum amyloid A (A-SAA) as a key initiating molecule.

Methods: We constructed ischemia/reperfusion injury (IRI)-induced AKI model in mice and analyzed renal tissue proteome changes at various post-surgery time points using mass spectrometry. Bioinformatics and mathematical modeling identified AKI initiating factors. A-SAA knockout mice were used to create IRI- or cisplatin-induced AKI models. We assessed kidney injury severity through histological, immunological, and molecular biology techniques. In vitro, hypoxia/reoxygenation-induced and cisplatin-induced models were used to study A-SAA's mechanisms. Primary cells and cell lines were used to examine A-SAA's function and tubule-macrophage interactions. A recombinant protein vaccine against A-SAA was designed and tested in mice for therapeutic potential. Additionally, serum A-SAA levels were measured in patients undergoing cardiac surgery to assess its predictive value for AKI.

Results: A-SAA levels surged in serum and kidney tissue within 4 hours post-IRI. Initially expressed in tubule epithelial cells, A-SAA later appeared in various kidney cells. Proteomic data analysis using the Hopfield model highlighted A-SAA as a critical AKI driver, significantly influencing other protein expressions. A-SAA knockout reduced IRI- or cisplatin-induced AKI in male mice, evidenced by decreased tubule cell injury and inflammation. Mechanistically, A-SAA bound to CD36 and TLR4, aggravating cell injury, apoptosis, and inflammatory response, creating a harmful inflammatory microenvironment. A-SAA also recruited and activated macrophages, further worsening the microenvironment. The A-SAA vaccine induced antibodies in mice and showed reno-protective effects against AKI. Serum A-SAA levels in cardiac surgery patients correlated with AKI severity.

Conclusions: A-SAA is a critical driver in early AKI stages. By binding CD36 and TLR4, A-SAA damages tubule cells and recruits activated macrophages, creating a detrimental inflammatory microenvironment that exacerbates AKI. Targeting A-SAA could mitigate kidney injury and serve as an early AKI warning signal.

Funding: Government Support - Non-U.S.

SA-PO094

HDAC1 Modulates Cell Cycle and Proliferation of Myofibroblasts in the Kidneys

Huy Nguyen, Kelly A. Hyndman, Luciano D. Mendoza. *The University of Alabama at Birmingham Division of Nephrology, Birmingham, AL.*

Background: Ischemia-reperfusion injury (IRI) can cause acute kidney injury (AKI) leading to renal interstitial fibrosis. Histone deacetylase 1 (HDAC1), a regulator of transcription, is implicated in mediating renal injury and fibrosis post-IRI. Understanding its role post-IRI may lead to novel therapeutic approaches for improving health outcomes. We hypothesized that fibroblast HDAC1 activation after IRI leads to fibrosis by promoting cell cycle progression and proliferation of myofibroblasts.

Methods: Male, floxed HDAC1 (control), and floxed HDAC1 mice with hemizygous Col1A2-CreER (iFibHDAC1KO mice, littermates) received tamoxifen i.p. in adulthood and this resulted in fibroblast HDAC1 knockdown in Cre+ mice. Mice underwent 18-min kidney bilateral IRI or sham surgery. AKI was confirmed 24 h post-surgery by serum creatinine levels and glomerular filtration rate (GFR). Interstitial fibrosis was evaluated after four weeks of recovery using picrosirius red. Normal rat kidney fibroblasts (NRK49F) were transfected with empty vector control or HDAC1 and cell cycle was determined by flow cytometry. Cells were also treated for 24 h with 2 ng/ml TGFβ1 to induce myofibroblast transition. Cells were collected for bulk RNA-seq to assess gene expression profiles.

Results: All IRI mice experienced a 50% reduction in GFR 24 h post-surgery compared to shams. iFibHDAC1KO IRI mice had significantly lower renal fibrosis compared to control IRI mice (0.47 ± 0.1% vs/ 1.16±0.2, p = 0.0011, n=5-7). HDAC1 overexpression in NRK49F cells led to a shift in the cell cycle with greater percentage of cells in the S (11 ± 0.2 vs 4 ±0.2, p< 0.001, n=3) and G2 phases (19 ± 0.4 vs 7 ± 0.1, p< 0.001). These cells also had increased expression of 44 cell cycle, and 65 proliferation related genes compared to control cells (adjusted P < 0.05). Although TGFβ1 treatment for 24 h didn't lead to a further shift in cell cycle, there were 2 additional cell cycle and 7 proliferation-related genes increased. HDAC1 overexpression lead to the cyclin gene *Ccna2* and proliferation marker *Mki67* upregulation in both conditions.

Conclusions: HDAC1 may be profibrotic through shifting the cell cycle and increasing fibroblast/myofibroblast proliferation. Targeting HDAC1-mediated pathways could offer a therapeutic solution for mitigating renal fibrosis progression.

Funding: NIDDK Support, Other NIH Support - R01DK126664, P30 DK 079337, Private Foundation Support

SA-PO095

Mechanisms of Injury and Protection in Ischemic AKI

Jillian R. Campbell,[1] Jesus H. Dominguez,[2] Meagan R. Troyer,[2] Katherine J. Kelly.[2,1] *[1]Richard L Roudebush VA Medical Center, Indianapolis, IN; [2]Indiana University School of Medicine, Indianapolis, IN.*

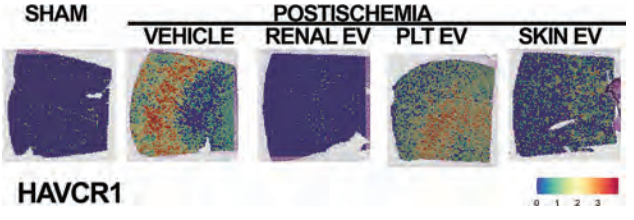
Background: AKI is frequent and deadly. Effective therapy is an unmet need. In experimental ischemia, we have shown rapid improvement in renal function and structure after therapy with extracellular vesicles (EV, exosomes) derived from kidney, when given 24 hours postischemia. We hypothesized that EV from platelets, a rich and readily available source, or from skin epithelia would be beneficial. Our hypothesis was not true, but the difference between therapeutic and ineffective EV allows exploration of injury/protection mechanisms in an unbiased manner.

Methods: Using an established model of ischemia/reperfusion, mechanism was examined using spatial transcriptomics.

Results: As in previous studies, serum creatinine and histological evidence of injury were improved within 24 hours of delivery of EV from tubular cells. Renal EV improved multiple pathways of injury with ~68% of transcripts altered postischemia improved with renal EV, including known markers of injury, such as HAVCR1 (KIM1, figure). Spatial analyses showed multiple alterations in all tubular segments, leukocytes, endothelia, glomeruli and regions of the kidney. Multiple pathways of immune and oxidant-mediated injury, including neutrophil extracellular trap formation and complement, were significantly altered with ischemia and improved with renal, but not platelet or skin, EV. In addition, only renal EV corrected alterations in mRNA involved in the programatic steps of peptide synthesis, cellular senescence and renal cytochrome p450. The latter is relevant because, as in liver, renal cytochrome enzymes may serve to preserve endothelial function and renal perfusion following ischemia.

Conclusions: The specific restoration by renal EV is consistent with the hypothesis that renal EV upload new sets of renal molecular instructions that reset the injured kidney towards rapid restoration of function and structure.

Funding: NIDDK Support, Veterans Affairs Support



Spatial distribution of KIM1 in postischemic kidneys. Expression levels of HAVCR1 (KIM1) overlaid upon hematoxylin and eosin stained sections are presented. Significantly less expression is seen with renal extracellular vesicle (EV, exosome) treatment as compared to EV from platelets (plt) or skin.

SA-PO096

Inhibition of PTP1b via Milk Exosome-Mediated Small Interfering RNA (siRNA) Delivery Is a Novel Therapeutic Approach for AKI

Myung-Gyu Kim, Yookyung Jang, Young Eun Choi, Ko Yoon Sook, Lee Hee Young, Sewon Oh, Sang-Kyung Jo. *Korea University Anam Hospital, Seoul, Republic of Korea.*

Background: Protein tyrosine phosphatase-1B (PTP1b) plays a crucial role in regulating insulin, leptin sensitivity, and inflammatory responses, rendering it a promising therapeutic target for diseases like diabetes, obesity, and neuroinflammation. Despite its well-established significance in various conditions, its involvement in kidney disease remains largely unexplored.

Methods: In this study, we developed an innovative siRNA delivery system using exosomes derived from milk to encapsulate PTP1b siRNA (PTP1b siR@mExo), with the aim of investigating its impact on acute kidney injury (AKI). C57BL/6 mice were subjected to bilateral ischemia reperfusion injury (IRI), and PTP1b siR@mExo was pretreated at -6, -4, and -2 hrs.

Results: In vitro studies demonstrated better cellular uptake of Cy3-labeled PTP1b siR@mExo by human proximal tubule cells (HK2) with superior stability compared to treatment with PTP1b siRNA alone. Moreover, in mice, PTP1b siR@mExo exhibited highly efficient kidney delivery, reaching maximum absorption at 2 hours, sustaining elevated levels up to 48 hours, followed by accumulation in the liver and spleen, indicating milk exosomes as a novel siRNA delivery system. PTP1b expression was notably observed on tubules and glomeruli, and pre-treatment with PTP1b siR@mExo in IRI effectively reduced PTP1b levels in the kidney. This reduction was accompanied by decreased expression of inflammatory cytokines (TNF-α, IL-6, IL-1β), alleviated endoplasmic reticulum stress (CHOP), diminished DMAP signal (HMGB1), and a significant improvement in renal function.

Conclusions: In conclusion, our study demonstrated that milk-derived exosomes, with superior structural stability, serve as efficient carriers for siRNA, and showed the efficacy of milk-derived exosomes carrying PTP1b siRNA in treating IRI. The inhibition of PTP1b emerges a promising novel therapeutic target for AKI, providing valuable avenues for further exploration and intervention strategies in kidney disease.

Funding: Government Support - Non-U.S.

SA-PO097

Circulating Extracellular Vesicles Exert Age-Dependent Immunomodulation in Acute Hypoxic Kidney Tubular Injury

Chia-Te Liao, Dora Livkisa, Tsung Lin Lee, David J. Lundy. *Taipei Medical University, Taipei, Taiwan.*

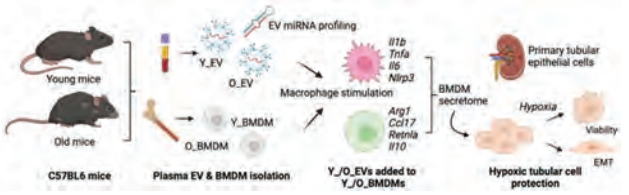
Background: Aging and paracrine secreted factors would affect systemic immune responses, and circulating extracellular vesicles (EVs) potentially play a role in these processes. This study aims to investigate the interaction of plasma EVs and bone marrow-derived macrophages (BMDMs) isolated from young and aged mice in the context of acute hypoxic renal tubular injury.

Methods: Plasma EVs from young (Y_EV) and aged (O_EV) C57BL/6 mice were first isolated by precipitation, then characterized by nanoparticle tracking analysis. EV miRNA were extracted and profiled, then miRNA targets were predicted using ingenuity pathway analysis. EVs stimulated BMDMs from young (Y_BMDM) and aged (O_BMDM) mice, both in naïve conditions and following hypoxic renal tubular injury. Macrophage M1/M2-related secretomes were assessed by quantitative PCR for comparison.

Results: Our results revealed distinct differences in the immunomodulatory effects of Y_EVs and O_EVs, and the corresponding responses of Y_BMDMs and O_BMDMs. Y_EVs tended to induce less pro-inflammatory cytokines, whereas O_EVs had a more varied impact, inciting both pro- and anti-inflammatory responses. However, neither EV population induced a distinct 'M1' or 'M2' phenotype. Notably, plasma EVs and whole plasma induced very different responses in BMDMs; plasma from aged mice was profoundly pro-inflammatory, whereas O_EVs were not. We further characterized and compared Y_EV and O_EV miRNA cargo, surprisingly finding only a very limited difference. In the context of hypoxic renal injury, Y_EVs suppressed inflammatory cytokine expression, but O_EVs were able to induce higher anti-inflammatory cytokine expression. However, both Y_EVs and O_EVs did not directly affect the degree of protection offered by macrophage secretomes following hypoxic renal tubular injury (Figure).

Conclusions: This study showed some age-related differences in the effects of EVs on macrophage function. In hypoxic renal injury, young EVs were able to reduce macrophage pro-inflammatory gene expression and increase anti-inflammatory gene expression. Further *in vivo* studies are warranted to decipher the exact role of circulating EVs in kidney diseases.

Funding: Government Support - Non-U.S.



SA-PO098

Nuclear-Localized Complement Factor B (CFB) Is a DNA-Binding Enzyme Regulating Histone Degradation

Md Tajmul,[1] Tilo Freiwald,[2,4] Jorge L. Trujillo-Ochoa,[1] Daniel Chauss,[1] Dhaneshwar Kumar,[1] Baktiar O. Karim,[3] Maja Gunkel,[2,4] Yubing Guo,[2,4] Julius F. Jäger,[2,4] Claudia Kemper,[5] Tobias B. Huber,[2,4] Thorsten Wiech,[6] Martin Kolev,[7] Scott D. Briggs,[8] Majid Kazemian,[8] Didier Portilla,[9] Behdad Afzali.[1] *[1]Immunoregulation Section, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD; [2]Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Leidos Inc, Reston, VA; [4]Hamburg Center for Kidney Health (HCKH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Complement and Inflammation Research Section, National Heart Lung and Blood Institute, NIH, Bethesda, MD; [6]Institute of Pathology, Section for Renal Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]Apellis Pharmaceuticals Inc, Waltham, MA; [8]Department of Biochemistry, Purdue University, West Lafayette, IN; [9]Division of Nephrology and Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia, Charlottesville, VA.*

Background: The complement (C') system is essential for innate immunity and pivotal to lytic pathogen destruction, recognition of danger signals, and orchestration of inflammatory responses. Although traditionally viewed as an extracellular, serum-based defense mechanism, recent insights have revealed critically important intracellular functions of C' components, suggesting roles beyond classical immune responses. Despite extensive studies on circulating factor B (CFB), its intracellular functions remain under-explored. We have observed inducible CFB expression in injured kidney epithelial cells, leading us to hypothesize that intracellular CFB also regulates cellular processes.

Methods: We studied mouse proximal tubular epithelial cells using primary cells, TKPTS cell lines, confocal imaging, a small molecule CFB inhibitor, CUT&Tag, electrophoretic mobility shift assay (EMSA), computational predictions with AlphaFold2 and GraphSite and protein assays with wild-type and mutated CFB.

Results: Confocal microscopy revealed significant nuclear accumulation of CFB in kidney epithelial cells. To explore potential DNA-binding by CFB, we employed CUT&Tag, identifying a consensus motif enriched at CFB binding sites within the genome. EMSA confirmed the binding of CFB to this motif, with a Kd of 0.71uM, indicating a meaningful interaction. *In silico* modeling suggested a DNA-binding pocket with 11 DNA-contacting residues, supported *in vitro* with CFB mutants showing reduced DNA binding. Considering the serine protease activity of CFB, we proposed that CFB targets and degrades DNA-associated proteins, such as histones, within its vicinity. *In vitro* experiments, including those with a CFB inhibitor, confirmed this hypothesis, showing the ability of CFB to degrade nucleosomal histones. Ongoing experiments aim to map specific histone cleavage sites to guide future functional studies

Conclusions: These findings expand understanding of intracellular C' functions and highlight a potential role for CFB in modulating transcriptional outcomes, with potential implications for therapeutic strategies targeting CFB in the intracellular or extracellular space in patients.

Funding: NIDDK Support, Other NIH Support - NHLBI, NCI, Commercial Support - Apellis Pharmaceuticals, Government Support - Non-U.S.

SA-PO099

Examining the Anti-inflammatory and Renoprotective Effects Resulting from Parasympathetic Nerve Stimulation after Inflammation

Sayumi Matsuo, Chia-Hsien Wu, Yasuna Nakamura, Norito Washimine, Ryusuke Umene, Tomoya Nishino, Tsuyoshi Inoue. *Nagasaki Daigaku Daigakuin Ishiyakugaku Sogo Kenkyuka, Nagasaki, Japan.*

Background: Recent reports have indicated that pre-injury stimulation of the parasympathetic nervous system, activating the cholinergic anti-inflammatory pathway (CAP), yields anti-inflammatory and renoprotective effects. However, it is unclear whether similar effects can be achieved with post-injury stimulation of the parasympathetic nervous system. This study aims to confirm whether post-inflammatory stimulation of the parasympathetic nervous system can indeed lead to anti-inflammatory and renoprotective effects, as well as to elucidate the underlying mechanisms.

Methods: The animal model employed in this study involved inducing acute kidney injury/sepsis using lipopolysaccharide (LPS). Due to concerns about the highly invasive nature of direct vagus nerve stimulation, we chose to activate the parasympathetic nervous system by administering 3-(2,4-Dimethoxybenzylidene)-anabaseine dihydrochloride (GTS-21), a selective α7 nicotinic acetylcholine receptor agonist. After inducing inflammation in wild-type C57BL/6 mice by administering LPS, we subsequently administered GTS-21 to evaluate its anti-inflammatory and renal protective effects. Furthermore, we induced inflammation in RAW 264 (mouse macrophages) and U937 (human macrophages) using LPS, followed by parasympathetic nerve stimulation, to evaluate their anti-inflammatory effects similarly. Furthermore, we conducted RNA-seq analyses on each cell type to elucidate the underlying molecular mechanisms.

Results: We confirmed that administering the selective α7 nicotinic acetylcholine receptor agonist, GTS-21, in the mouse model of acute kidney injury/sepsis induced by LPS, resulted in anti-inflammatory and renal protective effects. Moreover, based on the findings from RNA-Seq analysis, we elucidated that the expression of CCL2, a chemokine, in splenic macrophages is involved in mediating these effects.

Conclusions: Even after inflammation induction, stimulation of the parasympathetic nervous system yielded anti-inflammatory and renoprotective effects. This discovery holds significant promise for the development of novel treatments for sepsis and AKI.

SA-PO100

Inhibition of Plk1 Attenuates Cisplatin-Induced AKI via Upregulation of PERK/P-eIF2α Pathway

Yang Du, Xiuli Lin, Yaqiong Shang, Shuang Chen, Yan Guo, Weidong Cao, Zhanjun Jia, Yue Zhang. *Nanjing Medical University, Nanjing, China.*

Background: Acute kidney injury(AKI) is a common and serious clinical complication and lacks effective treatment except renal replacement therapy. PLK1 is an important cell cycle regulator with no study reported in AKI. In current study, we investigated the effect of Plk1 inhibition by BI6727 or knock down of Plk1 by siRNA in cisplatin induced AKI in mice or in cultured renal tubular epithelial cells.

Methods: AKI was induced in C57BL/6J mice by administration of cisplatin at dose of 25mg/kg(i.p.). Plk1 inhibitor BI6727 (7.5mg/kg) was given 6hrs prior to cisplatin injection. All Mice were executed 72hrs after cisplatin injection. Mice blood and kidney tissues were collected for histology or protein anaylsis. Renal proximal tubular epithelial cell line TKPT was pretreated with BI6727 or transfected with Plk1-shRNA, then cisplatin was added for 24hrs and cells were collected for apoptosis detection by flow cytometry.

Results: In BI6727 treated mice, increased serum creatinine caused by cisplatin was reduced by 65%. PAS staining showed tubular injury score was about 47% less. Protein expression of Kim1 and NGAL were reduced by 56% and 81%. mRNA of TNF-α and IL-6 were reduced by 85% and 77%. Tunnel staining showed about 46.1% less apoptotic cells. In cultured TKPT cells, BI6727 treatment reduced the apoptotic cells by 58% and knock-down of Plk1 reduced the apoptotic cells by 46.8% compared to cisplatin treated cells. Further, we found BI6727 upregulated PERK/P-eIF2α pathway, which is the central mechanism of the integrated stress response(ISR). Under conditions of stress, activation of the ISR inhibits protein translation and preserves energy for essential functions to support cell survival.

Conclusions: Inhibition of Plk1 by BI6727 protects against cisplatin-induced acute kidney injury. This effect is mediated by upregulation of PERK/P-eIF2α pathway. Our research suggests a pathogenic role of Plk1 in promoting AKI. Plk1 may be a potential target for AKI treatment.

Funding: Government Support - Non-U.S.

SA-PO101

PDZD8, a Tethering Protein of Endoplasmic Reticulum (ER)-Lysosome Interaction, Alters Tubular Inflammation in Mice with Cisplatin-Induced AKI

Yuto Takenaka,[1] Sho Hasegawa,[1] Yu Ah Hong,[1] Qi Li,[1] Hiroshi Maekawa,[2] Masaomi Nangaku,[1] Reiko Inagi.[1] *[1]Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu Seirigaku, Bunkyo-ku, Japan; [2]Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: The pathophysiological importance of organelle crosstalk in maintaining cellular homeostasis is a prominent trend. PDZD8, a tethering protein located on the ER lumen, facilitates interactions with other organelles and promotes homeostasis at organelle contact sites. We thus aim to elucidate the role of organelle crosstalk, specifically through PDZD8, in the context of AKI.

Methods: In vivo studies: 8-10 week-old male PDZD8 knockout (KO) and wild-type (WT) mice were administered 20mg/kg cisplatin and euthanized 48 hr later. Kidney injury was assessed by BUN, Cre, PAS, IHC for inflammatory molecules and RT-PCR. In vitro studies: human proximal tubular cell line (HK-2) was treated with 20mM cisplatin and assessed changes in organelle homeostasis and their effect on inflammatory response (TLR9-NFkB axis) using mass spectrometry-based immuno-precipitation proteomics and immunofluorescence microscopy for organelle function.

Results: PDZD8 KO mice improved cisplatin-induced kidney injury compared to WT mice, as indicated by lower BUN and Cre levels and less severe tubular damage. This was accompanied by a diminished activation of the NFkB inflammatory pathway and decreased NFkB-downstream inflammatory gene expression (IL6, CXCL10). In vitro studies revealed that cisplatin-induced inflammation was also reduced in PDZD8-knockdown (KD) HK-2 cells, while cisplatin damage, estimated by mitochondrial DNA leakage, was identical between WT and KD cells. Interestingly, such PDZD8-mediated tubular inflammatory signal was closely correlated with the TLR9 activation level: 1) cisplatin-exposed HK-2 cells induced the intracellular translocation of TLR9 (to the lysosome), which activates NFkB inflammatory signaling, 2) PDZD8-KD significantly impaired the TLR9 translocation/activation, leading to the reduction of NFkB-mediated tubular inflammation. Further, PDZD8-KD significantly affected the lysosomal functions, characterized by insufficient lysosomal pH, which hindered TLR9 activation. These findings suggested the critical role of PDZD8-TLR9-NFkB axis as a novel pathway for regulating tubular inflammation.

Conclusions: Tubular PDZD8 regulates TLR9-NFkB inflammatory pathway through its regulation of lysosomal function via ER-lysosome interaction.

SA-PO102

FBF1 Deficiency Protects against Chronic Progression of Cisplatin-Induced AKI

Jielu H. Robichaud,[1] Chuan Chen,[1] Kai He,[1] Xiaobo Sun,[1] Zheng Dong,[2] Jinghua Hu.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Augusta University, Augusta, GA.*

Background: Cisplatin-induced nephrotoxicity exhibits hallmarks of acute kidney injury (AKI), yest its long-term exposure results in chronic kidney disease (CKD). Recent evidence shows that senescence of renal epithelial cells contributes to chronic progression after injury. However, how senescence is initiated in the injured kidneys remains poorly defined.

Methods: C57BL/6 mice were exposed to repeated low-dose cisplatin (RLDC) treatment consisting of 4 weekly injections of 8 mg/kg cisplatin. Mouse proximal tubular (BUMPT) cells were exposed to 4 cycles of 2 μM cisplatin treatment, with 7-hour cisplatin exposure followed by 17-hour cisplatin-free culture medium incubation. The level of cellular senescence was determined by measuring Senescent Associated (SA)-b-Gal staining, and levels of senescence markers as well as inflammatory Senescence-Associated Secretory Phenotype (SASP) markers. *Fbf1* deficiency in mice were established by homozygous *Fbf1*$^{tm1a/tm1a}$ mutant using the ''knockout first strategy''. *FBF1* knockdown BUMPT cell lines were generated by using *shRNA*. Western blotting, confocal imaging were used to determine the expression and subcellular localization of key components. Histological/immunofluorescent stain, serum BUN, and creatinine level were detected to investigate the progression of kidney injury. Immunoprecipitation or chromatin immunoprecipitation assay were performed to analyze protein-protein or protein-DNA interaction.

Results: We discover that RLDC treatment of C57BL/6 mice induced FBF1 upregulation in injured kidney tubules, which develop characteristics of cellular senescence. RLDC prompted FBF1 nuclear translocation to initiate senescence in Cisplatin-exposed BUMPT cells. FBF1 depletion effectively reduce senescent burden of BUMPT cells, reversed the profibrotic phenotype, and increased regenerative capacity following RLDC treatment. Consistently, deficiency of FBF1 *in vivo* suppressed senescence initiation, attenuated renal fibrosis and improved tubular repair. Mechanistically, we discovered that nuclear-translocated FBF1 triggered the recruitment of transcriptional factor HNF-1β to promyelocytic leukemia nuclear bodies (PML-NBs) to regulate senescence responses in damaged cells.

Conclusions: Suppression of the FBF1 pathway ameliorates adverse senescence-associated impacts and prevents AKI-CKD transition in cisplatin-treated kidneys.

Funding: NIDDK Support

SA-PO103

Secretory Leukocyte Protease Inhibitor as an Early Protective Protein and Potential Biomarker in Ischemia-Reperfusion-Induced AKI

Fei Chen,[1,3] Yuanyuan Wu,[3] Bin Yang.[1,2] *[1]Affiliated Hospital of Nantong University, Nantong, China; [2]University of Leicester, Leicester, United Kingdom; [3]Nantong University School of Medicine, Nantong, China.*

Background: Ischemia reperfusion (IR) injury is one of main causes of acute kidney injury (AKI) that is a common syndrome characterized by a sudden decline of renal function and lacking early diagnosis and effective intervention. Secretory leukocyte protease inhibitor (SLPI) is an acute response protein that is associated with IR-induced AKI and repair, but its dynamic change, exact roles and underlying mechanisms remain unknown.

Methods: C57BL/6 mice was used to establish a time-course model of IR-AKI. Bilateral kidney pedicles were clamped for 30 minutes (min) followed by reperfusion for 6 hours (h) to 4 weeks (w), the expression and localization of SLPI were monitored. *In vitro*, a mouse kidney epithelial cell line TCMK-1 was treated with hydrogen peroxide (H_2O_2) to mimic IR injury. The effects of erythropoietin-derived helix B surface peptide (HBSP) or targeted siRNA on SLPI expression were further observed. The downstream cellular apoptosis and injury markers, as well as the phagocytic ability of TCMK-1 cells through uptaking fluorescent-labeled *E. Coli* were then assessed.

Results: The increase of serum SLPI in IR group mice was at 12 h earlier than that of serum creatinine. The renal expression of SLPI was also up-regulated as early as 12 h post IR injury, as well as in TCMK-1 cells, prior to the changes of inflammation and apoptosis related indicators. SLPI was mainly located in tubular epithelial cells of IR kidney. HBSP significantly increased SLPI expression in a dose-dependent manner. Moreover, SLPI siRNA further increased cellular apoptosis, cleaved-caspase3, HMGB1, IL-6 and TNF-α in TCMK-1 cells treated with H_2O_2, but inhibited the phagocytosis of TCMK-1 cells.

Conclusions: SLPI was increased early upon IR-induced kidney injury, acting as a protective factor to regulate apoptosis, inflammation and phagocytosis. The up-regulation of SLPI may be one of the mechanisms that HBSP protects IR-AKI. In summary, SLPI not only serves as a potential biomarker, but also a protector against AKI.

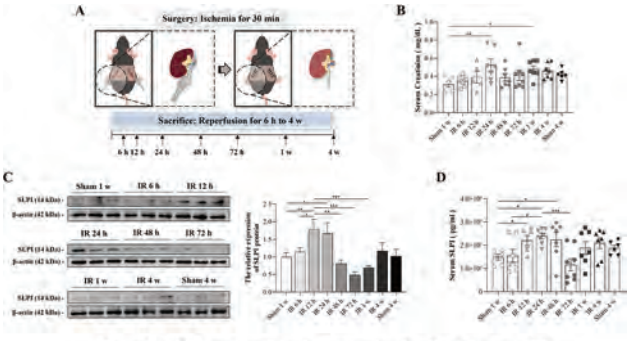


Figure 1. SLPI was significantly up-regulated at 12 h after renal IR.

SA-PO104

MG53 in Kidney Injury and Fibrosis

Min Zhang, Zhongguang Li, Pu Duann, Haichang Li, Sethu M. Madhavan, Brad H. Rovin, Pei-Hui Lin. Lin Lab. *The Ohio State University, Columbus, OH.*

Background: MG53 (TRIM72) is a muscle-predominant protein and functions as a circulating myokine that appears to confer tissue protection during ischemia-reperfusion (I/R) acute kidney injury and UUO-mediated kidney fibrosis. We discovered the functional duality of MG53 in kidney protection serving as a membrane repair protein and modulating the immune response during kidney inflammation. To further identify whether elevated level of either circulating MG53 or kidney proximal tubule-specific MG53 over-expression impact on kidney injury and fibrosis, we generated transgenic ctPA-MG53 mouse strain for conditional circulation and kidney MG53 over-expression to facilitate studying the role of MG53 in kidney disease and its impact on AKI-to-CKD transition.

Methods: We generated mouse strain "TRE-STOP^{flox}-tPA-MG53" ("ctPA-MG53") as conditional MG53 over-expression in kidney PTE cells and circulation. This mouse strain was bred to PEPCKcre (kidney PTE expression) mice. We examined and confirmed the doxycycline (DOX) induction of the ctPA-MG53 of kidney overexpression. We characterized these mouse strains – Control: "X/Y, ctPA-MG53" and the conditional overexpression "PEPCKcre/Y, ctPAMG53" on a DOX time-dependent MG53 expression. We established a kidney bilateral (bIRI) mouse model to study AKI-to-CKD transition. Additionally, using Lenti-viral gene transduction system, we successfully engineered in human PTE HKC8 cells with scramble knockdown, MG53 knockdown and MG53 overexpressing HKC8 cells as an *in vitro* system to study the cellular mechanisms.

Results: The transgenic "PEPCKcre/Y, ctPAMG53" mice follow a DOX-dependent and PTE specific MG53 induction. One week of DOX will induce a greater than 20-fold increase in kidney MG53 (protein) levels in proximal tubule cells and simultaneously high level of circulating MG53. Initial characterization of tissue expression of MG53 indicated an elevation in liver as well. We also did initial kidney functional characterization on these transgenic mice on DOX time-dependent induction. We subjected engineered HKC8 cells to various oxidative stress inducers and showed that MG53 over-expression confers better cell survival upon ROS stimulation.

Conclusions: We have established an *in vivo* animal system to study the impact of MG53 in AKI-to-CKD progression. We also established an *in vitro* system to investigate MG53 in ROS protection and its cellular mechanism.

Funding: NIDDK Support, Other NIH Support - NIA and NIAID

SA-PO105

Inflammatory Pathway in Crystalline Nephropathy: Modulation by Uromodulin and Its Potential Renoprotective Role

Larissa de Araujo,[1,2] Tarek M. El-Achkar,[2] Maria Oliveira-Souza.[1]
[1]Universidade de Sao Paulo Instituto de Ciencias Biomedicas, Sao Paulo, Brazil; [2]Indiana University School of Medicine, Indianapolis, IN.

Background: Uromodulin (UMOD) plays a crucial immunomodulatory role in the kidney. We hypothesize that this function is impaired in acute kidney injury (AKI) caused by crystalline nephropathy and that exogenous administration of UMOD may offer a renoprotective effect in this condition.

Methods: 8-week-old C57BL/6J mice were randomly allocated into four groups: 1. Control (saline 0.9%,i.p); 2. UMOD (exogenous UMOD–5µg/animal, single injection i.p); 3. NaOx (sodium oxalate–9mg/100g of body weight, single injection i.p); 4. NaOx administration and UMOD treatment. The animals were placed in metabolic cages for 24 hours before euthanasia and organ harvest. The results presented as mean ± S.D. were analyzed by two-way ANOVA and a Bonferroni post hoc test using GraphPad Prism software. p<0.05 was considered statistically significant.

Results: Crystal-positive medullary and cortical areas were increased in NaOx group. Co-treatment with exogenous UMOD prevented medullary crystal formation [NaOx+UMOD:1.3±0.8vsNaOx:5.0±1.6,p=<0.0001. Interaction p=<0.0001], but not cortical. Protein-positive medullary and cortical areas were increased in NaOx group. The co-treatment with exogenous UMOD prevented these changes [Medullary=NaOx+UMOD:2.0±2.2 vs NaOx:17.1±17.5,p=0.0250. Interaction p=0.0554/ Cortical =NaOx+UMOD:0.8±0.4 vs NaOx:2.7±2.2,p=0.0397. Interaction p=0.0717]. Treatment with NaOx significantly increased mRNA expression for KIM-1, NGAL, Ki67, MCP-1, TNFα, IL-1β, IL-6, CXCL1, and CXCL10, consistent with kidney injury. The mRNA expression for CCL19 significantly decreased in NaOx group. Co-treatment with exogenous UMOD prevented these changes (Fold change from control for NaOx+UMOD vs. NaOx, respectively):KIM-1 [95.2±121.7 vs. 730.0±182.5,p=<0.0001. Interaction p=0.0001],NGAL [2.5±2.1 vs. 86.4±19.3,p=<0.0001. Interaction p=0.0001],Ki67[2.0±1.0 vs. 5.7±1.7,p=0.0001. Interaction p=0.0006],MCP-1[1.9±1.8 vs. 8.2±3.8,p=0.0008. Interaction p=0.0030],TNFα[1.3±0.7 vs. 4.0±2.2, p=0.0087. Interaction p=0.0216],IL-6[5.4±7.5 vs. 84.4±46.2,p=0.0002. Interaction p=0.0010], CXCL1[8.4±15.9 vs. 1.2±0.4,p=0.0001. Interaction p= 0.0003],CXCL10[1.0±0.5 vs. 6.5±3.2,p=0.0005. Interaction p= 0.0030],CCL19[1.0±0.4 vs.0.1±0.1,p= 0.0066. Interaction p=0.0014].

Conclusions: The exogenous UMOD may have a renoprotective effect on nephropathy crystalline-induced AKI by modulating kidney inflammation.

Funding: Government Support - Non-U.S.

SA-PO106

The Tubular Epithelial Role of SMOC2 in Aristolochic Acid Nephropathy

Peng Gao,[1,2] Jonatan Barrera-Chimal,[2] Nathalie Henley,[2] Casimiro Gerarduzzi.[1,2]
[1]Universite de Montreal Departement de Pharmacologie et Physiologie, Montreal, QC, Canada; [2]Hopital Maisonneuve-Rosemont Centre de Recherche, Montreal, QC, Canada.

Background: Acute kidney injury (AKI) is a prevalent clinical condition with a rising incidence, posing an increased risk of chronic kidney disease (CKD) development characterized by interstitial fibrosis. Our lab has previously shown the effects of the matricellular protein SMOC2 on fibroblasts in regard to renal fibrosis present within CKD patients and in vivo kidney models. However, its involvement in tubular epithelial cell injury during AKI and its transition into CKD has not been previously examined.

Methods: Wild-type and SMOC2 knock-out (KO) mice were subjected to aristolochic acid I (AAI) injection to induce nephrotoxic AKI (known as aristolochic acid nephropathy, AAN). To evaluate the underlying mechanism, bulk RNAseq analysis of WT and KO kidneys 3 days after AAI injection was performed. Primary mouse tubular epithelial cells (mTECs) and human proximal tubular epithelial cells (HK-2) were exposed to recombinant SMOC2 (rSMOC2) protein alone or in combination with AAI.

Results: SMOC2 expression was increased in AAI-treated mTECs and renal tubules in AAI-injected mice, which was accompanied with tubular injury. On day 3 after injection, SMOC2 KO kidneys had increased tubular necrosis and histological damage scores compared to WT AAI-injected mice. Bulk RNAseq analysis revealed an increased expression of proliferation-related genes (CCND1 and Mki67) in SMOC2 KO AKI mice. In vitro studies showed that rSMOC2 treatment alone did not affect the proliferation of HK-2 cells; however, when combined with AAI treatment, it induced complete cell cycle arrest.

Conclusions: In contrast to the proliferative role of SMOC2 in fibroblasts during renal fibrosis, we unexpectedly discovered a cell cycle arrest role of SMOC2 on TECs. SMOC2 deficiency accelerates tubular cell proliferation after AKI, which renders them vulnerable to cell death signals. Therefore, SMOC2 may be a novel and important modulator of cellular injury after AKI by assisting in cell cycle arrest, which allows more time for DNA damage to be repaired, thus preventing the proliferation of cells with genotoxic insults and potentially avoiding maladaptive epithelial responses to injury.

Funding: Government Support - Non-U.S.

SA-PO107

Ischemic AKI Modifies Expression of Immune Checkpoint Inhibitor TIGIT Ligands and Co-signaling Partners

Radhika Kapoor, Shishir K. Patel, Qisen Guo, Mahta F. Gooya, Hamid Rabb, Sanjeev Noel. Hamid Rabb's Group. *Johns Hopkins University, Baltimore, MD.*

Background: T cell immunoreceptor with Ig and ITIM domains (TIGIT) increases in kidney T cells following ischemic AKI and participates in the pathogenesis of AKI in mice. To explore how TIGIT mediates AKI, we investigated the effects of ischemic AKI on TIGIT interacting ligands (CD155, CD112, CD113) and co-signaling molecules (CD226, CD96, CD127, PD1)

Methods: C57BL6 mice underwent bilateral ischemia reperfusion (IR) injury. TIGIT ligand/co-signaling molecule expression was initially measured with western blotting at 24h and 18 days post-AKI. Flow cytometry was performed to identify the cell types that express TIGIT ligands and co-signaling partners at baseline and 24h post-IR. TIGIT positive (TIGIT+) and TIGIT negative (TIGIT-) cells were analyzed to examine TIGIT relationship with these molecules

Results: Western blotting showed enhanced expression of CD155 (5.6±0.5 fold; P<0.001) and CD112 (2.4±0.5 fold; P<0.01) 24h after AKI. At 18 days, CD155 expression returned to normal levels however, CD112 remained elevated (2.7-fold). CD113 expression was reduced 24h after AKI (0.7±0.2 fold; P=0.04) with normalization at 18 days. CD155 expression by FACS increased significantly in CD11b+ cells at 24h (26.7±4.7 vs 1.5±0.3% P<0.0001) compared to control. Conversely, TIGIT co-stimulatory counterpart CD226 decreased in CD4 (67.1±19.0 vs 46.0±10.3%; P<0.05), double negative (DN) (92.1±5.1 vs 61.4±10.8%; P<0.001) and NKT (91.2±3.5 vs 71.2±5.9%; P<0.001) cells at 24h. CD96 expression was not affected by IR injury. Analysis of TIGIT+ cells showed significant decrease in CD155 (22.4±19.7 vs 6.8±8.6%, P<0.05) and CD127 (42.6±20.3 vs 10.7±6.5%, P<0.05) in NK cells from post-IR kidneys. TIGIT+ cells expressed PD1 both at baseline and after IR injury in CD4 (52.1±12.6 and 66.7±7.1%), CD8 (76.3±18.2 and 84.1±8.5%) and DN T (42.9±17.7 and 47.4±15.3%) cells. PD1 significantly increased at 24h in TIGIT+ CD4 (66.7±7.1 vs 16.5± 4.6%; P<0.001), CD8 (84.10±8.5 vs 12.3± 6.0%, P<0.01) and DN T cells (47.4±15.4 vs 16.6±7.4%; P<0.01) compared to TIGIT- cells.

Conclusions: Ischemic AKI leads to increased TIGIT ligands CD155 and CD112, and modulates TIGIT co-signaling molecules CD226 and CD127. TIGIT and PD1 are co-expressed by a subset of kidney T cells at baseline and during AKI. TIGIT ligand/ signaling molecule interactions likely underlie TIGIT effects on AKI

Funding: NIDDK Support

SA-PO108

Membrane Tumor Necrosis Factor (TNF) Drives Progression to Fibrosis after Kidney Injury via TNFR1 Activation

Charikleia Katsouridi, Andreas Herrlich, Eirini Kefalogianni.
Washington University in St Louis, St Louis, MO.

Background: Global TNF blockade reduces AKI-to-CKD transition, but the underlying mechanisms are unclear. TNF signaling is complex as it involves soluble and membrane-bound forms of TNF (sTNF and mTNF respectively) and of its two receptors, TNFR1 and TNFR2. As a result, TNF controls multiple signaling pathways with overlapping, separate, or even opposite functions. We hypothesized that targeting individual components of TNF signaling would increase our understanding of kidney disease progression and point to more specific targets for therapies.

Methods: We used mouse models of kidney injury and progression to fibrosis, wild-type mice, knockout mice, or mice with TNF or TNFR1 mutations that prevent cleavage and release of their soluble forms, and single-cell/nuclei RNAseq data analysis.

Results: Using pharmacological and genetic approaches, we show that mTNF, rather than sTNF, drives progression to fibrosis after kidney injury. In addition, mice that cannot cleave TNFR1, therefore cannot terminate its signaling, show increased fibrosis after injury. The latter phenotype is also mTNF-dependent. Serum creatinine and BUN levels on day 1 post-injury were not different between groups, suggesting that the observed outcomes are not the result of initial injury susceptibility differences. Kidney accumulation of macrophages, a key TNF-expressing cell type, accompanies mTNF-TNFR1-driven progression to fibrosis. Single-cell/nuclei RNAseq analysis showed that, during the transition to fibrosis, TNFR1 gene signature is enriched in endothelial and tubular cell subpopulations, suggesting that these cells potentially receive the profibrotic mTNF-TNFR1 signals.

Conclusions: Our results identify that the mTNF-TNFR1 signaling axis drives AKI-to-CKD transition and represents a potential target for therapeutic interventions.

Funding: NIDDK Support, Private Foundation Support

SA-PO109

Establishment of a New Detection Method for Senescent Cells in Injured Kidneys and Proof of Their Relationship to Failed-Repair Proximal Tubules

Ryo Yamada,[1] Yohei Iwashige,[1] Takuya Morinishi,[1] Koji Muro,[1] Shigenori Yamamoto,[1] Toshio Kitamura,[2] Motoko Yanagita.[1] Cell Cycle & Cellular Senescence Group. *[1]Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu, Kyoto, Japan; [2]Foundation of Biomedical Research and Innovation at Kobe, Kobe, Japan.*

Background: Cellular senescence occurs in response to repeated passages, persistent DNA damage, and oxidative stress and is characterized by permanent growth arrest. Recently, accumulation of senescent cells in vivo and their correlation with organ dysfunction has been reported; however, a highly sensitive method to identify senescent cells *in vivo* has not yet been established.

Methods: The cell cycle of the proximal tubular cells was evaluated in mice expressing the proximal tubule-specific G0 marker (*Ndrg1CreER^{T2} $^{/+}$: R26-mVenus-p27K$^{-/+}$*). The G0 marker is mVenus-p27K^{-} and is usually used to identify cells in the quiescent phase (G0 phase). We also performed spatial transcriptomics of G0 marker-positive cells using photo-isolation chemistry (PIC) based system.

Results: Using adult G0 marker mice, almost all proximal tubular cells (PTCs) were stayed at G0 phase under physiological conditions. In the chronic phase of kidney injury models, most PTCs became G0^{+}, but some G0^{+} cells exhibited nuclear abnormalities with Cyclin D1 positivity (G0 double positive cells: G0^{DP} cells). G0^{DP} cells exhibited various features of cellular senescence in tissue. In addition, G0^{DP} cells were included within the VCAM1^{+} failed-repair PTCs (FR-PTCs), which were recently attracted attention for their inflammatory features. After injury, most FR-PTCs were G0^{+} (≥ 90%), and Cyclin D1 positivity rate gradually increased up to 20-30% depending on the injury type. The PIC-based RNA-seq study also revealed that G0^{DP} cells exhibited features not only of FR-PTC but also of cellular senescence compared to G0^{+} cells in the vehicle group and Cyclin D1^{-} G0^{+} cells (G0 single positive cells: G0^{SP} cells) within FR-PTCs. Timelapse imaging of primary PTCs from G0 marker mice, treated with doxorubicin (DOXO), continuously expressed the G0 marker, and their cell cycle was permanently arrested. DOXO-treated primary PTCs further obtained Cyclin D1 positivity with senescent phenotypes.

Conclusions: G0 marker with Cyclin D1 expression can be a useful tool for identifying senescent proximal tubular cells under DNA damage conditions, both *in vivo* and *in vitro*.

SA-PO110

Deficiency of Hedgehog Interacting Protein (Hhip) in Endothelial Cells Prevents Kidney Ischemia-Reperfusion-Mediated Renal Tubular Cell Senescence

Yuchao Pang,[1,2] Junzheng Peng,[1] Xin-Ping Zhao,[1] Shiao-Ying Chang,[1] Min-Chun Liao,[1] Alain Rivard,[2] Julie R. Ingelfinger,[3] John S. Chan,[1,2] Shao-Ling Zhang.[1,2] *[1]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Universite de Montreal, Montreal, QC, Canada; [3]Harvard Medical School, Boston, MA.*

Background: Acute kidney injury (AKI) caused by renal ischemia/reperfusion (R I/R) injury is a major clinical issue lacking viable therapies, and with incompletely delineated underlying mechanisms. Given the important roles of hedgehog interacting protein (Hhip) in glomerular endothelial cells (ECs), we asked whether Hhip knockout (KO) in ECs prevents R I/R-induced kidney injury *in vivo* and *in vitro*.

Methods: Both male Hhip^{EC} KO and control Hhip$^{fl/fl}$ mice at 10-weeks of age were subjected to 45 minutes of unilateral R I/R or sham surgery along with contralateral nephrectomy. The time course of AKI was followed at Days 1, 3 and 7. We also studied naïve renal proximal tubular cells (IRPTCs) exposed to the conditioned media harvested from mouse endothelial cell (mECs) with or without Hhip (siRNA) ± cisplatin (20μM) treatment.

Results: Compared to the respective sham controls, R I/R mice (Hhip^{EC} KO and Hhip$^{fl/fl}$) lost body weight starting from Day 1 to Day 7. In line with the AKI time course, Hhip$^{fl/fl}$-R I/R mice had higher mortality with significant kidney apoptosis documented by IVISense™ Annexin-V 750 fluorescent imaging probe; increased urinary albumin-to-creatinine ratio; and displayed renal dysmorphology (PAS, Masson's trichrome and Sirius red) with enhanced Cystatin C- and kidney injury molecule-1 immunoexpression in their kidneys. Notably, renal tubular cell senescence (SA-β-galactosidase, p21, p16, MCP-1 staining) was significantly increased in Hhip$^{fl/fl}$-R I/R mice. In contrast, those changes were significantly ameliorated in the kidneys of Hhip^{EC} KO -R I/R mice. *In vitro*, naïve IRPTCs exposed to the conditioned media harvested from mECs treated with cisplatin exhibited higher cellular senescent activity with enlargment of nuclear size with both mono- or multi-nuclei and increased cytoskeleton destabilization as evidenced by dysmorphic patterns of α-tubulin and F-actin staining. Those changes were largely prevented in naïve IRPTCs exposed to the conditioned media from Hhip KO mECs treated with cisplatin.

Conclusions: Our data suggest that Hhip KO in ECs prevented or ameliorated AKI-induced renal tubular injury. This potential protection may be mediated, at least in part, by the inhibition of Hhip-mediated tubular cell senescence.

SA-PO111

Glutathione S-transferase Mu-1 (GSTM1) Deficiency Exaggerates Cisplatin Nephrotoxicity

Luojing Chen. *University of Rochester Medical Center, Rochester, NY.*

Background: Cisplatin is the first line chemotherapeutic agent for several cancers. However, its use is limited by significant toxicity, including acute kidney injury (AKI) in up to 30% of patients. Increased reactive oxygen species (ROS) generation plays a key role in cisplatin nephrotoxicity (CN). Glutathione-S-transferase Mu-1 (*GSTM1*) gene encodes GSTM1 enzyme that functions in the detoxification of electrophilic compounds. We previously reported that *Gstm1* knockout (KO) mice have increased oxidative stress and susceptibility to kidney injury in chronic kidney disease (CKD) models, and CKD patients carrying the highly common null variant of *GSTM1* gene are more susceptible to CKD progression. Here, we investigate the effect of GSTM1 in a chronic CN mouse model of AKI and in a human HK2 proximal tubular epithelial cell (PTEC) line model.

Methods: Wild-type (WT) and *Gstm1* KO male mice (12 weeks old) on FVB background were treated with cisplatin (9mg/kg) once per week for 4 weeks via IP injection. HK2 PTEC line deficient in *GSTM1* was used to generate a stable *GSTM1* overexpressing cell line (HK2-Tg). Cells were treated with cisplatin (60uM) for 24 hrs. Intracellular ROS was measured using ROS Assay Kit, and mitochondrial superoxide was measured by MitoSox. The color intensity of the images (three random fields of each image) was quantitated with Image J. Live cell numbers were counted with Trypan blue.

Results: After 4 weeks cisplatin treatment, *Gstm1* KO mice had a significant increase in serum creatinine measured by mass spec (0.13±0.157mg/ml), compared to WT mice (0.06±0.006 mg/ml) (n = 6 each, p=0.0043). There was a trend toward increase in BUN level (22.16 vs 14.77, p=0.309) in KO mice. Compared to HK2-Tg cells expressing *GSTM1*, HK2 cells deficient in *GSTM1* displayed fewer % of live cells: HK2 39±2.95 vs HK2-Tg 54±2.37; p=0.003. Compared to vehicle, cisplatin treatment resulted in a higher fold of intracellular ROS production in HK2 compared to HK2-Tg PTECs (6.6 vs 3.9; p=0.03). Similarly, HK2 PTECs showed a larger fold increase in mitochondrial ROS level compared to HK2-Tg PTECs (23.5 vs 17.6; p=0.01).

Conclusions: GSTM1 deficiency increases susceptibility to CN, which can be attributable to increased intracellular and mitochondrial ROS generation. Understanding how GSTM1 regulates ROS signaling pathway may lead to a novel therapeutic target in CN.

Funding: NIDDK Support

SA-PO112

Depletion of Salvage NAD+ Biosynthesis Exerts Opposing Effects in Inflamed Proximal Tubule vs. Microvascular Endothelium

Valerie Etzrodt, Liping Chen, Amanda J. Clark, Kyle Q. Vu, Marie Christelle Saade, Samir M. Parikh. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Nicotinamide phosphoribosyl transferase (NAMPT) is the rate-limiting enzyme of the nicotinamide adenine dinucleotide (NAD+) synthesizing salvage pathway. NAMPT's roles in the kidney, particularly in proximal tubule cells and adjacent microvascular endothelial cells, are of significant interest due to their vital functions in maintaining renal homeostasis. We hypothesized that NAMPT enzymatic function is necessary for renal tubular resilience to injury whereas its effects in the endothelium may be dispensable given the low metabolic activity of the latter.

Methods: In vivo disease models: LPS 17.5 mg/kgBW; in vitro models: human proximal tubule kidney cells (HK2), human umbilical vein EC (HUVECs), transendothelial electrical resistance, NAD(H) biochemical assessments.

Results: In a murine model of systemic inflammation, total kidney NAMPT was upregulated. This effect appeared to localize to ECs. HUVECs treated with inflammatory stimuli confirmed dose-dependent induction of NAMPT expression along with canonical markers of vascular inflammation such as intercellular adhesion molecular 1 (ICAM-1). In contrast, HK2 cells exhibited no induction of NAMPT following exposure to inflammatory stimuli. As expected, knockdown or pharmacological inhibition of NAMPT in HK2 cells depleted intracellular NAD+ and exacerbated the expression of kidney injury markers following inflammation. In contrast, knockdown or pharmacological inhibition of NAMPT in inflamed HUVECs significantly attenuated expression of ICAM-1. Interestingly, reintroduction of β-nicotinamide mononucleotide, in NAMPT deficient HUVECs abrogated the anti-inflammatory effect.

Conclusions: Kidney endothelial NAMPT may be markedly induced during systemic inflammation. Whereas NAMPT's major role in the renal tubule may be promote NAD+ homeostasis, NAMPT in the endothelium may be a potent regulator of vascular inflammation. Future studies have to clarify how NAMPT can be cell-specifically targeted in acute inflammation.

Funding: NIDDK Support, Other NIH Support - 5R01DK095072-10

SA-PO113

PDK4/SMAD3/HIF-1α Circle Enhances AKI Susceptibility in Diabetic Kidney Disease (DKD) through Fibrosis

Jianbo Guo,[1,2] Haidi Li,[3] Yifan Wang,[1,2] Baoyi Shao,[1,2] Jianan Wang,[3] Hai-Yong Chen.[1,2] *[1]School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [2]Department of Chinese Medicine, The University of Hong Kong-Shenzhen Hospital, Hong Kong, China; [3]Anhui Medical University, Hefei, China.*

Background: AKI poses significant risks of mortality and organ dysfunction, especially in DKD. Excessive accumulation of ROS is implicated in AKI pathogenesis. Pyruvate dehydrogenase complex is phosphorylated by pyruvate dehydrogenase kinase 4 (PDK4), leading to increased ROS. Previous studies have revealed that TGF-β/SMAD3 signaling activation promotes fibrosis in DKD, while HIF-1α could be activated by phosphorylated SMAD3. However, the regulatory relationship among PDK4, SMAD3, and HIF-1α in AKI susceptibility in DKD remains unclear.

Methods: The ischemia/reperfusion (I/R) induced AKI models were conducted in db/m and db/db mice. Kidney epithelial cells were treated high glucose with/without the hypoxia and reoxygenation (HG + H/R) conditions. Chromatin immunoprecipitation (ChIP)-qPCR were utilized to identify the promoter binding site at gene transcriptional level. Gain to loss-function of inter-players were used to further confirm the results.

Results: Oxidative stress levels were significantly increased in *vivo* and in *vitro* models, including increased SOD and GSH levels and decreased MDA levels. I/R-induced AKI in db/db mice and the HG + H/R model exhibited significant elevations in PDK4, p-SMAD3, HIF-1α, fibronectin and KIM-1. Inhibition of PDK4 by using PDK4-IN-1 hydrochloride down-regulated the expressions of p-SMAD3, HIF-1α, fibronectin and KIM-1. Inhibition of p-SMAD3 by using SIS3 down-regulated the expressions of PDK4, HIF-1α, fibronectin and KIM-1. Inhibition of HIF-1α by using YC-1 down-regulated the expressions of PDK4, p-SMAD3, Fibronectin and KIM-1. Besides, overexpressed PDK4, p-SMAD3, or HIF-1α by constructing plasmids up-regulated the expressions of other genes. ChIP results showed that p-SMAD3 protein could bind to HIF-1α promoter and up-regulate HIF-1α transcription.

Conclusions: PDK4, mediated by SMAD3, increases HIF-1α transcription and further up-regulate the PDK4 expression. The circular pathway increases the level of fibrosis and enhances AKI susceptibility in DKD.

Funding: Government Support - Non-U.S.

SA-PO114

Effect of Semaglutide in an Ischemic AKI Model

Juliana V. Silva, Guilherme H. Ferreira Vieira, Eloiza O. Silva, Maria De Fatima Vattimo, Camila Lima, Jessica P. García, Maikol L. Gonçalves, Carla D. Victoria, Alessandra Oliveira Maia. *Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Semaglutide is an antidiabetic drug analogous to human GLP-1, the scarcity of data on its effects on chronic and acute cardiovascular and kidney diseases limits its use by the general public. Acute kidney injury affects approximately 49% of patients undergoing major cardiovascular surgery, in addition to a mortality rate of over 50%, which justifies the possibilities of seeking to prevent AKI. Objectives: To evaluate the effect of oral semaglutide on the renal function of rats subjected to an animal model of ischemia/reperfusion

Methods: This is an experimental study with adult male Wistar rats, weighing 250-300g, planned in groups: SHAM(control, with simulated clamping of the renal pedicle); GLP-1(semaglutide, oral;3mg/day;5 days); Ischemia and Reperfusion (IR) (clamping of bilateral renal pedicles for 30 minutes, followed by reperfusion) and GLP-1+IR(semaglutide followed by IR). Renal function was assessed by inulin clearance, serum creatinine and urinary flow rate and oxidative profile was assessed by urinary peroxides FOX, lipid peroxides(TBARS) and nitric oxide(NO)

Results: The I/R group showed an increase in serum creatinine and urinary NGAL, a decrease in urinary flow, and a reduction in Clin, while the GLP-1+IR group showed an increase in Clin compared to the I/R group. Furthermore, the GLP-1+IR group showed an increase in oxidative metabolites(FOX, TBARS and NO) when compared to IR.

Conclusions: Semaglutide showed a renoprotective effect associated with its antioxidant role that prevented the reduction in renal function caused by ischemic AKI.

Funding: Government Support - Non-U.S.

Table 1 Renal Function

Groups	n	Urinary Flow (ml/min)	Serum creatinine (mg/dl)	Inulin *Clearance* (ml/min)	Urinary NGAL (ng/mL)
SHAM	5	0,013±0,002	0,31±0,06	0,81±0,06	55,1±18,0
GLP-1	5	0,030±0,013 [a]	0,51±0,1	0,75±0,13	50,1±13,3
IR	5	0,011±0,005 [b]	2,27±0,6 [ab]	0,24±0,03 [ab]	142,4±30,0 [ab]
GLP-1+IR	5	0,015±0,060 [c]	0,95±0,31 [ac]	0,51±0,08 [abc]	91,5±28,0 [c]

Results expressed as mean±standard deviation. SHAM: Control group; GLP-1: Glucagon Like Peptide; I/R: Ischemia and Reperfusion:

[a] p<0,0001 *vs* SHAM

[b] p<0,0001 *vs* GLP-1

[c] p<0,0001 *vs* IR

[d] p<0,0001 *vs* GLP-1+IR

Table 2. Oxidative and antioxidant profile.

Grupos	n	Urinary peroxides (nmol/g de urinary creatinine)	Lipid peroxidation(mnol/g de urinary creatinine)	Urinary nitrate (nmol/g de urinare creatinine)
SHAM	5	3,3±0,6	0,18±0,01	16,0±5,2
GLP-1	5	3,2±1,1	0,14±0,04	61,1±25,8 [a]
IR	5	15,9±2,8 [ab]	1,78±0,41 [ab]	174,5±13,0 [ab]
GLP-1 + IR	5	7,7±2,6 [abc]	0,20±0,05 [c]	68,0±20,1 [ac]

Results expressed as mean±standard deviation. SHAM: Control group; GLP-1: Glucagon Like Peptide; IR: Ischemia and Reperfusion:

[a] p<0.0001 *vs* SHAM

[b] p<0,0001 *vs* GLP-1

[c] p<0,0001 *vs* IR

[d] p<0,0001 *vs* GLP-1+IR

SA-PO115

Enhancing Glutathione Pathway Activity for Improved Resilience to Kidney Injury

Shun-Yang Cheng, Kari A. Koppitch, Andrew P. McMahon. *University of Southern California, Los Angeles, CA.*

Background: Males are more susceptible to AKI than females. What underlies superior resilience and increased tolerance to kidney injury in female? Our lab's analysis identified 984 genes with sex-biased expression: proximal tubule (PT), key target in many injury scenarios emerging as source of this sex-specific variability. Excessive ROS contribute to PT damage. Female-biased genes include glutathione pathway members, Gsts, that could potentially neutralize ROS. We hypothesize that female-enriched gene expression in glutathione pathway components may enhance resilience of female PT to IRI-induced oxidative stress. If so, activating these genes in male proximal tubules is predicted to increase resilience to IRI

Methods: To generate appropriate genetic tools, we identified and verified enhancers driving PT-restricted expression of HNF4a. Transgenic mice were generated that drive Gst transgene to PT and examined for effect on IRI response in male mice

Results: Identifying proximal tubule-specific enhancers ensures that overexpression is from target cell type. Using ATAC-seq, we identified conserved open chromatin, 5' and 3' of HNF4a promoter, in mouse and human PT cells that showed strong enhancer predictions in ENCODE datasets. Transgenic lacZ reporter studies using knock-in at a safe harbor locus demonstrated PT-restricted reporter activity of human enhancers in mouse kidney. Next, we generated a transgenic line in which Gst gene that shows marked female-enriched expression in PT cells is expressed under control of human HNF4A enhancer. To examine potential protective effects of elevated Gst levels in male mice, severe IRI was performed following unilateral nephrectomy, and serum creatinine levels and GFR determined to evaluate kidney function 2 and 28 days post IRI, respectively. Preliminary data suggests protective effect of ectopic Gst expression in male kidney: despite similar level of injury as measured by creatine levels 2 days after IRI, transgenics show improved post IRI survival and higher GFR at 28 days

Conclusions: Our research identified human HNF4A enhancers that will have broad utility for targeting gene expression to proximal tubule cells. Initial data addressing potential renal protective role for Gst, in male PT cells, are encouraging. Future studies will focus on earlier responses and rigorously assessing injury outcomes in transgenic and control male mouse kidneys

Funding: NIDDK Support

SA-PO116

Metabolomics Assessment Reveals Amino Acid Depletion in Skeletal Muscle after Ischemic AKI in Mice

Amy S. Li, Zhibin He, Kayo Okamura, Colin C. Anderson, Julie Haines, Sarah Faubel. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Acute kidney injury (AKI) is a systemic disease that affects energy metabolism in various remote organs, including heart, lungs, and liver, in murine models of AKI. However, AKI-mediated effects on skeletal muscle have not been comprehensively assessed.

Methods: Ischemic AKI was induced in 8-10-week-old male C57BL/6J mice via bilateral pedicle clamping for 25 minutes. Untargeted mass spectrometry metabolomics was performed on gastrocnemius samples at 24-hrs and 72-hrs after AKI with a targeted analysis on energy & redox metabolism. MetaboAnalyst 6.0 was utilized for normalization of the data via autoscaling and statistical analysis.

Results: Univariate ANOVA revealed that 166 of 175 (95%) named metabolites were significantly different among the 5 experimental groups (unmanipulated, 24-hr sham & AKI, 72-hr sham & AKI). The 24-hr AKI group exhibited the most distinct phenotype as demonstrated by principal component analysis (Fig. 1). 30% (50/166) and 16% (27/166) of analytes were significantly different at 24-hrs and 72-hrs after AKI, respectively, compared to sham controls. Hierarchical clustering analysis of the 50 analytes in the 24-hr AKI vs. sham group reveal that 66% (33/50) are reduced (Fig. 2), majority of which are amino acids and their derivatives, which was further supported by pathway analysis.

Conclusions: This is the first study to describe changes of the skeletal muscle metabolome after AKI in a murine model. The metabolome of murine gastrocnemius exhibits significant change after ischemic AKI, particularly at 24 hours. Multiple amino acids and their derivatives are significantly reduced, consistent with the notion that AKI is a hypercatabolic disease, which may lend insight into the mechanistic underpinnings of adverse sequelae associated with AKI in patients.

Funding: NIDDK Support

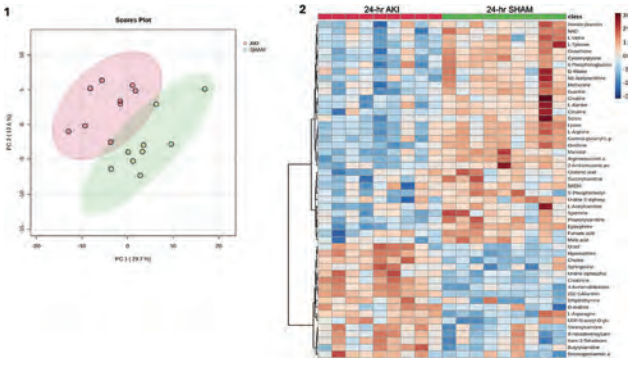


Fig 1. PCA plot of murine gastrocnemius metabolome at 24-hrs after AKI vs sham.
Fig 2. HCA heat map of top 50 analytes in murine gastrocnemius that are significantly different 24-hrs after AKI vs sham.

SA-PO117

Mitochondria Functional Study in Cisplatin-Induced AKI

Fnu Vikky, Rihab Bouchareb. *Temple University, Philadelphia, PA.*

Background: Acute kidney injury (AKI) results from a generalized or localized impairment of oxygen and nutrient delivery to the kidney. As a result of this imbalance, the tubular epithelial cells undergo injury, which manifests as cell death by apoptosis and necrosis, with reduced kidney function, impaired water and electrolyte homeostasis, and reduced excretion of waste products of metabolism. Administration of the chemotherapeutic agent cisplatin leads to acute kidney injury (AKI). Cisplatin-induced AKI (CIAKI) has a complex pathophysiological map, which has been linked to apoptosis, oxidative and stress. objective:Since the pathophysiology of AKI is reflected in mitochondrial function dysregulation, we aim to examine the role of mitochondria in the Cisplatin model of AKI in kidney tubular cells at different time points

Methods: We isolated tubular cells from *Pham* mice. The cell's mitochondria are tagged with Dendra2 (mito-Dendra2), a photo-convertible fluorescent protein, which enables us to examine the fission-fusion events in response to stimuli

Results: The confocal microscopy shows that upon treatment of the cells with cis-platin, mitochondria were more fragmented and profoundly affected photobleaching. The mitochondrial movement was significantly reduced as compared to untreated control, and the stress was delayed. The genes corresponding to mitochondrial function were analyzed by qPCR. It was interesting to find that the genes related to mitochondrial functionalities (COXI) and biogenesis (PGC1a) were upregulated in 12hr treatment with cisplatin; however, cells treated with cisplatin for 24hrs had increased oxidative stress (~2 folds). It was observed that the mitochondria biogenesis genes were drastically reduced in 24-hour treatment. Further, ALCLAT-1, a gene that promotes autophagy, was upregulated, indicating that the cells try to negate the stress due to cisplatin treatment; however, prolonged treatment reduces the transcriptional activity.

Conclusions: Our preliminary results suggest that cisplatin treatment leads to compromised mitochondrial functions and increased oxidative stress.

Funding: NIDDK Support

SA-PO118

Glucose-Pyruvate Metabolism in Sepsis-Associated AKI

Prabhleen Singh.[1,2] [1]*University of California San Diego, La Jolla, CA;* [2]*VA San Diego Healthcare System, San Diego, CA.*

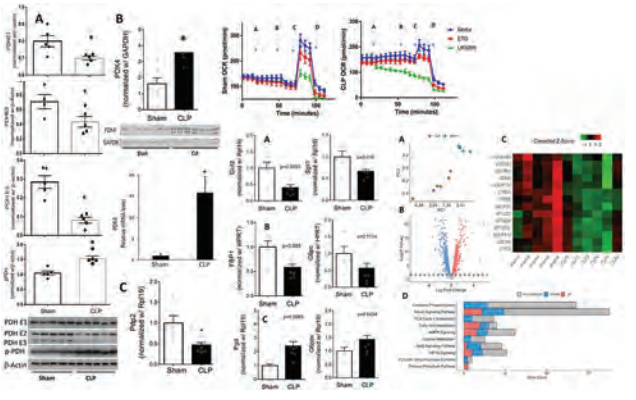
Background: *Metabolic reprograming* from oxidative to glycolytic in proximal tubules (PT) in AKI has been proposed. However, in the cecal ligation and puncture (CLP) model of sepsis-AKI (sAKI), we found dynamic changes with reduced oxidative metabolism (OXPHOS), increased glycolytic enzymes, but decreased functional glycolysis in PTs. Pyruvate, from glucose via glycolysis, can convert to lactate or fuel OXPHOS and is regulated by pyruvate dehydrogenase (PDH) and inhibited by PDH kinase (PDK). We examined the PDH-PDK axis, which is key in the control of OXPHOS and glycolysis, in sAKI.

Methods: Kidneys from sham or CLP mice were harvested at 24 hours. Protein and mRNA expression of key components of glucose and pyruvate metabolism were examined. *Seahorse Substrate Oxidation Stress kits were used* to interrogate substrates that fuel OXPHOS real-time with specific inhibitors- etomoxir (ETO) for fatty acids (FA) and UK5099 for pyruvate in fresh isolated PTs. RNA sequencing and metabolomics were also performed.

Results: PDH E1, E2, E3 were reduced, phospho-PDH and PDK4 were increased in CLP. PDP, which activates PDH, and PDH enzyme activity were decreased in CLP. Glucose transporters (GLUT2, SGLT1), gluconeogenic enzymes (FBP and G6pc) were decreased, but pentose phosphate pathway enzymes (G6pdx and Pgd) were increased in CLP. PTs from shams showed no change with ETO or UK5099 but in CLP PTs ATP-linked and maximal respiration were lower with UK5099 showing reliance on pyruvate. RNA sequencing showed differential regulation of OXPHOS, TCA, and glucose metabolism in CLP kidneys with gene expression changes consistent with above for pyruvate and glucose metabolism. Targeted metabolomics showed pyruvic acid as among the top 25 metabolites altered in CLP kidneys.

Conclusions: Our results advance the findings of dynamic and complex metabolic changes in CLP kidneys. Inactivation of PDH by increased PDK4 diverts pyruvate away from OXPHOS, which can lead to less ATP and more tubular injury, given the reliance of OXPHOS on pyruvate in CLP PTs. Therapeutics targeted to tubular metabolism via PDH-PDK axis can impact sAKI.

Funding: NIDDK Support, Veterans Affairs Support



SA-PO119

Protective Effects of Pemafibrate against Ischemia-Reperfusion-Induced AKI in Mice

Yuki Nakayama, Takayuki Nimura, Kosuke Yamaka, Daiki Aomura, Koji Hashimoto, Yuji Kamijo. *Shinshu Daigaku, Matsumoto, Japan.*

Background: The effect of peroxisome proliferator-activated receptor alpha (PPARα) on acute kidney injury (AKI) is unknown due to the limited literature investigating the renoprotective effect of PPARα in AKI using fenofibrate. Pemafibrate, a novel PPARα modulator, is characterized by high selectivity for PPARα. In this study, we aimed to explore the function of PPARα using pemafibrate in renal ischemic injury.

Methods: Twelve-week-old male C57BL/6J mice were divided into two groups: the pemafibrate group, which received mixed pemafibrate in their diet for 1 week before surgery, and the normal diet group. Bilateral 35-minute ischemia-reperfusion (I/R) was performed on the mice to produce an ischemic AKI model (n=9 in both groups). A sham

operation was also performed for control (n=3 in each group). All mice were sacrificed 24 hours after I/R or sham operation. Renal function, histology, and tissue gene expression were evaluated.

Results: Serum creatinine levels were significantly lower in the pemafibrate group than in the normal diet group. Pathological findings showed mild expansion of the urinary tubule lumen and slight loss of the brush border in the pemafibrate group compared to the normal diet group. RNA analyses revealed decreased expressions of urinary tubule injury markers and inflammatory genes. The renal PPARα expression was not significantly different between groups. However, oil red O staining showed less fat droplet accumulation, and the gene expressions of enzymes involved in fatty acid oxidation and anti-oxidative stress, which are target genes of PPARα, were up-regulated in the pemafibrate group.

Conclusions: Pemafibrate treatment attenuated ischemic AKI by activating fatty acid metabolism and reducing oxidative stress.

SA-PO120

Ablation of Type 2 IP3R, a Calcium Channel Located on the Organelle Contact Site, Improves the Repairment of Cell Survival and Endoplasmic Reticulum-Mitochondria Function in Tubular Cells

Qi Li, Sho Hasegawa, Yuto Takenaka, Masaomi Nangaku, Reiko Inagi.
Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Bunkyo-ku, Japan.

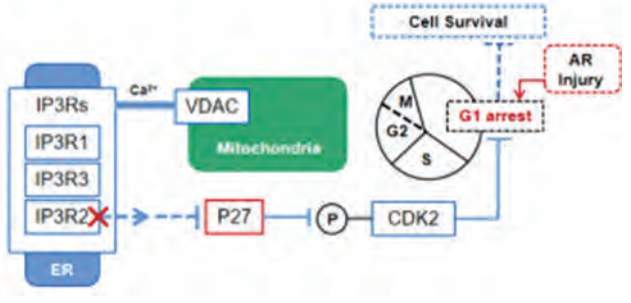
Background: The renal proximal tubules (PT) are susceptible to ischemia-reperfusion injury (IRI). The Inositol trisphosphate receptors (IP3Rs) are calcium-release channels located on endoplasmic reticulum (ER). IP3Rs, composed of 3 isoforms, mediate calcium flux from the ER to the mitochondria via mitochondria-associated ER membrane (MAM) and multiple cellular functions. However, isoform-specific IP3R function in PT cells still remains unknown.

Methods: To assess the isoform-specific IP3R function in kidney tubules, the isoforms were separately knocked down in the human proximal tubular cell line, HK-2 cells. As a mimic of IRI, HK-2 cells were exposed to 24h anoxia followed by 4h reperfusion (AR) and assessed the cell fate and organelle function by corresponding assays and fluorescent probes.

Results: Among 3 isoforms, knocking down IP3R2 in HK-2 cells decreased the cell number stacked in the cell cycle G1 phase and improved the cell proliferation rate under the AR conditions. In contrast, knocking down IP3R1 or IP3R3 did not protect the cells from G1 arrest. Interestingly, IP3R2 knockdown did not alter the AR-induced calcium flux after AR, a major MAM function in ER-mitochondrial interaction. Mechanistically, IP3R2 knockdown reduced the AR-induced p27 upregulation, which promotes the CDK2 activity, leading to the cell's entry to an efficient S phase. It was consistent with that induction of senescence-associated secretory phenotype (SASP: TGF-b1 and IL-6) by AR was significantly ameliorated by IP3R2 knockdown. Importantly, the IP3R2 knockdown ameliorated organelle stress caused by AR: ER stress and mitochondrial stress (depolarization and dynamics) were ameliorated by IP3R2 knockdown, but not IP3R1 and IP3R3.

Conclusions: IP3R2 knockdown improved cell cycle status and ER-mitochondria function in PT cells with AR injury, suggesting the novel pathophysiological significance for IP3R2 on cell fate and ER-mitochondrial homeostasis under IRI by a calcium flux-independent pathway.

Funding: Government Support - Non-U.S.



SA-PO121

Slc25a21 in Cisplatin-Induced AKI: A New Target for Renal Tubular Epithelial Protection by Regulating Mitochondrial Metabolic Homeostasis

Huimei Chen,[1] Aihua Zhang,[2,3] Xin Su.[2,3] *[1]Duke-NUS Medical School Cardiovascular & Metabolic Disorders Programme, Singapore, Singapore; [2]Nanjing Medical University, Nanjing, China; [3]Children's Hospital of Nanjing Medical University, Nanjing, China.*

Background: Acute kidney injury (AKI) is a global health issue frequently induced by cisplatin therapy. Dysfunctional mitochondria in tubular epithelial cells are key drivers of kidney injury, and the regulation of mitochondrial metabolites is proposed to be beneficial in kidney protection. Here, we highlighted that maintaining a mitochondrial 2-oxodicarboxylate carrier, Slc25a21 in cisplatin-induced AKI protected against tubular apoptosis and inflammation by restoring mitochondrial metabolic homeostasis.

Methods: Kidney samples from AKI patients and cisplatin-induced mice models were to evaluate the association of renal Slc25a21 expression and AKI progression. Slc25a21 expression was upregulated using AAV9 system via in situ injection and plasmid transfection in kidney proximal tubular epithelial cells. AKI severity was evaluated through histological assessments and kidney function tests. Cellular apoptosis and inflammatory response were assessed using TUNEL assays, flow cytometry, and ELISA for cytokines (e.g., IL-18 and TNFα). Additionally, mitochondrial function and metabolic alterations were examined through Seahorse assays and metabolomics analysis.

Results: It was observed that renal Slc25a21 is highly expressed in proximal tubular epithelial cells and showed a negative correlation with kidney function in both AKI patients and cisplatin-induced murine models. Maintaining renal Slc25a21 expression alleviated cisplatin-induced tubular injury by reducing cellular apoptosis and inflammatory responses. It also helped restore respiratory ATP production, mitochondrial biogenesis, and integrity in acutely injured tubular epithelial cells. Mechanistically, reduced Slc25a21 levels in AKI disrupted mitochondrial 2-oxoadipate transport, altering the influx of related metabolites, and particularly affecting the tricarboxylic acid cycle, while restoration of Slc25a21 reversed these effects in mitochondrial metabolic homeostasis.

Conclusions: Our findings suggest that suppression Slc25a21 contributes to AKI and sustaining Slc25a21 expression could prevent the progress of AKI via fuel metabolite transport and the restoration of mitochondrial homeostasis in tubular epithelial cells. We believe our findings will contribute to the advancement of mechanistic insights and potential therapeutic strategies to treat AKI.

Funding: Government Support - Non-U.S.

SA-PO122

Metabolic Alterations in Organs and Biofluids following Unilateral Ischemia-Reperfusion Kidney Injury in Pigs

Oliver Hahn,[1] Maria Chrysopoulou,[1] Johannes Jaegers,[1,3] Christoffer Laustsen,[4] Markus M. Rinschen.[1,2] Kidney Omics Group. *[1]Department of Biomedicine, Aarhus University, Aarhus, Denmark; [2]Department of Medicine, University Medical Center Hamburg Eppendorf, Hamburg, Germany; [3]Childrens Hospital, Pediatrics II, Pediatric Nephrology, University of Essen, Essen, Germany; [4]MR Research Centre, Aarhus University, Aarhus, Denmark.*

Background: The kidneys play a crucial role in eliminating metabolic waste products and regulating various metabolites. However, metabolic alterations in renal injury sometimes remain un-interpretable, since multiple organ systems may be affected.

Methods: We employed stable isotopes 13-Carbon glucose and 15-Nitrogen ammonium chloride to track metabolites across pig organs subjected to unilateral ischemia-reperfusion kidney injury for 2 hours and either one or four days of recovery. Utilizing ultra-high-pressure liquid chromatography-triple quadrupole tandem mass spectrometry, we accurately measured both labeled and unlabeled metabolites, enabling precise quantification of metabolite fluxes and fates. Additionally, we assessed changes in the proteome to correlate with metabolite fluxes.

Results: Using functional MRI, we accurately phenotyped the pigs and observed a significant decrease in the single kidney GFR of the injured kidney. Ammonia flux in the kidney medulla increased after 1 and 4 days of recovery in both the ipsilateral and contralateral kidneys compared to the kidneys of the control pigs. In contrast, ammonia flux remained unchanged in other organs, including the liver, heart, muscle, and brain. Additionally, measurements of metabolites from the citric acid cycle, urea cycle, and glycolysis indicated a strong metabolic rewiring to ischemia reperfusion injury. Proteome changes correlated with the observed findings, but subtle changes were also observed in the non-injured, contralateral kidney.

Conclusions: The metabolic epicenter of acute injury is the injured kidney, but distinct metabolic alterations are observed in the other kidney and, partly, other organs. These metabolic alterations are sequelae of renal injury and provide a first window into initial metabolic mechanisms conveying cardiovascular risk in renal injury.

Funding: Commercial Support - Novo Nordisk foundation

SA-PO123

Increased Severity of AKI in Obese Mice

Chathri Ratnayake,[1,2] Kurt Gleich,[2,3] Marina Katerelos,[2,3] Geoffrey Harley,[1,2] Mardiana Lee,[1,3] David A. Power,[1,3] Peter F. Mount.[1,3] *[1]The University of Melbourne Austin Clinical School, Heidelberg, VIC, Australia; [2]Kidney Laboratory, The Institute for Breathing and Sleep (IBAS), Austin Health, Heidelberg, VIC, Australia; [3]Department of Nephrology, Austin Health, Heidelberg, VIC, Australia.*

Background: Obesity is a lipotoxic state of abnormal and excessive fat accumulation. Although obesity is a well-known risk factor for chronic kidney disease, its role in acute kidney injury (AKI) is not well understood. We conducted this study to investigate the impact of obesity from a high fat diet (HFD) on AKI using the folic acid nephropathy (FAN) model.

Methods: Male mice aged 6-8-week-old received either HFD or control diet (CD) for 6 weeks. AKI was induced using FAN, in which intraperitoneal folic acid is given at 240 ug/g. Control mice were administered vehicle. Kidneys and bloods were collected 48 hours post FAN.

Results: HFD mice demonstrated more severe AKI compared to CD mice post FAN as evidenced by worse serum urea (HFD 48.9±4.9 mmol/L vs CD 32.3±19.8 mmol/L, P=0.035) (Fig 1A), worse creatinine (HFD 0.09±0.08 mmol/L vs CD 0.03±0.014 mmol/L, P=0.022), increased NGAL expression by Western blot (HFD 10.8±4.8-fold vs CD 2.1±1.3-fold) (Fig 1B) and RT-PCR (HFD 303.2±117.5-fold vs CD 184±77.6-fold, P=0.004). RT-PCR found that HFD increased the expression of inflammatory markers after FAN with increased IL-6 (HFD 214.6± 23.3-fold vs CD 108±87.8-fold, P = 0.014) and increased MCP-1 (HFD 32.3± 15.9-fold vs CD 12.8±8.5-fold, P<0.001). HFD mice showed worse histological injury score after FAN (HFD 3.43±0.6 vs CD 2.27±0.9, P<0.001). Notably, HFD increased tubular vacuolation in both FAN (HFD 3.5±0.6 vs CD 2.34±0.6, P<0.001) and vehicle treated (HFD 3.25±0.8 vs CD 1.93±0.4, P< 0.001) consistent with lipid accumulation in tubular epithelial cells (TEC).

Conclusions: Our data indicate that obese mice accumulate lipid in tubular epithelal cells and develop more severe AKI and inflammation following FAN. Strategies to reduce obesity may improve outcomes in AKI.

Funding: Government Support - Non-U.S.

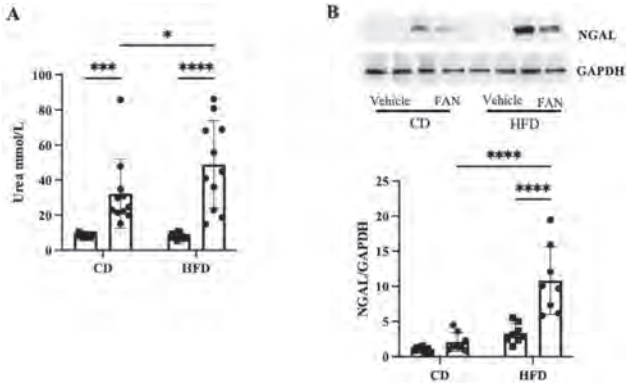


Figure 1.

SA-PO124

Adiponectin Alleviates AKI-Related Pyroptosis and Inflammation by Accelerating NLRP3 Degradation

Baoyi Shao,[1] Jianan Wang,[2] Haidi Li,[2] Jianbo Guo,[1] Yifan Wang,[1] Hai-Yong Chen.[1,3] School of Chinese Medicine. *[1]School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [2]Anhui Medical University, Hefei, China; [3]Department of Chinese Medicine, The University of Hong Kong-Shenzhen Hospital, Shen Zhen, China.*

Background: Adiponectin (APN), an adipose tissue-derived hormone, exhibits multifaceted effects on various tissues. The role of adiponectin in acute kidney injury (AKI) remains largely unclear. This study investigated whether adiponectin mitigates AKI by inhibiting pyroptosis and inflammation through the NLRP3/GSDMD-mediated pathway.

Methods: The levels of APN were tested in AKI-induced mouse models. Adiponectin knockout (KO) and wild-type (WT) mice were induced into AKI by injection of cisplatin, lipopolysaccharide, or folic acid. The effects of AdipoRon, an APN receptor agonist, were observed in three AKI models *in vivo* and in cisplatin-induced mouse tubular epithelial cells (mTECs). The role of AMPK in the renoprotective effects of APN was investigated and the relationship between AMPK and NLRP3 was researched.

Results: APN decreased in different AKI models. APN deletion exacerbated AKI-induced nephrotoxicity and inflammation as indicated by increased kidney injury scores and related inflammatory factors. APN deletion promoted the activation of pyroptosis-related NLRP3/GSDMD pathway across three AKI models rather than apoptosis, necroptosis or ferroptosis as expressed by relevant executioners *in vivo*. AdipoRon protected against AKI-induced nephrotoxicity and inflammation by directly activating AMPK and ameliorating pyroptosis-related pathways *in vivo* and *in vitro*. The renoprotective role of AdipoRon/APN was reversed by Compound C, an AMPK inhibitor. AICAR, an activator of AMPK, reduced the protein levels of NLRP3 without significantly affecting its mRNA levels, indicating NLRP3 undergoes post-translational modifications upon AMPK activation. AICAR-mediated NLRP3 reduction was prevented by MG-132 but not chloroquine, which suggested NLRP3 might be degraded through the ubiquitin-proteasome system. Indeed, AICAR enhanced NLRP3 ubiquitination as demonstrated by western blots in ubiquitin-transfected mTECs. Co-Immunoprecipitation followed by liquid chromatography–mass spectrometry identified several potential E3 ubiquitin ligases that could interact with NLRP3 and function as downstream transcription factors of AMPK.

Conclusions: APN mitigates AKI by inhibiting pyroptosis and inflammation via AMPK/NLRP3 pathways. Targeting APN/AMPK/NLRP3 represents a novel therapeutic strategy for addressing AKI-induced nephrotoxicity and inflammation.

Funding: Government Support - Non-U.S.

SA-PO125

Nicotinamide Phosphoribosyltransferase (NAMPT) Improves Kidney Injury and Promotes Kidney Regeneration of Adult Zebrafish

Young Sun Kang. *Korea University Ansan Hospital, Ansan, Gyeonggi-do, Republic of Korea.*

Background: NAMPT is a known adipokine which improves insulin resistance in obesity and have an anti-diabetic effect. However, its role remains uncertain in kidney injury and regeneration. In this study, we investigated the role of NAMPT on puromycin-induced kidney injury and regeneration of adult zebrafish model.

Methods: We injected 100ug of puromycin or/and 500ng of NAMPT via intraperitoneal injection into adult wild zebrafish, which were sacrificed at 1, 3, 5, 7, and 14 dpi. To investigate the role of NAMPT in kidney regeneration, we generated NAMPT knock-out zebrafish, then observed nephron injury and regeneration.

Results: Larva kidney showed only *namptb* gene expression and adult kidney presented both *nampta* and *namptb* gene expressions. Puromycin increased both *nampta* and *namptb* gene expressions. And puromycin also increased NAMPT protein expression of adult kidney. Compared to controls, puromycin-induced NAMPT protein synthesis was increased from 1 dpi until 7 dpi. NAMPT was not expressed on podocytes of glomeruli, but identified on interstitial and tubular cells of kidney in adult zebrafish. Especially, IF staining showed NAMPT expression on the apical area of tubular cells and intranuclear area of interstitial cells between 7 dpi and 14 dpi. NAMPT treatment recovered puromycin-induced nephron loss and tubular regeneration of adult zebrafish at 7 dpi and 14 dpi. This result also was identified by *in situ* hybridization of *lhx1a* as a regeneration marker. Finally, NAMPT knock-out zebrafish showed smaller number of nephrons in puromycin-induced kidney regeneration than that of puromycin-treated wild zebrafish.

Conclusions: From these results, NAMPT improved puromycin-induced kidney injury and enhanced kidney regeneration in adult zebrafish. Moreover, NAMPT showed the key role in nephron regeneration.

Funding: Government Support - Non-U.S.

SA-PO126

Humanin, a Mitochondrial-Derived Peptide, Mitigates the Progression of Acute Kidney Disease

Yung-Ho Hsu.[1,2] *[1]Taipei Medical University, Taipei, Taiwan; [2]Hsin Kuo Min Hospital, Taipei Medical University, Taoyuan, Taiwan.*

Background: Acute kidney disease (AKD) represents a critical period following acute kidney injury (AKI), during which preventing the onset of chronic kidney disease (CKD) becomes crucial. In this study, we investigated the impact of humanin, a mitochondrial-derived peptide, on AKD through both in vivo and in vitro experiments.

Methods: We analyzed the protective effect of humanin-G, a humanin analog, on rat renal tubular cells (NRK-52E) subjected to hypoxia/reoxygenation (H/R). We also established an AKD mouse model by performing right nephrectomy and inducing transient ischemic injury to the left kidney. One week after the operation, we administered 4 mg/Kg/week of humanin-G to AKD mice for 4 weeks.

Results: We found that H/R impaired mitochondrial function and triggered inflammatory and apoptotic responses, which were reversed by humanin treatment. Humanin treatment also reduced H/R led ROS levels. Humanin also upregulated PI3K III, downregulated phosphor-mTOR, and increased LC3 expression, all of which contribute to mitophagy. In hypoxic NRK-52E cells, humanin increased the levels of mitochondrial Complex I, which plays a crucial role in energy production within the mitochondria. Over a one-month period, humanin led to reduced serum creatinine and blood urea nitrogen levels in AKD mice. Additionally, renal fibrosis was mitigated in AKD mice treated with humanin.

Conclusions: Humanin shows promise as a potential intervention to prevent the transition from AKI to CKD. By enhancing mitochondrial function, it may play a crucial role in minimizing AKD progression.

Funding: Government Support - Non-U.S.

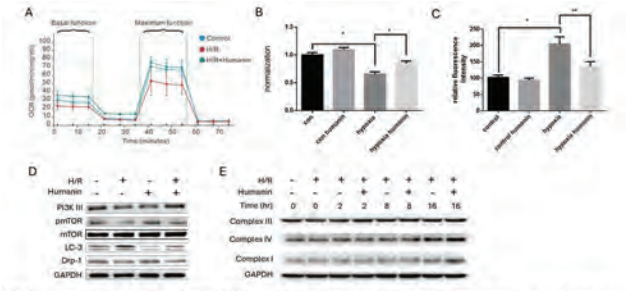


Figure 1. Humanin upregulated mitochondrial function in NRK-52E cells. (A) Oxygen consumption rate (OCR) curves. OCRs were measured 16 h after the humanin treatment (10 μM). Results are presented as the mean ± SD (n = 3). (B) The cell proliferation of hypoxic NRK-52E cells. The cells were treated with the hypoxia treatment overnight, cultured under normal conditions for 30 minutes, and then added 10 μM humanin for 24 hours. (C) The ROS in NRK-52E cells. We used DCFHDA staining for ROS detection and measured the fluorescence value by an ELISA reader. ROS in the hypoxia cells increased significantly compared to that in the control cells. ROS in the cells added humanin after hypoxia significant decreased. Results are presented as the mean ± SD (n = 3). *, P<0.05. (D) The Western blots of mitophagy-related signals in hypoxic cells. Humanin promoted the expression of PI3K III and LC-3, and reduced phospho-mTOR and Drp-1 expression. (E) The Western blots of mitochondrial complexes in hypoxic cells. The mitochondrial complexes were monitored 2, 8, or 16 h after the humanin treatment.

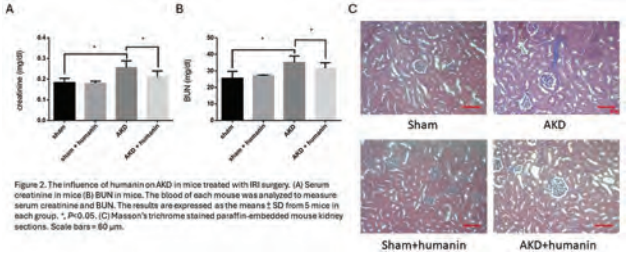


Figure 2. The influence of humanin on AKD in mice treated with IRI surgery. (A) Serum creatinine in mice (B) BUN in mice. The blood of each mouse was analyzed to measure serum creatinine and BUN. The results are expressed as the means ± SD from 5 mice in each group. *, P<0.05. (C) Masson's trichrome stained paraffin-embedded mouse kidney sections. Scale bars = 60 μm.

SA-PO127

Loss of Vascular Endothelial Growth Factor Receptor 2 (VEGF-R2) in the Renal Stroma Regulates Lipid Metabolism to Halt AKI-to-CKD Transition

Akira Oda, Sunder Sims-Lucas, Takuto Chiba. *University of Pittsburgh, Pittsburgh, PA.*

Background: A dire consequence of acute kidney injury (AKI) is a dramatically increased risk of developing chronic kidney disease (CKD). Understanding the mechanisms by which AKI progresses to CKD is essential for the development of therapies, for which none currently exist. The renal microvasculature, including pericytes and endothelial cells, is damaged in AKI, leading to recruitment of inflammatory cells that contribute to progression to CKD. Pericytes are a heterogeneous mesenchymal population and have been identified as a major source of myofibroblasts that drive CKD. Interestingly, VEGF-R2 (known as the master regulator of angiogenesis for endothelium) acts as a negative regulator of pericytes limiting angiogenesis *in vitro*. Understanding the molecular mechanisms that mediate maladaptive endothelial-pericyte crosstalk leading to exacerbated and prolonged inflammation may facilitate therapeutic exploitation of this phenomenon.

Methods: We generated genetic mouse models for renal stromal cell (RSC)-specific loss-of-function of VegfR2 with Foxd1-Cre (*VegfR2*$^{RSC-/-}$) to interrogate the role of *VegfR2* in the renal stroma, which includes pericytes, in the AKI-to-CKD transition. Mice were subjected to three CKD models induced by either renal ischemia/reperfusion injury (IRI), low/repeated cisplatin treatment, or unilateral urethral obstruction (UUO).

Results: Our RNA-seq analysis of isolated renal stroma with or without renal IRI revealed that injured renal RSCs decreased the expression of genes associated with lipid metabolism. We found that *VegfR2*$^{RSC-/-}$ mice consistently mitigated AKI-to-CKD transition in all three CKD models (IRI, UUO, and cisplatin). *VegfR2*$^{RSC-/-}$ mice have reduced inflammation, oxidative stress as well as reduced interstitial lipid deposition after renal IRI. Mechanistically, *VegfR2*$^{RSC-/-}$ kidneys have increased expression of a lipid metabolism associated genes, Bnip3 and Pyruvate dehydrogenase kinase1 (PDK1), contributing to the enhanced protection.

Conclusions: These data suggest that loss of VEGF-R2 in the renal stroma reduces oxidative stress and lipid metabolism to attenuate inflammation to halt CKD.

Funding: NIDDK Support

SA-PO128

GATM Ameliorates the Acute-to-Chronic Kidney Disease Transition through Enhancing Endogenous Creatine-Mediated Lipophagy

Xu Guan, Fan Li, Weijian Xiong. *Chongqing Hospital of Traditional Chinese Medicine, Chongqing, China.*

Background: Acute kidney injury (AKI), characterized by a rapid decline of kidney function in the short term, is a common clinical syndrome with complex pathogenesis. The incomplete recovery from AKI increases the risk of progression to chronic kidney disease (CKD). GATM, highly expressed in the mitochondria of renal tubular epithelial cells (RTECs), is a key rate-limiting enzyme in the endogenous creatine biosynthesis. Previous studies have found mutations in GATM gene in the kidney of patients with CKD contribute to the ROS production, mitochondrial damage and cell death in RTECs. Moreover, GATM mutations also upregulate the expression of the fibrotic cytokine IL-18 and accelerate CKD progression, indicating that GATM may play an important role in the pathogenesis of kidney diseases. However, the role of GATM in AKI-to-CKD transition remains unknown.

Methods: In this study, GATM adenovirus-overexpressed mice and cultured RTECs were used as subjects. Renal ischemia-reperfusion (IRI) mouse model, RNA sequencing, Immunofluorescence, Western blot and qRT-PCR were employed to reveal the crucial role and mechanisms of GATM in AKI-to-CKD transition.

Results: GATM was significantly reduced in the kidneys AKI patients and IRI mice. The analysis indicated GATM expression was positively correlated with kidney function. In vivo, GATM overexpression by adenovirus improved the transition from AKI to CKD. Primary RTECs were employed to RNA-seq analysis that GATM overexpression upregulated the expression of fatty acid degradation and autophagy-related genes while downregulated lipid droplet-related gene in RTECs through KEGG analysis. Transmission electron microscopy revealed that a large amount of lipid droplets were accumulated in RTECs after IRI, which could be reversed by GATM overexpression, accompanied by an increased autophagosomes enveloping-lipid droplets and reduced kidney injury. GATM promoted endogenous creatine synthesis and enhanced the lipophagy of RTECs. Collectively, our findings demonstrate that GATM deficiency contributes to AKI-to-CKD transition and GATM ameliorates AKI-to-CKD transition though enhancing endogenous creatine-mediated lipophagy.

Conclusions: GATM plays an important role in the transition of AKI to CKD and targeting GATM-lipophagy axis could serve as a promising therapeutic approach for retarding AKI-to-CKD transition.

SA-PO129

Reactivation of Pax2 in Proximal Tubular Epithelial Cells May Be Involved in the Directivity of Programmed Cell Death in Acute Tubular Necrosis

Kasumi Ohno, Keisuke Sako, Kiyoaki Ito, Shinji Kitajima, Ichiro Mizushima, Norihiko Sakai, Miho Shimizu, Yasunori Iwata. *Kanazawa university, Kanazawa, Japan.*

Background: Acute Tubular Necrosis (ATN) is a severe kidney injury, posing a critical issue due to its high mortality rate and the risk of progression to chronic kidney disease (CKD). In ATN, Paired box 2 (Pax2) reactivation in injured tubular epithelial cells has been known to occur. Pax2 is a transcription factor essential for kidney development and is reactivated in proximal tubular epithelial cells during recovery from injury. Previously, we reported that Pax2 reactivation is necessary to regenerate cells via cyclin-dependent kinase 4 (CDK4) in injured proximal tubules using a unilateral renal ischemia-reperfusion injury model. However, it is unclear whether the reactivation of Pax2 is an essential factor in the biological defense against ATN. Therefore, we hypothesized that inadequate Pax2 reactivation leads to exacerbating kidney injury and mortality.

Methods: To test our hypothesis, we conducted experiments using 8-week-old male mice with proximal tubule-specific Pax2 knockout (Pax2 KO mice) under endogenous androgen control. We administered aristolochic acid (AA) at a dose of 5 mg/kg intraperitoneally for three consecutive days. As a control group, we used C57BL/6 mice. Mice were sacrificed on days 1, 4, 7, and 42 after the end of AA administration. To evaluate the impact on mortality, we administered a single intraperitoneal dose of AA at 15 mg/kg.

Results: On the first and fourth days, the two groups showed no significant difference in kidney function. However, on the seventh day, serum creatinine levels increased in the Pax2 KO group (p=0.025). Kidney histological analysis revealed a clear obstruction of the Henle loop in the Pax2 KO group. In addition, TUNEL-positive cells were observed in both groups, while the number of Cleaved caspase 3-positive cells decreased in the cKO group (p=0.001). Instead, the number of p-Mlkl-positive cells increased (p=0.001). The experiment evaluating mortality showed a significant exacerbation in the Pax2 KO group (p=0.01).

Conclusions: Pax2 reactivation was shown to be protective against kidney injury and mortality. Our results suggest that non-apoptotic cell death is increased in tubular epithelial cells with inadequate Pax2 reactivation and may affect mortality and kidney function by inducing maladaptive cell death.

Funding: Government Support - Non-U.S.

SA-PO130

Nicotinamide N-methyltransferase (NNMT) Induction during AKI Reduces NAD+ and Durably Alters Global Gene Expression

Amanda J. Clark,[1,2] Kyle Q. Vu,[1] Samir M. Parikh.[1] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]Children's Medical Center Dallas, Dallas, TX.*

Background: NAD+ is a critical cofactor in cellular metabolism and is required for kidney tubular cell function. Reduced NAD+ abundance is a pathologic feature of both acute (AKI) and chronic kidney diseases (CKD). While NAD+ biosynthesis is suppressed

in AKI, multiple studies demonstrate an upregulation of nicotinamide N-methyltransferse (NNMT) during injury. NNMT catalyzes the methylation of nicotinamide (NAM), the most significant NAD+ precursor. Methyl-NAM is permanently removed from NAD circulation. Further, via production of methyl-NAM, NNMT permanently removes circulating methyl groups. Thus, NNMT induction during AKI may represent an actionable target to increase NAD+ to reduce AKI severity and also a mechanism where AKI induces long-term changes in gene expression that could underly the AKI to CKD transition.

Methods: NNMT expression was measured using qPCR of mouse kidneys after AKI induced by cisplatin, folic acid, ischemic reperfusion injury (IRI), and lipopolysaccharide (LPS). A novel, inducible renal tubule specific NNMT overexpression mouse (iNephNNMT) was created - Pax8rtTA, tetOCre, fl-STOP-fl-NNMT. iNephNNMT mice had kidney function (GFR) estimated via measurement of serum creatinine after 4 weeks of overexpression followed by IRI or sham. Wild type mice induced with IRI were treated with NNMT inhibitors methyl-NAM and JBSNF followed by GFR estimation. RNASeq and ATACSeq were performed on kidneys from iNephNNMT mice and littermate controls.

Results: NNMT induction was a conserved feature across 4 distinct AKI mouse models: cisplatin, folic acid, IRI, and LPS. iNephNNMT mice exhibited reduced GFR at baseline as well as more severe injury after IRI compared to littermate controls. Two structurally unrelated NNMT inhibitors increased kidney NAD+ and protected against IRI. RNASeq and ATACSeq data from iNephNNMT kidneys demonstrated that NNMT overexpression increased chromatin accessibility at the native NNMT locus and led to sustained NNMT overexpression.

Conclusions: NNMT induction during AKI may be a conserved, maladaptive feature. Transient NNMT induction during periods of stress can lead to persistently increased NNMT expression, which in turn could perturb kidney metabolism towards greater injury susceptibility and fibrosis. Finally, NNMT may be an attractive therapeutic target in the AKI-to-CKD transition.

Funding: NIDDK Support, Other NIH Support - 5R01AG027002

SA-PO131

Role of Lactate Dehydrogenase A (LDHA)-Mediated Glycolytic Switch in AKI

Yan Lu, Anna A. Zmijewska, Anupam Agarwal. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Acute kidney injury (AKI) is a detrimental and frequently irreversible loss of renal function that affects millions of individuals worldwide. Despite effective biomarkers, treatment options are limited, and outcomes from AKI remain poor. Proximal tubule cells (PTCs) are among the key functional renal cell populations significantly affected by AKI. In particular, the bioenergetics of PTCs are diminished during AKI, followed by maladaptive responses accompanied by hypoxia or endotoxin-induced inflammation. In this setting, lactate dehydrogenase A (LDHA), an enzyme involved in glycolysis, is activated in PTCs, although the impact of this activation and therapeutic potential of LDHA in AKI remain to be determined.

Methods: Nephron-specific LDHA knockout mice were generated by crossbreeding Pax8-rtTA/tetO Cre and LDHAfl/fl mice. Western blot, real-time PCR, and immunofluorescence analyses were used to determine LDHA levels in wild-type and LDHA-deficient mice. For an AKI model, ($LDHA^{Whole\ Nephron-/-}$) and LDHA wild-type ($LDHA^{Whole\ Nephron+/+}$) mice were subjected to Cisplatin (20 mg/kg; i.p., once) -induced injury. The severity of AKI, including serum creatinine levels, glomerular filtration rate (GFR), and Neutrophil gelatinase-associated lipocalin (NGAL) expression, was determined 4 days post-injection of Cisplatin.

Results: Both LDHA expression and protein levels were diminished in the whole nephron of LDHA knockout mice, while LDHB remained unchanged. Control groups of ($LDHA^{Whole\ Nephron-/-}$) mice showed no phenotype changes in proximal tubules. However, these mice developed more severe injury upon Cisplatin-induced AKI compared to wild-type counterparts. The severity of injury included increased serum creatinine levels, reduced glomerular filtration rate, and increased NGAL expression in ($LDHA^{Whole\ Nephron-/-}$) compared to wild-type mice.

Conclusions: Collectively, our findings indicate that LDHA deficiency increases the severity of Cisplatin-induced AKI, predominantly due to more significant dysfunction of proximal tubule cells. These results suggest that the accumulation of endogenous LDHA has a protective effect in AKI.

Funding: NIDDK Support

SA-PO132

Alternative Splicing of Uromodulin Enhances Mitochondrial Metabolism for Adaptation to Stress in Kidney Epithelial Cells

Azuma Nanamatsu, George Rhodes, Kaice A. LaFavers, Radmila Micanovic, Virginie Lazar, Daria Barwinska, Malgorzata Kamocka, Carrie L. Phillips, Katherine J. Kelly, Robert L. Bacallao, Pierre C. Dagher, Takashi Hato, Tarek M. El-Achkar. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Cells of thick ascending limb of the loop of Henle (TAL) are resistant to ischemic injury, despite high energy demands in a relatively hypoxic medullary milieu. This adaptive metabolic response is not fully understood even though the integrity of TAL cells is essential for recovery from acute kidney injury (AKI). TAL cells uniquely express uromodulin (UMOD), the most abundant protein secreted in healthy urine. The role of UMOD in this adaptation mechanism and the involvement of alternative splicing have not been previously described.

Methods: To explore alternative splice variants of UMOD, we assessed long-read RNA sequencing data of human and mouse kidneys. The expression of the spliced variant after AKI was evaluated using a renal ischemia-reperfusion injury (IRI) mouse model. To test the localization and function of the splice variant, its cDNA was overexpressed in Madin-Darby canine kidney (MDCK) cells. To evaluate its role during AKI, we designed splice-switching antisense oligonucleotides (SSOs) to induce this alternative splicing, and their efficacy was tested in immortalized mouse kidney TAL cells and IRI mice. We isolated primary TAL cells from IRI mice to confirm the cytoprotective effect of the splice variant.

Results: Long-read RNA sequencing showed the existence of alternatively-spliced UMOD (AS-UMOD) which skips exon 10 both in humans and in mice. AS-UMOD expression was induced by mild IRI, but not by severe IRI. This variant lacks a GPI-anchoring site and was localized intracellularly in mouse kidneys and MDCK cells. AS-UMOD was targeted to the mitochondria, interacted with SLC25 carriers, increased NAD^+ and ATP levels, and improved cell viability after hypoxic injury in MDCK cells. We identified SSOs that enhance AS-UMOD expression *in vitro* and *in vivo*. Augmentation of AS-UMOD using the SSO after severe IRI improved the course of injury by protecting TAL cells.

Conclusions: Alternative splicing generates a conserved intracellular isoform of uromodulin, which contributes to the metabolic adaptation of TAL cells to ischemic injury. Enhancing this protective splice variant in TAL cells might become a novel therapeutic intervention for AKI.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO133

Stearyl-Coenzyme A Desaturase 1 Regulates Tubular Cells Mitochondrial Homeostasis Exacerbates AKI

Han Wu, Ying Li, Mengru Gu, Chunsun Dai. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Acute kidney injury is a common clinical acute and critical condition, which is associated with increased mortality, prolonged hospital stay, and the risk of chronic kidney disease (CKD). Numerous studies have shown that renal tubular cell injury and death are the core events of AKI. The kidney is a high energy-consuming organ, and fatty acids become the preferred energy source for renal tubular cells due to their high performance, so mitochondrial dysfunction may be the main cause of renal tubular cell injury during AKI. SCD1 is a key enzyme in lipogenesis, mainly catalyzing production of monounsaturated fatty acids (MUFAs). Previous studies found that SCD1 may play an important role in maintaining mitochondrial homeostasis by participating in lipid metabolism, so we aimed to study whether SCD1 can participate in AKI by regulating mitochondrial homeostasis in tubular cells.

Methods: *In vivo*, we used SCD1 global knockout mice to construct ischemia-reperfusion-induced acute kidney injury model to study the role of SCD1 in AKI. *In vitro*, We primarily used primary tubular epithelial cells extracted from SCD1 knockout mice with H_2O_2 treatment and the role of SCD1 in AKI by metabolomics, proteomics, and transcriptomic methods.

Results: Firstly, we found that SCD1 mainly was expressed in the S3 tubular epithelial cells increased significantly during acute kidney injury. Further research showed that SCD1 knockout or inhibiting SCD1 significantly alleviated ischemia-reperfusion-induced acute kidney injury and H_2O_2-induced tubular cell death. Secondly, the results of electron microscopy showed that after H_2O_2 treatment, mitochondrial crest in SCD1 -/- tubular cells was more intensive and the mitochondrial structure was more complete. Thirdly, the metabolomics data demonstrated that SCD1 knockout significantly altered the tubular cells metabolic profile, in which the TCA cycle equivalent significantly increased. The data from transcriptomics and proteomics suggested that knocking out SCD1 significantly upregulated the mitochondrial oxidative phosphorylation proteins relative mRNA and protein expression.

Conclusions: Stearyl-Coenzyme A desaturase SCD1 aggravates acute kidney injury by regulating mitochondrial structure and function.

Funding: Government Support - Non-U.S.

SA-PO134

Mitochondrial Treatment Mitigates Hypoxia-Induced Renal Cell Injury

Edgar Maquigussa,[1,2] Bruno S. Bronel,[1] Mirian A. Boim.[1]
[1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil; [2]Universidade Nove de Julho, Sao Paulo, Brazil.

Background: Renal ischemia promotes renal hypoperfusion and hypoxia, leading to tubular epithelial damage, infiltration of inflammatory cells, and activation of pro-fibrotic pathways. Mitochondrial dysfunction plays a central role in cellular alterations induced by hypoxia. Mitochondria and their components can be secreted by cells and are found in the extracellular fluid in various forms: functional mitochondria, mitochondrial DNA, and mitochondrial vesicles. These mitochondrial components regulate cell metabolism, inflammation, and oxidative stress. Therefore, this study aimed to evaluate the role of mitochondria in an in vitro model of renal hypoxia.

Methods: Proximal tubular epithelial cells (mm55K) were cultured in normoxia (95% atmosphere air and 5% CO2) or hypoxia (94% N2, 5% CO2 and 1% O2) environment. The hypoxic stimulus length was previously determined using lactate levels by ELISA. Mitochondria were isolated from mm55K cells cultured in normoxia and hypoxia conditions and evaluated by flow cytometry and mitotracker-labeled. The mm55K cells cultured in normoxia or hypoxia were treated with either mitochondria isolated from normoxia or hypoxia conditions. The ability of mm55K cells to incorporate mitotracker-labeled mitochondria was evaluated by fluorescence microscopy. The gene expression of extracellular matrix markers (fibronectin, collagen IV, vimentin, and TGF-β), inflammation (p50 and p65), oxidative stress (NOX4, SOD-1, and UCP2), and apoptosis (caspase-3 and caspase-9) was assessed by RT-PCR.

Results: Hypoxia increased lactate concentration at 24, 48, and 72 hours in mm55K cells. There were no differences in the quantity of isolated mitochondria between the groups. Mitochondria stained with mitotracker were observed in the cytoplasm of mm55K cells, demonstrating the internalization of the isolated mitochondria by these cells. Under hypoxic stimulation, the gene expression of extracellular matrix markers, inflammation, oxidative stress, and apoptosis significantly increased. However, the effects on gene expression were attenuated with mitochondria treatment from both normoxia and hypoxia conditions.

Conclusions: Isolated mitochondria have a potential therapeutic role in reversing key markers in an in vitro model of cell injury caused by hypoxia.

SA-PO135

Effect of Ischemia-Reperfusion Injury on Mitochondrial Malondialdehyde Levels in Kidney Cortex and Medulla of Aged Rats

Marianna J. Zamlauski-Tucker, Bingwei Ye. *Ball State University, Muncie, IN.*

Background: The present study was undertaken to determine the effect of ischemia-reperfusion injury (IRI) on mitochondrial malondialdehyde (MDA) levels in kidneys from aged rats. MDA is a product of lipid peroxidation of cell and organelle membranes by free radiacals and is used as an indicator of oxidative stress. Kidney dysfunction in ischemia is associated with tissue damage caused by free radicals generated in IRI.

Methods: Anesthetized female Lewis rats (22 months of age) were used. Both renal pedicles were clamped for 60 min, followed by 60 min of reperfusion in the Experimental Group (n = 6). The kidneys were then harvested, separated into cortex and medulla, and homogenized. Kidneys in the Control Sham Group (n = 6) were not subjected to IRI before being harvested. The mitochondrial fractions were isolated by differential centrifugation and MDA levels were measured using a spectrophotometric assay. The water content of the cortex and medulla were determined to allow MDA levels to be expressed as nmol/g kidney dry weight. A Student's T Test was used to compare groups, and statistical significance was determined at $p< 0.05$. All data reported as X ± SEM.

Results: MDA levels were not changed in the kidney cortex of the Experimental Group.when compared to the Control Group. Mitochondrial MDA levels in the kidney cortex of the Experimental Group were 19.0 ± 1.8 nmol/ g kidney dry weight and 16.0 ± 1.6 nmol/g kidney dry weight in the Control Group. Mitochondrial MDA levels significantly decreased by 25% in the kidney medulla of the Experimental Group.when compared to the Control Group. Mitochondrial MDA levels of the kidney medulla were 30.5 ± 1.5 nmol/g kidney dry weight in the Experimental Group and 44.5 ± 2.6 nmol/g kidney dry weight in the Control Group.

Conclusions: The results suggest that in IRI the mitochondria in both kidney cortex and medulla may not be experiencing increased oxidative stress and damage, as indicated by no change or a decrease in MDA levels, respectively, after 60 min of ischemia.

SA-PO136

The FDA-Approved Drug Lasmiditan Augments Primary Mouse Renal Peritubular Endothelial Cell Wound Healing and Angiogenic Capacity

Austin D. Thompson,[1,2] Jaroslav Janda,[1] Rick G. Schnellmann.[1,3]
[1]The University of Arizona College of Pharmacy, Tucson, AZ; [2]Southwestern Environmental Health Sciences Center, Tucson, AZ; [3]Southern Arizona VA Health Care System, Tucson, AZ.

Background: Acute kidney injury (AKI) remains a significant public health concern with no FDA-approved treatments. AKI often involves mitochondrial dysfunction, tubular injury/necrosis, and microvascular damage/rarefaction, all of which exacerbate renal injury and increase the risk of developing chronic kidney disease. Pharmacological stimulation of mitochondrial biogenesis (MB) has been shown to enhance mitochondrial function and renal vascular recovery post-AKI; however, its role in relation to renal peritubular endothelial cell repair mechanisms remains unknown. To address this gap in knowledge, we conducted wound healing and tube formation assays using primary mouse renal peritubular endothelial cells (MRPEC) exposed to tumor necrosis factor-alpha (TNFα) in the presence/absence of lasmiditan, a HTR1F agonist known to induce MB in the renal cortices of mice.

Methods: Primary MRPEC were isolated as previously described by Thompson et al. (2023). For wound healing assays, MRPEC were seeded onto fibronectin-coated Ibidi wound healing dishes ($7x10^4$ cells/well) and incubated overnight in microvascular media (EGM-MV2). MRPEC were then treated with TNFα [100ng/mL] or vehicle [saline+0.1%DMSO], with/without lasmiditan [100nM], and chamber inserts were removed. Dishes were imaged 24h post-treatment. For tube formation assays, MRPEC were treated for 24h, as described above, and seeded onto growth factor reduced Matrigel-coated Ibidi 3D-angiogenesis μ-Slides ($1.5x10^4$ cells/well). Cells were incubated overnight in EGM-MV2 and imaged the following day. All images were analyzed via Ibidi FastTrackAI software.

Results: Lasmiditan-treated MRPEC exhibited 1.15- and 1.10-fold increases in wound closure and 2.40- and 7.21-fold increases in tubular branch formation, compared to vehicle- and TNFα-treated controls, respectively. Cells treated with both TNFα and lasmiditan exhibited 1.22- and 1.16-fold increases in wound closure compared to vehicle- and TNFα-treated controls, and a 2.98-fold increase in tubular branch formation compared to TNFα-treated cells.

Conclusions: Together, these data reveal that lasmiditan augments MRPEC wound healing and angiogenic capacity, independently and in response to TNFα-induced cellular injury, suggesting a potential role for lasmiditan treatment in promoting vascular recovery post-kidney injury.

Funding: Other NIH Support - NIEHS-T32 Trainee Award, Veterans Affairs Support

SA-PO137

Role of Sulfotransferase 1C2 in Vitamin D Signaling in Ischemic AKI Associated with Vitamin D Deficiency in Rats

Ana Carolina de Braganca,[1] Desiree R. Bernardo,[2] Mariana M. Nascimento,[2] Vitor A. dos Santos,[2] Maria H. Shimizu,[2] Antonio C. Seguro,[1] Daniele Canale,[2] Rildo A. Volpini,[1,3] Robert L. Bacallao,[4] David P. Basile,[4] Ana Carolina R. Viotto.[2]
[1]Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil; [3]Universidade de Sao Paulo Faculdade de Medicina de Ribeirao Preto, Ribeirao Preto, Brazil; [4]Indiana University School of Medicine, Indianapolis, IN.

Background: Cytosolic sulfotransferase enzymes (SULTs) facilitate inactivation/elimination of compounds from the body. SULTs expression is regulated by lipid-/xenobiotic-sensitive receptors, including vitamin D receptor (VDR). SULT1C2 seems to be regulated by vitamin D (VD) status via VDR, and may be an action pathway of VD in mitigating the renal disease progression. Our aim was to study the role of SULT1C2 in VD signaling in ischemic-AKI associated with VD deficiency in rats.

Methods: Male *Wistar* rats received a VD-depleted diet for 32 days (*protocol [P]1-48 h*), 37 days (*P2–7 days*) and 45 days (*P3–15 days*). Four groups of rats were assigned to each follow-up *P*: Sham; Renal ischemia/reperfusion (IR); IR with VD deficiency (d+IR); IR with VD replacement (R+IR). During the first 30 days of all *P*, only the rats in the Sham and IR groups received 40 IU/day of VD (maintenance dose [MD]) orally. On the 30th day of all *P*, the rats were submitted to sham or renal ischemia-reperfusion surgeries. On days 30th and 31st, VD was administered orally (80 IU/day attack dose) in the Sham, IR and R+IR groups of all *P*. Once *P1* was concluded, the VD MD was offered from the 32rd day until the end of *P2* and *3*. We evaluated plasma levels of 25(OH)D, creatinine and cystatin C as well as renal total tissue levels of VDR, immunoblotted for SULT1C2, and kinetic metabolite utilization rates (Biolog assay kit) in mouse S3 proximal tubule cells plus PAPS and SULT1C2 treated with VD.

Results: See figure 1. In vitro studies showed that VD treatment (125 pM-24 h) increased the utilization kinetics of malate, isocitrate, alpha-ketoglutarate, fumarate, and cis-aconitate.

Conclusions: Our study suggests that vitamin D status, via temporal modulation of VDR, regulated the expression of SULT1C2 in the progression of kidney disease after renal ischemia injury. Grants: FAPESP 2022/05519-3, 2022/07409-0, 2019/20840-0.

Table 1.

	Sham	IR	d+IR	R+IR
25(OH)D (ng/mL)				
48 h	114.3±0.41	107.8±3.64[c]	12.44±0.68[ad]	18.12±1.29[adf]
7 days	103.1±2.97	102.0±5.47	9.47±0.65[ad]	38.62±2.37[adg]
15 days	93.1±2.19	93.2±1.60	10.51±1.6[ad]	79.86±2.55[adg]
Creatinine (mg/dL)				
48 h	0.40±0.01	0.83±0.10[c]	0.77±0.16[c]	0.54±0.03
7 days	0.53±0.04	0.63±0.03	0.61±0.03	0.56±0.04
15 days	0.53±0.01	0.55±0.02	0.54±0.09	0.53±0.03
Cystatin C (ng/mL)				
48 h	1424±55	2945±226[a]	2680±262[a]	2230±100[c]
7 days	1253±55	1843±137[c]	2014±216[b]	1775±78[c]
15 days	1140±106	1574±129	1527±235	1368±155
VDR (ng/µg protein)				
48 h	0.26±0.01	0.18±0.02[c]	0.13±0.01[af]	0.22±0.01[h]
7 days	0.34±0.01	0.29±0.02	0.23±0.04[c]	0.29±0.02
15 days	0.37±0.05	0.27±0.04	0.17±0.03[c]	0.28±0.02
SULT1C2 (%)				
48 h	99.8±2.6	74.3±11.3	37.20±8.9[af]	42.8±10.2[af]
7 days	99.7±3.3	97.0±10.3	85.1±6.0	128.7±15.5[i]
15 days	99.8±1.5	97.1±3.6	69.0±9.8[ab]	93.1±2.8[h]

Data are expressed as mean±SEM. [a]$p < 0.001$, [b]$p < 0.01$, [c]$p < 0.05$ *vs.* Sham; [d]$p < 0.001$, [f]$p < 0.05$ *vs.* IR; [g]$p < 0.001$, [h]$p < 0.01$, [i]$p < 0.05$ *vs.* d+IR.

SA-PO138

The Nicotinic Acid Receptor HCA2 Regulates Progression of AKI and Development of CKD in Mouse Models of Sepsis and Postischemic Kidney Injury

Kambiz Zandi-Nejad,[1] Samir M. Parikh,[2] Ayumi Takakura.[3] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]The University of Texas Southwestern Medical Center, Dallas, TX; [3]Brigham and Women's Hospital, Boston, MA.*

Background: Patients with sepsis-associated AKI (SA-AKI) have longer ICU stay compared to patients with sepsis alone, higher mortality rate and higher requirement for renal replacement therapy. SA-AKI is also a risk factor for development and progression of CKD. However, pathophysiological mechanisms of SA-AKI remain poorly understood. We have previously shown that hydrocarboxylic acid receptor 2 (HCA2) is expressed in SA-AKI kidneys and in activated macrophages and that *Hca2* KO male mice have higher mortality than wild type mice in response to low-grade cecal ligation and puncture-induced sepsis (CLP-IS). We have also shown that renal tubular cell expression of the mitochondrial biogenesis factor PGC1α increases the local abundance of HCA2 ligand beta-hydroxybutyrate (β-OH B) and protects mice from experimental AKI. Thus, we hypothesized that activation of HCA2 may have a protective role in SA-AKI.

Methods: We used well-established models CLP (generate sepsis and SA-AKI), and ischemia reperfusion (IR).

Results: Here we show 100% of female *Hca2* KO mice died within 3 days after severe CLP whereas 77% of WT female mice were alive at 3 days after surgery and nearly 40% of the female WT mice were alive at 2 weeks. Conversely, activation of HCA2 by nicotinic acid or β-OH B improved survival in both male and female mice after severe CLP-IS by more than 40%. Deficiency of *Hca2* resulted in greater kidney interstitial fibrosis and pro-inflammatory cytokine production such as TNF-α after CLP-induced sepsis. Renal tubule specific overexpression of PGC1α (Pax8rtTA; tetO-PGC1α) improved survival and renal function during sepsis. However, deficiency of *Hca2* abolished the reno-protective effects of PGC1α during SA-AKI, suggesting that HCA2 may be required for PGC1α-induced renoprotection. Finally, we further investigated the role of HCA2 on AKI-to-CKD transition. In bilateral IR (a model of AKI) and in unilateral IR (a model of CKD), *Hca2*$^{-/-}$ mice exhibited greater renal damage (assessed by pathology and BUN) and increased pro-inflammatory cytokine production compared with wild-type mice.

Conclusions: Considered together, we propose that a positive feedback loop of HCA2 activation through PGC1α signaling may thwart maladaptive repair, thereby delaying or inhibiting transition from AKI to CKD.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO139

Abstract Withdrawnl

SA-PO140

A Novel Pharmacological Agent, MARY1, Induces Mitochondrial Biogenesis and Restores Kidney Recovery in a Mouse Model of AKI

Paul Victor Santiago Raj, Jaroslav Janda, Rick G. Schnellmann. *R Ken Coit College of Pharmacy, University of Arizona, Tucson, AZ.*

Background: Acute kidney injury (AKI) is a rapid decline in renal function that can increase mortality and morbidity. Ischemia reperfusion (I/R) injury, hypovolemia and drug induced nephrotoxicity are common initiators of AKI. As there is no FDA-approved drug for the treatment of AKI, we have studied chemicals that induce mitochondrial biogenesis (MB), generation of new functional mitochondria, and restore renal function and recovery following AKI. A novel small molecule, MARY1, was tested *in vitro* and *in vivo* for MB, and restoration of vascular integrity and renal function following I/R induced AKI in mice.

Methods: Male ~7-8-week-old C57B/6NCrl mice were administered either MARY1 (0.3mg/kg) or vehicle daily, beginning 24h after I/R-induced AKI and continuing for 6 days (n=4-6/group). Kidneys were harvested, and gene and protein expression were analyzed using q-RT-PCR and immunoblot analysis. One way ANOVA followed by TUKEY multiple comparison test was used to determine statistical significance between treatment groups. A p-value of $p \leq 0.05$ was used to identify statistical changes and correct for multiple comparisons.

Results: MARY1 induced MB in primary cultured renal proximal tubule cells and in naive mice. Following bilateral I/R induced AKI, serum creatinine, kidney injury molecule 1 (KIM1) and Lipocalin 2 (LCN2) were maximally elevated at 24h. Daily administration of MARY1 for 6 days post AKI decreased serum creatinine, KIM1, LCN2, microvascular leakage and mitochondrial damage score compared to vehicle group. qRT-PCR and immunoblot analysis revealed restoration of PGC1α, mitochondrial proteins (OXPHOS, NDUFB8, TFAM), mitochondrial copy number and total ATP in kidney cortex. In addition, treatment with MARY1 for 6 days restored beta oxidation proteins (AMPKα, ACSM2A, ACADM), tight junction proteins (CLDN1, CLDN2, CD9) and cell senescence (p21) in kidney cortex in mice. Interestingly, administration of MARY1 for 6 days post I/R injury had no effect on inflammation markers such as NF-κB and its downstream pro-inflammatory cytokines and eNOS in kidney cortex in mice.

Conclusions: MARY1 restored mitochondrial, vascular, renal function and recovery through the induction of MB. However, MARY1 had no effect on inflammation. Future experiments will determine the efficacy of MARY1 in other kidney diseases (CKD, DN).

Funding: Veterans Affairs Support

SA-PO141

Ischemia Precondition Attenuates Ischemia-Reperfusion (I/R)-Induced AKI by Activating CLpP

Wenjia Xie, Chunsun Dai, Lei Jiang. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Ischemic preconditioning (IPC) activates endogenous defense mechanisms to protect the kidney from ischemia-reperfusion (I/R) injury, but its protective mechanism is still unclear. The imbalance of mitochondrial protein homeostasis is closely related to the development of acute kidney injury (AKI). Casein hydrolytic protease P (CLPP) is a protease that maintains mitochondrial protein homeostasis by degrading unfolded proteins. In addition, the activation of mitochondrial unfolded protein response (UPR^{mt}) leads to the initiation of integrated stress response (ISR). Various stress factors promote phosphorylation of eukaryotic translation initiation factor 2α (eIF2α), inhibiting overall protein synthesis, and initiating stress response gene expression. However, it remains unclear whether activated eIF2α phosphorylation is involved in renal ischemic tolerance induced by IPC via upregulation of CLPP expression.

Methods: In vivo, I/R was used to induce AKI. To investigate the potential effects and mechanisms of different degrees of ischemia on renal injury, C57BL/6J mice underwent bilateral renal artery clamping for 5, 10, and 15 minutes followed by 6 hours of reperfusion to simulate mild, moderate, and severe renal injury. Subsequently, the protective effect of IPC on I/R was studied using ISRIB (ISR inhibitor), or systemic CLPP gene knockout.

Results: Moderate IPC significantly alleviates AKI induced by IRI in mice, as evidenced by decreased levels of BUN, Scr, KIM-1, and NGAL mRNA. In addition, IPC notably mitigates the morphological alterations induced by IRI, including loss of brush border, tubular formation, and reduced cell apoptosis. Mechanistically, we propose that IPC activates the ISR, thereby promoting upregulation of CLPP expression and reducing accumulation of unfolded proteins in mitochondria. Inhibition of the eIF2α activity, which is involved in the ISR, abolishes the protective effect of IPC on I/R-induced renal injury. Systemic CLPP gene knockout counteracts the protective effect of IPC on renal injury.

Conclusions: Phosphorylation of eIF2α and upregulation of CLPP contribute to the protective effect of IPC on I/R injury. This could offer more possibilities for clinical treatment, thereby improving patient prognosis and quality of life.

Funding: Government Support - Non-U.S.

SA-PO142

Effect of Renal Ceramidase on AKI

Xinling Liang, Yingwen Chen, Yuanhan Chen, Zhilian Li, Li Zhang, Jieyi Luo. *Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China.*

Background: This study was designed to explore the changes of renal metabolic enzymes related to sphingolipids in AKI and to clarify the important role of ceramidase, the metabolic enzymes of sphingolipids in AKI.

Methods: renal tissue of C57BL/6 mouse was taken on bilateral renal ischemia reperfusion injury (Bi-IRI) 2nd day and 28day for quantitative proteomic. Renal tissue ceramide and expression of renal tissue acid ceramidase and neutral ceramidase were performed at 6 hours, 12 hours, 18 hours, 24 hours, and 48 hours. Acid ceramidase inhibitor ARN14974, neutral ceramidase inhibitor C6-urea-ceramide, and ceramidase broad-spectrum agonist adiporon were administrated to IRI mice.

Results: Among the enzymes related to ceramide synthesis, serine palmitoyltransferase 1, serine palmitoyltransferase 2, and glucose ceramidase were elevated at both IRI 2d group and IRI 28d group, and ceramide synthase 2 was mildly elevated at IRI 2d group but the change was not statistically different at IRI 28d group. β-Hexosaminidase α-subunit was mildly elevated at IRI 2d group and markedly elevated. Among the ceramide-degrading enzymes, acid ceramidase was slightly elevated at IRI 2d group and significantly elevated at IRI 28d group, and neutral ceramidase was decreased at both IRI 2d group and at IRI 28d group. In the renal tissues of ischemia-reperfusion AKI mice, both total Cer(d18:1) and Cer(d18:1/16:0) levels were significantly elevated at 6 hours after IRI, but the levels gradually began to decline thereafter, and basically decreased to the level of the sham-operated group at 48 hours after IRI. The expression of renal acid ceramidase increased at IRI 48h group compared to the sham group, while the expression of neutral ceramidase decreased at IRI 48h group. Intervention with acid ceramidase inhibitor ARN14974 and neutral ceramidase inhibitor C6-urea-ceramide did not alleviate nor aggravate AKI. Ceramidase activator adiporon could significantly alleviate renal tubular injury, and improve renal function.

Conclusions: Renal ceramidase plays a protective role in AKI, activating ceramidase could promote renal function in AKI.

Funding: Government Support - Non-U.S.

SA-PO143

Spatially Resolved Metabolomics to Discover Metabolic Alterations in PHF14-Associated Kidney Protection after Acute Kidney Injury

Jiaxin Chen, Cheng Xue, Zhiguo Mao. *Shanghai Changzheng Hospital, Shanghai, China.*

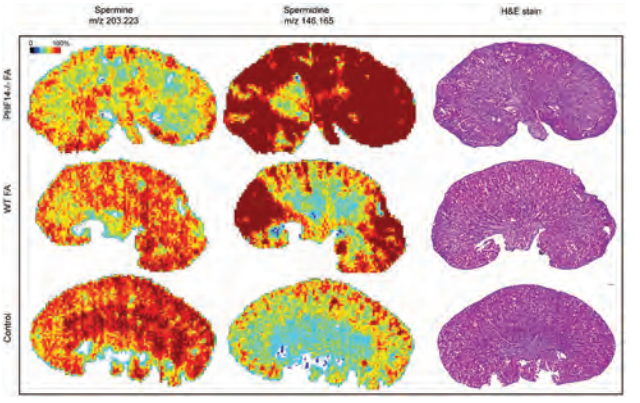
Background: Acute kidney injury (AKI) is a severe clinical syndrome,and a considerable part of AKI patients underwent maladaptive repair, resulting in renal fibrosis and chronic kidney disease. The epigenetic regulatory plant homologous domain Zinc finger protein-14 (PHF14) was proved to play a key role in inhibiting renal fibrosis after AKI, and its specific mechanism needs to be further clarified. This study aims to explore the mechanism of PHF14 inhibiting maladaptive repair after AKI from the metabolic level, so as to discover new therapeutic targets.

Methods: In this study, wild type (WT) and PHF14 knockout (PHF14-/-) mice were treated with folic acid (FA) to induce acute kidney injury. The renal function and histopathological were detected. Air-flow-assisted desorption electrospray ionization (AFADESI) was employed for metabolite analysis in cortical and medulla areas of mice kidney. Then the differential metabolites (DEMs) were identified respectively and KEGG enrichment was performed to identify the metabolic changes, and the DEMs were selected for mass spectrometry imaging analysis to determine their spatial distribution in the kidney.

Results: After 14 days of folic acid induction, renal function decreased, obvious inflammatory cell infiltration and fibrosis in kidney interstitial; while in PHF14-/- mice, were more serious. Compared with WT, different metabolites in the renal cortex and medulla of WT and PHF14-/- mice treated with FA were mainly concentrated in lipid metabolism, polyamine biosynthesis and TCA cycle, metabolites such as carnitine, glycerophospholipids, fatty acids, arginine, spermidine, succinic acid, malic acid and L-aspartic acid had significant changes in the kidney.

Conclusions: Spatial metabolomics was applied to investigate the changes of renal tissue metabolism after AKI, and the finding revealed the effect of PHF14 on renal metabolism after AKI, which proposed potential targets for the prevention and treatment of AKI.

Funding: Clinical Revenue Support



Distribution of Polyamine metabolites.

SA-PO144

Transcription Factor BACH1 in Promoting Mitochondrial Dysfunction of Kidney Ischemia-Reperfusion Injury via Mitochondrial Glutathione Depletion

Jun Li,[1,2] Xiaolin Li,[2] Hui Zhang,[2] Jingyao Lu.[2] *[1]Affiliated Hospital of Jiangnan University, Wuxi, China; [2]Jiangnan University Wuxi School of Medicine, Wuxi, China.*

Background: The hypothesis is that BACH1 induce mitochondrial glutathione(mtGSH) depletion through inhibiting SLC25A39 expression. The study aims to clarify the novel molecular pathogenesis of BACH1 on the renal ischemia-reperfusion induced-mitochondrial dysfunction, and provide a new intervention target for acute renal ischemia-reperfusion injury.

Methods: In vivo renal ischemia-reperfusion injury model(I/R) was established using C57BL/6J wild-type mice and BACH1 gene-knockout mice (BACH1-/-) respectively. Invitro anoxia-reoxygenation injury model(H/R) was established using human proximal tubular cells (HK-2) strain. BACH1 gene was silenced or overexpressed respectively, and SLC25A39 gene was also silenced. The effect of BACH1 on the transcriptional activity of SLC25A39 was detected by the luciferase reporter gene and Electrophoretic mobility shift assay (EMSA). The oxidative stress and mitochondrial function indexes were also measured.

Results: The renal expression of BACH1 increased, yet the renal expressions of SLC25A39 and mtGSH contents decreased significantly in patients with acute ischemic tubular injury and renal ischemia-reperfusion injury mice models. BACH1 deletion up-regulated renal expression of SLC25A39 and mtGSH contents, yet decreased mitochondrial oxidative stress index, leading to improved mitochondrial function in $BACH1^{-/-}$ mice following renal ischemia-reperfusion injury. In HK-2 cells subject to anoxia-reoxygenation injury, BACH1 gene overexpression down-regulated the expression of SLC25A39 and mtGSH contents, increased mitochondrial oxidative stress, leading to mitochondrial dysfunction. And BACH1siRNA up-regulated the expression of SLC25A39 and mtGSH contents, yet decreased mitochondrial oxidative stress, leading to improved mitochondrial function. Intriguingly, BACH1siRNA increased mtGSH contents and improved mitochondrial function in anoxia-reoxygenation HK-2 cells pretreated with GSH ethyl-ester. Luciferase reporter gene detection and EMSA confirmed the binding site between BACH1 and SLC25A39 promoter region.

Conclusions: BACH1 induced mitochondrial glutathione depletion through inhibition of SLC25A39 expression, leading to mitochondrial dysfunction of renal ischemia-reperfusion injury.

Funding: Government Support - Non-U.S.

SA-PO145

Protective Effect of Methylthioadenosine Phosphorylase (MTAP) Inhibition in AKI

Afaf Saliba, William B. Reeves, Kumar Sharma. Laboratory of Kumar Sharma, Center for Precision Medicine. *The University of Texas Health Science Center at San Antonio, San Antonio, TX*.

Background: Acute kidney injury (AKI) is sudden kidney failure, ranging from minor to severe, with multiple etiolgies. We identified adenine as a factor in diabetic kidney disease pathology, but its role in AKI is unknown. This study explores AKI metabolic mechanisms, focusing on adenine and the protective effects of inhibiting MTAP, the enzyme responsible for its production.

Methods: Male mice with ischemia-reperfusion injury (IRI) were prophylactically treated with dapaglifozin (10mg/kg) or MT-DADMe-ImmA (MTDIA 20 mg/kg) or vehicles with sham-operated mice as controls. For cisplatin-induced AKI, mice received MTDIA or vehicle before cisplatin (20 mg/kg), with saline controls. Plasma and kidney metabolomics were performed using capillary electrophoresis and liquid chromatography-mass spectrometry.

Results: Experimental IRI increased plasma metabolites, with adenine as the only nephrotoxic factor. Gene expression showed elevated inflammation and *Mtap*. Dapagliflozin modestly reduced kidney injury markers during ischemia, while MTAP inhibition significantly protected against AKI from IRI and cisplatin-induced models. MTAP inhibition normalized BUN, plasma creatinine levels and reduced kidney injury markers Kim-1 and Lcn2. PAS staining showed decreased necrotic tubules in MTDIA treated mice. MTAP inhibition reduced plasma LABA and pipecolate but not leucine and tyrosine. Kidney cortex adenine, pipecolate, GABA, and LABA were reduced, with increased MTA in MTDIA-treated mice. In cisplatin-induced AKI, MTDIA normalized BUN, Kim-1, and Lcn2 levels, and prevented tubular necrosis (Figure 1).

Conclusions: This study highlights the metabolic changes from IRI and identifies MTAP inhibition as a protective strategy against AKI. MTAP inhibition mitigates metabolic changes and improves cellular stress responses, suggesting its potential as a therapeutic target.

Funding: Other NIH Support - National Institutes of Health, National Center for Advancing Translational Sciences grant TL1 TR002647 (AS); National Institute of Diabetes and Digestive and Kidney Diseases UO1, 5U01DK114920-06 (KS), Veterans Affairs Support, Other U.S. Government Support

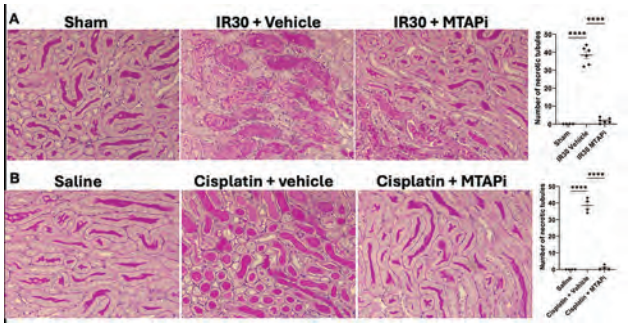


Figure 1. PAS staining of kidney FFPE sections (n=4/group) were evaluated blindly with quantification of necrotic tubules (average of 20 fields). IR30: 30 minutes bilateral ischemia. MTAPi: MTAP inhibitor (MTDIA).

SA-PO146

The IDH1-R132H Mutation Aggravates Cisplatin-Induced AKI by Promoting Ferroptosis through the Induction of NDUFA1 Methylation

Yanfang Xu. *Department of Nephrology, Blood Purification Research Center, the First Affiliated Hospital, Fujian Medical University, Fuzhou, China*.

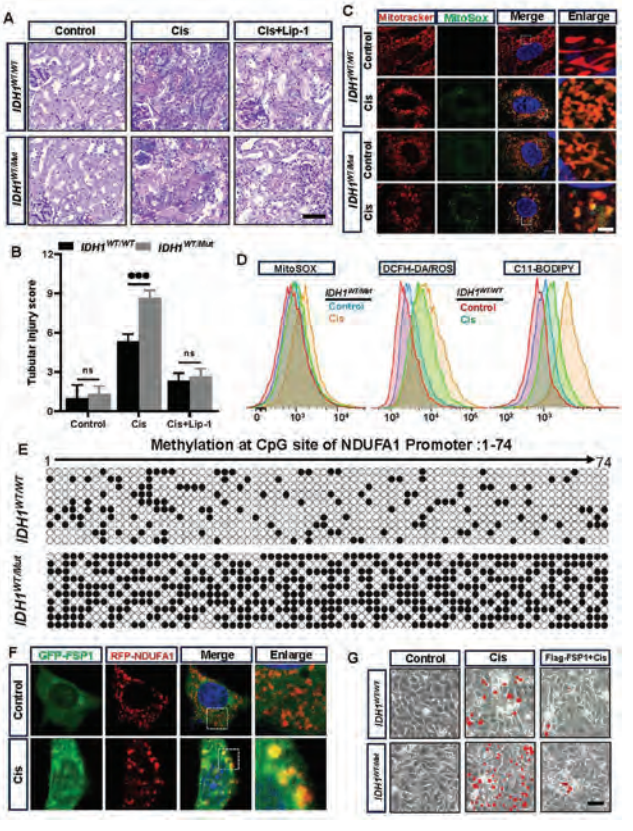
Background: The IDH1-R132H mutation is implicated in the development of various tumors. Whether cisplatin, a common chemotherapeutic agent, induces more significant renal toxicity in individuals with the IDH1-R132H mutation remains unclear.

Methods: We constructed a mouse model with the IDH1-R132H mutation to evaluate renal injury induced by cisplatin exposure. We explored key genes affected by the IDH1-R132H mutation using ferroptosis inhibitors, Reduced Representation Bisulfite Sequencing **(**RBBS) sequencing, and flow cytometry. Furthermore, we investigated the deeper mechanisms through overexpression and knockout of Ndufa1 and Fsp1.

Results: We revealed that the IDH1-R132H mutation exacerbates mitochondrial lipid peroxidation and dysfunction in renal tubules, rendering the kidneys more susceptible to cisplatin-induced ferroptosis. Further mechanistic investigations revealed that the IDH1-R132H mutation upregulates the methylation level of the NDUFA1, leading to the suppression of NDUFA1, disrupting the interaction between NDUFA1 and FSP1, resulting in the accumulation of lipid peroxidation and ferroptosis, thereby promoting AKI.

Conclusions: This study elucidates a novel mechanism underlying cisplatin-induced nephrotoxicity and provides valuable insights for the development of personalized treatment strategies for tumor patients carrying the IDH1-R132H mutation.

Funding: Government Support - Non-U.S.



IDH1-R132H mutation aggravates cisplatin-Induced AKI

(A, B) The IDH1-R132H mutation exacerbates kidney injury, which can be partially reversed by the ferroptosis inhibitor Lip-1. (C, D) IDH1-R132H mutation increases mitochondrial lipid peroxidation. (E) IDH1-R132H mutation leads to an upregulation of NDUFA1 methylation levels. (F) There is a direct interaction between NDUFA1 and FSP1. (G) Overexpression of FSP1 exerts a protective effect.

SA-PO147

Sex-Specific Differences in Branched Chain Amino Acid (BCAA) Catabolism and Mitochondrial Respiration in Healthy and Injured Kidneys

Samaneh DiMartino, Sandeep K. Mallipattu, Sian E. Piret. *Stony Brook University Renaissance School of Medicine, Stony Brook, NY.*

Background: Proximal tubule (PT) cells are highly susceptible to acute kidney injury (AKI) and undergo significant changes in cellular metabolism, directly contributing to injury. PT cells use fatty acid oxidation (FAO) and branched chain amino acid (BCAA) catabolism to generate ATP, however during AKI, both pathways are downregulated. Women and female mice are protected from AKI versus men and male mice. Our aim was to investigate BCAA catabolism in male and female human subjects and mice PT cells.

Methods: Publicly available RNA-sequencing data from kidney cortex of males and female subjects with and without AKI (three per group) were used for differential gene expression and pathway enrichment analysis using Seurat and EnrichR. Primary PT cells from *Bckdhb*$^{fl/fl}$ male and female mice were infected with adenoviral GFP (control) or CRE to excise *Bckdhb*, which encodes a crucial subunit of BCKDH, the rate-limiting enzyme in BCAA catabolism, followed by qRT-PCR. Wildtype (WT) primary PT cells were treated with aristolochic acid I to induce injury, and BT2 to activate BCKDH and increase BCAA catabolism. All primary PT cells underwent live cell metabolic assays using a Seahorse bioanalyzer.

Results: The BCAA catabolism pathway was significantly downregulated in males and females with AKI compared to healthy controls. However, more genes in the pathway were downregulated in males than females, and the downregulated genes were different between males and females. For example, *BCKDHB* was significantly downregulated in males but not females. To determine the specific role of *Bckdhb*, CRE recombination was undertaken in *Bckdhb*$^{fl/fl}$ primary PT cells, resulting in *Bckdhb* mRNA knockdown of 60% and 80% in male and female cells, respectively. Seahorse assays showed significant downregulation of basal respiration and mitochondrial ATP production rate in male cells but not in female cells upon *Bckdhb* knockdown, with no significant differences in glycolytic ATP production rate. BT2 treatment protected mitochondrial function in WT male primary PT cells treated with AAI but not female primary PT cells.

Conclusions: These findings suggest that BCKDH may play a more important role in males versus females, both in healthy and injured kidneys, which may have implications for targeted therapeutic strategies for AKI.

Funding: NIDDK Support, Other NIH Support - NYC-KUHR

SA-PO148

MicroRNA-mRNA Interactions in Cisplatin-Induced AKI to CKD

Hisakatsu Sone, Tae Jin Lee, Byung Rho Lee, Dan Heo, Sang-Ho Kwon. *Augusta University Medical College of Georgia, Augusta, GA.*

Background: Chemotherapy with cisplatin can lead to chronic kidney disease, complicating cancer prognosis. Understanding the interactions between microRNAs (miRNAs) and their target messenger RNAs (mRNAs) can shed light on the biological processes involved in cisplatin-induced kidney injury.

Methods: We used small and total RNA sequencing, and chimeric-eCLIP sequencing to identify pairs of miRNAs and their target mRNAs in the kidneys of cisplatin-injured male mice. These interactions were confirmed using various methods, including database searches, RNAscope, RT-qPCR, immunofluorescence, and immunoblotting.

Results: We identified 55,794 direct miRNA-mRNA interactions in the kidneys. Among the interactions, a group of cisplatin-induced miRNAs enriched with select mRNAs affects mitochondrial metabolic pathways. Specifically, the cisplatin-induced miRNAs, miR-429-3p and miR-21a-5p, suppress the pathway that breaks down branched-chain amino acids (BCAAs) in the proximal tubule, leading to ferroptotic cell death. In contrast, stimulating BCAA catabolism in the injured kidneys reduced ferroptosis and inflammation.

Conclusions: In vivo renal miRNA-mRNA interaction mapping identifies the role of branched-chain amino acid catabolism in ferroptotic proximal tubular cell death. Our findings suggest potential therapeutic benefits in modulating the branched-chain amino acid pathway to alleviate nephrotoxicity.

Funding: NIDDK Support

SA-PO149

Controlling p53 Responses in AKI

Shin-ichi Makino, Amy Zollman, Pierre C. Dagher, Takashi Hato. *Indiana University School of Medicine, Indianapolis, IN.*

Background: The guardian of the genome p53 is essential for controlling the cell cycle, genome integrity, and tissue repair. p53 is also an important determinant of AKI outcomes. However, limited strategies are available to control the p53 expression and facilitate tissue recovery.

Methods: Multiple models of AKI were used in our study. The full-length cDNA from endotoxin-treated mouse kidneys was sequenced using Nanopore long-read sequencing. CRISPR knock-out strategy was used to produce a cryptic exon knock-out mouse. For *in vitro* experiments, several antisense nucleotides targeting the short isoform were synthesized and transfected into HEK cells. CRISPR knock-in strategy was also used to generate p53 mutant human cell lines.

Results: We identified a previously uncharacterized short transcript consisting of the first p53 canonical exon and a cryptic exon embedded in the first p53 intronic region. We found that this short transcript emerges under various stress conditions. To determine the role of this transcript, we generated a mouse model in which the cryptic exon is genetically removed. We found that the lack of the cryptic exon heightens the expression of the canonical p53 upon stress challenges. Notably, mice lacking the short transcript were protected against ischemia-reperfusion injury with a significant increase in the expression of the canonical p53 in various cell types. Next, we designed and screened splice-switching antisense oligonucleotides. Our screening revealed specific antisense targeting sites that enabled us to differentially control the expression of the short transcript and canonical p53. Specifically, we found that targeting the transcription termination site results in the upregulation of the short transcript, linking transcription control and p53-mediated stress responses.

Conclusions: We have identified a strategy to control the expression of p53 in the kidney. This strategy involves targeting the stress-responsive cryptic exon, opening the door for finetuning p53 responses in AKI.

Funding: Other NIH Support - R01

SA-PO150

DHHC6-Mediated SDHB Palmitoylation Protects against Tubular Cell Death and AKI

Qing Hou, Chunsun Dai. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Acute kidney injury (AKI), a syndrome characterized by an abrupt of loss of kidney function, is associated with considerable morbidity and mortality. The tubular cell injury and death contributes to the initiation and progression of AKI. Palmitoylation, a reversible post-translational modification, is involved in the development of renal fibrosis. However, the role of palmitoylation in tubular cell survival and AKI remains unclear. We aimed to investigate the role and mechanism of palmitoylation in tubular cell survival and AKI.

Methods: 1.Acyl–biotin exchange,ABE; 2.Blue native polyacrylamide gel electrophoresis,BN-PAGE.

Results: 1. The level of protein palmitoylation was markedly downregulated in the kidney of mice after UNx+IRI surgery. Analysis of the transcription levels of DHHCx in the GSE98622 database revealed significant downregulation of *Zdhhc6* in the murine renal tissue of AKI. The expression of DHHC6 was reduced in tubular cells of AKI mice and patients. 2. To elucidate the role of DHHC6 in tubular cell survival and AKI, we generated DHHC6-deleted tubular cells mice by Cre/Loxp system and DHHC6 overexpressing mice by renal in situ injection of adeno-associated virus. We found that DHHC6 deficiency could exacerbate IRI induced renal injury, while overexpression of DHHC6 exerted renal protective effects. DHHC6 deficiency in vitro promoted tubular cell mitochondrial dysfunction and cell death, and significantly downregulated SDHB abundance. SDHB knockdown also promoted tubular cell death. 3. ABE assays showed that SDHB could be palmitoylated, and DHHC6 deficiency reduced, while DHHC6 overexpression elevated the palmitoylation level of SDHB. Immunoprecipitation and immunofluorescent analyses revealed the interaction of DHHC6 and SDHB. Furthermore, DHHC6 deficiency promoted the degradation of SDHB and reduced the activity of mitochondrial complex II. Based on the proteomics of palmitoylation modification and CSS/GPS-palm prediction results, the Cys115 site of SDHB was identified as its palmitoylation modification site. The palmitoylation of Cys115 was also associated with SDHB degradation and tubular cell death.

Conclusions: In summary, this study revealed that the palmitoyltransferase DHHC6 protects against UNx+IRI induced AKI and tubular cell death by catalyzing SDHB palmitoylation.

Funding: Government Support - Non-U.S.

SA-PO151

Dapagliflozin Attenuates Tubular Injury and Ferroptosis after AKI in Diabetic and Nondiabetic Mice

Tetta Sato,[1] Shintaro Ide,[1] Kana Ide,[1] Ayano Yamaguchi,[1] Naoya Teramoto,[1] Yoshiro Maezawa,[1] Koutaro Yokote.[2] *[1]Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu, Chiba, Japan; [2]Chiba Daigaku, Chiba, Japan.*

Background: Diabetes Kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) and end-stage renal disease. Diabetic patients are at a higher risk of acute kidney injury (AKI), which can lead to the rapid deterioration of kidney function, suggesting that AKI is a potential risk factor for DKD without albuminuria. Although several studies have shown sodium-glucose cotransporter 2 (SGLT2) inhibitors have a renoprotective effect in both diabetic and non-diabetic patients, it remains unclear whether SGLT2 inhibitors are protective in AKI and its transition to CKD, with or without diabetes.

Methods: To clarify the effect of an SGLT2 inhibitor in AKI and its mechanism, we performed unilateral ischemia-reperfusion injury (uIRI) in type 2 diabetic mice (db/db). We then divided these mice into two groups: one treated with Dapagliflozin (DAPA), an SGLT2 inhibitor, and the other treated with vehicle. We also performed uIRI on C57B6J (WT) mice and compared kidney phenotypes between the DAPA and vehicle groups to reveal this effect independently of glycemic control. We used histological analysis, immunofluorescence, and quantitative PCR to evaluate kidney injury.

Results: Db/db uIRI kidneys with vehicle showed severe tubular injury (ex. *Vcam1, Havcr1*), accumulation of inflammatory cells, and fibrosis. In contrast, treatment with DAPA significantly reduced tubular injury in db/db uIRI kidneys, indicating a protective effect of DAPA against AKI and AKI to CKD transition. This protective effect was also seen in WT uIRI kidneys. To understand the mechanism, we focused on ferroptosis, a non-apoptotic cell death process that plays a key role in diseases, such as DKD, AKI, and AKI to CKD transition. Db/db uIRI kidneys and WT uIRI kidneys with the vehicle showed increased ferroptosis, characterized by 4-Hydroxynonenal (4HNE) and TUNEL positivity. However, treatment with DAPA reduced these markers in both groups.

Conclusions: Our data demonstrate that Dapagliflozin attenuates kidney tubular injury and reduces ferroptosis, thereby mitigating AKI to CKD transition after AKI. The renoprotective effect of SGLT2 inhibitors appears to be mediated through suppressing ferroptosis. These findings would provide new insights into the potential treatment of AKI in patients with diabetes.

Funding: Government Support - Non-U.S.

SA-PO152

Sex Differences in Dynamics of Necroptosis in Ischemia-Reperfusion-Induced AKI

Minh H. Tran. *University of South Florida, Tampa, FL.*

Background: Ischemia reperfusion induced injury (IRI) is an important cause of acute kidney injury (AKI). Interruption of the arterial blood supply to a donor kidney leads to renal hypoxic injury and cell death, but blood flow restoration also result in reperfusion injury and organ dysfunction. Necroptosis has been recently identified as an essential factor in the pathogenesis of IR-AKI. However, sex differences in the dynamics of necroptosis in kidney IRI have not been a focus of study until now.

Methods: Male and female C57BL/6J mice (n=3-5 male or female mice/ group) were induced AKI via bilateral renal pedicle clamping for 18 minutes at 37 degrees Celsius. Plasma, urine and kidney tissue were collected at 0, 3, 6, 12, 24, 48, and 72 hours post reperfusion and plasma creatine, BUN and morphological damage were assessed by PAS staining and TUNEL staining. Necroptosis activation was equantified by the phosphorylation status of the necroptosis factors RIPk1, RIPk3, MLKL, and inflammatory factors (IL-6, IL-10 and TNF-α) post I/R injury. The effects of different sex hormone on the dynamic of necroptotic activation was assessed by ovariectomy to the female mice followed by IR-AKI. Kidney injury and function were evaluated and compared.

Results: Activation of necroptosis started at 3 hours post reperfusion in male mice, and around 6 hours after reperfusion in the female mice. The male mice exhibited a stronger and longer activated necroptosis status than females based on the phosphorylation measurement by western blotting. This sexual dimorphism closely correlated with sex differences in kidney injury dynamics. The plasma creatinine was 0.35±0.04 and 0.32±0.06 mg/dL for male and females, respectively, at 3 hours of reperfusion. Which dramatically increased to 2.05±0.18 at 48 hours of reperfusion for the males and gradually increased to 0.94±0.13 mg/dL. Deficiency in sex hormone mitigated the sex difference in the dynamic of the necroptotic activation and consequently in kidney injury.

Conclusions: Our study is the first to describe the sex differences in the dynamics of necroptosis and necroinflammation in a mouse model of IRI-AKI. Our findings provide a different time frame in monitoring kidney injury in males and females and suggest that although treatments targeting necroptosis may be effective even if given 3 hours after reperfusion, the treatment in male should start earlier than females.

SA-PO153

Tryptophan Breakdown Product 3-Hydroxyanthranillic Acid Promotes AKI Recovery under Hypoxic Conditions

James O'Sullivan, Gabriella Borkowski, Rajni Sharma, Ratnakar Tiwari, Pinelopi P. Kapitsinou. Kapitsinou Lab. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: We and others have demonstrated that hypoxic preconditioning is an effective strategy to protect against renal ischemia reperfusion injury (IRI). While more clinically relevant, however, the effect of hypoxia exposure after IRI remains undefined. Here, by profiling the effects of systemic hypoxia exposure on kidney repair after IRI, we identified the tryptophan metabolite 3-hydroxyanthranillic acid (3HAA) as a metabolite promoting adaptive repair. Beneficial effects of 3HAA reported include oxidative stress reduction via NRF2 activation, anti-ferroptosis, ROS-scavenging and enhanced longevity.

Methods: Male C57/BL6 mice were subjected to unilateral IRI and 6 hours later were placed in hypoxic chamber at 8% O_2 or normoxia for 72 hours post-IRI. Kidneys and serum collected for RNA-seq and HPLC metabolite profiling. HK2 cells were maintained under defined growth medium, treated with 3HAA (100μM or 200μM) and/or IL1β (10ng/mL) for 24 hours.

Results: 72 hours post-IRI, Hx mice had significantly lower injury scores histologically (2.2±0.4 Hx vs 3.3±0.5 Nx, P=0.02) and significantly lower KIM1 mRNA (0.8±0.2 Hx vs 2±0.5 Nx, P=0.0002). RNA-seq analysis followed by KEGG pathway analysis showed significant upregulation of tryptophan metabolism and glutathione metabolism, while inflammatory response was the top downregulated pathway. TRRUST implicated NRF2 as a key TF (P=3e-8), regulating many highly upregulated genes such as glutathione S-transferase alpha (GSTA) genes. Metabolite profiles indicated 3HAA as a key metabolite increased by hypoxia in serum (8.6-fold, P=0.02) and kidney (2.2-fold, P=0.005) compared to normoxia. In HK2 cells, 24-hour treatment with 3HAA 100μM increased GSTA1 expression by 3.1-fold (P=6e-4 vs untreated). Under IL1β-stimulation, 3HAA 100μM or 200μM reduced CCL2 expression by 4.3-fold (P=0.03) and 17.6-fold (P=0.01), respectively, compared to IL1β-stimulation alone.

Conclusions: Systemic hypoxia after IRI promotes adaptive kidney repair and reduces inflammation, a response that is associated with increased 3HAA and NRF2 activation. In vitro work indicated 3HAA alone counteracts inflammation in tubular epithelial cells and promotes anti-oxidative defense. Our findings identify a hypoxia/3HAA axis that can be exploited as therapeutic strategy in AKI, warranting further mechanistic investigation.

Funding: NIDDK Support

SA-PO154

Mechanism of Nicotinamide N-methyltransferase (NNMT) Regulating Heterogeneous Nuclear Ribonucleoprotein (HnRNP) D Promoting Ferroptosis in Renal Tubular Epithelial Cells and Aggravating Acute Kidney Injury

Yuebo Huang, Hui Peng. *Sun Yat-sen University, Guangzhou, China.*

Background: The study has shown that AKI is a significant risk factor for CKD and ESRD, seriously endangering human health. Exploring the mechanisms of AKI and finding effective treatment and intervention measures is of great clinical significance. Recently, Xu et al. used single-cell mRNA sequencing (scRNA-seq) to show that the ferroptosis pathway was significantly activated in proximal renal tubular epithelial cells (PTCs) of AKI mouse models. Therefore, ferroptosis could be a potential therapeutic target, which can provide new strategies for the treatment of AKI.

Methods: First, we screened the human GEO AKI database GSE30718, and enrichment analysis based on differential genes revealed significant enrichment of the ferroptosis pathway. Further screening of candidate gene nicotinamide N-methyltransferase (NNMT) in the ferroptosis pathway through machine learning for further research. Through combined human and mouse AKI scRNA-seq analysis, we found that NNMT is highly expressed in renal tubular epithelial cells of AKI renal tissue. Then, we overexpressed or silenced NNMT protein in HK-2 cells, changes in cell ferroptosis markers and release of inflammatory factors were detected by Western blot, real-time PCR, ELISA, immunofluorescence, and flow cytometry. Next, we used LC-MS/MS to detect potential binding proteins of NNMT and then validated it by using CO-IP and immunofluorescence.

Results: Silencing or overexpression NNMT can improve or exacerbates H/R and Cis-induced ferroptosis and inflammatory cytokine release in HK-2 cells. By using LC-MS/MS analysis, it was found that there is a potential interaction between HnRNPD and NNMT. Further validation of the binding between NNMT and HnRNPD was conducted through CO-IP and immunofluorescence, and NNMT increased the expression of HnRNPD protein by inhibiting the degradation of HnRNPD ubiquitinated proteasomes. RIP experiments confirmed that HnRNPD can stabilize the expression of ATF3 protein expression and lead to ferroptosis.

Conclusions: Our findings indicate an upregulation of NNMT expression in renal tubular epithelial cells during AKI. NNMT serves to stabilize ATF3 protein expression by impeding the ubiquitination and proteasome-mediated degradation of HnRNPD. This mechanism leads to lipid peroxidation and ferroptosis in renal tubular epithelial cells, thereby fostering the onset and progression of AKI

SA-PO155

Hydrogen Sulfide Alleviates Cisplatin-Induced AKI by Targeting Pyroptosis

Zhenyuan Han,[1,2] Yutao Jia,[1,2] Tianyu Deng,[1,2] Zhiyun Ren,[1,2] Weiwan Wang,[1,2] Xiaoyan Wang.[1,2] *[1]Department of Nephrology, Nanjing BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, Nanjing, China; [2]The Core Laboratory, Nanjing BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, Nanjing, China.*

Background: Our previous studies have demonstrated that GYY4137, a long-acting hydrogen sulfide(H_2S) donor, exerts a remarkable protective effect on diabetic renal damage by affecting multiple ROS-associated enzymes. According to animal experimental research reports, exogenous H_2S donors alleviate the renal toxicity caused by cisplatin, mainly through anti-inflammatory, antioxidant, autophagy, etc. However, the effect of H_2S on pyroptosis in cisplatin-induced AKI(cis-AKI) is currently unclear.

Methods: Male C57BL/6J mice (7-8 weeks old), were randomly divided into 3 groups (n=7/group). Cisplatin (20 mg/kg) was given by a single intraperitoneal injection to both cisplatin group and cisplatin+GYY group, the latter was given GYY4137(100mg/kg) by daily intraperitoneal injection for 4 times, a day before cisplatin. The control mice were given 0.9% saline. Blood and kidney samples were collected after the mice were sacrificed on day 3 of cisplatin. Data was shown as mean±SE, while significance($P<0.05$) was achieved by one-way ANOVA, and Holm-Sidak posthoc test.

Results: Compared to the control group, cis-mice showed an increase in serum creatinine (82.22±6.05 vs 57.3±2.4, umol/L) and urea nitrogen (23.3±1.1 vs 6.5± 0.3, mmol/L). Histological analysis also revealed severe damage to the renal cortex, characterized by vacuole-like degeneration of tubular epithelial cells, loss of brush border, and tubular cell necrosis. There were increases of NLRP3 (121.9±5.2) and GSDMD (127.3±1.7) in cis-group, indicating an activation of classical pyroptosis. In the non-classical pyroptosis pathway, caspase3 (132.9±2.1) and GSDME (209.1±8.2) were significantly elevated in response to cisplatin treatment. Treatment with GYY4137 mitigated serum creatinine levels (63.6±4.6) and blood urea nitrogen (18.1±1.7) and reduced histological damage to the renal cortex in cis-mice. Moreover, it normalized or reduced the cis-mediated increases in pyroptosis-related proteins, including caspase3 (106.9±5.9), GSDME (173.8±11.2), NLRP3 (88.3±4.3), and GSDMD (97.1±6.4).

Conclusions: Exogenous hydrogen sulfide may alleviate cis-AKI via inhibiting caspase3-dependent or independent pyroptosis.

Funding: Government Support - Non-U.S.

SA-PO156

NINJ1 Has a Pathogenic Role in Kidney Ischemia-Reperfusion Injury

Jianyong Yin, Niansong Wang. *Department of Nephrology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Programmed cell death (PCD) plays a pivotal role in the pathogenesis of AKI. It has been proved that various PCDS such as pyroptosis, necroptosis and ferroptsis can induce plasma membrane rupture (PMR) and release of damage associated molecular patterns (DAMPs), further activating inflammatory responses, and lead to kidney tissue damage. PMR is the common ultimate event in a variety of lytic cell death. Nerve injury-induced protein 1 (NINJ1) is a cell adhesion molecule highly expressed in immune cells and kidney. Recent studies indicate that NINJ1 is a key executive protein of PMR during various PCD. Therefore, we speculate that NINJ1 mediates PMR in tubule cells during PCD and subsequently activates inflammation, which may be the primary molecular mechanism of its pathogenic role in AKI.

Methods: We examined renal NINJ1 oligomerization in patients with AKI and AKI mice model. Male C57BL/6J were subjected to bilateral renal ischemia-reperfusion to induce AKI. Tubule cell-specific NINJ1 knockout mice was utilized to determine the pathogenic role of NINJ1 in AKI. Renal function, tubular cell death, release of HMGB1 and pro-inflammatory cytokines was assessed. Besides, we determined the role of NINJ1 in cell damage induced by hypoxia reoxygenation in primary renal tubular epithelial cells.

Results: The expression of NINJ1 was significantly increased in AKI model and kidney specimens of AKI patients. Tubular cell-specific knockout of NINJ1 remarkably ameliorated ischemia-reperfusion induced renal dysfunction and pathological injury. Moreover, tubular cell death and the levels of HMGB1, IL-1β were significantly blunted in NINJ1 knockout mice compared with WT mice. Additionally, hypoxia and reoxygenation induced NINJ1 oligomerization in renal tubular cells, while knockout of NINJ1 significantly decreased the LDH, which is the standard marker of PMR.

Conclusions: NINJ1 mediated PMR and subsequent release of DAMPs is critically involved in the pathogenesis of AKI and blockade of NINJ1 may be a novel therapeutic strategy for the treatment of AKI.

Funding: Government Support - Non-U.S.

SA-PO157

Estrogens Protect against AKI by Regulating Ferroptosis Sensitivity

Wulf Tonnus. Linkermann Lab. *Technische Universitat Dresden, Dresden, Germany*.

Background: Epidemiological studies demonstrated that premenopausal women experience less episodes of acute kidney injury (AKI) than males, and that estrogen supplementation protects concomitantly in menopause. This falls in line with the known phenomenon that female mice are protected against ischemia/reperfusion injury. However, molecular mechanisms of this phenomenon remain ill-defined. As ferroptosis, an iron-dependent form of regulated necrosis, plays a crucial role in the pathogenesis of AKI, we hypothesized that estrogens modulate sensitivity to ferroptosis.

Methods: The effects of estrogens on ferroptosis sensitivity were investigated in various cell culture assays. Mechanistic insights were derived from western blots, and confirmed by CRISRP-mediated knock-outs. Radical trapping mechanisms were tested in cell free systems, whereas translational relevance was established via isolated renal tubules of various species. Complex murine studies tested proposed mechanisms in AKI models.

Results: 17-beta-estradiol (E2) protected against ferroptosis and associated lipid peroxidation in cell culture. Mechanistically, E2 quinone derivates 2OH and 4OH were identified as potent lipophilic radical trapping antioxidants, which were regenerated by the oxidoreductase FSP1 (AIFM2). Interestingly, inhibition of FSP1 sensitized female cells to ferroptosis and increased the E2 doses required for protection. Furthermore, E2 induced several antiferroptotic programs via genomic functions, including increased expression of FSP1, generation of hydropersulfides, and downregulation of ether lipids via reduced AGPS expression. Knock-out studies confirmed the functional relevance of these mechanisms in cell culture, whereas isolated tubuli from several mammalian species demonstrated the conservation of these mechanisms. Studies utilizing the murine IRI model proved the functional relevance of these mechanisms upon AKI.

Conclusions: In summary, we describe the molecular underpinnings of ferroptosis resistance in female mammals. These findings may explain epidemiological data on female resistance to AKI, and could lead the path to sex-specific interventions in prevention and treatment of human AKI.

Funding: Government Support - Non-U.S.

SA-PO158

KRT20 Protects against Ferroptosis of Renal Tubular Cells by Inhibiting Extracellular Secretion of PRDX2 in AKI

Lijun Yin, Anqun Chen. *The Second Xiangya Hospital of Central South University, Changsha, China.*

Background: Acute kidney injury (AKI) exhibits high incidence and morbidity. Ferroptosis of renal tubular cells is a key event driving tubular injury in AKI, but the mechanism of which is unclear. Cytokeratin 20 (KRT20), a biomarker of tubular injury, is an intermediate filament protein whose role in renal tubular injury remain elusive. Intracellular peroxiredoxin2(PRDX2) is closely related to ferroptosis, but the relationship between KRT20 and PRDX2 has not been reported in any studies.

Methods: Bulk RNA-seq and snRNA-seq of kidneys from the AKI mouse model in public databases, were used to analyze transcript levels of KRT20 in AKI, which was validated in two AKI mouse models (cisplatin-induced AKI and ischemia-reperfusion(IR) AKI) and clinical kidney biopsy specimens. Renal proximal tubule-specific *Krt20* knockout mice in vivo, knockdown and overexpression of KRT20 in vitro, were used to construct two AKI models to assess the role of KRT20 in AKI. Luciferase reporter assays, CHIP-PCR and IP-MS were used to explore the transcription factors and the downstream candidates target of KRT20, respectively. CO-IP and truncating mutation were used to explore the binding domain between KRT20 and candidate targets. Whether urinary PRDX2 could be used as a promising predictor for AKI was investigated in a patient cohort.

Results: KRT20 was dramatically increased in renal tubules upon injury in the AKI mouse model and AKI patients, which might be regulated by the transcription factor Fosb. The renal tubular specific knockout of *Krt20* aggravated cisplatin- and IR-induced AKI in mice. The intervention of KRT20 affected ferroptosis of tubular cells in vitro. Mechanistically, KRT20 bound with PRDX2, whose secretion was dependent on ALG-2-interacting protein X(Alix), to retain its intracellular location to prevent renal tubular cell ferroptosis and attenuate AKI. KRT20 and Alix competitively bind to the NTD domain of PRDX2, thus affecting the secretion of PRDX2. Urinary concentrations of PRDX2 significantly increased in patients who underwent partial nephrectomy, which positively correlated with the renal tubular injury biomarker, such as KIM-1 and NGAL.

Conclusions: This study discovered a Fosb-KRT20-PRDX2 axis in the progression of AKI, which warrants future exploration as a therapeutic targets. In addition, PRDX2 may be a noninvasive biomarker for renal tubular injury.

Funding: Government Support - Non-U.S.

SA-PO159

Heat Acclimation Attenuates Ferroptosis and Prevents Heat Stress-Induced AKI by Enhancing Mitophagy

Yongwei Song,[1] Wenting Chen,[1] Wang Ling,[1] Yang Xuesen,[2,3] Dai H. Zi.[1] *[1]Department of Rheumatology and Clinical Immunology, Daping Hospital, Army Military Medical University, Chongqing, China; [2]Department of Tropical Medicine, Army Military Medical University, Chongqing, China; [3]Key Laboratory of Extreme Environmental Medicine, Ministry of Education of China, Army Military Medical University, Chongqing, China.*

Background: Exposure to a intense heat stress environment can lead to acute kidney injury (AKI), while heat acclimation(HA) can prevents the kidney against ischemic injury induced by intense heat stress. However, the mechanism underlying of the nephroprotective effect of HA remains unclear. It has been reported that ferroptosis is involved in heat stress-induced AKI. But,It is still unclear whether heat acclimation can exert renal protective effects by reducing ferroptosis. Furthermore, Mitophagy may influence the development of AKI through regulating intracellular iron metabolism, but it has not been reported in heat stress-induced AKI.

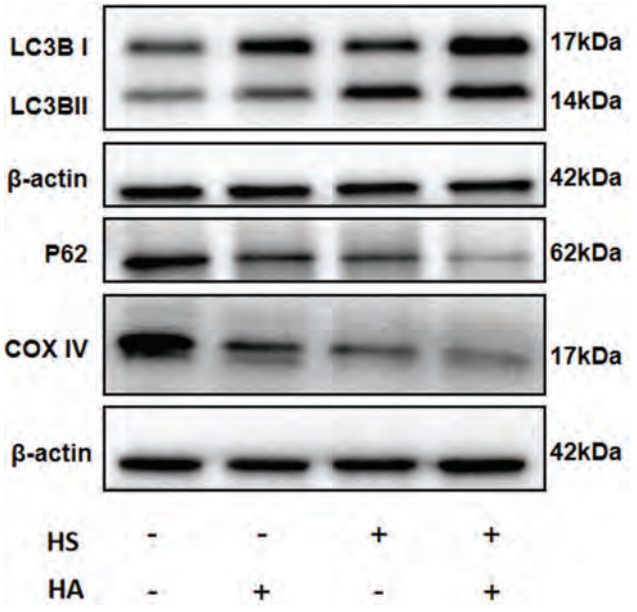
Methods: C57BL / 6 mice were divided into control group (CON), heat acclimation group (HA), heat stroke group (HS), heat stroke + heat acclimation group (HS+HA), and

heat stroke+heat acclimation+3-MA group (HS+HA+3-MA). Among them, the mice in the HS group were kept in a high-temperature environment to establish the HS model. The mice in the HS+HA group were kept in low-temperature environment for 30 days to establish the HA model, followed by inducing the HS model. Mice in the HS+HA+3-MA group were subjected to high heat stress after consecutive intraperitoneal injection of 3-MA (20 mg/kg/day) for the last 7 days of the constructed HA model. The levels of mitophagy and ferroptosis were assessed in each group of mice.

Results: In the HS group, there was a significant increase ferroptosis. Moreover, heat acclimation significantly enhanced mitophagy and alleviated HS-induced ferroptosis. In contrast, Inhibiting mitophagy exacerbated ferroptosis and reversed the renoprotective effect of the heat acclimation.

Conclusions: Heat acclimation may prevent heat stress-induced acute kidney injury by alleviating ferroptosis through enhanced mitophagy.

Funding: Clinical Revenue Support



Heat acclimation can enhance mitophagy

SA-PO160

Remote Ischemia Precondition Protects against Kidney Ischemia-Reperfusion Injury (IRI) through Apoptosis-Associated Vesicles Carrying MIF Protein

Nieke Zhang,[1,2] Yi Xia,[1,2] Ming Chen,[1,2] Guangyuan Zhang.[1,2] [1]*Southeast University, Nanjing, China;* [2]*Southeast University Zhongda Hospital Department of Urology, Nanjing, China*.

Background: Previous study showed remote ischemia precondition (rIPC) protected against kidney ischemia-reperfusion injury (IRI) through extracellular vesicles (EVs) delivering, however the mechanism remains unknown. It's showed apoptosis-induced compensatory proliferation signaling related vesicles (ACPSVs) could transmit proliferation signal to surrounding cells. In this study, we aim to investigate the role of ACPSVs in renal IRI after rIPC and its underlying mechanism.

Methods: We established a bilateral hind limb IPC followed by unilateral renal IRI rat model and a serum-starved apoptotic cell model. ACPSVs were isolated from rat plasma or cellular supernatant using differential centrifugation, ACPSVs size was analyzed by electron microscopy and nanoparticle tracking analysis and their contents were analyzed by ELISA and Western blot. Observing the effects on renal IRI by HE staining, Ki67 and serum creatinine tests after allogeneic injection of ACPSVs or plasma post-IPC. Using CCK8 and flow cytometry analysis to investigate ACPSVs impact on cell proliferation and apoptosis after co-culture with HK2 cell. Applying GO and KEGG analysis to explore the potential downstream molecular mechanisms.

Results: A stable rat model was established. The characterization of ACPSVs was confirmed, and plasma or ACPSVs after rIPC can alleviate kidney damage, the protective effect was diminished when ACPSVs were removed from plasma. A tenfold increase in plasma macrophage migration inhibitory factor (MIF) expression after rIPC was observed, mainly concentrated in ACPSVs. A HeLa cell model was established, the optimal condition for ACPSVs generation was to culture cell in EBSS containing 0.1% BSA and 0.1g/L $MgCl_2$ for 24 hours. HK2 cells can uptake ACPSVs, with peak uptake at 12h post co-culture. EVs of approximately 460.6 nm in size were obtained, its ACPSV marker (CrkI) was confirmed. Compared to the sham group, apoptosis rates reduced and cell viability increased in the ACPSVs+HK2 group. Analysis of ACPSV contents highlighted the significance of MIF. GO and KEGG analysis showed that proteins contained in ACPSVs were enriched in molecular complexes related to macrophages and cell proliferation pathways.

Conclusions: rIPC not only exerts cytoprotective effects but also confers protection against renal IRI through ACPSVs carrying MIF protein.

Funding: Government Support - Non-U.S.

SA-PO161

Fibroblast Growth Factor 23 (FGF-23) Inhibits Gasdermin E (GSDME)-Mediated Pyroptosis via Autophagy in Folic Acid-Induced AKI

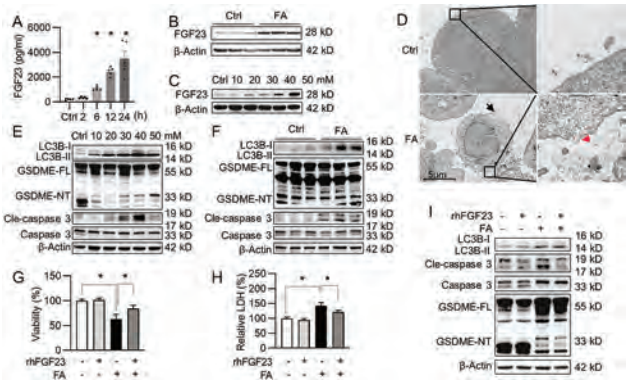
Lina Zhang,[1,2] Limeng Wang,[1] Fengmin Shao,[1] Wei Qin.[2] [1]*Henan Provincial People's Hospital, Zhengzhou, China;* [2]*Sichuan University West China Medical Center, Chengdu, China*.

Background: Fibroblast growth factor 23 (FGF23) increases rapidly after acute kidney injure (AKI); however, the precise role of FGF23 in AKI remains unclear.

Methods: In vitro and in vivo folic acid (FA)-induced AKI models were utilized to investigate the role of FGF23, via inhibition with FGFR inhibitors or enhancement with recombinant human FGF23 (rhFGF23) protein.

Results: Serum FGF3 and renal FGF23 protein levels were significantly increased in mice with FA-AKI (Fig. 1 A and B). In vitro, FGF23 levels were observed to rise progressively with higher FA concentrations and extended stimulation periods (Fig. 1 C). Transmission electron microscopy (TEM) strongly suggests the occurrence of pyroptosis in FA-AKI characterized by balloon-like bubbles on the cell membrane and membrane rupture (Fig. 1 D). The expression levels of GSDME-NT and cleaved-caspase 3 experienced an increase with higher concentrations of FA or extended stimulation periods (Fig. 1 E). Similarly, significant increases in GSDME-NT and cleaved-caspase 3 levels were detected in the kidney tissues of the mice with FA-AKI (Fig. 1 F). Furthermore, the presence of autophagy in FA-AKI was confirmed by the observation of autophagosomes and autolysosomes in the FA group, as well as the upregulation of LC3B-II proteins in both in vivo and in vitro FA-AKI models. The addition of the FGFR pan-inhibitor PD173074 led to reduced cell viability and increased LDH levels compared to the FA group. Additionally, the levels of LC3B-II were significantly reduced, while the levels of cleaved-caspase 3 and GSDME-NT were significantly elevated. The FGFR4 specific inhibitor BLU9931 showed similar results. In contrast, administration of rhFGF23 resulted in opposite results (Fig. 1G, H, and I). In summary, FGF23 can facilitate autophagy then inhibit caspase-3/GSDME-mediated pyroptosis in FA-AKI.

Conclusions: Our study elucidated the protective role of FGF23 in AKI and clarified its underlying mechanism by targeting GSDME-mediated pyroptosis through autophagy.



SA-PO162

KLF4/Galectin3 Signaling Axis Promotes Tubular Cell Death and AKI

Lishan Liu,[1] Kang Liu,[1] Juanjuan Jiang,[1] Jiafa Ren.[1,2] [1]*The First Affiliated Hospital of Nanjing Medical University, Nanjing, China;* [2]*Nanjing Medical University, Nanjing, China*.

Background: Acute kidney injury (AKI) is a serious clinical condition characterized by a rapid deterioration in renal function. Among the various components of the kidney, renal tubular cells are particularly vulnerable and often sustain the most significant damage during AKI. In clinical practice, AKI can stem from a diverse array of causes including ischemia, exposure to nephrotoxic agents, or sepsis. This diversity raises the question of whether there exists a common pathophysiological mechanism or pathway in renal tubular cells that underlies the development of AKI. Given the lack of effective therapies for the different etiologies of AKI, uncovering its common underlying molecular mechanisms across different causes could have a significant impact on human health.

Methods: We reanalyzed the single-cell RNA-sequencing atlas from four mouse AKI models to identify Galectin3 as a commonly expressed candidate in injured tubular cells. We then confirmed expression of Galectin3 protein in injured mouse and human tissues by immunofluorescence or western blotting. Furthermore, to determine the molecular

mechanisms regulating the galectin3 pathway, we utilized the "Cre-loxp" system, conducted bulk RNA-sequencing assays, and employed pharmacological interventions in a mouse model of AKI. Additionally, we examined the molecular mechanisms in an in vitro culture of the human kidney tubular cell line (HK2).

Results: We observed that Galectin3 is significantly up-regulated in all four AKI mouse models and shows a positive correlation with tissue injury in human kidneys affected by AKI. Our ChIP-PCR and luciferase-reporter experiments confirmed the direct binding of the transcription factor KLF4 to a specific sequence of the galectin3 gene promoter, supporting the predictions of the JASPAR database. Furthermore, mice with tubular-specific deletion of KLF4 displayed reduced kidney injury and inflammation, along with lower levels of galectin3 expression in both cisplatin and ischemia-reperfusion-induced AKI. Targeting the KLF4/Galectin3 axis with Kenpaullone and GB1107 demonstrated protective effects against cisplatin-induced cell death and acute kidney injury, respectively.

Conclusions: Our study highlights the critical role of KLF4/Galectin3 axis in the pathogenesis of AKI. Disrupting KLF4/Galectin3 signaling pathway may offer a promising therapeutic approach for the treatment of AKI.

Funding: Government Support - Non-U.S.

SA-PO163

Exposure of Viable Proximal Tubular Epithelial Cells (PTEC) to Apoptotic Cells Enhances Activation of Mixed-Lineage Kinase-3 (MLK-3) in PTEC

Sunho Park,[1,2] Saket Jha,[1,2] Sandeep Kumar,[1,2] Sowdhamini Mahendiran,[1,2] Sunil K. Singh,[1,2] Piush Srivastava,[1,2] Ajay Rana,[1,2] Jerrold S. Levine.[1,2]
[1]University of Illinois Chicago, Chicago, IL; [2]Jesse Brown VA Chicago Healthcare System, Chicago, IL.

Background: We have previously shown that receptor-mediated recognition of apoptotic targets by viable PTEC induces caspase 8- and BID-dependent apoptotic death of the PTEC. The signaling intermediates between target recognition and caspase-8 activation remain unknown. Separate studies have shown that MLK-3 mediates the death of kidney epithelial cells in response to a variety of toxic and inflammatory stimuli. We therefore hypothesized that MLK-3 may play a role in target-dependent death of PTEC.

Methods: BU.MPT cells, a conditionally immortalized PTEC line, were used as both viable responding cells and apoptotic targets. Responder cells were exposed to targets for 30 mins, followed by washing. Responder cells were then treated with vehicle, TNF-a, LPS, or both for 15 mins, either immediately after washing or after overnight incubation.

Results: Exposure to apoptotic targets led to increased activity of MLK-3, as shown by increased phosphorylation of MLK-3 and its downstream target JNK, on both Western blotting and immunofluorescence microscopy. The degree of MLK-3 activation was equal to or exceeded that induced by TNF-a and/or LPS. Activation by apoptotic targets alone occurred immediately after target exposure and persisted despite overnight exposure in the absence of targets.

Conclusions: We have shown that exposure of viable PTEC to apoptotic targets leads to activation of MLK-3, a kinase known to enhance the death of PTEC to a variety of injurious stimuli. Additional studies involving the overexpression or inhibition of MLK-3 are planned to determine whether MLK-3 is a key signaling intermediate connecting receptor mediated recognition of apoptotic targets and caspase 8-dependent apoptotic death. As most therapies for acute kidney injury (AKI) fail because efficacy depends on their administration before injury, activation of MLK-3 by apoptotic targets offers great promise because this mechanism of PTEC death is initiated *after* injury occurs.

Funding: Other NIH Support - National Cancer Institute

SA-PO164

Effect of PD-1 Blockade on Neonatal Sepsis and Septic Kidney Injury in Mice

Dong Li, Huiling Wu. *The First Affiliated Hospital of Dalian Medical University, Dalian, China.*

Background: Blocking the Programmedcelldeath-1 (PD-1) pathway can improve the prognosis and survival of patients with sepsis, and affect the occurrence of kidney injury in sepsis, but the mechanisms are still unclear. In this study we explored the effects of PD-1 blocking on neonatal sepsis and sepsis kidney injury, and aim to explore whether the kidney changes are mediated by glycolysis pathway.

Methods: C57BL/6 newborn mice at 7 days post birth (P7) were selected and randomly divided into four groups: Anti- PD-1-LPS group, neonatal mice were i.p. injected with anti PD-1 antibody (10mg/kg), 24 hours later followed i.p. injected with lipopolysaccharides(LPS) (15mg/kg); Anti-PD-1-NS group; NS-LPS group; and control group (NS-NS group). After injecting LPS or physiological saline, all mice were subdivided into 6 hour group, 12 hour group, and 24 hour group. Blood and renal tissue were collected separately. ELISA was performed to determine the soluble PD-1 (sPD-1) and IL-6 in serum. Renal tissue morpholog by HE, and the expression of PD-1 and PFKFB3 in renal tissue by IHC.

Results: The serum IL-6 levels in the NS-LPS group were significantly higher than those in the NS-NS group, while the serum IL-6 levels in the Anti-PD-1-LPS group were also significantly higher than those in the NS-LPS group. The proximal tubule epithelial cells in the Anti-PD-1-NS group showed mild edema changes, and the proximal tubule epithelial cells in the NS-LPS group showed serious damage, while the proximal tubule damage in the Anti-PD-1-LPS group was reduced. The expression of PD-1 in the kidneys of the NS-LPS group was significantly increased, the expression of PFKFB3 was not significantly different. The expression of PD-1 in Anti-PD-1-LPS group was decreased, while PFKFB3 expression was significantly increased (Fig 1).

Conclusions: Serum sPD-1 may involved in the neonatal sepsis. PD- 1 blockade can significantly increase the expression level of IL-6. PD-1 blockade can alleviate renal tubular injury in neonatal sepsis, which may be mediated by changes in glycolysis.

Funding: Government Support - Non-U.S.

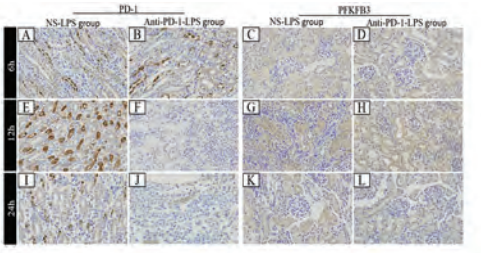


Figure1. The expression of kidney PD-1 and PFKFB3 in two groups of neonatal mice with sepsis was determined at different times (×40).

SA-PO165

Inhibition of ZC3H13 Attenuates G2/M Arrest and Apoptosis by Alleviating NABP1 m6A Modification in AKI

Zhimei Lv, Qinghao Sheng, Qun Yu, Jinxiu Hu, Yating Lang, Rong Wang.
Shandong Provincial Hospital, Jinan, China.

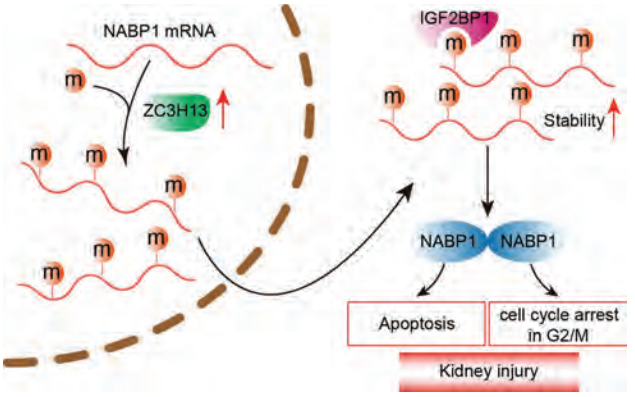
Background: Acute kidney injury (AKI) refers to a clinical syndrome caused by various etiologies, leading to rapid decline in renal function in a short period of time. M6A modification, which is the most common internal modification of mRNA, have been reported to play a vital role in AKI. ZC3H13, a kind of m6A methyltransferases, plays vital roles in canceer. However, the biological roles of ZC3H13 in the pathogenesis of AKI is still unknown.

Methods: Dot blot assay, and m6A ELISA were performed to detect the m6A modification in cisplatin-induced AKI mice and cisplatin-treated HK2 cells. Hematoxylin and eosin (H&E) and Periodic acid Schiff (PAS) were used to evaluate the histological and immunohistochemical change of the kidney. Flow cytometry and TUNEL staining were used to assess cell apoptosis rate in HK2 cells. Actinomycin was used to measure the stability of NABP1 mRNA. MeRIP-qPCR was used to detect the enrichment of NABP1 mRNA. RNA immunoprecipitation was performed to verify the binding of IGF2BP1 protein to NABP1 mRNA.

Results: We observed that m6A modification and the expression of ZC3H13 were substantially elevated in cisplatin-induced AKI mice and cisplatin-treated HK2 cells. Gain- and loss-of-function experiments showed silence of ZC3H13 attenuated G2/M cell cycle arrest and apoptosis both *in vivo* and *in vitro*. Mechanistically, we demonstrated that ZC3H13 mediated cisplatin-induced cell cycle arrest, apoptosis, and renal injury by regulating NABP1. Moreover, we confirmed that m6A modification mediated by ZC3H13 stabilized NABP1 mRNA and was discriminated by IGF2BP1.

Conclusions: In conclusion, ZC3H13 promoted the m6A modification of NABP1 and further enhanced its mRNA stability through IGF2BP1-dependent mechanism. The inhibition of ZC3H13 alleviated G2/M cell cycle arrest, apoptosis and kidney injury through regulating NABP1, showing that ZC3H13/NABP1 axis is a promising AKI treatment target.

Funding: Government Support - Non-U.S.



A simplified schematic diagram showing the effect of ZC3H13 in AKI.

SA-PO166

Dapagliflozin Protects against Cisplatin-Induced AKI on Primary Human Renal Proximal Tubular Epithelial Cells (hRPTECs)

Yuta Sekiguchi, Yutaro Mori, Makiko Mori, Yuki Nakao, Shintaro Mandai, Hiroaki Kikuchi, Fumiaki Ando, Koichiro Susa, Takayasu Mori, Eisei Sohara, Shinichi Uchida. *Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan.*

Background: The renal protective effects of SGLT2 inhibitors are widely known. However, the mechanism is not fully clear yet, although reduction of glomerular intraglomerular pressure and other factors are believed to be involved. We hypothesized that the direct actions of SGLT2 inhibitors on the tubular epithelium takes on a significant role to their renal protective effects, and we investigated them in unimmortalized human renal tubular epithelial cells (hRPTECs) in cisplatin induced acute kidney injury.

Methods: Our hRPTECs were obtained from the non-tumor kidneys removed from patients with malignancies with written informed concent. Renal cortex was diced and digested. Tubules were seeded on plates. And we obtained human primary renal proximal tubular cells. Then we administered cisplatin with or without dapagliflozin. We evaluated the expression of renal damage marker KIM-1 and other markers. To check the myofibroblast activation, potentially leading to tissue fibrosis through the secretion of paracrine factors from injured hRPTECs, we performed fibrosis bioassay, using culture supernatants with no cisplatin left over, and fibroblasts established from mouse renal cortex.

Results: Our hRPTECs express SGLT2 well unlike immortalized RPTEC (RPTEC/TERT). Tubular epithelial cells had increased expression of KIM-1 after cisplatin administration. Culture supernatants from these cells induced fibrosis, indicating injured hRPTECs excretes pro-fibrotic factors. When dapagliflozin administered simultaneously with cisplatin, KIM-1 expression was drastically suppressed, and the fibrosis-inducing effect of the culture supernatant was attenuated. Cisplatin treatment also increased the expression of the immune checkpoint ligand PD-L1, which induces immune tolerance against injured hRPTEC, and dapagliflozin suppressed it.

Conclusions: Dapagliflozin relieved cisplatin-induced acute kidney injury and attenuated myofibroblast activation through reducing the secretion of paracrine factors. Our findings demonstrate that dapagliflozin inhibits the progression from AKI to CKD. Immune tolerance may also be involved in these mechanisms.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO167

The Importance of Kidney Response over Hematologic Response in Predicting Kidney Outcomes in AL Amyloidosis

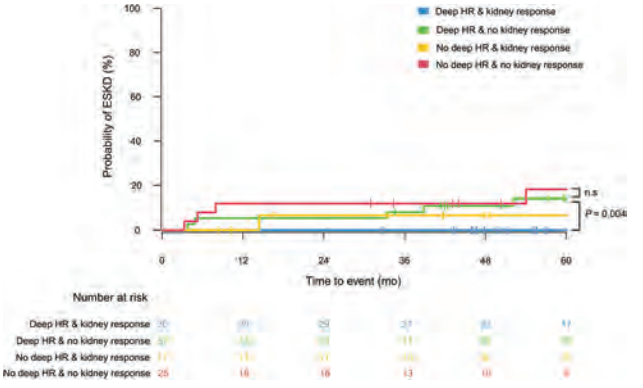
Sungmi Kim, Kyungho Lee, Junseok Jeon, Jung eun Lee. *Samsung Medical Center, Gangnam-gu, Seoul, Republic of Korea.*

Background: Light chain amyloidosis is a clonal plasma cell disorder characterized by amyloid fibril deposition in multiple organs. Kidney involvement of amyloidosis often leads to progression to end-stage kidney disease. This study aimed to identify predictors of kidney survival in patients with kidney amyloidosis, focusing on hematologic and kidney response.

Methods: This retrospective study included 138 patients diagnosed with kidney amyloidosis between 2011 and 2019. Palladini et al.'s criteria were applied for kidney stage and response, and the 2012 International Society of Amyloidosis criteria for hematologic response. Kidney and hematologic response were assessed at 6 months after treatment initiation. Deep hematologic response was defined as the achievement of at least very good partial response.

Results: Overall, 17 (12.3%) progressed to end-stage kidney disease. In multivariable analysis, kidney stage 2 was independently associated with an increased risk of end-stage kidney disease compared to stage 1 (hazard ratio [HR] 3.75; 95% confidence interval [CI] 1.38–10.15; P = 0.01). Compared to kidney response, the risk of end-stage kidney disease increased by 8.42 times (95% CI 1.71–41.35; P = 0.01) in stable disease and 7.36 times (95% CI 1.25–43.33; P = 0.03) in kidney progression. However, neither deep hematologic response nor the difference between involved and uninvolved free light chain, one component of hematologic response, showed an association with kidney outcome. Kidney survival was longer in patients with both deep hematologic response and kidney response than in those with only hematologic response (P = 0.004).

Conclusions: The study underscores the importance of kidney response over hematologic response in predicting end-stage kidney disease and emphasizes the need to establish treatment endpoints, considering organ response alongside hematologic response.



SA-PO168

An Atypical Cause of Kidney Amyloidosis: Combined Heavy and Light-Chain Amyloidosis

Dina R. Gonzalez Hernandez,[1] C. E. Cervantes.[2] *[1]MedStar Health, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD.*

Introduction: The kidney is the second most commonly affected organ in systemic amyloidosis. The International Society of Amyloidosis identifies 14 types of kidney-related amyloidosis, with most studies indicating that immunoglobulin (Ig) light chain (AL) amyloidosis is the predominant cause in over half of the cases. Heavy chain (AH) amyloidosis has been reported in 0.1 % to 2.3 % of kidney amyloidosis cases. However, combined heavy and light chain (AHL) amyloidosis is extremely rare.

Case Description: A 78-year-old man presented to the hospital with lower and upper extremities edema, dyspnea, and pulmonary edema. Workup revealed a serum creatinine of 1.25 mg/dL, and serum albumin of 2.7 g/dL. Urinalysis showed 3+ proteinuria with 22 g of proteinuria in a 24-hour collection. Serologic workup revealed high lambda light chains at 3,800 mg/L with kappa/lambda ratio of 0.01 and elevated IgM levels at 3,500 mg/L. A kidney biopsy showed mesangial expansion with negative periodic-acid-Schiff (Fig 1A) and positive Congo Red Stain (Fig 1B) with apple-green birefringence under polarized light. Immunofluorescence revealed diffuse mesangial staining for IgM (3+) (fig 1C), C3 (2+) and lambda light chains (2+). Mass spectrometry confirmed lambda light chain and mu heavy chain amyloidosis. The patient was diagnosed with AHL amyloidosis and initiated treatment with bendamustine and rituximab; however, his kidney disease progressed rapidly, necessitating dialysis initiation approximately 10 months after his initial presentation.

Discussion: AHL amyloidosis is extremely rare. Diagnosis requires a kidney biopsy and mass spectrometry to type the amyloidogenic protein given the highest sensitivity and specificity of this technique and the limitations of immunofluorescence. Compared to AL, AHL patients have a higher prevalence of IgM monoclonal gammopathy, longer overall survival (5-year survival rate of 66%), and less advanced disease. Although data are limited, our case underscores the potential rapid progression to dialysis in AHL patients with high proteinuria at diagnosis.

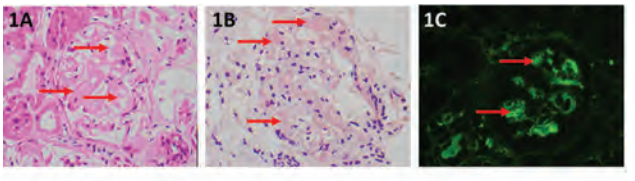


Figure 1A shows mesangial expansion, which is periodic-acid-Schiff (PAS) negative.
Figure 1B demonstrates a positive Congo Red Stain in the mesangium (salmon pink color).
Figure 1C reveals diffuse mesangial staining for IgM (3+) on immunofluorescence.

SA-PO169

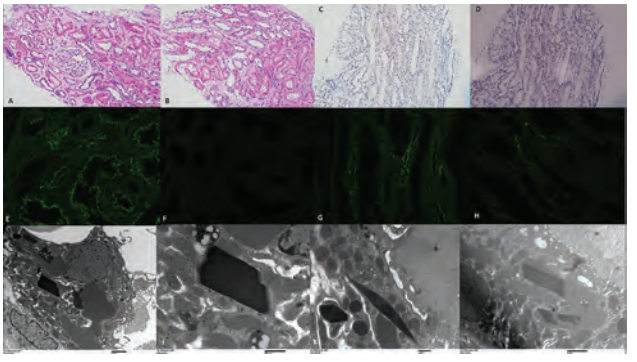
Monoclonal Gammopathy Manifested as Renal Interstitial Amyloidosis

Muhammad Qasim,[1] Kanza Mustafa,[2] Ann R. Finke,[1] Virgilius Cornea,[1] Taha Ayach.[1] *[1]University of Kentucky College of Medicine, Lexington, KY; [2]Yusra Medical and Dental College, Islamabad, Pakistan.*

Introduction: Amyloidosis is a disorder caused by deposition of insoluble misfolding proteins as fibrils leading to organ dysfunction. Incidence of AL Amyloidosis is 9 cases per million. Monoclonal gammopathy manifested as renal interstitial amyloidosis is a rare disorder.

Case Description: 54 yo F with history of hypothyroidism, covid 19 presents to primary care provider (PCP) with fatigue. Cr was noted to be 1.28 mg/dl, eGFR 50ml/min. Urinalysis was bland, and urine protein to creatinine ratio was 0.2 g/g. Renal U/S: Normal. SPEP: Normal. Serum free light chains (LC) K 249.23 mg/L[3.3-19.4], λ 10.90 mg/L [5.71-26.3], elevated K/λ LC ratio of 22.87[0.26-1.65]. Bone marrow biopsy(BMBx): plasma cell dyscrasia, 15% of the population of K-restricted plasma cells, negative Congo Red stain. Skeletal survey: negative. Renal Biopsy: proximal tubulopathy, monoclonal kappa light chain related and Interstitial renal amyloid deposition.

Discussion: Isolated K related monoclonal gammopathy manifested as renal interstitial amyloid is a rare disease entity scarcely reported in literature. We report a case of this patient with mild symptoms and minimal serum Cr elevation, no significant proteinuria with elevated K/λ LC ratio. BMBx: K-related plasma cell abnormality. Renal biopsy: K LC proximal tubulopathy along with interstitial amyloid deposits. Treated with lenalidomide, bortezomib, dexamethasone[6 cycles]. Achieved remission confirmed on BMBx. Had autologous hematopoietic stem cell transplant. Remains in remission on lenalidomide maintenance dose 20 months post auto-HCL. Renal function stable with serum Cr ~ 1-1.2 mg/dL with bland urine.



A&B- H&E. Proximal Tubulopathy, Acute Tubular Damage. C&D-Amyloid interstitial deposits- Congo Red. D:Apple-green; Polarized Light. E-H:(IF) E-Tubules, 2+ cytoplasmic staining after pronase digestion for K-LC. F-Tubules, no cytoplasmic staining after pronase digestion for λ-LC. G&H, interstitial staining for Kappa(G) and lambda(H) after pronase digestion. I-J:EM, enlarged atypical shaped lysosomes (J) and IC rhomboid and needle shaped crystals (I-L).

SA-PO170

Subphenotypes of Tumor Lysis Syndrome with AKI

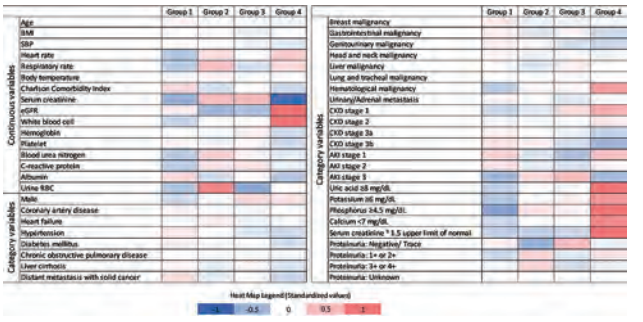
Ming-Jen Chan, Yi-Jiun Su, Chih-Hsiang Chang. *Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan.*

Background: The diverse clinical outcomes observed in tumor lysis syndrome (TLS) patients with acute kidney injury (AKI) suggest underlying heterogeneity within TLS. We aimed to elucidate the subphenotypes of TLS with latent class analysis (LCA) to better understand their clinical characteristics and outcomes.

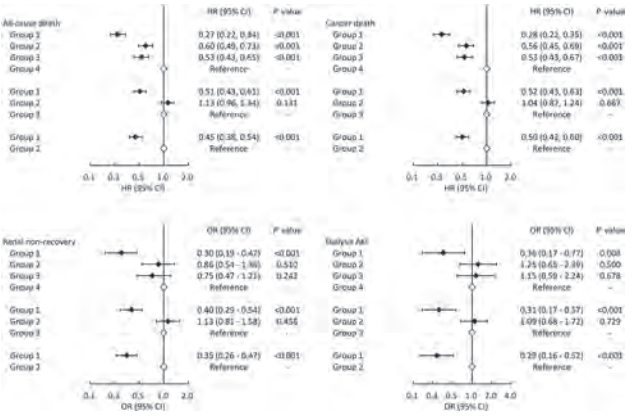
Methods: A cohort of 1,377 patients presenting with TLS-related AKI between 2005 and 2019 was enrolled. Analysis of total forty clinical variables, including baseline characteristics, malignancy type, metastatic site, AKI stage, and laboratory measurements, was conducted using LCA to identify distinct subphenotypes. All-cause death, cancer-specific death, non-recovery of renal function, and progression to dialysis requiring AKI, were compared among the identified subphenotypes.

Results: LCA revealed four distinct subphenotypes of TLS patients. Subphenotype 1 exhibited the lowest all-cause mortality (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.22-0.34), while subphenotype 4 had the highest mortality rate. Similar trend was observed in cancer-specific mortality with subphenotype 1 displaying the lowest risk (HR 0.28, 95% CI 0.22-0.35). Additionally, subphenotype 1 exhibited significantly lower risks of non-recovery of renal function (OR 0.30, 95% CI 0.19-0.47) and progression to dialysis-requiring AKI (OR 0.36, 95% CI 0.17-0.77) compared to the other subphenotypes.

Conclusions: Our study identifies four novel subphenotypes, with subphenotype 1 associated with the most favorable outcomes, while subphenotype 4 exhibits the worst prognosis. This subphenotyping approach holds promise in guiding future research.



Heat map of variable by subphenotypes



Subgroup analyses of clinical outcomes of subphenotypes.

SA-PO171

Impact of Hematopoietic Cell Transplantation Associated Thrombotic Microangiopathy on Kidney Failure Requiring Dialysis in Patients Aged 40 Years and Older Characterized by Pretransplant Kidney Health

Udit Nangia,[1] Deepak Chandramohan,[2] Hari Naga Garapati,[4] Prathap Simhadri.[3] *[1]UH Parma Medical Center, Parma, OH; [2]The University of Alabama at Birmingham, Birmingham, AL; [3]AdventHealth East Florida, Daytona Beach, FL; [4]Baptist Medical Center South, Montgomery, AL.*

Background: Allogeneic hematopoietic cell transplantation (all-HCT) associated thrombotic microangiopathy (TA-TMA) and pre-transplant renal dysfunction are recognized risk factors for mortality after all-HCT. In a recent observational study (Farhadfar et al, 2021), patients with pre-transplant decreased kidney function had higher risks of renal failure requiring dialysis (RFD). Using the same data from the Center for International Blood and Marrow Transplant Research (CIBMTR), we investigated the association between onset of TA-TMA and pre-HCT renal dysfunction on RFD.

Methods: All-HCT recipients of age ≥40 years between 2008-2016 were included in this secondary analysis. We evaluated TA-TMA as a time-dependent covariate, while pre-transplant renal health and other risk factors were included as fixed covariates in a multivariate Cox regression model for RFD. Cumulative hazards of RFD in patients with and without onset of TA-TMA were estimated.

Results: The incidence of TA-TMA was not significantly different between the renal function groups. As expected, renal dysfunction was a significant risk factor for RFD when compared to eGFR ≥60 mL/min group. TA-TMA was significantly associated with increased risk (5.9-fold compared to No TA-TMA) for RFD, the highest of all the significant risk factors (Table 1). Estimated cumulative hazard for patients with TA-TMA in the two pre-HCT renal function groups were significantly elevated when compared to similar patients with No TA-TMA (52% vs 9% for eGFR <60 mL/min and 22% vs 4% for eGFR ≥60 mL/min group, respectively) at 12 months post-HCT.

Conclusions: Our results demonstrate that the adjusted hazard ratio of renal failures requiring dialysis and cumulative hazard were much higher in patients with onset of TA-TMA vs No TA-TMA, emphasizing the need for therapies for preventing and addressing TA-TMA.

Table 1. Incidence of TA-TMA, Renal Failure Requiring Dialysis and Adjusted Risk Factors for Renal Failure Requiring Dialysis Post-Hematopoietic Cell Transplantation

Characteristic	Pre-HCT eGFR (mL/min)		
	<60 (n=1151)	≥ 60 (n=12025)	P-value
Incidence of TA-TMA	3.4%	2.8%	0.300
Incidence of Renal Failure Requiring Dialysis	12.2%	5.8%	<0.001
With No TA-TMA	11.8% (131/1112)	5.4% (627/11682)	<0.001
With TA-TMA	23.1% (9/39)	21.0% (72/343)	
[a]Significant Risk Factors for Renal Failure Requiring Dialysis Post-Hematopoietic Cell Transplantation			
Risk Factors		HR (95% CI)	P-value
TMA vs No TA-TMA		5.92 (4.23, 8.28)	<0.001
Renal Function Group eGFR <60 mL/min vs eGFR ≥60 mL/min		2.31 (1.89, 2.82)	<0.001
Hematopoietic cell transplantation-comorbidity index 2 vs 0		1.31 (1.01, 1.71)	0.045
Hematopoietic Cell Transplantation-Comorbidity Index 3 vs 0		1.49 (1.22, 1.82)	<0.001
Donor Age 40-49 (ref: identical sibling or other relative)		1.39 (1.04, 1.86)	0.027
Donor Age N/A - Cord Blood (ref: identical sibling or other relative)		1.54 (1.14, 2.08)	0.005
Donor Type: Unrelated vs Related		1.43 (1.11, 1.82)	0.005
Anti-thymocyte globulin and/or alemtuzumab: Yes vs No		0.77 (0.64, 0.92)	0.004
Chronic GVHD: Yes vs No		0.33 (0.28, 0.40)	<0.001
Conditioning Regimen: Bu-Cy (ref: Cy/TBI)		0.70 (0.51, 0.96)	0.027
Conditioning Regimen: Bu-Flu (ref: Cy/TBI)		0.49 (0.37, 0.66)	<0.001
Conditioning Regimen intensity: NMA vs Myeloablative		0.61 (0.46, 0.82)	<0.001
Disease Group: Lymphoma vs AML		1.56 (1.21, 2.01)	<0.001
Disease Group: MDS vs AML		1.25 (1.02, 1.53)	0.029
Disease Group: Other malignant hematologic disease vs AML		1.89 (1.43, 2.49)	<0.001
Veno-occlusive disease: Yes vs No		4.41 (3.30, 5.87)	<0.001
Idiopathic pneumonia syndrome: Yes vs No		2.19 (1.75, 2.75)	<0.001

[a]Cox multivariate regression, stepwise selection with a threshold of 0.05 for both entry and stay in the model.
Cy: cyclophosphamide; TBI: total-body irradiation; Bu: busulfan; NMA: Non-myeloablative; Flu: fludarabine

SA-PO172

Kidney Recovery Prognosis after Allogeneic Hematopoietic Stem-Cell Transplantation

Ping-Chi Tsai,[1] Bor-Sheng Ko,[2,3] Jenq-wen Huang,[1,2] Chi-Ting Su.[2,3]
[1]National Taiwan University Hospital, Taipei, Taiwan; [2]National Taiwan University College of Medicine, Taipei, Taiwan; [3]National Taiwan University Cancer Center, Taipei, Taiwan.

Background: Predictors of renal dysfunction should be thoroughly investigated to prevent compromising the success of HSCT in treating malignant and non-malignant hematological diseases. We aimed to determine the factors and effects of acute kidney injury (AKI), acute kidney disease (AKD), and chronic kidney disease (CKD) in patients receiving HSCT and investigate the impacts of the trajectory of renal recovery on outcomes.

Methods: We conducted a retrospective study of adult patients receiving allo-HSCT between 2015 and 2023. We identified incident AKI, AKD, and CKD as defined by changes in serum creatinine (sCr) levels based on the KDIGO criteria and ADQI consensus. Severe AKI and AKD were defined as a 100% increase in sCr within 7 and 90 days, respectively. Kidney recovery was based on the AKI resolution and subsequent sCr measurements below 1.5× the baseline at different timeframe. Multivariate Cox regression was used to assess known risk factors.

Results: The participants were 805 patients (mean age; 50.3 years; men; 53.3%; and median follow-up; 2.3 years). The incidence rates of AKI and AKD after 100 days of treatment were 53.8% and 65.3%, respectively. The cumulative incidence of CKD was 23.4%, whereas the non-relapse mortality was 11.8%. Severe AKI was independently associated with higher non-relapse mortality (hazard ratio [HR]; 2.01) and recovery after 3, 7, and 90 days of AKD were similar (HR; 2.90, p=0.004; HR; 2.39, p=0.01; and HR; 3.41, p=0.001, respectively). Non-recovery of AKI by 90 days was a risk factor for CKD (HR; 5.65/5.32, p<0.001), whereas AKI recovery by 3 and 7 days were not risk factors. Male sex, diabetes mellitus, hemorrhagic cystitis (HR; 2.40), and acute dialysis after HSCT (HR; 8.89) conferred higher risk of CKD incidence. Exposure to various nephrotoxic agents (HR; 1.76, p<0.001) increased risk of AKI. Cyclosporine levels was associated with AKI (HR for 1 standard deviation (SD) increase; 1.27, p<0.001) and exerted negative effect on recovery at 3 days (odds ratio for 1 SD increase; 1.52, p<0.001).

Conclusions: Recovery patterns of AKI stratify the risk of CKD and mortality. Moreover, the results highlighted cyclosporine levels, nephrotoxic agents, and hemorrhagic cystitis for further monitoring of the AKI-CKD continuum. Thus, transition from post-AKI to post-AKD and CKD should be prevented for patients receiving HSCT.

SA-PO173

Impact of Kidney Impairment Recovery on Survival of Patients with Newly Diagnosed Multiple Myeloma

Fernando L. Strufaldi, Luciana G. Lutf, Renato A. Caires, Francisco Z. Mattedi, Elerson Costalonga, Fernanda S. Seguro, Gracia A. Martinez, Veronica T. Costa e Silva. *Universidade de Sao Paulo Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil.*

Background: It has recently been suggested that recovery of Renal Impairment(RI) after treatment(AT) of patients(pts) with multiple myeloma (MM) is a better predictor of overall survival(OS) than RI at diagnosis(AD). Our aim is to assess the impact of RI recovery on the OS of pts with newly diagnosed(NDMM)

Methods: We screened adult pts with NDMM admitted for treatment at the Sao Paulo State Cancer Institute between January 2009 and September 2018. Estimated glomerular filtration rate(eGFR) was determined by the 2021 CKD-EPI creatinine(Cr) equation in ml/min/1.73m^2. RI was defined as eGFR<40 or serum Cr>2.0mg/dL. Chronic Kidney Disease (CKD) criteria was eGFR<60ml/min/1.73m^2, considering Cr in the previous three months before MM diagnosis. Acute Kidney Injury (AKI) was stratified according to the KDIGO criteria. Patients were classified into 3 groups: (1) no RI at diagnosis, (2)RI AD with recovery AT, (3)RI AD without recovery AT

Results: We enrolled 429 pts. Median age was 61.7(54.1–69.5)y, 58.1% male. Median Charlson comorbidity index was 4.0(3.0–5.0). International staging system III was found in 37.9%. Novel agents(bortezomib or thalidomide) were used in 70.8% pts. eGFR AD and AT were 70.9(40.7–98.7) and 93.2(62.7-104.1)ml/min/1.73m^2, respectively. AD, CKD, RI, and AKI stage 3 were observed in 26.3, 24.0, and 12.1% of patients, respectively. In the adjusted Cox regression models, among kidney variables, only the lowest eGFR AT was associated with worse OS(Table).

Conclusions: The lowest eGFR AT might be a better predictor of OS than RI AD in pts with NDMM

Variables	p value	Hazard Ratio (95% Confidence interval)
Renal impairment at diagnosis	0.54	1.11 (0.79 – 1.56)
eGFR at admission	0.88	1.0 (0.99 – 1.05)
Acute Kidney Injury stage 3	0.46	0.67 (0.51 – 0.89)
Chronic kidney disease	0.67	0.94 (0.70 – 1.26)
Renal recovery groups No Renal Impairment Renal impairment at diagnosis, recovery after treatment Renal impairment at diagnosis, no recovery after treatment	0.29 0.83 0.42	 1.04 (0.74 – 1.45) 1.62 (0.88 – 2.96)
Lowest eGFR in 6 months	0.004	0.99 (0.98 – 0.99)

Each model was adjusted for age, Charlson index, international staging system stage 3, body mass index categorization, and usage of novel chemotherapy agent(thalidomide or bortezomib).eGFR: estimated glomerular filtration rate

SA-PO174

Effects of Primer on Episodes of Hypotension during Therapeutic Plasma Exchange

Madhab Ray, Anna G. Macadam, Grace Monis. *University of California Davis, Davis, CA.*

Background: Plasma pheresis instruments are primed (pre-filled with a fluid) before Therapeutic Plasma Exchange (TPE) with saline solution or 5% albumin to prevent air embolism and hypovolemia from extracorporeal fluid shift. Changes in blood composition during TPE can cause various side effects, including hypotension through the involvement of the autonomic nervous system. No published study compares effect on hypotension when an albumin solution is used instead of normal saline. The purpose of this study was to characterize the blood pressure response during TPE when albumin is used for priming compared to normal saline.

Methods: Data was retrospectively collected from 118 TPE records of 26 patients who had one or more TPEs in the last two years at UC Davis Medical Center, California. TPE was done according to Spectra Optia System guidelines, and no patient had more than one exchange on a particular day. Five percent human albumin was used as the preferred replacement fluid, and the dose was calculated based on the body weight, height, sex, and age of the patients. Patients were closely monitored during the procedure. Changes in mean arterial blood pressures were compared to their respective baseline using unpaired two-tailed t-test. Episodes of hypotension (SBP <90 mm Hg or DBP <60 mmHg) during TPE were analyzed using Anova.

Results: The mean age of patients was 51 years and 42% were male. Hypotension was noted more frequently and with increased severity when 5% human albumin was used for priming the plasma apheresis system. Significant increase was noted both in severity (p-value < 0.01) and frequency of hypotensive episodes (p-value <0.001) when 5% human albumin was used for priming the plasma apheresis system (figure 1).

Conclusions: Episodes of hypotension were less frequent and less severe during therapeutic plasma exchange when the plasma apheresis system was primed with saline compared to 5% human albumin. Results may reflect the heterogenous pathophysiology of our study population. Further studies will be necessary to generalize these observations.

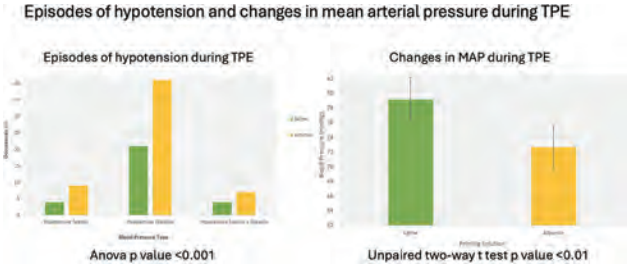


Figure 1

SA-PO175

Drug (Carfilzomib)-Induced Atypical Hemolytic Uremic Syndrome (aHUS)

Fnu Pariya,[1] Sandeep R. Sasidharan,[1] Tahir A. Jatoi,[1] Muhammad Azhar,[2] Isha Puri,[2] Mary C. Mallappallil,[2] Mohammad W. Abushawer.[1] *[1]SUNY Downstate Health Sciences University, New York City, NY; [2]Kings County Hospital Center, Brooklyn, NY.*

Introduction: MM, the second most common hematologic malignancy, accounts for 2.1% of all cancer deaths (1). TMA is a potentially organ and life-threatening condition affecting patients with MM. Risk for TMA in MM is from both the disease and drug used to treat (2). We present an elderly man with refractory MM on Carfilzomib who developed aHUS.

Case Description: 60-year-old male with history of prostate cancer in remission, refractory IgG Lambda chain associated MM, and was receiving chemotherapy with Carfilzomib presented with yellow productive cough for 3 days with fever and chills. On exam, Pt was febrile to 102 F, HR >100, and has rhonchi on lung fields. Labs showed Creatinine at 3.38 mg/dL (baseline 1.1mg/dl), WBC 10.57 K/uL with bands, Platelets 51K/uL and influenza A positive. CXR showed bibasilar opacities. The peripheral smear showed schistocytes with elevated LDH 795 U/L. ADAMS13 was negative and pt was diagnosed with aHUS. Patient was initiated on plasmapheresis followed by intermittent HD as the patient became oliguric with worsening renal functions. He was started on eculizumab after appropriate vaccinations. He had improvement in hematology labs but renal functions did not improve and remained dependent on iHD.

Discussion: TMAs in MM patients incur a high mortality risk with long-term morbidity like kidney failure as seen in our patient. MM- related TMA is poorly understood but thought to be due to VWF dysfunction mediates thrombotic thrombocytopenic purpura (TTP) (3), and uncontrolled complement activation mediates atypical hemolytic uremic syndrome (aHUS)(4). So Eculizumab, a complement inhibitor, is used with good results as in our patient but has not been studied as well. Influenza-associated TMA has been reported (5) which could be a trigger in our patient like other Carfilzomib TMAs (6, 7). It may be prudent to investigate if these patients need more frequent influenza vaccination. We report this case of TMA in MM especially with proteasome inhibitors to increase awareness for early detection and treatment thus can prevent morbidity and mortality.

SA-PO176

When Bad Becomes Worse: A Complex Case of Hypophysitis Causing Severe Hyponatremia in the Setting of Immune Checkpoint Inhibitor Therapy and Pituitary Metastasis

Rafael Portela, Ahmad Matarneh, Sundus Sardar, Aidaliz Llorens, Naman Trivedi. *Penn State Health Milton S Hershey Medical Center, Hershey, PA.*

Introduction: Immune checkpoint inhibitors (CPI) are immunotherapy drugs that have revolutionized cancer therapy by enhancing the immune response against tumor cells. However, their use is associated with life threatening complications such as hypophysitis, pituitary gland inflammation. Unrecognized secondary adrenal insufficiency in these cases could result in hyponatremia. We present a case of severe hyponatremia caused by CPI use and pituitary metastasis.

Case Description: 76-year-old woman with papillary thyroid cancer treated with thyroidectomy and metastasized angiosarcoma of the breast, presented with asymptomatic hyponatremia of 118 mmol/L. She had been receiving nivolumab and ipilimumab for 2 months prior to presentation. She was hemodynamically stable. Physical exam was unremarkable; patient was euvolemic. Chemistry showed a sodium 118 mmol/L with normal renal function. Other electrolytes were normal. Nephrology was consulted for management of hyponatremia. Further workup revealed urine sodium 123 mmol/l, urine osmolality 415 mmol/l and serum osmolality 255 mosm/kg; findings consistent with Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Interestingly, morning cortisol was 2.4 mcg/dL with a suppressed ACTH of <0.1 pg/mL consistent with SIADH caused by secondary adrenal insufficiency most likely due to CPI use. Brain MRI revealed an enlarged pituitary gland. She was started on hydrocortisone 25 mg twice daily which resulted in improvement of her sodium level from 118 mmol/L to 127 mmo/L in 24 hours. In 48 hours, sodium was 134 mmol/L and remained stable thereafter. Patient was discharged on hydrocortisone 15 mg in the am and 5 mg at 2 pm.

Discussion: We have portrayed a very interesting presentation of isolated hyponatremia due to central adrenal insufficiency due to CPI use. Understanding the mechanisms underlying CPI-induced hypophysitis is crucial for early detection and management. The current theory is that T-cell activation leads to immune-mediated destruction of pituitary cells, hence affecting synthesis of pituitary hormones. Severe hyponatremia could prompt a nephrology consult as a first approach by primary teams and therefore, recognizing this etiology for hyponatremia in the setting of CPI use could be essential in assertive treatment.

SA-PO177

A Rare Manifestation of Myeloma in a Kidney

Saieda Alleyne, Dhara Dave, Maryam Gondal. *Yale University, New Haven, CT.*

Introduction: Proteinuria and renal insufficiency are among the most common renal manifestations of Multiple Myeloma [MM] with cast nephropathy being the most common pathophysiology. There have been few case reports of plasma cell infiltration into the kidney resulting in renal dysfunction and proteinuria. Here we describe a case of nephrotic syndrome without deranged creatinine in a patient with long standing MM.

Case Description: 64-year-old female with history of anal cancer status post chemoradiation and Ig G multiple myeloma, diagnosed in 2016 refractory to numerous lines of treatment, including CAR-T and stem cell boost, currently on Blenrep and Pomalyst was found to have new onset nephrotic range proteinuria. Urine protein to creatinine ratio 3.74 mg/mg and urine albumin to creatinine ratio 16.1 mg/mg. Serum albumin 1 g/dl, creatinine 1.07 mg/dl [Baseline 0.8-1] and hemoglobin 8.2. Serum protein electrophoresis showed discrete abnormal band measuring 1.7g/dl in the gamma region and serum free kappa/lambda ration >665 unchanged from prior. Renal biopsy revealed diffuse and expansile plasma rich interstitial infiltration distorting the kidney architecture suggestive of infiltrative myeloma in the kidney. Unfortunately, due to the refractory nature and overall decline in her health she was made hospice.

Discussion: Renal involvement in multiple myeloma varies widely and there is a wide spectrum of pathologies noted on biopsy. Plasma cell infiltration of the kidney is a rare presentation of MM that showed itself as only proteinuria and no renal function impairment. It is, however, one that is usually associated with advanced myeloma and like in other reported cases, our patient succumbed to complications of advanced myeloma. With this case we emphasize the point that despite marked histologic changes one may not have significant renal dysfunction. It is important to note and recognize this advanced presentation that may otherwise disguise itself as a benign kidney involvement of MM.

SA-PO178

Membranoproliferative Glomerulopathy with Masked Monoclonal Deposit: A Case Report

Saieda Alleyne, Maryam Gondal. *Yale University, New Haven, CT.*

Introduction: Membranoproliferative glomerulonephritis [MPGN] is diagnosed on immunofluorescence. Some cases are influenced by the dysregulation of the alternative complement pathway. Larsen et al. have described the unmasking of immunoglobulin deposits when tissue is treated with paraffin and hence exposing immunoglobulin previously staining negative on immunofluorescence. Here, we describe a case of monoclonal gammopathy of renal significance presenting as MPGN with masked monoclonal deposit.

Case Description: 42-year-old male with history of intravenous drug use on methadone who presented with elevated creatinine and lower extremity swelling. No prior history of kidney disease or family history of kidney disease. Labs notable for creatinine 1.81, hemoglobin 7.9 [83.7] and albumin 3. Urine analysis showed +3 protein, RBC and WBC. Spot urine protein/creatinine ration showed 10 mg/mg with >4,400 mg/g albumin to creatinine ratio. Hepatitis B, C, Cryoglobulin, C3 and HIV were unremarkable. Serum kappa/lambda light chain ratio 1.91 and immunofixation positive for Monoclonal component detected in the gamma region in serum and characterized as IgM lambda. Renal biopsy revealed MPGN with masked monoclonal deposit with subsequent bone marrow aspirate showing findings are of a moderately hypocellular marrow with 10% lambda monoclonal plasma cells consistent with involvement by a plasmocytic neoplasm. CYBORD (Cyclophosphamide + Bortezomib + Dexamethasone) and lisinopril was started with improvement in protein/creatinine ratio to 3.42 mg/mg in 1 month and recent creatinine improvement to 1.2.

Discussion: This case is unique as it signifies the importance of Monoclonal gammopathy of Renal Significance. Early detection with renal biopsy and initiation of treatment was instrumental in preserving renal function

SA-PO179

Cast Nephropathy from Gamma Heavy-Chain Disease

Sai Prasad Desikan,[1] Raman Desikan.[2] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]White River Health System Inc, Batesville, AR.*

Introduction: In heavy chain disease, frame shift, point mutations, or somatic hypermutations result in the loss of portions of the heavy chain responsible for binding light chains. Gamma heavy chain disease in particular is uncommon. Here we present a patient with gamma heavy chain disease with nephrotic range proteinuria and heavy chain cast nephropathy.

Case Description: A 70-year old male presented with pancytopenia and declining renal function. CBC consisted of WBC of 1.6 x 10^3 /μL, Hgb 10.2 g/dL, and PLT of 90 x 10^3 / μL. Cr was 2.1 mg/dL. IgG was elevated at 2784 mg/dl. IgM and IgA were both low. 24 hour urine protein was elevated 8g/24 hours. Ig heavy chain made up 7.5g/24hr period. Bone marrow aspirate and biopsy evaluation was notable for 40% plasma cells on immunohistochemistry. Flow cytometry revealed 14.7% plasma cells, cytoplasmic

lambda light chain restricted CD38 bright plasma cells. FISH revealed loss of IgH and *FGFR3* genes. Renal biopsy revealed cast nephropathy with IgH and severe arteriolar nephrosclerosis. He received the VDT-ACE, Daratumumab protocol. Autologous SCT was performed. On follow up, proteinuria was significantly diminished at 150mg/24 hours and. Monoclonal protein was absent. Bone marrow biopsy revealed normocellular bone marrow 1% plasma cells observed in aspirate and 5-10% plasma cells in core biopsy. Minimal residual disease assessed by flow cytometric analysis was positive. He received velcade, revlimid and dexamethasone as well as stem cell infusion. Course complicated by pancytopenia. Upon recovery he received further consolidation with daratumumab and dexamethasone. He achieved MRD negativity. Cr continues to be elevated at 1.9 mg/dL.

Discussion: Our patient presented with the rare combination of gamma heavy chain disease, nephrotic range proteinuria, and cast nephropathy. Cast nephropathy is usually a result of light chains binding uromodulin; however, this is the first reported case of heavy chains resulting in cast nephropathy. This patient was successfully treated with induction, autologous transplant, and post transplant consolidation. To date, this is the first patient with gamma heavy chain disease managed with autologous transplant.

SA-PO180

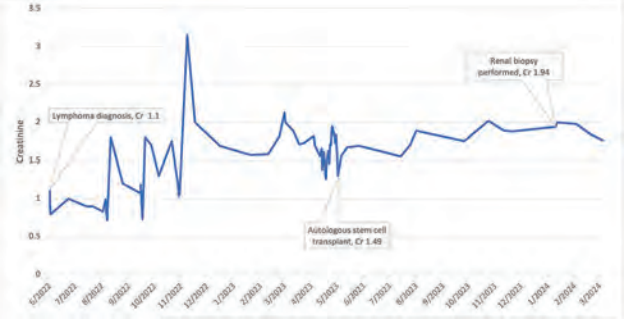
Unveiling the Link: Exploring the Association between Cancer and Leukocyte Chemotactic Factor 2 (ALECT2)-Associated Amyloidosis

Veena Ganesan, Rahul Maheshwari, Priya Deshpande, Matthew Abramson.
Icahn School of Medicine at Mount Sinai, New York, NY.

Introduction: We present a case of a 53-year-old Hispanic male diagnosed with mantle cell lymphoma with subsequent decline in glomerular filtration rate (GFR) found to have LECT2 amyloidosis on renal biopsy. Notably, following treatment of the lymphoma, his GFR stabilized. Given the correlation between his GFR and lymphoma course, we hypothesize that his lymphoma, possibly via dysregulated Wnt/β-catenin signaling, served as a trigger for ALECT2 amyloidosis.

Case Description: The patient was diagnosed with mantle cell lymphoma in June 2022 and underwent alternating R-CHOP and R-DHAP until December 2022. In May 2023, he had an autologous stem cell transplant with BEAM induction, followed by rituximab maintenance. Despite a normal baseline creatinine, his creatinine worsened to 1.5 mg/dL by May 2023. Post-transplant, creatinine continued to rise to 1.89 mg/dL by the time of initial nephrology consultation in December 2023. Urinalysis, urinary microalbumin and protein-to-creatinine ratio, monoclonal gammopathy screening, and renal sonogram were all unremarkable. Due to the unclear cause of worsening renal function, he had a renal biopsy in January 2024 showing tubulointerstitial amyloid deposition. Mass spectrometry was consistent with the ALECT2 type. As of March 2024, his creatinine was stable at 1.76 mg/dL

Discussion: ALECT2 amyloidosis is characterized by LECT2 protein accumulation, a molecule involved in neutrophil chemotaxis and implicated in multiple inflammatory conditions. Our patient's course and Hispanic origin align with other documented ALECT2 cases in the literature. However, no cases describe an association with lymphoma nor hypothesized treatment. Given the patient's course and the pathophysiology of ALECT2 amyloidosis, we suggest that a surge in LECT2 possibly occurred due to dysregulated Wnt/β-catenin signaling, a pathway implicated in carcinogenesis. We highlight the potential interplay between cancer and ALECT2 amyloidosis, with treatment addressing the underlying cause of amyloid accumulation.



SA-PO181

BK Nephropathy in a Patient with Multiple Myeloma Receiving Bispecific Antibody Therapy

Douglas R. Farrell, Matthew Abramson, Isaac E. Stillman, Daniel Stalbow.
Icahn School of Medicine at Mount Sinai, New York, NY.

Introduction: Human Polyomavirus BK (BKV) is typically a benign virus with seroprevalence in the adult population of 50-90%, but has been associated with interstitial nephritis (nephropathy) in kidney transplant and hemorrhagic cystitis in hematopoietic stem cell transplant (HSCT) recipients. While rare, BKV nephropathy has been described in native kidneys, though mostly in solid organ transplant and HSCT recipients. We describe a case of native kidney BKV nephropathy in a patient receiving the T-cell redirecting bispecific antibody (BsAb), talquetamab, for multiple myeloma (MM).

Case Description: A 66 yo woman with a history of relapsed/refractory IgG Kappa MM was admitted to our hospital for progressive kidney disease. Two months prior to her current admission, she had been started on talquetamab, a BsAb, for her 13th line of therapy for MM. Her creatinine at initiation of therapy was 2.45 mg/dL with a calculated eGFR of 22cc/hr/1.73m3. Her kidney function initially improved to a nadir of 1.89 mg/dL, but then over the duration of 2 months slowly increased to 4.47 mg/dL on day of admission. Her workup included well controlled light chains including a free kappa light chain 1.2mg/l and free lambda light chain1.6mg/l. Her Igs were low, despite treatment 1 month prior with IVIG, with undetectable IgA+IgM, and IgG of 699 mg/dL. She had bland UA, UPCR of 600mg/g, and urine immunofixation with faint monoclonal IgG protein. Kidney biopsy was performed and revealed marked IFTA with remaining tubular cells showing foci of viral cytopathy changes with >10% positive for SV40 Ag, diagnosed as polyomavirus nephritis Banff class 3. No evidence of myeloma kidney was seen. Urine BKV PCR after showed >100,000,000 iu/mL, confirmed the diagnosis of BKV nephropathy. Talquetamab was stopped and she as treated with monthly IVIG, but unfortunately never recovered kidney function.

Discussion: BsAbs are a novel therapy with two different binding domains, which bind one domain to a T-cell antigen (Ag) and another to a B-cell maturation Ag, thus allowing for T-cell destruction of MM cells. BsAbs have significant risk for infection, and some providers utilize prophylactic anti-virals and antibiotics with therapy. While infectious complications of BsAbs are common, BKV nephropathy has not be described, and thus this is the first description to our knowledge.

SA-PO182

Rare Glomerulopathy Associated with Renal Extramedullary Hematopoiesisin a Patient with Primary Myelofibrosis

Sami Mesgun,[1] Daniel Grosser,[1] Kwadwo A. Oduro,[2] Jing Wang,[1] Adily N. Elmi,[1] Richard Y. Chang,[1] Arash Rashidi.[1] *[1]University Hospitals, Cleveland, OH; [2]University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI.*

Introduction: Primary myelofibrosis (PMF) is a rare form of myeloproliferative neoplasm (MPN) that results in increased megakaryocytes and granulocytes, leading to marrow fibrosis, cytopenia, and splenomegaly due to extramedullary hematopoiesis (EMH). Glomerular involvement is rare and characterized by renal injury and proteinuria. MPN-related glomerulopathy is an underrecognized late complication of MPN.

Case Description: A 75-year-old woman with PMF and CKD presented with AKI and proteinuria. She was previously diagnosed with CALR type-1 myelofibrosis for which she began darbepoetin alfa. She was monitored without immune-modulation therapy. A kidney biopsy revealed EMH, notably present with atypical megakaryocytes on light microscopy. Interstitial fibrosis was also noted throughout most of the sampled cortex. She was diagnosed with PMF-related glomerulopathy with EMH.

Discussion: PMF findings vary by the phase of the neoplastic process from hypercellular marrow with myeloid predominance to hypocellular marrow with fibrosis and atypical megakaryocytes. Glomerular changes in MPN are sparsely described, with observed lesions possibly linked to the overproduction of cytokines and growth factors by clonal hematopoietic cells. Generally, the presence of EMH within glomerular capillaries, namely megakaryocytes, distinguishes MPN-related glomerulopathy from other glomerulopathies. EMH found in our case argues for direct involvement of the kidney by the neoplastic process. In sum, patients with PMF should be screened for proteinuria and kidney injury as early as possible, for the presence of renal dysfunction should be concerning for renal EMH and MPN-related glomerular disease.

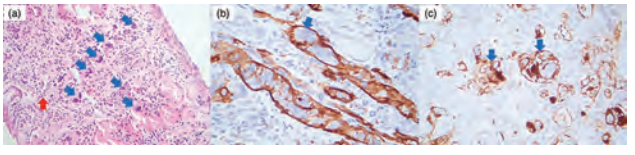


Figure 1. Kidney biopsy findings: (a) Renal interstitium is prominently infiltrated by hematopoietic elements, including erythroid precursors (red arrow on illustrative cluster), characterized by round hyperchromatic nuclei and eosinophilic to basophilic cytoplasm, and atypical megakaryocytes (blue arrows), characterized by clustering and bulbous hyperchromatic nuclei. Renal proximal tubules are visible at the top and bottom of the image. (b) Megakaryocytes are also found in vascular spaces, highlighted by CD34. (c) Megakaryocytes stain with Factor 8.

SA-PO183

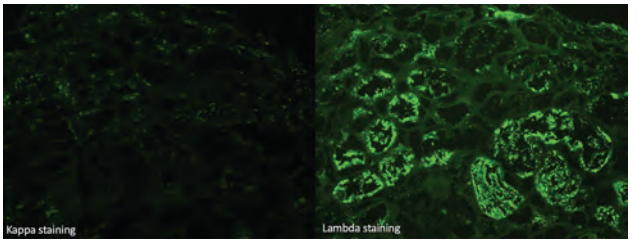
Where's Walden? Rare Manifestation of Waldenström Macroglobulinemia as Proximal Tubulopathy

Ethan N. Downes, Selvaraj Muthusamy, Jason M. Kidd. *Virginia Commonwealth University, Richmond, VA.*

Introduction: Waldenström's macroglobulinemia (WM) is an IgM monoclonal gammopathy that rarely effects the kidneys. We present a patient with WM with proximal tubulopathy that responded to treatment with Rituximab and Zanubrutinib.

Case Description: A 67-year-old man with CLL and mixed connective tissue disease manifested with Raynaud's phenomenon was seen for evaluation of proteinuria. Physical exam was significant for blood pressure of 127/85 and a vasculitic lower extremity rash. Serum creatinine was 1.2 mg/dl and spot urine protein/creatinine ratio (UPCR) was 1.4 g/g. Urinalysis was significant only for proteinuria and he was noted to have a positive urine immunofixation with elevated lambda light chains. A kidney biopsy was performed which showed findings consistent with a proximal tubulopathy and interstitial and perivascular clusters of mononuclear cells with a predominance of lambda staining on immunofluorescence (Figure 1). A bone marrow biopsy was significant for 5-10% CLL/SLL cells and 4% lambda monoclonal plasma cells. Further serologic testing revealed an elevated IgM level of 1493 mg/dl and type I cryoglobulins. A diagnosis of Waldenström's macroglobulinemia was made and treatment with rituximab was initiated. Two months later, proteinuria had decreased to 0.7 g/g but serum IgM failed to improve, and he developed acrocyanosis. He was started on the Bruton Tyrosine Kinase inhibitor (BTK), Zanubrutinib. Seven months after the initial presentation, UPCR decreased to 0.2g/g with stable kidney function.

Discussion: Kidney involvement in WM is rare and most often manifests as amyloidosis or cryoglobulinemic glomerulonephritis. Our patient presented with a light chain proximal tubulopathy without evidence of Fanconi syndrome. Proteinuria resolved by treating his WM with Rituximab and Zanubrutinib, before a hematologic response occurred.



Immunofluorescence staining of proximal tubular cells

SA-PO184

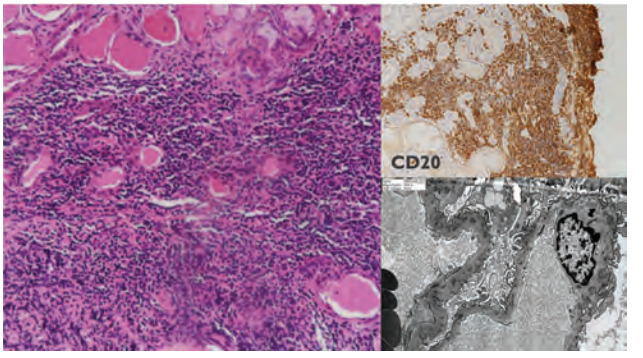
Acute Tubulointerstitial Nephritis with Membranous Nephropathy in a Patient with Newly Diagnosed Waldenstrom Macroglobulinemia

Napat Wongmat, Nitcha Suphatheerawatr, Oraphan Kongpanvijit, Solos Jaturapisanukul. *Navamindradhiraj University, Bangkok, Thailand.*

Introduction: Waldenstrom's macroglobulinemia (WM) is a rare B-cell lymphoproliferative neoplasm characterized by monoclonal immunoglobulin M (IgM) production. Renal involvement in WM is uncommon, often presenting as monoclonal-related kidney diseases like amyloidosis and cryoglobulinemia. Here, we report a rare case of WM associated with acute tubulointerstitial nephritis (ATIN) and membranous nephropathy (MN).

Case Description: A 62-year-old Thai woman was referred for rapid declining kidney function. 1 month prior to presentation, she had generalized edema, fatigue, and foamy urine. She had no prior medical history and was previously active. Physical examination revealed anemia, hepatosplenomegaly, and signs of volume overload. Laboratory results showed a serum creatinine level of 10.9 mg/dL and urine protein of 6 g/day without active urine sediment. Serum protein electrophoresis demonstrated IgM kappa monoclonal gammopathy. A bone marrow biopsy was consistent with lymphoplasmacytic lymphoma. Kidney biopsy findings included ATIN with B-cell lymphoma infiltration. Immunohistochemistry showed heavy interstitial staining for CD20+ and kappa light chain restriction. Electron microscopy revealed numerous subepithelial electron-dense deposits consistent with membranous nephropathy. The patient received a CHOP regimen, which improved the anemia; however, kidney function did not recover.

Discussion: In this case report, we describe a previously healthy woman presenting with rapidly progressive kidney function decline as the initial manifestation of her WM. Kidney pathology revealed ATIN due to lymphomatous infiltration and MN.



Light microscopy, immunohistochemistry for CD20+ shwoed acute tubulointerstitial nepritis from lymphomatous infiltration and electron microscopy show numberous subepithelial electron deposit.

SA-PO185

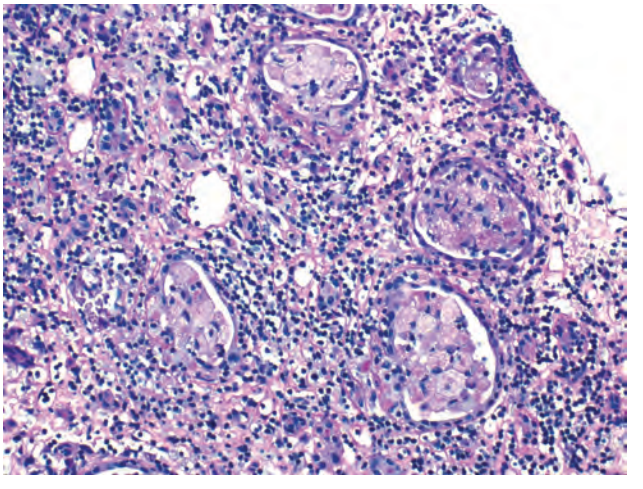
Unique Dystrophic Xanthomatous Reaction in Renal Parenchyma Due to T Cell Lymphoma

Sharmilee Vuyyuru, Rajib K. Gupta, Nasim Wiegley, Hiba Hamdan. *University of California Davis, Sacramento, CA.*

Introduction: While B-lymphocyte and plasma cell-associated kidney involvement have been described extensively in literature, kidney involvement by T-cell lymphoma remains a rare phenomenon. Rare case reports have described an interstitial nephritis-like picture in association with peripheral T cell lymphoma. We describe a unique dystrophic xanthomatous reaction in the kidney parenchyma in association with interstitial involvement with a CD8+ve T cell lymphoma.

Case Description: A 23-year-old woman with autoimmune encephalitis, seizure disorder hypogammaglobulinemia due to Common Variable Immune Deficiency (CVID), and CD3+/CD8+ T cell lymphoproliferative involvement of the liver and bone marrow, was admitted for seizures, and found to have non-oliguric acute kidney injury (Creatinine (Cr) of 4.42 mg/dL (baseline 1) with severe metabolic acidosis (serum bicarbonate of 9 mmol/L). Urine showed hematuria and proteinuria of 1.6g/g. Kidney ultrasound showed bilateral enlarged kidneys measuring 14.8cm and 16cm with diffuse infiltrative process. Kidney biopsy showed unremarkable glomeruli and an abnormal-appearing tubulointerstitium in the form of diffuse interstitial sheets and intra-tubular collections of foam cells/histiocytes, along with a patchy infiltrate of atypical T-lymphoid cells of CD3/CD8-lineage. (image 1) She was started on methotrexate 5mg/m2 weekly and prednisone 1mg/kg by her oncologist. On follow up, kidney function had improved with most recent Cr of 1.98mg/dL.

Discussion: We describe a unique histologic reaction (dystrophic xanthoma cells in the interstitium and within dilated kidney tubules) in association with interstitial involvement by a T-cell lymphoma, which has not been described before in the kidney, although such xanthomatous reaction has been described for cutaneous T-cell lymphomas. Awareness is vital in identifying such rare kidney histomorphology in association with T-cell lymphomas.



SA-PO186

Granulomatous Interstitial Nephritis Due to Small Lymphocytic Leukemia: A Management Conundrum

Ivette Gomez, Daniele Rios Leite, Sheena Pramod. *University of Florida, Gainesville, FL.*

Introduction: Granulomatous interstitial nephritis (GIN) is a rare morphological variant of interstitial nephritis defined histologically by the presence of interstitial inflammation and 1 or more interstitial granulomas, with a low incidence of 0.5% -5.9% of biopsies of acute interstitial nephritis. Small lymphocytic leukemia (SLL) can cause infiltration of kidneys in 60–90% of patients, however, renal dysfunction is uncommon

Case Description: We describe a 70-year-old male with history of hypertension, A. fib and BPH referred for declining renal function and hypercalcemia for 8-months, associated with weight loss and fatigue. Initial Creatinine was 3.57 mg/dL (baseline creatinine 0.57 mg/dl) and calcium level of 13 mg/dL with suppressed PTH. Patient's proteinuria was 1.2 grams per day with albuminuria of 50 mg per day. His SPEP was normal with k/l ratio of 2. Bone marrow biopsy showed small lymphocytic leukemia. Kidney biopsy showed B-cell infiltrates, few plasma cells, T cells and eosinophils and discrete noncaseating granulomas consistent with granulomatosis interstitial nephritis with Interstitial fibrosis and tubular atrophy (IFTA) of 70%. His presentation was consistent with GIN which is rarely associated with SLL. Patient was a started-on prednisone 60 Mg daily, with improvement of renal function to creatinine of 1.9 mg/dL. As soon as prednisone was discontinued, renal function worsened with creatinine increase to 3.2mg/dl, proving steroid sensitive GIN. Patient was started on Acalabrutinib for SLL along with prednisone and continued on prednisone 10mg with creatinine 1.7 to 1.9 mg/dL 14 months since presentation.

Discussion: GIN is suspected to be a local hypersensitivity reaction, which would explain its adequate response to steroids with or without SLL directed chemotherapy. There are no established management guidelines for these cases. Here we highlight the possibility of using low dose prednisone following a taper as an option for this uncommon entity to stabilize renal dysfunction. Another aspect of our case is the degree of response to steroids in spite of severe IFTA which is clinically important. GIN associated with SLL is a rare manifestation with overall poor outcomes.

SA-PO187

Worsening Proteinuria Reveals Lymphoplasmacytic Lymphoma

Iskandar Berbari, Fayaz A. Khan, Moarij A. Qazi, Madelyn Durhman. *TriHealth Inc, Cincinnati, OH.*

Introduction: A patient presented with worsening proteinuria diagnosed as Lymphoplasmacytic Lymphoma (LPL). Chemotherapy treatment was effective, significantly improving proteinuria and IgM levels

Case Description: A 59-year-old male with chronic lymphocytic lymphoma (CLL), Diabetes presented with new nephrotic range proteinuria of 3172 mg/g microalbumin/creatinine ratio from baseline of around 600, new foamy urine and creatinine elevation from 0.8 to 1 mg/dL. Further tests revealed elevated IgM (1243), kappa/lambda free light chain ratio (9.35), hypercalcemia, and IgM kappa spike (0.61 g/dL). Bone marrow biopsy showed a 30-40% cellular infiltrate of small lymphocytes. Kidney biopsy was pursued due to unexplained worsening proteinuria which revealed mild mesangial expansion with patchy dense mononuclear inflammatory infiltrates predominantly small lymphocytes (CD20+ve) with scattered plasma cells (figure 1), consistent with LPL. After 2 cycles of Rituximab-bendamustine, urine protein/creatinine ratio improved from 1.23 to 0.62; IgM level decreased to 327, M spike to 0.13 g/dL, creatinine back to baseline and urine appearance normalized.

Discussion: This case highlights the importance of proteinuria surveillance, especially in patients with CLL. Any changes in proteinuria should be aggressively investigated while other management strategies are pursued. A low threshold for kidney biopsy is crucial, as timely intervention can help preserve kidney function. Further research is essential to deepen our understanding of the pathogenesis and potential connections between CLL and LPL. While these conditions are distinct entities, cases of their co-occurrence have been documented. Investigating these associations more thoroughly could offer valuable insights into the mechanisms of disease and therapeutic strategies.

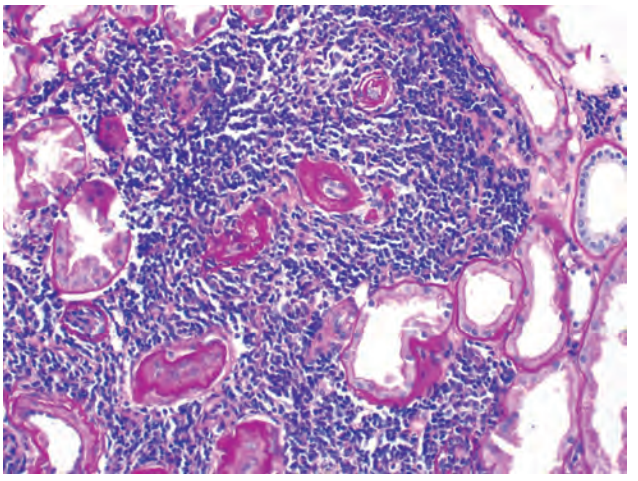


Figure 1

SA-PO188

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits Is Not Only a Disease in Elderly Patients but Also a Disease in Young Patients

Neeharik Mareedu, Hassaan Rasheed. *UPMC Western Maryland, Cumberland, MD.*

Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a special category of disease within the group of disorders, monoclonal gammopathy of renal significance (MGRS). Though it is an uncommon disorder, PGNMID is increasingly recognized in the recent times. Though PGNMID can occur at any age, the average age of onset is usually around 55 years.

Case Description: We report a young 31 year old female patient with history of resistant hypertension, type 2 diabetes mellitus and morbid obesity admitted to the hopsital with acute kidney injury and and noted to be having nephrotic syndrome with urine protein of 21 gm/24 hour, from biopsy-proven PGNMID with IgG3 kappa light chain deposistion. The patient failed treatments with Bortezomib, Lenalidomide, Dexamethasone (VRd) and daratumumab, bortezomib and dexamethasone. She had partial response to cyclophosphamide, bortezomib and dexamethasone (CyBorD) along with daratumamab with eventual worsening of proteinuria again. During the course of her disease, she continued to have significant problems with resistant hypertension as well as cardiac problems including coronary artery disease requiring 4-vessel bypass grafting. Unfortunately, despite multiple lines of chemoterapeutic/immunosuppressive agents the patient eventually progressed to end stage renal disease requiring initiation of hemodialysis.

Discussion: Though MGRS/PGNMID are rare causes of renal dysfunction, early recognition and early initiation of proper management of these patients is of utmost importance for improved renal outcomes. Unfortunately, due to unclear pathogenic mechanisms effective treatment options remains limited and usually treatment regimens are aimed at clone-directed therapies in patients with detectable clones as well as without detectable clones where the treatment is directed at potential hypotehtical clones. Moreover, our case also demonstrates that PGNMID can happen even in younger patients and may be associated with more aggressive disease with limited response to the traditional chemotherapeutic agents.

SA-PO189

Lysozyme Is No Lie! AKI in a Patient with Acute Myeloid Leukemia

David Lyu, Renuka Tolani, Shane A. Bobart, Lawrence Rice, Angelina Edwards, Ethan A. Burns, Tariq Shafi. HMH Nephrology. *Houston Methodist, Houston, TX.*

Introduction: In patients with leukemia who develop acute kidney injury (AKI) we often suspect tumor lysis syndrome and other common etiologies such as cytokine release syndrome. Lysozyme-induced nephropathy (LyN) is a less recognized cause of AKI. When monocytic cells release lysozyme, a small cation, it is filtered by the glomerulus and reabsorbed by the proximal tubule, resulting in toxic tubular injury. We present a case of a patient who was diagnosed with acute myelomonocytic leukemia (AMML) and had AKI with elevated lysozyme level in the blood that improved with treatment of the underlying leukemia.

Case Description: A 77 year old male with PMH of myelodysplastic syndrome (MDS) was noted to have 0.5 grams of proteinuria and AKI with serum creatinine of 1.9mg/dL from a prior baseline of 1.1 mg/dL. Serological studies and work up for paraproteinemia and thrombotic microangiopathy was negative. CBC showed worsening anemia, increasing leukocytosis (29.4 k/uL) with 18% monocytes and Pelger-Huët neutrophils, as well as thrombocytopenia and the patient was admitted for suspected acute leukemia. Bone marrow biopsy showed AMML, 28% blasts, hypercellular marrow (50%) with trilineage hematopoiesis and monocytosis. Given the severe thrombocytopenia, kidney biopsy was unable to be safely attempted. Given the new diagnosis of AMML, a lysozyme enzyme assay was ordered and the level was greater than 10 ug/mL (normal range < 4.5 ug/mL). Treatment with decitabine infusions commenced and one month after initiation, lysozyme levels decreased to 4.37 ug/mL and creatinine improved to near the patient's baseline (1.1 mg/dL). The clinical course was consistent with a diagnosis of lysozyme-induced AKI in the setting of AMML.

Discussion: While kidney biopsy remains the gold standard for diagnosis of AKI in the setting of acute leukemia, when unable to be safely performed, clinicians should be aware of the clinical entity of lysozyme-associated AKI. Checking and trending lysozyme enzyme levels can also be a useful tool to guide management of AKI in this setting. In our case, once treatment for AMML was started both lysozyme levels and serum creatinine improved.

SA-PO190

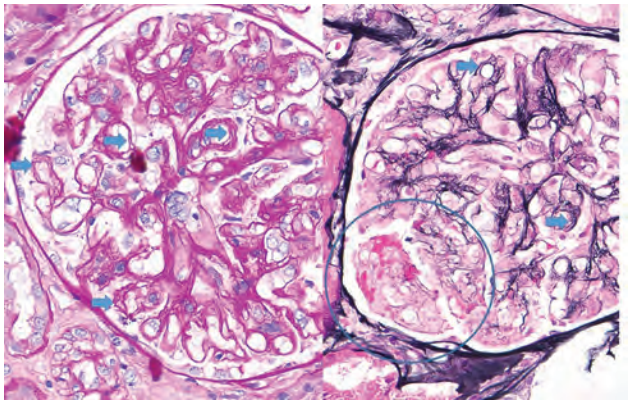
A Diagnostic Dilemma: Renal Limited Thrombotic Microangiopathy in a Stem-Cell Transplant Recipient

Virender S. Mahabir, Meghan Kapp, Arash Rashidi. *University Hospitals, Cleveland, OH.*

Introduction: Kidney disease following hematopoietic stem cell transplantation is attributed to a variety of etiologies

Case Description: A 59 year old male with history of diffuse large B cell lymphoma was seen in consultation for an elevated serum creatinine (SCr) of 1.8 mg/dL. He had previously failed therapy with multiple treatments, initially Rituximab, Etoposide phosphate, Prednisone, Vincristine sulfate, Cyclophosphamide, Doxorubicin hydrochloride (R-EPOCH), followed by CAR-T therapy, and most recently allogenic stem cell transplant. He was being treated with Epcoritamab (anti-CD20 agent) at time of consultation. He was not on a Calcineurin inhibitor. Urinalysis and imaging studies were unremarkable. Urine total protein creatinine ratio was mildly elevated at 0.32 mg/mg, with no monoclonal protein on urine electrophoresis. There were no schistocytes on peripheral smear and no thrombocytopenia on complete blood count. LDH was mildly elevated to 340. A renal biopsy was performed given no clear etiology of SCr elevation. Renal biopsy showed diffuse double contouring of glomerular basement membranes (arrows), focal segmental mesangiolysis with red cell fragmentation and microaneurysm formation (circle) and focal segmental endocapillary hypercellularity. There were no immune complexes by immunofluorescence. These findings were indicative of chronic endothelial injury (so-called Chronic Thrombotic Microangiopathy [TMA]).

Discussion: Early detection of transplant associated TMA is critical given potential for multiple organ dysfunction syndrome and death. Management options include Rituximab, Defibrotide and Eculizumab but evidence is limited to small cohorts and observational data. The patient was planned to start Eculizumab, and renal function remained stable at follow up visit. This case highlights the importance of renal biopsy in making this diagnosis since there were no obvious clues to suggest TMA from history and lab investigations.



SA-PO191

Battle Beyond the Bone Marrow! Case Report of Extramedullary Plasmacytoma with Multiple Myeloma

Aashvi R. Dalal, Michael Liben, Sein Y. See. *NewYork-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY.*

Introduction: Plasma cell neoplasms includes monoclonal gammopathy of undetermined significance, multiple myeloma (MM), and solitary plasmacytomas. Extramedullary plasmacytomas (EMPs), found in soft tissues, are rare, with mediastinal involvement even rarer. Only 5% of EMPs coexist with MM. We present a rare case of MM and concurrent mediastinal extramedullary plasmacytoma in a patient who presented with AKI.

Case Description: A 62 year old male patient with medical history of hypertension, hyperlipidemia with baseline creatinine of 1.1 mg/dl presented to the hospital, asymptomatic with abnormal labs of elevated creatinine to 6.9 mg/dl and anemia of 8.9 g/dl. Kidney injury was initially considered prerenal due to recent NSAID use. Incidental finding of anterior mediastinal mass on imaging was noted. Workup included elevated UPCR (7.56 gram), positive SPEP with monoclonal lambda light chain, elevated free Lambda light chains (13136.56 mg/L) and K/L Ratio of <0.01. Kidney biopsy confirmed monoclonal immunoglobulin deposition disease, monoclonal lambda light chains with light chain cast nephropathy and chronic tubulointerstitial disease without amyloid positivity. Bone marrow biopsy was notable for MM coexpressing lambda light chain. Mediastinal mass biopsy confirmed plasmacytoma. Due to worsening renal function, hemodialysis was initiated. Chemotherapy (bortezomib, cyclophosphamide, dexamethasone and daratumumab) led to significant reduction in lambda light chain allowing discontinuation of dialysis.

Discussion: Solitary osseous plasmacytomas are known to progress to MM, the likelihood of soft tissue EMPs (particularly involving anterior mediastinal) evolving into systemic disease is rare. In our case it is unclear which condition developed first, this case underscores the importance of considering a broad differential diagnoses in patients with acute kidney injury and associated mass. Renal complications like light chain cast nephropathy significantly impact morbidity and mortality. Treatment involves stem cell transplantation for eligible patients, radiation or chemotherapy. Early recognition and intervention, by nephrologists and oncologists, is crucial for improving survival.

SA-PO192

A Rare Case of Myelomatous Ascites with ESKD

Berk Celik, Unnati Bhatia, Sami S. Zarouk. *Corewell Health Beaumont Hospital, Royal Oak, MI.*

Introduction: Ascites is seen in less than 1% of patients with multiple myeloma (MM) and can be difficult to manage in the setting of concomitant kidney disease. Literature review revealed that myelomatous ascites has never been described concomitantly with end-stage kidney disease (ESKD). Here we describe an ESKD patient with relapsing MM presenting with refractory ascites.

Case Description: A 63-year-old African American male presented in February 2023 with acute kidney injury. He was initiated on hemodialysis (HD). Bone marrow biopsy showed more than 90% plasma cells. Flow cytometry showed lambda-restricted plasma cell myeloma. He was treated with CyBorD regimen (cyclophosphamide, bortezomib, dexamethasone). An autologous bone marrow transplant was done in November 2023 and showed relapse proven by bone marrow biopsy in January 2024. He presented with ascites in April 2024. Laboratory tests revealed decreased total protein but normal levels of albumin, ALT, AST, ALP, and total bilirubin. CT abdomen/pelvis showed a large amount of ascites with infiltration of the omentum. Paracentesis was done multiple times. Peritoneal cytology and flow cytometry showed CD138-positive plasma cells. Serum ascites albumin gradient (SAAG) was 1.4 g/dL, total nucleated cell count of 2742, and 2.8 g/dL total protein. Persistent hypotension prevented ascites control in spite of albumin use with hemodialysis.

Discussion: Myelomatous ascites is present in less than 1% of non-dialysis patients and significantly reduce the life expectancy. Rare cases of myelomatous ascites with acute kidney injury were previously described. ESKD patients dependent on HD have never been reported to have myelomatous ascites. It should be considered as a cause of ascites after other etiologies are excluded. Multiple studies showed SAAG is being helpful in diagnosing ascites with more than 90% sensitivity and specificity. A SAAG of less than 1.1 g/dL is expected in myelomatous ascites. However, in our case, SAAG was 1.4 g/dL on two different measurements. The presence of ascites makes dialysis ultrafiltration challenging without much benefit. In our case, abdominal paracentesis was helpful for immediate relief.

SA-PO193

No More Wandering To and Fro: Shedding Light on TAFRO

Nisarg Gandhi,[1] Xixi Zhao.[2] *[1]Stanford Medicine, Stanford, CA; [2]VA Palo Alto Health Care System, Palo Alto, CA.*

Introduction: TAFRO syndrome is a systemic inflammatory disease characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O), often accompanied by AKI. Recently described in 2010 through a case series of Japanese patients, TAFRO is now recognized as a subtype of human-herpesvirus 8 (HHV8) negative idiopathic multicentric Castleman disease (iMCD). Herein, we present a rare case of TAFRO syndrome with AKI requiring dialysis, who was successfully treated with rituximab-based chemotherapy.

Case Description: A 45-year-old previously healthy male presented with anasarca and was found to have new thrombocytopenia, leukocytosis, anemia, and extensive abdominal and axillary lymphadenopathy. After undergoing an excisional lymph node biopsy and a bone marrow biopsy, he was diagnosed with HHV8-negative iMCD, TAFRO subtype, and started on dexamethasone and siltuximab. Despite treatment, creatinine rose from 0.8 mg/dL to 3.11 mg/dL with hyperkalemia requiring hemodialysis. Labs were notable for IL-6 of 35.6 pg/mL (ref: <5 pg/mL) and VEGF of 446 pg/mL (ref: 31-86 pg/mL). UA was negative for proteinuria and hematuria. Renal biopsy showed intact glomerulus with mesangiolysis, glomerular basement membrane double contouring, and scattered fragmented RBCs consistent with thrombotic microangiopathy (TMA). Given severe features of the disease without improvement in renal function, he was initiated on a rituximab-based chemotherapy regimen (R-CHOP) with immediate response. His kidney function returned to its previous baseline two weeks later.

Discussion: TAFRO syndrome is an underrecognized condition that can result in AKI requiring dialysis. Despite the majority of TAFRO cases describing AKI as a central feature, descriptions of renal histology and treatment regimens have been limited in the literature. Prior kidney biopsies have commonly reported MPGN and TMA, which led to the postulated mechanism of injury to occur via IL-6 and VEGF leading to glomerular microangiopathy. Our patient was refractory to IL-6 blockade with siltuximab, suggesting the pleomorphic cytokine profile of iMCD and that IL-6 may not be the primary driver of inflammation. Due to the rarity of the condition and paucity of data guiding treatment, our case adds to the otherwise limited clinical description, renal histology, and treatment of TAFRO syndrome.

SA-PO194

A Rare Incidental Finding of Erdheim-Chester Disease

Maria A. Chilo Bejarano, Sonya D. Shah, Rohin Gurumurthy, Jeanine Hernandez, Celia P. Corona Villalobos, Nityasree Srialluri. *Johns Hopkins Medicine, Baltimore, MD.*

Introduction: Erdheim–Chester Disease (ECD) is a rare non-Langerhans histiocytic disorder marked by histocyte overproduction and tissue infiltration affecting the retroperitoneum, large vessels, heart, lung and central nervous system. Clinical presentation is nonspecific and varies depending on the organ involved. Here we report an incidental case of ECD in a patient with acute kidney injury (AKI).

Case Description: A 77-year-old white male with coronary artery disease, heart failure, and tobacco use presented for facial and shoulder burns after cardiac syncope and fall onto a space heater. He was found to have enterococcus faecalis bacteremia with right aortic valve vegetation, AKI and pulmonary embolism. Incidentally, CT abdomen pelvis showed irregular symmetric soft tissue infiltration of bilateral perirenal spaces, known as “hairy kidney” appearance, modest bilateral pelviectasis and soft tissue thickening surrounding the thoracic and intra-abdominal aorta (Fig. 1). Initial creatinine was 1.79 mg/dl which increased to 5.32 mg/dl in 24 hours. Biopsy of the lesion was deferred due to anticoagulant requirements and rapid clinical decline with volume overload and mental status changes. He was on hemodialysis briefly and transitioned to hospice per family wishes. Radiological features in this case, including the “hairy kidney” appearance, periaortic soft tissue, sparing of the vena cava and ureters, interlobular septal thickening and pleural effusion, are characteristic for ECD and support the diagnosis.

Discussion: ECD is a multiorgan disorder marked by sclerotic lesions of the long bones and perirenal infiltration. Less than 10% of cases occur without bone lesions, necessitating the consideration of histopathology and radiological characteristics for diagnosis. Given the nonspecific nature of ECD, early recognition of the radiological presentations as in our patient is crucial for timely diagnosis and management. Recent discoveries of underlying mutations, like the common BRAFV600E mutation, have shaped the use of targeted therapies such as BRAF inhibitors to prevent disease progression.

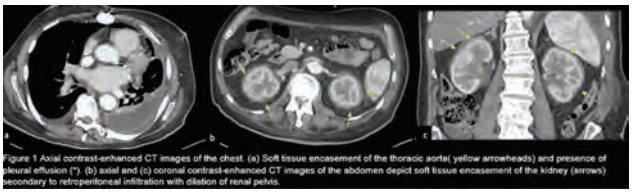


Figure 1 Axial contrast-enhanced CT images of the chest. (a) Soft tissue encasement of the thoracic aorta(yellow arrowheads) and presence of pleural effusion (*). (b) axial and (c) coronal contrast-enhanced CT images of the abdomen depict soft tissue encasement of the kidney (arrows) secondary to retroperitoneal infiltration with dilation of renal pelvis.

SA-PO195

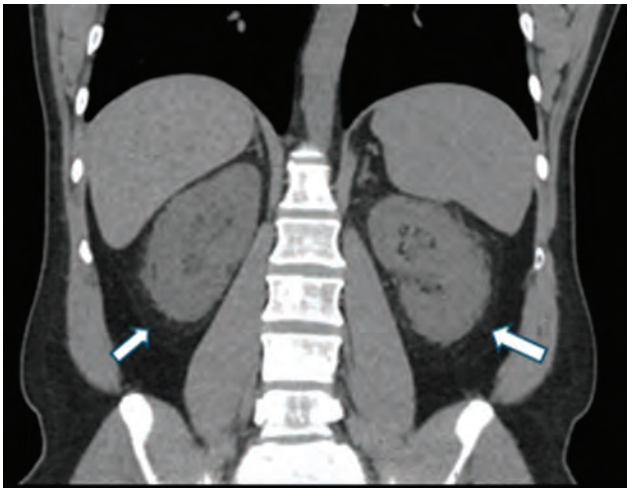
The Case of the Hairy Kidneys

Nazish Khan, Vimal K. Derebail, Ryan Bonner, Vanessa Moreno. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

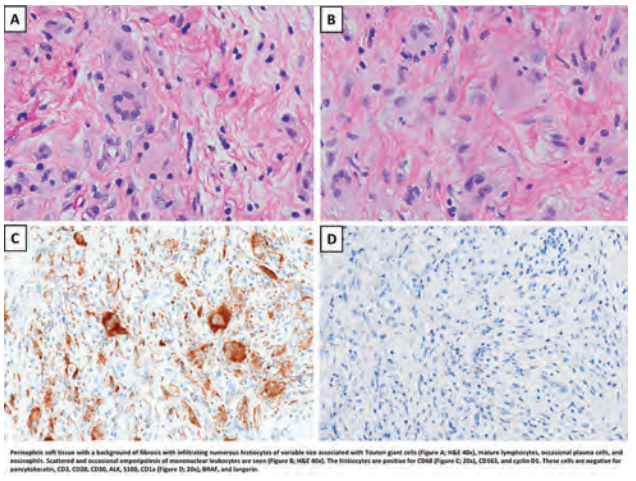
Introduction: Erdheim-Chester disease (ECD) is a multi-organ infiltrative disease due to to non-Langerhans histiocytosis, causing mostly bone and skin lesions. Kidney involvement occurs in 30% of patients.

Case Description: A 54-year-old male with hypertension experienced flank pain and was diagnosed with kidney stones 4 years prior. He had sclerotic bone lesions on imaging and biopsies demonstrated non-specific myelofibrosis. More recently, he had worsening flank pain and renal insufficiency. By computed tomography, extensive bilateral perinephric edema and fat stranding was seen, identified as “hairy kidney sign”, a finding pathognomonic for ECD. Kidney biopsy was performed to establish diagnosis and perform genetic sequencing and demonstrated macrophage-predominant histiocytic infiltrate. Tissue was BRAF negative by immunohistochemistry, but BRAF positive by molecular analysis. The patient was diagnosed with ECD based on his clinical, imaging, and biopsy findings and began MAPK/extracellular signal regulated kinase (MEK) inhibitor therapy.

Discussion: Fewer than 1,000 cases of ECD are reported. Somatic mutations of BRAF or other MAPK signaling pathway components result in myeloid progenitor cell proliferation. Kidney involvement presents as reduced glomerular filtration rate, perinephric stranding, hydronephrosis, renovascular hypertension, or flank pain with infiltration and enlarged kidneys. Tissue biopsy (often skin or kidney) establishes diagnosis and identifies mutations for targeted therapy.



CT scan with extensive bilateral perinephric stranding



Perinephric soft tissue with a background of fibrosis with infiltrating numerous histiocytes of variable size associated with Touton giant cells (Figure A; H&E 40x), mature lymphocytes, occasional plasma cells, and eosinophils. Scattered and occasional emperipolesis of mononuclear leukocytes are seen (Figure B; H&E 40x). The histiocytes are positive for CD68 (Figure C; 20x), CD163, and cyclin D1. These cells are negative for pancytokeratin, CD1, CD30, CD30, ALK, S100, CD1a (Figure D; 20x), BRAF, and langerin.

SA-PO196

Isosorbide Mononitrate (IMN) for Anti-vascular Endothelial Growth Factor (VEGF)-Induced Kidney Injury

Jaya Kala, Kevin W. Finkel. *The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.*

Background: Antiangiogenic drugs that target VEGF and its receptors are standard treatment for several cancers. Their action on VEGF expression has been associated with acute kidney injury(AKI), proteinuria and hypertension(HTN) which result in delay, interruption or reduction of effective dose in cancer patients. These effects have been attributed to the downregulation of nitric oxide(NO). Current recommendations for treatment of anti-VEGF induced HTN include use of ACE inhibitors and non-dihydropyridine calcium channel blockers but strategies to prevent proteinuria or AKI are lacking. NOdonors normalize blood pressure in anti-VEGF induced HTN. Studies have shown pre-treatment with long lasting NOdonors protect against development of anti-VEGF induced HTN. Paucity of large clinical studies using NOdonors for proteinuria, AKI and HTN prompted us to investigate this modality of treatment

Methods: Study-Population: Adult patients with AKI(≥ 25%decrease in eGFR)), HTN (systolicBP≥140mmHg and/or diastolicBP≥90 mmHg) and/or proteinuria(UPC of >500mg/g) while on anti-VEGF therapy. **Treatment:** Patients were randomized to treatment(IMN 60mg/d with dose escalation to 120mg/d in 4weeks if no response) or placebo arm. Criteria for Response(≥1) included improved eGFR≥25%; reduction in UPC by >500 mg/day;reduction in SBP≥10mm Hg and/or DBP≥5mmHg. **Follow-up:** UPC and eGFR were monitored monthly and blood pressure weekly. **PrimaryEndPoint:** Reduction in UPC by >500mg/day. **SecondaryEndPoints:** Improved eGFR≥25%;reduction in SBPof ≥10mmHg and/or DBP≥5mmHg

Results: 42 patients were screened and 9 were enrolled. Seven were randomized to treatment and two to placebo. In treatment arm, two patients showed proteinuria response but none showed eGFR response. Four showed responses in their SBP. The two patients who showed improvement in proteinuria had preceding improvement in HTN. Neither patient in placebo arm showed response in UPC or eGFR, but unexpectedly showed improved systolicBP. Unfortunately, COVID-19 pandemic precluded further recruitment and study was terminated

Conclusions: Treatment with NOdonors could be considered when ACEinhibition and non-dihydropyridine calcium channel blockers fail to control proteinuria in anti-VEGF treated patients. Larger population-based studies are needed to evaluate the use of NOdonors to improve renal prognosis in patients while allowing them to continue anti-VEGF treatment

Funding: Government Support - Non-U.S.

SA-PO197

Renal Adverse Events Associated with Atezolizumab Plus Bevacizumab, Carboplatin, and Paclitaxel (ABCP) Therapy in Patients with Non-small Cell Lung Cancer

Yusuke Watanabe, Koji Tomori, Tsutomu Inoue, Hirokazu Okada. *Saitama Ika Daigaku, Iruma-gun, Japan.*

Background: In recent years, the combination therapy comprising immune checkpoint inhibitors (ICIs), VEGF inhibitors, and cytotoxic anticancer drugs has gained prominence in treating various advanced cancers. ICIs, notably, can induce immune-related adverse events (irAEs) like acute interstitial nephritis (AIN), while VEGF inhibitors are associated with proteinuria, occasionally manifesting as nephrotic syndrome (NS). A novel regimen, ABCP therapy (atezolizumab + bevacizumab + carboplatin + paclitaxel), has emerged for non-small cell lung cancer. In the global phase III IMpower150 study of ABCP, renal adverse events included NS in 2.5%, severe AKI in 0.3%, and AIN due to irAE in 0.8%. This study aims to assess renal adverse events in such patients treated with ABCP at our institution, examining their clinical characteristics and risk factors.

Methods: We conducted a study involving 73 non-small cell lung cancer patients treated with ABCP therapy (up to 4 cycles of ABCP, followed by continuation of atezolizumab + bevacizumab combination therapy). We evaluated the incidence of nephrotic-level proteinuria and AKI.

Results: At the initiation of ABCP therapy, the median age was 70 years (IQR 64.5 - 73), UPCR was 0.11 g/gCr (IQR 0.07 - 0.16), and eGFR was 73.1 ml/min/1.73m2 (IQR 58.4 - 87). Patients underwent a median of 6 cycles of ABCP (IQR 2.3 - 11), with a median observation period of 10 months (IQR 5.5 - 15). Notably, 4 patients (5.5%) exhibited UPCR ≥3.5 g/gCr, and 1 patient (1.4%) experienced AKI due to irAE, necessitating steroid treatment. Patients with nephrotic-level proteinuria tended to have higher UPCR at treatment onset (0.24; 0.1- 0.38) vs (0.11; 0.07 - 0.15), lower BMI (18;17.3 - 20.1) vs (21.2; 19.2 - 24.2), and more frequent ABCP therapy sessions (10; 8.3 - 26.8) vs (6; 2 - 10.8) compared to those without.

Conclusions: The incidence of massive proteinuria may be higher during ABCP therapy in real-world clinical practice compared to the phase III trial. Possible contributing factors include patients with elevated UPCR prior to treatment initiation, potential excessive bevacizumab doses in patients with progressive emaciation, and the prolonged duration of ABCP treatment.

SA-PO198

Drug-Induced Thrombotic Microangiopathy from Cancer Therapies: A Clinicopathologic Series

Wai Lun Will Pak,[1,2] Andrea Knezevic,[3] Steven Salvatore,[4] Surya V. Seshan,[4] Ilya Glezerman,[1,4] Edgar A. Jaimes,[1,4] Insara Jaffer Sathick.[1,4] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]United Christian Hospital, Hong Kong, Hong Kong; [3]Memorial Sloan Kettering Cancer Center Department of Epidemiology & Biostatistics, New York, NY; [4]Weill Cornell Medicine, New York, NY.*

Background: Drug-induced thrombotic microangiopathy (di-TMA) is a major sequela of cancer therapies. The diagnosis of di-TMA is often presumptive, making accurate clinical characterization difficult. Herein we present our experience of biopsy-proven renal di-TMA due to cancer therapies.

Methods: We retrospectively reviewed kidney biopsies performed in a cancer center between 2001 and 2023. We included patients with biopsy-proven di-TMA and presentation consistent with a drug-induced process. We describe their clinical, laboratory, pathologic characteristics, and outcomes.

Results: We identified 53 patients with biopsy-proven di-TMA. Median age of this predominantly female (72%) cohort was 64 (range 44-81) years. Primary malignancies were pancreatic (19%), breast (15%), ovarian (15%) and lung (15%) cancers. Primary causative drugs were gemcitabine (49%), bevacizumab (25%), tyrosine kinase inhibitors (19%), and doxorubicin (15%). A secondary drug exposure was implicated in 28% patients. Hypertension was the commonest symptom (81%), followed by edema (53%). Hematological signs were anemia (77%), thrombocytopenia (29%), elevated LDH (67%), and low haptoglobin (46%). AKI occurred in 41 patients (77%), of which 53% was KDIGO stage 1, 20% was stage 2, and 27% was stage 3. Proteinuria occurred in 59% patients, nephrotic range proteinuria in 20% patients. Median creatinine at presentation was 2.0 (1.7-3.1) mg/dL and median eGFR was 29.2 (16.7-37.3) mL/min/1.73m^2. Majority (84%) had chronic TMA on biopsy, 36% with acute and 13% with subacute features. Cessation of offending drug was the mainstay management in 96%, other treatment included steroids (15%) and eculizumab (8%). Of patients with cessation of drug alone (40, 75%) who experienced AKI (30, 77%), renal recovery was observed in 47% after one year. One out of 9 patients requiring dialysis was weaned off.

Conclusions: We present the largest single institution cohort of patients with biopsy-proven di-TMA from cancer treatment. Though limited by its retrospective nature, our experience suggests that doxorubicin is an underrecognized cause of di-TMA. Many patients had chronic changes on biopsy indicating mild, ongoing endothelial injury before overt TMA develops. Clinical vigilance with early cessation of offending drug may allow for higher rates of renal recovery.

Funding: Other NIH Support - MSK Cancer Center Support Grant/Core Grant P30CA008748

SA-PO199

Gamma-Secretase Inhibitor-Associated Hypophosphatemia in Patients with Desmoid Tumors

Wai Lun Will Pak,[1,2] Edgar A. Jaimes,[1,3] Andrea Knezevic,[5] Jordyn Agins,[1] Kenar D. Jhaveri,[4] Aisha Shaikh.[1,3] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]United Christian Hospital, Hong Kong, Hong Kong; [3]Weill Cornell Medicine, New York, NY; [4]Northwell Health, New Hyde Park, NY; [5]Memorial Sloan Kettering Cancer Center Department of Epidemiology & Biostatistics, New York, NY.*

Background: Nirogacestat, a γ-secretase inhibitor (GSI), improved progression-free survival in adults with desmoid tumors (*DeFi trial, Gounder et al., NEJM, 2023*). Hypophosphatemia (HP), a class effect of GSI therapy, occurred in 42% of trial subjects. The mechanism of GSI-associated hypophosphatemia (GSI-HP) is unknown. The objective of the study was to elucidate the mechanism of GSI-HP.

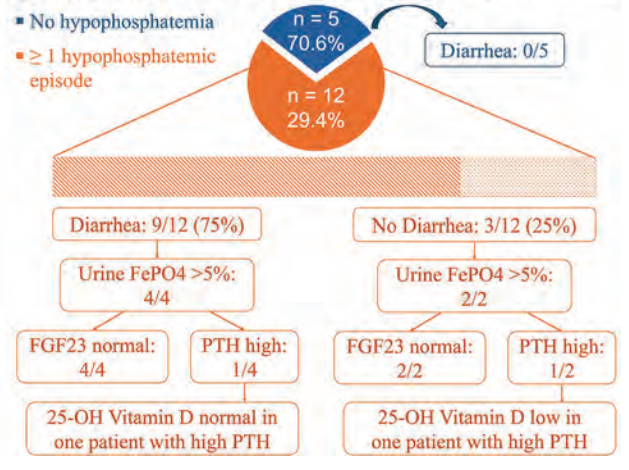
Methods: We used our institute's electronic medical record system to conduct a retrospective cohort analysis of the subjects in the DeFi trial, the RINGSIDE trial (an ongoing trial of AL102, another GSI), and those on compassionate use of nirogacestat at a single large cancer center. Clinical and laboratory data on all patients on a GSI were collected and analyzed.

Results: We identified seventeen patients who received nirogacestat or AL102 and had at least one episode of HP between 2020 and 2023 (Figure 1). Twelve patients had GSI-HP; nine of them had diarrhea. Urine fractional phosphate excretion (FePO4) was available in four patients with diarrhea and two without diarrhea. All six patients had a high urine FePO4 and a normal serum fibroblast growth factor 23 (FGF23), and two patients had high serum parathyroid hormone (PTH). 25-OH vitamin D level was low in one patient with a high PTH. In most patients, the hypophosphatemia was not severe (median serum phosphate 2.2, IQR: 1.9-2.2), and treatment with phosphate supplements and anti-diarrheal medications allowed the continuation of GSI therapy.

Conclusions: We conclude that the primary mechanism of GSI-HP is gastrointestinal loss due to diarrhea. High urine FePO4 may also contribute to GSI-HP in some patients, but FGF23 does not mediate it. This is the first study to describe the mechanism of GSI-HP. These findings will equip clinicians with the knowledge to assess the cause of GSI-HP and implement effective therapies to manage GSI-HP, ensuring better patient outcomes.

Funding: NIDDK Support, Other NIH Support - MSK Cancer Center Support Grant/Core Grant P30CA008748

Figure 1. Clinical and laboratory findings in patients who received GSI.



SA-PO200

AKI and Perioperative Complications Based on Modality of Nephrectomy for Treatment of Kidney Cancer

Maulinkumar N. Patel,[1] Edgar A. Jaimes.[2] *[1]The University of Texas Health Science Center at Houston, Houston, TX; [2]Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: Historically radical nephrectomy (RN) has been the standard of care for renal masses. However, the use of partial nephrectomy (PN) as a therapeutic modality has become more common. Laparoscopic (LAP) and robotic assisted (RAS) approaches are often used for either RN or PN. In this study we determined the rates of acute kidney injury (AKI) and peri-operative complications based on surgical approach

Methods: We used the National Inpatient Sample NIS 2020-2021 to identify kidney cancer patients who underwent PN or RN. Patients were stratified based on type of surgical approach, (open, LAP or RAS). Bivariate analysis was done using Kruskal Wallis test (for age and length of stay), chi-square test, and Fischer's exact test. Multivariable logistic and negative binomial regression models were used to assess the outcome rates. Multivariable models were adjusted for age, gender, race, hospital teaching status, and hospital region.

Results: Overall, 4,572 had PN, and 8,104 had RN. Median age was 63 years, 64% were male and 72% were whithe. In PN patients 21% had open, 9% had LAP, and 70% had RAS. In RN patients, 32% had open, 25% had LAP, and 43% had RAS. RN had greater risk of AKI (OR 1.73) as compared to PN. In PN patients, open approach had greater risk of AKI (OR 2.41), cardiac complications (OR 1.40), pulmonary complications (OR 2.34), and increased length of stay [rate ratio (RR) 1.81] as compared to RAS. A LAP approach had greater rsik of AKI (OR 1.61) and increased length of stay (RR 1.19,), as compared to RAS. In RN patients, compared to RAS, open approach had greater risk of AKI (OR 1.44), cardiac complications (OR 1.25), intraoperative complications (OR 2.26), pulmonary complications (OR 1.93), vascular complications (OR 3.41), postoperative bleeding (OR 2.6), and increased length of stay (RR 1.72). In RN patients length of stay (RR 1.08) was higher in LAP as compared to RAS.

Conclusions: Our results show a higher risk for AKI among patients undergoing RN as compared to PN. The use of LAP or RAS was associated with a lower risk for AKI and peri-operative complications as compared to open surgery. RAS was linked to a lower risk for AKI and peri-operative complications as compared to LAP. This study underlines the importance of surgical approach on the risk for AKI and perioperative complications in patients undergoing a nephrectomy for cancer.

Funding: NIDDK Support

SA-PO201

Impact of Ischemia Time on Kidney Function in Patients with Microcirculation Impairment during Partial Nephrectomy (PN) for Kidney Cancer

Francesco Trevisani, Francesco Cei, Daniele Cignoli, Federico Belladelli, Chiara Re, Giacomo Musso, Arianna Bettiga, Isaline Rowe, Roberta Lucianò, Giuseppe Rosiello, Daniela Canibus, Francesco Fiorio, Roberto Bertini, Andrea Salonia, Francesco Montorsi, Umberto Capitanio. *IRCCS Ospedale San Raffaele, Milano, Italy.*

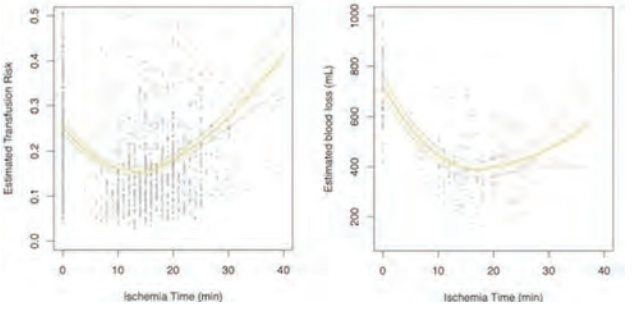
Background: The role of onco-nephrologists in renal cancer patients (RCC) is crucial due to the risk of surgical AKI and CKD. Despite the benefits of partial nephrectomy (PN) in preserving renal function, arterial clamping during surgery could lead to AKI and CKD, especially in RCC patients with comorbidities like hypertension, diabetes, or vascular diseases. This study aims to investigate the impact of PN on RCC patients with microcirculation impairment (MI)

Methods: Data are from 186 patients with microcirculation impairment undergoing elective partial nephrectomy (PN) for cT1-2 cN0 cM0 RCC. Impairments included hypertension, diabetes, peripheral vasculopathy, or vascular nephropathy. Ischemia time was the duration of clamping the renal artery without refrigeration. Primary outcome was the effect of warm ischemia time (WIT) on renal function postoperatively, at 6 months, and long term. Secondary outcome was hemorrhagic risk, defined as estimated blood loss (EBL) or peri-operative transfusions. Multivariable regression analyses were used

Results: A total of 139 patients (75%) underwent PN with WIT and 47 (25%) without. The baseline median eGFR was 71 mL/min/1.73m^2 for the on-clamp population and 61.4 mL/min/1.73m^2 for the off-clamp population. At multivariable analyses predicting renal function, longer WIT was associated with decreased postoperative eGFR (Est:−0.23, [P<0.001]). Conversely, no association between WIT and eGFR was recorded at 6-month or long-term follow-up (all P>0.1). At multivariable analyses predicting hemorrhagic risk, clampless resection with no ischemia time and PN with short WIT was associated with an increased EBL (Est:−25.77, [P=0.03]) and peri-operative transfusion rate (Est:−0.017, [P=0.04])

Conclusions: Patients and clinicians should know that performing partial nephrectomy (PN) with limited or zero warm ischemia time (WIT) in patients with microcirculation impairment does not improve long-term renal function and increases bleeding and transfusion risk. Our findings support hilum clamping even in these patients

Figure 1: Estimated blood loos and transfusion risk according to the duration of ischemia time in 186 patients with microcirculation impairment.



SA-PO202

Trend Analysis of Kidney Neoplasms-Related Mortality, 1999-2020

Mohammad Gul Yousaf Khan,[1] Mohammad Ammar ur Rahman,[2] Saleha Azeem,[2] Luqman Munir,[2] Amna Khalid,[2] Muhammad Talha Shaukat,[2] Ahsan Zil-E-Ali,[1] Umar Farooq,[1] Wania Rehman.[2] NEURALKEy.
[1]Penn State College of Medicine, Hershey, PA; [2]King Edward Medical University, Lahore, Pakistan.

Background: Renal neoplasms represent conditions with prognoses of varying severity depending on the tumor subtype. These neoplasms entail the abnormal proliferation of cells within kidney tissues, characterized by hematuria, localized flank or lumbar mass, extended pyretic episodes, weight reduction and edema in lower extremities. Early detection is critical to intervention, as renal neoplasms are amenable to treatment in their initial stages but may pose an imminent risk in advanced phases. This study aims to evaluate the incidence and mortality rates of kidney neoplasms from 1999 to 2020.

Methods: We examined mortality data for kidney neoplasms from 1999 to 2020 acquired from CDC Wonder Database. The AAMR per 100,000 people and annual percentage change (APC) with 95% confidence intervals were computed. We looked for substantial tests of parallelism that revealed different trends. To determine overall trends and variations in main demographic groupings (gender, race, age, and urban/rural), the Joinpoint Regression Programme was used.

Results: Between the years 1999 and 2020, a total of 275,905 fatalities linked to Kidney neoplasms were documented. An observed pattern of decreasing trend in the AAMR was significant throughout this period. Specifically, there was an APC of 2.34 from 1999 to 2001 followed by a decrease to -1.91 from 2001 to 2020. The analysis additionally demonstrated elevated rates of mortality in subpopulations characterized by male gender, African American and White ethnicities, as well as individuals residing in urban areas.

Conclusions: Between 1999-2020, the United States has witnessed a decline in mortality rates associated with kidney neoplasms, a trend ostensibly due to advancements in medical care and the deployment of comprehensive vaccination programs. Nevertheless, the persistently elevated mortality rates within certain demographic cohorts underscore a critical need for further research to address these disparities. It is imperative that future endeavors focus not only on the general population but also on those subgroups disproportionately affected by kidney neoplasms.

SA-PO203

Extent of Screening for CKD Development and Monitoring for CKD Complications in Childhood Cancer Survivors: A Single-Centre Retrospective Cohort Study

Carolyn Sun,[1,2] David A. Rubenstein,[1,2] Mahmudul Mannan,[1,2] Paul Nathan,[1,2] Tal Schechter,[1,2] Brandon Yip,[1] Anisa Mata,[1] Sham Haddad,[1] Yasmine Hejri-Rad,[1] Vedran Cockovski,[1] Stella Q. Wang,[1] Michael Zappitelli.[1,2]
[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada.

Background: Childhood cancer survivors (CCS) are at risk for CKD. The extent to which CCS are screened for CKD, or monitored for CKD complications is unknown. We evaluated: 1) the extent of screening for CKD in CCS ≥6 months post-cancer therapy; 2) in patients attaining CKD criteria, the extent of monitoring for CKD complications and of nephrology referral; and 3) the association of patient and cancer characteristics with CKD screening.

Methods: Retrospective cohort study of CCS, ≤18 years at cancer diagnosis from 2016–2020 at a quaternary care referral institution. Outcomes: 1) CKD screening (serum creatinine [SCr] or proteinuria); 2) CKD complications monitoring (i.e., repeat SCr/proteinuria; nephrology referral; vitamin D; PTH; hemoglobin; frequency per KDIGO guideline/CKD severity). CKD defined as: a) *"non-strict"*: any abnormal result; b) *"strict"*: ≥2 abnormal results (eGFR or proteinuria); ≥3 months apart; no normal results in between. Associations between characteristics and CKD screening were evaluated using distribution-appropriate univariable analyses.

Results: Of 443 CCS, only 240 (54.2%) and 132 (29.8%) were screened for non-strict and strict CKD, respectively; 41 (17.1%) and 15 (11.4%) attained criteria for non-strict and strict CKD, respectively. In CCS with non-strict and strict CKD respectively, percentages with complications monitoring: SCr measured (92.7%; 100.0%); urine protein measured (76.9%; 86.7%); nephrology referral (54.1%; 61.5%); vitamin D (36.8%; 61.5%); PTH (31.6%; 38.5%); hemoglobin (90.2%; 93.3%). Table: several variables were associated with CKD screening; many are recognized kidney risk factors.

Conclusions: Screening for CKD and monitoring for CKD complications in CCS are not ideal. Kidney guidelines and follow-up in CCS should be improved to reduce CKD and complications.

Funding: Government Support - Non-U.S.

Table. Comparison of characteristics for CCS who were vs. who were ***not*** screened for CKD, using the "non-strict" CKD definition (left) and "strict" CKD definition (right).

	Non-strict CKD		Strict CKD	
Characteristic	CKD screened (N=240)	CKD not screened (N=203)	CKD screened (N=132)	CKD not screened (N=311)
Age at cancer diagnosis (years)	6.5 [8.8]	6.8 [7.8]	8.5 [9.4]	6.0 [10.2]
Male sex	138 (57.5)	120 (59.1)	74 (56.1)	184 (59.2)
Cisplatin	33 (13.8)	30 (14.8)	***26 (20.0)***	***37 (11.9)†***
Carboplatin	***28 (7.5)***	***32 (15.8)****	11 (8.3)	39 (12.5)
Ifosfamide	19 (7.9)	26 (12.8)	11 (8.3)	34 (10.9)
High-dose methotrexate (dose ≥500 mg/m^2)	63 (26.3)	47 (23.2)	***22 (16.7)***	***88 (28.3)†***
Abdominal radiation	12 (5.0)	13 (6.4)	10 (7.6)	15 (4.8)
Hematopoietic stem cell transplant	27 (11.3)	25 (12.3)	***25 (18.9)***	***27 (8.7)†***
Nephrectomy	21 (8.8)	10 (4.9)	***16 (12.1)***	***15 (4.8)†***
Acute kidney injury during therapy (any stage)	***87/228 (38.2)***	***44/188 (23.4)****	47/128 (36.7)	84/288 (29.2)
Length of observation post-cancer therapy (years)	2.5 [1.6]	2.4 [1.9]	***2.7 [1.7]***	***2.4 [1.7]†***
Death	1 (0.4)	7 (3.4)	0 (0.0)	8 (2.6)

Data reported as median [IQR] or n (%).
*p<0.05 patients with non-strict CKD screening vs. no non-strict CKD screening.
†p<0.05 patients with strict CKD screening vs. no strict CKD screening.

SA-PO204

Late Kidney and Blood Pressure Outcomes after Pediatric Hematopoietic Stem-Cell Transplant: A Systematic Review and Meta-Analysis

Carolyn Sun,[1,2] Sahrish Masood,[1] Jenan-Jill Kiyingi,[1] Salma Abrahim,[1] Tal Schechter,[1,2] Victoria E. Lui,[1] Stella Q. Wang,[1] Michael Zappitelli.[1,2]
[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada.

Background: Pediatric hematopoietic stem cell transplant (HSCT) recipients are at risk for late kidney and blood pressure (BP) outcomes, but existing literature on their prevalence is unclear and outcome assessments differ widely. We evaluated 1) the proportion of patients with late kidney and BP outcomes after pediatric HSCT; 2) the proportion of studies that assess AKI in the first 100-days post-HSCT; 3) kidney and BP outcome definition methods reported.

Methods: Searched MEDLINE, Embase, CINAHL, Web of Science, and Scopus (January 2000–November 2022) for observational studies or clinical trials reporting kidney or BP outcomes, ≥6 months post-pediatric HSCT (excluded: N<20; conference abstracts; non-English/French). Categorical (e.g., CKD) and continuous (e.g., GFR) outcome measures were collected. Two reviewers independently reviewed articles, extracted data, and evaluated study quality; a third reviewer resolved disagreements. Stratified meta-analyses of pooled proportions were performed by HSCT indication (malignancy; non-malignancy; both) using a random-effects model. Heterogeneity was assessed; multiple sensitivity analyses were performed.

Results: 12,333 references identified, 45 selected: 36/45(80.0%) and 20/45(44.4%) evaluated late kidney and BP outcomes, respectively; 18/45(40.0%) assessed AKI. Pooled proportions of patients with late kidney and BP outcomes: 15.0% [95% CI 0.11–0.20, I^2=87.2%] and 9.0% [95% CI 0.06–0.13, I^2=92.2%], respectively. Sensitivity analyses (removing different studies) showed similar estimates. Highest proportions were observed for the malignancy HSCT indication. There was significant heterogeneity in pooled estimates (all, p<0.05). GFR, albuminuria, and proteinuria were used to assess kidney function in 26(72.2%), 4(11.1%) and 4(11.1%) studies, respectively. Definitions for late kidney and BP outcomes were at times undefined and varied greatly.

Conclusions: Late kidney and BP outcomes are common after pediatric HSCT, especially in malignancies, but the literature is exceedingly difficult to interpret. Future research should use well-defined kidney and BP outcome definitions with a goal to study data-driven interventions to reduce long-term kidney health burden.

Funding: Government Support - Non-U.S.

SA-PO205

Association between AKI during Cisplatin Therapy in Children with CKD and Hypertension at 12 and 36 Months after Therapy End

Salma Abrahim,[1] Asaf Lebel,[2,3] Kelly McMahon,[4] Vedran Cockovski,[1] Stella Q. Wang,[1] Jasmine Lee,[1] Michael Zappitelli,[1,2] Able Study Group.[1]
[1]The Hospital for Sick Children Child Health Evaluative Sciences, Toronto, ON, Canada; [2]The Hospital for Sick Children Department of Paediatrics, Toronto, ON, Canada; [3]Emek Medical Center, Afula, Israel; [4]McGill University Health Centre, Montreal, QC, Canada.

Background: Cisplatin (CisP) may cause acute kidney injury (AKI) in children treated for cancer. Predicting post-CisP chronic kidney disease (CKD) or elevated blood pressure or hypertension (≥eBP) remains elusive. We determined: 1) adjusted associations of AKI during CisP therapy with CKD and ≥eBP at 12 and 36 months(M) post-therapy end; 2) whether CKD and ≥eBP at 3M are associated with CKD and ≥eBP at 12 and 36M after CisP therapy end.

Methods: Multicenter prospective study of children treated with CisP followed throughout therapy and for 36M post-therapy end. Exclusion: pre-existing kidney conditions. Urine, blood, BP collected at 3, 12, and 36M post-CisP therapy. Exposures: a) serum creatinine (SCr)-AKI any time during CisP therapy, per KDIGO; b) severe

electrolyte-defined AKI (eAKI) during CisP therapy per National Cancer Institute (NCI) v4.0 criteria; c) composite AKI (SCr-AKI *and* severe eAKI); d) presence of CKD or ≥eBP at 3M post-CisP therapy end. Outcomes at 12 and 36M post-CisP therapy: a) CKD (per KDIGO); b)≥eBP (per AAP guidelines); c) composite of CKD *or* ≥eBP. Analysis: 1) multiple logistic regression (MLR) to evaluate AKI – outcome association (stepwise covariate selection); 2) MLR to evaluate association between 3M and 12M/36M outcomes (for AKI interaction).

Results: Table shows prevalence of CKD and ≥eBP at 12 and 36M. Patients with SCr-AKI, eAKI and composite AKI were more likely to have ≥eBP at 12M. CKD or ≥eBP at 3M did not predict outcome presence at 12 and 36M (Table 1). However, patients with vs. without CKD at 12M were 4.8 times more likely to have CKD at 36M (Table 1).

Conclusions: HTN and CKD were common at 12 and 36M post-CisP therapy. AKI during therapy was associated with ≥eBP at 12M, but the presence of kidney or BP outcomes at 3M did not predict later CKD or HTN. Novel methods to predict kidney health outcomes and interventions to reduce AKI during therapy should be investigated.

Table 1. Adjusted Odds Ratios for Relationship Between SCr-AKI, Severe eAKI and Composite AKI with 12 and 36 Month Outcomes

	12 Month Outcomes	
	CKD[B] n= 119: *48 (40.3%) CKD* Adj OR (95% CI)	≥eBP[C] n=127: *34 (26.8%) ≥eBP* Adj OR (95% CI)
SCr-AKI[A]	1.24 [0.56-2.75]	3.37 [1.39-8.19]
Severe eAKI	0.98 [0.42-2.27]	5.45 [2.09-14.23]
Composite AKI	0.91 [0.32-2.60]	5.18 [1.76-15.24]
3M CKD[D]	1.14 [0.48-2.68]	*NA*
3M ≥eBP	*NA*	0.54 [0.10-2.97]**
36 Month Outcomes		
	CKD[F] n= 81: *27 (33.3%) CKD*	≥eBP[G] n= 88: *26 (29.5%) ≥eBP*
SCr-AKI	0.58 [0.19-1.75]	1.74 [0.65-4.70]
Severe eAKI	1.11 [0.34-3.65]	0.91 [0.27-3.11]
Composite AKI	1.24 [0.27-5.62]	1.37 [0.32-5.86]
3M CKD	0.21 [0.35-1.22]**	*NA*
3M ≥eBP	*NA*	1.11 [0.32-3.83]
12M CKD	4.79 [1.62-14.18]	*NA*
12M ≥eBP	*NA*	2.94 [0.96-9.01]

Legend:

SCr-AKI: AKI defined based on KDIGO guidelines (peak SCr during cisplatin therapy over pre-cisplatin baseline SCr concentration).

eAKI: presence of low magnesium, phosphate or potassium during therapy. The presence of electrolyte abnormalities is common with cisplatin therapy, therefore severe eAKI was defined as NCI-CTCAE v4.0 ≥grade 3.

[A]All models evaluating relationship of 3M or 12M CKD or ≥eBP with 12M and 36M CKD or ≥eBP were adjusted for age and sex; models also included interaction term with SCr-AKI (and SCr-AKI) if the interaction term was statistically significant.

[A]All MLR were adjusted with age <3 at start of therapy and sex in addition to specific variables per outcome and follow up time.

[B]Adjusted with history of nephrotoxic medications 2 weeks before 12 months visit, history of veno-occlusive Disease.

[C]Adjusted with cancer diagnosis of Medulloblastoma; received vancomycin 1 month before visit.

[D]Adjusted with history of nephrotoxic medications 2 weeks before 36 months visit.

[E]Adjusted with baseline eGFR.

**AKI interaction term is significant ($p<0.05$).

SA-PO206

Psychiatric Disorders in Onconephrology Patients: Prevalence, Impact on Survival, and Quality of Life

Jorge I. Zamora Carrillo,[1] Sheila Bermejo Garcia,[2] Ana Callejo,[1] Marina López-Martínez,[1,2] Juan C. León-Román,[1] Marc Patricio-Liébana,[1] Maria Jose Soler.[1,2] *[1]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [2]Vall D'hebron Institut de Recerca (VHIR), Barcelona, Spain.*

Background: Onconephrology has emerged as a crucial subspecialty. Psychiatric disorders are common in cancer and kidney patients, but their impact in Onconephrology patients is not known. The aims of study are to investigate the prevalence and impact of psychiatric disorders on survival and quality of life in Onconephrology patients.

Methods: This prospective study included patients from the Onconephrology Unit (Nov-2021 to Feb-2023). Questionnaires assessed sleep disorders (Epworth scale), depression (GDS, PHQ), cognition (Montreal scale), and anxiety (GAD) at the first visit, 6 months, and 12 months. Clinical and analytical characteristics were collected.

Results: 182 patients were included (mean age 68(±11) years, 70(38.5%) women). 18(9.9%) lived alone, 152(83.5%) lived accompanied and 4(2.2%) in residence. At the first visit, (81)44.5% had sleep disorders, 52(32.7%) depression, 72(39.6%) cognitive impairment, and 14(7.7%) anxiety. Depression was more prevalent in people who lived in residence (p=0.013). Patients with cognitive impairment had a higher prevalence of DM(p=0.003), worse kidney function and were older(p<0.001). Sleep disorders were more prevalent in older patients(p=0.01), and anxiety in women(p<0.001). At six months, anxiety was higher in women(p=0.03) and those with progressive oncological disease(p<0.001). Living alone was linked to more depression(p=0.002). At twelve months, depression correlated with oncological progression(p=0.034). Multivariate analysis identified age as a risk factor for cognitive impairment(OR: 1.1; p<0.001) and female sex for depression(OR: 3.39; p=0.001). At 6 months, female sex was a risk factor for anxiety(OR: 8.6; p=0.01) and living alone for depression(OR: 10.8; p<0.001). 30(16.5%) patients died during follow-up. Kaplan-Meier analysis showed higher mortality in patients with sleep disorders(p=0.039), worse kidney function(p=0.003), and progressive disease(p=0.028)

Conclusions: Onconephrology patients had high rates of depression and anxiety, especially females and people living alone. Comprehensive approaches and early detection tools are essential to improve their survival and quality of life.

SA-PO207

Statewide Burden and Trend of Kidney Cancer in the United States, 1990-2021: A Benchmarking Secondary Analysis

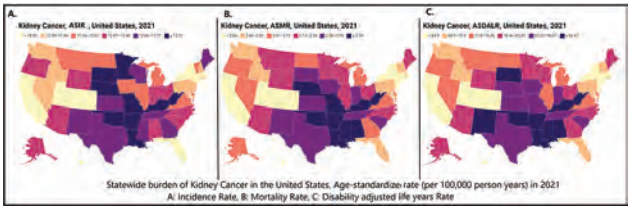
Abrisham Akbariansaravi,[1] Pragathi Munnangi,[2] Venkata Ramana Katikala,[3] Mankarn Hara,[5] Hardik Desai.[4] *[1]American University of Antigua, Coolidge, Antigua and Barbuda; [2]N.R.I Medical College, Guntur, India; [3]Konaseema Institute of Medical Sciences and Research Foundation Hospital, Amalapuram, India; [4]Gujarat Adani Institute of Medical Science, Bhuj, India; [5]Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, India.*

Background: In 2020, national expenditures for kidney cancer (KC) care in the United States were reported at $9.4 billion. This study is the first to assess the state-wide burden of KC over the past three decades, which includes the challenging first two years of the COVID-19 pandemic that impacted cancer management.

Methods: Using the Global Burden of Disease 2021 methodology, we analyzed the incidence, prevalence, deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) related to KC by age, sex, year, and location across the United States from 1990-2021. Using the Global Burden of Disease 2021 methodology, we analyzed the incidence, prevalence, deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) related to KC by age, sex, year, and location across the United States from 1990-2021.

Results: Over this period, the total percentage change (TPC) showed a 90% increase in KC prevalence (95% UI: 83-96%), a 61% rise in mortality (53-66%), and an 83% increase in YLDs (75-91%). The age-standardized incidence rate (ASIR) rose by 2%, and YLDs by 1%. Mississippi experienced the highest increase in ASIR by 26%, while Massachusetts saw a decrease of 27%. Regarding mortality rates, Mississippi saw an 11% increase, whereas the District of Columbia saw the greatest decrease at 38%. Among age groups, the highest number of deaths was observed in the 70-74 age group, totaling 2,863 (95% CI: 2,684-2,980), and the highest DALYs were recorded in the 65-69 age group, totaling 63,803 (95% CI: 60,635-66,470) in 2021. Males showed a higher burden compared to females, with a 3% increase in incidence rates, while females saw a 7% decrease from 1990-2021.

Conclusions: Kidney cancer accounted for 2.52% of all cancer-related deaths. These findings highlight the urgent need for focused efforts to manage the increasing burden of kidney cancer. Public health strategies should focus on improving early detection, optimizing treatment approaches, and ensuring widespread access to care to reduce the impact of this disease.



Statewide burden of Kidney Cancer in the United States. Age-standardize rate (per 100,000 person years) in 2021
A: Incidence Rate, B: Mortality Rate, C: Disability adjusted life years Rate

SA-PO208

Burden of Kidney Cancer Attributable to Smoking in 38 Organisation for Economic Cooperation and Development (OECD) Countries, 1990-2021: Insights from the Global Burden of Disease Study 2021

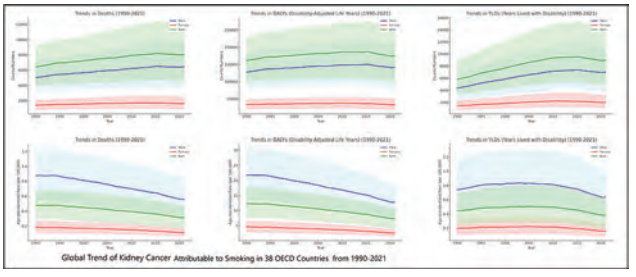
Harsha Choudary Pudhota,[1] Sree Abhilekha Purohit,[2] Sravani Bhavanam,[8,9] Ashwinikumar Shandilya,[4] Saif Syed,[7] Mohit Lakkimsetti,[5] Juhi Patel,[3] Hardik Desai,[6] Vishrant Amin.[3] *[1]Guntur Medical College, Guntur, India; [2]Shadan Institute of Medical Sciences College of Nursing, Hyderabad, India; [3]Gujarat Medical Education and Research Society Medical College & Hospital Valsad, Valsad, India; [4]Rural Medical College, Pravara Institute of Medical Sciences, Ahmednagar, India; [5]Mamata Medical College, Khammam, India; [6]Gujarat Adani Institute of Medical Science, Bhuj, India; [7]Royal College of Surgeons in Ireland, Dublin, Ireland; [8]Sri Devaraj Urs Medical College, Karnataka, India; [9]Brookdale University Hospital and Medical Center, New York, NY.*

Background: Kidney cancer (KC) is on the rise globally, presenting significant concerns. Among modifiable risk factors, this study focuses on the impact of smoking on KC across 38 Organization for Economic Cooperation and Development (OECD) countries over the past three decades. This study is pioneering in its assessment of the burden during the initial two years of the COVID-19 pandemic, a period that significantly challenged cancer management.

Methods: Utilizing the Global Burden of Disease (GBD) 2021 tool, we estimated the deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) attributed to KC attributable to smoking by age, sex, year, and location across these countries from 1990-2021.

Results: The total percentage change (TPC) in death counts increased by 26% (95% UI: 10-41%), DALYs by 9% (2-20%), and YLDs by 56% (39-71%) from 1990-2021. The highest number of age-standardized mortality rates (ASMR) was observed in Czechia at 0.69 cases, followed by Poland at 0.55, and while the US at 0.36 cases per 100,000 in 2021. Individuals aged 70-74 years recorded the highest number of deaths at 1,423 (821-2,122), while those aged 65-69 years showed the highest DALYs at 30,932 (18,383-45,164). In terms of gender differences over the last three decades, males experienced a higher burden compared to females, with TPC in deaths at 29% versus 15%, DALYs increased by 11% for males while decreasing by 1% for females, and YLDs at 61% versus 39%.

Conclusions: KC attributable to smoking accounted for 10.24% of all KC-related deaths in 2021. From the perspective of public stakeholders and policymakers, it is crucial to encourage smoking cessation and implement e-health or m-health education initiatives to reduce this burden.



Global Trend of Kidney Cancer Attributable to Smoking in 38 OECD Countries from 1990-2021

SA-PO209

Global Burden of Kidney Cancer Attributable to High Body Mass Index in 204 Countries and Territories, 1990-2021: Insights from the GBD 2021 Study

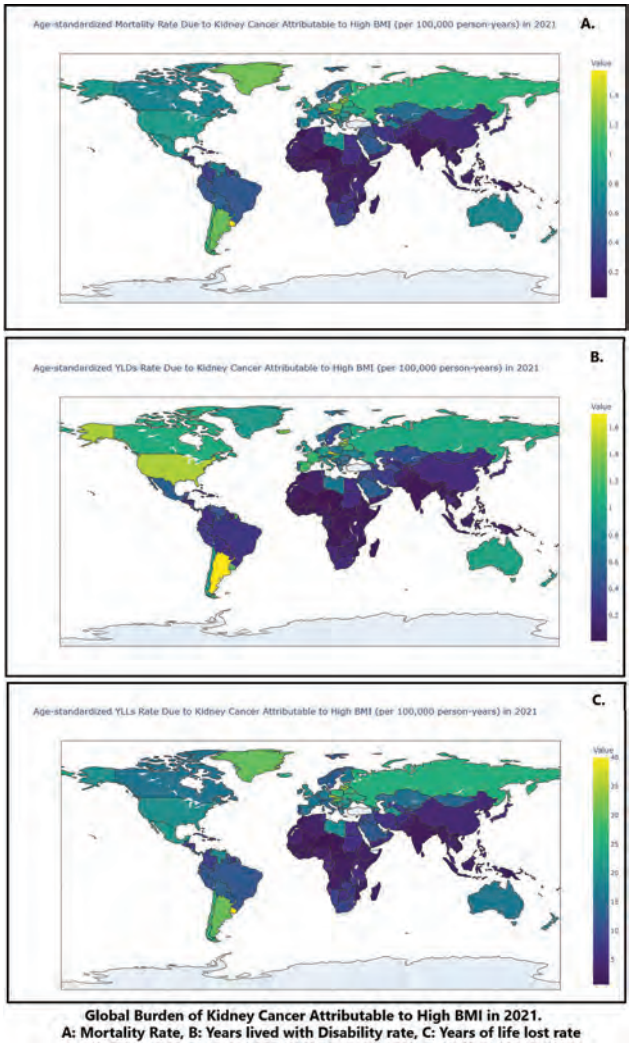
Ashwinikumar Shandilya,[1] Shruthi Katam,[3] Muhammad Waqas,[5] Sravani Bhavanam,[9,10] Shrey Goel,[6] Saif Syed,[8] Mohit Lakkimsetti,[7] Vishrant Amin,[2] Juhi Patel,[2] Hardik Desai.[4] *[1]Rural Medical College, Pravara Institute of Medical Sciences, Ahmednagar, India; [2]Gujarat Medical Education and Research Society Medical College & Hospital Valsad, Valsad, India; [3]Sri Venkateswara Medical College, Tirupati, India; [4]Gujarat Adani Institute of Medical Science, Bhuj, India; [5]Jinnah Sindh Medical University, Karachi, Pakistan; [6]Government Medical College and Hospital Chandigarh, Chandigarh, India; [7]Mamata Medical College, Khammam, India; [8]Royal College of Surgeons in Ireland, Dublin, Ireland; [9]Sri Devaraj Urs Medical College, Karnataka, India; [10]Brookdale University Hospital and Medical Center, New York, NY.*

Background: The burden of kidney cancer (KC) has escalated over the past three decades, alongside modifiable risk factors such as high body mass index (H-BMI). This pioneering study evaluates the burden of KC due to H-BMI over the last three decades, including the initial two years of the pandemic where non-COVID related excess mortality surged, and cancer patients faced challenges in accessing care.

Methods: Utilizing the GBD 2021 framework, we estimated the deaths, disability-adjusted life years (DALYs), years lived with disability (YLDs), and years of life lost (YLLs) due to KC attributable to H-BMI by age, sex, year, across 204 countries and territories from 1990-2021.

Results: The annual percentage change (APC) in age-standardized mortality rate (ASMR) increased by 20% (95% UI: 13-27%), with DALYs rate rising by 15% (9-22%) from 1990-2021. Regionally, the highest ASMR was observed in Southern Latin America at 1.18 per 100,000 population. High-income countries recorded the highest ASMR at 0.71 deaths per 100,000 in 2021. Czechia had the highest unadjusted mortality rate at 3.27 cases per 100,000. Among age groups, the highest number of deaths was observed in the 70-74 age group with 4,857 deaths, followed by the highest DALYs in the 65-69 age group with 119,593 in 2021. Males experienced a greater increase in deaths and DALY rates compared to females (96% vs 59% for deaths, 79% vs 46% for DALYs) from 1990-2021.

Conclusions: KC attributable to H-BMI accounted for 20.01% of all KC-related deaths in 2021. There is a pressing need to implement public health policies focused on managing BMI and to enhance awareness and education about the risks through health news media and public influencers.



Global Burden of Kidney Cancer Attributable to High BMI in 2021.
A: Mortality Rate, B: Years lived with Disability rate, C: Years of life lost rate

SA-PO210

Neuroendocrine Nephrotoxicity: A Case of Chromogranin A Tubulopathy

Madison B. Calder, Omar A. Ayah, Samin Sharma, Sarwat Gilani.
The University of Texas Health Science Center at San Antonio, San Antonio, TX.

Introduction: Neuroendocrine neoplasms (NENs) are capable of secreting functional peptides such as chromogranin A (CgA), an acidic glycoprotein that serves as a NEN biomarker. Although CgA is normally present at basal levels and is easily filtered, reabsorbed, and metabolized within the nephron, when filtered into the urinary space in large amounts, increased resorption can engorge proximal tubular epithelial cells beyond capacity causing cellular damage. We present a case of progressive renal insufficiency in the setting of metastatic NEN consistent with CgA tubulopathy.

Case Description: A 78-year-old female with known metastatic NEN maintained on somatostatin analog therapy was referred for progressive renal dysfunction. Urine microscopy was negative for hematuria or pyuria, and ultrasonography revealed structurally normal kidneys. Total proteinuria was elevated out of proportion to microalbuminuria in the setting of normal serum and urine protein electrophoresis but a rising serum CgA. Due to persistent renal function decline, kidney biopsy was performed, which demonstrated acute tubular injury with proximal tubular epithelial cell resorption granules identified as CgA by immunohistochemistry; these granules demonstrated neither light chain restriction on frozen or paraffin-based immunofluorescence nor evidence of Congo red staining (**Figure 1**).

Discussion: CgA tubulopathy has been described histologically as acute tubular injury resulting from intracellular CgA resorption granules or intratubular cast formation, both of which lead to direct epithelial cytotoxicity. Management centers on early detection and targeted NEN therapy; plasma exchange has been attempted without demonstrated effectiveness. Although rare, a keen awareness of the clinicopathologic consequences of CgA tubulopathy must be shared by oncologists and nephrologists to facilitate early and optimal diagnosis and management.

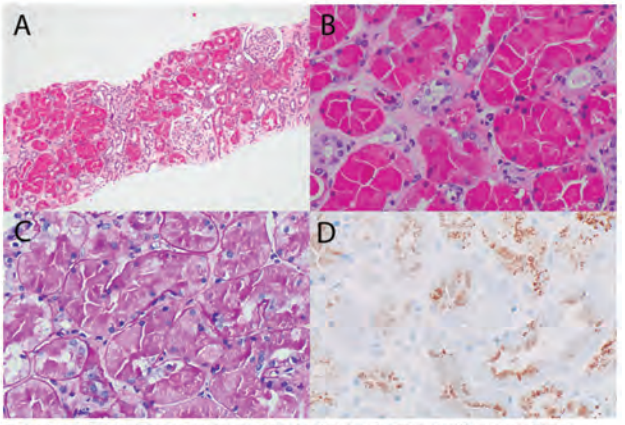


Figure 1. Histologic sections show proximal tubular epithelial cells engorged with intracytoplasmic eosinophilic (H&E stain, A. x200, B. x400) and PAS weak to negative (PAS section, C. x400) granules. The granules showed positivity with chromogranin A immunohistochemical stain (D. x400).

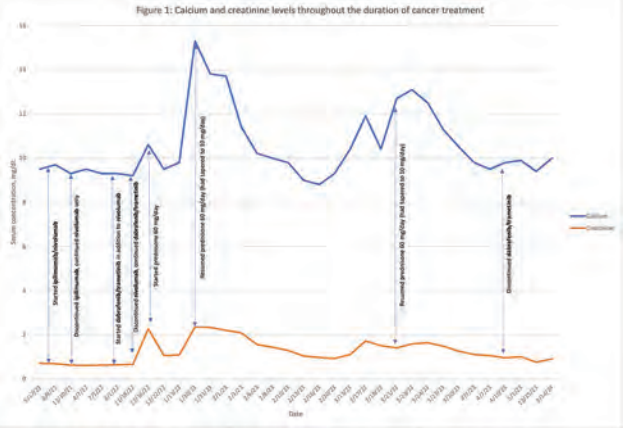


Figure 1

SA-PO211

Sarcoid-Like Reaction Causing Hypercalcemia and AKI in a Patient Treated with Dabrafenib and Trametinib

Stefanie Worwa,[1] Mayssaa Hoteit,[2] Sahar Koubar.[1] [1]*University of Minnesota Twin Cities, Minneapolis, MN;* [2]*Yale New Haven Health System, New Haven, CT.*

Introduction: Protein kinase B-raf (BRAF) and mitogen-activated protein kinase (MEK) inhibitors are pivotal in treating melanoma. Despite efficacy, they can induce adverse events. This case presents a unique instance of hypercalcemia-induced AKI due to a sarcoid-like reaction in a melanoma patient taking dabrafenib and trametinib. Two prior cases of sarcoid-like reactions with these drugs exist, but this is the first symptomatic case.

Case Description: A 53-year-old female was diagnosed with BRAF-positive metastatic melanoma. She started therapy with immune checkpoint blockade (ipilimumab/nivolumab) and later shifted to BRAF/MEK inhibition (dabrafenib/trametinib) with nivolumab. She developed fevers, fatigue, hypercalcemia, and AKI. A lung granuloma and hilar lymph nodes were seen on chest CT. The urinalysis was bland, and the renal ultrasound was normal. Nivolumab was stopped with concern for AIN; dabrafenib and trametinib were continued. She was placed on steroids with recovery, but with any taper, her AKI and calcium would worsen (figure 1). She eventually ended therapy and tapered off steroids as her creatinine and calcium stabilized.

Discussion: AKI recurred with steroid tapers despite the absence of nivolumab. Concomitant severe hypercalcemia and a bland urinalysis suggest the AKI was hypercalcemia-induced. Other etiologies of hypercalcemia were excluded (figure 2). The hilar lymph nodes and lung granuloma likely represented a granulomatous reaction, caused by dabrafenib/trametinib, and led to hypercalcemia. Calcitriol was normal, but hypercalcemia can occur in sarcoidosis despite this. In such cases, steroids decrease levels as they slow production of 1-25 $(OH)_2$ vitamin D. Her calcitriol level was markedly reduced with steroids.

Hypercalcemia Differential Diagnoses	
Bone metastasis	Alk phosphatase isoenzymes 611 U/L (NL 40-120 U/L) Liver 556 U/L (91%) Bone 55 U/L (9%)
Primary hyperparathyroidism	PTH 15 pg/mL (NL 10-65 pg/mL)
Hypercalcemia of malignancy	PTHrP 2.8 pmol/L (NL 0-3.4 pmol/L)
Hypervitaminosis D	25 OH Vitamin D 36 (NL 20-75 ug/L)
Medications	No history of lithium, thiazides, calcium supplements
Calcitriol-mediated	Before steroids: Calcitriol 48.5 (NL 19.9-79.3 pg/mL) With steroids: Calcitriol 15.7

Figure 2

SA-PO212

Acute Interstitial Nephritis Associated with Dabrafenib-Related Pyrexia: A Case Report

Yi-Ting Ong,[1] Ya Hwee Tan,[2] Hui Zhuan Tan.[1] [1]*Singapore General Hospital, Singapore, Singapore;* [2]*National Cancer Centre Singapore, Singapore, Singapore.*

Introduction: Acute kidney injury is common in patients receiving proto-oncogene B-Raf (BRAF) and mitogen-activated protein kinase (MEK) inhibitors, with a subset occurring in conjunction with BRAF/MEK-related pyrexia (Seethapathy *et al.* Nephrol Dial Transplant, 2022). We report a rare case of biopsy-proven acute tubulo-interstitial nephritis (ATIN) diagnosed in the setting of Dabrafenib-related pyrexia.

Case Description: A 69-year-old Chinese female with metastatic melanoma was referred for KDIGO Stage 3, non-oliguric acute kidney injury (AKI) [baseline sCr 54 μmol/L, peak sCr 195 μmol/L], occurring in the setting of Dabrafenib-induced pyrexia. She was reinitiated on Dabrafenib alone at a reduced dose of 75mg 3 weeks prior to presentation, after developing drug-induced liver injury to Dabrafenib/Trametinib (DT). Notably, she last received Nivolumab, an immune checkpoint inhibitor (ICI) 4 months prior, but had no recent exposure to proton pump inhibitors, non-steroidal anti-inflammatory drugs or antibiotics. Evaluation showed pyuria (urinary WBC 15/μL) and sub-nephrotic range proteinuria (uPCR 1.34g/g). Serum C-reactive protein was elevated at 17.8 mg/L. Autoimmune markers and virologies were negative. AKI was slow to improve despite supportive therapy and fever lysis. Kidney biopsy showed severe ATIN, with a small non-necrotising granuloma. There were no other clinical features suggestive of a systemic sarcoid-like reaction. She was started on prednisolone 60mg (1mg/kg), which was tapered over 7 weeks. Partial renal recovery was observed (sCr 76μmol/L). Dose-reduced DT was resumed 8 weeks later without prophylactic steroids. No recurrence of AKI was observed during 3 months of follow-up.

Discussion: AKI occurring with BRAF/MEK-related pyrexia can result from multiple etiologies. Cytokine release and NSAID use are common causes, but ATIN is an important differential. We postulate that previous ICI exposure could have contributed to the development of ATIN given their potential for longer-term modulation of immune tolerance. Diagnostic kidney biopsy should be strongly considered if AKI persists despite fever lysis and supportive therapy, especially in patients with past ICI exposure. Our case suggests that same-drug rechallenge is feasible, with or without prophylactic steroids, together with close monitoring for AKI recurrence.

SA-PO213

Hypophosphatemia in Midostaurin-Treated FLT3 Acute Myeloid Leukemia

Timothy M. Chow, Nityasree Srialluri. *Johns Hopkins Medicine, Baltimore, MD.*

Introduction: Midostaurin is a first in class, multiple protein kinase inhibitor approved in 2017 for treatment of FLT3-mutated acute myeloid leukemia with conventional therapy. It has activity against multiple protein receptors including the mutated and wild type FMS-related tyrosine kinases. Other kinase inhibitors have been previously described to contribute to hypophosphatemia and 5% of patients were found to have hypophosphatemia in a phase 3 trial of midostaurin. There have been no cases describing the course or nature of hypophosphatemia in midostaurin use. We present the first case of hypophosphatemia attributed to midostaurin use with resolution after discontinuation.

Case Description: A 51-year-old female with hypertension presented with encephalopathy and fevers and was found to have acute myeloid leukemia positive for the FLT3 IDT mutation. She underwent cytoreduction with hydrea and induction with

"7+3" cytarabine and anthracycline alongside midostaurin. Before induction therapy, phosphorous ranged from 3-4 mg/dL. By day 3, phosphorus was 1.0 mg/dL, requiring daily oral and intravenous replacement. On day 4, phosphorus was 0.8 mg/dL. Serum creatinine was at a baseline of 0.5 mg/dL, ionized calcium was 1.10mmol/L, serum calcium was 6.8 mg/dL. PTH was 222 pg/mL, Vitamin D level was 37 ng/mL, and uric acid was 1.2 mg/dL. Spot urine electrolytes were obtained. Urine creatinine was 26 mg/dL, urine phosphorus was 52.8 mg/dL, and urine potassium was 20.5 mg/dL. Urine sodium was 114 mg/dL. There was no glucosuria. The fractional excretion of phosphate was 59.7%. Midostaurin was switched to gilternitinib after day 15 and phosphorus and calcium levels improved without further supplementation.

Discussion: We describe the first case of hypophosphatemia attributed to midostaurin use. Like other kinase inhibitors, the exact mechanism of midostaurin related hypophosphatemia is unknown. Theories include PTH mediated hyperparathyroidism, FGF23 interaction, and proximal tubule wasting. Based on our patient's elevated fractional excretion of phosphate, the acuity and refractory nature of her phosphate depletion, she likely had at least contributions from proximal tubular injury. Use of midostaurin should have careful electrolyte monitoring and evaluation, with investigation of etiology if hypophosphatemic. In our patient, discontinuation was followed by resolution of the hypophosphatemia.

SA-PO214

A Rare Case of Severe Hypophosphatemia

Ryan M. Song, Marco A. Bonilla Arevalo. *The University of Chicago Medicine, Chicago, IL.*

Introduction: Tumor-induced osteomalacia (TIO) or oncogenic osteomalacia is a rare paraneoplastic syndrome characterized by excess production of fibroblast growth factor 23 (FGF23), which leads to hyperphosphaturic hypophosphatemia. Clinical manifestations are often nonspecific and the syndrome is underdiagnosed and recognized late. It is important to have a high index of suspicion when evaluating hypophosphatemia, as early intervention of TIO can prevent or reverse osteomalacia and lead to an expedited investigation of a culprit neoplasm.

Case Description: A 67-year-old male with actively-treated mesothelioma was referred to nephrology for hypophosphatemia despite aggressive oral repletion. History and physical revealed nonspecific symptoms of fatigue, myalgias, decreased appetite, and lower extremity swelling, but was negative for malnutrition, causative medications, or other specific etiology. Further labwork revealed a normal parathyroid level, low vitamin-D level, and elevated fractional excretion of urine phosphorous. An FGF23 level was markedly elevated, confirming the presence of a FGF23-mediated hypophosphatemia, consistent with TIO. Vitamin D supplementation and continued oral phosphorous repletion only mildly improved his serum phosphorous. Unfortunately, our patient's cancer was resistant to treatment and he ultimately passed away under hospice care.

Discussion: TIO is rare and underdiagnosed, with a prevalence of less than 1 per 100,000 adults in the general population. Correct diagnosis is often delayed by over 3 years on average after symptom onset, with treatment delayed further. As nephrologists, we routinely measure serum phosphate levels. Once hypophosphatemia is identified, it is paramount to rule out poor diet, medication effects, and other associated conditions (such as refeeding syndrome, hyperparathyroidism or vitamin D deficiency). Renal phosphorus wasting should be confirmed with an inappropriately elevated urinary phosphorous (fractional excretion > 5% or a ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate < 85%). In this setting, an elevated FGF23 level will be diagnostic of FGF23-mediated hypophosphatemia, after which localization of the culprit tumor should be performed with functional imaging studies. Early identification of TIO can lead to early intervention of a causative tumor, and limit the debilitating complications of osteomalacia and malignancy.

SA-PO215

Interleukins and Hyponatremia in Patients with Cancer

Joshua Pantanowitz,[1] Michelle N. Keyser,[2] Pooja D. Amarapurkar.[2] *[1]University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]UPMC, Pittsburgh, PA.*

Introduction: There is renewed interest in the use of targeted delivery systems and engineered forms of Interleukin-12 (eIL-12) for the treatment of several advanced cancers. We present a unique case of hyponatremia in a patient with eIL-12 therapy for pancreatic cancer that was unresponsive to 3% saline and tolvaptan and treated with tocilizumab.

Case Description: A 77 year old male with invasive poorly differentiated metastatic ampullary adenocarcinoma of the pancreas who failed multiple lines of therapy was seen in the hospital for altered mental status. Initial laboratory data showed a serum sodium of 121 mMol/L. 3% saline was administered after admission to the ICU and he remained hemodynamically stable. The serum sodium remained unchanged for 8 hours after 100 ml bolus and 25 ml/hr of 3% saline for several hours and tolvaptan 7.5 mg. Given the lack of response to 3% saline and tolvaptan, hyponatremia was thought to be related to eIL-12 infusions. After discussion with his oncologist, he received tocilizumab. Within hours of the tocilizumab administration his serum sodium increased to 127 mMol/L in 10 hours. Tocilizumab was repeated the following day with serum sodium stabilizing at 131mMol/L. 3 weeks prior to the current admission he started cycle 1 of eIL-12 and was found to have a hyponatremia with serum sodium of 127 mMol/l (baseline sodium 132-134 mMol/L). This was attributed to cancer-related syndrome of inappropriate anti-diuretic hormone and he was started on sodium chloride tablets 1 gram three times a day as an outpatient, but the hyponatremia persisted. 4 days prior to the current admission he received cycle 2 of eIL-12. Unfortunately, he developed severe cytokine release syndrome with subsequent infusions with disease progression and impending home hospice.

Discussion: With the increased use of immuno-modulatory therapies like eIL-12 and chimeric antigen receptor (CAR) T-cells, it is important to understand their kidney side effects. eIL-12 and CART-cells increase other pro-inflammatory cytokines such as interleukin-6 (IL-6). Evidence supports IL-6 causing a non-osmotic, non-volume-mediated increase in anti-diuretic hormone leading to hyponatremia. Tocilizumab (IL-6 receptor blocker) has been used to treat IL-6 side effects and in our case, hyponatremia. Our case highlights the unique immune mediated pathophysiology of hyponatremia and role of tocilizumab to treat the specific cause.

SA-PO216

New Therapies and New Challenges: Radioligand Therapy-Related Thrombotic Microangiopathy in the Kidneys

Michelle N. Keyser,[1] Joshua Pantanowitz,[2] Pooja D. Amarapurkar.[1] *[1]UPMC, Pittsburgh, PA; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA.*

Introduction: Radioligand therapy (RLT) has been increasingly used to treat metastatic castration-resistant prostate cancer. Intravenous (IV) 177Lu-PSMA and 225Ac-PSMA are two effective and well tolerated agents. Data on kidney-related side effects remain limited from initial clinical trials using these treatments. We present a unique biopsy-proven case of renal thrombotic microangiopathy (TMA) in a patient who received IV 177Lu-PSMA and 225Ac-PSMA resulting in rapid decline in kidney function, dialysis initiation and unresponsiveness to eculizumab.

Case Description: A 75-year-old male with stage 3b prostate adenocarcinoma was treated with radical prostatectomy, pelvic radiation, leuprorelin, bicalutamide, abiraterone. Therapy was changed to enzalutamide and darolutamide for new bone lesions. He traveled to Austria to receive IV RLT with 225Ac-PSMA and 177Lu-PSMA monthly for 8 months. 1 month after RLT his serum creatinine rose from 0.9–1.1 mg/dL to 1.3 mg/dL, and to 2.2 mg/dL at 6 months. Lower extremity edema and hypertension were noted at that time. 360 mg 24-hour urine protein, 516 mg/g UACr, normocytic anemia, elevated LDH, schistocytes on peripheral smear, elevated CH50, normal C3, C4, and SC5b-9 level were noted. A kidney biopsy showed subacute TMA, moderate (25%) interstitial fibrosis and tubular atrophy and 20-25% global glomerulosclerosis with double contour and subendothelial edema in the glomerular capillary walls. Losartan was started for hypertension and proteinuria. Eculizumab was added for possible complement-mediated process, but the kidney function declined rapidly. He started hemodialysis 10 months after his last dose of RLT. Eculizumab was trialed for 6 months without renal recovery.

Discussion: RLT such as 177Lu-PSMA and 225Ac-PSMA deliver targeted radiation to cancer cells. Despite being target specific, they may accumulate in the kidneys over time causing endothelial damage, hypertension, TMA and chronic kidney disease. Data on nephrotoxicity from the initial trials is sparse. Additionally, RLT-related kidney damage with use of dual agents 177Lu-PSMA and 225Ac-PSMA remains to be explored. Our case is a distinctive illustration of kidney side effects of RLT. With the expanding use of RLT, it is vital to educate nephrologists to recognize the kidney effects and develop strategies to prevent rapid decline in kidney function.

SA-PO217

Challenges in the Management of Giant Bilateral Renal Angiomyolipomas in a Young Woman with Tuberous Sclerosis Complex: A Case Report

Mark Gavin C. Dinsay. *Philippine General Hospital, Manila, Philippines.*

Introduction: Tuberous sclerosis complex-associated renal angiomyolipoma (AML) is a fast-growing tumor that develops earlier in life, with a propensity to achieve larger sizes and higher risks for life-threatening hemorrhage. We report a rare case of bilateral giant AMLs wherein a young patient presented with extensive involvement in both kidneys that limited treatment options recommended by current guidelines.

Case Description: A 23-year-old woman with tuberous sclerosis complex (TSC) presented with flank pain, abdominal fullness, hematuria, and hemodynamic instability. CT scan of the abdomen showed that both kidneys had been converted into large aggregates of heterogeneously enhancing and attenuating masses. The right kidney measured 17.4 x 9.7 x 10.3 cm (CC x W x AP) while the left measured 18.4 x 11.4 x 16.2 cm (CC x W x AP). She was transfused 2 units of packed red blood cells and closely monitored. Radiologic intervention with angioembolization was deemed unfeasible due to the diffuse involvement of both kidneys. Bleeding resolved spontaneously albeit with a high risk for recurrence. Prophylactic bilateral nephrectomy was considered but would render the patient in need of renal replacement therapies. After a multidisciplinary conference and discussion with the patient and her family, conservative management and therapy with mTOR inhibitor everolimus were pursued. The patient was apprised of the

need for nephrectomy should refractory life-threatening bleeding occur. On outpatient follow-up after a year, renal function was preserved with an eGFR of 87 mL/min. Although everolimus was discontinued after 1 month due to financial constraints, the patient reported subjective improvement in symptoms and no recurrence of anemia and bleeding.

Discussion: In our patient's case, extensive involvement of both kidneys and massive sizes of the angiomyolipoma presented a dilemma that required balancing the patient's preferences, risk for bleeding, and preservation of renal function. A conservative management approach involves close monitoring, intensive care, and blood transfusions. mTOR inhibition is employed to retard tumor size and growth and reduce the risk for bleeding. The challenge with managing such cases requires a multidisciplinary approach and shared decision-making to arrive at the best patient-centered outcomes.

SA-PO218

An Unusual Case of Steroid Refractory Allergic Interstitial Nephritis Related to Prior Ifosfamide Exposure

Sundus Sardar,[1] Ahmad Matarneh,[1] Victoria Gutgarts,[2] Naman Trivedi,[1] Nasrollah Ghahramani.[1] *[1]Penn State College of Medicine, Hershey, PA; [2]Memorial Sloan Kettering Cancer Center, New York, NY.*

Introduction: Tazemetostat, an EZH2 inhibitor, recently approved for treating solid and hematologic malignancies. EZH2 overexpression and mutations drive tumor growth. While Tazemetostat's side effects have been studied, further investigation is needed to establish their incidence. Reports suggest Tazemetostat can activate the innate immune response with T-cells against an antigen, which could be a medication, infection or an unknown factor. Our case report discusses allergic interstitial nephritis (AIN) presumed to be induced by Tazemetostat in the context of ifosfamide use.

Case Description: A 43-year-old male with metastatic epithelioid sarcoma was initially treated with ifosfamide and doxorubicin, developing Fanconi syndrome from ifosfamide toxicity. Tazemetostat was later initiated as secondary treatment. After 8 months, his renal function deteriorated, with creatinine increasing from 0.8mg/dL to 2.04mg/dL and proteinuria reaching 3.25 g/24h. Tests showed a normal blood count, negative (ANA, ANCA), normal complement levels, but positive PR3-ANCA antibodies. A kidney biopsy confirmed tubulointerstitial nephritis. Despite 6 weeks of oral steroids (60mg daily), renal function did not improve. Mycophenolate (MMF) was introduced for steroid-refractory AIN, but he developed anemia requiring blood transfusion, leading to a dose reduction. Renal function continued to decline, reaching 3.4mg/dL. A second kidney biopsy revealed severe tubulointerstitial nephritis with focal necrosis, suggesting ifosfamide-induced nephropathy. Imaging showed new inguinal lymph node enlargement, under evaluation. MMF is being tapered until biopsy result.

Discussion: Tazemetostat is a novel anticancer agent. Known side effects include nausea, headache, abdominal pain, and increased risks of T-cell lymphoma and myelodysplastic syndrome. No established link between Tazemetostat and AIN exists, necessitating further research. Studies suggest Tazemetostat may trigger an innate T-cell response to an antigen, potentially causing allergic interstitial nephritis. In our patient, we speculate ifosfamide acted as an antigen, triggering an immune response. AIN management involves discontinuing the offending agent and using immunosuppressants like steroids and MMF. Further research is needed to refine Tazemetostat's safety profile and optimize management strategies.

SA-PO219

Leukocyte Chemotactic Factor 2 (ALECT2)-Associated Kidney Amyloidosis in New Mexico: A Report of Two Cases and a Call for Attention to Epidemiologic Surveillance

George Vasquez-Rios,[1] Paul B. Avila,[2] Pablo Garcia.[2] *[1]Glomerular Disease Center, Renal Medicine Associates, Albuquerque, NM; [2]University of New Mexico Health Sciences Center, Albuquerque, NM.*

Introduction: LECT2-associated renal amyloidosis (ALECT2) was first described in the United States, predominantly affecting patients of Hispanic descent. The mechanisms, epidemiological drivers, and long-term prognosis of this disease remain poorly understood. Here, we present two cases from our GN clinic involving patients of Mexican descent residing in New Mexico for over 50 years.

Case Description: Case 1: An 80-year-old male with moderate CKD (sCr: 2 mg/dL), mild albuminuria (450 mg/g), hematuria. He presented with mild hypertension (142/60) and trace edema. **Case 2:** A 69-year-old male with moderate-severe CKD (serum Cr: 2.4 mg/dL), mild albuminuria (700 mg/g), hematuria. Both patients were referred by their PCPs due to slowly progressive kidney function decline over a span of 10-15 years. One of the patients had background of DM2. Comprehensive GN work-up showed mildly elevated ANA and ESR levels, no M-protein, negative SPEP/UPEP, and normal serum free light chain ratio. Bone marrow biopsy and imaging found no cell clonality or evidence of malignancy or clear source of hematuria. Given the concern for potential inflammatory versus MGRS presentations kidney biopsies were obtained. In both cases, kidney biopsies revealed amyloid deposits in glomeruli, blood vessel walls, and tubular interstitium with characteristic green birefringence. Immunohistochemical staining for amyloid A was negative. However, staining with anti-LECT2 antibody by an antigen retrieval technique at pH2 was positive; confirming the diagnosis of ALEC2 renal amyloidosis. Given the absence of cancer, asymptomatic presentation, and slowly progressive nature, we opted for conservative management (ACEi). On follow-up, both patients showed relatively stable CKD.

Discussion: The pathogenesis of ALECT2 remains to be elucidated. It is unclear if genetic or epidemiological factors contribute to its onset predominantly in Hispanics, and whether it can recur in post-kidney transplant patients, considering its major production in the liver. The preferred management includes RAS blockers. These cases highlight the need for increased epidemiologic surveillance and research into the mechanisms and prognosis of ALECT2. Given its prevalence in Hispanic populations, further studies are warranted to understand potential genetic or environmental factors influencing this condition.

SA-PO220

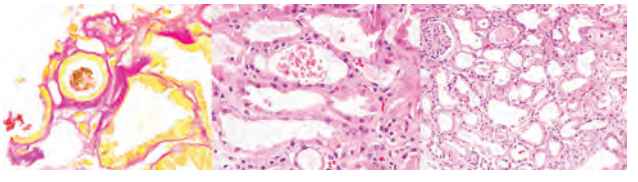
Bile-Cast Nephropathy in a Patient with Perihilar Cholangiocarcinoma

Joseph D. Nguyen,[1] Jill Nehrbas,[1] Monarch Shah,[1] Joel D. Murphy,[2] Uta Erdbruegger,[1] Tushar Chopra.[1] *[1]University of Virginia, Charlottesville, VA; [2]Arkana Laboratories, Little Rock, AR.*

Introduction: Bile cast nephropathy (BCN) is a rare cause of acute renal dysfunction in the setting of liver disease. Kidney injury in BCN is thought to be caused by multiple factors, including bile acid nephrotoxicity, tubule obstruction, and renal hypoperfusion. BCN is diagnosed by kidney biopsy in the appropriate clinical setting. Due to the rarity of the condition, there are few established treatment guidelines. We report a case of BCN diagnosed by kidney biopsy in a 70-year-old male.

Case Description: A 70-year-old male with intrahepatic cholangiocarcinoma with outflow hepatic vein obstruction treated with a single course of dose-reduced cisplatin/gemcitabine and durvalumab was admitted with biliary obstruction and anuria. Physical exam was notable for ascites and labs were notable for acute kidney injury (AKI) with creatinine 5 mg/dl (baseline 0.9 mg/dl), anion gap metabolic acidosis, total bilirubin 27.8 mg/dl, direct bilirubin 17.7 mg/dl, and alkaline phosphatase 1,440 mg/dl. Intermittent hemodialysis was initiated for volume overload. The patient underwent an endoscopic retrograde cholangiopancreatography with biliary sphincterotomy and bilateral biliary stents with transient improvement in serum bilirubin to 22 mg/dl before rising again. Kidney biopsy revealed severe acute tubular injury with bile casts (Fig 1). Due to the unresectable cholangiocarcinoma involving vasculature, cholestatic liver injury worsened. The patient's family elected comfort care due to his guarded prognosis.

Discussion: This case contains three major teaching points: 1) Cholemic nephrosis represents a spectrum of renal injury from proximal tubulopathy to intrarenal bile cast formation in patients with severe liver disease. Bile casts are thought to contribute to kidney injury by both obstruction and bilirubin toxicity. 2) Prevalence of BCN is likely underestimated as a definitive pathological diagnosis by kidney biopsy is often missing due to the increased bleeding risk in coagulopathic liver disease patients. 3) Renal replacement therapy may be necessary to manage severe AKI secondary to BCN. In refractory cases, extracorporeal liver support devices utilizing albumin dialysis may help to reverse AKI.



SA-PO221

Merkel Cell Carcinoma Preceding Renal Primary Amyloidosis: Coincidence or Causality?

Carolina Saldanha Neves Horta Lima, Beatriz Rizkallah Alves, Kelly A. Burdge. *Mass General Brigham Salem Hospital, Salem, MA.*

Introduction: We present a rare association of Merkle Cell carcinoma and nephrotic syndrome.

Case Description: 63-year-old female presented with new proteinuria and lower extremity swelling. She had recently taken 7 days of ibuprofen and amox/clav. She was initially started on furosemide, without improvement. Blood work revealed albumin of 2.3 g/dL and a 24h urine protein 4.35g. Her total cholesterol 449 mg/dL, LDL 319 mg/dL, triglycerides 274 mg/dL. One month prior, she was diagnosed with non-metastatic Merkel cell carcinoma of her right thigh. Further workup revealed normal complements, negative ANCA, negatuve ANA. Kappa and lambda free light chains ratio of 6. SPEP showed hypoalbuminemia. A kidney biopsy dmeonstrated lambda light chain amyloidosis. Bone marrow biopsy identified lambda light chain restricted plasma cell population. Fluorescence in situ hybridization was negative for t(11;14). She was referred to oncology and started on chemotherapy.

Discussion: AL amyloidosis is characterized by the existence of a plasma cell clone in the bone marrow that secretes immunoglobulin light chains. Their deposition leads to variety of presentations, including nephrotic syndrome, restrictive cardiomyopathy, peripheral and autonomic neuropathy. Screening of end-organ involvement is crucial for early treatment due to severity of prognosis. AL amyloidosis is not infrequently related to hematologic malignancies, such as monoclonal gammopathy of undetermined significant and multiple myeloma. Merkel cell carcinoma is a rare and aggressive cutaneous malignancy that affects older adults with light skin, especially in sun-exposed areas. Hematologic malignancies have been reported as a risk factor for Merkel cell carcinoma, most commonly chronic lymphocytic leukemia, more rarely multiple myeloma. Interestingly, patients with a preceding hematologic malignancy have a higher chance of being affected in an area not exposed to sun, such as our patient. This highlights 1) the non-coincidental occurrence of AL amyloidosis and an atypical presentation of Merkle cell carcinoma and 2) the need to further understand common physiopathological pathways. The question whether patients with an atypical Merkle cell carcinoma benefit from screening for hematologic malignancies remains.

SA-PO222

Partial Fanconi Syndrome following Ifosfamide

Piera A. Sosa,[1] Aaron Winer,[1] Sebastian Hinojosa,[1] Adriana Hung.[1,2]
[1]Vanderbilt University Medical Center, Nashville, TN; [2]VA Tennessee Valley Healthcare System, Nashville, TN.

Introduction: Partial or complete Fanconi syndrome is a rare yet known complication of ifosfamide administration. Fanconi syndrome characteristically results in metabolic derangements including metabolic acidosis, hypokalemia, hypophosphatemia, and proteinuria. Although Ifosfamide can lead to Fanconi syndrome, not all patients develop this complication. Therefore, pharmacogenomics, the study of how a person's genetic makeup affects their response to medications and drugs, should be considered when evaluating this disease process

Case Description: A male in his 70's with recently diagnosed dedifferentiated retroperitoneal liposarcoma presented to the ED 6 days after completing a first cycle of ifosfamide-based chemotherapy. His chief complaint was nausea, vomiting, and weakness. Labs on presentation were notable for hypokalemia, hypophosphatemia, and metabolic acidosis. Given his immunocompromised status, a thorough infectious work-up was obtained and he was found to have bacteremia secondary to chemotherapy port infection. Over the next several days, he continued to have profound electrolyte derangements requiring substantial repletion that were initially attributed to refeeding syndrome. However, further investigation into his significant electrolyte wasting revealed a urinalysis with newly developed proteinuria and phosphaturia, without glycosuria, and a transtubular potassium gradient (TTKG) of 8. Based on his clinical presentation and lab findings, along with his recent chemotherapy initiation with ifosfamide, the patient was ultimately diagnosed with partial Fanconi syndrome. Electrolyte repletion requirement slowly improved throughout admission, demonstrating evidence of renal tubular recovery. He was sent home with daily oral electrolyte supplementation with close outpatient monitoring.

Discussion: Close electrolyte monitoring in patients undergoing chemotherapy treatment with ifosfamide is imperative to avoid missing Fanconi syndrome diagnosis and its detrimental complications. Notably, not all patients undergoing treatment with ifosfamide develop nephrotoxicity leading to Fanconi syndrome. Understanding the role of pharmacogenomics, such as variations in genes encoding CYP3A4 and CYP2B6, is an important area of further investigation to minimize adverse effects from ifosfamide.

SA-PO223

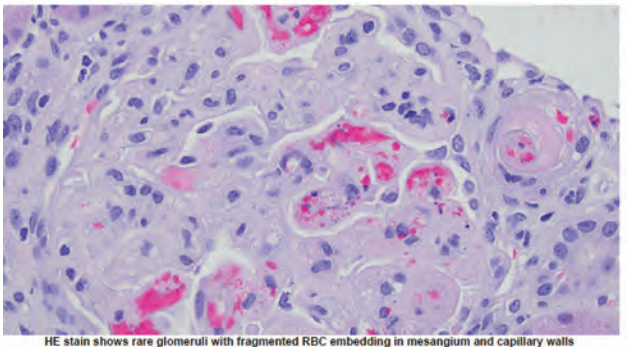
Atypical Presentation of Drug-Induced Thrombotic Microangiopathy: Time Does Not Matter

Nahomie I. Veguilla Rivera, Archi K. Dhamelia, Jan Paul Rosaly Martinez, Naveen Punchayil Narayanankutty. *University of South Florida, Tampa, FL.*

Introduction: Thrombotic Microangiopathy (TMA) is a disorder that causes disseminated occlusive microvascular thrombosis, thrombocytopenia, and end organ damage, commonly in the kidneys and brain. In cancer patients, especially those in multi-drug chemotherapy regimens, TMA is a diagnostic challenge due to overlap with other thrombotic disorders such as TTP, aHUS, and DIC. TMA can occur as a manifestation of the cancer itself and has been reported in mucin-producing adenocarcinomas. Chemotherapy-associated TMA can occur due to immune-mediated reaction or dose-dependent toxicity. TMA secondary to VEGF inhibitors has been described; however, literature reporting TMA due to Tyrosine Kinase Inhibitors (TKI) is limited. We present a case of TMA secondary to lenvatinib and bevacizumab.

Case Description: We report a case of a 31-year-old man with history of metastatic hepatocellular adenocarcinoma who was referred to the hospital with nephrotic-range proteinuria. Prior therapy regimen included bevacizumab and more recently Lenvatinib, last dose 3 weeks prior presentation of AKI. Creatinine increased to 4 mg/dL from a baseline of 1.5 mg/dL. Coagulation panel, ADAMST13 were normal. ALP and LDH were elevated. Other bloodwork revealed new thrombocytopenia and hypoalbunemia. TTP, aHUS and DIC were ruled out. Due to unclear cause, patient underwent renal biopsy that showed Chronic thrombotic microangiopathy with FSGS. After confirmation of results, patient remained on therapy for HCC and was offered hemodialysis.

Discussion: This case highlights the importance of evaluating the etiology of TMA, particularly in patients on chemotherapy independent of the time of administration of therapy. Distinguishing the cause of AKI in this patient is clinically important for appropiate treatment and avoidance of future drug toxicity. It also shows that renal biopsy can aid in the diagnosis. Restarting the offending medication a lower dose may help to avoid recurrent TMA.



HE stain shows rare glomeruli with fragmented RBC embedding in mesangium and capillary walls

SA-PO224

C-terminal Region of the TMEM174 Protein Regulates PTH-Induced NPT2A Endocytosis

Jose Miranda, Shinobu Miyazaki-anzai, Judith Blaine, Makoto Miyazaki. *University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO.*

Background: Sodium-dependent phosphate cotransporter 2a (NPT2A or SLC34A1) is a solute-carrier (SLC) transporter located in the brush border membrane of kidney proximal tubule that reabsorbs glomerular-filtered phosphate. We recently found that a proximal tubule-specific protein TMEM174 regulates phosphate reabsorption by inducing the degradation of NPT2A (PMID: 35459732). However, the molecular mechanism by which TMEM174 facilitates the degradation of NPT2A is unknown.

Methods: To obtain clues as to how TMEM174 induces the degradation of NPT2A, we examined which region of TMEM174 protein is essential to bind with NPT2A and induce the NPT2A endocytosis by the advanced microscope techniques such as Total Internal Reflection Fluorescence (TIRF) and Förster Resonance Energy Transfer (FRET) microscopy and the immunoprecipitation (IP) assay using DNA constructs containing full length TMEM174, TMEM174 lacking N-terminal 34 amino acids (TMEM174ΔN) and TMEM174 lacking C-terminal 130 amino acids (TMEM174ΔC).

Results: OK-P cells were transiently transfected with plasmids containing TMEM174 with moxCerulean3 (mC3) at its C-terminal and/or NPT2A with eYFP also at its C-terminal in the presence or absence of TMEM174 siRNA. TIRF microscopy analysis showed that treatment with TMEM174 siRNA blocked PTH induced-NPT2A endocytosis and increased the retention of NPT2A in the apical membrane of OK-P cells. In addition, FRET analysis showed that intact TMEM174 and TMEM174ΔN proteins are associated with NPT2A protein because upon PTH treatment NPT2A degradation is no decrease in the FRET ratio. Whereas TMEM174ΔC was significantly disassociated because under PTH treatment the FRET ratio decreased over-time signifying that NPT2A-eYFP was being degraded. IP assay confirmed that intact TMEM174 and TMEM174ΔN but not TMEM174ΔC were pull down with NPT2A.

Conclusions: The C-terminal region of TMEM174 protein is critical for regulating in the NPT2A endocytosis.

Funding: NIDDK Support

SA-PO225

Phosphate Transport through the Type II Sodium Phosphate Cotransporter Npt2a Regulates Metabolism Independent of Phosphate Level

Eleanor D. Lederer,[1,2] Kenneth B. Gagnon,[1] Adam E. Gaweda,[4] Hamid Baniasadi.[3] *[1]The University of Texas Southwestern Medical Center Department of Internal Medicine, Dallas, TX; [2]VA North Texas Health Care System, Dallas, TX; [3]The University of Texas Southwestern Medical Center, Dallas, TX; [4]University of Louisville School of Medicine, Louisville, KY.*

Background: Npt2a expression and function in proximal tubule (PT) are regulated by the Na-H Exchanger Regulatory Factor Isoform 1 (NHERF1). Absence of NHERF1 (NHERF1 KO) is associated with phosphaturia and a metabolic shift toward increased activity of the pentose phosphate pathway and altered glutathione levels. Whether the metabolic shift in NHERF1 KO cortex is due to phosphate (Pi) deficiency or decreased

functional Npt2a expression is unknown. We postulate that the metabolic shift is a result of decreased Npt2a-mediated Pi transport.

Methods: To address our hypothesis, we compared the kidney cortex metabolic profile from WT C57/Bl6 mice with kidney cortex from three models of hypophosphatemia: NHERF1 KO, Npt2a KO, and WT on low Pi diet (0.02%) for 2 weeks. Kidney cortices were subjected to targeted metabolomic assay followed by identification and pathway analysis of significantly different metabolites by Sparse Autoencoder Enabled Neural Network or Metaboanalyst 6.0 (principal component analysis) and pathway analysis.

Results: All hypophosphatemic conditions resulted in altered kidney cortex metabolomics when compared to wild type. WT compared to NHERF1 KO showed significant differences in metabolites related to arginine and proline metabolism, pentose phosphate pathway, and pyrimidine metabolism. WT compared to Npt2a KO showed significant differences in metabolites related to TCA cycle, glucose and pyruvate metabolism, the pentose phosphate pathway, and lysine degradation. WT compared to low Pi diet showed significant differences in their metabolomic profiles, primarily involving amino acid metabolism. Comparison of the metabolomic profiles of NHERF1 KO and Npt2a KO showed significant though not complete overlap (PC 1 42.9%, PC 2 18.7%). In contrast, comparison of NHERF1 KO and low Pi diet kidney cortex showed complete dissociation in metabolic profile.

Conclusions: We conclude that the metabolic shift associated wtih NHERF1 KO deficiency is largely due to loss of Npt2a-mediated Pi transport and not due to Pi deficiency. We also conclude that additional NHERF1-mediated transport processes may contribute to the metabolic shift seen in NHERF1 KO.

Funding: Veterans Affairs Support

SA-PO226

Tissue-Specific Deletion of Cyp24a1 Reveals Independent Systemic and Intestinal Vitamin D Regulation in Mice

Michaela A. Fuchs,[1] Alexander Grabner,[1,2] Melody Shi,[1] Susan L. Murray,[1] Emily Burke,[1] Nejla Latic,[3] Venkataramana Thiriveedi,[4] Shintaro Ide,[1] Koki Abe,[1] Hiroki Kitai,[1] Tomokazu Souma,[1] Myles Wolf.[1,5] *[1]Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, NC; [2]Department of Medicine, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [3]Veterinarmedizinische Universitat Wien, Wien, Austria; [4]Division of Gastroenterology, Department of Medicine, Duke University School of Medicine, Durham, NC; [5]Duke University Duke Clinical Research Institute, Durham, NC.*

Background: Dysregulation of vitamin D, a central regulator of mineral metabolism, is a severe complication of chronic kidney disease (CKD), leading to hypocalcemia, secondary hyperparathyroidism and increased risk of fractures. The most biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25D), is synthesized by the 1α-hydroxylase CYP27B1 in the kidney from its precursor, 25-dihydroxyvitamin D (25D). Catabolism of 1,25D is controlled by the expression of the 24-hydoxylase CYP24A1 in proximal tubules and other important Vitamin D target organs like the intestines or parathyroid glands. Human monogenic diseases and genome-wide association studies support a critical role for CYP24A1 in systemic regulation of mineral homeostasis, but little is known about its tissue-specific effects.

Methods: We used single cell RNA sequencing coupled with novel mouse models of tissue specific CYP24A1 deletion to address these questions. We analyzed the responses of mice with inducible global deletion, kidney-specific, and intestine-specific *Cyp24a1* deletion to standard calcium diet, high calcium diet and 1,25D injection.

Results: Global and kidney-specific *Cyp24a1* deletion caused similar phenotypes of systemic vitamin D intoxication: elevated circulating 1,25D and 25D levels, activation of vitamin D receptor target genes in the kidney and intestine, hypercalcemia, increased levels for fibroblast growth factor 23 and suppressed parathyroid hormone (PTH). In contrast, intestine-specific deletion of *Cyp24a1* led to no changes in systemic levels of 1,25D or 25D, yet vitamin D receptor target genes were activated in the intestine, and PTH was suppressed in response to high calcium diet without detectable changes to serum calcium levels.

Conclusions: These results implicate a central role for renal CYP24A1 in systemic vitamin D regulation, and highlight independent local effects of intestinal CYP24A1, inhibition of which can alter mineral homeostasis without precipitating hypercalcemia. These findings indicate that tissue specific modulation of CYP24A1 activity could present a new theraputical pathway for the treatment of secondary hyperparathyroidism in CKD with a reduced risk of hypercalcemia compared to current treatments with vitamin D and its analogs.

Funding: Other NIH Support - R01DK132060 , R01DK123097

SA-PO227

TBX2 Is a CKD-MBD Causal Gene by Regulating Calcium Homeostasis and Inflammation

Shen Li, Katalin Susztak. *University of Pennsylvania, Philadelphia, PA.*

Background: Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a syndrome characterized by biochemical mineral abnormalities, bone fragility, and vascular calcification, leading to increased morbidity and mortality. Genome-wide association studies (GWAS) have identified numerous loci associated with kidney diseases. However, the causal variants, genes, cell types, and disease mechanisms remain largely unknown.

Methods: We integrated GWAS, human kidney expression of quantitative trait analysis using Bayesian colocations, and summary-based Mendelian randomization studies to identify likely causal genes for CKD-MBD. We used single-cell RNA data to pinpoint causal cell types. Additionally, we generated TBX2 knockdown (KD) mice to study mechanism.

Results: We prioritized TBX2 (T-Box Transcription Factor 2) as a CKD-MBD risk gene. Human kidney single-cell epigenetic and immunostaining studies indicated kidney connecting tubular cells and vascular smooth muscle cells (VSMCs) as key disease-causing cell types. TBX2-KD mice exhibited increased urinary calcium excretion at baseline and showed heightened susceptibility to kidney injury in a chronic kidney disease model. These mice also demonstrated elevated tissue calcification, leading to activation of crystal-induced NLRP3 inflammasome pathways and increased inflammation.

Conclusions: In summary, our GWAS identified TBX2 as a risk gene for CKD-MBD. We showed that TBX2 regulates tissue calcification and crystal-induced inflammation, thereby influencing CKD-MBD risk and uncovering a novel mechanism for CKD-MBD development.

SA-PO228

Reduced miR122 Increases Fibroblast Growth Factor 23 (FGF-23) in Mice with CKD

Jane J. Thomas, Jadeah J. Spindler, Aline Martin, Valentin David. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Fibroblast growth factor 23 (FGF23) is associated with mortality in chronic kidney disease (CKD). Iron deficiency and inflammation stimulate the production and subsequent proteolytic cleavage of intact FGF23 (iFGF23) to yield C-terminal FGF23 peptides (Cter-FGF23) that play a protective role in iron metabolism. In CKD, FGF23 cleavage is impaired, but the mechanisms of impaired cleavage are unclear. O-glycosylation of iFGF23 cleavage site by GALNT3 prevents iFGF23 cleavage and we identified micro-RNA 122 (miR122) as an inhibitor of GALNT3. We hypothesized that reduction in osseous miR122 expression contributes to increased levels of GALNT3 and iFGF23 in CKD mice.

Methods: We crossed mice harboring a conditional deletion of miR122 in osteoblasts ($miR122^{Osx\text{-}cKO}$) with $Col4a3^{KO}$ mice with CKD to generate WT, $miR122^{Osx\text{-}cKO}$, $Col4a3^{KO}$, and compound (CPD) $Col4a3^{KO}$/$miR122^{Osx\text{-}cKO}$ mice. In all mice, we analyzed serum biochemical, hematological parameters and bone and liver gene expression at 18-weeks of age.

Results: Compared to WT mice, $miR122^{Osx\text{-}cKO}$ mice showed reduced bone miR122 levels, increased bone *Galnt3* expression, and reduced iron levels and transferrin saturation, but normal hemoglobin levels and red blood cells counts. As previously shown, $Col4a3^{KO}$ mice with advanced CKD displayed reduced iron levels and transferrin saturation and were overtly anemic compared to WT mice. They also showed a 2-fold reduction in bone miR122 levels, increased bone *Galnt3* expression (2.2-fold), and a dramatic increase in iFGF23 (7-fold). Further reduction in miR122 in CPD mice led to a 30% increase in bone *Galnt3* expression, a consequent 50% rise in iFGF23 circulating levels, and 20% increase in i/cFGF23 ratio vs. $Col4a3^{KO}$ mice, suggesting a further reduction of FGF23 proteolytic cleavage. As a consequence of reduced iron conserving Cter-FGF23 peptides, CPD mice also showed further reductions in hemoglobin and red blood cell.

Conclusions: Our study demonstrates that reduced expression of osseous miR122 in CKD leads to impaired FGF23 processing, resulting in reduced Cter-FGF23 but increased iFGF23. Therefore, administration of miR122 mimics to mice with CKD could lower iFGF23 and improve CKD-associated adverse outcomes.

Funding: NIDDK Support

SA-PO229

Skeletal Muscle Is a Novel Source of Fibroblast Growth Factor 23 (FGF-23) That Regulates Phosphate Homeostasis

Kylie Heitman, Abul Fajol, Madison Thomas, Qing Li, Svetlana Komarova, Christian Faul. *The University of Alabama at Birmingham Department of Cell Developmental and Integrative Biology, Birmingham, AL.*

Background: Fibroblast growth factor 23 (FGF23) is hormone that is secreted from bone in response to elevations in serum phosphate (Pi) levels (hyperphosphatemia) and that targets the kidney to increase Pi excretion. In chronic kidney disease (CKD), the kidney loses its ability to properly respond to FGF23 and to excrete Pi, leading

to elevations in systemic levels of Pi and FGF23 which might contribute to various CKD-associated pathologies. Previous studies suggest that bone might not be the sole source for systemic FGF23 elevations. Here we determine whether mouse models of hyperphosphatemia express FGF23 in skeletal muscle (SM) and whether elevated Pi can induce FGF23 expression in cultured myotubes

Methods: C2C12 and primary mouse and human myotubes were treated with increasing concentrations of Pi for 24 hours, followed by the analysis of FGF23 expression by qPCR and immunocytochemistry as well as ELISA from cell supernatants. We studied four mouse models of hyperphosphatemia: two CKD models, i.e. mice with deletion of collagen 4a3 and mice fed an adenine-rich diet for 14 weeks; and two non-CKD models: klotho deficient mice and mice fed a high-Pi diet for 6 months. Furthermore, we generated mice with SM-specific deletion of FGF23 (SM-FGF23-/-) and administered an adenine-rich or a high-Pi diet. We analyzed FGF23 production in SM tissue by qPCR, immunohistochemistry and ELISA as well as serum levels of FGF23 and Pi. We also injected SM-FGF23-/- with Pi and determined 24 hour urine excretion.

Results: Pi treatments increase the expression and the secretion of FGF23 in MT in a dose-dependent manner. We could detect FGF23 expression in SM of all four mouse models on mRNA and protein level. SM-FGF23-/- on an adenine-rich or a high-Pi diet had significantly reduced FGF23 levels in SM and serum when compared to control mice on the same diet. SM-FGF23-/- mice on a high Pi diet also showed further elevations in serum Pi. Acute Pi load of SM-FGF23-/- mice resulted in reduced urine Pi levels.

Conclusions: Hyperphosphatemia induces FGF23 expression in SM in the absence and presence of CKD. SM-derived FGF23 contributes to the pool of circulating FGF23 and seems to have physiologic activity by increasing renal Pi excretion.

Funding: NIDDK Support

SA-PO230

Fibroblast Growth Factor 23 Directly Contributes to CKD Progression in Col4a3 Knockout Mice

Dominik Kentrup, Hao-Hsuan Tsai, Xueyan Wang, Jane J. Thomas, Jadeah J. Spindler, Valentin David, Aline Martin. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Fibroblast growth factor 23 (FGF23) is a phosphate (Pi)-regulating hormone produced mainly by osteocytes. Increased levels of FGF23 are associated with increased mortality in CKD. Whether FGF23 has a direct role on CKD progression is unclear. In this study we tested the hypothesis that increased FGF23 levels accelerate CKD progression independently of phosphate.

Methods: First, we fed adult wild-type (WT) and *Col4a3*^{KO} male mice, an established model of progressive CKD, diets containing either 0.7% Pi (normal Pi, NP) or 2% Pi (high Pi, HP) continuously from 12 weeks of age to show the combined effects of FGF23 and Pi on CKD progression. Next, to separate the effects of FGF23 from hyperphosphatemia we deleted *Fgf23* in the bone (Osx-cre) of WT (*Fgf23*^{cKO}) and *Col4a3*^{KO} (*Col4a3*^{KO}/*Fgf23*^{cKO}) mice fed a NP diet. In all mice, we assessed lifespan, kidney function and markers of mineral metabolism.

Results: Compared to NP-WT mice, dietary Pi supplementation increased circulating FGF23 and PTH levels, resulting in increased urinary Pi excretion and reduced serum Pi levels in HP-WT. NP-*Col4a3*^{KO} mice with advanced CKD showed increased BUN, serum creatinine, FGF23, and PTH levels, late onset hyperphosphatemia, and a reduced lifespan compared to NP-WT mice. Dietary Pi supplementation in *Col4a3*^{KO} mice further increased serum creatinine, FGF23 and PTH levels, and led to earlier onset of hyperphosphatemia. As a result, HP-*Col4a3*^{KO} died on average 2.5 weeks earlier than NP-*Col4a3*^{KO} mice. In contrast, *Fgf23* deletion in WT mice slightly reduced FGF23 and increased serum Pi levels. In *Col4a3*^{KO} mice with CKD, *Fgf23* deletion corrected FGF23 levels by 60%, did not impact PTH levels, and further increased hyperphosphatemia. Despite further increases in Pi levels, BUN and serum creatinine levels were unchanged, and *Col4a3*^{KO}/*Fgf23*^{cKO} mice lived on average 2 weeks longer than *Col4a3*^{KO} mice.

Conclusions: In aggregate, FGF23 excess and hyperphosphatemia accelerated CKD progression whereas FGF23 reduction improved survival despite persistent hyperphosphatemia and hyperparathyroidism. This suggests that increased FGF23 in CKD directly contributes to CKD progression.

Funding: NIDDK Support

SA-PO231

Fibroblast Growth Factor 23 Bioactivity Induces General and Cell Type-Specific Kidney Genomic Reprogramming as Detected by Single-Cell Multiomics

Emmanuel Solis,[1] Rafiou Agoro,[1] Kayleigh N. Jennings,[1] Yamil Marambio,[1] Sheng Liu,[1] Mark B. Meyer,[2] Jun Wan,[1] Kenneth E. White.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]University of Wisconsin-Madison, Madison, WI.*

Background: FGF23 functions with its co-receptor Klotho (KL) to regulate phosphate and 1,25D synthesis in the kidney, and this control is dysregulated in diseases such as CKD. The identification of pathways regulated by FGF23 are limited by bulk methodologies, thus significant knowledge gaps remain. Herein, we undertook a novel approach to test FGF23 bioactivity at single-cell resolution, hypothesizing that FGF23 bioactivity would enact cell type-specific transcriptional and genomic changes that could provide insight into the processes driving regulation of phosphate and 1,25D.

Methods: Male and female C57BL/6 mice were injected with recombinant FGF23 over time (0, 1, 4, and 12h) and pooled male/female Multiome (scRNAseq/ scATACseq from the same cell) kidney datasets were generated. Female *Xist* gene and male Y chromosome markers were used to perform 'sex hashing' of cell populations. Data was validated by qPCR.

Results: Dimensionality reduction via UMAP identified 38 distinct clusters in the kidney including unique epithelial, endothelial, and immune cell populations based upon known gene markers. Sex-specific genes, female *Xist* and male *Kdm5d* and *Eif2s3y* showed segregation between female and male mice. *KL* was detected in PT, LOH, CNT, and DCT. In response to FGF23, *Cyp24a1* mRNA and promoter chromatin accessibility increased in PT-S1 whereas *Cyp27b1* had the converse regulation, showing that FGF23 induces rapid chromatin remodeling. Notably, *Hbegf* and *Egr1* mRNAs and accessibility increased across all KL-expressing cell types. Indeed, negative MAPK regulator *Dusp6* showed increased mRNA expression at 4 and 12h in both PT and DCT. Furthermore, within PT-S1, novel FGF23-regulated genes *Slc5a12*, *Fut9*, and *Pah*, all decreased at 4h. Finally, DCT showed decreased accessibility and mRNA of *Pde10a* and increased mRNA expression of *Dcdc2A* at 12h, supporting differential activity of FGF23 depending upon nephron site.

Conclusions: In summary, temporal FGF23 delivery paired with Multiome analyses demonstrated that FGF23 directs both rapid and more chronic renal cell events. Our studies pinpoint transcriptional and chromatin reprogramming that could provide novel pathways for treatment interventions.

Funding: NIDDK Support, Other NIH Support - R01-HL145528

SA-PO232

Renal Regulation of Fibroblast Growth Factor 23 Expression in Response to Inflammation Is Mediated by a Unique Genomic Mechanism

Seong Min Lee,[1] Mark B. Meyer,[1] J. W. Pike.[2] *[1]University of Wisconsin-Madison Department of Nutritional Sciences, Madison, WI; [2]University of Wisconsin-Madison Department of Biochemistry, Madison, WI.*

Background: Fibroblast growth factor 23 (FGF23) is a peptide hormone produced in bone to control phosphate homeostasis and vitamin D metabolism in the kidney. FGF23 is inappropriately upregulated in many tissues in response to inflammation and disease, potentially causing phosphate wasting and bone disorders. To model inflammation, we have shown that lipopolysaccharides (LPS) increased serum intact FGF23 (iFGF23) production *in vivo* via genomic mechanisms mediated by two distinct enhancers at -16 kb upstream and a large 4 kb proximal enhancer (PE) near the gene TSS in multiple tissues. However, the kidney LPS response is only in PE.

Methods: In this study, we generated 9 mouse strains to dissect the PE enhancer to examine the tissue specific regulation of LPS-induced *Fgf23*. Deletions were introduced by CRISPR/Cas9 editing in C57BL/6J mice and the levels of tissue *Fgf23* mRNA and serum iFGF23 in the mutants were compared with controls after LPS treatment for 6 h. ChIP-seq was performed in kidneys from wildtype mice for inflammatory factors after LPS treatment for 1 h.

Results: The results showed that while the induction in bone marrow, thymus, lung, and intestine was mediated by one region (PE1), a second, independent region (PE2) was responsible for renal *Fgf23* induction. *Fgf23* induction by LPS in bone, liver, and spleen was mediated by both regions (PE1 and PE2). Both PE1 and PE2 were further subdivided to explore mechanisms for *Fgf23* induction in the kidney where inflammation occurs under pathological conditions, such as chronic kidney disease. With these deletions, LPS-treated mice were resistant to *Fgf23* mRNA increases in the kidney, whereas the skeletal response remained. We confirmed complete loss of LPS-mediated *Fgf23* increases in both kidney and bone with a double knockout of the -16 kb region and PE together (DKO). Serum iFGF23 levels were unchanged in the DKO with LPS treatment. Following LPS treatment, ChIP-seq analysis showed increased binding of STAT3, p65, and p50 at these same regions in the kidney.

Conclusions: In conclusion, we have discovered that the regulation of FGF23 production in response to inflammation is orchestrated by a renal-specific enhancer. This leads to a unique mechanism by which tissues produce *Fgf23* and increase iFGF23 that modulates vitamin D metabolism and phosphate handling in disease.

Funding: NIDDK Support

SA-PO233

Differential Effects of Iron Overload and Iron Repletion on Bone and Mineral Metabolism in Growing Mice

Eduardo J. Duque, Jadeah J. Spindler, Xueyan Wang, Aline Martin, Valentin David. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Altered iron status is associated with bone and mineral metabolism disorders, including bone loss, increased risk of fracture and altered production and cleavage of the bone-derived phosphaturic hormone fibroblast growth factor 23 (FGF23). In mice and humans, iron deficiency is associated with increased risk of osteoporosis and stimulates FGF23 production and cleavage, leading to excess circulating carboxy-terminal (Cter)-FGF23 fragments, high total FGF23 (cFGF23) but only slightly elevated intact (i) FGF23. However, the effects of iron repletion on bone and mineral metabolism remain to be determined.

Methods: We fed 3-week-old male mice a control (Ctr), an iron deficient (ID) or a high iron diet (HI) for 3 weeks until 6 weeks of age. In addition, we fed 3 week-old male mice an ID diet for one week followed by HI for 2 weeks to study the effects of iron repletion (IR) on the skeleton. In all mice, we analyzed biochemical parameters of mineral metabolism, hematological parameters, and 3D bone microarchitecture.

Results: Compared to Ctr mice, ID mice developed anemia, marked by decreased serum iron and hemoglobin (Hb) content, and showed elevated serum iFGF23 (1.6-fold) and cFGF23 (3-fold) leading to a 7-fold decrease in intact to total (i/c)FGF23 ratio ($p<0.05$). As expected, IR increased serum iron and IR mice were no longer anemic, as shown by corrected Hb levels. IR also decreased iFGF23 (30%) with no impact on cFGF23 compared to Ctr. Interestingly, iron overload also led to anemia in HI mice, despite higher serum iron (2.5-fold) and TSAT (2-fold) levels, and to a 2-fold increase in cFGF23, but reduced iFGF23 and i/cFGF23 by 30 and 70%, respectively ($p<0.05$). ID and IR showed a modest impact on the skeleton. In sharp contrast, and in absence of changes in PTH and phosphate levels, iron overload led to a severe bone loss with a dramatic reduction in BV/TV (-38%), trabecular number (-32%), cortical thickness (-31%) and higher cortical porosity (+36%).

Conclusions: In aggregate, our findings show that dietary iron intake in iron depleted mice corrects anomalies associated with iron deficiency. However, excessive iron consumption leads to extensive skeletal alterations, demonstrating that dietary iron intake affects bone development and FGF23 regulation differently, depending on iron status.

Funding: NIDDK Support

SA-PO234

Effects of Intermittent Heparin Administration on Cardiac Tissue in Uremic Rats

Katia R. Neves, Luciene dos Reis, Luzia N. Furukawa, Vanda Jorgetti, Rosa M. Moyses. *Laboratório de Fisiopatologia Renal, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, UNiversidade de São Paulo, São Paulo, Brazil.*

Background: CKD-MBD plays a key role in CKD-associated myocardial hypertrophy (MH). Hyperphosphatemia, hyperparathyroidism and elevated fibroblast growth factor 23 (FGF23) are associated with MH in preclinical and clinical studies. Recently, it was shown that heparin mediates the binding of FGF23 to its receptor FGFR4, promoting MH in a adenine model of CKD in mice. However, this has never been tested in other experimental models or species. In this study, we tested whether intermittent unfractioned heparin (UFHep) or low molecular heparin (LMWHep) administration induces MH in rats submitted to 5/6 nephrectomy (Nx).

Methods: Male Wistar rats (n=50) were submitted to 5/6 Nx, or were sham operated. After a recovery period of one week, we divided the groups as follows, according to the administration: Sham (saline 0.9%), Nx (saline 0.9%), Nx+UFHep (125UI/Kg of UFHep) and Nx+LMWHep (1mg/Kg of LMWHep; enoxaparin). All groups received a standard rodent chow. Infusions were given subcutaneously, 3 times/ week. Tail cuff pressure and weight were measured weekly. After 2 months, serum and 24 hour-urine were collected, and myocardial histology was analyzed

Results: Initial and final body weight did not differ among the groups. Initial tail cuff pressure values were similar among all groups. However, all Nx rats developed hypertension, with no differences among them. Uremia and albuminuria were found in Nx animals (Table). Although no differences were found in serum calcium or phosphate among the groups, Nx rats had higher PTH. Also, Nx and Nx+UFHep rats had slightly higher FGF 23 levels than Sham animals. MH and cardiac fibrosis were found in all Nx groups, with no differences among them. Higher FGFR1 expression was seen in Nx+UFHep and Nx+LMWHep. However, no differences were seen in FGFR4 or TGFBeta expression.

Conclusions: Our data suggests that heparin is not able to worse MH in the absence of severe hyperparathyroidism or highly elevated FGF23. Whether this finding could be translated to clinical practice deserves future investigation.

Funding: Government Support - Non-U.S.

	CrCl (ml/min/100g)	Albuminuria (mg/24h)	Ca (mg/dl)	P (mg/dl)	PTH (pg/ml)	FGF23 (pg/ml)	HW/BW (g/100g)	Myocite Diamotar (μ)
Sham n=10	0.59±0.14*	0.5 (0.4-0.6) *	8.0±0.8	6.4±0.9	229 (177-361)*	307 (292-367) *	0.23 (0.21-0.24) *	10.6 (10.2-11.4)*
Nx n=8	0.29±0.14	87.5 (33.6-147.2)	8.7±1.1	5.7±1.0	748 (498-921)	493 (437-586)	0.29 (0.26-0.35)	12.8 (12.5-14)
Nx+UFHep n=12	0.26±0.10	52.2 (2.0-116.7)	8.1±1.2	5.9±1.5	513 (353-621)	396 (342-501)	0.29 (0.24-0.32)	13.7 (13.0-14.3)
Nx+LMWHep n=11	0.28±0.10	70.2 (29.8-136.9)	8.1±1.3	6.2±1.0	562 (500-1159)	343 (328-637)	0.28 (0.25-0.33)	15.1 (13.8-16.3)

Values are presented as mean ± SEM or median (25th-75th percentiles). CrCl: creatinine clearance/100g BW; Ca: total calcium, P: phosphate, HW/BW: heart weight/100 g body weight *=p<0.05 Sham vs. all. # =p<0.05 Sham vs Nx and Nx+NFHep

SA-PO235

Klotho KL1 Domain Directly Prevents Cardiac Fibrosis in a Rat CKD-MBD Model

Arvin Halim, Gayatri Narayanan, Shruthi Srinivasan, Kalisha O'Neill, Neal X. Chen, Sharon M. Moe, Kenneth Lim. *Indiana University School of Medicine, Indianapolis, IN.*

Background: α-Klotho has a bifunctional role as a co-receptor for FGF23 and exerts FGF23-independent cardioprotective effects. However, the fragment of Klotho responsible for direct cardioprotective effects is unknown. Our group's computational modeling suggests that the Klotho KL1 domain (which has a lipid raft binding site and lacks FGF23 binding elements) is the fragment responsible for these effects. This study aimed to assess whether KL1 can exert direct anti-fibrotic effects at the heart in CKD rats.

Methods: Cy/+ male rats (CKD rats) were fed a casein-based diet starting at 22 wks (~50% normal renal function), and then treated daily with intraperitoneal injections of 50 μg/kg KL1 (n=9) or vehicle (n=23) for 5-7 weeks starting at 27 wks. Normal littermates (NL, n=23) were used as controls. At 32-34 weeks (~15% normal renal function), tissues were harvested for molecular and histological analyses. For *in vitro* fibrosis experiments, human cardiac fibroblasts (HCFs) were exposed to 3.8mM phosphate and 2.0mM calcium (P+C) and treated daily for 5 days with 5nM KL1 or vehicle. For immunofluorescence (IF), HCFs were incubated with 500nM AlexaFluor-tagged KL1 and hybridized with anti-asialoGM1 (GA1) antibody to label lipid rafts.

Results: CKD rats had increased left ventricular (LV) and perivascular fibrosis as assessed by Masson's Trichome staining (P<0.0001), TGF-β (P<0.004), and LV mass index (LVMI P<0.0004) compared to NL. This was accompanied by mineral dysregulation (high phosphate, iFGF23 and iPTH (P<0.0006)) and reduced renal function (high BUN and creatinine (P<0.0001)) compared to NL rats. Significantly, KL1-treated rats exhibited reduced fibrosis (P<0.01) and TGF-β (P<0.02) in LV tissue. These effects were independent of changes in LVMI, mineral dysregulation, cardiac inflammatory markers (TNFα, IL-6, and MCP-1), and renal function. In HCFs, KL1 reduced collagen type I (P<0.0001) and α-SMA (P<0.02) cultured under P+C stress. IF demonstrated KL1 localization to the membrane, cytoplasm, and nuclei, but not with GA1-containing lipid rafts.

Conclusions: KL1 directly improved cardiac fibrosis independent of alterations in renal function, mineral metabolism, nor inflammation in CKD rats. Further studies are needed to validate these findings and elucidate the receptor(s) of KL1 responsible for its anti-fibrotic effects.

Funding: Other NIH Support - NIH career development award (K23 DK115683–01)

SA-PO236

Characterization of Renal Tubule-Derived Extracellular Vesicles (EVs) and EVs Carrying Klotho

Orson W. Moe,[1,2] Juan D. Salcedo Betancourt,[2] Taylor Davidson,[1,2] Isabelle Carroll,[1,2] Johanne V. Pastor.[1,2] *[1]The Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, Dallas, TX; [2]The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: EVs are cell-derived vesicles that act as organ-to-organ messengers and are studied as potential biomarkers of physiology, disease diagnosis and therapy response. Previous studies found Klotho highly associated with membrane fragments in cell culture supernatants. We aimed to interrogate whether Klotho is carried in EVs in body fluids. Additionally, we try to quantify renal tubule-derived EVs in urine and serum.

Methods: Urine (60 ml) and serum (10 ml) from healthy subjects underwent ultracentrifugation for EV isolation. We compared the concentration of free soluble Klotho (supernatant) with EV-Klotho (EV-enriched pellet) in urine and serum. A mouse model with renal epithelium-derived EVs selectively labeled with GFP (KSP-Cad16-Cre/TIGER CD9) was developed to characterize renal tubule-originated EVs. Isolated urinary EVs underwent fluorescence-activated vesicle sorting based on GFP positivity.

Results: Three methods of EV isolation were compared- size exclusion chromatography, immunoprecipitation and ultracentrifugation- with the latter method being most efficient. EVs from human urine and serum were confirmed by EV-markers (ALIX, Flotillin-1) by immunoblot. A minimal amount of Klotho was found in human urinary EVs compared to free soluble urinary Klotho and no Klotho was detected in human serum EVs. Renal fluorescent histochemistry confirmed tubular apical membrane localization of the GFP-CD9 EV marker. Renal tubule-derived urinary EVs were identified

by direct fluorescent microscopy and flow sorting. After flow sorting, only 23.1% of urinary EVs originated from the renal tubule (CD9+/GFP+ events = 2.8 million vs. GFP- events = 12.2 million). No renal tubule-derived EVs were observed in mice serum.

Conclusions: Only a minimal amount of Klotho is carried in urinary EVs, indicating that Klotho primarily exists in the soluble form in both human serum and urine. Only a subpopulation of urinary EVs in the mouse originated from the renal tubules. Tubular-derived EVs are present in the urine but not in serum, suggesting a selective destination for tubular EV secretion into the urine. One needs to take extreme caution to interpret data from urine EVs and draw conclusions about tubular function. Additional proteomic analysis is ongoing in our lab to assess the content of tubular vs non-tubular urinary-originated EVs.

SA-PO237

Simultaneous Transcriptional Reprogramming in Cortical Bone, Muscle, and Bone Marrow Uncovered by Spatial Transcriptomics in Modeled CKD

Lainey M. Hibbard, Sheng Liu, Yamil Marambio, Kayleigh N. Jennings, Steven S. Welc, Jun Wan, Kenneth E. White. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Musculoskeletal dysfunction in CKD-MBD is common, causing increased morbidity and mortality; however, the contribution of multi-tissue genetic reprogramming is not understood. Further, the interactions between bone and muscle, and among muscle fiber types have only been tested by candidate gene analysis and in individual tissues. Herein, we tested spatially unique transcriptional reprogramming occurring simultaneously across cortical bone, muscle, and marrow.

Methods: Visium spatial transcriptomics (ST) was used on femur-muscle cross sections from male mice with adenine diet-induced CKD (0.2%, 4 wks), or casein control diet.

Results: UMAP analyses paired with hallmark transcript mapping distinguished slow and fast twitch muscle fibers, including three fast-twitch subtypes (IIa, IIx, IIb), as well as cortical bone and bone marrow in the same histology sections. Consistent with disease phenotypes, atrophy-associated genes (Trim63, Fbxo32) were upregulated in CKD muscle, 1.76-1.92 and 1.67-1.94 log_2-fold, respectively. Interestingly, a novel increase in the structural gene Nrap was detected across CKD fast and slow-twitch muscle (1.24-2.29 log_2-fold), whereas fiber subtypes showed specific disturbances, including a slow-twitch muscle increase in Car3 (1.69 log_2-fold) and enrichment of ubiquitin-mediated proteolysis and transcriptional regulation by RUNX1 pathways in fast-twitch muscle. In cortical bone, differing effects of CKD on osteoblast gene expression occurred, with increased mRNAs for Tnc/Mmp13 and decreased expression of Bglap and Col3a1 (96.6% and 95.3%). Further, glycolysis pathways were downregulated in CKD cortical bone. Bone marrow showed expected changes with CKD, including enrichment of inflammation and downregulation of heme biosynthetic pathways. Additionally, we found a novel 89.3% decrease in expression of Hist1h1b, contributing to downregulation of chromatin-related pathways. Along with tissue specific changes, we also identified pathways shared across tissues, most notably increased intrinsic apoptosis signaling with CKD.

Conclusions: Unbiased ST identified novel effects of CKD concurrently within bone, bone marrow, and specific muscle subtypes associated with tissue-unique and -common musculoskeletal pathologies.

Funding: NIDDK Support, Other NIH Support - R01-HL145528

SA-PO238

Impact of Phosphate Binders on Bone Protein Expression in Rats Fed Diets with Different Phosphorus Concentrations

Tânia P. Truyts,[1] Juliana C. Ferreira,[1] Katia R. Neves,[1] Wagner Dominguez,[1] Rosilene M. Elias,[1,2] Vanda Jorgetti,[1] Rosa M. Moyses,[1] Luciene dos Reis.[1]
[1]*Laboratório de Fisiopatologia Renal, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, Sao Paulo, Brazil;*
[2]*Post-Graduation, Universidade Nove de Julho (UNINOVE), São Paulo, Brazil.*

Background: Managing hyperphosphatemia is important in treating chronic kidney disease (CKD) to prevent bone and cardiovascular complications. Phosphate (P) binders play a key role in this control. This study evaluated the efficacy of calcium carbonate (CaCO3) and sevelamer carbonate (Sev) on the bone expression of proteins involved in the Wnt/β-catenin pathway in nephrectomized (Nx) and parathyroidectomized (PTx) rats fed normal and high P diets.

Methods: Wistar rats underwent 5/6 nephrectomy (Nx), parathyroidectomy (PTx), and were fed diets with different P concentrations (0.6% and 1.2%). The animals were divided according to diet and treatment with the binders. Biochemical analyses were performed on all animals. Bone expression of sclerostin, DKK1, and β-catenin was evaluated using mRNA levels and immunohistochemistry (IH), whereas FGF23 was evaluated only by IH. Statistical analysis using the General Linear Model was applied to study the effects of diet and treatment in these animals.

Results: Table 1 describes the interaction between different P concentrations in the diet and the effects of both treatments on biochemical analysis, IH expression, and mRNA levels. Post-test analysis disclosed that serum P, fractional P excretion and ionized calcium (Cai) were influenced by both the different diets and the two binders, as well as osteocytic expression of sclerostin and FGF23, and mRNA levels of SOST.

Conclusions: Our results showed that treatment with both binders was effective in decreasing serum P and fractional excretion and increasing Cai. Phosphate overload increased FGF23 expression in the bone, and both binders were effective in reducing this expression. The Wnt/β-catenin pathway was blocked by sclerostin, with higher expression in animals with P overload, and both treatments reduced its expression, which was also observed in gene expression. These results demonstrated that P overload can inhibit the Wnt/β-catenin pathway and that both binders effectively reversed phosphate's effects.

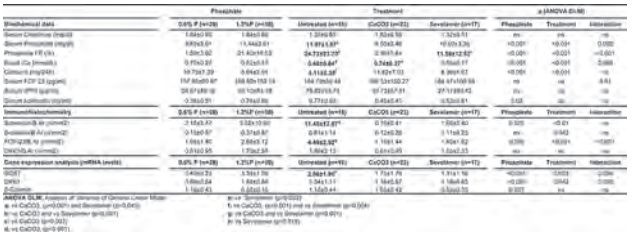


Table 1.

SA-PO239

Impact of Phosphate Binders on Bone Histomorphometry in Rats Submitted to Diets with Different Concentrations of Phosphorus

Tânia P. Truyts,[1] Juliana C. Ferreira,[1] Katia R. Neves,[1] Wagner Dominguez,[1] Rosilene M. Elias,[1,2] Vanda Jorgetti,[1] Rosa M. Moyses,[1] Luciene dos Reis.[1]
[1]*Laboratório de Fisiopatologia Renal, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil;*
[2]*Post-Graduation, Universidade Nove de Julho (UNINOVE), São Paulo, Brazil.*

Background: Managing hyperphosphatemia is important in treating chronic kidney disease (CKD) to prevent bone and cardiovascular complications. Phosphate (P) binders play a fundamental role in this control. This study evaluated the impact of calcium carbonate (CaCO3) and sevelamer carbonate (Sev) on bone tissue in nephrectomized (Nx) and parathyroidectomized (PTx) rats fed normal and high-phosphorus diets.

Methods: Wistar rats underwent 5/6 nephrectomy (Nx) and parathyroidectomy (PTx) and were fed diets with different P concentrations (0.6% and 1.2%). The animals were divided according to diet and treatment with the binders. Biochemical analyses and bone histomorphometry were performed on all animals. Statistical analysis using ANOVA General Linear Model was applied to study the effects of diet and treatment on bone tissue.

Results: Table 1 describes the interaction between different P concentrations in the diet and the effects of both treatments on biochemical analysis and bone histomorphometry. Post-test analysis showed that P excretion fraction and ionized calcium (Cai) were influenced by both different diets and CaCO3 and sevelamer. Also showed that formation parameters were influenced by P and treatment, significantly high in the rats treated with CaCO3. Resorption parameters were influenced by treatment but not by P, although no interaction was observed.

Conclusions: Our results demonstrated that, although CaCO3 was effective in reducing serum P, it significantly altered bone formation and resorption parameters, possibly due to calcium overload. In contrast, the use of sevelamer did not alter bone parameters. These findings reinforce the importance of considering the side effects related to calcium load when choosing phosphate binders. The study suggests that sevelamer may be a safer alternative to preserve bone health and control hyperphosphatemia in these experimental model.

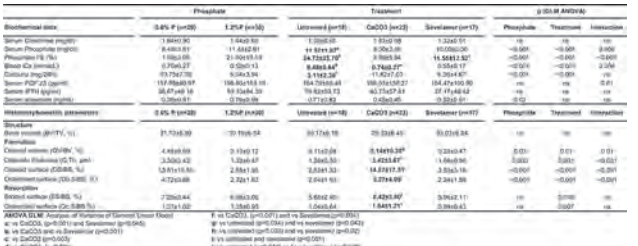


Table 1.

SA-PO240

Uremic Toxin Indoxyl Sulfate Increases Osteocyte Wnt Inhibitor Signaling and Decreases RANKL and Mineralization, Effects Negated by PTH

Neal X. Chen, Kalisha O'Neill, Hannah E. Wilson, Lynda F. Bonewald, Sharon M. Moe. *Indiana University School of Medicine, Indianapolis, IN.*

Background: In CKD, fractures can occur at both high and low PTH levels, indicating non-PTH mediated pathways. We hypothesized that uremic toxin indoxyl sulfate (IS), a potent ligand for the aryl hydrocarbon receptor (AhR), may be a factor in low bone turnover when PTH is not elevated.

Methods: We cultured IDG-SW3 osteocytes that differentiate from osteoblasts to early osteocytes (day 14) and mature osteocytes (day 35). We examined the effect of IS in short term 24 hour exposure, long term (14 or 35 day) exposure, and with and without PTH or CH223191 (an inhibitor of AhR nuclear translocation). We assessed osteocyte gene expression by RT-qPCR, alkaline phosphatase (ALP) activity, and mineralization. AhR canonical signaling was assessed by upregulation of the genes CYP1A1, CYP1B1, and AhRR.

Results: Short term exposure to IS for 24 hours dose dependently increased expression of the Wnt inhibitors SOST, Dkk1, and decreased RANKL in both early and mature osteocytes. IS dose dependently increased canonical AhR activation of CYP genes. Long term incubation of IS in early (IS for 14 days) and mature (IS for 35 days) osteocytes led to similar upregulation of Wnt inhibitors and decreased RANKL expression, ALP, and mineralization. CH223191 reduced AhR canonical CYP gene activation and reversed the IS inhibition of mineralization and alkaline phosphatase activity but did not reverse the IS induced expression SOST, Dkk1, or RANKL in osteocytes. Co-culture with both PTH and IS reversed the IS induced upregulation of SOST, Dkk1, and suppression of RANKL. In both early and mature osteocytes, AhR CYP genes were activated by IS but not PTH, but there was an additive effect of AhR CYP gene expression in the presence of both IS and PTH.

Conclusions: In summary, IS in the absence of PTH, activated canonical and non-canonical AhR signaling to increase osteocyte Wnt inhibitor signaling and decrease RANKL osteoclast activation and mineralization, which would translate to low remodeling. However, in the presence of PTH, these effects were reversed, suggesting IS is likely an important factor in the low turnover bone disease observed in CKD.

Funding: Commercial Support - Dialysis Clinic, Inc.

SA-PO241

Activin A Inhibition Reduces Kidney Fibrosis and Normalizes Bone Abnormalities in AKI

Anders Nordholm,[1,2] Andreas Lodberg,[3,4] Simone Snitgard Rosendal Nielsen,[5] Maria L. Mace,[2] Eva Gravesen,[6] Iain O. Bressendorff,[1] Marya Morevati,[2] Marco Eijken,[7] Christian B. Andersen,[3] Mads Hornum,[2,8] Jesper S. Thomsen,[3] Thomas L. Andersen,[5,9] Ditte Hansen.[1,8] *[1]Department of Nephrology, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark; [2]Department of Nephrology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [3]Department of Biomedicine, University of Aarhus, Aarhus, Denmark; [4]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; [5]Clinical Cell Biology, Research Unit of Pathology, Department of Pathology, Odense University Hospital, Odense, Denmark; [6]Department of Pathology, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark; [7]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [8]Department of Clinical Medicine, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark; [9]Department of Forensic Medicine, Aarhus University, Aarhus, Denmark.*

Background: Activin A inhibition (ActAi) ameliorates progressive kidney fibrosis and bone disease in CKD. In acute kidney injury (AKI) by unilateral ureter obstruction (UUO) activin A is secreted from injured kidneys leading to elevated levels in the circulation. We aimed to determine the effect of ActAi on kidney and bone in AKI.

Methods: Female C57BL/6 mice with UUO for 15 days received either ActAi with an anti-activin receptor type IIA/IIB antibody (s.c., 10mg/kg) twice weekly (UUO Ab, n=10) or vehicle (UUO Veh, n=10), while sham-operated controls received vehicle (Ctrl, n=8). At sacrifice, blood samples, kidneys, femora, and tibiae were collected. Analyses included ELISA, qPCR, histology, μCT, and bone histomorphometry.

Results: UUO Ab had reduced mRNA levels of type I collagen (20±5 vs 35±20, p<0,05) and fibronectin (8±2 vs 17±6, p<0.05) compared to UUO Veh. Histology confirmed diminished fibrosis in UUO Ab. Plasma Urea was similar in both UUO groups. UUO Ab mice had increased volumetric bone mineral density (130±13 vs 106±11 and 103±13mg/cm^3, p<0.001), and trabecular number (4.3±0.1 vs 3.9±0.2 and 3.9±0.2mm^{-1}, p<0.001) compared to similar levels in UUO Veh and Ctrl. In UUO Veh, osteoid surface increased (OS/BS 31±14 to 43±10%, p<0.05) and quiescent surface decreased (QS/BS 13±7 to 7±3%, p<0.05) compared to Ctrl. Both were restored in UUO Ab (p<0.05). Sclerostin mRNA was reduced in UUO Veh compared to Ctrl (0.5±0.3 vs 1.1±0.4, p<0.05) but restored in in UUO Ab (0.9±0.3, p<0.05). FGF23 mRNA levels was unaffected by UUO but decreased in UUO Ab (0.4±0.2 vs 1.2±0.5 and 1.1±0.4, p<0.01). Plasma FGF23 increased in UUO Veh compared to Ctrl (50±13 vs 34±10pg/mL, p<0.05) and was normalized in UUO Ab (33±6pg/mL, p<0.01). Plasma calcium, phosphate, and PTH were similar in all groups.

Conclusions: ActAi ameliorated progressive kidney fibrosis and restored bone-forming osteoid surfaces in AKI mice, indicating a normalization of a potential mineralization defect. ActAi increased bone mineral density and microstructure as well as restored mRNA levels of osteocyte-derived sclerostin. ActAi is a promising therapeutic approach to limit AKI induced renal fibrosis and to normalize bone homeostasis.

SA-PO242

Mitochondrial Dysfunction and Mitophagy Blockade Contribute to Renal Osteodystrophy in CKD-Mineral Bone Disorder

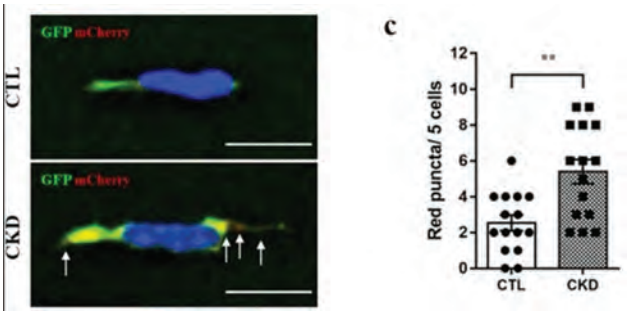
Shun-Neng Hsu,[1,2] Yu-Juei Hsu,[1] Colin Farquharson.[2] *[1]Tri-Service General Hospital Department of Medicine, Taipei, Taiwan; [2]The University of Edinburgh The Roslin Institute, Roslin, United Kingdom.*

Background: Chronic kidney disease–mineral and bone disorder (CKD-MBD) presents with extra-skeletal calcification and renal osteodystrophy (ROD). The origins of ROD likely lie with elevated uremic toxins and/or an altered hormonal profile but the cellular events responsible remain unclear. Here, we report that stalled mitophagy contributes to mitochondrial dysfunction in bones of a CKD-MBD mouse model, and also human CKD-MBD patients.

Methods: C57BL/6J wild-type male mice and *mito*-QC mice were obtained and CKD-MBD was induced using a casein-based diet containing 0.2% adenine for five weeks. 40 wild-type mice were allocated into control and CKD-MBD groups staggered from day 0 to day 35 to assess progressive changes. RNA-seq libraries were prepared and sequenced to provide comprehensive gene expression profiles. Blood serum, μCT of tibiae, and confocal microscopy of stained cryosections assessed CKD-MBD impact.

Results: RNA-seq analysis exposed an altered expression of genes associated with mitophagy and mitochondrial function in tibia of CKD-MBD mice. The accumulation of damaged osteocyte mitochondria and the expression of mitophagy regulators, p62/SQSTM1, ATG7 and LC3 was inconsistent with functional mitophagy, and in *mito*-QC reporter mice with CKD-MBD, there was a 2.3-fold increase in osteocyte mitolysosomes. Altered expression of mitophagy regulators in human CKD-MBD bones was also observed. To determine if uremic toxins were possibly responsible for these observations, indoxyl sulfate treatment of osteoblasts revealed mitochondria with distorted morphology and whose membrane potential and oxidative phosphorylation were decreased, and oxygen-free radical production increased. The altered p62/SQSTM1 and LC3-II expression was consistent with impaired mitophagy machinery and the effects of indoxyl sulfate were reversible by rapamycin.

Conclusions: Mitolysosome accumulation from impaired clearance of damaged mitochondria may contribute to the skeletal complications, characteristic of ROD.



Quantification of mitophagy in osteocytes from CTL and CKD-MBD mito-QC mice.

SA-PO243

Combination Oxylanthanum Carbonate and Tenapanor Lowers Urinary Phosphate Excretion in Rats

Satya Medicherla,[1] Guru Reddy,[1] Pramod Gupta,[1] Glenn M. Chertow,[2] Shalabh Gupta.[1] *[1]Unicycive Therapeutics Inc, Los Altos, CA; [2]Stanford University School of Medicine, Palo Alto, CA.*

Background: End-stage kidney disease(ESKD) affects >7 million people worldwide and ~70% of patients with ESKD have hyperphosphatemia. Tenapanor, sodium/hydrogen exchanger(NHE3) inhibitor, reduces paracellular phosphate(P) absorption by inducing conformational changes in intestinal epithelium. Oxylanthanum carbonate(OLC) is an investigational new drug being developed for treatment of hyperphosphatemia under FDA's 505(b)(2) regulatory pathway. If approved, OLC will share substantially the same product label and prescribing information as reference-listed drug Fosrenol®(lanthanum carbonate), although OLC tablets are smaller in size and swallowed whole with water and not chewed. This study evaluated effects of OLC+tenapanor on urinary P excretion in rats on a high phosphorus diet.

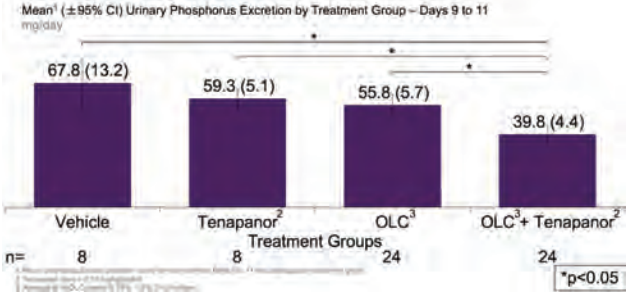
Methods: 64 male Sprague Dawley rats were fed standard chow 1 week prior to study start and then spiked with additional 0.4% inorganic phosphate [1:1 sodium:potassium salt, 1.1%(wt/wt) total phosphate content] for rest of the study. On study Day -1, animals were randomized into 8 groups(n=8 in each): 1) vehicle, 2) tenapanor 0.15mg/kg, 3) vehicle+OLC 0.75%, 4) vehicle+OLC 1.5%, 5) vehicle+OLC 3%, 6) OLC 0.75%+tenapanor 0.15mg/kg, 7) OLC 1.5%+tenapanor 0.15mg/kg, and 8) OLC 3%+tenapanor 0.15mg/kg. Vehicle and tenapanor were dosed PO twice daily whereas OLC was incorporated into the diets. 24-hour urine samples were collected using metabolic cages on day 9, 10, and 11 for urinary P measurements. OLC efficacy data are presented as average of all OLC doses(0.75%, 1.5%, and 3%).

Results: In tenapanor alone and OLC only groups, urinary P excretion was 8.5 and 12.0mg/day lower, respectively, compared to vehicle. In OLC+tenapanor groups, urinary P excretion was 28mg/day lower compared to vehicle.

Conclusions: Combination OLC+tenapanor demonstrates more pronounced P reduction than either agent used alone. The magnitude of P lowering suggests effect of OLC+tenapanor is synergistic rather than additive.

Funding: Commercial Support - Unicycive Therapeutics, Inc.

Figure 1. OLC + Tenapanor Effectively Decreased Urinary Phosphorus Excretion Compared to Tenapanor Only and OLC Only



SA-PO244

Systemic Phosphate Elevations Are Associated with Alveolar Calcification in Mice

Abul Fajol,[1] Seth Bollenbecker,[2] Parveen Kumar,[3] Kylie Heitman,[1] Madison Thomas,[1] Qing Li,[1] Svetlana Komarova,[1] Tanecia Mitchell,[3] Stefanie Krick,[2] Christian Faul.[1] *[1]The University of Alabama at Birmingham Division of Nephrology, Birmingham, AL; [2]Division of Pulmonary, Allergy and Critical Care Medicine, The University of Alabama at Birmingham, Birmingham, AL; [3]Department of Urology, The University of Alabama at Birmingham, Birmingham, AL.*

Background: Increases in serum phosphate levels (hyperphosphatemia) are associated with vascular calcification (VC) and mortality in patients with chronic kidney disease (CKD). Elevated phosphate can target vascular smooth muscle cells and induce inflammatory and osteogenic gene programs and VC. It is unknown whether high phosphate levels can also directly affect the lung.

Methods: We analyzed the lung phenotype of klotho-deficient (*kl/kl*) mice, which is a model for hyperphosphatemia and VC. Tissue calcifications were determined by μCT analysis, Alizarin red and von Kossa stainings, and tissue phosphate content by a colorimetric assay and ICP-MS. Nanoparticles in the bronchoalveolar lavage (BAL) fluid were quantified by NanoSight Technology and visualized by TEM. Cells in the BAL were analyzed by flow cytometry. Human alveolar epithelial cells (A549) and human lung fibroblasts (IMR-90) were cultured in the presence of high phosphate and analyzed by Alizarin red staining. Calcification events in lung tissue and cultured cells were also determined by qPCR analysis of osteogenic and inflammatory markers.

Results: We observed calcifications in the lung of *kl/kl* mice, especially in the alveolar region, as well as increased expression of osteogenic and inflammatory markers and elevated phosphate content. In the BAL of *kl/kl* mice, we detected increased numbers of macrophages and calcium-containing nanoparticles, which had a crystal-like morphology. No such alterations were observed in wildtype mice. A high magnesium diet reduced lung phosphate content and calcification. Exposure of A549 cells and IMR-90 to high phosphate induced osteogenic and inflammatory markers as well as calcium-phosphate deposition, which was abolished in cells co-treated with magnesium.

Conclusions: Our findings suggest that mice with hyperphosphatemia develop lung calcifications, which are accompanied by inflammation and by the appearance of calcium-phosphate crystals. Whether pulmonary calcification also occurs in CKD, needs to be determined. Our in vitro studies suggest that high phosphate can directly target lung cells and induce calcification. Therefore, lowering phosphate or preventing the formation of calcium-phosphate particles systemically or locally might have protective effects on the lung in diseases with hyperphosphatemia.

Funding: NIDDK Support

SA-PO245

Modeling Progression of Uremic Vasculopathy Using Machine Learning

Adam E. Gaweda,[1] Eleanor D. Lederer,[2,3] Michael E. Brier.[1] *[1]University of Louisville, Louisville, KY; [2]The University of Texas Southwestern Medical Center, Dallas, TX; [3]VA North Texas Health Care System, Dallas, TX.*

Background: KDIGO guidelines for Chronic Kidney Disease Mineral Bone Disorder (CKD-MBD) target Phosphate, Parathyroid Hormone, and Calcium as the primary clinical outcomes. To prevent vascular end organ damage due to CKD-MBD, we need better understanding of the mechanism behind uremic vasculopathy. We perform nonlinear analysis of biochemical parameters in the Chronic Renal Insufficiency Cohort (CRIC) and their association with coronary artery calcification (CAC).

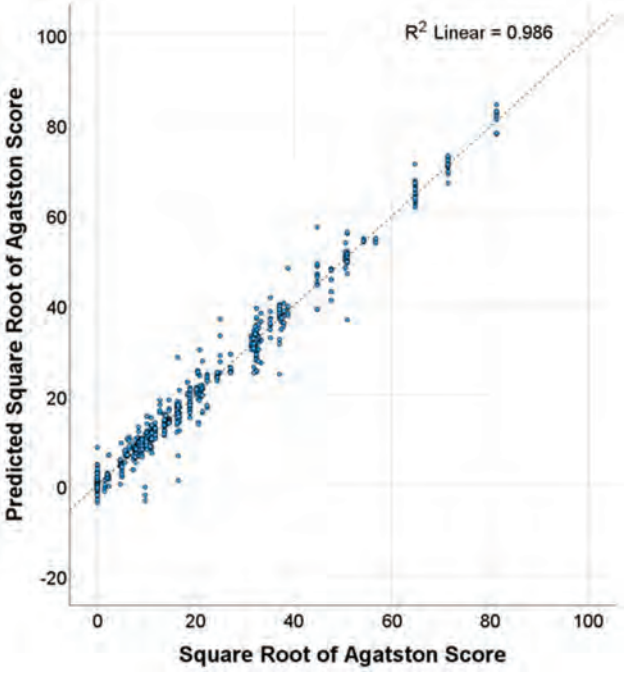
Methods: We abstracted 93 biochemical parameters from the CRIC data set and performed 10 data fitting sessions using Multilayer Perceptron Neural Network model, splitting the data into training (70%) and testing (30%) sets. Using sensitivity analysis, we selected the most important parameters from the trained model. We ranked these parameters and analyzed their association with CAC at different CKD stages. Data analysis was performed in IBM SPSS.

Results: The average CAC prediction RMSE was 0.08 (training) and 0.11 (testing). At early CKD stages, CAC appears to be influenced by oxidative stress, mitochondrial dysfunction, and alterations in protein translation and post-translational modification (YKL40, ADMA, succinic acid, NAG+, Tiglylglycine). High CAC scores in early CKD correlate with high FGF23, whereas high Calcitriol appears protective. At late CKD stages, high CAC scores reflect impaired tubular function including xanthosine, BTP, and B2M.

Conclusions: Uremic vasculopathy involves various pathways active at different CKD stages. Biomarker discovery enables identifying these pathways to better understand the disease process, leading to better diagnosis, prevention, and treatment.

Acknowledgment: CRIC data were provided by NIDDK Central Repository, a program of the National Institute of Diabetes and Digestive and Kidney Diseases.

Funding: Veterans Affairs Support



Regression plot for predicted vs actual CAC score.

SA-PO246

A Nonsteroidal Mineralocorticoid Receptor Antagonist Alleviates Vascular Aging in CKD

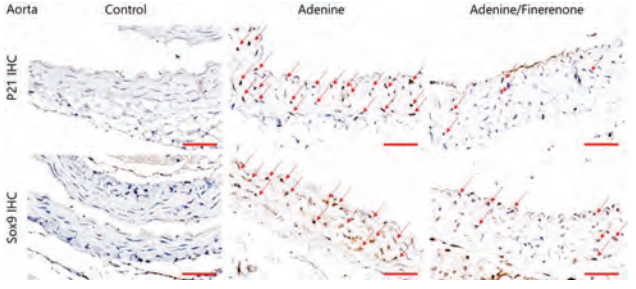
Yoonjoo Jang, Byung Min Ye, Seo Rin Kim, Il Young Kim, Soo Bong Lee, Dong Won Lee. *Pusan National University Yangsan Hospital, Yangsan, Republic of Korea.*

Background: Chronic kidney disease (CKD) is associated with early vascular aging processes, leading to increased morbidity and mortality. Aldosterone may exacerbate these processes, but the impact of mineralocorticoid receptor blocking on vascular complications in CKD remains unknown. This study aims to assess the impact of a novel nonsteroidal mineralocorticoid receptor antagonist, finerenone, on mitigating vascular aging in CKD.

Methods: CKD was induced in mice using an adenine-rich diet. Three groups of C57BL/6 mice were assigned to distinct dietary regimens: standard chow, a diet enriched with 0.25% adenine, and an adenine-enriched diet supplemented with finerenone (10 mg/kg) (n=6, 14, and 14, respectively). After a 6-week diet, renal function was assessed by serum creatinine and urine albumin levels. Vascular aging and calcification were studied on the aorta ex vivo to evaluate the effects of adenine and finerenone. (Figure)

Results: The adenine diet increased serum creatinine levels and urine albumin-to-creatinine ratios, but finerenone treatment improved these measures. Alkaline phosphatase levels in serum and calcium deposits in the aorta increased in mice fed adenine but normalized in the adenine/finerenone group. Whereas, serum aldosterone levels were upregulated in both adenine and adenine/finerenone groups compared to control mice. Aortic expressions of senescence and SASP markers *Cdkn1a, Tnfα,* and *Serpine1* increased in the adenine group but decreased with finerenone treatment. Finerenone also improved the expression of the osteogenic marker *Sox9* in the aorta, correlating with *Cdkn1a* expressions.

Conclusions: CKD triggers osteogenic changes and vascular aging in a murine model, but finerenone mitigates vascular aging, at least partly due to the improvement of Sox9 expression. These findings support the exploration of mineralocorticoid receptor blocking strategies for improving vascular aging in CKD.



SA-PO247

Disorder of Methionine Metabolism Triggers Vascular Calcification via DNMT3A in CKD

Fan He, Xue Xing, Qing Li. *Department of Nephrology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.*

Background: Vascular calcification is closely related to the occurrence and mortality of cardiovascular disease (CVD) in CKD patients, and the specific mechanism of its pathogenesis is not yet clear. Previous studies have found that elevated levels of methionine metabolites are risk factors for developing cardiovascular disease (CVD), but the mechanism remains unclear. This study aims to explore the role of methionine metabolism in vascular calcification in CKD.

Methods: Liquid chromatography-mass spectrometry was used to detect the levels of S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) in the plasma of CKD patients; 5/6 nephrectomy combined with high phosphorus diet and high phosphorus medium was used to establish in vivo and in vitro CKD vascular calcification models. Methylation-specific polymerase chain reaction (MSP) was used to detect whether the target gene has undergone methylation.

Results: The plasma levels of SAM, SAH, and SAM/SAH ratios in the CKD patient group were significantly increased. Also, CKD patients had significantly increased levels of 5-mC and DNMT3A expression in calcified arteries IHC staining. The proportion of 5-mC modification in the total DNA of blood vessels in CKD mice significantly increased;5Aza alleviated vascular calcification in vivo; Idownregulating the expression of DNMT3A can alleviate VC. Further validation experiments found that under high phosphorus stimulation, the intracellular arginine content of VSMC decreased, and the expression of arginine synthase ASS1 and ASL decreased. Knocking down DNMT3A can reverse the decrease in intracellular arginine content of VSMC caused by high phosphorus stimulation and simultaneously reverse the expression levels of key arginine synthase ASS1 and ASL; MSP detection showed that knocking down DNMT3A can reduce the high methylation levels of ASS1 and ASL under high phosphorus stimulation.

Conclusions: Disordered methionine metabolism in CKD patients with vascular calcification mediates hypermethylation of vascular tissue, accompanied by increased expression of DNMT3A. Inhibiting the expression of DNMT3A can alleviate CKD-related vascular calcification. DNMT3A silences the expression of arginine synthase ASS1 and ASL through DNA hypermethylation, inhibits arginine synthesis, and accelerates the occurrence of vascular calcification.

Funding: Government Support - Non-U.S.

SA-PO248

Inhibitory Dynamics of SBI-425 on Medial Arterial Calcification in Mice with CKD: A Therapeutic Perspective

Takashi Tani, Hitomi Tani, Akiko Mii, Rei Nakazato, Natsumi Kamijo, Akira Shimizu, Yukinao Sakai. *Nihon Ika Daigaku, Bunkyo-ku, Japan.*

Background: Daily oral administration of SBI-425, a TNAP inhibitor, prevents medial arterial calcification (MAC) in CKD mice. This study evaluated the efficacy of continuous TNAP inhibition via mixed feeding in MAC prevention and assessed its therapeutic effect on MAC progression when pre-existing MAC is present.

Methods: The Vehicle group of 10-week-old mice received 0.2% adenine. From 16 weeks, they were subjected to 0.2% adenine and 1.8% phosphorus for 10 weeks. Treatment groups, SBI-10W, SBI-6W, and SBI-4W, were switched to diets containing 0.03% SBI-425 at 16, 20, and 22 weeks, respectively, continuing the adenine and phosphorus load. The Control group was raised under normal conditions for 16 weeks from 10 weeks of age.

Results: Blood urea nitrogen, serum creatinine, serum phosphorus, FGF-23, and intact PTH were significantly elevated in the CKD group compared to the Control group, but there were no significant differences between the CKD groups. Animal CT images showed ectopic calcification in the aorta, heart, and bilateral kidneys in the Vehicle group, and the respective calcification volumes (mm^3) worsened over time after the start of the high-phosphorus diet. Control and SBI-10 groups showed almost no ectopic calcification throughout the experimental period. SBI-6 and SBI-4 groups showed ectopic calcification as in the Vehicle group, although ectopic calcification at all sites tended to be suppressed after the start of pharmacological intervention compared to the Vehicle group. In the aortic and renal histopathology, ectopic calcification with positive Von-kossa staining was observed in the CKD model groups. The area ratios (%) of calcified areas in the tissues of both aorta and kidney were in the order of Vehicle > SBI-4 > SBI-6 > SBI-10 group, indicating that the severity of calcification was inversely proportional to the length of treatment period with SBI-425.

Conclusions: Sustained TNAP inhibition with SBI-425 prevented MAC in CKD mice. TNAP inhibitors showed pharmacological effects proportional to the duration of drug administration, suggesting that they are effective in inhibiting the progression of ectopic calcification even in the presence of pre-existing MAC.

Funding: Government Support - Non-U.S.

SA-PO249

Calciprotein Particles (CPPs) Are Cleared Predominantly by Liver, Spleen, and Bone in a Rat Model of CKD

Jeroen H. De Baaij, Lara W. Zeper, Pieter A. Leermakers, Caro Bos, Joost Hoenderop. *Radboud Universitair Medisch Centrum, Nijmegen, Netherlands.*

Background: Calciprotein particles (CPPs) provide an efficient mineral buffering system to prevent the complexation of phosphate and calcium in the circulation. However, in chronic kidney disease (CKD), the phosphate load exceeds the mineral buffering capacity, resulting in the formation of crystalline CPP2 particles. CPP2 have been associated with cardiovascular events and mortality. Moreover, CPP2 have been demonstrated to induce calcification *in vitro.* In this study, we examined the fate of CPP2 in a rat model of CKD.

Methods: Calcification was induced in Sprague Dawley rats by a 5/6-nephrectomy (5/6-Nx) combined with a high phosphate diet. Control rats received a sham surgery and high phosphate diet. Twelve weeks after surgery kidney failure was significantly induced in 5/6-Nx rats as determined by enhanced creatinine and urea plasma levels and abnormal kidney histological architecture. Subsequently, radioactive and fluorescent (FITC)-labeled CPP2 ([^{89}Zr]Zr-CPP2-FITC) were injected *i.v.* to determine clearance *in vivo*.

Results: Using positron emission tomography scans and radioactive biodistribution measurements, it was demonstrated that [^{89}Zr]Zr-CPP2-FITC are mainly present in the liver, spleen, and bones in both 5/6-Nx and sham rats. Immunohistochemistry showed that [^{89}Zr]Zr-CPP2-FITC are predominantly taken up by Kupffer cells and macrophages. However, [^{89}Zr]Zr-CPP2-FITC could also be detected in hepatocytes. In the different parts of the aorta and in the blood, low values of [^{89}Zr]Zr-CPP2-FITC were detectable, independent of the presence of calcification.

Conclusions: CPP2 are cleared rapidly from the circulation by the liver, bones, and spleen in a rat model of CKD. In the liver, Kupffer cells, macrophages, and hepatocytes contribute to CPP2 clearance. Our results suggest that targeting liver CPP clearance may reduce the burden of crystalline CPP in the development of vascular calcification.

SA-PO250

Calprotectin Plays an Important Role in the Pathogenesis of Vascular Calcification in CKD

Zhang Jingxuan, Takashige Kuwabara, Ryosuke Date, Daisuke Fujimoto, Tomoko Kanki, Yutaka Kakizoe, Yuichiro Izumi, Masashi Mukoyama.
Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Cardiovascular complications are a major contributor to global mortality rates, with atherosclerosis and vascular calcification (VC) being significant factors. In particular, patients with CKD experience a higher prevalence of VC as their renal function deteriorates, well-known as CKD-MBD, leading to increased mortality rates. Calciprotein particles (CPPs) are colloidal nanoparticles that play a crucial role in the initiation and progression of VC, partly through TLR4 signaling. We recently reported that serum calprotectin (CPT, also known as MRP8/14 or S100A8/A9) levels, which amplify TLR4 signaling, have been found to have a predictive role in mortality among hemodialysis patients with high phosphatemia. The aim of this study is to clarify the pathogenic role of CPT on the cardiovascular calcification involving CPPs in CKD patients.

Methods: Secondary CPP (CPP2) was generated using a phosphate-enriched culture medium (DMEM/10% FBS) incubated at 37°C. Vascular smooth muscle cells (VSMCs) were stimulated by CPP2 concomitant with recombinant CPT or cultured supernatant of macrophages (RAW264.7) treated with LPS. To characterize the significant role of CPT in the calcification of VSMCs, RNA interference experiments using siMRP8 were performed. In in vivo experiment, the CKD-MBD model was developed in myeloid-lineage cell-specific MRP8 KO mice (MyMRP8KO) using adenine combined with a high-phosphate diet.

Results: In VSMCs, the addition of cultured medium from LPS-stimulated RAW264.7, which contains markedly increased CPT, aggravated calcification and Ca^{2+} deposition induced by CPP2. This phenotype was associated with the amplified expressions of pro-osteogenic and -inflammatory genes, which were effectively suppressed by CPT knockdown with siMRP8. In the CKD-MBD model, the aortic calcification was ameliorated in MyMRP8KO compared to WT.

Conclusions: Our study suggested that the inflammation can enhance the calcification through CPT. Inflammation-mediated release of CPT from macrophages exacerbates CPP2-induced VC. The pathogenic role of CPT in CPP2-induced calcification might support our previous cohort study in hemodialysis patients with high phosphatemia. CPT might become a novel therapeutic target to protect against VC in patients with CKD-MBD.

SA-PO251

An Oral Phosphate Challenge in Experimental CKD Reveals the Scope of Deficit in Calciprotein-Based Mineral Buffering Only If Both OsteoSense and T50 Are Used

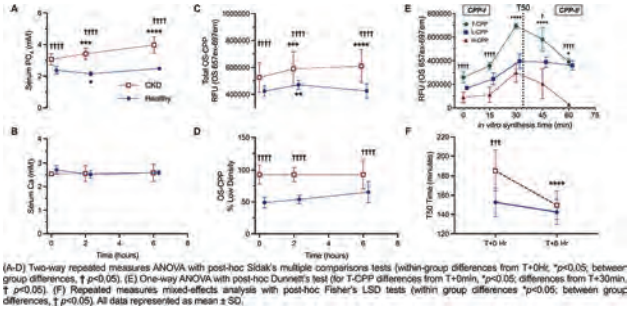
Eric B. Fernandes,[1] Tyler Rowsell,[1] Mandy E. Turner,[1,2] Rachel M. Holden,[1] Michael A. Adams.[1] *[1]Queen's University, Kingston, ON, Canada; [2]Brigham and Women's Hospital, Boston, MA.*

Background: In chronic kidney disease (CKD), disturbed phosphate (PO_4) homeostasis is linked to morbidity and mortality. Fetuin-based calciprotein particles (CPPs) are key to mineral buffering yet their role in health and disease is unclear. This study characterized the phenotype of CPPs in response to acute oral PO_4 challenges in both health and experimental CKD using a multi-modal approach.

Methods: CPPs were profiled in male Sprague-Dawley rats before and after CKD induction (n=10, 0.25% adenine, 6wks). After collecting fasted serum, animals rapidly ate a 1% PO_4 diet (10g, TD.08670) with serum collected at 2 and 6hrs. Serum minerals and OsteoSense detectable CPPs (OS-CPPs) were measured throughout, while type II CPP formation was assessed at 0 and 6hrs via T50 following an *ex vivo* mineral challenge. To contextualize OS-CPP observations, changes in OS-CPP detection versus *in vitro* T50-based CPP synthesis were compared. All differences stated are $p<0.05$.

Results: In CKD, both serum [PO_4] and total OS-CPPs increased by 12% at 2hrs post-challenge and by 30% and 16.6% at 6hrs. In contrast, in healthy rats at 2hrs, serum [PO_4] decreased (-8.7%) and OS-CPPs were elevated (11.5%), though by 6hrs no significant differences remained. Low-density OS-CPPs were much more prevalent than high-density forms in CKD (93±1%) vs healthy (56±8%) across all time points. The overall OS-CPP profile also revealed type II CPPs are poorly detected by OS. The T50 time was decreased in CKD rats (19%) vs healthy (6%) after mineral challenge.

Conclusions: The CPP profile in fasted rats showed near saturation of mineral buffering in experimental CKD as detected by the OS-CPP profile, but not by T50. The acute oral mineral challenge further revealed this near saturation of CPPs via a marked reduction in the T50 time. Given the issues regarding the detection of different forms of CPPs, these findings emphasize the critical need to use multiple protocols to properly evaluate changes in the CPP-based mineral buffering system.



(A-D) Two-way repeated measures ANOVA with post-hoc Sidak's multiple comparisons tests (within-group differences from T+0Hr, *p<0.05; between group differences, † p<0.05). (E) One-way ANOVA with post-hoc Dunnett's test (for T-CPP differences from T+0min, *p<0.05; differences from T+30min, † p<0.05). (F) Repeated measures mixed-effects analysis with post-hoc Fisher's LSD tests (within group differences *p<0.05; between group differences, † p<0.05). All data represented as mean ± SD.

SA-PO252

Correction of Paradoxical Mineralization in Murine CKD-MBD by ENPP1 Enzyme Biologics

Hajime Kato,[1] Hana Kim,[1] Tayyaba Ishaq,[1] Dominique Sims,[1] Shivani Srivastava,[1] Paul Stabach,[1] Thomas Carpenter,[2] W. Charles O'Neill,[3] Demetrios Braddock.[1] *[1]Yale University Department of Pathology, New Haven, CT; [2]Yale University Department of Pediatrics, New Haven, CT; [3]Emory University Renal Division, Atlanta, GA.*

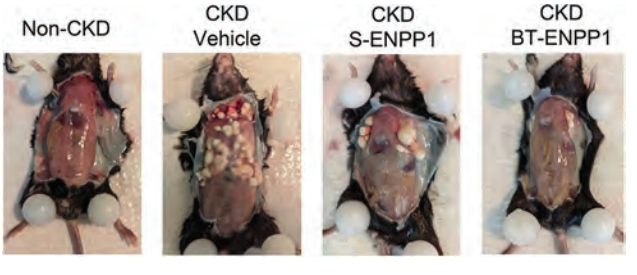
Background: Chronic Kidney Disease-Mineral & Bone Disorder (CKD-MBD) is a mineralization disorder characterized by medial arterial calcifications and loss of bone mass, a physiologic process known as 'Paradoxical Mineralization'. Reduced plasma pyrophosphate (PPi) levels in CKD patients suggest a role for the enzyme producing PPi, ENPP1, in the pathogenesis of this condition.

Methods: To induce CKD-MBD, mice were placed on a high phosphate, high calcium, low magnesium diet with alternating adenine (0.15%, 0.2%, or 0.3%) for 33 weeks, after the method of Jia *et al.* (BMC Nephrology 2013, **14**:116). Following the development of renal failure, animals were dosed weekly with either vehicle or soluble (S-) or bone-targeted (BT-) ENPP1-Fc. At 33 weeks, calcifications in the aorta, subcutaneous tissue, and heart were quantitated chemically, by weight, and by micro-CT, respectively. Bone mineralization was assessed using biomechanical testing of femurs and micro-CT analysis of tibial microarchitecture.

Results: The mice on the adenine diet showed progressive renal failure, characterized by elevated BUN and reduced plasma PPi levels. Both S- and BT-ENPP1 reduced aortic and subcutaneous calcification, comparable to the non-CKD control mice (Fig). Biomechanical testing showed improvements in maximum load, post-yield, and total work in both treatment groups compared with the vehicle CKD cohort. Micro-CT analysis showed improvement in trabecular number and spacing in the ENPP1-treated CKD cohort compared with the vehicle CKD controls. Finally, vehicle-treated CKD mice demonstrated an inverse correlation of vascular calcifications with bone mineralization parameters.

Conclusions: Our studies demonstrate that a modified version of the alternating adenine diet reproduces paradoxical mineralization in CKD-MBD which can be treated with an ENPP1 enzyme therapy, supporting the hypothesis that PPi deficiency may be a pathogenic mechanism driving the paradoxical mineralization in CKD-MBD.

Funding: NIDDK Support, Private Foundation Support



Subcutaneous calcifications of CKD-MBD cohorts at 33 weeks

SA-PO253

Magnesium Supplementation Reduces Vascular Calcification by Activating Calcium-Sensing Receptor (CaSR) in Vascular Smooth Muscle Cells

Qi Gao, Onur Cil. *University of California San Francisco, San Francisco, CA.*

Background: Pathological deposition of calcium-phosphate in the arterial wall leads to vascular calcification, which is an important risk factor for cardiovascular mortality in CKD patients. Higher dietary Mg^{2+} intake was shown to reduce vascular calcification and cardiovascular mortality in clinical studies, however the mechanisms of Mg^{2+} effect remain unclear. Extracellular Ca^{2+}-sensing receptor (CaSR) is a protein expressed in many tissues including vascular smooth muscle cells (VSMC). Although Ca^{2+} is considered as

its main physiological agonist, we recently showed that Mg^{2+} (an often neglected CaSR agonist) is a more potent CaSR activator in certain tissues such as gut and lung.

Methods: We studied the roles of CaSR in therapeutic effects of Mg^{2+} in cell and mouse models of vascular calcification.

Results: In both mouse and human primary aortic smooth muscle cells, calcium-phosphate treatment (3 mM Ca^{2+}, 2.5 mM PO_4^{3-} for 7 days) resulted in marked calcification. Increasing Mg^{2+} in culture media concentration-dependently reduced calcification by up to 90% at 1 mM. The protective effects of Mg^{2+} were essentially abolished by CaSR inhibitor NPS-2143. Mg^{2+} concentration had minimal effects on calcification in primary cells derived from VSMC-specific CaSR knockout mice (*SM22-Cre; Casr-flox*), confirming key roles of CaSR in its efficacy. CaSR activation assays showed that Mg^{2+} is 2-5 fold more potent CaSR agonist than Ca^{2+} in human and mouse primary VSMC. In high dose vitamin D-induced vascular calcification model, mice fed with low (0.02%) Mg^{2+} diet had severe aortic calcification which was reduced by 32% and 66% in mice fed with normal (0.2%) and high (0.5%) Mg^{2+} diets, respectively. Aortic CaSR protein expression was found to be reduced by 85% and 60% in mice fed with low and normal Mg^{2+} diets, respectively, compared to controls. Co-staining showed that CaSR expression was primarily reduced in calcified areas. High Mg^{2+} diet resulted in largely preserved aortic CaSR expression in mice.

Conclusions: These results collectively suggest that Mg^{2+} is the key CaSR agonist in VSMC for prevention of vascular calcification. Mg^{2+} deficiency results in reduced CaSR activity and expression, which can be restored by its supplementation. Mg^{2+} supplementation can potentially be used as a simple, safe and effective treatment for preventing vascular calcification in CKD.

Funding: NIDDK Support

SA-PO254

Quantitative Image Analysis Reveals the Benefits of Dapagliflozin on Glomerulosclerosis, Podocyte Effacement, and Kidney Fibrosis in the Spontaneously Diabetic Torii (SDT) Fatty Rat Model of Diabetic Nephropathy

Francois Briand,[1] Estelle Grasset,[1] Masami Shinohara,[5] Nicole Endlich,[2] Vedran Drenic,[2] Li Chen,[3] Mathieu M. Petitjean,[3] Blazej Dolicki,[4] Thomas D. Bel,[4] Yasushi Kageyama,[5] Thierry Sulpice.[1] *[1]Physiogenex, Escalquens, France; [2]Nipoka, Greifswald, Germany; [3]Pharmanest, Princeton, NJ; [4]Aiosyn, Nijmegen, Netherlands; [5]CLEA Japan Inc, Tokyo, Japan.*

Background: We aimed to optimize drug efficacy studies in the Spontaneously Diabetic Torii (SDT) fatty rat, a type 2 diabetic model, using quantitative image analysis of kidney. To demonstrate the accuracy of our imaging methods, dapagliflozin (DAPA) was evaluated in SDT fatty rats with unilateral nephrectomy (Unx).

Methods: Unx SDT fatty rats were fed a 0.3% salt diet and treated without or with DAPA for 10 weeks. Sham operated SDT fatty rats and Sprague Dawley (SD) rats were used as controls. Glomerular Filtration Rate (GFR) and urine parameters were measured at baseline, 5 weeks, and 10 weeks. Kidneys were collected at 10 weeks for histology and automated image analysis, including quantitative glomerulosclerosis and tubular impairments (Nephropath AI), Podocyte Exact Morphology Measurement Procedure (PEMP) and quantitative digital pathology of fibrosis (FibroNest platform).

Results: Sham rats showed higher proteinuria, urine albumin/creatinine ratio and KIM-1 levels (all $p<0.05$ vs SD). Those parameters were even higher in Unx rats (all $p<0.01$ vs sham). Hyperfiltration was only observed at baseline in sham rats (80% higher GFR, $p<0.05$ vs SD), while Unx rats showed a significant GFR decline from baseline to 10 weeks. In sham rats, Nephropath AI demonstrated higher number of dilated/atrophic tubuli and sclerotic glomeruli (all $p<0.01$ vs SD). Filtration slit density and filtration slit length measured by PEMP were significantly reduced, indicating podocytes effacement, while FibroNest demonstrated significant increase in phenotypic fibrosis composite scores. All these imaging parameters were significantly aggravated in Unx rats. DAPA significantly reduced hyperglycemia (-67% vs. untreated Unx rats), prevented the GFR decline ($p<0.05$ at 5 and 10 weeks) and reduced urine KIM-1 levels ($p<0.01$). DAPA significantly improved all imaging parameters and kidney inflammation (ED1 immunostaining).

Conclusions: Quantitative image analysis reveals the benefits of DAPA on glomerulosclerosis, podocytes effacement and kidney fibrosis in Unx SDT fatty rat. This experimental setting will help evaluating the efficacy of drugs targeting diabetic nephropathy.

SA-PO255

SGLT2 Inhibitors Attenuate Protein Abundance of Collectin Kidney 1 and Mannose-Binding Lectin in the Kidney and Liver in Mice with Experimental Diabetes

Mia Jensen,[1] Camilla Enggaard,[1] Steffen Thiel,[2] Yaseelan Palarasah,[3] Per Svenningsen,[1] Boye Jensen.[1] *[1]Unit for Cardiovascular and Renal research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark; [2]Department of Biomedicine, Aarhus University, Aarhus, Denmark; [3]Unit for Cancer and Inflammation Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark.*

Background: Diabetic nephropathy (DN) is a leading cause of end-stage renal disease. Sodium-glucose cotransport-2 (SGLT-2) inhibitors have significantly improved the treatment of DN and its cardiovascular complications. The mechanism behind the broad protection is elusive. We hypothesized that the lectin pathway of the complement system contributes to early kidney injury in DN. Here we investigate if 1) experimental diabetes in mice is associated selectively with increased collectin kidney 1 (CL-K1) abundance and binding, 2) if SGLT-2 inhibitors attenuate CL-K1 and complement activation, and 3) if a functional deletion of CL-K1 protects against diabetic kidney injury.

Methods: Streptozotocin (STZ) and vehicle were intraperitoneally injected in male wild-type (WT) FVB or CL-K1 knockout (KO) mice for 5 consecutive days to induce diabetes. Experiment 1: WT STZ(n=10) and WT vehicle (VEH)-treated(n=10) mice were sacrificed on day 14 and day 35. Experiment 2: WT STZ mice were orally treated with Dapagliflozin(n=10) or vehicle(n=10) for 10 days. Experiment 3: WT STZ(n=4), WT VEH(n=4), CL-K1 KO STZ(n=4), and CL-K1 KO VEH(n=4). Urine, plasma, and organs were collected. mRNA expression and protein abundance of complement products were determined by western blotting, qPCR, and RNAscope.

Results: STZ-treated mice exhibited increased plasma glucose, kidney weight, blood urea nitrogen, urinary excretion of albumin, and KIM-1. CL-K1 protein level increased significantly and progressively in kidney tissue and plasma but not in liver tissue in STZ-treated mice. MBL-C and MASP-1 increased in plasma following STZ. CL-K1 and MBL-C mRNA abundances increased in the kidney. Dapagliflozin lowered fasting plasma glucose (29.7 [5.50] vs. 33.3 [2.10] mmol/L,$p<0.01$) and protein abundance of CL-K1 in liver (0.38 ± 0.13 vs.1.0 ± 0.46 CL-K1/Beta-actin, $p<0.05$) and kidney (0.29 ± 0.34 vs.1.0 ± 0.52 CL-K1/Beta-actin, $p<0.05$), while corresponding mRNA levels were unchanged. CL-K1 KO did not affect kidney injury markers, but a trend toward lower levels of urinary excretion of albumin and KIM-1 was seen in STZ-treated CL-K1 KO mice compared to STZ WT.

Conclusions: CL-K1 increases in kidney and plasma with the progression of kidney injury, and SGLT-2 inhibitors may lower complement activation in diabetic kidneys.

Funding: Private Foundation Support

SA-PO256

Blocking Intracellular TXNIP Shuttling Attenuates Reactive Oxygen Species-Associated NLRP3 Inflammasome Activation Induced by Tubulointerstitial Fibrosis in Diabetic Kidney Disease

Li Wang, Bingbing Zhu, Shuang Liu, Yao Xingmei, Yuying Zhou. *Department of Nephrology, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China.*

Background: Accumulating evidence underscores the pivotal role of tubulointerstitial fibrosis (TIF) in the progression of diabetic kidney disease (DKD). TXNIP is an important regulatory protein that elicits the generation of reactive oxygen species (ROS) that involved in the fibrotic pathogenesis of DKD. However, the potential mechanism of TXNIP in DKD is not yet well understood.

Methods: RNA sequencing and RT-qPCR were used to detect the most significant expression of protein in high glucose-stimulated renal tubular epithelial cells (RTECs). Co-immunoprecipitation, ARE luciferase assay and chromatin immunoprecipitation assay were used to identify the transcriptional relationships between STAT6 and TXNIP. Immunofluorescence and western blot were used to detect the TXNIP shuttling. TXNIP-mediated NLRP3 inflammasome activation were examined via TXNIP siRNA and overexpression in vitro and knockdown in RTECs using AAV-shRNA in vivo. Correspondingly, the efficacy of Astragaloside IV (AS-IV), an active ingredient from traditional formula of Huangqi decoction, was examined in vitro and in vivo.

Results: We found that TXNIP was highly expressed in high glucose-stimulated RTECs and the renal tubules of patients with DKD. Experimental data showed that the TXNIP expression was positively associated with the development of TIF in DKD. p-STAT6 could bind to the promoter of TXNIP and promote its transcription in the nucleus and the interaction of STAT6 and TXNIP could enhance the NLRP3 inflammasome activation. Subsequent the TXNIP shuttling from nucleus to mitochondria increased the NLRP3-mediated TIF both in high glucose-stimulated renal tubular epithelial cells and in db/db mouse. Knockdown of TXNIP both in vitro and in vivo delayed the ROS associated inflammasome activation. Meanwhile, TXNIP was the target for Astragaloside IV to exert inhibitory effect on the STAT6/TXNIP/NLRP3-mediated inflammatory response.

Conclusions: These findings collectively substantiate a critical role of TXNIP shuttling to control inflammasome activation, and presenting AS-IV as a promising therapeutic ingredient for inhibiting TIF in DKD.

Funding: Private Foundation Support

SA-PO257

CircAkap7 Downregulation Promotes Renal Tubular Epithelial Cell Senescence in Diabetic Kidney Disease

Fenfen Peng, Yao Zeng, Yue Ji, Haibo Long. *Zhujiang Hospital of Southern Medical University, Guangzhou, China.*

Background: Diabetic kidney disease (DKD) exhibits an accelerated tubular epithelial cell senescent phenotype. Our previous studies showed that downregulation of circAkap7 promotes renal fibrosis in DKD.

Methods: Ultrasound mediated gene transfer of circAkap7 plasmids into the kidneys of db/db mice is used. Mouse primary renal tubular epithelial cells (mPTECs) was isolated and cultured in DMEM/F12 medium.

Results: As shown in Figure 1, the SA-β-gal activity and senescence markers P53, P21, and $P16^{INK4A}$ were significantly decreased in the db/db mice with circAkap7 overexpression. Two SASP factors, TGF-β1 and IL-6 were found to be decreased in db/db mice with circAkap7 overexpression. As shown in Figure 2, the mPTECs transfected with circAkap7 siRNA showed an increase in G1-phase cells and a decrease in S-phage cells. Knockdown of circAkap7 increased the level of SA-β-gal staining, P53, P21 and $P16^{INK4A}$ and renal injury marker NGAL, while circAkap7 overexpression decreased the SA-β-Gal activity and abolished the synthesis of P53, P21, and $P16^{INK4A}$ induced by the high-glucose. Medium derived from mPTECs transfected with si-circAkap7 can promotes the synthesis of fibronectin and α-SMA in fibroblast.

Conclusions: Downregulation of circAkap7 promotes renal tubular senescence in DKD.

Funding: Government Support - Non-U.S.

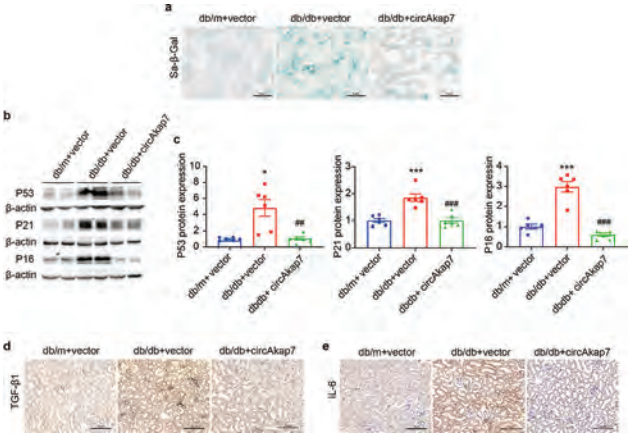


Figure1. In vivo expression of circAkap7 ameliorates renal tubular senescence in db/db mice.

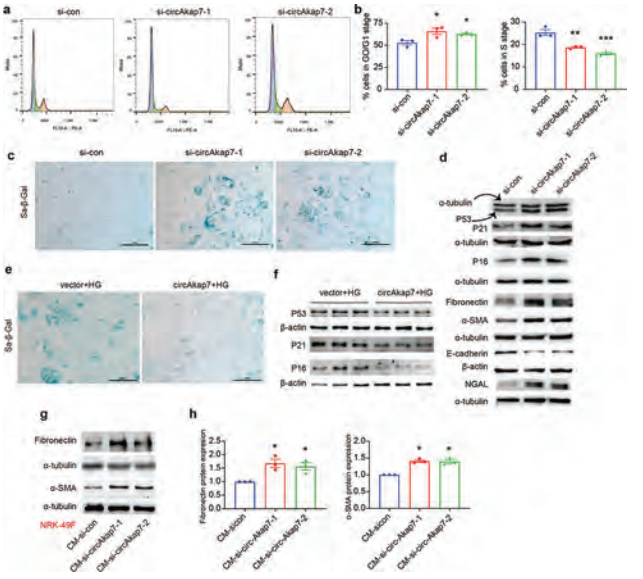


Figure2. CircAkap7 inhibits renal tubular epithelial cell senescence in vitro.

SA-PO258

Senolytics (Dasatinib/Quercetin) Inhibit Hedgehog Interacting Protein (Hhip)-Mediated Tubular Senescence in Diabetic Kidney Disease

Shiao-Ying Chang,[1] Min-Chun Liao,[1] Yuchao Pang,[1] Junzheng Peng,[1] Julie R. Ingelfinger,[2] John S. Chan,[1] Shao-Ling Zhang.[1] *[1]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Harvard Medical School, Boston, MA.*

Background: We recently reported that hedgehog interacting protein (Hhip) promotes tubular senescence-associated secretory phenotype in murine diabetic kidney disease (DKD) (*Diabetiologia, 2023*), the underlying mechanism(s) are not delineated. Here, we asked whether senolytics (dasatinib, D/quercetin, Q) could alleviate Hhip-mediated RPTC senescence in DKD *in vivo* and *in vitro*

Methods: The low-dose streptozotocin (LDSTZ)-induced diabetes in renal proximal tubules (RPTC)-specific *Hhip* transgenic (Tg) mice (*Hhip*-Tg) and their non-Tg littermates at the age of 10-week old were studied. Senolytics (D, 5 mg/kg and Q, 50 mg/kg) in combination were administered by gavage daily for three consecutive days every two weeks from 12 weeks until the mice were 24-weeks old. Vehicle-treated animals served as controls. Primary RPTCs and rat immortalized RPTC cells (IRPTCs) were used for *in vitro* studies.

Results: Diabetic mice displayed typical DKD characteristics (hyperglycemia, increased urinary albumin/creatinine ratio and glomerular filtration rate) and renal dysmorphology (renal hypertrophy, glomerulosclerosis and tubulopathy), and those features were more pronounced in diabetic Hhip-Tg (vs. non-Tg) mice. D/Q senolytics administration ameliorated DKD dysmorphology and renal tubular senescence as measured by heightened β-galactosidase activity in kidneys of diabetic mice. *In vitro*, excessive Hhip induced by overexpressing Hhip in RPTCs triggered the release of extracellular vesicles carrying Hhip, which facilitated RPTC turnover through accelerated cellular senescence, and fibrotic and apoptotic processes. In contrast, D/Q treatment reversed the effects of increased Hhip in RPTCs.

Conclusions: The treatment of senolytic D/Q prevents excessive Hhip-mediated RPTC senescence and DKD-related tubulopathy via the inhibition of Hhip carried by extracellular vehicles in DKD.

Funding: Government Support - Non-U.S.

SA-PO259

Transmembrane Protein 72, Expressed in the Distal Convoluted Tubule, May Play a Potential Role in Diabetic Kidney Disease

Jianteng Xie,[1,2] Min Lu,[1,2] Runli Jia,[1] Danfeng Liu,[1,2] Wenjian Wang.[1] *[1]Guangdong Provincial People's Hospital, Guangzhou, China; [2]South China University of Technology, Guangzhou, China.*

Background: Transmembrane protein 72 (TMEM72) is highly expressed in tubules of the kidney in patients with diabetic nephrology. This study is designed to explore the role and the potential mechanism of TMEM72 in the development of diabetic tubulopathy.

Methods: Serum TMEM72 concentration was tested in health control, patients with diabetes mellitus (DM) and diabetic kidney disease (DKD). The variation trend of TMEM72 was determined by immunohistochemistry on kidney tissues from patients in

different stage of DKD. Immunofluorescence staining was performed with TMEM72, SGLT2, NKCC2 and AQP2 to identify the expression site of TMEM72 in mice renal tubules. To investigate the potential cellular pathway that TMEM72 was involved, an immunofluorescence test was performed with TMEM72, LAMP1, Mito-tracker and Calnexin in cultured distal convoluted tubule (DCT) epithelial cells. Western blot was used to detect the activity of TMEM72 in HK2 cells following HG treatment.

Results: The concentration of serum TMEM72 was lower in DM and DKD groups compared to the health control (P<0.001). The expression of TMEM72 also decreased gradually in human kidney tissue of different stage of DKD following the progression of disease. Co-localization of TMEM72 and NKCC2 in immunofluorescence staining indicated that TMEM72 was mainly expressed in the lysosomes of distal convoluted tubule. In vitro, TMEM72 was markedly down-regulated in mouse tubular cell and HK-2 cells treated with high glucose. Overexpression or knock down of TMEM72 demonstrated a significant increased or decreased mitophagy in high glucose treated HK2. In vivo, tubules specific knock-out of TEME72 exhibited a significantly tubule injury evidenced by marked increase of KIM-1/Cr, NGAL/Cr, Albumin/Cr β-micro globin/Cr in the urine of mouse.

Conclusions: Our current study has revealed that TMEM72 may act as a novel participator in DKD by being involved in the renal tubular injury.

Funding: Government Support - Non-U.S.

SA-PO260

Transcriptomic Analysis of mRNA Expression in Peripheral White Blood Cells of Genes Encoding Circulating Proteins Associated with the Development of ESKD in Diabetes

Marcus G. Pezzolesi,[1] Katsuhito Ihara,[2,3] Eiichiro Satake,[2,3] Zaipul Md Dom,[2,3] Bozena Krolewski,[2,3] Andrzej S. Krolewski.[2,3] *[1]University of Utah Health, Salt Lake City, UT; [2]Joslin Diabetes Center, Boston, MA; [3]Harvard Medical School, Boston, MA.*

Background: Using global-untargeted proteomics, we recently identified 46 circulating proteins robustly associated the risk of development of end-stage kidney disease (ESKD) in individuals with Type 1 (T1D) or Type 2 diabetes (T2D) during 7-15 years of follow-up. In the present study, we performed transcriptomic analysis on mRNA to examine whether circulating levels of these proteins derive from expression of the risk-associated protein encoding genes in peripheral white blood cells (WBC).

Methods: RNA sequencing was performed on total RNA isolated from peripheral blood from a subset of individuals enrolled in the Joslin Kidney Study (23 T1D and 48 T2D). During 7-15 years of follow-up, 16 of these individuals developed ESKD and 55 remained without ESKD. The resulting sequencing reads were aligned to the GRCh38/hg38 reference genome and annotated using Ensembl (release 102). Differential gene expression analysis was then performed between controls and cases who progressed to ESKD during follow-up or had fast kidney function declining (eGFR slope <-5.0 ml/min/year).

Results: Transcriptome-wide, 4 out of ~22,000 genes (*GRB10*, *IGKV1-9*, *IGKV1-39*, and *NAV3*) were found to be differentially expressed between the two groups after correcting for multiple testing (Bonferroni-adjusted p $<2.26x10^{-6}$). Out of the 46 circulating proteins associated with risk of development of ESKD, 11 genes encoding these proteins were not expressed in WBC, 10 had low expression and 26 had moderate or high expression. Strikingly, and in contrast with our proteomic findings where concentrations of 10 ESKD risk-associated proteins in plasma collected at the same time as these WBC were significantly upregulated in cases relative to controls, expression of these genes was identical in those who progressed and those who did not progressed to ESKD.

Conclusions: These negative transcriptomic findings in WBC contrast with significant statistical differences in concentration of ESKD risk-associated proteins in plasma. These findings suggest that the high concentrations of ESKD risk associated proteins in circulation cannot be accounted for by increased transcription of these genes in WBCs.

Funding: NIDDK Support

SA-PO261

Molecular Mechanisms of Cobalt Chloride in the Treatment of Type 2 Diabetic Nephropathy

Tianyu Deng, Shiyue Yu, Xueqi Chen, Zhenyuan Han, Dechao Yan, Mingda Liu, Xiaoyan Wang. *Nanjing BenQ Medical Center, Nanjing, China*.

Background: Down-regulation of heme-oxygenases (HOs) induced by oxidative stress plays an important role in the pathogenesis of type 2 diabetic nephropathy (T2DN). COPP (cobalt chloride), a HO-1 agonist, has been used in experimental DN. To explore the underlying mechanism, caspase3, Gasdermin-E (GSDME), and other factors related to apoptosis and pyroptosis besides ROS-components were observed in the kidneys of type 2 DN mice with and without COPP treatment.

Methods: Male 7-week-old C57BL/6J mice were fed a 60% high-fat diet for 6 weeks, then injected intraperitoneally with STZ(60mg/kg/day) (DN) or vehicle (HFD) for 3 days. COPP at 3mg/kg was given to the STZ mice (DN+COPP) by weekly intraperitoneal injection (10 doses) while the background group (NFD) was given a 10% normal fat diet and vehicle injections until week 16 of the study (n=5-7/group).

Results: Fasting blood glucose levels in DN group(26.2±1.0, mmol/L) were higher than those in NFD(8.0±0.8) and HFD (8.7±0.6) groups but lowered slightly by COPP treatment (22.3±0.9). Serum creatinine (156.6±43.3, mmol/L) was higher than NFD(12.3±0.9) and HFD(21.9±6.1) groups but reversed after COPP treatment (65.8±9.7). Urinary albumin/creatinine exerts similar results in DN group(48.5±3.0, mg/g), NFD(3.0±0.6), HFD(20.7±5.2) groups and DN+COPP group (37.7±5.5). The glomerular basement membrane thickening and podocyte fusion seen in DN group by EM were reversed after COPP treatment. 8-OHdG, an oxidative stress index, increased (163.6±34.5, % of NFD, same as below) in the DN group and decreased after COPP treatment (130.8±22.6). HO-1(302.9±170.3) and PON1(63.0±8.1) was decreased in DN+COPP, after COPP treatment HO-1(701.7±171.1) and PON1(136.4±15.5) were reversed. Similarly, GSDME (139±7.2) and caspase 3(109.7±4.0) increased in DN group, and after COPP treatment GSDME (122.0±4.9) and caspase 3(100.7±2.3) were mitigated. In addition, BAX/Bcl-2, the key factor regulating apoptosis, increased in the DN group (159.0±21.6) and reversed after COPP treatment (94±6.3).

Conclusions: COPP may attenuate renal injury in type 2 diabetic mice by reducing apoptosis and pyroptosis along with its antioxidant effects.

Funding: Government Support - Non-U.S.

SA-PO262

Analysis of Single Urinary Extracellular Vesicles from Subregions of the Nephron as a Diagnostic Tool in Early Diabetic Nephropathy

Morgan Greig,[1] Indika V. Mallawaarachchi,[1] Jennie Z. Ma,[1] Clarissa J. Diamantidis,[2] Michael A. Harding,[1] Hayrettin Yavuz,[1] Luca Musante,[3] Michael Solga,[1] Samantha G. Upson,[1] Julia J. Scialla,[1] Uta Erdbruegger.[1] *[1]UVA Health, Charlottesville, VA; [2]Wake Forest University School of Medicine, Winston-Salem, NC; [3]University of Pennsylvania, Philadelphia, PA.*

Background: Urinary extracellular vesicles (uEVs) have been identified as early and sensitive biomarkers in kidney disease, however, their association with diabetic kidney disease (DKD) progression and DKD clinical traits is not yet clear. Characterization of uEVs may allow investigation into the relationship between uEVs of glomerular and tubular origin and distinct pathophysiological and clinical DKD phenotypes.

Methods: We attained uEVs from 24-hour urine collections in 116 adults with diabetes mellitus enrolled in the Simultaneous Risk Factor Control Using Telehealth (STOP-DKD). To determine uEV count, size and cargo, single EV characterization was performed via spectral flow cytometry (SFC) as a high throughput tool and SP-IRIS (Exoview R100) for small sample volumes. We used markers for CD26/DPP4(PT S1)+, CD35/CR1(podocyte)+, CD10/MME/NEP(PT S1,S2,S3)+, and tetraspanin, CD9(EV marker)+ labeled uEVs. Linear regression was used to assess the cross-sectional association of SFC data, kidney function and degree of microalbuminuria (UACR). SP-IRIS analysis compared a cohort of 10 healthy to 10 early DKD patients.

Results: Participants were 63.65±9.20 years of age; 50.4% female. Baseline eGFR was 81±22 ml/min/1.73m^2 and median UACR was 20.26(IQR 8.38 to 92.97mg/g). Higher counts of uEVs detected by SFC carrying DPP4 and MME were significantly associated with higher eGFR after adjustment for sex, race, age, log UACR and total urine creatinine. No markers demonstrated significant association with log UACR, and size was not considered further. SP-IRIS analyzed DPP4 and MME subpopulations captured by the CD63 and CD9 probes for exploration of small sample sizes. DPP4/Total Ratio was significantly higher in healthy patients when captured by CD63(p=0.0176), and results show sample size can be microscaled.

Conclusions: These results suggest that subgroups of tubular derived uEVs detected by SFC are associated with an increase in eGFR in a cohort of early DKD. However, tubular markers are also decreased in DKD when compared to HC. Further exploration is necessary to fully understand if these tubular derived uEVs derive from healthy tubular cells or are expressed more during tubular stress in early DKD.

Funding: Private Foundation Support

SA-PO263

Late Clinical-Stage Candidate Rilparencel's Effect on Kidney Function and Biological Pathways in a Type 2 Diabetes and CKD Patient Subset

Prakash Narayan,[1] Brooke Bauer,[1] Guido Filler,[2] Benjamin S. Freedman,[3] Howard Trachtman,[4] Joseph Stavas,[1] Emily L. Butler,[1] Andrew T. Bruce.[1] *[1]ProKidney, Winston-Salem, NC; [2]Western University, London, ON, Canada; [3]University of Washington, Seattle, WA; [4]Renal Strategies LLC, New York, NY.*

Background: Kidney cortical biopsy-derived rilparencel is a 1st-in-class autologous kidney epithelial cell platform being evaluated in late-stage clinical trials for patients with type 2 diabetes (T2D) & chronic kidney disease (CKD). Data from 2 Phase 2 studies suggest that kidney cortical injection of rilparencel may preserve estimated glomerular filtration rate (eGFR). In a proof-of-concept, limited retrospective cohort study we sought to evaluate biological pathways associated with rilparencel's effect on kidney function.

Methods: Banked rilparencel samples from 5 patients with T2D&CKD (NCT02836574) were analyzed with scRNAseq. Kidney cell types were identified with unsupervised clustering & projection on to the KPMP atlas. For each rilparencel cell

type, cell-level & pseudo-bulk differentially expressed genes (DEGs) were identified by Wilcoxon Rank Sum test & DESeq2, respectively, based on each patient's response to rilparencel, i.e. eGFR slope computed across 12 mo post-treatment. Biological pathways were identified with GO.

Results: KPMP-anchored molecularly profiled kidney cell types in rilparencel include glomerular parietal epithelial cells (PECs), adaptive proximal tubules (PT), ascending thin limb (ATL) & adaptive thick ascending limb-2 (TAL-2), distal convoluted tubule, connecting tubule & intermediate collecting ducts (DCT/CNT/IMCD). For each cell type, DEGs correlating with renal function were identified. Increased epithelial cell differentiation (PEC), negative regulation of inflammatory response genes (PT), increased expression of cell migration genes within Loop of Henle limbs & decreased cell adhesion (DCT/CNT/IMCD) appear to exhibit improved eGFR slopes.

Conclusions: In a limited retrospective cohort of T2D&CKD patients reparative & restorative pathways can be detected with rilparencel's effect on kidney function. Our approach might serve as a roadmap for unveiling the mechanism of action of cell-based therapies.

Funding: Commercial Support - ProKidney

rilparencel cell type	DEGs correlating with eGFR slope (0-12 mo)	biological pathway
PEC	TMEM220 (R~1, p<0.05)	increased epithelial cell differentiation
adaptive PTs	NETO2 (R~1, p<0.05)	reduced inflammation
ATL / adaptive TAL-2	SYTL2, TEX41, TINAG, ERBB4, CDHR1 (R~1, p<0.05)	increased cell migration
ATL / adaptive TAL-2	CNN3 (R~1, p<0.05)	increased cell migration
DCT/CNT/IMCD	ST14, CDH1, CPXM2, LINC02274, COL11A1, SAA2 (R~1, p<0.05)	decreased cell adhesion

Top. KPMP-defined cell types within rilparencel. Bottom. DEGs within each cell type correlating with kidney function & reparative & restorative pathways detected with rilparencel's effect on kidney function.

SA-PO264

C-reactive Protein Exacerbates Diabetic Kidney Disease through Smad3-ACSM3-Mediated Ferroptosis

Yifan Wang,[1] Yongke You,[2] Jianbo Guo,[1] Baoyi Shao,[1] Jianan Wang,[3] Haidi Li,[3] Hui Y. Lan,[4] Hai-Yong Chen.[1,5] *[1]School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [2]Department of Nephrology, Shenzhen University General Hospital, Shenzhen University, Shenzhen, China; [3]Anhui Medical University, Hefei, China; [4]Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China; [5]Department of Chinese Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China.*

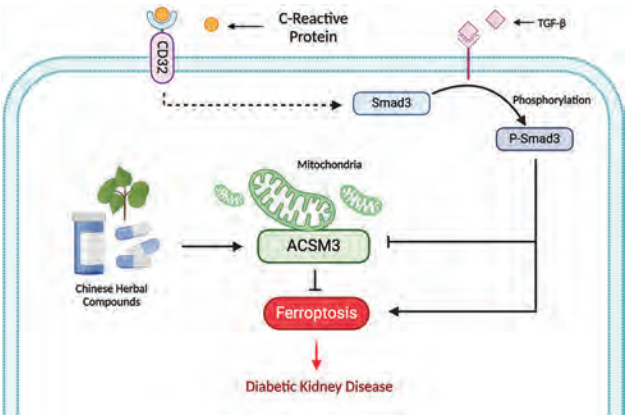
Background: Accumulated evidence indicated that C-reactive protein (CRP) enhances diabetic kidney disease (DKD) via Smad3 signaling pathway. Acyl-CoA synthetase medium-chain family member 3 (ACSM3) locates on the membrane of mitochondria to catalyze fatty acids. Ferroptosis is one type of cell deaths, featured with iron-dependent phospholipid peroxidation. This study determined whether CRP promotes DKD via Smad3-ACSM3 mediated ferroptosis and explore potential therapeutics.

Methods: CRP transgenic (Tg)×db/db, CRPtg×db/m, Smad3 knockout (KO)×db/db and Smad3 KO×db/m mice were used in the study. Differentially expressed genes in CRPtg×db/db mice were analyzed by RNA sequencing. To evaluate the protective role of ACSM3, AAVs with ACSM3 overexpression were administered into db/db mice. In vitro, HK-2 cells were treated with CRP with/without blocking of CRP receptor by CD32b antibody or treated with Smad3 inhibitor SIS3 were employed. Ferroptosis indexes were measured by IF, WB and qPCR. High through output molecular docking and cellular thermal shift assay (CETSA) were conducted to identify candidate compounds targeting ACSM3.

Results: Overexpression of CRP in diabetic mice significantly enhanced ferroptosis in kidneys. The RNAseq result indicated that ACSM3 level was significantly downregulated in CRPtg×db/db mice, compared to CRPtg×db/m mice. Interestingly, deletion of Smad3 alleviated ferroptosis and reversed ACSM3 deficiency in diabetic kidneys. Overexpression of ACSM3 in diabetic mice led to ferroptosis alleviation in kidneys. Consistently, the ferroptosis induced by CRP in vitro were reversed by SIS3, or the blockade of CRP receptor, or the overexpression of ACSM3. Furthermore, through the high through output molecular docking prediction and CETSA, we found that Rhapontin was one of potential compounds to suppress ferroptosis by targeting ACSM3.

Conclusions: Targeting on ACSM3 and SMAD3 have therapeutic potential for CRP induced ferroptosis in DKD.

Funding: Government Support - Non-U.S.



SA-PO265

Upregulated C1qa Signaling Antagonizes Glomerular Health in Aged Kidneys

Hyun Ji Lim, Tae Hoon Lee, Yoosun Joo, Young yoon Moon, Su Woong Jung, Yang Gyun Kim, Sangho Lee, Ju young Moon. *Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea.*

Background: Renal aging is closely associated with the prevalence of end-stage renal disease requiring renal replacement therapy and a higher incidence with lower recovery rates of acute kidney injury. The progressive structural changes and decline in glomerular number during renal aging contribute to a decrease in estimated glomerular filtration rate, an increase in albuminuria, and the development of age-related kidney diseases. Despite its clinical significance, the underlying mechanisms driving glomerular aging remain inadequately understood.

Methods: To investigate the specific changes occurring in glomeruli over time, we performed RNA-sequencing on glomeruli isolated from young (2 months old), intermediate (12 months old), and old (24 months old) mice. This approach allowed us to focus on the glomerular enrichment and identify age-related alterations. Our findings revealed significant alterations in genes associated with immune system processes, innate immune responses, inflammatory responses, and chemotaxis between 12- and 24-months old glomeruli.

Results: Among the upregulated complement pathways, the classical complement pathway stood out as the most prominent during glomerular aging. Specifically, the genes encoding complement 1 (C1) elements, including C1r, C1s, C1qa, C1qb, and C1qc, showed increased expression. These upregulated complement gene signatures were particularly observed in aged podocytes. Immunostaining of C1qa in human kidneys also demonstrated an age-dependent increase. To further investigate the role of C1qa in podocytes, we transduced C1qa lentivirus into podocytes and observed that the upregulated C1qa signaling significantly increased reactive oxygen species production and aggravated albumin permeability.

Conclusions: In summary, our transcriptome analysis has advanced our understanding of the molecular mechanisms involved in glomerular aging. Furthermore, it provides evidence for the crucial role of increased C1qa signaling in glomerular aging. These findings shed light on potential therapeutic targets and strategies to mitigate age-related kidney diseases.

SA-PO266

LXR/mTOR Signaling Axis Modulation: A Novel Approach for Regulating Autophagy in Diabetic Kidney Disease

Sahar Alkhansa, Sarah Almoussawi, Rachel Njeim, Sarah Hamade, Ghaith S. El Danaf, Nabih Habib, Fuad N. Ziyadeh, Assaad Antoine Eid. *American University of Beirut, Beirut, Lebanon.*

Background: Podocyte damage is crucial in diabetic kidney disease (DKD) pathogenesis. As podocytes have limited division capacity, autophagy is essential for their repair and homeostasis. Autophagy is described to be deregulated in diabetes. Yet, the underlying mechanism is still unclear. The mTOR complexes and oxidative stress have emerged as potential key players in mediating diabetes-induced autophagy imbalance. The role of the Liver-X-Receptor (LXR) in DKD has been mildly highlighted, but its role in autophagy and its crosstalk with key mechanistic pathways in DKD remains unclear. In this study, we investigate the role of the LXR/mTOR axis in autophagy and its possible link to podocyte injury in type 1(T1DM) and type 2 diabetes mellitus (T2DM).

Methods: An immortalized human podocyte cell line was used for our in vitro studies. Human podocytes were transfected with siRNA against LXR-α/β, Raptor, Rictor, or LC3B. For the in vivo model, T1DM and T2DM were experimentally induced in mice. Mice were treated with LXR activator T0 or DMHCA, mTORC1 inhibitor Rapamycin,

or the mTORC2 inhibitor JR-AB2-011. In parallel experiments, control mice were treated with autophagy inhibitor Hydroxychloroquine (HCQ). We assessed functional, histological, biochemical, and molecular parameters of the kidneys.

Results: Our results show that LXR activation attenuates podocyte and renal injury by inhibiting Nox4-dependent reactive oxygen species production and restoring autophagy. Mechanistically, this effect is mediated through the downregulation of both mTORC1 and mTORC2 activity. Interestingly, inactivation of either mTORC1 or mTORC2 pathways, both in vitro and in vivo, recapitulates the protective effects observed upon LXR activation, without altering the LXR pathway itself. Furthermore, our findings underscore the clinical relevance of autophagy signaling in DKD, as treatment with HCQ in control mice mimics the renal alterations seen in diabetes. Importantly, our study identifies mTORC2, in addition to mTORC1, as a key regulator of autophagy in the context of DKD.

Conclusions: This study highlights the interplay between LXR inactivation and mTORC1 activation, leading to autophagy dysregulation in DKD. Additionally, the activation of mTORC2 emerges as a critical factor in this process.

SA-PO267

Mapping Progression of Diabetic Kidney Disease (DKD) in Renin Adeno-Associated Virus (AAV) UNx db/db Mice Utilizing Time-Series RNA Sequencing

Adam B. Marstrand-Jørgensen,[1,2] Martin R. Madsen,[1] Ole Joergen Kaasboell,[3] Mette V. Østergaard,[4] Louise Dalbøge,[1] Michael Christensen.[1] *[1]Gubra A/S, Hørsholm, Denmark; [2]Kobenhavns Universitet, Kobenhavn, Denmark; [3]Tribune Therapeutics AS, Oslo, Norway; [4]Novo Nordisk A/S, Bagsvaerd, Denmark*.

Background: The adeno-associated virus-mediated renin overexpression (ReninAAV) uninephrectomized (UNx) db/db mouse model of diabetic kidney disease (DKD) recapitulates hallmarks of DKD complicated by hypertension. Gaps persist in our understanding regarding temporal patterns of glomerular gene expression and pathophysiology during hypertensive DKD. The present longitudinal study characterized glomerular transcriptome changes during disease progression in ReninAAV UNx db/db mice.

Methods: Female *db/db* (BKS.Cg-Dock7m +/+ Leprdb/J) received a single i.v. dose of renin-encoding AAV. Untreated db/m mice (BKS.Cg-Dock7m +/+ Leprdb/J) served as healthy controls. One week after AAV injection, ReninAAV mice underwent UNx and subsequently randomized and stratified into 4 groups according to fed blood glucose levels and body weight measured 3 weeks post-UNx. ReninAAV UNx mice were terminated at 4, 8, 12 and 16 weeks (w4-w12) after UNx. Healthy db/m mice were terminated at 12 weeks. Endpoints included urine and plasma biochemistry, kidney histology (Col1a1 and glomerulosclerosis scoring) and RNA sequencing of glomeruli isolated by laser-capture microdissection.

Results: ReninAAV UNx db/db mice showed onset of progressive glomerulosclerosis from w8 and albuminuria from w4. More than 3,000 differentially expressed genes (DEGs) were detected in glomeruli at each timepoint, including fibrosis, inflammation and glomerular injury markers. A subset of DEGs were also clinical drug targets. Shifting gene regulation was noted across all categories, including late downregulation of *Ednrb* and *Glp1r* and late upregulation of *Col1a1* and *Col3a1*. Additionally, temporal changes were seen in interacting targets, e.g. a shift from early temporary upregulation of *Adam17* to late upregulation of *Adam10*.

Conclusions: The ReninAAV UNx db/db mouse model of hypertensive DKD demonstrates progressive glomerulosclerosis and albuminuria paralleled by dynamic shifts in glomerular gene expression signatures. Notably, the identification of temporal patterns of gene expression provides novel insights into DKD pathophysiology and progression. This underscores the ReninAAV UNx db/db mouse as an applicable model of human DKD in preclinical target and drug discovery.

Funding: Commercial Support - Gubra A/S | Tribune Therapeutics AS

SA-PO268

Adenine Is a Marker and Potential Driver of Heart Failure in Cardiovascular-Kidney-Metabolic Syndrome

Ian M. Tamayo,[1] Hak Joo Lee,[1] Esmeralda Trevino,[1] Soumya Maity,[1] Richard Montellano,[1] Su-chi Lim,[2] Jan D. Lanzer,[3] Ravi Iyengar,[5] Petter Bjornstad,[4] Katherine R. Tuttle,[6] Vasan S. Ramachandran,[7] Ahmed Abdel-Latif,[9] Julio Saez-Rodriguez,[3] Jean C. Bopassa,[8] Kumar Sharma.[1] *[1]Center for Precision Medicine, University of Texas Health San Antonio, San Antonio, TX; [2]Clinical Research Unit, Khoo Teck Puat Hospital, Khoo Teck Puat, Singapore; [3]Heidelberg University, Faculty of Medicine, and Heidelberg University Hospital, Institute for Computational Biomedicine, Heidelberg, Germany; [4]Division of Nephrology, Department of Medicine and Section of Endocrinology, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO; [5]Department of Pharmacological Sciences and Institute for Systems Biomedicine, Icahn School of Medicine at Mount Sinai, New York, NY; [6]Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA; [7]Division of Cardiology, University of Texas Health San Antonio, San Antonio, TX; [8]Department of Cellular and Integrative Physiology, University of Texas Health San Antonio, San Antonio, TX; [9]Department of Medicine, University of Michigan, Ann Arbor, MI*.

Background: Cardiovascular-kidney-metabolic syndrome (CKM) is a risk factor for heart failure following the onset of diabetic kidney disease (DKD). Prior work identified a role for endogenous adenine in progressive DKD and urinary adenine to be predictive for progression. However, the underlying metabolic pathways of CKM are unknown.

Methods: Mass spectrometry imaging (MSI) and bulk tissue LC-MS were performed on human hearts from healthy and diabetic donors with left ventricular hypertrophy (LVH) (n = 5-6 per group). Sc-RNA-seq results from patient hearts with heart failure were analyzed for cell-specific changes in methylthioadenosine phosphorylase (MTAP) which produces adenine. Urinary adenine was measured in 661 participants with DKD as part of the Singapore Study of Macro-Angiopathy and Reactivity in Type 2 Diabetes (SMART2D), which tracked incident heart failure over a 10-year period. In addition, heart tissues from both a db/db diabetic mouse model (n=6 per group) and a high fat with L-NAME-treatment mouse model of heart failure (n=4-6 per group) were studied.

Results: In human hearts, MSI revealed an increase in adenine in coronary blood vessels from diabetics with LVH and was correlated with total heart weight. Sc-RNA-seq showed cardiac endothelial cells increase MTAP expression during heart failure. Results from the SMART2D studies show urinary adenine improves prediction of heart failure among DKD patients (unadjusted HR 1.54, 95% CI 1.15-2.05, adjusted 1.56, 95% CI 1.13-2.16). In the HFD+L-NAME mice heart tissues, vascular adenine and MTAP gene expression were increased. In db/db mice, urinary adenine correlated with heart adenine expression. Also, inhibition of MTAP in mice reduced urinary and vascular heart adenine, reduced heart size, and improved echocardiogram function.

Conclusions: Patients with CKM syndrome face a risk for both heart and kidney disease. MSI of human and mouse heart tissue revealed adenine to be localized to coronary blood vessels and intervention studies demonstrate a key role for adenine to mediate diabetic heart dysfunction. Taken together, adenine presents as a potentially actionable target in treatment of CKM syndrome.

Funding: Other NIH Support - K.S. is supported by UO1DK114920. K.R.T. is supported by NIH research grants R01MD014712, U2CDK114886, UL1TR002319, U54DK083912, U01DK100846, OT2HL161847, UM1AI109568, Veterans Affairs Support, Private Foundation Support

SA-PO269

Plasma and Urine Degradome Integration Reveals Sexual Dimorphic Prognostic Biomarkers for ESKD in Type 1 Diabetes (T1D)

Michael Merchant,[1] Gavin E. Arteel,[3] Daniel W. Wilkey,[1] Lauren T. Adams,[1] Rachel G. Miller,[2] Panayiotis Benos,[4] Tina Costacou.[2] *[1]University of Louisville School of Medicine, Louisville, KY; [2]University of Pittsburgh School of Public Health, Pittsburgh, PA; [3]University of Pittsburgh School of Medicine, Pittsburgh, PA; [4]University of Florida Health, Gainesville, FL*.

Background: DKD is a highly prevalent, severe microvascular T1D complication associated with altered expression/turnover of matrisomal proteins. Proteomics has identified several candidate surrogate biomarkers for DKD progression, but most studies did not consider urine/plasma proteome integration or sexual dimorphic responses. We hypothesized integration of plasma/urine low molecular weight proteome (degradome) could reveal sex-dependent differences associated with T1D ESKD incidence.

Methods: Paired urine & plasma samples for eight age/sex matched ESKD incident cases and non-ESKD controlswere randomly selected from the Pittsburgh Epidemiology of Diabetes Complications (EDC) T1D study biorepository. Samples were shipped to the University of Louisville and processed for degradome analysis using high resolution mass spectrometry in a data dependent analysis (DDA) fashion. De novo spectral assignments used PeaksX software. Uni-/multi-variate analysis compared feature abundances ($p<0.05$ for significance). MatrisomeDb and TopFinder assigned matrisome composition

and imputed likely protease activity. Comparisons were made using XIC areas for (1) individual peptides, (2) summed related, overlapping peptide sequences (degradome domains) and (3) peptides compiled for parent proteins. Exploratory confirmation studies of parent protein abundance were conducted by ELISA.

Results: More than 22,000 peptides, corresponding to 955 parent proteins were observed. 1,792 plasma and 1,041 peptides were observed in more than 50% of the samples with many unique to plasma (11) or urine (69). 191 matrisomal proteins were identified including known T1D DKD markers (COL1A1, BGN, AGT, TNFSF12, and EGF). Significantly enriched imputed proteases included MMP12, MMP7, MMP3, and MMP14. Fragments of fifteen proteins including PGRMC1, ORM1, A1BG, AGT, and APOA2 distinguished all cases from controls. Sexual dimorphic effects were observed for SerpinD1, MGP, AGT and EGF. EGF ELISA confirmed urine EGF degradome findings.

Conclusions: T1D DKD is associated with plasma and urinary degradomic changes observable ~12 yrs before ESKD onset. These differences may provide mechanistic insights into DKD progression and lead to novel surrogate diagnostic and target engagement biomarkers for ESKD intervention.

Funding: NIDDK Support, Other NIH Support - DK130294, AA028436, GM113226, ES030283

SA-PO270

Candidate Gene Product for Diabetic Nephropathy Protein 4.1O Locates to Ribosomes and Silences C-Myc Transactivation

Lorenz Sellin, Anica D. Biermann, Theresia Vienken, Lars C. Rump, Dennis Sohn, Eva Koenigshausen. *Heinrich-Heine-Universitat Dusseldorf, Dusseldorf, Germany*.

Background: Protein synthesis and its control are an important contributor to the pathogenesis of diabetic nephropathy. Previously FRMD3 coding for Protein 4.1O was identified as a potential target gene causing diabetic nephropathy in type 1 diabetes in a GWAS of the north American population. We were interested in the cellular functions of the Protein 4.1O.

Methods: Protein 4.1O isoforms and mutants were expressed HEK 293T cells and cos7 cells. Subcelluar fractionation was performed to track the appearance of Protein 4.1O and its mutants using a ultracentrifuge with 186.000xg. The samples of the different cellular compartments were subjected to SDS-PAGE and western blot analysis. Cos7 cells expressing Protein 4.1O were stained for Protein 4.1O and cellular organell markers by appropriate antibodies. Secondary antibodies with immunofluorecent dyes were used for visulization with an immunofluorecent microscope. Luciferase reporter assays were used to assess the c-myc transactivation in the presence of increasing doses of Protein 4.1O.

Results: Protein 4.1O its isoforms and mutants were detected in the ribosomal compartment by western blot which was generated by cellular farctionation. The rps3 was used as a positive control for adequate ribosomal preparation. By immunofluorecence Protein 4.1O was detected in the cytosol, ER and in submebranous regions. Protein 4.1O mutants were enriched in the nucleus sparing the nuceoli. Luciferase reporter assays show a dose dependent reduction for c-myc transactivation by Protein 4.1O.

Conclusions: Protein 4.1O can be deteced in the ribosomal fraction by subcellular fractionation with cosedimentation with established ribosomal markers. Immunofluorecent imaging confirms Protein 4.1O apperance in the ER. Increasing doses of Protein 4.1O silence c-myc transactivation in a dose dependet fashion. These finding shed new light on the potential cellular signficance of Protein 4.1O in the pathomechanism of diabetic nephropathy.

Funding: Private Foundation Support

SA-PO271

Identifying Key Genes and Mechanisms in Active Vitamin D Treatment for Diabetic Kidney Disease

Gao Ping. *Zhongnan Hospital of Wuhan University, Wuhan, China*.

Background: Diabetic kidney disease (DKD) presents a healthcare challenge with limited treatments. Active vitamin D may address DKD-related fibrosis, but its mechanisms are unclear

Methods: Utilized scRNA-Seq data from DKD mice treated with calcitriol and bulk RNA data from GEO. Employed Mendelian randomization and enrichment analyses to explore gene-immune cell interactions. Validated key gene expression with scRNA-Seq and GSE30529. Assessed renal function association with NephroseqV5 and confirmed protein expression with the Human Protein Atlas

Results: Active vitamin D reduced proliferative cells. Enrichment analyses highlighted FoxO signaling's role. SUMO3 and CD74 emerged as potential markers correlated with immune infiltration. Significant correlations found between SUMO3, CD74, creatinine levels, and eGFR. Confirmed higher SUMO3 and CD74 protein expression in DKD

Conclusions: Increased SUMO3 and CD74 expression in DKD is associated with active vitamin D treatment, affecting fibrosis via the FoxO pathway. They could serve as DKD protection markers

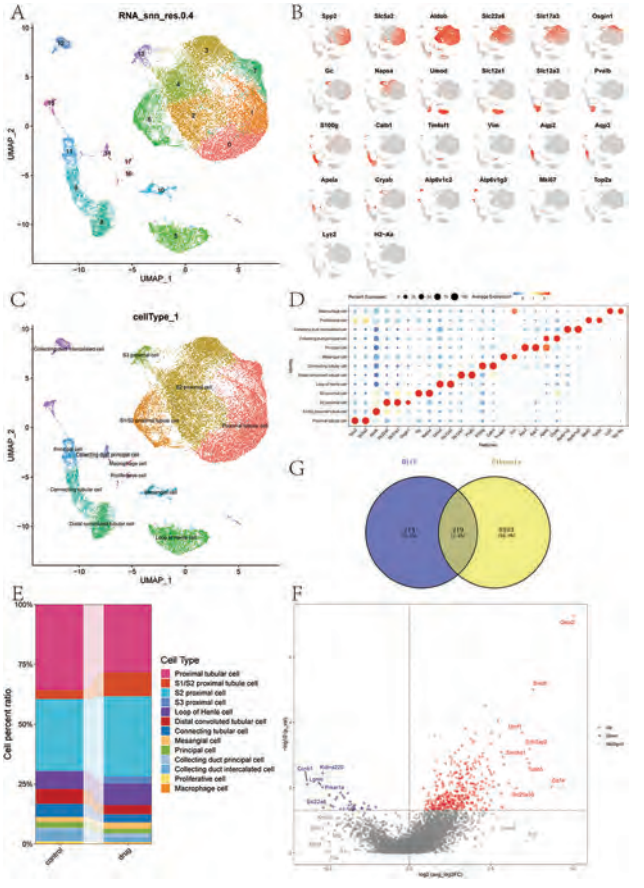


Figure 1. Cell Annotation and Analysis

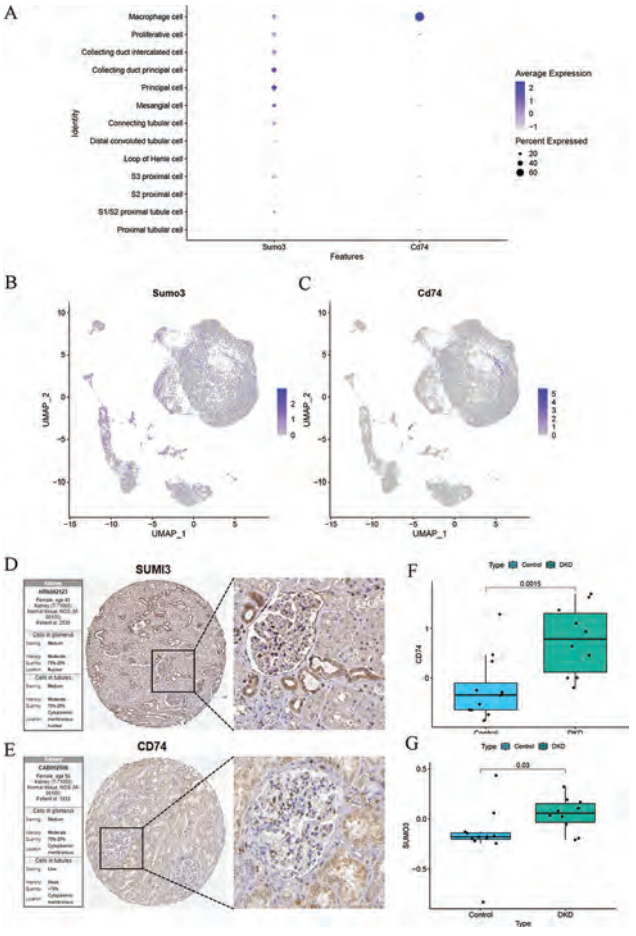


Figure 2. Gene Expression and Verification

SA-PO272

Effects and Dynamics of D-alanine under Diabetic Conditions

Tomonori Kimura,[1] Shinsuke Sakai,[1] Masashi Mita,[2] Masayuki Mizui,[1] Yoshitaka Isaka.[1] *[1]Osaka Daigaku, Suita, Japan; [2]Kagami Inc., Ibaraki, Japan.*

Background: D-Alanine, a rare enantiomer of alanine, protects from viral infections and mediates renal gluconeogenesis through the transcriptional network of circadian clock. These features of D-alanine are associated with the diabetic conditions; the aberrant circadian rhythm is a feature of diabetes, and diabetes is a worsening factor for Covid-19. This study investigated the effects and dynamics of D-alanine in the diabetic conditions.

Methods: The blood and urinary levels of D-alanine in diabetic model mice and in patients with diabetic kidney disease were measured using two-dimensional high performance liquid chromatography system. Gluconeogenetic activity of D-alanine was analysed using glucose production assay in *ex vivo*-cultured kidney cells. Glucose tolerance test was performed in mice treated with D-alanine.

Results: The circadian rhythm of D-alanine, which is clearly present in mice, was lost in mice model of diabetes. The urinary excretion profile of D-alanine was abnormal in patients with diabetic kidney disease. Like normal kidney, D-alanine induced gluconeogenesis in kidney from diabetic model mice. While treatment of D-alanine induced the transient increase of blood glucose level, repetitive treatment of D-alanine did not worsen the glucose tolerance.

Conclusions: D-Alanine also acts on the kidney from diabetic mice, whereas treatment of d-alanine does not worsen the diabetic conditions. D-Alanine may provide a therapeutic option for diabetes through the correction of circadian rhythm and treatment of viral infections.

SA-PO273

Expression and Distribution of Different Protein Kinase A Isoforms in Healthy and Diseased Kidneys

Sally S. Prueschenk,[1] Susan Taylor,[2] Jens Schlossmann.[1] *[1]Universitat Regensburg Fakultat fur Chemie und Pharmazie, Regensburg, Germany; [2]University of California San Diego School of Medicine, La Jolla, CA.*

Background: Diabetic nephropathy (DN) is a major universal problem caused by hyperglycaemia and might require dialysis or renal replacement. Still, the signalling events causing diabetic kidney disease and the effective treatment options are poorly understood. Alterations in the signalling of cyclic nucleotides and its regulated kinases might be involved in the development of this disease. Protein kinase A (PKA) signalling pathways are known to modulate extracellular matrix metabolism in diabetic kidneys. Multiple isoforms of PKA regulatory and catalytic subunits exist, leading to functional specificities of this kinase. However, localization of the specific PKA subunits, as well as other signalling proteins involved in this pathway, still need to be explored comprehensively. PKA, which is activated through cAMP, was described to exert antifibrotic effects and might therefore be important in prevention of fibrosis or DN. The aim of our project is to get an overview about distribution pattern of different PKA subunits in various cell types of the kidney. Furthermore, amount of PKA expression in healthy and diabetic kidneys is compared.

Methods: Type 1 diabetes was induced with streptozotocin in wild-type (WT) and endothelial NOS knockout (eNOS-KO) mice for 12 weeks. Kidneys were analysed by immunohistochemistry and stained with specific antibodies for different PKA subunits and markers for specialized renal cell types. Amount of catalytic subunit expression was quantified and compared between healthy and diabetic kidneys.

Results: The catalytic subunits PKA-Cα and PKA-Cβ reveal a different expression pattern in different segments of the kidney and interestingly the intracellular localization varies. Furthermore, PKA-Cα seems to be the predominant isoform in a lot of cell types. We also observe an altered amount of catalytic subunit expression in diabetic kidneys compared to healthy kidneys.

Conclusions: Our data show that catalytic subunits of PKA reveal a different distribution pattern in specialized cell types of the kidney as well as a different intracellular localization. Furthermore, the amount of catalytic subunit expression varies between healthy and diabetic kidneys. Therefore, PKA might play an important role in pathophysiology of DN and targeting the PKA signalling pathway could be a potential treatment approach.

Funding: Government Support - Non-U.S.

SA-PO274

5-Lipoxygenase Inhibition Ameliorates Diabetic Kidney Disease by Attenuating Renal Tubular Epithelial Cell Ferroptosis

Min Heui Ha, Hyun-Ju An, Min ji Sung, Hyeyun Jeong, Jihyun Baek, So-young Lee, Yu ho Lee. *CHA University Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea.*

Background: The enzyme 5-lipoxygenase plays a pivotal role in the conversion of arachidonic acid into 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which is a key source of lipid peroxides and leukotrienes. This study aims to elucidate the pathophysiological implications of 5-lipoxygenase in diabetic kidney disease (DKD), focusing on its impacts on lipid peroxidation and tubular cell ferroptosis.

Methods: HKC-8 cells, a human-derived renal proximal tubular cell line, was used to perform in vitro experiments. Diabetes induction in male C57BL/6J mice was achieved through streptozotocin injection. Zileuton was used to inhibit 5-lipoxygenase activity.

Results: Hyperglycemic stimuli upregulated the expression of 5-lipoxygenase both in HKC-8 cells. The overexpression of 5-lipoxygenase aggravated hyperglycemia-induced increases in the expression of profibrotic cytokines and reactive oxygen species (ROS) production, while its suppression mitigated these detrimental effects. High glucose also led to downregulations of glutathione peroxidase 4 (GPX4) and upregulations of Acyl-CoA synthetase long chain family member 4 (ACSL4), ferritin heavy chain 1 (FTH-1), and malondialdehyde (MDA), indicating the activation of pro-ferroptotic pathways. The overexpression of 5-lipoxygenase exaggerated hyperglycemia-induced ferroptotic cell death, which is attenuated by the inhibition of 5-lipoxygenase or ferrostatin-1 treatment. Additionally, streptozotocin-induced diabetic mice exhibited worse kidney function and interstitial fibrosis in association with decreased GPX4 and increased ACSL4 and FTH-1 levels compared to normoglycemic mice. Zileuton administration significantly ameliorated these hyperglycemia-induced kidney dysfunction and ferroptosis activation.

Conclusions: These findings demonstrate the central role of 5-lipoxygenase in intracellular lipid peroxidation and subsequent tubular cell ferroptosis under sustained hyperglycemic conditions. Inhibition of 5-lipoxygenase not only mitigates ferroptotic tubular cell death but also alleviates hyperglycemia-induced renal dysfunction. This suggests that 5-lipoxygenase could serve as a potential therapeutic target for the treatment of DKD.

SA-PO275

DNA Methyltransferase Inhibitor Alleviates Kidney Inflammation and Injury by Reversing DNA Hypermethylation-Associated Klotho Suppression in Diabetic db/db Mice

Qianling Liu, Xiaoyan Li, Jinjin Fan, Wei Chen. Dept of Nephrology, The First Affiliated Hospital, Sun Yat-sen University. *Sun Yat-Sen University, Guangzhou, China*.

Background: Klotho is a well-known anti-aging gene with anti-inflammatory effects. The renal expression of klotho is reduced both in patients with diabetic kidney disease (DKD) and diabetic mice. However, its mechanism is unclear. Studies have indicated elevated DNA methylation levels in the klotho promoter region of the kidney in DKD patients. Since DNA methylation can suppress gene expression, we speculate whether demethylation treatment can alleviate renal inflammation and improve DKD by upregulating renal klotho expression?

Methods: Male diabetic db/db (C57BLKS/J-LepR^{db}/LepR^{db}) mice and age-matched wild-type (BKS) mice were utilized in the study. At 8 weeks of age, db/db mice were given intraperitoneal injection of the DNA methyltransferase inhibitor 5-azacytidine (1 mg/kg body weight or 2 mg/kg body weight) or saline as control every other day. After 12 weeks of treatment, the blood, urine and kidney samples were collected for measurements.

Results: The renal expression of klotho in db/db mice is significantly reduced, along with an increase in DNA methylation levels in the promoter region. 5-azacytidine reduced the renal klotho DNA methylation level and increased klotho expression in db/db mice. This indicates that DNA methylation is involved in the downregulation of klotho in the kidney of DKD. In db/db mice, the renal expression levels of NF-κB and its downstream inflammation-related genes are elevated in db/db mice.5-azacytidine alleviated the renal expression of these inflammatory mediators. It also alleviated the activation of kidney inflammasome and macrophage infiltration. KEGG enrichment analysis of the RNA sequencing results showed that the differentially expressed genes were mainly enriched in NF-κB and TNF signaling pathways. In addition, 5-azacytidine concentration-dependently reduced serum levels of glucose and improved systemic insulin sensitivity. The urinary albumin excretion and serum creatinine in db/db mice were markedly decreased. This was accompanied by alleviation of glomerular hypertrophy, mesangial matrix expansion, glomerular basement membrane thickness and the extent of foot process effacement.

Conclusions: DNA methyltransferase inhibitor could alleviate renal inflammation and improve DKD by reversing DNA hypermethylation-associated klotho suppression in diabetic db/db mice.

SA-PO276

Dapagliflozin Significantly Suppresses Glomerular Hypertrophy in Rats with Type 2 Diabetes

Yuri Ishizaki, Masao Kikuchi, Koichi Kaikita, Shouichi Fujimoto. *Miyazaki Daigaku, Miyazaki, Japan.*

Background: Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor developed for the treatment of type 2 diabetes mellitus (DM), is a clinically very effective drug that inhibits the progression of chronic kidney disease with or without type 2 DM. However, the underlying mechanisms are unknown. We performed a histological evaluation to explore the renoprotective effects of SGLT2 inhibitors.

Methods: Twenty-four male SDT fatty rats, a model of type 2 diabetes, were divided into four groups: sham + placebo group (n=6), sham + dapagliflozin (dapa, 1.5 mg/kg/day) group (n=6), uni-nephrectomy (UNx) + placebo group (n=6), and UNx + dapa group (n=6). UNx or sham surgery was performed at week 6, rats were euthanized at week 12, and kidneys were harvested for histopathological evaluation. The number and size of podocyte nuclei were determined using Wilms tumor 1 (WT1) immunofluorescence staining, and glomerular tufts were estimated using the podocyte cytoplasmic marker glomerular epithelial protein 1 (GLEEP1) immunoperoxidase. Thirty glomeruli per rat were selected and evaluated using an image analyzer.

Results: Dapagliflozin significantly reduced glomerular hypertrophy in both the sham surgery and UNx groups (P<0.0001 and P=0.0099, respectively). However, the suppression was smaller in the UNx group. There were no significant differences in the number or density of podocytes.

Conclusions: Dapagliflozin significantly suppressed glomerular hypertrophy in a diabetic rat model. It was suggested that the renoprotective effect of dapagliflozin may be mediated through inhibition of glomerular hypertrophy.

SA-PO277

Inhibition of D-amino Acid Metabolism May Improve Glucose Metabolism via Reduction of Insulin Resistance

Eriko Hayashi, Keisuke Sako, Kiyoaki Ito, Shinji Kitajima, Ichiro Mizushima, Norihiko Sakai, Miho Shimizu, Yasunori Iwata. *Kanazawa Daigaku, Kanazawa, Japan.*

Background: D-amino acids are optical isomers of L-amino acids, and D-amino acid oxidase (DAO) is an enzyme that degrades certain D-amino acids. Risperidone, one of the major drug for schizophrenia, is also known to inhibit DAO. Previously, we reported a lower incidence of eGFR decline in the risperidone group in patients with schizophrenia, suggesting a renoprotective effect of risperidone via DAO inhibition. However, the significance of DAO activity inhibition in the pathogenesis of other diseases is unknown. We recently found that treatment with risperidone in type 1 diabetic mice model reduced fasting and postprandial blood glucose levels. Therefore, we further investigated the effect of risperidone on insulin resistance.

Methods: We administered risperidone to 7-week-old male C57BL/6J(B6) mice, non-diabetic mice, and DAO activity-deficient (DAO-KO) mice. We measured body weight, blood glucose levels, insulin levels, amount of food intake, urinary glucose levels, and urine volume. *In vitro*, we used C2C12 cells, a cell line derived from mouse rhabdomyosarcoma muscle. C2C12 cells were stimulated with risperidone at concentrations of 1 nM, 10 nM, and 50 nM. Glucose uptake experiments were performed to evaluate the glucose uptake capacity of the cells.

Results: Among B6 mice, administration of risperidone showed no significant change in body weight, blood glucose levels, insulin levels, amount of food intake, urinary glucose levels, or urine volume. However, in the glucose tolerance test, the risperidone-treated group showed decreased blood glucose at 0, 30, 60, 120, and 180 minutes. In addition, insulin levels also decreased at 0 minutes($p<0.05$). In DAO-KO mice, blood glucose levels decreased at 120 and 180 minutes. Insulin levels also showed a decreasing trend. These results indicated the potential role of risperidone via DAO inhibition in improving insulin sensitivity. In the insulin tolerance test, blood glucose levels were decreased in B6 mice treated with risperidone at 45 and 60 minutes ($p<0.05$), while no significant difference was observed in DAO-KO mice. *In vitro*, glucose uptake was enhanced in the risperidone groups at 1 nM and 10 nM concentrations ($p<0.05$).

Conclusions: Risperidone, an inhibitor of DAO metabolism, may improve insulin resistance.

Funding: Government Support - Non-U.S.

SA-PO278

Effects of Global SGLT2 Knockout on Heart Failure with Preserved Ejection Fraction

Margaret E. Fain,[1] Sol Misener,[1] Yalu Zhou,[1] Thomas Rousselle,[2] Valeria R. Mas,[2] Susan E. Quaggin.[1] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]University of Maryland School of Medicine, Baltimore, MD.*

Background: Until recently, there were no effective regimens for heart failure with preserved ejection fraction (HFpEF); however, clinical data from the EMPEROR-Preserved trial has shown that sodium glucose cotransporter 2 inhibitors (SGLT2is) reduce hospitalization and mortality in HFpEF patients. However, the mechanism(s) responsible for cardioprotection following inhibition of a kidney-restricted SGLT2 cotransporter is incompletely known. However, off- versus on- target drug effects remain unclear, and a clear explanation would allow for more directed drug therapy development.

Methods: To investigate the effect of SGLT2i on-target drug action, we used the SweetPee (SP) *Slc5a2* loss-of-function model on a high fat diet (HFD) L-NAME model of HFpEF to model the effects of on-target Sglt2 inhibition in new onset HFpEF. 8-10-week-old SP or wild type (WT) mice were maintained on either 60% HFD+L-NAME (0.5 g/L) or normal diet (ND) for 8 weeks. The animals were monitored every two weeks with echocardiography, blood pressure measurements, and weight surveillance, and were also tested for cardiovascular function using an exercise tolerance test before sacrifice and harvesting. The lung wet-to-dry weight ratio was also recorded in these animals as evidence of pulmonary edema.

Results: Echocardiography data showed no significant difference in ejection fraction, as is expected in HFpEF condition; however, the WT HFD+L-NAME group showed a trend towards an increase in E/e' relative to the SP HFD+L-NAME group, indicating an increase in left ventricular filling pressure which is a hallmark of heart failure. Furthermore, WT HFD-LNAME trended towards a higher systolic and diastolic blood pressure and lung wet-to-dry weight ratio and a decrease in running distance as measured via treadmill. These changes show that the SP genotype was protective against incipient HFpEF as induced by an HFD-L-NAME model.

Conclusions: These results show promise that cardioprotection observed in patients stems from on-target drug inhibition of the SGLT2 cotransporter. Future directions will identify potential molecular pathways underlying protection, as well as distinguish on-target from off-target effects.

Funding: NIDDK Support

SA-PO279

CDA1(TSPYL2) Deficiency Attenuates Kidney Fibrosis and Inflammation in db/db Diabetic Mice

Jiali Tang, Minling Huang, Tieqiao Wu, Mark E. Cooper, Zhonglin Chai. Diabetes Dept. *Monash University Faculty of Medicine Nursing and Health Sciences, Melbourne, VIC, Australia*.

Background: Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease worldwide, which increases morbidity and mortality in diabetes. Targeting Cell Division Autoantigen 1 (CDA1, also known as Tspyl2) has been demonstrated to retard diabetes-associated renal injury in type1 diabetes mouse models. However, whether such beneficial effects would extend to type 2 diabetes (T2D) is unknown.

Methods: This study investigated the effect of global genetic deletion of CDA1 on the development of DKD in a T2D mouse model. We generated a db/db CDA1 knockout (KO) mouse strain, assessed their kidney function and performed morphometric analysis at 16 weeks of age. To explore potential molecular mechanisms underlying the effects of CDA1 deficiency in the diabetic kidney, transcriptomic and proteomic analyses were performed on the renal cortex of these mice (n=6-10 mice/group).

Results: Deletion of CDA1 significantly reduced diabetes-induced albuminuria by ~40%, and normalized mesangial expansion and collagen deposition, without affecting glucose, body weight, or lipid levels. The expression levels of renal profibrotic and proinflammatory genes were increased in the db/db diabetic mice, such as collagens I, III and IV, fibronectin, alpha-smooth muscle actin, vascular cell adhesion molecule 1, monocyte chemoattractant protein 1, tumour necrosis factor-alpha and interleukin 6. These diabetes-induced changes were attenuated in db/db CDA1 KO diabetic mice to levels similar to those seen in non-diabetic db/h control mice. As observed in the previous studies using STZ-diabetes models, CDA1 deficiency reduced the gene expression levels of TGF-β ligands and its receptors in the diabetic kidney. These results demonstrate the anti-fibrotic and anti-inflammatory effects of CDA1 deletion. Transcriptomic and proteomic analyses confirmed these effects and revealed underlying potentially injurious pathways, such as the TGF-β and NFκB pathways, as well as complement/coagulation cascades, cellular senescence and other relevant pathways.

Conclusions: These results demonstrate the efficacy of targeting CDA1 in reducing renal injury as seen by targeting relevant proinflammatory and profibrotic pathways in the T2D model of db/db mice, thereby confirming that CDA1 is a promising therapeutic target for DKD in T2D.

Funding: Government Support - Non-U.S.

SA-PO280

Oral Butyrate Reduces Progression of Kidney Damage in a Diabetic Kidney Disease Mouse Model

Maria Novella Nicese, Angela Koudijs, Reshma Lalai, Cristina Avramut, Sander Kooijman, Roel Bijkerk, Bernard van den Berg, Joris I. Rotmans. *Universiteit Leiden, Leiden, Netherlands*.

Background: Patients with diabetic kidney disease (DKD) display an altered gut microbiome composition when compared to healthy subjects, with a lower prevalence of short chain fatty acids (SCFAs)-producing bacteria. Such reduction might exacerbate DKD, since SCFAs, including butyrate, are associated with health benefits. For this reason, we hypothesized that oral butyrate supplementation reduces DKD progression in mice.

Methods: For this study, L-NAME dissolved in drinking water was administered to diabetic BKS *db/db* male mice (80/mg/kg/day) for 4 weeks to accelerate DKD progression. Together with L-NAME, mice also received either standard diet or food with 5% sodium butyrate (n=10 per group), starting at the same time. In this period, blood pressure, glomerular filtration rate (GFR), besides total body water, glycemia and albuminuria were monitored during follow up period. After 4 weeks, animals were sacrificed whereupon blood samples and organs were collected.

Results: In animals fed with regular diet, L-NAME caused a reduction in GFR of 17% at 3 weeks, when compared to baseline. In contrast, mice treated with butyrate did not show any decline in GFR. Furthermore, mice on standard diet showed a significant increase in albuminuria when compared to baseline (p=0.03), which was not the case for the mice that received butyrate (p=0.5). Such difference in kidney function might explain the difference in total body water, which was higher in mice fed with regular diet (p=0.03). Interestingly, glycemia and blood pressure were comparable between groups, suggesting that other mechanisms underlie the effect of butyrate on kidney function. Analysis of kidney biopsies revealed smaller glomeruli (p=0.03) and less mesangial expansion (p=0.0082) in mice treated with butyrate, as well as less fibrosis in the medulla (p=0,04), when compared to mice fed with standard diet. This is also supported by a reduction in Collagen I mRNA expression extracted from whole kidney homogenate (p=0.08).

Conclusions: Our results show that oral sodium butyrate supplementation diminishes DKD progression by protecting against mesangial expansion and fibrosis. Future microbiome sequencing from feces and caecum content, together with metabolomic analysis on plasma samples, will help to further understand the effect of butyrate on DKD.

SA-PO281

Effects of Nucleobindin-2 on Tubular Cells and Mitochondria and Their Mechanisms

Yoshihisa Nakatani. *Kinki Daigaku Igakubu Daigakuin Igaku Kenkyuka, Osakasayama, Japan*.

Background: We have reported that serum NUCB2 (Nucleobindin-2) is a potential biomarker of tubular tissue damage and prognostic factor in DKD. However, the mechanism by which NUCB2 improves renal tubular damage remains unclear. In this study, we investigated the effects of Nucleobindin-2 on tubular cells and mitochondria and the mechanisms underlying these effects.

Methods: We analyzed the effects and mechanisms of NUCB2 on oxidative stress, apoptosis, and mitochondria under high glucose (HG) conditions using proximal tubular cells (HK2, RPTEC).

Results: In oxidative stress cultured HG, NUCB2 reduced ROS production by 20% (Ample Red method), SOD2 expression was unchanged, HO-1 expression was decreased, and oxidative stress scavenging gene expression was not enhanced. Nrf2 expression was decreased both in the nucleus and cytoplasm, P22phox expression was decreased, poldip2 expression was increased, and p47phox expression was increased. This suggests that the expression balance of NOX2/NOX4 is altered, which may reduce oxidative stress production at the basal level for cellular maintenance. Cleaved caspase 3 expression was reduced by 40%, while Bax was decreased and Bcl2 was increased in a NUCB2 concentration-dependent manner, pERK was increased at HG concentration with NUCB2, suggesting that mitochondria were affected via the cRaf-ERK pathway. Analysis of mitochondrial dynamics revealed changes in mitochondrial fusion and fission-related proteins at the protein level and by electron microscopy. Furthermore, NUCB2 enhanced the LC3 1/2 ratio, suggesting that autophagy may also be involved. When we examined metabolism, piruvate kinase, GAPDH, and lactate were unchanged regardless of blood glucose, but PEPCK expression was increased, suggesting an enhancement of the glycogenic system. This may be due to the increased activity of the pentose pathway, which may have suppressed oxidative stress by producing NADPH. In addition, the expression of lipolysis (beta oxidation) and synthesis was enhanced by NUCB2 administration, regardless of blood glucose level. These results may indicate a correlation between lipid profiles and serum NUCB2 concentrations in humans.

Conclusions: NUCB2 may reduce oxidative stress production, suppress apoptosis, and ameliorate mitochondrial damage at high glucose concentrations. NUCB2 may also have an effect on the metabolic system and lipid synthesis.

SA-PO282

TW-37, a Senolytic Agent and Inhibitor of KIM-1-Mediated Endocytosis, Reduces KIM-1 Expression, NF-κB-IL-1β Axis, and p16-Mediated Cellular Senescence

Yutaro Mori, Makiko Mori, Yuki Nakao, Yuta Sekiguchi, Shintaro Mandai, Fumiaki Ando, Koichiro Susa, Takayasu Mori, Eisei Sohara, Shinichi Uchida. *Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan*.

Background: Chronic KIM-1 expression is known to be detrimental. Previously, we identified TW-37 as an inhibitor for KIM-1 mediated endocytosis. We discovered KIM-1-mediated endocytosis of palmitic acid-bound albumin leads NLRP3 inflammasome activation, DNA damage response, cell cycle arrest, cellular senescence and inflammatory fibrotic cytokine production. TW-37 is also known as a senolytic which induce cell death on senescent cells. In this study, we tested relatively long-term effects of TW-37 on primary human renal proximal tubular epithelial cells (hRPTECs).

Methods: We established primary hRPTECs from a patient's resected kidney due to a malignancy with a written informed consent. Uninvolved parts of kidneys were cultured on serum-free media containing epidermal growth factor. We seeded 6 x 10^5cells on day 0 and changed the medium to 10% fetal bovine serum-DMEM (high glucose) containing TW-37 or control DMSO on day 2. We cultured the cells for 8 days (day 2-10) with changing media containing TW-37 or DMSO. KIM-1, NF-κB, IL-1β, p16, caspase-3 and PD-L1 were evaluated by western blotting.

Results: Treatment of TW-37 reduced KIM-1 expression. It also reduced NF-κB and IL-1β, probably indicating NF-κB-NLRP3 inflammasome-IL-1β axis was upregulated. In the control p16 was expressed. Treatment of TW-37 reduced expression of p16 but did not increase expression of caspase-3, suggesting that TW-37 may have non-apoptotic anti-senescence effects. Finally, TW-37 reduced PD-L1 expression.

Conclusions: TW-37 as known for a senolytic and an endocytosis inhibitor for KIM-1 mediated endocytosis may induce intracellular anti-inflammatory and anti-senescence process by downregulating KIM-1, which can be renoprotective effects.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO283

Myokine SIRPα Leads to Defective Heart-Kidney Fatty Acid Oxidation in Type 1 Diabetes

Helena Zhang, Jiao Wu, Sandhya S. Thomas. *Baylor College of Medicine, Houston, TX*.

Background: Dysregulated insulin signaling has been associated with maladaptive alterations in metabolism, cardiac dysfunction and adverse remodeling contributing to cardio-renal diseases. We have previous identified myokine signal regulatory protein alpha (SIRPα), an endogenous mediator of insulin resistance, is upregulated in response to hyperglycemia or uremia, modulating heart-kidney crosstalk. The impact of cardiac-specific SIRPα knockout (KO) regulation on heart-kidney metabolism in the absence of insulin is largely unknown.

Methods: A single dose of 150 mg/kg of STZ was administered to (Myh6Cre)-control and cardiac-specific (cs) SIRPα KO mice. At five weeks post-treatment, M-mode transthoracic echocardiography was performed by an experienced sonographer who was blinded to the study groups. Real-time PCR analysis was used to quantify relative mRNA transcript levels of fetal genes in the heart, fatty acid oxidation genes, fibrotic genes, and inflammatory cytokines. Statistical significance was calculated using 2-tailed unpaired Student's *t* test.

Results: Cardiac-specific SIRPα KO mice exposed to STZ exhibited improved cardiac output (ml/min), fractional shortening (%), and ejection fraction (%) compared to Myh6Cre-control mice with similar heart rates. STZ-treated csSIRPα KO mice displayed downregulation of fetal genes including ANP, BNP, and MHC-alpha as well as suppressed cardiac fibrosis when compared to control mice. These cardiac changes were importantly associated with a downregulation of transcripts encoding genes involved in fatty acid oxidation genes in both the heart and kidneys. Finally, kidney tissue from STZ-treated csSIRPα KO mice exhibited substantially decreased inflammatory markers and fibronectin when compared to control mice.

Conclusions: These results emphasize the role of myokine SIRPα in reprogramming of the fetal genes and cardiac dysfunction while contributing to kidney inflammation and fibrosis. Since chronic kidney disease is a significant independent risk factor for cardiovascular mortality, further examination is imperative in understanding the impact of dysregulated muscle metabolism, specifically myokine triggers on heart-kidney FAO responses independent of insulin in a model of type 1 diabetes.

Funding: Veterans Affairs Support, Private Foundation Support

SA-PO284

Physical Exercise Reduces the Morbidity of Diabetic Rats Exposed to Polymyxin B Nephrotoxicity

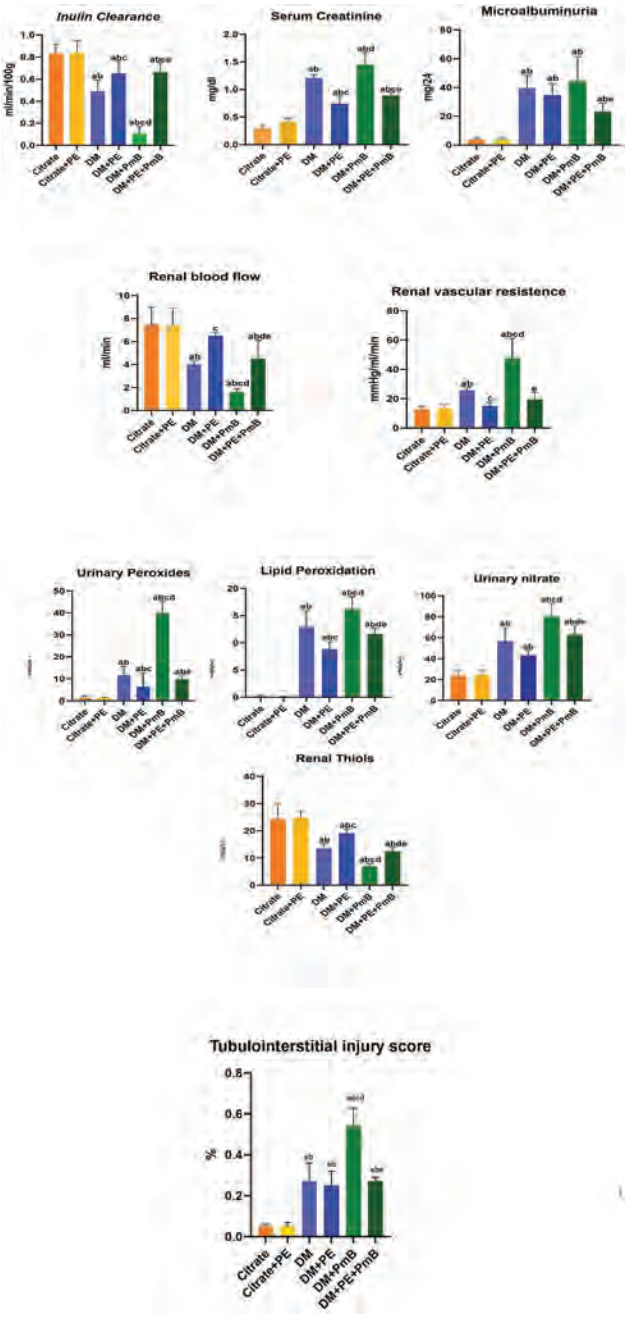
Eloiza O. Silva,[1,2] Carla D. Victoria,[1] Juliana V. Silva,[1] Maikol L. Gonçalves,[1] Jessica P. García,[1] Guilherme H. Ferreira Vieira,[1] Mykelly G. Alves,[1] Camila Lima,[1] Alessandra Oliveira Maia,[1] Luciana Soares C. Santos,[1,2] Maria De Fatima Vattimo.[1] Group of Studies on Acute Kidney Injury. *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Faculdade de Ciencias Medicas da Santa Casa de Sao Paulo, Sao Paulo, Brazil*.

Background: Diabetic kidney disease (DKD) is a significant global health concern and the leading cause of terminal chronic kidney disease (CKD). Polymyxin B (PmB), a nephrotoxic drug, precipitates acute kidney injury (AKI) on DKD patients, elevating risk of disease progression. Physical exercise (PE) is a non-pharmacological intervention that alleviates DKD complications. The objective of this study is to evaluate the impact of PE on renal function in rats with DKD that received PmB.

Methods: Adult Wistar rats were randomized in: Citrate (CT): rats receiving streptozotocin vehicle (citrate; i.v., caudal, single dose); Citrate+PE: citrate rats subjected to daily swimming training (1 hour, 4 weeks); Diabetes Mellitus (DM): rats receiving streptozotocin (STZ, 60 mg/kg; i.v.; single dose, up to the 28th day); DM+PE: DM rats subjected to swimming training; DM+PmB: DM rats receiving PmB (4 mg/kg/day, i.p., once a day, 5 days); DM+PE+PmB: DM rats receiving PmB and subjected to PE. Renal function, renal hemodynamics, oxidative profile and renal histology were evaluated.

Results: The DM+PmB group reduced Clin, RBF and renal thiol levels, while CrS, microalbuminuria, RVR, the excretion of oxidative metabolites and tubulointerstitial injury score significantly increased. PE attenuated the deterioration of renal function in the DM groups.

Conclusions: Findings revealed that DKD rats with PE did not manifest acute DKD when exposed to PmB. These results offer an innovative insight into the interplay between PE and nephrotoxicity in DKD and the renal disease morbidity and pave the way for promising interventions in management of the DKD.



SA-PO285

Combination of Renin AAV and L-NAME Accelerates the Progression of Kidney Disease in Diabetic Mice

Leah L. Porras, Brent Poling, Asim Dey. *Eli Lilly and Company, Indianapolis, IN*.

Background: Diabetic kidney disease (DKD) is a major cause of end stage kidney disease with increasing prevalence worldwide. Rodent models that recapitulate human disease are currently lacking, and many existing models show low proteinuria or take a longer time to develop the disease phenotype. Here we describe a rodent model with accelerated disease progression by combining hypertension and reduced nitric oxide bioavailability on the background of hyperglycemia.

Methods: Nine-week-old male *db/db* obese mice (BKS.Cg-+Leprdb/+Leprdb/OlaHsd-00642) from Jackson Laboratories were injected with Renin AAV (1×10^9 GC) or Lac-Z AAV and provided access to normal chow and water *ad libitum*. These two groups of mice were further divided into two subgroups each based on uACR and half of each subgroup was switched to drinking water containing L-Name (20 mg/L). The 4 subgroups (Lac-Z AAV + water, Lac-Z AAV + L-Name, Renin AAV + water, and Renin AAV + L-Name) were then followed for 5 weeks. Changes in proteinuria were evaluated every

two or three weeks for study duration. In addition, blood pressure was measured via tail cuff and 4 h fasted blood glucose levels measured with a glucometer. At study termination, animals were euthanized, and blood and organs were harvested for further analysis.

Results: Mice treated with a combination of Renin AAV and L-Name showed a significant increase in proteinuria compared to Lac-Z AAV + water group, at two weeks and renal dysfunction continued to progress up to five weeks. Blood pressure was not significantly increased during the study. All mice in the study showed hyperglycemia, with blood glucose levels above 600 mg/dL. Gene expression data from the kidney showed increases in markers of kidney injury and fibrosis in the Renin AAV + L-Name treated group compared to Lac-Z AAV + water group. Urinary biomarker data also showed an increased in kidney injury biomarker in the combination group compared to the Lac-Z groups.

Conclusions: Our results show that combination of Renin AAV and L-Name markedly accelerates the onset of DKD in male *db*/*db* mice, with signs of kidney dysfunction seen at 2 weeks. This model has the potential to be utilized for rapid evaluation of novel therapeutic interventions for DKD.

Funding: Commercial Support - Eli Lilly & Company

SA-PO286

Chronic Intermittent Hypoxia Aggravates Progression of Diabetic Nephropathy via Inducing Endoplasmic Reticulum Stress and Mitochondrial Dysfunction

Junjie Jia,[1,2] Haoran Feng,[1] Niansong Wang,[1] Ying Fan.[1] *[1]Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Huashan Hospital Fudan University, Shanghai, China*.

Background: Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common complication of diabetic nephropathy (DN), which has been found to exacerbate the progression of DN. Chronic intermittent hypoxia (CIH) is one of the most important pathophysiological mechanisms of OSAHS, but its exact impact on DN remains unknown.

Methods: Renal biopsy specimens and the clinical data of 18 biopsy-proven DN patients were collected to observe the correlation of the severity of OSAHS in these patients with their renal function indexes and renal pathological damage. An animal model of DN combined with OSAHS was established by subjecting type 2 diabetic db/db mice to in vivo CIH stimulation for 12 weeks. RNA-sequencing was performed on the kidney cortex tissue from mice to identify the factors CIH mediating the progression of DN. In vitro, HK-2 cells were induced by high glucose (HG) combined with CIH stimulation to confirm the effect of CIH on diabetic tubular injury.

Results: In the current study, we found that the severity of OSAHS was significantly correlated with renal function decline and tubular pathological damage in biopsy-proven DN patients. In vivo, the kidney damage, especially renal tubular injury of the 12-week-CIH-stimulating db/db mice was more severe as compared to normoxic controlled db/db mice and wild-type littermates. RNA-sequencing revealed that increased severity of tubular injury caused by CIH might be associated with activated endoplasmic reticulum stress (ERS), mitochondrial dysfunction, and the exacerbation of apoptosis as well. The *in vitro* experiments confirmed the results, demonstrating that HK-2 cells treated with HG combined CIH exhibited worsened cell apoptosis, ERS, and mitochondrial dysfunction.

Conclusions: This is the first basic research study to investigate the impact of OSAHS on the progression of DN. Our findings show that OSAHS is an important risk factor for the deterioration of renal function and aggravated tubular damage in the course of DN, in which the mechanism is related to the exacerbation of ERS and mitochondrial dysfunction caused by CIH.

SA-PO287

Phase 3 Clinical Candidate Rilparencel Demonstrates Distinct Secretomic Signatures at Key Points in Manufacturing, Suggesting a Reduced Inflammatory and Fibrotic Profile

Ashley Greenawalt, Mark A. Rohlfing, Brooke Bauer, Andrew T. Bruce, Dominic M. Justewicz. *ProKidney LLC, Morrisville, NC.*

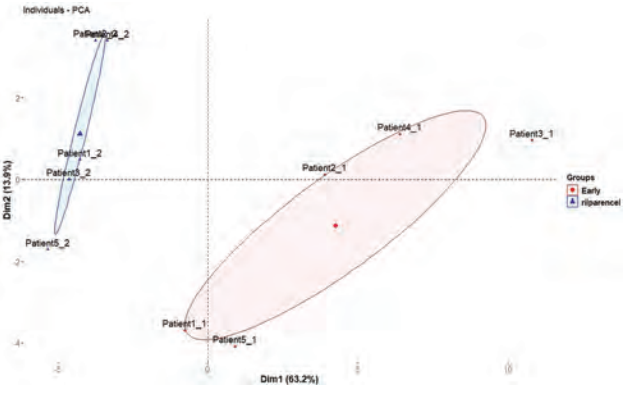
Background: Kidney cortical biopsy-derived rilparencel is a first-in-class autologous kidney epithelial cell platform in Phase 3 clinical trials for patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Data from two Phase 2 studies suggests that kidney cortical injection of rilparencel may preserve organ function as measured by estimated glomerular filtration rate (eGFR). T2D and CKD are associated with inflammation and tissue fibrosis. In a small pilot proof-of-concept study, we sought to characterize how the rilparencel secretome may facilitate kidney repair and restoration.

Methods: In a subset (NCT02836574) of 5 patients with T2D and CKD, conditioned-medium (CM, 24 hr) was collected from 2 stages, early and final product/rilparencel, during the manufacturing process. The CM was queried for 51 secreted inflammatory and fibrotic markers (Luminex xMAP, Intelliflex) whose expression levels were used to generate principal component analysis (PCA) plots.

Results: Secretomes exhibited distinct clustering with a secretory profile of reduced levels of inflammatory and fibrotic markers in rilparencel CM vs. early-stage CM.

Conclusions: This small pilot study suggests that our manufacturing process results in a product, rilparencel, that secretes reduced inflammatory and fibrotic markers, which may in part underlie its reparative and restorative activity. Secretomic profiling may also inform a potency assurance strategy for rilparencel.

Funding: Commercial Support - ProKidney LLC



PCA plot, based on inflammatory and fibrotic secretory markers, demonstrates distinct clusters between early-stage CM (red) and final-stage/rilparencel CM (blue).

SA-PO288

The Ketone Body β-Hydroxybutyrate Mitigates Diabetic Kidney Disease through Metabolic Reprogramming

Saroj Chakraborty, Manikanta S. Arnipalli, Judy J. Baek, Pradeep Kayampilly, Subramaniam Pennathur. Pennathur Lab. *University of Michigan, Ann Arbor, MI*.

Background: Diabetic kidney disease (DKD) is the most common cause of end-statge renal disease and need for renal replacement therapies. Metabolic dysregulation plays a pivotal role in the pathogenesis of DKD. Recent research has highlighted the link between ketone body, beta-hydroxybutyrate (BHB), and kidney function in humans; and the reno-protective effect in animal models via reduction of inflammation and fibrosis and a potential pathway through which SGLT2 inhibitors are effective. However, how BHB exerts its renoprotective effects is unknown and the focus of this work.

Methods: We collected the plasma, urine, and kidney from 24 weeks old diabetic db/db mice and control db/+ mice. BHB was measured by LC-MS based targeted metabolomics. In order to determine whether further increase in BHB would impact DKD, db/db mice were fed with 20% 1,3-Butanediol (v/v in drinking water; 1,3-BD), which is a precursor of BHB and DKD metrics including albuminuria were measured. We quantified post-translational beta-hydroxybutyrylation (BHBylation) of proteins in db/db vs. db/+ mice. In HK-2 cell, mitochondrial function and BHB's effect on TCA cycle metabolism were tested by LC/MS based metabolic flux analysis.

Results: We found that BHB level is significantly higher in plasma (db/+ 26.2±5.8 uM vs db/db 456.95±143.21 uM), urine (db/+ 0.234±0.04 M BHB per M creatinine vs db/db 119.87±33.43 M BHB per M creatinine), and kidney cortex (db/+ 4.48±0.97 pmole BHB per mg protein vs db/db 53.33±17.87 pmole BHB per mg protein) in diabetic mice. 1,3-BD feeding further reduced urinary albumin level (albumin/creatinine: db/db 6.58±2.12 vs db/db+1,3-BD 1.89±0.205) in diabetic mice. We found that diabetic mice have significantly higher BHBylated lysine levels compared to non-diabetic controls. BHB increased the flux of TCA cycle metabolites, implying improved mitochondrial function in HK-2 cells.

Conclusions: To summarize, BHB and BHBylated protein levels were higher in diabetic conditions, and supplementation with the BHB precursor, 1,3-Butanediol, led to lower urinary albumin excretion consistent with improved DKD. Increased in BHBylation associated with this protection suggests key role of this posttranslational modification in mediating improved mitochondrial function (enhanced TCA flux), metabolic rewiring in DKD and associated renoprotection.

Funding: NIDDK Support, Private Foundation Support

SA-PO289

Dissection of Key Molecular Events in Podocyte Response to Hyperinsulinemia and Its Implications in Prediabetic Microalbuminuria

Mengxuan Chen, Yan Ge, Lance D. Dworkin, Rujun Gong. *The University of Toledo Medical Center, Toledo, OH*.

Background: Epidemiological evidence suggests that insulin resistance, manifested as compensatory hyperinsulinemia, is an independent risk factor for chronic kidney disease. However, whether hyperinsulinemia *per se* is a cause for kidney injury is unknown.

Methods: Pre-diabetic *db/db* mice were examined for renal histology, glycemia, insulinemia and albuminuria. Insulin signaling profile was estimated in glomerular podocytes in *db/m* and *db/db* mice. Immortalized podocytes were exposed to high ambient insulin, following ectopic expression of a kinase-dead mutant of GSK3β (KD), a constitutively active GSK3β mutant (S9A), or treatment with a GSK3β inhibitor tideglusib. Cell injury and insulin signaling were examined.

Results: Hyperinsulinemia preceded hyperglycemia in pre-diabetic *db/db* mice, and was associated with microalbuminuria and early signs of podocyte impairment. In glomeruli isolated from young *db/db* mice, an exhausted insulin signaling was noted, marked by insulin receptor (INSR) depletion and hypoactivity of insulin signaling mediators like IRS1 and Akt. This was associated with loss of repression of the constitutively active GSK3β, as indicated by diminished inhibitory p-GSK3β^{S9}. GSK3β hyperactivity was also confirmed in glomerular podocytes in pre-diabetic *db/db* mice, correlating with the degree of hyperinsulinemia or microalbuminuria. Furthermore, GSK3β co-localized and physically interacted with IRS1 in podocytes, suggesting IRS1 acts as a putative substrate for GSK3β. In cultured podocytes, prolonged exposure to high ambient insulin depleted the expression of INSR, leading to GSK3β hyperactivity and inhibitory p-IRS1^{S332}. S9A reinforced inhibitory p-IRS1^{S332} and thereby desensitized insulin signaling, as evidenced by further reduction in Akt phosphorylation. This was associated with exacerbated podocyte injury. Conversely, KD mitigated the inhibitory p-IRS1^{S332} and thereby restored insulin signaling sensitivity, resulting in attenuated podocyte injury. This protective effect was mimicked by tideglusib.

Conclusions: Hyperinsulinemia elicits podocyte injury and microalbuminuria *via* a series of key molecular events, involving depletion of INSR, desensitization of insulin signaling, and GSK3β hyperactivity, which promotes inhibitory p-IRS1^{S332} and thereby forms a vicious cycle of insulin signaling resistance and podocyte injury.

Funding: NIDDK Support

SA-PO290

Modulation of IRS1 Activity by GSK3β Dictates Insulin Signaling Sensitivity in Podocytes: Implications for Diabetic Kidney Disease

Mengxuan Chen, Yan Ge, Lance D. Dworkin, Rujun Gong. *The University of Toledo Medical Center, Toledo, OH.*

Background: Insulin signaling in kidney cells, in particular podocytes, plays a critical role in kidney homeostasis independent of glycemic levels. As a critical transducer of insulin signaling, GSK3β also acts as a convergent point for myriad pathways implicated in kidney injury. However, its role in DKD remains elusive.

Methods: Mouse podocytes were exposed to insulin or a type 2 diabetic milieu, following GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with tideglusib, an inhibitor of GSK3β. Podocyte injury and insulin signaling were assessed and validated in kidneys from *db/db* or control mice.

Results: Upon insulin stimulation, insulin signaling mediators like Akt and GSK3β, were phosphorylated, associated with increased glucose uptake and expression of GLUT1 and 4. GSK3β silencing sensitized insulin signaling, marked by potentiated induction of p-Akt and p-ERK1/2 and enhanced glucose uptake and GLUT expression. Conversely, S9A de-sensitized insulin signaling and mitigated GLUT induction and glucose uptake. Among the many insulin signaling transducers, IRS1 co-precipitated and interacted with GSK3β. Moreover, *in silico* analysis indicated that IRS1^{S332}, which is known to negatively regulate IRS1 activity and target IRS1 for proteasomal degradation, resides in the consensus motifs for phosphorylation by GSK3β. Indeed, insulin-induced p-IRS1^{S332} was suppressed by GSK3β silencing but was enhanced by S9A. Furthermore, in podocytes exposed to a type 2 diabetic milieu, inhibitory p-GSK3β^{S9} was suppressed, denoting GSK3β hyperactivity. This was associated with enhanced p-IRS1^{S332}. Tideglusib treatment counteracted this effect, re-sensitized insulin signaling, and averted diabetic podocyte injury. In *db/db* mice, glomerular expression of p-IRS1^{S332} was augmented in glomerular podocytes. Based on immunoblotting of isolated glomeruli, the expression ratio of p-GSK3β^{S9}/GSK3β in glomeruli was repressed in *db/db* mice as compared with control mice, denoting GSK3β hyperactivity, and this was negatively correlated with the level of p-IRS1^{S332}.

Conclusions: Diabetes-associated GSK3β hyperactivity promotes IRS1 phosphorylation, contributing to desensitization of insulin signaling in podocytes. Therapeutic targeting of GSK3β could re-sensitize insulin signaling in podocytes *via* regulation of IRS1.

Funding: NIDDK Support

SA-PO291

Deletion of Angiotensinogen in Renal Tubule Attenuates Diabetic Kidney Disease Progression in Diabetic Mice

Wenxia Yang,[1] Ke Su,[1] Jing Zhou,[1] Min-Chun Liao,[1] Junzheng Peng,[1] Daniel N. Leal,[4] Michifumi Yamashita,[4] Kana Miyata,[5] Janos G. Filep,[3] Julie R. Ingelfinger,[2] Shao-Ling Zhang,[1] John S. Chan.[1] *[1]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Massachusetts General Hospital, Boston, MA; [3]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [4]Cedars-Sinai Medical Center, Los Angeles, CA; [5]Saint Louis University, St Louis, MO.*

Background: We previously reported that mice overexpressing angiotensinogen (AGT) in renal proximal tubular cells (RPTCs) developed hypertension and kidney injury Kidney Int. 2006). AGT is highly expressed in renal tubules (RTs) in mice and patients with diabetic kidney disease (DKD). We investigated whether genetic deletion of *Agt* only in renal tubules (RT) could attenuate DKD progression in type 1 diabetic Akita mice.

Methods: Male Akita mice with RT-specific *Agt* knockout (Akita RT-*Agt* KO) at 20 weeks of age were studied +/- selective A1 adenosine receptor inhibitor (A1aRi), which counteracts the effect of RT-*Agt* KO. Male Akita controls were also studied. We examined immunohistochemistry in kidney sections, electron microscopy to assess glomerulus basement membrane (GBM) thickness and podocyte foot process effacement, intra-vital confocal microscopy to determine the diameter of glomerular afferent and efferent arterioles, and Western blot and real-time qPCR of protein and gene expression in isolated renal proximal tubules (RPTs). HK2 (human immortalized RPTC cell line) cells were also studied.

Results: Akita RT-*Agt* KO mice had slightly lower systolic blood pressure and fasting blood glucose levels than Akita mice. Akita RT-*Agt* KO mice displayed significantly attenuated oxidative stress, decreased glomerular hyperfiltration, and decreased glomerulomegaly, tubular injury score, podocyte loss, GBM thickness and podocyte foot process effacement. These findings were associated with decreased urinary albumin/creatinine ratio (UACR), urinary AGT and Ang II levels and SGLT2 expression in RPTs. Intra-vital microscopy revealed decreased afferent arteriole (AA) diameter and increased efferent arteriole (EA) diameter in Akita RT-*Agt* KO mice cf. Akita mice. Treatment of Akita RT-*Agt* KO mice with A1aRi increased glomerular filtration rate. In cultured HK2 cells, Ang II stimulated SGLT2 expression, which was attenuated by losartan, NADPH oxidase inhibitors and antioxidants.

Conclusions: RT-specific *Agt* deletion mitigated DKD progression in Akita mice by reducing glomerular hyperfiltration and UACR, decreasing AA and increasing EA diameter, and decreasing podocyte loss, GBM thickness, podocyte foot process effacement and SGLT2 expression in RTs.

Funding: Government Support - Non-U.S.

SA-PO292

Deletion of Angiotensinogen in Renal Tubules Attenuates Tubular Senescence in Diabetic Kidney Disease

Wenxia Yang,[1] Ke Su,[1] Min-Chun Liao,[1] Junzheng Peng,[1] Kana Miyata,[2] Janos G. Filep,[3] Julie R. Ingelfinger,[4] Shao-Ling Zhang,[1] John S. Chan.[1] *[1]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Saint Louis University, St Louis, MO; [3]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [4]Massachusetts General Hospital, Boston, MA.*

Background: We reported previously that renal tubule (RT)-specific angiotensinogen (*Agt*) deletion attenuates kidney injury in type 1 diabetic Akita mice by reducing glomerular hyperfiltration, tubular injury score, urinary albumin-creatinine ratio and SGLT2 expression in renal proximal tubules (RPTs) (ASN'23, SA-PO423). Angiotensin II (Ang II) elicits reactive oxygen species (ROS), triggering oxidative DNA damage, cellular senescence and senescence-associated secretory phenotype (SASP). This study aimed to investigate whether RT-*Agt* deletion attenuates kidney injury by mitigating tubular senescence in Akita mice.

Methods: Diabetic Akita mice with RT-specific deletion of *Agt* (Akita RT-*Agt KO*) were generated by crossbreeding Pax8-Cre mice with *Agt*-floxed Akita mice. Male non-diabetic control, RT-*Agt* KO, Akita, and Akita RT-*Agt* KO mice were studied at 20 weeks of age. In vitro, Madin-Darby Canine Kidney (MDCK, a distal tubule (DT) cell line) cells and HK-2 (human immortalized proximal tubule cell line) cells were used.

Results: Akita mice exhibited increased urinary AGT and Ang II, as well as senescence-associated β-galactosidase positive renal tubules vs. control and RT-*Agt* KO mice and these were normalized in Akita RT-*Agt* KO mice. Notably, immunofluorescent staining of Ang II was increased and colocalized with the DT marker (lycopersicon esculentum lectin (LEL)) in Akita mice, along with elevated markers of oxidative DNA damage (8-Hydroxy-2'-deoxyguanosine (8-OHdG)) and senescence marker (p16) staining. These changes were normalized in Akita RT-*Agt* KO mice. Moreover, SASP components including CCL2, CXCL1, and TNF-α mRNA were upregulated in Akita mouse kidneys and attenuated in Akita RT-*Agt* KO mice. In vitro, Ang II-induced senescence in MDCK, which was attenuated by losartan (an AT1R blocker) or NAC

(N-acetyl L-cysteine, an ROS inhibitor). Finally, addition of senescent MDCK-derived conditioned medium to HK-2 culture facilitated the epithelial-to-mesenchymal transition, which was reversed by losartan or NAC treatment.

Conclusions: RT-derived Agt/Ang II triggers cellular senescence in renal tubules via ROS-mediated DNA damage and the p16 pathway, leading to SASP and increased tubular injury in Akita mice. These results highlight the importance of inhibiting intrarenal RAS to prevent DKD progression.

Funding: Government Support - Non-U.S.

SA-PO293

Improving the Histological Classification of Diabetic Nephropathy Based on Transformative Research in Diabetic Nephropathy (TRIDENT)

Samer Mohandes,[1] Amy K. Mottl,[2] Julia J. Scialla,[3] Salem Almaani,[4] Tamara Isakova,[5] Shweta Bansal,[6] Christos Argyropoulos,[7] Gaia M. Coppock,[1] J. Charles Jennette,[2] Katalin Susztak,[1] Matthew Palmer.[1] *[1]University of Pennsylvania, Philadelphia, PA; [2]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of Virginia, Charlottesville, VA; [4]The Ohio State University Wexner Medical Center, Columbus, OH; [5]Northwestern University Feinberg School of Medicine, Chicago, IL; [6]The University of Texas at San Antonio, San Antonio, TX; [7]University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Diabetic Nephropathy is the most common cause of kidney disease in the world. The diagnostic and prognostic utility of the current Renal Pathology Society Classification (RPS) system is not established. We aim to evaluate RPS system and compare it with our proposed Transformative Research in Diabetic Nephropathy (TRIDENT) histopathologic classification.

Methods: TRIDENT is a multicenter prospective observational study of subjects with diabetes mellitus undergoing a kidney biopsy. Unsupervised k-means clustering of 29 light microscopy features divided the cohort into 5 clusters. The association of this TRIDENT classification with kidney outcomes, defined as 40% change in eGFR or ESRD over 4 years of follow-up, was assessed by Cox proportional hazard models with Harrell's C-statistic for predictive accuracy. Decision curve analysis was used to compare the potential clinical utility of the TRIDENT and RPS classifications across risk thresholds.

Results: The RPS class showed some association with kidney outcomes, but not between classes 3&4 (65% of the cohort). The TRIDENT classification (table 1) grouped the cohort into risk groups with better predictive accuracy of renal risk at 1 year (AUC 0.75 vs 0.66) and 2 years (AUC 0.8 vs 0.74) compared to RPS. Class 5, which includes epithelial features, had the most rapid progression. Addition of the TRIDENT classification to the 2 year kidney failure risk equation resulted in improved discrimination (C statistic 0.759-0.766, ROC AUC at 2 years 0.803-0.837). A higher net benefit in the TRIDENT classification compared to RPS was seen using a decision curve analysis.

Conclusions: We developed a new TRIDENT classification system that improves on currently used methods to capture the severity of DN and predicts kidney outcomes. This classification identifies a subgroup with significant epithelial changes and a more severe kidney outcome.

Funding: Commercial Support - TRIDENT consortium

TRIDENT Classification System

TRIDENT Class	Description
1	GBM thickness without mesangial expansion
2	Mesangial matrix expansion without KW nodules
3	Mesangial matrix expansion and KW nodules without mesangiolysis
4	Mesangiolysis without epithelial hyperplasia
5	Mesangiolysis with epithelial hyperplasia

SA-PO294

Clinical Characteristics of Nodular Lesions in Patients with Diabetic Kidney Disease

Hisashi Kamido, Shigekazu Kurihara, Masayuki Yamanouchi, Tatsuya Suwabe, Yoshifumi Ubara, Naoki Sawa. *Toranomon Byoin Bunin, Kawasaki, Japan.*

Background: Nodular lesions are recognized as typical renal pathology findings in patients with diabetic kidney disease (DKD), although many cases without nodular lesions have also been documented. In diabetic animal models, maintaining a hyperglycemic state alone rarely results in nodular lesions, suggesting the involvement of other contributing factors. However, the pathogenesis remains unclear. This study investigates nodular lesions' clinical features in patients with DKD.

Methods: We conducted a retrospective study of 163 patients diagnosed with DKD via renal biopsy at our institution from 2008 to 2023. The patients were divided into two groups: those with nodular lesions and those without. We examined clinical and laboratory examinations, as well as renal pathology findings.

Results: Comparing the groups with and without nodular lesions, there were no significant differences in renal function (eGFR 34.2 ml/min/1.73m^2 vs. 36.4 ml/min/1.73m^2, p=0.92) or HbA1c (6.9% vs. 6.9%, p=0.43) at the time of biopsy. However, the group with nodular lesions was younger (56 years vs. 70 years, p<0.01) and had a shorter duration of type 2 diabetes (13 years vs. 18 years, p<0.02). Despite these factors, this group exhibited higher systolic blood pressure (152mmHg vs. 137mmHg, p<0.01), higher rates of hematuria (23% vs. 10%, p<0.03), and higher levels of proteinuria (6.2 g/gCr vs. 2.8 g/gCr, p<0.01). Additionally, the group with nodular lesions had higher rates of retinopathy (79% vs. 52%, p<0.01) and dialysis initiation (60% vs. 36%, p<0.01), as well as a shorter duration from biopsy to dialysis (4 years vs. 10 years, p<0.01). Light microscopy findings revealed that the group with nodular lesions had greater intimal thickening in interlobular arteries (p<0.01) and a higher incidence of exudative lesions (80% vs. 61%, p<0.02) and mesangiolysis (62% vs. 21%, p<0.01).

Conclusions: If hyperglycemia were the primary factor in the formation of nodular lesions, an increase in nodular lesions would be expected in older patients with a longer history of diabetes. However, our study found that the group with nodular lesions was younger with a shorter duration of diabetes. This group also exhibited higher blood pressure, more exudative lesions, and mesangiolysis, suggesting that endothelial cell injury plays a crucial role in the formation of nodular lesions.

SA-PO295

Challenge of Kidney Biopsy in Diabetic Patients: A Northwest Italy Large Cohort

Roberta Fenoglio, Dario Roccatello. *CMID-nephrology and Dialysis Unit, San Giovanni Bosco Hospital and University of Turin, Torino, Italy.*

Background: Diabetic kidney disease is one of the most severe long-term complications of diabetes. The aim of the study was to retrospectively analyze monocentric case history of kidney biopsies performed in diabetic patients over a period of 10 years. Patient's data were collected both at the time of histological examination and during follow-up

Methods: Data of renal biopsies (RB) performed in patients with diabetes mellitus from 1st January 2014 to 31th July 2023, were collected. Patient identification was performed by reviewing clinical histories and histopathological charts. Data on the indication for RB were collected from the medical report of the hospitalisation when the procedure was performed or from the visit when the indication was given.

Results: 297 patients were included in the study, regardless of diagnostic suspicion and histological findings. Histological examination revealed diabetic nephropathy (DN) in 112 cases (group 1), DN associated with another kidney disease in 56 cases (group 2) and nondiabetic renal diseases alone in the remaining 129 cases (62%) (group 3). In group 2 the kidney disease most frequently associated with DN was focal and segmental glomerulosclerosis, FSGS followed by IgA nephropathy, IgAN. The histological examination led to specific therapeutic indications in 22 pts. In group 3 the most frequently observed kidney disease was FSGS followed by ANCA-vasculitis, membranous nephropathy and IgAN. In this population, histological examination led to a specific therapeutic indication in 67 pts. During a mean follow up of 41.6±31.8 months, 53 pts reached ESKD (16.5 months). In our population the presence of DN associated with another biopsy-proven nephropathy was especially prevalent. Having double nephropathy conferred a relative risk-RR for dialysis of 1.8089 (95% CI 1.0094 to 3.2415, p=0.0464).

Conclusions: To our knowledge this is the largest cohorts of diabetic patients receiving renal biopsy even reported in a Western country. Our data proved kidney biopsy not to be an academic exercise in diabetic pts. Clinical and laboratory features do not predict histologic findings. Renal biopsy allowed the identification of unsuspecting nondiabetic kidney injuries and double nephropathies, which could be susceptible to different outcomes, and paved the pathway for treatment of potentially manageable histological changes.

SA-PO296

Utility of Kidney Biopsy in Patients with Diabetic Nephropathy: A Retrospective Study of 13,995 Cases

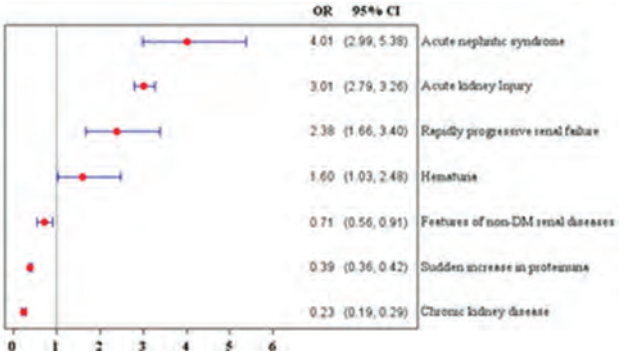
Tiffany Caza,[1] Vivek Charu,[2] Dao-Fu Dai,[4] Vicki G. Davis,[3] Patrick D. Walker.[1] *[1]Arkana Laboratories, Little Rock, AR; [2]Stanford University School of Medicine, Stanford, CA; [3]Statistical Consultant, Afton, VA; [4]Johns Hopkins Medicine, Baltimore, MD.*

Background: The number of renal biopsies performed in patients with diabetes has increased rapidly in the last twenty years. The value of the biopsy has been questioned because of the reported variability of finding a non-diabetic kidney disease (NDKD). We sought to determine the percentage of patients with a NDKD or diabetic nephropathy (DN) alone and to determine clinical indications, demographic factors, and histologic parameters that increase the odds of finding a NDKD on kidney biopsy.

Methods: A retrospective analysis of clinical and pathologic parameters from patients with DN received from 2001 through 2022 at Arkana Laboratories was performed. Inclusion criteria included a diagnosis of DN, available clinical information, and an adequate biopsy with ≥10 glomeruli.

Results: A total of 13,995 patients with DN were identified. A second diagnosis of a NDKD was identified in 27.1%. Of the 55 different NDKD diagnoses, acute tubular injury and infection-associated glomerulonephritis accounted for almost 50%. Acute kidney injury and acute nephritic syndrome had greater odds of a second diagnosis (Figure 1). The youngest (≤30 years) and oldest (≥60 years) patients had a higher prevalence of a second diagnosis. Higher chronicity indices on biopsy were associated with a lower prevalence of a second diagnosis.

Conclusions: Patient age and clinical indication for biopsy influences the odds of finding a NDKD on biopsy. Given the wide array of NDKDs found (55 diagnoses in total), the renal biopsy remains a critical tool in the care of diabetic patients.



Odds of a second diagnosis by clinical indication. Odds ratios (OR) and 95% confidence intervals (95% CI) for a second diagnosis are presented by clinical indication for N=13,995 renal biopsies with a diagnosis of diabetic nephropathy. ORs >1 (<1) imply a higher (lower) probability of a second diagnosis for patients presenting with that clinical indication versus patients with a different indication.

SA-PO297

Characterization of Diabetic Kidney Disease in 235 Patients: Clinical and Pathological Insights with or without Nondiabetic Kidney Disease

Qin Zhu. *Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, China.*

Background: Diabetic kidney involvement primarily manifests as diabetic kidney disease (DKD). However, some diabetic patients may solely present with diabetes mellitus or non-diabetic kidney disease (NDKD), or DKD combined with NDRD. This study statistically analyzed patients with DKD alone and DKD+NDKD, investigating their pathological and clinical characteristics, and identifying the independent factors associated with DKD+NDKD to aid clinical differentiation.

Methods: A retrospective analysis of 235 patients admitted to the Department of Nephrology at Hangzhou Hospital of Traditional Chinese Medicine was conducted between 2014-7 and 2022-12. These patients underwent renal biopsy and received a pathology-based diagnosis of DKD. They were categorized into the DKD alone group (93 cases) and the DKD+NDKD group (142 cases). DKD pathology grading criteria published in the American Journal of Kidney Diseases were used as a reference for grading.

Results: In the DKD alone group, gender distribution was even, with ages mainly between 50-59 years, and a disease duration of less than 5 years, primarily presenting nodular diabetic glomerulosclerosis. In contrast, the DKD+NDKD group had a higher male incidence, a wider age range, longer disease duration, and prevalent diffuse diabetic glomerulosclerosis. Acute and chronic tubulointerstitial lesions and IgA nephropathy were the predominant types of combined NDKD, accounting for 40.14% and 35.21%, respectively. Clinical correlation analysis revealed associations between glomerular grading, tubulointerstitial lesions, renal arteriolar vitelliform lesions, renal vascular atherosclerosis, and clinical parameters such as 24-hour urine protein, hemoglobin, and urinary specific gravity. Multifactorial logistic regression analysis identified independent factors affecting DKD+NDKD, including body mass index, serum creatinine (Scr), microscopic erythrocyte grade, urinary immunoglobulin G (IgG)/creatinine ratio, and serum immunoglobulin A (IgA).

Conclusions: Our research underscores distinctions in age, gender distribution, disease duration, and renal pathology between DKD alone and DKD+NDKD groups. Additionally, significant discriminative factors including BMI, Scr, microscopic erythrocyte grade, UIgG/urine creatinine ratio, and serum IgA levels help differentiate DKD from NDKD, thereby enabling personalized treatment approaches.

SA-PO298

Establishment and Validation of a Risk Prediction Model for Kidney Prognosis of People with Type 2 Diabetic Kidney Disease Diagnosed by Kidney Biopsy

Wenjian Wang,[1] Xiaojie Chen.[1,2] *[1]Department of Nephrology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China; [2]Department of Nephrology, the First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China.*

Background: Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD) and is associated with increased morbidity and mortality in patients with diabetes. Identification of risk factors associates with renal progression(50%eGFR decline and/or progressed to ESRD) of DKD is expected to result in early detection and intervention and improve prognosis.

Methods: Between January 2010 and December 2023, a total of 186 Chinese patients with T2DM and DKD confirmed by renal biopsy were enrolled and followed up for at least 90 days. Three machine learning algorithms (Logistic Regression, LASSO and stepwise AIC) were used to identify the critical clinical and pathological features and to build a risk prediction model for renal prognosis.

Results: There were 107 renal outcome events (57.53%) during the 2.27 year median follow up. The stepwise AIC algorithm showed the best performance at predicting progression to ESRD, showing the highest AUC (0.88). The stepwise AIC algorithm identified eight major factors: HDL-C, gender, hemoglobin (Hb), 24-hour urine urinary total protein, 24-hour urine urea nitrogen, baseline estimated glomerular filtration rate, age and renal hyalinosis of renal arterioles.

Conclusions: Our model can efficiently predict the incident renal prognosis in DKD patients. Compared with the previous models, the importance of 24-hour urine urea nitrogen, Hb, and renal hyalinosis of renal arterioles were highlighted in the current model.

Funding: Government Support - Non-U.S.

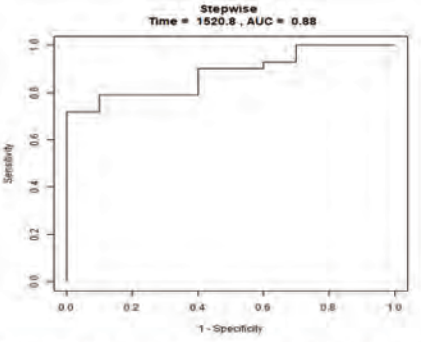


Figure 1. ROC for stepwise AIC algorithm predicts the results of renal prognosis in validate data set.

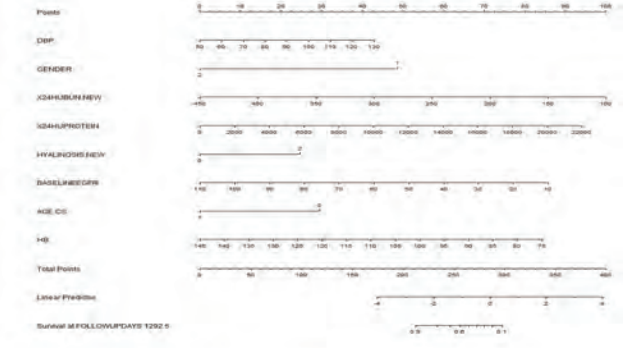


Figure 2. Prognostic nomogram to predict individual renal survival probability in T2DM patients with DKD diagnosed by biopsy. The nomogram allows the user to obtain renal survival corresponding to a patient's combination of variables. Points are assigned for each variable by drawing a straight line upward from the corresponding value to the "Points" line. Then, sum the points received for each variable, and locate the number on the "Total Points" axis.

SA-PO299

Exploring the Subtle, Novel, and Early Kidney Pathological Changes in Diabetic Nephropathy Using Clustering with Deep Learning

Tomohisa Yabe, Ai Fujii, Keiichiro Okada, Norifumi Hayashi, Keiji Fujimoto, Hitoshi Yokoyama, Kengo Furuichi. *Kanazawa Ika Daigaku, Kahoku-gun, Japan*.

Background: As diabetes mellitus (DM) is a leading cause of CKD, early diagnosis of diabetic kidney disease is essential to decrease the number of chronic kidney disease (CKD). However, the pathological changes occurred in early stages of diabetic nephropathy have not been fully elucidated yet.

Methods: Nephrectomized kidneys (partial/total) in Kanazawa Medical University from 1998 to 2019 were used in this study. We performed invariant information clustering (IIC)-based clustering on glomerular images obtained from nephrectomized kidneys of patients with and without diabetes. Visualizing techniques (gradient-weighted class activation mapping (Grad-CAM) and generative adversarial networks (GAN)) were also used to identify the novel and early pathological changes on light microscopy in diabetic nephropathy.

Results: Overall, 13,251 glomerular images (7,799 images from diabetes cases and 5,542 images from non-diabetes cases) obtained from 45 patients were clustered into 10 clusters by IIC. Diabetic clusters that mainly contained glomerular images from diabetes cases (Clusters 0, 1, and 2) and non-diabetic clusters that mainly contained glomerular images from non-diabetes cases (Clusters 8 and 9) were distinguished in the t-distributed stochastic neighbor embedding (t-SNE) analysis. Grad-CAM demonstrated that the outer portions of glomerular capillaries in diabetic clusters had characteristic lesions. Cycle-GAN showed that compared to Bowman's space, smaller glomerular tufts was a characteristic lesion of diabetic clusters.

Conclusions: The findings in this study would be the novel and early pathological changes on light microscopy in diabetic nephropathy and could be key to its early diagnosis to reduce the number of patients with CKD.

Funding: Government Support - Non-U.S.

SA-PO300

Morphometric Analysis of Different Nephron Segments in Patients with Diabetic Nephropathy and Overt Proteinuria

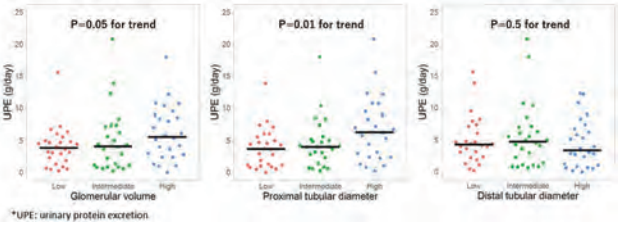
Akane Miura, Masahiro Okabe, Takaya Sasaki, Yusuke Okabayashi, Kotaro Haruhara, Nobuo Tsuboi, Takashi Yokoo. Dept of Nephrology and Hypertension, The Jikei University School of Medicine. *Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan*.

Background: Patients with diabetic nephropathy (DN) are characterized by kidney enlargement, and heavy proteinuria is associated with poor kidney function outcomes. The relationship between hypertrophic changes in single nephrons and the development of proteinuria has not been studied in DN patients.

Methods: Glomerular volume (V_{glom}), proximal tubular diameter (D_{prox}) and distal tubular diameter (D_{dist}) were measured using biopsy specimens from DN patients with overt proteinuria. Nephron-related parameters were estimated using combination of computed tomography imaging and biopsy stereology. These include number of total non-globally sclerotic glomeruli (N_{NSG}), number of globally sclerotic glomeruli (N_{GSG}) and single-nephron GFR (SNGFR), which was estimated by deviding eGFR by N_{NSG} of both kidneys. The proteinuria level at biopsy were compared among tertile groups based on V_{glom}, D_{prox}, and D_{dist}.

Results: A total 78 patients were included in this study (median 56 [quartile 46-67] years, 82% male, eGFR 40.0 [27.4-53.5] ml/min/1.73m^2, urinary protein 4.3 [2.0-6.9] g/day). Of the V_{glom}, D_{prox}, and D_{dist} tertiles, only D_{prox} showed a significant trend to correlate with urinary protein levels (**Figure**). Among the D_{prox} tertile, there were no differences in age, sex, hypertension, eGFR, and HbA1c among the groups, while body mass index showed an increasing trend with D_{prox}. N_{NSG}, N_{GSG}, and SNGFR were not statistically different among the D_{prox} tertile. D_{prox} showed an increasing trend with glomerular lesions characteristic of DN, but V_{glom}, and D_{dist} did not show such a trend.

Conclusions: The present study is the first to morphologically demonstrate the involvement of proximal tubular hypertrophy in the pathophysiology of proteinuria in DN. Morphological findings of different nephron segments, as shown in this study, may provide clinically useful insights when combined with response to treatment and kidney function outcomes.



Comparison of proteinuria levels according to morphological measurement of different nephron segments

SA-PO301

Enlarged Kidney Parenchymal Volume Predicts Poor Kidney Outcomes in Advanced Stage Diabetic Nephropathy

Akane Miura, Masahiro Okabe, Takaya Sasaki, Yusuke Okabayashi, Kotaro Haruhara, Nobuo Tsuboi, Takashi Yokoo. Dept of Nephrology and Hypertension, The Jikei University School of Medicine. *Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan*.

Background: Early diabetic nephropathy (DN) is characterized by enlarged kidneys, but its clinical significance in advanced stages is not well understood. This study aimed to determine whether total kidney parenchymal volume (V_{TKP}) is associated with renal outcomes in advanced stage DN patients with overt proteinuria.

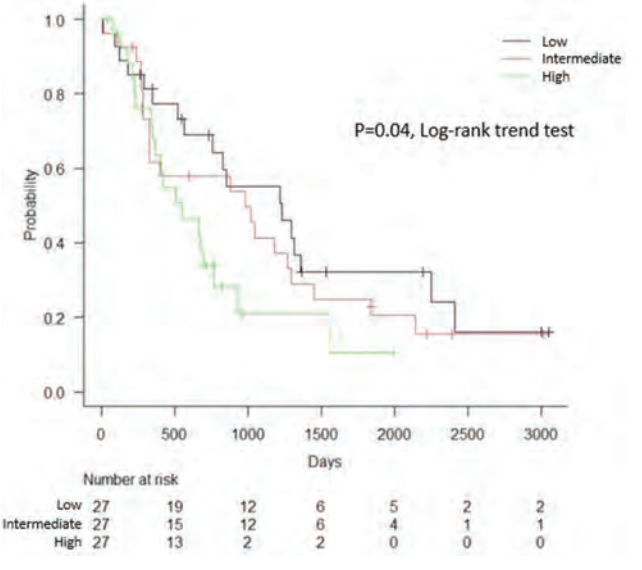
Methods: V_{TKP} was estimated in biopsy-proven DN patients using unenhanced computed tomography imaging. Clinicopathological findings, kidney morphometric parameters and renal outcomes were compared among tertile groups based on V_{TKP}. The end point was defined as a 50% reduction in eGFR or ESKD.

Results: A total 81 patients were included in this study (84% male, median 55 years, eGFR 38 [24-52] ml/min/1.73m^2, urinary protein 4.4 [2.2-7.0] g/day and median 1.8-year follow-up). Median values of V_{TKP} were 111 [98-121], 156 [149-164], and 214 [191-243] cm^3/kidney in the low, intermediate, and high V_{TKP} groups. There were no differences in sex, hypertension, HbA1c and BMI among groups. Age showed a decreasing trend, while eGFR and proteinuria showed an increasing trend with V_{TKP}. In the log-rank trend test, greater V_{TKP} was significantly associated with poor renal outcomes (**Figure**). Interestingly, the associations between V_{TKP} and renal outcomes were independent of age, eGFR and proteinuria levels at presentation (**Table**).

Conclusions: In patients with advanced stage DN, greater V_{TKP} at presentation is associated with poor renal outcomes, independent of kidney function and proteinuria levels.

Cox proportional hazard model

Variable	Hazard ratio	95% confidence interval	P value
Age, per year	1.01	0.99-1.04	0.2
Urinary protein, per g/day	1.10	1.04-1.16	<0.001
eGFR, per mL/min/1.73m2	0.97	0.95-0.98	0.001
VTKP, per 10cm3	1.09	1.01-1.18	0.001



eGFR ≥50% decline or ESKD

SA-PO302

Noninvasive Prediction Tool of Nondiabetic Kidney Diseases in Patients with Type 2 Diabetes

Narayan Prasad, Vamsidhar Veeranki, Jeyakumar Meyyappan, Brijesh Yadav.
Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.

Background: Despite being the gold standard in detecting non-diabetic kidney diseases(NDKD) in Type-2 Diabetes Mellitus, renal biopsy has an inherent risk of life-threatening complications. The current study is aimed to develop and validate a non-invasive scoring tool to predict NDKD using clinical and laboratory variables.

Methods: We developed a model to detect NDKD using multivariable binary logistic regression analysis with the backward Wald elimination method. A nomogram was developed from the multivariate logistic regression model and the probability of NDKD was assessed for each predictor variable using the strength of association. We included all patients of T2DM who had an indication kidney biopsy for NDKD during the study period. The model performance was analyzed using AUC-ROC curve on both the derivational (internal validation) and external cohorts from other centers (multicentric external validation).

Results: Out of 538 patients, 376 were included in the derivational, and 162 in the validation cohort. The model consists of the following variables, T2DM duration< 5 years(p=0.003), absence of coronary artery disease(p=0.05), absence of diabetic retinopathy(p=0.001), oliguria(p=0.02), acute rise in s.creatinine(p< 0.001) and low serum C3 level(p=0.001) significantly predicted NDKD on renal biopsy. Using a nomogram, statistical predictive models are converted into a single numerical estimate of probability of NDKD in the form of a graph(Figure.1,2). The model performance performed robustly with an AUC-ROC of 0.869(95% CI:0.805-0.933) in the validation cohort and 0.883(95%CI:0.830–0.937) on multicentric external validation.

Conclusions: The clinical and laboratory parameter-based non-invasive prediction model robustly predicted the NDKD among T2DM patients with renal dysfunction, and the prediction model has a high sensitivity of 86% and an equally good specificity of 80%.

Funding: Government Support - Non-U.S.

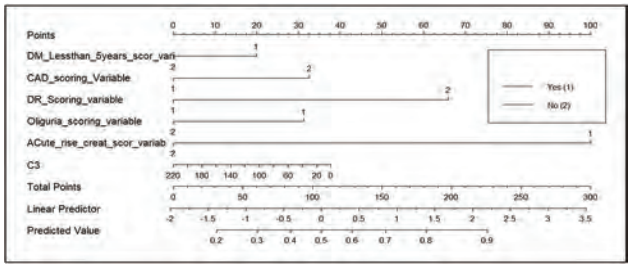


Figure.1 The nomogram depicting the statistical predictive models converted into a single numerical estimate of probability of NDKD in the form of a graph.

SA-PO303

Correlation Analysis between Extracapillary Hypercellularity, Segmental Sclerosis, and Clinical Features of Diabetic Nephropathy

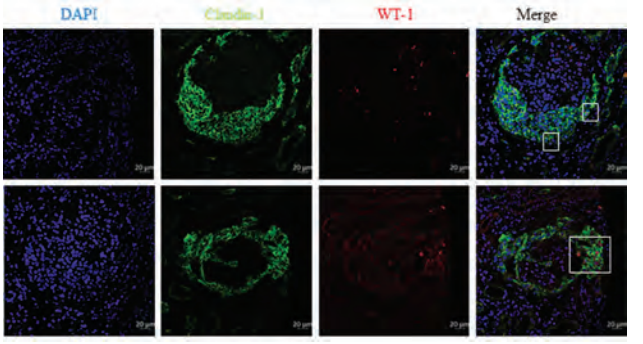
Huan Jiang, Jiaoqing Li, Haosen Xu, Peimin Liu, Ting Zhang, Xiaoyan Bai.
Guangdong Provincial People's Hospital, Guangzhou, China.

Background: Extracapillary hypercellularity(EXHC) and segmental sclerosis(SS) were poor prognostic features of diabetic nephropathy(DN). We stated the difference of EXHC and SS, and analyzed the correlation between EXHC or SS and clinical features. We also evaluated the pathological significance of EXHC and SS and studied the cellular origin of the EXHC structure.

Methods: Clinical and pathological information was collected from 115 biopsy-proven DN patients from 2021 to 2023. Welch t test, Chi-square test or Mann-Whitney U test was used to compare the difference. Correlation analysis was conducted using Spearman correlation analysis. The cellular component of EXHC was shown by immunofluorescence.

Results: The number of patients with EXHC and SS structure was 44 and 79, respcetively. There was significant difference in height between patients with EXHC and those without. There was significant difference in urea nitrogen, uric acid, 24-h proteinuria, urinary protein/creatinine ratio, urinary albumin/creatinine ratio, diabetic retinopathy in patients with SS compared with those without. A positive correlation was found between the number of EXHC and patients' height. Correlation analysis revealed that SS correlated with serum creatinine, e-GFR, urea nitrogen, 24-h proteinuria, urinary protein/creatinine ratio, urinary albumin/creatinine ratio, and diabetic retinopathy. Most of the EXHC structure consisted of Claudin-1 positive glomerular parietal epithelial cells and a little was WT1 positive podocytes.

Conclusions: We found in DN patients with SS, the level of serum creatinine, proteinuria, diabetic retinopathy and low e-GFR was higher than patients without SS. Although EXHC associated with height, the finding that podocytes were observed in the EXHC structure suggested that they may play a role in the formation of the unique structure.



Immunofluorescence staining for Claudin-1(green), WT1(red) in DN patients with EXHC.

SA-PO304

Diagnostic Accuracy of MicroRNAs in Diabetic Nephropathy: A Meta-Analysis

Gantsetseg Garmaa,[1] Tamás Kói.[2] *[1]Semmelweis Egyetem, Budapest, Hungary; [2]Budapesti Muszaki es Gazdasagtudomanyi Egyetem, Budapest, Hungary.*

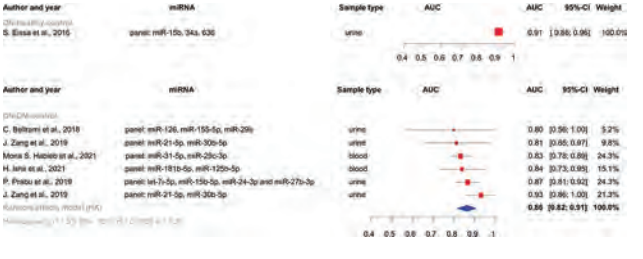
Background: MiRNAs play a significant role in the pathophysiology of diabetic nephropathy (DN), as demonstrated by numerous preclinical and cohort studies. They are potential diagnostic biomarkers but also promising therapeutic agents. However, to accelerate their clinical application, it is crucial to systematically review and summarize their diagnostic performance in various biological samples during DN.

Methods: The systematic search involves five databases following the PROSPERO CRD42021282785 protocol. The study includes individuals with DN and those without (healthy or with diabetes mellitus (DM)). MiRNA detection using qRT-PCR is the index test, while clinical diagnoses confirmed by biopsy or laboratory results serve as reference tests. For meta-analyses, the area under the curve (AUC) sensitivity (SEN), and specificity (SPE) of single or panel miRNAs from each study were extracted and analyzed using R software.

Results: Eighty-seven studies met the eligibility criteria, all included in the meta-analysis. The pooled SEN and SPE results in DN compared to healthy controls for single miRNAs were 0.91 (95% CI: 0.86–0.95) and 0.89 (95% CI: 0.77–0.95), respectively. When DN was compared to DM patients, the pooled SEN and SPE were 0.82 (95% CI; 0.76-0.87) and 0.81 (95% CI; 0.74-0.86) for single miRNAs. In the DN with healthy control, only AUC values for a panel of miR-15b, miR-34a, and miR-636 were reported (0.91, 95% CI; 0.86-0.96), and pooled AUC (pAUC) for single miRNAs was 0.85 (95% CI; 0.81-0.89). The pAUC of DN vs. DM was 0.86 (95% CI; 0.82-0.91) for panel miRNAs and 0.79 (95% CI; 0.75-0.82) for single miRNAs. Among the individual studies, a panel of miR-21 and miR-30-b-5p showed a higher AUC in DN patients than in DM patients, 0.93 (95% CI; 0.86–1.0). For DN, blood samples outperformed urine, with a pAUC of 0.87 compared to 0.84.

Conclusions: MiRNAs can differentiate between DN patients, healthy individuals, and patients with DM. Using miRNA panels for diagnosis is more effective than relying on a single miRNA. Additional large cohorts should investigate the diagnostic performance of miRNAs in different stages of DN and biological sample types.

Funding: Government Support - Non-U.S.



SA-PO305

Circulating Proteins Associated with Apoptosis Processes and Fast Progression to ESKD in Diabetic Kidney Disease

Katsuhito Ihara,[1,2] Eiichiro Satake,[1,2] Zaipul Md Dom,[1,2] Bozena Krolewski,[1,2] Andrzej S. Krolewski.[1,2] *[1]Joslin Diabetes Center, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: Many circulating proteins associated with risk of end-stage kidney disease (ESKD) have been identified in diabetic kidney disease (DKD). However, the biological pathways and disease processes they represent are unknown.

Methods: This global-untargeted proteomic study used the Olink platform to measure the concentrations of 455 proteins in plasma specimens obtained at baseline examination of 405 individuals with DKD. We used logistic regression to examine the associations between these proteins and the development of ESKD. This investigation consisted of two nested case-control studies from the Joslin Kidney Study. One study included individuals with T1D, and the other included individuals with T2D who were at risk of developing ESKD during a 7-15 year follow-up period. For pathway enrichment analysis of the differentially expressed proteins, we applied the Database for Annotation, Visualization, and Integrated Discovery (DAVID 6.8). Additionally, to assess whether the models based on apoptosis proteins captured all the predictive information for ESKD, we applied least absolute shrinkage and selection operator (LASSO) logistic regression.

Results: We identified 46 circulating proteins with elevated concentrations that were associated with the development of ESKD (n=149) during a 7-15 year follow-up period (p value $<10^{-5}$ for all 46 proteins). Twenty of these proteins were enriched in the apoptosis/TNF receptors signaling pathways. A small subset of 5 proteins out of the 46 (KIM-1, TNF-R27, IL-1RT1, TNF-R11A, and TNF-R6B in descending order of predictive ability), summarized as the apoptosis score, along with clinical variables, accurately predicted the risk of progression to ESKD.

Conclusions: Elevated levels of numerous circulating proteins, indicating apoptotic processes and TNF receptors signaling pathways, preceded fast progression to ESKD. These proteins may be used to predict and monitor the disease process leading to ESKD in DKD.

Funding: NIDDK Support, Commercial Support - Novo Nordisk Foundation

SA-PO306

Urine Biomarkers for Diabetic Kidney Disease Progression

Sarah J. Schrauben,[1] Joachim H. Ix,[2] Michael Shlipak,[3] Mirela A. Dobre,[4] Orlando M. Gutierrez,[5] Mark J. Sarnak,[8] Ana C. Ricardo,[9] Steven G. Coca,[10] Jason H. Greenberg,[14] Sushrut S. Waikar,[11] Chirag R. Parikh,[12] Debbie L. Cohen,[1] Chi-yuan Hsu,[13] Jonathan J. Taliercio,[15] Jeffrey R. Schelling,[4] Panduranga S. Rao,[16] Paul L. Kimmel,[6] Joseph V. Bonventre.[7] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of California San Diego, La Jolla, CA; [3]San Francisco VA Health Care System, San Francisco, CA; [4]Case Western Reserve University, Cleveland, OH; [5]The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; [6]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [7]Brigham and Women's Hospital Department of Medicine, Boston, MA; [8]Tufts Medical Center, Boston, MA; [9]University of Illinois Chicago, Chicago, IL; [10]Icahn School of Medicine at Mount Sinai, New York, NY; [11]Boston Medical Center, Boston, MA; [12]Johns Hopkins University, Baltimore, MD; [13]University of California San Francisco School of Medicine, San Francisco, CA; [14]Yale University School of Medicine, New Haven, CT; [15]Cleveland Clinic, Cleveland, OH; [16]University of Michigan, Ann Arbor, MI.*

Background: Urine biomarkers of proximal and distal kidney tubular health and inflammation may provide non-invasive ways to identify individuals with diabetes at risk for CKD progression since the extent of tubulointerstitial pathology is related to diabetic kidney disease progression. Prior studies were limited by use of incidence of end-stage kidney disease as an endpoint, focus on fewer biomarkers, and inconsistent findings.

Methods: We performed a case-cohort study among 898 participants in the Chronic Renal Insufficiency Cohort (CRIC). The subcohort (N=599) comprised a group of randomly selected CRIC participants with diabetes and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 with urine samples assayed for biomarkers. Cases (N=540) were participants with diabetes whose CKD progressed (incident ESKD or ≥40% eGFR decline). Urine biomarkers were assayed 1 yr after enrollment: monocyte chemoattractant protein-1 [MCP-1], kidney injury molecule-1 [KIM-1], a1-microglobulin, epidermal growth factor [EGF], and uromodulin. Weighted Cox regression models related biomarkers, standardized to urine creatinine (transformed as $\log_2$), with CKD progression and were adjusted for covariates, including eGFR and urine albumin-to-creatinine ratio (UACR).

Results: KIM-1/Cr, MCP-1/Cr, and UACR were most strongly correlated (rho = 0.47 - 0.58). In fully adjusted models, KIM-1/Cr was associated with increased CKD progression (HR 1.16 per 2-fold higher, 95% CI 1.05-1.29) and EGF/Cr was associated with decreased risk of CKD progression (HR 0.83 per 2-fold higher, 95% CI: 0.73-0.95) The highest quartiles of KIM-1/Cr and MCP-1/Cr, compared to the lowest quartile, were associated with increased CKD progression (HR 1.69, 95% 1.14-2.51, and HR 1.65, 95% CI 1.11-2.47, respectively). The highest quartile of EGF/Cr, compared to lowest, was protective against CKD progression (HR 0.59, 95% CI: 0.41-0.85).

Conclusions: Urine MCP-1, KIM-1, and EGF may provide non-invasive ways to assess tubule and interstitial disease and health in diabetes and help identify those at higher risk of CKD progression independent of GFR and albuminuria, and aid in the clinical monitoring of individuals with CKD and diabetes.

Funding: NIDDK Support

SA-PO307

Application and Mechanism of Renal Tubular Perilipin 2 in Predicting the Decline in Kidney Function in Patients with Diabetic Kidney Disease

Rui Shen, Qingqing Ke, Xin Yu, Chunsun Dai, Yang Zhou. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: To investigate whether the expression of perilipin 2 (PLIN2) in renal tubular cells could predict a decline in renal function in diabetic kidney disease (DKD) patients and to determine the potential mechanisms involved in renal tubular cell injury induced by PLIN2 during the progression of DKD.

Methods: Control individuals and DKD patients were enrolled in this retrospective cohort study. The relationship between expression of PLIN2 in kidney tubules and estimated glomerular filtration rate (eGFR) slope in DKD patients was predicted by Spearman correlation analysis and a generalized linear model. BKS-db/db diabetic mice and streptozotocin-induced diabetic mice were used. Primary renal tubular cells were treated with glucose and transfected with small interfering RNA or plasmid.

Results: The expression of PLIN2 was markedly greater in the tubules of DKD patients than in those of control subjects. After 24 (12, 39) months of follow-up, the eGFR slope of DKD patients was -7.42 (-19.77, -2.09) ml/min/1.73m^2/year. An increase in the baseline percentage of PLIN2-positive tubules was significantly associated with a change in the eGFR slope during the follow-up period (HR = 1.90, 95% CI: 1.00~3.58), indicating that tubular PLIN2 could predict a decrease in renal function in DKD patients. Both the accumulation of lipid droplets and the expression of PLIN2 were markedly greater in the tubules of diabetic mice than in those of control mice. Glucose treatment induced lipid droplet accumulation and PLIN2 expression in renal tubular cells. PLIN2 deficiency significantly alleviated glucose-induced lipid droplet accumulation, whereas PLIN2 overexpression aggravated glucose-induced lipid droplet accumulation. The decrease in mitochondrial oxygen consumption rate (OCR) in renal tubular cells induced by glucose treatment was alleviated after PLIN2 interference. However, overexpression of PLIN2 directly decreased the mitochondrial OCR.

Conclusions: PLIN2 expression in tubules predicts a decline in renal function in patients with DKD. PLIN2 suppresses mitochondrial aerobic respiration and contributes to the accumulation of lipid droplets in renal tubular cells to promote the progression of DKD.

Funding: Government Support - Non-U.S.

SA-PO308

Effects of Bardoxolone Methyl on Urinary Proximal Tubular Markers: A Subanalysis of the TSUBAKI Study

Michihiro Hosojima,[1] Shoji Kuwahara,[2] Hideyuki Kabasawa,[1] Shunji Kinoshita,[3] Tomohiro Ichikawa,[3] Akihiko Saito.[4] *[1]Department of Clinical Nutrition Science, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Laboratory of Clinical Nutrition, Department of Nutrition, Graduate School of Human Cultures, The University of Shiga Prefecture, Hikone, Japan; [3]Development Division, Kyowa Kirin Co., Ltd, Tokyo, Japan; [4]Department of Applied Molecular Medicine, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: Bardoxolone methyl (BARD) activates nuclear factor erythroid 2-related factor 2, exhibiting antioxidative and anti-inflammatory properties. BARD has been developed as a therapeutic agent for diabetic kidney disease (DKD). Previous clinical trials have demonstrated that BARD increases the estimated glomerular filtration rate (eGFR) and albuminuria. Animal experiments have suggested that the increase in albuminuria induced by BARD is associated with a decrease in the expression of megalin, a proximal tubule endocytic receptor involved in the reabsorption, metabolism, and degradation of glomerular filtrate proteins. However, the specifics of these effects require further elucidation. This study aimed to measure the urinary concentrations of markers associated with megalin in the proximal tubules using urine samples collected from the TSUBAKI study, a phase II clinical trial of BARD administration in DKD patients conducted in Japan, and to examine changes in these markers and their independent effects on eGFR.

Methods: In the TSUBAKI study, urine samples were collected at baseline and at 4, 8, 12, 16, and 4 weeks after administration. The urinary concentrations of A-megalin (megalin ectodomains), C-megalin (full-length megalin), α_1-microglobulin (α_1-MG), and N-acetyl-β-D-glucosaminidase (NAG) were measured. Statistical analyses were performed using mixed-effects models for repeated measures.

Results: Compared with the placebo group, the BARD group showed significantly increased urinary α_1-MG/creatinine (Cr) and A-megalin/Cr at all time points after the start of administration. However, this increase disappeared after the completion of administration. Similar results were found in urinary α_1-MG/Cr/eGFR and A-megalin/Cr/eGFR. In contrast, there were no changes in urinary C-megalin/Cr and NAG/Cr.

Conclusions: BARD administration resulted in changes in urinary proximal tubule markers. The increase in α_1-MG, a ligand of megalin, following BARD administration was consistent with the reduction in megalin expression observed in animal studies. The increase in urinary A-megalin levels suggests that BARD may stimulate the recycling and shedding of megalin, independent of its effect on increasing eGFR.

SA-PO309

Effects of Empagliflozin on Urinary Megalin and Its Ligand α1-Microglobulin in Patients with Diabetic Kidney Disease

Michihiro Hosojima,[1] Hideyuki Kabasawa,[1] Akihiko Saito.[2] *[1]Department of Clinical Nutrition Science, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Department of Applied Molecular Medicine, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors were initially marketed as oral hypoglycemic agents acting on proximal tubules (PTs) but have also begun to be used worldwide as renoprotective agents. However, the detailed mechanisms underlying these renoprotective effects remain unclear. Megalin is highly expressed in the apical membranes of PTs and serves as an endocytic receptor for various glomerular-filtered proteins, peptides, and drugs. Previous studies have demonstrated that megalin could play a role in the progression of renal injury as a "gateway molecule" for nephrotoxic substances. Furthermore, measuring urinary megalin excretion may help evaluate the severity and pathophysiology of diabetic kidney disease. In particular, A-megalin (megalin ectodomains) may serve as a novel urinary biomarker of the metabolic load in PTs. Therefore, this study aimed to explore whether measuring the excretion of A-megalin helps evaluate the efficacy of SGLT2 inhibitors, including the evaluation of other PT markers such as α_1-microglobulin (α_1-MG), an endocytic ligand of megalin.

Methods: Forty-seven adult patients with type 2 diabetes and mild to moderate renal dysfunction (HbA1c 7.6±1.2%, eGFR 65.8±17.9 mL/min/1.73 m^2, albuminuria 153.6±305.6 mg/g creatinine (Cr)) were enrolled (UMIN000023902). Urinary excretion of megalin, albumin, and PT markers such as α_1-MG was measured at baseline, one month after starting empagliflozin, and then every three months for 36 months, along with evaluation of changes in eGFR.

Results: There were no significant changes in urinary albumin levels at six months compared to baseline. Urinary α_1-MG showed an increasing trend from 9.2±8.7 mg/g Cr at baseline to 12.1±9.2 mg/g Cr at three months and 12.0±9.3 mg/g Cr at six months, and urinary α_1-MG/g Cr/eGFR exhibited a similar trend. Urinary A-megalin, which was 90.0±62.6 pmol/g Cr at baseline, showed a decreasing trend to 64.3±71.2 pmol/g Cr at three months and 56.3±43.1 pmol/g Cr at six months, and urinary A-megalin/g Cr/eGFR exhibited a similar trend.

Conclusions: Administration of empagliflozin led to decreased urinary A-megalin and increased α_1-MG in patients with diabetic kidney disease, even when considering changes in eGFR. Further detailed evaluations are needed to elucidate the relationship between the renal protective effects and megalin function.

SA-PO310

Renal Blood Flow during Adenosine-Stress by Magnetic Resonance Imaging in a Large Cohort of Patients with Type 2 Diabetes

Niclas Sunde,[1,2] Peter Gaede.[3,2] *[1]Kobenhavns Universitet, Kobenhavn, Denmark; [2]Slagelse Sygehus, Slagelse, Denmark; [3]Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Odense, Denmark.*

Background: Type 2 diabetes (T2D) affects most organs, and clinical evaluation is a task for most specialties in internal medicine, including not only endocrinology, but notably also cardiology and nephrology. Thus, premature morbidity and mortality in T2D is largely related to cardiovascular disease and to increased risk of renal failure. Diabetic nephropathy is a microvascular complication of T2D and a leading cause of end-stage renal disease.

Methods: 297 patients from Næstved/Slagelse/Ringsted Hospitals participated in the largest global study of its kind, with magnetic resonance imaging of the heart. Since T2D not only affects the heart and circulation but also the kidneys, these studies will not only focus on the heart but will utilize scans to determine, using a new technique, whether patients have normal or reduced kidney blood flow

Results: We found that perfusion of the renal cortex and medulla is lower in patients with T2D than in an age-matched control both during rest and adenosine-stress. During rest, blood perfusion of the renal cortex and medulla were 19% and 15% lower in patients with T2D than in normal age-matched control subjects (P=0.06 by unpaired t-test for renal cortex). The cortical/medulla-perfusion ratio was also lower in patients with T2D than in normal subjects. During adenosine-stress, renal cortical perfusion was 20% lower in patients with T2D than in normal subjects (P<0.001 by unpaired t-test). Renal medullary perfusion decreased to 103±46 SI units in normal subjects vs. 98±31 SI units in patients with T2D. Based on our findings, patients with T2D have comparable renal perfusion responses to adenosine but have lowered rest and stress renal cortical as well as medullary perfusions as compared to normal subjects. Further, patients with T2D during adenosine stress have comparably lower cortex/medulla-perfusion ratios than normal subjects, and hence do not seem to exhibit the same intra-renal redistribution of blood flow from the medulla to the cortex as noted in normal subjects.

Conclusions: We found a reduction in renal blood flow during rest and stress, within a cohort of patients with T2D and a board range of kidney function (uAER, eGFR) and diabetes medication compared to an age matched control group.

SA-PO311

Complement Pathway Correlates with Rapid Progression of Type 2 Diabetic Kidney Disease in Korean and American Cohorts

Donghwan Yun,[1] Dong Ki Kim,[1] Yon Su Kim,[1] Maryam Afkarian,[2] Seung Seok Han.[1] *[1]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [2]University of California Davis, Davis, CA.*

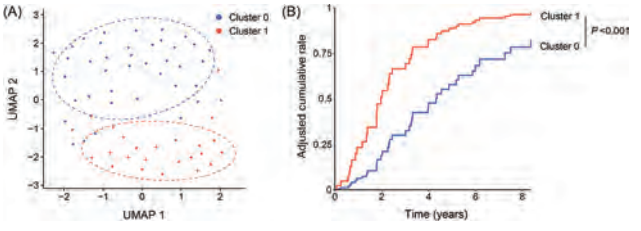
Background: Rapid progression of certain patients with diabetic kidney disease (DKD) remains a threatening issue despite existing treatments. However, their pathophysiological characteristics have not been well defined. This study addresses this gap by examining both Korean and American type 2 DKD cohorts through untargeted and targeted urinary proteomics, respectively.

Methods: We conducted untargeted proteomics on urine samples collected at the time of kidney biopsy from Korean patients diagnosed with biopsy-confirmed DKD (SNUH-DN cohort) in the context of type 2 diabetes (n=64) and validated the findings using targeted proteomics on those collected at the time of enrollment in the Chronic Renal Insufficiency Cohort study (n=282, CRIC-T2D cohort). Kidney progression as an outcome was defined as either doubling of serum creatinine, ≥50% decrease in eGFR, or the development of ESKD. For untargeted proteomics, analyses for pathways were employed to identify urinary biomarkers associated with kidney progression.

Results: A total of 1,877 proteins were quantified from the patients in SNUH-DN cohort with eGFR of 55 ml/min/1.73m^2 (IQR 44–75) and a random uPCR of 3.1g/g (1.7–7.0). The urinary proteins were clustered into two groups, and kidney progression was primarily observed in one group. This group, exhibiting a tendency for rapid kidney progression, had an elevated complement pathway as a proteomic set. When certain complement proteins were measured as a target in the patients from CRIC-T2D cohort with a baseline estimated glomerular rate of 42ml/min/1.73m^2 (37–49) and 24-hr urine protein of 0.48g (0.10–1.87), those with a high abundance of complements experienced rapid kidney progression compared to those with low abundance.

Conclusions: Urinary proteomic profiling confirms the involvement of the complement pathway in the rapid progression of type 2 DKD. The results will serve as the basis for studies aimed at manipulating relevant complements for the treatment of patients with type 2 DKD.

Funding: Clinical Revenue Support



(A) UMAP of untargeted proteomics. (B) Adjusted survival curves for kidney progression according to clustering in SNUH-DN cohort.

SA-PO312

Potential Defensive Role of TIM-3 on T Lymphocytes in the Inflammatory Involvement of Diabetic Kidney Disease

Guochun Chen, Xiaojun Chen, Runyan Tang. *The Second Xiangya Hospital of Central South University, Changsha, China.*

Background: The aberrant mobilization and activation of various T lymphocyte subpopulations play a pivotal role in the pathogenesis of diabetic kidney disease (DKD), yet the regulatory mechanisms underlying these processes remain poorly understood. The dysregulation of immune checkpoint molecules on T lymphocytes disrupts kidney homeostasis, instigates pathological inflammation, and promotes DKD progression, becoming a new derection for detecting the mechanism of DKD.

Methods: A total of 360 adult patients with DKD were recruited for this study. The expression of immune checkpoint molecules on T lymphocytes was assessed by flow cytometry for peripheral blood and immunofluorescence staining for kidney tissue. Single-cell sequencing (scRNA-seq) data from the kidneys of DKD mouse model were analyzed.

Results: Patients with DKD exhibited a reduction in the proportion of CD3+TIM-3+ T cells in circulation concurrent with the emergence of significant albuminuria and hematuria (p=0.008 and 0.02, respectively). Conversely, the incidence of infection during DKD progression correlated with an elevation of peripheral CD3+TIM-3+ T cells (p=0.01). Both univariate and multivariate logistic regression analysis revealed a significant inverse relationship between the proportion of peripheral CD3+TIM-3+ T cells and severe interstitial mononuclear infiltration (OR: 0.193, 95%CI: 0.040,0.926, p=0.04).

Immunofluorescence assays demonstrated an increase of CD3+, TIM-3+ and CD3+TIM 3+ interstitial mononuclear cells in the kidneys of DKD patients as compared to patients diagnosed of minimal change disease (p=0.03, 0.02 and 0.002, respectively). seq analysis revealed decreased gene expression of TIM3 on T lymphocytes in DKD compared to control. And TIM3's main ligands, Galectin-9 on immune cells showed a decreasing trend in gene expression as kidney damage worsened.

Conclusions: Our study underscores the potential protective role of TIM-3 on T lymphocytes in attenuating the progression of DKD and suggests that monitoring circulating CD3+TIM3+ T cells may serve as a viable strategy for identifying DKD patients at heightened risk of disease progression.

Funding: Government Support - Non-U.S.

SA-PO313

Artificial Intelligence in the Identification of Key Metabolites Associated with Diabetic Kidney Disease

Inha Jung,[1] Sungjin Park,[3] Soon hyo Kwon,[2] Ji A Seo,[1] Hyeong-Kyu Park,[2] Nan Hee Kim.[1] *[1]Korea University Ansan Hospital, Ansan, Gyeonggi-do, Republic of Korea; [2]Soonchunhyang University Hospital, Yongsan-gu, Seoul, Republic of Korea; [3]Korea University Anam Hospital, Seoul, Republic of Korea.*

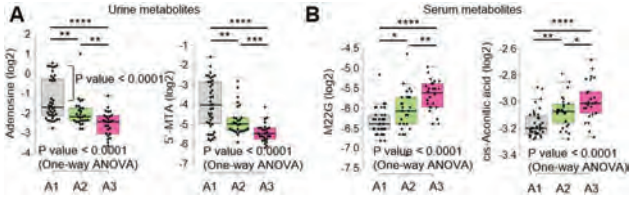
Background: Despite the increasing prevalence of DKD, reliable biomarkers for its early detection remain scarce. This study aimed to identify urine and serum metabolites that differentiate between DKD stages through bioinformatics analysis.

Methods: We analyzed 92 participants, categorizing them by eGFR and ACR combinations to identify criteria that best distinguish metabolites. Using these criteria, we trained and validated separate AI models. The criterion with the highest accuracy was selected for further investigation of metabolites that varied under this criterion. To understand the relationships and functions of these metabolites, we conducted a metabolic network analysis.

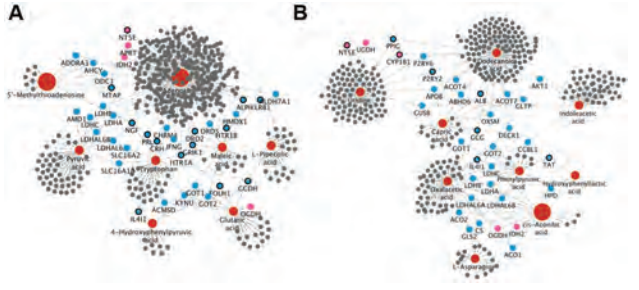
Results: The classification based on ACR achieved the highest prediction accuracy. We identified nine urine and thirteen serum metabolites common among the top 20 from each group. Four metabolites—Adenosine and 5-MTA in urine, and m2,2G and cis-Aconitic acid in serum—demonstrated significant differences across ACR groups (Fig 1). Metabolic network analysis revealed hub proteins and networks linking these metabolites, with significant mRNA expression differences in hub proteins between healthy controls and those with DKD in both urine and serum networks (Fig 2). Notably, IL4I1 mRNA was identified in both urine and serum.

Conclusions: The ACR-based classification demonstrated the highest accuracy. Urinary adenosine and 5-MTA, and serum m2,2G and cis-aconitic acid showed distinct patterns across ACR groups, highlighting their potential as biomarkers. Metabolic network analysis revealed hub proteins, including IL4I1, and networks connecting these differentially expressed metabolites. Further investigation into IL4I1's involvement in DKD is recommended.

Funding: Government Support - Non-U.S.



Differentially expressed metabolites according to DKD stages in urine (A) and serum (B).



Urine (A) and serum (B) metabolic networks.

SA-PO314

Mature MicroRNA (miRNA)-1287-5p and miRNA-197-5p Are Upregulated in Diabetic Kidney Disease

Jonathan M. Wilson,[1] Eiichiro Satake,[2] Behzad Najafian,[3] Kevin L. Duffin,[1] Andrzej S. Krolewski.[2] *[1]Eli Lilly and Company, Indianapolis, IN; [2]Harvard University, Cambridge, MA; [3]University of Washington, Seattle, WA.*

Background: Our previous study examined tissue expression levels of circulating risk miRNAs associated with end-stage kidney disease (ESKD) in diabetes (Satake et al, JASN 2021). The current study aims to extend these finding with larger cohorts and additional analyses of specific ESKD risk miRNAs to understand expression levels and cellular localization in diabetic kidney.

Methods: Localization and levels of mature miRNAs were examined in kidney specimens using a miRNAscope in situ hybridization (ISH) assay. Optimized in silico–designed miRNAscope probes for miR-1287-5p and miR-197-5p were utilized for analyses of kidney tissue expression. Probes were hybridized to formalin-fixed paraffin embedded sections of kidney biopsy tissue obtained from 8 healthy donors (controls), and persons with mild (N=6) or advanced (N=8) biopsy proven diabetic kidney disease (DKD).

Results: miR-1287-5p and miR-197-5p were detected more abundantly in DKD tissues than in controls. miRNA-197-5p was detected at a higher level than miRNA-1287-5p in DKD sections. In DKD, miR-1287-5p and miR-197-5p were detected in tubular epithelia (with more abundance in distal tubules) and glomeruli. Both miRNAs were detected in focal areas of infiltrating inflammatory cells. Both miRNAs were detected in the cytoplasm as well as the nuclei.

Conclusions: Our studies confirm that ESKD risk miRNAs (miRNA-1287-5p and miRNA-197-5p) have higher kidney tissue levels in DKD than normal, especially in tubular epithelial cells. miRNA-1287-5p was validated across multiple donor tissues to be present in DKD vs normal, while novel data show miRNA-197-5p was also present at higher levels in DKD tissue sections. Kidney may be a source of circulating ESKD miRNAs but cellular uptake of circulating miRNA into the kidney may also contribute to higher observed levels. Further studies of tissue expression patterns of ESKD miRNAs will help to advance our understanding of the pathology of DKD and the role of miRNA in disease signaling.

Funding: Commercial Support - Lilly

SA-PO315

Genetic Risk Factors for Kidney Disease in Type 1 Diabetes

Christine P. Limonte,[1] Xiaoyu Gao,[4] Ionut Bebu,[4] Amy B. Karger,[2] Gayle Lorenzi,[5] Bruce A. Perkins,[3] Ian De Boer,[1] Andrew Paterson.[3] *[1]University of Washington, Seattle, WA; [2]University of Minnesota Twin Cities, Minneapolis, MN; [3]University of Toronto, Toronto, ON, Canada; [4]The George Washington University, Washington, DC; [5]University of California San Diego, La Jolla, CA.*

Background: The genetic risk factors underlying kidney disease in type 1 diabetes (T1D) remain poorly understood. We examined whether previously-established genetic risk scores (GRS) for eGFR and albuminuria from general population cohorts correlate with these measures in adults with T1D beyond established demographic and clinical risk factors in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study.

Methods: We applied eGFR and albuminuria GRS derived previously in general population cohorts to 1,304 DCCT/EDIC participants with available genome-wide genotyping. Associations of eGFR GRS with continuous eGFR and of albuminuria GRS with continuous albumin excretion rate (AER) were assessed using linear regression models. Associations of eGFR GRS with incident eGFR <60 ml/min/1.73m^2 and of albuminuria GRS with sustained AER ≥ 30mg/24h and AER ≥ 300 mg/24h were assessed using Cox proportional hazards models. Models were adjusted for age, sex, hemoglobin A1c, diabetes duration, systolic blood pressure, triglycerides, and beta-blocker use.

Results: Overall, participants had a mean age of 60 years and 53% were male. 49% of participants were randomized to intensive versus conventional glucose-lowering therapy in the DCCT. Participants were followed for a median (IQR) 35 (33, 37) years. eGFR GRS was significantly associated with continuous eGFR (2.7±0.3 ml/min/1.73m^2 higher eGFR per 1 SD higher GRS; p<0.0001) and incident eGFR <60 ml/min/1.73m^2 (HR=0.83 [95% CI 0.74, 0.93] per 1 SD higher GRS; p=0.001). Albuminuria GRS was significantly associated with incident AER ≥30mg/24h (HR=1.12 [95% CI 1.03, 1.23] per 1 SD higher GRS; p=0.01), but not incident AER ≥300mg/24h or continuous AER. Associations were similar in analyses stratified by the original DCCT treatment group assignment (intensive versus conventional insulin therapy).

Conclusions: Genetic factors that predict eGFR and albuminuria in the general population are similarly associated with these measures in adults with T1D after adjusting for demographic and diabetes-related clinical risk factors, including glycemic exposure as measured by hemoglobin A1c and by the original DCCT randomization to intensive versus conventional insulin therapy.

Funding: NIDDK Support

SA-PO316

Urinary Growth Differentiation Factor 15 May Be a New Biomarker of Kidney Failure Progression in Diabetic Kidney Disease

Shun Watanabe,[1] Takafumi Toyohara,[1] Koichi Kikuchi,[1] Takehiro Suzuki,[1] Jun Wada,[2] Tetsuhiro Tanaka,[1] Takaaki Abe.[1,3] *[1]Tohoku University Graduate School of Medicine, Sendai, Japan; [2]Okayama University Graduate School of Medicine, Sendai, Japan; [3]Tohoku University Graduate School of Biomedical Engineering, Sendai, Japan.*

Background: Sensitive biomarkers can enhance the diagnosis, prognosis, and surveillance of chronic kidney disease (CKD), including diabetic kidney disease (DKD). Plasma growth differentiation factor 15 (GDF15) levels are a novel biomarker for mitochondria-associated diseases. However, plasma GDF15 levels increase with declining renal function, which may limit its utility in CKD. This study explores the potential of urinary GDF15 as a marker for CKD progression.

Methods: Plasma and urinary GDF15, along with 15 uremic toxins, were measured in 103 CKD patients. The relationship between the urinary GDF15-creatinine ratio and uremic toxins, as well as other clinical characteristics, was investigated. Furthermore, the relationship between the urinary GDF15-creatinine ratio and renal failure progression was examined. The urinary biomarker for the continuous and rapid progression of diabetic nephropathy (U-CARE) study was a multicenter, observational clinical study aimed at investigating urinary biomarkers in diabetic nephropathy (UMIN 00011525). Data from 342 patients in U-CARE study were used to evaluate the performance of the urinary GDF15-creatinine ratio as a biomarker for renal failure progression.

Results: Urinary GDF15-creatinine ratios were less related to renal function and uremic toxin levels compared to plasma GDF15 (eGFR and plasma GDF15 r = -0.46, $p < 0.01$, eGFR and urinary GDF15 $r = 0.13$, $p = 0.19$). However, higher urinary GDF15 levels were observed in patients with worsening renal function. In the U-CARE cohort (n = 342), multiple and logistic regression analyses revealed that baseline urinary GDF15-creatinine ratios predicted a decline in estimated glomerular filtration rate (eGFR) over 2 years (multiple regression: $p = 0.03$, logistic regression: $p = 0.05$), suggesting a predictive ability comparable to the existing urinary albumin-creatinine ratio.

Conclusions: Urinary GDF15 may serve as a useful prognostic marker for renal failure progression in patients with DKD, similar to the urine albumin-creatinine ratio. Integrating this marker into clinical practice could facilitate early therapeutic intervention for patients with progressing renal failure.

SA-PO317

Circulating Endotrophin Is an Early Marker of Kidney Disease Development in Persons with Type 2 Diabetes

Solveig S. Groen,[1] Federica Genovese,[1] Alexandra L. Møller,[1] Stefanie Thöni,[2] Felix Keller,[2] Christian Delles,[3] Morten Lindhardt,[4] Tine Hansen,[5,6] Gert J. Mayer,[2] Peter Rossing.[5,6] *[1]Nordic Bioscience, Herlev, Denmark; [2]Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria; [3]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, United Kingdom; [4]University Hospital Copenhagen, Holbæk, Holbæk, Denmark; [5]Steno Diabetes Center Copenhagen, Herlev, Denmark; [6]Copenhagen University, Department of Clinical Medicine, Copenhagen, Denmark.*

Background: Endotrophin (ETP), a pro-fibrotic fragment generated during collagen type VI formation, has been largely investigated as a biomarker of adverse outcome in persons with diabetic kidney disease. We investigated its potential to predict kidney disease onset in two independent type 2 diabetes (T2D) cohorts.

Methods: Levels of ETP were measured using the nordicPRO-C6™ ELISA (Nordic Bioscience A/S) in baseline plasma from 3226 people with T2D from the Prospective Cohort Study in Patients with Type 2 Diabetes Mellitus for Validation of Biomarkers (PROVALID) and serum from 151 participants with T2D from the PRIORITY trial (NCT02040441). Participants in PRIORITY were normoalbuminuric and with normal or slightly reduced estimated glomerular filtration rate (eGFR) and 976 of the participants in PROVALID had eGFR >90 ml/min/1.73 m^2 at baseline. The investigated outcome was a composite kidney endpoint (sustained 40% decline in eGFR, eGFR <60 ml/min/173 m^2, sustained 30% increase in albuminuria with transition in albuminuria stage, kidney replacement therapy or kidney death) in PROVALID and development of microalbuminuria in at least one morning void sample in PRIORITY. Median follow-up was 4 years in both studies. Cox proportional hazards regression models and Kaplan Meyer survival analysis (for PROVALID participants with eGFR >90 ml/min/1.73 m^2) were applied.

Results: A doubling of ETP was associated with a higher risk of outcome in both PROVALID, after adjustment for age, diabetes duration, HbA1c, history of atherosclerotic cardiovascular disease, systolic blood pressure (SBP), duration of hypertension, BMI, LDL- and HDL-cholesterol, and eGFR (hazard ratio (HR): 1.55, p=0.01; events: 293) and PRIORITY (HR: 1.52, p=0.036, events: 74) after adjustment for sex, age, SBP, eGFR, urinary albumin-creatinine ratio, HbA1c, and CKD273 score. Even in PROVALID participants with eGFR>90 ml/min/1.73 m^2 higher ETP was associated with an increased risk of experiencing the kidney endpoint (p=0.03; n = 69).

Conclusions: Circulating ETP was a risk marker for kidney outcomes in people with T2D without or with early kidney disease. This adds to the evidence that ETP is a relevant biomarker of kidney complications in T2D, even in persons with no or mild kidney disease at baseline.

Funding: Commercial Support - Nordic Bioscience

SA-PO318

Development of a Novel Assay to Quantify Circulating Endotrophin and Validation as a Risk Marker of Complications in Type 2 Diabetes

Federica Genovese,[1] Solveig S. Groen,[1] Alexandra L. Møller,[1] Tine Hansen,[2,3] Peter Rossing.[2,3] BNPCure Study Group. *[1]Nordic Bioscience, Herlev, Denmark; [2]Steno Diabetes Center Copenhagen, Herlev, Denmark; [3]Copenhagen University, Department of Clinical Medicine, Copenhagen, Denmark.*

Background: Endotrophin (ETP), a bioactive fragment of type VI collagen (COL6), has been widely evaluated as a biomarker of risk of outcome in type 2 diabetes (T2D). The most used assay to quantify ETP is a competitive ELISA employing an antibody targeting the C-terminal of the α3 chain of COL6, encompassing part of the ETP sequence (nordicPRO-C6™). We developed a sandwich ELISA targeting specifically the 77 amino acid sequence of ETP (nordicEndotrophin™), which employes a neo-epitope specific antibody targeting the N-terminal end of ETP after cleavage, and the antibody targeting the C-terminal end of COL6A3 (PRO-C6). We evaluated the potential of the two assays as risk markers of T2D adverse outcomes.

Methods: We quantified ETP employing the nordicPRO-C6™ and the nordicEndotrophin™ assays at baseline in serum of 194 individuals with T2D and microalbuminuria from an observational study conducted at Steno Diabetes Center Copenhagen. Endpoints included cardiovascular events (CV mortality, stroke, ischemic CVD, and HF), mortality, and kidney disease progression, defined as decline in estimated glomerular filtration rate (eGFR) of more than 30%. Median follow-up time was 4.9 to 6.3 years. Adjusted Cox-proportional regression analysis was employed to evaluate the association of a 2-fold increase in the biomarkers with the specified endpoints. Adjustment included baseline age, sex, BMI, HbA1c, systolic blood pressure, LDL cholesterol, urinary albumin excretion, eGFR and current smoking.

Results: The nordicEndotrophin™ had accepted linearity, precision, and accuracy in human serum. It showed a similar performance in terms of association to outcome than nordicPRO-C6™, potentially with a higher prognostic power for cardiovascular events than the competitive assay in this cohort (Table). The correlation between the two assay was: Spearman r=0.57, P<0.0001.

Conclusions: The nordicEndotrophin™ assay quantifies specifically the endotrophin molecule in circulation, presenting a similar, or possibly higher, prognostic power for complications of T2D than the competitive ELISA used so far to quantify ETP.

Funding: Commercial Support - Nordic Bioscience

Outcome	PRO-C6 HR (95% CI)	p	Endotrophin HR (95% CI)	p
All-cause mortality (n=25)	2.99 (1.60-5.62)	0.0006	4.97 (2.41-11.70)	0.0002
CV events (n=37)	1.61 (0.82-3.18)	0.17	3.51 (1.69-7.27)	0.0007
CKD progression (n=40)	3.22 (1.75-5.92)	0.0002	2.42 (1.22-4.80)	0.01

SA-PO319

Impact of Carbamylation on the Association of Glycated Albumin and Diabetic Kidney Disease (DKD) Progression

Mengyao Tang,[1,2] Anders H. Berg,[3] Sahir Kalim.[1,2] *[1]Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Cedars-Sinai Medical Center, Los Angeles, CA.*

Background: HbA_{1c} is widely used to estimate glycemia, yet it is less reliable in CKD due to factors such as anemia and competition from another post-translational protein modification, carbamylation, acting on the same amino groups. We previously showed that the association between HbA_{1c} and the risk of CKD progression was modified by anemia and carbamylation. While an alternative hemoglobin-independent glycemic marker, glycated albumin, could overcome the anemia-related limitation of HbA_{1c}, little is known about whether it is impacted by carbamylation in CKD.

Methods: We measured baseline serum glycated albumin and carbamylated albumin levels in 1,550 patients with co-existing CKD and diabetes enrolled in the prospective Chronic Renal Insufficiency Cohort study. A Cox regression model was used to test the association between glycated albumin and CKD progression (ESKD or 50% eGFR decline), with an interaction term of glycated albumin and carbamylated albumin to evaluate whether carbamylation modified this association.

Results: Participant characteristics included mean age 60 (SD 9) years; mean eGFR 38 (15) mL/min/1.73 m^2; median glycated albumin 22 (IQR 18-28) %; and median carbamylated albumin 8 (6-11) mmol/mol. Glycated albumin levels were higher in the higher carbamylated albumin quartiles. During a median 7-year follow-up, 805 (51.9%) individuals developed CKD progression. Overall, higher glycated albumin levels (restricted cubic spline or quartiles) were independently associated with greater risks of CKD progression (**Fig 1**): compared with quartile 1, those in quartile 4 had a 1.35-fold greater risk (95% CI, 1.10 to 1.66). Interaction testing between glycated albumin and carbamylated albumin was not significant (P = 0.43).

Conclusions: In patients with CKD and diabetes, the association between glycated albumin and CKD progression is not modified by carbamylation. This finding suggests that glycated albumin could overcome the carbamylation-related limitation of HbA_{1c} in CKD.

Funding: NIDDK Support, Private Foundation Support

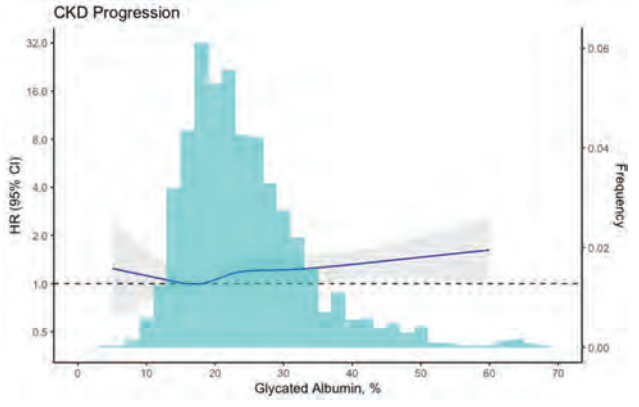


Fig 1. Adjusted HR for Glycated Albumin and Risks of CKD Progression

SA-PO320

Application of a Validated Prognostic Protein Biomarker Test for Kidney Decline in Type 2 Diabetes to Type 1 Diabetes

Kirsten E. Peters,[1] Wendy A. Davis,[2,3] Scott D. Bringans,[1] James K. Lui,[1] Tasha S. Lumbantobing,[1] Timothy Davis,[2,3] Richard Lipscombe.[1]
[1]Proteomics International, Perth, WA, Australia; [2]The University of Western Australia, Perth, WA, Australia; [3]Australian Centre for Accelerating Diabetes Innovations, Melbourne, VIC, Australia.

Background: Population-based studies have shown that the risk of chronic kidney disease (CKD) appears greater in type 1 diabetes (T1D) versus type 2 diabetes (T2D) across all age strata, and there is evidence of relative underutilization of renoprotective therapies in T1D. These observations argue for validated tests that reliably identify the risk of progressive renal disease at an early stage in T1D and pre-empt preventive management strategies. PromarkerD is a validated blood test developed for predicting renal decline over four years in T2D. This study assessed whether PromarkerD has similar clinical utility as a prognostic test in T1D.

Methods: PromarkerD scores were measured at baseline in 137 participants with T1D from the community-based Fremantle Diabetes Study. Plasma protein concentrations (ApoA4, CD5L, IGFBP3) measured by ELISA were combined with the concomitant age, serum HDL-cholesterol and eGFR to provide PromarkerD scores. Scores were categorised as low-, moderate- or high-risk as determined by pre-specified cut-offs. Renal decline was defined as incident CKD (eGFR <60 mL/min/1.73m^2 in people above this at baseline) or an eGFR decline of ≥30% over four years. Performance was assessed using the area under the receiver operating characteristic curve (AUC).

Results: At baseline, the 137 participants (mean age 45 years, 53% males, median diabetes duration 20 years) with PromarkerD classifying 83% low-risk, 10% moderate-risk and 7% high-risk for renal function decline in the next four years. Of these, 92 (67%) had renal function assessed at the four-year review, with 9 (9.8%) developing outcomes. The biomarkers ApoA4 and CD5L were significantly elevated at baseline in the people with prespecified renal outcomes while IGFBP3 showed no significant difference. The PromarkerD test scores were substantially higher in those with incident renal outcomes; the AUC was 0.93 (95% CI 0.87–0.99), with sensitivity 78%, specificity 98%, PPV 50% and NPV 97%.

Conclusions: The present data suggest that PromarkerD has strong clinical utility in identifying people with T1D at risk of adverse renal outcomes. Further validation studies are underway to confirm this promising performance of the PromarkerD test for predicting CKD in T1D, as has previously been shown for T2D.

Funding: Commercial Support - Proteomics International

SA-PO321

Unraveling the Mechanism of SGLT2 Inhibitors Using Urinary Proteomics in Patients with Diabetic Kidney Disease

Mark A. De la Rambelje,[1] Viji Nair,[2] Niels Jongs,[1] Michael K. Hansen,[3] Adriaan A. Voors,[1] Matthias Kretzler,[2] Wenjun Ju,[2] Hiddo J. Heerspink.[1]
[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]University of Michigan Department of Internal Medicine, Ann Arbor, MI; [3]Janssen Research and Development LLC, Spring House, PA.

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) confer kidney protection in patients with diabetic kidney disease (DKD). We studied the effect of the SGLT2i canagliflozin (CANA) on the urinary proteome, aiming to identify biological pathways involved in its protective effect.

Methods: We performed a post-hoc analysis in a subgroup of 392 participants with DKD from the phase 3 randomized placebo controlled CREDENCE trial. A total of 5284 proteins were quantified using the SomaScan platform in urine samples collected at baseline and week 52. Change in protein abundance was evaluated in patients receiving CANA after 1 year of treatment. Pathways were identified using ingenuity pathway analysis (IPA). Single-cell RNA expression of genes coding for proteins found to be affected by CANA was assessed in proximal tubule (PT) cells and thick ascending limb (TAL) cells in kidney biopsies from young patients with type 2 diabetes receiving either standard care + SGLT2i or only standard care.

Results: Placebo and CANA groups were well matched based on age (62 years), gender 141 (34.7%) female, albuminuria (median 1016 mg/g), eGFR (mean 60.4 mL/min/1.73m^2). After one year of treatment, 103 proteins were up-regulated (FDR < 0.05), these proteins are enriched in pathways related to gluconeogenesis, carbon metabolism, and hypoxia-inducing factor-1 signaling (Figure). Single cell analysis of young adults with T2D using SGLT2 inhibitors showed that more genes linked to these urinary proteins were upregulated in TAL cells compared to PT cells, suggesting that these urinary proteins more likely originate from TAL cells.

Conclusions: These results suggest that CANA treatment causes an increase in energy-demand in the distal tubule, possibly reflecting compensatory sodium reabsorption following sodium inhibition in the proximal tubule.

Funding: Commercial Support - Janssen

SA-PO322

Sex-Specific Methylation Indices Improve Risk Detection for Kidney Disease in the PROFIL Diabetes Study

Sam El-Osta,[1,2] Ishant Khurana,[1] Scott S. Maxwell,[1] Tine Hansen,[2] Tarunveer S. Ahluwalia,[2] Frederik Persson,[2] Peter Rossing.[2] *[1]Baker Heart and Diabetes Institute, Melbourne, VIC, Australia; [2]Steno Diabetes Center Copenhagen, Herlev, Denmark.*

Background: While sex-related differences in type 1 diabetic (T1D) are known to disproportionately affect the development and progression of diabetic kidney disease (DKD), genome wide association studies have failed to discern a genetic influence that stratify disease. This study assessed sex differences in the epigenetic architecture to define novel circulating biomarkers of DKD.

Methods: Despite recent improvements in BeadChip arrays we have used sequencing for broader genomic coverage to define methylation architecture of circulating leukocytes. Constructed on the Kidney Diseases, Improving Global Outcomes (KDIGO) classification of chronic kidney disease we characterised leukocyte methylation profiles by sequencing (methyl-seq) from the Steno Diabetes Centre Copenhagen PROFIL cohort (n=124). The case and control registry comprised of people living without diabetes (n=20) and a low-risk group without DKD (LR, n=36) as well as a moderate risk (MR, n=27), high risk (HR, n=21) and very high risk (VHR, n=20) groups living with DKD. To understand sex-related differences in methylation three-way analyses were performed to distinguish male and female profiles compared to combined sex analyses. Functional methylation analyses assessed pathways and regulatory elements associated with DKD. Differential methylation indices were used to characterise sex-specific biomarkers for DKD risk using eGFR for the prediction of disease progression.

Results: Methylation analyses identified exceptional gene body and promoter methylation in the PROFIL registry emphasizing the importance of sequencing methodologies to improve quantitative epigenetic classification by KDIGO. Methylation was disproportionally associated between sexes for the DKD groups (MR, HR and VHR) when compared to the LR group. Methylation was significantly reduced in females when

compared with increased quantitative methylation observed in males. Combinatorial ROC analysis for DKD risk and eGFR decline identified sex-specific methylation scores predictive of DKD progression.

Conclusions: PROFIL provides a T1D framework into the pathogenesis of kidney disease and define sex-specific methylation indices that improve diagnostic performance above clinical modelling alone.

Funding: Government Support - Non-U.S.

SA-PO323

Acetazolamide Therapy and Kidney Function in Persons with Type 1 Diabetes: The ATAK-DM1 Trial

Charles Ginsberg,[1] Jesse C. Seegmiller,[2] Volker Vallon,[1] Robert L. Thomas,[1] Joachim H. Ix.[1] *[1]University of California San Diego, La Jolla, CA; [2]University of Minnesota Medical School, Minneapolis, MN.*

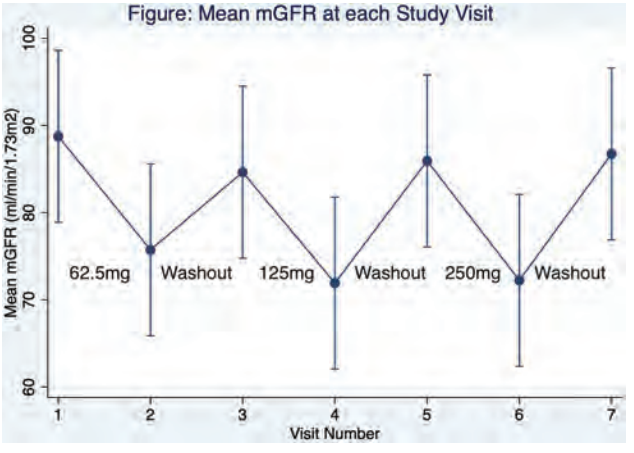
Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) lower risk of kidney failure through greater sodium delivery to the distal tubule and activation of tubuloglomerular feedback (TGF) thereby lowering glomerular pressure which lowers glomerular filtration rate (GFR). SGLT2i are not widely used in type 1 diabetes mellitus (T1DM) due to diabetic ketoacidosis (DKA) risk. Acetazolamide, a proximal tubule diuretic, delivers sodium to the distal nephron, and may activate TGF without glycemic effects. The kidney response and safety of acetazolamide in T1DM patients are not well known.

Methods: We conducted a dose escalation trial to study the effects of three doses of oral acetazolamide (62.5, 125, and 250mg, all twice daily) in 12 persons with T1DM and eGFR> 45ml/min/1.73m^2. Participants were treated for 2 weeks followed by a 2 week wash out before the next dose level. Blood chemistries were measured before and after each treatment interval. GFR was measured (mGFR) using iohexol. We hypothesized that acetazolamide would safely cause reversible reductions in GFR indicating stimulation of TGF.

Results: The 12 participants had mean age 46±17 years, all participants were White, and 9 were female. The mean mGFR was 89±18ml/min/1.73m^2 at baseline. Acetazolamide caused a 14.7(95%CI 8.5,21.0)%, 13.8(6.5,21.0)%, and 15.4(9.9,21.0)%, reduction in mGFR over 2 weeks on the 62.5, 125, and 250mg doses, respectively (**Figure**). These changes were not attenuated when accounting for body weight changes. GFR returned to baseline after a 2 week washout for each dose. Serum bicarbonate was reduced by 2.3(1.2,3.3), 4.1(3.3,4.8) and 4.4(2.3,6.5)mEq/L with the three escalating doses, respectively. There were no episodes of hypokalemia (serum potassium< 3.5 mEq/L) observed for any dose.

Conclusions: Among persons with T1DM, acetazolamide caused an acute reversible reduction in GFR with moderate concurrent reductions in serum bicarbonate.

Funding: NIDDK Support, Private Foundation Support



SA-PO324

Characteristics of Patients with Type 1 Diabetes (T1D) and CKD Receiving Novel Kidney Protective Therapies (KPT)

M. Luiza A. Caramori,[1] Enrico Repetto,[4] Christopher Perkins,[4] Ambarish Pandey,[3] Peter Rossing.[2] *[1]Cleveland Clinic, Cleveland, OH; [2]Steno Diabetes Center Copenhagen, Herlev, Denmark; [3]The University of Texas Southwestern Medical Center, Dallas, TX; [4]Roche Diagnostics Corp, Indianapolis, IN.*

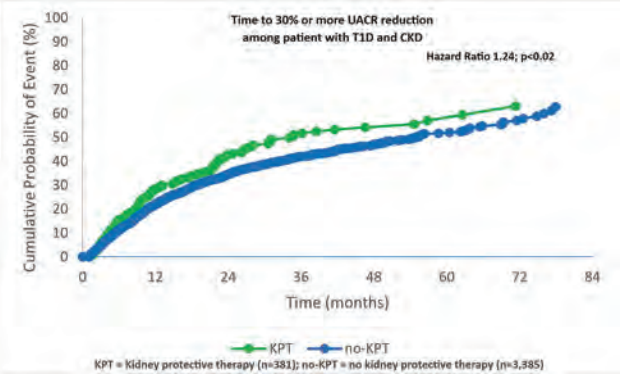
Background: KPT (SGLT2i, GLP-1RA and nsMRA) for pts with T2D and CKD have not been approved for pts with T1D and CKD. Regardless, a significant proportion of these pts receive these therapies. Herein, we used a case-control design to compare the characteristic of T1D pts with CKD treated or not with KPT and assessed kidney (Kd) outcomes.

Methods: Optum's De-identified Market Clarity database (1/1/2018-6/30/2023) was used to identify pts ≥18 yrs with T1D (Klompas algorithm) and CKD. CKD was defined as any two of CKD ICD-10 codes, eGFR<60 ml/min/1.73m^2, or UACR≥30 mg/g, ≥3 months apart. Pts on dialysis or who had a Kd transplant were excluded. KPT use was defined as any KPT prescription that was refilled ≤180 days from KPT start (index date). An index date was randomly assigned to pts not on KPT (no-KPT). Outcome analysis included T1D CKD pts who had UACR data available ≤540 days prior to and ≥30 days after index date.

Results: Among 408,951 pts with T1D, 128,675 (31.5%) had CKD. 1,970 pts (1.5% of T1D CKD pts) were on KPT, 41% of them on SGLT2i, 70% GLP-1RA, and 3% nsMRA; 14% were on more than one KPT. Pts on KPT were more often females (57 vs 50%), less often White (71 vs 78%), and had higher UACR [157 (114-200) vs 113 (92-135) mg/g] than pts not on KPT, respectively. Proportion of non-Hispanic (75 vs 76%), age (51±13 vs 52±17 yrs) and eGFR (60±28 vs 62±30 mL/min/1.73m^2) were not different. Time to 50% ≥30% UACR reduction (Fig) was 31 (25-47) vs 47 (43-53) months in the KPT (n=381) vs no-KPT (n=3385) cohort, respectively (HR1.24, p≤0.02).

Conclusions: We identified a large number of pts with T1D and CKD treated with off-label KPT. Pts on KPT were more often female and non-White and had more advanced Kd disease as evidenced by higher baseline UACR. The proportion of pts with T1D and CKD achieving clinically meaningful UACR reduction (≥30%) was greater among KPT users and comparable to what was observed among pts with T2D and CKD, supporting the need for trials in T1D.

Funding: Commercial Support - Roche: database acquisition, ER and CP efforts



SA-PO325

Glycemic Variability of Hemoglobin A1c-Based Metrics and Mortality in Patients with ESKD Undergoing Dialysis

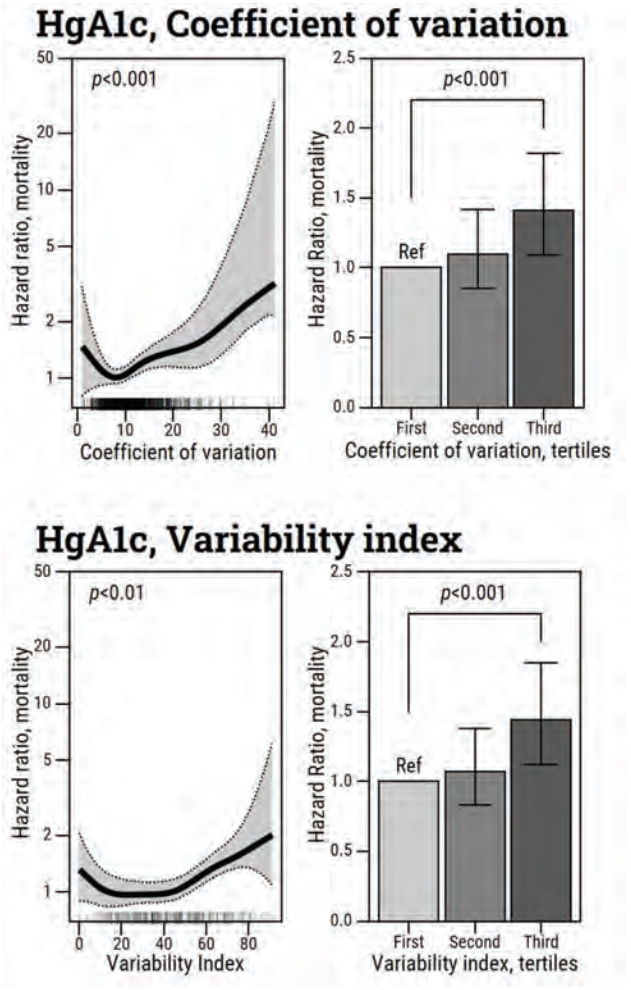
Jose E. Navarrete,[1] Jose Guevara,[2] Lucas Hernandez,[1] Guillermo Umpierrez.[1] *[1]Emory University, Atlanta, GA; [2]Universidad de Especialidades Espiritu Santo, Samborondon, Ecuador.*

Background: HbA1c has long been recommended as the gold standard for assessing glycemic control in patients with diabetes. However, the correlation between glycemic control by HbA1c and outcomes is less than optimal in end-stage kidney disease (ESKD). HbA1c variability has been proposed as a better tool to predict outcomes, including mortality in ESKD. We report the predictive value of HbA1c variability on all-cause mortality in patients undergoing dialysis

Methods: Patients with diabetes new to dialysis, enrolled in an academic dialysis program from 1/2010 to 12/2023. HbA1c was measured quarterly. Patients with at least 90 days on dialysis and 3 consecutive measures of HbA1c were included. The coefficient of variation (CV, standard deviation divided by mean HbA1c) and variability index (VI, change of 0.5% compared to previous value) were used as predictors of mortality. The association between CV, VI and mortality was assessed using Cox models, with CV and VI values as continued variables and tertile of distribution (Figure). Adjustments for age, body mass index (BMI), history of heart failure, and peripheral vascular disease were included in all models

Results: 979 patients were eligible, 91.5% with type 2 diabetes. The median age was 60.5 years (IQR: 50.8-68.7), 52.5% males, 89.2% African-Americans, BMI 27.6 kg/m2, and median follow-up of 3.3 years (IQR: 1.9-5.6). Glycemic variability indices-CV (p<0.001) and VI (p<0.01) were significantly associated with mortality. Their highest tertile- CV (HR 1.42, CI: 1.10-1.83) and VI (HR 1.44, CI: 1.12-1.85) were also associated with higher mortality compared to the lowest tertile

Conclusions: Glycemic variability of HbA1C - coefficient of variation and variability index- were strongly associated with all-cause mortality in ESKD undergoing dialysis



SA-PO326

Impact of Vertical Sleeve Gastrectomy (VSG) on Early Diabetic Nephropathy

Abhijit S. Naik,[1] Fadhl Alakwaa,[1] Jennifer A. Schaub,[1] Phillip J. McCown,[1] Viji Nair,[1] Francesca Annese,[1] Edgar A. Otto,[1] Ye Ji Choi,[2] Justin R. Ryder,[4] Laura Pyle,[2] Kristen Nadeau,[2] Frank C. Brosius,[3] Matthias Kretzler,[1] Petter Bjornstad.[2] *[1]University of Michigan, Ann Arbor, MI; [2]University of Colorado Anschutz Medical Campus, Aurora, CO; [3]Banner - University Medical Center Tucson, Tucson, AZ; [4]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL.*

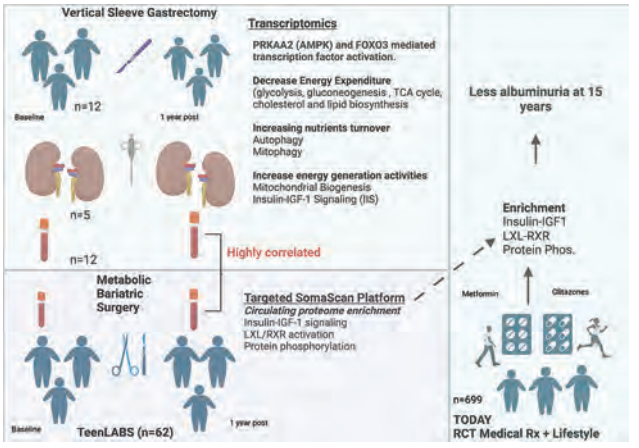
Background: We explored the impact of VSG on the progression of early diabetic nephropathy (DN) in an adolescent cohort with obesity and type 2 diabetes (T2D).

Methods: 5 of 12 patients from IMPROVE study had renal biopsies before and 1year after VSG. MRI measured change in total kidney volumes (TKV). Kidney tissue was profiled using histology, single-cell RNAseq (scRNAseq), and proteomics. Renal function was measured by assessing glomerular filtration rate (GFR) and albuminuria. Somascan data from TeenLABS study(n=62) was used to evaluate circulating proteomic changes pre- and post. The longitudinal TODAY study provided an association between change in circulating proteome with albuminuria.

Results: All participants had a reduction in weight, BMI, GFR, albuminuria, mean arterial pressure, and insulin resistance. The TKV decreased by 18%. Tissue morphometry showed reductions in glomerular volume, indicating resolving glomerular hypertrophy. scRNA-seq of the proximal tubule (PT) showed enrichment of evolutionarily conserved *PRKAA2 (*AMPK*)* and *FOXO3*-mediated transcription factors post-VSG, consistent with cells experiencing 'starvation stress.' There was a coordinated reduction in transcripts of gluconeogenesis, TCA cycle, ROS mitigation machinery and an increase in Insulin-IGF-1 Signaling (IIS), mitochondrial biogenesis, apoptosis and mitophagy. Circulating proteomic analysis from TeenLABS showed reduced IIS-mediated signaling aligned with the intrarenal transcriptional response after VSG. TODAY participants had decreased albuminuria at 15 years among pathways enriched in TeenLABS participants.

Conclusions: VSG induces a coordinated activation of *AMPK and FOXO3*-mediated transcription factors in youth-onset T2D, resetting molecular programs in the PT with reversal of early DN. These findings are currently undergoing proteomic validation.

Funding: NIDDK Support, Private Foundation Support



SA-PO327

Utilization Trends of Tirzepatide, Glucose-Lowering Medications, and Anti-obesity Medications in Patients with CKD with and without Type 2 Diabetes

Panupong Hansrivijit,[1,2] Janinne Ortega-Montiel,[1] Deborah J. Wexler,[3,2] Elisabetta Patorno,[1,2] Julie M. Paik.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Massachusetts General Hospital, Boston, MA.*

Background: Tirzepatide was approved by the U.S. FDA in May 2022 for glycemic control in adults with type 2 diabetes (T2D). Our study goal was to describe the utilization of tirzepatide, other glucose-lowering medications (GLM), and anti-obesity medications (AOM) in patients with chronic kidney disease (CKD), regardless of T2D status.

Methods: We obtained data from a large U.S. insurance claims database (Optum) from January 1, 2022, to September 30, 2023. We created two cohorts using validated algorithms based on ICD codes: 1) CKD with T2D and 2) CKD without any diabetes. Incident use of any medications was defined as no prior use in 365 days.

Results: We identified 455,047 patients with CKD and T2D treated with any GLM, and 5,978 patients with CKD without any diabetes treated with any AOM. For patients with CKD and T2D, tirzepatide initiation, regardless of dose, comprised 8.4% of all initiated GLM by the end of September 2023 (**Figure 1A**). Of 10,661 tirzepatide initiators, the mean age was 65.9 (9.7) years, 42.2% were male, and 64.2% were of white race. For patients with CKD without diabetes, initiation of tirzepatide was second to subcutaneous semaglutide ≤2 mg, with incidence rising from 0.5% in June 2022 to 36.5% of all initiated AOM in December 2022 (**Figure 1B**). Of 909 tirzepatide initiators, the mean age was 65.4 (10.1) years, 26.2% were male, and 74.4% were of white race.

Conclusions: Tirzepatide use increased over time in patients with CKD. Further studies are needed to assess tirzepatide's effectiveness and safety compared to other GLM and AOM in patients with CKD.

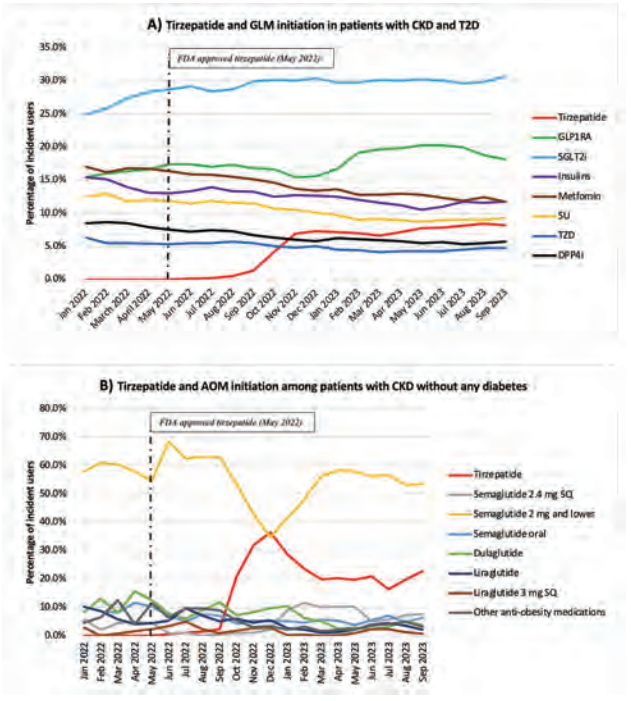


Figure 1. A) Trends of GLMinitiation in patients with CKD and T2D. **B)** Trends of AOM initiation in patients with CKD without any diabetes.

SA-PO328

A Novel Potassium Binder Sodium Zirconium Cyclosilicate to Enable RAAS Inhibitor (RAASi) Use in the Treatment of Patients with Diabetic Kidney Disease: The Crystal Study

Weiming Wang,[1] Leyi Gu,[2] Xiujuan Zang,[3] Na Liu,[10] Yangbin Pan,[11] Chunming Jiang,[4] Ying Li,[9] Gengru Jiang,[5] Zhiguo Mao,[6] Jun Xue,[7] Rong Zhou,[8] Hao Xu,[1] Jian Liu.[1] *[1]Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China; [2]Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital Baoshan Branch, Shanghai, China; [3]Songjiang Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [4]Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital, Nanjing, China; [5]Shanghai Jiaotong University School of Medicine Xinhua Hospital, Shanghai, China; [6]Shanghai Changzheng Hospital, Shanghai, China; [7]Huashan Hospital Fudan University, Shanghai, China; [8]Shanghai Yangpu District Central Hospital, Shanghai, China; [9]Shanghai Jiading Hospital, Shanghai, China; [10]Tongji University Dongfang Hospital, Shanghai, China; [11]Shanghai Pudong Hospital, Shanghai, China.*

Background: The key treatment strategy for diabetic kidney disease (DKD) involves optimizing the comprehensive management of blood glucose, blood pressure and proteinuria. Renin-angiotensin-aldosterone system inhibitors (RAASis) are preferred due to their effectiveness in lowering blood pressure, reducing urine protein and slowing kidney damage progression. However, RAASi may cause hyperkalemia (HK) in DKD patients, and RAASi reduction or discontinuation due to HK will affect its cardio-renal benefits. Therefore, it is crucial for DKD patients to receive RAASi at target dose while simultaneously managing hyperkalemia.

Methods: This is a multicenter, open-label, randomized clinical study to evaluate the efficacy of sodium zirconium cyclosilicate (SZC) in enabling RAASi usage in DKD patients (stage 3-4 chronic kidney disease). Patients are eligible if they experienced HK (sK>5.0 mmol/L) at least once in the 90 days prior to enrollment. Eligible patients will be randomized 1:1 to enter the SZC + RAASi or RAASi-only group and were followed up for 24 weeks, including a 12-week RAASi titration phase and a 12-week ACEIs/ARBs maintenance therapy phase. The primary endpoint is the proportion of patients with increased dose of RAASi at week 12. The exploratory endpoints include the distribution of patients with ≥50% of labelled maximum dose of RAASi and changes in UACR, serum creatinine and blood pressure at weeks 12 and 24.

Results: The CRYSTAL study has achieved 100% enrollment as of 2023 Dec, enrolling 86 patients with RAASi treatment. Results for the primary endpoint have been collected by March 2024 (week 12) and all follow-up data will be generated by June 2024 Jun (week 24). These results will be presented at the 2024 ASN congress.

Conclusions: This study will provide the first evidence on how SZC optimizes RAASi treatment while controlling hyperkalemia in the Chinese population.

Funding: Commercial Support - AstraZeneca China

SA-PO329

Association of Biopsy-Proven Diabetic Nephropathy with Obstructive Sleep Apnea-Hypopnea Syndrome

Qin Xue, Hui Liu, Niansong Wang. *Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Both obstructive sleep apnea-hypopnea syndrome (OSAHS) and diabetic kidney disease (DKD) are common disease. As one of the most common microvascular complications of DM, diabetic nephropathy (DN) has become a primary cause of end-stage renal disease (ESRD) worldwide. Previous reports show that patients with severe sleep apnea or sleep-disordered breathing (SDB) were more likely to have diabetes than those without sleep apnea or SDB. However, the correlation of renal pathology of DN with OSAHS is still unclear. The objective of this study is to explore the impact of OSAHS on renal pathology of DN and assess risk factors of OSAHS in patients with DKD.

Methods: We selected 87 patients with DKD who were hospitalized in department of our hospital from September 2020 to February 2023. All participants underwent full-night standard nocturnal polysomnography (PSG) monitoring in the sleep center. The apnea and hypopnea are scored following the definitions of the American Academy of Sleep Medicine guidelines. An apnea hypopnea index (AHI)>5 events/h was consistent with the diagnosis of OSA. 94 CKD Patients without DKD were recruited as control group in this study. Multiple linear regression is used for analysis the risk factors of OSAHS in patients with DKD. 20 biopsy-proven DN patients were divided into two groups based on the level of AHI to analyze the correlation between OSAHS-related parameters and renal pathological features.

Results: The prevalence of OSAHS was 90.8% (79 of 87), with 25.2% (22 of 87) mild, 35.6% (31 of 87) moderate and 29.8% (26 of 87) severe respectively. The Scr (P=0.001), cystatin C (P=0.030), 24h urine protein (P=0.006), AHI (P=0.022), ODI (P=0.011), and CT90 (P=0.046) levels in patients of DKD group were significantly higher than those within non DKD group. Multiple linear regression showed that diabetes course (p=0.048), BMI (p=0.042) were independent risk factors for eGFR. CT90 (p<0.001) was an independent risk factor for UACR. Regarding DKD renal pathology, the overall trend was that the higher the severity of OSAHS, the higher the renal interstitial tubule score and arteriolar hyalinosis score.

Conclusions: OSAHS is high prevalence in patients with DKD. Patients with DKD had more severe renal damage and hypoxemia than those without DKD. Patients of diabetic nephropathy with OSAHS tend to have higher risk of renal pathological impairment.

SA-PO330

Intensive Uric Acid-Lowering Improved Outcomes in Type 2 Diabetes with CKD: A Multicenter, Retrospective, Real-World Cohort Study

Zhang Shaogui X. Xiaoguizi, Danfeng Liu, Runli Jia, Jianteng Xie, Wenjian Wang. *Division of Nephrology, Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: To explorer the effects of intensive uric acid-lowering therapy on the outcomes in type 2 DM with chronic kidney disease (CKD).

Methods: Patients diagnosed of type 2 DM with CKD(DKD) were enrolled in the nephrology department of 8 hospitals from January 2013. The patients were followed up to the end of the follow-up period (October 2023). Primary outcomes encompass a composite endpoint, including doubling of Scr, 40%-decline in eGFR, initiate dialysis, progression to end-stage renal disease or all-cause mortality. The risk factors and the relationship with prognosis were analyzed. To further explore the influence of baseline SUA (B-SUA) and time average SUA (TA-SUA) level fluctuation on the prognosis of DKD patients, logistic and Cox proportional risk regression models were used to analyze. For the HUA group (n=772) and NUA group (n=300),1:1 propensity score matching was used to clarify the optimal range of SUA and explore the benefit of intensive uric acid-lowering therapy to prevent and slow down the kidney damage.

Results: 1651 patients were screened, 1072 patients with a median age of 56.5±10.4 years old, and 700 males (65.3%) were enrolled. The median of follow-up was 60.4±5.6 months. The overall prevalence of hyperuricemia incurrent cohort was 46.1%, which was higher in males than in females. The SUA level increased with age and was negatively correlated with renal function. After adjusting for confounding factors, we found that B-SUA and TA-SUA were independent risk factors for prognosis. In subgroup analysis, TA-SUA 360μmol/L was consistent among subgroups of age, sex, hemoglobin, glycosylated hemoglobin and lipid-lowering, glucose-lowering, blood-pressure lowering, and urico-lowering drug use. The spline curves demonstrated a U-shaped pattern after propensity score matching at B-SUA 360μmol/L and TA-SUA 300μmol/L respectively suggesting a potential threshold effect of SUA on prognostic risk.

Conclusions: In this study, we found that hyperuricemia was an independent risk factor for outcomes. Intensive uric acid-lowering therapy especially maintaining SUA levels around 300~360μmol/L, delays end-point events in DKD.

SA-PO331

Impact of Triglyceride-to-High-Density Lipoprotein Cholesterol Ratio as a Hyperinsulinemia Marker of Kidney Function Decline

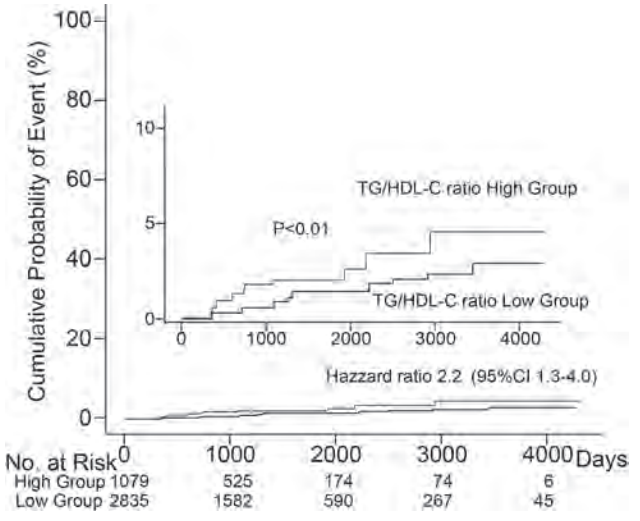
Makoto Araki. *Sapporo Tokushukai Hospital, Sapporo, Japan.*

Background: The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio is known as a surrogate marker for hyperinsulinemia, which underlies obesity, and is also an excellent predictor of progression to type 2 diabetes. This study aims to investigate whether hyperinsulinemia can predict renal function decline in the absence of diabetes and obesity using the proxy marker TG/HDL-C ratio.

Methods: This single-institutional observational study in Japan targeted individuals who had annual health check-ups measuring creatinine, TG, HDL-C, and body mass index (BMI) from 2012 to 2022. Exclusion criteria included individuals under 18, those with an initial estimated glomerular filtration rate (eGFR) below 45, blood test results for less than one year, and initial hemoglobin A1c (HbA1c) levels of 6.5% or higher. Participants were divided into two groups based on their baseline TG/HDL-C ratio and BMI. The TG/HDL-C threshold was set at 2.1, based on the previous report, and the BMI threshold was set at 23, according to Asian overweight criteria. The primary endpoint was the time to an eGFR decline below 45, analyzed using time-to-event analysis.

Results: A total of 3,914 individuals met the criteria (mean age: 50.0 years, 44.5% male, mean BMI: 23.0, mean eGFR: 75.1). During the observation period, 135 individuals (3.5%) developed diabetes, with the incidence rate being 2.51 times higher in the high TG/HDL-C group compared to the low group. Univariate analysis showed that the high TG/HDL-C group had significantly worse renal function (Log-rank p<0.01, hazard ratio 2.2 [1.3-4.0])(Figure). Further analysis of 2,022 non-obese individuals (BMI<23) showed similar results (Log-rank p<0.01).

Conclusions: The TG/HDL-C ratio, a surrogate marker for hyperinsulinemia, was associated with renal function decline in non-diabetic individuals. This association persisted even in non-obese individuals.



SA-PO332

Competing Risks of Kidney Failure and Death by Baseline eGFR in Diabetes

Katherine R. Tuttle,[1,2] Lindsey M. Kornowske,[1] Kenn B. Daratha,[1] Cami R. Jones,[1] Christina Reynolds,[1] Alain K. Koyama,[3] Fang Xu,[3] Yoshihisa Miyamoto,[3] Joshua J. Neumiller,[1,5] Radica Z. Alicic,[1,2] Susanne B. Nicholas,[4] Obidiugwu Duru,[4] Keith C. Norris,[4] Meda E. Pavkov.[3] The CURE-CKD Registry. *[1]Providence Health and Services, Spokane, WA; [2]University of Washington School of Medicine, Seattle, WA; [3]Centers for Disease Control and Prevention, Atlanta, GA; [4]University of California Los Angeles, Los Angeles, CA; [5]Washington State University College of Pharmacy and Pharmaceutical Sciences, Spokane, WA.*

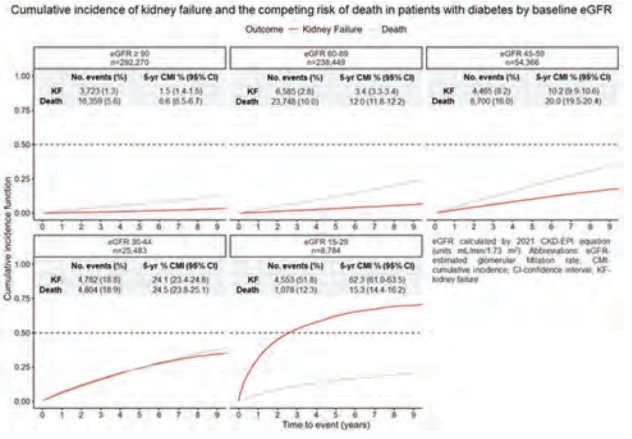
Background: The study aim was to assess the competing risks of kidney failure and death in a real-world population with diabetes by baseline estimated glomerular filtration rate (eGFR).

Methods: Providence and University of California Los Angeles health systems provided electronic health record registry data for patients aged ≥12 years with diabetes in 2013-2022. Kidney failure was defined by eGFR <15 mL/min/1.73 m², dialysis, or kidney transplant. Follow-up started at diabetes identification and ended at onset of kidney failure, death, or last encounter. Cumulative incidence functions were assessed by baseline eGFR. Fine-Gray multivariable models for kidney failure were constructed with death as a competing risk.

Results: Among 619,352 people with diabetes, risk of death exceeded kidney failure for eGFR ≥45 mL/min/1.73 m² (**Figure**). At eGFR 30-44 mL/min/1.73 m², these risks were equivalent. At eGFR 15-29 mL/min/1.73 m², 5-year cumulative incidences of kidney failure and death were 62.3% and 15.3%, respectively, with an adjusted hazards ratio for kidney failure of 55.5 (95% CI 51.6-59.6; reference eGFR ≥90 mL/min/1.73 m²). Accounting for competing risk of death, other significant kidney failure predictors were male sex, non-White race, non-commercial health insurance, Providence health system, macroalbuminuria, age 40-59 years, or hospitalization during a 1-year baseline period.

Conclusions: Death was more frequent than kidney failure at eGFR ≥45 mL/min/1.73 m², but the trend reversed at lower eGFR with kidney failure becoming more much common at eGFR <30 mL/min/1.73 m². In the diabetes population, kidney and survival-based risk stratification may help to target management according to risk status.

Funding: NIDDK Support, Other U.S. Government Support



SA-PO333

Trend Analysis of Kidney Failure and Diabetes Mellitus-Related Mortality, 1999-2020

Mohammad Ammar ur Rahman,[1] Ahmed J. Chaudhary,[2] Laiba Sarfraz,[1] Luqman Munir,[1] Amna Khalid,[1] Saleha Azeem,[1] Mahnoor Fatima.[1] NEURALKEy. *[1]King Edward Medical University, Lahore, Pakistan; [2]Detroit Medical Center, Detroit, MI.*

Background: The interrelation between renal failure and diabetes mellitus lies in insulin resistance. Diabetes mellitus type 2 is a metabolic syndrome resulting in hyperglycemia. High blood glucose causes nonenzymatic glycation of tissue proteins resulting in mesangial expansion. This increases the permeability of blood vessels by weakening the wall. This condition ultimately leads to renal failure as renal blood vessels are damaged. These negatively downgrade the quality of life of the survivors. The mortality due to kidney failure in diabetes mellitus patients is on the decline in the United States. In this study we explored these trends from 1999-2020, using age adjusted mortality rates (AAMR) to pinpoint incongruities between epidemiological groups.

Methods: Our study conducted an in-depth search of the CDC Wonder database, based on the incidence of sequalae of stroke-related Age-Adjusted Mortality Rate (AAMR) per 100,000 individuals. Employing Join point Regression Analysis, we assessed Parallelism and computed Annual Percent Changes (APC) with a 95% Confidence Interval. For a p<0.05, the test of parallelism was considered significant for unparallel.

Results: From 1999 to 2020, a total of 726654 deaths were reported due to the kidney failure due to diabetes mllitus. The overall AAMR showed a decline from 1999 to 2012, with an APC of -0.81. However, following this the AAMR had a rapid decline started to rise from 2012 to 2015, with an APC of -48.20. Following this a rise was seen from 2015 to 2020, with an APC of 13.88. The populations with the highest mortality rates were in males and African Americans. The geographical hotspots for mortality were urban and Black or African American. Tests for parallelism revealed disparate trends across gender (p=0.00022), Black and White races (p=0.06), urban versus rural demographics (p=0.12), and Large Central Metropolitan versus Large fringe Metropolitan (p=0.12).

Conclusions: The mortality due to the kidney failute and diabetes mellitus was on a decline in the US until 2013. However, the recent rise in the mortality is concerning. Furthermore, the disparity among the demographic variables warrant more investigation, and the planning of targeted interventions.

SA-PO334

Trend Analysis of Diabetic Kidney Disease-Related Mortality, 1999-2020

Mohammad Ammar ur Rahman,[1] Ahmed J. Chaudhary,[2] Gul S. Ghouri,[1] Luqman Munir,[1] Amna Khalid,[1] Natalia Azhar,[1] Abdullah Saeed.[1] NEURALKEy. *[1]King Edward Medical University, Lahore, Pakistan; [2]Detroit Medical Center, Detroit, MI.*

Background: A dangerous consequence of diabetes called diabetic kidney disease (DKD) is the progressive loss of kidney function. It results from long-term unchecked blood sugar levels that harm the kidneys' filtering organs. To lessen its influence on general health, early identification and treatment are essential. The mortality due to Diabetic Kidney Disease is on the rise in the United States. In this study we explored these trends from 1999-2020, using age adjusted mortality rates (AAMR) to pinpoint incongruities between epidemiological groups

Methods: Our study conducted an in-depth search of the CDC Wonder database, based on the incidence of sequalae of stroke-related Age-Adjusted Mortality Rate (AAMR) per 100,000 individuals. Employing Join point Regression Analysis, we assessed Parallelism and computed Annual Percent Changes (APC) with a 95% Confidence Interval. For a $p<0.05$, the test of parallelism was considered significant for unparallel.

Results: From 1999-2020, a total of 34195 deaths were reported due to diabetic kidney disease. The overall AAMR showed a rise from 1999-2014, with an APC of 30.62. Following this, the AAMR started to rise again from 2014-2020, with an APC of 11.5. The highest mortality populations were males and African Americans. The geographical hotspots for mortality were rural and west. Tests for parallelism revealed disparate trends across gender ($p=0.012$), African American races ($p=0.033$), urban versus rural demographics ($p=0.007$). However, the parallelism test in west ($p=0.029$) was not significant.

Conclusions: The recent rise in the mortality due to Diabetic Kidney Disease is concerning. Furthermore, the disparity among the demographic variables warrants more investigation, and the planning of targeted interventions.

SA-PO335

Evaluation of Plasma Proteins as Mediators of the Relationship between Kidney Disease and Heart Failure

Benjamin Lidgard,[1] Christine P. Limonte,[1] Jorge R. Kizer,[2] Bruce M. Psaty,[1] Leila R. Zelnick,[1] Nisha Bansal,[1] Jennifer A. Brody.[1] *[1]University of Washington, Seattle, WA; [2]University of California San Francisco School of Medicine, San Francisco, CA.*

Background: Patients with chronic kidney disease (CKD) are at high risk for heart failure (HF). Plasma proteins may indicate pathways associated with both reduced estimated glomerular filtration rate (eGFR) and HF. We tested if circulating proteins may mediate the associations between eGFR and HF.

Methods: We used the SomaLogic 5K platform to measure plasma proteins in 2,993 participants without prevalent HF in the Cardiovascular Health Study. We used linear regression to evaluate associations of each protein with eGFR (by the 2021 combined CKD-Epi equation), and proportional hazards models for associations with HF events. We used a quasi-Bayesian Monte Carlo method with 2,000 draws to test the adjusted mediation effects of proteins (which were associated with both eGFR and HF) on the eGFR-HF association. Bonferroni corrections were used for significance.

Results: The mean (SD) eGFR was 70 (16) mL/min/1.73 m^2; mean age was 74 (5) years. 1074 proteins were significant associated with eGFR. Of these, 44 proteins were significantly associated with incident HF; each was associated with statistically significant mediation effect on the association between eGFR and HF. These included COSA1 (proportion mediated 62%, 95% CI 39-93%) and NT-proBNP (proportion mediated 33%, 95% CI 24-47%).

Conclusions: Multiple plasma proteins were associated with significant mediation effect on association between eGFR and HF. These proteins may indicate pathways by which CKD increases HF risk. However, these statistical mediation analyses assume the directionality of associations. Ongoing work is investigating directionality of associations and joint mediation analyses.

Funding: Other NIH Support - NCATS KL2TR002317

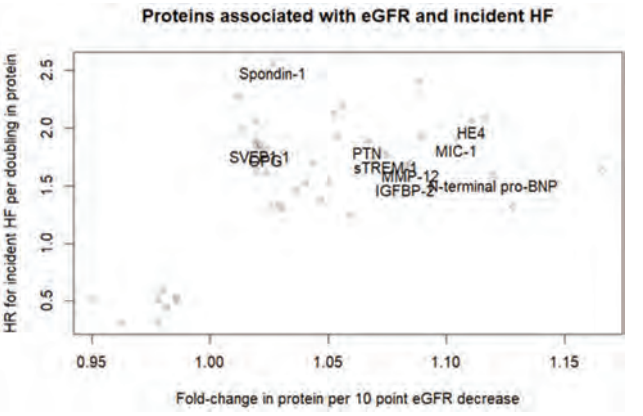


Table: Mediation by individual sphingolipids of the associations between eGFR and cardiovascular outcomes using a quasi-Bayesian Monte Carlo method with 2,000 draws

Protein	Average causal mediation effect (95% CI)	p-value	Proportion mediated (95% CI)	p-value
Cystatin C	-0.79 (-1.16, -0.45)	<2e-16	0.64 (0.37, 0.99)	<2e-16
COSA1	-0.76 (-1.08, -0.48)	<2e-16	0.62 (0.39, 0.93)	<2e-16
PXDN	-0.75 (-1.08, -0.47)	<2e-16	0.62 (0.38, 0.93)	<2e-16
HE4	-0.72 (-0.97, -0.49)	<2e-16	0.59 (0.4, 0.84)	<2e-16
MIC-1	-0.59 (-0.79, -0.41)	<2e-16	0.49 (0.34, 0.69)	<2e-16
b2-Microglobulin	-0.53 (-0.78, -0.3)	<2e-16	0.43 (0.25, 0.67)	<2e-16
ERBB2	-0.44 (-0.63, -0.28)	<2e-16	0.36 (0.23, 0.54)	<2e-16
NT-proBNP	-0.41 (-0.54, -0.31)	<2e-16	0.33 (0.25, 0.46)	<2e-16

Proportional effect is the percentage of the association between eGFR and HF that is mediated by the protein of interest. Adjusted for age, sex, race, smoking, BMI, LDL-C, HDL-C, triglycerides, total cholesterol, SBP, diabetes, prevalent HTN, and prevalent CVD.

SA-PO336

Heart Rate Variability in Dialysis Patients: Changes over the Dialysis Session and Evaluation of a Novel Device

Benjamin Lidgard, Nisha Bansal, Nathaniel Ashford, Leila R. Zelnick, Ian De Boer. *University of Washington, Seattle, WA.*

Background: Decreased Heart Rate Variability (HRV) is a measure of poor cardiovascular health and inability of the autonomic nervous system to respond to stress. Accumulation of uremic toxins in kidney failure, volume shifts, and clearance of uremic toxins by dialysis, may impact HRV. We sought to evaluate how HRV changes over the course of hemodialysis with gold-standard electrocardiogram (ECG) and a novel fingertip HRV sensor.

Methods: Among 22 participants treated with in-center hemodialysis, we evaluated time-domain and frequency-domain HRV metrics with an ECG (Schiller CARDIOVIT AT-10 Plus) and a novel fingertip sensor (EliteHRV CorSense) at five time points during 2 consecutive dialysis sessions. Changes over the session were evaluated by linear mixed models with random effect terms for participant and session. Devices were compared using correlation coefficients, T-tests, and linear regression.

Results: There were no significant changes in HRV metrics over the dialysis session (p-value for trend across ECG 0.11, across CorSense 0.58) (Figure). Time-domain HRV metrics were moderately correlated between the two methods (correlation coefficient for SDNN 0.72 and for RMSSD 0.66), while spectral methods were not (Table). Linear models comparing CorSense and EKG readings suggested strong association for time-domain metrics.

Conclusions: On average, HRV metrics did not significantly change over the course of hemodialysis sessions, suggesting that clearance of uremic toxins may not immediately impact cardiovascular health. A novel fingertip sensor accurately measured time-domain (but not frequency-domain) HRV metrics versus a gold-standard EKG device, which may provide a convenient way to assess autonomic neuropathy in dialysis patients.

Funding: NIDDK Support, Other NIH Support - NCATS KL2TR002317

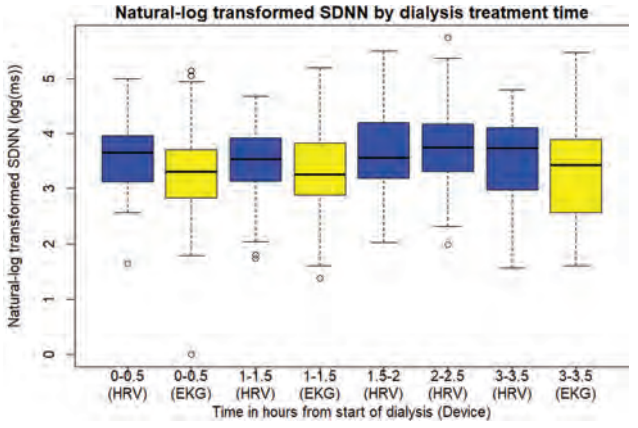


Table: Median (IQR) HRV values by each device with T-test p values and Pearson correlation coefficients

HRV domain	EKG	CorSense HRV	P value for difference	Correlation (Pearson)	Correlation p-value
Time-domain metrics					
SDNN	45.8	42.6	0.57	0.72	<0.0001
RMSSD	55.4	41.6	0.06	0.66	<0.0001
Frequency-domain metrics					
Low frequency (LF)	664.5	791.7	0.50	0.44	<0.0001
High frequency (HF)	1498.6	760.6	0.06	0.57	<0.0001
LF/HF ratio	1.38	7.17	0.32	-0.02	0.85

Abbreviations: Standard deviation of N-N interval, SDNN; root mean square standard difference, RMSSD

SA-PO337

Importance of the Cardiorenal Unit for the Management and Monitoring of Highly Complex Patients with Cardiorenal Syndrome

Juan C. León-Román, María Azancot, Marc Patricio-Liébana, Jorge I. Zamora Carrillo, Maria Jose Soler. *Hospital Universitari Vall d'Hebron, Barcelona, Spain.*

Background: Around 70% of patients with heart failure(HF) have kidney disease. The objective of the study is to evaluate the short and long-term clinical performance of patients with CRS who are followed-up by the cardiorenal units(CRU)

Methods: Fifty-four patients admitted in the CRU from April 1 to 30, 2022 at the Vall d'Hebron Hospital were included. Clinical follow-up was performed until October 31, 2023. Anthropometric measurements, signs of tissue and vascular congestion by US, and laboratory parameters were recorded

Results: A total of 47(87%) and 16(30%) patients completed follow-up in the CRU at 6 and 12 months. Baseline characteristics are shown in Table 1. Mean age 70 years(±1.6), 65% men, ischemic heart disease HF(48%), functional classes II and III were most frequent (60% and 35%, respectively). Cardiac ejection fraction (EF) of 40%(±1.6), and HFrEF reduced by 61%. Congestion studies: 15%of patients had pulmonary B lines, 23% vena cava>20mm, and 30% discontinuous renal venous pattern. NT-proBNP and CA-125 were 4623pg/mL[898-28229] and 20.2U/mL[3.9-171], respectively. Mean follow-up 8.6 months(±0.6). Comparing the baseline visit with the control at 6 months, treatment was optimized with sacubitril-valsartan 33% vs 49%(p=0.02) and SGLT2i 48% vs 72%(p=0.008) without significant deterioration in renal function, and a reduction of more than 50% in the number of hospital admissions(p=0.002). 22% required peritoneal dialysis and 20%hemodialysis. Ten(19%) patients died, 5of them due to cardiovascular(CV) events

Conclusions: We showed that the CRU is vital for the management of complex patients since it guarantees greater implementation of drugs that reduce CV mortality and the number of hospital admissions in HF

Table 1. Baseline characteristics of the 54 patients included in the study.

Variables	
Age (years), n (SD)	70,4 (±1.57)
Males, n (%)	35 (64.8)
Chronic medication	
ACEi/AIIRA, n (%)	12 (22.2)
Sacubitril-valsartan, n (%)	18 (33.3)
ARM, n (%)	23 (42.6)
SGLT2i, n (%)	26 (48.2)
Loop diuretic >80mg, n (%)	28 (56.0)
Chronic kidney disease	
eGF<60ml/min/1.73m², n (%)	45 (83.3)
eGF<20ml/min/1.73m², n (%)	17 (31.5)
CKD etiology	
CRS	17 (31.4)
Diabetes mellitus 2	14 (25.9)
Unknown	14 (25.9)
Others	9 (16.8)
HF etiology	
Ischemic, n (%)	26 (48.2)
Idiopathic, n (%)	10 (18.5)
Valvular, n (%)	11 (20.3)
Others, n (%)	7 (13.0)
HF classification	
HFrEF, n (%)	33 (61.1)
HFpEF, n (%)	15 (27.8)
Functional class	
II, n (%)	32 (59.3)
III, n (%)	19 (35.2)

SA-PO338

eGFR Variability in Heart Failure Patients with CardioMEMS Monitoring

Lawrence S. Ullman, Paige N. Beaudry, Gabriel Caldato Barsotti, Jeffrey M. Turner. Yale Nephrology Clinical Research. *Yale University School of Medicine, New Haven, CT.*

Background: Chronic variations in estimated glomerular filtration rate (eGFR) have been associated with an increased risk of stroke, myocardial infarction, and all-cause mortality. Patients with heart failure (HF) are a subpopulation that is commonly associated with variable eGFR. One approach to HF management is the implantation of the CardioMEMS device which allows patients' providers to remotely monitor their pulmonary artery pressure (PAP) to guide care in real-time. We hypothesized that HF patients who received a CardioMEMS implant may exhibit reduced eGFR variability due to the accessibility of acute PAP data to aid in treatment adjustments for volume regulation.

Methods: This retrospective observational study included HF patients identified from the Yale Heart Failure and Transplant CardioMEMS registry. Creatinine measurements were collected from the 12 months prior to the implantation and the 12 months following implantation. The 2021 CKD-EPI equation was used to calculate eGFR, and eGFR variability was quantified by the coefficient of variation (CV). The CV is defined as the standard deviation of the eGFR measurements divided by the mean eGFR. The primary outcome of interest was the difference in the CV in the pre-and post-CardioMEMS implantation periods.

Results: 429 patients received a CardioMEMS implant at Yale between 2017-2023. Of the 429 patients, 424 patients had available creatinine data and were included in the analysis. The mean eGFR of the patient cohort before CardioMEMS implantation was 49.4 mL/min/1.73m² and the mean eGFR post-CardioMEMS implantation was 43.6 mL/min/1.73m² ($p < 0.0001$). The CV of eGFR demonstrated a nonsignificant decrease of 0.0085 (p=0.2509) when comparing before and after CardioMEMS deployment.

Conclusions: In this cohort of heart failure patients who received a CardioMEMS implant, we did not observe an impact of the CardioMEMS intervention on eGFR variability. However, future research utilizing multivariate modeling to account for potentially confounding variables, such as comorbidities and outpatient medications, is warranted to better understand the impact of CardioMEMS-guided care on renal function.

SA-PO339

Cardiac Implantable Electronic Device Infections in Patients with Renal Insufficiency: A Meta-Analysis

Deepak Chandramohan,[1] Prathap Simhadri,[2,3] Prabhat Singh,[4] Hari Naga Garapati,[5] Raghunandan Konda,[1] Divya Chandramohan,[6] Nihar K. Jena,[7] Roopa Naik.[8] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]AdventHealth, Altamonte Springs, FL; [3]Florida State University, Tallahassee, FL; [4]Christus Spohn Health System, Corpus Christi, TX; [5]Baptist Medical Center East, Montgomery, AL; [6]The University of Texas at San Antonio, San Antonio, TX; [7]Trinity Health Oakland Hospital, Pontiac, MI; [8]Geisinger Health, Danville, PA.*

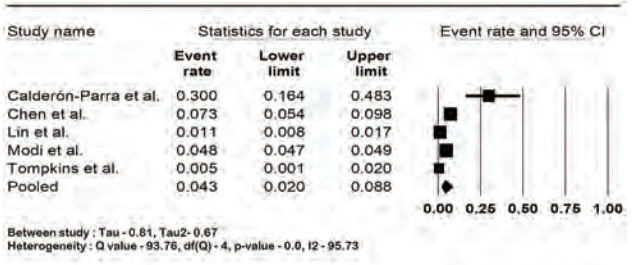
Background: Renal insufficiency is a risk factor for cardiac implantable electronic device (CIED) infection.

Methods: To identify studies, we conducted a comprehensive search of multiple electronic databases. Using the random effects model, we calculated the pooled rates and odds ratios. We utilized the Cochran Q and I2 statistics to detect heterogeneity.

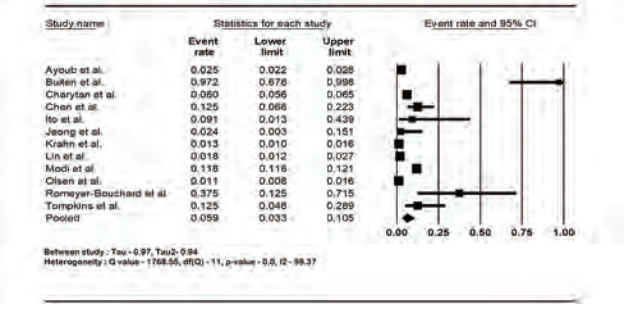
Results: A total of 17 studies comprising 263,819 chronic kidney disease (CKD) and 89,617 end stage renal disease (ESRD) patients were included. The mean age was 68.6 years (95% CI: 66.4-70.8; I2: 99.7). The pooled rate of CIED infection in patients with CKD was 4.3% (95% CI: 2-8.8; I2: 95.7) and ESRD was 5.9% (95% CI: 3.3-10.5; I2: 99.3). The pooled risk of CIED infection in the CKD population was OR 2.5 (95% CI: 1.9-3.3; p <0.001; I2: 21.1), and in ESRD was OR 2.4 (95% CI: 1.01-5.7; p = 0.046; I2: 88.8). ESRD was associated with higher mortality, OR 2.5 (95% CI: 1.4-4.4.8; p = 0.001; I2: 95).

Conclusions: The rates of CIED infections in renal insufficiency are significant. CKD and ESRD are associated with an increased risk of infection. ESRD patients have an increased risk of mortality.

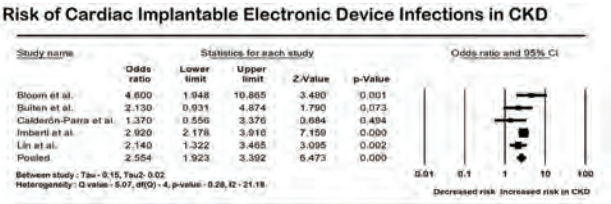
Rates of Cardiac Implantable Electronic Device Infections in CKD



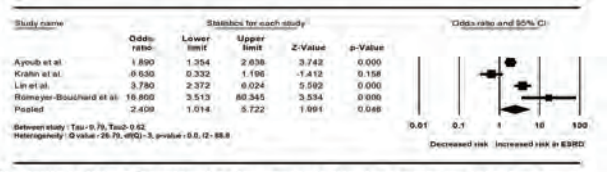
Rates of Cardiac Implantable Electronic Device Infections in ESRD



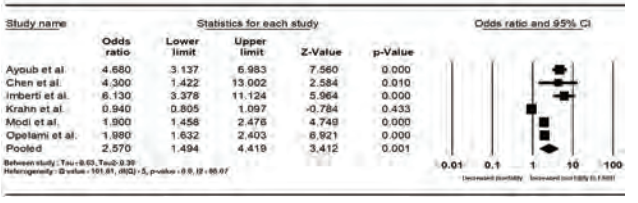
Risk of Cardiac Implantable Electronic Device Infections in CKD



Risk of Cardiac Implantable Electronic Device Infections in ESRD



Mortality in ESRD from Cardiac Implantable Electronic Device Infections



SA-PO340

Open vs. Endovascular Revascularization for Chronic Limb-Threatening Ischemia in CKD

Katherine R. Tuttle,[1,2] Mohammed Hamouda,[3] Matthew T. Menard,[4] Michael B. Strong,[4] Gheorghe Doros,[5] Alik Farber,[5] Mahmoud Malas.[3] On behalf of the BEST-CLI Trial. *[1]University of Washington School of Medicine, Seattle, WA; [2]Providence Inland Northwest Health, Spokane, WA; [3]University of California San Diego, La Jolla, CA; [4]Brigham and Women's Hospital, Boston, MA; [5]Boston University, Boston, MA.*

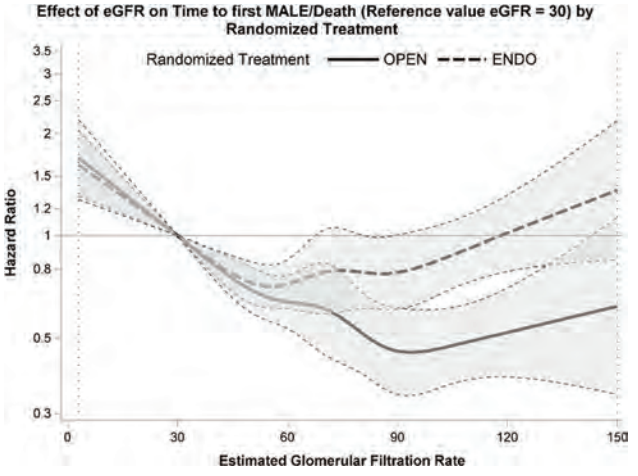
Background: Chronic kidney disease (CKD) increases risk of chronic limb threatening ischemia (CLTI). We assessed relationships between estimated glomerular filtration rate (eGFR) and clinical outcomes by surgical versus endovascular revascularization.

Methods: The Best Endovascular versus Surgical Therapy in Patients with CLTI (BEST-CLI) trial enrolled patients with CLTI inclusive of those with CKD. Spline modeling was performed across the range of eGFR observed in study participants to assess hazard ratios (HRs) for major adverse limb events (MALE: above ankle amputation, limb reintervention) or death, the primary trial outcome, by randomized assignment. Multiple variable Cox models were used to predict risks of MALE or death.

Results: At baseline, the mean±SD age was 67.4±9.7 years, 28.5% (500/1756) were women, and 27.5% (478/1740) identified as non-White race. CKD was present in 28.4% (499/1754). At eGFR <30 mL/min/1.73m^2, the HR for MALE or death increased with no difference in the primary outcome by randomized surgical versus endovascular revascularization (**Figure**). In adjusted Cox models, the HRs (95% confidence interval) for eGFR <30 versus ≥60 mL/min/1.73m^2 were 2.03 (1.68-2.43, p<0.001) and 3.46 (2.80-4.27, p<0.001) for MALE and death, respectively. In subgroup analyses by the same eGFR strata, antiplatelet agent non-users had increased risk of the primary outcome (HR 2.58, 1.71-3.89, p<0.001) versus no risk increase in users.

Conclusions: In patients with CLTI, risks of MALE and death increased sharply at eGFR <30 mL/min/1.73m^2 with no difference in the primary outcome by surgical or endovascular revascularization. Use of antiplatelet agents may mitigate risks of MALE and death in this high-risk population.

Funding: Other NIH Support - NHLBI, Commercial Support - Novo Nordisk



SA-PO341

Poststenotic Dilatation (PSD) in Human Renal Artery Stenosis (RAS)

Mina H. Al Saeedi,[1] Tarek Z. Arabi,[1,2] Jakob Nyvad,[1] Shivam Bajpai,[1] Mouaz Oudih,[1] Li Xing,[1] Bo Lu,[1] Lei Zhang,[1] Hui Tang,[1] Xiang yang Zhu,[1] Sanjay Misra,[1] Amir Lerman,[1] Lilach O. Lerman.[1] Nephrology and Hypertension. *[1]Mayo Foundation for Medical Education and Research, Rochester, MN; [2]Alfaisal University College of Medicine, Riyadh, Saudi Arabia.*

Background: A hemodynamically significant RAS may cause renal inflammation and development of PSD. However, beyond local remodeling, the functional significance of PSD, its link to renal function and inflammation, or its reversibility remain unclear. We hypothesized that PSD-RAS is associated with renal dysfunction and inflammatory marker levels in the stenotic renal vein (STK-RV) and would regress after percutaneous transluminal renal angioplasty (PTRA)

Methods: RAS patients with PSD (n=31, Table 1) underwent multidetector CT scanning and STK-RV sampling. In 3D CT images, PSD dilatation diameter ratio (DDR) was defined as the ratio between the maximal PSD diameter and the non-diseased segment proximal to RAS (Fig1). In 7 patients, studies were repeated 3 months after PTRA

Results: Patients had kidney dysfunction and hypertension (Table 1). DDR directly correlated with elevated serum creatinine, STK-RV levels of neutrophil gelatinase-associated lipocalin (NGAL), interleukin-6 (IL-6), and interferon-gamma (INF-γ) (Fig2), and 24h urinary protein levels. After PTRA renal function improved, inflammatory biomarkers declined, and PSD regressed (Fig3)

Conclusions: Development of PSD is reversible but associated with kidney dysfunction and inflammation and may reflect the severity of kidney injury in RAS. Detection of PSD may be beneficial in guiding treatment decisions

Funding: NIDDK Support

Table1 Demographics

Variables	Mean±SD
Age, Yrs.	71±7
MAP, mmHg	93±11
S.Cr, mg/dl	1.4±0.4
eGFR, ml/min/1.73m^2	48.2±18.7
Ras Severity, %	71±11

MAP: Mean Arterial Pressure, S. Cr: Serum Creatinine, eGFR: Estimated Glomerular Filtration Rate.

Figure 1

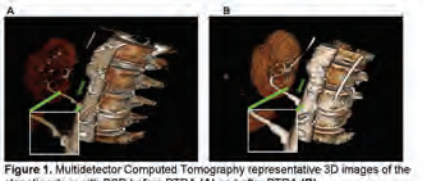


Figure 1. Multidetector Computed Tomography representative 3D images of the stenotic artery with PSD before PTRA **(A)** and after PTRA **(B)**.

Figure 2

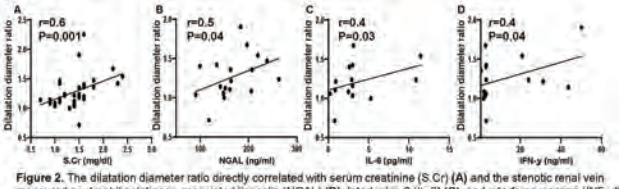


Figure 2. The dilatation diameter ratio directly correlated with serum creatinine (S.Cr) **(A)** and the stenotic renal vein measured neutrophil gelatinase-associated lipocalin (NGAL) **(B)**, Interleukin-6 (IL-6) **(C)**, and interferon-gamma (INF-γ) **(D)** levels

Figure 3

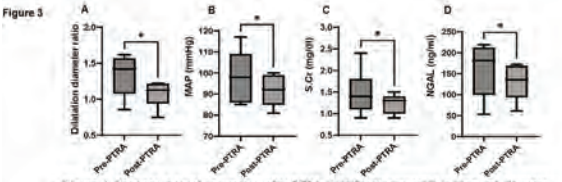


Figure 3. Changes in renal parameters after PTRA. Significant regression in dilatation diameter ratio **(A)** and levels of mean arterial pressure (MAP) **(B)**, serum creatinine (S.Cr) **(C)**, and NGAL **(D)**, *P<0.05 in post PTRA.

SA-PO342

Perceptions of Blood Pressure, Self-Monitoring, and Self-Management among Veteran Patients with CKD: A Qualitative Study

Mary K. Good,[1] Daniel D. Ball,[1] Sadaf Akbari,[1,2] Masaaki Yamada,[1,2] Elissa Z. Faro,[1,2] Heather Reisinger,[1,2] Diana I. Jalal.[1,2] *[1]VA Iowa City Healthcare System, Iowa City, IA; [2]University of Iowa Health Care, Iowa City, IA.*

Background: Hypertension, commonly found in Veterans with Chronic Kidney Disease (CKD), is a well-known risk factor for CKD progression, cardiovascular disease, and mortality. As part of a project to improve blood pressure (BP) management in Veterans living with CKD, this qualitative study examines Veterans' perceptions of BP monitoring and management.

Methods: In an ongoing clinical trial, 160 Veterans are randomized to test whether pharmacist-guided self-management of hypertension is more effective than self-monitoring and standard of care. We conducted semi-structured individual interviews covering participants' history and knowledge of hypertension and CKD; self-monitoring routine; perceptions of BP monitoring and management; and experiences with the clinical pharmacist. Transcripts were analyzed using MAXQDA 2024 qualitative software.

Results: The team completed 37 Veteran interviews. Most respondents spoke positively about their role in monitoring BP and interactions with clinical pharmacists. Self-reports of at-home BP monitoring indicated strong adherence to study instructions. Automated reminders promoted consistency in daily BP measurement and recording despite participants' mild irritation. Interest in tracking BP numbers varied by past experience monitoring BP, age, health literacy, and comorbidities like diabetes. Perceptions of BP measurements and trends influenced acceptability of pharmacist-guided self-management of BP. Veteran-specific factors affecting acceptability and adherence included a *Commitment to Serve*: Veterans hoped their participation would improve BP and CKD treatment for other Veterans in the future. Another factor was respect for *Chain of Command*: relationships with providers were seen through the lens of military hierarchy, with compliance interpreted as "following orders."

Conclusions: With proper instructions and technical support, consistent, correct self-monitoring of BP appears to be feasible for Veterans with CKD. Increased education on the importance of BP management and risks of hypertension for CKD patients could help to improve Veteran adherence with home BP monitoring and overall health understanding.

Funding: Veterans Affairs Support

SA-PO343

Unattended Compared with Attended Automated Office Blood Pressure Measurements: A Systematic Review and Meta-Analysis

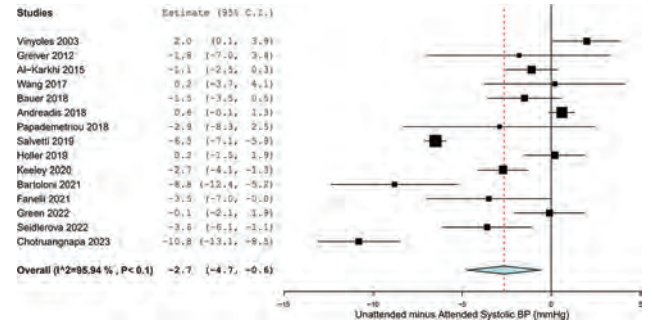
Valérie Deragon,[1] Youssef Baati,[1] Laurence Trudelle,[1] Amel Merabtine,[2,1] Dean S. Picone,[3] Remi Goupil.[2,1] *[1]Universite de Montreal, Montreal, QC, Canada; [2]Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada; [3]University of Sydney, Sydney, NSW, Australia.*

Background: Standardized automated office blood pressure (AOBP) measurement is widely accepted as the preferred method to monitor BP. However, disagreements persist as to the need to perform AOBP in an unattended manner, where the patient is left alone in a quiet room. In 2019, two meta-analyses assessing the differences between unattended and attended BP readings showed opposite results and prompting the publication of several more studies. Our objective was to reevaluate the BP differences between unattended and attended AOBP when both are performed in an identical manner.

Methods: This systematic review with meta-analysis was conducted according to the PRISMA guidelines. Studies were included if both unattended and attended AOBP were measured on the same participants in a randomized or alternating sequence manner during a single visit with the same device and an identical measurement protocol. The primary outcome was the difference between unattended and attended systolic (SBP) and diastolic (DBP) BP, expressed as weighted mean differences (95% confidence interval) using random-effects models.

Results: From 8,088 screened studies, data was extracted from 15 studies which met the inclusion criteria (n=1,747 participants). In the pooled analysis, the attended compared with unattended BP was higher for SBP by 2.7 mmHg (95%CI 0.6 to 4.7) and DBP by 0.9 mmHg (95%CI 0.1 to 1.8). In leave-one out analyses, results were similar except when excluding the study with the most extreme BP difference (Chotruangnapa 2023) where the difference became non-significant.

Conclusions: Standardized attended AOBP measurements result in slightly higher readings than unattended AOBP. Whether such small differences translate into clinically significant changes in management of BP remains uncertain. Therefore, standardized attended AOBP could remain a reasonable option for BP measurement in a real-life clinical setting.



SA-PO344

Measuring the Quality of In-Office Blood Pressure Measurements in Different Specialties

Artem F. Dadamyan, Neil S. Umles, Joel M. Topf. *Ascension St John Hospital, Detroit, MI.*

Background: In-office blood pressure measurements may be done routinely, or standardized. Both ACC/AHA and KDIGO recommend standardized in-office blood pressure measurements. Staffing issues, time constraints, and lack of widespread education of medical professionals may be barriers to proper measurements according to these guidelines. This study evaluated the technique of in-office BP measurements across internal medicine and nephrology specialties.

Methods: We conducted a quality improvement project collecting data by direct observation. The technique was scored by a ten-point checklist derived from ACC/AHA and KDIGO guidelines. Nephrology and Internal Medicine outpatient practices affiliated with Ascension St. John Hospital were observed and graded.

Results: Among nephrology offices, the overall checklist was followed correctly with a mean of 61% and 62% of the time, and an internal medicine clinic 46% of the time. The highest adherences were of patients with uncrossed legs (83%), correct cuff size (90%), and cuff over bare arm (73%). The lowest results were arm raised to level of sternum (13%), and sitting more than five minutes (3.3%). There were significant discrepancies between clinics among these data, with internal medicine clinic accounting for 4/5 of the patients with crossed legs, and having feet on the floor only 13% of the time.

Conclusions: Barriers to standardized blood pressure measurements are increased burden on medical professionals and time needed for proper measurement. This may be due to barriers of staffing, time constraints, and education. The concern for over or under-treatment is of significantly higher concern and therefore urges the need for updating clinic procedures of this standardized method. Home blood pressure monitoring (HBPM) has not been studied in the setting of chronic kidney disease, and although it likely has significant utility, needs to be used in addition to proper in-office measurements to guide appropriate therapy. Given the high recommendation for standardized BP measurement and its use in several clinical trials, the use of this method is of utmost importance to upkeep in general clinical settings in order to follow the recommendations made by clinical findings.

SA-PO345

Effect of Renal Denervation on Plasma Renalase Concentration in Patients with Resistant Hypertension

Marcin Adamczak,[1] Beata Czerwienska,[1] Michal Lelek,[2] Damian Gojowy,[1] Katarzyna Mizia-Stec,[2] Andrzej Wiecek.[1] *[1]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland; [2]1st Department of Cardiology, Medical University of Silesia, Katowice, Poland.*

Background: Renalase is an enzyme produced among others by proximal tubule cells in the kidneys and participates in the degradation of catecholamine. Results of experimental studies shown that renalase secretion is stimulated by increased plasma catecholamine concentration and to some extent also by an increase in blood pressure. Renal denervation (RDN), *i.e.*, percutaneous ablation of the sympathetic nervous system fibers located in the wall of renal arteries by radio frequency waves, is a method of patients with resistant hypertension. This single-center, interventional clinical study aimed to assess the effect of RDN on the plasma renalase concentration in patients with resistant arterial hypertension.

Methods: Twenty-five patients (12 women, 13 men) aged 54.4 ± 8.1 years with resistant hypertension who underwent renal denervation using Simplicity catheters (Medtronic, Inc., Northridge, CA) were enrolled in the study. Plasma renalase concentration was determined by enzyme-linked immunosorbent assay method (Cloud-Clone Corp., Houston, TX, USA) before RDN, 6 and 12 months after RDN. Results were presented as a mean with standard deviation.

Results: Systolic, diastolic blood pressure and heart rate were reduced after RDN (before RDN, 6 and 12 months after RDN, respectively: 190.4 ± 25.0, 161.1 ± 14.7, 155.5 ± 18.3; $p<0.001$; and 111.8 ± 19.3, 88.9 ± 8.5, 91.0 ± 10.4 mmHg; $p<0.001$ and 80.1 ± 16.3, 74.5 ± 11.1, 73.6 ± vs. 11.3 beats/min; $p<0.001$). Plasma renalase concentrations measured before RDN, 6 and 12 months after RDN in the studied group were 25.1 ± 7.5, 22.0 ± 7.1, and 23.1 ± 6.0 [μg/mL], respectively (ANOVA $p<0.001$, Fisher post hoc: before vs. six months $p = 0.01$, before vs. 12 months $p = 0.09$, six months vs. 12 months $p = 0.3$). There were no significant correlations between changes of plasma renalase concentration and decrease of blood pressure and heart rate during the follow-up after RDN.

Conclusions: 1. Renal denervation decreases moderately plasma renalase concentration, however this effect of RDN seems to be not associated with observed decrease of blood pressure. 2. Further studies are required to evaluate whether decrease in plasma renalase concentration is associated with change in plasma catecholamine concentration.

Funding: Government Support - Non-U.S.

SA-PO346

High Dietary Sodium Increases Urinary Endothelin-1 Excretion in Salt-Resistant Women but Not in Men

Rebecca C. Fetter,[1] Jazmine I. Benjamin,[1] Victoria L. Nasci,[1] Joseph M. Stock,[5] Nathan T. Romberger,[5] Joseph Watso,[2] Matthew C. Babcock,[3] Megan Wenner,[5] Austin Robinson,[4] Eman Y. Gohar.[1] *[1]Vanderbilt Department of Medicine, Nashville, TN; [2]Indiana University Bloomington Department of Kinesiology, Bloomington, IN; [3]Cardiovascular and Applied Physiology Laboratory, Florida State University, Tallahassee, FL; [4]Division of Geriatric Medicine, University of Colorado Denver, Aurora, CO; [5]Department of Kinesiology and Applied Physiology, University of Delaware, Newark, DE.*

Background: Endothelin-1 (ET-1) is a peptide thought to be implicated in gender differences in hypertension (HTN). In the kidney, ET-1 promotes natriuresis, and urinary ET-1 excretion reflects renal ET-1 production. Prior studies in our laboratory demonstrated that female rats exhibited higher urinary ET-1 than males on a normal salt diet. When switched to a high salt diet, only the male rats exhibited increased urinary ET-1. However, potential gender differences in the effect of dietary sodium on the renal ET-1 system in humans are unclear. Thus, we aimed to test the hypothesis that women would have higher overall ET-1 excretion than men and that increasing dietary sodium would augment ET-1 excretion only in men.

Methods: Salt-resistant participants (7 women; 14 men) with a baseline blood pressure (BP) of less than 140/90 mmHg followed recommended sodium (RS; 2300 mg/day) and high sodium (HS; 7000 mg/day) diets for 10 days, administered in random order with a washout of at least 4 weeks between interventions. At the end of each diet, 24-hour ambulatory BP was measured and 24-hour urine collected. ET-1 excretion was quantified

using the QuantiGlo (R&D) ET-1 ELISA. ET-1 excretion on the RS and HS diets in men and women was evaluated using a repeated measures two-way ANOVA with post hoc Sidak's test.

Results: Systolic, mean, and diastolic BP were not different between the RS and HS diets in either gender. Women exhibited higher urinary ET-1 than men, which was most evident on the HS diet (*P*=.0228). Only women experienced a significant increase in ET-1 excretion on the HS diet (196.01±18.40 pg/day) as compared to the RS diet (127.24±19.52 pg/day) (*P*=.0096). There was no significant gender difference or diet difference in urine flow rate (UFR).

Conclusions: Women exhibited higher urinary ET-1 excretion than men. Only women had significantly increased urinary ET-1 during the HS versus the RS diet, which opposes our hypothesis. Understanding gender differences in ET-1-mediated sodium regulation could potentially inform future studies toward developing gender-specific therapeutics for HTN.

Funding: NIDDK Support

SA-PO347

Clinical Characteristics and Progression in Patients with Malignant Hypertension and Thrombotic Microangiopathy Kidney Damage

Li Jin, Wanhong Lu, Xiangyun Dang. *The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China*.

Background: Malignant hypertension (MHT) is a group of syndromes characterized by severe hypertension and acute microvascular injury, often accompanied by thrombotic microangiopathy (TMA). This study aimed to establish a high-quality and standardized historical prospective study cohort to preliminarily investigate the possible mechanism of renal injury in MHT with TMA.

Methods: The MHT patients with TMA confirmed by renal biopsy were enrolled from July 2015 to December 2023. General information, clinical data, and renal pathology were collected. Patients were divided into two subgroups: the ESRD group (eGFR<15ml/min/1.73m^2) and the non-ESRD group (eGFR≥ml/min/1.73m^2).

Results: A total of 47 patients were enrolled with an age of 39.4±4.83 years, of which 43 (71.4%) were male. 17 (36.1%) of patients had a family history of hypertension. The highest systolic blood pressure was 204.8±15.0 mmHg and the highest diastolic blood pressure was 140.0±18.7 mmHg. Serum creatinine was 286.0 (158.0, 427.5) μmmol/L and eGFR was 23.6 (14.2, 49.6) ml/min/1.73m^2 at baseline. Renin, angiotensinogen II, and aldosterone were 130.0 (81.9, 301.0) IU/μl, 64.8 (46.6, 85.5) pg/μl and 530.0 (326.0, 1831.3) pg/μl respectively, all higher than normal. ACEI/ARB treatment was given to 30 patients (63.8%). During the follow-up period, 20 (42.6%) patients progressed to ESRD with a median time of 113 (4.5, 332.8) days. 1 patient (2.1%) died of heart failure. The level of baseline hemoglobin (t=5.151, P<0.001), eGFR (z=-4.769, P=0.005), immunoglobulin G (t=2.641, P=0.011), the proportion of ACEI/AERB use (χ^2=8.560, P=0.003) were lower in the ESRD group compared to the non-ESRD group. While the serum creatinine (*Z*=-4.688, P=0.005) and lactate dehydrogenase levels (z=-2.872, P=0.004) were higher in the ESRD group. Multivariate logistic regression analysis showed that lower hemoglobin level (OR=0.937, 95% CI 0.904-0.972, P<0.001) was associated with earlier progression to ESRD in MHT with TMA patients.

Conclusions: The renal prognosis for patients with MHT and TMA renal injury is poor. Patients with MHT and TMA kidney injury had secondary hyperaldosteronism. Baseline plasma hemoglobin level is an independent risk factor for progression to ESRD in patients with MHT and TMA kidney injury.

SA-PO348

Long-Term Efficacy of Renal Denervation in Patients with Resistant Hypertension: A Meta-Analysis of Randomized Controlled Trials

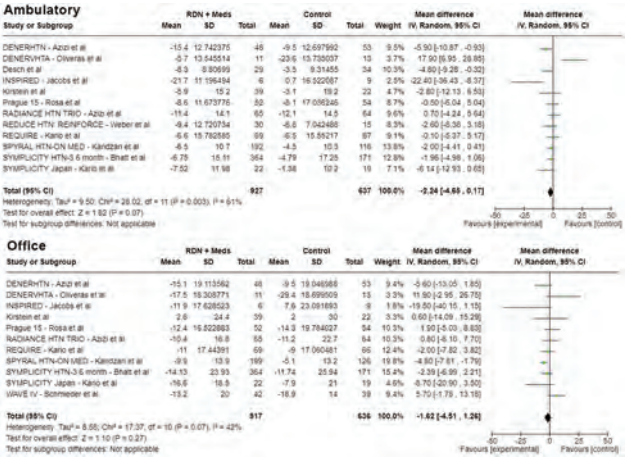
Rajiv Hans S. Menghrajani,[1] Mirtha C. Almanzar,[1] Maria Angela Matabang,[1] John Paul B. Aparece,[2] Edgar V. Lerma.[3] *[1]Lincoln Medical Center, Bronx, NY; [2]Texas Tech University Health Sciences Center El Paso, El Paso, TX; [3]University of Illinois Chicago College of Medicine, Chicago, IL*.

Background: Resistant hypertension, defined as blood pressure (BP) that remains elevated despite the concurrent use of three antihypertensive agents of different classes, represents a significant challenge in clinical practice. The persistent elevation of BP in these patients is associated with an increased risk of cardiovascular events and mortality. Renal denervation (RDN), a minimally invasive procedure targeting the sympathetic nerves within the renal arteries, has emerged as a promising intervention. This study aims to determine the long-term efficacy of RDN in controlling BP in patients with resistant hypertension.

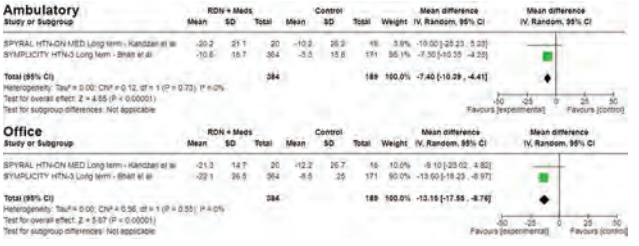
Methods: Electronic databases were searched until March 2024. Three reviewers screened the abstracts, reviewed the full texts, and appraised the quality of the included studies using the PRISMA guidelines. The primary outcomes were decrease in systolic BP at 6 months and 36 months.

Results: Out of 145 articles retrieved, 15 RCTs were included in the meta-analysis (n = 1564). At 6 months, there was a mean difference of -2.24 mmHg [-4.65, 0.17] p = 0.07 in the ambulatory systolic BP, while the office-measured systolic BP showed a mean difference of -1.62 mmHg [-4.51, 1.26] p = 0.27. There is moderate heterogeneity for both the ambulatory and office-measured systolic BP, I2 = 61% and I2 = 42%, respectively. At 36 months, there was a mean difference of -7.40 [-10.39, -4.41] p < 0.00001 in the ambulatory systolic BP, while there was a mean difference of -13.15 [-17.55, -8.76] p <0.00001 in the office measured systolic BP. The heterogeneity for both ambulatory and office-measured at 36 months was 0%.

Conclusions: RDN decreases office and ambulatory-measured systolic BP in resistant hypertension at both 6 and 36 months. However, this effect is only statistically significant in the long term basis (36 months). Studies with longer follow-up can further establish RDN's long term effect.



SBP at 6 months



SBP at 36 months

SA-PO349

Can Novel Ambulatory Blood Pressure Monitoring (ABPM) Parameters Change the Way We Treat Hypertension in CKD?

Bahaar S. Athavale, Hardik K. Shah, Dilip Kirpalani. *Bombay Hospital Institute of Medical Sciences, Mumbai, India.*

Background: Blood pressure control rates in CKD continue to remain abysmal, in spite of advanced diagnostics and therapeutics. Novel ABPM entities such as BP variability, morning masked hypertension, "Double Risers" (rise of both nocturnal heart rate and BP) and Early Morning BP Surge (EMBS) by moving average sleep trough method can facilitate efficient management of hypertension in CKD. Our study aims to detect and compare these parameters between CKD and non-CKD patients.

Methods: 100 hypertensive patients - CKD Group (Stage 1 to 4; n=50) and Non-CKD Group (n=50); underwent measurement of Single Office BP (SOBP), Automated averaged Office BP (AOBP) followed by 24 hours ABPM.

Results: In CKD group, 48% had nocturnal non-dipping pattern, 12% had rising pattern of nocturnal BP and 10% were double risers. This was significantly higher than the non-CKD group. The CKD group had significantly higher EMBS (36% vs. 22%; p=0.04) by the newer "moving" average sleep trough method. In this method difference between Average Morning SBP (Average of morning SBPs taken during the first 2 hours after waking up) and Moving Lowest Nighttime SBP (Average of 3 SBP readings centered on the lowest night (nadir) SBP value) is calculated. Masked hypertension was seen in 76% of CKD and 40% of non-CKD patients. However, in CKD group masked hypertension in morning time (between 6 am to 10 am) was significantly higher (70%) than non CKD (12%). BP variability assessment by Standard Deviation method revealed no statistically significant difference between the CKD and the non-CKD groups (15.12±4.05 vs. 15.86±4.20 respectively). However, novel method such as Average Real Variability revealed statistically significant difference between the two groups (12.9±4.18 vs 11.6±3.63; p=0.03). Similarly, while considering Variability Independent of Mean as a parameter, CKD patients had higher BP variability (24.74±16.25) as compared to the non-CKD group (22.2±13.3; p=0.03).

Conclusions: Hypertensive patients with CKD have a greater benefit from utilizing 24 hour ABPM as compared to those without CKD. Novel parameters such as morning masked hypertension, double risers, "moving" average sleep trough and average real variability can be assessed for better therapeutic interventions.

SA-PO350

Efficacy of the Combination of Acetazolamide with Loop Diuretics vs. Double-Dose Loop Diuretics for Decongestion in CKD Patients: A Randomized Controlled Trial

Jiranat Sriswasdi. *Phramongkutklao Hospital, Bangkok, Thailand.*

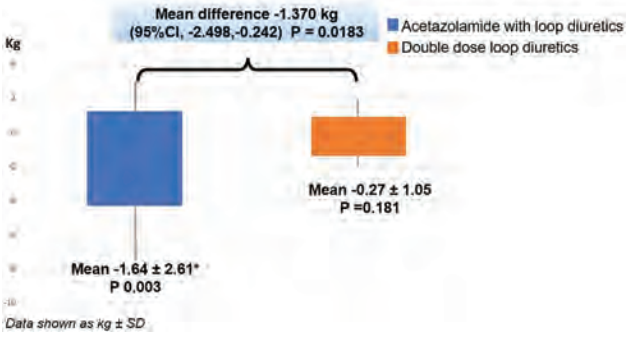
Background: The combination of acetazolamide and loop diuretics in the setting of hospitalized heart failure has shown promising results in improving diuresis and decongestion. However, the effectiveness of this combination in chronic kidney disease (CKD) with volume overload has yet to be determined.

Methods: CKD patients with fluid overload, confirmed by bioimpedance spectroscopy, were allocated to receive oral acetazolamide 250 mg/day plus furosemide or a doubled dose of furosemide. Volume status, changes of body fluid compartment from body composition monitoring, and urinary sodium were evaluated at baseline, 2, and 4 weeks. The main outcome was the proportion of body weight reduction (> 2 kg and 5%) and mean change of body weight at 2 weeks.

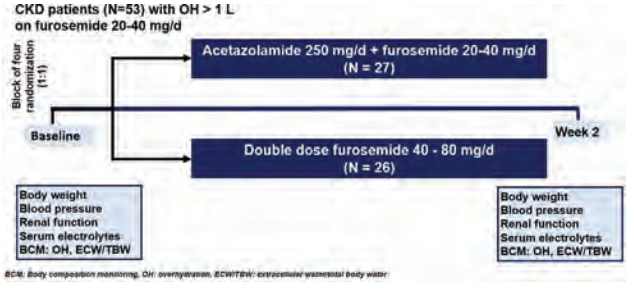
Results: Fifty-two CKD patients with an estimated glomerular filtration rate of 38 mL/min/1.73 m2 were included. Body weight reduction > 2 kg at week 2 (40.7% vs. 12%, risk ratio (RR) 3.39, 95% CI 1.06-10.7) and body weight reduction > 5% at week 2 (25.9% vs 0% RR 2.25, 95%CI 1.62-3.12) significantly occurred in the combination group compared to the doubled-dose group. Additionally, mean difference of body weight reduction between combination group and doubled dose group was -1.37 kg, 95% CI -2.498, -0.242). The combination group showed lower rates of alkalosis and hypokalemia at 4 weeks. No serious adverse events were found in either group.

Conclusions: Adding acetazolamide to loop diuretics ameliorates volume overload in CKD patients without significant or serious side effects.

Funding: Government Support - Non-U.S.



Primary outcome
Body weight reduction at week 2



SA-PO351

Effects of Dapagliflozin on Sodium Excretion and Blood Pressure in Patients with Type 2 Diabetes and CKD during Standardized Sodium Intake

Jelle Beernink,[1] Niels Jongs,[1] Vikas Sridhar,[2] Charlotte Mosterd,[5] Rosalie Scholtes,[5] Alyssa Caldwell,[3] Daniel I. Casillas,[3] Lynette M. Driscoll,[3] Peter J. Greasley,[4] Daniël H. van Raalte,[5,6] Petter Bjornstad,[3] David Cherney,[2] Hiddo J. Heerspink.[1] DAPASALT Investigators. *[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]University Health Network, Toronto, ON, Canada; [3]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [4]AstraZeneca, Mölndal, Sweden; [5]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [6]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands.*

Background: We previously demonstrated that dapagliflozin reduced blood pressure (BP) without altering natriuresis in patients with type 2 diabetes (T2D) and preserved kidney function. Chronic kidney disease (CKD) is often associated with salt-sensitive hypertension, which is resistant to many anti-hypertensive drugs. In this prospective study, we assessed the effects of dapagliflozin on sodium excretion and BP in patients with T2D and CKD during standardized sodium intake.

Methods: We conducted a prospective open-label study to evaluate the effects of dapagliflozin on 24-hour sodium excretion, 24-hour BP, and extracellular volume (EV) in patients with T2D with CKD (estimated glomerular filtration rate [eGFR] of ≥25 and ≤50 mL/min per 1.73m^2) at the start of treatment (ST) (days 2-4), end of treatment (ET) (days 12-14), and washout (days 15-18) during controlled sodium intake (150 mmol/day).

Results: Thirteen patients (mean age 70 ± 9.6 years, eGFR 41 ± 12.6 mL/min per 1.73m^2, 24-hour systolic BP 130 ± 23.1 mmHg) were included. Mean 24-hour sodium excretion did not change during the study (Table 1). Nominal decreases in 24-hour systolic and diastolic BP were observed, without changes in EV. Mean 24-hour urinary glucose excretion increased at ST and ET and reversed during wash-out.

Conclusions: In patients with T2D and CKD, dapagliflozin reduced BP during standardized sodium intake, without increasing natriuresis. These findings are consistent with those in patients with T2D and preserved kidney function, and suggest that BP lowering with dapagliflozin may be attributed to different mechanisms than natriuresis in patients with and without CKD.

Funding: Commercial Support - AstraZeneca

Table 1: Change from baseline (95% CI)

Outcome	ST	ET	Washout
Urinary sodium excretion, mmol/24-hour	-0.5 (-15.4, 14.5) P = 0.95	-11.7 (-30.4, 7.1) P = 0.20	-19.1 (-36.5, -1.7) P = 0.03
Urinary glucose excretion, mmol/24-hour	125.0 (55.6, 194.3) P = 0.006	85.5 (15.1, 156.0) P = 0.03	64.5 (-9.1, 138.1) P = 0.07
24-hour systolic blood pressure, mmHg	-6.1 (-19.8, 7.7) P = 0.31	-3.7 (-13.7, 6.2) P = 0.38	-7.9 (-12.3, -3.5) P = 0.006
24-hour diastolic blood pressure, mmHg	-3.0 (-9.6, 3.7) P = 0.30	-1.5 (-6.4, 3.3) P = 0.45	-4.0 (-6.8, -1.1) P = 0.02
Extracellular volume, L	-0.4 (-0.8, 0.1) P = 0.08	-0.4 (-0.9, 0.2) P = 0.18	0.1 (-0.6, 0.8) P = 0.79

SA-PO352

Comparison between Sacubitril-Valsartan and Thiazide Diuretics among Patients with Uncontrolled Hypertension in Japan

Kazuo Kobayashi,[1,2] Mari Sotozawa,[2] Kyoji Chiba,[3] Hiromichi Wakui,[2] Kouichi Tamura.[2] *[1]Committee of Hypertension and Kidney Disease, Kanagawa Physicians Association, Yokohama, Japan; [2]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [3]Department of Nephrology, Yokohama Sakae Kyosai Hospital, Yokohama, Japan.*

Background: The hypertension paradox is an urgent issue in clinical practice. Although ARBs and calcium channel blockers (CCBs) were widely used, less than 10% of patients used thiazide diuretics in Japan. Sacubitril valsartan can be used for not only patients with heart failure but also with hypertension. This study aimed to evaluate the differences of an efficacy and safety between sacubitril valsartan and thiazide diuretics in patients with poorly BP control.

Methods: Patients who showed ≥130/80 mmHg in the office despite a combination treatment of RAS inhibitors and CCBs were included. The comparison between patients treated with the addition of thiazide diuretics (THZ group, n=267) and those transferred from RAS inhibitors to sacubitril valsartan (SacVal group, n=381) was analyzed. A general linear mixed model (GLMM) was used for the analysis of clinical findings at baseline, 4 months, and 12 months. The rate of discontinuation was analyzed using the Cox proportional hazard model.

Results: The baseline backgrounds of the THZ /SacVal group were as follows; female 39/35 (%), mean age, body weight (BW), and eGFR at baseline were 67.8 ± 13.1/72.3±12.6 (years) (p<0.001), 68.1±15.7/66.2±14.2(kg), 61.2±20.9/56.8±20.3 (ml/min/1.73 m^2) (p=0.01), respectively. In the GLMM analysis, significant decrease in office and home BP after treatment was observed in both groups (p<0.001), however, no significant interaction effects between the type of drug and time course were observed for BP. Significant interaction effects were observed for eGFR, uric acid (UA), logarithmic value of ACR (LnACR), BW, and hemoglobin A_{1c} (HbA_{1c}) (all p<0.001). eGFR, UA, and LnACR were significantly decreased (p<0.001), increased (p<0.001), and decreased (p<0.001), respectively, in the THZ group during the time course. Significant decreases were observed in BW and HbA_{1c} in the SacVal group (p<0.001). Treatment discontinuation due to adverse effects was significantly more frequent in 34 cases (13%) in the THZ group, than 12 cases (3%) in the SacVal group with hazard ratio of 6.3 [95% CI, 2.7, 14.9] (p<0.001).

Conclusions: Both treatments decreased BP; however, compared to thiazide, sacubitril valsartan resulted in a superior reduction in BW, HbA_{1c}, and favorable changes in kidney function, with better treatment adherence.

SA-PO353

Effect of Baxdrostat on Albuminuria in Treatment-Resistant Hypertension

Hiddo J. Heerspink,[1] Dustin J. Little,[2] Robin Myte,[2] Nataliia Zaozerska,[2] Robert I. Menzies,[3] Shira Perl,[2] Glenn M. Chertow,[4] Jamie P. Dwyer.[5]
[1]University Medical Center Groningen, Groningen, Netherlands; [2]AstraZeneca Biopharmaceuticals R and D, Warsaw, Poland; [3]AstraZeneca Biopharmaceuticals R and D, Gothenburg, Sweden; [4]Stanford University School of Medicine, Stanford, CA; [5]University of Utah Health, Salt Lake City, UT.

Background: Baxdrostat is an aldosterone synthase inhibitor in development in combination with the sodium glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin for patients with CKD and hypertension (HTN). We performed a *post hoc* analysis evaluating baxdrostat's effect on urine albumin-to-creatinine ratio (UACR) in a phase 2 study in participants with resistant HTN.

Methods: BrigHTN was a randomized, placebo-controlled trial where qualifying participants with resistant hypertension (defined as treatment with at least 3 anti-hypertensive drugs, at least one of which was a diuretic) were randomized 1:1:1:1 to baxdrostat 0.5, 1, or 2 mg or placebo for 12 weeks. We analyzed geometric mean change from baseline to 12 weeks of log-transformed UACR and calculated the percent change within and between randomized groups. We excluded missing values (n=83).

Results: Overall, 275 participants were randomized of whom 39 (14.2%) had baseline eGFR <60 mL/min/1.73m^2 and 60 (21.8%) had UACR >30 mg/g. Baseline median UACR was 12 mg/g with quartile 1 and quartile 3 values of 6 and 36 mg/g, respectively. As reported previously, baxdrostat 1 mg and 2 mg resulted in statistically significant placebo-adjusted reductions in systolic blood pressure. All baxdrostat groups showed placebo-adjusted reductions in UACR (Table 1); changes in the baxdrostat 2 mg group met conventional levels of statistical significance (p=0.011).

Conclusions: In a placebo-controlled trial of baxdrostat for resistant hypertension, baxdrostat 2 mg daily reduced UACR. Relatively few BrigHTN participants had CKD, and any amount of albuminuria was allowed. The phase 3 Arctic trial (NCT06268873) of patients with CKD and hypertension will compare baxdrostat/dapagliflozin to placebo/dapagliflozin both on top of maximally tolerated ACE inhibitors or angiotensin receptor blockers to assess the primary endpoint of change in eGFR over time.

Funding: Commercial Support - AstraZeneca

Table 1: Post-hoc Analysis of Change from Baseline in UACR (mg/g) at 12 Weeks in Study CIN-107-121

Group	Treatment group, Participants (N)	Participants Evaluable (n)	Change, %	Comparison of treatment groups to placebo		
				Change, %	95% CI	p-value
All participants	Placebo (N = 69)	57	-2.8			
	0.5 mg (N = 69)	44	-21.6	-19.3	(-40.0, 8.6)	0.159
	1 mg (N = 70)	47	-19.9	-17.6	(-38.5, 10.4)	0.196
	2 mg (N = 67)	44	-33.7	-31.8	(-49.1, -8.6)	0.011

Change in % is obtained from geometric mean ratios from an ANCOVA model with change in log UACR from baseline as the dependent variable, treatment as a fixed categorical factor and baseline log UACR as a continuous covariate. Missing values are excluded. ANCOVA Analysis of Covariance; CI Confidence interval; n Number of participants included in analysis; N Number of participants per treatment group.

SA-PO354

Is It Nighttime Dipping or Sleep-Time Dipping?

Ali Mirza Onder,[1,2] Songul Onder.[3] *[1]Nemours Children's Hospital Delaware, Wilmington, DE; [2]Thomas Jefferson University Sidney Kimmel Medical College, Philadelphia, PA; [3]University of Maryland School of Medicine, Baltimore, MD.*

Background: Those subjects who work at night-time and sleep at daytime need to replicate the blood pressure dipping (BPD) phenomena during daytime. There is limited information on how well they can replicate night-time dipping.

Methods: 24-hour ambulatory blood pressure monitoring (ABPM) was used for 84 medical professionals during three different work- sleep schedules; work night-time and sleep during daytime, work daytime and sleep at night-time, and for an off-work day, awake at daytime and sleep at night-time. There were four groups within this cohort: *Group A;* subjects who only work at daytime and always sleep at night-time, Group B; subjects who switch from working day to night-time every 3-4 days, Group C; subjects who switch from working day to night-time every 3-4 months, and Group D; those who only work at night-time and always sleep during daytime. Sleep score is defined as the product of the sleep BPD percentage and duration of sleep (hours). The Kruskal Wallis test was used to compare differences among groups, and the Signed rank test was used to evaluate paired differences.

Results: Mean reported sleep durations were similar between the four groups for both periods of work schedule. When Group A was compared to Group D for the median BPD (15.5% vs. 12%) and the sleep score (112 vs. 90), they were statistically indifferent (p=0.31 and p=0.24, respectively). There was no difference for sleep BPD between two different work times for Groups B & C (p=0.47). However, the median sleep score was significantly better when subjects were sleeping at night-time (127.5 vs 103, P=0.02). There was no difference for sleep BPD (p=0.43) and for sleep score (p=0.36), when the four groups were compared for their BPD during an off-work day.

Conclusions: For this cohort, the BPD was associated with sleep-time rather than night-time. Subjects who work at night had similar sleep BPD compared to subjects who work at daytime. The personal history of night-time work did not impact the sleep BPD on an off-work day. A significantly higher sleep score was achieved by the alternating subjects when they slept at night-time, because of longer reported sleep duration.

SA-PO355

Effectiveness, Acceptability, and Feasibility of a School-Based Program for Detecting High Blood Pressure in Children

Jonathan P. Glenning,[1,2] Freya Sheeran,[1,2] Jon Quach,[1,2] Michael Cheung,[1,3] Stephanie Best,[1,2] Catherine Quinlan,[1,3] Jonathan P. Mynard.[1,2] *[1]Murdoch Children's Research Institute, Parkville, VIC, Australia; [2]The University of Melbourne, Melbourne, VIC, Australia; [3]The Royal Children's Hospital Melbourne, Parkville, VIC, Australia.*

Background: Childhood high blood pressure (BP) is associated with cardiovascular morbidity and mortality in mid-adulthood. Community-based BP screening may improve equitable access and awareness, but robust methodology is required. Accordingly, our aim was to assess the effectiveness, acceptability and feasibility of a two-stage school-based BP screening program incorporating targeted 24-hour ambulatory blood pressure monitoring (ABPM).

Methods: 198 children (59% male, 7.6–12.7 years) were recruited from three primary schools in Melbourne, Australia. Following an education session for all eligible children, auscultatory BP was measured five times, alternating between arms and after an initial five minutes of rest. Those with an average BP ≥85th percentile (AAP thresholds) or a risk factor for high BP had this repeated two weeks later, along with ABPM. Families and school staff completed a questionnaire about acceptability post-program.

Results: At the first assessment, 5.6% had elevated BP and 5.0% had a hypertensive BP (14.6% combined if using just the first measure). 29.8% were selected for the second assessment (including 10 with obesity, 15 born premature, four with a history of congenital heart disease, and nine with BP ≥85th percentile, but <90th percentile), of which 52 attended. ABPM indicated that 5.6% of the total cohort had white coat hypertension based on Assessment 1 and 2.5% based on Assessment 2, with a further 1.5% with sustained hypertension, and 1% with masked hypertension. An additional three participants each had either high BPs during school assessment but did not complete, or had inconclusive, ABPMs. Overall, 5.6% were referred for medical follow-up. The majority of participants (67%) who underwent ABPM reported it was tolerable with a 'bothersome' score <8/10 for day and/or night. 96% of families found the program acceptable and 90% welcomed it as part of their child's schooling.

Conclusions: These data indicate that a school-based BP screening program is effective for detecting high BP, acceptable to families and feasible to run in schools. Measuring BP on multiple occasions, with targeted ABPM, is pivotal for minimising false positives and unnecessary referrals.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO356

Incidence and Prevalence of Edema and the Effect of Aprocitentan Treatment Strategy in the PRECISION Study

Markus P. Schlaich,[1] George L. Bakris,[2] Parisa Danaietash,[3] Bruno Flamion,[3] Krzysztof Narkiewicz,[4] Mouna Sassi-Sayadi,[3] Jiguang Wang,[5] Michael A. Weber.[6]
[1]The University of Western Australia Medical School, Perth, WA, Australia; [2]The University of Chicago Medicine, Chicago, IL; [3]Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland; [4]Medical University of Gdansk Department of Hypertension and Diabetology, Gdansk, Poland; [5]Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China; [6]SUNY The State University of New York, New York, NY.

Background: Edema is an expected adverse event with Endothelin Receptor Antagonists (ERAs). PRECISION evaluated the effect of aprocitentan (APRO), a dual ERA in patients with resistant hypertension and increased CV risk (54% diabetes, 22% renal insufficiency, 20% history of heart failure). All patients were on a standardized fixed-dose combination of amlodipine (71% of patients at 10 mg), valsartan and hydrochlorothiazide. Results from PRECISION indicated a lower edema incidence in patients on 12.5 mg vs 25 mg APRO during the first 4 weeks. The objective of this analysis was to evaluate whether 12.5 mg APRO for 4 weeks followed by 25 mg APRO (12.5/25) decreased edema risk compared with 25 mg as initial dosing and throughout the study (25/25).

Methods: The study design included 3 parts: Part 1: double-blind placebo-controlled 12.5 mg or 25 mg APRO, or placebo for 4 weeks; Part 2: prolonged single-blind administration of 25 mg APRO to all patients; Part 3: double-blind placebo-controlled withdrawal phase (25 mg APRO vs placebo). Incidence (new and recurrent onset) and prevalence (new and ongoing events) of AEs indicating edema were evaluated up to 48 weeks by treatment regimen: a) 12.5/25 cohort or b) 25/25 cohort.

Results: The incidence of edema was lower in the 12.5 mg group (9.1%) vs the 25 mg group (15.9%) during the first 4 weeks of treatment (Fig 1). Most new events occurred during the first 8 weeks of treatment. After that, the incidence of edema in both APRO treatment sequences was comparable with the range reported for the placebo group during the first 4 weeks of treatment. The prevalence of edema during the 48-week study was consistently lower in subjects in the 12.5/25 cohort (11% to 17%) vs those in the 25/25 cohort (16% to 21%) throughout the study.

Conclusions: Initiation therapy with 12.5 mg APRO may represent a preferred clinical approach particularly in patients with risk of edema.

Funding: Commercial Support - Idorsia Pharmaceuticals Ltd.

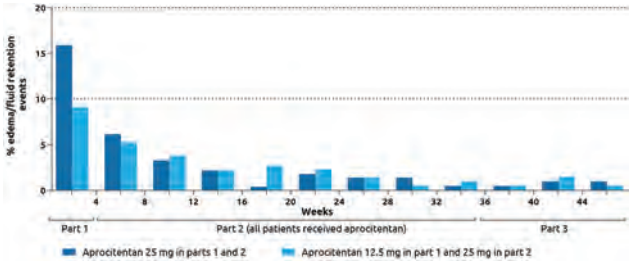


Figure 1: Incidence of edema in PRECISION

SA-PO357

Sodium-Mediated Blood Pressure Increase in CKD and Diabetic Kidney Disease Patients Coincides with Vasodysfunction

Robert E. van Duin,[1,2] Jetta J. Oppelaar,[1,2] Bert-Jan Van den Born,[1,2] Rik H. Olde Engberink,[1,2] Liffert Vogt.[1,2] Dept of Nephrology and Dept of Vascular Medicine. *[1]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [2]Amsterdam Cardiovascular Sciences Department of Internal Medicine, Amsterdam, Netherlands.*

Background: Chronic kidney disease (CKD) and diabetic kidney disease (DKD) patients are advised to limit salt intake because of its detrimental effects on blood pressure (BP) and albuminuria. The salt-sensitive BP response in these patients may be attributed to impaired renal ability to excrete sodium (Na+) resulting in fluid overload and/or vasodysfunction. To define which factor relates to BP sensitivity in both CKD and DKD, we studied the Na+-mediated BP response in these patients compared to healthy volunteers (HV).

Methods: In this randomized crossover study, CKD patients (KDIGO stage G2/3A, proteinuria >0.5 g/d), DKD patients (KDIGO stage G2/3A, proteinuria 0.2-0.5 g/d) and HV followed a 7-day low sodium diet (LSD, <50mmol/d) and high sodium diet (HSD, >200mmol/d), respectively. After each diet, assessment of hemodynamics included daytime BP (Mobil-O-Graph) and cardiac output (CO) measurements (NexfinTM), by which SVR was calculated accordingly. Extracellular fluid volume (ECV) change was assessed with multi-frequency body impedance spectroscopy (Fresenius).

Results: We included 20 CKD (mean age 48 yrs, median (IQR) proteinuria 0.7 (0.6-1.6) g/d, mean (SD) eGFR 60.7 (16.3) ml/min/1.73m2) and 8 DKD patients (age 68 yrs, proteinuria 0.3 (0.2-0.4) g/d, eGFR 59.0 (15.9) ml/min/1.73m2), and 16 HV (age 41 yrs). Dietary intervention was successful with mean difference in urine Na+ excretion of 185, 168, and 209 mmol/day in CKD, DKD and HV respectively. After HSD, mean (SD) systolic BP change was 9.3 mmHg (8.9; p<0.001) in CKD and 13.8 mmHg (10.4; p<0.01) in DKD, while systolic BP change (3.1 mmHg (6)) in HV was not significant. After HSD, we observed significant ECV expansion in all groups without differences between groups (CKD 1.6 L, DKD 1.6 L, HV 1.4 L, p=0.27), while no effects on CO were observed. After HSD, the mean (SD) SVR in CKD increased with 125.7 dyn*sec*cm-5 (247.9, p=0.04) and in DKD with 125.5 dyn*sec*cm-5 (142.6, p=0.04), while in HC a non-significant decline of -109.2 dyn*sec*cm-5 was observed (358.2, p=0.24).

Conclusions: Na+-mediated BP rise in both CKD and DKD coincides with an increase in SVR. The absence of differences in ECV and CO between the three groups indicates that salt sensitivity in both CKD and DKD is not completely based on fluid overload but might be due to an inability to induce vasodilation.

SA-PO358

A Simplified Lung Ultrasound-Guided Management Protocol of Pulmonary Congestion in Hemodialysis

Saleh Kaysi,[1,2] Abdullah I. Hamad,[3] Maxime Taghavi,[1] Rania A. Ibrahim,[3] Heba M. Ateya,[3] Mincy Mathew,[3] Mohamad M. Alkadi,[3] Hassan A. Al-Malki,[3] Joelle L. Nortier.[1,2] *[1]UVC Brugmann, Brussels, Belgium; [2]Universite Libre de Bruxelles, Bruxelles, Belgium; [3]Hamad Medical Corporation, Doha, Qatar.*

Background: Pulmonary congestion PC is frequent in Hemodialysis HD. We validated the first simplified LUS-guided PC management protocol in HD and evaluated its impact on blood pressure BP.

Methods: Prospective randomized multi-center trial: stable HD patients in 3 countries. Randomized: active A and control C groups. Bedside LUS after mid-week session at: Day 1, 15, 30, 45, 60. LUS according to the 8-zone method. B line score BLS of > 5 represented significant PC. Dry weight DW was adapted according to standard of care in the C group. In the A group, in addition, if BLS was > 5 at day 1 or 15 then DW was reduced by 500 g. Home BP monitoring HBPM weekly.

Results: 100 HD patients up until now. Age (60.5 ± 14.6) years, 60% diabetics. In the A group, mean BLS at day 1 (13.5 ± 9) decreased (8.32 ± 6.8) at day 60. (P<0.001). ***Figure 1,*** with a reduction in DW (P: 0.001) and greater UF (P: 0.047). ***Table 1*** A reduction in diastolic blood pressure was noted (*P: 0.001*) In the control group, BLS did not change.

Conclusions: Our simplified LUS guided management protocol was able to safely reduce the pulmonary congestion in HD patients in addition to better controlling their blood pressure.

Table 2: Evolution of parameters according to groups during the study

	Active group			Control group		
Variable	Baseline	Study end	P value	Baseline	Study end	P value
BLS	13.5 ± 9	8.3 ± 6.8	**<0.001**	15.6 ± 9.4	14.8 ± 13.2	0.805
Dry weight, kg	77.2 ±20.7	76 ± 21.2	**<0.001**	77.3 ± 16.7	75.9 ± 15.9	0.239
Ultrafiltration, ml	2512 ± 1177	2709 ± 1144	**0.047**	2590 ± 1059	2623 ± 1060	0.404
Mean SBP (HM)	139.5 ± 18.6	135.2 ± 21.1	0.085	138.2 ± 22.2	138 ± 23	0.914
Mean DBP (HM)	84.3 ± 36.8	74.4 ± 9.9	**0.001**	77.2 ± 10.9	76 ± 10.5	0.678
Kt/V	1.52 ± 0.24	1.5 ±0.23	0.183	1.51 ± 0.319	1.51 ± 0.29	0.603
K, mmol/l	5.15 ± 0.714	5.23 ± 0.8	0.462	5.12 ± 0.738	4.93 ± 0.56	0.056
Hemoglobin, g/dl	11.2 ± 1.5	11.5 ± 1.2	0.235	11.4 ± 1.7	11.5 ± 1.8	0.947
Albumin, g/l	38.2 ± 3.7	38.1 ± 4	0.848	36.8 ± 4.2	37.47 ± 4.1	0.122
PTH, ng/l	364 ± 353	389 ± 253	0.890	344 ± 209	411 ± 253	0.158

Continuous variables are presented with mean _ SDs or median (interquartile range) according to normality. Statistically significant P values are in bold type.
BLS: B lines score, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, K: Potassium, PTH: Parathormone, HM: Home monitoring.

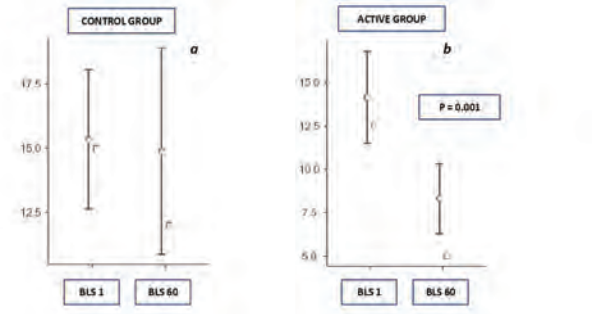


Figure 2 : Pulmonary congestion evolution in the control group (***a***) and the active group (***b***) from Day 1 to Day 60. BLS: B lines score.

SA-PO359

Cardiovascular Functional Capacity in Patients with CKD: Insights from the FIT-INDY Study

Nolan Groninger,[1] Nikita F. Samanani,[1] Cody A. Altherr,[2] Gayatri Narayanan,[1] Kenneth Lim.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Indiana Center for Musculoskeletal Health, Indianapolis, IN.*

Background: Patients with chronic kidney disease (CKD) exhibit a significantly increased risk of cardiovascular disease beginning in the early stages of kidney impairment. However, whether cardiovascular functional capacity is reduced in early-stage CKD and the pattern of its impairment is largely unknown. The goal of this study was to evaluate the natural history of impairment in cardiovascular functional capacity (by VO_2Peak) as assessed by Cardiopulmonary Exercise Testing (CPET) in patients with early-stage CKD.

Methods: We analyzed data from 139 patients in the ongoing Cardiorespiratory Fitness in Patients with Chronic Kidney Disease in Indiana (FIT-INDY) Study, an ambulatory referral cohort of patients who have undergone CPET as part of their standard of care from 2005 to 2023. Participants were stratified into three groups by estimated Glomerular Filtration Rate (eGFR): eGFR ≥90 (n=79); eGFR 60-89 (n=40); and eGFR <60 (n=20). Associations between eGFR and VO_2Peak were assessed using multiple linear regression modeling.

Results: Patients in the lowest eGFR group <60 (62 [45-71] y) were significantly older compared with the other groups (eGFR 60-89=47 [38-56] y; eGFR ≥90=36 [27-44] y; P<0.001). No significant differences in sex were observed between groups. We report an incremental impairment in VO_2Peak observed with declining kidney function (eGFR ≥90, 21.0 [14.8-26.2] mL/min/kg; eGFR 60-89, 16.2 [12.7-19.5] mL/min/kg; eGFR<60, 12.0 [8.8-13.2] mL/min/kg). Additionally, maximal workload declined serially with declining kidney function (eGFR ≥90, 120.0±49.6 W; eGFR 60-89, 117.0±48.8 W; eGFR<60, 70.9±19.7 W; P=0.002). After adjusting for age and hemoglobin, the relationship between eGFR and VO_2Peak remained significant (P=0.017).

Conclusions: Our study highlights that patients with mild to moderate CKD exhibit impaired cardiovascular functional capacity. These findings emphasize the importance of early cardiovascular assessment and management in individuals with CKD, and the need for further studies examining cardiovascular functional alterations in patients with kidney failure.

Funding: Other NIH Support - NCATS

SA-PO360

N-terminal Pro B-Type Natriuretic Peptide (NT-proBNP) and Cardiovascular Structure and Function in Advanced CKD

Monique O. Campos,[1] William Voors,[1] Thomas Hiemstra,[2] Gayatri Narayanan,[1] Kenneth Lim.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom.*

Background: NT-proBNP is a clinically used diagnostic marker in managing of heart failure. Unfortunately, interpretation of NT-proBNP levels is complicated in patients with CKD as the peptide is renally cleared. Furthermore, few studies, if any have assessed the diagnostic value of NT-proBNP in evaluating impaired cardiovascular functional (CVF) –a major complication in advanced CKD. Herein, we investigated the role of NT-proBNP levels in regulating CV structure and function in patients with advanced CKD.

Methods: We conducted a cross-sectional study of baseline data from 242 participants from the Cardiopulmonary Exercise Testing in Renal Failure and After Kidney Transplantation (CAPER) Cohort: advanced CKD stage 5 and 5D patients on the transplant list (n=159) and hypertension patients (n=83). All patients underwent cardiopulmonary exercise testing (CPET) to assess CVF capacity (VO_2Peak) and echocardiography. Participants were stratified into quartiles per NT-proBNP levels. One-way ANOVA was used for group comparisons and associations assessed using Pearson's Correlation.

Results: NT-proBNP levels across quartiles were: <8.1pg/ml (n=59), 8.2-43pg/ml (n=61), 43.1-262pg/ml (n=61), and >262.1pg/ml (n=61). Age did not significantly differ between the groups (p>0.05). However, patients in the lowest NT-proBNP quartile had higher BMI values (Q1:28.3±3.8 kg/m^2; p<0.0001). Patients with highest quartile had lower GFR (Q4:7.0[5,8] ml/min per 1.73 m^2, median [IQR]). Significantly, patients with higher NT-proBNP had reduced VO_2Peak (Q1:26.4±7.5; Q4:18.4±4.7 mL/min/kg;p<0.0001). Additionally, those in the higher NT-proBNP strata exhibited greater left ventricular mass index (LVMI) (Q1:87.7±18.1; Q4:129.4±40.1 g/m^2), lower heart rate (HR) at peak exercise (Q1:157±18; Q4:123±24 bpm), and ejection fraction (Q1:66 ±5;Q4: 60±10%), p<0.0001 for all. NT-proBNP levels were negatively associated with VO_2Peak (r=-0.18;p=0.006), HR (r=-0.27;p=0.0001), ejection fraction (r=-0.22;p=0.0004), and GFR (r=-0.77;p<0.0001) and a positive correlation with LVMI (r=0.44;p<0.0001).

Conclusions: Higher NT-proBNP levels were associated with impaired CV structure and function in patients with advanced CKD. The study suggests that NT-proBNP is a potential biomarker for assessing CVF impairment in advanced CKD.

Funding: Private Foundation Support

SA-PO361

Epimeric Vitamin D Is Not Associated with Arterial Stiffness in Patients with Advanced CKD

Monique O. Campos,[1] Eliott Arroyo,[2] Thomas Hiemstra,[3] Gayatri Narayanan,[1] Heather Burney,[1] Kenneth Lim.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Wake Forest University, Winston-Salem, NC; [3]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom.*

Background: 25-hydroxyvitamin D3 (25-(OH)D3) has the capacity for C-3 epimerization, resulting in the production of 3-epi-25(OH)D3. 3-epi-25(OH)D3 comprises up to ~54% of total 25(OH)D concentrations and therefore could significantly influence end-organ health. We recently demonstrated that 3-epi-25(OH)D3 levels are reduced in patients with advanced CKD and are associated with impaired cardiovascular (CV) functional capacity. However, its role in regulating vascular health in CKD is still largely unstudied. Herein, we investigated the association of serum 3-epi25(OH)D3 with arterial stiffness in patients with advanced CKD.

Methods: We conducted a cross-sectional study of baseline data from 270 participants from the Coventry-Cambridge Vascular Cohort that recruited patients with stage 5 CKD on the transplant list. All patients underwent arterial applanation tonometry to assess arterial stiffness (pulse wave velocity (PWV) and augmentation index at 75 bpm (AI75)). Serum 3-epi-25(OH)D3 was analyzed by liquid chromatography-tandem mass spectrometry. Participants were stratified into 3-epi-25(OH)D3 quartiles, with one-way ANOVA comparing differences and associations assessed using multiple linear regression.

Results: 3-epi-25(OH)D3 levels across quartiles were: < 0.30 ng/mL(n=64); 0.30-0.45 ng/mL(n=71); 0.46-0.73ng/mL(n=68); >0.73ng/mL(n=67). 3-epi-25(OH)D3 quartiles were well matched for age, gender, and BMI (p>0.05). There was a difference in race (<0.001) and dialysis status (p=0.016) among quartiles. The estimated glomerular filtration rate (eGFR) did not significantly differ among 3-epi-25(OH)D3 quartiles (Q1: 8.0 [80,101], Q4: 8.0 [5.3,12.0] ml/min per 1.73 m^2, median [IQR]) p>0.05). There were no differences among quartiles for either PWV (Q1: 7.9 [7.0,9.6], Q4: 7.8 [6.6,9.0] m/s, median [IQR]) p>0.05) and augmentation index (Q1: 20.5 ± 13.7; Q4: 20.4 ± 13.4 %, p>0.05). Multiple linear regression modeling demonstrated that 3-epi-25(OH)D3 was not associated with either PWV and AI75 after adjustment for race and dialysis status (p=0.72).

Conclusions: Our study demonstrates that epimeric vitamin D levels are not associated with modulating arterial stiffness in patients with advanced CKD. Therefore, its relationship with cardiovascular functional capacity in CKD may be mediated by non-vascular targets.

Funding: Private Foundation Support

SA-PO362

GFR-Adjusted Uric Acid Is Superior in Prediction of All-Cause Mortality Compared with Uric Acid or Uric Acid/Serum Creatinine

Eva Koenigshausen, Lars C. Rump, Lorenz Sellin. *Heinrich-Heine-Universitat Dusseldorf, Dusseldorf, Germany.*

Background: Elevated uric acid (UA) levels and serum UA to serum creatinine ratio (sUA/sCr) are associated with increased cardiovascular risk. We investigated GFR, age and sex-adjusted UA levels (eUA) to further increase precision in cardiovascular risk prediction.

Methods: The eUA formula was validated in the LURIC cohort. Due to GFR restrictions, a subpopulation of 2654 patients was evaluated. Outcome variables (mortality, cardiovascular events, heart failure NYHA > II) were analyzed in a risk group (eUA < UA) compared to the control group (eUA > UA). Uni- and multivariate regression analysis was performed for known risk factors as well as UA, eUA and sUA/sCr.

Results: eUA levels were calculated on the basis of the presented eUA formula. Mortality (OR 1.35; 95 % CI 1.09 -1.67; p = 0.006) and heart failure NYHA > II

(OR 1.91; 95 % CI 1.53 – 2.39; p < 0.001) were significantly increased in patients within the risk group (eUA < UA). Multivariate analysis revealed a better prediction of mortality with eUA (OR 7.41; 95 % CI 3.15 -17.47; p<0.001) compared to sUA/sCr (OR 1.12; 95 % CI 1.05 – 1.19; p < 0.001) or UA (OR 1.09; 95 % CI 1.02 – 1.16; p = 0.006) after adjustment for known cardiovascular risk factors. Cardiac events or heart failure NYHA > II was statistically not associated with eUA levels.

Conclusions: Assessment of the newly calculated eUA identifies patients with a particularly increased cardiovascular risk. eUA is superior in predicting mortality compared to established markers such as UA or sUA/sCr.

SA-PO363

Association of Insulin-Like Growth Factor 1 with Cardiovascular Outcomes in Individuals with or without CKD: The UK Biobank Study

Byounghwi Ko, Daseul Huh, Dong Hoon Kang, Ga Young Heo, Cheol Ho Park, Hyung Woo Kim, Jung Tak Park, Tae-Hyun Yoo, Shin-Wook Kang, Seung Hyeok Han. *Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.*

Background: Insulin-like growth factor-1 (IGF-1) has been implicated in chronic noncommunicable diseases. We aimed to explore the relationship between IGF-1 and adverse outcomes among individuals with or without CKD.

Methods: We included 359,739 participants without CKD (cohort 1) and 19,249 participants with CKD (cohort 2) from the UK Biobank cohort study. CKD was defined as an estimated glomerular filtration rate<60 ml/min/1.73m^2 or random urine-albumin-to-creatinine-ratio>30mg/g. The main predictor was IGF-1 levels, and the primary outcome was all-cause mortality. The secondary outcome included the 3-point major-cardiovascular-event (3P-MACE), defined as a composite of non-fatal myocardial infarct, non-fatal ischemic stroke, or cardiovascular death.

Results: There were 23,100 (6.4%) deaths (the corresponding incidence rate, 4.74) over a median follow-up of 13.6 years. In cohort 1 without CKD, the adjusted hazard ratios (aHRs) (95% CIs) for all-cause mortality were 1.24 (1.19-1.30), 1.00 (0.96-1.05), 0.98 (0.93-1.02), 1.03, (0.98-1.08), and 1.09 (1.08-1.19), for 1st, 2nd, 3rd, 5th, and 6th sextile groups, respectively, compared with 4th sextile as the reference group. The U-shaped association was similar in both cohorts. In cohort 2, the corresponding HRs (95% CIs) were 1.46 (1.29-1.66), 1.17 (1.02-1.34), 1.20 (1.04-1.37), 1.13 (0.98-1.30), and 1.17 (1.02-1.35), respectively. Notably, we observed a consistent U-shaped association with 3P-MACE, only in individuals with CKD. When effect modification was examined, no significant interaction between CKD and IGF-1 levels for the risk of all-cause mortality was observed, while a significant interaction was exhibited for the risk of 3P-MACE only in individuals with IGF-1 levels above the median.

Conclusions: This study revealed a U-shaped association between IGF-1 levels with all-cause mortality and cardiovascular outcomes in CKD patients. In individuals with IGF-1 levels above the median, this association was more pronounced in individuals with CKD, suggesting that IGF-1 may serve a more potent prognostic marker in this patient population.

SA-PO364

Comparison of Plasma B-type Natriuretic Peptide (BNP) Levels, N-terminal Pro B-Type Natriuretic Peptide (NT-proBNP) Levels, and the NT-proBNP-to-BNP Ratio in Patients with CKD

Hideki Fujii, Ken Hirabayashi, Keiji Kono, Shunsuke Goto. *Kobe University Graduate School of Medicine, Kobe, Japan.*

Background: Both B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are utilized for diagnosing and managing patients with heart failure in clinical settings. These parameters are also known to be elevated by other cardiovascular disease (CVD), such as coronary artery disease, arrhythmia, and valvular disease. However, their levels can also be influenced by numerous clinical factors including kidney function, and the details remain unclear in patients with chronic kidney disease (CKD). Then, we assess the clinical factors which can influence BNP levels, NT-proBNP levels, and the BNP/NT-proBNP ratio and their predictive availability for CVD in patients with advanced stage CKD.

Methods: This study included 1,037 patients who visited the division of Nephrology at our hospital between 2014 and 2015. For all study participants, both plasma BNP and NT-proBNP levels were measured simultaneously. Plasma BNP levels, NT-proBNP levels, and the BNP/NT-proBNP ratio were evaluated in each stage of CKD, and also examined a correlation of clinical factors with them. Furthermore, we assessed the correlation of BNP levels, NT-proBNP levels, the BNP/NT-proBNP ratio, and clinical parameters with CVD events in patients with CKD stage 4 and 5.

Results: Patients with CKD stage 1-5D were included in this study. Plasma BNP levels, NT-proBNP levels, and the NT-proBNP/BNP ratio increased and the relationship between BNP and NT-proBNP levels weakened with declining kidney function. In patients with CKD stage 1 to 5, common independent determining factors for BNP and NT-proBNP levels and the NT-proBNP/BNP ratio included Hb levels, phosphate levels, and intact PTH levels. In patients with advanced stage CKD (CKD4 and 5), those with higher levels of BNP, NT-proBNP, or the NT-proBNP/BNP ratio experienced a greater number of CVD events compared to those with lower levels. Additionally, multivariate Cox regression analysis showed that the occurrence of CVD was significantly correlated not with BNP and NT-proBNP levels, but only with the NT-proBNP/BNP ratio (HR [95%CI]: 1.064 [1.029-1.100], p<0.001) in these patients.

Conclusions: Given the complex influence of various factors on plasma BNP and NT-proBNP levels in patients with CKD, careful interpretation of these values is essential.

Funding: Commercial Support - Roche

SA-PO365

Elevated Serum Homocysteine Associated with Left Ventricular Remodeling in Patients with IgA Nephropathy

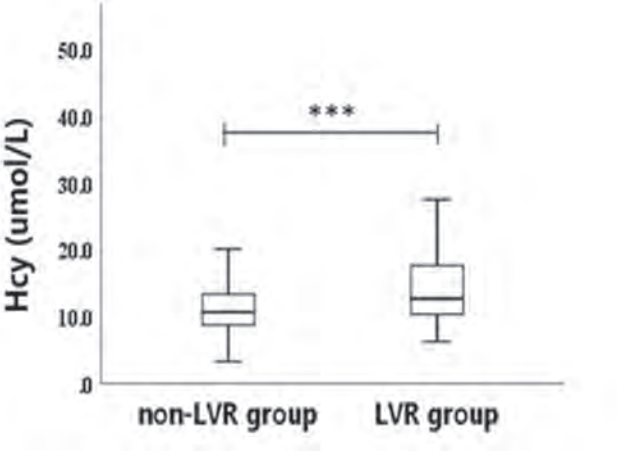
Hao Yu, Zizhen Li, Qianqian Han, Huicong Wu, Rui Zhang, Weicong Zeng, Jiajia Li, Qiongqiong Yang. *Department of Nephrology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China.*

Background: Homocysteine(Hcy) is a non-traditional independent risk factor for cardiovascular disease. Left ventricular remodeling(LVR) is a predictor of poor cardiovascular and renal outcomes in patients with chronic kidney disease(CKD). However, there is little known about LVR in IgA nephropathy(IgAN). We aimed to explore the association between serum Hcy and LVR in IgAN patients.

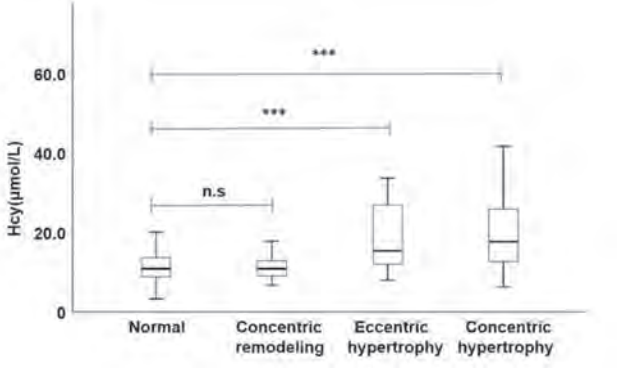
Methods: This retrospective study included 257 patients with IgAN who underwent echocardiography. LVR was defined as left ventricular mass index(LVMI)>115g/m^2 in men and>95g/m^2 in women or relative wall thickness(RWT)>0.42. Spearman correlation and logistic regression analysis were performed to explore the association between Hcy and LVR.

Results: In our study, 28.79% of patients had LVR, and the proportion increased with CKD progression. Patients with LVR were older and had higher serum Hcy[13.95(10.65,19.10) vs 10.90(8.80,13.70)μmol/L, *P*<0.001], body mass index(BMI), blood pressure(BP), serum creatinine(Scr), 24-hour urine protein, triglyceride(TG), and serum phosphorus(P), but lower haemoglobin(Hb) and serum bicarbonate compared to patients without LVR. An adjusted multivariate logistic regression model indicated that elevated serum Hcy was independently associated with increased risk of LVR(OR=1.072, 95%CI=1.001-1.149, *P*=0.047).

Conclusions: Serum Hcy was associated with LVR independent of traditional cardiovascular risk factors as BP, Scr and TG in IgAN patients.



Levels of serum Hcy in LVR group and non-LVR group. ***P<0.001



Levels of serum Hcy in groups according to heart structure. ***P<0.001

SA-PO366

Role of Inflammation and High-Sensitivity C-reactive Protein in Atherosclerotic Cardiovascular Disease and CKD: A Survey of Nephrologists

Vlado Perkovic,[1] David Cherney,[2] Edmundo Erazo Tapia,[5] Sofia Gerward,[6] Manisha Sahay,[4] Abhijit V. Shete,[5] Nikolaus Marx.[3] *[1]University of New South Wales, Sydney, NSW, Australia; [2]University of Toronto, Toronto, ON, Canada; [3]University Hospital RWTH Aachen, Aachen, Germany; [4]Aditya Hospital, Abids, Hyderabad, India; [5]Novo Nordisk, Zurich, Switzerland; [6]Novo Nordisk, Copenhagen, Denmark.*

Background: In patients (pts.) with atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD), systemic inflammation (SI) contributes to increased cardiovascular (CV) risk. The FLAME-ASCVD-Nephro survey assessed awareness and perception of SI among nephrologists (nephs).

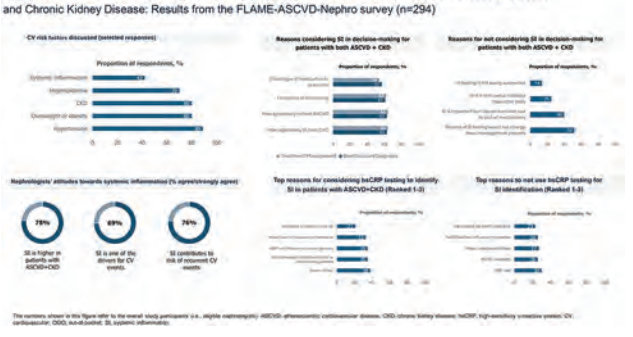
Methods: An online observational study (NCT06322641) of nephs (Feb-April 2024) across 10 countries (Australia, Brazil, Canada, China, France, Germany, India, Italy, Japan, and Saudi Arabia) who treat ≥20 pts. with ASCVD+CKD a month and in practice for ≥3 years, was analyzed using descriptive statistics.

Results: Of 3,778 participants, 294 completed the survey (~30/country). Traditional CV risk factors were most often discussed with pts.; SI to a lesser extent. 78% considered burden of SI higher in pts. with both ASCVD+CKD than CKD alone, and saw SI as an independent risk factor for ASCVD (66%) and linked to the development (63%) and progression of CKD (71%). 76% agreed SI as a contributor to the risk of recurrent CV events; 67% stated residual inflammatory risk persisted despite evidence-based preventive CV therapies. 7/10 reported testing SI to assist with clinical decisions, ie how aggressively to treat ASCVD (64%) and CKD (64%), and 83% used standard CRP. 74% would like to learn more about the role of SI in ASCVD and 35% agreed inclusion of high-sensitivity C-reactive protein (hsCRP) testing in guidelines would support clinical usage.

Conclusions: This survey among nephs show SI was considered a CV risk factor, but not to the level of traditional CV risk factors. There is a need for medical education on the role of SI and guidance on hsCRP testing in pts. with ASCVD+CKD.

Funding: Commercial Support - Novo Nordisk Health Care AG

Figure. Role of Inflammation and High-sensitivity C-reactive Protein in Atherosclerotic Cardiovascular Disease and Chronic Kidney Disease: Results from the FLAME-ASCVD-Nephro survey (n=294)



SA-PO367

Nuclear Magnetic Resonance Lipoprotein Analysis in Nephrotic Syndrome vs. Remission

Michael Hwang,[1,2] Rebecca Brown,[1] Lilian Howard,[1] Meryl Waldman.[1] *[1]National Institute of Diabetes and Digestive and Kidney Diseases Division of Intramural Research, Bethesda, MD; [2]National Institutes of Health, Bethesda, MD.*

Background: Nephrotic syndrome (NS) is associated with lipid abnormalities characterized by elevations in total chol, low density lipoprotein (LDL-C), triglycerides (TG), lipoprotein(a) & apolipoproteins. While dyslipidemia improves with remission (R), unfavorable lipid profiles may persist beyond R & in those with residual proteinuria. These changes have not been well characterized. Comprehensive lipid analysis using nuclear magnetic resonance (NMR) may provide more information about atherogenicity than standard lipid testing during active NS (ANS) compared to R. NMR assesses lipoprotein (LP), particle(P) size, # & concentration, apolipoproteins & inflammation.

Methods: Patients with non-diabetic glomerular disease with paired NMR profiles (Vantera Clinical Analyzer) available during ANS & R (proteinuria >3.5 & <1 g/d, respectively) were included. Statistical comparisons were done for ANS *vs* R, & both ANS & R *vs* healthy controls using paired *t* tests or Wilcoxon tests.

Results: Table 1. 19 patients with membranous nephropathy analyzed (68% male, mean age: 53 y); 68% on lipid lowering drugs. As expected, ANS was associated with an atherogenic lipid profile that improved at R, including ↓ in TG, LDL-C, LDL-P # & apoB. However, TG rich LP remained ↑, notably large & very small TRLP (VS-TRLP). While HDL-C did not change, both HDL -P # & apoA1 ↓ *vs* ANS. GlycA remained ↑ at R despite normal CRP.

Conclusions: This NMR analysis provides a granular snapshot of LP during contrasting disease states. Despite overall improvement in lipids with R consistent with ↓ atherogenicity, the pattern of ↓ apoA1, total & large HDL with persistently ↑ TRLP (particularly highly atherogenic VS-TRLP) may suggest residual atherogenicity. The clinical significance of high GlycA, which reflects systemic inflammation, warrants further investigation in NS as a CVD risk predictor.

Funding: NIDDK Support

	Active Nephrotic Syndrome (ANS) (N=19)	Remission (R) (N=19)	Normal Range	P-value (ANS vs R)	P-value (ANS vs Healthy)	P-value (R vs Healthy)
Clinical Measurements						
Protein Excretion, mg/day	12216 ± 8231	277 ± 250	<300	<0.0001		
Serum Albumin, g/dL	2.8 ± 0.7	4.3 ± 0.3	3.5 - 5.2	<0.0001		
eGFR, CKD EPI 2021 ml/min/1.73 m²	75 ± 28	74 ± 23	>70	0.8		
C-Reactive Protein, mg/L	4.3 (1.2, 10.3)	2 (0.7, 5.9)	1.0 - 3.0	0.5		
Total Cholesterol, mg/dL	286 (220, 344)	184 (175, 206)	0 - 200	<0.0001	—	—
Triglycerides, mg/dL	188 (124, 366)	128 (80, 197)	0 - 150	0.004		
LDL-C, mg/dL	181 ± 82	114 ± 30	0 - 100	0.002		
HDL-C, mg/dL	60.5 ± 21.8	53.5 ± 17.3	40 - 60	0.07		
BMI, kg/m²	33 ± 8.9	32.6 ± 9.5	18.5 - 24.9	0.56		
Triglyceride-Rich Lipoprotein Particle (TRL-P) Concentrations (nmol/L)						
Total TRL-P	313.3 (197.9, 507.8)	151.1 (89.1, 264.5)	81.4 (46.4, 135)	0.0001	0.002	0.02
Very Large TRL-P	0.8 ± 2.7	0.2 ± 0.2	0.2 ± 0.4	0.4	0.3	0.5
Large TRL-P	9.3 ± 26.5	6.5 ± 8.0	2 ± 4.5	0.2	0.2	0.02
Medium TRL-P	62 ± 90.5	33.2 ± 48.2	12.5 ± 17	0.07	0.03	0.08
Small TRL-P	188.1 ± 174.2	34.6 ± 24.2	28.9 ± 28.8	0.002	0.01	0.3
Very small TRL-P	218.7 ± 172.6	107.3 ± 88.3	56.7 ± 59.5	0.002	0.0007	0.02
LDL Particle (LDL-P) Concentrations (nmol/L)						
Total LDL-P	2502.7 ± 1083.2	1469.5 ± 346.1	1461.7 ± 468.4	0.0005	0.0006	0.9
Large LDL-P	570.3 ± 553.0	269.2 ± 283.1	221.9 ± 202.2	0.012	0.01	0.5
Medium LDL-P	694.0 ± 657.7	584.2 ± 340.6	528.3 ± 379.3	0.5	0.3	0.5
Small LDL-P	1238.5 ± 1234.2	616.1 ± 553.8	710.7 ± 499.6	0.006	0.08	0.5
HDL Particle (HDL-P) Concentrations (umol/L)						
Total HDL-P	24.4 ± 6.0	19.9 ± 2.6	19.9 ± 3.4	0.002	0.004	>0.00
Large HDL-P	2.2 (1.3, 3.3)	1.1 (0.6, 1.7)	2.2 (1.1, 3.8)	0.047	0.7	0.5
Medium HDL-P	2.6 ± 2.2	1.1 ± 1.8	4.2 ± 2.2	0.3	0.007	0.02
Small HDL-P	18.8 ± 7.2	14.4 ± 3.9	12.9 ± 3.9	0.004	0.002	0.1
Deconvolution-Derived Apolipoprotein Concentrations (mg/dL)						
Apolipoprotein A-1	148.5 ± 35.4	124.5 ± 25.3	132.1 ± 26.4	0.001	0.06	0.2
Apolipoprotein B	142 (107.7, 193.6)	82.0 (78.9, 96.3)	79.1 (64.2, 97.7)	<0.0001	0.0003	0.08
NMR Marker of Inflammation (umol/L)						
GlycA	476.5 ± 103.6	435.0 ± 90.2	371.8 ± 70.2	0.006	0.0003	0.007

Table 1: Standard Cholesterol and NMR profiles during NS and remission. NMR normal range is mean±SD or median (25^{th}–75^{th} %tile) from subjects (N=1335) healthy volunteers.

SA-PO368

Machine-Learning Approaches for Major Adverse Cardiovascular Events (MACE) Prediction in Patients on Hemodialysis

Cheng-Hsu Chen,[1,2] Shun Fang Hou,[1] Min-Shian Wang.[3,4] *[1]Division of Nephrology, Taichung Veterans General Hospital, Taichung City, Taiwan; [2]Doctoral Program in Tissue Engineering and Regenerative Medicine, National Chung-Hsin University, Taichung City, Taiwan; [3]Smart Healthcare Committee, Taichung Veterans General Hospital, Taichung, Taiwan; [4]Dept. of Applied Mathematics, National Chung Hsing University, Taichung, Taiwan.*

Background: Major Adverse Cardiovascular Events (MACE) are common complications of hemodialysis (HD) patients that include myocardial infarction (MI), stroke, cardiac arrhythmia and heart failure (HF). The objective of the current study was to predict MACE among our HD patients.

Methods: HD patients above 18 years old were recruited 29356 HD sessions for the study between 2014 to 2023 from our hospital database of the TSN-KiDiT (kidney, dialysis, and transplantation integrated software), which is integrated operation management system and quality control for Taiwan Society of Nephrology. Different Machine learning algorithms: including RandomForest (RF), XGBoost, logistic regression (LR), and KNN(K Nearest Neighbor) were employed. Clinical attributes, electrolytes, dialysis adequacy and blood flow (BF), cardiothoracic ratio (CT ratio) and biomarkers were explored in predicting MACE. The feature importance was determined using mean decrease accuracy.

Results: Overall, 28788 HD sessions were included in the analyses, there were 3791 events of MACE within 12-month. The XGBoost Model demonstrated a prediction accuracy of 88.92% with the area under the receiver operating characteristic curve (AUROC) 94.42%, which is higher as compared to the RF 84.54% [AUROC 94.95%], the LR model 65.23% [AUROC 65.23%], however, the KNN has the best accuracy 92.45% [AUROC 93.28%] with less sensitivity 59.47%, respectively. The classification accuracy of the models for cardiac arrhythmia was 89.01%, which was higher than prediction accuracy for AMI (83.67%), and heart failure (HF: 82.84%). Age, CT ratio, glucose, transferrin saturation, albumin, ferritin were the major predictors of MACE.

Conclusions: The ML models had shown acceptable performance in predicting MACE in HD patients. Age, CT ratio, glucose and other biomarkers were important predictors of MACE, which is consistent between the individual components of MACE, such as cardiac arrhythmia, MI, and HF. These parameters can be calibrated as prognostic parameters of MACE events in HD patients.

Table 1. Comparison of the performance of different models

		Validation					Testing				
	Classifier	Sens	Spec	Accuracy	AUROC	Precision	Sens	Spec	Accuracy	AUROC	Precision
Follow 12-month	Xgboost	82.75% (1.64%)	89.85% (0.78%)	88.90% (0.75%)	93.94% (0.35%)	55.72% (2.12%)	83.43%	89.70%	88.02%	94.42%	53.58%
	RF	89.49% (1.25%)	82.93% (0.45%)	83.80% (0.39%)	93.88% (0.52%)	44.67% (0.67%)	90.81%	83.65%	84.54%	94.95%	44.17%
	LR	66.22% (1.79%)	65.09% (1.06%)	65.24% (1.04%)	71.27% (1.10%)	22.62% (0.86%)	63.70%	65.44%	65.23%	70.75%	20.82%
	KNN	58.21% (3.33%)	97.32% (0.39%)	92.10% (0.57%)	92.44% (1.04%)	77.01% (2.86%)	59.47%	97.14%	92.45%	93.28%	74.78%
Follow 6-month	Xgboost	70.76% (2.54%)	91.37% (0.53%)	89.68% (0.56%)	91.49% (0.83%)	42.42% (1.84%)	77.46%	90.96%	89.06%	93.65%	40.64%
	RF	85.91% (2.82%)	77.36% (0.69%)	78.06% (0.78%)	90.25% (0.92%)	25.40% (1.03%)	89.44%	78.15%	78.99%	92.74%	24.64%
	LR	65.86% (2.62%)	65.44% (1.20%)	65.48% (1.04%)	71.29% (1.57%)	14.60% (0.52%)	67.37%	66.47%	66.53%	72.92%	13.83%
	KNN	32.56% (3.23%)	98.42% (0.17%)	93.00% (0.28%)	87.01% (1.20%)	64.82% (3.34%)	38.03%	98.37%	93.90%	90.34%	65.06%
Follow 3-month	Xgboost	53.96% (5.30%)	94.40% (0.56%)	92.64% (0.58%)	88.23% (1.93%)	30.65% (3.12%)	56.34%	93.70%	91.96%	89.33%	30.38%
	RF	79.52% (4.07%)	74.02% (0.58%)	74.26% (0.59%)	85.62% (1.89%)	12.26% (0.61%)	80.97%	74.23%	74.54%	85.44%	13.29%
	LR	64.41% (4.63%)	65.08% (1.00%)	65.05% (0.86%)	70.36% (2.82%)	7.76% (0.46%)	60.82%	66.02%	65.78%	68.63%	8.03%
	KNN	6.90% (1.46%)	99.28% (0.19%)	95.25% (0.22%)	81.84% (2.57%)	31.79% (9.41%)	10.45%	99.34%	95.21%	81.92%	43.75%

- This is an imbalanced dataset, and as the imbalance ratio increases, both sensitivity and AUROC deteriorate.
- The accuracy of predicting follow 12 months with major adverse cardiovascular events is 88.92%.

SA-PO369

Dynamic Prediction of Cardiovascular Events in Incident Patients on Peritoneal Dialysis with Multivariate Joint Models Adjusting for Phosphate, Albumin, and Calcium Trajectories and Competing Risks

Ivan Damgov,[1,2] Meinhard Kieser,[2] Simon J. Davies,[5] Muh Geot Wong,[6] Carol A. Pollock,[3] David W. Johnson,[4] Claus Peter Schmitt.[1] *[1]Center for Pediatric and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany; [2]Institute of Medical Biometry, University of Heidelberg, Heidelberg, Germany; [3]Kolling Institute, Sydney Medical School, University of Sydney, Royal North Shore Hospital, St Leonards, NSW, Australia; [4]Australasian Kidney Trials Network, University of Queensland, Brisbane, QLD, Australia; [5]Faculty of Medicine and Health Sciences, Keele University, Stoke-on-Trent, United Kingdom; [6]Department of Renal Medicine, Royal North Shore Hospital, St Leonards, NSW, Australia.*

Background: Joint models (JM) offer dynamic personalized risk predictions by exploring the link between longitudinal biomarkers and clinical outcomes. We investigated serum phosphate, albumin and calcium trajectories to predict cardiovascular events in peritoneal dialysis (PD) patients for the first time using innovative multivariate JM.

Methods: We evaluated the association of phosphate, albumin and calcium with composite cardiovascular events (CVE) in incident PD patients followed over 8 years in the Initiating Dialysis Early And Late trial. We adjusted time trajectories for non-linearities and considered non-cardiovascular death causes and transfer to hemodialysis as competing events. The complete dataset (N=318 patients) was used for model selection, while dynamic predictive performance was compared using a 4-fold and 10-repeat cross-validation. Individual patient CVE predictions were obtained for forecast horizons until 5 years on PD at cut-offs 1, 1.5 and 2 years utilizing biomarkers trajectory and 4 baseline risk factors.

Results: A median of 10 records per patient and a 28% CVE rate ensured convergence of all 8 JM models investigated. Multivariate JM demonstrated strong positive association of phosphate and strong inverse association of albumin with composite CVE, while calcium adjusted for albumin did not provide additional explanatory nor prognostic value. All JM demonstrated excellent to outstanding predictive performance in both short- and long-term CVE forecasts, regardless of competing risks adjustment. Multivariate JM with phosphate and albumin outperformed univariate JM (5-year forecast area under the curve (AUC) median values at 1, 1.5 and 2 years: 0.85, 0.84 and 0.80). Prediction performance of all multivariate JM surpassed the classical Cox model with baseline parameters only ignoring biomarker trajectories (median AUC = 0.79, 0.78, 0.77).

Conclusions: This first investigation of multivariate JM in PD patients outlines longitudinal phosphate and albumin as independent predictors of composite CVE with excellent potential in dynamic personized forecasts superior to the classical Cox approach.

SA-PO370

A Curious Case of Salt-Sensitive Hypertension

Madhumitha Rajagopal,[1] Joshua L. Rein.[1,2] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]James J Peters VA Medical Center, New York, NY.*

Introduction: Excess NaCl consumption is the top modifiable risk factor for HTN. Despite clear evidence, adherence to dietary NaCl restriction is low. HTN affects half of US adults and among them, half have salt-sensitive (SS)-HTN. We present a case of SS-HTN and its unique management.

Case Description: Patient is a 70 yo Black man with PMHx of resistant HTN (despite clonidine 0.3mcg TID, hydralazine 100mg TID, lisinopril 40mg TID, and labetalol 800mg BID). Over the years, he developed severe constipation from Ca^{2+} channel blockers, gynecomastia from spironolactone, and HCTZ induced hyponatremia. He weighed 95kg, had no edema, and BP was labile, 124-200/68-104 mmHg. Labs were notable for K^+ 3.5-4.0 mEq/L, TCO_2 23-28 mEq/L, creatinine (SCr) 1.3-1.6 mg/dL, and PAC/PRA < 1.0-2.3 ng/dL / 0.3-1.4 ng/mL/hr. Renal US was unremarkable and CT showed bilateral adrenal thickening. A positive correlation was observed between BP and NaCl intake based on 24h dietary recall (24H). Given suppressed RAAS (volume expanded state), low dose torsemide (10mg QD) and amiloride (5mg QD) were started, lisinopril was continued, and hydralazine, labetalol, and clonidine doses were halved. Two weeks later, he was hypotensive (90/60) with pre-renal AKI (SCr 2.8) that improved with IV fluids. Diuretics, lisinopril, and hydralazine were stopped, and clonidine dosing was decreased. However, BP rebounded over a few weeks to 158-190/88-108. Torsemide+amiloride were resumed and BP improved within 1 week to 106-144/68-85, allowing for a lower labetalol dose. Over the next 6 months, BP was controlled (106-144/68-85) and hypervolemia improved (PAC/PRA 6.5/0.8) with torsemide 10 QD, amiloride 5 QD, labetalol 200 BID, and clonidine 0.1 BID. Natera Renasight genetic testing revealed a heterozygous VUS in *NR3C1*, encoding the glucocorticoid (GC) receptor. Pathogenic homozygous mutations cause GC resistance, with elevated ACTH and cortisol levels leading to SS-HTN from mineralocorticoid receptor activation.

Discussion: After years of ineffective anti-HTN therapy missing the mechanism of SS-HTN, serial PAC/PRA measurements with 24H, prompted an unconventional diuretic combination to achieve HTN control and reduce pill burden. This case highlights: 1) the utility of serial PAC/PRA with 24H to diagnose SS-HTN; 2) the efficacy of non-thiazide distal diuretics to treat SS-HTN; and 3) an evolving role for genetic testing to further our understanding of SS-HTN.

SA-PO371

Liddle Syndrome and Recurrent Spontaneous Coronary Artery Dissection

Ritu Seethapathy,[1] Andrew Klufas,[2] Adina S. Voiculescu.[3] *[1]Landmark Medical Center, Woonsocket, RI; [2]Roger Williams Medical Center, Providence, RI; [3]Brigham and Women's Hospital, Boston, MA.*

Introduction: Liddle Syndrome is an autosomal dominant form of resistant hypertension (HTN) characterized by suppression of plasma renin activity and aldosterone secretion with early onset HTN and hypokalemia.

Case Description: A 45-year-old woman with treatment resistant HTN since her twenties, presented to the ED for chest pain. She was hypertensive, with elevated troponins and ST-segment elevation on EKG. In the Cath Lab she was found to have mid-LAD occlusion secondary to dissection with subsequent balloon angioplasty, and was discharged on Carvedilol, Losartan, HCTZ, and DAPT. Two years later she developed similar chest pain with recatheterization showing spontaneous dissection of first obtuse marginal artery. She was placed on regimen of five maximally tolerated medications (Losartan/HCTZ, Carvedilol, Diltiazem, Clonidine, and Isosorbide Mononitrate). Further workup showed low plasma renin activity and aldosterone, normal catecholamine levels, and chronic hypokalemia. Surveillance imaging showed a cavernous carotid artery aneurysm and renal artery beading suggestive of fibromuscular dysplasia (FMD), thought to demonstrate a shared pathophysiologic process. However, Renal Artery Doppler showed normal flow velocity bilaterally. Liddle Syndrome was suspected given unusual labs and lack of renal artery stenosis, and amiloride was recommended pending genetic test results.

Discussion: Liddle Syndrome is caused by mutations in genes encoding epithelial sodium channels (ENaC). Increased ENaC activity results in increased sodium reabsorption, causing HTN through intravascular volume expansion, and hypokalemia through high distal tubule potassium secretion. HTN also causes decreased renin and aldosterone production through JGA feedback. Treatment involves potassium sparing diuretics (triamterene and amiloride), which block ENaC channels. Mutant ENaC channels prevent action of mineralocorticoid receptor antagonists (spironolactone). Genetic studies are required for confirmation as phenotypic variability often leads to misdiagnosis; however, it cannot definitively rule out disease as not all associated mutations are known. Spontaneous coronary artery dissection (SCAD) has been associated with underlying connective tissue disease or arteriopathy, most commonly FMD. To our knowledge this is the first case reported of recurrent SCAD in the setting of possible Liddle Syndrome without evidence of FMD.

SA-PO372

Lisinopril-Induced Rhinorrhea: A Case Report

Alice Amudzi, Giro R. Samale, Xavier F. Parada. *Berkshire Medical Center, Pittsfield, MA.*

Introduction: A 47-year-old woman presents to our clinic with a chief complaint of rhinorrhea; she had a medical history of chronic hypertension managed with antihypertensive drugs, including Lisinopril. While dry cough is a well-known side effect of ACE inhibitors, this case highlights a common chief complaint yet less recognized side effect of ACE inhibitors. It further emphasizes that overall, angiotensin receptor blockers may be a better drug of choice in hypertension due to their favorable side effect profile.

Case Description: We present the case of a 47-year-old woman with chronic hypertension who presented to our clinic with a runny nose for more than a year. The patient denied cough, fever, facial pain, sneezing, polyps, pruritus, headaches, conjunctivitis, or sore throat. She had a sister with chronic hypertension who experienced rhinorrhea after starting Lisinopril and a father who similarly experienced facial flushing. After several office visits, Lisinopril was discontinued, and their symptoms resolved. Her physical exam was unremarkable. Given her strong family history and Losartan's low side effect profile, we substituted Lisinopril. Two weeks later, her rhinorrhea improved and resolved entirely by week four.

Discussion: Lisinopril belongs to a class of medications called ACE inhibitors. It works by inhibiting the conversion of angiotensin I to angiotensin II to regulate blood pressure. Lisinopril may result in the accumulation of bradykinin and substance P, which increases vascular permeability and fluid leakage from blood vessels into the surrounding tissues. This later mechanism mediates symptoms like postnasal drainage, rhinitis, and rhinorrhea. URTI is among the three top diagnoses in outpatient settings in the USA, and having a broad differential is crucial in treating patients to avoid unnecessary diagnostic testing. Most clinicians are aware of ACE-I-induced cough but less frequently recognize rhinorrhea as a side effect. Not everyone using an ACE-I will experience rhinorrhea, and some studies suggest a genetic predisposition. With the increasing prevalence of hypertension notwithstanding the benefits of ACE-I use, we favor the use of ARBs over ACE-Is when indicated in the management of hypertension and renal disease, more so in patients who are intolerant to ACE inhibitors, especially since ARBs are reasonably comparable in effectiveness and tolerability.

SA-PO373

Unmasking Secondary Hypertension: Renal Artery Stenosis Concealing Primary Hyperaldosteronism

Paul Wurtz, Alexandra Stewart. *Brooke Army Medical Center, Fort Sam Houston, TX*.

Introduction: In young adults with new onset hypertension, complete secondary workup is warranted. We present a patient ultimately found to have an aldosterone-secreting adenoma after a complex diagnostic journey.

Case Description: A 21-year-old woman with no medical history was found to have elevated blood pressures (BP) in both the home and office setting. Lab values were significant for hypokalemia and metabolic alkalosis with elevated plasma aldosterone concentration (PAC) of 16.1, plasma renin activity (PRA) of 0.442, and aldosterone to renin ratio (ARR) of 36.4. Subsequent values were non-diagnostic (Table 1) with normal 24-hour urine aldosterone and CT abdomen negative for adrenal adenoma. Additionally, renovascular workup revealed focal right renal artery stenosis of 40% concerning for fibromuscular dysplasia. One year later, due to increasing BP, angiogram revealed ~73% stenosis therefore angioplasty was performed. This did not improve her HTN, thus she sought opinion from an outside renovascular specialist re-visiting the possibility of primary hyperaldosteronism. Reassessment of primary hyperaldosteronism revealed elevated PAC and ARR levels with Adrenal MRI revealing a 1.7cm left adrenal adenoma. Adrenal venous sampling (AVS) confirmed the presence of a hyperfunctioning adenoma. Surgical removal of the adrenal gland resulted in successful weaning of all BP medications.

Discussion: We present a case with multiple confounders representing diagnostic dilemmas encountered with complex testing. Although the gold standard for diagnosing RAS is invasive angiography, the non-invasive tests such as doppler ultrasound and magnetic resonance angiography have reasonably high sensitivity and specificity. However, these tests are operator dependent which may impact reliability. Additionally, interpreting the plasma aldosterone and renin is nuanced with many factors affecting results including time of day, medications, and positioning of the patient. A multidisciplinary approach ultimately led to the diagnosis after an arduous evaluation.

Table 1

Date	Aldosterone	Renin	Aldosterone/Renin Ratio
04/28/2020	16.1	0.442	36.4
05/18/2020	4.2	1.621	2.6
06/10/2020	10.7	0.402	26.6
04/15/2022	8.3	0.468	17.7
06/12/2023	23.1	1.783	13
07/10/2023	2.4	3.118	0.8

SA-PO374

A New Cause of Glycyrrhizic Acid-Induced Apparent Mineralocorticoid Excess (AME) Syndrome with Hyperadrenergic Symptoms

John A. Szendrey, Gregory L. Braden, Daniel L. Landry, Anthony E. Poindexter, Jeffrey Mulhern. Kidney Care and Transplant Services of New England. *Baystate Medical Center, Springfield, MA*.

Introduction: AME is caused by genetic or drug-induced inhibition of renal 11Beta-hydroxysteroid dehydrogenase-2(11βDSH-2) inactivating conversion of cortisol to cortisone, leading to major cortisol activation of the renal mineralocorticoid receptor (MR). Acquired AME can occur due to the ingestion of glycyrrhizic acid(GA), found in licorice root and chewing tobacco. However, the brain contains 11βDSH-1 which can affect the level of brain catecholamines We present a new cause for AME from Advanced Liver Support supplements who also presented with never before reported hyperadrenergic symptoms associated with AME which we believe are due to the additional brain effects of 11BDSH-1 inhibition.

Case Description: A 65-year-old female developed accelerated hypertension, hypokalemia, metabolic alkalosis and adrenergic symptoms 4 months after daily ingestion of 4 tablets/day of Advanced Liver Support, Advanced BioNutritionals (Nacros, Georgia). Each pill contained 250 mg of GA. She had a BP 220/120 mmHg with episodes of palpitations, sweating & tremors. Her Na was 141 mmol/L, K 3.1 mmol/L, Cl 101 mmol/Land HCO3 30 mmol/L. Fasting free catecholamines were normal, plasma renin activity was reduced at 0.437 ng/mL/hr & serum aldosterone level was less than 1 ng/dL. Cessation of the liver supplement resulted in complete resolution of her hypertension, adrenergic symptoms & abnormal lab values within a few days, and her two blood pressure medications were discontinued. She has been followed for a year without reoccurrence of hypertension.

Discussion: GA is increasingly found in unregulated nutritional supplements and has the potential to induce a reversable syndrome of AME. Numerous other health supplements containing GA are available, which clinicians must consider in cases of AME. Acquired AME differs from genetic AME due to GA inhibition of both 11βDSH-1 and 2 enzymes. 11βDSH-2 inhibition increases local renal and CNS cortisol levels, while 11βDSH-1 inhibition increases pituitary hypothalamic tract mediated catecholamine release which can be responsible for additional hyperadrenergic effects of drug- induced AME.

SA-PO375

Pediatric Hypertension: A Case Series

Nikhila Aimalla, Divya Sai Vunnam, Rebecca Blonsky. *Marshfield Clinic Health System, Marshfield, WI*.

Introduction: Pediatric hypertension (HTN) is an increasingly common health concern. Essential HTN now surpasses secondary causes in prevalence amongst children. Early diagnosis and management are crucial. Pediatric HTN is diagnosed with three elevated systolic or diastolic blood pressure (BP) readings (≥ 95th percentile) adjusted for age, height, and sex.

Case Description: Case A: A 17-year-old female presented following an elevation of her blood pressure. On further history, she reported hot flashes, diaphoresis, palpitations, and lightheadedness in association with significantly elevated pressures. Pheochromocytoma was suspected, and serum catecholamines and CT confirmed the diagnosis. She underwent robotic resection, and pathology confirmed a paraganglioma with surgical correction of hypertension. **Case B:** A 9-year-old morbidly obese female was noted to have intermittently elevated BP for two years. She was evaluated for concerns about secondary HTN. Serologic evaluation and imaging were unremarkable. She was diagnosed with essential HTN and managed with medication and lifestyle modifications. **Case C:** A 16-year-old male presented for visual changes and was found to have optic nerve swelling with retinal hemorrhage due to a hypertensive emergency. The workup revealed an elevated serum creatinine, and a kidney biopsy was performed. The patient was found to have IgA nephropathy with extensive necrotizing and fibrous crescents with interstitial fibrosis. Hemodialysis was initiated, and he is awaiting a kidney transplant.

Discussion: The evaluation of pediatric HTN starts with a comprehensive history. Documenting dietary habits, physical activity, family history, and screening for obstructive sleep apnea is crucial. Annual BP measurements for children ≥3 years with more frequent checks for those at higher risk should be performed. Secondary causes such as endocrinologic, vascular, and renal disorders should be excluded. In addition to serologic evaluation, ambulatory BP monitoring can aid in determining the presence of true HTN. Pediatric patients, especially those presenting before puberty or with any laboratory abnormality, should trigger an evaluation for secondary causes of HTN.

SA-PO376

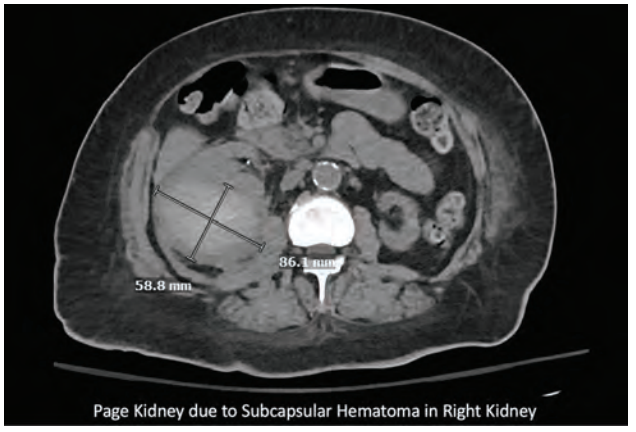
A Rare Case of Atraumatic Page Kidney in a Patient with ESRD

Jiya Mulayamkuzhiyil, Jonathan London, Shemrine Mark, Inaas Shirazi, Neeru Kumar. *Long Island Community Hospital, Patchogue, NY*.

Introduction: Page kidney is a rare cause of secondary hypertension occurring due to renal parenchymal compression from subcapsular hematoma which induces renal microvascular ischemia and activation of the renin-angiotensin-aldosterone system. The major causes include trauma, iatrogenic, tumor, and vasculitis. Rarely, Page kidney can be caused due to anticoagulation use. We describe a rare case of atraumatic Page kidney in ESRD due to anticoagulation use leading to malignant hypertension.

Case Description: A 60-year-old female with past medical history of ESRD, type 2 diabetes mellitus, hypertension, and CVA presented with fever, shortness of breath, and chest pain for 1 week. Patient denied abdominal pain and recent trauma. She was bedbound since having a CVA one month ago and was on heparin for DVT prophylaxis. On exam, patient was noted with elevated blood pressure 210/110 mm Hg. CT chest showed left lower lobe pneumonia with incidental finding of hematoma right kidney. Ultrasound of the kidney showed a large right renal subcapsular collection 12.5 x 6.9 x 8.0 cm with compression of the renal parenchyma suggestive of Page kidney with minimal vascular flow on color Doppler. CT abdomen showed similar findings with bilateral atrophic kidney. Labs were significant for WBC 19.8, Creatinine 5.7. Hemoglobin was 10.6 and was stable during hospital course. Blood pressure was controlled by starting antihypertensive medications, namely Amlodipine and Labetalol. Anticoagulation was held due to hematoma. Given stable hemodynamics, patient was conservatively managed with blood pressure control and renal function monitoring and was discharged with outpatient follow up for repeat renal ultrasound to ensure hematoma resolution.

Discussion: Our case is unique as it is one of the first cases of Page kidney occurring in the setting of anticoagulation use in ESRD. Page kidney should be considered a possibility for malignant hypertension in the setting of anticoagulation use in ESRD.



SA-PO377

A Case of Page Kidney Secondary to Spontaneous Bilateral Retroperitoneal Hemorrhage

Dao Le, Joshua M. Chan, Hugo Paz y Mar. *University of California Irvine, Irvine, CA.*

Introduction: Page kidney is an uncommon etiology for secondary hypertension and renal insufficiency in which outward mass effect causes stimulation of the renin-angiotensin-aldosterone system (1). Although the exact prevalence is difficult to estimate given its rarity, Page kidney is typically traumatic or iatrogenic with subcapsular hematoma formation (2). We report a case of Page kidney in an elderly male with spontaneous bilateral retroperitoneal hemorrhage and bilateral renal artery stenosis.

Case Description: An 83-year-old male with hypertension and chronic kidney disease presented for cough. His hospitalization was complicated by asymptomatic, severe hypertension with a systolic blood pressure ranging from 180 to 230 mm Hg. On hospital day 5, he developed abdominal distension and acute anemia from 9 to 7g/dl. There was no history of trauma or therapeutic anticoagulation. An abdominal computed tomography angiography revealed displacement of the left kidney by retroperitoneal hematoma and stenosis of bilateral renal arteries. On hospital day 7, he underwent a left iliolumbar and L4 lumbar artery embolization. Nevertheless, his renal dysfunction progressed. Continuous renal replacement therapy was initiated on hospital day 10, with successive transition to intermittent hemodialysis. He exhibited spontaneous renal function recovery without further dialysis requirements. However, he was transitioned to comfort care on hospital day 16 given an unrelated acute coronary syndrome with poor cardiac catheterization candidacy.

Discussion: This case is unique because it illustrates the interplay between two rare entities. Page kidney is commonly due to trauma or abdominal instrumentation. In our case, this phenomenon was secondary to spontaneous retroperitoneal hemorrhage (SRH), a rare condition on its own. The recognition of a reversible cause of secondary hypertension by external compression of the renal parenchyma prompted rapid treatment without unnecessary testing. Failure to identify extrinsic renal compression may result in irreversible kidney failure. Furthermore, the resultant hypertension may mask hemodynamic compromise, providing a false sense of stability in SRH, a potentially fatal condition. It is important to consider extrinsic renal compression as an etiology of hypertension and acute kidney injury in patients with spontaneous retroperitoneal bleeding.

SA-PO378

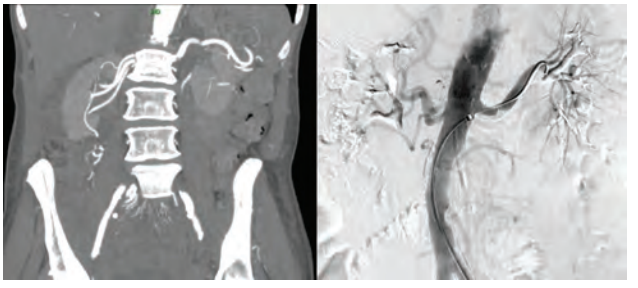
An Abundance of Anything Is Harmful: Accessory Renal Arteries as a Rare Cause of Flash Pulmonary Edema

Liliia Harris, Zaid M. Zahid, Jesus Diaz Acevedo, Nimrat K. Bains. *Hamilton Medical Center, Dalton, GA.*

Introduction: Flash pulmonary edema (FPE) typically develops from bilateral renal artery stenosis (RAS) or unilateral RAS with a solitary functional kidney. In rare instances, unilateral RAS with both functional kidneys can also trigger FPE. We describe a novel case of FPE stemming from unilateral RAS and multiple accessory RAs (ARA)

Case Description: A 68yo woman presented to ER with 3rd episode of FPE and HTN emergency Initial evaluation, including laboratory tests and RA ultrasound, showed no abnormalities. However, a CTA of the abdomen revealed a single heavily calcified L main RA with severe atherosclerosis extending into the lumen of the aorta and the proximal L main RA. Three RAs supply R kidney with questionable stenosis of superior, smaller R RA. Atherosclerotic plaque is present at the origin of the inferior R RA, but no definitive significant stenosis is detected Unilateral RAS and multiple ARAs were suspected as the cause of HTN and FPE. An aortogram with stenting was performed by vascular surgery. It confirmed > 75% stenosis in the L RA, prompting stent deployment. However, no significant stenosis was observed in R ARAs. BP control was achieved with a single agent

Discussion: FPE is a life-threatening syndrome. It is usually accompanied by cardiac systolic or diastolic dysfunctions. Recurrent FPE due to bilateral RAS was described by Pickering et al. Although its exact mechanism is not completely understood, it is believed to result from hypervolemia due to decreased sodium excretion Could the presence of ARA mimic the pathophysiology of RAS? It has been theorized that ARA may lead to HTN due to reduced blood flow to kidneys, caused by its longer and narrower caliber, leading to high resistance, hypoperfusion, stenosis. The Poiseuille equation, rearranged to $R=8\mu L/\Delta P\pi R4$ (where R=resistance, μ=viscosity, L=vessel's length, P=pressure, R=vessel's radius), suggests that radius and length of ARAs may play a role. In summary, ARAs are a common anatomical variation. Their specific characteristics may contribute to resistant HTN and FPE via renin-dependent hyperaldosteronism



SA-PO379

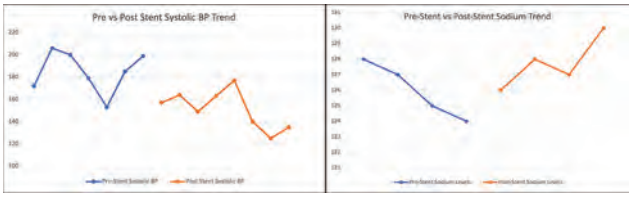
When Hyponatremia Meets Hypertension: The Impact of Renal Artery Stenosis

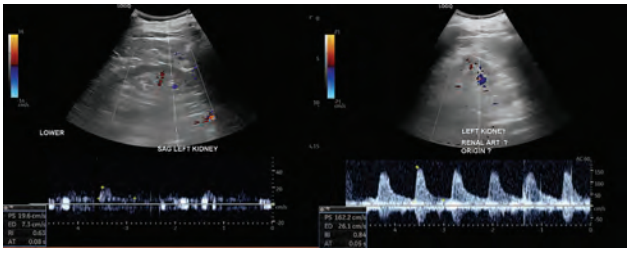
Muhammed Y. Jumani,[1] Yusra S. Jumani,[2] Murad Kheetan.[1] *[1]Marshall University, Huntington, WV; [2]Dow University of Health Sciences, Karachi, Pakistan.*

Introduction: Hyponatremic hypertensive syndrome (HHS) is characterized by severe hypertension and hyponatremia caused by unilateral renal artery stenosis (RAS). The ischemic kidney activates the renin-angiotensin system, causing hypertension. This leads to pressure diuresis in the non-ischemic kidney, with aldosterone and ADH secretion causing hyponatremia, hypokalemia, and polydipsia. Seemingly rare and under-diagnosed, this case report highlights HHS with underlying RAS in an elderly male with multiple comorbidities.

Case Description: 92-year-old male with HFpEF, aortic stenosis, CAD, and hypertension presented with confusion, lethargy, hyponatremia (Na 125), and hypertension (BP 200/100). Normal TSH and cortisol levels ruled out hypothyroidism or adrenal insufficiency. Ultrasound showed high-grade left kidney stenosis. CTA confirmed 85-90% stenosis in the left renal artery. Fluid restriction initially exacerbated hypertension. Left renal artery stenting was performed, improving sodium levels and blood pressure, with significant improvement in renal artery blood flow. Lisinopril and salt tabs were added upon discharge.

Discussion: Hyponatremic hypertensive syndrome (HHS), particularly in the presence of RAS, requires comprehensive clinical evaluation and diagnostic imaging. Unilateral renal artery stenosis leads to high renin release from the ischemic kidney, causing hypertension and pressure diuresis in the non-ischemic kidney. This results in polyuria, polydipsia, and urinary sodium loss, leading to hyponatremia. Early diagnosis is crucial to prevent complications and preserve renal function. Renal artery stenting improves perfusion and sodium levels, while ACE inhibitors reduce intraglomerular pressure and renal injury progression. In summary, managing HHS in the context of RAS requires understanding the pathophysiology, careful diagnostic workup, and a combination of interventional and pharmacologic treatments to improve outcomes.





Pre stent vs post stent in left renal artery

SA-PO380

Hypertensive Crisis Secondary to Afferent Baroreceptor Failure following Head and Neck Radiation

Christopher R. Showers, Nathaniel Reisinger, Jordana B. Cohen. *Penn Medicine, Philadelphia, PA.*

Introduction: Afferent baroreceptor failure is an uncommon cause of hypertension (HTN) that may result from carotid sinus injury. Characterized by labile HTN, postural blood pressure (BP) variation, orthostatic hypotension, and hypertensive crises, afferent baroreceptor failure is typically irreversible and often severely debilitating.

Case Description: A 67-year-old woman with labile HTN, hypothyroidism, and oral squamous cell carcinoma treated with hemiglossectomy and high dose radiation to the head and neck in 2009 presented to our hospital with headaches, BP of 230/120, and stage 1 acute kidney injury. She reported paroxysms of headache, visual blurriness, nausea, and lightheadedness since at least 2015. Inpatient BP values ranged from 90/60 to 190/100, including orthostatic hypotension, supine HTN, and wide variations with use of short acting intravenous medications. Daily home medications included amlodipine 10 mg, hydrochlorothiazide (HCTZ) 25 mg, valsartan 320 mg, and pramipexole for restless leg syndrome, which was stopped. Renin activity was 0.8 ng/mL/h and aldosterone concentration was 6.1 ng/dL. CT angiography showed right renal artery stenosis estimated at 70%. Echocardiography demonstrated mild concentric hypertrophy. Amlodipine was continued, HCTZ was stopped, valsartan was reintroduced at a lower dose, and a clonidine patch was started. Serum creatinine returned to her baseline. Lower extremity compression stockings and an abdominal binder were applied and postural maneuver training was performed with physical therapy. BP logs demonstrated markedly fewer BP fluctuations and attenuation of BP extremes; the patient reported a reduction in paroxysmal symptoms ascribed to BP extremes.

Discussion: Afferent baroreceptor failure from injury to carotid sinus neural structures may result in failure of counterregulatory signals during conditions that provoke extremes of blood pressure. Labile blood pressure, including paroxysms of HTN and symptomatic hypotension, can result in iterative end organ injury and disabling symptoms. Wider BP ranges are tolerated and avoidance of BP extremes is prioritized. Long-acting, central acting sympathetic blocking agents are often beneficial along with postural maneuver training, compressions stockings, and abdominal binders.

SA-PO381

A Case of Reninoma in a 42-Year-Old Patient with Recurrent Strokes

Michael Chau,[1] Solomon Dawson.[1,2] *[1]Cooper University Health Care, Camden, NJ; [2]Rowan University Cooper Medical School, Camden, NJ.*

Introduction: Secondary hypertension can be due to vasculopathy, endocrinopathy, or medications. Although uncommon, secondary hypertension can be due to a reninoma leading to secondary hyperaldosteronism. We discuss a case of a patient with a reninoma and describe his clinical presentation and medical course for this rare disorder.

Case Description: A 42-year-old male with a history of hemorrhagic strokes in 2016 and 2018 with and hypertension (HTN) diagnosed 8 years prior to admission presented to the hospital for acute onset aphasia and was found to have an acute ischemic left sided stroke. Vital signs were remarkable for a blood pressure of 204/130. Hospital labs showed a serum creatinine of 0.86 mg/dL, sodium of 140, potassium of 3.7, AM renin level of 11 ng/mL/h, AM aldosterone level of 2 ng/dL, and total serum metanephrine level of 279 pg/mL. A renal artery ultrasound did not show renal artery stenosis. A CT abdomen and pelvis without contrast revealed a 2.8 cm proteinaceous cyst in the right kidney. He was discharged on Hydralazine 75 mg twice a day, Quinapril 20 mg twice a day, and Labetalol 300 mg nightly. Repeat testing 3 months later in clinic showed an AM renin level of 46 ng/mL/h, AM aldosterone level of 71.2 ng/dL, serum creatinine of 0.87 mg/dL, sodium of 139, and potassium of 3.4. Urine metanephrine/catecholamine levels were within normal limits. His blood pressure remained uncontrolled averaging 150s systolic over 90s diastolic during his office visits and his regimen was uptitrated to Lisinopril 40 mg daily, Spironolactone 75 mg daily, Hydralazine 75 mg thrice daily, and Carvedilol 12.5 mg twice a day. He could not tolerate diuretics due to frequent urination or calcium channel blockers due to persistent headaches. An MRI of his kidneys was ordered to further assess the proteinaceous cyst and he was found to have a Bosniak 4 3.6 cm right renal lesion. He underwent a partial nephrectomy to address the mass with urology. Pathology showed a vascular-rich renal mesenchymal tumor that was compatible with a juxtaglomerular cell tumor. His blood pressure regimen improved to Lisinopril 5 mg daily 2 months after his surgery.

Discussion: Less than 100 cases of reninoma have been reported over the last 40 years. The mean age at diagnosis was 27 years with a mean duration of HTN of 47 months. Our case highlights the importance of keeping reninoma on the differential of causes of secondary HTN.

SA-PO382

Bilateral Nephrectomy as a Salvage Therapy for Resistant Hypertension in ESKD

Wajeeha Shahid,[1] Awiza Ali,[2] Waris Rafique,[2] Talha Shahid,[3] Mehdi Mushtaq.[2] *[1]The Wright Center for Graduate Medical Education, Scranton, PA; [2]Patel Hospital, Karachi, Pakistan; [3]Liaquat College of Medicine and Dentistry, Karachi, Pakistan.*

Introduction: Chronic hemodialysis patients face challenge with resistant hypertension and exhibit resistant to volume control and antihypertensive medications. Although bilateral nephrectomy has shown promising outcomes, it appears to be an underutilized option.

Case Description: 30 years male, past medical history of hypertension, hyperlipidemia, ESRD on intermittent hemodialysis admitted to the hospital with hypertensive emergency, systolic BP > 200, complicated with non-ST-elevation myocardial infarction, diastolic heart failure, pleural effusion. The patient's antihypertensive regimen included clonidine, hydralazine, methyldopa, lisinopril, doxazosin, nifedipine, and spironolactone. Minoxil was unavailable in country and was not used. The patient's BP was controlled with the addition of intravenous glyceryltrinitrate. The secondary causes of resistant hypertension in this patient were investigated, serum renin and aldosterone level came normal, plasma free metanephrine level was also unremarkable, renal angiogram was negative for large vessel stenosis only tortuous and anomalous origin of renal arteries was noted. The patient remained dependent on a glyceryltrinitrate drip despite >7 oral antihypertensives and daily four-hours hemodialysis sessions and intensive ultrafiltration. Choices for the treatment of this patient's refractory hypertension were considered, including renal denervation and bilateral nephrectomy. Interdisciplinary meetings resulted to proceed with bilateral nephrectomy. The option of renal denervation was postponed due to its invasive nature and unproven effectiveness. The patient underwent a bilateral nephrectomy without any significant complications. Following the procedure, the patient was closely monitored in the intensive care unit for a week. Subsequently, the patient's blood pressure gradually normalized over a three-month period. Post-surgery, Lisinopril was stopped, labetalol was discontinued after one month, and the doses of other antihypertensive medications were gradually reduced.

Discussion: The prevalence of bilateral nephrectomy as a treatment option ranges from 0 to 7% in various countries.[1] Bilateral nephrectomy leads to reduction in the levels of renin, angiotensin and aldosterone, which subsequently lowers the BP in resistant hypertension.[2] [1]doi: 10.1016/j.ijscr.2022.107566 [2]doi: 10.7759/cureus.9031

SA-PO383

More Than an Accessory: Renal Artery Stenosis in a Second Renal Artery Driving Uncontrolled Hypertension

Sunny R. Parmar, Ali Mehdi. *Cleveland Clinic, Cleveland, OH.*

Introduction: Renovascular hypertension may result from renal artery stenosis (RAS), because significant compromise in renal blood flow results in excessive renin release and drives renin-angiotensin system (RAAS) activation from the affected kidney. This may not be expected from a stenosed accessory artery, which would supply only a limited portion of the kidney. However, an uncommon anatomic variant with two ipsilateral renal arteries originating from the aorta does exist. We hereby present a case of uncontrolled renovascular hypertension emanating from RAS of one of two such renal arteries, initially confused for an accessory artery.

Case Description: A 51 year-old male presented to nephrology clinic with recently uncontrolled hypertension. Previously controlled on lisinopril and hydrochlorothiazide, blood pressure was now uncontrolled on five blood pressure agents of different classes. Secondary workup was pursued showing a direct renin concentration of 1,704 pg/mL (plasma renin activity of 324 ng/mL/h). A renal Doppler study described an "accessory" renal artery having 60-99% stenosis whereas the "main" left and right renal arteries showed 0-59% stenosis. Given renin elevation and worsening hypertension, a contrast enhanced CT scan was done showing two left renal arteries of similar caliber originating from the aorta with one having severe proximal stenosis. Angioplasty with stenting was done following which serial renal Dopplers confirmed resolution of stenosis up to two years later. On the most recent follow up, his blood pressure remained controlled on lisinopril-HCTZ 20-12.5mg daily alone.

Discussion: This case describes an unusual scenario where one of two ipsilateral renal arteries of similar size had severe stenosis, leading to renovascular hypertension.

The initial Doppler study might have been misleading pointing to a potentially insignificant, albeit stenotic, accessory renal artery. The severely high renin activity levels was the main clue that prompted further evaluation of this ultrasound finding ultimately leading to stenting which proved impactful on his hypertension management. In investigating renovascular hypertension, one should utilize renin levels and consider unusual anatomy when a stenosed accessory renal artery is described.

SA-PO384

Hereditary Paraganglioma Pheochromocytoma Syndrome (HPPS) Presenting as Resistant Hypertension in Patients with ESKD: A Rare Presentation

Arfa Amjad, Tahir A. Jatoi, Subodh J. Saggi, Sandeep R. Sasidharan, Fnu Pariya.
SUNY Downstate Health Sciences University, New York City, NY.

Introduction: End-stage renal disease (ESRD) is a growing public health concern, with uncontrolled hypertension (HTN) being a frequent complication. While pheochromocytoma, a catecholamine-secreting tumor, can cause HTN, its diagnosis in ESRD patients can be challenging. We present a rare mutation as the cause of pheochromocytoma in an ESRD patient.

Case Description: A 39-year-old AA woman with a history of ESRD, uncontrolled HTN with vitreous hemorrhage, MI, and CVA with family history of early MI & CVA presented with severe headaches and palpitations for many days and had 6 similar admissions for the last year. Her BP was uncontrolled with post HD BP noted to be >160/110 & with four antihypertensive. Normal physical exam with vitals stable except for BP of 210/125, confirmed with repeat. EKG was unchanged with T Inversion in a few leads. A secondary HTN workup showed low Dexamethasone <30 mg/ml, Urinary Dopamine <30 mcg, elevated Aldosterone 42.6 ng/dl, Renin 34.9 ng/ml/hr, normetanephrine 534 nmol/L. 24-hour urine showed Epinephrine 67 mcg, Norepinephrine 436 mcg, 24-hour normetanephrine 1041 mcg. CT abdomen scan showed a 1.4 cm left adrenal mass. Genetic testing revealed paraganglioma with SDHAF2 mutation. The 123I-MIBG scan was negative. She is to have a DOTATE 68 gallium PET scan for localization and paraganglioma surgery. She continues to be on HD with multiple antihypertensives.

Discussion: Hereditary Paraganglioma Pheochromocytoma Syndrome (HPPS) is characterized by elevated urinary metanephrines, catecholamine levels, and an SDHAF2 mutation. Pheochromocytoma diagnosis in ESRD patients presents challenges due to altered catecholamine metabolism and limited urine sampling. Our case highlights unique diagnostic features, including lower norepinephrine levels and a negative MIBG scan, along with a rare SDHAF2 mutation association. This syndrome is associated with the Succinate Dehydrogenase gene & manifests in four distinct syndromes. Our case corresponds to PGL type 2 with an SDHAF2 mutation. Families with SDHAF2 mutations are exceptionally rare and affected individuals typically present exclusively with head and neck paragangliomas. There is no case of this gene mutation reported in ESRD patients. Surgical removal remains the mainstay of treatment, often preceded by alpha-adrenergic blockade.

SA-PO385

An Unusual Case of High-Renin Hypertension

Adi Leiba,[1,2] Avital Angel-Korman.[1,2] *[1]Assuta Ashdod Hospital, Ashdod, Israel; [2]Ben-Gurion University of the Negev Faculty of Health Sciences, Beer-Sheva, Israel.*

Introduction: We present an unusual case in which negative sodium balance was the etiology of high renin hypertension

Case Description: A 75-year-old woman consulted us due to high blood pressure. **PMH:** LBP, history of excessive NSAIDS use, s/p partial colectomy **Meds :** amlodipine, zolpidem, bisacodyl, pregabalin, acetaminophen tramadol, brotizolam, atorvastatin, ezetimibe, esomeprazole **BP**- 150/84mmHg **Labs** - 24 hour urine collection – 240 mg protein (0 albumin), intermittent leukocytuia **Renal US –** echogenic diminished parenchyma On addition of low dose ARB (25mg losartan) her creatinine rose from 1.28 to 1.87 mg/dL, blood pressure dropped to 101/64 mmHg, and renin was found to be elevated to >500 microunits/ml. Aldosterone was also extremely elevated to 64.7ng/dl Renal artery doppler showed no evidence of renal artery stenosis. She reported keeping to a low salt diet as well self-prescribing 10 tabs of bisacodyl every evening (!) We suspected sodium malabsorption, and, indeed, her 24 hour urinary sodium was below detection limit. The patient was advised to liberalize sodium intake, to take salt tablets, and reluctantly agreed to cut down her laxative use into 3-4 tabs/day. Within a month her plasma creatinine improved, renin and aldosterone levels trended down, and sodium reappeared in her urine (Table 1). Despite sodium "loading" Her blood pressure was stable (132/74mmHg)

Discussion: Hypovolemia due to negative sodium balance can still cause hypertension due to the effect of the resultant high renin, angiotensin II and aldosterone. This case emphasizes the importance of the colon in sodium reabsorption and the complex interplay of the colon, the kidneys, and the adrenal gland. Secondary hyperaldosteronism would usually cause avid sodium reabsorption through colonic eNac, but, in our case, sodium malabsorption was dominant due to short colon and laxative abuse. Our intervention affected this colonic-renal-adrenal axis, relieving the patient from chronic hypovolemia, negative sodium balance, worsening kidney function and uncontrolled hypertension

changes related to liberalization of salt intake, addition of salt tabs and partial bisacodyl withdrawal

	April 2nd 2023	May 8th 2023
Creatinine	1.76 mg/dl	1.39mg/dl
24 hour urinary sodium	below detection limit	235 millimole
24 hour urinary potassium	16 millimole	26.4 millimole
Direct Renin	183.8 micro IU/ml	45.3 micro IU/ml
Plasma Aldosterone	64.7 ng/dl	19.5 ng/dl

SA-PO386

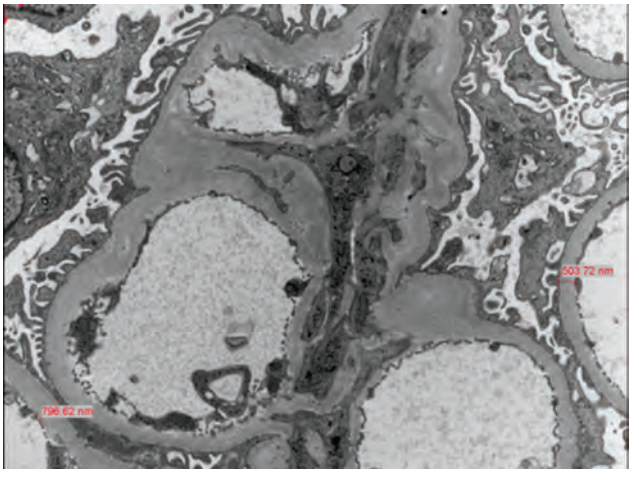
Cystinuria Screening Reveals Uncontrolled Hypertension and Subnephrotic-Range Proteinuria in a 20-Year-Old Patient: A Case Report

Muhammed Mumin,[1] Syed Mohammed Faizaan Zabiullah,[2,3] Viqarunnisa Faaiza Zahid,[4] Rebecca V. Levy,[1] Erika Drury,[1] Mohammad A. Yousuf,[1] Jerome L. Jean-Gilles.[1] *[1]University of Rochester, Rochester, NY; [2]Unity Hospital, Rochester, NY; [3]New York Medical College School of Medicine, New York, NY; [4]University of Minnesota Twin Cities, Minneapolis, MN.*

Introduction: Cystinuria is an autosomal recessive disorder caused by defects in the SLC3A1 gene that mediates sodium-independent transport of cysteine and dibasic amino acids in proximal tubule and small intestine. Cystinuria commonly presents as renal stones.

Case Description: A 20 y.o male with history of ADHD on amphetamine-dextroamphetamine presented for cystinuria screening. Family history was notable for a sister with cystinuria. He had no complaints. On examination, he is a young muscular man with BMI of 23.7 kg/m2. His office BP is 134/63 mm Hg. Physical examination is otherwise unremarkable. Urinalysis showed +1 protein. 24 hour urine showed proteinuria of 1842 mg/day, microalbuminuria of 1124.4 mg/day and cystinuria (1096 mg/day). The eGFR (CKiD U25) was 103 ml/min/1.73m2. Serology and immunological workup was normal. Renal biopsy revealed diffuse segmental mesangiolysis and IgM mesangial deposits of unclear significance. EM showed glomerular BM thickening (286-796 nm) with segmental lamina rara interna expansion and mesangiolysis. The overall findings were suggestive of chronic endothelial injury. Ambulatory BP monitoring showed markedly elevated BP readings(mean systolic 152 mm Hg). Preliminary diagnosis was masked hypertension with hypertensive kidney disease, lisinopril was started and stimulant was discontinued. Endocrine evaluation for secondary hypertension was negative. Echo revealed LV hypertrophy. Genetic testing showed biallelic pathogenic mutations in SLC3A1 consistent with known cystinuria.

Discussion: This case highlights a rare combination of cystinuria and hypertensive kidney disease. It is unclear in this patient whether the cystinuria and hypertension are linked. It also emphasizes the importance of screening of close family members for Cystinuria, which in this patient has led to early discovery of his hypertension and prevented severe end-organ damage.



SA-PO387

Implausible Hemolysis with the New Chinese Standard for Testing Dialyzer Hemocompatibility

Detlef H. Krieter,[1] Marieke Rueth,[2] Horst-Dieter Lemke,[2] Christoph Wanner.[1]
[1]University Hospital Würzburg, Nephrology, Würzburg, Germany; [2]eXcorLab GmbH, Obernburg, Germany.

Background: A new standard for testing dialyzer hemocompatibility (YY/T 1920-2023) has been introduced in China. With current international standards (e.g., EN ISO 10993-4 and ASTM F756) and the previous Chinese Standard (GB/T 14233.2 (2005)), certified dialyzers passed the hemolysis criteria easily (hemolysis <2%). In contrast, YY/T 1920-2023 led to aberrant results with several filters. Purpose of the present study was to analyze possible causes for these unexpected findings.

Methods: According to YY/T 1920-2023. (n=3), 0.5 g samples were cut from dialyzer membrane bundles and incubated for 30 min in saline at 37°C. Rabbit blood was added, slewed, incubated for 100 min at 37° C and then stirred with a pipette tip. Liquid was aspirated, centrifuged and the supernatant photometrically assessed at 545 nm. Hemolysis was calculated based on a positive control and two negative controls (A, saline; B, samples incubated only for 1 min). Baxter Revaclear 300 (PES; steam-sterilized), Bain DORA® B-16HF (PS; g-radiated), and Jafron JM 16H (PUREMA™ H; g-radiated, PET spacer yarn) were investigated. Native PUREMA™ (PES) was also tested: with and without PET; non-sterile and g-radiated; no cutting, stirring and suction.

Results: Hemolysis rates of the Revaclear, DORA®, and JM membranes were 5.1±1.1%, 1.1±0.1%, and 7.6±1.0%, resp. For PUREMA™, hemolysis for non-sterile/no PET bundles was 1.5±0.3%, γ-radiated/no PET 2.4±0.4%, non-sterile/with PET 4.3±0.7%, γ-radiated/with PET 6.3±0.1%, non-sterile/with PET/no-cutting 3.7±0.8%, non-sterile/with PET/no stirring and suction 0.9±0.4%. In the negative control B, which investigated the membrane samples with short incubation of 1 min, also hemolysis between 0.9±0.0 and 3.0±0.0% was observed.

Conclusions: Compared to current international standards, in vitro hemolysis determined with YY/T 1920-2023 can be significantly higher. Applying YY/T 1920-2023 is characterized by mechanical stress in form of compression from stirring and negative pressure from suction on blood cells which is particularly susceptible to operator influence. The outside surfaces of the dialysis membranes, which never come into contact with patient blood, also influence hemolysis as sterilization, the presence of a spacer yarn, and cut fragments have adverse effects. Consequently, the validity of the new Chinese Standard YY/T 1920-2023 must be questioned.

Funding: Commercial Support - 3M Healthcare

SA-PO388

Elevated Lipoprotein(a) Levels Are Associated with Endothelial Dysfunction Measured by Vascular Reactivity Index in Patients on Chronic Hemodialysis

Yu-Hsien Lai,[1,2] Yu Chi Chang,[1] Bang-Gee Hsu.[1,2] *[1]Division of Nephrology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan.*

Background: Lipoprotein(a)(Lp(a)) accelerates the formation of atherosclerotic plaque by its proatherogenic, prothrombotic, and proinflammatory actions and has a positive correlation with cardiovascular disease. We aimed to evaluate the association between serum Lp(a) levels and endothelial function in patients with maintenance hemodialysis (MHD).

Methods: We enrolled 123 MHD patients, and their blood samples and medical records were obtained. We measured endothelial function as vascular reactivity index (VRI) by a non-invasive digital thermal monitor, and serum Lp(a) concentration was measured by a commercial enzyme-linked immunosorbent assay.

Results: Eighteen (14.6%) MHD patients were classified as having poor vascular reactivity, 51 (41.5%) MHD patients as having intermediate vascular reactivity ($1.0 \le VRI < 2.0$), and 54 (43.9%) MHD patients were classified as having high vascular reactivity ($VRI \ge 2.0$). The serum alkaline phosphatase (ALP, $p = 0.002$) and Lp(a) ($p < 0.001$) levels significantly increased as VRI decreased. The logarithmic transformation of serum ALP (log-ALP, $r = –0.252$, $p = 0.005$) and log-Lp(a) ($r = –0.578$, $p < 0.001$) was negatively associated with the VRI values by univariate linear regression analysis. Multivariate stepwise linear regression analysis showed a significantly negative association of log-ALP (standardized $\beta = –0.212$, adjusted R^2 change = 0.040; $p = 0.001$) and log-Lp(a) (standardized $\beta = –0.562$, adjusted R^2 change = 0.328; $p < 0.001$) with VRI values in MHD patients. Serum Lp(a) was independently associated with vascular reactivity dysfunction (odds ratio (OR) = 1.006; 95% confidence interval (CI) = 1.002–1.009; $p = 0.001$) and poor vascular reactivity index (OR = 1.009, 95% CI = 1.004–1.014, $p < 0.001$) in MHD patients by logistic regression analysis.

Conclusions: In this study on MHD patients, along with serum ALP levels, the most significant clinical implication was that serum Lp(a) levels were negatively correlated to the VRI and can be used as a potential novel biomarker of endothelial dysfunction.

SA-PO389

Prognostic Value of Secretoneurin in Patients Treated with Chronic Hemodialysis

Caroline H. Liboriussen,[1,2] Louis Nygaard,[1,2] Magnus N. Lyngbakken,[3,4] Jens D. Jensen,[1] Rie I. Glerup,[1] Torbjorn Omland,[3,4] Helge Rosjo,[3,4] My Svensson.[1,2] *[1]Aalborg Universitetshospital, Aalborg, Denmark; [2]Aalborg Universitet, Aalborg, Denmark; [3]Akershus Universitetssykehus HF, Lorenskog, Norway; [4]Universitetet i Oslo, Oslo, Norway.*

Background: Secretoneurin (SN) is a novel biomarker with an upper reference limit (97.5th percentile) of 60 pmol/L in healthy subjects. High SN concentrations are associated with increased risk of mortality in patients with cardiovascular (CV) disease. This study investigated the association between SN and the risk of CV events and all-cause mortality in patients receiving hemodialysis (HD).

Methods: Prospective multicenter cohort study with 5 years of follow-up. Serum SN (pmol/L) was measured at baseline. Primary outcome was CV events; secondary outcomes were all-cause mortality and each component of CV events. The population was divided into tertiles according to SN concentrations (pmol/L): tertile 1 <110.7, tertile 2 from 110.7-143, and tertile 3 >143. The association between SN tertiles and outcomes was analyzed with adjusted Cox regression analysis.

Results: The study included 336 patients on HD. Median SN concentration was 126 (IQR 100-153) pmol/L. During follow-up 60% died and 42% had a CV event. After adjusting for relevant confounders neither SN tertile 2 nor SN tertile 3 were associated with the risk of CV events ($HR_{tertile2}$ 1.27 (95% CI 0.84-1.93) and $HR_{tertile3}$ 1.20 (95% CI 0.76-1.90)) or all-cause mortality ($HR_{tertile2}$ 0.84 (95% CI 0.60-1.18) and $HR_{tertile3}$ 0.90 (95% CI 0.62-1.31)), when compared to tertile 1 (**Fig. 1**).

Conclusions: Patients receiving HD have high SN concentrations; however, SN was not associated with CV events or all-cause mortality. High concentrations of SN, possibly explained by both impaired renal clearance and a high prevalence of cardiomyopathy, may limit its prognostic relevance in patients receiving HD.

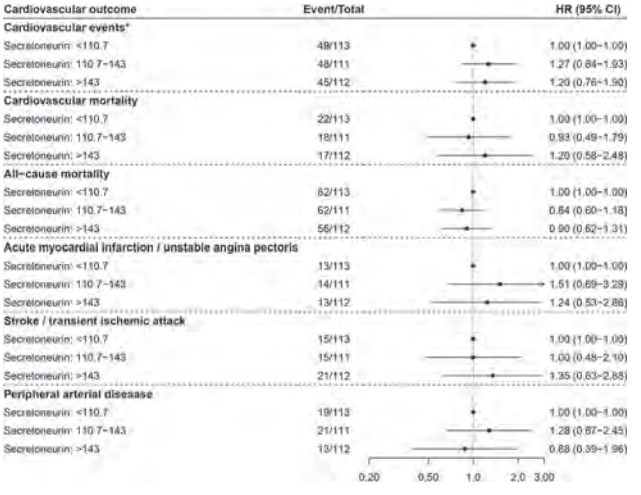


Fig 1. Association between secretoneurin tertiles and outcomes. *Cardiovascular (CV) events include acute myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, peripheral arterial disease, and CV mortality.

SA-PO390

Lectin Pathway Initiators Ficolin-1 and Collectin-11 Are Associated with Mortality in Patients on Hemodialysis

Philip De Laval,[1] Rie I. Glerup,[2] My Svensson,[2] Niclas Eriksson,[3] Laura Pérez Alós,[4] Peter Garred,[4,5] Bo Nilsson,[6] Kristina N. Ekdahl,[6,7] Bengt C. Fellstrom,[1] Inga Soveri.[1] *[1]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [2]Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark; [3]Uppsala Clinical Research Center, Uppsala, Sweden; [4]Department of Clinical Immunology, Copenhagen University Hospital, Copenhagen, Denmark; [5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [6]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; [7]Department of Chemistry and Biomedical Sciences, Linnaeus University, Kalmar, Sweden.*

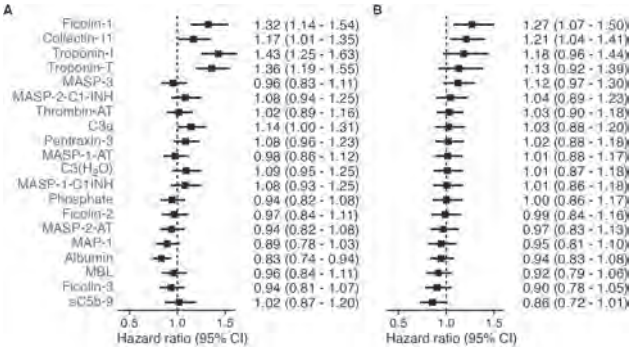
Background: Cardiovascular disease (CVD) is the leading cause of death in hemodialysis (HD) patients. The complement system may contribute to inflammation, which is considered a non-traditional risk factor for CVD, through activation of the lectin pathway during HD. Intradialytic complement activation has been linked to cardiovascular (CV) events but studies on the lectin pathway with regards to outcome in HD are few. We aimed to assess if baseline levels of lectin pathway factors are associated with clinical outcome in HD patients.

Methods: We conducted a cohort study with five years of follow-up. All patients > 18 years of age in five HD facilities in Jutland, Denmark without acute kidney injury were asked to participate. Plasma levels of complement factors C3a, sC5b-9, C3(H_2O), MBL, ficolin-1,-2,-3, pentraxin 3, collectin-11, MASP-1- and MASP-2-Antithrombin/C1-inhibitor complexes, MASP-3 and MAP-1 were analyzed using ELISAs. The endpoints were all-cause mortality, infection-related mortality, CV-mortality and CV-events. Hazard ratios (HR) were modeled using cox regression on one standard deviation increase in $\log_2$ complement levels. Known risk factors for mortality in HD were added in a second model. These were age, $\log_2$ dialysis vintage, diabetes mellitus, previous CVD and $\log_2$ albumin, CRP, troponin I, and troponin T.

Results: In total, 331 patients were included. During follow-up, 198 (60%) died. Ficolin-1 and collectin-11 levels were associated with all-cause mortality in both the crude (Fig. 1A) and adjusted (Fig. 1B) model. Collectin-11 was significantly associated with CV-mortality in the adjusted (HR 1.35 [95% CI 1.02-1.77]) but not in the crude model (HR 1.26 [95% CI 0.98-1.63]).

Conclusions: Lectin pathway initiators ficolin-1 and collectin-11 are associated with death in HD patients, independently of known risk factors. This suggests an adverse role for the lectin complement pathway in HD patients.

Funding: Private Foundation Support, Government Support - Non-U.S.



SA-PO391

A Comprehensive Skin Gas Analysis of Substances Related to Uremia

Toyohiro Hashiba,[1] Yosuke Hirakawa,[1] Hiroyasu Yamahara,[2] Yasuo Yano,[2] Yuka Yamada,[2] Hitoshi Tabata,[2] Masaomi Nangaku.[1] *[1]Division of Nephrology and Endocrinology, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Japan; [2]Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, Bunkyo-ku, Japan.*

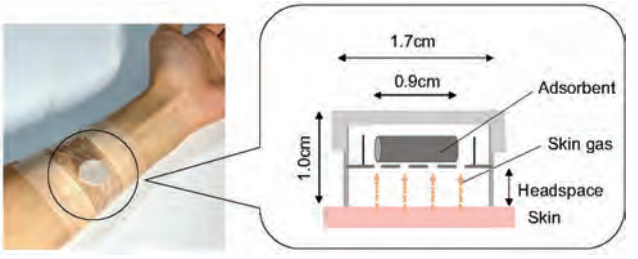
Background: Recent progress in gas-sensing technology has enabled highly sensitive analysis of skin gases associated with body odor, which are collected more continuously and unconsciously than blood or urine. Patients with end-stage kidney disease (ESKD) have a characteristic uremic odor, which fades after initiating kidney replacement therapy. We investigated the possibility of quantitatively evaluating the substances that cause uremia.

Methods: Skin gases were collected by placing a passive flux sampler on the forearm for 20 min (Figure), heating rapidly, and measuring peak intensity by gas chromatography-mass spectrometry. We investigated the changes in gases obtained from the hemodialysis (HD) group before and after the first HD session of patients undergoing incident dialysis. We compared skin gases between the ESKD (HD, non-HD), chronic kidney disease (CKD) stage G2, and the healthy group.

Results: Of the 176 volatile molecules collected from the HD group (N=5), we focused on 27 substances detected in all patients. Five volatile molecules included in 6-methyl-5-hepten-2-one derived from squalene specific to human sebum were detected in all participants: the ESKD (N=11), CKD stage G2 (N=6), and healthy (N=7) groups. In addition, benzaldehyde excreted in the urine as hippuric acid of uremic substances in the blood showed significantly higher intensities in the ESKD group than in other groups (p=0.012).

Conclusions: Although there were individual differences, a comprehensive skin gas analysis was helpful for inter-individual comparisons of uremia-related substances.

Funding: Government Support - Non-U.S.



The figure shows a passive flux sampler attached to the participant's left forearm to collect the skin gases and a cross-sectional view.

SA-PO392

Plasma Oxalate and Microbiome Assessment in Patients on Hemodialysis

Nadim Zaidan,[1] Karim Jaber,[2] Boyan Zhou,[2] David M. Charytan,[2] Laura M. Dember,[3] Lama Nazzal.[2] *[1]Staten Island University Hospital, Staten Island, NY; [2]NYU Langone Health, New York, NY; [3]University of Pennsylvania, Philadelphia, PA.*

Background: Uremic toxins accumulation in patients with end-stage kidney disease (ESKD) undergoing maintenance hemodialysis (HD) is associated with increased cardiovascular (CV) mortality. Plasma oxalate (POx) stands as a potentially significant contributor to CV complications in ESKD. Oxalate-degrading bacteria (ODB) are pivotal in oxalate metabolism, yet their prevalence and functional activity remain unexplored in ESKD patients. This pilot study explored the ODB community of ESKD patients.

Methods: Plasma (P) and fecal samples from 12 ESKD patients were obtained from the 8-week pretreatment phase of "The Microbiome and p-Inulin in Hemodialysis: A Feasibility Study" and used for our study. POx was calculated at both weeks 0 and 8 using a metabolomics platform (HPLC-MS) and colorimetric enzymatic assay. Fecal DNA from Week 1 and Week 8 were extracted using the Qiagen 96-well extraction kit and metagenomics sequencing was performed at NYU's Genome Technology Center. The raw sequencing data was processed and analyzed using the Kraken2 as well as our bioinformatics pipeline specific to ODB.

Results: The within-person percentage change of POx between weeks 0 and 8 was 10.67% + 62.93 % and -0.67% ±9.2% using the enzymatic assay and metabolomics platform, respectively. No significant variation between weeks 0 and 8 in both alpha and beta diversities indices highlighted microbiome stability across time for ESKD patients receiving hemodialysis. Several species were positively or negatively correlated with POx measured by the enzymatic and metabolomic assay (Table 1).

Conclusions: In conclusion, our study highlights the stability of the microbiome over time in patients with ESKD undergoing hemodialysis. Several ODB bacterial taxa are associated with POx levels in ESKD patients.

Species correlation with plasma oxalate

Positive correlation with plasma oxalate		Negative correlation with plasma oxalate	
Metabolomics Platform	Enzymatic Assay	Metabolomics Platform	Enzymatic Assay
Calditerrivibrio nitroreducens	Bifidobacterium breve	-Ruminococcus champanellensis -Thermotunaerobacterales bacterium -Eggerthella lenta -Gordonibacter pamelaeae -Mycoplasma conjunctivae -Muribaculaceae bacterium	Clostridiales bacterium

SA-PO393

Analysis of Characteristics of Patients on Maintenance Hemodialysis and Subjective Cognitive Decline Based on Intestinal Flora

Hua Liu. *The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: To study the relationship between intestinal flora and subjective cognitive decline (SCD) in patients with maintenance hemodialysis (MHD).

Methods: From July 2022 to July 2023,84 patients with MHD in the department of severe renal disease and blood purification, first affiliated hospital of the Xi'an Jiaotong University were enrolled, the subjects were divided into SCD Group (SCD group, N = 40, MMSE score≥24 and SCD-Q9 score≥5) and normal cognition group (NC Group, N = 44, MMSE score≥24), to investigate whether SCD is related to flora disturbance, the difference of flora at family and genus level was judged and the difference of KEGG function was predicted based on 16srDNA.

Results: SCD-Q9 score in SCD Group was significantly higher than that in NC Group ($P < 0.05$). There were 11 different bacterial families in the SCD Group, and Erysipelatoclostridiaceae and Enterobacteriaceae had higher relative abundance in the SCD group. Among the 9 major differential bacteria, the highest relative abundance in SCD group was in Escherichia-Shigella, Ruminococcus gnavus and erysipelato-clostridium, and the positive correlation between Escherichia-Shigella and SCD-Q9 was the strongest

($P < 0.01$), and the negative correlation between Escherichia-Shigella and MMSE was the strongest ($P < 0.01$). Ruminococcaceae had the strongest negative correlation with SCD-Q9($P < 0.01$) and Faecalibacterium had the strongest positive correlation with MMSE ($P < 0.01$). Rikenellaceae, Marinifilaceae, Alistipes, Ruminococcus gnavus and Odoribacter were more effective in identifying SCD. Compared with NC group, SCD increased bacterial invasion, Shigella and p-nitrotoluene degradation in epithelial cells, down-regulated the biosynthesis, Nonribosomal peptide structure, and biosynthetic function of neomycin, kanamycins and gentamicin Prodigiosin, it is suggested that the dysbacteriosis of SCD may lead to the increase of pathogenic metabolic pathway and the decrease of healthy metabolic function.

Conclusions: The results of this study suggest that the cognitive function of MHD patients has been altered during SCD, which is characterized by a decrease in the abundance of beneficial anti-inflammatory bacteria and an increase in the abundance of certain harmful pro-inflammatory bacteria, which indicates that intestinal flora disturbance is related to SCD and may predict SCD and become a target of intervention.

SA-PO394

Hepatic Function Is Impaired in Inflamed Haemodialysis Patients

Oscar Swift,[1,2] Bobby VM Dasari,[3,4] Malcolm A. Finkelman,[5] Yonglong Zhang,[5] Sivakumar Sridharan,[1,2] Enric Vilar,[1,2] Ken Farrington.[1,2] *[1]East and North Hertfordshire NHS Trust, Stevenage, United Kingdom; [2]University of Hertfordshire, Hatfield, United Kingdom; [3]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [4]University of Birmingham, Birmingham, United Kingdom; [5]Associates Of Cape Cod Inc, East Falmouth, MA.*

Background: Impaired hepatic function may drive inflammation in ESKD via reduced gut-derived toxin removal. (1-3)-β-D glucan (BDG), found in cell walls of bacteria and fungi, is often raised in ESKD and may reflect systemic translocation of gut material. This study evaluated hepatic function in inflamed and non-inflamed individuals on haemodialysis (HD). BDG was used as a surrogate marker of gut permeability.

Methods: 25 inflamed adults with ESKD (baseline hs-CRP >5mg/L) and 25 non-inflamed adults with ESKD (hs-CRP ≤5mg/L) were recruited from four UK outpatient HD units. Dynamic hepatic function was assessed by indocyanine green (ICG) clearance. ICG levels were measured transcutaneously to calculate plasma disappearance rate (ICG-PDR) and retention at 15 minutes (ICG-R15min). Fibroscan imaging assessed hepatic steatosis and fibrosis.

Results: ICG-PDR and ICG-R15min were, respectively, reduced and elevated, in inflamed individuals. Hepatic steatosis and fibrosis, and pre-HD BDG were similar between groups (Table 1). Post-HD BDG was higher in the inflamed group (Table 1), and in those with hepatic impairment (Figure 1).

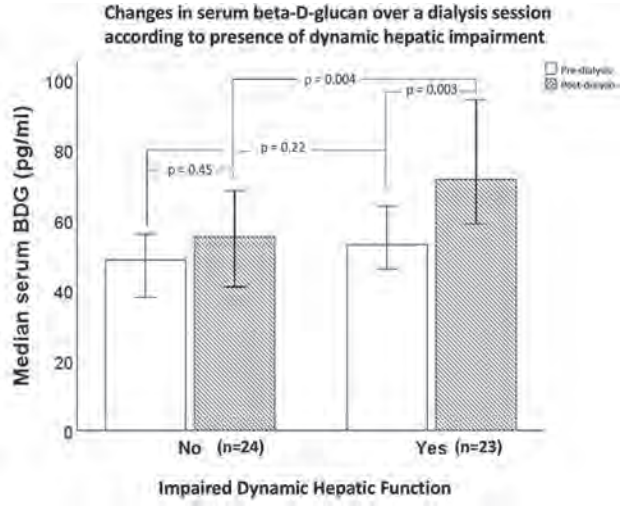
Conclusions: Hepatic function is impaired in inflamed individuals receiving HD. Impaired hepatic function associates with elevated BDG post-HD, suggesting that impaired hepatic removal of gut-derived toxins may propagate chronic inflammation in ESKD.

Funding: Other NIH Support - National Institute for Health and Care Research (NIHR) Research Capability Funding, East and North Hertfordshire Hospitals Charity, Commercial Support - Associates of Cape Cod provided assays for BDG measurement gratis

Comparison of hepatic function and BDG levels in non-inflamed and inflamed individuals receiving HD

	Non-inflamed (n=25)	Inflamed (n=25)	p-value
ICG-PDR (%/min)*	23.8(14.4)	19.4(8.7)	0.02
ICG-R15min (%)*	2.9(5.0)	5.4(7.6)	0.02
Liver Stiffness Measurement (kPa)†	4.8(2.1)	4.2(32.7)	0.69
Controlled Attenuation Parametography (dB/m)†	249±69	257±63	0.69
Pre-dialysis BDG (pg/ml)	49(12)	58(38)	0.13
Post-dialysis BDG (pg/ml)	58(27)	81(48)	<0.001

Continuous variables presented as mean±SD or median(IQR) according to distribution
*Data for 24 non-inflamed and 23 inflamed participants
†Data for 24 non-inflamed and 25 inflamed participants



SA-PO395

Protein-Bound Uremic Toxin-Lowering Effects of Sevelamer in Patients on Chronic Hemodialysis with Hyperphosphatemia: A Multicenter Randomized Controlled Trial: A Preliminary Report

Napas Srifa,[1] Jeerath Phannajit,[1] Sookruetai Lekhyananda,[2] Kamonrat Chongthanakorn,[3] Sipanan Thamratnopkoon,[3] Wannasit Wathanavasin,[3] Yingyos Avihingsanon,[1] Somchai Eiam-Ong,[1] Paweena Susantitaphong.[1] *[1]King Chulalongkorn Memorial Hospital Department of Internal Medicine, Bangkok, Thailand; [2]Priest Hospital, Bangkok, Thailand; [3]Charoenkrung Pracharuk Hospital, Bangkok, Thailand.*

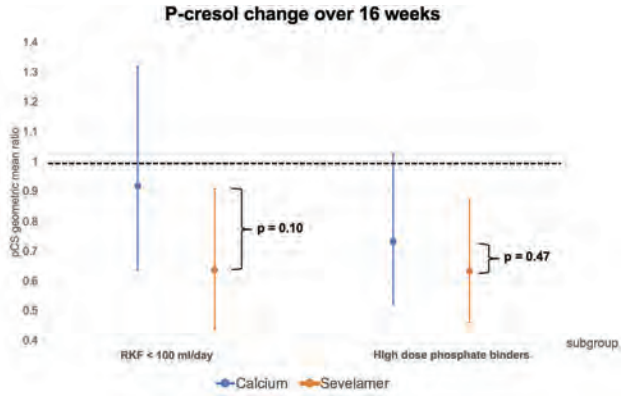
Background: P-cresol (pCS) is an important protein-bound uremic toxin (PBUT) linked with cardiovascular mortalites in chronic hemodialysis patients. Dialysis modalities have a limitation in removing PBUTs. Recent approaches focus on decreasing toxin generation, increasing gut absorbent, and preserving residual kidney function (RKF). Sevelamer, used as a phosphate binder, has limited data on pleiotropic effects on PBUTs in these patients. This study investigated the pCS-lowering effect of sevelamer in a open-label multicenter randomized controlled trial (TCTR20230530004).

Methods: Chronic hemodialysis patients with persistent hyperphosphatemia were randomly assigned to receive either sevelamer or calcium carbonate for 24-week using protocol-based dosage titration to achieve the target phosphate of 3.5-5.5 mg/dL. Blood samples were collected before and at 8, 16, 24 weeks. Mean differences between two groups including sub-group analysis stratified by RKF, phosphate binders dose, HD frequency, mean phosphate level and protein intake were analyzed using linear mixed model.

Results: Of the 73 initial participant, 3 patients dropped out leaving 35 in both treatment groups for the per-protocol analysis. Fifty-five percent were anuric (RKF < 100 ml/day). Significant phosphate lowering was observed in both groups. The mean changes in pCS were not different between groups. Interestingly, a trend towards reducing serum pCS levels was observed in sevelamer group among anuric patients and those using high dose phosphate binders (as figure). However, the changed were not significantly different when compared with calcium carbonate.

Conclusions: Sevelamer may reduce pCS in chronic hemodialysis with minimal RKF, suggesting potential pleiotropic effects. However, long-term follow-up is still required.

Funding: Commercial Support - Dr.Reddy's Laboratories (Thailand) Co., Ltd., Private Foundation Support



SA-PO396

Dynamics of Amyloid-β and Total Tau in Cerebrospinal Fluid and Plasma of Patients on Hemodialysis

Hassan Gorji,[1] Lin-Chun Wang,[1] Ohnmar Thwin,[1] Joshua E. Chao,[1] Ludovic Debure,[3] Nadja Grobe,[1] Xin Wang,[1] Hanjie Zhang,[1] Stephan Thijssen,[1] Thomas Wisniewski,[3] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai Department of Medicine, New York, NY; [3]NYU Langone Health, Department of Neurology Center for Cognitive Neurology Alzheimer's Disease Research Center - Biomarker Core, New York, NY.*

Background: While hemodialysis (HD) can reduce Amyloid beta protein (Aβ) in the blood, its impact on cerebrospinal fluid (CSF) Aβ levels has not been studied. This research is the first to investigate the dynamics of Aβ and total tau levels in both CSF and plasma of HD patients.

Methods: Three chronic HD patients with ventriculo-peritoneal shunts participated in this study. The patients underwent thrice weekly high-flux HD. During HD, plasma samples were collected at six different timepoints, shown in figures A1, B1, C1. Two patients had repeated VPS taps to collect CSF samples. One subject was withdrawn over safety concern. Aβ1-40, Aβ1-42, total tau in the CSF and plasma samples were quantified using the Neuro 3-Plex assays (Quanterix, MA, USA).

Results: Our findings indicate a decrease in plasma levels of Aβ1-40 and Aβ1-42 by 40% and 35% respectively, while total tau levels increased by 16% (Figures A1, B1, C1). The mean levels of these proteins in plasma and CSF during the intervals between HD sessions (interdialytic period) are shown in Figures A2, B2, C2. Notably, during the interdialytic intervals, there was an inverse relationship in protein levels: while plasma levels of Aβ1-40, Aβ1-42, and total tau increased, their respective CSF levels decreased (Table1, Figures A2, B2, C2).

Conclusions: This study is the first to demonstrate CSF dynamics of Aβ1-40, and 42, and total tau in HD patients. We observed that after HD, in the interdialytic period, the CSF levels of Aβ1-40 and 42, and total tau declined. Interestingly, while CSF levels of Aβs and total tau decreased during the interdialytic periods, their respective plasma levels tended to increase. The biological significance of these findings warrants further studies.

Figures: (A1, B1, C1) Mean plasma levels of Amyloid-βs and tau protein during dialysis sessions (Mean ± 95%CI, RM-ANOVA (A2, B2, C2)) Mean plasma and CSF levels of Amyloid βs and tau protein during the intervals between dialysis sessions (Mean ± 95%CI), p<0.05 was considered significant.

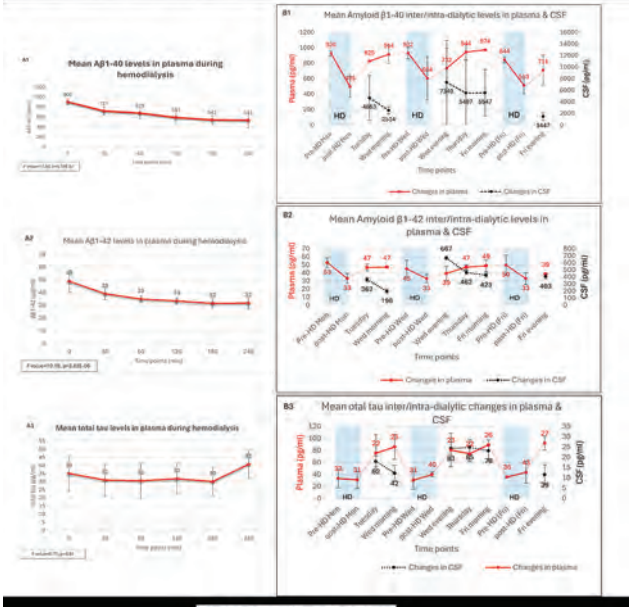


Table 1: Mean percent change of protein levels in plasma and CSF between dialysis sessions.

Dialysate	Plasma	CSF
Amyloid β1-40	0.22	-0.45
Amyloid β1-42	0.12	-0.41
Total tau	0.13	-0.18

SA-PO397

Does Hemodialysis Weaken GDF-15 Impairing Pulmonary Hypertension in Chronic Kidney Failure?

Yifang Tang, Zhu Zhou. *First Affiliated Hospital of Kunming Medical University, Kunming, China.*

Background: Pulmonary hypertension (PH) is a common complication of chronic renal failure (CRF) and contributes to mortality. However, the occurrence of mechanism or risk factors in CRF complicated with PH remains unclear.

Methods: One hundred and twenty subjects were prospectively recruited and divided into CRF group (n=79) and control group (n=41). The CRF group were subsequently divided into the pre-hemodialysis group (n=41) and the hemodialysis group (n=38). The GDF-15 levels of all subjects were tested by ELISA. The levels of GDF-15 in groups were compared each other. The association between GDF-15 and other clinical parameters was analyzed as well as the association between pulmonary artery pressure (PAP) and other factors with the stepwise regression analysis.

Results: GDF-15 levels in CRF group were significantly higher than that in control group. There was no difference between pre-hemodialysis and hemodialysis groups. Positive correlations between GDF-15 and PAP, urea, creatinine, or uric acid (UA) were found with or without adjusting for age, sex, and body mass index (BMI). Additionally, GDF-15 was positively associated with PAP or creatinine. Moreover, PAP was positively associated with hypertension other than GDF-15, while negatively with total bilirubin (TBIL) or glucose (GLU).

Conclusions: GDF-15 is significantly elevated and positively associated with PAP in CRF patients. GDF-15 may be a therapeutic target for PH in CRF. Hemodialysis can't weaken GDF-15 impairing PH because there is no difference in plasma levels of GDF-15 between pre-hemodialysis and hemodialysis patients with CRF. Moreover, PAP is negatively associated with TBIL or GLU in CRF.

Funding: Government Support - Non-U.S.

SA-PO398

Comparison of Platelet Aggregation Test before and after Hemodialysis in Patients with Kidney Failure

Sirihatai Konwai,[1] Suwikran Wongpraphairot,[1] Pirun Saelue,[2] Atthaphong Phongphithakchai,[1] Suntornwit Praditaukrit.[1] *[1]Nephrology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand; [2]Hematology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.*

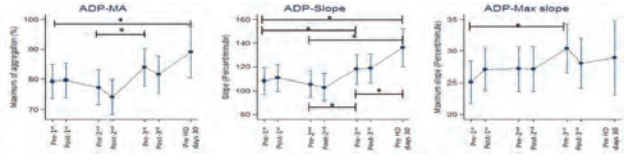
Background: One of the important signs of uremic toxin accumulation in renal failure patient is uremic bleeding. Renal replacement therapy is the way to stop uremic bleeding. However, opinions on how hemodialyis affects platelet function in uremia patients are divided.

Methods: This prospective cohort study included patients initiating hemodialysis with a blood urea nitrogen level more than 60 mg/dL. Blood samples were collected before and after the first, second, third, and day thirty of hemodialysis for the platelet aggregation test. The The primary outcome was the platelet aggregation test results before and after hemodialysis. Secondary outcomes included 30-day mortality and events of bleeding.

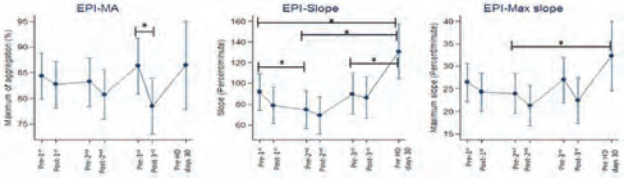
Results: Of the 15 cases that were included, 53.3% were female. There were 10 patients with chronic renal failure. The median values for hemoglobin, platelet counts, and fibrinogen were 9.00 mg/dL, 240000/microliter, and 758.4 mg/dl. Comparing the thirty-day pre-dialysis with the first pre-dialysis session, there was a higher percentage of platelet aggregation in adenosine diphosphate (ADP) (difference in aggregation level was 9.76, 95% CI 1.93-17.60). The first pre-dialysis session and the thirty-day pre-dialysis session show a significant difference in the slope after stimulation with ADP and epinephrine (difference 28.03, 95%CI 13.67-42.39 and 38.96, 95% CI 14.64-63.29). There was no death or bleeding for thirty days.

Conclusions: ADP and epinephrine-related platelet aggregation can be improved by initiating hemodialysis at least two sessions in advance. Hemodialysis can therefore be utilized to prevent uremic bleeding.

Funding: Private Foundation Support, Government Support - Non-U.S.



Platelet aggregation stimulated by adenosine diphosphate
* Significant difference
MA: maximum of platelet aggregation
Slope: slope at 1st minute
Max slope: slope at time to maximum aggregation



Platelet aggregation stimulated by epinephrine
* Significant difference
MA: maximum of platelet aggregation
Slope: slope at 1st minute
Max slope: slope at time to maximum aggregation

SA-PO399

Study of the Relationship between QTc Time Trends and Microglobulin during Hemodialysis

Yasuyuki Mimura, Akihiro Kuma, Masayoshi Nanami, Takahiro Kuragano. *Department of Cardiovascular and Renal Medicine, Hyogo Medical University, Nishinomiya, Japan.*

Background: Several studies have revealed a relationship between an abnormal QTc interval of electrocardiogram, mortality, and sudden death in patients undergoing hemodialysis (HD). However, only some studies have investigated the changes in the QTc interval during HD sessions and the determining factors. Therefore, our aim was to investigate the relationship between various parameters and QTc interval during HD.

Methods: This cross-sectional study enrolled 53 patients undergoing maintenance HD. The QTc was measured hourly from HD initiation. Blood samples were collected at the beginning of each HD session. Blood Ca, Mg, K, and HCO3-levels were evaluated at the beginning, 2 h after, and at the end of the HD session. The relationship between changes in the QTc interval and various parameters was analyzed using Spearman's correlation and multiple regression analyses.

Results: The patients were aged 37–91 years (Mean, 66.9) years, and the dialysis duration was 1–402 months (median, 2 months). Of the patients, 39.6% were diagnosed with a prolonged QTc interval (≥460 ms) at HD initiation (median, 455 ms). The QTc interval was shortened by 11 ms at 2 h and then increased by 3 ms at the end. Peak changes in the QTc interval occurred 2 h after HD initiation. Thus, we estimated the factors that affected the change in QTc 2 h after dialysis initiation (ΔQTc2h). HD treatment duration ($r = 0.312$, $P = 0.025$) and serum levels of β2MG ($r = 0.324$, $P = 0.019$) were positively correlated with ΔQTc2h. The 2 h change in corrected Ca (ΔcCa2h) ($r = -0.31$, $P = 0.03$), intact PTH ($r = -0.30$, $P = 0.035$), and α2MG ($r = -0.46$, $P = 0.001$) were negatively correlated with ΔQTc2h. The association between β2MG and ΔQTc2h was evaluated separately in the high and low β2MG groups. β2MG significantly suppressed the decline in QTc interval in the high β2MG group ($P = 0.03$). According to the multiple regression analysis, β2MG ($\beta = 0.389$, $P = 0.0027$) and α2MG ($\beta = -0.326$, $P = 0.020$) were significant predictors of ΔQTc2h.

Conclusions: The change in QTc time 2 h after dialysis initiation correlated significantly with β2MG and α2MG. The QTc time was expected to change proportionately to serum Ca; however, the QTc time was shortest after 2 h of dialysis. Removal of β2MG and α2MG by dialysis depends on HD treatment time, which may affect prolonged QTc interval in QTc 2 h after dialysis initiation.

SA-PO400

Small-Vessel Disease in Patients with ESKD Evidenced by Elevated Peak Width of Skeletonized Mean Diffusivity

Changmin Heo, Yang Wook Kim, Bongsoo Park, Sihyung Park, Yoo jin Lee, Eul Jo Jeong, Jiyae Yi. *Inje University Haeundae Paik Hospital, Busan, Republic of Korea.*

Background: The peak width of skeletonized mean diffusivity (PSMD) is a novel marker for small vessel disease. The aim of this study was to investigate the small vessel disease in patients with end-stage renal disease (ESRD) using PSMD.

Methods: We prospectively enrolled patients with ESRD, and also included age and sex-matched healthy controls. Diffusion tensor imaging (DTI) was performed using the three tesla MRI scanner in patients with ESRD and healthy controls. We obtained the PSMD based on the DTI by several steps including preprocessing, skeletonization, application of a custom mask, and histogram analysis. We compared the PSMD between the groups, and also performed correlation analysis between PSMD and clinical factors.

Results: We enrolled the 38 patients with ESRD and 38 healthy controls. There was significant difference of the PSMD between the patients with ESRD and healthy controls. The PSMD was higher in the patients with ESRD than that in the healthy control group (2.945 vs. 2.552×10^{-4} mm^2/s, $p<0.001$, Fig 1). In addition, the PSMD was positively correlated with age ($r=0.370$, $p=0.022$). However, PSMD did not differ depending on the types of dialysis or presence of diabetes mellitus.

Conclusions: We demonstrate that patients with ESRD exhibit higher PSMD compared to healthy controls, indicating greater small vessel disease. The findings provide crucial information for clinical management and treatment strategies, highlighting the importance of addressing small vessel disease in patients with ESRD.

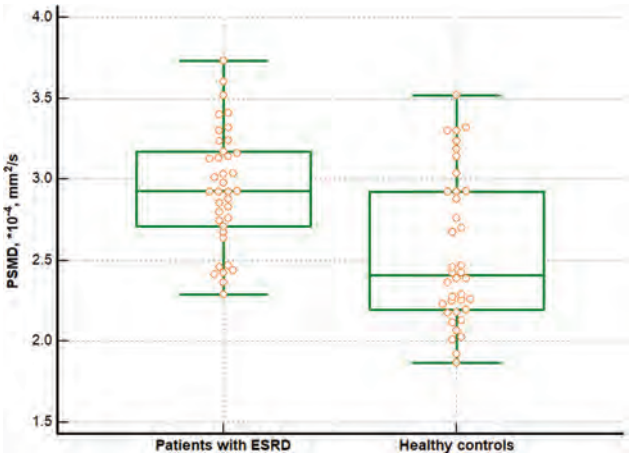


Figure 1. Difference in the PSMD between patients with ESRD and healthy controls

SA-PO401

Association of Diabetes with Heart Rate Variability in Hemodialysis

Brona Moloney,[1,2] Glenn M. Chertow,[3] Finnian R. McCausland.[1,2]
[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Stanford University School of Medicine, Stanford, CA.

Background: Autonomic dysfunction is common among patients with diabetes mellitus (DM) receiving hemodialysis (HD) and may contribute to a higher risk of intra-dialytic hypotension. We explored the association of DM with heart rate variability (HRV; a surrogate of dysautonomia) and explored if HRV modified the relation between DM and intra-HD systolic blood pressure (SBP).

Methods: In a post hoc analysis of the Frequent Hemodialysis Network Daily Trial, we used: 1) random effects linear regression to estimate the association of DM (vs. none) with log-transformed low-frequency power [LF], high-frequency power [HF], LF/HF, and standard deviation of the R-R interval [SDNN] measured on a per-visit basis (baseline and 12-months); 2) linear regression to explore associations with changes in HRV parameters over 12 months. We performed mediation analyses to explore if the association of DM with intra-HD SBP was related to HRV. Models adjusted for age, sex, designated race, height, access, HD vintage, heart failure, pre-HD SBP, heart rate, ultrafiltration rate, hemoglobin, albumin, calcium blockers, diuretics, LV mass, and randomized treatment.

Results: Of patients with available data and without atrial fibrillation (n=198), 82 (41%) had DM. Median values for HRV parameters at baseline and 12 months are shown in Table 1. In adjusted random effects models, DM (vs. none) was not significantly associated with differences in LF 9% (95%CI -18, 46), HF 9% (95%CI -10, 32), or LF/HF -1% (95%CI -16,17), but was significantly associated with SDNN -18% (95% CI -26, -8). DM was not associated with a change from baseline to 12 months in any HRV parameter. In mediation analyses, HRV was estimated to mediate -8% (95%CI -52, 15) of the association between DM and nadir SBP.

Conclusions: DM (vs. none) was associated with 18% lower SDNN, a surrogate of overall heart rate variability, among participants of FHN on a per-session level. SDNN does not appear to mediate the association of DM with intra-dialytic nadir SBP.

Funding: NIDDK Support

Table 1. Median [25-75th percentile] values for heart rate variability parameters at baseline and 12 months

	No Diabetes	Diabetes
Low Frequency power, ms²		
Baseline	105 [48, 194]	104 [52, 210]
Month 12	125 [45, 226]	105 [44, 194]
Delta (Month 12 - baseline)	4 [-52, 74]	6 [-49, 56]
High frequency component, ms²		
Baseline	45 [29, 60]	38 [30, 55]
Month 12	43 [31, 54]	38 [27, 56]
Delta (Month 12 - baseline)	-1 [-19, 13]	-1 [-14, 13]
LH/HF ratio		
Baseline	2 [2, 4]	2 [1, 4]
Month 12	3 [1, 4]	2 [1, 4]
Delta (Month 12 - baseline)	0 [-1, 2]	0 [-1, 1]
SDNN, ms		
Baseline	76 [58, 98]	56 [44, 89]
Month 12	74 [61, 90]	67 [42, 102]
Delta (Month 12 - baseline)	0 [-22, 20]	-1 [-18, 14]

SA-PO402

Association of Changes in Vector Length with Changes in Right Ventricular Magnetic Resonance Imaging Indices among Patients on Maintenance Hemodialysis

Enass Sayed,[1,2] Glenn M. Chertow,[3] Finnian R. McCausland.[2,1] *[1]Harvard Medical School, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Stanford University School of Medicine, Stanford, CA.*

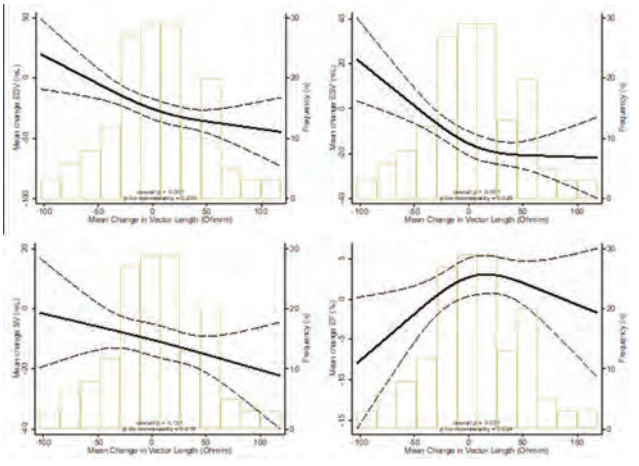
Background: Shorter vector length (a bioimpedance proxy of hypervolemia) is known to be associated with higher left ventricular volume indices among patients receiving maintenance hemodialysis (HD). However, the association of hypervolemia with right ventricular (RV) parameters is less clear.

Methods: Using data from the Frequent Hemodialysis Network Daily Trial (n=160), we used linear regression to assess the association of changes in vector length from baseline to month 12 with changes in magnetic resonance imaging (MRI) measures of RV parameters (RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RV stroke volume (RVSV), and RV ejection fraction (RVEF). We adjusted for baseline vector length, baseline outcome measurements, randomized treatment, age, sex, designated race, Quételet (body mass) index, access type, vintage (<2, 2-5, >5 years), pre-HD systolic BP, hypertension, heart failure, diabetes, residual urea clearance (0, ≤1, >1 to 3, >3 ml/min), hemoglobin, phosphate, ultrafiltration rate, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, log-transformed erythropoietin dose, and eKt/V.

Results: The mean age was 50 ±13 years; 35% were female. In the fully adjusted models, a decline in vector length (per 50 Ω/m; i.e., a proxy for an increase in volume) was associated with an increase of 14.4 (95%CI 5.8, 23.0), 9.7 (95%CI 4.2, 15.2), and 4.7 (95%CI -0.6, 10.1) mL in RVEDV, RVESV, and RVSV, respectively; the relation between change in vector length an RVEF was curvilinear. Continuous associations are presented in restricted cubic splines (Figure 1).

Conclusions: Change in vector length over 12 months, a bioimpedance-derived proxy of volume status, was inversely associated with RVEDV and RVESV measured by cardiac MRI in patients randomized to conventional or frequent hemodialysis.

Funding: NIDDK Support



Association of change in vector length with changes in right ventricular volume

SA-PO403

Proteomics-Based Machine-Learning Approach for Predicting Cardiac Dysfunction in Patients on Hemodialysis

Ping-Hsun Wu,[1,2] Yi-Ting Lin,[1,2] Yi-Wen Chiu,[1,2] Mei-Chuan Kuo,[1,2] Shang-Jyh Hwang.[1,2] *[1]Kaohsiung Medical University Chung Ho Memorial Hospital, Kaohsiung, Taiwan; [2]Kaohsiung Medical University College of Medicine, Kaohsiung, Taiwan.*

Background: Evaluating cardiac function is crucial for hemodialysis patients due to its association with cardiovascular mortality. Evaluating cardiac function in hemodialysis patients is crucial, and blood-based biomarker testing represents a potentially convenient and insightful approach for assessing cardiac function in this population. This study aims to explore using cardiovascular proteomics and machine learning (ML) to predict cardiac dysfunction in hemodialysis patients.

Methods: The study enrolled 347 hemodialysis patients who underwent cardiac ultrasonography to assess cardiac dysfunction, which was defined as an ejection fraction < 50% (primary analysis) or < 45% (sensitivity analysis). The proteomic analysis measured 184 proteins using proximity extension assays. ML techniques (classification and regression tree [CART], Least Absolute Shrinkage and Selection Operator [LASSO], random forest, Ranger, eXtreme Gradient Boosting [XgBoost]) were applied to develop predictive models using the proteomic and clinical data. Model performance was evaluated by area under the curve (AUC). The Significance of the Hierarchical Averaging of Shapley Values (SHAP) values identified key predictive features.

Results: The proteomic biomarkers outperformed routine clinical/laboratory variables in predicting cardiac dysfunction across ML models. LASSO and XgBoost models with feature selection highlighted N terminal pro B type natriuretic peptide (NT-ProBNP) as the top predictor, followed by Chitotriosidase 1 (CHIT1), Angiotensin-Converting Enzyme 2 (ACE2), and Matrix Metalloproteinase-2 (MMP-2). SHAP analysis confirmed these findings.

Conclusions: Cardiovascular proteomics combined with ML enables superior prediction of cardiac dysfunction compared to clinical variables alone in hemodialysis patients. The NT-proBNP and CHIT1 emerged as important protein biomarkers, potentially facilitating early interventions for preventing cardiovascular complications.

SA-PO404

Chronotropic Incompetence Rather than Stroke Volume Is the Main Driver of Impaired Cardiac Output Response in Patients on Hemodialysis

Aaron K. Wills, Monique O. Campos, Gayatri Narayanan, Heather Burney, Andrew R. Coggan, Sharon M. Moe, Kenneth Lim. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Impaired cardiovascular functional capacity (CFC) is a major complication in hemodialysis (HD) patients and contributes to diminished survival rates and compromised quality of life. Reduced CFC (as assessed by VO_2Peak) is known to arise from both reduced cardiac output (CO) response and impaired oxygen extraction at the level

of the contracting skeletal muscle (Fick Principle). However, at the CO level, it is unclear which determinant, heart rate (HR), or stroke volume (SV) primarily drives impaired response at peak exercise (PE) in patients on dialysis. Herein, we sought to determine the major cardiac determinants of impaired CO response during PE in HD patients.

Methods: We recruited seven HD patients and five healthy controls (CON). All participants underwent comprehensive breath-by-breath cardiopulmonary exercise testing (CPET) with simultaneous 12-lead EKG, pulse oximetry and CO monitoring via impedance cardiography. A t-test and a repeated measures two-way ANOVA were performed for analysis between groups, and a multiple linear regression to test for associations.

Results: Both groups were well-matched by age (HD:47±15,CON:51±8yr) and BMI (HD:28.2±5.0, CON:26.7±2.9kg/m^2). VO_2Peak was impaired in HD patients compared to CON (HD:12.9±4.5; CON:27.1±6.3mL/min^{-1}kg^{-1}, p<0.001). Both HD and CON patients demonstrated progressive increase in HR, SV, and CO during warm-up to the PE compared to resting measures (p<0.05). However, HD patients exhibited significant chronotropic incompetence at PE (HRR:+36±20%) compared to CON (HRR: +82±5.2%, p<0.05). The delta changes observed at rest to PE were significantly lower in the HD group compared to the CON group for HR (+34.±18;CON: +86±22 bpm;p=0.001), SV (+20±6;CON:+38±14mL;p=0.008), and CO (+4.7±1.5;CON:+14.8±4.6L.min-1; p=0.0002). Multiple linear regression modeling showed that delta changes in HR, but not in SV were associated with CO at peak exercise (β(standard error)= 0.08(0.02), p=0.008) in HD patients.

Conclusions: HD patients exhibited a smaller increase in HR and SV at peak exercise. However, our findings suggest that chronotropic incompetence is the major cardiac determinant of impaired CO response at PE in patients on dialysis.

SA-PO405

Real-Time Forecasting of Intradialytic Hypotension Using Deep Learning and Multimodal Data Integration

Yunfei Luo,[1] Siwei Zhao,[2] Subhasis Dasgupta,[1] Tauhidur Rahman,[1] Rakesh Malhotra.[1] *[1]University of California San Diego, La Jolla, CA; [2]Sanderling Renal Services, Nashville, TN.*

Background: Intradialytic hypotension (IDH) is a common and serious complication during hemodialysis and is linked to high morbidity and mortality. Early prediction of IDH can facilitate timely interventions and potentially reduce IDH rates.

Methods: We developed a transformer-based deep learning model to predict IDH events 30-60 minutes before their occurrence. IDH was defined using multiple criteria: Nadir 90, Nadir 100, Fall 20, Fall 30, Fall 20 plus Nadir 90, Fall 30 plus Nadir 90, KDOQI (SBP reduction ≥20 mmHg and associated symptoms), and HEMO (any drop in SBP resulting in an intervention). We utilized real-time physiological data from dialysis sessions and electronic health records (EHR), including demographics, past dialysis records, labs, and comorbidities. The model employed multimodal fusion methods and was trained using a multitask learning approach to account for different IDH definitions. We performed a 5-fold cross-validation by splitting the patients into five disjoint groups. Model performance was assessed using the area under the receiver operating characteristic curve AUROC.

Results: Our study included data from 1,452 patients, encompassing 21,129 dialysis sessions. The mean age was 65 years. The model achieved AUROC scores ranging from 0.85 to 0.94 across different IDH definitions as shown in Fig 1. The model performance was similar with or without integration of EHR module.

Conclusions: We successfully developed a rmodel using available clinical data to predict IDH during dialysis sessions. Future research should focus on validating our model within independent datasets. Implementing this predictive system could facilitate timely therapeutic interventions, and mitiogate the severe consequences of IDH.

Figure 1: Discriminative ability of the model expressed as AUC across different IDH definitions.

IDH Definitions	ROC AUC	Specificity	Sensitivity	Balance Accuracy
Fall 20	0.85±0.003	0.74±0.005	0.79±0.037	0.76±0.006
Fall 30	0.87±0.004	0.81±0.003	0.76±0.032	0.79±0.003
Nadir 90	0.94±0.006	0.92±0.006	0.80±0.017	0.86±0.011
Nadir 100	0.93±0.006	0.87±0.010	0.85±0.006	0.86±0.007
Nadir 90 Fall 20	0.91±0.004	0.97±0.004	0.50±0.022	0.74±0.010
Nadir 90 Fall 30	0.91±0.002	0.98±0.004	0.49±0.031	0.64±0.026
HEMO	0.81±0.002	0.71±0.025	0.76±0.023	0.73±0.002
KDOQI	0.81±0.004	0.93±0.016	0.34±0.067	0.64±0.026

SA-PO406

Noninvasive Blood Pressure Monitoring in Patients on Chronic Hemodialysis

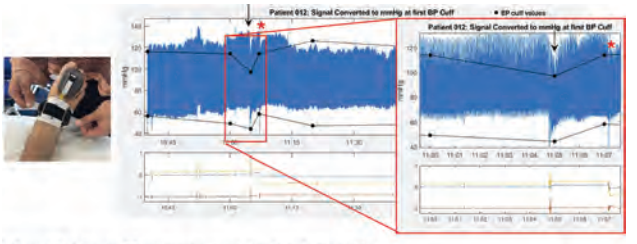
Frank Lee,[1] Tai Truong,[2] Whitney Li,[1] Abigail Cabush,[3] Akhil Chaudhari,[3] Parth Kumar,[2] Ekamol Tantisattamo,[2] Wei Ling Lau.[2] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Division of Nephrology, Department of Medicine, University of California-Irvine, Irvine, CA; [3]Vena Vitals, Irvine, CA.*

Background: Intradialytic hypotension (IDH) during hemodialysis is associated with adverse outcomes including cerebral ischemia and increased cardiovascular and all-cause mortality. Standard blood pressure (BP) monitoring is done every 30 min via an inflatable cuff, and data is lacking to guide optimal frequency of intradialytic BP measurements. Variability in cuff size, the patient's sitting position, and location of cuff placement (arm vs leg) may affect BP readings. Here, we present pilot data from a study evaluating a noninvasive continuous BP sensor during outpatient hemodialysis treatments.

Methods: The non-invasive BP sensor patch (AcuPulse) was provided by Vena Vitals, Inc. (Irvine, CA). The sensor detects pressure changes via conformal electrodes within a flexible silicone patch. Nineteen adults at the Fresenius Kidney Care Dialysis Center of Orange were enrolled for data collection. The BP sensor was secured over the radial or dorsalis pedis artery sites, to capture a continuous waveform during hemodialysis. Standard arm cuff BP readings were collected every 30 minutes for the duration of the hemodialysis treatment, with additional BP rechecks done per discretion of the dialysis staff. BP waveforms were analyzed and graphed on MATLAB.

Results: From the 19 subjects, 10 had usable datasets for analysis. Average age was 56 years and 7 of the 10 subjects were male. Excluded datasets were due to missing BP cuff readings (n=3), weak waveform due to improper device setup (n=1), signal artifact due to BP sensor placed on the same arm as BP cuff (n=1), and excessive motion artifact (n=4). Preliminary data shows that the BP sensor waveform tracks BP cuff measurements closely (example shown in Figure). The sensor detected IDH prior to the standard BP cuff in 3 subjects.

Conclusions: Our results demonstrate that a non-invasive sensor has potential utility for continuous BP monitoring during dialysis treatments, for timely detection of IDH. Technological refinements are ongoing to optimize sensor fidelity and to adjust for motion artifact.



Left panel: Non-invasive BP sensor secured over dorsalis pedis pulse on foot.
Right panel: Example of hypotensive episode (arrow) captured on the BP sensor waveform that correlated with BP cuff measurements. A "low diastolic" alarm on the dialysis machine prompted additional BP cuff checks by the dialysis staff. The tracing also shows an example of motion artifact (isolated spike after the hypotensive episode, red asterisk).

SA-PO407

Guideline-Concordant vs. Routinely Measured Predialysis Blood Pressure (BP), and Home BP in Prevalent Hemodialysis (HD) Patients

Judy A. Ukrainetz,[1,2] Branko Braam.[1,2] *[1]University of Alberta, Edmonton, AB, Canada; [2]Alberta Health Services, Edmonton, AB, Canada.*

Background: Pre-HD blood pressure is a pivotal vital sign in clinical decision-making. Yet, obtaining accurate measurements remains challenging. Pre-HD BP has been reported to poorly correlate with home BP. In this study, we investigated whether guideline-concordant measured pre-HD BP taken by the research team is better correlated to home BP than routine BP measurements taken by HD nurses.

Methods: Three automated and three manual BP measurements were obtained pre-HD by the research team strictly following Hypertension Canada guidelines. BP was also measured by the HD nurses as per program routines using the HD machine. Patients measured BP at home at 4 occasions. We observed and recorded whether nurses followed the 10 quality guidelines. Data are mean±sd.

Results: The 37 patients were 61±15 years of age, 49/51% female/male. HD vintage was 1 year and 7 months (2 months-8 years). Automated BP was 136/71±31/17 mmHg and manual BP was 135/69±31/17 mmHg (NS) as assessed by the research team. Routine nurse measured BPs averaged 140/63±29/19 mmHg. Pulse pressures were 60±18 by the research team, 77±26 by the nurses and 60±19 mmHg by patients at home (P<0.01, home vs. nurses). There was a significant correlation between SBP, DBP, and PP between measurements taken by the research team and nurses, but not between those and home BPs. A strong discrepancy was observed between research and nurse measurements, as assessed by the level of agreement for DBP, SBP, and PP (Bland Altman). None of the 36 observed BP measurements by 22 nurses were fully concordant with the guidelines. The time of resting before the measurement was highly variable (0-15 minutes). None

of the patients were asked whether food, drinks, or caffeine were consumed, or if people had smoked within 30 minutes prior to the measurement. No more than 1 pre-HD BP measurement was conducted in any of the cases. Nurses did not refrain from talking to patients during BP readings in 92% of the cases, which is known to potentially elevate readings by 25-40% within the first 30 sec of talking.

Conclusions: This study failed to show that not following guidelines for BP measurements could explain the previously reported discrepancy between home and pre-HD BPs, despite that guideline-concordant BP assessment in the HD unit was poor. Measuring BP accurately is essential in directing care for our HD patients.

SA-PO408

Nadir Systolic Blood Pressure during Hemodialysis Highly Correlates with Hospital Admission

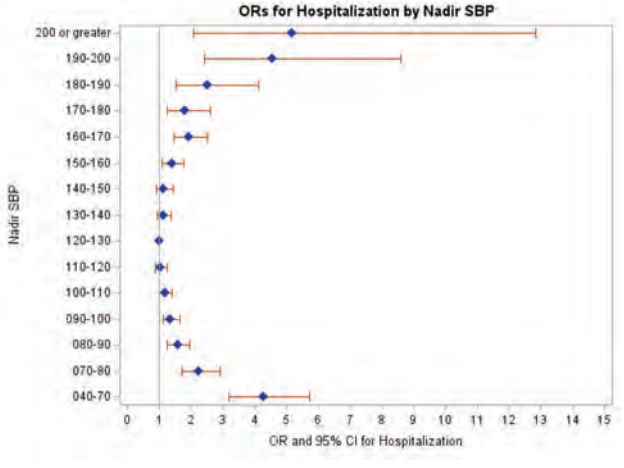
Heidi A. Bleyer, Anthony J. Bleyer, Carl D. Langefeld. *Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Establishing blood pressure (BP) targets during hemodialysis (HD) may improve the ability to achieve dry weight and avoid hospitalization. While Kt/V targets have been mandated and maximum fluid removal recommended, BP targets for HD have not been established. The purpose of this study was to identify whether the lowest systolic BP values attained during HD (LSBP) were associated with hospitalization. Hypothesis: LSBP < 100 or >160 mm Hg is associated with an increased risk of hospitalization

Methods: We performed a retrospective cohort study of 1668 HD patients cared for by nephrologists at Wake Forest School of Medicine from 1/1/2018 to 12/31/2023 and admitted to Atrium Health Wake Forest Baptist Medical Center for deteriorations in health. We performed a mixed model logistic regression where individual was the random effect, with the outcome variable being HD sessions occurring 0-3 days prior to a hospital admission vs. HD sessions unrelated to hospital admission and dependent variables including age, race, gender, LSBP, dialysis dose.

Results: There were 497,561 HD treatments during this time period and 1984 hospital admissions in 1668 HD patients (58% male, 54% White, 45% Black). During the study period there were 1984 admissions for patients who had undergone HD 0-3 days prior to admission. The figure shows the odds ratio for LBSP for HD treatments 0-3 days pre-admission vs. HD treatments not associated with admission, with a LSBP 120 to <130 mm HG as the reference range. LSBP readings from 100-150 mm Hg were associated with the lowest risk of hospitalization.

Conclusions: A nadir HD systolic BP <100 or >150 mm Hg is associated with an increased risk of hospital admissions. Targeting nadir systolic BP during HD may help to prevent morbidity and possibly mortality.



SA-PO409

Assessing the Role of Cooling on Hemodynamics of Patients on Dialysis in Inpatient Settings

Hui Xue,[1] In-Lu Amy Liu,[2] Aiyu Chen,[2] Edward Lin,[3] Beth Creekmur,[2] Antoine C. Abcar,[4] Josephine J. Chiu,[3] Paula S. Cho,[3] Patrick Fong,[3] John J. Sim,[4] Annie Suh,[3] Behzad Ali.[3] *[1]Kaiser Permanente Southern California, San Diego, CA; [2]Kaiser Permanente Southern California Department of Research & Evaluation, Pasadena, CA; [3]Southern California Permanente Medical Group, Pasadena, CA; [4]Kaiser Permanente Southern California, Los Angeles, CA.*

Background: The effect of cooling dialysate to reduce intradialytic hypotension (IDH) in the inpatient setting is unknown.

Methods: Retrospective Cohort: Session Level: 2019 inpatient (IP) HD sessions (n=17357) were evaluated at Kaiser Permanente Southern California (KPSC). Using multivariable repeated measure models; covariates included age, gender, race, IP utilization, IP duration, HD sessions, HD temp, blood pressure (Bp), fluid removed, BMI, and Elixhauser index (EI). Patient Level: 3243 patients received IP HD. Multivariable analysis (Fine and Gray, Cox proportional hazards, Robust Poisson, multiple regression) examined 30-day and 12-month outcomes: re-admissions (re-IP), total IP/day, 30-day-alive-at-home, hospice referral and death. Covariates included age, sex, race, index IP characteristics, prior utilization and comorbidity. **Prospective cross-over design cohort:** Session: Examined Cooled dialysate <36.5°C (CD) on IDH in 6 KPSC hospitals over 6-months in 2022. Each hospital served as its own control and was assigned to either 37.0°C or 35.5°C for the first 3 months, then switched in the 2nd 3 months. 6698 IP HD sessions were evaluated using a nested multivariable repeated measure model. Covariates included assigned temp (AT) and retrospective variables listed above. Patient: 1159 patients were followed for 12-months using models, covariates and outcomes similar to retrospective patient analyses with the addition of AT.

Results: Retrospective Cohort: Session: IDH risk factors were CD, older age, prior IP, lower ultrafiltration, under-weight, service area and higher EI. Higher Bp significantly reduce risk. Patient: IDH significantly increased risk of death, total IP/day and increased re-IP in 30-day. **Prospective cross-over design cohort:** Session: Lower AT (35.5 °C) and higher Bp could significantly reduce IDH risk. Patient: Lower AT tended to reduce outcomes for patients with less comorbidities (EI < 11) in 30-day. Due to small sample size, no risk reductions were significant. **Comparison:** Session: Prospective cross-over design reduced the effect of unmeasured confounders and shows AT (35.5 °C) could significantly reduce IDH risk (0.83 (0.71-0.97)).

Conclusions: CD reduced the risks of IP IDH, healthier patients had the greatest short-term benefits. Larger sample size needed for future work.

SA-PO410

Blood Pressure-Lowering Effects of Ultraviolet Light in Patients on Hemodialysis: Identification of Specific Wavelengths

Caroline Yovanovich,[1,2] Richard B. Weller,[3] Peter Kotanko,[4] Yuedong Wang.[2] *[1]Medtronic, Northridge, CA; [2]University of California Santa Barbara, Santa Barbara, CA; [3]The University of Edinburgh Division of Health Sciences, Edinburgh, United Kingdom; [4]Renal Research Institute, New York, NY.*

Background: Evidence from hemodialysis (HD) patients suggests an inverse correlation between solar ultraviolet (UV) radiation and systolic blood pressure (SBP) (Weller, *J Am Heart Assoc;* 2020). The exact nature of this relationship across the UV spectrum remains unknown.

Methods: Using longitudinal pre-dialysis SBP measurements and UV and temperature data from public sources, we explored whether distinct UV wavelengths (280 to 400 nm) are associated with SBP reduction. We used longitudinal SBP measurements from 2,214 HD patients and obtained daily ground-level UV spectral irradiance and temperature. Treating UV radiation over wavelengths as functional data, we fit functional linear mixed effects models with longitudinal SBP as the response variable and daily UV radiation functions as the independent variable, adjusting for hypertension, age, access type, BMI, IDWG, ESA dose, hemoglobin, serum albumin, Na^+, K^+, ambient temperature, and trend over time.

Results: Wavelengths <325 nm were associated with a decline of SBP, when adjusted for clinical variables. While still significant, adjusting for ambient temperature muted the effect size (Fig. 1).

Conclusions: These findings corroborate and expand previous findings of an association between solar UV light and SBP reduction. Narrow band 311 nm phototherapy lamps to treat psoriasis were developed based on the maximal divergence between therapeutic and erythemal/carcinogenic effects at this wavelength. We hypothesize that such lamps could similarly offer SBP lowering effects.

Funding: Commercial Support - Renal Research Institute

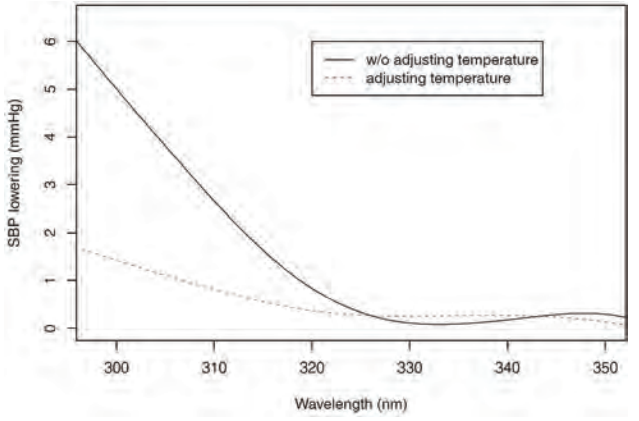


Fig. 1: Wavelength vs. SBP lowering effects. The solid black line indicates the effect with adjustment for clinical variables, the red dashed line with additional adjustment for ambient temperature.

SA-PO411

Pharmacologic and Nonpharmacologic Management of Intradialytic Hypotension in ESKD: A Systematic Review and Meta-Analysis

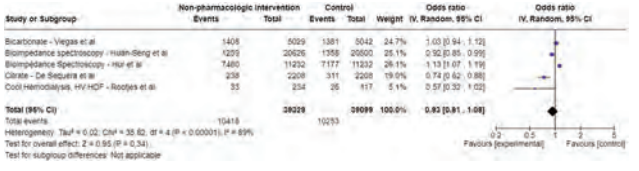
Rajiv Hans S. Menghrajani,[1] Mirtha C. Almanzar,[1] Maria Angela Matabang,[1] Kevin Elissandro Gumabon,[2] Ankur Shah,[3] Edgar V. Lerma.[4] *[1]Lincoln Medical Center, Bronx, NY; [2]Philippine General Hospital, Manila, Philippines; [3]Brown University Warren Alpert Medical School, Providence, RI; [4]University of Illinois Chicago College of Medicine, Chicago, IL.*

Background: Although life-saving, hemodialysis has many complications, intradialytic hypotension (IDH) being one of most frequently recognized occurring in ~10-12% of treatments. In this study, we aim to establish the efficacy of available strategies in managing IDH in end-stage kidney disease (ESKD) patients on hemodialysis (HD) or hemodiafiltration (HDF).

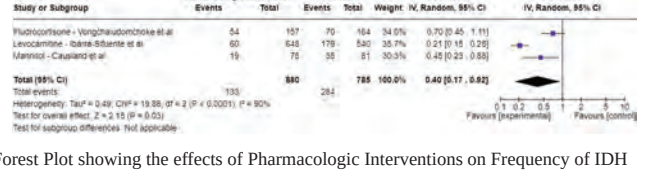
Methods: Electronic databases were searched up to March 2024. Three reviewers independently screened the abstracts, reviewed full-text papers, and critically appraised the quality of included studies using PRISMA guidelines. The primary outcome is the frequency of IDH per hemodialysis session among identified pharmacologic and non-pharmacologic interventions.

Results: Out of 412 articles retrieved, 17 randomized trials were included in a systematic review, 6 of which evaluated pharmacologic while 11 evaluated non-pharmacologic interventions. Of the 17 studies, 8 were included in the meta-analysis (n=745 patients, N=80, 093 dialysis sessions). Pharmacologic interventions (fludrocortisone, mannitol, levocarnitine) showed a significant decrease in IDH frequency [RR 0.40, p < 0.00001 95% CI: 0.17 - 0.92]. However, non-pharmacologic interventions (bicarbonate in HD solution, citrate in HD solution ultrafiltration (UF) profiling, body composition monitoring, UF biofeedback) did not significantly decrease IDH frequency [RR 0.93, p= 0.34 95% CI: 0.81 - 1.08]. Both groups had significant heterogeneity, with I2 = 90% and I2 = 89%, respectively.

Conclusions: Pharmacologic interventions lessened the frequency of IDH among ESKD patients on HD or HDF. However, larger randomized trials with more patients and HD sessions are needed to firmly establish its effect.



Forest Plot Forest Plot showing the effects of Non-Pharmacologic Interventions on Frequency of IDH



Forest Plot showing the effects of Pharmacologic Interventions on Frequency of IDH

SA-PO412

Controlling Sodium Balance in Maintenance Hemodialysis (MHD) Treatment: Study Protocol of a Randomized Controlled Registration Trial

Hui Hua Pang,[1] Leyi Gu,[1] Li Zuo,[2] Jiaxiang Ding,[3] Lihua Wang,[4] Hongtao Zhang,[5] Liang Wang,[6] Andreas Maierhofer,[7] Jennifer Braun,[7] Manuela Stauss-Grabo,[7] Weiwei Qi,[8] Qing Lin,[8] Yuanying Guo,[8] Kakiu Ho.[9] *[1]Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital Baoshan Branch, Shanghai, China; [2]Peking University People's Hospital, Beijing, China; [3]Peking University International Hospital, Beijing, China; [4]Second Hospital of Shanxi Medical University, Taiyuan, China; [5]Henan Provincial People's Hospital, Zhengzhou, China; [6]Wuxi People's Hospital, Wuxi, China; [7]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [8]Fresenius Medical Care Shanghai Co Ltd, Shanghai, China; [9]Fresenius Medical Care Asia Pacific Ltd, Hong Kong, Hong Kong.*

Background: Restoring and controlling fluid volume homeostasis remains a challenge in patients with end-stage kidney disease. Na plays an important role in this process. However, most MHD patients are treated with a fixed dialysate Na concentration, potentially resulting in intradialytic plasma Na shifts. Recently it has been demonstrated these shifts can be minimized by application of a Na control algorithm. The 6008 dialysis machine (Fresenius Medical Care) enables monitoring and control of intradialytic Na fluxes between dialysate and plasma.

Methods: We report the protocol of a multicenter, open-labelled, randomized, superiority registration trial with parallel groups and balanced randomization with a 1:1 ratio. The trial plans to enroll 136 -MHD adult patients with pre-dialysis plasma Na from last 3 routine tests between 130 to 150 mmol/L. After informed consent, patients will be randomized into two groups and stratified with centers and the pre-dialysis plasma Na concentration. The control group will receive dialysate Na concentration set according to current center practice by 5008 series machines (Fresenius Medical Care). The investigational group will receive zero diffusive Na balance setting on 6008 machines. All subjects receive 2-times high-flux HD and 1-time post-hemodiafiltration in a week. Other dialysis treatment parameters will be set per prescription. The primary outcome of this study will be the correlation between the intradialytic average dialysate Na concentration and the average pre-dialysis plasma Na concentration The main outcome will be reflected by the comparison of the value of the correlation coefficient R in both groups.

Results: The expectation is that applying zero diffusive Na control on 6008 machine results in a better correlation between the average dialysate Na concentration and the average pre-dialysis plasma Na concentration than with current center practice.

Conclusions: This will provide evidence that the Na control function individualizes dialysate Na prescription and minimizes the impact of diffusive Na transfer on plasma Na concentration during hemodialysis. This study is ongoing and will be completed in 2027.

Funding: Commercial Support - Fresenius Medical Care

SA-PO413

Comparison of Individualized Sodium Management vs. Standard Treatment in Hemodialysis: The SODIAH Study

Jennifer Braun,[1] Ngoc Pham,[1] Krister Cromm,[1] Andreas Maierhofer,[2] Manuela Stauss-Grabo.[1] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care Deutschland GmbH Werk Schweinfurt, Schweinfurt, Germany.*

Background: Conventional fluid and sodium (Na) management in dialysis patients includes adjusting dry weight based on clinical judgement and ancillary tools. An innovative approach to optimize Na management during dialysis has been developed with an automated Na control that has been evaluated in proof-of-concept studies (Kuhlmann et al.,2018; Sagova et al., 2019). However, the long-term clinical benefits were not addressed. Recently, Maduell et al. (2023) showed that automated Na control was potentially advantageous in reducing intradialytic weight gain (IDWG), improving blood pressure (BP) control, and decreasing intradialytic serum Na changes.

Methods: SODIAH (NCT06341452) is a prospective, parallel, randomized controlled trial with an intervention period of 12 weeks, to be conducted with the 6008 CareSystem (Fresenius Medical Care) in DE, CZ, ES, BE. The study will include 130 anuric HD-patients with a diffusive Na-load during standard dialysis and at least one of the following: IDWG>4% of dry weight, systolic BP (SBP)>180 mmHg, intradialytic morbid events (IMEs), and pre-dialysis fluid overload≥2.5L. To assess variables from patients' perspective, questionnaires covering fatigue, SBP issues, quality of life, thirst and xerostomia were included. These were translated into the local languages and culturally adapted after cognitive debriefing to ensure accuracy and cultural relevance in the target population.

Results: Our study is designed to assess the impact of Na zero-diffusive dialysis on performance indicators, particularly IDWG, intradialytic hemodynamic stability, IMEs, fluid status, and impact on symptom-related well-being of patients. Study results are planned to be reported in 2025.

Conclusions: SODIAH aims to broaden the knowledge of Na zero-diffusive dialysis and its clinical benefits. Culturally adapted questionnaires will be available in new languages supporting analysis of symptom-related well-being.

Funding: Commercial Support - Fresenius Medical Care

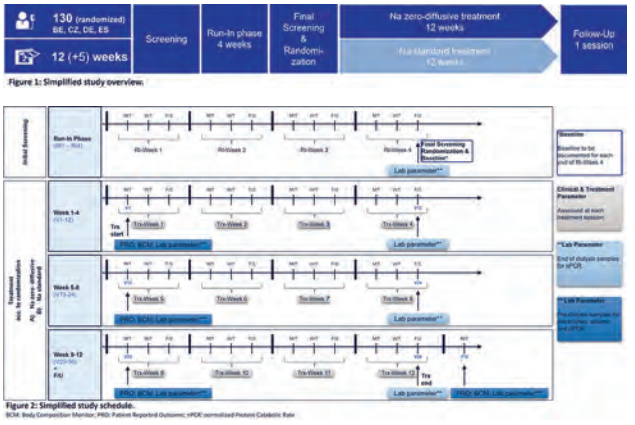


Figure 1: Simplified study overview.

Figure 2: Simplified study schedule.

SA-PO414

Hemodynamic Impact of High- vs. Low-Sodium Dialysate Concentrations in Patients with ESKD on Hemodialysis: A Crossover Clinical Trial

Diana Laura Muñoz,[1] Diana N. Sanchez,[2,1] Adriana Banda Lopez,[1] Salvador Mendoza Cabrera,[2] Caren D. Castro,[1,2] Jorge Andrade-Sierra,[1,2] Enrique Rojas-Campos,[2] Moises Cruz Landino,[2] Ricardo Parra Guerra.[2] Servicio de Nefrología y Trasplante, Hospital de Especialidades Centro Médico Nacional de Occidente, México. *[1]Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Guadalajara, Mexico; [2]Instituto Mexicano del Seguro Social Delegacion Jalisco, Guadalajara, Mexico.*

Background: The prescription of sodium dialysate concentration in the hemodialysis (HD) setting remains controversial. The aim of this study is to evaluate the hemodynamic impact of high versus low sodium dialysate concentrations in prevalent HD patients

Methods: A crossover clinical trial was conducted in chronic HD patients at one tertiary care center. Patients were randomized 1:1 into two arms: (1) dialysate sodium 135 mEq/L, and (2) dialysate sodium 145 mEq/L for 4 weeks, and a washout period with dialysate sodium at 138 mEq/L for 2 weeks. Figure 1 summarizes methods. Interdialytic weight gain (IDWG), blood pressure (BP), plasma sodium concentration, and C-reactive protein (CRP) concentrations were measured before and after each phase. Self-administered questionnaires were used to assess dialysis disequilibrium symptoms in each HD session.

Results: 27 patients were enrolled: 55% women, mean age: 37.5 ± 12.5 years, and mean time on HD: 7.6 ± 6.5 years. Main vascular access was arteriovenous fistula in 23 patients (79%), antihypertensive drugs were used by 15 patients (59%). The average BP at the beginning and end of each phase showed no statistically significant difference. The dialysate sodium prescription of 145 mEq/L showed an increase in CRP values (p = 0.004) and IDWG (p = 0.02), and showed a significant increase in thirst and edema.

Conclusions: Low sodium dialysate does not confer greater hemodynamic instability. This approach could reduce inter and intradialytic disequilibrium symptoms, as well as systemic inflammation.

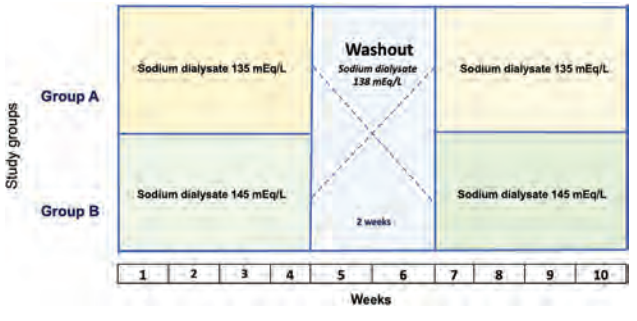


Figure 1 Study Methods

Variable	Dialysate Sodium 135 mEq/l (n= 27)		Dialysate Sodium 145 mEq/l (n= 27)		*Between Groups P value*	
	Baseline	End	Baseline	End	Basline	End
Systolic BP (mmHg)	138 ± 35	135 ± 32	136 ± 35	140 ± 32	0.82	0.6
Dyastolic BP (mmHg)	75 ± 15	75 ± 17	74 ± 20	77 ± 19	0.78	0.65
CPR	7.67 ± 6.76	6.54 ± 6.33	7.46 ± 8.41	9.07 ± 8.91	0.49	**0.004**
Interdialytic weight gain (kg)	2.17 ± 0.93	2.1 ± 0.75	2.37 ± 1.1	2.65 ± 0.95	0.47	**0.02***
Edema	1 (3.7)	0	11 (40.7)	6 (22)	**0.002***	**0.02***
Thrist	1 (3.7)	0	13 (48.1)	3 (11)	**<0.0001***	0.24

Figure 2 Results

SA-PO415

Plasma Refill Rate and Intradialytic Hypotension during Hemodialysis in Hospitalized Patients

Christina H. Brotman, Charlie Hull, Laura M. Dember. *University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: Fluid removal during hemodialysis (HD) is often complicated by acute illness and comorbid conditions that render patients susceptible to hemodynamic instability even with modest fluid removal goals. We previously developed a straightforward method to quantify the rate of plasma refilling during HD, plasma refill rate (PRR), and found that PRR was associated with intradialytic hypotension (IDH) among patients receiving outpatient HD. We sought to investigate whether PRR is associated with IDH in hospitalized patients.

Methods: We performed a prospective study of hospitalized patients receiving HD for either acute kidney injury (AKI) or end-stage kidney disease (ESKD) at a single center. Hematocrit monitoring (using CritLine-IV®) and ultrafiltration data were used to calculate PRR during HD, defined as the interval ratio of plasma refill volume to ultrafiltration volume, as previously established. Vital signs data, patient symptoms, and provider interventions were collected prospectively throughout HD. Cox proportional hazard regression was used to examine the relationship between PRR in the first 10 minutes of each HD session and time to IDH.

Results: In interim analysis, we analyzed data from 99 patients with 1 to 3 HD sessions per patient. HD was performed for ESKD in 70% and AKI in 30% or participants. Mean pre-dialysis systolic blood pressure was 136.9±22.9 mmHg, serum albumin was 2.8±0.6 g/dL, and ultrafiltration rate was 8.1±3.5 ml/kg/h. We found that PRR in the first 10 minutes of HD was associated with IDH even after adjusting for age, sex, and pre-dialysis blood pressure. Specifically, low (PRR <0.5) compared to adequate PRR ≥0.5 was associated with an increased risk of IDH in patients with acute kidney injury (HR 2.93; 95% CI:1.62, 5.29) and midodrine-dependence (HR 2.38, 95% CI:1.25, 4.52).

Conclusions: Low PRR early during the HD session was associated with an increased hazard of IDH, particularly in patients with AKI and midodrine-dependence. These results highlight the potential role of PRR for monitoring HD in patients with acute illness who may be susceptible to fluid shifts. Further studies are needed to understand the dynamics of PRR throughout the HD session and determine whether PRR is modifiable.

Funding: NIDDK Support

SA-PO416

Impaired Cerebrovascular Reactivity Is a Risk Factor for Cerebral Ischemia during Hemodialysis

Dawn F. Wolfgram,[1,2] Claire C. Seigworth,[1] Isabelle L. Grassl,[1] Yan Gao.[1] *[1]Medical College of Wisconsin, Milwaukee, WI; [2]VA Milwaukee Healthcare System, Milwaukee, WI.*

Background: Patients with end-stage kidney disease treated with hemodialysis (HD) have significant atrophy and ischemic type lesions noted on brain imaging. Circulatory stress during HD can lead to drops in systemic blood pressure. During change in blood pressure, cerebrovascular reactivity (CVR) is needed to maintain stable cerebral perfusion. Due to the high prevalence of vascular disease in HD patients, impaired CVR may be common and place patients at higher risk for cerebral hypoperfusion and ischemia during HD.

Methods: We used transcranial Doppler (TCD) to monitor change in cerebral blood flow velocity during induced hypercapnia to measure CVR in HD patients. We monitored intradialytic cerebral perfusion using continuous cerebral oxygen saturation measurements during HD sessions, calculating both maximum drop and overall decline in cerebral oxygen saturation during the HD session. We used linear regression to measure the association between CVR and decline in cerebral perfusion during HD, adjusting for covariates.

Results: We completed the CVR measure in 42 HD patients. The mean (SD) age of the cohort was 58.5 (11.0) years, 59.5% had diabetes, and 87.7% had hypertension. The mean CVR for the cohort was 2.7 (1.6) %/mmHg, with 42.9% having a CVR < 2.0%/mmHg, consistent with impaired CVR. The maximum drop in cerebral oxygen saturation was a decrease of 5.9% (2.8) and overall decline was 2.2% (2.5). A lower CVR was associated with greater drop and overall decline in cerebral oxygen saturation during HD ($p = 0.01$ for both). This relationship was strengthened when accounting for changes in blood pressure during HD.

Conclusions: Lower CVR is associated with decline in cerebral perfusion during HD. This measurement may be able to help identify patients who are at highest risk for cerebral ischemic injury during HD and help understand the pathophysiology of intradialytic cerebral hypoperfusion.

Funding: NIDDK Support

SA-PO417

Change of Central Venous Oxygen Saturation during Hemodialysis: A Real-Time Window into Intradialytic Hemodynamics

Andrea Nandorine Ban,[1] Vincent Filardi,[1] Lin-Chun Wang,[1] Xiaoling Ye,[1] Peter Kotanko,[1,2] Hanjie Zhang.[1] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Low central venous oxygen saturation ($ScvO_2$) is associated with morbidity and mortality in hemodialysis (HD) patients. However, the exact dynamic of $ScvO_2$ during HD remains unknown.

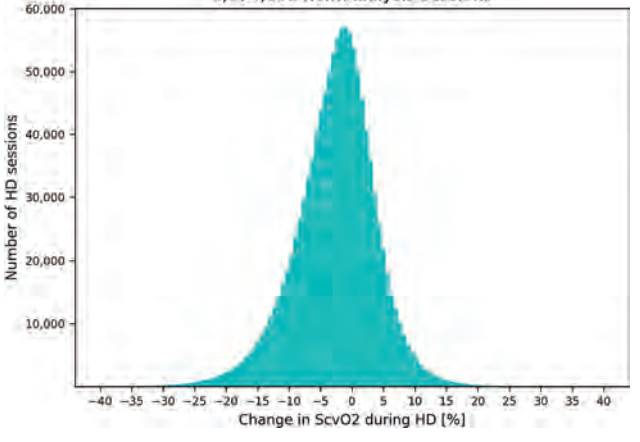
Methods: In patients with central venous catheter (CVC) as vascular access, we used the Crit-Line monitor (CLM; Fresenius Medical Care, Waltham, MA) to record $ScvO_2$ every 10 seconds. Data were uploaded to the cloud in real-time. We extracted CLM data between 1/14/2021, and 7/30/2023. Per Fick's principle, $ScvO_2$ is determined by the upper body blood flow (UBBF), arterial oxygen saturation (SaO_2) and oxygen content (1.34×Hgb), and the upper body oxygen utilization ($utilO_2$) as follows: $ScvO_2 = SaO_2 - (100 \times utilO_2) / (1.34 \times Hgb \times UBBF)$. For the derivation of this equation see Rosales et al. (Blood Purif, 2018). $ScvO_2$ at HD start is calculated as the mean $ScvO_2$ between minutes 5 and 20. $ScvO_2$ at the HD end is calculated as the mean $ScvO_2$ in the last 5-20 minutes. We dropped the treatments with less than 5 minutes measurements either at the beginning or at the end of the session.

Results: After data cleaning, our analytic cohort comprised over 1 million HD sessions in more than 31,000 patients with CVC. Average $ScvO_2$ at the beginning of the HD session was 64.7±8.3% and at the end 62.1±9.5%, indicating a mean intradialytic $ScvO_2$ decline of 2.65% (95% CI: 2.63 to 2.66) (Fig. 1).

Conclusions: Our results show a drop of $ScvO_2$ during HD. We hypothesize that an intradialytic decline of cardiac output, and consequently also of UBBF, is the predominant factor leading to the drop in $ScvO_2$. The goal of future research is to correlate $ScvO_2$ changes with clinical outcomes. Monitoring $ScvO_2$ during HD could provide real-time insights into intradialytic hemodynamics and may eventually result in improved HD procedures.

Funding: Commercial Support - Renal Research Institute, New York, NY, a wholly owned subsidiary of Fresenius Medical Care.

Figure 1



SA-PO418

Effect of Hemodialysis on Hemoglobin Oxygen Affinity

Shilpa Sharma,[1] Isidro B. Salusky,[1] Tomas Ganz,[1] Joachim H. Ix.[2] *[1]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [2]University of California San Diego, La Jolla, CA.*

Background: Hemoglobin (Hg) changes its affinity for oxygen (O_2) binding depending on ambient O_2 tension, acid/base status, 2,3 diphosphoglycerate (2,3 DPG) and other factors. 2,3 DPG is a key regulator of O_2 affinity within red blood cells and its levels are affected by blood phosphate. P50 is a marker of O_2 availability in tissues- A P50 reduction indicates increased Hg:O_2 affinity, decreased O_2 release and worsening tissue hypoxia. We measured P50 changes during hemodialysis (HD) and explored their predictors.

Methods: Venous blood gas, and other laboratory parameters were measured pre and post HD in 18 stable maintenance HD patients. We analyzed patients with tunneled dialysis catheters to avoid arterio-venous mixing. Associations of P50 with laboratory parameters and demographics were examined using linear regression models.

Results: Mean age was 72, 89% were male, and median dialysis vintage was 2.5 (IQR 0.9, 3.5) years. P50 levels decreased from a mean (±SD) of 27.1±0.9 mmHg to 26.2±0.7 mmHg during HD (**Figure**; $P<0.001$). Among 12 predictors evaluated, only higher baseline serum phosphate, and greater reductions in phosphate during HD were the predictors of P50 change (**Table**).

Conclusions: The HD procedure induces consistent reductions in P50, increasing Hg:O_2 affinity. The magnitude of mean P50 change was large – similar to that observed among Mt. Everest climbers (1). This observation provides a new potential mechanism leading to tissue hypoxia during HD. P50 changes were strongly associated with phosphate changes. Future studies should determine if intra-dialytic phosphate repletion may ameliorate tissue hypoxia and its adverse cardiac consequences in HD patients. Reference (1) Red cell function at extreme altitude on Mount Everest. *J Appl Physiol* 56: 109–116, 198 PMID: 6693310

Funding: Veterans Affairs Support

Figure: Change in P50 during hemodialysis. Colored lines show reduction between pre and post hemodialysis in individual patients. Black lines indicate range and median in the groups.

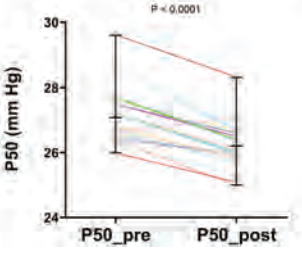


Table: Predictors associated with P50 change during hemodialysis

Predictors (per 1SD increase)	B coefficient (95% CI)
Age, per year	-0.19 (-0.41, 0.18)
Male sex	-0.19 (-1.12, 0.74)
Caucasian race (reference = AA)	0.32 (-0.26, 0.91)
Diabetes mellitus	-0.2 (-0.79, 0.39)
Urea reduction ratio, %	-0.23 (-0.51, 0.03)
Ultrafiltration, ml	0.14 (-0.15, 0.43)
Pre-dialysis serum phosphate (per mg/dL higher)	**0.29 (0.03, 0.55)***
Serum phosphate reduction during HD (per mg/dL reduction)	**0.28 (0.02, 0.55)***
Hemoglobin (pre-dialysis)	0.02 (-0.28, 0.33)
pH change during HD (per pH unit reduction)	-0.23 (-0.51, 0.04)
Dialysate Calcium	0.10 (-0.19, 0.41)
Dialysate Bicarbonate	0.14 (-0.15, 0.43)

* Indicates p<0.05

SA-PO419

In Patients on Hemodialysis, Relative Blood Volume Ranges Related to Improved Survival Are Associated with Increased Volume Reductions in Vascular and Interstitial Spaces

Felix J. Meigel,[1] Kevin Ho,[2] Peter Kotanko,[3,4] Doris H. Fuertinger.[1] *[1]Fresenius Medical Care AG, Bad Homburg, Germany; [2]Fresenius Medical Care Holdings Inc, Waltham, MA; [3]Renal Research Institute, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Observational research has identified in-target relative blood volume ranges (iRBV) that are associated with improved hemodialysis (HD) patient survival [1]. Employing an in-silico approach, we investigated differences in fluid removal between virtual patients (avatars) achieving RBV either within or above these iRBV ranges.

Methods: We generated 10,694 avatars based on real-world data from HD patients in an anonymized dialysis database (Apollo Dial DB). Data comprised weight, sex, treatment duration, and ultrafiltration volume. Pre-HD blood volume (Nadler formula) and fluctuating plasma refill rate (PRR) profiles were created to be statistically in line with published data [1,2]. Assuming constant ultrafiltration rates (UFR), we computed RBV profiles for each avatar. We compared the 'in-target' avatar group (RBV values within iRBV) with the 'above-target' group (RBV values above iRBV ranges).

Results: In-target and above-target groups differed by post-HD weight (79.3 ± 22.3 vs 86.0 ± 23.6 kg) and sex (58% vs 67% male). The in-target group had higher UFRs compared to the above-target group [median (IQR): 10.1 (8.2, 11.6) vs 7.1 (5.4, 9.0) ml/kg/h]. In the in-target group, volume reduction rates were increased in both vascular [2.5 (2.2, 2.9) vs. 1.2 (0.8, 1.5) ml/kg/h] and interstitial (PRR) spaces [7.5 (5.7, 9.0) vs. 5.9 (4.3, 7.8) ml/kg/h].

Conclusions: Volume reduction was greater in vascular and interstitial spaces in the in-target group compared to the above-target group. The increased blood volume reduction does not appear to translate to higher intradialytic hypotension rates in the in-target group [1]. **References:** [1] P. Preciado et al., 'All-cause mortality in relation to changes in relative blood volume during hemodialysis', *Nephrol Dial Transplant* (2019) [2] C. Wang et al., 'Plasma Refill Rate: A potential hemodynamic marker of intradialytic hypotension during hemodialysis', *ASN Kidney Week Abstract: PO1058* (2020)

Funding: Commercial Support - Fresenius Medical Care

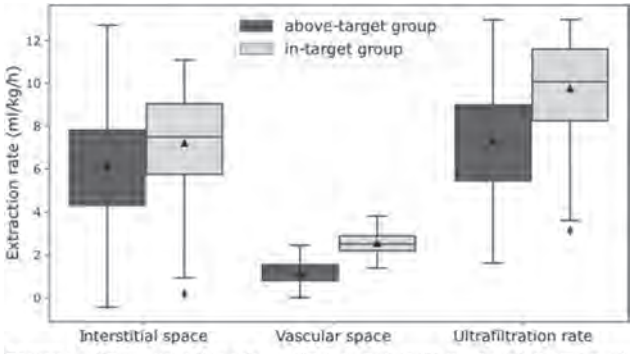


Figure 1: Volume reduction rates in the in-target (light gray) and above-target (dark gray) groups.

SA-PO420

Relationship between Fluid Overload and Anemia in the US Hemodialysis Population

Lin-Chun Wang,[1] Lemuel Rivera Fuentes,[1] Ariella E. Mermelstein,[1] Hanjie Zhang,[1] Ulrich Moissl,[3] Jochen G. Raimann,[1] Stephan Thijssen,[1] Frank van der Sande,[4] Jeroen Kooman,[4] Peter Kotanko.[1,2] [1]*Renal Research Institute, New York, NY;* [2]*Icahn School of Medicine at Mount Sinai, New York, NY;* [3]*Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany;* [4]*Maastricht Universitair Medisch Centrum+, Maastricht, Netherlands.*

Background: Current guidelines do not consider fluid overload (FO) when treating anemia in patients on hemodialysis (HD). Fluid status can be quantified using bioimpedance spectroscopy (BIS). We aimed to explore the association between FO and hemoglobin (Hgb) levels.

Methods: Pre-HD FO was assessed once per patient by BIS (Body Composition Monitor, Fresenius Medical Care, Germany). For each treatment within ±30 days from the BIS measurement, we calculated the pre-HD FO by assuming that differences in pre-HD body weight were equivalent to variations in FO. We built linear mixed effects models with Hgb as the dependent and FO as the independent variable. Inflammation was considered and adjusted with neutrophil-to-lymphocyte ratio (NLR). Patients were further divided into 3 groups according to fluid status (fluid depleted: <-1.1 l; normal hydrated: -1.1–1.1 l; fluid overloaded: >1.1 l).

Results: We studied 169 patients (61 years; 60% male), 78% were treated with erythropoietin stimulating agents (ESA). Hgb was inversely associated with increasing FO in the overall population [slope estimate -0.16 (95% CI: -0.20 to -0.12) g/dl per 1L of FO, P < 0.0001] (**Fig. 1a**). While significant in cohorts both with and without ESA, this effect was more pronounced in patients who did not receive ESA [slope estimate -0.20 (-0.30 to -0.095) g/dl per 1l of FO] (**Fig. 1b and 1c**). Adjustments for NLR did not alter the results. The comparison between the 3 sub-groups is shown in **Fig. 2**.

Conclusions: Hgb is inversely associated with FO in HD patients. While ESA administration mitigates the hemodilution effect, FO remains the main contributor to low Hgb. The present study showed that fluid status should be considered in the anemia management of patients on HD.

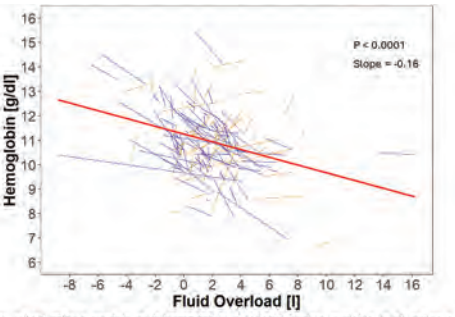


Figure 1a. Linear mixed effects models with hemoglobin as the dependent variable in all patients

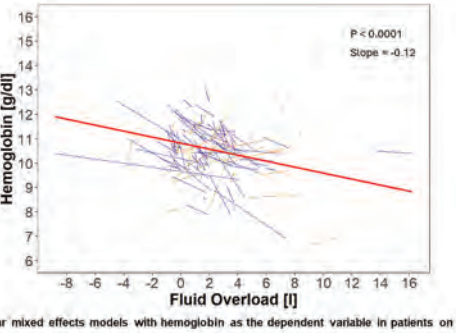


Figure 1b. Linear mixed effects models with hemoglobin as the dependent variable in patients on ESA

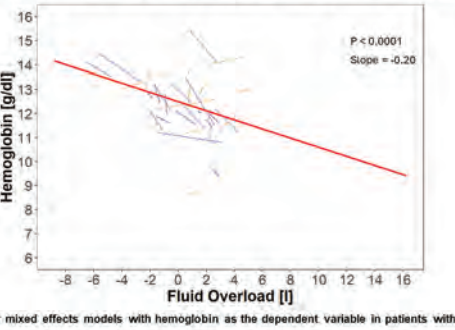


Figure 1c. Linear mixed effects models with hemoglobin as the dependent variable in patients without ESA

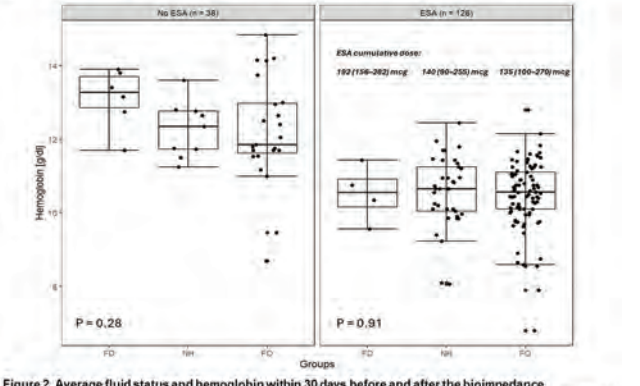


Figure 2. Average fluid status and hemoglobin within 30 days before and after the bioimpedance spectroscopy measurement. ESA, Erythropoiesis-Stimulating Agents; FD, fluid depletion; NH, normal hydration; FO, fluid overload. Majority of patients on methoxy polyethylene glycol-epoetin beta are shown on the ESA plot; cumulative doses are expressed in median (Q1-Q3). ANOVA was used to assess differences between groups.

SA-PO421

Impact of Anemia on Echocardiographic Parameters in Asymptomatic Patients with CKD on Hemodialysis

Paola Gomez-Aviles,[1,2] Pavel Martinez-Dominguez,[5] José R. Gómez,[6] Marianela Rodney,[4] Mario Jimenez Hernandez.[3,1] *[1]Universidad de las Americas Puebla, Cholula, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [3]Hospital Universitario de la Benemerita Universidad Autonoma de Puebla, Puebla, Mexico; [4]Instituto Cardiorenal de Puebla, Puebla, Mexico; [5]Instituto Nacional de Cardiologia Ignacio Chavez, Ciudad de Mexico, Mexico; [6]Hospital Angeles de Xalapa, Xalapa, Mexico.*

Background: Anemia and cardiac abnormalities play a crucial role in the complications associated with chronic kidney disease (CKD). However, there is insufficient information regarding the impact of anemia on cardiovascular outcomes

Methods: A cross-sectional multicenter study of hemodialysis patients with CKD was conducted. Data was collected from electronic medical records, cardiac function was assessed with echocardiography. Spearman rank correlation analysis and linear regression models adjusted for potential confounding variables were performed to assess anemia and cardiovascular remodeling. A p-value < 0.05 was considered statistically significant.

Results: Among the 124 individuals included (median age: 48 years), groups were divided by hemoglobin (Hb) level in non/mild anemia (Hb >10 mg/dL) and moderate/severe anemia (Hb <9.9 mg/dL) (Table). The moderate/severe anemia group had increased left ventricular (LV) posterior wall thickness (11mm vs. 10mm), increased left atrial (LA) volume (39 mL/m2 vs. 35 mL/m2), and decreased left ventricular ejection fraction (LVEF) (55% vs. 60%). Negative correlations (Figure) were found between Hb levels and LV posterior wall thickness (r= -0.22, p=0.013) and LA volume (r= -0.18, p=0.038). Linear regression models indicated a positive association between Hb and LVEF, and negative associations between Hb and LA volume, LV posterior wall thickness, and septum thickness.

Conclusions: Anemia degree was associated with multiple echocardiographic parameters, revealing complex interactions. This study highlights the importance of further prospective research to improve early identification and stratification of anemia in CKD patients to reduce subsequent cardiac complications.

Characteristic	Overall, N = 124[1]	Non/mild, N = 74[1]	Moderate/Severe, N = 50[1]	p-value[2]
Age	48 (34, 63)	53 (35, 66)	44 (32, 56)	**0.028**
Female Sex	58 (47%)	26 (35%)	32 (64%)	**0.002**
LV Posterior Wall	10.60 (9.00, 12.00)	10.00 (9.00, 12.00)	11.00 (10.00, 12.10)	**0.027**
LA Volume	36 (29, 48)	35 (26, 43)	39 (31, 55)	**0.004**
LVEF	59 (53, 63)	60 (56, 64)	55 (50, 61)	**0.013**

SA-PO422

Association of Erythropoiesis-Stimulating Agent Dose and Cardiac Magnetic Resonance Imaging Parameters in Patients Undergoing Hemodialysis

Armida Lefranc Torres,[1,2] Glenn M. Chertow,[3] Finnian R. McCausland.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Stanford University School of Medicine, Stanford, CA.*

Background: Erythropoiesis-stimulating agents (ESAs) are commonly prescribed to patients on hemodialysis (HD) to treat anemia; however, ESA use to target higher vs. lower hemoglobin has been linked with adverse cardiovascular (CV) outcomes. Using data from the Frequent Hemodialysis Network (FHN) Daily Trial, we explored the association of ESA dose with MRI metrics of cardiac structure and function.

Methods: Among patients with available baseline and 12-month MRIs (n=184), random effects linear regression models were fit to explore the association of mean weekly ESA dose (≤5000, >5000-≤20000, >20000 EPO equivalent units) with cardiac MRI parameters on a per-visit basis, including left ventricular (LV) and right ventricular (RV) end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), LV mass (LVM), and LV mass index (LVMI). Models were adjusted for age, sex, designated race, BMI, randomized treatment, access, pre-HD systolic BP, heart failure, diabetes, hypertension, residual urea clearance (0, ≤1, >1 to 3, >3 ml/min), ultrafiltration rate, ACE inhibitor or ARB use, hemoglobin, phosphate, dialysis vintage (<2, 2-5, >5 years), and eKt/V_{urea}.

Results: In adjusted models, compared with an ESA dose of ≤5000 U per week, the highest category was significantly associated with 12.7 (95%CI 2.2, 23.1) g higher LVM, 6.6 (95%CI 1.1, 12.0) g/m2 higher LVMI, 8.4 (95%CI 0.0, 16.8) mL higher LVSV, and 13.7 (95%CI 0.8, 26.6) mL higher LVEDV. No significant differences were observed with LVESV, LVEF, or any of the RV parameters (Table 1).

Conclusions: After adjusting for an array of potential confounders, higher mean weekly ESA dose was associated with significantly higher LVM, LVMI, LVEDV, and LVSV in patients receiving conventional and frequent HD. Future studies are needed to identify the mechanism(s) responsible for these associations and whether these findings, if directly related to ESAs, can be ameliorated or reversed.

Funding: NIDDK Support

Outcome	Weekly ESA dose (EPO equivalent units) ≤5,000	>5,000 – ≤20,000	>20,000
LVM, g	Ref	2.0 (-4.8, 8.9)	12.7 (2.2, 23.1)
LVMI, g/m²	Ref	1.4 (-2.1, 5.0)	6.6 (1.1, 12.0)
LVEDV, mL	Ref	3.9 (-4.7, 12.4)	13.7 (0.8, 26.6)
LVESV, mL	Ref	-0.1 (-6.2, 6.0)	5.0 (-4.1, 14.1)
LVSV, mL	Ref	4.0 (-1.9, 9.8)	8.4 (0.0, 16.8)
LVEF, %	Ref	1.2 (-1.0, 3.4)	1.3 (-1.9, 4.4)
RVEDV, mL	Ref	-1.0 (-12.3, 10.2)	9.8 (-6.3, 25.9)
RVESV, mL	Ref	-1.9 (-9.5, 5.7)	6.9 (-3.9, 17.7)
RVSV, mL	Ref	0.7 (-5.7, 7.1)	2.9 (-6.0, 11.7)
RVEF, %	Ref	0.2 (-2.3, 2.7)	-0.9 (-4.3, 2.5)

SA-PO423

Changes in Fluid Overload during the First 6 Months of Dialysis among More than 13,000 Patients

Melanie Wolf,[1] Linda Ficociello,[2] Meijiao Zhou,[2] Len A. Usvyat,[2] Stefano Stuard,[1] Jeffrey L. Hymes,[2] Franklin W. Maddux.[2] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care, Waltham, MA.*

Background: Fluid overload (FO) is a recognized risk factor for mortality in dialysis patients; however, less has been reported on factors related to changes in FO. Whole-body bioimpedance spectroscopy (BIS) has been validated for hydration assessment. We used Body Composition Monitor (BCM) data, a whole-body BIS, to evaluate changes in the degree of FO during the first 6 months of hemodialysis (HD) or hemodiafiltration (HDF) and characteristics associated with those changes.

Methods: Data was extracted from the global anonymized dialysis database, Apollo Dial DB. All patients with 2 BCM measurements separated by ~6 months, with the first being ≤90 days after HD/HDF start, were included. FO was dichotomized at ≥2.5L overhydration (OH) or at ≥15%/≥13% (for men and women, respectively) OH adjusted for extracellular water (OH/ECW). The patients were grouped into four groups (FO-FO, FO-No overload (NO), NO-FO, and NO-NO) by change in OH in liters (OH-L) and OH relative to ECW (OH-%) between these two measurements.

Results: A total of 13,221 adult HD/HDF patients were included who started dialysis treatment in 2018 or 2019. Baseline characteristics by change in fluid status (OH-L and OH-%) are shown in table 1. There was consistency between both methods of FO definition. Among patients starting with FO (n=8,147/8,354), 40%/37% were not FO at 6 months, for OH-L and OH-%, respectively. The two groups with FO at 6 months, were on average, older and diabetes was more prevalent.

Conclusions: In this first descriptive analysis, we observed improvement in many patients' fluid status within the first 6 months after initiating HD/HDF. Further research is needed to evaluate whether improvement in FO is associated with better patient outcomes.

Funding: Commercial Support - Fresenius Medical Care

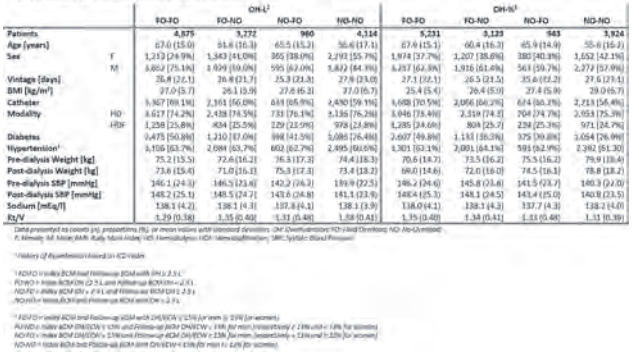


Table 1: Baseline Characteristics by change in fluid status (500 characters)

		OH-L[2] FO-FO	FO-NO	NO-FO	NO-NO	OH-%[3] FO-FO	FO-NO	NO-FO	NO-NO
Patients		4,575	1,772	960	4,114	4,231	1,123	643	3,924
Age [years]		67.0 (15.0)	61.6 (16.3)	65.5 (15.2)	56.6 (17.1)	67.6 (15.1)	60.4 (16.7)	65.9 (14.9)	55.6 (16.2)
Sex	F	1,213 (26.9%)	1,343 (41.0%)	365 (38.0%)	2,292 (55.7%)	1,974 (37.7%)	1,207 (38.6%)	380 (40.3%)	1,652 (42.1%)
	M	3,662 (73.1%)	1,029 (59.0%)	595 (62.0%)	1,822 (44.3%)	4,257 (62.3%)	1,916 (61.4%)	563 (59.7%)	2,272 (57.9%)
Vintage [days]		26.8 (22.1)	26.8 (21.7)	25.3 (23.3)	27.9 (23.0)	27.1 (22.1)	26.5 (21.5)	25.6 (22.2)	27.6 (23.1)
BMI [kg/m²]		27.0 (5.7)	26.1 (5.9)	27.8 (6.2)	27.0 (6.7)	25.4 (5.4)	26.4 (5.9)	27.4 (5.9)	29.0 (6.7)
Catheter		1,367 (29.1%)	2,301 (56.0%)	633 (65.9%)	2,490 (59.9%)	1,698 (70.5%)	2,056 (64.2%)	674 (65.2%)	2,213 (56.4%)
Modality	HD	3,617 (74.2%)	2,438 (74.5%)	733 (76.1%)	5,136 (76.2%)	3,946 (73.4%)	2,319 (74.2)	704 (74.7%)	3,953 (75.3%)
	HDF	1,258 (25.8%)	834 (25.5%)	229 (23.9%)	978 (23.8%)	1,285 (24.6%)	804 (25.7)	234 (25.3%)	971 (24.7%)
Diabetes		3,475 (50.8%)	1,210 (37.0%)	998 (41.5%)	5,088 (76.4%)	2,607 (49.8%)	1,133 (36.5%)	375 (39.8%)	3,054 (76.9%)
Hypertension[1]		3,105 (63.7%)	2,084 (63.7%)	602 (62.7%)	2,495 (60.6%)	3,301 (63.1%)	2,001 (64.1%)	591 (62.9%)	2,362 (61.3%)
Pre-dialysis Weight [kg]		75.2 (15.5)	72.6 (16.2)	76.3 (17.3)	74.4 (18.3)	70.6 (14.7)	73.5 (16.2)	75.5 (16.2)	79.9 (19.4)
Post-dialysis Weight [kg]		73.6 (15.4)	71.0 (16.1)	75.3 (17.1)	73.4 (18.2)	68.0 (14.6)	72.0 (16.0)	74.5 (16.1)	78.8 (18.2)
Pre-dialysis SBP [mmHg]		146.1 (24.1)	146.5 (23.6)	142.2 (26.2)	139.9 (22.5)	146.2 (24.6)	145.8 (23.6)	141.5 (23.7)	140.3 (22.0)
Post-dialysis SBP [mmHg]		148.2 (25.1)	148.5 (24.7)	143.6 (24.8)	141.1 (23.9)	148.4 (25.3)	148.1 (24.5)	143.4 (25.0)	140.8 (23.5)
Sodium [mEq/l]		138.1 (4.2)	138.1 (4.3)	137.8 (4.1)	138.1 (3.9)	138.0 (4.1)	138.1 (4.3)	137.7 (4.3)	138.2 (4.0)
Kt/V		1.29 (0.38)	1.35 (0.40)	1.31 (0.44)	1.38 (0.41)	1.35 (0.40)	1.34 (0.41)	1.33 (0.44)	1.31 (0.39)

SA-PO424

Rapid Fluid Assessment in Patients on Hemodialysis Using Portable Single-Sided Magnetic Resonance Sensor

Won-Seok Heo,[1] Sydney Sherman,[1,2] Alexa S. Zammit,[1,3] Houda Bouchouari,[4,5] Haley Higginbotham,[1,6] Oliver Nicholls,[1] Sahir Kalim,[4,5] Sagar U. Nigwekar,[4,5] Michael J. Cima.[1,3] *[1]Massachusetts Institute of Technology Koch Institute for Integrative Cancer Research, Cambridge, MA; [2]Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA; [3]Massachusetts Institute of Technology Department of Materials Science and Engineering, Cambridge, MA; [4]Massachusetts General Hospital Nephrology Division, Boston, MA; [5]Harvard Medical School, Boston, MA; [6]Massachusetts Institute of Technology Department of Mechanical Engineering, Cambridge, MA.*

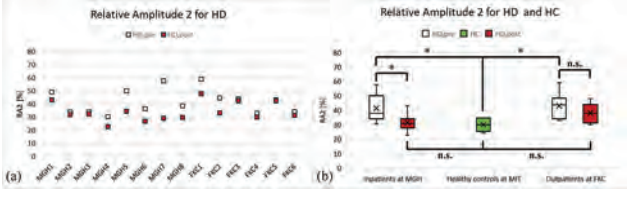
Background: Fluid overload poses health risks caused by hypertension among hemodialysis (HD) patients. Current fluid assessment methods, such as urine or blood screening and bioimpedance, are not sensitive to early-stage changes in volume. This study presents a noninvasive, rapid, and cost-effective method for assessing fluid status using a portable single-sided nuclear magnetic resonance (NMR) sensor, enabling multicomponent T2 relaxometry analysis of intra- and extra-cellular fluid in skeletal muscle tissues.

Methods: The NMR sensor (22×18×11 cm) consists of 0.5 in cube N52 Nd magnets, creating a homogeneous 0.2 T magnetic field 8 mm above the surface at 8.4 MHz. A CPMG pulse train is transmitted via a single surface transceiver coil, seated on a 0.5 mm AlN layer for heat dissipation. The clinical study measured T2 from end-stage renal disease (ESRD) patients' calves undergoing HD, excluding those with obvious signs of edema, compared to healthy controls (HC). T2 relaxation was modeled as tri-exponential decay using a nonlinear least squares optimization method to obtain relative amplitude 2 (RA2).

Results: We observed a decrease in RA2 from pre- to post-HD in every individual case. Population average RA2 values were approximately 41.5% and 31.5% for pre- and post-HD at MGH (p = 0.021), 43% and 38% for pre- and post-HD at Fresenius Kidney Care (FKC), and 30% for HC at MIT, showing lower RA2 compared to both pre-HD measurements at MGH (p = 0.014) and FKC (p = 0.022) (Fig. 1). Additional consented HD outpatients and HC volunteers will be measured in the coming months to support our findings.

Conclusions: This work demonstrates quantitative point-of-care volume status evaluation using an NMR sensor in vivo, providing noninvasive, real-time monitoring of fluid loss during dialysis by performing multicomponent T2 relaxometry localized to skeletal muscle, reducing system complexity and cost compared to MRI. These findings suggest that bedside NMR can effectively identify fluid overload or dehydration in ESRD patients and other hypervolemic conditions.

Funding: Other NIH Support - R01EB031813, NIH, NMR-Based Rapid Fluid Assessment: Device Design and Signal Processing



RA2 for 8 and 6 HD at MGH and FKC, respectively, and 7 HC at MIT.

SA-PO425

A Novel Approach to Monitoring Fluid Status of Patients on Maintenance Hemodialysis Using Remote Dielectric-Sensing Technology

Qiuling Fan. *Department of Nephrology, Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.*

Background: Remote Dielectric Sensing (ReDS) is a non-invasive radar wave lung water monitoring instrument, the ReDS technology allows quantification of lung fluid content. Due to its high efficiency and convenience, this instrument can help in the management of patients with heart failure. However, the role of the ReDS technology in predicting MHD patient's fluid status is unclear.

Methods: Patients undergoing MHD at the hemodialysis center of Shanghai General Hospital from March 2023 to April 2023 were examined using the ReDS technology before and after dialysis, and related clinical data were collected. Our objective is to evaluate the correlation between ReDS and BNP, and to analyze the significance of ReDS detection data through case studies using limited data;

Results: According to the inclusion and exclusion criteria, there were 31 patients with ReDS data before and after translucency, including 18 males (58%) and 13 females (42%), aged 19-83 years, with an average age of (59.8±15.6) years. There were 84 patients with ReDS data after translucency, including 48 males (57%) and 36 females (43%), aged 19-83 years, with an average age of (62.7±14.2) years. All selected patients have pre-treatment BNP data. The results showed a positive correlation between pre dialysis ReDS and BNP, and there was no direct relationship between the difference in pre-dialysis and post-dialysis ReDS and net ultrafiltration volume. We analyzed different cases and inferred that patients with pre dialysis ReDS greater than 36% may have excessive weight gain during the dialysis interval. For patients with ReDS greater than 36% after penetration, titration is required to reduce dry weight; If the ReDS after penetration is less than 24%, the ultrafiltration amount needs to be adjusted, and the dry body weight needs to be increased by titration; MHD patients with ReDS less than 24% before penetration should be analyzed based on their nutritional status and specific circumstances.

Conclusions: Our center's research preliminarily confirms that ReDS data has a certain guiding role in capacity load management for MHD patients. Further exploration is needed, such as the specific significance of the difference in ReDS before and after penetration.

SA-PO426

Utility of Point-of-Care Ultrasonography (POCUS) in Guiding Clinical Decision-Making

Kevin Zhang, Raphael J. Rosen. Stamford Health Nephrology. *Stamford Hospital, Stamford, CT.*

Introduction: Point-of-care ultrasound (POCUS) refers to ultrasound utilized by healthcare providers at the bedside for immediate clinical decisions, in contrast to consultative ultrasonography. POCUS is becoming more utlized in routine clinical practice across various medical specialties. In nephrology, POCUS has myriad applications, including rapid assessment of genitourinary tract, assessing volume and dialysis access, and differentiating causes of hypotension. POCUS also has utility across the spectrum of patient care, ranging from outpatient to inpatient to the dialysis unit. We present a case in which POCUS was used in the dialysis unit to personalize care and avioid harm.

Case Description: A 62-year-old woman with ESRD from HTN/DM on hemodialysis, CAD, and PVD developed progressive dyspnea. Echocardiogram demonstrated preserved LVEF but decreased RV function and elevated estimated PASP. Her cardiologist diagnosed presumed volume overload and recommended to decrease her target weight. The patient's dry weight was decreased but this resulted in worsening intradialytic hypotension and cramping. Nephrologist-performed POCUS in the dialysis unit demonstrated an IVC diameter < 2.1 cm with over 50% collapse with inspiration, suggesting low right atrial pressure. While RV dysfunction can cause plethoric IVC even without hypervolemia, on the contrary, small and collapsible IVC in this setting was felt to be reliable evidence of hypovolemia. The patient's estimated dry weight was increased, and intradialytic hypotension improved. A right heart catheterization demonstrated a right atrial pressure of 3 mmHg, a pulmonary artery pressure of 75/26 and a PCWP of 7mmHg, indicating normal LV filling pressures. She had no evidence of autoimmune etiologies, primary pulmonary etiology, or pulmonary embolism. Her diagnosis is presumed WHO type V pHTN from dialysis and is scheduled for follow up at a pHTN referral center.

Discussion: The integration of POCUS into nephrology practice provides additional tool for rapid and personalized patient assessment. In this case, nephrologist-performed POCUS in the dialysis unit mitigated harm by correcting an inappopriate dry weight reduction. Furthermore, an understanding of the strengths and limitations of cardiac ultrasonography avoided excess reliance on other providers' assessments, in this case a presumptive dry weight reduction based on an echocardiographic finding of pulmonary hypertension.

SA-PO427

Using Point-of-Care Ultrasonography (POCUS) in Volume Assessment in Patients on Hemodialysis

Leanna V. Ritchie, Michael A. Mao. *Mayo Foundation for Medical Education and Research, Jacksonville, FL.*

Background: The POCUS (point-of-care ultrasound) has been well studied in its superior ability to assess high volume status in the heart and lungs, however is not a standard of practice for volume assessment in dialysis patients. Hypervolemia in the end stage kidney disease (ESKD) population is associated with increased mortality and hospitalizations. We hypothesized that POCUS would identify hypervolemia with increased accuracy and safety to reduce hypervolemia complications compared to traditional physical exam.

Methods: This observational cohort study included 62 participants: 15 patients underwent POCUS and 45 patients had volume management by traditional physical exam. Hypervolemia criteria by POCUS included: IVC with < 50% diametric collapsibility, or the detection of at least 3 confluent B lines in >2/6 lung zones with at least one zone positive bilaterally. If exam met criteria for hypervolemia, then estimated dry weight (EDW) was adjusted to a delta of negative 0.5 kg for subsequent dialysis sessions. A traditional clinical physical exam was performed in all patients to assess for hypervolemia. Patients followed for total 6 months including 3 months post intervention for hospitaliztions, heart failure, medication changes, hypotension and death.

Results: In the POCUS group: 100% (15/15) met criteria for hypervolemia on initial POCUS exam and had their EDW adjusted after initial POCUS. However, 7/15 (46.67%) participants demonstrated persistent hypervolemia via second POCUS and

underwent a second EDW adjustment. Physical exam identified hypervolemia in 5/15 (33.33%) participants. The average length of POCUS exam decreased from 7.2 minutes to 6.1 minutes on first and second POCUS assessments, respectively. There were no hospitalizations related to hypervolemia in any of the POCUS participants compared to >15% of hospitalization related to complications of hypervolemia in control group.

Conclusions: The POCUS exam is efficient, timely and easy to learn. The use of POCUS is a safe adjunct to clinical volume assessment in the ESKD popoulation to reduce hypervolemia, hospitalization and improve quality of life.

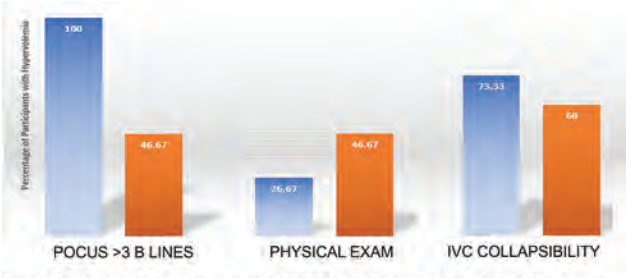


Figure 1. Comparing hypervolemia measurement by POCUS, physical exam and IVC collapsibility. Blue indicates POCUS Week 1. Orange indicates POCUS Week 3..

SA-PO428

Comparison between Lung Ultrasonography and Clinical Assessment for Volume Control in Patients on Chronic Hemodialysis

Sawinee Kongpetch. *Khon Kaen University, Nai Mueang, Thailand.*

Background: The management of volume overload to achieve dry weight improves hypertension and survival in hemodialysis patients. Several techniques are used for volume assessment, however, interventional studies with fluid-guided management are scarce. We aimed to compare between lung ultrasonography (LUS) and clinical assessment to guide volume reduction for blood pressure (BP) control.

Methods: The randomized control trial was conducted in chronic hemodialysis patients between December 2018 and March 2023. The study group was performed LUS every week for total 8 weeks to assess volume status and reduction of dry weight 0.05 and 0.1 kg/10-kg body weight if LUS score 16-30 and > 30, respectively. The control group was reduced dry weight as clinically indicated. Group-blindly investigators measured bioelectrical impedance analysis (BIA) in all participants at the start and finish times of study to assess the optimal dry weights and these results were concealed. At weeks 4 and 8, both groups were compared BP levels, dry weight achievement, cardiothoracic ratio evaluated by chest x-ray, number of antihypertensive drugs, N-terminal-pro-Brain Natriuretic Peptide (NT-proBNP) levels and intradialytic complications.

Results: A total of 83 patients with a mean age of 62.6±13 years and 72.5% male were randomized into the LUS group (n=41) and the clinical group (n=42). Baseline levels of the LUS vs. clinical groups were (a) systolic BP 146±17 vs. 143±11 mmHg, (b) cardiothoracic ratio 0.57±0.06 vs. 0.53±0.06, (c) median NT-proBNP 3,758 vs. 3,607 pg/mL. At weeks 4 and 8, systolic BP adjusted with baseline levels were significantly lower in the LUS groups (weeks 4; 134±13 vs.142±16, p <0.01 and weeks 8; 137±18 vs. 143±15, p=0.01). At the end of study, the LUS group also had (a) higher proportion of participants requiring less antihypertensive drugs (60% vs. 10%, p=0.002), (b) greater percentage of median cardiothoracic ratio reduction (-1.78% vs. 0.98%, p=0.03) and (c) closer levels of optimal dry weight obtained by BIA, than the clinical group. Incidences of intradialytic complications were similar in both groups.

Conclusions: LUS was helpful in volume assessment and fluid-guided management to achieve dry weight and control blood pressure. Further larger clinical trials should be conducted to prove benefit in survival of HD patients.

Funding: Government Support - Non-U.S.

SA-PO429

Comparing Ejection Fraction (EF) Using E-point Septal Separation from Point-of-Care Ultrasonography (POCUS) vs. Standard Two-Dimensional Echocardiography (ECHO) Using the Simpson Method in Patients with Stage 5 CKD on Hemodialysis at Victoriano Luna Medical Center: A Prospective Observational Study

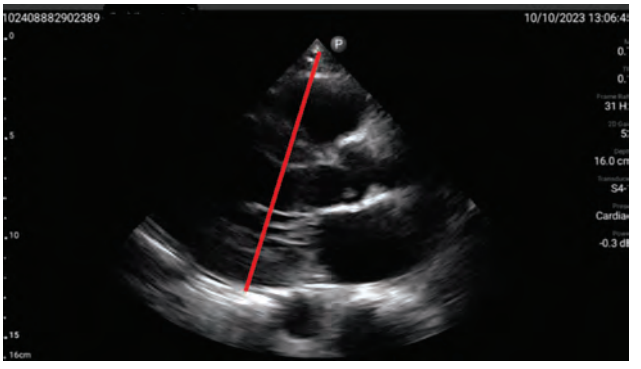
Yvonne P. Bulong. *Armed Forces of the Philippines, Quezon City, Philippines.*

Background: Patients with Chronic Kidney Disease Stage V undergoing Hemodialysis are at risk of developing cardiovascular complications including Coronary Artery Disease and Heart Failure which can be objectively evaluated through 2Dechocardiography. This study obtained the ejection fraction from POCUS through EPSS and compared to the standard 2Dechocardiography ultrasound using Simpson Method as an alternative screening test for Cardiovascular Complications.

Methods: Observational study design with prospective data collection was utilized in the study. Patient undergone both 2DECHO Ultrasound and Point of Care Ultrasound. EF was measured through Simpsons Method and E-point Septal Separation (EPSS). The difference in the mean ejection fraction between EPSS Method and Simpsons method was compared using Paired T-Test and Fischer's Exact Test and P values <0.05. Weighted kappa was used to determine the category of the EF on both methods.

Results: A total of 27 Chronic Kidney Disease Stage V patient were included. The mean EF for EPSS method is 55.4 with standard deviation of 15.4 while Simpson's Method was 59.2 with standard deviation of 16.5. Comparing the EF from the two methods, results showed that they are significantly different (t-value: -3.1995, p-value:0.0036). However, In the EF Category, both the Simpsons and EPSS has the same classification which is important in the deciding treatment of patients. Using both methods, 21 patients has preserved EF, 2 has mildly reduced EF and 4 has reduced EF. The weighted kappa is 1.000 which indicates perfect agreement between the two methods.

Conclusions: Point of Care Ultrasound using EPSS can be used as a screening method in determining the ejection fraction of patient with high risk of developing Cardiovascular Complication such as Chronic Kidney Disease Patients.



Measurement of Ejection Fraction using EPSS Method

SA-PO430

Rationale and Design of the NIH THYROID-HD Trial: A Randomized Controlled Trial of Thyroid Hormone Supplementation in Patients on Hemodialysis

Yoko Narasaki,[1] Andrea C. Daza Aguilar,[1] Alejandra Novoa Vargas,[1] Amy S. You,[1] Kamyar Kalantar-Zadeh,[2] Danh V. Nguyen,[3] Connie Rhee.[1] *[1]University of California Los Angeles, Los Angeles, CA; [2]Harbor-UCLA Medical Center, Torrance, CA; [3]University of California Irvine, Irvine, CA.*

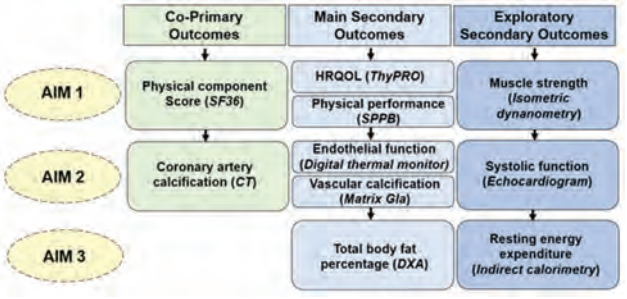
Background: Hypothyroidism is a highly prevalent yet under-recognized endocrine complication in CKD patients, affecting ~25% of those receiving dialysis. Prior evidence shows that higher TSH levels, even within the normal laboratory range, are strongly associated with impaired HRQOL and CV disease in this population. While levothyroxine is one of the most frequently prescribed medications in dialysis patients, its efficacy and safety in this population have not been well-studied.

Methods: The multi-center NIH THYROID-HD Trial is a randomized double-blind placebo-controlled trial enrolling dialysis patients with high-normal or subclinical hypothyroid range TSH levels to determine the effects of 24 weeks of levothyroxine vs. placebo on HRQOL assessed by the Short Form 36 and coronary artery calcification (co-primary endpoints). The main secondary endpoints include assessment of HRQOL measured by the ThyPRO survey, physical performance, endothelial function, vascular calcification inhibitors, and total body fat. A subcohort of patients are also undergoing exploratory endpoints of muscle strength, systolic function, and resting energy expenditure (Figure 1).

Results: The THYROID-HD Trial's enrollment target is 336 patients, based on an anticipated 10% attrition rate. Among 242 patients recruited and randomized thus far, baseline characteristics show that the mean ± SD age is 54±13 years old; 42% are female; 9%, 6%, 3%, 80%, and 3% are of Asian, Black, NHOPI, White, or Other race; 75% are of Hispanic ethnicity; and 71% vs. 29% have TSH levels in the high-normal vs. subclinical hypothyroid range.

Conclusions: The THYROID-HD Trial will determine the effects of thyroid hormone replacement on patient-reported outcomes, CV endpoints, and metabolic health in dialysis patients with high-normal or subclinical hypothyroid range TSH levels, and inform the management of this prevalent endocrine complication in ESKD patients.

Funding: NIDDK Support



SA-PO431

Altered Lactate Metabolism at Peak Exercise in Patients on Dialysis

Nolan Groninger,[1] Eliott Arroyo,[2] Heather Burney,[1] Gayatri Narayanan,[1] Sharon L. Karp,[1] Kenneth Lim.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Wake Forest University, Winston-Salem, NC.*

Background: Patients with end-stage kidney disease (ESKD) on hemodialysis commonly exhibit exercise intolerance, as reflected by decrements in oxygen uptake at peak exercise (VO_2Peak). Cardiopulmonary exercise testing (CPET) is the gold-standard for obtaining VO_2Peak and requires participants to exercise past their anaerobic threshold, leading to increased blood lactate concentrations. The purpose of this study was to compare lactate response to maximal exercise in patients with ESKD versus healthy controls.

Methods: We analyzed data from the ongoing "Comparison of the Self-Paced versus Ramp Incremental Exercise Protocols on Patients with Kidney Failure (SPARK)" trial. Participants completed CPET and capillary blood samples were taken at rest, warm-up, and every 2 minutes of exercise and analyzed for blood lactate levels. Wilcoxon tests were conducted to compare blood lactate values between patients with ESKD and healthy controls. Adjusted analysis was conducted using multiple linear regression modeling.

Results: A cohort of 10 patients with ESKD (n=4 men, mean [SD] age=49 [11] years, dialysis vintage=27 [IQR: 14-45] months) and 21 healthy controls (n=10 men, age=55 [9] years) were included in this analysis. Hemoglobin was significantly lower in ESKD patients (11.5 [1.7] g/dl) compared to healthy controls (14.3 [1.0] g/dl; P<0.001). There were no differences in age (P=0.10) or sex (P=0.99) between groups. Resting lactate levels were significantly greater in ESKD patients (1.3 [0.4] mmol/L) than in healthy controls (0.9 [0.3] mmol/L; P=0.029). Significantly, lactate levels at peak exercise were lower in ESKD patients (3.4 [2.7-4.3] mmol/L) compared with healthy controls (7.8 [7.0-9.2] mmol/L; P<0.001), even after adjusting for hemoglobin (P<0.001).

Conclusions: ESKD is complicated by lactatemia in the resting state and may in part, be a direct consequence of impaired renal clearance. The lower levels of lactate at peak exercise in patients with ESKD are reflective of impaired exercise intolerance in the anaerobic phase and indicate a reduced capacity to sustain exercise above the lactate threshold.

SA-PO432

Optimal Protocol for Cardiopulmonary Exercise Testing (CPET) in Patients on Dialysis

Nolan Groninger,[1] Eliott Arroyo,[2] Heather Burney,[1] Gayatri Narayanan,[1] Sharon L. Karp,[1] Kenneth Lim.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Wake Forest University, Winston-Salem, NC.*

Background: Patients with end-stage kidney disease (ESKD) on hemodialysis commonly present with impaired physical function which is linked to adverse outcomes including frailty, fractures, reduced quality of life, and mortality. Peak oxygen uptake (VO_2Peak) is usually obtained by standard ramp incremental testing, but this protocol may underestimate VO_2Peak. To determine the most accurate method for obtaining VO_2Peak in patients on dialysis, we sought to compare the ramp protocol with two novel CPET protocols, the self-paced (SP), and RISE (ramp incremental step exercise) that are considered alternative options to the traditional incremental ramp test.

Methods: We analyzed data from the ongoing "Comparison of the Self-Paced versus Ramp Incremental Exercise Protocols on Patients with Kidney Failure (SPARK)" study, a randomized cross-over study comparing patients on dialysis versus healthy controls. Participants completed three CPET protocols on three separate visits: 1) standard ramp 2) SP (five 2-min stages with self-selected workload) and 3) RISE. Testing was completed for patients with ESKD on a non-dialysis day. A repeated measures ANOVA test was performed to compare VO_2Peak values between each protocol.

Results: A cohort of 11 ESKD patients (n=5 men, mean [SD] age=49 [10] years, dialysis vintage=30 [IQR: 10-48] months) and 21 healthy controls (n=10 men, age=55 [9] years) participated in the study. No significant differences in sex or age were observed (P>0.05) but there was significant difference in race (P=0.003) and ethnicity (P=0.002). There was no significant difference in VO_2Peak between protocols in ESKD patients (ramp=13.5 [1.2] mL/min/kg; SP=13.2 [0.9] mL/min/kg; RISE=13.2 [0.8] mL/min/kg; P=0.77). However, there were significant differences in healthy controls (ramp=30.3 [1.4] mL/kg/min; SP=28.7 [1.4] mL/min/kg; RISE=30.9 [1.2] mL/min/kg; P=0.017). Time-varying covariates remained the same across all visits.

Conclusions: We found that the RISE protocol resulted in higher VO_2Peak averages in healthy controls, but there were no differences in VO_2Peak values between the three protocols in ESKD patients. Therefore, the ramp protocol is the most established CPET methodology and should be selected for objectively determining cardiovascular functional capacity in patients with ESKD.

SA-PO433

Associations between Physical Function Questionnaires and VO2Peak in Patients on Hemodialysis

Nolan Groninger, Drake Dillman, Gayatri Narayanan, Kenneth Lim. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Cardiopulmonary exercise testing (CPET) is well-recognized as the gold standard tool for quantifying cardiovascular functional capacity (as assessed by oxygen uptake at peak exercise, VO_2Peak). VO_2Peak is a strong predictor of survival in patients with chronic kidney disease (CKD). It is currently unknown whether physical function questionnaires can reliably predict VO_2Peak in patients with advanced CKD. Herein, we sought to assess the predictive value of the International Physical Activity Questionnaire (IPAQ) and Patient Reported Outcomes Measurement Information System (PROMIS) evaluations for VO_2Peak in patients on hemodialysis.

Methods: We analyzed data from the "Effects of long interdialytic intervals on Cardiovascular Functional Capacity (ECON)" study, a randomized crossover trial of patients on hemodialysis. All participants underwent CPET and completed questionnaires on a non-dialysis day. A total of 31 patients completed ECON, however 2 patients were excluded in this analysis due to incomplete questionnaire data. Multiple linear regression analysis was used to assess the association between IPAQ and PROMIS results with VO_2Peak.

Results: 29 patients were dichotomized based on the median VO_2Peak value of 11.3 mL/min/kg into a High group (n=15, 11 [73%] men, age=53 [11]; VO_2Peak=14.9 [12.2-16.5] mL/min/kg) and a Low group (n=14, 4 [50%] men, age=54 [12]]; VO_2Peak=10.2 [9.3-10.8] mL/min/kg). The High group had a lower BMI (26.7 [23.5-27.5] kg/m2) compared to the Low group (33.2 [27.8-38.9] kg/m2; P=0.021). No group differences were observed in age, sex, race/ethnicity, dialysis vintage, hypertension, or diabetes (all P's>0.05). The High group had a higher median number of days walked per week (P=0.037) on the IPAQ and a higher average score on the PROMIS Mobility questionnaire (P=0.006). The PROMIS Function questionnaire and all other IPAQ results were not statistically different between groups (P>0.05). The number of days walked per week (P=0.15) and PROMIS Mobility questionnaire (P=0.06) were not significantly associated with VO_2Peak after adjusting for age and sex.

Conclusions: Our results indicate that physical function questionnaires are not effective for predicting VO_2Peak in dialysis patients. CPET is therefore recommended to objectively determine cardiovascular functional capacity and exercise intolerance.

Funding: Private Foundation Support

SA-PO434

Evolution of Nutritional Status in Patients on Hemodialysis after 1 Year of Intervention by a Team of Kidney Dietitian-Nutritionists: Is It Possible to Correct Malnutrition from More Severe Stages?

Shaira Martinez Vaquera, Ascension Lupiañez-Barbero, Christian I. Alfaro Sanchez, Sonia C. Molina, Antoni B. Gil, Maria Paz Sorribes López, Teresa Martinez Sanchez. Diaverum Spain Team. *Diaverum Renal Services, Catalonia, Spain.*

Background: Given the complexity of protein energy wasting (PED) in hemodialysis (HD), prevention and treatment options are complex. There is no single treatment approach. Objective: To retrospectively evaluate the evolution of the nutritional status of HD patients.

Methods: Descriptive, retrospective and multicenter study of 130 HD patients. We performed individualized nutritional intervention by Dietitians-Nutritionists (DN) integrated in a multidisciplinary team. We collected demographic, clinical, nutritional and nutritional screening variables, MIS1 and DPE2, at baseline and one-year follow-up. Parametric and non-parametric statistics for related groups.

Results: Median age 75.77 years [65.43-83.83], time on HD 33.91 months [23.06-57.26], Charlson index 7 [5-9], BMI 24kg/m2 [21-27], LVEF 54.6%, DM 45.4%, diabetic nephropathy 22.3%, history of previous RF 30.8%, men 64.6%, non-EU origin 15.4%. In the annual follow-up, 82.3% of the patients remain active. A total of 5.4% were transplanted, 9.2% died and 3.1% were discharged. All patients receive dietary education (DE). Patients with moderate-severe malnutrition without improvement only with DE were added: 33.7% Oral nutritional supplementation (ONS) through hospital coordination, 16.8% intradialytic phosphosoda, 9.3% appetite stimulants, 7.5% food support by social services in coordination with the social work unit. An improvement in

MIS screening scores was observed (baseline 7 [5-10] vs follow-up 5 [5-7]), especially those who received ONS (baseline 10 [7-13] vs follow-up 7 [6-9]). Even more evident in patients who received ONS during the entire period evaluated (baseline 12 [9-13] vs follow-up 7 [5-9]). A progression of malnutrition was observed and, likewise, a decrease in severe malnutrition ($p \leq 0.05$).

Conclusions: Individualized dietary advice in combination with different nutritional strategies from a multidisciplinary approach contributes to improve MIS scores and reverse malnutrition in more severe stages.

Funding: Private Foundation Support

SA-PO435

Evaluation of Intradialytic Parenteral Nutrition Indication: Mirage or Reality?

Shaira Martinez Vaquera, Ascension Lupiañez-Barbero, Christian I. Alfaro Sanchez, Sonia C. Molina, Jose Luis Pizarro Leon, Teresa Martinez Sanchez, Maria Paz Sorribes López. Diaverum Spain Team. *Diaverum Espana, Madrid, Spain.*

Background: The estimated prevalence of protein energy wasting (PEW) in haemodialysis (HD) is between 28-54%, and may be even higher[1]. Different nutritional strategies are available: dietary advice by a Dietitian-Nutritionist (DN), oral nutrition (ONS) or Intradialytic parenteral nutrition (IDPN), among others[2]. The economic cost or the lack of DN in dialysis units are barriers that limit its use. Objective: To determine the prevalence of HD patients who are potential candidates for IDPN.

Methods: Descriptive, retrospective and multicentre study of 3544 patients who responded to the KDQOL-SFTMV[1,3] surveys during 2022. We analysed the generic part (SF-36), the Summative Physical (ISF) and Mental Index (ISM)[3]. We collected demographic and clinical data, used the DPE scale[4] and the expert consensus[5] as screening for PIND. We assessed normality and performed non-parametric statistics.

Results: 62.4% male, 73 years, BMI 25.8kg/m2, albumin 3.93g/dl, creatinine 6.5mg/dl, CRPn 0.98 g/kg/d, FSI 49.14 [39.58-55.69], MSI 34.88 [27.75-42.55]. 45.4% had DM, 60.9% were on dialysis with AVF and 35 months on HD [15-67]. According to DPE screening components: 33% albumin <3.8g/dl; 4.1% creatinine <3.8mg/dl; 26.3% BMI <23kg/m2; 20.8% nCRP <0.8g/kg/d. 59.2% had some degree of malnutrition. 21.3% could be candidates for NPID due to moderate-severe malnutrition. According to expert consensus: 27.4% albumin <3.8g/dl plus creatinine <8mg/dl; 3% BMI <18.5kg/m2; 14.4% CRPn <0.75g/kg/d; 0.6% weight loss> 10% in the last 6 months. Only 0.23% met at least 3 of these criteria and would be candidates for NPID. We observed association between nutritional status and quality of life (QoL) (table 1).

Conclusions: We found huge discrepancy in the prevalence of patients who were candidates for NPID according to the criteria used. The decision to provide NPID not only impacts on the clinical prognosis and QoL of the patient, but also entails relevant costs that could be avoided.

Funding: Private Foundation Support

Table 1. Characteristics of patients according to the selected nutritional screening to assess the indication of intradialytic parenteral nutrition

	Nutritional screening based on the abbreviated DPE scale 2018* N=3,401					Nutritional screening based on NPID criteria from expert group N=3,634			
KDQOL-SFTM V 1.3 Generic Part [Median (p25-p75)]	No NPID indication: Normal nutrition (n=1,367, 40.18%)	Assess indication for ONS + NPID + appetite stimulants: Mild malnutrition (n=1,289, 37.9%)	Moderate malnutrition (n=592, 17.4%)	Severe malnutrition (n=153, 3.9%)	P value	No NPID indication (n=3,526, 99.72%)	Indication for INDP (n=8, 0.23%)	P value
• SF12-PH	49.67 (40.67-56.05)	49.74 (39.12-55.52)	46.33 (38.4-53.95)	47.75 (34.84-55.02)	0.001*	49.14 (39.59-55.79)	49.84 (47.25-54.11)	NS
Physical Functioning	50 (40-55)	45 (30-55)	35 (20-45)	30 (10-50)	<0.001*	50 (30-55)	45 (37.5-46.5)	NS
Physical Role	25 (0-100)	25 (0-100)	0 (0-75)	0 (0-50)	<0.001*	25 (0-100)	75 (0-87.5)	NS
Bodily Pain	55 (42.5-90)	55 (32.5-90)	55 (32.5-77.5)	55 (32.5-77.5)	0.001*	55 (35-90)	45 (35.25-56.25)	NS
General Health	52 (25-65)	47 (25-65)	45 (30-65)	45 (30-65)	<0.001*	50 (35-65)	51 (51.5-51.5)	NS
• SF12-MSI	36.19 (29.08-43.05)	34.99 (28.12-42.78)	32.66 (26.63-40.48)	31.79 (25.41-39.26)	<0.001*	35.42 (27.64-41.65)	38.03 (37.05-38.45)	<0.001
Mental Health	64 (52-68)	64 (52-76)	60 (52-76)	60 (48-76)	0.001*	64 (52-80)	66 (64-82)	NS
Emotional Role	100 (16.33-100)	100 (0-100)	100 (0-100)	100 (0-100)	0.001*	100 (0-100)	100 (66.66-100)	NS
Vitality	30 (20-45)	30 (20-50)	25 (20-55)	25 (20-55)	<0.001*	30 (20-50)	40 (20-47.5)	NS
Social Functioning	62.5 (50-87.5)	62.5 (50-75)	50 (37.5-75)	50 (37.5-75)	<0.001*	62.5 (50-87.5)	62.5 (43.75-81.25)	NS
CLINICAL VARIABLES								
• Albumin (g/dl)	4.07 (3.84-4.23)	3.89 (3.7-4.11)	3.64 (3.43-3.76)	3.52 (3.23-3.65)	<0.001*	3.94 (3.72-4.14)	3.42 (2.99-3.52)	<0.001
• Creatinine (mg/dl)	7.3 (6-8.65)	6.5 (5.4-7.8)	5.7 (4.7-6.9)	5.4 (4.4-6.4)	<0.001*	6.8 (5.6-8)	5.05 (4.3-6.1)	0.015
• nPCR (g/kg/d)	1.08 (0.95-1.21)	0.97 (0.85-1.12)	0.79 (0.69-1)	0.72 (0.64-0.77)	<0.001*	0.98 (0.83-1.13)	0.84 (0.57-0.89)	<0.001
• BMI (kg/m2)	27.7 (25.3-31.5)	25 (21.5-28.9)	22.5 (20.7-26.1)	21 (19.7-22.2)	<0.001*	25.6 (22.8-29.5)	18.65 (17.05-18.85)	<0.001
• >10% PP in 6m	11 (1.2-15.7)	0.7 (-3.3-0.85)	-1.8 (-4.8-0)	-1.8 (-4.9-0)	NS-	0.6 (-3-0.9)	-1.75 (-9.1-0)	<0.001
• Albumin (mg/dl)	134 (96-154)	100 (82-120)	75.5 (57-104.5)	68 (50-78)	<0.001*	104 (84-124)	66.5 (54-70.5)	<0.001
• Phosphorems (mg/dl)	4.6 (3.87-5.37)	4.24 (3.59-5.19)	3.81 (3.13-4.72)	3.42 (2.92-4.05)	<0.001*	4.22 (3.57-5.04)	4.5 (3.9-4.73)	NS
• GMD (%)	2.33 (1.58-4.12)	2.26 (1.33-3.71)	2.18 (1.25-2.99)	2.06 (1.5-3.21)	0.016*	2.27 (1.4-3.3)	3.08 (2.15-6.21)	0.042
• K/V	1.8 (1.61-1.99)	1.85 (1.66-2.1)	1.88 (1.66-2.1)	1.98 (1.68-2.21)	<0.001*	1.86 (1.64-2.06)	1.6 (1.49-2.02)	NS
• Time on HD (months)	12 (15-64)	49 (16-67)	50 (14-74)	52 (15-77)	NS	51 (14-68)	13.5 (10-75)	NS
• Vascular access (%)					<0.001			0.008
AVF	59.6	58.2	58.4	48.9		57.4	50	
CVC	37.1	40.3	40.6	48.9		41.1	37.5	
Synthetic graft	1.5	1.5	1.2	2.1		1.5	12.5	
• Comorbidity (%)					<0.001			NS
Mild	6.9	7.8	5.7	9.6		6.4	0	
Moderate	17.1	19.2	9.8	15.7		17.5	25	
Severe	75.9	73.1	84.5	74.5		76.1	75	
• Primary renal cause (%)					NS			NS
Diabetic nephropathy	34.4	32.4	33.8	38.3		33.3	37.5	
Hypertension	12.3	14.6	15.9	16.6		12.5	0	
Glomerulonephritis	7.1	7.4	5.9	3.6		6.6	0	
Others	18.1	18.6	17.8	15.7		18	12.5	
• DM: yes (%)	44	41.9	43.6	40.8	<0.001	40.1	50	NS
DEMOGRAPHIC VARIABLES								
• Age (years)	70 (60-78)	73 (61-81)	76 (65-81)	77 (68-82)	<0.001*	73 (63-80)	68 (64-75.5)	NS
• Gender: male (%)	62.5	60.8	64.5	66.9	NS	62.7	62.5	NS

P1: Significant Kolmogorov-Smirnov test. Non-parametric tests applied: Kruskal-Wallis and Jonckheere-Tepstra for quantitative variables. Expressed as median and 25th and 75th percentiles. Chi-square for categorical variables. Expressed as proportions. *Significant Jonckheere-Tepstra trend test (p<0.001)

P2: Significant Kolmogorov-Smirnov test. Non-parametric tests applied: Mann-Whitney U for quantitative variables. Expressed as median and 25th and 75th percentiles. Chi-square for categorical variables. Expressed as proportions.

HRQoL: Health-Related Quality of Life; DM: Diabetes Mellitus; NS: Not significant; PF: Weight loss; SF12-PSI: Physical Summary Index of the Short Form Health Survey SF-36; SF12-MSI: Mental Summary Index of the Short Form Health Survey SF-36.

Notes: a)Moreau-Gaudry X, et al. A simple protein–energy wasting score predicts survival in maintenance hemodialysis patients. J Ren Nutr. 2014 Nov;24(6):395-400.b)Cárrero JJ, et al. Recommendations from an expert group. 20 questions and 20 answers on intradialytic parenteral nutrition. 2022. c Hays R, et al. Kidney Disease Quality of Life Short Form (KDQOL-SFTM version 1.3: A Manual for Use and Scoring. Santa Monica CA: RAND; 1997. d Based on the decision tree for nutritional support according to nutritional status by Cárrero JJ, et al. Recommendations from an expert group. 20 questions and 20 answers on intradialytic parenteral nutrition. 2022. *Patients in HD program who would potentially be candidates to receive NPID according to expert committee criteria and whose data we have collected in our electronic records are selected. Patients who meet 3 or more of the following criteria: Albumin < 3.8 g/dL in addition to serum creatinine < 8 mg/dl for 3 or more months; >10% decrease in usual weight and/or >20% decrease in ideal weight in the last 6 months; BMI < 18.5 kg/m2; Protein intake <0.75g/kg of body weight/day. It is unknown if they are undergoing nutritional treatment with oral supplementation.

SA-PO436

Extra Domain A-Spliced Fibronectin Variant Contributes to Peritoneal Inflammation and Fibrosis in a Murine Model of Peritoneal Fibrosis

Sami Ullah, Susan Yung, Rafter Y. Wu, Tak Mao D. Chan. *Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong SAR, Hong Kong.*

Background: Peritoneal dialysis (PD) is an important mode of renal replacement therapy but preservation of the structural and functional integrity of the peritoneal membrane is a major challenge limiting the feasibility of long-term treatment. Onset of tissue fibrosis is characterized by the presence of fibronectin (FN) isoforms including extra domain A-spliced FN variant (EDA-FN). We investigated the role of EDA-FN in a murine model of PD.

Methods: Male wild-type (WT) and EDA-FN knockout (KO) mice were randomized to receive saline (Control Group) or glucose-based PD fluid containing 40 mM methylglyoxal (PDF Group) by intra-peritoneal injection twice daily for 4, 8 and 12 weeks, after which time the parietal peritoneum was harvested to investigate peritoneal membrane histology and expression of mediators of inflammation and fibrosis using a combination of qPCR, Western blot analysis and cytochemical staining. Human peritoneal mesothelial cells were isolated from omentum to investigate the mechanism of EDA-FN induction.

Results: PDF-treated WT mice developed submesothelial thickening after 12 weeks compared to saline-treated mice, accompanied by a marked influx of immune cells and mesothelial cell denudation. EDA-FN gene expression was increased in the peritoneal membrane of PDF-treated mice (1.00 ± 0.13 vs 15.46 ± 9.83 arbitrary units, saline vs PDF, $p = 0.0095$), accompanied by increased gene and/or protein expression of TGF-β1, IL-1β, IL-6, native FN, collagen I and III, α-smooth muscle actin and Adgre1 (F4/80). PDF-induced peritoneal membrane pathology and thickening were markedly reduced in EDA-FN KO mice compared to WT mice, with reduced immune cell infiltration and mediators of inflammation and fibrosis. In cultured mesothelial cells, PDF induced native FN and EDA-FN expression through the synergistic effect of TGF-β1 and IL-1β.

Conclusions: Our data suggest that increased peritoneal EDA-FN expression in PDF-treated mice contributes to peritoneal inflammation and fibrosis in PD.

Funding: Government Support - Non-U.S.

SA-PO437

Peritoneal Fibrosis Activated by Glucose-Based Peritoneal Dialysis Solutions Can Be Reverted by XyloCore

Valentina Masola,[1] Luciano D'Apolito,[3,2] Angelo D'Alessandro,[4] Luigi Vecchi,[5] Mario Bonomini,[6] Giovambattista Capasso,[3,2] Francesco Trepiccione,[3,2] Maurizio Onisto,[1] Tommaso Prosdocimi,[7] Jose C. Divino-Filho,[8] Arduino Arduini.[7]
[1]Department of Biomedical Science, University of Padova, Padova, Italy; [2]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Napoli, Italy; [3]Biogem, Institute of Molecular Biology and Genetics, Ariano Irpino, Italy; [4]Department of Biochemistry and Molecular Genetics, University of Colorado, Denver – Anschutz Medical Campus, Aurora, CO; [5]Unit of Nephrology, Santa Maria Hospital, Terni, Italy; [6]Department of Medicine, University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy; [7]Iperboreal Pharma Srl, Pescara, Italy; [8]Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden.

Background: One of the major drawbacks of peritoneal dialysis (PD) is the decline in ultrafiltration capacity. Prolonged exposure to traditional high glucose-based PD fluids can induce severe pathological conditions such as peritoneal fibrosis, angiogenesis and epithelial-mesenchymal transition (EMT), ultimately leading to membrane failure. The introduction of new glucose-sparing PD solutions may provide a means to restore peritoneal filtration capacity.

Methods: Mesothelial cells were initially exposed to conventional PD solution for two days, followed by treatment with XyloCore (a novel glucose-sparing PD solution maintaining iso-osmolality by replacing glucose with L-carnitine and xylitol) for the subsequent three days, along with appropriate controls. Similarly, rats were subjected to peritoneal dialysis for 15 days with daily intraperitoneal injections of conventional glucose-based PD fluids, followed by XyloCore or appropriate controls for another 15 days. Multi-photon microscopy (MPM) was utilized to assess blood flow, grade of fibrosis, and vessel spreading. Gene and protein expression of TGF-b, VEGF, EMT, and inflammatory markers were investigated in both in vitro and in vivo samples.

Results: Both in vitro and in vivo findings demonstrated that XyloCore treatment mitigated the upregulation of TGF-b, VEGF, EMT, and inflammatory markers induced by conventional PD fluids. Moreover, XyloCore treatment in rats led to decreased collagen deposition in the sub-mesothelium and reduced compactness of collagen fibers. Additionally, the number of vessels and their branching were contracted.

Conclusions: XyloCore appears to have the ability to reverse the fibrotic process initiated by conventional PD fluids. This potential could facilitate functional recovery and potentially extend the functional life of the peritoneal membrane, even in individuals undergoing peritoneal dialysis with conventional solutions for prolonged periods of time.

Funding: Private Foundation Support

SA-PO438

Nicotinamide Nucleotide Transhydrogenase Is Critically Involved in High Glucose-Mediated Peritoneal Damage

Margarete C. Ohse,[1] Song Rong,[1] Michael S. Balzer,[2,1] Sibylle Von Vietinghoff,[3,1] Hermann Haller,[1,4] Yulia Kiyan,[1] Nelli Shushakova.[1,5] Dept of Nephrology and Hypertension, Hannover Medical School. *[1]Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; [2]Medical Department, Division of Nephrology and Internal Intensive Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany; [3]Nephrology Section, Medical Clinic 1, University Hospital Bonn, Bonn, Germany; [4]Mount Desert Island Biological Laboratory, Salsbury Cove, ME; [5]Phenos GmbH, Hannover, Germany.*

Background: High glucose (HG)-induced mitochondrial dysfunction contributes to peritoneal membrane damage during peritoneal dialysis (PD). Nicotinamide Nucleotide Transhydrogenase (NNT) is critically involved in maintaining the mitochondrial redox balance and energy metabolism. The enzyme catalyzes the transfer of redox potential between the mitochondrial NAD(H) and NADP(H) pools by utilizing the inner mitochondrial membrane potential.

Methods: The role of NNT in peritoneal membrane damage was investigated *in vivo* using a mouse model of PD applied in C57BL/6N wild-type and NNT-deficient C57BL/6J mice. *In vitro*, NNT silencing was performed in mouse peritoneal mesothelial cell line (MPMC), mouse primary peritoneal macrophages and NIH3T3 fibroblasts.

Results: Exposure of the peritoneum to PD fluid in C57BL/6N mice resulted in the loss of the mesothelial cell monolayer, peritoneal membrane fibrosis, neoangiogenesis, an inflammatory response, and macrophage infiltration, which was paralleled by reduced ultrafiltration capacity. In contrast, C57BL/6J NNT-deficient mice demonstrated much less structural and no functional damage of the peritoneal membrane. *In vitro*, a reverse NNT reaction in fibroblasts has been shown to contribute to HG-induced mitochondrial ROS accumulation. NNT silencing prevented mitochondrial ROS accumulation, decreased pro-inflammatory mediator release from MPMC and fibroblasts, prevented pro-inflammatory M1 macrophage polarization, and strongly decreased fibroblast proliferation under HG conditions.

Conclusions: Acting in reverse mode NNT contributes significantly to HG-induced PM damage. Inhibition of NNT activity could have therapeutic implications.

Funding: Government Support - Non-U.S.

SA-PO439

Proteomic Analysis of Extracellular Vesicles in Peritoneal Dialysis Effluent from Patients with Ultrafiltration Failure

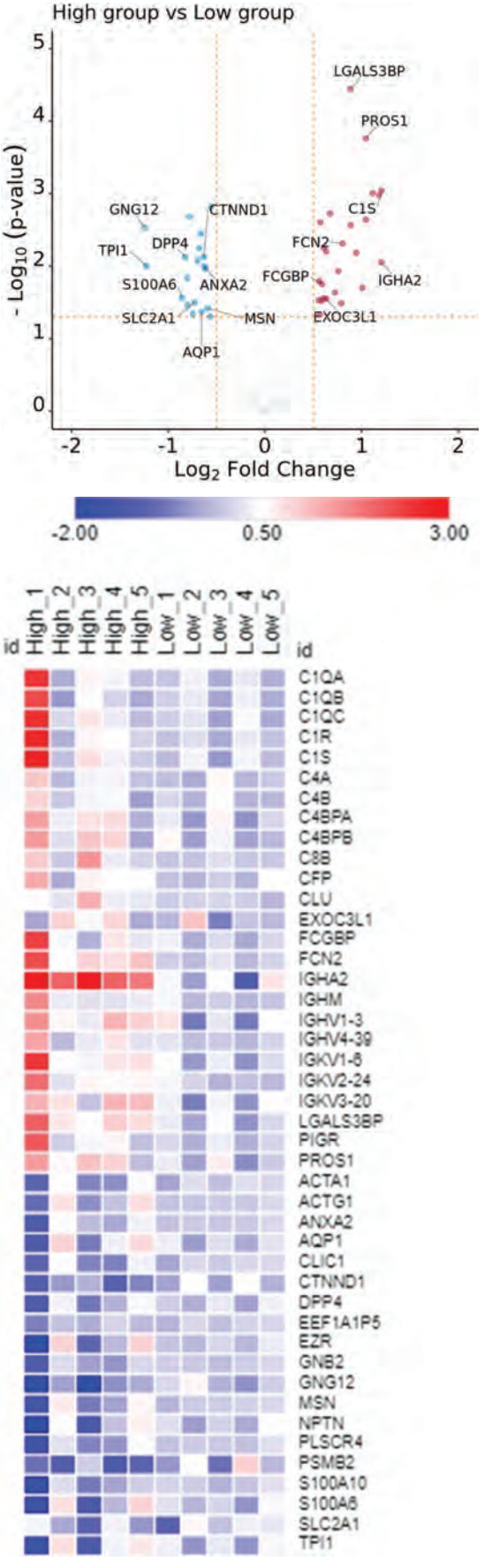
Chi Wei Shih, Chih-Chien Sung. *Tri-Service General Hospital, Taipei, Taiwan.*

Background: Ultrafiltration failure (UFF) is a critical problem in patients with peritoneal dialysis (PD). Although Aquaporin-1 level in the PD effluent (PDE) has been reported as a non-invasive biomarker to predict PD efficiency and UFF, comprehensive analysis in UFF patients remains lacking.

Methods: PDE was collected from 70 patients, divided into two groups based on peritoneal membrane transport type: High (high and high average, n=35) and Low (low and low average, n=35). PDE extracellular vesicles (PDE-EV) were isolated by ultracentrifugation and analyzed using LC–MS/MS, followed by bioinformatic analyses.

Results: PDE-EV was confirmed by nanoparticle tracking analysis and immunoblotting of CD9 and Mesothelin. Of the 390 identified proteins, 44 were differentially expressed ($p<0.05$, $|\log2(\text{High/Low})|>0.5$), with 25 upregulated and 19 downregulated (Figure 1A and 1B). AQP1 and SLC2A1 transporters were significantly downregulated in the High group. Gene ontology analysis of upregulated proteins highlighted immune response and complement activation, indicating an inflammatory response.

Conclusions: This study demonstrated the PDE-EVs could be a non-invasive approach way to evaluate the peritoneal membranous function and understand the pathogenesis of UFF.



SA-PO440

Metabolomic Analysis of Peritoneal Dialysis Effluent across Different Peritoneal Transport Types

Xiaoling Wang,[1] Hasib Absar,[1] Nadja Grobe,[1] Mark Kakembo,[1] Xin Wang,[1] Gabriela Ferreira Dias,[1] Lela Tisdale,[1] Fansan Zhu,[1] Laura Rosales M.,[1] Lin-Chun Wang,[1] Maggie Han,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

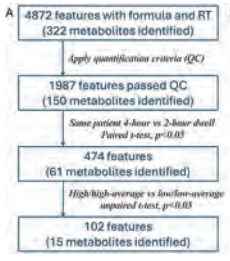
Background: The efficiency of peritoneal dialysis (PD) depends on the peritoneal transport rate, which varies among patients. High transporter characteristics are associated with PD technique failure and increased mortality. Understanding the biochemical changes in different transport types over time is crucial for optimizing PD.

Methods: Sixteen PD patients participated in this study. All patients completed a 2-hour PD session using 2-liter 2.5% dextrose dialysis fluid. Additionally, six patients underwent a separate 4-hour PD session with the same solution on another day. PD effluent (PDE) was collected at the end of each PD session, with serum collected midway. Patients' transport types were determined using dialysate-to-serum creatinine ratio and D/D0 of glucose at 2 hours and were classified as high/high-average (H/HA) and low/low-average (L/LA). Untargeted metabolomics of PDE was conducted using semi-quantitative liquid chromatography mass spectrometry.

Results: A total of 1,987 features (predicted formula and retention time) met quantification criteria. We first selected features with intensities differing between the 2-hour and 4-hour PD sessions within the same patient (paired t-test threshold of $p<0.05$) for 6 patients. Subsequently, the remaining 474 significantly different features were compared between the H/HA and L/LA groups (unpaired t-test; **Figure 1A**). We observed significant differences ($p<0.05$) in 102 features between the two transport types. Among these, 15 metabolites were identified (**Figure 1B**).

Conclusions: Our analysis revealed 150 metabolites in PDE. Notably, 15 metabolites showed potential as biomarkers indicating transport status and/or membrane function under the same prescription regimen. Further validation and exploration of these findings are warranted to understand their clinical applications.

Funding: Commercial Support - Renal Research Institute



B

Name	average MS intensity	4h vs 2h		High/high-average vs Low/low-average	
		Fold change	p-value	Fold change	p-value
L-Tryptophan	24188	1.5	0.0123	1.5	0.0007
2-Methoxy-2-methylpropanoic acid or 2-hydroxy-3-methyl-butyric acid	18871	1.5	0.0005	2.6	0.0015
L-Glutamine	561960	1.5	0.0017	1.4	0.0027
L-Phenylalanine	100335	1.5	0.0014	1.5	0.0041
L-Leucine	87554	1.6	0.0445	1.6	0.0096
L-Serine	42951	1.3	0.0064	1.5	0.0096
L-α-Glycerophosphorylcholine	291524	1.4	0.0344	1.6	0.0100
cis-Cinnamic acid	7746	1.4	0.0057	1.5	0.0139
L-Tyrosine	59653	1.4	0.0264	1.6	0.0201
Uric acid	690323	1.6	0.0008	1.3	0.0241
L-Histidine	12506	1.7	0.0084	1.4	0.0246
N1-Acetylspermidine	20676	1.5	0.0244	1.5	0.0373
L-Isoleucine	51259	1.5	0.0315	1.6	0.0373
5'-Methylthioadenosine	27689	1.6	0.0025	1.3	0.0379
4-Hydroxybenzoic acid	2883	2.4	0.0331	1.8	0.0447

Figure 1: Feature and metabolite identification. (A) Metabolite identification workflow. (B) 15 metabolites showed differences between transport types H/HA and L/LA.

SA-PO441

A Multicohort Biomarker Study in Patients with Advanced CKD on Peritoneal Dialysis or Hemodialysis and in Healthy Volunteers Investigating Inflammatory Markers

Guido Junge,[1] Fabienne Aregger,[2] Dominik E. Uehlinger,[2] Martin K. Kuhlmann,[5] Eric Seibert,[3] Fernanda Do Valle Duraes,[1,4] Romy Höppli,[1] Anette C. Orjuela Leon,[1] Claire Malinverni,[1] Karine Jeanneau,[1] Grazyna Wieczorek,[1] Abdelkader Seroutou,[1] Bernd Hohenstein.[3] *[1]Novartis Pharma AG, Basel, Switzerland; [2]Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [3]Nephrology Center, Villingen-Schwenningen, Germany; [4]Nouscom AG, Basel, Switzerland; [5]Department of Nephrology, Vivantes Clinic in Friedrichshain, Berlin, Germany.*

Background: CKD and ESKD lead to a significant increase in inflammatory cytokines contributing to long-term complications such as anemia, malnutrition, atherosclerosis, and CV disease. This trial explores the potential role of the NLRP3 inflammasome and complement system for the underlying chronic inflammation in CKD patients w/wo KRT.

Methods: BASICHR0052 is a multi-center, prospective biomarker study conducted in pre-KRT CKD4/5, and ESKD patients on KRT (PD or HD at RRT start, month(M) 2-6, or >M12) to assess inflammatory markers in plasma and PD dialysate. Healthy volunteers' (HVs) samples from 12 subjects were collected as part of another study.

Results: 46 subjects (17 CKD4/5, 16 HD, 13PD) were enrolled. We observed a stepwise increase of apoptosis-associated speck-like protein containing CARD (ASC), a marker of NLRP3 activation, IL-18, IL-18BPa and CXCL9 plasma concentrations from HV to CKD and ESKD patients. Key inflammatory cytokines such as IL-1RA, IL-18 and IL-6 were higher in all CKD groups compared to HV. ASC and CXCL9 were removed during HD. IL-6 was higher in the PD dialysate compared to plasma levels, suggesting a modality related, inflammatory peritoneal component. Alternative complement pathway activation was evidenced by significant increase of iC3b and Bb in CKD and HD compared with HV. Dialysis raised levels of both fragments. Significant increase of FD in CKD and HD pre-dialysis were also observed. No significant difference was observed in TCC, FB and C3.

Conclusions: Overall, subjects with advanced CKD stages and especially those under KRT presented evidence of chronic activation of the NLRP3 inflammasome and the complement system. HD resulted in reduction of ASC and CXCL9 and an increase of iC3b and Bb. IL 6 concentrations were comparable between HD and PD patients but were higher in dialysate of PD patients compared to plasma. Further studies are required to validate those findings as potential new therapeutic targets for patients with advanced CKD w/wo RRT.

Funding: Commercial Support - Novartis Pharma AG

SA-PO442

Association between Serum Leptin Levels and Vascular Reactivity Index in Patients on Long-Term Peritoneal Dialysis

Yu Chi Chang,[1] Yu-Hsien Lai,[1,2] Bang-Gee Hsu.[1,2] *[1]Division of Nephrology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan.*

Background: Leptin directly affects vascular function, including atherosclerotic effects, endothelial dysfunction resulting from the long-term effect of leptin on nitritic oxidase synthesis, and disturbed bioavailability. This study investigated the correlation between serum leptin levels and endothelial dysfunction in patients undergoing peritoneal dialysis (PD).

Methods: This cross-sectional, single-center study included 74 patients with long-term PD for end-stage kidney failure. A digital thermal monitoring device calculated the vascular reactivity index (VRI) to measure endothelial function, and an enzyme immunoassay was used to determine serum leptin levels. In this study, VRI < 1.0 denoted poor vascular reactivity, 1.0 ≤ VRI < 2.0 intermediate vascular reactivity, and VRI ≥ 2.0 good vascular reactivity.

Results: Out of the long-term PD patients, thirty-four (45.9%) displayed poor vascular reactivity (VRI < 1.0), while 29 (39.2%) exhibited intermediate vascular reactivity (1.0 ≤ VRI < 2.0), leaving the remaining 11 patients demonstrating good vascular reactivity. Higher waist circumference ($P < 0.001$), elevated serum C-reactive protein (CRP, $P = 0.003$), and leptin levels ($P < 0.001$) were found to be associated with poor vascular reactivity. Waist circumference ($r = –0.336$, $P = 0.003$), log-transformed serum levels of CRP (log-CRP, $r = –0.552$, $P < 0.001$), and serum leptin levels ($r = –0.497$, $P < 0.001$) exhibited a negative correlation with VRI values in long-term PD patients. Following the multivariate linear regression test, serum log-CRP level (β = –0.431, adjusted R^2 change = 0.295, $P < 0.001$) and leptin level (β = –0.346, adjusted R^2 change = 0.098, $P = 0.001$) emerged as significantly and independently associated with VRI values among PD patients. Using the Spearman correlation analysis, the log-PD vintage ($r = –0.234$, $P = 0.048$) was negatively correlated, while waist circumference ($r = 0.412$, $P < 0.001$) and log-CRP level ($r = 0.351$, $P = 0.002$) was positively correlated with serum leptin level.

Conclusions: In patients with long-term PD, a negative association was observed between serum log-CRP and leptin levels and endothelial dysfunction determined by VRI values.

SA-PO443

Impact of Peritoneal Dialysis on Peritoneal Macrophage Immunometabolism and Its Relation to Systemic Inflammation and Cardiac Function

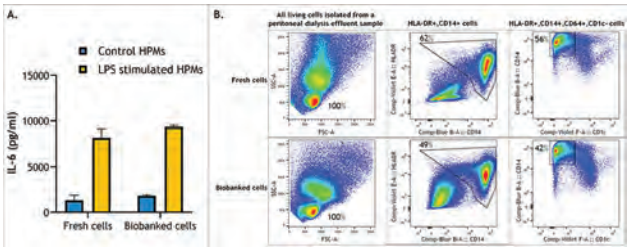
Micky Karsten,[1,2] Nico Hahn,[3,2] Puck Vree,[1,3] Marc G. Vervloet,[4] Jan Van den Bossche,[3,2] Lily Jakulj.[1,5] *[1]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [2]Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands; [3]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands; [4]Radboud Universiteit, Nijmegen, Netherlands; [5]Dianet Dialysis Center Amsterdam, Amsterdam, Netherlands.*

Background: Heart failure with a preserved ejection fraction (HFpEF), is in part driven by invading macrophages and is common in peritoneal dialysis (PD) patients. The glucose rich PD-effluent (PDE) triggers peritoneal inflammation, alike to what is seen in HFpEF. However, the role of macrophages in PD-induced peritoneal injury is unknown. We hypothesize that human peritoneal macrophages (HPMs) of PD-treated patients exhibit an inflammation-driven immunometabolic profile that may ultimately aggravate damage in remote tissues such as the myocardium.

Methods: In adult PD-patients, we collected PDE-derived HPMs and peripheral blood mononuclear cells (PBMC) and performed echocardiography to measure left ventricular global longitudinal strain (LVGLS). We evaluated the impact of biobanking by comparing fluorescence-activated cell sorting (FACS) and (LPS-stimulated) IL-6 production between fresh and thawed HPMs. We will obtain complex immunometabolic HPM and PBMC profiles by lactate, resazurin and SCENITH analysis. Phenotype will be analyzed with FACS and functionality is assessed by in vitro exposure to M1 and M2 inducers. We will relate HPM characteristics to systemic PBMC profiles and other markers of systemic inflammation and LVGLS.

Results: We successfully isolated HPMs from 16 PD-patients (mean age 61,9 (±19,3) years, median PD-vintage 9,5 [4-44,3] months and median LVGLS -17% [-18;-13]). Phenotype and functionality was evaluated both in fresh and thawed HPMs. FACS showed stable high percentages of CD14+HLA-DR+CD64+ macrophages and IL-6 production was maintained after biobanking both with and without lipopolysaccharides (LPS) stimulation.

Conclusions: We successfully isolated and biobanked HPMs from the easily accessible PDE, with maintained functionality. With the proposed protocol we will obtain in depth immunometabolic HPM profiles and relate these to cardiac function and systemic inflammation.



Panel A: No difference in IL-6 production of fresh and biobanked HPMs with or without LPS; Panel B: FACS showed no difference between fresh and biobanked HPM populations

SA-PO444

Estimating Transport in Peritoneal Dialysis Using Sodium Kinetics

Jakob Helman, Carl M. Öberg. *Lunds Universitet Institutionen for Kliniska Vetenskaper Lund, Lund, Sweden.*

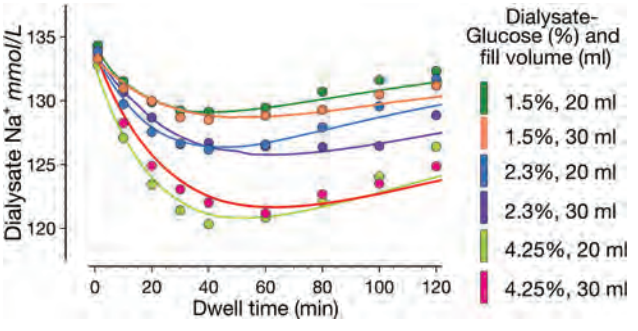
Background: Reliable tests to assess membrane function in peritoneal dialysis are critically needed to individualize prescription, monitor membrane integrity, and improve outcomes of patients treated with peritoneal dialysis. Dialysate sodium kinetics could theoretically be used to estimate both osmotic water transport and solute diffusion across the peritoneal membrane. Here we tested the hypothesis that solute and water transport can be predicted solely from sodium kinetics.

Methods: We derived a modified version of the three-pore model based on the Nernst-Planck equation, which accounts for the Gibbs-Donnan and plasma water effects. Computer simulations were compared with data from an experimental rat-model of peritoneal dialysis (n = 25), divided into six groups by dialysate glucose strength (1.5%, 2.3% and 4.25%) and fill volume (20 ml and 30 ml). The diffusion capacity of sodium and the area to diffusion length ratio were set as parameters and fitted to data consisting of sodium measurements during dialysis, using a non-linear least squares algorithm.

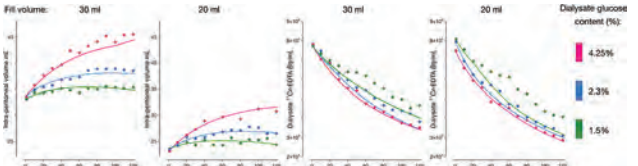
Results: After running the regression, the model fit sodium data well (figure 1). Intraperitoneal fluid volume over time closely matched experimental data for all glucose strengths (figure 2). Predictions of the concentrations of ^{51}Cr-EDTA over time in dialysate closely matched experimental data for most groups, but there was a slight deviation from datapoints in lower glucose strengths (figure 2).

Conclusions: In conclusion, we demonstrate that sodium kinetics can predict changes in intraperitoneal volume and transport of small solutes, such as ^{51}Cr-EDTA. This is in line with earlier results where sodium kinetics have been shown to closely correspond to changes in peritoneal fluid volume. The model should be further validated for other solutes, which might require adjustments of the model.

Funding: Government Support - Non-U.S.



Simulations (line) vs data (dots) for sodium



Simulations (line) vs data (dots) for Cr-EDTA and interaperitoneal volume

SA-PO445

Ultrafiltration Patterns during Automated Peritoneal Dialysis

Osama El Shamy,[1] Ankur Shah,[2] Nicole Wyatt,[3] Sagar Patel,[4] Naief N. Abudaff,[5] Thomas A. Golper,[3] Andrew Guide,[3] Robert Greevy,[3] Juan Pablo Arroyo Ornelas.[3]
[1]The George Washington University, Washington, DC; [2]Brown University Warren Alpert Medical School, Providence, RI; [3]Vanderbilt University Medical Center, Nashville, TN; [4]Renal Associates LLC, Columbus, GA; [5]Arizona Kidney Disease and Hypertension Center, Phoenix, AZ.

Background: With the growing use of automated peritoneal dialysis (APD), it is important to improve our knowledge of the clinical patterns and physiology of APD treatment sessions. The ultrafiltration achieved during each cycle of an APD treatment is assumed to be relatively linear if the delivered prescription is the same. We set out to determine if that is case.

Methods: Single-center, cross-sectional study of APD patients > 18 years old, who had been on APD for ≥3 months were included. CAPD patients or those with peritonitis within 3 months were excluded. Individual treatment data from 7 consecutive APD treatment sessions with consistent dialysate composition were collected.

Results: 39 subjects were enrolled. A total of 273 APD treatment days were analyzed. The probability of yielding a positive UF was 48.9% for cycle 1, gradually rising to 90.5% by cycle 6. Adjusting for average dextrose concentration, dwell time, tidal PD status, fill volume, solute transfer rate, and number of cycles, we observed that cycles 2 through 6 achieved progressively higher UF volumes than cycle 1 ($p < 0.001$). To adjust for a potential "last cycle effect", assessment of a middle cycle compared to the first and last cycles demonstrated statistically significantly cycle UF volumes (-230 ml and 277 ml, respectively, $p < 0.001$), in-line with our other findings.

Conclusions: This is the first study investigating variations in UF volumes achieved between APD cycles. Adjusting for all potentially confounding factors, as the APD treatment progressed, the UF achieved per cycle increased. While the exact explanation of these findings is unclear, peritoneal surface area recruitment, mesenteric elasticity, and cumulative glucose concentration in the interstitium are possible factors.

Table 1. Predicting cycle ultrafiltration using the Generalized Estimating Equations (GEE) longitudinal model analysis, adjusting for average dextrose concentration, dwell time, tidal PD status, fill volume, transfer status, and cycle number*

Variable	Estimate (Std Error)	p-value
Average Dextrose Concentration		
1.5%	32.39 (64.01)	0.613
2.5%	77.20 (27.19)	0.005
3.38%	124.51 (24.41)	< 0.001
Dwell Time	-0.09 (0.86)	0.917
Fill Volume	31.45 (31.23)	0.314
Transfer Status		
High Average	22.78 (24.38)	0.350
Low Average	136.54 (32.49)	< 0.001
Low	66.82 (63.32)	0.291
Unavailable	12.22 (45.33)	0.788
Cycle Number		
2	197.74 (40.41)	< 0.001
3	258.31 (44.44)	< 0.001
4	322.28 (76.01)	< 0.001
5	420.50 (76.31)	< 0.001
6	417.47 (93.55)	< 0.001

SA-PO446

Examining Ultrafiltration Variance across Two Peritoneal Dialysis Prescriptions of the Automated Wearable Artificial Kidney (AWAK) in a Porcine Model

Arsh Jain,[1] Siti N. Huda,[2] Sridhar Chirumarry,[2] Jason T. Lim,[2] Sheena Gow,[2] Mandar Gori,[2] Suresha B. Venkataraya,[2] Sanjay Singh.[2] *[1]London Health Sciences Centre, London, ON, Canada; [2]AWAK Technologies Pte Ltd, Singapore, Singapore.*

Background: AWAK PD uses sorbent-based tidal therapy that regenerates spent dialysate into clean dialysate fluid that returns to the peritoneum. Our aim was to study the ultrafiltration (UF) generation per gram of glucose exposed and absorbed (UF efficiency – UFE) under 2 AWAK PD prescriptions.

Methods: This study was conducted in a 5/6 nephrectomised porcine (*Sus Scrofa, male*). The animal (Low transporter; $D/P_{creatinine}$ at 4 hour = 0.40) was maintained on automated PD therapy (5 exchanges of 2L fills of 1.5% Dianeal® over 10 hours) in between the test periods. During the test period, daily 9-hour AWAK PD therapy was conducted; it consists of a 7-hour tidal sorbent phase and a 2-hour non-sorbent dwell phase (initial fill 2L, 1.5% Dianeal®). Glucose was dosed using AWAK's glucose management system Setting 3; 4 settings are available, ranging from 0.3 – 6.8mL of Glucose 70%, every 7.5 minutes in the first 7 hours of tidal dialysis and during the 2-hour non-sorbent dwell, glucose was dosed every 7.5 minutes (Test A) or 15 minutes (Test B). The animal also had daily last fills (1L, 2.5% Dianeal®) throughout the study period. Post-AWAK PD therapy dialysate data were collected for glucose analysis and UF calculation.

Results: The difference in UF between the 2 tests was statistically insignificant (p-value = 0.81). The UF ranges and UFE rates are shown in Table 1. Higher UFE (exposed and absorbed) were observed for Test B and would be a preferred treatment prescription as it was able to achieve similar UF with lowered glucose exposure. This experiment was performed on a porcine model with a low transport status and the results may vary for a high transport status peritoneal membrane.

Conclusions: With a reduced requirement of glucose, the device size can be improved. Further long-term studies in both animals and humans are needed to ascertain the efficacy of the glucose management system and prescription implications of AWAK PD therapies.

Funding: Commercial Support - AWAK Technologies Pte Ltd

Table 1: Summary of UF results from 2 glucose prescriptions

Glucose dosing in non-sorbent phase	Test A - every 7.5 minutes [n = 14 days]	Test B - every 15 minutes [n = 14 days]
Average UF volume (mL); min-max	852 (413 – 1046)	867 (448 - 1064)
UFE – exposed (mL/g)	9.4	10.3
UFE – absorbed (mL/g)	18.0	19.2

SA-PO447

Peritoneal Equilibration Test: Comparison of Different Cutoff Values

Noemi Del Toro-Cisneros,[1] Rosario Guadalupe H. Ortega,[2] Erick Y. Zuñiga Gonzalez,[1] Alejandro Quinonez-Flores,[1] Omar Fueyo,[1] Rodolfo Rincon-Pedrero.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Department of Nephrology, ISSEMyM Ecatepec, State of Mexico, Mexico.*

Background: The aim of this study was to compare the type of peritoneal transport using the Peritoneal Equilibration Test (PET) performed at 2 and 4 hours with the cut-off values described by Twardowski (1) and Cueto-Manzano (2) and to propose neu cut-off values for the test at 2 and 4 hours.

Methods: This was a retrospective study, we included patients on peritoneal dialysis with PET in two tertiary care centers in Mexico between 2016-2023. The type of peritoneal transport obtained from Creatinine D/P was compared at 2 hours vs. 4 hours, depending on the result it was classified as high (H), high average (HA), low average (LA) and low (L). In addition, new cut-off values are proposed using the method initially described by Twardowski (1) based on the mean and +/- standard deviation.

Results: Two hundred and two PET studies were included. Eighty-three patients (41%) were men, median age was 43 years (interquartile range 27-58 years). The main causes of chronic kidney disease (CKD) were diabetes 39% (79 patiens) and unknown cause 35% (71 patients). The median time in dialysis was 18 months. The indications for performing PET were initiation of dialysis 48% (97), failure of ultrafiltration 8% (16), after peritonitis 7% (15), and the rest for therapy adequacy. **Table 1** presents the type of peritoneal transport according to the cut-off values described in the literature as well as the values proposed from this study. As can be seen, the cut-off values at 2 hours described bye Cueto-Manzano and Twardowski compared to 4 hours incorrectly classify 13 and 6% respectively as high transporters, while in the low transportes they classified 13 and 8% less patients in the category.

Conclusions: In this study we found that the cut-off values established for the PET study at 2 hours overestimate patients with high transport and underestimate those with low transport. The new proposed value appropriately classifies patients with high and low solute transport.

Solute Transport	Creatinine D/P 2h, Cueto-Manzano	Creatinine D/P 4h, Cueto-Manzano	Creatinine D/P 2h, Twardowski	Creatinine D/P 4h, Twardowski	Creatinine D/P 2h, new cut-off	Creatinine D/P 4h, new cut-off
High	55 (27)	29 (14)	40 (20)	29 (14)	30 (15)	29 (14)
Cut-off	0.58-0.75	0.81-0.94	0.63-0.87	0.82-1.03	0.65-0.96	0.80-1.07
High Average	54 (27)	56 (28)	78 (39)	83 (41)	61 (30)	83 (41)
Cut-off	0.49-0.57	0.69-0.80	0.49-0.62	0.66-0.81	0.52-0.64	0.66-0.80
Low Average	68 (34)	67 (33)	70 (35)	59 (29)	83 (41)	59 (29)
Cut-off	0.39-0.48	0.57-0.68	0.34-0.47	0.50-0.64	0.38-0.50	0.50-0.64
Low	25 (12)	50 (25)	14 (7)	31 (15)	28 (14)	28 (14)
Cut-off	0.20-0.38	0.41-0.56	0.23-0.33	0.34-0.49	0.23-0.37	0.18-0.49

Table 1. Comparison of solute transport with the original cut-off values proposed by Twardowski at 2 and 4 hours and assessed in the Mexican population by Cueto-Manzano, as well as the new proposed cut-off values.

SA-PO448

Effect of Icodextrin on Volume and Metabolism: A Multicenter Clinical Study

Yao Li, Zhu Zhou. *First Affiliated Hospital of Kunming Medical University, Kunming, China.*

Background: Icodextrin is a novel peritoneal dialysis fluid that enhances fluid clearance. It works through the formation of colloidal osmotic pressure, so it maintains effective ultrafiltration for a longer period of time, and the incidence of ultrafiltration (UF) failure is much lower than that of glucose peritoneal dialysis solution. The aim of this study was to compare the changes in volume and metabolism of patients before and after icodextrin treatment, expecting more evidence to support the effectiveness of icodextrin.

Methods: After screening for inclusion and exclusion criteria, we included 20 cases of continuous ambulatory peritoneal dialysis (CAPD) patients from seven hospitals of Yunnan Province. These patients were given a 3-month long-stay nocturnal treatment with icodextrin. We compared nocturnal net UF, peritoneal creatinine clearance(Ccr), and body weight, BNP. And related metabolic parameters, including fasting blood glucose(FBG), cholesterol(TC), and triglycerides(TG), before and after icodextrin treatment.

Results: After 3 months of treatment with icodextrin, patients showed significant increase in nocturnal long-stay abdominal net UF and peritoneal Ccr. The mean nocturnal long-stay net abdominal UF was (57.78±257.63) ml at baseline and (681.85±168.23) ml after treatment (difference -624.07, 95% CI -742.69 –-505.45, t=-11.10, P<0.001). The patient's peritoneal Ccr was (2.10±0.40) ml/min at baseline and (3.10±0.48) ml/min after treatment (difference -1.00, 95% CI -1.31–0.68, t=-6.72, P<0.001). Pre-treatment weight (64.98±10.79) kg Post-treatment weight (63.09±10.28) kg, (difference 1.89, 95% CI 0.58–3.21, t=3.05, P=0.007). After treatment, the patients' BNP decreased, but the difference was not statistically significant (P>0.05); FBG, TG and TC increased afterward, but the mean values were still in the normal range, and the difference was not statistically significant (P>0.05).

Conclusions: In this study, icodextrin was found to increase UF and peritoneal Ccr as well as improve volume control in patients. It can remove more water and reduce patients' body weight. But no significant effect of icodextrin in improving glycolipid metabolism and lowering BNP has been detected for the time being, and the effect of icodextrin on cardiac function needs to be further explored, and its long-term effects and potential application in specific patient groups need to be further investigated.

Funding: Government Support - Non-U.S.

SA-PO449

Identification of Body Fluid Distribution in Patients on Hemodialysis and Peritoneal Dialysis Using Whole-Body and Segmental Bioimpedance Analysis

Fansan Zhu,[1] Samer R. Abbas,[1] Laura Rosales M.,[1] Peter Kotanko.[1,2] [1]*Renal Research Institute, New York, NY;* [2]*Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The understanding of fluid transport in dialysis patients is based on a two-compartment model between the whole body's extracellular volume (ECV) and the intravascular compartment. We developed a segmental method to measure ECV in the arm, trunk, and leg. This study aims to evaluate change in ECV in the segments of hemodialysis (HD, Fig.1) and peritoneal dialysis (PD, Fig. 2) patients during dialysis.

Methods: Twenty HD (9 females, age 68.7±24.4 year) and 19 PD patients (10 females, age 54.6±11.6 year) were studied. Whole body and segmental bioimpedance spectroscopy (Hydra 4200) were performed pre and post-treatment (Fig. 3). Changes in the whole body ECV (ΔECV_W) and in the arm (ΔECV_A), trunk (ΔECV_T), and leg (ΔECV_L) were estimated (post – pre ECV). Ultrafiltration volumes (UFV) were recorded. The difference between UFV and ΔECV_W was calculated (DIFF=UFV – ΔECV_W). The ratios of changes in segmental ECVs to UFV ($2*\Delta ECV_A$/UFV; ΔECV_T/UFV; and $2*\Delta ECV_L$/UFV) were defined as *effective removed volume* (ERV, %).

Results: UFV in HD patients was larger compared to PD patients (2.65±0.83 L vs. 0.36±0.22 L, p<0.0001), but treatment time did not differ (3.82±0.67 h vs. 4.00 h, p=0.27). DIFF in HD was larger than in PD patients (Fig. 4). In HD patients, the mean of leg ERV (-44±45 %) was larger than in the trunk ERV (-29±20 %; p=0.23), as well as larger than in the arms (-4±28 %; p<0.01) (Fig. 5). In contrast, in PD patients, trunk ERV (-57±21%) was larger compared to ERV of leg (-33±26%, p=0.1) and arms (-9±55 %, p=0.07) (Fig. 6).

Conclusions: In HD patients, more than 40% of UFV was removed from the legs, while in PD patients more than 50% of UFV was removed from the trunk. These different fluid distributions may cause errors in the estimation of fluid removed by the whole body bioimpedance method. Fluid distribution models may further make a better understanding of fluid dynamics in patients treated with different dialysis modalities, and therefore, improve precision care.

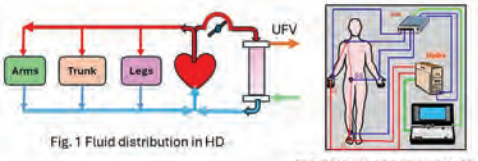


Fig. 1 Fluid distribution in HD

Fig. 3 Whole and segmental BIS

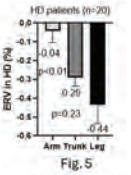


Fig. 5

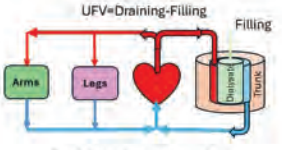


Fig. 2 Fluid distribution in PD

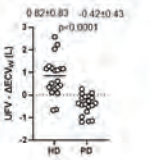


Fig. 4

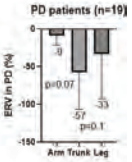


Fig. 6

SA-PO450

Initial Feasibility Pilot Study of Interdialytic Peritoneal Ultrafiltration to Manage Volume Status in Patients on Hemodialysis (iPUF-HD)

Patrik Deleaval,[1,2] Jarrin D. Penny,[1] Amy Freeman,[1] Christopher W. McIntyre.[1,3] [1]*London Health Sciences Centre London Kidney Clinical Research Unit, London, ON, Canada;* [2]*NephroCare Tassin-Charcot, Saint Foy-les-Lyon, France;* [3]*Western University, London, ON, Canada.*

Background: Increased dietary sodium (Na) and reduced Na excretion drive interdialytic weight gain (IDWG). High ultrafiltration (UF) rates are associated with mortality in hemodialysis (HD) patients. Achieving complete removal of IDWG is often challenging with conventional HD. Combination therapy with peritoneal dialysis (PD) allows additional UF but significantly increases treatment burden. We report first use of short dwell PD, delivered passively, immediately after HD for 2/3 sessions per week. To maximize Na removal and address congestion we instilled low volume 0% sodium fluid with short dwell time.

Methods: We studied 5 anephric HD patients with history of difficult to manage IDWG [(> 4% of dry weight) within conventional HD regimen. After catheter implantation/healing, patients underwent two short dwell (2 hours) peritoneal treatment sessions per week (immediately after HD), using 10% dextrose. Low volume (500ml) was used to limit glucose exposure (no more than conventional 2.5% dextrose/sodium containing PD fluid). Patients were treated for 3 weeks with additional one-washout. IDWG, hemodynamics, effluent composition, tolerability, serum sodium/osmolality and intradialytic serial echocardiography (HD-induced myocardial stunning) were assessed.

Results: Low volume Na-free peritoneal solution effectively removed 4.83±1.37g of Na and 251±190ml UF per session. Na-free 10% dextrose PD solution was well tolerated without treatment interruption (pain score 0 -1/5). During intervention period, IDWG progressively decreased (from 1820 to 950ml), markedly greater than achieved peritoneal UF. Serum potassium, hs-troponin, calcium, and hemoglobin concentrations remained stable. Serum Na modestly decreased from 136.64±4.46 to 132.11±2.96mmol/L (p < 0.0001), with no adversity attributable to hyponatremia. Systolic blood pressure and continuous intradialytic hemodynamics remained unchanged throughout. Of those with viable echo images (for strain analysis), HD-induced myocardial stunning was reduced in 2/3 patients.

Conclusions: This pilot study suggests that additional Na removal can be achieved with use Na-free peritoneal fluid delivered post-dialytic. Such a regimen appears to be capable of improving the congestive state (and its consequences) in patients otherwise unable to be adequately managed with conventional HD.

SA-PO451

Impact of Peritoneal Dialysis Modality on Quality of Life in Hypervolemic Patients

Suchai Sritippayawan,[1,2] Usa Chaikledkaew,[3] Piyatida Chuengsaman,[5] Montarat Thavorncharoensap,[3] Nipa Aiyasanon,[4] Sasima Tongsai.[4] APDICO Project Group. *[1]Division of Nephrology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2]Nephrology Society of Thailand, Bangkok, Thailand; [3]Mahidol University Faculty of Pharmacy, Bangkok, Thailand; [4]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [5]Banphaeo General Hospital, Samut Sakhon, Thailand.*

Background: Hypervolemia significantly affects outcomes and quality of life (QOL) in peritoneal dialysis (PD) patients. Limited data compare the QOL across the PD modalities. Our study aims to study the QOL in hypervolemic patients treated with Continuous Ambulatory Peritoneal Dialysis (CAPD), CAPD with 1 cycle of icodextrin (ICO) and nighttime Automated Peritoneal Dialysis (APD).

Methods: 180 CAPD patients with systolic blood pressure (BP) >140 mmHg, diastolic BP >90 mmHg, edema from volume excess or a history of heart failure within the past year from 16 hospitals were randomized into 3 groups of 60 each: CAPD, ICO and APD. Hypertonic solutions, antihypertensive drugs and daily dialysate volume were adjusted based on patients' BP, symptoms and total weekly Kt/Vurea. QOL was assessed using the EQ-5D-5L and KDQOL-36 questionnaires at week 0, 24, 48, 104 and 156. The relationship between the treatment groups and the QOL scores was analyzed using Generalized Estimating Equations in linear regression. The model coefficients determined the intensity and direction of these correlations.

Results: At enrollment, the groups showed no significant differences in age, urine volume, PD duration, Charlson Comorbidity Index (CCI) score, blood pressure, serum albumin, previous peritonitis rate, total weekly Kt/Vurea, or QOL scores. By week 156, 20, 21, and 11 patients remained in the study, while 30, 19, and 32 had died in the CAPD, ICO, and APD groups, respectively. Two patients each withdrew from the CAPD and ICO groups. Patients on ICO and APD showed significantly better utility and VAS scores on EQ-5D-5L compared to those on CAPD ($p<0.05$). KDQOL-36 also revealed higher scores in all domains for the ICO group compared to the CAPD group (significant or trending). The APD group achieved higher KDQOL-36 scores in the Effects and Burden of Kidney Disease and SF-12 Physical Component Summary domains compared to the CAPD group. There were no differences between APD and ICO groups in any domain.

Conclusions: In hypervolemic patients, treatment with ICO offered better QOL than CAPD alone, but was similar to APD. APD offered advantages in specific aspects of QOL compared to CAPD. The ICO group also had a higher survival rate than the CAPD and APD groups. This suggests ICO may improve QOL for PD patients.

Funding: Government Support - Non-U.S.

SA-PO452

Impact of Hydrolysis on the Change of Icodextrin Amount during Peritoneal Dialysis

Joanna Stachowska-Pietka,[1] Jacek Waniewski,[1] Bengt Lindholm.[2] *[1]Instytut Biocybernetyki i Inzynierii Biomedycznej im Macieja Nalecza Polskiej Akademii Nauk, Warszawa, Poland; [2]Karolinska Institutet, Stockholm, Sweden.*

Background: During peritoneal dialysis (PD), icodextrin (Ico), a mixture of glucose polymers, disappears from peritoneal cavity (PC) due to various processes: absorption (A), diffusion (D), convection (C), and hydrolysis (H) of Ico in PC leading to shortening of glucose polymers. The impact of H on amount of Ico molecules (Ico_M, mmol) and their fractions during PD was not investigated so far. We analysed changes of Ico_M in PC using three pore model (TPM) applied to clinical data.

Methods: Extended TPM, which includes hydrolysis of Ico, was applied to clinical data from 8 Ico-naïve PD patients during 16 h dwell with Ico-based solution and frequent sampling of dialysate and blood. Based on the measured polymers distribution, Ico was described by 7 fractions of different molecular weights, Tab.1. The change of Ico_M was calculated for the 16 h dwell time.

Results: The decrease of Ico_M (ΔIco_M in mmol) in dialysate was around 40% of Ico initial amount after 16-hour dwell and was mostly due to A (91% of ΔIco_M) as the decrease due to D&C (74% of ΔIco_M) was almost counterbalanced by enhanced Ico_M caused by H (65% of ΔIco_M). For the fractions, the decrease in Ico_M was the highest for F2-F4 (88, 25 and 13% of ΔIco_M, respectively); however we observed the increase of F1 (31% of ΔIco_M), Tab.1. The impact of A, D, C and H on the decrease of F1-F7 amount is presented in Tab.1. For F1, overall amount increased (solely due to H); this increase was higher than the F1 decrease related to D, C and A, Tab.1.

Conclusions: Decrease of Ico amount from PC was mostly due to A and mainly related to the decrease of F2 amount, and to some extent also of F3-F4, whereas F1 was increased at the dwell end. The increase of F1 amount was solely due to H that greatly exceeded the F1 removal caused by A, D&C. For fractions F2 and F5, H and A have similar impact on the decrease of fraction amount, whereas for F3 and F4 the observed decrease was mostly due to A. On the contrary, H was the main contributor to the observed decrease of the fractions F6-F7 amount, while the contribution of A was smaller.

Tab 1. Share (in %) of total decrease of Ico fraction amount in the overall Ico amount decrease, and the share (in %) of Ico fraction amount decrease by various processes: peritoneal absorption (**A**), Ico transport by diffusion and convection (**D&C**) and Ico hydrolysis (**H**), in the overall decrease of Ico fractions F1-F7 amount and MW - molecular weight.
Negative sign denotes increase of the amount of molecules and MW - molecular weight

Fractions		Share of Ico frac. amount decrease in total Ico amount decrease	Share of Ico frac. amount decrease by process in Ico frac. amount decrease		
Symbol	MW range	Total, %	A, %	D&C, %	H, %
F1	up to 1.08 kDa	-30.79	84	184	-368
F2	1.08 - 4.44 kDa	87.77	37	19	44
F3	4.44 - 9.89 kDa	24.90	74	1	25
F4	9.89 - 21.4 kDa	12.51	98	1	1
F5	21.4 - 43.5 kDa	5.11	44	0	56
F6	43.5 - 66.7 kDa	0.47	20	0	80
F7	over 66.7 kDa	0.03	10	0	90

SA-PO453

Mechanism of Macrophage Extracellular Traps Involved in the Formation of Encapsulating Peritoneal Sclerosis

Juan Sun, Hui Peng. *The Third Affiliated Hospital of Sun Yet-sun University Department of Nephrology, Guangzhou, China.*

Background: Encapsulating peritoneal sclerosis (EPS) is one of the most severe complications of peritoneal dialysis and poses a serious threat to the lives of peritoneal dialysis patients. However, the mechanism of the development of EPS is still unclear, and there is a lack of effective treatment.

Methods: We collected cells from the peritoneal dialysis effluent of EPS patients for single-cell transcriptome sequencing and used scanning electron microscopy and immunofluorescence to co-localize and identify macrophage extracellular traps(METs), while using fluorescent tracer cells to observe the "netting effect" of METs in vitro. We also used the EPS mouse model and PAD4 knockout mice for in vivo experiments. We stimulated fibroblasts with purified METs in vitro to explore the downstream molecular mechanism.

Results: The ratio of myofibroblasts in the peritoneal cavity of EPS patients was significantly increased compared with that of other patients by using scRNA-seq analysis. In addition, the macrophage-fibroblast interaction was significantly increased and the proportion of pro-inflammatory macrophages (S100A8+ Macro) was significantly higher in EPS patients. Immunofluorescence also showed that fibroblasts and macrophages were the most predominant cellular components in the adhesion region of the abdominal. Intrestingly, the METs formation pathway was significantly enriched in this celltype. The level of METs was positively correlated with the severity of EPS. Both PAD4 knockdown and injection of DNase-I effectively reduced METs and adhesion in EPS mice. In vitro study showed that METs induced fibroblast activation via p38/MAPK pathway.

Conclusions: Our study found that Macrophages in the peritoneal cavity produce METs under severe stimulation, and the reticular structure of METs can act as a scaffold to form "adhesion bridges" between cells in the peritoneal cavity and induce fibroblast activation through the p38/MAPK signaling pathway, which promotes peritoneal thickening and adhesion formation. Both knockdown of PAD4 and inhibition of METs by DNaseI were effective in improving EPS.

SA-PO454

Clinical Outcomes of Encapsulating Peritoneal Sclerosis Treated with Tamoxifen in Patients with ESKD: A Retrospective, Single-Center Analysis

Soy Kang, Binna Park, Dongeun Yang, Won Suk An. *Dong-A University, Busan, Republic of Korea.*

Background: Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis(PD). Patients with EPS showed 25-55% mortality rate, but the optimal treatment for EPS is not clear. EPS treated with tamoxifen is associated with lower mortality, but other studies showed no difference in outcome. This study aimed to evaluate the clinical outcomes of EPS treated with tamoxifen in end-stage kidney disease patients.

Methods: We conducted a 20-year (from January 2004 to December 2023) retrospective observational study. We included 34 EPS patients (mean age: 59.0 ± 11.7 years, male: 55.9%) who were diagnosed with abdominal computed tomography and treated with tamoxifen in Dong-A university hospital. We also analyzed data according to 10-year period (period 1: 2004-2013, n=24, period 2: 2014-2023, n=10).

Results: The mean duration of PD before diagnosis of EPS was 79.0 ± 45.0 months (range 27-192). Four patients had treated with hemodialysis prior to diagnosis of EPS. The length of hospital stay was 40.1 ± 28.4 days at time of diagnosis and survival time was 32.0 ± 32.2 months. Prescribed dose of tamoxifen was 22.3 ± 7.4 mg and prescribed days were 106.6 ± 172.1 (range 5-880). Four patients were also treated with low dose prednisone and five patients were treated with tamoxifen over 5 months. The length of hospital stay was shorter at period 2 compared to period 1 (26.0 ± 18.2 vs. 46.0 ± 30.1).

Four patient required surgical treatment and one patient died after surgery. The peritoneal culture at diagnosis of EPS showed fungus (32.4%), no growth (29.4%) and gram-negative bacteria (26.5%). The overall mortality rate was 14.7%. No adverse reaction related to tamoxifen was found.

Conclusions: Tamoxifen may be safe and essential for EPS treatment in patients with history of PD treatment. Further studies are necessary to evaluate the effectiveness of long term treatment with tamoxifen.

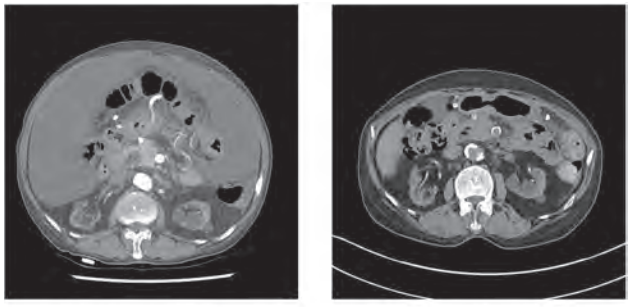


Figure 1. CT images of a EPS patient treated with Tamoxifen

SA-PO455

Association of Hypokalemia Duration and First Episode Peritonitis in Patients on Peritoneal Dialysis: A Single-Center, Retrospective Analysis

Geraldine P. Cercado. *National Kidney and Transplant Institute, Quezon City, Philippines*.

Background: Hypokalemia is a common condition in end-stage renal disease (ESRD) patients undergoing peritoneal dialysis (PD). Peritonitis is one of the most common complications associated with peritoneal dialysis. PD-associated peritonitis (PDAP) carries high morbidity for PD patients, which can cause catheter loss and transition to hemodialysis. First episode of peritonitis affects survival of peritoneal membrane as well as survival of PD patients. Several previous studies were done to determine association the association of hypokalemia and peritonitis. However, previous studies have differing results on the association of hypokalemia and PDAP.

Methods: A single center retrospective study design was conducted in the National Kidney and Transplant Institute, Philippines, reviewing patients initiated with peritoneal dialysis and had first-episode peritonitis from January 2018 to December 2022. A total of 336 patients were included. Hypokalemia duration was calculated as the total number of months that a patient's serum potassium level was continuously below 3.5 mmol/L.

Results: Most patients (246, 73.4%) with first-episode peritonitis had hypokalemic episodes. Shorter duration of hypokalemia had significant association with the peritonitis (p=0.004). Specifically, 50.4% (169) had hypokalemia for a duration of 1-3 months, while 12.2% (41) for 4-6 months and 10.7% (36) for >6 months. It is noteworthy that among hypokalemic patients with peritonitis in the first year, 41% (49 of 117) had early-onset peritonitis and most of these patients (39, 73%) had hypokalemia in the first 3 months of peritoneal dialysis. *Pseudomonas aeruginosa* in Gram-negative, and *Streptococcus spp* in Gram-positive bacteria were the main organisms in this study. Hypokalemic patients had significantly higher incidence of *Staphylococcus aureus* than patients without hypokalemia.

Conclusions: Most patients with PD-associated peritonitis were hypokalemic and most had hypokalemia duration of only 1-3 months. This signifies that PDAP can occur even with the shortest duration of hypokalemia.

SA-PO456

Au@PDA Nanotag-Based Lateral Flow Immunoassay Platform for Highly Sensitive Screening of Pathogenic Bacteria and Fast Evaluation of Antibacterial Agents

Fangfang Zhou, Qun Luo. *Ningbo No 2 Hospital, Ningbo, China*.

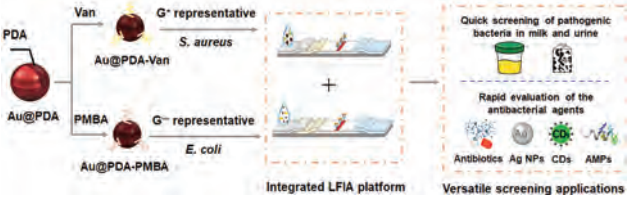
Background: Peritoneal dialysis associated peritonitis (PDAP) is one of the most common complications of PD. Timely and accurate diagnosis of PDAP is the key to improving the dialysis quality and survival rate of PD patients.

Methods: We developed lateral flow immunoassays (LFIAs), which had the merits of low cost, quick screening, and on-site detection are competitive technologies for bacteria detection, but their detection limits depend on the optical performance of the adopted nanotags. Herein, we presented a LFIA platform for bacteria detection using polydopamine (PDA) functionalized Au nanoparticles (denoted as Au@PDA) as the nanotag. The introduction of PDA could provide enhanced light absorption of Au, as well as numerous functional groups for conjugation. Small recognition molecules i.e. vancomycin (Van) and p-mercaptophenylboronic acid (PMBA) were covalently anchored to Au@PDA, and selected as the specific probes towards Gram-positive (G+) and Gram-negative (G-) bacteria, respectively. Taken Staphylococcus aureus (S. aureus) and Escherichia coli (E. coli) as the representative targets of G+ and G- bacteria, two LFA strips were successfully constructed based on the immuno-sandwich principle.

Results: The LFIA platform could quantitatively detect S. aureus and E. coli both down to 102 cfu/mL, a very competitive detection limit in comparison with other colorimetric or luminescent probes-based LFIAs. Furthermore, the proposed two strips were applied for the quantitative, accurate, and rapid screening of S. aureus and E. coli in food and human urine samples with good analytical results obtained. In addition, they were integrated as a screening platform for quick evaluation of diverse antibacterial agents within 3 hours, which is remarkably shortened compared with that of the traditional bacterial culture (over 3 days) and the common plate coating method (over 24 hours).

Conclusions: Au@PDA nanotag-based lateral flow immunoassay platform is highly sensitive screening of pathogenic bacteria and fast evaluation of antibacterial agents for peritoneal dialysis associated peritonitis.

Funding: Government Support - Non-U.S.



SA-PO457

Changes of Incidence and Microbiological Spectrum of Hospitalized Patients with Peritoneal Dialysis-Associated Peritonitis over Time: Results from the TRI-PoD Consortium

Moritz Schanz,[1] Tina Oberacker,[1] Severin Schricker,[1] Gabriele C. Eden,[3] Benedikt Kolbrink,[2] Jan T. Kielstein,[3] Roland Schmitt,[2] Kevin Schulte,[2] Joerg Latus.[1] *[1]Robert-Bosch-Krankenhaus GmbH, Stuttgart, Germany; [2]UKSH Campus Kiel Klinik für Innere Medizin IV mit den Schwerpunkten Nieren- und Hochdruckkrankheiten, Kiel, Germany; [3]Braunschweig Municipal Hospital, Braunschweig, Germany*.

Background: PD-associated peritonitis is the most common infectious complication of PD. The incidence and microbiological spectrum in hospitalized patients with PD-associated peritonitis in Germany is not known, which holds especially true for the time of the SARS-CoV-2 pandemic. The TRI-PoD project, a consortium of three major German nephrology centers (Braunschweig Municipal Hospital, Kiel University Hospital and Robert Bosch Hospital Stuttgart) investigated this topic as part of our mission to overcome barriers to PD initiation and improving PD care.

Methods: The incidence, baseline data and microbiological spectrum of hospitalized patients with PD-associated peritonitis in the period 2017-2023 from the three nephrological centres in Braunschweig, Kiel and Stuttgart were prospectively recorded and retrospectively evaluated.

Results: A total of n=368 patients were included in the analysis. Median (IQR) age was 62 years (50-75). 42.4% of the patients were of female sex. Median body mass index (BMI) was 28.0 kg/m^2 (24.4-32.0). Median initial cell count from the peritoneal dialysate was 6,306/µL (1,980-14,123). Median hospital stay was 9 days (5-18). In 19.8% of the cases catheter removal was necessary. Microbiological results showed sterile peritonitis in 22.0% of the cases. In total, 48.1% were gram positive and 24.2% gram-negative pathogens. A mixed spectrum with gram-positive and negative pathogens was found in 7.1% of cases.

Conclusions: Incidence of PD-associated peritonitis requiring hospitalization has declined over the 5 years, possibly due to increased outpatient management. Beyond that, our data showed a trend towards a lower rate of hospitalized patients with PD associated peritonitis and an increased percentage of gram-positive results in PD dialysate during the SARS-CoV-2 pandemic. A high rate of sterile cultures was found, presumably due to outpatient pretreatment. In addition, a high rate of gram-negative bacteria found. The latter one was related to a high catheter explantation rate. This relative increase in risk might be attributed to the fact that only more severe cases of PD associated peritonitis had been hospitalized.

SA-PO458

Predictive Value of Gram Stain in Peritoneal Dialysis-Associated Peritonitis: Preliminary Results of a Single-Center Pilot Study

Bhavya Chatragadda,[1] Christina A. Raker,[3] Susie L. Hu,[2] Ankur Shah.[2] *[1]University of Rhode Island, Kingston, RI; [2]Brown University Warren Alpert Medical School, Providence, RI; [3]Lifespan Health System, Providence, RI*.

Background: Peritoneal dialysis-associated peritonitis (PDAP) is a common and serious complication in patients undergoing peritoneal dialysis (PD). Early diagnosis and appropriate treatment are crucial for optimal patient outcomes. Gram stain is a rapid

diagnostic tool that may help guide initial treatment decisions. This pilot study aims to evaluate the ability of gram stain to predict culture results in PDAP.

Methods: This single-center, retrospective observational study included all adult patients with PDAP at our institution over a 5-year period (*** to (***). Electronic medical records were reviewed to collect data on peritoneal fluid gram stain and culture results at the time of peritonitis. Gram stain results were categorized as gram-positive, gram-negative, or no organisms seen. Culture results were considered the gold standard for diagnosis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of gram stain were calculated.

Results: A total of 56 patients with PDAP (n = 87 episodes) were included. The mean age was 54 years, and 62.5% were male. Median time on peritoneal dialysis was 1.2 years. Gram stain results showed 29.9% gram-positive, 16.1% gram-negative, 6.8% yeast/polymicrobial, and 47.1% no organisms seen. Culture results were positive in 69.3% of cases, with the most common organisms being coagulase-negative staphylococci (28.8%), Staphylococcus aureus (10.2%), and Klebsiella pneumoniae (10.2%). The overall sensitivity and specificity of gram stain for predicting culture results were 72.9% and 92.3%, respectively. The sensitivity for gram-positive was 79.3%, and for gram-negative, 63.2%. The PPV was 88.5% for gram-positive and 92.3% for gram-negative. The NPV was 89.8% for gram-positive and 90.3% for gram-negative organisms.

Conclusions: While we demonstrate a high sensitivity, specificity, PPV, and NPV of gram stain in predicting culture results it is important to exercise caution when interpreting gram stain results, as inappropriately narrowing antibiotic coverage based solely on gram stain findings can result in undertreatment. Our study provides preliminary information to support larger, multicentric trials to evaluate the potential of gram stain to decrease antibiotic exposure.

SA-PO459

Incidence and Outcomes of Nontuberculous Mycobacterium Infections in Patients Undergoing Peritoneal Dialysis

Rachael Lazar,[1] Meredith L. Zywno,[1] Eric D. Weinhandl,[2,4] Mihran V. Naljayan.[1,3]
[1]DaVita Inc, Denver, CO; [2]Davita Clinical Research, Minneapolis, MN; [3]LSU School of Medicine, New Orleans, LA; [4]University of Minnesota Twin Cities, Minneapolis, MN.

Background: Nontuberculous mycobacterium (NTM) infections in peritoneal dialysis (PD) can lead to morbidity, including hospitalization and catheter removal. Our aim was to describe demographics and outcomes associated with NTM infections among a population of PD patients.

Methods: The study population comprised PD patients with at least one positive exit site or PD fluid culture collected between 1/1/19 and 12/31/23. Data included lab results, demographics, and hospital admission and dialysis treatment dates obtained from electronic medical records at a large dialysis provider (average 26,000 PD patients treated annually). Infection events were defined by positive cultures. Cultures resulting in any NTM organism were categorized as NTM infection events, and cultures resulting in non-NTM organism(s) were categorized as "other." Outcomes were hospital admission and discontinuation of PD within 30 days of culture collection date.

Results: Over the 5-year period, NTM (N=305) showed greater tropism for exit site (vs PD fluid) than other organisms (79% vs 44% infections at exit site). Regarding demographics among patients with NTM infection, median age at infection was 60 years; 62% were male and 46%, 24%, and 18% were non-Hispanic White, Hispanic, and non-Hispanic Black, respectively. At the time cultures were collected, median time on PD was 5 months (IQR: 2-13). The majority of cases occurred in the Southeast (49%) or Southwest (21%) regions of the US. Thirty-day risks for hospital admission and discontinuation of PD were greater following NTM infection events (35%, 28%, respectively) than following non-NTM infections (21%, 7%, respectively): adjusted odds ratio (aOR) 3.1, 95% CI: 2.8-3.3 for hospital admission and aOR 8.3, 95% CI: 8.0-8.6 for PD discontinuation. Exit site infection-specific risks for outcomes were also greater for NTM infections (aOR 2.0, 95% CI: 1.7-2.3 for hospital admission and aOR 7.9, 95% CI: 7.5-8.2 for PD discontinuation).

Conclusions: NTM infections among PD patients most commonly occurred among patients treating in the southern US and as exit site infections rather than PD fluid infections. Even after controlling for culture source and demographic factors, NTM infection events were associated with more frequent negative outcomes, including hospitalization and discontinuation of PD, compared with other infections.

SA-PO460

Development of Risk-Prediction Tool for Peritoneal Dialysis-Associated Peritonitis and External Validation in the PDTAP Cohort

Yumeng Qiao, Jie Dong. *Peking University First Hospital, Beijing, China.*

Background: Although peritoneal dialysis related peritonitis is a common complication among peritoneal dialysis (PD) patients, there is no validated and recognized tool to predict disease prognosis. This limits patient-specific risk stratification and treatment decisions.

Methods: A single-center peritonitis cohort was used for model derivation and Peritoneal Dialysis Telemedicine-assisted Platform (PDTAP) cohort was used for external validation. Logistic regression models were used to analyze the risk of treatment failure within 1 month of peritonitis, i.e. a composite of peritonitis-related mortality and transferring to hemodialysis. The discrimination and calibration were evaluated using C statistics, Hosmer-Lemeshow (HL) test, Akaike information criterion (AIC), Bayesian information criterion (BIC) and calibration curves. Predictors were weighted to calculate a risk score.

Results: Totally, 528 and 1190 first-episode peritonitis were included in the derivation cohort and validation cohort, respectively. A total point of 5 in basic model was developed including baseline albumin <35g/L and PD duration >25months, and a total point of 29 in extended model was developed including age >60 years old, PD duration >25months, the white cell count >300/mm3 in dialysis effluent on the day 3, and causative organism. Compared with basic model, the extended model performs better with higher C statistic [0.744 (95%CI 0.684-0.804) vs. 0.635 (95%CI 0.574-0.696), P = 0.012], HL statistic [6.73 (8df; P = 0.566) vs. 3.27 (2df; P = 0.195) and lower AIC (389.10 vs. 509.74) and BIC (421.99 vs. 522.50). Both models in the validation cohort performed similar or better discrimination and calibration, as shown in C statistics [0.620 (95% CI 0.579-0.661) in basic model; 0.871 (95%CI 0.837, 0.905) in extended model] and HL statistic [0.31 (2df; P = 0.858) in basic model; 7.86 (8df; P = 0.447) in extended model].

Conclusions: In this study, the basic and extended models for predicting treatment failure of peritonitis were established based on commonly used clinical data, which were applicable to different clinical scenarios and facilitated clinical doctors to identify high-risk individuals and adjust treatment decisions.

SA-PO461

High Effluent Lactic Acid Levels Predict the Adverse Outcomes of Peritoneal Dialysis-Associated Peritonitis: A New Role for an Old Marker

Xiao Yu,[1,2] Ying Ma.[2] *[1]The Second Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang, China; [2]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: Peritonitis remains the major complication of peritoneal dialysis(PD). Acute inflammation promotes glycolysis and increases the production of lactic acid by increasing the NADH-NAD^+ ratio. The role of monitoring effluent lactic acid levels during treatment of peritoneal dialysis-associated peritonitis(PDAP) deserves attention.

Methods: We retrospectively collected effluent and serum lactic acid levels, and other laboratory and clinical characteristics, as well as treatment outcomes of PDAP occurred between November 2022 and October 2023. Adverse outcomes of PDAP were defined as no cure, including recurrent, relapse, catheter removal, transfer to hemodialysis and death. According to treatment outcomes, PDAP episodes were divided into cure group and no cure group. Characteristics at the beginning of PDAP were compared between the 2 groups. Factors associated with clinical outcome were analyzed using logistic regression modeling.

Results: Totally, 80 PDAP episodes were recorded in 67 PD patients. Their baseline average age was 52.4±13.8 years old, among which 64.2% were men. As for the clinical outcomes of the PDAP, 60 episodes were cured, while 20 episodes experienced adverse outcomes (no cure), among which relapse was the leading one (n=12, 15.0%), followed by catheter removal. No difference was observed in age, gender, Charlson's Comorbidity Index, blood pressure, BMI, PD duration, peritoneal membrane transport type or Kt/V microbiologic cause between cure group and no cure group. Effluent lactic acid levels was significantly higher in no cure group[7.95(6.43,12.1) Vs 6.45(3.13,8.9), p=0.006], accompanied by a higher Day-5 effluent WCC. Multiple Logistic regression analysis showed higher effluent lactic acid levels was the independent risk factors for peritonitis adverse outcomes(odds ratio(OR)=0.822, p=0.012). ROC analyses of effluent lactic acid levels yielded a moderate discriminative capacity for adverse outcomes (area under curve(AUC)=0.71, p=0.006). The threshold values with the highest Youden's index were 5.25 mg/L (sensitivity=100%, specificity=45%). Calibration for the ROC curve of effluent lactic acid concentration in diagnosing adverse outcome of PDAP was 0.291(Hosmer-Lemeshow goodness-of-fit test:x^2=13.667, p=0.091).

Conclusions: Higher effluent lactic acid levels could predict adverse outcome of PDAP independently.

SA-PO462

Peritonitis Trends and Patient Outcomes in Peritoneal Dialysis from a Portuguese Center: Decades of Data Unlocked

Joana P. Dias,[1] Vitória V. Paes de Faria,[1] Maria B. Bessa,[1] Rute Carmo,[1] Daniela Lopes,[1] Clara Almeida,[1] Ana Marta Gomes.[1,2] *[1]Unidade Local de Saude de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; [2]Universidade do Porto Unidade Multidisciplinar de Investigacao Biomedica, Porto, Portugal.*

Background: Peritonitis is a common and severe complication of peritoneal dialysis (PD). This study aims to ascertain how the rate of peritonitis is evolving in our center, examine the factors that influence these cases and their outcomes, including the causative infectious agent, hospitalization and technique transference.

Methods: Between January 1, 1999, and December 31, 2023, 152 patients who started PD at our institution were included in the study. All PD-related peritonitis episodes were collected. Complicated peritonitis included recurrent, relapsing, repeating or refractory cases, guided by ISPD 2022 recommendations.

Results: The rate of peritonitis showed a steady decline over the study period, dropping from 0.7 episodes/patient in 1999 to 0.27 by the study's end. The majority of infections (76.3%) were managed on an outpatient basis and 72.4% progressed to healing. The most common causative agents were Gram-positive (GP) (57.9%), including coagulase-negative staphylococci (22.6%). GP infections were significantly linked to recent antibiotic exposure (p=0.017). Moreover, fungal peritonitis was found to be more common among male patients (p=0.032) and those with diabetes (p=0.046). Cases involving Gram-negative (GN) and fungal microorganisms exhibited worse outcomes, as depicted in Table 1.

Conclusions: Over the years, our center observed a notable decline in PD-related peritonitis, with most cases being effectively treated on an outpatient basis due to improved aseptic techniques, enhanced patient education, advancements in PD equipment, better antibiotic protocols, and regular monitoring and follow-up care. GP organisms remained the major cause of PD-related peritonitis, while GN and fungal peritonitis were associated with worse outcomes and a higher rate of PD failure, which is aligned with current literature. Understanding the trajectory of our center's experience provides invaluable insights for the development and continuous growth of our practices, enhancing patient outcomes and elevating the standards of care in PD.

Outcome	Gram Positive (n=208)	Gram Negative (n=44)	Fungal (n=9)	Polymicrobial (n=16)
Complicated peritonitis	80 (38.5%), p = 0.711	24 (54.5%), p = 0.051	8 (88.9%), p = 0.003	11 (68.8%), p = 0.014
Catheter removal	49 (32.5%), p = 0.010	18 (40.9%), p = 0.009	9 (100%), p < 0.001	8 (50%), p = 0.036
Hospitalization	45 (29.8%), p = 0.024	18 (40.9%), p = 0.004	6 (66.7%), p = 0.007	5 (31.3%), p = 0.546
Technique transference	28 (18.5%), p = 0.007	11 (25%), p = 0.011	5 (55.6%), p = 0.002	3 (18.8%) p=0.446

SA-PO463

Technique Survival after Relapsing Peritonitis: Experience from a Center in Mexico

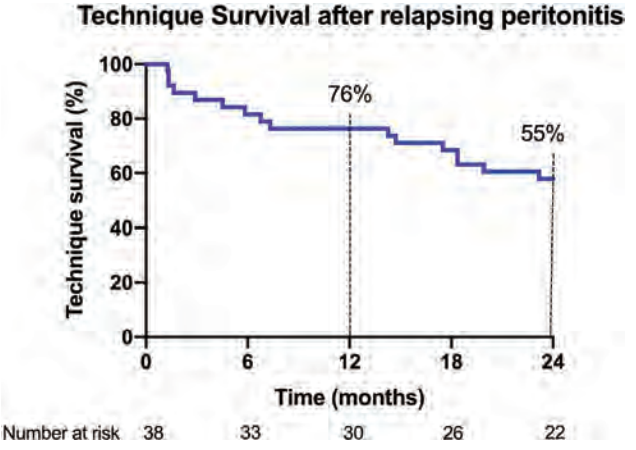
Miguel Angel Franco Barrera, Luis A. Camacho-Murillo, Hugo Sergio Breien Alcaraz. *Hospital Regional Valentin Gomez Farias ISSSTE, Zapopan, Mexico.*

Background: Relapsing peritonitis significantly impacts the outcomes of peritoneal dialysis patients. Catheter removal and temporary migration to hemodialysis are part of the routine management in some cases. In these instances, the response or failure of antibiotic treatment guides therapeutic decisions and patient outcomes. An alternative approach involves simultaneous or short-term catheter removal and repositioning in episodes where infection control is evident.

Methods: A retrospective cohort analysis was conducted from January 1, 2013, to December 31, 2023, at a peritoneal dialysis center in Guadalajara, Jalisco, Mexico. The entire population enrolled in the peritoneal dialysis program was included in the study. The aim of this research is to describe the outcomes (technique survival, 30-day mortality) observed in patients with relapsing peritonitis that remained in peritoneal dialysis.

Results: Total population of the program included 854 patients. Among 281 patients, 585 episodes of peritonitis were recorded, and 51 episodes were classified as relapsing and included in the analysis. Of them 13 (25%) were transferred to hemodialysis, and 38 (75%) remained in peritoneal dialysis. Among patients who remained on peritoneal dialysis, the median technique survival was 32 months. Seventy-six percent maintained the technique at 12 months, and 65% at 24 months. Among the population that remained on dialysis, 2 (4%) patients died within 30 days following the recurrence event.

Conclusions: In patients with relapsing peritonitis, continuation of peritoneal modality is achievable with an acceptable technique survival.



SA-PO464

Trends, Outcomes, and Economic Implications of Peritoneal Dialysis-Associated Peritonitis: A National Cohort Study

Shagun Vashisth,[1] Christina A. Raker,[2,1] Susie L. Hu,[1,2] Ankur Shah.[1,2] *[1]Brown University Warren Alpert Medical School, Providence, RI; [2]Rhode Island Hospital, Providence, RI.*

Background: Peritoneal dialysis-associated peritonitis (PDAP) is a serious complication of peritoneal dialysis, associated with significant morbidity, modality transition, and mortality. We provide an update on the national burden of this significant complication in the US, highlighting trends in demographics, treatment practices, and in-hospital outcomes of PDAP from 2016 to 2020.

Methods: Utilizing a national all-payer dataset of hospitalizations in the US, we conducted a retrospective cohort study of adult hospitalizations with a primary diagnosis of PDAP from 2016 to 2020. We analyzed demographic, clinical, and hospital-level data, evaluating in-hospital mortality, PD catheter removal, length of stay, and healthcare spending. Multivariable logistic regression adjusted for demographic and clinical covariates was employed to identify risk factors associated with adverse outcomes.

Results: This study included 17,335 PDAP hospitalizations from 2016 to 2020. In-hospital mortality was observed in 3.29% of cases and 23.2% of episodes resulted in removal of the PD catheter. Healthcare expenditures associated with PDAP totaled over $75,000 per admission. Additionally, geographic variations in treatment patterns were present, with treatment at western and teaching hospitals associated with increased rates of catheter removal relative to northeastern and non-teaching centers and a mean cost of nearly $55,000 more in Western states compared to Midwest states. Risk factors associated with adverse outcomes are represented in Table 1.

Conclusions: PDAP is a major cause of mortality among PD patients, and there is a vital need for future studies to examine the impact of hospital location and teaching status on PDAP outcomes, which can inform treatment practices and resource allocation.

Table 1. Adjusted Odds Ratios for Catheter Removal and Mortality by Risk Factors

Risk Factor	Adjusted Odds Ratio (95% CI) for Catheter Removal	Adjusted Odds Ratio (95% CI) for Mortality	Adjusted Odds Ratio (95% CI) for Catheter Removal or Mortality
Age (per year)	1.00 (1.00 - 1.01)	1.03 (1.02 - 1.05)	1.01 (1.00 - 1.01)
Female	0.86 (0.73 - 1.02)	1.44 (0.96 - 2.15)	0.91 (0.78 - 1.07)
Race			
White	1.00 (ref)	1.00 (ref)	1.00 (ref)
Black	0.97 (0.80 - 1.18)	0.51 (0.30 - 0.89)	0.93 (0.77 - 1.12)
Hispanic	0.83 (0.64 - 1.08)	0.68 (0.34 - 1.36)	0.80 (0.62 - 1.03)
Asian/Pacific Islander	0.92 (0.63 - 1.33)	1.37 (0.67 - 2.79)	0.89 (0.62 - 1.28)
Native American	0.85 (0.43 - 1.66)	1.93 (0.43 - 8.67)	1.03 (0.55 - 1.96)
Other	1.42 (0.80 - 2.51)	0.56 (0.08 - 3.83)	1.40 (0.80 - 2.44)
Charlson Comorbidity Index (per point)	1.17 (1.04 - 1.32)	1.55 (1.18 - 2.03)	1.21 (1.09 - 1.36)
Congestive Heart Failure	0.99 (0.80 - 1.21)	1.26 (0.81 - 1.97)	1.02 (0.84 - 1.25)
Peripheral Vascular Disease	1.14 (0.76 - 1.69)	2.01 (1.03 - 3.95)	1.24 (0.86 - 1.81)
Hypertension	0.91 (0.63 - 1.33)	0.49 (0.24 - 1.02)	0.92 (0.63 - 1.34)
Diabetes	0.91 (0.71 - 1.16)	0.48 (0.28 - 0.82)	0.89 (0.71 - 1.13)
Need for Pressors	2.12 (1.12 - 4.01)	18.90 (8.45 - 42.27)	4.04 (2.09 - 7.78)
Teaching Hospital	1.28 (1.03 - 1.60)	0.93 (0.56 - 1.54)	1.28 (1.03 - 1.59)
Hospital Region			
Northeast	1.00 (ref)	1.00 (ref)	1.00 (ref)
Midwest	1.17 (0.88 - 1.56)	0.70 (0.35 - 1.40)	1.05 (0.80 - 1.38)
South	0.97 (0.74 - 1.26)	1.03 (0.57 - 1.85)	0.92 (0.72 - 1.19)
West	1.45 (1.08 - 1.95)	0.96 (0.50 - 1.84)	1.33 (1.00 - 1.77)
Hospital Bed Size			
Small	1.00 (ref)	1.00 (ref)	1.00 (ref)
Medium	1.09 (0.84 - 1.43)	0.61 (0.34 - 1.09)	1.03 (0.80 - 1.33)
Large	1.09 (0.86 - 1.37)	0.72 (0.45 - 1.19)	1.05 (0.84 - 1.32)
Hospital Location			
Rural	1.00 (ref)	1.00 (ref)	1.00 (ref)
Urban	1.11 (0.69 - 1.80)	1.12 (0.43 - 2.91)	1.10 (0.70 - 1.73)

Models adjusted for age, gender, race, Charlson comorbidity, diabetes, hypertension, PVD, CHF, hospital region, teaching vs nonteaching hospital, rural vs urban hospital, hospital bed size, and payer.

SA-PO465

Peritonitis and Stool Burden on Plain Abdominal Radiographs in Patients on Peritoneal Dialysis

Kentaro Nakai, Yuho Ota, Mako Ochiai, Sonoda Shinichiro, Keitaro Uehara, Masanori Tokumoto. *Fukuoka Sekijuji Byoin, Fukuoka, Japan.*

Background: Peritonitis is a significant and troublesome complication of peritoneal dialysis. It is imperative to overcome peritonitis to preserve peritoneal function and prolong peritoneal dialysis. Bacterial translocation from the intestinal tract is the most probable candidate for a bacterial portal of entry in peritonitis associated with peritoneal dialysis, and it has been postulated that constipation may be related to this mechanism. The definition of constipation is based on stool characteristics and subjective evaluation, which is often difficult to assess objectively. Attempts have been made to assess the degree of stool burden with plain abdominal radiographs, which can be obtained routinely.

Methods: This was a retrospective study comprising 45 patients who were on peritoneal dialysis at the end of 2020. Patients were divided into two groups according to the median score of stool retention on plain abdominal radiographs. The three-year clinical outcomes of transition to hemodialysis and peritonitis were calculated for each group using the Kaplan-Meier method, and adjusted hazard ratios were calculated using the Cox regression model.

Results: There were no significant differences between the two groups in age, gender, diabetes status, dialysis vintage, history of peritonitis, and biochemical parameters. A total of 13 patients (29%) developed peritonitis related to peritoneal dialysis. Of these, 22 patients (49%) were converted to hemodialysis, 1 patient (2%) died, and 1 patient (2%) underwent renal transplantation. The Kaplan–Meier analysis demonstrated that patients in the high-score group exhibited a significantly shorter time to first peritonitis than those in the control group, even after adjusting for confounding factors. However, no significant association was found between radiographic scores and transition to hemodialysis.

Conclusions: The stool burden score was evaluated by plain abdominal radiographs and demonstrated a significant independent correlation with the time to first peritonitis, though no such correlation was observed with death or transition to hemodialysis. The results of this study may be utilized to assess the efficacy of potential interventions aimed at reducing peritonitis.

SA-PO466

Gut Microbiota in Patients on Peritoneal Dialysis

Shutov Evgeny, Stepan B. Alexeevich, Irina Fedoseeva. *Botkin Hospital, Moscow, Russian Federation.*

Background: In recent years, the research of the structure and role of the gut microbiota in patients with CKD has been of increasing interest due to the cumulation of data on the involvement of intestinal microflora in the onset of typical complications. The investigation of the gut microbiota in patients on peritoneal dialysis is especially relevant given the high frequency of dialysis peritonitis caused by intestinal flora, up to 40%.

Methods: In our study we included 39 patients, age 55±16.4 years (22 f/17 m), who received peritoneal dialysis at our nephrology center. The intestinal microbiota was analyzed using 16s rRNA sequencing. Correlation analysis was carried out using the Pearson and Spearman coefficient.

Results: Fig.1 shows microorganisms at the phylum, class, order, family and genus level in patients receiving PD. The visual shows that, on average, the prevailing phylum in the samples was Bacillota, and the second largest phylum was Bacterioidota. Bacterioidia of the Bacterioidota phylum and Clostridia and Bacilli of the Bacillota phylum were significant at the class level. The phylum Actinomycetota included the classes Coriobacteriia and Actinobacteria. At the order level, the 10 most represented taxonomic groups included Lachnospirales, Oscillospirales, Lactobacillales, Erysipelotrichales, Christensellales, Peptostreptococcales, Bacteroidales, Bifidobacteriales, Coriobacteriales and Enterobactertales. A high positive correlation (R =0.7, p<0.005) was found for ferritin and bacteria of the genera Citrobacter, Ligilactobacillus, Lactococcus, Porphyromonas, Klebsiella, Leuconostoc, Lachnoclostridium and Fusobacterium. The analysis of alpha diversity showed an inverse correlation (R -0.5,p<0.001) between the Simpson, inverted Simpson and Shannon indices and the number of peritonitis transferred, The decrease in alpha diversity was significantly inversely correlated with ferritin levels (p < 0.01).

Conclusions: A decrease in the alpha diversity of microorganisms correlates with high ferritin levels and the frequency of dialysis peritonitis. There were no significant correlations with age and the studied biochemical parameters.

Funding: Government Support - Non-U.S.

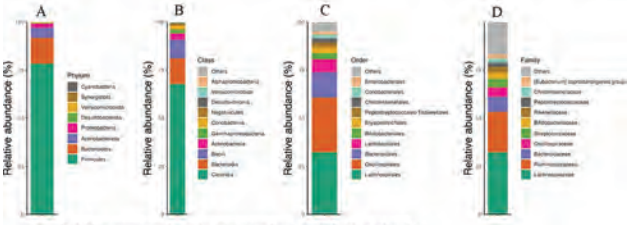


Figure 1. Relative average number of bacteria in samples at the level of A - phylum, B - class, C - order, D – family.

SA-PO467

Defining the Optimal Frequency of Dialysis Adequacy Test for Patients on Peritoneal Dialysis

Jack K. Ng, Winston W. Fung, Cheuk-Chun Szeto. *The Chinese University of Hong Kong, Hong Kong, Hong Kong.*

Background: Peritoneal Dialysis (PD) is a cost-effective treatment for end-stage kidney disease, with the adequacy of small solute clearance being a key factor in determining the PD regimen. Although regular monitoring of small solute clearance is recommended, recent guidelines emphasize a person-centered approach. We hypothesize that peritoneal Kt/V(urea) remains stable in most patients and does not require frequent monitoring.

Methods: We reviewed 11427 PD adequacy tests in 1874 PD patients. The serial change in Kt/V-PD was compared. The effect of daily exchange volume, peritonitis episodes, PD solution osmolality, duration of dialysis, and other baseline parameters were explored.

Results: The median duration between two dialysis adequacy tests was 7.0 months (IQR 5.6 to 11.0 months). The average change in Kt/V-PD between two tests was 0.024 ± 0.319. The change in Kt/V-PD was significantly higher after an increase in exchange volume than those with a static PD exchange volume (0.176 ± 0.453 vs 0.012 ± 0.302, p<0.0001). When dialysis adequacy test pairs that had a static PD exchange volume were analyzed, the change in Kt/V-PD did not differ between tests that were interposed with peritonitis episodes and those without (0.006 ± 0.317 vs 0.013 ± 0.300, p = 0.4). The change in Kt/V-PD was similar when the adequacy test was repeated after an increase in PD solution osmolality as compared to those with a static PD regimen (-0.011 ± 0.367 vs 0.014 ± 0.296, p = 0.1). There was no correlation between the change in Kt/V-PD and the duration between two adequacy tests (r = 0.002, p = 0.8).

Conclusions: Our result shows that Kt/V-PD remains stable in most patients within 12 months and does not require frequent monitoring.

SA-PO468

Decline of Kidney Function before and after Start of Peritoneal Dialysis (PD)

Markus Björksten,[2,1] Abdul Rashid T. Qureshi,[2] Peter Stenvinkel,[2,1] Olof Heimburger.[2,1] *[1]Karolinska Universitetssjukhuset, Huddinge, Sweden; [2]Karolinska Institutet Institutionen for Klinisk Vetenskap Intervention och Teknik, Huddinge, Sweden.*

Background: Residual kidney function (RKF) is a key component for PD adequacy and is associated with improved volume status, and clinical outcome. The RKF decline rate has been reported to diminish after PD initiation. The aim was to compare kidney function decline, and diuresis decline, before and after start of PD, and to compare eGFR and GFR from urine collections (uGFR) predialysis.

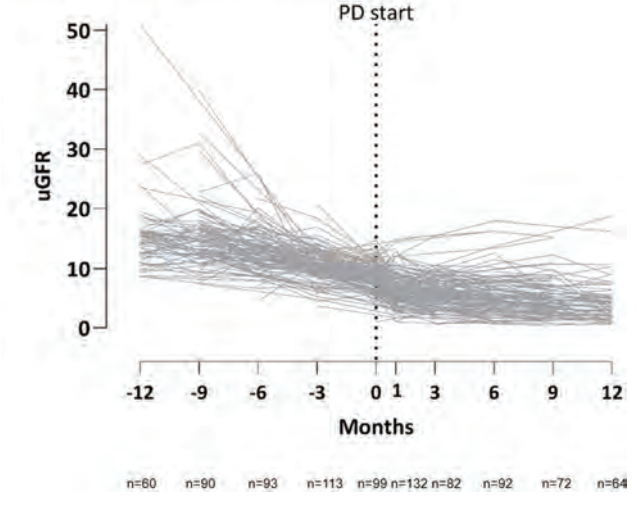
Methods: We studied 138 patients (42% females, mean age 55±13 years) starting PD during 2000-2019 in a prospective study. Inclusion criteria were ≥ 1 urine collection before, and ≥ 1 after PD initiation, PD initiation < 6 months after study inclusion and > 6 months of PD. Data was collected from 12 months before to 12 months after PD start. uGFR was calculated as average of creatinine and urea clearance from 24-hour urine collections corrected for BSA. eGFR was calculated using CKD-epi 2021.

Results: The mean uGFR was 15.5±6.2 and eGFR 12.1±5.8 at 12 months before PD start, and PD was started at mean uGFR 8.5±2.3 and eGFR 5.8±1.9 ml/min/1.73m². The GFR decline rate before PD start was similar using eGFR or uGFR. However, uGFR was higher than eGFR. The uGFR decline rate was slower after PD start. Notably, there was a marked attenuation at 1 month of PD. However, urine volume decline rate increased after PD start, likely because of peritoneal ultrafiltration.

Conclusions: The results could suggest that an earlier initiation of PD may be beneficial for preservation of RKF.

Funding: Private Foundation Support

Decline of uGFR before and after PD start



Decline of kidney function and diuresis before and after PD start[1]

	Before PD initiation	After PD initiation
GFR	-0.59	-0.34
eGFR	-0.52	NA
Diuresis	-26	-106

[1]Values are described as average decline rate per month. uGFR and eGFR are presented as mL/min/1.73m². Diuresis is presented as ml/day.

SA-PO469

A Single-Centre Experience with Assisted Home Hemodialysis in Long-Term Care Facilities: A Cost-Feasibility Study

Gihad Nesrallah,[1,2] Jessica Wang,[1] Monica Silva,[1] Justin M. Ashley,[1] Shabnam Hamidi,[1] Danica Lam,[1] David C. Mendelssohn.[1,2] *[1]Humber River Health, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada.*

Background: For hemodialysis (HD) recipients residing in long-term care (LTC), the COVID-19 pandemic created several barriers to care. To address these challenges, we established a pilot program of fully-assisted HD provided on-site to LTC residents (LTC-HD) by registered nurses (RNs), registered practical nurses (RPNs) and personal support workers (PSWs).

Methods: We performed a cost-feasibility analysis from the provider perspective using a bottom-up micro-costing approach based on real costs incurred between March 2020-March 2023. We examined a range of staffing models (in-sourced vs. out-sourced/agency and 1:1 vs higher patient:staff ratios) for providing daily (6/week, 2hrs) and conventional (3/week, 4hrs) HD. Direct costs included labor, medical supplies, and dialysis consumables using standard (Fresenius 4008K) and portable (NxStage) equipment. Indirect costs included equipment maintenance, injectables, travel, and staff replacement costs. We excluded capital, patient-borne, non-dialysis costs, and physician fees. Costs are reported in CAD/year using FY2022/23 prices.

Results: During follow-up, 44 patients received LTH-HD at 15 facilities. Bundled rates were $50,076 and $83,467 for conventional and daily HD, respectively. Conventional HD with PSWs (1:1) yielded a net loss of $2,947 vs. net surplus of $3,076 with out- vs. in-sourcing, respectively. Staffing with in- and out-sourced RNs and RPNs yielded net losses with 1:1 staffing but generated surpluses of $17,426 and $20,546 when insourced RPNs and RNs treated provided 2:1 and 3:1 clustered HD. Daily HD with NxStage cost $13,681/yr more vs. standard equipment resulting in net losses in all scenarios. Daily HD yielded a surplus when staffed by in-sourced staff with further savings under clustered models.

Conclusions: Fully-assisted LTC-HD is financially feasible under current bundled rates in Ontario, with greater savings in clustered settings with in-sourced staff.

Table 1. Cost-feasibility of LTC-HD under varying operating models for daily and conventional hemodialysis. Operating models are ranked by net cost; red font denotes net deficit.

Staff Type	Care Setting/Location	In vs. Out-Sourced	Patient:Staff Ratio	HD Equipment	Bundle Amount	Direct Labour Costs	Consumable Costs	Total Expenses	Surplus/Deficit per Annualized Patient
Daily HD									
RPN	Home or Individual LTC pt	Out	1:1	NxStage	$83,467	$81,606	$30,096	$117,152	$(33,685)
RN	Home or Individual LTC pt	In	1:1	NxStage	$83,467	$78,063	$30,096	$113,609	$(30,142)
RPN	Home or Individual LTC pt	Out	1:1	Fresenius	$83,467	$81,606	$16,415	$104,471	$(21,004)
RN	Home or Individual LTC pt	In	1:1	Fresenius	$83,467	$78,063	$16,415	$100,929	$(17,462)
PSW	Home or Individual LTC pt	Out	1:1	NxStage	$83,467	$60,881	$30,096	$96,427	$(12,960)
RPN	Home or Individual LTC pt	In	1:1	NxStage	$83,467	$60,466	$30,096	$96,012	$(12,545)
PSW	Home or Individual LTC pt	In	1:1	NxStage	$83,467	$51,102	$30,096	$86,848	$(3,381)
PSW	Home or Individual LTC pt	Out	1:1	Fresenius	$83,467	$60,881	$16,415	$83,746	$(279)
RPN	Home or Individual LTC pt	In	1:1	Fresenius	$83,467	$60,466	$16,415	$83,332	$135
PSW	Home or Individual LTC pt	In	1:1	Fresenius	$83,467	$55,748	$16,415	$78,613	$4,854
RN	LTC (Congregate)	In	2:1	Fresenius	$83,467	$39,032	$16,415	$60,147	$23,320
RPN	LTC (Congregate)	In	2:1	Fresenius	$83,467	$30,233	$16,415	$51,348	$32,119
RN	LTC (Congregate)	In	3:1	Fresenius	$83,467	$26,021	$16,415	$46,553	$36,914
Conventional HD									
RPN	Home or Individual LTC pt	Out	1:1	Fresenius	$50,076	$49,458	$9,675	$65,583	$(15,508)
RN	Home or Individual LTC pt	In	1:1	Fresenius	$50,076	$47,215	$9,675	$63,340	$(13,264)
PSW	Home or Individual LTC pt	Out	1:1	Fresenius	$50,076	$36,898	$9,675	$53,073	$(2,947)
RPN	Home or Individual LTC pt	In	1:1	Fresenius	$50,076	$36,550	$9,675	$52,675	$(2,599)
PSW	Home or Individual LTC pt	In	1:1	Fresenius	$50,076	$30,875	$9,675	$47,000	$3,076
RN	LTC (Congregate)	In	2:1	Fresenius	$50,076	$23,607	$9,675	$37,983	$12,093
RPN	LTC (Congregate)	In	2:1	Fresenius	$50,076	$18,275	$9,675	$32,650	$17,426

SA-PO470

A Single-Centre Experience with Assisted Home Hemodialysis in Long-Term Care Facilities

Justin M. Ashley,[1,2] Shayne K. Joseph,[3] Shabnam Hamidi,[1] Gihad Nesrallah,[1,2] Danica Lam,[1] David C. Mendelssohn.[1,2] *[1]Humber River Health, Toronto, ON, Canada; [2]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [3]McMaster University, Hamilton, ON, Canada.*

Background: To address challenges imposed by the COVID-19 pandemic, our renal program expanded assisted home hemodialysis (HD) services to provide on-site HD to patients residing in long-term care (LTC) facilities. The purpose of this study was to describe the patient and treatment characteristics and outcomes in a cohort of patients undergoing home HD in LTC facilities.

Methods: We conducted a retrospective review of all consecutive patients across 15 LTC facilities within our catchment area in Toronto who converted from in-centre HD to LTC-HD between March 2020 and March 31, 2023. We included all adult patients who received assisted conventional (3 HD/week, 3-4 hr) and short-daily (5-7 HD/week, 2-3 hr) HD provided by a registered nurse, registered practical nurse, or personal support worker during the study period. We extracted all data from our hospital electronic record system, including baseline demographics, comorbidities, dialysis prescriptions, deaths, hospitalizations, COVID-19 related and unrelated infections.

Results: The mean age among 44 eligible patients was 75.6 years with 30 (70%) male patients and 13 (30%) female patients. Thirty-one (67%) patients had type two diabetes. There were 20 patients (45%) on conventional HD and 24 patients (54%) on daily HD at the time of enrolment. Eighty-five percent had limited mobility or were bedbound and

33% had dementia. During follow-up, there were 23 deaths with a one-year mortality rate of 45%. There were 69 hospitalization events, including 13 intensive care unit (ICU) admissions, with an average length of stay of 11 days. The number of access related complications was 18. There were 10 COVID-19 infections.

Conclusions: Assisted hemodialysis in LTC facilities is a patient-centered means by which to provide dialysis to a frail and vulnerable patient population. As expected, clinical outcomes were relatively poor. Additional analyses with control data as well as costing and ethical evaluations are ongoing and will be reported separately.

SA-PO471

Connected Home Hemodialysis Machine Use and Transition to In-Center Hemodialysis

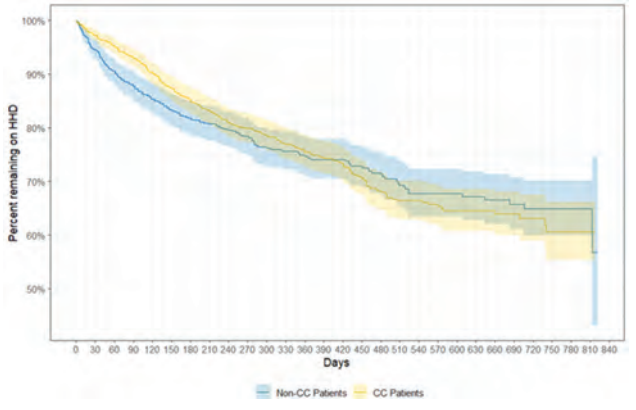
Miranda Hurtado,[1] Meredith L. Zywno,[1] Eric D. Weinhandl,[2] Mihran V. Naljayan.[1,3] *[1]DaVita Inc, Denver, CO; [2]Davita Clinical Research, Minneapolis, MN; [3]LSU School of Medicine, New Orleans, LA.*

Background: Although home hemodialysis (HHD) has been growing rapidly, ongoing expansion is constrained by relatively high rates of transition to in-center hemodialysis (ICHD) during the first year of therapy. We aimed to assess whether the use of an internet-connected home hemodialysis machine (CC), which employs a tablet and relays treatment data to dialysis providers, was associated with a decreased rate of transitioning to ICHD.

Methods: The study population included all HHD patients who began treatment in a large dialysis provider organization between July 2021 and December 2022 and initiated use of a CC [NxStage System One with Nx2me Connected Health, Fresenius Medical Care] within 30 days of first documented treatment. Patient data were obtained from electronic medical records and initiation of CC was ascertained from electronic treatment records. Patients were followed from 30 days after HHD initiation until the earliest of transition to ICHD, death, kidney transplant, or end of study follow-up. Kaplan-Meier estimation and Cox regression were used to compare technique survival in CC and non-CC patients at 90 days and 360 days; death and transplantation were classified as censoring events.

Results: The study cohort included 1,563 patients, among whom 930 (60%) used a CC. Mean age among patients was 55.8 years, and 39% of patients were female. In the HHD patient population, CC and non-CC patients had no significant difference in risk of transitioning to ICHD (HR: 1.00, 95% CI: 0.82, 1.21). However, when follow-up was limited to the first 180 days, CC patients experienced a 22% lower rate of transition to ICHD, compared to non-CC patients (HR: 0.78, 95% CI: 0.61, 1.00).

Conclusions: The use of a CC was not associated with a differential risk of transition to ICHD from HHD in our study population, although there was evidence of potential benefit during the first 6 months. More study is needed to determine whether this technology could positively impact home modality retention.



SA-PO472

Association of Connected Cycler Use with Rate of Transition from Peritoneal Dialysis to In-Center Hemodialysis

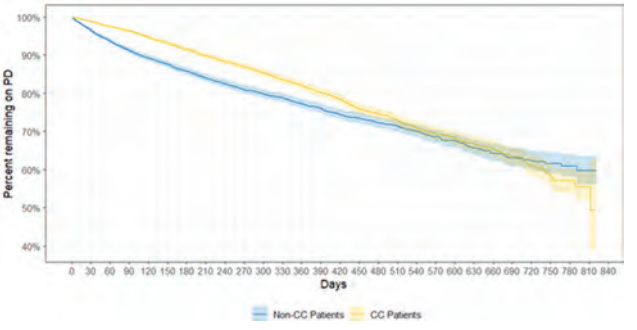
Miranda Hurtado,[1] Meredith L. Zywno,[1] Eric D. Weinhandl,[2] Mihran V. Naljayan.[1,3] *[1]DaVita Inc, Denver, CO; [2]Davita Clinical Research, Minneapolis, MN; [3]LSU School of Medicine, New Orleans, LA.*

Background: Attrition from home dialysis is an ongoing challenge, sometimes attributable to the difficulty of assessing prescription adherence in real time. With increasing use of remote monitoring platforms, we aimed to assess whether the use of an internet-connected automatic peritoneal dialysis cycler (CC), which transmits treatment data to the dialysis provider on a daily basis, was associated with lower rate of transition to in-center hemodialysis (ICHD).

Methods: The study population included all peritoneal dialysis (PD) patients who began treatment in a large dialysis provider organization between July 2021 and December 2022 and initiated use of a CC [Homechoice Claria or Amia, Baxter International] within 30 days of first documented treatment. Patient data were obtained from electronic medical records and initiation of CC was ascertained from electronic treatment records. Matched pairs of CC PD patients and non-CC PD patients were constructed, based on clinical and demographic factors, to address measurable confounding. Patients were followed from 30 days after PD initiation until the earliest of transition to ICHD, death, kidney transplant, or end of study follow-up. Kaplan-Meier estimation and Cox regression were used to compare technique survival in CC and non-CC patients; death and transplantation were classified as censoring events.

Results: The study cohort included 5,308 pairs of CC and non-CC PD patients. Mean age was 60.5 years, and 41% of patients were female. Among CC patients, 5% experienced transition to ICHD after 90 days, compared to 10% of non-CC patients. After 360 days, 18% of CC patients experienced transition to ICHD, compared to 25% of non-CC patients. CC patients had a 16% lower rate of transition to ICHD, compared to non-CC patients (HR: 0.84, 95% CI: 0.78, 0.91).

Conclusions: The use of a CC for peritoneal dialysis was associated with a significantly lower risk of transition to ICHD. Broader use of this technology may facilitate improvement in retention of patients undergoing PD.



SA-PO473

Teledialysis: The First Northeast Italy Experience of Telehealth in Peritoneal Dialysis

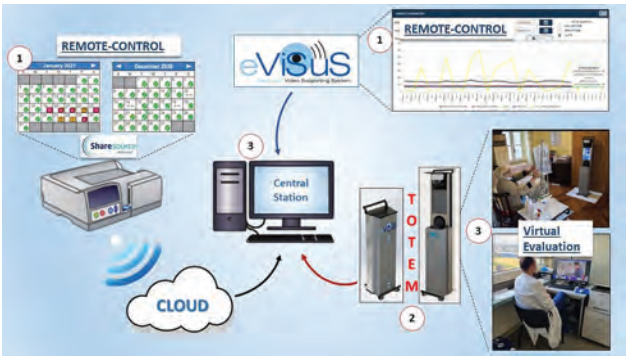
Paolo Lentini, Claudia Benedetti, Antonino Previti, Giorgio Laudadio. *Nephroloy, "S.Bassiano Hospital", Bassano del Grappa, Italy.*

Background: Telehealth may facilitate patient care in peritoneal dialysis(PD). We report our experience with Teledialysis(TD), a combination of PD technique and new technology devices that we used together to overcome clinical, social and psychological barriers toPD.

Methods: Pilot study-25 consecutive Automated Peritoneal Dialysis(APD)pts. TD was perform by the combination of 2 systems A- A Web platform *Sharesource*(Baxter®) that supports remote patient management and provide to the clinician the ability to act on that assessment by updating the cycler. B-*Totem eVISUS* System(TesiSquare®);a plug-play system consisting of two units:1) a transportable remote station**(Totem)**equipped with high performance camera, touchscreen monitor, speaker microphone, internet routers for fixed and mobile phone, wireless access point and remote control to answer calls remotely and 2) a **Control Station** used form our healthcare personnel to connect to one or more pts at the same time [Fig 1]. We check all PD sessions by Sharesource and we perform clinical evaluation status with eVISUS System for medications/monitoring of catheter, PD effluent color and to give instructions for PD training/session management.

Results: On 24 months-25 consecutive pts(14M/11F) with an average age of 73 yrs [Fig 2]. We perform 103 TDsessions with an average duration of 26' mins/each visit. We don't detect any exitSite Infection, Tunnel infection or Peritonits; none of our pts require hospital admission.

Conclusions: Our results shown that TD is safe, reliable and is easy to use for our pts;we assert that technology can help nephrologist to improve PD program and aid patients to overcome barriers to select PD. Teledialysis promote a real integration between Hospital and our territory by a new care pathway.



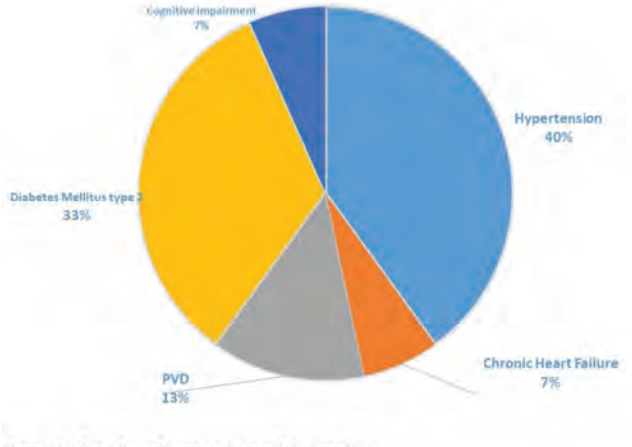


Figure 2: Baseline characteristcs of the patients

SA-PO474

Caregiver Support on Tablo Home Hemodialysis

Cynthia J. D'Alessandri-Silva,[1] Christopher Gunter,[1] Michael A. Aragon,[1] David E. Henner.[2] *[1]Outset Medical, San Jose, CA; [2]Bershire Medical, Pittsfield, MA.*

Background: The treatment of End-Stage Renal Disease (ESRD) at home can significantly impact daily activities and health-related quality of life (QOL) for patients. With home hemodialysis (HHD), care partners often share in the physical, mental, and social burden of self-care at home. Understanding and quantifying that burden provides opportunity to create technology and develop resources to better support patients and families performing home hemodialysis.

Methods: The HOME Registry Study (NCT04526301) is an ongoing multi-center, prospective, single-arm study investigating clinical and QOL outcomes on patients receiving HHD with the Tablo® Hemodialysis System (Tablo). In this interim analysis, the Care Partner-Net Promotor Score (NPS), Care Partner-Post Training Questionnaire, and Zarit Burden Interview (ZBI) were analyzed to quantify the impact of Tablo training on the care partner's perception of readiness and QOL once home assisting with treatment.

Results: Ninety-nine participants were enrolled into the HOME Registry Study, mean age 57, 73% male, 78% non-Hispanic/Latino, with 70% married or in a domestic relationship, and 50 care partners reporting at baseline. Of care partner responses after completing training, 96% agree or strongly agree with "being satisfied with Tablo training received", 98% agree or strongly agree they are "confident in supporting my partner's dialysis treatment with Tablo System", and 100% of care partners agree or strongly agree with being "satisfied with what is being asked of them as a care partner". At month 12, 100% of responses reported: Sometimes, Rarely, or Never "feeling stressed between caring for their relative and meeting my own responsibilities" and to "feeling that I've lost control of my life since my relatives' sickness". In addition, 89% reported: Sometimes, Rarely, or Never "feeling I don't have enough time for myself due to my relative's HHD". Mean care partner NPS at month 12, reported on a 10 point scale from 1 "not at all likely" to 10 "extremely likely", was 8.94 at month-6 and 8.90 at month-12.

Conclusions: Care partners surveyed in the HOME Registry study report confidence in their training and their ability to care for their loved one with little impact on their own QOL. In addition, based on their experience, care partners of patients on Tablo at home were very likely to recommend Tablo HHD to others.

SA-PO475

Improvement of Depressive Symptoms and Quality-of-Life in Patients on Home Hemodialysis

Cynthia J. D'Alessandri-Silva,[1] Christopher Gunter,[1] Michael A. Aragon,[1] David E. Henner.[2] *[1]Outset Medical, San Jose, CA; [2]Berkshire Health Systems, Pittsfield, MA.*

Background: Patients with end-stage renal disease (ESRD) commonly report depressive symptoms (e.g., feeling hopeless, suicidal thoughts), significantly impacting quality-of-life (QOL) and feelings of self-worth (e.g., feeling like a failure, letting your family down). These symptoms can impact a patient's overall sense of well-being as well as treatment recovery time. The HOME Registry Study (NCT04526301) is a multi-center, prospective, study on patients receiving home hemodialysis (HHD) with the Tablo® Hemodialysis System.

Methods: In this interim analysis of HOME we report results from the Patient Health Questionnaire-9 (PHQ-9), Time-to-Recovery (TTR), and Participant Net Promotor Score (NPS) to quantify the impact of Tablo HHD on participants' mental health and perceived QOL.

Results: 99 subjects were enrolled into the HOME Registry, with mean age of 57, 73% male, 78% non-Hispanic/Latino, and 70% married or in a domestic relationship. PHQ-9 responses from baseline to month-12 are as follows- Q1: no incidence of "feeling down, depressed, or hopeless"- baseline 68%, 12 month 74%; (90% reported this feeling ≤2 times over a 2-week period at 12 months); Q2: no incidence of "feeling bad about yourself-or that you are a failure"- baseline 65%, 12 months 77% (84% reported this feeling ≤2 times over a 2-week period at 12 months). Q3: no incidence of "thoughts that you would be better off dead or hurting yourself"-baseline 89%, 12 months 94%; (7% reporting this feeling ≤2 times over a 2-week period). Over 80% of participants at month-12 reported their HHD making no/some impact on their ability to work, take care of their home and getting along with others. TTR of <60min trended positively over 12 months of HHD, increasing 5.5%. Mean NPS score for likelihood of recommending HHD with Tablo to other ESKD patients on a point scale from 1 "not likely" to 10 "extremely likely" was 9.2 at month-6 and 9.3 at month-12 visit.

Conclusions: HOME Registry patients on Tablo report improvement in depressive symptoms and low time to recovery out to 12 months. At both 6 and 12 months at home performing self-care, patients are extremely likely to recommend home hemodialysis via Tablo to other patients.

SA-PO476

Provider Perspectives on Patient Burnout in Peritoneal Dialysis

Spencer A. King,[1] Karine E. Manera,[2] Jenny I. Shen.[1] *[1]Harbor-UCLA Medical Center, Torrance, CA; [2]The University of Sydney, Sydney, NSW, Australia.*

Background: Peritoneal dialysis (PD) can provide more independence and flexibility for patients compared with in-center hemodialysis (ICHD). However, this self-adminstered home-based modality can also cause burnout, which we define as mental, emotional, or physical exhaustion leading to negative attitudes towards PD. These attitudes can lead to poor outcomes, including depression, increased risk of peritonitis, and transfer to ICHD. We aimed to describe the perspectives on PD burnout by nephrologists with patients on PD.

Methods: We conducted semi-structured interviews of 29 nephrologists with experience with treating patients on PD in Australia, Canada, Columbia, Hong Kong, Japan, New Zealand, Singapore, US, UK, Uruguay, and Thailand from Apr 2017 to Nov 2019. Transcripts were analyzed thematically.

Results: Two major themes were identified that was similar to previous themes noted from a parallel study on patients'/carers' perspectives on burnout. 1) Suffering an unrelenting responsibility: providers viewed their patients and carers being overwhelmed by the daily regimen and bearing alone the burden and uncertainty of what to expect from PD. 2) Adapting and building resilience: providers witnessed patients drawing hope and support from family and finding meaning in other activities. A third theme was coping with the aid of therapy: providers oberved patients and caregivers benefitting from meeting with a psychologist, psychiatrist, social worker and support groups, but also noted that such resources are not always readily accessible.

Conclusions: Nephrologists with patients on PD are aware of burnout among their patients on PD and of means of coping. Further work is needed to identify effective ways for providers, patients, and families to openly communicate about burnout and to more broadly implement interventions to prevent it.

Illustrative Quotes

Theme	Quote
Suffering an unrelenting responsibility	"I think the long PD treatment can cause the patient to feel burnout. And the high frequency of the bag exchange by themselves, many times of the bag exchange cause patients feeling burnout." "If they find that they don't have enough time in their day to do their daily activities as well...they really burnout and they are really down in the dumps."
Adapting and building resilience	"And we see a lot of cases have caregiver burnout...But normally in Asian countries, I think we have a big family. So they can rotate to the other son, or daughter." "But I think having a family, children around for elderly is helpful."
Coping with the aid of therapy	"I think it would be good to have early psychological support or counseling if they, if we find that they're really struggling, because we can only do so much to help them, but we need to be able to refer them early on to a professional that can help, if they're feeling like they're starting to burn out or they're not coping with their diagnosis and their medical conditions, and the burden of debt. Because sometimes it hits them really hard, starting treatment." "And then we don't have a lot of resource. So we have one psychiatrists, but she just retired. And like every centers, we don't have that much help."

SA-PO477

Patient and Care Partner Perspectives on Challenges of Home Dialysis and Interventions to Prevent Dropout

Christina E. Tse,[1] Ayesha Anwaar,[3] Wael F. Hussein,[3] Karine E. Manera,[2] Nicole J. Scholes-Robertson,[2] Jenny I. Shen.[1] *[1]Harbor-UCLA Medical Center, Torrance, CA; [2]The University of Sydney, Sydney, NSW, Australia; [3]Satellite Healthcare, San Jose, CA.*

Background: High rates of transition from home dialysis to in-center hemodialysis (ICHD) place a strain on patients and healthcare systems. We explored patients' and care partners' difficulties with home dialysis and their recommendations to prevent transitioning to ICHD.

Methods: Participants were patients and their care partners who had transitioned from home dialysis to ICHD or were at high-risk for transitioning. Focus groups were conducted via ZOOM Aug 2021-Jan 2022 and analyzed thematically. Participants ranked their top 3 preferred interventions to reduce transitions using nominal group technique.

Results: There were 29 participants: 16 had transitioned (11 patients, 5 care partners) and 13 were on home dialysis (7 patients, 6 partners). They were aged 30-75, 48% female, 45% white, and were on home dialysis <1 to 5 years. 78% had care partners; 45% were employed. Challenges of home dialysis included management of comorbidities, machine issues, prep and dialysis time, storage needs, isolation, dependency on dialysis, and fear of making an error. The top ranked interventions to prevent transitions were in-home assistance, family involvement in modality education, and peer support programs.

Conclusions: Participants identified challenges with home dialysis and expressed the need for further support and education from providers and peers for both patients and their families.

Interventions to prevent transition to ICHD, as ranked by participants

Intervention	Total Ranking Score
In-home assistance	35.5
Family involvement in modality education	23
Peer support program	20
Early & continuous education about life on home dialysis	15.5
Respite care	13.5
Prolonged training or re-training	13
Dialysis prescription change (cycler, fewer hours)	13

Participant reported challenges and interventions

SA-PO478

Capacity Coaching: A Pilot Randomized Trial of a Self-Management Intervention for Patients on Dialysis

Maria B. Mateo, Ricardo J. Loor Torres, Vicky L. Hines, Victor Montori, Maria Lourdes Gonzalez Suarez, Kasey Boehmer. *Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: End Stage Kidney Disease (ESKD) patients are trusted to handle numerous healthcare tasks associated with managing their disease, often overwhelming their capacity. This can lead to poor health outcomes and increased healthcare use. Capacity Coaching (CC) aims to bolster patients' ability to manage their treatment load. This pilot study evaluates the feasibility of CC in ESKD care and its potential effects on clinical and patient-reported outcomes (PROs).

Methods: This randomized mixed-methods pilot trial involved English-speaking adult ESKD patients receiving in-center or home dialysis care at a large academic medical center. Intervention consisted of 6 CC sessions with a board-certified wellness coach embedded in their clinical care plan. Clinical outcomes included hospitalizations, Emergency Department (ED), primary care (PC) visits, shortened or missed dialysis sessions, interdialytic weight, and serum albumin levels. PROs analyzed included treatment burden, self-efficacy, fatigue, emotional distress, and illness intrusiveness. Mixed models were used, adjusting for fixed effects of arm, time (baseline, 3 and 6 months), their interaction, and the random effect of the patient. Secondary analysis results were adjusted based on adherence to the intervention (≥ 3 CC sessions) using the FREQ procedure.

Results: Of the 93 patients approached, 33 consented and were randomized (16 to CC, 17 to usual care [UC]). Of the 16 patients randomized to CC, 11 were adherent to the intervention. CC was feasible within the team, with patients attending an average of 3.6 (SD 2.13) sessions overall, and 4.8 (SD 1.17) when adjusted for adherence. CC patients had fewer ED visits compared to the control group in the overall analysis (p=0.03), with increased significance when adjusted for adherence (p=0.008). While CC showed reduced shortened and skipped dialysis sessions, this was not statistically significant. Moreover, fatigue was significantly decreased (p=0.047) in the CC arm compared to the UC arm when adjusted for adherence.

Conclusions: Capacity Coaching appears effective in reducing ED visits and fatigue for ESKD patients who adhere to the intervention, suggesting its potential for larger trials. The pilot highlights the need for improved patient-reported outcome data collection.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO479

Psychosocial Barriers to and Enablers of Peritoneal Dialysis Utilization: A Literature Review

Janice J. Tng, Melissa Chew. *Woodlands Health, Singapore, Singapore.*

Background: With an ageing population comes the concomitant increase in Chronic Disease prevalence. In Singapore, most patients with End-Stage Renal Disease (ESRD) are on Haemodialysis (HD). Peritoneal Dialysis (PD) take-up rate is rather low at 21% of the total number of dialysis patients compared to other countries. Our Ministry of Health aims to boost PD uptake to 30% by 2025. With rising ESRD prevalence and insufficient HD centres to meet demand, it is crucial for patients to opt for PD. This review aims to identify the psychosocial barriers and enabling factors to PD, service gaps and areas for improvement.

Methods: Medline (OVIDsp) and the Cumulative Index to Nursing & Allied Health Literature databases were used to find studies published in English from year 2000 to present, using relevant key words. Reference lists of selected studies were also perused for relevant literature.

Results: 18 studies were selected from databases and 11 met the inclusion criteria. Of these, 6 relevant studies were chosen from the reference lists. A total of 17 studies were reviewed - 3 analytical studies, 1 cross-sectional survey, 2 literature reviews, 4 observational studies, 1 prospective study and 6 qualitative studies. Lack of social support or PD caregiver are common reasons for choosing HD, especially those who are unable to perform PD on their own. Fear is a salient theme - fear of the failure to perform PD adequately to prevent infection and medical complications, and the fear of social isolation. PD is usually done at home while HD allows for social interactions at the HD centres. Patient's health beliefs and insight into their health are enablers to increase PD uptake. Performing PD allows a sense of perceived control as it is done independently in the comforts of their home. Regular reviews by the hospital's renal team and external PD nurse can motivate patients to cope better and helps the healthcare team to build relationships with patients.

Conclusions: Dialysis is physically demanding and emotionally intensive. There are many factors that influence patients' decision-making when it comes to choosing a dialysis modality and psychosocial factors play a major role. Reducing barriers and increasing enablers can help boost PD uptake. Majority of the existing literature focuses on barriers to PD and this is a good chance for further research to better understand the psychosocial enablers to PD.

SA-PO480

Caregiver's Word Choices, Definitions, Roles, and Functions in Peritoneal Dialysis Caregiving: A Systematic Scoping Review

Piyawat Kantagowit,[1] Krit Pongpirul,[2] Talerngsak Kanjanabuch.[3]
[1]Chulalongkorn University Faculty of Medicine, Bangkok, Thailand; [2]King Chulalongkorn Memorial Hospital Department of Preventive and Social Medicine, Bangkok, Thailand; [3]King Chulalongkorn Memorial Hospital Division of Nephrology, Bangkok, Thailand.

Background: Caregivers are vital in peritoneal dialysis (PD) care, with the understanding and classification of PD self-care tasks crucial in defining caregiver roles. Due to inconsistencies in the existing literature, we conducted a systematic exploration of the variations surrounding the term 'caregiver' in PD studies.

Methods: We conducted a thorough systematic search using PubMed, Embase, and CENTRAL databases for English-language studies relevant to caregiver support for PD patients up to June 2, 2023. Our analysis focused on word choices, definitions, caregiver identities, and their associated functions.

Results: Out of 4,130 potential studies, 468 articles were screened, of which 177 met the criteria. These studies involved 102,180 patients across 38 countries. 'Caregiver(s)' was used in 88.7% of studies, 'carer(s)' in 15.3%, and other terms in 11.3%. Multiple terms were found in 15.3% of studies. However, only 8.5% provided explicit definitions. Caregiving roles were referenced in 53.7% of studies, primarily identifying parents (38.4%), spouse (33.9%), other family members (33.9%), descendants (31.1%), non-relative non-healthcare workers (21.5%), friends (15.8%), and healthcare workers (14.1%). Functions were delineated in 38.4% of studies, with PD-specific tasks in 33.3%, instrumental activities of daily living (IADLs) in 9.0%, and basic activities of daily living (ADLs) in 7.3%.

Conclusions: Our findings reveal a wide variability in definition and scope of PD caregivers across studies. To facilitate accurate assessment of PD caregiver impact and inform policy development, we advocate for consistent definitions and detailed functional descriptions within the field.

Summary of Key Findings and Proposed Components Defining a Peritoneal Dialysis Caregiver

Component	Key Findings
Word Choice	'Caregiver' was the most used term (89%) 27 studies (15%) used more than one term for 'caregiver'.
Definitions	Only 15 out of 177 studies provided a definition.
Persons Performing Caregiving	Approximately 46% of studies did not specify.
Functions	Only 38% of studies mentioned caregiver functions. Most studies identified caregivers based on PD-specific tasks (87%).
Additional Findings	Certain studies grouped patients and caregivers together.
Suggestions	Use consistent terminology with clear, detailed definitions. Address caregivers separately from patients.

Abbreviations: PD, Peritoneal dialysis.

SA-PO481

Effects of Shared Decision-Making on the Prognosis of Patients with Peritoneal Dialysis

Hark Rim,[1,2] Byeonghwa Bak,[1,2] Ye na Kim,[1,2] Ho Sik Shin,[1,2] Yeonsoon Jung.[1,2] *[1]Kosin University Gospel Hospital, Busan, Republic of Korea; [2]Transplantation Research Institute, Kosin University College of Medicine, Busan, Republic of Korea.*

Background: Patients with chronic kidney disease (CKD) require shared decision-making (SDM) processes when choosing a dialysis method. Peritoneal dialysis (PD) guarantees patient autonomy; thus, SDM is even more important. Based on these findings, we aim to highlight the benefits of PD and increase the rate in which patients choose PD. In order to increase the rate of PD implementation, patients must actively participate in dialysis decisions, and SDM process is necessary between doctors and patients. So, we investigated the effect of SDM on the prognosis of patients with CKD. We focused on the effects of SDM on patient death, survival rates, hemodialysis conversion, emergency room visits, hospitalization days, and outpatient visits. The results of this study suggest that SDM has a positive impact on increasing the number of patients who choose PD and reduce unneccessary medical cost

Methods: Among patients with chronic kidney failure from eight hospitals in Korea who started dialysis, 256 who participated in a pilot project for home management of PD were included in the present study. A mixed-methods study was conducted using questionnaires and semi-structured interviews. Our study focused on the effects of SDM on patient death, survival rate, hemodialysis conversion, emergency room visits, hospitalization days, and outpatient visits.

Results: A significant difference was observed in the number of days of hospitalization per admission ($p = 0.0044$) between the SDM and non-SDM groups. However, no significant differences were observed in survival rate, rate of conversion to hemodialysis (HD), survival rate after conversion to HD, emergency room visit rate, number of hospitalizations per patient, outpatient visit rate, medical cost, hospitalization cost, outpatient cost, and phosphate-binding agent prescription rate.

Conclusions: The number of hospitalization days per admission decreased throughout the SDM process. Continued communication between patients and medical staff on how to manage PD in the long term after making the decision to undergo dialysis will be beneficial in promoting the home management of PD patients.

Table 1
Basic characteristics of patients with educational counseling for dialysis type confirmation.

		Shared decision making (IBS11)
Number		408
Age (yr)		58.9 ± 13.3
Sex	Male	247 (60.5%)
	Female	161 (39.5%)
Training sessions (times)		1.07 ± 0.26
Education target	Patient	275 (67.6%)
	Patient & Guardian	132 (32.4%)
Educational materials provided	Yes	380 (93.1%)
	No	28 (6.9%)
Patient understanding		3.40 ± 0.98

SA-PO482

Addressing Cognitive Impairment in Peritoneal Dialysis: A Systematic Review of Prevalence, Risk Factors, and Outcomes

Noppawit Aiumtrakul,[1] Charat Thongprayoon,[2] Pitchaporn Yingchoncharoen,[5] Chalothorn Wannaphut,[1] Supawadee Suppadungsuk,[2,3] Pajaree Krisanapan,[2,4] Wisit Cheungpasitporn.[2] *[1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; [2]Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN; [3]Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand; [4]Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand; [5]Department of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX.*

Background: Cognitive impairment (CI) is a critical complication in peritoneal dialysis (PD), associated with increased hospitalization and mortality rates. Despite its significant impact, the prevalence and consequences of CI in PD patients are not well understood. This study aimed to determine the prevalence, risk factors, and outcomes of CI in PD.

Methods: We performed systematic reviews in OVID Medline, Embase, and Cochrane databases until January 2024 to identify cross-sectional and cohort studies on CI (identified by cognitive exams) in PD patients. Data on sample size, mean age, sex, prevalence of CI, risk factors, and outcomes were extracted. Pooled meta-analysis of prevalence was performed using a random-effects model. Risk factors for CI were ranked based on odds ratios (ORs) and other available metrics. Longitudinal studies were analyzed for objective data on CI-related outcomes. The protocol was registered in the International Prospective Register of Systematic Reviews (CRD42024526057).

Results: A total of 19 studies were identified, involving 2,882 PD patients. The weighted mean age was 55.02±9.42 years, and 52.38% of participants were male. The pooled prevalence of CI in PD patients was 47.7% (95% CI: 35.8-59.9%). Continuous Ambulatory PD (CAPD) (OR=7.7), depressive symptoms (OR=7.67), being female (OR=3.3), diabetes mellitus (DM) (OR=1.67), older age (OR=1.1), and fewer years of education (OR=0.78) were identified as significant risk factors for CI. Multiple linear regression showed that Automated PD (R^2 =0.64) and Serum Na (R^2=0.56) were significantly associated with a decline in MoCA score. Cohort studies found that CI was significantly associated with higher rate of hospitalizations (HR=1.96) and peritonitis (HR=1.51), compared to those without CI. However, there was no difference in mortality in PD with CI, compared to non-CI groups (HR=0.58-1.18).

Conclusions: CI is common and appears to be underrecognized in PD patients. CAPD, depression, female, age, and DM are major risk factors for CI. CI in PD is associated with an increased rate of hospitalization and peritonitis. Further research is needed to establish standardized cognitive exams and guidelines for the timely management of risk factors of CI in PD patients.

SA-PO483

Patient Perspectives on Incremental Peritoneal Dialysis: A National Survey

Jeffrey Perl,[1,2] Arti Dhoot,[3,2] Michael Spigler,[5] Bruce M. Robinson.[4]
[1]St Michael's Hospital, Toronto, ON, Canada; [2]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [3]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [4]University of Michigan, Ann Arbor, MI; [5]American Kidney Fund, Rockville, MD.

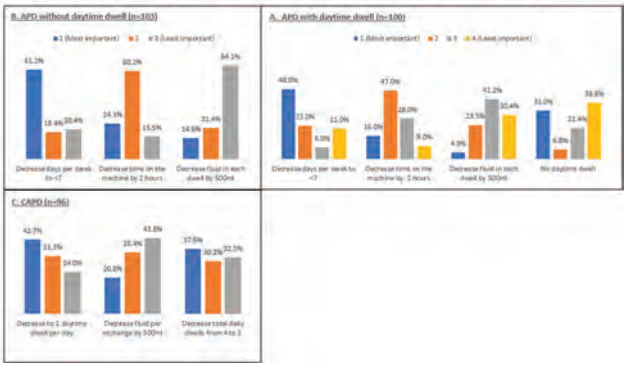
Background: Incremental peritoneal dialysis (PD) may improve quality of life, reduce therapy burden and ease transition to PD. Incremental approaches for automated PD (APD) include: less than 7 days a week, carrying no daytime dwell, reduced dwell volumes or less time on the cycler. For CAPD, decreasing the exchange frequency or reducing dwell volumes are also strategies. We sought to understand patient preferences for various strategies via the dissemination of a national survey to individuals on PD.

Methods: A pilot tested, anonymous, voluntary survey was administered in Aug-Sep 2023. The American Kidney Fund (AKF) distributed the survey via an online link to those receiving charitable assistance from AKF, social media platform, and AKF's monthly newsletter. The survey was for those over 18 years, on PD now or in the past year, and the goal was "to learn about ways that PD can help patients have a good quality of life". Descriptive results were analyzed.

Results: Of the 564 respondents, 9.6% were aged 18- 39 years, 75.9% between 40-69 years and 23.8% over 70 years with 59.1% females, 62.5% Caucasian, and 15.5% identifying as black. PD was initiated ≤1 year in 35.1% of patients. Within 6 months of PD-start, 70.6% of patients reported performing PD treatment 7 days a week. Patients ranked various initial preferred PD prescriptions between 1-4, with 1 as most important as shown in figure 1. Less days of PD treatment per week consistently emerged with the highest priority rankings (ranging from 48- 61.2%) among those receiving APD versus reducing to a single daily dwell for CAPD (42.7%).

Conclusions: Patients value less days of PD treatment per week or a single daily exchange over other approaches to incremental PD. Days off from PD as a strategy is currently underutilized in most patients at time of PD initiation. Further research should evaluate the safety and feasibility of providing these prescription variations in select incident individuals.

Figure 1: Ranked patient responses to the following APD/CAPD prescription changes in order of importance to their quality of life.



SA-PO484

Assessing Global and Regional Interest in Home Dialysis Modalities, 2004-2024

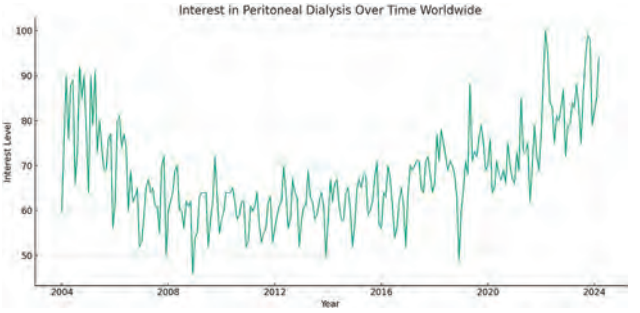
Paul W. Davis,[1] Charat Thongprayoon,[1] Jing Miao,[1] Supawadee Suppadungsuk,[1,2] Iasmina Craici,[1] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Chakri Naruebodindra Medical Institute, Samut Prakan, Thailand.*

Background: Home dialysis, including peritoneal dialysis and home hemodialysis, represents crucial renal replacement therapy options for patients with end-stage kidney disease. With the internet becoming a primary source for healthcare information, this study aimed to analyze global and regional interests in home dialysis using Google Trends™ data from January 2004 to March 2024.

Methods: A comprehensive analysis was conducted using Google Trends™ with the search terms "Peritoneal Dialysis" and "Home Hemodialysis." The study extracted worldwide trends and detailed regional interests within the United States. Interest levels were quantitatively assessed based on Google Trends™ indices, providing insights into temporal patterns and geographical distributions of public interest.

Results: The study found fluctuating global interest in PD, with a peak in March 2022 and the lowest interest in December 2008. The most recent data from March 2024 showed a significant interest level of 94, indicating a recent upward trend. Notably, Mexico exhibited the highest relative interest in PD. Within the United States, Tennessee demonstrated the highest interest. For Home Hemodialysis, peak interest was recorded in July 2004, with the most recent data from March 2024 showing a modest increase in interest. The United States led in relative interest for Home Hemodialysis, followed by Australia, Canada, and the United Arab Emirates. Mississippi was the state with the highest interest within the United States.

Conclusions: This study offers crucial insights into the global and regional landscape of interest in home dialysis modalities, highlighting the significance of leveraging online platforms to increase public awareness, education, and engagement in peritoneal dialysis and home hemodialysis. By understanding the temporal and geographical patterns of interest, healthcare providers, policymakers, and patient advocacy groups can develop targeted strategies to promote the benefits of home dialysis, address knowledge gaps, and improve access to these life-sustaining treatments.



SA-PO485

What Are the Keys to Promoting Home Dialysis in a Country Where In-Center Hemodialysis Is Highly Developed?

Ikuto Masakane. *Yabuki Byoin, Yamagata, Japan.*

Background: In the past decade, the promotion of home dialysis has been recognized as a pressing global issue for several view points; to reduce the medical costs for chronic dialysis, to improve the accessibility to dialysis therapy, and to avoid "dialysis-related pandemic" which was recognized during the COVID-19 pandemic. Another aspect of promoting home dialysis is to create a home care environment for chronic kidney disease patients in the highly aging society. However, Japan's rate of home dialysis, peritoneal dialysis (PD) and home hemodialysis (HHD) remain the lowest of the countries listed in the USRDS annual reports. The aim of this study is to clarify the keys to promoting home dialysis in Japan where in-center HD has highly developed.

Methods: The data about home dialysis was extracted from the Japanese Society for Dialysis Therapy Renal Data Registry. The data of reimbursement was referred to those of our facilities. The data was evaluated in relation to the social and reimbursement events.

Results: As of the end of 2022, the total number of chronic dialysis patients was 347,474, and 10,531 (3.0%) patients were treated by PD including 2,138 patients, and 827 (0.2%) patients. The number of PD patients had increased until 1997, but plateaued until 2020. It seemed to be the result from the shock of the life-threatening complication of PD, encapsulating peritoneal sclerosis. After the installation of an additional payment for providing proper options of renal replacement therapy, the number of PD patients are gradually increased. The number of HHD patients had been around between 100 and 150 until 1997, but it suddenly dropped because of the penalty to the doctor and the facility for false billing suspicion. Since government reimbursement for HHD was installed in 1998, the HHD patients have gradually increasing, and it was accelerated by the two positive revisions of reimbursement for HHD. There are several regulations to limit the promotion of both PD and HHD.

Conclusions: The government policy, proper reimbursement and deregulation of certain regulations are important key to promote home dialysis in countries where in-center HD was highly developed.

SA-PO486

Enhancing Peritoneal Dialysis Access: Overcoming Catheter Insertion Barriers for Patients Who Are Older or Have Obesity

Michael Corr,[1] Stephen O'Neill.[2] *[1]Queen's University Belfast, Belfast, United Kingdom; [2]Belfast City Hospital, Belfast, United Kingdom.*

Background: With rising numbers of patients with end-stage kidney disease, peritoneal dialysis PD is a cost-effective alternative to haemodialysis (HD), aligning with international goals for home-based dialysis. Our study aimed to demonstrate how access to PD was successful expanded in our region, particularly for older frail patients and those with obesity, populations typically underrepresented in PD due to perceived risk of complications from catheter insertion.

Methods: Changes included appointing a PD surgical lead and having a dedicated interventional radiologist for fluoroscopically guided PD catheter insertion. Data were prospectively collected on all patients who had a PD catheter inserted in 2020-2022. Patient demographics, insertion techniques, and outcomes up to 1-year post insertion were summarised. Additionally, a comparison was made between outcomes of PD catheter insertion in patients with and without obesity.

Results: The annual number of PD catheter insertions doubled following service change. Patients receiving percutaneous insertions and able to avoid anaesthesia were older (median age 76 vs. 56, $p < 0.0001$) and had less previous abdominal surgery (25% vs. 54%, $p=0.05$. Outcomes showed a primary patency rate of 85%, primary assisted patency of 94%, and secondary patency of 97%. For patients with obesity, primary and primary-assisted patency rates were similar to those without obesity. However, individuals with obesity exhibited lower secondary patency rates. Patients with obesity showed a trend towards higher transfer rates to haemodialysis within the first-year post-insertion.

Conclusions: We have effectively doubled the annual incident PD population in our region, including older, frailer patients and those with obesity. This study highlights the

benefits of a flexible, multi-faceted approach to PD catheter insertion, improving access and offering an effective alternative to HD for a wider range of patients. The inclusion of laparoscopic and fluoroscopically guided techniques allowed a tailored approach, ensuring appropriate patient selection and timely catheter insertion. Our results suggest that such reconfigurations can significantly enhance PD accessibility, benefiting both patients and healthcare systems.

SA-PO487

Development and Validation of a Formative Objective Structured Clinical Examination (OSCE) Assessing Home Hemodialysis (HHD) Clinical Skills

Jason A. Jones,[1] Trevor W. Tobin,[6] Maria Bermudez,[2] Gregory L. Braden,[3] Nupur Gupta,[4] Evan I. Fisher,[1] Daniel L. Landry,[3] Robert Nee,[1] Bret N. Pasiuk,[5] Christina M. Yuan.[1] Nephrology Education Research and Development Consortium. *[1]Walter Reed National Military Medical Center, Bethesda, MD; [2]Geisinger Medical Center, Danville, PA; [3]Baystate Medical Center, Springfield, MA; [4]Indiana University School of Medicine, Indianapolis, IN; [5]SSM Health Care of Wisconsin, Fond du Lac, WI; [6]Eisenhower Army Medical Center, Fort Gordon, GA.*

Background: The Accreditation Council for Graduate Medical Education(ACGME) requires that graduating nephrology fellows demonstrate competence in HHD. Because low patient numbers may lead to gaps in training, there is an opportunity to enhance clinical experience using simulation. We designed a case-based formative OSCE assessing clinical care of an uncomplicated patient initiating HHD.

Methods: The blueprint, test and rubric were developed by a nephrology fellow, an academic nephrologist, and 4 nephrologists practicing HHD (2 academic, 2 community-based). It was further refined by a 9-member test committee: 5 in HHD practice; 5 in academic nephrology; 1 in regulatory administration; 1 nephrology fellow (who had been a HHD partner). The final test consisted of 27 items (31 points), 4 (10 points) of which were evidence based. Median time in practice: 12 years. Pass threshold was set at 20/31 points (with one possible negative point). 3/27 items were assessed as "hard", the others were of "medium" to "easy" difficulty. Median relevance for all items was "important" or "essential", with a test content validity index of 0.84.

Results: 11 validators, all board-certified, 4 with outpatient HHD practices, took the test. Median years of practice: 10 (range 3-35) All passed: percentage correct 77-97%, mean score 28 ± 2 points. Inter-grader agreement was high; Kappa: 0.83 (95% CI 0.667-0.992). 24 fellows at 4 programs have thus far taken the test, 15 have been graded. 100% (15/15) passed (percentage correct 65-89%); mean score 24 ± 1 points. 73% (8/11) validators vs. 80% (12/15) fellows correctly indicated 4 benefits/2 risks associated with HHD, 64% (7/11) vs. 27% (4/15) correctly defined minimum recommended standard weekly Kt/V, 91% (10/11) vs. 87% (13/15) correctly defined flow fraction, and 100% (11/11) vs. 80% (12/15) described risks associated with buttonhole cannulation.

Conclusions: The HHD OSCE may be used as a formative assessment of fellow knowledge and confidence in prescribing HHD. Disclaimer: The views expressed are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. government.

SA-PO488

Home Hemodialysis (HHD) Practice and Curriculum Recommendations among Graduates of a Training Program without a HHD Clinic Experience

Andrew J. Howard,[1] Nupur Gupta,[2] Christina M. Yuan.[1] *[1]Walter Reed National Military Medical Center, Bethesda, MD; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: The 2019 Advancing American Kidney Health initiative set a goal for ≥ 80% of new ESRD patients to receive home dialysis or kidney transplant by 2025. Home hemodialysis (HHD) rates have remained low (about 15K patients in the U.S.) and not evenly distributed between states. One barrier to increasing HHD prevalence may be a lack of familiarity among nephrologists, and lack of sufficient training during nephrology fellowship.

Methods: We performed an anonymous survey of 92/94 graduates of the Walter Reed program (1984-2023) regarding their HHD practice and training. The program's home dialysis program is limited to peritoneal dialysis patients, and HHD training is limited to didactics and training with machines used for low-flow home dialysis. The survey was conducted from 12/4/2023-2/4/2024.

Results: 52/92 (57%) responded with 50/52 (96%) completing the survey. All were in clinical practice. 75% (38/51) had been in practice ≦20 years. 43% (22/51) had (or had at one time) an HHD practice, and 54% (12/22) had been HHD directors/co-directors. Of those who practiced HHD, 73% (16/22) had started within the last 10 years. The majority of HHD practitioners were in the southern (50%) or western (23%) U.S., and 32% had rural practices. 54% (12/22) followed 6-10 patients. "On the job" training (68%) was the predominant way they reported learning HHD skills. Barriers most commonly cited by HHD practitioners were lack of patient interest (41%), lack of patient partners (27%), and lack of nursing staff to train patients (27%). Respondents indicated that the minimum effective curriculum to achieve HHD competence should include block/longitudinal HHD clinic (84%), familiarization with HHD machines (82%), didactic lectures (80%), and training in effective counselling for HHD (80%).

Conclusions: Among graduates of a training program without an HHD clinical experience, 43% reported subsequently practicing HHD. The majority learned their skills "on the job". Overall, graduates felt that a block/longitudinal HHD clinic was the most effective way for fellows to learn HHD skills during training. Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. government.

SA-PO489

Assessment of Body Composition by Whole-Body Bioimpedance and Body Cardio Scale in Patients on Peritoneal Dialysis

Jun Yi,[1] Fansan Zhu,[1] Laura Rosales M.,[1] Lela Tisdale,[1] Maricar Villarama,[2] Valeria Gusmao Bittencourt,[1] Barbara M. Murphy,[1] Amir Golnabi,[1] Peter Kotanko.[1,3] *[1]Renal Research Institute, New York, NY; [2]Mount Sinai Health System, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Quantitative assessment of body composition is important for optimizing individualized treatment regimens in peritoneal dialysis (PD) patients. This study aims to compare body composition using the body cardio scale (BCS) and whole-body bioimpedance based on a body composition model (BCM).

Methods: Nine PD patients (6 males, age 50.1±12.8 years) were stuided. BCS (Withings) was used (Fig.1) with the patient standing on the scale. Total body water (TBW_{BCS}), fat (Fat_{BCS}), and muscle mass (MM_{BCS}) were provided. Whole body bioimpedance spectroscopy (Hydra 4200) was used to estimate extracellular (ECV) and intracellular (ICV) volume. Four electrodes were donned on the hand and foot (Fig 2). Overhydration (OH), fat (Fat_{BCM}), muscle mass (MM_{BCM}) andTBW_{BCM} (ECV+ICV) were calculated (Chamney, Am J Clin Nutr 85:80-9, 2007). Linear regression analysis and Bland-Altman plots were applied to evaluate the correlation and agreement between BCS and BCM.

Results: A strong correlation was observed between TBW_{BCS} and TBW_{BCM} (R^2=0.94, p<0.0001), with a minor bias (0.67±2.47 kg) (Fig.3a and 3b). Fat_{BCS} and Fat_{BCM} were also highly correlated (R^2=0.97, p<0.0001), albeit with a substantial negative bias (-12.06±7.92 kg) which inversely correlated with fat mass (Fig.3c and 3d). MM_{BCS} correlated reasonably well with MM_{BCM} (R^2=0.82, p<0.001), but MM_{BCS} overestimated muscle mass (bias, 12.75±4.68 kg) (Fig.3e and 3f). Furthermore, BCM indicated the degree of overhydration (OH =1.47±2.0 kg).

Conclusions: While BCS offers easy-of-use and no specific electrodes, the big biases limit its applicability in dialysis patients. The bias may be attributed to a calculation of fat-free mass (FFM) by a general formular (FFM=TBW/0.73) which may not be appropriate for dialysis patients. We refrain from recommending it as a precise assessment of body composition in dialysis patients.

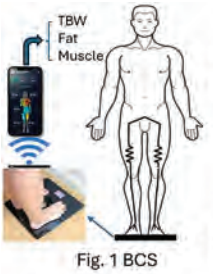


Fig. 1 BCS

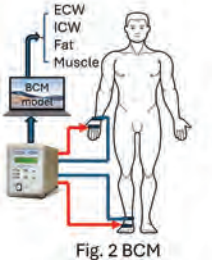


Fig. 2 BCM

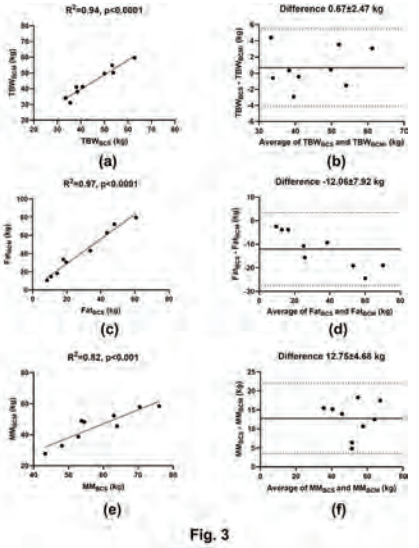


Fig. 3

SA-PO490

Reversible Encephalopathy after Exposure to Glyphosate-Based Herbicide (GBH) in a Patient with ESKD

Joseph H. Brezin. *Drexel University College of Medicine, Philadelphia, PA.*

Introduction: GBH are known to be neurotoxic and often lethal following ingestion. Environmental exposure leads to respiratory and transdermal absorption and prompt renal elimination. However, GBH may be toxic in patients with CKD.

Case Description: A 60 year old man with ESKD attributed to diabeties presented to the ER with progressive symptoms of speech apraxia, jerking movements of his upper extremities, and an unsteady gait over the past five days. Fully compliant with CCPD for the past 11 months; recent weekly Kt/V was 1.95. No history of fever, trauma, foreign travel, or substance abuse. Medications: vitamins, calcium acetate, omeprazole, and antihypertensives. He prepared 2 gallons of RoundUp in his garage and sprayed his property for 30-60 minutes wearing a surgical mask 36 hours befor symptoms arose. Exam: 78 kg man with normal vital signs. Oriented to person and place; responded slowly to simple questions without dysarthria or aphasia; positive myoclonic jerkes of extremities, asterixis, and unsteady gait. Rest of neurological and general exam was unremarkable. BUN 43 mg/dL, creatinine 12.8 mg/dL, normal electrolytes; Hemoglobin 13.3 gm/dL, WBC 16,500 /uL, normal differential. Glucose 124 mg/dL, ammonia <9 umol/L TSH 0.78 mIU/mL. CT, MRI/MRA of brain without acute findings. CSF clear with 3 WBC's, 112 RBC's, protein concentration 74 mg/dL (15-45), and glucose 78. PCR panel negative for CNS pathogens. Urine drug screen negative. He was empirically given loading doses of IV acyclovir and piperacillin-tazobactam after the LP and then underwent 4 hours of high efficiency hemodialysis for presumed glyphosate neurotoxicity. He was sedated during the LP and line placement but awakened within 30 minutes and manifested myoclonic jerks and slow speech. These symptoms abated throughout the treatment and he was able to speak in complete sentences and drink a cup of water without difficulty by the end of dialysis. A full neurologic recovery was noted the following morning and he walked without assistance. He received another hemodialysis treatment and was discharged to resume nocturnal PD. An assay for serum levels of glyphosate was not available.

Discussion: Glyphosate is a glycine based substance with MW 169 daltons. It binds to the NMDA receptor leading to calcium influx and excititoxicity. Heavy routine household exposure in a PD patient led to an encephalopathy consistent with this pathway.

SA-PO491

Revisiting the Urinary Anion Gap: A Sound Concept during Hyperchloremic Metabolic Acidosis

Bilal Khan Mohammed, Ahmed Ismail, Mohammed Z. Rehman, Robert M. Rosa, Daniel Batlle. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: The urine anion gap (UAG) has been used since the late 80s with the primary idea of estimating if urine ammonium (NH_4^+) increases appropriately, as in patients with hyperchloremic metabolic acidosis MA of gastrointestinal etiology, or not as in patients with with distal renal tubular acidosis or chronic kidney disease in whom its excretion is markedly diminished. The use of the UAG as a marker of urinary NH4+ has been criticized because there is a very poor correlation between urine NH_4^+ and UAG in large databases. Here we go over the concept of the UAG measured as the difference in unmeasured anions (UA) and unmeasured cations (UA) to illustrate how in MA a robust rise in NH4+ results in a corresponding fall in the UAG.

Methods: We used published data from Leman et al (JCI, 1966, many years before the UAG was introduced) where all the anions and cations were measured before and after MA induced by NH_4Cl. This way, the UAG could be calculated using measured anions and compared to the the calculated by the formula UAG = $(Na^+ + K^+) - Cl^-$. The following are the reported mean values (mEq/day): **NH_4^+: Before NH4Cl = 28, NH_4Cl = 171 Ca^{++}:** Before NH4Cl = 4, NH4Cl = 7 **Mg^{++}:** Before NH4Cl = 11, NH_4Cl =12 **SO_4^{--}:** Before NH4Cl = 34, NH4Cl = 38 **OA:** Before NH4Cl = 29, NH4Cl = 27 **PO_4^{---}:** Before NH4Cl = 20, NH_4Cl=23

Results: Based on the principle of electroneutrality, the sum of all anions and all cations should be equal; $(Cl^- + HCO_3^-) + (UA) = (Na^+ + K^+) + (UC)$ After rearranging, **= UA – UC = $(SO_4$+P+OA) – (Ca+Mg+ NH_4) = Measured UAG** Before NH4Cl = (34 + 20 + 29) – (4 + 11 + 28) = 40 NH_4Cl = (38 + 23 + 27) – (7 + 12 + 171) = -105 **Calculated UAG = $(Na^+ + K^+) - Cl^-$** Before NH4Cl = (127 + 49) – 135 = 41 NH_4Cl = (136 + 67) – 316 = -113

Conclusions: Ammonium chloride induced MA in normal people results in a marked decrease in the UAG, both measured and calculated, that matches perfectly the induced increase in urine NH4+ excretion. Such perfect correlation, is not seen or expected in the clinical setting where other changes in urine anions and cations take place but the UAG still roughly reflects if there is or not an increase in ammonium excretion in response to hyperchloremic MA supporting its use as an initial diagnostic tool.

SA-PO492

The Citrate and Oxalate Association Is Likely Driven by Diet

Megan Prochaska, Elaine M. Worcester. *University of Chicago Division of the Biological Sciences, Chicago, IL.*

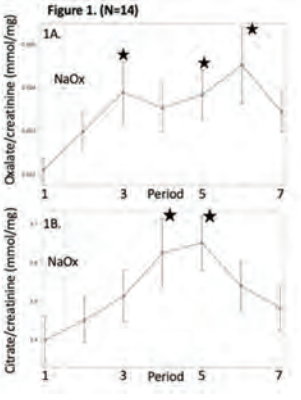
Background: Higher urine oxalate excretion has been associated with higher urine citrate excretion. The mechanism for this association may be due to simultaneous dietary intake oxalate and citrate in food or transporter linkage of SLC26A6 and NaDC1 in the kidney.

Methods: Nineteen participants were admitted to the clinical research center and given sodium oxalate. Timed pre-sodium oxalate (3) and post-sodium oxalate (6) urine samples were collected every hour. Fourteen participants also consumed a low oxalate, low citrate breakfast at the time of the sodium oxalate and 5 participants remained fasting for the duration of the protocol. Means of baseline values and ratios of oxalate (mmol)/creatinine (mg) and citrate (mmol)/creatinine (mg) were calculated. Mean and standard error were graphed per period and mixed methods longitudinal models were generated to compare change over time versus pre-oxalate value (mean 3 values, Period 1).

Results: Ten of the 19 participants were female with mean age 54 years. For the 14 who had breakfast, urine oxalate/creatinine was higher than baseline in periods 3, 5, and 6 and urine citrate/creatinine was higher than baseline in periods 4 and 5 (Figure 1A and 1B). For the 5 who had no breakfast, urine oxalate was higher than baseline in periods 3, 5, 6, and 7 and urine citrate did not increase above baseline in any period (Figure 2A and 2B).

Conclusions: After consumption of sodium oxalate participants had a rise in urine oxalate excretion, as expected. However, only participants who had food at the time of sodium oxalate administration also had a rise in urine citrate. The association between oxalate and citrate excretion is likely driven by dietary intake though additional participants need to complete the protocol.

Funding: NIDDK Support



SA-PO493

Association of Dietary Acid Load and Its Dietary Sources with Aciduria in Community-Dwelling Japanese Adults

Keiko Kabasawa,[1] Michihiro Hosojima,[1] Hideyuki Kabasawa,[1] Ribeka Takachi,[2] Kazutoshi Nakamura,[1] Junta Tanaka,[1] Ichiei Narita,[1,3] Yumi Ito.[1] *[1]Niigata University, Niigata, Japan; [2]Nara Women's University, Nara, Japan; [3]Niigata Institute for Health and Sports Medicine, Niigata, Japan.*

Background: The composition of certain diets, such as contemporary Western diets, leads to chronic subclinical metabolic acidosis, which can lead to urine acidification. Methods for estimating dietary acid load have been established in Western countries, but such estimates have not been fully evaluated in Asian populations, which have different dietary habits. Here, we evaluated associations of dietary acid load and the corresponding nutrient compositions with aciduria.

Methods: This study was based on data from a Japanese community-based cohort comprising 6,274 adults aged ≥40 years, 51.0% women). We cross-sectionally assessed dietary acid load and aciduria (spot urine pH <6.0). Dietary acid load was estimated by net endogenous acid production (NEAP) score and its components, calculated from energy-adjusted nutrients based on a validated food frequency questionnaire. Associations with aciduria were analyzed by using multivariable logistic regression analysis with adjustment for potential confounders.

Results: Median NEAP and eGFR were 38.8 mEq/day and 74.0 mL/min/1.73m^2, respectively. Higher NEAP was significantly associated with aciduria (P for trend <0.001, Figure). When intake of dietary protein and protein sources were analyzed separately from potassium, higher potassium intake showed a significant inverse association with aciduria, while relatively high animal protein intake, but not total protein, was positively associated with aciduria (both P for trend <0.05, Figure).

Conclusions: Our findings suggest that estimated diet-dependent net acid load was associated with aciduria, and low potassium intake and relatively high animal protein out of total protein intake may be contributors to aciduria in Japanese community-dwelling adults.

Funding: Government Support - Non-U.S.

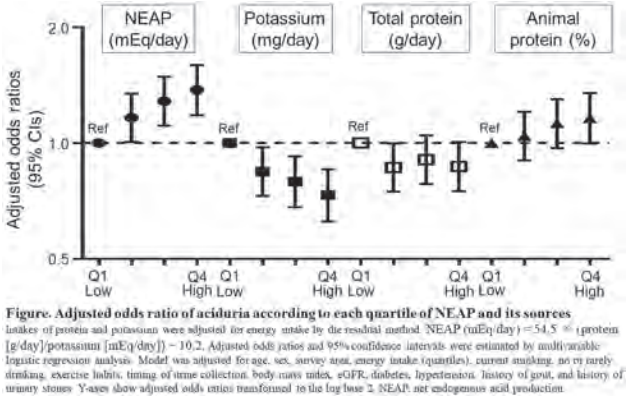


Figure. Adjusted odds ratio of aciduria according to each quartile of NEAP and its sources
Intakes of protein and potassium were adjusted for energy intake by the residual method. NEAP (mEq/day) = 54.5 × (protein [g/day]/potassium [mEq/day]) − 10.2. Adjusted odds ratios and 95% confidence intervals were estimated by multivariable logistic regression analysis. Model was adjusted for age, sex, survey year, energy intake (quartiles), current smoking, no or rarely drinking, exercise habits, timing of urine collection, body mass index, eGFR, diabetes, hypertension, history of gout, and history of urinary stones. Y-axes show adjusted odds ratios transformed to the log base 2. NEAP, net endogenous acid production.

Adjusted odds ratio of aciduria according to each quartile of NEAP and its sources

SA-PO494

Effect of Sodium Bicarbonate Therapy on Calciprotein Particles in Patients with CKD Stages 3 and 4 and Mild Metabolic Acidosis

Wei Chen,[1,2] Mirela A. Dobre,[3] Seiji Koike,[4] Jodi A. Lapidus,[4] Garry A. Graham,[1] Matthew K. Abramowitz,[1,2] Thomas H. Hostetter,[5] Alfred K. Cheung,[6] Kalani L. Raphael,[6] Michal L. Melamed.[7,1] *[1]Albert Einstein College of Medicine, Bronx, NY; [2]Montefiore Medical Center, New York, NY; [3]University Hospitals, Cleveland, OH; [4]Oregon Health & Science University, Portland, OR; [5]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; [6]University of Utah Health, Salt Lake City, UT; [7]NYU Langone Health, New York, NY.*

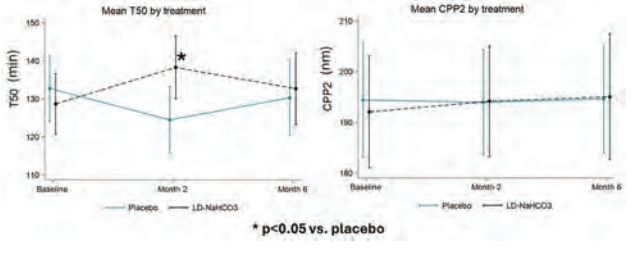
Background: Animal studies suggest that sodium bicarbonate, used to treat metabolic acidosis of CKD, may worsen vascular calcification. Calciprotein particles (CPPs) are nanoparticles of calcium phosphate crystals and calcification inhibitors. Faster transformation (i.e., low T_{50}) from primary to secondary CPP (CPP2) and larger CPP2 indicate a reduced mineral buffering capacity in blood and are associated with mortality. In people with CKD, we tested the hypothesis that sodium bicarbonate therapy reduces T_{50} and increases CPP2 size.

Methods: We performed secondary analyses of a double-blind, placebo-controlled trial, in which 149 participants with CKD stage 3 or 4 with serum bicarbonate levels 22-26 mEq/L were randomized to receive either sodium bicarbonate 0.4 mEq/kg/day or placebo. In the stored serum samples at baseline, month 2 and 6, we measured the time for half maximal CPP transformation (T_{50}) using nephelometry and CPP2 size using dynamic light scattering. Linear mixed effect models were used to test the effects of sodium bicarbonate on the changes in T_{50} and CPP2.

Results: 54% were women and 58% were Black. At baseline, mean (±SD) age was 62±10 years; serum bicarbonate was 24.0±2.2 mEq/L; eGFR was 36±11mL/min/1.73m^2; T_{50} was 131±36 min; and CPP2 was 193±49 nm. At Month 2, serum bicarbonate in the intervention group increased to 26.4 mEq/L and T_{50} increased by 10 min. These changes were significantly higher than placebo ($p<0.001$ and $p=0.03$, respectively). At Month 6, mean serum bicarbonate was 25.5 mEq/L and there was no change in T_{50} compared to placebo. There was no significant change in CPP2 at either Month 2 or 6.

Conclusions: In contrary to our hypothesis, oral sodium bicarbonate therapy in people with CKD increased T_{50} after 2 months, suggesting improved mineralization capacity; however, this effect was not sustained at 6-month follow-up. Further studies are required to confirm these findings and to investigate whether this increase in T_{50} improves vascular calcification and survival.

Funding: NIDDK Support



SA-PO495

Oral Sodium Bicarbonate in Patients on Maintenance Hemodialysis: A Systematic Review and Meta-Analysis

Adrian L. Santos, Jayson M. Villavicencio, Maxine Camela S. Sta. Maria. *Philippine General Hospital, Manila, Philippines.*

Background: Metabolic acidosis, one of the complications of chronic kidney disease (CKD), can lead to malnutrition and increased protein catabolism. Oral sodium bicarbonate supplements have been used to address this consequence among non-dialytic CKD patients. However, the evidence of their continued use among patients already on regular maintenance hemodialysis is still the subject of many studies. This study aims to determine the effect of oral sodium bicarbonate supplements on the nutritional status and interdialytic potassium gain of CKD patients on maintenance hemodialysis.

Methods: Searches for eligible studies were done on PubMed, ProQuest, the Cochrane Library, and ClinicalTrial.gov until December 2023. Studies included were randomized controlled trials of CKD patients on maintenance hemodialysis given oral sodium bicarbonate supplements. The primary outcome is change in nutritional status which was assessed by different parameters, while the secondary outcome of interest is interdialytic potassium gain. Three reviewers independently screened the studies and assessed the quality using the Cochrane RoB tool. Random-effects meta-analysis was done using Review Manager 5.4.

Results: Two studies, both moderate quality RCTs, were included in this review, involving a total of 93 patients. The parameters employed for the assessment of nutritional status included normalized protein catabolic rate (nPCR), interdialytic weight gain, and handgrip. Pooled analysis showed that sodium bicarbonate was as effective or better in terms of in nPCR, mean difference 0.09 g/kg/day (95% CI -0.05 to 0.23, I2=37%; associated with an increase in interdialytic weight gain compared to control, mean difference of 0.43 kg (95% CI 0.01 to 0.84, I2=39%), and as effective compared to control (no sodium bicarbonate) in terms of improving handgrip, mean difference of 3.57 kg (95% CI -10.72 to 17.85, I2=80%). The sodium bicarbonate group also showed lower levels of pre-dialysis potassium, mean difference of 0.33 mmol/L (95% CI -0.58 to -0.11, I2 = 0%).

Conclusions: There is low certainty of evidence to suggest that oral sodium bicarbonate supplementation among patients on hemodialysis may result in a slight improvement in the nutrition and interdialytic potassium gain of these patients.

SA-PO496

Among Patients Meeting the KDIGO CKD Practice Point Criterion for Treatment of Metabolic Acidosis, Higher Serum Bicarbonate Concentrations Are Associated with Slower CKD Progression

Bhupinder Singh,[1] Navdeep Tangri,[2] Glenn M. Chertow,[3] Pablo E. Pergola,[4] Stewart A. Turner,[1] Jessica B. Kendrick,[6] Donald E. Wesson.[5] *[1]Renibus Therapeutics, Southlake, TX; [2]University of Manitoba, Winnipeg, MB, Canada; [3]Stanford University, Palo Alto, CA; [4]Renal Associates PA, San Antonio, TX; [5]University of Texas, Austin, TX; [6]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Lower serum bicarbonate concentrations in patients with CKD and metabolic acidosis are associated with worse clinical outcomes including faster CKD progression. Less clear is to what extent raising bicarbonate delays CKD progression. The 2024 KDIGO CKD guideline recommends, as a practice point, the use of pharmacological treatment in patients with serum bicarbonate < 18 mEq/L. We explored the relation between achieved serum bicarbonate and CKD progression using data from the VALOR-CKD study, which evaluated the safety and efficacy of veverimer, a non-absorbed polymer that removes hydrochloric acid from the gastrointestinal tract. In this study, 1,480 patients with CKD (eGFR 20-40 mL/min/1.73 m^2) and metabolic acidosis (serum bicarbonate 12-20 mEq/L) were randomized, after a single-blind active treatment period, to veverimer or placebo and followed for a median of 24.5 months. The difference in achieved serum bicarbonate concentrations between treatment groups was only 1.3 mEq/L and the trial failed to show a slowing of CKD progression.

Methods: In a post-hoc analysis restricted to patients with baseline serum bicarbonate ≤18 mEq/L, we evaluated the relation between the average serum bicarbonate concentration achieved over the course of the randomized treatment period (<20, ≥22 mEq/L, ie ≥ 4 mEq/L serum bicarbonate increase), and CKD progression using a Cox proportional hazards model. CKD progression was defined as the time to the first kidney composite endpoint (KCE) of a confirmed reduction in eGFR ≥40%, ESKD (requiring dialysis or transplantation), or death.

Results: The patients who achieved average serum bicarbonate concentrations ≥22 mEq/L, irrespective of treatment received, experienced a significantly reduced risk of KCE, HR=0.52 (CI 0.36 to 0.75), p <0.0005, relative to those with serum bicarbonate concentrations <20 mEq/L.

Conclusions: This post-hoc analysis from the VALOR-CKD trial provides supportive evidence that in a CKD population with serum bicarbonate concentrations meeting the KDIGO practice point criterion for treatment of metabolic acidosis (< 18 mEq/L), higher achieved serum bicarbonate concentrations are associated with slower CKD progression.

SA-PO497

Variability in the Delta Anion Gap/Delta Bicarbonate (ΔAG/ΔHCO3) Ratio in Lactic Acidosis

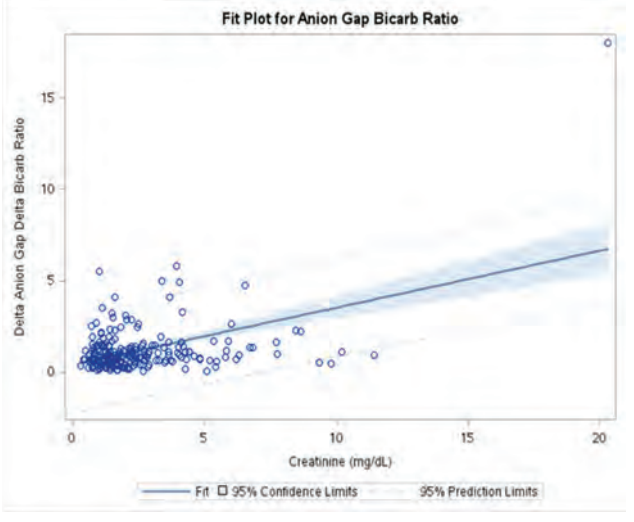
Garrett Yu,[1,2] In-Lu Amy Liu,[3] Richard M. Treger.[1,4] *[1]Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA; [2]Cedars-Sinai Medical Center, Los Angeles, CA; [3]Kaiser Permanente Department of Research and Evaluation, Pasadena, CA; [4]Kaiser Permanente Bernard J Tyson School of Medicine, Pasadena, CA.*

Background: The delta anion gap (AG) to delta bicarbonate (HCO_3) ratio ($\Delta AG/\Delta HCO_3$) is useful for detecting complex acid-base disorders in the setting of elevated anion gap metabolic acidosis. Consistent with published studies, our data demonstrated that $\Delta AG/\Delta HCO_3$ in lactic acidosis has significant variability, ranging from 0.07-5.79. This variability is not well explained. This study aims to better understand what factors explain the variability in $\Delta AG/\Delta HCO_3$.

Methods: This is a retrospective cohort study of adult ICU patients with sepsis and lactic acidosis. $\Delta AG/\Delta HCO_3$ was calculated using albumin-corrected AG and each patient's baseline AG and HCO_3. Pearson correlation was used to determine the association between creatinine, BUN, BUN/Cr, chloride, and potassium and $\Delta AG/\Delta HCO_3$.

Results: 484 patients were included. Creatinine (Figure; $R^2 = 0.225$; $p < 0.0001$), BUN ($R^2 = 0.0233$; $p < 0.026$), and serum chloride ($R^2 = 0.045$; $p = 0.002$) were significantly correlated with $\Delta AG/\Delta HCO_3$. No association was found between $\Delta AG/\Delta HCO_3$ and serum potassium or BUN/Cr

Conclusions: Creatinine and BUN were significantly correlated with $\Delta AG/\Delta HCO_3$, likely due to accumulation of organic and inorganic anions that occurs with renal dysfunction. Serum chloride was significantly associated with $\Delta AG/\Delta HCO_3$, but only explained 4.5% of variance in $\Delta AG/\Delta HCO_3$, suggesting that concurrent normal AG metabolic acidosis (NAGMA), as with large volume saline infusion, diarrhea, or early renal failure did not play a clinically significant role in the variability in $\Delta AG/\Delta HCO_3$. Lack of statistically significant association between $\Delta AG/\Delta HCO_3$ and serum potassium, as well as BUN/Cr, supports the absence of diarrhea (as a cause of NAGMA) or concurrent metabolic alkalosis, respectively. Additional work needs to be done to identify other important factors that can further explain the variability in $\Delta AG/\Delta HCO_3$, which limits the utility of $\Delta AG/\Delta HCO_3$ in diagnosing mixed acid-base disorders.



SA-PO498

Sodium Bicarbonate Supplementation May Be Harmful in Septic Patients with Severe Lactic Acidosis: A Retrospective Analysis

Dongeun Yang, Binna Park, Soy Kang, Won Suk An. *Dong-A University, Busan, Republic of Korea.*

Background: Lactic acidosis is a common cause of metabolic acidosis in severely ill patients. Administrating sodium bicarbonate may be considered in lactic acidosis with pH <7.0, however the effect of sodium bicarbonate on mortality remains controversial. We aimed to evaluate the effect of sodium bicarbonate on mortality in patients with severe septic lactic acidosis.

Methods: Single-center analysis was conducted from May 2011 to April 2021 at Dong-A University Hospital, Korea. We screened 1987 patients with initial pH<7.2, lactate<19.8mg/dL(2.2mmol/L), and positive blood culture. 695 patients with pCO2>45mmHg or without follow-up lactate were excluded. We classified 1292 patients into two groups depending on sodium bicarbonate supplementation.

Results: Sodium bicarbonate group was 746 and control group was 545. Mean age was 66.8±13.3 years and male was 60.4%. Sodium bicarbonate group had significantly higher 7-day(25.2% to 15.0%) and 28-day(48.5% to 32.1%) mortality rate. More patients were treated with CKRT(continuous kidney replacement therapy), ventilator, and catecholamine in the sodium bicarbonate group. The difference of 7-day and 28-day mortality rate between two groups was prominent in patients below pH<7.0, whereas patients with pH 7.1-7.2 showed no difference of mortality rate. Similar results were shown in the Kaplan-Meier curve(Figure 1). Sodium bicarbonate was associated with 7-day(HR=1.800, p<0.001) and 28-day(HR=1.601, p<0.001) mortality in the Cox regression model. Sodium bicarbonate was only associated with 7-day(HR=2.245, p=0.034) and 28-day(HR=2.285, p=0.004) mortality in patients below pH<7.0.

Conclusions: Administrating sodium bicarbonate may be harmful in septic patients with severe lactic acidosis. Sodium bicarbonate should be carefully administered in septic lactic acidosis even with pH<7.0.

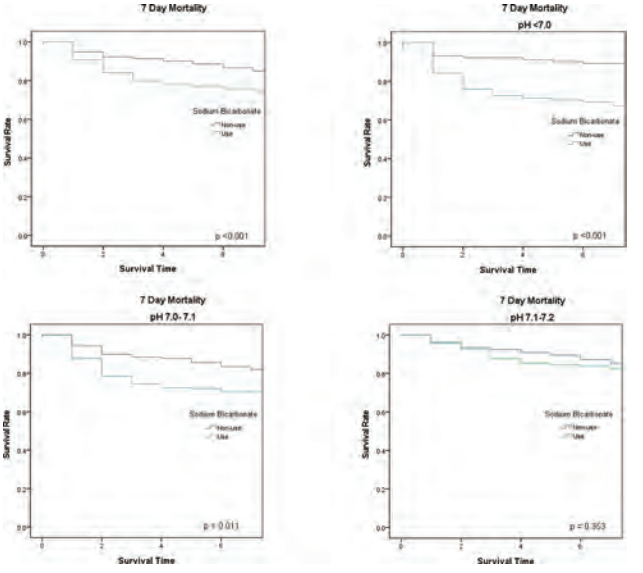


Figure 1. Kaplan-Meier Curve of 7 day Mortality

SA-PO499

Tris(hydroxymethyl)aminomethane Reverses Tumor-Induced Lactic Acidosis

John A. Szendrey, Daniel L. Landry, Gregory L. Braden, Jeffrey Mulhern. Kidney Care and Transplant Services of New England. *Baystate Medical Center, Springfield, MA.*

Introduction: Tumor-induced(TI) lactic acidosis (LA) occurs in lymphomas due to impaired liver L metabolism & the Warburg effect of anaerobic glyolysis in the tumor. We describe a patient with large B cell lymphoma with severe respiratory distress & Kussmaul breathing from TI LA. The use of tris-hydroxymethyl aminomethane (THAM) which provides HCO3 without the generation of CO2, rapidly cleared his lactic acidosis.

Case Description: A 73 yr old man had severe dyspnea after 1 month of an enlarging groin mass He had a RR of 30/min with Kussmaul respirations. Lungs were clear & heart exam normal. A V/Q scan showed no pulmonary embolus. Table 1 shows a severe anion gap LA on admission. His glucose, BUN & creatinine, CPK, aspirin, acetaminophen & beta-hydroxybutyrate levels were normal. He was transfered to the ICU due to severe respirtory fatigue. THAM at a dose of 575 ml via a 0.3 mmo/L solution was given. Four hours later his LA dropped from 14.7 to 8.7 & his HCO3 rose to 20 mEq/L with markedly improved breathing & no intubation. The next day this same THAM dose was repeated with a greater fall in LA. A biopsy showed diffuse large cell B-lymphoma. & methylprednisolone was started. By the fourth day his LA was gone.

Discussion: Sodium bicarbonate IV in TI LA worsens LA. We chose to use THAM in our patient as it rapidly alkalinizes tissue & the liver within three minutes. This patient's LA quickly reversed with THAM doses calculated to increase the serum bicarbonate by 5 mmol/L per dose, prreventing intubation. We conclude that THAM can reverse TI LA without liver mets by the following mechanisms: a) alkalosis Increases lactate uptake & metabolism by hepatocytes, b) alkalosis increases liver conversion of lactate to pyruvate by stimulation of lactate dehydogenase (LHD) A and inhibition of LDH B, & c) reversal of the Warburg effect by increasing pyruvate dehydogenase(PDH) by inhibition of (PDH) kinase its breakdown enzyme with enhanced shuttling of pyruvate into the alkalosis-stimulated Krebs cycle. THAM is a new therapy for TI LA.

	Day 1	Day 2	Day 3	Day 4
Na	133	131	134	131
HCO3	10	20	19	23
Lactate	14.7	8.7	7.4	1.7
AG	27	16	19	12
pH	7.34	7.43	7.40	7.41
CO2	23	33	33	38

SA-PO500

Lactate Gap: A Diagnostic Clue for Diagnosing and Managing Ethylene Glycol Poisoning

Prathap Simhadri,[1] Deepak Chandramohan,[2] Renish Contractor,[1] Prabhat Singh,[3] Pradeep Vaitla,[4] Michelle Neuman,[5] Ujjwala Murari.[5] *[1]Florida State University, Tallahassee, FL; [2]The University of Alabama at Birmingham, Birmingham, AL; [3]Christus Spohn Health System, Corpus Christi, TX; [4]The University of Mississippi Medical Center, Jackson, MS; [5]West Virginia University, Morgantown, WV.*

Introduction: Ethylene glycol(EG) is a type of toxic alcohol, and its ingestion is associated with the development of an osmolar gap and elevated anion gap metabolic acidosis. Early identification and aggressive management of this condition are critical in improving outcomes. We used lactate gap as a diagnostic tool in two patients with ethylene glycol poisoning.

Case Description: A 59-year-old male with a history of Hepatitis C and hypertension was brought for altered mental status(AMS) and had a GCS of 3. Labs showed serum osmolality of 319 mOsm/Kg with an osmolar gap of 69; Chemistry showed an anion gap(AG) of 28 mmol/l and bicarb of 8 mmol/L, ABG showed pH of 7.02, with blood gas lactate of > 17 mmol/L. Serum lactate was 1.5 mmol/L. EG poisoning was suspected, given the significant lactate cap. He was started on fomepizole and aggressive intermittent hemodialysis. EG level later came back as 1205 mg/dl and was undetectable by 48 hours with aggressive treatment. A 60-year-old male was admitted for AMS, acute respiratory failure, and shock. He also had an osmolar gap of 135; chemistry showed an AG of 35, bicarb of <5 mmol/L; ABG showed pH of < 7.00, and lactate of > 18 mmol/L and serum lactate of 2.5 mmol/L. EG poisoning was suspected, given the significant lactate cap; the patient was started on fomepizole and aggressive CRRT. EG level later came back as 344 mg/dl, and the CRRT was discontinued once the EG level was < 20 mg/dl.

Discussion: Ethylene glycol metabolizes into glycolic acid and oxalic acid; these metabolites are responsible for elevated anion gap metabolic acidosis. It is also associated with minimal lactic acid production. Lactic acid can be measured using lactate oxidase and lactate dehydrogenase methods. The lactate oxidase method measures the hydrogen peroxide generated from the metabolism of lactic acid to pyruvate via lactic oxidase. Glycolic acid is structurally similar to lactate, and it can also generate hydrogen peroxide, which causes a false elevation of lactic acid. Conversely, the measurement of lactic acid by the dehydrogenase method is not interfered with by glycolic acid. The closure of the lactate gap can hint at the successful removal of ethylene glycol metabolites through dialysis. Conclusion: The lactate gap can be a diagnostic tool to diagnose and manage ethylene glycol poisoning.

SA-PO501

Fireball Whiskey-Induced Severe Lactic Acidosis

Priya Kumari Maheshwari,[1,2] Michel J. Sabra,[1,2] William W. Goldsmith,[1,2] Maro Issac,[3] Anil Harrison,[1,2] Peter Fahim.[1,2] *[1]HCA Florida West Hospital, Pensacola, FL; [2]University of Central Florida, Orlando, FL; [3]German University in Cairo, New Cairo, Egypt.*

Introduction: Propylene glycol (PG) is metabolized by alcohol dehydrogenase in the liver into lactate, which further converts to pyruvate. Excessive consumption of Fireball whiskey, containing PG, can lead to lactic acidosis.

Case Description: A 36-year-old patient with a history of alcoholism presented to the ED due to increased work of breathing and SOB. Upon arrival, the patient was afebrile with a heart rate of 128 bpm, BP of 112/52 mmHg, RR of 28 breaths per minute, and SpO2 of 98% on room air. He was encephalopathic, and the rest of his physical examination was unremarkable. Initial laboratory investigations were significant for severe anion gap metabolic acidosis with a bicarbonate level of 13 mmol/L and an anion gap of 31, elevated lactic acid of 19.3 mmol/L, hyponatremia, hypomagnesemia, hypophosphatemia, elevated transaminases, elevated total bilirubin, and neutrophilic leukocytosis. A chest CT scan with IV contrast was unremarkable. Additionally, an EKG revealed sinus tachycardia. ABG revealed a pH of 7.4, pCO2 of 16, and bicarbonate of 8.8. The ethanol level was negative. The patient received fluid resuscitation with 30 ml/kg and empiric antibiotics and was admitted to the medical floor. Subsequently, the patient was transferred to ICU due to respiratory distress and concerns regarding potential intubation needs. In the ICU, serum osmolality was measured at 281 mosm/kg with no osmolar gap, and a urine drug screen returned negative. Further inquiry revealed heavy Fireball whiskey consumption over recent days with concern for PG intoxication. Treatment included fluid resuscitation and aggressive electrolyte replacement, resulting in the clearance of lactic acid. However, the patient's hospital course was complicated by acute respiratory failure secondary to aspiration pneumonia, necessitating intubation, critical illness myopathy leading to extubation failure and requiring tracheostomy, and acute kidney injury which resolved. Fortunately, the patient was successfully decannulated before discharge.

Discussion: This case illustrates a low threshold to consider PG intoxication in alcoholic patients presenting with severe lactic acidosis. Our patient didn't have a high osmolar gap as the PG had already been metabolized to lactic acid. Hence, fomepizole was not administered, and given that he cleared lactic acid with fluid resuscitation, hemodialysis was not performed.

SA-PO502

Case of 2,4-Dinitrophenol Intoxication: A Lethal Weight-Loss Alternative Returns

Javier A. Ortega, Pooja Maknoor, Stephen B. Tanner. *Baylor Scott and White Central Texas, Temple, TX.*

Introduction: Initially used as a weight loss suplemment, 2,4 Dinitrophenol (DNP) was banned due to its toxicity. However, its use resurfaced among bodybuilding and dieting groups as a weight loss alternative pushed by online blogs and marketplaces seemingly circumventing heavy regulation.

Case Description: A 43-year-old man with history of depression and previous suicide attempts was transferred to our institution following ingestion of a weight loss supplement. He was brought by police officers who responded to a welfare check by his ex-wife. They stated the patient earlier expressed desire to commit suicide with ingestion of 10 instead of his usual daily 3 drops of DNP. He was started on cooling measures due to hyperpyrexia (41C), dantrolene was administered, then airlifted to our institution. Laboratories showed acute kidney injury, worsening lactic acidosis, and elevated creatinine kinase, with refractory hyperkalemia. Clinical deterioration ensued, with worsening diaphoresis, tachycardia, tachypnea, yellowing of distal extremities, and hypotension requiring escalating vasopressor support, mechanical ventilation and dialysis. Complications included rhabdomyolisis with bilateral lower extremity compartment syndrome requiring bedside fasciotomies and lastly, DIC. Unable to sustain adequate perfusion despite four vasopressors, the patient expired 30 hours after ingestion.

Discussion: Identified in both accidental and intentional intoxications, once ingested DNP is a potent decoupler of oxidative phosphorylation at the mitochondria, shifting to anaerobic respiration. Pyrexia and rhabdomyolysis are common complications along with characteristic discoloration of skin culminating in multiorgan failure. No known antidote is available at this time, and mortality remains high with scarce data to guide treatment. Therefore, it is crucial to raise awareness as preventing ingestion is likely the best available strategy to save lives.

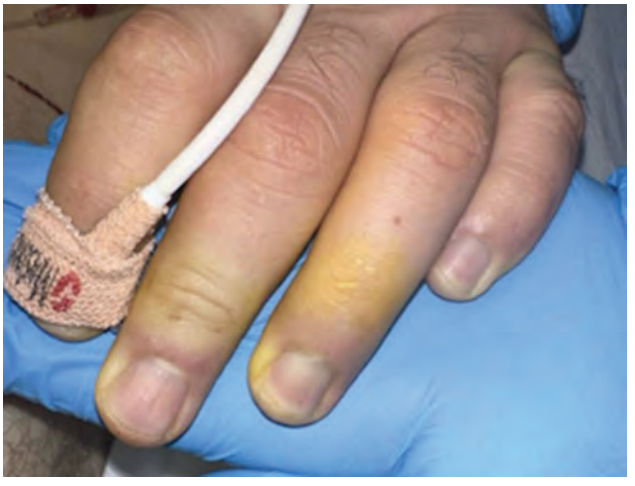


Figure 1

SA-PO503

The Warburg Effect: A Case of Severe Lactic Acidosis and Hypoglycemia

Juan J. Adams Chahin, Janice M. Cuevas Rivera, Ileana E. Ocasio Melendez, Carlos G. Rivera-Bermudez. *Universidad de Puerto Rico Recinto de Ciencias Medicas, San Juan, Puerto Rico.*

Introduction: The Warburg effect, observed in cancer cells, is a type of cellular adaptation where lactate fermentation is favored for biosynthetic needs regardless of oxygen levels leading to type B lactic acidosis. Additionally, due to heightened glucose demand by malignant cells, hypoglycemia may be present. The Warburg effect is predominantly observed in aggressive lymphoproliferative disorders and is linked to a poor prognosis due to significant tumor burden.

Case Description: We present a 36-year-old male with history of diffuse B-cell lymphoma, complicated by pulmonary embolism and deep vein thrombosis on anticoagulation. The patient was brought to ED with complaints of respiratory distress and altered mental status. On exam, the patient appeared disoriented and tachypneic (respiratory rate of 34) with a peripheral oxygen saturation of 95% on room air. Physical exam revealed a prominent mass in the right thigh. Laboratory showed hypoglycemia (45), elevated creatinine and azotemia consistent with non-oliguric acute kidney injury type 1, alongside severe metabolic acidosis (pH: 6.8, pCO2: 14, HCO3: 3.1) with high anion gap (31.9) (delta ratio: 1.2), attributed to lactatemia (151 mg/dL). Aggressive intravenous hydration and bicarbonate drip failed to improve acidosis, necessitating intermittent hemodialysis (IHD). Despite four days of daily IHD, severe lactic acidosis persisted (pH: 7.2, HCO3: 7, and lactic acid: 130 mg/dL), requiring intubation. Induction chemotherapy was initiated, leading to marked improvement in acidosis (HCO3: 16, pH: 7.3) by day two for which dialysis was discontinued.

Discussion: The Warburg effect presents as a rare, complex, and challenging clinical situation in patients with hematologic malignancies, necessitating early identification and intervention to improve prognosis. Tachypnea without low oxygen levels is a characteristic manifestation. Treatment primarily focuses on prompt initiation of chemotherapy alongside supportive measures, yet efficacy of bicarbonate or hemodialysis is uncertain, often offering partial or no correction. Further research into kidney replacement therapy's potential benefits is warranted.

SA-PO504

Severe Lactic Acidosis in Hemophagocytic Lymphohistiocytosis

Andrea Broka, Juan P. Moreno-Ortiz, Nandakishor Kapa. *UC Davis Health, Sacramento, CA.*

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a catastrophic disease with multiple triggers, and often results in poor outcomes. We present a case of severe, persistent lactic acidosis in a rare presentation of HLH secondary to parvovirus B19 infection that improved after steroids and IL-1 inhibitor treatment.

Case Description: A 79-year-old man with diabetes mellitus and cirrhosis presented after a fall, 5 days of progressive malaise, fever, nausea, vomiting, melena, and hematemesis and was to be found febrile to 101° F and hypertensive. Workup showed serum creatinine 1.28 mg/dL, lactic acid (LA) 15.9 mmol/L, pancytopenia, and VBG pH of 7.2 with severe metabolic acidosis (HCO3 9 mEq/L). IV fluids and antibiotics were started, and GI ulcer was treated on EGD. His clinical condition deteriorated with persistent lactic acidosis, shock, decreased urine output, worsening transaminitis, elevated LDH, low haptoglobin, and with concern for potential metformin toxicity, hemodialysis was initiated. Lactic acid decreased from 20 to 13 mmol/L but increased to 20 mmol/L after stopping dialysis. A viral blood panel was positive for Parvovirus B 19 IgG. With ongoing fevers, pancytopenia, elevated ferritin at 8378 ng/mL and hypertriglyceridemia, he met 7 of 9 HLH-2004 criteria (H-score 284). Soluble IL-2Ra/CD25 was elevated at 4778.9 pg/mL. Bone marrow biopsy showed hypercellularity 70% with hemophagocytic lymph histiocytosis. Treatment with dexamethasone and anakinra improved the pancytopenia, liver enzymes, and lactic acidosis. Due to refractory septic shock, he was ultimately transitioned to comfort care.

Discussion: HLH is a rare, aggressive syndrome with dysregulated cytokine release, histiocyte activation, and multiorgan failure. Studies have reported an increased activity of lactate dehydrogenase A and inhibition of pyruvate dehydrogenase due to inflammatory cytokines increasing the production of lactate. The Warburg effect, where cells may preferentially use the lactic fermentation pathway even in the presence of oxygen and without significant mitochondrial dysfunction may also play a role. Lactic acidosis in patients with HLH is underrecognized, but if identified may prompt earlier treatment and improved outcomes.

SA-PO505

Linezolid-Induced Lactic Acidosis

Ritu Seethapathy,[1] Andrew Klufas,[2] Michael J. Monsour.[1] *[1]Landmark Medical Center, Woonsocket, RI; [2]Roger Williams Medical Center, Providence, RI.*

Introduction: Linezolid inhibits bacterial protein synthesis by preventing formation of 70S initiation complex needed for bacterial reproduction. This site of action is unique to linezolid, distinguishing it from other protein synthesis inhibitors.

Case Description: A 93-year-old woman presented to the hospital after nursing home labs showed elevated creatinine, nitrite positive urinalysis, and normal lactic acid. Urine culture grew VRE susceptible to linezolid and she was discharged on a course of linezolid. Two weeks post-discharge, the patient was readmitted with dyspnea, with labs showing AKI and significant lactic acidosis (LA). CT C/A/P revealed bilateral opacities consistent with pneumonia. She was started on a bicarbonate drip per Nephrology recommendations. Her FeUrea was consistent with prerenal AKI and urine output was ~400 cc/dy. Unfortunately, the patient then became hypotensive requiring pressor support, thought to be secondary to her significant LA causing her hemodynamic instability, rather than the inverse. Linezolid toxicity was the leading diagnosis and she was switched to meropenem and started on IV thiamine. Although the patient's pH normalized, her LA worsened. Hemodialysis was declined per the family's wishes and patient was made CMO after extensive goals of care discussion.

Discussion: Linezolid Induced Lactic Acidosis (LILA) is due to an interaction between the drug and mitochondrial ribosomes; inhibition of mitochondrial protein synthesis causes impaired oxidative phosphorylation, thus limiting aerobic energy production. LILA is a diagnosis of exclusion after ruling out common causes of LA and has been found to cause hemodynamic instability in patients. Previous studies have shown that mortality from LILA does not have a strong correlation with age, gender or duration of treatment, however, mortality is as high as 50% in patients with shock. LILA can often be associated with hypoglycemia however our patient was normoglycemic throughout hospitalization. Management of LILA consists of withdrawal of the drug and supportive care. Previous case reports suggest that critically ill patients further benefit from concurrent renal replacement therapy, like treatment of metformin induced lactic acidosis. LILA is a poorly understood side effect of patients treated with even a short course of linezolid. Given high rate of mortality, further investigation is warranted to study etiology of LILA to prevent its occurrence.

SA-PO506

Severe Lactic Acidosis in a Patient with Type 2 Diabetes Mellitus on Metformin

Dean Mellas, Xueguang (Gary) Chen. *Southern Illinois University School of Medicine, Springfield, IL.*

Introduction: Metformin-associated lactic acidosis (MALA) is a complication of altered lactate and hydrogen metabolism leading to life-threatening lactic acidosis in the setting of Metformin use or overdose. The major risk factors for developing MALA include poor renal function, impaired hepatic metabolism, and diseases that can cause increased production of lactate.

Case Description: A 67-year-old female with type 2 diabetes mellitus on Metformin and chronic kidney disease (baseline creatinine: 1.4) presented to a local ER with nausea, vomiting, diarrhea, and abdominal pain for three days. She was found to have severe lactate metabolic acidosis (pH: 6.84, bicarbonate: 8, lactate: 11.6) without hemodynamic instability. The patient underwent emergent hemodialysis for severe acidosis and hyperkalemia (K: 8.2) in the setting of acute kidney injury (serum creatinine: 7.47, BUN: 56). She was transferred to our hospital with persistent metabolic acidosis (pH: 6.97, bicarbonate: 7, lactate: 17) despite 4 hours of hemodialysis at the local hospital. On arrival to the ICU, the patient remained hemodynamically stable. CRRT was initiated urgently and lasted about 48 hours. Her lactic acidosis resolved, and the patient was discharged 8 days later with serum Cr 2.19. At 2-week follow up at renal clinic, her kidney function improved with creatinine back to baseline (1.4).

Discussion: Metformin is widely used to treat type 2 diabetes mellitus, and is generally considered a safe drug. However, patients with preexisting chronic kidney disease are at increased risk of developing a potentially fatal lactic acidosis. This case demonstrated the importance of early recognition and treatment of MALA as evidenced in this patient with known history of Metformin use and severe lactic acidosis. Hemodialysis continues to be the definitive treatment of MALA and should be initiated in any patient with severe acidosis.

SA-PO507

Dapagliflozin-Associated Ketoacidosis in the Absence of Diabetes

Loai Dweik,[1] Wesam Aleyadeh,[1] Pratik Rath,[1] Dania Salih Bacha,[2] Natthavat Tanphaichitr.[1] *[1]Cleveland Clinic Akron General, Akron, OH; [2]Cleveland Clinic, Cleveland, OH.*

Introduction: Dapagliflozin is a sodium-glucose transport protein 2 (*SGLT-2*) inhibitor developed for diabetes management and has emerged as a therapeutic option for heart failure. Use of these agents in the perioperative period remains an area of concern, with growing reports of adverse events and perioperative complications. We describe a case that highlights the importance of management and monitoring of SGLT-2 inhibitors in non-diabetic patients during the perioperative period.

Case Description: A 71-year-old female with a history of hypertension, restless leg syndrome, and depression presented with left hemiparesis. Physical examination revealed normotension, left lower facial droop, left hemiparesis with left upper extremity strength 4/5, left lower extremity 3/5 and ataxia. Complete blood count and creatinine were within normal range. She was subsequently diagnosed with a right middle cerebral artery (MCA) infarct. She underwent cerebral angiogram with right MCA thrombectomy. Post-procedurally, she was found to have an elevated anion gap (19 mmol/L), low bicarbonate (14 mmol/L), and high beta hydroxybutyrate (>2.00 mmol/L). A venous blood gas showed acidemia with primary metabolic acidosis and respiratory compensation. Her hospital course was complicated by new onset atrial fibrillation and systolic dysfunction with findings of a low ejection fraction (35%) on echocardiogram and initiation of dapagliflozin for heart failure with reduced ejection fraction. Nephrology was consulted for progressively worsening serum bicarbonate. Workup showed normal renal function, absence of diabetes (HbA1c: 5.2%), unremarkable ethylene glycol, methanol, and salicylate levels.

Discussion: The patient's serum bicarbonate levels continued to downtrend with persistent acute high anion gap metabolic acidosis (HAGMA). The patient had no history of Type 1 diabetes making euglycemic diabetic ketoacidosis (DKA) unlikely. Suspicion fell on dapagliflozin, which had been prescribed shortly after admission and post-thrombectomy. It was subsequently discontinued with HAGMA resolution. Despite lacking a history of diabetes, the patient's prolonged fasting, surgical stress, and dapagliflozin use may have contributed to the observed metabolic disturbance. Clinicians must exercise caution when continuing SGLT-2 inhibitors during the perioperative period, even in non-diabetic heart failure patients.

SA-PO508

Metformin Toxicity and Euglycemic DKA: A Tale of Two Acidosis

Aditya Yelamanchi,[1,2] Sharmilee Vuyyuru,[1] Andrea Chau,[1] Amanda Nguyen,[1] Brian Y. Young.[1] *[1]University of California Davis, Davis, CA; [2]NorthShore University HealthSystem, Evanston, IL.*

Introduction: Metformin associated lactic acidosis (MALA) and euglycemic diabetic ketoacidosis (euDKA) from SGLT2 inhibitor use are well known life-threatening metabolic disorders where immediate recognition and treatment is imperative to decrease mortality in patients. However, MALA and euDKA have rarely been cited in literature to occur simultaneously, as seen in our case.

Case Description: A 60 year old male with chronic kidney disease stage 3B, diabetes mellitus with retinopathy and peripheral neuropathy was admitted from a nursing facility with altered mental status, abdominal pain, decreased oral intake, and emesis. History was limited on admission. He was found to have a severe anion gap metabolic acidosis and anuric acute kidney injury. Admission creatinine was 10.06mg/dL (baseline ~ 2), serum bicarbonate level was 10mmol/l, anion gap was 44mmol/L, blood glucose was 154mg/dL, and pH on venous blood gas was 7.17. Nephrology was consulted, which prompted a more extensive workup revealing urinalysis with trace ketones and many granular casts, serum beta-hydroxybutyrate level at 6.84mmol/L, and lactic acid level at 6.4mmol/L. This combination of findings was concerning for dual euglycemic DKA and metformin toxicity. Given the high mortality of untreated metformin toxicity, empiric emergent hemodialysis was initiated. Post 2 dialysis treatments, there was significant renal recovery, with creatinine stabilizing at 2.2mg/dL and normalization of lactic acid. It was later found that the patient was taking both metformin 500mg bid and empagliflozin 10mg daily before admission. Metformin level sent prior to dialysis returned 2 weeks later at 23mcg/mL (therapeutic range 1-2; toxic level 5).

Discussion: MALA is a rare and lethal diagnosis with mortality rates ranging from 25-50%, without a significant correlation between degree of acidosis. While concurrent euDKA and MALA is rare, this scenario should be considered given increasing use of both agents. When clinical suspicion is high for this dual acidosis, waiting on serum metformin levels should not delay dialysis given the high mortality. Treatment of euDKA should also be initiated simultaneously.

SA-PO509

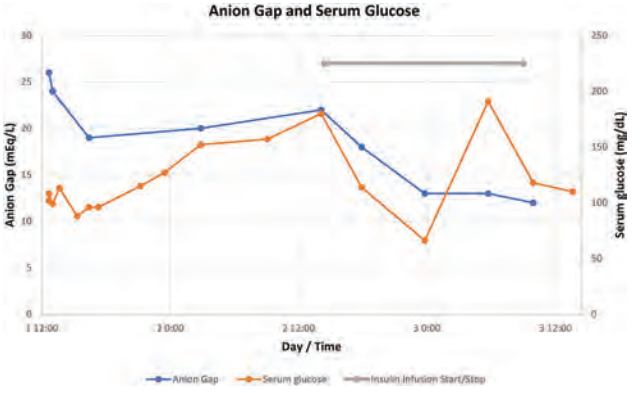
A Case of Cocaine-Induced Euglycemic Diabetic Ketoacidosis

Amir Moghaddam, Zan Shareef, Song Liu, J. Pedro Teixeira. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Introduction: Severe anion gap metabolic acidosis (AGMA) may be life-threatening and often requires specific therapy, but prompt diagnosis may be challenging. We present a case of euglycemic diabetic ketoacidosis (euDKA) likely triggered by cocaine use.

Case Description: A 69-year-old man with diabetes, hypertension, and polysubstance use presents after being found unresponsive by his son. He is intubated for airway protection and is found to have acute kidney injury and severe acidosis with creatinine 3.5 mg/dL, BUN 75 mg/dL, pH 7.13, pCO2 35 mmHg, bicarbonate 10 mEq/L, anion gap 26 mEq/L, lactate 2.0 mmol/L, negative toxic alcohol panel, and serum glucose 66-191 mg/dL. Urinalysis reveals ketonuria and serum beta-hydroxybutyrate is 3.2 mmol/L. Urine drug screen is positive for cocaine. Despite treatment with IV dextrose and IV bicarbonate for >24 h, anion gap remains >20 (Figure). Nephrology is consulted and recommends IV insulin with dextrose which results in normalization of his anion gap within 24 h, at which point his mental status improves sufficiently for extubation.

Discussion: The severity of the AGMA, lack of response to dextrose alone, need for insulin, and glucose consistently <200 mg/dL all strongly suggest euDKA in this case rather than starvation ketosis or classic DKA. Though increasingly identified in patients taking sodium-glucose cotransporter-2 inhibitors, euDKA may be triggered by stressful events such as pregnancy, surgery, or pancreatitis. A classic trigger of DKA, cocaine stimulates counterregulatory hormones like epinephrine and cortisol which normally raise blood glucose, inhibits insulin secretion, and stimulates breakdown of free fatty acids into ketones. One study found 14% of DKA cases to be related to cocaine. However, cocaine may less commonly trigger euDKA via suppression of feeding centers that results in oral intake poor enough to prevent hyperglycemia. Given the specific therapy required, nephrologists and intensivists alike must recognize cocaine-induced euDKA as a potential cause of unexplained severe AGMA.



SA-PO510

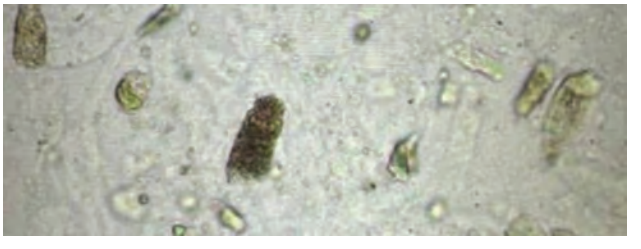
Unveiling the Deceptive Diagnosis: Exploring False-Positive Ethylene Glycol Poisoning

Aakriti Jain, Hafsa Jawaid, Pulkit Gandhi, Roopali G. Gandhi. *Rochester General Hospital, Rochester, NY.*

Introduction: Ethylene glycol (EG) poisoning can lead to significant mortality if left untreated. When unable to elicit exposure history, determining blood EG levels becomes critical for diagnosis and guides antidote administration. While gas chromatography is gold standard for diagnosis, its utility is limited due to restricted availability. Surrogate diagnostic tests are often used and should be interpreted with caution.

Case Description: A 66-year-old female with history of alcohol use disorder and COPD presented with dyspnea and confusion. History of EG ingestion could not be obtained. She was hypotensive, tachycardic, in respiratory distress and had decreased breath sounds bilaterally. Laboratory work showed pancytopenia, respiratory and metabolic acidosis (pH 6.87), anion gap of 31 mmol/L, osmolol gap of 9 mOsm/kg, and lactic acidosis (17.4 mmol/L). A right lower lobe lung opacity on CT raised suspicion for respiratory source of septic shock. She was emergently intubated, treated with IV fluids, antibiotics, vasopressors, and initially got fomepizole for severe EG toxicity after spectrophotometric assay revealed elevated EG levels of 49 mg/dL. Since no calcium oxalate crystals were present on urine sediment (Image) and the osmolal gap was normal, the blood sample taken upon admission, which indicated elevated EG levels, was subjected to gas chromatography coupled with mass spectrometry. It resulted negative for EG. Due to worsening acidosis and anuria, CRRT was initiated with no improvement and she passed away. Respiratory culture resulted positive for staphylococcus, making pneumonia and sepsis a likely diagnosis.

Discussion: EG levels can be falsely elevated by spectrophotometry in presence of severe lactic acidosis. It uses enzymatic method to detect nicotinamide adenine dinucleotide levels produced by oxidation of both EG and lactic acid. This leads to misdiagnosis and use of inappropriate and costly therapies. Thus, laboratory tests should be interpreted with caution. When suspicion for EG toxicity is high in patients with lactic acidosis, gas chromatography coupled with mass spectrometry should be used.



Urine without calcium oxalate crystals.

SA-PO511

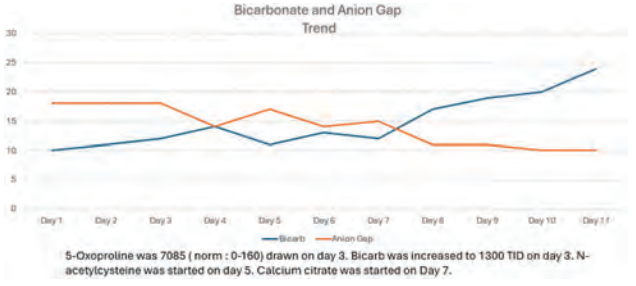
Treatment of 5-oxyproline Anion Gap Acidosis with N-acetylcysteine

Ryan Fields, Harold A. Franch. *Emory University, Atlanta, GA.*

Introduction: Over 60 million Americans use acetaminophen (APAP) weekly. Mitochondrial APAP metabolism requires the consumption of glutathione which is produced by the glutathione cycle (GC) consuming the amino acid, cystine. 5-oxoproline anion gap (AG) metabolic acidosis occurs when high dose APAP therapy combined with inadequate protein intake leads to depletion of cystine. Low cystine levels block the GC causing accumulation of 5 oxyproline. N-Acetylcysteine, used to threat APAP overdose, restores the GC and should reduce 5-oxoproline production.

Case Description: 81 y.o. woman with past Roux-n-Y gastric bypass, leukemia s/p bone marrow transplant, cervical vertebral collapse s/p surgeries was admitted for cervical and abdominal pain and anorexia and found to have UTI and severe constipation. Her pain does not respond to narcotics: she took APAP 650 BID and 2 tablets of Fioricet (APAP 600 mg) q 8 hours at home. She received IV APAP 1000 mg BID and 2 Fioricet BID in hospital. Her baseline normal gap metabolic acidosis is treated with Ca citrate, but on admission patient had mixed non-gap and AG metabolic acidosis with normal ketones, lactate, eGFR. Urine electrolytes showed sodium 35 mEq/L but chloride was undetectable, suggesting anion drag. On Day 2 riifaxamin was started for presumed bacterial overgrowth AG acidosis. She refused to stop APAP, but reduced to ~ 2200 mg daily and N acetyl cysteine 35 mg/kg BID stared day 5. AG normalized day 8. Samples obtained day 2 showed serum d-lactate normal and urine organic a 5-oxoproline was 44-fold top of normal range with no other organic acid elevated more than 6-fold (lactate 4-fold).

Discussion: Clinical recognition of 5-oxoproline metabolic acidosis is important given delays in urinary organic acid results. Treatment is discontinuing APAP and feeding protein. This first report of N-acetylcysteine treatment may provide an option if APAP cannt be discontinued when adequate protein intake is not possible.



5-Oxoproline was 7085 (norm : 0-160) drawn on day 3. Bicarb was increased to 1300 TID on day 3. N-acetylcysteine was started on day 5. Calcium citrate was started on Day 7.

SA-PO512

GOLD MARK "S": A Unique Cause of High-Anion Gap Metabolic Acidosis

Hassan H. Allahrakha, Akash Hazari, Roberto L. Collazo-Maldonado. *Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Calcific uremic arteriolopathy (CUA) is a serious disorder characterized by vascular calcifications that can affect patients with advanced chronic kidney disease. Currently, there is no approved therapy for CUA, but sodium thiosulfate (STS) has been used off-label for CUA. Mehta et. Al proposed a new anion gap mnemonic for the 21st century: GOLD MARK. TS is also a cause of high anion gap metabolic acidosis (HAGMA). We present two cases of STS-induced HAGMA.

Case Description: The first patient was a 58-year-old male with end-stage renal disease (ESRD) who presented with left toe gangrene. He was diagnosed with chronic CUA. He received STS (50 g) and underwent dialysis. Eleven days following admission, he developed HAGMA (anion gap: 27 mEq/L, CO_2: 17 mEq/L). The second patient was a 32-year-old female with ESRD secondary to diffuse proliferative lupus nephritis who was admitted for central retinal artery occlusion. She was diagnosed with a painful ulcer on the right thigh secondary to CUA. She received STS and developed HAGMA during her hospitalization (anion gap: 22 mEq/L). In both cases, HAGMA resolved following discontinuation of STS.

Discussion: The mechanism of how STS causes HAGMA is unknown. It is presumed to be due to oxidation of thiosulfate to sulfate by the liver or intestinal bacteria, which is enhanced in patients with ESRD due to reduced clearance of the medication. A new HAGMA mnemonic has been proposed: GOLD MARK (**G**lycols [ethylene and propylene], **O**xoproline, **L**-lactate, **D**-lactate, **M**ethanol, **A**spirin, **R**enal failure, and **K**etoacidosis). We propose that STS be considered in the differential diagnosis of HAGMA, and that "S" for STS be added to the end of the mnemonic GOLD MARK.

SA-PO513

Severe Metabolic Acidosis in a Patient with Spinal Muscular Atrophy

Joyita Bharati, Kevin Tong, Afolarin A. Amodu. *Boston Medical Center, Boston, MA.*

Introduction: Ketogenesis starts early after starvation in healthy individuals. However, ketoacidosis develops after ~2 weeks of starvation. We report a case of severe ketoacidosis after a short period of fasting in a patient with spinal muscular atrophy (SMA).

Case Description: A 59-year-old wheelchair-bound male with SMA and a recent history of percutaneous cholecystostomy presented to the hospital with purulent drainage. His food intake mainly comprised ground vegetables and protein. The patient was nil per oral overnight on day 2 for cholecystostomy tube exchange and reported abdominal pain and vomiting on day 3 of admission. Home medications included baclofen and sertraline. Physical examination was noted for muscle atrophy without any distress. Blood pressure was 124/66 mm Hg, pulse rate was 85/min, respiratory rate was 22/min, and oxygen saturation was 98% on room air. Laboratory evaluation: serum bicarbonate 11 mmol/L, anion gap 22, pH 7.17 with partial pressure of carbon dioxide of 30 on day 3 of admission. Severe high anion gap metabolic acidosis (without adequate respiratory compensation) was confirmed with repeat tests. Sodium bicarbonate infusion was started due to severe acidosis while being further evaluated. Serum creatinine was 0.49 m/dl, and electrolytes were within range. Serum lactate was 0.8 mmol/L (0.5 to 2 mmol/L), osmolar gap was 4 (<10), serum ethanol, methanol, ethylene glycol, salicylate, and acetaminophen, respectively, were negative. The urine dipstick showed 2+ ketones, serum acetone was 20 mg/dL (0-5 m/dL), and serum beta-hydroxybutyrate was 8.52 mmol/L (0.28 mmol/L). His blood sugar was 93 mg/dl on day 1 and 63 mg/dl on day 3 of admission. Low-normal blood sugar and ketoacidosis in the setting of ~18 hours of fasting prompted a diagnosis of starvation ketoacidosis. Serum bicarbonate remained ~12 mmol/L on bicarbonate infusion. Dextrose infusion normalized bicarbonate (25 mmol/L) within four hours.

Discussion: Starvation ketoacidosis is described within 12-24 hours of starvation in patients with SMA in isolated case reports. Poor ketone body consumption by low muscle mass is postulated to cause severe ketoacidosis in SMA patients upon a short period of starvation. Timely treatment and prevention with dextrose, including during fasting for procedures, are crucial to prevent this complication in SMA patients.

SA-PO514

Therapeutic Plasma Exchange Complicated by Hyperchloremic Metabolic Acidosis in a Patient with Myasthenia Gravis and CKD

Michael Gilleo, Hassan Mahmoud. *Maine Medical Center, Portland, ME.*

Introduction: Therapeutic plasma exchange (TPE) is commonly associated with metabolic derangements such as hypocalcemia and hypomagnesemia. Hyperchloremic metabolic acidosis is a rare complication previously reported in patients undergoing multiple days of consecutive TPE. We present a case of hyperchloremic acidosis in a patient with baseline renal dysfunction undergoing TPE every other day.

Case Description: An 88 year old with CKD 3B was admitted for acute myasthenia gravis with respiratory failure, a category I indication for plasma exchange. They underwent TPE treatment on two consecutive days, followed by another three treatments each separated by 48 hours. Plasma was replaced at 105% fluid balance with 50 g/L albumin in saline solution (3-4L per treatment). Citrate anticoagulation was used for the apheresis circuit. The patient developed hyperchloremic acidosis following initial TPE treatment (Figure 1). The anion gap was normal. The acidosis persisted throughout the duration of TPE therapy and corrected two days after therapy completion.

Discussion: This case highlights the rare complication of hyperchloremic acidosis during TPE. The acidosis was likely caused by replacement of plasma with large volumes of chloride-containing fluids, with underlying renal dysfunction impairing excretion of excess chloride. Chloride concentrations of 109-145 mmol/L have been reported in albumin solutions, but this measurement was not made for the albumin used in this patient. Citrate toxicity was not a factor, as hepatic function and total-to-ionized calcium ratio were normal. Hyperchloremic acidosis may result in reduced renal perfusion, increased ventilatory needs, and symptoms such as nausea, vomiting, or myalgias. Providers must be aware of this risk associated with TPE, even when treatment frequency is reduced to every 48 hours. Early recognition may allow for treatment of the acidosis, or changes to replacement fluids used during plasma exchange.

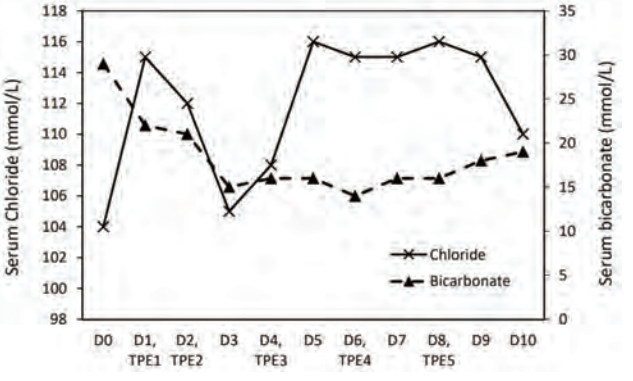


Figure 1: Serum chloride and bicarbonate throughout TPE treatment

SA-PO515

Distal Renal Tubular Acidosis as Initial Presentation of Sjogren Syndrome in Pregnancy

Chintan V. Shah, Issa R. Haddad. *Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida College of Medicine, Gainesville, FL.*

Introduction: Sjogren's syndrome (SS) is a chronic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, leading to dryness of mucosal surfaces. While renal involvement in SS is not uncommon, its initial presentation as distal renal tubular acidosis (dRTA) in pregnancy is rare. dRTA is a renal tubulopathy characterized by impaired acid secretion in the distal nephron, resulting in metabolic acidosis.

Case Description: A 44-year-old female physician with a history of Hashimoto's thyroiditis was referred to the nephrology clinic for elevated creatinine levels at 19 weeks of gestation without any specific symptoms. Laboratory investigations revealed serum potassium of 3.7 mmol/L, serum CO2 of 12 mmol/L with a normal anion gap of 13, and serum creatinine level of 1.4 mg/dL. Urinalysis showed persistent alkaline urine pH >7. dRTA was suspected and confirmed with 24-hour urine demonstrating undetectably low citrate with ammonium of 14 mmol/24hr. Further rheumatology evaluation revealed positive antinuclear antibodies (ANA), elevated SSA and SSB antibodies, and a positive Schirmer test (right eye 4mm, left eye 4mm) after 5 minutes, suggesting Sjogren's syndrome (SS). Renal US did not show evidence of nephrocalcinosis or hydronephrosis. Treatment with oral potassium citrate 30 mEq twice a day was initiated with normalization of serum CO2 to 23 mmol/L. Kidney biopsy revealed acute on chronic tubulointerstitial nephritis. Consequently, the patient was initiated on prednisone 60 mg/d, followed by a taper. Despite initial clinical improvement, symptoms recurred with prednisone less than 20 mg/d. Azathioprine 50 mg/d was added, and the dose increased gradually while simultaneously tapering off steroids. Significant improvements have been noted in the patient's symptoms and fetal growth, demonstrating a positive shift from the 3rd to the 13th percentile with immunosuppression.

Discussion: Extra-glandular renal manifestations are not uncommon presentations of Sjögren's syndrome. SS is associated with various renal manifestations, including tubulointerstitial nephritis and renal tubular acidosis. This case highlights the challenges in managing Sjogren's syndrome during pregnancy and emphasizes the importance of tailored treatment strategies to alleviate the patient's symptoms and mitigate fetal complications.

SA-PO516

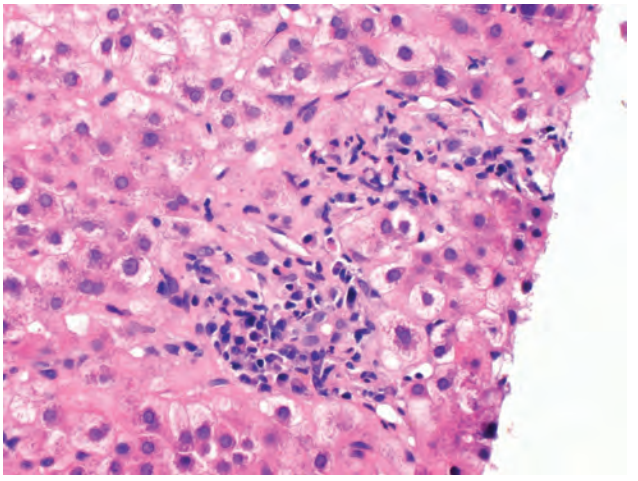
Worsening of Distal Renal Tubular Acidosis (dRTA) as a Sign of Recurrent Autoimmune Hepatitis after Liver Transplant

Samir A. Elshouny,[1] Ayat S. Al saeed,[2] Ahmed F. Elfar.[1] *[1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [2]Royal Commission for Jubail and Yanbu, Jubail, Saudi Arabia.*

Introduction: dRTA is characterized by hyperchloremic non-anion gap metabolic acidosis, marked hypokalemia and alkaline urine. Patients with dRTA almost always have hypocitraturia which increase the risk of calcium phosphate stones and nephrocalcinosis. dRTA develops because of autoimmune diseases including Sjögren's syndrome, autoimmune hepatitis and other causes.

Case Description: A 32 years old female with a history of autoimmune hepatitis complicated with cirrhosis underwent living related liver transplant. Her family history was negative for any autoimmune diseases. Few years prior to liver transplant, she was diagnosed with dRTA secondary to autoimmune hepatitis. Her disease was complicated by kidney stones which required surgical removal. Post-transplant, she has remained stable clinically and biochemically. 6 months after the transplant surgery, she presented to our hospital with fatigability, low energy, continuous vomiting, and poor appetite. Blood pH 7.14. Serum creatinine 129 umol/L (close to baseline), K 2.9 mmol/l, HCO3 10 mmol/L. T.Bilirubin 216 umol/L, D.Bilirubin 187 umol/L, ALT 176 U/L, AST 156 U/L alk. phosphatase 323 U/L. Urine pH 7, urine K 8.55 mmol/L, urine creatinine 1.1 mmol/l. Urine K/C Ratio 7.77 mmol/mmol indicating renal potassium wasting. MRCP showed focal biliary anastomotic stricture with minimal intrahepatic biliary dilatation. She underwent ERCP mediated dilatation and stenting. A biopsy of the liver was consistent with recurrent autoimmune hepatitis. The patient was discharged on steroid tapering dose and K citrate.

Discussion: We present a new correlation between worsening dRTA and recurrence of autoimmune hepatitis in a post liver transplant patient. Our case highlights that worsening dRTA could be a sign of recurrence of the primary disease in the transplant graft. To our knowledge, this finding has never been reported in the literature.



SA-PO517

A Case of Fanconi Syndrome with Biopsy-Proven Acute Proximal Tubular Injury Induced by a Dietary Supplement, Benikoji

Masato Habuka, Michihiro Hosojima, Hideyuki Kabasawa, Asa Ogawa, Yumi Ito, Suguru Yamamoto, Akihiko Saito. *Niigata Daigaku Igakubu Igakuka Daigakuin Ishigaku Sogo Kenkyuka, Niigata, Japan.*

Introduction: Fanconi syndrome is a common consequence of drug-induced nephrotoxicity characterized by diffuse injury of the proximal tubules that results in the malabsorption of various electrolytes and substances. However, cases of dietary supplement-induced Fanconi syndrome are rare and there is no report on renal histology in these patients. Herein, we present a case of dietary supplement-induced Fanconi syndrome confirmed by renal biopsy.

Case Description: A 49-year-old woman who had been taking a lipid-lowering dietary supplement, Benikoji, was referred to our hospital due to anorexia and nausea over the past 13 days. Blood examinations revealed renal dysfunction, hypokalemia, hypophosphatemia, hypouricemia, and metabolic acidosis. Urinalysis showed proteinuria, glycosuria, hematuria, aminoaciduria, increased excretion of potassium, phosphorus, and uric acid levels, which were not explained by plasma concentration, along with high levels of urinary β_2-microglobulin and N-acetyl-beta-D-glucosaminidase. A drug-induced lymphocyte stimulation test of her serum showed positive for the dietary supplement. A percutaneous kidney biopsy was performed on the second day after admission. Light microscopy analysis showed significant tubular changes, with 50% of the tubular epithelial cells showing simplification, vacuolization, and shedding, indicating acute tubular necrosis. Immunohistochemical staining with an anti-megalin antibody, a proximal tubule marker, was positive for the damaged tubules. Acute proximal tubular injury due to the intake of the dietary supplement was found based on her medical history, laboratory examination, and pathological findings, which led to diagnosis of Fanconi syndrome. Her general condition and clinical laboratory data markedly improved after discontinuation of the dietary supplement and correction of dehydration and electrolyte imbalance. She was discharged 14 days after admission.

Discussion: Clinicians should consider dietary supplement-induced Fanconi syndrome as a differential diagnosis if patients are taking dietary supplements. Kidney biopsy is useful for diagnosing and determining the pathogenesis of dietary supplement-induced Fanconi syndrome. However, further reports are warranted to investigate the exact mechanism of dietary supplement-induced Fanconi syndrome.

SA-PO518

Sheep in Wolf's Clothing: Pseudohypobicarbonatemia in a Patient with Multiple Myeloma

Ziad Alahmadi, Zain Haq, Joshua D. King, Ami M. Patel. *University of Maryland Medical Center, Baltimore, MD.*

Introduction: There are multiple methods to measure serum bicarbonate level which is crucial for diagnosis and management of acid-base disturbances. The most common method is directly measuring the total serum carbon dioxide (CO2) concentration in basic metabolic panel (BMP) via a method based on phosphoenolpyruvate carboxylase (PEPC); another method is by indirect calculation of the bicarbonate concentration via the Henderson-Hasselbalch equation using the measured pH and partial pressure of CO2 (pCO2) in plasma. Multiple confounders can cause discrepancies in the measured bicarbonate in each method, such as increased concentration of serum proteins that can affect the PEPC assay leading to spuriously low bicarbonate values.

Case Description: A 47 year old male patient with multiple myeloma, chronic kidney disease (CKD) and hypertension who presented with hypoxia due to pneumonia

and volume overload in the setting of hypertension and acute kidney injury on top of CKD. Patient improved after antibiotics, intravenous (IV) diuresis, and blood pressure control. He was noted to have significantly low total CO2 level in BMP on admission to 10 mmol/L with anion gap (AG) of 23 mmol/L. Patient was thought to have high anion gap metabolic acidosis and was treated with an IV bicarbonate infusion. Patient had a normal lactate, normal blood sugar, and no apparent contributing factor that would explain this acid-base disturbance. A simultaneous venous blood gas (VBG) showed a pH of 7.35, pCO2 of 42 mmHg and bicarbonate of 22 mmol/L. IgA level and lambda light chain were both significantly elevated at 3804 mg/dL and 1788.97 mg/L respectively. The discrepancy of bicarbonate level between VBG and BMP was explained by increased paraproteins, which have resulted in artifactual errors in PEPC-based laboratory analysis of serum HCO3. The patient's AG and accuracy of serum bicarbonate level measurement improved as their IgA and lambda light chain levels subsequently decreased.

Discussion: Interpretation of serum CO2 is usually accurate; rarely, there are factors that can cause false readings. Arterial or venous blood gas bicarbonate value can guide you to detect pseudohypobicarbonatemia in the appropriate clinical setting.

Discrepancy in HCO3 levels based on paraprotein levels

	HCO3 BMP	Anion Gap BMP	pH VBG	CO2 VBG	HCO3 VBG	Lambda light chain	IgA level
Day 1 of MM treatment	10 mmol/L	23	7.35	42 mmHg	22 mmol/	1788.97 mg/L	3804 mg/dL
Day 7 of MM treatment	19 mmol/L	13	7.41	37 mmHg	23 mmol/L	812.98 mg/L	2276 mg/dL

SA-PO519

A Case of Metabolic Alkalosis, Hyponatremia, and Hypokalemia Secondary to Dietary Chloride Deficiency Syndrome in a J Tube-Dependent Patient

Amitha N. Kapyur,[1,2] John C. Ong,[1,2] Sapna Shah.[2,1] *[1]Los Angeles General Medical Center, Los Angeles, CA; [2]Keck Hospital of USC, Los Angeles, CA.*

Introduction: Chloride deficiency is a well-established contributor of metabolic alkalosis. Hypochloremia results predominantly from renal and extra-renal losses, and rarely from decreased intake. Here, we report a case of metabolic alkalosis, hyponatremia, and hypokalemia from insufficient chloride content in enteral formula in a J-tube dependent patient.

Case Description: A 36 year-old-male with past medical history of caustic injury secondary to alkali ingestion with laryngeal, esophageal, and pyloric strictures who is J-tube dependent for nutrition presents for routine J tube exchange, and is admitted for electrolyte abnormalities. He is otherwise in normal health without any gastrointestinal symptoms or abnormal gastrostomy output. Laboratory tests were notable for pH7.64, PaCO2 53 mm Hg, bicarbonate >50 mEq/L, Na 130 mEq/L, K 2.6 mEq/L, Cl 65 mEq/L, BUN 119 mEq/L and Cr 2.67 mEq/L. XR demonstrated appropriate positioning of his GJ tube. His outpatient enteral nutrition prescription was 5 cartons of TwoCal formula daily. The nutritional chloride content of this prescription is 1.1g/day which is significantly below the daily recommended intake

Discussion: Metabolic alkalosis is one of the most common acid-base disturbances encountered in the hospital setting and is associated with an increased mortality. In a population where nutrition is entirely dependent on an artificial formulation, insufficient electrolyte additions can lead to severe complications. TThere are hundreds of formulations available for enteral feeding, with each varying in their composition. Per USDA, the recommended amount of intake of chloride in an adult is thought to be about 2.3 - 3.1g, though no standardized number has been established. Electrolytes such as sodium and potassium often receive a lot of focus due to their role in metabolic homeostasis while chloride is often overlooked. We suggest that clinicians should include chloride content in their decision making when choosing enteral artificial nutrition in order to avoid an under-recognized potential complication of metabolic alkalosis, hyponatremia, and hypokalemia due to chloride deficiency syndrome.

SA-PO520

Detergent Pica Causing Alkalemia, Life-Threatening Hypokalemia, and Profound Hypochloremia

Munsef Barakat, Anand Achanti, Waleed A. El Sheikh Mohammed. *Medical University of South Carolina, Charleston, SC.*

Introduction: Metabolic alkalosis is characterized by elevated serum bicarbonate and result from either a net loss of acid via the renal or GI tracts or via accumulation of exogenous base. History may reveal unusual cause like detergent PICA. Renal handling of excess bicarbonate is limited by the low GFR, hypovolemia, hypokalemia and hypochloremia.

Case Description: 32 years old lady presented with progressive lower limb weakness, nausea and one episode of vomiting without hematemesis. On further history she reported drinking detergent (Gain & Oxiclean). **Examination:** BP125/70mmHg, HR 77bpm (no orthostatic changes), and normal oxygen saturation 96%. Neurological exam showed mild weakness in proximal lower limbs muscle with normal reflexes. **Labs:** BMP: K 1.3mmo/l, Cl 65mmol/l, HCO_3- 49mmol/l, CPK 3042U/L. Normal TSH, genetic testing was negative for Bartter, Gitelman and Liddle syndrome. PH 7.71, PCO_2 51mmHg, HCO_3- 62mmol/l, ionized calcium 0.93mmol/l. **Urine study:** Cl 87mmol/l, K 8.6mmol/l, Na 24 mmol/l and Cr 90mmol/l **ECG:** prolonged QTc interval and low T- wave amplitude with U-wave. Based on presentation, the likely diagnosis was metabolic alkalosis secondary to pica disorder with consumption of bicarbonate found in detergents which is exacerbated further by the hypokalemia and hypochloremia which limited the kidney ability to mitigate such high alkali load. Furthermore, her severe hypokalemia caused mild rhabdomyolysis as evident by the elevated creatine kinase level. She was admitted to the ICU for telemetry monitoring, started IV chloride rich IV fluids, aggressive parenteral potassium replacement via central venous catheter, she required total of 560mEq of potassium chloride and another 360mEq of oral potassium chloride. 72 hours post admission alkalemia resolved with resolution of the hypokalemia and correction of hypochloremia.

Discussion: Approach to metabolic alkalosis should takes into consideration its different phases of development, the generation, maintenance, and recovery phase. Both hypochloremia and hypokalemia have an inhibitory effect on the pendrin exchanger in the B-intercalated cells as hypochloremia impair the bicarbonate secretion and hypokalemia will downregulate the pendrin expression. In conclusion the correction of metabolic alkalosis require correction of concomitant hypokalemia, hypochloremia and volume resuscitation when clinically appropriate.

SA-PO521

Rapid Correction of Chronic Respiratory Alkalosis Leading to Profound Hyperphosphatemia in a Patient in the Cardiac Intensive Care Unit (ICU)

Kirollos Eskander,[1] Akshita Sahi,[1] Talha Siddique,[1] Jarrod B. Post.[2] *[1]UConn Health, Farmington, CT; [2]Hartford HealthCare, Hartford, CT.*

Introduction: In critically ill patients, changes in extracellular buffer (i.e. bicarbonate) concentrations are expected and usually trigger further work-up into the underlying acid-base disorder. However, hyperphosphatemia in a patient with acute renal failure is often thought to be in the setting of reduced creatinine clearance. But what about 'bone buffering'?

Case Description: Our patient is a 59-year-old female with mixed ischemic and nonischemic cardiomyopathy status post orthotopic heart transplant with a post-transplant course complicated by biopsy-negative rejection with subsequent cardiogenic shock. She developed acute kidney injury and respiratory failure in the setting of hypervolemia. She was initiated on pulse dose steroid and continuous veno-venous hemodialysis with improvement in her oxygenation. The patient had been tachypneic for several months with mild respiratory alkalosis. In light of hypocapnia and normal oxygen saturation, we hypothesize this to be due to alveolar capillary J-receptor stimulation in the setting of chronic pulmonary edema secondary to decompensated heart failure. [1] However, blood gas indicated worsening alkalemia and change in mentation. Labs showed pH 7.60, pCO2 23, bicarbonate 23, and an anion gap of 12. She underwent serum electrolyte mass removal with normal saline replacement to induce therapeutic dilutional acidosis. However, the patient developed concomitant steroid-induced diabetic ketoacidosis the following day with repeat labs showing pH 7.40, pCO2 19, bicarbonate 12, and an anion gap of 28. Within 24 hours, her phosphorus increased from 2.5 to 11.8 with a slight increase in serum calcium from 7.2 to 8.3. Her hyperphosphatemia improved with insulin therapy and with a subsequent increase in pH to 7.56.

Discussion: Our patient's pH, while within the acceptable range at 7.40, reflected a rapid increase in serum H^+ concentration with a drop from 7.60 overnight. Our patient's respiratory compensation was already maximized due to her persistent tachypnea, and she was unable to renally excrete acid due to her AKI. Therefore, we believe this case highlights bone resorption and intracellular buffers such as phosphate in strict control of serum hydrogen ion concentrations. This is congruent with the concomitant increase in serum calcium.

SA-PO522

Acute Hypophosphatemia Due to Rapid Correction of Respiratory Acidosis

Sruthi Sundaram, Payaswini Vasanth, Mohammad Kazem Fallahzadeh Abarghouei. *Emory University Woodruff Health Sciences Center, Atlanta, GA.*

Introduction: Acute respiratory alkalosis is a known cause of acute hypophosphatemia. Here we describe a case of acute hypophosphatemia due to rapid correction of respiratory acidosis in a patient with acute kidney injury (AKI) superimposed on chronic kidney disease (CKD).

Case Description: A 59-year-old male with end stage renal disease due to focal segmental glomerulosclerosis status post renal transplant 17 years prior, chronic kidney disease stage 3b of the allograft, scoliosis with restrictive airway disease, obstructive sleep apnea, and chronic hypercapnic respiratory failure, presented with encephalopathy and acute on chronic respiratory acidosis requiring intubation and mechanical ventilation. He was also noted to have an AKI. As expected in a patient with AKI on CKD, he had hyperphosphatemia on presentation, but did not require renal replacement therapy. However, after intubation and mechanical ventilation, which resulted in an acute decline in his pCO2 level from 88 mmHg to 31 mmHg and an acute rise in pH to 7.53, his phosphorus level acutely dropped to 1.0 mg/dL. His serum phosphorous levels rose to 3.0 mg/dL after being given 20 mmol of intravenous sodium phosphate, which was still within low-normal range despite remaining in an AKI state suggesting these values were true.

Discussion: Hypophosphatemia in acute respiratory alkalosis can occur from a rapid decline in pCO2 and an increase in intracellular pH which induces phosphofructokinase activity and glycolysis, leading to intracellular phosphorus consumption as phosphorylated glucose precursors are produced. As a result, extracellular phosphorus shifts intracellularly acutely dropping serum phosphorus levels. The correction of our patient's hypercapnic respiratory failure with intubation and mechanical ventilation induced a rapid decline in pCO2, which subsequently resulted in a similar decline in serum phosphorus levels likely through a similar mechanism. This case illustrates the importance of monitoring serum phosphorous levels in patients being treated for hypercapnic respiratory failure to avoid complications from acute hypophosphatemia.

SA-PO523

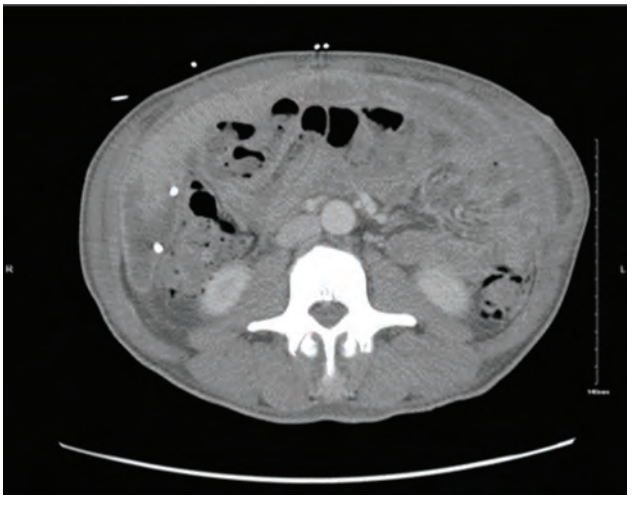
A Case of Hypercalcemia Due to Peritoneal Sarcoidosis Presenting as Appendicitis and Recurrent Sterile Intra-abdominal Abscess with Skin Fistula

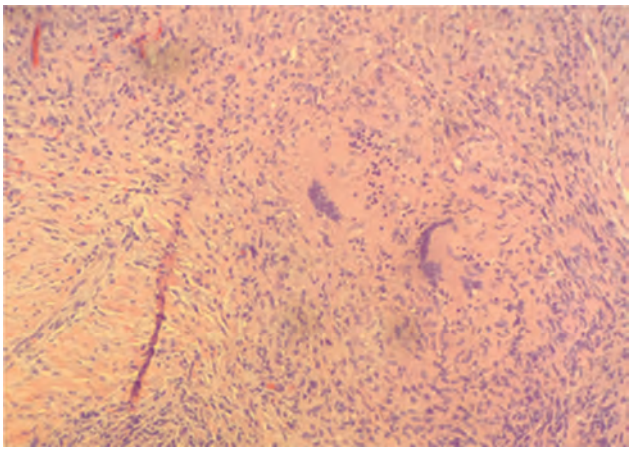
Thin Thin Soe,[1,2] Ao Wang,[1,2] Isha Puri,[1,2] Muhammad Azhar,[1,2] Mary C. Mallappallil.[1,2] *[1]New York City Health and Hospitals Corporation, New York, NY; [2]SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Sarcoidosis is a systemic inflammatory disease which affects multiple organs. The lungs and lymphatic systems are most commonly affected. We present a case of peritoneal involvement.

Case Description: A 47 year old man who had no prior history presented to ED with sudden onset abdominal pain, was diagnosed with acute appendicitis, and underwent laparoscopic appendectomy. The hospital course was complicated by intermittent fevers without leukocytosis, sterile intraabdominal pus like fluid collection and provoked pulmonary embolism. He was discharged with indwelling intraabdominal Jackson-Pratt drain and oral metronidazole. One month later, he presented with abdominal pain, swelling at the surgical site and 20 lbs weight loss. His serum calcium was 16.3, repeated CT abdomen and pelvis revealed mass-like consolidation along the right anterior greater omentum, multiple intra-abdominal rim-enhancing fluid collection (see image). Hypercalcemia workup showed: PTH 8.4, PTHrP <2.0, 25OH VitD 7.03 and 1,25OH VitD 101, ACE level 176. Due to high suspicion of granulomatous disease all infectious causes and malignancy were ruled out with peritoneal fluid cytology. Omental biopsy was done which showed Fibro adipose tissue with non-necrotizing granulomas, Acute and Chronic inflammation with Giant cell reaction (see image). He was diagnosed with sarcoidosis and started on Prednisone after which he clinically improved and hypercalcemia resolved

Discussion: As sarcoidosis is a diagnosis of exclusion, sometimes diagnosing sarcoidosis can be challenging because of its indolent nature, and similar presentation to inflammatory, chronic infectious diseases or malignancy. Peritoneal involvement of sarcoidosis is a rare manifestation.





SA-PO524

Utility of N-terminal Parathyroid Hormone-Related Protein in Evaluating Hypercalcemia in Patients with CKD

Vincent Anthony S. Tang, Anthony Russell Villanueva. *Division of Adult Nephrology, Department of Medicine, University of the Philippines - Philippine General Hospital, Manila, Philippines.*

Introduction: Humoral hypercalcemia of malignancy (HHM) is commonly seen among patients with cancer, and its incidental finding in asymptomatic individuals may be the first indication of an occult malignancy. Parathyroid hormone-related protein (PTH-RP) has been implicated as the circulating factor mediating HHM. However, the diagnostic evaluation of HHM in the setting of CKD can be challenging due to associated alterations in parathyroid (PTH) physiology as well as impaired clearance of PTH-RP metabolites among these patients.

Case Description: A 48-year old female, with CKD 5 from Diabetic Kidney Disease on hemodialysis since 2018, consulted for incidental finding of hypercalcemia. 8 months prior, she was diagnosed with secondary hyperparathyroidism given her hyperphosphatemia, hypocalcemia, and elevated PTH levels. Interim, she was prescribed dietary modifications and non-calcium-based phosphate binders. However, on her most recent laboratory tests, she was noted to have mild hypercalcemia, normophosphatemia, normal vitamin D3 levels, and low-normal PTH levels. She was asymptomatic and denied intake of calcium or vitamin D supplements. Rest of the ancillary history was non-contributory. Her vital signs were normal, and systemic physical exam was unremarkable. Since a PTH-independent cause was considered, N-terminal PTH-RP assay was requested, which came out elevated thus confirming the suspicion of HHM. Screening mammogram revealed an irregularly-shaped, high-density right breast mass. Core needle biopsy and immunohistochemistry staining showed invasive ductal carcinoma (pT2N1M0; grade I; positive for estrogen and progesterone receptors; negative human epidermal receptor-2 status). She was then scheduled for lumpectomy, and adjuvant hormonal therapy. Post-operatively, her calcium levels gradually normalized.

Discussion: Historical trends of calcium, phosphate, and vitamin D levels can aid clinicians to identify concomitant PTH-independent hypercalcemia among patients with CKD. When an occult malignancy is suspected, clinicians should specifically request for N-terminal PTH-RP assays to accurately confirm the diagnosis of HHM. Although more commonly available, C-terminal PTH-RP levels can be falsely elevated in patients with CKD without cancer due to reduced glomerular filtration in this population.

SA-PO525

A Modern and Hip Cause of Profound Hypercalcemia

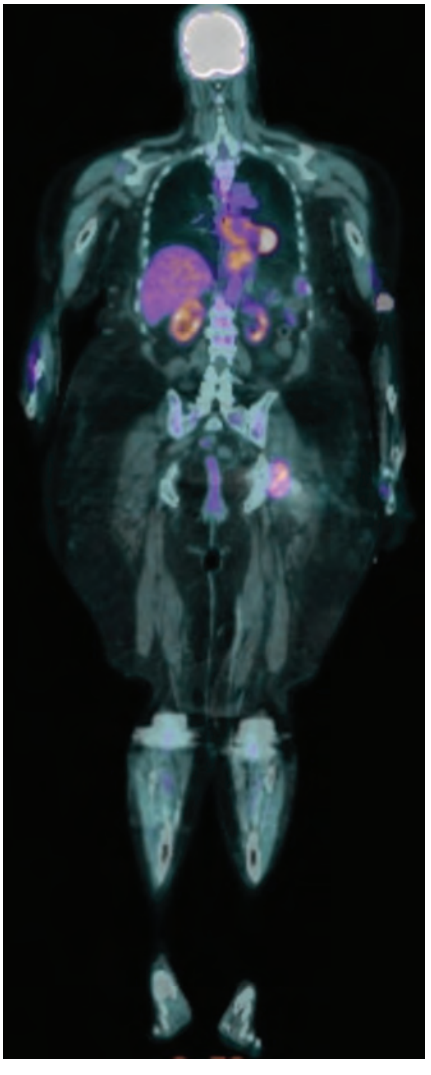
Saud A. Alsaleh, Trevor C. Stevens, William H. Fissell. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) is triggered by adjuvants causing abnormal immune responses. Though usually linked to vaccines and medical products, its link to arthroplasty and cement leak is unexplored. We describe a hypercalcemia case due to ASIA after left hip arthroplasty.

Case Description: A 69-year-old woman with chronic kidney disease had a left hip replacement complicated by dislocation. During revision, there was cement leak into her intramedullary canal. Post-operatively, she developed intermittent episodes of hypercalcemia, which progressed to hypercalcemia (14.7 mg/dL) four years later. Work-up in (see table) was suggestive of granulomatous disease. A PET scan showed intense uptake around the hip arthroplasty and iliac adenopathy, soft tissue biopsy was unrevealing. Therapy with steroids improved her condition along with Vit D 1,25 level, tapering led to return of hypercalcemia and chorioretinitis. Symptoms and response to steroids suggested ASIA with a sarcoid-like reaction.

Discussion: The cement leak from arthroplasty exposes individuals to components, potentially acting as adjuvants and triggering ASIA-like symptoms. ASIA is linked to manifestations such as granulomas, hypercalcemia, uveitis, and CKD. The temporal relationship in this case between cement leak and the onset of autoimmune symptoms suggests ASIA as a potential complication of arthroplasty. More research is needed to establish diagnostic criteria and treatment for ASIA.

Test	Result	Test	Result
PTH	14 pmol/L	Free light chain	Normal ratio
25 Vitamin D	23 pg/mL	Serum Histoplasmosis	Negative
1, 25 OH Vitamin D	150 pg/mL	Serum Blastomycosis	Negative
PTHrp	8 pmol/L	Immunoglobulins	Normal levels
ACE	95 U/L	IGRA	Negative
SPEP/UPEP	No monoclonal disease	HIV	Negative



SA-PO526

Recurrent Hypercalcemia in a Patient with Hodgkin Lymphoma with Concurrent Elevated Parathyroid Hormone-Related Peptide (PTHrP) and Vitamin D

Zachary Appelbaum, Christina H. Brotman. *University of Pennsylvania, Philadelphia, PA.*

Introduction: Hypercalcemia occurs in approximately 30 percent of patients with malignancy. Malignancy-associated hypercalcemia has been attributed to several distinct mechanisms: osteolytic metastases, humoral production of parathyroid hormone-related peptide (PTHrP), excess 1-alpha hydroxylase associated production of 1,25 dihydroxyvitamin D (1,25(OH)2D), and rarely ectopic parathyroid hormone (PTH) secretion. We report a case of hypercalcemia associated with elevated levels of both 1,25(OH)2D and PTHrP in a patient with newly diagnosed Hodgkin lymphoma.

Case Description: A 68 year old man with a history of hypertension initially presented for inguinal hernia repair and was found to have a mediastinal mass on cross sectional imaging. A biopsy revealed Hodgkin's lymphoma. He was scheduled to start chemotherapy as an outpatient, but was found to have severe hypercalcemia with a serum calcium level of 14.7 mg/dL and impaired kidney function with serum creatinine of 2.85 mg/dL. He was hospitalized and received intravenous normal saline, calcitonin 8 units/kg twice daily for 48 hours, and intravenous pamidronate. A workup revealed a suppressed PTH level of 1.4 pmol/L, elevated PTHrP of 3.6 pmol/L, and elevated 1,25(OH)2 D of 220.8 pg/mL. His calcium improved to 9.6 mg/dL and the creatinine improved to 2.0 mg/dL prior to discharge. The following week, his calcium was elevated to 11.4 mg/dL, and he was prescribed prednisone 100 mg for five days. The calcium continued to rise to 13.9 mg/dL and he was again hospitalized and received intravenous fluids, calcitonin, and bisphosphonate therapy.

Discussion: Hypercalcemia of malignancy can be due to a single or a combination of disparate mechanisms. Solid organ tumors are typically associated with PTHrP production while hematologic malignancies are typically associated with increased activity of 1-alpha hydroxylase. We report a case of a patient with Hodgkin lymphoma associated hypercalcemia with elevated levels of both PTHrP and 1,25(OH)2D. His hypercalcemia was not responsive to oral corticosteroids despite the elevated 1,25(OH)2D, suggesting that the hypercalcemia was at least partially attributable to the PTHrP. There have been a few cases of co-secretion of PTHrP and 1,25(OH)2D in Non-Hodgkin's lymphoma; this appears to be the first reported case in a patient with Hodgkin lymphoma.

SA-PO527

Abnormally Normal? A Patient with Hypercalcemia of Malignancy Presenting with Normal PTH

Amelito Manuel L. Andaya,[1] Amelito Miguel L. Andaya.[2] Piedmont Athens Regional GME. *[1]Piedmont Athens Regional Internal Medicine Residency Program, Athens, GA; [2]University of Santo Tomas Faculty of Medicine and Surgery, Manila, Philippines.*

Introduction: In malignancy-related hypercalcemia, serum PTH are usually suppressed with noted elevation in PTHrP. We present a case of hypercalcemia of malignancy due to suspected lung cancer with normal PTH levels.

Case Description: A 73 year old man with multiple substance use including tobacco and alcohol, hypothyroidism, and hypertension presented with a several-day history of confusion and eventually unresponsiveness. He was hypotensive on presentation that responded to normal saline bolus. On exam, he was somnolent, tachycardic, had severely dry oral mucosa, impaired skin turgor, and generalized abdominal tenderness. Pertinent workup showed hypercalcemia at >18, hypernatremia at 154, elevated creatinine at 2.18 and BUN at 66. Ionized calcium was high at 1.81. On further investigation, PTH was normal at 24.30 but PTHrP was elevated at 85. Chest CT scan with contrast demonstrated multiple pulmonary nodules, right hilar and mediastinal adenopathy, lymphangitic carcinomatosis, and bilateral small pleural effusions. Aggressive IV hydration with IV lactated ringers at 150 mL/hr was done. IV zoledronic acid and calcitonin were started. Serum calcium then improved and stabilized to 10.7 however patient's altered sensorium persisted, eventually becoming more agitated. He was then assessed to have metastatic lung cancer and was transitioned to hospice after extensive discussion with the patient and his family.

Discussion: Excessive secretion of PTHrP is said to be the most common cause of hypercalcemia of malignancy. This patient presented with normal PTH levels of 24.30 which would have otherwise led the diagnostic trail to other non-malignant causes of hypercalcemia. Although there is no standard, any PTH greater than 20 pg/mL is considered unsuppressed. In addition, another interesting development was the persistence of the patient's mentation despite eventual successful lowering of the serum calcium. This was hypothesized to be likely secondary to other factors including possible CNS metastasis, hypothyroidism, or undiagnosed dementia. Hence, with the findings of this case, clinicians should not always expect suppression of PTH and at the same time, must be careful in interpreting parameters of improvement in hypercalcemia especially in patients with multiple risk factors.

SA-PO528

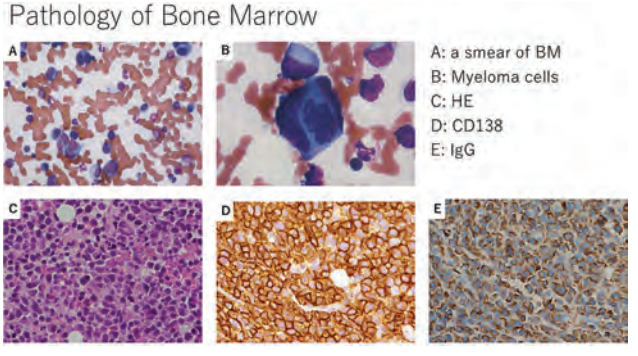
A Rare Case of Nonsecretory Multiple Myeloma: Pitfall of Hypercalcemia

Hitomi Miyata. *Kyoto Katsura Byoin, Kyoto, Japan.*

Introduction: Hypercalcemia is a common disorder normally caused by primary hyperparathyroidism or malignancy. Basically some disease signals seem to come out on the process of differential diagnosis. However, non-secretory multiple myeloma (NSMM) is a rare case and might not show any signs and lead us hard to diagnose it.

Case Description: An 80-year-old man was urgently admitted to our hospital with lower back pain, appetite loss and progressed his limitation of movement and weakness. He had type 2 diabetes and hypertension in his past history. The laboratory data just showed acute kidney injury(serum creatinin 1.63mg/dl) with hypercacemia(serum calcium 1.32mg/dl, calcium ion 1.61mmol/L), moderate higher CRP(5.59mg/dl), hyperuricemia (13.2mg/dl) and metabolic alkalosis. Computed tomography was not detected any abnormality. Both of Urinary BJP and M protein was negative. On Day 21, we rechecked abdominal CT and it showed newly osteolytic lesion on the left ischium. Bone marrow aspiration revealed eventually malignant myeloma and non-producer and non-secretory myeloma cells with both negative findings of M protein and deviation of free light chains.

Discussion: We experienced a rare case of NSMM with acute kidney injury and hypercalcemia. We struggled about differential diagnosis of hypercalcemia without M peak in serum and urinary Bence Jones protein (BJP). Only osteolytic lesions in the lumbar, appeared in three weeks after admission, led us to diagnosis of multiple myeloma. We should seek the examination of bone marrow aspiration and smear of peripheral blood if we get nothing of causes in regard to hypercalcemia.



SA-PO529

Denosumab-Associated Severe Symptomatic Hypocalcemia in a Patient with Multiple Myeloma and AKI

Nerihan Hadji, Hitesh H. Shah. *Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY.*

Introduction: Denosumab, a human monoclonal antibody has several FDA-approved indications including treatment of hypercalcemia of malignancy. Hypocalcemia is a known side effect of this medication however severe symptomatic hypocalcemia has been rarely described in patients with hypercalcemia of malignancy. We present a case of severe symptomatic hypocalcemia following a single dose of Denosumab in a patient with AKI and hypercalcemia from multiple myeloma.

Case Description: 78-year-old male with recent history of multiple myeloma, AKI and hypercalcemia presented to our hospital for abdominal discomfort, back pain, tremors and confusion. Admission labs were significant for severely low serum calcium (SCa) level of 4.8 mg/dL and an elevated serum creatinine (SCr) level of 4.06 mg/dL. Two weeks prior to current presentation, our patient was hospitalized for back pain, AKI and hypercalcemia. During that hospital stay, patient was found to have multiple myeloma on bone marrow biopsy. Scr on that admission was elevated at 2.56 mg/dL and SCa was elevated at 12.0 mg/dL. Patient initially received two doses of calcitonin however as serum calcium remained elevated a dose of Denosumab was administered. SCa normalized to 8.9 mg/dL on discharge. During this hospital stay, patient received multiple doses of intravenous calcium with daily oral calcium and calcitriol therapy for several days for management of persistent hypocalcemia. SCa finally improved to 8.4 mg/dL on discharge. Pt. was discharged on oral calcium and calcitriol therapy with close outpatient monitoring of SCa.

Discussion: Our patient with AKI and hypercalcemia in setting of multiple myeloma developed severe symptomatic hypocalcemia following a single dose of Denosumab treatment. Our patient required prolonged hospitalization for management of severe and persistent hypocalcemia. Based on our experience, we recommend caution with Denosumab use in patients with AKI and hypercalcemia of malignancy. We also recommend very close outpatient monitoring of SCa following Denosumab treatment in this patient population.

SA-PO530

Stepwise Teamwork Approach Saves Patients Extensive Work-Up

Anas R. Alshwayat, Nithin Karakala, Ahmed Abdallah. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Hypercalcemia is a relatively common clinical entity that can arise from a variety of etiologies, including primary hyperparathyroidism, malignancies or medications. In most of these cases, the underlying cause can be determined through a thorough clinical evaluation, including a detailed patient history, physical examination and targeted laboratory testing. We present a case with significant hypercalcemia, highlighting the diagnostic approach taken to identify the underlying cause through systematic analysis of the patient's symptoms, laboratory results and imaging studies

Case Description: 77-year-old male with past medical history of hypertension, prostate cancer status post-excision and CKD stage IIIB, was transferred from an outside hospital for evaluation of suspected multiple myeloma. Physical exam was stable but initial laboratory work up showed a serum calcium level of 15.3 mg/dL. He was started on IV fluids with a slight improvement in serum calcium level to 12 mg/dl however it rebounded to 13 g/dl the next day prompting a consultation for Nephrology for management of acute kidney injury and hypercalcemia. A bone marrow biopsy ruled out for multiple myeloma, leading to consideration of other differentials. Parathyroid hormone (PTH) was appropriately low, and 25-Hydroxyvitamin D level was normal, but 1,25-Dihydroxyvitamin D was elevated at 108 pg/mL. This raised the suspicion of hypervitaminosis D due to granulomatous disease (sarcoidosis vs. infection). Detailed history revealed that the patient lived on a farm with various animals, including birds raising suspicion for an inhalational insult. CT scan of the lung that showed a left lung nodule. This was followed by a bronchoscopy that revealed high beta-D-glucan levels and fungal culture showed growth of Pneumocystis Carinii pneumonia. The patient was subsequently treated for PCP. After two months, his hypercalcemia was completely resolved.

Discussion: Pneumocystis pneumonia is recognized for triggering a granulomatous response that stimulates the overproduction of 1,25-dihydroxyvitamin D, resulting in hypercalcemia and a range of complications, including AKI. Hypercalcemia associated with PCP proves resistant to standard treatments and should trigger a thorough patient history inquiry. In many cases, a comprehensive history and examination offer vital diagnostic insights even for non-immunocompromised patients.

SA-PO531

Hypercalcemia-Associated AKI and Nephrogenic Diabetes Insipidus in the Hospital Setting: A Cohort Study

Fnu Suman, Juan Carlos Q. Velez. Ochsner Group. *Ochsner Health, New Orleans, LA.*

Background: Hypercalcemia (hyperCa) can cause acute kidney injury (AKI) through a variety of mechanisms that include renal vasoconstriction, a loop diuretic-like effect, nephrogenic diabetes insipidus, and nephrocalcinosis. Although these clinical associations are well-recognized, their incidence and interrelationship are sparsely reported. We examined the rate of AKI and hypernatremia (hyperNa) during episodes of hyperCa in hospitalized patients.

Methods: A retrospective review of medical records was conducted searching for inpatient adults with hyperCa at Ochsner Medical Center over a 1-year period. Hypercalcemia was defined as serum calcium (sCa) > 11.0 mg/dL. Etiology of hyperCa was determined based on history and available laboratory and imaging data. We examined the rate of AKI (by KDIGO) registered during the hyperCa event, as well as the rate of hyperNa. Patients with end-stage kidney disease or kidney transplant were excluded.

Results: A total of 102 patients with in-hospital hypercalcemia were included. Median age was 72, 35% women, 48% White, 29% Black. Etiology of hyperCa was malignancy in 58 (57%) (multiple myeloma, metastatic bone disease, PTH-related peptide production, or 1,25-vitamin D), exogenous calcium or vitamin D supplements in 29 (28%), thiazide in 3 (3%), sarcoidosis in 3 (3%), and immobilization in 9 (9%). Median peak sCa was 12.1 (11.2-17.8) mg/dL. Corrected sCa was available in 65%, with a median of 12.8 (11.7-15.4) mg/dL. High ionized Ca was verified in 36%. AKI was present in 14 (14%). Hypernatremia was present in 8 (8%). The most severe case of hyperNa had a serum Na 168 mEq/L and a urine osmolality of 110 mOsm/kg, suggesting nephrogenic diabetes insipidus. The second most severe case of hyperNa had a serum Na 150 mEq/L and a urine osmolality of 603 mOsm/kg, suggesting absence of ongoing water losses. Urine osmolality was not measured in the remaining 6 hyperNa cases. Concomitant AKI and hyperNa only occurred in 2 (2%).

Conclusions: AKI occurred in 1 in 7 cases of hyperCa, whereas hyperNa occurred in 1 in 12 cases. Urine osmolality is seldom obtained in cases of hyperNa. Because hyperNa was only present in 2/14 (14%) of AKI cases, the primary mechanism of AKI in hyperCa may not relate to nephrogenic diabetes insipidus. Further investigation is warranted.

SA-PO532

Antineoplastic Agents Associated with Hypomagnesemia and Effect Modifiers for the Associations

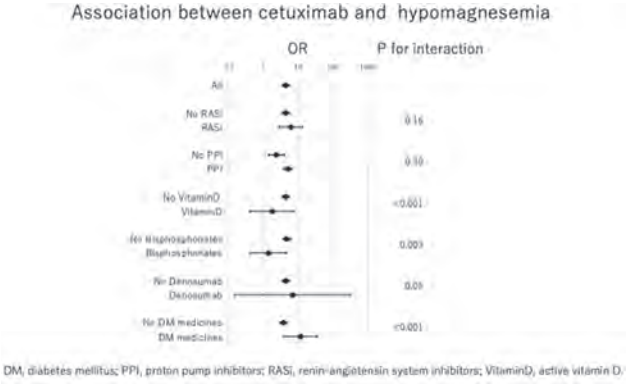
Kodai Suzuki, Miho Murashima, Yuki Miyaguchi, Takahisa Kasugai, Tatsuya Tomonari, Minamo Ono, Masashi Mizuno, Takayuki Hamano. *Nagoya Shiritsu Daigaku Daigakuin Igaku Kenkyuka Igakubu, Nagoya, Japan.*

Background: Hypomagnesemia (hypoMg) is common and associated with worse outcomes among patients with malignancy. In this study, we aimed toidentify anti-neoplastic agents associated with it and modifiable factors for the associations.

Methods: In this retrospective cohort study, we enrolled patients receiving antineoplastic agents at Nagoya City University Hospital from 2018 to 2020. We employed mixed-effects logistic regression models to identify factors associated with hypoMg (Mg<1.8mg/dL) and effect modifiers for the associations. As a sensitivity analysis, missing data for dipstick proteinuria were multiply imputed and the data were analyzed by Poisson regression with frequency of laboratory measurements as an exposure variable.

Results: A total of 2644 patients were included. The mean age was 63.8 (16.5) years and the mean eGFR was 71.9 (21.1) mL/min/1.73m2. Serum magnesium (Mg) was measured at least once in 1692 (64.0%) patients, of these, 718 (42.4%) developed hypoMg (15.5 events/100 patient-measurements). Cetuximab was most strongly associated with hypoMg (OR 4.36 [3.44-5.54]), followed by platinum drugs (2.20 [1.87-2.59]). Loop diuretics were negatively associated with hypoMg (0.76 [0.61-0.96]), while eGFR was not. Cetuximab was associated with hypoMg among non-users of vitamin D recptor activator (VDRA) (4.36 [3.44-5.54]) and non-users of bisphosphonates (4.70[3.65-6.04]) but not among users of these agents (p for interaction <0.001 and 0.003, respectively). In the sensitivity analyses, the effect modification by VDRA was consistent, while the effect modifications by bisphosphonates were not observed. Proteinuria was not associated with hypoMg and no effect modifications were seen by eGFR or proteinuria.

Conclusions: HypoMg was common among those with malignancy, while only about two-thirds of patients had Mg measurements. Cetuximab was the agent most strongly associated with hypoMg, and cetuximab-induced hypoMg might be prevented by using vitamin D or bisphosphonates.



DM, diabetes mellitus; PPI, proton pump inhibitors; RASi, renin-angiotensin system inhibitors; VitaminD, active vitamin D.

SA-PO533

Evaluating the Prognostic Significance of Magnesium Levels in Emergency Department Admissions: The Largest Retrospective Cohort Study

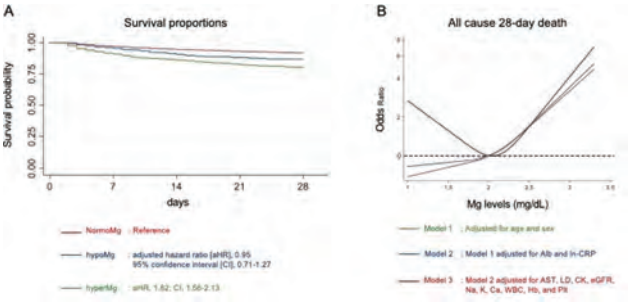
Keita Hattori, Nobuhiro Nishibori, Masaki Okazaki, Nobuhide Endo, Kazuhiro Furuhashi, Shoichi Maruyama. *Nagoya Daigaku, Nagoya, Japan.*

Background: Previous research has reported hypermagnesemia (hyperMg) in the emergency department (ED) as an independent mortality factor, however there are no studies which evaluated consecutive cases because magnesium (Mg) is routinely measured. On the other hand, hypomagnesaemia (hypoMg) in the ED is controversial. Our study aims to address these limitations and provide a comprehensive analysis of the relationship between Mg levels and mortality.

Methods: We conducted a retrospective cohort study of patients admitted in the ED of the Anjo Kosei Hospital, Japan. Consecutive patients more than 18 years old from January 2017 to December 2019 were included. Patients were divided into three groups according to Mg categories (Mg ≦ 1.5, 1.5 < Mg ≦ 2.4, and Mg < 2.5 mg/dL). We investigated association Mg levels and 28-day death using multivariable Cox proportional hazard model. Restricted Cubic Spline (RCS) analysis was also performed for evaluation of non-linear relationship.

Results: There were 43,100 ED visits and 43,808 cases of Mg data are available. Among included 11,532 patients (mean age, 75 years; 58% male; mean Mg, 2.1 mg/dL; mean length of hospital stay, 11days), 404 (3.6%), 9,826 (85.2%), and 1,302 (11.2%) patients were classified as hypoMg, normoMg, and hyperMg, respectively. Survival curves are shown in Figure A. RCS analysis in Figure B showed no significant increase in the hazard ratio for hypomagnesemia, but a significantly higher hazard ratio for hypermagnesemia in multivariate-adjusted models after adjustment for CRP and Alb.

Conclusions: In patients admitted from the ED, HyperMg was associated with 28-day mortality, while hypoMg was not associated.



SA-PO534

Correlation between Ionized and Total Magnesium in Children on Continuous Kidney Replacement Therapy

Shruthi Mohan,[1] Denise C. Hasson,[2] James Rose,[1] Stuart Goldstein,[1,3] Stefanie W. Benoit.[1,3] *[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]NYU Langone Health Hassenfeld Children's Hospital, New York, NY; [3]University of Cincinnati College of Medicine, Cincinnati, OH.*

Background: Abnormal magnesium (Mg) levels are associated with poor outcomes in critically ill children. Regional citrate anticoagulation (RCA) during continuous renal replacement therapy (CRRT) may deplete Mg by chelating ionized Mg (iMg) and lead to negative Mg balance. iMg data in children on CRRT are sparse, and existing concordance data between iMg and total Mg (tMg) levels are conflicting. We assessed iMg/tMg correlation in critically ill children during CRRT with RCA.

Methods: Blood samples collected prospectively to measure iMg immediately before, 1-2, and 18-24 hours after the first CRRT start. We compared iMg to tMg levels obtained for clinical purposes. Normal iMg and tMg were based on reference ranges of 0.44-0.65 and 0.66-1.07 mmol/L, respectively.

Results: 17 patients provided 48 iMg and 37 tMg samples. Low iMg was seen in 12% (2/17) at CRRT start, 35% (6/17) at 1-2 and 70% (12/17) at 18-24 hours. iMg decreased over time (β = - 0.005, $p < 0.001$). iMg and tMg levels showed moderate correlation ($r = 0.71$, $p < 0.0001$). The citrate dose, CRRT effluent dose, CRRT fluid type, or Mg dose in parenteral nutrition did not differ between patients with normal *vs.* low iMg at 24 hours after CRRT initiation.

Conclusions: iMg and tMg showed moderate correlation in critically ill children receiving CRRT with RCA. Increased prevalence of low iMg within 24 hours of CRRT initiation highlights the need for vigilant Mg monitoring and further exploration of Mg trends after 24 hours.

Funding: Commercial Support - Nova Biomedical provided critical care blood gas analyzer and supplies for research

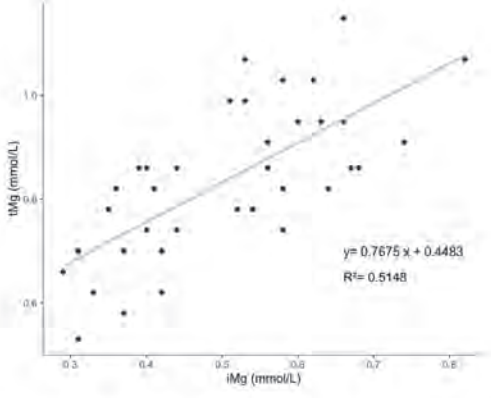


Figure 1: Correlation between iMg and tMg in CRRT. Grey line indicates the simple linear regression line. Pearson's Correlation coefficient for iMg and tMg showed moderate association ($r = 0.717$, $p < 0.0001$)

Table 1: Comparison of normal vs. low iMg groups 24 hours after CRRT initiation. Median, IQR for numeric variables, and N (%) for categorical variables are shown. Mann Whitney U test or Fisher Exact test showed no significant differences between the groups.

Variables	Normal iMg (n = 5/17) Median (IQR)	Low iMg (N = 12/17) Median (IQR)	P value
Age (years)	14 (2 -14)	3 (0.9 – 14.3)	0.49
Gender, Female, N (%)	3 (60)	7 (58)	1.0
Race, White, N (%)	4 (80)	9 (75)	0.56
Ethnicity, Non-Hispanic, N (%)	5 (100)	10 (83.3)	1.0
Weight (Kg)	26.2 (20 - 70)	13.5 (9.1 – 62.5)	0.31
BSA (m2)	1 (0.7 - 2)	0.6 (0.4 – 1.6)	0.32
CRRT effluent rate (ml/hour/1.73 m2)	2090 (1950 - 2160)	2170 (2108 - 2392)	0.17
Acid Citrate Dextrose dose (ml/m2/hour)	150 (138 - 209)	175 (152 - 202)	0.75
No Magnesium in TPN, N (%)	2 (40)	6 (50)	0.62
Magnesium in TPN (mg/day)	517 (954)	94 (619)	
CRRT fluid Type			0.54
Prismasate (Mg = 0.5 mmol/L), N (%)	3 (60)	10 (83.4)	
Phoxilium (Mg = 0.75 mmol/L), N (%)	2 (40)	1 (8.3)	
HBiofluid (Mg = 0.75 mmol/L), N (%)	0 (0)	1 (8.3)	

SA-PO535

Genome-Wide Association Study of Candidate Genes Associated with Hypomagnesemia in the MyCode Population

Adwait S. Chafale,[1] Ian Dinsmore,[2] Tooraj Mirshahi,[2] Alexander R. Chang.[2] *[1]Geisinger Commonwealth School of Medicine, Scranton, PA; [2]Geisinger Health, Danville, PA.*

Background: Magnesium is the second most common intracellular cation with many critical roles in enzymatic reactions the body. Consequently, hypomagnesemia has been linked to dysfunction of multiple diseases. Our aim in this study was to identify potential genetic causes of hypomagnesemia.

Methods: We conducted a genome-wide association study (GWAS) using data from 68620 participants with outpatient serum magnesium levels in the Geisinger MyCode DiscovEHR study, a health system-based cohort in central and northeast Pennsylvania. Cases of hypomagnesemia were defined as magnesium levels <1.75 mg/dL (n=7704; 11.2%).

Results: Using a genome-wide significance cutoff ($p < 5x10^{-8}$), we identified numerous significant loci (Figure). The top loci associated with hypomagnesemia identified included rs11255473 located near the *TAF3* gene (p =7.02E-14), rs2070803 located near *MUC1/TRIM46* (p = 2.25E-13), rs7133329 located near MIR4491 (p=1.41E-10), rs78116544 located near *HERC2P3* (p=1.07E-10), rs11079428 located near *BCAS3* (p=1.26E-9), rs11079428 located near TBX2-AS1 (p=1.26E-9), rs1210864775 located near 5_8S-rRNA (p=3.78E-09), and rs2844882 on chromosome 14 (p=2.81E-09).

Conclusions: Our hypomagnesemia GWAS confirms an association between *TAF3* and hypomagnesemia, and identifies several other novel loci associated with magnesium.

Funding: NIDDK Support

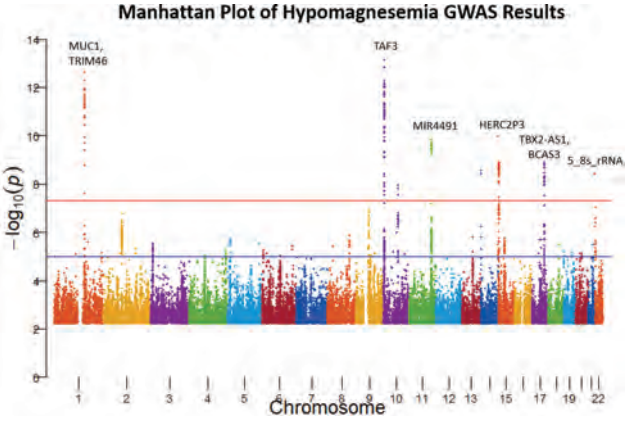


Figure. **Manhattan Plot of Hypomagnesemia GWAS Results**. Blue line p = 1x10^-5; red line p = 5x10^-8.

SA-PO536

Critical Hypermagnesemia Induced by Excessive Milk of Magnesia in Acute Kidney Failure

Pooja V. Nangrani, Shikha Jaiswal. *UC Health Medical Center, Cincinnati, OH.*

Introduction: Hypermagnesemia is rare, usually caused by excessive magnesium intake, impaired renal excretion, or both, with most cases being mild and asymptomatic. Here, we present a case of severe Hypermagnesemia in the setting of Peptic Ulcer disease and Acute Renal Failure.

Case Description: 68-year-old Male with a history of Heart Failure with Reduced Ejection Fraction, EF 45%, Mobitz II, status-post pacemaker, and prior percutaneous cholecystostomy, normal baseline renal function, presented with nausea, vomiting, and epigastric pain. Initial CT showed pneumonia but no intraabdominal abnormalities. Labs were unremarkable, with a magnesium of 1.5 mg/dL. Suspecting Peptic ulcer disease, he was given 3 doses of 400 mg magnesium oxide and 2 doses of 2400 mg Milk of Magnesia. Thereafter, He left Against Medical Advice (AMA), only to return 12 hours later with worsening abdominal pain, hypotension, and tachycardia. Repeat CT showed large pneumoperitoneum. EKG was notable for paced rhythm and prolonged QTc. He was emergently taken for exploratory laparotomy for suspected duodenal perforation, even before labs could be obtained. Post-op labs showed critically elevated magnesium at 11.6 mg/dL, and serum creatinine at 2.5, with oliguria. He was started on normal saline, with Lasix and calcium gluconate as a temporizing measure. He then underwent urgent intermittent hemodialysis (HD), followed by continuous Renal replacement therapy for 24 hours. Magnesium gradually improved to 4.7, and to 2.5 over the next 24 hours. He admitted to drinking ¾ bottles of Milk of Magnesia after leaving AMA. After discontinuing HD, magnesium levels remained in the normal range, and urine output and creatinine gradually improved.

Discussion: Significant exogenous magnesium intake can exceed the kidneys' excretory capacity, especially in cases of renal impairment. Gastrointestinal inflammation can lead to increased absorption. Magnesium levels greater than 10mg/dl can lead to neuromuscular paralysis and even cardiac arrest and require emergent hemodialysis. Calcium gluconate antagonizes hypermagnesemia's neuromuscular and cardiac effects and should be given promptly. This case highlights the need for concise patient history, judicious medication administration, emergent therapies for electrolyte abnormalities, and patient education to prevent risks associated with self-medication and AMA discharges.

SA-PO537

Making Haste in Magnesium Waste: A Case for Genetic Testing

Andrea Chau, Michael T. Sim, Brian Y. Young. *UC Davis Health, Sacramento, CA.*

Introduction: Hypomagnesemia is estimated to affect between 2-15% of the general population. While the most common etiologies of hypomagnesemia are acquired, genetic causes need to be considered and can be associated with additional complications. Our case describes a patient found to have an HNF1B gene mutation.

Case Description: A 22-year-old female with multiple sclerosis and borderline primary hyperparathyroidism was found to have hypomagnesemia during work up for chronic headaches and fatigue. Despite discontinuation of a PPI, the patient had persistent hypomagnesemia requiring intermittent IV repletion. Laboratory testing showed isolated hypomagnesemia as low as 1.0mg/dL, with normal serum potassium and other electrolytes, high-normal calcium, and creatinine of 0.7mg/dl. Renal ultrasound was unremarkable. Her initial FeMg at 2% was borderline and non-diagnostic for renal wasting. A 24-hour urine magnesium was done, with results suggestive of renal wasting at 155mg in the presence of hypomagnesemia (normal < 30mg/24 hours). Of note, the patient was still receiving IV magnesium repletion, which may confound 24-hour urinary testing. Ultimately, genetic testing was pursued given diagnostic uncertainty, and it revealed a heterozygous mutation in HNF1B.

Discussion: Unlike most patients with HNF1B mutations who have renal cystic disease or hypoplasia, our patient's kidneys were anatomically normal. Her only clinical manifestation was hypomagnesemia, which occurs in up to 50% of patients. Of its many roles, HNF1B regulates the transcription of a subunit of Na/K-ATPase in the kidney and is involved in distal convoluted tubule magnesium reabsorption. The HNF1B mutation may also explain this patient's hyperparathyroidism, as mutations can cause loss of PTH transcription repression. Absent clear indicators for the etiology of hypomagnesemia, genetic testing was imperative. Providers may now screen for associated complications of HNF1B mutations, such as early-onset diabetes, chromophobe renal cell carcinoma, CKD, and abnormal liver function. HNF1B is only one of many genetic causes of hypomagnesemia and has variable phenotypic manifestations. Genetic testing should be considered in the evaluation of hypomagnesemia because diagnosis can allow for early identification and prevention of comorbidities, as well as referrals to genetic counseling.

SA-PO538

Overlooked Cause of Hypomagnesemia

Nidhi Gupta, Golnaz Vahdani. *Banner - University Medical Center Tucson, Tucson, AZ.*

Introduction: Hypomagnesemia can occur due to GI losses or renal wasting. Genetic causes of hypomagnesemia usually include Bartter/ Gitelman syndrome or isolated hypomagnesemia. We present a case of hypomagnesemia that was initially misdiagnosed as Gitelman syndrome, however later diagnosed as HNF1beta mutation.

Case Description: A 25-year-old female with history of Gitelman syndrome presented to our hospital for evaluation of jaundice. Jaundice that began at age 17, with prior liver biopsies revealing idiopathic ductopenia. Nephrology was involved in the treatment of electrolyte abnormalities. At age 18, the patient was noted to have hypokalemia and hypomagnesemia with fractional excretion of magnesium at 32%. Renin was elevated and the patient was diagnosed with Gitelman syndrome. On admission, she was noted to have hypocalcemia which did not fit the diagnosis of Gitelman syndrome. Genetic testing was recommended in addition to replacing her electrolytes. Patient underwent a liver biopsy and genetic testing, and was eventually discharged on spironolactone, potassium chloride, oral magnesium and calcium carbonate supplementation along with outpatient appointment for iv magnesium infusions. She was readmitted for decompensated cirrhosis and acute kidney injury requiring renal replacement therapy and underwent liver transplantation. Kidney imaging revealed bilateral simple cysts measuring upto 2.1 cm. Genetic reports showed 17p-12 deletion syndrome which explained her liver and kidney disease. Patient to date continues to receive iv magnesium infusions weekly. She was recently started on dapagliflozin.

Discussion: 17p-12 deletion encompasses 23 known genes, one of which includes hepatocyte nuclear factor 1 beta mutation. This mutation is associated with renal magnesium wasting due to dysfunction of distal convoluted tubule with 100% occurrence by at 13.8-18 years. These patients may be misdiagnosed as Gitelman syndrome, hence early recognition of this mutation in patients presenting with liver and kidney disease should be considered to avoid extensive diagnostic evaluation and economic burden to the health system.

SA-PO539

"Tubular Intoxication": Phosphatidylethanol Testing to Diagnose Alcohol-Induced Hypomagnesemia

Sophia M. Cima,[1] Aj Lowe,[1] Jay L. Hawkins,[2] Prasanth Ravipati.[2]
[1]University of Nebraska Medical Center College of Medicine, Omaha, NE; [2]University of Nebraska Medical Center, Omaha, NE.

Introduction: Hypomagnesemia occurs with chronic alcohol (EtOH) use through multiple pathways including intestinal malabsorption, decreased dietary intake, and importantly, renal magnesium wasting. Previous data has shown that discrepancy between patient reported EtOH consumption and true EtOH intake is common. A new test, called Phosphatidylethanol (PEth), is an invaluable tool in identifying EtOH consumption patterns and alcohol-related disorders. PEth accumulates with repeat ethanol exposure, and thus, PEth reliably indicates a person's EtOH consumption over the prior 28 days. We present a case series of 3 patients with uncertain etiology of hypomagnesemia, in which PEth testing confirmed a diagnosis of chronic EtOH consumption resulting in renal magnesium wasting.

Case Description: A 68-year-old man and 58-year-old woman were referred to nephrology clinic for hypomagnesemia refractory to supplementation. They had chronic magnesium levels of 1.2-1.4 mg/dL and 1.1-1.5 mg/dL, respectively. A 33-year-old man was admitted to the hospital due to muscle spasms and weakness and was found to have magnesium level of 0.9 mg/dL. Fractional excretion of magnesium on a random urine sample was greater than 8% in all patients. All patients had normal renal function, were without additional risk factors for renal magnesium wasting, and reported consuming less than 6 drinks per week. PEth levels (ng/mL) were 1,401, 206, 337 – indicating severe EtOH consumption (level > 200) and consistent with EtOH intake beyond the patients' report.

Discussion: In the setting of hypomagnesemia associated with renal magnesium wasting, the differential is broad, including EtOH consumption. EtOH consumption as reported by patients can be difficult to quantify and can be misleading. With the novel use of PEth testing, these three patients were ultimately diagnosed with EtOH use disorder as the cause of their hypomagnesemia and referred to addiction services. In the evaluation of hypomagnesemia, PEth testing can help clinicians identify EtOH use disorder and help optimize management strategy, potentially reducing the need for additional work up (genetic testing, medication adjustments, additional consultations).

SA-PO540

Severe Hypomagnesemia Due to Renal Magnesium Wasting in Patient with HNF1B Mutation and Pseudogout

Michael Che, Peter Magner, Caitlin Hesketh, Pierre-Antoine Brown. *University of Ottawa, Faculty of Medicine, Division of Nephrology, Ottawa, ON, Canada.*

Introduction: Hepatocyte nuclear factor 1β (HNF1B) is a transcription factor that is essential for proper development of the kidney and pancreas. Here, we report a case of severe hypomagnesemia and cystic kidney disease due to *HNF1B* mutation in a patient with pseudogout.

Case Description: A 41-year-old female with hypothyroidism and frequently flaring pseudogout with severe chondrocalcinosis in multiple joints was referred to nephrology for assessment of hypomagnesemia refractory to oral magnesium (Mg) supplementation. There was no history of gastrointestinal losses, offending medications, or family history of hypomagnesemia. Plasma Mg was 0.35 mmol/L and she had metabolic alkalosis with total CO2 of 32 mmol/L but normal plasma calcium, potassium, sodium, phosphate, creatinine, and parathyroid hormone. Plasma Mg was very low for at least one year prior to nephrology assessment. Urine fractional excretion of Mg (FEMg) was 3.9%, consistent with renal Mg wasting. Genetic testing for hereditary causes of renal Mg wasting revealed a heterozygous pathogenic *HNF1B* gene variant, identified as 1.26 Mb deletion, seq[GRCh37] del(17)(q12), chr17:g.34842466_36104935del. An abdominal CT scan revealed a congenital agenesis variant of the dorsal pancreas and multiple left renal cysts, both in keeping with her *HNF1B* mutation. She was treated with amiloride, titrated to 15 mg BID, to reduce renal Mg wasting, in addition to oral Mg glycinate supplementation, but her Mg continued to remain low. Consequently, she was also started on IV Mg sulfate 5 mg weekly. Plasma Mg improved slightly to 0.5 mmol/L but FEMg remained high at 5.5%. Dapagliflozin 10 mg daily was further added and FEMg improved to 2.6%. Her plasma Mg fluctuates depending on timing relative to weekly IV Mg infusion but has been as normal as 0.9 mmol/L. She continues on oral Mg supplementation, weekly IV Mg infusions, and amiloride and dapagliflozin.

Discussion: Severe hypomagnesemia is known to cause increased chondrocalcinosis likely contributing to the patient's poorly controlled pseudogout. Numerous renal manifestations are associated with *HNF1B* mutations including cystic kidney disease and renal Mg wasting as demonstrated in this case. Hypomagnesemia when associated with *HNF1B* variants may be severe, refractory to oral Mg supplementation, and consequently may benefit from IV Mg infusions and diuretic therapy.

SA-PO541

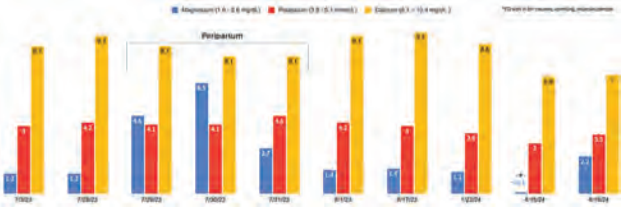
Severe Hypomagnesemia in Pregnancy

Ankita Ashoka, Monica L. Reynolds. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Introduction: Hypomagnesemia in pregnancy has been associated with a higher risk for perinatal complications. We report a case of severe hypomagnesemia of unknown etiology in a woman presenting for prenatal care. Genetic testing revealed mutations in the transient receptor potential cation channel membrane 6 (TRPM6) gene leading to intestinal and renal magnesium(Mg) wasting with secondary hypocalcemia.

Case Description: A 37-year-old woman with a history of infantile seizures was referred to nephrology clinic for prenatal evaluation of hypomagnesemia. She reported pediatric work-up revealing hypomagnesemia and one episode of breakthrough seizure in adolescence after stopping chronic Mg supplements. Family history was noted to be unremarkable. Laboratory values were notable for Creatinine 0.65mg/dL, fractional excretion(Fe) of Mg 2.5%, Fe calcium(Ca) 1.9%. Trends for Mg, Ca, and potassium are noted in the image. Kidney-centered genetic testing identified two mutations in TRPM6: one known to cause intestinal losses (c.1081C>T; p. Gln361*) and a variant of uncertain significance (c.1732-3C>G; p.?). At 36 weeks 3 days, the patient developed preeclampsia with severe features and was treated with intravenous (IV) Mg, maintaining levels > 4 mg/dL at time of delivery, and was discharged on oral Mg supplements. At 8 months postpartum, she presented to the hospital with seizures and was noted to have a Mg level of <0.1 mg/dL requiring IV Mg supplementation.

Discussion: For most women in the United States, prenatal care is their sole contact with the health care system, offering a rare opportunity to diagnose and optimize chronic disease. Through nephrology referral and genetic testing, our patient was able to secure a diagnosis and understand implications for inheritance in her offspring. Though it is uncertain if the mutations found in our case are biallelic, her clinical history and lab findings suggest these mutations together are pathogenic in an autosomal recessive manner. We advocate for early genetic testing in patients presenting with severe hypomagnesemia to improve diagnosis and management. Aggressive management of hypomagnesemia during the prenatal period is also warranted, given its association with pre-eclampsia and preterm birth.



SA-PO542

A Case Study of Treatment-Resistant Hypomagnesemia in a Young Adult with HNF1B Mutation

Ryan M. Trimble. *Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC.*

Introduction: It is well-established that genetic mutations can cause familial hypomagnesemia syndromes. One of the most common inherited causes of renal malformation is mutation in the transcription factor hepatocyte nuclear factor 1B (HNF1B) which can result in renal tubular dysfunction, leading to magnesium wasting (1). HNF1B plays a role in the regulation of FXYD2 gene transcription, involved in the tubular handling of magnesium through encoding the γ a-subunit of the Na+-K+-ATPase. HNF1B is important in nephrogenesis and maintaining tubular function (2). In addition to these renal manifestations, HNF1B mutations have been linked to other clinical issues including exocrine pancreatic insufficiency, renal cysts, liver dysfunction, gout, and genital tract malformations (3). This high clinical variability can hamper clinical diagnosis.

Case Description: We report a 35 year old female patient with a history of migraines, chronic hypokalemia, and hypomagnesemia presenting with refractory hypomagnesemia despite supplementation. She had several episodes of syncope and consistently low magnesium level ranging between 0.8-1.1 mmol/l for the past 7 months while on 8 tablets of magnesium supplementation (64 mg). Her potassium levels were normal with daily supplementation of 40 mEq. A 24-hour urinary magnesium test revealed hypermagnesuria and hypocalcuria. Genetic study revealed a whole gene deletion of HNF1B.

Discussion: The patient's persistent hypomagnesemia raised concern for a genetic disorder affecting magnesium regulation. The presence of high magnesium and low calcium levels on a 24-hour urinary test further suggests this. Genetic analysis revealed a complete deletion of the HNF1B gene aligning with a diagnosis of HNF1B-related autosomal dominant tubulointerstitial kidney disease, a condition characterized by kidney cysts, diabetes, and issues with electrolyte regulation, including low magnesium and potassium levels. This case emphasizes the importance of considering genetic mutations in patients with stubborn hypomagnesemia and underscores the need for healthcare providers to refer such patients to a nephrologist or genetic counselor for thorough assessment. In summary, mutations in HNF1B are a common genetic cause of kidney malformations and tubular dysfunction. Identifying and addressing these related conditions are essential for providing optimal care to individuals with HNF1B syndrome.

SA-PO543

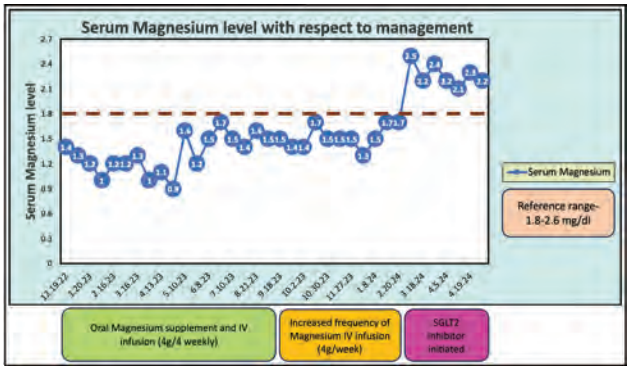
SGLT2 Inhibitors: Unlocking the Solution for Refractory Hypomagnesemia in Suspected Gitelman Syndrome

Irtiza Hasan, Bhaktidevi Makadia, Vishal Jaikaransingh, Charles W. Heilig. *University of Florida College of Medicine - Jacksonville, Jacksonville, FL.*

Introduction: Hypomagnesemia is a rare and poorly understood magnesium (Mg+) disorder, often resistant to conventional therapies. Emerging studies suggest sodium-glucose cotransporter 2 inhibitors (SGLT2i) may help. We present a case of complex refractory hypomagnesemia with suspected Gitelman Syndrome successfully treated with SGLT2 inhibitors.

Case Description: A 70-year-old woman with PMH of CKD stage 2, DM T2, HTN presented with chronic severe hypomagnesemia & frequent muscle cramps. She was on Pantoprazole & HCTZ for >7 years, discontinued 1 year before presentation. Workup as follows: Na+ 140 mmol/L, K+ 3.4 mmol/L, CO2 27 mmol/L, BUN 8 mg/dL, Creatinine 0.8 mg/dL, Glucose 205 mg/dL, Ca+ 9.9 mg/dL, & Mg+ ranging between 1.0 to 1.3 mg/dl. 24-hour urine lytes: Mg+ 59.4 mg, Ca+ 68 mg/dL, K+ 50 mmol, Na+ 90 mmol. Creatinine 0.8 g. Fractional excretion (FE) of Ca+ 0.01% & Mg+ 6.9%. Suspected a case of Gitelman Syndrome (genetic test pending) and initially started on oral Mg+ as well as Mg+ IV infusion (4g/4 weeks), which was later increased to 4g weekly for 4 weeks with maintenance at 4g-biweekly. Due to the refractory nature, she started on an SGLT2i (Empagliflozin 10 mg daily), resulting in dramatic improvement & stable Mg+ levels (>2.0 mg/dl) without any further infusion. Interestingly, three of her four children also developed low magnesium after age of 50, requiring supplements, currently under investigation.

Discussion: To the best of our knowledge, this is the first reported case of Gitelman treated with SGLT2i. Studies suggest SGLT2i can improve magnesium homeostasis, especially in diabetic patients. Possible mechanisms include glycemic control with magnesium redistribution and enhanced intestinal absorption/renal resorption via TRPM6-medicated transport. Further research is needed to define the role of SGLT2i in treating hypomagnesemia & its inclusion in treatment guidelines for refractory cases.



SA-PO544

Developing a Highly Sensitive Meso Scale Discovery (MSD) SLIT Immunoassay for Chronic Kidney and Eye Disease

Easton J. Liaw,[1,2] Sudhir Kumar,[1,3] Xueping Fan,[1,3] Courtney Huynh,[1,3] Insa M. Schmidt,[1,3] Sara I. Shoushtari,[1] Zahra Sheikh,[1,3] Manju L. Subramanian,[1,3] Sushrut S. Waikar,[1,3] Weining Lu.[1,3] *[1]Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [2]Boston University Sargent College of Health & Rehabilitation Sciences, Boston, MA; [3]Boston Medical Center, Boston, MA.*

Background: Both kidney failure and blindness are common complications of poorly controlled diabetes mellitus, which afflicts over 150 million people around the world. The kidney and eye share several structural similarities and developmental pathways that may account for their shared susceptibility as end-organ complications of diabetes. SLIT is a ligand for ROBO receptors. SLIT/ROBO pathway plays essential roles in kidney and eye development. Published ELISA results showed upregulation of SLIT protein expression in both chronic kidney and eye diseases. Recently, a novel SLIT inhibitor has advanced to a phase II clinical trial for proteinuric kidney disease. However, the low sensitivity and dynamic range of the ELISA assay have made the SLIT immunoassay results unreproducible.

Methods: We developed a highly sensitive Meso Scale Discovery (MSD) immunoassay using an electrochemiluminescence detection technique with a greater dynamic range that may replace previously developed ELISAs for SLIT detection. In a process similar to a sandwich ELISA assay, we detected and quantified standard SLIT recombinant protein and unknown SLIT concentration in human and mouse samples using the MESO QuickPlex SQ120 instrument.

Results: Our data showed a greater dynamic range and more precise and accurate readings on a lower concentration of SLIT using the MSD assay (LLoD=5 pg/ml, ULoD=20,000 pg/ml) compared to regular ELISA (LLoD=1,000 pg/ml, ULoD=50,000 pg/ml). We also found the optimal concentrations of the capture and detection antibodies that best suit the SLIT measurements. Besides the newly developed SLIT MSD assay able to detect low protein levels, we also discovered 7-fold higher SLIT levels in vitreous humor compared to blood samples in humans and an 80% serum SLIT level reduction in mice treated with a SLIT inhibitor.

Conclusions: We have developed a highly sensitive MSD assay across 4 orders of magnitude for SLIT in humans and mice. This assay may be used in clinical trials as a target engagement biomarker for SLIT inhibitors and in preclinical animal models of diabetic kidney and eye diseases.

Funding: NIDDK Support, Other U.S. Government Support, Commercial Support - Pfizer, Private Foundation Support

SA-PO545

Developing a Model of Urosepsis Using a Kidney and Lung-on-a-Chip System

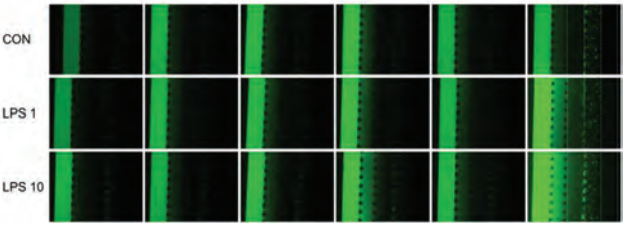
Eun Mi You, Eun-Jeong Kwon, Sejoong Kim. *Seoul National University Bundang Hospital, Seongnam, Republic of Korea.*

Background: The emergence of organ-on-a-chip models has revolutionized preclinical investigations, yet a crucial gap persists in the absence of an in vitro model for lung injury resulting from urosepsis. To address this, we engineered a novel 3D microfluidic chip capable of mimicking urosepsis within the kidney, lung, and vascular microenvironments.

Methods: Our kidney and lung-on-a-chip platforms were designed with five channels, facilitating co-culture of HK-2 (human kidney proximal tubule epithelial) cells, HUVEC (human umbilical vein endothelial) cells, lung fibroblasts, and BEAS-2B (immortalized bronchial epithelial cell) cells. Confocal imaging was employed to assess tubular formation induced by shear stress. Urosepsis was simulated by administering LPS (lipopolysaccharide) to HK-2 cells over a 3-day period. Subsequent to LPS treatment, cell injury was evaluated, including cell-to-cell distance measurement via CK8 staining, cadherin expression analysis in HUVEC cells to gauge cell adhesion, and assessment of cell permeability and protein expression using FITC and dot blot analysis. The observation of Beas2B cell death due to LPS was inconclusive in our findings.

Results: Application of shear stress during cell culture led to increased cell proliferation and the formation of well-defined tubular structures. Following induction of urosepsis via LPS exposure to HK-2 cells, we observed a dose-dependent increase in FITC permeability, compromised cell integrity. This was concomitant with an elevation in cell-to-cell distance among HK-2 cells and a reduction in cadherin expression in HUVEC cells, suggesting rapid dissemination of LPS to lung cells. Urosepsis-induced lung injury was associated with heightened expression of IL-6 and NGAL. But, The observation of Beas2B cell death due to LPS was inconclusive in our findings

Conclusions: Utilizing a kidney and lung-on-a-chip system, we developed a model for urosepsis, enabling the sequential observation of tubular damage, vascular impairment, and the effects of urosepsis on bronchial cells. This approach enhances our comprehension of urosepsis-related lung injury, thereby providing a promising platform for future therapeutic investigations.



SA-PO546

Exploring Monocyte Trafficking: Unveiling MicroRNA (miRNA) Contributions with Organ-on-Chip Vessel Models

Miguel Hueso,[1,2] Adrián Mallén Bareas,[2] Estanis Navarro,[3] Jordi Bover.[4,3] *[1]Hospital Universitari de Bellvitge Servei de Nefrologia, L'Hospitalet de Llobregat, Spain; [2]Institut d'Investigacio Biomedica de Bellvitge, Barcelona, Spain; [3]Fundacio Institut d'Investigacio en Ciencies de la Salut Germans Trias i Pujol, Badalona, Spain; [4]Hospital Universitari Germans Trias i Pujol, Badalona, Spain.*

Background: Monocytes play pivotal roles in numerous inflammatory disorders, including vascular and renal diseases. Environmental signals at site of inflammation mediate rapid monocyte migration and dictate differentiation programs. However, the molecular mechanisms of the migration of monocytes remain poorly understood. Since, proinflammatory activation of monocyte-derived macrophages were associated with a concomitant increase in miR-125b we will study if miR-125b contribute to the regulation of the traffic of monocytes using in vivo and in vitro models.

Methods: In the ApoE$^{-/-}$ mice model fed with a high fat diet for 14 weeks, we inhibited miR-125b using an antagomir over a 4-week period. We explored the mechanism using a Vessel-on-Chip adhesion assay, constructed with Human Aortic Endothelial Cells (HAoEC) stimulated with TNFα, along with Transwell studies.

Results: We observed a significant reduction in infiltration of F4/80 macrophages and attenuation of NF-κB^{+} activation in vascular lesions. We observed an impairment in the trafficking of miR-125b transfected THP-1 monocytes, accompanied by the downregulation of the CD11b/CD18 integrin and the CCR7 receptor. Furthermore, we demonstrated a direct regulation of the CCR7 receptor by miR-125b using a reporter plasmid construct (p_CCR7.WT) containing the 3'UTR region of CCR7 gene fused with a luciferase coding sequence. In addition, miR-125b transfected monocytes inhibited CCR7 cell migration induced by the CCL21 ligand but did not affect migration induced by others ligands such as MCP1. Finally, we confirmed the downregulation of CCR7 in coronary plaques in both ApoE$^{-/-}$ mice and patients with coronary artery disease.

Conclusions: Organs-on-chip, engineered to mimic the complexity of organs and replicate specific microenvironments are valuable models for studying biological mechanisms. In our study, we demonstrated that miR-125b contributes to monocyte trafficking by downregulating the CD11b/CD18 integrin and the CCR7 receptor. Thus, miR-125b could be a potential therapeutic target in renal or vascular inflammatory disorders.

Funding: Government Support - Non-U.S.

SA-PO547

Kim-1 Targeted Black Phosphorus Nanoplatforms: Antioxidation and Efferocytosis Recovery for AKI Treatment

Zhiwen Wang, Chun Zhang. *Huazhong University of Science and Technology Tongji Medical College Union Hospital, Wuhan, China.*

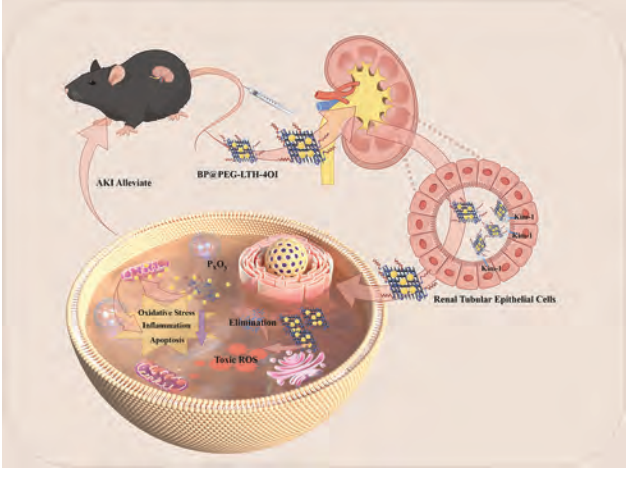
Background: Acute kidney injury (AKI) is a global public health issue with high morbidity and mortality rates. Past research on AKI treatment has predominantly focused on antioxidation and anti-inflammation, with little attention given to the clearance of apoptotic cells post-AKI. The clearance of apoptotic cells, or efferocytosis, is crucial for resolving inflammation. However, the inflammation triggered by oxidative stress in the damaged tissue region of AKI often impedes efferocytosis, hindering the clearance of apoptotic cells and exacerbating inflammation, thereby causing tissue damage.

Methods: In this study, we designed a kidney dual-targeted nanotherapy platform utilizing the Kim-1 protein-targeting peptide LTH combined with the therapeutic agent 4-octyl itaconate (4OI), based on novel two-dimensional black phosphorus nanosheets, to treat AKI induced by various etiologies.

Results: The nanoplatform rapidly anchors to damaged renal tubular epithelial cells, clearing intracellular ROS overload, thereby reducing tubular dilation and inhibiting cast formation. Following intervention, the expression of NGAL in the kidneys of AKI mice significantly decreases, indicating substantial alleviation of tissue damage. Moreover, the improvement in efferocytosis facilitates the clearance of apoptotic cells, effectively mitigating renal tissue injury following rhabdomyolysis and renal ischemia-reperfusion injury.

Conclusions: The novel kidney dual-targeted nanoplatform achieves rapid targeting and anchoring to damaged renal tubular epithelial cells post-AKI. Through antioxidative stress and enhancement of efferocytosis, it enables specific treatment of AKI in the affected regions. We believe this platform presents a new solution for AKI treatment induced by various causes and holds promise as an innovative drug delivery system for the treatment of other diseases.

Funding: Government Support - Non-U.S.



SA-PO548

Engineered Renal-Targeting Nanozyme Achieves Sequential Treatment of AKI through Reactive Oxygen Species Clearance and Immune Modulation

Zhiwen Wang, Chun Zhang. *Huazhong University of Science and Technology Tongji Medical College Union Hospital, Wuhan, China.*

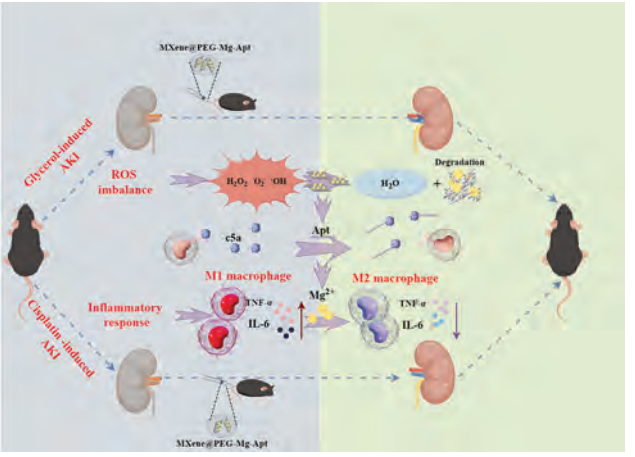
Background: Effective countermeasures for acute kidney injury (AKI) remain unsatisfactory. During AKI progression, the appropriate and timely transition of macrophages from pro-inflammatory to anti-inflammatory states is crucial for promoting the resolution of acute inflammation and tissue repair. Timely clearing excess reactive oxygen species (ROS) and promoting M2 polarization of macrophages determines the extent of AKI progression.

Methods: In this study, we designed an engineered renal-targeting nanozyme constructed from a novel two-dimensional nanomaterial, MXene nanosheets, through surface conjugation of the anticomplement component 5a aptamer (ac5a-Apt) and magnesium ions (Mg^{2+}).

Results: The results revealed that after AKI, the engineered nanozyme can not only target the kidneys but also navigate towards inflammatory areas under the guidance of the ac5a-Apt, clear excessive ROS, inhibit the C5a-C5aR complement system activation and promote M2 polarization of macrophages. Importantly, after MXene reacts with ROS and degrades, the surface-loaded Mg^{2+} is released, which can further suppress the MAPK/ NF-κB signaling pathway to achieve sequential therapy.

Conclusions: The engineered renal-targeting nanozyme provides a novel strategy based on ROS clearance and immune modulation for AKI sequential treatment. And as a novel engineered nanozyme, its remarkable biocompatibility and excellent therapeutic effectiveness establish the foundation for its substantial potential in clinical translation.

Funding: Government Support - Non-U.S.



SA-PO549

Integrative Systems Analyses Reveal Calcineurin Inhibitor-Mediated Control of Human Podocyte Biophysics and Physiology

Jacob M. Wright,[1] Anthony Mendoza,[1] Jonathan C. Haydak,[1] Jenny Wong,[1] Linda M. Rehaume,[2] Kirk N. Campbell,[1] Evren U. Azeloglu,[1] Maria Paola Santini.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Aurinia Pharmaceuticals Inc, Victoria, BC, Canada.*

Background: Calcineurin inhibitors (CNIs), such as cyclosporine A (CsA), tacrolimus (TAC), and voclosporin (VCS), have been used to regulate the immune response in a number of conditions, including kidney transplantation, lupus nephritis and other autoimmune disorders. Whereas the immunosuppressive functions of CNIs are regulated by the calcium-calmodulin pathway, the mechanisms by which they control glomerular cell biology remain elusive. We previously showed that CsA treatment in LPS-induced proteinuria was associated with cytoskeletal stabilization of podocytes leading to preserved glomerular integrity.

Methods: We combine network, enrichment and pathway analyses of transcriptomics, isobaric-tagged quantitative phospho- and total proteomics, atomic force microscope elastography and high content image analytics with classical cell biological assays to understand the role of CNIs in podocyte biology and biomechanics.

Results: We discovered that podocyte physiology is significantly modulated by all CNIs, and that this regulation converged on the cytoskeletal architecture. Divergent phosphoproteomic signatures highlighted the differential impact of each drug in microtubule organization, post-translational modifications, and histone methylation. Downstream gene transcription showed a significant upregulation of focal adhesion molecules, GEF/GAPs and cytoskeletal-adhesion organizers. Our phoshoproteomic observations recapitulated several previously known targets, such as synaptopodin, and detected a number of novel cytoskeletal posttranslational modifications. Interestingly, we observed that at maximal clinically relevant concentrations lower than CsA and TAC, VCS affected these signaling pathways for enhancing cytoskeletal stability, which is confirmed via focal adhesion morphometrics, spreading area and cellular elasticity.

Conclusions: Based on these findings, our study contributes significantly to the understanding of the role of CNIs in podocyte function, independently from other cell biological impacts, and it represents an integrative cellular and molecular atlas to guide the discovery of novel drug-induced modulators of glomerulopathies and evaluate the effect of new CNIs on podocyte biophysical and biomechanical features.

Funding: Commercial Support - Aurinia Pharmaceuticals

SA-PO550

Kidney-Targeting Mesoscale Nanoparticles for Delivery of Gene Therapy in CKD

Edgar A. Jaimes,[1] Anastasiia Vasylaki,[2] Arantxa Roach,[2] Pratyusha Ghosh,[2] Melis Baltaci,[1] Ryan Williams.[2] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]The City College of New York, New York, NY.*

Background: Despite the rapidly increasing number of gene therapies being introduced into clinical practice, no such treatment is available for kidney diseases. One of the major obstacles in gene therapy implementation is the difficulty in delivering biological molecules to the disease site due to their easily degradable nature, immunogenicity, and inability to permeate through cell membranes. Here, we developed a polymer nanoparticle gene delivery system for chronic kidney disease.

Methods: We optimized the formulation of kidney-targeted polymeric mesoscale nanoparticles (MNPs) to maximize the encapsulation of siRNA and mRNA gene therapies for kidney diseases. Specifically, we formulated MNPs from poly-lactic-co-glycolic polyethylene glycol di-block (PLGA-PEG) polymer. This process was optimized for loading of a luciferase reporter mRNA, which was evaluated for renal delivery and protein expression in hairless mice. Separately, it was optimized for loading of cytokine-specific siRNA (IL-6, IL-1B, and TNFa), which were evaluated for therapeutic efficacy in a mouse model of unilateral uretral obstruction (UUO) and a rat model of Dahl Salt-Sensitive (DSS) salt-induced hypertension. We evaluated blood and urine markers of renal function in both models, as well as performed histology.

Results: We optimized mesoscale nanoparticles for maximal siRNA and mRNA therapy loading while maintaining a 300 – 400 nm polymeric MNP diameter. In healthy immunocompetent hairless mice, we found that MNPs specifically localize to the kidneys and deliver functional luciferase reporter mRNA via in vivo bioluminescence imaging. In both mouse and rat chronic kidney disease models (UUO and DSS, respectively), we administered inflammatory cytokine-silencing siRNA-loaded MNPs. These studies demonstrated substantial therapeutic efficacy and reduction of inflammation from kidney-targeted siRNA delivery as measured by renal fibrosis and injury markers. MNPs localize to the kidneys with up to 26-fold specificity compared to other organs with little to no off-target delivery or toxicity.

Conclusions: We anticipate further pre-clinical development of both mRNA and siRNA-targeted delivery to the kidneys for chronic kidney diseases will result in a highly specific novel therapy with minimal off-target effects for CKD and other renal diseases.

Funding: Other NIH Support - NCI, Private Foundation Support

SA-PO551

Growth, Maturation, and Light Sheet Microscopy of Autologous Induced Pluripotent Stem Cell-Derived Kidney Organoids in Tunable Gelatin Methacrylate (GelMA) Hydrogels

Ivan Krupa,[1] Shane Clerkin,[1] Jessie Davis,[1] Sara Knezevic,[1] Robert Lees,[2] Dermot F. Brougham,[1] John Crean.[1] *[1]University College Dublin, Dublin, Ireland; [2]Science and Technology Facilities Council, Swindon, United Kingdom.*

Background: Recent advances in the generation of hiPSC derived kidney organoids have successfully established their use as a novel disease-modelling platform. Here we describe the utility of gelatin methacryloyl (GelMA) hydrogels as support matrices for kidney organoids in which manipulation of biophysical parameters like stiffness and shear flow acts as a mechanism for control of cell composition and structure.

Methods: Kidney organoids were generated from hiPSCs using established methods (Treacy et al., *Bioactive Matertials*, 2023). Light sheet fluorescence microscopy (LSFM) imaging was conducted on a Leica SP8 Digital Light sheet microscope. Hydrogel rheology was conducted using the Anton Parr Physica MCR301 rheometer. For experiments investigating the effects of shear flow via the use of an orbital shaker system, a modified version of a protocol published by Przepiorski et al., (2021) was utilised in conjunction with GelMA hydrogel encapsulation of kidney organoids.

Results: Rheological measurements show that chemically crosslinked GelMA hydrogels retain their mechanical storage moduli over a prolonged period of time in culture. Therefore, this biomaterial provides a means of studying the effects of a constant storage modulus of the surrounding matrix on the growth of organoids. We have recently evaluated the utility of LSFM as a technique for rapid 3D imaging of organoid samples and a means for characterising the effects of the biophysical microenvironment on kidney organoid generation. In this pilot study, we imaged the development of $MAFB^{+ve}$ cells, representing developing podocytes, within kidney organoids grown in GelMA, with live low-phototoxicity light sheet imaging. We also observed $CD31^{+ve}$ endothelial cells in GelMA supported kidney organoids with fixed and cleared light sheet imaging. The extent of the vascularisation observed was comparable to that previously described (Ryan et al., *Developmental biology,* 2021).

Conclusions: Overall, our study suggests that modification of biophysical properties such as matrix stiffness and shear flow can be used as an instructive cue to modify kidney organoid maturation. With this work we hope to inform the development of increasingly physiologically authentic kidney organoids for the advancement of 3D models of disease and drug responses.

Funding: Government Support - Non-U.S.

SA-PO552

Electrospun Polyacrylamide Nanofiber Mats for Renal Cell Tissue Culture

Harold D. Love,[1] Shuvo Roy,[3] William H. Fissell.[1,2] The Kidney Project. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Veterans Health Administration, Washington, DC; [3]University of California San Francisco, San Francisco, CA.*

Background: We have previously used soft polyacrylamide (PA) based hydrogels for renal cell tissue culture. PA gels functionalized with amino groups promote robust attachment and differentiation of primary proximal tubule cells under fluid shear stress. We have now developed a method of electrospinning (ES) PA nanofibers with 50-200 nm diameters. When functionalized with ECM protein, renal cells attach on the ES nanofiber mats and express increased levels (up to 10X) of several transporters, exceeding those cultured on non-permeable PA gels.

Methods: Linear PA was prepared by polymerizing a 3.75% solution of acrylamide monomer without bis-acrylamide at room temperature. The linear PA was precipitated with isopropanol and redissolved at ~10% concentration in water. Glutaraldehyde and HCl were added to crosslink the linear PA into stable fibers. Crosslinking required incubation at 60ºC overnight after spinning. ES was performed at 0.1-0.2 ml/hour at 15KV. Atomic force microscopy was used to measure the elastic modulus of the resulting mats. The crosslinked mats were mounted in transwell supports, functionalized using Sulfo-SANPAH and Geltrex and sterilized with 70% ethanol. PA gels incorporating N-(3-Aminopropyl) methacrylamide (APMA) were used as non-permeable controls. Primary proximal tubule cells (Lonza) were then seeded on mats and gels. Cultures were placed on oscillating platforms at 72 RPM for 2-4 weeks.

Results: ES mats consisted of randomly oriented fibers 50-200 nm diameter with an elastic modulus of ~0.9 kPa. Cells attached rapidly to fibers and APMA gels and maintained attachment up to 4 weeks. Cells formed confluent patches on the mats but did not form complete monolayers as seen on APMA gels. The expression (qPCR) of several renal markers (LRP2, NHE3, OAT1-3, NKCC2 and SGLT2) were 3-10 fold higher in cells on ES mats than on APMA gels.

Conclusions: Primary human renal cells were found to attach to PA nanofiber mats functionalized with ECM. Cells formed confluent patches and remained attached for at least 4 weeks, under fluid shear stress (~2 dyn/cm^2). RNA levels for several renal genes in cells on mats were increased 3-10 fold compared to levels seen on non-permeable APMA gels. We conclude that our linear PA spun nanofiber mats can significantly increase expression levels of several important genes in cultured renal cells in standard media over those seen on non-permeable PA gels.

Funding: Private Foundation Support

SA-PO553

Organized Tubular Scaffolds to Build Vascularized Kidney Proximal Tubules

Anne Metje van Genderen,[1] Sebastian Beusink,[1] Thibault Sampon,[1] Marta Garcia Valverde,[1] Tina Vermonden,[1] Jitske Jansen,[2] Silvia M. Mihaila,[1] Rosalinde Masereeuw.[1] *[1]Universiteit Utrecht Utrechts Instituut voor Farmaceutische Wetenschappen, Utrecht, Netherlands; [2]Division of Nephrology and Clinical Immunology, Institute of Experimental Medicine and Systems Biology, Medical Faculty RWTH Aachen University, Aachen, Germany.*

Background: Kidney tubular engineering requires structures of small sizes (≲1mm) to mimic curvature of native kidney proximal tubule (PT), which is key for cellular functionality and maturation. Here, we created highly porous rhombus tubules using melt-electrowriting (MEW) to build a vascularized PT.

Methods: A MEW device was used to print small polycaprolactone tubular scaffolds (inner ø: 1 mm) with defined rhombus microarchitectures (winding angles of 30°, 50° and 70°). Human conditionally immortalized PT epithelial cells (ciPTEC) and glomerular endothelial cells (ciGEnC) were seeded alone or consecutively in the scaffolds and evaluated via immunofluorescent stainings for monolayer formation and tightness (zonula occludens-1, cluster of differentiation 31 (CD31)), cell directionality (F-actin), polarization (a-tubulin, Na^+K^+-ATPase) and extracellular matrix (ECM) production (collagen IV). Furthermore, gene expression of endothelial (CD31 and Von Willebrand Factor) and PT (organic cation transporter-2, P-glycoprotein (P-gp), multidrug resistance protein) markers was measured via RT-qPCR, and P-gp transport was studied in the tubular scaffolds.

Results: Tubular scaffolds (length: 2 cm, inner ø: 1 mm) with different rhombus microarchitectures were manufactured by controlling key instrument parameters. Both ciPTEC and ciGEnC formed tight monolayers within the tubular scaffolds and generated collagen IV-enriched ECM. The 30° winding angles induced preferential cell alignment along the scaffold fiber direction for ciPTEC and ciGEnC, and facilitated formation of polarized monolayers. Consecutive seeding of first ciPTEC and, after monolayer formation, ciGEnC enabled growth of endothelial cells on the ECM deposited by ciPTEC, thereby forming a vascularized PT, maintaining high gene expression of PT markers, and showing increased functionality of P-gp in co-culture.

Conclusions: MEW tubes with highly controlled microarchitectures advance ciPTEC and ciGEnC organization and ECM deposition. Our results show the first prototype of a vascularized scaffold, where the basement membrane formed by ciPTEC supports ciGEnC adhesion and growth. This innovative approach not only shows the potential of MEW in tissue engineering but also sets a new benchmark for the creation of functional, bioengineered kidney models.

Funding: Private Foundation Support

SA-PO554

Tubuloid Production from Primary Cultured Renal Tubular Epithelial Cells Derived from Resected Unfunctional Kidneys of Patients on Dialysis

Makiko Mori, Yutaro Mori, Yuki Nakao, Yuta Sekiguchi, Shintaro Mandai, Hiroaki Kikuchi, Fumiaki Ando, Koichiro Susa, Takayasu Mori, Eisei Sohara, Shinichi Uchida. *Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.*

Background: Renal tubular organoids (tubuloids) developed by our technology have the potential to serve as an alternative, more human-like model of human pathology. Tubuloids are made from patient kidney-derived primary cells, not stem cells, and mimic kidney tubules. We have previously produced tubuloids from normal and mild chronic kidney disease (CKD) kidneys. Here, cells from unfunctional kidneys of dialysis patients will be 3D engineered.

Methods: 5 patients receiving hemodialysis and 5 patients with normal kidney function were joined to this study with written informed consents. Using kidneys obtained from patients by surgery for malignancy, only primary cultures of renal tubular epithelial cells were selectively grown. Growth factors and Matrigel were then added. After several days of culture, tubuloids are obtained. In primary cultured cells in 2-dimensional condition and tubuloids, Western blotting and immunostaining are used to determine renal tubular and CKD properties.

Results: Primary cultured renal epithelial cells of normal kidneys show a large number of fine, swollen epithelial cells. On the other hand, those of unfunctional kidneys from dialysis patients are elongated, and some cells are giant in size. At the beginning of 3-dimentional culture, the speed of growth of normal tubuloids is faster than that of renal cells from unfunctional kidneys. Eventually, however, the size difference between normal renal tubuloids and tubuloids from dialysis patients is not very discernible. Western blotting of the completed tubuloids showed that p16, a marker of cellular senescence, was predominantly expressed in the dialysis tubuloids. KIM-1, which appears in damaged kidneys, was confirmed in two of the dialysis tubuloids strongly.

Conclusions: We have established primary renal epithelial cells from patient kidneys derived from healthy kidneys and from unfunctional kidneys of hemodialysis patients, and now we have successfully produced tubuloids derived even from unfunctional kidneys. The results also revealed that tubuloids derived from unfunctional kidneys have the properties of cellular senescence. These tubuloids are expected to be used as a simple model for a new type of human pathology, more similar to humans than mice.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO555

Optimized Culture Media Extends Human Kidney Organoid Longevity to 6 Months

Sophie M. Blackburn, Arjun Sen, Benjamin S. Freedman. *University of Washington - Division of Nephrology, Department of Medicine, Kidney Research Institute, and Institute for Stem Cell and Regenerative Medicine, Seattle, WA.*

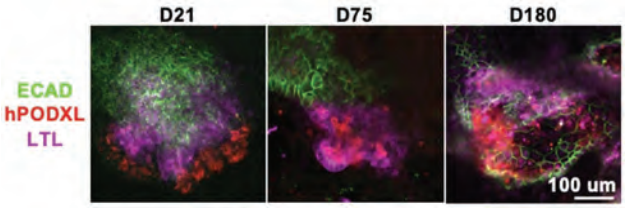
Background: Although kidney organoids, derived from human pluripotent stem cells (hPSC), mature *in vitro* in approximately 3 weeks, there is an interest in using this model to study the effects of microgravity on the kidney during long-term space flight. The most widely used kidney organoid protocols consider their structures mature between day 16 and day 28 of differentiation, generally completing experimental assays at that time or shortly thereafter.

Methods: Standard kidney organoid differentiation was performed until cultures reached the renal vesicle stage. We then supplemented our standard differentiation media with organoid tubular enhancing media (OTEM) which contains components proposed to promote epithelial cell growth and limit de-differentiation. Organoid counts were obtained using full-well brightfield images and nephron segments were visualized using immunostaining. Viability was assessed with a colorimetric assay. Transcriptomic analysis was performed via single-cell RNA sequencing of kidney organoid cultures at days 25 and 180 of differentiation.

Results: OTEM drastically improved the longevity of kidney organoids, whereas no kidney organoids survived past day 100 when treated with standard media. After six months of culture, structural and transcriptomic analyses showed viable podocytes, proximal tubules, and distal tubules present in OTEM treated kidney organoids. We also identified an early glomerular epithelial cell cluster that grew relative to other cell types over the course of the experiment. At day 26 of differentiation, cultures treated with OTEM had four-fold more kidney organoids than those grown in standard media. Furthermore, the OTEM-treated cultures had less stromal overgrowth and contained twice as many viable cells compared to controls.

Conclusions: Our findings indicate that OTEM is improving the stability of kidney organoids and supporting the proliferation of cell types that indicate increasing maturity of the structures. This is a simple yet powerful change to our differentiation protocol that sets the stage for future studies of organoid aging on earth and in space.

Funding: Other U.S. Government Support



Timecourse of OTEM-treated kidney organoids

SA-PO556

Recapitulation of Cellular Senescence, Inflammation, and Fibrosis in Human Kidney-Derived Tubuloids by Repeated Cisplatin Treatment

Yuki Nakao, Yutaro Mori, Makiko Mori, Shintaro Mandai, Tamami Fujiki, Hiroaki Kikuchi, Fumiaki Ando, Koichiro Susa, Takayasu Mori, Eisei Sohara, Shinichi Uchida. *Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.*

Background: In the pursuit of more accurate pathophysiological models for assessing renal drug response, the development of kidney organoids derived from human pluripotent stem cells represents a significant step forward. However, recapitulating aging/senescence associated pathophysiology within these models remains challenging. Here, we present an innovative approach to generate more homogeneous epithelial-like structures known as “tubuloid” using primary human renal proximal tubular epithelial cells (hRPTECs) cultured from human resected kidneys as a refined alternative and try to evaluate their ability to show aging/senescence associated pathophysiology.

Methods: Primary hRPTECs were established from the non-tumor kidney tissue removed from patients with malignancies with written informed consents. Cells were cultured on ultra-low attachment plates in media containing basement membrane gel and multiple growth factors. To assess the disease-modeling potential of tubuloids, we evaluated the efficacy of tubuloids using cisplatin treatment at three different concentrations: 0.2, 2.0, and 20.0 μg/mL.

Results: Upon exposure to cisplatin, γH2AX expression increased in a dose-dependent manner, indicating DNA damage. Cisplatin treatment also resulted in the expression of Kidney Injury Molecule-1 (KIM-1) and Cleaved Caspase-3, which are indicators of kidney injury and apoptotic signaling, respectively. Repeated cisplatin administration resulted in upregulation of the cellular senescence marker p16, alongside increased secretion of inflammatory cytokines IL-1β and IL-6, indicating the induction of a senescence-associated secretory phenotype (SASP). Furthermore, supernatant collected from repeated cisplatin treated tubuloids induced myofibroblast activation, indicating the onset of renal fibrosis.

Conclusions: We successfully established a tubuloid-based model that goes beyond the immediate effects of cisplatin nephrotoxicity to simulate the transition from AKI to CKD, or even model CKD itself, using hRPTECs. Tubuloids can recapitulate cellular senescence, SASP, and fibrosis, making them a promising pathophysiological model for chronic kidney disease (CKD) providing insights into the disease’s fibrotic mechanisms.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO557

Surgical Refinement of Silicon Nanopore Membrane Devices for Implantable Kidney Replacement Therapy: 7-Year Experience across 90 Prototypes

Jarrett Moyer,[1] Charles Blaha,[1,3] Mark W. Wilson,[1] Shant M. Vartanian,[1] Lynda Frassetto,[1] William H. Fissell,[2,3] Shuvo Roy.[1,3] *[1]University of California San Francisco, San Francisco, CA; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Silicon Kidney, LLC, San Francisco, CA.*

Background: Silicon nanopore membranes (SNM) are highly permeable and selective filters providing a pathway to next-generation implantable renal replacement therapies (RRT). SNM enable needle-free hemodialyzers, low-resistance hemofilters, and immuno-protective renal tubular cell bioreactors. Implantation of these first-of-their-kind prototypes requires strategies to overcome the recipient anatomy, immune response, and blood-materials interactions. Here we describe iterative refinement of surgical technique over seven years and 90 implants of SNM RRT prototypes.

Methods: Surgical refinement was iterative with experimental results from of each of the 90 implants informing subsequent ones. Initial prototypes housed 2 cm^2 of SNM surface area, progressing to 832 cm^2 over the seven-year period. Implants occurred in the dorsolateral neck or retroperitoneum of swine with vascular anastomoses to the cervical or iliac vessels, respectively. The retroperitoneum accommodated devices with more SNM area (mean 204 cm^2 compared to 20 cm^2 in the neck). Prototypes were implanted for 3-32 days with subjects receiving anti-platelet agents. Patency was assessed using angiography and direct visualization upon retrieval.

Results: Patency across all prototypes was 67% (60/90) for up to 32 days. An advanced hemofilter housing 166 cm^2 of SNM surface area exhibited 100% patency

(n=9). Of 30 thrombosed prototypes, 17 were due to mechanical obstruction from graft kinks. The largest SNM RRT prototypes were more likely to kink (5 of 8, compared to 10 kinks in 82 small-scale prototypes, p=0.005). Following observation of kinks in 75% of initial implants, a series of protective silicone graft sleeves was applied leading to a reduction to 16% kink rate (p=0.020).

Conclusions: Iterative adaptation of surgical approach and SNM RRT prototypes across 90 implants achieved patency for up to 32 days, while enabling a 416-fold increase in blood-contacting silicon surface with no systemic anticoagulation. Mechanical obstruction to blood flow proved to be the most common cause of device failure and was more likely to occur in the largest prototype. Protection of the vascular graft interface with a silicone sleeve reduced the rate of graft kinks.

Funding: NIDDK Support, Other NIH Support - NIH-NIBIB Support, Other U.S. Government Support, Private Foundation Support

SA-PO558

Transport and Barrier Function in Cultured Primary Tubule Cells Are Preserved after Brief Cold Storage

Rachel C. Evans,[1] Shuvo Roy,[2] H. David Humes,[3] William H. Fissell.[1]
The Kidney Project. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of California San Francisco, San Francisco, CA; [3]University of Michigan Michigan Medicine, Ann Arbor, MI.*

Background: Implantable bioartificial kidneys will need to be distributed to clinical sites distant from the point of manufacture. Renal allografts are typically shipped cool surrounded by ice-water baths with or without perfusion, while suspended cells are typically shipped frozen in dry ice. Freezing a device to -78ºC is likely impractical as it subjects a device to destructive mechanical stresses from thermal expansion, and there may be incomplete survival of cells upon thawing, jeopardizing function. We simulated cold transport by examining survival and function of primary renal proximal tubule cells in monolayer culture after storage at 5ºC.

Methods: Primary human renal proximal tubule cells were grown on permeable supports in serum-supplemented 50:50 DMEM:F12 with an inhibitor of TGF-βR1 on a rotary shaker table at 37ºC and 5%CO_2/air for 28 days. Baseline apicobasal barrier was assessed by leak of TRITC-labeled dextrans from apical to basolateral compartments, and function was assessed by diuretic-inhibitable apicobasal volume transport assessed by weighing apical and basolateral supernatants. Cells were removed from the incubator and culture trays wrapped in sterile parafilm. Cell culture trays were placed in a conventional household 5ºC refrigerator for 24, 48, 72, and 96 hours (n=3 wells each condition) without any media exchanges. After the specified chill time, cell culture trays were removed from the refrigerator and chilled media exchanged for fresh warmed media. Cell culture plates were returned to culture at 37ºC and 5%CO_2/air. At 1, 12, and 40 days after chill exposure, cell barrier and transport function were again measured.

Results: Cells chilled for 24,48, and 72 hours maintained barrier integrity and transport function out to 40 days post chill. Cells chilled for 96 hours had an initial 28-fold increase in leak that persisted at lower levels to 40 days post exposure.

Conclusions: Renal tubule cells in bioartificial kidneys need to present a barrier to reabsorption of toxins and need to transport salt and water to concentrate filtered toxins. Primary renal tubule cells grown on permeable supports retained function and barrier even after 72 hours at 5C. Transport of bioartificial kidneys from manufacturing facilities to clinical sites may be possible with non-hazardous simple ice-water refrigeration.

Funding: Private Foundation Support

SA-PO559

Machine Perfusion of Mice Kidneys to Deliver a Protective Bioengineered Soluble ACE2 Protein

Cosimo Cianfarini, Fatmah N. Yamani, Jan Wysocki, Dinesh Jaishankar, Zheng J. Zhang, Daniel Batlle. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Machine perfusion of donor kidneys has emerged as a promising approach to improve transplant outcomes by decreasing storage-related injury and reducing the occurrence of delayed graft function (DGF). Activation of the renin-angiotensin-system (RAS) has been shown to play a role in the pathophysiology of DGF and countering this overactivity may improve transplant outcomes. Here we investigated the delivery of a short soluble ACE2 protein, bioengineered in our lab and termed ACE2-618-ABD, to mice kidneys using hypothermic machine perfusion as a strategy to reduce RAS activity.

Methods: Kidneys from c57bl6 ACE2 Knock-Out (ACE2-KO) and c57bl6 wildtype (WT) mice were harvested and the renal artery cannulated. We adapted a perfusion system previously used for rats to be used with mice kidneys. The mice kidneys were perfused with phosphate buffered saline (PBS) either alone or with added ACE2 618-ABD for four hours at four degrees celsius through the cannulated renal artery in a closed-circuit perfusion system using a peristaltic pump. ACE2 enzymatic activity was then measured using a fluorogenic assay and ACE2 protein levels determined by Western Blot.

Results: While ACE2 enzymatic activity and protein were undetectable in non-perfused ACE2-KO kidneys, enzymatic activity and protein by Western Blot were found in ACE2-618-ABD perfused ACE2-KO kidneys. In WT kidneys perfused with ACE2-618-ABD, Western Blot showed two distinct bands for ACE2 protein at ~100kD and ~85kD. The ~100kD band reflects the native ACE2, the ~85kD represents the perfused short soluble ACE2-618-ABD which was not found in the PBS- and non-perfused WT kidneys. In kidney lysates, the cytosolic compartment of ACE2-618-ABD perfused kidneys had increased ACE2 enzymatic activity and protein demonstrating intracellular uptake.

Conclusions: Delivery of a bioengineered, short soluble ACE2 protein to mice kidneys can be accomplished via machine perfusion of the renal artery which results in passage of the glomerular filtration barrier and tubular uptake. Ex-vivo perfusion of kidneys with ACE2-618-ABD results in cytosolic uptake as demonstrated by increased protein and enzymatic activity. This approach may result in improved quality of kidneys prior to transplantation.

Funding: Other NIH Support - NIAID Grant to Daniel Batlle, Private Foundation Support

SA-PO560

A Bypass Flow Model to Study Endothelial Cell Mechanotransduction across Diverse Flow Environments

Zhuotao Xiao,[1,2] Rudmer J. Postma,[1] Anton J. Van Zonneveld,[1] Bernard van den Berg,[1] Wendy M. Sol,[1] Nicholas White,[1,4] Asad M. Mirza,[3] Jun Wen,[5] Roel Bijkerk,[1] Joris I. Rotmans.[1] *[1]Leids Universitair Medisch Centrum, Leiden, Netherlands; [2]First Affiliated Hospital of Soochow University, Suzhou, China; [3]Florida International University, Miami, FL; [4]Technische Universiteit Delft, Delft, Netherlands; [5]Southwest University of Science and Technology, Mianyang, China.*

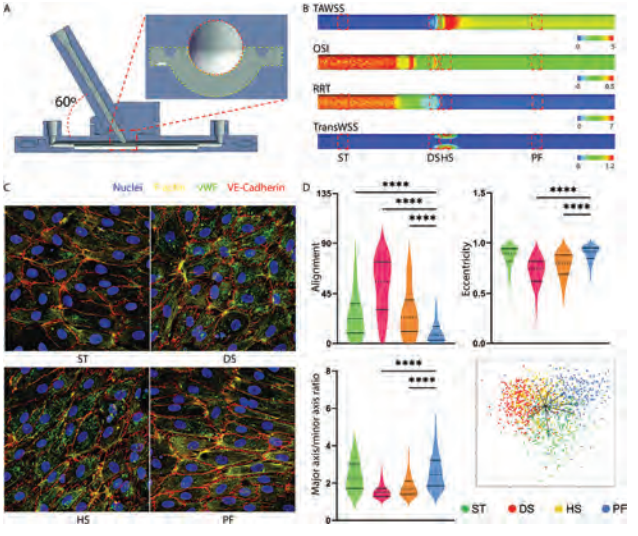
Background: Disturbed flow is one of the pathological initiators of endothelial dysfunction in intimal hyperplasia (IH) which is commonly seen in vascular bypass grafts, and arteriovenous fistulas. Various *in vitro* disease models have been designed to simulate the hemodynamic conditions found in the vasculature. Nonetheless, prior investigations have encountered challenges in establishing a robust disturbed flow model. In the present study, we aim to address this gap by introducing an *in vitro* bypass flow model capable of inducing disturbed flow and other hemodynamics patterns through a pulsatile flow in the same model, Fig. A.

Methods: We employed computational fluid dynamics (CFD) to simulate hemodynamics and compared the morphology and functions of human umbilical venous endothelial cells (HUVECs) under disturbed flow conditions to those in physiological flow or stagnant conditions.

Results: CFD analysis revealed the generation of disturbed flow within the model, pinpointing the specific location in the channel where the effects of disturbed flow were observed, Fig. B. High-content screening, a single-cell morphological profile assessment, demonstrated that HUVECs in the disturbed flow area exhibited random orientation, and morphological features were significantly distinct compared to cells in the physiological flow or stagnant condition after a two days of flow exposure, Fig. C D. HUVECs exposed to disturbed flow underwent extensive remodeling of the adherens junctions and expressed higher levels of endothelial cell activation markers compared to other hemodynamic conditions.

Conclusions: In conclusion, our *in vitro* bypass flow model provides a robust platform for investigating the associations between disturbed flow pattern and vascular diseases.

Funding: Private Foundation Support



SA-PO561

Green Tea Polyphenol Sandwich-Assisted Construction of Endothelial Biomimetic Coatings with Hyaluronic Acid Platform and Nitric Oxide Release for Hemodialysis Access Stents to Prevent Thrombosis and Restenosis

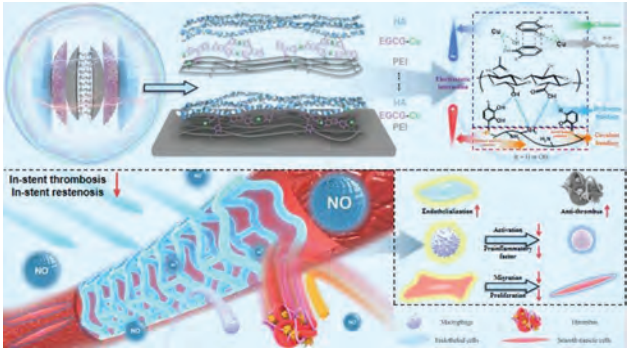
Chong Chen, Liang Ma, Ping Fu. *West China Hospital of Sichuan University, Chengdu, China.*

Background: Vascular stent is one of the main means of treating dialysis access stenosis. However, in-stent thrombosis (IST) and in-stent restenosis (ISR) always limit effectiveness of stents in clinical applications. Vascular endothelial cells play an important role in regulating the physiological structure and function of vessels, so endowing vascular stents with the bionic function of endothelial cells is an effective solution to address complications such as IST and ISR.

Methods: In this paper, an endothelial bionic coating for stents constructed by layer-by-layer self-assembly method was developed. We used positively charged polyethyleneimine (PEI) and negatively charged hyaluronic acid (HA) as polyelectrolytes, assisted construction by a chelate sandwich of epigallocatechin gallate (EGCG) with copper (Cu). The biocompatibility of the coatings was verified by systematic materialogical characterization, in vitro and ex in vivo hemocompatibility experiments, in vitro cell culture experiments, and in vivo experiments of subcutaneous implantation and stent implantation.

Results: The results showed that this strategy was able to improve the loading, stability and homogeneity of the coating through various interations, such as electrostatic adsorption, hydrogen bonding, π-π stacking, and chemical cross-linking of phenalkamines. The coating was able to synergistically improve the antithrombotic ability of vascular scaffolds with HA and nitric oxide, and promote the rapidly endothelialization of the stents, inhibit intimal hyperplasia and regulate the inflammatory response.

Conclusions: This polyelectrolyte endothelial biomimetic coating constructed by metal polyphenol sandwich can effectively reduce complication such as IST and ISR of stents and improve the clinical outcomes of vascular stenting for dialysis access stenosis.



The scheme of coating for hemodialysis access stents to prevent IST and ISR.

SA-PO562

Prolonged Bactericidal Activity in Extracorporeal Hemoadsorption with Vancomycin-Functionalized HA380 Sorbent Cartridge

Gerd Klinkmann,[1,2] Anna Lorenzin,[1,3] Massimo de Cal,[1,3] Anna Italia Toscano,[1] Gonzalo Ramirez Guerrero,[1,4] Thiago A. Reis,[1,5] Monica Zanella,[1,3] Claudio Ronco.[1,3] *[1]Fondazione IRRIV, Vicenza, Italy; [2]Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Medical Center Rostock, Rostock, Germany; [3]Ospedale San Bortolo di Vicenza, Vicenza, Italy; [4]Hospital Carlos Van Buren, Valparaiso, Chile; [5]Fenix Nephrology, São Paulo, Brazil.*

Background: Blood purification therapies hold promise in addressing complications linked to bacteremia, a key predictor of mortality in sepsis. However, antibiotic treatment, the current standard therapy, poses risks of organ toxicity. To alleviate this burden and expand the scope of sorbent technology, we propose using surface-modified adsorption cartridges to reduce circulating bacteria. The current study investigates the in vitro efficacy of a sorbent device (mini-module with HA380 beads, Jafron Medical, China) functionalized with vancomycin, evaluating its impact on circulating *Staphylococcus aureus* and compare it to standard of care antibiotic treatment in a simulated circulation model.

Methods: In an *in vitro* model, 1400 mL of heparinized blood containing bacterial load were split in 2 reservoirs. In Setting 1, 700 ml of blood circulated through a cartridge functionalized with vancomycin. In Setting 2, 500 mg of vancomycin were added to blood reservoir 2 and, circulated through a non-functionalized cartridge. Closed-loop hemoadsorption circuits were set up using 2 HA380 mini-modules. Circulations were maintained at 250 mL/min for 1 hour, blood reservoirs were heated to 37°C, and stirred. Samples were drawn at predefined time points, to determine time to positivity (TTP) for bacterial replication, vancomycin levels and cytokine profiles. Reservoir 2 underwent Setting 2 twice consecutively.

Results: Dynamics of TTP exhibited a similar trajectory in both settings after 60 minutes of hemoadsorption. Following an additional hour of incubation, TTP remained unchanged in Setting 1, whereas a significant decline occurred in Setting 2. Notably, the concentration of vancomycin in Reservoir 2 decreased significantly after the first cycle of hemoadsorption. Following a second dose (500 mg) of vancomycin into Reservoir 2, TTP increased significantly again. These dynamic changes were observed again after the second cycle of hemoadsorption with the non-functionalized cartridge.

Conclusions: Using antibiotic-functionalized cartridges for bacteremia may mitigate drug toxicity concerns. Delayed bacterial growth post-vancomycin cartridge passage hints at benefits. Early adjunctive use with standard therapy may aid infection resolution, pending confirmatory clinical trials.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO563

Myoglobin Adsorption Kinetics: An In Vitro Model

Matteo Marcello,[1] Anna Lorenzin,[1] Massimo de Cal,[1] Gonzalo Ramirez Guerrero,[2] Claudio Ronco.[1] *[1]Ospedale San Bortolo di Vicenza, Vicenza, Italy; [2]Hospital Carlos Van Buren, Valparaiso, Chile.*

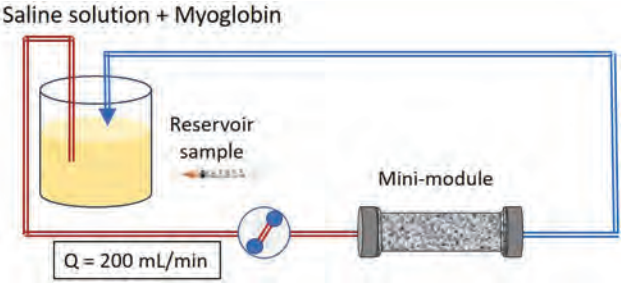
Background: Rhabdomyolysis is a condition in which a severe injury to the muscles leads to the release of muscle cells' content, including myoglobin, into the blood with consequent acute renal injury. Myoglobin is a middle molecular weight uremic toxin presents a two-compartment model of distribution in the body. A possible therapeutic option is the use of high cut-off membranes but with the risk of significant loss of albumin and other proteins. The use of adsorption cartridges can overcome these limitations. Our study aimed to assess the adsorption capacity of neutral microporous styrene-divinylbenzene copolymer sorbent towards myoglobin.

Methods: Using a downscaled module of HA380 cartridge, we set up an *ex-vivo* circulation experiment in which 1 liter of saline solution with high concentration of myoglobin was pumped through the cartridge. We collected samples (3 mL) at different time points to measure myoglobin concentration. We calculated the removal ratio (RR) and mass adsorbed at given time points.

Results: Initial myoglobin concentration was 326,338 μg/L. Final myoglobin concentration after 4 hours of experiment was 2,042 μg/L. Removal Ratio at the end of the experiment was 99.4 % with a mass adsorption of 324.30 mg of myoglobin.

Conclusions: To our knowledge, this is the first experiment that assessed the adsorption capacity of polistyrene-divinylbenzene sorbent towards myoglobin and demonstrated high affinity to bind this molecule. Our results confirmed adsorption treatment as an effective option in rhabdomyolysis, avoiding complications associated to current dialytic treatment.

Time (min)	Concentration in the reservoir (μg/L)	Mass in the reservoir (mg)	Mass adsorbed (mg)	RR (%)
0	326,338	326.34	0.00	0.0
10	196,761	194.99	129.58	39.7
30	130,211	128.65	196.13	60.1
60	76,338	75.19	250.00	76.6
120	40,070	39.35	286.27	87.7
180	12,958	12.69	313.38	96.0
240	2,042	1.98	324.30	99.4



Schematic representation of the circuit utilized for the experiment. The flow rate was set at 200 mL/min.

SA-PO564

Metyos K-Patch: A Novel Biowearable for Real-Time Potassium Level Monitoring

Olga Chashchina, Alexandre Boulanger, Maroua Hamami, Louis X. Cacheur, Paul Durand Estebe, Frederic Abboud, Emilie Jemmi. *Metyos, Paris, France.*

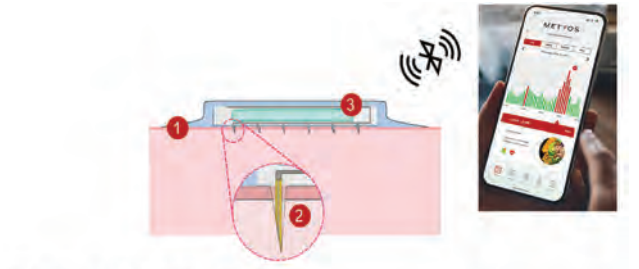
Background: Abnormal serum potassium (K+) levels or dyskalemia are dangerous due to the risk of cardiac rhythm disturbances. The reference method of K+ monitoring based on venous blood sampling is invasive, painful and takes up to several days to provide a result. The ability to dynamically and non-invasively monitor changes in K+ levels could reduce the morbidity and mortality due to dyskalemia in both acute and chronic situations.

Methods: Metyos K-Patch is a remote patient monitoring solution integrating a biowearable for monitoring K+ in real time thanks to a microneedle array inserted in the patient's dermis. The sensor sticks to the skin with medical adhesive and is worn for 8 consecutive days. Despite the efficiency of transdermal penetration, microneedles do not exceed 1mm in length and cause no pain upon device's placement. They are modified with ion selective membrane for specific reaction with K+. The electrochemical sensor generates an electrical response proportional to the concentration of K+ that can be measured as a potential difference. The registered signal is then transmitted via Bluetooth to the patient's smartphone.

Results: The potentiometric cell based on the microneedles was sufficiently sensitive for detecting real-time changes in K+ concentrations. It exhibits linear behavior with Nernstian slope 59mV for the complete range of physiological K+ concentrations (2-10mM) when tested in complex matrix. Its analytical performance remains stable during 8 days. No needle deformation or degradation has been registered upon the insertion of the device both in pig skin and volunteers' skin. General ease of use has been tested by 10 volunteers of age 34-72 y.o.

Conclusions: The wearable Metyos K-Patch has shown promising results for continuous K+ tracking. These results pave the way towards remote K+ monitoring in patients with dyskalemia.

Funding: Commercial Support - Metyos



1. Skin interface with microneedles network
2. Microneedle-shaped electrochemical sensors for specific analytes measurement
3. Embedded electronics, Bluetooth module and rechargeable battery

SA-PO565

Evaluation of Clinical Performance of an In Vitro Diagnostic Medical Device for Detecting Microalbuminuria Using a Smartphone Application

Jiwon Ryu,[1] Yun Jung Oh,[2] Dong-Hoon Lee,[3] Eung-Kyu Park.[3] *[1]Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [2]H Plus Yangji Hospital, Seoul, Republic of Korea; [3]QSTAG Incorporation, Seoul, Republic of Korea.*

Background: Microalbuminuria indicates kidney damage and can serve as a marker for treatment and prognosis in patients with kidney disease or diabetes mellitus. Urine albumin tests are typically conducted in hospitals, which is impractical for daily patient monitoring. We assessed the feasibility of using a commercially available in-vitro diagnostic medical device to measure urine microalbumin in daily life.

Methods: In our study, we enrolled 303 patients from three tertiary care hospitals who tested positive for urine protein using dipstick tests. We utilized a self-checking semi-quantitative urine test strip with QR code technology to evaluate urinary microalbumin and creatinine levels. Integrating QR code technology and correction color pads significantly enhanced QR code recognition and color reaction extraction accuracy. The device utilizes pH indicators and benzoic acid for precise microalbumin and creatinine measurement. A mobile application scans the QR code to provide semi-quantitative values of microalbumin and creatinine. These results were compared to those obtained from a hospital's benchtop machine, with a predefined class agreement for semi-quantitative data set at 95%.

Results: Variations in application environments, laboratory conditions, and hospital settings impacted QR code recognition and the detection of urine microalbumin and creatinine, necessitating adjustments to the colorimetric extraction formula. Comparing results between patients and experts, the agreement rates for urine microalbumin were 92.9%, 92.5%, 97.4%, and 97.3% for normal range, 1 positive, 2 positive, and 3 positive, respectively. After accounting for urine creatinine, the agreement rates for the urine microalbumin/creatinine ratio were 97.1%, 100%, and 98.0% for "Good", "Moderate", and "High", respectively. Expert data on urine microalbumin correlated well with semi-quantitative results from the benchtop machine, with agreement rates of 66.7%, 94.1%, 100.0%, and 87.0% for normal range, 1 positive, 2 positive, and 3 positive in the dipstick test, respectively.

Conclusions: Using this in-vitro diagnostic medical and software enable semi-quantitative urine microalbumin assessment outside hospitals, supporting disease management and patient prognosis in real-life settings.

Funding: Commercial Support - QSTAG Incorporation

SA-PO566

Artificial Diuresis: Development of a Mathematical Model to Assess Ultrafiltration

Anna Lorenzin,[1,2] Alessandra Brendolan,[2] Claudio Ronco,[2] Monica Zanella.[1] *[1]Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy; [2]International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy.*

Background: Fluid overload (FO) is associated with adverse outcome both in heart failure and critically ill patients admitted to intensive care. Extracorporeal ultrafiltration (UF) represents a solution to avoid acute kidney injury due to FO; an UF miniaturized device AD1 has been developed. Reduced priming volume, low pressures and flows at which it operates make AD1safer and smaller than the conventional machines. AD1 has been already tested in vitro and in animal studies, no adverse events have been reported. The aim of this study was to develop an UF mathematical formulation capable to mimic the UF behaviour of AD1. Data collected from the animal study were used to validate the model.

Methods: AD1 is equipped with a peristaltic pump for blood flow (Q_b) and a polysulfone mini-filter. Transmembrane pressure (TMP) is modulated by Q_b setting and the height at which is hanging the bag for UF. This generate a negative pressure in the filter UF compartment: higher is the gap between AD1 and the bag, greater the negative pressure, increasing TMP and ultrafiltration rate (Q_{UF}). In animal study, 6h UF sessions were scheduled in 3 pigs with a Q_b=30mL/min and the bag placed 20cm below AD1. Clinical parameters and UF data were collected. The UF mathematical formulation is based on hydrostatics and hydrodynamics laws. Parameters considered are Q_b, height of the bag, haematocrit, catheter features. Experimental data were compared with the formulation.

Results: In the animal sessions the Q_{UF} was in a range of 3-5ml/min. Average data of target Q_{UF}, observed Q_{UF} during the animal study and the model estimation are reported. In all treatments the Q_{UF} was obtained in the absence of major clinical or technical problems with a maximum deviation from the target Q_{UF} lower than 10%. Formulation reported a maximum error compared to the experimental data less than 10%.

Conclusions: The model reported data comparable with the results observed in the animal study. The selected parameters and the implementation adequately estimate the Q_{UF} in the animal model. Data derived from clinical trials will be necessary to further assess and improve the model.

Animal ID	Htc	Target Q_{UF} (mL/min)	Observed Q_{UF} (mL/min)	Estimated Q_{UF} (mL/min)
I31	26.8%	4.16	4.40	4.00
I29	31.3%	4.16	4.17	4.09
I50	25.9%	4.16	4.28	3.97

SA-PO567

In Vitro Per- and Polyfluoroalkyl Substances (PFAS) Adsorption Assessment through Mesoporous Styrene-Divinylbenzene Sorbent Cartridge

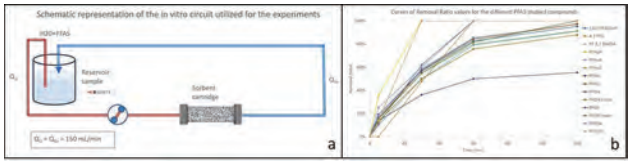
Anna Lorenzin,[1,2] Natascha Perin,[1,2] Massimo de Cal,[1,2] Alessandra Brendolan,[2] Monica Zanella,[1] Claudio Ronco.[2] *[1]Department of Nephrology, Dialysis and Transplantation, St. Bortolo Hospital, Vicenza, Italy; [2]International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy.*

Background: Per- and polyfluoroalkyl substances (PFAS) are chemical substances used in a wide range of fields as construction materials, biocides, flame retardants etc. Due to their high stability in the environment and resistance to biodegradation, all PFAS are persistent, and many are highly mobile in global waters. High blood levels of PFAS have been associated with adverse health effects including increased risk of kidney or testicular cancer. Classic extracorporeal therapies have demonstrated limited efficiency and new approaches based on adsorption should be explored. The aim of this study was to assess the potential adsorption capacity of HA380 cartridge towards PFAS from patients with high blood levels.

Methods: We developed an *in-vitro* model of hemoadsorption using GALILEO testing platform. We recirculated a highly polluted batch of water (4 liters) through a HA380 cartridge (Jafron medical, Zuhai, China) for 120 minutes at a flow rate of 150mL/min (Figure a). We collected samples after 5,30,60, and 120 minutes from the initiation of circulation and analyzed 39 different PFAS compounds. Removal Ratio (RR) was calculated to assess PFAS adsorption.

Results: PFAS compounds with concentrations significantly above normal showed a RR close to 90% already within the first 60 minutes of circulation leading to almost complete elimination of all pollutants at the end of the circulation (Figure b). RR is remarkably high already at the outset of the adsorption process demonstrating a high capacity of removal of HA380 cartridge. This is likely dependent on the interaction of the different solutes with the molecular structure of the sorbent.

Conclusions: The *in-vitro* model of hemoadsorption suggests the possible application *in-vivo* of this technique to reduce/normalize the concentrations of PFAS in patients exposed to water or environmental pollution. Hemoadsorption may therefore be considered as a new possible approach in patients with high blood levels of PFAS.



SA-PO568

Kidney Prognosis in Patients with TSC2/PKD1 Contiguous Gene Deletion Syndrome

Mateus Guerreiro,[1] Eduardo Valle,[1] Jose O. Reusing,[2] Elieser H. Watanabe,[1] Luiz F. Onuchic.[1] Disciplinas de Nefrologia e Medicina Molecular. *[1]Universidade de Sao Paulo Faculdade de Medicina, São Paulo, Brazil; [2]Serviço de Transplante Renal, Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.*

Background: Patients with TSC2/PKD1 contiguous gene deletion syndrome (CGS) have classically been associated with a much more severe kidney phenotype than observed in isolated autosomal dominant polycystic kidney disease (ADPKD), displaying childhood onset and progression to end-stage kidney disease (ESKD) within the three first decades of life. Recent reports, however, revealed a more variable clinical course.

Methods: A survey of all reports of CGS was conducted using the terms "TSC2" and "PKD1" or "tuberous sclerosis" and "polycystic" on Pubmed. Thirty studies including patients with genetically confirmed CGS were selected, comprising 74 such cases. The addition of 11 cases from two novel pedigrees totalized 85 evaluated patients, who were analyzed at the demographic, clinical, and genetic levels.

Results: The median kidney survival of CGS patients was 35 (28-43) years. The age of ESKD onset did not differ between patients with germline deletion and cases in whom germline deletion could not be confirmed and mosaicism could not be excluded (Unknown group) (28 [20-37] vs 33 [31-43] years, respectively; p=0.09). Mosaic patients did not reach ESKD during the follow-up. Deletion extension did not affect kidney survival. The relative prevalences of TSC manifestations did not differ between CGS and TSC patients, except for higher frequencies of lymphangioleiomyomatosis and retinal hamartomas in CGS.

Conclusions: CGS patients have a slower progression to ESKD than previously believed, though usually faster than severe ADPKD cases (Figure 1). Thereby, CGS should be considered in ADPKD or significantly cystic TSC patients with severe CKD progression, particularly before the 5th decade. Our data suggest that the frequencies of most TSC clinical features do not significantly differ between CGS and TSC individuals.

Funding: Government Support - Non-U.S.

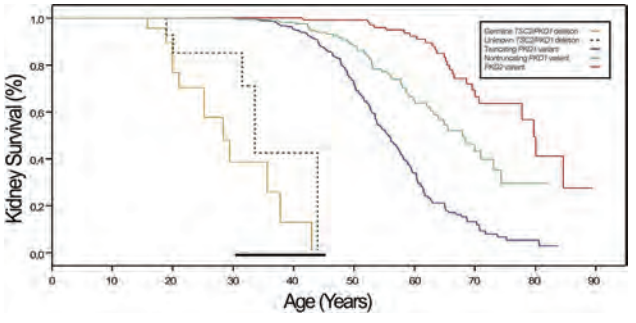


Figure 1. Cumulative kidney survival according to the variant type/classification (adapted from Cornec-Le Gall et al, J AmSoc Nephrol, 24:1006-1013, 2013). The ESKD onset age overlap between the most severe ADPKD cases and the milder CGS cases is depicted by the black bar.

SA-PO569

Genetic Characteristics of Autosomal Dominant Polycystic Kidney Disease in a Greek Population

Dimitra Gkalitsiou,[1] Eirini Evangelou,[1] Danai Palaiologou,[2] Maria Konsta,[3] Leandros Lazaros,[2] Niki Markou,[1] Tsielestina Poulli,[1] Aggeliki Poula,[1] Emmanouel Kanavakis,[2] George I. Tsirpanlis.[1] *[1]Department of Nephrology, General Hospital of Athens "G. Gennimatas", Athens, Greece; [2]Genesis Genoma Lab, Genetics Diagnosis, Clinical Genetics & Research, Athens, Greece; [3]Department of Rheumatology, Sismanoglion General Hospital, Athens, Greece.*

Background: Autosomal Dominant Polycystic Kidney Disease is the predominant monogenic renal genetic disorder. Confirmatory genetic testing defines the disease, provides prognostic information and may support therapeutic management. This study aims to investigate the genetic characteristics of a cohort of ADPKD patients from a single Greek center.

Methods: Ninety-three patients (46 females, 47 males, mean age: 34±15 years) were enrolled from 59 distinct families attending our outpatient ADPKD clinic. Genetic analysis included Targeted next-generation sequencing of over 600 genes, Sanger sequencing, and Multiplex ligation-dependent probe amplification. MRI was performed in 74 patients, revealing more than 10 renal cysts in all but one patient. Children with positive family history (FH) displayed at least one cyst, while two without FH had multiple renal cysts.

Results: Genetic diagnosis was established in 88 of 93 patients (94.5%). Seventy patients (75%), had single nucleotide variants (SNVs) and large deletions (4 patients) in the PKD1 gene, whereas SNVs and large deletions (5 patients) in the PKD2 gene were identified in 15 (16%) cases. Other gene mutations were found in 3 patients (3.5%). Two cases, involving a father and son, revealed a SEC61B variant; the father displayed more than 10 renal and liver cysts in the MRI, while the son had only liver cysts. Another patient with nephrolithiasis and over 10 renal cysts, had a SLC3A1 variant. Five patients (5.5%) had negative genetic analyses. Truncating mutations in PKD1 were observed in 43 cases, (61%), while the rest (39%) had non-truncating mutations. Variants were classified as Pathogenic (45.5%), Likely Pathogenic (36%), and Variants of Uncertain Significance (VUS 13.5%), according to the guidelines of the American College of Medical Genetics. Reclassification to Likely Pathogenic could be proposed for 6 VUS cases with noted family segregation. Finally, 52% and 82% of the detected variants have not been previously reported in ClinVar and gnomAD databases, respectively.

Conclusions: In this ethnically homogenous population, truncating mutations in PKD1 gene were the predominant genetic cause of ADPKD, followed by PKD1 non-truncating mutations, PKD2 gene variants and other rare or undefined genetic etiologies.

SA-PO570

Integrating Genotype and Phenotype Data Is Required for Kidney Survival Prediction in Autosomal Dominant Polycystic Kidney Disease

Dimitra Gkalitsiou,[1] Eirini Evangelou,[1] Maria Konsta,[3] Kiriaki Vasiliou,[1] Aggeliki Poula,[1] Niki Markou,[1] Tsielestina Poulli,[1] Leandros Lazaros,[2] Paraskevi Liaveri,[1] George I. Tsirpanlis.[1] *[1]General Hospital of Athens Georgios Gennimatas, Nephrology Department, Athens, Greece; [2]Genesis Genoma Lab Genetics Diagnosis, Clinical Genetics & Research, Athens, Greece; [3]Department of Rheumatology, Sismanoglion General Hospital, Athens, Greece.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the cause for 5-10% of End Stage Kidney Disease (ESKD) worldwide. Accurate renal prognosis is essential for effective disease management. Investigation of the prognostic value of combining genetic and phenotypic characteristics in a cohort of ADPKD patients is attempted.

Methods: In 66 ADPKD patients (mean age 33 ± 12 years, 32 males), the genetic diagnosis (using targeted Next Generation, tNGS, or Sanger Sequencing or Multiplex ligation-dependent probe amplification, MLPA) and the Mayo Clinic Imaging Category (MCIC) (through Renal Magnetic Resonance Imaging, MRI, for Total Kidney Volume measurement) were assessed. The prediction of ESKD was performed using the Mayo Clinic formula (Irazabal MV et al JASN, 2015). The calculation incorporated variables such as sex, age, e-GFR, and the MCIC. The PROPKD score was derived by considering both phenotypic factors (sex, hypertension and urologic events before the age of 35 years) and genetic data (PKD1-truncating, PKD1- non truncating and PKD2).

Results: Adjusted for age, the e-GFR was on average, 26 and 27 ml/min higher in PKD2 patients compared to ADPKD-PKD1-truncating and ADPKD-PKD1-non-truncating patients, respectively (p = 0.001). The median prediction of ESKD for ADPKD-PKD1-truncating, ADPKD-PKD1-non-truncating and PKD2 patients was 22 (11-31) years, 22 (11-34) years and 31 (21-59) years, respectively (NS). In patients categorized as high risk according to PROPKD (score 7-9) the predicted time to ESKD was 16 (9-30) years, for those at intermediate risk (score 4-6), 25 (13-34) years and for those at low risk (score 0-3), 28 (16-55) years (NS). Finally, the PROPKD score showed an inverse correlation to the years of ESKD prediction, as determined by the Mayo Clinic formula; a higher PROPKD score was associated with a shorter prediction period for ESKD (Spearman r = -0.3, p = 0.04).

Conclusions: Prognosis of renal survival in ADPKD patients requires not only a specific genetic diagnosis but also consideration of the phenotypic data, as incorporated in the PROPKD score, enhancing the accuracy of renal survival prediction.

SA-PO571

Exploring the Personal Narratives of Patients with Autosomal Dominant Polycystic Kidney Disease: The NaMe-PKD Study

Anuva Mittal, Jessica Porras, Samar Chackerreza, Kayvon Solaimanpour, Nuria M. Pastor-Soler. *USC/UKRO Kidney Research Center, Keck School of Medicine of University of Southern California, Los Angeles, CA.*

Background: For patients with chronic diseases, including autosomal dominant polycystic kidney disease (ADPKD), previous studies have shown that patients' disease progression, outcomes, and goals can be impacted by their illness perceptions. Specifically, in the case of genetic diseases, patients' perceptions may be shaped even before their own diagnoses by observing their family members' experiences with the disease. Few studies contrast patients' perceptions of their genetic disease before and after their diagnoses and how this information may inform their management goals. Our study asks patients with ADPKD, specifically those who observed family members with the disease prior to their diagnosis, to reflect on the way their understanding of ADPKD pre-diagnosis may have influenced their experience post-diagnosis.

Methods: This study was approved by the Social Behavioral Institutional Review Board. An IRB-approved questionnaire was administered in person with verbal responses from participants. Using a grounded theory approach, a thematic analysis of these transcribed interviews was performed.

Results: While recruitment is ongoing, five participants have met inclusion criteria and have been interviewed. Men and women from ages 36 to 53 years old are represented. Thematic analysis led to the creation of three categories of themes: 1) Illness perception pre-diagnosis, 2) Illness perception initially post-diagnosis, and 3) Acceptance of the diagnosis. Illness perception pre-diagnosis entailed secrecy, surprise, and misinformation; post-diagnosis entailed a sense of isolation, denial, and guilt; and acceptance entailed inevitability and resilience.

Conclusions: Patients expressed ideas of protective secrecy and sometimes misinformation surrounding the discussion of ADPKD before their diagnosis, with some mentioning the complete lack of discussion of the disease in their families and others equating ADPKD with dialysis. Furthermore, as patients came to terms with their diagnosis and related to their family members' experiences, they described shifts in their attitude from denial and helplessness to later incorporating disease management into their lifestyle. Ultimately, we hope to use our findings to help clinicians more effectively approach conversations related to the trauma around the initial diagnosis of ADPKD.

SA-PO572

Patient Experience with Genetic Testing in ADPKD

Diana Etwaru, Ying Gao, Meyeon Park. *University of California San Francisco, San Francisco, CA.*

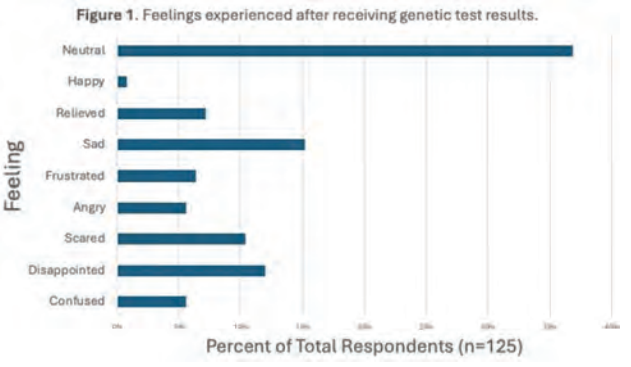
Background: Genetic testing for diagnosis in autosomal dominant polycystic kidney disease (ADPKD) has become more common since the development of panel tests including PKD1 and PKD2 and related cystic genes. We sought to explore attitudes about genetic testing among individuals with ADPKD.

Methods: We generated a web-based Qualtrics survey comprising 23 questions and incorporating a validated survey about public attitudes toward genetic testing (Henneman PMID 16792518). The survey was pilot-tested by volunteers from our clinical center. The survey was distributed to 16,773 individuals with PKD above the age of 18 through the PKD Foundation e-mail listserv.

Results: 226 individuals responded. 70% were female and 88% were White / Caucasian. 127 out of 201 individuals answered "No, never discussed" to the question, "has the possibility of getting a genetic test to detect a PKD variant (mutation or abnormality) been discussed with you by a doctor or healthcare provider?" Out of 113 individuals who did undergo genetic testing, 54 were unable to remember their results. 39 out of 94 individuals reported that the results "did not change anything" about their feelings about their kidney disease, while 10 felt more "optimistic / positive," 14 felt more "pessimistic / negative," and 31 were "not sure." The range of feelings expressed are shown in Figure 1.

Conclusions: Many individuals with ADPKD have not participated in discussions about genetic testing with healthcare providers. Among individuals who have undergone testing, the majority do not recall their results. Most individuals with testing felt that the tests did not change their feelings, while many were unsure. A wide range of feelings associated with testing were reported. Given the growing role of genetic knowledge in ADPKD, further work is needed to ensure patients are educated about genetic testing and its potential implications for management, and to include patients of all backgrounds in studies investigating this evolving area. This is an investigator sponsored study which was funded by Otsuka Pharmaceutical Development and Commercialization, Inc.

Funding: Commercial Support - Otsuka Pharmaceutical Development and Commercialization, Inc.



SA-PO573

Effect of Genotype on Kidney Outcomes among Patients with Inherited Cystic Kidney Disease

Hayne C. Park,[1] Dha Woon Im,[2] Yong Chul Kim,[3] Yaerim Kim,[4] Yun Kyu Oh.[5] *[1]Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea; [2]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [5]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea.*

Background: Inherited cystic kidney disease is a constellation of heterogenous genetic diseases that commonly share renal cystic phenotype. We have analyzed renal outcome (annual change of estimated glomerular filtration rate (eGFR) and total kidney volume (TKV)) among Korean genetic cohort of inherited cystic kidney disease.

Methods: Primary genetic analysis was conducted using a targeted gene panel including 89 ciliopathy-associated genes. A total of 705 patients were included in the cross-sectional analysis. A total of 375 patients with longitudinal data without history of Tolvaptan treatment were included in the renal outcome analysis. Genotypes were classified into PKD1, PKD2, minor genotypes, or double variants (DV).

Results: PKD1 group showed younger age at diagnosis of cystic kidney disease and hypertension, and higher proportion of rapid progressor. Interestingly, the patients with minor genotypes showed better renal function but smaller kidneys than PKD1 group. The DV group demonstrated similar profiles with PKD1 group. PKD1 genotype showed faster eGFR decline (-2.69± 9.2 mL/min/1.73m^2/yr) compared to PKD2 (-0.15 ± 8.1 mL/min/1.73m^2/yr) and minor genotypes (0.68 ± 9.5 mL/min/1.73m^2/yr, p=0.03). The DV group demonstrated faster eGFR decline rate than PKD1 genotype (-3.53 ± 7.4 mL/min/1.73m^2/yr). PKD1 group (59.2 ± 93.0 mL per year) and PKD2 group (47.5 ± 79.5 mL per year) demonstrated TKV growth during study period while minor genotypes showed shrinkage of kidneys (-8.6 ± 55.8 mL per year, p=0.052).

Conclusions: PKD1 genotype demonstrated poorer renal outcome compared to other genotypes. Minor genotypes showed favorable renal outcome with shrinkage of kidneys.

Funding: Government Support - Non-U.S.

Renal outcome according to genotypes

	PKD1-PT	PKD1-NT	PKD1-IFindel	PKD2	Minor genotypes	P-value
Annual change of eGFR (n=375)	-2.78 ± 9.7	-2.36 ± 8.57	-3.89 ± 5.9	-0.15 ± 8.09	0.68 ± 9.53	0.043
Annual change of TKV (n=102)	63.0 ± 107.1	60.3 ± 55.8	-1.4 ± 49.0	47.5 ± 79.5	-8.6 ± 55.8	0.026

Minor genotypes: COL4A5, HNF1β, TSC1, COL4A3, GANAB, UMOD, DYNC2H1, TSC2, AHI1, AVP, COL4A1, CPLANE1, HSPA6, NEK8, PAX2, PRKCSH, SEC31B, TRPV1, WFS1

SA-PO574

Exome Sequencing "Firsthand" for Polycystic Kidney Diseases: Impact beyond PKD1/PKD2 Identification on ADPKD Clinical Management

Laurent Mesnard,[1,2] Ilias Bensouna,[1,2] Marine Serveaux Dancer,[3] Thomas Robert,[4] Alice Doreille.[5] *[1]Sorbonne Universite, Paris, France; [2]Inserm UMR S1155, Paris, France; [3]Eurofins Biomnis Lyon, Lyon, France; [4]Assistance Publique Hopitaux de Marseille, Marseille, France; [5]Montreal General Hospital, Montreal, QC, Canada.*

Background: Genetic testing is currently considered non-mandatory for managing typical autosomal dominant polycystic kidney disease (ADPKD) patients. However, an increasing number of genes are associated with ADPKD. For atypical forms of ADPKD, the diagnostic yield may be lower with targeted genetic analysis. Genome-wide analysis can highlight incidental findings that could impact clinical management. Recent studies suggest that exome sequencing (ES) could be as efficient as standard methods, even for PKD1/PKD2 analysis.

Methods: Among 3523 index cases undergoing ES genetic testing at Sorbonne University, Paris, France, 721 patients were categorized as having cystic diseases (149 with typical ADPKD and 572 with atypical ADPKD). We compared the diagnostic yield in both typical and atypical ADPKD. Then, we analyzed the rate of incidental findings impacting ADPKD clinical management (pathogenic variants not anticipated that explain part of the phenotype, or for which the patient is not/pre-symptomatic, or variants of interest in genetic counseling) among patients with a pathogenic variant in PKD1/PKD2 genes and compared this to the entire cystic nephropathy cohort.

Results: Of the 721 patients with cystic nephropathy, 239 had a positive genetic test with a pathogenic or likely pathogenic variant (33%). The diagnosis rate was 59.1% for typical ADPKD patients compared to 26.4% in the atypical cystic nephropathy population. In the typical ADPKD group, PKD1 and PKD2 represented only 60.3% of pathogenic variants found by ES. Double hits represented 13.1% of patients with a positive genetic test, reaching 20.6% in the PKD1/PKD2 population.

Conclusions: Our results showed a great diversity in genes responsible for adult's cystic nephropathies, even in the typical ADPKD population. We observed a significant rate of incidental findings impacting clinical ADPKD management. Our work suggests that ES should be considered a first-tier test for any ADPKD patients to optimize their clinical management.

Percentage of patients carrying a second variant in a second gene among patients with a positive genetic diagnosis.

SA-PO575

ADPKD Progression by Variant Type and Molecular Domain: An Evaluation of Time-Series Disease Trajectories among HALT Participants

Robert L. Sucholeiki,[1] Elena Jochum,[1] Arlene B. Chapman,[2] Peili Chen,[2] Oliver Wessely.[3] University of Chicago Medicine Section of Nephrology. *[1]University of Chicago Division of the Biological Sciences, Chicago, IL; [2]University of Chicago Pritzker School of Medicine, Chicago, IL; [3]Cleveland Clinic, Cleveland, OH.*

Background: As the leading monogenic cause of kidney failure, autosomal dominant polycystic kidney disease (ADPKD) affects over 12 million people worldwide. Understanding predictors of ADPKD severity is important for prognosis, long-term management, and treatment. Disease severity has been shown to depend on the gene affected by the pathogenic variant (*PKD1* vs *PKD2*) and its truncating effect. However, the association between ADPKD disease phenotype and the location of genetic variants in functional polycystin protein domains is not understood.

Methods: We studied time-series height-adjusted total kidney volume (htTKV), eGFR, and Mayo Imaging Class (MIC) distribution among 334 early-stage patients with ADPKD in the HALT A dataset (a randomized clinical trial dataset of early-onset ADPKD individuals) to examine the impact of variant location in the *PKD1* gene on disease progression over time. HALT A provided Sanger sequencing information for the pathogenic variant of each patient. We referenced the UniProt and cBioPortal genetic databases for protein domain information. We assigned non-truncating genetic variants (n=110) by location to key structural or functional domains in polycystin-1 or polycystin-2. We used RStudio to plot time-series htTKV and eGFR progressions and ran linear regressions for each participant. We compared patients' longitudinal disease trajectories for truncating vs non-truncating variant status and the protein domain location of non-truncating *PKD1* variants.

Results: *PKD1* non-truncating pathogenic variants in the REJ (90.5 ml/m/year; 95% CI [66.5–112.5]) and PLAT (80.3 ml/m/year; 95% CI [58.0–102.6]) domains demonstrated rapid htTKV growth, while variants in the C-type lectin (26.8 ml/m/year; 95% CI [10.8–42.8]) and PKD repeat (19.6 ml/m/year; 95% CI [1.3–37.8]) domains demonstrated significantly slower growth ($p<0.0001$). Variants in these fast- and slow-progressing regions also showed clinically and statistically significant differences in MIC distribution ($p<0.0001$) and eGFR rate of change (-4.26 vs -2.67 ml/min/year; $p<0.0001$).

Conclusions: Our findings shed light on protein domain location as a clinically substantive marker of ADPKD disease progression that can be valuable for disease prognosis in early-stage patients with non-truncating variants in *PKD1*.

SA-PO576

Comparative PKD1 and PKD2 Missense Variant Profiling Aids Molecular Diagnoses and Reveals Common Pathomechanisms and Variant Subtypes across the ADPKD Spectrum

Cynthia J. Sieben,[1] Vladimir G. Gainullin,[1,2] Christina M. Heyer,[1] Doaa E. Elbarougy,[1] Sarah R. Senum,[1] Zhifei Wang,[3] Xiaobo Sun,[1] Hana Yang,[1] Ines Sturmlechner,[1] Yong Yu,[3] Peter C. Harris.[1] *[1]Mayo Clinic Research Rochester, Rochester, MN; [2]Exact Sciences Corporation, Madison, WI; [3]St. John's University, Queens, NY.*

Background: ADPKD is characterized by the formation and growth of fluid-filled renal cysts, often leading to kidney failure (KF). Typically, monoallelic *PKD1* or *PKD2* (encoding PC1 and PC2) variants cause ADPKD, however, complex inheritance and a broad phenotypic spectrum exist. The advent of genomewide variant screening emphasizes the importance of ADPKD molecular diagnostic methods to reliably determine the pathogenicity of variants of uncertain significance (VUS).

Methods: Here, we evaluated the pathogenicity/penetrance of 48 *PKD1* and 44 *PKD2* missense variants using *in silico* (ACMG guidelines [clinical] and Variant Strength Group [VSG; research] categorization) and *in vitro* (PC1 maturation/trafficking to the cell surface [sPC1; requires PC1/2 complex formation] using a cell-based flow cytometry assay, and PC1/2 channel activity employing *Xenopus* oocytes) methods. The *in vitro* results were correlated with *in silico* predictions and patient phenotypes (htTKV, eGFR, and KF), including employing the population-based, Mayo Clinic Biobank (MCBB).

Results: The majority of proposed monoallelic *PKD1* and *PKD2* variants assayed close to fully penetrant (~68%, <20% sPC1), whereas biallelic and digenic *PKD1* and *PKD2* variants ranged from strong hypomorphs (25% biallelic *PKD1*; 20-40% sPC1) to mild or benign (75% biallelic *PKD1*, 100% biallelic/digenic *PKD2*; 50-110% sPC1). Most were associated with aberrant folding (~85% *PKD1*, 68% *PKD2*). Analysis of Ca^{2+} channel activity for mild/benign sPC1 variants (12 *PKD1* and 14 *PKD2*, monoallelic and complex), occasionally suggested channel defects (~8% *PKD1*, 14% *PKD2*). Variant sPC1 levels showed correlations with clinical endpoints (htTKV, eGFR, and KF). Analyses of two hypomorphic variants (*PKD1* p.Arg3277Cys and p.Ile3167Phe) in the MCBB, revealed correlations between sPC1 levels (~27 and 64%) and disease penetrance (~20 and 5% with ICD cystic codes).

Conclusions: Together, these studies reveal: 1) the value of combining *in silico*, functional, and population data for *PKD1* and *PKD2* variant evaluation, 2) aberrant PC1 trafficking as a common *PKD1/2*-mediated pathomechanism and disease determinant, and 3) enhanced PC1/2 folding as a potential therapy in ADPKD.

Funding: NIDDK Support, Private Foundation Support

SA-PO577

A Microhomology-Mediated End-Joining (MMEJ)-Based F0 Assay in Zebrafish for Rapid Screening of Genetic Modifiers of Kidney Cysts

Ping Zhu, Xiaolei Xu, Xueying Lin. *Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Autosomal-dominant polycystic kidney disease (ADPKD) is one of the most prevalent and potentially lethal genetic diseases. ADPKD patients exhibit highly variable phenotypes, of which genetic modifiers are thought to play an important role. However, the identity of the genetic modifiers remains largely unknown because of the lack of an efficient method. Prompted by the success of applying microhomology-mediated end joining (MMEJ)-based genome editing technology for the identification of genetic modifiers of cardiomyopathy in the F0 generation, we decided to explore the F0-based genetic assay for discovering genetic modifiers of ADPKD.

Methods: We generated zebrafish mutants of *IFT140*, a newly identified ADPKD gene. All *ift140* mutants exhibited distinctive pronephric cysts and were otherwise normal till approximately 2 weeks of age. Injection of a MMEJ-inducing sgRNA against *ift140* consistently resulted in pronephric cysts in >90% of the injected embryos, and the cysts can be easily scored under a light microscope at 4-6 dpf. To test the feasibility of developoing a modifier screen platform, we co-injected MMEJ-inducing sgRNAs targeting *ift140* and a gene of interest into one-cell staged wild type embryos and assessed kidney cysts at 5 dpf.

Results: In a pilot screen, we tested 18 genes that are implicated in the signaling pathways known to be dysregulated in ADPKD. Inactivation of genes that were previously suggested beneficial, such as *mtor*, was found to reduce the number of $ift140^{MJ}$ embryos with pronephric cysts. By contrast, inactivation of genes that were previously suggested detrimental did not suppress pronephric cyst formation. Besides genes with known modifying effects, novel protective modifiers such as *ulk1a* have been suggested from our pilot screen. Using *mtor* and *ulk1a* stable mutants, we confirmed the protective modifying effects of mTor and Ulk1a inhibition in *ift140*-based as well as *pkd1*-based kidney cyst development.

Conclusions: Thus, $ift140^{MJ}$ embryo can be used as a surrogate to rapidly discover candidate protective modifiers of kidney cysts, which can be validated by generating stable mutants and extended to *pkd1*-based cystogenesis.

Funding: NIDDK Support

SA-PO578

Assessment of Key Indicators of Pathogenicity in PKD1/2 Variants

Dinah Clark, Robert T. Burns, Michelle Bloom, Elizabeth Garrity, Sumit Punj, Stephen Andrews. *Natera Inc, Austin, TX.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is primarily caused by pathogenic (P) and likely pathogenic (LP) variants in *PKD1* and *PKD2*, with ~5% of affected individuals remaining genetically unresolved. Due to the high rate of novel variants seen in *PKD1/2*, many will be variants of uncertain significance (VUS) with insufficient evidence to be classified as either LP or likely benign (LB), and may comprise a significant proportion of the unresolved cases. According to ACMG, evidence including phenotypic and prevalence data in affected and/or unaffected populations can be used to support VUS reclassification. Here we utilized unaffected population prevalence and renal phenotypes to assess VUS in *PKD1/2*.

Methods: A retrospective analysis of *PKD1/2* variants identified via a 385 renal gene panel (the Renasight™ test) was performed. The gnomAD database (v2.1.1) was queried for variant population prevalence. Claims information were abstracted from the Komodo Health database to assess phenotypes based on the absence or presence of kidney cystic ICD codes (Q61.0-.9 and/or N28.1).

Results: Across 61057 cases with test results, 4002 cases had a P/LP variant (1565 unique variants) and 5409 had a VUS in *PKD1/2* (2900 unique variants) with no P/LP in a cystic gene. 97.3% of P/LP *PKD1/2* variants were absent from gnomAD and none were present in >3 alleles (excluding 2 hypomorphic variants). Likewise, 70% (n=2025) of VUS were present in ≤ 3 alleles in gnomAD, of which 1310 (64.7%) were absent. 22.8% (n=661) of all VUS were both absent and had ≥1 patient with a cystic ICD code. Patients with the remaining absent VUS (n=649) had incomplete clinical profiles, preventing further evaluation by the testing lab.

Conclusions: Absence of a variant from gnomAD and cystic disease ICD-10 codes are examples of evidence supporting pathogenicity, yet they are not sufficient to enable reclassification without additional evidence. Here we demonstrate that less than a quarter of VUS identified in *PKD1/2* satisfy these pieces of evidence, edging these variants closer to LP. For an additional 22%, phenotypic information was lacking but could support reclassification. These findings highlight the important role physicians have in providing phenotypic information to the testing lab for patients with rare VUS.

SA-PO579

Population Frequency of Undiagnosed Pathogenic Variants in PKD Type 1 and Type 2

Santosh Varughese, Judith A. Savige. *The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, Melbourne, VIC, Australia.*

Background: The estimated population frequency of AD polycystic kidney disease in recent epidemiologic studies has varied from one in 1000 to one in 2000 but when based on a genetic analysis is closer to one in 1000 (PMID:30135240). This study has reexamined the commonest genes affected, *PKD1* and *PKD2*, for pathogenic variants including assessing missense changes with highly stringent criteria, with Alamut and REVEL, in order to more accurately determine the ADPKD population frequency.

Methods: *PKD1* and *PKD2* variants were downloaded from gnomAD v2.1 and annotated in ANNOVAR. Structural and null variants were considered pathogenic and missense variants assessed for pathogenicity based on rarity, positivity in three computational tools and whether they affected a residue conserved in vertebrates. The occurrence of these variants in people of different ancestries was also examined. Our approach for assessing missense variants was compared with positivity in Alamut (scores ≥5 or ≥6), and REVEL (≥0.932), and the accuracy of these approaches evaluated using 20 benign and 20 pathogenic variants reported in LOVD.

Results: One in 1500 of the population have a null *PKD1* variant and one in 2500 have a null variant in *PKD2*. Thus the population frequency of null variants is greater than one in 1000 (8/7500) and 60% of variants affect *PKD1*. Null variants are most frequently found in people of African/African American, East Asian and South Asian ancestries. Our strategy for assessment of missense changes in *PKD1* had a sensitivity of 65% and a specificity of 95%, and missense changes in *PKD2* had a sensitivity of 40% and specificity of 100%. However the population frequencies of missense variants were more variable with different approaches.

Conclusions: These results suggest that *PKD1* and *PKD2* pathogenic null and missense variants occur more often in the population than the previously-estimated one in 1000. Missense changes in *PKD1* and *PKD2* remain difficult to evaluate accurately for pathogenicity.

Population frequencies of predicted pathogenic structural, null and missense variants and strategy evaluation

	PKD1	Sensitivity	Specificity	PKD2	Sensitivity	Specificity
Structural and null variants						
Total null and structural variants	70 or one in 1500			44 or one in 2500		
Comparison of evaluation of missense variants						
Our assessment	569 or one in 178	65%	95%	81 or one in 1357	40%	100%
Alamut > or equal to 5	One in 183	55%	100%	One in 1221	55%	90%
Alamut > or equal to 6	One in 1400	20%	75%	One in 2389	20%	100%
REVEL > 0.932	One in 52,534	0%	100%	One in 18,318	25%	100%

SA-PO580

ADPKD-Spectrum Phenotype in Carriers of IFT172 Pathogenic Variants

Doaa E. Elbarougy,[1] Rohail Jameel,[1] Hana Yang,[1] Rachel S. Schauer,[1] Sean Rogers,[1] Shannon K. McDonnell,[1] Jacob A. Frank,[1] Jun Ma,[1] Nikola Zagorec,[3] Marie-Pierre Audrezet,[3] John A. Sayer,[2] Emilie Cornec-Le Gall,[3] Nicholas B. Larson,[1] Peter C. Harris.[1] *[1]Mayo Clinic Research Rochester, Rochester, MN; [2]Newcastle University, Newcastle upon Tyne, United Kingdom; [3]INSERM, Paris, France.*

Background: ADPKD is mainly due to *PKD1* and *PKD2* mutations. However, ~10% are genetically unresolved or due to other loci, including *IFT140*. Here, we link another ciliary structural protein gene, *IFT172* to the ADPKD like-phenotype.

Methods: We screened ADPKD-like patients on a 356 gene panel (Mayo PKD Center) or a custom gene panel (CHU Brest). In addition, we screened the Mayo Clinic Biobank (MCBB), UK Biobank (UKBB) and Genomics England 100kG Project cohorts, for *IFT172* loss of function (LoF) variants. MCBB carriers of *IFT140* LoF variants were also identified for comparison.

Results: In the cystic population, we identified 6 monoallelic *IFT172* probands with LoF variants and clinical and imaging data. The mean age ±SD was 54.2±20.8, and the mean eGFR 62.8±32.3. The kidney cyst count ranged from 5 to >50. Two probands (33%) had a family history of kidney cysts. In the 52,786 MCBB individuals, we identified 66 (0.13%) with *IFT172* LoF variants and 83 (0.16%) with *IFT140* LoF variants. Of the 38 *IFT172* patients with imaging, nine (24%) had kidney and liver cysts, 18 (47%) only kidney cysts, and four (10.5%) ICD codes for kidney cysts, including three with ADPKD codes. Of the 48 *IFT140* individuals with imaging, nine (18.8%) had kidney and liver cysts, 32 (67%) only kidney cysts, and nine (18.8%) ICD codes for kidney cysts, including two with ADPKD codes. The mean eGFR ±SD were similar, 72.9±22 in the *IFT172* group and 70.2±20 in the *IFT140* group. Figure 1 shows the number of kidney (A) or liver (B) cysts per patient in both groups; 14.3% and 2.3% of the *IFT172* and 23% and 10% of the *IFT140* had ≥10 kidney or liver cysts, respectively. In the UKBB, *IFT172* LoF variants were associated with cystic kidney disease ICD code Q61 (burden test p-value: 0.0114). In the 100kG project, 37 *IFT172* LoF alleles were identified in a rare disease cohort of probands (n=34,082); 2 probands (5.4%) had a cystic kidney phenotype.

Conclusions: *IFT140* and *IFT172* LoF heterozygous variants show incomplete penetrance. The *IFT172* kidney phenotype in affected patients is mild PKD with large cysts and few liver cysts, similar to monoallelic *IFT140*.

Funding: NIDDK Support

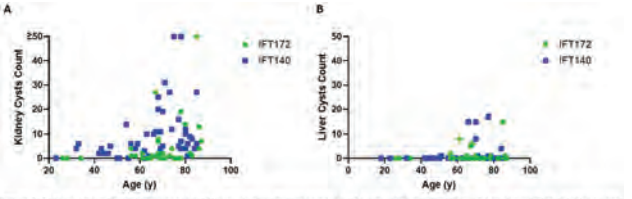


Figure 1. A: Plot of cysts in the kidney of the IFT172 individuals (green) and the IFT140 individuals (blue), in the MCBB population, relative to age. **B:** Plot of cysts in the liver of the IFT172 individuals (green) and the IFT140 individuals (blue), in the MCBB population, relative to age.

SA-PO581

Characterizing Kidney and Liver Cysts in Monoallelic PKHD1 Individuals Identified in a Population-Based Study

Doaa E. Elbarougy,[1] Tabinda Jawaid,[1] Hana Yang,[1] Shannon K. McDonnell,[1] Jacob A. Frank,[1] Jun Ma,[1] Adriana Gregory,[1] Vicente E. Torres,[1] Fouad T. Chebib,[2] Christian Hanna,[1] Timothy L. Kline,[1] Nicholas B. Larson,[1] Peter C. Harris.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic in Florida, Jacksonville, FL.*

Background: Biallelic-*PKHD1* pathogenic variants are associated with ARPKD, while monoallelic-*PKHD1* mutations have recurrently been related to mild liver or kidney cysts. Here, we employed the population-based Mayo Clinic Biobank (MCBB) cohort with whole exome sequencing data to clinically characterize monoallelic-*PKHD1* individuals.

Methods: A cohort of 52,786 MCBB individuals was screened for known pathogenic variants in *PKHD1* and clinical records were screened using Mayo Data Explorer. Kidney and liver cysts were counted via automated segmentation or manually, respectively.

Monoallelic-*PKHD1* individuals identified from ARPKD families and through genetic screening of cystic subjects in the Mayo PKD Center (MPC) were also characterized and compared to the MCBB *PKHD1* carriers.

Results: A total of 975 *PKHD1* carriers were identified in MCBB (1.85%); 267 (27.4%) had protein truncating and 708 (72.6%) non-truncating pathogenic variants. Based on radiology reports of the 581 with abdominal imaging, 142 (24.4%) had both kidney and liver cysts, 149 (25.6%) only kidney cysts, and 57 (9.8%) only liver cysts; 30.6% with appropriate imaging had nephrolithiasis. ICD9/10 codes for kidney or liver cysts were positive in 37 (6.5%) patients, including three with ADPKD codes. Figure 1 shows the number of kidney (A) or liver (B) cysts per patient out of 259 MCBB individuals with analyzed imaging; 17% and 15.8% had ≥10 kidney or liver cysts, respectively. Corresponding frequencies were 12.5% and 25% in 16 ARPKD family members and 70.6% and 51.5% in 33 MPC sporadic individuals. With age adjustment, the mean eGFR ±SE was higher in the MCBB group (74.9±0.7), than in the ARPKD families (62.5±5.8; p=0.04) and the MPC sporadic individuals (57.2±5; p<0.001). A total of 25 *PKHD1* MCBB cases had CKD5, but in each case other comorbidities were identified.

Conclusions: Carriers of *PKHD1* pathogenic variants are common and kidney and/or liver cysts are often seen, but polycystic kidneys and/or livers are quite rare (<20% of individuals), as is eGFR decline.

Funding: NIDDK Support

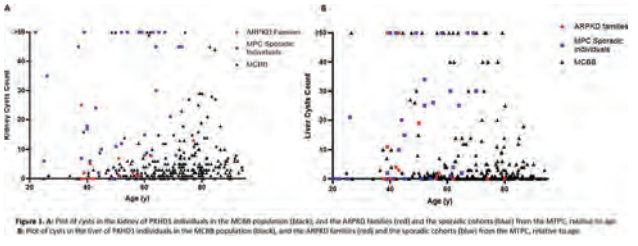


Figure 1. A: Plot of cysts in the kidney of PKHD1 individuals in the MCBB population (black), and the ARPKD families (red) and the sporadic cohorts (blue) from the MTPC, relative to age. B: Plot of cysts in the liver of PKHD1 individuals in the MCBB population (black), and the ARPKD families (red) and the sporadic cohorts (blue) from the MTPC, relative to age.

SA-PO582

Determining the Pathogenic Mechanism Underlying Childhood ADPKD Caused by a Monoallelic Pathogenic Variant in NEK8

Chuan Chen, Peter C. Harris, Kun Ling. *Mayo Clinic Minnesota, Rochester, MN.*

Background: While autosomal dominant polycystic kidney disease (ADPKD) typically manifests in adults, a fraction present early and rapidly progress to kidney failure during infancy and childhood. We recently identified a monoallelic variant in *NEK8* (c.133C>T (p.Arg45Trp)), resulting in an enzymatic deficient serine/threonine kinase that resides in primary cilia. Unlike biallelic pathogenic *NEK8* variants causing systemic ciliopathies, the p.Arg45Trp variant causes early-onset ADPKD with few extrarenal defects. Thus, NEK8^{R45W} seems specific for renal cystogenesis and is a unique tool to dissect the pathogenic mechanism of PKD in children.

Methods: Mouse renal epithelial cell lines null for NEK8 were generated using CRISPR/Cas9 and wild type (WT) or R45W human NEK8 constructs were reexpressed: Ciliary biogenesis, structure, and signaling were analyzed. Phospho-site and proximity-dependent proteomics were conducted using the cell lines to identify proteins that are differentially phosphorylated, deposited into cilia, or associated with NEK8 variants. We constructed a mouse model to study the physiological role of NEK8^{R45W}.

Results: Although Nek8-null cilia are shortened, NEK8^{R45W} cilia retained comparable length and overall structural integrity to the WT cilia, but the PKD1/PKD2 proteins, PC1 and PC2, were significantly reduced in NEK8^{R45W} cilia. Although the ciliary level of GPR161 remained unchanged, SAG induced less accumulation of Smoothened and Gli3 in NEK8^{R45W} cilia than WT, indicating a weaker activation of the Hedgehog (Hh) signaling. Phospho-site proteomics results supported the defective kinase activity of NEK8^{R45W} and revealed mis-regulated pathways in cells expressing NEK8^{R45W}. Importantly, *Nek8*$^{+/R45W}$ mice showed aggressive renal cystogenesis within 3 weeks after birth, recapitulating the early-onset ADPKD phenotype in patients.

Conclusions: We further study the characteristics of the monoallelic *NEK8* p.Arg45Trp and determined that the kinase activity of NEK8 in cilia is necessary for the ciliary trafficking of the PC complex, activation of Hh signaling, and epithelial morphogenesis. These signaling pathways may collectively contribute to the establishment and maintenance of renal tubule structures. Understanding the crosstalk between these pathways via studying the role of NEK8^{R45W} may reveal potential drug targets for the treatment of ADPKD in children.

Funding: Other U.S. Government Support

SA-PO583

Functional Analysis of a De Novo Monoallelic NEK8 Variant Supports Pathogenicity for a Polycystic Kidney Disease Phenotype

Whitney Thompson, Chuan Chen, Hana Yang, Tracy A. Baker, Carl H. Cramer, Peter C. Harris, Kun Ling, Christian Hanna. *Mayo Clinic Minnesota, Rochester, MN.*

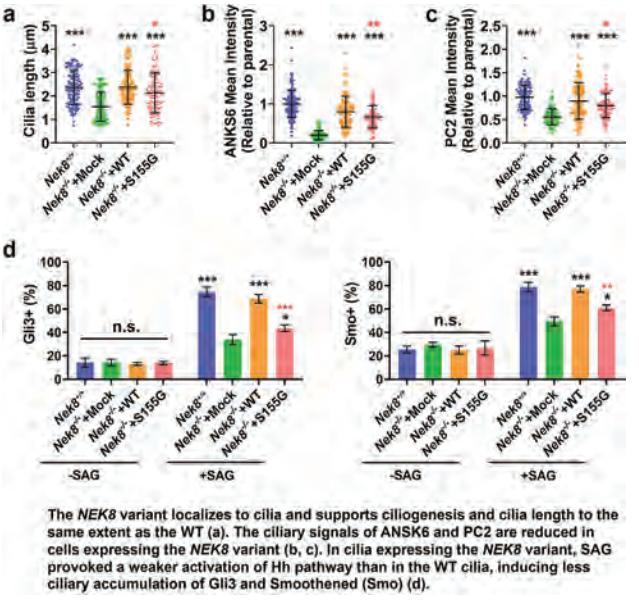
Background: While *PKD1* and *PKD2* pathogenic variants are most common in ADPKD, additional genes linked to primary cilia are increasingly recognized in ADPKD. One such gene, *NEK8*, encodes a ciliary serine/threonine kinase involved in renal and cardiovascular development. Biallelic pathogenic variants in *NEK8* cause renal-hepatic-pancreatic dysplasia-2; however, certain monoallelic *NEK8* variants have been recently linked to ADPKD, causing phenotypes ranging from childhood-onset kidney failure to typical ADPKD. Decreased polycystin-2 (PC2) in cilia have been reported in Nek8 null cells. Herein, we report studies on a novel monoallelic *NEK8* variant (c.463A>G, p.Ser155Gly) in a pediatric patient.

Methods: Genetics and the clinical phenotype were characterized and the *NEK8* variant was stably expressed in Nek8 null cells. The ciliary biogenesis, protein composition, and Hedgehog (Hh) signaling were compared between the empty vector (Mock), the Myc-tagged *NEK8* wild type (WT), and *NEK8* (p.Ser155Gly).

Results: A 12-year-old male was diagnosed incidentally with bilateral medullary kidney cysts. PKD panel screening found a de novo *NEK8* variant of uncertain significance (VUS), c.463A>G (p.Ser155Gly), as the most likely pathogenic change. This *NEK8* variant localizes to cilia and supports ciliogenesis and cilia length to the same extent as the WT (Fig 1a). Yet, the ciliary signals of ANSK6 and PC2 are reduced in cells expressing the *NEK8* variant (Fig 1b, c). In *NEK8* variant cilia, SAG weakly activated the Hh pathway compared to WT cilia, inducing less ciliary accumulation of Gli3 and Smoothened (Smo) (Fig 1d).

Conclusions: Functional analysis supports the pathogenicity of our patient's *NEK8* VUS. Monoallelic *NEK8* should be considered in childhood ADPKD cases.

Funding: Other U.S. Government Support



The *NEK8* variant localizes to cilia and supports ciliogenesis and cilia length to the same extent as the WT (a). The ciliary signals of ANSK6 and PC2 are reduced in cells expressing the *NEK8* variant (b, c). In cilia expressing the *NEK8* variant, SAG provoked a weaker activation of Hh pathway than in the WT cilia, inducing less ciliary accumulation of Gli3 and Smoothened (Smo) (d).

SA-PO584

Cystic Development in Ift140 Knockout Mice Depends on Knockout Timing

Hana Yang, Zoey Mann, Kristian M. Kennedy, Cynthia J. Sieben, Gurparneet K. Sohi, Peter C. Harris. *Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN.*

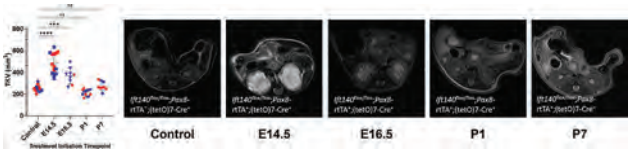
Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disease, causing kidney failure, and is primarily caused by mutations in *PKD1* (~81%) or *PKD2* (~13%), however, >8 minor genes, including *IFT140*, have been identified. The ADPKD-*IFT140* phenotype is distinct, featuring a lower number of large cysts. IFT140, an intraflagellar transport protein, is critical for the generation and function of primary cilia, but the monoallelic cystic disease pathomechanisms are unclear.

Methods: We employed an inducible conditional mouse model (*Ift140*$^{flox/flox}$;*Pax8*-rtTA;(tetO)7-Cre) to achieve kidney tubule-specific *Ift140* knockout (KO) at different stages. Doxycycline treatment (*Ift140* KO) via food was introduced to pregnant or nursing dams at embryonic day (E) 14.5 and 16.5, or postnatal day (P) 1, and 7. To monitor PKD severity/progression, MRI and total kidney volume (TKV) were assessed at 1, 3, and 6 months (m) in living animals, and histological and kidney function analyses performed post-sacrifice.

Results: TKV was significantly increased at 1m in E14.5 and E16.5-induced mice (Fig. 1), but P1 and P7-induced mice were unaffected. The degree of cystic severity at 1m differed greatly between the E14.5 and E16.5 groups, showing a steep decline from E14.5 to E16.5. Furthermore, P1 and P7-induced mice did not develop cysts up to 6m. However, E14.5-induced mice had severe disease, with lethality by 1m, whereas E16.5 mice, with milder disease, survived beyond 3m in some cases.

Conclusions: The timing of *Ift140* removal greatly influenced the rate of cyst development in mice between E14.5 and E16.5, while no cysts formed at or after P1. This dramatically contrasts with the later kidney development switch point between severe and mild PKD for *Pkd1* (~P13). This raises questions about when embryonic reduction of IFT140 in ADPKD-*IFT140* may be critical for cyst development and how this contrasts with ADPKD-*PKD1*. To further elucidate IFT140 pathomechanisms, we will analyze ciliary protein trafficking and structure at different time points.

Funding: NIDDK Support



SA-PO585

Heterozygous Mutations in Three Novel Candidate Genes, IFT122, WDR19, and WDR35, Cause Autosomal Dominant Polycystic Kidney Disease

Dan Colombo,[1] Denisse Romero Cruz,[1] George W. Wan,[1] Adriana C. Barreiro-Rosario,[1] Ahona Dam,[1] Alexandra Diamond,[1] Giada Bianchi,[2] Christopher S. Oglivy,[1] Samer S. Nasser,[1] Elizabeth A. Phipps,[3] Walter P. Mutter,[4] Emily Robinson,[2] Katherine S. Ravi,[2] Peter G. Czarnecki.[1]
[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Mount Auburn Hospital, Cambridge, MA; [4]Newton-Wellesley Hospital, Newton, MA.

Background: Autosomal-dominant polycystic kidney disease (ADPKD) is one of the most common monogenic diseases in mankind. Despite the identification of two major and various minor causative genes, many cases remain genetically unresolved ("ADPKD-NMD", "no mutation detected"). We sought to identify novel disease-causing genes by analyzing the genotypes of patients with ADPKD-NMD, and we found numerous variants in IFT122, WDR19 and WDR35. Given the similarity of disease phenotypes and the common biochemical function of the ADPKD gene, IFT140, with the 3 novel candidate genes, we hypothesize that our newly discovered variants are causative in PKD.

Methods: Chart review to identify patients with ADPKD-NMD Family pedigree genotype-phenotype correlation CRISPR/Cas9 gene knockout Lentiviral transduction Immunofluorescent confocal microscopy Co-immunoprecipitation/Western blot

Results: Chart analysis revealed 3 families with heterozygous alleles in IFT122 and WDR19, segregating with a clinical PKD phenotype across two generations. We further identified 3 additional IFT122 and 2 WDR35 alleles in singletons, coinciding with clinical PKD. In summary, we found a truncation in WDR19, 2 truncations in WDR35, a truncation and a large in-frame deletion in IFT122, and three missense variants in IFT122. After CRISPR/Cas9-knockout of the endogenous IFT122, WDR19 and WDR35, and lentiviral add-back transduction, none of the truncation or in-frame deletion alleles rescued the ciliogenesis defect in mIMCD-3 cells. Although the missense variants in IFT122 allowed for cilia formation, ciliary length was significantly reduced compared to the wildtype. We further show by co-immunoprecipitation and Western blot that the truncation mutations disrupt IFT-A subcomplex formation between IFT140, IFT122, WDR19 and WDR35. IFT122 missense variants exhibit a significantly reduced affinity to their native binding partner, WDR35.

Conclusions: We present the discovery of 3 novel ADPKD genes, IFT122, WDR19 and WDR35. Along with the recently identified ADPKD gene, IFT140, the novel genes represent components of the IFT-A complex that is essential for ciliary handling of PKD1 and PKD2.

Funding: NIDDK Support, Private Foundation Support

SA-PO586

Characterization of IFT140 Phenotype in Patients with ADPKD Using Advanced Imaging Biomarkers

Ahmad Ghanem,[1] Fadi George Munairdjy Debeh,[1] Abdul Hamid Borghol,[1] Stefan N. Paul,[1] Bassel Alkhatib,[1] Nay Nader,[1] Adriana Gregory,[2] Hana Yang,[2] Christian Hanna,[2] Neera K. Dahl,[2] Timothy L. Kline,[2] Peter C. Harris,[2] Fouad T. Chebib.[1] *[1]Mayo Clinic in Florida, Jacksonville, FL; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is commonly caused by pathogenic variants in *PKD1* and *PKD2* genes. This study aims to characterize the phenotype of ADPKD-*IFT140*, the third most common pathogenic variant associated with milder ADPKD, and compare it with the phenotypes of nontruncating-*PKD1* (*PKD1NT*) and *PKD2* pathogenic variants.

Methods: In this retrospective cohort study, ADPKD patients with pathogenic variants in *IFT140*, *PKD2*, or *PKD1NT*, and imaging prior to any event that may affect total kidney volume (TKV) were identified and matched by sex, age, and closest htTKV. Advanced imaging biomarkers were assessed using an automated cyst segmentation deep learning model as shown in **Figure**.

Results: Of the included ADPKD patients (27 each in *IFT140*, *PKD1NT*, *PKD2*), 48% were male with a mean (±SD) age at imaging of 57.7 (±13.3) years. Imaging biomarkers analyses across the 3 groups is shown in **Table**. Although no significant difference was observed in total cyst volume (TCV) between the 3 groups, ADPKD-*IFT140* patients were characterized by a smaller total number of cysts (median TCN: 42 in *IFT140* vs. 277 in *PKD2* vs 217 in *PKD1NT*, p<0.01) and larger average cyst volumes (median: 12.1 mL in *IFT140* vs. 2.2 in *PKD2* and 1.0 mL in *PKD1NT*, p<0.01). Furthermore, the cyst-parenchymal surface area was significantly smaller in the ADPKD-*IFT140* group (median: 182.3 cm^2 in *IFT140* vs. 1222.4 cm^2 in *PKD2* and 678.3 cm^2 in *PKD1NT*, p<0.01).

Conclusions: ADPKD-*IFT140* patients develop enlarged kidneys with fewer but significantly larger cysts compared to ADPKD-*PKD2* and ADPKD-*PKD1NT.*

Table

	IFT140	*PKD2*	*PKD1NT1*	p-value
Height-adjusted total kidney volume (htTKV) (mL/m), median (Q1-Q3)	424.8 (263.7 - 858.7)	915.8 (345.2 - 1402.1)	448.0 (312.5 - 1141.1)	0.13
Total cyst volume (TCV) (mL), median (Q1-Q3)	399.4 (110.7 - 1063.9)	815.6 (217.9 - 1412.6)	223.5 (83.4 - 1007.5)	0.18
Renal parenchymal volume (RPV) (mL), median (Q1 - Q3)	364.9 (293.2 - 529.2)	603.7 (393.5 - 1043.8)	550.8 (412.5 - 1106.6)	<0.01
Cyst-parenchymal surface area (CPSA) (cm^2), median (Q1 - Q3)	182.3 (100.3 - 382.4)	1222.4 (421.3 - 1888.8)	678.3 (347.4 - 1734.8)	<0.01
Total cyst number (TCN), median (Q1 - Q3)	42 (18 - 56)	277 (121 - 614)	217 (144 - 470)	<0.01
Average cyst volume (mL), median (Q1 - Q3)	12.1 (4.0 - 17.1)	2.2 (0.9 - 3.4)	1.0 (0.5 - 2.2)	<0.01

Figure: Advanced imaging biomarkers assessed using an automated cyst segmentation deep learning model.

SA-PO587

Characterization of GANAB Phenotype in Patients with ADPKD Using Advanced Imaging Biomarkers

Fadi George Munairdjy Debeh,[1] Vineetha Rangarajan,[1] Ahmad Ghanem,[1] Abdul Hamid Borghol,[1] Stefan N. Paul,[1] Bassel Alkhatib,[1] Nay Nader,[1] Adriana Gregory,[2] Hana Yang,[2] Christian Hanna,[2] Neera K. Dahl,[2] Timothy L. Kline,[2] Peter C. Harris,[2] Fouad T. Chebib.[1] Chebib's Clinical Team. *[1]Mayo Clinic in Florida, Jacksonville, FL; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Autosomal dominant polycystic kidney disease (ADPKD), primarily caused by pathogenic variants in the *PKD1* and *PKD2* genes, is the most prevalent inherited kidney disorder leading to kidney failure. Rarely, other genes like *GANAB* can cause ADPKD with a lower risk of kidney failure. This study aims to characterize the renal and hepatic manifestations of ADPKD-*GANAB* and compare them with nontruncating-*PKD1 (PKD1NT)* and *PKD2* pathogenic variants.

Methods: In this retrospective cohort study, ADPKD patients with pathogenic variants in *GANAB*, *PKD2*, or *PKD1NT*, and imaging prior to any event that may affect total kidney volume (TKV) were identified and matched by sex, age, and closest htTKV. Advanced imaging biomarkers were assessed using an automated cyst segmentation deep learning model.

Results: Of the included ADPKD patients (14 each in *GANAB*, *PKD1NT*, *PKD2*), 78% were female with a mean (±SD) age at imaging of 56 ±11.5 years. Imaging biomarkers analyses across the 3 groups is shown in **Table**. Median total liver volume and percentage of patients with >100 liver cysts were similar between the 3 groups. However, ADPKD-*GANAB* patients had a significantly lower htTKV (median: 214.5 in *GANAB* vs. 324 in *PKD2* vs. 288.3 in *PKD1NT*, p=0.03), total cyst volume (TCV) (median: 4.1 in *GANAB* vs. 119 in *PKD2* vs. 69.2 in *PKD1NT*, p=0.02), and total cyst number (TCN) (median: 12.5 in *GANAB*, vs. 145 in *PKD2* vs 98 in *PKD1NT*, p<0.01).

Conclusions: Compared to ADPKD-*PKDNT1* and ADPKD-*PKD2*, ADPKD-*GANAB* patients have similar hepatic manifestations, but milder renal manifestations characterized by significantly smaller kidneys with a fewer number of cysts. These findings suggest that *GANAB* pathogenic variants lead to a liver-dominant phenotype with milder renal cystic burden.

Table

	GANAB	*PKD2*	*PKDNT1*	p-value
Height adjusted kidney volume (htTKV) (mL/m), median (Q1 – Q3)	214.5 (156.8 – 264.1)	324 (252.2 – 756.1)	288.3 (226.2 – 452.4)	0.03
Total cyst volume (TCV) (mL), median (Q1 – Q3)	4.1 (1.47 – 125.5)	119.7 (57.3 – 560.6)	69.2 (23.53 – 286.5)	0.02
Renal parenchymal Volume (RPV) (mL), median (Q1 – Q3)	316.1 (245.8 – 374.7)	379.3 (320.5 – 675.5)	412 (382.8 – 523.6)	0.02
Cyst parenchymal surface area (CPSA) (cm^2), median (Q1 – Q3)	25.1 (9.96 – 124.1)	356.1 (138.9 – 991.3)	206 (92.5 – 692.3)	<0.01
Total cyst number (TCN), median (Q1 – Q3)	12.5 (6.5 – 27.7)	145 (73.5 – 333.7)	98 (56 – 183.7)	<0.01
Percentage of patients with >100 liver cysts	71.4%	64.3%	78.6%	0.70
Liver volume (mL), median (Q1 – Q3)	1990.4 (1392.5 – 3167.6)	2439.5 (1582.2 – 5123.1)	2000.2 (1595.6 – 4074.0)	0.59

SA-PO588

The Co-chaperone DNAJB11 in Polycystic Kidney Disease: Molecular Mechanisms and Cellular Origin of Cyst Formation

Bjoern Neubauer, Tilman Busch, Lars Schmitt, Lukas Westermann, Alexis Hofherr, Michael Kottgen. *Department of Medicine IV - Nephrology and Primary Care, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany*.

Background: Autosomal dominant polycystic kidney disease (ADPKD) arises due to mutations in the genes *PKD1* and *PKD2*, which encode the membrane proteins polycystin-1 (PC1) and polycystin-2 (PC2). PC1 and PC2 form a receptor-ion channel complex participating in the regulation of the renal tubular diameter. Loss of polycystin function results in cyst formation from epithelial cells of all nephron segments. Mutations in genes, which encode endoplasmic reticulum (ER)-resident proteins have been previously demonstrated to cause atypical forms of ADPKD. Here, we investigate the function of DNAJB11, an ER co-chaperone, in the development of ADPKD.

Methods: Murine models with constitutive and inducible *Dnajb11* inactivation as well as *Dnajb11*-deficient renal epithelial cells were generated to investigate the genetic mechanism underlying autosomal dominant inheritance, the specific cell types driving cyst formation, and molecular mechanisms that lead to DNAJB11-dependent polycystic kidney disease.

Results: Through the use of mouse models with constitutive and conditional *Dnajb11* inactivation, we show that homozygous loss of *Dnajb11* results in polycystic kidney disease, while heterozygous animals are healthy. This suggests that cyst formation is recessive at the cellular level. The formation of cysts begins *in utero* and the timing of *Dnajb11* inactivation significantly influences the severity of the phenotype. In contrast to classical ADPKD, cysts in *Dnajb11*-related kidney disease originate almost exclusively from proximal tubular cells. In addition, we identify impaired processing of Polycystin-1 as a molecular mechanism contributing to cystogenesis, but also find additional proteins that are dysregulated in *Dnajb11* deficient cells.

Conclusions: We show that biallelic loss of *Dnajb11* causes cystic kidney disease and fibrosis in mice, closely resembling human disease characteristics. These findings contribute to a better understanding of the pathogenic mechanisms of DNAJB11-related kidney disease. The observation that cysts already form in embryonic kidneys and emanate exclusively from proximal tubules has important implications since the knowledge of disease-specific time points and cell types is critical for the future development of therapeutic approaches.

Funding: Government Support - Non-U.S.

SA-PO589

New Mutation Associated with Polycystic Kidney Disease Type I: A Case Report

Vanya Rai,[1] Manisha Singh,[2] Joseph H. Holthoff.[2] *[1]Mayo Clinic Research Rochester, Rochester, MN; [2]University of Arkansas for Medical Sciences, Little Rock, AR*.

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most prevalent heritable disorders, characterized by the progressive development of kidney cysts leading to renal failure. The disease is primarily caused by mutations in the PKD1 and PKD2 genes, which account for approximately 85% and 15% of cases, respectively. The PKD1 gene, encoding polycystin-1, plays a crucial role in maintaining renal tubular structure and function. This case report describes a previously unreported mutation in the PKD1 gene, identified in a family involving an aunt and her niece, both diagnosed with ADPKD.

Case Description: The index case, a 56-year-old female with chronic kidney disease stage 3b secondary to ADPKD and hypertension, exhibited a strong family history of polycystic kidney disease (PKD). Initial genetic evaluations did not identify any recognized pathogenic mutations, leading to a more detailed genetic investigation, which revealed a novel in-frame deletion in the PKD1 gene, a mutation previously not known to be pathogenic. This mutation was also found in her niece, who presented with severe manifestations of the diease from an early age. The familial consistency of these presentations prompted the investigation into this genetic mutation's potential significance in disease phenotype and progression.

Discussion: The identification of a heterozygous six-nucleotide deletion, c.2084_2089del, resulting in the in-frame deletion of two amino acids, p.Pro695_Ala696del, in the PKD1 gene has significant implications for the clinical outcomes in both patients. The discovery of this novel PKD1 mutation highlights the necessity of considering novel genetic variants in patients with typical clinical presentations but without identifiable mutations in the common loci associated with ADPKD. It also emphasizes the need for continuous updates to genetic data and the benefits of comprehensive genetic screening in families with a history of the disease.

SA-PO590

Liddle Syndrome in a Family Presenting with Early-Onset Hypertension, Sudden Death, and Bilateral Kidney Cysts

Janewit Wongboonsin,[1,2] Nadine N. Channaoui,[5] Anna Verwillow,[1,3] Carolyn Ho,[1] Ana C. Onuchic-Whitford.[1,4] *[1]Brigham and Women's Hospital, Boston, MA; [2]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [3]Massachusetts General Hospital, Boston, MA; [4]Boston Children's Hospital, Boston, MA; [5]Mass General Brigham Inc, Boston, MA*.

Introduction: Liddle syndrome is an autosomal dominant form of monogenic hypertension (HTN). Caused by gain-of-function variants in genes encoding subunits of ENaC, classical presentation includes early-onset HTN, hypokalemia and metabolic alkalosis. Here, we describe a family with early-onset HTN referred for history of sudden death and bilateral kidney cysts, found to have Liddle syndrome.

Case Description: A 40-year-old (yo) female with early-onset HTN presented for evaluation of kidney cysts. Diagnosed with HTN at 18 yo, imaging revealed small bilateral kidney cysts, attributed to polycystic kidney disease (PKD). She was treated with lisinopril, HCTZ and metoprolol, with normal serum potassium (mid-high 3s) and renal function. A prior cystic kidney genetic panel was negative. At our clinic, a broad kidney genetic panel was sent to further explore her cystic disease/HTN, revealing a heterozygous pathogenic variant in *SCNN1B* c.1853C>T (p.Pro618Leu) consistent with Liddle syndrome (LS). No variants were found in PKD-related genes. 24-hour urine study showed undetectable aldosterone and high potassium. A younger sister with early HTN had sudden death at 37yo, during a high-altitude trip after episodes of vomiting. Autopsy revealed cardiomegaly and hypertrophic cardiac remodeling due to HTN, with multiple small bilateral kidney cysts. Cardiomyopathy gene panel (not inclusive of *SCNN1B*) was negative, with insufficient DNA for further testing. Their 70 yo father had early HTN, stroke, hypokalemia, bilateral kidney cysts, and found to have the same *SCNN1B* variant. The patient and father were transitioned to amiloride with excellent control of HTN.

Discussion: LS is a tubulopathy typically characterized by hypokalemic HTN and metabolic alkalosis. Lack of this full triad may result in delayed diagnosis and HTN-associated end-organ damage. Although kidney cysts are not regarded as part of LS, here all affected family members had small bilateral cysts, independent of hypokalemia. Additionally, association of LS with sudden cardiac death was suspected due to hypertensive cardiomyopathy, potassium loss, and likely arrhythmia. Increased genetic testing in nephrology may contribute to phenotypic expansion of Mendelian diseases, enable earlier molecular diagnoses, and support inclusion of relevant genes in phenotype-driven panels.

SA-PO591

An Unusual Case of Cystic Kidney Disease in a Patient with CACNA1H Mutation and Hyperaldosteronism

Jerin Karingattil, Yinelka G. Silverio De Castro, Minesh Khatri.
NYU Langone Health, Mineola, NY.

Introduction: Studies have reported an elevated prevalence of renal cysts in patients with primary aldosteronism. A proposed mechanism is that chronic hypokalemia results in renal tubular cell injury and cyst expansion. We report a case of a patient with chronic kidney disease (CKD) who was found to have numerous bilateral renal cysts and a variant of uncertain significant (VUS) mutation in CACNA1H, associated with Familial Hyperaldosteronism Type IV. Our case highlights the role of hyperaldosteronism on the development of renal cysts. Especially unique here is the absence of hypokalemia, suggesting an alternative mechanism by which aldosterone influences renal cyst formation and growth.

Case Description: A 68-year-old female was evaluated in our clinic for hypertension and CKD. She has no family history of cystic kidney disease. Imaging revealed bilateral renal cysts mostly at the corticomedullary junction, suspicious for medullary cystic kidney disease (MCKD). She also had two stable pancreatic cysts concerning for autosomal dominant polycystic kidney disease (ADPKD) or Von Hippel-Lindau (VHL). Genetic testing was negative for mutations in MCKD1-2, PKD 1-2, VHL genes, but it detected a VUS mutation in CACNA1H. Lab data revealed an aldosterone level of 57.9 ng/dL, plasma renin activity of 0.6 ng/mL/hr, and aldosterone/renin ratio 96.5, suggesting primary aldosteronism. There was no hypokalemia or metabolic alkalosis. She was started on spironolactone to mitigate effects of hyperaldosteronism.

Discussion: While initial presentation of numerous renal cysts and CKD suggested ADPKD, MCKD or acquired cystic kidney disease, genetic testing eventually discovered a CACNA1H VUS mutation. This has been associated with Familial Hyperaldosteronism type IV and is the likely cause of the medullary renal cysts in this patient. While prior studies have postulated that chronic hypokalemia leads to cyst formation and growth, our patient's hyperaldosteronism was without hypokalemia. One should consider alternative mechanisms, such as aldosterone inducing signaling cascades that enhance cell multiplication and modify ion transport activities in renal cells. Along with broadening the differential for cystic kidney disease to include CACNA1H mutation, further research is needed to determine mechanistic pathways by which aldosterone influences cyst growth.

SA-PO592

Unmasking the Mimickers: HNF1B Variants in Pediatric Kidney Diseases

Jordy Salcedo-Giraldo, Krista R. Wink, Andrew Freiman, Louise C. Pyle, Ashima Gulati. *Children's National Hospital, Washington, DC.*

Introduction: Hepatocyte nuclear factor 1 beta (*HNF1B*) variants are associated with a spectrum of phenotypic manifestations including renal, pancreatic, and metabolic disorders. These variants can pose diagnostic dilemmas due to their diverse clinical presentations, often mimicking other congenital kidney conditions.

Case Description: A retrospective case series of 12 pediatric patients (age 4 months to 10 years) referred to our Renal Genetics Clinic with varied kidney phenotypic findings ultimately attributed to heterozygous disease-causing *HNF1B* variants. Each case exhibited unique clinical features, including cystic and non-cystic renal abnormalities, early-onset diabetes, and abnormal liver tests. Table 1 lists the clinical, laboratory, and kidney imaging findings at clinical presentation. Genetic investigation revealed two types of *HNF1B* defects: (i) whole gene deletion (67%); and (ii) truncating or missense variant predicted to be pathogenic (33%), which were *de novo* in all cases but one.

Discussion: Our findings highlight the importance of considering *HNF1B* variants in the differential diagnosis of pediatric patients presenting with structural kidney abnormalities with or without cystic kidney disease or specific multisystemic features. Despite disparate presentations, the genetic evaluation revealed a unifying etiology in all cases. Enhanced awareness of the protean nature of *HNF1B*-related disorders is valuable for accurate prognostication and optimization of multidisciplinary management strategies.

Table 1

Pt	Variant	Cystic	Non-Cystic	Abn LFT	DM	↓ Mg	↑ U	GD	FH
1	c.494G>A: p.R165H	-	+	+	+	-	-	+	-
2	17q12 deletion	+	-	-	-	-	-	-	-
3	c.26C>T: p.Q9*	+	-	-	-	-	-	-	+
4	17q12 deletion	+	-	-	-	-	-	-	-
5	17q12 deletion	-	+	-	-	+	-	-	-
6	whole gene deletion	+	-	-	-	-	-	-	-
7	17q12 deletion	-	+	-	-	-	-	-	-
8	whole gene deletion	+	-	-	-	-	-	+	-
9	c.395A>G: p.H132R	+	-	+	-	-	-	+	-
10	c.826C>T: p.R276*	-	+	-	-	-	-	+	-
11	17q12 deletion	+	-	-	-	+	+	-	-
12	whole gene deletion	-	+	-	-	-	-	-	-

Key: Cystic = cystic renal disease, Non-Cystic = non-cystic/functional renal disease, Abn LFT = abnormal liver test, DM = diabetes, ↓ Mg = hypomagnesemia, ↑ U = hyperuricemia, GD = growth delay, FH = family history

SA-PO593

COL4A1 Mutation: Hereditary Angiopathy with Nephropathy, Aneurysms, and Muscle Cramps (HANAC) Syndrome, an ADPKD Mimicker

Harshil Fichadiya,[1] Vraj Patel,[2] Andrew J. Bentall.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Canton Medical Education Foundation, Canton, OH.*

Introduction: Type 4 collagen(T4C) has 6 alpha subunits(A1-6) and is responsible for synthesis of most basement membranes. Alport syndrome involving defect in synthesis of A5 and rarely A3/A4 subnits is the most common known genetic syndrome resulting from faulty T4C synthesis. While A3,4,5 collagen network replaces A1,1,2 network during embryogenesis in the GBM, A1,1,2 network is the most common network in Bowmans space, tubular BM, rest of the body, including blood vessels HANAC syndrome (Heridetary Angiopathy, Nephropathy, Aneurysm and Muscle Cramps) has been described with AD inheritance in families with defective A1 subunit synthesis. Kidney disease is characterized by mild hematuria and renal cyst. Emmanuelle etal characterized phenotypes from 3 families having HANAC syndrome and reported glycine mutation in exon 24 and exon 25

Case Description: 74 year old female referred for evaluation of preemptive kidney transplant. She first presented with microhematuria and was first diagnosed with CKD at age 30. CKD progressed gradually over multiple years to stage 4 CKD in 2023. She has persistent microhematuria and proteinururia has gradually progressed to 1.5g/24hrs, reported strong family history of PKD in aunts, uncles and cousins. Multiple USG over the years revealed small kidneys with 2-3 partially regressing cyst bilaterally, largest cyst 3cm. Genetic analysis using next generation sequencing revealed mutation in COL4A1 gene. She described experiency occasional muscle cramps. MRA revealed 3 mm right and left ICA aneursyms She is listed for DDKT

Discussion: Since most ADPKD cases are diagnosed based on imaging criteria and positive family history when available, COL4A1 mutation can be easily confused for ADPKD when genetic testing is not performed. It is important to make this distinction as specific therapies available for ADPKD may not be as effective in patients with COL4A1 mutation. HANAC syndrome is a rare genetic syndrome characterized by cystic kidney disease aneurysm involving mutiple organ systems & retinal vessel (vs mainly CNS in ADPKD), cardiac, and muscular abnormalities causing cramping and occasionally hypotonia with developmental delay. Additionally digenic genotype with both COL4A1-PKD mutation have been identified with earlier progress to ESRD,50 years age. Our case presented with small kidneys, hematuria, 2-3 renal cyst and mild CNS aneurysms with ocassional cramping and slow progression

SA-PO594

Oral-Facial-Digital Syndrome Type 1: An Underestimated Differential Diagnosis of PKD in Women

Constantin A. Wolff,[1] Marie-Pierre Audrezet,[2] Emilie Cornec-Le Gall,[2] Jan Halbritter.[1] AG Halbritter, AG Cornec-Le Gall. *[1]Klinik m. S. Nephrologie und internistische Intensivmedizin, Charité - Universitätsmedizin, Berlin, Germany; [2]Service de Néphrologie, Centre Hospitalier Régional Universitaire de Brest and INSERM UMR1078, Brest, France.*

Background: OFD1 (oral-facial-digital syndrome type 1) is an X-linked inherited multi-systemic disorder with variable presentation. Although first identified in 2001, little is known about the true prevalence, natural course, and outcomes of *OFD1*-related kidney disease. With this case series, we aim to highlight *OFD1*-related kidney disease as an underestimated phenocopy of autosomal-dominant polycystic kidney disease (ADPKD) in women.

Methods: We performed a retrospective study of patients with a genetically confirmed *OFD1* diagnosis who presented to multiple centers in European renal clinics between 2006 and 2024. We collected demographic, clinical, laboratory, imaging, and histopathological data for statistical analysis.

Results: We identified 19 females from 15 families with *OFD1*-related kidney disease (mean age: 54y ± 4y). The median age at diagnosis was 38y ± 4y. Erroneously 11 patients were classified as typical ADPKD, and partially treated with tolvaptan (n=6). Genetically, all patients harbored monoallelic truncating variants N-terminal of the SDCCAG8-interaction domain (Fig.1). Phenotypically, all patients presented with majorly non-enlarged PKD. Estimated glomerular filtration rate varied widely and showed no overall trend even within families and age groups. Eight patients developed kidney failure (KF) at a mean age of 47.5 years. In addition to PKD, typical extra-renal features (e.g. frenulum, syndactyly, epilepsy, cleft lip and palate, intellectual disability) were observed in 11 patients (58%) to variable degrees.

Conclusions: Our study highlights the importance of considering OFD1 in the differential diagnosis of normal-sized PKD with or without further extra-renal abnormalities, particularly in young females. Early detection and timely initiation of general kidney protection measures may improve treatment outcomes and delay progression to KF. Further studies are required to evaluate specific treatment options for *OFD1*-related PKD, as the benefit of otherwise licensed tolvaptan has not been demonstrated.

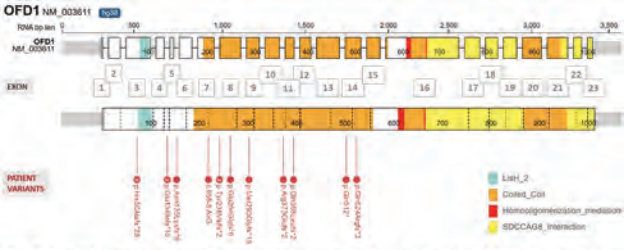


Fig. 1: A modified protein structure with protein length, patient variants and structure of OFD1 is shown in this figure. All patient variants are located in the Coiled-Coil domain, likely resulting in protein truncation of the SDCCAG8 domain. Image made with proteinpaint.stjude.org

Fig.1: A modified protein structure of OFD1 with patient variants.

SA-PO595

Cystic Phenotypes Associated with Monoallelic COL4A3/A4/A5 Pathogenic Variants Identified in a Population-Based Cohort

Gurparneet K. Sohi, Doaa E. Elbarougy, Hana Yang, Rachel S. Schauer, Shannon K. McDonnell, Jacob A. Frank, Jun Ma, Neera K. Dahl, Marie C. Hogan, Vicente E. Torres, Peter C. Harris. *Mayo Foundation for Medical Education and Research, Rochester, MN*.

Background: In Alport syndrome, mono/biallelic *COL4A3*/*COL4A4* or hemizygous *COL4A5* pathogenic variants cause glomerular disease, leading to hematuria, proteinuria and kidney failure. A milder, monoallelic (including *COL4A5*), glomerular phenotype can be evident, while kidney cyst development has also been described. We screened the Mayo Clinic Biobank (MCBB) patients (pts) cohort with available electronic medical records (EMR) and whole exome sequencing (WES) for *COL4A3/4/5* monoallelic individuals.

Methods: We screened 52,786 MCBB individuals for likely pathogenic (LP) variants and renal/hepatic cyst-related ICD codes in the *COL4A3/4/5* genes. Those with LP variants were evaluated using EMR and imaging to determine cystic phenotype penetrance.

Results: We identified 459 individuals with single LP variants: 232: *COL4A3*, 201: *COL4A4*; 26, *COL4A5*. Phenotypes included hematuria (microscopic/gross) (COL4A3: 62%, COL4A4: 65.6%, COL4A5: 61.5%), proteinuria (>150 mg/day) (COL4A3: 36%, COL4A4: 233%, COL4A5: 42.3%) and hypertension (COL4A3: 52%, COL4A4: 57.7%, COL4A5: 65.3%). Using 15 renal/hepatic cyst related ICD codes in pts with imaging (n=281) we identified 27 (9.6%) pts with cysts, 8.6%: *COL4A3*, 11%: *COL4A4*, and 6.2%: *COL4A5*; 0.7% coded for ADPKD. By image analysis, kidney cysts were present 56% of *COL4A3*, 45.2% of *COL4A4* and 30.7% of *COL4A5* (see Fig1); median eGFR was 74, 75 and 78 ml/min/1.73 m^2. Additionally, 2.5% *COL4A4* and 7.7% *COL4A5* monoallelic individuals had FSGS.

Conclusions: Monoallelic LP variants in *COL4A3/A4/A5* often have glomerular phenotypes and cyst development seen in 30-50% of cases, although multiple cysts are rarer. Therefore, genetic screening panels for PKD pts should encompass *COL4A3/A4/A5*.

Funding: NIDDK Support

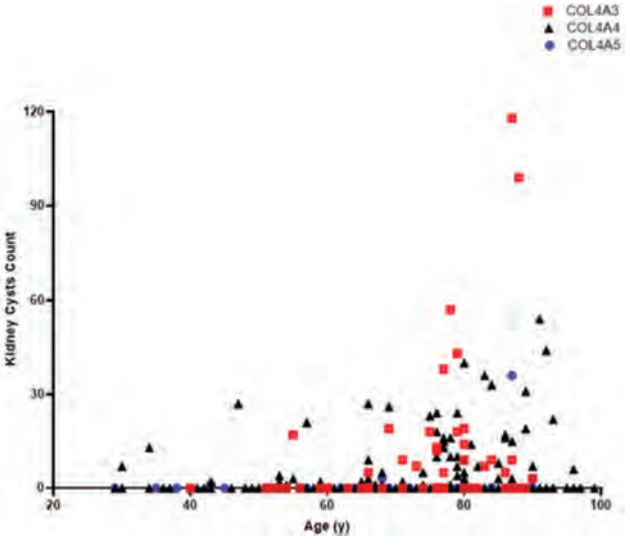


Fig1: Kidney Cysts by age in COL4A3/A4/A5 mutation individuals

SA-PO596

Genetics behind the Phenotypic Spectrum of Polycystic Kidney Disease

Raquel Martínez Pulleiro,[1,2] Ana Barcia de la Iglesia,[1] Catarina A. Toscano,[2] Noa C. Carrera Cachaza,[1] Miguel A. Garcia-Gonzalez.[1] [1]*Instituto de Investigacion Sanitaria de Santiago de Compostela, Santiago de Compostela, Spain;* [2]*Universidade de Santiago de Compostela, Santiago de Compostela, Spain*.

Background: Polycystic kidney disease (PKD) is an inherited disorder with a broad range of clinical presentations. The most common form is autosomal dominant PKD (ADPKD), caused by mutations in *PKD1* or *PKD2* genes. ADPKD typically manifests in adulthood, leading to bilateral kidney cysts, kidney enlargement, and end-stage chronic kidney disease (ESKD). Autosomal recessive PKD (ARPKD), caused by *PKHD1* gene mutations, is more severe and usually appears in childhood or adolescence. Atypical presentations exist, characterized by variations in family history, renal imaging patterns, and phenotypic variability. Here, we want to analyse the genetics behind the cases in our cohort of atypical PKD.

Methods: A retrospective cohort study was performed. Inclusion criteria were 1) having a request for genetic analysis specifying the condition of atypical polycystic disease or mentioning the presence of multiple cysts among its clinical manifestations, 2) having a pathogenic variant in one of the less common cystic genes after genetic analysis, regardless of clinical suspicion.

Results: In our preliminary cohort of 142 patients, 60.68% have received a genetic diagnosis. In 36.75% of cases, no mutation was detected (NMD), and 2.56% remain inconclusive pending further testing. Preliminary data suggest that 14.53% of atypical polycystic disease cases result from *PKHD1* gene mutations. *COL4A3* and *COL4A4* mutations account for 15.38% of cases, presenting with bilateral renal cysts and microhematuria. The next gene that explains more atypical cases is *HNF1B*, which shows great phenotypic heterogeneity. Other mutated genes in our cohort include *ALG8*, *GANAB*, *IFT140*, *DNAJB11*, *PKD1*, *SEC63*, and *TSC1*.

Conclusions: Our preliminary atypical PKD cohort has a mutation detection rate of 60,68% The gene responsible for 14% of cases is *PKHD1* in heterozygosity *COL4A3* and *COL4A4* are responsible for approx. 14% of cases. In general, the inheritance pattern is dominant When analyzing genetic results in an atypical PKD case, it's crucial to consider multiple polycystic disease-associated genes. Additionally, we shouldn't overlook different modes of inheritance and the variable impact of genetic variants.

Funding: Government Support - Non-U.S.

SA-PO597

Prevalence and Severity of Polycystic Liver Disease (PLD) in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Taher Dehkharghanian,[1] Mauricio A. Miranda Cam,[1] Sol M. Carriazo Julio,[1] Xuewen Song,[1,2] Yasmina Sarie,[2,1] Saima Khowaja,[1] Timothy L. Kline,[3] York Pei.[1,2] [1]*University Health Network, Toronto, ON, Canada;* [2]*University of Toronto, Toronto, ON, Canada;* [3]*Mayo Clinic Minnesota, Rochester, MN*.

Background: Liver cysts are common in patients with ADPKD, but the prevalence of clinically significant PLD has not been well defined. Here we report the prevalence, severity and clinical characteristics of PLD from the Toronto Genetic Epidemiology Study of PKD (TGESP), a large prospective cohort study of patients with ADPKD from the Greater Toronto Area.

Methods: All study patients underwent a research protocol with detailed clinical, laboratory (including genetic testing) and abdominal MRI between 2013-2023. An automate liver segmentation model was applied on coronal T2 MRI to calculate TLV and HtTLV. We analyzed baseline clinical characteristics and liver volume measurements of 617 study patients who were found to have a PKD1 protein-truncating (PT), PKD1 (inframe insertion/deletion), PKD1 non-truncating (NT), or PKD2 mutation. Patients were divided into quartiles based on their HtTLV and clinical characteristics, shown in Table 1.

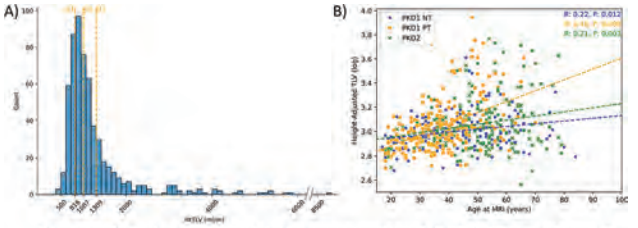
Results: The mean ± sd of TLV and HtTLV of the study cohort were 2163 ± 1466 ml and 1251 ± 856 ml/m; 57% were female. In total, 25% of patients had high HtTLV ranging between 1309 to 8810 ml/m (Figure 1A). The average HtTLV was larger in patients with PKD1 PT mutations in all age groups. However, the difference was only significant between PKD1 NT and PKD1 PT of age 50-59 years (p value: 0.02). Statistically significant positive correlations between HtTLV and TLV were seen among the three mutation classes (Figure 1B).

Conclusions: Up to 25% of patients with ADPKD have moderate to severe PLD (i.e. 2.5 to 10x normal LV). TLV and volume growth rate appeared to be higher in PKD1 PT patients. Multivariate analysis including age, sex, body mass index will be performed to delineate the effects of mutation class on PLD severity.

Funding: Government Support - Non-U.S.

	Q1 (< 817 ml/m)	Q2 (818-1007 ml/m)	Q3 (1008-1308 ml/m)	Q4 (1309 ml/m <)	Overall
Age	39 (± 16)	42 (± 13)	43 (± 12)	50 (± 12)	44 (± 14)
Sex	63% F	51% F	43% F	67% F	57% F
Weight (kg)	67 (± 13)	74 (± 13)	83 (± 16)	81 (± 22)	76 (± 18)
BMI	24 (± 4)	25 (± 4)	28 (± 5)	28 (± 6)	26 (± 5)
PKD1 NT (134)	30%	27%	22%	21%	
PKD1 PT (274)	28%	25%	24%	24%	
PKD2 (209)	29%	25%	23%	23%	

Clinical characteristics of the patients divided into 4 groups based on their HtTLV quartiles.



A) Distribution of HtTLV of our cohort. Orange dashed lines represent quartile cut-offs. B) HtTLV in logarithmic scale versus age shows a positive correlation for all 3 mutation classes, with *PKD1* PT having a higher growth rate.

SA-PO598

Patients with Polycystic Kidney Diseases with Normal Kidney Function Report Poor Sleep Quality

Erin C. Hanlon, Stephanie N. Sintetas, Elizabeth Salvo, Qiyi Ding, Arlene B. Chapman. *University of Chicago Division of the Biological Sciences, Chicago, IL.*

Background: In general, kidney disease has been reported to be associated with poor sleep quality, sleep disturbances, and sleep disorders including obstructive sleep apnea (OSA). While these abnormalities have been reported in CKD population, little is known about sleep characteristics in patients with autosomal dominant polycystic kidney disease (ADPKD), the most common monogenic kidney disorder worldwide. It is possible that aspects unique to ADPKD (increased kidney and liver volumes) may contribute to altered respiratory mechanics that can contribute to sleep abnormalities. These increases in organ volume occur in the setting of normal kidney function. Thus, in this pilot, we examined self-reported sleep characteristics in ADPKD patients with normal kidney function (eGFR > 90 mL/min) compared to a group of BMI, age, and sex matched healthy controls.

Methods: ADPKD and matched controls were asked to fill out gold-standard questionnaires that assess aspects of sleep quality (Pittsburgh Sleep Quality Index - PSQI) and risk for the sleep disorder OSA (Stop-Bang). Chronotype was also assessed with the Owl/Lark Questionnaire in all individuals.

Results: Seven individuals with PKD (4 women, 3 men) with a mean age of 34 years (± 9.5) and body mass index (BMI) of 30.9 kg/m^2 (± 9) were compared to seven matched controls (4 women, 3 men) with a mean age of 32 years (± 8) and a BMI of 34 kg/m^2 (± 10). Both groups reported to be morning types with similar scores on the Owl/Lark Questionnaire (PKD: 55.3 ± 11.3 vs Control: 57.5 ± 13.9) and were both at low to intermediate risk for OSA according to the STOP-Bang questionnaire (ADPKD: 1.9 ± 1.1 vs Control: 1.5 ± 0.8). Six ADPKD individuals completed the PSQI, and interestingly, when compared to their six matched controls, ADPKD subjects had significantly higher PSQI ratings than controls (ADPKD: 5.3 ± 1.8 vs Control: 3.7 ± 0.8, p = 0.019) indicating that they had poorer sleep quality.

Conclusions: These data suggest that ADPKD individuals may experience poor sleep quality when compared to healthy matched controls, that is not a product of diminished kidney function. The contributions to reduction in sleep quality in ADPKD may be multifactorial including increased abdominal girth due to liver and kidney cyst burden, chronic pain and/or the psychological impact of having a hereditary kidney disorder.

SA-PO599

Monoallelic PKHD1 Loss-of-Function Variants Could Be a Cause of Adult Polycystic Kidney Disease

Takuya Fujimaru,[1,2] Takayasu Mori,[1] Akinari Sekine,[3] Motoko Chiga,[4] Shintaro Mandai,[1] Hiroaki Kikuchi,[1] Yutaro Mori,[1] Yu Hara,[1] Tamami Fujiki,[1] Fumiaki Ando,[1] Koichiro Susa,[1] Soichiro Iimori,[1] Shotaro Naito,[1] Tatsuya Suwabe,[3] Yoshifumi Ubara,[3] Shinichi Uchida,[1] Eisei Sohara.[1] *[1]Tokyo Ika Shika Daigaku Daigakin Ishigaku Sogo Kenkyuka, Bunkyo-ku, Japan; [2]Sei Roka Kokusai Byoin, Chuo-ku, Japan; [3]Toranomon Byoin, Minato-ku, Japan; [4]Tokyo Ika Shika Daigaku Byoin, Bunkyo-ku, Japan.*

Background: *PKHD1* is known as a causative gene of autosomal recessive polycystic kidney disease (ARPKD). Recently, it has been suggested that heterozygous *PKHD1* variants may cause autosomal dominant polycystic kidney disease (ADPKD). However, there are few reports that have investigated the clinical characteristics and genetic background of such patients. We investigated the presence of *PKHD1* pathogenic variants in patients with adult polycystic kidney disease.

Methods: We performed a comprehensive genetic analysis in 236 adult polycystic kidney families using either the cystic kidney disease-associated gene panel or the chronic kidney disease-associated gene panel.

Results: In our cohort, 166 patients (70.3%) did not have polycystic kidneys in their parents. Through this analysis, 92 patients (39%) had pathogenic variants in *PKD1* or *PKD2* genes. Additionally, 17 patients (7.2%) had pathogenic variants in other genes (*IFT140*, n = 7; *HNF1B*, n = 3; homozygous *PKHD1*, n = 2; *COL4A3*, n = 1; *MUC1*, n = 1; *NPHP4*, n = 1; *OFD1*, n = 1; *PRKCSH*, n = 1). In 6 of 127 patients (4.7%) who did not have any apparent pathogenic variant in known causative genes, heterozygous loss-of-function (LOF) variants of *PKHD1* were detected (nonsense, n = 4; frameshift, n = 1; splicing, n = 1). In the patients with heterozygous LOF variants in *PKHD1*, age at the time of genetic analysis ranged from 35 to 64 years, and total kidney volumes ranged from 135 to 1193 ml. Two patients had end-stage renal disease, and the remaining four had eGFR ranging from 11 to 61 ml/min/1.73m^2. Furthermore, two of the six patients had heterozygous truncated variants of other autosomal recessive cystic kidney disease related genes.

Conclusions: It has been suggested that heterozygous LOF variants of *PKHD1* may acquire pathological phenotypes due to the coexistence of modifiers such as modifier genes.

Funding: Government Support - Non-U.S.

SA-PO600

Sex Differences and Aging Influence the Association between Kidney Prognosis and Intracranial Aneurysms in Patients with ADPKD: Attribute-Based Medicine (ABM) Insights

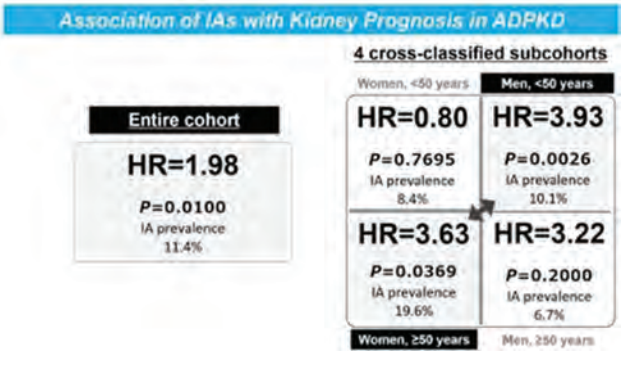
Yusuke Ushio, Hiroshi Kataoka, Toshio Mochizuki, Shun Manabe, Momoko Seki, Shiho Makabe, Ken Tsuchiya, Kosaku Nitta, Junichi Hoshino. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Background: There is a recognized tendency for intracranial aneurysms (IAs) to occur more frequently in elderly women. We aimed to elucidate the association of IAs on kidney disease progression in ADPKD patients, taking into account age and sex as pivotal factors.

Methods: Our study included 494 patients with ADPKD. Renal outcome, defined as a 50% reduction in estimated glomerular filtration rate or initiation of renal replacement therapy, was evaluated using Cox regression analysis and Kaplan-Meier analysis.

Results: Multivariable Cox analyses indicated that IAs were significantly associated with kidney disease progression across the entire cohort (hazard ratio [HR]=1.93). Sub-group analyses showed significant associations between IAs and kidney disease progression in men with <50 years (HR=3.93) and in women ≥50 years (HR=3.63). Kaplan–Meier analysis demonstrated that kidney survival rates were significantly lower in patients with IAs compared to those without, across all cohorts. The 5-year renal survival rate of ADPKD patients with IAs was 51.2% for the entire cohort, 73.5% for women <50 years, 46.2% for men <50 years, 39.9% for women ≥50 years, and 37.5% for men ≥50 years, indicating a extremely poor renal prognosis.

Conclusions: IAs were associated with a poor renal prognosis in patients with ADPKD, especially in men <50 years and women ≥50 years. Susceptibility to IAs in ADPKD patients varies by age and sex. Younger patients are primarily affected by genetic mutations, while older patients, particularly elderly women, may be influenced by a combination of genetic mutations and lifestyle factors, potentially impacting their kidney prognosis.



SA-PO601

Sex- and Age-Related Variations in Intracranial Aneurysms among Patients with ADPKD: Significance of Middle Cerebral Artery Aneurysms in Elderly Women

Yusuke Ushio, Hiroshi Kataoka, Toshio Mochizuki, Shun Manabe, Momoko Seki, Ken Tsuchiya, Kosaku Nitta, Junichi Hoshino. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Background: The effects of sex differences on intracranial aneurysms (IAs) in patients with autosomal dominant polycystic kidney disease (ADPKD) are not fully elucidated.

Methods: We enrolled 519 patients with ADPKD. Logistic regression analyses using sex, age ≥50 years, hypertension, family history of IA or subarachnoid hemorrhage (IA/SAH), and chronic kidney disease (CKD) stages 4–5 or height-adjusted total kidney volume (htTKV) were conducted to identify factors related to IAs.

Results: Sex disparities in intracranial aneurysms (IAs) were evident among ADPKD patients. Women showed a higher prevalence of anterior circulation IAs compared to men (62.7% vs. 44.8%; P=0.0403), with women also experiencing SAH at an older age than men (46 years vs. 37.5 years; P=0.0490). In the entire cohort, female sex was significantly linked with IA (OR=1.78). Stratified by sex, CKD stages 4–5 (OR=4.21), family history of IA/SAH (OR=3.11), and hypertension (OR=2.22) were significantly associated with IA in females, while in males, only family history of IA/SAH (OR=2.35) and CKD stages 4–5 (OR=2.21) were risk factors for IA. Interestingly, when classified by sex and age (≥50 years), gender disparities in IAs were pronounced among patients aged ≥50 years. Anterior circulation IAs (OR=4.58: 71.4% in women vs. 35.3% in men; P=0.0173), particularly middle cerebral artery IAs (OR=10.88: 40.5% in women vs. 5.9% in men; P=0.0113), were more prevalent in women aged ≥50 years compared to men. Moreover, women aged ≥50 years had a significantly higher prevalence of hypertension (OR=4.11), CKD4–5 (OR=10.60), IAs (OR=3.06), and middle cerebral artery IAs (OR=5.93) compared to those <50 years. Additionally, women over 50 years exhibited an increased incidence of middle cerebral artery aneurysms, with multivariate logistic analysis associating these aneurysms with female gender and hypertension.

Conclusions: IAs in patients with ADPKD were affected by attributes (age and sex). Sex and age-specific medical treatment might be desirable, especially, women should pay attention to the incidence of middle aortic aneurysm and its risk factors, which increase with age.

SA-PO602

Progressive Intrarenal Microvascular Damage Presents Early On and Is Preceded by Vascular Molecular Changes in ADPKD

Santu K. Singha,[1] Ahmed Abdelfattah,[1] Christian Hanna,[1] Marie C. Hogan,[1] Alejandro R. Chade,[2] Alfonso Eirin,[1] Maria V. Irazabal.[1] *[1]Mayo Clinic, Rochester, MN; [2]University of Missouri, Columbia, MO.*

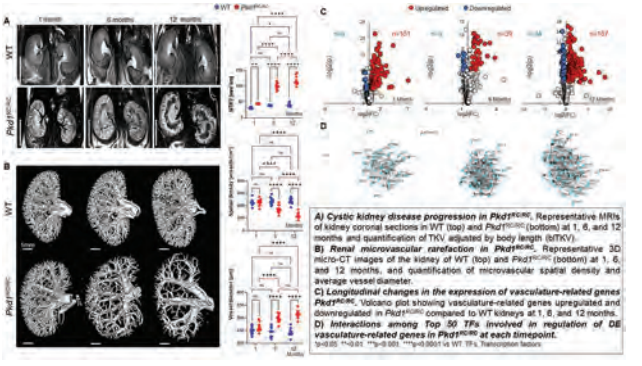
Background: Autosomal dominant polycystic kidney disease (ADPKD) progression has been mainly attributed to the continuous development and expansion of kidney cysts, but the role of the intrarenal microvasculature and the mechanisms leading to vascular damage are still unclear. We hypothesized that intrarenal microvascular structural abnormalities are present from early stages and preceded by vascular molecular changes.

Methods: ADPKD (*Pkd1*$^{RC/RC}$) and WT mice (n=16 each, 8M/8F) were studied at 1, 6, and 12 months (mo). Disease severity and progression were evaluated by kidney weight/body weight (KW/BW), body-length adjusted total kidney volume by MRI (blTKV), cystic area (CA), fibrotic area (FA), and BUN, and intrarenal microvasculature architecture by 3D (micro-CT), capillary density (H&E), and perivascular fibrosis (Trichrome). In randomly selected *Pkd1*$^{RC/RC}$ and WT kidneys (n=5, each per time point, 30 animals), mRNA-sequencing (seq) was performed to identify vasculature-related differentially expressed genes (DEGs). Transcription Factors (TFs) of the DEGs were predicted and ranked, and their gene expression examined.

Results: KW/BW, blTKV, and CA were higher in *Pkd1*$^{RC/RC}$ from 1mo, but FA and BUN were similar until 12mo. Spatial density of cortical and medullary microvessels was preserved at 1mo but progressively decreased at 6 and 12mo **(Figure)**, associated with vessel tortuosity (vascular immaturity), capillary loss, and perivascular fibrosis. A total of 110, 48, and 201 vasculature-related genes were DE at 1, 6, and 12mo, respectively. Interactions among the Top 50 TFs involved in regulating DE vasculature-related genes in *Pkd1*$^{RC/RC}$ increased from 1 to 12mo, and the expression of 18 Top TFs followed the same pattern as their targeted genes.

Conclusions: In ADPKD, intrarenal microvasculature abnormalities are present early on and may constitute a synergistic therapeutic target. Early vascular molecular signatures may serve as biomarkers for disease progression.

Funding: NIDDK Support



SA-PO603

Intracranial Aneurysms Are Detected in 11.2% of Polycystic Patients Undergoing Kidney Transplant Assessment, Particularly in Tall and Hypertensive Patients

Tana Berisha, Laurence Seidel, Vinciane Dideberg, Laurent E. Weekers, Francois Jouret. ULiege Transplant Group. *Universite de Liege, Liege, Belgium.*

Background: The risk of developing an intracranial aneurysm (ICA) is quadrupled in autosomal dominant polycystic kidney disease (ADPKD) compared with the general population, with a prevalence of ~13%. Some risk factors have been suggested in the ADPKD population, such as family history of ICA, *PKD1* genotype, smoking, hypertension and female gender. A systematic screening for ICA during the pre-transplant work-up enabled us to study (i) the prevalence and (ii) the risk factors for ICA in ADPKD patients with end-stage renal disease (ESRD).

Methods: The presence of an ICA was systematically sought in all ADPKD patients undergoing a pre-transplant work-up between 01/2002 and 12/2023 in our center. The clinical, genetic and radiological parameters, as well as comorbidities, were statistically compared between the 2 groups of patients with *versus* without ICA, with an uncertainty level of 5%.

Results: Our cohort included 169 patients, 81 of whom were women (47.9%). The median age at first dialysis and at transplantation was 52.4 [46.7; 62.7] and 54.8 [49.1; 64.1] years respectively. There were 27 pre-emptive transplants, and 30 patients still on the waiting list. Median body mass index was 25.9 [23.1; 29.2] kg/m^2. Hypertension and/or diabetes were diagnosed in 167 (98.8%) and 57 (33.7%) patients, respectively. The median age at diagnosis of hypertension was 41.4 [31.3; 50.4] years. Left ventricular hypertrophy was detected in 75 patients (46%). Smoking was found in 98 (58%) patients. A family history of ICA was reported in 35 patients (23%). Molecular confirmation of PRAD was carried out in 57 patients, 43 of whom had a *PKD1* variant, 8 *PKD2* and 6 others. In this cohort of 169 transplant candidates with ADPKD, the prevalence of ICA reached 11.2%. These 19 patients with ICA were significantly taller than ICA-negative patients: 176 ± 9 *vs* 170 ± 9 cm, p=0.015. Blood pressure levels were significantly higher in ICA-positive patients (systolic: 152 ± 15 *vs* 136 ± 18 mmHg, p=0.0002; diastolic: 86 ± 11 *vs* 81 ± 12 mmHg, p=0.11).

Conclusions: ICA is a frequent complication of ADPKD, which is associated with higher height and systolic hypertension. The other above-mentioned risk factors were not statistically confirmed in our retrospective monocentric cohort including ESRD patients.

SA-PO604

Genetic Mutation Type and Cerebral Aneurysm Screening in Patients with ADPKD

Noella Ahn,[1] Evgenia Preka,[3] Joshua K. Mulligan,[2] Daniel P. Gale.[2,1] *[1]Royal Free London NHS Foundation Trust, London, United Kingdom; [2]University College London, London, United Kingdom; [3]Paris Centre de Recherche Cardiovasculaire, Paris, France.*

Background: Subarachnoid haemorrhage (SAH) is a devastating complication of Autosomal Dominant Polycystic Kidney Disease (ADPKD) due to increased rate of intracranial aneurysm (IA) formation in this population compared to the general population. The cause of IA formation is thought to be due to *PKD1* and *PKD2* gene mutation however, genetic risk factors or a geneotype-phenotype relationships are unclear unlike the correlation seen in renal manifestations of ADPKD. We report outcomes of our targeted screening of patients with personal or positive family history of IA or SAH with a five-yearly scans at a single large tertiary centre, alongside their genetic variants, to identify genetic risk factors or the presence of genotype-phenotype relationships in IA formation.

Methods: A retrospective review of 701 ADPKD patients in Royal Free Hospital between January 2012 to October 2022. Their medical records were reviewed for the development of IA, SAH, adherence to screening policy and their genetic tests.

Results: Of the 701 patients, 127 (18.1%) underwent screening as per the local guideline. 12 (1.7%) were eligible for screening but had not been screened. Within those screened, 21 (16.5%) had IA with zero SAH in this group. Of those unscreened, 8 (1.4%) had IA and 17 (3.0%) had SAH. Of the 701, 499 (71.2%) had genetic tests with clinically diagnostic variants in *PKD1* in 260 (52.1%) with 169 truncating mutations, *PKD2* in 102 (20.4%) with 78 truncating mutations, other genes in 78 (15.6%) and no reportable findings in 59 (11.8%). In 46 patients with IA or SAH, 33 (71.7%) had genetic tests of whom 21 (63.6%) had *PKD1* which 13 were truncating, 6 (18.2%) had *PKD2* which 4 were truncating, 6 (18.2%) had no genetic variants reported. These figures did not differ significantly from the overall patient cohort. 11 (8.6%) of the 127 screened patients received intervention for their aneurysms.

Conclusions: Cerebral aneurysm screening is a key part of ADPKD management. Amongst the screened group, no SAH were observed, although this did not differ significantly from the event rate of the unscreened group. The lack of evidence of increased risk of IA or SAH in those with truncating *PKD1* mutations suggest that the mechanism mediating this manifestation of ADPKD differs from the somatic loss of the normal allele that is thought to be important in kidney cyst formation and hence renal failure in ADPKD.

SA-PO605

Ryanodine Receptor 3 (RYR3) as a Candidate Modifier of Aneurysm Formation in ADPKD

Kasturi Roy,[1] Ashima Gulati,[3] Jianlei Gu,[1] Melissa M. Shaw,[1] Zhaoxia Sun,[1] Whitney Besse,[1] Terry J. Watnick,[2] Stefan Somlo.[1] *[1]Yale University School of Medicine, New Haven, CT; [2]University of Maryland, College Park, MD; [3]Children's National Hospital, Washington, DC.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the primary inherited cause of kidney failure, caused by mutations in *PKD1* or *PKD2*. Among its extrarenal manifestations, intracranial aneurysms (ICA) pose a significant mortality risk, with a prevalence approximately five times higher than the general population, and further elevated when a family member has ADPKD and ICA. We hypothesize that the development of ICA in ADPKD involves one or more genetic modifiers in addition to the germline PKD mutation.

Methods: To investigate this hypothesis, we established a cohort comprising individuals with ADPKD and ICA, alongside controls. Whole exome sequencing (WES) was performed to identify germline PKD mutations and to assess for enrichment of genes or pathways with rare genetic variants in those with ADPKD and ICA vs. control cases. To investigate candidate targets, a zebrafish model with *pkd2* mutation (*pkd2*^{hi4166Tg}) was employed. Candidate modifiers were inactivated using CRISPR/Cas9 system and scored for intracranial hemorrhage (IH) without knowledge of genotype.

Results: We identified *RYR3* as having increased occurrence of rare predicted deleterious missense variants in ICA-ADPKD cases compared to ADPKD controls without known ICA (p=2.75e-8; OR=11.6). Given this enrichment of *RYR3* variants within the cohort, we proceeded with a secondary validation screen in zebrafish models. *ryr3* was inactivated by CRISPR/Cas9 in heterozygous *pkd2*^{hi4166Tg} fish and both acute and germline transmission of *ryr3* knockout (*ryr3*$^{-/-}$) were examined. Acute *ryr3*$^{-/-}$ resulted in a 2-fold increase in brain bleeds while germline *ryr3*$^{-/-}$resulted ~4-fold increase in brain bleeds in heterozygous *pkd2*^{hi4166Tg} fish compared to respective *ryr3*$^{+/+}$ controls observed at 56 hpf. Imaris analysis showed a 0.6-fold reduction in vascular branching in *ryr3*$^{-/-}$; *pkd2*$^{hi4166Tg/+}$ fish compared to *ryr3*$^{+/+}$; *pkd2*$^{hi4166Tg/+}$ fish.

Conclusions: *RYR3* is a potential modifier of vascular integrity in the context of ADPKD mutations. Further replication and validation studies are warranted.

Funding: Other U.S. Government Support

SA-PO606

Genetic and Clinical Characterization of Patients with ADPKD and Intracranial Aneurysms: The PKD-VASC Cohort

Puja Patel,[1] Whitney Besse,[2] Ashima Gulati,[11] Melissa M. Shaw,[2] Jon D. Blumenfeld,[3] York Pei,[7] Berenice Y. Gitomer,[4] Ronald D. Perrone,[5] Yasar Caliskan,[6] Hayne C. Park,[12] Alan S. Yu,[8] Neera K. Dahl,[9] Frederic F. Rahbari-Oskoui,[10] Stefan Somlo,[2] Terry J. Watnick.[1] *[1]University of Maryland Baltimore, Baltimore, MD; [2]Yale University School of Medicine, New Haven, CT; [3]Rogosin Institute, New York, NY; [4]University of Colorado Anschutz Medical Campus, Aurora, CO; [5]Tufts Medical Center, Boston, MA; [6]Saint Louis University School of Medicine, St Louis, MO; [7]University Health Network, Toronto, ON, Canada; [8]The University of Kansas Medical Center, Kansas City, KS; [9]Mayo Clinic Minnesota, Rochester, MN; [10]Emory University School of Medicine, Atlanta, GA; [11]Children's National Research & Innovation Campus, Washington, DC; [12]Hallym University Kangnam Sacred Heart Hospital, Yeongdeungpo-gu, Seoul, Republic of Korea.*

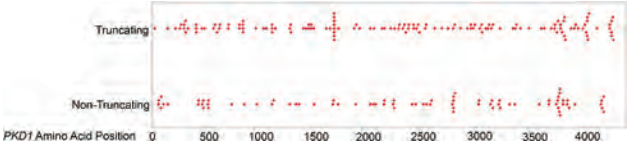
Background: ADPKD is associated with a ~4-5-fold increase in the prevalence of intracranial aneurysm (ICA) compared with the general population. This risk is intensified ~4-fold in ADPKD families with a history of ICA suggesting an inherited predisposition.

Methods: To investigate the genetic underpinnings of ICA in ADPKD, we assembled an international cohort of individuals with ADPKD and ICA: the PKD-Vasc cohort. We collected clinical data and DNA for whole exome sequencing (WES) from 289 self-referred participants or colleague-referred de-identified cases with both ADPKD and ICA.

Results: The PKD-Vasc cohort is ~70% female and 46% had either a ruptured ICA or required neurosurgical intervention. The remaining 54% had an unruptured ICA of at least 2mm and 22.5% had more than one ICA. Most participants (85%) had a family history of ADPKD and 38% had a family history of ADPKD with ICA. Of note 19% had a history of ICA in a family member without a diagnosis of ADPKD. Most participants (89%) were hypertensive, most had never smoked cigarettes, and a minority (18%) had ESKD at the time of their ICA diagnosis. As has been reported, most unruptured ICA were small (<5mm) and located in the middle cerebral, internal carotid, and anterior communicating arteries. WES identified a *PKD1* mutation in 220/289 (76%), a *PKD2* mutation in 38/289 (13%) and there was no causative mutation detected in 11%. A small number of cases had disease caused by minor ADPKD genes. These cases were excluded from primary analysis. Among participants with truncating *PKD1* variants, 55% had a ruptured ICA or an ICA requiring intervention. We looked at the distribution of truncating and non-truncating *PKD1* mutations and we found that variants were scattered along the gene with no obvious genotype/phenotype correlation.

Conclusions: Genetic modifiers in the setting of *PKD1/PKD2* may influence the risk of ICA. The PKD-Vasc cohort will be a valuable tool for investigating this question.

Funding: Other U.S. Government Support



Distribution of PKD1 mutations plotted against their amino acid location within the PKD1 protein.

SA-PO607

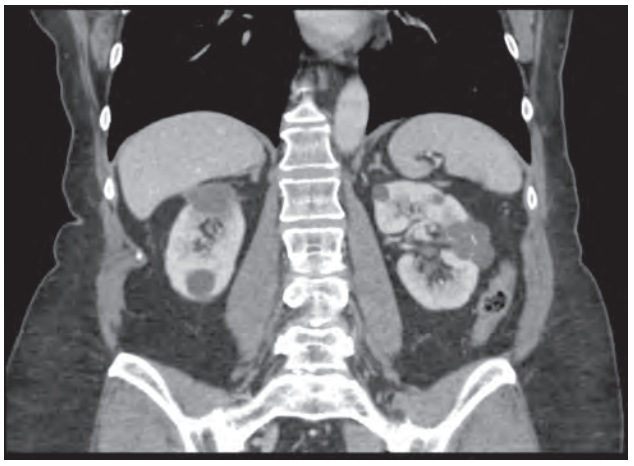
Unraveling Rarity: Atypical Presentation of Polycystic Kidney Disease

Jessica E. Lowe,[1] Angelina Edwards.[1,2] *[1]Houston Methodist Hospital, Houston, TX; [2]Division of Kidney Disease, Hypertension and Transplantation. Houston Methodist Hospital, Houston, TX.*

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder commonly associated with mutations in *PDK1* and *PDK2* and presents with enlarged kidneys seen on imaging due to cyst formation, typically classified by the Mayo Clinic Imaging Classification. However, genetic testing increasingly identifies other pathogenic variants leading to a spectrum of ADPKD. We present a case of an individual with poorly controlled hypertension and bilateral renal cysts whose imaging was not concordant with ADPKD but ultimately was positive based on genetic testing.

Case Description: A 73-year-old Caucasian woman with history of resistant hypertension presented for evaluation of elevated serum creatinine. One year prior, a CT scan performed for evaluation of abdominal pain showed incidental bilateral renal cysts. She was referred to Urology for further evaluation and underwent drainage of an 8 cm right renal cyst, without significant improvement in blood pressure control or abdominal pain. She then presented to nephrology clinic for referral for elevated creatinine and concern for chronic kidney disease. Laboratory testing revealed creatinine 1.51 mg/dL, blood urea nitrogen 31 mg/dL, and no proteinuria. Given the atypical cysts, genetic testing was pursued. Results confirmed pathogenic variant in the *IFT140* gene, a rare cause of atypical ADPKD.

Discussion: Biallelic mutations in *IFT140* are known to cause Mainzer-Saldino syndrome, a severe ciliopathy that causes skeletal and kidney abnormalities including cysts. However, monoallelic *IFT140* loss of function variants have been emerging as a cause of atypical ADPKD beyond *PKD1*/*PKD2*, associated with large renal cysts, mild renal insufficiency, few liver cysts, and unknown extra-renal manifestations. This case highlights the critical role of genetic testing, particularly when imaging is equivocal, and may help with in widening the group of atypcial ADPKD-spectrum disorders.



Sagittal CT image of bilateral renal cysts

SA-PO608

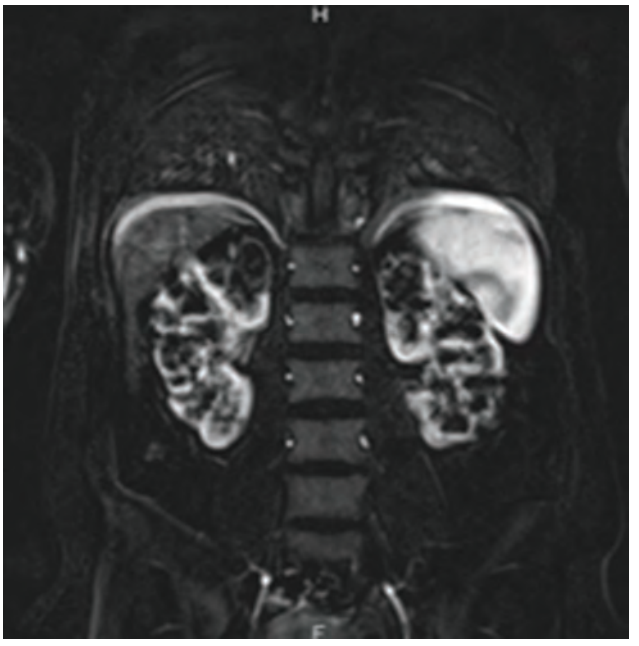
Cerebral Aneurysm in an Adult with Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Songul Onder, Terry J. Watnick. *University of Maryland School of Medicine, Baltimore, MD.*

Introduction: Intracranial aneurysms (ICA) are seen in 8-12 % of patients with autosomal dominant polycystic kidney disease (ADPKD). There are only a few case reports of ICA in autosomal recessive polycystic kidney disease (ARPKD) published to date.

Case Description: We present a 24-year-old woman with a genetic diagnosis of ARPKD. Abdominal MRI showed normal liver. The left kidney volume was 254.3 cc and the right kidney volume was 242.8 cc. She presented with chronic kidney disease stage 4 with eGFR of 22 ml/min. There was no family history of ADPKD or ICA. Her mother was with history of post traumatic subarachnoid hemorrhage (SAH). Due to intermittent headaches and family history of SAH, MRA of head was performed as part of kidney transplant evaluation. MRA revealed a 6 mmx5 mm unruptured ICA. aneurysm. She underwent to microsurgical clip reconstruction of unruptured anterior circulation aneurysm. Due to the negative family history of ADPKD and relatively small kidney size in the setting of advanced CKD, a whole exome panel genetic testing done. There were two heterozygous missense variants in the *PKHD1* gene.

Discussion: There are only a few cases with ARPKD and ICA reported within the last decade. To our knowledge, this is the 8th reported case of ICA with ARPKD. Previously reported cases presented with aneurysm rupture or were diagnosed during the investigation of neurologic symptoms. In addition, there have been two cases of extracranial aneurysm reported in ARPKD. Although most experts agree that ADPKD patients with a family history of ICA should undergo MRA screening, there are no recommendations for individuals with ARPKD. Taken together these cases suggest that there may be a link between ARPKD and vascular aneurysms that may warrant additional investigation. Screening patients for ICA in ARPKD should be considered in appropriate settings.



MRI of Abdomen

SA-PO609

Unveiling Kidney Disease Progression in Autosomal Recessive Polycystic Kidney Disease with Hypertension: Insights from the SS-PCK Rat Model

Aya Yoshimura,[1] Takahiro Shirozu,[1] Masanori Kugita,[1] Kanako Kumamoto,[1] Akiko Takizawa,[2] Melinda R. Dwinell,[2] Masumi Hirabayashi,[3] Kazuo Takahashi,[4] Harold M. Aukema,[5] Tamio Yamaguchi,[6] Shizuko Nagao.[1]
[1]Fujita Health University, Toyoake, Japan; [2]Medical College of Wisconsin, Milwaukee, WI; [3]National Institute for Physiological Sciences, Okazaki, Japan; [4]Fujita Health University School of Medicine, Toyoake, Japan; [5]University of Manitoba, Winnipeg, MB, Canada; [6]Suzuka University of Medical Science, Suzuka, Japan.

Background: The SS-PCK rat model offers a novel approach to investigate autosomal recessive polycystic kidney disease (ARPKD) complicated by salt-sensitive hypertension. This model integrates the mutated human orthologous *Pkhd1* allele from PCK rats into a Dahl salt-sensitive (SS) background, providing a unique platform to explore the influence of salt sensitivity on cyst formation and renal pathology. Intriguingly, male SS-PCK rats demonstrated significantly elevated blood pressure and renal pathology even under normal salt conditions, presenting distinct medullary cyst formation and reduced renal cyst size compared to PCK rats. Histological examination revealed small cysts in both cortical and medullary regions of SS-PCK kidneys, with renal function parameters declining progressively with age. We examined cellular mechanisms and the effects of an ACE inhibitor.

Methods: PCK and SD rats were obtained from The Jackson Laboratories Japan, Inc, and SS and SS-PCK rats were from Medical College of Wisconsin. Males were given standard chow with a normal salt level. Furthermore, Enalapril was administrated in SS-PCK rats from 5 to 16 weeks of age. Kidney samples were prepared for analytical studies.

Results: Expression analyses indicated decreased levels of Cytochrome P450 4 (*Cyp4*) family genes, including *Cyp4a3* and *Cyp4a8*, in SS-PCK rats compared to PCK rats, while epithelial sodium channel (*ENaC*) expressions, specifically β-*ENaC* and γ-*ENaC*, were significantly elevated. Additionally, Aquaporin-2 (*AQP2*) expression was notably higher in SS-PCK rats. Enalapril treatment in SS-PCK rats improved renal function, evidenced by significantly lower serum urea nitrogen and creatinine levels, along with increased *Cyp4a1* expression. Furthermore, Enalapril treatment reduced β-ENaC and γ-ENaC expressions, without affecting AQP2 expression.

Conclusions: These findings elucidate the complex mechanisms underlying ARPKD progression, emphasizing the involvement of the Cyp4 signaling pathway and Angiotensin II-induced ENaC expression. Enalapril treatment effectively mitigated hypertension and renal complications, highlighting the therapeutic potential of ACE inhibitors in managing ARPKD and hypertension-associated renal disease.

Funding: Government Support - Non-U.S.

SA-PO610

Disruption of the Human Cystin-1 Myristoyl-Electrostatic Switch Causes Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Chaozhe Yang,[1] Naoe Harafuji,[1] Jacob Watts,[1] Claire Moran,[5] Jenna Clements,[5] Kailyn M. Price,[5] Natalie Burrill,[2] Juliana S. Gebb,[2] Shelly Soni,[2] Edward R. Oliver,[2] Jill Savla,[2] Avni Santani,[3] Erum A. Hartung,[2] Rudolfo Karl,[4] Dagmar Wachten,[4] Zsuzsanna M. Bebok,[7] Landon S. Wilson,[6] Ljubica Caldovic,[1,5] Lisa M. Guay-Woodford.[1,2] *[1]Children's National Hospital, Washington, DC; [2]The Children's Hospital of Philadelphia, Philadelphia, PA; [3]Veritas Genetics, Danvers, MA; [4]Universitatsklinikum Bonn, Bonn, Germany; [5]The George Washington University School of Medicine and Health Sciences, Washington, DC; [6]The University of Alabama at Birmingham Department of Pharmacology and Toxicology, Birmingham, AL; [7]The University of Alabama at Birmingham Department of Cell Developmental and Integrative Biology, Birmingham, AL.*

Background: Autosomal recessive polycystic kidney disease (ARPKD; MIM#263200) is primarily caused by pathogenic variants in *PKHD1*. The *Cys1*$^{cpk/cpk}$ (*cpk)* mouse expresses a renal lesion that closely phenocopies ARPKD. *Cys1* encoded cystin is a myristoylated protein that traffics to the primary cilium and the nucleus, where it regulates gene expression.

Methods: Clinical characterization of siblings with ARPKD and Cystin-1$_{G2S}$ variant. Bioinformatics analysis of mammalian cystin sequences. Immunofluorescence (IF) staining and optogenetic stimulation assay to determine subcellular localization of wild-type and mutant cystin. Tandem affinity purification (TAP) and mass spectroscopy (MS) to identify cystin-binding partners. Evaluation of cystin serine-17 (S17) phosphorylation.

Results: The homozygous Cystin-1$_{G2S}$ variant identified in the siblings is predicted to disrupt the G2 myristoylation site within the cystin MGxxxSx N-terminal motif. Alignment of 97 mammalian cystin sequences showed high conservation of a putative myristoyl-electrostatic switch that can regulate reversible protein binding to membranes. The conserved region includes the N-myristoylation site and an adjacent arginine-rich stretch flanked by S17 residues. Using IF staining and site-directed mutagenesis, we confirmed that S17 phosphorylation modulates cystin membrane association and intracellular trafficking. In turn, optogenetic activation of ciliary cAMP signaling reduced the cystin ciliary localization in a PKA-dependent manner. TAP-MS identified the protein phosphatase PPM1A as a cystin-interacting partner. Inhibition of PPM1A with sanguinarine impeded cystin S17 de-phosphorylation confirming functional interaction.

Conclusions: Our study demonstrates that cystin intracellular trafficking and nuclear function are regulated by a myristoyl-electrostatic switch mechanism, and further supports *CYS1* as a disease-causing gene for human ARPKD, providing the first mechanistic insight for disease pathogenesis.

Funding: NIDDK Support, Private Foundation Support

SA-PO611

Role of the Proto-oncogene c-KIT in Tuberous Sclerosis Complex Renal Cystogenesis

Sharon L. Barone,[1,2] Kamyar A. Zahedi,[1,2] Nathan Zaidman,[3] Marybeth Brooks,[1,2] Manoocher Soleimani.[1,2] Soleimani Lab. *[1]University of New Mexico Health Sciences Center, Albuquerque, NM; [2]Veterans Health Administration, Albuquerque, NM; [3]University of New Mexico School of Medicine, Albuquerque, NM.*

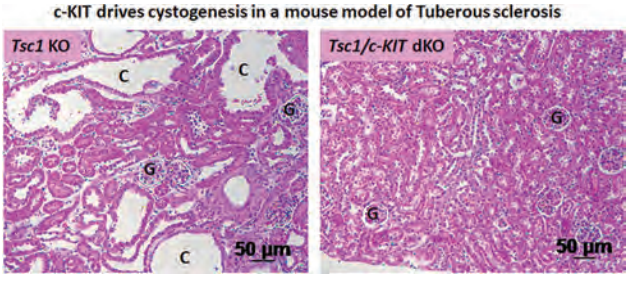
Background: Tuberous sclerosis complex (TSC) is caused by mutations in *TSC1* or *TSC2* genes. In the kidney, TSC presents with cysts and angiomyolipomata that can lead to renal failure. The cyst epithelium in TSC mouse models and in TSC patients is comprised of A-intercalated (AIC) cells. Deletion of Foxi1 abrogates the kidney cysts in TSC.

Methods: To identify the molecules critical to kidney cystogenesis in TSC, RNAseq analyses were performed in *Tsc1*KO (which display many cysts) and *Tsc1/Foxi1*dKO (that display no cysts) vs. WT mice. The mRNA and protein expression of differentially expressed transcripts (DET) was confirmed, their localization was ascertained and the effect of their ablation on cystogenesis was determined.

Results: RNAseq identified c-*Kit* as a vigorously up-regulated DET in the kidneys of *Tsc1*KO mice, with a profound downregulation in *Tsc1/Foxi1*dKO mice. Confirmatory analyses proved robust expression of c-*Kit* in the kidneys of *Tsc1*KO mice, and immunofluorescence microscopy showed its localization to the basolateral membrane of cyst epithelia. Ablation of c-*Kit* gene in *Tsc1*KO mice by generating *Tsc1/c-Kit* dKO mice completely abrogated kidney cysts and inhibited mTORC1 activity. Expression of c-*Kit* in M1 CCD cells increased their proliferation, along with the activation of ERK1/2 and RSK1 signaling. The potentiation of ERK1/2 and RSK1 signaling were also demonstrated in kidneys of *Tsc1*KO mice and inhibited in *Tsc1/c-KIT* dKO mice.

Conclusions: Activation of c-KIT, a proto-oncogene and a resident molecule in AIC cells in *Tsc1*KO mice point to a novel pathway that disrupts the regulation of mTORC1 function and leads to unregulated cell growth and cystogenesis in TSC. The effect of *c-Kit* ablation in *Tsc1*KO mice strongly suggest that the modulation of KIT signaling may be a novel treatment for TSC renal cysts.

Funding: NIDDK Support, Other NIH Support - NIH/NHLBIT32HL007736, Veterans Affairs Support, Private Foundation Support



SA-PO612

Role and Mechanism of mTOR Signaling Activation in Nephronophthisis Type I

Liangzhong Sun, Baojuan Zou, Qianying Wang. *Southern Medical University Nanfang Hospital, Guangzhou, China.*

Background: Nephronophthisis (NPH), a group of autosomal recessive ciliopathies, is a lead- ing genetic cause of renal failure in children and adolescents. Over 20 NPH genes have been identified, among which *NPHP1* is the most frequent. It is generally believed that dysfunctional ciliary signa- ling leads to uncontrolled cellular growth and proliferation by activating the mTOR signaling, which leads to organ cystogenesis such as polycystic kidney disease (PKD). However, NPH is prominently featured by extensive tubular atrophy and interstitial fibrosis, whereas its cystic load are relatively mild. Hence, it's of great interest whe- ther abnormal ciliary signaling in NPH activates mTOR signaling along with cell proliferation similar to PKD.

Methods: In this study, wild-type and *NPHP1*-knockout (*NPHP1*$^{-/-}$) MDCK cells, an well as mice, are used to explore the role of mTOR signaling in NPH and figure out whether mTOR inhibition can rescue renal lesions in NPH type I.

Results: *NPHP1* deletion activates mTOR signaling in MDCK cells and mouse kidneys, featured by a significant increase of p-S6/S6 and p-4EBP1/4EBP1. Expression of Deptor, a natural mTOR inhibitor, declines singularly with *NPHP1* deletion in vitro and in vivo. Proliferation decreased in *NPHP1*$^{-/-}$ cells and mRNA analysis showed an alteration in p21, with a 1-fold higher expression compared with wild-type. Knockdown of Deptor, which activates mTOR signaling, promotes proliferation in wild-type but not in *NPHP1*$^{-/-}$ MDCK cells. p21 expression was induced in *NPHP1*$^{-/-}$ but suppressed in wild-type MDCK cells by Deptor-siRNA. *NPHP1*$^{-/-}$ MDCK cells shows increased resistance to rapamycin, which further reduces Deptor expression. Rapamycin alleviates renal fibrotic, cystic, and inflammatory lesions of *NPHP1*$^{-/-}$ mice and improves their renal function. However, it brings about adverse effects, including loss of weight gain and aggravated cell senescence in kidney.

Conclusions: mTOR signaling is excessively activated in renal tubular cells of NPH type I, due to a decreased expression of Deptor. Despite mTOR activation, *NPHP1* deficiency restrains proliferation in renal tubular cells. Rapamycin significantly alleviates renal fibrotic, cystic and inflammatory lesions and improves renal function of *NPHP1*$^{-/-}$ mice. However, adverse effects include loss of weight gain and aggravated cell senescence of kidney in rapamycin treatment.

Funding: Government Support - Non-U.S.

SA-PO613

NBL1 Correlates with Kidney Disease in a Mouse Model for Alport Syndrome, but Is Not Causal

Courtney Willey,[1,2] Rei Bufi,[1] Abigail Brackett,[1] Susan M. Sheehan,[1] Ron Korstanje.[1,2] *[1]The Jackson Laboratory, Bar Harbor, ME; [2]The University of Maine, Orono, ME.*

Background: Alport syndrome (AS) is a rare genetic condition that often results in progressive loss of kidney function and end-stage kidney disease. Although the causal genes for AS are well characterized, individuals with AS still display a wide range of variation in kidney function and age of onset, suggesting the presence of modifiers. Recently, several studies identified levels of neuroblastoma suppressor of tumorigenicity 1 (NBL1) in the blood to be strongly and independently associated with more severe progression of diabetic nephropathy and IgA nephropathy. We decided to investigate the role of NBL1 in a genetically diverse population of Diversity Outbred (DO) mice with X-linked Alport Syndrome (DO-XLAS) and found a significant correlation between NBL1 and kidney function. However, it is still unclear whether NBL1 is causal or consequential to kidney disease.

Methods: To test causality, we created an NBL1 knockout (KO) mouse model and confirmed that heterozygous (HET) animals have significantly lower NBL1 levels in their blood compared to wildtype (WT). We then induced AS by breeding a mutated Col4a5 allele into our NBL1 KO mice and investigated differences in kidney function and damage.

Results: We did not find a difference in GFR or albuminuria between HET and WT animals, suggesting that NBL1 does not have a causal role in disease progression. We are performing a genetic analysis on 600 DO-XLAS mice to identify the drivers of increased plasma NBL1 levels and better understand the underlying mechanism and relationship with kidney disease.

Conclusions: NBL1 does not appear to have a causal role in disease progression and increased NBL1 levels are more likely to be a consequence of kidney disease. The exact role of NBL1 in kidney disease remains to be elucidated.

Funding: NIDDK Support, Other NIH Support - 5T32GM132006

SA-PO614

Systematic Metabolomics Study in the Serum and Urine of a Mouse Model of Alport Syndrome

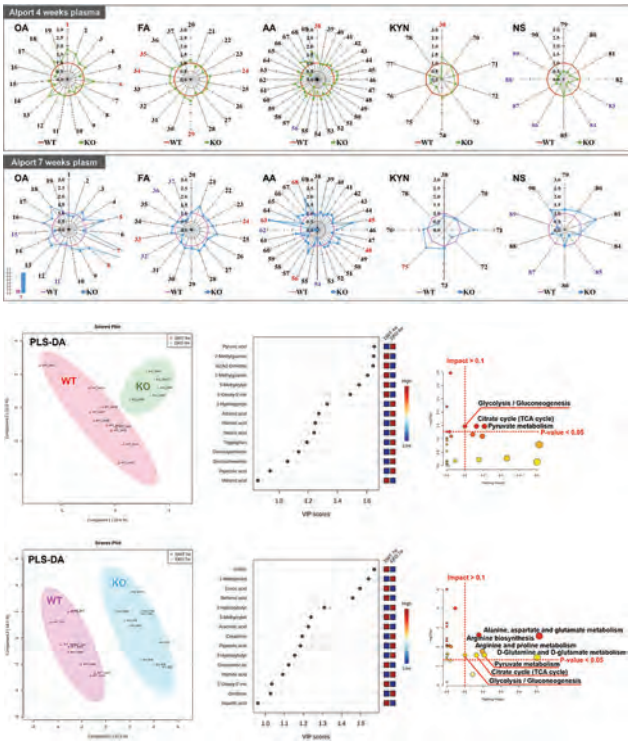
Hong Sang Choi,[1,2] Sang Heon Suh,[1,2] Chang Seong Kim,[1,2] Eun Hui Bae,[1,2] Seong Kwon Ma,[1,2] Soo Wan Kim.[1,2] *[1]Chonnam National University Medical School, Gwangju, Gwangju, Republic of Korea; [2]Chonnam National University Hospital, Gwangju, Gwangju, Republic of Korea.*

Background: Alport syndrome (AS) is a hereditary nephropathy characterized by progressive kidney disease and hearing loss, which is caused by mutations in the genes encoding the alpha 3, 4, or 5 chain comprising the type IV collagen that forms glomerular basement membrane. There is a limited understanding of the metabolites related to progressive kidney disease in AS.

Methods: Metabolomics study was performed for monitoring of biomarker and altered metabolism related with disease progression in serum and urine from male *Col4a3* knockout mice and age-matched wild-type mice at 4 and 7 weeks. Profiling analysis for metabolites, including organic acids, amino acids, fatty acids, kynurenine pathway metabolites, and nucleosides in the serum and urine was performed using gas chromatography-tandem mass spectrometry and liquid chromatography-tandem mass spectrometry combined with star symbol patterns and partial least squares discriminant analysis (PLS-DA).

Results: A total of 29 and 44 metabolites from the serum and urine of *Col4a3*$^{-/-}$ mice were distinguished from those of wild-type mice, respectively, based on P-value (< 0.05) and variable importance in projection scores (> 1.0) of PLS-DA. In the serum of 4 weeks AS mice, metabolites of the glycolysis, gluconeogenesis, pyruvate metabolism and TCA cycle were increased, whereas those involved in alanine, aspartate and glutamate metabolism, arginine and proline metabolism, arginine biosynthesis and D-glutamine and D-glutamate metabolism were altered in serum of 7 weeks AS mice.

Conclusions: Altered metabolic pathway and metabolites are associated with progressive kidney disease in AS.



SA-PO615

Dysregulated Glomerular Proteins in 1-Day-Old Col4a3 Knockout Mice

Vanessa S. De Gregorio,[1] Akanchaya Rana,[2] Emine B. Caparali,[1] Samantha Ricardo,[1,3] Ana Konvalinka,[1,4] Moumita Barua.[1,4] *[1]Toronto General Hospital Research Institute, Toronto, ON, Canada; [2]Princess Margaret Hospital Cancer Centre, Toronto, ON, Canada; [3]Institute of Medical Science, University of Toronto, Toronto, ON, Canada; [4]Division of Nephrology, University Health Network, Toronto, ON, Canada.*

Background: Alport syndrome (AS) is a hereditary disorder caused by pathogenic variants in *COL4A3*, *COL4A4* and/or *COL4A5*, encoding the α3α4α5 chains of type IV collagen typically expressed in the mature glomerular basement membrane (GBM) of the kidney. In AS due to truncating variants, podocytes do not form the α3α4α5(IV) basement membrane and instead, there is persistence of the flexible α1α1α2(IV) trimer normally present during development. To understand the earliest mechanisms of disease in AS, we elected to study glomerular changes in *Col4a3* $^{-/-}$ (knockout; KO) mice at postnatal-day 1 (P1), when trimer switching is occurring.

Methods: P1 *Col4a3* KO and wildtype mouse glomeruli were isolated using Dynabeads. Protein extracts from glomerular samples were subjected to mass spectrometry. Pathway analysis was performed using Gene Ontology and protein interactors were identified using STRING.

Results: More than 1,000 proteins from glomerular extracts were significantly dysregulated in P1 female KO compared to wildtype. In assessing protein-protein interactions between significantly dysregulated proteins, those with the greatest number of interactors included ACTB, GAPDH, ATP5B, EEF2, and SDHA. Over 70 pathways were identified as significantly different in female P1 KO compared to wildtype. Notably, these pathways were related to K63-linked deubiquitinase activity, alternative mRNA splicing, via the spliceosome, establishment or maintenance of transmembrane electrochemical gradient, actin filament binding, and NF-κB binding. In P1 male KO compared to wildtype, 17 proteins from glomerular extracts were identified as significantly dysregulated but no significantly different pathways were identified.

Conclusions: Pathways related to alternative splicing, cell maintenance, actin binding, and inflammation are dysregulated in the glomerulus at the earliest stage of disease in *Col4a3* KO mice. These dysregulated pathways will be further explored to understand biological mechanisms in disease and to inform therapeutic development in the future.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO616

Development and Assessment of Col4a5 Missense Mouse Model of Alport Syndrome

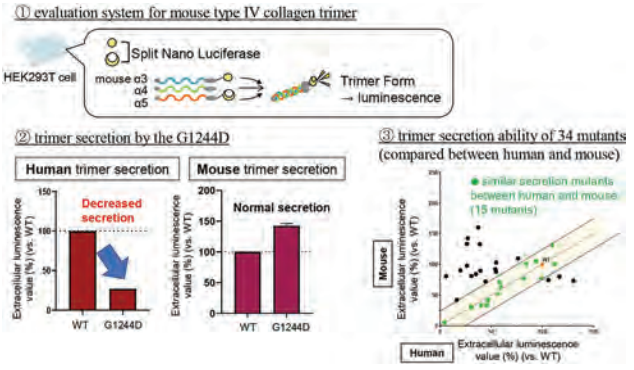
Aimi Owaki, Yuya Sannomiya, Jun Horizono, Mary Ann Suico, Tsuyoshi Shuto, Hirofumi Kai. Dept of Molecular Medicine. *Kumamoto University, Kumamoto, Japan.*

Background: Mutation in type IV collagen α3, α4 or α5 results in the abnormal formation and secretion of α345(IV) trimer causing Alport syndrome (AS), a progressive hereditary nephritis. Missense mutations in α5(IV) are the most frequently reported. Current symptomatic therapies are unable to prevent the progression to end-stage renal failure. Therefore, the development of novel drugs is needed but is hampered by the lack of a mouse model of missense mutant AS that enables the evaluation of drug efficacy.

Methods: We previously developed a nanoluciferase-based trimer evaluation system (Cell Chem Biol 2018) and focused on the human α5(IV) G1244D mutation, whose secretion is significantly decreased and is reported to be clinically severe. We generated mutant mice using the kick-in method that can generate knock-in mice.

Results: The results showed that while the α5(IV) G1244D mutation causes severe renal disease in humans it does not cause renal disease in mice, indicating a phenotypic divergence. To elucidate the cause of this species difference, we constructed an evaluation system for mouse type IV collagen trimer. We assessed clinically reported 34 missense mutations in α5(IV) and evaluated the trimer function. The results showed that the trimer secretion by the G1244D mutation in mouse α5(IV) was normal, unlike that in human. Furthermore, when the trimer secretion ability of 34 mutants was compared between human and mouse, only 15 mutations showed similar secretion. These results indicate that the trimer behavior of human and mouse mutants does not necessarily coincide. Furthermore, we are currently generating mouse models of missense mutations that cause a significant decrease in mouse trimer secretion. Phenotypic analysis will be performed to provide much-needed information for a new AS missense mouse model.

Conclusions: Human and mouse α345(IV) trimer behavior diverges, necessitating a thorough assessment of each mouse mutant to produce a missense mouse model that recapitulates the clinical phenotypes of human AS missense mutant pathologies.



SA-PO617

Nephrotic Syndrome-Associated Variants Dysregulate TRIM8 Functions in Biomolecular Condensates, Cell Adhesion, and Glomerular Injury

Vineeta Sharma,[1] Hari R. Singh,[2] Sunwoo Hong,[1] Alexander Rubin,[1] David A. Ball,[1] Victoria C. Gauntner,[1] David J. Salant,[3] Friedhelm Hildebrandt,[1] Amar J. Majmundar.[1] *[1]Boston Children's Hospital, Boston, MA; [2]Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany; [3]Boston University Chobanian & Avedisian School of Medicine, Boston, MA.*

Background: C-terminal truncating TRIM8 variants (tripartite motif containing 8) cause human nephrotic syndrome (NS) and mislocalization of TRIM8 from nuclear bodies. However, the effects of these variants at the physicochemical, molecular, cellular and whole organism levels are poorly understood.

Methods: Tagged TRIM8 constructs were expressed in U2OS cells or immortalized human podocytes. Time lapse fluorescence microscopy, immunofluorescence staining, confocal microscopy, coimmunoprecipitation and immunoblotting were performed. CRISPR/Cas9-mediated gene editing in immortalized human podocytes and in mice was performed to generate disease mimicking C-terminal truncating variants.

Results: Tagged TRIM8 nuclear bodies exhibited rapid fluorescence recovery after photobleaching (T-half=10s) and fusion consistent with liquid-like condensates in U2OS cells. Supporting this classification, as bulk tagged TRIM8 concentration increased to 4 μM, its concentration within nuclear bodies increased up to 20 μM while remaining low outside (<2 μM). In silico algorithms (ESpritz, IUPred, PrDOS, PONDR) detected intrinsically disordered region (IDR) features in the TRIM8 C-terminus. In correlation, truncation of the IDR impaired TRIM8 condensate formation in vitro. In immortalized podocytes, NS-associated C-terminal IDR truncating variants impaired tagged TRIM8 polyubiquitination and 26S-dependent degradation, suggesting potential gain-of-function. Endogenous proteasome components (PSMD4, PSMD12) co-localized with tagged wildtype TRIM8—but not NS mutants—in condensates, implicating these condensates in proteasome-dependent TRIM8 regulation. TAK1 is a published TRIM8 substrate that regulates cell adhesion and murine podocyte homeostasis. TAK1 co-localized with wildtype TRIM8 in condensates and coimmuoprecipitated, which NS variants reduced. Rather, TRIM8 NS mutant protein caused reduced TAK1 protein levels. At the cellular level, CRISPR-mediated TRIM8 variants led to reduced immortalized podocyte adhesion. As compared to wildtype controls, Trim8 mutant mice developed increased albuminuria after nephrotoxic serum injury.

Conclusions: TRIM8 forms proteasome-associated biomolecular condensates that may impact its regulation of TAK1, cell adhesion, and podocyte injury.

Funding: NIDDK Support, Private Foundation Support

SA-PO618

Pathogenic Variants in NFATC1 and NFATC3 Can Cause Nephrotic Syndrome

Sue Zhang,[1] Hariel G. Peters,[1] Megan Chryst-Stangl,[1,2] Guanghong Wu,[1,2] Rasheed A. Gbadegesin,[1,2] Brandon M. Lane.[1,2] *[1]Duke University, Durham, NC; [2]Duke Molecular Physiology Institute, Durham, NC.*

Background: Nephrotic syndrome (NS) is a kidney condition that is characterized by disruption of the glomerular filtration barrier leading to proteinuria and progressive kidney damage. While dysregulation of the calcineurin (*CN*) signaling pathway has been implicated in the pathogenesis of NS, the role of pathogenic variants in calcineurin signaling pathway (CNP) genes in the etiology of genetic NS remains unclear. To address this, we performed whole exome sequencing on >500 children with nephrotic syndrome and performed targeted analysis of 67 CNP genes.

Methods: We carried out whole exome sequencing in >500 children with NS and use previously published filtering algorithm to identify pathogenic variants in CNP genes in these children. To determine the pathogenicity of the variants on podocyte homeostasis, we used lentiviral shRNA and plasmid transduction to modulate *NFATC1* and *NFATC3* gene expression in immortalized podocyte cell lines and examined changes in cell migration using automated live-cell imaging.

Results: We identified two variants in NFAT genes (*NFATC1* c.insC2463; p.G821fs and *NFATC3* c.G1519A; p.A507T) in two families with steroid resistant nephrotic syndrome (SRNS). The two variants segregate with disease in the family. Knockdown of NFATC1 and NFATC3 in immortalized human podocyte cell lines reduces podocyte motility and disruption of cytoskeleton regulation.

Conclusions: Our data suggests that *NFATC1* and *NFATC3* are new candidate genes for nephrotic syndrome.

Funding: NIDDK Support

SA-PO619

Transgenic Human Nephrin in Drosophila Nephrocytes Facilitates Variant Analysis

Julia M. Wolff,[1] Konrad Lang,[1] Julian Milosavljevic,[1] Mengmeng Chen,[1] Martin Helmstädter,[1] Sami Bahar,[3] Maximilian H. Ulbrich,[2] Tobias F. Hermle.[1] *[1]University Medical Center Freiburg Department of Medicine, Divison of Nephrology, Freiburg, Germany; [2]University of Freiburg, Faculty of Medicine, Department of Anatomy and Cell Biology, Department of Neuroanatomy, Freiburg, Germany; [3]An-Najah National University, Faculty of Medicine and Health Sciences, Department of Medicine, Nablus, Palestine, State of.*

Background: Nephrin, the key structural protein of the slit diaphragm, is encoded by *NPHS1*. Pathogenic variants in this gene are the primary cause of congenital nephrotic syndrome. About 400 variants have been described but functional characterization is curtailed by the lack of slit diaphragm formation within *in vitro* models. A molecularly conserved and accessible slit diaphragm can be found in the *Drosophila* nephrocyte model.

Methods: Human nephrin was transgenically expressed in *Drosophila* nephrocytes in combination with silencing of the nephrin ortholog *sns*. Nephrocytes were phenotypically characterized by immunofluorescence, tracer studies, and transmission electron microscopy including immunogold labeling. Automated image annotation was employed to quantify distinct staining patterns. A novel nephrin variant was identified in a patient with congenital nephrotic syndrome using whole exome sequencing. Transgenes reflecting this novel and another variant of *NPHS1*, previously identified as deleterious, were generated for functional analysis in *Drosophila*.

Results: Transgenic human nephrin assembled into a complex linear architecture in nephrocytes after silencing of *Sns*. This suggests lateral clustering of nephrin into a macromolecular configuration within the podocyte-like cells. Transgenic nephrin colocalized with the endogenous slit diaphragm protein Pyd, ortholog of ZO-1, suggesting a hybrid multi-protein complex. Upon transgenic co-expression of murine Neph1, nephrin similarly recruited its binding partner. However, the linear nephrin exhibited an atypical, tubular ultrastructure and did not adequately direct actin remodeling, underscoring the need for further indispensable co-factors. The linear nephrin assembly was disrupted in transgenes reflecting canonical patient variant S366R as well as novel variant V1241G, which affects the nephrin C-terminus. Automated annotation of Pyd staining patterns provided a quantitative read-out for investigation of these patient-derived variants.

Conclusions: Transgenesis of *NPHS1* in nephrocytes is a viable approach for investigation of basic steps of slit diaphragm formation and functional characterization of patient variants in *NPHS1*.

Funding: Government Support - Non-U.S.

SA-PO620

Mutation in NUP155 Causes Activation of Autophagy in Podocytes through Retraining the YAP in the Cytoplasm to Induce Podocyte Loss and Subsequent Nephrotic Syndrome

Anqun Chen, Zhuoyuan Jiang. *The Second Xiangya Hospital of Central South University, Changsha, China.*

Background: Hereditary nephrotic syndrome (HNS) is a clinical syndrome characterized by increased permeability of the glomerular filtration barrier. Recently, mutations in a class of genes encoding nucleoporins (NUPs) have been found to cause NS.

Methods: First, whole-exome sequencing, and Sanger sequencing were performed in Chinese familial patients with NS. A Drosophila model with Nup154 (the NUP155 ortholog) knockdown (KD) was established. NUP155-Knockdown stably transfected cell lines of human immortalized podocytes were constructed and the rescued experiments were performed by overexpressing the mutants and wild NUP155 in NUP155-KD cells. Co-IP mass spectrometry was used to explore the downstream mechanism of *NUP155* mutation causing NS.

Results: We identified mutations in the *NUP155* gene, coding an inner ring sub-unit of the nuclear pore complex, in Chinese familial patients with NS, manifested as FSGS.

The missense variant (c.397G>T) results in p.Asp133Tyr. The other mutation in the splice region (c.4037+2T>C) led to four kinds of alternative splicing transcripts, all encoding premature proteins. The intensity of NUP155 in the patients' kidneys was diffusely decreased compared with the control. Meanwhile, podocyte-specific expression of WT1 and NPHS2 was significantly reduced, showing podocyte loss. In adult Nup154-KD drosophila, the number of nephrocytes is decreased. NUP155-KD podocytes exhibit reduced proliferation and migration abilities and heightened susceptibility to injury. Recovering two mutant proteins cannot rescue these phenotypes. The variants in NUP155 affected the interaction with NUP133 and NUP93, causing disrupted nuclear pore complex (NPC) assembly. Additionally, autophagy activation, an increase in YAP phosphorylation, and a reduction of nuclear YAP localization in NUP155-KD podocytes and proband kidney, suggesting NUP155 is essential for YAP nuclear import and aberrant nuclear localization of YAP leads to increased autophagy.

Conclusions: We show that the mutations in *NUP155* could cause NS, which led to abnormal NPC, retraining nucleocytoplasmic shuttling of YAP, and activation of autophagy, eventually leading to dysplasia and impaired function of glomerular podocytes.

SA-PO621

In Vivo Mechanisms of LAMB2 Variants in Isolated Nephropathy: Insights from Knock-In Mouse Models

Mika Okutsu,[1,2] Taeko Hashimoto,[5] Yamato Kikkawa,[3] Akira Shimizu,[4] Yutaka Harita.[1] *[1]Tokyo Daigaku, Bunkyo-ku, Japan; [2]Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan; [3]Tokyo Yakka Daigaku, Hachioji, Japan; [4]Nihon Ika Daigaku, Bunkyo-ku, Japan; [5]Yamagata Daigaku, Yamagata, Japan.*

Background: Loss of function mutations of *LAMB2* encoding laminin β2 (β2) cause Pierson syndrome. Typical *LAMB2* mutations found in Pierson syndrome are truncating mutations or mutations that inhibit extracellular secretion of β2. In recent years, a series of missense variants within specific domains of β2 (e.g. p.G699R) have been identified in cases of isolated nephropathy without extrarenal symptoms. The allele frequency of these mutations varies greatly regionally, with p.G699R being more frequent in East Asians (0.0085). We previously demonstrated that these variants have biochemical features distinct from loss-of function mutations causing Pierson syndrome. The variants found in isolated nephropathy preserved extracellular secretion of β2, but enhanced interactions between β2 and components in the glomerular basement membrane (GBM) (Kikkawa et al. JCI Insight 2021). To date, the in vivo effects of these variants are unknown.

Methods: We generated knock-in (KI) mice with the mutation corresponding to the *LAMB2* p.G699R. We investigated the phenotype of KI mice, including the effects of adriamycin (ADR)-induced nephropathy.

Results: In the homozygous KI mice, β2 secretion in the GBM was maintained, which supports the results of the in vitro analysis. Long-term observation showed increased proteinuria in some homozygous KI mice. After ADR administration, KI mice had significantly more proteinuria than wild type mice. KI mice showed significantly increased mesangial area enlargement, focal thickening of the GBM and FSGS lesions in the renal tissue after ADR administration, and markedly enlarged subendothelial lumen and abnormal endothelial fenestrae by the electron microscopy. RNA-seq analysis suggests that KI mice have more intense changes in tissue inflammation than wild-type mice.

Conclusions: *LAMB2* p.G699R exerts changes in the plasticity of glomerular injury by altering the adhesive capacity of the GBM, and could act as a risk factor for the development of renal disease.

SA-PO622

Deletion of Gapvd1 Sensitizes Murine Podocytes to Adriamycin-Induced Injury

Lea Gerstner, Dominik Spitz, Julian Milosavljevic, Lina L. Kampf, Marc Brettel, Camille Lempicki, Martin Helmstädter, Wibke Bechtel-Walz, Gerd Walz, Tobias F. Hermle. *Renal Division, Department of Medicine, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany.*

Background: DNA variants in *GAPVD1*, an activator of endosomal protein Rab5, are a monogenic cause of nephrotic syndrome. The encoded protein interacts with nephrin and previous studies in podocyte-like nephrocytes in *Drosophila* suggested a crucial function for slit diaphragm integrity. However, the role of this gene remained unexplored in mammalian animal models.

Methods: To generate a conditional knockout, we established a *Gapvd1* allele with loxP sites flanking exon 4. Gapvd1$^{fl/fl}$ mice were crossed with *Nphs2*-Cre for podocyte-specific deletion and *Six2*-Cre for deletion in nephron progenitor cells. To apply toxicity stress, sixteen week old *Nphs2*-Cre; Gapvd1$^{fl/fl}$ mice and control animals (Gapvd1$^{fl/fl}$) were treated with intravenous Adriamycin. For phenotypic characterization, we determined serum creatinine and urinary albumin-to-creatinine ratios (ACR) and further applied histochemistry, immunofluorescence and electron microscopy.

Results: In situ hybridization indicated a successful conditional knockout of Gapvd1. However, unstressed animals using *Nphs2*-Cre or *Six2*-Cre for deletion of *Gapvd1* revealed no overt phenotype including changes in glomerular architecture, renal function and urinary ACR. In contrast, Adriamycin-injected *Nphs2*-Cre, *Gapvd1*$^{fl/fl}$ mice presented with elevated proteinuria compared to the control group. Periodic acid-Schiff staining of kidney sections indicated focal segmental glomerulosclerosis in stressed knockout animals, which further exhibited significantly less WT1-positive podocytes per glomerulus in immunofluorescence. Analysis of glomeruli with scanning electron microscopy revealed shortened and partially fused foot processes and transmission electron microscopy confirmed foot process effacement.

Conclusions: *Gapvd1* seems dispensable for podocyte homeostasis in unstressed mice, likely due to compensation by another Rab5-regulating protein. However, loss of Gapvd1 sensitized animals to Adriamycin-induced podocyte injury resulting in podocyte loss and proteinuria.

Funding: Government Support - Non-U.S.

SA-PO623

Characterization of Steroid-Resistant Nephrotic Syndrome-Associated Motor Domain Mutations in MYO1E

Kazi Sayeeda, Mira Krendel. *SUNY Upstate Medical University, Syracuse, NY.*

Background: Myosin1e (Myo1e) is a cytoskeletal protein highly expressed in podocytes and localized to cell-cell junctions/slit diaphragm complexes, which are required for these cells' structural and functional integrity. As podocytes are the final gatekeepers of the filtration barrier, they rely on the actin cytoskeletal organization to maintain their intricate architecture and respond to mechanical stresses from fluid flow and capillary distension. Myo1e binds to actin and may modulate actin cytoskeletal assembly and dynamics. Mutations in the gene encoding Myo1e have been found in patients with steroid-resistant nephrotic syndrome (SRNS) and focal segmental glomerulosclerosis (FSGS). In this project, we have analyzed recently identified *MYO1E* mutations associated with SRNS/FSGS (Warejko et al. Clin J Am Soc Nephrol 2018, Krendel et al. Pediatr Nephrol 2023) that have not been functionally characterized.

Methods: EGFP-tagged Myo1e constructs (mutant or wild-type (WT)) were introduced into the Myo1e-KO podocyte-derived cells via adenovirus-mediated transduction to test the effects of these mutations on Myo1e localization and podocyte junctional properties.

Results: Similarly to Myo1e localization in the WT podocytes, WT Myo1e was enriched at cell-cell contact points and colocalized with actin. Unlike WT Myo1e, the mutants showed primarily cytoplasmic subcellular localization. One of the mutants, G562R, was partially localized at the cellular junction, but its enrichment at the cell-cell junctions was significantly lower than that of the WT. Although none of the mutants colocalized with actin at the podocyte-podocyte intersection, their expression as the sole source of Myo1e did not affect the actin enrichment at those sites.

Conclusions: WT Myo1e frequently localizes at the cell-cell contacts and may play a role in regulating junctional integrity. Mis-localization of the Myo1e mutants that we have studied indicates that these disease-associated mutations disrupt the ability of Myo1e to perform its functions at the sites of cell-cell contact.

Funding: NIDDK Support

SA-PO624

Potentiated JAK-STAT Signaling Differentiates Stem Cell-Derived Podocytes of Patients with APOL1-Associated FSGS from Those of Healthy Carriers with a High-Risk APOL1 Genotype

Somenath Datta, Karen Soldano, Daniel P. Silas, Guojie Li, Sarah Nystrom, Melanie E. Garrett, Allison Ashley-Koch, Opeyemi A. Olabisi. *Duke University, Durham, NC.*

Background: An estimated 20% of the 6 million Black Americans who carry *APOL1* high-risk genotype (HRG) will develop APOL1-kidney disease (AKD) in their lifetime, while the remaining 80% will remain free of AKD. There is an urgent, unmet need for predictive biomarkers that could distinguish the 20% at risk of AKD prior to the onset of the disease. Podocytopathy, including FSGS, is a key manifestation of AKD. We hypothesized that genetically-encoded differences in podocyte in response to AKD triggers, such as interferons, could explain the incomplete penetrance of AKD among carriers of HRG.

Methods: To identify potential differences in interferon-gamma (IFN-γ)-induced podocyte gene expression that might lead to risk or protection from AKD, we generated iPSC-podocytes from 21 adults with HRG and biopsy-proven FSGS (high-risk (HR) cases) and 12 adults with HRG and normal eGFR and no proteinuria (HR controls). The iPSC-podocytes were treated with or without IFN-γ followed by whole genome transcriptomic analysis and compared with published transcriptome of laser-captured glomeruli of FSGS cases from the NEPTUNE cohort.

Results: We discovered that IFN-γ induced higher expression of several genes including *CXCL9, CXCL10 CXCL11,* and *APOL1* in iPSC-podocytes of HR cases versus HR controls. The expression of these genes is regulated by JAK-STAT signaling. At baseline, there were no differences in JAK-STAT signaling between HR cases and HR controls. Our comparative analysis of iPSC-podocyte transcriptome with published glomeruli transcriptome from the NEPTUNE cohort confirmed that elevated JAK-STAT signaling is a common feature of HR cases in iPSC-podocytes and glomeruli.

Conclusions: Our results identified potentiated JAK-STAT-mediated gene expression including chemokines in human iPSC-podocytes, which could serve as a predictive biomarker of APOL1-kidney disease. This promising finding suggests that measurement of IFN-γ-induced chemokine expression in iPSC-podocytes of HRG carriers could serve as a tool for predicting the likelihood of future incidence of AKD. Validation in a larger sample size would facilitate clinical translation of this finding.

Funding: NIDDK Support, Other NIH Support - NIH Common Fund

SA-PO625

Differential Pathway Activation by APOL1 G1 and G2 Variants in Induced Pluripotent Stem Cell (iPSC)-Derived Endothelial Cells: Insights from Proteomic Analysis

Miguel Carracedo, Meztli Matadamas-Guzman, Bojana Lazovic, Ramesh Tati, Orsolya Bilkei-Gorzo, Grzegorz Sienski, Pernille B. Laerkegaard Hansen, Mark Lal. *AstraZeneca, Mölndal, Sweden.*

Background: Apolipoprotein-L1 (APOL1) risk variants (RV), named G1 and G2, are associated with increased risk of chronic kidney disease (CKD) in people of African ancestry. Recent evidence has highlighted the role of APOL1 RVs as drivers of endothelial cell (EC) activation. However, the specific molecular mechanisms driving APOL1-mediated EC activation in humans and the differences between G1 and G2 variants remain unknown.

Methods: We employed CRISPR Xential, a novel CRISPR/Cas9-based method to select and enrich for cells with two edited copies of a gene of interest, to engineer induced pluripotent stem cells (iPSCs) with inducible APOL1 expression. iPSCs were differentiated into ECs and treated with doxycycline for 24 or 48 hours to induce expression of APOL1 variants G0 (control), G1, and G2. We assessed EC viability and conducted global proteomics and bioinformatics analyses.

Results: APOL1 induction reduced EC viability in a time-dependent manner, most significantly with G2 followed by G1 and G0. Proteomics analysis revealed more protein changes (119) after 24h in the G2 expressing ECs when compared with G1 (75) and G0 (6). After 48h, G2 and G1 showed similar amount of differentially regulated proteins, 154 and 175, respectively, whereas G0 expressing ECs presented 44. Among these proteins, IL8 and GLUT1 were upregulated in all conditions. Pathway enrichment analysis revealed inflammatory response and TNFa pathways to be common between G1 and G2 expressing ECs. Interestingly, after 48h, G1 expression led to changes in pathways related with EMT transition and hypoxia, whereas G2 enhanced pathways related with cell cycle and DNA replication.

Conclusions: Our findings corroborate APOL1's role in EC activation and unveil distinct pathways influenced by G1 and G2 variants, underscoring their differential contribution to endothelial dysfunction.

Funding: Commercial Support - AstraZeneca

SA-PO626

APOL1 Induction Increases Cytosolic Calcium in 293 Cells but Not HeLa or Isogenic Induced Pluripotent Stem Cell (iPSC)-Derived Podocytes

Korey Bartolomeo, John F. O'Toole, Yaping Gu, Leslie A. Bruggeman, Uyen Tran, Oliver Wessely, John R. Sedor. *Cleveland Clinic, Cleveland, OH.*

Background: Coding variants in APOL1 are associated with a spectrum of kidney diseases, but the biology underlying this genetic association remains uncertain. The channel function of APOL1 imparts its trypanolytic activity and *in vitro* models demonstrate APOL1 can insert into lipid bilayers conferring a non-selective cation transport without variant-dependent differences. Recently overexpression of APOL1 kidney disease variants in cell culture models of 293 cells were shown to increase intracellular calcium. However, these model systems rely on APOL1 overexpression that may lead to aberrant APOL1 trafficking and cytotoxic phenotypes that may not reflect the pathogenesis of human APOL1 kidney disease. Our data suggests that APOL1-mediated cytosolic calcium elevations are cell line dependent.

Methods: We utilized isogenic induced pluripotent stem cell (iPSC) with APOL1-G0 and gene edited to G1 or G2, and differentiated to podocytes using a differentiation protocol developed in our lab. We also used tetracycline regulated G0, G1 or G2 in HeLa or 293 cells. We performed surface biotinylation with streptavidin pulldowns, SYTOX microplate viability assays and fura-2 microplate calcium assays after 6h (293), 24h (HeLa and iPSC) and 72h (iPSC) of tetracycline or IFN-γ induced APOL1 expression.

Results: In 293 cells APOL1 localizes to the plasma membrane after 6h of induced expression and is associated with an increase in intracellular calcium in a variant independent manner ($p < 0.05$ Kruskal-Wallis). In HeLa cells after 24 hours of APOL1 induction APOL1 does not localize to the plasma membrane and there is no APOL1 mediated cell death ($p > 0.05$ Kruskal-Wallis). Similarly, iPSC-derived podocytes do not have APOL1 localization at the plasma membrane even after 72h of IFN-γ induction and there is no variant-dependent differences in cell viability or intracellular calcium at 24h, 48h or 72h ($p > 0.05$ Kruskal-Wallis).

Conclusions: Our data indicates that overexpression of APOL1 in 293 cells results in plasma membrane insertion and variant independent intracellular calcium elevations and cell death. On the other hand, tetracycline induced APOL1 induction in HeLa cells and IFN-γ APOL1 induction in isogenic iPSC derived podocytes do not have APOL1 plasma membrane localization, intracellular calcium differences or cytotoxicity.

Funding: NIDDK Support, Private Foundation Support

SA-PO627

The Novel MYH9 Variant, c.1270C>G, p.Arg424Gly, Causes Epstein-Fechtner Syndrome by the Modification of Nonmuscular Myosin IIA Contraction

Lena Pollinger,[1] Johannes N. Greve,[5] Sara Kaliman,[6] Shada Abuhattum,[6] Martin Kräter,[6] Antje Wiesener,[4] Francesca Pasutto,[4] Melanie Grosch,[1] Jan René Haak,[1] Cathiana Kolb,[1] Christoph Daniel,[3] Kerstin U. Amann,[3] Mario Schiffer,[1,2] Dietmar J. Manstein,[5] Michael S. Wiesener,[1,2] Tilman Jobst-Schwan.[1,2] *[1]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [2]Research Center On Rare Kidney Diseases (RECORD), University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [3]Department of Nephropathology, Institute of Pathology, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [4]Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [5]Institute for Biophysical Chemistry, Fritz-Hartmann-Centre for Medical Research, Hannover Medical School, Hannover, Germany; [6]Max-Planck-Institut fur die Physik des Lichts, Erlangen, Germany.*

Background: The *MYH9* gene encodes the heavy chain of non-muscular myosin IIA (NMMIIA). Mutations in *MYH9* cause autosomal-dominant monogenic disorders that include macrothrombocytopenia, proteinuric kidney disease and elevated liver enzymes.

Methods: Whole exome sequencing was performed in a patient with end-stage renal disease. Segregation analysis in all affected family members was done by Sanger sequencing. Patient tissue biopsies were analyzed. Primary skin fibroblasts were used in migration assays. Immortalized human podocytes were transfected and stained for NMMIIA. Blood smears were inspected by light microscopy and stained for NMMIIA. Blood cell deformability was analyzed by microfluidic technique. Functional analysis of recombinant protein was performed using *in vitro* motility assays.

Results: We identified the putative deleterious *MYH9* variant *c.1270C>G*, p.Arg424Gly (ACMG class 4, CADD score 22, evolutionary highly conserved), heterozygous in 5 affected family members. The variant affects the O-helix in the upper 50k subdomain of the motor domain, which contributes to the conformational coupling between the actin binding site, the nucleotide binding site and the lever arm region. All 5 patients presented with proteinuria, elevated liver enzymes and intermittent thrombocytopenia. No Döhle-like bodies and NMMIIA-positive conglomerates were found in granulocytes. However, granulocytes had modified deformability compared to healthy controls. Patient skin fibroblasts showed elongated morphology and reduced surface area. *MYH9 c.1270C>G* transfected immortalized human podocytes displayed NMMIIA -positive conglomerates. Further functional assays revealed a 22% increase in motility at molecular level compared to wild-type protein.

Conclusions: We identified a novel variant in the *MYH9* gene in a family with hepato-renal disease as the major phenotype of the intrafamilial syndrome. Functional data confirmed the predicted pathogenicity of this variant by identifying altered mechanical properties and highlighted the multicellular function of the protein, even though typical intracellular findings in granulocytes could not be detected.

Funding: Government Support - Non-U.S.

SA-PO628

Biallelic Variant in ENPP6 Alters Choline Metabolism in Humans and Conveys Loss of Enzymatic Function In Vitro

Nils D. Mertens,[1,2] Kuniyuki Kano,[4] Gijs A. Franken,[1,2] Sherif M. El Desoky,[3] Jameela A. Kari,[3] Shirlee Shril,[1,2] Friedhelm Hildebrandt.[1,2] *[1]Boston Children's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]King Abdulaziz University Hospital, Jeddah, Saudi Arabia; [4]Tokyo Daigaku Daigakuin Yakugakukei Kenkyuka Yakugakubu, Bunkyo-ku, Japan.*

Background: Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT) are the leading cause of chronic kidney disease before 25 years of age. In previous studies, we have proposed *ENPP6*, encoding a membrane-bound choline-specific phosphodiesterase, as a potential novel candidate gene for monogenic CAKUT.

Methods: Segregation analysis of a potentially pathogenic *ENPP6* variant (c.727A>G; p.M243V) was performed via exome sequencing in a family with CAKUT and correlated with choline metabolites in urine samples measured via mass spectrometry. A fluorescent probe cell assay was established to quantify the enzymatic activity of full-length human wildtype and mutant ENPP6.

Results: In parents and four brothers, we detected a potentially pathogenic homozygous *ENPP6* variant (c.727A>G; p.M243V) in a boy with posterior urethral valves and neurogenic bladder. Both parents and two brothers are unaffected heterozygous

carriers. One brother is biallelic wildtype. We collected urine samples from the whole family and detected the phosphocholine metabolite beta-GPC exclusively in the urine of the affected boy. These findings are consistent with urine analysis on published *Enpp6* knockout mice. Next, we demonstrated that wildtype full-length human *ENPP6* transiently overexpressed in HEK293 cells catalyzes the release of strongly fluorescent 2-Me-4OMe TG from a non-fluorescent synthetic probe (TG-mPC) consisting of the ENPP6 substrate phosphocholine linked to the fluorophore Tokyo green in a time and concentration-depended manner. Mutated ENPP6^{M243V} had reduced release of fluorescent 2-Me-4OMe TG compared to wildtype ENPP6.

Conclusions: This study provides functional evidence that biallelic variants in *ENPP6* can cause human CAKUT.

Funding: NIDDK Support, Private Foundation Support

SA-PO629

A Novel CLC-Kb Pore Mutation Disrupts Glycosylation and Associates with Distal Tubular Remodeling

Robin H. Lo,[1] Yogita Sharma,[1] Victor N. Tomilin,[2] Holly A. Deremo,[1] Wuxing Dong,[1] Vivek Charu,[1] Neeraja Kambham,[1] Kerim Mutig,[3,4] Oleh Pochynyuk,[2] Vivek Bhalla.[1] *[1]Stanford University School of Medicine, Stanford, CA; [2]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX; [3]Charite Universitatsmedizin Berlin, Berlin, Germany; [4]Pervyj Moskovskij Gosudarstvennyj Medicinskij Universitet Imeni I M Secenova, Moskva, Russian Federation.*

Background: Bartter's and Gitelman's syndromes are inherited, monogenic autosomal recessive tubulopathies resulting in defects of renal electrolyte handling with a propensity for chronic kidney disease. One type of Bartter's syndrome involves inactivating mutations in *CLCNKB*, a gene encoding the chloride channel CLC-Kb expressed on the basolateral membranes of the thick ascending limb and the distal tubule. Here, we identified a family with a mixed Bartter's/Gitelman's phenotype and early-onset kidney failure and employing a candidate gene approach, discovered a novel mutation (ntG499T, G167C) in exon 6 of *CLCNKB* in the index patient.

Methods: The mutation was identified via Sanger and whole exome sequencing. Wild type and mutant *CLCNKB* plasmid constructs were generated and transfected *in vitro* for electrophysiological analysis via patch-clamp experiments. Wild type and mutant CLC-Kb N-link glycosylation patterns were analyzed by Endo H or PNGase F digestion and localization by cell surface biotinylation or subcellular fractionation. Nephrectomy samples from the index patient and healthy controls were used for histology, morphometry, and qualitative immunofluorescence.

Results: Compared to wild type CLC-Kb, the G167C mutant conducted less current. The G167C mutation also caused impaired N-linked CLC-Kb glycosylation. By targeted mutagenesis of potential CLC-Kb glycosylation sites, we demonstrated that complex N-linked glycosylation at Asn-364 glycosylation is required for proper channel function but not for its surface expression. Moreover, using other known CLC-Kb mutations, we deduced that lack of glycine rather than gain of cysteine is responsible for the findings. Morphologic evaluation of kidney biopsies revealed basolateral localization of mutant G167C CLC-Kb in cortical distal tubular epithelia. However, we detected attenuated expression of distal sodium transport proteins, changes in abundance of distal tubule segments, and hypokalemia-associated intracellular condensates from the index patient compared to control nephrectomy specimens.

Conclusions: We demonstrate a novel regulatory mechanism of CLC-Kb activity by glycosylation and demonstrate nephron remodeling caused by mutant CLC-Kb, with implications for renal electrolyte handling, blood pressure control, and kidney disease.

Funding: NIDDK Support, Private Foundation Support

SA-PO630

Characterization of a Novel Mutation Associated with Renal Tubular Acidosis

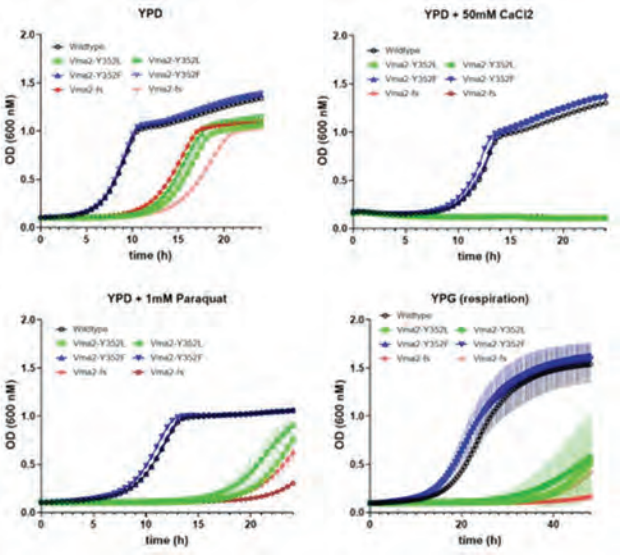
Christopher M. Bernert,[1] Bryce Mendelsohn,[2] Anne S. Salyer,[2] Anna K. Breen,[1] Brian Wasko.[1] *[1]Western University of Health Sciences College of Osteopathic Medicine of the Pacific-Northwest, Lebanon, OR; [2]Kaiser Permanente, Oakland, CA.*

Background: Primary Distal Renal Tubular Acidosis (dRTA) is a condition involving an impaired ability of the distal renal tubules to remove protons from blood. *ATP6V1B1* encodes a kidney specific protein subunit of the V-ATPase proton pump involved in acid secretion into urine. A patient with classic dRTA has been identified with a de novo single nucleotide polymorphism (SNP) in *ATP6V1B1*, resulting in a Phe365Leu mutation of uncharacterized pathogenicity. Evolutionary conservation between *Homo sapiens ATP6V1B1* and *Saccharomyces cerevisiae* (yeast) *VMA2* allows for the use of yeast to elucidate the impact of the novel *ATP6V1B1* mutation on V-ATPase function.

Methods: CRISPR/Cas9 was used to generate yeast strains expressing *VMA2* Tyr352Leu, which serves as an analogous mutation to *ATP6V1B1* Phe365Leu. Additional yeast strains were generated containing Tyr352Phe as well as a frameshift mutation for use as controls. V-ATPase function was assessed by assaying *S. cerevisiae* growth under conditions previously shown to inhibit growth of V-ATPase mutants. The growth assays included control YPD media, YPD with 50 mM $CaCl_2$, YPD with 1 mM paraquat (forming reactive oxygen species), and glycerol containing YPG media (to induce respiration).

Results: *S. cerevisiae* haploid strains containing a *VMA2* Tyr352Leu mutation were found to exhibit growth phenotypes consistent with a complete loss of V-ATPase activity, including an inability to grow when exposed to 50 mM $CaCl_2$, an inability to grow under respiratory conditions, and sensitivity to reactive oxygen species. Yeast containing the humanized *VMA2* Tyr352Phe mutation were not found to display these phenotypes.

Conclusions: Our results provide supportive evidence that a Phe365Leu mutation within *ATP6V1B1* results in a loss of function and thus is highly probable to contribute to dRTA.



Growth of haploid yeast *VMA2* mutants under various assay conditions.

SA-PO631

Identification of Pathogenetic Pathways in Autosomal Dominant Tubulointerstitial Kidney Disease Due to Mutations in REN

Celine Schaeffer,[1,2] Maurizio De Fusco,[1] Elena Pasqualetto,[1] Caterina Scolari,[1,3] Santo Diprima,[1] Claudia Izzi,[4,5] Francesco Scolari,[4,5] Luca Rampoldi.[1,2] Molecular Genetics of Renal Disorders Unit. *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Universita Vita Salute San Raffaele, Milano, Italy; [3]Universita degli Studi di Torino, Torino, Italy; [4]Universita degli Studi di Brescia, Brescia, Italy; [5]Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia, Brescia, Italy.*

Background: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) is a rare genetic disorder leading to progressive chronic kidney disease. ADTKD is caused by mutations in different genes including *REN* encoding for renin. Renin is a secreted protein composed of 3 domains: the leader peptide allowing its insertion in the endoplasmic reticulum (ER), a pro-segment regulating its protease activity, and the mature part. Mutations in mature renin lead to ER retention of mutant protein and to a late onset disease, while mutations in the leader peptide, associated with defective ER translocation, and mutations in the pro-segment, accumulating in the ER-to-Golgi compartment, lead to early onset disease.

Methods: We used transiently and stably transfected cells to further investigate the effect of mutations on renin trafficking and performed RNA sequencing on cells expressing renin isoforms under an inducible Tet-ON promoter.

Results: We demonstrate an unprecedented effect of mutations in the leader peptide and pro-segment leading to full or partial mistargeting of mutated protein to mitochondria. The pre-pro sequence of renin, carrying mutation in either the leader peptide or the pro-segment, is necessary and sufficient to drive mitochondrial rerouting. In turn, this leads to mitochondrial import defect and mitochondria fragmentation. Transcriptome profiling of cells expressing mutant renin isoforms in the leader peptide (L16R, L16del), pro-segment (E48K) and mature part (L381P) clearly shows that mutants mislocalised to mitochondria induce similar cellular responses that are only partly overlapping with the ones observed for the ER retained mutant. Specific responses are consistent with the observed trafficking defect (i.e ER stress and Unfolded Protein Response for the ER retained mutant and signs of mitochondrial dysfunction in mutants misrouted to mitochondria). However, all mutants converge to the induction of similar stress molecules as CHOP.

Conclusions: Despite the different cellular phenotype (mitochondrial vs ER localisation) and the severity of the associated clinical features, all ADTKD renin mutations converge to similar kidney damage. We are currently investigating how this endpoint is reached starting from stress signals emerging from the ER and mitochondria.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO632

Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Is Indispensable for Maintaining Mitochondrial Homeostasis in Uromodulin-Associated CKD

Yili Fang,[1] Chuang Li,[1] Chenjian Gu,[1] Anuradhika Puri,[1] Meredith Jackrel,[1] Maria Lindahl,[2] Ying M. Chen.[1] *[1]Washington University in St Louis, St Louis, MO; [2]Helsingin yliopisto, Helsinki, Finland.*

Background: Autosomal dominant tubulointerstitial kidney disease due to uromodulin mutations (ADTKD-*UMOD*), a leading hereditary kidney disease, has no targeted therapies. UMOD is expressed in the thick ascending limb (TAL) tubules, and mutant UMOD causes endoplasmic reticulum (ER) stress. Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a novel ER resident molecular chaperone and ER stress-inducible secreted protein. The biological role of endogenous MANF in the regulation of mitochondrial function has not been studied.

Methods: CRISPR was utilized to generate the first *Umod* deletion mutation mouse model carrying *Umod* p.Y178-R186del, analogous to human H177-R185del, the most prevalent human mutation. To assess the function of MANF in ADTKD, tamoxifen-inducible TAL-specific MANF knockout mice were generated. Meantime, stable HEK cell line harboring WT or H177-R185del UMOD was established, and shRNA was employed to knockdown MANF *in vitro*. Bood urea nitrogen was monitored along the disease course. Immunoblotting, q-PCR and immunofluorescence staining were employed. Mitochondria function was assessed by electron transport chain protein expression, OROBOROS Oxygraphy system and Seahorse assay.

Results: MANF is induced in the TALs carrying the *Umod* deletion mutation. Genetic ablation of MANF in the mutant TALs suppresses phosphorylation of AMP-activated protein kinase (AMPK) and downstream expression of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) and forkhead box O3 (FOXO3) in isolated primary TAL cells, resulting in impaired mitochondrial biogenesis/oxidative phosphorylation and mitophagy, respectively. The *in vitro*results are in line with the *in vivo* findings. Consequently, MANF deficiency in TALs activates mitochondrial DNA leak-induced STING (stimulator of interferon genes) signaling and hyperinflammation, leading to accelerated renal fibrosis and kidney dysfunction in ADTKD.

Conclusions: For the first time, we discover that MANF is required to maintain mitochondrial homeostasis and acts as a critical molecular linker between ER and mitochondria homeostasis in ADTKD. The key role of MANF in mediating ER-mitochondria crosstalk may also have important implications in other protein misfolding diseases, such as Alzheimer.

Funding: NIDDK Support, Other NIH Support - R21 DK131557A1, Other U.S. Government Support

SA-PO633

Unraveling the Role of Mitochondrial Dysfunction in the Pathogenesis of Clc-k2-Deficient Bartter Syndrome Mice

Amir Zaidi, Emily Morrison, Yiwen Chen, Chih-Jen Cheng. Cheng Lab. *University of Iowa, Carver College of Medicine, Iowa city, IA.*

Background: Mutations in human ClC-Kb (Clc-k2 in mice) lead to Bartter syndrome (BS) type 3, a congenital renal tubulopathy. Our previous research showed the constitutive deletion of Clc-k2 in mouse kidneys hindered the postnatal development of thick ascending limbs (TALs) through mechanisms not yet fully understood. Our recent extracellular flux analysis revealed that low transport activity in renal tubules resulted in low mitochondrial mass and respiratory capacity. This alarming discovery prompted us to delve deeper into the mitochondrial functions in Clc-k2-deficient TALs and explore the potential of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α), the master activator of mitochondrial biogenesis, in rescuing Bartter syndrome.

Methods: We analyzed the mitochondrial biogenesis and bioenergetics in isolated TALs using mitochondrial DNA copy numbers, seahorse-based mitochondrial assays, and electron microscopy. We also conducted a comparative transcriptome analysis using isolated Clc-k2 KO vs. wild-type TALs. Uromodulin-positive TAL/DCT cells were pulled down and used for cell cycle and proliferation assays. Pseudohypoaldosteronism type 2 (PHA2) WNK4$^{D561A/+}$ mutant knockin mice and PGC1-α transgenic mice were crossed with Clc-k2 KO mice to rescue the transport activity/mitochondrial function, respectively. Mouse phenotypes then analyzed and compared.

Results: Clc-k2-deficient TALs had reduced mitochondrial-to-nuclear DNA ratio and mitochondrial respiratory capacities, indicating downregulated mitochondrial biogenesis and bioenergetics. Transcriptome analysis confirmed suppression of mitochondrial genes in Clc-k2-deficient TALs. These cells were prone to G1-S cell cycle transition and proliferation delay. PHA2 WNK4$^{D561A/+}$ mutant improved the mitochondrial mass/function, cell cycle, and proliferation of Clc-k2-deficient TAL cells and rescued the activity of NKCC2 and NCC cotransporter of Clc-k2-deficient mice. Overexpression of PGC1-α in Clc-k2 KO mice improved mitochondrial function of TAL, NKCC2/NCC activities, and BS phenotype.

Conclusions: Our results support that low transport activity suppresses mitochondrial biogenesis/bioenergetics in renal tubules, thereby aggravating renal salt wasting, cell cycle delay, and TAL hypoplasia in Clc-k2-deficient BS mice. Mitochondrial-targeting therapy could be promising to BS.

Funding: Other NIH Support - R01

SA-PO634

Novel Models to Study Fanconi Syndrome and CKD Due to Heterozygous GATMP341L Mutations

Daniel F. Arroyo Ariza,[1] Rhea Singal,[1] Andrew S. Allegretti,[2] Benjamin D. Humphreys,[1] Harald Jüppner,[2] Ignacio A. Portales Castillo.[1] *[1]Washington University in St Louis, St Louis, MO; [2]Massachusetts General Hospital, Boston, MA.*

Background: Autosomal dominant Fanconi syndrome due to *GATM* mutations (GATM-FS) presents during childhood with evidence of proximal tubular (PT) dysfunction and progresses to end stage kidney disease in adults. Kidney biopsies of patients with GATM-FS show PT injury and Arginine:glycine amidinotransferase (AGAT), the enzyme encoded by *GATM*, accumulates in PT mitochondria. Besides renal dysfunction, we found lower levels of guanidinoacetate (GAA) and creatine in patients with *GATM* P341L mutations. To further study the pathophysiology of this disease, we tested the enzymatic function of AGAT P341L using patient-derived cells, generated human kidney organoids and a novel Gatm^{P341L} mouse.

Methods: GAA synthesis by the AGAT mutant was measured in patient-derived immortalized lymphocytes using stable isotopes of arginine and glycine, and the effect of creatine on *GATM* expression was assessed in wild-type kidney organoids. We generated mice carrying the Gatm^{P341L} mutant, using CRISPR/Cas9 methodologies.

Results: In comparison to wild-type cells, GAA synthesis by patient-derived GATM$^{P341L+/-}$ LCL cells was reduced by ~50%, consistent with our findings of low GAA and creatine in plasma and urine of affected patients. Creatine supplementation (5 g daily) restored plasma creatine levels in a patient with GATM-FS, and in vitro creatine (10 mM) down-regulated AGAT expression in kidney organoids. At 4 weeks of age, Gatm$^{P341L/+}$ mice showed higher phosphate excretion than wild-type littermates (median Pi/Cre: 0.97 vs 0.42, $p<0.05$). At 8 weeks, blood urea nitrogen also tended to be higher in plasma of Gatm$^{P341L/+}$ vs wild-type mice, 66.5 vs 21.8 mg/dl in males.

Conclusions: Our results support the hypothesis of deficient creatine metabolism in GATM-FS and the possible use of low levels of GAA as biomarker of this disease. We now developed several promising experimental models, kidney organoids, LCLs, and Gatm$^{P341L/+}$ mice for evaluating the role of abnormal creatine metabolism in renal disease and the potential therapeutic effect of creatine supplementation in GATM-FS.

SA-PO635

Establishment of a Quantitative Evaluation System for Interferon Pathways in Patients with Lupus Nephritis

Jiahui Zhang, Yangyang Zhang, Ying Jin, Changming Zhang, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Jingling Hospital, Nanjing University School of Medicine, Nanjing, China.*

Background: The interferon (IFN) pathway is one of the important pathogenic factors of lupus nephritis (LN), however, there is currently a lack of unified and clear quantitative assessment scoring system for its expression level, making difficulties in its applications in clinical practice.

Methods: RNAseq of 271 LN patients (before IFN-inhibition: n=261; after IFN-inhibition: n=10) and 94 healthy controls were conducted. ROC analysis were used to analyze the best performing scoring model. Data distribution analysis were made by R-mclust.

Results: Pivotal IFN genes in LN were highly expressed in patients, and decreased after JAK inhibitor therapy (**Fig 1A)**. The analyses based on different datasets of LN patients resulted in two sets of genes, named 11-gene and 14-gene **(Fig 1B)**. The z-score algorithm was used to calculate IFN scores based on each gene sets. The set of 11-gene had the best performance as LN biomarkers, followed by 14-gene set. And the previous reported gene sets generated from wider spectrum of autoimmune diseases had relatively lower AUC values **(Fig 1C)**. Besides, the 11-gene score (IFN11) had bimodality of expression with different data distribution ranges and trends in different cells **(Fig 1D)**, indicating the necessity to establish different thresholds for whole blood and PBMCs, two common materials for clinical tests, and the bimodality can provide basis for threshold delineation.

Conclusions: It is very feasible to develop a specialized IFN scoring system for LN patients, and IFN11 has good clinical application prospects in assessing disease status, guiding treatment, and predicting the risk of recurrence in clinical practise.

Funding: Government Support - Non-U.S.

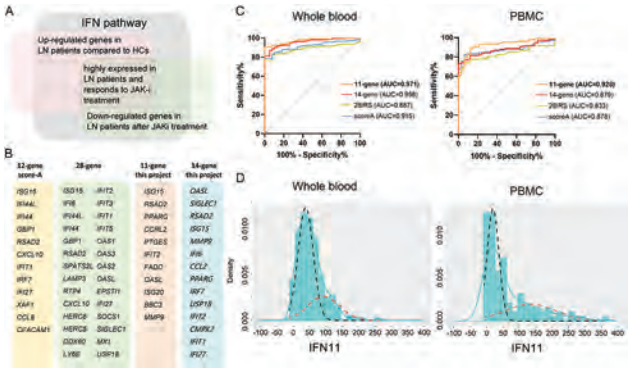


Fig 1. Comparison of LN-specific IFN scores.
A. The preliminary screening of characteristic genes in the IFN pathway through differential expression analysis. **B.** IFN gene sets previously reported (28IRS and score A) and obtained from this study (11-gene and 14-gene). **C.** ROC analysis of several IFN gene sets. **D.** The bimodality of 11-gene IFN score.

SA-PO636

Chromatin Conformation and Histone Modification Profiling across Human Kidney Anatomic Regions

Dian Li,[1] Haikuo Li,[1] Pierre Isnard,[1] Benjamin D. Humphreys.[1,2] *[1]Division of Nephrology, Department of Medicine, Washington University in St. Louis, St. Louis, MO; [2]Department of Developmental Biology, Washington University in St. Louis, St. Louis, MO.*

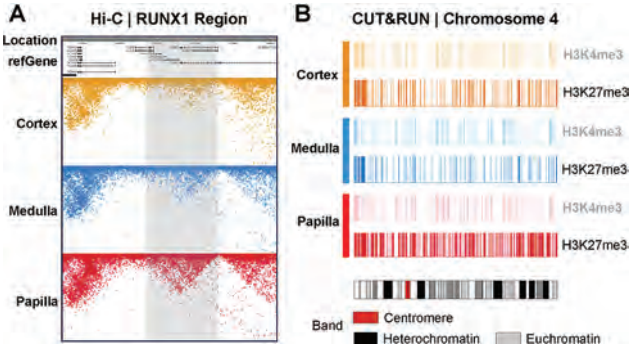
Background: Delineating human kidney anatomical structures using high-throughput transcriptomic methodologies has provided a deeper understanding of region-specific function and pathophysiology. Less is known concerning epigenetic mechanisms, such as 3D chromatin architecture and histone modification and how this changes in different kidney cell types and regions.

Methods: We leveraged our recently developed high-yield nuclei extraction method to simultaneously profile chromatin conformation capture with Hi-C and H3K4me3/H3K27 histone modification with Cleavage Under Targets and Release Using Nuclease (CUT&RUN) sequencing samples of human kidney cortex, medulla, and papilla dissected from a healthy donor. We also performed inter-study comparisons of 3 previously published CUT&RUN datasets.

Results: We generated 6 Hi-C and 18 CUT&RUN libraries, at an average depth of 578 million and 19 million reads. We built Hi-C chromatin contact maps for each kidney region at a resolution of 5,000 bp and inter-region difference maps. We observed that long-cis interactions (>20 kb apart), accounted for >50% of the contact events. Interestingly, we identified region-specific contact enrichments along with their marker genes (RUNX1, Fig. 1A). Regarding CUT&RUN, we detected that over 75% of H3K4me3 (enhancer) peaks were localized to the promoter regions, and 34% to 51% of H3K27me3 (repressor) peaks over distal intergenic regions. Similarly, we identified variations in peak abundances across different kidney regions, with the medulla accounting for the fewest peaks for both histone modifications (Fig. 1B).

Conclusions: We describe a comprehensive epigenetic landscape across human kidney anatomical regions. Importantly, we identified region-specific epigenetic modifications which further emphasizes at a molecular level the importance of segment-specific differentiation of the human kidney.

Funding: NIDDK Support



SA-PO637

Targeted Delivery of Small Interfering RNA (siRNA) to Proximal Tubule Cells in the Kidneys

Shiying Ding,[1] Kimberly R. Long,[2] Jeremy Cunniff,[1] Johnny Lucas,[1] Haojing Rong,[1] Adam Belanger,[1] Hongmei Zhang,[1] Jonathan F. Lawrence,[1] Youssef Rbaibi,[2] Ora A. Weisz,[2,3] Alfica Sehgal.[1] *[1]Judo Bio, Cambridge, MA; [2]University of Pittsburgh Department of Medicine, Pittsburgh, PA; [3]University of Pittsburgh Department of Cell Biology, Pittsburgh, PA.*

Background: Small interfering RNA (siRNA) is a clinically validated therapeutic modality, which silences gene expression via RNA interference (RNAi). Although siRNAs are secreted through the kidney, siRNA mediated knock-down in the kidney is still limited, largely due to challenges with optimal delivery. Proximal tubule epithelial cells (PTECs) within the nephron are attractive targets for utilizing RNAi, where the primary mode of entry is likely endocytic uptake. Here we describe a targeted approach to deliver conjugated siRNAs exploiting the PTECs' internalizing receptors. Understanding the mechanisms of siRNA uptake in kidney PTECs is pivotal for developing efficient and safe delivery platforms targeting renal diseases.

Methods: In the present study, we investigated siRNA uptake in vitro and in vivo using conjugated siRNAs. A well-differentiated, opossum kidney (OK) PTECs cell line was used as a model system to mimic proximal tubule biology both morphologically and functionally, for studying siRNA uptake. Fluorescently tagged siRNAs were employed to observe uptake and intracellular trafficking. Additionally, siRNAs conjugated with target ligands were administered in mice to assess exposure in vivo, measured by mass spectrometry and microscopy. We further measured siRNA mediated knock-down across multiple genes in mouse kidneys.

Results: The siRNAs were taken up by OK cells in both time and concentration dependent manners, predominantly from the apical surface. We further studied the mechanism of conjugated siRNA uptake using specific inhibitors and cell specific knockouts of various PTEC endocytic receptors. Conjugation with selected ligands of megalin significantly enhanced siRNA uptake both in OK cells and in mouse kidneys. In addition, these conjugations led to significant gene knock-down across multiple targets.

Conclusions: The work suggests that PTECs employ megalin to facilitate siRNA uptake via endocytosis and can be used for gene silencing. Elucidating the mechanism(s) for siRNA uptake in the proximal tubule aids in the development of RNA-based therapeutics. Future work will focus on ligand conjugation optimization and chemical modification to improve kidney specific silencing activity.

Funding: Commercial Support - Judo Bio

SA-PO638

Towards a Translatable Model for Studying Therapeutic Efficacy in Alport Syndrome

Yanling Zhang, Linda Nghiem, Hai Wang, Kerri Thai, Chiara Oliveira, Richard E. Gilbert. *Unity Health Toronto, Toronto, ON, Canada.*

Background: Reducing GFR loss is the primary outcome for studying therapeutic effectiveness in Alport syndrome (AS). Unlike humans, standard dose ACE inhibition (ramipril 10 mg/kg) almost completely normalizes the kidney in the Col4a3 KO (AS) mouse. We sought to establish a model with more similarity to its human counterpart by (1) comparing the reliability of GFR methods, and (2) using GFR as the primary outcome to establish a model for testing agents on top of ACE inhibition.

Methods: *Study 1* GFR was measured (mGFR) in wild type and Col4a3 KO mice comparing the gold standard of fluorescein-labeled sinistrin (inulin analogue) with plasma creatinine, BUN and cystatin C. In *Study 2*, having established cystatin C as a preferred method, we assessed the ACE inhibitor dose-response relationship, aiming for an approximate 50% improvement in GFR, akin to human disease. Urinary ACR, glomerulosclerosis and interstitial fibrosis were also assessed.

Results: *Study 1.* At 8 weeks of age, the between group difference between WT and Col4a3 KO was 11-fold for sinistrin-GFR, 4.9 fold for plasma creatinine, 2.6 fold for BUN and 6.9 fold for cystatin C. All comparisons $p < 0.001$. *Study 2 (Table 1).* In comparison with untreated Col4a3 KO mice, ramipril induced dose-dependent reductions in cystatin C. ACR, glomerulosclerosis and interstitial fibrosis while near-normalized by ramipril 10 mg/kg were unaffected by lower doses.

Conclusions: Changes in cystatin C most closely resemble sinistrin-based mGFR. ACE inhibition with ramipril provided dose-dependent improvements in cystatin C with an approximate 50% reduction at 1 mg/kg, akin to findings of standard of care in humans. Accordingly, 1 mg/kg may be an appropriate dose to use in studies testing the efficacy of new additive agents. The dynamic range for UACR, GSI and IF may be too narrow to allow for such testing.

Funding: Government Support - Non-U.S.

Renal function parametres and histologic analysis

	WT	RO water	ramipril 0.1	ramipril 1	ramipril 10
cystatin C (mmol/l	306 ± 21	2360 ± 158	1450 ± 168†	1129 ± 191†‡	502 ± 52†‡§
UACR (mg/mmol)	3.1 (2.9 – 7.9)	423 (292 – 635	484 (325 – 807)	303 (187 – 474)	15 (7 – 126)†
GSI	0.2 (0.2 – 0.7)	3.8 (3.3 – 3.9)	3.7 (2.4 – 3.9)	3.7 (2.9 – 3.9)	0.5 (0.4 – 1.0)†
BP (%)	1.2 ± 0.3	11 ± 2.5	10 ± 4.6	6.9 ± 2.6	2.2 ± 1.0*

* p<0.05 versus RO water ; † p≤0.001 versus RO water; ‡ p<0.01 versus 0.1 ramipril; § p<0.01 versus 1 ramipril

WT, wild type; RO, reverse osmosis water. RO water and ramipril-treated mice were all studied in Col4a3 KO mice.

SA-PO639

Oral L-lysine Treatment Ameliorates Proximal Tubular Damage in Mice with Alport Syndrome

Suresh K Ramakrishnan,[1] Jiayi Li,[1] Verena Rickert-Zacharias,[1] Jeffrey H. Miner,[2] Matias Simons.[1] *[1]UniversitatsKlinikum Heidelberg, Heidelberg, Germany; [2]Washington University in St Louis School of Medicine, St Louis, MO.*

Background: Chronic kidney disease (CKD) is characterized by a long-term decline of kidney function. Proteinuria induced by glomerular damage is one of the hallmarks of CKD. Apart from the glomerular damage, the increased tubular load of proteins and protein-bound lipids can damage proximal tubular cells (PTC), causing tubulointerstitial fibrosis. Treatment with the basic amino acid L-lysine, which is shown to be safe in humans, has been shown to inhibit protein uptake in PTC. Therefore, we hypothesized that blocking PTC protein uptake via L-lysine might protect against tubulointerstitial damage in glomerular diseases, such as Alport syndrome.

Methods: *Col4a3* Wildtype (WT) and knockout (Alport mice) in 129/Sv background were treated with and without L-lysine chloride (50mg/ml) in drinking water from 5 weeks of age for 3 weeks. Blood gas analysis and transdermal glomerular filtration rate (GFR) was measured. Kidney samples were analyzed for histology and injury markers. Induced renal epithelial cells (iRECs) grown on filters were used. Albumin-Alexa 647 uptake studies were performed upon treatment with different concentrations of L-Lysine chloride. Lipotoxic effects were studied upon treatment with albumin-bound palmitic acid.

Results: We observed a significant increase in albuminuria on day 1 of the L-Lysine treatment in both WT and Alport mice. Interestingly, there was a progressive decrease of albuminuria in L-Lysine-treated Alport male mice starting from week 1 to the end of the study. Gene expression of kidney injury and fibrosis markers were significantly ameliorated in the Alport male mice treated with L-lysine. No change in GFR was found between the groups. Albumin uptake was reduced in iRECs treated with L-lysine. We confirmed that iRECs express megalin and cubilin on the apical surface when plated on Transwell filters. L-lysine treatment significantly decreased the lipotoxicity exhibited upon addition of palmitic acid.

Conclusions: Our preliminary data suggests that oral L-Lysine treatment has beneficial effects in Alport mice. We are currently performing proteomics and metabolomics on renal cortical samples on these mice to identify the mechanisms underlying the protective effects. In the future, L-Lysine could be proposed as an efficient and safe therapeutic strategy to prevent proximal tubular damage in glomerular diseases.

SA-PO640

Kidney Protection by a Novel Keap1-Nrf2 Protein-Protein Interaction Inhibitor for a Mouse Model of Alport Syndrome

Jun Horizono,[1] Shota Kaseda,[1,4] Yuya Sannomiya,[1] Mary Ann Suico,[1] Hirohiko Fukiya,[2] Hidetoshi Sunamoto,[2] Hiroshi Watanabe,[3] Takehiro Nakano,[3] Kai Tokumaru,[3] John B. Davenport,[4] Tsuyoshi Shuto,[1] Rachel Lennon,[4] Kazuhiro Onuma,[2] Hirofumi Kai.[1] *[1]Department of Molecular Medicine, Graduate School of Pharmaceutical Science, Kumamoto University, Kumamoto, Japan; [2]Pharmaceuticals Research Laboratory, UBE Corporation, Yamaguchi, Japan; [3]Department of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto City, Japan; [4]Wellcome Centre for Cell-Matrix Research, University of Manchester, Manchester, United Kingdom.*

Background: Keap1-Nrf2 pathway plays an important role in the defense mechanism against oxidative stress in the kidney. We have shown that UBE-1099, a Keap1-Nrf2 protein-protein interaction (PPI) inhibitor, exerts renoprotective effects in Alport syndrome (AS) mice (*Kidney 360*, 2022). Furthermore, we found a more promising Keap1-Nrf2 PPI inhibitor UD-051 having a high Nrf2 activation potency at lower concentrations. In the present study, we aim to elucidate the effects of UD-051 on AS pathophysiology.

Methods: We studied the effects of UD-051 using AS (Col4a5-G5X) and Nrf2 KO-AS mice. In addition, we evaluated the survival of AS mice treated with UD-051 in combination with losartan, an angiotensin II receptor blocker (ARB).

Results: UD-051 improved the glomerular and tubular damage, renal inflammation, and fibrosis in AS mice. UD-051 transiently increased proteinuria in AS mice. The renoprotective effect of UD-051 and the transient increase in proteinuria were abolished in Nrf2 KO-AS mice. Interestingly, UD-051 suppressed the albumin accumulation in the proximal tubules of AS mice, and decreased the expression of albumin reabsorption transporter megalin. These results suggest that UD-051 inhibits excessive albumin reabsorption in the tubules of AS mice and exerts a tubular protective effect. Moreover, UD-051 decreased oxidized albumin ratio (OAR), the clinical biomarker for the progression of kidney disease in the plasma of AS mice. Importantly, OAR highly inverse correlated with the expression level of *Nqo1* which is the Nrf2 target gene in vehicle- and UD-051-treated AS mice kidney tissue, suggesting that OAR is a highly sensitive biomarker that reflects Nrf2 activity in kidney tissue. Notably, survival studies showed that UD-051 (3 mg/kg, *p.o.*) increased the median survival of AS mice by 22 %, losartan alone by 8.4%, and the combination of UD-051 (3 mg/kg, *p.o.*) and losartan extended the median survival by 65% more than the vehicle-treated AS mice.

Conclusions: The present study demonstrated a renoprotective effect of UD-051. The results also suggest that the combination treatment with UD-051 and ARBs may be useful for AS and other chronic kidney diseases.

Funding: Commercial Support - UBE Corporation, Japan

SA-PO641

Protective Effect of Ambrisentan on Proteinuria in Patients with Alport Syndrome

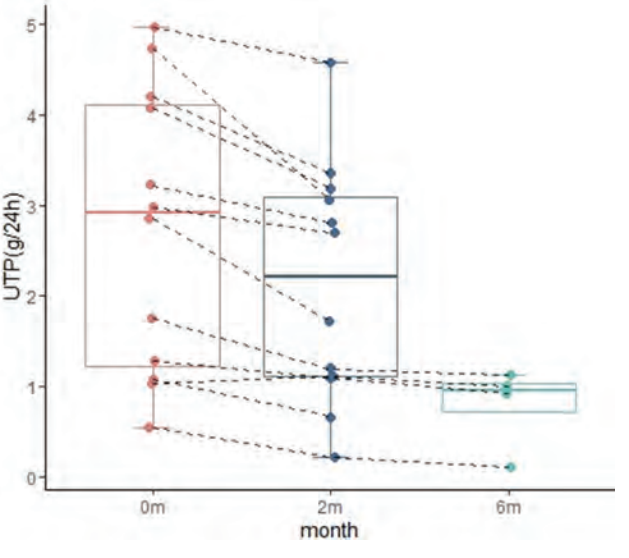
Zhuoran Song, Yang Li, Hong Zhang, Xu-jie Zhou. *Peking University First Hospital Department of Nephrology Renal Division, Beijing, China.*

Background: In recent years, endothelin receptor antagonists (ERAs) have stepped into the spotlight of chronic kidney disease treatment, showing a significant reduction in proteinuria and preservation of kidney function, such as SONAR study in diabetic nephropathy, DUPLEX trial in focal segmental glomerulosclerosis (FSGS) and PROTECT trial in IgA nephropathy. However, whether they are effective in Alport syndrome (AS) is unclear.

Methods: This was a real-world study. AS patients that had been treated with RAASi or RAASi combined with sodium-dependent glucose transporters 2 inhibitors (SGLT2i) / mineralocorticoid receptor (MRA) in stable doses for at least 3 months but still with proteiuria (>0.5g/d)and eGFR>25 ml/min/1.73m^2 were included. All of them received ambrisentan 5 mg daily. Efficacy was assessed by the changes in proteinuria. The safety outcomes included renal function change and tolerance.

Results: In total, 12 patients with AS were included. The mean baseline 24-hour urinary protein (UTP) (±SD) was 2.73 ± 1.56g/d and decreased to 2.14 ± 1.32g/d after two-month treatment (P=0.001). The mean eGFR was stable in the two months (mean 57.08 vs. 58.98 ml/min/1.73m^2 at baseline). 2 patients discontinued due to edema and 2 due to headache in the second month. Other patients never reported any side effects. Among the patients, four have been followed over 6 months with additional 4 months follow-up data. We observed a continued decrease trend in urinary protein, additional 20.85±10.67% from the second month in the UTP reduction, and 36.61±16.06% reduction from the baseline. The eGFR remained stable.

Conclusions: The pilot study suggests that introducing of ERA on top of RAASi with or without SGLT2i/MRA provides an additional antiproteinuric effect in AS.



SA-PO642

Adeno-Associated Virus (AAV)-Mediated Gene Therapy in Nphs1 Knockout Mice: A Strategy for Treating Congenital Nephrotic Syndrome

Ken Saida,[1] Seyoung Yu,[1] Alina Braun,[1] Gijs A. Franken,[1] Kraisoon Lomjansook,[1] Katharina Lemberg,[1] Caroline M. Kolvenbach,[1] Bshara Mansour,[1] Kirollos Yousef,[1] Korbinian M. Riedhammer,[1] Nils D. Mertens,[1] Izzeldin Elmubarak,[1] Ronen Schneider,[1] Shirlee Shril,[1] Florian Buerger,[1,2] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]University Children's Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: Finnish-type congenital nephrotic syndrome (CNS) causes nephrin dysfunction and disrupts glomerular filtration barrier. Podocyte-specific *Nphs1* knockout mouse models recapitulate the human CNS phenotype and have a median survival of 18 days (Buerger F. *Am J Physiol Renal Physiol* 2024). Establishing AAV-based gene therapy in neonatal mice is crucial for treating CNS. Although AAV serotypes exhibit broad organ tropism, efficient kidney targeting, particularly in podocytes, remains challenging. In addition, the efficiency of AAV-mediated gene expression in neonatal mouse kidneys remains unclear.

Methods: Retro-orbital (RO) and intrarenal injections of AAV capsids (AAV9, AAV-PHP.S, AAV-DJ, and AAV-KP1) carrying the CAG promoter and tdTomato were administered to P1 mice (*Nphs1*$^{tm1.1Pgarg}$/J *Nphs2*-Cre^{+} vs. control). The injected AAV dose was >1E+14 vg/kg. For RO injections, 10 µL of AAV was injected into each eye using a 31-gauge insulin syringe under cryo-anesthesia. For intrarenal injections, 10 µL AAV was percutaneously delivered into the left kidney over a minute using a syringe pump. The mice were dissected three weeks post-injection, and transduction efficiency was assessed by immunofluorescence (IF) and flow cytometry (FC).

Results: RO injection in P1 mice resulted in transduction of the proximal tubules and glomeruli. In glomeruli, distinct podocyte transduction was confirmed by super-resolution microscopy. FC analysis of AAV9 and AAV-PHP.S injected mice shows transduced podocytes accounting for >13%, as indicated by the presence of podocalyxin-positive cells expressing tdTomato. Intrarenal injection of AAV-KP1 into the left kidney of P1 mouse resulted in significant tdTomato expression in both tubular and glomerular cells, whereas the uninjected right kidney showed only glomerular transduction. We achieved a podocyte transduction rate of >50% in most of the mature glomeruli via intrarenal injection.

Conclusions: This study demonstrated the feasibility of podocyte transduction, providing a proof-of-principle for AAV gene therapy in a CNS mouse model. Further optimization is required to enhance the efficiency of AAV delivery to podocytes.

SA-PO643

Treatment of Autosomal Dominant Tubulointerstitial Kidney Disease Uromodulin (ADTKD-UMOD) with Antisense Oligonucleotides

Kathy Y. Morgan, Nino Jungels, Christopher Greer, Stephanie Garcia, Emily G. Thompson, Tushare Jinadasa, Xuyu Tan, Kailash Adhikari, Vincent Guerlavais, Ryan Oliver. *Sarepta Therapeutics Inc, Cambridge, MA.*

Background: Autosomal Dominant Tubulointerstitial Kidney Disease-Uromodulin (ADTKD-UMOD) is a genetic disease caused by destabilizing mutations in uromodulin (UMOD). Misfolded UMOD protein aggregates and accumulates inside the loop of Henle and the distal convoluted tubule, leading to progressive and irreversible chronic kidney disease. We hypothesized that peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs) could knock down *UMOD* expression and potentially reduce the disease-causing UMOD aggregation inside the cells.

Methods: A library of PPMOs was designed to bind to the complementary sequences of the mouse *Umod* gene and induce nonsense-mediated decay. These PPMOs were screened in mIMCD-3 cells, which express endogenous *Umod* to identify the most active compounds. The most efficacious PPMO compound was tested in both wildtype and UMOD C93F mice, a well characterized disease model of ATDKD, to determine the ability of the PPMO to reduce UMOD expression at the transcript and protein levels.

Results: A single dose of PPMO resulted in a 70% knockdown of UMOD protein in WT mice. The reduction in UMOD protein was sustained for at least 28 days. Two subsequent weekly doses of PPMO increased the amount of UMOD knockdown further, demonstrating an additive effect of PPMO dosing over a two week period. Furthermore, Umod MOD protein expression was reduced in the UMOD C93F animals after a single dose of PPMO.

Conclusions: PPMO technology can be used to reduce UMOD transcript and protein levels *in vitro and* in vivo. These findings demonstrate that PPMOs have the potential to preserve renal function in patients with ADTKD.

Funding: Commercial Support - Sarepta Therapeutics

SA-PO644

Ccr2 Targeting Does Not Ameliorate Disease Phenotype in a Model of UMOD-Related Autosomal Dominant Tubulointerstitial Kidney Disease

Mariapia Giuditta Cratere,[1,2] Francesca Nicola,[1,2] Matteo Trudu,[1,2] Celine Schaeffer,[1,2] Luca Rampoldi.[1,2] Molecular Genetics of Renal Disorders Unit. *[1]Universita Vita Salute San Raffaele, Milano, Italy; [2]IRCCS Ospedale San Raffaele, Milano, Italy.*

Background: Mutations in *UMOD*, encoding uromodulin, cause *UMOD*-related Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD-*UMOD*). The common gain-of-function effect of *UMOD* mutations is endoplasmic reticulum (ER) retention and aggregation of mutant uromodulin. In a transgenic mouse model of the disease (Tg^{UmodC147W}) we detected significant upregulation of pro-inflammatory chemokines already at one day *post-natal*, well before any sign of kidney damage, suggesting a key role of early inflammation in disease pathogenesis. All upregulated chemokines are ligands of the C-C Motif Chemokine Receptor Ccr2, mainly expressed by circulating monocytes and important for their migration to inflamed sites. Here, we investigated the effect of targeting Ccr2-axis on ADTKD-*UMOD* kidney disease.

Methods: We adopted a genetic approach by generating Tg^{UmodC147W}/*Ccr2*$^{-/-}$ mice that were characterized at 1 week (presymptomatic) and 24 weeks (late disease) of age and compared with both Tg^{UmodC147W}/*Ccr2*$^{+/+}$ and WT/*Ccr2*$^{+/+}$ mice (non-transgenic littermates).

Results: *Ccr2* ablation did not affect *Umod* expression levels nor mutant uromodulin ER retention in kidneys of Tg^{UmodC147W} mice. Following extensive phenotype analysis, we did not observe decreased inflammation, fibrosis and expression of tubular damage markers at any studied timepoint in kidneys of Tg^{UmodC147W}/*Ccr2*$^{-/-}$ mice compared to age-matched Tg^{UmodC147W}/*Ccr2*$^{+/+}$, demonstrating that deletion of *Ccr2* receptor is not sufficient to improve phenotype of Tg^{UmodC147W} mice. To assess possible compensatory inflammatory pathways acting in response to loss of Ccr2 signalling, we studied Ccr1, Ccr3 and Ccr5 axes. Tg^{UmodC147W}/*Ccr2*$^{-/-}$ mice showed increased expression of *Ccr5* (24-weeks of age) and *Ccr1* (1 and 24 weeks of age). These data suggest that *Ccr2* ablation in Tg^{UmodC147W} mice induces compensatory activation of inflammatory pathways contributing to disease onset (*Ccr1*) and sustainment (*Ccr5*) in Tg^{UmodC147W}/*Ccr2*$^{-/-}$ mice.

Conclusions: Our results demonstrate that Ccr2 targeting is not sufficient to block inflammation and prevent kidney disease progression in ADKTD-*UMOD*. These data provide evidence for the context-dependent redundance of Ccr receptors in triggering the inflammatory process.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO645

Developing New Therapies for Autosomal Dominant Tubulointerstitial Kidney Disease Caused by Uromodulin Mutations by Screening a Small Molecule Library

Matthias T. Wolf, Rory A. Sebastian, Krish D. Patel, Sung Wan An, Huiyuan Wu. *University of Michigan Michigan Medicine, Ann Arbor, MI.*

Background: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) caused by Uromodulin (*UMOD*) mutations, is the third most common inherited kidney disease. *UMOD* mutations result in a misfolded UMOD protein which is less secreted and accumulates intracellularly resulting in apoptosis and kidney failure. We want to identify new therapies for patients with ADTKD caused by *UMOD* mutations applying a high-throughput screening (HTS) assay.

Methods: We developed stable cell lines expressing C150S or wild-type (WT) UMOD tagged to luciferase. We used the luciferase activity in the cell culture supernatant as the readout how well a compound improved C150S UMOD secretion. 8,000 compounds from the UT Southwestern HTS core library were screened. Best candidates were counter-screened for cell viability, effect on apoptosis, restoring TRPV5 current density (applying patch-clamp recording), and UMOD secretion using an ELISA assay.

Results: The initial screen resulted in 124 candidates which increased C150S UMOD secretion to at least 20% of WT UMOD. We picked the best 99 candidates and confirmed them in triplicates at three different concentrations. Next, we chose the best 24 candidates which increased UMOD secretion to 40% of WT UMOD. To exclude any cytotoxic compounds, we removed 14 of the 24 candidates which reduced cell viability by more than 40%. Out of the 10 remaining candidates three small compounds increased UMOD secretion to 80-100% of WT UMOD. All three small molecules reduced apoptosis by more than 20%. Dose-response curves were performed for all three compounds. Compounds restored TRPV5 current density with C150S UMOD comparable to WT UMOD, and UMOD ELISA assays confirmed UMOD secretion. Western blot studies after treatment with these candidates showed a reduction of caspase 3 and an increase of the endogenous chaperone Hsp70.

Conclusions: Our proof-of-concept study shows that screening of a small molecule library allows to identify potential new therapies for kidney diseases. Thorough counter-screening is required to remove false positive candidates. Further experiments including analysis of the targeted molecular pathway, structure-activity relationships, pharmacokinetics and -dynamics, and *in vivo* experiments in mutant UMOD mice will be required.

Funding: NIDDK Support

SA-PO646

Characterization and Regulation of the Disease-Causing Mucin 1 Frameshift Protein in Patient-Derived Cells Affected by Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)-MUC1

Hannah Schwarz,[1] Karl X. Knaup,[1] Florian J. Wopperer,[1] Mario Schiffer,[1] Maike J. Buettner,[2] Kerstin U. Amann,[2] Michael S. Wiesener.[1]
[1]Universitatsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; [2]Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany.

Background: Autosomal Dominant Tubulointerstitial Kidney Diseases (ADTKD) are rare monogenic diseases of the kidney, which are mainly caused by germline mutations of *UMOD* and *MUC1*, leading to end-stage renal disease (ESRD) usually in mid adulthood. ADTKD-*MUC1* is caused by a characteristic frameshift mutation, leading to the *de novo* protein MUC1-fs. MUC1-fs is believed to play a distinct role in terms of a "toxic proteinopathy", mainly accumulating in TMED9-containing vesicles (Dvela-Levitt et al., Cell 2019). The substance BRD4780 is reported to re-route MUC1-fs towards lysosomal degradation, with interventional trials being in preparation. Therefore, we aimed to gain more insights into MUC1-fs temporal and spacial regulative characteristics with respect to (pharmacological) intervention with TMED9.

Methods: To analyze MUC1-fs protein in more detail, we generated iTCs (immortalized Tubular Cells) from huPTC (human urinary Primary Tubular Cells) of several patients with ADTKD-*MUC1*. Clonal selection of cells was performed to retrieve immortalized clones with MUC1-fs expression. From these cells functional studies including immunoblotting, immunofluorescence and electron microscopy (EM) were performed to analyze the temporal and special expression of MUC1-fs and TMED9 in more detail.

Results: Immunofluorescence studies confirmed that MUC1-fs accumulates in the cytoplasm, possibly the secretory pathway. Co-localization was only partially observed with TMED9 (which localizes to COP vesicles), being involved in protein trafficking within the early secretory pathway. TMED9 negative components of this pathway also showed MUC1-fs staining, such as the Golgi apparatus and Early Endosomes. Immunogold EM of iTCs reveals MUC1-fs expression within the ER and vesicular structures, compatible with the secretory pathway. BRD4780 led to profound reduction of MUC1-fs. However, this effect was not specific. Protein half-life and reconstitution of MUC1-fs after blockade comprise a few hours.

Conclusions: Our data confirm and extend previously published information on intracellular MUC1-fs localization and regulation. The small molecule BRD4780 is effective, but not specific.

Funding: Government Support - Non-U.S.

SA-PO647

Proximal Tubule-Targeted Adeno-Associated Virus (AAV) Gene Therapy for Cystinuria

Jennifer L. Peek,[1,2] Alan Rosales,[3] Julie Qi,[4] Anna Menshikh,[4] Richard C. Welch,[4] Fabian Bock,[4] Lauren E. Woodard,[4,5] Aravind Asokan,[3,6] Matthew H. Wilson.[4,5] *[1]Vanderbilt University Medical Scientist Training Program (MSTP), Nashville, TN; [2]Vanderbilt University Department of Cell and Developmental Biology, Nashville, TN; [3]Duke University Department of Biomedical Engineering, Durham, NC; [4]Vanderbilt University Division of Nephrology and Hypertension, Nashville, TN; [5]VA Tennessee Valley Healthcare System, Nashville, TN; [6]Duke University Department of Surgery, Durham, NC*.

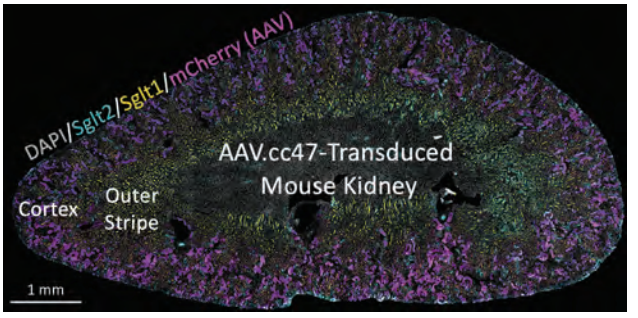
Background: Gene therapy for kidney disease remains a challenge primarily due to lack of gene delivery. Cystinuria, the most common inherited kidney stone disorder, results from deficiency of cystine transport and reabsorption in the proximal tubule. Cystinuria patients suffer from cystine stones, obstruction, and CKD development; effective treatments are lacking for this lifelong disease. We have previously shown significant reductions in urinary cystine levels in murine models of type A (*Slc3a1*$^{-/-}$) cystinuria through plasmid delivery of *Slc3a1*, which encodes rBAT. However, gene transfer was estimated to be <5% of proximal tubular epithelial cells (PTECs) and therefore did not affect stone formation.

Methods: Recent innovations in viral vectors have improved kidney transduction. With novel adeno-associated viruses (AAV) including AAV.cc47, we have shown efficient kidney delivery *in vivo*, *in vitro*, and in human kidney organoids. We have used AAV.cc47 to deliver fluorescent reporters and therapeutic transgenes in both healthy and cystinuric mice. Immunofluorescence analysis and statistics were performed in QuPath and GraphPad Prism, respectively.

Results: We observed that AAV.cc47 consistently targeted the kidney, with >80% of PTECs transduced in all mice injected with at least 1x10^{11} viral genomes (p=0.0011). Further quantification revealed a dose-dependent increase in the % transduced PTECs and strength of transduction. We next identified AAV.cc47 specifically targets S1 and S2 PTECs in the kidney, as >90% of all transduced cells were SGLT2+ (p=0.0009). Finally, we have shown rBAT expression post-delivery of AAV.cc47-*Slc3a1* to cystinuric mice and investigation of phenotypic changes is ongoing.

Conclusions: We have shown *Slc3a1* gene delivery for type A cystinuria gene therapy *in vivo* utilizing a proximal tubule-targeted vector, AAV.cc47. Phenotypic correction of a kidney disease remains a challenge, but our current efforts to optimize the delivery and stable expression of desired transgenes provide hope for overcoming the barriers to kidney gene therapy.

Funding: NIDDK Support, Veterans Affairs Support



SA-PO648

2,8-Dihydroxyadenine Impacts Kidney Cell Health and Barrier Integrity in an In Vitro Model of Adenine Phosphoribosyltransferase (APRT) Deficiency

Hildur R. Helgudottir,[1] Runolfur Palsson,[1,2] Vidar O. Edvardsson,[1,3] Thorarinn Gudjonsson.[1,4] *[1]Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland; [2]Division of Nephrology, Landspitali University Hospital, Reykjavik, Iceland; [3]Children's Medical Center, Landspitali University Hospital, Reykjavik, Iceland; [4]Division of Laboratory Hematology, Landspitali University Hospital, Reykjavik, Iceland*.

Background: Adenine phosphoribosyltransferase (APRT) deficiency is a rare genetic disorder that results in excessive generation and excretion of 2,8-dihydroxyadenine (DHA), leading to kidney stones and crystal nephropathy. This condition causes inflammation and fibrosis of the kidneys. Although the effects of other types of crystal nephropathies and kidney stone diseases have been studied in cell culture models, the mechanism of DHA-mediated kidney injury is not well understood. This study aimed to establish a comprehensive cell culture model to investigate DHA crystal-induced kidney injury and identify therapeutic targets for clinical intervention.

Methods: Three kidney cell lines, MDCK, HK-2, and HEK293, were tested in both monolayer and 3D cultures, including liquid-liquid interface (LLI) and "on-top" of Matrigel methods. Cells were exposed to DHA at concentrations similar to those found in the urine of APRT-deficient patients. Cell viability and migration assays, RT-PCR, western blotting, phase-contrast microscopy, and immunostaining were used as read-out assays. Immunohistochemistry (IHC) was used to analyze kidney tissue samples from APRT deficiency patients and healthy controls obtained from Landspitali University Hospital Biobank.

Results: DHA exposure decreased kidney cell viability and migration across all cell lines. Rising DHA concentrations increased CD44 expression, suggesting enhanced crystal-binding potential of the kidney cells. In a 3D environment "on-top" of Matrigel, MDCK cells maintained polarized structures despite DHA accumulation and did not show an increase in the EMT phenotype compared with TGFβ-treated cells. MDCK cells formed a polarized cell layer grown on Transwell polyester membranes and demonstrated trans-epithelial electrical resistance (TEER) in LLI, which decreased when the cells were treated with DHA. Analysis of patient kidney tissue samples revealed increased collagen I and III expression, well-known markers of fibrosis, in APRT deficiency patients.

Conclusions: Our findings demonstrate the deleterious effects of DHA on kidney cell health, barrier function, and its potential role in promoting fibrosis in APRT deficiency. Future studies in 3D cultures will focus on further exploring the phenotypic changes in kidney cells after exposure to DHA both at the cellular and molecular level.

Funding: Government Support - Non-U.S.

SA-PO649

Clinical Utility of a Novel Ultraperformance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-MS/MS) Plasma 2,8-Dihydroxyadenine Assay in Patients with Adenine Phosphoribosyltransferase (APRT) Deficiency

Unnur A. Thorsteinsdottir,[1,3] Hrafnhildur L. Runolfsdottir,[2] Finnur F. Eiriksson,[1,3] Vidar O. Edvardsson,[2,1] Margret Thorsteinsdottir,[1,3] Runolfur Palsson.[2,1] *[1]Heilbrigdisvisindasvid - Haskoli Island, Reykjavik, Iceland; [2]Landspitali, Reykjavik, Iceland; [3]ArcticMass, Reykjavik, Iceland.*

Background: Treatment with a xanthine oxidoreductase inhibitor (XORi), allopurinol or febuxostat, reduces urinary 2,8-dihydroxyadenine (DHA) excretion and slows CKD progression in adenine phosphoribosyltransferase deficiency (APRTd). We have developed and validated an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) plasma assay for the simultaneous quantification of DHA, adenine, allopurinol, oxypurinol and febuxostat in human plasma. The aims of the current study were to assess the clinical applicability of the assay.

Methods: DHA, allopurinol, oxypurinol and febuxostat were quantified in 82 bio-banked plasma samples using the novel assay. Clinical patient data were obtained from our APRT Deficiency Patient Registry. Plasma DHA concentration was correlated with age, sex, XORi treatment status and estimated glomerular filtration rate (eGFR).

Results: The average plasma concentration was 323 ng/mL for DHA and 292 ng/mL for adenine in untreated (n=28) APRTd patients. When treated with allopurinol 400 mg/day (n= 29) or febuxostat 80 mg/day (n=25), the average concentration of DHA was 61 ng/mL and below the limit of quantification, respectively, and of adenine 818 and 1264 ng/mL, respectively. DHA was not detected in plasma samples from controls (n=9). The average plasma concentration of allopurinol, oxypurinol and febuxostat in patients receiving XORi therapy was 1695 ng/mL, 11612 ng/mL and 313 ng/mL, respectively. There was a moderate negative correlation between the plasma DHA concentration and eGFR in untreated patients. No significant correlation was found between age and sex and the DHA plasma concentration.

Conclusions: The UPLC-MS/MS plasma assay for quantification of DHA, adenine, allopurinol, oxypurinol and febuxostat in human plasma can be used for therapeutic monitoring in APRTd. Measurement of plasma DHA will also be a useful test for the diagnosis of APRTd.

Funding: Government Support - Non-U.S.

SA-PO650

Effect of Allopurinol and Febuxostat on Plasma and Urine 2,8-Dihydroxyadenine: A Clinical Trial

Hrafnhildur L. Runolfsdottir,[1] Unnur A. Thorsteinsdottir,[2,3] Inger M. Agustsdottir,[1] Margret Thorsteinsdottir,[2,3] Runolfur Palsson,[1,2] Vidar O. Edvardsson.[1,2] *[1]Landspitali, Reykjavik, Iceland; [2]Haskoli Islands, Reykjavik, Iceland; [3]ArcticMass, Reykjavik, Iceland.*

Background: In patients with adenine phosphoribosyltransferase (APRT) deficiency, treatment with allopurinol or febuxostat reduces urinary 2,8-dihydroxyadenine (DHA) excretion, preventing stone formation and progression of chronic kidney disease. The aim of this study was to determine the effects of allopurinol 400 and 800 mg/day and febuxostat 40 and 80 mg/day on plasma and urinary DHA levels in patients with APRT deficiency.

Methods: Patients with estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m^2 listed in the APRT Deficiency Registry of the Rare Kidney Stone Consortium were enrolled in a 168-day clinical trial. Following a 4-week washout period, patients were randomized to a single daily dose of allopurinol 400 mg or febuxostat 40 mg for 28 days, after which the dose was elevated to 800 mg of allopurinol and 80 mg of febuxostat. A second washout period was then followed by cross-over to the alternative study drug. Plasma and urine levels of DHA were measured using an ultra-performance liquid chromatography-tandem mass spectrometry assay, and the urinary excretion expressed as DHA/creatinine ratio.

Results: Seven patients completed the study. Their median (range) age was 57.7 (37.3-65.1) years; 3 were female. The median urinary DHA/creatinine ratio was 7.5 (4.3-14.0) ng/mmol off treatment, 2.1 (1.0-4.9) and 0.79 (0.2-2.2) on 400 and 800 mg of allopurinol, respectively, and 0.6 (0.3-1.0) and 0.6 (0.2-5.4) on 40 and 80 mg of febuxostat, respectively. The median plasma DHA concentration was 289 (216-432) ng/mL during both washout periods and 50 (32-95) ng/mL on 400 mg of allopurinol in 4 patients, while the other 3 patients had concentrations below the level of quantification (BLQ). On allopurinol 800 mg/day, the plasma DHA concentration was BLQ in all but 2 patients, and BLQ in all but 1patient on both doses of febuxostat.

Conclusions: Urinary DHA excretion and plasma concentration was lower in patients on allopurinol 800 mg/day compared to 400 mg/day. There was no apparent difference in DHA plasma concentration or urinary DHA excretion between the two prescribed febuxostat doses. Febuxostat was more efficacious than allopurinol in the prescribed doses.

Funding: Government Support - Non-U.S.

SA-PO651

Burden of Illness of Primary Hyperoxaluria with CKD

David S. Goldfarb,[1] Jing Voon Chen,[3,4] Olivia Li,[2] Jeffrey R. Skaar,[2] Sandra Salem,[4] Frank Modersitzki.[1] *[1]NYU Langone Health, New York, NY; [2]Trinity Partners LLC, Waltham, MA; [3]Genesis Research LLC, Hoboken, NJ; [4]Novo Nordisk Inc, Plainsboro, NJ.*

Background: Primary hyperoxaluria (PH) is a rare genetic disorder characterized by the overproduction of oxalate, which combines with calcium to form calcium oxalate crystals, leading to kidney stones, CKD, and kidney failure. The burden of illness for people with PH and CKD (PH-CKD) relative to people with CKD alone (non-PH-CKD) is unclear. This study aims to understand epidemiology, patient characteristics, treatment, healthcare resource utilization, and cost of care of people with PH who have normal or impaired kidney function.

Methods: This retrospective, non-interventional, observational study uses real-world US administrative data from the 2017-2021 Merative MarketScan® Commercial Claims and Encounters databases and the 2017-2021 CMS Medicare Fee-For-Service Limited Data Set. The study includes people with PH (at least 1 medical claim with PH diagnosis in 2020-2021 and no secondary hyperoxaluria or Crohn's disease), PH-CKD (PH criteria and at least 1 medical claim with CKD diagnosis in 2017-2021), and non-PH-CKD (no PH or secondary PH diagnosis in 2017-2021 and CKD criteria).

Results: There were ~4,500 people with diagnosed PH in US in 2021; 37% presented with early (stage 1-3; 65%) or advanced (stage 4-5 or end-stage kidney disease [ESKD]; 33%) CKD. People within the PH-CKD group were ~5 years older than the overall PH population. Pharmacotherapy, particularly potassium citrate (33%), was more common in people with PH and early-stage CKD, while people with PH and advanced CKD were more likely to undergo procedural interventions, including dialysis (48%) and kidney transplant (16%). People with PH and advanced CKD had ~13x and ~5x higher median all-cause semi-annual healthcare costs compared to people with only PH or PH-CKD (stage 1-3), respectively. The PH-CKD cohort had higher burden compared to the matched non-PH-CKD group, including higher rates of kidney stones and urinary tract infections ($p<0.05$). The PH-CKD cohort had higher use of potassium citrate (stage 1-3; $p<0.05$) and dialysis (stage 4-5/ESKD; $p<0.05$) compared with the non-PH-CKD. PH-CKD (stage 1-3) had higher utilization and cost differences (~2x) compared to a matched non-PH-CKD cohort.

Conclusions: People with PH-CKD show a higher clinical and economic burden of illness compared to non-PH-CKD people. Among people with PH, the health burden increases with CKD stage.

Funding: Commercial Support - Novo Nordisk Inc.

SA-PO652

Evaluation of the Impact of SGLT2 Inhibitor Treatment in a Mouse Model of Dent Disease

Elise de Combiens, Nadia Frachon, Stéphane Lourdel. *Centre de Recherche des Cordeliers, Paris, France.*

Background: Dent's disease is a rare disorder affecting the proximal tubule. It is characterized by urinary loss of low-molecular-weight proteins (LMWPs), and other electrolytes such as calcium. It generally progresses to chronic kidney disease (CKD), and is due to a mutation in the CLCN5 gene encoding the ClC-5 protein which plays a crucial role LMWPs endocytosis. To study the mechanisms involved in the progression of this disease to CKD, we created a Knock In (KI) mouse model carrying a CLCN5 mutation. The transgenic mice develop the main clinical features observed in patients, presents fibrosis and inflammation with age, as well as an alteration of their glomerular filtration rate. In an attempt to slow-down the progression of the disease to CKD, we treated our mice with empagliflozin, a SGLT2 inhibitor which have been described to display nephroprotective effects in many diabetic and non-diabetic CKD patients.

Methods: empagliflozin was administered in the diet of mice for 8 months at a dose of 30mg/kg of mice per day. At 10 months, mouse kidneys were collected to evaluate fibrosis and inflammation and quantify the tubular damage marker NGAL.

Results: Surprisingly, the treatment did not slow-down the progression of Dent's disease, as the mice showed significant inflammation and fibrosis at 10 months, as well as high levels of NGAL compared with WT mice.

Conclusions: Contrary to other murine models of CKD, empagliflozin does not appear to slow-down the progression of Dent's disease. Some clinical studies suggest that SGLT2 inhibitors act synergistically with inhibitors of the renin angiotensin system, another treatment commonly administered in patient with CKD. It would therefore be interesting to evaluate the effect of these 2 treatments on our mouse model.

Funding: Government Support - Non-U.S.

SA-PO653

Nedosiran in Pediatric Patients with PH1 (PHYOX8)

David J. Sas,[1] Sevcan A. Bakkaloglu,[2] Vladimir Belostotsky,[3] Wesley N. Hayes,[4] Jing Zhou,[5] Verity Rawson,[5] María Gema Ariceta Iraola.[6] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Gazi Universitesi, Ankara, Turkey; [3]McMaster University, Hamilton, ON, Canada; [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [5]Novo Nordisk A/S, Bagsvaerd, Denmark; [6]Hospital Infantil i l'Hospital de la Dona de Vall d'Hebron, Barcelona, Spain.*

Background: Primary hyperoxaluria type 1 (PH1) is a rare genetic disorder leading to excessive hepatic production of oxalate, which can cause deposition of calcium oxalate crystals in the form of recurring kidney stones and nephrocalcinosis.PH1 often presents in childhood and, if left untreated, may result in progressive damage to kidneys and other organs. Nedosiran is a synthetic RNA interference (RNAi) agent designed to selectively reduce hepatic LDH (encoded by the *LDHA* gene) to decrease oxalate burden. Nedosiran is administered as a monthly subcutaneous injection and is FDA-approved for patients with PH1 (≥9 years of age; eGFR ≥30mL/min/1.73 m^2).

Methods: PHYOX8 (NCT05001269) is a phase 2 clinical trial evaluating the efficacy and safety of nedosiran in lowering urinary oxalate (Uox) excretion in pediatric participants (birth to 11 years) with PH1 and eGFR ≥30mL/min/1.73m^2. Reported here are the results of 15 pediatric patients (2 to 10 years of age) with PH1 who received nedosiran once monthly for 6 months in PHYOX8 (Feb 2022 to Aug 2023).

Results: A substantial reduction in spot Uox:creatinine (cr) ratio was observed in patients treated with nedosiran (**Figure 1**): the least squares (LS) mean of percent change in spot Uox:cr ratio from baseline to month 6 was -64.1% (95% CI: -83.8, -44.4). At the month 6 visit, 6 (40%) participants had normal (i.e. ≤ULN) spot Uox:cr ratios, whereas 11 (73%) had Uox:cr ratios ≤1.5 x ULN. Further, there was a mean reduction of 10% in the surface area of kidney stones from baseline to month 6. The mean eGFR remained stable. Nedosiran was well tolerated; 3 participants experienced treatment-related AEs that did not result in discontinuation of treatment or from the study. There were no treatment-related serious AEs. One participant (6.7%) experienced an injection-site reaction. No muscle pain or weakness was observed.

Conclusions: Nedosiran appeared to be safe and well-tolerated in children aged ≥2 years with PH1. Nedosiran treatment led to a substantial reduction of spot Uox:cr in this population.

Funding: Commercial Support - Dicerna Pharmaceuticals, a Novo Nordisk Company

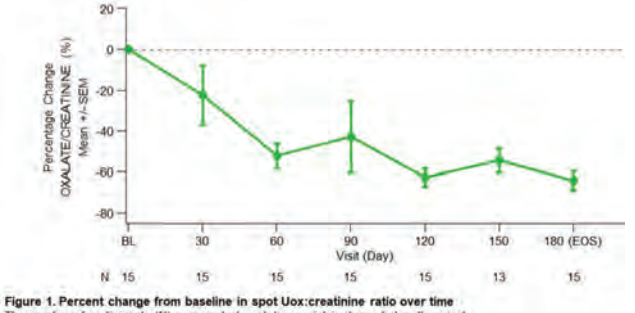


Figure 1. Percent change from baseline in spot Uox:creatinine ratio over time
The number of participants (N) assessed at each time point is shown below the graph
Abbreviations: Uox, urinary oxalate; SEM, standard error of the mean; EOS, end of study

SA-PO654

Lucerastat Effect on Kidney Function in Patients with Fabry Disease: Results from the Phase 3 Clinical Program

Eric L. Wallace,[1] Dominique P. Germain,[5] Derralynn Hughes,[6,7] Peter Nordbeck,[4] Martine Clozel,[2] Aline Frey,[2] Christoph Wanner.[3] *[1]University of Alabama at Birmingham, Birmingham, AL; [2]Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland; [3]Fabry Center for Interdisciplinary Therapy, Würzburg, Germany; [4]University Hospital of Würzburg, Würzburg, Germany; [5]University of Versailles, Versailles, France; [6]University College London, London, United Kingdom; [7]Royal Free London NHS Foundation Trust, London, United Kingdom.*

Background: Substrate reduction therapy with lucerastat, an oral glucosylceramide synthase (GCS) inhibitor, aims to reduce Gb3 synthesis and prevent further Gb3 accumulation in patients with Fabry disease. Here, we describe a surprising effect of lucerastat on kidney function from the ongoing global Phase 3 clinical trial, MODIFY, and its open label-extension (OLE).

Methods: MODIFY (NCT03425539)(Wanner et al. 2022) randomized adult patients with Fabry disease 2:1 to lucerastat 1000 mg b.i.d. orally (dose adjusted based on eGFR) or placebo for 6 months. Participants who completed MODIFY were eligible to enter the OLE (NCT03737214) for up to 72 months. Prespecified efficacy endpoints included the change from baseline to Month-6 in eGFR in MODIFY and the annualized eGFR slope in the OLE.

Results: Of 118 participants randomized, 117 received study treatment (80 lucerastat, 37 placebo), 107 (91%) enrolled in the OLE, and 78 (67%) were ongoing at the Month-18 OLE interim analysis. Participants' demographic and baseline characteristics were similar across treatment groups. Kidney function remained stable in lucerastat-treated participants in MODIFY, and in the 39 participants with baseline renal impairment (eGFR <90 mL/min/1.73m^2), eGFR increased at Month-6 with lucerastat (mean [SE] 3.8 [2.2] mL/min/1.73m^2) and decreased with placebo (-1.6 [4.0] mL/min/1.73m^2). This unexpected renal effect was confirmed at Month-18, where lucerastat markedly slowed eGFR decline in the 93 participants with pre-randomization eGFR data, including in subgroups with severe disease course (baseline eGFR <90 mL/min/1.73m^2, classic males) and independent of gene variant amenability to migalastat. Lucerastat was well tolerated.

Conclusions: GCS inhibition with lucerastat might be a novel approach to stabilize or slow the progression of kidney dysfunction, a major therapeutic goal in patients with Fabry disease.

Funding: Commercial Support - Idorsia Pharmaceuticals Ltd

SA-PO655

A Phase 4 Study to Evaluate the Safety and Tolerability of Higher Infusion Rates of Agalsidase Beta to Shorten Infusion Duration in Fabry Disease: Interim Analysis

Maryam Banikazemi,[1] Ozlem Goker-Alpan,[2] Khan J. Nedd,[3] Manish Maski,[4] Chase Lee.[4] *[1]Department of Human Genetics, New York Medical College, New York, NY; [2]Lysosomal Disorders Research and Treatment Unit, Fairfax, VA; [3]Infusion Associates, Grand Rapids, MI; [4]Sanofi, Cambridge, MA.*

Background: Recombinant human α-galactosidase A (agalsidase beta), an enzyme replacement therapy (ERT) for treatment of Fabry disease (FD), is dosed biweekly at 1 mg/kg body weight, and infusion rates can be increased based on tolerability. The FDA label specifies ≥ 90 min infusions for all patients and maximum infusion rate of 15 mg/hr in patients ≤ 30 kg. The present study is evaluating the safety and tolerability of agalsidase beta at approved dose at an increased infusion rate with reduced total infusion volume.

Methods: This ongoing Phase 4 (NCT06019728), open label, single arm study will enroll 18 participants (≥2 to ≤65 years) with confirmed diagnosis of FD into five cohorts. The primary endpoints are percentage reduction of infusion duration from prestudy mean of the most recent three infusions and from an initial 120 minutes, along with shortest infusion duration each participant can tolerate. Here we present data from Cohort 1 and part of Cohort 2, with three heterozygous females and one male with variants in the *GLA* gene. All 4 patients were previously treated with agalsidase beta without any infusion associated reaction (≥ 30 kg).

Results: Three female patients aged 22, 19, and 49 years (mean body weight, 70.7 kg) and one male patient (age: 61 years, body weight: 100 kg) were enrolled. The duration of previous agalsidase beta treatment was 132, 60, 58, 43 months, and the prestudy mean duration of the three most recent infusions was 133, 136, 120, 90 minutes, respectively. The initial duration for first infusion in all three female patients was 120 minutes and was 60 minutes for the male patient. In subsequent infusions (four for the female patients and 2 for the male patient), the infusion time was gradually reduced to 20 minutes without any patient experiencing any infusion associated reaction (IAR). The plasma lyso-GL3 remained low and stable, and antidrug antibodies to agalsidase beta remained negative, in all four patients throughout the study.

Conclusions: Agalsidase beta infusion was given safely at a final time of 20-minute infusion duration in ERT-experienced female and male patients without any IAR. Further findings from this study will help in establishing a protocol to reduce duration of agalsidase beta infusion and minimize the treatment burden.

Funding: Commercial Support - Sanofi

SA-PO656

Early Intervention with Angiotensin Blockade to Reverse Proteinuria in Glycogen Storage Disease Type Ia (GSD Ia)

Feng-Jung Yang,[1,2] Yin-Hsiu Chien.[1,3] *[1]National Taiwan University Hospital, Taipei, Taiwan; [2]National Taiwan University Hospital Yun Lin Branch, Douliou, Taiwan; [3]National Taiwan University, Taipei, Taiwan.*

Introduction: Glycogen storage disease type Ia (GSD Ia) is caused by a deficiency in glucose-6-phosphatase (G6Pase) activity. This enzyme deficiency affects not only the liver but also the kidneys. In adolescents with GSD Ia, "silent" glomerular hyperfiltration commonly develops, progressing to microalbuminuria and, eventually, overt proteinuria. The progression to decreased glomerular filtration rate (GFR) is attributed to focal segmental glomerulosclerosis and interstitial fibrosis. Angiotensin blockade has long been employed to reduce proteinuria and slow GFR decline in renal diseases characterized by hyperfiltration injury, such as diabetes mellitus. Emerging evidence suggests that similar therapeutic benefits are observed in GSD Ia patients, with angiotensin blockade improving glomerular hyperfiltration and temporarily restoring normal GFR rates.

Case Description: Between January 2002 and July 2024, we retrospectively reviewed the clinical profiles and renal outcomes of patients diagnosed with GSD Ia at National Taiwan University Hospital. Thirteen patients were included in our study, four

of whom had a history of proteinuria. Among these, two patients experienced complete resolution of proteinuria following treatment with angiotensin receptor blockers (ARBs). One patient, treated with ARBs showed a reduction in proteinuria but subsequently developed acute renal failure, which resolved after discontinuing Diovan. Only one patient experienced a rapid decline in renal function, ultimately requiring dialysis and receiving a renal transplant one year later.

Discussion: Angiotensin blockade appears to decelerate the progression of GFR loss in patients with GSD Ia once it commences. Although systematic studies on angiotensin blockade in GSD Ia are lacking, early intervention upon the onset of persistent microalbuminuria holds potential as a strategy to mitigate the factors leading to accelerated glomerular obsolescence, microalbuminuria, proteinuria, and renal insufficiency. Given the generally favorable tolerance of these agents and the likelihood of their eventual use in the lifelong management of GSD Ia, early initiation of angiotensin blockade presents minimal risk and may alter the natural progression of GSD-associated nephropathy. Therefore, early administration of ARBs should be considered to optimize renal outcomes in GSD Ia patients.

SA-PO657

Hospitalization in Children: Experience of the Italian Registry of Pediatric Dialysis

Edoardo La Porta,[1] Rachele Spagnol,[2] Ester Conversano,[3] Enrico Vidal.[2] *[1]Istituto Giannina Gaslini, Genova, Italy; [2]Universita degli Studi di Padova Scuola di Medicina e Chirurgia, Padova, Italy; [3]Ospedale Pediatrico Bambino Gesu, Roma, Italy*.

Background: Children in dialysis experience complications leading to hospitalizations. This nationwide retrospective observational study, performed within the Italian Registry of Pediatric Chronic Dialysis (IRPCD), aims to describe complications in children on chronic dialysis and to compare hospitalization rates between dialysis modalities

Methods: Pediatric patients receiving HD or PD were recorded from 2000 to 2019 by the IRPCD. Hospitalization was defined as an admission involving at least one overnight stay, excluding hospitalizations for dialysis initiation and kidney transplantation. Reasons for hospitalization were categorized into infections related to dialysis, non-infectious complications related to dialysis, other infections, other non-infectious conditions, diagnostic tests, procedures or surgery, and other complications

Results: 847 incident dialysis patients (493 PD, 354 HD) were enrolled. The median age at dialysis initiation was 5 (1.0-10.7) years for PD and 13 (9.6-15.3) years for HD, females in both groups (59.6% and 54.8%). The primary cause of ESKD was CAKUT in both groups (41.6% in PD, 32% in HD); a significant difference was noted for glomerulonephritis, with a higher prevalence in the HD group (25.4 vs. 16.1%). Of the 847 patients, 418 (49.3%) required hospitalization, predominantly in the PD group (314 [75%] vs. 104 [24%] in HD). Median hospitalization duration was 6 days in HD (IQR 4.5-11) and PD (4-9) patients. Infections related to dialysis were the main cause of hospitalization (35%), followed by other non-infectious medical conditions (18%) and other ESKD-related complications (14%). The hazard of hospitalization over time was significantly lower for HD compared to PD patients (aHR 0.54[0.42;0.70]) and it decreased with increasing patient age (aHR 0.97[0.95;0.98]) and calendar year since dialysis initiation (aHR 0.97[0.96;0.98]). The hazard of hospitalization was not related to the primary renal disease but increased significantly with the number of complications. Children on PD for over 1 year had a higher aHR (1, ref) for changing treatment compared to HD patients (0.29[0.10;0.81])

Conclusions: The risk of hospitalization is linked to younger age at dialysis initiation and decreases in more recent calendar years. Children on PD face a higher risk of hospitalization resulting in a higher chance of switching dialysis modality.

SA-PO658

Assessment of Medication Adherence among Children with Glomerular Diseases

Jill Krissberg,[1] Maria Larkina,[2] Margaret Helmuth,[2] Abigail R. Smith,[3] Chia-Shi Wang,[4] Tetyana L. Vasylyeva,[7] Richard A. Lafayette,[5] Katherine R. Tuttle.[6] Cure Glomerulonephropathy. *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]University of Michigan, Ann Arbor, MI; [3]Northwestern University, Evanston, IL; [4]Emory University, Atlanta, GA; [5]Stanford University School of Medicine, Stanford, CA; [6]University of Washington School of Medicine, Seattle, WA; [7]Texas Tech University Health Sciences Center, Lubbock, TX*.

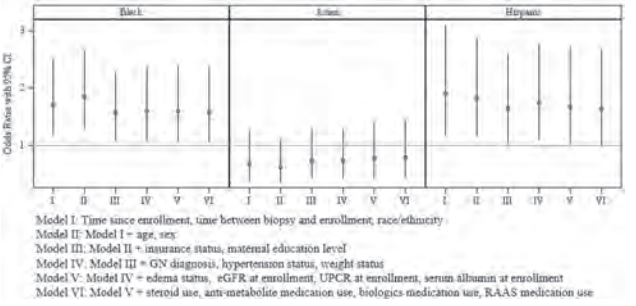
Background: Children with glomerular disease (GD) are subjected to complicated medication regimens where a high frequency of nonadherence has been described. While adult studies in kidney disease have identified differences in adherence for patients of racial or ethnic minorities, little is known in children with GD, and what may be driving any observed differences. This study aims to assess patient, treatment, and disease characteristics associated with medication nonadherence practices.

Methods: CureGN is a prospective cohort study of patients with GD diagnosed by biopsy within 5 years prior to enrollment. Adherence is assessed at enrollment and longitudinally by child (≥8 years) or parent (<8 years) completed questionnaires (adapted Medication Adherence Scale or Morisky MGL Medication Adherence Scale). We used multivariable mixed effects logistic regression models to explore associations between race and ethnicity and odds of nonadherence, sequentially adjusting for socioeconomic status, disease characteristics, and medications.

Results: In 692 children with GD (63% Non-Hispanic White, 21% Black, 6% Asian, 10% Hispanic White; 42% female; median [IQR] age of 11 [6, 14] years; 46% privately insured [US] at enrollment) 534 (77%) reported medication nonadherence at least once (median follow-up of 14 [4, 36] months with 4 [2, 6] completed surveys). Odds of nonadherence was higher for Black children (OR 1.58, 95% CI 1.06-2.38) and Hispanic White children (OR 1.64, 95% CI 1.00-2.68) vs Non-Hispanic White children, and for children with obesity (OR 1.99, 95% CI 1.43-2.79). Older age, international public insurance, hypertension, and presence of edema were associated with lower odds of non-adherence.

Conclusions: Medication non-adherence is common in children with GD and associated with Black race, Hispanic ethnicity and obesity, while lower odds of nonadherence were observed with older age, insurance type, and markers. These characteristics may help inform strategies to support medication adherence.

Funding: NIDDK Support



SA-PO659

Incidence and Severity of Extra-Kidney Manifestations and Outcomes in Pediatric Hemolytic Uremic Syndrome: A Retrospective Cohort Study

Keval Yerigeri, Rupesh Raina. *Department of Nephrology, Akron Nephrology Associates/Cleveland Clinic Akron General Medical Center, Akron, OH*.

Background: Hemolytic uremic syndrome (HUS) is a relatively uncommon disease amongst children with an annual incidence rate of 5.08 per 100,000. Through data analysis gathered using an electronic health record (EHR), we aimed to assess incidences of extra-renal manifestations involved with HUS, explore clinical outcomes, and conduct an epidemiological analysis on the renal profiles of these patients.

Methods: An observational, retrospective analysis was conducted using the data analytics program TriNetX. We assessed the cumulative incidence and 1-year mortality risk of extra-renal manifestations of hemolytic uremic syndrome (HUS) in pediatric patients at 3-, 6- and 12-months following diagnosis: hypertension, noninfective colitis, acute upper respiratory tract infections, disorders of GI tract, GERD, pulmonary edema and ARDS, epilepsy, heart disease, stroke, muscular disorders, and abnormal serum enzyme levels. We also analyzed clinical outcomes (incidence of ICU admissions, mechanical ventilation, hospitalizations, emergency department (ED) visits), mortality, and treatment over a 1-year follow-up period and the progression of overall kidney disease.

Results: Hypertensive diseases were the most prevalent cumulative incidence outcome, with a cumulative incidence of 25.7% and a survival probability of 70.4% at 1-year post-diagnosis. At 1-year post HUS diagnosis, 44/2,142 (2.1%) patients were deceased, 460/2,142 (21.5%) patients had an ED visit, 760/2,142 (35.5%) patients were hospitalized, 137/2,142 (6.4%) patients were admitted to the ICU, and 171/2,142 (8.0%) patients were mechanically ventilated/intubated. At 1-year post diagnosis in pediatric HUS patients 154/2,142 (7.2%) patients received treatment with Eculizumab, 86/2,142 (4.0%) patients received a transfusion of non-autologous platelets, and 248/2,142 (11.6%) patients ended up receiving hemodialysis. At 1-year post HUS diagnosis, 726/2,142 (34.0%) patients developed AKI and 85/2,142 (4.0%) patients developed ESRD. 323/2,142 (15.1%) patients developed CKD.

Conclusions: We present short term outcomes of pediatric HUS from a large database, including novel findings of the rates of hospitalization and ED visits, outcome of hypertension and extrarenal manifestations, as well as mortality and kidney disease progression over 1-year follow-up.

SA-PO660

Kidney ANCA-Associated Vasculitides (AAV) Manifestations and Outcomes in a Diverse Pediatric Cohort: A Single-Center Experience

Alvaro H. Orjuela, Emily Frierson, Sharanya Joginpalli. *Baylor College of Medicine, Houston, TX.*

Background: Renal involvement and long-term outcomes in childhood ANCA-associated vasculitides (AAV) has been understudied in various racial and ethnic minority groups.

Methods: This is a retrospective analysis of pediatric patients with renal AAV diagnosed between 2011 and 2023, followed at Texas Children's Hospital. We report the clinical features, histopathology, renal outcomes, and prognostic factors in a diverse pediatric patient cohort.

Results: A total 37 cases of pediatric renal AAV were identified. 17 (46%) patients presented with rapidly progressive glomerulonephritis (RPGN). At diagnosis, 3 (8%) patients had normal kidney function, 25 (68%) had an AKI, and 8 (22%) patients had an AKI that required acute renal replacement therapy (RRT). 24 (65%) patients received induction immunosuppression with cyclophosphamide and rituximab. 10 patients had therapeutic plasma exchange for RPGN. 8 of these patients were dialysis-dependent from diagnosis. As creatinine increases, the odds of dialysis dependency increases (OR=2.23, 95%CI [1.41, 3.5], p=0.001). Presentation with AKI not requiring RRT is associated with less dialysis dependency (OR=0.04, 95%CI [0.01, 0.29], p=0.001), while presentation with an AKI requiring RRT is associated with dialysis dependency (OR=60.67, 95% CI [5.26, 699.82], p=0.001). Kidney biopsies were scored using the renal ANCA renal risk score (ARRS) by Brix et al. The AUC for Brix score predicting dialysis dependency is 0.944 (95% CI=0.876-1.00) with a sensitivity of 88.89% and specificity of 88.46% for a score of >=9.

Conclusions: In a racially and ethnically diverse pediatric cohort, approximately a third of patients developed ESKD. As Brix score increases, the odds of dialysis-dependency increases.

Table 1. Demographic Characteristics

	N	(%)
Female	30	(81.81)
NH White	6	(16.7)
NH Black	5	(13.9)
Asian	3	(8.3)
Hispanic	22	(61.1)
English	27	(73)
Spanish	9	(24.3)
GPA	9	(24.3)
MPA	25	(67.5)
Other	3	(8.2)
Anti-MPO +	26	(70.2)
Anti-PR3 +	8	(21.6)
EGFR at diagnosis		
HTN	23	(62.2)
Proteinuria	34	(91.9)
Hematuria	33	(89.2)

SA-PO661

Clinicopathological Differences between Young Children and Adolescents in Childhood IgA Nephropathy

Yuko Shima,[1] Hironobu Mukaiyama,[1] Yu Tanaka,[1] Wataru Shimabukuro,[2] Hiroshi Kaito,[3] Ryojiro Tanaka,[3] Kandai Nozu,[4] Kazumoto Iijima,[4] Daisuke Tokuhara,[1] Norishige Yoshikawa,[5] Koichi Nakanishi.[2] *[1]Wakayama Kenritsu Ika Daigaku, Wakayama, Japan; [2]Ryukyu Daigaku Igakubu Daigakuin Igaku Kenkyuka, Nakagami-gun, Japan; [3]Hyogo Kenritsu Kodomo Byoin, Kobe, Japan; [4]Kobe Daigaku, Kobe, Japan; [5]Shakai Iryo Hojin Aijinkai Takatsuki Byoin, Takatsuki, Japan.*

Background: Proteinuria remission is the most significant predictive factor for kidney outcome in childhood IgA nephropathy (c-IgAN). In our previous study, younger children were more likely to achieve proteinuria remission and less likely to proteinuria recurrence. Among c-IgAN, there might be differences in clinicopathological findings depending on age regardless of the timing of kidney biopsy. So, the purpose of this study is to clarify the clinicopathological features between younger children whose onset age〈 10 years old and adolescents whose onset age ≧ 10 years old in this study.

Methods: From July 1976 to December 2022, among 567 children with biopsy-proven IgAN at Kobe University and Wakayama Medical University, those with age at onset were available in 557. We investigated clinicopathological differences in 213 (38.2%) younger c-IgAN and the other 344 (61.8%) adolescent c-IgAN. A 1:1 propensity score matching was performed to account for between-group differences (duration from onset to kidney biopsy and kidney biopsy before or after 1990), and 204 matched pairs were obtained.

Results: Adolescent c-IgAN were more detected by school screening program (80.4 vs. 71.1%, p=0.04). Proteinuria was more in younger c-IgAN (0.8 vs. 0.5 g/gCr, p=0.02). The prevalence of tubular atrophy/interstitial fibrosis present was higher in adolescent c-IgAN (44.3 vs.54.9%, p=0.04). The Kaplan-Meier analysis of proteinuria remission showed that younger c-IgAN achieved significantly higher proteinuria remission than ad adolescent c-IgAN (75.4 vs 54.9% at 10 years; 95%CI: 67.4-82.1 vs. 44.8-64.5, p=0.0004).

Conclusions: In adolescent c-IgAN, tubular atrophy/interstitial fibrosis are more likely to be formed regardless of the timing of kidney biopsy, making it difficult to achieve proteinuria remission.

SA-PO662

Single-Cell Transcriptome Sequencing Identifies New Molecular Markers for Pathogenicity of IgA Deposition in the Mesangial Region

Wan JunLi,[1,2] Qilin Chen,[1,2] Li Qiu.[1,2] *[1]Children's Hospital of Chongqing Medical University National Clinical Research Center for Child Health and Disorders, Chongqing, China; [2]Children's Hospital of Chongqing Medical University Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China.*

Background: In a variety of glomerular diseases represented by IgA nephropathy, significant IgA deposition can be seen in the glomerular mesangial area. However, the biomarkers of the pathogenic changes of mesangial cells caused by it are still unclear.

Methods: Children with nephrotic syndrome who had minimal change disease (MCD) with IgA deposition in the mesangial area who were referred to our center in the past 10 years were enrolled as IgA+MCD group. MCD without IgA deposition were enrolled as MCD group. IgAN nephropathy with nephrotic syndrome were defined as NS-IgAN group. The general data, laboratory examination, treatment and follow-up informations of patients were collected and analyzed. Single-cell transcriptome sequencing (scRNA-seq) was performed on renal biopsy tissues. Finally, the findings of scRNA-seq were verified by immunohistochemical staining of renal tissue.

Results: The albumin of all the enrolled patients was less than 30g/L, there was no significant difference between the group IgA^+MCD and the group MCD, but they both were lower than that of group NS-IgAN ($P<0.05$). There was no significant difference in the efficacy of glucocorticoid therapy between group IgA^+MCD and group MCD. The analysis of proportion of cell subtypes and the similarity of transcription levels by scRNA-seq of renal biopsy tissue suggested that the transcription level of children with IgA+MCD was similar to that of children with MCD. Comparative analysis of different expression genes in mesangial cells suggested that the expression level of FN1 in children with NS-IgAN was significantly higher than that in children with IgA+MCD. Whether mesangial cells or podocytes, IgAN group was related to molecular characteristics such as extracellular matrix and fibrosis, while other groups were not obvious. Immunohistochemical staining of FN in renal tissue showed that the expression of FN in kidneys of children with NS-IgAN was significantly higher than that of group IgA+MCD and group MCD.

Conclusions: The chilid with IgA^+MCD was similar to MCD in clinical features and molecular status of renal tissue. The deposition of IgA in the mesangial region did not cause the increase of extracellular matrix represented by the increase of FN expression and the enhancement of pro-fibrotic function, which meant that the deposition of IgA did not have a pathogenic effect

SA-PO663

Impact of Proteinuric Glomerular Disease on Educational Outcomes in the Cure Glomerulonephropathy (CureGN) Study

Mahie M. Abdullah,[1,2] Matthew Schuchman,[1,2] Laura J. Castellanos,[1,2] Pamela Singer,[1,2] Abby M. Basalely,[1,2] Carol L. Shen,[1,2] Rachel Frank,[1,2] Suzanne Vento,[1,2] Christine B. Sethna.[1,2] On behalf of CureGN. *[1]Northwell Health, New Hyde Park, NY; [2]Cohen Children's Medical Center, Queens, NY.*

Background: Children with chronic health disorders frequently experience difficulties within the educational system, which can result in poorer educational outcomes (EO). However, EO in proteinuric glomerular diseases remain understudied. The objective was to assess how glomerular disease diagnosis (GDD) and kidney function affect school enrollment, special education and educational attainment.

Methods: Longitudinal analysis included all visits from children aged 5-18 years enrolled in CureGN. Main exposures were GDD (minimal change disease [MCD], focal segmental glomerulosclerosis [FSGS], membranous nephropathy [MN], IgA nephropathy [IgA]) and glomerular filtration rate (eGFR, CKID U25). EOs were absenteeism (>15 days of missed school/year), school enrollment (part-time/home schooled/not enrolled), special education and grade repetition. Generalized estimating equations (GEE) examined the association of GDD and eGFR individually with EOs in models adjusted for age, sex, maternal education and duration of diagnosis.

Results: Of 901 children (12.65±3.56 years, 58.8% male, 28.23 months follow-up), the prevalence of absenteeism was 11.1%, part-time enrollment was 1.4%, not enrolled was 2.8%, special education was 12.5%, and grade repetition was 1.9%. In adjusted models, the diagnosis of IgA was associated with lower odds of absenteeism compared to MCD. eGFR was not associated with any EO. (Table)

Conclusions: In CureGN, GDD was associated with absenteeism, highlighting the importance of developing individualized approaches to decrease the risk of adverse EOs and promote academic success. Further research is needed to understand the underlying mechanisms of GDD that promote such disparities in this vulnerable population.

Funding: NIDDK Support

Table: Generalized Estimating Equations of Educational Outcomes in Relation to Glomerular Diseases and eGFR

Outcomes		Exposure Variables						
		Diagnosis				eGFR		
		MCD*	OR	(95% CI)	p	OR	(95% CI)	p
Primary	Absenteeism	FSGS	1.028	(0.731-1.444)	0.875	0.996	(0.991-1.001)	0.088
		MN	0.938	(0.496-1.775)	0.845			
		IgA	0.685	(0.502-0.936)	0.017			
Secondary	Part-time	FSGS	0.900	(0.336-2.411)	0.834	0.997	(0.987-1.008)	0.593
		MN	1.524	(0.272-8.549)	0.632			
		IgA	0.441	(0.171-1.138)	0.090			
	Home-schooled	FSGS	2.034	(0.968-4.276)	0.061	1.001	(0.993-1.009)	0.823
		MN	2.565	(0.854-7.705)	0.093			
		IgA	1.030	(0.458-2.316)	0.943			
	Not-enrolled	FSGS	2.669	(0.878-8.117)	0.084	0.998	(0.989-1.007)	0.642
		MN	2.227	(0.485-10.233)	0.304			
		IgA	0.833	(0.218-3.173)	0.788			
	Received special education	FSGS	1.554	(0.910-2.655)	0.106	0.997	(0.991-1.003)	0.282
		MN	1.376	(0.520-3.642)	0.520			
		IgA	1.035	(0.604-1.771)	0.901			
	Repeated a grade	FSGS	1.222	(0.336-4.448)	0.761	0.994	(0.985-1.003)	0.185
		MN	2.445	(0.678-8.822)	0.172			
		IgA	0.403	(0.088-1.839)	0.241			

* MCD is the reference group | OR = odds ratio; CI = confidence interval; p = p-value

SA-PO664

Predictors of Lack of Remission in Pediatric Patients with IgA Vasculitis with Nephritis: A Retrospective Review

Virginia Hoch,[1,2] Sandra G. Yang,[3] Carlos E. Araya,[4] Ali Mirza Onder.[2]
[1]Christiana Care Health Services Inc, Wilmington, DE; [2]Nemours Children's Hospital Delaware, Wilmington, DE; [3]Thomas Jefferson University Sidney Kimmel Medical College, Philadelphia, PA; [4]Nemours Children's Clinic, Orlando, FL.

Background: Despite favorable outcomes in the majority of cases, 3-5% of children with IgA vasculitis with nephritis (IgAVN) fail to respond to treatment and progress to advanced chronic kidney disease or end stage renal disease (ESRD). It is therefore crucial to predict early markers of progressive disease so that treatment regimens can be quickly escalated. This retrospective study was conducted to investigate predictors of lack of remission in pediatric IgAVN patients.

Methods: We identified pediatric patients from two hospital campuses at our academic institute diagnosed with biopsy-proven IgAVN from 2013 to 2023. We retrospectively collected demographic, clinical, laboratory and histopathologic variables at diagnosis and during 2 years of follow-up. The primary outcome was lack of remission at 6 months follow-up. Secondary outcomes were progression to ESRD and lack of remission at last data point. To assess for association with lack of remission, we performed logistic regressions as well as Mann-Whitney U tests and Pearson's chi-squared or Fisher's exact tests for numerical and categorical variables, respectively.

Results: Thirty-one patients were identified for analysis in our study (23 male and 8 female) with mean age of 10 years at diagnosis. Remission was achieved in 26/31 (84%) of cases, with 15/31 (48%) achieving remission by 6 months. Lack of remission at 6 months was associated with presence of gross hematuria (p=0.024) and nephritic-nephrotic syndrome (p=0.022) during the study period. Three patients (9.6%) progressed to ESRD during the study period; no variables were significantly associated with this outcome. Full remission was associated with lower serum albumin (p=0.03) and higher eGFR (p=0.023) at 9 months.

Conclusions: In the studied cohort, presence of gross hematuria and nephritic-nephrotic syndrome was associated with lack of remission at 6 months. We found no early predictors for progression to ESRD. Our ESRD prevalence is higher than that in previous reports, which may be due to our sample size. We also found a lower rate of full remission and a slower rate of achieving full remission in our cohort. Further research including larger patient populations is needed to better identify predictors of lack of remission and progression to ESRD for pediatric IgAVN patients.

SA-PO665

Association of Serum Free Cortisol and Kidney Function in Children and Adolescents with Type 1 Diabetes Mellitus

Lance A. Sloan,[1] Katia P. Sloan,[1] Eduardo F. Chagas,[2] Sandra M. Barbalho,[2] Jesselina F. Haber.[2] *[1]Texas Institute for Kidney and Endocrine Disorders, Lufkin, TX; [2]Universidade de Marilia Faculdade de Medicina e Enfermagem, Marilia, Brazil.*

Background: The treatment of Type 1 Diabetes mellitus (DM1) has always been a challenge for health care professionals due to the difficulties of achieving good glycemic control. Poor glycemic control can result in hyperfiltration and the development of diabetic kidney disease. Cortisol plays an essential role in the body's metabolism and chronic elevation or dysregulation of cortisol levels can have adverse effects on renal function and glycemic control. Our objective was to investigate the association between serum free cortisol and renal function in children and adolescents with DM1

Methods: A cross-sectional observational study was conducted with 61 individuals of both sexes (6-19 years) diagnosed with DM1 for at least 12 months and with C-peptide values < 0.3ng/ml. Renal function was measured as glomerular filtration rate (eGFR) using CKiD equation. Serum albumin (g/dL), creatinine (mg/dL), urea (mg/dL), and free cortisol (µg/dL) were collected in the morning in a fasting state. An early morning urine sample was collected for urine albumin to creatinine ratio (uACR). A multiple linear regression was used to explore the effect of cortisol (independent variable) on the dependent variables (eGFR, Creatinine, urea, albumin, uACR) controlling the effect of the independent covariates (sex, age, BMI-z, HbA1C and length of diagnosis).

Results: Increases in Cortisol, length of diabetes, HbA1c and being female was associated with an increase in eGFR and possibly hyperfiltration. Age was associated with a reduction in the eGFR. A significant effect of serum cortisol and gender explained 13.6% (R^2) of the creatinine variation and 19.0% (R^2) of the urea variation. Increases in cortisol in males was associated with an increase in creatinine and increases in cortisol in females was associated with a decrease in urea. An increase in cortisol was positively associated with uACR and inversely related to serum albumin.

Conclusions: There is a direct relationship between cortisol, eGFR, and uACR in children and adolescents with DM1. Cortisol may be having an impact on renal function which in the long term could potentially play a role in the progression of kidney disease in this population.

Funding: Private Foundation Support

SA-PO666

Urinary DKK3 as a Novel Biomarker for Kidney Function Decline in Children with Alport Syndrome

Jan Boeckhaus, Oliver Gross. *Universitatsmedizin Gottingen, Gottingen, Germany.*

Background: CKD progression in children with Alport syndrome (AS), a common genetic kidney disease, is hard to predict. DKK3 predicts declining kidney function in adults and advanced CKD children, but its usefulness in early AS detection is unknown.

Methods: Urine samples from 50 children enrolled in the EARLY PRO-TECT Alport trial were analyzed to address this hypothesis.

Results: DKK3 levels were higher than those of the general population reported in the literature. DKK3 levels were also higher elevated in patients with later AS stages. Furthermore, children, who were not treated with RASi, had higher DKK3 levels compared to treated children. Children with above-average DKK3 levels were more likely to experience increased albuminuria compared to children with below-average DKK3 levels after 2 years of follow-up.

Conclusions: This study demonstrated that urinary DKK3, a biomarker for CKD progression, is significantly increased in children at very early stages of AS. Children with above-average DKK3 had higher risk of disease progression.

Age (years)	9.0±4.2
Male no. (%)	49 (98)
Mode of inheritance	–
X-linked	44 (88)
Autosomal	5 (10)
Unknown	1 (2)
BMI (kg/m2)	18±4
Systolic/diastolic blood pressure (mmHg)	105±13/60±9
Creatinine (mg/dl)	0.5±0.2
eGFR (ml/min/1.73 m2)	127±25
Albuminuria (mg/g creatinine)	54 (160)
RASi	42 (84)
AS stage	–
0	22 (44)
I	19 (38)
II	9 (18)

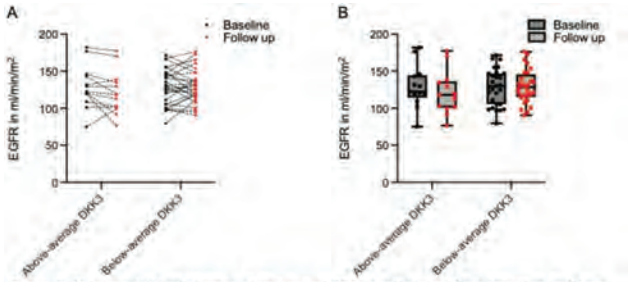


Figure 2: A) intraindividual change of estimated GFR in ml/min/m² from baseline to follow up after 2 years seperated by mean DKK3 levels (n=41). B) group comparison of estimated GFR in ml/min/1.73m² in children with above- and below average DKK levels at baseline and after two year follow up (n=41).

SA-PO667

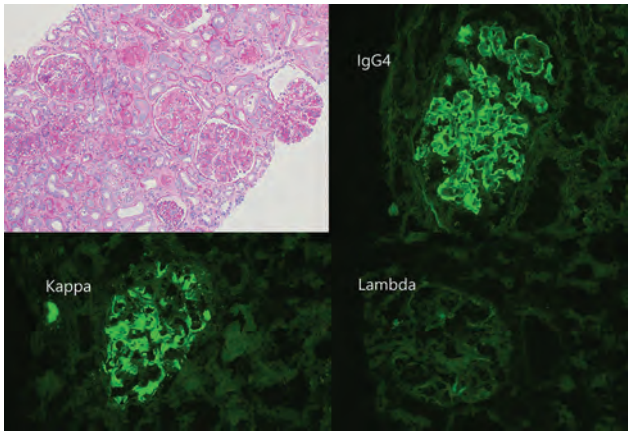
Pediatric Proliferative Glomerulonephritis with Unique IgG4

Gabriela Rocha, Jessamyn S. Carter. *University of Michigan Michigan Medicine, Ann Arbor, MI.*

Introduction: Proliferative Glomerulonephritis with monoclonal IgG deposits (PGNMID) is a recently established diagnosis defined by monoclonal immunoglobulin deposition in the glomerulus. PGNMID is rare and typically found in the adult population. Here, we present a unique case of pediatric PGNMID secondary to IgG4 deposition.

Case Description: A 10-year-old female with history of metastatic neuroblastoma status post extensive chemotherapy and abdominal radiation in remission on long-term difluoromethylornithine developed hematuria, proteinuria (protein:creatinine ratio 14), glycosuria, and hypertension. She was determined to have stage 3a chronic kidney disease and was started on amlodipine. While awaiting renal biopsy she developed hypoalbuminemia, edema, and acute kidney injury requiring admission for augmented diuresis. Biopsy showed proliferative glomerulonephritis with IgG4 and kappa immunoglobulin deposits with moderate glomerular scarring and 15% interstitial fibrosis and tubular atrophy. Bone marrow biopsy was negative for clonal disorder. Serum protein electrophoresis was nondiagnostic due to oligoclonal bands from recent IVIG infusion. Urine Bence-Jones screen showed lambda light chain M-protein, an unexpected finding as the biopsy showed kappa. For her PGNMID versus IgG4-related disease, the patient was recently started on steroids and rituximab.

Discussion: PGNMID is a recently described diagnosis, more commonly seen in adults, which can be a source of progressive kidney disease in children. PGNMID is most often caused by IgG3 and can be a monoclonal gammopathy of renal significance. In this case, PGNMID would not explain glycosuria which, along with IgG4 restriction and the light chain mismatch, leads to diagnostic uncertainty. Her disease may instead represent an overlap with IgG4 disease. Our goal in sharing this case is to raise awareness for both PGNMID and IgG4 disease in pediatric patients and emphasize the potential overlap in pathophysiology.



SA-PO668

Assessment of Kidney Size in African American Children with Sickle Cell Disease: A Matched-Pair Analysis

Asma B. Shaoba, Yaoping Zhang, Angelika C. Gruessner, Okwudili Nnaji, Anil K. Mongia, Oluwatoyin F. Bamgbola. *SUNY Downstate Health Sciences University, New York City, NY.*

Background: Sickle cell disease (SCD) is caused by a beta-globin gene mutation that produces sickling of red blood cells. Increase in cardiac output from sickle cell anemia produces hyperfiltration that results in a progressive increase in renal size. We aim to examine the impact of SCD morbidity on kidney size using renal ultrasound.

Methods: The study included 31 African Americans with SCD aged 3 to 20 years and 57 matched controls who were seen in outpatient clinic from 01/ 2018 to 12/2022. Cases were matched with controls at 1:2 ratio. We examined the impact of the severity of hemoglobinopathy on kidney size by stratification of subjects based on HBSS and HBSC subtypes, and SCD morbidity score.

Results: Four subjects had HBSC and 27 had HBSS genotypes. The right and the left kidney volume of SCD cases were significantly larger than of controls [$p < 0.0001$] (Table 1). There was a significant difference in eGFR between subjects and controls, and among individuals with HBSS and HBSC genotypes (Table 1 and Fig. 1). A unit increase in SCD morbidity score was associated with 5.7 and 5.1 cm3 volume increase for right and left kidneys respectively.

Conclusions: Severity of sickle cell anemia positively correlates with a greater eGFR and (therefore) volume of hyperfiltration, which in turn, are the primary determinants of nephromegaly.

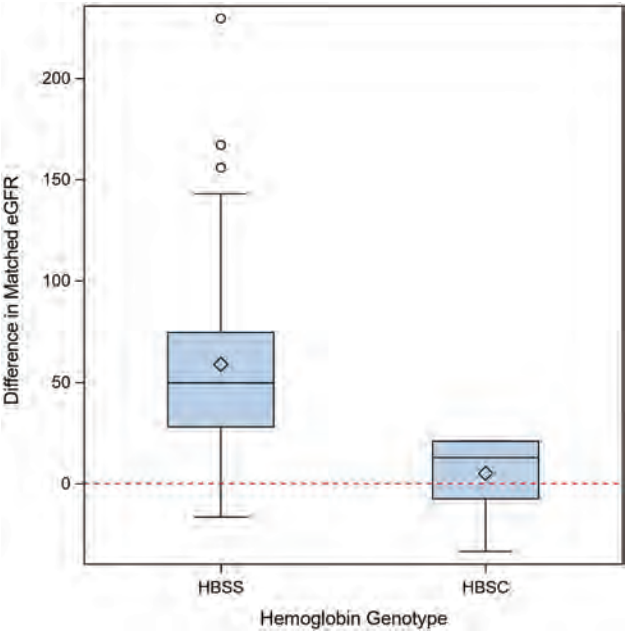


Fig 1: Box plot of eGFRs for the difference between matched subjects by hemoglobin genotypes.

Table 1: Comparison of the kidney volume, hemoglobin concentration and estimated GFR between Sickle cell disease subjects and controls.

Parameters	Number of SCD subject-control matches	Difference in the median values between SCD cases and Controls	p-values
Right kidney volume (cm^3)	57	36 (-166 – 27)	< 0.0001
Left kidney volume (cm^3)	57	28 (-133 – 48)	< 0.0001
Hemoglobin (gm/dL)	49	-3.8 (-8.4 – 2)	< 0.0001
Estimated GFR (ml/min/1.73 m^2)	52	43 (-34 – 230)	< 0.0001

SA-PO669

Kidney Pathological Findings in MYH9-Related Disease

Ryo Nakatani,[1] Kenichiro Miura,[1] Yoko Shirai,[1] Yasufumi Ohtsuka,[4] Yoko Ohwada,[5] Takao Konomoto,[7] Tamaki Morohashi,[9] Koji Tsugawa,[6] Sekiko Taneda,[1] Kazuho Honda,[2] Shinji Kunishima,[8] Kenji Ishikura,[3] Motoshi Hattori.[1]
[1]Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan; [2]Showa Daigaku Daigakuin Igaku Kenkyuka Igakubu, Shinagawa-ku, Japan; [3]Kitasato Daigaku Igakubu, Sagamihara, Japan; [4]Saga Daigaku Igakubu Daigakuin Igakukei Kenkyuka, Saga, Japan; [5]Dokkyo Ika Daigaku, Shimotsuga-gun, Japan; [6]Hirosaki Daigaku Igakubu Daigakuin Igaku Kenkyuka, Hirosaki, Japan; [7]Miyazaki Daigaku Igakubu Daigakuin Ikagaku Kangogaku Kenkyuka, Miyazaki-gun, Japan; [8]Gifu Iryo Kagaku Daigaku, Seki, Japan; [9]Nihon Daigaku Igakubu Daigakuin Igaku Kenkyuka, Itabashi-ku, Japan.

Background: *MYH9*-related disease (*MYH9*-RD) is characterized by congenital macrothrombocytopenia, progressive kidney failure, and sensorineural hearing loss. There are limited data of kidney pathological findings of *MYH9*-RD because of the low platelet count. Although focal segmental glomerulosclerosis (FSGS) and glomerular basement membrane (GBM) abnormalities similar to Alport syndrome have been anecdotally described, no comprehensive studies have been performed.

Methods: We conducted a cross-sectional nationwide survey in Japan. Questionnaires were initially sent to 145 institutions. We asked the eligible patients if a kidney biopsy had been performed. Eight kidney biopsy samples from seven patients were finally included in the study. All pathological samples were examined by pediatric nephrologists and pathologists at our institution. This study was supported by "Research on Rare and Intractable Diseases, Health and Labor Sciences Research Grants" from the Ministry of Health, Labour and Welfare (Grant No. 20FC1028), Japan.

Results: All seven patients had pathogenic variants in the *MYH9* gene: R702C in three patients, R702H in two patients, D1424H in one patient, and Q1068_L1074dup in one patient. The median ages at onset of proteinuria and kidney biopsy were 7 years and 11 years, respectively. Mesangial matrix expansion was observed in all samples, and two samples also showed FSGS. Immunofluorescence study showed significant depositions of immunoglobulin and complement in two samples: IgG and C1q in one patient and IgA and C3 in one patient. Electron microscopy showed segmental foot process effacement, endothelial cell swelling, and electron-dense deposits (EDD) in eight, six, and five samples, respectively. GBM abnormalities such as thinning, thickening, and splitting of the lamina densa were observed in three samples.

Conclusions: Mesangial matrix expansion and focal foot process effacement were commonly observed in *MYH9*-RD patients. In addition, a variety of pathological findings including immunoglobulin and complement depositions with EDD and GBM abnormalities were also observed. These results may have important implications for the disease mechanism and treatment of *MYH9*-RD.

SA-PO670

Utility of Adult-Derived Biomarkers for Assessment of Kidney Function in Pediatric ANCA-Associated Vasculitis

Kelly Brown,[1,2] Simranpreet K. Mann,[3,2] Kirandeep Toor,[3,2] Else S. Bosman,[4] Audrea Chen,[5] Cherry Mammen,[4,1] David A. Cabral,[4,1] Kimberly Morishita.[4,1]
On behalf of the Pediatric Vasculitis (PedVas) Investigator Network.
[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]BC Children's Hospital Research Institute, Vancouver, BC, Canada; [3]The University of British Columbia, Vancouver, BC, Canada; [4]BC Children's Hospital, Vancouver, BC, Canada; [5]The Hospital for Sick Children, Toronto, ON, Canada.

Background: In adults with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), measures of ANCA positivity and antigen specificity, estimated glomerular filtration rate (eGFR), and urine proteins are informative of kidney function and aid treatment decisions. Despite aggressive therapy, two-thirds of pediatric AAV patients have persistently reduced renal function. The objective of this study is to evaluate the utility of adult-derived kidney markers in pediatric AAV.

Methods: Eligible participants < 18 yrs of age in the ARChiVe/PedVas initiative had a diagnosis of small vessel vasculitis including AAV, ANCA positive pauci-immune glomerulonephritis, and unclassified primary vasculitis. Kidney disease activity was defined by the renal component of the pediatric vasculitis activity score. Kidney function was categorized by eGFR into KDIGO stages. Predictive analysis of ANCA and baseline eGFR for 1- to 2-year outcomes were conducted using adjusted regression models and/or a proportional odds logistic regression model. Concentrations (ELISA) of MCP-1, sCD25, and sCD163 in time-of-diagnosis urine was measured for correlations with baseline and 1-year kidney state using R statistical language.

Results: At diagnosis, patients with MPO-ANCA had similar levels of overall disease activity to those with PR3-ANCA but had 2.4 times higher odds of kidney involvement ($P = 0.008$) and 6.0 times higher likelihood of worse kidney dysfunction ($P < 0.001$). Time-of- diagnosis eGFR was informative to future kidney function with the odds of worse kidney function at 1-year being 18.2 times higher for children with moderately-severely reduced function at onset. Urine proteins performed poorly as indicators of kidney disease activity at onset and follow up.

Conclusions: The results of this study show mixed utility of adult derived biomarkers for use in the pediatric population, with severe kidney disease at onset and function over the first 1-year being best informed, respectively, by MPO-ANCA seropositivity and baseline eGFR. The study illustrates the need for pediatric AAV-focused studies for novel kidney biomarker discovery.

Funding: Government Support - Non-U.S.

SA-PO671

Rapidly Progressive Kidney Failure in a Patient with Longstanding Juvenile Dermatomyositis

Sarah Rogal,[1] Donghyang Kwon,[2] Sun-Young Ahn.[1] *[1]Children's National Hospital, Washington, DC; [2]MedStar Georgetown University Hospital, Washington, DC.*

Introduction: Juvenile dermatomyositis (JDM) is an inflammatory myopathy characterized by proximal muscle weakness, heliotrope rash and Gottron papules. Collapsing focal segmental glomerulosclerosis (cFSGS) and glomerulocystic disease have not been previously reported with JDM.

Case Description: A 21 year-old male with JDM (diagnosed 9 years ago), osteoporosis, calcinosis, and restrictive lung disease presented with a 3-week history of left knee and foot pain concerning for cellulitis. He recently discontinued mycophenolic acid and tofacitinib for a low white blood cell count but continued hydroxychloroquine, prednisone, and monthly intravenous immunoglobulin. Initial labs were concerning for serum creatinine of 2.9 mg/dl, increased from baseline of 0.92 mg/dl, serum albumin 1.7 g/dl, and urine protein to creatinine ratio 4.8. An ultrasound showed increased renal echogenicity. C3 was 84(nl>90 mg/dl), C4 and creatinine kinase normal, ANA 1:80, while anti-dsDNA, HIV, hepatitis B and C were negative. His cellulitis was treated with IV clindamycin and cefepime. A kidney biopsy showed cFSGS, glomerulocystic changes, and tubules with microcystic dilatation(Fig 1). Widely scattered immune complex deposits were seen on electron microscopy and IV methylprednisolone was given for 3 days. However, his kidney function continued to worsen leading to the initiation of hemodialysis.

Discussion: Renal involvement in JDM is rare with acute kidney injury secondary to myoglobinuria and nephrotic syndrome reported. Collapsing FSGS has been reported in patients with parvovirus B19 and HIV, both of which were absent in our patient. It has also been observed in patients who received high doses of pamidronate; however, our patient's cumulative dose(given for osteoporosis) was much lower than the reported cases(300 mg vs. 1170-3960 mg). This is the first report to our knowledge of cFSGS and glomerulocystic features in a patient with JDM. Further investigation is needed to elucidate whether there is a genetic or immunologic predisposition for patients with JDM to develop cFSGS and glomerulocysts.

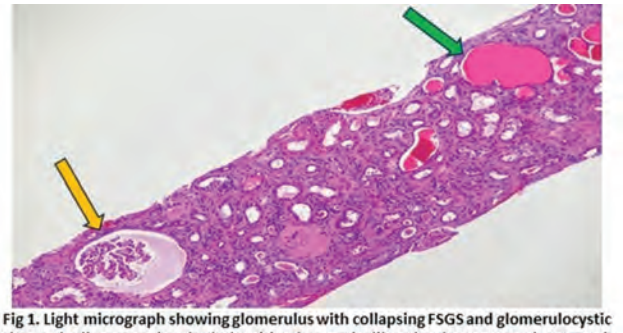


Fig 1. Light micrograph showing glomerulus with collapsing FSGS and glomerulocystic change (yellow arrow) and tubule with microcystic dilatation (green arrow); H&E stain.

SA-PO672

ACTION3 Phase 3 Clinical Trial Assessing the Efficacy and Safety of DMX-200 (Repagermanium): Mid-trial Safety Assessment and Pharmacometric Model-Informed Pediatric Dose Selection

David E. Fuller,[1] Erno van Schaick,[2] Alisha J. Smith,[1] Robert Shepherd,[1] Carl White.[1] *[1]Dimerix Bioscience Pty Ltd, Melbourne, VIC, Australia; [2]Calvagone, Amsterdam, Netherlands.*

Background: DMX-200 (repagermanium) is a C-C chemokine receptor type 2 (CCR2) inhibitor which when administered with an angiotensin II receptor blocker (ARB) inhibits CCR2/AT1R complex function. This modulates the aberrant response to inflammation, blocking attraction of inflammatory cells into the kidneys and reducing

both proteinuria and podocyte loss. Following encouraging Phase 2 data, Dimerix have commenced a Phase 3 randomized double-blind placebo-controlled study (ACTION3) investigating the efficacy and safety of DMX-200 (120 mg BID) compared with placebo in patients with FSGS on a stable ARB dose. In March 2024 the study passed an interim futility assessment, and following safety review, PK assessment and pharmacometric modelling, will now include adolescent patients aged 12-17 years.

Methods: An interim safety analysis covered the first n=91 patients randomised in ACTION3. PK data from n=46 DMX-200 evaluable patients was assessed in a population PK model (popPK) built on previous data from Phase 1 and 2.

Results: Median duration of exposure to DMX-200 or placebo was 9.1 months (range 0.5-17.3) with median total exposure of 65.76 g (range 3.6-124.56 g). 277 individual adverse events (AEs) were reported by 72/91 (79%) patients. 80% of AEs were rated as "mild" and reflected the underlying disease (FSGS) and associated comorbidities. DMX-200 has a half-life ($t_{1/2}$) of 3.6 hrs and is not metabolised. PK data were variable with a wide exposure range due to the short $t_{1/2}$ of DMX-200 but were comparable with prior data and supported the use of the popPK model to predict adolescent exposure. Simulations of exposure in renally impaired adolescent patients (AP) showed that AP will generally have similar drug exposures to adults. APs with a combination of very low body weight and poor renal function may experience higher exposure that is likely covered by the observed exposures in adults.

Conclusions: No safety signal that would preclude paediatric dosing was identified. Based on this comprehensive review of safety, PK data and PopPK modelling of predicted exposure, a dose of 120mg BID will be used for adolescents (12-17 years) who are now being recruited into the ACTION3 study.

Funding: Commercial Support - Dimerix Biosciences Pty Ltd

SA-PO673

Pediatric Peritoneal Dialysis after Cardiopulmonary Bypass: Long-Term Outcomes

Sarah Couser, Stuart Goldstein, David L. Morales, David S. Cooper, Michael A. Carlisle. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Acute kidney injury (AKI) with fluid overload is a common complication for children undergoing congenital heart surgery and is associated with increased mortality and extended length of hospital stays (LOS). We and others have demonstrated early initiation of peritoneal dialysis (PD) in the post-operative period is associated with decreased fluid accumulation, ICU LOS and mortality. Since 2010, our institution developed a systems-wide practice to electively place PD catheters at the time of cardiopulmonary bypass (CPB) surgery in a child deemed to be at high risk for AKI. Although outcomes for these patients are often excellent, there has been no investigation into the outcomes of patients who continue to require PD beyond AKI. We aimed to further understand the outcomes our population in order for providers to better counsel families on goals on care.

Methods: This is a retrospective cohort study of patients aged birth to 18 years deemed at risk for AKI who received placement of a PD catheter in the OR after CPB between 2018 and 2023.

Results: 342 patients received a PD catheter over the study period. 112 (33%) had continuous PD for a median time of 2 days (IQR 1-5 days, range 1-157 days). 9/112 (8%) of these patients required PD for >14 days. Of these 9 patients, 5/9 survived until CICU discharge and 4/9 survived until hospital discharge. 2/4 patients who survived until hospital discharge never recovered kidney function. 1/8 patients survived until a year after PD initiation, with an additional patient surviving, but currently only 11 months old. 5/9 patients became tracheostomy and ventilator dependent, 2/9 remained intubated until time of death, and 2/9 were discharged home with low flow nasal cannula oxygen supplementation.

Conclusions: The requirement of PD for >14 days was associated with more than 50% in-hospital mortality, poor respiratory outcomes, and 1-year survival less than 25%. Despite the excellent clinical outcomes we have observed for patients receiving PD in the post-operative AKI period, patients who require PD for prolonged courses appear to have poor clinical outcomes and may need different care counseling.

SA-PO674

Association of Sleep-Disordered Breathing with Isolated Diastolic Hypertension in Youth Referred for Hypertension Disorders

Ashna Pudupakkam,[1] Sahar Siddiqui,[1] Fallon Campbell,[1] Andrew M. South,[2] Elizabeth A. Onugha.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Sleep-disordered breathing is associated with an increased risk of hypertension. Studies have shown that adults with sleep-disordered breathing have a higher prevalence of isolated diastolic hypertension. While youth with sleep-disordered breathing have higher daytime diastolic blood pressures, the association of sleep-disordered breathing with isolated diastolic hypertension in youth is unclear. We aimed to determine the association of sleep-disordered breathing with isolated diastolic hypertension in youth referred for hypertension disorders.

Methods: Cross-sectional analysis of baseline data from the Study of the Epidemiology of Pediatric Hypertension (SUPERHERO), a multisite Registry that retrospectively collects electronic health record data validated by manual record review. We included patients with ICD-10 codes for hypertension disorders at the index visit at subspecialty hypertension clinics who were aged <19 years. We excluded patients with ICD-10 code-identified pregnancy, kidney failure on dialysis, or kidney transplantation. Our exposures were an ICD-10 code visit diagnosis for sleep-disordered breathing at the index visit. Our outcomes included blood pressure severity at the index visit. We used unadjusted generalized linear models.

Results: In our cohort, 5% of participants (560 of 10,968) had an ICD-10 code for sleep disordered breathing. Participants with an ICD-10 code for sleep-disordered breathing had higher odds of having blood pressure at the isolated diastolic hypertension level at baseline.

Conclusions: In our large cohort of youth referred for hypertension disorders, we found that sleep disordered breathing was associated with isolated diastolic hypertension at baseline. This study may have been impacted by lack of longitudinal blood pressure data and variation in pharmacologic management of hypertension. In future studies, we plan to investigate the association of sleep-disordered breathing with target organ injury to determine the long-term impact of isolated diastolic hypertension in youth.

Table 2: Association of sleep-disordered breathing with isolated diastolic hypertension at the index visit in youth referred for hypertension disorders

Outcome	Unadjusted OR (95% CL) n=6,790	Adjusted[a] OR (95% CL) n=6,744
Isolated diastolic hypertension (reference isolated systolic hypertension)	1.4 (1.02 to 1.92)	1.55 (1.13 to 2.13)
Isolated diastolic hypertension (reference combined hypertension)	1.99 (1.43 to 2.78)	1.99 (1.42 to 2.8)
Isolated systolic hypertension (reference combined hypertension)	1.42 (1.11 to 1.83)	1.28 (0.996 to 1.66)

Generalized estimating equations with generalized logit link function and multinomial distribution. Red font indicates statistically significant results. [a]Multivariable models included directed acyclic graph-informed adjustment set containing obesity.

SA-PO675

Risk Factors for Incident Hypertension in Children with Mild-Moderate CKD (CKiD Study)

Smitha R. Vidi,[1] Mark Mitsnefes,[2] Joseph T. Flynn,[3] Bradley A. Warady,[4] Susan L. Furth,[5] Wanpen Vongpatanasin.[1] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]Seattle Children's Hospital, Seattle, WA; [4]Children's Mercy Kansas City, Kansas City, MO; [5]The Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Hypertension (HTN) affects > 50% of children with chronic kidney disease (CKD). Increased aortic stiffness contributes to the development of hypertension and left ventricular hypertrophy in adults. Electrolyte disturbances including hyperphosphatemia and hypercalcemia are known to be associated with vascular stiffness in adults as CKD progresses. However, the role of hypercalcemia and hyperphosphatemia in the development of arterial stiffness and incident HTN in the early stages of pediatric CKD is unknown.

Methods: We studied children aged 5-18 years with CKD (U25 eGFR 30-90 ml/min/1.73m2) who were normotensive without anti-HTN medications at baseline using data from the CKiD cohort. Aortic stiffness index (ASI) was measured by echocardiography; serum electrolytes and 24-hour ambulatory BP were measured at baseline and during at least one follow-up visit. HTN was defined as either wake/sleep mean SBP/DBP ≥ gender/height-specific 95th percentile for <13 yrs of age and ≥ 130/80 mmHg for wake BP or ≥ 110/65 mmHg for sleep BP or mean ambulatory 24 hr BP ≥ 125/75 mmHg for ≥ 13 yrs of age.

Results: Out of 132 participants included in our study, 50 were not on anti-HTN medications. 26 participants had a follow up 24-hour ABPM study conducted 2 years after study entry. Mean age (76% males) was 11.6±3.7 yrs; mean eGFR 50±15 ml/min/1.73m2. 96% of participants on anti-HTN therapy and 92% without antihypertensives had abnormally high ASI compared to healthy controls. Higher baseline ASI and serum calcium were not associated with incident HTN at 2 years. Similarly, low serum potassium and phosphorous levels were not associated with incident HTN (Table) in unadjusted and adjusted analyses for age and eGFR.

Conclusions: Higher aortic stiffness index and serum calcium, potassium, and phosphorous were not associated with development of HTN after 2 yrs in children with CKD. Additional studies in larger cohorts or with longer follow-up times are needed.

Funding: NIDDK Support, Other NIH Support - The CKiD Study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U24-DK-137522, U24-DK-66116).

Association of aortic stiffness and serum electrolytes with development of HTN

Exposure	Unadjusted Odds Ratio, 95% CI	Adjusted Odds Ratio, 95% CI
Aortic Stiffness	1.17 CI (0.62 -2.19)	1.26 CI (0.66-2.4)
Serum potassium	0.25 CI (0.03-1.89)	0.24 CI (0.03-2.2)
Serum phosphorous	0.74 CI (0.17-3.1)	0.63 CI (0.12-3.4)
Serum calcium	2.9 CI (0.33-25.1)	2.29 CI (0.24-22.23)

SA-PO676

COVID-19-Associated Worry and Emotional Distress in Children with CKD

Joann M. Carlson,[1] Erin M. Jones,[6] Matthew Matheson,[7] Sharon L. Manne,[5] Cynthia Wong,[9] Camille Wilson,[8] Amy Kogon,[2] Judith Jerry-Fluker,[7] Marc Lande,[11] Lyndsay Harshman,[10] Susan L. Furth,[2] Bradley A. Warady,[3] Stephen R. Hooper,[4] Rebecca J. Johnson.[3] *[1]Rutgers University New Brunswick, New Brunswick, NJ; [2]The Children's Hospital of Philadelphia, Philadelphia, PA; [3]Children's Mercy Kansas City, Kansas City, MO; [4]The University of North Carolina at Chapel Hill Libraries, Chapel Hill, NC; [5]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [6]Emory University School of Medicine, Atlanta, GA; [7]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [8]Nationwide Children's Hospital, Columbus, OH; [9]Stanford University, Stanford, CA; [10]University of Iowa Health Care, Iowa City, IA; [11]University of Rochester, Rochester, NY.*

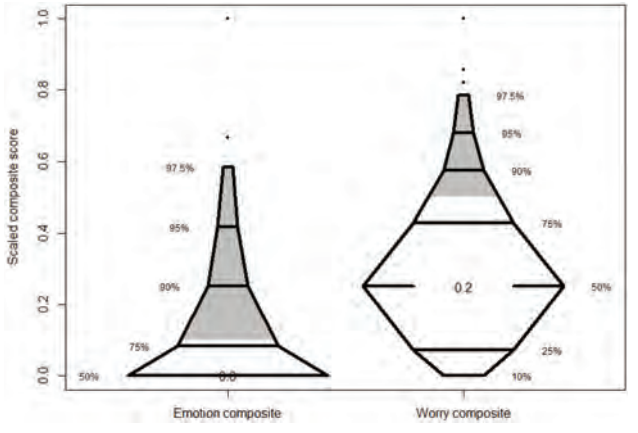
Background: The COVID-19 (C19) pandemic impacted youth mental/behavioral health, with 26% reporting significant emotional distress. Little is known about the emotional impact of C19 for youth with chronic kidney disease (CKD). We examined rates of C19 associated worry and emotional distress in youth with CKD and associations with socioeconomic and disease-related variables.

Methods: Caregivers completed the C19 questionnaire adapted from the Women's Interagency HIV Study and Multicenter AIDS Cohort Study. Covariate data was collected at or prior to C19 questionnaire. Analyses examined rates of C19 emotional distress and worry and included logistic regression to identify associations with covariates.

Results: Sample included 320 participants from the Chronic Kidney Disease in Children Study: 63% male, 18% African American, 10% Hispanic, median age 16 years, median estimated GFR 52 ml/min/1.73m2 among pre-ESKD participants and median urine P:C 0.27. 27% were post-kidney replacement, 29% had household income <$36,000 and 29% had maternal education of high school or less. 19% and 17% endorsed C19 emotional distress and worry, respectively (see Figure 1). Having eGFR <30 pre-KRT was associated with endorsement of emotional distress (OR 3.34; p= 0.046). Low household income was associated with endorsement of C19 worry (OR 5.43; p=0.01).

Conclusions: Youth with CKD endorsed C19 associated emotional distress and worry at rates lower than what has been observed nationally. Being pre-KRT with eGFR <30 was associated with increased C19 emotional distress, and low household income was significantly associated with C19 worry. This study did not assess social-emotional health broadly among youth with CKD but suggests those with poorer kidney function and lower income were more likely to endorse distress and worry related to C19.

Funding: NIDDK Support



SA-PO677

Energetic Profiles of Children with CKD Compared with Profiles of Healthy Controls

Amy Kogon, Jonathan Mitchell, Susan L. Furth, Sandra Amaral, Babette Zemel. *University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: Children with CKD who are obese develop earlier cardiovascular disease (CVD), a leading cause of mortality. Understanding how the components of energy balance, which include resting energy expenditure (REE), physical activity (PA) and energy intake, affect obesity in pediatric CKD is critical to prevent it and reduce CVD risk.

Methods: Participants were 8-21 years old with CKD stages 3-5 not on dialysis or healthy controls (HC) of similar age, sex and BMI category. REE was measured by open circuit indirect calorimetry, PA by child PROMIS PA measure, energy intake by 24-hour dietary recall, and body composition by DXA. Linear regression models were used to determine if the components of energy balance differed between CKD and HC participants, adjusting for age and sex and for lean body mass (LBM), the primary determinant of REE, when evaluating group differences in REE.

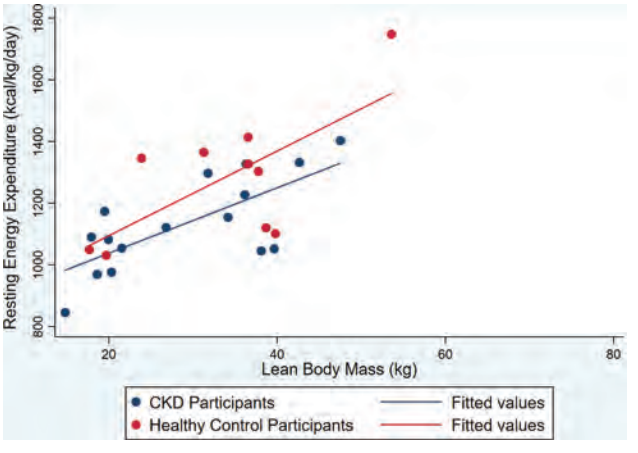
Results: Twenty-two participants with CKD and 14 HC completed baseline studies. REE was measured in 16/22 CKD and 10/14 HC participants. Self-reported PA levels and energy intake were similar between groups. After adjusting for age and sex, for a given LBM, REE was 116 kcal/day lower in CKD participants (p=0.026).

Conclusions: Total energy intake and PA levels were similar between CKD and HC participants, but REE was significantly lower in the group with CKD, even after consideration for LBM. This suggests that energy imbalance in CKD may be related to lower-than-expected energy utilization by LBM.

Funding: NIDDK Support

Factor	CKD Mean (SD) or N (%)	Control Mean (SD) or N (%)	p-value
N	22	14	
Age (year)	14 (4)	14 (3)	0.82
Female sex	8 (36%)	7 (50%)	0.42
Race			
White race	13 (59%)	11 (79%)	0.29
Black race	8 (36%)	6 (43%)	0.74
Asian Race	3 (14%)	0 (0%)	0.27
Hispanic Ethnicity	2 (9%)	1 (7%)	0.84
Transplant recipient	2 (9%)	0 (0%)	
Glomerular filtration rate	30 (17)	100 (14)	<0.001
BMI category based on CDC			
Grade 1 thinness	2 (9%)	2 (14%)	0.91
Normal weight	14 (64%)	9 (64%)	
Overweight	3 (14%)	2 (14%)	
Obese	3 (14%)	1 (7%)	
Waist to height ratio	0.5 (0.1)	0.4 (0.0)	0.36
Lean body mass	31512.2 (12992.8)	32653.8 (10028.6)	0.78
Average resting energy expenditure (KCal/day)	1145 (151)	1280 (217)	0.078
Average total daily energy intake (kcal)	1562 (314)	1639 (519)	0.58

Baseline Characteristics



Resting Energy Expenditure Relative to LBM

SA-PO678

Body Mass Index Trajectories among Adolescents and Young Adults with CKD

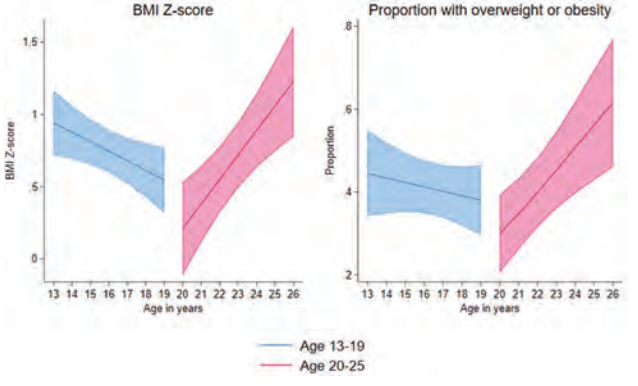
Pierina P. Parraga,[1] Caleb W. Easterly,[2] Guido Filler,[4] Donna B. Gilleskie,[3] Maria E. Ferris.[1] *[1]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; [2]The University of North Carolina at Chapel Hill Gillings School of Global Public Health, Chapel Hill, NC; [3]The University of North Carolina at Chapel Hill College of Arts and Sciences, Chapel Hill, NC; [4]London Health Sciences Centre, London, ON, Canada.*

Background: Nearly 1 in 5 US children and adolescents have obesity, a risk factor for cardiovascular disease. We examine longitudinal body mass index (BMI) patterns among adolescents and young adults (AYA) with chronic kidney disease (CKD) during the age of transition to adulthood.

Methods: We conducted an historical cohort study of AYA with CKD stages 1-5 aged 13-25 at a southeastern health system in the USA. Electronic medical record (EMR) appointment and laboratory data from Jan 2005-May 2015 were extracted, and CKD patients with ≥4 height and weight measurements were included (*N*=7,978 observations from 255 patients). Age- and sex-specific BMI Z-scores and percentiles were calculated using the 2000 CDC growth chart (normal weight: BMI >5th and <85th percentile; overweight: BMI ≥85th and <95th percentile; obese: BMI >95th percentile). We modeled BMI Z-score as a linear function of age allowing for different intercepts and slopes for adolescents (aged 13-19) and young adults (aged 20-25), adjusting for sex, race/ethnicity, birth year, and CKD etiology (glomerular, non-glomerular, other primary diagnosis). Logistic regression estimated the proportion of patients with overweight or obesity by age.

Results: At baseline, patients' mean age was 14.9 years, 53% were male; 35% had glomerular conditions, 32% non-glomerular conditions, and 33% had other primary diagnoses. BMI Z-scores decreased with age among adolescents (-0.066 standard deviations [SD] per year of age; P = 0.022) and increased with age for young adults (0.170 SD per year of age; P < 0.001). The proportion of adolescents with overweight or obesity did not change with age (P = 0.643), but the proportion of young adults with overweight or obesity increased by 0.037 with each year of age (P < 0.001), reaching 0.62 by age 25.

Conclusions: Trends in BMI increase as adolescents with CKD move into young adulthood.



Adjusted for age, race/ethnicity, birth year, and CKD etiology. 95% confidence intervals are shaded.

SA-PO679

Global Health Burden of Pediatric CKD of Varying Etiologies: A Longitudinal and Comparative Analysis

Raghav Shah,[1] Manan Raina,[2] Bryce Pember,[1] Thomas J. Cahill,[1] Sidharth K. Sethi.[3] *[1]Northeast Ohio Medical University, Rootstown, OH; [2]Hawken High School, Cleveland, OH; [3]Medanta The Medicity Medanta Institute of Kidney and Urology, Gurugram, India.*

Background: Chronic Kidney Disease (CKD) affects >10% of the adult global population. Data on the incidence of CKD in the pediatric population is scarce and the epidemiology is not clear. This study estimates: the distribution of pediatric-CKD (pCKD) by geography, sociodemographic indices (SDI), age, and gender; 2-decade pCKD-trends between 1990 to 2019; and compares its different etiologies (diabetes type 1 (T1DM), diabetes type 2 (T2DM), hypertension (HTN), and glomerulonephritis (GN)).

Methods: Using the Global Burden of Disease 2019 database, the incidence, prevalence, death rates, and DALY rates per 100,000 children and adolescents with CKD identified 4 major etiologies: T1DM, T2DM, GN, and HTN. Average annual percentage change (AAPC) over 20 years at global and regional levels was measured and stratified by age, gender, and socio-demographic index (SDI). The SPSS package was utilized.

Results: Globally, the overall pCKD incidence rates increased over 20 years in all 4 etiologies: GN (AAPC 0.478), T1DM (AAPC 0.490), T2DM (AAPC 1.022) HTN (AAPC 1.026). Overall prevalence rates increased for T2DM (AAPC 0.249), T1DM (AAPC 0.504), GN (AAPC 0.649), and HTN (AAPC 0.828). The increase in overall incidence/prevalence was higher in boys than girls and in older versus younger ages. Regarding SDI, AAPC was greater with lower SDI. Concerning geography, the incidence of AAPC was two-fold higher in Asia, America, and Africa than in Europe. Globally, death rates decreased for CKD due to T1DM (AAPC -1.377), GN (AAPC -0.976), T2DM (AAPC -0.862), and HTN (AAPC -0.474). Similarly, the overall DALY rates decreased for T1DM (AAPC -0.849), GN (AAPC -0.755) and T2DM (AAPC -0.745) and increased for HTN (AAPC 0.139). Overall death/DALYs decreased more sharply in females than males, and in younger children than older. Similarly, lower SDIs showed higher death/DALY AAPC. For geography, the decrease in death/daily AAPC was observed to be higher among those in Europe as compared with America, Asia, or Africa.

Conclusions: In conclusion, there has been an overall significant increase in the global incidence and prevalence of pediatric CKD over 20 years as indicated by varied distribution patterns of etiology, SDI, DALY rates, and geography underscoring the need for targeted public health interventions, especially in vulnerable populations.

SA-PO680

Pediatric and Adult Kidneys Have Largely Similar Gene Expression in CKD and Non-CKD

Marvin Sinsakul,[1] Maria Ryaboshapkina,[2] Dianne Acoba,[2] Stefanie Breitenstein,[3] Mario Berger,[3] Anna Reznichenko.[2] *[1]AstraZeneca, Gaithersburg, MD; [2]AstraZeneca, Gothenburg, Sweden; [3]Bayer AG, Pharmaceuticals, Wuppertal, Germany.*

Background: Understanding the molecular similarities between kidney diseases in children and adults is important for pediatric drug development. Here, we assessed age-related changes in kidney gene expression.

Methods: We surveyed public pediatric transcriptomics data and analyzed 5 cohorts (non-diseased GSE11024, GSE70503, GSE147451, mostly glomerular CKD GSE104954 and GSE68127). Differential expression analysis was adjusted for batch as appropriate and APOL1 risk group in GSE68127. Genes with false discovery rate < 5% were considered significant. CKD molecular category (Reznichenko et al. 2024 PMID38286178) was predicted for children in GSE68127.

Results: In total, the 5 cohorts included 53 children from 0 to 17 and 388 adults from 18 to 90 years. Pediatric and adult kidney samples did not clearly segregate on principal component analysis (PCA), neither in CKD nor in non-CKD cohorts (**Fig 1A**). We detected no to minimal differential expression changes, which constituted < 0.5% of measured genes in every cohort (**Fig 1B**). All adult CKD molecular categories were detected among children, with relative proportions and technical mapping quality similar to the adult CKD (**Fig 1C**).

Conclusions: Age *per se* had minimal effect on kidney gene expression. Instead, the gene expression profile in CKD was driven by molecular pathophysiology of CKD.

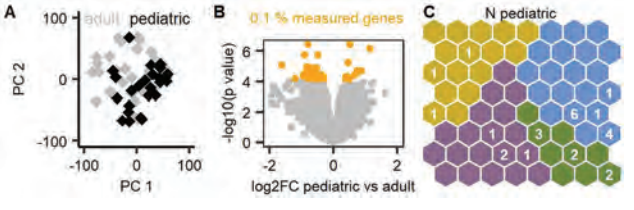


Fig. 1. Representative results in tubulointerstitium. 26 children (6-17 years) and 29 adults (18-74 years) with nephrotic syndrome GSE68127. **A.** PCA. **B.** Differential expression (significant genes in orange). **C.** Children mapped on to the adult CKD molecular categorization map.

SA-PO681

Resolution of Pica with Kidney Transplant

Nicole Vegh,[1,2] Diego H. Aviles.[1,2] *[1]LSU Health New Orleans, New Orleans, LA; [2]Children's Hospital New Orleans, New Orleans, LA.*

Introduction: Pica, compulsive consumption of non-nutritive substances, has been documented in end stage renal disease (ESRD) requiring dialysis with a prevalence of 38-42% in adults and 46% in pediatric patients. Pica is often thought to be secondary to iron deficiency (ID), which is common in ESRD, however, it is debated if the ID drives the compulsion or the compulsion results in ID through impaired absorption of iron. Majority of patients who experience pica endorsed ice pica; hard pica is the ingestion of other substances aside from ice that can result in significant health consequences including death. A prior study in pediatric dialysis patients showed that the presence of anemia and dialysis duration >5 years was associated with increased odds ratio of pica and showed no statistical difference between hemodialysis (HD) vs peritoneal dialysis (PD) modalities or Kt/V between those with pica and those without. They also suggested an underlying cultural or stressful state of ESRD as risk factors for pica (Katsoufis et al, 2012).

Case Description: We present an African American male with ESRD secondary to focal segmental glomerulonephritis (FSGS) on PD for approximately 5.5 years with pica

ingestion, most frequently laundry detergent and carpet cleaner. He developed profound and persistent metabolic alkalosis which led to the discovery of pica. Despite maintaining adequate hemoglobin, iron stores and treatment for depression, his pica persisted. He developed pica near the onset of his kidney disease and 5 years before the initiation of dialysis. Pica resolved immediately following kidney transplantation.

Discussion: This case highlights the need for further evaluation of underlying causes of pica in patients not only in ESRD but also those with chronic kidney disease. Though previous studies have not demonstrated an association between decreased Kt/V and increased risk of pica, this case makes an argument for further investigation. The onset of his symptoms at the time of decreasing GFR, and resolution of symptoms with transplant and normalization of eGFR suggests significant renal insufficiency as a risk factor for pica. Kt/V is not a one-size fits all. Does the onset of pica symptoms suggest a need for improved clearance and a more personalized dialysis prescription?

SA-PO682

Derivation and Validation of a Novel Automated Algorithm for Staging Infant Blood Pressures

Chloe N. Williams,[1] Tasha A. Jawa,[2] Vedran Cockovski,[1] Sophia Nunes,[1] Adree Khondker,[3] Chia Wei Teoh,[1] Seetha Radhakrishnan,[1] Michael Zappitelli.[1] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Queen's University, Kingston, ON, Canada; [3]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada.*

Background: Infant blood pressure (BP) is assessed by visual evaluation of sex and age specific BP curves (i.e., "manual staging"). Manual staging is time consuming and error prone, but is the standard method to assess infant BP. We developed and evaluated accuracy of a novel computerized algorithm to stage BP category in infants.

Methods: We retrospectively acquired BP data in electronic health records (EHRs) from infants hospitalized at a quaternary healthcare center between June 2018-August 2019. Infants <1 year old with paired systolic/diastolic BP were included. First or last admission BP was randomly selected for evaluation. An algorithm to estimate published BP curves was created by digitizing age and sex-based infant BP cutoff curves into a series of points, then deriving each curve's equation of best fit via regression. All BP's were staged manually by two raters (normal, elevated or hypertensive [stage 1 or 2]). The algorithm was evaluated for agreement (using Cohen's kappa and % agreement) with manual staging.

Results: Of 2407 BP measurements, 1304 patients were staged as normal, 298 elevated BP, and 805 hypertensive by manual staging (inter-rater agreement for manual staging was kappa 0.82 [0.58-1.00]). By the algorithm, 1368 had normal BP, 323 elevated BP and 716 hypertensive. Agreement between manual and algorithm classification was 89.4% (kappa 0.83 [0.82-0.85]). Discrepancy between manual vs. algorithm BP staging was noted for 255 BPs. Five BPs (2% of errors) were incorrectly staged by the algorithm and correctly staged by manual staging; 63 BP's (24.7% of errors) were incorrectly staged by manual staging and correctly staged by the algorithm. The remaining discrepancies (73.3% of errors) were BPs on/near the curve at the border of normal vs. abnormal BP. The algorithm has been made into a ShinyApp (developed by A. Khondker), available at https://sickkidsnephrology.shinyapps.io/InfantHypertension/ (Figure 1).

Conclusions: The new infant BP staging algorithm has strong agreement with manual staging and may be used to stage BP in infants in the clinical setting and within EHRs.

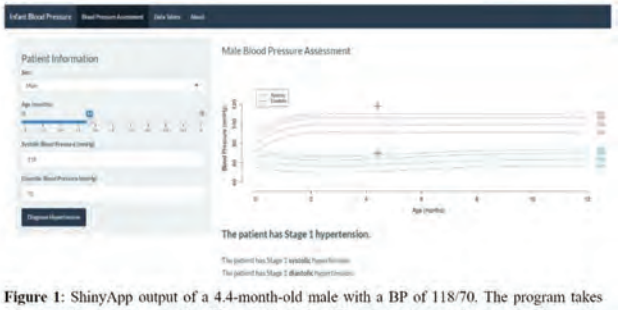


Figure 1: ShinyApp output of a 4.4-month-old male with a BP of 118/70. The program takes sex, age (in months), systolic BP, and diastolic BP input values and automatically stages hypertension using the computerized algorithm.

SA-PO683

Late Relapse of Atypical Hemolytic Uremic Syndrome 36 Months after Discontinuation of Complement Blockade Therapy

Ganesh Prasanna, Abhijeet Pal. *The University of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Introduction: Complement-mediated atypical hemolytic uremic syndrome (aHUS) manifests as microangiopathic hemolytic anemia, renal failure, and thrombosis, stemming from dysregulated complement system activation. The outcomes include end-stage kidney disease and death. The advent of complement blockade therapy has improved the prognosis, but with prohibitive costs and the inconvenience of infusions. So, discontinuation is often considered, though there is a 30% risk of relapse, which typically happens within weeks of stopping the treatment. In our case, the relapse occurred years later, raising new questions about this contentious subject.

Case Description: In 2020, a five-year-old boy presented with fever, non-bloody diarrhea, and a rash shortly after an influenza infection. He was hypertensive and febrile, along with jaundice and petechiae. Lab results indicated anemia (Hb 10 g/dL) with schistocytes, thrombocytopenia (platelets 17,000/mm3), and acute kidney injury (BUN 44 mg/dL; creatinine 3 mg/dL). Normal ADAMTS-13 activity (99%), and negative stool culture and ELISA for shigella led to the diagnosis of atypical HUS. Along with supportive therapy and plasmapheresis, eculizumab, a complement 5 blocker, was started, inducing remission. Genetic analysis showed a heterozygous mutation of the C3 gene at the binding site for factor H, predisposing to complement dysregulation. Remission was maintained with eculizumab, which was changed to ravulizumab given its longer half-life. During a year of therapy, he was asymptomatic with normal hematological and renal parameters. Ravulizumab was stopped in March 2021. Thirty-six months later, a relapse occurred in March 2024, with another influenza infection. Thus, eculizumab was restarted.

Discussion: Prior studies have indicated a median relapse time of 13 weeks after discontinuation of complement blockade. However, our case underscores the potential for delayed relapse, and advocates for extended periods of surveillance. Our decision to discontinue Ravulizumab was guided our patient's negative C3 deposition assay and his mother's asymptomatic status, though she had the same mutation. Secondly, influenza might have been a "second hit", triggering the relapse. Clinicians must recognize that aHUS can recur despite pre-discontinuation risk assessment. Further research is needed to inform the optimal treatment duration.

SA-PO684

Combined Liver-Kidney Transplant in Children

Amber J. Kazi,[1] Juhi Kumar,[2] Jodi M. Smith,[1] Nicole A. Hayde,[3] Lyndsay Harshman,[4] Chloe E. Douglas,[1] Sarah J. Kizilbash,[5] Sharon M. Bartosh,[6] Rachel M. Engen.[6] *[1]Seattle Children's Hospital, Seattle, WA; [2]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA; [3]Montefiore Medical Center, New York, NY; [4]University of Iowa Health Care, Iowa City, IA; [5]University of Minnesota Twin Cities, Minneapolis, MN; [6]University of Wisconsin-Madison, Madison, WI.*

Background: Data describing outcomes of pediatric combined liver-kidney transplant (CLKT) are limited.

Methods: Retrospective cohort study of pediatric CLKT, liver-alone transplants (LT), and kidney-alone transplants (KT) in US from 1/1/2001 to 12/31/2019 using SRTR data. Primary outcomes include demographic and clinical characteristics, graft, and patient survival.

Results: There were 284 CLKT recipients with a median age of 10 yrs; 22.5% had polycystic kidney disease and 18.7% had primary hyperoxaluria (Table 1). CLKT recipients were more likely to have a history of prior transplant, be listed at multiple centers, and be on dialysis prior to CLKT. CLKT were more likely to receive a whole liver and be listed with exception points compared to LT. CLKT were more likely to have en bloc kidney transplants, KDPI 35-85% donor kidneys, and DGF compared to KT. CLKT graft survival was superior to LT but inferior to KT long term (Fig 1). CLKT patient survival was inferior to KT but similar to LT.

Conclusions: CLKT recipients have different transplant characteristics and outcomes compared to LT or KT alone recipients. Further research is needed to understand the factors driving these differences.

Characteristics[1]	CLKTs n=284	KT n=17,175	LT n=10,490	p Value
Age (y)	16(5-15)	13(8-16)	3(0-10)	<0.001
Kidney Diagnosis				<0.001**
Polycystic Kidney	64(22.5%)	552(3.2%)		
Primary Hyperoxaluria	53(18.7%)	16(0.1%)		
CAKUT	6(2.1%)	5822(33.9%)		
Other	140(49.3%)	9233(54.1%)		
Liver Diagnosis				<0.001*
Acute liver failure	0		1099(10.5%)	
Biliary Atresia	0		3836(36.6%)	
Other	174(61.3%)		4654(44.4%)	
Primary Hyperoxaluria	41(14.4%)		35(0.3%)	
PELD score				<0.001*
<34	115(40.5%)		4605(43.8%)	
≥34	136(47.9%)		3367(32.1%)	
Status 1A and 1B	65 (29.9%)		3693(35.2%)	
Prior Transplant				<0.001
Kidney (alone)	34(12.0%)	1594(9.3%)	0	
Liver (alone)	19(6.7%)	159(0.9%)	1029(9.9%)	
Dialysis History	168 (59.2%)	8959 (52.1%)	427 (4.1%)	<0.001
Waitlist time <6 months	177 (62.3%)	7058 (41.1%)	8343 (79.5%)	<0.001
Listed at multiple centers	32(11.3%)	1185(6.9%)	703(6.7%)	0.02
Liver listing with exception status*	218(76.8%)		4373(41.7%)	<0.001
KDPI (Deceased)				<0.001**
0 - 34%	154 (68.4%)	9361 (90.9%)		
35% - 100%	87 (30.7%)	904 (8.8%)		
En-Bloc Kidney transplant**	25(8.9%)	109(0.6%)		<0.001
Liver Graft				<0.001*
Liver – Whole	218(76.8%)		6275(59.8%)	

[1] Reported as median [IQR] for continuous variables and n (%) for categorical variables. * Only comparing CKLT vs Liver ** Only comparing CKLT vs Kidney

Table 1. Pt Characteristics

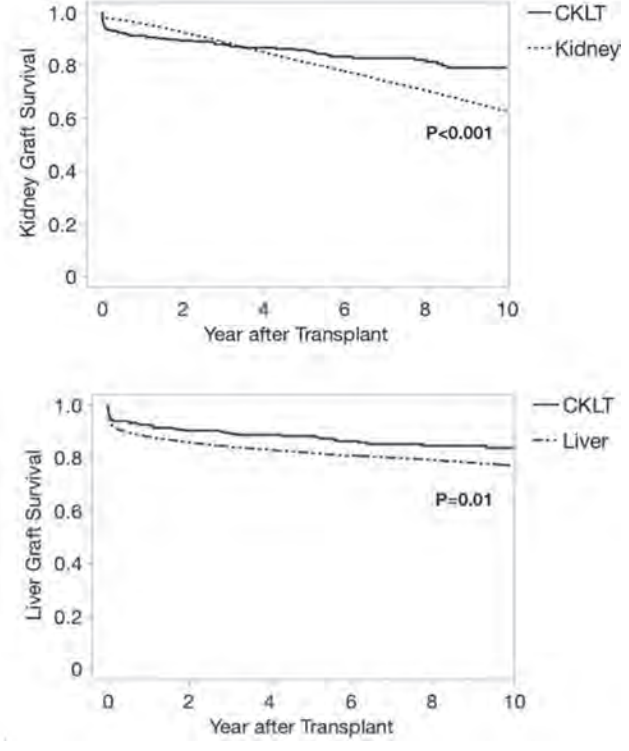


Figure 1. Graft Survival

SA-PO685

Role of Angiopoietins in Pediatric Heart Transplant Recipients with and without Kidney Dysfunction

Melvin Chan,[1] Stephanie J. Nakano,[1] Shelley Miyamoto,[1] Scott R. Auerbach,[1] Gabriel M. Cara-Fuentes.[2] *[1]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [2]Nationwide Children's Hospital, Columbus, OH.*

Background: Angiopoietins have been implicated in worse cardiac outcomes but haven't been studied in pediatric heart transplant recipients (HT) with or without chronic kidney disease (CKD).

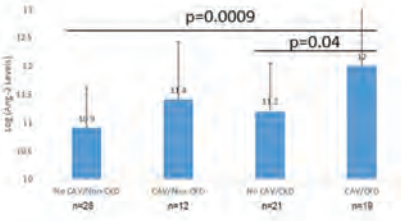
Methods: We included 17 healthy subjects and 82 HT recipients. In the latter group, patients were matched with and without CKD based on gender, age at the time of collection +/- 4 years, time from transplant +/- 3 years. Estimated glomerular filtration rate (eGFR) was based on serum creatinine using the CKiD U25 calculator. By commercial ELISA kits, we measured Angiopoietin-1 (Ang-1), Ang-2, and Tie-2 levels a single serum sample per subject. Clinical outcomes included HT rejection, diagnosis of coronary allograft vasculopathy (CAV) at the time of sample collection and decline in eGFR.

Results: A total of 41 CKD patients were matched to 41 patients without CKD. About 90% of those with CKD were stage 2. There were no differences in the distribution of age at time of collection, gender, race, ethnicity, primary cardiac diagnosis, time from transplant at collection time, and presence of CAV or any rejections. For healthy controls, biomarker levels were similar to those with HT but no CAV and/or CKD. Ang-2 levels and Ang-2/Ang-1 levels were higher in those with CAV and/or CKD as compared to those with HT but no CAV and/or CKD (Figure 1). Higher Ang-2 levels were also seen in those with any rejections. None of these markers were associated with worsening eGFR after a median of 3 year follow-up from time of collection.

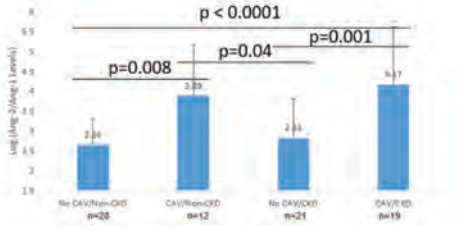
Conclusions: Angiopoetins appear to play a role in predicting CAV with and without CKD and rejections. More studies involving severe CKD patients need to be conducted to see if Ang-2 and Ang-2/Ang-1 levels are higher in those with CAV and rejections based on renal function.

Figure 1: Ang-2 and Ang-2/Ang-1 Levels in Patients with Coronary Vasculopathy (CAV) and Chronic Kidney Disease (CKD)

(a) Ang-2



(b) Ang-2/Ang-1



SA-PO686

Prevalence and Consequences of Glomerular Hyperfiltration (HF) in Pediatric Solid-Organ Transplant (SOT) Recipients

Melvin Chan, Amy Feldman, Scott R. Auerbach. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: The prevalence and sequalae of glomerular HF are unknown in pediatric SOT. We aimied to describe HF in a pediatric SOT cohort.

Methods: We reviewed all actively followed SOT at a large quatenary pediatric referral center from 2002-2023. Patients were excluded if they had muscular dystrophy or were under the age of 2. The primary outcome was estimated renal function (creatinine based CKiD U25) yearly during the first 5 years post-transplant and the most recent visit. HF was defined as 2 standard deviations above the mean eGFR for age at anytime. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of less than 90mL/min/1.73m2. Secondary outcomes included any rejections and hypertension (HTN). We used a contigency table to determine odds ratio.

Results: A total of 402 patients were eligible. Of the 129 kidney transplant recipients, only one had HF. The clinical characteristics of the remaining patients are shown in Table 1, with 44 (16%) demonstrating HF at some point during the first 5-years post-transplant. Table 2 depicts the clinical associations based on renal function in liver and heart transplant recipients. Patients in both the HF and CKD groups had a 2.22 higher odds of having HTN compared to those with normal function (p=0.024 and 0.008, respectively). The non-renal transplant CKD group also had a 1.8 higher odds of having any episodes rejection (p=0.02).

Conclusions: While HF is uncommon in pediatric kidney transplant recipients, it is prevalent in pediatric liver and heart transplant recipients. HF and CKD are both independently associated with an increased risk for HTN in these non-renal transplant patients. Close follow-up for progression and sequalae of CKD is thus warranted in this high risk SOTr population.

Table 1: Clinical Characteristics

Mean (STD)/Count (%)	Non-Hyperfiltration (n=229)	Hyperfiltration (n=44)
Age at Transplant (Years)	5.9 (6.4)	4.2 (5.5)
Sex		
Females	116 (51%)	19 (43%)
Males	113 (49%)	25 (57%)
Race		
Caucasian	127 (55%)	20 (45%)
Hispanic	56 (24%)	15 (34%)
Asian	5 (2%)	1 (2%)
African-American	9 (4%)	1 (2%)
Native American	10 (5%)	1 (2%)
Other	22 (10%)	6 (15%)
Organ		
Heart	148 (65%)	21 (48%)
Liver	81 (35%)	23 (52%)
Primary Diagnosis		
Cardiomyopathy	65 (28%)	4 (9%)
Congenital Heart Disease	80 (35%)	17 (39%)
Biliary/Cholestatic	45 (20%)	17 (39%)
Hepatic	36 (16%)	6 (13%)
Missing	3 (1%)	0 (0%)

Table 2: Clinical Associations Based on Renal Function

	Hypertension		Any Rejections	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Hyperfiltration*	2.22 (1.087-4.543)	0.024**	0.711 (0.359-1.4)	0.209
Chronic Kidney Disease*	2.22 (1.22-4.178)	0.008**	1.812 (1.061-3.09)	0.02**

*Groups were compared to those with normal renal function, defined as those from >= 90mL/min/1.73m2 to 2 standard deviations above the mean estimated glomerular filtration rate for that age.

**p < 0.05

SA-PO687

Utility of Donor-Derived Cell-Free DNA in Pediatric Kidney Transplantation: Initial Results from the NAPRTCS Registry Centers

Vikas R. Dharnidharka,[1] Sara A. Boynton.[2] NAPRTCS Investigators.
[1]Washington University in St Louis, St Louis, MO; [2]Johns Hopkins University, Baltimore, MD.

Background: Peripheral blood donor-derived cellfree DNA (dd-cfDNA) percentage is a novel biomarker for acute rejection (AR) in adults, but studies in a large cohort of children are lacking. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), a voluntary multi-center consortium that has been collecting data on children with kidney transplants (pKT) since 1987, expanded the registry with a CareDx grant in 2022 to collect dd-cfDNA data.

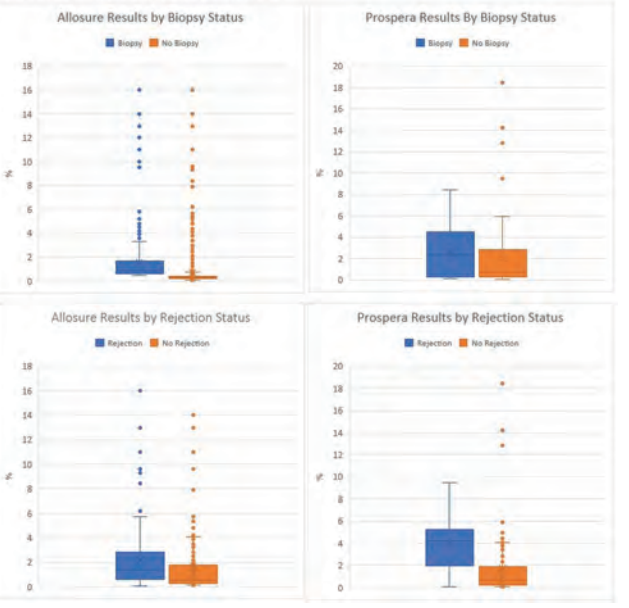
Methods: In addition to pKT data routinely collected by NAPRTCS, dd-cfDNA percentage results obtained as part of standard care were collected. Centers provided the assay type used (Allosure; Prospera or other) and whether the test was associated with a biopsy or an episode of AR.

Results: To date, we have 1386 dd-cfDNA results, from 305 unique recipients (median 3 results per patient, IQR 2, 6), from test dates 10/8/18 to 2/2/24, representing pKT dates 10/8/08 to 4/2/24, from 14 different centers, median 16 patients and 58 results per center. Recipient demographics mirrored the overall population. The dd-cfDNA test used was Allosure in 1294 (93.3%; median result 0.34%, range 0.04-16.0) and Prospera in 92 (6.7%; median 0.83, range 0.04-18.44). On the forms, test results were associated with a biopsy for 706 Allosure (median dd-cfDNA 1.1%; range 0.07-16, Fig 1 panel A) and 64 Prospera results (median 2.9%; range 0.1-9.46, panel B) and to AR in 122 Allosure (median 1.4%, range 0.07 -13, panel C) and 11 Prospera results (median 4.2%, range 0.1-9.46, panel D).

Conclusions: In this large pediatric cohort study, higher dd-cfDNA levels associated with pKT biopsy or an AR event. Further analyses will calculate AR test efficacy via ROC curves, separated by surveillance or for-cause detailed biopsy results.

Funding: Commercial Support - CareDx grant to NAPRTCS

Figure 1. Test Results by Biopsy or Acute Rejection Status



SA-PO688

Use of the Seraph 100 Microbind Affinity Blood Filter in a Pediatric Patient with Persistent BK Nephropathy

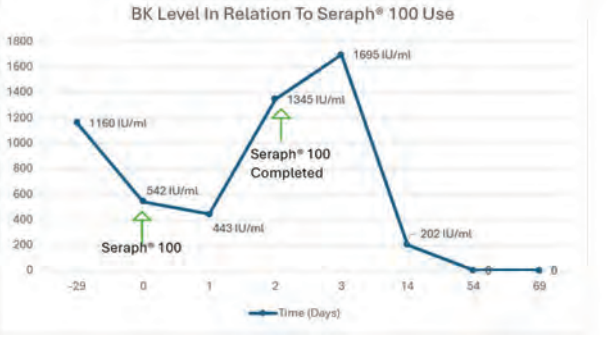
Meredith Harris, Mahima Keswani, Theresa A. Mottes, Priya S. Verghese.
Ann and Robert Lurie Children's Hospital of Chicago, Chicago, IL.

Introduction: BK nephropathy (BKN), a cause of kidney failure in solid organ transplant recipients, has no approved treatment strategy. Most providers trial immunoreduction which risks rejection of the transplanted organ. The Seraph® 100 Microbind® Affinity Blood Filter (Seraph® 100) (ExThera Medical Corporation) mimics the action of the natural glycocalyx to bind pathogens via heparin sulfate proteoglycans in patients on Continuous Renal Replacement Therapy (CRRT). It has been used to treat COVID-19, Adenovirus, Epstein-Barr Virus, and Cytomegalovirus with variable efficacy. Based on aforementioned viral load reduction with the Seraph® 100, we hypothesize this filter will reduce BK viral load in our patient.

Case Description: A 14 yo female with dilated cardiomyopathy presented 8 years following cardiac transplant with new onset BK viremia (BKV). Her BK PCR titers peaked at 9,600,000 IU/ml. She was treated with Leflunomide, IVIG and immunoreduction. Despite reduction in BK titers, her glomerular filtration rate progressively declined. Persistent BKV was considered a contraindication to kidney transplant for which she would have otherwise qualified. With her impending need for dialysis, CRRT was initiated using the Seraph® 100 for 48 hours with a filter change at 24 hours. No adverse effects were noted. The patient was discharged to continue outpatient hemodialysis. **Figure 1** shows trends of BK levels from time of initiation of Seraph® 100. Two months post Seraph® 100, BK level was undetectable without any new interventions. She underwent kidney transplant and is 3 months post-transplant without recurrent BKV. Surveillance biopsy at 3 months demonstrates no evidence of BKN.

Discussion: We demonstrate the clearance of BKV in a heart transplant patient with BKN related end stage kidney disease, 2 months post utilizing the Seraph® 100 filter, allowing for successful kidney transplant. Ongoing studies are needed to confirm and evaluate continued success of the Seraph® 100 in patients with BKV.

Figure 1: BK viral load in relation to initiation of Seraph® 100 use. Time 0 is the time of initiation of the Seraph® 100 filter.



SA-PO689

Immune Monitoring by Torque Teno Virus Load in Addition to Virus-Specific T Cells after Pediatric Kidney Transplantation

Lars Pape. *Universitatsklinikum Essen, Essen, Germany.*

Background: Pharmacokinetic monitoring alone is insufficient to estimate the intensity of immunosuppression after kidney transplantation (Tx). The IVIST RCT demonstrated that additional steering of immunosuppressive therapy by virus-specific T cells (Tvis) is safe and reduces exposure to immunosuppressants. Another promising biomarker is the torque teno virus (TTV) load that was associated with risk for rejections and infections in some observational trials. We have now evaluated a possible benefit of additional analysis of TTV load to improve immune monitoring in the IVIST cohort.

Methods: In the IVIST trial, 31 pediatric kidney recipients were randomized to the intervention group with additional steering by Tvis levels. The immunosuppressive regimen consisted of cyclosporine A (CsA), everolimus (Eve) and glucocorticoids. In 27/31 patients of the intervention group (11.7±3.3 years) a retrospective analysis of TTV-DNA was performed by PCR in frozen plasma samples obtained from 20 visits (1-24 months after Tx). TTV and Tvis changes from baseline levels have been evaluated by paired t-test, the correlations to CsA and Eve trough levels by Pearson correlation coefficients.

Results: Median TTV-DNA of all plasma samples (n=474) was 2.5E4 cop/ml (2.3E1 to 2.8E9). High TTV loads were found under the intensified immunosuppression during the initial post-transplant period (2 mo post Tx: mean log number 11.6) and a significant TTV-decrease after reduction of immunosuppression (6 mo post Tx: 9.8, p=0.009; 22 mo post Tx: 9.3, p=0.005). In contrast, ADV-Tvis levels increased over time: from 1.47 cells/µl (2 mo post Tx) to 1.98 (6 mo post Tx, p=0.056) and 2.36 (22 mo post Tx, p=0.008). (Figure 1). TTV-load showed weak correlations to trough levels of CsA and Eve (24 mo post Tx: TTV vs. CsA r=0.33; vs. Eve r=0.37).

Conclusions: The first combined analysis of TTV load and ADV-Tvis showed an opposite course over the first two years after Tx. Both biomarkers were related to the intensity of immunosuppression but with high interindividual variations and weak correlations to trough levels of immunosuppressants. Therefore, a combined post-Tx monitoring may have an additional value to identify over- and underimmunosuppression. Further randomized controlled trials are needed to confirm the benefit of a combined use of TTV and Tvis to optimize dosing of immunosuppressants.

SA-PO690

Outcomes Using Alemtuzumab Induction in Pediatric Kidney Transplant Recipients

Yifeng Zhang, Juhi Kumar. *UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA.*

Background: No standard guidelines for induction immunosuppression exist in pediatric kidney transplant and the choice is usually institution specific. Alemtuzumab (Campath) is a humanized monoclonal antibody that binds to the CD-52 membrane glycoprotein and causes profound depletion of T and B lymphocytes. Recent review of the NAPRTCS Registry showed that only 17.5% of patients received Alemtuzumab, compared to 48.5% thymoglobulin and 30.1% Basiliximab. It is the least used agent with minimal data on its longitudinal effects. Alemtuzumab has been associated with the development of de novo donor specific antibodies (DSAs) which has been shown to increase risk for allograft loss. Our center uses one dose of Alemtuzumab as induction with tacrolimus and mycophenolate mofetil maintenance immunosuppression. Aim of the study is to review our institution's transplant outcomes with Alemtuzumab induction.

Methods: We did a retrospective chart review of 170 kidney transplant patients, aged 2 to 26 years old, transplanted between January 2010 to December 2023 who received Alemtuzumab as induction therapy. We examined incidence of viremia (CMV, BKV, EBV), BK viruria, DSAs, acute rejections, and patient and allograft survival rates.

Results: Median age at transplant was 12 years, (IQR 6-23). 60% of the patients were male. 50% received a deceased donor transplant. Incidence of viremia 6 months and 1 year post transplant for CMV was 3.6% and 2%, EBV 23% and 28%, BKV was 16% and 14%, and BK viruria was 31.9% and 31.2%, respectively. Incidence of Class II DSAs was 2% at 6 months, 3.4% at 1 year, 6.9% at 3 years, and 7.7% at 5 years post-transplant. Incidence of rejection at 6 months and 1 year post-transplant was 5.8% and 8.3%, respectively. Graft survival was 99.4% at 1 year, 94.7% at 3 years, and 93.5% at 5 years post-transplant. Patient survival was 96.4% and graft survival was 91.1% over the study period duration.

Conclusions: Alemtuzumab is a reasonable option for induction immunosuppression given its ease of administration with outcomes that are comparable to those reported for other induction agents in the literature.

SA-PO691

Metabolic Screening to Assess Cardiovascular Risk in Pediatric Kidney Transplant Recipients

Yifeng Zhang, Juhi Kumar. *UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA.*

Background: Post-transplant immunosuppression, such as steroids and calcineurin inhibitors, have been implicated in the development of new onset diabetes after transplantation (NODAT) and dyslipidemia increasing the risk of cardiovascular events affecting allograft and patient survival. The estimated incidence of NODAT in the pediatric transplant population is around 3-20%. Yet the incidence of metabolic syndrome, defined as a constellation of cardiovascular risk factors such as obesity, dyslipidemia, insulin resistance, and hypertension, has been difficult to establish among pediatric kidney transplant recipients. A contributing factor is a lack of guidelines to effectively screen these patients. We implemented a quality improvement (QI) project to streamline how our patients are screened. Our aim is to identify at-risk patients earlier with the goal of decreasing the morbidity and mortality related to the metabolic syndrome.

Methods: Non-fasting lipid panel, random plasma glucose and hemoglobin A1c (HgbA1c) were obtained annually. 162 pediatric kidney transplant patients aged 2 years to 20 years old were screened. Patients were referred to endocrinology if BMI was > 90% percentile, HgbA1c > 6 %, and abnormal fasting lipid profile was present. Primary outcome of interest is the percentage of patients who received metabolic syndrome screening labs pre and post implementation. Secondary outcome is the incidence of metabolic syndrome.

Results: Prior to QI initiation, only 18 patients (0.1%) had metabolic syndrome screening labs. After initiation, 91 patients (56%) received screening labs. HgbA1c level > 6% was found in 4 patients and they were referred to endocrinology and 7 patients had HgbA1c in the pre-diabetic range (5.6-6%). 4 patients had abnormal non-fasting lipid panels that will require reassessment on a fasting sample. The prevalence of patients with a component of metabolic syndrome was 18%.

Conclusions: Early identification and regular screening for metabolic syndrome in pediatric kidney transplant recipients is critical for the overall health and survival of the patient and their allograft. Without a standardized process to screen these patients, there is a risk of missing a group of patients with early signs of disease. The results of this QI intervention show that standardized screening is feasible and leads to early recognition of abnormal metabolic profile.

SA-PO692

Sex Disparities in Access to Second Kidney Transplantation among Adolescents

Alexandra Bicki, Sang M. Nguyen, Gabriela Accetta Rojas, Charles E. Mcculloch, Elaine Ku. *University of California San Francisco, San Francisco, CA.*

Background: Prior work has demonstrated disparities in access to kidney transplantation by sex, with women being less likely to receive a first transplant compared to men. We aimed to determine whether this disparity persists in relation to access to second kidney transplantation.

Methods: We performed a retrospective cohort study of people ≥13 years with first graft failure from 2006-2019 according to the United States Renal Data System. Using Cox proportional hazards models, the primary predictor was sex and the primary outcome was receipt of a second transplant overall, living, or deceased donor transplantation. We tested for interaction between age at first graft failure and sex.

Results: Of the 36,215 individuals included, median age at first graft failure was 48 years (IQR 37-58 years; 59% male). Median vintage of the first graft was 8 years (IQR 4-13 years), with no difference by sex (p=0.44). Over the observation period, 6,935 individuals (19%) died prior to second transplant receipt, and 18,610 individuals (51%) received a second transplant. There was an interaction between age and sex (p_{int}<0.05) such that girls 13-<18 years at first graft failure had reduced access to second transplant as compared to same-aged boys (HR 0.65, 95% CI 0.55-0.76). This relationship was not observed among older age groups. Findings were more prominent for deceased (vs living) donor transplantation in the adolescent age group.

Conclusions: Adolescent girls had substantially reduced access to second transplant compared to adolescent boys, a disparity that was not observed in other age groups. Given the high priority of children on the national waitlist, further studies are needed to understanding the sources of this disparity.

Funding: NIDDK Support

Hazard of second kidney transplant by sex, stratified by age at first graft failure

Hazard and 95% CI for women vs. men (reference)	Any transplantation	Living donor transplantation	Deceased donor transplantation
Overall	1.02 (0.99-1.05)	1.06 (1.01-1.11)	1.00 (0.97-1.03)
13-<18 years	0.65 (0.55-0.76)	0.89 (0.64-1.24)	0.59 (0.49-0.72)
18-<40 years	1.05 (1.00-1.11)	1.05 (0.96-1.13)	1.06 (1.00-1.13)
40-<65 years	1.04 (1.00-1.08)	1.09 (1.02-1.16)	1.01 (0.97-1.06)
≥65 years	0.92 (0.83-1.00)	0.94 (0.78-1.13)	0.91 (0.81-1.02)

Models adjusted for age and body mass index at first graft failure, sex, race/ethnicity, neighborhood income, calendar period (before vs. after 2014 Kidney Allocation System changes were made), insurance type, ABO blood group, and comorbidities.

SA-PO693

Need to Know, Want to Know: Characterization of Pediatric Kidney Transplant Education Materials

Taylor R. House,[1] Makayla Thomas,[1] Aaron G. Wightman,[2] Ari Pollack,[2] Susan P. Wong.[3] *[1]University of Wisconsin-Madison, Madison, WI; [2]Seattle Children's Hospital, Seattle, WA; [3]University of Washington, Seattle, WA.*

Background: Educational materials are meant to empower patients and families with information about kidney transplant, making their content and accessibility vital to supporting family-centered care and optimizing outcomes.

Methods: We conducted a mixed inductive and deductive content analysis of educational materials used by pediatric kidney transplant centers associated with a national research consortium to assess readability and relevance to four established priorities shared by patients, parents, and clinicians: kidney function, infection, life participation, and survival. We assessed readability using validated measures and summarized data descriptively.

Results: We obtained educational materials from 23 centers (32% response rate), averaging 81±69 pages in total length. Six centers (26%) used materials targeted to pediatric patients. All centers' materials addressed kidney function and infection, 22 (96%) also addressed life participation, and 18 (78%) addressed survival. Materials tended to feature more pages addressing infection (12±8 pages) and kidney function (10±6 pages) than life participation (7±7 pages) and survival (3±4 pages). Among aspects of life participation, psychological well-being was most frequently addressed (Figure). Over one-third (38%) of all life participation references were negatively framed – discouraging or cautioning aspects of life post-transplant. Mean grade level readability of materials was 8.9±1.7 with Simple Measure of Gobbledygook and 9.5±1.8 with Flesch-Kincaid Grade Level.

Conclusions: Pediatric kidney transplant centers use educational materials that are infrequently targeted to children, exceed recommended readings levels, and unevenly address stakeholder priorities. There is an opportunity to better address child and caregiver prioritized outcomes, particularly life participation, to promote greater goal concordance and shared expectations among patients, families, and clinicians.

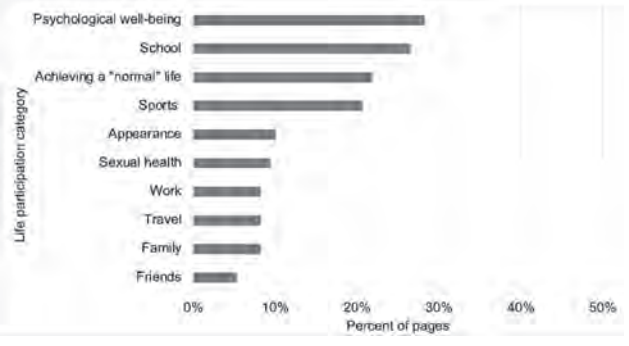


Figure: Of pages referencing life participation, percent discussing varying categories of life participation.

SA-PO694

Pediatric-to-Adult Kidney Transplant Transition Clinic in a Single Center: 3-Year Experience

Namita Singh, Craig S. Wong, Amy Staples. *University of New Mexico School of Medicine, Albuquerque, NM.*

Background: The transition of adolescents from child-centered to adult-oriented health care systems is a complex phenomenon. It is unique for each individual, affected by demographic, personal, ecological factors, as well as degree and specific features of one's disease. Failure of proper transition in kidney transplant (KT) recipients can lead to medical non-adherence, and subsequent loss of graft and return to dialysis.

Methods: We present the framework and findings of the KT Transition clinic at an academic center serving predominantly American Indian and Hispanic population. The clinic consists of a multi-disciplinary team including a lead nephrologist, nurse, pharmacist, social worker, dietician, and psychologist. Regular transition care meetings are conducted between pediatric and adult transplant teams to discuss each eligible patient at length, to understand the medical and social history, as well as to identify any potential barriers for successful transition which can be addressed in a timely and efficient manner. Pre-transition stage occurs at ages 14- 18 years, under the care of pediatric team, where the individual and caregivers are assessed for readiness to transition. Active transition stage starts at 18-21 years age and management is collaborative between the pediatric and adult teams. Complete transition to adult care happens with consensus among the patient, caregivers, and providers. These KT recipients are followed in the transition clinic for up to 26 years age with routine labs and office visits at least every 3 months.

Results: Since the re-establishment of the transition process and protocols in January 2021 and until December 2023, we have managed about 30 patients in the clinic with majority identifying as Hispanics (76%). Compliance with clinic visits has increased and remained consistently above 85%. Three out of 4 allograft failures were noted due to biopsy-proven chronic rejection, with none in the past year.

Conclusions: We report improved patient compliance and graft outcomes in young adult KT recipients in a single center, achieved through a standardized transition protocol and efficient crosstalk between pediatric and adult provider teams.

Time period	Number of rejections	Number of allograft failure
Jan- June 2021	2	0
July- Dec 2021	1	1
Jan- June 2022	1	2
July- Dec 2022	0	1
Jan- June 2023	0	0
July- Dec 2023	0	0

SA-PO695

Impact of a Health Care Transition (HCT) Clinic on Health Outcomes in Patients with Kidney Diseases: A Single-Center Experience

Demah Alobaidi, Sai Kaumudi Saridey, Cortney T. Zimmerman, Sahar Siddiqui. *Baylor College of Medicine, Houston, TX.*

Background: HCT from pediatric to adult focused care in patients with renal disease can be a challenging process. Inadequate HCT can cause interruption in continuity of care, which can lead to poor health outcomes like disease progression. A HCT clinic can be effective tool in building trust, communication and better health outcomes in adolescents and young adults (AYA). This abstract highlights the impact of a HCT on patients who utilized this at a Children's hospital in collaboration with an affiliate hospital in southwest USA.

Methods: We included patients who utilized the HCT clinic from 2021-2023 comprising of two visits (pediatric and adult clinics) to achieve thorough hand-off. We collected data on health related outcomes by manual review of EHRs. Our outcomes were: 1. Retention in adult renal care as measured by regular follow up with adult provider 2. Adequate communication between patient and provider measured via MyChart utilization 3. Significant events by noting adverse events such as hospitalization, renal transplant rejection & unplanned pregnancies.

Results: 29 patients utilized the HCT clinic (8 M, 21 F). 16(55%) with renal transplants, 7(24%) with Lupus Nephritis and 6(20%) with CKD. Retention in adult renal care was good 96%(28 out of 29) followed up regularly with their renal provider and only one patient was lost to follow up. All patients (100%) utilized MyChart to communicate with their adult renal providers. There were adverse events: 2(6%) patients who experienced complications of renal transplant requiring hospitalization and disease management. Patients were sent to transplant team in the same hospital for closer monitoring. 3 female patients got pregnant.

Conclusions: We found that AYA can benefit with HCT clinic. Overall retention in adult renal care was favorable and majority of the patients maintained good communication with their pediatric and adult renal providers. Outcomes for patients utilizing the HCT clinic appear positive with only 2 patients developing transplant rejection. In the future, we plan to look in to women's health especially after HCT with pregnancy and disease progression.

Health Outcomes from HCT clinic

1) Retention in adult health care	28/29 patients followed up with adult renal provider 1 patient with ESRD – transitioned to local dialysis unit 1 patient with insurance issues transitioned to in-network renal 1 patient was lost to follow up
2) Communication between patient and provider	29/29 patients active on my chart
3) Significant events	Two patients with transplant complication transitioned to transplant team in same adult hospital Three patients had pregnancies

SA-PO696

Barriers to Caring for Adolescents and Young Adults with Kidney Diseases

Angelina M. Dixon,[1] Anna Ostrow,[1] Andrew Vissing,[2] Eliza Blanchette,[1] Jessica B. Kendrick.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Adolescents and young adults (AYA) with CKD experience morbidity and mortality outcomes at unacceptably high rates, and a lack of knowledge and communication among nephrology providers is a contributing factor to adverse outcomes. Here, we evaluate adult nephrology providers' self-perceived education gaps, comfort, and reported barriers in transitioning patients from pediatric to adult care.

Methods: An anonymous, on-line survey of US nephrologists was undertaken from January 30 to May 7, 2024. The survey included questions regarding awareness and implementation of healthcare transitions (HCT) guidelines and knowledge of childhood-onset kidney disease, pediatric nephrology treatment guidelines, and AYA care.

Results: 152 adult nephrologists and 22 pediatric nephrologists submitted the survey. 71% of adult respondents were unfamiliar with the American Academy of Pediatrics (AP) Six Core Elements (vs.18% of pediatric nephrologists, p<0.001) and 63% were unfamiliar with the ISN/IPNA consensus statement on transitioning patients from pediatric to adult nephrology care (vs. 27% of pediatric nephrologists, p<0.001). In addition, adult nephrologists report they are not familiar or slightly familiar with youth health/adolescent medicine (68%), childhood/congenital causes of kidney disease (27%), and medications approved for patient <18 with kidney disease (51%). 48% of respondents had not received training in HCT. Of those who had received HCT training, 73% received training after completion of their formal training. 65% of respondents felt that further training in HCT would be useful and felt it should be included in residency training (37%), fellowship training (96%), and after completion of formal training (37%).

Conclusions: Most adult nephrologists are unaware of HCT guidelines and unfamiliar with caring for AYA with CKD. The creation of a HCT curricula that addresses these topics is imperative.

SA-PO697

Barriers to Communication with Providers among Pediatric Kidney Transplant Patients and Their Caregivers

Kaushalendra Amatya,[1,2] Kristen Sgambat,[1,2] Mesgana Dagnachew,[3] Asha Moudgil.[1,2] *[1]Children's National Hospital, Washington, DC; [2]The George Washington University School of Medicine and Health Sciences, Washington, DC; [3]Georgetown University, Washington, DC.*

Background: Effective communication between pediatric transplant patient/families and the treatment team is essential to adjustment and adherence to medical regimen. Barriers to communication such as language, health literacy, trust and comfort in providers, and cultural beliefs can impact outcomes and thus should be identified and addressed. This project aimed to obtain baseline data on the major barriers to healthcare communication in transplant patients and families.

Methods: Participants were patients (n=30) and caregivers (n=29, total n=59) presenting to the post-kidney transplant clinic in a pediatric hospital. A survey of healthcare communication consisting of demographics and factors related to healthcare communication was developed and administered to patients or caregivers using an electronic tablet.

Results: The self-reported racial distribution was 21 Latinx (35.6%), 19 Black (32.2%), 10 White (16.9%), 4 Asian (6.7%), 3 Middle Eastern (5.08%), and 2 Other. 28 patients (47.4%) identified English and 15 (25.4%) identified Spanish as their primary language; others reported were Arabic, Korean, and Urdu. Participants noted being most comfortable talking to the treatment team about medications and least comfortable talking about emotional health and financial concerns. 2 participants noted feeling uncomfortable or somewhat uncomfortable reaching out to providers between visits and 1 noted feeling their healthcare providers are not invested in the patient's health. 94.9% participants noted they think the healthcare providers' advice is very important (others neutral) and 81.3% noted completely trusting their providers (others neutral or somewhat trust).

Conclusions: Patients presenting to our pediatric kidney transplant clinic are racially diverse and a significant portion do not use English as their primary language. While most patients and families are comfortable discussing medications with providers and trust provider's advice, some may not feel comfortable reaching out to providers as needed and may not want to discuss certain topics that have direct and indirect implications on healthcare outcomes. It is imperative that these barriers be identified and adequately addressed. Future research should further explore barriers to communication and identify remedial methods to improve transplant outcomes.

SA-PO698

It Takes Two to Tango: Pediatric and Adult Kidney Transplant Providers' Perspectives and Practices for Transition of Care

Omar Alomar,[1] Beverly Kosmach-Park,[2] Tarek Alhamad,[1] Song C. Ong.[3] On behalf of the AST KPCOP-PCOP Transition of Care Workgroup. *[1]Washington University in St Louis, St Louis, MO; [2]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA; [3]The University of Alabama at Birmingham, Birmingham, AL.*

Background: Kidney transplant (KT) recipients aged 17-24 face the highest graft failure risk, coinciding with their transfer to adult care. Healthcare transition (HCT) can help preparing young adults (YA) for adult care, yet practices of American Society of Transplantation (AST) members serving this vulnerable population have not been studied.

Methods: An on-line survey developed by the AST Kidney-Pancreas and Pediatric Communities of Practice was distributed between July 2023 and March 2024.

Results: There were 131 responses: 60 Pediatric Providers (PP) and 71 Adult Providers (AP), mostly US attending physicians (PP 78%, AP 83%). Out of 69 KT centers where UNOS ID was disclosed, 80% had one respondent. Most PP and AP (91%, 84%) agreed that transition is a joint responsibility and valued having a transition program (PP 97%, AP 94%). More PP had transition programs (70% vs 48%), and both groups were familiar with their centers' transition programs (PP 82%, AP 73%). A formal transition policy was often lacking, with AP more likely to lack one (79% vs. 57%, p=0.008). PP were more likely to have a transition coordinator (67% vs 48%). Multidisciplinary transition clinics were rare (PP 27%, AP 23%). Both groups felt Transition Readiness Assessment was key to timing transfer (PP 87%, AP 73%). 62% of PP had no age limit in their centers and would delay transfer if needed. Both cited mental health status, inadequate self-management and self-advocacy skills as significant barriers. Systemic barriers included the YA relationship with PP, fragmentation of adult care, lack of community resources, and staffing/training issues. Only 19% of AP felt YA were well-prepared for transfer, few continued transition training post-transfer (15%). Outcome measures were tracked by 34% of PP and 42% of AP. Feedback from YA/caregivers was rarely obtained by PP (24%/18%) or AP (37%/24%).

Conclusions: This is the first AST survey on AP and PP perspectives regarding HCT. PP and AP endorse transition as a collaborative process and share similar concerns on barriers to successful HCT. With increased awareness of HCT's importance for improving outcomes, efforts should focus on program development starting with the pediatric team and continued into young adulthood post-transfer, both systemically and locally.

SA-PO699

The State of Pediatric Nephrology in the United States: Survey of Division Directors

Priya S. Verghese,[1] Joseph T. Flynn.[2] ASPN Division Director Interest Group. *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Seattle Children's Hospital, Seattle, WA.*

Background: Targeted interventions to address the conflict in demand with a workforce shortfall in pediatric nephrology services require a better understanding of current state.

Methods: The American Society of Pediatric Nephrology interest group of 92 Pediatric Nephrology Division leaders, developed a survey to describe the scope of practice and faculty activity for pediatric nephrology, with operational details of their programs.

Results: Survey completion was 83% and 56% respondents were from small programs (≤4 faculty). The number of nephrologists were 1-21 (median 4); with 1-12 purely clinical faculty(cFTE>0.7) per group. Small groups had significantly greater fraction of primarily clinical (>0.7 cFTE) faculty. Large programs had more outreach, ancillary staffing, independent transplant programs, diverse renal replacement options, and on-site outpatient dialysis. Small programs have a disproportionately large outpatient volume per cFTE until recruitment / transition to the large program model. Heterogenous operations for transplant/dialysis/fellowship programs did not mitigate the administrative burden, which were often minimally supported.

Conclusions: These results highlight the diversity of academic pediatric nephrology divisions and identify areas where increased administrative support is needed to maintain division operations.

	All Programs	Small Programs <=4 faculty	Large Programs >4 faculty	p-values
Continuous Renal Replacement Therapy (CRRT) Practices				
CRRT orders				
Nephrology only	33/39 (84%)	7/12(58%)	26/27(96%)	< 0.005
Critical care only	4/39 (10%)	4/12(33%)	0/27(0%)	
Both	2(5%)	1/12(8.3%)	1/27(4%)	
CRRT set up				0.02
Nephrology nurses	15/39(38%)	1/12(8.3%)	14/27(52%)	
Critical care nurses	20/39 (51%)	10/12(83%)	10/27(37%)	
Both	4/39 (10)	1/12(8.3%)	3/27 (11%)	
In-person nephrologist presence at CRRT initiation				
First time	11/39(28%)	5/12 (42%)	6/27 (22%)	0.2
Re-starts	7/39 (18%)	4/12 (33%)	3/27 (11%)	0.1
Use HF20 on Prisma flex/Prismax.	17/42	2/12 (17%)	15/30(50%)	0.05
Other Extracorporeal Modalities				
Aquadex	8/42 (19%)	0	8/25 (32%)	0.01
Carpe Diem	3/42 (7.1%)	0	3/25 (12%)	0.14
PD in ICU	42/42 (100%)	17/17(100%)	25/25(100%)	1.0
Apheresis	20/42 (48%),	3/18(17%)	17/24(71%)	< 0.005
Diagnostic Procedures				
Renal Biopsies				0.04
Nephrology	17/37 (46%)	6/15 (40%)	11/22 (50%)	
Interventional Radiology	16/37 (43%)	5/15 (33%)	11/22 (50%)	
Surgery	4/37 (11%)	4/15 (27%)	0/22 (0%)	
Point of Care US	10/42 (24%)	6/10 (60%)	4/32 (12.5%)	< 0.005
Point of Care Urinalysis	32/42 (76%)	10/10 (100%)	22/32 (69%)	0.04
Ambulatory BP Monitoring	39/41 (93%)	2/10 (20%)	31/31 (100%)	<0.005
Nephrology Faculty Call/Coverage				
In-House Nephrology overnight	0/73	0	0	N/A
In-person Satellite Clinics	9/68 (13%)	3/68 (4.4%)	6/30 (20%)	0.01
# Hospitals Covered				< 0.002
1	42/68 (62%)	30/38 (79%)	12/30 (40%)	
2	11/68 (16%)	6/38 (16%)	5/30 (17%)	
3	9/68 (13%)	2/38 (5.2%)	6/30 (20%)	
4	5/68 (7%)	(0%)	5/30 (17%)	
5	1/68 (1.5%)	(0%)	1/30 (3.3%)	
Hospital Support				
24/7 Hospitalist	28/39 (72%)	7/16 (44%)	21/23 (91%)	< 0.001
PICU attending	36/41 (88%)	14/17 (82%)	22/23 (96%)	0.14
NICU attending	33/41(80%)	13/17 (76%)	20/23 (87%)	0.37

Funded Directorships				
	Any support	0.05-0.14 FTE	0.15-0.3 FTE	>0.3 FTE
Division	83.3%	0	63.9%	19.4%
Chronic Dialysis	82.1%	10.2%	43.6%	12.8
Transplant	58.8%	29.4%	29.4%	0
Fellowship	48.7%	12.2%	36.5%	0
Quality Improvement	14.5%	14.5%	0	0
Acute Dialysis	8.5%	6.3%	2.2%	0
Hypertension	2.5%	2.5%	0	0
Apheresis	2.2%	0	2.2%	0
Funded Ancillary Services				
	Any Staff	Dialysis Service	Transplant Service	General Renal
Social Worker	95%	95%	43%	43%
Pharmacist	80%	39%	80%	8%
Nutritionist	66%	66%	58%	12%
Psychologist	50%	8%	50%	6%
Child Life	21%	21%	15%	3%
Funding for Fellowship Training Positions				
	Hospital/Dept	Training Grant	Individual Grants	Philanthropy
1st Year/Clinical	95.2%	0	0	4.8%
2nd-3rd Year/Research	66.7%	19.0%	9.5%	4.8%

SA-PO700

Small Molecule Inhibition of APOL1 Channel Activity Protects Podocytes from Mitochondrial Dysfunction, Cell Death, and Barrier Disruption Induced by APOL1 Risk Variants

Sylvain Galvani, Kelly E. Sullivan, Heather Weber, Michael Parsons, James J. Mann, Prachi Matsye, Timothy J. Senter, Leslie Dakin, Evanthia Nanou, Brinley Furey, Brandon Zimmerman. *Vertex Pharmaceuticals Incorporated, Boston, MA.*

Background: The presence of two copies of *apoliprotein L1 (APOL1)* genetic variants, *APOL1 G1* or *G2*, along with a 'second hit' (IFNg, HIV, cytokines, etc.), can cause damage to specialized kidney cells called podocytes. We sought to examine the impact of *APOL1* variants in podocytes and the potential impact inhibition of APOL1-mediated ion flux could have on these effects.

Methods: To enable this effort, we developed tetracycline inducible, human immortalized podocyte lines expressing *APOL1 G0* (reference allele), *APOL1 G1* or *APOL1 G2* and examined cell survival following APOL1 induction using a cell death assay. We also studied the potential for APOL1 variants to disrupt cell adhesion, cell-cell junctions and mitochondrial function and the ability of APOL1 ion channel inhibition to modulate these effects.

Results: APOL1 G1 and G2 induction led to a loss in podocyte viability that was rescued by treatment with Compound 3, a close analog of our clinical candidate inaxaplin. We also demonstrate that prophylactic inhibition of APOL1 prevents cell detachment and mitochondrial dysfunction and preserves podocyte barrier formation. Further, therapeutic administration of compound enabled restoration of these three outcomes, highlighting the potential to rescue damaged podocytes.

Conclusions: These data highlight the critical importance of APOL1-mediated ion flux in APOL1 driven cell injury and suggest that damaged podocytes can be recovered to restore their critical filtration barrier.

Funding: Commercial Support - Vertex Pharmaceuticals, inc.

SA-PO701

Small Molecule APOL1 Channel Inhibitor Reduces Proteinuria, Rescues Podocyte Injury, and Reverses eGFR Decline in an APOL1-Mediated Kidney Disease Mouse Model

Angelo Blasio, Gizelle Mccarthy, Shyamesh Kumar, Kathy Stavropoulos, Timothy J. Senter, Leslie Dakin, Jennifer Proctor, Brinley Furey, Brandon Zimmerman. *Vertex Pharmaceuticals Incorporated, Boston, MA.*

Background: APOL1-mediated kidney disease (AMKD) is a progressive, proteinuric nephropathy caused by gain-of-function variants (G1 or G2) in APOL1. There are currently no treatments addressing the underlying cause of AMKD. We reported results from a proof-of-concept clinical study with inaxaplin (IXP, VX-147), a small molecule inhibitor of APOL1, which has potential to become the first genetically-targeted therapy for kidney disease. Our previous preclinical data demonstrated that therapeutic intervention with a small molecule APOL1 channel inhibitor with similar structure and potency to IXP (Compound 3) reduced proteinuria and podocyte injury in a chronic AMKD mouse model.

Methods: To develop a chronic AMKD mouse model with glomerulopathy, we used transgenic *APOL1* mice homozygous for the *APOL1 G2* variant ($G2_{SC}$). A plasmid encoding interferon γ (IFNγ) was hydrodynamically injected (HDI) into $G2_{SC}$ mice to continuously secrete IFNγ from the liver. Mice were treated for 7 days with Compound 3 or vehicle at two therapeutic timepoints after HDI. Proteinuria and eGFR were assessed throughout the study. Morphological assessment of podocyte health was evaluated using 3D-structural illumination microscopy.

Results: HDI of IFNγ plasmid into $G2_{SC}$ mice led to a dramatic and sustained increase in proteinuria and progressive glomerulopathy. Therapeutic intervention with Compound 3 at both intervention timepoints dramatically reduced proteinuria. Morphological assessment of podocytes showed that loss of filtration slit density was present prior to treatment initiation and was reversed with Compound 3, highlighting the recovery of effaced podocytes. Furthermore, therapeutic intervention with Compound 3 preserved the eGFR when administered early, and reversed eGFR decline back to near baseline level at a later timepoint of intervention.

Conclusions: Here we demonstrate that APOL1 channel inhibition by Compound 3, a close analog of the clinical candidate inaxaplin, reduces proteinuria and glomerulopathy and reverses eGFR decline after APOL1-mediated glomerular damage is well established.

Funding: Commercial Support - Vertex Pharmaceuticals, inc.

SA-PO702

A Kidney-Specific Fasting-Mimicking Diet Induces Podocyte Reprogramming and Restores Kidney Function in Glomerulopathy

Valentina Villani,[1] Xiaogang Hou,[1] Paolo Cravedi,[3] Sean P. Monji,[1] Roberta Buono,[4] Stefano Da Sacco,[1] Silvia Lai,[5] Alessandro Laviano,[5] Diana G. Eng,[6] Stuart J. Shankland,[6] Kevin V. Lemley,[1] Roger E. De Filippo,[1] Valter Longo,[2] Laura Perin.[1] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]University of Southern California, Los Angeles, CA; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]University of California Irvine, Irvine, CA; [5]Universita degli Studi di Roma La Sapienza, Rome, Italy; [6]University of Washington Division of Nephrology, Seattle, WA.*

Background: Dietary changes are recommended for chronic kidney disease (CKD) patients. Yet no dietary intervention has shown glomerular regeneration. Cycles of a fasting-mimicking diet (FMD) were previously shown to promote regeneration and reduce damage in the pancreas, blood, gut, and nervous systems but its effect in glomerulopathies are yet unknown.

Methods: We applied cycles of a low-salt FMD (LS-FMD) to puromycin aminonucleoside-induced nephrotic (PAN) rats and monitored renal function and performed histological analysis. We performed qPCR arrays on whole glomeruli and whole kidney snRNA seq during one cycle of LS-FMD and refeeding. Alport syndrome (AS)-FUCCI (Fluorescence Ubiquitin Cell Cycle Indicator) mice were fed with FMD and used to track the cell cycle specifically in podocytes. To determine whether parietal epithelial cells (PECs) contribute to the replacement of podocytes, inducible dual transgenic PEC-Podo mice that lineage trace PECs (red) and podocytes (green) simultaneously were fed LS-FMD following adriamycin-induced nephropathy. To translate these findings, we also performed a pilot clinical trial on CKD patients receiving three 5-day cycles of the human version of the FMD and monitored renal and other physiological parameters up to 1 year post treatment.

Results: Cycles of a LS-FMD lowered proteinuria, and restored nephron structure and function in PAN rats. LS-FMD induced the expression of nephrogenic markers, mimicking kidney developmental processes in multiple kidney structures. Specifically in the glomerulus, LS-FMD prevented podocyte loss by preventing entrance to G1/S phase, in addition to activating PEC-podocyte-lineage reprogramming, as evidenced by lineage tracing studies. In the pilot randomized cross-over study in CKD patients, FMD cycles promoted renoprotection including long-term reduction of proteinuria and improved endothelial function.

Conclusions: We have developed a dietary intervention with the potential to limit and even reverse kidney damage by preserving the number and function of podocytes, and reducing inflammation and glomerulosclerosis.

Funding: Private Foundation Support

SA-PO703

Canagliflozin Reduces Podocyte Hypertrophic Stress and Progression of Nephropathy by Suppressing the mTOR/p70S6K/cyclin D1 Signaling Pathway in a Model of Obesity-Related Nephropathy

Miho Suzuki, Akihiro Fukuda, Ryo Kurimoto, Akiko Kudo, Takeshi Nakata, Hirotaka Shibata. *Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan.*

Background: We recently suggested that SGLT2 inhibitors (SGLT2i) suppressed podocyte hypertrophy in models of obesity-related nephropathy (ASN2023). In this study, we examined the underlying mechanisms of the podocyte-protective effects of SGLT2i.

Methods: Zucker fatty rats with non-diabetic obesity were divided into three groups (non-treated: n=6, SGLT2i: n=6, calorie restriction (CR): n=6). Starting at 12 weeks, both the non-treated and SGLT2i groups were fed same quantities of diet. From 24 weeks, the SGLT2i group received canagliflozin (10 mg/kg/day) for 8 weeks, while the CR group was on a diet restricted to match the urinary glucose excretion of the SGLT2i group. Kidney tissue and urine samples were collected at 32 weeks to assess podocyte injury through measurements of urinary protein, urinary sediment podocin (U-sed pod) mRNA using qRT-PCR, glomerular volume (GV), podocyte volume (PV), and podocyte density (PD). To investigate the underlying mechanism, RNA sequencing of the renal cortex was performed for a Zucker Lean (ZL) group as a control, and for the non-treated and SGLT2i groups. Additionally, the IGF-1/mTOR pathway was examined through phosphorylated S6 (pS6) immunostaining and IGF-1 expression using ELISA in the kidney cortex of all four groups.

Results: In the SGLT2i group, body weight, urinary protein, GV, PV, and U-sed pod mRNA significantly decreased, while PD increased, compared to the non-treated group. These effects were more pronounced than those observed in the CR group. RNA sequencing revealed a significant increase in cyclin D1 expression in the non-treated group, which plays an important role in cell cycle and hypertrophy, but a decrease in the SGLT2i group. Western blot analysis confirmed these trends in cyclin D1 expression. Additionally, the expression of the IGF-1/mTOR pathway components (IGF-1 and phosphorylated S6), which are upstream of cyclin D1, was upregulated in the non-treated group but downregulated in the SGLT2i group. The CR group had intermediate levels between the non-treated and SGLT2i groups.

Conclusions: In obesity-related nephropathy, SGLT2i may protect podocytes and reduce hypertrophic stress by suppressing the mTOR/p70S6K/cyclin D1 signaling pathway, independently of reductions to body weight.

Funding: Government Support - Non-U.S.

SA-PO704

MAP4K1 Downregulation by Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists Alleviates Podocyte Injury and Inflammation via the cGAS-STING Pathway in Glomerular Diseases

Aili Cao, Qiye Liu, Ying Chen, Li He, Jiayin You, Niansong Wang. *Department of Nephrology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.*

Background: GLP1R agonists, widely known for their role in glycemic control, have also been observed to confer renal protective effects independent of their blood glucose-lowering properties. Despite these benefits, the underlying mechanisms by which GLP1R agonists exert renoprotective effects remain inadequately understood.

Methods: Our study aimed to elucidate these mechanisms, focusing on the effects of the GLP1R agonist liraglutide on podocyte function and gene expression. We employed RNA-seq sequencing to analyze gene transcription in podocytes treated with liraglutide. Additionally, we investigated the role of the gene MAP4K1 by generating podocyte-specific MAP4K1 knockout mice and inducing nephropathy with adriamycin (ADR) and lipopolysaccharide (LPS) models.

Results: RNA-seq sequencing revealed that liraglutide significantly modulates gene transcription in podocytes, notably causing substantial downregulation of MAP4K1 expression. Data from the Nephroseq database indicated that MAP4K1 is upregulated in focal segmental glomerulosclerosis (FSGS) patients, suggesting its significant role in kidney pathology. In the ADR nephropathy model, liraglutide administration resulted in a marked decrease in MAP4K1 expression in podocytes, correlating with improved kidney functions. Podocyte-specific MAP4K1 knockout mice exhibited significant amelioration of podocyte injury upon ADR-induced nephropathy, associated with suppression of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway. Additionally, in the LPS model, MAP4K1 knockout mice showed reduced levels of inflammatory cytokines and notable improvements in podocyte integrity and kidney functions.

Conclusions: These findings underscore the pivotal role of MAP4K1 in mediating podocyte injury and the inflammatory response in kidney disease. Targeting the MAP4K1-cGAS-STING axis could be a viable strategy for developing new treatments for chronic kidney disease (CKD), highlighting the therapeutic potential of GLP1R agonists in renal protection.

SA-PO705

Reversal of Established CKD by Weekly Subcutaneous Recombinant Human Mutated Angiopoietin-Like 4

Jose L. Sanchez Gloria,[1] Ariadna J. Ortega Lozano,[1] Ranjan Das,[1] Joubert B. Kharlyngdoh,[1] Maria Del Nogal Avila,[1] Hector Donoro Blazquez,[1] Eduardo Molina-Jijon,[1] Camille E. Mace,[1] Carmen Avila-Casado,[2] Lionel C. Clement,[1] Sumant S. Chugh.[1] Glomerular Disease Therapeutics Laboratory. *[1]Rush University Medical Center, Chicago, IL; [2]Toronto General Hospital, Toronto, ON, Canada.*

Background: We investigated the therapeutic potential of recombinant mutated human Angiopoietin-like 4 (ANGPTL4), previously shown to reduce proteinuria in diabetic and FSGS (Buffalo Mna) rats (*Clement LC Nat. Med. 2014*), in established chronic kidney disease (CKD). ANGPTL4 binds integrins β_1 and β_5 (podocyte $\alpha_3\beta_1$, glomerular endothelial $\alpha_v\beta_5$, interstitial capillary endothelial $\alpha_1\beta_1$), and has potent anti-apoptotic activity.

Methods: Included with results.

Results: As a proof of concept, transgenic expression of wild type rat *Angptl4* from adipose tissue in Buffalo Mna rats (372-B. Mna) prevented doubling of serum creatinine (measured by LC-MS) between age 6 to 8 months ($P<0.001$), eliminated tubulo-interstitial fibrosis, and improved glomerular morphology compared to B. Mna rats (n = 4 to 6 rats / group). Interstitial infiltrate in 372-B. Mna rats contained mostly macrophages. Recombinant human mutated ANGPTL4 protein 8520 (Nat. Med. 2014) was purified and ultra-purified from HEK 293 stable cell lines grown in FiberCell systems. In a declining dose study (starting with 500 μg weekly subcutaneous 8520 or control rat albumin, n = 5 ZSF1 diabetic rats / group), serum creatinine was lower in the 8520 group compared to control between week 5 (dose 500 μg; $P<0.001$) and week 9 (dose 125 μg; $P<0.05$), but not at subsequent lower doses. Within the 8520 group, serum creatinine was lower on week 9 than Day 0 ($P<0.05$). Upon euthanasia (week 28), interstitial capillary endothelium apoptosis (TUNEL stain) was lower in 8520 compared to control ($P<0.001$). Using the lowest effective 8520 dose (125 μg / week) with or without ACE inhibitor (enalapril 5 mg/Kg/day), inulin clearance GFR at 16 weeks was higher in 8520 ($P<0.05$) and 8520 + enalapril ($P<0.01$) groups, tubulo-interstitial fibrosis lower ($P<0.01$ both groups) and interstitial capillary endothelial apoptosis lower ($P<0.001$ both groups) compared to control treated

ZSF1 rats (age on Day 0, 19 weeks; n = 4-5 rats / group). Enalapril alone did not improve GFR. Studies with higher doses of 8520 are in progress.

Conclusions: 8520 reverses established CKD to improve GFR via a multi-compartment anti-apoptosis effect that keeps capillaries open for repair.

Funding: NIDDK Support

SA-PO706

Trametinib Ameliorated Adriamy-Induced Podocyte Injury In Vivo and In Vitro by Inhibiting METTL3-Mediated RCAN1 m6A RNA Methylation

Hua Zhou, Feifei Miao, Yonghe Zhang, Junjun Luan. *Shengjing Hospital of China Medical University, Shenyang, China.*

Background: Trametinib can protects mice from adriamycin(ADR)-induced focal segmental glomerulosclerosis (FSGS). Recently, METTL3, a m^{6}A writer, is reported to involve in pathogenesis of kidney diseases. We aimed to investigate whether Trametinib can attenuate podocyte injury through regulating METTL3 and its modified downstream gene in ADR-induced FSGS mice and injured podocytes.

Methods: TREW database was used to find regulator calcineurin 1(RCAN1) as METTL3 modulated mRNA. First we examined WT-1, METTL3, and RCAN1 in biopsied kidney tissue from FSGS patients. Second, FSGS was induced by ADR injection in BALB/c mice in both normal and pretreated with trametinib. Urinary albumin to creatinine ratio (UACR) and serum albumin (sALB) were measured. Kidney damages were evaluated by PAS, Masson and EM. Third, overexpression and knockdown of METTL3 were performed in human podocytes *in vitro*. Podocyte specific gene WT-1 and synaptopodin (SYNPO); Profibrotic COL-1, α-SMA, and fibronectin (FN); and RCAN1 were assessed at mRNA by qPCR and protein levels by western blotting and immunostaining both *in vivo* and *in vitro*. The level of total m6A was measured by the m6A colorimetric qPCR and m^{6}A methylated mRNA of RCAN1 wwa examined by SELECT qPCR.

Results: WT-1 was downregulated, METTL3 was increased, and RCAN1 was decreased in biopsied kidney sections compared with normal control kidney sections. Trametinib alleviated ADR-induced proteinuria, hypoalbuminuria, hyperlipidemia, and renal dysfunction; podocyte foot process effacement, and sclerotic glomeruli. It also reverted the downregulation of WT-1 and SYNPO as well as reduced production of profibrotic COL-1,α-SMA, and FN protein in FSGS mice. Importantly, Trametinib inhibited the increment of METTL3 and decrease of RCAN1. In vitro study, overexpression of METTL3 in normal podocyte or knockdown of METTL3 by siRNA or Trametinib in ADR-treated podocyte, the changes of podocyte markers and profibrotic proteins displayed similar to those in vivo. The change directions of total level of m^{6}A RNA methylation and relative level of METTL3 methylated mRNA of RCAN1 in podocytes were same as the expressiom changes in vivo.

Conclusions: Trametinib attenuated podocyte injury in FSGS mice and ADR-treated podocyte by regulating METTL3/RCAN1 axis. Trametinib might serve as a potential agent to protect podocyte injury

Funding: Government Support - Non-U.S.

SA-PO707

Autophagic Inhibitor ROC-325 Ameliorates Glomerulosclerosis and Podocyte Injury via Inhibiting Autophagic Flux in Experimental FSGS Mice

Xinling Liang, Li Zhang, Jiaying Li, Yan Yang, Lu-an Li. *Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China.*

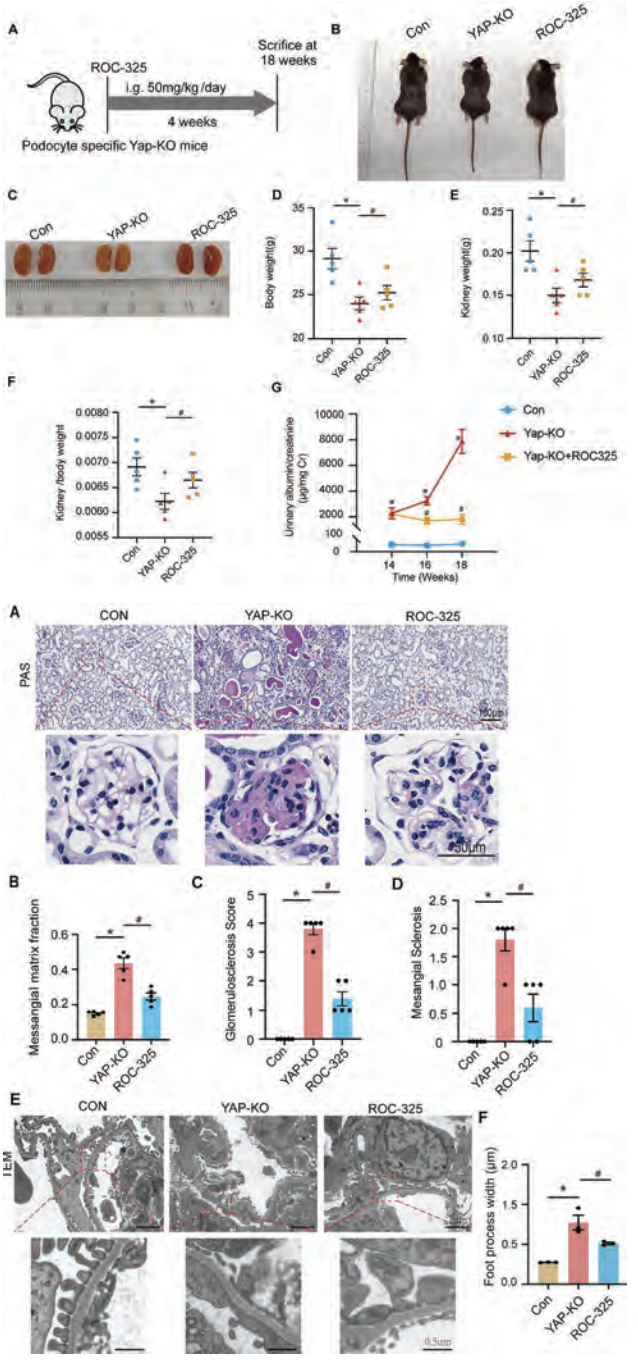
Background: Podocyte-specific Yes-associated protein (YAP) deletion mice(YAP-KO mice), is considered a new animal model to study the underlying mechanism of FSGS. We sought to determine the therapeutic benefit of ROC-325, a novel small-molecule lysosomal autophagy inhibitor in FSGS model.

Methods: Mass spectrometry were used to profile the downstream pathways in YAP-KO mice. Foot process morphology and autophagy level were detected by transmission electron microscopy. Immunofluorescence measured autophagy level and autophagic flux.

Results: Mass spectrometry showed the processes linked to lysosome dysregulation have been significantly enrich in the YAP-KO mice. The results showed albuminuria, mesangial matrix expansion, and focal segmental glomerulosclerosis in YAP-KO mice were significantly attenuated by ROC-325. Corrugated capsule formation was greatly altered by ROC-325. Furthermore, ROC-325 treatment inhibited the autophagy activaty induced by YAP-KO by inhibiting autophagosome-lysosome fusion, and accumulation of LC3 and p62. Meanwhile, preapplication of ROC-325 in podocyte markedly suppressed autophagic flux.

Conclusions: These results showed that the role of autophagic activity in FSGS and ROC-325 could be a promising agent for the treatment of FSGS.

Funding: Government Support - Non-U.S.



SA-PO708

Pharmacologic Inhibition of Urokinase-Type Plasminogen Activator Receptor (uPAR)-Formyl Peptide Receptor (FPR) Signaling Prevents Podocyte Damage in Primary Podocytopathies

Manuel A. Podestà,[1] Deborah Mattinzoli,[1] Masami Ikehata,[1] Min Li,[1] Silvia Armelloni,[1] Francesca Zanoni,[1] Carlo Alfieri,[1,3] Piergiorgio Messa,[1] Alberto Diana,[3] Luca Del Giacco,[3] Vincenzo Pavone,[2] Giuseppe Castellano.[1,3]
[1]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;* [2]*Universita degli Studi di Napoli Federico II, Napoli, Italy;* [3]*Universita degli Studi di Milano, Milano, Italy.*

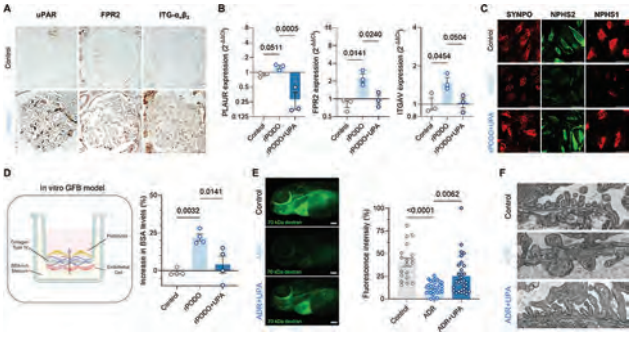
Background: Primary podocytopathies are a group of disorders characterized by nephrotic syndrome and frequent progression to kidney failure in patients not responding to treatment, with high rates of recurrence after transplantation. Glomerular upregulation of the urokinase-type plasminogen activator receptor (uPAR) has been linked to podocyte dysfunction in these disorders. We tested the hypothesis that inhibition of uPAR signaling via the formyl peptide receptor (FPR) would ameliorate podocyte damage in primary podocytopathies.

Methods: Renal biopsies and serum from patients with recurrent primary podocytopathies were collected. Podocyte and podocyte-endothelium co-cultures to model the glomerular filtration barrier were carried out according to previously published protocols. RT-PCR and immunostaining were performed with standard methodology. Zebrafish larvae exposed to adriamycin were used as a podocytopathy in vivo model. The peptide UPARANT was used in all experiments to inhibit the uPAR-FPR crosstalk.

Results: uPAR upregulation in kidney biopsies of patients with primary podocytopathies was accompanied by increased expression of FPR2 and integrin-αvβ3 (Fig1A). The same molecules were upregulated in podocytes exposed to sera from patients with recurrent disease (Fig1B), and pharmacologic inhibition of the uPAR-FPR interaction led to normalization of this effect. uPAR-FPR crosstalk inhibition prevented podocyte damage induced by recurrent sera (Fig1C), resulting in significant functional rescue in an *in-vitro* model of the glomerular filtration barrier (Fig 1D). Consistently, targeting of uPAR-FPR crosstalk in a zebrafish larval model of podocytopathy led to functional (Fig1E, high-MW dextran clearance) and ultrastructural (Fig1F) rescue of the disease phenotype.

Conclusions: Pharmacologic targeting of the uPAR-FPR axis confers protection against podocyte damage and may preserve renal function in primary podocytopathies.

Funding: Government Support - Non-U.S.



SA-PO709

Voclosporin Ameliorates Proteinuria and Directly Protects Podocytes in a Model of Noninflammatory Glomerular Disease

Yu Kamigaki,[1] Julie Dougherty,[1] Amanda P. Waller,[1] Linda M. Rehaume,[2] Laura Biederman,[3,5] Bryce A. Kerlin,[1,4] William E. Smoyer.[1,4] *[1]The Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Aurinia Pharmaceuticals Inc, Victoria, BC, Canada; [3]The Ohio State University Wexner Medical Center, Columbus, OH; [4]The Ohio State University College of Medicine, Columbus, OH; [5]Nationwide Children's Hospital Department of Pathology, Columbus, OH.*

Background: Idiopathic nephrotic syndrome (INS) is one of the most frequent glomerular diseases in children. There is a critical need for the development of more effective and less toxic treatments. Voclosporin (VCS) is a second generation calcineurin inhibitor (CNI) approved in the USA, EU, Great Britain, and Switzerland on a background of immunosuppressive therapy for the treatment of adults with active lupus nephritis. VCS does not require therapeutic drug monitoring due to an improved pharmacokinetic profile. We investigated whether VCS could reduce proteinuria in a non-inflammatory animal model of NS.

Methods: Rats received 50 mg/kg puromycin aminonucleoside (PAN) or saline via tail vein injection and were gavaged twice daily with vehicle (VEH, vitamin E-TPGS, MCT oil, Tween 40, and 95% ethanol 4:2:2:1, by weight), VCS (4 mg/kg/dose), or cyclosporine (CsA, 10mg/kg/dose) as clinically relevant doses. Rats were euthanized on day 11, and proteinuria, lipid profile, glomerular cell injury, hypercoagulability, and histopathology were assessed. To validate the direct protective effect of VCS on podocytes, cultured human podocytes were also treated with PAN (5 μg/ml) + vehicle (DMSO), VCS (0.1 μg/ml), or CsA (0.1 μg/ml) for 72 hours and podocyte viability and actin stress fiber changes were analyzed.

Results: VCS improved proteinuria, hypercoagulopathy, lipid profile, and TUNEL positivity of glomerular podocytes. PAN + VCS rats exhibited a significantly decreased mean total tubular injury score (1.07 ± 0.23) compared with PAN + VEH (2.00 ± 0.37, $P < 0.05$), while PAN + CsA mean total injury score (1.75 ± 0.34, $P = 0.66$) was only slightly better than PAN + VEH. Cultured podocyte viability of the PAN + VCS group was significantly improved (100% ± 2.6%, $P < 0.01$) compared with PAN + DMSO (91% ± 2.5%), while PAN + CsA (94% ± 4.4%, $P = 0.28$) was mildly better than PAN +DMSO. Also, PAN + VCS cells had more intact actin-fiber cells and fewer actin-fiber-disrupted cells than PAN + DMSO and PAN + CsA.

Conclusions: Compared to CsA, a clinically relevant dose of VCS more effectively ameliorated PAN-induced proteinuria, hypercoagulopathy, NS-associated dyslipidemia, and tubular injury in rats, as well as cell viability and actin cytoskeleton of cultured podocytes.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc

SA-PO710

Similarities and Differences in Gene Expression between Glucocorticoids and Pioglitazone in a Rodent Model of Nephrotic Syndrome

Yu Kamigaki,[1] Julie Dougherty,[1] Sagar Bhayana,[1] Amanda P. Waller,[1] Bryce A. Kerlin,[1,2] William E. Smoyer.[1,2] *[1]The Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University College of Medicine, Columbus, OH.*

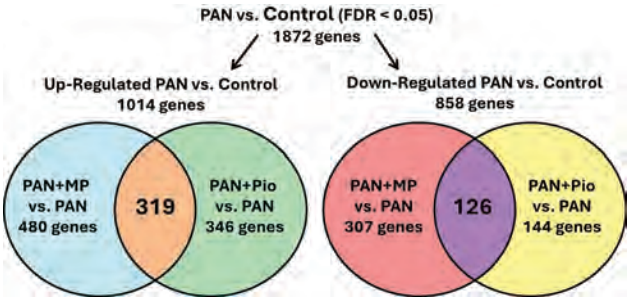
Background: Idiopathic nephrotic syndrome (INS) is one of the most frequent glomerular diseases in children with first line treatment of glucocorticoids (GCs), an immunosuppressant with myriad side effects. Thus, there is a critical need to develop more effective and less toxic options. Pioglitazone (Pio), a non-immunosuppressant, is FDA-approved for type 2 diabetes mellitus. Pio has been associated with proteinuria reduction in adults and children with NS, so it has potential as a non-immunosuppressive alternative or supplement to GC treatment. Therefore, we wanted to compare changes in gene expression and pathways between the two drugs.

Methods: Male Wistar rats received 50 mg/kg puromycin aminonucleoside (PAN) or saline injection and treated daily with vehicle, methylprednisolone (MP, 15 mg/kg), or Pio (10 mg/kg). Rats were euthanized on day 11 and glomerular RNA was sequenced. Differentially expressed genes were analyzed for pathway activation, upstream regulators, and causal networks.

Results: MP and Pio significantly improved proteinuria compared to PAN-only treated animals. We filtered glomerular data for genes significantly up- or down-regulated in PAN-treated animals compared to controls, then compared expression of PAN + MP and PAN + Pio. Our recent article addressed PAN-induced up-regulated genes ameliorated by both drugs. This study analyzed the PAN-induced down-regulated genes commonly improved by both drugs. Common upstream regulators included calcitriol, EGLN family, KRAS, MYOD1, and SORL1. We also analyzed expression changes unique to either drug. MP had 46 unique upstream regulators, including immune regulators and transcription regulators such as HDAC1/2, TBX3, and ATF3. The list of uniquely altered genes for Pio was too short for pathway analysis but included CD36, IL34, RHOQ, and SHPRH, among others.

Conclusions: These studies illustrated the common and unique changes in glomerular gene expression in a rodent NS model treated with immunosuppressive (MP) and non-immunosuppressive (Pio) drug.

Funding: NIDDK Support



SA-PO711

miR-193a and Nanoparticle Technology: A Novel Therapeutic Approach for Alport Syndrome

Laura Perin,[1,2] Paola Aguiari,[1] Astgik Petrosyan,[1,2] Yi Huang,[2] Qi Zhang,[1] Xiaogang Hou,[1] Roger E. De Filippo,[1,2] Kevin V. Lemley,[1,2] Eun ji Chung,[2] Stefano Da Sacco.[1,2] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]University of Southern California, Los Angeles, CA.*

Background: Significant molecular changes in podocyte cell cycle regulation are responsible for the progression of renal damage. miR-193a has been reported to regulate podocyte phenotype and to ensure maintenance of their differentiated G0 state. We observed elevated levels of miR-193a in human podocytes from Alport Syndrome (AS) biopsies and in AS mice. Here, we study the role of miR-193a in Alport podocytes and if miR-193a inhibition by podocyte-targeting nanoparticles could restore podocyte quiescent state.

Methods: To study the effects of miR-193a, we used miR-193a mimic and antagomir on podocytes from AS FUCCI mice (cell cycle indicator mouse model) and in the glomerulus-on-a-chip system (GOAC), generated with AS patient-derived podocytes. Podocyte-targeted nanoparticles (micelles) were developed and tested for specificity in vitro and in the GOAC and for assessing the efficiency of a miR-193a inhibition therapy. In situ hybridization, Digital Spatial Profiling (DSP, Nanostring), and protein arrays were used to investigate changes in miR-193a targets in murine podocytes and human AS biopsies.

Results: We observed specific upregulation of miR-193a in podocytes vs other glomerular cells, and upregulation of miR-193a targets osteopontin, VEGFA, and ItgαV, and downregulation of WT1 in AS glomeruli. Our data shows that miR-193a regulates

the cell cycle: WT podocytes re-enter the cell cycle when exposed to miR-193a (G1/S), while miR-193a inhibition rescues the AS podocyte G0 and modulates P18, cyclin A1 and cyclin C, important cell cycle regulators. We successfully generated miR-193a inhibitor-mediated micelles enhancing targeting to podocytes and preliminarily proved effective in safeguarding the glomerular filtration barrier. In human AS glomeruli, DSP revealed changes in gene expression in miR-193a targets and cell cycle regulators.

Conclusions: Our data indicate that the elevation of miR-193a plays a key role in regulating podocyte biology by controlling the podocyte cell cycle. Inhibiting miR-193a using micelle technology may re-establish glomerular function by modulating important molecular pathways responsible for podocyte survival to prevent further injury representing a therapeutic target for AS.

Funding: NIDDK Support

SA-PO712

Dapagliflozin in Addition to Ramipril Ameliorates Kidney Disease Progression in Mice with Alport Syndrome

Kana Miyata,[1] Denise Smith,[1] Michifumi Yamashita,[2] Shimok Kim,[1] Faith A. Yeargin,[1] Melisa Beganovic,[1] Daniel N. Leal,[2] John C. Edwards,[1] Shao-Ling Zhang,[3] John S. Chan,[3] Jeffrey H. Miner.[4] *[1]Saint Louis University School of Medicine, St Louis, MO; [2]Cedars-Sinai Medical Center, Los Angeles, CA; [3]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [4]Washington University in St Louis, St Louis, MO.*

Background: Renin-angiotensin-aldosterone system inhibitors (RAASi) have been the most extensively studied treatment for Alport syndrome, demonstrating established benefits for renal function and survival in both animals and humans. We presented that Ramipril (an angiotensin-converting enzyme inhibitor) had more renoprotective effects in mice with Alport syndrome than sodium glucose cotransporter 2 inhibitors, Dapagliflozin (ASN Kidney Week 2023). The objective of this study is to investigate whether combination treatment with Dapagliflozin and Ramipril exerts a better kidney-protective effect than treatment with Ramipril alone in Col4α3 knockout (KO) mice (an Alport syndrome model).

Methods: We studied both sexes of Col4α3 KO and wild-type (WT) mice (129S1/SvImJ background). Dapagliflozin (1.5 mg/kg/day), Ramipril (10 mg/kg/day), or a combination of both were orally administered via drinking water for 6 weeks, starting at 4 weeks of age (N=8-10/group). The control mice received vehicle for the same duration. Glomerular filtration rate (GFR) was measured by inulin-FITC clearance in conscious mice, and kidneys were processed for histology (PAS, Masson's Trichrome staining and electron microscope). Another set of mice were monitored for their survival.

Results: At 10 weeks of age, Col4α3 KO mice developed a significant weight loss, decreased GFR/body weight, elevated BUN and urine albumin/creatinine ratio. These findings were attenuated by Ramipril, and further improved by the combination treatment. Histologically, Col4α3 KO kidneys showed the severe degree of global and segmental glomerulosclerosis, tubulointerstitial fibrosis, and thickened glomerular basement membrane, which were more significantly improved by the combination treatment than by Ramipril alone. Furthermore, the combination treatment prolonged the life of Col4α3 KO mice; median survival was 157 days in combination treatment while 127 days in Ramipril alone ($p<0.01$).

Conclusions: The combination of Dapagliflozin and Ramipril had more favorable outcomes on preservation of renal function and histology than Ramipril alone in Col4α3 KO Alport mice. Studies are currently ongoing to investigate the underlying mechanisms of action.

Funding: Private Foundation Support

SA-PO713

Reducing Proteinuria by Antagonizing αVβ3 Integrin with a Novel Inducible Co-stimulator Ligand-Based Peptide

Alexis P. Jimenez Uribe,[1] Yan Xu,[1] Yanxia Cao,[1] Ryan Spear,[1] Kwi Hye Koh,[2] Adrian P. Mansini,[1] Ariana G. Alcantar,[1] Felix Kliewe,[3] Nicole Endlich,[3] Jochen Reiser,[4] Steve Mangos,[1] Eunsil Hahm.[1] *[1]Rush University, Chicago, IL; [2]Morphic Therapeutic Inc, Waltham, MA; [3]Universitatsmedizin Greifswald, Greifswald, Germany; [4]The University of Texas Medical Branch at Galveston, Galveston, TX.*

Background: Activation of $\alpha_V\beta_3$ integrin has been linked to early stages of glomerular diseases, leading to podocyte injury and proteinuria. To date, no $\alpha_V\beta_3$ antagonists have been successful in clinical trials. Our group has recently discovered a novel protective role for the inducible co-stimulator ligand (ICOSL) in the kidney, functioning as an antagonist of $\alpha_V\beta_3$integrin independently of its canonical immune function and mitigating glomerular damage through its RGD-motif. Here, we developed a 19-mer peptide based on the human ICOSL structure (hICOSL-19) and evaluated its therapeutic potential *in vitro* and *in vivo*

Methods: Data were obtained from the Nephroseq database. The interactions between ICOSL or its derived peptide and integrins were analyzed using surface plasmon resonance (SPR) and proximity ligation assay (PLA). The antagonistic effects of peptides were evaluated through podocyte adhesion, cancer cell proliferation and invasion assays, and western blotting. PEGylation was applied to extend the peptide half-life. The in vivo efficacy of ICOSL-based peptides was tested in mice injected with lipopolysaccharide (LPS) or nephrotoxic serum (NTS).

Results: Analysis of the Nephroseq database confirmed the reduction of ICOSL expression in the glomeruli across several kidney diseases. SPR analysis revealed the preferential binding of ICOSL to $\alpha_V\beta_3$ integrin over other RGD-binding integrins. PLA tests confirmed this ICOSL-$\alpha_V\beta_3$ interaction at both cellular and tissue levels. Similar to the full-length hICOSL protein, hICOSL-19 demonstrated a high affinity for $\alpha_V\beta_3$ integrin. In vitro assays demonstrated that hICOSL-19 effectively blocks $\alpha_V\beta_3$ integrin-mediated downstream signaling. Additionally, unlike cRGDfV, hICOSL-19 maintained its antagonistic effects even at low concentrations. Treatment with hICOSL-19 peptide reduced proteinuria in a mouse model of LPS-induced kidney damage. PEGylation of this hICOSL-19 extended its plasma half-life and maintained its antagonistic effect against $\alpha_V\beta_3$ integrin in vitro and in vivo.

Conclusions: The hICOSL-19 peptide is a promising therapeutic option for treating glomerular disease associated with $\alpha_V\beta_3$activation. Its applications might also extend to conditions involving $\alpha_V\beta_3$ integrin activation, including cancer and fibrotic disease.

Funding: NIDDK Support

SA-PO714

Stabilization of Integrin a3b1 with Novel Activating Antibodies Protects against FSGS

Santiago Balza Pineda,[1] Darlah M. Lopez-Rodriguez,[1] Mohamed Youssef,[2] Sheri Brackman,[2] Antonio Barbosa,[1] Vineet Gupta.[2] *[1]149 Bio, LLC, Miami, FL; [2]The University of Texas Medical Branch at Galveston, Galveston, TX.*

Background: Healthy podocytes maintain the normal function of the glomerulus. The cell surface integrin a3b1 helps podocytes adhere to the extracellular basement membranes. Inflammatory injury, mutations in a3b1 or associated protein CD151, or defects in the integrin-linked cytoskeleton result in reduced cell adhesion, podocyte detachment and urinary loss. This weakening of the filtration barrier contributes to progressive glomerular diseases, including focal segmental glomerulosclerosis (FSGS). Enhancing podocyte retention through increased integrin-mediated cell adhesion presents a promising therapeutic strategy in FSGS.

Methods: Podocytes were used in High-Content Screening (HCS) assays to measure cell damage induced by puromycin aminonucleoside (PAN) and measure the protective effects of integrin agonists. To identify a3b1-activating antibodies (Abs), we employed a naive human phage display library. For discovery and in vitro characterization assays, we used recombinant integrin constructs, K562 cells stably expressing a3b1, differentiated podocytes, and human SK-OV3 cells. Albuminuria was assessed in a lipopolysaccharide (LPS)-induced mouse model of FSGS.

Results: Results from the HCS assay revealed observable changes in F-actin fiber formation, focal adhesion formation, and active integrin levels in podocytes following PAN injury. Notably, known b1 integrin agonists (Ab 9EG7 and Pyrintegrin) and novel a3 Abs demonstrated protective effects against PAN-induced injury in podocytes. The agonist Abs also increased cell adhesion and decreased cell migration *in vitro*. Ab mapping experiments show selective and allosteric binding of the new Abs to the a3 head-domain, away from the ligand binding pocket. In an animal model of FSGS, treatment with the new a3 Ab resulted in a significant reduction in albuminuria compared to control groups, highlighting the therapeutic potential of a3b1 activation in mitigating glomerular dysfunction.

Conclusions: Activation of integrin a3b1 in podocytes enhances adhesion to matrix proteins and confers protection against cellular damage. Ongoing *in vivo* efficacy studies will provide additional insights into the therapeutic potential of this approach, offering a promising strategy against various glomerular diseases.

Funding: Commercial Support - 149 Bio, LLC

SA-PO715

Activation of Podocyte-Specific MC5R Signaling by Melanocortin Therapy Protects against THSD7A-Associated Membranous Nephropathy

Jing Liu, Yan Ge, Lance D. Dworkin, Rujun Gong. *The University of Toledo Medical Center, Toledo, OH.*

Background: Melanocortins, exemplified by adrenocorticotropic hormone (ACTH), have demonstrated a unique beneficial effect in membranous nephropathy (MN). The underlying mechanism remains elusive. This study tested the role of melanocortin 5 receptor (MC5R), one of the 5 MCRs of the melanocortin system and reported to be expressed in podocytes.

Methods: Wild-type (WT) and MC5R knockout (KO) mice were injected with a rabbit anti-THSD7A antibody to develop MN. Beforehand, some KO mice received hydrodynamic transfer of a plasmid encoding MC5R driven by *Nphs2* promoter. Subsequently, melanocortins were given, including repository corticotropin injection (RCI; Purified Cortrophin® Gel, ANI Pharmaceuticals, Inc.), the nonsteroidogenic

pan-MCR agonist NDP-MSH, and the selective MC5R agonist PG901. Glomerular disease was evaluated. *In vitro*, primary podocytes from WT or KO mice were exposed to the anti-THSD7A antibody in the presence or absence of melanocortins and cellular injury was assessed.

Results: After anti-THSD7A antibody insult, WT mice developed massive proteinuria and a pathology resembling human MN. Despite granular subepithelial deposition of the rabbit IgG in glomeruli to a comparable extent, KO mice sustained more severe glomerular injury than WT mice, as evidenced by heavier proteinuria, worsened podocytopathy, and increased expression of the podocyte injury marker. Melanocortin treatment with RCI, NDP-MSH or PG901 ameliorated proteinuria and glomerular damage in WT mice, coinciding with an improvement in podocyte injury. The beneficial efficacy of melanocortins was drastically blunted in KO mice. Mechanistically, MC5R is expressed in glomeruli in WT mice, and co-localized with podocyte markers like podocalyxin. Melanocortin treatment directly protected WT podocytes against the anti-THSD7A antibody-elicited cytopathic changes, including actin cytoskeleton disruption, cellular hypermotility, oxidative stress, and apoptosis. This protective effect was abolished in cultured KO podocytes. In contrast, glomerular podocyte-specific reconstitution of MC5R in KO mice attenuated the experimental MN, and restored the beneficial efficacy of melanocortins.

Conclusions: Our findings suggest that podocyte-specific MC5R signaling protects against glomerular injury and proteinuria in MN, and may serve as a novel therapeutic target for treating MN.

Funding: Commercial Support - ANI Pharmaceuticals, Inc.

SA-PO716

A Novel IKKβ Inhibitor Ameliorates Podocyte and Kidney Injuries

Yiqing Guo,[1] Nehaben A. Gujarati,[1] Andrew K. Chow,[1] Navjot Pabla,[2] Sandeep K. Mallipattu.[1] *[1]Stony Brook University Renaissance School of Medicine, Stony Brook, NY; [2]The Ohio State University, Columbus, OH.*

Background: Previous studies showed that Krüppel-Like Factor 15 (KLF15) plays a protective role in the kidney through maintaining of podocyte differentiation. We developed a high-throughput screening (HTS) to identify KLF15 agonists as a therapy for proteinuric kidney diseases. Based on the structural activity relationship from the HTS, we designed and synthesized a novel compound, BT503 that was found to be protective in both *in vitro* and *in vivo* proteinuric models. Here, we demonstrate that BT503, directly inhibits IKKβ activity, resulting in loss of NFκB signaling.

Methods: IKKβ kinase activity was measured using either wild type IKKβ or gatekeeper mutant (M96V, in the ATP binding pocket) with BT503 as compared to vehicle. *in vitro* and *in vivo* profiling of BT503 was conducted using HPLC/MS/MS to characterize the drug properties. RNA-sequencing, in-silico drug-docking studies, and western blot analysis were also performed.

Results: Initial unbiased RNA-sequencing, in-silico drug-docking studies, and western blot analysis demonstrate that the salutary effects of BT503 in the podocyte are due to inhibition of IκBα phosphorylation, thereby preventing the nuclear translocation of p50/p65 and subsequent downregulation of KLF15. BT503 inhibits IKKβ kinase activity, which was abolished using an IKKβ gatekeeper mutant, suggesting that BT503 directly targets IKKβ. Thermal shift assay showed BT503 directly binds to IKKβ, but not IKKα and TAK1. BT503 also demonstrates low toxicity in cultured human podocytes and in mice. Expression of p50/65 was reduced in BT503-treated as compared to VEH-treated mice in proteinuric mouse models (HIV-1 transgenic mice, NTS-treated mice). Furthermore, knockout of KLF15 in podocytes attenuated the salutary effects of BT503, suggesting that the effects of IKKβ-p50/p65 are in part mediated by KLF15.

Conclusions: These data suggest that the salutary effects of a novel KLF15 agonist (BT503) are mediated through the direct inhibition of IKKβ kinase activity and subsequent canonical NFκB signaling.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO717

Lymphatic Dysfunction and Perirenal Adiposity: Role of Glucocorticoids

Jianyong Zhong, Haichun Yang, Elaine L. Shelton, Valentina Kon. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Glucocorticoids (GCs) are commonly prescribed to treat proteinuric kidney injury, but their use often leads to negative side effects such as visceral adiposity. The impact of GCs on adipocyte growth is well-established, however, their effect on lipid clearance via lymphatic vessels is not understood. This study investigated GCs effects on lymphatic endothelial cell (LEC) permeability which underlies reabsorption of fluids, solutes and lipids from the interstitium and lymphatic vessel contractile functions which regulates transport of lipids.

Methods: Primary cultured mouse LECs were exposed to vehicle, dexamethasone (DXMS), or DXMS+glucocorticoid receptor (GR) antagonist (D06). RNA sequencing was performed and related genes were validated by rtPCR. Additionally, barrier integrity was analyzed by Transepithelial electrical resistance (TEER). Ex vivo pressure myography assessed the contractile function of renal lymphatic collecting vessels of rats treated with DXMS or vehicle x 2 weeks.

Results: GR was detected in both lymphatic vessels and cultured LECs. RNA sequencing revealed DXMS upregulated 771 genes and downregulated 693 genes, with DXMS+D06 reversing expression of 615 genes. GO enrichment and KEGG pathway analysis revealed changes in cell junction-related genes and rtPCR confirmed DXMS upregulation of *TJP1* and *Ocln* junctional genes, reversed by D06. In TEER assays, DXMS increased barrier integrity of LECs. This effect could be reversed with addition of D06. Lymphatic vessels from DXMS-treated rats had reduced amplitude of contraction and ejection fraction. In vivo, DXMS increased perirenal fat by around 56% vs vehicle.

Conclusions: In conclusion, GCs expand perirenal adiposity and blunt lymphatic contractility together with increasing LECs tight junctions and reducing permeability through GR which we propose contribute to development of visceral adiposity.

SA-PO718

Inhibiting STAT3-Mediated Glutathione Metabolism Attenuates Parietal Epithelial Cell Activation in Proliferative Glomerulopathy

Yogesh Gowthaman,[1] Joseph Kim,[1] Yiqing Guo,[1] David J. Salant,[2] Sandeep K. Mallipattu.[1,3] *[1]Stony Brook University, Stony Brook, NY; [2]Boston University, Boston, MA; [3]Northport VA Medical Center, Northport, NY.*

Background: The activation of STAT3 is seen in podocytes and parietal epithelial cells (PECs) in mouse models of proliferative glomerulopathy and human RPGN and subtypes of FSGS. We reported that the loss of STAT3 in PECs reduced PEC activation, and eventual FSGS in nephrotoxic serum (NTS) treated mice. To elucidate the mechanims of STAT3-mediated PEC activation, we performed bulk RNA-sequencing in *Stat3* knockout PECs and identified glutathione (GSH) metabolism as a significantly downregulated pathway. GSH is the major antioxidant in the body which functions to maintain cellular redox homeostasis, however, an overabundance of GSH may fuel pathologic PEC activation.

Methods: CRISPR/Cas9 generated PECs with deletion of *Stat3*. ChIP-qPCR was performed for GSH metabolism genes on *Stat3* KO and control PECs after incubation with total STAT3 and phospho-STAT3 antibodies. GSH metabolism was targeted using an inhibitor of glutamate–cysteine ligase, L-buthionine sulfoximine (BSO). Control PECs were treated with increasing doses of BSO (62.5 - 500 μM), and MTT and mitostress seahorse assays were performed. BSO was given to mice injected with NTS, a mouse model of proliferative glomerulopathy. Osmotic pump released BSO at a dose of 10 mg/kg daily until the mice were collected on day 7, and proteinuria and PEC activation were evaluated.

Results: *Stat3* KO PECs showed a reduction in GSH synthesis and peroxidase activity levels compared to control PECs. STAT3 occupancy in the promoter region of 8 genes involved in GSH metabolism (*Gpx4, Gss, Gstz1, Gsta4, Gstm4, Gstm5,* and *Mgst2*) was significantly reduced in *Stat3* KO PECs as compared to control PECs. Increasing doses of BSO resulted in significantly lower cell viability via MTT assay, and in significantly lower OCR via seahorse assay. Compared to vehicle, BSO treatment reduced albuminuria and crescent formation 7 days post-NTS. Immunostaining and quantification for markers of activated PECs and quiescent PECs, CD44 and AKAP12, respectively, reveals that BSO treatment reduces CD44 expression, but increases AKAP12 expression, suggesting a reduction in pathogenic PEC activation post-NTS treatment.

Conclusions: These data suggest that inhibition of GSH metabolism might be a key target in attenuating PEC activation, proliferation, and crescent formation in proliferative glomerulopathy.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO719

Selective Peroxisome Proliferator-Activated Receptor γ Modulator, GQ-16, Provides Therapeutic Efficacy in a Murine Model of Rapidly Progressive Glomerulonephritis

Antonio S. Novaes, Shipra Agrawal. *Stony Brook University, Stony Brook, NY.*

Background: Rapidly proliferating glomerulonephritis (RPGN) is clinically characterized by rapid decrease in glomerular filtration accompanied with pathologic findings of glomerular epithelial hypercellularity. It often leads to irreversible kidney failure and is a significant health problem globally. Current treatments for RPGN focus on suppressing the immune system, but they are not curative and have serious side effects. Therefore, safer and more effective therapies are needed. We have previously demonstrated therapeutic potential of GQ-16, a selective modulator of peroxisome proliferator-activated receptor γ (PPARγ), in minimal change disease model. We hypothesized that GQ-16 can also provide therapeutic efficacy in a more severe and immunological model of RPGN.

Methods: RPGN was induced by two doses of intraperitoneal administration of rat nephrotoxic serum (NTS) preceded by IgG sensitization, in 7 weeks old male 129/Sv mice. The treatment group received GQ-16 (40 mg/kg) daily by oral gavage, while the control group received vehicle (n=4) for 7 days. Albuminuria and Transdermal Glomerular Filtration Rate (GFR) was measured serially, and kidneys and glomeruli were harvested at the end of the study for analyses.

Results: Robust albuminuria was observed with NTS injury on Day 3 (73.4 ±33.2 mg/mg vs Control 0.22±0.06 mg/mg), which was significantly decreased up to 80% with

GQ-16 treatment (p=0.0025). On Day 7, NTS injured group showed a reduction in GFR, whereas no differences were observed in GFR in the GQ-16 treatment group compared to baseline. Histopathological examination demonstrated segmental sclerosis, hyalinosis, and hypercellularity in Bowman's space in the NTS group (17.7% ± 4.3 glomeruli affected), tubular protein casts (90% ± 2.8) and interstitial inflammation (13% ± 6.0). These pathological findings were not observed in the GQ-16 treatment group. There were no changes in the weight among the groups. Additionally, gene expression of podocyte markers, nephrin, podocin, and WT1 was increased in GQ-16 group treatment compared with the NTS injury group.

Conclusions: Together, our findings suggest that GQ-16 might be an attractive and promising pharmacological intervention for treating RPGN.

Funding: NIDDK Support

SA-PO720

Therapeutic Targeting of Antibody-Secreting Cells for the Treatment of Autoimmune Kidney Diseases

Marie Eggers,[1,2] Alessa Z. Schaffrath,[1,2] Thomas Eden,[3] Ming Huang,[1,2] Natalie Tode,[3] Renke Lucas,[1,2] Stephan Menzel,[3] Friedrich Koch-Nolte,[3] Nicola M. Tomas.[1,2] *[1]University Medical Center Hamburg-Eppendorf, Department of Medicine, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Hamburg Center for Kidney Health (HCKH), Hamburg, Germany; [3]University Medical Center Hamburg-Eppendorf, Institute of Immunology, Hamburg, Germany*.

Background: Antibody-secreting cells (ASCs) are the main source of antibodies and represent an important therapeutic target in antibody-mediated autoimmune diseases. However, molecular targets suitable for the elimination of pathogenic ASCs are sparse. The aim of this study was the identification and evaluation of novel ASC targets for the treatment of antibody-mediated disease.

Methods: We used available cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) datasets to identify surface molecules with high specificity for ASCs. We then generated nanobody-based heavy chain antibodies (hcAbs) against the identified target and tested their cytotoxic effects in vitro, ex vivo and in vivo. We further used a model of experimental autoimmune membranous nephropathy (EAMN) to evaluate the therapeutic potential of this treatment.

Results: We identified a new potential therapeutic target protein with high membrane expression on both human and murine ASCs. In vitro and ex vivo, hcAbs against this target protein mediated potent cellular lysis of human and murine plasma and myeloma cells. Application of these hcAbs in mice induced a strong depletion of ASCs in bone marrow and spleen. Finally, anti-target protein hcAb treatment strongly reduced the levels of antigen-specific antibodies as well as the degree of podocyte damage and improved clinical outcome in the EAMN disease model.

Conclusions: Our study introduces a promising new target protein for the depletion of ASCs in autoimmune diseases. Considering the global burden of severe autoimmune diseases, further investigation of this potential therapeutic strategy is warranted.

Funding: Government Support - Non-U.S.

SA-PO721

Felzartamab Selectively and Potently Targets CD38+ Antibody-Secreting Cells from Patients with Immune-Mediated Kidney Diseases

Tess A. Delfino,[1] Kristina M. Ilieva,[2] Karin Landgraf,[2] Rainer Boxhammer,[2] Stefan Steidl,[2] Donna Flesher.[1] *[1]Human Immunology Biosciences Inc, South San Francisco, CA; [2]MorphoSys AG, Planegg, Germany*.

Background: CD38+ antibody secreting cells (ASC) such as plasmablasts and plasma cells have been implicated in the pathology of many immune-mediated diseases (IMD). Variability in the efficacy of therapies that target earlier B lineage cells in IMD highlights the need to selectively target the pathogenic cellular drivers of disease. Felzartamab (felza) is a fully human monoclonal antibody that binds to CD38 and has the potential to selectively deplete CD38+ ASC that contribute to IMD through secretion of pathogenic antibodies.

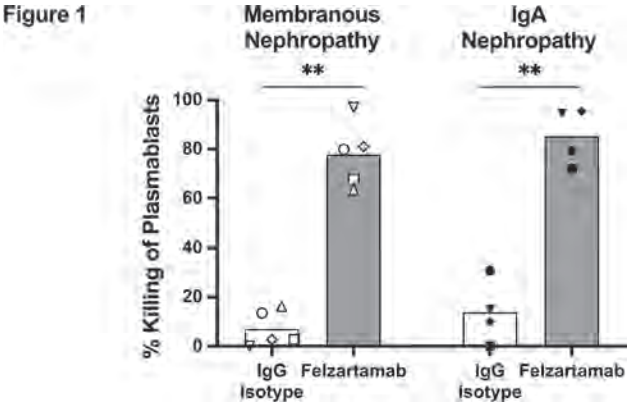
Methods: Flow cytometry based CD38 quantification was evaluated on immune cells from peripheral blood, bone marrow, and *in vitro* differentiated healthy donor and IMD patient ASC. Depletion of ASC after treatment with felza was assessed in an antibody-dependent cell cytotoxicity (ADCC) assay *in vitro* and in NSG-SGM3 mice engrafted with human CD34+ cord blood cells *in vivo*.

Results: CD38 is highly expressed on ASC and other cellular drivers of IMD in peripheral blood, bone marrow, and *in vitro* differentiated ASC from healthy and IMD donors. Felza demonstrated potent ADCC activity on *in vitro* differentiated ASC from healthy donors and IMD patients with Membranous Nephropathy (MN) and IgA Nephropathy (IgAN) (Figure 1), while sparing earlier B lineage cells. Furthermore, felza treatment reduced spleen and bone marrow CD38+ ASC and human immunoglobulin titers in engrafted humanized NSG-SGM3 mice, suggesting depletion activity *in vivo*.

Conclusions: These *in vitro and in vivo* proof of concept studies highlight the capacity of felza to selectively deplete CD38+ ASC, suggesting the potential for clinical utility in antibody-driven IMD. Clinical trials assessing the safety and efficacy of felza in immune-mediated kidney diseases including MN, IgAN, antibody-mediated kidney rejection and lupus nephritis are currently ongoing.

Funding: Commercial Support - Human Immunology Biosciences, Inc

Figure 1



SA-PO722

Moss-Produced Human Factor H (CPV-104): Pioneering Rebalancing Therapies for Kidney Complement Disorders

Todor A. Tschongov,[1] Swagata Konwar,[1,2] Paulina Dabrowska-Schlepp,[3] Andreas Busch,[3] Andreas Schaaf,[3] Karsten Häffner.[1] *[1]Universitatsklinikum Freiburg Abteilung Innere Medizin IV Nephrologie und Allgemeinmedizin, Freiburg, Germany; [2]Albert-Ludwigs-Universitat Freiburg Fakultat fur Biologie, Freiburg, Germany; [3]Eleva GmbH, Freiburg, Germany*.

Background: Dysregulation of the complement system can lead to various pathological conditions, particularly in the kidneys. Beside aHUS and C3G, other renal diseases are often associated with unbalanced complement activation. Drugs targeting the complement system often aim to inhibit either specific components or the entire cascade. Utilizing factor H (FH), a natural regulator of the alternative pathway, offers an alternative treatment option by restoring complement balance. Through a moss-based expression system, we developed a recombinant FH variant (CPV-104) with pharmacokinetics and pharmacodynamics comparable to native FH *in vivo*. In this study, we investigated dosing intervals and explored the feasibility of subcutaneous (s.c.) administration of CPV-104 in preclinical models.

Methods: B-cell and CD4 T-cell depletion was performed by injecting FH deficient mice with anti-CD20 antibody SA271G2 and anti-CD4 antibody GK1.5 at certain intervals, respectively. Depletion was confirmed by flow cytometry. Mice were treated intravenously (40 mg/kg) or s.c. (40 mg/kg; 200 mg/kg) with CPV-104 every 3, 4 or 5 days for a total of 3 injections. Blood samples were collected and the amount of FH and C3 quantified using ELISAs. Kidneys were harvested and stained for FH and glomerular C3 deposits. FH antibody formation was tested by incubating mouse sera on FH coated wells and detecting bound mouse IgGs.

Results: B- and CD4 T-cell depletion in mice allowed multiple injections of CPV-104 without causing antibody response. In FH-deficient mice, repeated CPV-104 injections normalized serum C3 levels and degraded kidney C3 deposits. Additionally, the feasibility of s.c. CPV-104 injections was explored. Initial results indicate that multiple s.c. injections lead to prolonged FH availability in mouse sera, resulting in sustained elevation of serum C3 levels and reduced kidney C3 deposits.

Conclusions: By optimizing dosing intervals and exploring s.c. administration, FH availability was significantly improved in conjunction with sustained reduction of glomerular C3 deposits in preclinical models. These findings provide valuable insights into the clinical translation of CPV-104 as a new therapeutic strategy for complement-mediated renal diseases, enabling physiological complement functionality.

Funding: Commercial Support - Eleva GmbH

SA-PO723

Pharmacologic Activation of CD11b Suppresses TLR7-Driven Proinflammatory Myeloid Signaling and Protects against Lupus Nephritis

Xiaobo Li,[1] Viviana Jimenez,[2,1] Billy Nguyen,[2] Nishant Ranjan,[1] David J. Cimbaluk,[3] Jochen Reiser,[1] Vineet Gupta.[1] *[1]The University of Texas Medical Branch at Galveston, Galveston, TX; [2]Rush University, Chicago, IL; [3]Rush University Medical Center, Chicago, IL*.

Background: Lupus Nephritis (LN) is a severe complication of Systemic Lupus Erythematosus (SLE) and occurs in approx. 50% of all patients. Single nucleotide polymorphisms (SNPs) in ITGAM gene, coding for CD11b, shows a high correlation with risk for SLE and LN. We previously showed that ITGAM SNPs that result in less functional protein show heightened inflammatory signaling via toll-like receptors (TLRs), resulting in enhanced systemic immunity. However, how these are linked to increased kidney disease is unclear.

Methods: Human PBMCs from LN patients, primary macrophages, RAW264.7 cells, MRL/lpr genetic and humanized mouse model were utilized in our study. Two orthogonal approaches, genetic and pharmacologic, were utilized to activate CD11b and to measure its effect on TLR7-dependent inflammatory signaling in myeloid cells *in vitro* and in LN *in vivo*.

Results: We found that LN patients carrying *ITGAM* SNPs have significantly elevated serum suPAR levels, suggesting a strong link between the variants and kidney disease. TLR7-stimulation increased suPAR, IFN I, IL-6 and other pro-inflammatory markers in myeloid cells and absence of CD11b exacerbated this response. Conversely, CD11b activation using an oral allosteric agonist called Ontegimod or a gain-of-function point mutation in CD11b (constitutively active) significantly reduced serum suPAR, pro-inflammatory markers, anti-dsDNA antibodies, and ameliorated proteinuria and glomerulonephritis. CD11b activation also reduced splenomegaly and $CD11b^+$ cells infiltration in kidney. Mechanistically, CD11b activation reduced TLR7-dependent NF-kB and IFN-I signaling to suppress suPAR generation, demonstrating therapeutic modality for LN.

Conclusions: CD11b activation reduced TLR7-dependent suPAR levels in LN models. This study provides pre-clinical evidence supporting CD11b activation as a promising therapeutic for treating SLE and LN.

Funding: NIDDK Support, Other NIH Support - R01DK084195, R01DK106512 and R21CA176055

SA-PO724

Targeting M2b Macrophages by Selenium Nanomedicine for the Treatment of Lupus Nephritis

Yiming Zhou,[1] Haoran Lv,[2] Hanzhi Liang,[2] Le Wang,[1] Siweier Luo,[1] Qinghua Liu.[2] *[1]Sun Yan-sen Memorial Hospital, Sun Yan-sen University, Guangzhou, China; [2]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China.*

Background: Excessive activation of macrophages, particularly M2b macrophages, plays a pivotal role in the progression of lupus nephritis (LN); however, effective treatment strategies remain limited. Selenium possesses immunomodulatory properties; nevertheless, its high toxicity and instability hinder its application. Here, we designed and constructed novel selenium nanoparticles for the treatment of LN by targeting M2b macrophages.

Methods: Primary mouse macrophages were used to observe the toxicity and targeting ability of selenium nanomedicine on macrophages, as well as the immune-regulation of macrophage activation by LPS. RNA-seq and qPCR experiments were used to explore the molecular mechanism of selenium nanoparticles on macrophage activation. Finally, a lupus mouse model was used to investigate the renal protective effect of selenium nanoparticles *in vivo*.

Results: Selenium nanoparticles exhibited excellent stability and biocompatibility. By coating mannose to the selenium nanoparticles, they could selectively target M2b macrophages both in vitro and in vivo, and display increased retention time in kidneys of lupus mice. Selenium nanoparticles significantly inhibited macrophage activation and reduced the expression and releasing of pro-inflammatory cytokines and chemokines. In addition, selenium nanoparticles significantly attunated the ROS production and improved the mitochondrial function in M2b macrophages. Mechanistically, we discovered that selenium nanoparticles regulate M2b macrophages via the JAK1/JAK2-STAT1 pathway through GPX1 expression. In animal, these nanoparticles significantly improved the renal function, preserved the renal structure, and reduced the renal fibrosis by inhibiting M2b macrophage activation in mice with lupus nephritis.

Conclusions: In this study, we developed a novel selenium nanomedicine that selectively targets M2b macrophages and suppresses their activation by attenuating the ROS production and inhibiting the JAK1/JAK2/STAT1 pathway through GPX1 expression, thereby achieving therapeutic efficacy in LN. Our findings provide a new idea for the treatment of LN by targeting specific macrophage population.

SA-PO725

Sinomenine Alleviates Lupus Nephritis in MRL/lpr Mice by Suppressing the Noncanonical NF-kB Pathway

Anqun Chen, Baiyu Feng. *The Second Xiangya Hospital of Central South University, Changsha, China.*

Background: Systemic lupus erythematosus (SLE) is a severe autoimmune disease with significant mortality, often progressing to lupus nephritis (LN), which affects over 50% of patients and can lead to end-stage renal disease. Urgent attention is needed for new drugs in treating LN due to severe complications associated with traditional therapies. Sinomenine, a natural alkaloid with proven anti-inflammatory properties, holds promise for therapeutic efficacy in LN given its success in treating rheumatoid arthritis.

Methods: At 10 weeks, MRL/lpr mice were grouped: vehicle (i.g., PBS, n=6), sinomenine (i.g., 50mg/kg/day, n=6), and dexamethasone (i.p., 1mg/kg/day, n=6). MPJ mice served as controls (i.g., PBS, n=5). At week 18, mice were euthanized. Lymph node and spleen size, renal function, histopathology, autoimmune antibodies, inflammatory cell infiltration, and immune complex deposition were assessed. Spleen cell flow cytometry was conducted, and kidneys underwent single-cell RNA sequencing (scRNA-seq) analysis (n=2/group). Sinomenine's binding affinity to target protein was confirmed via molecular docking, cellular thermal shift assay (CESTA), and drug affinity-responsive target stability (DARTS) assay.

Results: Sinomenine improved renal function in MRL/lpr mice, reducing UACR and Scr while increasing GFR. It also alleviated renal histological injury and suppressed adaptive immunity, evidenced by reduced splenomegaly, serum anti-dsDNA titers, splenic CD8+ T cells, and splenic Th1/Th2 ratio. scRNA-seq data indicated alleviation of tubule cell inflammation and dedifferentiation in sinomenine treatment group. Dexamethasone exhibited a strong inhibitory effect on immune cells in the kidneys, notably promoting the differentiation of mononuclear cells and macrophages towards an immunosuppressive phenotype in the kidneys. Sinomenine decreased Relb regulon activity, inhibiting the non-canonical NF-kB pathway. In vitro, sinomenine suppressed nuclear translocation of RelB-p52 complex, validated by CESTA and DARTS assays confirming its binding to Relb.

Conclusions: Sinomenine protects against LN in MRL/lpr mice by reducing immune cell infiltration and tubular damage through modulating non-canonical NF-kb signaling pathways, suggesting its promise as a therapeutic option for patients with LN.

Funding: Government Support - Non-U.S.

SA-PO726

SGLT2 Inhibition in Nondiabetic CKD: Results in Experimental Lupus Nephritis (LN)

Jordi Vilardell,[1] Conxita Jacobs Cachá,[1] Nerea Martos,[1] Carmen Llorens Cebrià,[1] Aku Enam Motto,[1] Maciej Lech,[2] Irene Martínez Díaz,[1] Hans J. Anders,[2] Maria Jose Soler.[1] Nephrology and Transplantation Research Group. *[1]Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus. Nephrology and Transplantation Research Group., Barcelona, Spain; [2]University Hospital, Ludwig-Maximilians-University. Department of Medicine IV, Division of Nephrology, Munich, Germany.*

Background: Sodium glucose cotransporter type 2 inhibitors (SGLT2i) attenuate cardiovascular morbidity and progression of CKD in type 2 diabetes patients. It has been proposed that SGLT2i may also elicit renoprotection in non-diabetic CKD. Our goal is to evaluate if the SGLT2i treatment improves kidney disease progression in a mouse model of LN.

Methods: Female MRLlpr/lpr mice were randomly assigned to (1) vehicle (VH) or (2) empagliflozin (EMP) (10 mg/kg/day) treatment once signs of active systemic lupus erythematosus appeared: proteinuria >100mg/dL or lymphadenopathy in minimum 2 bilateral sites with proteinuria >30mg/dL. 13 mice/group were treated for 4 weeks. Reduction of urinary albumin to creatine ratio (UACR) was the primary endpoint. Glomerular Filtration Rate (GFR), renal histology (LN activity/chronicity index, glomerulosclerosis, interstitial fibrosis) and SLE markers (total serum IgG, anti-dsDNA IgG, IgG deposits, lymph node and spleen weight) were considered secondary endpoints.

Results: After 4 weeks of treatment, no significant differences in glicemia were found between groups. Empagliflozin inhibited SGLT2 in the tubular cells supported by a significant increase of glucosuria (EMP 12.3±5.3 mg/g; VH 1.2±5.3 mg/g, $p<0.001$) and reflected with the increased water intake observed in this group (EMP 7.0±0.95 mg/g; VH 5.0±0.3 mg/g; $p<0.001$). At the end of the experiment, vehicle treated mice showed a significant increase in UACR (post-UACR 3.3±0.7 vs pre-UACR 2.2±0.7mg/g; $p<0.001$) consistent with LN progression that was not reduced by empagliflozin. Empagliflozin did not modify GFR and LN activity/chronicity indexes, glomerulosclerosis or interstitial fibrosis. Regarding SLE markers, empagliflozin was not able to decrease total serum IgG, anti-dsDNA IgG, glomerular IgG deposits or lymph node weight. Only spleen weight decreased significantly in empagliflozin treated mice (EMP 8.5±1.6mg/g; VH 12.1±3.4 mg/g; $p<0.001$).

Conclusions: In our experimental setting, empagliflozin reduced spleen weight suggesting a protective role in SLE in MRLlpr/lpr mice. However, empagliflozin did not modify LN progression probably because the acute LN phase. It is expected that positive effect in terms of reducing proteinuria will be observed in patients with LN and residual proteinuria.

Funding: Government Support - Non-U.S.

SA-PO727

Assessing the Therapeutic Potential of a Myeloperoxidase Inhibitor in a Preclinical Rat Model of MPO-ANCA Autoimmune Vasculitis

Vandana Veenit,[1] Maria Prendecki,[2] Stephen P. McAdoo,[2] Asha Seth,[1] Lorna J. Hale,[1] Birgitta E. Rosengren,[1] Pernille B. Laerkegaard Hansen,[1] Anna Collén,[1] Julie Williams.[1] *[1]AstraZeneca R&D Cambridge, Cambridge, United Kingdom; [2]Imperial College London, London, United Kingdom.*

Background: Antineutrophil cytoplasmic antibody (ANCA)- associated vasculitis (AAV) is a rare systemic autoimmune disease characterised by the inflammation of blood vessels and involves multiple organ systems. ANCA binds to proteins on the neutrophil surface, particularly myeloperoxidase (MPO) which is a major disease driver of AAV.

Methods: We evaluated a tool MPO inhibitor- AZM198 on human AAV relevant readouts using a well characterised preclinical rat model of AAV which involves immunising adult male WKY rats with human MPO followed by an intravenous administration of 1:100 dilution of nephrotoxic serum (NTS) on day 14. We first assessed AZM198 in a prevention setting by dosing AZM198 at 125 mg/kg peroral from day 7 until day 27. We then conducted an intervention study where one group received AZM198 from day 16 until day 35 (early intervention) and another group received AZM198 from day 25 until day 35 (late intervention). Animals were sacrificed one day after the last treatment (AZM-198 or vehicle).

Results: In prevention and early intervention groups, but not in the late intervention group, AZM198 treated rats showed reductions in human AAV pertinent readouts - haematuria, proteinuria, kidney/lung injury and inflammatory cell infiltration compared to vehicles. There was no change in MPO antibody titre or MPO mass in response to AZM198 treatment. However, there was a significant reduction seen for the MPO activity/mass ratio both in plasma and kidney in AZM198 treated animals in prevention and early intervention groups but not in the late intervention group. Interestingly, we also saw a significant correlation between kidney MPO activity and proteinuria in both studies which corroborates the role of MPO activity in driving AAV pathogenesis.

Conclusions: Our preclinical data confirms a key role of MPO activity in AAV aetiology and suggests strongly that inhibition of MPO activity might offer protection in AAV patients.

SA-PO728

Genome Editing to Delete the Proteinase 3 Autoantigen as a Treatment Strategy for ANCA-Associated Vasculitis

Uwe Jerke,[1,2] Claudia Eulenberg-Gustavus,[1,2] Dimitrios L. Wagner,[3,4] Adrian Schreiber,[1,5] Ralph Kettritz.[1,5] *[1]Experimental and Clinical Research Center, a cooperation between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association and Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [3]BIH Center for Regenerative Therapies (BCRT), Berlin Institute of Health (BIH) at Charité - Universitätsmedizin Berlin, Berlin, Germany; [4]Berlin Center for Advanced Therapies (BeCAT), Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health (BIH), Berlin, Germany; [5]Department of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Berlin, Germany.*

Background: Proteinase 3 (PR3) is a major autoantigen in ANCA-associated vasculitis (AAV). We performed a proof-of-principle study using ex-vivo genome editing to eliminate the PR3 autoantigen in CD34+ human hematopoietic stem cells (HSC) and assessed functional consequences in a neutrophil differentiation model.

Methods: A ribonucleoprotein (RNP) complex of an endonuclease and a sgRNA was transfected into human CD34+ HSC by electroporation to disrupt PR3 protein expression. Effects on neutrophil differentiation, PR3 protein abundance, and ANCA-dependent and independent neutrophil responses were assessed. Only low-risk off-targets were predicted, which are currently analyzed by amplicon sequencing.

Results: $PR3^{KO}$-HSCs and non-transfected Ctrl-HSCs showed similar neutrophil differentiation at day 10 by flow cytometry using the CD15 differentiation marker (5,515±1,163 MFI in $PR3^{KO}$-HSCs and 5,289±1,393 in Ctrl-HSCs, n=5). Gene editing reduced the PR3 protein efficiently as demonstrated by immunoblotting and the complete absence of PR3-specific proteolytic activity by FRET analysis. In contrast, human neutrophil elastase was not affected. Flow cytometric analysis showed that, while the amount of the PR3-presenting CD177 receptor on the cell surface was unaffected in neutrophil-differentiated $PR3^{KO}$-HSCs, membrane-PR3 was significantly reduced to isotype control levels (p=0.011, n=8). Consequently, extracellular reactive oxygen species (ROS) production in differentiated $PR3^{KO}$-HSCs activated with either monoclonal or human PR3-ANCA was significantly reduced, whereas ROS production with MPO-ANCA stimulation was not affected. PR3-ANCA independent defense functions in neutrophil-differentiated HSCs showed similar responses for $PR3^{KO}$- and Ctrl-HSCs. For neutrophil-differentiated $PR3^{KO}$-HSCs was the phagocytosis index of E.coli bioparticles 91.3%±6.9 of controls, phorbol ester-stimulated intracellular ROS production 95.4%±10.2 of controls, and extracellular superoxide production 98.8%±1.2 of controls.

Conclusions: Our proof-of-principle study showed the feasibility to effectively knock out PR3 in human CD34+ HSCs using genome editing. Our data could provide the basis for developing a drug-free treatment strategy in AAV patients.

SA-PO729

RNK288: A MASP2-Targeting Small Interfering RNA (siRNA) for the Treatment of IgA Nephropathy by Blocking the Activation of Lectin Pathway

Ling Pan,[1] Guofeng Meng,[1] Wei Liu,[2] Cong Huang,[1] Yang Xiaoyan,[1] Guoqing Cai,[1] Xin X. Xu,[1] Ming Yue,[1] Tao He,[1] Lei Wang,[2] Jinyu Huang,[1] Jianwu Fang,[1] Bo Chen,[2] Yibin Shi.[1] *[1]Rona Therapeutics, Shanghai, China; [2]Keymed Biosciences Inc, Chengdu, China.*

Background: IgA nephropathy (IgAN), the most prevalent primary glomerulonephritis, is a major contributor to renal failure, including in young individuals. Accumulating evidence suggests that the overactivation of the lectin pathway critically contributes to the pathogenesis of IgAN. RNK288, a MASP2-targeting siRNA, is developed as a therapeutic agent for IgAN by blocking the activation of the lectin pathway. Here, we demonstrate the efficacy and safety profile of RNK288 in preclinical studies.

Methods: RNK288 was developed by RAZOR™ platform to achieve an optimized PD and safety profile. The knockdown potencies of RNK288 were evaluated using both in vitro and in vivo models, including primary human hepatocytes (PHH), primary cynomolgus monkey hepatocytes (PCH), humanized MASP2 (hMASP2) transgenic mice and non-human primates (NHP). The safety of RNK288 was investigated by in vitro assay, RNA-seq and repeated-dose toxicity studies in rat and NHP. The efficacy of RNK288 was evaluated in rodent disease models, including grouped ddY mice.

Results: RNK288 suppressed MASP2 expression in PCH and PHH with the half-maximal inhibitory concentrations (IC_{50}) of 0.02nM and 0.03nM, respectively. In hMASP2 mice, RNK288 reduced serum MASP2 protein by up to 94% after a single subcutaneous injection of 3 mg/kg. In NHP, a single dose of RNK288 significantly lowered MASP2 protein levels to 3.8% even after 3 months, indicating a robust and long-lasting efficacy. In addition, the activity of lectin pathway, was shown to be reduced to a minimum of 13% of the pre-dose level. In repeated-dose toxicity studies (Q2W, 3 doses), no adverse findings were observed in either rats or monkeys and the No Observed Adverse Effect Levels (NOAEL) were 300 mg/kg (the highest dose) for both species. RNA-seq and in silico analysis also indicated low off-target risk, confirming the good safety profile of RNK288. Moreover, RNK288 demonstrated signs of IgAN improvement in rodent disease models.

Conclusions: RNK288 is a novel siRNA drug candidate for the treatment of IgAN by blocking the activation of lectin pathway. A series of preclinical studies demonstrated the robust and long-lasting efficacy of RNK288 with good safety and tolerability. RNK288 represents a potential therapeutic option for patients with IgAN.

Funding: Commercial Support - RONA Therapeutics

SA-PO730

First-in-Class Antigen-Specific Extracellular Protein Degrader, BHV-1400 for IgA Nephropathy, Selectively Targets Galactose-Deficient IgA for Rapid and Efficient Endolysosomal Degradation in the Liver

Seong Lee,[1] Charlotte B. Spliid,[1] Ana Estrella,[1] Kathleen Mcgrath,[1] Hanna Yousuf,[1] Ann Marie Rossi,[1] Brett Rasile,[1] Scott Conroy,[1] David Spiegel,[2] Gene Dubowchik,[1] David Pirman,[1] Bruce D. Car,[1] Lawrence R. Marcin,[1] Anna Bunin,[1] Vlad Coric.[1] *[1]Biohaven Ltd, New Haven, CT; [2]Yale University School of Medicine, New Haven, CT.*

Background: IgA nephropathy (IgAN) is the most prevalent form of glomerulonephritis, affecting 2.5 of 100,000 people worldwide. The production of galactose-deficient IgA1 (Gd-IgA1), and the subsequent formation and deposition of Gd-IgA1-IgG immune complexes in the kidney mesangium drive the onset and progression of IgAN. Targeting pathogenic Gd-IgA1 in IgAN patients offers a promising strategy to decrease immune complex formation, potentially leading to a reduction in kidney inflammation and pathology.

Methods: Biohaven engineered a novel, bifunctional antibody-based, protein degrader, BHV-1400, that specifically targets extracellular Gd-IgA1 for degradation via the ASGPR-mediated endolysosomal pathway in the liver. Here, we present data illustrating the reactivity of BHV-1400 with IgAN patient samples.

Results: In *in vitro* assays, BHV-1400 mediates efficient specific cellular internalization and degradation of monomeric and multimeric deglycosylated IgA (dg-IgA). Pharmacological data indicates that BHV-1400 facilitates a rapid reduction of exogenous dg-IgA both in the bloodstream and tissues, most notably within kidney glomeruli.

Conclusions: Thus, Gd-IgA1 degradation with BHV-1400 offers significant promise as a novel and effective precision, disease-modifying approach for treating IgAN.

Funding: Commercial Support - Biohaven Pharmaceuticals

SA-PO731

mTOR Inhibition: A Novel Regulator of Soluble CD89 Activity via the Mesangial Transferrin Receptor and Its Therapeutic Potential in IgA Nephropathy

Cambier Alexandra,[1] Jennifer Da Silva,[2] Julie Bex,[2] Aurelie Sannier,[2] Amandine Badie,[1] Renato C. Monteiro.[2] *[1]Research Centre Sainte Justine Hospital, Montreal, QC, Canada; [2]Inserm U1149, Paris ile de France, Paris, France.*

Background: IgA nephropathy (IgAN) is the predominant primary glomerulonephritis worlwide. We have recently shown that soluble IgA receptor CD89 induces mesangial cell proliferation via the PI3K/Akt/mTOR axis (Cambier, Kidney Int 2022). Transferrin receptor (TfR), an IgA1 receptor overexpressed in mesangium, is associated with IgAN progression (Tamouza, Kidney Int 2012). sCD89 binds also to TfR (Berthelot, J Exp Med 2012). As mTOR is involved in sCD89-TfR signaling, we explore its inhibitor, the everolimus, in a IgAN model, the $\alpha1^{KI}CD89^{Tg}$ mouse, that express human IgA1 and CD89. Single-cell kidney biopsy techniques were used to delve TfR1 and mTOR expression in mesangial cells from IgAN patients.

Methods: 20 adult $\alpha1^{KI}CD89^{Tg}$ and 6 young rCD89-injected $\alpha1^{KI}$ mice constituted two groups. Treated arms received everolimus (2 mg/kg) for 8 weeks or 4 weeks, respectively, while the control arms underwent a placebo water. Weekly urine collections monitored proteinuria and mice were sacrificed for renal function, immune complex analysis, and histological examination. PI3K/Akt/mTOR activation under sCD89 stimulation was studied with human mesangial cells. Single cell analysis were performed to quantify mTOR and TfR1 expression in 5 patient kidney biopsy and 1 healthy kidney tissue.

Results: Everolimus treatment showed a reduction in mesangial TfR expression, IgA1 and C3 deposits in kidneys of both groups ($p<0.001$, respectively). It also decreased cell proliferation, as indicated by Ki67 staining in glomeruli ($p<0.05$). This treatment led to decreased proteinuria ($p<0.05$). Levels of immune complexes (sCD89-IgA1, IgG-IgA1) were impaired by everolimus treatment. Rec sCD89 induced activation of PI3K/Akt/mTOR pathway in human mesangial cells. Using single cells from kidney biopsies we found overexpression of TfR1 and mTOR in mesangial cells from IgAN patient biopsies but not in healthy kidney.

Conclusions: mTOR inhibitor prevents and treats IgAN in a pre-clinical model. These results open new avenues for future clinical trials in IgAN.

Funding: Government Support - Non-U.S.

SA-PO732

Quantitative Image Analysis Uncovers the Efficacy of the Selective Endothelin A Receptor Antagonist Atrasentan in a Rat Model of IgA Nephropathy

Francois Briand,[1] Estelle Grasset,[1] Nicole Endlich,[2] Vedran Drenic,[2] Blazej Dolicki,[3] Thomas D. Bel,[3] Thierry Sulpice.[1] *[1]Physiogenex, Escalquens, France; [2]Nipoka, Greifswald, Germany; [3]Aiosyn, Nijmegen, Netherlands.*

Background: Our aim was to validate and optimize a rat model of IgA nephropathy for drug efficacy studies using quantitative image analysis of kidney. To demonstrate the accuracy of our imaging methods, we evaluated atrasentan, a selective Endothelin A receptor Antagonist currently evaluated in phase III clinical trials.

Methods: On day 0, Wistar male rats received a single i.v. injection of Thy1.1 antibody to induce IgA glomerulonephritis and were then treated orally BID with vehicle or atrasentan 10mg/kg until day 7. A group of rats were injected i.v. with PBS as control. Urine parameters were measured at day 2 and day 7, while Glomerular Filtration Rate (GFR) was measured at day 7. Kidneys were then collected for histology and automated image analysis, including quantitative mesangial expansion and tubular impairments (Kidney AI suite) and Podocyte Exact Morphology Measurement Procedure (PEMP).

Results: Compared to control, rats injected with Thy1.1 antibody showed significantly higher proteinuria, urine albumin/creatinine ratio (ACR), cystatin-C and KIM-1 levels at both day 2 and day 7, and significantly reduced GFR at day 7. Although it did not improve GFR decline significantly, atrasentan markedly improved all urine parameters above, as compared with vehicle. Compared to control, Thy1.1 antibody injection also led to a significantly higher kidney histopathological scoring (including greater proliferative glomerulonephritis, inflammation scores and tubule alterations), mean glomerular size and % alpha-SMA labelling, and all these parameters were again improved with atrasentan treatment. Filtration slit density and filtration slit length by PEMP were significantly reduced with Thy1.1 injection, indicating podocytes effacement, and both parameters increased in rats treated with atrasentan. Kidney AI suite demonstrated significant increase in glomeruli with mesangial expansion in rats injected with Thy1.1, which was also significantly reduced by atrasentan.

Conclusions: Quantitative image analysis uncovers the efficacy of atrasentan on glomerulonephritis in the Thy1.1 antibody rat model. This experimental setting will help evaluating the efficacy of drugs targeting IgA nephropathy.

SA-PO733

Development of GE8820 for Selective and Rapid Removal of Pathogenic Autoantibodies in Primary Membranous Nephritis (PMN) and Other IgG4-Mediated Diseases

Tanmoy C. Ganguly, Jonathan Back, Melinda Hanes, Michela Manni, Stephen Hesler, Hanumantha Rao Madala, Oaklyne Billion, Courtney Oconnell, Kellie Cotter, Tina Schelbert, Manuela Mally, Dominique N. Sirena, Jan L. Hillson, Ganesh V. Kaundinya. *Glycoera Inc, Newton, MA.*

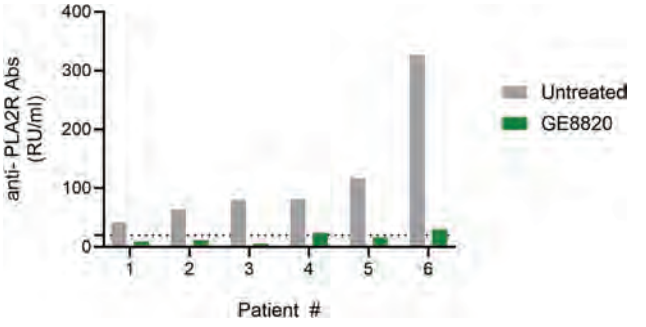
Background: In PMN, anti-PLA2R autoantibodies are used as a diagnostic, levels are associated with disease activity, and most are of the IgG4 isotype. Disease can be transferred to models, and a mechanism of injury was demonstrated with the IgG4 fraction. GE8820 is a bifunctional biologic that selectively binds to human IgG4 and through a glycan mediated engagement of ASGPR on hepatocytes, targets it for liver degradation.

Methods: GE8820 a selective high affinity human IgG4 binder was expressed using the proprietary BiND™ platform. Immuno-depletion experiments were performed in normal and PMN patient sera. In vivo experiments in rodents were performed by exogenously administering human IgG4 followed by GE8820 via iv route.

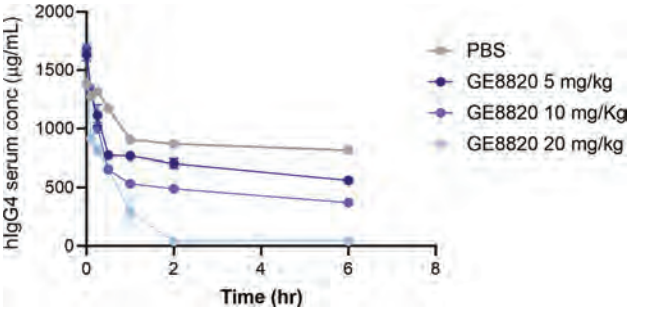
Results: Human IgG4 was selectively and completely depleted in both normal human sera and PMN sera. Depletion of IgG4 in pMN patient sera resulted in removal of PLA2R autoantibodies to levels below the threshold for serological positivity scores for pMN diagnosis. GE 8820 resulted in rapid (≤ 2hrs) and near complete (≥95%) depletion of IgG4 in a dose dependent manner.

Conclusions: Through selective depletion of the IgG4 subclass, GE8820 removed PLA2R autoantibodies from patient sera. GE8820 is being developed for the treatment of autoimmune diseases driven by pathologic IgG4 autoantibodies such as primary membranous nephropathy, muscle specific kinase driven myasthenia gravis and pemphigus vulgaris.

Funding: Commercial Support - Glycoera Inc



Immunodepletion of PLA2R autoantibodies in PMN patient sera



Rapid, deep and dose dependent depletion of human IgG4

SA-PO734

General, Nervous System, Eye, and Skin Involvement in the Phase 3 Trial of Avacopan for the Treatment of ANCA-Associated Vasculitis

Duvuru Geetha,[1] Rula Hajj-Ali,[2] Raashid A. Luqmani,[3] Christian Pagnoux,[4] Darcy Trimpe,[5] David R. Jayne,[6] Peter A. Merkel.[7] ADVOCATE Study Group. *[1]Johns Hopkins University, Baltimore, MD; [2]Cleveland Clinic, Cleveland, OH; [3]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [4]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; [5]Amgen Inc, Thousand Oaks, CA; [6]University of Cambridge, Cambridge, United Kingdom; [7]University of Pennsylvania, Philadelphia, PA.*

Background: The most common types of ANCA-associated vasculitis, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), can affect many organs. The phase 3 ADVOCATE trial compared avacopan vs a prednisone taper to treat patients with GPA or MPA. Patients receiving avacopan had improvements in sustained remission and kidney outcomes, with less glucocorticoid (GC) exposure and GC-related toxicity than those receiving a prednisone taper.

Methods: This post hoc analysis of the ADVOCATE trial reports rates of active general, nervous system, mucous membranes/eyes, and skin involvement based on the Birmingham Vasculitis Activity Score (BVAS) at weeks 4, 26, and 52, and changes from baseline to week 52.

Results: In the 330-patient ADVOCATE trial, active involvement of the general, nervous system, mucous membranes/eyes, and skin domains affected 68.2% (n=225), 20.9% (n=69), 20.0% (n=66), and 14.2% (n=47) of patients, respectively; most patients had at least one of these manifestations (**Table**). Similar and substantial improvements in the control of active disease in these domains were achieved in both groups: reductions from baseline to week 52 in the proportion of patients with active manifestations in the avacopan vs prednisone taper group, respectively, were 97.3% vs 96.5% (general), 100% vs 93.5% (nervous system), 100% vs 95.0% (mucous membranes/eyes), and 83.3% vs 100% (skin).

Conclusions: In the ADVOCATE trial, treatment with either avacopan or a prednisone taper was associated with the reversal of nearly all active general, nervous system, mucous membranes/eyes, and skin manifestations of GPA or MPA.

Funding: Commercial Support - Amgen

Table: Proportions of Patients With Active General, Nervous System, Mucous Membranes/Eyes, or Skin Involvement in Prednisone Taper and Avacopan Groups Over Time

	Prednisone taper (N=164)					Avacopan (N=166)				
	Baseline, n (%)	Week 4, n (%)	Week 26, n (%)	Week 52, n (%)	Week 52 % Change from Baseline†	Baseline, n (%)	Week 4, n (%)	Week 26, n (%)	Week 52, n (%)	Week 52 % Change from Baseline†
General	114 (69.5)	10 (6.1)	10 (6.1)	4 (2.4)	-96.5	111 (66.9)	15 (9.0)	6 (3.6)	3 (1.8)	-97.3
Myalgia	46 (28.0)	6 (3.7)	4 (2.4)	4 (2.4)	-91.3	47 (28.3)	7 (4.2)	3 (1.8)	2 (1.2)	-95.7
Arthralgia/arthritis	69 (42.1)	8 (4.9)	8 (4.9)	4 (2.4)	-94.2	63 (38.0)	9 (5.4)	3 (1.8)	2 (1.2)	-96.8
Fever (≥38°C)	23 (14.0)	1 (0.6)	1 (0.6)	0 (0.0)	-100	24 (14.5)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Weight loss (≥2 kg)	56 (34.1)	0 (0.0)	1 (0.6)	0 (0.0)	-100	53 (31.9)	4 (2.4)	0 (0.0)	0 (0.0)	-100
Other	4 (2.4)	1 (0.6)	1 (0.6)	0 (0.0)	-100	5 (3.0)	1 (0.6)	0 (0.0)	0 (0.0)	-100
Nervous system	31 (18.9)	6 (3.7)	3 (1.8)	2 (1.2)	-93.5	38 (22.9)	9 (5.4)	0 (0.0)	0 (0.0)	-100
Headache	13 (7.9)	2 (1.2)	2 (1.2)	1 (0.6)	-92.3	9 (5.4)	4 (2.4)	0 (0.0)	0 (0.0)	-100
Meningitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Cerebrovascular accident	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	-100	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Organic confusion	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	-100	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Spinal cord lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Cranial nerve palsy	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	-100	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	-100
Sensory peripheral neuropathy	15 (9.1)	2 (1.2)	1 (0.6)	0 (0.0)	-100	19 (11.4)	1 (0.6)	0 (0.0)	0 (0.0)	-100
Mononeuritis multiplex	10 (6.1)	2 (1.2)	0 (0.0)	1 (0.6)	-90.0	11 (6.6)	2 (1.2)	0 (0.0)	0 (0.0)	-100
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Mucous membranes/eyes	40 (24.4)	7 (4.3)	1 (0.6)	2 (1.2)	-95.0	26 (15.7)	7 (4.2)	1 (0.6)	0 (0.0)	-100
Mouth ulcers	9 (5.5)	1 (0.6)	0 (0.0)	0 (0.0)	-100	5 (3.0)	3 (1.8)	0 (0.0)	0 (0.0)	-100
Significant proptosis	3 (1.8)	1 (0.6)	1 (0.6)	1 (0.6)	-66.7	3 (1.8)	1 (0.6)	0 (0.0)	0 (0.0)	-100
Scleritis/episcleritis	15 (9.1)	2 (1.2)	0 (0.0)	1 (0.6)	-93.3	10 (6.0)	3 (1.8)	0 (0.0)	0 (0.0)	-100
Conjunctivitis/blepharitis/keratitis	7 (4.3)	1 (0.6)	0 (0.0)	0 (0.0)	-100	13 (7.8)	1 (0.6)	0 (0.0)	0 (0.0)	-100
Blurred vision	5 (3.0)	2 (1.2)	0 (0.0)	0 (0.0)	-100	3 (1.8)	0 (0.0)	1 (0.6)	0 (0.0)	-100
Sudden visual loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Uveitis	7 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	-100	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Other	5 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	-100	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Skin	23 (14.0)	1 (0.6)	2 (1.2)	0 (0.0)	-100	24 (14.5)	7 (4.2)	3 (1.8)	4 (2.4)	-83.3
Infarct	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	-100	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	-100
Purpura	15 (9.1)	1 (0.6)	1 (0.6)	0 (0.0)	-100	14 (8.4)	5 (3.0)	3 (1.8)	3 (1.8)	-78.6
Ulcer	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	-100	2 (1.2)	1 (0.6)	0 (0.0)	1 (0.6)	-50.0
Other skin vasculitis	6 (3.7)	0 (0.0)	1 (0.6)	0 (0.0)	-100	9 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	-100
Other	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	-100	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA

Organ involvement was defined as at least one activity item in the relevant domain of the Birmingham Vasculitis Activity Score Version 3. Seizures (not hypertensive) in the nervous system domain; genital ulcers, adnexal inflammation, and retinal changes in the mucous membranes/eyes domain; and gangrene in the skin domain were not listed, as there was no involvement in either treatment group at any time point.
†"Week 52 % Change from Baseline" indicates the difference in the proportion of patients with activity at week 52 from the proportion with activity at baseline: $((n_{w52}-n_{bl})/n_{bl})*100$.

SA-PO735

Antineutrophil Cytoplasmic Autoantibody Levels in Patients in the Avacopan Phase 3 Trial

Frank B. Cortazar,[1] Duvuru Geetha,[2] Salem Almaani,[3] Christina Song,[4] Tomasz M. Wilmanski,[4] Alana M. Bozeman,[4] Peter A. Merkel,[5] David R. Jayne.[6] ADVOCATE Study Group. *[1]New York Nephrology Vasculitis and Glomerular Center, Saint Peter's Hospital, Albany, NY; [2]Johns Hopkins University, Baltimore, MD; [3]The Ohio State University Wexner Medical Center, Columbus, OH; [4]Amgen Inc, Thousand Oaks, CA; [5]University of Pennsylvania, Philadelphia, PA; [6]University of Cambridge, Cambridge, United Kingdom.*

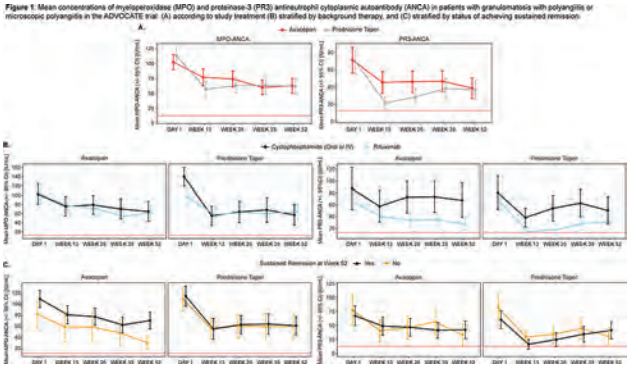
Background: The utility of measuring serial antineutrophil cytoplasmic autoantibody (ANCA) levels to guide treatment in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) is controversial. This analysis reports on circulating myeloperoxidase (MPO) and proteinase-3 (PR3) ANCA levels in patients in the avacopan and prednisone taper arms of the phase 3 ADVOCATE trial.

Methods: Serum MPO- and PR3-ANCA levels were measured by a central laboratory using an enzyme-linked immunosorbent assay for the following timepoints: day 1 (pre-treatment), week 13, 26, 39, and 52. Linear mixed effect models were used to evaluate the association of a) avacopan and a prednisone taper; b) background therapy (rituximab [RTX] or cyclophosphamide [CYC]); and c) treatment response (sustained remission at week 52) on MPO- or PR3-ANCA levels.

Results: In patients with MPO-ANCA (n=142) or PR3-ANCA (n=188), baseline mean MPO-ANCA levels were higher than PR3-ANCA levels, but both decreased from baseline over time. At week 13, mean ANCA levels decreased more in patients in the prednisone taper arm vs the avacopan arm (both PR3/MPO p=0.002), but levels converged by week 26 for MPO-ANCA and week 39 for PR3-ANCA (**Figure 1A**). While the decrease in mean PR3-ANCA was greater in patients treated with RTX vs CYC regardless of study treatment (p<0.001), the mean MPO-ANCA trajectories were similar between background therapies (p=0.49) (**Figure 1B**). When stratified by treatment response, the reduction in mean ANCA levels was independent of sustained remission status (**Figure 1C**).

Conclusions: The addition of avacopan to RTX or CYC for treatment of GPA or MPA does not appear to impact ANCA levels. The lack of correlation between ANCA levels and outcome of treatment in the ADVOCATE trial suggests that ANCA levels are an unreliable marker of treatment response.

Funding: Commercial Support - Amgen



SA-PO736

Baseline Characteristics of the First Patients in AvacoStar, a Real-World Study of Avacopan in ANCA-Associated Vasculitis

Achim Obergfell,[1] David R. Jayne,[2] Raashid A. Luqmani,[3] Benjamin Terrier,[4] Shaun Flint,[1] Marie E. Boff,[1] Monica Balcells-Oliver,[1] Bernhard Hellmich.[5] *[1]CSL Vifor, Glattbrugg, Switzerland; [2]University of Cambridge, Cambridge, United Kingdom; [3]University of Oxford, Oxford, United Kingdom; [4]Hôpital Cochin (Hôpitaux Universitaires Paris Centre), Paris, France; [5]Medius Kliniken, University of Tübingen, Kirchheim unter Teck, Germany.*

Background: Avacopan, an oral, selective C5a receptor antagonist, was approved by the EMA in January 2022 for the treatment of adults with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), in combination with rituximab or cyclophosphamide. The safety of avacopan is now studied in a real-world cohort followed beyond 1 year.

Methods: AvacoStar (NCT05897684) is a non-interventional, multinational, prospective, post-authorization safety study (≤6 months of data may be collected retrospectively). It will enroll 500 patients in Germany and the UK, in two cohorts of 250: (1) avacopan treated, and (2) receiving a cyclophosphamide- or rituximab-based induction regimen without avacopan. Patients aged ≥18 years with severe, active GPA or MPA in the opinion of the investigator, at the time of commencing avacopan or non-avacopan standard of care induction therapy are eligible. The primary objective is the incidence of defined medical events of special interest (MESI) in the avacopan cohort. MESIs are liver injury, cardiac safety, serious infections, and malignancy. Patients will be followed for up to 7 years. We present the baseline characteristics of the first patients enrolled.

Results: Between Sep 2023 and Mar 2024, 122 patients were enrolled and 118 included in this analysis (n=60 avacopan cohort; n=58 non-avacopan cohort). To date, most patients enrolled are newly diagnosed with renal involvement (Table). Other baseline characteristics are also tabulated.

Conclusions: AvacoStar baseline characteristics are currently similar between groups and consistent with clinical practice, suggesting study outcomes may yield generalizable insights on safety and use patterns of avacopan.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma AG

Baseline Characteristic	Avacopan cohort N=60	Non-avacopan cohort N=58	Combined groups N=118
Age at consent (years)	63.3 (16.9)	65.4 (11.9)	64.4 (14.7)
Male, n (%)	30 (50.8)	36 (62.1)	66 (56.4)
Race[a], n (%)			
White	51 (92.7)	53 (94.6)	104 (93.7)
Asian	2 (3.6)	2 (3.6)	4 (3.6)
Other	2 (3.6)	1 (1.8)	3 (2.7)
Missing/unknown/not reported	5	2	7
Body mass index (kg/m^2)	27.1 (5.2)	26.2 (4.6)	26.7 (4.9)
Duration of AAV since diagnosis (years)	2.9 (6.4)	1.6 (4.1)	2.3 (5.4)
Median (range)	0 (0–32)	0 (0–18)	0 (0–32)
AAV phenotype[a], n (%)			
MPA	26 (43.3)	31 (53.4)	57 (48.3)
GPA	34 (56.7)	27 (46.6)	61 (51.7)
AAV status[a], n (%)			
Newly diagnosed	43 (71.7)	47 (81.0)	90 (76.3)
Relapsed	17 (28.3)	11 (19.0)	28 (23.7)
Currently or ever ANCA positive[a, b], n (%)	55 (98.2)	52 (92.1)	107 (94.7)
Currently or ever PR3 positive[c]	32 (58.2)	30 (62.5)	62 (60.2)
Currently or ever MPO positive[c]	28 (50.9)	30 (63.8)	58 (56.9)
Pattern of organ involvement[a, b, d], n (%)			
Renal	46 (76.7)	41 (70.7)	87 (73.7)
General	27 (45.0)	24 (41.4)	51 (43.2)
Chest	19 (31.7)	18 (31.0)	37 (31.4)
Ears, nose and throat	18 (30.0)	12 (20.7)	30 (25.4)
Pulmonary nodule/mass	13 (21.7)	9 (15.5)	22 (18.6)
Mucous membranes/eyes	9 (15.0)	8 (13.8)	17 (14.4)
Cutaneous	8 (13.3)	6 (10.3)	14 (11.9)
Nervous system	8 (13.3)	6 (10.3)	14 (11.9)
Pauci-immune GN on biopsy	5 (8.3)	6 (10.3)	11 (9.3)
eGFR[a] (mL/min/1.73 m^2)	32.6 (27.4)	33.9 (27.1)	33.3 (27.0)
Missing, n	27	26	53
Patients with treatment exposure/concomitant medication for AAV[a, b], n (%)	44 (73.3)	44 (75.9)	88 (74.6)
Rituximab	29 (65.9)	25 (56.8)	54 (61.4)
Cyclophosphamide	18 (40.9)	19 (43.2)	37 (42.0)
Glucocorticoids	36 (81.8)	30 (68.2)	66 (75.0)
Plasma exchange	5 (11.4)	0	5 (5.7)

Data are mean (standard deviation) unless otherwise indicated.
As noted in the table, some data are missing due to the observational nature of the study.
[a]Categories in sub-rows are not mutually exclusive; a patient can be counted in more than one category.
[b]Calculated among patients in the full analysis set, by treatment group and with non-missing information.
[c]Percentages calculated among patients who were currently or ever ANCA-positive, by treatment group and with non-missing information.
[d]List limited to organ involvement occurring in >5 patients in either treatment group.
[e]Includes only patients with renal involvement at baseline and with non-missing information.
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

SA-PO737

Characteristics and Treatment Patterns before Initiation of Avacopan in the United States

Sushmitha Inguva,[1] Pallavi Rane,[1] Darcy Trimpe,[1] Jasjit Multani,[2] Hsiu-Ching Chang,[2] Duvuru Geetha,[3] Peter A. Merkel,[4] Zachary S. Wallace.[5] *[1]Amgen Inc, Thousand Oaks, CA; [2]IQVIA, Wayne, PA; [3]Johns Hopkins University, Baltimore, MD; [4]University of Pennsylvania, Philadelphia, PA; [5]Massachusetts General Hospital, Boston, MA.*

Background: The FDA approved avacopan to treat adults with severe active granulomatosis with polyangiitis or microscopic polyangiitis in Oct 2021. Real-world data on patients receiving avacopan are sparse.

Methods: In a retrospective cohort study using the United States (US)-based IQVIA open-source pharmacy and medical claims data, patients with ≥1 avacopan claim from Oct 2021 to Sep 2023 were identified, with the first avacopan claim date being the index date. Patients ≥18 years old with ≥12 months of pre-index continuous data were included. Demographics on the index date and clinical characteristics in the 12-month pre-index period are shown.

Results: Overall, 701 patients were identified: mean [SD] age: 55.8 [15.9], 60.6% female, 61.1% commercially insured (**Table 1**). Index avacopan was mostly prescribed by rheumatologists (66.0%) or nephrologists (23.1%). Before starting avacopan, 92.3% received systemic glucocorticoids (GCs) with a median duration of GC use of 102 days (IQR: 45-210) and a cumulative oral prednisone-equivalent dose of 2660 mg (IQR: 900-4905). 56.6% received other immunosuppressive therapy before avacopan. In the pre-index period, 54.5% had kidney involvement, including chronic kidney disease/end-stage kidney disease (ESKD; 40.7%), glomerulonephritis (26.1%), proteinuria (22.3%), hematuria (21.5%), or dialysis (3.4%). Pulmonary (56.5%), constitutional (40.9%), and ear, nose, or throat (34.4%) involvement was also commonly observed.

Conclusions: Among initial users of avacopan in the US, most had kidney (including ESKD and dialysis) and pulmonary involvement, and used GCs in the year before starting avacopan. Future studies will assess outcomes following treatment with avacopan in a real-world setting.

Funding: Commercial Support - Amgen

Table 1. Demographics and clinical characteristics in the 12-month pre-index period among early avacopan users

Patients with ≥1 claim for avacopan (N)		N = 701	
Characteristic	**Statistic/Category**	**Value**	**Percent**
Demographics			
Age (years)	Mean	55.8	
	SD	15.9	
Sex (n, %)	Female	425	60.6%
	Male	276	39.4%
Geographic region (n, %)	South	247	35.2%
	West	157	22.4%
	Northeast	151	21.5%
	Midwest	146	20.8%
Payer type (n, %)	Commercial	428	61.1%
	Medicare Part D	190	27.1%
	Medicaid	79	11.3%
	Other/unknown	4	0.6%
GPA or MPA-related medication use			
Index avacopan prescriber specialty (n, %)	Rheumatology	463	66.0%
	Nephrology	162	23.1%
	Other[a]	74	10.6%
	Unknown	2	0.3%
Systemic glucocorticoids (n, %)[b]	Any systemic glucocorticoids	647	92.3%
Immunosuppressive therapy (non-glucocorticoid: n, %)[b]	Any immunosuppressive drug	397	56.6%
	Rituximab	227	32.4%
	Methotrexate	87	12.4%
	Azathioprine	79	11.3%
	Mycophenolate mofetil	61	8.7%
	Cyclophosphamide	45	6.4%
Any immunosuppressive and/or systemic glucocorticoids (n, %)		659	94.0%
Patients with ≥1 claim for oral glucocorticoids (n, %)		614	87.6%
Duration of oral glucocorticoid use (days)	Median	102.0	
	IQR	(45, 210)	
Cumulative oral prednisone-equivalent dose during the baseline period (mg)	Median	2660.0	
	IQR	(900, 4905)	
Total oral prednisone-equivalent dose per day (mg, 12-month pre-index)	Median	7	
	IQR	(3, 14)	
Total oral prednisone-equivalent dose per day (mg, 90-days pre-index)	Median	8	
	IQR	(0, 23)	
Renal involvement (n, %)[b,c]		382	54.5%
Chronic Kidney Disease/End-Stage Kidney Disease		285	40.7%
Glomerulonephritis		183	26.1%
Proteinuria		156	22.3%
Hematuria		151	21.5%
Dialysis		24	3.4%
Kidney transplant		0	0.0%
Extrarenal involvement (n, %)[b,c]		612	87.3%
Chest		396	56.5%
Constitutional[d]		287	40.9%
Ear, Nose, or Throat		241	34.4%
Cardiovascular		159	22.7%
Nervous system		149	21.3%
Mucous membranes/eyes		90	12.8%
Cutaneous		82	11.7%
Abdominal		16	2.3%

SD = Standard Deviation, GPA = Granulomatosis with Polyangiitis, MPA = Microscopic Polyangiitis, IQR = Interquartile Range, mg = milligram
[a] "Other" included miscellaneous specialty types. Examples include internal medicine, nurse practitioner, physician assistant, pulmonologist etc.
[b] Categories are not mutually exclusive.
[c] Renal and extrarenal involvement was identified using diagnosis and procedure codes.
[d] "Constitutional" includes myalgia, arthralgia, fever, and weight loss.

SA-PO738

Avacopan for ANCA-Associated Vasculitis in Ireland: A Report on All Patients Who Received Avacopan in the Irish Health Care System

Eithne M. Nic an Riogh,[1] Andy G. Cummiskey,[2] Sinead Stoneman,[3] Michael Clarkson,[3] Sarah M. Moran,[3] Ciara N. Magee,[4] Susan M. McAnallen,[5] Mark A. Little.[1] *[1]Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland; [2]Mater Misericordiae University Hospital, Dublin, Ireland; [3]Cork University Hospital, Cork, Ireland; [4]Beaumont Hospital, Dublin, Ireland; [5]St James's Hospital, Dublin, Ireland.*

Background: Avacopan is a selective C5a receptor antagonist that inhibits neutrophil chemoattraction and activation. It is indicated for the treatment of severe, active granulomatosis polyangiitis or microscopic polyangiitis in combination with rituximab or cyclophosphamide and is considered a steroid sparing alternative. The aim of this report is to describe the first clinical experience with avacopan in ANCA Associated Vasculitis (AAV) in Ireland.

Methods: To date ten patients have received avacopan for AAV between December 2017 and April 2024 through the Irish early access programme and ADVOCATE trial. For these patients, disease relevant information was extracted from the RITA Ireland Vasculitis (RIV) database and through collaboration with the treating nephrologists. Data collected included commencement date and indication for avacopan initiation, duration of treatment, ANCA subtype, organ involvement, number of flares, immunosuppression medication usage and adverse events experienced.

Results: The average age of patients receiving avacopan in Ireland is 51 years (range 18-69 years). 50% were male and 50% were female. Six patients were MPO positive and four were PR3 positive. The majority of patients had renal involvement (90%). Avacopan was predominately commenced in cases where steroid sparing regimens were sought, e.g. severe osteoporosis, history of steroid induced psychosis, patient preference not to take steroids. Avacopan treatment duration ranged from 1 to 20 months, with an average duration of 4 months. 50% of patients remain on avacopan. On average patients received a total of 2.37 gm of Methylprednisolone prior to avacopan commencement (dose range 0mg to 6.5gm). While most patients tolerated avacopan and had no adverse events, reported side effects in this Irish cohort included headache, limited maculopapular rash as well as neutropenia and persistent liver dysfunction.

Conclusions: This is the first report of real-world experience of all patients who have received avacopan in Ireland. Two minor relapses and no major relpases have been reported in this cohort. Although the number of patients receiving avacopan in Ireland is small, avacopan appears to have a good safety profile in this population.

SA-PO739

Elicitation of Physician Opinions of the Impact of Dynamic Changes in Biomarkers on Perceived Relapse Propensity in ANCA-Associated Vasculitis: Impact of Individual Expert and Patient Characteristics

Eithne M. Nic an Riogh,[1] Maren Hackenberg,[2] Moritz Hess,[2] Cathal D. Walsh,[3] Arthur White,[3] Mark A. Little.[1] *[1]Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland; [2]Institute of Medical Biometry and Statistics, University of Freiburg, Freiburg, Germany; [3]School of Computer Science and Statistics, Trinity College Dublin, Dublin, Ireland.*

Background: ANCA-associated vasculitis(AAV) has a relapsing and remitting course. Accurate predictive algorithms do not exist. Prior knowledge can help to specify Bayesian prior distributions or generate synthetic observations to augment available data. To elicit prior knowledge on changes in time-varying variables and clinical endpoints, we assessed the beliefs of experts on how biomarker changes affect relapse probability and treatment intention.

Methods: We devised 10 synthetic clinical cases. Experts (immunology n=1, nephrology n=5, rheumatology n=4) with an average of 20.4 years' experience were recruited from Ireland, UK, Spain, Netherlands, Germany and Australia. 10 time-varying biomarkers were selected: creatinine, anti-MPO, anti-PR3, sCD163, lymphocyte count, urine protein, urine blood, IgG level and CD19 count. We assessed the perception of relapse risk and intention to change immunosuppression(IS) over 9-24 months. The questionnaire was refined using a Delphi approach. We assessed biomarker rise and fall, positive to negative, or negative to positive switch. The 290-question survey was conducted using a dimensionless scale with a slider to capture responses with extremes of responses labelled on opposite ends.

Results: Reduction in anti-PR3 and anti-MPO were associated with intention to reduce IS (median 46.5 and 38.5) and reduced relapse risk perception (41.0 and 42.0). A rise in anti-PR3 and anti-MPO were strongly associated with a decision not to reduce IS (81.0 and 82.5) and increased relapse risk perception (72.0 and 68.0). Clinicians intended to reduce IS if lymphocyte count (33.5) or IgG (30.0) levels fell, but this did not influence perception of relapse risk (50.0 - lymphocyte count, 50.0 - IgG). There were higher discrepancies in the responses on stable patient characteristics.

Conclusions: Clinical experts were more confident in reducing IS than relapse probability. This reflects the challenge of accurately identifying long term remission in AAV. Greater variability in responses regarding IS reduction reflects variation in clinical practice. Greater concordance was seen in responses on relapse prediction. This study guides future development of predctive algorithms using Bayesian methodologies.

SA-PO740

Avacopan for Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) in a Real-World Setting

Zachary S. Wallace,[1] Sam S. Oh,[2] Darcy Trimpe,[2] Sushmitha Inguva,[2] Naomi J. Patel.[1] *[1]Massachusetts General Hospital Department of Medicine, Boston, MA; [2]Amgen, Thousand Oaks, CA.*

Background: Avacopan is approved for use in adults with severe active GPA/MPA in the US. Data on avacopan in the real-world setting are limited.

Methods: This is an ongoing retrospective cohort study including patients from 12/1/21 to 4/1/24 prescribed avacopan for GPA/MPA at Mass General Brigham. Data are extracted by manual review and as structured data. Data from -12 to +6 months are reported. Complete remission (CR) is defined as Birmingham Vasculitis Activity Score (BVAS v3)=0 at month 6 and no glucocorticoids (GC) after month 5.

Results: At the prescription date in the first 80 patients (Fig. 1), mean age was 59 years, and most were female (70%), newly diagnosed (65%), MPO-ANCA+ (60%), and had MPA (53%). Nephrologists were the most frequent prescribers (56%). Of these 80 patients, 67 initiated avacopan. At initiation, 46% had renal involvement by BVAS (median eGFR 24 ml/min/1.73m^2; urine protein-to-creatinine ratio (UPCR) 1.9g/g). Among the 67 initiators at month 6, median cumulative GC dose was 1,011mg, 82% had BVAS=0, and 66% achieved CR. All 5 patients with ≥1 dialysis session ±30 days of initiation stopped dialysis by month 6; 4 newly initiated dialysis ≥30 days post-avacopan start. Of the 11 with eGFR <20 ml/min/1.73m^2 at initiation, 5 had eGFR ≥ 30 ml/min/1.73m^2 by month 6. By month 6, UPCR was 0.5g/g. Of the 35 GC users who discontinued GC by month 6, the median time from avacopan initiation to GC discontinuation was 50 days. At month 6, 43 remained on avacopan; 8 completed a planned 6-month course and 9 discontinued for AEs.

Conclusions: In this real-world GPA/MPA cohort, avacopan was commonly used in patients with severe renal involvement. Most users discontinued GC by month 5, achieved CR, and had favorable renal outcomes.

Funding: Commercial Support - Amgen

Figure 1: Characteristics and 6 Month Outcomes of Patients Prescribed Avacopan at Mass General Brigham

N Prescribed Avacopan	80
Characteristics at Prescription	
Age (in years) – mean (SD)	58.7 (15.9)
Female – n (%)	56 (70.0)
Race – n (%)	
White	62 (77.5)
Black	4 (5.0)
Asian	5 (6.3)
Other	9 (11.3)
Hispanic Ethnicity – n (%)	7 (8.8)
ANCA Type – n (%)	
MPO-ANCA+	48 (60.0)
PR3-ANCA+	26 (32.5)
ANCA-negative	6 (7.5)
AAV Phenotype – n (%)	
Granulomatosis with Polyangiitis	38 (47.5)
Microscopic Polyangiitis	42 (52.5)
AAV Status – n (%)	
Newly diagnosed	52 (65.0)
Relapsed	28 (35.0)
BVAS v3 – median (IQR)	10 (4, 14)
Setting of Avacopan Prescription – n (%)	
Inpatient	22 (27.5)
Outpatient	58 (72.5)
Prescribing Provider – n (%)	
Rheumatology	32 (40.0)
Nephrology	45 (56.3)
Pulmonary	3 (3.8)
Concomitant Treatment – n (%)	
Rituximab	41 (51.3)
Cyclophosphamide	4 (5.0)
Rituximab and Cyclophosphamide	28 (35.0)
Other	4 (5.0)
None	3 (3.8)
Cumulative GC Exposure in the 3 Months Prior to Prescription – prednisone-equivalent mg, median (IQR)	1,250 (540, 3,465)
Cumulative GC Exposure in the 12 Months Prior to Prescription – prednisone-equivalent mg, median (IQR)	2,073 (980, 4,325)
Characteristics Among Those Who Initiated Avacopan – n (%)	67 (83.8)
Median Time to Avacopan Initiation from Prescription – days, median (IQR)	13 (3, 28)
Initiated in ≤ 14 days of prescription – n (%)	37 (55.2)
Initiated in ≤ 21 days of prescription – n (%)	42 (62.7)
Prednisone-equivalent Dose at Time of Initiation – mg, median (IQR)	35 (20, 60)
BVAS v3 at Prescription – median (IQR)	10 (4, 14)
BVAS v3 at Initiation – median (IQR)	8 (1, 3)
Baseline eGFR – ml/min/1.73m^2, median (IQR)	63 (25, 92)
≥ 1 Dialysis session +/- 30 days of initiation – n (%)	5 (7.5)
Renal Involvement[a] at Prescription and/or Initiation – n (%)	31 (46.3)
Baseline eGFR among those with renal involvement (n = 31)	24 (16, 46)
eGFR < 20ml/min/1.73m^2 among those with renal involvement (n = 31) – n (%)	11 (35.5)
Urine Protein:Creatinine Ratio[†] among those with renal involvement (n = 31) – g/g median (IQR)	1.93 (0.68, 2.65)
6 Month Outcomes Among Those Who Initiated Avacopan	
Complete Remission: BVAS v3 of 0 at Month 6 and No GC Exposure After Month 5 – n (%)	44 (65.7)
BVAS v3 of 0 at month 6 – n (%)	55 (82.1)
≤5mg/day of Prednisone-e Equivalent Dose at Month 6 – n (%)	57 (85.1)
No GC at month 6 – n (%)	49 (73.1)
Cumulative GC Exposure Between Initiation and Month 6 – prednisone-equivalent mg, median (IQR)	1,011 (553, 1,624)
Time to GC Discontinuation Among those Off GC at Month 6 – days, median (IQR)	50 (33, 87)
Relapse[a] Between Initiation and Month 6 – n (%)	5 (7.5)
Major – n (%)	0 (0)
Minor – n (%)	5 (7.5)
Time to Relapse – days, median (IQR)	149 (102, 184)
eGFR Among Those with Renal Involvement – median ml/min/1.73m^2 (IQR)	40 (22, 65)
eGFR ≥ 30ml/min/1.73m^2 Among Those with eGFR < 20ml/min/1.73m^2 at prescription (n=11) – n (%)	5 (45.5%)
Dialysis-free Among Those on Dialysis at Prescription (n=5) – n (%)	5 (100)
Newly Initiated Dialysis >= 30 days after initiation – n (%)	4 (6.0)
Urine Protein:Creatinine Ratio[†] Among Those with Renal Involvement (n = 31) - g/g, median (IQR)	0.5 (0.27, 1.08)
% Change in Urine Protein:Creatinine Ratio[†]	-74.1%
Absolute Change in Proteinuria[†] – g/g, median (IQR)	-0.79 (-0.06, -1.63)
eGFR Slope[‡] – ml/min over 6 months	+9.9 (+5.4, +16.1)
Remained on avacopan at 6 months – n (%)	43 (64.2)

[†]Spot urine measurement; [a]Defined by presence of renal items on BVAS v3; [a]Relapse was defined as the return (after prior improvement) of vasculitis activity on the bases of ≥1 major BVAS/WG item, ≥3 minor BVAS v3 items, or one or two minor BVAS v3 items for at least two consecutive clinical visits. Relapse is assessed after 1 month and completion of rituximab induction doses.
[‡]Linear mixed models were used to estimate the GFR slope using all available eGFR between initiation and month 6 (median 13 (IQR 6, 20) measurements per person). The analysis was limited to individuals with renal involvement who initiated avacopan.
IQR: Interquartile range; eGFR: estimated glomerular filtration rate; BVAS v3: Birmingham Vasculitis Activity Score Version 3; GC: Glucocorticoid; AAV: ANCA-associated vasculitis; PR3: Proteinase 3; MPO: Myeloperoxidase; ANCA: Anti-neutrophil cytoplasmic antibody

SA-PO741

Use of Avacopan outside the ADVOCATE Inclusion Criteria

Ranjoy Sen, Louise R. Moore, Ajay P. Dhaygude, Lauren Floyd, Adam Morris. *Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom.*

Background: The ADVOCATE (Avacopan Development in Vasculitis to Obtain Corticosteroid elimination and Therapeutic Efficacy) trial was a large randomized controlled trial which has demonstrated the beneficial use of Avacopan in the management of Antineutrophil Cytoplasmic antibody (ANCA)-associated Vasculitis (AAV). However, patients with the most severe disease including those with estimated glomerular filtration rate (eGFR) <15, significant pulmonary haemorrhage and dual positive with anti-GBM antibody were excluded. We report 3- and 6-months outcomes of the use of Avacopan outside the ADVOCATE inclusion criteria in AAV patients with severe and life-threatening disease.

Methods: We reviewed patients with AAV and renal involvement treated with Avacopan outside the ADVOCATE inclusion criteria. The response to treatment was measured on change in eGFR at diagnosis, 3 and 6 months, as well as the resolution of lung haemorrhage.

Results: A total of 37 patients were treated with Avacopan with 15 patients falling outside the ADVOCATE inclusion criteria. The demographics and the serology of the patients is shown in table 1. Two were dialysis dependent at presentation and later regained renal function to become independent of renal replacement therapy (RRT) and two had dual positive antibodies with ANCA and anti-GBM. Two patients had diffuse pulmonary haemorrhage and one was ANCA negative. All patients showed an improvement in their renal functions at 3 and 6 months.

Conclusions: This small case series demonstrate successful use of Avacopan outside ADVOCATE inclusion criteria. Further real-life data is likely to support use of Avacopan for a wider and more severe presentations of AAV.

Age (years)	Sex	Indication outside the ADVOCATE criteria	eGFR at diagnosis (ml/min/1.73m²)	eGFR at 3months (ml/min/1.73m²)	eGFR at 6months (ml/min/1.73 m²)	Overall change in eGFR (ΔeGFR)
74	Female	ANCA & anti-GBM Ab+ve eGFR<15	05	08	10	05
52	Male	eGFR<15	10	52	61	51
61	Male	eGFR<15	14	23	21	07
86	Female	eGFR<15	12	15		03
77	Male	eGFR<15	08	16	16	08
68	Female	eGFR<15	08		51	43
73	Male	eGFR<15	07	23	35	28
74	Female	eGFR<15	09	12		03
70	Male	eGFR<15	07	10		03
68	Male	eGFR<15	06	21		15
64	Male	ANCA & anti-GBM Ab+ve eGFR<15	06	17	18	12
61	Female	eGFR<15 Pulmonary haemorrhage	09	62		53
65	Male	Pulmonary haemorrhage	18	34		16
72	Male	eGFR<15	04	10		06
74	Female	ANCA negative Vasculitis	44	47	50	06

Table 1: Change in eGFR at 3 and 6 months of treatment with Avacopan.

SA-PO742

Incidence and Severity of Pediatric-Onset ANCA-Associated Vasculitis (AAV) Glomerulonephritis (GN) during the COVID-19 Pandemic: A Large Tertiary Center Experience

Alvaro H. Orjuela, Sharanya Joginpalli, Emily Frierson, Sameer Thadani. *Baylor College of Medicine, Houston, TX.*

Background: During the SARS-CoV-2 virus global pandemic, there were concerns that changes in access to care would negatively impact both the timely diagnosis and severity of disease at presentation. This study sought to determine the incidence and severity of disease at presentation in patients with AAV seen in our center during the pandemic (03/2020-05/2023) compared to those seen prior to the pandemic (01/2017-2/2020).

Methods: We retrospectively reviewed patients with AAV from 2017 to 2023. Abstracted data included patient demographics, clinical characteristics, durations of symptoms prior to presentation, clinical features on presentation, renal biopsy findings, and renal outcomes. Data were evaluated using standard descriptive statistics

Results: In the study period, 29 patients were identified. ***Figure 1 shows the patient demographic data and clinical characteristics on presentation.*** **The pre-pandemic cohort (N=12)**, 58% had MPA (N=7) and 42% GPA (N=5). Mean onset of symptoms to diagnosis of 1.5 months. At presentation, 68% had reno-pulmonary involvement, 16% ENT/Orbital, 8% isolated pulmonary, and 8% isolated renal disease.**The pandemic cohort (N=15)**, 53% had MPA (N=8) and 47% GPA (N=7). Mean onset of symptoms to diagnosis was 1 month. Organ involvement in presentation: 53% renal-pulmonary, 20% isolated pulmonary involvement, 13% isolated renal disease, and 13% ENT/orbital (P=0.4).

Conclusions: While there was a demonstrable 25% increase in the incidence in patients with AAV during the pandemic with a concurrent increase the frequency of both RPGN and CKD/ESKD (P=0.4), the duration of symptoms prior to presentation was not impacted. These data suggest that there was only a limited impact on access to care during the Pandemic. Factors that impacted disease severity and renal involvement need further investigation

Figure 1	Pre-Pandemic Cohort (Pre-PC) N=12	Pandemic Cohort (PC) N=15
Mean age at presentation	11.8 years (range: 4 to 19 years)	11.7 years (range: 6 to 17 years)
<10 years	41% (N=5)	40% (N=6)
> 10 years	64% (N=7)	60% (N=9)
Sex (P>0.9)	83% female	87% female
Race (P=0.2)	34% Hispanic	60% Hispanic
	42% non-Hispanic white	13% non-Hispanic white
	16% Black	13% Black
	8% Asian	13% Asian
Renal Involvement at Diagnosis (P=0.13)		
Proteinuria, Hematuria, HTN	33% (N=4)	20% (N=3)
Acute Kidney Injury (AKI)	33% (N=4)	20% (N=3)
Rapidly Progressive Glomerulonephritis (RPGN)	8% (N=1)	46% (N=7)
No renal involvement	25% (N=3)	13% (N=2)
Biopsy Findings of Pauci-immune Crescentic GN		
< 50% glomeruli involvement	33% (N=4)	13% (N=2)
> 50% glomeruli involvement	25% (N=3)	46% (N=7)
Renal Outcomes (P=0.4)		
Normal renal function	75% (N=9)	33% (N=5)
CKD Stage 1-2	16% (N=2)	26% (N=4)
CKD Stage 3-4	0	20% (N=3)
ESRD	8% (N=1)	20% (N=3)

SA-PO743

French Vasculitis Study Group Score: A Predictor of Outcome or a Tool for Guiding Remission-Induction Therapy?

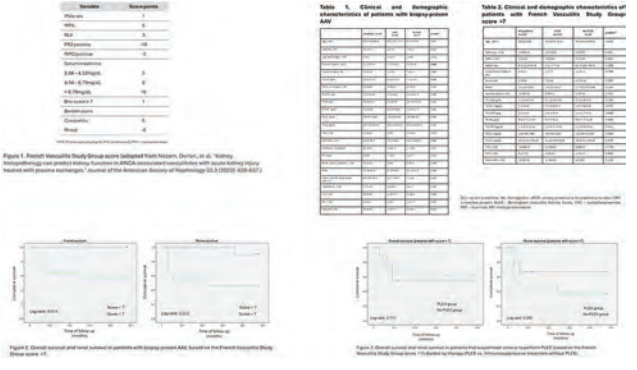
Afonso Santos, Andreia Curto, Fábio D. Henriques, Ana C. Brás, Pedro Campos, Joana E. Santos, Patricia S. Carrilho, Rita Theias Manso, Maria A. Serra, Fernando Domingos. *Hospital Professor Doutor Fernando Fonseca EPE, Amadora, Portugal.*

Background: Patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) develop end-stage kidney disease, despite progress in therapy. To choose patients for whom PLEX would be helpful, the French Vasculitis Study Group (FVSG) suggested a score combining clinical and histopathologic data (Fig. 1). The aim of our study was to evaluate this score's clinical usefulness in patients with AAV.

Methods: This is a retrospective, single-center cohort study. We enrolled adult patients with AAV (kidney biopsy, suggestive clinical features and/or ANCA positivity) between 2011 and 2023. The use of PLEX was uncontrolled. Patients were classified according to the FVSG score and divided in two groups (score >7 the threshold above which PLEX was recommended and <7). Baseline parameters, overall survival, and renal survival were compared. We further compared the subpopulation that received PLEX with those receiving only immunosuppressive drugs, using the same threshold.

Results: The baseline data of the 33 patients are described in table 1. PLEX was performed in 16 patients (48.4%). Serum albumin and creatinine levels were significantly different between the two groups (PLEX vs. no-PLEX, p=0.008). The overall survival and renal survival of patients with score >7 was lower than the patients with score <7 (p=0.015 and p=0.012, respectively, Fig 2.). We found no differences between groups (PLEX vs no-PLEX) for patients with a clinical score >7 (table 2 and Fig. 3).

Conclusions: The FVSG score was successfully used to predict overall and renal survival using the threshold proposed. However, in our retrospective cohort, the patients that would have a survival benefit with PLEX, had similar outcomes to those who did not receive it. In conclusion, in our cohort, this score was predictive of clinical outcome, however it was not helpful at differentiating patients who would benefit from receiving PLEX.



SA-PO744

Urinary Complements as a Predictor of Kidney Outcomes in Patients with ANCA-Associated Vasculitis

Kenta Fujimoto, Masao Kikuchi, Shoko Ochiai, Akiko Baba, Koichi Kaikita, Shouichi Fujimoto. *Miyazaki Daigaku, Miyazaki, Japan.*

Background: Anti-Neutrophil Cytoplasmic Antibody (ANCA) -associated vasculitis (AAV) is a systemic vasculitis characterized by inflammation of small blood vessels that can lead to rapidly progressive glomerulonephritis. Recent research has underscored the significance of C5a in the pathogenesis of this condition. Although there are reports of elevated urinary complement levels during the active phase of AAV, the exact relationship between elevated complement and renal outcome is unclear.

Methods: This study included 36 patients (median age 73 [69, 78] years, 38.9% male, serum Cr 2.26 [1.2, 5.5] mg/dL) with newly diagnosed MPO-ANCA positive AAV with renal involvement who were admitted to our hospital from March 2019 to November 2023. Urine samples were collected at the beginning of treatment and stored in a -30 °C freezer. Urinary complement levels (specifically C5a and C3a) were measured using each ELISA kits (Becton, Dickinson and Company, Franklin Lakes, NJ). Patients were classified into three groups (low, intermediate, and high) based on their respective C5a/Cr and C3a/Cr ratios and their progression to end-stage kidney disease (ESKD) was evaluated. In addition, the relationship between urinary complement levels and renal biopsy findings was also examined (n=32).

Results: Five patients developed ESKD during the 2-year follow-up period, and Kaplan-Meier analysis showed no significant difference among the three groups in C5a/Cr ratio (P=0.053), but there was a significant difference in C3a/Cr ratio among the groups (P=0.025). Histopathological examination showed an associations between C3a/Cr ratio and cellular crescent formation (|ρ|=0.3947, P=0.025) and tubulointerstitial lesions (|ρ|=0.4002, P=0.023), while C5a/Cr ratio was correlated with tubulointerstitial lesions (|ρ|=0.4563, P=0.010).

Conclusions: Urinary complement levels in newly diagnosed AAV patients may be a useful biomarker for assessing the risk of developing ESKD. It also correlates with renal involvement in patients with AAV and may be an alternative to kidney biopsy.

SA-PO745

Risk of ESKD in ANCA-Associated Glomerulonephritis at Presentation and during the Disease Course

Sjoerd Timmermans,[1,2] Daan P. van Doorn,[1,2] Floris T. Voorde,[1,2] Pieter van Paassen.[1,2] Limburg Renal Registry; Expert Center for Immune-mediated Kidney Diseases and Vasculitis. *[1]Maastricht Universitair Medisch Centrum+, Maastricht, Netherlands; [2]Universiteit Maastricht Cardiovascular Research Institute Maastricht, Maastricht, Netherlands.*

Background: Kidney involvement in ANCA vasculitis is common and impacts quality of life and survival. Tools to determine disease activity and predict risk for ESKD may optimize intensity and duration of immunosuppression. The ANCA kidney risk score (AKRiS) predicts ESKD. The AKRiS, however, is based on cross-sectional data. Here, we validated AKRiS in two well-defined cohorts of patients with *de novo* ANCA glomerulonephritis (AGN) and studied the effect of kidney recovery and relapsing AGN on kidney survival.

Methods: We analyzed patients with *de novo* AGN recruited from the Limburg Renal Registry (i.e., historical cohort; *n*=290) and prospective PROMAVAS cohort (*n*=36). Kidney recovery at 12 months and slope of eGFR from 12 months onward were studied, using a two-slope mixed-effects linear spline model.

Results: The historical cohort included 126 (63%), 43 (21.5%), 28 (14%), and 3 (1.5%) patients with low, moderate, high, and very high risk, with follow-up of 10 (IQR, 6-15) years. Creatinine was 2.4 (IQR, 1.4-4.5) mg/dL and 164 (82%) patients were treated using a cyclophosphamide-based regimen. Kidney survival varied from 97.5%, 87.9%, 74.5%, to 33.3% at 36 months, validating AKRiS with good discrimination (C statistic, 0.84). The PROMAVAS cohort (creatinine, 2.4; IQR, 1.8-3.5) mg/dL, including 21 (58.3%) patients treated using a rituximab-based regimen, corroborated these observations (C statistic, 0.92). The eGFR improved +10.4 (95%CI, 7.8 to 12.9) mL/min/1.73m^2 at 12 months, with no differences between patients with an eGFR <30 mL/min/1.73m^2 as compared to those with better kidney function at presentation. eGFR's mean annual slope was -1.0 mL/min/1.73m^2 (95%CI, -1.7 to -0.3) in remitted AGN, contrasting -3.3 mL/min/1.73m^2 (95%CI, -4.4 to -2.2; *P*=0.001) in relapsing AGN. ESKD was associated with eGFR <30 mL/min/1.73m^2 at 12 months.

Conclusions: AKRiS predicts the risk of ESKD in *de novo* AGN. Moreover, CKD stage at 12 months, and relapsing AGN affect eGFR's slope and progression to ESKD. Treatment should therefore focus on maximal kidney recovery using novel drugs, such as, C5aR inhibition, and prevention of relapsing AGN, particularly in patients with eGFR <30 mL/min/1.73m^2 at 12 months, to maintain kidney function. Future trials should focus on the effects of treatment on kidney recovery and eGFR's slope.

Funding: Commercial Support - Vifor Pharma Group

SA-PO746

Prediction of Recovery of Kidney Function in Severe ANCA-Associated Glomerulonephritis

Megan Leffek,[1] Kavita Gulati,[3] Jennifer Scott,[4] Gavin Chapman,[12] Benoit Brilland,[5] Cecilia Barnini,[6] Vojtech Kratky,[7] Jens Rathmann,[14] Minhyung Kim,[8] Li Jin Ooi,[2] Zdenka Hruskova,[7] Maria J. Stangou,[15] Ajay P. Dhaygude,[9] Abdulmecit Yildiz,[10] Jean Francois Augusto,[5] Jung eun Lee,[8] Andrea Hinojosa-Azaola,[11] Juan M. Mejia-Vilet,[11] Andreas Kronbichler,[6] Neeraj Dhaun,[12] Marten Segelmark,[14] Mark A. Little,[4] Duvuru Geetha,[13] Stephen P. McAdoo,[3] Silke R. Brix.[1,2] AKRiS Working Group. *[1]The University of Manchester, Manchester, United Kingdom; [2]Manchester University NHS Foundation Trust, Manchester, United Kingdom; [3]Imperial College London, London, United Kingdom; [4]The University of Dublin Trinity College, Dublin, Ireland; [5]Centre Hospitalier Universitaire d'Angers, Angers, France; [6]University Innsbruck, Innsbruck, Austria; [7]Prague City University a s, Praha, Czechia; [8]Samsung Medical Center, Gangnam-gu, Seoul, Republic of Korea; [9]Royal Preston Hospital, Preston, United Kingdom; [10]Bursa Uludag Universitesi, Nilufer, Turkey; [11]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [12]University of Ediburgh, Edinburgh, United Kingdom; [13]John Hopkins University, Baltimore, MD; [14]Lunds Universitet, Lund, Sweden; [15]Aristoteleio Panepistemio Thessalonikes, Thessalonike, Greece.*

Background: Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis often involves the kidneys and kidney failure confers significant morbidity and mortality. An improved prognostication of kidney function recovery will enable tailoring treatment to patients' needs.

Methods: Multicentre, retrospective analysis of newly diagnosed ANCA glomerulonephritis (GN) patients requiring kidney replacement therapy (KRT) at time of diagnosis of 16 registries and vasculitis referral centres. Unadjusted and adjusted multivariable Cox regression for primary outcome of kidney function recovery.

Results: 372 patients required KRT at time of diagnosis and 137 of these recovered kidney function during follow-up (36.8%). The median age was 67 years (interquartile range, IQR, 56 – 74 years) and 57.4% were male. 159 patients were anti-myeloperoxidase positive (42.7%), 174 patients were anti-proteinase 3 positive (46.8%), and 39 patients were ANCA negative (10.5%). Median creatinine and estimated glomerular filtration rate (eGFR) at time of diagnosis were 618mmol/l (IQR 470 – 844mmol/l) and 6.2mls/min (IQR 4.7 – 9mls/min). 243 patients developed ESKD (65.3%) during median follow-up of 3.6 years (IQR 0.6 – 6.2 years). 120 patients died during follow-up (32.3%). Patients recovering kidney function showed a median of 22.8% normal and 33.5% crescentic glomeruli, patients remaining KRT-dependent demonstrated a median of 5.7% normal and 27.3% crescentic glomeruli in their biopsies. The percentage of normal glomeruli, interstitial fibrosis and tubular atrophy (IFTA), creatinine and eGFR associated with kidney function recovery. In a multivariable adjusted analysis, the percentage of normal glomeruli and creatinine correlated with outcome (p<0.001, p<0.001, respectively) while antibody subtype and diagnosis did not.

Conclusions: Kidney function and the percentage of normal glomeruli were predictive of kidney function recovery in patients with newly diagnosed ANCA GN requiring KRT. The percentage of crescentic glomeruli did not differ between patients recovering from kidney failure and patients remaining on KRT.

Funding: Government Support - Non-U.S.

SA-PO747

Temporal Trends in the Utilization of Hydralazine and Diagnoses of ANCA-Associated Glomerulonephritis

Juarez R. Braga,[1] Swathi Muni Reddy,[1] Clarissa A. Cassol,[2] John M. Arthur.[1] *[1]University of Arkansas for Medical Sciences, Little Rock, AR; [2]Arkana Laboratories, Little Rock, AR.*

Background: Hydralazine is used in clinical praactice in the management of hypertension and heart failure. However, hydralazine is associated to the development of ANCA antibodies which can then in turn cause pauci-immune glomerulonephritis (GN). We designed this study to examine temporal trends in the use of hydralazine and in the number of individuals diagnosed with biopsy-proven hydralazine-associated ANCA-GN.

Methods: This study included 2 analyses: (i) a repeated cross-sectional study examining the use of hydralazine among Medicare beneficiaries using Part D Prescription data from 2013 to 2021; (ii) an observational study of ANCA-GN diagnosed with a kidney biopsy at a single renal pathology center, Arkana Laboratories, from 2016 to 2021. From the Medicare part D files, we extracted the number of beneficiaries, the total number of claims, and claims according to provider specialty for hydralazine. Prescription rate was expressed per 100,000 beneficiaries and per 1,000 providers. From the pathology laboratory, we identified cases diagnosed with pauci-immune GN using the ICD code N01.7. Electronic records were then reviewed for a history of positive ANCA antibodies and exposure to hydralazine.

Results: The number of Part D enrollees increased from 35.1 million in 2013 to 46 million in 2021. Meanwhile, the proportion of beneficiaries receiving hydralazine increased from 2% to 2.9%. In absolute numbers, that represented an increase from 718,433 to 1,324,532 beneficiaries in use of hydralazine ($P < .001$). There was an increase in the prescription rate of hydralazine among cardiologists from 1,271 claims per 100,00 beneficiaries in 2013 to 1,639 per 100,000 in 2021 ($P < .001$). The prescription rate, when examined per 1,000 providers, also increased from 41,287 claims in 2013 to 52,795 in 2021 among cardiologists ($P < .001$). This trend was not observed among nephrologists or internists. The number of individuals in use of hydralazine diagnosed with biopsy-proven ANCA-GN increased from 16 cases in 2016 to 36 in 2021 ($P < .001$).

Conclusions: The number of Medicare beneficiaries using hydralazine and the number of biopsy-proven hydralazine-associated ANCA-GN increased significantly over time. Those trends could have broad implications for Medicare spending with dialysis.

Funding: Commercial Support - Arkana Laboratories

SA-PO748

Clinical Profile, Histologic Profile, and Outcome of Patients with Rapidly Progressive Glomerulonephritis: Experience from Ethiopia

Hamelmal G. Hailegiorgis.[1,2] *[1]Saint Paul Millennium Medical College, Addis Ababa, Ethiopia; [2]University Teaching Hospital of Kigali, Kigali, Rwanda.*

Background: Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome defined by the rapid loss of renal function, accompanied by features of the nephritic syndrome with proteinuria, glomerular hematuria, and often oliguria. Although relatively uncommon, early recognition and prompt treatment are crucial to prevent irreversible loss of renal function. Data are scarce regarding RPGN in Africa. This study aims to determine the clinical profile and outcomes of RPGN among patients treated at a tertiary hospital in Addis Ababa, Ethiopia.

Methods: A retrospective study was conducted including all eligible RGPN patients who were managed at St. Paul Millennium Medical College from January 2020 to January 31, 2023. Data from 120 RPGN patients was collected. Patient characteristics are presented using frequencies, mean ± standard deviation (SD), or median with Inter Quartile range (IQR) values. To identify predictors of treatment outcome, a multinomial logistic regression analysis was used and an adjusted odds ratio (AOR), with 95% used for the interpretation of the results

Results: 120 patients diagnosed with rapidly progressive glomerulonephritis (RPGN) were included in the study. The mean age of patients was 40.25 ± 14.6 years. Oliguria and hypertension were the most common presenting symptoms (74.41 and 73.62% respectively).62.5% (n=75) underwent kidney biopsy. Of these 44% showed crescentic RPGN and DPGN in 19 (33.3%) patients. Of the 120 RPGN cases, 28% developed ESRD 13.6% died, and 30.4% achieved CR. Among crescentic RPGN patients, 27.3% developed ESRD,24.2% died, and only 18.2% achieved CR.

Conclusions: In our population, crescentic GN was found to be the most common histopathological diagnosis in patients with clinical RPGN. However, it is important to note that alternative diagnoses without histologic evidence of crescentic GN are also common. Renal histology plays a crucial role in both the diagnosis and prognosis of patients with clinically suspected Rapidly Progressive Glomerulonephritis (RPGN). Routine ancillary serologic tests for this patient group can significantly impact the diagnosis and prognosis of cases.

SA-PO749

Clinical Presentation and Outcomes of SARS-CoV-2 Infection in Patients with Pauci-Immune Glomerulonephritis

Angeliki Sardeli,[1] Evangelia Dounousi,[7] Dimitra Gkalitsiou,[3] Konstantia Kantartzi,[4] Vassilios Liakopoulos,[5] Smaragdi Marinaki,[2,6] Georgios Moustakas,[3] Minas Karagiannis,[1] Petros Nikolopoulos,[1] Stylianos A. Panagoutsos,[4] Sophia Lionaki.[1,2] *[1]Panepistemiako Geniko Nosokomeio Attikon, Athens, Greece; [2]Ethniko kai Kapodistriako Panepistemio Athenon, Athens, Greece; [3]Geniko Nosokomeio Athenon Giorgos Gennematas, Athens, Greece; [4]Demokriteio Panepistemio Thrakes, Komotini, Greece; [5]Aristoteleio Panepistemio Thessalonikes, Thessalonike, Greece; [6]Laiko General Hospital, Athens, Greece; [7]Panepistemio Ioanninon, Ioannina, Greece.*

Background: SARS-CoV-2 infection is characterized by multi-system involvement, affecting not only the respiratory system[1,2]. This study aimed to outline the clinical presentation and outcomes of SARS-CoV-2 infection in patients with pauci-immune GN (PIGN).

Methods: A retrospective analysis was conducted on 29 individuals with PIGN and positive SARS-CoV-2 PCR test, excluding those in end-stage kidney disease (ESKD) prior to infection. Data encompassed immunosuppressive regimens at PIGN diagnosis, treatment outcomes, SARS-CoV-2 infection's clinical course and outcome of PIGN post infection.

Results: The mean age of patients was 61.0(±16.4) years, with 16(55.1%) being female. Upon SARS-CoV-2 infection, 12(41.3%) were on immunosuppressive therapy, of whom 4 (13.7%) were on rituximab maintenance therapy. Almost all patients were symptomatic in terms of the infection and 7(24.1%) required hospitalization. 23(88.4%) experienced complete recovery from Covid-19, 3(3.1%) had prolonged symptoms and 3(11.5%) died due to Covid-19. Among patients in remission, 1(3.8%) experienced a relapse of PIGN following SARS-CoV-2 infection.

Conclusions: In this cohort of patients with PIGN, SARS-CoV-2 infection impacted morbidity and mortality of this vulnerable population.

Demographics, baseline patients' characteristics, symptoms and outcomes of SARS-CoV-2 infection and GN.

Parameter N(%) or mean (SD)	N=29
Age at diagnosis of GN (years)	61.0 (16.4)
Gender (males)	13/29
Time since diagnostic biopsy (months)	61.2(56.2)
Induction treatment Corticosteroids Cyclophosphamide Mycophenolate mofetil Rituximab	29(100) 20 (95.2) 1(3.4) 7 (26.9)
First outcome of GN Remission Relapse	27 (96.4) 1 (3.5)
Immunosuppressive treatment at SARS-CoV-2 infection Mycophenolate mofetil Glucocorticoids Rituximab AZA	N=12 2 3 4 3
Symptoms Arthralgias Myalgias Fever Fatigue Cough Shortness of breath	2(6.9) 1(3.4) 22 (75.8) 3 (10.3) 9 (31.0) 1 (3.4)
Hospitalization requirement	7 (24.1)
Mechanical ventilation requirement	1(14.3)
SARS-CoV-2 outcome Complete recovery Death Long COVID	26 23 (88.4) 3 (11.5) 0
Relapse of GN after SARS-CoV-2 infection	1 (3.8)

SA-PO750

SARS-CoV-2 Vaccination in Patients with Pauci-Immune Glomerulonephritis: A Multicenter Study

Angeliki Sardeli,[1] Evangelia Dounousi,[7] Dimitra Gkalitsiou,[3] Konstantia Kantartzi,[4] Kriki Pelagia,[4] Vassilios Liakopoulos,[5,6] Smaragdi Marinaki,[2,8] Giannakopoulos Panagiotis,[1] Georgios Moustakas,[3] Sophia Lionaki.[1,2] *[1]Panepistemiako Geniko Nosokomeio Attikon, Athens, Greece; [2]Ethniko kai Kapodistriako Panepistemio Athenon, Athens, Greece; [3]Geniko Nosokomeio Athenon Giorgos Gennematas, Athens, Greece; [4]Demokriteio Panepistemio Thrakes, Komotini, Greece; [5]Aristoteleio Panepistemio Thessalonikes, Thessalonike, Greece; [6]Ahepa Hospital, Thessalonikes, Greece; [7]Panepistemio Ioanninon, Ioannina, Greece; [8]Laiko General Hospital, Athens, Greece.*

Background: SARS-CoV-2 vaccination has been shown crucial in stemming the pandemic. This study aimed to describe adverse events associated with SARS-CoV-2 vaccination in patients with a history of pauci-immune glomerulonephritis (PIGN).

Methods: A retrospective analysis was conducted in individuals with PIGN who received the SARS-CoV-2 vaccine, excluding those in ESKD prior to vaccination. Recorded data included histopathological diagnosis, immunosuppressive regimens, clinical outcomes, vaccination type, and related adverse events.

Results: A cohort of 69 individuals diagnosed with PIGN, with an age of 59.6 (±17.5) years, was studied, of whom 36(53.7%) were females. Of these, 34(50.7%) had a medical history of hypertension, and 16(23.9%) type 2 diabetes. Induction therapy was administered in 66(98.5%) cases, with 87.7% of them achieving remission. 50(74.6%) patients received maintenance therapy and 50 (94.3%) were vaccinated against SARS-CoV-2, within 79.5(±70.8) months from the diagnostic biopsy with 3.2(±1.0) doses. At vaccination, 90% of patients were in remission and 44% were on immunosuppression. 26% of patients reported systemic adverse events and 62% local reactions after vaccination. 2(4.3%) patients experienced a relapse of PIGN, within 5.7 (±3.4) months from the first dose.

Conclusions: SARS-CoV-2 vaccination was well-tolerated, with non-significant impact on PIGN relapse probability. Local side effects were common, seen in the majority of patients, while systemic ones occurred in 20.4% of them.

Demographics, baseline characteristics and adverse events of patienst with PIGN following vaccination SARS-CoV-2 vaccination.

Parameter N (%) or mean (SD)	N=69
Age at PIGN diagnosis (years)	61.75(15.55)
Sex (male)	32 (46.3)
Time since kidney biopsy (months)	76.1 (60.9)
Induction treatment	
Glucocorticoids	65 (97,0)
Cyclophosphamide	55 (83.3)
Mycophenolate mofetil	2 (3,0)
Rituximab	11 (18,0)
Maintenance treatment	
Rituximab	20 (39.2)
AZA	23 (45.0)
First outcome of PIGN	N=63
Remission	58 (92.0)
Resistant disease	5 (7,9)
Number of doses	3.2 (1)
Adverse Events	10 (20,4)
Systematic	2 (4,25)
Arthralgias	5 (10,6)
Myalgias	7 (14,9)
Headache	5 (10.9)
Fever	2 (4,25)
Diarrhea	27 (55.1)
Local	12 (24.5)
Pain	

SA-PO751

Clinical, Serologic, and Histologic Characteristics of Pauci-Immune Renal Vasculitis and Its Response to Treatment in a Mexican Population

Martin B. Yama Estrella, Mario Alamilla-Sanchez, Jose H. Cano Cervantes, Mayra M. Matias Carmona, Citlali Fernandez Vivar, Carolina Gonzalez-Fuentes, Manuel Camacho Luna, Nicte Alaide R. García, Michelle Sánchez, Fani G. Ruiz Rivera, Enrique F. Morales Lopez, Regina C. Hernandez. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico.*

Background: Small-vessel vasculitis presents an adverse renal prognosis that can be life-threatening, so it is relevant to know its characteristics and response to treatment

Methods: Retrospective cohort study, conducted between April 2018 and April 2024. The objective was to analyze the characteristics of pauci-immune renal vasculitis and its response to treatment in a third level hospital in Mexico. Patients older than 18 years with a biopsy-proven diagnosis, who had a follow-up of at least 12 months were included

Results: 19 patients were evaluated, with average age 54 years, 13 (68.42%) women. 14 (73.68%) had extra-renal manifestations. In the histological classification 6 (34.58%) were mixed, 5 (26.32%) focal, 4 (21.05%) sclerotic, 3 (15.79%) crescentic and 1 not classified. 9 (47.37%) were associated with MPO, 7 (36.84%) with PR3, and 3 (15.79%) seronegative. 7 (36.84%) had decreased Complement C3 (< 90 mg/dl). At diagnosis, 16 (84.21%) patients had deterioration of the glomerular filtration rate (eGFR < 60 ml/min/1.73m2) and 9 (47.37%) required renal replacement therapy (RRT). As induction treatment all patients received steroids, 6 (31.58%) cyclophosphamide (CYC), 6 (31.58%) rituximab (RTX), 5 (26.32%) CYC + RTX and one mycophenolic acid (Table 1). Until April 2024, patients were followed up for a mean of 31 months, 14 (73.68%) are free of RRT and one (5.26%) died

Conclusions: Deterioration of the GFR was the main renal manifestation. The most common serology was associated with MPO (47.37%). Although not frequently reported, we found C3 hypocomplementemia in 7 (36.84%) patients. The survival of the patients (94.74%) and their renal prognosis (78.95% without RRT) were better than those reported in other populations. The efficacy of the treatments is similar among the regimens we evaluated

Table 1. Follow-up on response to induction therapy

Treatment	Basal	6 months	12 months	18 months	24 months
STR + CYC:					
Patients	6	6	6	5	3
eGFR ml/min/1.73m2	43.33 +/- 28.35	55 +/- 31.96	44.17	34.8 +/-25.93	18 +/- (6.92)
Proteinuria g/24h	0.937 +/- 0.821.77	0.375 +/- 0.129	0.541 +/- 0.620	0.575 +-0.521	2.04 +/-1.28
Patients on RRT (%)	2	1	1	1	1
Deaths	0	0	0	0	0
STR + CYC+ RTX:					
Patients	5	5	5	4	4
eGFR ml/min/1.73m2	12.8 +/- 6.58	30 +/- 19.91	27+/- 14.75	27.75 +/-17.19	26 +/- 19.71
Proteinuria g/24h	361.89 +/- 426.84	272.21 +/- 389.86	135.58 +/- 132.52	164.41 +/- 36.47	173.61+/-155.96
Patients on RRT (%)	4	2	2	2	2
Deaths	0	0	0	0	0
STR+ RTX:					
Patients	6	5	5	3	2
eGFR ml/min/1.73m2	34.17 +/- 31.27	34.6 +/- 27.16	39.2 +/- 28.05	35.33+/-26.41	19+/-13.73
Proteinuria g/24h	1357 +/- 1153.5	1179.27 +/- 2039.96	1896+/-779.68	392.96 +/- 176.58	No data
Patients on RRT (%)	2	1	0	0	0
Deaths	0	1	1	1	1

CYC: Cyclophosphamide; eGFR: estimated glomerular filtration rate; RRT: renal replacement therapy; RTX: Rituximab; STR: steroid.

SA-PO752

National Trends and Outcomes of Hospitalizations among Patients with Renal Vasculitides

Chikodili N. Nebuwa,[1] Nnenna A. Ukoha,[2] Victor N. Oboli,[3] Ede Omosumwen,[4] Evaristus Asobara.[5] *[1]Nuvance Health, Vassar Brothers Medical Center, Poughkeepsie, NY; [2]East Tennessee State University, Johnson City, TN; [3]Lincoln Medical Center, Bronx, NY; [4]Richmond Gabriel University, Arnos Vale, Saint Vincent and the Grenadines; [5]Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.*

Background: Renal vasculitides are a rare and often debilitating diseases characterized by inflammation of blood vessels within the kidneys with risk for severe renal complications. This study aims to characterize recent trends in hospitalization and clinical outcomes for renal vasculitides.

Methods: We used data from NIS between 2017 and 2020 for vasculitides among patients hospitalized for diseases of the kidney and urinary tract (Major Diagnostic Category 11). Diagnoses and comorbidities were identified using CCSR and ICD 10th edition codes. We used pearson chi-square tests to compare baseline characteristics. The primary outcome was in-hospital mortality. Secondary outcomes were length of stay (LOS) and need for dialysis. Cochran-Armitage tests were used for trend analysis with statistical significance set at P<0.05.

Results: We analyzed a total of 9,090 hospitalizations for renal vasculitides. The frequencies were: Granulomatosis with polyangiitis (GPA) (28.5%), anti-glomerular basement membrane disease (anti-GBM) (24.8%), hypocomplementemic urticarial vasculitis syndrome (24.8%), cryoglobulinemic vasculitis (12.5%), Bechet's disease (16.7%), eosinophilic granulomatosis with polyangiitis (8.5%), and polyarteritis nodosa (PAN) (8.9%). The cohort was predominantly female (51.7%), mean age of 55.2 ± 0.4 years. The annual hospitalizations reduced from 2,730 in 2017 to 1,740 in 2020 (P<0.001). A total of 255 mortalities (2.8%) were recorded in the study period, mostly among females (130), White Americans (160). Mortalities reduced from 85 in 2017 to 35 in 2020 (P<0.001). The greatest mortalities were recorded in the GPA (112; 4.3%) and PAN cohorts (34; 4.25%). Mean LOS was 9 days overall. Patients with Bechet's disease spent 5.5 days compared to GPA (11.2 ± 0.5 days). No significant change in LOS was recorded from 2017 to 2020 (8.9 vs 9.4 days; p=0.749). About 795 (8.7%) required dialysis. Most patients dialyzed were men (410) and patients with anti-GBM disease (400) or GPA (274). The mean cost of hospitalization over the study period was $110,895.4 =/-4,003, with increase in cost from $95,891 in 2017 to $125,695 in 2020 (p<0.0001)

Conclusions: The study highlights the hospitalization pattern of renal vasculitides. Hospitalization for renal vasculitides, in-hospital mortality and dialysis requirement decreased significantly over the study period.

SA-PO753

Monoclonal Gammopathy and Its Associations with Kidney Failure in Patients with ANCA-Associated Vasculitis

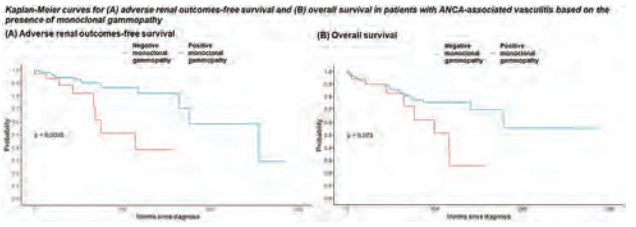
Poemlarp Mekraksakit,[1] Maria Jose Vargas-Brochero,[1] António d. Inácio,[2] Yeshwanter Radhakrishnan,[1] Patrícia A. Domingues,[2] Alessia Buglioni,[1] Ladan Zand.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Centro Hospitalar de Setubal EPE, Setubal, Portugal.*

Background: Up to 30% of patients with ANCA-associated vasculitis (AAV) and kidney involvement progress to end-stage kidney disease (ESKD) despite therapy. The role of monoclonal gammopathy (MG) in disease progression among patients with AAV is not well understood.

Methods: We retrospectively reviewed records of 167 AAV patients with renal involvement tested for MG from January 2000 to December 2023. Patients were divided into monoclonal positive (n=34) and negative (n=133) groups. Multivariate Cox analysis identified predictors of adverse renal outcomes (>40% decline in eGFR or ESKD) and mortality.

Results: The median age of the cohort was 68 years [58.5-74.5], with 85 (50.8%) males. 65.8% tested positive for MPO, and 64.6% received rituximab as induction therapy. Both groups had similar baseline characteristics, but the MG positive group had more moderate/severe Mayo Clinic Chronicity Score (MCCS) (56.7% vs. 33.3%, p=0.01) and less crescentic Berden classification (6.7% vs. 24.8%) on kidney biopsy. Patients in the MG positive group had higher rates of adverse renal outcomes (23.5% vs. 11.3%), ESKD (20.6% vs. 9.8%), death (26.5% vs. 18%), and relapse (35.3% vs. 27.1%) compared to those with no MG. After adjusting for baseline eGFR, hypertension, proteinuria, moderate/severe MCCS, sclerotic Berden class, and induction therapy, MG was associated with adverse renal outcomes (HR 4.64 [95% CI 1.24-17.35]), but not mortality (HR 2.0 [95% CI 0.92-4.3]). Other predictors of adverse renal outcomes were sclerotic Berden classification (HR 12 [2.02-71.9]), proteinuria (HR 1.53 [1.15-2.04] per 1 g/24 hr), and lack of induction therapy (HR 6.3 [1.18-33.5]). Achieving renal remission was associated with lower mortality (HR 0.03 [0.003-0.3]).

Conclusions: AAV patients with renal involvement and MG are at a higher risk of adverse renal outcomes even after adjusting for factors such as eGFR and the degree of chronicity, both of which are known predictors of renal outcomes. The mechanism by which MG worsens outcomes is unclear and requires further research.



SA-PO754

Association of Urinary Adhesion Molecules Derived from Endothelial Cells and Kidney Pathology in ANCA-Associated Glomerulonephritis

Tomoki Tanaka,[1] Ryosuke Umeda,[1] Shun Minatoguchi,[1] Joichi Usui,[2] Kunihiro Yamagata,[2] Midori Hasegawa,[1] Naotake Tsuboi.[1] *[1]Fujita Ika Daigaku, Toyoake, Japan; [2]Tsukuba Daigaku Igaku Iryokei, Tsukuba, Japan.*

Background: Although renal biopsy provides valuable histological information, it is an invasive procedure carrying a risk of bleeding in patients with ANCA-associated glomerulonephritis (ANCA-GN). Therefore, non-invasive urinary biomarkers reflecting renal pathology are highly desirable. ICAM-1 and VCAM-1 belong to the immunoglobulin superfamily serving as cell adhesion molecules and their expression on the cell surface is induced in response to inflammatory stimuli. The aim of the current study is to evaluate the clinical significance of ICAM-1 and VCAM-1 as urinary biomarkers in relation to the pathological findings in ANCA-GN.

Methods: The Japanese nationwide cohort (RemIT-JAV-RPGN cohort, n = 44) and our institutional cohort (FHU cohort, n = 76) for ANCA-GN were subjected to the current study. Urinary concentrations of soluble ICAM-1 and VCAM-1 measured by ELISA were standardized with urinary creatinine (UICR or UVCR), and urine VCAM-1 to ICAM-1 ratio (UVIR) was also obtained. We investigated the association of both biomarkers with renal pathology.

Results: In the RemIT-JAV-RPGN cohort, a correlation between UVIR and the severity of interstitial fibrosis and tubular atrophy (IF/TA) was observed, and similar associations for both UVCR and UVIR were also observed in the FHU cohort. Furthermore, UVIR was found to be a superior indicator for assessing the severity of IF/TA compared with UVCR. In the FHU cohort, when categorizing interstitial damages to interstitial inflammatory cell infiltration (ICI) and interstitial fibrosis (IF), UVIR was consistently increased according to the severity of ICI, but not to IF. Association of urine ICAM-1 or VCAM-1 with cellular crescents was not observed in either cohort. ROC analysis demonstrated that UVIR has superior predictive ability for IF/TA ≥25% in both cohorts. Although the predictive performance of UVIR was comparable to that of urine α1-microglobulin to creatinine ratio (Uα1MGCR) in the FHU cohort, multivariate ROC analysis of UVIR combined with Uα1MGCR improved the prediction ability compared to Uα1MGCR alone.

Conclusions: The urinary ICAM-1 and VCAM-1 are reliable biomarkers that reflect renal pathological activity related to acute interstitial inflammation in ANCA-GN.

Funding: Commercial Support - Bayer Yakuhin, Ltd, Chugai Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Sumitomo Pharma Co., Ltd.

SA-PO755

Identification of Kidney Transcripts Associated with Prognosis in ANCA-Associated Glomerulonephritis

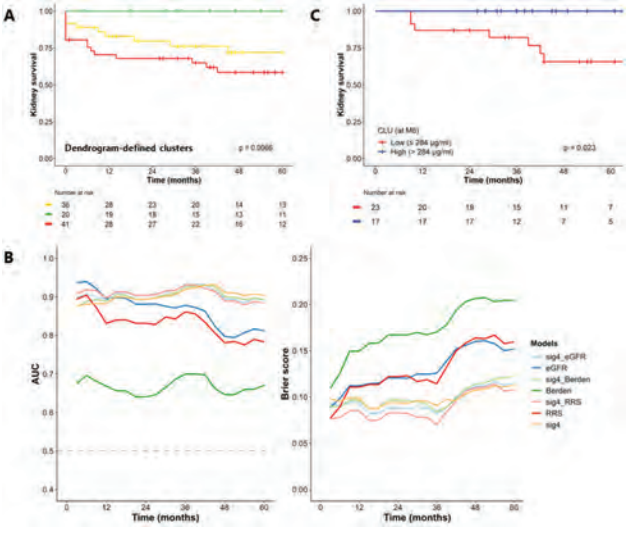
Benoit Brilland,[1] Jérémie Riou,[1] Andrea Boizard-Moracchini,[2] Nathalie Merillon,[1] Maïa Despre,[1] Giorgina B. Piccoli,[3] Assia Ilham Djema,[4] Nicolas Henry,[5] Marie-Christine Copin,[1] David Langlais,[6] Patrick Blanco,[1] Jean Francois Augusto.[1] Maine-Anjou Registry Research Group. *[1]CHU Angers, Angers, France; [2]Centre Hospitalier Universitaire de Bordeaux Groupe hospitalier Pellegrin, Bordeaux, France; [3]Centre Hospitalier du Mans, Le Mans, France; [4]Centre Hospitalier de Cholet, Cholet, France; [5]CH Laval, Laval, France; [6]McGill University, Montreal, QC, Canada.*

Background: Kidney involvement in ANCA-associated vasculitis (AAV-GN) predicts poor patient and kidney survival. To get insights into pathogenic mechanisms or identify biomarkers for refining prognosis, we aimed to investigate the potential prognostic value of kidney transcripts associated with kidney survival.

Methods: Immune gene transcript analysis was performed on RNA extracted from 97 adult AAV-GN kidney biopsies from the French Maine-Anjou Registry using NanoString technology. Transcripts of interest were selected, and their prognostic performance was compared to current histological-based classifications. Following the identification of a possible role for clusterin (CLU), the relationship between serum CLU and prognosis was assessed.

Results: Among the 750 evaluated transcripts, we identified a 4-gene signature (XRCC6, PRKCD, TEK, and CLU) strongly associated with kidney survival (**Figure 1A**). This signature predicted kidney survival better than histological-based classifications (global C-Index 0.87 vs. 0.65 for Berden classification or 0.81 for Renal Risk Score, with better time-dependent AUC and Brier scores) (**Figure 1B**). Among these 4 transcripts, the expression level of the CLU transcript had the highest correlation with glomerular involvement, kidney function at diagnosis, and kidney survival. Serum CLU levels were associated with kidney survival, especially when assessed at 6 months from diagnosis (**Figure 1C**, p = 0.023).

Conclusions: Transcriptomic analysis of kidney biopsies of AAV-GN identified potential transcripts that may improve prediction of kidney survival. This transcriptomic signature may help us gain a deeper understanding of the AAV-GN pathogenesis and provide insights for developing new therapeutic options.



SA-PO756

Immune Profiling-Based Targeting of Pathogenic T Cells with Ustekinumab in ANCA-Associated Glomerulonephritis

Jonas Engesser,[1] Robin Khatri,[1,2] Darius P. Schaub,[1,2] Hans-Joachim Paust,[1] Zeba Sultana,[1] Nariaki Asada,[1] Varshi Sivayoganathan,[1] Victor G. Puelles,[1] Ulrich O. Wenzel,[1] Oliver M. Steinmetz,[1] Elion Hoxha,[1] Hans-willi Mittrücker,[1] Thorsten Wiech,[1] Tobias B. Huber,[1] Stefan Bonn,[1,2] Christian F. Krebs,[1] Ulf Panzer.[1] *[1]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Universitatsklinikum Hamburg-Eppendorf Zentrum fur Molekulare Neurobiologie Hamburg, Hamburg, Germany.*

Background: Antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis is a life-threatening autoimmune disease that often results in kidney failure caused by crescentic glomerulonephritis (ANCA-GN). To date, treatment of most patients with ANCA-GN relies on unspecific immunosuppressive drugs that are often only partially effective and harbor serious adverse effects. This underscores the unmet need for the development of pathogenesis-based and safer therapies.

Methods: Here, we performed combined spatial and single cell transcriptome analysis to characterize the inflammatory niches in the kidneys of 34 patients with ANCA-GN. Digital pharmacology was used to predict the most promising drugs for treatment of kidney inflammation. Subsequently, we treated four relapsing ANCA-GN patients in a proof-of-concept study with ustekinumab (90 mg s.c. at weeks 0, 4, 12 and 24) in combination with low dose cyclophosphamide and steroids. Patients were followed up for 26 weeks.

Results: Spatial transcriptome analysis revealed distinct inflammatory niches in both glomerular and tubulointerstitial regions, each associated with T cell activation. By using unsupervised single-cell transcriptomics and epitome mapping of renal T cells, we identified a predominance of proinflammatory, cytokine-producing Th1/Tc1 and Th17/Tc17-like effector T cells. Ensuing digital pharmacology pinpointed ustekinumab, a human monoclonal antibody binding the common p40-subunit shared by IL-12/IL-23, thus blocking Th1 as well as Th17 responses, as the most promising drug to target these pathogenic T cells in a pathogenesis-based treatment approach. The treatment of four ANCA-GN patients with relapsing disease using ustekinumab led to a rapid clinical response in all four patients, including improved kidney function and lower Birmingham Vasculitis Activity Scores. No treatment related adverse effects were observed during the follow up period.

Conclusions: Our findings suggest that immune profiling-based targeting of pathogenic T cells in ANCA-GN patients with ustekinumab is a promising approach and warrants further investigation in clinical trials.

Funding: Government Support - Non-U.S.

SA-PO757

Low Albumin Levels Are Associated with Intrarenal Complement C4d Deposits in Critically Ill Patients with ANCA-Associated Renal Vasculitis

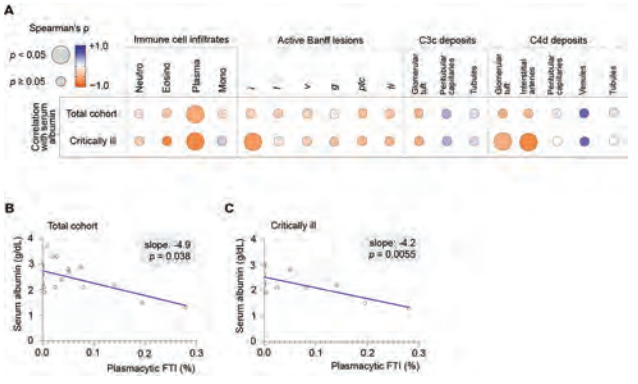
Eva Baier, Bjoern Tampe. *Universitatsmedizin Gottingen Klinik fur Nephrologie und Rheumatologie, Gottingen, Germany.*

Background: Despite serum albumin levels being predictive for clinical outcome in ANCA-associated renal vasculitis (AArV), implications providing a direct link between low serum albumin levels and intrarenal lesions remain elusive. Thus, we here aimed to systematically assess the clinical relevance of low albumin levels and scrutinize clinicopathological correlations to expand our knowledge.

Methods: We retrospectively enrolled biopsy-proven cases of AArV between 2015 till 2020 in a single-center observational study. Survival-curve analyses on short-term clinical recovery were performed. Correlative analyses between serum albumin levels, laboratory parameters, proteinuria levels, and histopathological lesions including tubulointerstitial immune cell infiltrates, lesions analogous to the Banff score and intrarenal complement deposition of C3c and C4d were performed.

Results: Critically ill patients with serum albumin levels below the median of 2.4 g/dL featured an affected short-term clinical recovery (p=0.0082, HR: 3.6, 95% CI: 1.1-11.7). An extrarenal causation of hypoalbuminemia in the critically ill was assumed, since serum albumin levels did not correlate with the urinary marker of tubular damage (β=-0.5, p=0.07). We identified plasmacytic infiltrates to correlate with low albumin levels (β=-0.7, p=0.005) and Banff-scored interstitial inflammation (i) to be inversely correlated with albumin levels (β=-0.7, p=0.02). Intrarenal C4d deposition showed a significant correlation with low serum albumin levels in the glomerular tuft (β=-0.4, p=0.04).

Conclusions: In conclusion, short-term recovery was predicted by low albumin levels in critically ill patients with AArV. We here provide evidence that low levels of serum albumin might directly affect tubulointerstitial inflammation as reflected by plasmacytic immune-cell infiltration, and intrarenal C4d complement deposition in AArV.



SA-PO758

Clinical Phenotype Identifies Individuals with ANCA-Associated Vasculitis Who Do Not Require Kidney Biopsies for Diagnosis of Kidney Involvement

Ayman Al Jurdi, Christopher El Mouhayyar, Gabriel Sauvage, Anushya Jeyabalan, Orhan Efe, Harish Shanthanu Seethapathy, Katherine M. Cosgrove, Karen A. Laliberte, John Niles. *Massachusetts General Hospital, Boston, MA.*

Background: Kidney involvement is common in ANCA-associated vasculitis (AAV). The most common finding on kidney biopsy in AAV is crescentic glomerulonephritis (GN). Guidelines recommend kidney biopsy in individuals with AAV and kidney abnormalities to confirm kidney involvement. Kidney biopsies are associated with a risk of bleeding and may delay treatment for active AAV. Therefore, identification of characteristics associated with a high likelihood of finding crescentic GN on biopsy can avoid the need for kidney biopsy in these individuals and its associated risks and costs.

Methods: We conducted a single-center retrospective cohort study of all individuals with a positive ANCA test and a kidney biopsy between 2000 and 2023 at the Vasculitis and Glomerulonephritis Center at Massachusetts General Hospital. The positive predictive value (PPV) for finding crescentic GN on biopsy based on various clinical findings was evaluated.

Results: 142 individuals met the study's inclusion criteria. The median age was 64 and 55% were female. The median serum creatinine was 2.49 mg/dL, and 89% had microscopic hematuria. 73%, 24%, and 3% were positive for antibodies to myeloperoxidase, proteinase 3, or both, respectively. Crescentic GN was found in 85% of biopsies (Fig. 1A). 100% of individuals with ANCA positivity and rapidly progressive GN (defined as ≥50% eGFR loss in ≤6 months, n = 45) had crescentic GN on biopsy. Over 93% of individuals with ANCA positivity, microscopic hematuria, and ≥1 extra-renal system involvement had crescentic GN on biopsy (Fig. 1B).

Conclusions: The rate of kidney function decline, microscopic hematuria, and extra-renal symptoms identify individuals with AAV who do not require kidney biopsy to establish kidney involvement.

Funding: Veterans Affairs Support

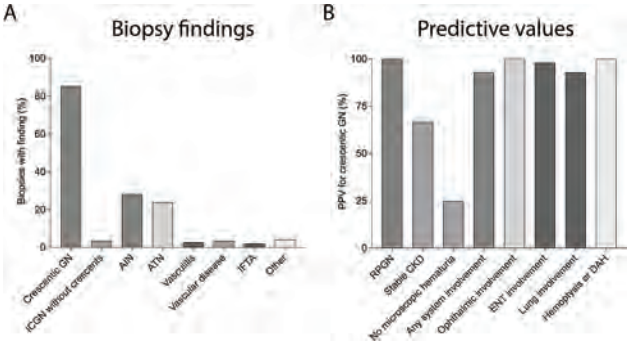


Figure 1. Diagnostic value of ANCA testing for kidney involvement by vasculitis. (A) Kidney biopsy results. (B) Positive predictive value of different clinical presentations.

SA-PO759

Retrace-Clustering Creatinine Trajectory and Baseline Features for Predicting ESKD

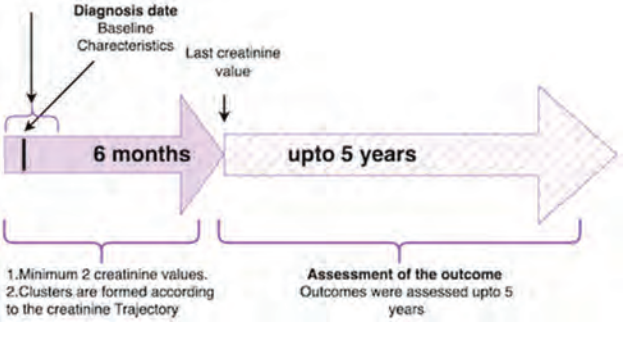
Dearbhail Ni Cathain, Jamsheela Nazeer, James Ng, Jennifer Scott, Eithne M. Nic an Riogh, Angel Mary George, Arthur White, Mark A. Little. *The University of Dublin Trinity College, Dublin, Ireland.*

Background: Patients with ANCA-associated vasculitis (AAV) may experience end-stage kidney disease (ESKD) and mortality. We aim to investigate the connection between the longitudinal trajectory of creatinine and the occurrence of ESKD and mortality.

Methods: We included patients with a minimum of two creatinine measurements, encompassing the baseline period and the following six months (Figure). Creatinine trajectories were formulated using six months of creatinine readings from AAV patients with kidney involvement. We excluded patients who presented with end-stage kidney disease (ESKD). In instances where a patient had multiple creatinine values within a given month, the average of those values was employed. Percentage delta creatinine values, representing the percentage difference between a creatinine value and its baseline, were then calculated. The K-means algorithm for longitudinal data was employed to cluster the creatinine trajectories of AAV patients. The quality of clustering was evaluated using the Calinski-Harabasz Index. We conducted a time-to-event analysis for ESKD and death, assessing the survival rates of the clusters over a five-year follow-up period through Kaplan-Meier Survival analysis.

Results: The study incorporates 273 patients with >1 creatinine values, amounting to a total of 2022 creatinine readings. We identified three renal trajectory groups: A-Stable (140), B-Recovered (N=100), and C- Declining (N=33). The baseline features varied across clusters, specifically in terms of baseline creatinine (284uM, 390uM and 151uM respectively, p<0.001) and ENT involvement (p=0.001). When considering the composite outcome of ESKD and death, Cluster A exhibited a 3-year incidence rate of 23%, Cluster B at 8%, and Cluster C at 28% (p<0.0069).

Conclusions: Trajectory clustering allows for the identification of patients who may require closer monitoring, or targeted interventions based on their cluster assignment and associated risk profile.



SA-PO760

Kinetic eGFR Ratio Predicts Active Lesions and Prognosis in ANCA-Associated Glomerulonephritis

Rina Oba, Go Kanzaki, Takaya Sasaki, Kotaro Haruhara, Masahiro Okabe, Shinya Yokote, Akihiro Shimizu, Kentaro Koike, Keita Hirano, Hideo Okonogi, Nobuo Tsuboi, Takashi Yokoo. *Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.*

Background: Antineutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-GN) is a typical vasculitis syndrome presenting with rapidly progressive glomerulonephritis (RPGN). Kinetic estimated Glomerular Filtration Rate (KeGFR) has been proposed to approximate true GFR under non-steady-state conditions. We investigated the clinicopathologic and prognostic significance of KeGFR in patients with ANCA-GN.

Methods: We retrospectively identified 66 patients with ANCA-GN from 3 hospitals in Japan (2004–2020). KeGFR ratio was defined as the ratio of KeGFR difference to baseline eGFR. The primary composite endpoints included end-stage kidney disease and death. We compared clinicopathologic features and long-term outcomes between the high KeGFR ratio group and the low KeGFR ratio group. We also assessed the factors associated with treatment resistance.

Results: Patients with a high KeGFR ratio had a higher incidence of treatment resistance and a higher percentage of cellular crescents and interstitial inflammation (Tables 1 and 2). The cumulative event-free survival rate at 5 years was significantly lower in the high KeGFR group than in the low KeGFR group (Figure 1). In addition, the KeGFR ratio was significantly associated with treatment resistance after adjusting for age, ANCA renal risk score (which included % normal glomeruli, baseline eGFR, and % Interstitial fibrosis/tubular atrophy), and treatment (Table 3).

Conclusions: KeGFR ratio is associated with disease state and acute lesions in ANCA-GN and may be useful in assessing long-term prognosis and treatment resistance.

Table 1. Comparison of clinical features of the KeGFR ratio groups

KeGFR ratio groups	Low <48	48≤ High	P value
Age, years	76 (60-83)	73 (70-78)	0.75
Male, n (%)	10 (30.3)	8 (24.2)	0.58
Lung involvement, n (%)	23 (69.7)	18 (54.5)	0.21
Immunosuppressors			0.75
PSL, n (%)	25 (75.8)	27 (81.8)	-
PSL+IVCY, n (%)	5 (15.1)	3 (9.1)	-
Others, n (%)	3 (9.1)	3 (9.1)	-
Treatment resistant, n (%)	2 (6.1)	11 (33.3)	0.01
Baseline eGFR (mL/min/1.73m²)	39.3 (21.0-58.1)	51.7 (32.8-70.7)	0.07
UPE (g/day)	0.5 (0.3-1.4)	1.0 (0.4-2.2)	0.17
U-RBC (/HPF)			0.23
<0-5, n (%)	2 (6.1)	3 (9.1)	-
<50, n (%)	16 (48.5)	11 (33.3)	-
≥50, n (%)	7 (21.2)	4 (12.1)	-
≥100, n (%)	8 (24.2)	15 (45.5)	-
ANCA Renal Risk Score	2 (0-2)	5 (4-6)	0.001

Table 2. Comparison of histologic features of the KeGFR ratio groups

KeGFR ratio groups	Low <48	48≤ High	P value
Berden classification			0.16
Focal, n (%)	14 (42.4)	8 (24.2)	-
Mixed, n (%)	12 (36.5)	10 (30.4)	-
Crescentic, n (%)	3 (9.1)	4 (12.1)	-
Sclerotic, n (%)	4 (12.1)	11 (33.3)	-
% normal glomeruli	42.1 (33.3-76.8)	30.0 (13.1-50.8)	0.01
% global sclerosis	21.4 (11.1-40.3)	28.6 (7.5-50.0)	0.39
% cellular crescents	14.3 (5.83-25.8)	25.0 (10.4-43.3)	0.03
% fibrous crescents	0.0 (0.0-5.9)	2.8 (0.0-9.8)	0.24
% IF/TA	30.0 (20.0-52.5)	50.0 (25.0-72.5)	0.06
% Inflammation	39.0 (15.0-50.0)	40.0 (30.0-75.0)	0.01
Arteritis, n (%)	8 (24.2)	7 (21.2)	0.77
Arteriosclerosis, n (%)	23 (69.7)	21 (63.6)	0.60
Granuloma, n (%)	5 (15.1)	6 (18.2)	0.74
Mayo Clinic Chronicity Score	5 (5-7)	7 (5-8)	0.13

Table 1. and Table 2.

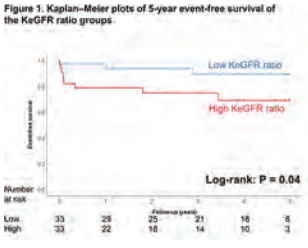


Figure 1. Kaplan–Meier plots of 5-year event-free survival of the KeGFR ratio groups

Table 3. Factors associated with treatment resistance

Predictor of treatment resistance	Multivariate	
	OR (95%CI)	P value
KeGFR ratio (%)	1.037 (1.002-1.073)	0.04
Age (years)	0.950 (0.887-1.017)	0.14
ANCA Renal Risk Score	1.088 (0.865-1.368)	0.47
Treatment: PSL only	reference	-
PSL pulse vs PSL	0.442 (0.065-3.014)	0.41
PSL+IVCY vs PSL	0.633 (0.053-7.613)	0.72
Others vs PSL	1.150 (0.095-13.907)	0.91

Figure 1. and Table 3.

SA-PO761

Long-Term Kidney Outcomes in ANCA-Associated Vasculitis in a Mexican Hispanic Cohort

Adriana Hernández Andrade, María F. Zavala Miranda, Valeria Navarro Sanchez, Alberto Nordmann-Gomes, Andrea Hinojosa-Azaola, Juan M. Mejia-Vilet. *Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: The kidneys are frequently involved in anti-neutrophil cytoplasm antibody-associated vasculitis (AAV). Kidney outcomes are variable among centers and have been scarcely reported in the Latin American region

Methods: Retrospective cohort study including all patients diagnosed with AAV and kidney involvement between 2001 and 2022. All patients were followed for ≥12 months, kidney failure, or death. All outcomes were evaluated by time-to-event analyses.

Results: The cohort included 154 patients with AAV and kidney involvement, 133 (86%) diagnosed by kidney biopsy, with a median follow-up of 74 months (IQR 32-126). The median age was 52 years (IQR 38-61), 104 (67%) female, 82 (53%) diagnosed as granulomatosis with polyangiitis (GPA), 47 (31%) microscopic polyangiitis, and 25 (16%) as renal-limited vasculitis. At presentation, median serum creatinine was 2.4mg/dL (IQR 1.7-4.5), eGFR 23ml/min/1.73m2 (IQR 12-36), and proteinuria 1.8g/g (IQR 1.1-3.2). In the kidney biopsy, the median normal glomeruli were 18% (IQR 0-37), global sclerosis 39% (IQR 6-56%), interstitial fibrosis 30% (IQR 15-50), tubular atrophy 30% (10-60). 52 (34%) patients had renal replacement therapy requirements at presentation, of which x 19 (36%) recovered kidney function. Over long-term follow-up, 54 patients progressed to kidney failure with 5- and 10-year progression rates of 73% and 56%, respectively (Figure 1-A). Twenty-four patients died over follow-up, with patient survival being 88% and 83% by 5 and 10 years (Figure 1-B). The main cause of death was infection (75%)

Conclusions: The kidney outcomes in this Mexican cohort are worse than those described in European and US cohorts. The percentage of patients with initial kidney replacement therapy requirements and advanced sclerosis is higher than in other cohorts, suggesting that late diagnosis is one of the factors associated with dismal prognosis in this cohort.

SA-PO762

Clinical Frailty as a Proxy Measure for Infection Risk in ANCA-Associated Glomerulonephritis

Joshendra Durailingam,[1] Kavita Gulati,[3] Gavin Chapman,[4] Neeraj Dhaun,[4] Stephen P. McAdoo,[3] Silke R. Brix.[1,2] *[1]The University of Manchester, Manchester, United Kingdom; [2]Manchester University NHS Foundation Trust, Manchester, United Kingdom; [3]Imperial College London, London, United Kingdom; [4]University of Edinburgh, Edinburgh, United Kingdom.*

Background: Frailty is a functional term referring to a decline in physiological function that leads to dependency, vulnerability and a high risk for poor health-related outcomes. Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis affects the elderly and often results in a rapid decline in the general health. We aim to better understand the interaction between the rapid evolving ANCA associated inflammation and the impression of frailty to improve prediction modelling for adverse outcomes. Here, we investigated clinical frailty scale (CFS) at time of diagnosis for its association with clinical outcomes.

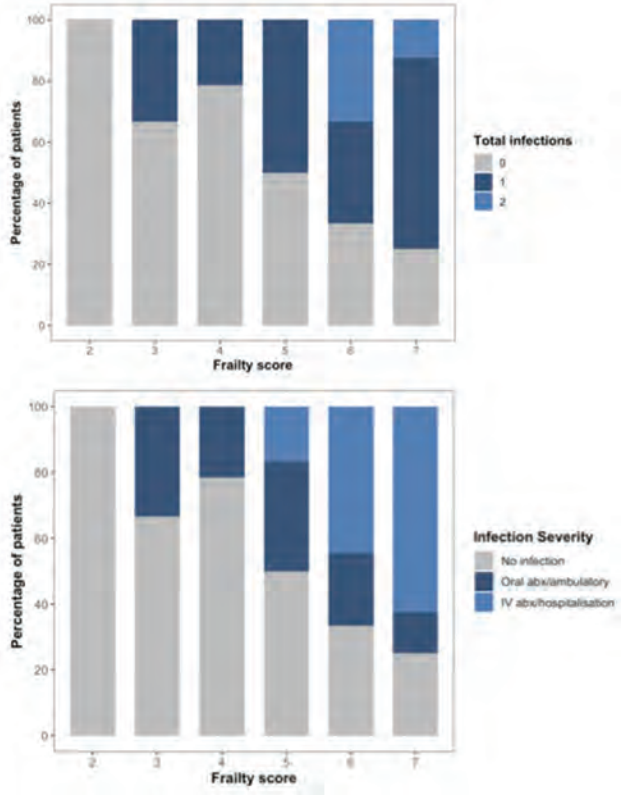
Methods: We performed a three-centre, retrospective analysis of newly diagnosed ANCA glomerulonephritis (GN) patients in the UK. Wilcoxon-Rank-Sum, Kruskal-Wallis and Fisher-Exact testing were used to analyse the relationships of age, CFS and infections, end stage kidney disease (ESKD) and death.

Results: A total of 275 patients were included, median follow-up 3.8 years (interquartile range, IQR, 2.1 – 5.3 years). The median age at presentation was 66.3 years (IQR, 54.7 – 74.5 years) and 145 were of male gender (52.3%). A total of 86 patients developed ESKD (31.3%), and 77 patients died (28%) during follow-up. Data on infection during the first year was available on 158 patients. Age and CFS did not influence the development of ESKD (p=0.4 and p=0.21). Higher age and CFS were both associated with deaths during follow up (p=0.004 and p=0.002). The frequency and severity of infections did not differ across age (p=0.4 and p=0.2). CFS however associated with infections in frequency and severity (p=0.01 and p<0.001, Figure 1).

Conclusions: An initial frailty assessment at the time of diagnosis might assist in predicting infections in patients with newly diagnosed ANCA GN.

Funding: Government Support - Non-U.S.

Figure 1



	AAV+aGBM N (%)	aGBM+AAV N (%)
Gender		
Male	4 (57.1)	10 (43.5)
Median BVAS at diagnosis	14	15
Median CRP (mg/L) (IQR)	26.5 (81)	76 (103.5)
Median creatinine (µmol /L) (IQR)	412 (103.5)	425 (404.5)
Antibody		
Anti-MPO+	5 (71.4)	16 (69.6)
Anti-PR3+	2 (28.6)	7 (30.4)
Induction Treatment		
Yes	7 (100)	23 (100)
Maintenance Treatment		
Yes	4 (57.1)	18 (90)
RRT		
Yes	2 (28.6)	15 (65.2)
Recovery of renal function		
Yes	1 (50)	3 (20)
ESKD		
Yes	2 (28.6)	6 (26.1)
Relapse		
Yes	1 (14.3)	9 (39.1)
Death		
Yes	1 (14.3)	6 (26.1)

SA-PO763

ANCA and Anti-glomerular Basement Membrane (GBM) Dual Antibody Positivity: A Case Series and Proposal for a Clinical Classification

Tara O'Sullivan,[1] Michael Clarkson,[1] Niall P. Conlon,[2] Matthew D. Griffin,[5] Edward P. Mc Monagle,[4] Mark A. Little,[3] Sarah M. Moran.[1] *[1]Cork University Hospital, Cork, Ireland; [2]St James's Hospital, Dublin, Ireland; [3]The University of Dublin Trinity College, Dublin, Ireland; [4]University Hospital Limerick, Dooradoyle, Ireland; [5]Galway University Hospitals, Galway, Ireland.*

Background: Anti-glomerular basement membrane (aGBM) disease and the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are rare vasculitides. ANCA and aGBM dual positivity can occur; up to 40% of patients with a clinical diagnosis of aGBM disease have a positive ANCA (aGBM+AAV) and up to 5% of patients with a clinical diagnosis of AAV have detectable aGBM antibodies (AAV+aGBM). Literature on clinical phenotyping and prognosis is lacking, with no current clinical consensus on definitions. We report a case series of aGBM+AAV and AAV+aGBM from RITA-Ireland, with the following proposed definitions: 1. aGBM+AAV: aGBM disease with linear IgG staining on kidney biopsy and no clinical features of vasculitis outside lung or kidney, with co-existent ANCA positivity in serum 2. AAV+aGBM: clinical AAV with aGBM antibody (pauci immune kidney biopsy findings)

Methods: Dual positive patients with documented renal biopsy were identified from the European reference Network RITA-Ireland Vasculitis (RIV) Registry and Biobank. Clinical and biochemical features, aGBM methodology, renal biopsies, requirement for RRT, progression to ESKD, recovery of renal function, treatment, relapse, and death were retrospectively compared between the two groups.

Results: Thirty patients meeting the inclusion criteria were identified, 7 (23.3%) with AAV+aGBM and 23 (76.7%) with aGBM+AAV. Anti-myeloperoxidase (MPO) antibody was detected in 70%. See figure 1 for results and comparison between groups.

Conclusions: AAV and aGBM disease are rare vasculitides, whose overlap occurs at a higher frequency than determined by chance. There is currently no consensus on nomenclature of aGBM+AAV and AAV+aGBM. This case series highlights differences between these diseases, most notably the higher proportion of relapse in aGBM+AAV, and informs a proposal for a clinical classification to guide future care pathways.

SA-PO764

Efficacy and Safety of Rituximab in Anti-glomerular Basement Membrane (GBM) Disease

Vanja Ivkovic,[1,2] Ingeborg M. Bajema,[3] Annette Bruchfeld,[4,5] Stephen P. McAdoo,[6,7] Marten Segelmark,[8,9] Andreas Kronbichler.[10] *[1]UHC Zagreb, Department of Nephrology, Hypertension, Dialysis and Transplantation, Zagreb, Croatia; [2]University of Rijeka Faculty of Health Studies, Rijeka, Croatia; [3]Department of Pathology and Medical Biology, University of Groningen, University Medical Center, Groningen, Netherlands; [4]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; [5]Department of Renal Medicine, Karolinska University Hospital and CLINTEC Karolinska Institutet, Stockholm, Sweden; [6]Centre for Inflammatory Disease, Department of Immunology and Inflammation, Imperial College London, Hammersmith Campus, London, United Kingdom; [7]Imperial College Renal and Transplant Centre, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom; [8]Department of Clinical Sciences, Lund University, Lund, Sweden; [9]Department of Endocrinology, Nephrology and Rheumatology, Skåne University Hospital, Lund, Sweden; [10]Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck, Innsbruck, Austria.*

Background: Anti-glomerular basement membrane (GBM) disease is a vasculitis caused by pathogenic antibodies targeting the NC1 domain of the α3 chain of type IV collagen and presenting as RPGN and diffuse alveolar haemorrhage (DAH). Decreasing production of these antibodies and their clearance are imperative to achieve patient and kidney survival. The mainstay of therapy is the combination of plasma exchange (PLEX), glucocorticoids and cyclophosphamide. Rituximab, an anti-CD20 monoclonal antibody causing B-cell depletion, has been proposed as a potential treatment for anti-GBM disease, but there is still a paucity of evidence of its efficacy and safety.

Methods: We have performed a systematic review of case reports/series providing individual patient-level data on the efficacy and safety of rituximab in anti-GBM disease. A search strategy of studies indexed in PubMed was performed followed by synthesis and analysis of the collated data.

Results: Twenty-two studies with data on 43 patients (M:F=18:15; median age 34 years, IQR: 20-63) were included who received rituximab in the first (N=18) or second line (N=25). Median serum creatinine was 416 µmol/L (IQR 212-706) with 21 (49%) patients being dialysis-dependent on presentation and 19 (44%) having DAH. Ten patients were positive for ANCA, 8 of them for MPO-ANCA. Almost all patients received pulse and oral glucocorticoids and PLEX (88%, 100% and 95%, respectively) and 62% of them received cyclophosphamide. Patients received a median of 4 (2-4) doses of rituximab with 5 patients (12%) having adverse effects which were all transient. After a median of 14.8 (5.0-33.0) months follow-up, patient survival was 100% and kidney survival 63% (33% in initially dialysis-dependent patients vs. 90% in initially non-dialysis-dependent patients, p<0.001). There were no differences in kidney survival between ANCA-positive and negative patients, those with and without DAH or those who received rituximab in first or second line.

Conclusions: In this, the largest group of anti-GBM disease patients receiving rituximab to date, the treatment had a favourable toxicity and efficacy profile. However, there is a great risk of publication bias and prospective trials are necessary to determine if rituximab should replace cyclophosphamide or be used in conjunction with cyclophosphamide as first line treatment.

SA-PO765

Rituximab in Addition to Plasma Exchange, Cyclophosphamide, and Steroids for the Treatment of Anti-glomerular Basement Membrane (GBM) Disease

Mukunthan Srikantharajah,[1] Jacob Chappell,[2] Maria Prendecki,[1] David Makanjuola,[2] Bhrigu Raj Sood,[2] Stephen P. McAdoo.[1] *[1]Imperial College London, London, United Kingdom; [2]Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.*

Background: Anti-GBM disease is a rare antibody-mediated vasculitis, usually treated with plasma exchange (PEX), cyclophosphamide (CYC) and steroids. There are limited data regarding the use of B-cell depleting therapies such as rituximab (RTX).

Methods: Two-centre retrospective cohort study of patients presenting from 2003-2023 with anti-GBM disease treated with or without RTX, in addition to standard care, as first-line therapy.

Results: Seventy-eight patients are included; baseline demographics, disease characteristics, treatments and outcomes are summarised in Table 1. All patients were treated with PEX, CYC (oral or IV), and steroids. The addition of RTX treatment was associated with non-significant trends to reduced number of PEX (10 *versus* 14 with no RTX, p=0.30) and lower total CYC dose (3.3g *versus* 3.6g, p=0.78), with reduced time to anti-GBM negativity (2.1 *versus* 3.5 months with no RTX, p=0.67). In the Cox-proportional hazards regression model incorporating age, sex, ANCA status, dialysis need at presentation, lung haemorrhage, CYC and RTX treatment, increasing age was associated with risk of death (HR 1.07 [95% CI 1.01-1.17]) and risk of infection (HR 1.03 [95% CI 1.00-1.06]). Dialysis need at presentation was associated with ESKD-risk (HR 0.05 [95% CI 0.01-0.14]). The addition of rituximab was not significantly associated with risk of death (HR 1.45 [0.38-6.93]), ESKD (HR 0.97 [0.50-1.91]) or infection 0.48 [0.23-1.02].

Conclusions: Addition of RTX to standard treatment for anti-GBM disease was not associated with improved renal or overall survival. However, RTX use permitted lower cumulative doses of CYC and reduction in the number of PEX, without an increased risk of infection. RTX may have a role as a CYC- and PEX-sparing treatment in patients with anti-GBM disease.

Table 1: Demographics, disease features, and outcomes
(data reported as median [IQR])

	All	RTX	No RTX
Demographics			
Number	78	31	47
Age, years	61 [45-73]	61 [44-74]	59 [46-73]
Sex, M:F	39:39	13:18	26:21
Disease at Baseline			
Dialysis need (%)	47/78 (60)	20/31 (65)	27/47 (57)
Creatinine, µmol/L	546 [317-901]	800 [302-1343]	499 [339-795]
Lung Haemorrhage (%)	23/78 (29)	8/31 (26)	15/47 (32)
ANCA (neg/MPO/PR3)	47/24/7	17/10/4	30/14/3
Anti-GBM, iu/L	111 [40-308]	103 [41-659]	115 [40-217]
Treatment			
PEX, number	12 [7-16]	10 [7-14]	14 [7-16]
CYC dose, g	3.6 [2.2-5.3]	3.3 [2.2-4.6]	3.6 [2.3-5.3]
Outcomes			
Time to anti-GBM negative, months	3.2	2.1	3.5
1 year survival (%)	66/78 (87)	28/31 (90)	38/47 (81)
1 year ESKD-free survival (%)	36/78 (46)	13/31 (42)	23/47 (49)
1 year infection-free (%)	47/78 (60)	15/31 (48)	32/47 (68)
Hypogammaglobulinemia (%)	5/78 (6)	5/31 (16)	0/47
Post-treatment diabetes (%)	4/78 (5)	3/31 (10)	1/47 (2)
Malignancy (%)	3/78 (4)	1/31 (3)	2/47 (4)

SA-PO766

Pulmonary-Renal Syndrome from Cocaine-Induced ANCA-Associated Vasculitis: A Case Report

Christopher C. Shrack, Carrie L. Phillips, Simit Doshi. *Indiana University School of Medicine, Indianapolis, IN.*

Introduction: Approximately 71% of cocaine samples obtained in the United States are adulterated with Levamisole, an anthelminthic drug with immunomodulatory properties that is used to increase the weight and potency of cocaine. Case reports have linked Levamisole-contaminated cocaine with an ANCA-associated vasculitis (AAV). We present a case of AAV manifesting as a pulmonary-renal syndrome with undetectable complement levels following cocaine use.

Case Description: A 75-year-old African American man with a past medical history of type 2 diabetes mellitus, hypertension, COPD, heart failure with reduced ejection fraction, paroxysmal atrial fibrillation, chronic Hepatitis C infection, and MGUS presented with chest pain and leg edema without a rash. He reported nasal inhalation of cocaine 3 days prior to admission. Serum creatinine on presentation was 3.22 mg/dL and continued to worsen. Urine microscopy showed muddy brown casts. His hospital course was complicated by new-onset hemoptysis which progressed to diffuse alveolar hemorrhage (DAH) requiring intubation and critical care support. Serum complement levels were undetectable. Hepatitis C titers showed 541,000 copies, however, rheumatoid factor assay and test for cryoglobulinemia remained negative. ANCA titers showed positivity for MPO antibodies. Kidney biopsy specimen showed focal necrotizing and crescentic glomerulonephritis (50% active lesions) in the absence of immune complex deposits compatible with AAV. He received immunosuppression with steroids and cyclophosphamide, underwent 7 rounds of plasmapheresis, and was initiated on renal replacement therapy. He had complete resolution of DAH and was extubated while on pheresis. He remained dialysis dependent at 2 month follow up at the time of discharge to subacute rehabilitation.

Discussion: Cocaine-induced AAV can present with a variety of symptoms and signs due to involvement of multiple organ systems including life-threatening pulmonary-renal syndrome. While role of pheresis is limited in levamisole-induced AAV, resolution of DAH was noted in our patient.

SA-PO767

Rituximab Induction in Rheumatoid-Associated, ANCA-Negative, Pauci-Immune Glomerulonephritis

Chunzi Song,[1] Maurice I. Khayat.[1,2] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]VA North Texas Health Care System, Dallas, TX.*

Introduction: Rheumatoid vasculitis (RV) is a serious complication of rheumatoid arthritis (RA). Adoption of disease modifying antirheumatic drugs (DMARDs) has decreased its incidence. Renal involvement is rare, but pauci-immune glomerulonephritis (GN) with detectable antineutrophil cytoplasmic antibodies (ANCA) has been reported. The optimal therapy for ANCA-negative RV is unknown. Rituximab (RTX) is frequently used to treat articular symptoms, but no cases using RTX for ANCA-negative RV are described.

Case Description: A 68 year-old man with a history of RA presented with anasarca, acute kidney injury and nephrotic syndrome. His RA was diagnosed 15 years prior with erosive arthritis, positive antinuclear antibodies, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies. He was started on methotrexate, but after 5 years he was lost to follow up. On re-presentation after 10 years, labs were notable for a serum creatinine between 2.6-3.0 mg/dL, albumin of <1 mg/dL, and urine protein-to-creatinine ratio between 5.4-14 g/g. Renal biopsy revealed pauci-immune focal crescentic GN, global and segmental glomerulosclerosis without interstitial fibrosis or tubular atrophy (IFTA). Congo red stain was negative. Serologic work up including serum ANCA was negative except as outlined above. No extrarenal manifestations of vasculitis were noted. RTX 1000mg, 2 weeks apart resulted in reduction of proteinuria with unchanged serum creatinine and albumin. Repeat renal biopsy after 3 months revealed resolution of crescentic vasculitis, development of moderate IFTA and focal segmental glomerulosclerosis (FSGS). Complications included hypervolemia requiring temporary renal replacement therapy and persistent nephrotic syndrome. A short course of empiric corticosteroids was stopped due to disease quiescence following biopsy results.

Discussion: ANCA-negative RV with crescentic GN is rare, and the optimal treatment is uncertain. Of the three described cases, all received corticosteroids, two were given cyclophosphamide, and one was treated with plasma exchange. To our knowledge, this is the first reported case utiliizing RTX induction. For our patient, rituximab resulted in remission of active crescentic disease, but not the development of chronic sequelae. While RTX remains an attractive potential treatment option for ANCA-negative RV, further investigation is warranted.

SA-PO768

A Case of Pulmonary-Renal Syndrome (PRS) in ANCA-Negative, Pauci-Immune Necrotizing Glomerulonephritis with High IntelliSep Index

Caroline Stafford, Hollis R. O'Neal, Christopher B. Thomas, Matthew Foy. *LSU Health New Orleans, Baton Rouge, LA.*

Introduction: Pauci-Immune Necrotizing Glomerulonephritis (PING) results from inflammatory vasculitis, often associated with antineutrophilic cytoplasmic antibodies (ANCA). ANCA-negative PING is rare. The role of neutrophils with PING is highly implicated in ANCA-negative cases. We present a case of ANCA-negative PING with PRS. It highlights early recognition and postulates potential methods for utilizing IntelliSep Index (ISI), a rapid (<10 min) assay quantifying immune activation via biophysical properties of leukocytes, to support treating PING.

Case Description: A 67-year-old woman with tobacco use and primary hypertension presented to the hospital with progressive dyspnea and hemoptysis. Labs included creatinine (Cr) 0.71 mg/dL, serum albumin 1.9 g/dL, Hgb 10.3 g/dL and WBC count 14.7 1000/uL; urinalysis positive for protein, large Hgb, 5-10 WBC/hpf and 10-20 RBC/hpf. Chest imaging showed bilateral moderate airspace opacities. ISI Index was 8.8, ISI Band 3. Blood and sputum cultures were negative. Given high suspicion for PRS from small vessel vasculitis, pulse dose steroids were started. Autoimmune workup including ANCA was negative. Renal biopsy revealed necrotizing crescentic glomerulonephritis with granular mesangial staining for C3, IgM, kappa and lambda, but all other stains negative. She was discharged on prednisone, cyclophosphamide (CYC) and

trimethoprim-sulfamethoxazole (TMP-SMX) for Pneumocystis prophylaxis. She had transaminitis 6 weeks later and CYC and TMP-SMX were held. CYC was resumed 2 weeks later and prednisone reduced. She represented to the hospital with a flare 3 weeks later. Workup with proteinuria, hematuria, and Cr elevated to 1.8 mg/dL. Repeat ISI Index was 9.0, ISI Band 3. Prednisone therapy was increased to 60 mg daily. Three months later, after prolonged steroid course and taper, her Cr improved to 1.3 mg/dL, pulmonary symptoms resolved, and she was transitioned to mycophenolate mofetil.

Discussion: Diagnosing PING requires high clinical suspicion to initiate therapy. Standard diagnosis of PING may take several days for biopsy and serology. This case shows a high ISI level on presentation as well as with her flare. Considering clinical context, ISI may be beneficial in stratifying patients to consider early PING induction treatment as well as monitoring treatment response.

SA-PO769

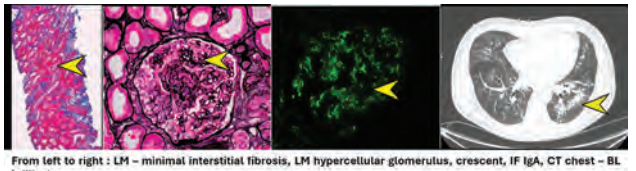
Co-occurrence of Crescentic IgA Nephropathy and Borderline Positive ANCA-Associated Vasculitis: A Perilous Pairing!

Divya Sharma Divyadarshini,[1] Gargi Sharma Priamvada,[2] Kirolos Iskander,[1] Zahid B. Ahmad.[1] *[1]The University of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]East Carolina University, Greenville, NC.*

Introduction: The convergence of IgA nephropathy (IgAN) and Antineutrophil cytoplasmic antibody associated vasculitis (AAV) represents a rare but clinically significant condition. This combination presents with severe clinical manifestations, characterized by biopsy-confirmed IgAN, serological positivity for ANCA, rapid progression of renal failure, and pronounced pulmonary involvement. In this case, we underscore the complexities in management and emphasize the grim prognosis associated with IgAN/ANCA-positive vasculitis.

Case Description: 46-year-old male with alcoholic cirrhosis presented with epistaxis, anemia, and rapidly increasing creatinine levels (from 6.26 mg/dl to 10 mg/dl within 3 days, baseline unknown) necessitating hemodialysis. Urine-protein creatinine ratio of 2.2 g/g, dysmorphic microhematuria, and borderline positive PR3-ANCA at 1.1 U (normal range: 0.0 - 0.9 U) were noted. Renal biopsy showed minimal interstitial fibrosis, endocapillary hypercellularity, 33% cellular crescents, and granular mesangial staining of IgA and C3 on immunofluorescence. CT imaging detected bilateral lung infiltrates. Bronchoalveolar lavage showed nasal ulcers and extensive diffuse alveolar hemorrhage (DAH). Crescentic IgAN with concurrent AAV was diagnosed. Despite aggressive treatment with high-dose steroids, cyclophosphamide, and plasmapheresis, the patient deteriorated due to persistent DAH complicated by infections, resulting in death.

Discussion: This case of IgAN/ANCA+ highlights the importance of thorough serological assessment and early kidney biopsy in individuals with acute pulmonary-renal syndrome. IgAN infrequently presents as rapidly progressive glomerulonephritis and indicates a poorer prognosis necessitating swift intervention. Per literature review, clinicopathological combination of IgAN/ANCA+ is associated with worse clinical outcomes like DAH and acute renal failure, when compared to IgAN/ANCA- or AAV. Management of such mixed glomerulonephritis is inadequately documented. While high-dose steroids, cyclophosphamide/rituximab, and plasmapheresis are potential treatments, their effectiveness is limited by the risk of fatal infections.



From left to right : LM – minimal interstitial fibrosis, LM hypercellular glomerulus, crescent, IF IgA, CT chest – BL infiltrates.

SA-PO770

Case Series of Avacopan in Dual-Positive Anti-glomerular Basement Membrane (GBM) and ANCA Disease

Lauren Floyd,[1] Louise R. Moore,[1] Ranjoy Sen,[1] Ajay P. Dhaygude,[1] Stephen P. McAdoo,[2] Adam Morris.[1] *[1]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; [2]Imperial College London, London, United Kingdom.*

Introduction: Anti-glomerular basement membrane(GBM) disease is characterised by rapidly progressive glomerulonephritis(RPGN) & pulmonary haemorrhage & up to 40% can have dual positivity with circulating ANCA antibodies. Treatment include steroids, plasma exchange(PLEX) & cyclophosphamide(CYC). The recent ADVOCATE trial showed Avacopan as a steroid-sparing agent but its effectiveness in other RPGNs including dual positive patients remains uncertain.

Case Description: We present 3 cases of dual positive ANCA & anti-GBM disease treated with Avacopan. The first was a 73yr old lady presenting with severe non-oliguric AKI(eGFR 5ml/min) and dual positivity with MPO-ANCA(Fig1). Renal biopsy showed focal segmental necrotising GN with added tubular injury. She was treated with CYC, rituximab & PLEX. Prior to admission she had a significant GI bleed with erosive gastritis & duodenal ulcers. Consequently, she was managed steroid free, opting for Avacopan as a steroid sparing agent. Case 2 was a 64yr old male presenting with AKI (eGFR 8ml/min) and dual antibody positive with MPO-ANCA. The biopsy showed fibrocellular & cellular crescents and linear IgG. He was treated with PLEX, CYC, rituximab & a rapidly weaning course of steroids alongside Avacopan(Fig.2) The final case was a 22yr old lady presenting with myalgia & cough progressing to pulmonary haemorrhage(Fig 3). She was anti-GBM & PR3-ANCA positive with significant anaemia & proteinuria. She received CYC, PLEX, rituximab & Avacopan alongside a 6week tapering course of steroids. She made a good recovered & is in remission with Avacopan as maintenance treatment

Discussion: We demonstrated the role of Avacopan in anti-GBM disease to facilitate rapid steroid weaning, even in those with severe disease. One patient was managed without steroids, a rare approach in the management of anti-GBM disease & all maintained independent renal function. We suggest Avacopan should be considered in the management of patients with dual positive antibodies

Figure 1: Trend in eGFR for case 1

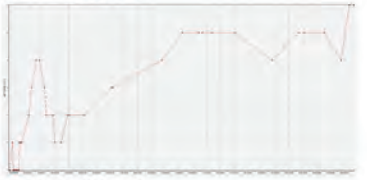


Figure 2: Trend in eGFR for case 2

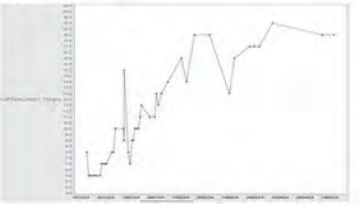
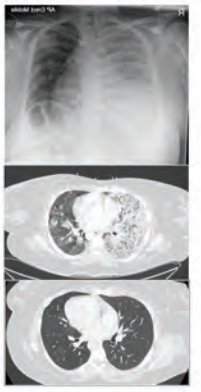


Figure 3: Pulmonary haemorrhage on chest imaging



SA-PO771

Evolving ANCA Serotype in a Patient with Dialysis-Dependent ESKD

Peter Dock,[1] James F. Dylewski.[2,1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Denver Health Main Campus, Denver, CO.*

Introduction: ANCA antibody serotype PR3 and MPO has become an increasing focus of care in patients with ANCA associate vasculitis (AAV) since antibody serotype seems to be a more reliable marker for prognosis, response rate, relapse risk, and outcome compared to a clinical diagnosis of GPA or MPA. Furthermore, these serotypes have been reported to have different geographic and genetic factors. Below is a case of a patient who switched serotypes which, to our knowledge, has not been previously described.

Case Description: Ms G is a 49 yo Latina female who initially presented in 2018 with diffuse alveolar hemorrhage and AKI. ANCA testing showed +MPO/+p-ANCA-AAV consistent with a clinical diagnosis of microscopic polyangiitis (MPA). Kidney biopsy was also consistent with ANCA associated pauci-immune GN. Unfortunately, Ms G's disease was difficult to control, and she suffered from multiple disease relapses despite maintenance therapies. While she would clinically improve with re-induction therapies, she remained serologically positive. In December 2019, after multiple disease flares, she became dialysis dependent. After approximately 1 year on dialysis, ANCA and MPO antibodies became negative, and she no longer had features of active AAV. (Table 1) In 2021, 2 years after becoming dialysis dependent, Ms G presented with increasing dyspnea. ANCA serologies were checked and yielded a new positive PR3 antibody (Table 1). Ultimately, her symptoms were attributed to non-ANCA related disease. However, she continued to have a PR3 antibody. In 2024, Ms G presented with upper respiratory symptoms and rash. Biopsy of the rash demonstrated a small vessel vasculitis consistent with AAV. though repeat ANCA testing was negative at that time.

Discussion: To our knowledge, Ms G is the first reported patient to have an evolution in her ANCA vasculitis from an MPO to a PR3 serotype. Additionally, this evolution occurred after the patient had been dialysis dependent for several years, a time when most AAV disease typically becomes inactive. This would suggest the AAV serotype in this patient represents a spectrum of disease rather than a distinct phenotype.

Table 1

Date	12/18	12/19	12/19	6/20	12/20	7/21	11/21	05/22	1/23	3/24
ANCA (ref.: <1:20)	p-ANCA; 1:160	p-ANCA; 1:320	ESKD on dialysis	p-ANCA; 1:320	<1:20	<1:20	<1:20	<1:20	p-ANCA; 1:80	<1:20
MPO (ref.: <19)	66	135		57	12	8	6	5	5	15
PR3 (ref.: <19)	2	0		0	2	1	87	616	58	15

SA-PO772

Rapidly Progressive Glomerulonephritis (RPGN) Due to Myeloperoxidase Anti-neutrophil Cytoplasmic Antibodies (MPO-ANCA)-Associated Vasculitis and Anti-glomerular Basement Membrane (GBM) Disease

Ji-Min Park,[1] Rafael Sancillo,[1] Jesse M. Wickham,[1] Sarwat Gilani.[2]
[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]The University of Texas Health Science Center at San Antonio, San Antonio, TX.

Introduction: RPGN is a type of nephritic syndrome characterized by rapid decline of kidney function with associated proteinuria, hematuria, and presence of urinary dysmorphic red blood cells/casts. RPGN caused by both MPO-ANCA associated vasculitis and anti-GBM disease (Goodpasture syndrome) is rarely reported and generally results in poorer outcomes. We present such a case in an otherwise healthy 32 year-old woman.

Case Description: A 32 year-old woman with no prior history of kidney disease presented with bilateral lower extremity edema and right flank pain of 1 day duration with associated gross hematuria. Physical exam showed 1+ bilateral lower extremity edema extending up to mid-shins. Initial labs revealed serum creatinine of 5.71 mg/dL (no prior baseline), ESR 62 mm/hr, CRP 68.9 mg/L, and urinalysis with >50 RBCs/HPF and 6-10 WBCs/HPF. Urine protein/creatinine ratio was 5.85 g/g. Additional labs showed elevated myeloperoxidase (MPO) antibody at 2.9 AI and positive IgG glomerular basement membrane antibody (anti-GBM) with negative serine protease 3 (PR3) antibody, cryoglobulins, anti-nuclear antibody, and double stranded DNA antibody. Infectious workup was negative for hepatitis, syphilis, HIV, and tuberculosis. Renal ultrasound showed bilateral echogenic kidneys. Computed tomography of abdomen and pelvis showed mild right renal hydronephrosis. Subsequent kidney biopsy showed crescentic, necrotizing, and sclerosing glomerulonephritis with linear glomerular basement membrane staining for IgG, consistent with anti-GBM nephritis. Interestingly, patient had an isolated renal involvement with no neurologic, cardiac, pulmonary, or gastrointestinal manifestations. She was ultimately diagnosed with RPGN secondary to anti-GBM disease with dual positivity for MPO-ANCA. She was treated aggressively with corticosteroids and cyclophosphamide followed by plasma exchange and rituximab, with reduction of antibody titers and disease regression.

Discussion: RPGN secondary to renal MPO-ANCA associated vasculitis and anti-GBM disease is extremely rare. Currently, there are only three reported cases in the literature. In the absence of signs suggestive of infection, clinicians should initiate prompt investigation of autoimmune causes of RPGN to guide optimal treatment.

SA-PO773

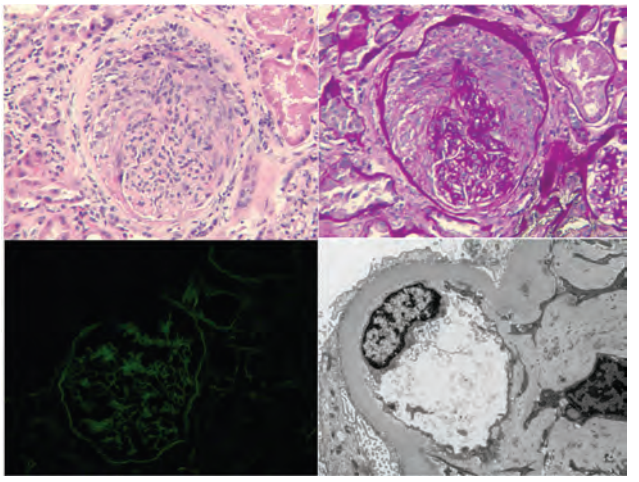
Sweet Syndrome-Associated ANCA-Negative Vasculitis

John Stathopoulos, Bhavana Movva, Casey N. Gashti, David J. Cimbaluk.
Rush University Medical Center, Chicago, IL.

Introduction: Sweet syndrome (SS) is characterized histologically as a neutrophilic dermatosis. It typically presents with fever and an asymmetric, painful, erythematous rash. Lab abnormalities include leukocytosis with predominant neutrophilia, elevated ESR and CRP. It can be drug-induced, infection-related, malignancy associated, or part of a systemic inflammatory disease. SS has been associated with ANCA-associated vasculitis (AAV). The syndrome can predate, occur simultaneously, or follow the onset of AAV. Treatment includes glucocortocoids (GC) in addition to other immunologic agents. We present, to our knowledge, the first case of ANCA-negative crescentic glomerulonephritis associated with sweet syndrome.

Case Description: A 52 y/o male presented with new onset weakness and painful skin rash. His autoimmune and malignancy work up were negative. A diagnosis of SS was established based on skin biopsy. Treatment comprised of GC with a 9-week taper. Four months later, he presented with fever, nausea, and vomiting. His serum creatinine was elevated to 4.48 mg/dL from a baseline of 1.2 mg/dL. Urinalysis showed proteinuria and hematuria. Kidney biopsy revealed pauci-immune necrotizing glomerulonephritis with crescents. Despite negative ANCA serology, treatment mimicked that of AAV, involving GC and rituximab, resulting in renal function and proteinuria improvement.

Discussion: Although association of SS with AAV has been previously reported, we present the first case of such association with ANCA-negative vasculitis. Treatment with GC and rituximab resulted in improvement of acute kidney injury and proteinuria, suggesting that similar immunosuppressive regimen may be efficacious regardless of the ANCA status.



H&E stain (top L) and PAS stain (top R) Active segmental necrotizing lesion with cellular crescents. IMF (Bottom L) pseudo-linear IgG staining. EM (Bottom R) Thickened GBM with no immune deposits

SA-PO774

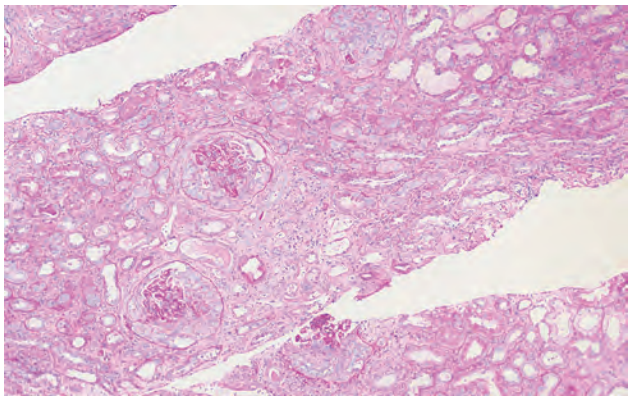
From Lice to the Heart and Kidneys

Carlos A. Rueda Mantilla, Zach Kisley, Carla L. Ellis, Yusra R. Cheema, Ayotunde Ositelu. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Introduction: Bartonella henselae and quintana, accounting for more than 95% of all Bartonella infections, are the most common cause of culture negative endocarditis in the US. There are many case reports of proteinase-3 (PR3) ANCA vasculitis associated with Bartonella endocarditis. Here we present a case of Bartonella-associated dual-positive myeloperoxidase (MPO) and PR3 renal-limited ANCA vasculitis

Case Description: A 55-year-old male with a history of stage 3 chronic kidney disease, heart failure with preserved ejection fraction (HFpEF), severe mitral regurgitation (MR), Hepatitis B on entecavir, and Hepatitis C presented with shortness of breath, lower extremity edema, and abdominal distention. Initial labs were consistent with a nephritic presentation, acute renal failure with Cr 9.32 mg/dL (baseline 1.7 mg/dL), hematuria, proteinuria, hypocomplementemia, elevated BNP, and hypoalbuminemia. Serologies were notable for strongly positive MPO and PR3 titers. Echocardiogram revealed severe MR with vegetations. Initial blood cultures were negative, but subsequent Bartonella quintana IgG (> 1:1,024) and microbial cell–free DNA were positive. The patient required urgent initiation of hemodialysis and underwent mitral valve replacement. Tissue confirmed Bartonella endocarditis and he was started on doxycycline and rifampin. Renal biopsy showed diffuse crescentic pauci-immune GN and diffuse podocyte foot process effacement. ANCA associated vasculitis (AAV) treatment included pulse dose steroids and induction therapy with RTX ten days following the initiation of definitive antimicrobial therapy and Avacopan two weeks following the completion of rifampin therapy. He demonstrated early signs of renal recovery at dischage

Discussion: We present a case of dual positive MPO/PR3 AAV associated with Bartonella endocarditis leading to diffuse crescentic pauci-immune GN. The severity of findings on renal biopsy prompted an aggressive approach to management despite underlying endocarditis and planned valvular surgery. Treatment with immunosuppression began within days of starting antimicrobial therapy and resulted in early signs of renal recovery nearing discharge. Early initiation of Avacopan therapy (post completion of rifampin to avoid its inducing effects) can be utilized to expedite a prednisone taper in patients with underlying infectious complications or need for adequate wound-healing



10x magnification of PAS stain showing diffuse cellular crescents

SA-PO775

Overlap Syndrome of ANCA-Associated Crescentic Glomerulonephritis, Autoimmune Hepatitis, and Rheumatoid Arthritis

Luis Ng, Duvuru Geetha. *Johns Hopkins Medicine, Baltimore, MD.*

Introduction: The most common renal histopathological in Rheumatoid Arthritis (RA) is Amyloidosis. Conflicting data exist about frequency of other types of glomerulonephritis in RA

Case Description: 46 y.o. female with focal nodular hyperplasia and hemangioma of the liver, hypothyroidism admitted with constitutional symptoms, joint and abdominal pain. Laboratory data revealed abnormal LFTs (AST 336, ALT 498, Alk Phos 227, Albumin 3.0, TBili 5.6, DBili 4.6) and Creatinine 1.8 mg/dL (baseline 1.4). UA: 2+ protein, moderate Hb, 1 WBC, 22 RBC, UPCR 2.2 g/g and UACR 1.3 g/g. Urine microscopy showed granular casts. Serologies were positive for RF 27, Anti CCP >2776.8, ANCA 1:320, MPO>100, Smooth muscle Ab 46.0. C3 and C4 were normala. Sed rate 91 mm/h, C-Reactive protein 3.1 mg/dL. Hepatitis A, B, C, and HIV serology was negative. Simultaneous liver-kidney biopsy obtained. Renal biopsy showed a crescentic glomerulonephritis with fibrous (6/9 glom) and fibrocellular crescents (3/9 glom); reported as inactive associated with chronicity features (45% IFTA) and no activity (endocapillary proliferation, necrosis or thrombi). IF was nonspecific and EM did not show deposits. Liver biopsy showed severe acute hepatitis with extensive necrosis. Given inactive crescents and no activity, the decision was to treat autoimmune hepatitis with Prednisone and start Rituximab for Rheumatoid Arthritis with some collateral benefit on the kidney function. After weeks of treatment, she had improvement in LFTs and symptoms resolved. Kidney function did not significantly change after treatment.

Discussion: This case displays a rare coexistence between three autoimmune entities including MPO ANCA related crescentic glomerulonephritis, Rheumatoid Arthritis and Autoimmune hepatitis. In majority of reported cases, ANCA vasculitis occurs a few years following the diagnosis of RA. Our case is unique for the simultaneous diagnosis of RA, ANCA vasculitis, and autoimmune hepatitis. The lack of improvement of renal despite Rituximab therapy is most likely related to the chronicity findings shown in her kidney biopsy, that was most likely damage from the ANCA related glomerulonephritis. RA can have different histopathologic renal manifestations and it is not limited to Amyloidosis. In the presence of significant proteinuria and hematuria, kidney biopsy needs to be considered in patients with RA.

SA-PO776

Crescentic Glomerulonephritis (GN) with Anti-glomerular Basement Membrane (GBM) Antibodies and ANCA: Double Trouble

Arundhati Sharma, Mugdha Kulkarni, Jacob A. Nysather, Manish Anand, Stephanie M. Bryant. *University of Cincinnati, Cincinnati, OH.*

Introduction: Crescentic GN is characterized by rapid deterioration of kidney function and is caused by antibodies against glomerular basement membrane (anti-GBM), immune complex or pauci-immune etiologies. We present a case of RPGN with anti-GBM Ab and Myeloperoxidase (MPO)-ANCA positivity.

Case Description: 37-year-old male with no prior medical history presented with abdominal pain, hematuria and oliguria. On admission, serum creatinine was 19.72 mg/dL and potassium 7.3 mEq/L. Urine with protein >500 mg/dL and hematuria. Hemodialysis(HD) was started for metabolic abnormalities. Serologies revealed ANA positive, MPO >8units, GBM-Ab >8units, and P-ANCA titer >1:640. Kidney biopsy was obtained after 3 sessions of HD and 10 days after presentation. Biopsy revealed 39/49 glomeruli with circumferential cellular crescents (fig 1) as well as necrotizing arteritis. Immunofluorescence showed GBM linear positivity with IgG 3+ (fig 2), kappa 3+, lambda 3+ and C3 3+. Electron microscopy showed breaks in GBM, and no immune complexes seen. He was transferred to our hospital for further management. Course was complicated by hemoptysis and retroperitoneal hematoma requiring embolization of left renal artery pseudoaneurysm. Steroid induction was promptly started. After stabilization, he received 18 sessions of plasmapheresis and oral Cytoxan 1 mg/kg daily with steroid taper resulting in a drop in anti-GBM Ab to 1.8units. He remains dialysis dependent.

Discussion: Anti-GBM Ab and ANCA associated GNs are rare, but approximately 20%-30% of patients with anti-GBM disease have MPO antibodies. Dual antibody positivity has a worse renal prognosis compared to patients with ANCA related GN. Patient survival is worse in those presenting with acute renal failure requiring dialysis. Our patient's age is much lower than the mean age of presentation for double positive cases. Prompt treatment needs to be started without waiting for biopsy due to fulminant nature of anti-GBM disease followed by longer maintenance therapy due to relapsing nature of ANCA disease.

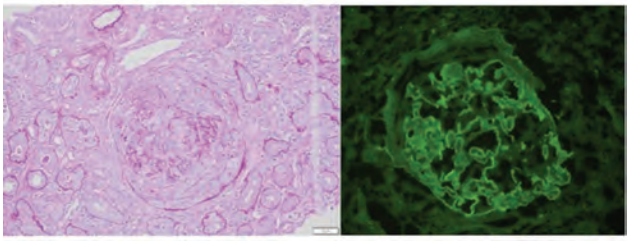


Figure 1(fibro cellular crescent), figure 2(linear pattern of anti GBM antibodies)

SA-PO777

Rapidly Progressive Glomerulonephritis Due to Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS) Masquerading as ANCA-Associated Vasculitis: A Rare Presentation

Sumbal Wajid, Aman Pal, Lilit Grigoryan, Swati Mehta, Krishnakumar D. Hongalgi. *Albany Medical Center, Albany, NY.*

Introduction: Hypocomplementemic urticarial vasculitis syndrome (HUVS) is an immune-complex mediated small-vessel vasculitis with low complement levels. Due to the rarity of HUVS, the existing literature on renal involvement is limited. We present a case of an 87-year-old male who developed rapidly progressive glomerulonephritis (RPGN) due to HUVS.

Case Description: An 87-year-old female was referred to the nephrology clinic with a creatinine surge to 3.5 mg/dL from 0.9 mg/dL a year prior. Urinalysis showed proteinuria and hematuria, with subsequent urine albumin-creatinine ratio of 2g/g and an unremarkable renal ultrasound. Immunological studies indicated normal C3, low C4, elevated p-ANCA and elevated MPO antibody. Concerns for RPGN in the context of ANCA-associated vasculitis (AAV) prompted a renal biopsy, revealing focal crescentic glomerulonephritis with mesangial C3-dominant immune complex deposition. A detailed history revealed episodes of burning facial rash lasing recurring over the past two years alongside arthralgias, weight loss, eye redness and floaters. Physical examination revealed periorbital edema and pitting edema to the ankles. Repeat lab assessment again showed elevated anti-MPO, now with both low C3 and C4 levels. Despite lab findings consistent with microscopic polyangiitis (MPA), the history of urticarial rash, periorbital edema, normal CRP, low complement levels, and C3-predominant immune complex deposition in the mesangium raised suspicion for HUVS. Subsequent testing confirmed low C1Q levels, supporting the diagnosis. Induction therapy was started with cyclophosphamide, rituximab, and steroids, followed with avacopan. She has demonstrated ongoing improvement in creatinine, most recently measuring 2.17 mg/dL.

Discussion: RPGN is characterized by a rapid decline in kidney function and although its etiologies are broad, 40-50% of cases in adults are deemed to be secondary to AAV. However, in our patient, renal biopsy findings contradicted the typical pauci-immune pattern, instead revealing immune complex deposits in the mesangium. This, in addition to the angioedema and low complements, raised suspicion for HUVS, as confirmed using the Schwartz criteria. This case highlights the need for HUVS as consideration of RPGN differentials and emphasizes the necessity for further research on optimal management strategies for this rare condition.

SA-PO778

Rare Biopsy Findings of IgA and C3 on Immunofluorescence in ANCA-Associated Vasculitis

Nazia Habib, Muhammad R. Khan, Sidrah Abid, Geovani Faddoul. *Albany Medical College, Albany, NY.*

Introduction: ANCA associated vasculitis includes GPA, MPA and renal limited vasculitis. It is a severe pauci-immune vasculitis with high mortality which requires prompt management. Some cases have been reported with immune deposits and glomerular C3 deposits. Such cases are now increasingly recognized and associated with worse outcomes. Very rarely there can also be glomerular IgA deposits. Immune

deposits of C3 and IgA are also seen in IRGN and IgA nephropathy which can also be associated with ANCA positivity. This poses a diagnostic challenge which requires ruling out infections as immunosuppressives can be detrimental in such cases.

Case Description: 55-year-old male admitted with recurrent upper respiratory symptoms started 2 months ago. He was initially treated with antibiotics for otomastoiditis. CT chest revealed cavitary lung lesions and was started on appropriate antibiotics for pneumonia. Admission wbc 18 10*3/UL, creatinine (Cr) 1 mg/dl and worsened to 9mg/dl, Positive ANCA 1:80 AI, PR3 30 U/ml, CRP 130mg/L. Anti GBM negative. Kidney biopsy revealed necrotizing and crescentic glomerulonephritis with leukocytoclastic vasculitis, C3/IgA-codominant glomerulonephritis, likely infection-related, mild to moderate interstitial fibrosis and tubular atrophy. Rheumatology and ID were consulted. Any active infection was ruled out before initiating patient on immunosuppressive regimen. He received cyclophosphamide, steroids with taper and transition to Avocapan, PLEX and rituximab. Renal function remained stable but had to be dialyzed once, Clinically, he improved and respiratory symptoms resolved.

Discussion: Our case is unique in which a multispecialty approach was used for management. Although Overlap of ANCA with IRGN possible, this patient received multiple courses of antibiotics during and prior to this admission with no improvement favoring ANCA vasculitis as primary diagnosis. There are no previous cases reported with PR+ ANCA vasculitis with glomerular C3 and IgA deposition. Clinical history, physical examination and characteristic biopsy findings were used together to promptly start management of ANCA associated vasculitis with stabilization of renal function and improvement in respiratory symptoms. A case like this poses a diagnostic challenge for physicians as initiating the appropriate treatment in a timely fashion is extremely important for a patient's recovery.

SA-PO779

Infective Endocarditis-Associated Pauci-Immune Crescentic Glomerulonephritis with Complete Remission after Immunosuppression

Raghunandan Konda, Huma Fatima, Dana V. Rizk, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Kidney disease due to infective endocarditis (IE) was first described over 100 years ago. Although initially believed to be primarily embolic, it later became clear that majority of cases represented focal, segmental, or diffuse proliferative glomerulonephritis. Currently, the most common kidney biopsy findings in IE are necrotizing and crescentic GN (~50%), followed by endocapillary proliferative GN (~40%). We describe a rare case of crescentic GN in the setting of renal limited PR3 ANCA Vasculitis (AAV) in a patient with Streptococcus mitis aortic valve (AV) infective endocarditis with complete renal recovery after valve replacement and immunosuppression.

Case Description: 24-year-old male with asthma presented with fevers, chills, and weight loss. Workup revealed bicuspid AV and aortic vegetation. Blood cultures were persistently negative, and he had no prior h/o IV drug use. He received antibiotic therapy, underwent mechanical AV replacement with lifelong anti-coagulation deemed necessary. PCR testing of native AV revealed Streptococcus Mitis. Despite source control and AV replacement, patient developed RPGN. Cr 4.7 mg/dL, Sr albumin 2.3 g/dL, UPCR 2519 mg/g, urinalysis revealed acanthocytes. C3 48 (low), C4 13. PR-3 25. Rest of comprehensive serological workup (incl. Anti-GBM) negative. Kidney biopsy revealed crescentic GN that was pauci-immune with no immune complex or electron dense deposits. Given source control of IE with antibiotics and valvular replacement, induction immunosuppression (IS) with intravenous cyclophosphamide [total - 3g] and glucocorticoids [pulse followed by oral taper] lead to serological remission of AAV [BVAS=0] and complete kidney function recovery with no further RBCs in the urine. He received intravenous rituximab [5 doses of 500 mg so far] for remission maintenance with no flare-ups so far.

Discussion: IE related pauciimmune crescentic GN carries a poor prognosis with a mortality rate of 40-50%. Outcomes have not really improved over time. Treatments have ranged from isolated antibiotic use [~ 60%] and antibiotics with supportive care [35%]. Data on use of IS is lacking and often shows mixed results. Through our case, we postulate the role of IS after early source control has been attained, especially in young patients with no other comorbidities.

SA-PO780

I ANCA Kidding: ANCA-Associated, Pauci-Immune Crescentic Glomerulonephritis with Normal Kidney Function Presenting with Transverse Myelitis

Timothy E. Yen, Maria Clarissa Tio, Ramya Krishna Velagapudi, Neville R. Dossabhoy. *The University of Mississippi Medical Center, Jackson, MS.*

Introduction: Microscopic polyangiitis (MPA) frequently (>80%) manifests with kidney involvement, often presenting with rapidly progressive glomerulonephritis. However, MPA can have a variable presentation with normal kidney function, underscoring the importance of recognizing the extrarenal manifestations of the disease.

Case Description: A 63-year-old Black female was admitted with a 2-week history of falls and progressive lower extremity weakness. Vital signs and electrolytes were normal with creatinine at a baseline of 0.8 mg/dL. Spinal MRI revealed longitudinally extensive transverse myelitis extending from the corticomedullary junction to the thoracic cord. A broad workup for inflammatory, neoplastic, and infectious etiologies was performed and revealed positive ANA (1:320), anti-RNP (1.2U), and anti-myeloperoxidase (1.5U) autoantibodies with P-ANCA positivity raising the concern for MPA with CNS involvement. The patient started plasma exchange (x6) and pulse steroids before being tapered to 1 mg/kg. Despite normal creatinine, nephrology was consulted due to hematuria (RBC >100) and pyuria (WBC >500) on urinalysis and 0.4g/g UPCR. Further, CT chest done for trauma/fall evaluation had revealed asymptomatic lung infiltrates which together with ANCA and renal findings raised concern for a pulmonary-renal syndrome. A transbronchial biopsy was performed first. The initial pathology report from our institution suggested capillaritis, but a second, specialty evaluation reported no vasculitis. The patient subsequently underwent a kidney biopsy which showed pauci-immune crescentic glomerulonephritis (5/20 glomeruli with crescents--3 fibrocellular/2 fibrous crescents; negative immunoglobulins and complements on immunofluorescence) with minimal (~5%) interstitial fibrosis/tubular atrophy. These findings were consistent with MPA and a rituximab-based regimen was started. At four months, the patient's neurologic sequelae have completely resolved while her kidney function has remained at baseline.

Discussion: Although MPA commonly involves the peripheral nervous system, severe central nervous system manifestations such as transverse myelitis are uncommon. In this case, early recognition of the underlying pulmonary-renal syndrome was crucial to ensuring adequate therapy and preserving kidney function.

SA-PO781

Mycobacterium Avium Complex (MAC)-Induced Pauci-Immune Necrotizing Glomerulonephritis

Said Sharawi, Khaled Al-Baqain, Zeid Khitan. *Marshall University, Huntington, WV.*

Introduction: Rapidly progressive glomerulonephritis (RPGN) is a rare syndrome with rapid loss of renal function that has a high rate of renal failure. Histologically, there are numerous glomerular crescents. It is classified according to immune complex deposition. Pauci-immune represents up to 80% of RPGN cases and the incidence in the US is around 7-10 cases per 1 million people per year. ANCAs are negative in approximately 10-30% of patients with pauci-immune necrotizing glomerulonephritis (PING).

Case Description: A 64-year-old male with COPD, OSA, CAD presented with a recent MAC diagnosis awaiting susceptibility. He was doing well until he started having pleuritic chest pain, dyspnea, foamy white sputum, fatigue, nausea, swelling of the lower extremities, and dark urine with reduced urine output. Labs were significant for creatinine of 9.42 from 0.78 a month earlier, BUN 101 from 12, negative ANCA, serology and blood cultures. Active UA. Negative renal ultrasound. PET/CT showed new cavitated lesions within the lungs, diffuse pleural thickening and nodular hypermetabolic activity demonstrated within the left hemithorax, hyperdense material within the right lobe of liver. Echo showed LV thrombus with no vegetations. A kidney biopsy showed severe crescentic GN with ATN and negative IF representing pauci-immune GN. A multidisciplinary team was formed including nephrology, infectious disease and ICU team to discuss this challenging case with recent MAC diagnosis and how to treat in the need of immunosuppression. The patient was started on hemodialysis and the decision was not to start immunosuppression.

Discussion: PING has no deposits or very scant deposits of IgM, IgG or C3 on IF. To our knowledge, our case is the first to link MAC with ANCA negative PING. In a recent unique case series, 9 patient was diagnosed with PING associated with an acute bacterial infection [Staph. A (4), E.coli (1), Klebsiella pneumoniae (1), Strep. parasanguinis (1), and Staph. Epi.(1)]. Bacterial infection-associated PING has no endocapillary proliferation or intense C3 glomerular deposition in contrast to postinfectious glomerulonephritis. Differentiating between infection-associated and other forms of PING is crucial in the management, as the use of immunosuppressive drugs without associated specific treatments may have negative consequences.

SA-PO782

Atypical ANCA-Associated Vasculitis Relapse in ESKD

Veena Aswath, Deanna N. Jones. *Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC.*

Introduction: Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) are a group of autoimmune diseases affecting small-sized arteries. Despite treatment, many patients have progressive kidney disease. In patients with renal-limited AAV, relapse is rare once dialysis is started. We present a patient with a granulomatous with polyangiitis (GPA) flare four years after diagnosis and one year after starting peritoneal dialysis (PD).

Case Description: A 73 year old male originally presented to the hospital with fatigue, elevated creatinine (3.0 mg/dl), microscopic hematuria (26-40 RBC) and non-nephrotic range proteinuria (800 mg/g). Work-up and kidney biopsy at that time were consistent with AAV. His induction treatment included intravenous (IV) cyclophosphamide for 6 months; and he continued prednisone as maintenance therapy, as he could not tolerate azathioprine. He continued to have mild hematuria and proteinuria, and progressed from chronic kidney disease stage 4 to ESRD three years later. He was started on PD; prednisone was stopped at that time. One year later, he presented with new onset hemoptysis for one week. Serology workup revealed elevated cytoplasmic-ANCA (1:4096), proteinase-3 antibody (4.5 units). Pulmonary hemorrhage was suggested on imaging and confirmed with bronchoscopy--all consistent with active AAV, despite no previous pulmonary involvement.

Discussion: Relapse is recurrence of signs or symptoms of active vasculitis in any organ system after remission is achieved, not due to another cause. Residual proteinuria can reflect active vasculitis or previous, scarred areas in the glomeruli. Risks of continued immunosuppression may outweigh benefits on kidney function. In this case, the patient had only a partial response to his initial treatment, as signified by persistent hematuria, proteinuria, and progression of kidney disease over the next few years. With new symptoms of systemic vasculitis a year later, could he have benefited from continued immunosuppression? However, relapse of renal-limited AAV is rare after progression to ESRD. Uremic toxins are thought to cause a quiescene of the immune system. This "functional" immunosuppression reduces risk of autoimmune disease relapse as compared to those with normal renal function. This case illustrates the need to consider AAV relapse in ESRD patients with recurrent or new systemic symptoms.

SA-PO783

Missed Primary Aldosteronism with HydrANCAzine Consequences

Elias Bassil, Sunny R. Parmar, Georges Nakhoul, Jonathan J. Taliercio, Jagmeet S. Dhingra, Ali Mehdi. *Cleveland Clinic, Cleveland, OH.*

Introduction: Primary aldosteronism (PA) is responsible for up to 25% of treatment resistant hypertension (TRH). However, less than 4% of eligible patients undergo screening. This leads to escalating antihypertensive regimens subjecting patients to otherwise circumventable side effects. We hereby present 3 cases of missed PA sub-optimally managed with hydralazine complicated by drug induced ANCA associated vasculitis (AAV).

Case Description: These are 3 cases of p-ANCA/MPO positive biopsy proven hydralazine induced pauci-immune glomerulonephritis sharing striking similarities (Table 1). All 3 had a diagnosis of TRH on 6 blood pressure medications on average. Notably, none were on mineralocorticoid receptor antagonists. Despite multiple providers spanning many specialties and suggestive biochemical profiles PA testing was not done. In addition to discontinuing hydralazine, significant immunomodulatory therapy was employed to achieve disease remission. PA was diagnosed thereafter, and blood pressure control achieved with only 2-3 medications (including an MRA). Patient #3 also underwent adrenalectomy for unilateral disease.

Discussion: Autonomous hyperaldosteronism has well documented deleterious end-organ effects. Underrecognized PA can lead to unwarranted side effects in attempts to control blood pressure with non-targeted and suboptimal treatments. These cases describe a potentially life-threatening idiosyncratic hydralazine side effect. More importantly they highlight the persistent poor rates of PA screening, underutilization of MRAs, and overreliance on agents relegated to the bottom of our antihypertensive arsenal. Realizing that PA can even have a milder phenotype without overtly obvious biochemical profiles, expanded screening to achieve an accurate diagnosis is instrumental in choosing the right therapy and circumventing significant adverse events such as hydrANCAzine.

	Patient #1	Patient #2	Patient #3
Age	71	65	61
Number of Antihypertensives (pre diagnosis)	7	5	6
Potassium Levels	3-3.5 mEq/L	3-3.3 mEq/L	2.5-3 mEq/L
Aldo/PRA	15	26	130
Number of Antihypertensives (pre diagnosis)	3	3	2
AAV Presentation	AKI	AKI + Alveolar Hemorrhage	AKI + Arthralgias
AAV Management	Prednisone PLEX Cyclophosphamide Rituximab	Prednisone PLEX Cyclophosphamide Rituximab	Prednisone
Kidney Outcomes	CKDIIIa	CKDIIIb	CKDIIIb

Table 1 - Patient Characteristics

SA-PO784

Unveiling the Enigma: ANCA-Negative Granulomatosis with Polyangiitis

Ali Shah, Shila Simkhada, Wajeeha Shahid. *The Wright Center for GME, Scranton, PA.*

Introduction: Granulomatosis with polyangiitis (GPA) is a systemic inflammation of small to medium blood vessels, often linked with anti-neutrophil cytoplasmic antibodies (ANCAs). Diagnosis can be challenging due to diverse symptoms, potentially delaying treatment. Tissue biopsy typically reveals necrotizing granulomatous inflammation, though about 10-20% of cases lack ANCAs complicating identification.

Case Description: A 78-year-old man with COPD, hypertension, high cholesterol, and psoriasis experienced recurrent upper respiratory symptoms, denying hemoptysis or dyspnea. Despite using antihistamines, he had no relief and sought help from his primary care provider. He also had painless hematuria, leading to a scheduled cystoscopy. His recent blood work, ordered by his showed a decrease in hemoglobin from 11.3 to 9.7, an increase in serum creatinine from a baseline of 1.0 to 4.35, and a decrease in glomerular filtration rate (GFR) to 12 prompting an ER visit. Urinalysis revealed proteinuria at 1+, hematuria at 3+, and a high concentration of red blood cells. Renal ultrasound showed non-obstructive right renal calculi without hydronephrosis. Although his potassium levels remained stable, his creatinine continued to worsen (now 7.1), and his urine output decreased, prompting initiation of hemodialysis. Tests for hepatitis and HIV were negative, as were serum tests for various autoimmune markers including ANCA, PR3, anti-MPO, anti-GBM antibodies, and complement levels. Kidney biopsy revealed pauci-immune glomerulonephritis with circumferential fibrous crescents. He was subsequently treated with high-dose intravenous steroids and rituximab in the setting of ANCA-negative Granulomatosis with polyangiitis.

Discussion: The inflammation seen in GPA prompts an immune response, often leading to high ANCA titres. Around 82–94% of GPA patients are ANCA positive, leaving about 10% ANCA negative. These cases without ANCA are often overlooked. Initial symptoms vary, including sinusitis (67%), pulmonary signs like cough, renal failure, skin/mucous membrane ulcers, and abdominal pain with vasculitis. The diagnosis of GPA includes urinalysis showing red blood cell casts, abnormal chest x-ray, oral/nasal ulcers, and granulomatous inflammation on biopsy. Survival without treatment averages 5 months, with a 20% 1-year survival rate. Treatment involves corticosteroids and immunosuppressants.

SA-PO785

When Interstitial Nephritis Hides Vasculitis: A Case of ANCA-Associated Vasculitis

Zachary D. Stello, Deepak Chandramohan, Huma Fatima, Ashita J. Tolwani. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: We present a case of anti-myeloperoxidase (MPO) antibody-positive Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) presenting as subacute interstitial nephritis on renal biopsy.

Case Description: The patient is a 75-year-old male with a history of pulmonary fibrosis, hypertension, dyslipidemia, and coronary artery disease who presented with worsening renal function following a recent hospitalization where he was diagnosed with new-onset polymyalgia rheumatica. Labs showed a serum creatinine of 1.5mg/dL (known baseline of 1.0), and urinalysis showed trace protein and 1+ hematuria. Acute kidney injury was initially presumed to be secondary to NSAIDs and was stopped. Since the hospital discharge, he also experienced worsening peripheral neuropathy-like symptoms and a new-onset right foot drop. He was seen a week later, and his serum creatinine had continued to rise and was 2.8 mg/dL. His urine protein-creatinine ratio was 688mg/g, and his symptoms remained unchanged. Urine microscopy was negative for dysmorphic RBCs and casts. Serologic studies returned and were notable for perinuclear-ANCA titer of 1:160, rheumatoid factor level of 56U/mL, and anti-MPO antibody level of 33U/mL. Renal biopsy revealed focal subacute tubulointerstitial nephritis with no evidence of crescents, negative immunofluorescence for IgA, IgM, IgG, C3, C1q, and fibrinogen and electron microscopy showed subtotal foot process effacement. He was treated with intravenous methylprednisolone daily and then transitioned to a prednisone taper. Additionally, he was given Rituximab 1000mg with plans for continuation. About 1 month later, his renal function and overall symptom burden improved, and the anti-MPO antibody titers became undetectable.

Discussion: This case represents a rare presentation of AAV with interstitial nephritis and without classical crescentic glomerulonephritis. These patients are usually older and have more nonspecific symptoms.

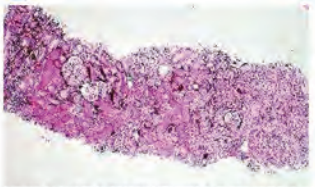


Figure 1: There is patchy interstitial mononuclear inflammatory infiltrate. The glomeruli are unremarkable. Jones Silver x10

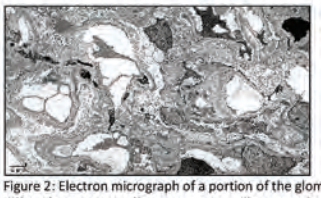


Figure 2: Electron micrograph of a portion of the glomerulus shows features of podocyte injury as diffuse foot process effacement, microvillous transformation and cytoplasmic vacuolization. TEM x2500

SA-PO786

B Cells Unhinged: Concurrent PR3+ ANCA-Associated Vasculitis and Diffuse Large B Cell Lymphoma Treated Effectively

Eliot Sachsenmeier, Yinelka G. Silverio De Castro, James Drakakis, Minesh Khatri. *NYU Langone Hospital - Long Island, Mineola, NY.*

Introduction: We present a case of PR3+ ANCA vasculitis diagnosed simultaneously with diffuse large B-cell lymphoma (DLBCL). Both improved after rituximab and chemotherapy. This appears to be the third case of DLBCL-associated ANCA vasculitis described in the literature. The mechanisms of this association and implications for therapy warrant future investigation.

Case Description: 71-year-old man with hypermetabolic lung and left tonsillar masses on outpatient PET-CT presented for fatigue, anorexia, and weight loss. Laboratory testing showed an elevated creatinine of 5.87 mg/dL. Serologic workup revealed an elevated proteinase-3 level of 183. CT chest confirmed a spiculated right upper lobe nodule measuring 3.1 cm with architectural distortion. He received three dialysis treatments and was started on pulse dose steroids. He underwent renal and lung biopsy, showing diffuse necrotizing and crescentic pauci-immune glomerulonephritis (Fig. 1), and pulmonary parenchyma effaced by sheets of large, atypical B-lymphocytes compatible with DLBCL. Two months later, after daily prednisone, 4 doses of weekly rituximab, and 2 cycles of Pola-CHP, his creatinine was 1.31 mg/dL. Repeat PET-CT showed complete resolution of the hypermetabolic left tonsillar mass and near complete resolution of the right upper lobe mass.

Discussion: While uncommon, malignancy is diagnosed more frequently in patients with ANCA vasculitis, especially granulomatosis with polyangiitis (GPA). The most common cancers diagnosed include bladder cancer, non-melanoma skin cancer, leukemia, and lymphoma. Association with the latter two may relate to overexpression of PR3 in response to granulocyte colony stimulating factor. The overexpression of PR3 may trigger an immune response that harms normal and malignant tissue. Alternatively, PR3-specific B cell clones may proliferate to become lymphoma. Our patient's improvement with combination therapy may support a common cause.

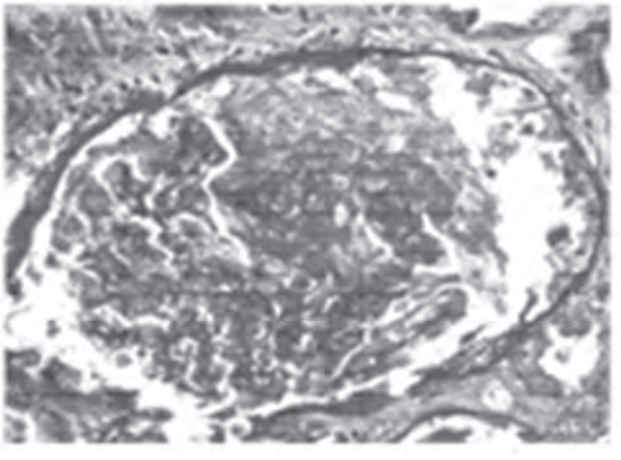


Fig. 1

SA-PO787

Uncommon Presentation of Pauci-Immune Crescentic Glomerulonephritis in a Young Adult with Normal Kidney Function

Nicholas P. James, Ubaid Naeem, Vishwajeeth Pasham, Natalie T. Freidin. *Medical University of South Carolina, Charleston, SC.*

Introduction: Crescentic glomerulonephritis is common in pauci-immune reno-pulmonary disorders, typically presenting with acute kidney injury (AKI) and diffuse alveolar hemorrhage (DAH). We present a case of pauci-immune crescentic glomerulonephritis (PICGN) with migratory polyarthralgia, DAH and remarkably preserved kidney function.

Case Description: 19 year old male presented with seborrheic dermatitis and polyarthralgia with associated recurrent "sinus infections." Workup revealed microscopic hematuria, nephrotic range proteinuria (>5g/24 h), serum creatinine (0.8-1 mg/dl), and positive serology for proteinase-3 (PR3) and c-ANCA. Later developed hemoptysis with bronchoscopy notable for diffuse alveolar hemorrhage. Renal biopsy showed fibro-cellular crescents in 34/45 glomeruli consistent with pauci-immune crescentic GN. Treated with cyclophosphamide and methylprednisone along with plasma exchange with subsequent improvement in symptoms and proteinuria.

Discussion: PICGN is typically associated with rapid eGFR loss correlated with extent of crecent formation. Despite renal biopsy Figure 1 revealing extensive crescents GFR was preserved. Main prognostic factor in PICGN is clinical vigilance and maintaining low threshold for aggressive treatment. Literature review suggests renal biopsy if clinical concern for ANCA vasculitis regardless of presenting renal function. Our case highlights the clininical importance of renal biopsy in long term prognostication and significant pathologic findings despite preservation of GFR. In a cohort of 70 biopsy proven PICGN patients, mean serum creatinine at presentation was 5.5 ± 2.1 mg/dl and mean proteinuria of 2.5 g/24 h. This signifies the importance of clinical diagnosis and management in atypical presentation of cases. The successful management of this case, involving the identification and subsequent initiation of cyclophosphamide, pulse dose steroids, and plasma exchange, highlights the importance of early and aggressive treatment to prevent progression and preserve renal function.

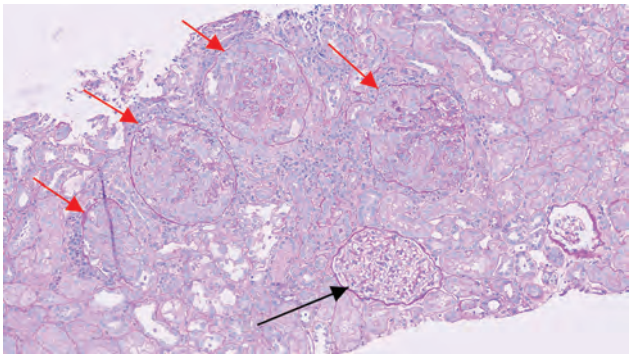


Fig. 1

SA-PO788

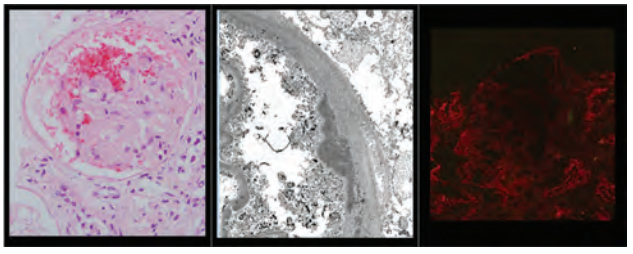
ANCA-Negative Pauci-Immune Crescentic Glomerulonephritis in a 26-Year-Old Postpartum Woman Treated with Oral Steroid and Azathioprine

Joel John C. Mejos, Ruben A. Maguad, Grecia Darunday. *Perpetual Succour Hospital, Cebu City, Philippines.*

Introduction: Pauci-immune crescentic glomerulonephritis (PICGN) is a rapidly progressive condition leading to rapid loss of kidney function within days to weeks and potentially life threatening. PICGN is an idiopathic form of crescentic GN that typically lacks significant immune deposits within glomeruli and often associated with antineutrophil cytoplasmic antibody (ANCA). However, some patients with PICGN are ANCA negative. Treatment for PICGN with or without ANCA includes IV methylprednisolone pulse therapy followed by tapering of oral steroid and cyclophosphamide either IV or orally.

Case Description: A 26 year old Filipina presented with anuria, jaundice and elevated creatinine hours after an emergency cesarian section secondary to arrest of labor. She had BP elevation, edema and blurring of vision. No other signs and symptoms. Her D-dimer, phosphorus and triglycerides were high. Coomb's test are negative, C3/C4 are normal. She underwent hemodialysis (HD) for couple of sessions until her clinical status improved. Renal biopsy showed PICGN with cellular crescents and global glomerulosclerosis. P and C-ANCA were negative. She was given oral steroid and azathioprine (AZA) for 6 months which showed remarkable clinical improvement. Serum creatinine fall to 5mg/dL from 10mg/dL, UPCR to 0.8mg/dL from 3.9 mg/dL. HD was discontinued with stable kidney function and continuously monitored as outpatient.

Discussion: PICGN is the most common cause of RPGN in adults and often associated with the presence ANCA's. Around 10-30% of patients with PICGN lack the ANCA's. The mechanisms of ANCA-negative PICGN are still vague. Neutrophils (PMNs) are the major effector cells in ANCA-positve PICGN. PMNs are also thought to be the major effector cells in ANCA-negative PICGN. The presence of PMNs in pathological lesions exist separately from circulating ANCA's and may include other autoantibodies or T-cell dependent mechanisms. Treatment of patients with ANCA-negative PICGN are usually based on those patients who are ANCA-positive. In our patient, oral steroid and AZA have shown excellent results.



SA-PO789

Pauci-Immune Crescentic Glomerulonephritis Linked to Candida parapsilosis Fungemia

Long Qian,[1] Hugh Carey.[2,1] *[1]Yale New Haven Hospital, New Haven, CT; [2]Metabolism Associates, New Haven, CT.*

Introduction: Infectious endocarditis (IE) typically correlates with infectious glomerulonephritis (GN), presenting as membranoproliferative GN (MPGN) with positive C3 and immunoglobulin staining. However, there are rare instances of pauci-immune GN associated with infectious endocarditis, sometimes with ANCA positivity, but occasionally negative for any ANCA or PR3 or MPO. Here we present a case of Candida parapsilosis endocarditis associated with p-ANCA positive, PR3-negative, MPO-negative pauci-immune GN.

Case Description: A 59-year-old man with a history of intravenous drug use on methadone, compensated cirrhosis due to HCV and alcohol, and HIV, presented with abdominal pain. Creatinine was newly elevated to 4.4 mg/dL (baseline 0.8). Echocardiogram revealed a 1.1 x 0.7cm aortic valve vegetation. Blood cultures grew Candida parapsilosis. Serological testing showed negative PR3 and MPO, positive p-ANCA (1:40), low C3, normal C4, negative cryoglobulin, negative HIV, HBV, and HCV PCR. Kidney biopsy showed crescentic necrotizing GN with negative to trace immunofluorescence for immunoglobulins, C3, and kappa and lambda, and electron microscopy showed no deposits. Immunosuppression was withheld due to fungemia persistent for 4 weeks despite receiving liposomal amphotericin B, flucytosine, and fluconazole. Hemodialysis (HD) was started 3 weeks post-presentation for uremia. After blood cultures cleared, he was started on 60mg/day of prednisone. However, he later developed methicillin-sensitive Staphylococcus aureus bacteremia, thus prednisone was tapered. He received cefazolin with continued antifungals. Aortic valve replacement was performed 2 months post-presentation without complications. He received one session of HD post-surgery but had kidney recovery and HD was stopped. He completed 6 weeks of amphotericin; fluconazole continues for lifelong suppression. He remains off HD.

Discussion: Pauci-immune necrotizing GN is a rare cause of AKI associated with IE. To our knowledge this is the second reported case of MPO, PR3 negative GN associated with Candida parapsilosis IE. The potential mechanism of IE triggering ANCA is unknow and has been hypothesized to be via autoantigen complementarity or molecular mimicry. For treatment, balancing immunosuppression against ongoing infection can be challenging. Favorable prognosis may be achieved with definitive infection control and cautious immunosuppressive therapy.

SA-PO790

Not-So-Pauci-Immune Crescentic Glomerulonephritis: A Management Challenge with Poor Kidney Survival

James B. Hughes, Megha R. Joshi. *Walter Reed National Military Medical Center, Bethesda, MD.*

Introduction: Glomerulonephritis (GN) caused by antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV) classically presents on renal biopsy as a pauci-immune GN. However**,** glomerular immune complex deposition is becoming increasingly recognized as a potential pathologic presentation. Studies have reported significant immune complex deposition (26%-41%) in patients diagnosed with AAV. Reported immune deposits on direct immunofluorescence (DIF) have included IgG, IgM, IgA, C3, C4, and C1q in varying combinations. Higher degrees of proteinuria and worse renal outcomes have been associated with reported immune complexes on DIF in AAV patients, particularly with myeloperoxidase (MPO) positivity. Low serum C3 and glomerular IgG deposits are also indicators of poor renal prognosis.

Case Description: We present a patient, previously healthy, who was hospitalized with hypertensive emergency, mixed nephritic and nephrotic syndrome, and acute renal failure requiring initiation of hemodialysis. Labs were notable for MPO positivity with normal C3 and C4. All other serologies were negative. The patient was initiated on empiric induction with intravenous cyclophosphamide and methylprednisolone. Renal biopsy revealed a crescentic GN and DIF positivity for IgG, C3, C1q, kappa, and lambda. Despite induction therapy for over three months duration, the patient remained dialysis dependent with continued positive MPO serologies. Rheumatology evaluation revealed no evidence of extrarenal disease. He was transitioned to mycophenolate mofetil maintenance therapy and is undergoing evaluation for renal transplantation.

Discussion: This case exemplifies the severe nature and therapeutic challenge posed by ANCA-associated RPGN with immune complex deposition and may indicate that current standard therapies may not be adequate for this pathologic variant. Further research is needed to elucidate effective immunosuppressive therapy for these patients.

SA-PO791

First Reported Case of Rapidly Progressive Glomerulonephritis (RPGN) Due to Combined Renal-Limited ANCA-Associated Vasculitis and Anti-glomerular Basement Membrane (GBM) Disease in a Young Man with Koolen-de Vries Syndrome

Vijaya Chelikani, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Koolen-de Vries syndrome (KdVS) is characterized by congenital malformations, developmental and intellectual disability, hypotonia, epilepsy, and behavioral features. Other findings include speech and language delay (100%), epilepsy (~33%), congenital heart defects (25%-50%), and renal and urologic anomalies (25%-50%) that include cryptorchidism, hypospadias, hydronephrosis/VUR, and renal duplication. Concomitant glomerular disease has not been reported to date. We describe the first case of combined renal limited ANCA Vasculitis (AAV) and Anti-GBM Disease in a patient with KdVS.

Case Description: A 24-year-old male with KdVS and morbid obesity presented with reduced energy levels and rapid loss of kidney function. He did not have pulmonary manifestations including hemoptysis. His baseline serum creatinine level was unknown. On presentation, Sr Cr 4 mg/dL [was 1.7 mg/dL 1 month prior], Sr albumin 4.3 g/dL, UACR 346 mg/g and UPCR 755 mg/g. Urinalysis revealed acanthocytes. Serological workup revealed ANA (+), 1:320 [homogenous], negative ds-DNA, c-ANCA >1:1280; p-ANCA 1:220; anti-MPO titer of 96, anti-PR-3 titer of 23, anti-GBM titer of 4.7. Remainder of comprehensive serological testing was negative. Kidney USG revealed mild right pelviectasis. Patient refused PLEX and kidney biopsy. Pulse dosing of methylprednisolone and one dose of intravenous cyclophosphamide 1000 mg was given followed by oral cyclophosphamide at 200 mg/day. After 8 months, UPCR 600 mg/g, no acanthocyturia; he has attained serological remission of his MPO, PR-3, and Anti-GBM serologies and has a Sr Cr stable at 2.4 mg/dL.

Discussion: AAV with concomitant anti-GBM disease is a rare, potentially life-threatening disease. Prompt diagnosis with a kidney biopsy is warranted to ascertain extent of cellular activity. Early treatment with PLEX, cyclophosphamide, and glucocorticoids is warranted. Dual AAV (+) Anti-GBM mandates immunosuppression for remission maintenance as well as portend a poor prognosis. We describe the first case of RPGN due to combined renal limited AAV and Anti-GBM Disease in a patient with Koolan-De Vries Syndrome, and the associated challenges with treatments.

SA-PO792

A Case of Bartonella henselae Infection-Related Glomerulonephritis and Endocarditis with Negative Blood Culture Mimicking PR3-ANCA-Associated Vasculitis

Yui Mohri, Shinya Yamamoto, Keisuke Morita, Motoko Yanagita. *Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.*

Introduction: A case of *Bartonella henselae* infection-related glomerulonephritis and endocarditis with negative blood culture mimicking PR3-ANCA associated vasculitis.

Case Description: A 70-year-old female with a history of aortic stenosis was admitted to our hospital because of fever and fatigue. The laboratory data revealed cytopenia and an elevated creatinine level from 0.50 mg/dL to 0.97 mg/dL with hematuria and urinary protein of 0.5 g/gCr. Immunological tests revealed positive PR3-ANCA (52 U/mL), rheumatoid factor (90.4 IU/mL), and reduced C3 (71.7 mg/dL). Blood culture was negative. Renal biopsy revealed endocapillary proliferation and endothelial cell swelling without crescent formation. Immunofluorescence showed the deposition of IgM and C3c on the capillary wall. The pathological diagnosis was consistent with IRGN. Considering the habit of keeping 30 wild cats, blood polymerase chain reaction (PCR) testing was performed, which was positive for *B. henselae*. Echocardiography and brain MRI revealed newly noted aortic valve regurgitation and subacute cerebral infarction. The diagnoses of *B. henselae* IRGN and IE were confirmed. We initiated rifampicin and doxycycline, which were eventually changed to gentamycin and minocycline due to

adverse events of nausea and vomiting. Cytopenia, renal function, and urinalysis results improved. Subsequently, the patient underwent aortic valve replacement, and the excised valve was positive for *B. henselae* PCR.

Discussion: The differential diagnosis of PR-3 ANCA-positive IRGN and AAV is often challenging, particularly in cases with negative blood or tissue cultures. *B. henselae* cannot be easily isolated from clinical specimens owing to its fastidious nature. In the present case, PCR testing and renal biopsy were essential for confirming *B. henselae* infection and treatment decisions.

SA-PO793

Correlations in Histology and Complement Biomarkers in C3 Glomerulopathy

Jillian R. Hall, Monica D. Hall, Lauren O. Fergus, Patrick D. Walker, Yuzhou Zhang, Richard J. Smith, Carla M. Nester. Molecular Otolaryngology and Renal Research Laboratories. *University of Iowa Health Care, Iowa City, IA.*

Background: C3 Glomerulopathy (C3G) is characterized by complement dysregulation and C3 deposition in glomeruli. We reviewed characteristics of baseline kidney biopsies to determine whether features of activity and/or chronicity correlate with clinical parameters and/or complement biomarkers at presentation.

Methods: Data from the University of Iowa's C3G Natural History Study were used. Criteria for entry included baseline native biopsy diagnosis of C3G and complement biomarkers within 1 year of biopsy. Patients with a history of dialysis, transplant, or anti-complement therapy were excluded. Significance was assessed using Pearson correlation coefficients with two-tailed p values (95% confidence) and one-way ANOVA analysis; p-values <0.05 were considered significant.

Results: 57 of 104 subjects (54.8%) presented with an activity score of ≥9; 18 (17.3%) presented with a chronicity score of ≥4 (the a priori determinants of increased risk for progression to renal failure). Higher activity scores were associated with elevated C5Nefs (p = 0.012, R = 0.255) and soluble C5b-9 (p = 0.013, R = 0.259) levels. Higher chronicity scores were associated most strongly with an increase in Ba (p = 8.183e-10, R = 0.677) and a lower GFR (p = 1.665e-9, R = -0.558) and less strongly with increased C3 (p = 0.022, R = 0.265), C5 (p = 0.014, R = 0.331) and Bb (p = 0.037, R = 0.263) levels, and decreased C5Nefs (p = 0.012, R = -0.262 and soluble C5b-9 (p = 0.026, R = -0.232) levels.

Conclusions: The association of higher C5Nefs and soluble C5b-9 levels with increased activity scores is consistent with terminal pathway activity being a driver of inflammation, while the association of increased chronicity scores with a lower GFR and higher Ba reflects declining renal function independent of complement activity. While the increase in C3 and C5 and the decrease in soluble C5b-9 levels reflect decreased complement activity, Bb levels suggest some component of continued alternative pathway activity. In aggregate, these data support a role for complement biomarker testing in C3G.

Funding: NIDDK Support

SA-PO794

Clinical and Histological Predictors of Outcomes in C3 Glomerulopathy

Malak A. Ghaddar,[1,2] Hannah J. Lomax-Browne,[5] H. Terence Cook,[5] Erica Daina,[3] Marina Noris,[3] Giuseppe Remuzzi,[3] Manuel Praga,[4] Fernando Caravaca-Fontan,[4,6] Dilshani Induruwage,[2] Matthew C. Pickering,[5] Sean Barbour.[1,2] *[1]The University of British Columbia, Vancouver, BC, Canada; [2]BC Provincial Renal Agency, Vancouver, BC, Canada; [3]Istituto di Ricerche Farmacologiche Mario Negri Centro Aldo e Cele Dacco, Ranica, Italy; [4]Universidad Complutense de Madrid Facultad de Medicina, Madrid, Spain; [5]Imperial College London Department of Immunology and Inflammation, London, United Kingdom; [6]Hospital Universitario 12 de Octubre Servicio de Nefrologia, Madrid, Spain.*

Background: C3 glomerulopathy (C3G) is a rare disease that has significant overlap with idiopathic membranoproliferative glomerulonephritis (MPGN). Risk factors for kidney outcomes remains poorly defined, limited by small cohorts. We aimed to determine risk factors for kidney outcomes and to incorporate them into a prediction model

Methods: Using a cohort of 225 patients with C3G or idiopathic MPGN from three international centers, we evaluated the association between clinical and histologic variables at biopsy and the composite outcome of 30% decline in eGFR or ESKD using Cox proportional hazards models. A prediction model was derived and internally validated through bootstrap resampling

Results: In a multivariable model, lower eGFR, paraprotein presence, and interstitial fibrosis were associated with higher risk of outcome, while native (versus transplant) disease and lower C4 levels were associated with lower risk (Table1). The prediction model including these variables performed well (R^2_D: 53.14%, C-statistic: 0.84 (95% CI 0.82-0.86), integrated calibration index: 0.31), maintaining robustness after internal validation. Adding proteinuria over time showed that a 50% reduction from baseline to <1g/day was associated with a lower risk of outcome (HR 0.35, 95% CI 0.12-0.97)

Conclusions: In the largest C3G/MPGN study to date, baseline eGFR, paraprotein, interstitial fibrosis, low C4 and transplant status were independently associated with kidney outcome. These factors can be used in a prediction model to predict individual patient risk. A 50% reduction in proteinuria to <1g/day was associated with lower kidney risk, suggesting it may be an evidence-based definition of proteinuria remission to use in clinical trials

Covariates for the risk of progression to the composite outcome in a multivariable model

Parameter	Adjusted HR (95% CI)	P value
eGFR (per 1 log base 2-unit decrease)	2.11 (1.66-2.67)	<0.001
Native kidney (versus transplant)	0.35 (0.20-0.60)	<0.001
Paraprotein	4.42 (2.00-9.77)	<0.001
Low C4	0.51 (0.29-0.90)	0.02
Interstitial fibrosis		
1	2.03 (1.03-4.01)	0.04
2	3.01 (1.56-5.83)	0.001
3	4.68 (2.05-10.68)	<0.001

Interstitial fibrosis score: 0 (<10%), 1 (10%-25%), 2 (26%-50%) and 3 (>50%)

SA-PO795

Clinical Burden of Native vs. Post-transplant Complement 3 Glomerulopathy (C3G) in the United States: A Retrospective Claims Analysis

Briana C. Ndife,[1] Anirban Bose,[1] Karishma Thakkar,[1] Rahul Khairnar,[1] Xiaolei Li,[2] James B. Young,[2] Hemanth Nair,[2] Mohanram Narayanan.[3] *[1]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [2]Clarivate, PLC, Toronto, ON, Canada; [3]Baylor Scott & White Medical Center Temple, Temple, TX.*

Background: C3G is caused by overactivation of the alternative complement pathway leading to deposition of C3 in the glomeruli. It is a rare disease; its clinical burden has not been well studied. Using medical claims data, this analysis characterized disease progression in a US cohort of patients (pts) with C3G in native kidney (NK) and post-transplant (TK).

Methods: We performed a retrospective cohort analysis of pts ≥12 years of age, diagnosed with C3G (defined by diagnosis codes) within the Clarivate Real-World Data Product database (Jan 2017–Sep 2022). Included pts had database records for ≥12 months (mo) prior to, and ≥6 mo post, the index (date of diagnosis). Pt demographic/clinical characteristics were assessed at index and stratified by transplant status (NK, TK). Time to chronic kidney disease (CKD) progression and/or kidney failure was assessed using Kaplan–Meier analyses.

Results: Of 350 pts with C3G, 244 (69.7%) had NK and 106 (30.3%) had TK; median follow-up was 23.7 mo (interquartile range: 13.9–46.9). Pt characteristics are shown in the **Table**. The median time to first CKD progression was 13.3 mo (95% confidence interval [CI]: 4.5–28.3) for NK and 3.5 mo (95% CI: 1.0–25.5) for TK. A higher proportion of TK pts (90.9%) progressed to kidney failure vs NK (45.8%). Median time to kidney failure was shorter in pts with TK C3G (27.1 mo [95% CI: 12.2–45.0]) vs NK C3G (43.5 mo [95% CI: 32.9–85.7]).

Conclusions: Disease progression to a higher CKD stage and/or kidney failure is faster in pts with TK C3G compared to pts with NK C3G. Given the disease characteristics and progression, these data highlight the need for novel therapies to treat both NK and TK C3G.

Funding: Commercial Support - Novartis Pharmaceutical Corporation

Table

Patient demographic/clinical characteristic		Overall (n=350)	Native kidney (n=244)	Post-transplant (n=106)	*P*-value (native kidney vs post-transplant)
Age, mean (SD)		49.9 (19.3)	53.7 (19.3)	41.2 (16.3)	<0.001
Male, n (%)		190 (54.3)	141 (57.8)	49 (46.2)	0.06
CCI score, mean (SD)		3.7 (2.1)	4.0 (2.3)	2.9 (1.3)	<0.001
Associated comorbidities, n (%)	Acute kidney injury	192 (54.9)	154 (63.1)	38 (35.8)	<0.001
	Atrial fibrillation	36 (10.3)	30 (12.3)	6 (5.7)	0.092
	Heart failure	101 (28.9)	89 (36.5)	12 (11.3)	<0.001
	Hypertension	299 (85.4)	208 (85.2)	91 (85.8)	0.008
	Myocardial infarction	26 (7.4)	20 (8.2)	6 (5.7)	0.542
Treatment use, n (%)	ACEi	62 (17.7)	47 (19.3)	15 (14.2)	0.318
	ARB	81 (23.1)	59 (24.2)	22 (20.8)	0.575
	ACEi and ARB	12 (3.4)	10 (4.1)	2 (1.9)	0.523
	Eculizumab	15 (4.3)	2 (0.8)	13 (12.3)	<0.001
	Immunosuppressive agents	113 (32.3)	55 (22.5)	58 (54.7)	<0.001
	Corticosteroids*	178 (50.9)	122 (50.0)	56 (52.8)	0.711

*Including oral and intravenous.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; SD, standard deviation.

SA-PO796

Health Care Resource Utilization (HCRU) Burden in C3 Glomerulopathy (C3G) in the United States: A Retrospective Linked Electronic Medical Records (EMR) and Claims Database Analysis

Briana C. Ndife,[1] Rahul Khairnar,[1] Anirban Bose,[1] Karishma Thakkar,[1] Marley K. Boyd,[2] Claudia Leiras,[2] Swastina Shrestha,[2] Laura H. Mariani.[3] *[1]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [2]Genesis Research LLC, Hoboken, NJ; [3]University of Michigan, Ann Arbor, MI.*

Background: C3G is a chronic, rare glomerulonephritis in which pathological deposition of C3 in the glomeruli leads to progressive chronic kidney disease (CKD). This analysis aimed to evaluate C3G-related HCRU in the US.

Methods: We performed a retrospective analysis of patients (pts) diagnosed with C3G (Jan 2017–Sep 2022), with EMRs and linked medical claims in the HealthVerity database. Pts were ≥12 years (y) of age and had records ≥12 months prior to and following first diagnosis (index). Annual, per patient HCRU was assessed by CKD stage (defined as: mild [stage 1–2, reference], moderate [stage 3–4], severe [stage 5]) and proteinuria level (<1, ≥1 g/g) at index. HCRU rate ratios (RRs) for proteinuria groups and CKD stages were estimated using a generalized linear model with log link and negative binomial distribution, with 95% confidence intervals (CIs) and p-values.

Results: At index, the final cohort of 677 pts was majority female (63%), with a mean (standard deviation [SD]) age of 44y (19). Comorbidities included hypertension (55%), type II diabetes (24%), congestive heart failure (11%), atrial fibrillation (4%) and myocardial infarction (3%). Mean estimated glomerular filtration rate (n=152) was 78 (SD 37) mL/min/1.73m^2 and median proteinuria was 1.5 (n=49, interquartile range 0.3–3.3) g/g. Mean number of total visits was 65.7 (SD 74.8). Proteinuria level ≥1 g/g was associated with a 2-fold increase in total visits versus those with levels <1 g/g (RR 2.08, 95% CI 1.18–3.69, p=0.012). Increasing CKD stage associated with increasing total visits (moderate CKD: RR 1.78, 95% CI 1.42–2.23, p<0.0001; severe CKD: RR 2.68, 95% CI 2.04–3.51, p<0.0001) (**Table**).

Conclusions: Pts with higher proteinuria and CKD stage have a higher HCRU burden, highlighting the need for therapies that reduce proteinuria and prevent CKD progression.

Funding: Commercial Support - Novartis Pharmaceutical Corporation

Visits, mean (SD)	Overall (N=677)	Index proteinuria (n=49)		Index CKD stage (n=310)		
		<1.0 g/g (n=20)	≥1.0 g/g (n=29)	Mild (n=128)	Moderate (n=118)	Severe (n=64)
Total visits	65.7 (74.8)	51.0 (65.1)	106.4 (92.1)	58.3 (71.3)	103.9 (78.2)	156.2 (96.1)
Emergency department visits	2.1 (2.8)	2.4 (2.6)	3.2 (3.6)	2.0 (2.7)	2.6 (3.3)	3.9 (3.9)
Inpatient visits	1.7 (2.0)	1.0 (1.2)	2.4 (2.3)	1.7 (2.4)	2.3 (2.4)	2.7 (2.4)
Outpatient visits	48.0 (70.0)	37.3 (64.0)	73.4 (93.2)	38.6 (62.1)	75.0 (79.7)	132.7 (97.7)
Pharmacy visits	23.9 (21.2)	17.4 (14.5)	35.4 (24.3)	23.7 (20.9)	37.5 (20.9)	36.9 (29.3)

SA-PO797

Experience with Iptacopan in Patients with Recurrent Complement 3 Glomerulopathy (C3G): Early Access Program Data

Serge Smeets,[1] Soudeh Ansari,[2] Sviatlana Rizk,[1] Induja Krishnan,[3] Nicholas J. Webb,[1] Matthias Meier.[1] *[1]Novartis Pharma AG, Basel, Switzerland; [2]Novartis Institutes for Biomedical Research, Cambridge, MA; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ.*

Background: C3G is a severe primary glomerulonephritis driven by alternative complement pathway (AP) dysregulation; >50% of patients (pts) progress to kidney failure in <10 years and there is high risk of recurrence after successful kidney transplantation. Iptacopan is an oral proximal complement inhibitor that specifically binds Factor B and inhibits the AP; Phase 2/3 studies have shown efficacy in proteinuria reduction and favorable safety. An early access program (EAP) was initiated in 2018 (NCT05222412) to provide iptacopan for C3G pts (native and recurrent) with progressive renal insufficiency not eligible for any clinical trial who have exhausted all available therapies. We here focus on outcomes in pts with recurrent C3G post transplantation.

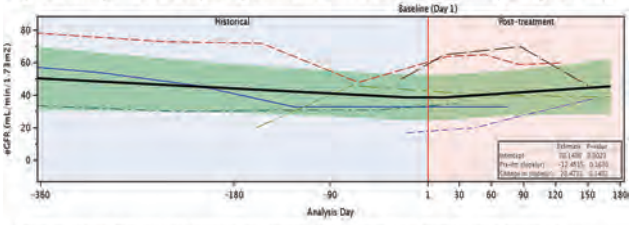
Methods: Unsolicited requests submitted to the EAP were approved if meeting eligibility criteria and applicable local laws/regulations. Recurrent C3G had to be biopsy confirmed. Physicians received a 3-month supply of iptacopan (200 mg twice daily). Resupply requests were submitted generally every 3 months and estimated glomerular filtration rate (eGFR) values collected. Adverse events (AEs) were collected by spontaneous reporting. Cutoff for data collection: 27-Feb-2024.

Results: 12 pts with recurrent C3G received iptacopan: median age 40 y (17-76); 75% male; median iptacopan treatment duration 214 days (15-1017); baseline mean eGFR 44.4 mL/min/1.73m^2 (SD 21.6). Analysis comparing eGFR slope post-transplant prior to and after start of iptacopan treatment suggested potential stabilization of kidney function (**Figure**). 3 pts reported 26 AEs, of which 12 were serious (all judged not related to iptacopan except 1 of bacterial pneumonia).

Conclusions: Following a historic period of eGFR decline post-transplantation without iptacopan treatment, recurrent C3G pts demonstrated potential stabilization of progression with iptacopan treatment. AEs were consistent with the known safety profile of iptacopan; no new safety signals were identified.

Funding: Commercial Support - Novartis Pharma AG

Figure. Change in eGFR trajectory based on historical data (sensitivity analysis*; n=6)



*Includes only patients with both historical and on-treatment data available, more than one resupply of iptacopan, and a period of ≤60 days between eGFR reported at the initial request and treatment initiation. Day 1 denotes start of iptacopan treatment.

SA-PO798

Kidney AA Amyloidosis in a Liver Transplant Recipient

Long Qian, Jeffrey M. Turner. *Yale University, New Haven, CT.*

Introduction: Renal AA amyloidosis is a rare cause of proteinuric AKI occuring in chronic inflammatory states from amyloid A protein deposition in the kidney. AA amyloidosis is rare in immunosuppressed transplant recipients. Such cases can present a diagnostic challenge as potential etiologies include autoimmune disease recurrence, occult infections, and inflammation from graft rejection. We report a case of renal AA amyloidosis in a liver transplant recipient that highlights the spectrum of potential pathologies in such patients.

Case Description: A 34-year-old man with a liver transplant 13 years ago for autoimmune hepatitis/primary sclerosing cholangitis (AIH/PSC) overlap syndrome presented with abdominal pain. Creatinine was newly elevated to 4.5 mg/dL (baseline 1.0) and urine protein creatinine ratio was 5g/g. Kidney biopsy showed deposits positive for Congo red with apple green birefringence, with positive immunohistochemistry for serum amyloid A protein. He had multiple risk factors for AA amyloid including injection drug use, cystic liver lesions on imaging resembling abscesses, and long-standing liver enzyme elevations with prior liver biopsy findings suggestive of recurrent AIH/PSC versus cellular rejection. ANA titer was elevated at 1:1280. Liver-kidney microsomal antibody and smooth muscle antibody were negative. AST, ALT, and ALP fluctuated between normal to elevated. Multiple blood cultures were negative. Direct sampling of the liver lesions was not obtainable due to their small size and difficult anatomical location. The patient received 4 weeks of cefuroxime/metronidazole for potential abscesses, but the liver lesions persisted on repeat imaging. Repeat liver biopsy showed amyloidosis as well as inflammatory changes suggesting AIH/PSC versus rejection. The patient's immunosuppression was modified: sirolimus was replaced with azathioprine, while tacrolimus and low dose prednisone continued. In addition, losartan was started. The patient abstained from further injection drug use. His creatinine improved to 1.57; proteinuria persisted.

Discussion: AA amyloidosis in an immunosuppressed patient with substance use poses diagnostic challenges. In this case, injection drug use seems a likely cause, as renal function improved with self-reported abstinence. However, the liver lesions remain of unclear etiology, and a potential link between AIH/PSC recurrence and AA amyloidosis remains a consideration.

SA-PO799

ADX-097, a Tissue-Targeted Complement Inhibitor for the Treatment of Kidney Diseases: Phase 1 Results in Healthy Participants and Model-Informed Phase 2 Dose Selection

Bernd Jilma,[1] Katherine A. Vernon,[2] Hong Wu,[2] Stefan Wawersik,[2] David Rezendes,[2] Ryan Faucette,[2] Richard Leigh-Pemberton,[2] Justin L. Hay,[3] Christina L. Mayer,[4] Shelia Violette,[2] Jason Campagna.[2] *[1]Medical University of Vienna, Vienna, Austria; [2]Q32 Bio Inc, Waltham, MA; [3]Certara, Radnor, PA; [4]Semivida Research, LLC, Dallas, TX.*

Background: Alternative complement pathway (AP) activation is implicated in the pathogenesis of various autoimmune renal diseases. ADX-097, a C3d mAb – fH_{1-5} fusion protein, was designed to inhibit complement in diseased kidney while avoiding systemic blockade, providing the potential for enhanced activity and safety profile. In preclinical studies, ADX-097 durably inhibited glomerular complement activity and reduced urine protein and sC5b-9 without any impairment of systemic complement. ADX-097 is being evaluated in a Phase 2 renal basket trial in IgA nephropathy, lupus nephritis and complement component 3 glomerulopathy. Here we report results from a Phase 1 study evaluating the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ADX-097.

Methods: A randomized, double-blind, placebo-controlled study of ADX-097 with single ascending and multiple doses was performed in heathy participants. ADX-097 was administered in single dose cohorts IV at 0.1-30 mg/kg, or SC at 3.75 and 10 mg/kg and in one multiple dose cohort of 450 mg SC QW for 5 doses. Circulating AP activity was measured by Wieslab assay. An exploratory PK/PD model was used to project a dose that maintains circulating drug concentrations in a target range of 0.3 - 3.2 µg/ml, which is associated with maximal tissue pharmacology in preclinical models.

Results: ADX-097 was well tolerated across all dose levels with no clinically significant drug-related safety findings or ADAs observed. ADX-097 demonstrated a robust PK/PD relationship with a systemic AP IC_{50} of 56.3 µg/ml. These data confirmed the in vivo integrity of the fusion protein. PK/PD simulations projected that 450 mg ADX-097 SC QW can attain circulating concentrations in the target range for maximal tissue pharmacology in preclinical models, with a $C_{max,ss}$ ~5-fold below the IC_{50} for systemic AP inhibition.

Conclusions: ADX-097 demonstrated a favorable safety profile and desired PK/PD properties in healthy participants, supporting a Phase 2 dose that is predicted to provide tissue inhibition of complement in glomerular diseases while sparing systemic complement activity.

Funding: Commercial Support - Q32 Bio Inc

SA-PO800

Pegcetacoplan for Post-transplant Recurrent C3 Glomerulopathy (C3G) or Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN) in NOBLE: 52-Week Patient Evolution

Anuja Java,[1] Andrew S. Bomback,[2] David Kavanagh,[3] Giuseppe Remuzzi,[4] Gere Sunder-Plassmann,[5] John Kanellis,[6] Erica Daina,[4] Patrick D. Walker,[7] Zhongshen Wang,[8] Zurish Ahmad,[8] Fadi Fakhouri.[9] *[1]Washington University in St Louis School of Medicine, St Louis, MO; [2]Columbia University Irving Medical Center, New York, NY; [3]Newcastle University, Newcastle upon Tyne, United Kingdom; [4]Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; [5]Medizinische Universitat Wien, Vienna, Austria; [6]Monash Medical Centre, Clayton, VIC, Australia; [7]Arkana Laboratories, Little Rock, AR; [8]Apellis Pharmaceuticals Inc, Waltham, MA; [9]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.*

Background: Pegcetacoplan (Peg; targeted C3/C3b inhibitor) may prevent kidney damage in C3G and primary IC-MPGN. NOBLE (NCT04572854) randomized 13 patients with post-transplant recurrent C3G or primary IC-MPGN. At week 12, Peg was well tolerated and showed improvements in histologic, clinical, and biomarker parameters of disease.

Methods: We conducted a post-hoc analysis of 9 NOBLE patients treated with subcutaneous Peg 1080 mg twice weekly plus standard of care for 52 weeks; of these, treatment completers had >80% compliance (n=7).

Results: At week 52, 5/9 (55.6%) patients had reduced C3c staining (p=0.0423 vs baseline). 7/9 (77.8%) had decreased activity score compared to baseline and 2/8 (25%) had absent electron microscopy deposits at week-52 biopsy. Patients with >1 g/g proteinuria at baseline had a median 56.4% decrease in proteinuria (**Table**). 7/9 (77.8%) patients had stable/improved estimated glomerular filtration rate, and 8/9 (88.9%) had both increased serum C3 and decreased sC5b-9. No meningitis cases, graft losses, or deaths were reported. Non-serious rejection episodes were reported for 2/9 (22.2%) patients. 1 patient (11.1%) discontinued for serious adverse event of weight loss.

Conclusions: By inhibiting the breakdown of C3, Peg achieved meaningful histology improvements for 8/9 (88.9%) patients while also improving disease parameters, increasing serum C3, and decreasing plasma sC5b-9. The Phase 3 VALIANT (NCT05067127) trial will further evaluate the safety and efficacy of Peg in patients with native kidney or post-transplant C3G or primary IC-MPGN.

Table. Histological, clinical, and biomarker parameters of disease activity for patients who received 52 weeks of pegcetacoplan

Parameter		Pegcetacoplan Weeks 0–52 (n=9)	Pegcetacoplan Weeks 0-52 Treatment Completers (n=7)
C3c staining intensity on renal biopsy[a]	# of patients with a decrease by ≥2 orders of magnitude compared to baseline, n (%)	5 (55.6) p=0.0423[b]	5 (71.4) p=0.0423[b]
	# of patients with zero staining intensity, n (%)	4 (44.4)	4 (57.1)
Absent EM deposits, n (%)		2 (25.0), n=8[c]	2 (33.3), n=6[c]
Absent podocyte effacement, n (%)		8 (88.9)[d]	6 (85.7)[e]
Histology activity index	# of patients that decreased from baseline, n (%)	7 (77.8)	6 (85.7)
	Score, n/total # pts, n (%)	5 (55.6)	4 (57.1)
	% Change from baseline, median (IQR)	-100 (-100.0, -54.3)	-100 (-100.0, -80.0)
Proteinuria, % change from g/g baseline, median (IQR; n=4)		-56.4 (-84.5, -23.6)	-56.4 (-84.5, -25.8)
Serum C3, % change from baseline, median (IQR)		247.37 (272.98, 314.29)[e]	247.29 (272.98, 314.29)[e]
Plasma sC5b-9, % change from baseline, median (IQR)		-84.2 (-97.8, -48.1)	-84.1 (-97.8, -48.1)
eGFR change from baseline, mL/min/1.73m², median (IQR)		10.0 (-2.0, 26.0)	22.0 (3.0, 27.0)

eGFR, estimated glomerular filtration rate; EM, electron microscopy; IQR, interquartile range; SD, standard deviation.
[a]Study inclusion required ≥2 orders of magnitude in C3c staining.
[b]Analyzed by Cochran-Mantel-Haenszel test.
[c]At baseline, all patients (n=9 for whole group and n=6 for treatment completers; 100%) with available data had EM deposits present.
[d]At baseline, 3/8 (37.5%) patients with available data had absent podocyte effacement.
[e]At baseline, 2/6 (33.3%) patients with available data had absent podocyte effacement.

SA-PO801

Long-Term Safety and Efficacy of Pegcetacoplan in Patients with C3 Glomerulopathy or Primary Immune-Complex Membranoproliferative Glomerulonephritis: The Long-Term VALE Extension Study

Carla M. Nester,[1] María Gema Ariceta Iraola,[2] Anwesha Mukherjee,[3] Li Li,[3] Johan Szamosi,[4] Luis López Lázaro.[4] *[1]University of Iowa, Stead Family Children's Hospital, Iowa City, IA; [2]Universitat Autonoma de Barcelona, Barcelona, Spain; [3]Apellis Pharmaceuticals Inc, Waltham, MA; [4]Swedish Orphan Biovitrum AB, Stockholm, Sweden.*

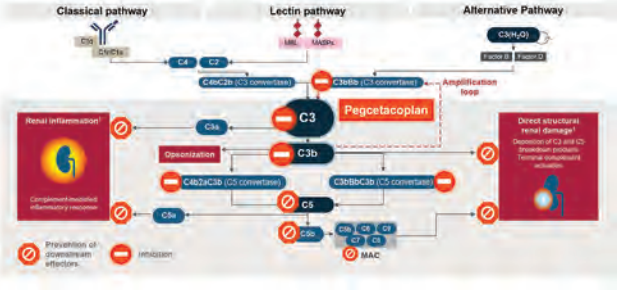
Background: C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) are rare diseases caused by complement overactivation leading to excessive deposition of C3 breakdown products in the kidney, causing inflammation, renal damage, and renal failure. Pegcetacoplan (PEG; C3/C3b inhibitor) blocks overactivation of alternative and classical complement pathway by inhibiting both C3 and C5 convertases (Figure). In the phase 2 trials, PEG demonstrated clinical benefit and was well tolerated. The Phase 3 VALIANT (NCT05067127) trial, in patients with C3G or primary IC-MPGN in native kidney or post-transplant, will further evaluate the safety and efficacy of PEG. Here we describe VALE (NCT05809531), a phase 3 extension study designed to evaluate long-term efficacy and safety of PEG in C3G and primary IC-MPGN.

Methods: Patients ≥12 years old who completed VALIANT through week 52 and achieved clinical benefit will continue to receive twice-weekly doses of PEG for a minimum of approximately 2.5 years. The primary efficacy endpoint is the log-transformed urine protein-to-creatinine ratio vs baseline. Secondary endpoints will evaluate changes in estimated glomerular filtration rate, proteinuria, and patient-reported outcomes, and disease progression defined by a composite clinical outcome. Safety endpoints will assess treatment-emergent adverse events.

Results: Not available.

Conclusions: The VALE extension will assess long-term efficacy and safety of PEG in C3G and primary IC-MPGN.

Figure. Proposed mechanism of action for pegcetacoplan in C3G and primary IC-MPGN[1–4]



MAC=membrane attack complex; MBL=mannose-binding lectin; MASP=MBL-associated serine protease

1. Obata S et al. *Transplant Rev (Orlando)* 2024;38(2):100839; 2. Kolev M et al. *Nat Rev Immunol* 2014;14:811–20; 3. Holers VM. *Annu Rev Immunol* 2014;32:433–59; 4. Dunkelberger JR, Song WC. *Cell Res* 2010;20:34–50.

SA-PO802

Efficacy of Pegcetacoplan in Children with C3 Glomerulopathy

Maria Cristina Mancuso,[1] Antonio Mastrangelo,[1] Letizia Dato,[2] Simona Verdesca,[1] Massimo Cugno,[1] Gianluigi Ardissino.[1] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Università del Piemonte Orientale, Novara, Italy.*

Background: C3 glomerulopathy (C3G) is a rare chronic kidney disease caused by a dysregulation of the alternative complement pathway leading to glomerular deposition of complement component 3 (C3) followed by inflammation and tissue damage. Pegcetacoplan is an inhibitor of both C3 and of its active fragment C3b, that can prevent their glomerular deposition. A phase III registration protocol is currently ongoing in patients (adolescents and adults) with C3G, with promising results. Herein we describe our recent experience with Pegcetacoplan in 5 pediatric patients with C3G.

Methods: This retrospective, observational study presents the efficacy and safety of Pegcetacoplan in pediatric patients with biopsy proven C3G over a 12-week treatment period. The drug was administered subcutaneously, twice a week for the first month, then weekly. The primary endpoint was the change in urinary protein-to-urinary creatinine ratio evaluated by the mean of 3 samples collected on different days before each visit at baseline, 8 and 12 weeks. The changes in serum C3, albumine, creatinine and urinary erythrocytes (number/µL) were also evaluated.

Results: Detailed results are shown in Fig.1. Median C3 level increased of more than 600% while proteinuria decreased to 30% of baseline value. Some of the patients with decreased renal function exhibited an improvement of eGFR. No adverse event has been recorded except for some transient discomfort at the injection site.

Conclusions: All our patients showed a rapid over-normalization of the C3 levels, a significant reduction of proteinuria and a significant increase in albuminemia. We think that the present case series, although small and with a short follow up period, may be important to support other physicians to consider this treatment as an opportunity for their C3G patients.

Table 1

Patient	Gender	Age at diagnosis (Yrs)	Age at Peg (Yrs)	C3 (mg/dl)		eGFR (ml/min/1.73m²)		Proteinuria (mg/mg)		sAlbumin (g/dl)		Urinary RBC (n/microL)	
				Wk0	Wk12	Wk0	Wk12	Wk0	Wk12	Wk0	Wk12	Wk0	Wk12
1	M	7.6	12.5	45	364	26	41	7.7	2.8	1.8	3.9	1380	29
2	F	2.2	13.1	113	429	45	46	3.5	3.4	3.8	3.5	65	40
3	F	19.1	20.0	67	335	45	46	5.0	1.3	3.0	4.0	395	27
4	M	9.0	10.8	28	222	104	114	3.5	1.3	3.7	4.4	99	41
5	F	8.7	9.5	18	185	63	61	7.1	1.5	2.3	3.6	425	315

SA-PO803

C3 Nephrotic Factor at Diagnosis Is Associated with Better eGFR Preservation in Patients with C3 Glomerulopathy (C3G): Findings from the European Rare Kidney Disease Registry (ERKReg)

Jonas Hofstetter,[1] Marina Vivarelli,[5] Victor Perez-Beltran,[2] Peter J. Conlon,[3] Enrico Vidal,[4] Franz Schaefer.[1] *[1]European Rare Kidney Disease Reference Network, Heidelberg, Germany; [2]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [3]Beaumont Hospital, Dublin, Ireland; [4]Azienda Ospedale Universita Padova, Padova, Italy; [5]Ospedale Pediatrico Bambino Gesu, Roma, Italy.*

Background: C3G and ic-MPGN are complement-mediated rare kidney disorders with variable responsiveness to standard immunosuppressive protocols. Information regarding biomarkers of therapeutic responsiveness is scarce. ERKReg, a longitudinal pan-European registry for rare kidney diseases is currently following >9,000 patients with rare glomerulopathies, including 484 patients with C3G/ic-MPGN. We assessed the database for risk factors associated with a progressive disease course.

Methods: Retrospective diagnostic and prospective follow-up information was extracted from a total of 208 C3G/ic-MPGN patients enrolled in ERKReg between 10/2018 and 05/2024, most commonly (84%) as prevalent patients with a median (IQR) total disease duration of 5.8 (2.9; 9.3) years. Serum C3NeF at time of diagnosis was available for 55 C3G patients (cohort 1) and serum C3 for 146 C3G and 62 ic-MPGN patients (cohort 2). Multivariable, linear mixed-effects models were fitted to longitudinal eGFR adjusted for sex, eGFR and age at first visit (baseline), hypertension and RASi therapy for each cohort to investigate whether C3NeF status and/or serum C3 levels at diagnosis were associated with prospective eGFR change.

Results: Disease onset was observed at childhood age in 77%. Prospective observation time accounted for a median of 21% (0%; 52%) of total disease duration. eGFR at baseline was 103 (66;127) ml/min/1.73m². Systolic hypertension was documented in 21% and RASi therapy in 69% of visits. In cohort 1, eGFR improved with time in C3G patients positive for C3NeF at diagnosis (ß=1.1, p =0.039) whereas C3NeF-negative patients exhibited a negative eGFR slope (ß=-3.9, p <0.01). In cohort 2, low vs. normal C3 levels at time of diagnosis tended to associate with improved eGFR preservation ($ß^{\Delta}$=2.69, p = 0.078). Among the potential confounder variables accounted for in the models, adult age at baseline had a distinct negative association with eGFR over time in both cohorts.

Conclusions: In patients with C3G undergoing standard-of-care management in the past 5 years, the detection of C3NeF at time of diagnosis was associated with better kidney function. We speculate that C3NeF identifies a subset of patients with greater sensitivity to standard immunosuppressive therapies.

Funding: Commercial Support - Novartis

SA-PO804

Real-World Effectiveness of Ravulizumab among C5 Inhibitor-Naive Patients with Atypical Hemolytic Uremic Syndrome (aHUS): A Physician Panel-Based Chart Review Study (aHUS IMPACT)

Ramy M. Hanna,[1] Shruti Chaturvedi,[2] Moh-Lim Ong,[3] Dr. Arpita Nag,[3] Rui Song,[4] Lynn Huynh,[4] Jordan Burdeau,[4] Mei Sheng Duh,[4] Yan Wang.[3] *[1]University of California, Irvine, CA; [2]John Hopkins University, Baltimore, MD; [3]Alexion, AstraZeneca Rare Disease, Boston, MA; [4]Analysis Group, Inc., Boston, MA.*

Background: aHUS is a rare disease and form of thrombotic microangiopathy (TMA) caused by complement dysregulation. Ravulizumab (RAV; a C5 inhibitor [C5i]) is approved for aHUS based on registrational clinical studies, but real-world evidence is limited.

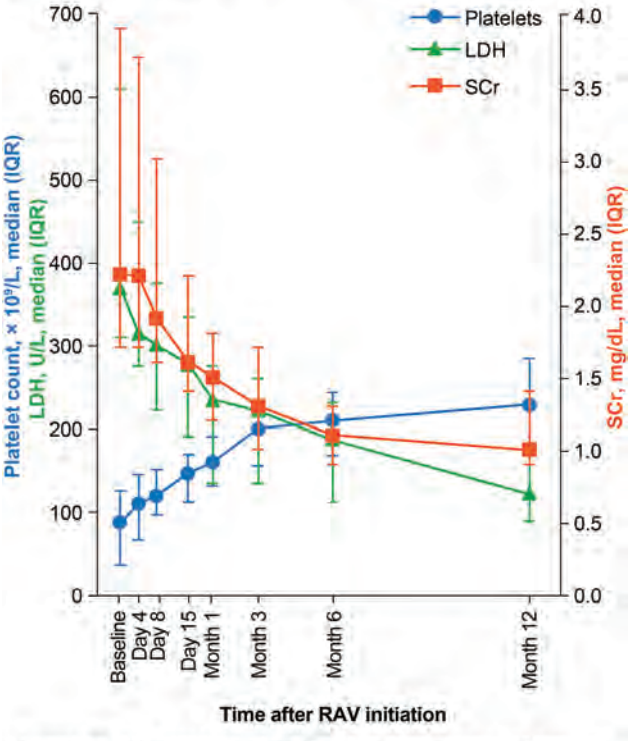
Methods: This was a retrospective, longitudinal, physician panel-based chart review of C5i-naive patients (pts) in the USA treated with RAV. Physicians with medical and laboratory records for ≥1 pt with aHUS randomly selected 1–5 pts with aHUS who had ≥6 months of medical records after RAV initiation, unless the pt died.

Results: Overall, 79 C5i-naive pts with aHUS (enrolled by 31 physicians) initiated RAV. Median (IQR) pt age at RAV initiation was 44 (27–54) years; 3 pts (4%) had a kidney transplant before RAV initiation and 20 (25%) received dialysis 12 months before to ≤2 weeks after RAV initiation. Laboratory parameters over time are shown in the **Figure**. Statistically significant changes from baseline occurred as early as Day 4 (LDH and percent change in serum creatinine [SCr]; both $p<0.001$) and Day 8 (platelet count, $p<0.001$). The proportions of pts with normalization of platelets, LDH and ≥25% improvement in SCr were 19/59 (32%), 17/51 (33%) and 19/58 (33%) at Day 8 and 40/48 (83%), 35/38 (92%) and 42/48 (88%) within 12 months after RAV initiation. Complete TMA response rates were 61% and 70% within 6 and 12 months after RAV initiation, respectively, and the median (IQR) time to complete TMA response was 3 months (1–13).

Conclusions: This study supports the immediate and sustained benefits of initiating with RAV in pts with aHUS as seen by the early response and continued improvement.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease.

Figure. Platelet count, LDH and SCr from baseline to Month 12 after RAV treatment.



Complete TMA response was defined as normalization of platelet count (≥ 150 × 10⁹/L), normalization of LDH (≤ 246 U/L) and ≥ 25% improvement in SCr.
IQR, interquartile range; LDH, lactate dehydrogenase; RAV, ravulizumab; SCr, serum creatinine; TMA, thrombotic microangiopathy.

SA-PO805

Safety and Effectiveness of Switching to Ravulizumab from Eculizumab in Kidney Transplant Recipients with Atypical Hemolytic Uremic Syndrome: A Global Registry Analysis

Anja H. Gaeckler,[1] Imad Al-Dakkak,[2] Nuria Saval,[2] Hans H. Dieperink,[3] Margriet Eygenraam,[7] Larry A. Greenbaum,[4] Nicole Isbel,[5] Johan Vande Walle.[6] *[1]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [2]Alexion, AstraZeneca Rare Disease, Boston, MA; [3]Odense University Hospital, Odense, Denmark; [4]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA; [5]The University of Queensland and Princess Alexandra Hospital, Brisbane, QLD, Australia; [6]Ghent University Hospital, Gent, Belgium; [7]aHUS Canada, Brampton, Brampton, ON, Canada.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a disease of complement dysregulation that causes kidney failure and has a propensity to recur after kidney transplant (KTx) with graft loss. Ravulizumab (RAV) and eculizumab (ECU) are

C5 inhibitors approved for the treatment of aHUS. We assessed the real-world safety and effectiveness of switching from ECU to RAV in KTx recipients with aHUS for immediate, complete, and sustained terminal complement inhibition.

Methods: The Global aHUS Registry is a multicenter study (NCT01522183) enrolling patients (pts) with aHUS since 2012. Safety and effectiveness outcomes were assessed in KTx recipients with aHUS who switched from ECU to RAV up to April 22, 2024. Safety analyses included pts with a KTx before RAV initiation; pt characteristic and effectiveness analyses included KTx recipients who received RAV for ≥3 months and had ≤1 month between ECU discontinuation and RAV initiation.

Results: Overall, 29 pts (25 adults) were included in safety analyses; 21 adverse events (AEs) were reported in 15 pts at or after RAV initiation, and none were unexpected. During RAV treatment, no new AEs of thrombotic microangiopathy or kidney impairment, and no meningococcal infections or deaths were reported. Among 21 pts (20 adults) included in the pt characteristic and effectiveness analyses, median (range) age at RAV initiation was 35 (11–72) years, and 67% had a reported pathogenic complement variant or anti-complement factor H antibodies. Median (range) time on treatment was 66 (4–158) months for ECU and 24 (5–43) months for RAV; median (range) time from last KTx to RAV initiation was 56 (4–184) months. Mean (standard deviation) estimated glomerular filtration rate was 50 (25) mL/min/1.73m^2 at last record before or at RAV initiation and 50 (28) mL/min/1.73m^2 at last follow-up after RAV initiation. Among 29 KTx events in these 21 pts, no rejections or graft failures were reported after RAV initiation.

Conclusions: This analysis from the Global aHUS Registry provides real-world evidence of the successful transition from ECU to RAV in KTx recipients with aHUS, with stable kidney function and no unexpected safety concerns.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease

SA-PO806

Design of an Observational, Longitudinal Data Platform of Patients with C3 Glomerulopathy (C3G) and Idiopathic Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN) in the United States

Ali Poyan-Mehr,[1] Rahul Khairnar,[2] Anirban Bose,[2] Jackson Tang,[3] Claire Buchan,[3] Tayler Buchan,[3] Briana C. Ndife.[2] *[1]The Permanente Medical Group Inc, San Francisco, CA; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [3]Asclepius Analytics, New York, NY.*

Background: C3G and IC-MPGN are rare renal diseases characterized by overactivation of the complement system. The absence of a comprehensive United States (US) real-world data (RWD) platform for these diseases limits our understanding of the challenges faced by patients (pts) and their healthcare providers. Here, we describe the development of a national RWD platform to capture, harmonize, and report comprehensive information for pts with C3G and idiopathic IC-MPGN.

Methods: This living data platform will include longitudinal data from prospective and retrospective cohorts of US-based pts of all ages with a diagnosis of C3G or idiopathic IC-MPGN, compiled using coordinated recruitment strategies. Site-based recruitment in collaboration with The GlomCon Foundation (a non-profit consortium of medical centers, clinicians, and pathologists overcoming challenges in glomerular disease through research partnerships) will generate retrospective and prospective cohorts of harmonized patient-level data from various single-center cohorts and patient registries. A patient cohort will also be generated from data collected via retrospective chart review. Variables collected will include demographic and clinical characteristics, comorbidities, biopsy findings, genetic studies, treatment patterns, genetic testing, laboratory values, and key outcomes of interest, including dialysis, transplant, and kidney failure. A data model will harmonize retrospective cohorts for pooled analyses. In a patient-centric recruitment approach, we will complement these center-specific, patient-level data with patient-reported outcomes, including the Functional Assessment of Chronic Illness Therapy–Fatigue *Scale and the EuroQol-5D* Measure of Health-Related Quality of Life.

Results: The site and patient recruitment are ongoing. The first analyses from this data platform are anticipated in 2025.

Conclusions: The development of an RWD platform for pts with C3G and idiopathic IC-MPGN will improve our understanding of the epidemiology, clinical burden, and determinants of clinical outcomes in these rare diseases, across a geographically diverse population in multiple centers and healthcare settings.

Funding: Commercial Support - Novartis Pharmaceutical Corporation

SA-PO807

Proteinuria as a Surrogate Predictor of Kidney Failure in Both C3 Glomerulopathy and Primary Immune-Complex Membranoproliferative Glomerulonephritis

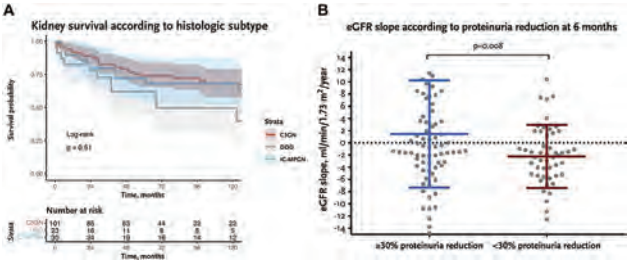
Fernando Caravaca-Fontan,[1] Manuel Praga.[2] GLOSEN Group. *[1]Instituto de Investigacion Hospital 12 de Octubre, Madrid, Spain; [2]Universidad Complutense de Madrid, Madrid, Spain.*

Background: C3 glomerulopathy (C3G) and primary immune complex membranoproliferative glomerulonephritis (IC-MPGN) are rare glomerular diseases sharing similar etiology and pathogenesis. While some studies have shown association between changes in proteinuria and kidney outcomes in C3G, the prognostic significance of proteinuria changes in IC-MPGN remains largely unexplored.

Methods: Multicenter, retrospective cohort study in 37 nephrology departments belonging to GLOSEN group. All patients fulfilling diagnostic criteria of C3G were included, and secondary causes of IC-MPGN were carefully ruled out. A joint modelling of linear mixed-effects models was applied to assess the underlying trajectory of a repeatedly measured proteinuria at 0,1,3,6,12,24,60 or last follow-up, and a Cox model to evaluate the association with the risk of kidney failure.

Results: The study group consisted of 154 patients: 124 with C3G (81%) and 30 IC-MPGN (19%), with a mean age of 33±17 years. Median baseline eGFR was 55 ml/min/1.73m^2 (IQR 24–106) and proteinuria 3 g/day (IQR 1.7–6). No significant clinical or histologic baseline differences were observed across groups. During a median follow-up of 65 months (IQR 30–123), 55 patients (36%) reached kidney failure, without differences between groups. The longitudinal change in proteinuria exhibited a robust association with this outcome, where each 1g/day increase was linked to a 3.4-fold rise in the risk. A ≥30% proteinuria reduction over time was associated with a lower risk of kidney failure (HR 0.97; 95% CI 0.94–0.99; p<0.001), as was a ≥50% proteinuria reduction over time (HR 0.92; 95% CI 0.85–0.95; p<0.001). Results were consistent in both C3G and IC-MPGN. A ≥30% proteinuria at 6 months or a ≥50% proteinuria reduction at 12 months were associated with a slower eGFR decline over time. These results were also confirmed in patients aged >12 years at baseline, eGFR ≥30 ml/min/1.73m^2 and proteinuria ≥1g/day at baseline.

Conclusions: Proteinuria reduction is associated with improved kidney outcomes in both C3G and primary IC-MPGN.



SA-PO808

Analytic Performance of MicroVue Enzyme Immunoassay (EIA) for Measurement of Ba and sC5b-9 for Urine

Cameron Droste, Eric Gorzkowski, Manuel Galvan. *National Jewish Health, Denver, CO.*

Background: Complement mediated kidney diseases, including C3 glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), lupus nephritis (LN), and immunoglobulin A nephropathy (IgAN) are chronic inflammatory conditions characterized by dysregulated complement activation. Traditionally, complement activation is measured in plasma. However, patients with kidney disease often have an abundance of complement activation fragments in their urine – including Ba and soluble C5b-9 (sC5b-9), markers of alternative pathway activation and terminal pathway activation respectively– highlighting the potential value of Ba and sC5b-9 measurement in urine for diagnosis and risk management in patients with C3G, aHUS, LN, IgAN, and other kidney diseases. Herein we evaluated the analytical performance of the Quidel MicroVue Plus EIA Ba and sC5b-9 for urine samples.

Methods: The Quidel MicroVue Ba and sC5b-9 Plus EIA were evaluated using randomly collected healthy urine samples or healthy urine samples spiked with a known concentrations of Ba and sC5b-9, as well as chronic kidney disease (CKD) urine samples.

Results: The analytical performance of the assays met acceptability criteria for accuracy and precision. Assay accuracy was (100 ± 20%) and intra-assay precision as well as inter-assay precision was ≤ 20 % coefficient of variability (CV) for both assays. Ba was detected in healthy urine samples (N=40), but sC5b9 was not. Positive linearity was observed in both assays over a wide range of concentrations. Ba and sC5b-9 measured in urine was stable following three freeze-thaw cycles. Lastly, Ba and sC5b-9 measured in urine was stable when stored at -20°C and -80°C for 4 weeks. Long term stability testing at -80°C is underway.

Conclusions: Quidel MicroVue Ba and sC5b-9 Plus EIA are accurate, and reliable assays for detection of Ba and sC5b-9 in urine samples, making it a viable alternatibe to plasma.

Accuracy and Precision

Accuracy

	Validation samples (% RE)			
Assay	1	2	3	4
Ba	114%	105%	103%	112%
sC5b-9	101%	112%	106%	93%

Precision

	Validation Samples (% CV)			
Assay	1	2	3	4
Intra Ba	6%	1%	3%	2%
Inter Ba	14%	7%	19%	6%
Intra sC5b-9	11%	3%	5%	4%
Inter sC5b-9	9%	4%	4%	6%

SA-PO809

Retrospective Analysis of Membranoproliferative Glomerulonephritis and C3 Behavior in a Large Brazilian Center

Liliana M. Kassar, Karoline W. Silva, Felipe Carvalho Barros Sousa, Vinícius S. Silveira, José Guilherme R. Gonçalves, Viktoria Woronik, Luis Yu, Cristiane B. Dias, Lectícia Jorge. *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil*.

Background: Membranoproliferative glomerulonephritis (MPGN) is a disease pattern on kidney biopsy that comprises a series of different diagnostic possibilities. Clinical evaluation and laboratory workup are essential steps on the investigation, although renal biopsy is still mandatory on classification between immunocomplex associated MPGN and C3 glomerulopathy. This study aims to describe the profile of MPGN patients in a large center in Brazil.

Methods: Patients with MPGN pattern on kidney biopsy from June 1999 to December 2023 were included. Variables of interest were age, gender, creatinine, estimated glomerular filtration rate (eGFR) by CKD-EPI, proteinuria, intensity of C3 staining on immunofluorescence and serum C3 levels on admission and after 1 year follow-up.

Results: A total of 136 renal biopsies were performed on the studied period, 65% of patients were male, 72% white, 46% had hypertension. Mean age was 46 years old (±16), median creatinine 1.8 mg/dL (0.6-15.8) with median eGFR 40 mL/min (4-135), serum albumin 2,7 g/dL (1-4.5), proteinuria 4.6 g (0.1-20.1), 79% hematuria, serum C3 levels 84 (± 39) on diagnosis and 90 (± 34) after a year follow-up. In our cohort 10% of the patients had schistosomiasis, 13% hepatitis C, 4% hepatitis B, 4% HIV and 9% had a paraprotein on immunofixation tests. There was no correlation between C3 levels and initial creatinine and proteinuria, however lower C3 levels were associated with a stronger C3 staining on kidney biopsy (p 0.016) on Kruskal-Wallis test. Additionally, a serum C3 < 80 was not associated with specific biopsy patterns (p 0.25) and immunosuppressive treatment was not an influencing factor on the rise of serum C3.

Conclusions: Complement activation is a part of the physiopathological pathway on GNMP, therefore lower serum C3 was observed in patients with stronger C3 staining on kidney tissue showing the association with a higher activation on kidney tissue. Although GNMP can be classified between immunocomplex mediated and C3 glomerulopathy, serum complement levels were not able to identify those patterns.

SA-PO810

Long-Term Prognosis after Kidney Transplantation in Patients with Membranoproliferative Glomerulonephritis

Rune Bjoerneklett, Lars S. Bostad, Thomas Knoop, Leif H. Bostad. *Department of Clinical Medicine, University of Bergen, Bergen, Norway*.

Background: Membranoproliferative glomerulonephritis (MPGN) is a distinctive light microscopic damage pattern caused by a wide variety of disease states. About 50% of patients with MPGN progress to end-stage kidney disease (ESKD) and kidney transplantation (KTX) is the preferred treatment. However, recurrence of MPGN in KTX with subsequent graft loss (GL) is a known risk. The prognosis after KTX for patients with MPGN in Norway has not previously been systematically examined. We have therefore analysed the risk of GL in patients with MPGN who have undergone KTX.

Methods: Cases of biopsy-verified MPGN in the period 1991-2012 were identified in Norwegian kidney biopsy registry. The cohort was linked to the Norwegian Kidney Registry, and patients who had received KTX as well as the course after transplantation until May 2024 were identified. GL and death with functioning kidney transplant (DFG) are reported separately. We also analysed risk of GL stratified for C1q +/- in the kidney biopsy, as an indicator of immune complex-MPGN.

Results: We identified 60 patients who had received at least 1 KTX during the course of MPGN. Among these 60, there were 19 cases of GL, 11 of these <5 years after KTX. Furthermore, there were 17 cases of DFG. The average function time for the remaining 24 functioning KTXs was 14.5 years (SD 9). 15 patients were transplanted at least 2 times. Among these, there were 7 cases of GL, 6 of these after <5 years after KTX 2 and 3 cases of DFG. The average function time for the remaining 5 functioning KTX 2 was 6.3 years (SD 5). 4 patients were transplanted 3 times. Among this 1 case of GL, after <5 years. No cases of DFG. The average function time for the remaining 3 KTX 3 was 8.5 years (SD 4). 33 biopsies were C1q positive, this was not associated with risk of GL.

Conclusions: As expected, there were relatively many GL and frequent need for re-transplantations in this cohort of patients with KTX due to MPGN. However, the majority of patients, 52 out of 60, as of May 2024 have functioning KTX or they died with functioning KTX. Følsomhet Intern (gul) Unfortunately, the registry data do not have information about the etiology of MPGN and the causes of GL. This will be further investigated using biopsy material and medical record information.

Funding: Commercial Support - Novartis

SA-PO811

Long-Term Risk and Risk Factors for ESKD in Membranoproliferative Glomerulonephritis

Rune Bjoerneklett, Lars S. Bostad, Thomas Knoop, Leif H. Bostad. *Department of Clinical Medicine, University of Bergen, Bergen, Norway*.

Background: Membranoproliferative glomerulonephritis (MPGN) is a distinctive light microscopic injury pattern caused by a wide range of different disease conditions. The classification of MPGN has changed over time, it is now common to divide MPGN caused by immune complexes (IC-MPGN) and MPGN caused by dysregulation of the alternative activation pathway in the complement system, complement C3 nephropathy (C3G). The utility of division by IC-MPGN/C3G versus etiological division for diagnosis, treatment, and prognosis, however, is still uncertain. There is a need for more information about the long-term prognosis of MPGN, including risk factors for progression to end-stage kidney disease (ESKD). We have therefore analyzed the risk of ESKD for patients with MPGN registered in the Norwegian Kidney Biopsy registry (NKBR) in the period 1991-2012.

Methods: Cases of biopsy-verified MPGN 1991-2012 including demographic, clinical, laboratory, and histological variables at the time of diagnosis were retrieved from NKBR. Cases of MPGN due to SLE and thrombotic microangiopathy were excluded. The cohort was linked with the Norwegian Kidney Registry for identification of patients with ESKD by May 1, 2014

Results: We identified 158 patients with biopsy-verified MPGN. Male; 85 (54%), age; 47 years (SD 23), systolic BP; 151mmHg (SD 28), diastolic BP; 86 mmHg (SD 16), hypertension; 155 (67%), mean eGFR; 50 ml/min/1.73m2 (SD 35), eGFR<15; 18 (11%), eGFR 15-29; 26 (16%), eGFR 30-59; 49 (31%), s-albumin 28 g/l (SD 7), proteinuria 5.6 g/24h (SD 3.4), nephrotic syndrome; 79 (50%), crescents; 28 (18%), tubulointerstitial fibrosis >50%; 77 (49%) and C1q positive; 111 (70%). During an average observation period of 11 years, 61 (39%) of patients progressed to ESKD. 45 (28%) of the patients died, without ESKD. Cumulative risk for ESKD after 5/10/15/25 y; 25%/37%/43%/48%. A low eGFR was the only significant risk factor of ESKD, 42 vs 55, p=0.03.

Conclusions: A cumulative long-term risk for ESKD in patients with MPGN of around 50% corresponds well with previously published studies. The registry data unfortunately does not allow precise classification by IC-MPGN/C3N. C1q positivity is, however, indicative of IC-MPGN and in this study not a significant prognostic factor.

Funding: Commercial Support - Novartis

SA-PO812

C3 Glomerulopathy: A Pediatric and Adult Case Series in New Mexico

Paul B. Avila,[1] Namita Singh,[2] Amy Staples,[2] Darren W. Schmidt,[2] Pablo Garcia.[2] *[1]Universidad de San Carlos de Guatemala, Ciudad de Guatemala, Guatemala; [2]University of New Mexico Health Sciences Center, Albuquerque, NM.*

Introduction: C3 glomerulopathy (C3GN) results from alternative complement pathway dysregulation. C3G manifests with proteinuria, decreased kidney function, and low serum C3 levels. Therapeutic options are limited. Improving diagnostic criteria and treatment strategies is essential for better outcomes in C3GN. Here, we report a case series of five cases in our pediatric and young adult population of C3GN with long term follow up in New Mexico.

Case Description: Five patients, aged 8 to 15 years, were diagnosed with C3GN based on kidney biopsy findings or clinical presentation and genetics. All were treated with C5 inhibitor therapy (C5IT), with two receiving additional immunosuppressive therapy (IST) and three undergoing PLEX therapy. Details of each case are summarized in table 1. During C5IT treatment lasting 1 to 9 years, 4 patients showed kidney function improvement. Three patients experienced reduced proteinuria (urine protein-to-creatinine ratio, UPCR), with those initially presenting with lower eGFR and higher C3 levels responding better. Two patients achieved complete remission (UPCR <0.3 g/g), and four showed significant improvement in eGFR post-treatment.

Discussion: In this case series, C3G treated with C5IT showed positive results regarding kidney function. The effect of C5IT on proteinuria reduction was not clear. The role of PLEX in pediatric cases is promising. Two achieved complete remission (UPCR <0.3 g/g). These findings support C5IT as a promising therapy for C3GN. Larger multicenter studies in pediatric and young adult populations are needed. Furthermore, novel therapies are needed to improve outcomes as the degree of proteinuria could correlate with disease activity.

Pt.	Age at Diagnosis (y)	Follow-up (y)	Sex	Cr. at Diagnosis	UPCR at Diagnosis (g/g)	Hx	Genetic Abnormalities	Serum C3 Level (mg/dl)	eGFR at Diagnosis	GS/IFTA	PLEX	IST	C5IT Duration (y)	UPCR on Follow-Up (g/g)	eGFR on Follow-Up
1	8	11.9	F	0.4	5.1	+	Yes	8	107.6	None/<5%	No	P, MMF, T	8	0.06	48
2	13	9.5	F	0.56	4.8	+	Yes	9	122	None/<10% (initial MPGN type 1 C3 3+)	No	P, MMF, T	7.3	0.4	147
3	8	9.5	F	6.9	9.6	+	None	73	<10	2 globally sclerosed, 75% necrotic/none	yes	none	9	1.67	44
4	9	8	F	4.69	3.7	+	Yes	101	15	n/a	yes	none	7	0.07	99
5	15	2.5	F	1.3	22	+	Yes	99	44.7	n/a	yes	none	1.3	0.06	86

Pa = patient; Cr = serum creatinine; H+ hematuria; eGFR = estimated glomerular filtration rate (mL/min/1.73 m2); GS/IFTA = Global glomerulosclerosis/interstitial fibrosis and tubular atrophy; UPCR = urine protein/creatinine ratio; C5IT = C5 inhibition therapy; IST = immunosuppression therapy; PLEX = plasma exchange. P = prednisone; MMF = mycophenolate mofetil; T = tacrolimus

Clinical characteristics, treatment, and outcomes of followed patients diagnosed with C3GN

SA-PO813

Novel Therapy for Recurrent Dense Deposit Disease in an Adolescent Kidney Transplant Recipient

Khaing S. Wei,[1] Carla M. Nester,[2] Nasir Khan.[1] *[1]University of Arkansas System, Little Rock, AR; [2]University of Iowa Health Care, Iowa City, IA.*

Introduction: Dense deposit disease (DDD) is a rare C3 glomerulopathy caused either by genetic or acquired drivers of overactivation of the alternative complement pathway. It most frequently affects children and young adults, and 50% progress to ESKD within 10 yrs of diagnosis. It poses a significant challenge in post-kidney transplant care due to high recurrence rates associated with allograft failure. To date, no specific targeted interventions have consistently improved outcomes for either primary or recurrent C3G. We present a compelling case of early recurrent DDD in a renal transplant adolescent recipient managed with Iptacopan, an oral complement factor B inhibitor.

Case Description: A 19-year-old Caucasian female diagnosed with hypocomplementemic DDD at the age of 6. Disease was associated with high titer nephritic factors and normal genetic studies. She was initially treated with cyclosporine and later switched to tacrolimus (Tac). Persistent proteinuria with UPCR15mg/mg led to a switch to mycophenolate (MMF). Her renal function progressively declined necessitating PD dependence for ESKD at age 14. She underwent DDKT 1.5 months before turning 19. She received ATG and prednisone taper for induction and post-transplant immunosuppressants, including Tac, MMF and prednisone. She suffered primary allograft dysfunction necessitating HD on post-op day 4. An allograft biopsy was performed 1 week postoperatively, which showed recurrent DDD and was negative for acute rejection. The patient was started on Iptacopan 200 mg BID on day 26th post-transplant. Prior to Iptacopan, her C3 was 8, C5 was 8.7, FB was 18.7, soluble C5b-9 was 0.69. 3 days after Iptacopan, C3 increased to 90, C5 to 19.9, FB to 24. C5b-9 decreased to 0.12. After 1 week, C3 increased to 111 and creatinine decreased from 2.6 to 1.8 mg/dl and proteinuria decreased.

Discussion: Iptacopan is an oral, first-in-class and selective inhibitor of factor B, a key component of the alternative pathway. In our patient, after failed conventional treatments, leading to a quick recurrence of disease in the allograft. Iptacopan lead to a significant clinical and biochemical remission of disease. Our case highlights the possibility that this aggressive renal disease is salvable even in the transplant settings by using a targeted treatment approach and further supplements the clinical trial results from native kidney C3G.

SA-PO814

C3 Glomerulonephritis in a Child with Elevated Anti-streptolysin O (ASO) Titer

Jessica M. Rosario-Falero,[1] Ihor V. Yosypiv.[2] *[1]Louisiana State University, Baton Rouge, LA; [2]Tulane University School of Medicine, New Orleans, LA.*

Introduction: C3 glomerulopathy in children is rare with an estimated incidence of 1-4 cases per million population. Most children with C3 glomerulopathy have C3 glomerulonephritis (C3GN). C3GN carries a poor kidney prognosis, with a median time to kidney failure of around 10 years from diagnosis. We report the case of a pediatric patient presenting with features of acute glomerulonephritis (GN) and elevated ASO titer who was promptly diagnosed with C3GN.

Case Description: A previously healthy 14 y.o. male presented to his pediatrician with dark urine color, facial and lower extremity swelling, and headache for 3 days. Family history was non-contributory. Blood pressure was elevated. Laboratory workup showed unremarkable CBC, normal creatinine-based eGFR of 105 ml/min/1.73m2, serum albumin 3.0 mg/dL, normal C4 and reduced C3 (23 mg/dL; ref. range 80-173) complement levels, elevated ASO titer (563 IU/ml; ref. range <350), normal CRP and ESR. Urinalysis had 2+ protein, 3+ blood, 51-99 WBC, >100 RBC and spot protein/creatinine ratio 4.0 mg/mg. Physical exam on admission showed BP at stage 2 hypertension level, mild facial and 2+ pitting edema in lower extremities, and mild ascites. Although presentation was consistent with acute postinfectious GN (APIGN), presence of nephrotic range proteinuria prompted us to perform renal biopsy on admission. Histology showed 4+ staining for C3, +/-peripheral granular staining for C1q, +/- mesangial granular staining for IgM, with no staining for IgG or IgA. EM showed endothelial swelling occluding glomerular capillary lumens, subendothelial electron dense deposits, basement membrane reduplication and extensive foot process fusion. Diagnosis of C3GN was made. Expanded infectious workup was negative. Complement studies showed: normal Factor H auto-antibody, negative *C3*, *CD46*, *CFB*, *CFD*, *CFH*, *CFHR2*, *CFHR5*, *CFI* gene sequence panel and positive C3 Nephritic factor of 13.5 (ref. range 0.0 unit/ml). Therapy with mycophenolate mofetil, oral prednisone and lisinopril was initiated.

Discussion: This case emphasizes the need to consider C3GN in a child presenting with findings consistent with APIGN. As therapies of APIGN and C3GN differ, establishing correct diagnosis promptly is critical. In this case, timely performance of kidney biopsy established correct diagnosis, enabled to initiate in-depth evaluation of alternative complement pathway (ACP) and targeted therapy.

SA-PO815

Complement Chaos: A Perplexing Case of C3G and Seminoma in a Young Man

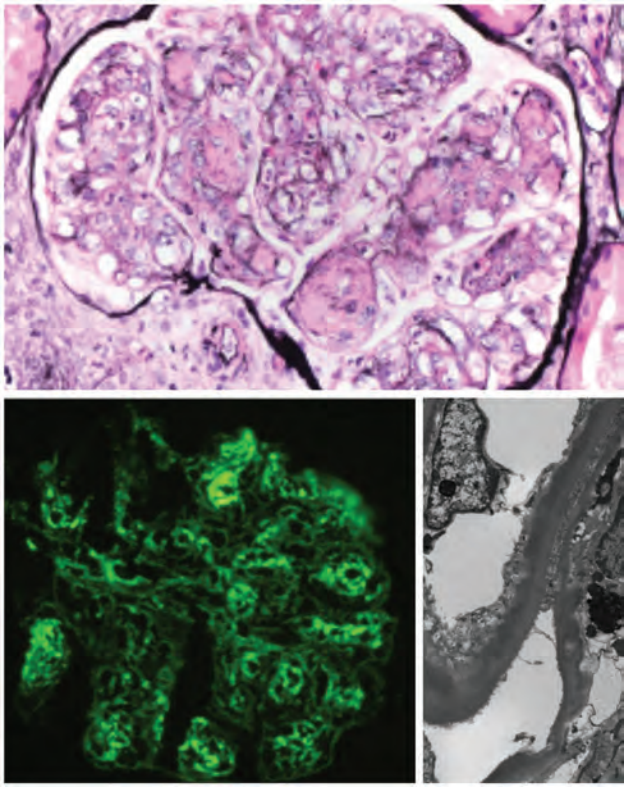
Saud A. Alsaleh, Yihan Wang, Neil S. Sanghani. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: C3G represents a spectrum of glomerular diseases characterized by dysregulation of the alternative complement pathway. Concurrent presentation of solid tumors and C3GN is rare and yet to be reported. Here we present a case of C3G with partial resolution after radical orchiectomy of a seminoma, highlighting the novel interplay between testicular malignancy and complement-mediated injury.

Case Description: A 38-year-old male presented with testicular swelling, severe hypertension, and renal dysfunction. Further evaluation revealed a testicular mass, elevated b-HCG, and histological changes suggestive of C3GN on renal biopsy. Work up for plasma cell dyscrasias and C3 Nephritic factor were unrevealing however, genetic testing revealed a heterozygous mutation in the CFH gene. Following radical orchiectomy for seminoma, renal function showed partial improvement. After initiation of mycophenolic acid and steroids, renal function and proteinuria continued to improve with normalization of C3 levels.

Discussion: In addition to genetic mutations and autoantibodies, this case suggests a potential link between testicular seminoma and C3G. The interplay between testicular seminoma, CFH gene mutation, and complement activation may have contributed to renal dysfunction. Resection of the seminoma, combined with immunomodulatory therapy, likely mitigated immune dysregulation and led to the resolution of renal dysfunction. This highlights the need to consider malignancy as a potential trigger for complement-mediated renal injury in patients with C3G, warranting further investigation into the underlying mechanisms and optimal therapeutic strategies.

Test	Initial evaluation	Post-Orchiectomy	6 months of IS therapy
Cr (mg/dl)	3.6	2.1	1.4
C3 (mg/dl)	N/A	69	143
Urine Protein-Cr ratio (mg/mg)	N/A	7.2	3.6



SA-PO816

C3 Glomerulonephritis and Neuromyelitis Optica in a Patient with Systemic Lupus Erythematosus (SLE)/Sjogren Overlap Syndrome

Vijaya Chelikani, Frida Rosenblum, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: C3 glomerulopathy (C3G) that includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) are rare glomerular disorders triggered by dysregulation of the alternative complement pathway with an estimated incidence of 2-3 cases per million. We describe a rare case of C3GN and neuromyelitis optica in a patient with known SLE/Sjogren overlap syndrome.

Case Description: 51-year-old African-American female with SLE/Sjogren overlap syndrome presented with proteinuric AKI on CKD and newly diagnosed transverse myelitis. Baseline Cr 0.8 mg/dL. Labs on admission: Cr 1.7 mg/dL, Sr albumin 2.8 g/dL, UPCR 5511 mg/g, urinalysis revealed acanthocytes. C3 152, C4 38, ANA 1:320 [speckled], ds-DNA (-), SSA > 150, SSB 106, NMO/AQP4 (+) at 1:10000. Rest of serological workup negative. No e/o infection. Kidney USG unremarkable. Kidney biopsy - LM: 35 glomeruli, no segmental or global sclerosis. Glomeruli normal, no endocapillary hypercellularity noted. IFTA <5%. Mild to moderate arterial and arteriolar sclerosis. IF: Fine granular reactivity for C3 [3+] along capillaries and in mesangium that are chunky. Rest of immunoreactants negative. Pronase IF negative. EM: Few scattered medium to large-sized electron dense deposits present in the mesangium and paramesangial area. Alternative complement pathway functional panel revealed low APFA and Fb levels and elevated C5 levels. C3GN genetic panel revealed a VUS in the THBD and MPLA gene. Patient received repeated doses of rituximab and has attained complete remission of proteinuria and resolution of AKI.

Discussion: C3GN affecting younger patients usually are mediated by genetic abnormalities of the alternative complement pathway. In addition to renal manifestations, a number of other extra-renal manifestations have also been associated with C3G including retinal involvement [drusen] and lipodystrophy, particularly in DDD. To date, concomitant NMO (+) transverse myelitis presenting concomitantly with C3GN has not been described. It remains unclear if the C3G-dominant immune complex-mediated glomerulonephritis was precipitated by the underlying SLE/Sjogren overlap syndrome.

SA-PO817

Possible Link between C3 Glomerulonephropathy and Ulcerative Colitis

Sean P. Mahoney, John Anaya, Aldo E. Torres Ortiz. *Tulane University School of Medicine, New Orleans, LA.*

Introduction: C3 glomerulopathies include both C3 glomerulonephritis (C3GN) and Dense Deposit Disease (DDD). These rare diseases occur from dysregulation of the complement pathway causing C3 deposits in the glomerular basement membrane without immunoglobulins (such as IgG).

Case Description: A 74 year old male with a past medical history of hypertension and ulcerative colitis (UC), with dialysis-dependent AKI on CKD due to colitis flare two months prior, presented with symptomatic COVID pneumonia. The AKI from the recent admission was attributed to a pre-renal state secondary to diarrhea. Further chart review determined that the patient was admitted with creatinine of 1.5, 300mg/dL of proteinuria, and hematuria before dialysis was initiated. During his time with us, the patient failed to show any signs of renal recovery. Workup revealed positive “atypical ANCA,” common in UC. Given suspicion for a glomerulonephritis, a renal biopsy was performed that showed focal proliferative necrotizing glomerulonephritis with no chronicity and C3 deposition with minimal IgG deposits, suggesting C3 Glomerulopathy. Additional tests included persistently low C3 and negative C3 nephritic factor, but genetic testing showed multiple complement pathway abnormalities including a likely pathogenic heterozygous complement Factor B variant.

Discussion: The main differential for our patient was infection-related GN. However, given lack of other immunoglobulins on biopsy and little evidence for infection, the diagnosis was more consistent with C3 glomerulopathy. Risk factors for C3 glomerulopathy have been difficult to identify. Inflammatory bowel disease (IBD) has been linked, and complement factor B gene mutations have previously been tied to familial C3GN. Furthermore, the link between the complement system and IBD has been theorized before. We surmise that C3 glomerulopathy should be considered in patients with renal failure and a history of inflammatory bowel disease, and genetic testing along with biopsy should be employed as part of the workup to help guide diagnosis, treatment, and further research. C3 glomerulopathy is a serious kidney pathology with poor prognosis, especially with late diagnosis. Multiple case studies of patients with IBD and the disease exist, and its association with complement Factor B abnormalities suggest unique associations that may lead to diagnostic or therapeutic breakthroughs.

SA-PO818

Mesoamerican Nephropathy and C3 Glomerulonephritis Leading to Kidney Failure in a Young Male from Guatemala

Devansh H. Patel, Deepak Chandramohan, Frida Rosenblum, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Mesoamerican nephropathy (MeN) refers to nonproteinuric CKD that presents in young, agricultural workers predominantly in Central America, in the absence of common etiologies for CKD. C3 glomerulopathy that includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) are glomerular disorders triggered by dysregulation of the alternative complement pathway. We present a rare case of a young Central-American male with kidney biopsy features suggestive of C3GN and MeN.

Case Description: A 28-year-old Hispanic male without significant medical history presented with reduced urine output and uremic symptoms. He worked on a sugarcane ranch in Guatemala prior to moving to the US. He did not take any medications. Physical exam was unremarkable. Workup revealed BUN 116 mg/dL, Cr 11 mg/dL, Sr albumin 4 g/dL, and UPCR 5700 mg/g. Urinalysis revealed acanthocytes and RBC casts. C3 level was low at 80 mg/dL; C4 level was normal. Comprehensive GN workup was negative; infection was ruled out. Kidney USG revealed bilateral shrunken kidneys. Kidney biopsy revealed 13/21 globally sclerosed glomeruli. The interstitium contained moderate inflammatory infiltrates, mainly monocytes, and IFTA was 60%. IF revealed granular and smudgy C3 (3+) along the capillaries and mesangium; rest of immunoreactants were negative. Functional C3G panel revealed elevated C5 and C5b-9 levels. Genetic C3G panel was negative. Given evidence of advanced chronicity features, immunosuppression was not offered and dialysis was started.

Discussion: C3GN affecting younger patients usually are mediated by genetic abnormalities of the alternative complement pathway. Our patient had a negative genetic C3G panel highlighting the fact that his C3GN is truly not mediated by a genetic abnormality or that he has a genetic abnormality that our current assays are not detecting (unlikely given the significant advancements made in this area). The co-existing severe tubulointerstitial disease likely points to a concomitant MeN given his place of origin and occupation. It is more likely that the patient had 2 different pathologies affecting the glomeruli (C3GN) and tubulointerstitium (MeN).

SA-PO819

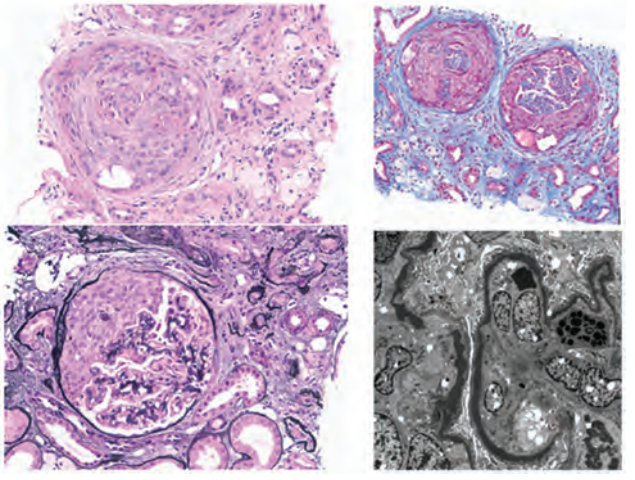
Rapidly Progressive Glomerulonephritis Due to Dense Deposit Disease Overlapping Alport Syndrome

Ruchi J. Sahota. *Mayo Clinic Minnesota, Rochester, MN.*

Introduction: Alport's syndrome is a rare X-linked mutation resulting in structural abnormalities in the glomerular basement membrane. C3 glomerulonephritis (C3GN), specifically dense deposit disease (DDD) is unique due to complement dysregulation of the alternative pathway. There are few cases reported of co-existance of Alport's with DDD. We will be discussing a case of Alport's syndrome complicated by rapidly progressive glomerulonephritis (RPGN) in the setting of DDD.

Case Description: 21 year old male diagnosed with X-linked COL4A5 Alport's variant admitted for hematuria, nephrotic range proteinuria, and elevated creatinine developed RPGN which resulted in the initiation of dialysis. Serology workup was negative for ANA, ANCA, anti-GBM, cryoglobulin, hepatitis, and HIV. Complements, Factor B and Factor H antigen were normal. Biopsy showed crescentic glomerulonephritis in setting of C3GN favoring DDD along with previous glomerular basement changes. Results were compatible with alternative pathway hyperactivation and C3GN was treated with Eculizumab as he had failed immmunosuppression and prednisone trial.

Discussion: Alport's nephropathy has a broad range of progression from advanced age with normal kidney function to rapidly progressive renal failure depending on sex and COL4A genotype. Initial management for both Alport's and C3GN require angiotensin-converting enzyme inhibitor (ACE-I); non-specific therapies include immunosuppressants, steroids, or plasmapheresis. Goal of the immunosuppression is to inhibit cellular immune response to decrease C3a and C5a production; early treatment with immunosuppression can have 100% renal recovery in C3GN. Currently, studies are ongoing for eculizumab and ravulizumab which bind with high affinity to C5 to prevent activation of MAC and C5a. This is one of the unique presentations where DDD occured upon Alport's and patient failed all conservative therapies, leaving renal transplant as the last option.



SA-PO820

Thrombotic Microangiopathy Multidisciplinary Team Assessment: Single-Center Case Series

Matthew D. Nguyen,[1] Samir D. Patel,[1] Fawaz Al Ammary,[1] Minh-Ha Tran,[2] Stefan O. Ciurea,[3] Sheetal Desai,[4] Alpesh Amin,[5] Hongyu Zhao,[1] Omid Vadpey,[5] Tai Truong,[1] Antoinette Abdelmalek,[1] Jordan Perkins,[1] Rebecca S. Ahdoot,[1] Fatima T. Malik,[1] Antoney J. Ferrey,[1] Uttam G. Reddy,[1] Ekamol Tantisattamo,[1] Yongen Chang,[1,6] Wei Ling Lau,[1] Yulian Khagi,[6] Lisa Lee,[3] Zahra Pakbaz,[3] Ramy M. Hanna.[1] *[1]University of California Irvine Nephrology Hypertension & Kidney Transplantation, Orange, CA; [2]University of California Irvine - Department of Medicine - Division of Transfusion Medicine, Irvine, CA; [3]University of California Irvine - Department of Medicine - Division of Hematology & Oncology, Irvine, CA; [4]University of California Irvine - Department of Medicine - Division of Rheumatology, Irvine, CA; [5]University of California Irvine - Department of Medicine, Irvine, CA; [6]University of California Irvine - VA LBMC Department of Medicine - Division of Nephrology, Irvine, CA.*

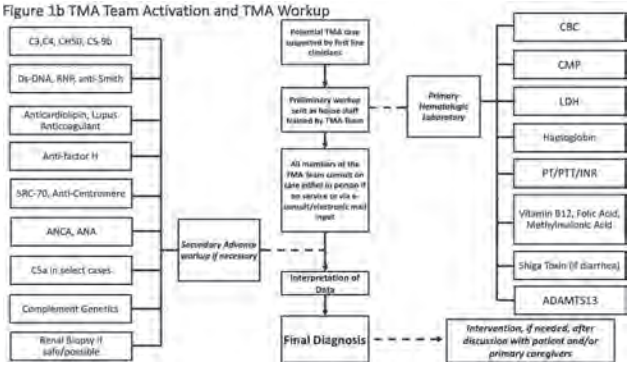
Background: Thrombotic Microangiopathies (TMAs) include an etiological diverse group of phenotypically similar disorders. While individually rare, they are seen as an aggregate with regularity. Prior reports suggested the importance of approaching TMAs in a multidisciplinary fashion. We present the design, structure, evaluation workflow and data in the initial 3-year period of the established University of California Irvine (UCI) TMA team.

Methods: This is a single-center retrospective case series of 51 diverse patients demonstrating demographics, diagnoses, triggers, treatments applied, and outcomes for patients with the diagnosis of TMA

Results: Of the 51 patients, 31 were females with an age range between 18 and 83. Twenty patients were diagnosed with atypical hemolytic uremic syndrome (aHUS). Five patients were diagnosed with Hematopoetic Stem Cell Transplant associated TMA (HSCT-TMA), 2 patients had Thrombotic Thrombocytopenic purpura (TTP). Of the 20 aHUS patients, 13 were treated with anti-complement blockade and 7 were evaluated for potential future use of complement blockade. All patients treated with anti-complement blockade (100%) demonstrated a hematologic response, 75% (9 of 12) of patients requiring renal replacement therapy remain off dialysis after 6-18 months of treatment with anti-complement blockade. HSCT-TMA patients were treated with anti-complement blockade had a less positive response.

Conclusions: This case series highlights the importance of TMA multidisciplinary team to improve diagnosis and optimize outcomes of this rare condition. Future research is needed to assist efficacy and implementation of TMA-multidisciplinary care.

Figure 1b TMA Team Activation and TMA Workup



SA-PO821

IgA Nephropathy with Complement-Associated Thrombotic Microangiopathy: A Case Series

Ryan E. Fekrat,[1] Gayathri Dileep,[1] Matthew D. Nguyen,[1] Omid Vadpey,[2] Jonathan E. Zuckerman,[3] Ramy M. Hanna.[1] *[1]University of California Irvine Nephrology Hypertension & Kidney Transplantation, Orange, CA; [2]University of California Irvine Department of Medicine, Orange, CA; [3]University of California Los Angeles – David Geffen School of Medicine - Department of Pathology and Lab Medicine, Los Angeles, CA.*

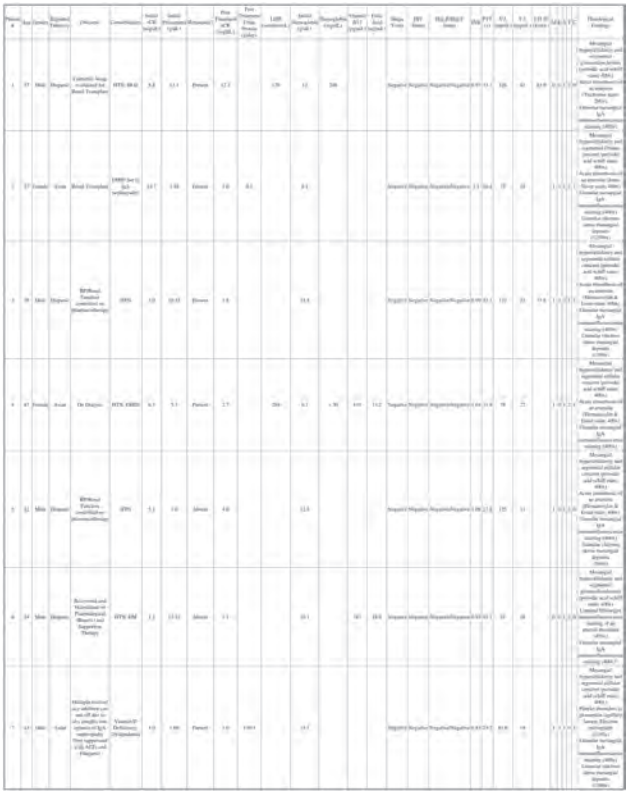
Background: Presentation of immunoglobulin A nephropathy (IgAN) with TMA has been commonly documented, however the relationship betwen IgAN and complement activation requires further exploration. Here we present a series of 7 patients with histological findings consistent with IgA nephropathy and TMA with supplementary serological data, suggesting a linkage between complement pathology and IgA nephropathy.

Methods: Coded datasets here are identified by our team using Epic software under consent of participating patients. Patients' biopsy data with histological specimen is complemented by data from patient records. Histological specimen was read by UCLA Health Renal Pathology.

Results: The collected data shown in Table 1 shows 7 patients evaluated at UCI with the average age being 41.6 ± 8.1 years, 5/7 being male and 4/7 being Hispanic. 1/7 of the patients showed evidence of acute systemic TMA while 6 patients had renal limited TMA supported by histological slides. Average initial serum creatinine for all patients was 5.17 ± 4.74 mg/dL, average initial urine protein was 6.75 ± 5.11 g/day, and 5/7 patients had evidence of hematuria in their urine. Serological evaluation of complement levels show 2/7 (28.6%) of patients had low C3 complement levels. 1/7 (14.3%) of patients showed elevated C4 levels.

Conclusions: The patterns of histology show typical IgA nephropathy deposition and TMA. It is suggested that mesangial IgA activates mesangial cells, activating complement through the lectin and alternative pathways. This would not be the first time complement disorder is implicated as the conception of IgA TMA as reflected in some of our patients having lower C3 levels while having normal C4, however this finding may present a precedent for future research and clinical identification.

Patient Lab Values and Outcomes



HTN = Hypertension; ESRD = End Stage Renal Disease, HLD = Hyperlipidemia, DM = Diabetes Mellitus, sCR = serum creatinine

SA-PO822

Kidney-Limited Thrombotic Microangiopathy (TMA) Is Prevalent along the Spectrum of TMA and Does Not Exclude Complement Defects

Daan P. van Doorn,[1,2] Sjoerd Timmermans,[1,2] Pieter van Paassen.[1,2] Limburg Renal Registry; Expert Center for Immune-mediated Kidney Diseases and Vasculitis. *[1]Maastricht Universitair Medisch Centrum+, Maastricht, Netherlands; [2]Universiteit Maastricht Cardiovascular Research Institute Maastricht, Maastricht, Netherlands.*

Background: The syndromes of TMA are associated with acute kidney injury and risk of ESKD. Patients typically present with systemic hemolysis, that is, thrombocytopenia and microangiopathic hemolytic anemia. Kidney-limited TMA, however, can occur but is often overlooked and undertreated. Here, we studied morphologic features on kidney biopsy and their clinical correlates in patients with TMA.

Methods: Patients with TMA on kidney biopsy were recruited from the Limburg Renal Registry and classified as definite complement-mediated (C-)TMA (i.e., ≥1 pathogenic complement gene variant), probable C-TMA (i.e., massive *ex vivo* C5b9 formation, either with ≥1 complement gene variant of uncertain significance or not), and secondary TMA (i.e., normal *ex vivo* C5b9 formation without complement gene variants). Morphologic features, including activity and chronicity indices, were studied in relation to clinical presentation and outcome.

Results: Patients were classified as definite C-TMA (*N*=14, 18%), probable C-TMA (*N*=21,27%),orsecondaryTMA(*N*=42,55%),including52(66%;*n*/*N*=8/14,10/21,and33/42) patients with kidney-limited TMA. Definite and probable C-TMA presented with higher creatinine (11.0 [IQR, 4.0-13.3] and 5.7 [IQR, 4.0-8.2] vs. 3.2 [IQR, 2.2-5.3] mg/dL; *P*<0.001) and at younger age (33 [IQR, 25-29] and 33 [IQR, 28-44] vs. 40 [IQR, 35-52] years; *P*=0.01) as compared to secondary TMA. Glomerular thrombosis was not associated with systemic hemolysis, but appeared more common in definite and probable C-TMA as compared to secondary TMA (79% and 76% vs. 43%; *P*=0.005). Morphologic features neither defined etiology nor differed between systemic TMA and kidney-limited TMA. Kidney remission, that is, recovery of kidney function and/or ≥25% increase in eGFR, occurred more often in eculizumab treated patients with definite (100% vs. 11%; *P*=0.001) and probable C-TMA (86% vs. 29%; *P*=0.009) but not secondary TMA (60% vs. 67%; *P*=0.7) as compared to untreated patients; chronicity indices did not predict kidney remission.

Conclusions: Kidney-limited TMA is common along the spectrum of TMA, including definite and probable C-TMA. Thus, a kidney biopsy is often needed to detect the TMA but cannot define etiology. Chronicity indices should not be used to withhold complement-specific drugs in patients with definite and probable C-TMA.

Funding: Commercial Support - Alexion Pharmaceutical Inc. (AstraZeneca), Private Foundation Support

SA-PO823

Abstract Withdrawn

SA-PO824

Biological Parameters in Biopsy-Proven Renal Thrombotic Microangiopathies

Jean-Michel Halimi,[1,2] Valentin Maisons,[1] Etienne Chardon,[2] Sophie Caillard,[3] Marie Frimat,[4] Laurent Mesnard,[5] Sophie Chauvet,[6] Eric Piver.[1] MATRIX Consortium Cohort Study (NCT05991245). *[1]Centre Hospitalier Regional Universitaire de Tours, Tours, France; [2]INSERM U1327, Tours, France; [3]Universite de Strasbourg, Strasbourg, France; [4]Universite de Lille, Lille, France; [5]Hopital Tenon, Paris, France; [6]Hopital Europeen Georges Pompidou Cancerologie, Paris, France.*

Background: Thrombotic microangiopathies (TMA) are suspected in the presence of anemia, high LDH, low haptoglobin, thrombocytopenia and schistocyte>1%. The kidney is the most frequently affected organ. However, interpreting biological parameters in this context is unclear.

Methods: Biological parameters were studies in 967 patients with biopsy-proven renal TMA from 25 French hospitals during the 2009-2023 period.

Results: Median age was 49 (IQR: 36-64), 53.2% were male. All TMA KDIGO causes were represented. Biomarker sensitivity (ie. proportion of patients with the parameter) ranked as follows: anaemia (81.7%), high LDH (75.4%), low haptoglobin (53.7%), thrombocytopenia (40.3%), schistocytes>1% (34.0%) but varied widely according to fibrinogen, prothrombin time (PT) and serum creatinine. The sensitivity of these biological parameters was preserved (>75%) only in patients with both fibrinogen levels <5 g/L and serum creatinine ≥300 µmol/L, ie 29% of the population. Laboratories used 11 different ways to report schistocytosis: various threshold values and reporting (binary, qualitative, semi-quantitative, quantitative, adjective-based vs numerical) were found. Schistocyte>1% had been used as the sole criterion, suspicion of TMA would have been missed in 66.0% of patients (23.8% to 86.4% according to TMA causes). Unsupervised cluster analysis revealed that biological parameter structuring is strongly linked to specific renal TMA causes. Using fibrinogen, serum creatinine, anemia, LDH and haptoglobin, A simple algorithm identified patients with infrequent (sensitivity <10%) or very frequent (sensitivity: 75-90%) phenotypes.

Conclusions: Schistocyte reporting varies widely and "schistocyte>1%" misses two-thirds of renal TMAs. Biological parameters' results should be interpreted according to fibrinogen, creatinine and PT but careful analysis of these parameters can help differentiate among TMA causes. A simple algorithm provides crucial information regarding the necessity of kidney biopsy, indicating when renal TMA is either unlikely or highly probable.

SA-PO825

A Tale of Two Findings: Thrombotic Microangiopathy and Podocytopathy Due to Graft vs. Host Disease

Jonathan Hall, David A. Mcmillan, Nathaniel Leonardi, Prasanth Ravipati, Ryan Mullane. *University of Nebraska Medical Center, Omaha, NE.*

Introduction: Acute kidney injury (AKI) following hematopoietic stem cell transplantation (HSCT) is common, and typically multifactorial in etiology related to infections, medications, and graft versus host disease (GVHD). Thrombotic microangiopathy (TMA) following HSCT is not uncommon and can be associated with GVHD. When TMA is due to GVHD, it is often refractory to treatment with steroids. Nephrotic syndrome, however, is a rare presentation of kidney disease following HSCT.

Case Description: A 56-year-old female with myelodysplastic syndrome that progressed to acute myeloid leukemia for which she had undergone allogenic HSCT 8 months ago was found to have a serum creatinine of 2.9 mg/dL (prior serum creatinine of 1.0 mg/dL). She reported recent development of leg edema with weight gain. Her serum albumin was 2.5 g/dL, a urine protein to creatinine ratio was 14.7, and urine microscopy revealed microscopic hematuria. A kidney biopsy was performed, and the patient was begun on IV methylprednisolone. Light microscopy revealed mesangiolysis, duplication of basement membranes, and intracapillary red cell fragmentation, consistent with TMA. Electron microscopy showed subendothelial widening with accumulation of flocculent material and podocyte effacement of at least 90% of the sampled capillary surface area. Despite treatment with IV methylprednisolone, the patient had progression of kidney failure and required hemodialysis. Given the biopsy findings of TMA, treatment was started with eculizumab. The patient had subsequent improvement in her kidney function,

and hemodialysis was stopped. Over the next 4 weeks, her serum creatinine decreased from a peak of 5.6 mg/dL to 2.2 mg/dL, and her serum albumin normalized.

Discussion: Co-presentation of TMA with diffuse podocytopathy is a rare cause of kidney dysfunction in patients post-HSCT. TMA due to GVHD is typically refractory to treatment with steroids and is thought to be due to alternative complement pathway dysfunction, necessitating treatment with complement blockade. Combination therapy with eculizumab and corticosteroids in this unusual case of concurrent TMA and podocytopathy led to improvement in the patient's renal function and normalization of the patients' serum albumin.

SA-PO826

Castleman Disease and Kidney Thrombotic Microangiopathy

Wenchy Tan, Melissa Notis, Miriam Chung, John C. He. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Idiopathic Multicentric Castleman Disease (iMCD) is a rare, life-threatening disorder that causes multiorgan dysfunction, generalized lymphadenopathy and systemic hyperinflammation that rarely affects the kidney. Thrombotic microangiopathy (TMA) is characterized by microvascular thrombosis due to vessel wall abnormalities in arterioles and capillaries. Kidney TMA is a rare manifestation of iMCD. We report a rare case of iMCD with kidney TMA in a young patient.

Case Description: 19 year-old male presented with diarrhea, night sweats, leg swelling and dark urine. Initial workup included creatinine 1.5 mg/dL, albumin 1.9 g/dL, C-reactive protein 310 mg/L, LDH 317 U/L, and platelet 90 K/μL. Urinalysis showed 2+ protein and small blood, urine protein-creatinine ratio 0.3 mg/mg. Kidney biopsy showed glomerular mesangiolysis with fragmented red blood cells and platelets, subendothelial widening and focal areas of glomerular basement membrane duplication consistent with membranoproliferative pattern of TMA. He was started on eculizumab. Further studies revealed normal complements, negative ANA, anti-ds DNA, anti-cardiolipin antibodies, HHV-8, and HIV. CT scan showed multiple retroperitoneal lymph nodes and adrenalitis, concerning for Castleman Disease with supportive excision lymph node biopsy results. His kidney function continued to decline, and hemodialysis was started after three weeks. Siltuximab and high-dose steroids were started after iMCD diagnosis.

Discussion: iMCD has an estimated yearly incidence of 3-4 cases nationwide. Kidney complications are very rare, though kidney TMA and AA amyloidosis have been reported. The pathogenesis of kidney TMA in iMCD is unclear; may involve increased production of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) by proliferating plasma cells within lymph nodes. Elevated serum levels of VEGF and IL-6 are reported to decrease VEGF expression within glomerular podocytes, which may have a role in thrombotic glomerular injury. There is no standard treatment for iMCD; IL-6 inhibitors, tocilizumab and siltuximab have demonstrated kidney recovery. In our patient, kidney function rapidly declined requiring dialysis. This highlights the importance of having iMCD as a differential diagnosis for kidney TMA with an atypical presentation and promptly starting treatment.

SA-PO827

Penicillin-Induced Thrombotic Microangiopathy

Huanchun N. Lai.[1,2] [1]*McLaren Health Care Corp, Mt Clemens, MI;* [2]*Michigan State University, East Lansing, MI.*

Introduction: Thrombotic microangiopathies (TMA) are characterized by features of thrombocytopenia, microangiopathic hemolytic anemia, acute kidney injury, combined with cardiac and neurologic abnormalities. Drug-induced thrombotic microangiopathy (DITMA) is an acquired condition due to either immune (antibody-mediated) or non-immune (direct toxicity) mediated organ dysfunction secondary to medication exposure. DITMA is an uncommon condition that can be fatal if the diagnosis is missed. It must be considered in the presence of characteristic features, without evidence of systemic causes of TMA. Here, we describe a case of penicillin-induced TMA in a previously healthy individual.

Case Description: A 25-year-old male with no medical history presented with three-day history of hematuria and non-bloody diarrhea. Patient was treated one week prior for a dental infection with penicillin VK for four days. On admission, patient had no other complaints other than persistent hematuria. Initial lab work showed significant thrombocytopenia of 23K/mcL, PBS 2+ schistocytes, haptoglobin <10mg/dL, LDH 2,600U/L, creatinine of 2.1mg/dL, and UA had RBC count of 27. Serologic workup showed normal C3 and C4, ANA, dsDNA, GBM, MPO and PR3 were all negative. DAT, SPEP, and HIV were negative. ADAMTS13 activity was normal. Patient was started on prednisone with improvement of platelets and renal function, without the need for plasma exchange. Patient completed a six week prednisone taper with resolution of symptoms and renal recovery.

Discussion: DITMA is uncommon but poses potential life-threatening complications. It is under-recognized due to diagnostic challenges and lack of standardized testing. Therefore, it is difficult to establish a causal relationship with the implicated agent. Most commonly, DITMA is associated with quinine and chemotherapy agents. There are rare reports of penicillin as cause of DITMA in literature. This case further highlights penicillin as a cause of TMA and illustrates the management and anticipated recovery after the cessation of the offending medication.

Days since initial exposure to Penicillin VK and the progression of DITMA

Labs	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 42
Hgb (g/dL)	15.1	12.9	11.4	10.9	10.9	11.0	11.9	13.6
Platelets (K/mcL)	23	16	21	29	60	123	269	214
BUN (mg/dL)	22	21	20.7	19.8	19.8	16.9	16	14.1
Creatinine (mg/dL)	2.1	2.13	2.0	23	1.6	1.6	1.48	0.9
LDH (U/L)	-	2600	-	2091	1740	1250	1046	207

SA-PO828

Use of Eculizumab in the Management of Drug-Induced Thrombotic Microangiopathy: A Case Report

Afsheen Afzal, Thangamani Muthukumar, Steven Salvatore. *Weill Cornell Medicine, New York, NY.*

Introduction: The use of complement pathway inhibitor, Eculizumab, for managing drug-induced thrombotic microangiopathy (TMA) is controversial. We describe a patient with cancer who developed TMA and acute kidney injury (AKI) associated with the use of bevacizumab/oxaliplatin. Early identification and use of eculizumab resulted in complete recovery of kidney function.

Case Description: 64-year-old female with stage IIb colon cancer on FOLFOX (folinic acid, fluorouracil [5FU], oxaliplatin [Oxa]) & Bevacizumab(Bev) for 6 months, later maintained only on Bev/5FU.2 days after resumption of FOLFOX&Bev infusions, patient was sent to ER by Oncology clinic for reduced urine output, and elevation in serum creatinine (sCr) to 4.96 from 0.65 2 days ago. She was normotensive at presentation, denied diarrhea, reduced fluid intake, NSAIDs or recent IV contrast use. Her hemoglobin was 9.8 (11.3 two days ago) and platelets were 27,000 (90,000 one week ago). Direct and indirect bilirubin were 0.9, AST 97 from 25, LDH 1208 and haptoglobin < 8. Peripheral blood smear revealed 8-10 schistocytes per HPF. Urinalysis revealed hematuria(17 RBCs), proteinuria(>500), glucosuria (50, new). Urine electrolytes were indicative of intrinsic kidney injury. Urine protein/Cr ratio was 2.8g/g and urine microalbumin/Cr ratio was 0.8g/g. ADAMTS-13 levels were normal. The constellation of anemia, thrombocytopenia, elevated LDH, low haptoglobin, schistocytes on peripheral smear and AKI were indicative of microangiopathic hemolytic anemia likely due to Bev/Oxa. Skin biopsy revealed +ve staining for C5b-9 in 8-10 dermal capillaries. Patient was started on Eculizumab 900mg on day 1. There was immediate improvement in hematological markers; however, sCr continued to rise upto 14 over next few days. She underwent a kidney biopsy(10 days after presentation), which revealed severe acute tubular injury with intraluminal material suggestive of hemoglobin casts, diffuse C5b-9 positivity, and focal subacute endothelial injury involving glomeruli with thickening of capillary walls. Patient continued to receive Eculizumab weekly then biweekly with sCr trending down to 1.0 over the course of a month.

Discussion: This case highlights the immediate reversal of microangiopathic hemolytic anemia with the use of Eculizumab. Early use of eculizumab likely reduced the severity of kidney injury and aided in the complete recovery of kidney function.

SA-PO829

Infection-Related Glomerulonephritis with Thrombotic Microangiopathy following Treatment for Streptococcal Bacteremia: A Case Report

Keisuke Onishi, Tadashi Sofue, Tetsuo Minamino. *Kagawa Daigaku, Takamatsu, Japan.*

Introduction: Post-streptococcal acute glomerulonephritis (PSAGN) occurs 1-3 weeks after infections of the upper respiratory tract or skin. Infection-related glomerulonephritis can be accompanied by anemia and thrombocytopenia; however, the detailed mechanism remains unknown. Here, we report a case of PSAGN complicated by thrombotic microangiopathy (TMA) after treatment for streptococcal bacteremia.

Case Description: A 64-year-old woman with no relevant medical history was admitted to our hospital with fever and abdominal pain. Antibiotics were administered because a blood culture revealed group A *Streptococcus*, although the fever and right-sided chest pain persisted. Surgical thoracic drainage was performed after a diagnosis of pyothorax based on CT and pleural fluid analysis. Postoperative fever persisted, and 14 days after admission, serum Cr was 1.2 mg/dL and urinalysis results were normal; however, low C3 and CH50 levels were observed. On day 21 after admission, gross hematuria developed, and urinalysis revealed proteinuria. Based on the patient's medical history and positive ASO findings, she was clinically diagnosed with PSAGN. Progressive thrombocytopenia and hemolytic anemia were also observed, requiring differentiation from TMA. One month after PSAGN onset, serum Cr level had elevated to 1.8 mg/dL. Renal biopsy was performed, and light microscopy revealed membranoproliferative glomerulonephritis with tubulointerstitial nephritis. Immunofluorescence revealed C3 and IgG deposition in the glomerular tuft, and electron microscopy showed dense subepithelial deposits, leading to the diagnosis of PSAGN. Six weeks after the onset of PSAGN, 30 mg prednisolone was administered because her renal function, anemia, and complement levels did not improve. Renal function and hemolytic anemia improved rapidly after treatment initiation, followed by steroid tapering and complete remission of proteinuria after 3 months.

Discussion: There have been few reports of cases of secondary TMA after severe streptococcal infection or of TMA complicated by PSAGN. In this report, we captured the natural history of PSAGN development by observing gross hematuria followed by a drop in complement levels after streptococcal infection. Because TMA occurred simultaneously with PSAGN, a common underlying pathogenesis is hypothesized for both diseases.

SA-PO830

Spectrum of Monoclonal Gammopathy of Renal Significance (MGRS) in a Tertiary Care Hospital in India

Atanu Pal, Rajnarayan Mukherjee, Tathagata Mukherjee, Bibek Maulik. KOLKATA IPGMER Nephrology. *Institute of Postgraduate Medical Education and Research, Kolkata, India*.

Background: MGRS is a heterogeneous group of kidney disorders characterized by direct or indirect kidney injury caused by toxic monoclonal immunoglobulin that does not meet the current hematological malignancy criteria. The concept of MGRS was introduced in 2012 by IKMG. The diagnosis of MGRS is typically made by nephrologist through kidney biopsy. The followings are the Aims of the study: 1.Histopathological spectrum of MGRS patients, 2.Different clinical & pathological variable in MGRS patients, 3.Response to standard of care

Methods: All MGRS patients (IKMG guidelines) attending IPGME & R hospital are included in this study over a period of 1st January'23 - December'23. All data are captured by using preformed proforma & analysed by SPSS software.

Results: 15 patients were included. Median age - 52 years, (2 patients < 40 years). Male : Female 1:1. Diabetes was found in 5/15, one hypothyroid, 3 patients had hypertension, one patient had Urinary bladder Carcinoma. **Presentations**: Nephrotic syndrome - 8, RPRF - 3, AKI - 2, CKD3b -1, CKD4-1. Peripheral blood - Eosinophilia (Absolute count > 500/microlitre) found in 10. **Renal biopsy**: AL amyloidosis - 8, PGNMID - 3, MIDD (LCDD) - 3, C3 glomerulopathy - 1 **Serum Protein Electrophoresis & Immunefixation**: M band was detected in 60% of study population. AL amyloidosis (8) - M band in 5. Immunefixation showed IgG lambda in 6, 2 patients had IgG Kappa. PGNMID (3) - 1 had no M band & Immunefixation failed to detect any monoclonal intact immunoglobulin & or freelight chain. Renal biopsy showed IgG3kappa. Other two patients had no M band, Immunefixation showed IgG Kappa & lambda. LCDD (3) - one patient had no M band, but IgG Kappa was found in one patient, two patients showed IgG lambda. Serum Free light chain ratio was altered in 8, lambda dominance among 5, rest were Kappa.

Conclusions: The MGRS group of kidney diseases often produces diagnostic challenges. So it requires multidisciplinary coordination. Cardiac death is common both pre and post therapy, particularly in AL amyloidosis patients. Therefore early & timely detection are required to improve overall & renal prognosis of patients & also reduces the chance of progression into overt hematological malignancy. Clone based therapy followed by HSCT may be curative.

Funding: Government Support - Non-U.S.

SA-PO831

A Clinicopathological Study of IgA Variant-Proliferative Glomerulonephritis with Monotypic Ig Deposits (PGNMID)

Margot Poux, Marguerite Vignon, Elise Michelon, Vincent Javaugue, Frank Bridoux, Khalil El Karoui. *Assistance Publique - Hopitaux de Paris, Paris, France*.

Background: Proliferative glomerulonephritis with monotypic immunoglobulin deposits (PGNMID) is a rare form of monoclonal gammopathy of renal significance (MGRS) related to glomerular non-organized monotypic Ig deposits, usually IgG. The IgA variant of PGNMID has been rarely described. We aimed at describing a large cohort of IgA-PGNMID to detail population characteristics, treatment, and renal and hematological outcome.

Methods: We conducted a multicentric retrospective study of all French patients with monotypic IgA glomerular deposits with a PGNMID diagnosis between May 2012 and May 2023. Patients were classified in two groups according to the presence of a detectable monotypic IgA component (blood, urine, or blood marrow). Renal, and hematological, baseline characteristics and long-term follow-up were analyzed.

Results: Forty-three patients were identified. Eighteen (41,8%) patients had a detectable monoclonal IgA clone (IgA-MGRS) and 25 (58,1%) (unproven MGRS) had no identified clone in blood and/or blood marrow. Most patients were men (65%), and the mean age was 52 years. Renal function impairment was frequent at diagnosis (DFG < 60 ml/min in 77,7 % and 68%, in the IgA-MGRS and unproven MGRS groups, respectively) and proteinuria > 1 g/g in 15/18 (83,3%) and 22/25 (88%) cases, in the IgA-MGRS and unproven MGRS groups, respectively. There were no significant differences between groups at baseline, except for hypertension. After treatment with anti-plasmocytic drugs, patients with a detectable clonal IgA and eGFR > 30 ml/min/m2 had a correlation between hematological and renal response after one year follow-up (Fisher p=0,04). 3/7 patients (42,8 %) had disease recurrence after renal transplantation, and all of them had hematological relapse. Four patients developed overt malignancy with MM. At last follow-up, renal survival was significantly lower in IgA-MGRS group than unproven MGRS and primitive polytypic IgA nephropathy groups.

Conclusions: In conclusion, IgA-PGNMID is a distinct entity from IgA nephropathy, with renal outcome correlated with hematological outcome after anti plasmocytic treatment. A pathogenic plasma cell clone is identified in 42% cases and is associated with a worse renal prognosis.

SA-PO832

Monoclonal Gammopathy in ANCA-Negative Pauci-Immune Crescentic Glomerulonephritis: Is There Causality? Case Series

Maria Jose Vargas-Brochero, Poemlarp Mekraksakit, António d. Inácio, Patrícia A. Domingues, Fernando C. Fervenza, Alessia Buglioni, Ladan Zand. *Mayo Clinic Minnesota, Rochester, MN*.

Background: In a subset of patients with diagnosis of ANCA-associated vasculitis, no antibodies(MPO or PR3) can be identified, and these cases are referred to as"ANCA-negative". The antibody or trigger for the disease in this subset of patients has remained elusive. Monoclonal gammopathy(MG) has been shown to directly activate neutrophils. We hypothesized that MG may be the cause for the renal presentation in such patients. We therefore explored the role of MG and its association with disease presentation in cases of ANCA-negative vasculitis.

Methods: We retrospectively analyzed database between Jan2000 through Dec2023 and identified patients with a diagnosis of pauci-immune crescentic glomerulonephritis who had undergone testing for MPO, PR3, and monoclonal gammopathy (MG). Patients positive forMPO, PR3, or anti-GBM and those with a kidney transplant, were excluded. Time-to-event analysis was conducted using the Kaplan-Meier method, death as the event of interest

Results: 14 patients diagnosed with ANCA-negative vasculitis who had undergone monoclonal testing. 8(57%) had evidence of MG, prevalence significantly higher than the anticipated (3%) in the general population over 50 years of age. Mean age of this group was 60.3 (12.2) years, 75% were female, with mean serum creatinine of 4.3(1.92) mg/dL. Most common histological characteristics were Focal Berden Classification(n=5, 62.5%) and Mayo Clinic/Renal Pathology Society Chronicity Score(MCS) of moderate(n=5, 62.5%). Most common heavy chain was IgG(n=4, 50%), and Kappa light chain(n=4, 50%) with serum free light chain ratio of 2.3[1.01-3.41] for involved to uninvolved light chain. Median follow-up time was 3.2 years. At the last follow-up, 3 patients progressed to end-stage kidney disease, and 4 patients died (2 without ESKD). Mean time to death of 3.0(4.1) years. Estimated one-year survival was 85.7%(95% CI 13.2 to 63.3) and two-year survival was 68% (95% CI:18.6 to 40.3).

Conclusions: Our study shows that majority of patients with ANCA-negative vasculitis have evidence of MG and it is possible that the MG is involved in the pathogenesis of the disease and may need to be considered as MGRS lesion in the future. Additional research is needed to better understand the role of MG in causing pauci-immune crescentic GN.

SA-PO833

Collaborative Study: Identifying Risk Factors for ESKD in Leukocyte Chemotactic Factor 2 (ALECT2)-Associated Amyloidosis

Maria Jose Vargas-Brochero,[1] Lisa E. Vaughan,[1] María F. Zavala Miranda,[2] Norma O. Uribe-Uribe,[2] Juan M. Mejia-Vilet,[2] Nelson Leung.[1] [1]*Mayo Clinic Minnesota, Rochester, MN;* [2]*Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico*.

Background: ALECT2 represents the third type of kidney-involved amyloidosis; its clinical prognosis and natural history are uncertain.

Methods: This was a retrospective cohort study of adults diagnosed with kidney biopsy-proven ALECT2 by immunohistochemistry or mass spectrometry between 1/1/2000 and 12/31/2022 at two institutions. Patients with end-stage kidney disease (ESRD) at diagnosis or without follow-up were excluded. ESRD-free survival was estimated using the Kaplan-Meier method. Cox regression was used to evaluate associations between characteristics at diagnosis and risk of incident ESRD

Results: There were 54 patients meeting inclusion criteria for this study (mean (SD) age 63.7 (7.2) years, 28 (51.8%) male and 48 (88.8%) Hispanic. There were a total of 19 (35.2%) ESRD events occurring during a mean (SE) follow-up of 7.1 (0.8) years. Estimated survival was 92% (95%CI: 85%-99%) at one year, 79% (95%CI: 67%-92%) at two years, and 70% (95%CI: 55%-88%) at 5-year follow-up. Patients with a higher percentage of glomerulosclerosis, serum creatinine, proteinuria, interstitial fibrosis/tubular atrophy, and a lower eGFR had a significantly higher risk of incident ESRD (P<0.05 for all; see **Table 1**)

Conclusions: This study reports long-term renal survival for ALECT2 patients and identifies several promising biomarkers associated with worse renal survival

Table 1. Univariable associations between patient characteristics at the time of diagnosis and risk of ESRD

Baseline Patient Characteristic	HR (95% CI)	P
Percent of Glomerulosclerosis (%) (per 10 %)	1.27(1.05-1.53)	0.01
Serum creatinine (per 1 mg/dl)	1.96(1.25-3.08)	0.003
eGFR (per 1 ml/min/1.73m^2)	0.90(0.90-0.98)	0.004
Proteinuria (per 1g/24hr)	1.11(1.03-1.20)	0.006
Interstitial Fibrosis/Tubular Atrophy (per 10%)	1.31(1.04-1.64)	0.018

SA-PO834

Longitudinal Clinical Outcomes with Membranous-Like Nephropathy with Monoclonal Light-Chain Deposition: A Case Series

Elaine Park,[1] Blaithin A. McMahon,[1] Guangchen Zou,[2] Mohamed G. Atta,[2] Benjamin R. Teruel.[1] [1]*Medical University of South Carolina, Charleston, SC;* [2]*Johns Hopkins Medicine, Baltimore, MD.*

Background: Membranous-like nephropathy with monoclonal light chain deposition is a rare entity first described in 2014. This pathological entity is very distinct from primary idiopathic membranous nephropathy, with the prominent feature of masked IgG-kappa deposits on immunofluorescence. The purpose of this small case series is to examine the treatment and long-term outcomes for 6 with patients with this disease.

Methods: This six-patient series was identified at Johns Hopkins Medicine and Medical University of South Carolina. We examined demographics, clinical characteristics at presentation, light microscopic findings, glomerular immunofluorescence staining, and long-term renal outcomes. The median duration of follow-up was 12.5 years.

Results: The patients most commonly presented with edema and had a mean 24 hr urine protein of 3.09 g/day. Only one patient had an identifiable MGUS at presentation. All renal biopsies stained positive for IgG kappa light chain. Half of all patients had electron dense deposits at other sites other than at the sub-epithelial membrane (including sub-endothelial and mesangial site). 5 out of the 6 patients were found to have intramembranous deposits. Treatment included no treatment, RAAS blockade, and immunosuppressants. Of the 6 cases, 4 achieved complete remission and 2 progressed to ESRD.

Conclusions: Although this is a small case series, membranous-like nephropathy with IgG kappa light chain deposition can still contribute to ESRD. None of these patients who progressed to ESRD received cyclophosphamide. Additional observational studies are needed to better understand the response to immunosuppressive therapy.

SA-PO835

Kidney Prognostic Value of Serum Monoclonal Immunoglobulin in Nonautoimmune Diseases Related to Cryoglobulinemic Glomerulonephritis

Lei Ma, Dandan Liang, Yuanyuan Xia, Feng Xu, Shaoshan Liang, Dacheng Chen, Xinchen Yao, Fan Yang, Xiaodong Zhu, Caihong Zeng. *National Clinical Research Center for Kidney Diseases, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, NanJing, China.*

Background: To explore the clinicopathological features and renal outcome in patients with cryoglobulinemic glomerulonephritis (Cryo-GN) without evidence of autoimmunity disorders.

Methods: Sixty-nine patients with Cryo-GN from a single center were recruited in this retrospective study. Their clinical, pathologic, and follow-up data were collected and analyzed. According to whether the serum monoclonal immunoglobulin (MIg) and HBV-DNA/HBV markers or HCV-RNA/anti-HCV antibodies were positive or not, they were classified into four groups: positive serum MIg only (MIg group), positive HBV-DNA/HBV markers or HCV-RNA/anti-HCV antibodies (HBV/HCV) only (HBV/HCV group), positive serum MIg and HBV/HCV (MIg+HBV/HCV group), and all MIg/HBV/HCV negative group.

Results: The male-to-female ratio was 1.38:1 with a mean age of 50.4±14.7 years in the patient cohort. Hypertension was presented in 59.4% of cases, anemia in 73.9%, renal insufficiency in 58.0%, nephrotic proteinuria in 44.9% and microscopic hematuria in 94.2%. The MIg group had significantly lower eGFR levels, higher cryoglobulin levels, and higher rates of abnormal serum-free light chain ratios than the MIg/HBV/HCV negative group. The most common histological pattern of Cryo-GN was membranoproliferative glomerulonephritis (MPGN), and the MIg group had significantly higher scores of the severity of intracapillary cryo-Plugs than the MIg+HBV/HCV group and the MIg/HBV/HCV negative group. Sixty-three patients had a median follow-up of 31.2 months, and 25.4% of them progressed to end-stage renal disease (ESRD). The renal survival was inferior for MIg group than for HBV/HCV group. Multivariate analysis showed that serum MIg and the severity of intracapillary cryo-plugs were independent prognostic factors.

Conclusions: Regardless of the presence of HBV/HCV infection, non-autoimmune diseases related Cryo-GN patients with serum MIg had worse renal function and renal survival. Serum MIg and severity of intracapillary cryo-Plugs were independent risk factors for renal survival in Cryo-GN patients without autoimmune diseases.

Funding: Government Support - Non-U.S.

SA-PO836

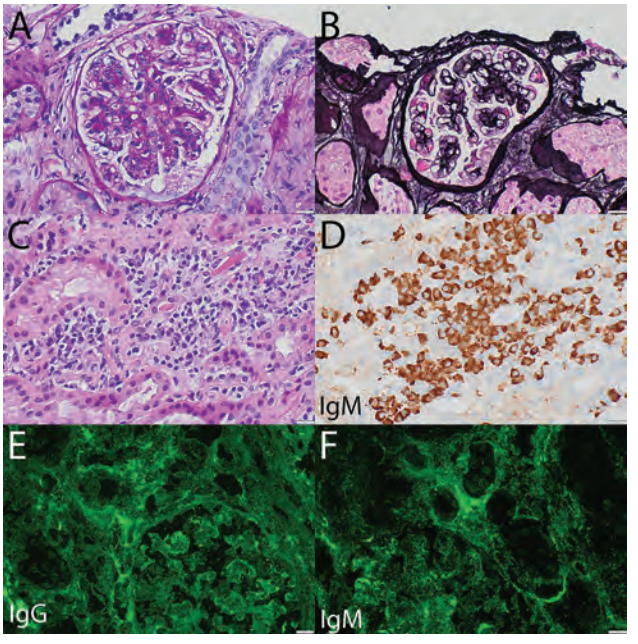
Plasma Exchange to Prevent Cyroglobulinemic Vasculitis Flare in Sjogren Membranoproliferative Glomerulonephritis

Patrick J. Palacios, Akwe Nyabera, Omar A. Ayah, Sarwat Gilani, Mir T. Ali. *The University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Introduction: Cryoglobulinemia related membranoproliferative glomerulonephritis (MPGN) is a described manifestation of renal disease in Sjogren's. Treatment involves steroid therapy and rituximab. Plasma exchange (PLEX) can reduce the incidence of rituximab induced cyroglobulinemic vasculitis (CV) flare. There are differences in literature on when to initiate PLEX prior to rituximab. We describe a case of Sjogren's related MPGN requiring PLEX prior to rituximab in order to prevent CV flare.

Case Description: 73y.o female with PMH of Sjogren's, HTN, HF, noted to have 2.8 g/g of proteinuria and a rise in serum Cr from 1 mg/dL-1.5 mg/dL over a 2-month period. Serology showed positive:anti-SSA (>8), ANA (>1:640), anti-smooth muscle (23.84), cryocrit (79%) and rheumatoid factor (RF) (69.86). Decreased:C3 (89 mg/dL) / C4 (3 mg/dL) and elevated IgM (1139 mg/dL). Hepatitis B/C and HIV were negative. Kidney biopsy showed MPGN and tubulointerstitial nephritis. She was initiated on a prednisone taper, and underwent PLEX prior to rituximab.

Discussion: Risk factors for rituximab induced CV flare are:an elevated cryocrit percentage, extremely low C4 and positive RF. Vascular damage is related to classical pathway activation by both RF-positive IgM cryoglobulin and IgG1 of rituximab. PLEX reduces the incidence of flare. There are differences in the literature on what criteria should be used to determine PLEX prior to rituximab. One recommendation is for IgM levels >4g/dL; our pts levels were lower at 1.1 g/dL. However, other sources recommend PLEX for a cryocrit percentage of >10%, and her cryocrit level was 79%. We suggest that patients with cryoglobulinemic MPGN that meet any of the criteria for possible rituximab induced flare, PLEX therapy should be considered prior to rituximab.



A) MPGN injury
B) Tubulointerstitial inflammation
C) IgM+ plasma cells

SA-PO837

Membranoproliferative Glomerulonephritis with Striated Ultrastructural Deposits: A New Pathological Entity? A Case Report and Literature Review

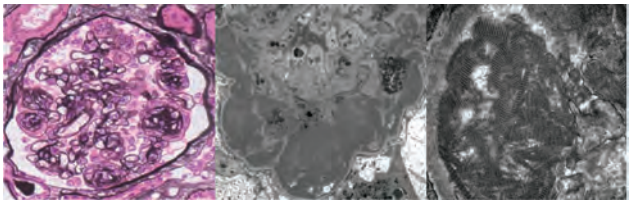
Manna Ishida,[1] Shinya Yamamoto,[1] Yohei Iwashige,[1] Akiko Mii,[2] Akira Shimizu,[2] Motoko Yanagita.[1] [1]*Kyoto Daigaku Igakubu Fuzoku Byoin, Kyoto, Japan;* [2]*Nihon Ika Daigaku, Bunkyo-ku, Japan.*

Introduction: Glomerular diseases with organized deposits can be classified into various etiologies. A diagnostic algorithm based on clinical and pathological findings has been proposed; however, some cases cannot be diagnosed using existing algorithms.

Case Description: A 77-year-old man presented to our hospital with proteinuria, hematuria, and lower leg edema that had developed 1 month prior. Renal biopsy revealed membranoproliferative glomerulonephritis (MPGN). Electron microscopy showed microfilament-like substructures with regularly stacked, straight bands arranged in parallel in the subendothelial space. The examinations and clinical findings were incompatible with known glomerular diseases with organized deposits with organized deposits. During

2 years without immunosuppressive drugs, he developed nephrotic syndrome, and renal impairment. A second renal biopsy revealed that the area occupied by the deposits was prominently extended (Figure). Hemodialysis was initiated 10 months after the second biopsy. We also performed mass spectrometry (MS) and estimated exponentially modified protein abundance index (emPAI) and, significant levels of fibrinogen and fibronectin were detected. Immunostaining for fibrinogen, fibrin, and fibronectin was also positive in the subendothelial space.

Discussion: Our case pathologically showed rare fibril structure mimicking striated fibrin bundles, and clinically showed progressive renal impairment. MS and emPAI analysis suggested the possibility of new disease entity which was associated with endothelial injury induced by fibril structure composed of a fibrin-fibronectin complex. Clinicians should be aware of the findings of glomerulonephritis with striated ultrastructural deposits because these patients do not respond to steroids and have a poor prognosis.



SA-PO838

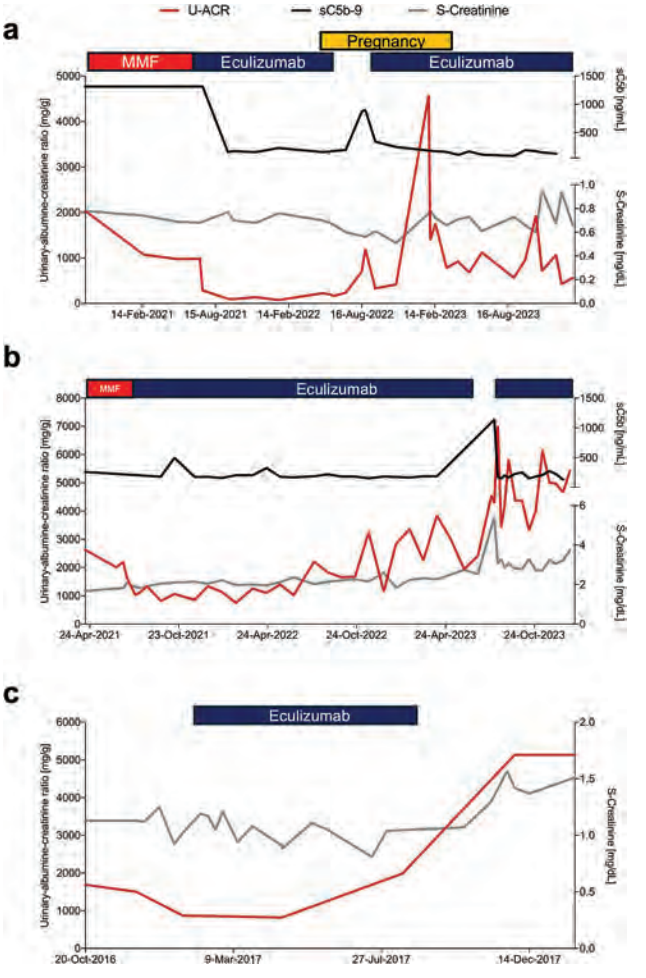
Rebound Albuminuria after Discontinuation of Eculizumab in Three Cases of Idiopathic Membranoproliferative Glomerulonephritis

Max Schuller,[1] Christof Aigner,[3] Marion J. Pollheimer,[2] Alexander R. Rosenkranz,[1] Kathrin Eller.[1] *[1]Medical University of Graz, Division of Nephrology, Graz, Austria; [2]Medical University of Graz, Institute of Pathology, Graz, Austria; [3]Medical University Vienna, Division of Nephrology and Dialysis, Vienna, Austria.*

Introduction: Idiopathic membranoproliferative glomerulonephritis (MPGN) is a rare, clinically challenging entity that frequently affects young individuals and is associated with a poor prognosis. Evidence for an involvement of the complement system in the pathogenesis of MPGN has resulted in the testing of C5 convertase inhibition by eculizumab, but response to treatment has been heterogenous.

Case Description: Here, we describe three patients (two female patients and one male patient) from two different centers with idiopathic MPGN (one IC-MPGN and two C3-GN), who showed a substantial increase in albuminuria and serum-creatinine that was paralleled by a substantial increase in sC5b-9 after stopping eculizumab due to pregnancy in one case and non-response in the other two. Reintroduction of eculizumab resulted in a prompt decrease in sC5b-9 and albuminuria.

Discussion: Our observations highlight the potential risk of increased albuminuria following treatment cessation of eculizumab in MPGN, irrespective of apparent treatment response. It is tempting to speculate that C5 convertase inhibition may suppress disease activity even in apparent non-responders. One may hypothesize that treatment of MPGN might need another form of complement blockade that more effectively inhibits complement activation or inhibits the complement system at an earlier activation step in the complement cascade. Additionally, our report supports eculizumab continuation for MPGN during pregnancy.



SA-PO839

Clinicopathological Profile and Outcomes of Kidney Amyloidosis: A Single-Centre Retrospective Biopsy Registry Cohort Study

Elenjickal E. John,[1,2] Rizwan Alam,[1] Vinoi G. David,[1] Santosh Varughese,[1] Suceena Alexander.[1] *[1]Christian Medical College Vellore, Vellore, India; [2]McGill University, Montreal, QC, Canada.*

Background: Kidney is the most common organ involved in systemic amyloidosis. The two most common types of amyloidosis affecting the kidneys are immunoglobulin (Ig)-derived and AA amyloidosis. Although classified under the same bracket of amyloidosis, each of these subtypes vary in their presentation, histology and outcomes which is not well defined.

Methods: This was an observational retrospective biopsy registry cohort study. done at a single centre in South East Asia. In total, 260 consecutive patients of amyloidosis who underwent kidney biopsy between January 2005 and December 2022 were included in this study.

Results: The mean age of the cohort was 52.5 ± 11.4 years and 67.3% were males. The most common histological type of amyloidosis was Ig amyloidosis (73.1%) followed by AA (14.6%) and undifferentiated amyloidosis (11.5%). Ig amyloidosis included 186 patients of AL amyloidosis and 4 patients of AHL amyloidosis. Extra-kidney involvement was seen in 22.7% patients. Patients with AA amyloidosis were younger, had a lower baseline estimated glomerular filtration rate (eGFR) and none of the patients had cardiovascular involvement. Patients with Ig amyloidosis were older, and almost half of the patients presented with nephrotic syndrome. Histologically, half of the patients had both glomerular and vascular deposits. Vascular and interstitial involvement was less commonly seen in undifferentiated amyloidosis. Majority (82%) of patients with Ig amyloidosis had lambda monoclonal light chain deposits. CyBorD was the most used chemotherapeutic regimen in Ig amyloidosis (38%). Of the 121 patients with follow-up >3months, 21 (17%) patients progressed to kidney failure over a median period of 11 (IQR, 8.5-29.5 months). The predictors of kidney failure were baseline eGFR < 30 ml/min, extensive glomerular amyloid deposits, moderate to severe IFTA and persistent proteinuria at follow-up. On Cox proportional hazard model, the only significant predictor was baseline eGFR < 30 ml/min [HR 4.37 (95% CI 1.01-18.88)]. Patients of Ig amyloidosis who did not attain VGPR were more likely to have persistent proteinuria at follow up (73% vs. 42%).

Conclusions: Clinicopathological presentation and outcomes differ based on the type of amyloidosis. Attainment of VGPR is associated with better kidney outcomes in Ig amyloidosis.

SA-PO840

Fibrillary Glomerulonephritis Treated with Rituximab and Cyclophosphamide Combination Therapy: A Retrospective Cohort Study

Gabriel Sauvage,[1] Reza Zonozi,[1,2] Orhan Efe,[1,2] Anushya Jeyabalan,[1,2] Katherine M. Cosgrove,[1] Karen A. Laliberte,[1] John Niles,[1,2] Ayman Al Jurdi.[1,2]
[1]Vasculitis and Glomerulonephritis Center, Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA.

Background: Fibrillary glomerulonephritis (FGN) is a rare kidney disease with a poor prognosis. Over 50% of patients progress to end-stage kidney disease (ESKD) within two years of diagnosis. Currently, no treatments have been shown to reduce the risk of ESKD in individuals with FGN. In this study, we aimed to describe the outcomes of FGN patients treated with a combination induction regimen of rituximab, low-dose oral cyclophosphamide, and prednisone.

Methods: We conducted a single-center retrospective cohort study including all patients with FGN treated at the Vasculitis and Glomerulonephritis Center at the Massachusetts General Hospital in Boston, MA between 2008 and 2024. The primary outcome was defined as the doubling of serum creatinine or the development of ESKD. Progression of kidney disease at the end of the follow-up period was the secondary outcome subdivided into the following categories: non-progressive (increase in serum creatinine by < 25%), progressive (increase in serum creatinine by > 25%), and ESKD (dialysis initiation or transplantation during the study period).

Results: We identified 14 consecutive patients with biopsy-proven FGN. 13 patients were treated with rituximab, low-dose cyclophosphamide, and prednisone, while one patient was treated with rituximab monotherapy. The median (IQR) follow-up was 3.0 (0.9-5.5) years. Five of 14 reached the primary outcome of doubling of serum creatinine or ESKD at a median of 2.8 years. At the end of follow-up, seven (50%) patients were non-progressors, two (14%) were progressors, and five (36%) had developed ESKD. To evaluate the effectiveness of the combination induction regimen, we compared the outcomes of individuals in our cohort to two historical cohorts (Hogan et al. *Nephrology Dialysis Transplantation* 2014, and Javaugue et al. *Am J Kidney Dis* 2013). Multivariable Cox regression showed that combination induction immunosuppression was associated with an 80% reduction in the incidence of ESKD (HR = 0.20, 95% CI 0.05-0.83, P = 0.03).

Conclusions: Our results suggest that combination therapy with rituximab, low-dose cyclophosphamide, and prednisone, is associated with a slower progression to ESKD in FGN. Clinical trials are needed to confirm these findings.

SA-PO841

A Rare Case of Waldenstrom Macroglobulinemia-Associated AHL Amyloidosis and Nephrotic Syndrome

Alexander M. Smith,[1,2] William Da Silva,[1,2] Swetha Rani Kanduri,[1,2] Ayaa M. Zarm,[1,2] Juan Carlos Q. Velez,[1,2] Chien-Wen Yang.[1,2] Ochsner Group.
[1]Ochsner Medical Center, New Orleans, LA; [2]The University of Queensland, Brisbane, QLD, Australia.

Introduction: AHL amyloidosis (combined heavy and light chain) is a rare subtype of amyloidosis, accounting for 4.2% of the Ig-related amyloidosis. Waldenstrom macroglobulinemia (WM), is linked to 5–7% of the Ig-related amyloidosis. Herein, we present a very rare case of WM-associated AHL amyloidosis who presented with normal serum *kappa/lambda* free light chain (FLC) ratio and positive Congo-red staining for amyloid on renal biopsy and confirmed by mass spectrometry.

Case Description: A 65-year-old woman presented with a 2-month history of bilateral lower legs swelling. Her medical history was pertinent for a remote stage III colon cancer. She had been diagnosed with WM 2 years prior and was managed with rituximab and bendamustine, and switched to acalabrutinib, a BTK inhibitor. On examination, she was hypotensive (86/56 mmHg), had marked bilateral 3+ pitting edema. Laboratory work up revealed a serum creatinine 0.7 mg/dL, albumin 1.8 g/dL, and urine protein-to-creatinine ratio 10 g/g. Serum protein electrophoresis (SPEP) showed a paraprotein peak near gamma. IgM level was high (1590 mg/dL) and *kappa/lambda* FLC ratio was normal (0.83/1.11). Cryoglobulin, anti-PLA2R, RPR, C3/C4 levels were normal. Renal biopsy revealed 25% glomerulosclerosis, 10-20% interstitial fibrosis and tubular atrophy, with immunofluorescence positive for IgM and *lambda* light chain restriction in glomeruli, and positive Congo-red stain. Mass spectrometry confirmed AHL-type amyloidosis. Bone-marrow biopsy showed 5-10% involvement by *lambda* light-chain restricted plasma cells and Congo-red stain positive. Bortezomib-based therapy was contraindicated due to severe neuropathy from prior oxaliplatin exposure, so zanubrutinib, a BTK inhibitor, was started based on efficacy consideration. She remains on this regimen and is being evaluated for bone marrow transplantation.

Discussion: This case exemplifies a very rare presentation of AHL amyloidosis in a patient with previously diagnosed WM. Interestingly, despite significant light chain deposition in renal pathology, serum *lambda* chain levels were normal. Hence, confirmatory tests including Congo-red staining on tissue biopsy and mass spectrometry were required for diagnosis. Renal prognosis is closely related to hematological responses.

SA-PO842

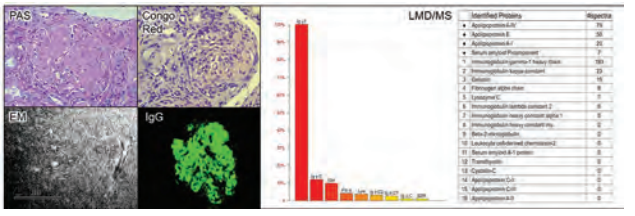
AH Amyloidosis Treated with Rituximab

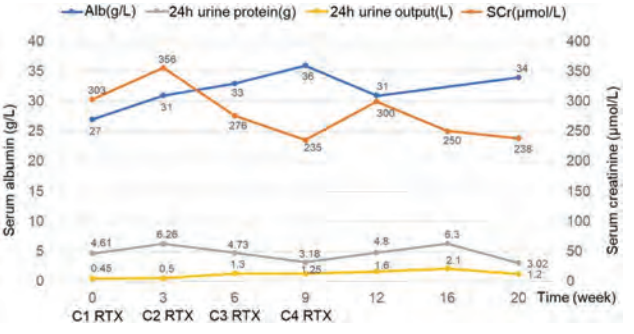
Yan Yang, Shi Jin, Yiqin Shi. *Zhongshan Hospital Fudan University, Shanghai, China.*

Introduction: Heavy chain amyloidosis is a rare type of amyloidosis caused by deposition of monoclonal immunoglobulin heavy chain usually produced by clonal plasma cells. Here we report a case of renal AH amyloidosis caused by clonal B lymphocytes and showed good prognosis after Rituximab treatment.

Case Description: A 67-year-old woman presented with nephrotic syndrome and progressively renal insufficiency was admitted. Laboratory results revealed sCr 303μmol/L, proteinuria 4.6 g/d, serum albumin 27g/L, and pancytopenia. Elevated κ/λ ratio 5.3, IgG κ monoclonal protein were detected. Anti-aCL IgM, aβ2GPI and anti-platelet were strongly positive. Bone marrow biopsy showed 0.2% abnormally mature small B lymphocytes and 0.1% plasma cells expressing κ light chain restriction. Kidney biopsy (figure 1) showed weakly PAS-positive nodules in glomeruli, with bright mesangial and capillary wall staining for IgG by IF and fibrillary deposits under EM. However, Congo red was negative. Laser microdissection/mass spectrometry studies confimed the AH (IgG) amyloidosis by detecting large signature amyloid spectra of IgG1, apo E, and A-IV. Therefore, renal AH amyloidosis was diagnosed. The patient was given rituximab, and kidney function improved with decreased urinary protein (figure 2).

Discussion: LMD/MS analysis is crucial in the diagnosis of rare amyloidosis. The choice of treatment should consider affected organs and the source of malignant cells. The prognosis is relatively good after appropriate therapy.





SA-PO843

A Rare Case of Renal AA Amyloidosis Secondary to Infectious Etiology

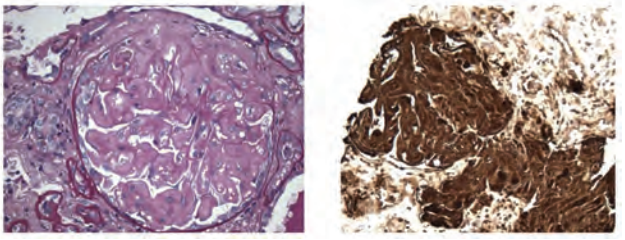
Irvianny Madera, Lorgis I. Jimenez Perez, Bessy Suyin Flores Chang.
SBH Health System, Bronx, NY.

Introduction: AA amyloidosis, characterized by the deposition of serum protein amyloid AA, typically arises in inflammatory settings, such as active infections. While renal involvement is common, cases directly linked to pneumonia leading to end-stage renal disease (ESRD) are exceedingly rare. Here, we present such a case, shedding light on its clinical course and management challenges.

Case Description: 62-year-old male with history of HIV presented to the hospital due to worsening diarrhea and shortness of breath. On admission, he presented with serum creatinine of 9.2 mg/dL (0.6-1.2 mg/dL) (baseline 0.9 mg/dL, two months prior) and a protein/creatinine ratio of 10. He was found to have cavitary lesions in a Computerized Tomography (CT) scan suggesting unresolved necrotizing pneumonia when compared to previous imaging. In the meantime, he required hemodialysis. Due to nephrotic range proteinuria of unknown etiology, a kidney biopsy was performed which showed severe AA amyloidosis with moderate tubular atrophy and interstitial fibrosis. Unfortunately, the patient remains in hemodialysis.

Discussion: We describe a patient with a rapid decline in renal function for whom we hypothesize that the ongoing infection in his immunosuppressive state led to reactive AA amyloidosis. Renal AA amyloidosis is presented rarely in adult-age patients. One case is described similar to our patient where renal AA amyloidosis was caused by pulmonary

Mycobacterial infection associated with diarrhea. However, in our patient, none of the acid-fast bacilli cultures were positive. The standpoint in management is decreasing the inflammatory environment in the patient, however since our patient already had moderate tubular atrophy, prognosis remained poor.



Kidney histology showing AA amyloidosis in H&E stain (left) and immunohistochemistry (right).

SA-PO844

Postkidney Transplant Outcomes among Patients with Prior Diagnosis of Leukocyte Chemotactic Factor 2 (ALECT2)-Associated Amyloidosis: A Case Series

Pablo Garcia,[1] Paul B. Avila,[2] George Vasquez-Rios,[3] Namita Singh,[1] Saeed K. Shaffi,[1] Christos Argyropoulos.[1] *[1]The University of New Mexico, Albuquerque, NM; [2]Universidad de San Carlos de Guatemala Facultad de Ciencias Medicas, Guatemala, Guatemala; [3]Renal Medical Associates, Alburquerque, NM.*

Introduction: ALECT2 amyloidosis, a prevalent form of amyloidosis in the Soutwestern US mainly New Mexico, predominantly affects Hispanic patients and often leads to kidney failure 35%. Notably, long-term outcomes in kidney transplant recipients with ALECT2-associated kidney failure remain understudied. This study fills this gap by analyzing long-term outcomes in this specific patient population.

Case Description: Three patients, aged 45 to 78 years, were diagnosed with ALECT2 based on kidney biopsy findings. All patients underwent kidney transplantation and received immunosuppressive therapy, which included various combinations of envarus, mycophenolate, tacrolimus, and/or prednisone. Details of each case are summarized in the accompanying table. During the follow-up period, ranging from 8 to 60 months, all patients remained stable with preserved estimated glomerular filtration rate (eGFR) and minimal or no urinary protein-to-creatinine ratio (UPCR).

Discussion: The most comprehensive cohorts in ALECT 2 with a follow-up of 30-50 months indicate a higher risk of rapid progression to ESKD in patients with biopsy-proven ALECT2. However, in this post-kidney transplant cohort with long-term follow-up – up to 60 months, there is no evidence of clinically significant renal ALECT2 recurrence. Further research is needed to determine the long-term kidney outcomes among post-transplant recipients with ALECT2.

Age at Txp	Gender	Race/Ethnicity	ESKD	DM	Post Txp eGFR*	Post Txp UPCR**	Follow-up time (months)	Follow-up eGFR	Follow-up UPCR	ISR	Other therapies	ALECT2 post Txp
45	F	Hispanic	Yes	Yes	90	0.2	60	107	0.13	Envarsus, MMF	Carvedilol, lisinopril	N/A
71	F	American Indian	Yes	No	90	0.16	8	90	0	TAC, MMF	None	N/A
78	M	Hispanic	No	No	50	0	10	49	0	TAC, MMF, prednisone	None	No

Txp = Transplan ESKD = End-Stage Kidney Disease DM = Diabetes Mellitus eGFR = estimated Glomerular Filtration Rate UPCR = Urine Proteine/Creatinine Ratio ISR = Immunosuporessive therapy MMF = Mycophenolate TAC = Tacrolimus *30 days post-transplant **90 days post-transplant

SA-PO845

A Rare Case of Cryoglobulinemic Membranoproliferative Glomerulonephritis in the Setting of Negative Hepatitis Serologies

Anastasios Papanagnou,[1] Sanjeev Gupta.[2] *[1]NewYork-Presbyterian Hudson Valley Hospital, Cortlandt Manor, NY; [2]Westchester Medical Center, Valhalla, NY.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) accounts for approximately 7-10% of all cases of biopsied glomerulonephritis, characterized (histologically) by mesangial hypercellularity, subendothelial deposition of immune complexes, and duplication of the glomerular basement membrane (tram-track appearance). MPGN is classified as being mediated by immune complexes, complement dysregulation, or neither of the two. MPGN can be caused by chronic infections (especially hepatitis), autoimmune diseases, and paraproteins (including cryoglobulinemia). Cryoglobulinemic MPGN is reported to be highly associated with chronic hepatitis C virus (HCV) infection but there are only a few case reports documenting cryoglobulinemic MPGN in the absence of chronic hepatitis.

Case Description: We present a case of an 81 y/o woman without any underlying hepatitis, with mild to moderate AS, CHF, HTN, LBBB, osteopenia, polymyalgia rheumatica, who presented to the hospital with worsening SOB and LE edema. Labs showed AKI with associated microscopic hematuria and nephrotic range proteinuria (Urine protein/creatinine ratio of 8.18). She was admitted for management of a CHF exacerbation, started on IV Lasix with improvement in her symptoms. Proteinuria work-up revealed ANA (+) 1:1280, C3 83 (mildly depressed), atypical p-ANCA pattern (1:640) and positive cryoglobulins. SPEP/serum immunofixation: no monoclonal proteins, serum FLC ratio 1.48. Blood cultures did not show any growth. HIV and Hepatitis B/C panels were both negative. Renal biopsy showed diffuse endocapillary proliferative and focal crescentic glomerulonephritis with membranoproliferative features with IgM-dominant deposits, mild tubular atrophy, interstitial fibrosis and mild acute tubular injury. The patient was started on a prednisone taper and mycophenolate. She was subsequently discharged with close outpatient renal follow-up. Serial outpatient labs, over the span of 6 months, showed resolution of her AKI and microscopic hematuria, with dramatic improvement of her proteinuria down to trace levels.

Discussion: We discussed a rare case of cryoglobulinemic MPGN with strong IgM staining, without underlying hepatitis, which led to a positive outcome after receiving combination steroid/mycophenolate therapy. Moreover, there is still much to be learned about establishing the standard of care for managing cases, like this one, appropriately.

SA-PO846

A Case of Heavy Chain Deposition Disease

Stela Teferici,[1,2] Aaron S. Stern,[1,2] Nitzy N. Munoz Casablanca.[1,2] *[1]Elmhurst Hospital - Main Campus, Elmhurst, NY; [2]Mount Sinai Health System, New York, NY.*

Introduction: Monoclonal Immune Deposition Disease (MIDD) is a rare manifestation of monoclonal gammopathy of renal significance, with non-organized deposition of monoclonal proteins in the glomerulus. Deposition that only involves the heavy chain portion of a monoclonal immunoglobin is even rarer. We present a case of Heavy Chain Deposition Disease (HCDD).

Case Description: A 61-year-old female was referred to our clinic for edema and nephrotic syndrome. She had facial and pedal edema, hypoalbuminemia and a Urine Protein/Creatinine Ratio of 4. Further work-up revealed antinuclear antibody: 1: 320, Complement 3: 72mg/dL (mildly low), Complement 4: 32mg/dL (normal), Serum protein electrophoresis (SPEP) had a weak gamma paraprotein, Immunofixation electrophoresis (IFE) was positive for immunoglobulin G (IgG) kappa. Serum free light chain kappa (K)/lambda (λ) ratio was 9.1. Renal biopsy showed a pronounced nodular mesangial appearance on light microscopy. Congo-red staining was negative. Immunofluorescence showed deposits composed of IgG along glomerular, tubular, and basement membranes, with negative staining for K and λ light chains, findings consistent with HCDD. The heavy chain subclass was not performed. Electron Microscopy revealed a powdery appearing deposition in the basement membrane.

Discussion: In elderly patients with nephrotic syndrome, diabetes and amyloidosis are common culprits. Our case supported this suspicion with a positive SPEP, IFE, and free light chain assay. However, while the kidney biopsy showed a nodular sclerosis pattern suggestive of amyloidosis, further analysis with staining and immunofluorescence revealed a rarer diagnosis: heavy chain deposition disease (HCDD) associated with a paraproteinemia. On review of the previously reported cases of HCDD, common clinical presentations include nephrotic syndrome, renal insufficiency, hematuria, and, in some cases, hypocomplementemia. Hematologic workup to assess for a plasma cell dyscrasia is ongoing.

SA-PO847

Rituximab for Patients with Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID): A Case Series

Sai Prasad Desikan, Samir V. Parikh. *The Ohio State University Wexner Medical Center, Columbus, OH.*

Introduction: Monoclonal gammopathy of renal significance (MGRS) is defined is a clonal disorder characterized by renal monoclonal immune deposition without adequate criteria for a specific malignancy. PGNMID, a subtype of MGRS, is further defined by granular deposits without organization that are predominantly located in the mesangium and / or subendothelium on electron microscopy. Here we present a case series of 5 patients treated with regimens including rituximab.

Case Description: Patients were aged between 17 and 72. Creatinine on presentation ranged from 0.66 to 3.22 mg/dL. All patients had proteinuria with 4 patients with nephrotic range proteinuria. Three patients had monoclonal IgG3 with kappa predominant deposits. One patient had both kappa and lambda deposits. One patient had lambda restricted deposits. All patients received rituximab and steroids. One patient received cyclophosphamide. Of the 5 patients, three patients responded (> 30% reduction in proteinuria without decrease in GFR >25%) to therapy. These three patients have maintained response to date with progression free survival of 42, 70 and 91 months respectively. None of these patients have required dialysis to date. Two patients did not respond to therapy. One patient later responded to velcade, dexamethasone, and daratumumab. The other patient required dialysis prior to treatment and eventually passed away with a survival of 3.2 months.

Discussion: Here we present a case series of 5 patients that received rituximab-based regimens. Three patients had durable renal remissions with rituximab-based regimens. Two patients did not respond. One of these patients did eventually respond to a plasma

cell directed therapy. This case series suggests that for some patients a rituximab-based regimen is adequate to induce and maintain a renal remission; however, there is a subset of patients that may benefit from plasma cell directed treatment.

SA-PO848

Pregnancy-Associated Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition

Ram Sinha, Chintan V. Shah, Amer A. Belal. *University of Florida, Gainesville, FL.*

Introduction: Proliferative glomerulonephritis with monoclonal immune deposits (PGNMID) is a rare form of monoclonal gammopathy of renal significance. Although it has been rarely reported at a young age, pregnancy-associated PGNMID represents a unique and rare clinal presentation that requires further understanding. Diagnosis of the condition is challenging as the clinical presentation and lab findings upon presentation are non-specific.

Case Description: A 32-year-old female without any significant past medical history presented at 35 weeks of gestation with elevated blood pressure, a serum creatinine (S. Cr) of 0.58 mg/dL, and proteinuria of 2.8 grams/d. Serum creatinine increased to 1.2 mg/dL. A presumed diagnosis of pre-eclampsia was made, and vaginal delivery was induced at 37 weeks. Six weeks later, the patient was re-admitted with peripheral edema, uncontrolled hypertension, and acute kidney injury with a peak S. Cr of 4.5 mg/dL. Her 24-hour urine protein was 9.4 grams/d, and S. albumin was 1.7 gm/dL. A kidney biopsy showed IgG3-Lambda PGNMID with 80% cellular crescents. A detailed workup to identify pathological clone was negative, including serum protein electrophoresis, serum immunofixation, light chain ratio, peripheral blood flow cytometry, and bone marrow biopsy. Although kidney function improved with high-dose steroids initially with S. Cr of 1.4 mg/dL, the patient remains with persistent and severe nephrotic syndrome after 6 weeks of high-dose steroids (Prednisone 1mg/kg/d) and is being considered for empirical clone-directed therapy, pending insurance approval, at the time of writing this report.

Discussion: The pathogenesis of PGNMID associated with pregnancy requires further understanding. Pregnancy is a state of dramatic immune modulation. The fetus/placenta unit could induce a maternal immune response, as part of the pro-inflammatory state or working as an alloantigen, producing nephrotoxic monoclonal protein resulting in PGNMID. Notably, while two previously reported cases improved after delivery, our patient failed to show clinical improvement with steroids after delivery and requires further treatment with clone-directed therapy. Thus, Pregnancy-associated PGNMID requires further understanding of pathophysiology, treatment options, and clinical prognosis.

SA-PO849

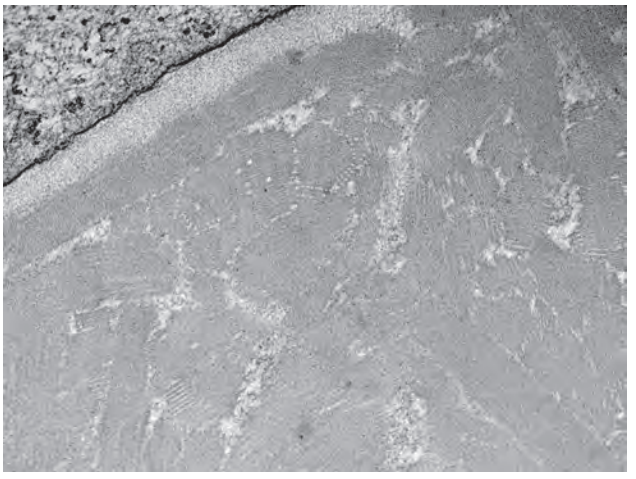
Novel Grid-Like Substructure in a Case of Paracrystalline Monoclonal Gammopathy of Renal Significance (MGRS)

Rajib K. Gupta,[1] Sajid Melvin George,[2] Xin Gu,[3] Lois J. Arend.[4] *[1]UC Davis Medical Center, Sacramento, CA; [2]Richmond Nephrology Associates, Richmond, VA; [3]LSU Health Shreveport, Shreveport, LA; [4]Johns Hopkins University, Baltimore, MD.*

Introduction: Monoclonal deposits with substructure in the kidney are essentially of 3 types – fibrillary, microtubular and crystalline deposits. Grid-like substructure, also known by other descriptors like mesh-like, lattice-like or striated muscle-like, has been described as a rare electron microscopic (EM) appearance of monoclonal deposits occurring in association with monoclonal gammopathy of renal significance (MGRS), most commonly involving the glomeruli. Here we describe a rare case with abundant grid-like monoclonal deposits.

Case Description: Patient is a 62-year-old Caucasian male with pancytopenia, acute kidney injury and a recent diagnosis of MGUS. SPEP showed a monoclonal M-spike 1.1 gm/dL with IgG kappa on serum and urine immunofixation. Bone marrow biopsy showed 5% kappa-restricted plasmacytosis, and a kappa to lambda ratio of 2.7. Serum complements were low. The patient also had motor neuropathy. Urinalysis showed 3+ protein and 3+ blood. Rheumatoid factor, serum cryoglobulin, ANCA and anti-GBM antibodies were negative. ANA was mildly positive. Kidney biopsy revealed glomeruli with a membranoproliferative pattern along with occlusive, large, intracapillary hypereosinophilic pseudothrombi which showed IgG1 and kappa restriction on immunofluorescence. EM revealed massive intraluminal and subendothelial electron-dense deposits having an extremely compact grid-like paracrystalline substructure, vaguely resembling the EM appearance of striated muscle.

Discussion: Grid-like substructure has been described in association with monoclonal renal disease in few reports, most typically type 1 cryoglobulinemic glomerulonephritis (CryoGN) although rare association with proliferative GN with monoclonal immunoglobulin deposits (PGNMID) has also been described. In this patient, the overall histologic findings favored a type 1 seronegative CryoGN. Awareness of such rare substructure and its association with monoclonal glomerular deposits is important for timely diagnosis of MGRS.



SA-PO850

A Case of MGRS-Associated C3 Glomerulonephritis following Acute COVID-19 Infection

Keith L. Saum, Jeffrey B. Hodgin, Jennifer A. Schaub. *University of Michigan, Ann Arbor, MI.*

Introduction: C3 glomerulonephritis (C3GN) is a proliferative GN resulting from mutations or functional inhibition of regulatory proteins in the alternative complement pathway. Rarely, inhibition of complement-regulating proteins may result from monoclonal gammopathy. We present a case of C3GN associated with monoclonal gammopathy of renal significance (MGRS) following acute COVID-19 infection.

Case Description: A 60-year-old female with a history of hypertension developed new edema one month following acute COVID-19 infection which had been managed conservatively as an outpatient. She was subsequently admitted for nephritic syndrome with worsening hypertension, serum creatinine of 1.9 mg/dl, and proteinuria of 2.4g/24hr. Urinalysis was positive for protein and blood with dysmorphic RBCs on urine sediment. Serologic evaluation was notable for a new IgG Lambda M-protein on SPEP with a normal free-light chain ratio and low C3 level. Blood cultures, C4, ANA, cryoglobulins, ANCA, HIV, HBV, HCV, and were normal/negative. Despite adequate blood pressure control with nifedipine and irbesartan, proteinuria and hematuria persisted for >8 weeks. Kidney biopsy showed neutrophilic glomerulitis with a membranoproliferative pattern. Immunofluorescence showed only mesangial and capillary C3 deposits. Pronase digestion of paraffin samples did not reveal masked immunoglobulin deposits. Functional complement testing demonstrated increased C3 convertase activity and negative for autoantibodies to complement regulatory proteins. Subsequent bone marrow biopsy revealed a 5% IgG Lambda plasma cell clone, consistent with MGRS-associated C3GN. She was treated with six cycles of cyclophosphamide, bortezomib, and dexamethasone resulting in improvement in proteinuria and serum creatinine.

Discussion: C3GN is a rare variant of MGRS not associated with infection. Although causality between the preceding COVID-19 infection and the subsequent C3GN cannot be proven, other cases of post-viral MGRS, have been reported. Nephrologists should be aware that not all kidney disease occurring after COVID-19 is due to tubular injury or collapsing glomerulopathy.

SA-PO851

Double Jeopardy: Monoclonal Gammopathy of Renal Significance (MGRS) in the Shadow of Lupus Nephritis

Yara Mouawad, Amanda Tchakarov, Dia R. Waguespack. *The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.*

Introduction: Monoclonal gammopathy of renal significance remains a clinical challenge given the rarity of the condition and lack of literature regarding treatment and outcomes.

Case Description: This is the case of a 56 year old female with diagnosed APLS, SLE, and cryoglobulinemia. Her disease course was complicated by multiple thrombotic events requiring adjustment of her anticoagulation. She had quiescent disease, and was off treatment except for anticoagulation, when work up showed a rising creatinine, elevated dsDNA titers, and hematuria. A renal biopsy was considered to be high risk given her anticoagulation and thrombocytopenia, therefore she was assumed to have lupus nephritis and was started on Plaquenil, prednisone and later azathioprine. Despite treatment, she had worsening proteinuria up to nephrotic levels. She was switched to mycophenolate, however was unable to tolerate it. At the same time, she complained of a worsening rash on her lower extremities. A renal biopsy was then performed which

revealed "Proliferative Glomerulonephritis with Monoclonal IgG Deposits, specifically IgG kappa restricted deposits". The biopsy did not show evidence of lupus nephritis, APLS or cryoglobulinemic vasculitis. She initially had a normal SPEP and a bone marrow biopsy was normal ruling out any hematological malignancy, MGUS, or MM. Repeat SPEP showed an IgG kappa monoclonal band consistent with deposits seen on renal biopsy. Given the lack of data on treatment of monoclonal gammopathy of renal significance in patients with underlying autoimmune diseases, the decision was made to treat with Rituximab as a clone depleting agent.

Discussion: This case highlights the importance of considering monoclonal gammopathy of renal significance as a cause of glomerulonephritis, particularly in patient with SLE despite its rarity.

SA-PO852

Semaglutide-Associated Minimal Change Disease: A Potential Rare Complication of a Novel Medication

Gary Tan, Kenar D. Jhaveri, Omar Muhammad, Ming Wu, Spencer Weintraub. *Northwell Health, New Hyde Park, NY.*

Introduction: Glucagon-like peptide 1 receptor agonists (GLP1-RAs) are a class of antihyperglycemic medications that have demonstrated benefits for obesity and cardio-renal protection. The increased utilization of these therapies may reveal previously undocumented adverse effects.

Case Description: An 83-year-old male with CKD (baseline Cr 1.7), hypertension, hyperlipidemia, congestive heart failure, hypothyroidism, and obesity (BMI 33) presented to the hospital with 5 days of dyspnea and bilateral leg swelling. He was recently started on Semaglutide in Israel. The patient reports no use of NSAIDs or over-the-counter medications. On exam, he had diminished breath sounds at the lung bases and 2+ bilateral lower extremity pitting edema. Labs showed BUN 34mg/dL, creatinine 2.06mg/dL, and albumin of 2.2g/dL. He had a total serum cholesterol level of 213 mg/dL and triglyceride of 170mg/dL. Urinalysis had 4+ proteinuria. The urinary protein to creatinine ratio (UPCR) was 17.2g/g. Serologic testing of ANCA-ab, ANA, GBM-ab, PLAR2R-ab were all negative. HIV, viral hepatitis, and renal ultrasound studies were unremarkable. A renal biopsy was performed, and light microscopy revealed global glomerulosclerosis. Electron microscopy showed complete visceral epithelial cell foot process effacement, which was consistent with minimal change disease (Figure 1). He was treated with pulse solumedrol for 3 days and transitioned to a 3-month prednisone taper. The patient also received 2 doses of Rituximab during the admission. UPCR improved from 17.2g/g to 9.2g/g. His creatine peaked at 4.1mg/dL and improved to 3.2mg/dL at discharge.

Discussion: Podocytopathies can be associated with certain medications (i.e. NSAIDS, lithium, interferon), but their link with GLP-RAs has not been well described. Therefore, new edema or proteinuria associated with GLP1-RA initiation should prompt investigation for glomerular disease and discontinuation of the medication.

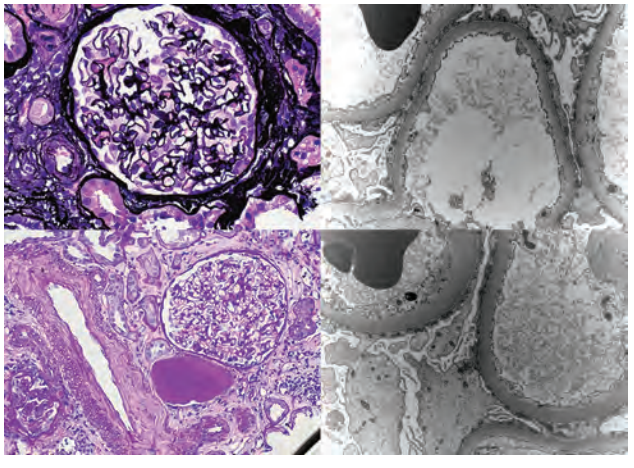


Figure 1

SA-PO853

Mesalamine-Induced Minimal Change Disease

Sahar A. Bhai, Ryan A. Parrish, Jatayah Sheed, Folasade Arinze. *Wellstar Kennestone Regional Medical Center, Marietta, GA.*

Introduction: Minimal change disease frequently manifests as a nephrotic syndrome that is mediated by inflammatory effacement of podocytes, either due to a hypersensitivity reaction or direct toxin effect. The etiology is often idiopathic, but some inciting factors include cancer, infections, and medications. Mesalamine, also known as 5-aminosalicylic acid (5-ASA), is commonly used to treat IBD. Nephrotoxicity is a known but rare adverse effect of 5-ASA with an incidence of 0.17% per year. The most common manifestations include chronic interstitial nephritis, renal calculi, papillary nephritis, idiopathic nephrotic syndrome, and FSGS. However, minimal change disease remains a rare complication and has only been described with the chronic use of mesalamine. We present a case of rapid development of acute nephrotic syndrome after 5-ASA overdose.

Case Description: A 24-year-old man with a history of ulcerative colitis on mesalamine presented with generalized swelling after ingestion of extra doses of his mesalamine. On the day of presentation, he noticed lower extremity and abdominal swelling. His exam was remarkable for 4+ pitting edema of the lower extremities, abdominal distention, and mild periorbital edema. Labs were notable for Na+ 128 mmol/L, creatinine 1.44 mg/dL, albumin 1.4 g/dL, CK 128 IU/L. Urinalysis showed 4+ protein and 2+ blood. His 24-hr urine protein was 16.3g. Testing for HIV, hgb A1C, syphilis, ANA, C3, C4, anti-GBM, and ANCA panel were normal. Renal biopsy showed effacement of podocytes on electron microscopy. He was treated with prednisone during admission with symptom improvement and near-resolution of proteinuria at 3 month follow up with full remission expected.

Discussion: This case report illustrates rapid development of MCD within days of overdose of mesalamine. While previous case reports described patients who developed MCD with chronic mesalamine use, it remains a rare adverse effect. While most adult patients with MCD remain in remission following adequate treatment, approximately 5% will develop a relapsing-remitting disease course that progresses to end-stage renal disease despite treatment. Several organizations have proposed routine intervals to monitor serum creatinine and 24-hour urine protein in patients on 5-ASA. However, recommendations vary and no consensus for monitoring exists. Future guidelines should promote standardization of monitoring.

SA-PO854

Rifampin-Induced Minimal Change Disease

Robert Kosalka, Fitsum T. Hailemariam. *Thomas Jefferson University Sidney Kimmel Medical College, Philadelphia, PA.*

Introduction: Latent *Mycobacterium tuberculosis* affects around 25% of the international and 3.1% of the American population. One of the most common treatments is rifampin. In the past, there have been cases of rifampin-associated interstitial nephritis and nephrotic diseases which have typically resolved with cessation of the offending agent and a short course of steroids. Although rituximab and calcineurin inhibitors (CNI) are effective treatments in frequently relapsing/steroid-dependent patients with primary minimal change disease (MCD), this is the first reported case of their use in rifampin-induced MCD.

Case Description: This is a 33-year-old female with a history of latent tuberculosis who presented to the hospital with edema, nausea, and vomiting. One month before, she was initiated on rifampin 600mg daily with a planned 4-month course. On initial blood work, she had an elevated creatinine of 1.46mg/dL from a baseline of 0.7mg/dL, and an albumin of 2.1g/dL. Urinalysis revealed 3+ protein and 2+ blood. The urine protein-creatinine ratio was 26.2mg/mg. She had negative anti-MPO, anti–PR3, ANA, anti-dsDNA, and anti-GBM antibodies, and normal C3 and C4 levels. Renasight genetic testing revealed no known disease-causing variants. Rifampin was discontinued. Solumedrol 500mg was given and followed with prednisone at 1mg/kg. A kidney biopsy was obtained. Light microscopy was unremarkable, but electron microscopy revealed diffuse podocyte foot process effacement, vacuolization of cell bodies, and villous transformation of the cytoplasm consistent with MCD. Creatinine peaked at 4.18 mg/dL before trending down to baseline. Prednisone was rapidly tapered. Once steroid therapy was completed, the proteinuria returned and prednisone was resumed. Due to refractory proteinuria, she received rituximab 1g twice two weeks apart and tacrolimus (target trough of 3-5mg/dL) and a short steroid taper owing to weight gain and hypertension.

Discussion: When evaluating patients with drug-induced nephrotic syndrome, clinicians should be aware that removing the offending agent is not always enough. This case shows that the principles of treating primary MCD can apply to secondary MCD. This patient with relapsing disease eventually responded to rituximab and CNIs. It is important to monitor proteinuria in these patients to choose the most appropriate treatment.

SA-PO855

Minimal Change Disease Secondary to Adalimumab

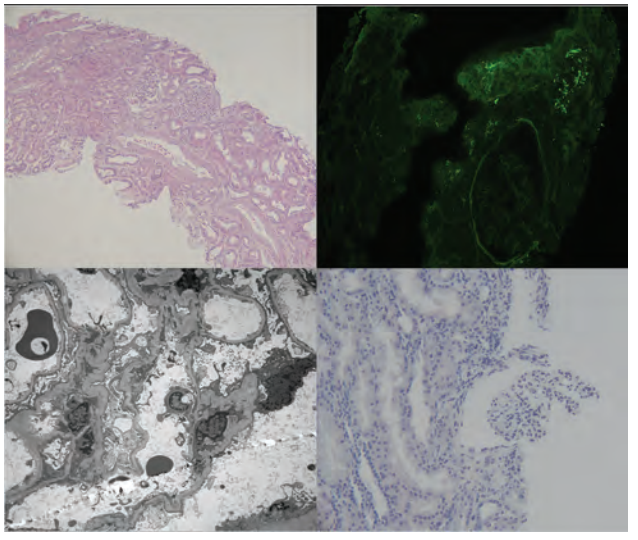
James Allen, Joshua Kaplan, Smita Mahendrakar. *Rutgers University Newark, Newark, NJ.*

Introduction: Adalimumab is a fully human recombinant monoclonal antibody against TNFa. There have been case reports of patients developing proteinuria following treatment with adalimumab for rheumatoid arthritis (RA). Renal pathology demonstrating membranous glomerulopathy, pauci-immune necrotizing and crescentic glomerulonephritis have been reported. We describe a patient who developed minimal change disease as an adverse effect of treatment with the anti-TNFa adalimumab.

Case Description: A 63-year-old female with seropositive RA treated with adalimumab presented to the hospital with generalized swelling. Symptoms started seven days prior to admission after she received her fifth injection of adalimumab. Generalized

swelling was noted the morning after her dose. She met clinical criteria for nephrotic syndrome with nephrotic range proteinuria, hypoalbuminemia, peripheral swelling, and hyperlipidemia. Significant labs included cholesterol and triglycerides of 413mg/dL and 392mg/dL, up from 208mg/dL and 178mg/dL prior to adalimumab injection. Albumin was up from 4.1gm/dL four months prior to 1.6gm/dL on admission. 24-hour urine protein was greater than 3.9g/day. Renal biopsy was obtained which showed minimal glomerular alterations with marked effacement of foot processes ultra-structurally and negative immunofluorescence studies consistent with minimal change disease. Treatment was initiated with 1mg/kg/day of prednisone with following taper after one month. Supportive management including statins and diuretics was prescribed. With the protein to creatinine ratio decreasing to 0.106g/day and albumin improving to 4.2gm/dL on the two month follow up, steroids were discontinued.

Discussion: We present a case of a rare cause of adult-onset minimal changed disease secondary to adalimumab. Patients on anti-TNF therapy should be monitored for signs of nephrotic syndrome including peripheral edema, proteinuria, and hypoalbuminemia.



SA-PO856

Minimal Change Disease and Overlapping IgA Nephropathy Associated with Peripheral Inflammatory Spondyloarthropathy

Hannah Angle, Gilda M. Portalatin, Narender Annapureddy, Anna M. Burgner. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Spondyloarthritis (SpA) describes a group of seronegative rheumatic disorders that cause skeletal inflammation. They are often associated with HLA-B27 and have been linked with kidney disease, specifically IgA nephropathy. However, associations between SpA and other glomerular diseases have not been well elucidated. Here, we present a rare case of minimal change disease (MCD) associated with peripheral SpA.

Case Description: A 50-year-old male with HTN presented with AKI and nephrotic syndrome with Cr 2.9mg/dL and urine protein creatinine ratio (UPCR) 18.6g/g. A few months prior, he developed right knee pain treated with NSAIDs. Kidney biopsy revealed MCD with mild IgA nephropathy. He was treated with prednisone 1 mg/kg daily for 4 weeks until remission was achieved. After a 4-month taper, he developed severe pain and stiffness of multiple distal joints. Labs notable for CRP 86.7 mg/L and UPCR 7.5g/g. Further workup included positive HLA-B27 and synovial fluid analysis consistent with inflammatory arthritis, raising suspicion for peripheral SpA. Prednisone was resumed, and his joint symptoms and proteinuria subsequently resolved. Unfortunately, due to recurring arthritic flares at lower steroid doses, prednisone could not be tapered. Methotrexate was initiated without response. Then, adalimumab was initiated and steroids were tapered off. Over 2 months, CRP and UPCR normalized, arthritis symptoms resolved, and MCD remission was achieved.

Discussion: Kidney involvement is seen in many rheumatic diseases, whether from direct pathologic effect or secondary to treatment. Nephrologists and rheumatologists must work together to manage these patients. SpA with HLA-B27 positivity has previously been linked with kidney disease, specifically ankylosing spondylitis and IgA nephropathy. Our patient with primary MCD associated with peripheral SpA is discordant with existing literature. His joint symptoms were primarily peripheral, unlike ankylosing spondylitis, and there was no clinical evidence to suggest reactive arthritis or arthritis associated with psoriasis or IBD. With adalimumab, his joint symptoms and proteinuria quiesced. This case emphasizes the temporal relationship between MCD and peripheral SpA. Recognizing the interconnection between the diseases played a key role in successfully treating this patient.

SA-PO857

Refractory Primary Podocytopathy: Any Role for Daratumumab?

Victor Martinez Leon, Abdallah Sassine Geara. *University of Pennsylvania, Philadelphia, PA.*

Introduction: Primary Podocytopathy is an autoimmune injury of the podocytes with a characteristic histopathologic lesion of focal and segmental glomerulosclerosis (FSGS) or minimal change disease (MCD). It is associated with abrupt onset of nephrotic syndrome and treated with corticosteroid and anti-B cell therapy.

Case Description: 30-year-old male previously healthy presented with peripheral edema and shortness of breath, his urine protein to creatinine ratio (UPCR) was 5.8 g/g for which he underwent kidney biopsy showing MCD. The patient had a complete remission following a prednisone course however he relapsed at 4 months (during the prednisone tapering) and had a prolonged course of steroid-refractory nephrotic syndrome a repeat kidney biopsy showed FSGS tip lesion. The immunosuppressive therapies and adverse events (AE) were sequentially: 1. Prednisone 80mg for additional 4 months (AE: retinal detachment) 2. Rituximab 1g x2 with successful depletion of CD19+ B cells without decrease in proteinuria (AE: hypogammaglobulinemia) 3. Obinutuzumab 1g x2 followed by 1g at 6 months with worsening proteinuria to 6.4 g/g (AE: fungal pneumonia) 4. Repeat steroid course, tacrolimus (trough: 5-7 µg/l) and Dapagliflozin 10 mg daily (AE: AKI) The patient received Daratumumab 1800mg SC weekly for 8 doses with improvement of the UPCR to to 0.89 g/g, increase albumin to 3.4 g/dL and resolution of the edema that was persistent for more than 2 years.

Discussion: Guidelines recommend high-dose steroids as first-line the treatment for primary FSGS and MCD. Tip glomerular lesion has been described to respond to glucocorticoid therapy more than patients with the other FSGS variants. Calcineurin inhibitors and rituximab (anti-CD20 mAb) can be used for the treatment of frequently relapsing MCD or FSGS. Although not yet widely use, the anti-CD38 mAb, Daratumumab, has been used in some cases of post-transplant recurrent FSGS with promising results. Further randomized control trials of patient with multi-drug resistant primary podocytopathy are needed to determine the efficacy of daratumumab.

Clinical course and treatment

SA-PO858

Refractory Nephrotic Syndrome Resulting in Bilateral Achilles Tendon Rupture Due to Relapse by Vaccination after Recovery from COVID-19: A Case Report

Jun Takeoka,[1] Ryo Sato,[1] Kansei Otsuka,[1] Naohiro Toda,[1] Kyoka Fujita,[1] Satoshi Kurahashi,[1] Kosuke Mochizuki,[1] Hisako Hirashima,[1] Toshiyuki Komiya,[2] Eri Muso,[1] Akira Ishii.[1] *[1]Kansai Denryoku Byoin, Osaka, Japan; [2]Otsu Sekijuji Byoin Toshoshitsu, Otsu, Japan.*

Introduction: There are several reports suggesting the involvement of SARS-CoV-2 (COVID-19) infection and COVID-19 messenger RNA (mRNA)-based vaccine respectively in the development and severity of nephrotic syndrome. We report a case of refractory nephrotic syndrome resulting in bilateral Achilles tendon rupture due to relapse by vaccination shortly after recovery from COVID-19.

Case Description: A 60-year-old man was diagnosed with minimal change nephrotic syndrome (MCNS) 37 years ago and was in remission with steroid therapy. Although it recurred a total of five times over the next 36 years, the disease remained relatively stable, Two months before admission, he developed a COVID-19 pneumonia and was cured by treatment. Just two months later, he received the third dose of COVID-19 vaccine and was admitted to our department with generalized edema, rapid weight gain of 12 kg in 2 weeks, proteinuria (3.3 g/gCr) and hypoalbuminemia (2.9 mg/dL). After admission, steroid pulse therapy was started, and renal biopsy revealed MCNS recurrence. The patient was treated with steroid pulse therapy for three times and LDL apheresis, but the response was poor. Eight months after relapse, rituximab therapy was started. Although proteinuria gradually decreased, gait disturbance appeared and bilateral Achilles tendon ruptures were discovered.

Discussion: Although there have been scattered reports suggesting that COVID-19 infection and COVID-19 vaccine respectively have been implicated in the development and severity of nephrotic syndromes, including MCNS, the precise mechanism is not fully understood. In this case, vaccination shortly after COVID-19 recovery may have acted as a booster, causing the immune system to become abnormally activated and trigger a recurrence with severe edema leading to Achilles tendon rupture.

SA-PO859

Minimal Change Disease in a Patient with Sickle Cell Disease

Alexa E. Golbus, Ashley Golbus, Natalie T. Freidin. *Medical University of South Carolina, Charleston, SC.*

Introduction: Renal complications of sickle cell disease (SCD) are common, however, minimal change disease (MCD) as a cause of nephrotic syndrome in SCD patients, to our knowledge, has not been reported. While controversial, there is evidence that focal segmental glomerulosclerosis (FSGS) and MCD may represent different presentations of the same disease process. We present an interesting case of nephrotic syndrome in a patient with SCD, with MCD demonstrated on biopsy and a clinical course detailed over a 9-year period. We propose that our patient's case provides further support that idiopathic MCD and FSGS are presentations of the same disease process.

Case Description: A 17-year-old female with history of SCD presented with one week of fever, left plank pain, and hematuria. BP was 128/74, HR 78, RR 14, and SpO2 98%. No edema was present. sCr was 2.3 mg/dL and she had 24 g/d proteinuria. Hemoglobin variants revealed Hgb S 64%. Renal biopsy showed diffuse foot process effacement, moderate to severe interstitial fibrosis and tubular atrophy, and no glomerular basement membrane changes. Biopsy findings were consistent with MCD. Our patient was initially treated with IV steroids for 3 days, then continued on oral prednisone and ACE-i, with reduction in Cr to 0.5 after 12 months. At extended follow-up 9 years later, Cr has remained stable at 0.8, however mild proteinuria of 1g/g has persisted. Urine protein to creatinine ratio remains elevated at 1600 mg/g and urine microalbumin remains elevated at 698.8 mg/L. At this time, she has CKD stage G2A3, attributed to a combination of previous biopsy proven MCD with interstitial fibrosis and tubular atrophy, hypertension, and sickle cell disease.

Discussion: We propose that while our patient's renal biopsy was consistent with MCD, her persistent steroid resistant nephropathy and significant interstitial fibrosis and tubular atrophy which has likely progressed given her prolonged proteinuria, suggests progression to FSGS. This aligns with ongoing study suggesting that MCD and FSGS are presentations of the same progressive disease. While both MCD and FSGS are histopathological forms of idiopathic nephrotic syndrome, potentially caused by circulating permeability factors, abnormal T cell function, or cytokine alterations impacting glomerular membrane permeability, these pathologies may be related with steroid resistant MCD potentially progressing to FSGS.

SA-PO860

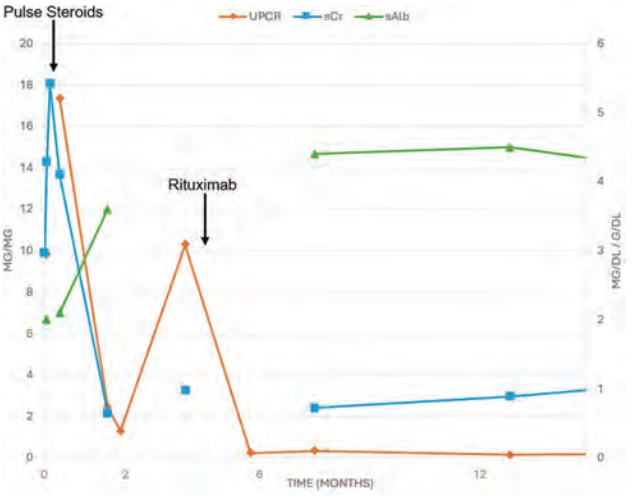
Partial Remission of Minimal Change Disease on Steroids: A Real-Life Case Report

Erica Marnet,[1,2] Kaltrina Sedaliu.[1,2] *[1]Yale New Haven Health System, New Haven, CT; [2]Bridgeport Hospital, Bridgeport, CT.*

Introduction: Minimal change disease (MCD) is a significant cause of primary nephrotic syndrome (NS). Less frequent in adults, around 10-15% of cases, and courses more frequently with hypertension, incomplete remission and steroid dependence. Management is generally extrapolated from pediatric data, highlighting the need to assess different therapies for the adult population.

Case Description: A 49-year-old male, with a history of hyperlipidemia, hypothyroidism presented with nausea, vomiting, oliguria, ascites and gravitational edema up to the abdomen. BP was 155/84 mmHg, serum creatinine (sCr) 2.97, serum albumin (sAlb) 1.8, UA with 4+ protein, 1+ glucose, urine protein/creatinine ratio (UPCR) 9.81. C3/C4, liver function, serologic evaluation and lymphoproliferative disorder work up were negative. Kidney biopsy demonstrated no sclerosis or immune complex deposition, but extensive effacement of foot processes suggestive of MCD. He was started on solumedrol then prednisone with good response. His edema was controlled with diuretics, those not needed on discharge. He did not tolerate steroids due to diabetes and myopathy. This rendered adherence to steroids difficult and his proteinuria worsened (Figure 1). Due to the financial burden of cyclophosphamide (CP) and dosing, he received 2 infusions of rituximab (RTX), followed by complete remission with no relapses, severe infection, or need of additional doses.

Discussion: MCD in adults differs from childhood in various factors as clinical course, relapses, secondary causes and treatment response. Limited data is available on adults. Frequent relapse or steroid dependence in MCD can occur up to 30% of patients. Despite RTX high remission rates in MCD refractory to other immunosuppressants, its role as a first agent after steroids is unknown. RTX is well tolerated in other causes of NS and requires fewer doses when compared to CP. This case shows RTX as a safe and cost-effective option for adult-onset MCD.



SA-PO861

A Minimal Change: Obesity-Related Glomerulopathy (ORG) and Intermittent Nonsteroidal Anti-inflammatory Drug (NSAID) Use as a Precursor to Minimal Change Disease in an Adult Patient

Frederick D. Parks, Jamie Pham, Mahesh Shrestha. *St Francis Emory Healthcare, Columbus, GA.*

Introduction: Minimal change disease (MCD) is predominantly idiopathic and rare in adults, accounting for only 10-15% of proteinuric glomerulopathy cases. The proportion caused by NSAID use is even lower. Typically, obesity-related glomerulopathy (ORG) presents as Focal Segmental Glomerular Sclerosis (FSGS) or Membranous Nephropathy (MN). We present a unique case of adult-onset MCD in an obese female precipitated by intermittent NSAID use.

Case Description: The patient is a 19-year-old Egyptian female studying in the US who abruptly develops edema. She has a BMI of 34.71 kg/m2. Her urinalysis revealed a 3+ proteinuria. The patient admits to taking Advil intermittently one week per month during her menstrual cycle. She has no family history of renal disease or dialysis. The patient exhibited hypercholesterolemia, random urine protein/creatinine ratio of 9.28 g, 24-hour urine collection of over 7.5 g of proteinuria, and hypoalbuminemia of <2.5 g/dL. CT-guided renal biopsy showed global foot process effacement on electron microscopy, with no deposits, sclerosis, crescent formation, or spikes. Serological workup was negative for C3, RPR, RF factor, ANA, MPO/PR3, HIV, and hepatitis. Post-stabilization, she was discharged on anticoagulation, an ACE inhibitor, steroids with GI and bone prophylaxis, lipid-controlling agents, and advised on lifestyle modifications.

Discussion: FSGS is far more commonly seen in ORG, and MCD is less common in adults. However, recent studies identify obesity as an independent risk factor leading to glomerular enlargement and proteinuria. Obesity also triggers biochemical pathways, such as TGF-β and RAAS, exacerbating kidney damage and altering gene expression related to lipid metabolism and inflammation. Studies also reveal ORG increasing in incidence, especially in BMIs ranging from 30.9-62.7 kg/m2. The mechanism of NSAIDs in adult onset MCD is also poorly understood. This case suggests that obesity may lead to MCD in adults, with NSAID use potentially lowering the threshold confounded by underlying immunological effects from obesity. Obesity may also increase the metabolic clearance rate of steroids, necessitating higher doses for full remission. Understanding these dynamics is crucial for managing MCD-type nephrotic syndrome in a growing population of obese patients.

SA-PO862

A Case of Pediatric Steroid-Resistant FSGS Evolving into a Steroid-Sensitive Profile in Young Adulthood

Antonio M. Fontanella,[1] Meghan R. Grewal,[1] Veronica A. Ortigosa Serrano,[3,2] George W. Burke,[1] Alessia Fornoni,[1] David Roth.[1] *[1]University of Miami Miller School of Medicine, Miami, FL; [2]Hospital Beneficente Sao Carlos, Rio Grande do Sul, Brazil; [3]The William J. Harrington Medical Training Programs for Latin America and the Caribbean and Global Observaerships, University of Miami, International Medicine Institute, Miami, FL.*

Introduction: Recurrent focal segmental glomerulosclerosis (rFSGS) is a challenging complication affecting 30-40% of transplanted FSGS patients, which can lead to loss of graft function and end-stage kidney disease. In this case report, I, the first author, will share my recent experience with rFSGS and hope to showcase the use of glomerular biomarkers to monitor disease evolution and guide treatment.

Case Description: I received a kidney transplant at 14 years old due to FSGS and PKD and developed rFSGS within 24 hours. Post-reperfusion renal biopsy showed that I was B7-1 positive, and I have been effectively treated with abatacept at the time and during various episodes of recurrence until the current case. I presented to transplant follow-up with fatigue, edema, and abdominal discomfort. Urine dipstick had shown +2 proteinuria, and labs showed a UPCR of 6.5, with a SCr of 0.9. Over the next 2 months, I received 4 doses of abatacept 1 g IV to no effect, with UPCR increasing to 10.8 and serum albumin falling to 1.8 with worsening symptoms. A cytokine panel found significant elevations in multiple cytokines. (Table 1). Standard treatment with plasmapheresis and rituximab 700 mg IV showed little effect, leading us to pursue allograft biopsy. The glomeruli demonstrated non-collapsing segmental sclerosis (tip variant) and mild mesangial expansion, as well as foot process effacement, consistent with rFSGS. B7-1 staining was negative, marking a shift from my previous status from B7-1 positive. [Figure 1] Plasmapheresis was continued for a total of 10 exchanges, accompanied by bolus steroid dosing followed by oral prednisone taper, and a repeat dose of rituximab 700 mg IV. There was a rapid response with decreasing proteinuria and clinical improvement in symptoms. Follow-up labs obtained 1 week after completion of treatment showed a UPCR of 0.2 with an albumin of 4.1 and SCr of 1.2. [Figure 2]

Discussion: Here, we report the first case of a pediatric patient with steroid resistant B7-1 positive rFSGS who transitioned to a B7-1 negative profile responsive to steroids in adulthood. It is crucial to observe the growing cohort of pediatric rFSGS patients reaching adulthood to determine the effect of age on pathology, outcomes, and treatment response.

SA-PO863

Steroid-Responsive FSGS Secondary to Bisphosphonate Use

Omar Ali, Aman Pal, Geovani Faddoul, Mauricio Monrroy. *Albany Medical Center, Albany, NY.*

Introduction: Focal segmental glomerulosclerosis (FSGS) is a histopathologic renal injury pattern with varying clinical features that poses diagnostic and management challenges. Current KDIGO guidelines recommend immunosuppression to treat primary FSGS, which is associated with nephrotic syndrome and diffuse podocyte effacement (DPE). Secondary FSGS presentations are highly variable, allowing primary and secondary FSGS to have overlapping features. Our case highlights an excellent response to steroids in a patient with secondary FSGS with DPE.

Case Description: A 71-year-old female presenting with an acute on chronic kidney disease stage 3 in the setting of a 2-week history of persistent nausea, vomiting, and diarrhea. Her creatinine was 15.68 mg/dL from a baseline of 1.3mg/dL, with nephrotic-range proteinuria of 4.96g/day and hypoalbuminemia. She started emergent dialysis for acute renal failure and had a renal biopsy showing collapsing FSGS with 100% foot process effacement. Genetic testing revealed a heterozygous mutation for Fanconi anemia. She was on ibandronate for postmenopausal osteoporosis, which was discontinued. She started daily prednisone 60mg and came off dialysis after one month of treatment, with creatinine returning to 1.2mg/dL. A few months later, she continued to have an adequate urine output with appropriate creatinine levels and was tapered to 10mg of prednisone daily. She has remained off dialysis since then and was recently transitioned to oral tacrolimus 0.5mg twice daily due to concerns of steroid-induced myopathy.

Discussion: In our case of FSGS secondary to ibandronate use, the biopsy revealed DPE. Bisphosphonates' exact mechanism of nephrotoxicity remains unclear. However, it was found to directly induce podocytes' loss of differentiation and loss of vital cytoskeletal proteins. This direct insult is similar to the postulated podocyte-toxic factor injury in primary FSGS. The prevalence of bisphosphonate-induced FSGS is well documented. However, its treatment with steroids and immunosuppressants is uncommon. There are reports of successful steroid treatment of secondary FSGS. Our patient demonstrated remarkable recovery after discontinuing ibandronate and starting steroids. She remained off dialysis and returned to her baseline renal function within a few weeks. More studies are needed to validate the role of steroids in secondary FSGS with diffuse podocyte involvement.

SA-PO864

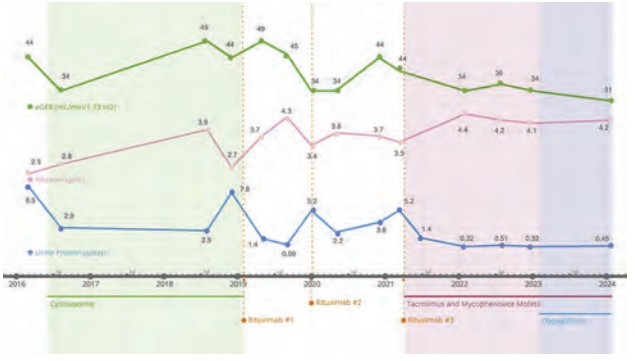
Successful Management of Relapsing Primary FSGS with Tacrolimus and Mycophenolate Multitarget Therapy

Frank Lee,[1] Marrey Ruby L. Quizon,[2] Wei Ling Lau.[2] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Division of Nephrology, Department of Medicine, University of California-Irvine, Irvine, CA.*

Introduction: Focal segmental glomerulosclerosis (FSGS) is a leading cause of nephrotic syndrome in adults. Multitarget immunosuppressive therapy has shown promise in lupus nephritis, but there is limited evidence in primary FSGS. Here, we describe a case of relapsing FSGS treated using a combination of tacrolimus and mycophenolate with years of stable disease remission.

Case Description: A 75-year-old female presented with recurrent nephrotic syndrome flares over several years. She had 2 native kidney biopsies (done 3 years apart) that showed FSGS (NOS variant with diffuse podocyte foot process effacement, 30% glomeruli with segmental sclerosis, 35% interstitial fibrosis). Other medical history is significant for CKD stage 3b, hypertension, type 2 diabetes mellitus and dyslipidemia. At time of initial diagnosis, the patient had 8.5 g/day of proteinuria and was treated with cyclosporine, on which she achieved partial remission with decrease in proteinuria to 3.5 g/day. The patient declined steroid therapy due to concerns about potential side effects. After 2 years on cyclosporine, she had proteinuria flare 7 g/day and therapy was changed to rituximab (375 mg/m^2 weekly x4 doses). She had good response with decrease in proteinuria <1 g/day, but had annual FSGS flare with nephrotic syndrome requiring repeat rituximab dosing (3 courses over 3 years). In early 2021, the patient was started on multitarget therapy with low-dose tacrolimus and mycophenolate mofetil. SGLT2 inhibitor therapy was added in early 2023. Patient is doing well after 3 years on this combination therapy, with stable proteinuria around 500 mg/day.

Discussion: This case demonstrates the feasibility of using tacrolimus and mycophenolate multitarget therapy to achieve successful long-term management of primary FSGS.



SA-PO865

FSGS in an Adult Transplant Recipient Possibly Linked to a New Antibody against WT1

Khaing S. Wei, Christian Herzog, Sushma Bhusal, John M. Arthur. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Focal segmental glomerulosclerosis (FSGS) is a histologic pattern of glomerular injury primarily affecting the glomerular podocytes, characterized by segmental scarring of select glomeruli. Primary FSGS involves circulating factors and can recur after transplant.

Case Description: A 66-year-old female with PMH of hypertension, microscopic hematuria, CKD diagnosed at the age of 30 progressed to ESKD at age 58 requiring HD. She had minimal proteinuria prior to ESKD. Her native biopsy contained only a single glomerulus but revealed thin basement membranes with podocyte effacement. She underwent DDKT at age 61. She had immediate graft function with UPCR of 0.67 mg/mg. Proteinuria resolved (UPCR undetectable) after one year but she again developed proteinuria of 2.1 g at 16 months and 11 g at 18 months. Her eGFR was 19-22 ml/min and serum albumin 3.2g/dl. An allograft biopsy showed FSGS with some collapsing features. Genetic analysis revealed a WT1 gene mutation (Ser466Phe). She underwent regular therapeutic plasma exchange (TPE) with stable Cr levels at 1.8 -2.2 mg/dl and UPCR at 2.0mg/mg. Plasma was collected prior to the first TPE. We performed western blot analysis using her plasma as the source of the primary antibody to determine if she could have an antibody against WT1. Normal human glomerular lysates were separated, transferred to PVDF and incubated with sera of the FSGS patient and two controls. Western blots were probed with secondary Ab against human IgA, IgG/M, IgM and developed with ECL reagent. A strong band at about 50kDa detected in the patient serum probed with anti IgM but not with IgG or IgA, suggested the presence of an antibody against WT1. The band was not present in two control plasma samples.

Discussion: The presence of an antibody that recognizes a glomerular protein at about 50 kDa suggests that this patient could have developed an autoantibody against WT1 after transplantation. Since the patient's kidney expressed a different sequence of WT1, this would be a novel antigen to her immune system. Since WT1 is expressed on podocytes, this antibody could interfere with the glomerular permeability barrier. Disease causing antibodies against nephrin have been described in children with nephrin mutations after kidney transplantation.

SA-PO866

Unveiling the Second Hit: Cytomegalovirus-Induced Collapsing Glomerulopathy in a Patient with Lupus

Vidya K. Bollavaram, Aric Gonter, Maria Bermudez, Kartik Kalra. *Geisinger Medical Center, Danville, PA.*

Introduction: Collapsing glomerulopathy (cGN) is a histological type of focal segmental glomerulosclerosis (FSGS) best described in association with human immunodeficiency virus (HIV). It has been increasingly seen in association with drugs, autoimmune disease, viruses (SARS-CoV2), and in rare cases, with cytomegalovirus (CMV). We present the case of a patient with lupus found to have cGN in the setting of CMV viremia.

Case Description: A 33-year-old African American female with a history of biopsy-proven Class V lupus maintained on hydroxychloroquine and mycophenolate, presented with 1 week of dyspnea and fevers. Lab investigations revealed Serum Creatinine (Cr) of 2.7 mg/dL (baseline 1.1mg/dL), pancytopenia, low C3 (80mg/dL), and C4 (7mg/dL) with negative dsDNA. Urinalysis showed 5-10 RBC. Spot urine Protein/Cr ratio was 10 gm/gm. Her clinical course was complicated by diarrhea and worsening acute kidney injury (AKI) requiring dialysis. The etiology of AKI was initially thought to be a lupus flare, and a kidney biopsy was done. Biopsy showed podocyte hyperplasia, collapse of the underlying glomerular tuft with segmental glomerulosclerosis, 40% interstitial fibrosis, and tubular atrophy. No evidence of an active immune complex-mediated process was noted. Viral studies were positive for CMV (CMV DNA 1,310,085 IU/ml). The patient was started on high-dose steroids and valganciclovir while other immunosuppression was held.

Discussion: cGN represents a variant of FSGS typically presenting with severe nephrosis and AKI. In our case, CMV likely acted as a 'second hit' with a possible underlying high-risk APOL-1 gene mutation, given her ancestry. The mechanism driving development of cGN has been proposed to be mediated by an interferon-chemokine pathway. Second hits such as HIV or SARS-CoV2 activate an inflammatory cascade that interacts with high-risk APOL-1 variants to precipitate cGN. Lupus has been associated with high interferon activity and thus may be another predisposing factor. CMV overall, remains a rare cause for cGN. While flares and class switching are sound differentials for AKI in lupus patients, this case highlights the importance of testing for CMV and considering cGN as a cause for AKI, especially in patients with African American ancestry. It further emphasizes the importance of ruling out opportunistic infections before preemptively adding more immunosuppression.

SA-PO867

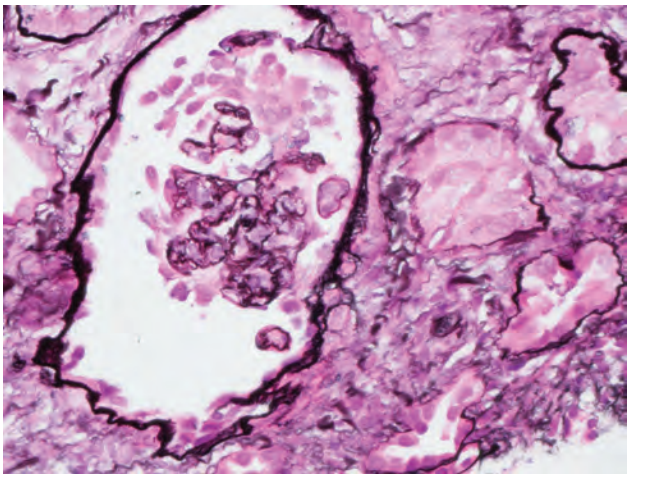
A Rare Cause of Collapsing FSGS: Hemophagocytic Lymphohistiocytosis-Associated with Epstein-Barr Virus

Keyana Khedmati, Josephine Abraham, Sarah Gilligan, Nirupama Ramkumar, Monica P. Revelo Penafiel. *University of Utah Health, Salt Lake City, UT.*

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a severe, life-threating syndrome of pathologic immune system activation. Viral infection, such as Epstein Bar Virus (EBV) infection, is a known trigger of HLH. Collapsing focal segmental glomerulosclerosis (FSGS), an aggressive variant of FSGS, that may be idiopathic or occur with infectious or inflammatory conditions. Here we present a case of a patient who presented with AKI (acute kidney injury) requiring hemodialysis who was later diagnosed with HLH associated EBV and collapsing FSGS/ATN on renal biopsy.

Case Description: A 42-year-old Somalian male with hypertension and new diagnosis of ESRD presented to the emergency department for hemodialysis (HD). He had presented two weeks prior at an outside hospital with renal failure ultimately thought to be ESRD from hypertension as his serologies were negative and ultrasound did not show obstruction. He had no prior baseline renal function as he did not follow routinely with primary care. During HD, he was found to be tachycardic and febrile, requiring admission. He underwent extensive workup for infectious etiologies and was ultimately diagnosed with HLH associated EBV. Genetic HLH panel was negative. He also underwent renal biopsy during this admission with evidence of FSGS with collapsing features and extensive ATN. He was started on rituximab and dexamethasone with improving results in his EBV titers from 21,000 to 10,000 after dose #4 and was discharged in stable condition. He remained on hemodialysis without evidence of renal recovery. Unfortunately, he presented a month later and was found to be hypotensive, febrile and tachycardic on dialysis. There was evidence of relapse with EBV PCR >110,000 and ferritin >40,000. He was also found to have disseminated cryptococcal infection, encephalopathy, and shock requiring multiple pressors and CRRT and eventually passed during admission.

Discussion: Collapsing FSGS may be idiopathic or occur with infectious or inflammatory conditions. HLH secondary to EBV infectious resulting in collapsing FSGS is rare and the exact mechanism is unknown. This case highlights the important association between HLH associated EBV, and collapsing FSGS in a rapidly progressive course leading to ESRD as well as the need for thorough evaluation of patients with presumed hypertensive kidney disease



SA-PO868

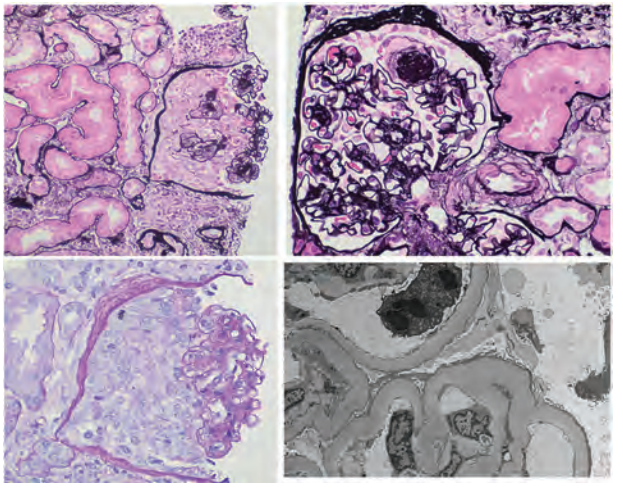
Once in a Blue Moon: Crescentic Diabetic Kidney Disease

Manjot Singh, Bushra Syed, Mohamed Hassanein, Pradeep Vaitla, Ramya Krishna Velagapudi, Mohammad Atari. *The University of Mississippi Medical Center, Jackson, MS.*

Introduction: Diabetic nephropathy is the leading cause kidney disease worldwide. Crescentic diabetic nephropathy is a rare occurrence and herein we present a case of diabetic kidney disease (DKD) with crescents formation in a kidney transplant recipient.

Case Description: A 65-year-old male with type 2 diabetes, hypertension, and atrial fibrillation who received a deceased donor kidney transplant in 2011 presented for routine follow up in clinic. His post-transplant course was unremarkable except for the development of low-grade prostate cancer managed with active surveillance and reduction in immunosuppression. The patient started to have worsening proteinuria up to 4.95 g/d and declining kidney function with creatinine of 1.7 mg/dL. HLA-DSA, PLA2R-Ab, and ANCA all were negative. No monoclonal protein detected by SPEP or UPEP and FLC ratio was normal. Kidney biopsy was pursued which showed characteristic diabetic changes. Interestingly, three glomeruli showed cellular crescents. There was no deposits or linear IgG staining on immunofluorescence. Electron microscopy showed severely thickened glomerular basement membrane without any deposits or fibrils. The patient was started on ARBs and proteinuria started to improve.

Discussion: While DKD is the most common cause of ESKD globally, the formation of crescents within the context of DKD is relatively rare. Crescents formation in the setting of DKD is mainly seen in association with other glomerular pathologies commonly known to present with crescentic glomerulonephritis. The presence of crescents in the setting of DKD is associated with a worse prognosis and points toward a more aggressive diabetic nephropathy. The absence of deposits in our patient with negative serological and monoclonal work up in addition to the absence of linear IgG staining by IF, rules out other pathology responsible for crescents formation.



SA-PO869

Collapsing Focal Segmental Glomerulosclerosis (cFSGS) and Its Association with Influenza A and Positive Cytoplasmic ANCA (C-ANCA) Serology: A Case Report

Amnah T. Kashkari, Ahmed F. Elfar, Rawan Alquaiz. *King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.*

Introduction: Collapsing FSGS is aggressive variant of glomerular diseases characterized by a rapid decline in renal function and poor prognosis. This report contribute to the existing literature by presenting a case of cFSGS associated with influenza A infection and positive C-ANCA.

Case Description: A 35-year-old male presented with flank pain preceded by upper respiratory tract infection symptoms. Physical examination was unrevealing. Laboratory findings were significant for creatinine of 1013 umol/L, albumin of 28 g/L. Urine studies showed microscopic hematuria, 24 hours urine collection was 300 ml with 2 g of proteins. He tested positive for influenza A. He was admitted and started on pulse steroid. Serology revealed high C-ANCA titer. Renal biopsy showed cFSGS as described in figure 1. He required hemodialysis for refractory hyperkalemia. He was discharged with tapering dose of steroids and hemodialysis twice weekly that was stopped few weeks later. After 6 months, his labs showed stable creatinine with GFR of 27, reduction in proteinuria, and normal serum albumin.

Discussion: The exact etiology of cFSGS is unknown. Several reports highlighted the association with various viral infections. In our case, influenza A virus appeared to have a crucial role in triggering cFSGS. The presentation of rapid decline in renal function, microscopic hematuria and positive C-ANCA may lead to incorrect initial diagnosis of rapidly progressive glomerulonephritis thus signifying the importance of confirming diagnosis with renal biopsy before commencing the patient on aggressive immunosuppressive therapy. Overall, the association between cFSGS, influenza A infection, and positive C ANCA serology suggests a complex interplay between viral triggers, and immune dysregulation.

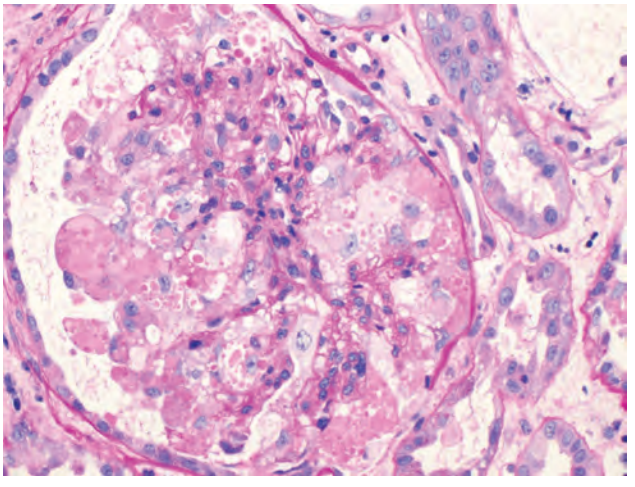


Figure 1: Segmental collapse of glomerular tufts, acute tubular injury and mild interstitial fibrosis and tubular atrophy

SA-PO870

A Diagnostic Dilemma of Lupus Nephritis and ANCA-Associated Vasculitis Overlap Syndrome

Kimberly Remedios,[1] Mateo Montalvo Campana,[1] Erica Marnet,[1] Deepthi Gunasekaran.[2] *[1]Yale New Haven Health - Bridgeport Hospital, Bridgeport, CT; [2]Yale University School of Medicine, New Haven, CT.*

Introduction: Systemic lupus nephritis (SLE) is characterized by the development of antinuclear antibodies (ANAs) and immune complex deposition in the kidney. Antineutrophilic cytoplasmic antibodies (ANCA) associated vasculitis (AAV) predominantly affects small vessels and is typically without immune complex deposition. It is challenging to determine if ANCA positivity in SLE patients is part of lupus nephritis (LN), or whether two different processes occur concurrently

Case Description: An 18-year-old female, without co-morbidities presented with hematuria, dysuria, and headache for one week. She was febrile on presentation. Laboratory tests were significant for acute kidney injury (AKI) and anemia. Treatment started with intravenous fluids and antibiotics. Subsequently, she developed hemoptysis, with a consequent drop in hemoglobin. She became hypoxic, with worsening AKI and required intubation, mechanical ventilation and initiation of hemodialysis. Bronchoscopy showed DAH. She was initiated on steroids and plasma exchange for concern of rapidly progressive glomerulonephritis and pulmonary renal syndrome. Serologies were positive for antinuclear antibodies (1:320), anti-double stranded DNA (51 IU/ml) antibodies, Myeloperoxidase antibodies. Light microscopy showed mesangial hypercellularity with one fibrocellular crescent (Figure 1). IF was positive for IgA, IgM, IgG, C1q negative. She was started on cyclophosphamide and steroid. She was extubated and remained on dialysis

Discussion: It is a challenge to distinguish AAV from LN and the dilemma in treatment options for the two cases. ANCA positivity has been reported to be associated with more severe lupus nephritis in some cases while others have discounted it as a laboratory artefact. Her presentation of DAH is more often associated with ANCA vasculitis along with classic pathology of lupus nephritis in the form of immune complex deposition supports the diagnosis of SLE/ANCA vasculitis overlap syndrome

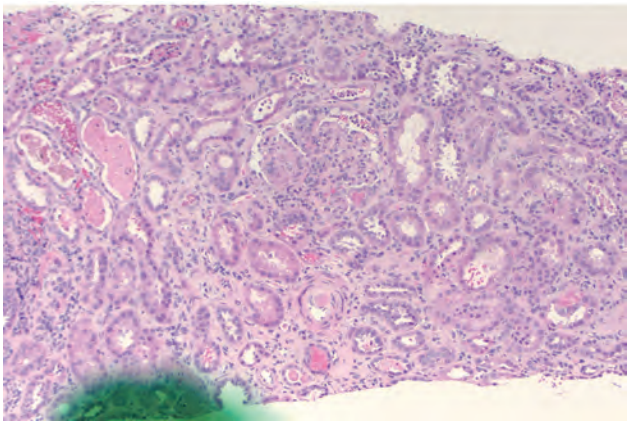


Figure 1: Light microscopy

SA-PO871

Glomerulonephritis (GN) Due to Systemic Lupus Erythematosus in a Seronegative Patient: A Lupus Criteria Dilemma

Sumbal Wajid,[1] Lilit Grigoryan,[1] Aman Pal,[1] Ruben A. Peredo-Wende.[2] *[1]Albany Medical Center, Albany, NY; [2]Albany Stratton VA Medical Center Albany, Albany, NY.*

Introduction: Systemic Lupus Erythematosus (SLE) is a well-recognized autoimmune disease with varying clinical and immunological manifestations. According to the 2019 American College of Rheumatology lupus consensus criteria, a positive ANA at any time is required as an entry criterion. Our case highlights a clinical and pathological diagnosis of SLE with negative ANA and anti-dsDNA.

Case Description: A 54-year-old African-American woman presented with cough, dyspnea, orthopnea, and leg swelling. Initial work up showed hemoglobin 10.2 g/dL, unremarkable EKG, troponin, and BNP. CT chest showed a large pericardial effusion, with TTE confirming tamponade physiology. A pericardial window was performed. All infectious work up including blood and pericardial fliuid cultures remained negative. Further testing was pursued that showed positive direct Coombs test, proteinuria and hematuira on urine analysis, and low C3 and C4 levels. This prompted further work up for renal disease in the context of multisystem disease. Serology came back negative for ANA, anti-dsDNA, ENA panel, and antiphospholipid antibodies, as well as c-ANCA, p-ANCA, anti-MPO and anti-PR3 antibodies. Protein electrophoresis and hepatitis panel were unremarkable. Ultimately, kidney biopsy revealed diffuse mesangial and focal segmental endocapillary proliferative GN with positive immunofluorescence to IgG, IgM, C3 and C1, suggesting immune-complex type GN. Although serologic work up remained negative, a presumptive diagnosis of SLE with lupus nephritis was made, in setting of Coombs positive anemia, serositis, hypocomplementemia and immune-complex type GN. Patient was started on steroids and mycophenolate mofetil. 7 years later, she remains on mycophenolate mofetil with stable creatinine and kidney function.

Discussion: The 2019 EULAR/ACR classification criteria diagnose SLE with a score of 10 or greater. However, these criteria exclude SLE if the ANA is negative. If we were to follow this updated criteria for the diagnosis of SLE, our patient would not be classified as having lupus, even though their score is well over 20, neglecting the negative ANA. Although ANA-negative lupus is quite rare, with only a prevalence of around 2%, it is still crucial to properly diagnose these patients as both early diagnosis and initiation of therapy can greatly benefit our patients.

SA-PO872

Case of Eosinophilic Granulomatosis with Polyangiitis with Kidney Involvement

Ram Sinha, Ivette Gomez, Amer A. Belal. *University of Florida, Gainesville, FL.*

Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic small-vessel vasculitis characterized by asthma, eosinophilia, and ANCA positivity in 40% of patients. Though predominantly a rheumatological process, we present a case with severe renal disease.

Case Description: A 42-year-old male with a history of asthma and tobacco abuse presents complaining of fever, abdominal pain, pleuritic pain, weakness, and weight loss. On admission he was febrile to 101.1F, lab studies were significant for WBC of 13.1, PLT 521, eosinophils 2.11, Cr 2.10 mg/dL from a baseline of 1.0, CRP 285. CT chest abdomen pelvis revealed moderate paraseptal emphysema. Blood and urine cultures, TB, RPR, HIV, and Hepatitis serologies were negative. Urine microscopy revealed acanthocytes and thus renal biopsy was sought. The patient had normal ANA and complement levels however ANCA serologies were positive with p-ANCA pattern at > 1:1250, PR3 Ab 75, and MPO Ab 193. His PLA2R Ab and GBM Ab were negative. The renal biopsy showed severe pauci-immune necrotizing crescentic glomerulonephritis and glomerular cellular crescents involving 66% of the glomeruli with prominent podocyte effacement. Rheumatology was consulted and diagnosed the patient with EGPA. The patient was given methylprednisolone at 1 g daily for 3 days followed by an initial dose of Rituximab 1 g when his Cr was 4.02 mg/dL. His Cr peaked at 4.57 mg/dL the following day before downtrending, and he was discharged on prolonged prednisone taper with follow-up with Rheumatology, Pulmonology, and Nephrology. The patient had IgG 1476, IgM 44, and IgA 197 baseline immunoglobulin levels. His 2nd dose of Rituximab was 3 weeks later and at a reduced dose of 800 mg IV due to issues with insurance authorization. The renal response stalled with a Cr level of 3 mg/dL 6 weeks after his 2nd dose of Rituximab and proteinuria worsened to 13 g/d. Adjunct therapy with Mepolizumab or Cytoxan was discussed with Rheumatology. His follow-up IgG 481, IgM 23, and IgA 108 precluded repeated dosing of Rituximab. Given the patient's refractory EGPA with severe symptoms, the decision was made to proceed with Cytoxan therapy.

Discussion: Renal involvement in EGPA occurs in about 25% of cases compared with other ANCA vasculitis and impacts the patient's prognosis and treatment. Treatment of EGPA with renal involvement is challenging and involves a multidisciplinary approach

SA-PO873

A Rare Case of Concurrent IgA Nephropathy and Anti-glomerular Basement Membrane (GBM) Disease

Phoenix Xu, Rahul Maheshwari, Sebastian Gandarillas Fraga, Stephen C. Ward, Joseph A. Vassalotti, Miriam Chung, Samuel Mon-Wei Yu. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Anti-glomerular basement membrane (anti-GBM) disease is a rare disorder, characterized by rapidly progressive glomerulonephritis (RPGN) with or without pulmonary involvement. Here, we report a patient presenting with RPGN due to anti-GBM disease, who was found to have mesangial IgA staining on immunofluorescence (IF), suggesting concurrent IgA nephropathy (IgAN).

Case Description: A 38-year-old male with no known past medical history, presented with several days of abdominal pain, nausea, and vomiting. He was found to have acute kidney injury with initial serum creatinine of 7.9 mg/dL requiring hemodialysis. Initial workup included a urinalysis with +4 protein; innumerable RBCs and 5-10 WBCs per HPF; a urine protein-to-creatinine ratio of 3.10 g/g; and an unremarkable kidney ultrasound. Serologic workup was notable for an IgG anti-GBM titer of 2.5 units/mL (reference < 0.9), and anti-nuclear antibody (ANA) titer of 1:320. Other serological studies including MPO, PR3, C3, C4, hepatitis B and C, and PLA2R were normal or negative. Kidney biopsy light microscopy showed 25 glomeruli (20 with cellular and/or fibrous crescents, and 1 with mesangial expansion and hypercellularity). There was moderate interstitial scarring. IF showed linear staining of glomerular basement membrane for IgG (1+) and lambda/kappa (2+) consistent with anti-GBM glomerulonephritis. Additionally, mesangial regions were positive for IgA (1-2+), IgM (1+) and C3 (1+), consistent with IgA nephropathy. Patient received pulse dose glucocorticoids, oral and intravenous cyclophosphamide, and 10 sessions of plasmapheresis. He remained on kidney replacement therapy after induction treatment with an anti-GBM titer of 0.2 units/mL.

Discussion: Concurrent IgAN with anti-GBM disease has been described sporadically in the literature with heterogeneous findings. These findings include linear IgA staining of GBM, concurrent mesangial IgA and linear IgG staining, and linear IgG staining with circulating IgA anti-GBM antibodies. The moderate scarring, mesangial involvement, and variable stages of crescent formation suggest that our patient may have had ongoing undiagnosed IgAN that preceded development of anti-GBM disease. Unlike other similar reported cases, he unfortunately did not have kidney function recovery.

SA-PO874

Diffuse Alveolar Hemorrhage (DAH) Secondary to Influenza B in a Kidney Transplant Recipient with Anti-glomerular Basement Membrane (Anti-GBM) Disease

Muhammed N. Rehmani, Sean Hebert. *The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.*

Introduction: DAH is a potentially life-threatening syndrome requiring immediate recognition and treatment. In kidney transplant recipients with known Anti-GBM disease in native kidneys, recurrent anti-GBM disease should be suspected if they present with microscopic hematuria, proteinuria, and/or acute kidney injury. However, isolated DAH is rare and poses a diagnostic challenge, particularly if it is secondary to infection.

Case Description: A 48-year-old male with Anti-GBM disease presented to the emergency department with hemoptysis. He had been diagnosed with Anti-GBM disease twelve years earlier, resulting in rapidly progressive glomerulonephritis that was refractory to first and second-line treatments. He became dialysis dependant until his kidney transplant 10 years later. His disease had remained quiescent since transplant and his allograft function was normal on immunosuppression. Upon presentation, his vitals were stable except for a temperature of 100.5 F. Chest radiography revealed infiltrates in the left middle and lower lung lobes. A computed tomography (CT) scan of the chest confirmed these infiltrates and showed surrounding ground glass opacities. Serum electrolytes, creatinine and urinalysis were normal. Bronchoscopy revealed progressively bloody aliquots consistent with DAH. He was treated with daily plasmapheresis for possible recurrent disease for 2 days. This treatment was discontinued when his serum Anti-GBM antibody returned negative, and no evidence of anti-GBM disease was found on lung pathology. Consequently, his DAH was suspected to be secondary to viral pneumonia, specifically Influenza B, and all treatments except antiviral therapy were discontinued.

Discussion: Isolated DAH in a patient with Anti-GBM disease is typically either an initial presentation or an indicator of disease recurrence. However, in this case, the patient presented with alveolar hemorrhage without laboratory findings suggestive of disease recurrence, indicating that the DAH was secondary to viral pneumonia. Infection, although rare, should be considered a possible cause of DAH once more common causes have been excluded. This case highlights the importance of considering infectious etiologies in patients with DAH. Early identification and appropriate management of the underlying cause are crucial for improving patient outcomes.

SA-PO875

Diabetic Nephropathy Complicated by an IgA-Dominant Infectious-Related Glomerulonephritis: A Case Report

Leonardo R. Ramirez Botana. *LSU Health Shreveport, Shreveport, LA.*

Introduction: Acute post-infectious glomerulonephritis (APIGN), in adulthood is common in diabetic, alcoholic, and intravenous drug-abusing patients. APIGN is usually secondary to Staphylococcus aureus infection, occurring after skin infection, deep-seated abscesses and presents a histological pattern identical to acute poststreptococcal glomerulonephritis. This case reported a diabetic nephropathy complicated by an IgA-dominant infectious related glomerulonephritis

Case Description: A 27-year-old female with past medical history of hypertension, diabetes mellitus type 1 and chronic kidney disease was admitted due to acute renal failure, high blood pressure and uncontrolled diabetes mellitus. Physical examination showed bilateral periorbital edema, lower extremities pitting edema, and the presence of left frontal skin abscess. Uncontrolled blood glucose, anemia, hyperkalemia, impaired renal function was documented. Urinalysis revealed moderate urine blood with high total protein. The C4 /C3 complements and anti streptolysin O were within normal rage. Immunological workup was normal including antinuclear antibody and anti-DNA. Head abscess culture was positive for Staphylococcus aureus, and due to a massive proteinuria, renal biopsy was performed. The mesangium biopsy shows PAS-positive nodular mesangial expansion and interstitial fibrosis. Immunofluorescence findings showed capillary loops staining for IgA, C3 and lambda, subepithelial immune type electron dense deposits and global effacement of foot processes consistent with diabetic injury, likely with superimposed port-infectious glomerulonephritis.

Discussion: Few cases have been reported in Puerto Rico, and a major shift has occurred in the epidemiology of this disease. Worldwide numerous cases of APIGN have been identified with intense deposits of IgA as the sole or dominant immunoglobulin on immunofluorescence, similar to our case, characterizing a new entity named IgA-dominant acute post infection glomerulonephritis (GN) The massive proteinuria and the rapid deterioration of renal function in our diabetic patient should suggest that an additional pathologic condition is affecting the kidneys. An IgA-dominant infection related GN was diagnosed, and after treated with antibiotic therapy our patient recovered from the disease and was discharge to home.

SA-PO876

A Case of Nephrotic-Range Proteinuria and False-Positive Anti-phospholipase A2 Receptor (PLA2R) Antibodies

Ying-ying Seow, Ivan Wei Zhen Lee, Swee Ping Teh. *Sengkang General Hospital, Singapore, Singapore.*

Introduction: Autoantibodies to the M-type phospholipase A2 receptor (anti-PLA2R AB) have been demonstrated to be highly specific for the diagnosis of primary membranous nephropathy (MN). We present a case of anti-PLA2R AB positivity with no membranous glomerular pathology.

Case Description: A 45-year-old Malay female was referred for the evaluation of nephrotic-range proteinuria and elevated serum creatinine (sCr). She was admitted for uncontrolled hypertension and acute decompensated heart failure with reduced ejection fraction. She did not have diabetes mellitus. On admission, sCr was 147 umol/L (eGFR 37 ml/min/1.73m^2), serum albumin 42 g/L, urine albumin/creatinine ratio (uACR) 361.1 mg/mmol, protein/creatinine ratio 4 g/g and minimal hematuria (5 cells/uL). 24-hour total urine protein was 0.57 g/d on a suboptimal collection. Serological testing revealed faintly positive antinuclear antibody titer (1:160, homogeneous pattern) and positive anti-PLA2R AB 49.6 RU/ml (IgG ELISA Euroimmun). She was started on goal-directed therapy for heart failure. Serial repeated measurements of anti-PLA2R AB remained elevated over the next 5 months (49.6, 68.46 RU/ml) with persistent proteinuria. A kidney biopsy was obtained, revealing focal segmental glomerular sclerosis, arteriolar hyalinosis and focal arteriolar thrombosis, without features of MN. Immunofluorescence was weakly positive (1-2+) for IgM and C3 along glomerular capillary walls but negative for IgG. Electron microscopy showed mild basement membrane thickening, moderately extensive podocyte foot effacement (30-40% capillary wall surface area), but no subepithelial electron dense deposits were found. The diagnosis of hypertensive nephropathy with thrombotic microangiopathy (TMA) and FSGS was made. Her dose of valsartan was optimized and dapagliflozin was added. Over the next year, her sCr was stable at 151 umol/L (eGFR 36 ml/min/1.73 m^2) and uACR regressed to 39.8 mg/mmol.

Discussion: The specificity of anti-PLA2R AB for MN has been described to be as close to 100%, allowing patients with nephrotic syndrome and positive serology to forego biopsy. Other cases of anti-PLA2R AB positivity without MN have described minor glomerular, FSGS or diabetic nephropathy changes but not TMA. Our case adds to the body of literature of false-positive anti-PLA2R AB and supports pursuing a kidney biopsy especially when nephrotic syndrome is absent.

SA-PO877

Nephrotic-Range Proteinuria in Patient with Syphilis and HIV

Karishma Iyer, Kaitlin Markoja, Lukman Cheraghvandi, Keiko I. Greenberg, Chanigan Nilubol, Donghyang Kwon. *MedStar Georgetown University Hospital, Washington, DC.*

Introduction: Syphilis is a curable sexually transmitted infection caused by Treponema Pallidum. Infection develops in stages (primary, secondary, latent and tertiary), each associated with different signs and symptoms. Kidney manifestations are rare but can be a feature of secondary syphilis. Membranous nephropathy is most commonly observed; syphilis associated kidney disease can also present as nephrotic syndrome, acute kidney injury, membranoproliferative glomerulonephritis, or interstitial nephritis.

Case Description: 34 year old male with newly diagnosed human immunodeficiency virus (HIV), history of gonorrhea, and recent positive syphilis screen (RPR 1:512) presented with bilateral vision loss. He underwent lumbar puncture and was diagnosed with secondary syphilis with ocular/CNS involvement (CSF VDRL 1:16). Treatment with IV penicillin was initiated. His kidney function was normal but a routine urinalysis (UA) was positive for proteinuria. Repeat UA confirmed the presence of albuminuria and was also notable for 8 RBC/hpf. Urine protein creatinine ratio was 4.1 g/g. Serum albumin was normal at 4.0g/dL. His physical examination was notable for improving rashes and no peripheral edema. Further infectious testing was notable for HIV viral load 65,897 copies/mL and CD4 count 171 cells/uL. Hepatitis B surface antigen and hepatitis C antibody were negative. Further workup for nephrotic syndrome was initiated: complement levels were normal, ANA negative, kappa:lambda ratio normal and no monoclonal spike on SPEP or UPEP. Renal biopsy was pursued which showed marked subepithelial deposits along with numerous tubuloreticular structures consistent with membranous glomerulopathy. Immunofluorescence positive for IgG, IgA, IgM, and C3. C1q was negative.

Discussion: Syphilis is re-emerging in the US - in 2022, the highest number of cases of syphilis were reported since 1950 with an increase of 17.3% since 2021. Most cases reported were primary or secondary syphilis. Individuals who present with proteinuria should be screened for syphilis. Although membranous nephropathy has also been reported in HIV, it seemed most likely that this patient's membranous nephropathy was related to syphilis. Proteinuria usually resolves with treatment of syphilis. Our patient was unfortunately lost to follow up so it is unknown if his proteinuria improved following treatment.

SA-PO878

Varicella zoster: A Rare Cause of Membranoproliferative Glomerulonephritis

Anuj Gupta, Muhammed Mumin, Janany J. Sabescumar. *University of Rochester Medical Center, Rochester, NY.*

Introduction: A rare association of Varicella Zoster (VZV) with renal disease was first discovered in 1884 by Henoch[1]. There is scarce literature on the evidence of glomerulonephritis following the incidence of VZV. We are presenting a case of a 72-year-old man who was diagnosed of membranoproliferative glomerulonephritis (MPGN) post shingles.

Case Description: A 72-year-old male with a past medical history of hypertension presented to primary care with profound anasarca and uncontrolled hypertension. Two months ago, he experienced shingles and responded well to antiviral therapy and prednisone. His labs were significant for spot protein/creatinine ratio of 11.35 g/dL and serum creatinine increase from 0.9 mg/dL at baseline to 1.16 mg/dL. Serological work up was revealing for low C3 level 78 mg/dL only. Subsequently after nephrology consultation, he underwent renal biopsy which revealed membranoproliferative glomerulonephritis with 3+ IgM and C3 deposition on immunofluorescence. He was started on weight-based 1 mg/kg of oral prednisone daily followed by steroid taper over a course of three months. Subsequently, his proteinuria reduced to 7.62 g/day whilst on treatment and improvement of anasarca and hypertension.

Discussion: VZV associated with nephritis is uncommon and was proven with only 3 (0.1%) out of 2534 developing clinical nephritis in a 1935 study[2]. Molecular pathologic method (in situ hybridization) verified VZV's growth and reproduction in kidneys causing glomerulonephritis[3]. The mechanism of VZV induced MPGN could be direct or immune mediated[1]. Membranoproliferative glomerulonephritis shows a pattern of injury with distinctive mesangial cellularity and glomerular capillary walls thickening due to subendothelial deposition of complement factors like strong C3 deposition or IgM immune complexes which was noticed in our patient[6-8]. Literature shows that these results are suggestive of immune complex mediated glomerulonephritis[9,10]. Proteinuria occurring in patients post varicella infection should caution clinicians to check for the possible diagnosis of membranoproliferative glomerulonephritis

SA-PO879

When You Close a Door, a Window Opens: A Case of Dupilumab-Induced Autoimmune Glomerulonephritis

Meshaal Alanzi, Avrum Gillespie, Kishore Kumar Mani, Suzanne Boyle, Sheetal Koul. *Temple University, Philadelphia, PA.*

Introduction: Dupilumab, a monoclonal antibody that blocks IL-4 and 13, is indicated for atopic dermatitis management. Eosinophilic granulomatosis with polyangiitis (EGP) has been reported with dupilumab use. We report a case of AKI from lupus-like glomerulonephritis following dupilumab, suggesting that blocking IL-4 and 13 may be linked to autoimmunity.

Case Description: A 61-year-old man with a history of an orthotopic liver transplant for HCV-related cirrhosis five years prior and non-proteinuric CKD (baseline creatinine 2.3 mg/dl) was admitted for generalized fatigue, mild abdominal pain, nausea, and poor appetite. Serum creatinine was 8 mg/dl. Four months before, he started Dupilumab for resistant atopic dermatitis. Further testing revealed normocytic anemia with Hb of 6.5 g/dL and thrombocytopenia 103 K/mm^3. Urinalysis showed hematuria; urine protein to creatinine ratio 4216 mg/gram. Complement C3/C4 normal, ANA, anti-ds DNA, and rheumatoid factor negative. c-ANCA titer was 1:320 (negative for anti-PR-3 and MPO). An ANCA-mediated GN was initially suspected. However, a kidney biopsy revealed a membranoproliferative glomerulonephritis with cellular crescents and a diffuse tubulointerstitial inflammatory infiltrate with "full house" staining on immunofluorescence, consistent with lupus-like nephritis. The patient was managed with steroids (500 mg methylprednisolone for three days, then 1 mg/kg with taper). Ultimately, he needed regular hemodialysis.

Discussion: In this case, Dupilumab was the most likely cause of this "full-house" ANCA-positive nephritis. Dupilumab has also been associated with EGP. The potential mechanism is that blocking IL4 increases autoimmunity. IL-4 is considered an immunoregulatory cytokine with pleiotropic effects on antibody production, inflammation, and T-cell responses. It is suggested that IL-4 has a protective role against autoimmunity as it suppresses T-cell activity and tissue inflammation. In one mouse strain, the pathogenic autoantibody subclasses (IgG21 and IgG3) were suppressed by IL-4. Thus, mice with increased IL-4 had low levels of IgG3 and IgG2a subclasses of anti-DNA antibodies with high IgG1 levels, which is considered protective against lupus-like nephritis development. Consequently, suppressing IL-4 might lead to increased autoantibody subclasses that deposit in the kidney, inducing inflammation.

SA-PO880

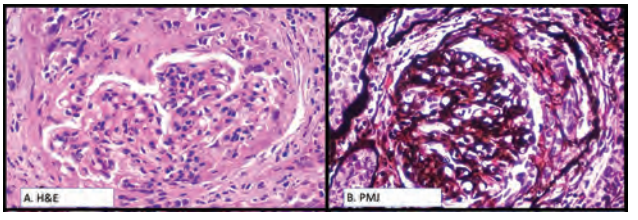
Anti-neutrophil Cytoplasm Antibody-Associated Vasculitis as Paraneoplastic Glomerular Disease

Belén Gallegos, Laura G. Amador Reyes, Gonzalo Ruiz Saucedo, Laura d. Fuentes-Mendez, Angela M. Cordoba Hurtado, L. M. Perez-Navarro, Virgilia Soto, Diana L. Figueroa Gamiño, Ingrid R. Velasquez Lorenzo. *Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico*.

Introduction: Paraneoplastic glomerulonephritis (PGN) is a rare complication of a malignant tumor, with glomerular lesions induced by products of tumor cells. ANCA-associated vasculitis (AAV) occurs in 14-20% of paraneoplastic syndromes associated with renal tumors; 71% are clear-cells carcinoma. In Latin America there are no cohorts that evaluate the association of AAV and renal cell carcinoma.

Case Description: CASE 1: 51 years old male, admitted requiring KRT. We found active urinary sediment and positive anti-MPO. An image of a kidney tumor was found in the echography, later confirmed with CT. Patient had a partial nephrectomy, with pathology result showing clear cell renal cell carcinoma and pauci-immune crescentic glomerulonephritis with focal and segmental sclerosis and grade II interstitial fibrosis. CASE 2: 56 years old male, admitted due to uremic syndrome, and behavior of rapidly progressive glomerulonephritis, starting KRT. We found positivity for anti-MPO, evidence of a kidney tumor in echography and TC. A renal biopsy was performed, reporting active pauci-immune crescentic glomerulonephritis and grade II interstitial fibrosis. He was treated with complete nephrectomy four months later, pathology confirmed clear cell renal carcinoma. CASE 3: 44 years old male, with granulomatosis with polyangiitis since 2020, referred because of proteinuria and chronic kidney disease. Ecography showed a renal tumor, CT was performed suggesting clear cell renal carcinoma.

Discussion: The course of PGN is a rare diagnostic and a therapeutic challenge, so early identification and treatment with close follow-up could help improve the prognosis. It is reasonable to treat AAV with standard immunosuppression, including steroids and/or cyclophosphamide and/or rituximab, given the high associated morbidity and mortality, along with planned cancer treatment.



SA-PO881

Unexplained Chylous Pleural Effusions Diagnosed by Kidney Biopsy

Aju Jose,[1] Amy Ludwig,[1] John T. Ludwig.[2] [1]*Northwestern University McGaw Medical Center, Chicago, IL;* [2]*University of Michigan, Ann Arbor, MI*.

Introduction: Amyloidosis is a group of diseases characterized by extracellular protein deposition of beta-sheet fibrils. Renal amyloidosis is found in about 2% kidney biopsies and is usually secondary to systemic disorders. Here we describe an atypical case of renal AA amyloidosis presenting with chylous pleural effusions and ascites.

Case Description: Patient is a 47 year old paraplegic male with neurogenic bladder, chronic indwelling urinary catheter, chronic sacral wounds, history of osteomyelitis and malnutrition. History of presenting illness included insidious onset of shortness of breath which started 18 months prior to presentation. He was evaluated by his primary care physician who found bilateral pleural effusions and was sent to a thoracic surgeon. He had multiple serial thoracentesis underwent VATS with talc pleurodesis which was unsuccessful. Bilateral pleurX catheters were placed for symptom management. He was referred to our center due to increased drainage from his catheters, anasarca and worsening shortness of breath and consideration of lymphangiogram with interventional radiology. Labs were significant for serum albumin < 1.5 and pleural fluid triglycerides > 135 consistent with chylous efusion and UPCR > 40 g/g. Lymphangiogram showed a patent thoracic duct with no evidence of leak. Renal Biopsy showed changes of amyloidotic nephropathy. Laser dissection and tandem mass spectroscopy confirmed AA amyloid. Pleural fluid cultures revealed VRE and he was treated with daptomycin and ciprofloxacin. Supportive care was provided with nutrition management, wound care and diuresis. Drainage from left pleurX catheter decreased and was eventually removed. He continued to require frequent paracentesis. He was discharged with plans for close follow up but unfortunately passed away 14 days after discharge.

Discussion: Chylous pleural effusions and ascites is a rare presentation of amyloidosis, in this case diagnosed on kidney biopsy. This diagnosis is challenging and requires a high index of suspicion. AA amyloidosis is a rare but serious complication from underlying chronic inflammatory disorders with a sustained acute phase reactant response. Renal dysfunction with proteinuria is the most common manifestation of AA amyloidosis, with high mortality (median survival of 133 months after diagnosis)1. Management typically consists of targeting the underlying inflammatory response.

SA-PO882

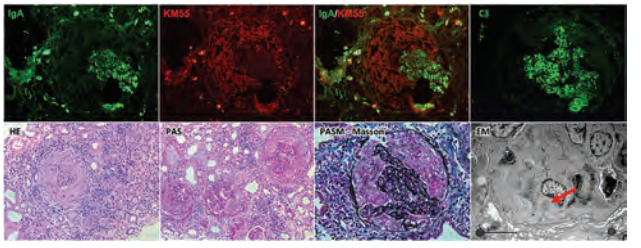
IgA-Dominant Postinfectious Crescentic Glomerulonephritis after a Cervical Smear

Shi Jin. *Zhongshan Hospital Fudan University, Shanghai, China*.

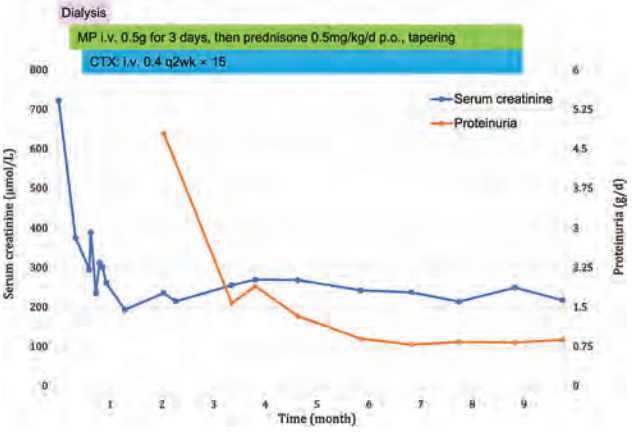
Introduction: IgA-dominant infection-associated glomerulonephritis(IRGN) usually presents diffuse endocapillary and/or mesangial proliferation with a few crescents. Here we report a rare case of IgA-dominant IRGN with diffuse necrotizing cellular crescents, which benefited from corticosteroid and cyclophosphamide treatment.

Case Description: A 29-year-old woman developed rapidly progressive edema and anuria with fever and persistent vaginal discharge of pus after a cervical smear for health checkup. Laboratory analyses revealed serum creatinine of 723μmol/l, serum albumin of 17.4g/l, C-reactive protein of 172mg/l, hypocomplementemia and prominent proteinuria and hematuria. Anti-GBM and ANCA were negative. *Enterococcus faecium* were isolated from culture of vaginal discharge. Kidney biopsy (Figure 1) showed starry sky patten of IgA and C3 deposition along GBM by immunofluorescence. Light microscope showed 90% of glomeruli with necrotizing cellular crescents, endocapillary infiltration and Bowman's capsule rupture. Electronic microscope showed major subepithelial and subendothelial electron-dense deposits with mild mesangial deposits. Therefore, IgA-dominant IRGN was diagnosed. Pulse therapy of methylprednisolone and intravenous cyclophosphamide (CTX) were given after infection controlled. Her urine output began to increase after 3 days and reached dialysis independence after two weeks. She was treated with i.v. CTX 0.4g every 2 weeks with tapering oral methylprednisolone, and maintained stable renal function for ten months(Figure 2).

Discussion: IgA-dominant IRGN can mimic ANCA glomerulonephritis with diffuse necrotizing lesions and crescents. Prompt immunosuppression besides infection control is crucial for kidney function restoration and preservation.



Histopathologic findings of kidney biopsy



Clinical course after presentation

SA-PO883

Don't Forget the Topical Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Golriz Jafari, Phuong-Chi T. Pham, Hoang Anh Nguyen, Sapna Gopal, Anirudh V. Chandra, Anita Kamarzarian. *UCLA Medical Center Olive View, Sylmar, CA*.

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are known to cause multiple adverse effects to the kidneys including acute kidney injury, interstitial nephritis, hyperkalemia, membranous glomerulonephritis, minimal change disease (MCD) or papillary necrosis. Topical NSAID use is usually considered safe and low risk for these adverse effects; however, it still needs to be considered.

Case Description: A 53-year-old male with poorly controlled diabetes mellitus (DM) type 2 (HgA1C 9.8%) presents with acute onset of bilateral lower extremity, abdominal distention and shortness of beath. Patient was found to have urine albumin/creatinine ratio (UACR) or 6215 mg and nephrotic syndrome. Urine did not show any active

sediment and he had no know personal or family history of kidney disease. Patient had been using regularly topical diclofenac for back and knew pain. Differential diagnosis included DM nephropathy, focal segmental glomerulosclerosis (FSGS) due to obesity, primary FSGS and MCD. All proteinuria serology including hepatitis B and C, HIV, syphilis, immunofixation, phospholipase A2R, ANCA, complement, kappa/lambda, QuantiFERON gold were all within normal limits and patient did not have any evidence of diabetic retinopathy. Given acute onset of nephrotic syndrome and no evidence of retinopathy, patient underwent kidney biopsy which revealed minimal change disease. Patient did not have any history of atopy, or lymphoproliferative disorder. He was instructed to discontinue topical NSAIDs and follow up UACR in 1 month normalized to 7.2 mg.

Discussion: Diabetic kdiney diease is the most common cause of proteinuria and can often cause nephrotic syndrome, however it usually presents insidiously and coincides with diabetic retinopathy. In patients who do not have the typical natural history, kidney biopsy evaluation is imperative to not miss other etiologies. Additionally, although nephrologist often screen for oral NSAIDs during history evaluation, often topical NSAIDs are considered safe. However, if used in excessive amounts this may lead to systemic complications such as MCD in this case.

SA-PO884

Crescentic Glomerulonephritis and Pancytopenia Secondary to Bartonella henselae Bioprosthetic Valve Endocarditis

Juan Salvatierra,[1] Rohini Rao,[2] Rasha Nasri,[1] Liliia Harris,[1] Ahmad Alayyat,[1] Keelan T. Tuel,[1] Rafael O. Duchesne,[1] Lee Connor.[1] *[1]Hamilton Medical Center, Dalton, GA; [2]Riverview Regional Medical Center, Gadsden, AL.*

Introduction: *Bartonella* spp may cause diverse clinical manifestations including endocarditis and cytopenias. The new 2023 Duke-ISCVID criteria include *Bartonella* serology as this infection is often culture-negative. Infection-related glomerulonephritis (IRGN) can be secondary to *Bartonella* endocarditis and usually has an immune-complex deposition pattern.

Case Description: A 53-year-old man with insulin-dependent type 2 diabetes presented to the emergency department with epistaxis, abdominal pain and vomiting for three days. He noted 7-pound weight loss and a leg rash for three weeks. He owns cats. He denied fever or joint swelling. He had undergone bioprosthetic valve replacement for mitral valve prolapse 5 years before. Examination revealed a petechial and purpuric rash on his lower extremities but no heart murmur or lymphadenopathy. Laboratory analyses showed pancytopenia, creatinine 11 mg/dL, 3+ hematuria and proteinuria, and negative ANA and ANCA. Kidney biopsy revealed crescentic glomerulonephritis with codominant IgM and C3 deposits. Hemodialysis was initiated for worsening renal function. Due to negative blood cultures and no vegetation on echocardiogram, he received rituximab and methylprednisolone. Expanded infectious workup returned positive for *B. henselae* titers IgM 1:20 and IgG >1:1024. He was started on doxycycline 100 mg twice daily indefinitely and rifampin 300 mg for 2 weeks and discharged home on a steroid taper.

Discussion: Crescent formation may be indicative of IRGN and should prompt extensive testing if no causative organism is initially identified. We present a rare case of *B. henselae* causing endocarditis, glomerulonephritis, and pancytopenia. Although there are no guidelines for the treatment of *B. henselae* bioprosthetic valve endocarditis, treatment with doxycycline and rifampin followed by permanent suppressive treatment with doxycycline may be reasonable.

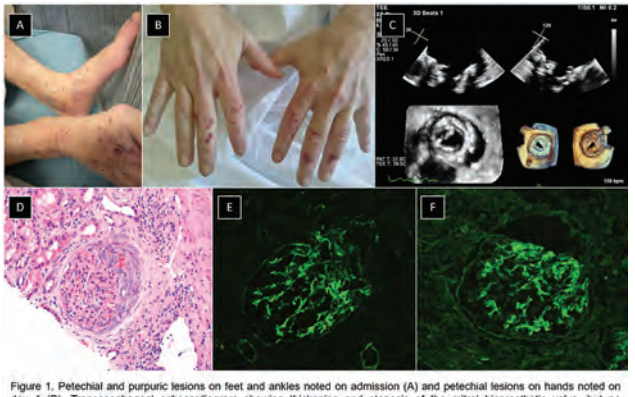


Figure 1. Petechial and purpuric lesions on feet and ankles noted on admission (A) and petechial lesions on hands noted on day 4 (B). Transesophageal echocardiogram showing thickening and stenosis of the mitral bioprosthetic valve, but no vegetation identified (C). Left kidney biopsy showing necrotizing, cellular or fibrocellular crescent formation on H&E stain; representative glomerulus shown (D). Immunofluorescence demonstrating co-dominant C3 (E) and IgM (F) deposition.

SA-PO885

A Unique Case of Primary Renal Sarcoidosis

Bhoomi Shah, Rupinder Kaur, Nabeel Siddiqui, Sreenidhi Kosuri, Benjamin M Easow. *Southeast Health, Dothan, AL.*

Introduction: Renal sarcoidosis is usually associated with other extra-renal sarcoidosis, it usually involves the lungs and renal involvement is only 0.7%. Initial lab work shows elevated serum creatinine, a bland urine sediment or sterile pyuria and high or high-normal calcium. Kidney biopsy is not diagnostic but is useful in making the diagnosis and ususally shows noncaseating granulomas in the interstitium. Treatment of choice is glucocorticoids and is started at 1mg/kg/day with maximum of 80 mg/day followed by a slow taper. Glucocorticoid doses required for renal sarcoidosis are higher than extra-renal sarcoidosis.

Case Description: 44-year-old male patient with past medical history significant for kidney stone, hypertension presents with complaints of high blood pressure and worsening kidney functions, on further investigation it was found that he had a left-sided renal biopsy in Miami about 4 years ago which showed nephrosclerosis with 50% sclerotic glommeruli, focal moderate interstitial fibrosis and mild arteriolosclerosis, chronic inflammatory infiltration with focal tissue calcinosis. At the time of initial diagnosis, his lab work revealed elevatded creatinine, calcium levels with proteinuria. No pulmonary lesions were found. He was started on 50 mg of prednisone daily and gradually taper down to 10 mg every other day and he has been on this dose for about 1.5 year now. He has not had any kidney stones since he started treatment for sarcoidosis and currently he requires supplements for low vitamin D levels.

Discussion: Though primary renal sarcoidosis is uncommon it is important to keep it as a differential in a person with no other extrarenal manifestation of sarcoidosis who presents with elevated creatinine and calcium levels. Patients with renal sarcoidosis are well managed with corticosteroids, though most patients require a higher dose of corticosteroids but some of them can be well managed on lower doses like our patient who was started only on 50 mg of prednisone and was gradually tapered down to 10 mg every other day. He continues to have CKD stage 3B even on this lower doses of corticosteroids and he has been stable there for the last few years. Also another noticeable point is that the patient has low vitamin D stores and requires supplementation currently after being treated for sarcoidosis for a 4 years.

SA-PO886

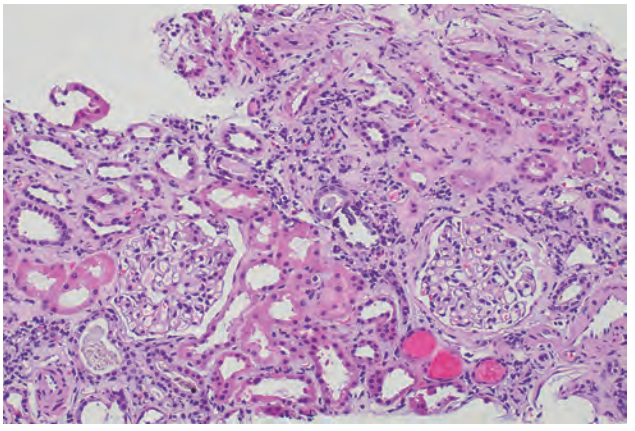
A Genuine Cat's Cradle: An Elusive Case of Bartonella Endocarditis-Associated Glomerulonephritis

Sameer Ahmed,[1] Patricia J. Allen,[2] Virgilius Cornea.[3] *[1]University of Kentucky College of Medicine, Lexington, KY; [2]Veterans Administration Hospital, Lexington, KY; [3]University of Kentucky, Lexington, KY.*

Introduction: We present a 73 yo male patient with Bartonella endocarditis–associated GN. The following describes his initial presentation, the ensuing diagnostic dilemma, and the eventual diagnosis which lead to proper resolution of the infection but unfortunate permanent loss of the patient's kidney function.

Case Description: 1 year after recieving a prosthetic aortic valve, a 73 yo male began developing weight loss, fatigue, and pancytopenia. The patient's pancytopenia and 80lb weight loss led to a malignancy workup that was non-revealing. After 6 months of worsening symptoms the patient was admitted with progressive kidney dysfunction and hematuria. Serological workup revealed low C3 & C4, +ANA, +dsDNA, +PR3, and an RF titer of >256. This led to an initial impression of lupus nephritis. However, a kidney biopsy revealed either infection-related GN or C3 nephritis. The patient's blood cultures were negative for typical organisms, but a TEE showed vegetation in the aortic valve. A search for atypical organisms revealed a Bartonella henselae IgG titer >1.256 and an IgM titer >1.800. As renal function deteriorated the patient was started on HD. The patient was placed on a combination of Rifampin and Doxycycline for 3 months. The patient's overall condition improved except for his kidney function, which progressed to ESKD.

Discussion: B. henselae is one of the most common causes of culture-negative IE. Kidney involvement is seen in up to half of patients with IE, and these patients can exhibit hematuria, infarction of the parenchyma, and glomerulonephritis. Delays in the rapid identification of the causative organism due to a negative blood culture can confuse the differential and delay treatment. B. henselae endocarditis is most associated with an exposure to cats and pre-existing valvular disease. This patient's affection for his feline companions was to a degree that it was noted in a PCP note months prior to admission, revealing the odd ways a patient's history can illuminate etiology.



SA-PO887

A Case of Scabies-Induced Glomerulonephritis

Aditya Ragunathan. *Boston Medical Center, Boston, MA.*

Introduction: Scabies is caused by the parasitic mite *Sarcoptes scabiei var. hominis*. Patients with this disease can present with diffuse skin itching and the excoriations can predispose them to bacterial cellulitis. There have been documented cases of post-streptococcal glomerulonephritis (PSGN), rheumatic fever, and systemic sepsis as a complication. Typically, the treatment of PSGN is supportive, and requires treating the underlying infection. Here, we present a case of scabies causing post-infectious glomerulonephritis (PIGN) requiring dialsyis that recovers with supportive therapy

Case Description: 63 y.o.male with a history of scabies and noted to be homeless who presented with fever, nausea, vomiting and an AKI. Initial exam was noted for bilateral crackles, peripheral edema, diffuse erythematous rash and distended abdomen. Infectious work-up included a chest X-ray without infiltrates, CT abdomen and pelvis with a thickened bladder wall and mild diffuse abdominal pelvic ascites, urinalysis with >100 white blood cells and red blood cells per high powered field. Blood and urine cultures were negative. He was treated for a presumed urinary tract infection with ceftriaxone 1 g daily for 7 days and permethrin baths. Baseline creatinine was 0.7-0.9 mg/dL, but was elevated to 4.2 mg/dL on admission. Serum creatinine increased to 7.37 mg/dL and patient became more volume overloaded. Ultimately, patient was started on dialysis. Serologic work-up of kidney injury was positive for ANA at 1:80, C3 <20 mg/dL, C4 of 12 mg/dL. Protein electrophoresis of serum and urine were negative for monoclonal bands. All other antibody tests performed were negative. A kidney biopsy was perfomed exhibiting the classic appearance of PIGN. Patient underwent dialysis, but was eventually weaned off after two weeks. At follow-up two months later, his serum creatinine had mostly recovered to 1.21 mg/dL

Discussion: Scabies is a common condition across the globe, affecting 300 million people worldwide, and can be associated with concomitant skin infections. PIGN is a complication of this condition and can be treated with supportive care. Patients on dialysis can have their kidney function improve even with severe acute injury, but do not require additional therapy. It is important to note the possibility of multiple infections in patients with scabies infections and keep the possibility of other complications of those infections in minds as a nephrologist.

SA-PO888

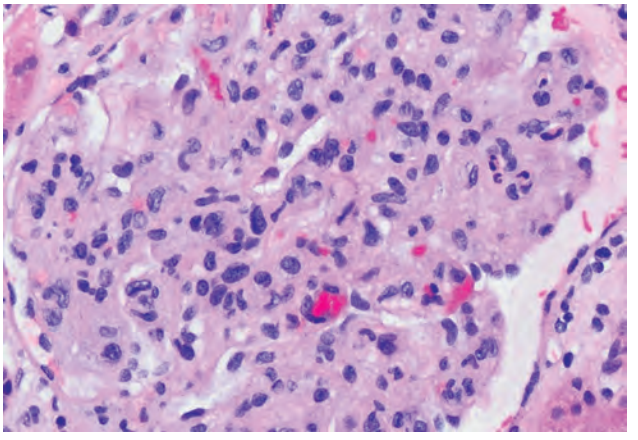
An Unsuspected Case of Idiopathic Multicentric Castleman Disease (iMCD) Presenting with Renal Microangiopathy

Jay V. Dominguez, Ramon A. Lopez. *University of South Florida, Tampa, FL.*

Introduction: iMCD remains an elusive diagnosis because of the non specific clinical manifestations that are common in other systemic diseases. Renal manifestations are rare, but can provide insight in the diagnosis of this elusive disease.

Case Description: A 20-year-old caucasian male presented with fevers, anemia, thrombocytopenia, hepatosplenomegaly, anasarca and unclear etiology of multiorgan failure that required vasopressors, ventilator support and dialysis. He was treated initially empirically for sepsis with antibiotics and then with steroids for autoimmune disease of unknown etiology. After improvement in his respiratory and hemodynamic status he had a renal biopsy with evidence of widespread glomerular endotheliosis with rare RBC fragments and no evidence of immunecomplexes by IF and EM. TTP was ruled out and no other common causes of microangiopathy was found. Bone marrow biopsy had no evidence of malignancy, but excisional axillary lymph node biopsy was consistent with mixed hyaline vascular and plasma cell Castleman disease, HHV8 negative.

Discussion: HHV8 negative iMCD is an uncommon lymphoproliferative disorder characterized by inflammatory systemic manifestations mediated by increased IL-6 and VEGF. Renal manifestations are rare and usually associated with severe disease manifestations as TAFRO syndrome. It can present as a microangiopathy with severe diffuse glomerular capillary endoteliosis and reduction in glomerular filtration rate to require dialysis. Fibrin thrombi or fibrinoid necrosis may not be present as seen in other causes of thrombotic microangiopathy. Some patients have a paradoxical downregulation in renal VEGF expression with similar histologic features as seen with VEGF antagonists. Delayed diagnosis and severity of the disease is associated with worst outcomes. iMCD is difficult to diagnose since the systemic manifestations are non specificic and should be suspected in renal microangiopathies of unclear etiololgy so early therapy can be prescribed.



SA-PO889

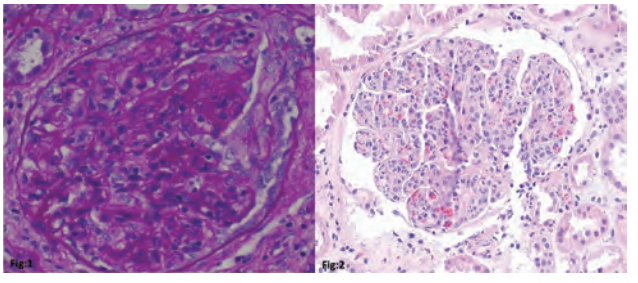
Donor-Derived Proliferative Glomerulonephritis

Kanza Haq,[1] Sami Alasfar,[2] Avi Z. Rosenberg,[1] Fizza F. Naqvi.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]Mayo Clinic Arizona, Phoenix, AZ.*

Introduction: Pre-existing glomerular disease in renal allografts is rarely reported in the literature. A majority of the cases are diagnosed retrospectively following transplant on reperfusion biopsy, or on discovery of the same lesion in both allografts from the donor.

Case Description: Two patients underwent deceased donor kidney transplant from a adult donor who had anoxic brain death in the setting of sepsis due to Streptococcus pneumoniae bacteremia. He was noted to have hematuria and proteinuria on pre-procurement urinalysis. 1st recepient was 50-year-old female with end-stage renal disease (ESRD) from diabetic nephropathy. She received Induction with thymoglobulin and methylprednisolone. Initial maintenance IS included tacrolimus, mycophenolate mofetil, and prednisone. The patient had delayed graft function (DGF). Urinalysis continued to demonstrate hematuria & proteinuria. Renal biopsy on POD 60 showed diffuse proliferative and exudative glomerulonephritis with focal cellular crescents (fig 1). Immunofluorescence was negative and no discrete electron dense immune deposits were seen. Follow-up biopsy 90 days post-transplant showed persistent exudative glomerulonephritis with severe tubulointerstitial scarring. Recipient serological work-up was negative. She remained on dialysis and has no evidence of renal recovery to date. Second recipient was a 52-year-old male with ESRD due to type 2 diabetes mellitus who also developed DGF. Post perfusion biopsy (Fig 2) showed similar diffuse proliferative and exudative glomerulonephritis. A follow-up biopsy 30 days post-transplant showed persistent glomerulonephritis with reduced neutrophilic inflammation and no signs of active immune-mediated rejection. EM was negative for deposits and IF remained negative. 2nd recipient was able to come off dialysis and the creatinine slowly improved to a nadir of 2.5 mg/dL.

Discussion: Preexisting diseases in renal allografts can follow variable courses which often are disease and recipient dependent. This case highlights the importance of pre-engraftment biopsies as current clinical parameters used for donor selection are inadequate to assess pre-existing disease etiology and severity.



SA-PO890

Scleroderma Renal Crisis Requiring Kidney Replacement Therapy

Michael Liben, Aashvi R. Dalal, Varun Madireddy. *NewYork-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY.*

Introduction: Systemic Sclerosis (SSc) is an autoimmune disease characterized by vascular dysfunction, and fibrosis of the skin and internal organs. Although cutaneous, pulmonary and renal manifestations are most common, every organ system is vulnerable. SSc often presents with acute flares that can be life threatening if not promptly recognized and managed.

Case Description: A 73-year-old woman with SSc presented to the hospital with exertional dyspnea and decreased oral intake. Given prior intolerance to mycophenolate and inability to obtain insurance authorization for Tocilizumab, she was only taking prednisone 20mg. Upon presentation, vital signs were within normal limits except a blood pressure of 180/83. Pertinent labs are shown in Table 1. Further results showed a white blood cell count of 12.3x10^3/uL, hemoglobin of 7.0g/dL, proBNP of 38,000pg/mL, phosphate of 9.0mg/dL, anion gap of 22mmol/L, and lactate of 0.6mmol/L. Urinalysis showed moderate blood, 11/HPF RBCs, 300mg/dL of protein, and a specific gravity of 1.014 without casts. Anti-topoisomerase I antibody titers were elevated. The next day, she developed hyperkalemia and hypervolemia requiring placement of a dialysis catheter and urgent hemodialysis (HD). She was started on captopril which was titrated to maximum tolerated dose.

Discussion: Despite guideline-directed medical therapy, our patient developed a life threatening Scleroderma Renal Crisis (SRC). Ultimately, renal failure necessitated renal replacement therapy and she was discharged with outpatient HD. Three months later, she requires regular HD, and is compliant with ACE inhibitor, prednisone 10mg, and Tocilizumab. SRC affects 2-15% of patients with SSc. It is not managed with high dose steroids, but with ACE inhibitor uptitration. One study showed that after 45.8 months, 54% of patients developed ESRD and 41% died. Another study found that renal recovery could occur after 3 to 18 months of HD and ACE inhibitor use. Although our patient's medication regimen was suboptimal, we highlight the importance of raising clinical suspicion and prompt identification of SRC in the outpatient setting.

	On Arrival	Next Day
Creatinine (mg/dL)	9.85	10.17
Blood Urea Nitrogen (mg/dL)	169	176
Potassium (mmol/L)	5.1	5.7
pH	7.25	7.24
Bicarbonate (mmol/L)	8	9

SA-PO891

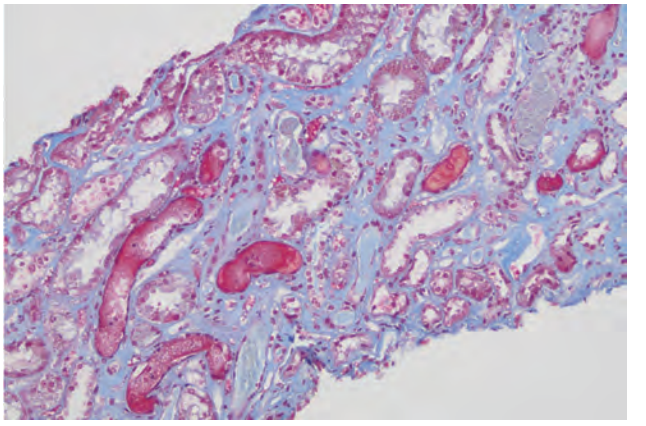
Beyond Blood: A Case Report on Anticoagulation-Related Nephropathy

Divmehar Kaur, Elizabeth A. Phipps. Mount Auburn Hospital. *Mount Auburn Hospital, Cambridge, MA.*

Introduction: Anticoagulation related nephropathy (ARN) is thought to be a frequently undiagnosed complication of anticoagulant therapy. Typically manisfesting as gross hematuria and AKI in individuals on therapeutic anticoagulation doses, its diagnosis remains rare. Its confirmation through renal biopsy is tough, as it may be missed or underreported due to the presence of concurrent pathologies.

Case Description: A 76-year-old male with pertinent history of hypertension, BPH was started on Apixaban for a new diagnosis of atrial fibrillation. Soon after, his creatinine levels nearly doubled from their baseline of 1-1.3 within a year which prompted nephrology involvement. Initial work up showed microscopic hematuria with acanthocytes, raising suspicion for underlying nephropathy. Shortly, this progressed to gross hematuria and was initially attributed to severe BPH causing bilateral hydronephrosis found on renal ultrasound. However, the persistence of hematuria and AKI despite relieving post renal obstruction warranted a kidney biopsy which showed ATN, IgA nephropathy and numerous RBC casts. This raised suspicion for ARN, which was confirmed with improvement in renal function after stopping Apixaban.

Discussion: ARN is known to cause glomerular hemorrhage and occlusion of renal tubules with RBC casts. This is reflected in typical renal biopsy findings showing near complete occlusion of the tubular lumen by numerous RBC casts lacking Uromodulin. Patients with underlying pathologies compromising the glomerular filtration barrier integrity such as IgA nephropathy (identified in our patient) are prone to develop ARN. Ongoing research is looking into thrombin driven activity of PAR-1(expressed in endothelial cells and podocytes) causing local inflammation at the filtration barrier, which along with free iron release (from trapped RBCs) may cause ARN. These insights emphasize the need for further research to better understand ARN and improve patient management and outcomes.



SA-PO892

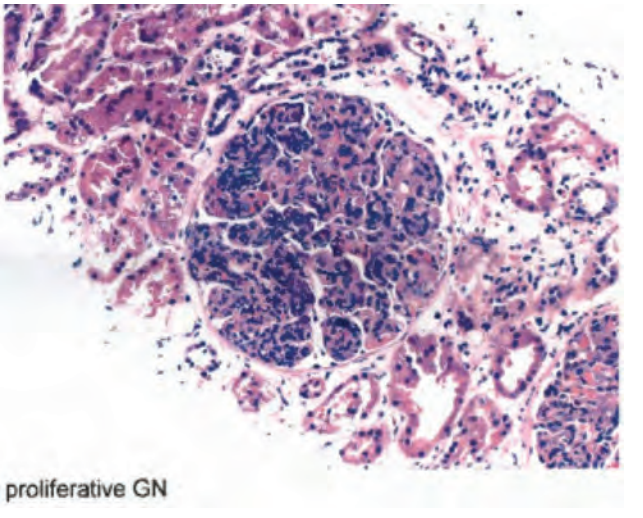
A Case of Type II Cryoglobulinemic Membranoproliferative Glomerulonephritis Associated with Marginal Zone B Cell Lymphoma

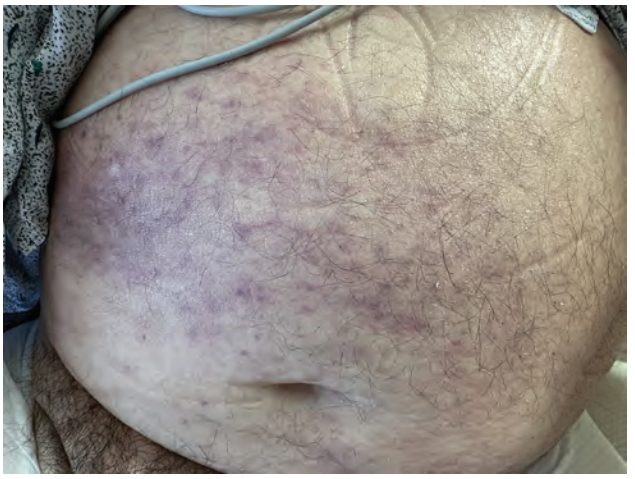
Pooja V. Patel. *Mercy Fitzgerald Hospital, Darby, PA.*

Introduction: Cryoglobulinemia is rare. Renal involvement is seen some cases associated with type II cryoglobulinemia. We present a case of type II Cryoglobulinemic MPGN associated with Marginal Zone B-cell Lymphoma and response to the treatment.

Case Description: A 74-year-old male with history of HTN, DM II, recent LE DVT presented to the hospital with worsening SOB, lower extremity edema, intermittent abdominal pain associated with nausea for 2 days. Upon arrival his BP was 168/79 mmHg. On exam, bibasilar crackles and +1 LE pitting edema. Labs revealed SCr 5.8 mg/dl (baseline 1.5 mg/dl). UA was positive for protein & RBC. Complements C3 and C4 were low. ANA was negative and RF level 1104. Cytology revealed positive cryoglobulin, Hep B core total and sIgG antibody positive with undetectable viral load. Hep C and HIV were negative. Immunofixation showed prominent IgM kappa. Kidney biopsy revealed B-cell lymphoma associated type II cryoglobulinemic glomerulonephritis. Immunofluorescence studies revealed glomerulus immune deposits of IgM and Kappa. Omental mass biopsy showed Marginal zone B-cell lymphoma. He was started on Rituximab and Methylprednisolone. After 3 months of treatment, his renal function improved to 1.5 mg/dl. He developed rash after first few doses of Rituximab.

Discussion: Noninfectious type II cryoglobulinemic GN associated with marginal zone lymphoma is uncommon. Management and prognosis is dependent on disease severity and treatment of underlying cancer.





Rash after Rituximab

SA-PO893

Intermittent Hematuria in a Patient with Crohn Disease: A Case Report

David M. Warner,[1] Prakash S. Gudsoorkar,[2] Jacob A. Nysather.[2]
[1]University of Cincinnati College of Medicine, Cincinnati, OH; [2]UC Health Medical Center, Cincinnati, OH.

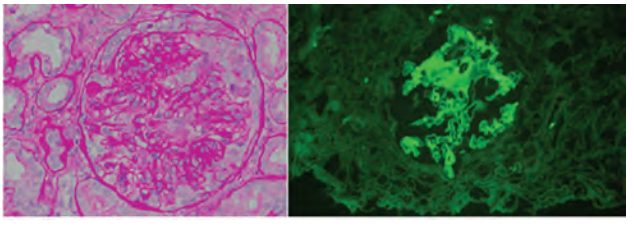
Introduction: There are a variety of secondary causes of IgA vasculitis (IgAV) and glomerulonephritis in adults. We report a rare case of IgAV with crescentic glomerulonephritis in a patient with Crohn Disease (CD) treated with infliximab.

Case Description: A 30-year-old male with biopsy-proven CD on infliximab developed intermittent gross hematuria, elevated serum creatinine (SCr), and a palpable purpuric lesion. Genitourinary cancer, hemorrhagic cystitis, and infectious etiologies were ruled out and his infliximab was held. He was referred to nephrology after 6 months of symptom onset. Glomerular serology work-up revealed polyclonal IgA and IgG on immunofixation with a protein gap of 5.1 g/dL; the rest was unremarkable. A kidney biopsy (Figure 1) showed focal fibrocellular crescents with diffuse mesangial expansion and hypercellularity. Immunofluorescence (IF) confirmed IgA glomerulonephritis M1, E1, S0, T1, C1. Pulse steroids with a slow taper and valsartan were started, with improvement in SCr and hematuria (Table 1).

Discussion: Secondary causes of IgA nephropathy (IgAN) include HIV, HBV, HCV, renal cell carcinoma, celiac disease, and lymphoma. Less common secondary causes include inflammatory bowel disease (IBD) and infliximab treatment. CD is thought to cause IgAN through increased IgA glycosylation, which correlates with disease severity, and elevated levels of the apoptosis inhibitor of macrophages (AIM), leading to co-localization of IgA, IgG, and IgM in the glomeruli. Infliximab has been shown to cause secondary IgAN; however, his intermittent hematuria and worsening SCr persisted despite discontinuing infliximab, suggesting CD progression linked to IgAV and nephritis. A recent Japanese study showed patients with IBD have a higher cumulative incidence of IgAN compared to non-IBD (p=0.0028), with CD having a strong association compared to ulcerative colitis.

Pre- and Post-Treatment Labs

Lab Value	Pre-Biopsy	Post-Treatment	Reference Value
Serum Cr	1.84 mg/dL	1.09 mg/dL	0.60-1.30 mg/dL
Serum Cystatin C	2.23 mg/dL	1.77 mg/dL	0.60-1.00 mg/dL
Urine Protein/Cr	3.16	3.05	<0.15
Urine RBC	>100/HPF	25/HPF	0-3/HPF



SA-PO894

Recurrent Dialysis-Dependent Rapidly Progressive Glomerulonephritis

Alexandra Stewart,[1] Gabriela Dande.[2] *[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]The University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Introduction: IgA nephropathy is the most common primary glomerulonephritis. Clinical presentations and kidney outcomes are variable, ranging from asymptomatic microscopic hematuria to nephrotic syndrome with rapidly progressive glomerulonephritis (less than 10 percent).

Case Description: A 69-year-old male with PMHx of microscopic hematuria with negative urologic evaluation and no prior nephrology evaluation, T2DM, HTN, small vessel disease with history of CVA was admitted to the hospital after a fall with rib fractures and a L hemopneumothorax complicated by MRSA empyema s/p thoracotomy. After 3 weeks, he developed nephrotic syndrome with anuric renal failure and volume overload. Physical exam was notable for elevated blood pressures and anasarca. Urine microscopy revealed 40-50 RBC/hpf with at least 30% dysmorphic. Serologic workup was negative for monoclonal protein with normal FLC ratio, vasculitis panel negative for ANCA, negative HIV/ RPR/ Hepatitis B and C, and normal complements. Had 6 g proteinuria on 24 hour urine collection. Prednisone was started at 1 mg/kg/day and renal biopsy was obtained with findings of IgA nephropathy (Oxford score: M1, E1, S0, T0, C1) and diabetic glomerulosclerosis with extensive foot process effacement. Initially had good response to steroids and diuretics, but developed worsening volume overload and was started on hemodialysis. Required a few sessions of HD with renal recovery and was discharged home on prednisone. 1 week after discharge, patient presented again to the hospital for symptomatic hypoglycemia and was found to have worsening renal failure. He was again started on dialysis for uremic symptoms and another renal biopsy was obtained. Biopsy findings were consistent with RPGN with IgA nephropathy (Oxford score: M1, E1, S0, T0, C2) and <10% IF/TA. Despite pulse steroids and 4 cycles of cyclophosphamide, he had no evidence of renal recovery and declared ESKD after 3 months of HD; CYC therapy was discontinued and he was started on a rapid steroid taper.

Discussion: Rapid progression to ESKD in uncommon in patients with IgAN and prognosis is generally poor. Treatment has not been evaluated in randomized trials; and observational trials have used a treatment approach similar to those in idopathic RPGN. We hope to demonstrate the challenges and the need for early intervention/ treatment approach in RPGN in IgAN.

SA-PO895

Unveiling IgA Nephropathy with Crescents: A Prognostic and Therapeutic Dilemma

Fnu Versha, Viral Patel, Kristi Pejo. *Baptist Hospitals of Southeast Texas, Beaumont, TX.*

Introduction: Limited data exists regarding the outcomes, clinical significance, and management strategies for IgA Nephropathy (IgAN) with crescents. The KDIGO 2021 guidelines assert that neither the presence nor the relative number of crescents should predict IgAN progression or dictate the use of immunosuppression. However, some uncontrolled studies suggest otherwise. We present a challenging clinical case that underscores the need for further discussion on this topic.

Case Description: A 62-year-old Caucasian male presented with worsening shortness of breath and bilateral lower extremity edema over two weeks. Initial evaluation revealed a serum creatinine level of 6.4 mg/dL and nephrotic-range proteinuria, indicating severe renal impairment. His baseline eGFR was previously normal. Insufficient follow-up data necessitated a renal biopsy, which identified IgAN with 47% crescents, moderate interstitial fibrosis and tubular atrophy (30%), and a MEST-C score of M1, E1, S0, T1, C2. Refractory hyperkalemia required emergent hemodialysis, continued as outpatient therapy due to lack of renal function recovery. The patient was treated with prednisone, cyclophosphamide, and lisinopril. After six months, although still on hemodialysis, there was partial renal function improvement as evidenced by decreased proteinuria. A follow-up biopsy to assess disease progression is pending.

Discussion: The KDIGO 2021 guidelines recommend that crescents on renal biopsy should not predict disease progression or influence immunosuppression choice in IgAN cases. Contrary evidence suggests the importance of crescents should not be overlooked. Our case indicates potential benefits of steroid-immunosuppression therapy, as demonstrated by partial renal function recovery within a short follow-up period. We propose that evaluating crescents alongside other MEST scores, clinical data, and novel biomarkers can facilitate a personalized therapeutic approach for patients with IgAN.

SA-PO896

IgM Dominant Proliferative Glomerulonephritis (GN), Undetectable Serum C4, and Chronic Lymphocytic Leukemia (CLL) with Persistently Negative Serological Testing for Type 1 Cryoglobulins

Raghunandan Konda, Dana V. Rizk, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Cryoglobulins are immunoglobulins (Ig) that precipitate at < 37°C and dissolve on rewarming. Type I cryoglobulinaemia consists of 1 isotype of monoclonal Ig, whereas type II and type III are classified as mixed cryoglobulinaemia [include IgG & IgM]. We describe a likely longstanding type 1 cryoglobulinemia with persistently negative serological testing in a patient with chronically suppressed/undetectable C4 levels, leukocytoclastic vasculitis, IgM kappa paraproteinemia, and IgM dominance in the kidney biopsy with CLL eventually being diagnosed much later.

Case Description: 87-year-old male with diabetes mellitus, chronic leukocytoclastic vasculitis, and persistently low C4 presented with AKI on CKD. Baseline Cr 1.3 mg/dL. Had serum cryoglobulins checked multiple times at different labs that were all negative. Exam sig. for purupuric lesions in LE. Cr 2.3 mg/dL, Sr albumin 3.7 g/dL, UA 1(+) protein, UPCR 340 mg/g, C3 102, C4 <1, RF 72, Sr Kappa (376) and Lambda (138) with FLC 2.7. SPEP/SIFE negative. UPEP/UIFE revealed M-spike with monoclonal IgM kappa LC. Sr cryoglobulin, HCV [Ab & Quant], CCP, and comprehensive GN screen (-). Blood cultures and testing for indolent infections including Bartonella/coxiella (-). ECHO [TTE/TEE] normal. Kidney bx revealed focal proliferative glomerulonephritis. IFTA 50%. IF: Diffuse global granular mesangial staining for IgM [3+], C3 [2+], kappa [2+], and lambda [3+]. Pronase IF negative. EM: No immune deposits. Congo red (-). Patient became sick with worsening abdominal lymphadenopathy that demonstrated IgM kappa CLL [BM Bx neg]. Serum testing for cryoglobulin again (-). Patient subsequently died.

Discussion: Testing for cryoglobulins is complicated by lack of reference range, standards, and stringency in maintaining testing temperature conditions. Despite the overall diagnosis favoring a likely an indolent Type 1 cryoglobulinemic process, our case is rare in that it was never detectable [blood, kidney, skin biopsy] and that the eventual diagnosis of CLL appeared 7 years after initial clinical manifestations. Better modalities to diagnose Type 1 cryoglobulins are therefore warranted.

SA-PO897

A Cascade of Viral Infection to Cardiomyopathy and Lupus Nephritis

William M. Parkinson, Jesse M. Wickham. *Brooke Army Medical Center, Fort Sam Houston, TX.*

Introduction: Systemic Lupus Erythematosus (SLE) affects over 1.5 million Americans, causing significant morbidity and mortality. Lupus onset and flares can be triggered by a range of insults including medications, infections, and environmental factors. Lupus nephritis (LN) is a common manifestation of SLE with symptoms often including edema, hypertension or proteinuria. Lupus myocarditis highlights SLE cardiac involvement with heart failure symptoms. The wide spectrum of organ involvement with Lupus further complicates diagnosis. Appropriately phrased, Hickam's dictum states, "A man can have as many diseases as he damn well pleases". We present a case that highlights Hickam's dictum with a tenuous presentation and multiorgan involvement.

Case Description: A 24-year-old active-duty female with a recent admission for pancreatitis presented to the emergency department with edema, fatigue, and found to be in cardiogenic shock. Previously, she was in excellent health, exercising, and fulfilling military requirements. Labs revealed proteinuria with dysmorphic red blood cells, elevated creatinine, ANA titer 1:320, and positive dsDNA. Kidney biopsy confirmed class III Lupus Nephritis. Cardiogenic shock was initially attributed to Lupus myocarditis. Cardiac MRI revealed an ejection fraction of 20%, dilated cardiomyopathy, severe valvular disease, but no myocarditis. Without myocarditis, Lupus is unlikely causative for cardiomyopathy. Further workup aimed at possible infectious etiologies revealing positive coxsackie antibody titers. The hospital course was further complicated by progressive biventricular failure requiring an intra-aortic balloon pump. Ultimately, the patient was stabilized and transferred for cardiac transplant evaluation. The presentation is thought to be a cascade of coxsackie virus infection driving both cardiomyopathy and new onset lupus with nephritis.

Discussion: The work up for complex patients requires a broad differential without bias. In this case, the initial concern was for Lupus induced myocarditis driving cardiogenic shock. However, further investigation revealed positive antibody titers for coxsackie virus and imaging not consistent with Lupus myocarditis. Broadening the differential to include infectious causes allowed the identification of prior coxsackie infection. This case highlights an interesting cascade from viral infection to cardiomyopathy and nephritis.

SA-PO898

Failure Is a Learning Experience: A Case of Lupus Vasculopathy without Clinical Response to Rituximab

Seshma Ramsawak, Leal C. Herlitz, John R. Sedor, Corey J. Cavanaugh. *Cleveland Clinic, Cleveland, OH.*

Introduction: Lupus vasculopathy (LV) is a rare entity and the pathogenesis is poorly understood. Renal involvement in systemic lupus erythematosus (SLE) is typically an immune complex glomerulonephritis. LV however is a non-inflammatory form of vascular injury. The prognosis is poor and currently there is no standard recommended treatment available. We hereby describe a case of LV that progressed to ESKD despite treatment with high dose corticosteroids, plasmapheresis and rituximab.

Case Description: A 29 year old female with a history of SLE, hypertension and multiple ischemic strokes presented with a 3-week history of malaise and weight loss. The onset of chest pain and shortness of breath prompted medical evaluation with concern for lupus myopericarditis. On presentation serum creatinine was 1.2 mg/dL (baseline 0.7) and UPCR was 4.8 (previously 0.1-0.15). These findings together with hypocomplementemia and elevated dsDNA raised suspicion for lupus nephritis. A kidney biopsy performed revealed findings of lupus nephritis class II. Notably, half of the glomeruli sampled had ischemic changes, likely a result of prominent luminal narrowing of small arteries and arterioles due to immune complexes admixed with hyalin and fibrin. The diagnosis was consistent with LV. The non-ischemic glomeruli on this biopsy were preserved without features of glomerulonephritis. Serological testing for scleroderma and antiphospholipid syndrome were negative. 5 sessions of plasmapheresis were performed followed by rituximab infusions in conjunction with high dose steroids. Despite this, renal function progressively worsened over two months requiring initiation of dialysis without recovery.

Discussion: There is a paucity of data on LV and the existing literature is limited to isolated case reports. Most of these cases have an associated severe lupus nephritis, and use of cyclophosphamide was often reported. Immunosuppressive medications however are "glomerulocentric" and are stratified based largely on the ISN/RPS lupus nephritis classification. There is no standardized treatment of LV alone, and future studies are needed to determine optimal treatment for LV specifically. This report uncovers another rare case of lupus vasculopathy, and highlights the need for a clinically effective treatment.

SA-PO899

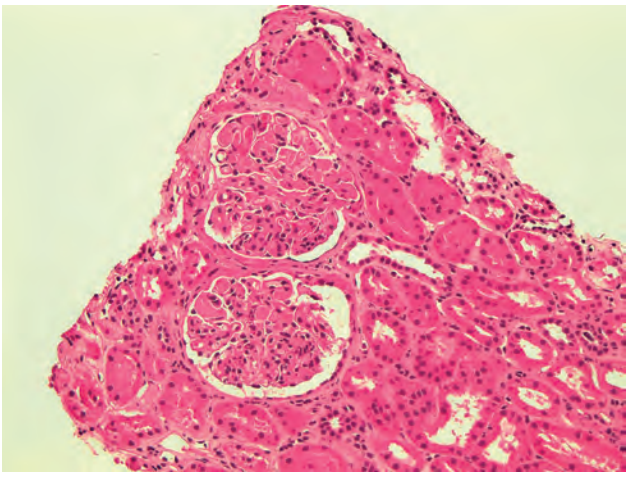
A Rare Case of Lupus Nephritis with Hemophagocytic Lymphohistiocytosis

Sam Beavin, Sameer Ahmed, Fritz E. Lower. *University of Kentucky College of Medicine, Lexington, KY.*

Introduction: In this case, we present a 19 yo female with SLE and lupus nephritis complicated by HLH. The following describes her initial presentation and diagnosis, followed by the treatment of this uncommon complication of SLE.

Case Description: A 19 yo female with a family history of autoimmune disease reported fatigue, joint pain, and a rash on her feet 6 months prior to admission. 3 days prior to admission, she experienced nausea, vomiting, and abdominal distension. On admission, the patient was found to have pancytopenia, severe AKI with proteinuria, and imaging suggestive of cirrhosis with ascites and splenomegaly. Her ANA and anti-DS DNA were positive. Subsequent workup, including a kidney biopsy and bone marrow biopsy, led to a diagnosis of SLE complicated by LN class IV and HLH/MAS. The patient was treated with dexamethasone per the HLH-94 protocol, in addition to HCQ and MMF for SLE and LN. Her inflammatory markers normalized, and AKI resolved. At 6-month follow-up, she had tapered off steroids and continued on HCQ and MMF.

Discussion: Hepatic involvement is rare in SLE and suggests a secondary complication such as aPL-related TMA, autoimmune hepatitis, secondary Still disease, or, as in this patient, HLH. sHLH is a rare disorder that is life-threatening if not promptly treated. It is a diagnostic challenge for clinicians given the overlap in presentation between autoimmune disease and infection. sHLH is an uncommon but severe complication of SLE, where it is called macrophage activation syndrome. It is described in ~8% of new SLE cases, mostly in children. Differentiating features for MAS are high fever, elevated AST, LDH, ferritin, TG, and neutropenia. SLE patients presenting with MAS are more likely to have renal disease. Treatment options for sHLH include disease-specific therapy or chemotherapy. In this patient, disease remission was achieved by combining SLE induction treatment with a higher-than-typical steroid regimen guided by HLH treatment protocols.



SA-PO900

Late-Onset Systemic Lupus Erythematous in a Man with Antiphospholipid Antibody Syndrome and Lupus Nephritis

Yinelka G. Silverio De Castro, Jerin Karingattil, Eliot Sachsenmeier, James Drakakis. *NYU Langone Hospital - Long Island, Mineola, NY.*

Introduction: Late onset systemic lupus erythematosis (SLE) is a subgroup of SLE, with age 50 considered minimum age of onset. As with early onset disease, the incidence here is also higher in females. There is little available data characterizing males with SLE and biopsy proven lupus nephritis. That which is available notes the late onset SLE patients have less renal involvement and historically receive less aggressive treatment. We present a case of a 72 year old male with newly diagnosed SLE with positive antiphospholipid antibodies and proteinuria/hematuria. Renal biopsy ultimately revealed a class III lupus nephritis.

Case Description: 72 year old male with a history of hypertension, presented to ER with pleuritic chest pain. He was found to have left lower extremity DVT. Hypercoagulable testing showed high titer anti cardiolipin & anti beta2 glycoprotein IgG. Additionally, ANA 1:1280 (nuclear, homogeneous), double stranded (ds) DNA antibody 79 IU/mL, C3 89 mg/dL (low), C4 11 mg/dL. Urinanalysis with 3+ protein, large blood and >100 RBCs. Urine protein to creatinine ratio (UPCR) 2112 mg/g. Kidney biopsy revealed focal endocapillary proliferative & crescentic immune complex mediated glomerulonephritis, and endothelial cells containing tubuloreticular inclusions. Rare glomerulus with small active crescent. This was felt to represent focal proliferative lupus nephritis, class III. 3 days of pulse steroids given, transitioning to Prednisone 60 mg daily (tapering). Cellcept added and escalated to 3 g/day. After 3 months of therapy, PCR down to 260 mg/g with negative ANA, ds DNA antibody 4 IU/mL and normal C3. Serum creatinine remained stable at 1.1 - 1.3 mg/dL.

Discussion: This case illustrates the importance of constructing a broad differential diagnosis in older patients presenting with non specific symptoms. Early recognition and diagnosis proved critical to our patient's management. Antiphospholipid antibodies were found on hypercoagulable workup, which in turn prompted consideration of SLE. The active UA was the key to determining the presence of renal involvement, despite the literature noting decreased incidence of nepritis in this population. More information is needed to better characterize this late onset subtype, especially in males. Clincians need maintain a high index of suspicion regardless of age and gender.

SA-PO901

Myeloperoxidase (MPO)-ANCA: From Confounding to Confirming a Case of Lupus Nephritis (LN) in a Silent Patient

Jackson Rajendran,[1,2] Katherine Toma,[1] Sheilabi Seeburun.[1,2] *[1]RWJBarnabas Health, Toms River, NJ; [2]Rutgers The State University of New Jersey, New Brunswick, NJ.*

Introduction: ANCA is positive in up to 23% of LN cases, of which 82% represent MPO-ANCA. Despite this, SLE-ANCA overlap syndrome is very rare (2%). We present a case of an 18-year-old female with supposed Acute Renal Failure (ARF) whose high MPO-ANCA titer confounded her treatment course.

Case Description: An 18-year-old African American female with developmental delay presented with malaise, periorbital edema, oliguria, nausea, and vomiting for one week. No joint pain/swelling, oral ulceration, rash, or alopecia were noted by family. Past medical and surgical histories were otherwise unremarkable. There was no family history of kidney or rheumatologic disease. Upon examination, the patient weighed 51 kg and was hypertensive (205/145 mmHg) and tachycardic (133 beats per minute). She had generalized facial edema without peripheral edema. No cutaneous lesions were found. Labs revealed ARF (Blood Urea Nitrogen 57 mg/dL, creatinine 5.08 mg/dL), anemia (hemoglobin 8.6 g/dL), nephrotic range proteinuria (Protein-creatinine-ratio 4.818) and metabolic acidosis (bicarbonate 18 mEq/L, anion gap 10). She was also found to have a large pericardial effusion with tamponade, which was evacuated. Pathology eventually yielded granulation tissue. Empiric high-dose methylprednisolone and hemodialysis were initiated. Kidney biopsy revealed Class IV and Class V Lupus Nephritis with minimal activity and severe chronicity. Further serology evaluation is summarized in the table. The end-stage nature of the pathology did not warrant aggressive immunosuppression. She was placed on a steroid taper and was given one dose of Rituximab (1 gram) due to the very high MPO-ANCA titer and unclear systemic involvement. Further rheumatologic evaluation confirmed no systemic ANCA-mediated disease. A second dose of Rituximab was therefore not given. The patient remains dialysis-dependent and will eventually undergo renal transplant evaluation.

Discussion: Our patient with limited ability to provide a history presented with severe ARF, pericardial tamponade, and anasarca with nephrotic range proteinuria. Clinical suspicion for LN was confirmed with renal biopsy. High MPO-ANCA titer caused concern for a second autoimmune process but ultimately confirmed the chronicity of her silent chronic renal failure.

Positive serology: MPO-ANCA (521 units), ANA, Smith antibody, Anti-RNP
Negative serology: Anti-dsDNA, Lupus anticoagulant, Anti-cardiolipin, Anti-Beta 2 Glycoprotein, Anti-SSA/ SSB, Anti- PLA2R, C ANCA, Anti-GBM, Antimitochondrial antibodies

SA-PO902

Diffuse Lupus Nephritis Secondary to Ixekizumab Therapy: A Case Report and Literature Review

Nusiba H. Elamin, Essa Abuhelaiqa, Awais Nauman. *Hamad Medical Corporation, Doha, Qatar.*

Introduction: Drug-induced lupus (DIL) is a recognized category of illnesses associated with lupus. There are no standards for diagnosis, DIL differs from the conventional form of SLE in several ways, one of which being the pattern of organ involvement. DIL is often accompanied by constitutional and cutaneous symptoms. Renal system involvement is rare. Management usually is by stopping the offending agent. Up to date several drugs have been identified as being linked in DIL, the introduction of novel medications and the relative decline in the usage of more traditional ones have altered the epidemiology of DIL

Case Description: 69-year-old woman who developed diffuse lupus nephritis after receiving ixekizumab for psoriasis. She exhibited symptoms of lower limb edema and uncontrolled hypertension, and was found to have impaired renal function, positive ANA, anti-double strand DNA antibody, anti-ribonucleoprotein antibodies, significant proteinuria, hypoalbuminemia, and low serum complement levels. Ixekizumab was discontinued, and she was treated with prednisolone and mycophenolic acid, resulting in a favorable clinical and laboratory response as shown in figure 1.

Discussion: There is a growing number of reported cases of lupus erythematosus induced by IL-17 inhibition. Ixekizumab, an IL-17 inhibitor, are approved for the treatment of active psoriatic arthritis and Ankylosing spondylitis. Lupus nephritis after IL-17 inhibition is not well known or documented as a possible adverse effect, it has been reported before only once after secukinumab therapy (another anti-IL17). To our knowledge this is the the first reported case of drug induced lupus nephritis due to Ixekuzumab. The relationship between IL-17 inhibitors and lupus nephritis not yet well established and Further research are needed.

Figure 1. Proteinuria

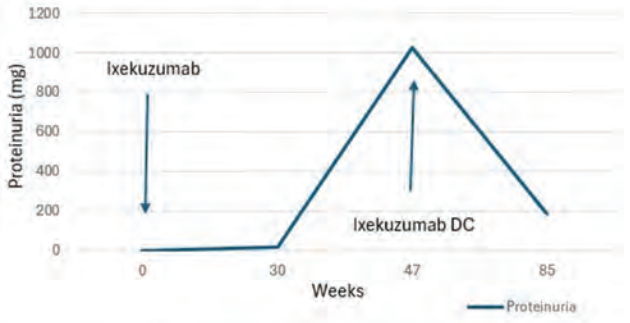
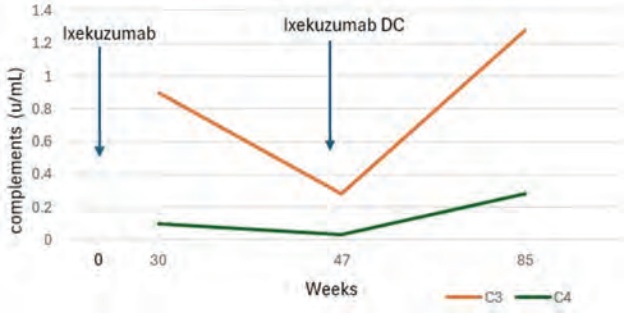


Figure 2. C3 and C4 levels



SA-PO903

Postpartum Diagnosis of Lupus Nephritis in a Patient with Preeclampsia Presenting with AKI and Decompensated Heart Failure

Tanya Geranpayeh, Jeannette Crew, Elissa Foster, Gates Colbert.
Baylor Scott & White Health, Dallas, TX.

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease that frequently affects women of the childbearing age. Myocarditis complications in SLE are rare and affect less than 10% of patients. Peripartum cardiomyopathy is an idiopathic condition of heart failure. Both diseases can present as acute decompensated heart failure in the postpartum state. We present a unique case of a young woman who presented 6 weeks postpartum with heart failure symptoms and new onset of lupus nephritis.

Case Description: A 19-year-old G1P1 woman presented at 6 weeks postpartum with shortness of breath. She underwent induction for delivery at 37-weeks due to significant hypertension and concerns for pre-eclampsia. Physical examination revealed lung crackles, malar rash, and lower extremity edema. A transthoracic echocardiogram showed an ejection fraction of 36-40%. Laboratory work revealed acute kidney injury with serum creatinine 2.9 (normal baseline) and urine protein to creatinine ratio 3 g/g. Urine microscopy revealed dysmorphic red blood cells with acanthocytes. She was initiated on IV furosemide, metoprolol, spironolactone, hydralazine and isosorbide dinitrate for heart failure treatment. Further workup showed positive ANA (1/160), anti-dsDNA (1/640) and anti-histone (7.5 U) antibodies. C3 (28 mg/dL) and C4 (3 mg/dL) levels were low. Hydralazine was discontinued due to the concern for drug-induced lupus. Kidney biopsy resulted as Class IV lupus nephritis. The patient was initiated on systemic steroids and mycophenolate mofetil, then discharged with plans for outpatient follow up.

Discussion: Differentiating lupus nephritis versus pre-eclampsia in proteinuric pregnant patients without prior history of SLE can be difficult. This patient was recently diagnosed with pre-eclampsia, now presented with acute decompensated heart failure postpartum. The elevated ANA titer, low complement levels and acute kidney injury made SLE a possible differential diagnosis. Definitive diagnosis was solidified by kidney biopsy showing class IV lupus nephritis. This case highlights the challenging diagnosis of SLE myocarditis in patients presenting with peripartum acute heart failure without history of SLE. Clinicians are required to have a high index of suspicion for SLE in these patients to achieve diagnosis and treatment in a timely manner.

SA-PO904

Don't Be Fooled by the Full House

Mingyue He. *Temple University Hospital, Philadelphia, PA.*

Introduction: Lupus nephritis (LN) is a common and serious systemic lupus erythematosus (SLE) complication. Some patients exhibit histological features of LN, characterized by the "full house" pattern on immunofluorescence (IF), despite the absence of other criteria for SLE. This rare entity is referred to as non-lupus full-house nephropathy (FHN). Herein, we present a rare case of non-lupus FHN in a kidney transplant recipient.

Case Description: A 37-year-old female with a history of type 1 diabetes and ESRD s/p simultaneous pancreas-kidney transplant in 2004, and recurrent ascites presented with abdominal pain and was found to have cardiac tamponade with pericardial fluid negative for infection and malignancy. Her creatinine levels had increased for months, from 1.9 to 3 mg/dl with 2.2 g proteinuria and bland urine sediment. She had a functioning pancreas. The initial ANA test was 1:160 positive but repeated ANA and dsDNA were negative. Renal graft biopsy revealed membranoproliferative glomerulonephritis (MPGN) with a "full-house" linear pattern on IF and 60% IFTA. Concerned about de novo LN, she was treated with pulse steroid. However, there was no clinical response, and she returned to dialysis. Electron microscopy (EM) results came back later, which did not reveal any immune-type deposits. After a multidisciplinary discussion with pathologists and rheumatologists, the positive IF was interpreted as a nonspecific accumulation of serum protein constituents due to chronic endothelial and membranoproliferative injury associated with transplant glomerulopathy rather than true immune complex (IC) deposition disease.

Discussion: This case presents a diagnostic challenge in distinguishing between de novo LN and non-lupus FHN secondary to transplant glomerulopathy. The combination of pericardial effusion, ascites, an initial ANA of 1:160, and a renal biopsy with full-house features could classify her as having SLE. However, this diagnosis relied heavily on the kidney biopsy interpretation. The development of lupus in a chronically immunosuppressed patient is unusual. Considering the absence of IC and the alternative diagnosis of transplant glomerulopathy, her presentation is not compatible with SLE and can be explained by other factors such as volume overload. This case underscores the importance of EM in diagnosing LN, highlighting that a full-house pattern does not necessarily indicate LN or immune complex deposition disease.

SA-PO905

Nonlupus Full-House Nephropathy Presenting with Rapidly Progressive Glomerulonephritis, Hypertensive Emergency, and Heart Failure

Aakash Padodara, Shawn Alonso, Gabriel Contreras, Yelena Drexler.
University of Miami Health System, Miami, FL.

Introduction: Nonlupus full house nephropathy (NLFHN) is a rare and heterogenous clinical entity that is distinct from lupus nephritis. Here, we describe a case of NLFHN presenting with rapidly progressive glomerulonephritis and hypertensive emergency with new onset systolic heart failure.

Case Description: A 43-year-old male with a past medical history only of COVID-19 infection presented with several weeks of headaches, blurry vision, and leg swelling. He was found to have severely elevated blood pressure (224/138 mmHg), severe hypertensive retinopathy, and 3+ pitting lower extremity edema. Laboratories revealed serum creatinine 3.8 mg/dL, serum albumin 2.8 g/dL, hematuria (682 RBC/hpf), and proteinuria (UACR 7723 mg/g). Echocardiogram revealed moderately reduced left ventricular systolic function with ejection fraction 35-40%. Serologies were notable for low total complement and low-normal C3 complement levels, elevated rheumatoid factor, and negative ANA and dsDNA antibodies. Kidney biopsy revealed a light microscopy pattern of membranoproliferative glomerulonephritis with cellular crescents and a full house pattern on direct immunofluorescence with 3+ staining for IgG, 3+ IgM, 2+ IgA, 3+ C3, and 1+ C1q. Workup for secondary causes was negative including testing for HIV, syphilis, hepatitis B/C, anti-neutrophil cytoplasmic antibody, and cryoglobulin.

Discussion: NLFHN is an immune complex glomerulonephritis that can present with different light microscopy patterns accompanied by a typical full-house immunofluorescence pattern, without clinical or laboratory features of lupus. It can be categorized as secondary or idiopathic. Secondary causes include infections, autoimmune diseases, lymphoid neoplasms, or drugs. NLFHN typically has male predominance, higher proteinuria, and less complement consumption than lupus nephritis. Our case highlights that NLFHN can present with clinically challenging conditions including rapidly progressive glomerulonephritis, hypertensive emergency, and heart failure. While a preceding viral illness may have been causative, the patient is being followed for the potential development of an overt autoimmune condition with ANA and dsDNA every 6 months. He is doing well with a partial renal response and recovered left ventricular systolic dysfunction on mycophenolate and tapered prednisone.

SA-PO906

Hepatitis B-Related Cryoglobulinemia: A Case Report of Renal-Pulmonary Syndrome

Mahdi Beydoun, Emily A. Christie. *University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada.*

Introduction: The World Health Organization estimates that approximately 296 million individuals were chronically infected with hepatitis B in 2019, with an annual incidence of 1.5 million new infections. Hepatitis B infection can lead to severe hepatic complications, including cirrhosis, liver failure and hepatocellular carcinoma. Rarely, patients with hepatitis B infection will develop extrahepatic manifestations such as mixed cryoglobulinemia.

Case Description: 47-year-old man with untreated chronic hepatitis B (HBeAg negative) presented with hypoxia, pleuritic chest pain, hemoptysis, and pitting edema. He was noted to have a new normocytic anemia and a stage III AKI with proteinuria and hematuria on urine sediment. A CT pulmonary angiogram showed bilateral pleural effusion, pulmonary nodules and no evidence of embolism. Patient subsequently decompensated requiring intubation due to diffuse alveolar hemorrhage confirmed on bronchoscopy. His kidney biopsy was consistent with cryoglobulinemic glomerulonephritis and serum cryoglobulin testing was positive for mixed cryoglobulinemia. Patient was treated with intravenous pulse corticosteroids and started on entecavir. He responded well to the treatment and was successfully extubated. Following his course of intravenous corticosteroids, he was transitioned to high-dose oral prednisone once daily. His renal function returned to baseline and patient was discharged from hospital with outpatient follow-up.

Discussion: This highlighted a case of HBV-related cryoglobulinemia with renopulmonary syndrome. Cryoglobulinemia is rarely seen in patients with hepatitis B infection and does not commonly lead to diffuse alveolar hemorrhage. Current guidelines recommend treatment for hepatitis B infection if there is evidence of liver injury either through elevated ALT or liver biopsy. The guidelines favor treating chronic hepatitis B infection with evidence of extrahepatic manifestations, however there are no recommendations on how to effectively screen patients. Diffuse alveolar hemorrhage is a life-threatening complication, and physicians should consider a lower threshold to treat patients with chronic hepatitis B infection. Given the rarity of HBV-related cryoglobulinemia with renopulmonary syndrome, there are no definitive guidelines on management; existing literature suggest treating with antiviral and corticosteroids, which was effective in this case.

SA-PO907

Long-Read Single-Cell RNA Sequencing Reveals the Alternative Splicing Landscape across Mouse Kidney Epithelial Cells

Megan L. Noonan, Haojia Wu, Benjamin D. Humphreys.
Washington University in St Louis School of Medicine, St Louis, MO.

Background: There is surprisingly little known regarding alternative splicing (AS) in kidney health and disease, and to date no study has reported cell-specific AS patterns using long-read single-cell RNA-seq (scRNA-seq) in the kidney. Long-read sequencing more accurately identifies full-length gene isoforms to better determine AS that differentiates kidney cell types and can identify cell type-specific transcripts to refine kidney cell identities.

Methods: A 15-week-old C57BL/6J male mouse kidney was dissociated into single cells and barcoded using the 10X Genomics Single Cell 3' GEM kit (v3.1). The library was prepared using Oxford Nanopore Technologies (ONT) PCR-cDNA SQK-PCS111 kit and sequenced on a PromethION flow cell. QC and gene/transcript quantification was performed using ONT's EPI2ME Labs wf-single-cell workflow. Seurat was used for gene- and transcript-level PCA and clustering. DTUrtle was used to determine differential transcript usage (DTU) between cell types.

Results: Gene-level clustering identified known kidney cell types and was used to determine differentially expressed transcripts (DET) and DTU. Long-read scRNA-seq detected differential transcript usage (DTU) in all kidney cell types, with most DTU events observed between epithelial cells such as the proximal tubule (PT), thick ascending limb (TAL), and distal convoluted tubule (DCT). We compared all PT cells to all other cell types in the dataset and found isoform Miox-201 (myo-inositol oxygenase) as the most significant DET and expression was highly specific to PT cells compared to all other cell types, identifying a novel PT cell-specific isoform. DTU analysis between PT-S1 and TAL identified 37 genes and 76 transcripts with significant DTU. DTU genes between these two cell types were in pathways related to Na/K transport, cellular communication, and cell adhesion. The isoform Cldn10-201 (claudin-10) had a 76% increase in usage in PT-S1 versus TAL. This isoform switch results in preferring anions over cations, which corresponds to its function along the nephron.

Conclusions: We show for the first time the single-cell full-length isoform landscape of the murine kidney. Cell type-dependent DTU adds an additional layer of gene regulation, therefore, understanding the mechanisms of AS in the kidney could lead to new targets for future therapeutics to treat kidney diseases.

Funding: NIDDK Support

SA-PO908

Adjudication of Kidney Biopsy Histopathology to Establish Consensus Diagnosis of Tubulointerstitial Nephritis

Sagar S. Sadarangani,[1] Melissa M. Shaw,[1] Gilbert W. Moeckel,[1] Deepika Kumar,[1] Michael B. Kuperman,[2] Avi Z. Rosenberg,[3] Randy L. Luciano,[1] Steven Menez,[3] Mark A. Perazella,[1] Francis P. Wilson,[1] Amrita Makhijani,[1] Kyra A. Shelton,[1] Chirag R. Parikh,[3] Dennis G. Moledina.[1] *[1]Yale University School of Medicine, New Haven, CT; [2]Cleveland Clinic, Cleveland, OH; [3]Johns Hopkins University, Baltimore, MD.*

Background: The absence of consensus histological criteria for tubulointerstitial nephritis (TIN) diagnosis leads to high variability and low inter-rater agreement in its reporting. Here, we establish consensus TIN diagnosis through an adjudicated process and test the association of interstitial histological features recorded on a standardized ordinal scale with TIN.

Methods: We selected biopsies from 147 participants enrolled in Yale's kidney biobank including all biopsies with clinically reported TIN (n=106) and a subset of controls (n=41). The adjudication process included two renal pathologists independently reviewing whole slide scans of kidney biopsies, reporting their diagnosis, and rating histological features using a standardized scale. Disagreements were resolved by joint slide review or, if consensus could not be achieved, by a third pathologist. We report inter-rater agreement and test association of reported histologic features with TIN diagnosis.

Results: After independent review, the pathologists reached agreement on 111 cases (agreement, 75%; κ, 0.50; P<0.001), which increased after joint slide review to 144 cases (agreement, 98%; κ, 0.96; P<0.001). Interstitial features associated with consensus TIN diagnosis included severity of infiltrate in preserved areas and tubulitis (**Table**). Among the 106 biopsies that were clinically reported as TIN, consensus diagnosis was TIN in 91 (86%) and 20 were reclassified as non-AIN. Among the 41 without TIN reported clinically, 38 (93%) were adjudicated as non-AIN, where 3 (7%) were reclassified as TIN.

Conclusions: We noted moderate agreement on TIN diagnosis that improved after joint review of slides, which can be used as a gold-standard for research into diagnostic biomarkers and dysregulated pathways in TIN. Our analysis also provides preliminary data on histopathological features associated with TIN that could support future work on establishing consensus criteria for TIN diagnosis.

Funding: NIDDK Support

Table. Association of interstitial features with consensus interstitial nephritis

Feature	Severity	Odds Ratio (95% CI)	
		Univariable	Multivariable selected by LASSO
infiltrate, preserved areas	<10 %	Ref.	Not selected
	10-25%	8.2 (4.2, 16.0)	3.8 (1.8, 8.0)
	>25%	19.5 (8.2, 46.4)	6.1 (2.4, 15.7)
Tubulitis	Present	10.3 (1.2, 87.0)	3.4 (1.7, 6.6)
Infiltrate, fibrosed	<10 %	Ref.	Not selected
	10-25%	6.5 (3.1, 13.8)	
	>25%	8.5 (3.8, 19.3)	
Interstitial Edema	Present	1.0 (0.2, 4.8)	
Eosinophils	None	Ref.	
	1-5/HPF	2.9 (1.2, 7.4)	
	>5/HPF	7.1 (2.1, 24.5)	
Mesangial expansion	Present	2.2 (1.5, 3.3)	

SA-PO909

Association between eGFRcystatin C-to-eGFRcreatinine Ratio and the Nonkidney Factors Muscle Mass, Muscle Strength, and Sarcopenia

Rona Dawar, Agne Laucyte-Cibulskiene, Anders Christensson, Linnea Malmgren, Kristina Åkesson. *Lunds Universitet, Malmö, Sweden.*

Background: Selective glomerular hypofiltration syndromes (SGHS), are linked to cardiovascular disease and mortality, and defined by a low eGFRcysC/eGFRcreat ratio. To correctly define SGHS, non-renal factors potentially affecting creatinine and cystatin C should be accounted for. The aim of our study was to investigate the association between muscle mass, muscle strength, sarcopeni and eGFRcysC/eGFRcreat ratio.

Methods: This study was based on 1044 females from the Osteoporosis Prospective Risk Assessment (OPRA) cohort, all aged 75 at inclusion with additional investigations after 5 (n=683) and 10 (n=355) years. Estimated glomerular filtration rate (eGFR) was based on creatinine and cystatin C using the CKD-EPI equation, and $eGFR_{cysC}/eGFR_{creat}$ ratio was determined. Muscle strength was measured as maximal knee extension and muscle mass measured by dual-energy x-ray absorptiometry (DXA). Sarcopenia was defined according to European Working Group on Sarcopenia in Older People (EWGSOP)2, defined as low muscle strength *plus* low muscle mass. Linear regression models examined the association between the dependent variable, low eGFR ratio, and the independent variables, muscle mass, muscle strength and sarcopenia. Analyses were adjusted for inflammation (CRP), smoking and glucocorticoid treatment. Results are presented as regression coefficients with 95 % confidence intervals (CI), p-value and partial explained variation (R^2).

Results: Sarcopenia was present in 32, 33 and 36 individuals at ages 75, 80 and 85 years respectively. At age 75, sarcopenia was significantly associated with the eGFR ratio (β_{adj}=-0,09, 95% CI = -0,2 to -0,02, p=0,012, R^2=4,9%) (Table). Similar results were observed at age 85, but not at 80. Muscle mass was associated with the eGFR ratio at

age 75 (β_{adj}=0,03, 95% CI = 0,01 to 0,05, p=0,008, R^2= 4,7%) and at age 80, but not at 85. Muscle strength showed a significant association across all ages, with the explained variation decreasing with age (9%, 7,8%, 4,1%).

Conclusions: While the eGFRcysC/eGFRcreat ratio was associated with non-renal factors such as muscle mass, muscle strength and sarcopenia, these parameters explained only a small portion of the variation in the ratio, suggesting limited clinical impact. Further investigations in older populations are warranted to confirm these findings.

SA-PO910

Quantification of Globotriaosylceramide (GL3) in Peritubular Capillary (PTC) Endothelial Cells (ECs) in Kidney Biopsies from Patients with Fabry Disease (FD) Using Machine Learning

David D. Smerkous,[1,2] Michael Mauer,[3] Alex Amedson,[1] Zian Wang,[1] Lexeigh A. Kolakowski,[1] Vanessa Delombaerde,[1] Frank Dastvan.[1]
[1]University of Washington, Seattle, WA; [2]Oregon State University, Corvallis, OR; [3]University of Minnesota Twin Cities, Minneapolis, MN.

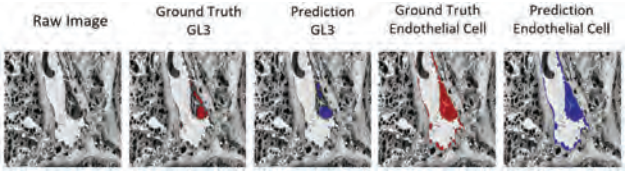
Background: Intracellular GL3 accumulation is a hallmark of FD. Clearance of kidney PTC EC has been accepted by FDA as a valid clinical trial endpoint. Current light microscopy PTC EC GL3 inclusion quantitative methods are insensitive for partial clearance, time consuming, and subjective. We aimed to develop an automated electron microscopy (EM) approach for quantification of GL3 inclusions.

Methods: A pre-trained vision transformer (ViT) model was developed using masked auto-encoders (MAE) on ~190K EM images from human kidneys. ~200 EM images of PTC at 5000x from FD patients and controls biopsies were segmented for EC cytoplasm, GL3 inclusions and nuclei using a segmentation utility to serve as the ground truth. Segmentation models were trained on ground truth images using the ViT with minor modification and tested on validation segmentations.

Results: The train and test dices (shown respectively) for PTC EC segmentation were 0.82 ± 0.12 and 0.80 ± 0.07; for GL3 inclusions were 0.83 ± 0.30 and 0.84 ± 0.24; and for EC nuclei were 0.84 ± 0.26 and 0.87 ± 0.13. The intersection over union (IOU; 1=perfect; 0=none) of predicted and ground truth masks for GL3 inclusions, EC and nuclei ranged between 0.8 - 0.87 in test images. Fraction of EC occupied by GL3 [Vv(Inc/EC)] in the Fabry images studied was 0.097 ± 0.117 in manually segmented images and 0.107 ± 0.127 by model prediction. Vv(Inc/EC) in control (non-Fabry) biopsies was 0 by either manual segmentation or model prediction. The absoloue error of segmentation in test images was 0.03 ± 0.07.

Conclusions: Pre-training vision models using self-supervised methods is an effective way to develop performant and robust segmentation models, from large pools of unlabeled data. As exemplified by our GL3 quantification in PTC EC, these models can then be used with limited supervised training data. This approach provides a rapid, automated reproducible approach for GL3 quantification in PTC for clinical trial endpoints, research studies, or clinical purposes.

Funding: Other NIH Support - NCATS



Raw, ground truth and model predictions for EC and GL3 inclusions

SA-PO911

CKD of Unknown Etiology (CKDu): Histopathology of the Disease in Patients from Nicaragua

Alexei V. Mikhailov,[1] Michael H. Carstens,[1] Sreedhar A. Mandayam,[2] Biruh Workeneh,[2] Nelson B. Garcia Salazar.[3] *[1]Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Mauricio Abdalah Hospital Departamental, Chinandega, Nicaragua.*

Background: Chronic kidney disease of uncertain origin (CKDu) is an endemic disease mainly affecting young male agricultural workers in tropical countries. CKDu displays an inexorable course with rapid deterioration of renal function. Since kidney biopsies are unavailable in endemic countries, our knowledge about the CKDu etiology is limited.

Methods: Patients with CKDu stages 3A-3B were identified by nephrologists in several Nicaraguan agricultural communities. All underwent clinical study, including ultrasonography. 2-3 cores were obtained for each patient via ultrasound-guided percutaneous renal biopsy. Light, electron microscopy, and immunofluorescence studies on pronase-treated paraffin-embedded material were performed.

Results: 21 patients were selected for this study, age 21 to 59 years (mean 41 y.o.), serum creatinine at biopsy 1.9±0.3 mg/dL, eGFR 40±9 mL/min/1.75m^2, resistance index 0.67±0.08, renal volume 131±51 cm^3. The major findings were global glomerulosclerosis affecting 30-88% of glomeruli in 80% of patients and glomerular capillary deflation. Perihilar FSGS was found in 1 biopsy. Tubules displayed fixation artifacts; chronic changes seen in 80% of patients were those of mild to rarely severe focal or diffuse interstitial fibrosis and tubular atrophy associated with mononuclear infiltration. 5 patient biopsies showed mild or moderate arteriosclerosis. Low-intensity segmental IgM deposition was noted in 50% of biopsies on the glomerular capillary walls or in the mesangium. Electron microscopy showed wrinkling of the glomerular capillary walls in 50% of biopsies. One biopsy showed thin glomerular basement membranes (GBMs), and another one- GBM remodeling; podocyte foot process effacement was segmental and rare. Toxic lysosomal inclusions were only rarely observed in the tubular epithelium by light and electron microscopy.

Conclusions: The most common pathological changes in Nicaraguan patients clinically diagnosed with CKDu were those of marked glomerulosclerosis and chronic tubulointerstitial lesions with associated inflammation. The concomitant pathology included arteriosclerosis, perihilar FSGS, and thin basement membrane disease. Our current research explores the treatment of CKDu with intraarterial injection of autologous stromal vascular fraction.

Funding: Private Foundation Support

SA-PO912

Targeting Alternative Splicing of Fibronectin (Fn) to Reduce Extra Domain A (EDA)+ Fn Production and Inhibit Kidney Fibrosis

Mysore K. Phanish,[1] Felicia Heidebrecht,[1] Pritpal S. Virdee,[1] Frank Rigo,[2] Mark E. Dockrell.[1] Research Team, SW Thames Institute for Renal Research.
[1]SW Thames Institute for Renal Research, Renal Unit, St helier Hospital, Epsom and St Helier University hospitals NHS Trust, St Georges' University of London, London, United Kingdom; [2]Ionis Pharmaceuticals Inc, Carlsbad, CA.

Background: EDA+ isoform of Fn is overexpressed in fibrosis. We investigate the effect of blocking 'splicing in' of EDA exon with antisense oligonucleotides (ASO) on EDA+Fn production and TGFβ1-induced fibrotic events in human primary proximal tubule cells (PTEC) and murine model of aristolochic acid (AA)-induced tubular injury.

Methods: PTEC were treated with TGFβ1 for 48 h, transfected with RNase H-independent ASO designed to block EDA exon inclusion (ASO5, selected after screening targeting 20 ASOs). EDA+Fn RNA and protein expression were analysed along with the expression of pro-fibrotic TGFβ target genes. In vivo, we assessed the expression of EDA+ Fn in murine AA model (IP inj of AA, 3.5mg/kg, D1 & 5; kidney lysate analysed by PCR for target genes on D0, D12, D20 & D100. We assessed the effect of ASO5 (50mg/kg) in mouse models: Short model (D-1 ASO5, neg control, NC or PBS S/C inj followed by a single dose of IP AA, cull D3) and long model (ASO5 or NC-ASO or PBS D-1, D3, x2/wk for 3 wks, weekly until cull D96, IP AA D1 and D5).

Results: ASO5 was effective and selective in reducing EDA+Fn RNA and protein in human PTEC (n=6, p<0.0001). TGFβ1 induced endogenous TGFβ, αSMA, MMP2, MMP9 and Col I mRNA and reduced K-Cadherin expression. These changes were attenuated by ASO5 (n=3-9, p <0.0001). Further increases in αSMA, MMP2, MMP9 (N 3-6, p<0.001) observed 48h after removal of TGFβ was inhibited by ASO5 (P<0.001). In vivo, compared to D0, there was a significant increase in EDA+/EDA- RNA ratio (30-fold, N=6, P<0.0001) on D12 which dropped to 2-fold on D100 (P<0.01). Similar pattern of induction was observed for CTGF, TGFβ1 and LTBP1 mRNA. The effect of ASO5 (50mg/kg) in mouse models: Short model (D-1 ASO5, neg control, NC or PBS S/C inj followed by a single dose of IP AA, cull D3) and long model (ASO5 or NC-ASO or PBS D-1, D3, x2/wk for 3 wks, weekly until cull on D96, IP AA D1 and D5). ASO5 treatment significantly reduced the mRNA levels of EDA+Fn, TGFβ1 (short and long models) and LTBP1 (long model P<0.05). Immunostaining for EDA+ Fn was attenuated in animals treated with ASO5.

Conclusions: EDA+ Fn plays a key role in TGFβ driven pro-fibrotic responses in renal tubule cells and blocking its production with ASO (in vitro and vivo) offers a potential therapy to limit the progression of renal fibrosis.

SA-PO913

m6A RNA Methylation Drives Kidney Fibrosis by Upregulating β-Catenin Signaling

Yinyi Long, Haiyan Fu, Youhua Liu. *Southern Medical University Nanfang Hospital, Guangzhou, China.*

Background: The N^6-methyladenosine (m^6A) methylation plays a crucial role in various biological processes and the pathogenesis of human diseases. However, its role and mechanism in kidney fibrosis remain elusive.

Methods: The level of m^6A methylation and the expression of METTL3 were assessed in mouse models and human kidney biopsies of chronic kidney disease (CKD). Conditional knockout mice with proximal tubule-specific deletion of METTL3 and mice with overexpression of METTL3 were used to corroborate a role of METTL3/β-catenin in kidney fibrosis.

Results: The overall level of m^6A methylated RNA was upregulated and the m^6A methyltransferase METTL3 was induced in kidney tubular epithelial cells in mouse

models and human kidney biopsies of chronic kidney disease (CKD). Proximal tubule-specific knockout of METTL3 in mice protected kidneys against developing fibrotic lesions after injury. Conversely, overexpression of METTL3 aggravated kidney fibrosis in vivo. Through bioinformatics analysis and experimental validation, we identified β-catenin mRNA as a major target of METTL3-mediated m^{6}A modification, which could be recognized by a specific m^{6}A reader, the insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3). METTL3 stabilized β-catenin mRNA, increased β-catenin protein and induced its downstream profibrotic genes, whereas either knockdown of IGF2BP3 or inhibiting β-catenin signaling abolished its effects.

Conclusions: These results indicate that METTL3 promotes kidney fibrosis by stimulating the m^{6}A modification of β-catenin mRNA, leading to its stabilization and its downstream profibrotic genes expression. Our findings suggest that targeting METTL3/IGF2BP3/β-catenin pathway may be a novel strategy for the treatment of fibrotic CKD.

Funding: Government Support - Non-U.S.

SA-PO914

A Novel Morphometric Approach to Estimate Interstitial Fibrosis from Trichrome-Stained, Whole-Slide Images

Ambarish Athavale,[1] Tushar Patel,[2] Hemant Kulkarni.[3] *[1]University of California San Diego, La Jolla, CA; [2]University of Illinois Chicago, Chicago, IL; [3]M&H Research LLC, San Antonio, TX.*

Background: Interstitial fibrosis (IF) is estimated by visual assessment which leads to significant interobserver variability. Using an image processing approach, we developed a novel algorithm (TRI_IF) to estimate IF from Trichrome whole slide images (WSI).

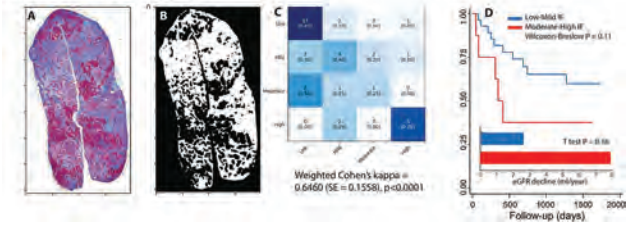
Methods: TRI_IF (developed in Python) masks out non-cortical area and estimates the proportion of blue stained area in the total cortical area (Figure 1A, 1B). 57 Trichrome WSI from the NEPTUNE study were used. Quality control excluded images with significant over/under staining and those beyond limits of agreement established by Bland-Altman plots. Cortex and glomeruli were manually annotated using QUPath. TRI_IF estimated IF was compared with NEPTUNE pathologists' consensus estimate (NP_IF). Categorization of IF was done using the Banff classification for NP_IF and latent class thresholds (using item response theory) for TRI_IF. Comparisons were made using Pearson's correlation for raw estimates, quadratically weighted Cohen's kappa for clinical classification of IF and association with two clinical endpoints: a) composite of ESRD or 40% reduction of eGFR and b) slope of eGFR decline per year.

Results: Of 57 Trichrome WSI, 16 were excluded after quality control and 41 were included in the analysis. Pearson's correlation between TRI_IF and NP_IF estimates was 0.69 (p<0.0001) and weighted Cohen's kappa for categorized IF was 0.65 (p<0.0001, Figure 1C). Compared with low-to-mild IF (<35% for TRI_IF), Moderate-to-high IF ≥35% for TRI_IF) was associated with a higher risk of the composite outcome (Figure 1D) and faster decline of eGFR (Figure 1D, inset).

Conclusions: A novel algorithm (TRI_IF) for automated estimation of IF on Trichrome WSI showed good agreement with pathologist's estimate of IF. Future studies need to validate this on a larger dataset.

Funding: NIDDK Support

Figure 1. Performance of TRI_IF. (A-B) Example biopsy core and generated IF mask (C) Agreement analysis (D) Association with progression to composite outcome (D, inset) Association with eGFR decline.



SA-PO915

Indoxyl Sulfate as Potential Kidney Tubular Function Marker across Kidney Disease Models

Sabbir Ahmed,[1,2] Sebastiaan Knoppert,[2] Rachel V. Harwood,[3] João Faria,[1] Paul J. Besseling,[2] Rolf Sparidans,[1] Silvia M. Mihaila,[1] Patricia Murray,[3] Tri Q. Nguyen,[2] Karin G. Gerritsen,[2] Rosalinde Masereeuw.[1] *[1]Universiteit Utrecht, Utrecht, Netherlands; [2]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [3]University of Liverpool, Liverpool, United Kingdom.*

Background: Kidney tubular damage is a strong predictor of end-stage kidney disease (ESKD) progression. Tubular function involves active secretion via transporters, such as organic anion transporters (OATs), to eliminate waste and metabolites, including protein bound uremic toxins (PBUTs). In tubular dysfunction, PBUT accumulation has been associated with many ESKD comorbidities. We hypothesized that PBUTs may be used as sensitive markers for tubular dysfunction.

Methods: We evaluated this in experimental models of chronic (rat nephrectomy and mouse IRI) and acute (mouse and *in vitro* IRI) kidney disease.

Results: In rats, PBUT parameters correlated with urinary tubular injury markers (kidney injury molecule-1 (Kim-1; p<0.001), neutrophil gelatinase-associated lipocalin (NGAL; p= 0.965 to <0.001), Beta-2-microglobuline (B2M; p<0.001) and cystatin C (p<0.001)). Moreover, indoxyl sulfate (IS) correlated better in a subgroup with the lowest tubular injury (p= 0.06 to <0.05) than filtration markers (GFR and plasma creatinine, cystatin C and urea (p= 0.54 to 0.07)). In chronic IRI mice, plasma IS and its clearance correlated with tubular atrophy scores, plasma NGAL and NGAL excretion (p<0.05 to <0.001), whereas filtration markers did not correlate. In acute IRI mice, IS and hippuric acid (HA) clearance correlated with plasma NGAL (p=0.058). Among all PBUTs, IS parameters showed the most consistent correlations with tubular injury markers across the animal models. Furthermore, proximal tubule transporters Oat1/3 expression was downregulated in mouse models and correlated with PBUT parameters. In agreement, OAT1-mediated transport of IS was decreased after inducing IRI *in vitro* using a human kidney proximal tubule cell line.

Conclusions: Our findings suggest that plasma IS and its clearance represent kidney transporters-related tubular function and may serve as sensitive clinical biomarkers for tubular dysfunction in kidney diseases.

Funding: Private Foundation Support

SA-PO916

Stenosis of Glomerulotubular Necks in a CKD Model

Eric P. Cohen,[1,2] Ann M. Farese,[3] George A. Parker,[4] Thomas J. Macvittie.[3] *[1]New York University Grossman School of Medicine, New York, NY; [2]VA NY Harbor Healthcare System Manhattan Campus, New York, NY; [3]University of Maryland School of Medicine, Baltimore, MD; [4]Charles River Laboratories International Inc, Durham, NC.*

Background: Fibrosis is a marker of injury and a predictor of future loss of renal function. Its intra-renal location may have more significance than its generalized presence. Histological studies of single time points show that fibrotic constriction of the glomerulotubular neck (GTN) may play a mechanistic role to impair nephron function (Cohen, *J Lab Clin Med* 129:567, Sato, *J Pathol* 197:14). We thus evaluated the time-course of the presence of GTN in a non-human primate (NHP) model of chronic kidney disease (CKD) and show that stenotic GTN increase over time in parallel with loss of renal function.

Methods: 38 NHP underwent 10 or 11 Gy partial-body irradiation (PBI) with tibial bone marrow sparing. Eleven NHP were non-irradiated (0 Gy). This model reliably causes progressive fibrotic CKD within months after irradiation (Cohen, *Radiat Res* 188:741). Kidneys were obtained at planned or for-cause euthanasia, whole kidney sections stained with Trichrome, then analyzed in a masked fashion using whole slide scanning. 40 or more glomeruli were identified in each section. Where seen, stenotic GTNs were defined as a narrowing at the beginning of the proximal tubule, while patent GTNs showed no narrowing at that site.

Results: 5%, 3%, and 4% of all glomeruli had visible necks in the 0, 10, and 11 Gy NHP, respectively. 15%, 21%, and 40% of visible necks were stenotic in the 0, 10, and 11 Gy NHP, respectively. The ratio of stenotic to normal necks was 0.2, 0.3, and 0.6 in the 0, 10, and 11 Gy NHP, respectively. The number of patent necks decreased over time after irradiation (figure). The % of visible necks that were stenotic increased progressively over time after irradiation. The serum creatinine increased in parallel to the increase in stenotic necks.

Conclusions: In conclusion, stenosis of the glomerulotubular neck is a definite feature of fibrotic chronic kidney disease. Further study is needed to identify the mechanisms whereby stenotic GTN form, and to identify markers of their presence in life.

Funding: Other NIH Support - HHSN272201500013I, Veterans Affairs Support

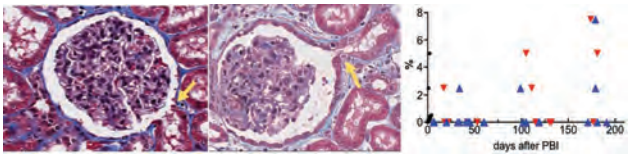


Figure 1: The left hand panel shows a glomerulus with a normal patent neck, the middle panel shows a stenotic neck, and the right hand panel shows the % of stenotic necks per 40 glomeruli for non-irradiated (●), 10 Gy (Δ), and 11 Gy irradiated NHP (,).

SA-PO917

Stenosis of the Glomerulotubular Neck Is Associated with Progressive CKD

Eric P. Cohen,[1,2] Aleksandar Denic,[3] Ian W. Gibson,[4] Fnu Aperna,[3] Andrew D. Rule.[3] *[1]New York University Grossman School of Medicine, New York, NY; [2]VA NY Harbor Healthcare System Manhattan Campus, New York, NY; [3]Mayo Clinic Minnesota, Rochester, MN; [4]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada.*

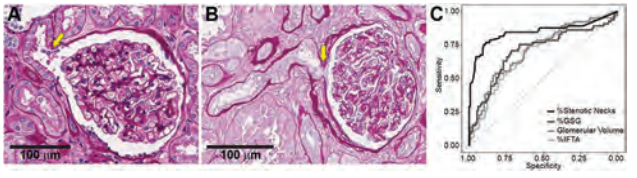
Background: Histopathologic evaluation can clarify the pathophysiology of chronic kidney disease (CKD). We tested whether the occurrence of glomerulotubular neck stenoses associates with progressive CKD.

Methods: We evaluated the non-cancerous parenchyma from radical nephrectomies for tumor between 2000 and 2021 and analyzed the cortex for stenoses of the glomerulotubular neck. Stenosis was defined as a focal narrowing at the neck for which the draining tubule had a greater diameter than at the neck (**Figure 1B**). Progressive CKD was defined as dialysis, kidney transplantation, sustained eGFR <10 ml/min per 1.73m^2 or sustained 40% decline from the post-nephrectomy eGFR during follow-up. Each case of progressive CKD was age-sex-matched to 2 controls without progressive CKD. Logistic regression models assessed the risk of progressive CKD with stenotic necks adjusting for other histological features, kidney function, and CKD risk factors.

Results: There were 65 cases with a mean of 255 glomeruli and 130 controls with a mean of 329 glomeruli. Among both cases and controls, 5% of glomeruli showed visible glomerulotubular necks. The proportion of necks that were stenotic was higher in cases than controls (35% vs. 11%, p<0.0001). Stenotic necks associated with progressive CKD independent of other histologic and clinical characteristics. ROC curves for histological morphometric measures showed that the proportion of stenotic necks was superior to glomerular volume, %GSG, and % IFTA as a classifier for predicting progressive CKD (**Figure 1C**).

Conclusions: Glomerulotubular neck stenosis predicts progressive CKD.

Funding: NIDDK Support, Veterans Affairs Support



Representative images of glomerulotubular necks that are **A**) normal (non-stenotic), and **B**) stenotic. **C**) ROC curves for histological pathology by morphometry as a classifier for subsequent progressive CKD among patients who underwent radical nephrectomy for tumor. The area under the curve (AUC) was 0.847 (95%CI: 0.776 to 0.917) for % stenotic glomerulotubular necks, 0.715 (95%CI: 0.638 to 0.793) for glomerular volume, 0.707 (95%CI: 0.623 to 0.790) for % globally sclerotic glomeruli (%GSG), and 0.695 (95%CI: 0.617 to 0.772) for % interstitial fibrosis and tubular atrophy (%IFTA).

SA-PO918

Urinary Extracellular Vesicle Analysis Reveals Early Signs of Kidney Inflammation and Damage in Single-Ventricle Pediatric Patients after Fontan Operation

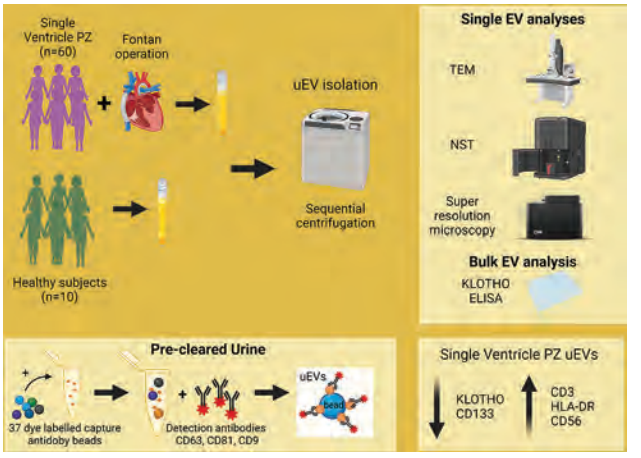
Cristina Grange, Diego Prudente, Benedetta Bussolati. *Universita degli Studi di Torino, Torino, Italy.*

Background: Extracellular vesicles present in urine (uEVs) are gaining considerable interest as biomarkers, to monitor and predict kidney physio-pathological state. Patients with single ventricle defects and hemodynamic stabilization by Fontan intervention may develop kidney dysfunction as one of the most prevalent extracardiac co-morbidity. Our study aimed to identify markers for monitoring and predicting kidney function in children with single ventricle heart defects who underwent Fontan surgery, as well to get physio-pathological insights on possible mechanisms of tissue damage and progression.

Methods: We isolated uEVs from urine of 60 paediatric patients affected by single ventricle defects, and from 10 healthy subjects. We analysed uEVs for the expression of the reno-protective hormone Klotho, using super- resolution microscopy of single EVs and ELISA. Moreover, we analysed the level of marker of kidney regeneration, such as CD133 and CD24, and of inflammation using a bead-based cytofluorimetric multiplex analysis. Marker expression was correlated with demographical, clinical and surgical data of patients.

Results: uEVs from children with single ventricle defects showed reduced levels of Klotho and CD133, compared with the one of healthy subject. In parallel, the levels of inflammatory markers (CD3, CD56, and HLA-DR) were significantly higher. Interestingly, levels of inflammatory markers correlated with age of patients and distance from surgery.

Conclusions: This study demonstrates that EVs isolated from the urine of single ventricle patients. present distinct expression of biomarkers of fibrosis, regeneration and inflammation in respect to those of healthy subjects, suggesting the presence of early signs of kidney damage.



Experimental scheme

SA-PO919

Development and Validation of an Enzyme-Linked Immunosorbent Assay (ELISA)-Based Method for Quantitative Evaluation of Urinary Extracellular Vesicles as Biomarkers for CKD

Tatsuya Nishimura,[1] Yosuke Hirakawa,[2] Keiichi Takizawa,[1] Yuko Kajiho,[1] Shoichiro Kanda,[1] Yutaka Harita.[1] *[1]Department of Pediatrics, The University of Tokyo Hospital, Bunkyo-ku, Japan; [2]Division of Nephrology and Endocrinology, The University of Tokyo Hospital, Bunkyo-ku, Japan.*

Background: Urinary extracellular vesicles (uEVs) are emerging as promising biomarkers for various diseases. Our previous work highlighted the potential of MUC1 expression levels on uEVs as an indicator for chronic kidney disease (CKD) in children (iScience 2022). We have developed an ELISA-based method for the quantitative assessment of uEVs (STAR Protocols, 2023; ASN 2023). Despite the existence of several techniques for uEVs purification on ELISA plates, their optimization remains incomplete. Furthermore, storage and processing of urine samples suitable for uEVs-ELISA have not been established.

Methods: We generated monoclonal antibodies against MUC1 and evaluated their performance across two uEVs purification methods (Tim4 and CD9 antibodies) on ELISA plates. Selecting the optimal antibody and plate combination, we analyzed urine samples from 160 adult patients (83 males) with varying kidney functions. The median age was 50 years, and the median estimated glomerular filtration rate (eGFR), calculated using serum creatinine, was 57.6 ml/min/1.73m^2.

Results: Among the developed monoclonal antibodies, the most sensitive one, in conjunction with both Tim4 and CD9 antibodies for uEVs purification on ELISA plates, effectively captured variations in MUC1 levels in uEVs. The CD9 plate method more accurately mirrored clinical outcomes. The area under the curve (AUC) values from receiver operating characteristic (ROC) curve analysis for predicting the presence of eGFR <60 or <45, standardized with urine creatinine value, were 0.912 and 0.928, respectively. This predictive accuracy was consistent across gender-specific analyses. This method has been found to provide stable results when storing urine at 4°C for up to a week and over a long period when stored at -80°C.

Conclusions: Given the stability of urine for uEVs-ELISA analysis, this system offers a non-invasive approach, demonstrating significant potential as a clinical biomarker for adult CKD patients as well as children.

SA-PO920

Progressive Changes in Urine Extracellular Vesicle Molecular Signatures Predict Phase of AKI

Monica S. Ng,[1,2] Sophie C. Chiang,[1,2] Xiangju Wang,[1,2] Helen G. Healy,[1,2] Andrew J. Kassianos.[1,2] *[1]Kidney Health Service, Royal Brisbane and Women's Hospital, Herston, QLD, Australia; [2]Conjoint Internal Medicine Laboratory, Chemical Pathology, Pathology Queensland, Herston, QLD, Australia.*

Background: Acute kidney injury (AKI) carries risks of severe complications including kidney failure and death. Urine extracellular vesicles (uEVs) released by cells in the urinary tract may have biomarker potential for assessing phase of AKI.

Methods: 50ml urine collected from people with evolving (n=3) and recovering (n=3) stage 3 AKI. Evolving AKI group had rise in serum creatinine and recovering AKI group had improving serum creatinine. uEVs were isolated using sequential centrifugation and size exclusion chromatography. uEVs were confirmed using electron microscopy and uEV related proteins were confirmed with mass spectrometry. uEVs were stained for cell source (podocyte: podocin; mesangial: CD90; endothelial: CD31; tubular: mucin-1; proximal

tubule: CD10, CD13) and inflammatory cytokine receptors (interleukin (IL)-1R1, IL-1R2, IL-6R, IL-2R). Stained uEVs were measured by multiparametric spectral flow cytometry. Counts were normalised to urine creatinine and compared using t-tests with correction for multiple comparisons.

Results: People with recovering AKI had increased uEVs compared to people with evolving AKI (mean: 7.89 x 10^6 uEVs/µmol creatinine vs 1.64 x 10^6 uEVs/µmol creatinine, p=0.048). Compared to people with evolving AKI, people with recovering AKI excreted more uEVs expressing CD90 (mean: 2,605 uEVs/µmol creatinine vs 407 uEVs/µmol creatinine, p=0.039), CD31 (mean: 8,833 uEVs/µmol creatinine vs 2,772 uEVs/µmol creatinine, p=0.012), mucin-1 (mean: 464,330 EVs/µmol creatinine vs 81,535 uEVs/µmol creatinine, p=0.015), IL-1R1 (mean: 8,481 uEVs/µmol creatinine vs 727 uEVs/µmol creatinine, p=0.030) and IL-2R (mean: 58,799 uEVs/µmol creatinine vs 1,671 uEVs/µmol creatinine, p=0.003) [Fig 1].

Conclusions: People with recovering AKI excrete more uEVs from mesangial, endothelial and tubular cells compared to people with evolving AKI. The inflammatory signatures of uEVs have biomarker potential for profiling AKI phase.

Funding: Government Support - Non-U.S.

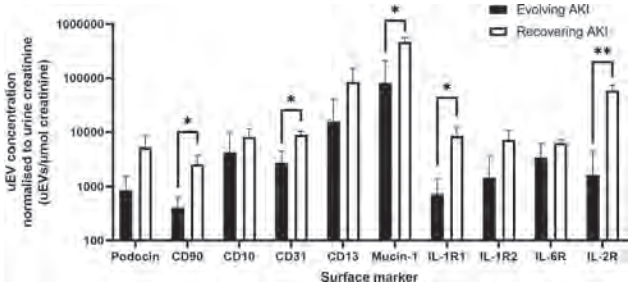


Fig 1-Concentration of uEVs expressing different surface markers from people with evolving and recovering AKI. * p<0.05, ** p<0.01.

SA-PO921

Measured GFR Implemented in a US Clinical Practice: Comparing 4-Hour and 10-Hour Plasma Iohexol Clearance

Shane A. Bobart, Jacob Nielsen, Xin Yi, Angelina Edwards, Tariq Shafi.
Houston Methodist Hospital, Houston, TX.

Background: It is well recognized that estimated glomerular filtration rate (eGFR) can be highly inaccurate in assessing measured GFR (mGFR) for individual patients. mGFR using non-radiolabeled plasma iohexol clearance is straightforward and easily implementable in clinical practice, but it is not widely available in the US. In 2019, we implemented mGFR by a 4-hour plasma iohexol clearance as part of clinical care at Houston Methodist Hospital. The mGFR is orderable via an Epic order set. Recent studies (White CA; PMID: 32750458) and European Kidney Function Consortium (EKFC; under review) guidelines emphasize the importance of a long plasma clearance interval (10-hours) if the GFR is expected to be low (<30 mL/min/1.73 m^2). We have now updated our mGFR protocols to include both the standard (4-hour) and the long (10-hour) clearances. We present these case studies as an educational tool to enhance the understanding of mGFR and promote dissemination of mGFR protocols.

Methods: We describe 3 patients that had simultaneous measurement of creatinine, cystatin C, and mGFR by 10 hour plasma iohexol clearance. We compared the 4-hour and 10-hour mGFRs with eGFRs. We defined eGFR to be accurate in assessing the mGFR if the eGFR was within ±5 ml/min/1.73 m^2 of the 10-hour mGFR.

Results: See Table 1.

Conclusions: mGFR is the best available test of kidney function and it is not influenced by age, sex, or race. We have successfully implemented standard (4-hour) and long (10-hour) mGFR in routine practice at a busy clinical center in the US. Our cases provide important educational opportunities for nephrologists interested in learning and implementing mGFR in routine clinical care.

Table 1

Characteristic	Patient #1	Patient #2	Patient #3
mGFR indication	CKD in the setting of lung transplant	CKD in the setting of lung transplant	CKD at an old age
Age, years	64	68	83
Race/Ethnicity	W	W	W
CVD	No	Yes	No
Diabetes	Yes	Yes	No
Hypertension	Yes	Yes	Yes
Immunosuppression	Yes	Yes	No
Body surface area, m^2	1.81	1.85	1.84
BMI, kg/m^2	27	30	27
Urine ACR, mg/g	3	63	8
Serum Creatinine, mg/dL	1.92	1.46	1.05
Serum Cystatin C, mg/L	2.83	2.13	1.56
Iohexol GFR (10 hr) mL/min/1.73m^2	**30**	**43**	**41**
Iohexol GFR (4 hr) mL/min/1.73m^2	32	48	43
Overassessment by 4 hr mGFR	7%	11%	4%
CKD-EPI eGFR mL/min/1.73m^2			
Creatinine	**29**	52	52
Creatinine-cystatin C	22	37	**45**
Cystatin C	18	27	**36**
Teaching Points	eGFR creatinine is accurate. Cystatin C is not the "gold standard" for GFR assessment.	None of the eGFRs are accurate.	eGFR using cystatin C equations are accurate but discordant

SA-PO922

Theoretical Analysis of D-serine and D-asparagine as Biomarkers for Glomerular Filtration Rate

Tomonori Kimura,[1,2] Ryo Tanaka,[1] Yoko Higa,[1] Shigeaki Nakazawa,[1] Yoichi Kakuta,[1] Shinsuke Sakai,[1] Masayuki Mizui,[1] Shiro Takahara,[2] Norio Nonomura,[1] Yoshitaka Isaka.[1] *[1]Osaka Daigaku, Suita, Japan; [2]Kansai Medical Clinic for Renal Transplantation, Toyonaka, Japan.*

Background: As biomarkers that potentiate the precise measurement of glomerular filtration rate (GFR), two rare enantiomers of amino acids, D-serine and D-asparagine, are expected in use. This study aimed to analyze why the levels of these D-amino acids reflect GFR.

Methods: We utilized a cross-sectional observational study of 210 living kidney transplant donors and recipient, for whom GFR was measured using clearance of inulin. The levels of D-amino acids in blood and urine were measured using two-dimensional high performance liquid chromatography. The validity as GFR markers was assessed based on four criteria proposed previously: (i) free filtration at the glomeruli, (ii) constant clearance from plasma, (iii) no reabsorption at the tubules, (iv) no secretion at the tubules, (iv) endogenously present preferentially. We added two more criteria: (iv) endogenously present, preferentially, and (v) stable dynamics, regardless of GFR.

Results: D-Serine and D-asparagine are endogenously-present small molecules that are considered to pass through glomerular filtration barrier freely. Scatter plot analysis using clearance of inulin (C-in) as a reference showed that clearances of D-serine (C-dSer) and asparagine (C-dAsn) were well-correlated with C-in. These clearances are close to C-in with small proportional biases; the slope was 1.178 for C-dSer and 0.995 for C-dAsn, while the slope for C-cre was 0.674. Therefore, (i) D-serine and D-asparagine are subject to minor reabsorption and secretion in the tubules, or (ii) the reabsorption and secretion of these D-amino acids is balanced. Blant-Altman plot showed that the dissociations of C-dSer and C-dAsn from C-in were small and unaffected with the reduction of GFR.

Conclusions: D-Serine and D-asparagine are unaffected by tubular reabsorption and secretion after glomerular filtration. Additionally, tubular handling of D-serine and D-asparagine are unaffected by the reduced glomerular filtration. These features are the basis of D-serine and D-asparagine as biomarkers for GFR.

SA-PO923

Detection of Chronic Glomerular Nephritis in Nephrotic Patients Using D-amino Acids

Tomonori Kimura,[1] Shinsuke Sakai,[1] Yukimasa Iwata,[2] Hiroki Okushima,[1] Terumasa Hayashi,[3] Masayuki Mizui,[1] Yoshitaka Isaka.[1] *[1]Osaka Daigaku, Suita, Japan; [2]Sakai Shiritsu Sogo Iryo Center, Sakai, Japan; [3]Osaka Kyuseiki Sogo Iryo Center, Osaka, Japan.*

Background: Patients with chronic glomerular nephritis (CGN) is often complicated with diabetes, and it is often a diagnostic challenge to detect CGN in patients with diabetes. D-amino acids, rare enantiomers of amino acids, are kidney biomarkers that are useful to assess glomerular filtration rate and prognosis of kidney disease. Furthermore, combinational assessment of D-serine, one of D-amino acids, in blood and urine has the diagnostic potential to identify the origin of kidney diseases. We aimed to differentiate diabetic nephropathy from chronic glomerular nephritis in patients with higher level of urinary proteins by broadening the range of D-amino acid measurements.

Methods: Patients with biopsy-proven diabetic nephropathy, minimal change disease, and IgA nephropathy, and participants without kidney disease, were analyzed. The levels of four major D-amino acids in blood and urine were measured using two-dimensional

high-performance liquid chromatography. Multivariate analysis was performed to identify the ideal marker for the diagnosis of CGN from diabetic nephropathy (DN).

Results: A total of 566 patients were analyzed. Multivariate analysis identified that the parameters calculated from the combination of D-amino acids have the diagnostic value to differentiate CGN from DN. ROC curve analysis showed that area under the curve of 0.833 for the differentiation of CGN from DN in patients with the nephrotic range of urinary protein.

Conclusions: Combinational analysis of D-amino acids in blood and urinary excretion is useful in the differentiation of CGN from DN. Profiling of D-amino acids may help the diagnosis of origin of kidney disease in nephrotic patients.

SA-PO924

Development of a Novel Metabolite Filtration Marker Panel to Improve GFR Estimation

Jesse C. Seegmiller,[1] Seiei Shiba,[1] Nora F. Fino,[2] Tom Greene,[2] Benjamin Haaland,[2] Josef Coresh,[3] Ogechi M. Adingwupu,[4] Andrew S. Levey,[4] Lesley A. Inker.[4] CKD-EPI. *[1]University of Minnesota Medical School, Minneapolis, MN; [2]University of Utah Health, Salt Lake City, UT; [3]New York University Department of Medicine, New York, NY; [4]Tufts Medical Center, Boston, MA.*

Background: The GFR is estimated (eGFR) in clinical practice by analyzing endogenous filtration markers creatinine and/or cystatin C. However, current estimates of GFR are not sufficiently accurate across all populations and clinical settings. Using non-targeted metabolomic approaches, we previously identified 32 possible metabolite filtration markers yielding high correlation to measured GFR (mGFR). The goal of these analyses was to identify metabolites providing acceptable analytical properties to develop a targeted measurement procedure for subsequent clinical validation and translation.

Methods: A total of 32 metabolites were pursued based upon mGFR correlation and commercial availability. Analysis was performed in a single measurement procedure using liquid chromatography tandem mass spectrometry employing positive and negative ionization switching to capture this diverse set of metabolites and to allow for maximal quantitative multiplexing. Validation studies included linearity, recovery and imprecision determined from N=21 batches to determine analytical performance.

Results: Of the 32 metabolite filtration markers, 11 passed analytical validation studies (figure). All 11 metabolites displayed a % coefficient of variation (%CV) of < 6.4% over the entire analytical ranges investigated. The lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ) were determined empirically and are displayed in figure along with results from the low, medium, and high-quality controls (QC) with imprecision given at each level.

Conclusions: The performance of the novel metabolite filtration marker panel displayed excellent reproducibility < 6.4% CV over the entire endogenous range in QC specimens. Assessing these metabolites may allow for more robust eGFR approaches in patients. Future steps include clinical validation and development of algorithm to estimate the GFR.

Funding: NIDDK Support

Compound Name	LLOQ (µM)	ULOQ (µM)	QC Concentration (µM)			Inter-assay %CV N=21		
			Low	Med	High	Low	Med	High
Pseudouridine	0.25	50	1.208	5.034	24.791	1.7%	1.7%	1.6%
2-(α--D-Mannopyranosyl)-tryptophan	0.02	4	0.100	0.394	1.979	6.2%	5.7%	4.6%
SDMA	0.05	10	0.245	1.017	5.059	3.9%	3.1%	2.5%
L-Homocitrulline	0.05	10	0.236	0.985	4.885	3.3%	2.1%	2.3%
Kynurenic acid	0.006	1.2	0.029	0.120	0.594	4.2%	2.1%	1.7%
N2,N2-Dimethylguanosine	0.006	1.2	0.030	0.119	0.592	5.3%	3.2%	1.9%
N-Acetylserine	0.15	30	0.748	3.046	14.846	5.0%	2.6%	2.1%
N-Acetylneuraminic acid	0.1	20	0.470	1.977	9.699	6.3%	3.1%	3.3%
Acetyl-L-threonine	0.06	12	0.295	1.200	5.912	2.1%	1.3%	1.6%
N-Acetyl-L-alanine	0.1	20	0.501	2.049	9.993	2.0%	1.3%	1.1%
4-Acetamidobutanoic acid	0.05	10	0.253	1.033	5.091	1.8%	1.9%	1.7%

SA-PO925

Cell Type-Specific Effects of Zinc on Human Kidney Cells in Culture

Zakeya A. Baalawy,[1,2] Zeynep Ulker,[1,4] Christer Hogstrand,[1] Mark E. Dockrell.[2,3] *[1]King's College London, London, United Kingdom; [2]SWT Institute for Renal Research, London, United Kingdom; [3]St George's University of London, London, United Kingdom; [4]Sabanci Universitesi, Istanbul, Turkey.*

Background: Zinc is a nutritionally essential trace element for all living organisms; it is required for development, growth, and tissue repair. However zinc excess is harmful and potentially lethal. High zinc has been shown to cause embryological damage in fish. In adult fish Zinc Chloride ($ZnCl_2$) caused reduction in antioxidant defence systems and neurotoxicity. In man approximately 15% of zinc is cleared through the kidney. Although CCN2/CTGF (Connective Tissue Growth Factor) is considered pathological particularly in fibrotic diseases, expression of CCN2/CTGF is crucial to embryonic development. CCN2/CTGF knockout mice have multiple skeletal dysmorphisms and raised perinatal lethality. In this work we examined the effect of sub-lethal zinc concentrations on human embryonic and adult renal cells with a focus on CCN2/CTGF expression.

Methods: Human Embryonic Kidney cells (HEK 293) and adult human primary proximal tubule epithelial cells (PTEC) were treated with a range of concentrations of $ZnCl_2$. Cell toxicity was measured using CellTox Green Cytotoxicity Assay. Cellular expression of Zinc transport channels (ZIP) was assessed by immunofluorescence microscopy.

Results: $ZnCl_2$ induced a dose and time dependent increase in HEK 293 cell cytotoxicity, which reached statistical significance at 300 µM at 24h. Primary human PTEC appeared more sensitive to $ZnCl_2$ with significant cytotoxicity at 100 µM at 24h. $ZnCl_2$ treatment (20 µM, 24h) significantly reduced CCN2/CTGF expression in HEK 293 cells but had no effect on human primary PTEC CCN2/CTGF expression. Both cell types expressed Zip10 (SLC39A10) zinc channels.

Conclusions: The inhibition of CCN2/CTGF expression in embryonic renal cells may indicate the potential for raised levels of Zinc to induce renal malformation in utero. Zip10 expression has previously been reported in the apical membrane of proximal tubule cells and provides a possible mechanism for zinc entry into the cells however a more comprehensive investigation of Zip protein expression is lacking. An important caveat in the interpretation of our results is that although HEK 293 cells are derived from human embryonic kidney and have an epithelial morphology, the original cells were not fully characterised. Furthermore the cell line is a result of adenovirus transformation.

Funding: Private Foundation Support

SA-PO926

Analysis of PD-L1 on Kidney Vascular Endothelial Cells

Yoichi Imai, Yoriaki Kaneko, Masato Kinoshita, Junya Suwa, Hiroko Hamatani, Hidekazu Ikeuchi, Keiju Hiromura. *Gunma University Graduate School of Medicine Department of Nephrology and Rheumatology, Maebashi, Japan.*

Background: Programmed death ligand 1 (PD-L1), expressed on various types of cells including vascular endothelia, inhibits T cell activity via PD-1. Anti- PD-L1/ PD-1 antibodies block this interaction and enhance T cell cytotoxicity, which has been utilized as cancer immunotherapy. However, Anti-PD-L1/PD-1 antibodies sometimes induce interstitial nephritis with unclear etiology. This study examines PD-L1 expression on kidney endothelial cells (ECs) and its effects on T cells in mice.

Methods: Female C57BL/6j mice were used. Kidney and lung cells were isolated by collagenase treatment and density gradient centrifugation, then analyzed by flow cytometry (FCM). Glomerular cells were separated using a mesh and collagenase treatment. Specific cell populations were separated using CD45 and CD31 microbeads. Mice received intraperitoneal injections of LPS, anti- PD-L1, or anti-CD3ε antibodies.

Results: FCM analysis in healthy mice showed PD-L1 expression in ECs ($CD31^+CD45.2^-$) of both kidneys and lungs, with higher expression in kidneys. These cells also expressed other EC markers like ICAM-1 and VEGFR2. Immunofluorescence staining (IF) revealed PD-L1 co-staining in CD31+ glomerular ECs, peritubular capillary ECs, and interlobular artery ECs. Glomerular ECs had lower PD-L1 expression compared to peritubular capillary and arterial ECs. Co-culturing renal ECs with splenic cytotoxic T cells ($CD8\alpha^+$) induced IFN-γ secretion, significantly increased by anti-PD-L1 antibody. LPS administration increased PD-L1 expression in ECs of both kidneys and lungs. IF showed enhanced PD-L1 in glomerular and peritubular capillary ECs in kidneys with LPS injection. Anti-CD3ε antibody, inducing high IFN-γ levels, also increased PD-L1 expression in renal ECs, as shown by FCM. Blocking PD-L1 on ECs with anti-PD-L1 antibody before anti-CD3ε treatment led to increased leukocyte infiltration into the renal interstitium and elevated blood urea nitrogen levels.

Conclusions: In healthy mice, PD-L1 is primarily expressed in peritubular capillaries of the kidney, and its expression increases during inflammation. PD-L1 on kidney ECs may inhibit T cell immune activation, suggesting a protective role for the kidneys.

SA-PO927

Microplastics and Bisphenol A Coexposure on Human Kidney Proximal Tubular Cells

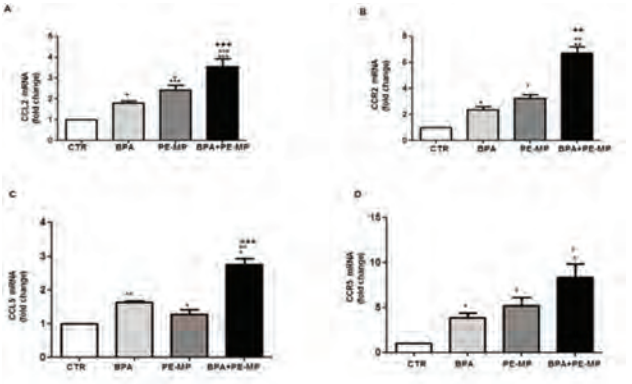
Luca Estienne,[1] Daniela Verzola,[3] Pasquale Esposito,[3] Francesca Viazzi,[3] Andrea Angeletti,[2] Paolo Cravedi,[4] Marco Quaglia,[1] Edoardo La Porta.[2] *[1]Azienda Ospedaliera Nazionale Santi Antonio e Biagio e Cesare Arrigo Alessandria, Alessandria, Italy; [2]Istituto Giannina Gaslini, Genova, Italy; [3]IRCCS Ospedale Policlinico San Martino, Genova, Italy; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Microplastics (MPs) accumulate in human tissues, including kidney. Beyond direct harmful actions, MPs can also adsorb a wide range of toxic substances, such as Bisphenol A (BPA) and so, enhancing their toxicity. MPs have been found in human blood, urine, and several human tissues, including lungs, placenta, blood, heart, and the kidney by Massardo et al. Moreover, it have recently demonstrated that patients with evidence of MPs in carotid artery plaque experience an increased risk of death and cardiovascular event compared with those without MPs.

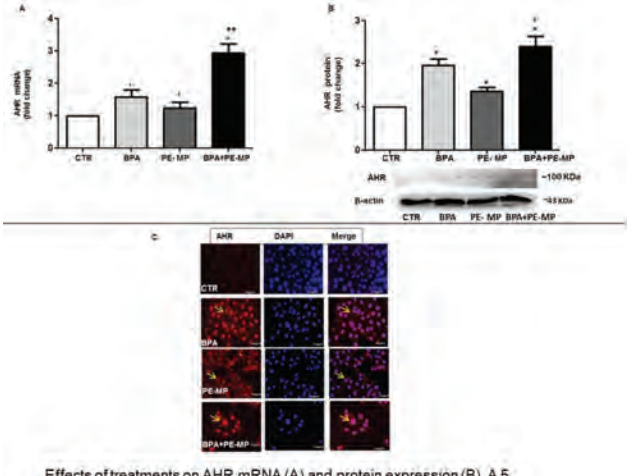
Methods: We exposed a proximal tubular cell line for 5-24 hours to polyethylene (PE)-MPs and BPA alone or combined. MP characterization was performed by by means of Dynamic Light Scattering analyses. We analyzed molecules involved in renal damage through mRNA Analysis, Immunofluorescence and immunocytochemistry and Western Blot Analysis

Results: Compared with the single exposure, the co-treatment was more powerful, reducing cell viability and boosting the pro-oxidant a pro-inflammatory response. Exposition to co-treatment induced a 3.5 and 2.7 fold increase of CCL-2 and -5 (both $p<0.05$ vs CTR). In addition, Heat Shock protein (HSP90), a chaperone involved in multiple cellular functions, was reduced, while Aryl hydrocarbon receptor (AHR) expression, a transcription factor which binds multiple environmental ligands, was increased.

Conclusions: Our study demonstrates that all the treatments influenced the cell behavior, but the co-exposure was more incisive. The combination of PE-MPs and BPA can negatively modify the cellular homeostasis, contributing to the induction of kidney damage.



Effects of treatments on inflammatory molecules. 5 hour exposition increased CCL2 (A), CCL5 (C) and their receptors CCR2 (B) and CCR5 (D), mRNAs were evaluated by rt-PCR. The results represent means ± SEM



Effects of treatments on AHR mRNA (A) and protein expression (B). A 5 hour exposition increased AHR levels. By immunofluorescence (C), AHR was observed in nuclei as pointed out by the yellow arrows. mRNA was evaluated by rt-PCR and protein by western blot. Blots were stripped and reprobed with antibody to β-actin. The results represent means ± SEM

SA-PO928

Kidney Localization of Cardiac Protein in Acute Cardiorenal Syndrome

Daiki Aomura,[1,2] Yoshio Funahashi,[1,2] Adam C. Munhall,[1,2] Tahnee Groat,[1,2] Michael Hutchens.[1,2] *[1]Oregon Health & Science University, Portland, OR; [2]Portland VA Medical Center, Portland, OR.*

Background: In a translational acute cardiorenal syndrome (CRS) model, mouse cardiac arrest and cardiopulmonary resuscitation (CA/CPR), heart-specific cardiac LIM protein (CSRP3) filters into the proximal tubule (PT), and mediates renal fibrosis. In the heart, CSRP3 undergoes stress-induced nuclear translocation and participates in fibrosis signaling. However, how endocrine CSRP3 acts in PT is unknown. Therefore, we characterized CSRP3 appearance in PT after CA/CPR using immunohistochemistry (IHC).

Methods: CA/CPR was performed on wild-type C57/B6J mice. CA was induced with potassium chloride; CPR, started after 8 minutes CA, included chest compressions and epinephrine. Mice were sacrificed on day (d) 1, 3, 7, or 49 after CA/CPR or sham (n=3/group). Kidneys were stained for CSRP3 with IHC. The volume of CSRP3 positivity with respect to kidney (V_{CSRP3}/V_{Kidney}, by Cavalieri method) was quantified using unbiased stereology on whole kidney sections to reduce IHC bias. Kidney compartments were independently segmented on 5 random high-power sections per mouse using machine learning (ilastik) to test localization of CSRP3. Segmentation was manually validated. Plasma CSRP3 was quantified by ELISA. Group differences were assessed with ANOVA and post-hoc tests.

Results: CSRP3 was heterogeneously stained at low level in sham. After CA/CPR (d1-7), CSRP3 was abundant in PT, concentrated at the apical brush border and in intratubular cell punctae. V_{CSRP3}/V_{Kidney} increased after CA/CPR (0.14±0.00 in sham vs 0.16±0.02 on d1 and 0.16±0.00 on d49, p=0.01). PT and nuclear segmentation was adequate (F=0.88). PT-associated CSRP3 increased after CA/CPR ($p<0.001$) and correlated with V_{CSRP3}/V_{Kidney} (r=0.58, p=0.02). Apical-basal distribution of CSRP3 within PT did not vary much with time, however, perinuclear CSRP3 localization within PT was persistently increased after CA/CPR (0.47±0.09 in sham and 0.58±0.10 on d49, $p<0.001$). Plasma of CSRP3 peaked on d1 and declined to baseline by d3 (sham 1.4±0.2, d1 20±4.2 p=0.003 vs sham, d3 3.7±4.0 p=0.9 vs sham, ng/mL).

Conclusions: CSRP3 is present at the renal brush border and in tubular punctae at baseline. PT CSRP3 increases after CA/CPR. Perinuclear distribution of CSRP3 increased immediately after CA/CPR, persisting for weeks. Therefore, CSRP3 is taken up by PT after CA/CPR in a manner suggesting intracellular trafficking.

Funding: Veterans Affairs Support

SA-PO929

Upregulation of Tissue Factor Is Associated with Increased Levels of D-dimer and Decreased Levels of Thrombin Generation in ESKD

Hamzah Hussain,[1,2] Fakiha Siddiqui,[1,3] Debra Hoppensteadt,[1] Elyse Fairand,[1] Emma Abulencia,[1] Jawed Fareed,[1] Vinod K. Bansal.[1] *[1]Loyola University Medical Center, Chicago, IL; [2]Hurley Medical Center, Flint, MI; [3]Universidad Catolica San Antonio de Murcia, Murcia, Spain.*

Background: End-stage renal disease (ESRD) is often associated with vascular complications. Tissue factor (TF) plays a very important role in triggering the thrombogenesis and biomarkers associated with thrombin generation (TG) such as D-Dimer (DD). TF levels in chronic kidney disease are known to be upregulated, however such a study in ESRD patients is not reported. In this study, we sought to measure TF antigen and activity levels and their association with DD and TG potential.

Methods: 72 patients plasma with confirmed ESRD was collected in the Hemodialysis Clinic at Loyola University Medical Center (LUMC). 50 healthy plasma samples from a commercial source and 12 healthy plasma samples from LUMC served as control. Sandwich ELISA methods were used to measure TF antigen and DD levels and a chromogenic substrate method was used for TF activity. TG was quantified by using a fluorogenic method. Applicable statistical methods were performed and $p<0.05$ were considered significant.

Results: ESRD patients showed marked increase in TF and DD levels compared to the control. DD increased from 7.08 to 905.8ng/mL (128-fold, $p<0.05$) and TF concentration increased from 107.5 to 283.6pg/mL (2.6-fold, $p<0.05$). Peak thrombin levels reduced in the patient cohort from 138.4 to 109.9nM (-1.3-fold, $p<0.05$), while lag time increased from 1.7 to 2 minutes (1.2-fold, $p<0.05$). TF activity and ETP showed no significant difference. Table 1 represents the composite results in the patient cohort and controls.

Conclusions: These studies demonstrate that while TF activity is undetectable, TF antigen is quantifiable in ESRD patients. Simultaneously, the peak thrombin level decreased and DD levels increased. These results suggest that coagulation system is activated where thrombin is consumed leading to DD formation. Thus, TF upregulation plays a central role in the pathogenesis of ESRD and its measurement may be helpful in prognostic management.

Table 1

Biomarkers	Controls Median (IQR)	ESRD Median (IQR)	p-value
DD (ng/mL)	7.08 (7.08-44.3)	905.8 (616.5-1831.4)	<0.05
TF Immunologic (pg/mL)	107.5 (60.2-125.1)	283.6 (243.3-352.7)	<0.05
TF Activity (optical density)	0.08 (0.07-0.15)	0.09 (0.07-0.12)	0.66
Peak Thrombin (nM)	138.4 (126.6-155.6)	109.9 (58.1-142.5)	<0.05
Lag Time (min)	1.7 (1.7-2.0)	2.0 (1.6-2.3)	<0.05
Endogenous Thrombin Potential (nM*min)	583.7 (532.8-651.7)	592.0 (388.5-704.2)	0.46

SA-PO930

Novel High-Resolution Three-Dimensional Fluorescent Confocal Imaging Resolves Differences in Urinary Sediment

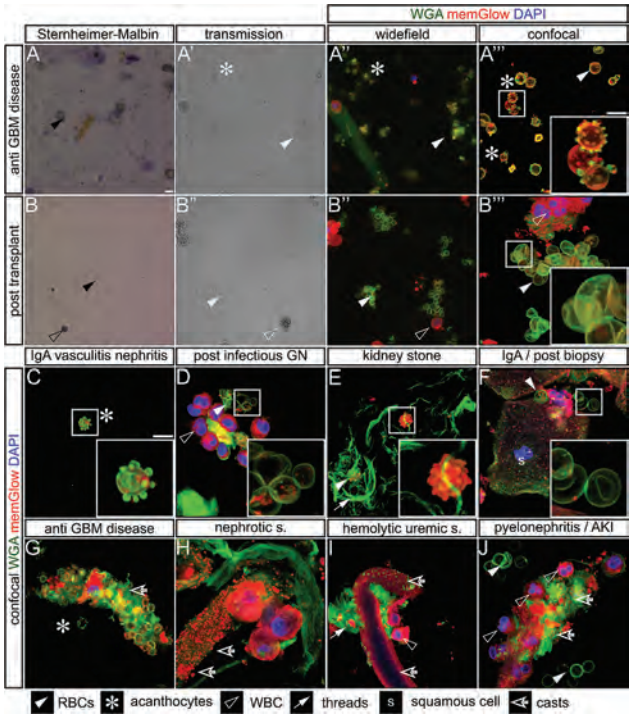
Sarah N. Lipp, Andrew L. Schwaderer. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Although microscopic urinalysis is used as a liquid biopsy to determine kidney disease etiology, it is limited by poor resolution, few stains, and sample instability.

Methods: Fixed urine sediment from pediatric patients with kidney disease was fluorescently stained with lectins, membrane markers, and nuclear stains and imaged using high-resolution confocal microscopy.

Results: Fluorescent stains followed by high-resolution 3D confocal imaging resolved urine sediment structures including of acanthocytes, red blood cells (RBC), white blood cells (WBC), mucus fibers, and casts in higher resolution than standard urine microscopic examination. Widefield fluorescent images (A″-B″) and 3D confocal (A‴-B‴) renderings of urine sediment stained for wheat germ agglutinin (WGA, green), memGlow (red), and DAPI (blue) resolved structure better than transmission (A″-B″) or Sterheimer-Malbin (A-B). Confocal images of urine sediment in disease showed (C) acanthocyte, (D) WBCs, (E) mucous threads, (F and J) eumorphic RBCs, (G) RBC cast, (H) lipid cast, (I) hyaline cast, and (J) WBC cast. GBM=glomerular basement membrane, GN=glomerulonephritis, s.=syndrome, AKI=acute kidney injury. A-B″: 60×, widefield, A″-B‴, C-J: confocal 63×, z=5 µm, inset 3× zoom. Scale bar=10 µm.

Conclusions: The improved resolution of confocal imaging will provide the foundation for quantification and comparison between disease type and response to therapy when affected patients are followed longitudinally. Enhanced analysis of the urine sediment offers a strategy to increase diagnostic insight beyond the standard microscopic evaluation that has been used relatively unchanged for decades.



SA-PO931

Changes in the Composition of Urine Using Urinalysis and Automated Microscopy over 6 Hours at Room Temperature

Pranav C. Parikh,[1] Serena D Souza,[2] Wassim Obeid.[2] *[1]Gilman School, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD.*

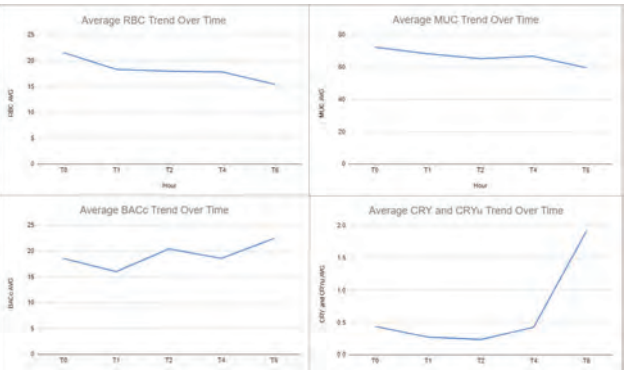
Background: Urinalysis (UA) is a commonly performed test for the diagnosis and prognosis of kidney disease in hospitalized patients. UA involves examining the chemical composition of the urine as well as microscopy to examine the cells and casts. In clinical settings, there is a frequent delay of several hours to perform UA after sample collection. The purpose of this study is to investigate the changes in urine composition over set time intervals in order to confirm the reliability of UA when there are delays in performing the tests.

Methods: We obtained 15 mL of urine from the Foley catheters of five ICU patients. We utilized the state-of-the-art IDEXX Sedivue machine to perform urine microscopy and the Siemens CLINTEK Status+ Urine Analyzer to perform the dipstick tests. We performed both microscopy and dipstick tests at 0, 1, 2, 4, and 6 hours. The samples were left at room temperature between measurements. We altogether tested 30 individual components in the urine. We calculated the %CV for each component by taking 4 repeated measurements at one time period for multiple samples.

Results: After calculating the %CV for each component, we analyzed the trend for each constituent over the 6-hour period. If the percent change over the six-hour interval was significantly more than the %CV, we determined time to have an influence on the results. Significant changes were seen in bacteria (BACc), as the levels increased, RBC and mucus (MUC) where the levels decreased, and crystals (CRY and CRYu) levels were determined inconclusive due to fluctuations in the results (*see figure*). All other components were found to remain unchanged.

Conclusions: The majority of the components were unchanged suggesting that UA results for these could be helpful even if the processing of the sample is delayed in clinical settings. The changes in the levels of bacteria and blood could lead to an incorrect clinical diagnosis. Additionally, changes in some components are highly variable and cannot be compensated for with certainty.

Funding: NIDDK Support



SA-PO932

Continuous Antithrombin III Infusion in a Clinically Relevant Sepsis Model

Naoki Hayase, Rohit R. Chari, Yoshitaka Naito, Alef Aragao Carneiro dos Santos, Xuzhen Hu, Peter S. Yuen, Robert A. Star. *National Institutes of Health, Bethesda, MD.*

Background: Despite unacceptably high mortality and economic burden, effective therapeutic strategies for sepsis remain elusive. Discrepancies between drug responses in septic patients and animal models may be caused by differences in drug pharmacokinetics and timing of drug administration. Antithrombin III (AT) is an anticoagulant that might ameliorate sepsis-induced multiple organ dysfunction. Clinical trials using bolus AT infusions are conflicting. AT has a short half-life in mice, so we devised a method to continuously infuse drugs starting 6-12 h after cecal ligation and puncture (CLP) surgery (the time needed for clinical diagnosis of sepsis). We asked, "Is AT effective in our clinically relevant sepsis model?"

Methods: We catheterized mouse jugular veins, then connected catheters to osmotic minipumps containing saline. After 1-week stabilization, we performed CLP surgery and replaced each minipump with one containing AT or saline. We set a 6-12-h time delay between sepsis induction and treatment by incorporating a 4 cm saline-filled catheter in the circuit and validated the delay by using FITC-sinistrin. Infusion continued for 7 days. Survival studies were conducted. In separate experiments, we collected blood, kidney, liver, and lung at 48 h for biochemical, histological, and microbiological analyses. To examine effect of administration route, we also compared continuous AT infusion with a conventional bolus AT injection.

Results: First, continuous AT infusion significantly improved 7-day survival compared to saline-infusion (65% vs. 29%, $p = 0.018$). Additionally, continuous AT infusion markedly increased survival vs. a single injection of AT (65% vs. 19%, $p = 0.003$). Continuous AT attenuated liver injury but not renal and lung injury. Furthermore, vascular leakage and inflammatory cytokine were suppressed only in the liver. Focusing on liver in CLP sepsis, we detected the highest accumulation of bacteria and thrombin production, the target of AT, in the liver at 48 h after CLP.

Conclusions: In summary, continuous AT infusion improved 7-day survival after abdominal sepsis. Continuous AT infusion attenuated vascular leakage, inflammation, and organ injury in the liver in late phase of CLP sepsis. Liver may be a critical site of intervention because bacteria accumulate there and induce thrombin generation.

SA-PO933

Urine Protein to Albumin Gap without Monoclonal Gammopathy

Matthias Bergmann, George J. Kavalam, Rucci Marcus C. Foo, Solab Chitrakar, Nathan H. Raines. *Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: The urine protein-to-albumin gap (UPAG) describes the difference between total urine protein excretion and urine albumin excretion. The UPAG is usually considered significant when less than 50% of the urine protein consists of albumin. If the UPAG is elevated, this may raise suspicion for monoclonal gammopathies such as multiple myeloma where increased immunoglobulin or light chain excretion in the urine results in proteinuria that is composed of a relatively smaller proportion of albumin. We present the case of a 61-year-old man with elevated UPAG without evidence of monoclonal gammopathies.

Case Description: A 61-year-old man with a past medical history of type 2 diabetes mellitus was admitted with endocarditis in the setting of *Staphylococcus aureus* bacteremia from cellulitis complicated by septic shock and multiple septic emboli involving the brain. He developed acute kidney injury (AKI) and required temporary hemodialysis. His renal function improved and creatinine normalized to 0.8 mg/dL. Urinalysis during the AKI was positive for blood and protein. After resolution of the AKI, hematuria resolved but proteinuria persisted. Urine protein quantification showed a UPCR of 3.2 g/g and a UACR of 533 mg/g, resulting in a UPAG of 2.5 g with albumin only accounting for 16.7% of the proteinuria. The results were confirmed with repeat testing. Urine protein electrophoresis (UPEP) showed multiple protein bands with albumin predominating but no monoclonal immunoglobulins identified. Serum fibrinogen was 565 mg/dL and CRP 122 mg/L. Total serum protein was 6.8 g/dL with hypoalbuminemia of 2.2 g/dL. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia with elevated IgG 2332 mg/dL and IgA 677 mg/dL, decreased IgM 38 mg/dL, and no monoclonal immunoglobulins identified.

Discussion: A 61-year-old man who was admitted with endocarditis was incidentally found to have a UPAG without monoclonal pattern on UPEP. CRP, fibrinogen, and polyclonal IgG and IgA were elevated in the setting of endocarditis. The UPAG is best explained by inflammatory proteins released in the setting of the systemic infection. While a UPAG is commonly considered to be an indicator of monoclonal gammopathies, this case illustrates that inflammatory proteins may reach quantities that can lead to a significant UPAG when excreted in the urine.

SA-PO934

Confounded Magnetic Resonance Imaging Contrast Agent Exposures and Gadolinium Retention in Organs

Karol Dokladny,[1,2] Joshua Deaguero,[1,2] Abdul Mehdi S. Ali,[3] Ian Henderson,[2] James H. Degnan,[3] G. P. Escobar,[1,2] Brent Wagner.[1,2] *[1]University of New Mexico Health Sciences Center, Albuquerque, NM; [2]Kidney Institute of New Mexico, Albuquerque, NM; [3]University of New Mexico, Albuquerque, NM.*

Background: In 2006, gadolinium-based contrast agents (GBCAs) were linked to nephrogenic systemic fibrosis, a rare but highly disabling and often fatal condition. GBCAs can also induce kidney injury and fatal encephalopathy. The US Food and Drug Administration ordered a black box warning for all gadolinium-based contrast agents. There are two general classes of GBCAs: linear (e.g., Omniscan) and macrocyclic (Dotarem). Our previous research indicated that prior GBCA exposures influence gadolinium retention in the kidney or liver. The present study aimed to test whether a similar paradigm holds for other vital organs.

Methods: 18 male mice were randomized to five experimental groups: (1) saline-treated controls; gadolinium-based contrast agent-treated (2) Omniscan (OMN), (3) Dotarem (DOT), or in combination (4) OMN (1 week) followed by DOT administration for 3 weeks or (5) DOT (1 week) followed by OMN treatment for 3 weeks. Per our established protocols, saline or contrast agents were administered via intraperitoneal injections 5 days a week for 4 weeks. Lung, heart, adipose tissue, and skeletal muscle tissue were excised and snap-frozen in liquid nitrogen. On average, 15 mg of tissue were digested in nitric acid, and gadolinium concentrations were quantified using PerkinElmer NexION 5000 inductively coupled plasma mass spectrometry (ICP/MS) with a detection limit of 0.01 ppb.

Results: A 4-week treatment of OMN or DOT alone or in combination (OMN-DOT or DOT-OMN) resulted in a significant accumulation of gadolinium in the lung and heart. Gadolinium deposition was equal for Omniscan, OMN-DOT, and DOT-OMN. No differences existed among any group for Zn or P, regardless of the organ.

Conclusions: Gadolinium is retained in the heart and lung for linear, macrocyclic, and confounded agent exposure. Adipose retains macrocyclic agents. Skeletal muscle retains linear agents. Our study is underpowered with respect to the other experimental groups for adipose and skeletal muscle. Future studies are required to determine those tissue-specific differences.

SA-PO935

Interaction of Gadolinium-Based Contrast Agents with Endogenous Compounds: Effect on Stability

Ian Henderson,[1] Karol Dokladny,[2,1] G. P. Escobar,[2,1] Joshua Deaguero,[2,1] Brent Wagner.[2,1] *[1]Kidney Institute of New Mexico, Albuquerque, NM; [2]University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Gadolinium-based contrast agents (GBCAs) are widely used in contrast-enhanced magnetic resonance imaging (MRI), improving tissue discrimination by increasing proton relaxation. GBCA complications can be catastrophic, including nephrogenic systemic fibrosis (NSF) and gadolinium encephalopathy. The stability of the metal-ligand bond correlates with gadolinium retention *in vivo*, with stabilities generally expressed in terms of equilibrium constants and kinetic stability. Equilibrium constants do not account for a physiologic milieu and endogenous compounds. We investigated two endogenous compound-mediated mechanisms of GBCA decomposition *in vivo*: associative ligand exchange (direct attack) by oxalic acid (OA) and decomposition through protein-ligand interaction.

Methods: GBCAs reacting with OA were followed spectrophotometrically at 605 nm. We measured precipitation rates. We characterized the products using elemental analysis, thermogravimetric analysis (TGA), and X-ray photoelectron spectroscopy (XPS). Contrast agents were incubated with bovine serum albumin (BSA) for 4 days. We analyzed the nanoparticulate product using transmission electron microscopy and X-ray energy-dispersive spectroscopy.

Results: Linear agents (gadodiamide and gadobenate dimeglumine) reacted with OA, forming gadolinium oxlate. Macrocyclic GBCAs (gadoteridol, gadoteric acid, and gadopiclenol) underwent two-step ligand exchange upon exposure to OA with a wide range of rates, ranging from k ~ 10-2 (gadoteridol) to <<10-6 (gadopiclenol). The presence of BSA (4%) resulted in an increased rate. Incubation of GBCAs with BSA over 4 days formed nanoparticles with a similar morphology to those found in pathologic gadolinium retention.

Conclusions: Oxalic acid, a biologically endogenous compound, can directly attack GBCAs, with linear contrast agents being particularly vulnerable. Protein enhances the rate of gadolinium oxalate formation. Simple protein/ligand interactions destabilize GBCAs. We can detect gadolinium-rich nanoparticles in vitro.

SA-PO936

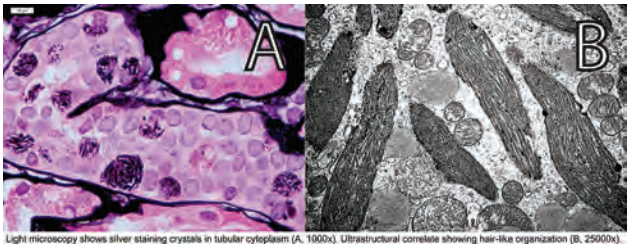
Impaired Kidney Function with Renal Tubular Vacuolization and Paracrystals in Adult Refsum Disease: A Case Report

Chen Yu (Jamie) Lee,[1] Mark Elliott,[3] Anna Lehman,[4] Susanna A. Mcrae,[1,2] Maziar Riazy.[1,2] *[1]Department of Pathology, University of British Columbia, Vancouver, BC, Canada; [2]Department of Pathology, St. Paul's Hospital, Vancouver, BC, Canada; [3]Division of Nephrology, University of British Columbia, Vancouver, BC, Canada; [4]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada.*

Introduction: Classic, or adult, Refsum disease (ARD) is a rare peroxisomal disorder characterized by an inability to metabolize the fatty acid phytanic acid (PA). Accumulation of PA leads to polyneuropathy and potentially lethal cardiac arrhythmias. Renal impairment is rarely seen and there is a paucity of information on the histopathology. We present a case of renal impairment due to tubular involvement by ARD.

Case Description: A 55-year-old Fijian female with genetically proven ARD presented with a reduced eGFR without proteinuria or overt tubular dysfunction. Her past medical history includes ARD-related retinitis pigmentosa, DM2, recent MI with PCI, and chronic knee osteoarthritis. Physical examination showed shortened toes consistent with ARD. Serum PA at diagnosis was 180 mcg/mL (ULN 3 mcg/mL). A renal biopsy was performed to assess for diabetic nephropathy versus another cause for her renal impairment. The biopsy showed diffuse vacuolization of renal tubular epithelium, with rare foci of intracytoplasmic crystals (Figure 1A). Ultrastructurally, these crystals were electron dense with unusual parallel linear arrays (or 'paracrystalline formation') (Figure 1B). She continues to be very adherent to her low PA diet and avoidance of fasting, but despite this has experienced a progressive decline in her eGFR. Her PA level remains elevated at 270 mcg/mL.

Discussion: To the best of our knowledge, this is the first description of intracytoplasmic crystals on light microscopy in ARD. The etiology and pathologic effects of these crystals are not yet known, but they may share features with other crystalline nephropathies. This case provides evidence to support renal function monitoring in ARD, which is currently not suggested by the literature. The morphology of the intracytoplasmic crystals are rather distinct but subtle and can be overlooked. Nephropathologists should be vigilant for additional findings in the setting of tubular epithelial abnormalities without a known explanation. Limiting dietary PA is the first-line treatment of choice but may not be sufficient to prevent complications.



Light microscopy shows silver staining crystals in tubular cytoplasm (A, 1000x). Ultrastructural correlate showing hair-like organization (B, 25000x).

SA-PO937

Pregnancy-Related Complications and Snake Bites Are Leading Causes of Renal Cortical Necrosis in India

Anila A. Kurien,[1] Jansi Prema K.S,[1] Malathi Cv,[1] Tiffany Caza.[2] *[1]Renopath Center for Renal and Urological Pathology Pvt Ltd, Chennai, India; [2]Arkana Laboratories, Little Rock, AR.*

Background: Renal cortical necrosis is present in 1-3% cases of severe acute kidney injury and <1% of kidney biopsies. Due to its relative rarity, potential etiologies are incompletely understood and studies are limited to small series. Here, we present the largest kidney biopsy series of renal cortical necrosis from a study of 227 patients who underwent native kidney biopsy in India.

Methods: Patients who underwent native kidney biopsy from 2013-2023 with a diagnosis of cortical necrosis were identified from the renal pathology archives at the Renopath Center for Renal and Urological Pathology in Chennai, India. Demographics, clinical data, and histopathology were reviewed.

Results: A total of 227 patients with renal cortical necrosis were identified. The mean patient age was 32.2 ± 14.2 years. There was female predominance (75.3%). Of the 227 cases, 150 had concurrent thrombotic microangiopathy (TMA, 66.1%), one had membranous glomerulopathy (0.4%), and one biopsy had a concurrent abscess (0.4%). A known etiology for cortical necrosis was identified in 170 cases (74.9%). For those with known etiology, 95 were due to pregnancy-related complications (55.9%), 32 from snake bites (19.8%), 13 from acute pancreatitis (7.6%), 8 from sepsis (4.7%), 5 from NSAID-associated papillary necrosis (2.9%), 5 from ingestion of other substances (2.9%), 4 from other animal and insect bites (2.4%), 3 due to non-pregnancy-related post-op complications (1.8%), 2 due to obstruction (1.2%), 2 due to connective tissue disorders (scleroderma and lupus, 1.2%), and one from venous thrombosis. A similar distribution of diagnoses was seen in patients with and without concurrent TMA, with pregnancy-related complications comprising the majority of cases.

Conclusions: Pregnancy-related complications and snake bites were the leading etiologies of renal cortical necrosis from a large kidney biopsy series in India. The majority of cases demonstrated concurrent thrombotic microangiopathy.

SA-PO938

Epidemiology of Biopsy-Confirmed Kidney Disease: A Single-Practice Study in South Texas

Klarissa A. Saldivar, Umar Khan, Julio P. Zavala Georffino. *University of the Incarnate Word, San Antonio, TX.*

Background: Prevalence of biopsy-proven kidney disease in the United States (US) is fairly limited, especially in Hispanic populations who experience a large burden of kidney disease. This study is aimed to determine the patterns and epidemiological features of kidney disease in a predominantly hispanic population of South Texas.

Methods: Using data from a single nephrology practice in Laredo, TX, we identified patients who underwent kidney biopsies from April 2014 to April 2024. Retrospective analysis was done to obtain demographics, histopathologic diagnosis, and clinical/laboratory data. Results were stratified by age, gender, race/ethnicity, and comorbidities to identify epidemiologic patterns.

Results: Of 260 patients, transplant biopsies and those with insufficient data were excluded, leaving 240 patients for analysis. The median age was 50 years, with 57% female patients. Racial/ethnic demographics included 97% Hispanic patients. Secondary Glomerular Diseases (SGD) were most common with prevalence of 50%, followed by Primary Glomerular Diseases (PGD) (38%) and Tubulointerstitial Diseases (TID) (12%). Diabetic kidney disease (DKD) (*n*=94, 39%) and lupus nephritis (LN) (*n*=17, 7%) were the most common SGD, whereas IgA nephropathy (IgAN) (*n*=17, 7%), AA amyloidosis (*n*=13, 5), membranous nephropathy (MN) (*n*=11, 5%), and focal segmental glomerulosclerosis (FSGS) (*n*=11, 5%) were the most common PGD. The most common TID was acute tubular necrosis (ATN) (*n*=20, 8%). Of patients with FSGS, MCD, and LN ≥ 70% were female. Of patients with amyloidosis, FSGS, Thrombotic microangiopathy (TMA), and LN > 85% were ≤ 50 years of age.

Conclusions: Our study describes the prevalence of biopsy-proven kidney diseases in a Hispanic population. This provides a foundation to better understand patterns for kidney disease in a population underrepresented in literature, and contributes to the current lack of kidney biopsy data in the US.

	Total N(%)	Female N(%)	Median Age (y)	Avg Serum Cr mg/dL
PGD	**90 (38)**	**51 (57)**	**46**	**4.0**
IgAN	17 (7)	10 (59)	48	2.9
AA Amyloidosis	13 (5)	6 (46)	36	3.1
MN	11 (5)	5 (45)	32	1.8
FSGS	11 (5)	9 (82)	43	2.6
MCD	10 (4)	7 (70)	67.5	2.6
TMA	7 (3)	2 (29)	40	6.0
Misc	21 (9)	12 (57)	48	5.2
SGD	**120 (50)**	**72 (60)**	**51**	**3.9**
DKD	94 (39)	52 (55)	52.5	3.9
LN	17 (7)	15 (88)	29	2.1
Misc	9 (4)	5 (56)	69	4.1
TID	**30 (12)**	**13 (43)**	**52**	**5.1**
ATN	20 (8)	8 (40)	58	5.0
AIN	6 (2)	2 (33)	51	5.9
Misc	4 (2)	3 (75)	39.5	6.0

SA-PO939

Comparative Efficacy and Safety of Kidney Biopsies Performed by Nephrologists vs. Interventional Radiologists: A Study in Two Level III Hospitals in Lima, Peru

Hemily Z. Chimoy,[1] Juan O. Lluncor.[2] *[1]Hospital Nacional Alberto Sabogal Sologuren, Callao, Peru; [2]Hospital Nacional Dos de Mayo, Lima, Peru.*

Background: Renal biopsy is an invasive procedure. Formerly, this procedure was exclusive to nephrologists, but currently it is also performed by interventional radiologists. An adequate sample is crucial for the diagnosis, prognosis and treatment of the renal disease. Also, it is important to avoid associated complications.

Methods: All renal biopsies was performed from January to December 2023 in two level III hospitals in Lima, Peru. In the first hospital, renal biopsies were performed exclusively by interventional radiologists without the involvement of nephrologists, while in the second hospital, they were performed by nephrologists (real-time ultrasound guidance or marking point). Quality of the sample was evaluated according to the number of glomeruli reported in the analysis. Pre-biopsy laboratory variables, post-biopsy hemoglobin control, post-renal biopsy events and/or complications were compared as safety variables of the procedure.

Results: A total of 93 renal biopsies were reported during this period (47 renal biopsies performed by interventional radiologists and 46 by nephrologists). The efficacy of the procedure was evaluated by the quality of the sample. The mean number of glomeruli in the first group was 22, and in the second group, it was 18, with no significant difference found between the two groups ($p = 0.343$). No relationship was found between the number of reported glomeruli and any variables such as age, urea, creatinine, pre-procedure hemoglobin, longitudinal diameter, and kidney parenchyma, except for the anteroposterior diameter of the kidney ($p = 0.03$). In terms of safety, a significant difference was found for the presence of post-procedure pain ($p < 0.01$) and renal hematoma ($p = 0.048$) in the group of renal biopsies performed by interventional radiologists. There was also no significant difference in the variation of pre- and post-procedure hemoglobin levels in both groups.

Conclusions: This study demonstrated that the nephrologist-performed biopsies are equally effective and often safer than those performed by radiologists. Considering that the nephrologist is the one who has the initial contact with the patient and provides follow-up for the underlying condition throughout the treatment, it is important not to lose procedural skills for the benefit of our patients.

SA-PO940

Low Prevalence of Class 1 Indications for Coronary Revascularization in Patients Undergoing Prekidney Transplant Screening for Coronary Disease

Avantika Israni, Bronya L. Sandorffy, Celina S. Liu, Daniela I. Fraticelli Ortiz, Haley Gross, Joey Nicholson, Miri Cazes, Qandeel H. Soomro, David M. Charytan. *New York University, New York, NY.*

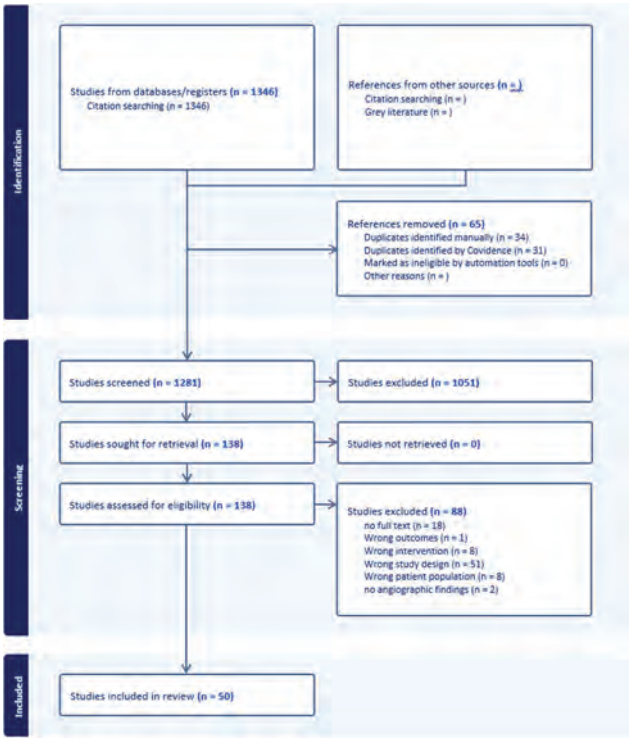
Background: CVD is the most common cause of morbidity and mortality in kidney transplant recipients. Screening for coronary disease is to reduce the risk of perioperative cardiovascular complications, long term cardiovascular morbidity and mortality is frequently required but coronary intervention has not been shown to be beneficial except in complex coronary disease. The likelihood of finding significant coronary artery disease and benefit of routine pre-transplant screening is uncertain.

Methods: We performed a systematic review and meta-analysis to quantify the frequency of detecting significant coronary lesions for which--there are AHA Class 1 indications for revascularization: a) >50% left main stenosis; or b) multi-vessel disease

with EF < 35%. Medline & Embase were searched to identify manuscripts reporting the results of pre-transplant screening published between 1998 and 2024. Screening and data collection was performed by 4 independent authors with disagreements resolved by consensus. Quality assessment was performed using the Joanna Briggs Institute scale. This review was registered with PROSPERO.

Results: We identified 1281 studies, 148 required full text review out of which 50 met eligibility criteria. We extracted data from 50 studies, 17 studies did not report ejection fraction. The mean prevalence of a class 1 indication across these studies was 5.35 %. Analysis of the number of patients with left main disease, triple vessel disease (without an EF < 35%) will be updated.

Conclusions: Identification of class I indications for revascularization during pre-transplant coronary screening is rare and routine screening may not be warranted.



SA-PO941

Accuracy of Myocardial Perfusion Imaging (MPI) in Predicting Post-transplant Cardiovascular Events among Asymptomatic Diabetic Kidney Transplant Candidates

Bilal Mohsin, Yasir Alfi, Shahad Alaydarous, Naief M. Alhowaiti, Nasser O. Odah, Wael T. Habhab. *King Faisal Specialist Hospital and Research Centre - Jeddah, Jeddah, Saudi Arabia*.

Background: Cardiovascular risk assessment is crucial prior to kidney transplantation especially in diabetic patients as nearly 6.6% of recipients have a major adverse cardiovascular event (MACE) within 3 years. This study aims to evaluate the predictive role of MPI among asymptomatic diabetic candidates for post-kidney transplant cardiovascular events.

Methods: This is a retrospective, single center study. We included adult diabetic patients who underwent MPI prior to kidney transplant with a post kidney transplant follow up of 2 years. The primary outcome was a composite of death, ACS, coronary revascularization, hospitalization for heart failure (ADHF), and CVA. These were also studied individually as secondary outcomes. Sensitivity, specificity, PPV and NPV for MPI in detecting obstructive CAD were evaluated in candidates that underwent pre-transplant coronary angiography.

Results: Out of 121 candidates, 76 had normal-MPI and 45 had abnormal-MPI. Primary composite outcome was seen in 9 pateints (11.8%) in the normal-MPI group and in 4 (8.9%) in the abnormal-MPI group. More patients in abnormal-MPI group had ADHF (not statistically significant). Out of the 4 normal-MPI patients that had ACS, 3 required post-transplant revascularization, 2 of them did not undergo pre-transplant coronary angiography. In normal-MPI patients, 55 underwent pre-transplant coronary angiography, 8 of them had obstructive CAD. MPI had a sensitivity, specificity, NPV and PPV of 60%, 59.7%, 85% and 27.9% respectively in identifying obstructive CAD as compared to pre-transplant coronary angiography.

Conclusions: Diabetic candidates with abnormal-MPI had similar incidence of mortality and MACE post-kidney transplant as compare to normal-MPI patients. MPI had a NPV of 85% in ruling out obstructive CAD. The predictive role of MPI pre kidney transplant remains unclear and needs further study.

	Normal-MPI (n=76)		Abnormal MPI (n=45)		p-value*
	(n)	(%)	(n)	(%)	
Primary Composite Outcome	9	11.8	4	8.9	0.765
Death	3	3.9	0	0	0.293
ACS	4	5.2	3	6.7	0.710
Revascularization	3	3.9	0	0	0.293
ADHF	1	1.3	4	8.9	0.063
CVA	1	1.3	0	0	0.628

* Significance of Fisher's Exact test

SA-PO942

Prognostic Role of Hypertension Remission in Kidney Transplant Recipients with Pretransplant Hypertension

Minji Kim, Kyungho Lee, Junseok Jeon, Jung eun Lee, Wooseong Huh, Hye Ryoun Jang. *Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*.

Background: Hypertension is commonly associated with advanced chronic kidney disease and end-stage kidney disease. Kidney transplantation (KT) in patients with pre-transplant hypertension has the potential to lead to remission of hypertension. However, the remission rate of hypertension after KT and its prognostic impact on KT outcomes remain unknown.

Methods: KT recipients (2006–2015) who had pre-transplant hypertension were identified and categorized into two groups based on their post-KT hypertension status: "persistent hypertension" and "hypertension remission", using data from the Health Insurance Review & Assessment Service and Korean National Health Insurance System. Cox proportional hazard analyses were performed for death-censored graft failure and all-cause mortality.

Results: A total of 3,109 (27%) among 11,342 KT recipients with pre-transplant hypertension experienced hypertension remission after KT. The patients who experienced hypertension remission had lower prevalences of delayed graft function and major comorbidities including diabetes, ischemic heart disease, and stroke, compared to those with persistent hypertension. Graft failure (incident rate [IR], 6.8 vs 12.0) and mortality rates (IR 5.5 vs 11.1) were both lower in the hypertension remission group (per 1,000 person-years, log-rank P <0.001 for both) than the persistent hypertension group. Hypertension remission was associated with 0.58-fold (95% confidence interval 0.48–0.72) and 0.50-fold (0.40–0.62) lower risks for graft failure and all-cause mortality, respectively, in unadjusted analyses. The adjusted hazard ratio of hypertension remission was 0.59 (0.49–0.73) for graft failure and 0.59 (0.48–0.73) for mortality compared to the persistent hypertension group after adjusting multiple covariates. There were significant interactions with sex for graft failure (stronger protection in females, P for interaction=0.045) and with diabetes status for mortality (weaker protection in recipients with diabetes, P for interaction=0.033).

Conclusions: Kidney transplantation can lead to hypertension remission in a substantial number of patients. Remission of pre-transplant hypertension was associated with better graft survival as well as overall patient survival. We suggest that hypertension remission can be used as an indicator of favorable outcomes in KT recipients.

SA-PO943

Cardiorenal Outcomes, All-Cause Mortality, and Arterial Stiffness Parameters in Stable Kidney Transplant Recipients

Zbigniew Heleniak,[1] Alicja Debska-Slizien,[1] Fabian Halleck,[2] Klemens Budde.[2] *[1]Gdanski Uniwersytet Medyczny, Gdansk, Poland; [2]Charite Universitatsmedizin Berlin, Berlin, Germany*.

Background: The objective of the study was to evaluate the predictive value of pulse pressure (PP) and carotid-femoral pulse wave velocity (cfPWV), in relation to cardio-renal outcomes and all-cause mortality in stable renal transplant recipients (RTRs).

Methods: 344 stable RTRs with a median age of 52.7 years, were enrolled. At baseline PP and cfPWV were measured during a routine visit in RTRs without cardiac symptoms and heart failure exacerbation. The follow-up was 54 months.

Results: The mean creatinine level, the value of estimated glomerular filtration rate, and transplantation vintage were 1.47mg/dl, 50.5ml/min/1.73m$^{2.}$ and 73 months, respectively. The median PP and cfPWV were 55mmHg and 7.9m/s respectively. Cut-off values for all-cause mortality, CV events, and renal outcomes were: PP 60, 68, 60mmHg cfPWV 9.90, 8.0, and 10.0 m/s respectively. During the follow-up, the likelihood of patient survival, and cardio-renall outcomes based on PP and cfPWV values (established using the Youden method) were shown in Figures 1 and 2.

Conclusions: Both PP and cfPWV have significant predictive ability for mortality and renal events outcomes in RTRs. Only the cfPWV value was predictive in terms of the incidence of CV events, significantly.

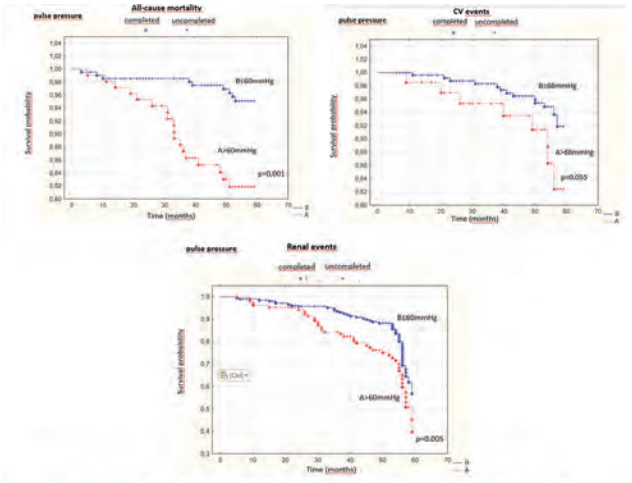


Figure 1 The predictive role of PP in terms of all-cause mortality, cardiovascular (CV) and renal events.

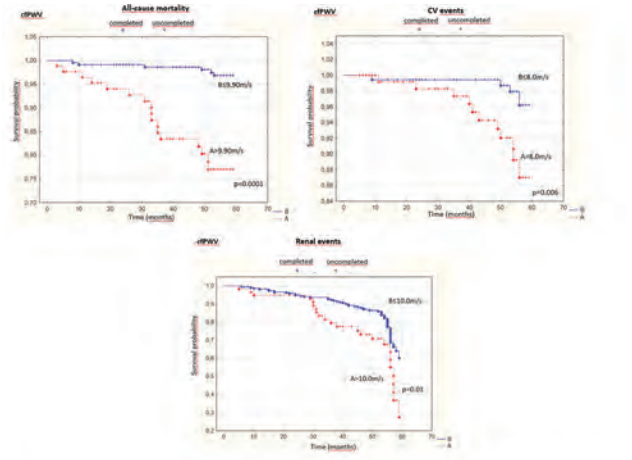


Figure 2 The predictive role of carotid-femoral pulse wave velocity (cfPWV) in terms of all-cause mortality, cardiovascular (CV) and renal events.

SA-PO944

Pulse Pressure: A More Relevant Risk Factor for Graft Outcomes in Deceased Donor Kidney Transplantation than Living Donor Transplantation

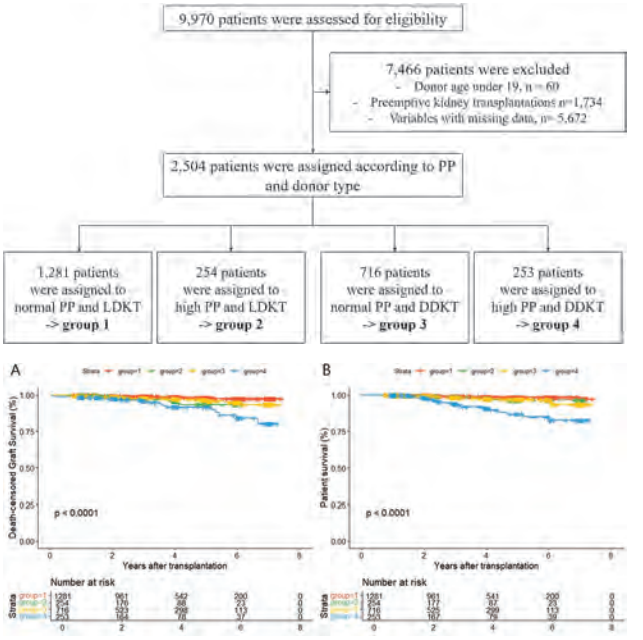
Ji Eun Kim. KOTRY Study Group. *Seoul St. Mary's hospital, Seoul, Republic of Korea.*

Background: Pulse pressure (PP) is a hemodynamic indicator associated with arterial stiffness. However, its role in kidney transplant remains unclear, especially in the context of living donor kidney transplantation (LDKT) versus deceased donor kidney transplantation (DDKT). This study aims to investigate the impact of PP according to donor type in kidney transplant.

Methods: A total of 2,504 kidney transplant patients were analyzed between 2014 and 2022 from the Korea Organ Transplantation Registry database. PP was calculated from systolic and diastolic blood pressure at 1-year post-transplantation. High PP is defined as exceeding 60 mmHg. Patients were stratified into four groups based on PP and donor type: LDKT with normal/high PP, and DDKT with normal/high PP. Primary outcomes were graft loss and mortality over an 8-year period.

Results: Among the kidney transplant recipients, only the group with high PP in DDKT represented markedly higher graft loss (HR 2.260, 95% CI 1.183-4.317, p=0.014) and mortality (HR 2.202, 95% CI 1.098-4.417, p=0.026). Conversely, no significant differences in graft loss or mortality were observed among the other groups. Furthermore, high PP with DDKT group maintained consistently lower estimated glomerular filtration rates throughout the 5-year follow-up period. Additionally, the DDKT group exhibited significantly higher PP compared to the LDKT group at 1-year post-transplantation, with a higher prevalence of high PP in DDKT.

Conclusions: In DDKT, elevated PP is associated with inferior graft survival and increased mortality rates, whereas LDKT recipients show a lesser susceptibility to the effects of PP. When considering higher prevalence and impact of elevated PP in DDKT, it essentially should be considered a crucial risk factor in DDKT.



SA-PO945

Major Cardiovascular Events and Hyperuricemia as an Effect-Modulating Factor in Kidney Transplant Recipients

Inese Folkmane.[1,2] [1]*Faculty of Medicine, University of Latvia, Riga, Latvia;* [2]*Pauls Stradins Clinical University Hospital, Centre of Nephrology, Riga, Latvia.*

Background: Major cardiovascular events (MACE) remain the leading cause of morbidity and mortality in patients with kidney transplants (KT). The risk for MACE is affected by the accumulation of a wide range of traditional and transplant-associated nontraditional cardiovascular (CV) risk factors (RFs). In the last years, studies have shown that many other cardiovascular RFs may be involved, including hyperuricemia (HU).

Methods: We investigated the association between CV risk factors related to KT with MACE, and their effect modification by HU in a cohort of 545 patients transplanted between 2008 to 2019. Univariate and multivariate Cox proportional hazards regression analyses were performed to determine the RFs associated with MACE. To investigate the possibility of effect modification of the uric acid (UA) for the associations of independent factors with MACE, patients were stratified as having a low (< 6 mg/dL), normal (6-7 mg/dL), high (7-8 mg/dL) and very high (> 8 mg/dL) UA level.

Results: MACE occurred in 145 of 545 (26.6 %) KT recipients. Most of the independent variables investigated in this study were univariately related to the MACE. On the multiple logistic regression main model that described 62.1% of changes in MACEs, the most prominent factors associated with MACE were previous CV event (OR = 70.6, 95% CI 24.9 – 200.1), left ventricular hypertrophy (LVH) (OR = 12.6, 95% CI 2.74 – 58.3), HU treatment (OR = 4.29, 95% CI 2.44 – 7.57), anemia (OR = 5.32, 95% CI 2.89 – 9.8). Effect modification by hyperuricemia showed that independent factors associated with MACE were age (OR = 1.03, 95% CI 1.03 – 1.09), previous CV events (OR = 41.70, 95% CI 13.62 – 127.64), LVH (OR = 15.33, 95% CI 2.02 – 116.60), HU treatment (OR = 2.45, 95% CI 1.31 – 4.59) and anemia (OR = 5.36, 95% CI 2.75 – 10.45). Effect modification by very high levels of UA showed that HU treatment was not associated with MACE either for those with or for those without very high levels of UA. The variables that were significantly associated with MACE for those with very high UA were previous CV events (OR = 72.82, 95% CI 9.09 – 583.34) and anemia (OR = 6.46, 95% CI 2.46 – 16.95).

Conclusions: HU was found to be an effect-modifying factor for MACE, especially in association with RFs such as age, previous CV events, LVH, and anemia.

SA-PO946

Kidney Transplant Candidates with Reduced Ejection Fraction: Risky Business or Not?

Alice H. Won, Ashwin Kelkar, Maria Karas, Darshana M. Dadhania. New York Presbyterian-Weill Cornell Medicine. *Weill Cornell Medicine, New York, NY.*

Background: Heart failure with reduced ejection fraction (HFrEF) is prevalent among patients with advanced chronic kidney disease. Data remains limited on whether HFrEF at the time of transplant is associated with an increased risk of graft failure and mortality. In this study, we sought to compare the patient and graft survival between the cohorts of patients with or without HFrEF undergoing kidney transplantation (KTx).

Methods: In this retrospective case-control study, we performed a 1:2 matched cohort analysis of 103 KTx patients with pre-transplant EF ≤45% (HF cohort) and 206 patients with EF >45% (control cohort), transplanted between January 2011 - December 2021. Two cohorts were matched based on age, sex, donor type, and transplant year. Simultaneous liver-kidney transplants were excluded.

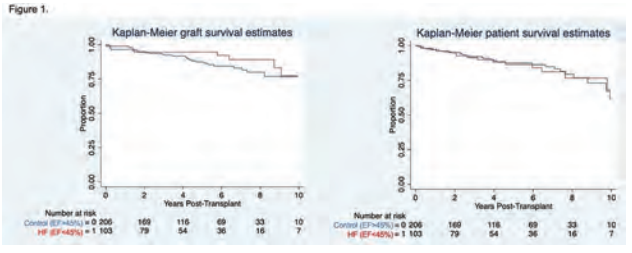
Results: Baseline characteristics were similar except pre-emptive transplant and thymoglobulin induction were less frequent in the HF cohort. Despite increased delayed graft function (DGF) in the HF cohort, there was no statistically significant difference in the mean creatinine levels at 3-months (1.51 vs. 1.56) and 1-year (1.41 vs. 1.57) post-KTx between the control and HF cohorts (Table 1). At a mean follow-up period of 4.7 years, the two cohorts demonstrated similar overall graft survival and patient survival (Figure 1), with no statistically significant difference in the rates of graft loss due to acute rejection or death due to cardiovascular cause (Table 1).

Conclusions: In our investigation, the graft and patient survival of control and HF cohorts were similar and comparable to the published ten-year KTx outcomes (PMID:26285695). Our data suggests low EF alone should not be a contraindication to KTx and is associated with acceptable long-term survival.

Table 1.

Patient Baseline Characteristics	Control cohort (n=206)	HF cohort (n=103)	p value
Average Age (yr.)	55.5	55.7	0.99
Male sex	157 (76.2%)	76 (73.8%)	0.07
Ethnicity			0.41
White	46%	43%	
Black	23%	28%	
Other / Declined	23%	22%	
Asian	8%	7%	
Repeat transplant	30 (15.6%)	13 (12.6%)	0.64
Pre-emptive transplant	65 (31.6%)	12 (11.7%)	0.0001
Living donor kidney	124 (60.2%)	55 (53.4%)	0.25
Immunosuppression induction			
Thymoglobulin	174 (84.5%)	47 (45.6%)	<0.0001
Simulect	31 (15.0%)	53 (51.5%)	
Left ventricular ejection fraction (LVEF), pre-transplant , mean (SD)	61.7% (6.2)	37.5% (6.8)	<0.0001
Minimum LVEF, Maximum LVEF	47.0%, 80.0%	15.0%, 45.4%	
25% percentile-, Median-, 75% percentile- LVEF	57%, 60%, 66%	35%, 40%, 43%	
Post-transplantation Clinical Outcomes	**Control cohort (n=206)**	**HF cohort (n=103)**	**p value**
Delayed graft function (DGF)	38 (18.4%)	28 (27.2%)	0.03
Hospitalization within 1 year	109 (52.9%)	55 (53.4%)	0.45
Acute rejection within 1 year	15 (7.3%)	14 (13.6%)	0.22
Total graft loss	29 (14.0%)	10 (9.7%)	0.36
Graft loss due to acute rejection	6 (2.9%)	1 (1.0%)	0.43
Total deaths	35 (17.0%)	16 (15.5%)	0.25
Death due to cardiovascular cause	7 (3.4%)	5 (4.9%)	0.54
Mean creatinine at 3-months (mg/dL), mean (SD)	1.51 (0.67); n=197	1.56 (0.68); n=100	0.44
Mean creatinine at 1-year (mg/dL), mean (SD)	1.41 (0.47); n=197	1.57 (0.97); n=95	0.25

Figure 1.



SA-PO947

Hurry Up and Wait: Modeling Kidney Transplant Wait Times under Wait-List Expansion Scenarios

Jillian Caldwell, Xingxing S. Cheng, Glenn M. Chertow, Jeremy D. Goldhaber-Fiebert. *Stanford University School of Medicine, Stanford, CA.*

Background: Kidney transplantation offers survival benefits and superior quality of life compared with maintenance dialysis for patients with end-stage kidney disease (ESKD). While over 500,000 Americans currently receive dialysis, deceased donor transplantation is limited to approximately 20,000 patients annually. Expanding access to kidney transplant is a top priority of public policy. Strategies involve adding more patients to the waitlist and increasing organ supply. However, the effect of these interventions on transplant wait times has not been explored.

Methods: We constructed a decision analytic Markov model to simulate a cohort of approximately 660,000 patients with chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR) <20ml/min and ESKD on dialysis over a ten-year period. We then used Kaplan-Meier survival analysis to estimate median wait time by counting time on the waitlist until transplantation, censoring for waitlist removal and death. We compared current wait times (status quo) to three strategies: 1) waitlist expansion by 10%, 2) waitlist expansion by 50%, and 3) waitlist expansion by 50% combined with a 50% reduction in the kidney nonuse rate.

Results: Under the status quo, median wait time was 48.2 months (4.01 years). Under the 10% expansion strategy, wait times increased to 53.1 months (4.43 years; + 5.0 additional months). Under the 50% expansion strategy, median wait times increased substantially to 74.2 months (6.2 years; + 26.1 additional months). 50% waitlist expansion combined with 50% reduction in the kidney nonuse rate attenuated the increase in wait times to 67.5 months (5.6 years; + 19.4 additional months) and resulted in 2,252 additional kidney transplants.

Conclusions: Alternate strategies prolonged the median time to kidney transplant by 5 to 26 additional months depending on the degree of expansion and presence of additional organ supply. Efforts to expand access to transplantation without concomitant increases in organ supply would likely result in longer wait times. Systems-level efforts to increase organ supply and enhance allocation efficiency should be prioritized in conjunction with measures which substantially add to the transplant waitlist.

Funding: NIDDK Support, Private Foundation Support

SA-PO948

Barriers to Obesity Management in Kidney Transplant Candidates

Linda-Marie U. Lavenburg,[1,2] Harry Morford,[2] Sanjana S. Kamat,[3] Michele Molinari,[2] Susan A. Stark,[2] Chethan M. Puttarajappa.[1,2] *[1]University of Pittsburgh, Pittsburgh, PA; [2]UPMC, Pittsburgh, PA; [3]Conemaugh Memorial Medical Center, Johnstown, PA.*

Background: Obesity poses significant barriers to kidney transplantation (KT). Transplant waitlisting is 30-70% lower for candidates with body mass index (BMI; kg/m^2) ≥ 40 compared to BMI ≥18.5 to <25. Although no consensus exists, KT centers often require candidates to have a BMI <35-40 prior to KT. KT candidates are often referred to weight loss programs (WLPs) (e.g., dietitian support, medical weight management, or bariatric surgery) but patients' acceptance for WLP referral and their subsequent follow through are unknown.

Methods: Through a quality improvement project, patients with BMI>43 referred for KT evaluation at our center were offered referral to WLP. A proportion of patients accepting referral and those eventually contacting WLP were evaluated. Differences in patient characteristics among those that accepted vs declined referral and among those that contacted vs did not contact a WLP were evaluated using descriptive statistics and multivariable logistic regression.

Results: Cohort had 59 patients with a median age of 57 years (IQR 49-65), 49% were male, 44% were Black or other race and 56% White, 79% were on dialysis, and 53% were from high social distress areas (area deprivation index ≥80). Of 59 patients, 30 patients (50.8%) accepted referral to a WLP but only 9 contacted WLP. Patients accepting referral had a higher median (IQR) BMI [47 (45-50) vs 45 (41-46); p=0.002] and resided closer to the KT center [20 (3-41) vs 48 (17-67) miles; p=0.010]. In multivariable models, referral acceptance decreased 2% with each mile away from KT center (OR 0.98; 95% CI: 0.96-1.00) and increased by 22% (OR 1.22, 95%CI: 1.03-1.45) with every 1 unit increase in BMI. Among patients accepting referral, every 1 year increase in age reduced odds of contacting WLP by 17% (OR 0.83, 95%CI: 0.74-0.96).

Conclusions: A large share of KT candidates with obesity do not establish care with WLPs. Increasing age and distance to KT center were major barriers. Efforts aimed at obesity management in KT should consider these barriers. WLPs integrated within KT programs may overcome barriers to establishing care with WLPs. Future steps in this study will compare weight trajectories, transplant waitlisting and receipt of a kidney transplant between patients who accepted vs declined WLP referrals.

Funding: NIDDK Support, Private Foundation Support

SA-PO949

Expedited Main Obstacles of Prekidney Transplant Workup: A Quality Improvement Study

Abdelrahman Elsebaie,[1] Natalie Witton,[2] Wilma M. Hopman,[1,2] David C. Holland,[1,2] M. Khaled Shamseddin.[1,2] Kingston Kidney Transplant Program (KKTP). *[1]Queen's University, Kingston, ON, Canada; [2]Kingston Health Sciences Centre, Kingston, ON, Canada.*

Background: Failure to complete a comprehensive pre-kidney transplant workup in a timely fashion results in increased dialysis exposure, poorer post-transplant survival, and higher resource demands. Candidates undergo workup by our transplant program post-referral rather than by their dialysis programs. We aimed to assess quality metrics at our program, focusing on variability in the duration of pre-transplant workup after adopting a more frequent and scheduled chart review process by our newer coordinator to expedite pre-transplant workup.

Methods: This is a retrospective study evaluating the duration and obstacles of the pre-kidney transplant workup of all candidates evaluated at our transplant program between January 1, 2021, and December 31, 2022, after adopting a more regular chart review process by our coordinator, with a follow up until March 1, 2024. Data were also compared with historical candidates' workup evaluated at our program before January 1, 2021.

Results: 101 candidate's files were reviewed [Mean age 55.4±13.1 years, female (42.6%), Caucasian (76.2%)]. By March 1, 2024, 86.1% of candidates were on dialysis, with 79.3% of those on dialysis by the time of assessment. 78 (77.2%) candidates received a transplant decision while 23 patients stayed in workup, including 5 candidates who were referred, after completing their workup, to another center for combined organ transplantation. Median time from assessment to transplant decision was significantly shorter with more regular pre-transplant chart review at 12.8 (7.2-20.4) months, compared with historical candidates' workup of 23.3 (14.3-37.1) months (P <0.001). At the time of transplant decision, 64 (63.4%) patients were on dialysis (12 on dialysis <1 year). Median

time from dialysis to transplant decision was 24.1 (12.3-43.2) months, compared with historical candidates' time of 31.6 (5.9-52.4) months (*P* 0.89). Dialysis vintage can be reduced further with earlier referral to transplant since median time from dialysis to initial assessment was longer in our cohort, 7.9 (2.9-32.1) months, compared with historical candidates' time of 5.6 (-7.0-20.8) months (*P* 0.12).

Conclusions: Frequent and scheduled chart review of pre-transplant candidates results in shorter workup and dialysis vintage.

SA-PO950

"Survival after Listing": A Metric That Helps Transplant Patients Compare Different Transplant Centers

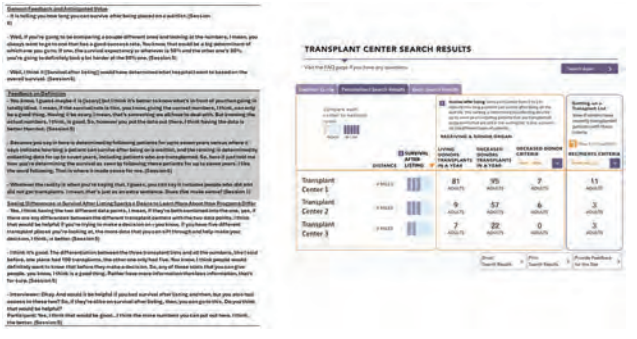
Cinthia Lozano,[1] Warren T. Mckinney,[1] Lucero V. Vazquez Loyola,[1] Cory Schaffhausen,[1] David P. Schladt,[1] Jon J. Snyder,[1] Arthur J. Matas,[2] Ajay K. Israni.[1] *[1]Hennepin Healthcare Research Institute, Minneapolis, MN; [2]University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Previous research has found that using reports to make informed decisions involves processing a large amount of information, which challenges the decision-making process. The Transplant Center Search (TCS) tool was developed to provide patients with comparative information about transplant centers to support decision making on center selection (www.transplantcentersearch.org). To reduce patients' cognitive efforts, we are developing TCS prototypes with a new metric, "survival after listing" which incorporates the current metrics and assesses survival among waitlisted candidates and recipients as provided by the Scientific Registry of Transplant Recipients (SRTR).

Methods: We gathered qualitative data from local kidney transplant candidates. Participants evaluated mockups of the TCS site (Figure 1), including different labels and definitions describing the new metric. Participants were asked to share their impressions of how useful the new metric would be for decision making.

Results: 15 kidney transplant candidates were enrolled in the study with the following characteristics: 60% female, median age 58 (*SD* 7.4), 60% White and 26.7% Black. 13.3% of participants reported needing assistance interpreting printed health materials. Feedback from candidates was generally positive and shows that the new metric supports distinguishing between centers. They also suggested that TCS should continue to provide the current metrics to facilitate decision making (Table 1).

Conclusions: Efforts to reduce the complexity of comparative information on transplant programs are supported by patients. Survival after listing, provides a singular measure of comparative survival among candidates and recipients. We are recruiting national kidney transplant recipients and patients from other solid organ groups to further refine the presentation of the new metric.



SA-PO951

CKD Management and Hemodialysis Planning in Stage 5 Transplant vs. Native CKD Patients

Ricardo A. Macau,[1,2] Afonso V. Ferreira,[2] Joana Gameiro,[1,2] Filipe Marques,[1,2] Fernando Abreu,[1,2] Alice Santana,[1] Jose A. Lopes.[2,1] *[1]Unidade Local de Saude Santa Maria, Lisboa, Portugal; [2]Centro Academico de Medicina de Lisboa, Lisboa, Portugal.*

Background: CKD management and renal replacement therapy (RRT) planning is challenging, especially in patients with graft failure and transitioning to dialysis (dialysis after graft loss), whose complications may not be properly managed, comparing to native CKD patients initiating dialysis.

Methods: We compared patients with native CKD (NKD) and those with graft loss (Tx) initiating hemodialysis (HD) at a Portuguese University Hospital between 2021 and 2023 at a ratio of 3:1. We considered: Age, sex, transplant or native kidney failure, cause of CKD, comorbidities, laboratory at HD start (T0) and three months prior (T3), type of vascular access at HD start and planned start of RRT. We considered as outcomes: type of HD start [outpatient / elective (vs hospitalisation / urgent) and Catheter as vascular access] as well as the patients' status regarding therapeutic levels of haemoglobin and bicarbonate.

Results: The study comprised 112 participants, including 78 (69.6%) NKD and 34 (30.4%) Tx recipients. Participants ranged from 25 to 90 years, (average 65.8 years). Among them, 66 (58.9%) were male. NKD patients demonstrated a higher prevalence of planned RRT initiation (88.5% vs. 47.1%, $p < 0.001$) and elective RRT start (91.0% vs. 32.4%, $p < 0.001$). They were notably younger at RRT initiation than Tx patients (52.1 years vs. 70.2 years, $p < 0.001$). At RRT start, significant differences were observed in bicarbonate levels (21.39 mmol/L in NKD vs. 19.26 mmol/L in Tx, $p = 0.011$) and patients achieving haemoglobin targets (65.4% in NKD vs. 41.2% in Tx, $p = 0.017$). At T3, consistent trends were observed, with differences in bicarbonate and haemoglobin targets.

Conclusions: This retrospective analysis may reveal disparities in CKD management between transplant and native kidney disease patients, notably at the initiation of dialysis. Transplant recipients seem to exhibit a less programmed start, often requiring emergent interventions, while native CKD patients demonstrate better anaemia and metabolic acidosis control. These findings emphasize the impact of transplantation status on CKD management trajectories and highlight the need for further research to understand these differences comprehensively and develop tailored interventions.

SA-PO952

Comparisons of Mortality, Wait-Listing, and Transplantation Outcomes of Young Adults in the United States Renal Data System (USRDS)

Jaya S. Parulekar,[1,2] Marciana Laster,[2,1] Neha D. Pottanat,[2,1] Mengyu Di,[3] Jade Buford,[3] Rachel E. Patzer.[3,1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Riley Hospital for Children at Indiana University Health, Indianapolis, IN; [3]Regenstrief Institute, Indianapolis, IN.*

Background: Young adults are a unique patient population, with the highest incidence of end-stage kidney disease (ESKD) among pediatric subgroups. Despite differences in ESKD cause, comorbidities, and social factors between younger and older adults, young adults are placed in a composite adult category of 18-44 years. Our goal is to better characterize young adults with ESKD (ages 18-25) and compare outcomes with those of older adults (ages 26-44).

Methods: Using data from USRDS, we identified 87,411 incident dialysis patients aged 18-44 starting dialysis from 2015-2020, 9.5% aged 18-25 years and 90.5% aged 26-44 years, following to 2021 for waitlisting and transplant. Multivariable Cox proportional hazards models studied time to mortality, waitlisting, and transplant by age, adjusting for demographics, ESKD cause, comorbidities, pre-ESKD care, transplant awareness, insurance, neighborhood and dialysis-facility variables.

Results: Glomerulonephritis (43%) was the most common cause of ESKD in young adults vs. diabetes (40%) in older adults (Table 1). More older adults had hypertension (86% vs. 76%) and obesity (27% vs. 15%). Younger adults had a 29% lower mortality risk and higher likelihood of waitlisting (33%), transplantation among dialysis-started (32%), and transplantation among waitlisted (18%) (Table 2).

Conclusions: Our analysis provides initial insights into characterizing the broad adult group aged 18-44. Younger adults showed decreased mortality and better transplant outcomes. Future research is needed to define critical age groups with notable outcome differences.

Funding: NIDDK Support

Table 1: Patient comparisons by age group

Variable		Age 18-25 N=8277	Age 26-44 N=79134
Sex	Female	3835 (46.33)	32099 (40.56)
	Male	4442 (53.67)	47035 (59.44)
Race/Ethnicity Group	Non-Hispanic White	2825 (34.25)	26943 (34.17)
	Non-Hispanic Black	2463 (29.87)	28011 (35.53)
	Hispanic	2363 (28.65)	17679 (22.42)
	Non-Hispanic Other	596 (7.23)	6208 (7.86)
Attributed Cause of ESRD	Diabetes	815 (10.01)	31240 (40.06)
	Hypertension	1743 (21.4)	22271 (28.56)
	Glomerulonephritis	3530 (43.34)	12563 (16.11)
	Cystic Kidney	569 (6.99)	3081 (3.95)
	Other	1488 (18.27)	8824 (11.32)
Insurance Status	Medicaid	3463 (42.51)	32773 (42.02)
	Medicare	200 (2.46)	6033 (7.74)
	Employer	2254 (27.67)	20653 (26.48)
	Other	1082 (13.28)	7932 (10.17)
	None	1147 (14.08)	10605 (13.6)

Table 2: Comparison of Mortality and Transplant Outcomes by age group

Event	Age (years) [N=87411]	Crude HR (95% CI)	Adjusted HR (95% CI)
Death among Dialysis Started	18-25 (N=8277)	0.49 (0.46-0.52)	0.71 (0.66-0.76)
	26-44 (N=79134)	Reference	
Wait-listing among Dialysis Started	18-25	1.75 (1.68-1.82)	1.33 (1.27-1.39)
	26-44	Reference	
Transplant among Dialysis Started	18-25	1.96 (1.88-2.03)	1.32 (1.27-1.38)
	26-44	Reference	
Transplant among Waitlisted	18-25	1.35 (1.29-1.42)	1.18 (1.12-1.24)
	26-44	Reference	

SA-PO953

Outcomes of Kidney Transplantation from Deceased Diabetic Donors

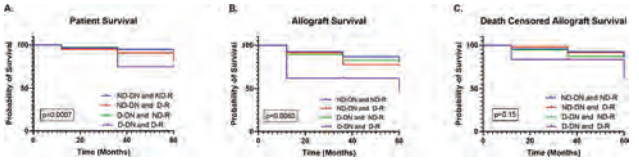
Ahmed Emara,[1] Abigail Hobill,[2] Ria Nagpal,[2] Felix W. Karst,[2] Azhar A. Khan,[2] Maryam Javed,[2] Alice M. Gage,[2] Amy Needleman,[2] Raymond Fernando,[2] Gareth L. Jones,[2] Rhys Evans.[3] *[1]Ain Shams University Faculty of Medicine, Cairo, Egypt; [2]Royal Free London NHS Foundation Trust, London, United Kingdom; [3]University College London, London, United Kingdom.*

Background: Diabetes mellitus (DM) is an increasing comorbidity in the kidney donor population. Utilization of kidneys from donors with DM and subsequent recipient selection is challenging due to limited data on outcomes in this group. To address this gap, we investigated the outcomes of kidney transplantation from deceased diabetic donors over a 10-year period.

Methods: We undertook a retrospective observational study of adult patients who underwent kidney alone transplantation from deceased donors at a single centre between 2012-2022. We stratified patients according to the diabetic status of both donor and recipient. We determined patient and allograft survival at 1-, 3- and 5-years post-transplant.

Results: 985 kidney transplant recipients (KTRs) were included, of whom 64 (6.5%) underwent transplantation from a diabetic donor. Diabetic donors were older, a higher proportion had hypertension, and they had a higher Kidney Donor Profile Index and implant Karpinski score. Recipients of diabetic donor kidneys were also older, and had a higher baseline clinical frailty score. Creatinine levels at 1, 3, and 5 years were higher in KTRs of diabetic donors; rejection rates did not differ according to donor diabetes status. Patient and allograft survival were worst in diabetic recipients of diabetic kidneys (**Figures A-C**). Outcomes were similar in non-diabetic recipients regardless of the diabetic status of the donor. In multivariable analyses, recipient age (HR 1.05, 95% CI 1.03-1.08) and recipient diabetes (HR 2.22, 95% CI 1.32-3.67) increased the hazard of patient mortality but not death censored graft survival and donor diabetes had no effect on any recipient outcomes.

Conclusions: Utilizing kidneys from diabetic donors is associated with acceptable recipient outcomes and offers a potential mechanism to expand the deceased donor pool. Recipient diabetes status should be considered during organ allocation



(**A**) Patient survival, (**B**) Allograft survival (**C**) Allograft survival censored for patient death stratified by donor and recipient diabetes status.
D-DN: Diabetic Donor
D-R: Diabetic recipient
ND-DN : Non-Diabetic Donor
ND-R: Non-diabetic Recipient

SA-PO954

Pilot Randomized Trial to Define the Benefits and Harms of Deceased Donor Kidney Procurement Biopsies

Krista L. Lentine,[1] Vidya Fleetwood,[1] Tiffany Caza,[2] Yasar Caliskan,[1] Gary F. Marklin.[3] *[1]Saint Louis Univ., St. Louis, MO; [2]Arkana, Little Rock, AR; [3]Mid-America Transplant, St. Louis, MO.*

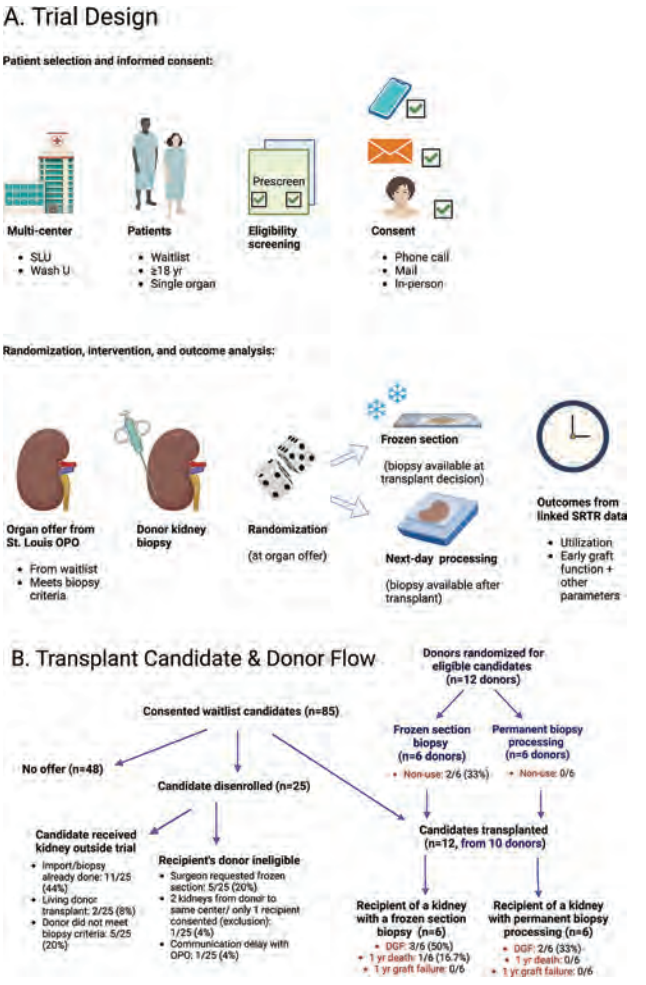
Background: Kidney biopsies obtained during organ procurement are often used in acceptance decisions, but supporting evidence is controversial. We conducted a pilot randomized controlled trial (RCT) to help assess impacts of deferring release of procurement biopsy information at the time of offer (in this design, through permanent processing).

Methods: This pilot, multicenter RCT involved 1 Midwest organ procurement organization (OPO) and 2 local transplant centers (7/2019-7/2022 | *ClinicalTrials.gov* **NCT03837522**). Waitlisted candidates were approached for consent, such that if offered a kidney from an eligible deceased donor (DD), the DD could be randomized (**Fig 1A**). Criteria for routine DD biopsy included KDPI >50% or KDPI components. Eligible DDs for consented recipients were randomized to immediate (frozen) versus delayed (permanent) biopsy processing. Outcomes were assessed in linked SRTR data.

Results: 85 candidates were consented; 25 were disenrolled (**Fig 1B**), most commonly due to receipt of an imported and/or previously biopsied kidney at another OPO, surgeon request for immediate biopsy (25%), or DD not meeting routine biopsy criteria (20%). 12 DDs were randomized for eligible candidates. 2 kidneys from 2 study DDs were not used, both in the frozen group. 12 kidneys from 10 randomized DDs were transplanted in study recipients. Delayed graft function (DGF) occurred in 3/6 (50%) in frozen and 2/6 (33%) in permanent groups. There were no graft failures within 1 y, and 1 death (frozen group).

Conclusions: An RCT of impacts of DD procurement biopsy information on transplant outcomes faces challenges, including effort to consent waitlist candidates and high disenrollment for reasons including rising organ imports. This pilot did not suggest safety concerns for delayed biopsy information.

Funding: Private Foundation Support



SA-PO955

Managing the Costs of Kidney Paired Donation: A Survey of Contemporary US Practice and Challenges

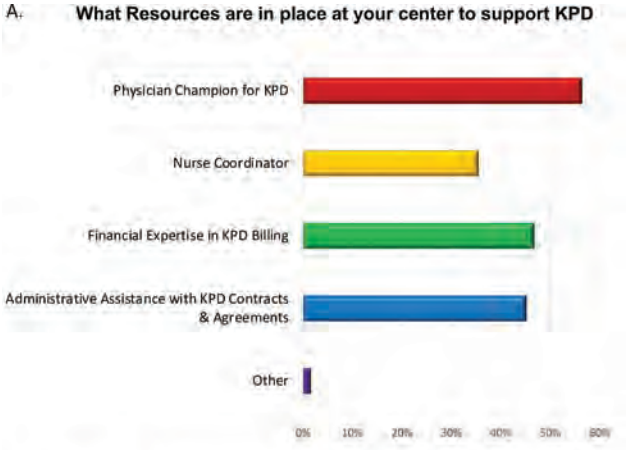
Krista L. Lentine,[1] Geoffrey Gheorghian,[1] Gwen E. McNatt,[2] Robert Howey,[7] Vidya Fleetwood,[1] Didier A. Mandelbrot,[4] Hossein Tabriziani,[6] Cody Wooley,[1] Fawaz Al Ammary,[5] Andrea Tietjen.[3] *[1]Saint Louis Univ., St. Louis, MO; [2]Univ. Iowa, Iowa City, IA; [3]St. Barnabas, Livingston, NJ; [4]Univ. Wisconsin, Madison, WI; [5]UC Irvine, Irvine, CA; [6]Natera, San Carlos, CA; [7]Toyon Assoc., Franklin, TN.*

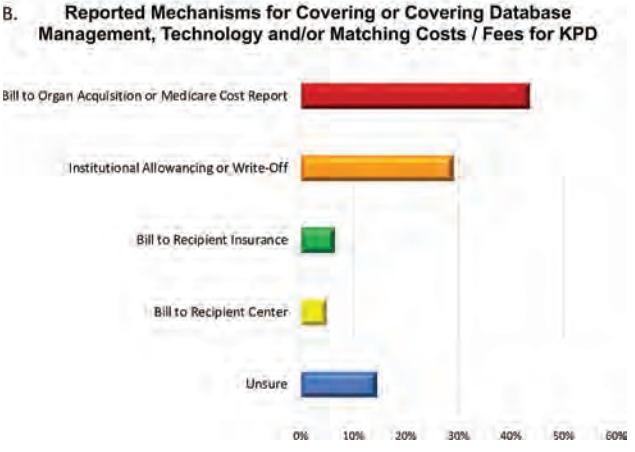
Background: Kidney paired donation (KPD) is increasingly used to provide access to living donor kidney transplantation (LKDT), but concerns related to managing costs pose barriers to transplant center participation. To help inform community discussions of strategies, we surveyed U.S. LDKT program staff on experiences and practices for managing KPD-related costs.

Methods: A survey instrument was designed by a multidisciplinary workgroup of professionals in transplant administration and practice. We distributed the survey to staff at U.S. LDKT transplant programs by email and posting to professional society list-servs in 2024 using the Qualtrics survey platform.

Results: Among 62 programs that participated to date, 95% report KPD participation, with 34% reporting >10 exchanges per year. For external changes, 72% use the National Kidney Registry alone or combined with other programs, and 11% use the Alliance for Paired Donation alone or with other programs. Reported resources for KPD include physician champions (56%), nurse coordinators (35%), financial expertise (47%) and contracting assistance (45%)**(Fig A)**. Heterogenous methods are used to cover database costs (**Fig B**) and other costs including evaluation, nephrectomy, and organ shipping. 42% of centers report standardized policies and procedures for handling KPD costs, while 21% are uncomfortable discussing methods to cover costs of KPD with administration.

Conclusions: Based on a pilot survey of U.S. LDKT programs, a variety of approaches are used to cover costs of KPD practice, and many centers are uncomfortable discussing resource needs with administration. Up-to-date resources on handling KPD finances will be useful to support programs in expanding KPD practice.





SA-PO956

Adjusted Donor-Age (ADA) Score as a Tool for Characterizing Deceased Donor Kidneys: Multicentre Validation Study for a German Eurotransplant Cohort

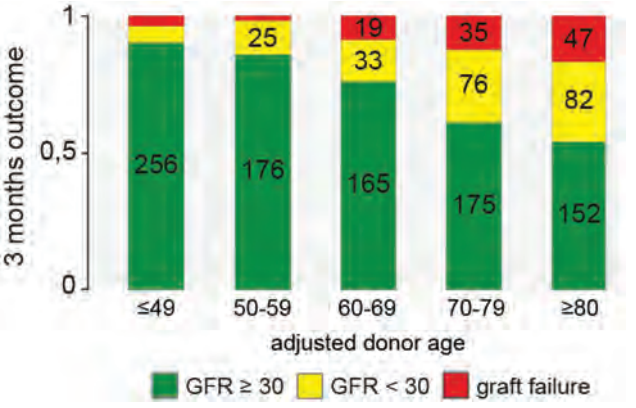
Christoph F. Mahler,[1,2] Felix Friedl,[1] Christian Nusshag,[1] Claudius Speer,[1] Louise Benning,[1] Matthias Schaier,[1] Claudia Sommerer,[1] Markus Mieth,[3] Martin G. Zeier,[1] Can C. Süsal,[4] Vedat Schwenger,[4] Christian Morath,[1] Fabian Echterdiek,[4] Florian Kälble.[1] *[1]Nierenzentrum Heidelberg eV, Heidelberg, Germany; [2]Clinician Scientist Program, Universität Heidelberg, Heidelberg, Germany; [3]Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg, Heidelberg, Germany; [4]Department of Nephrology, Klinikum Stuttgart, Stuttgart, Germany.*

Background: ADA adjusts the donor age according to risk factors (A: ADA<49, B: 50-59, C: 60-69, D: 70-79, E: >80 years) and stratifies the adjusted age into quintiles (A-C advantageous, D moderate, E unfavorable). The aim of this multicentre study is to explore, whether the ADA score can be validated for a Eurotransplant cohort.

Methods: We conducted a retrospective analysis of all kidney transplants from cadaveric donations at centers in Heidelberg, Stuttgart, and Munich (Technical University) between 2015 and 2021. Donor data were recorded using the Eurotransplant database to calculate the ADA score. The prognostic accuracy was assessed based on graft function after three months.

Results: Out of a total of 1353 transplanted kidneys, 1273 were included in the analysis. After three months, 924 (73%) recipients achieved an eGFR of >30 ml/min/1.75m². In 9% of the cases, graft failure occurred within the first three months. There was a significant correlation between higher ADA quintiles and poor transplant outcome (eGFR < 30 ml/min at 3 months in 10% (A), 14% (B), 24% (C), 39% (D), 46% (E) of patients; p<0.001). For patients with good graft function, the 3-month eGFR was associated with ADA (c-statistic = 0.66) and decreased with higher ADA quintiles (A: 60, B: 49, C: 43, D: 35, and E: 36 ml/min).

Conclusions: The ADA score proves to be a suitable, intuitive method for the evaluation grafts. Our multicentric analysis shows good predictive accuracy for graft function after three months. Although organs with an ADA over 80 years have an increased risk of graft failure, more than 50% of patients in this group show good graft function. Future studies should investigate this group in more detail to adapt the ADA score to the specific characteristics of the Eurotransplant donor pool.



SA-PO957

Perceived Patient Interest in Pursuing Kidney Transplantation: A Qualitative Study

Adam S. Wilk,[1] Jennifer L. Mcdonnell,[1] Megan Urbanski,[1] Stephen O. Pastan,[1] Kimberly Arriola,[1] Cam Escoffery,[1] Rachel E. Patzer.[2] *[1]Emory University, Atlanta, GA; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: Kidney transplantation improves patient survival and quality of life compared to dialysis for many patients, yet dialysis care teams do not refer all qualified candidates for transplant evaluation. Dialysis professionals often cite "Patient not interested" as a key reason for not providing comprehensive transplant education or completing referrals, yet little is known about how dialysis professionals assess patient interest or use these assessments to guide education and referral practices.

Methods: We conducted 39 in-depth telephone interviews during June-August 2022 with dialysis professionals in Georgia, North Carolina, and South Carolina about their processes leading up to referral decisions. We recruited dialysis social workers, nurse managers, nephrologists, and administrators using purposive sampling to capture diversity by participants' role, years of experience, and county median household income. Interviews were recorded and transcribed and data were managed using MAXQDA software. We used thematic analysis to identify themes, with 3 coders developing the codebook, analyzing, and interpreting data.

Results: Dialysis professionals described assessing patients' interest in transplant as part of transplant education, directly asking patients if they are interested during initial discussions or regularly "checking in" about care options across later care encounters. Most described concurrently assessing and influencing patients' thinking, using distinct approaches. Some encourage nearly all patients to consider transplant given its benefits for most patients. Others are selective, choosing when to bring up transplant and how much transplant education to provide based on assumptions about the patient's interest in transplant and transplant eligibility. These assumptions are based on perceived innate characteristics (e.g.,"really want it") or social constraints (e.g.,"too far to the center," "cannot afford…post-transplant medications") of the patient.

Conclusions: Many dialysis professionals provide transplant education selectively based on how interested they perceive patients are, based on subjective perceptions of patient characteristics and circumstances. Future research should examine whether standardized transplant education practices minimize implicit biases and increase equity in transplant access.

Funding: NIDDK Support

SA-PO958

Organ Donation: A Cross-Sectional, Descriptive Study from an Inner-City Hospital in the Bronx

Htun M. Aung,[1] Juan Diego Rodriguez Salazar,[1,2] Anjali Acharya,[1] Roxanne Todor.[1] *[1]New York City Health and Hospitals Corporation, New York, NY; [2]Albert Einstein College of Medicine, Bronx, NY.*

Background: Renal transplant is the treatment of choice in patients with end-stage renal disease. However, organ donation rates in NYC are relatively low, at approximately 18%, with the Bronx borough having the lowest rate, at around 11%, despite having the highest number of patients on the waiting list. We have been recognized as a high performing donor hospital and are part of the CMS ETCLC initiative. We carried out this retrospective study where we aimed to look at our patients with brain-death diagnosis in a public hospital in the Bronx where health equity and disparities are front and foremost.

Methods: A descriptive cross-sectional study was conducted, during which relevant information was gathered from the electronic medical records of patients diagnosed with brain death between 2020 and 2023. Children under 18 years of age were excluded from the study. The focus was on collecting data related to organ donation, timely referral to our OPO Live On NY, electrolyte and renal function abnormalities, as well as nephrology referral. Data analysis was performed using Excel.

Results: Information was collected from 115 patients, of whom 63.48% were men. LiveOnNY was consulted in more than 95% of cases, and 42.61% of patients diagnosed with brain death ended up being donors. 57.39% were diagnosed with acute kidney injury, of which 20% were classified as KDIGO 3. Additionally, 76.52% and 59.13% of patients exhibited significant alterations in sodium or potassium levels, respectively. Furthermore, 14.78% of the cases required renal replacement therapy. Finally, the nephrology service was consulted in 27.83% of the cases.

Conclusions: Based on the results of our study, we can conclude that despite been an inner-City hospital from the Bronx, the rate of organ donation on death brain patients is encouraging. The rates of AKI and electrolytes disturbances were significant. We would like to encourage the significance of involving nephrology experts in managing the renal complications and increasing the chances of transplantation and decrease organ discard rate.

SA-PO959

A Cross-Sectional, Descriptive Web-Based Survey on Knowledge of the Organ Donation Process among Internal Medicine Residents

Htun M. Aung,[1] Juan Diego Rodriguez Salazar,[1] Roxanne Todor,[1] Anjali Acharya.[1,2] *[1]New York City Health and Hospitals Jacobi, Bronx, NY; [2]Albert Einstein College of Medicine, Bronx, NY.*

Background: Jacobi Medical Center is recognized as a major organ donor hospital by CMS and play a prominent part of the CMS ETCLC initiative. Our resident physicians are on the front lines, taking care of critically ill patients and working with the organ donor network for referrals of potential organ donors. We wanted to improve our understanding of organ donation practices and see how to serve our patients better.

Methods: A cross-sectional, descriptive, web-based 13-item survey was developed. Internal medicine residents at our institution were invited to participate in the survey. All variables were reported descriptively, and free-text responses were summarized.

Results: Out of 102 residents, 25 residents responded to the survey. The survey results are shown in Table 1. Six residents described potential barriers to organ donation as follows: not knowing who to reach out to; hard to work with the organ donor program; resident education; work burden; patients' families and social issues.

Conclusions: Most survey respondents were knowledgeable about the referral process for organ donation. However, there were knowledge gaps regarding electrolyte abnormalities in patients after brain death, renal consult for acute kidney injury or electrolyte abnormalities for these patients, and the First Person Authorization. Subsequently, education sessions were planned to improve the organ donation process.

Table 1: Survey Responses

	Yes	No	Others
1. Do you know the criteria for brain death?	92%	8%	
2. Are you aware of donation after cardiac death?	96%	4%	
3. Do you know when to refer a patient to LiveOnNY?	88%	12%	
4. Do you know the process of referring a patient to LiveOnNY?	80%	20%	
5. Do you know the electrolyte abnormalities that might occur with brain death?	56%	44%	
6. How often do you call renal consult for acute kidney injury in a patient after brain death?	Not applicable	Not applicable	Always (4%), usually (20%), sometimes (20%), rarely (24%), and never (32%)
7. How often do you call renal consult for electrolyte abnormalities in a patient after brain death?	Not applicable	Not applicable	Always (4%), usually (8%), sometimes (24%), rarely (40%), and never (24%)
8. Do you think organ donation is helpful in saving lives?	100%	0%	
9. Have you encountered potential barriers at Jacobi Medical Center to organ donation?	24%	76%	
10. Are you a registered organ donor?	48%	52%	
11. If you are not a registered organ donor, are you interested in becoming one?	20%	36%	I am already registered (44%)
12. Do you know what First Person Authorization (FPA) is?	8%	92%	
13. In your opinion, can First Person Authorization be used for both donation after brain death (DBD) and donation after cardiac death (DCD)?	52%	48%	

SA-PO960

Human Leukocyte Antigen (HLA) Histocompatibility and Kidney Graft Survival

Ada Noemi Chavez. *Hospital General San Juan de Dios, Ciudad de Guatemala, Guatemala.*

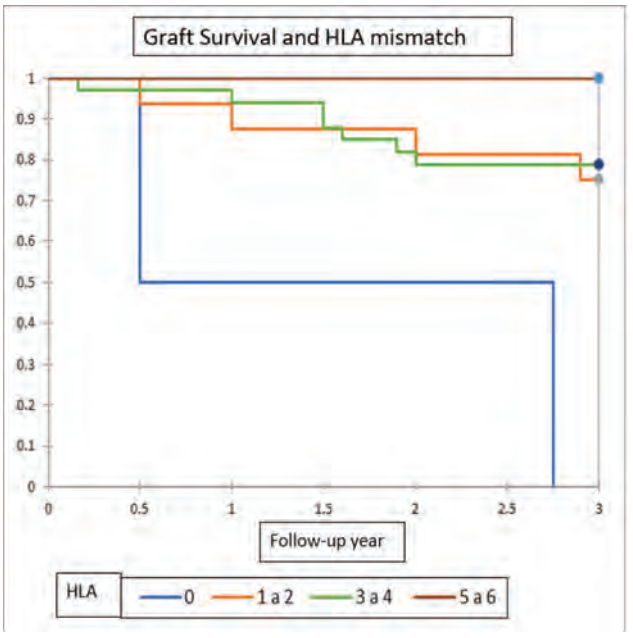
Background: Renal transplantation is the treatment of choice for chronic kidney disease and its survival is known to be related to multiple risk factors. Regarding HLA matching, the number of acute rejection episodes in renal transplantation has been associated with the degree of incompatibility for HLA-DR, as well as a beneficial correlation has been observed between better HLA matching (both HLA-DR and HLA-A and -B) with long-term graft survival.

Methods: Descriptive retrospective, 55 post-renal transplant patients were evaluated during January 1, 2018 to December 31, 2019 and followed up for 3 years.

Results: Graft survival was evaluated at the first year of follow-up 94% of the grafts had survived out of a total of 55 grafts, at the second year, of the 52 grafts that still had survival 6 (12 of the remaining grafts, and at the third year of follow-up 4 more grafts were lost, the patients who presented HLA-DR compatible had a mean graft survival of 2.85 years. (Figure 1) The survival of the graft was also evaluated in relation to the number of compatibilities that the patients presented, dividing the patients into 4 groups according to the number (0, 1- 2, 3- 4 and 5- 6) in which it was evidenced that the patients who presented 0 compatibilities 100% lost the graft, and those who presented compatibility group 5-6, had 100% survival (CI: 95%) at 3 years of follow-up of patients, among patients who were among the groups 1-2 and 3-4, had a graft survival at the end of the study in 78.2% and 80.1% respectively, and very similar data. (Figure 2)

Conclusions: HLA matching was significant for graft survival, mainly HLA-DR. It is important to continue investigating in our population with longer follow-ups as well as the follow-up approach to patients who do not share HLA

Graft Survival	1 year	2 year	3 year	Total
Yes	52 (94%)	46 (83.6%)	42 (76.3%)	42 (76.2%)
No	3 (6%)	6 (16.4%)	4 (23.7%)	13 (23.8%)



SA-PO961

Preemptive Registration in Hispanic Kidney Transplant Candidates: When Is Early Not Early Enough?

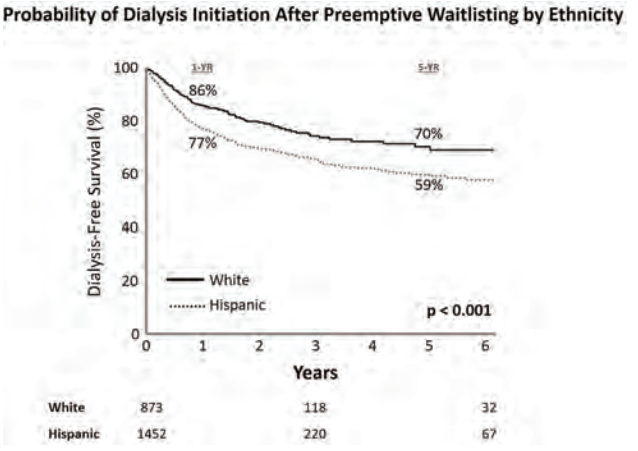
Nassir Thalji, Tamer Shaker, Ranjeeta Chand, Matthias M. Kapturczak.
Methodist Specialty and Transplant Hospital, San Antonio, TX.

Background: Preemptive registration promotes time accrual, waitlist priority, and an opportunity for preemptive kidney transplantation. Hispanic patients with kidney disease enjoy fewer preemptive waitlist registrations. We evaluated the fate of preemptively listed Hispanic kidney transplant candidates.

Methods: We studied adult patients preemptively added to the kidney transplant waitlist at our center between 2003–2022, excluding multiorgan listings. Rates of transplantation, living donor kidney transplant (LDKT), preemptive transplant and dialysis initiation were compared in Hispanic vs. non-Hispanic White patients.

Results: We evaluated 2,624 patients with a median age of 51 years and 58% were male. Hispanic patients accounted for 55% (1,452) and 33% (873) were White. Hispanics had more obesity and diabetes, but were less likely to have higher-level education or paid employment (all p<0.001). Overall 50% of Hispanics and 62% of Whites were transplanted, with Whites 75% more likely to be transplanted preemptively (both p<0.001). Hispanic were 40% less likely to have LDKT (OR 0.61) or preemptive LDKT (OR 0.59) (both p<0.001). Considering dialysis initiation as a time-dependent endpoint, Hispanics were 66% more likely than Whites to start dialysis after preemptive listing (Figure). Accounting for age, sex, diabetes, living donor availability and private insurance, Hispanic ethnicity independently predicted waitlist dialysis initiation (HR 1.34; p=0.009).

Conclusions: Preemptive listings in Hispanic patients yield fewer kidney transplants, LDKTs, or preemptive transplants compared to Whites, and more readily culminate in dialysis initiation. The prognostic value of preemptive registration is thus incompletely realized in Hispanic transplant candidates. Coordinated efforts are needed to bolster capacity for self-advocacy in Hispanic patients while augmenting access to providers able to guide them through early kidney transplant evaluations.



SA-PO962

Disparities in Access to Upstream Steps in the Kidney Transplant Pathway among Young Adults with New-Onset Kidney Failure

Kelsey M. Drewry,[1,2] Jade Buford,[2] Arrey-Takor Ayuk-Arrey,[2] Jaya S. Parulekar,[1] Marciana Laster,[1] Rachel E. Patzer.[2,1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Regenstrief Institute Inc, Indianapolis, IN.*

Background: Despite the benefits of kidney transplantation compared to dialysis, access to transplant remains limited, especially among marginalized populations. Inequities in access to the transplant waitlist persist even among young, otherwise healthy patients with kidney failure who may be best suited for transplant. This study used the only multi-regional referral data to assess whether disparities in access to waitlisting among young patients arise from inequitable access to the pre-waitlisting steps of referral for transplant and evaluation initiation.

Methods: Young adults (age 18-40 years) with new-onset kidney failure in Georgia, North Carolina, and South Carolina (2015-2020) were identified using the United States Renal Data System. Primary outcomes included timely referral for evaluation (within one year of dialysis initiation) and evaluation initiation (within three months of referral among all referred patients), assessed via linkage to the Early Steps to Transplant Access Registry. The odds of timely referral and evaluation were compared using multivariable logistic regression.

Results: Among 13,291 patients (mean [SD] age: 33 [6]; 7528 [57%] male; 1756 [13%] Hispanic, 6535 [49%] Black), 6374 [48%] were referred for evaluation within 1 year of dialysis initiation, and 5448 [41%] began the evaluation within 3 months of referral. In adjusted logistic regression models, White race, full time employment, private health insurance, and longer durations of pre-kidney failure nephrology care were positively associated with timely referral and evaluation. Hispanic ethnicity was associated with lower odds of referral (aOR 0.57 [95% CI 0.49-0.68]), but not evaluation start (aOR 0.80 [95% CI 0.58-1.10]).

Conclusions: This retrospective cohort study found racial, ethnic, and socioeconomic inequities in access to timely referral and evaluation for kidney transplant among young patients likely to be highly suitable for transplant. To improve equity in access to transplantation and subsequent outcomes in this key age group, interventions should focus on increasing the proportion of young patients from underserved populations who are referred for transplant evaluation within the first year of kidney failure diagnosis, and ensuring referred individuals progress to initiating the evaluation.

Funding: NIDDK Support, Other NIH Support - NIMHD

SA-PO963

Does Live Donor and Preemptive Kidney Transplantation Reduce the Impact of Socioeconomic Deprivation on Graft Outcome?

Michael Corr,[1] Jenni Beck,[2] Alexander P. Maxwell,[1] Ciaran O'Neill,[1] Gareth J. McKay.[1] *[1]Queen's University Belfast, Belfast, United Kingdom; [2]Belfast City Hospital, Belfast, United Kingdom.*

Background: Socioeconomic deprivation has been reported to adversely affect transplant outcomes from access to wait listing to post-transplant care. Individuals from lower socioeconomic backgrounds have lower rates of living donor transplants and face significant challenges post-transplant leading to higher rates of graft loss. The aim of this study was to assess the impact of socioeconomic deprivation on transplant outcomes in Northern Ireland, a region with universal healthcare but high socioeconomic deprivation.

Methods: A single-centre retrospective study included all 1,581 kidney transplant recipients from 2000-2020. A national tool allowed determination of socioeconomic deprivation status, using a multi-dimensional deprivation score. Concentration curves were calculated for pre-emptive and living donor transplantation across the study

population ranked by summary deprivation score. For analysis of each individual deprivation score the population was divided into quintiles. Cox regression was used to assess risk of graft failure compared to least deprived quintile. Other variables such as age, live donor and pre-emptive transplantation were investigated for association with graft survival in a regression model.

Results: Concentration curves for pre-emptive and living donor transplantation lie above the line of equality suggesting both are more prevalent in lower socioeconomic groups. Univariate cox proportional hazards failed to identify significant associations between socioeconomic status and graft survival which remained non-significant following adjustment for pre-emptive transplantation (HR 0.64 $p < 0.05$), live donor transplantation (HR 0.79 $p < 0.01$) and increasing recipient age (HR 0.77 $p < 0.05$).

Conclusions: Our results differ from previous reports on impact of socioeconomic deprivation on transplant outcomes. The higher proportion of pre-emptive and live donor transplants in more deprived groups likely represents equitable access to transplantation, despite unequitable burden of end-stage kidney disease. Our region has high pre-emptive (24%) and live donor (42%) rates which may mitigate impact of deprivation on graft survival. These data demonstrate an opportunity to reduce the burden of socioeconomic deprivation on transplant outcomes through expanded access to pre-emptive and live donor transplantation.

SA-PO964

Racial Disparities Exist in the Transplant Process among Hispanic Patients on Dialysis

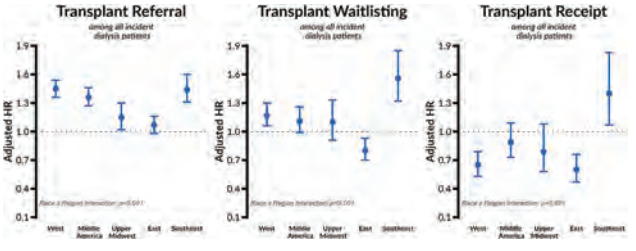
Adam G. Walker,[1] Carey Colson,[1] Danelle Radney,[2] Unini Odama,[2] William D. Maixner,[2] Francesca Tentori,[1] Steven M. Brunelli.[1] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO.*

Background: Kidney transplantation is considered the best long-term treatment for patients with end-stage kidney disease (ESKD). Previous results revealed that African American patients are 54% less likely to receive a kidney transplant than White patients; we sought to examine if any disparities exist for Hispanic patients.

Methods: This retrospective study used electronic health records and county-level indices of socioeconomic deprivation at the time of dialysis initiation at a kidney care organization. Patients included in the study (n=50,102) were those who initiated dialysis between July 2015 and June 2018, were 18-80 years old, either Caucasian or Hispanic, and began care with a kidney care organization within 30 days of first ever dialysis. Patients with prior transplant or transplant evaluation/ listing were excluded. Patients were followed from date of first eligibility until 30 June 2022 or until censoring for death, transfer, withdrawal from dialysis, renal recovery, or loss to follow up. Outcomes included transplant referral, waitlisting, or receipt and were compared using time-to-event models. Models were adjusted for differences in patient demographic factors, comorbidities, laboratory values, and socioeconomic factors across exposure categories.

Results: Results indicate that the progression of Hispanic patients through the transplant process (referral, waitlisting, and receipt) varies by US region. Nearly half (47.1%) of all Hispanic patients on dialysis reside in the West region of the US, where they are ~35% less likely to receive a kidney transplant, primarily driven by a lower rate of conversion from waitlist to transplant. In the East region of the US, Hispanics are 40% less likely to receive a kidney, primarily driven by a lower rate of conversion from referral to waitlist. In all areas of the country, Hispanic patients were more likely to be referred for transplant evaluation.

Conclusions: In this sample, from the period 2015-2022, there were large and systematic biases against Hispanic patients that resulted in a lower likelihood of receiving a kidney transplant despite higher referral rates.



SA-PO965

Kidney Transplantation Outcomes by Dialysis Modality in an Underserved Population

Ali Huzair,[1,2] Jiten Patel,[1,2] Anisha Ganguly,[2] Jaspreet Sian,[1,2] Jillian L. Smartt,[2] Michael Harms,[2] Ramesh Saxena.[1,2] *[1]The University of Texas Southwestern Medical Center, Dallas, TX; [2]Parkland Health, Dallas, TX.*

Background: While in-center hemodialysis (HD) is delivered by trained healthcare providers, peritoneal dialysis (PD) involves active patient-engagement in dialysis treatment. This process of self-care can be associated with a range of potential collateral health benefits that can positively impact clinical and patient-centered outcomes. Kidney transplantation (KT) is the major outcome goal among kidney failure (KF) patients who initiate dialysis. Several studies have shown that PD patients are more likely to receive KT, compared to HD patients. However, baseline differences among HD and PD patient populations such as age, race/ethnicity, education and socioeconomic status, may confound differences in receipt of KT. In this retrospective study, we compared transplant evaluation and listing status among propensity matched incident HD and PD patients initiating dialysis at Parkland Health, a safety net health system caring for underserved populations in Dallas County.

Methods: We included adult patients, who were newly initiated on HD or PD at Parkland Health from January 2012 to December 2022. PD Patients were propensity matched 1:1 with HD patients based on language, race/ethnicity, age and comorbidities. The primary outcome was proportion of patients evaluated for transplantation, while key secondary outcomes included proportion of patients listed for transplantation, reasons for not listing, and proportion transplanted.

Results: During the study period 155 patients were initiated on PD, and were matched with 155 patients initiating on HD. Of patients initiated on PD, 133 (85.8%) were evaluated for KT, compared to 109 (70.3%) patients on HD (p=0.001). Eventually, 78 (50.3%) PD patients and 50 (35.5%) HD patients were listed for transplantation (p=0.001). Of the patients evaluated but not listed, medical ineligibility was the predominant reason in PD group (38/54, 70.3%), while in HD group 36/56 (65%) were not listed due to lack of interest and non-adherence to treatment. Finally, 27 HD patients and 33 PD patients underwent KT (p=0.108).

Conclusions: We observed that more PD patients presented for transplant evaluation compared to HD individuals in a safety net system. This led to higher KT listing of PD versus HD patients. These findings suggest that patient engagement through PD may improve distal KF outcomes, including KT, among underserved population.

SA-PO966

Increasing Transplant Access with a Novel Care Model Employing Transplant Peer Navigators (TPNs)

Eliot C. Heher, Rachel A. Eaton, Katherine E. Norris, Laurie R. White, Jullie Hoggan. *Square Knot Health, Boston, MA.*

Background: Kidney transplantation requires multidisciplinary planning and high levels of patient engagement. Geography, ethnicity, and other social determinants of health impact access to transplantation. We sought to improve access by identifying and removing barriers to transplant.

Methods: A transplant nephrologist (EH) and TPNs (RE, JH, KN, LW) assessed patients with chronic kidney disease (CKD) referred by primary nephrologists. Medical record review, virtual visits, and transplant planning were independent of any one transplant center. TPNs are kidney recipients and donors who received additional formal training. TPNs partnered with patients through the life cycle of transplant, helping them address barriers, search for living donors, and secure care. Outcomes measured included referral, listing, transplant rates, and “net promoter score.”

Results: Patients (Table 1) were referred between Oct 1, 2021 and Sept 30, 2023 from ME, NH, and MA. Results are in Figure 1. 43 (38%) had been referred to a transplant center but never listed, due to high BMI, medical and communication challenges, poor support, failure to complete tasks, and other barriers. We referred 21 of these to a 2nd center, and 5 to a 3rd, resulting in 16 listings and 5 transplants. 6 of 19 transplants occurred at the 2nd or 3rd center. 32 of 34 respondents rated the service a “10” (highly likely to recommend), and 2 others rated it 9 and 8.

Conclusions: Using a novel TPN led, transplant center agnostic, and community-based model, 37% of patients were added to the kidney waitlist after previous denial. Patient satisfaction was high. Further study of our model’s impact on access in other underserved populations is warranted.

Funding: Clinical Revenue Support

	Totals	On Dialysis	Pre-Dialysis
Total number referred CKD patients	**175**	–	–
Number of CKD patients enrolled	**112 (64%)**	81 (72%)	31 (28%)
Previously evaluated but not listed	**43 (38%)**	35 (81%)	8 (19%)
Average age (range)	**57 (24-85)**	57 (24-85)	57 (27-85)
Gender: Male/Female	**71%/29%**	78%/22%	52%/48%
Number of Deaths (%)	**7 (6%)**	7 (100%)	0 (0%)
Median follow up in days (range)	**565 (89-903)**	–	–

Table 1

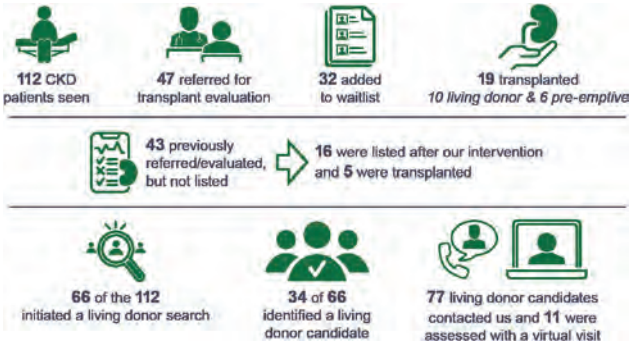


Figure 1

SA-PO967

Impact of Victorian Quality Indicator (QI) on Kidney Transplant Wait-Lists for Indigenous and Nonindigenous Australians

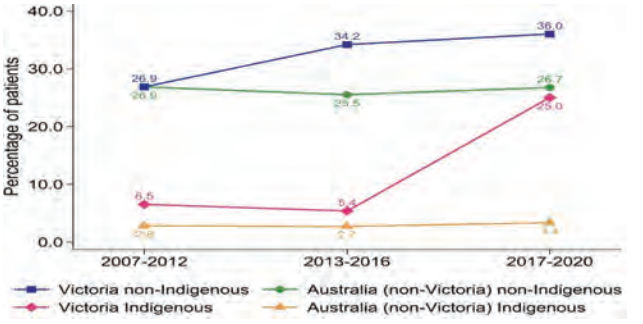
Rebecca Ling,[1] Christopher E. Davies,[2,3] Tia-Maria Mark,[5] Stephen P. McDonald,[2,3] David J. Goodman.[1,4] *[1]Department of Renal Medicine, St Vincent's Hospital, Melbourne, VIC, Australia; [2]Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia; [3]Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia; [4]The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, Melbourne, VIC, Australia; [5]Monash Health Kidney & Pancreas Transplant Unit, Melbourne, VIC, Australia.*

Background: In 2012, Victoria introduced a 6monthly reportable renal QI for proportion of patients waitlisted or pre-emptively transplanted by set time points following start of dialysis. In 2019, renal QI was modified to include patients aged 18-70 at 6 and 12 months after commencing dialysis. We aimed to determine if QI influenced timeliness of placement on kidney transplant waiting list for Victorians, including Indigenous (ATSI; Aboriginal and Torres Strait Islander People) Victorians.

Methods: Dialysis start date, date of waitlisting or pre-emptive transplantation, medical co-morbidities, type of kidney replacement therapy (KRT) for patients aged 18-70 commencing KRT between 2007-2020 was extracted from ANZDATA. Data was divided into three eras and four sub-cohorts. Primary outcome was percentage of patients waitlisted or transplanted at 6, 12 and 24 months from starting dialysis.

Results: Of 25,836 (14.7% ATSI) patients on dialysis, 8,587 (5.7% ATSI) were listed for transplant and 1,103 had pre-emptive transplants by December 2021. A higher proportion of non-ATSI (49%) and ATSI Victorian (31%) patients were waitlisted or had pre-emptive transplants compared to Australians (non-Victorian) (44% and 13% respectively). The proportion of Victorian patients waitlisted or had pre-emptive transplants at all timepoints improved substantially in 2017-2020, compared to 2007-2012. The proportion of Victorian patients waitlisted by 6months improved significantly (aOR 1.85 (1.55-2.21), P<0.001) following QI implementation, but there was no significant change in Australians (non-Victorian). Victorian ATSI patients were three times more likely to be waitlisted or transplanted than ATSI patients in rest of Australia (aOR 3.59 (1.45, 8.87), P = 0.006).

Conclusions: Following introduction of the Victorian QI, the percentage of dialysis patients on waitlist or had pre-emptive transplants at 6 and 12 months increased. Victorian ATSI patients were more likely to be waitlisted than Australian ATSI patients.



SA-PO968

Genetic Evaluation of Living Kidney Donor Candidates: Results from the LDGen Registry

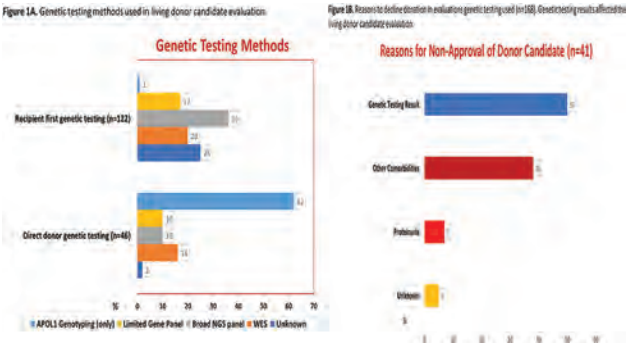
Yasar Caliskan,[1] Ozgur A. Oto,[8] Tarek Alhamad,[2] Halil Yazici,[3] Abdulmecit Yildiz,[11] Arzu Velioglu,[9] Neetika Garg,[12] Karim Soliman,[13] Arksarapuk Jittirat,[14] Ondrej Viklicky,[10] Zeynep Ural,[4] Christina Irene Mejia,[15] Reem Daloul,[5] Danilo Radunovic,[6] Brian Lee,[16] Christie P. Thomas,[17] Hernando Trujillo Cuellar,[18] Roslyn B. Mannon,[7] Krista L. Lentine.[1] LDGen Consortium. *[1]Saint Louis University, St Louis, MO; [2]Washington University in St Louis, St Louis, MO; [3]Istanbul Yeni Yuzyil Universitesi, Istanbul, Turkey; [4]Gazi Universitesi, Ankara, Turkey; [5]Allegheny Health Network, Pittsburgh, PA; [6]Klinicki Centar Crne Gore, Podgorica, Montenegro; [7]University of Nebraska System, Lincoln, NE; [8]Istanbul Universitesi, Fatih, Turkey; [9]Marmara Universitesi, Istanbul, Turkey; [10]Institut Klinicke a Experimentalni Mediciny, Praha, Czechia; [11]Bursa Uludag Universitesi, Nilufer, Turkey; [12]University of Wisconsin-Madison, Madison, WI; [13]Medical University of South Carolina, Charleston, SC; [14]Case Western Reserve University, Cleveland, OH; [15]Johns Hopkins University, Baltimore, MD; [16]Dell Seton Medical Center at The University of Texas, Austin, TX; [17]University of Iowa Hospitals and Clinics, Iowa City, IA; [18]Hospital Universitario 12 de Octubre, Madrid, Spain.*

Background: We describe our preliminary experience with the launch of a novel international Registry – "LDGen" – as a repository to study current and evolving practices in genetic testing as part of living donor (LD) candidate evaluation.

Methods: A cross-sectional, electronic REDCap registry was developed to collect information on LD candidates and their genetic test results. LD candidates who either 1) underwent genetic testing, and/or 2) had a family history of genetic kidney disease, or 3) are looking to donate to a related recipient with kidney disease of unknown etiology were registered. Data reported here were collected between June, 2023 and May, 2024.

Results: Data on 1004 LD evaluations were obtained representing 12 U.S. and 9 international centers. 39% (n=305) of intended recipients had possible genetic kidney disease. Genetic testing was performed in 17% (n=168) of LD evaluations. Testing in recipient candidate was performed before the LD candidate in 73% (n=122) of cases while it was performed only in the donor candidate in 27% (n=46) of evaluations (Fig. 1A). 125 LD candidates underwent genetic testing and 81% of these donors received formal pre-test genetic counseling. Single gene/limited gene panel (42%) and broad kidney disease gene panel (29%) were the most common methods. 33% (n=41) of the LD candidates who underwent genetic testing during evaluation were not accepted, of which 51% (n=21) of declinations were due to the genetic testing result [Pathogenic/Likely pathogenic variant (n=9), renal risk variants (n=2), VUS (n=10)] (Fig.1B).

Conclusions: Our initial experience supports the feasibility of international collaboration in creating a registry of genetic kidney disease testing practices among LD candidates. With more data, the findings of the LDGen registry will provide value information on global LD evaluation practice patterns.



SA-PO969

Increase in Arterial Stiffness in Living Kidney Donors after Kidney Donation

Dennis Kannenkeril,[1] Merve Günes-Altan,[1] Agnes Bosch,[1] Kristina Striepe,[1] Mario Schiffer,[1] Kerstin U. Amann,[2] Roland E. Schmieder.[1] *[1]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg (FAU), Erlangen, Germany; [2]Department of Nephropathology, Department of Pathology, University Hospital Erlangen, Erlangen, Germany*.

Background: Low glomerular filtration rate (GFR) is associated with high cardiovascular mortality and morbidity. Living kidney donor's vascular characteristics have been poorly investigated till now. In this analysis, living kidney donors were followed up with respect to vascular parameters for one year after renal donation.

Methods: Blood pressure (BP) and different arterial stiffness parameters were assessed before, 6 months and 1 year after renal donation using a 24-hour blood pressure device (Mobil-o-graph®). Cortical, medullary and total renal perfusion of the donors were assessed using Arterial Spin Labeling MRI before and 6 months after donation. Preimplantation biopsy of the donor kidney was obtained. Biopsies were scored for glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis.

Results: Twenty-five living kidney donors with mean age of 54±9.4 were followed up for one year. The estimated GFR fell significantly (87.7±15.9 vs. 55.6±10.9 ml/min/1.73m^2; p<0.001) and urinary albumin creatinine ratio remained similar to baseline (19.5±18.4 vs. 19.5±12.2 mg/g creatinine; p=0.204) 1 year after donation. Pulse wave velocity (7.5±1.4 vs. 7.8±1.4; p=0.001), peripheral resistance (1.1±0.19 vs. 1.23±0.19;p=0.003), and augmentation index (heart rate corrected) (24.4±5.5 vs. 26.7±6.1;p=0.025) over 24 hours increased significantly 12 months after donation, while no change was observed in systolic and diastolic BP. A relationship has been found between eGFR at baseline and mean 24-hour pulse wave velocity at 12 months (r=-594, p=0.002). An increase in renal cortex perfusion was found 6 months after donation (351±53.4 vs. 388±40.7; p=0.013). The 24-hour systolic BP (116.6±6.8 vs. 129.1±10.7;p=0.011), -diastolic BP (73.2±4.4 vs. 81.3±5.6;p=0.006) and -central systolic BP (118.6± 8.9 vs. 128.9±7.7;p=0.013) at 12 months post donation was significantly higher in donors with renal histological changes compared to donors without renal histological changes, while no difference in BP was noticed at baseline between these groups.

Conclusions: Our data indicates that arterial stiffness increases after living kidney donation. This can be interpreted as an early change before increase in BP. Living donors with chronic renal histological changes tend to develop high BP after donation.

SA-PO970

Race-Neutral 2021 CKD-EPI Creatinine eGFR and Iohexol-Measured GFR in Living Kidney Donor Candidates

Walaa Dabbas, Ruchi H. Naik, Lorenzo G. Gallon, Ignatius Y. Tang. *University of Illinois Chicago, Chicago, IL*.

Background: The race neutral 2021 CKD EPI creatinine (Cr) eGFR was approved by the OPTN to calculate kidney function for transplant candidates on the national waitlist to address disparities in kidney transplantation. The 2021 CKD EPI Cr equation estimates a lower GFR for Black patients and a higher GFR for non -Black patients for the same creatinine value. Hence the 2021 CKD EPI Cr eGFR may not provide an accurate estimate of kidney function of potential living kidney donors

Methods: single center retrospective review of charts of potential kidney donors who had measured GFR by Iohexol clearance between January 1, 2021 and December 31, 2023. Data collected include demographics, eGFR calculated by race neutral 2021 CKD EPI Cr equation and Iohexol GFR test. Subjects were divided into 2 groups, Black and Non Black.

Results: Iohexol clearance was done in 333 kidney donor candidates, 62.7% were female and 23.7% were black. The average BMI was 30.4 kg/ m 2. There was a positive correlation between 2021 CKD EPI Cr eGFR and Iohexol GFR in both groups. Black donor candidates had lower eGFR calculated by 2021 CKD EPI Cr compared to non black, p=0.002. See table. There was no significant difference between Iohexol clearance between the 2 groups. The race neutral 2021 CKD EPI Cr eGFR overestimated GFR in non black compared to black individuals, p=0.02.

Conclusions: 2021 CKD EPI Cr eGFR correlated with the Iohexol GFR in black kidney donor candidates, however it overestimated GFR in non black kidney donors.

N=333	
Female, n (%)	209 (62.7)
Age, years, median [IQR]	41 [32-52]
African American, n (%)	79 (23.7)
Weight, kg, median [IQR]	83 [72-97]
Height, cm, median [IQR]	168 [160-173.5]
BMI, kg/ m^2, median [IQR]	30 [26-34]
HTN, n (%)	37 (11)
S.Cr, mg/dl, median [IQR]	0.79 (0.69-0.9]
Race neutral 2021 CKD EPI eGFR, ml/min, 1.73m^2, median [IQR]	103 [92-115]
BSA, m^2 median [IQR]	1.987 [1.82-2.176]
Iohexol GFR, ml/min, 1.73m^2, median [IQR]	98 [87-109]

Race neutral 2021 CKD EPI Cr eGFR, eGFR ml/min/1.73m^2, Mean (median [IQR]) All Black, n=79 Non-Black, n=254	 102.5 (102.5 [92-115]) 97.8 (97 [86-111) 104 (104 [95-116])	p=0.002
Iohexol GFR, ml/min/1.73m^2, mean(median[IQR]) All Black, n=79 Non-Black, n=254	 98 (98 [87-109]) 96.3 (98 [86-105]) 98.7 (98 [88-110])	p=0.24
Difference between 2021 CKD-EPI Cr eGFR and Iohexol GFR Mean median [IQR]) All Black, n=79 Non-Black, n=254	 4.5 (5 [-5-15]) 1.43 (0 [-9-13]) 5.5 (5.5 [-4.7-16])	p=0.02

SA-PO971

Postdonation Weight Gain Is Associated with Lower Likelihood of Recovering Predonation eGFR

Rhiannon D. Reed, Marshall C. Mcleod, Paul A. Maclennan, Vineeta Kumar, Jayme E. Locke. *The University of Alabama at Birmingham, Birmingham, AL*.

Background: Living kidney donors with obesity (body mass index (BMI) ≥ 30 kg/m^2) at donation have a lower likelihood of recovery of estimated glomerular filtration rate (eGFR) post-donation. We sought to understand whether early post-donation changes in weight are also associated with the likelihood of eGFR recovery.

Methods: Using data from the Scientific Registry of Transplant Recipients, we examined 91,653 adult living kidney donors (1999-2023) with pre-operative serum creatinine and height/weight measurements and at least one creatinine and weight measurement post-donation. We utilized the 2021 CKD-EPI equation to estimate eGFR, and Cox proportional hazards regression with a time-varying covariate for change in BMI was utilized to estimate the likelihood of recovering at least 60% of pre-donation eGFR, censoring for last creatinine measurement.

Results: Among a cohort that was majority female (63%) and white (85%), donors were median age 43 years (IQR: 33-52) and median BMI 26.6 kg/m^2 (IQR: 24.0-29.6). Median pre-donation serum creatinine was 0.80 mg/dL (IQR: 0.70-0.93), with a median mean arterial pressure of 90 mmHg (IQR: 83.3-96.3). On unadjusted analyses, gaining > 5% BMI (a clinically relevant threshold for risk of cardiovascular and obesity-related complications) was associated with a 7% lower likelihood of recovering 60% of pre-donation eGFR (HR: 0.93, 95% CI: 0.92-0.94, p< 0.001), while losing > 5% BMI was positively associated with recovery (HR: 1.02, 95% CI: 1.00-1.03, p=0.01). After adjusting for relevant baseline factors, gaining > 5% BMI remained significantly associated with a lower likelihood of eGFR recovery (aHR: 0.91, 95% CI: 0.90-0.93, p < 0.001) (Figure).

Conclusions: Weight change in the early post-donation period is a modifiable factor that is associated with recovery of kidney function. These findings highlight the need for a greater commitment to support living donors in maintaining healthy lifestyles post-donation and prospective studies of living donor follow-up.

Funding: NIDDK Support

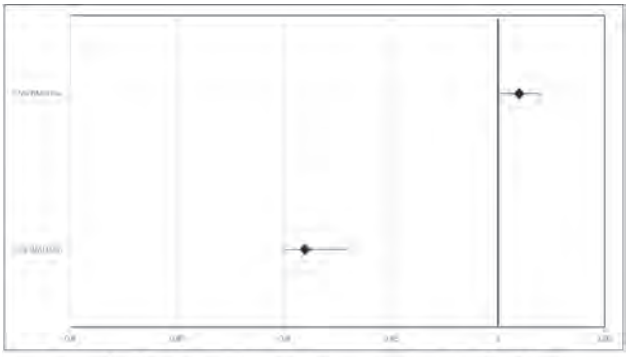


Figure. Forest plot of the likelihood of 60% eGFR recovery post-donation (ref=BMI Stable)

SA-PO972

Using Machine-Learning Techniques to Predict Postdonation Kidney Function in Living Kidney Donors

Junseok Jeon, Kyungho Lee, Jung eun Lee, Wooseong Huh, Hye Ryoun Jang. *Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*.

Background: Predicting kidney function after kidney donation is critical to properly selecting donors for living kidney donation. We aimed to predict postdonation kidney function after a living kidney donation using machine learning techniques.

Methods: This retrospective cohort study included 823 living kidney donors from 2009 to 2020. The dataset was randomly divided into training (80%) and test (20%) sets. The main outcome was the postdonation estimated glomerular filtration rate (eGFR) at 12 months after kidney donation. We compared the performance of various machine learning techniques, traditional regression models as well as model from previous study. The best-performing model was selected using the mean absolute error (MAE) and root mean square error (RMSE).

Results: The mean age was 45.2 ± 12.3 years, and 48.4% were males. The mean predonation and postdonation eGFRs were 101.3 and 68.8 ± 12.7 mL/min/1.73 m^2, respectively. The XGBoost model showed the best performance with an MAE of 6.23 and RMSE of 8.06 with feature importance, including eGFR, age, serum creatinine, 24-hour urine creatinine, 24-hour urine sodium, creatinine clearance, cystatin C, cystatin C-based eGFR, computed tomography volume of the remaining kidney/body weight, normalized GFR of the remaining kidney measured through a diethylenetriaminepentaacetic acid (DTPA) scan, and sex. An easy-to-use web application titled Kidney Donation with Nephrologic Intelligence (KDNI) was developed.

Conclusions: The prediction model using XGBoost accurately predicted the postdonation eGFR after living kidney donation. This model can be applied in clinical practice using KDNI, the developed web application.

Funding: Government Support - Non-U.S.

SA-PO973

Evaluation of Renal Functional Reserve in Adult Living Kidney Donors

Jose L. Ortega, Mario Alamilla-Sanchez, Enrique F. Morales Lopez, Ydris Z. Rosillo-Salgado, Jose L. Torres Cuevas, Carolina Gonzalez-Fuentes, Victor M. Ulloa Galvan, Jesús O. Rubio, Martin O. Carbajal. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico*.

Background: Renal functional reserve (RFR) assessed by renal response to a protein load is considered to reflect functional reserve capacity and is believed to be a tool for screening living donors

Methods: A descriptive, observational and prospective study was carried out in a single center where 22 living kidney donors, over 18 years of age, clinically healthy, were considered between the month of July 2023 to May 2024. RFR was measured with a test of the glomerular stress using an oral protein loading test

Results: Of a total of 22 patients included, the median age was 39 (18-56) years, 77% (17) women. Body mass index was 25.5 (20.2 to 32.7). Median baseline Cr was 0.67 (0.47-1.04) mg/dl, median baseline cystatin was 0.67 (0.40-0.9) mg/dl versus post-cystatin. stress was 0.6 (0.30-0.90) mg/dl. The median values of bGFR and sGFR were statistically different (123.54 [56.38 -250.11] vs. 178.71 [84.88 - 418.43] ml/min/1.73 m2, p = 0. 0017. A difference will be observed between bGFR and sGFR, with an RFR = 45.9% (11.87-132.62) equivalent to an increase in GFR after a protein load of 48.81 ml/min (16.24- 161.56) having a bGFR > 90 ml/min was associated with a risk of presenting borderline FRR < 30). ml/min OR 1.2 95% CI (1.0- 1.05) and a BMI < 30 estimated an OR 0.76 95% CI (0.60-0.96) protective factor to preserve an RFR > 30ml /min.

Conclusions: The results suggest that glomerular renal stress testing by oral protein loading could be useful before transplantation to establish the original global filtration capacity of the donor kidneys. The results provide a previous global renal function of 48 ml/min, a result similar to that reported in the literature, drawing attention to the tendency in obese patients to present a low RFR, as well as the no association in the level of basal normality. creatines and RFR that may represent an inadequate estimate and present the patient's susceptibility to developing kidney injury before it becomes clinically evident

SA-PO974

Long-Term Risk of ESKD in Kidney Donors with Diabetes Mellitus Using eGFR 6 Months after Donation

Lovy Gaur, Manoj K. Singhal. *Max Superspeciality Hospital Vaishali, Ghaziabad, NCR, India*.

Background: Traditionally, diabetes mellitus was considered contraindication for kidney donation. Guidelines now recommend evaluation of such donors on case-to-case basis. Estimated GFR at 6 months post-donation (eGFR6) may be surrogate for long-term risk of ESKD. As per a study, 15-year cumulative incidence of ESKD with eGFR6 >70 ml/min was estimated to be 11.7/10000 donors against 33.7/10000 donors if eGFR6< 50ml/min. We demonstrate potential safety of donors with diabetes using eGFR6.

Methods: Potential kidney donor with diabetes mellitus were evaluated only after exploring other voluntary family members' feasibility to donate. As per KDIGO recommendations, older diabetic candidates with well-controlled glycemia, not requiring insulin & without end-organ damage were considered. Donors were deemed eligible only if pre-donation projected 15-year-risk of ESKD was <1% as estimated by ESRD-Risk tool for living kidney donors(NYU Langone's Center for Surgical & Transplant Applied Research(C-STAR)). Independent assessment of potential donors by Internal Hospital Medical Board was also done.

Results: 345 patients received kidney transplantation from Jan 2019 to Dec 2023. 9 kidney donors with diabetes (mean age-60.7yrs), with follow-up of > 6months were included.8 donors were detected to have diabetes during work-up for donation & 1 had been diabetic for 5 years and 5 had hypertension. Mean HbA1C was 6.7%. Mean pre-donation creatinine was 0.75 mg/dl(eGFR- 92.84 ml/min), urine albumin-creatinine ratio was 20.29. Mean DTPA-GFR of retained kidney was 41.42 ml/min. Mean follow up was 20.6 months (6-48 mon). Average eGFR at 6 months was 59.8 ml/min. Only 1 donor (aged 72 years) had eGFR6 < 50ml/min (38 ml/min). On her last-follow-up at 24 months, she continues to do well (creatinine-1.29,UACR <30). Graft outcomes were good. Only 1 graft was lost to plasma-cell rich rejection at 6 months post-transplant. Another patient who was biopsied 2 weeks after transplant had mild ATN, which recovered gradually. None of these patients had histopathological changes of diabetic nephropathy.

Conclusions: Our study demonstrates safety of diabetic kidney donors using eGFR6 as a surrogate for long-term risk of ESKD. More long-term studies are required to substantiate this risk. In certain exceptional circumstances, donation from diabetic donors may be considered, considering intangible effects of recipient health on donor well-being.

SA-PO975

Relationship between New-Onset Proteinuria and Remnant Kidney Hypertrophy and/or Pre-donated Kidney Volumes

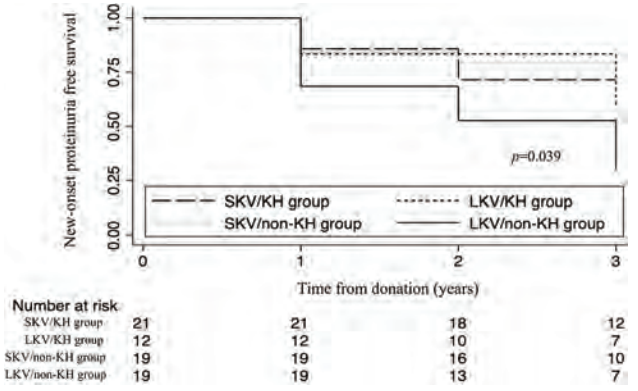
Masatomo Ogata,[1] Takamasa Miyauchi,[1] Kiyomi Osako,[1,2] Naohiko Imai,[1] Yuko Sakurai,[1] Kazunobu Shinoda,[1] Yugo Shibagaki,[1] Masahiko Yazawa.[1] *[1]St. Marianna University School of Medicine, Kawasaki, Japan; [2]Shiraishi hospital, Kagoshima, Japan*.

Background: Some living kidney donors (LKDs) develop proteinuria, which is generally associated with end-stage kidney disease. Previous reports have shown new-onset proteinuria correlates with preoperative preserved kidney volume (PKV) and remnant kidney hypertrophy (%PKV change). We explored the association between the combination of preoperative PKV and %PKV change after donation and new-onset of proteinuria.

Methods: This single-center, retrospective, observational study included eligible LKDs who donated kidneys between January 2008 and July 2022 (N=195). Of these, 71 LKDs who had their PKV calculated via non-contrast computed tomography (CT) volumetry before and 1 year after donation and who were evaluated for proteinuria were included. They were divided into four groups according to the mean body surface area (BSA)-adjusted PKV (large [LKV] and small [SKV]) and mean %PKV change (hypertrophy [KH] and non-hypertrophy[non-KH]), and the association with new-onset proteinuria was investigated. Time-to-event analysis was performed using log-rank tests. Significant factors for event occurrence were calculated using Cox proportional hazards model adjusted by age and sex.

Results: Mean age was 59.7 ± 7.9 years and 71.8% were female (N=51). The mean %PKV change and BSA-adjusted PKV were 20.3 ± 7.0%, and 161.6 ± 24.0 cm^3, respectively. During the 2.3 years follow-up period (mean), the LKV/non-KH group had significantly higher proteinuria events than the other groups (log-rank test, p = 0.039). The LKV/non-KH group had a significantly higher hazard ratio (HR) of new-onset proteinuria than the SKV/KH group (adjusted HR: 2.87, 95% confidence interval: 1.03–8.06).

Conclusions: Post-donated proteinuria is more likely to occur in kidneys already enlarged before donation and is not sufficiently hypertrophic change after donation in LKDs. This imaging study before and shortly after donation might authorize personalized follow-up in LKDs.



SA-PO976

Measurement and Estimation of Kidney Length Using Computed Tomography and Predictor Formulas in Kidney Transplant Donors

Moises Cruz Landino,[1] Diana Laura Muñoz,[1,2] Adriana Banda Lopez,[1,2] Enrique Rojas-Campos,[1] Ricardo Parra Guerra,[1] Salvador Mendoza Cabrera,[1] Luis Alberto Evangelista-Carrillo,[1] Diana N. Sanchez,[1] Maria Santisbais Beas.[1,2]
[1]Instituto Mexicano del Seguro Social Delegacion Jalisco, Guadalajara, Mexico; [2]Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Guadalajara, Mexico.

Background: Kidney length measurement is fundamental in the diagnosis of chronic kidney disease. The aim of this study is to evaluate the relationship between kidney length measured by computed tomography (CT) and the estimation by three predictive formulas in the Mexican population.

Methods: This was a cross-sectional, analytic study performed in kidney donors who had renal length measured by CT. Age, body height, weight, blood pressure, and serum creatinine concentrations were measured. Based on body height and weight, we calculated kidney length using three distinct formulas. Pearson correlation coefficients were obtained between kidney length measured by CT and the results obtained using the formulas

Results: A total of 212 kidney donors were included. Mean age 39.5 ± 11 years, men 97 (47%), body weight 71.5 ± 6 kg, height 1.65 ± 0.1 m, eGFR 106 ± 12 ml/min. Mean right kidney length: 103 ± 8 mm, left kidney length: 104 ± 8 mm. Right kidney volume 130 ± 33 cm3, left kidney volume 132 ± 34 cm3. Figure 1. There was a significant correlation between CT kidney length, and the estimation by formulas. The strongest correlation significance was observed by using Formula 3 for left kidney (r=.041) and right kidney (r=0.38). Table 1 and Figure 2 resume study findings

Conclusions: The kidney length estimation by formulas show a significant correlation with the measurement by CT. Formula 3 better estimates kidney lenght in Mexican population.

Table 1: Correlation between kidney length by CT and estimation by formulas

		Correlation coefficient	p
Left Kidney	Formula 1	0.4	0.01
	Formula 2	0.34	0.01
	Formula 3	0.41	0.01
Right Kidney	Formula 1	0.36	0.01
	Formula 2	0.28	0.01
	Formula 3	0.38	0.01

	All N=212	Men n=97	Women n=115
Age (years)	39.5 ± 11	37.1 ± 12	41.4 ± 9.5
Weight (kg)	71.5 ±	78.7 ± 9.6	65.5 ± 7
Height (m)	1.65 ± 0.1	1.7 ±0.1	1.59 ± 0.1
BMI (kg/m2)	26.1 ± 2.7	26.4 ± 2.7	25.8 ± 2.7
BSA(m2)	1.8 ± 0.17	1.9 ± 0.15	1.7 ± 0.11
SBP (mmHg)	116 ± 9.1	115 ± 8	117 ± 10
DBP (mmHg)	75 ± 7	75 ± 7	75 ± 7
Glycemia (mg(dL)	86 ± 8	84 ± 8	87 ± 8
Right Kidney Length, CT (mm)	103 ± 8	105 ± 8	102 ± 8
Left Kidney Length, CT (mm)	104 ± 8	106 ± 8	102 ± 7
Right Kidney Volume, CT (cm3)	130 ± 33	143 ± 37	120 ± 26
Left Kidney Volume, CT(cm3)	132 ± 34	148 ± 37	118 ± 25
Serum Creatinine (mg/dL)	0.78 ± 0.1	0.9 ± 0.1	0.68 ± 0.09
eGFR (ml/min/1.73m2)	106 ± 12	107 ± 12	105 ± 12

SA-PO977

Sociodemographic Correlates of Mortality after Living Kidney Donation: Informing the Need for Nondonor Controls

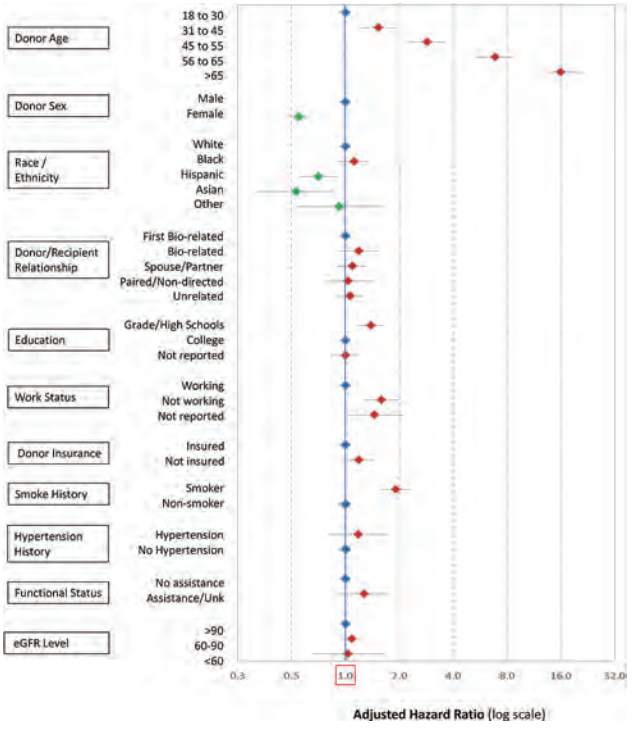
Krista L. Lentine,[1] Yasar Caliskan,[1] Amy D. Waterman,[2] Ajay K. Israni,[3] Jon J. Snyder,[3] Allyson Hart,[3] Vidya Fleetwood.[1] *[1]Saint Louis Univ., St. Louis, MO; [2]Houston Methodist, Houston, TX; [3]Hennepin County, Minneapolis, MN.*

Background: Mandated follow-up of living kidney donors (LKDs) in the U.S. is limited to 2 years postdonation. Recently, an expanded linkage of death records to the national transplant registry was conducted, enabling capture of intermediate-term death events after living donation.

Methods: We examined Scientific Registry of Transplant Recipients (SRTR) data incorporating updated linked national death records to examine the incidence and adjusted correlates of mortality (adjusted hazard ratio, $_{95\%\ LCL}$ aHR $_{95\%\ UCL}$) after donation, censored at 09/02/23. LKDs were registered in 1987-2023.

Results: Among 179,977 LKDs in the registry, overall mortality at 10 years was <1%. 10-year mortality rose with older donor age, up to 4.9% in donors aged >65 years at donation (vs 0.3% in those who donated at age 18-30; aHR; $_{11.5}$ 15.9 $_{21.8}$). Mortality was lower in women (vs men: 0.6% vs 0.9%; aHR, $_{0.48}0.55_{0.63}$), and in Hispanic and Asian (vs White) LKDs, but slightly higher in spousal donors. Mortality trended higher in uninsured LKDs, was higher in those not working, and nearly twice as high in smokers (vs nonsmokers: 0.9% vs 0.7%; aHR, $_{1.57}1.91_{2.31}$). 10-year death risk did not vary significantly according to hypertension history or predonation eGFR.

Conclusions: Intermediate-term mortality after living kidney donation varies with age, sex, race, relationship, education, employment, and smoking status. While trends are similar to general population patterns, comparison to nondonor controls through mechanisms such as the SRTR Living Donor Collective candidate registry are needed for continuous monitoring of donation-attributable risks. Sociodemographic correlates of mortality in LKDs warrant attention for risk mitigation to support optimal long-term outcomes in all donors.



SA-PO978

Racial Disparities in Access to Deceased Donor Kidney Transplantation in the United States, 1999-2023

Fawaz Al Ammary,[1] Krista L. Lentine,[2] Deidra C. Crews,[3] Abimereki Muzaale,[3] Simeon Adeyemo.[1] Living Donor Transplant Outcome Collaborative (LDTOC).
[1]University of California Irvine, Irvine, CA; [2]Saint Louis University, St Louis, MO; [3]Johns Hopkins University, Baltimore, MD.

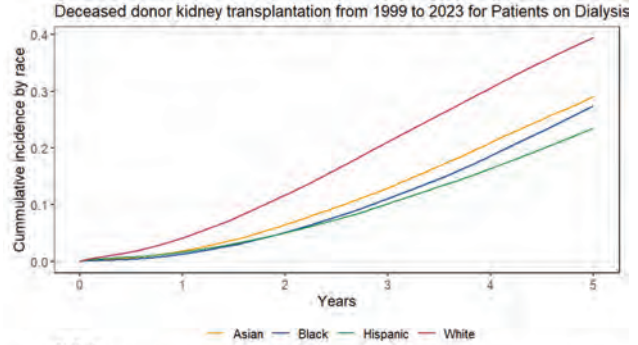
Background: The Kidney Allocation System was revised in December 2014 to provide priority from start of dialysis rather than listing date to improve equity in access to transplantation. We examined the interplay between race/ethnicity and duration of dialysis in access to deceased donor kidney transplantation over time.

Methods: We used the Scientific Registry of Transplant Recipients of 350,516 adult first-time kidney transplant candidates on dialysis between 1999 and 2018. Outcome was dialysis time to deceased donor kidney transplantation, and exposure was race/ethnicity. We used competing risk survival to estimate the cumulative incidence of the outcome competing with death and multivariable Cox regression models to adjust for confounders. Analyses stratified by era (1999–2003, 2004–2008, 2009–2013, and 2014–2018). Patients were followed for 5 years, ending in December 2023.

Results: Overall, the cumulative incidence of deceased donor kidney transplantation for patients on dialysis varied by race [Figure]. In adjusted models compared to White patients, in the eras 1999–2003, 2004–2008, 2009–2013, and 2014–2018, Black patients were less likely to be transplanted by 45%, 37%, 35%, and 27%; Hispanic patients by 45%, 50%, 43%, and 38%; and Asian patients by 42%, 37%, 31%, and 30%, respectively [Table].

Conclusions: Although there has been increase in deceased donor kidney transplantation in recent years for U.S. dialysis patients, racial disparities remain. Gaps are narrowing for Black and Asian patients but remain unchanged for Hispanic patients on dialysis. Programs are needed to address systemic barriers and enhance policies to support equitable access to transplantation for racial minorities.

Funding: NIDDK Support



At Risk						
Asian	24156	22749	20128	17093	13802	10603
Black	115245	111264	101587	88309	72738	56237
Hispanic	72492	68527	61756	53607	44627	35275
White	138623	121644	97554	73589	52048	34810
Events						
Asian	0	431	1475	2857	4460	5953
Black	0	1468	5688	12031	19620	27795
Hispanic	0	1168	3464	6764	10506	14473
White	0	5482	14668	24865	33991	41421

Deceased Donor Kidney Transplantation by Era, Adjusted HR (95% CI)

Patients on dialysis	1999-2003	2004-2008	2009-2013	2014-2018
White	Ref	Ref	Ref	Ref
Black	0.55 (0.53-0.57)	0.63 (0.61-0.65)	0.65 (0.63-0.67)	0.73 (0.71-0.75)
Hispanic	0.55 (0.52-0.57)	0.50 (0.48-0.52)	0.57 (0.55-0.59)	0.62 (0.59-0.64)
Asian	0.58 (0.54-0.62)	0.63 (0.60-0.67)	0.69 (0.65-0.73)	0.70 (0.66-0.73)

All models were adjusted for age at listing, sex, race, ABO blood type, BMI, and DM as the cause of ESRD

SA-PO979

Evolution of Biologically Related Living Kidney Donations in the United States over 35 Years

Fawaz Al Ammary,[1] Simeon Adeyemo,[1] Krista L. Lentine,[2] Abimereki Muzaale.[3]
[1]University of California Irvine, Irvine, CA; [2]Saint Louis University, Saint Louis, MO; [3]Johns Hopkins University, Baltimore, MD.

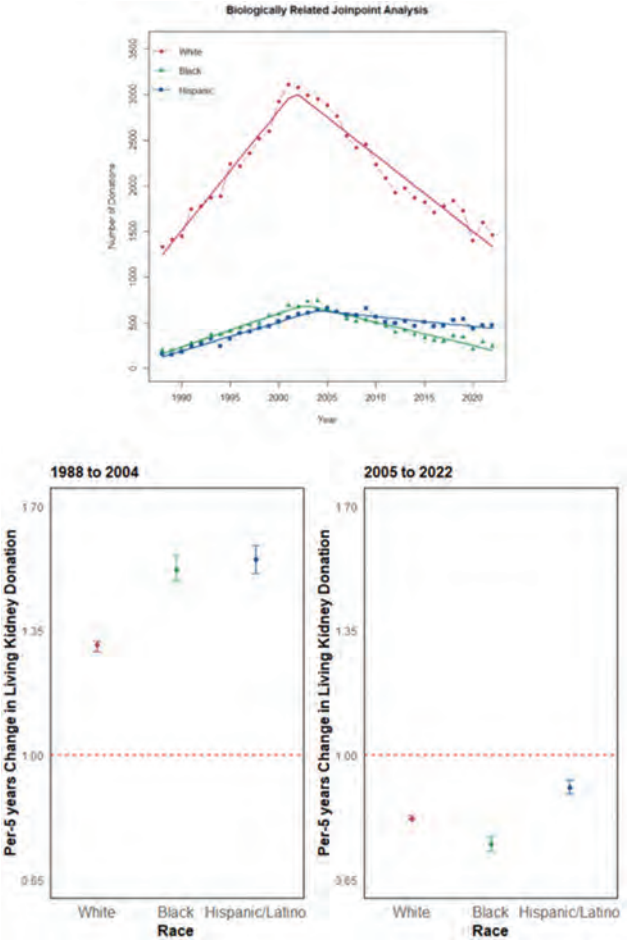
Background: Living kidney donors have declined over the last two decades, mainly driven by biologically related donors with the recipient. We sought to understand the interplay of biological donor-recipient relationship and race to guide future interventions.

Methods: We used the Scientific Registry of Transplant Recipients to examine changes in biologically related living kidney donations over time. *A priori*, we stratified the analyses by era (1988–2004 and 2005–2022) and donor race (Black, Hispanic, and White/others). We used Poisson regression to estimate change in number of donors per 5-year increment (incidence rate ratio, IRR).

Results: Of 106,033 biologically related donors (43% full sibling, 25% offspring, 20% parents, and 12% non-first-degree relative donors) 71% were White, 14% Black, and 15% Hispanic. The rates of biologically related donors between 1988 and 2004 increased across race. For every 5-year increment, White related donors increased by 31% (IRR $_{1.29}1.31_{1.32}$), Black related donors increased by 52% (IRR $_{1.49}1.52_{1.56}$), and Hispanic related donors increased by 55% (IRR $_{1.51}1.55_{1.59}$). Conversely, the rates of biologically related donors between 2005 and 2022 decreased across race. For every 5-year increment, White related donors decreased by 18% (IRR $_{0.82}0.82_{0.83}$), Black related donors decreased by 25% (IRR $_{0.73}0.75_{0.77}$), and Hispanic related donors decreased by 9% (IRR $_{0.89}0.91_{0.93}$).

Conclusions: Our study highlights opportunites to reduce barriers to biologically related donations among racial/ethnic minorities and the socioeconomically disadvantaged healthy adults. Efforts are needed to reduce hurdles for biologically related donors, potentially by providing outreach education, easing access to donor evaluation, offering social and financial support, and assuring post-donation follow-up care.

Funding: NIDDK Support



SA-PO980

Perioperative Donor Nephrectomy Risks in Living Kidney Donors with Obesity: A Systematic Review and Meta-Analysis

Fawaz Al Ammary,[1] Simeon Adeyemo,[1] Abimereki Muzaale,[2] Asad Naveed.[3]
Living Donor Transplant Outcome Collaborative (LDTOC). *[1]University of California Irvine, Irvine, CA; [2]Johns Hopkins University, Baltimore, MD; [3]University of Toronto, Toronto, ON, Canada.*

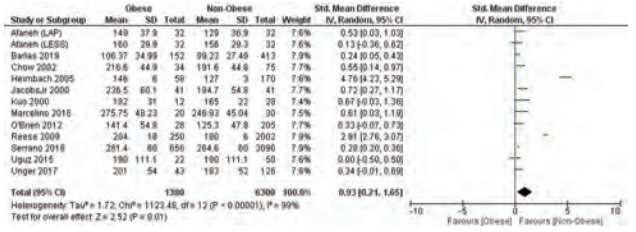
Background: Obesity is a global public health concern. Given the shortage of living kidney donations, transplant centers have been more willing to accept obese donor candidates in recent years. To better counsel obese donor candidates about donor nephrectomy risks, we aimed to summarize evidence for the perioperative risks for obese living kidney donors compared to non-obese living kidney donors across studies.

Methods: A systematic search of standard databases was conducted to identify studies comparing obese and non-obese living kidney donors. Outcome data were extracted and synthesized. Obesity was defined as BMI ≥ 30. The risk of bias was assessed using Cochrane's risk of bias in non-randomized studies - of interventions (ROBINS-I) tool.

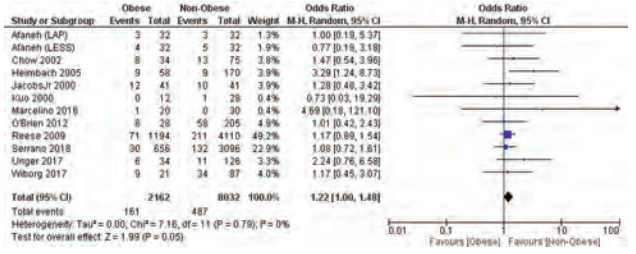
Results: Fifteen cohort studies were included in the final review. Obese patients have significantly longer operative times compared to non-obese patients, with a standardized mean difference of 0.93 (95% CI: 0.21 to 1.65, P=0.01), favoring non-obese donors (Figure 1). Additionally, Obese donors have significantly higher odds of surgical complications compared to non-obese patients, with an odds ratio of 1.22 (95% CI: 1.00 to 1.48, P=0.05), favoring non-obese patients (Figure 2).

Conclusions: Living kidney donors with obesity have increased risks of longer operating time and perioperative complications. These findings highlight the need for interventions to minimize perioperative risk for obese donors and tailored follow-up care to ensure best outcomes for this group of donors, who provide a vital source for living kidney donation.

Funding: NIDDK Support



Operative time



Surgical complications

SA-PO981

Racial and Relationship Trends in Living Kidney Donation: A Retrospective Analysis from Miami Transplant Institute

Daniel S. Del Castillo Rix,[1] Veronica A. Ortigosa Serrano,[2] Adriana Medina,[3] Rojin Esmail,[3] Franco H. Cabeza Rivera.[1] *[1]Jackson Memorial Hospital, Miami, FL; [2]University of Miami, Coral Gables, FL; [3]Ross University School of Medicine - Barbados Campus, Bridgetown, Barbados.*

Background: Living kidney donation is pivotal in combating end-stage renal disease, offering superior outcomes and reduced waiting times compared to deceased donor transplants. Understanding the relationship between donors and recipients, particularly across various racial and ethnic groups, is crucial for developing targeted strategies to increase donor recruitment and improve transplant equity, ultimately enhancing patient outcomes in transplant medicine.

Methods: We retrospectively reviewed the clinical data of seven hundred seventy donors who underwent nephrectomy for living donor kidney transplantation at the Miami Transplant Institute from 2011 to 2021. We evaluated the relationships between living kidney donors and recipients and how they varied across racial and ethnic groups over time. We used descriptive statistics to describe the changes in living kidney donors and chi-squared to determine its statistical significance. Logistic regression was used to determine differences in relationships by race over time statistical significance was set at a p-value <0.05, with analyses performed using STATA/BE, version 17.

Results: We included 770 patients, who were categorized into three primary groups: White (266 participants, 34.8%), Black (155 participants, 20.1%), and Latino (347 participants, 45.1%). Within these groups, the total number of related donors varied: 122 (45.5%) in the White group, 107 (69%) in the Black group, and 192 (55.3%) in the Latino group. Logistic regression revealed no significant differences in the trends of kidney donation over time.

Conclusions: This retrospective analysis underscores the complexities of living kidney donation across our different groups. Despite variances in the proportion of related donors among White, Black, and Latino groups, our findings indicate no significant changes in the trends of kidney donation relationships over time. However the proportion of related donors is notably higher in the Black and Latino group compared to white. This suggests underlying social and cultural differences in living kidney donation attitudes that could be addressed by incentivizing culturally sensitive programs. Further studies need to be done to better understand what factors influence differences in relationships.

SA-PO982

Quality of Life in Kidney Donors: A Single-Center Experience

Amgad E. El Agroudy. *Arabian Gulf University, Manama, Bahrain.*

Background: Living kidney donation is used to treat ESRD, but it poses risks and decision-making challenges for donors. This study examines kidney donors' long-term quality of life (QOL).

Methods: We conducted a cross-sectional survey on kidney donors between 1982 and 2018. We used the SF-36 (Arabic version) to measure the donors' quality of life (QOL). Out of 60 donors contacted, 44 agreed to participate and responded. Demographic information, donor-recipient relationships, and specific questions about the donation were collected and analyzed.

Results: The mean age of the donors was 50.1 ± 11.7 years at follow-up, and 26 (59.1%) were males. Most donors were siblings and parents, accounting for 36.4% (n=16) each. The time since the donation was 111.5 ± 97.1 months. All donors decided voluntarily to donate and all of them would do it again if given a chance. However, one donor (2.3%) complained that the donation had caused problems in his marriage, while 6 donors (13.4%) experienced clinically relevant distress, and 2 donors (4.5%) experienced financial disadvantages. Donors had high QOL scores, with a mean score of 73.1 and 96.9 (on a scale of 1-100) for the 8 subscales. The highest score was for role social functioning, while the lowest was for Energy/Fatigue. The mean scores for the four fatigue subscales were low, ranging from 61.8 to 86.8. The lowest score was for feeling calm and reassured, while the highest was for feeling frustrated. In social functioning, the highest score was for the effect of mental health on work performance (97.2). We analyzed various demographic factors and their correlation with QOL and found no significant correlation in most domains regarding sociodemographic characteristics.

Conclusions: Our research indicates that most kidney donors have had a positive experience over the past four decades. Both male and female donors of all ages reported good long-term quality of life, further enhanced by recognition and support from their families and friends. These findings provide further support for our current policy on organ donation.

SA-PO983

Simultaneous Liver-Kidney Transplant vs. Safety Net Kidney after Liver Transplant: How Has the Policy Change Impacted Graft and Patient Outcomes?

Anjana Murali, Srijan Tandukar, Mary Ann C. Lim. *University of Pennsylvania, Philadelphia, PA.*

Background: The policy governing the eligibility criteria for simultaneous liver-kidney transplant (SLK) was implemented on Aug 10, 2017. After policy change, liver transplant patients can be listed for kidney transplants (KAL) by the safety net criteria between posttransplant days 60 to 365 if they have a qualifying eGFR of ≤20 ml/min. The impact of this policy change for transplant recipients at our center is not known.

Methods: Demographic information for recipients and donors, chronic kidney and liver disease history, transplant characteristics, graft function and patient survival information were collected by chart review for transplants occurring between Aug 10, 2017 and Mar 31, 2023. Rates of primary non function (PNF), death, rejection, and time between waitlisting and transplant were collected for all patients listed for liver and kidney transplant.

Results: There was a total of 49 SLK recipients and 16/37 liver transplant patients who were listed for KAL received a kidney transplant. The proportion of patients on dialysis at the time of listing for SLK and KAL was 57% (N=21) vs 63% (N=23). Hepatorenal syndrome was a cause of kidney disease in 31% (N=15) vs 46% (N=17) patients of SLK vs KAL recipients. 2 SLK recipients developed PNF whereas none of the KAL recipients developed PNF. 14 KAL patients (88%) received the kidney transplant within 2 years of a liver transplant. Among KAL listing, 81% (N=30) occurred within the safety net period. The mean eGFR at 1 year post transplant was 55 and 61 ml/min for SLK vs KAL. Two patients on KAL waitlist recovered kidney function and were removed from the waitlist.

Conclusions: Most patients receiving a liver alone received a kidney transplant within 2 years of the liver transplant, most often through the safety net criteria. The patients receiving KAL had comparable allograft function, rejection and patient survival rates to SLK patients. Some patients on KAL waitlist recovered kidney function and were removed from the waitlist allowing these kidneys to be allocated to patients listed for a kidney transplant alone. Identification of patients that may be able to get KAL transplant may allow for improved access to kidney transplant for others on the deceased donor kidney transplant waitlist.

SA-PO984

Outcomes of Kidney after Liver Transplantation by Induction Type, Stratified by Intertransplant Interval and Immunologic Risk

Gabriel Cojuc,[1] Stalin Canizares,[1] Maria B. Rivera,[1] Ritah R. Chumdermpadetsuk,[1] Kalathil K. Sureshkumar,[2] Devin Eckhoff,[1] Martha Pavlakis,[1] Bhavna Chopra.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Allegheny Health Network, Pittsburgh, PA.*

Background: There is no standard induction immunosuppression (IS) for kidney after liver transplants (KALT). Time from liver engraftment and immunologic risk have been hypothesized as effect modifiers for induction therapy-related outcomes. We aimed to assess outcomes in KALT according to induction type, further stratified by inter-transplant intervals and immunologic risk.

Methods: Retrospective UNOS registry cohort study. We selected KALT between 2010 and 2022 who received mycophenolate- and tacrolimus-based maintenance IS. We compared patient death, graft loss, and death-censored graft failure (DCGF) using Cox proportional hazards models in KALT according to induction type (depleting vs. non-depleting), inter-transplant intervals (<1, 1–3, >3 years), and calculated panel reactive

antibody (cPRA) (<20, 20–49, 50–80, >80) adjusting for gender, age, ethnicity, steroid use, dialysis vintage, HLA mismatch, cold ischemic time, body mass index, kidney donor profile index, diabetes, and donor characteristics.

Results: We included 1640 KALT (31% female, age 58.5±11 yrs), 61% received depleting, and 39% non-depleting induction IS. There were no statistically significant differences between induction IS groups in patient death (HR 1.01, 95% CI 0.79–1.30), graft loss (0.96, 95% CI 0.76–1.22), and DCGF (HR 1.14, 95% CI 0.86–1.52). The results were consistent when stratifying into inter-transplant intervals; no differences were observed in KALT with <1, 1–3, or >3 years between transplants. Similarly, there were no differences in the outcomes categorized by cPRA (Table).

Conclusions: Induction IS therapies did not impact patient death, graft loss, and DCGF in KALT stratified by inter-transplant intervals and cPRA. The selection of induction IS should be individualized based on immunologic and infection risk.

Depleting (D) vs. non-depleting (ND) induction in KALT	Adjusted patient death HR (95% CI); p value	Adjusted graft loss HR (95% CI); p value	Adjusted death censored graft loss HR (95% CI); p value
All KALT (D = 996; ND = 644)	1.01 (0.79–1.30); 0.91	0.96 (0.76–1.22); 0.75	1.14 (0.86–1.52); 0.37
<1 yr post LT (D = 163; ND = 135)	0.70 (0.22–2.23); 0.55	0.49 (0.19–1.25); 0.14	1.09 (0.51–3.81); 0.89
1–3 yr post LT (D = 182; ND = 138)	1.23 (0.61–2.50); 0.56	0.89 (0.46–1.71); 0.73	1.35 (0.54–3.37); 0.52
>3 yr post LT (D = 651; ND = 371)	0.98 (0.74–1.30); 0.90	0.97 (0.73–1.28); 0.82	1.13 (0.81–1.55); 0.47
cPRA <20 (D = 561; ND = 459)	1.15 (0.84–1.57); 0.39	1.07 (0.79–1.43); 0.68	1.16 (0.82–1.65); 0.40
cPRA 20-49 (D = 93; ND = 63)	0.48 (0.15–1.51); 0.21	0.59 (0.18–1.88); 0.37	1.96 (0.39–9.80); 0.41
cPRA 50–80 (D = 138; ND = 66)	0.81 (0.33–1.95); 0.63	0.63 (0.27–1.48); 0.29	1.20 (0.40–3.61); 0.75
cPRA >80 (D = 204; ND = 56)	0.59 (0.28–1.25); 0.17	0.64 (0.30–1.33); 0.23	0.91 (0.34–2.46); 0.85

SA-PO985

Comparative Analysis of Infection and Rejection Rates for Recipients of Kidney-after-Liver (KALT) Compared with Simultaneous Liver and Kidney Transplant (SLK)

Sarah Abu Kar, Laura Binari, Scott A. Rega, Irene Feurer, Saed Shawar. *Vanderbilt University Medical Center, Nashville, TN.*

Background: We investigated 1- and 3 year kidney allograft and patient outcomes for recipients of (KALT) compared to (SLK). Analysis of infection and rejection outcomes by induction type and panel reactive antibody (PRA) was performed.

Methods: Data were collected from the records for patients who had SLK or KALT at Vanderbilt University Medical Center between 1983 and 2022. Patients with multiple kidney transplants or insufficient data were excluded. Data were analyzed using summary statistics, chi square, ANOVA, and Kaplan-Meier survival and multivariable logistic regression analysis.

Results: 59 patients, 39 KALT and 20 SLK recipients, were included. Age at kidney transplant was 57±10 years. Among all patients, kidney induction therapy was 44% alemtuzumab, 27% basiliximab, 24% methylprednisolone and 5% thymoglobulin. A higher proportion of KALT received alemtuzumab (62% vs 10% SLK), whereas more SLK patients (60% vs 5% KALT) received methylprednisolone (p<0.05). Maintenance IS did not differ between the two groups. Mean serum creatinine and GFR at 1-year (1.29±0.39 mg/dL, 57.31±19.9 ml/min/1.73m2) and 3-years (1.32±0.37 mg/dL, 54±17.6 ml/min/1.73m2) did not differ between the two groups. Point estimates of 3-year patient and death-censored graft survival were 84.6% (SE= 4.7%) and 93.1% (SE= 3.3%), respectively. Univariate analyses showed no difference in rate of rejection within 1 and 3 years by induction regimen or between SLK and KALT patients. Among person with at least 33 months follow-up after adjusting for induction regimen, the multivariable analysis may suggest that SLK recipients had increased likelihood of rejection within the first 3 years (p=0.051). Rates of infection within 1 and 3 years did not differ by induction regimen or between SLK and KALT. Mean PRA for patients who had alemtuzumab induction (44.7±41.6%) was higher than mean PRA for methylprednisolone induction (11.3±24.6 %) (p =0.045). Mean PRA did not differ significantly among patients experiencing at least one infection or one rejection within 1 and 3 years compared to those who did not.

Conclusions: Infection and rejection rates did not differ between SLK and KALT recipients within 1 year after adjusting for different induction therapies. Additionally, PRA levels were not related to infection or rejection rates.

SA-PO986

Successful Simultaneous Liver-Kidney Transplantation in a Patient with Nonuremic Calciphylaxis (NUC) Secondary to Alcoholic Cirrhosis

Issa R. Haddad, Shawna Lord, Rohan V. Mehta, Alfonso Santos. *Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida College of Medicine, Gainesville, FL.*

Introduction: Calciphylaxis is a rare condition characterized by painful, non-healing skin lesions due to arterial calcification and thrombosis. While typically associated with end-stage renal disease (ESRD), calciphylaxis can also occur in the absence of renal dysfunction, known as non-uremic calciphylaxis (NUC). Common causes include primary hyperparathyroidism, alcoholic liver disease, and malignancy.

Case Description: A 45-year-old male with end-stage liver disease secondary to alcohol (EtOH) cirrhosis presented with worsening bilateral lower extremity necrotic wounds over 6 months. He was initially diagnosed with livedo reticularis. At the time of lesion appearance, renal function was normal (GFR 123 mL/min), but as liver failure progressed, renal dysfunction ensued, necessitating dialysis. Skin biopsy confirmed calciphylaxis, prompting treatment with vitamin K and sodium thiosulfate (STS), along with wound care and prophylactic antibiotics. Significant labs revealed PTH of 68 pg/ml, 25 OH Vit D of 22 ng/ml, calcium of 8.3 mg/dl, PO4 of 5 mg/ml, and albumin of 1.8 g/dl. The patient underwent simultaneous liver and kidney transplantation attaining a baseline creatinine of 0.9 mg/dl. Maintenance Immunosuppression included tacrolimus and mycophenolate. Continuation of STS therapy for 6 weeks post-transplantation led to complete resolution of lesions.

Discussion: We present a case of successful simultaneous liver and kidney transplantation in a patient with active NUC. Although NUC complicates pre-transplant evaluation due to associated high mortality and infection risks, aggressive medical management and continued STS therapy can yield favorable outcomes. While the literature on NUC and transplantation is limited, existing reports suggest favorable outcomes with STS post-transplantation. This case emphasizes that a diagnosis of NUC may not preclude transplantation or immunosuppression.

SA-PO987

Prolonged Cold Ischemia Time in Pancreas Transplantation Yields Similar Outcomes Compared with Standard of Care Outcomes: Single-Center Experience, a Call to Action to Decrease Nonuse Rates

Georges Aboukasm, Mariella O. Goggins, George W. Burke. *Miami Transplant Institute University of Miami School of Medicine Jackson Memorial Hospital, Miami, FL.*

Background: Overall number of deceased donor pancreas transplant have decreased overtime and the rate of nonuse pancreas have reached its highest at 28.6% in 2022. There are many reason for nonuse pancreas, with newer allocation schemes, broader organ sharing, increase ischemia times, decrease risk tolerance and lack of center/surgeon expertise playing a role. We aim to evaluate our single center experience on the use of pancreas with prolonged cold ischemia time(CIT) and outcomes. Standard of care is to place the pancreas within 12 hours(hrs) of CIT. We report our single-center experience in the use of pancreas with over 12hrs of CIT.

Methods: Single center retrospective review of all simultaneous kidney/pancreas(SPK) and pancreas transplant alone(PTA) from January 2014 to September 2023 with at least 6m of follow up. Pancreas graft failure was defined as allograft pancreatectomy or recipients' fully dependency of insulin and/or c-peptide levels <2.0 ng/ml

Results: We had 190 SPK/PTA recipients during the study period, we divided them by less or more than 12hrs of pancreas CIT.Table1. Shortest CIT was 3.5hrs and longest was 23hrs, significantly higher among the groups (p<0.001). Enteric-drained recipients were more likely to have CIT<12hrs and bladder-drained more likely to have >12hr CIT (p<0.00001). Table2: Mean follow-up was longer in the group with >12hrs CIT, 5yrs vs 2.8 yrs (p=0.03). Patient survival was lower among the group with CIT>12hrs (p=0.007). However, there were no difference in pancreas graft survival among the groups. A1c,c-peptide and fasting blood glucose was similar up to 5yrs of follow-up.

Conclusions: In the current environment of high nonuse rate for pancreas transplantation, allowing longer pancreas CIT and total pancreas preservation time, may increase the rates of pancreas transplantation. We are evaluating our outcomes with regards to post-op complications, enteric leak, intra-abdominal abscess and length of stay, between both groups, under and longer than 12hrs CIT.

Table 1 Baseline Characteristics

	Pancreas CIT <12 hours (n = 183)	Pancreas CIT >12 hours (n = 38)	P value
Recipient Mean Age	42	42	0.977
Male n (%)	91 (52.3%)	25 (71.4%)	0.0394
Race/Ethnicity n (%)			
Black	36 (20.7%)	9 (25.7%)	0.757
Hispanic	91 (52.3%)	17 (48.6%)	0.697
White	46 (26.5%)	9 (25.7%)	0.881
Mean (range) CIT Pancreas (hours)	8.7 (3.5 - 12)	16 (12 - 23)	<0.001
Mean (range) Total Pancreas Preservation time (hours)	9.17 (3.50 - 13.13)	16.29 (8.52 - 33.48)	<0.001
Recipient Mean C-peptide	1.04	0.884	0.252
Recipient Mean A1C (%)	7.8	7.9	0.178
Recipient Mean BMI	25.25	23.99	0.102
Drainage Type			
Enteric	133 (85.9%)	8 (22.9%)	<0.0001
Bladder	22 (14.2%)	27 (77.1%)	<0.0001

Table 2: Recipient Post Transplant Characteristics

	CIT <12 hours	CIT >12 hours	P value
Mean (range) follow up (years)	2.5 (2.5 - 8.8)	5 (0.5 - 9.0)	0.030
Patient Survival	95.8%	92.9%	0.907
Pancreas Graft Survival	93.5%	100%	0.124
Mean A1C (%) at 3 months	5.0	5.2	0.318
Mean C-peptide at 3 months	4.21	4.00	0.835
Mean FBG at 3 months	90	89	0.901
Mean A1C (%) at 6 months	5.0	5.7	0.058
Mean C-peptide at 6 months	3.96	3.51	0.086
Mean FBG at 6 months	94	93	0.831
Mean A1C (%) at 1 year	5.0	5.5	0.217
Mean C-peptide at 1 year	3.77	3.14	0.141
Mean FBG at 1 year	93	90	0.850
Mean A1C (%) at 5 years	5.8	5.4	0.197
Mean C-peptide at 5 years	2.54	4.30	0.005
Mean FBG at 5 years	90	97	0.168

*FBG = Fasting Blood Glucose

SA-PO988

Trends in Discard of Kidneys from Hepatitis C Viremic Donors in the United States, 2020-2023

Krutika P. Chauhan,[1] Su-Hsin Chang,[1] Siobhan Sutcliffe,[1] Massini Merzkani,[1] Krista L. Lentine,[2] Bekir Tanriover,[3] Louai Alrata,[1] Dema Yaseen Alsabbagh,[1] Tarek Alhamad.[1] *[1]Washington University in St Louis, St Louis, MO; [2]Saint Louis University, St Louis, MO; [3]The University of Arizona College of Medicine Tucson, Tucson, AZ.*

Background: With the introduction of direct-acting antiviral (DAA), the discard rate of hepatitis C viremic (HCV) has decreased remarkably. With the continuous shortage of organs and the change in the allocation system, it is not clear if the HCV organs continue to have a higher risk of discard in the new era 2020 – 2023.

Methods: We used the 2020-2023 Organ Procurement and Transplantation Network (OPTN) to identify deceased donor kidneys recovered for transplant. We utilized our inclusion-exclusion criteria (Fig 1) to formulate our analytic cohort. The exposure was donor HCV antibody and viremia status. We did a multivariable logistic regression throughout the years to assess the association of HCV and discard while adjusting for donor characteristics. We also did another model where we adjusted for the COVID status of donors along with donor characteristics.

Results: Among the 101,088 kidneys recovered from 2020-2023, 5,718 (5.7%) were HCV viremic donors (NAT+) and 4,768 (4.7%) were aviremic seropositive (NAT-, Ab+) donors. Compared to HCV aviremic seronegative kidneys (NAT-, Ab-), the odds of HCV viremic kidney discard slightly increased from 27% in 2020 (aOR 1.27, 95% CI, 1.07 to 1.51), to 33% in 2022 (aOR 1.33, 95% CI, 1.31 to 1.57). The results were not significant for 2021 and 2023 (2021, aOR 1.06; 95% CI, 1.31 to 1.57, and 2023, aOR 0.99; 95% CI, 0.83 to 1.18). (Figure 1A). We saw a similar trend when we adjusted for donor COVID status (Figure 1B). Kidneys from aviremic seropositive donors did not carry a higher risk of discard during the entire period.

Conclusions: Discard of HCV viremic kidneys has been fluctuating in the last few years with odds of 30% in 2020 and 2022 while not significant in the other years. With the prevalent organ shortage and safety of DAA, more efforts are needed to eliminate the discard of HCV viremic kidneys.

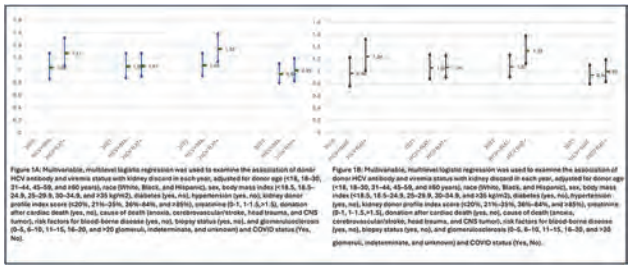


Figure 1A: Multivariable, multilevel logistic regression was used to examine the association of donor HCV antibody and viremia status with kidney discard in each year, adjusted for donor age (<18, 18–30, 31–44, 45–59, and ≥60 years), race (White, Black, and Hispanic), sex, body mass index (<18.5, 18.5–24.9, 25–29.9, 30–34.9, and ≥35 kg/m2), diabetes (yes, no), hypertension (yes, no), kidney donor profile index score (≤20%, 21%–35%, 36%–64%, and ≥65%), creatinine (0–1, 1–1.5,>1.5), donation after cardiac death (yes, no), cause of death (anoxia, cerebrovascular/stroke, head trauma, and CNS tumor), risk factors for blood-borne disease (yes, no), biopsy status (yes, no), and glomerulosclerosis (0–5, 6–10, 11–15, 16–30, and >30 glomeruli, indeterminate, and unknown) and COVID status (Yes, No).

Figure 1B: Multivariable, multilevel logistic regression was used to examine the association of donor HCV antibody and viremia status with kidney discard in each year, adjusted for donor age (<18, 18–30, 31–44, 45–59, and ≥60 years), race (White, Black, and Hispanic), sex, body mass index (<18.5, 18.5–24.9, 25–29.9, 30–34.9, and ≥35 kg/m2), diabetes (yes, no), hypertension (yes, no), kidney donor profile index score (≤20%, 21%–35%, 36%–64%, and ≥65%), creatinine (0–1, 1–1.5,>1.5), donation after cardiac death (yes, no), cause of death (anoxia, cerebrovascular/stroke, head trauma, and CNS tumor), risk factors for blood-borne disease (yes, no), biopsy status (yes, no), and glomerulosclerosis (0–5, 6–10, 11–15, 16–30, and >30 glomeruli, indeterminate, and unknown) and COVID status (Yes, No).

SA-PO989

Simultaneous Heart-Kidney Transplant Is the Best Treatment Option for Patients with CKD and ESKD vs. Heart Transplant Alone

Krutika P. Chauhan, Qingyuan Tan, Siobhan Sutcliffe, Su-Hsin Chang, Tarek Alhamad, Massini Merzkani. *Washington University in St Louis, St Louis, MO.*

Background: Simultaneous heart and kidney transplantation has been considered for patients who had advanced CKD and ESRD who have an indication for heart transplantation. In this study, we analyzed whether there is an increase in patient survival and heart transplant graft survival.

Methods: We analyzed data from the OPTN patients who received heart transplant with CKD/ESRD 1/2020-12/2023. Our inclusion criteria were adults aged >18 years old receiving a solid organ heart transplant with evidence of CKD, defined as eGFR less than 60 or on dialysis for heart transplant alone, and who were ABO compatible. Our outcomes were heart graft loss, defined as receiving another heart transplant or death, and death was defined patient expiring as per UNOS. Multivariable Cox regression was used to evaluate defined patient survival and graft survival while adjusting for recipient, donor, and graft characteristics.

Results: A total of 22,111 transplants were performed, 86.6% of which were HTx and 13.4% of which were SHKTx. The prevalence of graft loss was 40.7% and death was 41.6% overall. We see better patient and graft survival with simultaneous heart-kidney compared to heart alone in all stages of CKD and including the different stages of CKD in graft failure and death as shown in Table 1 and Figure 2 and 3. Our study have the limitation of selection bias as it is unclear why there are patients with CKD/ESRD who did not receive simultaneous heart and kidney transplantation. The other bias the eGFR were calculated by using serum creatinine as a marker and unclear it will be the ideal marker given the patient with end-stage heart failure usually have cachexia with low muscle mass.

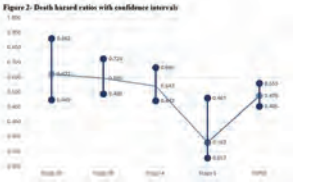
Conclusions: SHK transplantation has an increased benefit in patient and heart transplant survival compared to patients who received heart transplantation alone. Prospective studies should be performed to determine the ideal eGFR cutoff for patient listing.

Table 1 Outcomes in Simultaneous Heart Kidney Transplant

	Hazard ratio	Pvy	Low CI	High CI
Graft failure				
All stages	0.540	<0.001	0.493	0.592
Stage 3A	0.617	0.004	0.444	0.859
Stage 3B	0.585	<0.001	0.479	0.715
Stage 4	0.515	<0.001	0.418	0.633
Stage 5	0.126	<0.001	0.041	0.386
ESRD	0.464	<0.001	0.304	0.548
Death				
All stages	0.556	<0.001	0.506	0.609
Stage 3A	0.622	0.004	0.449	0.862
Stage 3B	0.595	<0.001	0.488	0.724
Stage 4	0.543	<0.001	0.443	0.665
Stage 5	0.362	0.001	0.057	0.461
ESRD	0.479	<0.001	0.405	0.569

Figure 1- Graft failure hazard ratios with confidence intervals

Figure 2- Death hazard ratios with confidence intervals



SA-PO990

Decreased Risk for Rejection in Simultaneous Heart-Kidney Transplant

Krutika P. Chauhan, Qingyuan Tan, Siobhan Sutcliffe, Su-Hsin Chang, Tarek Alhamad, Massini Merzkani. *Washington University in St Louis, St Louis, MO.*

Background: Simultaneous heart and kidney(SHKTx) is one of the best choice for patient with advanced CKD and ESRD. Recent data and basic science research have suggested that kidney transplant has an immunoprotective effect to heart transplant. In this large retrospective cohort study we reviewed the rejection rate in the heart transplant in patient who received a SHK compared with the ones who had heart transplant alone with CKD/ESRD.

Methods: We analyzed the OPTN data that had CKD with heart transplants in the period of 1/1/2020 to 12/31/2023. Our inclusion criteria were adults aged 18 and older who receive solid organ heart transplants with evidence of CKD defined as eGFR being less than 60 or being on chronic dialysis for the HTx and were ABO compatible. Our outcome of interest was Rejection. The aim of this study is to determine in the study population if SHKTx has a better outcome defined as no rejection in all stages of CKD and individual stages of CKD. Multivariable logistic regression was performed to evaluate defined patient survival and heart graft survival while adjusting for recipient, donor, and transplant characteristics.

Results: During the study period, there was a total of 19,141Htx and 2,970 of SHKTx. The prevalence of rejection was 19.2% with 3,078 in heart alone and 170 in simultaneous heart kidney. Highly prevalent CKD stages were Stage 3A Moderate CKD with 49.7%. We see better odds for SHKTx for stages 3A (OR 0.43, CI-0.24 and 0.77), stage 3B (OR 0.49, CI-0.33 and 0.70), stage 4 (OR 0.43, CI-0.27 and 0.67) and ESRD stage (OR 0.31, CI-0.21 and 0.45) with significant values. We see similar results for overall, all stages of CKD and only for Stage 5 of CKD were not a higher risk.

Conclusions: In this we found that Simultaneous heart and kidney was protective for rejection in the heart transplant compared with heart transplant alone. More studies should be done to determine the long-term benefits and pathophysiology of these findings.

Table 1 Logistic Regression Rejection of Simultaneous heart kidney transplant compare with heart transplant alone with CKD/ESRD

Logistic regression	Odds ratio	P>z	[95% conf.	interval]
Simultaneous heart kidney				
Overall	0.3838485	<0.001	0.3191892	0.461606
Stage 3A	0.4304939	0.005	0.2406274	0.7701744
Stage 3B	0.4904629	<0.001	0.3391254	0.709336
Stage 4	0.4314344	<0.001	0.2776691	0.6703506
Stage 5	0.0327811	0.225	0.0001316	8.16594
ESRD	0.3168649	<0.001	0.2197457	0.4569071

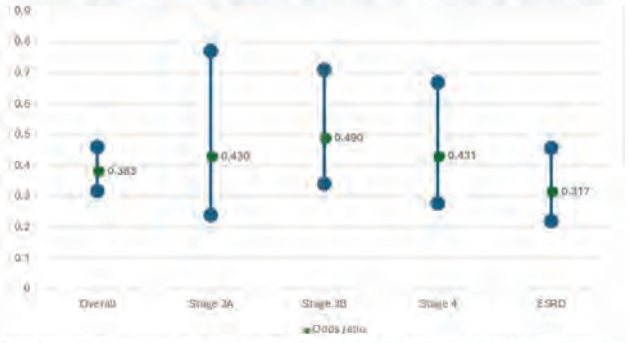


Fig 1 Logistic Regression Rejection of Simultaneous heart kidney transplant compare with heart transplant alone with CKD/ESRD

SA-PO991

Assessing Kidney Function in Combined Heart-Kidney Transplant Candidates: Challenges and Opportunities

Krishna A. Agarwal, Aman Srivastava, Andrew S. Levey, Lesley A. Inker.
Tufts Medical Center, Boston, MA.

Background: Heart transplant candidates often have concomitant kidney disease, necessitating simultaneous heart-kidney transplantation (SHKT). UNOS outlined GFR cutoffs for allocating heart-kidneys in 2023. A heart transplant (HT) candidate with baseline CKD can qualify for SHKT with GFR<=30 or with sustained AKI if GFR<=25. Unfortunately, there is no guidance for appropriate methods of assessing GFR in these patients with heart failure who can be volume expanded and sarcopenic and hence have inaccurate creatinine based GFR (eGFRcr). While cystatin based GFR (eGFRcys) is an alternative, it is known to have high error rates as well.

Methods: We present 5 cases of HT candidates who were evaluated for SHKT. Only one of them (#2) had peripheral edema on exam. As part of pre-transplant evaluation, eGFRcr, eGFRcys, eGFRcr-cys (CKD-EPI 2021), 24-hour urinary creatinine clearance (mClcr) and measured GFR using plasma iohexol clearance (mGFR) were obtained. For mGFR, blood samples were drawn at 2, 4, 6 and 24 hours after iohexol injection and GFR was determined using a two-compartment model with the Brochner-Mortenson correction.

Results: There was wide discrepancy between eGFRcr and mGFR, with eGFRcr overestimating mGFR for all five patients (Table 1). eGFRcys and eGFRcr-cys were more similar to mGFR. Urine mClcr did not corelate with mGFR.

Conclusions: In HT candidates being evaluated for SHKT, it is essential to have an accurate assessment of GFR. eGFRcr alone is fraught with inaccuracies. Our findings support the use of guideline-recommended eGFRcr-cys (CKD-EPI 2021) with comprehensive evaluation using cystatin C and mGFR. Transplant centers should consider collaborating with laboratory scientists to implement measurement protocols for cystatin C and mGFR for assessing dual organ transplant eligibility.

ID	Creatinine (mg/dL)	eGFRcr (mL/min/1.73m2)	Cystatin C (mg/L)	eGFRcys (mL/min/1.73m2)	eGFRcr-cys (mL/min/1.73m2)	mClcr (mL/min/1.73m2)	mGFR (mL/min/1.73m2)
1	1.25	54	2.08	29	38	45	42
2	2.98	24	3.55	15	18	UNK	17
3	1.70	34	2.50	21	26	32	21
4	1.26	49	1.71	36	41	26	35
5	2.27	38	1.96	35	36	23	37

SA-PO992

Lymphocyte Immune Assays for the Management of Immunosuppression of Kidney Transplant Patients in Sepsis

Emiliya Bakhshiyeva,[1] Marie Kranefuß,[2] Mario Schiffer,[1] Carsten Willam,[1] Regine Brox,[2] Johanna T. Kurzhagen.[1] *[1]University Hospital Erlangen Department of Nephrology and Hypertension, Erlangen, Germany; [2]University Hospital Erlangen Department of Transfusion Medicine, Erlangen, Germany.*

Background: Kidney transplanted (KT) patients are on high risk for infections including sepsis. However, by date there is no guideline on the management of immunosuppression in these patients in sepsis and management is based on clinical decision making with little evidence. We therefore aim to study different lymphocyte immune assays as potential biomarkers in septic patients with and without IS.

Methods: T- and B-cell markers were examined in 3 groups of patients: Healthy controls (HC), patients with sepsis without IS and patients with sepsis with IS. Sepsis was diagnosed based on Sequential Organ Failure Assessment (SOFA) Score. Determination of T- and B-cell markers was performed at different time points of sepsis, at day 0, 3 and 7 using flow cytometry.

Results: Study participants were 69.8 (standard deviation, SD: ±18.6) years old in average. Mean SOFA-Score at baseline was 4.5 (±0.7) in patients without IS vs. 4 (±0.0) in patients with IS. CD3+ lymphocytes and CD8+ T-cells were less frequent in both groups compared to HCs. However, patients with IS showed recovery by day 7. CD4+ T-cell frequency was decreased in patients with IS in comparison to patients without IS. In CD4+ T-cells, expression of pro-inflammatory markers such as CD4+TNF-α+, CD4+IFN-γ+ and CD4+IL-17+ was reduced in patients with IS compared to patients without IS. The anti-inflammatory marker CD4+IL-10+ was downregulated in both groups compared to HCs. CD8+IFN-γ+ cells were more upregulated, whereas CD8+IL17+ in patients with IS compared to patients without IS. CD8+IL10+ cells were downregulated and CD8+TNF-α+ showed no differences in both groups compared to HCs. Expression of T-cell activation markers CD25 and CD71 declined over the course of sepsis in both groups compared to HCs. The B-cell activation marker CD86 showed less expression in patients with IS on d0. CFSE revealed no changes in proliferation in different groups.

Conclusions: Preliminary data show differences in T- and B-cell markers between immunosuppressed and non-immunosuppressed patients in different phases of sepsis. This may provide deeper understanding of lymphocyte function and potentially allow a more individualized management of immunosuppression in KT patients in sepsis in future.

SA-PO993

Survival of Kidney Transplantation in People Living with HIV/AIDS: A Systematic Review and Meta-Analysis

Ka chun Leung,[1] Wincy Wing Sze Ng.[2] *[1]Tuen Mun Hospital Department of Medicine and Geriatrics, Hong Kong, Hong Kong; [2]Queen Mary Hospital, Hong Kong, Hong Kong.*

Background: As of 2022, nearly 40 million individuals are affected by HIV/AIDS, with 1.3 million new cases annually. The high effectiveness of antiretroviral therapy (ART) has made kidney transplantation a possibility for people living with HIV/AIDS (PLWHA) who are suffering from chronic kidney disease (CKD). The HIV Organ Policy Equity (HOPE) Act in the US lead to research in different aspects of transplant complexities including drug interactions and co-infections. This review aimed to evaluate kidney transplantation outcomes in PLWHA.

Methods: Databases were searched up to Nov 2023. Prospective and retrospective clinical trials were included. Primary outcomes centered on graft survival(GS), rejection(GR), infections, and patient survival(PS) post-transplantation. Secondary outcomes assessed the impact of ART and co-infections.

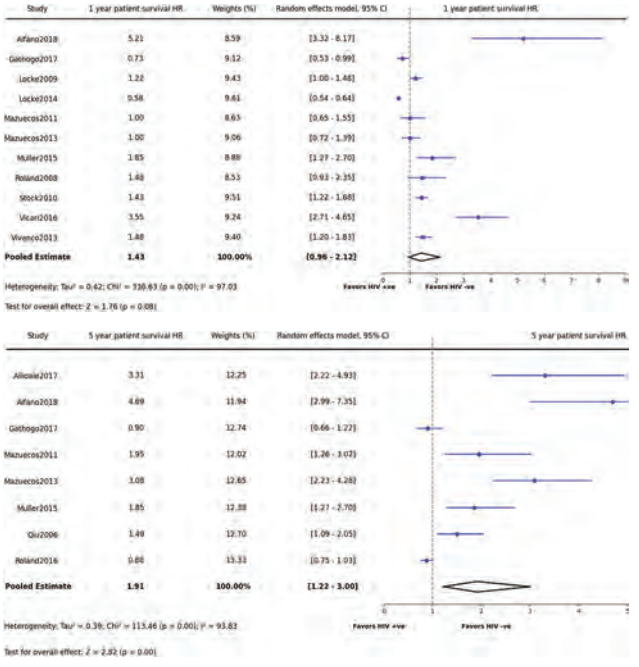
Results: 601 potentially eligible studies were identified with 48 included in analysis. No significant survival disadvantage for PLWHA in short term survival despite a higher long term risk (1yr PS 94%, hazard ratio(HR) 1.43, p=0.077; ≥5yr PS 83%, HR 1.91, p=0.005; 1yr GS 90%; ≥5yr GS 71%)(Table1, Figure1). There are positive impact of integrase inhibitor-containing ART regimens on PS and GS.

Conclusions: Kidney transplantation is an effective option for PLWHA, with outcomes comparable to the general population. Research on long-term outcomes, newer ART regimens, and tailored post-transplant monitoring protocols for PLWHA are essential to improve patient outcomes.

Table 1. Primary outcome

	Time Frame (years)	Outcome(%)[95%CI]	Hazard Ratio[95%CI]	I2(%)	p
Patient Survival	1	93.90[92.8–94.9]	1.43[0.96–2.11]	97.04	0.077
	3	89.50[87.3–91.5]	1.09[0.81–1.47]	92.81	0.585
	>5	82.80[76.6–87.7]	1.91[1.22–2.99]	93.94	0.005
Graft Survival	1	90.20[88.8–91.5]	2.11[1.50–2.95]	95.34	<0.0001
	3	77.90[72.7–82.3]	1.89[1.14–3.15]	97.62	0.014
	>5	70.60[64.3–76.2]	1.76[0.87–3.59]	97.29	0.118
Graft Rejection	1	25.90[18.7–34.8]	0.71[0.61–0.84]	72.84	0.005
	3	32.70[22.9–44.2]			
	>5	38.50[28.3–49.9]	0.62[0.46–0.84]	82.75	0.002

I2 and p are the heterogeneity assessment of hazard ratio data synthesis



SA-PO994

Association of 25-Hydroxyvitamin D Levels with BK Viremia and Nephropathy in Kidney Transplant Recipients

Suseela A. Raj, Angela L. Zhou, Ekaterina Fedorova, Zhongyu Yuan, Didier A. Mandelbrot, Brad C. Astor, Sandesh Parajuli. *University of Wisconsin-Madison, Madison, WI.*

Background: In kidney transplant recipients, BK virus reactivation and subsequent viremia (BKV) and nephropathy (BKN) are significant causes of morbidity and mortality. Limited treatment options make these complications particularly detrimental. Vitamin D supports immune function, yet low 25-hydroxyvitamin D [25(OH)D] levels are common in kidney transplant recipients. The association between 25(OH)D and BKV and BKN in kidney transplant recipients remains undefined.

Methods: The relationship between serum 25(OH)D level, measured 61 days to 2 years post-transplant, and BKV and BKN was examined in 3308 kidney transplant recipients. Recipients received kidney transplants from 2010 to 2019. Only recipients with 25(OH)D level measured before BKV were included.

Results: Out of 3308 recipients, 399 (12%) were vitamin D deficient [25(OH)D <20 ng/mL], and 916 (27.7%) were insufficient [25(OH)D 20-29 ng/mL]. 184 recipients had BKV, and 44 recipients had BKN. The incidence rate for BKV/100 person-years was 2.88 in the 25(OH)D sufficient group, 2.22 in the insufficient group, and 2.37 in the deficient group. With reference to sufficient 25(OH)D, there was no significant association for BKV after adjustment for multiple baseline characteristics. Similarly, the incidence rate/100 person-years for BKN was 0.30 in the 25(OH)D sufficient group, 0.75 in the insufficient group, and 1.28 in the deficient group. After adjustment for multiple baseline characteristics, with reference to sufficient 25(OH)D, deficiency (aHR: 3.92; 95% CI: 1.66-9.23) and insufficiency (aHR: 2.22; 95% CI: 1.11-4.45) were significantly associated with increased risk for BKN (Figure 1).

Conclusions: Low serum 25(OH)D is associated with increased risk of BKN but not BKV. Further studies are needed to explore the effects of vitamin D supplements to mitigate complications associated with BKN.

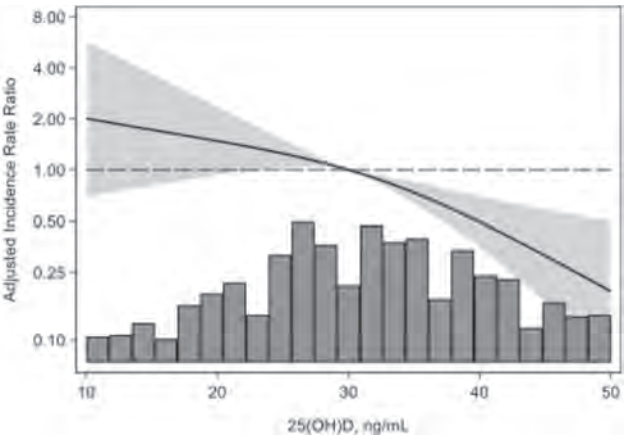


Figure 1. Incidence of BKN decreased with increasing 25(OH)D.

SA-PO995

Association of Post-transplant 25-Hydroxyvitamin D and Infection in Kidney Transplant Recipients

Zhongyu Yuan,[1,2] Michal L. Melamed,[3] Margaret R. Jorgenson,[4] Didier A. Mandelbrot,[2] Sandesh Parajuli,[2] Brad C. Astor.[1,2] *[1]University of Wisconsin-Madison Department of Population Health Sciences, Madison, WI; [2]University of Wisconsin-Madison Department of Medicine, Madison, WI; [3]NYU Langone Health, New York, NY; [4]UW Health, Madison, WI.*

Background: Infection is a leading cause of morbidity and mortality in kidney transplant recipients (KTRs). There is a growing interest in the immunoregulatory effect of vitamin D. While vitamin D inadequacy is common among KTRs, the association of serum 25-hydroxyvitamin D [25(OH)D] and infection remains unclear.

Methods: KTRs with at least one serum 25(OH)D measurement from 5 to13 months after transplant at our center from 2005 to 2020 were included. All 25(OH)D measurements thereafter were included as a time-varying variable. Infections within 365 days of each 25(OH)D measurement were identified. Marginal rates models were fitted to account for multiple infection episodes for each KTR. Models adjusted for recipient age, sex, race, cause of kidney failure, donor status, delayed graft function, prior kidney transplant, human leukocyte antigen-mismatch, immunosuppression, infection and acute rejection history, transplant year, season of 25(OH)D measurement, serum albumin, proteinuria and estimated glomerular filtration rate.

Results: A total of 2251 infection episodes were identified in 2207 KTRs followed for a median of 6.6 years after transplant. 23% and 10% of KTRs had vitamin D insufficiency (21-29ng/ml) and deficiency (≤ 20ng/ml), respectively, at baseline. Vitamin D deficiency was associated with a 1.22-fold (adjusted rate ratio [aRR]=1.22; 95% CI: 1.03-1.43; p=0.02) higher incidence of infection compared with vitamin D sufficiency. The association was strongest for bacterial infection (aRR=1.40; 95%CI: 1.14-1.73; p<0.01), especially urinary tract infection (aRR=1.55; 95%CI: 1.24-1.94; p<0.01).

Conclusions: Vitamin D deficiency is independently associated with a higher incidence of infection in KTRs, especially urinary tract infection. Further research is needed to determine the causal relationship.

Table 1. Clinical characteristics of post-transplant infection episodes.

Characteristics	Frequency, N (%)
Overall infection	2251
Site of infection	
Urinary tract infection	1020 (45)
Viremia	281 (12)
Pneumonia	213 (9)
Skin and soft tissue infection	209 (9)
Gastrointestinal infection	131 (6)
Upper respiratory tract infection	128 (6)
Pathogen	
Bacteria	1256
Escherichia coli	325 (28)
Klebsiella pneumoniae	102 (8)
Enterococcus faecalis	63 (5)
Clostridium difficile	67 (5)
Coagulase-negative staphylococcus	46 (4)
Virus	684
CMV	173 (26)
BK polyoma virus	172 (25)
Norovirus	47 (7)
Epstein-barr virus	39 (6)
Fungi	170
Candida	88 (52)
Yeast	18 (11)
Aspergillus	13 (8)

CMV, cytomegalovirus.

Table 2. Association of post-transplant serum 25(OH)D and incidence of infection.

Incident infection	Serum 25(OH)D			
	< 20 ng/ml	21 – 29 ng/ml	≥ 30 ng/ml	Per 5 ng/ml lower
Overall infection (2251 events)				
Adjusted RR (95% CI)	1.22 (1.03, 1.43)	1.17 (1.05, 1.31)	Reference	1.05 (1.03, 1.07)
P value (adjusted)	0.02	< 0.01		< 0.01
Bacterial infection (1256 events)				
Adjusted RR (95% CI)	1.40 (1.14, 1.73)	1.22 (1.06, 1.41)	Reference	1.07 (1.04, 1.10)
P value (adjusted)	< 0.01	< 0.01		< 0.01
Viral infection (684 events)				
Adjusted RR (95% CI)	1.25 (0.93, 1.68)	1.08 (0.89, 1.31)	Reference	1.04 (1.00, 1.08)
P value (adjusted)	0.14	0.43		0.03
Fungal infection (170 events)				
Adjusted RR (95% CI)	1.35 (0.76, 2.42)	1.48 (1.04, 2.12)	Reference	1.07 (1.00, 1.14)
P value (adjusted)	0.31	0.03		0.05
Urinary tract infection (1020 events)				
Adjusted RR (95% CI)	1.55 (1.24, 1.94)	1.22 (1.04, 1.43)	Reference	1.08 (1.05, 1.12)
P value (adjusted)	< 0.01	0.02		< 0.01

25(OH)D, 25-hydroxyvitamin D; RR, rate ratio; CI, confidence interval.

SA-PO996

Treating Refractory BK Virus Nephropathy with Allogenic BK Virus-Specific T Cells in Kidney Transplant Recipients

Suraj J. Chandwani, Eike Lonnemann, Zhejia Tian, Alena Richter, Sabine Tischer-Zimmermann, Agnes Bonifacius, Astrid Wintering, Rainer Blasczyk, Kai M. Schmidt-Ott, Wilfried Gwinner, Britta Eiz-Vesper, Britta Maecker-Kolhoff, Christian Hinze. *Medizinische Hochschule Hannover, Hannover, Germany*.

Background: Refractory BK virus nephropathy (BKVNP) is a significant risk factor for graft loss in kidney transplant recipients. Currently, there are no targeted therapies available for BKVNP. Given the importance of cellular immunity in viral clearance, we investigated the effects of allogeneic BK virus-specific T cell transfer on graft function, BKV-specific T cell levels, and BKV replication in patients' blood.

Methods: We included three kidney transplant recipients with refractory BKVNP. Refractory BKVNP was defined by persistent BKV replication (>1000 IU/ml), minimum possible immunosuppression, low BKV-specific T cell levels, and histologic evidence of BKVNP. For two patients, donors for virus-specific T cells were selected from the third party T cell donor registry (alloCELL), ensuring the best possible HLA compatibility with the transplanted organ and the recipient. For one patient, the related living organ donor was selected, thus resulting in a haploidentical T cell transfer. BKV-specific T cells were produced from leukapheresis, short-term stimulation with LT and VP1 overlapping peptide pools, followed by cytokine selection and magnetic separation. Patients received at least four T cell transfusions (first fresh, subsequent cryopreserved) every three weeks. BKV load was quantified by qPCR, and BKV-specific T cells were enumerated using interferon-γ Elispot assay.

Results: We observed significant declines in BKV load in all cases (93.16%, 78.10%, 71.11% decrease compared to pre-therapy levels), along with significant increases in BKV-specific T cells in recipients' blood. The most pronounced reduction in BKV load (93.16%) was observed in the haploidentical transplant patient, emphasizing the relevance of HLA compatibility to ensure an adequate T-cell milieu. Graft function remained stable throughout therapy, and no infusion-related adverse events were observed.

Conclusions: Allogeneic BK virus-specific T cell therapy shows promise in treating refractory BKVNP in kidney transplant recipients. Patient selection based on BKV-specific T cell levels, BKV blood levels, graft function, and histology is essential. Further evaluation is needed to determine its clinical efficacy.

SA-PO997

Experience of Utilizing Low-Dosage Belatacept and Cyclosporine in Patients with Refractory BK Polyoma Viremia

Irfan A. Moinuddin, Nouman Akbar, Dhiren Kumar, Akshay Athreya, Gaurav Gupta. *Virginia Commonwealth University Health System, Richmond, VA.*

Background: There are no proven therapeutic options for BK polyoma virus (BKPyV) nephropathy apart from immunosuppression reduction. In-vitro studies have shown that tacrolimus (FK) promotes BKPyV replication through FK binding protein-12 pathyway, while cyclosporine (CsA) inhibits BKPyV replication. Belatacept, CD80/86-CD28 co-stimulation blocker, may have theoretical benefits by avoiding calcineurin inhibitor related nephrotoxicity and FKBP-12 mediated BKPyV replication. We present our experience of CsA and low dose belatacept in refractory BKPyV viremia on FK-based immunosuppression.

Methods: 15 adult kidney transplant patients with refractory BKPyV viremia despite reduction in immunosuppression and IVIg were included. Patients with worsening eGFR were switched to low dose belatacept 2.5mg/kg every 2 weeks for first 5 doses, then monthly (BELA group) and ones with stable eGFR were converted to CsA (CsA group). eGFR and BKPyV PCR between the groups were compared at 3- and 6-months post conversion.

Results: 10/15(67%) patients were in BELA group and 5(33%) were in CsA group. BELA group was transitioned to belatacept at 6±3 months after diagnosis. Mean FK trough was 7.5±2.8ng/ml and median daily dose of mycophenolate(MMF) was 0 mg (range 0-500 mg) at conversion. Mean follow up was 34±19 months. Mean eGFR improved from 24.7±8.3 to 30.4±7.5(p=0.01) at 6 months. BKPyV viral load improved from a median of 87100 COPIES/ml (range 5290-1880000) to 2055 COPIES/ml (range 0-26000;p=0.08). 6/10(60%) patients had resolution of viremia. CsA group were switched to CsA at 21±10 months after diagnosis. Mean FK trough was 6.1±0.6ng/ml and patients were off MMF at the start of CsA. Mean follow up was 13.8±3.3 months. Mean eGFR remained stable, 55±12.5 at conversion vs 54.4±10.7 at 6 months. BKPyV viral load at 6-month improved from a median of 61500 COPIES/ml (range 11500-94800) to 4130 COPIES/ml (range1100-6460;p=0.08). 3/5(60%) patients had resolution of viremia. No rejection was reported in either group.

Conclusions: In our experience, there was a significant reduction in BKPyV viral loads with both strategies. The kidney function improved with belatacept conversion and it remained stable with CsA conversion. Longer follow up is needed to understand the graft outcomes with these strategies. These results provide a framework for prospective studies.

SA-PO998

Effect of Conversion from Tacrolimus to Cyclosporine on BK Viremia among Kidney Transplant Recipients: The TACCsA-SWITCH Study

Shaikha R. Ali,[1,2] Hon Shen Png,[1,2] Abdullah A. A. AlGhamdi,[1,2] Azim S. Gangji.[1,2] *[1]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada; [2]McMaster University, Hamilton, ON, Canada*.

Background: There is no established treatment strategy for BK-polyomavirus (BKPyV) infection among kidney transplant recipients (KTRs) after initial reduction of immunosuppression. In vitro studies suggest an inhibitory role of cyclosporine on replication of BKPyV. We investigated effect of conversion of tacrolimus to cyclosporine (TAC-CsA switch) on BKPyV viral load (VL) among KTRs.

Methods: We conducted a retrospective cohort study with a pre-post study design investigating effect of TAC-CsA switch among KTRs with persistent BKPyV-VL of more than 10,000 IU/ml (equivalent to 4 $\log_{10}$IU/ml) for more than 3 months before TAC-CsA switch. We ensured 6 months of follow up after conversion, between 2020 to 2023. We calculated the slope of change for log-BKPyV-VL in $\log_{10}$IU/ml/month using least-square method and compared the mean results before and after TAC-CsA switch.

Results: 32 patients were included in the analysis. 25 (78.1%) patients had deceased kidney transplantation (KT), and 17 (53.1%) patients received anti-thymocyte globulin. Before TAC-CsA switch, 17 (53.1%) had a change of mycophenolate to leflunomide, 4 (12.5%) and 14 (43.8%) were given cidofovir and intravenous immunoglobulin, respectively. Median time from last immunosuppression adjustment/ therapy given prior to TAC-CsA switch was 112.5 (interquartile range (IQR) 225.75) days. At time of TAC-CsA switch, median BKPyV-VL was $321x10^3$ (IQR $2.49x10^6$) IU/ml, equivalent to median log-BKPyV-VL of 5.50 (IQR 1.39) $\log_{10}$IU/ml. The mean slope of change for log-BKPyV-VL before and after TAC-CsA switch were 0.304 (95% confidence interval (CI) 0.139, 0.469) and -0.279 (95% CI -0.353, -0.204) $\log_{10}$IU/ml/month respectively. Mean difference between the slopes before and after TAC-CsA switch was -0.583 (95% CI -0.807, -0.358) $\log_{10}$IU/ml/month ($p < 0.001$). 21 (65.6%) patients achieved log-BKPyV-VL improvement of at least 0.2 $\log_{10}$IU/ml/month (equivalent to 16 fold VL reduction in 6-month period) after TAC-CsA switch.

Conclusions: TAC-CsA switch is a useful strategy for difficult to treat BKPyV viremia among KTRs.

SA-PO999

Pre- and Post-transplant BK Virus-Specific Enzyme-Linked Immunospot (ELISPot) Assay for Predicting the Outcome of BK Virus Infection in Kidney Transplant Recipients

Do-hyun Na,[1] Eun jeong Ko,[2] Byung ha Chung.[1] *[1]The Catholic University of Korea Seoul St Mary's Hospital, Seocho-gu, Seoul, Republic of Korea; [2]The Catholic University of Korea College of Medicine, Bucheon, Seoul, Republic of Korea*.

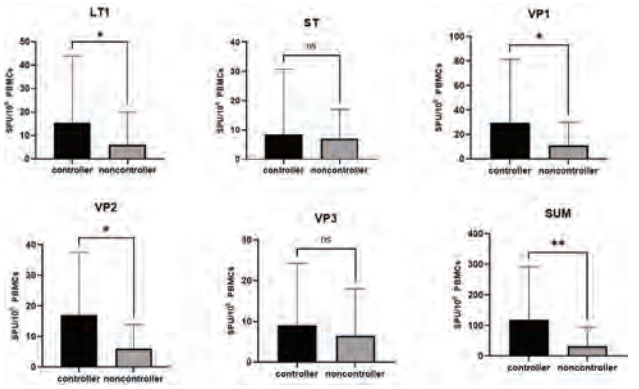
Background: It is needed to plan optimal therapeutic strategies for controlling BK viremia. Our previous study showed that BK virus (BKV)-specific T-cell immunity measured by an interferon-γ enzyme-linked immunospot (ELISPOT) are related to outcome of BKV infections. However, there was limitations about difference of time and viremia status.

Methods: We included 84 KTRs who experienced at least one BK viremia at RQ-PCR of BKV-DNA. BKV-ELISPOT were measured in all included recipients at the time of pre-transplant, post- 4 weeks, post- 12 weeks transplant, and when viremia were detected. We divided into two groups Controller and Noncontroller according to sustained duration of BKV infection. We compared BKV-ELISPOT results at each times.

Results: We reduced or stop mycophenolic acid in 88.6% of BK viremia patients and used leflunomide for 48% patients (38.6% and 70% for each group). BKV-ELISPOT results were higher in controller groups at the time of pre-transplant, 4 weeks post-transplant, 12 weeks post-transplant, first viremia detected. When first viremia detected, we analyzed BKV ELISPOT including five BKV peptide mixes. Controller group had higher LT, ST, VP1, VP2 ELISPOT results. Also, those who had no biopsy proven BKVAN had higher LT, ST, VP1, VP3 ELOSPT results.

Conclusions: Pre- and Post- BKV-ELISPOT assay may help to distinguish patients with well controlling BK Viremia from those who have persisting BK Viremia who need more intensive therapy to prevent BKVAN.

Funding: Government Support - Non-U.S.



SA-PO1000

Burden of BK Virus Infection and BK Virus-Associated Nephropathy in Kidney Transplant Recipients: Scoping Review Reveals Gaps in Patient-Centered Research

Maja Kuharic,[1] Courtney N. Hurt,[1] Kevin J. Fowler,[2,3] Alexander W. Bastian,[2] Juergen Beck,[4] Erik J. van den Berg,[4] John D. Peipert.[1] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Memo Therapeutics Consultant, Schlieren, Switzerland; [3]The Voice of the Patient, Inc., Saint Louis, MO; [4]Memo Therapeutics, Schlieren, Switzerland.*

Background: BK virus (BKV) infection and BKV-associated nephropathy (BKVN) are significant complications affecting kidney transplant recipients, leading to impaired graft function and increased risk of graft loss. This scoping literature review aimed to synthesize the current evidence of the burden of BKV infection and BKVN in kidney transplant recipients.

Methods: A scoping literature search focused on patient-centered research in BKV among kidney transplant recipients was conducted in PubMed and Embase databases from inception to January 2024. Studies were eligible for inclusion if they met the following criteria: (1) included kidney transplant recipients with BK virus infection; (2) reported on clinical, economic, or humanistic burden of BK virus; (3) were published in English; and (4) were original research articles, systematic reviews, or meta-analyses.

Results: Sixty-three studies were included in the review, with most (47%) published within the last five years. No studies examined impacts on quality of life, mental health, and daily functioning. Similarly, no studies reported on economic impact on patients and their families, such as the ability to continue working, opportunity costs of receiving treatment, time off work, and fear of losing jobs. Viruria and viremia were detected in approximately 30% and 12% of kidney transplant recipients, respectively. The incidence of BKVN ranged from 1.4% to 7%. Risk factors for BK virus infection and BKVN included degree of immunosuppression, tacrolimus use, older age, male sex, and donor/recipient ethnic mismatch among others. Graft loss (35% vs. 21%), rejection (42% vs. 25%), and death (18% vs. 13%) were more common in the BKVN group compared to those without BKVN.

Conclusions: This review provides insights into the incidence and risk factors of BK virus infection and BKVN in kidney transplant recipients. However, it also highlights gaps in the literature, particularly regarding the humanistic burden on patients' quality of life, mental health, daily functioning and the economic impact on patients and their families. Future research should prioritize patient-reported outcomes and qualitative studies to better understand the full burden of BK virus infection and BKVN on kidney transplant recipients.

SA-PO1001

An Unusual Suspect: A Case of BK Nephropathy (BKVN)

Gaoyuan Huang,[1] Mabel A. Bodell,[2] Aanand A. Patel,[1] Shreeram Akilesh,[1] Yue-Harn Ng,[1] Karen S. de Wolski.[1] *[1]University of Washington School of Medicine, Seattle, WA; [2]Confluence Health, Wenatchee, WA.*

Introduction: BK viral reactivation is known to occur in non-kidney solid organ transplant (NKSOT) recipients, but patients are not routinely screened for BK viremia/viruria, nor are there studies of the associated long-term kidney prognosis. Importantly, chronic kidney disease (CKD) in Orthotopic Heart-transplant (OHT) patients is often attributed to other causes, such as calcineurin-inhibitor (CNI) toxicity, leading to late or missed diagnosis of BKVN. Here, we report a case of BKVN of native kidneys causing advanced CKD in an OHT recipient.

Case Description: A young male with a history of OHT for viral cardiomyopathy 7 years prior and CKD initially attributed to CNI use (serum creatinine [SCr] 1.3-1.5mg/dl) was referred to nephrology for an increase in SCr to 3.8 over the last year. He had been on immunosuppression (IS) with tacrolimus (goal 8-10ng/ml) and mycophenolate (MMF). Due to concern for CNI toxicity, IS was switched to a CNI minimization regimen with reduction in tacrolimus, continuation of MMF, and addition of sirolimus one year before. However, Scr continued trending up and proteinuria increased to 3g/d, with otherwise bland urine and negative serologic workup, so sirolimus was discontinued. Unfortunately, kidney function continued to decline rapidly, prompting renal biopsy, which showed BKVN (Figure 1) with both chronic and active tubulointerstitial nephritis, 90% globally sclerosed glomeruli, and evidence of mild CNI toxicity. He was concurrently found to have high-titer BK viremia and viruria. MMF was reduced by 50%. He is starting dialysis. OHT has been functioning well without rejection based on routine TTE and endomyocardial biopsies. He will not be a candidate for kidney transplant until resolution of BK viremia.

Discussion: Due to a lack of routine screening, BKVN of native kidneys may be an underreported etiology of CKD in NKSOT patients. Delayed diagnosis of BKVN can result in ESKD and be a barrier for kidney transplant, as is seen here. There may be a role for BK screening in NKSOT patients with kidney dysfunction as a means of early diagnosis of BKVN.

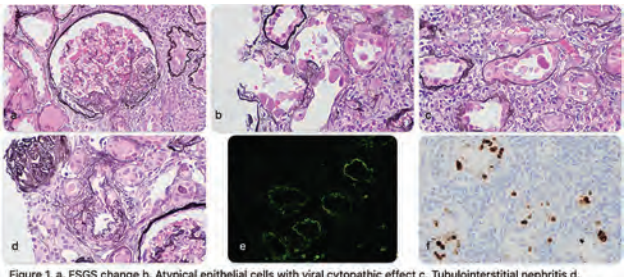


Figure 1. a. FSGS change b. Atypical epithelial cells with viral cytopathic effect c. Tubulointerstitial nephritis d. Arteriolar hyalinosis e. Tubular basement membrane staining for IgG (IF) f. Positive SV40 staining in tubular nuclei

SA-PO1002

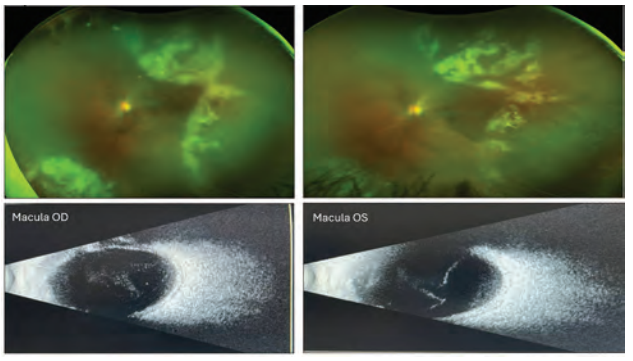
A Complicated Case of Severe Cytomegalovirus (CMV) Retinitis after 2 Decades of Kidney Transplant

Hafsa Habib,[1] Muneeba Sarosh,[2] Shahzad Chaudhry,[2] Beje S. Thomas,[1] Aisha Batool.[1] *[1]Medical College of Wisconsin, Milwaukee, WI; [2]Advocate Aurora Health Inc, Milwaukee, WI.*

Introduction: CMV stands as the primary pathogen following kidney transplantation especially within the initial 6 months post-transplantation, CMV manifests through primo-infection, reactivation of latent infection, or reinfection with a distinct strain. While CMV retinitis is infrequent among kidney transplant recipients compared to its prevalence in HIV-infected individuals.

Case Description: A 44-year-old female with a history of ESRD from type 1 diabetes, who underwent renal transplantation thrice with most recent DDKT in 2002. She was Transitioned from tacrolimus to belatacept 18 years after her DDKT, she has been on belatacept therapy for 40 months. She presented with progressive eye pain and declining vision. Outpatient eye examination revealed retinal infiltrate in the right eye surpassing the left eye, along with subacute posterior vitreous detachment in the right eye. She was admitted with initial CT Head, MRI Brain and CSF were negative for CMV. Serum CMV PCR NAAT revealed 157,000 copies. She started on IV and intravitreal Ganciclovir. She remains admitted inpatient with slight improvement of her visual symptoms. Visual acuity at 20/100 OD and 20/50 OS. OCT reveals no subretinal fluid, while Optos photography shows similar lesion size and distribution overall, with a potential slight increase in the size of an inferior lesion in the right eye. She is planned for IVIGG infusion and transitioning from belatacept to CNI.

Discussion: First-line treatment for CMV retinitis involves systemic and intravitreal ganciclovir, although prolonged therapy may lead to resistance due to mutations in viral genes. Kidney transplant recipients with CMV retinitis have shown multidrug resistance in some cases. The advent of belatacept underscores the importance of identifying potential new side effects of this treatment, particularly considering the cellular-mediated immune response against the virus by CMV-specific T-lymphocytes. The safety of belatacept concerning CMV infection remains inadequately studied.



SA-PO1003

A Patient with Severe Post-transplant Anemia Due to Parvovirus B19 Infection Treated with Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI): Desidustat

Arvind Conjeevaram. *Trustwell Hospitals Pvt Ltd, Bangalore, India.*

Introduction: Anemia is a common complication following kidney transplantation, influenced by factors such as immunosuppressive medications, increased susceptibility to infections, hemorrhage, nutritional deficiencies, reduced erythropoietin levels, hyperparathyroidism, and specific post-transplant medications.

Case Description: A 52-year-old male with h/o T2DM, hypertension & ESKD underwent a deceased donor kidney transplant in March, 2023. Postoperatively, the patient developed anemia with an initial Hb level of 9.3 g/dl, with a declining trend. By May 2023, Hb had dropped to 5.8 g/dl, with normocytic normochromic anemia, normal iron/B12 levels & Stool OB -ve. A Bone Marrow Aspiration revealed pure red cell aplasia & giant proerythroblasts with features of "Lantern" cells of Parvovirus B19 infection. Diagnosis was confirmed by detection of B19 DNA through NAAT. Multiple interventions including blood transfusions (x8 units), IVIg at recommended doses, lowering TAC dose, adding everolimus at low dose, reducing steroid/MMF doses, adding erythropoietin inj, were ineffective in sustaining Hb levels (see Fig). In Nov-2023, Desidustat (Oxemia®), an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), was started at 100mg 3/wk. Initial improvement in Hb to 8.3 g/dl was observed but was not sustained. The Desidustat dose was subsequently increased to 400mg/wk, resulting in improvement in Hb. By Feb 2024 Hb had increased to 11.1 gm/dl & by Mar 2024, Hb had stabilized at 13 g/dl. The Transplant kidney function remained stable with the serum creatinine of 1.01 mg/dl upon last review in March 2024.

Discussion: This case illustrates the potential efficacy of Desidustat in managing refractory post-transplant anemia, particularly in complex cases involving Parvovirus B19-related anemia and is the first description noted in literature for this particular indication. The observed sustained improvement in Hb with adjusted dosing of Desidustat suggests a promising therapeutic avenue that warrants further research to optimize dosing and ensure long-term efficacy.

SA-PO1004

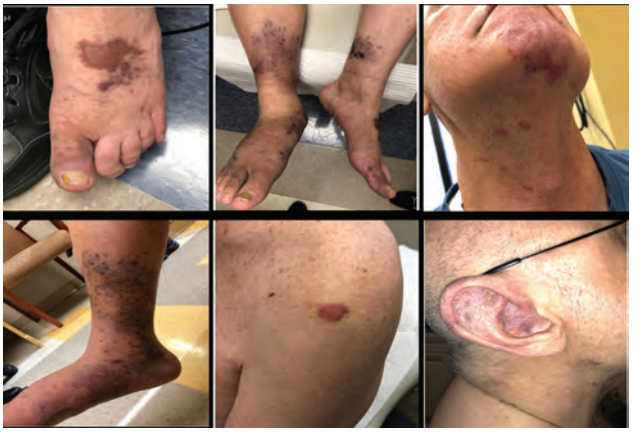
An Unusual Case of Lymphangioma-Like Kaposi Sarcoma in a Kidney Transplant Patient

Sujay D. Paudel, Syed S. Hasni, Mohammed Javeed Ansari.
Northwestern University Feinberg School of Medicine, Chicago, IL.

Introduction: Lymphangioma-like Kaposi sarcoma (LLKS) is a rare histologic presentation of Kaposi sarcoma (KS). LLKS has been described in acquired immunodeficiency syndrome and in endemic African-type as well as classic indolent KS. Here we present a rare case of transplant-associated iatrogenic immunosuppression–induced LLKS

Case Description: 71 yrs old Caucasian male with PMH of ESRD 2/2 PKD who underwent DDKT, presented with skin lesions at 1 yr post-transplant follow-up. He initially noticed the lesion around the time of transplantation as a bruise-like spot on his right foot and over the past one year gradually developed numerous skin lesions affecting multiple sites. HHV8-pcr was positive. His immunosuppressant at that time comprised of tacrolimus 2mg bid and MMF 1250mg bid. Dermatology referral was done who described the lesion as violaceous discoloration and edema with erythematous patches, ill-defined vascular plaque, purplish-blue papules and nodules, with edema and induration of right foot and lower leg. Skin biopsy revealed grossly dilated and anastomosed vascular channels with prominent hobnail endothelial cells, adjacent stroma showed fibroplasia with a proliferation of atypical spindled-shaped cells, numerous erythrocytes in the adjacent stroma as well as mononuclear cells and plasma cells. Immunohistochemistry was positive for HHV-8 and podoplanin. C-MYC was negative. Tacrolimus was changed to everolimus with improvement and stabilization of the Kaposi's lesions

Discussion: LLKS is a rare histologic presentation of KS which is strongly associated with HHV-8 infection. Incidence of Kaposi sarcoma in renal transplant is 1.5%, however the incidence of LLKS in renal transplant patient is extremely rare. mTOR inhibits the HHV-8 lytic replication cycle and has an antineoplastic and antiangiogenic effects. This case report represents further evidence of the utility of an mTOR inhibitor as a treatment for kidney transplant–associated iatrogenic immunosuppression–induced Kaposi sarcoma



SA-PO1005

The Ticking Time Bomb: A Case of Hemophagocytic Lymphohistiocytosis Triggered by Ehrlichiosis in a Kidney Transplant Recipient

Aung Sitt Naing,[1,2] Sean Bademian,[1,2] Ralph Rogers,[3] Harlan C. Rust,[2,1] Thomas R. McCune.[2,1] *[1]Eastern Virginia Medical School, Norfolk, VA; [2]Nephrology Associates of Tidewater LTD, Norfolk, VA; [3]Sentara Medical Group, Norfolk, VA.*

Introduction: Human Monocytic Ehrlichiosis (HME) is rare in kidney transplant recipients despite immunosuppression and risk of direct transmission from the donor kidney. Disease severity ranges from mild symptoms to life-threatening illness in immunocompromised patients. There are cases of Hemophagocytic Lymphohistiocytosis (HLH) triggered by HME. However, there have been no such reports in adult kidney transplant recipients.

Case Description: A 60-year-old female with a history of living donor kidney transplant 3 years prior presented with a few days of altered mental status and fever. Initial labs showed pancytopenia, elevated liver enzymes, acute kidney injury. Her hospital course was marked by worsening encephalopathy and pancytopenia requiring serial platelet and RBC transfusions. Empirical antibiotic therapy was initiated for meningitis. CSF analysis was unremarkable. Her condition rapidly deteriorated into profound shock requiring intubation and CRRT. She was started on dexamethasone 10 mg Q12 hours for suspected HLH due to ferritin of 44,000, persistent coagulopathy, pancytopenia, hypertriglyceridemia, liver injury and sCD25 of 14856. Despite no known tick bites, further workup was pursued for tickborne disease due to known association of HLH and HME which revealed a positive E. chaffeensis DNA PCR. A 21-day course of doxycycline was initiated and other anti-infectives discontinued. She improved drastically with resolution of pancytopenia, coagulopathy and shock. She was extubated and taken off CRRT.

Discussion: The incidence of HME has risen significantly from 2000-2019 in Southeastern regions of US. While serology tests in an acute phase has poor sensitivity, PCR testing can be diagnostic. HLH is an exceedingly rare but life-threatening condition caused by dysregulated activity of immune system characterized by consumptive coagulopathy and shock. While HME is effectively treated with doxycycline, treating secondary HLH includes moderate-dose dexamethasone and addressing the underlying cause. Etoposide, IVIG and plasma exchange have been used in severe cases. Mortality ranges from 20-88%. Diagnosis of HME and HLH remains very challenging for clinicians. HME-induced HLH can be considered in fever, pancytopenia, coagulopathy and worsening shock when there is no clear cause identified in kidney transplant recipients living in endemic areas.

SA-PO1006

A Double Therapeutic Challenge: Handling Acremonium sp. Hyalohyphomycosis and Atypical Mycobacteriosis in Tandem in a Kidney Transplant Recipient

Felipe Pascoal, Caroline F. Carrera, Jose O. Reusing. *Universidade de Sao Paulo, São Paulo, Brazil.*

Introduction: Acremonium sp. hyalohyphomycosis and Mycobacterium cheloane mycobacteriosis are opportunistic infections, often resistant to medical therapy and requiring prolonged antibiotic treatment. Despite rare, they have become more frequent as imunnosupression efficacy enhances. Herein, we present the first case of succesfully treated concurrent Acremonium sp. hyalohyphomycosis and atypical M. chelonae cutaneous mycobacteriosis in a kidney transplant recipient.

Case Description: A 66-year-old 0% PRA kidney transplant recipient from 2013 with a history of wayward compliance to standard immunossupression and multiple opportunistic infections presented with a one-year history of dorsal right hand erythematous-violaceous, nodular lesions, impaired 2nd to 5th finger flexion and purpuric plaques on abdomen and right thigh (figure 1). Magnetic Resonance Imaging (MRI) of his right hand is also shown (figure 2). Direct examination and culture of his hand and thigh lesions yielded positive for Acremonium sp., while abdominal lesions were biopsied and cultured, revealing Mycobacterium chelonae positivity and chronic inflamation. Oral voriconazole was prescribed to address the fungal infection for twelve months, whereas a combination of Levofloxacin, Linezolid and Azithromycin was initiated for the atypical mycobacteriosis. One year later, marked inflamation control and clinical response was achieved (figure 3), corroborated by follow-up MRI findings (figure 4).

Discussion: To our knowledge, this is the first case of concomitant hyalohyphomycosis and atypical mycobacteriosis in a kidney transplant recipient. While transplantation stands as a top renal replacement choice, suspicion for these rare but highly morbid infections must be raised given their demanding follow-up. When combined, they challenge even experienced nephrologists and infectious disease specialists, but therapy can be effective and optimal response achieved when adequate surveillance and care are provided.

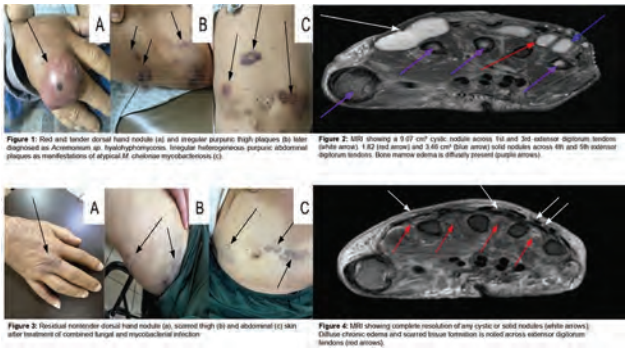


Figure 1: Red and tender dorsal hand nodule (a) and irregular purpuric thigh plaques (b) later diagnosed as *Acremonium sp. hyalohyphomycosis*. Irregular heterogeneous purpuric abdominal plaques as manifestations of atypical *M. chelonae* mycobacteriosis (c).

Figure 2: MRI showing a 0.07 cm² cystic nodule across 1st and 3rd extensor digitorum tendons (white arrow). 1.62 (red arrow) and 3.46 cm² (blue arrow) solid nodules across 4th and 5th extensor digitorum tendons. Bone marrow edema is diffusely present (purple arrows).

Figure 3: Residual noninodular dorsal hand nodule (a), scarred thigh (b) and abdominal (c) skin after treatment of combined fungal and mycobacterial infection

Figure 4: MRI showing complete resolution of any cystic or solid nodules (white arrows). Diffuse chronic edema and scarred tissue formation is noted across extensor digitorum tendons (red arrows).

SA-PO1007

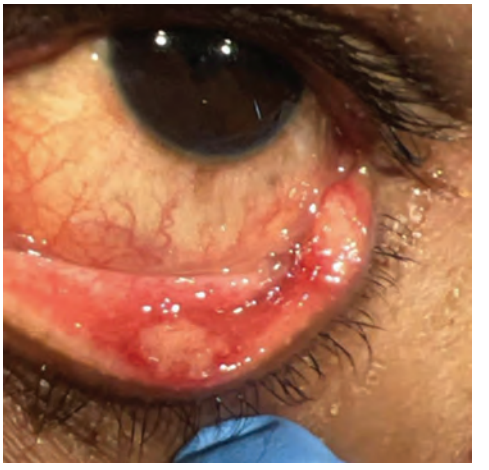
Central Nervous System (CNS) and Ocular Involvement of Systemic Blastomycosis in a Kidney Transplant Recipient

Hanna Larson,[1] Drishti Jain,[2] Ritu Garg.[1] *[1]Loyola University Medical Center, Maywood, IL; [2]Loyola University Chicago Stritch School of Medicine, Maywood, IL.*

Introduction: Blastomycosis dermatitidis is a fungal pathogen primarily affecting lungs. Immunocompromised patients, specifically solid organ transplant recipients, are at increased risk of disseminated blastomycosis. We describe a rare case of disseminated blastomycosis in a kidney transplant recipient with pulmonary, cutaneous, ocular, and CNS manifestations.

Case Description: A man aged 45 status post renal transplant due to post-streptococcal glomerulonephritis presented with fatigue, cough, and fever. Initial workup revealed leukocytosis and pulmonary micronodular lesions, tree-in-bud opacities and ground glass nodules on CT. Post admission the patient developed lower leg painless, flat, red macules that progressed to diffuse painful umbilicated pustules and papules. Skin biopsy showed broad-budding yeast cells, suggesting systemic blastomycosis. IV Amphotericin B was initiated. The patient then developed neck stiffness and encephalopathy. Blastomyces antigen in CSF confirmed leptomeningeal involvement. Palpebral fissure granulomas and culture identified mold, confirming chorioretinitis. During 4-weeks of Amphotericin B, the patient's symptoms improved significantly. Due to high tacrolimus levels, hypovolemia, and Amphotericin B an AKI developed, resolving with tacrolimus reduction and IV fluids. He transitioned to voriconazole for a year of therapy.

Discussion: Disseminated blastomycosis CNS and ocular involvement is rare. It is challenging to diagnose given the range of clinical symptoms, especially in transplant recipients. This case emphasizes early recognition and treatment, specifically for ophthalmologic and neurologic manifestations, to prevent severe complications.



Inferior palpebral conjunctiva with 2 large granulomatous appearing lesions.

SA-PO1008

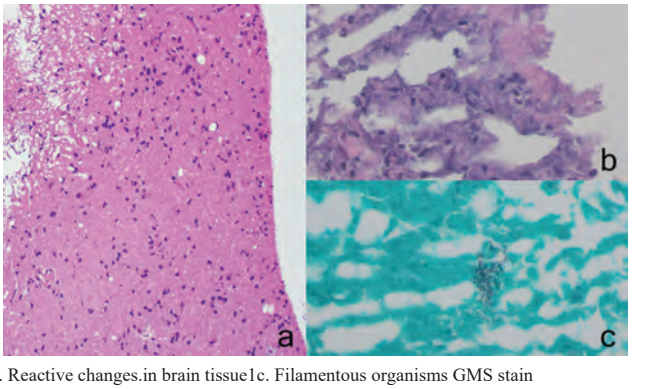
Nocardia Brain Abscess and Cytomegalovirus Meningoencephalitis in a Kidney Transplant Patient

Irmaris R. Quinones Vargas, Namita Singh, Pablo Garcia, Faye Oakes, Karen S. Santacruz, Laura E. Shevy, Pooja P. Singh. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Introduction: Nocardia mainly affects immunosuppressed people with 20-50% infections disseminating to the brain. CMV infection can result in meningoencephalitis in the immunocompromised. Both Nocardia and CMV infections can cause significant morbidity for transplant recipients. We present a kidney transplant (KT) recipient with co-existing CMV meningoencephalitis and Nocardia brain abscess.

Case Description: 75 YO woman, 6 months s/p DDKT, presented to the hospital with AMS and fever. Brain MRI demonstrated a 3 cm abscess in the left frontal lobe. LP was performed with detection of CMV by PCR and isolation of *Nocardia veterana* in the CSF. Brain abscess biopsy demonstrated purulent and necrotic debris within brain tissue. GMS stain revealed finely filamentous organisms, and *Nocardia veterana* was isolated in AFB culture. Source of infection was felt to be soil inhalation given pulmonary nodules on chest CT. Her immunosuppression regimen was adjusted. She was treated with IV trimethoprim-sulfamethoxazole and meropenem for the *Nocardia* brain abscess, and with IV ganciclovir for the CMV meningoencephalitis. She had full neurological recovery at 7 weeks and is now 26 weeks out from initial diagnosis with excellent allograft function.

Discussion: A dual diagnosis of CMV meningoencephalitis and *Nocardia* brain abscess post KT is rare; with no other cases reported in the literature. The outcomes of nocardiosis and delayed post-prophylactic CMV disease depend on the site of infection and host immune status. Nocardial CNS infections confer a high mortality rate – up to 85% in immunosuppressed patients. However, early diagnosis and prompt treatment can achieve cure rates up to 50-85%. CMV disease in kidney transplant recipients can increase the risk of mortality by more than 50%. This case demonstrates the importance of early diagnosis and treatment of these virulent infections in transplant recipients so that successful outcomes can be achieved.



1a. Reactive changes.in brain tissue1c. Filamentous organisms GMS stain

SA-PO1009

Fatal Pulmonary Mucormycosis in a Kidney Transplant Patient: Missed "Opportunism"

Tatiana Correa, Barbara A. Greco, Kenneth Brand, Umair Khan, Gregory L. Braden. *Baystate Medical Center, Spring ield, MA*.

Introduction: Pulmonary mucormycosis (PM) has a high mortality rate if not diagnosed promptly. We present a fatal case in a patient presenting seven months post-transplantation whose diagnosis was delayed, and emphasize the need for early diagnosis of opportunistic infections.

Case Description: A 55-year-old man with ESRD and prior failed deceased donor kidney transplant (DDKT) underwent a second DDKT complicated by delayed graft function and antibody-mediated rejection treated with apheresis and IVIG. Seven months post-transplant, he presented with cough, fever, diarrhea, and weight loss. He was on tacrolimus, mycophenolic acid, and prednisone. Imaging revealed diverticulitis and a cavitating thick-walled right lower lung lesion. He was treated with ampicillin/sulbactam but had continued fevers and respiratory distress. Serologic infectious workup was unrevealing; galactomannan test was negative. Bronchoalveolar lavage on hospital day 4 identified Streptococcus species; piperacillin/tazobactam was given for seven days. The patient worsened and required noninvasive ventilation. Repeat imaging demonstrated a pleural effusion with invasion of the RLL mass into the right middle lobe, diaphragm, and liver. Thoracentesis was performed on hospital day 12 and a lung biopsy on day 19. Pleural fluid and tissue histology was consistent with mucor. Amphotericin was started and he was transferred for surgical debridement, but died within 24 hours.

Discussion: Kidney transplant patients are immunosuppressed and at risk for opportunistic infections. Mucormycosis accounts for 2-6% of fungal infections and emerges usually after 6 months post-transplantation as rhinocerebral, PM, skin, or disseminated disease. Concomitant bacterial pneumonia occurs in 30% of PM cases. A negative galactomannan test is expected as mucor lacks this cell wall antigen. Reverse halo sign on imaging is suggestive but histology is necessary for diagnosis. The presence of characteristic non-septate, right-angled branching hyphae confirms diagnosis. Treatment requires intravenous liposomal Amphotericin B and surgical debridement. PM is rapidly progressive, invasive, and carries a 60-70% mortality rate. This case highlights the pitfalls of empiric approaches to infections in immunocompromised hosts and the need for early suspicion for opportunistic infection and tissue diagnosis to optimize outcomes.

SA-PO1010

Hypercalcemia Due to Disseminated Histoplasmosis in a Kidney Transplant Recipient with Negative Histoplasma Antigen Testing

Michael I. Tabet, Lemuel R. Non, M. Lee Sanders. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Introduction: Histoplasmosis is a fungal infection that can lead to disseminated disease in immunosuppressed patients. Hypercalcemia can occasionally result, as it is a granulomatous disease. We present an interesting case of disseminated histoplasmosis complicated by hypercalcemia but negative histoplasma antigen testing.

Case Description: A 68-year-old male with kidney transplanted in 2002 on sirolimus, mycophenolate mofetil, and prednisone presented to clinic complaining of fevers, night sweats, 35-lb weight loss, fatigue, and intermittent diarrhea. He was found to have enteropathogenic E coli on stool enteric panel and esophagitis on upper endoscopy. With ongoing treatment, his serum calcium rose from normal to 11.0 mg/dL. Initial work-up showed PTH was mildly low, 25-hydroxyvitamin D was normal, but 1,25-dihydroxyvitamin D was elevated. CT imaging showed innumerable miliary lung nodules with multiple cavitary nodules and calcified splenic lesions, consistent with granulomatous infection. An extensive infectious work-up was performed, including bronchoalveolar lavage, and was unremarkable. His hypercalcemia and symptoms improved, and he was discharged home, only to return months later with similar symptoms and a calcium of 13.1 mg/dL. Infectious testing was again unrevealing; therefore, he underwent video-assisted thoracoscopic surgery with pleural fluid sampling and lung wedge resection biopsy. Pleural fluid studies and cultures were unremarkable, but lung biopsy both showed necrotizing granulomas with silver-stained yeast forms and grew Histoplasma capsulatum on culture. He was started on itraconazole. A follow-up CT scan eight months later showed contraction of cavitary lesions to smaller nodules and resolution of his symptoms and hypercalcemia.

Discussion: Histoplasmosis is a concern for immunosuppressed patients in certain geographic areas. While hypercalcemia can occur with disseminated granulomatous disease, it is relatively uncommon. The usual testing performed when histoplasmosis is suspected is checking blood and/or urine for the histoplasma antigen, which is usually positive in disseminated disease. Interestingly, in this case, both blood and urine antigen were negative at two different time points prior to diagnosis, despite dissemination. Persistent testing including tissue biopsy may be needed in such cases to make a diagnosis.

SA-PO1011

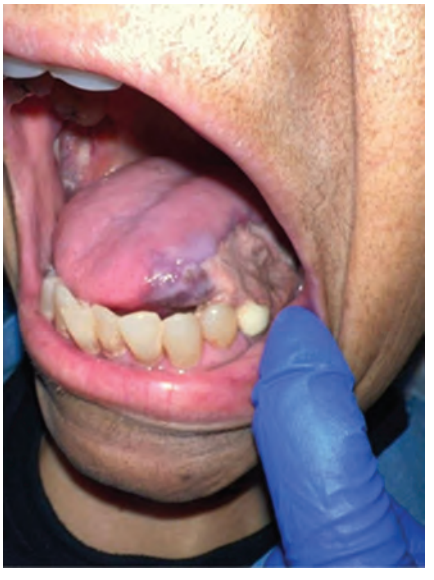
Disseminated Histoplasmosis Manifesting as Oral Lesions in a Kidney Transplant Patient

Sebastian Hinojosa,[1] Alexis Nguyen,[2] Piera A. Sosa,[1] Trey H. Richardson,[1] Levan Gakhokidze,[1] Alissa A. Ice,[1] Anthony J. Langone, [1] Heidi M. Schaefer.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Wayne State University School of Medicine, Detroit, MI.*

Introduction: Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum,* is often asymptomatic in immunocompetent individuals. In immunocom-promised hosts, Histoplasmosis can become disseminated and severe. Oral manifestations of histoplasmosis are rare and can pose a diagnostic challenge.

Case Description: A 72-year-old female who had undergone renal transplant 3 years prior presents to the ED with a 1-month history of painful oral lesions and weight loss of 20lbs. Her immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. Physical examination revealed a painful, irregularly shaped left lateral tongue ulceration with superficial sloughing and similar ulceration over the right buccal mucosa. There was palpable lymphadenopathy of the left anterior cervical chain. Workup was notable for pancytopenia, elevated β-d-glucan, and positive urine histoplasma antigen. CT of the chest revealed ground glass nodular opacities bilaterally and abnormal bone marrow signal. Biopsies were performed revealing budding yeast forms consistent with*Histoplasma capsulatum*.

Discussion: This case illustrates several important points about histoplasmosis in the post-transplant population. Firstly, disseminated histoplasmosis can present with nonspecific symptoms such as mucosal ulcers and weight loss, which can mimic other post-transplant complications like drug reactions, malignancy, or other infections. Secondly, the diagnosis of histoplasmosis should be considered in immunosuppressed patients presenting with unusual lesions or systemic symptoms in endemic areas. In our patient, management included reducing immunosuppression and treatment with amphotericin B followed by oral posaconazole. The patient improved after several weeks of treatment.



SA-PO1012

Feline Footprints in Transplant Realms

Kamil Sardarli,[1] Adolfo Del Bosque-Aguirre,[2] Scott Mullaney.[1] *[1]University of California San Diego, La Jolla, CA; [2]Tecnologico de Monterrey Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico.*

Introduction: Bartonella henselae is a zoonotic pathogen with clinical presentations influenced by the immune status of the human host. While cat scratch disease is common in immunocompetent hosts, solid organ transplant recipients typically present with a different spectrum of symptoms. Bartonella species are increasingly acknowledged as significant pathogens, but diagnosing Bartonella infection in this population can be challenging due to overlapping clinical manifestations with other conditions, such as malignancy, and the potential risks associated with invasive procedures like biopsies.

Case Description: 35 years old female patient presented with fever and myalgia. She had past medical history of lupus nephritis and atypical HUS complicated by end stage kidney disease and received a deceased donor kidney transplant 6 months prior to presentation, She received thymoglobulin induction and had been taking tacrolimus, mycophenolate, and prednisone for immunosuppression. On initial presentation, she was febrile (103 F), but hemodynamically stable. Initial laboratory work yielded WBC 11.6 cells/mm^6, Hgb 7 g/dl, platelet 74/mm^6, creatinine 1.7 g/dl from baseline 1.2 g/dl, ALP 139 U/L, ALT 39 U/L and AST 47 U/L. Initial imaging revealed an unremarkable transplant kidney but hepatosplenomegaly with multiple hypoechoic lesions throughout the liver and spleen. MRI identifed enhancing lesions in the liver, spleen, and bones with retroperitoneal lymphadenopathy, read as "primarily concerning metastatic disease with atypical infection felt to be less likely." The patient was started on vancomycin, cefepime, metronidazole, micafungin. A broad infectious work up was ordered and interventional radiology consulted for liver biopsy. The biopsy had to be postponed by two days due to scheduling constraints. B. henselae serology returned with a positive IgM titer of 1:32 and IgG > 1:1024. She was started on azithromycin and rifampin. Further history revealed she owned three cats.

Discussion: Bartonella infection should be considered in the differential diagnosis of transplant recipients presenting with fever, lymphadenopathy and hepatosplenic lesions, especially when imaging suggests multifocal involvement. Serology offers a safer alternative to biopsy in confirming the diagnosis. Early recognition and appropriate antimicrobial therapy are crucial in managing Bartonella infection in immunocompromised hosts to prevent complications.

SA-PO1013

Abstract Withdrawn

SA-PO1014

Late Pneumocystis jiroveci Pneumonias in Kidney Transplant Recipients in Central Norway

Marius A. Øvrehus,[1,2] Jakob Lund,[1] Robin K. Kehreman.[1] *[1]Norges Teknisk-Naturvitenskapelige Universitet, Trondheim, Norway; [2]St Olav's Hospital HF, Trondheim, Norway.*

Background: *Pneumocystis jirovecii* pneumonia (PCP) can be life threatening in kidney transplant recipients (KTR). We know little about the course of late onset PCP - occurring later than one year after transplantation - in KTR.

Methods: Retrospective study using electronic patient charts in KTR diagnosed with PCP between 2006 and 2021 in Central Norway, which has a population of 697,000. We collected clinical data (table).

Results: We found 38 kidney transplant recipients with PCP. Median age 60 years, most on standard immunosuppression. Median length of hospitalization was 2 weeks, 32% received organ support treatment. Total mortality 18,4% within 180 days. The incidence was 0,4 cases/100,000 inhabitants.

Conclusions: We found that PCP had a serious course with organ failure, need of organ support, and 180 day mortality of 18%. In spite of the recommendation of life-long prophylaxis after PCP, 30% were not started on TMS at discharge.

Funding: Government Support - Non-U.S.

PCP patients (n)	38
Age, median, (q1-q3)	60 (50-66)
Male, n (%)	25 (65,8)
Last eGFR (stable phase), mL/min (n = 31), median, (q1-q3)	36 (27-54)
In dialysis, n (%)	7 (18,4)
Years since kidney tx., median, (q1-q3)	8 (4,8-18)
Years on immunosuppression, median, (q1-q3)	
Corticosteroids (n = 38)	8 (4-14)
CNI (n = 36)	8 (3,8-14)
MMF/MMS (n = 35)	6 (3,5-11)
Azathioprin (n = 7)	18 (7,5-20)
Everolimus/sirolimus (n = 6)	2,5 (1,3-3,8)
Days from symptom onset to diagnosis, median, (q1-q3)	11,5 (7-22)
CRP median, (q1-q3) (n = 38, mg/L) at diagnosis.	84 (52-112)
Leukocytes, median, (q1-q3) (n = 38, x 109/L) at diagnosis	7,8 (5,4-9,8)
Chest X ray pathology, any (n = 36) at diagnosis	97%
CT thorax pathology, any (n = 36) at diagnosis	100%
Microbiological diagnosis: bronchoscopy with BAL, n (%)	34 (89,5)
Microbiological diagnosis: other n (%)	7 (18,4)
Antibiotic treatment: trimethoprim-sulfametoxazol, n (%)	34 (89,5)
Antibiotic treatment: clindamycin + primaquine, n (%)	10 (26,3)
Days in hospital, median, (q1-q3) (n = 38)	17 (11-27)
Days in ICU, median, (q1-q3) (n = 10)	22 (17-24)
Days on respirator, median, (q1-q3) (n = 8)	15 (12-23)
Days with new onset dialysis, median, (q1-q3) (n = 5)	15 (12-15)
Mortality, in hospital, n (%) (n = 38)	6 (15,8)
Mortality, within 180 d after discharge, n (%) (n=32)	1 (3,1)
Mortality, total, n (%) (n =38)	7 (18,4)
Prophylaxis against P. jirovecii at discharge (n = 32), n (%)	23 (71,9)

SA-PO1015

Risk of Post-transplantation Hepatocellular Carcinoma, Cirrhosis, and Liver Failure in Kidney Recipients with Hepatitis C Infection

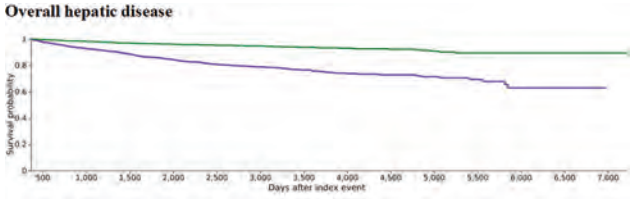
Tung-Min Yu, Yu-Nong Kao, Chih Wei Chiu, Shih T. Huang. *Taichung Veterans General Hospital, Taichung, Taiwan.*

Background: Hepatitis C virus (HCV) infection is prevelant in patients with end stage renal disease (ESRD). Compared to ESRD with dialysis, kidney transplantation offers a survival advantage for ESRD patients. To the present, ESRD with HCV infection remains an acceptable candidate for kidney transplantation. However, HCV is the leading cause resulting in hepatic complications after transplantation. Data to elucidate the liver issue in renal transplant patients with HCV infection are scarce. In the present study, we aimed to investigate the hepatic outcomes of renal transplantation with HCV infection.

Methods: Data Source TriNetX is a multicenter federated health research network. Our study population is drawn from 89 Healthcare Organization (HCOs). Patients received kidney transplantation [ICD-10: Z94.0] and those with HCV were case group in this study, while those without HCV were control group. Propensity score matching (PSM) with ratio 1:1 was applied including sex, age at index, and comorbidities.

Results: A total of 6,605 renal recipients with HCV infection and 188.466 renal recipients without HCV infection were enrolled. After PSM, 6,473 were in each group, respectively. In the study population, over 60% of the patients were male and aged between 40-65. After matching, our findings showed that subjects with HCV infecton had significantly higher risk of hepatoma, cirrhosis, hepatic failure, and overall hepatic disease than those without HCV infection. (hepatoma: HR: 8.957; CI: 5.324-15.069; cirrhosis: HR: 5.378; CI: 4.363-6.631; hepatic failure: HR: 3.258; CI: 2.527-4.200; overall hepatic disease: HR: 4.128; CI: 3.428-4.971)

Conclusions: In the present study, our findings show that renal recipients with HCV infection is significantly associated with a remarkably high risk of hepatic complications including hepatoma, cirrosis and liver failure post-kidney transplanttaion and that has been ignored previously. Professionals should pay more attention while taking care of renal recipients with HCV infection. The eradication of HCV therapy by Direct-acting antivirals (DAAs) should be considered.



RTX with HCV in purple color and RTX without HCV in green color; P<0.0001 in Log-Rank Test

SA-PO1016

IgG4 Hypogammaglobulinemia Associated with Urinary Tract Infection in Kidney Transplant Recipients at the Centro Médico Nacional de Occidente, Guadalajara, Jalisco, Mexico

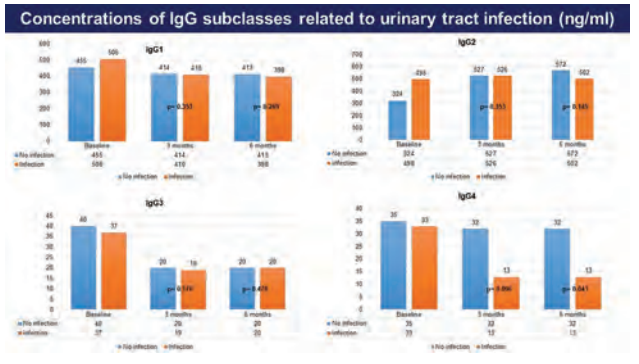
Javier Israel Ruiz, Luis Alberto Evangelista-Carrillo, Adriana Banda Lopez, Caridad A. Leal, Cynthia M. Lujano Navarro. Resident. *Hospital de Especialidades del Centro Medico Nacional de Occidente IMSS, Guadalajara, Mexico.*

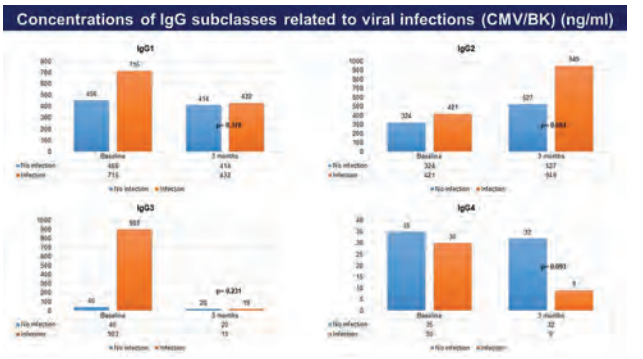
Background: In the era of precision medicine, the evaluation of IgG subclasses represents an attractive tool that could open a new scenario in the personalized pharmacological treatment of the patient. The measurement of immunoglobulins, specifically IgG, has taken importance in recent years as an instrument that allows reducing the risk of complications such as infectious processes in patients with a kidney transplant.

Methods: Single-center, retrospective cohort study. 1-year follow-up. IgG subclasses were quantified using Luminex equipment.

Results: The study included 143 patients diagnosed with chronic kidney disease who underwent kidney transplantation and 20 donors for reference values. Urinary tract infection events at 3 (20.4 ng/ml, p = 0.09) and 6 months (28.4 ng/ml, p = 0.04) were related to low IgG4 concentrations. IgG subclasses concentrations were not related to the presence of viral infections in patients.

Conclusions: IgG4 subclass levels appear to be associated with urinary tract infection events, but not with viral processes. This is the first study, that analyzes the immunoglobulin G subclass profiles of transplant patients and relates them to clinical events (urinary tract infection and viral infections) using magnetic microspheres in Luminex equipment as a measurement technique in the Mexican population. Serum levels of IgG subclasses can be a surrogate in the management of immunosuppression in patients with kidney transplants, since it is not a one-dimensional measurement but rather the final result of a complex interaction of pathways that culminate in their formation.





SA-PO1017

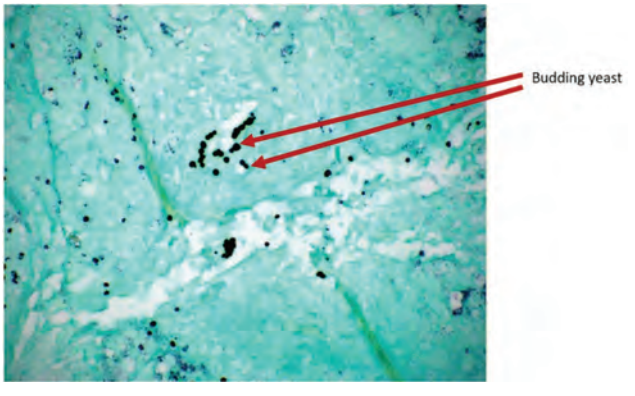
Successful Resolution of Fungal Pyelonephritis in a Kidney Transplant Recipient

Gina G. Suarez,[1,2] Gretchen N. Marrero Lozada,[2] Shawn Alonso,[2] Marco A. Ladino Avellaneda.[2] *[1]Jackson Memorial Hospital, Miami, FL; [2]University of Miami Miller School of Medicine, Miami, FL.*

Introduction: Fungal pyelonephritis in the context of a kidney transplant refers to a renal infection caused by fungi, which can complicate the post-transplant course and potentially lead to delayed graft function. This condition is relatively rare but can be severe, leading to serious consequences such as graft loss and even death if not promptly identified and treated. Various fungi can cause pyelonephritis in kidney transplant recipients. Candida glabrata has been reported to cause emphysematous pyelonephritis, a serious necrotizing infection. Surgical interventions such as graft nephrectomy may be required in severe cases. However, the specific treatment approach, including the choice of antifungal agent and the duration of therapy, should be individualized based on the patient's clinical condition, the causative organism, and the presence of any complications.

Case Description: A 52-year-old male with a history of IgA Nephropathy and a deceased donor kidney transplant presented two months post-transplant with fevers alongside stage II acute kidney injury. Despite isotonic intravenous fluids, his renal function did not improve, necessitating a kidney biopsy to elucidate the underlying cause of his deteriorating condition. He was diagnosed with fungal pyelonephritis from Candida glabrata, and was ultimately treated with fluconazole. The patient did not lose the allograft and has maintained stable renal function with lifelong antifungal therapy.

Discussion: This case represents the first documented instance within the scientific literature of a successful therapeutic resolution of fungal pyelonephritis attributable to Candida glabrata in a kidney transplant recipient. The treatment efficacy delineated in this scenario is particularly noteworthy given the complexity often associated with opportunistic fungal infections in immunocompromised hosts.



The Grocott's Methenamine Silver (GMS) stain revealed the presence of an abundant number of yeast cells.

SA-PO1018

Biopsy-Proven Fungal Pyelonephritis in a Kidney Transplant Recipient

Vikramjeet Kakade, Sri Vibhavari Guntupalli, Sudha Tata, Alton B. Farris, Stephen O. Pastan, Mohammad Kazem Fallahzadeh Abarghouei. Emory University Div of Renal Medicine. *Emory University School of Medicine, Atlanta, GA.*

Introduction: Acute pyelonephritis due to bacterial infections is a common cause of acute kidney injury in kidney transplant recipients but fungal pyelonephritis is rare with only a few cases reported.

Case Description: A sixty-year-old man with a history of end-stage kidney disease attributed to hypertension who had an unrelated living donor kidney transplant in Iraq, with no known complications presented five months after transplantation with fever, and confusion. He was found to have an acute kidney injury. His urine culture was positive for methicillin-susceptible Staphylococcus aureus and his blood culture was positive for Salmonella. He was treated with empiric ceftriaxone therapy. He had two sessions of hemodialysis due to concern for uremic encephalopathy with improvement in his mental status. Due to a lack of improvement in his kidney function, he had a transplant kidney biopsy that showed fungal forms (Figure 1). He had extensive workup including fungal culture and molecular studies of biopsy tissue, but no organism was identified. His immunosuppression regimen was reduced. He received empiric amphotericin followed by oral isavuconazonium resulting in significant improvement in kidney allograft function and no further need for hemodialysis.

Discussion: Fungal pyelonephritis is a rare but serious cause of acute kidney injury in kidney transplant recipients. Observing fungal forms on kidney biopsy is instrumental in the diagnosis. If there is a suspicion of fungal pyelonephritis, for example in patients with systemic fungal infection with acute kidney injury, a kidney biopsy tissue sample should be sent for fungal culture. Our case shows that cases of fungal pyelonephritis in which no specific organism is identified could be successfully treated with empiric amphotericin followed by long-term oral isavuconazonium with close clinical monitoring.

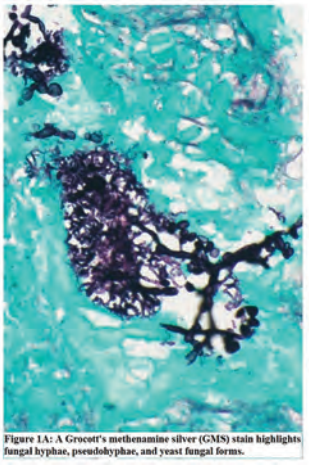


Figure 1A: A Grocott's methenamine silver (GMS) stain highlights fungal hyphae, pseudohyphae, and yeast fungal forms.

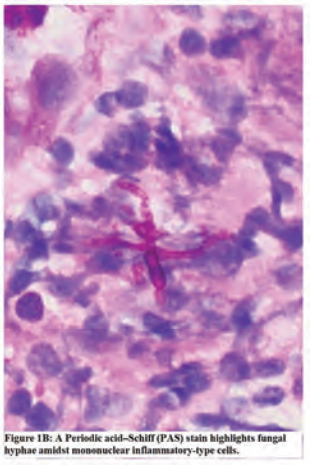


Figure 1B: A Periodic acid–Schiff (PAS) stain highlights fungal hyphae amidst mononuclear inflammatory-type cells.

Figure 1: Kidney allograft pathology

SA-PO1019

AKI Due to Asymptomatic Pyelonephritis in a Kidney Transplant Recipient

Jae H. Son, Payaswini Vasanth, Mohammad Kazem Fallahzadeh Abarghouei. *Emory University, Atlanta, GA.*

Introduction: Kidney transplant recipients with a positive urine culture but no symptoms of urinary tract infection (UTI) are typically diagnosed with asymptomatic bacteriuria and usually do not receive antibiotic treatment. However, in this report, we describe a case of acute kidney injury (AKI) due to asymptomatic pyelonephritis, which responded to antibiotic therapy.

Case Description: A 62-year-old woman with a history of end-stage kidney disease due to hypertension underwent a deceased donor kidney transplant. Her post-transplant course was complicated by delayed graft function and early borderline acute cellular rejection, which was treated with high-dose oral prednisone. One month post-transplant, she had removal of ureteropelvic stent. Two months post-transplant, she developed a symptomatic urinary tract infection (UTI) caused by multidrug-resistant Klebsiella pneumoniae, accompanied by acute kidney injury (AKI), and was treated with intravenous antibiotics. Three months post-transplant, she presented again with AKI. Although her urine culture was positive for the same organism, she did not exhibit any UTI symptoms and was initially not given antibiotics. A kidney biopsy performed for evaluation of AKI revealed severe tubulointerstitial inflammation with neutrophil casts, indicative of acute pyelonephritis. Consequently, she was treated with intravenous antibiotics, resulting in an improvement in her serum creatinine levels.

Discussion: Monitoring for and treating asymptomatic bacteriuria is typically not recommended beyond two months post-kidney transplant due to a lack of evidence for improved outcomes and concerns about antibiotic resistance. However, our case demonstrates that biopsy-proven acute pyelonephritis, severe enough to cause AKI, can be asymptomatic in kidney transplant recipients. Therefore, acute pyelonephritis should be considered as a potential cause of AKI in patients with asymptomatic bacteriuria when no other clear etiology for AKI is present.

SA-PO1020

Urinary Tract Infections Caused by Carbapenemase-Producing Enterobacteriaceae in Kidney Transplant Patients

Ariane B. Monteiro,[1] Ana Clara E. Perotti,[1] Gisele Meinerz,[1] Elizete Keitel.[1,2] *[1]Universidade Federal de Ciencias da Saude de Porto Alegre, Porto Alegre, Brazil; [2]Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil.*

Background: Patients undergoing kidney transplantation, due to changes in urogenital anatomy and the use of immunosuppressive medications, are more susceptible to infections, with urinary tract infections (UTI) being the most common. The emergence of carbapenemase-producing enterobactéria (CPE) as causes of infectious events in this population is a concern. This study aims to describe kidney transplant patients who presented CPE urinary tract infection and the outcome of these patients in the first year after the procedure. **Objective:** to describe kidney transplant patients who presented CPE urinary tract infection and the outcome of these patients in the first year after the procedure.

Methods: Retrospective observational study of adult and pediatric patients undergoing kidney transplantation between January 2014 and December 2022, in a hospital in southern Brazil, who presented with asymptomatic bacteriuria, simple cystitis and complicated CPE UTI in the first year after the procedure. The project was approved by the Ethics and Research Committee of Santa Casa de Misericórdia de Porto Alegre, CAAE 54930022.9.0000.5335.

Results: During the period, 2119 patients underwent kidney transplantation, 59 (2,8%) presented with asymptomatic bacteriuria and 128 (6,0%) at least one UTI episode due to CPE (figure 1) with a median of 26 days after surgery. Recurrent infection occurred in 62 (48,4%) of UTI patients. The most prevalent microorganism was *Klebsiella pneumoniae* and the resistance mechanism was Klebsiella pneumoniae carpapenemase (KPC). Patient outcomes are detailed in figure 1.

Conclusions: Almost 6% of patients had at least one episode of UTI by CPE. The median time until the first UTI was 26 days. One year graft loss and mortality rate in patients with UTI were 23,4% and 13,3%, respectively. The findings of this cohort highlights the incidence and the negative repercussion of this infection on renal transplant recipients.

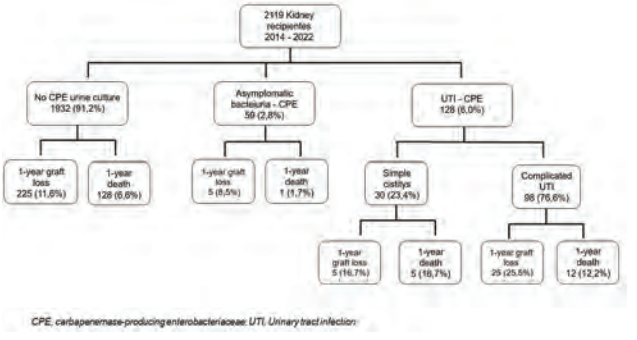


Figure 1. Kidney transplant patients flow during the study.

SA-PO1021

Case Report of Nontyphoidal Salmonella Aortitis in a Kidney Transplant Recipient

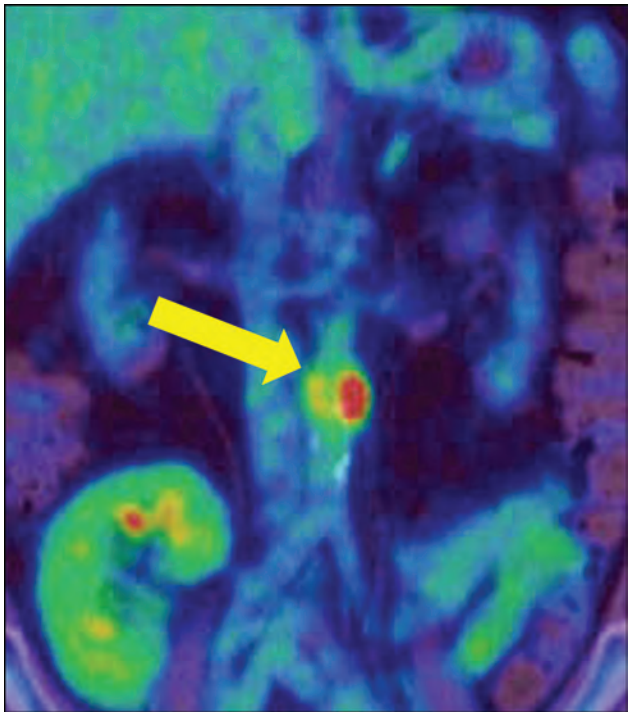
Suguru Muraoka, Yasuhiro Mochida, Kunihiro Ishioka, Machiko Oka, Hidekazu Moriya, Takayasu Ohtake, Sumi Hidaka. Kidney Disease Transplant Center. *Shonan Kamakura Sogo Byoin, Kamakura, Japan.*

Introduction: Immunosuppressive therapy predisposes kidney transplant recipients to various infections. While Salmonella infection after transplantation typically manifests as enteritis or urinary tract infection, there are limited reports of aortitis. We present a case of Salmonella enterica-induced abdominal aortitis.

Case Description: A 49-year-old man with diabetic nephropathy underwent ABO-incompatible living donor kidney transplantation. Five years later, he presented to the emergency department with fever and chills persisting since the previous day. His serum creatinine ranged from 2 to 3 mg/dL. Blood cultures isolated Salmonella enterica, and computed tomography (CT) on day 6 of hospitalization confirmed abdominal aortitis. Conservative management with antibiotics and blood pressure control was initiated, and the aortic diameter was monitored via CT. The maximum aortic diameter reached 27 x 25

mm but subsequently decreased. C-reactive protein (CRP) levels normalized on day 31, and the patient was discharged on day 34.

Discussion: This case highlights infectious aortitis secondary to Salmonella bacteremia post-transplantation. Transplant recipients, particularly those with diabetes, are at heightened risk of Salmonella bacteremia and infectious aortitis due to immunosuppression and atherosclerotic lesions. Given the predominant fecal-oral transmission of Salmonella, dietary counseling for kidney transplant recipients is crucial to mitigate this risk.



PET-CT shows FDG accumulations on a slightly diliated stie of abdominal aorta.

SA-PO1022

Shanghai Fever in Los Angeles: A Solid-Organ Transplant Recipient

Andrea L. Urrutia,[1] Claudia G. Olano,[2] Sami M. Akram.[3] *[1]Universidad de San Carlos de Guatemala Facultad de Ciencias Quimicas y Farmacia, Ciudad de Guatemala, Guatemala; [2]Harbor-UCLA Medical Center, Torrance, CA; [3]Loma Linda University, Loma Linda, CA.*

Introduction: Shanghai fever is a rare presentation of pseudomonas aeruginosa sepsis. The core symptoms are fever, diarrhea and ecthyma gangrenosum (EG) (1). The enteric disease caused by pseudomonas aeruginosa has been reported in pediatric patients (2,3,4); cases in adults are extremely rare (5). To the best of our knowledge this is the first case report of shanghai fever in an adult solid organ transplant (SOT) recipient. EG frequently occurs in immunocompromised and neutropenic patients (6,7). Sixty percent of EG lesions are in the gluteal perineal region (6,8) and can be overlooked if skin is not thoroughly examined

Case Description: This is a 49-y-old female who had simultaneous pancreas kidney transplant 15 months ago. She presents with oral ulcers, severe diarrhea, which progressed to sepsis followed by gastrointestinal bleeding. She required intensive care support and transfusions. She had perirectal pustular and nodular lesions with central necrosis. Histology was consistent with ecthyma gangrenosum. Tissue cultures grew pseudomonas aeruginosa. A clinical diagnosis of pseudomonas sepsis with ecthyma gangrenosum was made, I.e. shanghai fever

Discussion: This is the first case report of shanghai fever in a kidney transplant patient in a suburb of Los Angeles, California. Shanghai fever is a well described enteric disease due to pseudomonas sepsis in pediatric patients. A PubMed search using the terms, [shanghai fever + adults +case report] revealed only one publication (5). While uncommon, shanghai fever or pseudomonas enteric disease (PED) can occur outside of Asia (8). PED can be fatal and in one case series the mortality was 15% (1). The clinical features of PED cases are fever, diarrhea (enteric illness) and ecthyma gangrenosum (1). Our patient had all components of PED. The differential diagnosis of fever in a immunosuppressed patient is challenging because of increased frequency of unusual microbes and other non-infectious mimics. However, our case illustrates that common organisms may have uncommon presentations in immunosuppressed patients. Shanghai fever can occur in Los Angeles. A thorough physical exam and microbiological evaluation is needed for accurate diagnosis. We report the first case of Shanghai fever in an adult kidney-pancreas recipient. We want to inform the clinicians about pseudomonas enteric disease therefore, describe its diagnosis and management

SA-PO1023

Post-transplant Lymphoproliferative Disorders (PTLD) in Kidney Transplant

Mariarosaria Campise,[1] Silvia Malvica,[1] Carlo Alfieri,[1,2] Simona Verdesca,[1] Anna Regalia,[1] Giuseppe Castellano.[1,2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Universita degli Studi di Milano, Milano, Italy.*

Background: PTLD are serious complications in solid organ (SO) and allogeneic hematopoietic stem cell transplants (T), ranging from benign proliferations to malignant lymphomas. PTLD accounts for 21% of cancers in SOT. Risk factors include Epstein-Barr virus (EBV) serostatus, recipient age, organ type, immunosuppression (IS), and genetic predispositions. Most PTLD originate from EBV-infected B cells proliferation due to IS but some 30-40% are not EBV-related. IS reduction (ISR) for immune function restoring, and chemotherapy (CT) is the treatment. We report our single center experience about incidence, risk factors, and treatment outcomes of PTLD in kidney transplant (KT) patients (pts).

Methods: Between January 1, 1969, and August 31, 2023, 3024 adult pts underwent KT. Pts with a confirmed PTLD diagnosis (biopsy/clinical suspicion) were included in the study and PTLD cases classified according to the WHO criteria. KT pts without PTLD transplanted in the same period served as control. All the relevant clinical data before and after PTLD diagnosis were collected. End of follow-up was the last outpatient visit, death, or dialysis. After ISR, chemotherapy was coordinated with hematologists.

Results: Monomorphic PTLD was diagnosed in 26 pts (0.8%):18 B-cell non-Hodgkin Lymphoma (nHL) (68%), 3 T-cell nHL, and 4 multiple myelomas. No early/polymorphic PTLD were detected. PTLD was diagnosed with a median (m) of 121 months (mos) after Tx (IQR 88-165). M-observation time was 187 mos (IQR 93-326). PTLD was EBV-related in 52% of cases. At diagnosis m-plasma creatinine was1.6 mg/dl (IQR 1.2-1.9) and m-proteinuria 0.3 g/24 hours (IQR 0.1-0.5). ISR was done in all but the 3 pts with a smoldering myeloma. In 24% of cases calcineurin inhibitor (CNI) was withdrawn, halved in 16%, discontinued in 8%. mTOR replaced CNI in 24% of pts. Steroid therapy was given at doses prescribed for CT. Pts survival was 44%. Twenty pts (75%) died for PTLD or its complications. Pts m-survival time was 12 mos (IQR 3-145), 77% of pts died with a m-creatinine of 1.9 mg/dl.

Conclusions: In our series PTLD frequency of 0.8% and a mortality of 50% at one year are lower than literature rates. One and 5-year survival rate are 52% and 32% for monomorphic PTLD. Molecular-targeted drugs and immunomodulators may enable international multicenter studies to improve PTLD unfavorable prognosis.

SA-PO1024

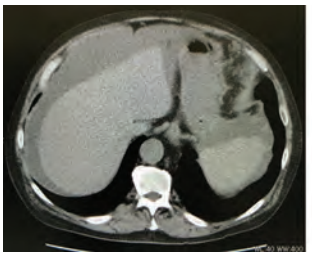
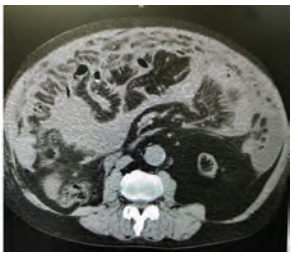
Late-Onset Post-transplant Lymphoproliferative Disorders Presenting with Sudden Massive Abdominal Ascites Effusion: A Case Report

Kana Shirai, Marie Murata, Masatomo Ogata, Takamasa Miyauchi, Kazunobu Shinoda, Yugo Shibagaki, Masahiko Yazawa. *St. Marianna University School of Medicine, Kawasaki, Japan.*

Introduction: Late-onset post-transplant lymphoproliferative disorders (PTLD) are increasingly recognized in recent literature. Late-onset PTLD exhibits distinct characteristics regarding the primary lymphoma lesion, Epstein-Barr virus (EBV) association, and risk factors. Here, we present a case of non-EBV-associated late-onset PTLD marked by sudden massive abdominal ascites, later diagnosed as peritoneal lymphomatosis.

Case Description: A 65-year-old man underwent ABO-compatible living-donor kidney transplantation (KT) 8 years ago for end-stage kidney disease due to nephrosclerosis. Both donor and recipient were EBV-seropositive pre-KT. Post-transplantation, the patient maintained a stable course under a standard immunosuppression with steroids, tacrolimus, and mycophenolate mofetil. Eight years post-KT, however, he presented with anorexia and sudden massive abdominal ascites (Figure). Ascitic fluid cytology revealed diffuse large B-cell lymphoma (DLBCL). Because of negative serum EBV-DNA, non-EBV-associated PTLD was diagnosed. Imaging studies showed diffuse omental and peritoneal thickening without solid organ tumors or lymphadenopathy (Figure), indicating that the primary lesion of PTLD was peritoneal lymphomatosis. Reduced immunosuppression and R-CHOP chemotherapy induced DLBCL remission, resolving ascites without graft function deterioration.

Discussion: Late-onset PTLD often presents with extranodal lesions and involves extra-transplanted organs. Peritoneal lymphomatosis is rare not only as a primary lesion of PTLD but also as a primary lesion of lymphoma in non-transplant patients. Notably, literature of peritoneal lymphomatosis lacks KT case reports, with focus mainly on liver transplantations. Although PTLD with peritoneal lymphomatosis is a rare condition, clinicians should consider it as a differential diagnosis when encountering sudden massive abdominal ascites following kidney transplantation.

SA-PO1025

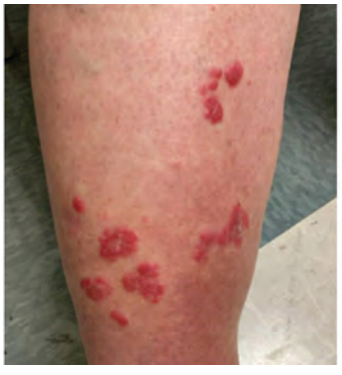
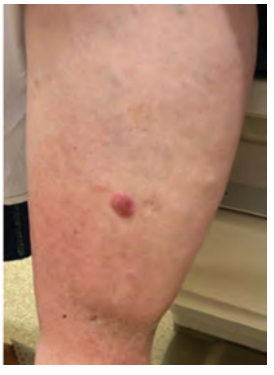
Recurrent Cutaneous Plasmacytoma: Atypical Presentation of Post-transplant Lymphoproliferative Disorder

Kavindya Wickramasinghe, Sarthak Virmani. *University of Virginia School of Medicine, Charlottesville, VA.*

Introduction: Post Transplant Lymphoproliferative Disorder (PTLD) usually affects the allograft, GI tract or CNS. Plasmacytic PTLD is an unusual variant notable for lack of CD20 expression with limited reports in the literature. We present a complex case of cutaneous plasmacytic PTLD.

Case Description: A 70-year-old lady s/p DDKT for IgAN in 2008 and a 2nd transplant for failing allograft in 2018 presented with multiple skin lesions on her right lower extremity (RLE). There was clinical concern for SCC but a biopsy surprisingly showed plasmacytic PTLD instead. Immunosuppression(IS) reduction & radiotherapy (RT) led to successful treatment. She unfortunately developed new lesions within 3 months of completing RT. An 8-week course of s/c daratumumab infusion was given after which her lesions appeared stable on PET-CT with low-level FDG uptake. Within 6 months, she developed multiple new skin lesions that remained consistent with plasmacytic PTLD. She was then treated with bortezomib but did not tolerate it due to significant GI side effects & weight loss. PET-CT showed more new nodular densities with increased uptake suspicious for recurrent PTLD. She was then transitioned to dara-CyBorD with resolution of all lesions except one small nodule on the RLE after 4 cycles that was surgically excised. A second new lesion appeared approximately one year after discontinuing dara-CyBorD but began to recede on its own. The patient completed 4 doses of rituximab and has had no new lesions as of her last follow-up.

Discussion: Isolated cutaneous PTLD is very rare. Prior cases of plasmacytic PTLD describe responses with a combination of IS reduction & RT. Those with more advanced or relapsed disease have received myeloma-based therapies with varying levels of success. Given the absence of a standard of care for plasmacytic PTLD and our patient's localized disease, we opted to gradually escalate treatment intensity over 4 years as the lesions recurred. To our knowledge, this is the first case report demonstrating successful use of dara-CyBorD in a KTR with cutaneous-limited PTLD.

SA-PO1026

Chylous Ascites in a Patient on Peritoneal Dialysis with Recurrent T Cell Post-transplant Lymphoproliferative Disorder after Transplantation from a Living Unrelated Kidney Donor

Christopher R. Showers, Vishnu S. Potluri, Rebecca K. Seshasai. *Penn Medicine, Philadelphia, PA.*

Introduction: Chylous ascites is a rare manifestation of abdominal lymphatic system disruption; ascites fluid appears cloudy and is characterized by elevated triglyceride levels. Few reports exist of chylous ascites in patients on peritoneal dialysis (PD) or in patients following solid organ transplantation. We report a case of chylous ascites in a patient on peritoneal dialysis with recurrent post-transplant lymphoproliferative disorder (PTLD) following a living unrelated kidney transplant (LUKT).

Case Description: A 54 year old man with ESKD due to IgA nephropathy who received a LUKT in 2018 that was complicated by T-cell mediated rejection in 2022 leading to allograft failure and initiation of peritoneal dialysis (PD) in 2023 presented with cloudy PD fluid and mild abdominal discomfort. Additional history included T-Cell lymphoma characterized as PTLD in 2021 treated to complete metabolic response. Both donor and recipient were EBV seropositive at the time of LUKT. Gross examination revealed cloudy PD fluid; initial PD fluid studies demonstrated 84 total nucleated cells per microliter with 1% neutrophils. PD fluid cultures and smears for acid-fast bacilli were both negative. Ascites fluid triglyceride level was 412 mg/dL (serum 133 mg/dL). A CT abdomen and pelvis demonstrated bulky lymphadenopathy and a PET-CT scan confirmed severe progression of lymphoma. A PD catheter was appropriately positioned. PD was limited by inability to tolerate therapeutic fill volumes and persistent chylous ascites. Hemodialysis was initiated. Following initiation of chemotherapy, the patient developed tumor lysis syndrome and eventually expired.

Discussion: We report chylous ascites as the initial presentation of severe recurrent PTLD following LUKT. Cloudy PD fluid warrants immediate and thorough evaluation and may raise suspicion for PTLD in post-transplant patients. Large volumes of chylous ascites may impair continuation of PD.

SA-PO1027

A Case of Post-transplant Lymphoproliferative Disorder Developed 45 Years after Kidney Transplantation

Nobuaki Nishima, Yoshifumi Hamasaki, Yosuke Hirakawa, Masaomi Nangaku. *The University of Tokyo, Tokyo, Japan.*

Introduction: Post-transplant lymphoproliferative disorder (PTLD) affects 1-3% of renal transplant recipients, with the majority of cases occurring within the first year or around 5 years post-transplant. PTLD presents with a variety of symptoms depending on the affected organs and requires treatment including reduction or discontinuation of immunosuppressive agents. Very late-onset PTLD (VL-PTLD), developing more than 10 years after transplantation, is rare and requires different management strategies from early or late-onset PTLD due to its characteristics.

Case Description: A 61-year-old male pharmacist, who had undergone kidney transplant 45 years ago due to purpura nephritis and was maintained on AZA+PSL, developed fever and shortness of breath. Blood test showed inflammation and worsening kidney function but EBV was negative. Computed tomography showed multiple nodules and masses in lung and liver, and bronchoscopy revealed a tumor exposed in the left bronchus. A lung biopsy confirmed monomorphic PTLD (diffuse large B-cell lymphoma type, stage IVB). Treatment was initiated with change in immunosuppressive agents from AZA to everolimus and chemotherapy (R-CHOP). His symptoms improved and he was discharged on day 45. However, sudden bleeding from his airway led to cardiopulmonary arrest and death on day 66.

Discussion: Three percent of post-kidney transplant patients at our hospital have presented with PTLD, of which this case was the only case of VL-PTLD with the oldest age. It has been reported that VL-PTLD cases are often older and on classical immunosuppressive agents such as AZA, and present monomorphic type pathologically. Previous reports have indicated that the 1- and 5-year survival rates for VL-PTLD are 56% and 29%, respectively, and poor prognostic factors include age 65 or older, male gender, and CyA+AZA maintenance therapy. Continued attention to PTLD should be paid even long after kidney transplantation. Further case collection and research is needed to establish the optimal treatment strategy for VL-PTLD.

SA-PO1028

Long-Term Outcome of a Deceased Donor Kidney Transplant in a Patient with Active Chronic Lymphocytic Leukemia at Time of Transplantation

Nathaniel Leonardi, Brian J. Benes, Clifford D. Miles, Ryan Mullane, Scott G. Westphal. *University of Nebraska Medical Center, Omaha, NE.*

Introduction: While active malignancy is often considered a contraindication to kidney transplantation, certain malignancies have an increased survival with medication advancements. Chronic lymphocytic leukemia (CLL) is such a disease with an 88% 5-year survival and median survival of nearly 10 years. Concerns for organ transplantation in patients with CLL include risk of immunosuppression on disease progression, potential leukemic infiltration of allograft, and increased risk of infection. Transplant experience in patients with CLL is limited. Published experiences report high rates of graft failure and mortality and no long-term follow-up data. We present a patient with CLL treated with a Bruton Tyrosine Kinase inhibitor, ibrutinib, who underwent successful kidney transplant with excellent long-term outcome.

Case Description: A 50-year-old male was diagnosed with CLL/small lymphocytic lymphoma Rai stage 0 with favorable genetics and was initially treated with monitoring approach. Due to CLL progression and kidney function decline, cyclophosphamide and rituximab were initiated. Kidney biopsy revealed IgA Nephropathy with CLL involvement characterized by lymphocytic interstitial infiltrate. He progressed to end-stage kidney disease and completed two years of rituximab followed by maintenance ibrutinib. Prior to transplant, ibrutinib was stopped with concern of increased bleeding

risk. He underwent successful deceased donor kidney transplantation with basiliximab induction and maintenance immunosuppression with tacrolimus, mycophenolate sodium (MPS), and prednisone. Three years post-transplant, progression of CLL developed with worsening lymphadenopathy and lymphocytosis. MPS and tacrolimus doses were reduced. Ibrutinib was resumed and his CLL responded to treatment with improvement in lymphocytosis. Eight years from transplant, serum creatinine is 1.16, without infectious complication or adverse allograft injury related to CLL.

Discussion: While patients with CLL have frequently been excluded from kidney transplant consideration, newer therapies and improved understanding of favorable prognostic markers may allow for safe kidney transplantation in lower risk patients. This case demonstrates potential longevity following transplant with appropriate treatment and immunosuppression adjustments.

SA-PO1029

Renal Whodunit: The Paraprotein Connection

Jessica Boldridge,[1] George P. Bayliss,[1] Anthony Chang.[2] *[1]Brown University, Providence, RI; [2]University of Chicago Division of the Biological Sciences, Chicago, IL.*

Introduction: A monoclonal gammopathy is an abnormal increase in the synthesis of one of the five immunoglobulin (Ig) isotypes. These monoclonal Igs are also referred to as paraproteins which can be nephrotoxic. Manifestations can range from tubulopathies to glomerular disease. Known paraprotein diseases include multiple myeloma, Waldenstrom macroglobulinemia, CLL and malignant lymphoma. All other B cell lymphoproliferative and plasma cell proliferative disorders that result in kidney disease are referred to as monoclonal gammopathy of renal significance.

Case Description: A 68 yo male with a PMH of ESRD secondary to FSGS status post (s/p) living donor kidney transplant in 2020 who was admitted to the hospital for acute kidney injury (AKI). Six weeks prior to presentation, he was diagnosed with IgM paraprotein associated with a low-grade lymphoproliferative disorder most consistent with CD5 positive marginal zone lymphoma. Per hematology/oncology, the initial plan was to not treat unless the patient had systemic involvement. There was no known systemic involvement at that time. Fast forward six weeks and labs are now significant for a creatinine (Cr) of 3.2 mg/dL. Urinalysis positive for 1+ for blood, 30 protein. Tacrolimus level was 6.7. He tested covid positive. Biopsy was pursued which showed no signs of rejection but acute tubular necrosis and ongoing ischemic changes possibly related to tacrolimus. Four of 24 glomeruli were globally sclerosed. There was also severe hyalinosis and moderate IFTA 30%. The plan at that time was to start belatacept and to titrate down tacrolimus. Routinely, immunofluorescence (IF) is not obtained on transplant biopsies. Given new onset AKI and recently diagnosed malignancy, pathology was asked to review the allograft biopsy samples. IF showed evidence of light chain cast nephropathy, kappa light chain restricted.

Discussion: We present a rare case of a light chain cast nephropathy in a renal allograft. As described in this case, the preliminary plan was to hold treatment as he had no known systemic manifestations. The plan changed once AKI developed. Initial result of the biopsy was suggestive of tacrolimus toxicity with plans to alter immunosuppression accordingly. Maintaining monoclonal gammopathy of the allograft as a differential diagnosis is essential in relevant patients as it can alter treatment and important to remain as a differential for all learners.

SA-PO1030

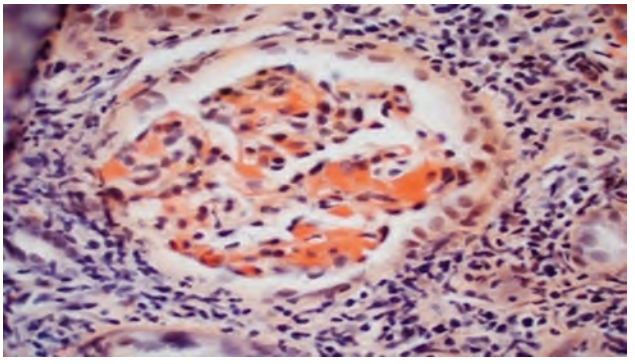
Donor-Derived AA Amyloidosis in a Kidney Allograft

Vamsee K. Chirumamilla, Kiran M. Goli, Sharon E. Maynard, Ravindra Bollu. *Lehigh Valley Health Network, Allentown, PA.*

Introduction: AA amyloidosis in renal allograft is an exceptionally rare occurrence. It typically arises in the context of chronic inflammatory or infectious diseases. We present a distinctive case of AA amyloidosis in a renal allograft.

Case Description: A 62-year-old man with end-stage kidney disease secondary to diabetes mellitus underwent a preemptive deceased donor kidney transplant. Immunosuppresion consisted of thymoglobulin and methylprednisolone, followed by belatacept, mycophenolate mofetil and prednisone. Post-transplant serum creatinine (Cr) improved to 2.5 mg/dl. Urine-protein creatinine ratio (UPCR) improved to 3.97 g/g compared to 6.08 g/g pre-transplant. Five months post-transplant, the Cr increased to 3.95 mg/dl and UPCR increased to 9.36 g/g. Allograft biopsy showed Banff 1A acute cellular rejection (ACR), moderate expansion of mesangium and glomerular capillary walls by an amorphous pink material with apple-green birefringence on Congo red stain, signifying amyloid deposition. Liquid chromatography-tandem mass spectrometry analysis revealed AA type amyloid. The patient had no known chronic inflammation, infection, or autoimmune disorder. The donor had a history of intravenous drug use and died of necrotizing pneumonitis. The mate kidney thrombosed within a week of being implanted and required explantation. Donor kidney biopsy at the time of donation revealed eosinophilic material in the glomeruli, which in hindsight may have represented amyloidosis. The clinical impression was donor-derived AA amyloidosis. His ACR was treated with corticosteroids. Repeat biopsy confirmed resolution of acute rejection but kidney function worsened, and hemodialysis was initiated 7 months after transplantation.

Discussion: Donor-derived AA amyloidosis in a kidney allograft has not been reported. Despite successful treatment of acute rejection, the patient developed graft failure. This complication may be avoidable by thorough pathologic evaluation of donor biopsy prior to transplantation.



Note the deposition of amorphous pink material in the glomerulus

SA-PO1031

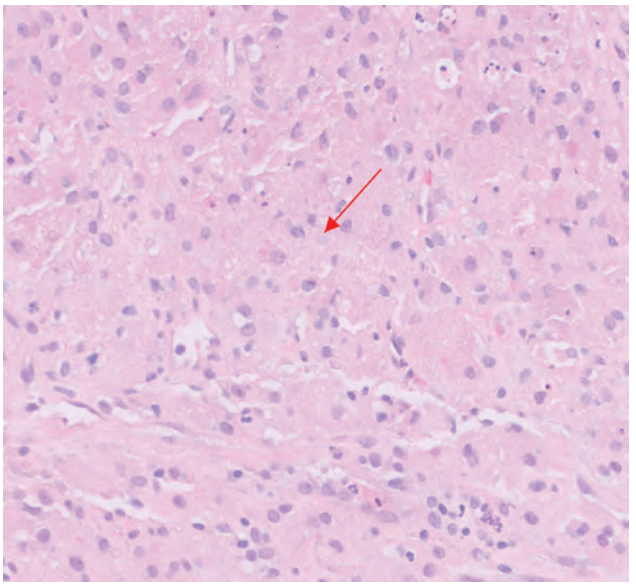
Malakoplakia in a Kidney Transplant Recipient

Samira M. Samant, Camilo Cortesi. *Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA.*

Introduction: Malakoplakia (MK) is a rare inflammatory condition of impaired phagocytosis, often linked to gram-negative infections. It can be devastating in kidney transplant recipients. Presentations vary, from renal dysfunction to extra-renal involvement.

Case Description: A 57-year-old female with end-stage renal disease due to hypertensive nephrosclerosis underwent a kidney transplant five months prior, with recurrent urinary infections post-transplant. She presented with a 50-pound weight loss, three weeks of dysuria, weakness, and hematuria. Labs showed severe acute kidney injury, metabolic acidosis, and elevated lactate. Blood and urine cultures detected E. coli. Ultrasound revealed a hypoechoic focus in the graft, on CT an ill-defined mass suggestive of pyelonephritis or abscess. MRI showed fingerlike masses extending into the cortex, suspicious for post-transplant lymphoproliferative disorder or malignancy. Biopsy showed no malignancy, but identified Michaelis-Gutmann bodies (MGBs). Her immunosuppression was reduced, and long-term antibiotics started. She succumbed to septic shock complications three months later.

Discussion: Malakoplakia is poorly understood due to its rarity. In renal transplant patients, urinary infections, graft dysfunction, or new masses should prompt consideration of MK. Its pathophysiology involves impaired phagocytosis, likely due to inadequate cyclic GMP release, hampering macrophage bactericidal activity and increasing infection risk. Pathognomonic biopsy findings include intracytoplasmic Periodic acid-Schiff positive inclusions (MGBs) and histiocytes with granular cytoplasm (von Hansemann cells). Management includes prolonged antibiotics, reduction of immunosuppression, and occasionally surgical excision. Despite this regimen improving mortality, morbidity remains high due to graft failure. Early recognition and timely biopsy are crucial to optimizing outcomes.



MGBs on biopsy

SA-PO1032

Unmasking Malakoplakia: A Rare Complication in Kidney Transplantation

Alexandra Rosario Aulet,[1] Akash Hazari,[1] Wael A. Hanna,[1,2] Muhammad R. Qureshi.[1,2] *[1]Methodist Dallas Medical Center, Dallas, TX; [2]Dallas Nephrology Associates, Dallas, TX.*

Introduction: Malakoplakia is a rare granulomatous inflammatory disease associated with poor graft and patient survival. Although it frequently involves the bladder, it can also affect transplanted kidneys. Presentation varies from asymptomatic kidney dysfunction to lower urinary tract symptoms or palpable mass.

Case Description: A 38 y/o Puerto Rican male with a history of ESRD secondary to obstructive uropathy from posterior urethral valve, s/p deceased donor kidney transplant. One week post-transplant, his course was complicated with COVID-19 infection and UTI cause by multi-sensitive E. coli. Slow graft function with negative donor-specific antibodies was reported. Serum creatinine did not improve as expected when compared to mate kidney, for which decision was made to proceed with a biopsy of the transplanted kidney. Biopsy reported nuclear inclusion highlighted with Von Kossa stain, known as Michaelis Gutman bodies, supportive of a diagnosis for malakoplakia. As recommended immunosuppression regimen was adjusted, MPA dose was decreased, tacrolimus target level was lowered and started on four weeks of oral antibiotics. A follow up Scr stabilized around 2.4mg/dL, and biopsy was schedule after completion of medical therapy.

Discussion: The risk of malakoplakia increases in immunocompromised states. Treatment includes reduction of immunosuppression and targeted antimicrobial therapy. This pathology must be considered transplanted patient that presents with AKI associated with UTI. If missed can lead to significant morbidity. Kidney biopsy remains the gold standard for diagnosis.

SA-PO1033

Delayed Presentation of Donor-Derived Allograft Squamous-Cell Carcinoma in a Kidney Transplant Recipient

Ricardo A. Pagan, Madhu C. Bhaskaran. *Northwell Health, New Hyde Park, NY.*

Introduction: We present an unusual case of allograft squamous cell carcinoma (SCC) in a kidney transplant recipient, presenting as a mass in the allograft. While kidney transplants notably enhance life expectancy and quality of life, there is a risk of malignancies. Despite SCC of the skin being one of the most common malignancies in transplant recipients it is an rare neoplasm in the allograft.

Case Description: 58 years old male, with history of end stage renal disease related to diabetes, received deceased donor renal transplant. Other comorbidities included hypertension and nephrolithiasis. Post-transplant course included CMV viremia, managed with Valganciclovir. He had a kidney biopsy when due to presentation of persistent generalized weakness, oliguria, elevated creatinine and dark urine. An ultrasound revealed a focal mass lesion of allograft kidney which was followed by a MRI showing a 4.9 cm mass in the transplanted kidney. Biopsy revealed SCC and due to declining GFR and oliguria, patient required hemodialysis. Nephrectomy was performed, immunosuppression discontinued and the patient remains on hemodialysis with oncology follow-up. Interestingly the recipient of the other kidney from the same donor was tracked and was found to be undergoing treatment for metastatic squamous cell carcinoma.

Discussion: Among post-transplant malignancies, SCC of the renal allograft stands out as a rare case. Chronic inflammation and irritation play a crucial role in the development of primary SCC, with the urothelium potentially converting to squamous cells due to irritants like kidney stones and recurrent infections. Additionally, oncogenic viruses like Epstein Barr Virus (EBV) and CMV may contribute to oncogenesis. Immunosuppression is well known to predispose to malignancies. Renal cell carcinoma and papillomas are reported in transplanted kidneys, with donor age, especially over 45, being a significant risk factor for cancer transmission. Even though donor derived malignancies are a known risk in solid organ transplant there are reports of successful outcomes of kidney transplantation with well circumscribed small tumor after they are resected. The atypical presentation of SCC in renal allograft raises questions about donor screening methods prior to organ allocation and reminds the need to keep donor derived malignancies in mind on delayed post-transplant period.

SA-PO1034

An Unusual Case of Late-Onset Profound Granulomatous Interstitial Nephritis Due to Adenovirus in a Kidney Allograft

Syed S. Hasni, Carla L. Ellis, Sujay D. Paudel, Mohammed Javeed Ansari, John J. Friedewald. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Introduction: Adenovirus (AV) is a common infection in transplant recipients with wide clinical presentations, ranging from subclinical and self-limiting to lethal disease. Most often, AV infection occurs within weeks to months after transplantation, suggesting reactivation of a latent AV in the immunosuppressed recipient as the source of infection. This report describes a case of AV infection in the renal allograft 19 years after transplantation.

Case Description: A 71 year old male with analgesic nephropathy, status post DDKT was seen for annual f/u 19 yrs later. Immunosuppression included MMF and Sirolimus. Recently had AKI of unclear etiology and 1g proteinuria which was stable. UA showed hematuria, BK blood/uine and Adenovirus PCR in blood were negative. Urine Adenovirus DNA was barely detected. DSA, non-invasive gene expression profile, and donor-derived cell-free DNA were negative. Kidney biopsy showed granulomatous interstitial nephritis. Adenovirus immunohistochemistry was equivocal. PCR testing for Adenovirus on the paraffin embedded block was positive. Patient's wife was treated for large B cell lymphoma with chemotherapy and had hemorrhagic cystitis 2/2 Adenovirus and was receiving Cidofovir. Given the negative PCR test in the blood and low level of Adenovirus in the urine, no intervention was done. Cr is stable and back to baseline, UA is bland and proteinuria is stable at 6 month follow up.

Discussion: Asymptomatic AV viremia is common in solid organ transplant recipients, estimated at 7.2% of patients and it was estimated that AV is excreted by 11% of patients with renal transplant. Since most AV infections occur during childhood, it is believed to be reactivation of an endogenous latent infection. This late onset of AV infection suggests that this is a de novo infection. In addition, this case highlights the perseverance that may be required to make a definitive diagnosis. Identification of AV contact tracing, prompted us for PCR testing for AV on the paraffin embedded block after immunohistochemical staining for the AV antigen on the biopsy was equivocal. A negative serological test and the absence of diagnostic viral cytopathic changes in a renal biopsy do not rule out AV infection and hence both the clinician and the pathologist need to remain alert to the possibility of this diagnosis.

SA-PO1035

Kaposi Sarcoma Inflammatory Cytokine Syndrome in an HIV-Positive Kidney Transplant Patient

Karishma Iyer, Kaitlin Markoja, Metin Ozdemirli, Nadiesda Costa, Parichi V. Buch. *MedStar Georgetown University Hospital, Washington, DC.*

Introduction: Kaposi sarcoma (KS) is a malignancy that typically appears as skin or mucosal lesions but can develop in other organs. HHV-8 is an oncogenic herpes virus that causes KS. KS is rare but can develop in HIV+ and kidney transplant (KT) patients. A highly fatal presentation is Kaposi Sarcoma Inflammatory Cytokine Syndrome (KICS), which causes multisystem organ failure.

Case Description: A 39 year old male with HIV on ART (CD4 <50 cells/mm3, viral load undetectable) and ESKD status post living donor kidney transplant one year prior (CMV +/+, EBV +/+) presented with febrile illness, acute kidney injury (AKI) and pancytopenia. Prior induction was thymoglobulin and maintenance immunosuppression (IS) was belatacept (due to CNI toxicity), mycophenolate and prednisone; tacrolimus was recently discontinued. Extensive infectious evaluation revealed CMV and EBV viremia, treated with valganciclovir. His condition deteriorated and he developed shock and acute hypoxic respiratory failure requiring mechanical ventilation. Due to persistent cytopenias, bone marrow biopsy was done which showed metastatic KS. HHV-8 returned at 505,000 copies/mL and IL-6 at 183 pg/mL. He was treated with rituximab and liposomal doxorubicin; HHV-8 and IL-6 levels rose, so Tocilizumab was added. IS was changed to sirolimus. AKI required continuous renal replacement therapy. He developed ARDS and died after two months.

Discussion: There is an increased incidence of KS in HIV+ patients as well as KT recipients. There is no consensus guidance regarding HHV-8 screening in the pre or post transplant period in HIV+ KT recipients. Reduction in IS and transition to sirolimus have been associated with KS regression, while the role for antiviral therapy is uncertain. KICS should be considered in at-risk patients with shock, respiratory failure, cytopenias and elevated inflammatory markers. In our patient, this catastrophic syndrome manifested prior to diagnosis of KS becoming evident, as he had no cutaneous lesions and KS was only identified on bone marrow biopsy. Optimal treatment for KICS is uncertain and may include chemotherapeutic and immunomodulatory drugs. It is associated with a high mortality rate, underscoring the importance of consideration of an HHV-8 screening strategy, as well as awareness of this condition among transplant nephrologists.

SA-PO1036

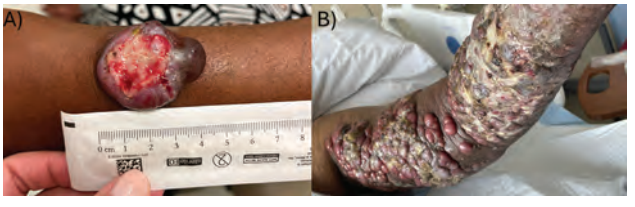
An Unusual Aggressive Skin Cancer in a Kidney Transplant Recipient

Joseph D. Nguyen, Swati Rao, Angie G. Nishio Lucar. *University of Virginia, Charlottesville, VA.*

Introduction: Merkel cell carcinoma (MCC), a rare and aggressive neuroendocrine skin cancer, has a poor prognosis in immunocompromised patients. In advanced stages, radiotherapy, chemotherapy, and immunotherapy have been used with variable success. Immunotherapy is relatively contraindicated in transplant recipients due to the risk of allograft rejection and loss. We report a complex case of aggressive metastatic MCC in a kidney transplant recipient (KTR).

Case Description: A 66-year-old female with ESKD due to hypertension receiving a kidney transplant 4 years prior was diagnosed with stage IIIB MCC of the left wrist (Figure 1A). Her disease progressed rapidly despite undergoing radical local resection and axillary dissection. Within a month post excision, she had developed numerous new MCC lesions on her left arm and axilla which were deemed unresectable and had a suboptimal response to radiotherapy. After deliberation, immunotherapy with pembrolizumab was initiated, but stopped after 4 cycles (of 35 planned) due to extensive disease progression (Figure 1B) and patient progressed to hospice care. Throughout her pembrolizumab course, she remained on prednisone, low dose tacrolimus, and mycophenolate. She had no episodes of rejection and maintained good allograft function.

Discussion: Indications for checkpoint inhibitors in the treatment of malignancies are growing. Pembrolizumab, a PD-1 ligand blocker, enables lymphocytes to target and destroy cancer cells. KTRs are often excluded from checkpoint inhibitor trials due to the risk of allograft loss (40-70% incidence). Despite this risk, KTRs can benefit from immunotherapy to treat aggressive malignancies such as MCC. In our patient, we elected to continue immunosuppression along with pembrolizumab to balance the risk of rejection and anti-cancer effect. Although immunosuppression protected the graft, it may have compromised immune-mediated tumor regression. Our case supports the literature that pembrolizumab can be utilized in certain settings in KTRs without graft loss and highlights the need for additional research for the optimal management of aggressive cancers in KTRs.



SA-PO1037

Immune Checkpoint Inhibitor Therapy Use in Kidney Transplant Recipients: A Single-Center Study

Elena-Bianca Barbir, Ali Ghaffar, Clark Otley, Arkadiusz Z. Dudek, Aleksandra Kukla. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Immune checkpoint inhibitors (ICI) have radically improved cancer outcomes. Due to concerns regarding graft rejection, ICI's were infrequently offered to KTR's despite significant cancer related mortality. We report the cancer and allograft outcomes of patients receiving ICI therapy at our center.

Methods: We retrospectively reviewed all KTR's undergoing ICI therapy at our center that were referred to our transplant clinic for immunosuppression (IS) management from December 1, 2018 to May 1, 2024. All patients continue to be followed, unless deceased. Indication biopsies were performed for acute kidney injuries.

Results: 21 patients met inclusion criteria. Patient characteristics and outcomes are described in Table 1. No acute rejection was noted. 1 patient had biopsy evidence of chronic antibody mediated rejection and recurrent PLA2R positive membranous nephropathy after 11 months of Pembrolizumab. This patient had a complete response with a stable creatinine of 1.5-1.8 mg/dL 2 years post therapy completion. Of 16 evaluable patients, 1 had complete response, 3 had partial response, and 2 had stable disease. Therapy limiting extra-renal immune related adverse events were noted in 1 patient with colitis.

Conclusions: The absence of acute rejection or frequently recurrent native disease in our cohort is encouraging, though objective response is low. Many patients were frail with advanced disease at the time of ICI initiation, likely contributing to the poor objective response, though degree and type of IS may also have influenced outcomes. Additional prospective studies comparing IS regimens while controlling for disease burden are needed.

Table 1

	Total Patients (n=21)
Median Age at ICI Therapy Initiation (years)	65 (range 52-78)
ESRD Secondary to Glomerulopathy (%)	43
Advanced Cutaneous Squamous Cell Carcinoma (%)	57
Metastatic Melanoma (%)	19
Patients on PD1 Inhibitor (%)	95
Maintenance Post ICI (Calcineurin Inhibitor/Pred) (%)	67
Maintenance Post ICI (Mammalian Target of Rapamycin Inhibitor/Pred) (%)	28
Rejection (%)	4.8
Median Follow Up (months)	3 (range 0.25 – 44)
Objective Response in 16 evaluable patients (%)	25
Stable Disease in 16 Evaluable Patients (%)	12.5
Median Overall Survival For Patients with Progressive Disease (months)	3 (range 0.25-8)
Median Time from Transplant to ICI Initiation (years)	8 (range 1-29)

SA-PO1038

Rapid Acute Rejection with Cortical Necrosis after First-Dose Cemiplimab in a Living Donor Kidney Transplant

Ahmed I. Abdelkader, Sakshi Vaishnav, Ahmed Daoud, Karim Soliman, Munsef Barakat, Vishwajeeth Pasham, Maria Aurora C. Posadas, Michael Casey. *Medical University of South Carolina, Charleston, SC.*

Introduction: Transplant recipients (TR) have an increased risk of squamous cell carcinoma (SCC) 65-250 times that of general population. There are few treatment options for advanced SCC in the setting of immunosuppression (IS) which has carcinogenic effect. Cemiplimab (CMP) is a checkpoint inhibitor (CPI) directed at PD-1 which has had promising responses in advanced SCC, but its use has also been associated with acute rejection. However, a recent prospective study using CPM showed safe use in TR with sirolimus (SRL).

Case Description: A 71-year-old male, CKD/V due to IgA nephropathy received a living donor TR. He has a history of BCC treated with Moh's surgery 5 months (Ms) pretransplant. He received basiliximab induction and maintained on a standard IS of tacrolimus (TAC), mycophenolate (MMF), and prednisone. Creatinine (Cr) settled at 1.4 mg/dL. 5 Ms post-transplant (PTx), 15 spots of actinic keratoses were treated with cryotherapy. *A month later*, he had neutropenia, so MMF was changed to everolimus. *By 8 Ms PTx*, he had CMV disease so everolimus was held kept him on prednisone and TAC. He had 2 biopsies at 2 and 9 Ms PTx which showed no rejection. A year PTx, he developed DSA treated with IVIG. Then, he was diagnosed with multiple BCC and SCC involving his face, ear, and hands. He had multiple facial surgeries to control his SCC but the lesions progressed. 19 Ms PTx, CMP was given as salvage therapy for advanced SCC. TAC was switched to SRL while Cr was 1.3 mg/dL. 1 week after the first dose of CMP, he experienced fever and malaise with rise in Cr to 3 mg/dl. He was admitted with oliguria and Cr of 4.7 mg/dL and treated with IV steroid then biopsy showed acute cortical necrosis and vascular inflammation. The patient started on dialysis.

Discussion: Until recently, TR were excluded from CPI's treatment for the risk of organ rejection. A recent prospective study reported favorable outcomes for 12 subjects who used CMP for the treatment for advanced SCC along with SRL with no rejection at 6 months. Our patient suffered from a rapid aggressive acute rejection at 1 week after first dose of CMP that resulted in cortical necrosis and graft loss. This is the first case of rapid renal allograft loss due to acute rejection and cortical necrosis after the CMP reported in literature.

SA-PO1039

Mesenteric Desmoid Tumor in a Transplant Patient

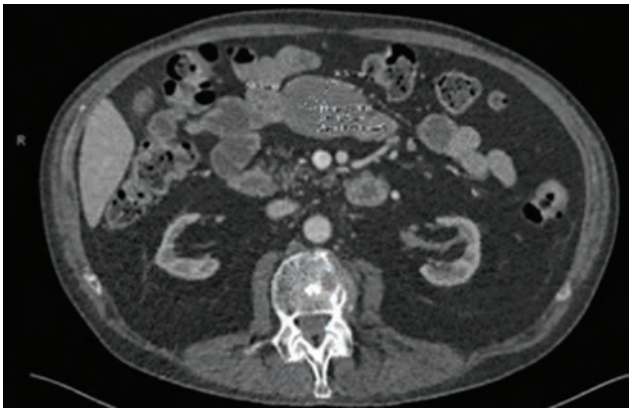
Dominik Thomas, Sarah Gilligan, Suayp Oygen, Duha A. Jweehan, Isaac E. Hall, Miklos Z. Molnar, Divya Raghavan. *University of Utah Health, Salt Lake City, UT.*

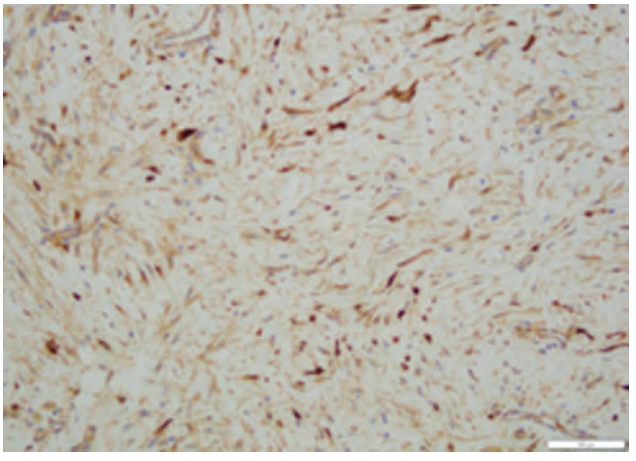
Introduction: Desmoid tumors (DTs) are deep, locally aggressive, benign connective tissue neoplasms that originate most commonly in the extremities, intraperitoneal cavity and abdominal and thoracic walls. They are rare with reported incidence of 2–4 per million population per year and account for 0.03% of all neoplasms. DTs have a high rate of local recurrence but do not metastasize. We present an unusual case of a DT found two years after kidney transplant.

Case Description: 61 year-old man with end-stage renal disease due to diabetic nephropathy who underwent a deceased donor kidney transplant presents with abdominal pain starting six months after transplant. He underwent robotic inguinal hernia repair without improvement in pain. He reports night sweats, fatigue, and unintentional weight loss of 15lbs over two months. CT abdomen/pelvis showed a mid-abdomen, mesenteric soft tissue mass measuring 5.4 x 3.5 cm which was mildly hypermetabolic on PET-CT.

Surgical biopsy of the mass revealed a DT. Resection of the mass was not pursued due to areas of fibrosis along the mesentery suggestive of a more diffuse process. Consequently, the oncology team started Pazopanib with good response.

Discussion: The differential diagnosis for an abdominal mass is broad with high concern for post-transplant lymphoproliferative disorder. When suspecting malignancy, tissue diagnosis is always important for diagnosis and guiding treatment. For DT, asymptomatic patients can be managed with active surveillance while symptomatic patients may require surgery, systemic therapy, and/or radiation therapy.





SA-PO1040

Postkidney Transplant Cancer: Incidence, Risk Factors, and Future Perspectives in a Real-World Analysis of a Single Italian Center

Carlo Alfieri,[1,2] Giulia V. Re Sartò,[2] Mariarosaria Campise,[1] Anna Regalia,[1] Simona Verdesca,[1] Paolo Molinari,[1] Margherita Di Naro,[1] Sara Moscardino,[1] Maurizio Gallieni,[2] Giuseppe Castellano.[1,2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Universita degli Studi di Milano, Milano, Italy*.

Background: Our study aims to outline cancer epidemiology post-KTx, examine risk factors, and assess the impact on treatment and survival in a large cohort of kidney transplant patients. We'll analyze the link between changes in immunosuppressive therapy post-cancer diagnosis and survival outcomes.

Methods: Retrospective collection of data in KTx-ps transplanted between January 2004 and December 2021, subjected to outpatient follow-up with a median follow-up of 7 [1-19] years.

Results: Our study included 930 KTx-ps, average age 49yrs. 91% had pre-KTx dialysis for about 52 months. Most received KTx from a deceased donor (84%). 74% had Basiliximab induction therapy, 26% ATG. Maintenance therapy mostly involved steroids (87%), tacrolimus (92%), ciclosporin (8%), and mycophenolate (94.6%). 177 patients (19%) had at least one cancer (CAN+). The mean time from KTx to oncological diagnosis was 83 months. Non-melanoma skin cancers (NMSC) were the most common tumors (55%), while solid tumors were observed in 38.6% of cases. Deceased donor was more represented in CAN+. CAN+ were older and with higher BMI. They had greater presence of vasculitis as basic nephropathy. In the period between 2016 and 2021, induction therapy with ATG was significantly associated with CAN+. In multivariable analysis, ATG emerged as an independent risk factor for CAN+ (p=0.014) and, in survival analyses, ATG was strongly and significantly related to the earlier development of CAN+ (p=0.010). During follow up, cancer-related causes were the second cause of mortality (23%); the average time from cancer diagnosis to death was 23 months. The median survival from Ktx was 148 (CAN+) and 82 months (CAN-). After oncological diagnosis, significant evidence on tumor survival was derived from the shift to mTOR inhibitors compared to the group with definitive drug suspension (p=0.004).

Conclusions: Our study confirms cancer's significance as a KTx complication. ATG is an independent cancer risk factor, emphasizing the need for personalized immunosuppressive therapy at KTx to mitigate neoplastic risk. In KTx-ps, future research should focus on therapeutic strategies with antineoplastic agents and post-malignancy immunosuppression management.

SA-PO1041

Feasibility Study of a Randomized Controlled Trial Investigating Renal Denervation as a Possible Treatment Option in Patients with Loin Pain Hematuria Syndrome

Bhanu Prasad,[1] Aarti Garg,[2] Aditi Sharma.[2] *[1]Regina General Hospital, Regina, SK, Canada; [2]University of Regina, Regina, SK, Canada*.

Background: Loin Pain Hematuria Syndrome (LPHS) is a poorly understood clinical condition characterized by severe pain localized to the kidney but in the absence of identifiable urinary tract disease. Several studies have shown promise in observational studies but have been unable to replicate the results when compared with a sham arm in a randomized controlled trial. To address this gap, we conducted a feasibility study that involved a randomized controlled trial comparing renal denervation (RDN) with a sham arm. The primary objectives were to ensure that 80% of the study patients underwent the procedure (roll-in, treatment or sham) within 6 months and that 80% of the randomized patients (treatment or sham) completed the follow-up measures at 6 weeks, 3 and 6 months.

Methods: We conducted a single-center double-blinded, parallel-group, partial crossover, sham-controlled, randomized feasibility trial. 13 LPHS patients who required >100 mg of morphine milligram equivalent were randomized (treatment or control or roll-in) and they completed the follow-up for 6 months. The participants who received the sham procedure were crossed over into the treatment group and were followed for 6 months. The pain was assessed using Brief Pain Inventory Score (BPI) and quality of life was measured by EuroQol-5D and SF-36.

Results: 100% of patients underwent the procedure within the initial 6-month period. 100% patients in the roll-in and 80% each in the treatment and sham group completed the follow-up assessments throughout the study duration. Improvements in pain severity and interference seem to have continued up to the 3-month follow-up in roll-in, RDN, and crossover. Percentage gain in VAS at 3 months was 100%, 60%, and 60% respectively (Table 1).

Conclusions: This is the first randomized controlled study that shows that RDN is associated with improvement in pain and quality of life. Our results suggest that percutaneous catheter-based radiofrequency energy delivery is a safe, rapid treatment option for all patients with LPHS.

Characteristics	Roll in (n=3)	RDN (n=5)	Sham (n=5)	Cross-over (n=3)
Mean age (years)	43.33±5.5	36±12.5	40±6	39±5.2
Sex (n, female)	3	4	5	3
BPI Percent reduction (baseline to 3 months)	78.8%	34.7%	-17.3%	57%
VAS % gain in scores (baseline to 3 months)	100.2%	60%	21.4%	60%

RDN: renal denervation; BPI: brief pain inventory

SA-PO1042

Quiescent Sex Differences in C57BL/6J Mice

Han Eckenrode, Rohan S. Balkawade, Lisa M. Curtis. *The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL*.

Background: Many studies focus on male animals, with fewer studies explicitly studying female animals. Studies have found sex differences in various kidney disease states, such as acute kidney injury and chronic kidney disease, although sex differences in unaltered animals remain underexplored.

Methods: Male and female C57Bl6/J mice were purchased from Jackson labs at 6 weeks of age. Mice had access to standard chow, ad libidum. During the study period, glomerular filtration rate (GFR), plasma creatinine (PCr), and whole blood parameters, including electrolytes, were measured. At 18 weeks of age, mice were euthanized, tissues collected, and complete blood count parameters were measured

Results: Neutrophil count and absolute percent were lower in female mice, although absolute percent of lymphocytes were higher. Male mice had higher red blood cell distribution width, and mean platelet volume, compared to female mice. Hemoglobin and hematocrit did not persistently differ between sexes. Slight differences in electrolyte balance were found, with higher sodium and lower potassium in female mice. Chloride levels did not differ. Although pH and PCO_2 was not different between sexes, HCO_3- levels were higher in male mice, and anion gap was higher in female mice. Direct and indirect measures of renal function, including PCr, GFR, and BUN, did not persistently differ between male and female mice.

Conclusions: Our study provides insight into sex differences at baseline in parameters that directly and indirectly affect kidney function. These quiescent differences may reflect in a sex differential in the capacity to respond to renal insults.

Funding: NIDDK Support

SA-PO1043

Sex Differences in the Impact of Heat Stress on Kidney Function in a Large Taiwanese Population Study

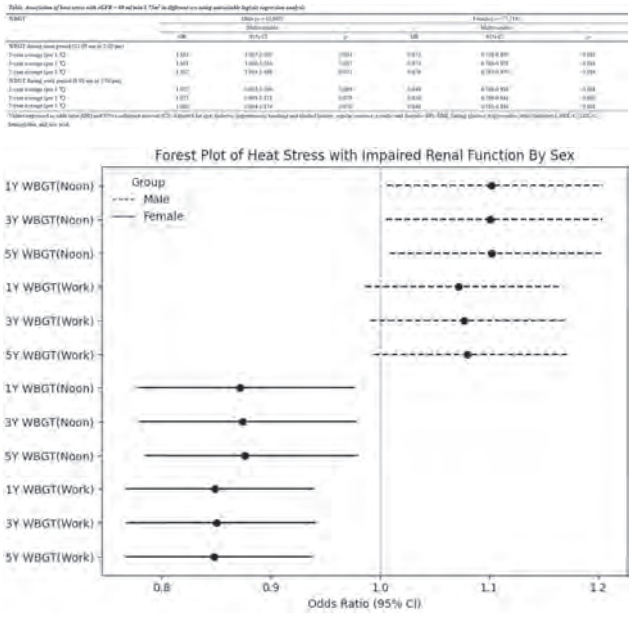
Yi-Kong Chen,[1,2] Yi-Ting Lin,[2,3] Ming-Yen Lin,[2,1] Ping-Hsun Wu,[2,1] Mei-Chuan Kuo,[2,1] Shang-Jyh Hwang,[2,1] Jer-Ming Chang,[2,1] Yi-Wen Chiu,[2,1] Szu-Chia Chen.[2,1] *[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Kaohsiung Medical University Chung Ho Memorial Hospital, Kaohsiung, Taiwan; [3]Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.*

Background: Taiwan, a region with high dialysis incidence and prevalence, prioritizes mitigating chronic kidney disease (CKD) and declining kidney function. Heat stress is a significant CKD risk factor and impairs kidney function. Yet, the impact of heat stress differs between males and females and remains unexplored.

Methods: We conducted this retrospective cross-sectional analysis using data from the Taiwan Biobank (TWB), incorporating records of the wet bulb globe temperature (WBGT) during midday (11 AM - 2 PM) and working hours (8 AM - 5 PM) periods based on the participants' residential address. Average 1-, 3-, and 5-year WBGT values prior to the survey year were calculated and analyzed using a geospatial artificial intelligence-based ensemble mixed spatial model, covering the period from 2010 to 2020.

Results: Our study included 114,483 TWB participants, of whom 35.9% were male and 1,053 showed impaired kidney function (eGFR < 60 ml/min/1.73 m²). Multivariable analysis revealed that for male participants during midday, increases in 1-, 3-, and 5-year average WBGT values were significantly positively linked to impaired kidney function. No significant associations were observed during working hours. For female participants, during both midday and working hours, increases in 1-, 3-, and 5-year average WBGT values were significantly negatively associated with impaired kidney function.

Conclusions: In conclusion, our results revealed that a high WBGT was associated with impaired kidney function in males, whereas a low WGBT was associated with impaired kidney function in females. Further studies are needed to elucidate the exact mechanisms underlying these findings.



SA-PO1044

Reproductive Health and CKD: A Cross-Sectional Survey of Patient Knowledge and Educational Needs

Andrea L. Oliverio,[1] Kelcie Brophy,[1] Corey C. Powell,[2] Michelle A. Hladunewich,[3] Sarah Hawley,[1] Julie A. Wright Nunes.[1] *[1]University of Michigan Medical School, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI; [3]Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Background: Female reproductive health is affected by kidney disease, but is often not addressed in nephrology care. Our objective was to better understand patient educational needs on this topic to better facilitate family planning care for people with CKD.

Methods: We conducted an online survey of people with CKD assigned female sex at birth, aged 18-45, in English. Survey topics included current knowledge satisfaction, self-ranked education needs, communication preferences, health history, and demographics. Univariate(UV) and multivariable(MV) logistic regression were used to determine associations between individual patient characteristics and overall knowledge satisfaction.

Results: 209 surveys were completed; 77% of participants self-identified as white, 11% Black, 4% Asian; 11% Hispanic. 23% had limited health literacy. Many were dissatisfied with their knowledge of contraception and pregnancy outcomes with CKD (49% and 36%, respectively). Pregnancy planning was associated with lower knowledge satisfaction and glomerular disease with higher knowledge satisfaction. However, after adjustment in MV analysis only health literacy was significantly associated with knowledge satisfaction (β -0.5, 95% CI -0.9 to -0.02) (Table 1). Understanding CKD impact on fetal development and menstruation, and kidney function changes after pregnancy were topics ranked as high priority by participants. The majority were open to receiving a recommendation about contraception (76%; n=159/209) or pregnancy timing (77%; n=161/209) from their nephrologist.

Conclusions: These findings suggest priority topics that should be included in family planning during CKD care. Patients are open to receiving this advice in nephrology clinics. Findings also reinforce the need for education tools to address family planning for all patients, including those with limited health literacy.

Funding: NIDDK Support

UV and MV associations of patient characteristics with knowledge satisfaction about reproductive health and CKD

Patient characteristics	Estimated univariate effect	95% CI	P	Estimated adjusted effect*	95% CI	Adjusted P
Multigravid vs nulligravid	0.2	-0.1 – 0.5	0.17	0.04	-0.4 – 0.4	0.86
Planning a pregnancy vs not or unsure	-0.4	-0.7 - -0.1	0.009	-0.3	-0.7 – 0.1	0.19
Stage 1-2 vs stage 3-5 CKD	0.2	-0.04 – 0.5	0.10	0.2	-0.2 – 0.5	0.37
Glomerular disease vs/not glomerular disease etiology	0.3	0.01 – 0.5	0.043	0.3	-0.1 – 0.6	0.12
Additional year of age	0.02	-0.002 – 0.03	0.087	0.002	-0.03 – 0.03	0.90
Assistance with reading hospital materials (ever vs never)	-0.2	-0.6 – 0.1	0.16	-0.5	-0.9 - -0.02	0.043

*Adjusted model included race, ethnicity, educational attainment, and income

SA-PO1045

Reproductive Planning in Kidney Disease (REPKID): A Survey of Female Patients with CKD

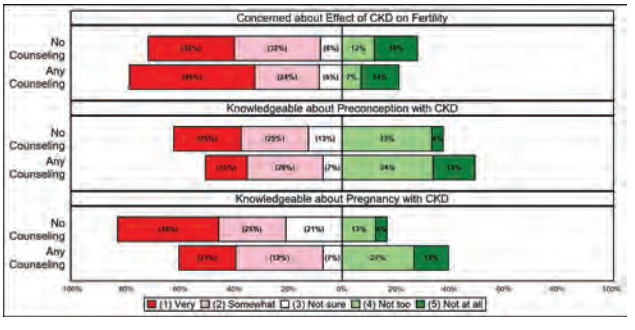
Niloofar Nobakht,[1] Gwendolyn Lee,[2] Maha Al Baghdadi,[1] Yaquelin Arevalo Iraheta,[1] Lorna Kwan,[1] Christina S. Han.[1] *[1]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [2]University of California San Francisco, San Francisco, CA.*

Background: CKD is associated with high rates of maternal, obstetrical & fetal complications in pregnancy. Although preconception counseling (PCC) is recommended by the CDC as primary prevention for pregnancy complications, the frequency of its utilization in CKD is unknown. We hypothesize that PCC in CKD remains suboptimal.

Methods: A cross-sectional survey was distributed to reproductive-aged females at nephrology clinics within a quaternary care health system between 01-05/2024. Data were analyzed using Chi-square (or Fisher's exact tests). Uni- & multi-variable logistic regressions were performed to explore characteristics associated with inadequate PCC.

Results: Of 119 surveys distributed, 98 (82%) were completed. Subjects included those with history of dialysis (54%), transplant (48%), and long duration of disease (32.7%). No PCC was reported in 26% of respondents. In a multivariable logistic regression (Table 1), lack of PCC was more common in individuals who had no college education or did not report loss of libido. Compared to counseling by non-nephrologists, counseling that included a nephrologist were more likely to include discussions on birth control, future childbearing, medication safety, and fetal and maternal complications. Receipt of PCC improved patient's self-reported knowledge about preconception and pregnancy with CKD. (Figure 1)

Conclusions: Preconception counseling for reproductive-aged female patients remains suboptimal in CKD. The underlying causes of this insufficiency and inequity warrants investigation and intervention.



Effect of preconception counseling on concern and self-reported knowledge

Table 1: Crude and adjusted odds ratios for no inclusion of preconception counseling in care

	Crude OR (95% CI)	Adjusted OR (95% CI)
Ethnicity (Not Hispanic as referent)	2.0 (0.8, 5.1)	1.9 (0.6, 5.5)
Education Level (Some College as referent)	**2.9 (1.0, 8.0)**	1.7 (0.5, 5.7)
Insurance (Private or Self-Pay as referent)	2.3 (0.9, 5.8)	1.9 (0.6, 5.6)
Duration of CKD (1-5 years as referent)		
< 12 months	2.2 (0.6, 8.8)	2.3 (0.5, 10.8)
6-10 years	0.4 (0.1, 1.7)	0.4 (0.1, 2.1)
>11 years/Don't recall	0.8 (0.2, 2.6)	0.9 (0.2, 4.4)
Loss of Libido (Yes as referent)	**3.4 (1.2, 9.6)**	**3.5 (1.1, 11.0)**
Management		
Current Use of Contraindicated Medication (No as referent)	1.2 (0.5, 3.0)	0.9 (0.3, 2.8)
History of Transplant (No as referent)	1.0 (0.4, 2.5)	0.8 (0.2, 2.7)

Crude and adjusted odds ratios for no inclusion of preconception counseling in care

SA-PO1046

Fertility, Sexual Function, and Endothelial Health in Premenopausal Women with Kidney Diseases

Angie S. Lobo,[1] Lisa E. Vaughan,[2] Vesna D. Garovic,[2] Andrea G. Kattah.[2]
[1]University of Minnesota Twin Cities, Minneapolis, MN; [2]Mayo Clinic Minnesota, Rochester, MN.

Background: Women with advanced chronic kidney disease (CKD) face reproductive health challenges, including reduced fertility, sexual dysfunction, and increased pregnancy risks. This study examined changes in sex hormones with CKD progression and their correlation with sexual function.

Methods: This study recruited women aged 18-51 with CKD stages 3b-5 from nephrology clinics and dialysis units. Exclusions included active pregnancy, menopause, prior hysterectomy/bilateral oophorectomy, or hormonal contraceptive/therapy use. Demographics, clinical characteristics, female sexual function index (FSFI) surveys, and hormone levels were collected at enrollment. Comparisons across CKD stages used Kruskal-Wallis or Chi-square tests, and associations between sex hormones and sexual function were evaluated using Spearman's correlation coefficients.

Results: Thirty-eight subjects were enrolled in the trial (8 in CKD stage 3b, 10 in CKD stage 4, and 20 in CKD stage 5/5D). Patient characteristics are detailed in Figure 1. Patients in more advanced CKD stages had significantly higher blood urea nitrogen (BUN) and prolactin levels, and lower hemoglobin levels, compared to those in CKD stage 3b ($p<0.05$ for all). Significant negative correlations existed between prolactin levels and desire, arousal, lubrication, orgasm and total FSFI score ($P<0.05$ for all, data not shown).

Conclusions: This study highlights major reproductive health challenges in women with advanced CKD, including progressive hormonal imbalances. Women in later stages of CKD had higher levels of BUN and prolactin, and lower hemoglobin levels, indicating more severe disease and its impact on reproductive health. Further research is needed to develop effective strategies to improve the quality of life for women with CKD.

Funding: Other NIH Support - Fulk Career Development Award (Mayo Clinic), National Institutes of Health on Aging, Office of Research on Women's Health grant 3K12AR084223-18S1 (University of Minnesota), Private Foundation Support

Baseline Characteristic	CKD Stage 3B (N=8)	CKD Stage 4 (N=10)	CKD Stage 5/5D (N=20)	Total (N=38)	P-value
Age (years), mean (SD)	37.8 (10.4)	40.0 (6.3)	32.7 (7.4)	35.6 (8.3)	0.05
Blood Urea Nitrogen (mg/dL), median (IQR)	24.5 (22.5, 29.0)	37.5 (34.0, 46.0)	49.0 (38.0, 63.0)	39.0 (32.0, 51.0)	<0.001
Hemoglobin (g/dL), median (IQR)	12.4 (11.0, 13.8)	11.5 (10.8, 13.4)	10.5 (9.2, 12.0)	11.0 (10.1, 12.7)	0.027
Follicle-Stim hormone (mIU/mL), median (IQR)	6.7 (4.6, 22.3)	7.4 (3.5, 10.5)	4.1 (3.2, 5.7)	5.0 (3.5, 8.2)	0.076
Prolactin (ng/mL), median (IQR)	16.1 (12.6, 23.6)	20.9 (16.7, 30.0)	38.5 (24.6, 48.0)	25.3 (16.7, 43.0)	0.007
FSFI total score, mean (SD)	22.0 (8.1)	22.0 (10.0)	16.6 (11.9)	20.0 (10.7)	0.48

SA-PO1047

The TIMING Study: Patients' and Clinicians' Perspectives on Reproductive Health Care and Autosomal Dominant Polycystic Kidney Disease

Margriet Gosselink,[1] Robin Mooren,[1] Rozemarijn Snoek,[1] Neeltje Crombag,[1] Paul Vos,[2] Mandy G. Keijzer-Veen,[1] Albertien M. van Eerde,[1] Titia Lely.[1]
[1]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [2]Haga Ziekenhuis, Den Haag, Netherlands.

Background: Family planning and reproductive care are essential yet complex aspects of lifecycle management for individuals with Autosomal Dominant Polycystic Kidney Disease (ADPKD), given the potential genetic transmission and pregnancy-related complications. This qualitative study studied the experiences and perspectives of ADPKD patients and clinicians to identify areas for potential improvement in reproductive lifecycle care.

Methods: Focus group discussions were conducted in the Netherlands with ADPKD patients, both men and women, who had children through varied reproductive choices, and clinicians, including (pediatric) nephrologists, obstetric gynecologists, geneticists. Thematic analysis, utilizing a grounded theory approach, was performed on verbatim transcriptions of recordings, followed by consensus discussions to finalize themes.

Results: Nine focus groups involving 31 participants (16 patients and 15 physicians) identified six key themes. These included the need for timely and comprehensive information dissemination, understanding patient-specific decision-making factors, improving tailored psychosocial guidance and communication, the need for systematic efforts to take care of missed (minor) at-risk patients, addressing inequities in access to care, and improving multidisciplinary collaboration.

Conclusions: This study represents the first qualitative study of patient and physician perspectives on reproductive lifecycle care for ADPKD. We present valuable insights into factors influencing patients' reproductive decision-making, a comprehensive comparison between the perspectives of patients and clinicians on family planning, and follow-up care of minors at risk for ADPKD, and recommendations for enhancing overall care quality. Incorporating these insights into clinical care could enhance patient-centered care and foster interdisciplinary collaborations to further improve the quality of reproductive healthcare services for individuals with ADPKD.

Funding: Private Foundation Support

SA-PO1048

Unplanned Pregnancy in Women with Lupus Nephritis Is Common and Is Associated with Poor Fetal Outcomes

Hannah K. Beckwith,[1,2] Hannah R. Wilson,[2] Tabitha Turner-Stokes,[2,1] Marlene Pluess,[1,2] Marie B. Condon,[1] Tom Cairns,[1] Philip Webster,[1] Liz Lightstone.[2,1]
[1]Imperial College Healthcare NHS Trust, London, United Kingdom; [2]Imperial College London, London, United Kingdom.

Background: Lupus Nephritis (LN) is a frequent organ manifestation of Systemic Lupus Erythematous among women of childbearing age. Whilst disease activity is known to correlate negatively with pregnancy outcomes(1), the frequency of unplanned pregnancies in people with LN and subsequent maternal-fetal outcomes have not yet been reported.

Methods: All women <35yrs at the time of diagnostic renal biopsy at our centre (01/01/1996-31/12/2016) were included in the study. Our standard practice is to offer pre-pregnancy counselling (PPC). Case notes were manually reviewed and clinical and biochemical data extracted. Pregnancies prior to LN diagnosis were excluded. Pregnancies were considered unplanned when: a. PPC had not occurred or b. teratogenic medication(s) were used peri-conception or c. when pregnancies were reported as unintended.

Results: There were 179 pregnancies in 87/201 women (43%). The median length of follow up was 14.2 years (range 9.4-19.5). 37/179 (21%) pregnancies were unplanned and 128/178 (72%) pregnancies* resulted in a live birth. Unplanned pregnancy resulted in significantly worse fetal outcomes (Table 1) and 50% of unplanned pregnancies did not progress >20 weeks gestation (P=0.0004). 25/201 women (12%) sought help for primary or secondary infertility following a diagnosis of LN and 3 were diagnosed with premature ovarian failure (1.5%).

Conclusions: This study is the largest single centre cohort of LN pregnancies reported to date. Planned pregnancies have excellent outcomes, however 1 in 5 pregnancies are unplanned: these are associated with poor fetal outcomes and high rates of pregnancy loss.

Reference 1. Bundhun et al (2017). Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016. J Autoimmun;79:17-27.

Table 1

Fetal outcome	Planned pregnancies (n=142)	Unplanned pregnancies (n=36*)	P Value
Spontaneous death before 20 weeks gestation n (%)	21 (15%)	10 (28%)	0.084[a]
Spontaneous death after 20 weeks gestation n (%)	4 (3%)	1 (3%)	1.000[a]
Therapeutic termination of pregnancy n (%)	6 (4%)	8 (22%)	**0.0016[a]
Live birth after 20 weeks gestation n (%)	111/115 (97%)	17/18 (94%)	0.523[a]
Birth weight (kg) (SD)	2.71 (0.51)	1.90 (1.03)	***0.0005[b]
Mean gestational age of live births, days (SD)	263 (15)	239 (35)	***0.0002[b]

a 2-tailed Fisher's exact t test
b Unpaired t test
*One person is currently pregnant

SA-PO1049

Kidney Disease in Pregnancy and Associated Maternal Outcomes

Cynthia Chalk, Bruce F. Folck, Lue-Yen Tucker, Aida Shirazi, Ali Poyan-Mehr.
Kaiser Permanente, San Francisco, CA.

Background: Maternal hypertension and CKD have increased over the last thirty years. In this study, we evaluate the prevalence of CKD as defined by GFR and proteinuria at the time of pregnancy and its impact on maternal outcomes during pregnancy.

Methods: We identified 353,735 adult female members of an integrated healthcare system who had one or more pregnancies from 1/2011 to 6/2023. We stratified the cohort into KDIGO's CKD subcategories and assessed the risk of maternal and prenatal outcomes of patients with versus without CKD.

Results: We identified a substantial number of patients with CKD. Clinically and statistically significant differences in maternal and prenatal outcomes exist between those with CKD versus those without. (Please see images for results: Cohort Distrubution and Maternal and Prenatal Outcomes)

Conclusions: Understanding individual risks associated with maternal and prenatal outcomes is critical for CKD patients. Additional analysis is being conducted to define risk in individual CKD subgroups and additional predictors of outcome such as comorbidities, age, and ethnicity.

			Proteinuria Categories			
			ACR (mg/g) < 30 mg/g Dipstick negative Or UPCR <0.2 g/g	ACR (mg/g) 30-300 Or dipstick trace to 2+ Or dipstick 30-100 UPCR 0.2-0.5 g/g	ACR (mg/g) > 300 Or dipstick > 2+ Or dipstick >100 Or UPCR >0.5 g/g	
			A1	A2	A3	Total
No baseline creatinine			134,314 (44.3)	16,466 (37.1)	244 (4)	151,024 (43)
eGFR Categories (ml/min/1.73m²)	≥90	G1	161,924 (53.4)	27020 (60.8)	5,378 (88.5)	194322 (54.9)
	60-89	G2	6,869 (2.3)	929 (2.1)	381 (6.3)	8,179 (2.3)
	45-59	G3A	61 (0.02)	16 (0.04)	32 (0.5)	109 (<0.1)
	30-44	G3B	34 (0.01)	10 (0.02)	21 (0.4)	65 (<0.1)
	15-29	G4	9 (<0.1)	2 (<0.1)	20 (0.3)	31 (<0.1)
	<15	G5	0	1 (<0.1)	4 (<0.1)	5 (<0.1)
Total			303,211 (85.7)	44,444 (12.6)	6,080 (1.7)	

Table 2. Cohort distribution. Adult female members who had one or more pregnancies from January 2011 to June 2023 were categorized into CKD groups according to their eGFR and proteinuria levels, n (%).

Cohort Distrubution

Maternal and Prenatal Outcomes

	Total	No CKD	CKD	P value
Total, n	353,735 (100)	296,826 (83.9)	56,909 (16.1)	
Gestational Hypertension	64,714 (18.3)	48,253 (16.3)	16,461 (28.9)	<0.0001
Gestational Diabetes	40,606 (11.5)	33,506 (11.3)	7,100 (12.5)	<0.0001
Pre-eclampsia	23,667 (6.7)	12,875 (4.3)	10,792 (19)	<0.0001
Pre-eclampsia (severe)*	15,881 (4.5)	9,082 (3)	6,799 (12.1)	<0.0001
Eclampsia	35 (<0.1)	16 (<0.1)	19 (<0.1)	<0.0001
Placenta Accreta	556 (0.2)	466 (0.2)	90 (0.2)	0.95
Placenta Previa	4,332 (1.2)	3,702 (1.3)	630 (1.1)	0.005
Placental Abruption	4,494 (1.3)	3,655 (1.2)	839 (1.5)	<0.0001
Postpartum Hemorrhage	1,272 (0.4)	961 (0.3)	311 (0.6)	<0.0001
Uterine Rupture	323 (0.1)	273 (0.1)	50 (0.1)	0.755
Chorioamnionitis	39,652 (11.2)	33,303 (11.2)	6,350 (11.2)	0.870
Intrauterine Growth Restriction	11,202 (3.2)	9,242 (3.1)	1,960 (3.4)	<0.0001
ICU admission	1,014 (0.3)	726 (0.2)	288 (0.5)	<0.0001

Table 3. Maternal outcomes. Significant testing was performed between those with any level of CKD versus those without any kidney impairment. *Severe pre-eclampsia is defined as Systolic blood pressure >160 in 2 measurements at least 15 minutes apart or Diastolic blood pressure >105 in 2 measurements at least 15 minutes apart, and any of the following: thrombocytopenia, elevated liver function tests, elevated LDH, uric acid, creatinine, urine protein-to-creatinine ration (source: Kaiser Permanente Perinatal Obstetrics Database). P- values were computed using Chi-square and Fisher's exact test for categorical variables.

Maternal and Prenatal Outcomes

SA-PO1050

Effective Management of Gitelman Syndrome with Amiloride during Pregnancy and Breastfeeding: A Case Report

Abdelrahman Ibrahim, Christof Westenfelder, Aylin R. Rodan, Laith Al-Rabadi.
University of Utah Health, Salt Lake City, UT.

Background: Gitelman Syndrome (GS) is an autosomal-recessive tubulopathy marked by hypokalemia, hypomagnesemia, metabolic alkalosis, hyperreninemic hyperaldosteronism, and normotension. Managing GS during pregnancy and lactation is challenging due to physiological renal changes and concerns about the teratogenicity of conventional treatments.

Methods: We document the case of a 20-year-old pregnant female diagnosed with GS, which was characterized by persistent hypokalemia and hypomagnesemia despite oral supplementation. Genetic testing confirmed GS through the identification of two pathogenic mutations in the SLC12A3 gene. Due to inadequate control with supplementation alone, amiloride was initiated and adjusted during pregnancy and postpartum periods. In this specific instance, the use of amiloride managed the patient's electrolyte imbalances effectively, without observable adverse effects on the neonate.

Results: The patient's treatment comprised the administration of amiloride, along with potassium and magnesium supplements. Initially, amiloride was paused during the first trimester and resumed thereafter. Post-delivery, amiloride was temporarily halted during the initial weeks of breastfeeding and reintroduced due to persistent hypokalemia. Monitoring indicated no significant electrolyte disturbances in the neonate directly attributable to amiloride.

Conclusions: While the extant literature about the use of amiloride during pregnancy is limited, this case highlights amiloride as a potential and viable option, under specific conditions, for managing electrolyte imbalances in GS during pregnancy and breastfeeding. It controlled persistent hypokalemia and hypomagnesemia effectively, with no significant adverse effects observed in the mother or infant. This report supports the consideration for cautious, heavily monitored use of amiloride in similar clinical scenarios. Nevertheless, further studies are recommended to thoroughly evaluate its safety and efficacy during pregnancy and lactation.

SA-PO1051

Assessment of Obstetric and Kidney Outcomes in Women Who Underwent Hemodialysis during Pregnancy in Brazil

Fernanda B. Roberto, Carlos A. Balda, Gianna Mastroianni-Kirsztajn.
Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil.

Background: Pregnant women with renal disease have worse obstetric outcomes than their healthy pairs, and risks are greater when dialysis is needed. Our main goal is to analyze maternal, fetal and renal outcomes of pregnant women who performed hemodialysis (HD) sessions due to acute kidney injury (AKI) or chronic kidney disease (CKD) during their hospital stay.

Methods: Single center retrospective observational study conducted to assess the features of pregnant women with CKD or AKI who needed HD and were followed by the Nephrology department of UNIFESP-EPM during the years between 2005-2019. These patients were compared between each other and sorted in three groups: AKI, non-dialytic CKD (NDCKD) and end-stage renal disease (ESRD).

Results: Our sample consisted of 36 pregnant women. Overall, 10 (27.8%) women presented with AKI, 14 (38.9%) with NDCKD and 12 (33.3%) with ESRD. Demographic data were similar between the groups, with a mean age of 30,7 years. All of the women in the AKI group dialyzed in the puerperium, while all the women in de NDCKD group started dialysis during pregnancy, with 69.2% starting in the 2nd trimester, and 60% of the ESRD women increased their dialysis schedule in the 1st trimester. Preeclampsia was more common in patients with AKI (50%) comparing to patients with NDCKD (27.3%) or with ESRD (no cases described). Furthermore, 4 patients (40%) in the AKI cohort evolved to death and no patients in the CKD groups. Regarding the live birth rate, we found a 60% rate in the AKI group, 57.1% in the NDCKD group and 58.3% in the ESKD women. Concerning the prematurity, there was a 66.7% frequency in the AKI patients, 87.5% in the NDCKD women and 85.3% in the ESKD group, considering only the live newborns. In the three groups, we did not find any statistical difference concerning the fetal outcomes. In our research, the weekly dialysis time were related only to the birth weight of the newborns, in a way that, the longer the weekly dialysis time, the greater the birth weight ($p = 0.037$).

Conclusions: Pregnant women with AKI needed dialysis later (in the puerperium) and had greater mortality. The negative pregnancy outcomes were similar between the three groups and worse than the general Brazilian population. The longer weekly dialysis schedule was related to greater birth weight.

SA-PO1052

Addressing Hypertensive Disorders of Pregnancy through a Combined Renal-Maternal Fetal Medicine Clinic

Jaya S. Parulekar, Elizabeth Taber-Hight. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Pregnancy marks a thrilling yet precarious time for women with underlying renal disorders, marked by unique physiologic, immunologic, and hemodynamic changes. These changes, complicated by progression of chronic kidney disease (CKD) and development of hypertensive disorders of pregnancy (HDOP), can endanger mother and fetus if left untreated. Establishing interdisciplinary practices through co-management of CKD and HDOP by nephrologists and maternal fetal medicine (MFM) providers, thus, offers great potential. Through collaborative clinic visits with laboratory and blood pressure monitoring, our study aims to better understand and address gaps in maternal and fetal health outcomes when treating CKD and HDOP.

Methods: This retrospective study followed 24 pregnant patients establishing care in our combined Renal-MFM Clinic from September 2022-May 2024. Data encompassed demographics (age, race, zip code, and insurance), obstetric history, estimated gestational age (EGA) at consultation, timing of aspirin initiation, comorbidities, laboratory results, blood pressures, hospitalizations, and delivery outcomes, all cataloged in a Redcap database.

Results: Women aged 17-43 years (mean 31.3, median 32) were studied, of whom 54% were White, 29% Black, 8% Hispanic, and 4% Asian. Referrals spanned gestational ages between 9-36 weeks. Around 67% sought care for HDOP, 29% for CKD, 25% for proteinuria, and 13% for nephrolithiasis. Among HDOP cases, 59% had chronic hypertension, 29% chronic hypertension with superimposed pre-eclampsia, and 11% gestational hypertension. Of those with HDOP, 82% were treated with medications, of whom 29% required 2 or more agents to manage blood pressure. Beta-blockers were more frequently selected (used in 57% of patients, alone and in combination with other agents). Prophylactic low-dose aspirin commenced at 13.1 weeks EGA on average. Of the 18 patients who delivered during the study period, 11% had term deliveries, 44% early term, and 44% pre-term delivery, with 2 cases of fetal demise before 20 weeks EGA.

Conclusions: This initial study outlines baseline characteristics and outcomes for our combined Renal-MFM clinic. Future directions include evaluating optimal medication management for target blood pressure attainment, expanding patient recruitment statewide, and integrating pre-conception counseling into our combined clinic framework.

SA-PO1053

Pregnancy, Peritoneal Dialysis, and a Dive into Some Unchartered Territories

Randall R. Rainwater,[1] Salima Valiani,[1,2] Manisha Singh.[1,2] *[1]University of Arkansas for Medical Sciences, Little Rock, AR; [2]Dialysis Clinic Inc, Little Rock, AR.*

Introduction: Pregnancy with end-stage-kidney disease (ESKD) is challenging at all levels, even more so with peritoneal dialysis (PD). The pregnancy rate on peritoneal dialysis is about half that of patients on hemodialysis, and usually, all such patients are transitioned to hemodialysis to support better outcomes. There are only a few reported cases of pregnancy that were carried beyond 32 weeks' gestation on PD alone. We report such a case in a 41 yo Pacific islander woman with spontaneous conception and continuation on PD through pregnancy and postpartum, using Icodextrin when needed.

Case Description: We present a case of a 41-year-old pacific islander woman with ESKD secondary to ureteral reflux with multiple infections who had been on PD for over two years at the time of natural conception. As the pregnancy progressed, the need for better clearances arose, but the patient was adamant not to transition to hemodialysis due to her fear of blood infections and tunnel catheters. The patient is in the medical profession and would read up on her options. She was aware of the risks and benefits of the alternatives discussed, thus enabling us to carry out a genuinely patient-centered and patient-led plan. With the patient's consent and multiple discussions with our team, division, and the pharmacy medical liaison, at 30 weeks of pregnancy, her PD regimen was modified to include a 1.5-liter Icodextrin to support her adequacy and volume control. This adjustment aided in her pregnancy reaching a higher gestation age of 32w4d when she delivered a viable 1630g female infant with Apgar scores of 1 and 8 at 1 and 5 minutes after birth. Though our patient underwent a cesarean section, she stayed on PD by modifications as appropriate, given her residual renal function, diuretic use, and renal diet, not needing hemodialysis at any time.

Discussion: We present the challenges and report a successful outcome of such a pregnancy, along with the first off-label use of icodextrin in pregnancy. We opine that Icodextrin did not adversely impact the course; it helped carry the pregnancy forward a few more critical weeks. As far as we are aware, this is also the first case report of a pacific islander and only one of two cases of pregnancy on PD in women aged 40 and over.

SA-PO1054

Gestational Changes in eGFR among Patients with CKD

Sharon E. Maynard, Anam Ali, Shae Duka. *Lehigh Valley Health Network, Allentown, PA.*

Background: Chronic kidney disease (CKD) affects ~3% of women of childbearing age and is a risk factor for adverse pregnancy outcomes. In normal pregnancy, glomerular filtration rate (GFR) increases by 40-50%. Pregnant patients with CKD may have a blunted gestational increase in GFR. This study aimed to explore if lower baseline eGFR is associated with a lower gestational increase in eGFR among pregnant patients with CKD.

Methods: This was a single-center retrospective study of pregnant women age ≥18 who received care at a multidisciplinary high-risk obstetric nephrology clinic between 2011-2023. All subjects had CKD, defined as eGFR < 60 ml/min/1.73m2 or urine protein:creatinine ratio (UPCR) >150 mg/mg prior to pregnancy, or UPCR >300 mg/mg prior to 20 weeks gestation. eGFR was calculated using the 2021 CKD-EPI Cr equation. Baseline eGFR was calculated from the last serum Cr prior to and within 2 years of pregnancy. Gestational % change in eGFR was calculated from the baseline eGFR and the peak mid-pregnancy eGFR, measured between 13-28 weeks gestation. Pearson's correlation was used to assess the correlation between baseline eGFR and gestational change in eGFR.

Results: 47 patients were included in the study. 5 (10.6%) had diabetes mellitus, and 15 (31.9%) had chronic hypertension. At the initial prenatal visit, 41 (87.2%) had proteinuria, 13 (37.1%) had eGFR 30-59, and 2 (5.7%) had eGFR 15-29. Median eGFR prior to pregnancy was 91.2 ml/min/1/73 m2 (IQR 58.8-119.0), and median peak eGFR during pregnancy was 105.2 (IQR 59.6-133.9). The median absolute change in eGFR was 11 ml/min/1.73 m2 (IQR 3.9-18.6), and median percent change was +13% (IQR +4-26.9%). There was no correlation between baseline eGFR and gestational change in eGFR (Pearson correlation coefficient -0.065, p=0.6647). 18 patients (39.1%) developed preeclampsia.

Conclusions: We found no correlation between baseline eGFR and gestational change in eGFR in patients with CKD. Limitations included a small number of patients with very low eGFR. Our patients with CKD had a smaller gestational increase in GFR than has been reported in pregnant patients with normal kidney function.

SA-PO1055

Kidney Cortical Necrosis after Placental Abruption

Anthony T. Nguyen, Haiyan Zhang, Margaret Ivanov. *University of California San Diego, La Jolla, CA.*

Introduction: Renal cortical necrosis (RCN) is a rare cause of kidney failure related to obstetric complications such as sepsis, placental abruption, and eclampsia. Incidence of RCN in developed countries is low, accounting for <2% renal failure cases. Prognosis is poor due to abrupt renal function loss, but improving with wider availability of renal replacement therapy (RRT). We present a case of RCN after placental abruption with massive hemorrhage.

Case Description: A 39 year old G5P2122 woman at 32w6d gestation presented for vaginal bleeding. Upon EMS arrival she was found to have placental abruption, with 0.75L of blood loss en route to the OR for emergent C-section. An additional 2L blood loss was reported intraoperatively. Her postoperative course was notable for AKI and anuria. Due to high suspicion for RCN a MRI abdomen/pelvis was obtained showing renal cortical diffusion restriction (Fig 1) suggestive of RCN. Subsequent renal biopsy showed 30% overall patchy cortical infarct and ATN, 10% IFTA, with segmental glomerular TMA-like changes (Fig 2). After 18 days she remained anuric and RRT was initiated; she remains on hemodialysis 2 months later.

Discussion: Obstetric complications account for a majority of RCN cases, possibly attributed to a combination of hypoperfusion, endotoxin-endothelial injury, and vascular thrombosis. There are two histological patterns of RCN: diffuse and patchy. Differing recovery rates are associated with type of injury, with patchy RCN having a more favorable prognosis. Anuria develops in 70-80% of RCN cases. Early RRT initiation in RCN may help reduce hospital length of stay, but further studies are needed on whether it provides a mortality benefit. Prognosis remains poor with 38-56% of patients able to withdraw dialytic support several months after initiation.

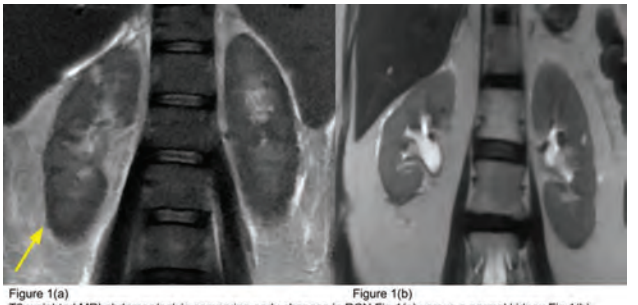


Figure 1(a) Figure 1(b)
T2-weighted MRI abdomen/pelvis comparing early changes in RCN Fig 1(a) versus a normal kidney Fig 1(b).
Fig 1(a) (arrow) showing a dark cortical rim of diffusion restriction and cortex/medullary separation seen in RCN

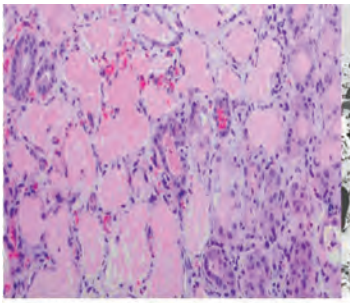


Figure 2(a) H&E staining showing patchy necrosis with areas of necrotic tubules as pink amorphous material

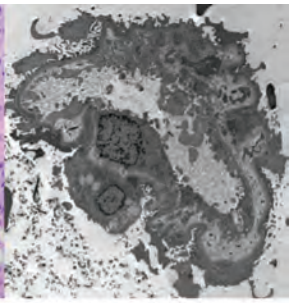


Figure 2(b) Electron microscopy showing glomerular TMA-like changes which can be seen with post-partum related RCN

SA-PO1056

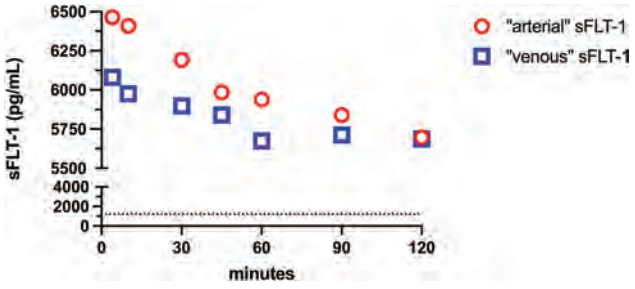
Seraph 100: A New Tool to Decrease Elevated sFlt-1 in Preeclamptic Plasma? An In Vitro Analysis

Amelie Gienapp, Kijanosh Lehmann, Torsten M. Meyer, Jan T. Kielstein. Kielstein Lab. *Stadtisches Klinikum Braunschweig gGmbH, Braunschweig, Germany*.

Introduction: There is an unmet need to treat pre-eclampsia. To reverse endothelial dysfunction caused by elevated soluble fms-like tyrosine kinase -1 (sFlt-1) and therefore antagonizing placental growth factor (PIGF), extracorporeal techniques have been tested including unselective therapeutiic plasma exchange (TPE) and specific adsorprive devices. Since sFlt-1 binds to heparin, we hypothesized that the Seraph® 100, that consists of small polyethylene beads with endpoint attached heparin, lowers sFlT-1.

Case Description: We used the plasma of a 33-year-old woman with severe preeclampsia during her 23rd week of gestation (blood pressure 190/110 mmHg, sFlT1/PIGF ratio 1433, platlets 36.000/µl, ALT 238 U/l). She and her son survived thanks to prolongation of the pregnancy by TPE. For the *in vitro* testing the Seraph® 100 was used in hemoperfusion mode. The Seraph® 100 adsorber clearance (CL) of sFlT-1 as calculated based on the plasma perfusion rate and extraction ratio (C_{pre} - C_{post}) / C_{pre}, using the equation $CL_{sFlT-1} = Q_e * (C_{pre} - C_{post}) / C_{pre}$, where Q_e is the effective plasma flow through the adsorber and C_{pre} and C_{post} are pre and post adsorber concentrations, respectively [Figure].

Discussion: *In vitro* the Seraph® 100 lowered sFlT-1 by roughly 12 % in the plasma of our patient. The median plasma clearance of the Seraph® 100 for sFlT-1 based on seven pre- and post Seraph® 100 plasma levels at a pump speed of 200 mL/min was 8.9 (0.4 – 13.5) mL/min. Interestingly the clearance decreased during the treatment, which could reflect saturation. of the device. A total amount of 3.5 µg sFlT-1 had been removed. Further data are needed to clarify whether the Seraph® 100 decreases sFlT-1 to a clinically relevant degree.



Serum levels of s-FLT-1 in a life size *in vitro* treatment with 4500 ml pre-eclamptic plasma using the Seraph® 100 on a Multifiltrate® Fresenius Medical Care machine in hemoperfusion mode at a pump speed of 200 mL/min for 120 min. "Arterial" levels refer to the plasma before entering the Seraph® 100 "Venous" levels refer to the plasma leaving the Seraph® 100.

SA-PO1057

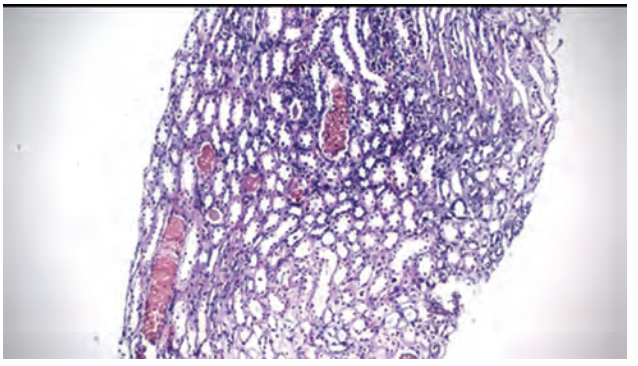
Kidney Involvement in Plasmodium falciparum Infection in a Pregnant Patient

Enzo C. Vasquez Jiménez,[1] Sabrina V. Castillo,[1] Virgilia Soto,[2] Octavio R. Garcia-Flores.[1] *[1]Hospital Juarez de Mexico, Mexico City, Mexico; [2]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico.*

Introduction: In Mexico, cases of malaria are becoming more frequent due to the effects of global warming and the migratory phenomenon. There are various mechanisms that can cause AKI in patients with *P. falciparum* infection: due to a hemodynamic effect associated with parasitemia, parasite sequestration, endothelial dysfunction, intravascular hemolysis, oxidative stress and immunological damage.

Case Description: A 29-year-old pregnant woman from Equatorial Guinea was admitted with abdominal pain, jaundice and fever, anemia (8.9 g/dL), thrombocytopenia ($10x10^9$ /L), hyperbilirubinemia (21 mg/dL), direct bilirubin (15 mg/dL), BUN (21 mg/dl), Cr (0.7 mg/dl). At the time of admission, the patient was 17.5 weeks of pregnancy. Urinalysis showed granular and biliary casts. Diagnosis was confirmed by a thick blood smear and a real-time PCR assay; therefore, antimalarial treatment were started. During stay in the ICU, mechanical ventilation, norepinephrine and CRRT were started due to neurological deterioration, hypotension and severe AKI (creatinine 3.7 mg/dL and anuria). Kidney biopsy was performed due to AKI and a urinary P/C ratio of 4 g/g and revealed an active tubulointerstitial nephritis with acute tubular lesion and pigment tubulopathy with negative IF. Recovery of kidney function was observed and follow-up was carried until the successful resolution of the pregnancy withouth deterioration in kidney function or proteinuria.

Discussion: Malaria is a serious disease in pregnant women. The indications for RRT in pregnant patients with AKI are similar to the general population. However, the thresholds are controversial due to the importance of maintaining an environment without uremia and acidosis to reduce fetal complications. The decision to perform a kidney biopsy in a pregnant patient is less clear and in this case a malaria manifestation was observed. Fortunately, the patient recovered kidney function after specific antimalarial treatment and completed her pregnancy without complications.



SA-PO1058

Lupus Nephritis Masquerading as Preeclampsia: A Treatment Dilemma

Samiya Yasin, Fatima Khalid, Akinwande A. Akinfolarin. *Baylor Scott & White Health, Dallas, TX*.

Introduction: Systemic Lupus Erythematosus (SLE) increases pregnancy related maternal and fetal risk when compared to healthy women. Active disease has been associated with poorer pregnancy outcomes. Differentiating between active lupus nephritis (LN) and preeclampsia is a diagnostic challenge making management difficult.

Case Description: A 21-year-old female was diagnosed with SLE, eight months prior to presentation. She had been on Cellcept which was discontinued at conception. She was admitted at 22 weeks of gestation with abdominal pain, nausea and vomiting. Vital signs were significant for BP of 166/110 mmHg. Physical examination revealed malar rash, mid epigastric tenderness but no peripheral edema. Laboratory data was significant for hemoglobin 9.2 g/dl, platelet count 83 K/uL, Creatinine (Cr) 1.17 mg/dl (baseline 0.6), serum albumin 3.2 g/dl and normal liver enzymes. Urinalysis revealed RBC > 100/hpf, WBC 100/hpf, 3 + proteinuria. A 24-hour urine protein/creatinine ratio was 2.6 g. Serologic work up revealed elevated antinuclear antibody (ANA) titer 1: 1280 and low complement C4 level. Serum Uric acid level was normal. Antineutrophil cytoplasmic antibodies (ANCA), anti-double stranded DNA (dsDNA), anti-Glomerular Basement Membrane Antibody (Anti-GBM), HIV, hepatitis panel, Antibody to SSA-Ro and SSB-were negative. She was initiated on therapy for a LN flare with hydroxychloroquine and prednisone. However, she had clinical and laboratory deterioration with large pleural effusion, pulmonary edema, worsening liver and kidney function and anemia requiring packed RBC transfusions. A kidney biopsy could not be safely done. A suspicion of preeclampsia was entertained and a 24-hour urine calcium collection was 14 mg/d confirming the diagnosis. She was treated with betamethasone, magnesium sulfate and underwent an urgent cesarian section. Subsequently, her renal function and hematologic parameters improved. A subsequent renal biopsy showed mesangial proliferative lupus nephritis class II for which she received Cellcept therapy.

Discussion: Active LN can mask the presentation of preeclampsia making diagnosis challenging due to the similarity of symptoms and laboratory features. A renal biopsy can clarify these differences; however, it is usually avoided during pregnancy. A high index of suspicion can help clarify this diagnostic and treatment dilemma which can otherwise be life threatening.

SA-PO1059

Navigating Recurrent Immune-Mediated Thrombotic Thrombocytopenic Purpura (iTTP) in Pregnancy: A Case Report

Niloufar Ebrahimi, Mohadese Golsorkhi, Sayna Norouzi, Amir Abdi Pour. Postdoctoral Scholar Research Program. *Loma Linda University, Loma Linda, CA.*

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a rare and potentially fatal condition characterized by thrombocytopenia and microangiopathic hemolytic anemia. Primarily affecting women of childbearing age, pregnancy is a significant precipitating factor for TTP. The condition's symptoms often overlap with other pregnancy-related disorders, such as pre-eclampsia or HELLP syndrome, making accurate diagnosis particularly challenging.

Case Description: A 32-year-old woman, gravida 2 para 1, with a body mass index of 39, presented at 11 weeks gestation with a syncopal episode following a blood draw, along with petechiae, bruising, and thrombocytopenia. Her obstetric history includes a similar clinical presentation during her first pregnancy three years earlier, initially diagnosed as HELLP syndrome, necessitating the emergent delivery of a healthy baby at 34 weeks gestation. However, persistent postpartum thrombocytopenia led to further investigation and a definitive immune TTP (iTTP) diagnosis due to anti-ADAMTS-13 antibodies. She was successfully treated with plasma exchange (PLEX) and high-dose steroids at that time. She remained in remission on low-dose steroid, which eventually was tapered off. In her current pregnancy, she experienced a recurrence of iTTP at 11 weeks GA, notably earlier than her previous episode. Laboratory evaluations showed a platelet count of 41,000/μL, anemia (Hb=8.3 g/dL), elevated lactate dehydrogenase (LDH=400 U/L), normal creatinine, and scant schistocytes on the blood smear. Given her medical history, prednisone and PLEX were initiated. Following three PLEX sessions, her thrombocytopenia and clinical signs resolved, and her platelet count increased to 298,000/μL. The patient was subsequently discharged in a stable condition.

Discussion: The incidence and frequency of iTTP increase during pregnancy and can often be misdiagnosed as severe preeclampsia or HELLP syndrome. Plasma-based therapies have significantly improved the prognosis for these patients. Additionally, serial evaluation of ADAMTS-13 activity is recommended both at the preconception stage and throughout pregnancy for women with a history of TTP. This case emphasizes the critical need for heightened awareness and vigilance for TTP relapse during pregnancy.

SA-PO1060

The Proteinuria Puzzle of Pregnancy: Membranous Nephropathy Unmasked

Sandeep Kaur, Ratib T. Mahfouz, Snigdha Reddy. *Henry Ford Hospital, Detroit, MI.*

Introduction: The evaluation of proteinuria in pregnancy can be a challenge. While proteinuria is commonly associated with conditions like pre-eclampsia during pregnancy, it is important to recognize that there can be other underlying causes as well. Membranous nephropathy is one such cause.

Case Description: In this case, a 23-year-old female G5P1031 with a family history of IgA nephropathy presented at 36 weeks of gestation due to oligohydramnios. On admission, she displayed elevated blood pressure (146/82 mmHg) accompanied by headaches, along with facial and leg swelling persisting for several months. Further investigation revealed significant proteinuria, indicating nephrotic syndrome. Tests showed a notably high urine protein to creatinine ratio 11 mg/mg. Diagnosis of pre-eclampsia with severe features was made, necessitating induced labor. Post-delivery, the patient continued to exhibit nephrotic-range proteinuria. Serum albumin level was low 2.5 g/dL, prompting additional tests that revealed elevated phospholipase A2 receptor (PLA2R) level 17 RU/mL with uptrend to 47 RU/mL. Subsequent kidney biopsy showed positive staining for PLA2R in the glomerular deposits (see figure 1), confirming the diagnosis of primary membranous glomerulopathy. Treatment commenced with ACE inhibitor, leading to favorable response characterized by decreasing PLA2R levels to <2 RU/mL and improved proteinuria.

Discussion: This case underscores the intricate relationship between pregnancy-related complications such as pre-eclampsia and underlying renal conditions like primary membranous nephropathy. Effective management requires a comprehensive approach addressing both maternal and fetal health considerations.

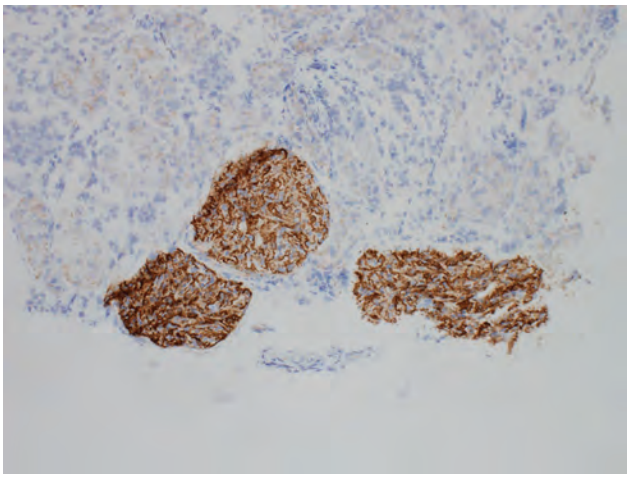


Figure 1: Immunohistochemistry for PLA2R

SA-PO1061

Placental Extracellular Vesicles from Preeclampsia Alter the Transcriptome of Murine Renal Proximal Tubule Epithelial Cells

Priyadarshini Pantham,[1,2] Jennifer N. Chousal,[1] Tyler Ostrander,[1,2] Scott A. Lindsay,[1,2] Anushka R. Edlabadkar,[1,2] Willi Cheung,[1,2] Subhashini Bolisetty,[3] Prabhleen Singh.[1,4] *[1]University of California San Diego, La Jolla, CA; [2]Sanford Consortium for Regenerative Medicine, La Jolla, CA; [3]University of Alabama at Birmingham, Birmingham, AL; [4]VA San Diego Healthcare System, San Diego, CA.*

Background: Preeclampsia (PE), a deadly hypertensive disorder of pregnancy, is associated with maternal kidney damage indicated by proteinuria, increased risk of chronic kidney disease, and cardiorenal syndrome. The placenta plays a key role in the etiology of PE and releases extracellular vesicles (EVs) containing RNA cargo into the maternal circulation throughout pregnancy, which can modulate distant organs including the maternal kidney. The role of renal proximal tubule epithelial cells (rPTECs) in the etiology of kidney damage and their interaction with placental EVs in PE has never been studied. We aimed to characterize the effect of human placental EVs isolated from PE pregnancies compared to normal pregnancies on the transcriptome of murine rPTECs.

Methods: Placental EVs (70-100nm) were isolated using size exclusion chromatography following placental explant culture from normal (n=3) or preeclamptic (n=3) pregnancies. Murine rPTECs were isolated from non-pregnant female mouse kidneys (n=2) and treated with normal or PE placental EVs on day 7 at a dose of $1x10^{10}$EVs/mL for 24 hours. RNA was isolated from murine rPTECs, RNA libraries were constructed using the KAPA RNA HyperPrep Kit, and RNA-Seq was performed (Illumina NovaSeq X Plus). Reads were aligned using STAR, gene abundances quantified using RSEM, and differential expression analysis was conducted using DESeq2.

Results: An average of $41x10^6$ reads per sample was obtained, and >5000 transcripts were dysregulated in murine rPTECs treated with EVs from PE compared to normal pregnancies (FDR<0.001, Figure 1). Analysis of molecular pathways using gProfiler showed that these transcripts were significantly enriched for mRNAs involved in oxidative phosphorylation (42 mRNAs, FDR<0.01).

Conclusions: We have shown that placental EVs isolated from PE pregnancies alter the transcriptome of murine rPTECs, particularly in transcripts involved in mitochondrial electron transport. Current efforts are aimed at measuring mitochondrial oxygen consumption in proximal tubules isolated from pregnant mice injected with placental EVs from PE and normal pregnancies, to establish whether increased oxidative stress in rPTECs plays a key role in inducing the kidney damage seen in PE.

Funding: Other NIH Support - This work was supported by NIH/NICHD R00HD096125 and the UC San Diego Center for Perinatal Discovery Pilot grant to PP, and VA Merit BX002175 to PS., Veterans Affairs Support

SA-PO1062

Perinatal Outcomes and Risk Factors for Fetal Growth Restriction in Kidney Transplant Recipients: A Retrospective Cohort Study

Nada Alamri,[1] Hatoon Altaifi,[2] Hassan A. Aleid.[3] *[1]Madinah Health Cluster, Ministry of Health, Madinah, Saudi Arabia; [2]Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; [3]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.*

Background: Pregnancy outcomes have significantly improved in women with end-stage renal disease following renal transplantation. Despite this, these women still face higher rates of adverse outcomes, including intrauterine growth restriction (IUGR). This study aims to report perinatal outcomes and identify risk factors for IUGR in kidney transplant recipients.

Methods: This retrospective cohort study included 40 women who conceived after receiving a kidney transplant. We compared pregnancies complicated by IUGR with those that had normal fetal growth, focusing on identifying significant risk factors.

Results: IUGR was identified in 8 (21%) cases, with fetal weight below the 10th percentile. Significant risk factors for IUGR included proteinuria (P = 0.03), nulliparity (P = 0.04), and age at the time of transplant (P = 0.03). No significant associations were found with anemia, hypertension, maternal age, or pre-pregnancy creatinine levels. Increased incidences of pre-eclampsia (40%), placental abruption (12.5%), preterm delivery (29%), and cesarean section (66%) were observed.

Conclusions: IUGR is a common adverse outcome among pregnant women post-renal transplantation. Proteinuria, nulliparity, and age at transplant are significant risk factors for IUGR. These findings highlight the importance of targeted monitoring and management in this high-risk population. Future research should include long-term pediatric follow-up to better understand the outcomes for children born to this group of women.

	Renal transplant since 2-4 years before pregnancy N=26	Renal transplant more than 4 years before pregnancy N=11	P value	OR (95%CI)
Fetal \ neonatal				
Stillbirth \ neonatal death	1	2	P = 0.4265	2.8571 (0.2149 - 37.9915)
Preterm delivery	5	4		
NICU admission	5	3		
Maternal				
preeclampsia	3	2	P = 0.2660	0.9429 (0.0520 - 2.2611)
worsening HPT	5	3		
PPROM	2	0		
Placental abruption	1	2		
placenta previa	1	0		

Prenatal Outcome in Relation to Pregnancy Timing After Renal Transplant

SA-PO1063

Maternal Kidney Disease and Offspring Neurodevelopmental Outcomes: A Nationwide Population-Based Study

Jeongin Song,[1] Seung hyun Han,[2] Sehoon Park,[3] Hajeong Lee.[3] *[1]Dongguk University Medical Center, Goyang, Gyeonggi, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; [3]Seoul National University Hospital Department of Internal Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: Maternal immune activation, triggered by both acute and systemic chronic inflammation, is considered a predisposing factor for offspring neurodevelopmental conditions. However, there is no data about the effect of mothers' chronic kidney disease on their offspring's neurodevelopmental diseases.

Methods: We extracted the data on pregnant women from the National Health Information Database from 2008 to 2017 in South Korea. We categorized the subjects into four groups based on their pre-pregnancy kidney function: no CKD, CKD, kidney replacement therapy (KRT), and kidney transplantation (KT). The outcomes are defined as offspring's neurodevelopmental diseases, including motor and cognitive developmental delay, autism spectrum disorders, attention deficit hyperactivity disorder, tics, stereotypic behavior, and seizures based on ICD-10-CM codes.

Results: A total of 3,794,031 children were born to 2,680,092 mothers during the study period. We included 488,208 mothers without kidney diseases, 46,930 mothers with CKD, 49 mothers with ESKD, 187 mothers with KT, and 3,637,903 children after the exclusion of multiple pregnancies. Mothers with CKD, KRT, and KT had older ages and more co-morbidities than those without. They suffered from more adverse pregnancy outcomes, such as preeclampsia, preterm birth, and placenta previa/abruption. Their offspring's neurodevelopmental disease occurred in 8.7%, 10.9%, 31.7%, and 16.3% of the no CKD, CKD, KRT, and KT groups, respectively. Mothers with CKD (adjusted OR [95% CI]: 1.29 [1.26-1.33], p<0.001), KT (1.87 [1.28-2.65], p=0.001), and ESKD (3.73 [2.12-6.37], p<0.001) showed a higher risk of offspring's neurodevelopmental diseases even after adjusting for maternal age, nulliparity, underlying hypertension, smoking history, maternal BMI, gestational diabetes, preeclampsia, neonatal sex, preterm birth, and low birth weight.

Conclusions: In this nationwide cohort study, we first found that maternal pre-pregnancy kidney function was associated with offspring's adverse neurodevelopmental diseases in dose-responsive manners.

SA-PO1064

Association of Marital Status with CKD Progression and Mortality: Analyses from the CRIC Study

Karela B. Herrera-Enriquez,[1,2] Finnian R. McCausland.[1,2] *[1]Brigham and Women's Hospital Department of Medicine, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: Being married is associated with lower mortality among patients with several disease types. Whether marital status is associated with future risk of kidney failure among patients with chronic kidney disease (CKD) is not clear.

Methods: Using data from the Chronic Renal Insufficiency Cohort (CRIC; n=5,625), we explored the association of marital status (never, former, current) with a composite kidney outcome (≥50% decline in estimated glomerular filtration rate [eGFR], eGFR <15, transplant, or dialysis) and mortality. Unadjusted and adjusted Cox models were fit, adjusting for age, race, body mass index, education, income, systolic blood pressure, diabetes, myocardial infarction or revascularization, peripheral vascular disease, heart failure, current smoking status, eGFR, 24-hour urine protein, hemoglobin, serum albumin, and medications (beta-blocker, calcium blocker, ACEi or ARB, aspirin, statin, or diuretic). We also explored if associations differed according to sex.

Results: Mean age was 60 ±11 years; 44% were female; 43% self-reported as Black; baseline eGFR was 49 ±16 ml/min/1.73m2. At baseline 2,994 (53%) reported being married, 1,830 (33%) formerly married, and 801 (14%) never married. Over a median follow-up of 5.1 years, there were 1,501 (27%) kidney composite events and 1,890 (34%) deaths. In adjusted analyses, compared with never married, those currently married had a lower risk of the kidney composite (HR 0.80; 95%CI 0.66, 0.96) and all-cause mortality (HR 0.76; 95%CI 0.63, 0.91). The association of marital status with the kidney composite and death appeared to differ according to sex (P-interaction=0.16 and 0.04, respectively), such that lower risks were observed for males, versus females (Table 1).

Conclusions: Marital status is independently associated with a lower risk for adverse kidney outcomes and death among patients with CKD. These associations appeared to be most potent among male patients.

Table 1 Risk of outcomes according to marital status in sub-groups of females and males

Outcome	Never Married HR (95%CI)	Formerly Married HR (95%CI)	Currently Married HR (95%CI)
FEMALES			
Kidney Composite events, n (%)	122/388 (31%)	251/955 (26%)	238/937 (25%)
Adjusted	Ref	0.94 (0.70, 1.25)	0.98 (0.72, 1.33)
Death, n (%)	124/424 (29%)	361/1028 (35%)	255/1005 (25%)
Adjusted	Ref	0.87 (0.67, 1.13)	0.82 (0.62, 1.09)
MALES			
Kidney Composite events, n (%)	129/357 (36%)	214/736 (29%)	547/1869 (29%)
Adjusted	Ref	0.79 (0.60, 1.04)	0.66 (0.51, 0.85)
Death, n (%)	124/377 (33%)	376/802 (47%)	650/1988 (33%)
Adjusted	Ref	1.02 (0.80, 1.30)	0.73 (0.58, 0.93)

SA-PO1065

Association between Health Literacy and Body Mass Index among Patients with CKD

You-Chi Chen,[1] Pei-Ni Hsiao,[2] Shang-Jyh Hwang,[1,3] Yi-Wen Chiu,[1,3] Yi-chun Tsai.[1,3] *[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan; [2]Department of Nursing, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan; [3]Faculty of Renal Care, Kaohsiung Medical University, Kaohsiung, Taiwan.*

Background: Patients with chronic diseases need to have sufficient health literacy to establish the ability of self-care. Variation of body mass index (BMI) has been related to chronic kidney disease (CKD) progression. Limited studies examined the association between BMI and health literacy in CKD patients. This study aims to explore the relationship between health literacy and BMI in CKD patients.

Methods: The cross-sectional study enrolled CKD patients in Interdisciplinary CKD Care Program conducted at Kaohsiung Medical University Hospital in southern Taiwan. Health literacy was measured at study interview using multidimensional health literacy questionnaire. The proposed scale covers the following five dimensions including accessing, understanding, appraising, applying health information, and communication and interaction. The total scores of health literacy was calculated as (the average scores of the sum of five dimensions -1)*50/3. According to the total scores, health literacy could be graded as inadequate (score range (SR): 0~25), limited/insufficient (SR: 26~33), sufficient (SR: 34-42), and excellent (SR: 43~50).

Results: Among 240 CKD patients, 33.4% had limited and insufficient health literacy. BMI was negatively correlated with total scores and five dimensions of health literacy

in multivariable linear regression (r: -0.25, p=0.02). Late CKD patients with high BMI had lower health literacy scores than early CKD patients with high BMI. CKD patients with high total scores of health literacy and accessing or applying health information had decreased risk of obesity (BMI > 27 kg/m^2).

Conclusions: The significant relationship between BMI and the grade of health literacy was found in CKD patients. Improvement of health literacy may assist in reducing the risk of obesity.

SA-PO1066

Association between Parity and Prevalence of CKD

Haeun Lee, Hee-Chan Moon, Ju hwan Oh, A young Cho, In O Sun.
Presbyterian Medical Center, Jeonju, Jeollabuk-do, Republic of Korea.

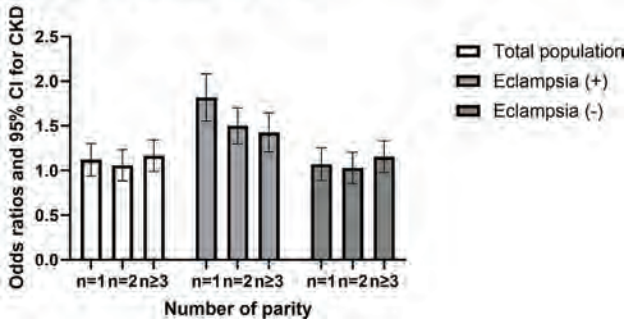
Background: Previous studies have demonstrated that women with a history of adverse pregnancy outcomes, such as eclampsia, are at increased risk of developing chronic kidney disease (CKD). However, only a limited number of studies investigated the association between parity and CKD. Under the assumption that physiologic and anatomic changes during pregnancy, such as in glomerular filtration rate, renal plasma flow, renin-angiotensin-aldosterone system and size of kidneys could impact on kidney, we investigated whether the number of parity affects the prevalence of CKD.

Methods: We analyzed the health examinee data from the Korean Genome and Epidemiology Study (KoGES-HEXA), which comprises participants from Korea between 2004 and 2013. After excluding individuals with histories of pre-existing CKD and participants with incomplete records, 100,433 participants were included in this study. CKD was defined as an estimated glomerular filtration rate below 60 mL/min/1.73 m^2, calculated using the CKD-EPI (Epidemiology Collaboration) formula or the presence of proteinuria. We compared the prevalence of CKD across four groups, categorized by the number of parity; 0, 1, 2, and ≥3.

Results: Women with 3 or more parities, compared to those with no parity, were older with more co-morbidities, less likely to smoke or drink, and had higher body mass index, elevated fasting blood sugar and low density lipoprotein cholesterol. CKD prevalence seemed higher in women with three or more parities than in no parity group (5.3% vs. 3.1%, *P*<0.05), but this association disappeared after adjusting for risk factors (**Figure 1**). Among women with a history of eclampsia, 1 and 2 parity groups showed higher risk of CKD compared to 0 parity group (**Figure 1**).

Conclusions: Exposure to eclampsia was associated with higher risk of CKD. On the other hand, parity may not independently affect the prevalence of CKD in Korean women. Further studies are needed to determine whether parity itself increases the prevalence of CKD.

Figure 1. Odds ratios and 95% confidence intervals for CKD based on the number of parity



SA-PO1067

Prognostic Influence of Physical Activity and Sedentary Behavior in Patients with CKD: The CKD-REIN Study

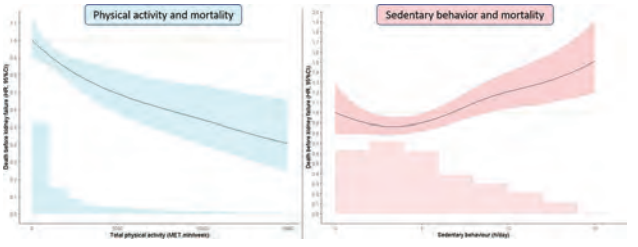
Aghiles Hamroun,[1,2] Raphael Bentegeac,[1,2] Natalia Alencar de Pinho,[3] Celine Lange,[4] Luc Frimat,[5] Denis Fouque,[6] Ziad Massy,[7] Benedicte Stengel,[3] Abdou Omorou.[5] *[1]Centre Hospitalier Universitaire de Lille, Lille, France; [2]Institut Pasteur de Lille, Lille, France; [3]Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; [4]Agence de la biomedecine, La Plaine Saint-Denis, France; [5]Centre Hospitalier Regional Universitaire de Nancy, Nancy, France; [6]Hospices Civils de Lyon, Lyon, France; [7]AURA Paris, Paris, France.*

Background: Although the benefits of adapted physical activity (APA) programs have been demonstrated, including among the population with chronic kidney disease (CKD), there is currently limited data on daily physical activity (DPA) in real life among these patients.

Methods: All patients included in the CKD-REIN prospective cohort (CKD stage 2-5) who completed the Global Physical Activity Questionnaire (GPAQ) at baseline were analyzed. The medical and psychosocial determinants of DPA were studied using a multivariable Poisson regression model. The associations between DPA, sedentary behavior and the risks of kidney failure and all-cause mortality were estimated using cause-specific Cox models adjusted for age, sex, CKD characteristics, medical history, and lifestyle factors. The variables for DPA and sedentary behavior were modeled both continuously (using restricted cubic splines) and categorically, in accordance with recommendations.

Results: Within the 2528 patients included (65% male, median age 69 years, median GFR = 32.8 mL/min/1.73m^2), 48%, 25%, and 27% had low (< 600 MET.min/week), moderate (600-1500), and high (≥ 1500) DPA, respectively, defined by the WHO guidelines. Female sex, advanced age, obesity, and depression were significantly associated with lower DPA. We observed a strong linear association between the level of DPA and the risk of mortality in the fully adjusted models. Conversely, this risk increased non-linearly with the duration of sedentary behaviour per day (Figure 1). For instance, higher DPA was significantly associated with better survival (HR = 0.84 [0.66 to 1.07], HR = 0.63 [0.47 to 0.82] for moderate and high activity, respectively, compared to low activity, p for trend < 0.001), with no association with the risk of kidney failure. Conversely, sedentary behavior (> 9 hours/day) was independently associated with an increased risk of death (HR = 1.39 [1.17 to 1.66], p < 0.001).

Conclusions: Like APA, real-life DPA is associated with better survival among the population of patients with CKD, independantly of sedentary behavior.



SA-PO1068

Snoring and Self-Reported Apnea Are Risk Factors for Albuminuria and CKD: A Retrospective Data Analysis

Shruti Kore, Savneek S. Chugh, Sanjeev Gupta, George N. Coritsidis.
Westchester Medical Center Health Network, Valhalla, NY.

Background: Obstructive sleep apnea is a well-known cause of albuminuria. However, many patients are reluctant to undergo a sleep apnea study due to the time and effort involved, often requiring significant persuasion. It would be beneficial if there is some data to demonstrate to patients that snoring or episodes of sleep apnea are linked to chronic kidney disease. In this study, we present a retrospective data analysis comparing the effects of snoring and self-reported apnea episodes on albuminuria.

Methods: We conducted data analysis of a retrospective survey from 2017-2020 pre-pandemic using National Health and Nutrition Examination Survey (NHANES). We explored variables for sleep disturbance such as self-reporting snoring, and episodes of apena and compared it with Urine albumin and creatinine ratio (UACR). All the demographic variables were included for participants above 20 years of age and data was alanlyzed on 9,232 adults using Stata software.

Results: Episodes of apnea were seen higher in age group of 45-65 years (53.51%). Similarly, episodes of snoring seen higher in the same age group 50.48%, followed by 25.39 % in age group 20-40 years. Snoring and apneic events were higher in males 53.97% and 58.57 % respectively. About 58.42 % of individuals with episodes of apnea and 61.27 % with snoring slept between 7 to 9 hours. Unadjusted logistic regression for episodes of apnea showed 1.34 OR with p value 0.003 for UACR OF 30-299 mg, 1.77OR with p value of 0.002 for UACR of >300 mg/dl. Unadjusted logistic regression for snoring showed 1.19 OR with p value 0.011 for UACR OF 30-299 mg, 1.57 OR with p value of 0.002 for UACR of >300 mg/dl. When adjusted for diabetes and hypertension the results for episodes of apnea showed 1.04 OR for 30-299mg/dl, 1.15 OR for >300mg/dl.

Conclusions: Our study adds to the body of data that sleep disturbances are strongly associated with albuminuria and develpment of chronic kidney disease. We recommemd primary care physicians to check albuminuria in patients with history of snoring and episodes of sleep apnea with timely referral to nephrologist to improve Kidney health.

SA-PO1069

Impact of Smoking Status on Hemoglobin Levels and Progression of CKD in Patients in a Metabolic Disorder Cohort

Hoon Young Choi,[1,2] Hyo Jeong Kim,[1,2] Hyeong cheon Park.[1,2] *[1]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [2]Gangnam Severance Hospital, Seoul, Republic of Korea.*

Background: Smoking has been known as one of the leading causes of preventable deaths worldwide. Smoking has also known as the risk developing chronic kidney disease (CKD). The hemoglobin level for incident CKD in metabolic patient groups can vary depending on various factors such as age, gender, the specific metabolic disorder, the

stage of CKD, and smoking status. This study investigated the relationship between hemoglobin levels and the progression of CKD depends on smoking status.

Methods: In the data from the medical records database in Gangnam Severance Hospital from 2006 through 2020, a longitudinal analysis included participants with CKD. Progression of CKD was defined by a reduction in the GFR ≥30% of baseline. Logistic regression analyses were used to determine the association between hemoglobin level and progression of CKD according to smoking status by adjusting for the influence of confounders.

Results: The study included 4,176 patients, of whom 986 had smoking status. Mean hemoglobin levels were 13.7 ± 1.9 g/dl (non-smoker) and 14.2 ± 1.9g/dL (smoker) according to smoking status. Among non-smoker, highest and second highest quartiles of hemoglobin levels was decreased with the risk progression of CKD [OR 0.664, OR 0.405, P<0.001] after adjusting for age, sex, hypertension status, diabetes status, and alcohol status. However, the risk progression of CKD was significantly decreased only in the second highest quartile of hemoglobin levels among smoker [OR 0.669, P=0.017].

Conclusions: Our study provides evidence that smoking is associated with elevated hemoglobin levels, and hemoglobin levels may have varying implications for CKD progression depending on smoking status.

SA-PO1070

Baseline and Longitudinal Self-Reported Physical Function and Important Clinical Outcomes in CKD

Sarah J. Schrauben,[1] Vanessa-Giselle Peschard,[2,3] Rebecca T. Brown,[1] Xiaoming Zhang,[1] Michael Shlipak,[2] Navdeep Tangri,[4] Wei Yang.[1]
[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]San Francisco VA Health Care System, San Francisco, CA; [3]UCSF Medical Center, San Francisco, CA; [4]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada.

Background: Physical function is essential for independent living and good health. However, it's evolution and association with important clinical outcomes is unknown among people with CKD. We aimed to describe self-reported physical function over time and its relationship to heart failure events, incident end-stage kidney disease (ESKD), and death in a CKD cohort.

Methods: Using annual data from the prospective CRIC Study, we calculated the physical composite summary (PCS) score from the SF-12 survey, a validated summary measure of physical health (range, 0-100, higher scores indicate better function). Linear regression models were used to calculate yearly PCS change for each participant using annual PCS scores from baseline to year 3 visits. After the year 3 visit, Cox models were used to examine the association of baseline PCS score and yearly PCS change with incident heart failure, incident ESKD and death. We also assessed effect modification by age, sex, race, and eGFR groups.

Results: Among 5,495 CRIC participants at baseline, mean age was 60 yrs, 42.7% were non-Hispanic Black, 51.5% had diabetes and mean eGFR was 48.1 ml/min/1.73^2. Median (IQR) follow up was 9.4 (7.6-16.8) yrs. Mean (SD) PCS yearly change in the first 3 yrs was -0.17 (3.99). Lower baseline PCS and declining PCS slope were associated with 20-29% increased risk of incident heart failure and death and declining PCS slope was associated with 11% increased risk of incident ESKD (Table). Interactions were found for PCS-12 slope decline between eGFR groups and incident heart failure (HR for eGFR ≥30: 1.21, 95% CI: 1.05-1.39; HR for eGFR <30: 0.82, 95% CI: 0.61-1.09), and between race groups and ESKD (HR for Non-Hispanic White group: 1.09, 95% CI: 0.91-1.31; HR for Non-Hispanic Black group: 0.99, 95% CI: 0.87-1.13; HR for Hispanic group: 1.45, 95% CI: 1.09-1.93).

Conclusions: Baseline and longitudinal changes in self-reported physical function were associated with important clinical outcomes in CKD, highlighting the importance of monitoring self-reported physical function over time in CKD care to identify those at risk and who may benefit from early and targeted interventions.

Funding: NIDDK Support

	Incident Heart Failure	Incident ESKD	Death
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Baseline PCS per 10-unit decrease	1.20 (1.05-1.37)	0.99 (0.92-1.07)	1.29 (1.22-1.36)
PCS yearly change per 1-SD decline	1.20 (1.01-1.44)	1.11 (1.01-1.32)	1.22 (1.13-1.32)
Adjusted for: age, sex, race, smoking, diabetes, cardiovascular disease, systolic blood pressure, body mass index, eGFR, urine protein, baseline PCS, and recruitment site			

SA-PO1071

Metabolic Risk Factors, Genetic Risk Score, and Risk of Incident CKD

Ga Young Heo, Hyung Woo Kim, Jung Tak Park, Tae-Hyun Yoo, Shin-Wook Kang, Seung Hyeok Han. *Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.*

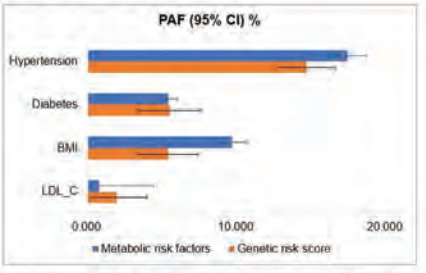
Background: Multiple modifiable risk factors are associated with chronic kidney disease (CKD). However, the combined effect of metabolic risk and genetic risk on CKD remains unexplored.

Methods: This study investigated the association between metabolic risk factors (Obesity, high low-density lipoprotein cholesterol [LDL-C], hypertension, diabetes), genetic risk score and incident CKD, using data from UK Biobank. We used polygenic risk scores (PRS) for hypertension, diabetes, body mass index (BMI), and LDL-C, utilizing PRS data by Genomics PLC as part of UK Biobank project. The primary outcome was the incident CKD. Cox proportional model were used and population attribution fraction (PAF) were analyzed in risk of CKD.

Results: This study included 171,955 participants, with a mean age 55.7 years and 86,153 (50.1%) being men. During the 12.8-year follow-up period, 8,641 incident CKD occurred. Prevalent hypertension exhibited the highest PAF at 17.4% (95% CI, 16.1, 18.7). Regarding the total CKD risk, 5.4% (95% CI, 5.0, 6.0) and 9.6% (95% CI, 8.7-10.7) were attributable to prevalent diabetes or obesity, respectively; while high LDL-C did not show significant attribution to CKD risk. Similar to the metabolic risk factors, PRS_hypertension, PRS_diabetes, and PRS_BMI contributed to CKD risk; PAF 14.7 (95% CI, 12.7-16.6), 5.5 (95% CI, 3.3-7.6), and 5.4 (95% CI,.3.4-7.4), respectively. The risk of CKD was more significantly attributable to hypertension in the high PRS_hypertension and PRS_diabetes group. Prevalent diabetes, and obesity were more significantly attributed to the risk of CKD in the highest quintile of PRS_hypertension.

Conclusions: In this prospective cohort study, both metabolic risk factors and genetic risk were contributed to the development of CKD, except LDL-C. Notably, in the genetically high-risk subgroup, metabolic risk factors showed a more pronounced and significant contribution to CKD risk.

Figure 1. Population attribution fraction of metabolic risk factors and genetic risk score for chronic kidney disease



Abbreviation PAF, population attribution fraction; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol

SA-PO1072

CKD Awareness among US Adults by Kidney Disease: Improving Global Outcomes (KDIGO) Risk Classification

Jennifer L. Bragg-Gresham,[1] Jenna Kiryakos,[1] Michael Heung,[1] Tiffany C. Veinot,[2] Brenda W. Gillespie,[3] Hal Morgenstern,[3] William H. Herman,[1] Yoshihisa Miyamoto,[4] Fang Xu,[4] Rajiv Saran.[1] *[1]University of Michigan Medical School, Ann Arbor, MI; [2]University of Michigan School of Information, Ann Arbor, MI; [3]University of Michigan School of Public Health, Ann Arbor, MI; [4]Centers for Disease Control and Prevention, Atlanta, GA.*

Background: Nearly 1 in 7 U.S. adults have chronic kidney disease (CKD); however, 9 in 10 adults with CKD do not know of their diagnosis. Improving awareness is particularly important because newer therapies are now available that can significantly improve kidney and cardiovascular outcomes in these patients. We sought to quantify awareness of CKD by eGFR and albuminuria categories among adults with a focus on stages G1–G2 with albuminuria (A2–A3), an at-risk population for CKD progression and cardiovascular disease.

Methods: Using the National Health and Nutrition Examination Survey (2017–March 2020), CKD was based on the CKD-EPI 2021 formula and albuminuria testing (urine albumin to creatinine ratio) among U.S. adults aged ≥ 20 years (*N*=7,671). Awareness was defined as a self-reported affirmative response to the question "Have you ever been told by a doctor or other health professional that you had weak or failing kidneys?" Analyses accounted for complex survey design and weights.

Results: Awareness of CKD was markedly lower among adults in the earlier stages of CKD (Table), especially for those with A2 category of albuminuria with eGFR ≥ 60 ml/min/1.73m^2. Extrapolating to the US population, this represents over 18 million U.S. adults with CKD who are unaware of the disease. Adults with CKD G5 had the highest awareness, yet 15-25% (approximately 52,000 adults) were unaware.

Conclusions: While earlier stages of CKD (G1–G3) are more prevalent in the U.S. population than advanced stages (G4–G5), adults with early-stage CKD are much less likely to be aware of their diagnosis. Most adults with albuminuria and eGFR ≥ 60 ml/min/1.73m^2 are unaware of having kidney disease. A limitation is that this analysis uses single measurements of these kidney markers. Raising awareness of CKD in earlier stages of the disease through increase in screening among those with risk factors may help to prompt earlier implementation of preventive strategies and could be studied further.

Funding: Other U.S. Government Support

Awareness of CKD among adults with confirmed CKD based on laboratory testing, National Health and Nutrition Examination Survey 2017—March 2020

GFR categories (ml/min/1.73 m²)				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g (<3 mg/mmol)	30–300 mg/g (3–30 mg/mmol)	>300 mg/g (>30 mg/mmol)
	G1	Normal to high	≥90	1.12%	2.26%	4.26%
	G2	Mildly decreased	60–89	2.53%	7.32%	29.42%
	G3a	Mildly to moderately decreased	45–59	15.17%	22.58%	21.36%
	G3b	Moderately to severely decreased	30–44	31.47%	46.94%	41.12%
	G4	Severely decreased	15–29	24.90%	62.86%	83.35%
	G5	Kidney failure	<15	NA	76.23%	84.84%

*Green=Low risk; Yellow=Moderately increased risk; Orange=High risk; Red=Very high risk

SA-PO1073

Screening Programs for Early Detection of CKD: A Systematic Literature Review

Pamela R. Kushner,[1] Christian W. Mende.[2] [1]*University of California Irvine, Irvine, CA;* [2]*University of California San Diego, La Jolla, CA.*

Background: Early detection of chronic kidney disease (CKD) allows intervention to delay progression and other adverse outcomes. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines advise screening high-risk groups with albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR); diagnostic if abnormality in one/both for ≥ 3 months. We investigated CKD screening programs in the US, Canada, Australia, and UK.

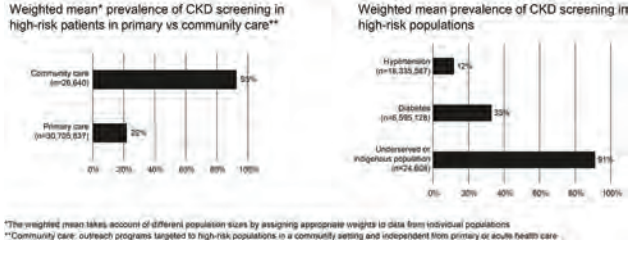
Methods: Systematic literature review (SLR) of CKD screening programs in patients with diabetes and/or hypertension between Jan 2018 – Oct 2023.

Results: Of 2361 records screened, 52 full-text reports were assessed, and 23 publications (of 21 studies) included. In addition to diabetes and/or hypertension (13 studies), high-risk groups included indigenous populations (4 studies), underserved areas (3 studies) and older population (1 study). Of the 21 studies, 5 reported screening prevalence and 16 described screening programs. Also, 7 studies reported 1 test (ACR or eGFR), 9 used ACR + eGFR, 5 used ACR + serum creatinine. Of the 16 screening programs, 9 were in community care and 7 in primary care. Prevalence (mean weighted) of screening in high-risk patients was 4-fold greater in community vs. primary care. Low screening rates were reported for patients with hypertension and diabetes (Fig. 1). Of 10 studies reporting assessment frequency, only 3 repeated ACR within 1 year.

Conclusions: This SLR suggests a low prevalence of CKD screening of high-risk patients, particularly in primary care. Contrary to KDIGO guidelines, approximately one-third of studies performed incomplete screening (only 1 test); follow-up testing was infrequent or not reported. Inadequate testing for CKD and lack of adherence to KDIGO guidelines are delaying CKD diagnosis and appropriate early therapy.

Funding: Commercial Support - Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) & Lilly, USA LLC

Fig. 1: Prevalence of CKD screening in high-risk patients



*The weighted mean takes account of different population sizes by assigning appropriate weights to data from individual populations
**Community care: outreach programs targeted to high-risk populations in a community setting and independent from primary or acute health care

SA-PO1074

Hypertensive Patients Should be Routinely Screened for CKD

Adi Leiba,[1,2] Avital Angel-Korman.[1,2] [1]*Assuta Ashdod Hospital, Ashdod, Israel;* [2]*Ben-Gurion University of the Negev Faculty of Health Sciences, Beer-Sheva, Israel.*

Background: Hypertension is a well-established risk factor for CKD, but awareness for early detection of CKD especially among non-diabetic hypertensive patients is lacking. Early detection of CKD can promote treatment with novel therapies such as SGLT-2 inhibitors or new MRAs. The aim of this study was to estimate referral rates and the extent of positive screening results for CKD (i.e. reduced eGFR and/or proteinuria), in a large scale community-based registry.

Methods: In this real-life, retrospective, observational study we utilized the Maccabi Healthcare Services (MHS) database. Included in the study, were patients over the age of 18 years, who had entered the MHS HTN registry in the past 10 years before February, 2024, and did not have diabetes or CKD. Early detection of CKD was defined as a PCP referral for blood test (serum creatinine (sCr)) and urine protein quantification (either uACR, uPCR or 24 hour urinary albumin/protein) within 12 months of HTN diagnosis, between 2014 and 2024. CKD diagnosis was defined according to the KDIGO guidelines as eGFR<60ml/min/1.73 square meter and/or urine albumin >30 mg or protein >150 mg per 24 hours or as a ratio to urine creatinine. Only those who had both a sCr test for eGFR estimation and a urine test for protein quantification, were considered as being screened for early detection of CKD.

Results: A total of 1,875,479 MHS members were over 18 years on February 2024, and 121,056 of them had a diagnosis of HTN within the past 10 years (2014-2024). Of those, 76,425 (63.1%) examinees had both urine and blood tests sent within a year after HTN diagnosis. CKD according to the above indices was found in 9958 examinees (13%). Importantly, lifetime prevalence of CKD within all adult MHS members is significantly lower - 5.7%, which indicates the extra burden of disease among those with HTN. Considering a 13% prevalence of CKD in the hypertensive population, early referral of the remaining 36.9% of patients who were not sent for the full blood and urine workup, would be expected to detect an extra 5815 patients with CKD (13% of 44,631 patients), 4.8% of the overall hypertensive cohort.

Conclusions: A one-time referral of every new hypertensive patient, for both urinary sCr and urine protein estimation, is a cost effective and simple tool for early CKD detection and may have a positive impact on CKD progression and cardiovascular complications of both HTN and CKD.

SA-PO1075

Assessment of Public Interest in CKD: A Google Trends Analysis

Cristian A. Milla, Mohammad W. Abushawer, Arfa Amjad, Thin Thin Soe, Dinah Goodman. *SUNY Downstate Health Sciences University, New York City, NY.*

Background: Chronic Kidney Disease (CKD) is a critical global health problem, that affects millions of patients worldwide, leading to severe health complications and increased mortality. Understanding the public interest in CKD is essential for awareness and prevention efforts. Google Trends serves as a valuable tool in this regard, offering insights into the general public's search behaviors and interest patterns, providing a resource for healthcare professionals and policymakers to tailor their strategies more efficiently.

Methods: Google Trends was utilized to analyze searches for the term "chronic kidney disease", from January 2004 to January 2024, focusing on English-Language queries within the United States of America. The gathered data encompassed search frequency over time, location distribution, frequent topic of interest, and related searches. Search frequency is reported on a normalized scale, with a value of 100 representing peak in search popularity.

Results: The number of google searches related to the term chronic kidney disease has significantly increased over time, from a mean of 14% in 2004 to 76% interest in 2024. Regarding interest by subregion in 2024, the state of West Virginia leads the frequency of searches, followed by South Dakota, Alabama, Tennessee and Mississippi. Top searched terms by frequency were the following: chronic kidney disease stage 3, chronic kidney disease treatment, what is kidney disease, assessment of kidney function, and dialysis.

Conclusions: The substantial increase in Google searches for chronic kidney disease over the past two decades reflects a rising public interest and awareness of CKD. This trend, particularly pronounced in some geographic regions, highlights the public's growing concern and need for information about CKD stages, treatments, and kidney function assessment. Physicians should integrate this information to provide better patient care by addressing common concerns, offering targeted education and tailoring prevention strategies.

SA-PO1076

Advancing Nephrology Care Access for Veterans: Implementation and Insights from a Telenephrology Program

Melissa L. Swee,[1,2] Mary V. Sarrazin,[1,2] M. Lee Sanders,[1,2] Heather Reisinger,[2] Kantima Phisitkul,[1] Angie R. Thumann,[1] Bradley S. Dixon,[1] Diana I. Jalal.[1,2] [1]*Iowa City VA Medical Center, Iowa City, IA;* [2]*University of Iowa Health Care, Iowa City, IA.*

Background: Chronic kidney disease (CKD) is a significant health concern among Veterans, often compounded by delayed nephrology referrals. A Telenephrology program was introduced at the Iowa City Veterans Affairs Health Care System (ICVA) in 2018. A dashboard alerted the nephrology service when CKD or acute kidney injury were noted prompting either an e-consult or an outpatient consult to the nephrology service. Here, we evaluated the impact of the program on nephrology encounters.

Methods: We conducted a retrospective cohort study involving Veterans receiving care in Veterans Integrated Service Network (VISN) 23, which consists of 8 medical centers and affiliated clinics. The cohort included patients with at least one eGFR <60 during from 2014 to 2016. Patients with nephrology encounters before 2014 or who died before 2016 were excluded. Annual outpatient virtual and face to face nephrology encounters from 2016 to 2020 were identified. Poisson regression was used to compare nephrology encounters per months alive before and after the intervention to other VISN 23 sites during the same time period, controlling for patient characteristics.

Results: We identified 5161 eligible patients in Iowa City and 44618 in other VISN 23 sites. Veterans in ICVA were older with higher rates of heart failure, peripheral vascular disease, and hypertension. Nephrology encounters rose by ~78% and 114% during 2018-2019 and 2019-2020 compared to the average annual encounters during 2016-2018 [Rate ratios were 1.78 (95% CI, 1.62-1.95; p<.001) and 2.14 (95% CI, 1.97-2.32; p<.001)]. Compared to other sites in VISN23, nephrology encounters per month increased to a lesser extent in ICVA. In the period March 2018-February 2019, the increase in encounters in ICVA was 86% of that observed in other VISN 23 sites (relative rate = 0.86; 95% CI, 0.79-0.95; p<.001). During 2019-2020, the rate of increase in Iowa City was 85% of the increase observed in other VISN 23 sites (relative rate = 0.85; 95% CI, 0.78-0.93; p<.001).

Conclusions: The Telenephrology program in Iowa City improved access to nephrology care but the annual increase in virtual and face-to-face encounters was smaller than seen in other VISN23 facilities. Future studies will explore the impact of the Telenephrology program on clinical outcomes.

Funding: NIDDK Support, Private Foundation Support

SA-PO1077

Prevalence of Albuminuria in US Adults with Obesity and Its Possible Impact on CKD Screening: A Cross-Sectional Analysis of NHANES Data, 2003-2020

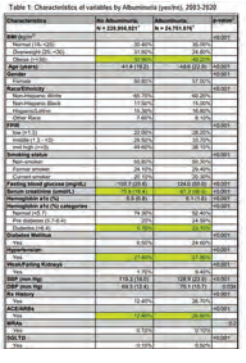
Aisha Batool,[1] Hafsa Habib,[1,2] Shahzad Chaudhry,[3] Ashraf El-Meanawy.[1]
[1]Medical College of Wisconsin, Milwaukee, WI; [2]Nishtar Medical College and Hospital, Multan, Pakistan; [3]Advocate Aurora Health Inc, Milwaukee, WI.

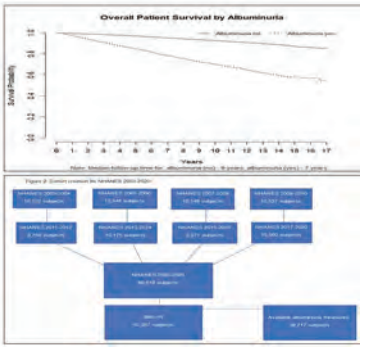
Background: About 37 million US adults are reported to have CKD and those with proteinuric CKD have higher mortality. There's no agreement on whether albuminuria screening is beneficial for the general US population or individuals who are obese. Our study aims to determine a correlation between obesity and albuminuria, and b) relationship of albuminuria with mortality.

Methods: This study utilized data from NHANES 2003-2020 with urine albumin and creatinine ratio>30 (uACR) to identify albuminuria and BMI>30 to identify obesity. The final dataset comprised 59,717 adults. Employing a series of multivariable-adjusted regression models, we assessed the IDR to evaluate the association between uACR and obesity with overall mortality.

Results: The demographic analysis indicated that among those with albuminuria, 40% were obese, 57% women, and 61% were low-middle income category based on FPIR. Within the albuminuria group, 24% were diabetics, with an average A1C level of 6.1%. Additionally, 52% of those with albuminuria were identified as hypertensive and only 26% were utilizing RAAS blockade. Logistic regression model weighted results by albuminuria and obesity when adjusted for socioeconomic risk factors OR of 1.36 with 95% CI 1.23-1.50 p value <.001. The age-adjusted mortality rate exhibited an upward trend across albuminuria group.

Conclusions: In a nationally representative US adult population, we have observed robust, progressively increasing corelation between albuminuria and obesity. We have also observed that individuals with albuminuria have higher likelihood of all-cause mortality within all segments of sex, race or ethnicity, and concurrent health conditions. Our study underscores the underutilization of albuminuria-reducing agents in approximately 75% of individuals with albuminuria. This emphasizes a missed opportunity for screening a potentially at-risk population of obese individuals who could benefit from therapies aimed at reducing albuminuria.





SA-PO1078

Factors Associated with CKD Awareness and Impact on Kidney Prognosis

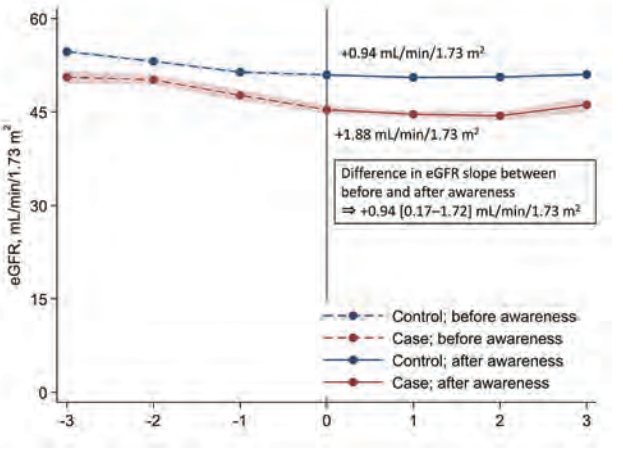
Takahiro Imaizumi, Akiko Hattori, Shoichi Maruyama. *Nagoya Daigaku, Nagoya, Japan.*

Background: Behavioral change and awareness of healthy living are important elements for caring for patients with chronic kidney disease (CKD). Despite the importance of CKD awareness, few patients, even those diagnosed with CKD, are aware of their disease. We aimed to investigate the factors associated with CKD awareness and its impact on renal prognosis. In this study, we focused on urine tests and nutritional guidance, which are typical clinical quality indicators in CKD practice

Methods: The study examined the proportion of participants with CKD who underwent health checkups from 2013 to 2022 and responded that they were aware of CKD in the questionnaire. The outcome was the change from CKD "unaware" to "aware", and multivariable logistic regression analysis was used to examine the association of urine testing or nutritional guidance with CKD awareness. A control group was randomly selected from the unaware group and matched for age, sex, and estimated glomerular filtration rate (eGFR). The change in eGFR slopes before and after the occurrence of awareness was compared using mixed-effects models.

Results: Of the 13,489 participants, 372 (2.8%) were aware of having CKD at baseline, and of the 1,614 participants who had CKD-related diseases in their claims data, only 316 (19.6%) were aware of their CKD status. The odds ratios of urine test or nutritional guidance associated with the occurrence of awareness were 1.72 (95% confidence interval [CI] 1.13–2.62) and 2.91 (95% CI 1.41–6.01), respectively. Compared to the pre-occurrence of awareness, the post-occurrence eGFR slope improved by 0.94 mL/min/1.73 m^2 per year (95% CI 0.17–1.72, P=0.017) (**Figure**).

Conclusions: Our findings suggest that urine tests and nutritional guidance may promote CKD awareness, which may help slow its progression.



SA-PO1079

Development and Validation of a Prediction Model of Early Mortality for Conservative Management vs. Dialysis among US Veterans with Advanced CKD

Connie Rhee,[1] Yoko Narasaki,[1] Amy S. You,[1] Csaba P. Kovesdy,[2] Alejandra Novoa Vargas,[1] Danh V. Nguyen,[3] Kamyar Kalantar-Zadeh.[4] *[1]University of California Los Angeles, Los Angeles, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]University of California Irvine, Irvine, CA; [4]Harbor-UCLA Medical Center, Torrance, CA.*

Background: Given that dialysis may result in greater healthcare utilization, loss of physical function/independence, and high early-mortality in certain subgroups (elderly, multi-morbid), there is growing interest in conservative management (CM) as an alternative patient-centered treatment strategy for advanced CKD. We developed and validated a prediction model to provide individualized predicted probability of survival with CM vs. dialysis transition among a national cohort of advanced stage CKD patients.

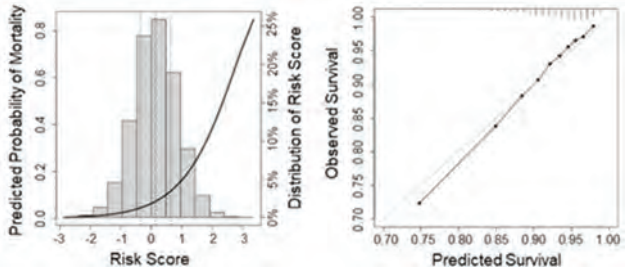
Methods: Using the national VA database linked to USRDS and Medicare data, we developed a risk prediction tool for mortality in US Veterans with advanced CKD (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis (defined as non-receipt vs. receipt of dialysis within 2-years of 1st eGFR <25) over 2010-19. Patients were divided into a 2/3rds development set and a 1/3rd validation set. Prediction models for 1-year mortality were developed on the basis of survival data up to 2-years after the index eGFR date (1st eGFR <25) using Cox models.

Results: Among a cohort of 61,118 Veterans (43,197 vs. 17,921 receiving CM vs. dialysis), selected characteristics associated with higher overall mortality included older age; higher index eGFR, UACR, and VA frailty index; faster eGFR decline; lower serum albumin and BMI; prior 1-year hospitalization; presence of heart disease, sepsis,

and tobacco use; and dialysis transition. Model discrimination was good with similar C-statistics in the development and validation cohorts: 0.704 (95% CI 0.697-0.708) and 0.704 (95% CI 0.696-0.711), respectively. Model goodness-of-fit tests showed adequate fit in the validation cohort (P=0.65). Risk score and model calibration plots are shown in Fig 1.

Conclusions: In a national cohort of US Veterans with advanced CKD, we developed a clinical prediction tool for survival for CM vs. dialysis to inform individualized treatment and improve the shared decision-making process between clinicians and patients.

Funding: NIDDK Support



SA-PO1080

Medication Reconciliation at the Time of Admission and Discharge by Pharmacists in the Adult Nephrology Wards of a Referral Hospital in Iran

Iman Karimzadeh.[1,2] *[1]Shiraz University of Medical Sciences, Shiraz, Fars, Islamic Republic of Iran; [2]University of Pittsburgh, Pittsburgh, PA.*

Background: Medication reconciliation is the process of identifying a precise list of drugs taken by a patient and comparing it to his/her current medications. The aim of the present research was investigating the impact of medication reconciliation by pharmacists at both admission and discharge in hospitalized patients with different kidney diseases.

Methods: A prospective, interventional study was conducted in two adult nephrology wards of a teaching, referral hospital in Iran from September 2020 to March 2021. All patients hospitalized in the nephrology ward for at least 1 day received the minimum of one medication during their ward stay within the study period were considered eligible. The best-possible medication history taken from each patient by an educated pharmacist was compared with prescribed medications at the time of ward admission and discharge from the ward. Medications were evaluated for possible intentional as well as non-intentional discrepancies.

Results: At ward admission and discharge, 178 and 134 patients were included. The mean number of un-intentional drug discrepancies per patient at ward admission and discharge was 6.13±4.13 and 1.63±1.94, respectively. The mean ± SD number of prescribed medications for patients before ward admission detected by pharmacist was significantly higher than that by nursing/physician (9.22±4.71 and 6.06±3.53, respectively [P=0.0001]). The number of unintentional medication discrepancies at ward admission has a significant association with the number of comorbidities (P = 0.043) and the number of administered medications (P = 0.023). At the time of ward discharge, only the number of comorbidities was significantly associated with the number of unintentional medication discrepancies (P = 0.031). Drug-drug interactions were observed in 97 (59.49%) of patients. At the time of ward discharge, all 134 subjects were given medication consult.

Conclusions: The rate of reconciliation errors at the time of ward admission and discharge was high in the adult nephrology ward. Implementing medication reconciliation program as a regular practice, preferably by pharmacists, in different phases of patient care in the hospital, especially for patients with numerous comorbidities like kidney diseases, is crucial.

SA-PO1081

Accuracy of Smartphone-Enabled Urinary Albumin-to-Creatinine Ratio (uACR) Testing

Danielle Jeddah,[1] Nicholas J. Bevins,[2] Matan Ronen,[1] Ron Zohar,[1] Navdeep Tangri.[3] *[1]Healthy.io, Boston, MA; [2]Birdrock Laboratories, San Diego, CA; [3]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada.*

Background: Urinary albumin to creatinine ratio (uACR) testing is crucial for diagnosing, staging, and managing chronic kidney disease (CKD), yet testing rates remain short of guideline recommendations. Guidelines recommend semi-quantitative point-of-care testing (POCT) with ≥85% sensitivity when lab access is limited or when POCT offers advantages like convenience, immediate results, and elimination of sample transportation. We evaluated the accuracy of the Minuteful-Kidney Test (MKT), an FDA-cleared, smartphone-enabled, semi-quantitative test of uACR for home use, improving accessibility to kidney health assessment

Methods: We conducted a diagnostic study comparing the Minuteful-Kidney Test to the Beckman Coulter AU 480 Analyzer, a gold standard laboratory method, in a population at risk for kidney disease. From January to March 2024, we analyzed 615 urine samples in an accredited U.S. laboratory. Inclusion criteria were medical conditions or risk factors for kidney damage based on EMR data. Exclusion criteria were extreme urine pH, diluted samples, and samples with preservatives. Sensitivity, specificity, PPV, and NPV were calculated

Results: Among 615 samples, 60 met exclusion criteria, leaving 555 for analysis. The Minuteful-Kidney Test showed a sensitivity of 96.2% (95% CI 94.2%-98.2%) and specificity of 84.2% (95% CI 80.7%-87.7%), with an NPV of 98.6% (95% CI 97.4%-99.8%) and PPV of 66.8% (95% CI 60.3%-73.3%). Albuminuria was identified in 24.9% (95% CI 21.3-28.5) of the samples based on the quantitative device. The test accurately classified 85.6% of samples into KDIGO albuminuria categories, identifying all 25 (100%) laboratory-confirmed A3 samples as abnormal

Conclusions: The Minuteful-Kidney Test demonstrated high sensitivity (96.2%), exceeding the guideline-required 85%, and robust specificity for detecting albuminuria in high-risk CKD populations. The device can streamline CKD screening and enable early intervention, for patients with or at risk for CKD.

Funding: Private Foundation Support

Comparative Analysis of Minuteful - Kidney Test and Quantitative Analyzer for Albuminuria Detection

	Beckman Coulter AU 480 Analyzer				
	Normoalbuminuria	Albuminuria		Total	
Minuteful - Kidney Test	(A1) uACR ≤30 mg/g	(A2) uACR 30-300 mg/g	(A3) uACR ≥300 mg/g		
(A1) uACR ≤30 mg/g	351	5		356	NPV 98.6%
(A2) uACR 30-300 mg/g	65	102	3	170	PPV 66.8%
(A3) uACR ≥300 mg/g	1	6	22	29	
Grand Total (n)	417	113	25	555	
Positivity Rate 24.9%	Specificity 84.2%		Sensitivity 96.2%		

SA-PO1082

Predictive Value of Current KDIGO CKD Screening Criteria in Women and Men across Ethnic Groups: The HELIUS Study

Taryn G. Vosters,[1] Vianda S. Stel,[1] Kitty J. Jager,[1] Liffert Vogt,[1] Frans J. van Ittersum,[2] Bert-Jan Van den Born,[1] Irene van Valkengoed.[1] *[1]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [2]Amsterdam UMC Locatie VUmc, Amsterdam, Netherlands.*

Background: Unequal burden of chronic kidney disease (CKD) amongst women and men and amongst ethnic groups poses a public health issue. Early detection of disease enables faster initiation of treatment as well as efficient deceleration of further disease progression. It is unclear whether the current screening guidelines are equally detecting women and men across ethnic groups with CKD.

Methods: Cross-sectional analyses were performed to determine the predictive value of the current available screening criteria recommended by KDIGO 2024, hypertension, diabetes mellitus and cardiovascular disease, in 12384 women and 9046 men from the HELIUS Study (2011-2015, Amsterdam, the Netherlands). Additionally investigating whether the optional variables such as low education, obesity, high risk occupations and genetic risk factors improve detection rates. This was done using Poisson regression analyses, including Likelihood ratio tests and AIC estimations in women and men. Significantly associated variables were added to the base criteria to create a final model. Base- and final model AUC, sensitivity, specificity, positive- and negative predictive values in women and men and across ethnic groups were compared.

Results: Current screening criteria showed higher sensitivity (Sens: 80.4 vs 58.3) and lower AIC (AIC: 3419.6 vs 4273.0) rates in men than women. Both low educational level and obesity in women, but not high risk occupations and genetic risk factors, significantly improved the prediction measures. As was the case for obesity in men. An improvement in predictive measures was observed for the final models (AUC : 0.64 (basemodel women); 0.66 (final model women); 0.75 (base model men); 0.76 (final model men)). These results were consistent across ethnic groups.

Conclusions: Current screening criteria may not be equally detecting women and men across ethnic groups. Different optional criteria, specifically low educational level for women or obesity for men, may improve detection rates in women and men.

Funding: Private Foundation Support

SA-PO1083

Health Care Costs and Utilisation for CKD among Hospitalised Patients in the Republic of Ireland

Leonard Browne,[1] Meera Tandan,[1] Rajiv Saran,[2] Austin G. Stack.[1,3] National Kidney Disease Surveillance System and Quality Assurance Programme. *[1]University of Limerick, Limerick, Ireland; [2]University of Michigan Michigan Medicine, Ann Arbor, MI; [3]Health Service Executive, Dublin, Ireland.*

Background: To facilitate effective healthcare planning and resource allocation, comprehensive knowledge of the frequency, length of stay and costs of inpatient hospitalisation for chronic kidney disease (CKD) is crucial. To fill this deficit, we assesed rates of hospitalisation, length of stay (LOS), and associated costs for all CKD-related hospitalisations in Ireland.

Methods: A retrospective study of the National Hospital In-Patient Enquiry (HIPE) database in 2022. Non-coded hospitalisations and patients aged <1 year were excluded. All ICD-10 coded hospital admissions with a principal or additional CKD diagnoses were included. Age-standardised rates of hospitalisation and inpatient mortality were computed. We assessed hospitalisation, inpatient mortality, length of stay and costs by demographic factors, Charlson comorbidity score and region.

Results: In 2022, 13.1% of all coded hospitalisations in Ireland (n=225,164/1,711,564) recorded CKD as a principal diagnosis and/or additional diagnoses, costing €427 million. CKD-related hospitalisations excluding dialysis and transplantation as principal diagnoses represented 2.1% of all hospitalisations nationally, with 35,409 admissions from 23,261 patients, culminating in a total stay of 422,738 days, costing €320.3 million. The average LOS was 11.9 days and increased from 4.5 to 16.1 days with rising Charlson Comorbidity score. Stratified by comorbidity score, admissions, LOS, and costs rose significantly with increasing comorbidity burden. The leading principal diagnoses in 2022, when CKD was listed as an additional diagnosis included acute kidney failure, sepsis, heart failure, diabetes and pneumonia. CKD hospitalisation rates and inpatient mortality were higher in men and increased with age. Age standardised hospitalisation rates varied significantly across health regions and were lowest in the West and highest in the Midland regions of Ireland, P<0.01).

Conclusions: CKD exerts a substantial impact on healthcare utilisation and cost to the Irish health system. Increasing length of stay, resource utilisation, and in-hospital mortality, are especially common in older patients with higher comorbidity burden. Demographic and regional disparities in CKD hospitalisation rates highlight the need for targeted interventions and healthcare planning to address this public health issue effectively.

Funding: Government Support - Non-U.S.

SA-PO1084

Statin Use in Patients with CKD (Nondialysis) in Ambulatory Care: A Quality Improvement Project at a Rural Community Hospital

Waleed Hassan, Vernon Rayford. North Mississippi Medical Center. *North Mississippi Medical Center, Tupelo, MS.*

Background: Chronic kidney disease (CKD) is a known risk factor for cardiovascular disease (CVD). Statins have been shown to reduce CVD risk in CKD (Non-Dialysis) with or without diabetes.

Methods: This is a quality improvement project at North Mississippi Medical Center as a retrospective analysis of 304,575 observations in a total of 178,722 patients. Data were extracted from an office or wellness visit at any Epic clinic between 7/1/2021 and 7/1/2022. CKD diagnosis was made based on an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 for > 3 months. The estimated GFR was calculated by the CKD-EPI creatinine equation (2021). The 10-year atherosclerotic cardiovascular (ASCVD) risk was calculated using Pooled Cohort Equations, the risk was categorized as <5%, 5-7.4%, and ≥7.5-10% in patients who met CKD criteria.

Results: Out of the total observations of 119,557 representing 43,557 patients, 8538 patients (20%) met the CKD criteria by eGFR. Demographic characteristics are shown in table 1. For patients with CKD (Non-Dialysis) and diabetes with a 10-year ASCVD risk of ≥7.5-10%, the majority (~75%) were on statins versus 18% being not on statins (figure1). Differently, only 65 % of CKD patients without diabetes with a 10-year ASCVD risk of ≥7.5-10% were found to be taking statins versus 25% not on statins (figure2).

Conclusions: Statin is an underused protective shield in patients with CKD (Non-Dialysis) in the ambulatory setting.

Table 1. Demographic characteristics of patients who meetCKD criteria by eGFR

	n=8,538
Age, median (IGR), y	75(68-81)
Gender	
Female *n* (%)	5,823 (68)
Male n (%)	3,437 (37)
Race	
White *n* (%)	6,365 (68)
Black or African American *n* (%)	2,518 (29)
American Indian or Alaska native *n* (%)	114 (1.34)
Unknown or decline to answer *n* (%)	75 (< 2%)
Age group	
< 40	39 (<1)
40-60	943(11)
< 60	7,556 (89)
Last BMI kg/M2, median (IGR)	29.6 (25.65-34.35)
Last SBP, median (IGR)	130 (120-140)
Last DBP, median (IGR)	74 (66-80)
Have a CKD diagnosis documented.	
Yes *n* (%)	5,789 (68)
Diabetes Mellitus	
Yes *n* (%)	4,578 (54)
Hypertension	
Yes *n* (%)	7,630 (89)

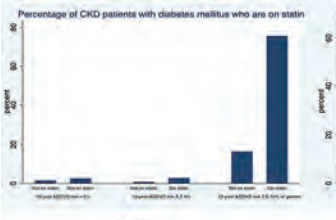


Figure 1.

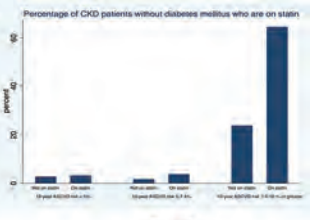


Figure 2.

SA-PO1085

Identifying Barriers to SGLT2 Inhibitor Use in Patients with CKD: A Qualitative Analysis

Rema Elmostafa, Justin A. Dower, Angela M. Victoria Castro, Lisa Chan, Gabriella M. Riwes, Shelli L. Feder, Sherry Mansour. *Yale University, New Haven, CT.*

Background: Despite clearly stated guidelines by KDIGO recommending Sodium-glucose cotransporter-2 inhibitor (SGLT2i) use in CKD, prescription of SGLT2is among providers remains suboptimal. In this study, we aimed to understand the utilization patterns of SGLT2is and to identify barriers hindering their broader implementation.

Methods: We conducted semi-structured interviews with providers from January to April 2024 in a large academic center in New Haven, CT. Participants were asked open-ended questions about their experiences with prescribing SGLT2is, what factors facilitated or limited their use, and ideas on future directions to promote SGLT2i utilization. Each interview was recorded and transcribed. We used a hybrid approach of deductive and inductive content analysis using NVIVO analytic software.

Results: A total of 8 providers participated in the semi-structured interviews. Providers included cardiologists, nephrologists and internal medicine physicians and nurse practioners. The median age of providers was 33 (range: 29-63) years. The cohort consisted of 50% women, with 15% identifying as Black and 29% as Hispanics. Provider comfort level and preference to defer to a specialist were mentioned most frequently as barriers to prescription. Other barriers included side effects, medication costs, and polypharmacy. Most providers believed that SGLT2is were well-tolerated and had significant benefits in slowing CKD progression, but most reported that KDIGO guidelines were not promoted in their workplace. The most common solutions provided by participants to overcome barriers to using SGLT2is were education for providers and patients, EPIC pathways to guide provider decision, and cost assistance for patients.

Conclusions: While most providers agreed that SGLT2is are essential in the treatment of CKD, there exists a need and opportunity to improve education and comfort around their use among providers and patients.

SA-PO1086

Effect of Oral Absorbent Therapy on Kidney Progression According to the Cause of CKD

Hyunjin Cho, Jee Young Lee, Young-Il Jo. *Konkuk University Medical Center, Gwangjin-gu, Seoul, Republic of Korea.*

Background: Oral absorbent therapy with DW-7202 (Renemezin®) and AST-120 (Kremezin®) slows the progression of CKD. The aim of this study is to investigate whether the mitigating effect of oral absorbents on CKD progression varies according to the etiology of CKD.

Methods: This retrospective study included 490 patients at Konkuk University Medical Center who took absorbents for over three months between January 1, 2016, and August 31, 2023. Serum Cr levels were compared annually from the start of treatment until April 30, 2024, or the initiation of renal replacement therapy. The slope of serum Cr was compared among CKD patients with different causes using multilevel mixed-effects linear regression.

Results: The most common cause of CKD was DM (54.9%), followed by HTN (22.7%), GN (7.7%), ADPKD (2.8%), and unknown etiology (11.9%). Baseline Cr levels were not significantly different among the groups (P=0.39), but were significantly different after one year (P=0.02). After drug administration, serum Cr levels significantly increased compared to baseline in all groups (Figure 1, p<0.05), with the highest increase observed in the GN group. Compared to the GN group, the slope of serum Cr increases was significantly lower in the HTN, DM, ADPKD, and unknown etiology groups (Table 1, p<0.01).

Conclusions: These findings suggest that oral absorbent therapy has different effects depending on the cause of CKD. The treatment significantly alleviated CKD progression in patients with HTN, DM, ADPKD, and unknown etiology compared to those with GN.

Funding: Commercial Support - DAEWOONG PHARMACEUTICAL CO.,LTD

Table 1. Comparison of the Slope of Creatinine Increase in Each Etiology Group Following Oral Absorbent Therapy

Cause of CKD	Slope of Creatinine Increase (μmol/L/year) (95% CI)	p Value
HTN	19.3 (4.63 - 33.8)	<0.01
DM	28.3 (18.3 - 38.3)	<0.01
GN	84.4 (62.2 - 106.6)	Reference
ADPKD	22.9 (-12.7 - 58.4)	<0.01
Unknown	19.6 (-1.48 - 40.7)	<0.01

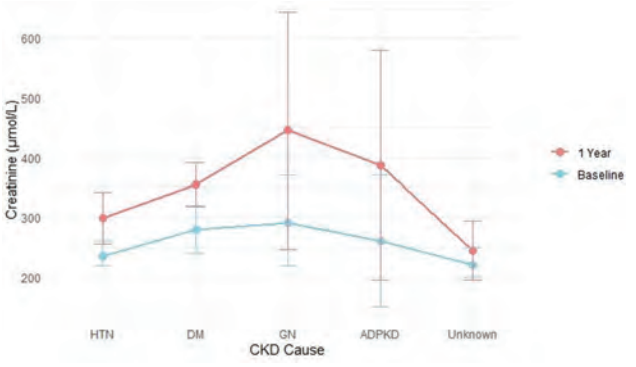


Figure 1. Changes in Serum Cr Before and After Drug Therapy Over One Year in Each Etiology Group

SA-PO1087

Hyperuricemia Treatment Reduces ESKD Risk and Mortality in Patients with CKD: A Causal Inference Analysis Using the G-formula Approach

Ara Ko,[1,2] Jeonghwan Lee,[3,2] Chun Soo Lim,[3,2] Jung Pyo Lee.[3,2] *[1]Seoul National University Hospital Department of Internal Medicine, Jongno-gu, Seoul, Republic of Korea; [2]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [3]Seoul National University Hospital Boramae Medical Center, Seoul, Republic of Korea.*

Background: Hyperuricemia is recognized as an independent predictor of chronic kidney disease(CKD), but the role of treating it in CKD, especially when asymptomatic, remains under debate. The g-formula, valuable for epidemiological causal inference, allows estimation of effects in complex relationships among time-varying covariates. We used the g-formula to assess the impact of treating hyperuricemia in CKD patients using urate-lowering agents(ULAs).

Methods: Employing the g-formula, we analyzed data from 27,260 CKD patients to build regression models, evaluating relationships among time-varying covariates: serum urate(sUA), creatinine, and ULA prescription status, measured every 6 months. We also adjusted for time-invariant factors like diabetes and hypertension. Our focus was the impact of various strategies for managing hyperuricemia (treating if sUA ≥7, 8, 9, or 10mg/dL, or never treating) on end-stage kidney disease(ESKD) and all-cause mortality, supported by 1,000 bootstrap replicates for 95% confidence intervals(CIs).

Results: Of the cohort, 5,361 patients had been prescribed allopurinol, febuxostat, or benzbromarone. We found that hyperuricemia treatment generally decreased ESKD and all-cause mortality risks compared to never treating. Lower sUA thresholds were linked to dose-responsive decrease in risk, particularly at 7mg/dL [RR of 0.960 for ESKD (95% CI: 0.956 to 0.964), and 0.988 for mortality (0.984 to 0.992) compared to never treating]. Compared to no intervention, initiating treatment ≥9 or 10mg/dL, or never treating, significantly increased ESKD and mortality with a protective effect observed only at the threshold of 8mg/dL or below.

Conclusions: Our study demonstrates that treating hyperuricemia in CKD patients significantly reduces the risk of ESKD and mortality. This suggests potential harm in not treating hyperuricemia at urate levels of 9mg/dL or higher.

Outcome	Intervention	Observed risk*	Risk†	Risk ratio (RR)	95% CIs of RR	
ESRD	No intervention‡†	0.1719	0.1833	1	1	1
	Never treating	-	0.1864	1.0205	1.0158	1.0253
	Treating if sUA ≥10mg/dL	-	0.1851	1.0118	1.0086	1.0144
	Treating if sUA ≥9mg/dL	-	0.1841	1.0052	1.0033	1.0062
	Treating if sUA ≥8mg/dL	-	0.1825	0.9945	0.9926	0.9953
	Treating if sUA ≥7mg/dL	-	0.1502	0.9755	0.975	0.9835
All-cause mortality	No intervention‡†	0.2736	0.2689	1	1	1
	Never treating	-	0.2711	1.0042	1.0018	1.0065
	Treating if sUA ≥10mg/dL	-	0.2705	1.0021	1.0007	1.0033
	Treating if sUA ≥9mg/dL	-	0.27	1.0002	0.9998	1.0007
	Treating if sUA ≥8mg/dL	-	0.2691	0.9971	0.9959	0.9982
	Treating if sUA ≥7mg/dL	-	0.2678	0.9921	0.9885	0.9956

Table 1. Simulated risk estimates using the g-formula under hypothetical interventions on management of hyperuricemia in CKD patients

*1-year cumulative risk calculated based on the observed data
†Risks estimated by the g-formula
‡"No intervention simulation" in the g-formula uses real-world data for time-varying covariates instead of covariate estimations to represent the real-world practice. If the risk under "no intervention simulation" is close to the observed risk, it suggests the absence of model misspecification.

SA-PO1088

Renin-Angiotensin System Blockade Does Not Alter Long-Term Kidney Outcomes in Sickle Cell Disease

Kabir O. Olaniran. *The University of Texas Southwestern Medical Center Department of Internal Medicine, Dallas, TX.*

Background: Sickle disease (SCD) is associated with faster kidney function decline compared to normal hemoglobin phenotypes. The role of renin angiotensin system inhibitors (RASI) in modifying long-term kidney outcomes in SCD is not well described despite several studies showing antiproteinuric effects of RASI in SCD. This study aimed to describe long-term kidney outcomes in adult SCD patients on RASI.

Methods: A single-center observational study of adult patients with SCD on RASI (exposure) and SCD not on RASI (reference) between 2010 and 2021 was performed. Inclusion criteria were patients with a baseline eGFR≥15 ml/min/1.73m^2, ≥3 estimated glomerular filtration rate (eGFR) values, and ≥1 year between first and last eGFR values. The outcomes of interest were the difference in the mean change in eGFR per year (evaluated using linear mixed models), rapid eGFR decline (≥3 ml/min/1.73m^2/year), incident stage 5 chronic kidney disease (CKD), and mortality (described using Cox proportional hazard models). Propensity score matching (1:3) adjusted for 16 baseline characteristics. Time-updated RASI use was utilized in all models. All other covariates (demographics, comorbidities, medications, labs) were baseline values.

Results: In total 1,960 SCD patients (476 RASI, 1,484 reference) were identified. After matching, 442 reference patients were used. Matched cohort median follow-up was 4.6 (IQR 2.5-8.3) years with a median of 24 (IQR 10-60) eGFR values, a mean±SD age of 43±16 years, 59% female, and mean baseline eGFR±SD of 97±29 ml/min/1.73m^2. All results were compared to the matched reference. The adjusted mean eGFR change in RASI users was +0.02 (95% confidence interval [CI] -1.06 to +1.08) ml/min/1.73m^2/year. Rapid eGFR decline (hazard ratio [HR] 0.80; 95% CI 0.51-1.25), incident stage 5 CKD (HR, 0.28; 95% CI 0.06-1.21) and mortality (HR, 0.61; 95% CI 0.30-1.25) were not significantly different. Among RASI users only, the adjusted mean eGFR change pre- vs. during-RASI use was -0.13 (95% CI -0.30 to +0.03) ml/min/1.73m^2/year.

Conclusions: In the largest observational study to date of adult SCD RAS blockade, RASI use was not associated with adverse or improved long-term kidney outcomes compared to no RASI use. Therefore, if RASI are indicated in SCD, adverse long-term kidney outcomes should not be a concern. Conversely, RASI should not be started solely to slow kidney function decline in SCD.

Funding: Other NIH Support - KL2

SA-PO1089

Kidney and Mortality Outcomes on Renin-Angiotensin System Inhibitors in Nonproteinuric CKD: Findings from the CRIC Study

Rachel Shulman, Debbie L. Cohen, Wei Yang, Peter P. Reese, Jordana B. Cohen. *University of Pennsylvania, Philadelphia, PA.*

Background: The kidney benefits of renin angiotensin system inhibitors (RASIs) in patients with absent or minimal proteinuria in CKD is not known. We evaluated the long-term kidney outcomes and survival in those with non-proteinuric CKD treated with RASIs vs. other antihypertensive drugs.

Methods: Among participants with CKD and less than 0.5 g/day of proteinuria in the Chronic Renal Insufficiency Cohort Study, we evaluated baseline RASI use vs other antihypertensive medications (i.e. intention-to-treat approach) with inverse probability of treatment weighting (IPTW) and Cox proportional hazards modeling to determine the association of RASIs with (1) CKD progression (halving of eGFR, dialysis, or transplant) and (2) all-cause mortality. Secondary analyses included censoring with drug discontinuation (i.e. per-protocol) and a new user, time-updated RASI use approach (i.e. cumulative exposure) to evaluate the association of RASI use with CKD progression.

Results: A total of 2664 participants with non-proteinuric CKD met inclusion criteria. In the baseline RASI use approaches, use of RASIs was not significantly associated with CKD progression. The time-updated approach was underpowered but showed a higher risk of CKD progression among low level RASI users (RASI use during 0-25% of follow-up) vs. non-users but no higher risk of CKD progression among higher level RASI users (RASI use during >25% of follow-up) vs. non-users. RASI users had a lower mortality risk vs. non-users in the per-protocol analysis (adjusted HR 0.63, 95% CI 0.49-0.80) and a non-significantly lower mortality risk among higher level RASI users (>25%) vs. non-users.

Conclusions: Among people with non-proteinuric CKD, RASI use is not associated with CKD progression but may be associated with lower mortality risk compared to other antihypertensive medications. For people with non-proteinuric CKD, RASIs may not provide a kidney benefit, but may still confer a mortality benefit for hypertension management.

Funding: NIDDK Support

Table 1. Risk of kidney events and mortality by RASI use: Intention-to-treat, per-protocol, and cumulative exposure analyses

	Kidney HR (95% CI)	p-value	Mortality HR (95% CI)	p-value
IPTW intention-to-treat analyses				
	1.01 (0.81-1.25)	0.96	0.90 (0.76-1.07)	0.23
IPTW per-protocol analyses				
	0.94 (0.69-1.28)	0.68	0.63 (0.49-0.80)	<0.001
Cumulative exposure analyses: New user cohort				
0% on RASI	Reference		Reference	
0-25% on RASI	2.99 (1.79-4.98)	<0.001	1.49 (0.82-2.69)	0.19
25-50% on RASI	1.67 (0.94-2.96)	0.08	1.00 (0.50-1.98)	0.99
>50% on RASI	1.72 (0.83-3.54)	0.14	0.62 (0.25-1.52)	0.29

Abbreviations: CI, confidence interval; HR, Hazard ratio

SA-PO1090

Kidney Protective Effect of SGLT2 Inhibitors Based on Fractional Excretion of Total Protein

Hideaki Kuno, Go Kanzaki, Saeko Hatanaka, Hirokazu Marumoto, Takaya Sasaki, Kotaro Haruhara, Kei Matsumoto, Kentaro Koike, Hiroyuki Ueda, Nobuo Tsuboi, Takashi Yokoo. *The Jikei University School of Medicine, Tokyo, Japan.*

Background: An initial dipping in eGFR occurs after initiation of SGLT2 inhibitors (SGLT2i), reflecting a decrease in intraglomerular pressure. Changes in proteinuria in response to the initial dipping in eGFR are variable and the impact on renal prognosis is not clear. Fractional excretion of total protein (FETP) which was protein clearance divided by creatinine clearance is an indicator of protein leak that accounts for glomerular filtration rate. This study investigated the association between initial dipping in FETP after initiation of SGLT2i and renal prognosis in CKD.

Methods: This retrospective observational study included 112 CKD patients who received SGLT2i from 2016 to 2022 at our Hospital. The FETP was calculated as follows: FETP = (urinary total protein / serum total protein) / (urinary creatinine / serum creatinine) %. According to the decline in FETP, patients were divided into two groups. The primary outcome was eGFR slope for 2 years (Figure1).

Results: Their median age was 58.0 (interquartile range, 50.0–66.0) years, 69.6 % of which were male. eGFR was 45.0 (33.0–59.9) ml/min/1.73 m^2, and FETP was 0.010 (0.004-0.024) %. The eGFR slope for 2 years was significantly slower in the FETP dipper group than in the non-dipper group (Figure 2). We found that initial dipping in FETP was an independent risk factor for eGFR slope for 2 years in multivariate analysis (P=0.030).

Conclusions: We found that a greater initial dipping in FETP after initiation of SGLT2i was associated with a better renal prognosis. FETP may be a useful and convenient marker that accurately reflects changes in intraglomerular pressure after initiation of SGLT2i.

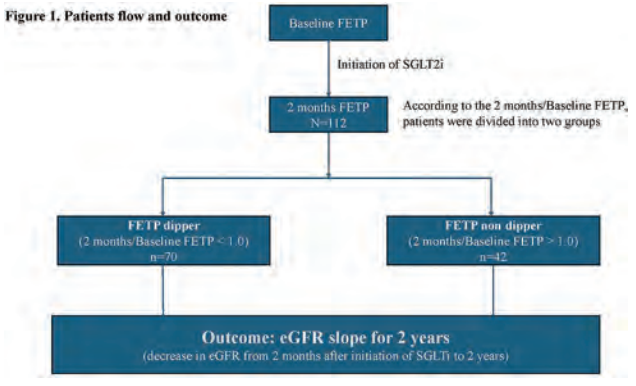


Figure 1

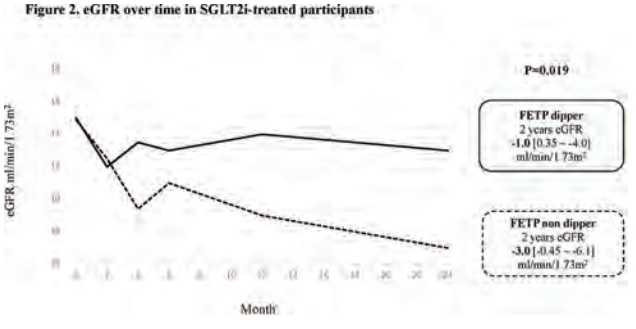


Figure 2

SA-PO1091

Changes in Kidney Function Associated with Discontinuation of Lithium Treatment

Gisli Gislason,[1,2] Olafur S. Indridason,[1] Engilbert Sigurdsson,[1,2] Runolfur Palsson.[1,2] *[1]Landspitali, Reykjavik, Iceland; [2]Heilbrigdisvisindasvid - Haskoli Island, Reykjavik, Iceland.*

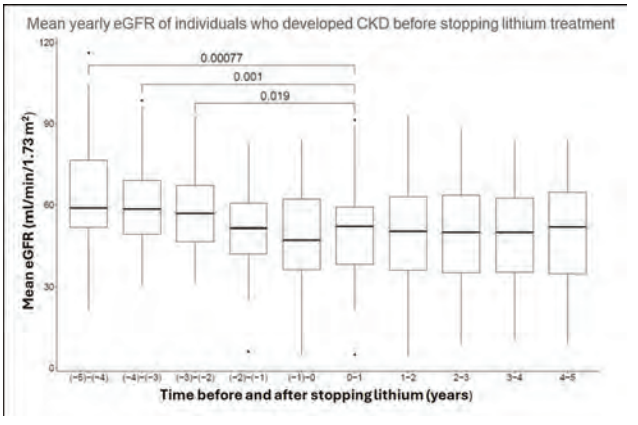
Background: Lithium treatment for mood disorders has been associated with a decrease in estimated glomerular filtration rate (eGFR) and the development of chronic kidney disease (CKD). It is not clear whether or to which degree discontinuation of lithium improves kidney function. This study examined changes in eGFR when lithium treatment is stopped.

Methods: This was a retrospective study of all persons in Iceland using lithium in the years 2003-2018 for whom serum creatinine (SCr) measurements were available more than a year after their last lithium exposure. Lithium exposure was defined as at least one lithium prescription or at least two serum lithium measurements with detectable levels. CKD stages 3-5 were defined according to the KDIGO GFR criteria. eGFR was calculated using the SCr-based CKD-EPI$_{2009}$ equation. Mean eGFR was calculated for every individual in each year from five years before to five years after lithium discontinuation. Analysis of variance was used to assess the difference in eGFR between time periods.

Results: A total of 682 individuals had SCr measurements performed more than a year after lithium discontinuation, 81 of whom had developed CKD stage 3 or above before cessation of lithium treatment. For all individuals the mean eGFR declined from an initial level of 90.4±20.9 ml/min/1.73 m^2 five years before lithium discontinuation to 84.6±24.8 ml/min/1.73 m^2 in the year of lithium discontinuation (p=0.006), but remained stable in the ensuing years, concluding at 83.4±23.7 ml/min/1.73 m^2 five years after lithium was discontinued (p>0.1). In individuals with CKD stages 3-5 before lithium discontinuation, the mean eGFR was 63.5±19.6 ml/min/1.73 m^2 five years before discontinuation, 50.2±16.3 ml/min/1.73 m^2 at the time of discontinuation (p<0.001) and 48.6±21.0 ml/min/1.73 m^2 five years later (Figure).

Conclusions: Discontinuation of lithium therapy appears to stabilize the decline in kidney function and halt the progression of CKD.

Funding: Government Support - Non-U.S.



SA-PO1092

Evaluation of the Effect of Racial Differences on Longitudinal Trajectories of Kidney Function in People with HIV (PWH) on Tenofovir Alafenamide (TAF)-Based Antiretroviral Treatment (ART) Regimens

Myra A. Kleinpeter,[1] Jihad Slim,[2] Sarjita Naik,[3] Xiwen Huang,[3] Amy R. Weinberg,[3] Lauren Temme,[3] Li Tao,[3] Anand Chokkalingam,[3] Samir K. Gupta,[4] Betty Chiang,[3] Robert B. Canada.[5] *[1]Tulane University School of Medicine, New Orleans, LA; [2]Saint Michael's Medical Center, Newark, NJ; [3]Gilead Sciences Inc, Foster City, CA; [4]Indiana University School of Medicine, Indianapolis, IN; [5]The University of Tennessee Health Science Center, Memphis, TN.*

Background: HIV can contribute to chronic kidney disease (CKD), as do some older antiretrovirals. PWH are also subject to traditional risk factors for CKD affecting the general population including but not limited to race, age, and hypertension. Along with variations in prevalence of HIV, racial differences are associated with differences in risk for CKD. We aim to explore the impact of Black race on renal function change in routine clinical practice in a non-CKD population of PWH on TAF-based regimens.

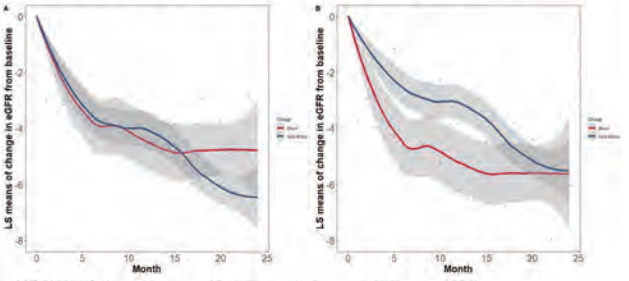
Methods: Individuals with HIV who initiated TAF-based regimens (2015-2023) and had ≥1 estimated glomerular filtration rate (eGFR calculated by CKD-EPI Equation 2021) measurements within 1 year pre- and post-ART initiation were identified using IQVIA Ambulatory EMR-US. Individuals maintained on TAF were followed up until the end of the observation period. eGFR changes were calculated by subtracting post-ART initiation measurements from the pre-initiation 1-year average eGFR and analyzed using a mixed-effects model adjusted for age, sex, and baseline eGFR. Least square means of the adjusted model were plotted.

Results: At baseline, Black (n=1,195) and non-Black PWH (n=1,601) on TAF-based regimens had an average eGFR of 89.9 and 92.4 mL/min. Black PWH were more likely to be female and younger. After adjusting for baseline eGFR and covariates, decline in eGFR at 15 months was -4.5 vs. -2.9 (p>0.05) in Black and non-Black PWH, respectively. The long-term trend became similar between groups at 24 months (Figure). Stratified by baseline eGFR, discrepancies in eGFR changes between groups was mostly driven by baseline eGFR ≥90 mL/min.

Conclusions: Black and non-Black PWH experienced similar changes in eGFR over 24 months of ART including TAF. These results suggest TAF does not increase risk of renal decline in Black PWH.

Funding: Commercial Support - Gilead Sciences

Figure 1. Least-squares mean eGFR change from baseline over time for Black and non-Black PWH on TAF-based regimens (A) unadjusted; (B) adjusted.



SA-PO1093

Ketamine Use as a Cause of CKD: A Case Series

Lina Alatta, Bruce S. Spinowitz, Ritesh Raichoudhury, Zainulabdeen S. Al-saedi, Sheng F. Kuo, Mohammed A. Miqdad. *New York Presbyterian Queens, Flushing, NY.*

Background: Use of ketamine has been associated with urinary tract pathology, including contraction of urinary bladder and lower urinary tract obstruction, leading to secondary renal injury. Clinical presentation and image findings include contracted bladder, ureteral stricture, and hydronephrosis. Ketamine is excreted in bile and urine. It has been proposed that tissue damage is related to the duration of exposure and contact with ketamine metabolites in the urinary system, and that bladder wall is usually the first organ to present with lower urinary tract symptoms followed by the lower third of the ureter and renal pelvis. We present a series with history of ketamine abuse resulting in obstructive uropathy and chronic kidney disease.

Methods: Chart review of deidentified patient records with history of ketamine abuse who presented to New York Presbyterian Queens Hospital The following features were extracted: baseline demographic data, serum creatinine, BUN, estimated glomerular filtration rate, and renal imaging.

Results: Seven patients presented to the hospital with abnormal renal function and history of ketamine abuse, all with hydronephrosis on imaging. Six were Asian and one African American. They were predominantly female (5:1). The median age of presentation was 32 (range, 31-56) years. Three patients had hypertension. Serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate were 2.2 mg/dL(range 1.03 to 3.07), 36.2 mg/dL (range 21.4 to 64.3), 34 cc/min (25 to 45), respectively. All had the following abnormalities: elevated liver enzymes (median alanine aminotransferase of 47.5 U/L, aspartate aminotransferase of 65 U/L, and alkaline phosphatase of 1060 U/L; bile duct dilation; bladder wall thickening with moderate to severe hydronephrosis. All required urological intervention (six patients had bilateral ureter stents and one patient had bilateral percutaneous nephrostomy). One patient required transient hemodialysis and one died.

Conclusions: Our experience of Ketamine abuse is consistent with findings in the literature. Image findings of obstructive uropathy are typical and when present, is associated with chronic kidney disease. It is associated with high morbidities and requires frequent hospitalizations and procedures. Cases are likely underreported as most patients may not have symptoms.

SA-PO1094

Potential Reduction of Proteinuria by Oral Care Using Chlorhexidine Gluconate

Taro Misaki,[1,2] Shuhei Naka,[4] Seigo Ito,[5] Yasuyuki Nagasawa,[6] Ryota Nomura,[7] Michiyo Matsumoto-Nakano,[4] Kazuhiko Nakano.[3] *[1]Seirei Hamamatsu Byoin, Hamamatsu, Japan; [2]Seirei Kurisutofa Daigaku, Hamamatsu, Japan; [3]Osaka Daigaku, Suita, Japan; [4]Okayama Daigaku Daigakuin Ishiyakugaku Sogo Kenkyuka, Okayama, Japan; [5]Koku Jieitai Iruma Kichi, Sayama, Japan; [6]Hyogo Ika Daigaku, Nishinomiya, Japan; [7]Hiroshima Daigaku, Higashihiroshima, Japan.*

Background: Chlorhexidine mouthwash is widely used as an antimicrobial agent to reduce bacterial load in the oral cavity. However, its effects on systemic conditions in patients with chronic kidney disease (CKD) are still unknown. In the present study, we examined the relationship between the number of *Streptococcus mutans* in the oral cavity and proteinuria.

Methods: The patients with CKD gargled with chlorhexidine mouthwash three times daily for one year. We investigated the relationship between changes in the number of *S. mutans* and proteinuria.

Results: The *S. mutans* ≥1000 group at 0 month was significantly associated with higher number of *S. mutans*, urinary protein (g/gCr) and higher % urinary protein 2 + or higher in over time. Mean of the number of *S. mutans* in the oral cavity in whole patients decreased significantly over time. Proteinuria also decreased significantly with a delay. Relationship between the degree of decrease in the number of *S. mutans* after 12 months and proteinuria less than 0.3 g/gCr after 12 months remained significantly different in logistic regression analysis adjusted for age, sex, and proteinuria(g/gCr) at baseline (0 month). Additionally, the rate of proteinuria less than 0.3g/gCr at 12 months was significantly higher in the group that achieved S. mutans <1000 at 12 months.

Conclusions: These results suggest that there was a relation between the number of *S. mutans* in the oral cavity and proteinuria in patients with CKD and oral care with chlorhexidine mouthwash may reduce the proteinuria.

SA-PO1095

Association of Changes in Albuminuria with Change in Estimated Glomerular Filtration Rate (eGFR) in Macroalbuminuric CKD (CKD): Post Hoc Analysis of a 5-Year Randomized Trial

Nimrit Goraya,[1] Jan Simoni,[3] Maninder Kahlon,[2] Nazan Aksan,[2] Donald E. Wesson.[2] *[1]Baylor Scott & White Medical Center Temple, Temple, TX; [2]The University of Texas at Austin Dell Medical School, Austin, TX; [3]Texas Tech University System, Lubbock, TX.*

Background: Previous studies show changes in albuminuria associate inversely with the rate of eGFR change in patients with CKD and normoalbuminuria (urine albumin [mg]-to-creatinine [g] ratio [UACR] < 30) or microalbuminuria (UACR 30 to <300). In this post hoc analysis, we hypothesized that this inverse association also holds for patients with macroalbuminuric (UACR ≥ 300) kidney injury and non-diabetic CKD with initially normal eGFR (> 90 ml/min/m2 or stage G1).

Methods: One hundred fifty-three macroalbuminuric, non-diabetic G1 participants on ACEI were randomized to receive F&V (n=51), oral NaHCO3 (HCO3, n=51), or Usual Care, n=51. They were followed annually for 5 years, measuring eGFR (CKD-EPI) and UACR. Mixed linear regressions with random person intercepts tested differential group trajectories, p-values from relevant interaction terms are included below. We conducted preliminary causal mediation analyses examining participant level improvements in eGFR from the first year after randomization until the last study year (time-5) as the outcome. We examined the cumulative impact of change from first year after randomization to year 4 in UACR. In both the mediator and the outcome equations, baseline levels of eGFR and UACR were partialled out.

Results: Baseline eGFR and UACR were not different among groups. The observed mean rate of eGFR decline [mean (SE)] from baseline to year 5 for F&V [-1.08 (0.06) ml/min/1.73m2/ yr] and HCO3 [-1.17 (0.07) ml/min/1.73m2/ yr] were both lower (p<0.001) than UC [-1.94 (0.11) ml/min/1.73m2/yr. Interaction terms indicated that the UACR trajectories for F&V and HCO3 were each lower (consistent with less kidney injury) than UC (p<0.001). Although the direction of the UACR change vs. eGFR change varied among groups, the interaction for the entire sample was inverse (r= -0.41) and significant (p<0.001).

Conclusions: Like in patients with CKD and normoalbuminuria or microalbuminuria, this post hoc analysis showed that directional changes in albuminuria associate inversely with the rate of eGFR changes in patients with CKD and baseline macroalbuminuria. The data support future studies to test if interventions that reduce albuminuria might also be kidney protective in patients with macroalbuminuric level of kidney injury.

SA-PO1096

Association of Calcium-to-Magnesium Intake Ratio with Albuminuria in Community-Dwelling Japanese Adults

Keiko Kabasawa,[1] Michihiro Hosojima,[1] Kazutoshi Nakamura,[1] Ribeka Takachi,[2] Junta Tanaka,[1] Ichiei Narita,[1,3] Yumi Ito.[1] *[1]Niigata University, Niigata, Japan; [2]Nara Women's University, Nara, Japan; [3]Niigata Institute for Health and Sports Medicine, Niigata, Japan.*

Background: Calcium and magnesium both work together and counteract each other. In the kidneys, filtered calcium and magnesium are reabsorbed in consecutive segments from the proximal tubule to the connecting duct, where both are used in albumin handling. Previous studies have suggested that the calcium-to-magnesium intake ratio is associated with chronic health conditions such as cardiovascular disease; however, its relationship with albuminuria is not known.

Methods: This study analyzed data from 6,849 Japanese community-dwelling adults age ≥40 years (51.3% women). We cross-sectionally assessed the calcium-to-magnesium intake ratio and each nutrient using a validated food frequency questionnaire and spot urine albumin-to-creatinine ratio (ACR). Linear regression analyses were performed for the relationships of natural log-transformed intake ratio, calcium intake, and magnesium intake with natural log-transformed ACR, with adjustments for potential confounders.

Results: Median values of the calcium-to-magnesium intake ratio and eGFR were 1.65 and 73.5 mL/min/1.73 m^2, respectively. In the multivariable linear regression analysis, the calcium-to-magnesium intake ratio was inversely associated with log-transformed ACR [β(95%CI), –0.085 (–0.15, –0.021)]. When calcium and magnesium intake were analyzed individually, each nutrient was inversely associated with log-transformed ACR but the relationship with magnesium intake was not independent of calcium intake (Table).

Conclusions: The calcium-to-magnesium intake ratio was inversely associated with albuminuria. The balance of calcium and magnesium intake may be a potential modifiable factor for preventing albuminuria, and calcium intake may be a main contributor to this association.

Funding: Government Support - Non-U.S.

Table: Multivariable linear regression analysis for the relationship of natural logarithms of calcium-to-magnesium intake ratio, calcium intake, and magnesium intake with the natural logarithm of ACR

Note Calcium and magnesium intake were adjusted for energy intake by the residual method. Model 1 was adjusted for age, sex, survey area, no or rarely drinking, current smoking, regular exercise habit, energy intake (quartiles), diabetes, hypertension, history of urinary tract stone, body mass index, and eGFR. Model 2 was further adjusted for magnesium or calcium intake. ACR, urine albumin-to-creatinine ratio.

	Calcium-to-magnesium intake ratio	Calcium intake	Magnesium intake
	β (95%CI)	β (95%CI)	β (95%CI)
Model 1	−0.085 (−0.150, −0.021)	−0.110 (−0.164, −0.057)	−0.172 (−0.270, −0.074)
Model 2		−0.084 (−0.149, −0.019)	−0.085 (−0.204, 0.035)

Multivariable linear regression analysis for the relationship of natural logarithms of calcium-to-magnesium intake ratio, calcium intake, and magnesium intake with the natural logarithm of ACR

SA-PO1097

Association of Transthyretin Val122Ile Variant with Kidney Outcomes in Black Participants of REGARDS

Soumya Khanna,[1] Katharine L. Cheung,[2] Mary Cushman,[2] Titilayo O. Ilori,[3] Marguerite Irvin,[1] Orlando M. Gutierrez.[1] *[1]The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; [2]University of Vermont The Robert Larner MD College of Medicine, Burlington, VT; [3]Boston University Chobanian & Avedisian School of Medicine, Boston, MA.*

Background: A *TTR* gene variant (Val122Ile) causes misfolded tetrameric transthyretin protein, accumulating as extracellular amyloid fibrils and causing the most common form of hereditary transthyretin amyloidosis in Black Americans associated with incident heart failure. Whether this variant impacts kidney function through amyloid protein deposition is unclear.

Methods: In 8669 Black participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study with complete data on *TTR* genotyping and kidney function measures, we examined the association of the TTR Val122Ile (rs76992529) genotype with (1) estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR) at the baseline visit and (2) risk of incident end-stage kidney disease (ESKD). We used linear regression and Cox proportional hazards models adjusted for genetic ancestry and socio-demographic and clinical factors.

Results: A total of 265 participants carried the *TTR* Val122Ile variant while 8404 participants were non-carriers. There were no significant differences in baseline characteristics between the two groups, including baseline eGFR and ACR (Table). In linear regression adjusted for genetic ancestry, sociodemographic and clinical factors, there were no significant associations of *TTR* Val122Ile carriage with eGFR (1.22±1.48; p=0.41) or ACR (-0.007±.09; p=0.43). After a mean 8±3 years of follow-up, 400 participants developed ESKD. There was no significant association of *TTR* Val122Ile carriage with incident ESKD in fully adjusted analyses (hazard ratio 0.59, 95%CI 0.25,1.44).

Conclusions: Despite an association with left ventricular hypertrophy and heart failure via extracellular amyloid fibril deposition, the *TTR* Val122Ile variant was not associated with kidney function or development of ESKD in a community-based sample of Black Americans.

Funding: Other NIH Support - U01NS041588

Characteristics	Carriers (n= 265)	Non-carriers (n=8404)
Demographics		
Age, mean (SD), y	63 (9)	63 (9)
Male Sex, %	37	39
Social factors		
Income < $20,000, %	25	25
Less than high school graduate, %	19	18
Risk factors		
Current smoker, %	79	82
No exercise, %	34	36
Body mass index, mean (SD)	30 (6)	31 (7)
Blood pressure, median (IQR), mm Hg		
Systolic	130 (17)	131 (17)
Diastolic	78 (10)	78 (10)
eGFR, mean (SD), mL/min/1.73 m^2	84 (23)	83 (23)
ACR, median (IQR), mg/g	7.6 [4.9,18.6]	8.0 [4.7,20.77]
Comorbidities, %		
Coronary heart disease	15	14
Diabetes status	29	29
Hypertension	66	65
Stroke	8	7

SA-PO1098

Short-Term Kidney Function Decline in Patients with Nondiabetic Kidney Disease and Albuminuria with and without APOL1 High-Risk Variants

Carina M. Flaherty, Morgan Grams. On behalf of CRIC and AASK Authors. *New York University, New York, NY.*

Background: Having two *APOL1* high-risk kidney variants has been associated with higher risk of developing end-stage kidney disease (ESKD). Less is known about short-term kidney outcomes in patients with decreased kidney function and albuminuria.

Methods: The study population included participants of recent African Ancestry with CKD, urine protein-creatinine ratios (UPCR) >=0.2 g/g, and no diabetes who were genotyped for *APOL1* kidney risk variants in the African American Study of Kidney Disease and Hypertension (AASK) and the Chronic Renal Insufficiency Cohort (CRIC). Unadjusted GFR slopes were estimated using linear mixed effect models with random intercept and random slope, and change in albuminuria estimated as percent change in UPCR. Outcomes were estimated over the total study follow-up as well as three years.

Results: There were 223 and 273 participants included in AASK and CRIC, respectively, with 35.9% and 33.7% having the high-risk genotype (G1/G1, G1/G2, or G2/G2). In AASK, baseline measured GFR was 39 ml/min/1.73 m^2 and similar by risk status; UPCR was higher among those with the high-risk genotype (median 0.7 g/g vs. 0.5 g/g, p=0.02). Over 12 years, risk of ESKD was higher in high-risk individuals compared with low-risk individuals (77.5% vs. 56.6%, p=0.002), as was eGFR slope (-4.3 vs. -3.7 ml/min/1.73 m^2 per year, p=0.05). Shorter-term eGFR slope and percent change in UPCR were not different by genotype. In CRIC, baseline eGFR was 40 ml/min/1.73 m^2 and similar by genotype; UPCR was also similar between genotypes (median 0.7 g/g vs. 0.6 g/g, p=0.7). Patients in the high-risk genotype were younger and had a lower proportion of cardiovascular disease than patients in the low-risk genotype. Over 18 years, there was a non-significant trend toward higher risk of ESKD in individuals with the high-risk genotype (65% vs. 59%, p=0.3), similar to that for eGFR slope (-3.1 vs. -2.8 ml/min/1.73 m^2 per year, p=0.16). Shorter-term eGFR slope and percent change in UPCR were not different by genotype.

Conclusions: When conditioned on established CKD, UPCR ≥0.2 g/g, as well as the absence of diabetes in two prospective cohorts, short-term eGFR slope and change in UPCR were not meaningfully different by *APOL1* genotype, although long-term ESKD risk appeared to be higher in the high-risk genotype.

Funding: Private Foundation Support

SA-PO1099

Kidney Prognostic Role of a Temporal Relationship between Onset of Diabetes and Hypertension in Patients with Coexisting Diabetes and Hypertension

Seungmin Song,[1] Kyungho Lee,[1,2] Minhyung Kim,[1] Junseok Jeon,[1,2] Jung eun Lee,[1,2] Wooseong Huh,[1,2] Hye Ryoun Jang.[1,2] *[1]Samsung Medical Center, Gangnam-gu, Seoul, Republic of Korea; [2]Sungkyunkwan University School of Medicine, Suwon, Republic of Korea.*

Background: Diabetes and hypertension are well-established risk factors for chronic kidney disease(CKD) and end-stage kidney disease(ESKD). These conditions frequently coexist, potentially due to bidirectional mechanisms. Prognostic differences between hypertension preceding diabetes and diabetes preceding hypertension remain unclear. We aimed to evaluate whether onset of diabetes before or after hypertension differentially influences risk of developing ESKD.

Methods: We identified all adult patients with diabetes and hypertension who participated in national health insurance service(NHIS) in Korea between 2015 and 2016. Patients were categorized into two groups based on order of onset of diabetes and hypertension: those with diabetes preceding hypertension(termed "diabetes first") and hypertension preceding diabetes(termed "hypertension first"). Demographic and laboratory data were obtained from NHIS database. Cox proportional hazards analyses were performed for ESKD.

Results: Among 995,484 patients, 468,072(47%) and 527,412(53%) developed diabetes and hypertension first, respectively. Incidence rates for ESKD were 4.53 in diabetes first group and 1.46 in hypertension first group(1,000 person-years, log-rank p<0.001). In unadjusted analysis, diabetes first group had a 3.10-fold(95%CI 2.99–3.22) higher risk of developing ESKD compared to hypertension first group. After adjusting for multiple covariates, including demographics, lifestyle factors, dyslipidemia, eGFR, blood pressure, blood glucose levels, proteinuria, duration of diabetes and hypertension, adjusted hazard ratio for ESKD was 1.55(95%CI 1.49–1.61) for diabetes first group. Stratified analyses by glucose and blood pressure status consistently showed an increased risk in diabetes first group. Subgroup analyses revealed significant interactions with age, smoking status, and CKD status, with stronger risks in younger patients, current smokers, and non-CKD.

Conclusions: In patients with coexisting hypertension and diabetes, sequence in which these conditions develop plays a significant prognostic role in predicting risk of ESKD. An earlier onset of diabetes than hypertension is associated with a higher risk. Considering order of onset of each condition could be a practical approach to enhance kidney-focused prognostication.

SA-PO1100

Discrepancy between Lifetime Risk of ESKD vs. 3-Year Risk of CKD Progression in US Adults with Diabetes

Yoshitsugu Obi,[1] Xiaoqian Zhu,[1] Maria Clarissa Tio,[1] Timothy E. Yen,[1] Michael E. Hall,[1] Neville R. Dossabhoy,[1] Tariq Shafi.[2] *[1]University of Mississippi School of Medicine, Jackson, MS; [2]Houston Methodist, Houston, TX.*

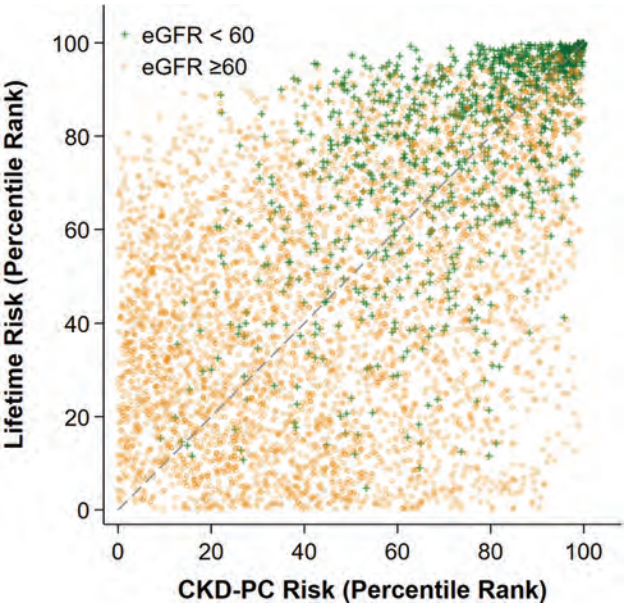
Background: The CKD Prognosis Consortium developed a model predicting CKD progression (i.e., ≥40% eGFR decline or end-stage kidney disease [ESKD]) in three years (Grams, Diabetes Care 2022). However, the risk of CKD progression is cumulative over time and the lifetime risk of ESKD is also important to assess. We sought to compare the 3-year CKD progression risk with the lifetime ESKD risk using the Swedish prediction model (Østergaard, CJASN 2022).

Methods: Among 5,284 US adults with diabetes who participated in the 1999-2020 NHANES, we estimated the lifetime ESKD risk by calibrating baseline hazards for mortality and ESKD in the Swedish prediction model. Since ESKD incidence was not available, we used the Kidney Failure Risk Equation and obtained the calibration factor for ESKD. We then evaluated their correlation by comparing risk percentiles using spearman's rho and risk quartiles using concordance kappa.

Results: Mean age was 63 years, 47% were women, median HbA1c was 7.0%, and median diabetes duration was 12 years. Mean eGFR was 82 (SD, 21) mL/min/1.73 m^2, with 65% and 32% having moderate and severe albuminuria, respectively. Median [interquartile range] 3-year CKD progression risk was 2.6% [1.5% to 5.2%], and median lifetime ESKD risk was 1.6% [0.9% to 3.0%]. There was only a fair correlation between the two risk estimates (rho=0.49, **Figure**) and only a slight agreement between the risk quartiles (kappa=0.17). The correlation and concordance were poorer among people with eGFR ≥60 mL/min/1.73 m^2 (rho=0.34; kappa=0.11). Additionally, the lifetime ESKD risk percentiles were higher than the 3-year CKD progression risk percentiles among people with longer life expectancies, and vice versa.

Conclusions: Shorter term risk of CKD progression may not be sufficient to identify individuals with high lifetime ESKD risk. Clinicians should consider lifetime ESKD risk in addition to short-term CKD progression risk when counseling people with diabetes.

Funding: Other NIH Support - the National Institute of General Medical Sciences of the National Institutes of Health



SA-PO1101

Trend Analysis of Chronic Kidney Failure-Related Mortality, 1999-2020

Luqman Munir,[1] Ahmed J. Chaudhary,[2] Sara Sohail,[1] Kanwal Fatima,[1] Amna Khalid,[1] Mohammad Ammar ur Rahman,[1] Saleha Azeem.[1] NEURALKEy. *[1]King Edward Medical University, Lahore, Pakistan; [2]Detroit Medical Center, Detroit, MI.*

Background: The hallmark of chronic renal failure, also called chronic kidney disease, is a progressive decline in kidney function over time. Multiple etiologies for the illness may exist, such as glomerulonephritis, diabetes, and hypertension. High risk of heart failure, weak bones, and anemia are just a few of the many complications that may result.

Methods: We reviewed the CRF mortality data obtained from the CDC WONDER (Wide-Ranging Online Data for Epidemiological Research) Database, which spans the years 1999 to 2020. Using 95% confidence intervals, the Joinpoint Regression Program computed annual percent changes (APC) and AAMR per 1,000,000 individuals. For p<0.05, the parallelism test was deemed significant for non-parallel results.

Results: A total of 1,938,505 CRF-related deaths were reported between 1999 and 2020. With an APC of 1.33, AAMR demonstrated an increasing trend. Between 2010 and 2012, there was a noticeable peak, which was followed by a decline. Blacks or African Americans, males, non-metropolitan population, and people 85 years or older showed higher death rates. Disparate trends were found in the tests for parallelism among gender (p=0.0002), Blacks and Whites (p=0.002), Northeast and Midwest (p=0.004), Midwest and South (p=0.02), and Midwest and West (p=0.02). However, the parallelism test between urban and rural areas was not significant (p=0.07).

Conclusions: In the United States, the number of deaths from CRF has increased significantly over the last 20 years, possibly because early-stage CKD is frequently asymptomatic. Certain demographic groups continue to have higher death rates, which emphasizes the need for more research.

SA-PO1102

Albuminuria, eGFR, and Cancer Risk: The Chronic Kidney Disease Prognosis Consortium

Yejin Mok, Jennifer S. Lees. *CKD Prognosis Consortium, New York, NY.*

Background: Studies examining the association of chronic kidney disease (CKD) with cancer risk have demonstrated conflicting results. We quantified the independent associations of albuminuria and estimated glomerular filtration rate (eGFR) with cancer risk overall and among selected site-specific cancers in the CKD Prognosis Consortium (48 cohorts).

Methods: We performed individual-participant data meta-analysis of 715,713 individuals without a history of cancer. Adjusted Cox models were used to quantify the associations of urine albumin-to-creatinine ratio (ACR) and serum creatinine-based eGFR with overall and site-specific cancer risk.

Results: 94,417 incident cancer cases occurred during 17,416,991 person-years of follow-up (incidence rate of 22.2 per 1000 person-years). Higher ACR was positively associated with cancer risk [HR 1.07 (1.05-1.09 per 8-fold increase in ACR], whereas no consistent association of eGFR with cancer risk was seen [HR 1.01 (0.99 - 1.03) per 15 ml

decrease in eGFR]. For the cross-categories of ACR and eGFR, higher ACR was associated with higher risk for overall cancer risk, irrespective of eGFR levels. For site-specific cancer, lower eGFR showed a significant association with urological cancer, multiple myeloma, and prostate cancer, whereas higher ACR was related to many types of cancer (i.e., head/neck, colorectal, liver, pancreas, lung, hemolymphatic, leukemia, and multiple myeloma), in addition to kidney-related cancer. Results were similar after excluding incident cases within 1 year to minimize the possibility of reverse causation.

Conclusions: CKD measures, particularly albuminuria, were independently associated with subsequent risk of cancer. Our result warrant investigation into the pathways from albuminuria to cancer.

Funding: NIDDK Support, Private Foundation Support

Table. Adjusted hazard ratios (95% CI)* of overall cancer incidence by cross-categories of eGFR and ACR

	ACR, mg/g				
eGFRcr, mL/min/1.73m²	<10	10-29	30-299	≥300	Combined
≥105	0.88 (0.83 - 0.94)	1.00 (0.94 - 1.07)	1.01 (0.92 - 1.11)	1.26 (1.12 - 1.40)	0.91 (0.86 - 0.96)
90-104	REF	1.03 (0.99 - 1.07)	1.15 (1.10 - 1.20)	1.23 (1.13 - 1.34)	REF
60-89	0.98 (0.95 - 1.02)	1.06 (1.03 - 1.10)	1.12 (1.07 - 1.17)	1.18 (1.10 - 1.28)	1.00 (0.98 - 1.02)
45-59	1.07 (1.02 - 1.12)	1.08 (1.02 - 1.14)	1.14 (1.07 - 1.22)	1.28 (1.17 - 1.39)	1.03 (1.00 - 1.06)
30-44	1.03 (0.94 - 1.13)	1.08 (0.99 - 1.17)	1.12 (1.03 - 1.23)	1.23 (1.13 - 1.33)	1.00 (0.95 - 1.05)
<30	1.09 (0.95 - 1.26)	1.24 (1.09 - 1.41)	1.17 (1.06 - 1.30)	1.25 (1.13 - 1.37)	0.99 (0.93 - 1.06)
Combined	REF	1.06 (1.04 - 1.09)	1.12 (1.08 - 1.16)	1.19 (1.14 - 1.24)	

*Adjusted for age, sex, race, smoking status, systolic blood pressure, antihypertensive medication, diabetes, body mass index, total cholesterol, history of cardiovascular disease (i.e., history of coronary heart disease, stroke and heart failure), aspirin use

SA-PO1103

Risk Stratification of Delayed Postpolypectomy Bleeding in Patients with and without Kidney Diseases: A Large, High-Dimensional Propensity Score-Matched Cohort Study

Hae-Ryong Yun, Tae-Hyun Yoo. *Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.*

Background: The assessment of the risk of delayed bleeding following polypectomy in patients with chronic kidney disease (CKD), including those undergoing kidney failure with renal replacement therapy, has not been established. To address this issue, we conducted a high-dimensional propensity score-matched study to investigate whether CKD contributes to an increased risk of delayed post-polypectomy bleeding (PPB).

Methods: A large cohort study and retrospective analysis of 20,052 patients who underwent colonoscopy and polypectomy, between 2005 and 2022 in Korea. Propensity score matching with adjustments for patient-related, polyp-related and procedure-related factors was used to account for differences between patients based on the stage of CKD. The primary end points were the risks of delayed PPB, and the secondary end points were the risks of bleeding depending on the stage of CKD.

Results: A total of 16,895 patients were selected including 2,349 (13.9%) patients with CKD. Based on the estimated glomerular filtration rate (eGFR), 892 (38.0%) patients had CKD at stages 1 and 2, 1163 (49.5%) at stages 3 and 4, and 294 (12.5%) at stages 5 and ESRD. The prevalence of PPB in patient with CKD was 1.3 %. Adjusted propensity matching analysis, the risk of delayed PPB was significantly increased according to the stage of CKD (hazard ratio [HR] = 1.676, 95% confidence interval [CI] 1.100–2.552 for stage 1-2, HR 2.045, 95% CI 1.441–2.901 for stage 3-4, and HR 2.189, 95% CI 1.203–3.982 for stage 5 or ESRD, all $p<0.05$).

Conclusions: CKD is an independent risk factor for delayed PPB, and it showed an association with a substantially increased risk of CKD stage. Consequently, greater caution should be treated when undergoing polypectomy on patients with CKD.

SA-PO1104

Effect of Urolithiasis and Recurrent Urinary Tract Infection on Estimated GFR in CKD

Sameena Iqbal, Song-ah Chai, Celena Scheede-Bergdahl. *McGill University, Montreal, QC, Canada.*

Background: Urolithiasis is a known renal disease cause dependent on stone burden and number of interventions. Urinary tract infections (UTIs) are often associated with urolithiasis given the inflammatory state due to urinary flow obstruction. These two reversible risk factors can further cause progressive Chronic kidney disease (CKD).

Methods: Objective: The primary study objective is to report the association of urolithiasis and urinary tract infection (UTI) with eGFR decline in CKD. Methods: A retrospective cohort study was conducted in a community nephrology clinic in Quebec, Canada that included laboratory and radiologic data collection from April 1, 2015 until June 30, 2022.

Results: Upon review of 310 medical charts, the subjects had a median age of 73 years (IQR 29-99), and 58.1% of the cohort was male. The prevalence of Grade 1 and 2, Grade 3, Grade 4 and Grade 5 CKD was 10.3%, 50%, 32.3%, and 7.4%. The median follow-up time was 1555 days (28-4864). Urolithiasis was seen in 14.5%. The rate of UTIs was 0.107 events per patient-days. The multivariate generalized linear models (GLM) documented the proportionally reverse relationships between more than one UTI and decline in the individual slope of estimated GFR, reaching statistical significance. In the adjusted GLM, for every unit of ml/min/1.73m2/per day of decline in GFR slope, a 2% increase risk that is measured for recurrent UTI event (RR 1.02 (95%CI 1.00-1.04) p=0.0446. A tendency towards urolithiasis diagnosis was associated negatively with the slope of estimated GFR, as the RR for urolithiasis was 1.01 (95% CI 0.99-1.33), p=0.1136. There is an association of urolithiasis and average kidney size on GLM, p=0.0464. Recurrent UTI is associated with CKD grades with on trend analyses, p=0.049. The recurrent UTI proportions were 11%, 9% and 33% in CKD grade 3, 4 and 5, respectively among those with no urolithiasis. Majority of the UTIs were E. coli species (59%).

Conclusions: Our study demonstrated an overall association between urolithiasis, recurrent UTIs and estimated GFR slope. Recurrent UTI is not associated with kidney size. Methods to prevent recurrent urolithiasis and urinary tract infection episodes should be assessed in a prospective manner.

Funding: Commercial Support - Ortho Janssen

SA-PO1105

Association between Plasma Alpha 1-Antitrypsin Levels and Kidney Failure in Patients with CKD

Antoine Créon,[1] Julie Klein,[2,3] Sophie Liabeuf,[4,5] Celine Lange,[1,6] Christian Jacquelinet,[1,6] Joost Schanstra,[2,3] Natalia Alencar de Pinho,[1] Ziad Massy.[1,7] Centre for Research in Epidemiology and Population Health. *[1]Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; [2]INSERM 1297, Toulouse, France; [3]Universite Toulouse III-Paul Sabatier, Toulouse, France; [4]Centre Hospitalier Universitaire Amiens-Picardie, Amiens, France; [5]MP3CV Laboratory, Amiens, France; [6]Agence de la Biomedecine, La Plaine Saint-Denis, France; [7]AURA Paris, Paris, France.*

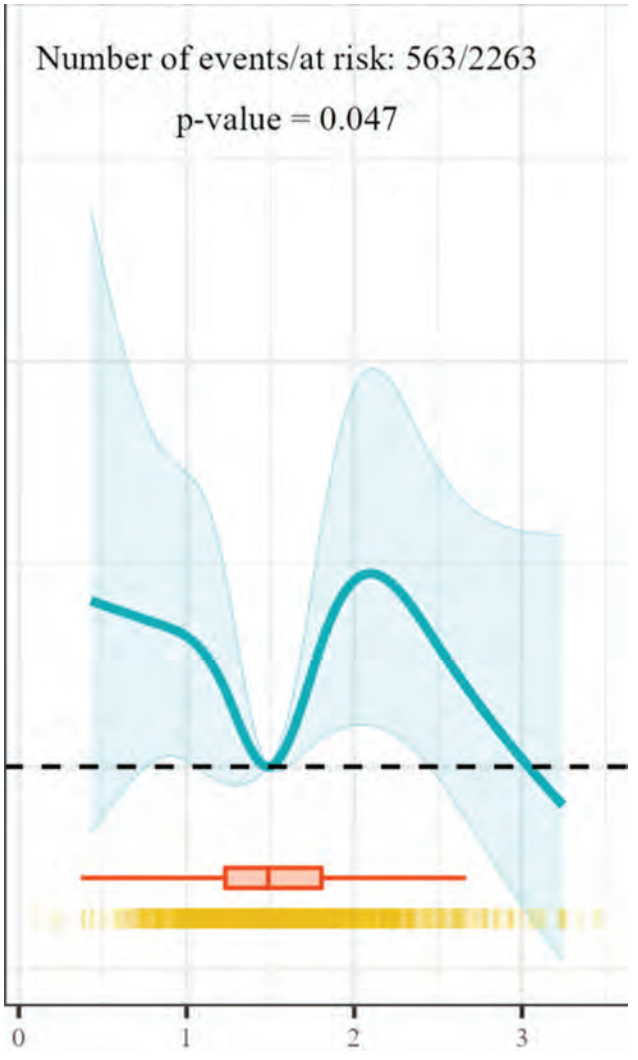
Background: Chronic kidney disease (CKD) is overrepresented in persons with alpha-1-antitrypsin (AAT) deficiency, and previous studies suggest that AAT may play a role in kidney fibrosis. This study assessed the relationship between plasma AAT and kidney failure (KF) in patients with CKD.

Methods: National, prospective cohort of 2263 patients with CKD stage 2-5. Baseline plasma AAT was measured centrally with ELISA (Bio-techne, DY1268, normal ranges from 0.9 g/l to 1.8 g/l). Cause-specific Cox models were used to estimate hazard ratios (HR) for KF, defined as initiation of kidney replacement therapy, adjusted for demographics, eGFR, albuminuria, albumin, hemoglobin, CRP, cardiovascular comorbidities, and use of RAAS, diuretics, MRAs, and corticosteroids.

Results: Patients had a mean age (±SD) of 66 years (±13) and 34% were females. The mean eGFR was 35 (±13) ml/min/1.73 m2 and median AAT (Q1-Q3) was 1.49 g/l (1.23-1.80). Over a median follow-up of 5.8 (5.4-6.3) years, 563 patients experienced KF. The relationship between AAT and KF followed a U-shaped pattern (**figure 1**). The adjusted HR (95% CI) of KF associated with a 0.5 g/l-lower baseline AAT relative to its median value was 1.33 (1.02 -1.73), while that for a 0.5 g/l-higher baseline AAT value was 1.45 (1.10-1.92).

Conclusions: A U-shaped relationship between plasma AAT and KF suggests a relative imbalance between systemic inflammation and anti-inflammatory AAT in patients with low baseline plasma AAT. Clinical studies are needed to clarify whether therapy with AAT, currently indicated only for the treatment of the severe forms of genetic AAT deficiency, may be helpful to correct AAT levels and potentially protect the risk of progression from CKD to KF.

Funding: Government Support - Non-U.S.



SA-PO1106

Effect of Ambient Temperature on Renal Colic: A Systematic Review and Meta-Analysis

Csaba P. Kovesdy,[1] Hoimonty Mazumder,[2] Farah Faizah,[2] Naznin Alam,[2] Xichen Mou,[2] Hongmei Zhang,[2] Abu Mohd Naser.[2] *[1]University of Tennessee Health Science Centre, Memphis, TN; [2]The University of Memphis, Memphis, TN.*

Background: Renal colic is a clinical manifestation characterized by spasmodic pain in the lower back, which is commonly caused by kidney stones. Although limited, recent evidence suggests increased risk of kidney outcomes in exposure to elevated ambient temperature. In this meta-analysis, we aimed to elucidate the effect of ambient temperature on renal colic.

Methods: We systematically searched four leading bibliographic databases (PubMed, CINAHL complete, Scopus, and Web of Sciences) and additional sources from the inception of each database to February 12, 2024. Epidemiological studies that met a pre-determined eligibility criteria following PECOS (population, exposure, comparator, outcome, and study design) were included. The effect sizes from individual studies were standardized to Cohen's d and we performed a meta-analysis with a random-effects model to estimate a pooled Cohen's d and constructed a 95% confidence interval. We performed further sub-group analyses by study region, sample size, study design, and mean age of study participants.

Results: Out of 1463 primarily retrieved articles, seven articles representing 758666 study participants underwent meta-analysis. Most of the studies were conducted in the US (3) followed by China (2), Canada (1), and Israel (1). Ambient temperature demonstrated a significant effect on renal colic [Cohen's d: 0.30, 95% CI: 0.18, 0.41, p-value < 0.001, I^2 = 99.08%]. Subgroup analyses for potential explanation of heterogeneity demonstrated statistically significant between-group variance for study region [America- Cohen's d: 0.25, (95% CI: 0.11, 0.39); Asia - Cohen's d: 0.44, (95% CI: 0.42, 0.45)] and study design [Case-crossover- Cohen's d: 0.46, (95% CI: 0.01, 0.93); Retrospective cohort - Cohen's d: 0.44, (95% CI: 0.42, 0.45); Time-series - Cohen's d: 0.21, (95% CI: 0.17, 0.25)].

Conclusions: These findings suggest a moderate effect of ambient temperature on renal colic.

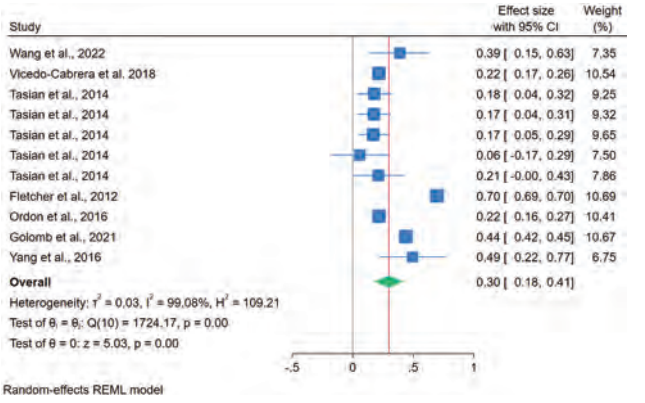


Figure 1: Forest plot showing summary-effect.

SA-PO1107

Deoxycholic Acid and the Risk of Death and Cardiovascular Events among Patients with Advanced CKD

Jun Ha Gu, Michel Chonchol, Cole L. Hoffman, Makoto Miyazaki, Shinobu Miyazaki-anzai, Kristen L. Nowak, Anna Jovanovich. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Circulating levels of the secondary bile acid, deoxycholic acid (DCA), are elevated in chronic kidney disease (CKD) and may contribute to vascular calcification in CKD patients. Whether circulating DCA levels are associated with death and cardiovascular events (CVE) among advanced chronic kidney disease patients is unknown.

Methods: The Homocysteine Study was a randomized double-blind trial evaluating the effects of high doses of folic acid and B vitamins on all-cause mortality (ACM) and CVE in subjects with advanced CKD and elevated serum homocysteine levels. Fasting serum DCA levels were measured in stored serum samples obtained at 3 months in a cohort of 1,054 patients with mainly stage 4 CKD (mean eGFR 18.1± 6.5 mL/min/1.73m^2). The study population was divided into quartiles according to plasma DCA levels. We used Cox proportional-hazards models to examine the association between DCE levels with ACM and a composite of CVE (combining myocardial infarction, stroke, and amputation).

Results: Participants had a mean age of 69±11 years. The median DCA level was 119 [63-232] ng/mL. During a median follow-up of 3.0 years, 445 (42%) patients died from any cause and 210 (20%) had a CVE. Higher DCA levels were not associated with higher risks of death. Compared to the first (lowest) quartile, the HR (95% CI) for death were as follows: second quartile, 0.89 (0.74-1.06); third quartile, 0.98 (0.82-1.18) and fourth quartile, 0.88 (0.73-1.06) after adjustment for potential confounders available in the database. Similar results were obtained when DCA was examined as a continuous variable: 0.97 (0.93-1.02). Compared to the lowest quartile, the two highest quartiles of DCA were also not associated with a significantly elevated risk of CVE (HR 0.98, 95% CI 0.82-1.78) and (HR 0.87, 95%CI 0.73-1.05), respectively after multivariate adjustment.

Conclusions: Among HOST participants, DCA was not associated with death and cardiovascular events in patients with advanced CKD not requiring dialysis.

Funding: Veterans Affairs Support

SA-PO1108

Association of Serum Complement 3 (C3) with Renal Arteriolar Hyalinosis and Blood Pressure-Dependent Proteinuria in Patients with Non-nephrotic CKD

Kentaro Kohagura,[1] Nanako Oshiro,[1,2] Yuki Shinzato,[2] Ryo Zamami,[2] Kenya Kusunose.[2] *[1]Ryukyu Daigaku Igakubu Fuzoku Byoin, Nakagami-gun, Japan; [2]Ryukyu Daigaku Igakubu Daigakuin Igaku Kenkyuka, Nakagami-gun, Japan.*

Background: Renal arteriolar hyalinosis may be associated with proteinuria by disrupting the autoregulatory system in the afferent arteriole. Deposition of complement C3 (C3) is commonly seen in hyaline lesions of arteriolosclerosis. Serum C3 has been suggested to play a pathogenic role as an adipocytokine. However, an association of serum C3 with renal arteriolar hyalinois and blood pressure dependent proteinuria in patients with non-nephrotic chronic kidney disease (CKD) is unknown.

Methods: A total of 174 consecutive patients who underwent renal biopsy at our department were considered for the study. We excluded patients with serum albumin less than 3.0 mg/dl, vasculitis, lupus nephritis, etc. leaving us with 122 patients. Arteriolar hyalinosis was assessed using a semiquantitative grading system. We divided the patients into four subgroups based on the high systolic blood pressure (hSBP) and high serum C3 (hC3), defined as equal or above of their median value. We investigated an association of serum C3 with renal hSBP/hC3 subgroups with proteinuria.

Results: Median age, blood pressure, estimated glomerular filtration rate (eGFR), urine protein, and serum C3 were as follows: 42.0 years, 123/74 mmHg, 71.3 ml/min/1.73 m^2, 0.7 g/gCr and 104.5mg/dl, respectively. Serum C3 was positively associated with body mass index, HbA1c, low-density lipoprotein cholesterol, oxidative stress index, high-sensitivity C-reactive protein (hs-CRP), urine protein, and arteriolar hyalinosis index. In the multiple regression analysis, serum C3, but not C4, was associated with arteriolar hyalinosis index independent of age, sex, and potential confounders (β=0.195, P=0.026). SBP was significantly associated with urinary protein in patients with hC3 but not in those without hC3. In the multiple logistic regression analysis with hC3-/hSBP- as reference, hC3+/hSBP+ was independently associated with high proteinuria, defined as the highest tertile (OR 5.67, 95%CI 1.32-34.29, P=0.02), but its significance disappeared after additional adjustment for the arteriolar hyalinosis index.

Conclusions: These results suggest that serum C3 may be elevated as an adipocytokine and may be associated with increased BP-dependent proteinuria by inducing arteriolar hyalinosis in non-nephrotic CKD patients.

SA-PO1109

Association of Biomarkers of Fibrosis with the Progression of CKD

Jayanta Gupta,[1] Anvesha Srivastava,[2] Richard L. Amdur,[3] Dominic S. Raj.[2]
[1]Florida Gulf Coast University, Fort Myers, FL; [2]The George Washington University School of Medicine and Health Sciences, Washington, DC; [3]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY.

Background: Fibrosis of the kidney is the hallmark and the final common pathway of chronic kidney disease (CKD) progression, regardless of underlying etiology. Fibrosis is characterized by excessive production and deposition of extracellular matrix (ECM) proteins mainly in the kidney interstitium and results in structural damage, impairment of renal function, and eventually end-stage renal disease (ESRD). The most abundant collagens in the interstitial matrix of the kidney are collagen type I (COL I) and III (COL III). In renal fibrosis, these collagens are upregulated and the activity of the proteases responsible for their remodeling is altered. In this study, we used a sub-cohort of the Chronic Renal Insufficiency Cohort (CRIC) to examine the association of serum PRO-C6, a biomarker for type VI collagen formation and urine C3M, a biomarker for type III collagen degradation with a composite endpoint (ESRD or 50% decline in eGFR).

Methods: Urine C3M was adjusted for 24-hour urinary creatinine excretion. Subjects were categorized into three groups based on tertiles of the biomarker (serum PRO-C6 and urine C3M) levels. The association of biomarkers with the composite outcome was investigated using Kaplan-Meier curves and multivariable Cox proportional hazards regression models after controlling for age, sex, race, income, BMI, diabetes at baseline, hypertension, use of ACEI/ARB, history of CVD, history of smoking, baseline eGFR and UACR.

Results: The number of events in the serum PRO-C6 and urine C3M groups were 426 (out of 998 participants used in the Cox model) and 417 (out of 985 participants used in the Cox model) respectively. The multivariable-adjusted hazard ratios (HRs) comparing the upper to the lower tertiles of serum PRO-C6 and urine C3M for the composite outcome was 1.85 (95% CI: 1.29 - 2.66) and 0.72 (95% CI: 0.56 - 0.94) respectively.

Conclusions: Serum PRO-C6 and urine C3M levels were directly and inversely associated with the composite outcome respectively. These biomarkers may be useful in predicting early events in renal fibrosis.

Funding: NIDDK Support

SA-PO1110

Prognostic Implications of Relative Eosinophil Counts in Nephrosclerosis

Haruki Mae, Go Kanzaki, Kotaro Shimoyama, Hideaki Kuno, Saeko Hatanaka, Hirokazu Marumoto, Takaya Sasaki, Kotaro Haruhara, Nobuo Tsuboi, Takashi Yokoo. The Jikei University School of Medicine. *The Jikei University School of Medicine, Minato-ku, Japan.*

Background: The interplay between atherosclerosis and chronic inflammation has gained considerable recognition, with elevated eosinophil counts identified as a risk factor for cardiovascular diseases. Nonetheless, the effect of eosinophils on the kidney prognosis of patients with nephrosclerosis remains unclear.

Methods: This retrospective observational study was conducted in a single hospital. Patients diagnosed with nephrosclerosis via kidney biopsy between January 2010 and December 2023 were included in the study. Clinical data were extracted from hospital records at the time of biopsy to evaluate the association between blood relative eosinophil count (REC; percentage of eosinophil in WBC) and renal outcomes. Logarithmic transformation was performed for continuous variables to make data conform more closely to the normal distribution. The primary endpoint was dialysis initiation during follow-up. Patients were categorized into three groups based on their REC levels (REC grade 1, lower group [0.7-2.6%]; 2, middle group [2.7-4.0%]; and 3, higher group [4.2-20.5%]), and a log-rank test was performed. Cox regression analysis was conducted and adjusted for REC, age, sex, BMI, and mean arterial pressure.

Results: The cohort comprised 76 patients (median age 54.9 years, 81.6% male, with a median follow-up duration of 68.7 months [interquartile range 21.8-106.8]). Fifteen patients (19.7%) underwent dialysis. Kaplan-Meier curves with the log-rank test for time to events showed no significant difference (Log-rank p = 0.07; Figure 1). However, Cox regression analysis demonstrated that REC, as a continuous variable, was significantly associated with the initiation of dialysis (hazard ratio 1.41, 95% confidence interval 1.21-13.9).

Conclusions: Eosinophil counts may serve as a significant prognostic marker for kidney outcomes in patients with nephrosclerosis.

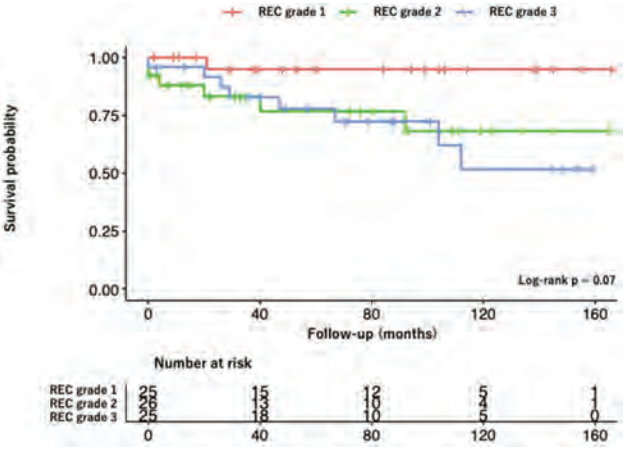


Figure 1

SA-PO1111

Value of Histopathologic Assessment for Nephrosclerosis in Predicting Kidney Function Decline

Haekyung Lee,[1,2] Soon hyo Kwon,[1,2] Hyunjin Noh.[1,2] *[1]Soonchunhyang University Hospital, Seoul, Republic of Korea; [2]Soonchunhyang University Hospital Kidney Center, Seoul, Republic of Korea.*

Background: Accurate prediction of kidney failure risk is crucial for the effective management of kidney diseases. While demographic and laboratory parameters have been utilized to stratify the risk of kidney failure, the potential of histopathologic assessments—specifically evaluating chronic changes such as glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis—to improve the prediction of kidney function decline remains to be elucidated.

Methods: This study retrospectively analyzed patients who underwent native kidney biopsy from 2014 to 2022 at Soonchunhyang University Seoul Hospital in South Korea. Two kidney pathologists performed semiquantitative visual inspections for glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis. We evaluated the value of these histopathologic changes in predicting the risk of a decrease in estimated glomerular filtration rate (eGFR) by 30% or more.

Results: Among 491 patients, 183 (37.3%) experienced a decrease in eGFR by 30% or more. Multivariable analyses, which included demographic and laboratory parameters, revealed that severe tubular atrophy (>50%) (hazard ratio [HR] 2.74, 95% CI 1.68–4.46, P < 0.001) and severe interstitial fibrosis (>50%) (HR 2.09, 95% CI 1.31–3.34, P = 0.002) were independently associated with the risk of an eGFR decline of 30% or more. Additionally, incorporating these histopathologic changes into traditional clinical parameters significantly improved the prediction of eGFR decline.

Conclusions: The integration of histopathologic assessments of chronic kidney changes into clinical information significantly improves the prognostic assessment of eGFR decline. This suggests that histopathologic evaluation of chronic kidney changes should be considered to improve risk stratification in patients with kidney diseases.

SA-PO1112

Need and Efficacy of Add-On Opt-Out Strategy to Promote Delivery of Kidney Replacement Therapy (KRT)-Directed Comprehensive Pre-ESKD Education (CoPE) for All Patients with Advanced CKD

Popy Shell,[1] Malea Joyce,[1,2] Grant D. Scheiffele,[1] Shobha Subhash,[1] Teresa A. Lyles,[1] Huanguang Jia,[1] Ashutosh M. Shukla.[1,2] *[1]VA North Florida South Georgia Veterans Health System, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: CoPE is a must for informed KRT selection and use; however, only a minority of advanced CKD patients receive CoPE before KRT. We lack evidence-based estimations for patients' interest for CoPE and effective strategies to facilitate CoPE for all patients with advanced CKD. Mail-inviting eligible patients derived from an electronic health record database can improve advanced CKD identification and aid CoPE dissemination; however, its efficacy has not been tested.

Methods: We conducted secondary analysis of recruitment processes for the ongoing TEACH-VET study aimed to evaluate the benefits of CoPE (vs. usual care) on many patient-level outcomes among Veterans with advanced CKD. TEACH-VET employs a mail-based opt-out strategy; all advanced, stage 4 and 5 CKD patients are extracted from the clinical database, and mail-invited to receive CoPE or usual care (opt-in cohort). Patients not self-responding to study invite within two-week period are actively contacted (opt-out cohort). We examined the rates and efficiency of CoPE interest assessed by enrollment as co-primary outcomes, and successful contact with patients and final randomization as secondary outcomes.

Results: Of the 1130 patients eligible for the opt-in cohort, 90 (8%) enrolled for education with passive, strategy. Significantly higher fraction (n=293, 48%, p<0.001) of the eligible 617 approached through active outreach were enrolled for education. Overall, 77% of all CoPE enrollments required an active outreach. Both, upstream successful contacts (72% vs. 10%, p<0.001) and the downstream randomizations into study (34% vs. 7%, p=0.01) were higher for active outreach group. Subgroup analysis of those successfully contacted with either method showed that enrollments were higher among passive approach (80%), compared to active outreach (66%, p=.02) group. The efficiency of add-on active outreach was significantly better, with time per successful approach 29±8 vs. 169±183 mins, p<.001, per successful enrollment 25.33±11.57 vs. 140.11±157, p<0.001, and randomization 92±34 vs. 319±385, p<0.001, compared to passive strategy.

Conclusions: Adopting a process of active outreach allows higher and more efficient enrollments for the provision of CoPE, necessary for informed KRT decision-making.

Funding: Veterans Affairs Support

SA-PO1113

Longitudinal Study of Conservative Kidney Management by Using Tools to Identify Palliative and End-of-Life Care Needs

Ying-ying Seow,[1] Swee Ping Teh,[1] Ivan Wei Zhen Lee,[1] Koey Cheng,[2] Angelica Lee,[2] Lee Ying Yeoh.[1] *[1]Sengkang General Hospital, Singapore, Singapore; [2]Lee Kong Chian School of Medicine, Singapore, Singapore.*

Background: Trajectory of end-stage kidney disease (ESKD) patients on conservative care varies. The objective of study was assessing the utility of objective assessment tools and mortality outcome.

Methods: This is a single center, prospective study of conservative kidney management patients from April 2021 to February 2024. Palliative trained community nurse performed monthly home visit and assessment. Edmonton symptom assessment system revised (ESASr version 2016), resource utilization groups activities of daily living (RUG-ADL) and palliative performance scale (PPS) were used and monitored longitudinally. SPSS version 27 was used for analysis, $p < 0.05$ is considered significant.

Results: A total of 103 patients with median follow-up of 11.1 months (IQR: 0.4, 15.8). Forty-seven patients passed away during the study. The baseline characteristics including female 64.1%, Chinese 80.6%, mean age 79.6±7.7 years, estimated glomerular filtration rate 10.5±3.4ml/min and Charlson comorbidity index 8.4±1.9. No significant difference between the survived versus demised group. However, those demised patients had higher ESASr (4.4 vs 2.0), RUG-ADL (6.3 vs 4.9) but lower PPS (59 vs 67) at baseline. Mixed model using repeated measurements for ESASr, RUG-ADL and PPS were done. The variance within each time point for RUG-ADL, ESASr and PPS were 1.5, 6.5 and 27.4, whereas covariance between any 2 time-points were 7.2, 11.3 and 136.9 respectively. There was no interaction with PPS model. The CKM patients have relative stable PPS until last few weeks of life (figure1).

Conclusions: This study demonstrated the high degree of symptom burden and functional decline toward the end of life for CKD patients managed conservatively. Optimal community care allow close monitoring of symptoms with optimization of care and timely referral to hospice service to reduce hospitalization for end-of-life care.

Funding: Government Support - Non-U.S.

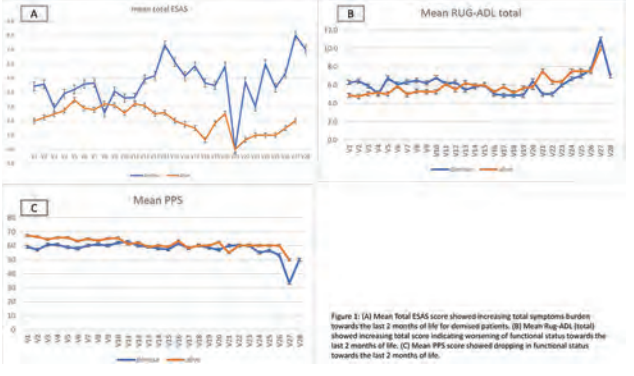


Figure 1: (A) Mean Total ESAS score showed increasing total symptoms burden towards the last 2 months of life for demised patients. (B) Mean Rug-ADL (total) showed increasing total score indicating worsening of functional status towards the last 2 months of life. (C) Mean PPS score showed dropping in functional status towards the last 2 months of life.

SA-PO1114

Age-Stratified Cost of Care in CKD: Real-World Data from a Retrospective Cohort Study

Satabdi Chatterjee,[1] Adrian R. Levy,[2] Sydnie Stackland,[3] Lindsay Bengtson,[1] Bonnie M. Donato.[1] *[1]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; [2]Dalhousie University, Halifax, NS, Canada; [3]Panalgo LLC, Boston, MA.*

Background: Chronic kidney disease (CKD) affects an estimated 14% of US adults, and is more common in those aged 65 years or older, than younger age groups. Little is known regarding the costs of CKD by age. In a large cohort of patients with prevalent CKD, this study described the mean total and direct medical costs accrued in the overall and age-stratified cohorts.

Methods: A retrospective longitudinal cohort study was conducted using Optum® Market Clarity electronic health record-linked claims data. The study cohort included adults with 2 estimated glomerular filtration rates <60 ml/min/1.73m^2 (3-12 months apart) followed by an ICD 9/10 code for CKD, and 1-year of continuous enrolment pre- and post-CKD diagnosis. These included patients diagnosed before January 1, 2020 plus new cases arising in 2020 (prevalent cohort); subjects who died or disenrolled in 2020 were excluded upon censoring. Total costs including direct medical costs (inpatient, outpatient, emergency department) as well as medications were calculated for the prevalent CKD cohort for the year 2020. Mean costs per patient were computed for the overall cohort and by age groups.

Results: In 2020, there were 214,631 patients with CKD, consisting of: 7,270 (3.4%) aged 18-49 y; 44,879 (20.9%) aged 50-64 y; 115,070 (53.6%) aged 65-80 y; and 47,412 (22.1%) aged ≥81 y. The mean (SD) total and medical costs were $68,095 (139,099) and $48,379 (104,185), respectively. Cost breakdown by age groups showed annual mean total costs of: $82,958 (203,481), $76,073 (170,039), $69,675 (135,308), and $54,432 (95,669), among the 18-49, 50-64, 65-80, and ≥81 y subgroups, respectively. Total medical costs were $53,388 (139,247), $50,826 (126,435), $49,614 (101,644), and $42,297 (76,868), respectively, ranging from 64% in those aged 18-49 to 78% among those ≥81 y.

Conclusions: In a large cohort of insured patients with prevalent CKD, medical costs accounted for nearly two-thirds of the total costs, and this proportion increased in older age groups. Better understanding of the drivers of medical costs by age along with other sociodemographic and clinical characteristics can provide critical insights on surveillance of CKD, and consequently, informing optimal strategies for reducing the burden of CKD.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO1115

Timeliness of Documentation and Costs of Care in Adults Newly Diagnosed with CKD

Satabdi Chatterjee,[1] Adrian R. Levy,[2] Sydnie Stackland,[3] Lindsay Bengtson,[1] Bonnie M. Donato.[1] *[1]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; [2]Dalhousie University, Halifax, NS, Canada; [3]Panalgo LLC, Boston, MA.*

Background: Among persons with new onset chronic kidney disease (CKD), previous research has found considerable delay between laboratory evidence and documented diagnosis of the condition. However, the consequences of diagnostic delay are not known. Among adults with laboratory evidence (two estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 measured between 3-12 months apart) and a documented diagnosis of CKD (using ICD 9/10 codes), the study described the mean annual costs, among those with a documentation of the diagnosis within six months ("timely"), and greater than six months ("delayed") of laboratory-based CKD.

Methods: A retrospective longitudinal cohort study was conducted using 2009-2020 Optum® Market Clarity electronic health record-linked claims data among adults with an incident diagnosis of CKD. The study computed the mean total annual costs, which included direct medical (inpatient, outpatient, emergency department) costs and pharmacy costs (in 2022 United States Dollars) between cohorts stratified by the timing of CKD diagnosis. Mean annual costs for each component were calculated by dividing the costs incurred during follow up for each patient divided by the number of years of follow-up that the patient contributed, and represented cost per patient per year.

Results: A total of 193,539 individuals with incident diagnosis of CKD were included; of them, 55,154 (28.5%) had a timely documented diagnosis of CKD, while 138,385 (71.5%) recorded a delayed documentation. The mean (SD) total annual costs were $46,030 (194,293) among those with timely diagnosis, and $50,151 (463,278) among the delayed cohort. Breaking down those totals, the annual mean medical costs were $37,054 (190,103) among those with timely diagnosis, and $41,007 (461,608) with delayed diagnosis. The mean annual pharmacy costs were $8,977 (31,296) and $9,145 (30,035) in timely diagnosed and delayed cohorts, respectively.

Conclusions: In large cohort of US adults with incident CKD, our descriptive analysis found that, less than 30% had a timely documentation, and incurred lower costs than the cohort with delayed documentation. While this could be partially driven by the selection of patients in the timely and delayed groups, our preliminary findings suggest the need for timely documentation of CKD.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO1116

RevOCE CKD: Revolutionising Outpatient Care for Patients with CKD

Hannah M. O'Keeffe,[1] Saif Al-Chalabi,[1] Ivona Baricevic-Jones,[1] Pierina Kapur,[2] Carlie A. Gardner,[3] Fiona Mendell,[3] Jude Allen,[1] Schanhave Santhirasekaran,[1] Paul W. Robinson,[1] James Ritchie,[1] Philip A. Kalra,[1] Dimitrios J. Poulikakos,[1] Smeeta Sinha.[1] *[1]Northern Care Alliance NHS Foundation Trust, Salford, United Kingdom; [2]Chapel Group Medical Centre, Manchester, United Kingdom; [3]Newbury Green Medical Centre, Manchester, United Kingdom.*

Background: Early detection of chronic kidney disease (CKD) including testing for urine albumin:creatinine ratio (uACR), and risk stratification using tools like the kidney failure risk equation (KFRE) enables proactive management. This facilitates the initiation of renoprotective therapies and earlier identification of patients at risk of progression who should be seen in specialist care. This programme is a multifaceted Quality Improvement intervention to improve CKD management, including the establishment of a virtual multidisciplinary meeting (MDT) to provide specialist advice to General Practitioners (GPs), the creation of a pharmacy medications optimisation pathway, and the utilisation of data to highlight high risk patients.

Methods: Virtual MDTs were established as a pilot with two primary care practices, commencing March 2023. Five MDTs have been carried out in these practices, with an educational component, and approximately 6 patients discussed at each. The virtual MDTs have now been scaled to a third practice, and a primary care network where 8 practices meet together. The MDTs have been iterative, with changes made based on feedback. Patients have been selected by GPs for discussion and data from the practices has been used to identify high risk patients.

Results: Of patients (n=38) discussed at MDT, the majority were managed remotely (n=29, 76.3%) avoiding onward referral. More than 50% of patients discussed had medication changes (e.g. recommendation to commence an SGLT2 inhibitor). The two practices involved in the project since commencement now have CKD coding significantly above average in the region; prevalence of 4.85% and 3.41%, compared to an average of 3.06%. They have uACR screening rates above average; 60.6% and 70.6%, compared to 45.2%. They have SGLT2 inhibitor prescribing rates above average at 35.9/1,000 and 45.8/1,000, versus 29.8/1,000 for the region.

Conclusions: This model has proven acceptable to primary care and can improve patient care, with quicker access to specialist input without the need for patients to be seen in clinic and the associated waiting times. We plan to scale this to additional practices and primary care networks with ongoing assessment of the outcomes and impact.

SA-PO1117

Preemptive Outpatient Clinic Experience: Holistic Approach vs. Standard of Care

Carmen Sivo,[1] Raffaella Guido,[1] Emanuela Cataldo,[2] Ilario Russo,[1] Francesca Annese,[1] Paola M. Acquaviva,[1] Gloria Rana,[1] Gianvito Caggiano,[1] Marco Fiorentino,[1] Adele Mitrotti,[1] Loreto Gesualdo.[1] *[1]Universita degli Studi di Bari Aldo Moro, Bari, Italy; [2]Poliambulatorio Altamura, Altamura, Italy.*

Background: Pre-emptive kidney transplantation (PKT) represents the best option of renal replacement therapy (RRT), but it is still underused.

Methods: We analyzed lab parameters at baseline, at the last follow-up and RRT initiation outcomes in a cohort of 404 chronic kidney disease (CKD) patients with G4-G5 KDIGO-stages, afferent to pre-emptive outpatient clinic at Policlinico of Bari (Apulia, Italy), from January 2017 to January 2024. Inclusion criteria: age within 18 e 80 years, eGFR CKD-EPI < 30 ml/min. We compared different parameters of CKD progression in a group of patients treated with a multidisciplinary holistic approach (that included a nutritional and psychological counseling) and a group of patients managed with standard of-care approach.

Results: Patients (262 M and 142 F) had a mean age of 55 years, with follow-up mean timing of 686,3 days. Of the 404 patients, 139 started hemodialysis, 122 are still in follow-up, 69 chose peritoneal dialysis, 43 underwent PKT, of which 36 from living donors and 7 from deceased donors, while 23 were lost at follow up and 8 died. Patients treated with multidisciplinary holistic approach (N=73) had a lower cumulative probability of initiating RRT (LogRank test: p=0.003) rather than the standard of care group (Fig. 1). Specific nutritional approach was associated with a significative azoturia reduction in the holistic group (15,5 vs 20,3 g/24h); while the use of music- therapy intervention determined a reduction in anxiety and tiredness patients' perception.

Conclusions: Multidisciplinary approach could represent an opportunity to slow CKD progression and increase the number of PKT. These preliminary data lay the foundations for a careful management of advanced CKD patients.

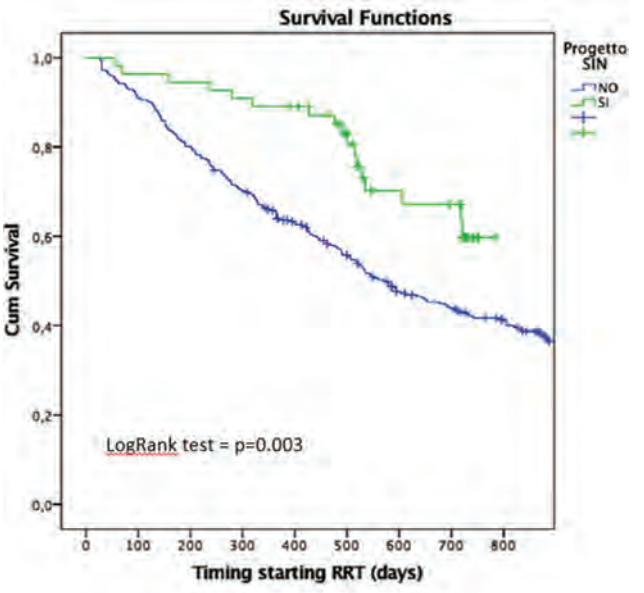


Fig. 1 Cumulative probability of initiating RRT in the holistic and standard- of- care groups.

SA-PO1118

Slicer Dicer as a Potential Tool for Self-Assessment

Richard Hae,[1,2] Sunchit Madan,[1,3] Anita Acai,[1,2] Steven Wong,[1,2] Azim S. Gangji.[1,2] *[1]McMaster University, Hamilton, ON, Canada; [2]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada; [3]William Osler Health System, Brampton, ON, Canada.*

Background: Self-assessment is a crucial competency for physicians, yet the evidence suggests that physicians have limited ability to do so and assessment of competence requires external feedback. Slicer Dicer is a self-service reporting tool on Epic that enables efficient patient data collection, providing a potential tool to self-assess practice patterns. Our study aims to explore whether Slicer Dicer can collect meaningful data for physicians to practise self-assessment. We piloted this question collecting data on prescribing patterns of sodium-glucose co-transporter 2 inhibitors (SGLT2i) in nephrology clinic patients with diabetes mellitus (DM) and chronic kidney disease, aligning with current care standards for this cohort.

Methods: Slicer Dicer was used to collect data from July 1, 2023 to December 31, 2023. Patients were captured using filters by provider, context, visit type, and medical history. "Slices" by medications were created to determine the number of patients on an SGLT2i.

Results: Slicer Dicer captured 1357 patients in the nephrology clinic amongst thirteen nephrologists with a diagnosis of DM who may benefit from an SGLT2i. Of these, 627 (46.2%) of these patients were found to be on an SGLT2i. The percentage of patients on an SGLT2i ranged from 32.9% to 61.4%.

Conclusions: We highlight the potential for Slicer Dicer as an innovative method to collect data using easily accessible EMR tools. Future directions will be aimed at how physicians can use this objective data to self-assess their practice by closer analysis of patients who are not meeting current care standards.

	Patients on SGLT2i	Total number of patients	Percentage (%) of patients on SGLT2i
Nephrologist #1	53	161	32.9
Nephrologist #2	94	225	41.8
Nephrologist #3	55	108	50.9
Nephrologist #4	87	205	42.4
Nephrologist #5	33	63	52.4
Nephrologist #6	62	101	61.4
Nephrologist #7	64	151	42.4
Nephrologist #8	37	91	40.7
Nephrologist #9	77	168	45.8
Nephrologist #10	58	105	55.2
Nephrologist #11	88	166	53.0
Nephrologist #12	54	115	47.0
Nephrologist #13	20	41	48.8
Total	627	1357	46.2

Patients in nephrology clinic with DM from Jul 1-Dec 31, 2023 by nephrologist

SA-PO1119

A LUCID Approach to CKD Care Using Collaborative Primary and Secondary Care Virtual Clinics

Rupert Major,[1,2] James Burton.[1,2] LUCID (Leicester, Leicestershire, and Rutland Chronic Kidney Disease Integrated Care Delivery Project). *[1]University of Leicester, Leicester, United Kingdom; [2]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom.*

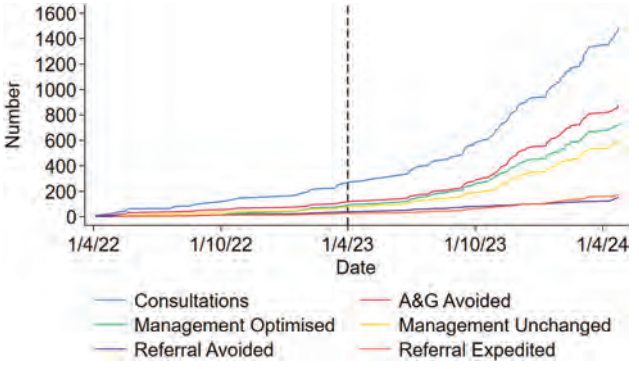
Background: Most people living with CKD are managed in a traditional primary care setting but more collaborative working with secondary care physicians may improve cardiovascular and ESKD outcomes. Standardized systems for CKD screening at a federal level are currently being considered and incentive systems, such Medicaid's merit-based incentive payment system value pathways, may face implementation barriers to improving care.

Methods: We developed and implemented a novel education and virtual CKD service in the UK - "The **L**eicester, Leicestershire, and R**U**tland **C**hronic Kidney Disease **I**ntegrated Care **D**elivery Project" (LUCID) - across an area of ~1.2 million people with ~60,000 people living with CKD. The programme focused on four core LUCID principles for people living with CKD: 1. Identification of cases at a population level 2. Optimisation of guideline directed medical therapy 3. Surveillance of the known CKD population 4. Education for public and professionals

Results: In April 2022 virtual clinics were piloted in an area of ~150,000 people with the focus on the four key principles including education during virtual clinics. Virtual clinics were delivered by an attending nephrologist in collaboration with primary care physicians and pharmacists. The program was expanded in April 2023 to make virtual clinics available to 130 primary care practices with support via an EHR-based CKD dashboard to support the four LUCID principles. Upto 1st April 2024, 1341 consultations have occurred across 102 virtual clinics. 590 episodes of medicines optimisation (Figure 1) have occurred for people living with CKD and often other co-morbidities such as hypertension (75%), diabetes (56%) and heart failure (14%).

Conclusions: LUCID can lead to the delivery of identification, optimization, surveillance and education for people living with CKD and other co-morbidities at a population level. LUCID may represent a clinical model that can promote efficient care, especially in the context of Medicaid's incentive systems and if federal CKD screening were to be implemented.

Funding: Commercial Support - AstraZeneca UK



SA-PO1120

A Collaborative Approach: Pharmacist-Led CKD Clinic in the Primary Care Setting

Erica Reinhardt, Joanna N. Peduzzi, Nathan Jaworsky, Jessica Zuik, Nissreen El Fadawy. *University Hospitals, Cleveland, OH.*

Background: Chronic Kidney Disease (CKD) affects a growing number of US adults every year, with many unaware of their condition. To address this, our ambulatory care pharmacy team has initiated a pharmacist-led CKD clinic in the primary care setting. We aim to identify and provide free Telepharmacy services, treatment, and monitoring for at least 100 patients in the early stages of CKD within our internal medicine practice over the course of a year and measure the impact of our services.

Methods: Patients were selected for pharmacist intervention based on specific criteria, including diagnoses of diabetes, hypertension, and/or CKD, and GFR <90 ml/min and/or urine ACR >30 mg/mmol. Initially, 124 patients were identified candidates for the pilot program, and as of May 2024, 108 patients are participating. Among these patients, 100 have diabetes and 31 have a urine ACR >30 mg/mmol. After identification, patients had a telepharmacy visit with a pharmacist, who completed a medication reconciliation, reviewed lab results, initiated appropriate medications, and provided instructions for lab tests and follow-up visits. The pharmacy team tracked medication adherence, referrals to nephrology, and lab data.

Results: Iinitial findings indicate the pharmacist-led program is impactful. Regarding medication adherence, all patients were prescribed an SGLT2i, and 75% were prescribed an ACE/ARB. Twelve patients were originally under the care of a nephrologist. No new referrals to nephrology were made. Additionally, 59% of patients experienced an increase or no change in their GFR.

Conclusions: The pharmacist led team will continue to follow these patients through July 2024. To this point, the impact of a pharmacist-led CKD clinic has demonstrated increased compliance on medication access and adherence with 100% of patients being treated with an SGLT2i and 75% an ACE/ARB as appropriate. Additionally no new referrals were made to nephrology for these patients throughout the pilot program. And finally, 59% of patients to date have seen a plateau or increase in their GFR indicating preservation of kidney function.

SA-PO1121

Perspectives and Current Practices in the Provision of Sexual Health Support for People with CKD: A Survey of Canadian Health Care Providers

Meghan J. Elliott,[1] Shannan Love,[1] Sabrina Jassemi,[1] Dwight Sparkes,[4] Sandi M. Dumanski,[1] Brenda Hemmelgarn,[2] Clare Mckeaveney,[5] Janine Farragher,[3] Katie B. Ahrenholz,[1] Gillian Crysdale,[1] Nancy Verdin,[4] Maoliosa Donald.[6] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; [3]University of Toronto, Toronto, ON, Canada; [4]Can-SOLVE CKD Network, Vancouver, BC, Canada; [5]Queen's University Belfast, Belfast, United Kingdom; [6]University of Calgary, Calgary, AB, Canada.*

Background: People living with chronic kidney disease (CKD) have identified sexual health as an important aspect of their wellbeing and kidney care. However, limited information is available to integrate sexual health support within multidisciplinary CKD care. We aimed to explore the perceptions, practices, and needs of healthcare providers in Canadian multidisciplinary CKD clinics related to sexual health support for individuals with non-dialysis CKD.

Methods: We administered an online survey to healthcare providers (i.e., nephrologists, nurses, allied health professionals) from multidisciplinary CKD clinics across Canada. The survey included questions related to providers' understanding of sexual health, current practices, and perceived gaps in how patients' sexual health is addressed in routine CKD care. We conducted semi-structured interviews with interested respondents to expand on survey responses. Data were analyzed descriptively for the survey and using content analysis for the qualitative data.

Results: Thirty nurses, 23 nephrologists, 8 allied health professionals, 5 managers, and 5 other team members (e.g., unit clerk) completed the survey between September and December 2023. Participants most commonly defined sexual health as physical symptoms related to sexual function, prevention of sexually transmitted infections, and pregnancy and fertility care. Most respondents reported not having any formal training in the area (80%) and having discussed sexual health with less than one quarter of their patients (71%). While respondents reported that sexual health was most often discussed when patients introduced the topic (39%), they indicated that less than one quarter of patients raised concerns during clinic visits (89%). Qualitative findings complemented survey results and elaborated on key barriers to integrating sexual health into routine care, including lack of knowledge, inadequate training, and time constraints.

Conclusions: We identified variability in sexual health definitions and care practices among healthcare providers from multidisciplinary CKD clinics. Identified barriers will inform strategies to enhance sexual health supports for individuals with CKD.

SA-PO1122

Patient and Caregiver Perceptions of Health Risks Associated with CKD: A Thematic Synthesis of Qualitative Studies

Meghan J. Elliott,[1] Shannan Love,[1] Kathryn M. King-Shier,[3] Ping Liu,[2] Heather Dumka,[1] Caitrin O'Connor,[1] Pietro Ravani.[1] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]University of Calgary, Calgary, AB, Canada; [3]University of Calgary Faculty of Nursing, Calgary, AB, Canada.*

Background: People with chronic kidney disease follow varying disease trajectories, but it is unclear how they understand and use information about their individual risk of adverse outcomes. We aimed to thematically synthesize the published qualitative literature on how patients with chronic kidney disease not receiving kidney replacement therapy and their care partners perceive their individual risk of disease progression, kidney failure, and death.

Methods: We searched relevant electronic databases for qualitative studies in adults with chronic kidney disease not receiving kidney replacement therapy or their care partners, and that explored perceptions of individual risks of progression to kidney failure or death. Studies were excluded if participants had committed to a kidney replacement therapy or were receiving palliative or end-of-life care. Two research team members screened titles and abstracts and retrieved relevant full-text articles for review. Disagreements were resolved through discussion. We extracted details of included studies and conducted a thematic synthesis of findings captured descriptively or as participant quotes from primary studies.

Results: Of the 7671 citations screened, we included 39 studies. All studies involved patients living with chronic kidney disease, and 5 involved care partners. Only 4 studies addressed perspectives on risk and prognosis as the primary research objective. We characterized 5 themes – Participants conveyed a lack of personalized conversations (*Theme 1*) and limited prognostic understanding (*Theme 2*), which contributed to decisional conflict when choosing between kidney failure treatment options that they perceived as equally unappealing (*Theme 3*). Individuals' readiness and acceptance of information about their individual risks influenced if and how they took action to modify potential outcomes (*Theme 4*) and anticipated implications for life participation (*Theme 5*).

Conclusions: Few qualitative studies have explored the perspectives of patients and their care partners specifically related to their individual risks of kidney failure and death. Our findings highlight a lack of discussions about perceived risk and need for additional supports to facilitate decisions as patients' chronic kidney disease progresses.

SA-PO1123

Comparison of Claims-Based Definitions vs. Measured Frailty in Patients with CKD

Hailey V. Hildebrand,[1,2] Oksana Harasemiw,[1] Ranveer S. Brar,[1,2] Paul Komenda,[1,2] Claudio Rigatto,[1,2] Bhanu Prasad,[3] Clara Bohm,[1,2] Navdeep Tangri.[1,2] *[1]Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, MB, Canada; [2]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [3]Saskatchewan Health Authority, Saskatoon, SK, Canada.*

Background: Frailty is common in patients with Chronic Kidney Disease (CKD), and those affected by both conditions are at increased risk of adverse outcomes including worsened disability, hospitalization, and death. Collecting data on frailty status as part of routine clinical care could enhance care by identifying patients at high risk of adverse events. Clinical assessment of frailty is time and resource intensive. Frailty definitions based on administrative data might provide a feasible and efficient alternative. The primary objective of this study was to compare agreements between administrative claims-based definitions for frailty versus objectively measured frailty in adults with advanced (Stage G4+), non-dialysis CKD.

Methods: The cohort consisted of Manitoba participants from the Canadian Frailty Observation and Interventions Trial (CanFIT). This multicentre cohort study followed 442 adults with an eGFR < 30mL/min/1.73 m^2 longitudinally. At each visit, an assessment was conducted to determine frailty status using the Fried Frailty Index, Short Physical Performance Battery, and healthcare providers impression. The CanFIT database was linked to several administrative health databases at the Manitoba Centre for Healthy Policy to calculate two claims-based frailty indices, the Segal Frailty Index and the Pre-operative Frailty Index, which have been previously validated in the non-CKD literature.

Results: Of participants included, the mean age was 65.8±13.9 years and 58.4% were male; 87.8% had hypertension, 61.3% dyslipidemia, and 57.5% diabetes. The prevalence of frailty varied from 18.1% to 69.5% depending on definition. Agreement between claims-based frailty indices and objective and subjective measures of frailty was low to modest (κ 0.08–0.31). Individuals considered frail, using both administrative or measured definitions, had an increased risk of all-cause mortality and hospitalization.

Conclusions: This study suggests that claims-based definitions of frailty developed in the general population are poor substitutes for identifying frailty in individuals with advanced, non-dialysis CKD. Efforts to integrate valid and efficient frailty assessments in clinical practice are needed to improve clinical decision making.

SA-PO1124

A Contemporary Economic Model of CKD in the United States

Andrew Briggs,[1] Ciaran Kohli-Lynch,[3] Satabdi Chatterjee,[5] Bonnie M. Donato,[5] Adrian R. Levy,[4] Csaba P. Kovesdy.[2] *[1]London School of Hygiene & Tropical Medicine, London, United Kingdom; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [3]Northwestern University, Evanston, IL; [4]Dalhousie University, Halifax, NS, Canada; [5]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT.*

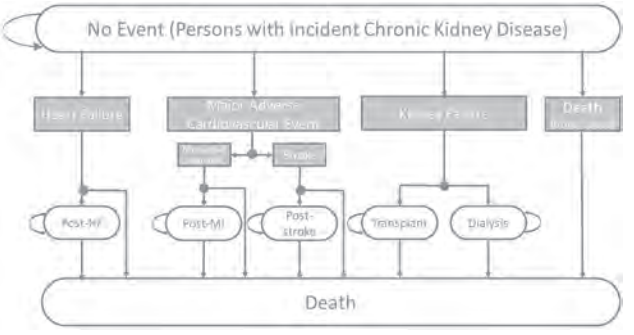
Background: Chronic kidney disease (CKD) impacts an estimated 14% of US adults, and is associated with reduced quality of life, progression to kidney failure, and cardiovascular disease (CVD), resulting in high healthcare costs. The recently updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have highlighted the importance of CVD management to improve CKD outcomes and including a role for sodium-glucose cotransporter-2 (SGLT2) inhibitors in delaying disease progression and improving CVD outcomes.

Methods: A state transition model was developed (see figure) to follow a hypothetical cohort of US adults with CKD over their lifetime. Progression of CKD was tracked through KDIGO health states defined by estimated glomerular filtration rate (eGFR) and urine albumin creatinine ratio (uACR). Individuals with CKD could transition to kidney failure, major adverse cardiovascular event (myocardial infarction or stroke), heart failure, or death from other causes. Probability of a first event was determined by eGFR, uACR, and diabetes status, with age and sex determining the background mortality risks. Individuals who had a non-fatal first event were followed until death. Resource utilization, costs, transition probabilities, and utilities were derived from peer-reviewed studies.

Results: The model predicted clinical events associated with current management as well as healthcare costs and quality adjusted life years (QALY). Under usual care, the model estimated lifetime outcomes of 6.8 QALYs and $150,386, with time prior to a clinical event contributing most to the QALYs, and dialysis contributing most to the healthcare costs. KDIGO guidelines for optimizing CVD treatment and SGLT2 inhibitor treatment were shown to be cost-effective (cost-per-QALY<$100,000).

Conclusions: The current model can predict clinical events and consequent impacts on healthcare costs and QALYs. This enables estimation of the value of various guideline-recommended strategies designed to treat patients at all stages of CKD.

Funding: Commercial Support - Boehringer Ingelheim



SA-PO1125

Experience of Patients and Caregivers During the Predialysis Period: A Thematic Analysis

Annie-Claire Nadeau-Fredette,[1,2] Émilie Robitaille,[1] Guylaine Cyr,[1] Karthik K. Tennankore,[3] Kelley Kilpatrick.[4,1] On behalf of the TRANSIT-CARE Study Group. *[1]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [2]Universite de Montreal Faculte de Medecine, Montreal, QC, Canada; [3]Nova Scotia Health Authority, Halifax, NS, Canada; [4]McGill University, Montreal, QC, Canada.*

Background: Patients living with advanced chronic kidney disease (CKD) often plan to initiate dialysis when their kidney function declines. While several studies have explored components associated with dialysis modality choice, little is known as to how patients and their caregivers experience the period preceding dialysis initiation.

Methods: In this qualitative study, semi-structured interviews were performed with patients (n = 9) followed in an advanced multidisciplinary CKD clinic with an eGFR <12 ml/min/1.73 m^2 who had already chosen their dialysis modality and with caregivers (n = 9). Thematic analysis was used to identify patients and caregivers' experiences during the predialysis time.

Results: Patients participants were 69 ±7 years, included 4 women and 5 men. Among them, 5 patients had chosen home dialysis and 4 facility hemodialysis. Caregivers were mostly women (n=7/9) and most were living with the patient with CKD. Four main themes described patients and caregivers experience: ***successive shocks of announcements*** (from CKD diagnosis to imminent need for dialysis), ***minimizing repercussions on lifestyle*** regardless of the choice of dialysis therapy, ***personality type influencing feelings*** linked to dialysis anticipation (optimist versus pessimist, hope versus despair), ***reassurance through support network*** (including loved one and healthcare professionals). Patients and caregiver pairs had mostly concordant experience and overall, emotions toward dialysis were more often positive (hope of better future), although grief was also often identified.

Conclusions: This work highlights the need to individualize care of patients planning to start dialysis, not only at time of modality selection, but also as patients and caregivers near the initiation of dialysis.

Funding: Government Support - Non-U.S.

SA-PO1126

Patients' Experiences Receiving a CKD Diagnosis: Opportunities for Clarity, Empowerment, and Support

Leah C. Bush,[1] Eleanor Rivera,[2] Sarah J. Schrauben.[1] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of Illinois Chicago, Chicago, IL.*

Background: Chronic kidney disease (CKD) is a highly prevalent condition, affecting >1 in 7 US adults. Advances in basic science and clinical management of CKD have improved clinical outcomes, but gaps remain in the understanding of patient experiences with the diagnosis of CKD. Such an understanding is crucial to mitigate psychological challenges experienced with receiving a CKD diagnosis and to establish the patient knowledge, agency, and support necessary for optimal patient-driven CKD management.

Methods: We conducted semi-structured interviews with patients with CKD stage 3 or 4 from nephrology clinics using an interview guide related to experiences about being diagnosed with CKD. Interviews were audio recorded, transcribed verbatim, and analyzed inductively using thematic analysis.

Results: We interviewed 30 patients. We identified 5 themes clustered around reactions to receiving a CKD diagnosis: 1) surprise, shock, and fear attributed to the unexpected nature of the diagnosis and the uncertainty about potential need for dialysis or transplant; 2) reluctance to disclose CKD diagnosis to friends and/or family given the lack of overt symptoms and stigma around having a chronic disease; 3) bidirectional relationships between CKD and mental health, in that a CKD diagnosis poses a mental health stress test, and adequate mental health is necessary for optimal CKD management; 4) lack of social support from friends and family; and 5) progression through the stages of grief toward acceptance of the diagnosis (Table).

Conclusions: Our findings describe patients' experiences receiving the diagnosis of CKD, which informs practical recommendations for diagnosis communication, including a focus on patient empowerment and facilitating support services via the CKD care team. Opportunity also exists for greater public understanding of the role of the kidneys for overall health and for greater public familiarization with CKD.

Funding: NIDDK Support

Themes related to Receiving and Coping with CKD Diagnosis

1. Alarming Reaction to Diagnosis	"it was just shock… it was very sudden… It was just kind of like, where did this come from? Like what's going to happen?" -participant #3
2. Reluctance to Disclose Diagnosis	"When you hear the words chronic and disease together – chronic, means I'm going to have this forever, and a disease, something I can't do anything about. Of course, I didn't tell my family. I still haven't told them…they'd probably say, "you have a disease?" -participant #9
3. Linkage of Mental health and CKD	"I'm scared all the time. Am I doing the right thing?" - participant #25 "I get depressed thinking about dialysis." - participant #1
4. Lack of social support	"people I thought were my friends weren't because they were afraid I was gonna ask them for something." - participant #24 "I don't turn to anybody [for support]. I handle everything myself." - participant #6
5. Stages of Grief and Acceptance of Diagnosis	"you start accepting things for what they are. [CKD] is something that has to be managed and you can take control over it." -participant #3

SA-PO1127

Patient-Reported Outcomes and Associations with Clinical Events in a Cohort of People with Nondialysis-Dependent CKD

Dipal M. Patel,[1] Dingfen Han,[1] Chirag R. Parikh,[1] Jung-Im Shin,[2] Kristin Riekert,[1] Deidra C. Crews.[1,2] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

Background: People with CKD face substantial disease burden and impairments to quality of life (QOL). The distribution and severity of these patient-reported outcomes (PROs), and whether they are associated with clinical outcomes, is underexplored for people with non-dialysis dependent CKD.

Methods: We quantified general health, QOL, and physical and mental health symptoms, as reported by people with CKD G3-5 who completed an electronic PRO assessment tool prior to Johns Hopkins (JH) nephrology clinic follow-up visits. We performed multivariable regression analyses to investigate the association of PROs with dialysis initiation and 1-year hospitalization.

Results: We collected 2180 PRO assessment tool responses from 1091 individuals with CKD G3-5 (**Figure**). QOL, general health, and some symptoms were worse for people with advanced stages of CKD compared to earlier stages. Among the full cohort, 99 individuals (9%) were hospitalized within 1 year (231 total number of hospitalizations), and 177 (16%) started dialysis. After adjustment for age, sex, comorbidities, and individual measures of socioeconomic status, low self-reported general health was associated with higher risks for hospitalization and dialysis initiation, with every one-point increase in general health scores being associated with a 12% reduction in incidence of hospitalization and a 17% reduction in the risk of dialysis initiation.

Conclusions: People with non-dialysis-dependent CKD experience several symptoms and impairments to QOL and self-perceived general health. Our findings highlight the utility of PRO assessment in identifying people at high risk for adverse outcomes including hospitalization and dialysis initiation.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities; National Heart, Lung, and Blood Institute, Private Foundation Support

	Average PRO assessment tool score, mean +/- S.D.				Regression coef. for CKD G5 (CKD G3a as reference)* (95% CI)	Incidence rate ratio for hospitalization** (95% CI)	Odds ratio of dialysis initiation (95% CI)***
	CKD G3a (n=297)	CKD G3b (n=534)	CKD G4 (n=519)	CKD G5 (n=428)			
Overall quality of life (1-10, 10 = best)	7.4 ± 1.7	7.3 ± 2.1	6.7 ± 2.0	6.8 ± 1.8	-0.3 (-0.7, 0.2)	1.03 (0.99, 1.08)	0.88 (0.81, 0.96)
General health (1-5, 5 = best)	3.1 ± 0.8	3.0 ± 0.9	2.8 ± 0.9	2.7 ± 0.8	-0.2 (-0.4, 0.0)	0.88 (0.80, 0.96)	0.83 (0.7, 0.97)
Physical symptoms (0=100, 100 = no symptoms)							
Cramps	89 ± 19.4	86.7 ± 21.3	82.7 ± 23.2	84.8 ± 20.3	-5.0 (-9.7, -0.2)	1.29 (1.21, 1.38)	0.86 (0.77, 0.96)
Pruritis	82.8 ± 24.3	85.2 ± 24.0	77.4 ± 26.7	83.8 ± 22.7	-0.5 (-6.1, 5.0)	1.07 (1.02, 1.11)	0.89 (0.82, 0.96)
Shortness of breath	89.7 ± 17.3	85.9 ± 22.5	83.8 ± 23.5	84.3 ± 22.8	-6.5 (-11.2, -1.8)	0.96 (0.9, 1.01)	0.9 (0.8, 1.01)
Lack of appetite	93.6 ± 16.5	92.1 ± 18.4	87.7 ± 21.6	88.0 ± 20.6	-5.4 (-9.7, -1.0)	1.43 (1.31, 1.56)	0.9 (0.77, 1.04)
Feeling washed out/drained	78.3 ± 25.3	74.7 ± 27.2	70.7 ± 27.2	71.1 ± 27.2	-7.6 (-13.7, -2.0)	1.02 (0.98, 1.05)	0.95 (0.9, 1.02)
Nausea or upset stomach	92.9 ± 16.7	90.7 ± 19.8	89.7 ± 19.5	88.4 ± 19.9	-6.3 (-10.3, -2.2)	1.45 (1.33, 1.59)	0.88 (0.76, 1.02)
Composite physical symptoms score	86.8 ± 12.4	85.4 ± 13.2	82.3 ± 14.8	84.6 ± 12.3	-3.0 (-6.0, 0.1)	1.13 (1.10, 1.16)	0.91 (0.86, 0.96)
Frequent urination at night (0=100, 100 = no symptoms)	79.0 ± 24.5	75.2 ± 26.1	75.3 ± 26.5	74.0 ± 27.0	-5.5 (-11.4, 0.5)	1.03 (0.99, 1.07)	1.08 (1.01, 1.15)
Mental health symptoms (0=100, 100 = no symptoms)							
Not feeling calm/peaceful	71.6 ± 22.7	71.7 ± 24.2	66.8 ± 25.2	67.9 ± 23.8	-3.6 (-8.8, 1.6)	1.09 (1.06, 1.11)	0.97 (0.92, 1.02)
Lack of energy	55.9 ± 25.7	51.8 ± 27.7	45.9 ± 25.3	47.4 ± 25.7	-6.9 (-12.4, -1.4)	1.00 (0.98, 1.03)	0.95 (0.9, 1.00)
Composite mental health score	69.3 ± 19.1	67.8 ± 20.3	63.3 ± 19.1	64.6 ± 19.2	-3.9 (-8.1, 0.3)	1.04 (1.01, 1.06)	0.94 (0.89, 0.99)

*Mixed regression models considering the clustering of individual patients was performed after adjustment for age, sex, comorbidities (heart failure, coronary artery disease, hypertension, and diabetes), Charlson comorbidity index, and quartiles of area deprivation index.
**Poisson and ***logistic regression for clinical outcomes were performed after adjustment for the same variables as above, plus eGFR. Point estimates for hospitalization and dialysis are reported for each decile change in physical symptom and mental health scores.

Select PRO assessment tool scores and associations with clinical outcomes. Lower scores represent lower QOL and general health, and more prevalent physical and mental health symptoms.

SA-PO1128

Real-World Utilization of a Patient-Reported Outcome (PRO) Assessment Tool in Nephrology Clinic: Patient and Provider Perspectives

Dipal M. Patel,[1] Mary Ann C. Stephens,[1] Jessica M. Gotay-Lehmer,[1] Kristin Riekert,[1] Deidra C. Crews.[1,2] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

Background: Patient-reported outcome (PRO) assessment is a key component of person-centered care; however, approaches for utilizing PRO assessment tools in nephrology clinic are understudied. We integrated a PRO assessment tool into the electronic health record at Johns Hopkins (JH) and distributed it to people with CKD G3-5 prior to nephrology follow-up appointments. We evaluated determinants of patient and provider utilization of the PRO assessment tool.

Methods: We conducted surveys and individual semi-structured interviews of nephrology providers and people with CKD. We quantified questionnaire responses using descriptive statistics and performed thematic analysis of semi-structured interview transcripts.

Results: We surveyed 17 JH nephrology providers and 102 JH CKD patients. Answering Likert-scale questions (1=strongly disagree, 5=strongly agree), patients more strongly agreed with a need for symptom assessment compared to providers (mean ± S.D.: 3.9 ± 0.7 for providers and 4.5 ± 0.5 for patients, $p < 0.01$). Patients also more strongly agreed that PRO assessment tools would make patients "feel heard and understood" (mean ± S.D.: 3.5 ± 0.6 for providers and 4.2 ± 0.7 for patients, $p < 0.01$). Providers were uncertain if they would independently review and discuss PRO assessment tool scores during each clinic visit (mean ± S.D.: 2.6 ± 0.9). From semi-structured interviews of 15 providers and 21 patients, we identified key themes influencing utilization of the PRO assessment tool (Figure).

Conclusions: While the importance of PRO assessment is recognized by people with CKD and nephrology providers, we identified several barriers which should be addressed in order to improve the capability, opportunity, and motivation of care teams to incorporate PRO assessment tools into routine clinical care.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities; National Heart, Lung, and Blood Institute, Private Foundation Support, Clinical Revenue Support

Themes	Exemplary quotations
While symptom assessment is a routine part of CKD care, the role of nephrologists in discussing quality of life (QOL) and mental health is less clear.	"Well, if I needed to talk about it, I feel like I could talk about anything. I just don't really bring it up. Most visits, I'm just so fixated on the numbers and that they remain stable. That's pretty much what I focus on with her. Not really this bigger picture of my everyday health, 'cause I don't hadn't really associated that with the kidney disease." (*Person with CKD*)
Nephrologists may benefit from additional knowledge in symptom and QOL management.	"I think the barrier for me is how do I make them better with those symptoms. And I may not have all the tools necessary to improve those symptoms. And that's where I think we, as nephrologists, may fall short because we are not trained to manage those symptoms necessarily or even to make a good diagnosis of why they have those symptoms." (*Nephrology provider*)
Additional clinical support is needed to optimize utilization of PRO assessment tools in routine care.	"I feel, in terms of quality of life, easier access to allied health professional support, social work support, nutrition, definitely, palliative…having a team to address multiple issues that sometimes it's a little bit hard to be handled by the physician alone, I think, helps." (*Nephrology provider*)

Themes and exemplary quotations.

SA-PO1129

Symptoms and Impacts Experienced by People Living with Nondiabetic CKD (ndCKD) and Diabetic Kidney Disease (DKD): Qualitative Interview Findings

Sara Tadesse Bell,[1] Julia Stein,[2] Lara Ayala-Nunes,[2] Eleanor Scouler,[2] Sophi Tatlock,[2] Patricia Corey-Lisle,[3] Sharan Randhawa.[2] *[1]Genentech Inc, South San Francisco, CA; [2]Adelphi Values Ltd, Bollington, United Kingdom; [3]Formerly Genentech Inc, San Francisco, CA.*

Background: The congruence of the non-diabetic chronic kidney disease (ndCKD) and diabetic kidney disease (DKD) patient experience is not well-known. This study aimed to compare/contrast symptoms and health-related quality-of-life [HRQoL] impacts reported by ndCKD and DKD patients to provide initial insights as to whether a consistent patient-reported outcome (PRO) measurement strategy could be applied across both populations in clinical trials.

Methods: Semi-structured, concept elicitation interviews were conducted to explore patients' experiences of ndCKD/DKD. Interviews were audio recorded and verbatim transcripts were subject to thematic analysis in ATLAS.ti. Concepts identified were compared to explore similarities/differences in the patient experience of ndCKD and DKD.

Results: The sample was racially and ethnically diverse, comprising 24 participants (n=12 ndCKD [83.3% female]; n=12 DKD [66.7% female]), across CKD stages 2-5 and mean age 57 years (range 28-84). Almost all symptoms and impacts elicited were reported across both samples, though frequency of elicitation varied. Most participants (ndCKD n≥10/12; DKD n≥11/12) reported fatigue, low energy or weakness, frequent urination, swelling and nocturia. Erectile dysfunction (ED) was only reported in the DKD sample (n=2/12), which had a higher proportion of males. Restless legs was only reported in the ndCKD sample (n=1/12). Difficulty urinating, weight changes, gastrointestinal symptoms, and vision problems were reported by more DKD participants (n≥3). Muscle cramps were reported more frequently by ndCKD participants (n≥3). HRQoL impact reports were broadly comparable; impacts on diet/drinking were reported by more DKD participants (n≥3). All participants described emotional wellbeing impacts, and most (≥22/24) reported disruptions to daily activities and sleep. Other impacts included physical and social functioning, work and cognition.

Conclusions: Apart from ED and restless legs, all concepts were reported across both samples with small differences in elicitation frequency. Fatigue, frequent urination, swelling and nocturia were most frequently reported across both samples. Patients were also aligned on HRQoL impacts, suggesting that using the same PRO strategy in ndCKD/DKD may be appropriate, depending on the concepts of interest.

Funding: Commercial Support - This study was funded by Genentech, Inc., a member of the Roche Group

SA-PO1130

The National Kidney Foundation's CKD Learning Collaborative: Transforming Care across University Health in Kansas City, Missouri

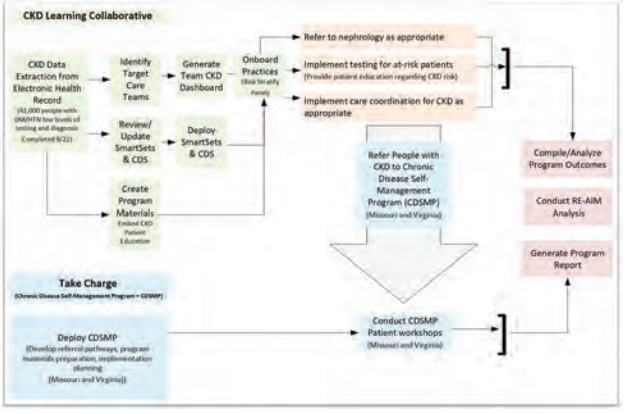
Jignesh Shah,[1,2] Rajib Bhattacharya,[1,2] Megan Schultz.[3] *[1]University of Missouri-Kansas City, Kansas City, MO; [2]University Health Truman Medical Center, Kansas City, MO; [3]National Kidney Foundation Inc, New York, NY.*

Background: National Kidney Foundation (NKF) implemented a CKD intercept project in collaboration with University Health(UH) to improve CKD diagnosis and recognition and clinician confidence and engagement in CKD management. This is done to implement a chronic disease self-management program (CDSMP) tailored for people living with CKD, using primary care outreach as the referral mechanism to Nephrology, and introduce a CKD learning collaborative model to provide integrated care delivery.

Methods: We assessed current CKD testing and diagnosis levels in select clinics at UH. We reviewed existing workflows for diabetes, hypertension, and wellness and worked with the technical team to include EHR data for risk stratification of the initial patient cohort. We determined the individual practices of participating clinicians, provided clinician decision support and workflow-related tools, then utilized them in partnership with clinicians and measured their confidence and engagement throughout interventions.

Results: We improved the identification of proteinuria and eGFR calculation of the at-risk patient population by 62.8%. Identification of patients with eGFR lower than 60, screened, identified, and staged appropriately improved by 60%. ARB and Statin use increased by, 89.9% and 28.5 %, respectively, across all CKD stages. We did not see significant improvements in SGLT2i, GLP-1 agonist, and MRA prescription patterns.

Conclusions: NKF and University Health (UH) partnered to introduce the CKD intercept project in select clinics. The comprehensive interventions covered various aspects of CKD management, improved CKD recognition in primary care, tested eGFR and Urine Albumin Creatinine Ratio, and referral patterns. Clinician confidence and engagement improved regarding CKD identification, self-management, NSAID avoidance ACEI/ARB, and SGLT2i use. We suggest community-level efforts to enhance CKD testing and management.



CKD collaborative model

SA-PO1131

Real-World Evaluation of Best Practice Patterns in CKD Management

Yan Ting Chua,[1] Clara L. Ngoh,[1] Priyanka Khatri,[4] Shilpa Rastogi,[2] Sky Wei Chee Koh,[5] Valerie Ma,[3] Wui Heng Goh,[3] Horng-Ruey Chua.[1] *[1]National University Hospital, Singapore, Singapore; [2]Ng Teng Fong General Hospital, Singapore, Singapore; [3]National University Health System, Singapore, Singapore; [4]Alexandra Hospital, Singapore, Singapore; [5]National University Polyclinics, Singapore, Singapore.*

Background: The incidence of kidney failure continues to rise amid an evolving landscape in chronic kidney disease(CKD) management, with improved therapeutics that prompted a series of practice guidelines. However, real-world uptake of CKD therapeutics, against a backdrop of polypharmacy, is unclear. We used our information systems to track adoption of best CKD practices in a regional healthcare cluster.

Methods: We performed a multicenter ambi-directional cohort study of patients with CKD, aged≥21, from 7 primary care institutions and 3 acute hospitals. We extracted quarterly anonymized demographics, laboratory and prescription data from electronic health records from March 2022 to March 2024 to evaluate aggregated measures in CKD care. We defined CKD by ICD-10 diagnosis codes and ≥2 estimated glomerular filtration rate(eGFR)≥90 days apart of <60mL/min/1.73m². We excluded patients with kidney failure.

Results: We studied 34,217 patients. Mean age was 72±12years. Clinicians did not monitor 33% of patients for albuminuria or proteinuria. Less than half of diabetic patients aged<80 with CKD G1-3b achieved Hba1c<7%. Of patients aged<80 with eGFR<60, diabetes, ischemic heart disease, stroke or peripheral vascular disease, 71% received statins; 69% had lipids measured, of whom 72% achieved low-density lipoprotein<2.6mmol/L. Use of angiotensin II receptor blockers(ARB) or angiotensin-converting enzyme inhibitors(ACEi) in albuminuric patients was 74%; only 40% received ceiling doses despite 4% prevalence of hyperkalemia and 4% with mean systolic blood pressure<110mmHg. Penetrance of sodium-glucose co-transporter-2 inhibitors(SGLT2i) increased from 21% to 40% among albuminuric patients during the study period. Of patients aged<80 with albuminuric CKD G1-3b, 21% received ACEi/ARB at≥50% ceiling doses, SGLT2i and statins; fewer non-diabetic vs diabetic patients received SGLT2i (12% vs 49%,p<0.01) or statins (65% vs 83%,p<0.01). In contrast, patients with obesity or worse albuminuria were more likely to be on a combination of ACEi/ARB, SGLT2i and statins.

Conclusions: We visualize a disconnect between CKD practice guidelines and their real-world adoption. We will examine a systems approach to scale up population-level CKD management in patients yet to be optimized with evidence-based therapeutics, such as for non-diabetic CKD.

Funding: Commercial Support - AstraZeneca. The pharmaceutical company was not involved in the conduct, analysis or reporting of the study

SA-PO1132

Encouraging a Standardized ESKD Transition Pathway in Value-Based Care (VBC) Patients Is Associated with a High Optimal Dialysis Start Rate

Roy G. Marcus, Katherine W. Kwon, Rohit Sharma, Dave M. Miller, Douglas Eckhardt, Nirav Vakharia. *Panoramic Health, Tempe, AZ.*

Background: In 2022, Panoramic Health and several physician leaders from four practice groups developed a standardized ESKD transition pathway (Pathway) as part of a value-based care program. The Pathway led to a substantially higher optimal dialysis start rate, defined as initiation without a central venous catheter. This study aimed to determine if the Pathway could improve optimal start rates in other practice groups participating in the same program.

Methods: The Pathway was taught to all physicians involved. Monthly feedback was provided on ESKD preparation, highlighting patients who were off-track based on Pathway guidelines. Dialysis starts were recorded, and the proportion of optimal starts was determined.

Results: In 2022, the original four practice groups had a historical optimal start rate of 29% prior to Pathway implementation. By Q3, this rate increased to 37%, and by Q4, it reached 53%. In 2023, these groups achieved a 64% optimal start rate. Fourteen other practice groups, with a historical optimal start rate of 28%, reached 53% by the end of 2023. Additionally, two practice groups achieved over 70% optimal starts. One new practice group had a 76% optimal start rate with 50 starts, and one original practice group had a 78% rate with 91 starts. These successful groups shared ESKD preparation data transparently, held each other accountable, celebrated successes, and reviewed non-optimal starts to identify and address local access issues.

Conclusions: The deployment of the Pathway is associated with a large increase in optimal starts. The Pathway can be taught to nephrologists that were not part of the development process with comparable results. and can be effectively taught to nephrologists not involved in its development. Transparent data sharing, peer accountability, and attention to local access processes may further enhance the Pathway's impact. Future efforts will focus on making the Pathway available to all patients.

SA-PO1133

Identifying Key Outcomes for Optimal CKD Management: A UK-Based Delphi Study

Naeema A. Patel, Matthew Graham-Brown, Courtney J. Lightfoot, Alice C. Smith. *University of Leicester College of Life Sciences, Leicester, United Kingdom.*

Background: Effective self-management is crucial for people with chronic kidney disease (CKD). Robust evaluation of resources to support self-management in research and clinical practice settings should be based on outcomes that are meaningful and valued by stakeholders. This study aimed to establish stakeholder consensus on priority outcomes for CKD self-management.

Methods: A 3-round online Delphi survey was conducted. Invited participants included CKD patients, relatives, carers, healthcare professionals and policy-makers. Round 1: Participants were asked to describe in free text their top three most important outcomes for non-dialysis CKD self-management. Responses were analysed using conventional content analysis to generate items for consideration by participants in subsequent rounds. Round 2: Participants rated each item on a 9-point Likert scale. Items scoring ≥70% at 7-9 (critically important) progressed to Round 3. Round 3: Participants ranked items in order of importance to reach a consensus. A ranking-weighted score was used to identify highly ranked outcomes

Results: 64 patients/relatives and 69 kidney professionals contributed to Round 1. 28 outcome items were identified and categorised into 5 themes: 'Clinical', 'Behaviour and self-care', 'Knowledge, skills and confidence to manage own health', 'Healthcare usage' and 'Psychological and social factors'. In Round 2, 44 patients/relatives and 53 kidney professionals participated. Three items did not meet the progression criteria and were subsequently removed (2 items from 'Healthcare usage' category and 1 from 'Psychological and social factors'). In Round 3, 25 patients/relatives and 37 kidney professionals participated. The top three ranked items were: 1) Prevent or slow the decline of kidney function; 2) Feeling more in control of own health and kidney disease, feeling empowered and independent; and 3) Improve life expectancy.

Conclusions: All the items identified as the top three priority outcomes of self-management by patient and professional participants fell into the "Clinical" or "Knowledge, Skills and Confidence" themes. Identification of these key outcomes will be important for future resource design, clinical trials, healthcare service assessment, and strategies to support the commissioning and uptake of self-management resources.

SA-PO1134

Advanced CKD Veterans' Perspectives on Ideal KRT-Targeted Educational Modalities

Darin Ftouni,[1,2] Rebecca Campbell-Montalvo,[1] Shobha Subhash,[1] Popy Shell,[1] Kailyn Pearce,[1] Ashutosh M. Shukla.[1,2] *[1]VA North Florida South Georgia Veterans Health System, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: Awareness of KRT and KRT-targeted kidney disease education (KDE) is a necessity for informed dialysis selection for advanced CKD patients. We currently lack clear understandings of these patients' preferences for receiving such KDE.

Methods: Approaching enrollees for the ongoing mixed-method randomized Trial to evaluate and assess the impact of Comprehensive KRT-directed KDE on home dialysis among Veterans (TEACH-VET), we evaluated advanced CKD Veterans' preferences for the resources and methods for receiving KDE. Qualitative interviews were conducted using a structured interview guide grounded in theoretical domains framework. We oversampled women and individuals from racial/ethnic minorities to ensure broad applicability of findings. In addition to emergent themes related to KDE's influence on lack/gaps in knowledge, thematic analysis also focused on participant views on the preferential forms of future KDE dissemination.

Results: We enrolled 42 Veterans with advanced stage 4 and 5 CKD – 7(17%) women, 13(31%) African Americans, 1 Asian and 2 Latinx individuals. Most (n=32, 79%) had some college education, 60% were married, 26% divorced, and 69% retired; 60% lived with one other person and 24% lived alone. Forty-one provided education modality preferences and engaged in further discussions. Qualitative analysis revealed key social-psychological mechanisms influencing patients' KDE choices. A majority (80%) preferred receiving KDE from the providers. Individual concerns, such as psychological, social anxiety, ease of access, etc., were identified as key factors deterring patients from participating in group sessions, though, 2/3rd (66%) preferring this mode. Peer-Veteran supported KDE was among the least preferred method, with 44% of advanced CKD interviewees rejecting this method. Internet and phone apps were popular with 49% of veterans. Veterans' preferred methods for education provision were audio, podcasts, and video recordings, with an overall 85% interest rate.

Conclusions: This analysis provides a crucial insight into Veterans' preferences for KRT-directed KDE. Veterans have a strong preference for audio, podcasts, and video recordings as well as provider-delivered KDE. These results highlight the need for ongoing efforts to better understand and optimize KRT-directed KDE, guided by patients' own preferences.

Funding: Veterans Affairs Support

SA-PO1135

Optimizing Patient Outcomes in Advanced CKD: Insights from Predialysis Care in Qatar

Tarek A. Ghonimi,[1] Abdullah I. Hamad,[1] Tarek Ahmed Elsayed Fouda,[1] Hany E. Ismail,[1] Farooq Ahmad,[1] Muhammad A. Baig,[1] Mohamed T. Abdellatif,[2] Heba M. Ateya,[1] Mincy Mathew,[1] Hoda Tolba,[1] Fadwa S. Al-Ali,[1] Hassan A. Al-Malki.[1] *[1]Hamad Medical Corporation, Doha, Qatar; [2]Misr University for Science and Technology College of Medicine, 6th of October City, Egypt.*

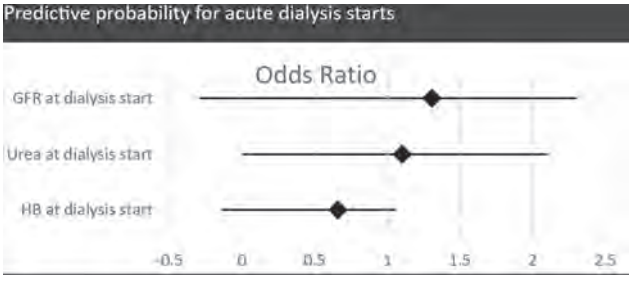
Background: A pre-dialysis multidisciplinary clinic (MDC) program improves the quality of care for advanced CKD patients. This study assesses the impact of such a program on the quality of CKD patients outcomes.

Methods: This report outlines the first-year findings of a three-year prospective study initiated on December 5, 2022, at Hamad General Hospital. We enrolled 695 patients with advanced CKD from multidisciplinary Low Clearance Clinics and analyzed demographic and laboratory data retrieved from electronic health records.

Results: Among 695 study patients, initial eGFR was 15.7 ± 5.4 mL/min/1.73m^2, decreasing to 14.9 ± 6.7 mL/min/1.73m^2 at study initiation. 39% had eGFR < 15 mL/min/1.73m^2 at referral. 43.7% received dialysis education, and 43% were referred for transplant evaluation. During follow-up, 24.3% started dialysis (55% acutely, 45% electively). Predictors for acute dialysis were low HB, low eGFR, and high urea (odds 0.662, 1.306, 1.101 respectively). Late referral (eGFR < 15 mL/min/1.73m^2) correlated with shorter time to dialysis (log rank value = 0.004). Mean eGFR at dialysis initiation was 6.3 ± 3.6mL/min/1.73m^2. Hemodialysis (73.3%) was primary, with temporary lines (36.6%) and AVF (28.4%) common. 2.4% had preemptive renal transplant, and mortality rate during follow-up was 1.7%.

Conclusions: Multidisciplinary pre-dialysis care is crucial for advanced CKD management and transitioning to kidney replacement therapy. This report emphasizes its role in enhancing outcomes, stressing early referral for interventions like dialysis education and transplant evaluation to optimize CKD care.

Funding: Private Foundation Support



SA-PO1136

Factors Associated with Decision Change through Shared Decision-Making Process Regarding Kidney Replacement Therapy

Shunsuke Kitamura,[1] Masaru Matsui,[2] Marumi Yamamoto,[1] Kosuke Tansho,[1] Hideo Tsushima,[1] Kazuhiko Tsuruya.[2] *[1]Department of Nephrology, Nara Prefectural General Medical Center, Nara, Japan; [2]Department of Nephrology, Nara Medical University, Nara, Japan.*

Background: In Japan, 97% of patients with end-stage kidney disease (ESKD) choose hemodialysis (HD) as their kidney replacement therapy (KRT), with few patients opting for peritoneal dialysis (PD) or transplantation. Although recent studies have revealed the implementation of shared decision-making (SDM) for KRT increases the number of patients choosing PD and transplantation, decision changes often occur through the SDM process until the development of ESKD. We thus explored the factors associated with decision changes in patients with advanced chronic kidney disease (CKD) who made a decision for KRT.

Methods: We conducted a cohort study involving 317 CKD patients who underwent KRT discussions through SDM process and provided their decisions between 2019 and 2022. The primary endpoint was a time-to-event analysis for changes from the initial decisions made during SDM, and we identified factors associated with decision changes.

Results: The mean age was 73 ± 12 years, with 192 (61%) being male. The baseline eGFR was 15.3 ± 6.4 mL/min/1.73m^2 at the time of SDM. The distribution of the initial decisions was as follows: HD for 124 (39%), PD and transplantation for 118 (37%), conservative kidney management (CKM) for 10 (3%), and 65 patients (21%) remained undecided. Eighty-six patients (27%) changed their initial decisions, with a median of 381 days. In the multivariable logistic regression model, factors associated with decision change (odds ratios [95% confidence intervals]) were male (1.85 [1.01–3.36]), having family support (2.44 [1.24-4.77]) and decisions of PD and transplantation (10.9 [4.27–27.6]) and CKM (7.5 [1.48–38.1]). In fact, approximately 30% of patients who initially decided on PD and transplantation or CKM changed to desire for HD treatment during the study period.

Conclusions: Following the KRT discussion through the SDM process, decisions of PD and transplantation or CKM may be changed to another KRT modality.

SA-PO1137

Nephrologist Visits Lower Rates of Hospitalization, Mortality, and ESKD Transition in Patients with CKD

Steph Karpinski,[1] Michael H. O'Shea,[2] Steven M. Brunelli.[1] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO.*

Background: Chronic kidney disease (CKD) patients require integrated care from a network of healthcare professionals including primary care physicians (PCP) and nephrologists. While it is hypothesized that increased exposure to nephrology care can slow CKD progression and reduce costs, evidence of the impact of primary care has been mixed. Therefore, we sought to determine if CKD stage 4/5 patients benefit clinically because of nephrologist visits, independent of primary care physician exposure.

Methods: This was a retrospective study of 8,941 adult CKD 4/5 patients. For this analysis, we used Optum's® de-identified Integrated Claims-Clinical Dataset that links administrative claims and clinical data from providers across the continuum of care.[1] The primary exposure (outpatient nephrologist visit: Y/N) was considered over a 6-month period. Outcomes were examined in the subsequent 6 months from exposure and included hospitalizations, mortality, and transition to end-stage kidney disease (ESKD). We modeled the hospitalization outcome using a quasi-Poisson distribution and modeled the ESKD transition and mortality outcomes using binomial distributions, adjusting for age, race, sex, insurance type, baseline CKD state, AKI events, and number of PCP visits (during exposure period). A sensitivity analysis also adjusted for albumin.

Results: After accounting for demographic and clinical factors results indicate that seeing a nephrologist is specifically associated with lower rates of hospitalization [RR (95% CI) 0.81 (0.69, 0.94)], ESKD transitions [OR (95% CI) 0.80 (0.66, 0.98)], and mortality [OR (95% CI) 0.63 (0.48, 0.81)]. The sensitivity analysis yielded similar results.

Conclusions: Among stage 4/5 CKD patients, nephrologist visits over a 6-month period have positive impacts on clinical outcomes.[1] Optum's de-identified Integrated Claims-Clinical dataset (2007-2021)

Outcome	Adjusted Effect
Hospitalization	0.81 (0.69, 0.94)
ESKD Transition	0.80 (0.66, 0.98)
Mortality	0.63 (0.48, 0.81)

Adjusted for number of PCP visits, age, AKI diagnosis, CKD stage (4/5), cohort ID, sex, race, and insurance type.

SA-PO1138

Understanding the Kidney Replacement Therapy Decision-Making Journey

Suma Prakash,[1] Spoorthy Vangala,[1] Kauser S. Razvi,[2] Matthew Taylor,[1] Erika Drury,[1] Marcus D'Alfonso,[1] Igor Oliveira,[1] Peter J. Veazie,[1] Scott Mcintosh.[1] *[1]University of Rochester Medical Center, Rochester, NY; [2]Strategic Urban Solutions Inc., Cleveland, OH.*

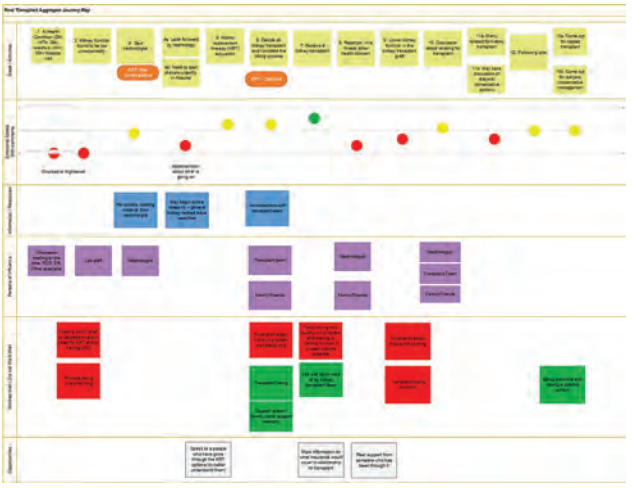
Background: This study aimed to better understand kidney replacement therapy (KRT) decision-making. It is unknown whether the KRT decision-making journey is similar across chronic kidney disease (CKD) groups and when interventions would be most helpful.

Methods: A qualitative study was done using journey mapping and focus groups. Journey mapping is a technique in which a visual representation of the process experienced sequentially by the person with their corresponding emotional journey is created. It provides information on what went well and did not at particular points in the journey allowing the participant to point out what and where in the process tailored interventions would be beneficial. Individual journey maps were done in the following CKD groups: stage 4 decided on KRT option, CKD 5 decided, CKD 4/5 undecided, post-transplant CKD 4/5, and patients with underlying stage 3-5 CKD requiring unplanned hospital dialysis start. Individual journey maps were aggregated by group and reviewed in a focus group for accuracy. Two provider focus groups were done to obtain additional perspective and validation. Theme coding was used to aggregate the journey maps and analyze the focus group data.

Results: There were 40 patient participants from a single center (8 per group) and 11 provider participants from multiple institutions. An aggregate map from the post-transplant CKD group is shown in figure 1. A group specific finding from the journey map analysis was the unplanned start group has a different set of steps in their process than the other 4 groups. A common finding across groups was the shock or grief at the time nephrologists suggest the need for KRT.

Conclusions: Journey mapping provides unique information that can be used to tailor the KRT decision-making process to the above CKD groups and may be a useful technique to look at other renal processes.

Funding: Other NIH Support - National Center for Advancing Translational Sciences (NCATS)



Post Transplant Map

SA-PO1139

Factors Associated with Major and Minor Complications of Percutaneous Kidney Biopsy: A Quality Improvement Project

Kayla Lett,[1] Lindsay Richels,[1] Ameer Abusada,[1] Shubrandu Sanjoy,[2] Bonnie R. Richardson.[2] *[1]University of Saskatchewan College of Medicine, Regina, SK, Canada; [2]Saskatchewan Health Authority, Regina, SK, Canada.*

Background: Percutaneous kidney biopsies are commonly performed in the evaluation of acute and chronic kidney disease. Due to physiologic, anatomic, and equipment factors, complications are not uncommon. Fortunately, most complications are minor and self-resolving. Life-threatening complications include bleeding requiring blood transfusion, need for angioembolization, and death. Recent literature suggests that these major complications are exceedingly rare. This study aimed to determine the rate of major and minor complications in both outpatient and inpatient kidney biopsies at a tertiary centre and to understand the factors associated with these complications.

Methods: A retrospective chart review of patients who received a kidney biopsy between 2020 and 2023 was conducted. Patients who were at least 15 years of age and underwent a biopsy in the outpatient or inpatient setting were included. Primary endpoints were minor complications (pain, hematoma formation, gross hematuria) and major complications (blood transfusion, admission to hospital, embolization, death). Factors including use of anticoagulation, use of antiplatelet agents, baseline blood pressure, hemoglobin, and platelet count were obtained.

Results: Data from 120 patients were analyzed with 52.5% being male. Median age was 65 years (IQR 50-74) and 70.6% of biopsies were performed in the outpatient setting. All biopsies were performed by interventional radiology staff and the median number of needle passes was 3. Anti-platelet agents were held for a median of 4 days (IQR 1-7). Major complications were observed in 4.2% of patients (n = 5), including blood transfusion (1.67%), need for angiography (1.67%) and death (0.83%).

Conclusions: The rate of major complications at this tertiary centre was higher compared to recently published literature. Significant practitioner variation was observed with respect to the use of anti-platelet medications and blood pressure targets peri-biopsy. Interventions to improve patient safety could include protocols to review all anti-platelet and anti-coagulant medications prior to percutaneous kidney biopsy, practitioner order sets to manage blood pressure, and education surrounding the use of post-procedure imaging when blood products or fluid resuscitation is required.

SA-PO1140

Validation of a Risk Calculator for Predicting Major Bleeding Complications from Percutaneous Kidney Biopsy

Jordan Thorne,[1,2] Keigan More,[1,2] Amanda J. Vinson,[1,2] David Clark,[1,2] Karthik K. Tennankore.[1,2] Kidney Research Institute Nova Scotia. *[1]Nova Scotia Health Authority, Halifax, NS, Canada; [2]Dalhousie University, Halifax, NS, Canada.*

Background: Percutaneous kidney biopsy (PKB) is valuable for the diagnosis of kidney disease but may be associated with adverse events including major bleeding (the most concerning complication of PKB). A prior study developed a risk calculator for the prediction of major bleeding following PKB, however this calculator has not been externally validated.

Methods: We analyzed all adults that received diagnostic PKB at a large, tertiary care center from 2012-2019. Predictors of major bleeding (defined as the need for blood transfusion, surgical intervention/embolization following PKB or death) included age, body mass index (BMI), platelets, hemoglobin, kidney length and transplant versus native kidney biopsy (the same factors included in the "Risk of bleeding complications after kidney biopsy" calculator; https://perioperativerisk.com/kbrc). Similar to the derivation study, continuous variables were converted to cubic splines and the risk of major bleeding complications were analyzed using logistic regression. Discrimination was assessed using the concordance statistic and calibration was analyzed using the Hosmer-Lemeshow test.

Results: Of 714 patients, 568 with complete data for each predictor were included. 82% of biopsies were from native kidneys. Mean age was 56±16 years, mean BMI was 29.3±6.9 and mean kidney length was 11.3±1.5 cm. Mean platelet and hemoglobin count was 248X10^9/L and 109 g/L, respectively. A model incorporating these variables demonstrated excellent discrimination (area under the curve 0.858, figure 1a) and good calibration (P=0.9170, figure 1b).

Conclusions: In this external validation study, a risk calculator for patients receiving diagnostic PKB demonstrated excellent calibration and discrimination emphasizing its utility in predicting the risk of major bleeding following PKB.

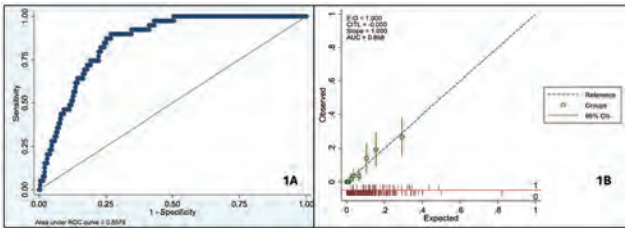


Figure 1: External validation of "Risk of bleeding complications after kidney biopsy calculator" – receiver operating characteristic curve (1A) and calibration plot (1B)

SA-PO1141

Are Waxy Casts in the Urinary Sediment Associated with Advanced Kidney Disease?

Khalid M. Mohammed,[1] Vipin Varghese,[4] Dustin R. Chalmers,[5] Muner Mohamed,[2,3] Juan Carlos Q. Velez.[2,3] Ochsner Nephrology. *[1]Tanta University, Tanta, Egypt; [2]Ochsner Health, New Orleans, LA; [3]The University of Queensland, Brisbane, QLD, Australia; [4]University of Michigan, Ann Arbor, MI; [5]Louisiana State University, Baton Rouge, LA.*

Background: Casts are clusters of urinary sediment elements formed in the kidney tubules, and the contents of the cast indicate the nature of clinical associations. The waxy casts probably represent the last stage of granular or cellular cast degeneration. Such casts thought to be form in chronic kidney disease when there is renal stasis and tubular atrophy.

Methods: We reviewed cases at Ochsner Medical Center who underwent kidney biopsies and have waxy casts in their urinary sediments around the same time of kidney biopsy. The pathology reports were reviewed and we collected the pathological findings of the presence of acute tubular injury (ATI), glomerular diseases (GD) and the pathological markers of chronic kidney disease which includes the percentage of interstitial fibrosis and tubular atrophy (IFTA) and global sclerosis (GS). We used the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to assess the significance of clinical association between the presence of waxy casts and different combinations of the above mentioned pathological findings.

Results: We have total 100 patients who underwent kidney biopsy and have microscopic examination of their urinary sediments. In relation to the pathological finding waxy casts seen in 15 of 58 with ATI (sensitivity 26, specificity 21, PPV 63, and NPV 57), in 6 of 26 with ATI/IFTA (sensitivity 18, specificity 27, PPV 33, and NPV 45), in 6 of 23 with GD/IFTA (sensitivity 25, specificity 27, PPV 50, and NPV 53), in 9 of 32 with ATI/GD/IFTA (sensitivity 38, specificity 19, PPV 67, and NPV 43), in 6 of 25 with ATI/GS (sensitivity 17, specificity 26, PPV 17, and NPV 26), in 6 of 23 with GD/GS (sensitivity 20, specificity 28, PPV 17, and NPV 24) and in 9 of 31 with ATI/GD/GS (sensitivity 40, specificity 27, PPV 22, and NPV 14). Serum creatinine levels were

Conclusions: Waxy casts are not specific or pathognomic findings for chronic kidney disease, their presence in urinary sediment should be interpreted carefully in addition to the other clinical findings.

SA-PO1142

Patterns of Low-Frequency Physiological Fluctuations in the Human Kidney Detected by Resting-State Magnetic Resonance Imaging

Edwin Baldelomar,[1] Cihat Eldeniz,[1] Jennifer R. Charlton,[2] Kevin M. Bennett.[1] *[1]Washington University in St Louis School of Medicine, St Louis, MO; [2]University of Virginia School of Medicine, Charlottesville, VA.*

Background: Many mechanisms in the kidney, including autoregulation, act as feedback systems and cause natural fluctuations in perfusion. Detecting these spontaneous hemodynamic fluctuations could provide patient-specific signatures of early disease progression. Non-contrast resting-state magnetic resonance imaging (rsMRI) was

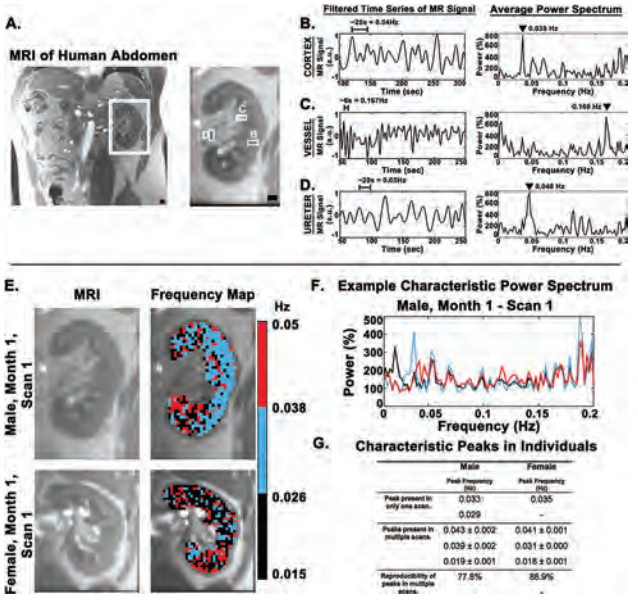
recently developed to detect spontaneous physiological fluctuations in the human kidney, *in vivo*. Here, we examined the spatial patterns and reproducibility of these measured fluctuations.

Methods: We performed rsMRI at 3T over 10 minutes (gradient echo, TE/TR=2.27/4.2ms, resolution=2.5mm^3, temporal resolution = 0.605sec) of the kidneys of two healthy subjects (1 male, 1 female, ages 46-47, no reported history of kidney disease). Individuals were imaged twice on the same day, and again ~16 months later. Imaging and image processing were performed using published protocols.

Results: rsMRI demonstrated spontaneous physiological fluctuations throughout the human kidney (Figure 1A-D). Strong fluctuations at ~0.03Hz occurred in the cortex in 60.5±13.6% of voxels (Figure 1B). Specific fluctuations appeared in other tissue compartments: e.g. vessels, 0.1-0.2Hz; ureter, ~0.05 Hz (Figure 1C-D). rsMRI spectra from cortex and medulla exhibited characteristic peaks in frequency ranges of 0.015-0.026, 0.027-0.038, 0.039-0.05 Hz (Figure 1,E-G). Characteristic spectra were reproducible between scans and over 16 months (77.8% in the male and 88.9% in the female kidney).

Conclusions: rsMRI can be used to map spontaneous hemodynamic fluctuations at frequencies in the healthy human adult kidney. Patterns of these fluctuations are specific to individual subjects and are reproducible over 16 months. rsMRI may detect physiological biomarkers that reflect disease progression or response to therapies.

Funding: NIDDK Support, Private Foundation Support



SA-PO1143

Mild CKD Is Predictive of Higher Mortality in Rural Uganda and Kenya

Anthony N. Muiru,[1] James Ayieko,[2] Jane Kabami,[3] Mucunguzi Atukunda,[3] Gordon O. Orori,[2] Erick M. Wafula,[2] Debbie Adam,[1] Edwin Charlebois,[1] Maya Petersen,[4] Diane Havlir,[1] Moses Kamya,[3] Michelle M. Estrella,[1] Chi-yuan Hsu.[1] *[1]University of California San Francisco, San Francisco, CA; [2]Kenya Medical Research Institute, Nairobi, Kenya; [3]Infectious Diseases Research Collaboration, Kampala, Uganda; [4]University of California Berkeley, Berkeley, CA.*

Background: Few studies have quantified the strength of the association between CKD and death in rural East Africa.

Methods: Within 22 communities of a cluster-randomized HIV trial conducted in Uganda and Kenya (NCT01864603), we randomly selected 100 households with at least one HIV-positive adult and 100 without any HIV-positive adults. We then chose 1 HIV-positive and 1 HIV-negative adult from the respective households to participate in a CKD sub-study. We determined the community-representative prevalence of CKD in 2016–2017 using weighting to account for sampling (PMC7055898). We then ascertained all-cause mortality through interviews with informants in 2023-4. We employed weighted multivariable logistic regression models to evaluate the association of baseline eGFR categories and all-cause mortality.

Results: So far, we have tracked 1,757 participants from 12 of 22 study communities. The population-weighted mean age at baseline was 39 years, and 54% were female. Prevalence of HIV was 9% (95% CI 8-11%), diabetes 5% (95% CI 4-7%), and hypertension 19% (95% CI 16-22%). An estimated 6% (95% CI 4-7%) had dipstick proteinuria, and only 1% (95% CI 0.7-2%) had eGFR<60 ml/min/1.73m^2 (mean 109 ±19 ml/min/1.73m^2). Follow-up visits were carried out after an average of 6.3 (±0.5) years, with 1,419 (81%) consenting to participate, 232 (13%) were deemed lost to follow-up, and 106 (6%) were deceased. Among those with baseline eGFR <60 ml/min/1.73m^2, 38% were deceased, compared with 5% with eGFR ≥90 ml/min/1.73m^2. An eGFR<60 (vs. ≥ 90) ml/min/1.73m^2 was associated with a seven-fold increased risk of death (aOR 7.6 95% CI: 2.2-26.2, P=0.001) after adjusting for geographic region, social demographics, health habits, diabetes, hypertension, HIV, and proteinuria. This effect size surpassed the other modifiable risk factors considered in our model.

Conclusions: CKD is a very strong risk factor for future mortality in rural Uganda and Kenya. The strength of association exceeds that observed between stage 5 CKD and deaths in resource-rich settings. This underscores the urgent need to uncover the specific causes of death related to CKD and to develop effective interventions in resource-poor settings.

Funding: NIDDK Support

SA-PO1144

Clinicopathological Characteristics and Outcomes of Nondiabetic Kidney Disease in Patients with Type 2 Diabetes

Ting Zhou,[1,2] Qiye Liu,[1] Niansong Wang,[1] Ying Fan.[1] *[1]Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: There is limited research on the characteristics and prognosis within the non-diabetic renal disease (NDRD) categories itself. We aim to investigate the clinicopathological characteristics, specific predictors and renal outcomes of various subtypes of NDRD in patients with Type 2 diabetes mellitus (T2D).

Methods: A total of 646 adult T2D patients who underwent renal biopsy were collected from Jan 2008 to Nov 2023. Among which 197 patients were diagnosed NDRD with different types of renal pathology. We conducted analysis on 123 patients with the top three subtypes of NDRD: IgA nephropathy (T2D-IgAN, n=52), membranous nephropathy (T2D-MN, n=48), and podocytopathies (T2D-Podo, n=23). Multivariate Cox regression models were used to analyze the predictors of renal outcomes in NDRD patients. The median follow-up time was 80 months (IQR: 62-102).

Results: Clinically, T2D-MN were older and had higher level of nephrotic proteinuria, total cholesterol as well as lower levels of serum albumin as compared to T2D-IgAN or T2D-Podo. T2D-MN patients were more likely to develop atherosclerotic plaques or unstable plaques in both carotid and lower extremity arteries (LEA), and are more prone to thromboembolism, infections as compared to other two groups. Pathologically, patients in T2D-IgAN group showed more pronounced glomerular sclerosis, interstitial inflammation and C3 deposit. Kaplan-Meier survival curves demonstrated that T2D-MN group had poorer renal survival, although it's not statistically significant. Multivariate Cox regression showed glomerular C3 deposit (HR 2.777, 95%CI 1.008-7.653), estimated glomerular filtration rate (eGFR) more than 60ml/min/1.73m^2 (HR 0.348, 95%CI 0.133-0.909) and T2D duration over 10 years (HR 3.866, 95%CI 1.326-11.275) were independent predictors for renal endpoints.

Conclusions: This is the first study to compare the clinicopathological characteristics of MN, IgAN, and podocytopathies and evaluate the renal outcome in T2D patients, which could help clinicians to initiate early intervention and prevent complications in those NDRD patients with poor prognosis. Novel immunosuppressants and biologics with minimized glucocorticoids strategies might bring more optimized options to NDRD patients.

SA-PO1145

Application of Functional Kidney Magnetic Resonance Imaging to Improve Assessment of CKD: The AFiRM Study

Nicholas M. Selby,[1,2] Mark S. Gilthorpe,[3] Philip A. Kalra,[4] Iosif A. Mendichovszky,[5] Steven Sourbron,[6] Maarten W. Taal,[1,2] Susan Francis.[1] On behalf of the AFiRM Investigators. *[1]University of Nottingham, Nottingham, United Kingdom; [2]University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom; [3]Leeds Beckett University, Leeds, United Kingdom; [4]Salford Royal Hospital Manchester Centre for Clinical Neurosciences, Salford, United Kingdom; [5]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [6]The University of Sheffield, Sheffield, United Kingdom.*

Background: Current kidney imaging techniques for chronic kidney disease (CKD) are limited. Better methods that can determine cause and prognosis of kidney diseases are required for improved patient stratification, targeting of therapies and new drug development. Renal multiparametric MRI provides whole kidney structural and functional measurements, assessing multiple aspects of kidney pathophysiology including altered tissue microstructure (inflammation/fibrosis), oxygenation and perfusion. The AFiRM study is a UK multi-centre study to evaluate the utility of multiparametric renal MRI to study CKD progression. This abstract describes the study design and baseline study population characteristics.

Methods: AFiRM is a prospective cohort study of people with CKD across 10 UK centres, collecting renal multiparametric MRI (comprising MRI measures of morphology, microstructure, flow and perfusion) at baseline and Year 2. Inclusion criteria include eGFR <60ml/min/1.73m^2, or persistent albuminuria (ACR >30mg/mmol). Annual follow-up visits collect eGFR, albuminuria and change in clinical status until Year 4. Long-term outcomes will be determined with individual patient tracking via the UK Renal Registry to ten years. Cause and effect between the renal MRI measures (alone and in combination) and the progression of CKD will be determined. A mechanistic sub-study is embedded to compare MRI measures to kidney histology.

Results: Between June 2021 and November 2023, 653 patients with CKD were screened for inclusion, of whom 421 were eligible, consented to participate and completed baseline multiparametric MRI. Mean age was 55 ± 13yrs and 64% were male. Mean eGFR was 38 ± 5ml/min/1.73m^2 and distribution across CKD stages was: stage G1/2 14%; stage G3A 22%; stage 3B 34%; and stage G4 30%. Albuminuria was present in 86% (A2/A3). The most common CKD aetiology was IgA nephropathy (21%), 15% had diabetic kidney disease but a large proportion (17%) had CKD of unknown cause.

Conclusions: The AFiRM study is a UK-wide multicentre clinical study of renal multiparametric MRI in people with CKD, which utilises a harmonised renal MRI acquisition, centralised image upload and quality assurance, and analysis.

Funding: Government Support - Non-U.S.

SA-PO1146

Higher Glycolysis in Circulating Leukocytes in Patients with CKD

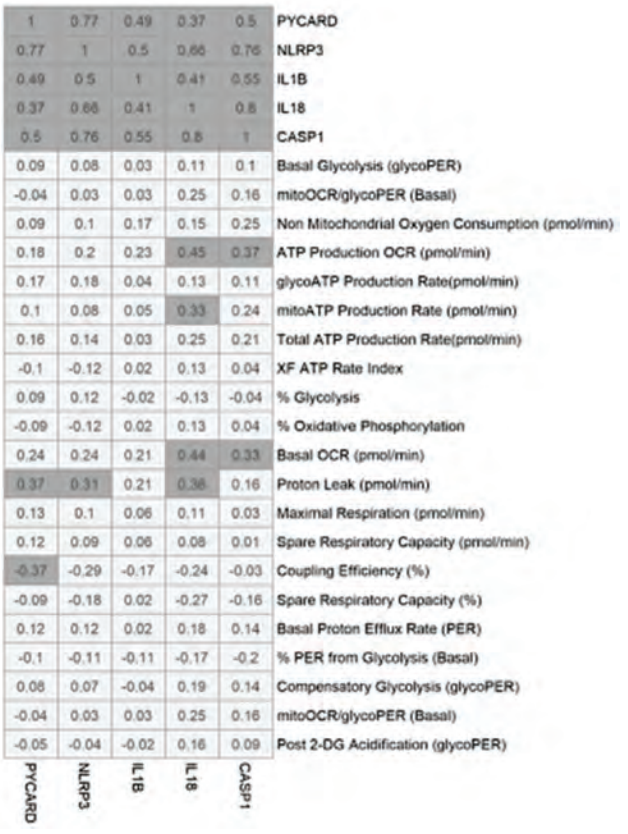
Lucas R. Johnson, Nishank Jain, Yasir Rahmatallah, Jon Coca Juaristi, Rajshekhar A. Kore. *University of Arkansas for Medical Sciences, Little Rock, AR.*

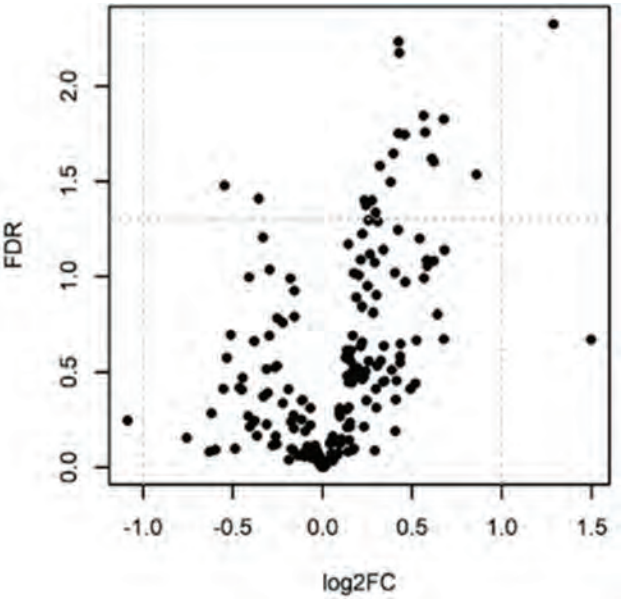
Background: Increased expression of glycolytic enzymes in kidney tissue correlates with CKD progression in the subtotal nephrectomy murine model. There are also higher levels of inflammatory cytokines with worsening CKD. These proinflammatory cytokines promote glycolysis in human endothelial cell lines. It is unknown whether glycolysis is altered in the circulating immune cells of patients with CKD that's associated with the pro-inflammatory phenotype of these patients.

Methods: We collected peripheral blood mononuclear cells from outpatients with CKD with eGFR <30 (n=37) and controls with normal kidney function (n=29) using ficoll high-density gradient leukoseparation. We identified pathways that were significantly different between groups using HALLMARK analysis. We also performed DEseq analysis for differentially expressed genes that met threshold fold change of 1.5 at false discovery rate of 0.1. Seahorse assays measured ATP production from leukocytes via glycolysis and non-glycolytic pathways.

Results: The glycolytic pathway was significantly upregulated in the CKD group in unadjusted analysis; and remained significant even after adjusting for presence of diabetes, age, race and gender. We also found 7 differentially expressed genes in CKD leukocytes - 2 of them from the glycolytic pathways- IDH1 (Isocitrate dehydrogenase 1) and SLC16A3 (Solute carrier). There was higher ATP generation via glycolysis pathways in CKD leukocytes that positively correlated with patients' serum CRP levels.

Conclusions: There is overexpressed glycolytic pathway with differentially overexpressed genes of glycolytic pathways in the immune cells of patients with CKD. In addition, CKD leukocytes rely more on glycolysis for energy production that the controls which positively correlates with their proinflammatory burden.





SA-PO1147

Sarcoidosis Found in the Bone Marrow

Alyssa C. Weyer, Sanjana Bukkapatnam, Arda Akoluk. *The University of Texas Health Science Center at Tyler, Tyler, TX.*

Introduction: 90% of patients who present with hypercalcemia are likely due to primary hyperparathyroidism or malignancy, with the alternative diagnosis of sarcoidosis. Sarcoidosis tends to affect the lung in 95% of cases and about 4% of cases affect the bone marrow. Patients tend to present with vague symptoms of faigue, shortness of breath, arthralgias, and fevers. We present a case of a patient who presented with hypercalcemia and the work-up that it entailed.

Case Description: Patient is a 69-year-old woman with a history of hypertension, microcytic anemia, atrial fibrillation, chronic kidney disease stage 4, proteinuria, and insulin dependent diabetes mellitus type 2 who presented to the Nephrology clinic due

to acute renal failure which was presumed due to acute tubular necrosis and overdiuresis. Patient was undergoing work up with Hematology due to microcytic anemia and was noted to have hypercalcemia. There was concern for multiple myeloma, so extensive work up consisted of negative Serum protein electrophoresis, flow cytometry, and kappa/lambda. Bone marrow biopsy was obtained for further clarification and was found to have granulomas in the bone marrow (Fig. 1). Extensive infectious work up performed including fungal etiologies which was negative. The angiotensin converting enzyme was elevated at 178 U/L. Kidney involvement was highly suspected due to intrinsic pathology consistent with urinalysis. She started on prednisone and her kidney function has normalized, her calcium as well as her angiotensin converting enzyme level is normal currently and prednisone is being weaned. Her fatigue and tiredness have resolved.

Discussion: Sarcoidosis presenting only with bone marrow granulomas and no lung finding is a very rare presentation. Our patient did not have any joint symptoms. Common findings for bone marrow sarcoidosis involve cytopenias, lymphadenopathy, and hypersplenism. Treatment involves steroids, and if not responsive, addition of immunosuppressants. It is important to base decision of obtaining a bone marrow biopsy when sarcoidosis is highly suspected in the setting of hypercalcemia.

SA-PO1148

Bleeding Complications and Insufficient Samples after Percutaneous Native Kidney Biopsy

Hisashi Kamido, Shigekazu Kurihara, Masayuki Yamanouchi, Tatsuya Suwabe, Yoshifumi Ubara, Naoki Sawa. *Toranomon Byoin Bunin, Kawasaki, Japan.*

Introduction: Insufficient samples in kidney biopsies (total number of glomeruli ≤7) significantly impact diagnostic accuracy. Recently, the rate of inadequate kidney biopsy samples in the United States has risen to 14%, posing a substantial issue. This study analyzes the frequency and influencing factors of inadequate samples and bleeding in kidney biopsies at our institution.

Case Description: This retrospective study included 70 cases of kidney biopsies performed between August 2022 and March 2023. Variables analyzed included the presence of insufficient samples, bleeding events, age, gender, height, weight, eGFR, position, laterality, and number of punctures. The results are presented as medians (IQR). Among the patients, 36 were male (52%), with a median age of 56 years (45-68), BMI of 22 kg/m^2 (22-24), and eGFR of 57 ml/min/1.73m^2 (39-72). There were 11 cases (16%) of left kidney biopsies, 2 cases (2.9%) performed in the lateral position, with a median of 5 punctures (4-6), 3 biopsy cores obtained (2-4), and 33 glomeruli collected (22-42). Insufficient samples (total number of glomeruli ≤10) occurred in 3 cases (4.4%), and bleeding events in 5 cases (7.3%). No clear correlation was observed between the number of punctures, hypertension, abdominal circumference, and bleeding events.

Discussion: Since bleeding complications did not increase with the number of punctures, it is recommended that a sufficient number of punctures be performed to collect an adequate volume of specimens for diagnosis.

SA-PO1149

Beyond Anemia of CKD: A Tale of Discovering Post-transplant Lymphoproliferative Disorder by Colonoscopy

Hira Tahir, Farah Daccueil, Katherine Andrade, Henry Yip. *Stony Brook University Hospital, Stony Brook, NY.*

Introduction: In young patients seldom are drops in hemoglobin investigated with colonoscopy. In chronic kidney disease (CKD) patients, anemia is attributed to CKD and further testing is often met with resistance especially in younger population. Our rare case describes how a nephrologists referral for anemia diagnoses post-transplant lymphoproliferative disorder (PTLD) in the form of colon lymphoma. This highlights the important role nephrologist play in caring for transplant patients.

Case Description: A 31-year-old male with congenital nephrotic syndrome (Finnish type) post living related kidney transplant 3/30/2006 is referred by nephrologist for inpatient workup of diarrhea and anemia. Exam revealed pale and toxic appearing young male with admission labs of Na 125, K 5.9, Cl 96, HCO3 16, BUN 73, Cr 3.64 and WBC 12.99, Hb 6.6, Hct 20.8 and PLT 403. Stool pathogen was positive for Yersinia Enterocolitica and E.coli (EPEC). CT imaging revealed pleural effusion and no lymphadenopathy. Although patient responded to transfusion, nephrology team had extensive discussion to pursue endoscopy which gastroenterology finally agreed. EGD/Colonoscopy revealed multiple polypoid non-obstructing medium sized masses in descending colon, transverse colon and ascending colon and multiple superficially ulcerated nodules in recto-sigmoid and sigmoid colon. Pathology diagnosed diffuse large B-cell lymphoma (DLBCL) negative for CD-20. Immunosuppression was reduced and patient was discharged however outpatient PET found mesenteric lymphadenopathy. Even though oncology initiated chemotherapy, the patient suffered septic shock due to enterotoxigenic E.coli after first treatment and expired.

Discussion: Immunosuppressed kidney transplant recipients are at higher risk of developing malignancy including gastroenterology cancer. However current guidelines for testing and screening do not differ between the transplant and general population. Therefore continued sense of awareness and advocacy for screening is important. Evidence based guidelines in this population is needed to improve life expectancy in kidney transplant patients.

SA-PO1150

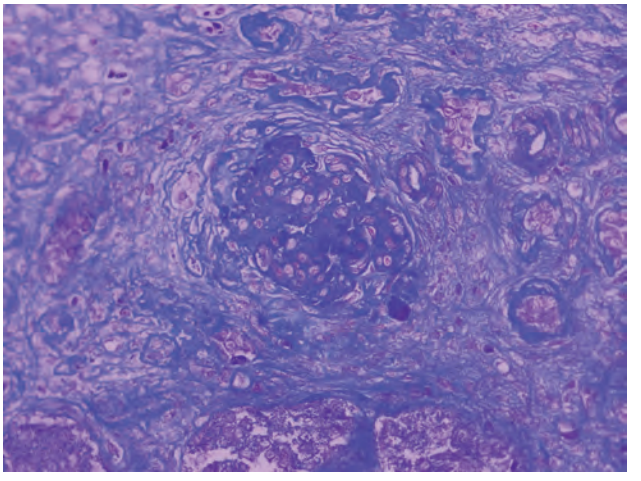
Chronic Organophosphate Intoxication Developed End-Stage Kidney Failure

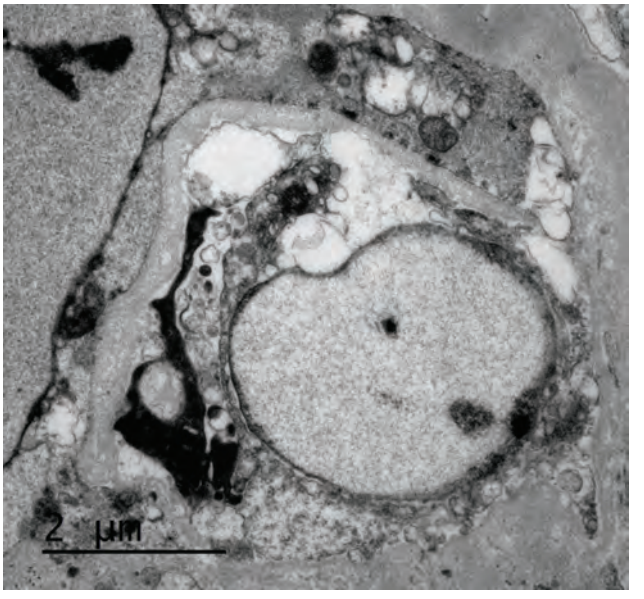
Maite Hurtado Uriarte,[1] Johanna Alvarez.[2] [1]*Baxter Renal Care Services, Bogota, Colombia;* [2]*Fundacion Santa Fe de Bogota, Bogota, Colombia.*

Introduction: Organophosphates, which are commonly used as pesticides, are highly toxic and can enter the body through the skin, lungs, and gastrointestinal tract. They directly affect acetylcholinesterase (AChE), leading to overstimulation of cholinergic neurons. Exposure to organophosphates has been identified as a significant non-traditional cause of chronic renal failure.

Case Description: A nineteen-year-old fumigator with no prior medical history presented with symptoms including headache, cramps, palpitations, fatigue, anorexia, and seizures over the past 20 days. Upon arrival at the emergency room, he was found to have metabolic acidosis and compromised kidney function, requiring ventilator support and immediate renal replacement therapy. Infectious and autoimmune causes were ruled out. A renal biopsy was performed, revealing 66% global sclerosis, 15% segmental sclerosis, retracted basement membrane, cortical infarction, and changes consistent with thrombotic microangiopathy.

Discussion: Chronic kidney disease is a significant global health concern, leading to premature mortality, increased cardiovascular risk, and reduced quality of life. Pesticide exposure, particularly in agriculture, heightens the risk of kidney damage. It is crucial to remain alert about this public health issue.





SA-PO1151

Unknown Disease or Unusual Mesoamerican Nephropathy?

Pooya Zardoost, Sidney Elston, Alexander Prouty, Henry L. Wehrum. *OhioHealth, Columbus, OH.*

Introduction: Mesoamerican Nephropathy (MeN) is a known disease in patients from Central and North America with history in manual labor industries. Aside from ruling out HTN, DM, and AKI, diagnosis requires GFR below 60 ml/min, urine P/C ratio below 2, biopsy showing tubular atrophy, fibrosis, and glomerulosclerosis. We had a patient with nephrotic proteinuria and biopsy consistent with MeN. Whether the proteinuria indicated an unknown disease or an unsual case of MeN is an area of uncertainty.

Case Description: A 31-year-old male with no past medical history was hospitalized after routine labs showed creatinine of 3.9 mg/dL and bicarbonate of 17 mmol/L. He recently moved from Mexico and spent years working in the textile industry. He denied any other symptoms. Vitals were 135/74 mmHg, 72 bpm, 15, 98.6 F and 98%. Exam was non-revealing. CT and ultrasound were negative for obstruction, revealing increased renal cortical echogenicity. Urine studies showed intrinsic disease, and proteinuria with P/C ratio of 3.7. Workup for autoimmune disease, vasculitis, diabetes, and infection were negative. He was initiated on bicarbonate supplementation, and creatinine improved the day after to 3.6 mg/dL; acidosis resolved. He was discharged with renal biopsy scheduled outpatient, which later showed diffuse tubulointerstitial fibrosis with atrophy and global glomerulosclerosis (Figure 1). He was scheduled to see nephrology outpatient.

Discussion: Our patient presented with a picture consistent with MeN despite proteinuria above the maximum level for diagnosis. His history in the textile industry suggests exposure to silica. It is unclear whether this may have resulted in a variant of MeN, or if he had another unknown disease. Atypical presentations of renal disease associated with occupational exposures demand further attention.

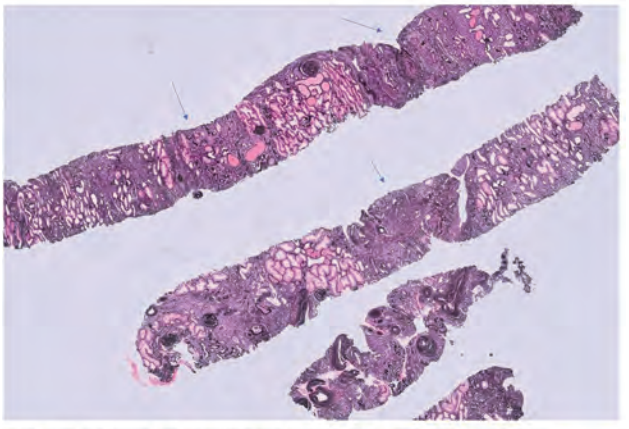


Figure 1 Jones' Methenamine Silver Stain showing zonal areas of interstitial fibrosis and atrophy (blue arrows).

SA-PO1152

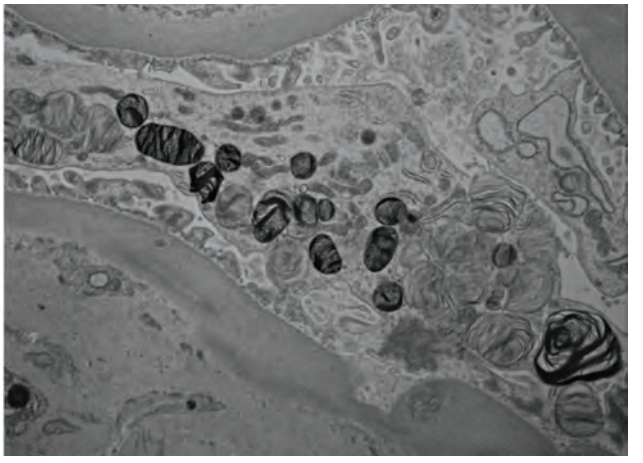
When You Hear Hoofbeats: An Interesting Presentation of Zebra Bodies Associated with Hydroxychloroquine Use

Adileen Sii, Aisha Batool, Carl S. Dernell, Anna R. Gaddy. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: The presence of zebra bodies in kidney biopsy is a distinctive characteristic of Fabry disease. However, certain medications such as hydroxychloroquine may also induce zebra body formation by mimicking the phospholipidosis of Fabry disease. First developed as antimalarial drugs, chloroquine and hydroxychloroquine are widely used today in management of autoimmune disorders. While both medications have been generally regarded as safe, serious side effects such as retinopathy, myopathy, and cardiomyopathy have been reported. Hydroxychloroquine in particular has been associated with the presence of zebra bodies in the kidney but the clinical significance of this finding is not well-known. We present a case illustrating zebra bodies in a patient with long-term hydroxychloroquine use.

Case Description: A 75 year-old female with history of rheumatoid arthritis was evaluated for proteinuric Stage 3 CKD. Serum electrophoresis revealed a monoclonal band and biopsy was performed. Histologic examination revealed C3 dominant mesangioproliferative glomerulonephritis, but also ultrastructural evidence of podocyte lipid accumulation consistent with Fabry disease. Medication history confirmed that the patient had been on the amphiphilic drug hydroxychloroquine for many years.

Discussion: The prevalence of zebra bodies attributable to hydroxychloroquine has been low and the clinical significance remains unclear. While there is an association of zebra bodies and increased phospholipidosis, the histological difference between drug-induced zebra bodies and those observed in Fabry disease requires further clarification. Understanding these differences will allow for further assessment regarding the implications of long-term usage of drugs such as hydroxychloroquine. Our patient was referred to hematology for bone biopsy due to her C3 disease but hydroxychloroquine was not thought to be causative of her kidney disease and was continued.



SA-PO1153

Chronic Interstitial Nephritis in Agricultural Communities: Two Potential Belgian Cases

Sylvina da Silva Fernandes,[1,2] Isabelle Simon,[5] Karl M. Wissing,[6] Joelle L. Nortier,[4] Eva M. Buhl,[2] Caroline Geers,[6] Cynthia C. Nast,[3] Peter Boor,[2] Marc E. De Broe,[1] Benjamin A. Vervaet.[2,1] *[1]Universiteit Antwerpen, Antwerpen, Belgium; [2]Universitatsklinikum Aachen Institut fur Pathologie, Aachen, Germany; [3]Cedars-Sinai Medical Center, Los Angeles, CA; [4]UVC Brugmann, Brussels, Belgium; [5]Hopital Erasme, Bruxelles, Belgium; [6]Universitair Ziekenhuis Brussel, Brussel, Belgium.*

Introduction: Chronic Interstitial Nephritis in Agricultural Communities (CINAC) is a chronic kidney disease of unknown etiology. Currently, CINAC can be diagnosed when patients are active in a farming context, present no or mild hypertension, have no overt proteinuria, and show light microscopic indication of chronic tubulo-interstitial nephritis on biopsy. A histopathological study of our group discovered enlarged (>1,2 μm) dysmorphic lysosomes containing dispersed round aggregates in proximal tubular cells as a prevalent feature of CINAC. Therefore, we hypothesize that verifying this lesion strengthens the CINAC diagnosis when observed in the aforementioned clinico-epidemiological context and helps uncover new cases.

Case Description: In 2023 two Belgian nephrologists independently admitted CKD patients for renal biopsy who fitted the minimal criteria for CINAC (Table). Patient 1, a 50-year-old male, originated from El Salvador where he assisted and worked in pesticide spraying, without protection, from the age of 10 to 32 before moving to Belgium in 2016 with developing CKD. Patient 2, a 71-year-old male, has been a floriculturist for 50 years with often use of pesticides, although with mask protection. Both patients had features of chronic interstitial nephritis in biopsy with a range of healthy and damaged tubuli, some of which showed the abnormal lysosomal lesions. Electron microscopy confirmed the presence of several enlarged, dysmorphic lysosomes containing moderate- to well-defined electron-dense aggregates.

Discussion: We describe two cases of suspected CINAC, that show the presence of abnormal lysosomal lesions, the first cases identified in Belgium. Albeit rare outside of the typical geographic localization, CINAC should be considered in the differential diagnosis of CKD cases of unknown etiology.

	Patient 1	Patient 2
Creatinine (mg/dl)	2.50	1.91
Proteinuria (g/g creatinine)	0.42	0.06
Hypertension	treated	treated
Kidney size on ultrasound	decreased in size	decreased in size
Histopathology	Chronic Interstitial Nephritis	Chronic Interstitial Nephritis

SA-PO1154

A Rare Case of Nonuremic Calciphylaxis in a Patient with Mild Macroalbuminuric CKD

Michelle N. Keyser, Jyotsana Thakkar. *UPMC, Pittsburgh, PA.*

Introduction: Nonuremic calciphylaxis (NUC) is a rare, poorly understood entity that can occur in patients without end-stage kidney disease (ESKD) and kidney transplantation. Sparse data has shown several risk factors associated with NUC, but these associations are not well understood. We present a case of NUC in a patient with mild macroalbuminuric chronic kidney disease (CKD G2A3).

Case Description: A 61-year-old female with long-standing uncontrolled type 2 diabetes, peripheral vascular disease, hypertension, coronary artery disease, uterine cancer status post total hysterectomy, hypothyroidism, and mild macroalbuminuric chronic kidney disease (CKD G2A3, eGFR 70-80 ml/min/1.73 m2, BUN 18, UACr 749 mg/g) who presented with a painful, ulcerated skin lesion on her right leg following mild trauma. She was evaluated by vascular surgery and underwent angioplasty of the right peroneal artery and anterior tibial arteries. Despite angioplasty, the ulcerated lesion did not improve, and she was referred to a dermatologist. Subsequently, a skin biopsy was performed which showed acute ulceration with necrosis and inflammatory exudate with associated dermal sclerosis and vascular peri-eccrine calcifications concerning for atypical nonuremic calciphylaxis. Calcium, phosphorus, and PTH levels (77 pg/ml) were within normal limits. She was taking vitamin D supplementation for many years and her vitamin D-25-OH was elevated to 72 ng/ml, which was stopped. Serologies were only notable for an elevated rheumatoid factor. She was started on sodium thiosulfate which led to improvement in the skin lesion and pain.

Discussion: Calciphylaxis is typically seen in patients with ESKD and kidney transplantation. However, it has rarely been described in patients with nonuremic causes. It is important to report these cases to better understand the risk factors associated with NUC. Our patient had mild CKD, vitamin D deficiency, uterine cancer, uncontrolled type 2 diabetes, peripheral artery disease, elevated rheumatoid factor, and was on dual anti-platelet therapy. All of these are proposed triggers for NUC. There is currently no standard treatment for NUC, but sodium thiosulfate has shown promise, was trialed in this patient, and led to clinical improvement.

SA-PO1155

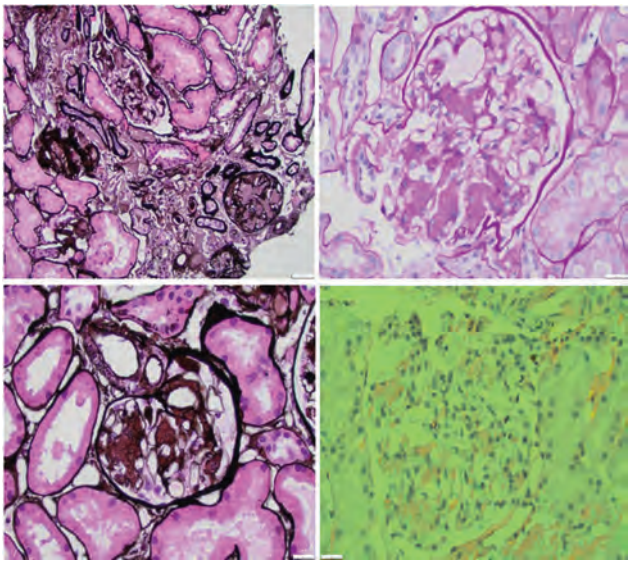
Leukocyte Chemotactic Factor 2-Related Amyloidosis Presenting with a Rash and Unexplained CKD

Zohreh Gholizadeh Ghozloujeh, Yan Chen Wongworawat, Amir Abdi Pour, Niloufar Ebrahimi, Sayna Norouzi. *Loma Linda University, Loma Linda, CA.*

Introduction: Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a recently described type of amyloidosis predominantly affecting the kidneys. ALECT2 has a relatively benign course, rare cardiac involvement, and a specific ethnic distribution. Recognizing ALECT2 is crucial to avoid unnecessary and potentially harmful treatments intended for more common subtypes like AL or AA amyloidosis. We present a case of ALECT2 with unusual clinical presentation and renal histology.

Case Description: A 60-year-old Hispanic female with a history of prediabetes (HbA1c = 5.7%) and hypertension presented with a pruritic skin rash on her hands. Upon reviewing historical laboratory findings, the patient was found to have elevated serum creatinine (Cr = 1.20 mg/dL) with an estimated glomerular filtration rate of 48 mL/min/1.73m^2 (CKD stage 3) without proteinuria for the past 20 months. Renal ultrasound showed increased echogenicity consistent with CKD. Despite controlling her hypertension, her serum creatinine continued to rise (1.39 mg/dL) over the next 2 months, necessitating a biopsy to investigate the underlying etiology of her CKD. The kidney biopsy revealed LECT2 amyloidosis, predominantly glomerular and less dominant interstitial amyloid deposition, which was Congo red-positive with light green birefringence under polarized light (Image1). No diagnostic features of paraprotein-associated renal deposition disease, immune complex-mediated glomerulonephritis, or interstitial nephritis were observed, and urine protein electrophoresis was negative. The echocardiography did not suggest cardiac involvement with an ejection fraction of 60-65%.

Discussion: We report an unusual case of biopsy proven ALECT2 presenting with skin rashes resembling other autoimmune diseases.



SA-PO1156

Incidental Diagnosis of Lymphoplasmacytic Lymphoma in a Patient with CKD

Muhammad R. Khan, Mauricio Monrroy. *Albany Medical Center, Albany, NY.*

Introduction: Lymphoplasmacytic lymphoma (LPL) is a rare B cell lymphoma, predominantly affecting whites and males, with a median onset age of 65. It mainly targets the bone marrow, and less frequently the spleen and lymph nodes, with kidney involvement being exceptionally rare. LPL often harbors mutations in the MYD88 gene and may not present with typical B symptoms. It is commonly associated with IgM monoclonal gammopathy, known as Waldenström gammaglobulinemia. This report describes an incidental finding of LPL in the kidney of an asymptomatic patient.

Case Description: A 76-year-old male with a history of chronic kidney disease (CKD) stage 3A presented for CKD management. Diagnosed concurrently with hypertension eight years prior, he had no known CKD risk factors. He was a non-smoker without illicit drug use. His medication regimen included irbesartan, hydrochlorothiazide, nifedipine, levothyroxine, atorvastatin, and multivitamins. He had a history of surgically treated prostate cancer and thyroid papillary carcinoma, 11 years ago. No family history of kidney disease was reported. Physical examination showed elevated blood pressure and 1+ lower extremity edema. Labs showed creatinine 1.38 mg/dl and no proteinuria with bland urinalysis. Kidney ultrasound identified bilateral simple renal cysts and a persistent complex cyst in the right kidney. Regular surveillance of the cyst was advised. During subsequent follow-up he reported 9 kg weight loss but no other symptoms. Repeat labs showed creatinine 1.48 mg/dl and normal blood counts. Renal biopsy was done which revealed LPL with a MYD88 mutation. Subsequent diagnoses included Waldenström gammaglobulinemia, with immunoelectrophoresis detecting IgM kappa paraprotein. He was referred to hematology/oncology for further evaluation and treatment, receiving six cycles of Rituximab, Bendamustine, and Neulasta, resulting in normalized IgM levels and creatinine remained stable at 1.46 mg/dl.

Discussion: LPL in the kidney is exceedingly uncommon, with few case reports available. This case emphasizes the significance of renal biopsy in patients with stable renal function and unidentified causes of CKD, highlighting its utility in revealing unusual pathologies even when initial evaluations are inconclusive.

SA-PO1157

CKD Induced by Cholesterol Crystal Embolization (CCE)

Shohan Pervaze, Nirmay Sonar. *Ballad Health, Norton, TN.*

Introduction: CCE typically impacts individuals with widespread erosive atherosclerosis. This occurs when fragments of atherosclerotic plaques detach and travel to distant locations, causing the partial or complete blockage of numerous small arteries, including glomerular arterioles, leading to ischemia in affected tissues or organs.

Case Description: 68-year-old man with CAD post-left heart catheterization with stent placement 4w ago, CKD3, HTN, DM and Afib presented to the ED with fatigue and melena for 3 days. His meds include amlodipine, metformin, aspirin, Plavix and Eliquis. In the ED, he was stable and labs with slight leukocytosis, Cr 3.8, K 5.8, BUN 71, and lactate 2.8. He received 1uPRBC, and a positive FOBT with general surgery consultation for GI bleed workup. Initially, his AKI was thought to be prerenal due to GI bleed from anticoagulation intolerance. However, EGD and colonoscopy were benign. Eliquis was held. He responded well to transfusion and received maintenance IVF. Repeat labs showed improved BUN

but Cr at 5.3 by day 5. A repeat UA on day 3 revealed hyaline and granular casts. Despite good urine output, Cr levels did not improve. Renal US showed a slightly atrophic right kidney. Autoimmune workup and complement levels were normal. A renal biopsy of the right kidney showed light microscopy findings consistent with tubular injury and cholesterol emboli in vessels. Electron microscopy revealed mild thickening of the glomerular basement membrane and focal effacement of podocyte foot processes. The IF study was negative. With a stable chonic renal injury and HPE findings, he was diagnosed with CCE.

Discussion: CCE requires suspicion, especially with AKI, hypereosinophilia, livedo reticularis, or blue toe syndrome in elderly men with atherosclerosis or recent vascular interventions like cardiac cath, with fever, weight loss, anorexia, fatigue, and myalgias. Labs may show elevated WBCs, ESR, CRP, reduced C3/C4, anemia and low Plts. Hypereosinophilia is seen in 80% of cases, mediated by cytokines potentially IL 5 from vascular endothelium. Biopsy, preferably of affected skin or muscles remains the gold standard. Treatment focuses on supportive care for end-organ damage and preventing recurrent cholesterol embolization episodes. Addressing atherosclerosis risk factors like smoking, hypertension, and cholesterol is crucial. Mention on statin, antiplatelets and revascularization therapy is made.

SA-PO1158

Postsurgical Outcomes in Veterans with Advanced CKD vs. ESKD on Chronic Dialysis

Austin L. Mallory, Mary V. Sarrazin, Masaaki Yamada, Diana I. Jalal, Benjamin R. Griffin. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Patients with advanced chronic kidney disease (CKD) have poor post-surgical outcomes, perhaps due in part to negative uremic impacts on immune function, hemostasis, and wound healing. We hypothesized that end stage kidney disease (ESKD) patients on chronic dialysis would have better post-surgical outcomes due to reduced uremic toxin burden compared to patients with advanced CKD, particularly for post-surgical infection and bleeding. We compared outcomes following surgery between patients with advanced CKD not on chronic dialysis to patients with ESKD on chronic dialysis within the Veterans Affairs Health Care System.

Methods: We analyzed data from the VA Surgical Quality Improvement Program (VASQIP) database from 2013 to 2019. Veterans with an eGFR <20 mL/min based on pre-operative creatinine or ESKD on chronic dialysis were included. Exclusion criteria were emergent surgery, pre-operative acute kidney injury, or pre-operative sepsis. Outcomes including mortality, infection, cardiac events, and hematologic and respiratory complications were assessed over a 30-day period from surgery. The two groups were compared using a General Estimating Equation (GEE) model that adjusted for age, comorbidities, frailty, urgent case status, and operative stress score.

Results: A total of 3,097 patients were included, of which 643 had CKD with eGFR <20 mL/min and 2,454 had ESKD. The ESKD patients were younger but had higher frailty and comorbidity scores. After adjustments, CKD patients had 56% increased odds of having a post-surgical complication **(Table)**.

Conclusions: Veterans with advanced CKD had higher rates of post-surgical complications than Veterans with ESKD on chronic dialysis, particularly cardiac and infectious complications. It is possible that uremic burden may contribute to poor post-surgical outcomes in advanced CKD, though additional research is needed to further understand this association.

Outcome (CKD vs ESKD)	Adjusted Odds Ratio	95% Confidence Interval	P-value
30-Day Mortality	1.22	0.74 - 2.03	0.4
30-day Readmission	0.91	0.72 – 1.14	0.4
Any Post-Surgical Complication	1.56	1.23 – 1.97	0.0003
Adverse Cardiac Events	1.67	1.09 – 2.55	0.02
Post-Surgical Infections	1.37	1.00 – 1.86	0.048
Hematologic Complications	0.81	0.27 – 2.40	0.7
Respiratory Complications	0.99	0.58 – 1.70	0.9

SA-PO1159

Mitofusins by Regulating Lung Macrophage-Derived Immune Signals Modulate Monocyte Migration and Interorgan Cross-Talk during Kidney Fibrosis

Divya Bhatia, Edwin Patiño, Eleni Kallinos, Maria Plataki, Augustine M. Choi, Mary E. Choi. *Weill Cornell Medicine, New York, NY.*

Background: Chronic kidney disease (CKD)-associated lung injury is under-recognized. Coexistence of lung dysfunction with CKD increases rates of kidney failure and mortality. We studied alveolar macrophage (AM) and type 2 alveolar epithelial cell (AEC2)-specific roles of mitochondrial fusion proteins, mitofusin (MFN)1 and MFN2 in kidney fibrosis-associated lung injury and interorgan crosstalk.

Methods: Myeloid-(*LysM-Cre*$^{+/-}$) or AEC2 (*Spc-Cre*$^{+/-}$)-specific *Mfn1*$^{+/-}$ and/or *Mfn2*$^{+/-}$ & control mice were subjected to unilateral ureteral obstruction (UUO) or sham surgery (7-days), or adenine or control diet (4 or 8-weeks). Lungs, kidneys, & bronchoalveolar lavage fluid (BALF) were analyzed by western blot, Masson's trichrome staining, & flow cytometry. Blood was assessed for blood urea nitrogen (BUN), creatinine, chemokine analysis (bead array) & flow cytometry. THP-1 cells were treated with TGF-β1 and/or PGC-1α agonist.

Results: CKD-associated monocyte infiltration in the lungs, AM-derived inflammatory (mitochondrial-specific reactive oxygen species (mROS), Ly6C^{high}) & fibrotic (CX3CR1, galectin-3, arginase-I) signals were suppressed in myeloid-specific *Mfn1*$^{+/-}$ and/or *Mfn2*$^{+/-}$ mice. Protection in myeloid-specific *Mfn1*$^{+/-}$ and/or *Mfn2*$^{+/-}$ mice was mediated by AEC2-specific compensatory inductions of MFN1/MFN2 during CKD. AEC2-specific *Mfn1*$^{+/-}$ and/or *Mfn2*$^{+/-}$ mice after UUO had increased monocytes in the lungs and BALF. After UUO, interstitial, monocyte-derived, and tissue-resident alveolar macrophages from lungs and BALF of AEC2-specific *Mfn1*$^{+/-}$ and/or *Mfn2*$^{+/-}$ mice displayed increased mROS & galectin-3. AEC2-specific *Mfn1*$^{+/-}$ and/or *Mfn2*$^{+/-}$ mice after UUO had increased levels of i) BUN & creatinine, ii) circulating CCL-17, 22, TGF-β1, IL-12p40, & iii) CCR2+, Ly6C^{high}, mROS+ monocytes. TGF-β1 promoted, while PGC-1α agonist suppressed migratory, inflammatory, and profibrotic functions of THP-1 monocytes.

Conclusions: Myeloid lineage-specific *Mfn1*/*Mfn2* ablation attenuated CKD-associated lung injury via a compensatory induction of MFN1/MFN2 in AEC2. AEC2-specific loss of *Mfn1*/*Mfn2* accelerated kidney fibrosis-associated lung macrophage-derived local and circulating inflammatory signals. Circulating immune signals by promoting monocytes' infiltration into the kidney, can exaggerate kidney inflammation and fibrosis.

Funding: Other NIH Support - NHLBI (2T32HL134629-06A1)

SA-PO1160

Nano Delivery of Sinomenine Targeting Mitochondria to Improve Mitochondrial Autophagy against Kidney Fibrosis through PINK1/Parkin Pathway

Hong Dong Huang.[1,2] [1]*Capital Medical University, Beijing, China;* [2]*Capital Medical University Affiliated Beijing Friendship Hospital, Beijing, China.*

Background: Mitophagy plays a key role in maintaining kidney function and impaired in pathologic states. This study investigated the protective effect of mitochondria-targeted nano sinomenine on renal fibrosis and its molecular mechanism.

Methods: Synthesis mitochondria-targeting nanomaterials. Cell fibrosis cell and animal model were established. Different concentrations of nano sinomenine were used to interfere with cell fibrosis and animal model. Western blot/ flow cytometry were used to detect the expression of LC3, CollagenI, α-SMA and ROS. The expression of PINK1/Parkin were analyzed by RNA-SEQ. The mitochondria and autophagosomes of mitochondria-like organelles were observed by electron microscope. Western blot and immunofluorescence were used to compare the expressions of fibrotic proteins CollagenI, α-SMA, Fibronectin, and mitochondrial autophagy in renal tissues of mice in each group. The renal tubule boundary destruction, atrophy and collagen deposition were observed by PAS and Masson staining.

Results: Nanometer sinomenine targeting mitochondria was successfully established. Cell experiments induced by TGF-β1 and animal experiments on adenine and UUO surgical models confirmed that mitochondrial autophagy was enhanced and TGF-β1 was decreased in the group treated with nano sinomenine. Nano sinomenine decreased the expression of CollagenI, α-SMA, Fibronectin proteins. PINK1 was highly enriched, and the expression level of LC3B decreased after silencing PINK1. The levels of urea nitrogen and creatinine of mice with Nanometer sinomenine treatment were lower than those of control group. The ROS, fibrotic proteins CollagenI, α-SMA, Fibronectin were significantly lower than that of control group, and the expression level of mitochondrial autophagy protein was significantly increased. Renal tubule boundary destruction, atrophy and collagen deposition were significantly lower than those in the control group.

Conclusions: Mitochondria-targeted nano sinomenine had a strong mitochondrial targeting effect on renal tubules, significantly enhances mitochondrial autophagy, inhibits ROS, CollagenI, α-SM production, and against renal fibrosis. It provides a new idea for the treatment of renal fibrosis and the transformation of basic experimental results.

Funding: Government Support - Non-U.S.

SA-PO1161

Knockout of Integrin αvβ6 Protects against Kidney Inflammation in CKD by Reduction of Proinflammatory Macrophages

Chang-Jian Zhu,[1,2] Ruilin Zheng,[1,2] Zhou Liang,[1,2] Yi Zhou.[1,2] [1]*Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China;* [2]*NHC Key Laboratory of Clinical Nephrology (Sun Yat-sen University) and Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, China.*

Background: Integrin αvβ6 holds promise as a target for organ fibrosis, yet targeted therapies are hampered by concerns of inflammatory-related side effects. The role of αvβ6 in renal inflammation remains unknown, and clarifying this issue is crucial for αvβ6-targeted treatment of chronic kidney disease (CKD).

Methods: The correlation between αvβ6 and renal inflammation was investigated in CKD patients and mouse fibrotic models. *Itgb6* systemic or proximal tubular cells (PTCs)-specific conditional knockout mice were established to explore the effect of αvβ6 on the renal inflammation during fibrosis. *In vitro*, PTCs transfected with si-NC or si-*Itgb6* were co-cultured with macrophages to elucidate the mechanism of crosstalk.

Results: A positive correlation was revealed between overexpressed αvβ6 in PTCs and renal inflammation in CKD patients and mouse models. Notably, knockout of αvβ6

not only alleviated renal fibrosis but also reduced inflammatory responses in mice, especially the infiltration of pro-inflammatory macrophages. Conditional knockout of αvβ6 in PTCs *in vivo* and co-culture of PTCs with macrophages *in vitro* showed that depleting αvβ6 in PTCs suppressed the migration and pro-inflammatory differentiation of macrophages. Screening of macrophage activators showed that αvβ6 in PTCs activates macrophages via secreting IL-34. IL-34 produced by PTCs was significantly diminished by αvβ6 silencing, and reintroduction of IL-34 restored macrophage activities, while anti-IL-34 antibody restrained macrophage activities enhanced by αvβ6 overexpression. Moreover, RNA-sequencing of PTCs and verification experiments demonstrated that silencing αvβ6 in PTCs blocked hypoxia-stimulated IL-34 upregulation and secretion by inhibiting YAP expression, dephosphorylation, and nuclear translocation, which resulted in the activation of Hippo signaling. While application of a YAP agonist recurred IL-34 production by PTCs, enhancing the subsequent macrophage migration and activation. Besides, reduced IL-34 expression and YAP activation were also observed in global or PTCs-specific αvβ6-deficient injured kidneys.

Conclusions: Our research elucidates the pro-inflammatory function and YAP/IL-34/macrophage axis-mediated mechanism of αvβ6 in renal inflammation, providing a solid rationale for the use of αvβ6 inhibition to treat kidney inflammation and fibrosis.

Funding: Government Support - Non-U.S.

SA-PO1162

Myeloid Ferritin Heavy Chain Regulates Macrophage Differentiation towards Iron Recycling Phenotype in CKD

Tanima Chatterjee, Sarah E. Machado, Kellen A. Cowen, Abolfazl Zarjou. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Chronic kidney disease (CKD) is a worldwide public health problem affecting ~850 million people. Dysregulation in iron metabolism is a hallmark of advanced CKD. Myeloid cells, particularly macrophages (MΦ), play a crucial role in establishing the delicate balance of iron homeostasis. Ferritin, a spherical shell composed of heavy (FtH) and light (FtL) chains, is paramount in maintenance of this process. Our overarching hypothesis is that myeloid FtH orchestrates iron distribution and regulates MΦ plasticity under injurious/inflammatory conditions through controlling Spic expression.

Methods: To investigate the role of myeloid FtH in relation to kidney iron metabolism, mice deficient in FtH in the myeloid compartment ($FtH^{LysmΔ/Δ}$) were generated. Experiments were carried out using bulk RNA sequencing, single cell RNA sequencing, real-time PCR, western blot, flow cytometry, immunohistochemistry.

Results: Using unbiased transcriptome analysis, significant upregulation of Spic, a transcription factor that selectively controls the development of iron recycling MΦ (Fe-MΦ) was observed in kidneys of $FtH^{LysmΔ/Δ}$ mice following iron administration. This observation was further validated by other markers expressed by this subset of MΦ and was accompanied by higher degree of tubular iron deposition when compared to their wild-type counterparts ($FtH^{fl/fl}$). Moreover, we observed marked induction of Spic in different kidney injury models including ischemia-reperfusion, aristolochic acid, and sepsis mediated kidney injury. Notably, Fe-MΦ are responsible for the resolution stage of the injury and inflammation. Functional significance of myeloid FtH was validated by worse kidney outcomes as evidenced by higher serum creatinine, increased fibrosis, and leukocyte expansion.

Conclusions: Our findings suggest a potential contribution of myeloid FtH to calibrate the iron recycling MΦ phenotype during kidney injury and resolution however, the functional significance of spic in the context of CKD remain to be elucidated.

Funding: NIDDK Support

SA-PO1163

Macrophage Iron Dyshomeostasis Promotes Aging-Related Kidney Fibrosis

Lingzhi Wu, Hongchun Lin, Hui Peng. *The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Renal aging, marked by the accumulation of senescent cells and chronic low-grade inflammation, leads to renal interstitial fibrosis and impaired function. However, the mechanism of macrophages in renal aging remains unclear. Here, by analyzing single-cell RNA sequencing data and constructing aging models in vivo and in vitro, we further explore the role and mechanism of macrophages in promoting kidney aging.

Methods: We analyzed kidney single-cell RNA sequencing data (GSE198832) of C57BL/6J mice aged 8 weeks to 24 months to describe the dynamic changes in the proportion and function of kidney cell types during kidney aging. CellChat analysis uncovered changes in the intercellular communications between macrophages and tubular cells. SCENIC analysis revealed key regulons in a network of aging-related genes within kidney macrophages. Molecular docking and virtual screening revealed potential anti-aging agents.

Results: Our findings elucidate the dynamic changes in the proportion of kidney cell types during renal aging and reveal that increased macrophage infiltration contributes to chronic low-grade inflammation, with these macrophages exhibiting senescence and activation of ferroptosis signaling. CellChat analysis indicates enhanced communications between macrophages and tubular cells during aging. Suppressing ferroptosis alleviates macrophage-mediated tubular partial epithelial-mesenchymal transition in vitro. Using SCENIC analysis, we infer Stat1 as a key age-related transcription factor promoting iron dyshomeostasis and ferroptosis in macrophages by repressing the expression of Pcbp1, an iron chaperone protein that inhibits ferroptosis. Knockdown of Pcbp1 aggravated the drug-induced macrophage senescence phenotypes, whereas overexpression of Pcbp1 alleviated macrophage senescence phenotypes. Through virtual screening and molecular docking from a library of anti-aging compounds, we construct a docking model targeting Pcbp1, which indicates that the natural small molecule compound Rutin can suppress macrophage senescence and ferroptosis by preserving Pcbp1.

Conclusions: Our study underscores the crucial role of macrophage iron dyshomeostasis and ferroptosis in renal aging. Our results also suggest Stat1 and Pcbp1 as intervention targets in aging-related renal fibrosis, and highlight Rutin as a potential therapeutic agent in mitigating age-related renal chronic low-grade inflammation and fibrosis.

SA-PO1164

Role of Nephrotoxic Serum-Driven Ferroptosis in Ncf1-p.R90H KI Female Mice

Mariia Stefanenko,[1] Lei Wang,[1] Mykhailo Fedoriuk,[1] Alena Cherezova,[2] Daria Ilatovskaya,[2] Sun-sang J. Sung,[3] Betty Tsao,[1] Oleg Palygin.[1] *[1]Medical University of South Carolina, Charleston, SC; [2]Augusta University, Augusta, GA; [3]University of Virginia, Charlottesville, VA.*

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder characterized by deposition of autoantibodies and immune complex formation, leading to inflammation and impaired organ function. The activation of NOX2, facilitated by efferocytosis, is disrupted by the substitution of arginine (R) for histidine (H) in the NCF1/p47phoxprotein, which reduces NOX2's ability to produce reactive oxygen species, exacerbating autoimmune responses and affecting redox balance in SLE pathogenesis in humans and mouse models on the C57BL/6 background. This study explores the mechanisms of ferroptosis in the renal proximal tubules (PT) of the H90.B6 knock in (KI) mice and examines potential sexual dimorphism in nephrotoxic serum (NTS)-driven tubulointerstitial disease.

Methods: The R90.B6 wild-type (WT) and H90.B6 KI female littermates were injected with either sheep (control) or NTS and kidneys were harvested after two weeks. Prussian blue histochemical staining was performed on fixed tissue to detect ferroptosis and PT damage. Freshly isolated PT was obtained by vibrodissociation, and *ex vivo* confocal imaging with fluorescent indicators was performed to assess ferrous ion (Fe^{2+}) presence (Mito-FerroGreen) and mitochondrial membrane potential (ΔΨm, JC1) in PT cells, respectively.

Results: Histochemical staining revealed elevated ferroptosis in NTS-treated H90.B6 compared to the NTS-treated R90.B6 littermates ($P<0.05$) but not in control-treated groups. The confocal microscopy confirmed a high prevalence of mitochondrial ferrous ion in PT of female H90.B6 NTS- treated group that control-treated and NTS-treated WT and KI were 4±3, 2±1, 4±2, 17±4 % of PT ferroptosis (n≥74 tubule/ group, $P<0.05$). The accumulation of mitochondrial ferrous iron in PT was also confirmed by acute ammonium iron (II) sulfate applications. Compared to control serum treatment, the NTS-treated R90.B6 and H90.B6 groups showed a reduced ΔΨm.

Conclusions: The human SLE causal variant NCF1-H90 variant promotes ferroptosis in PT of non-autoimmune mice. These findings underscore the importance of understanding the role of redox mechanisms in linking ferroptosis, nitrosative stress, and lipid peroxidation in NCF1-p.R90H (H90) variant, highlighting the need to better understanding of tubulointerstitial disease in SLE.

Funding: NIDDK Support, Other NIH Support - R01 DK126720, R21 AR081933-01A1., Private Foundation Support

SA-PO1165

Single-Cell RNA Sequencing Identifies a Unique Population of Macrophages in the Aristolochic Acid-Induced AKI-to-CKD Transition Murine Model

Xiangchen Gu, Yaodong Gu, Lin Xie, Ye Cheng, Yi Wang, Min Chen. *Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai, China.*

Background: The transition from acute kidney injury (AKI) to chronic kidney disease (CKD) is a significant contributor to kidney injury progression, and effective treatments to prevent or slow this transition are lacking. Macrophages are known to play a pivotal role in this process, but the specific subtypes involved and their interactions with other cell types remain unclear.

Methods: We induced AKI in mice via intraperitoneal injections of Aristolochic Acid I (AAI) every 3 days for 2 weeks, followed by a 2 week remodeling phase without injections. Single-cell RNA sequencing (scRNA-seq) was then performed on kidney samples from control, AKI, and CKD phases using 10x Genomics. Following stringent quality control and feature selection using Scanpy, SoupX, and scDblFinder, we harmonized gene symbols and integrated the data using deep generative modeling (scVI). We identified cell subclusters, cell-to-cell communication, and cellular trajectories

using Scanpy, LIANA, and scVelo. Differentially expressed genes (DEGs) and enriched pathways were determined using edgeR. Immunofluorescence of the unique population of macrophages was confirmed in both human CKD kidney samples and the murine AAI-induced AKI to CKD model.

Results: We profiled 56,325 single cells representing 30 major cell types across three time points. Significant changes in immune cell clusters, particularly macrophages, were observed during the AKI to CKD transition. Enriched pathways in the CKD phase included mitochondrial ATP synthesis and electron transport, while the AKI phase was characterized by inflammatory and innate immune responses. A unique population of Ctsk+ and Mmp9+ macrophages was identified in the CKD phase. These macrophages interacted with T cells (via Lgals1/Ptprc and Calr/Itgav), injured proximal tubules and fibroblasts (via Apoe/Lrp2), and dendritic cells and basophils (via Vim/Cd44). Increased expression of CTSK and MMP9-positive macrophages was confirmed by immunofluorescence staining in both the CKD phase of the murine model and human CKD samples.

Conclusions: ScRNA-seq of the murine AAI model identified a unique population of CTSK and MMP9-positive macrophages as critical responders in the AKI to CKD transition. Targeting these macrophages may present a valuable therapeutic strategy for preventing the progression from AKI to CKD.

Funding: Government Support - Non-U.S.

SA-PO1166

Involvement of Protein-Tyrosine Phosphatase ζ Receptor on the Progression of Kidney Fibrosis in Mice with Unilateral Ureteral Obstruction

Tetsuya Abe, Yukihiro Wada, Masashi Satoh, Takayuki Imanishi, Makoto Otsu, Tadahiro Suenaga, Yasuo Takeuchi. *Kitasato Daigaku Igakubu, Sagamihara, Japan.*

Background: Intrarenal expressions of protein-tyrosine phosphatase ζ receptor (PTP-ζ), the second receptor of interleukin (IL)-34 for macrophage (Mø) proliferation, have been demonstrated in several experimental renal disease models. However, role of PTP-ζ on the progression of renal diseases remains elusive. We investigated the influence of PTP-ζ on renal fibrosis caused by unilateral ureteral obstruction (UUO).

Methods: 10-week-old male wild type (WT) C57BL/6 (B6) mice (WT, n = 14) and age-matched male PTP-ζ knockout (KO) B6 mice (KO, n = 16) were induced UUO. Four age-matched male B6 mice received sham operation as control. All mice were sacrificed on day 14. *In vitro*, mouse Mø cell line (RAW 264.7) or mouse bone marrow-isolated Møs (BMMøs) were stimulated with TGF-β (5 ng/mL), and then treated with or without recombinant IL-34 (r-IL-34) (500 pg/mL) for the effects of PTP-ζ analyses.

Results: Compared to the sham-operated control, the UUO kidneys of WT mice exhibited remarkable intrarenal IL-34 and PTP-ζ expressions. Meanwhile, the KO mice showed deficiency of intrarenal PTP-ζ expression despite comparable IL-34 expression to the WT mice. Compared to the WT mice, tubular injury and sirius red-stained fibrosis area were significantly attenuated in the KO mice kidney (9.0% ± 0.7 vs. 4.8% ± 0.7/HPF, $p<0.001$). The KO mice significantly suppressed the number of $F4/80^+$ Mø, $PDGF\text{-}\beta^+$ fibroblasts, and $\alpha\text{-}SMA^+$ myofibroblast in damaged kidneys of UUO by immunofluorescence (IF) analysis. Intrarenal mRNA levels for TGF-β, COL-1, fibronectin, Yim1/Chil3, and Timp-1 were lower in the KO mice. IF revealed significant suppression of intrarenal $F4/80^+CD206^+$ Mø infiltration in the KO mice. Flow cytometry analysis showed that the ratio of CD206/CD11c in the population of intrarenal $CD11b^+F4/80^+$ Mø was higher in the KO mice. *In vitro*, expressions of PTP-ζ were confirmed in TGF-β stimulated RAW264.7 cells and BMMs. Administration with TGF-β and rIL-34 significantly up-regulated the mRNA level for Timp-1 in RAW264.7 cells compared to TGF-β- and vehicle-treated group.

Conclusions: Up-regulation of PTP-ζ in the damaged kidneys is involved in the progression of renal fibrosis. IL-34/PTP-ζ pathway on Mø might skew Mø into M2-like Mø, contributing to renal fibrosis via enhancing profibrotic response.

SA-PO1167

Single-Cell Spatial Transcriptomics Unveil Platelet-Fueled Cycling Macrophages for Kidney Fibrosis

Jun Liu. *Children's Hospital of Soochow University, Suzhou, China.*

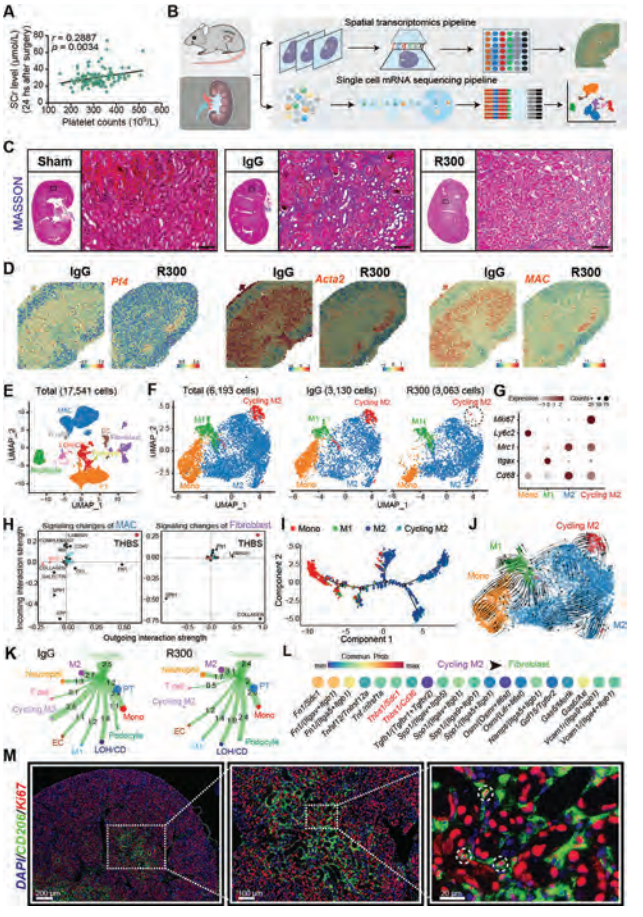
Background: With the increasing incidence of kidney diseases, there is an urgent need to develop therapeutic strategies to combat post-injury fibrosis. Immune cells, including platelet, play a pivotal role in this repair process. However, the specific role of platelet in kidney injury and subsequent repair remains underexplored.

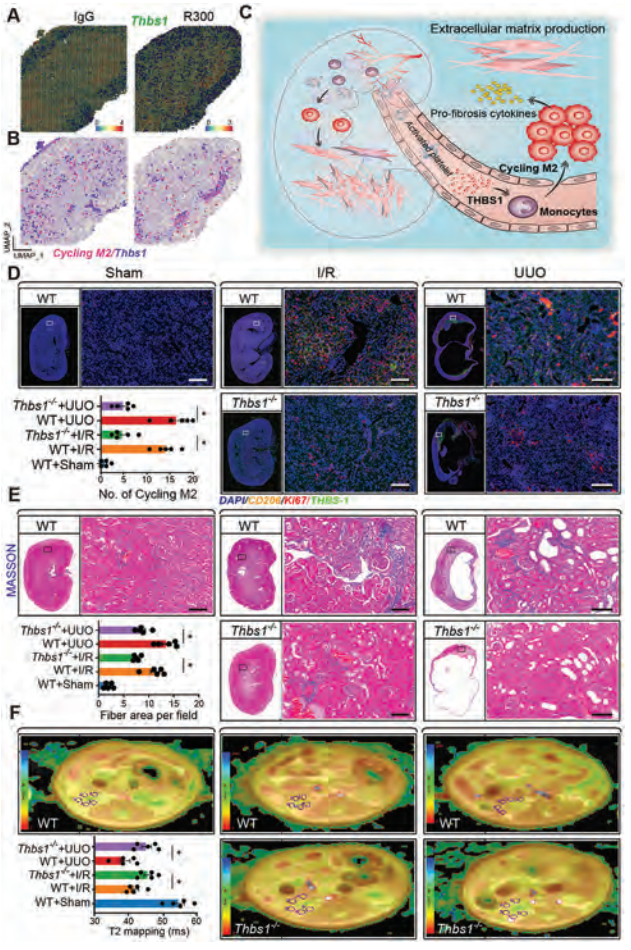
Methods: The surgery of bilateral I/R-induced kidney injury was performed on Wild-type and *Thbs1* knock-out mice to induce kidney injury and fibrosis. Single-cell and spatial transcriptomics and Magnetic Resonance Imaging (MRI) scanning were applied.

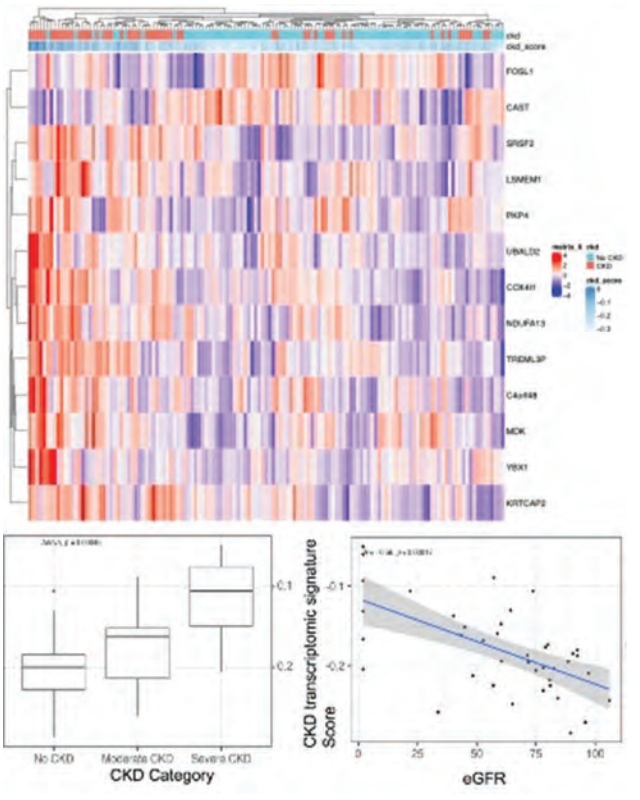
Results: We show that depleting platelet accelerates injury resolution and significantly reduces fibrosis. We identify a novel subset of macrophages, termed "cycling M2", which exhibit an M2 phenotype combined with enhanced proliferative activity. This subset emerges in the injured kidney during the resolution phase and is modulated by platelet-derived THBS1 signaling, acquiring profibrotic characteristics. Targeted inhibition of THBS1 reduces the cycling M2 macrophage, thereby mitigating fibrotic progression.

Conclusions: Our findings highlight the adverse role of platelet THBS1-boosted cycling M2 macrophages in renal injury repair and suggest platelet THBS1 as a promising therapeutic target for alleviating kidney fibrosis.

Funding: Government Support - Non-U.S.







SA-PO1168

Platelet Transcriptome Analysis in CKD Provides Insight into Cardiovascular Events

Avantika Israni, Matthew Muller, David M. Charytan, Jeffrey S. Berger.
New York University, New York, NY.

Background: Platelet dysfunction is common in patients with CKD and contributes to hemorrhagic tendencies as well as CVD, but to our knowledge effects of CKD on the platelet transcriptome have not been analyzed.

Methods: We compared the platelet transcriptome from prospectively recruited patients with peripheral artery disease according to eGFR and CKD class: moderate CKD (eGFR of 30-<60 mL/min/1.73m²), severe CKD (eGFR of < 30 mL/min/1.73,2), or chronic dialysis. Results were adjusted for age, sex, ethnicity and race.

Results: 54 participants had CKD (28% male, mean age 72, and 12% Black) and 81 had preserved kidney function (62% male, mean age 69, and 15% Black). After adjusting for age, sex, race, ethnicity, and multiple comparisons, we identified 17 differentially expressed genes in moderate CKD (13 upregulated, 4 downregulated), & 344 in severe CKD (188 upregulated, 156 downregulated), and 560 in chronic dialysis (274 upregulated, 286 downregulated) compared with preserved kidney function. We defined a transcriptomic signature of 13 genes differentially expressed in CKD, and showed that this signature associated with CKD severity in a test cohort (N=40). This signature was correlated with epinephrine and ADP induced platelet aggregation and was significantly associated with mortality and major adverse cardiovascular events in adjusted analyses. In additional analyses multiple genes were significantly correlated with eGFR. Mitochondrial function and RNA function processes were particularly impacted (Figure)

Conclusions: These findings demonstrate a unique platelet transcriptomic signature in CKD that is associated with future risk of cardiovascular events.

SA-PO1169

Cardiac Dysfunction in C57Bl/6J Mice with CKD: Comparison of Dietary Adenine and 5/6 Nephrectomy Models

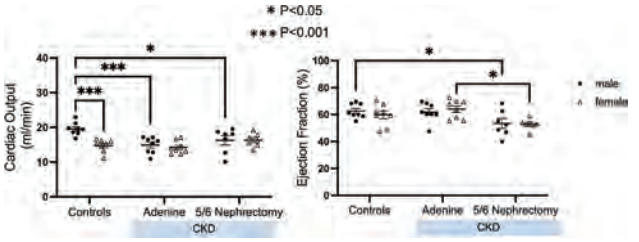
Yitong Zhao,[1] Karen Yang,[2] Hongmei Wu,[1] Han Liu,[1] Leandro Velez,[3] Jin Kyung Kim,[4] Marcus Seldin,[3] Wei Ling Lau.[1] *[1]Division of Nephrology, Department of Medicine, University of California-Irvine, Irvine, CA; [2]University of California Riverside School of Medicine, Riverside, CA; [3]University of California Irvine Department of Biological Chemistry, Irvine, CA; [4]Division of Cardiology, Department of Medicine, University of California-Irvine, Irvine, CA.*

Background: Cardiovascular disease (CVD) is the leading cause of death among patients with chronic kidney disease (CKD). Gut-derived uremic toxins contribute to vascular injury and cardiomyopathy in CKD. In this study, we compared echocardiogram parameters between dietary adenine and 5/6 nephrectomy CKD models and examined associations with gut-derived uremic toxins stratified by sex.

Methods: Male and female adult C57Bl/6J mice were randomly assigned to control, adenine-induced CKD and 5/6 nephrectomy CKD groups. Echocardiography was performed on all mice at 5 weeks after CKD induction. Serum creatinine, cystatin C and gut-derived uremic toxins (trimethylamine N-oxide, TMAO; indoxyl sulfate, IS; and p-cresyl sulfate, pCS) were analyzed at study termination. Data was analyzed using two-way ANOVA and Spearman correlation analysis.

Results: Serum markers of kidney dysfunction (creatinine and cystatin C) were significantly elevated in both CKD models. TMAO was significantly increased in adenine CKD mice, IS was elevated in both CKD models, and pCS was increased in the nephrectomy group. Left ventricular volume was increased in nephrectomy animals. Cardiac output (CO) was decreased in male CKD animals from both models compared to male controls, and ejection fraction (EF) was decreased in male 5/6 nephrectomy mice (figure). Female controls had lower CO than male counterparts, and female CKD animals were not significantly different from female controls in terms of CO and EF. In female animals, higher serum pCS and IS were positively correlated with increased left ventricular volume; higher pCS were inversely correlated with EF ($r = -0.501$, $P<0.05$). These associations were not seen in male animals.

Conclusions: Our work highlights sex differences in cardiac function and serum toxin levels in two established preclinical CKD models. Gut-derived uremic toxins may impact cardiorenal pathophysiology in female but not male CKD animals.



SA-PO1170

Gut Microbiota Drives Kidney Damage and Cardiac Remodeling in Experimental CKD

Wibke Anders, Alex Yarritu, Istvan A. Szijarto, Arne Thiele, Sara A. Hassan, Carina Hoffmann, Ariana Rauch, Franziska Fuckert, Natnael Gebremedhin, Paul Moritz Bonnekoh, Olena Potapenko, Johannes Holle, Hendrik Bartolomaeus, Nicola Wilck. *Charite Universitatsmedizin Berlin, Berlin, Germany.*

Background: Chronic kidney disease (CKD) represents a major, often overlooked cardiovascular (CV) risk factor. CV disease (CVD) is the leading cause of mortality in CKD. Alterations in gut microbiome composition and function are evident in CKD, leading to increased production of detrimental metabolites of bacterial origin, impacting inflammation and end-organ damage. We hypothesize that CV remodeling and preservation of kidney function are influenced by the microbiome.

Methods: Experimental CKD was induced in *129/Sv* mice by subtotal nephrectomy (STNx). To suppress the microbiome mice received antibiotics (Abx) orally over the course of 13 weeks. CV damage was quantified by echocardiography, histological and gene expression analysis, as well as radiotelemetry blood pressure measurements and analysis of endothelial function.

Results: Compared to STNx, STNx+Abx mice exhibited a significantly improved kidney function quantified by plasma cystatin c (0.66±0.41 mg/l vs. 1.14±0.54 mg/l; p = 0.012). This was confirmed by the expression of renal damage markers (e.g. *Ngal, Tgfb, Ctgf*) and histological analyses. We observed an increase in heart weight/tibia length in STNx (10.1±0.5 g/m) that was attenuated by Abx (7.0±0.2 g/m; p < 0.001). Hearts of STNx+Abx mice displayed significantly less remodeling, independent of similarly elevated blood pressures in both groups. Cardiac expression of hypertrophy and pro-fibrotic markers were reduced in STNx+Abx (e.g. *Nppb, Myh7, Ctgf*). Histological analysis of the left ventricle by picrosirius red revealed STNx-induced cardiac fibrosis (PSR-positive area 12.0±1.5%), that was ameliorated by Abx (5.8±1.8%; p=0.008). Vascular function, as assessed by wire myography of mesenteric arteries, indicated an impaired endothelium-dependent relaxation in STNx that was improved in STNx+Abx. In addition, we performed functional analysis by echocardiography, organ-specific immune phenotyping, and bulk RNA sequencing of the heart.

Conclusions: In experimental CKD, kidney function and cardiac remodeling depend on the dysbiotic microbiome, highlighting the interplay between the microbiome, CKD progression, and the development of CV complications in CKD.

SA-PO1171

Associations of Urine Epidermal Growth Factor with Kidney and Cardiovascular Outcomes in Individuals with CKD in SPRINT

Merve Postalcioglu,[1] Ronit Katz,[2] Simon Ascher,[4] Pranav S. Garimella,[3] Stein I. Hallan,[5] Joachim H. Ix,[3] Michael Shlipak.[1] *[1]UCSF Medical Center, San Francisco, CA; [2]University of Washington, Seattle, WA; [3]University of California San Diego, La Jolla, CA; [4]University of California Davis, Davis, CA; [5]St Olav's Hospital HF, Trondheim, Norway.*

Background: Urine epidermal growth factor (uEGF) marks kidney tubule function and lower urine concentrations are associated with faster kidney function loss. Its associations with cardiovascular disease (CVD) and mortality are unknown.

Methods: We measured uEGF among 2,346 Systolic Blood Pressure Intervention Trial (SPRINT) participants with an eGFR<60 ml/min/1.73m^2. Linear mixed-effects models were used to investigate associations with the annual eGFR change, and Cox models evaluated associations with the ≥30% eGFR decline, cardiovascular disease (CVD), and mortality. To account for the competing risk of death, Fine and Gray method was utilized for acute kidney injury (AKI) and end-stage kidney disease (ESKD) outcomes.

Results: Mean (SD) age was 73±9 years, mean eGFR was 46±11 ml/min/1.73m^2 and median UACR of 15 mg/g (interquartile range: 7-49). In analyses adjusting for baseline albuminuria and eGFR, each 50% lower uEGF concentration was associated with 0.74% (95% confidence interval:1.19, 0.29) per year faster decline in eGFR. **(Table)** During 3.1 (median) years of follow-up, lower uEGF was also associated with higher risk of ≥30% eGFR decline. Lower uEGF concentrations were associated with ESKD, AKI, incident CVD, and mortality in initial models, but associations were substantially attenuated by adjustment for albuminuria and eGFR. **(Table)**

Conclusions: Among hypertensive adults with CKD, lower uEGF is associated with faster eGFR decline independent of baseline albuminuria and eGFR; but not with ESKD, AKI, CVD, or mortality.

Funding: NIDDK Support

Table. Associations of baseline uEGF concentrations with kidney outcomes, CVD and all-cause mortality among SPRINT participants with prevalent CKD

Outcome (N=2346) (per 50% lower uEGF concentration)	Multivariable adjusted model*	Multivariable adjusted model +UACR+eGFR*
Annualized percent change in eGFR (% year)	β (95% CI)	β (95% CI)
	-1.41 (-1.76, -1.06)	-0.74 (-1.19, -0.29)
≥30% eGFR Decline (N=418)	HR (95% CI)	HR (95% CI)
	1.39 (1.23, 1.56)	1.17 (1.00, 1.36)
Acute kidney injury (N=183)	SHR (95% CI)	SHR (95% CI)
	1.63 (1.35, 1.98)	1.11 (0.85, 1.45)
End-stage kidney disease (N=73)	SHR (95% CI)	SHR (95% CI)
	4.14 (3.06, 5.61)	1.24 (0.81, 1.89)
Cardiovascular disease[1] (N=180)	HR (95% CI)	HR (95% CI)
	1.32 (1.09, 1.59)	0.98 (0.76, 1.27)
All-cause mortality (N=158)	HR (95% CI)	HR (95% CI)
	1.61 (1.31, 1.99)	1.08 (0.82, 1.43)

[1]CVD composite outcome includes myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes.
* Adjusted for age, sex, race, randomized treatment arm, urine creatinine, smoking status, body mass index, history of cardiovascular disease, systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoprotein, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blocker, calcium channel blockers, and diuretics.
†Additionally adjusted for baseline urine albumin and eGFR.
Abbreviations: uEGF, urine epidermal growth factor; CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SPRINT, systolic blood pressure intervention trial; HR, hazard ratio; SHR, sub-distribution hazard ratio.

SA-PO1172

Indoxyl Sulfate Dysregulates Choline Acetyltransferase-Mediated Cognitive Impairment in Patients with ESKD by Extrinsic Apoptosis in the Neuronal Cells during the Differentiating Process

Yi-Chou Hou. *Cardinal Tien Hospital, New Taipei City, Taiwan.*

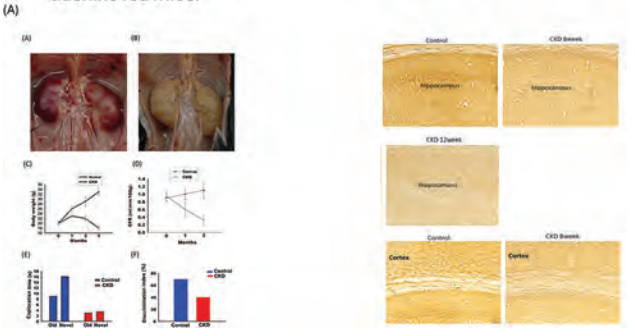
Background: This study investigates the correlation between indoxyl sulfate (IS) levels and cognitive impairment in end-stage renal disease (ESRD) patients from human study, in vivo and in vitro study.

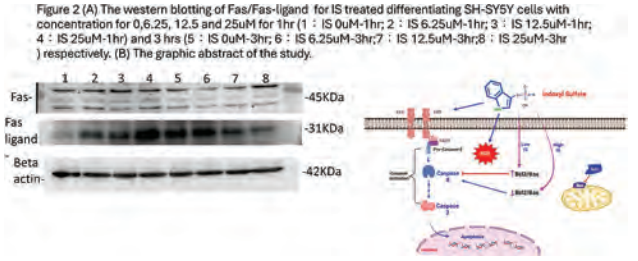
Methods: A CKD animal model induced renal impairment in adenine-fed C57BL/6 mice, assessing memory loss and behavioral changes. Immunohistochemistry evaluated choline acetyltransferase. Differentiating SH-SY5Y cells were treated with IS to assessing cell viability. Reactive oxidized species generation was measured using DCFCA fluorescence.

Results: IS levels were significantly higher compared to healthy controls, along with older age. CKD mice exhibited renal impairment and memory loss, accompanied by altered choline acetyltransferase. IS treatment induced early apoptosis in SH-SY5Y cells, associated with increased cleaved caspase 3 levels and Fas/Fas-ligand activity, altered Bax/Bcl2 ratio, and reactive oxidized species generation.

Conclusions: IS levels was associated with cognitive impairment and neuronal apoptosis with choline transferase dysfunction. IS could be a therapeutic target for cognitive dysfunction in CKD.

Figure 1. (A) The impairment in NOR test in adenine-fed mice; (B)The decrease of Choline transferasein CA1 of hippocampus and cortex in adenine fed mice.





SA-PO1173

Klotho Mitigates Indoxyl Sulfate-Induced Oxidative Stress through Modulation of the AKT/Nrf2 Pathway

Chien Yao Sun,[1,2] Chia-Ter Chao,[3] Yu T. Chang.[1] *[1]National Cheng Kung University Hospital, Tainan, Taiwan; [2]University of California San Francisco Department of Medicine, San Francisco, CA; [3]National Taiwan University Hospital, Taipei, Taiwan.*

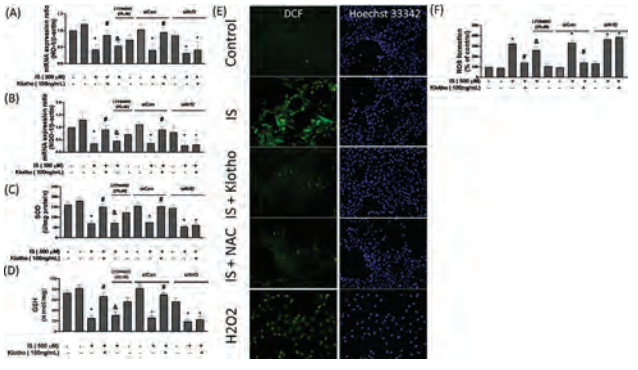
Background: Chronic kidney disease (CKD) is a progressive condition with significant global prevalence. The uremic toxin indoxyl sulfate (IS) induces tubulotoxicity and oxidative stress in CKD patients. It has been shown that IS downregulates the expression of the anti-aging protein klotho in proximal tubule cells and kidneys. The detailed mechanism of reduced klotho's role in nephropathy and oxidative stress is unclear.

Methods: We treated renal proximal tubule epithelial cells (HK-2 cells) with 500μM IS to induce oxidative stress. Antioxidant gene expression was studied by real-time PCR, and ROS levels were investigated by DCF-DA.

Results: Our results showed that the mRNA expression levels of HO-1 and NQO1 were suppressed in IS-treated cells, but administration of klotho counteracted this effect. Blocking AKT/Nrf2 signaling with an AKT inhibitor (LY2780301) or silencing Nrf2 impeded klotho's rescue effect on HO-1 and NQO1 expression, suggesting that IS inhibits HO-1 and NQO1 via the klotho/AKT/Nrf2 axis. We also examined superoxide dismutase (SOD) expression and found that IS treatment reduced SOD levels, which were restored by recombinant klotho. Inhibition of AKT/Nrf2 signaling negated Klotho's beneficial effect on SOD concentration. IS-stimulated cells showed elevated ROS formation, while recombinant klotho hindered this upregulation. Suppression of AKT/Nrf2 signaling restrained Klotho's protective effect against IS-induced ROS production.

Conclusions: Our findings suggest that IS increases oxidative stress in HK-2 cells by elevating ROS and inhibiting antioxidant capacity, as evidenced by lower expression of HO-1, NQO1, and SOD via the Klotho/AKT/Nrf2 signaling pathway.

Funding: Other NIH Support - Ministry of Science and Technology (MOST) 111-2314-B-006 -034 (Taiwan)



Klotho reduces IS-increased oxidative stress.

SA-PO1174

ARNTL Regulates Endoplasmic Reticulum Stress and Mitochondrial Apoptosis through NRF2 and Plays a Crucial Role in the Development of CKD

Li He, Aili Cao, Niansong Wang. *Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.*

Background: The core molecular clock protein, ARNTL, contributes to kidney tubular injury and fibrosis. Endoplasmic reticulum (ER) stress is implicated in the pathogenesis of chronic kidney disease (CKD), yet the interaction between ER stress and circadian clock pathways in kidney tubular cells remains unclear.

Methods: In this study, we observed ARNTL expression and ER stress markers in both CKD patients and CKD rats. In vitro experiments involved treating HK2 cells with the ER stress activator tunicamycin (Tm) and the ER stress inhibitor Tauroursodeoxycholic acid (TUDCA). Additionally, ARNTL was silenced using siRNA to assess the effects on ER stress markers and mitochondria-related apoptosis. The regulation of NRF2 by ARNTL was studied through direct E-box binding to the Nrf2 promoter.

Results: We found a decrease in ARNTL expression and a significant increase in ER stress markers in both CKD patients and CKD rats. In vitro experiments showed that the ER stress activator tunicamycin (Tm) markedly reduced ARNTL expression, while treatment with Tauroursodeoxycholic acid (TUDCA), an effective ER stress inhibitor, significantly increased ARNTL protein levels and reduced ER stress markers. Silencing ARNTL with siRNA in HK2 cells resulted in the upregulation of ER stress markers and activation of mitochondria-related apoptosis. NRF2, crucial in the innate immune response and apoptosis regulation, is shown to be regulated by ARNTL through direct E-box binding to the Nrf2 promoter. Loss of ARNTL diminished NRF2's response to ER stress, leading to increased production of the proinflammatory cytokine IL-1β and subsequent mitochondria-related apoptosis in HK2 cells.

Conclusions: These findings underscore the pivotal role of ARNTL in modulating NRF2 activity and the ER stress response in HK2 cells, providing insights into the mechanisms underlying CKD. Our study highlights the importance of ARNTL, ER stress, and NRF2 in the apoptosis and injury of renal tubular cells, contributing to the pathology of CKD.

Funding: Private Foundation Support

SA-PO1175

Empagliflozin Attenuates CKD-Induced Cognitive Impairment by Improving Blood Brain Barrier Integrity in Mice and Endothelial Cells

Lung-Chih Li,[1,2] Chia-An Chou,[1] Chiang-chi Huang,[1] Jenq-Lin Yang.[2] *[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [2]Institute for Translational Research in Biomedicine; Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan.*

Background: Chronic kidney disease (CKD) is characterized by progressive loss of renal function and complicated with varies comorbidities, including cardiovascular disorders (CVD) and neurological dysfunction. The evidence of our previous study has suggested that uremic toxins, including indoxyl sulfate (IS) and p-cresyl sulfate (PCS), could pass blood brain barrier (BBB) promoting neuroinflammation that eventually contributes to CKD-induced cognitive dysfunction. Empagliflozin (EMPA), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, has emerged as a novel therapeutic approach for CVD and neurodegenerative disorders. This study aims to investigate pathogenic mechanisms of CKD-induced cognitive impairment, furthermore, to determine whether EMPA improves CKD-induced neurological dysfunction.

Methods: Eight-week-old male C57B6 wide type mice received sham and 5/6 nephrectomy to mimic CKD status. EMPA was given orally for 12 weeks. The Morris water maze (MWM) testes was applied to evaluate cognitive function, including the short-term and long-term memory in shame, CKD, and EMPA-treated CKD mice. Fe^3O^4 Brain MRI and Evans blue were used to evaluate the permeability of BBB in mouse brain. Trans-well assay was used to evaluate the permeability of in vitro BBB model, constructed by bEnd3 cell, an endothelial cell from mouse brain. Western blot was used to identify the protein expression of target molecules in the brain tissue and endothelial cells.

Results: The results of *in vitro* study revealed that 20 μM IS, but not PCS, dysregulated permeability of brain endothelial cells (bEnd3) via disruption of tight-junction integrity. The brains of 5/6-nephrectomy-induced CKD mice also showed BBB leakage by Fe^3O^4 tail vein-injected magnetic resonant images (MRI). In addition, MWM tests indicated the impaired learning capability and long-term memory in CKD mice. The treatment of EMPA restored permeability of bEnd3 cells as well as ameliorated CKD-induced cognitive impairment that were consequences of EMPA maintaining BBB integrity of CKD mice. The evidence was demonstrated by Evans blue brain perfusion, brain MRI, MWM, and transwell permeability assay.

Conclusions: EMPA effectively improved BBB integrity and attenuated CKD-induced cognitive impairment in brains of CKD mice.

Funding: Government Support - Non-U.S.

SA-PO1176

Empagliflozin Reduces Progressive Proteinuria by Potentially Reprogramming Energy Metabolism in Proximal Tubules in Young, Nondiabetic, Obese, Dahl Salt-Sensitive Rats

Sautan Mandal, Anukool A. Bhopatkar, Ubong S. Ekperikpe, Ngoc Hoang, Karen Brooks, Kristin Edwards, Jan M. Williams. *The University of Mississippi Medical Center, Jackson, MS.*

Background: Prepubertal obesity has become a major health problem and has been associated with early signs of proteinuria. Recently, we reported that the non-diabetic obese Dahl salt-sensitive leptin receptor mutant (SS^{LepR}mutant) rat develops proteinuria prior to puberty. Renal proximal tubules (PTs) are highly energy demanding primarily

relying on fatty acid oxidation (FAO) for energy production. Previous studies have demonstrated that PT energy metabolism shifts to glycolysis during the development of diabetic renal injury. We recently observed the expression of SGLT2 was upregulated in the PTs of SS^{LepR}mutant rats before puberty. This suggests there may be energy metabolic alterations in the PTs of young SS^{LepR}mutant rats contributing to proteinuria. Therefore, the current study examined whether treatment with the SGLT2i, empagliflozin (EMPA), shifts energy metabolism in the PT and reduces the early proteinuria in SS^{LepR}mutant rats.

Methods: Four-week-old SS and SS^{LepR}mutant rats were treated with either vehicle (orally) or EMPA (30mg/kg/day) for 4 weeks. Proteinuria was measured every two-weeks. At the end of the protocol, one kidney was used to measure mitochondrial bioenergetics, and PTs were isolated from the other kidney to measure glycolysis.

Results: Proteinuria was significantly higher in SS^{LepR}mutant vs SS rats (401±51 vs. 27±4 mg/day; $p<0.05$), and treatment with EMPA reduced proteinuria in SS^{LepR}mutant rats (252±23 mg/day; $p<0.05$). We observed a 3-fold increase in GFR in SS^{LepR}mutant rats compared to SS rats, and EMPA markedly decreased GFR in SS^{LepR}mutant rats by 50%. Renal cortical FAO was reduced and PT glycolysis was increased in SS^{LepR}mutant rats when compared to SS rats suggesting a shift in the source of energy metabolism in PTs. Chronic treatment with EMPA significantly increased FAO in the renal cortex and markedly decreased glycolysis in the PTs in SS^{LepR}mutant rats.

Conclusions: Overall, these data indicate that the early proteinuria observed in SS^{LepR}mutant rats during PPO is associated with an energy metabolic shift in PTs that may involve increased SGLT2 activity. Moreover, these results also suggest that SGLT2 inhibition could be of great potential in non-diabetic obese children with early signs of proteinuria.

Funding: NIDDK Support

SA-PO1177

Neuropilin 1 Expressed in Resident Fibroblasts Protects Kidneys from Development of Fibrosis

Yunzhu Shen, Christos Chatziantoniou, Amelie Calmont. *Inserm UMR-S 1155 Common and Rare Kidney Disease, Paris, France.*

Background: Renal fibrosis is the common end point of Chronic Kidney Disease (CKD), the hallmark of which is the deposition of pathological extracellular matrix by myofibroblasts. Experiments with lineage tracing in mice and single-cell RNAseq in humans revealed that resident fibroblasts/pericytes are the major sources of myofibroblasts during CKD progression. Neuropilin 1 (NRP1) is a membrane-bound coreceptor for class 3 semaphorins and for specific isoforms of vascular endothelial growth factor. Importantly, NRP1 plays a critical role in fibrosis progression in various pathophysiological conditions such as liver cirrhosis and tumor proliferation and metastasis. In the kidney, NRP1 is expressed in resident fibroblasts/pericytes of the renal interstitium. We therefore tested the possibility that NRP1 could participate in a cell-autonomous manner in the development of renal fibrosis

Methods: We used the myelin protein zero-Cre (*P0-Cre*) strain of mice to invalidate the expression of *Nrp1* constitutively in resident fibroblasts of the kidney. *Nrp1-ko* mutants (P0-Cre, $Nrp1^{flox/flox}$, $Rosa^{YFP}$) and wildtype littermates were subjected to two well-characterized models of renal fibrosis: the folic acid (FA) nephrotoxicity model and the unilateral ureteral obstruction (UUO) model. In separate experiments, we used angiotensin II (Ang II) administration through an osmotic minipump to generate cardiac fibrosis.

Results: We found that *Nrp1-ko* displayed proliferative defects that affected renal recovery after acute kidney injury. Accordingly, the renal function and structure of *Nrp1-ko* were significantly more impaired than those of their wildtype littermates in FA-induced renal disease. Similar observations were done in *Nrp1-ko* subjected to UUO. Our lineage tracing experiments showed that renal and cardiac interstitial cells derived from the same P0-Cre positive progenitors. This observation led us to investigate the role of NRP1 in the progression of cardiac fibrosis. We found that after continuous Ang II infusion, the fibrotic lesions are more pronounced in the hearts of *Nrp1-ko* mice compared to those of their wildtype littermates.

Conclusions: Our data suggest that NRP1 expressed in resident fibroblasts is a protective mechanism against the progression of fibrosis, and this mechanism appears to be common in the kidney and heart.

Funding: Government Support - Non-U.S.

SA-PO1178

Targeting Neuropilin-1 in Distal Tubules Improves Kidney Injury and Fibrosis

Yinzheng Li, Rui Zeng, Gang Xu, Ying Yao. *Huazhong University of Science and Technology Tongji Medical College Tongji Hospital, Wuhan, China.*

Background: Transforming growth factor-beta (TGF-β) is a critical driver of organ fibrosis, but current strategies to target it are clinically ineffective. One reason for this inefficiency is due to co-receptor surrogacy. Notably, Neuropilin-1 (NRP1), a broad-spectrum co-receptor for various cytokines, has been identified as a potential therapeutic target for liver and pulmonary fibrosis in recent years. However, its role in renal injury and renal fibrosis is still unclear. Therefore, this study aimed to investigate the role of NRP1 in kidney injury and fibrosis and its specific mechanisms.

Methods: Renal puncture specimens from patients with transplant renal insufficiency and kidney samples from ischemia-reperfusion (IR) mice were analyzed. Additionally, multi-omics analyses including single-cell RNA sequencing (scRNA-seq), transcriptomics, proteomics, and post-translational modified proteomics were conducted to investigate the role of NRP1 in renal injury and fibrosis.

Results: NRP1 expression was found to been upregulated in DT of patients with transplant renal insufficiency and mice with IR injury. Knockdown of NRP1 in DT reduced IR-induced kidney injury and fibrosis in mice. Increased TNF-α after renal injury promoted NFKB1 expression by promoting the binding of NRP1 to TNR1A (TNF-α receptor), thereby inhibiting its downstream target protein ACOX3. The downregulation of ACOX3 lead to a decrease in lysine crotonylation modification level of cytochrome c oxidase subunit COX4, which consequently resulted in mitochondrial damage and a decrease in oxidative phosphorylation level. This lead to increased cell death in DT, ultimately exacerbating renal injury. Meanwhile, NRP1-positive DT secrete collagen and communicate with myofibroblasts, exacerbating renal fibrosis by activating TGF-β-dependent/independent SMAD3 signaling in renal DT.

Conclusions: NRP1 worsens renal injury and fibrosis by inhibiting the lysine crotonylation modification level of cytochrome c oxidase subunit COX4 and bi-activation of TGF-β-dependent and -independent SMAD3 signaling. Intervention against NRP1 represents a promising strategy for the treatment of chronic kidney diseases.

Funding: Other U.S. Government Support

SA-PO1179

Fibroblast-Selective Smoothened Sensing of the Fibrotic Microenvironment by Controlling Energy Metabolism

Yuan Gui, Yuanyuan Wang, Saiya Zhu, Dong Zhou. *University of Connecticut School of Medicine, Farmington, CT.*

Background: Smoothened (Smo) is a serpentine transmembrane protein that regulates hedgehog signaling through an intracellular conformational switch controlled by electrostatic interactions and multiple phosphorylations. Our previous study found that the loss of fibroblast-Smo decreased tyrosine phosphorylation on GSK-3β, activating the Wnt signaling pathway to mitigate acute kidney injury. However, the role of fibroblast-selective Smo in kidney fibrosis remains unclear.

Methods: We generated two strains of inducible fibroblast-specific Smo conditional knockout (cKO) mice using Gli1-Cre and Pdgfrβ-Cre drivers. These mice underwent unilateral renal ischemic reperfusion injury combined with nephrectomy (UIRI [10 days] + Nx [7 days]) or unilateral ureter obstruction (UUO [7 days]) to induce kidney fibrosis. Global, phospho-, and spatial-proteomics were employed to analyze the results.

Results: Following UIRI + Nx or UUO, both strains of fibroblast-Smo cKO mice showed improved renal function and reduced kidney fibrosis. Global proteomics identified 5,945 differential candidates out of 8,024 proteins in fibrotic kidneys. Among these, 67 significant core-matrisome proteins were highlighted, with fibulin-2 being the most notably altered. Phosphoproteomics identified 10,740 phospho-sites corresponding to 3,351 non-redundant phosphoproteins. KEGG enrichment analysis indicated that the epidermal growth factor (EGF) signaling pathway was inactivated in cKO mice compared to controls. Notably, the phosphorylation of most EGF downstream proteins was substantially reduced at multiple serine and tyrosine sites. Mechanistically, fibroblast-released fibulin-2 directly interacted with tubular EGFR, causing EGFR phosphorylation and mitochondrial translocation. This suborganelle translocation induced acetyl-CoA acetyltransferase 1 (ACAT1), as confirmed by spatial proteome analysis. Consistent with Gene Ontology analysis of the global- and phospho-proteome showed upregulated fatty acid β-oxidation and amino acid metabolism in cKO kidneys, as a mitochondrially localized enzyme, ACAT1 indeed processed amino acids and fatty acids in energy metabolism, facilitating the alleviation of kidney fibrosis in fibroblast-Smo cKO mice.

Conclusions: Fibroblast-specific deletion of Smo reduced EGFR phosphorylation and its mitochondrial translocation, improving the fibrotic kidney microenvironment.

Funding: NIDDK Support

SA-PO1180

Deciphering Endoplasmic Reticulum Stress Activation and Its Role in Kidney Disease Progression via the STING Pathway

Magaiver A. Silva, Andrea Sanchez Navarro, Dhanunjay Mukhi, Kolligundla L. Prasanna, Jonathan Levinsohn, Katalin Susztak. Susztak Lab. *University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: Endoplasmic reticulum (ER) stress is crucial in the pathogenesis of kidney disease, yet the mechanisms initiating ER stress remain largely unexplored. Viruses are known to manipulate ER-related processes, potentially aiding their replication and pathogenesis. The adaptor molecule STING, which detects double-strand DNA in viral and bacterial infections, has also been implicated in sterile chronic kidney inflammation and may influence ER stress. Given these insights, we investigated the relationship between STING, ER stress, and the development of kidney disease.

Methods: We utilized STING N153S mice, which exhibit constitutive STING activation, and mice with conditional STING deletion in kidney tubules. In vitro

experiments included silencing of STING or ER stress pathways, and molecular events were analyzed through immunofluorescence, qPCR, Western blotting, and immunoprecipitation techniques. Gene expression data were scrutinized through RNA sequencing from human control and diseased samples, as well as mouse kidney disease models

Results: In both cisplatin and UUO models, we observed consistent activation of STING and the ER stress–activated eIF2α kinase (PERK) pathway. STING was found to physically interact with and activate PERK in tubule cell, leading to ER stress and subsequent renal fibroinflammation. Conversely, deletion of STING or inhibition of PERK provided protection against disease development. sc-RNA-Seq and spatial transcriptomic analysis of human CKD patients and mouse kidney injury models reinforced the association between renal dysfunction and activation of the ER stress pathway.

Conclusions: Our findings reveal a novel mechanism whereby STING activation triggers ER stress via the PERK pathway, resulting in kidney tubule injury and fibrosis. This breakthrough offers promising avenues for developing strategies to modulate ER stress and create effective therapies for fibroinflammatory kidney diseases.

Funding: NIDDK Support

SA-PO1181

Autophagy Attenuation-Induced LSD1 Enrichment Promotes Renal Tubular Cell Senescence and Kidney Aging

Yingying Zhang, Xiaoyan Li, Chen Yu, Xiaogang Li. *Mayo Clinic Minnesota, Rochester, MN.*

Background: The process of population aging will inevitably lead to an increase in age-related comorbidities, including CKD. Alterations of epigenetic modifications are associated with aging at various levels, making them promising targets for interventions against age-related CKD. Lysine-specific demethylase 1 (LSD1) as the first identified histone demethylase plays a critical role in a variety of diseases. However, the role of LSD1 in senescence and kidney aging remains unknown.

Methods: To explore the role and mechanisms of LSD1 in renal tubular senescence and kidney aging, we treated renal tubular epithelial cells with oxidative stress injury agent D-Gal and DNA damaging agent etoposide (ETO) and wild type mice with ionizing radiation (IR) plus an LSD1 specific inhibitor, ORY1001.

Results: The protein level of LSD1, but not its mRNA, was increased in 22-month-old mouse kidneys compared to that in 2-month-old mouse kidneys. The expression of LSD1 protein was also increased in mouse IMCD cells treated with D-gal or ETO. Inhibition of autophagy with its inhibitor Lys05 resulted in a dose-depedent increase of LSD1 protein. We found that LSD1 interacted with autophagy proteins, LC3 and Beclin1, and these interactions subjected to autophagy mediated LSD1 degradation, suggesting a mechanism of that the downregulation of autophagy contributes to the upregulation of LSD1 in senescent cells and aged kidneys. We further found that LSD1 bound to the promoters of $p16^{ink4a}$ and $p21^{cip-2}$, two senescence markers, in renal tubular epithelial cells and targeting LSD1 with its specific inhibitor, ORY100, or siRNA decreased their expression in those cells induced by ETO, supporting a promoting role of LSD1 in senescence. Irradiation(IR) induces high levels of DNA damage which often leads to cellular senescence in vivo. We found that treatment with IR increased LSD1 protein in IR treated kidneys, and administration of ORY-100 demonstrated a protection from IR-induced gray hairs seen in vehicle treated wild type mice and decreased IR-induced accumulation of senescent cells in kidneys.

Conclusions: This study indicates a role of LSD1 in promoting senescence and kidney aging, and a mechanism of that the upregulation of LSD1 is subjected to impaired autophagy in these processes. Our study places an emphasis that LSD1 has potential as a therapeutic target for the delay of kidney aging.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO1182

Distal Convoluted Tubule (DCT)-Specific Disruption of the COP9 Signalosome Induces Autophagy Leading to Kidney Injury and DCT Atrophy

Ryan J. Cornelius,[1] Xiao-Tong Su,[1] Jonathan W. Nelson,[2] David H. Ellison,[1] Chao-Ling Yang.[1] *[1]Oregon Health & Science University, Portland, OR; [2]University of Southern California Keck School of Medicine, Los Angeles, CA.*

Background: Regulated maintenance of protein degradation is accomplished by two main systems: the ubiquitin-proteasome system and autophagy-lysosome system. Proteasomal degradation selectively ubiquitinates substrates via E3 ubiquitin ligases, the largest family of which are Cullin-RING ligases (CRLs). All CRLs are regulated by the COP9 signalosome (CSN), which interacts with the CRL to turn off ubiquitin ligase activity. To investigate the role of impaired CSN dysfunction in the kidney, we inactivated the CSN by deleting *Jab1* (the key CSN catalytic subunit) along the entire nephron (KS-*Jab1*$^{-/-}$). The mice developed progressive kidney injury with specific atrophy of the distal convoluted tubule (DCT) that culminated in chronic kidney disease (CKD). Autophagy is known to be associated with exacerbating CKD and can be activated due to cellular stress. We hypothesized that CSN dysfunction activates autophagy leading to atrophy of the DCT and CKD.

Methods: Inducible DCT-specific NCC-Cre-ERT2 mice were bred to INTACT (Isolation of Nuclei TAgged in specific Cell Types, which fluorescently labels nuclei) and *Jab1* floxed mice to generate DCT-INTACT-*Jab1*$^{-/-}$ mice. At six-weeks nuclei from kidney cortex was isolated and the DCT was enriched using Fluorescence-Activated Nuclei Sorting (FANS). GFP-positive nuclei were used for single-nucleus RNA-sequencing (snRNA-seq). Additionally, we impaired the autophagy pathway utilizing *Atg5* floxed mice to generate JAB1 and ATG5 double knock out mice (DCT-*Jab1*$^{-/-}$/*Atg5*$^{-/-}$).

Results: snRNA-seq of DCT enriched cells from DCT-INTACT-*Jab1*$^{-/-}$ mice showed four distinct populations: DCT1, DCT2, damaged DCT1 (dDCT1), and damaged DCT2 (dDCT2) cells. The damaged DCT cells showed downregulation of Differentially Expressed Genes (DEGs) associated with ion transport and metabolic processes and upregulation of DEGs associated with apoptosis, which is known to activate autophagy. Like KS-*Jab1*$^{-/-}$ mice, DCT-*Jab1*$^{-/-}$ mice developed tubule injury and atrophy of the DCT. Inhibition of autophagy in DCT-*Jab1*$^{-/-}$/*Atg5*$^{-/-}$ mice attenuated kidney injury and reduced DCT atrophy.

Conclusions: DCT-specific CSN disruption causes activation of apoptosis and autophagy pathways leading to tubule injury and atrophy of the DCT.

Funding: NIDDK Support

SA-PO1183

KLF5 Is Upregulated via NFkB to Promote Maladaptive Kidney Repair after Ischemia-Reperfusion Injury

Zhengwei Ma,[1] Zheng Dong.[1,2] *[1]Augusta University Medical College of Georgia, Augusta, GA; [2]Charlie Norwood Department of Veterans Affairs Medical Center, Augusta, GA.*

Background: Kruppel Like Factor 5 (KLF5) is a transcriptional factor that has been implicated in the pathogenesis of diabetic kidney disease and lupus nephritis. However, its role and regulation in acute kidney injury (AKI) and post-AKI kidney repair are unknown.

Methods: KLF5 expression was analyzed in C57BL/6 mice after renal ischemia-reperfusion injury (IRI) in vivo and TGFβ-treated kidney proximal tubule cells in vitro. A proximal tubule-specific *Klf5* knockout (PT-Klf5-KO*)* mouse model was established to examine the role of KLF5 in AKI and post-AKI repair. In vitro, the effect of *klf5* knockdown was investigated in TGFβ-treated proximal tubular cells.

Results: KLF5 was induced by IRI in the kidney and the induction was mainly in proximal tubule cells in immunohistochemistry staining. Renal IRI was more severe in PT-Klf5-KO mice than in wild-type mice as shown by BUN and creatinine levels and the percentage of injured tubules, suggesting a protective role of KLF5 at the acute injury phase. However, PT-Klf5-KO mice showed a significantly better kidney repair after renal IRI. At 2 weeks after renal IRI, PT-Klf5-KO mice had higher eGFR, lower BUN and serum creatinine, and markedly less renal fibrosis. K*lf5* KO mice also showed less senescence as indicated by less β-Gal staining and P16 expression. In addition, PT-*Klf5* KO decreased TNFα and Cxcl2 mRNA expression and macrophage infiltration in the kidneys. KLF5 was also induced in TGFβ-treated proximal tubular cells, and knockdown of *Klf5* decreased the induction of fibronectin and profibrotic cytokines in these cells. The induction of KLF5 during renal IRI was attenuated in proximal tubule-specific NF-kB/P65 knockout mice. It was also suppressed by the pharmacological inhibitor of NF-kB, JSH23. Chromatin immunoprecipitation (ChIP) assay further showed that KLF5 was a direct transcriptional target of NF-kB.

Conclusions: KLF5 is upregulated via NF-kB during renal IRI and post-injury kidney repair. While KLF5 may play a protective role against acute injury, it promotes maladaptive kidney repair by inducing renal inflammation, senescence, fibrosis, and deterioration of kidney function.

Funding: NIDDK Support

SA-PO1184

A Cost-Effective, High-Throughput, Three-Dimensional Coculture Model of Kidney Fibrosis for Drug Discovery

Long T. Nguyen,[1,2] Sonia Saad,[1,2] Carol A. Pollock.[1,2] Renal Research Group. *[1]Kolling Institute of Medical Research, St Leonards, NSW, Australia; [2]The University of Sydney Faculty of Medicine and Health, Sydney, NSW, Australia.*

Background: Acute kidney injury (AKI) can cause permanent damage to the kidneys, leading to chronic kidney disease (CKD). Recent advances in system biology revealed thousands of novel molecules involved in the transition of AKI to CKD. Nevertheless, there is a lack of efficient and reliable platforms to validate their biological functions and therapeutic potentials. Stem cell-derived kidney organoids and three-dimensional (3D) tissue culture have been shown to be able to capture key characteristics in kidney development and pathology. However, most of these models are not suitable for studying fibrosis, the common hallmark in CKD. The aim of this study is to develop a cost-effective and high throughput 3D coculture model of kidney fibrosis for drug screening.

Methods: Renal proximal tubular epithelial cells, fibroblasts and endothelial cells were seeded on polymerised Matrigel at a specific ratio to form a 3D network of vascularised tubules with interspersed fibroblasts. The 3D coculture was treated with Transforming

Growth Factor beta (TGFb) and Cyclosporin A (CsA) simultaneously to induce AKI and fibrosis. Telmisartan was used as the standard therapy to attenuate these effects.

Results: The 3D coculture produced a stable tubular network that is rich in Collagen type 1A (COL1A), which was otherwise not expressed in 2D and 3D monocellular culture even when being stimulated by TGFb, suggesting that the addition of fibroblasts was essential for fibrotic responses. TGFb and CsA treatment for 48 hours induced cell death to the tubular cells while stimulated cell growth of fibroblasts. In association, the expression of inflammatory markers MCP-1 and TNFa as well as fibrotic markers Fibronectin and COL1A were significantly increased. Such effects were partially attenuated by treatment of telmisartan, suggesting that the 3D coculture mimics pathology and drug responses in patients with kidney diseases.

Conclusions: In conclusion, We have successfully developed a 3D coculture model of tubulointerstitial fibrosis to be used as a low-cost, high throughput fibrotic assay for studying intercellular interaction and drug effects.

SA-PO1185

Multiplexed Imaging of Senescent Chromatin State in Single Cells in the Kidneys

Hannah S. Perry, Benjamin C. Mustonen, Madeline K. Wong, Stuart J. Shankland, Joshua C. Vaughan. *University of Washington, Seattle, WA.*

Background: The gradual loss of kidney function with age and disease can be linked to changes in physiology and single cell epigenetics. As cells become stressed or damaged from these conditions, they undergo the process of becoming senescent, a state of permanent cell cycle arrest associated with massive chromatin rearrangement and telomere shortening, as a way to mitigate further damage. The order of events and extent of epigenetic changes within single cells and their correlation to physiological alterations as the kidney ages or becomes diseased and senescence forms are not fully understood.

Methods: Super-resolution optical microscopy techniques were used with advanced chemical labeling methods to concurrently study epigenetic states and nanoscale physiology in mouse kidney slices. We used multiplexed imaging to simultaneously study histone marks, telomeres, and tissue morphology at the single cell level.

Results: The use of optical super-resolution techniques allows for ~70 nm spatial resolution. Multiple histone modifications have been detected and quantified throughout the nucleus and at locations of repetitive DNA sequences (telomeres and major satellites) in single cells with a high degree of accuracy. In the same sample, these single cell epigenetic signatures were correlated with nanoscale features within glomeruli and proximal tubules. Telomeres in aging samples have been shown to shorten using imaging techniques. The quantification of these nanoscale features includes the glomerular basement membrane thickness, width of individual podocyte foot processes, and the size of endothelial fenestrations.

Conclusions: The combination of these advanced labeling methods and super-resolution optical microscopy techniques allows for an unprecedented view and correlation of single cell epigenetic states and nanoscale physiology in kidney tissue at many age points. Our approach has implications for identifying specific epigenetic changes in the kidney that precede the development of senescence and related diseases and their physiological markers. Understanding the sequence of events may assist in predicting disease formation along with studying the effectiveness of various treatments.

Funding: NIDDK Support

SA-PO1186

Targeted Pulsed Ultrasound of the Spleen Protects against AKI and CKD and Permits Kidney Regeneration

Eibhlin S. Goggins,[1] Yanjun Xie,[2] Yi Huang,[2] Carson A. Brantley,[1] Junlan Yao,[1] William Nash,[1] Sylvia Cechova,[1] John Hossack,[2] Mark D. Okusa.[1]
[1]Division of Nephrology, Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia, Charlottesville, VA; [2]University of Virginia Department of Biomedical Engineering, Charlottesville, VA.

Background: Our group has demonstrated that unfocused pulsed ultrasound (pUS) protects against ischemic AKI. The efficacy of pUS targeted directly to the mouse spleen and in kidney injury caused by other insults is unknown. Here, we aimed to 1) Develop an effective and reproducible pUS protocol specifically targeting the mouse spleen to block inflammation and prevent ischemia induced AKI 2) To test the hypothesis that pUS can prevent toxin induced AKI and the transition to CKD and that 3) pUS permits regeneration in the kidney microenvironment.

Methods: The US configuration consists of a power amplifier and waveform generator paired with a 1 MHz single element transducer with a stand-off of 1mm. The optimized stimulation parameters used were tonebursts of 150 cycles, pulse repetition frequency of 2kHz, and a peak-negative pressure of 280kPA. 4 min of pUS was delivered to the spleen 24h prior to folic acid (FA, 250mg/kg IP), lipopolysaccharide (LPS, 3.5mg/kg IP), or bilateral kidney ischemia reperfusion injury (bIRI, 25min).

Results: Mice that received spleen targeted pUS demonstrated significantly reduced plasma TNFα 1h after LPS. The increase in plasma creatinine (Cr) and BUN 24h after bIRI was significantly reduced in splenic pUS mice. In the FA model, the increase in Cr (Sham: 1.14±0.25, pUS: 0.32±0.04 mg/dL) and BUN (Sham: 155.8±23.2, pUS: 45.9±4.6 mg/dL) on day 2 was reduced in pUS mice. Analysis of H&E and PAS stained kidney sections demonstrated reduced injury in pUS treated mice. 23% of sham treated mice died over the 14d study period. On day 14, kidney mRNA levels of the fibrotic markers, *Col1α1*, *Col3α1*, and *Fn-1* and proinflammatory cytokines, *IL-1β*, *IL-6*, and *Ccl2* were decreased in pUS treated mice. pUS mice displayed reduced kidney tubulointerstitial fibrosis and collagen deposition by blinded assessment of Masson trichrome sections. Kidney mRNA expression of *Wnt2*, *Wnt4* and the acute epithelial stress response gene, *Sox9* remained persistently elevated in sham treated mice compared to pUS mice.

Conclusions: We developed a spleen targeted pUS protocol that reduces inflammation and prevents AKI/CKD in multiple mouse models. Future work is focused on understanding the mechanism by which pUS may promote a microenvironment conducive to kidney regeneration.

Funding: Other NIH Support - 5TL1DK132771-03

SA-PO1187

Low-Intensity Pulsed Ultrasound Stimulation to Treat Kidney Fibrosis through Inhibition of Tubular IL-1R

Zhimin Huang, Jiaxin Dong, Ziqi Fu, Jiafa Ren, Huijuan Mao. *The First Affiliated Hospital with Nanjing Medical University, Nanjing, China.*

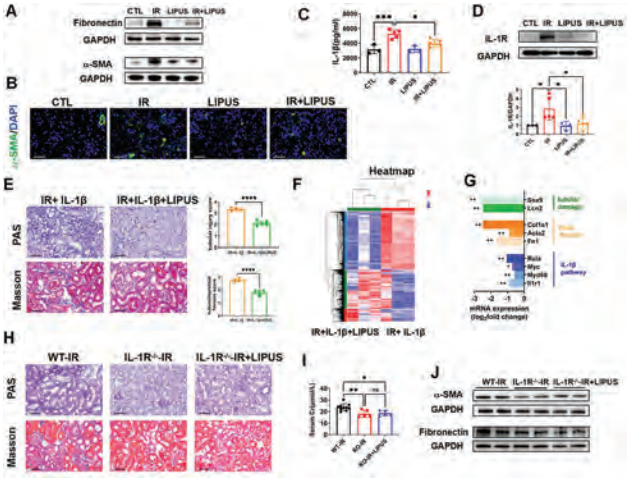
Background: Low intensity pulsed ultrasound (LIPUS) has become increasingly appreciated for kidney diseases. However, its mechanisms for chronic kidney disease (CKD) remain poorly defined.

Methods: Under different parameters of LIPUS, histological tests and molecular biology were determined. We detected IL-1β/IL-1R and its downstream in unilateral renal ischemia/reperfusion (IR) induced renal fibrosis and IL-1β-induced tubular partial epithelial-to-mesenchymal transition with or without LIPUS treatment. In addition, we evaluated the IL-1R dependence of LIPUS in treating IR-induced CKD models using tubular IL-1R$^{-/-}$ mice.

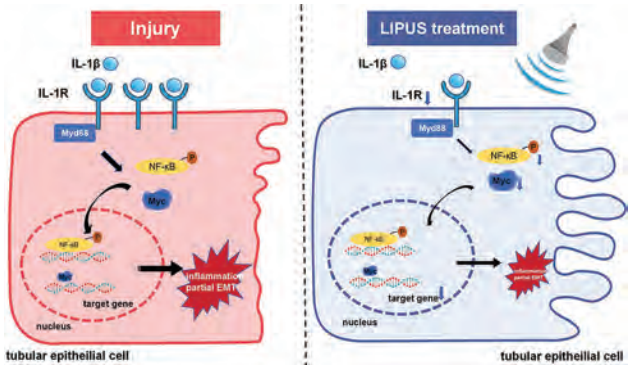
Results: Daily LIPUS treatment at 315 mW/cm^2 reduced the IR-induced tubular injury and fibrosis, accompanied by the remarkable amelioration in IL-1β and IL-1R[Fig.1A-D]. Transcriptome sequencing showed a significant reduction of IL-1R and its downstream(p-NF-κB, Myc) in the LIPUS-treated IR-injured plus IL-1β stimulation, compared to the untreated diseased group[Fig.1E-G]. LIPUS treatment reversed IL-1β induced tubular injury and profibrotic cytokines by reducing IL-1R in vivo and in vitro. Knockout mice lacking tubular IL-1R expression exhibited less renal tubular injury and retained a more preserved renal function after IR injury. However, LIPUS treatment showed no more improvement in tubular IL-1R Knockout mice after IR injury[Fig.1H-J].

Conclusions: Daily LIPUS treatment at 315 mW/cm^2 could reduce IR-induced tubular injury and fibrosis by ameliorating tubular IL-1R[Fig.2].

Funding: Government Support - Non-U.S.



1.LIPUS treating renal fibrosis through inhibition of tubular IL-1R



2. A diagram of the molecular mechanism of LIPUS treatment in renal fibrosis

SA-PO1188

Optimized Protocol for the Multiomics Processing of Cryopreserved Human Kidney Tissue

Sydney Elisabeth Gies,[1,3] Sonja Haenzelmann,[1,2] Dominik Kylies,[1,4] Moritz Lassé,[1,3] Nikolay Zolotarev,[1,3] Robin Khatri,[3,2] Manuela Poets,[1,2] Shun Lu,[1,3] Shuya Liu,[1,3] Fabian Hausmann,[2,3] Jan Czogalla,[1,3] Fabian Braun,[1,3] Markus M. Rinschen,[1,3] Victor G. Puelles,[1,3] Stefan Bonn,[2,3] Maja Lindenmeyer,[1,3] Tobias B. Huber.[1,3] *[1]Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Institute of Medical Systems Biology, Center for Biomedical AI (bAIome), Center for Translational Immunology (HCTI), Center for Molecular Neurobiology (ZMNH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Hamburg Center for Kidney Health, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4]Massachusetts Institute of Technology Picower Institute for Learning and Memory, Cambridge, MA.*

Background: Immediate processing of fresh kidney tissue obtained from needle biopsies is challenging in clinical routines. To address this, tissue samples can be harvested in (cryo-) preservative agents such as RNA*later* (Rl) or CellCover (CC), that rapidly preserve the integrity of cellular molecules already at room temperature. In this study, we examined the effects of *Rl* and CC on the single nucleus transcriptome, on tissue architecture and immunofluorescence stainings and on the proteome.

Methods: Biopsy cores from pig kidneys received from a slaughterhouse were either snapfrozen (sf) or put into Rl or CC. For human kidney tissue, the second core of a kidney needle biopsy and healthy kidney tissue from tumor nephrectomies were either sf or put in Rl. For single nucleus RNA sequencing (snRNAseq) with the Chromium 10X platform, 3-4 mm of a thawed kidney biopsy core was dissociated. For proteomic analysis, 2-3 mm sections of biopsies were analyzed by mass spectrometry. For immunohistochemical analysis, samples were thawed and subjected to fluorescent immunolabeling (IF).

Results: Each data set from sf, Rl and CC stored pig kidney tissue contributed to 31 clusters of both common and rare kidney cell types. Enrichment analysis detected a similar activation of the stress response pathways in all preservation methods. Applying snRNAseq to human kidney tissue stored in Rl resulted in diverse cell type clustering. Proteome analysis of pig kidney tissues showed the highest correlation between Rl and sf tissues. Classical histology with OCT-embedded kidney tissue as control indicated better preservation in Rl stored kidney compared to CC. IF-staining signal quality in Rl and CC preserved tissue was comparable to OCT-embedded kidney tissue.

Conclusions: Our study demonstrates that Rl can facilitate the collection and storage of kidney tissue without the need for snap freezing, supporting snRNAseq, proteome and histopathological analysis. As our optimized protocol requires only 3-4 mm of a biopsy core for high-throughput snRNAseq, the remaining part of a biopsy core can be utilized to generate other omics data.

SA-PO1189

Regulation of NLRP3 Inflammasome Expression through Inhibition of Podocyte-Specific Lysyl Oxidase-Like 2 as a New Therapeutic Target for AKI on CKD

Hoon Young Choi,[1,2] Nara Jeon,[1,2] Beom Jin Lim.[1,2] *[1]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [2]Gangnam Severance Hospital, Seoul, Republic of Korea.*

Background: The NLRP3 inflammasome activation has been suggested a potential role in renal inflammation and thus contribute to the progression of kidney disease. Lysyl oxidase-like 2 (LOXL2) has been known to play an important role in target organ fibrosis including heart, liver and lung. In this study, we investigated the expression of LOXL2 in human kidney and podocyte, and its contribution to the NLRP3 inflammasome expression in the progression of acute kidney injury (AKI) on chronic kidney disease (CKD).

Methods: A podocyte cell line that suppresses LOXL2 expression was generated to investigate the role of LOXL2 in podocytes. And also, the podocyte-specific LOXL2-inhibiting mice (Nphs2-Cre:Loxl2-/-) was constructed to determine the role of LOXL2 in renal podocytes mice to determine the role of LOXL2 in renal podocytes in an animal model of AKI on CKD progression using lipopolysaccharide (LPS) and streptozotocin injection.

Results: Gene silencing of LOXL2 significantly reduced NLRP3 mRNA and protein expression in human podocytes (1.19±0.16 vs. 1.87±0.16, P<0.05). In hyperglycemic mice treated with LPS, podocyte-specific LOXL2 deficiency significantly reduced NLRP3 mRNA and protein expression in human kidney glomerulus. Western blot analysis also showed that TGF-beta 1, collagen I and phosphorylated Smad2 protein expression were significantly decreased in podocyte-specific LOXL2 deficiency mice.

Conclusions: Our results demonstrated that the genetic manipulation of podocyte-specific LOXL2 expression on NLRP3 inflammasome expression in AKI on CKD, suggesting its potential as a new therapeutic target for the mechanism of AKI on CKD.

Funding: Government Support - Non-U.S.

SA-PO1190

The Early Renal Profibrotic Phenotype Caused by 5/6 Nephrectomy in Mice Depends on CD11c+ Antigen-Presenting Cells Population

Javier I. Reyes Osorio,[1] Patricio A. Araos,[2] Stefanny M. Figueroa,[1] Javiera Saez,[1] Maria J. Fuenzalida,[3,1] Rodrigo Pacheco,[3,1] Cristián A. Amador.[1] Laboratory of Renal Physiopathology. *[1]Universidad San Sebastian Facultad de Medicina y Ciencia, Santiago, Chile; [2]Universidad Autonoma de Chile - Campus El Llano Subercaseaux, Santiago, Chile; [3]Fundacion Ciencia & Vida, Santiago, Chile.*

Background: The recruitment and activation of antigen-presenting cells (APC) represent key mechanisms for the pro-inflammatory stages that lead to fibrosis in the progression of chronic kidney disease (CKD). Our revious experimental studies indicate that dendritic cells-like APC (APC-CD11c$^+$) are essential for inflammation, renal dysfunction, and heart fibrosis in mice with hypertensive nephropathy. Although that we have previously demonstrated that APC-CD11c$^+$ would not contribute to the inflammatory processes in the experimental unilateral ureteral obstruction, it is still unknown whether these cells contribute to the renal pro-fibrotic status in a model of CKD with reduction of renal function. Our objective was to determine whether the depletion of APC-CD11c$^+$ prevents the early renal pro-fibrotic status in a 5/6 nephrectomy model ($Nx_{5/6}$).

Methods: Male CD11c.DOG mice (8-12 wo, n=3-7), which can be depleted of APC-CD11c$^+$ by using diphtheria toxin (DT), underwent to the $Nx_{5/6}$ or Sham surgery (control) for 5-days. These groups received vehicle (Vh) or DT (8ng/g/d, ip) from the beginning of the experiment, where those animals-DT+ with a reduction >60% of APC-CD11c$^+$ were selected. Biochemical, histological and molecular analyses were performed.

Results: $Nx_{5/6}$ caused a trend increase in plasma creatinine (p=0.16 vs Sham-Vh), and in blood urea nitrogen (p=0.08 vs Sham-Vh). In addition, $Nx_{5/6}$ caused a significant increase in renal fibrotic area and was associated with the overexpression in the mRNA for the following pro-fibrotic markers: Collagen (COL)1A1, COL3A1 and Fn-I (p<0.05 vs Sham-Vh), and the pro-inflammatory mediators: Interleukin (IL)-6 and Lipocalin-2 (NGAL). Depletion of APC-CD11c$^+$ in $Nx_{5/6}$ animals did not alter the plasma parameters analyzed for determining renal function, but it did prevent renal fibrosis (3.79% vs 5.80% $Nx_{5/6}$-Vh; p<0.05), and the increase of mRNA for COL3A1 (p<0.05). In addition, the use of DT was associated with a lower abundance of COL1A1 and Fn I (p=0.07 and p=0.12, vs $Nx_{5/6}$-Vh, respectively), without affecting any pro-inflammatory mediator.

Conclusions: APC-CD11c$^+$ depletion prevents the early renal profibrotic phenotype in the $Nx_{5/6}$ model, providing new background related to the importance of APCs in the early progression of CKD.

Funding: Government Support - Non-U.S.

SA-PO1191

Genetic Ablation of SLC6A19 Is Protective against Kidney Damage in Mouse Models of CKD

Laura Sanman, Richa Sarwaikar, Amelia Joslin, Sheela Crasta, Lisa Pang, Perryn Wong, Terry Satterfield, Nina Oberbeck, Yonghong Xiao, Yannan Xi, Maarten Hoek, Julie Ullman. *Maze Therapeutics Inc, South San Francisco, CA.*

Background: SLC6A19 is a sodium-dependent neutral amino acid transporter expressed in the small intestine and proximal tubule of the kidney. SLC6A19 has emerged as a novel target for the treatment of CKD based on analyses of large human data sets that have identified a link between loss of function gene variants with protection from CKD, and that individuals carrying heterozygous putative loss-of-function (LOF) variants in SLC6A19 have improved eGFR while gain of function variants carriers have diminished eGFR. In agreement with the protection from CKD observed in humans, ablation of SLC6A19 in mice has been shown to protect animals from renal injury induced by the proximal tubule toxin aristolochic acid (AAI).

Methods: Maze Therapeutics has developed a new SLC6A19 KO mouse model to further investigate published findings. These mice were tested in the AAI model of CKD

and biomarkers of kidney injury were assessed. In order to understand mechanistically how SLC6A19 LOF protects from renal injury samples were evaluated using transcriptomic, metabolomic, and immunostaining assays.

Results: When tested in the AAI CKD model the SLC6A19 KO mice were protected from chronic renal injury with evidence of normalization of kidney injury markers KIM1 and NGAL, as well as attenuation of UACR. Metabolomics from KO and WT animals reveals distinct redistribution of metabolic pathways consistent with SLC6A19's role as an amino acid transporter. Transcriptomic analysis of kidney samples from the AAI study suggest KO protection is mediated through alterations in metabolic pathways including downregulation of glycolysis and upregulation of oxidative phosphorylation.

Conclusions: Though the exact mechanism by which SLC6A19 LOF protects the kidney is not completely understood, we hypothesize this could be through a combination of decreasing workload on the proximal tubule, decreasing proximal tubule mTOR activity mediated by amino acid uptake, and decreasing intraglomerular pressure by restoring tubule-glomerular feedback via increased sodium delivery to distal regions of the nephron. In addition to direct effects on the kidney, reduction of SLC6A19 activity in the gut may lead to reduction of whole-body amino acid and metabolite intake that benefits multi-system physiology.

Funding: Commercial Support - Maze Therapeutics

SA-PO1192

Urea Suppresses the Alternative Activation of Murine Macrophages

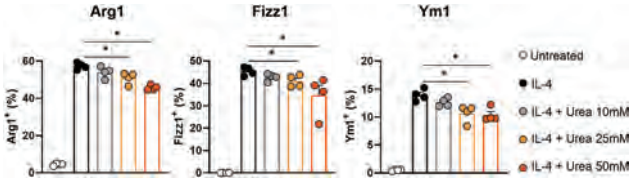
Seung Yun Chae,[1,2] Kyoung Il Min,[1,2] You-Me Kim.[2] *[1]The Catholic University of Korea Seoul St Mary's Hospital, Seoul, Seocho-gu, Republic of Korea; [2]Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea.*

Background: Although urea is generally considered harmless, it has been documented to obstruct the intracellular transport of arginine in vascular endothelial cells and inhibit glycolysis in pancreatic beta cells. This study aims to determine whether elevated extracellular urea concentrations impact macrophage functions.

Methods: Peritoneal macrophages and bone marrow-derived macrophages (BMDMs) were exposed to LPS and IL-4 to induce M1 and M2 polarization, respectively, in the presence of varying urea concentrations. Flow cytometry was utilized to examine the expression of markers of macrophage polarization including arginase-1 and iNOS. Additionally, M2 marker gene expression was analyzed using qPCR. Bulk RNA sequencing was performed to elucidate the transcriptomic changes induced by urea in BMDMs. The Seahorse real-time cell metabolic analysis was conducted to measure the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) in IL-4-treated BMDMs.

Results: Our study discovered that physiologically high urea concentrations reduce IL-4-induced upregulation of arginase-1 in murine macrophages in a dose-dependent manner at both mRNA and protein levels. Urea also significantly decreased the expression of other M2 macrophage markers, such as Fizz1 and Ym1. However, urea had minimal impact on LPS-induced M1 polarization. RNA sequencing of M2-polarized BMDMs indicated that urea downregulates genes associated with mTOR signaling, glycolysis, and oxidative phosphorylation. Correspondingly, urea treatment reduced phosphorylation of S6 protein and AKT, targets of mTORC1 and mTORC2, respectively. Additionally, ECAR and OCR were lower in urea-treated M2 BMDMs. The attenuation of M2 polarization by urea was not evident in the presence of Torin, a pan mTOR inhibitor, indicating that urea's inhibitory effect is mediated through downregulation of mTOR signaling.

Conclusions: Based on these findings, we propose that, contrary to the traditional view of urea as an inert molecule, urea suppresses M2 polarization in murine macrophages, likely through the attenuation of mTOR signaling.



Flow cytometry analysis of M2 marker expression in BMDMs

SA-PO1193

Microbes Regulate Glomerular Filtration Rate in Health and Disease in Mice

Jiaojiao Xu, Eesha Verma, Jason Sanchez, Sepideh Gharaie, Mahta F. Gooya, Kunal Gupta, Hamid Rabb, Jennifer L. Pluznick. *The Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: We hypothesized that the microbiome modulates glomerular filtration rate (GFR).

Methods: Microbiota were depleted using antibiotics in drinking water (ABX: ampicillin, neomycin, vancomycin). Germ-free (GF) mice were born in the Johns Hopkins GF Facility. GFR was measured by transcutaneous detection of FITC-sinistrin clearance. Mice were treated with adenine to model chronic kidney disease (CKD).

Results: GFR was significantly increased after microbiota depletion (ABX) in both sexes (Table 1, Study I). GFR was also significantly elevated in GF as compared to both control (ctrl) and conventionalized GF (CGF) mice in both sexes (Table 1, Study II). To determine if ABX increases GFR in CKD, mice were given adenine or adenine+ABX (simultaneously). Adenine decreased GFR. In females, adenine+ABX improved GFR (vs adenine) on weeks 4 and 6. In males, GFR improvement was seen on week 2 (Table 1, Study III). Plasma creatinine was significantly increased on adenine but normalized by ABX treatment in females (chow 0.19 mg/dl ±0.03 vs adenine 0.31±0.02, p=0.04; adenine vs adenine+ABX 0.15±0.03, p=0.005, n=7-9) and males (chow 0.17±0.03 vs adenine 0.65±0.07, p<0.0001; adenine vs adenine+ABX 0.40±0.04, p=0.005, n=7-9). Histological studies revealed that adenine increased collagen; ABX suppressed this increase in both females (chow 2.9±2.1 collagen area% vs adenine 7.2±7.4, p=0.0008; adenine vs adenine+ABX 4.5±4.0, p=0.02) and males (chow 2.2±2.1 vs adenine 8.7±6.6, p<0.0001; adenine vs adenine+ABX 6.2±4.6, p=0.02). 16S rRNA analysis on female feces indicated that *Akkermansia muciniphila* was elevated in adenine than chow diet, but adenine+ABX treatment decreased it.

Conclusions: Both the absence (GF) and suppression (ABX) of gut microbes increased GFR in healthy females and males. Moreover, ABX partially improved kidney function in an adenine-induced CKD model.

Funding: NIDDK Support

Table 1. GFR (µl/min/100 g body weight), mean ± SEM.

	Females				Males			
Study I (n=8)								
	GFR	p value: week 0 vs 5	p value: week 0 vs 9	p value: week 5 vs 9	GFR	p value: week 0 vs 5	p value: week 0 vs 9	p value: week 5 vs 9
week 0	1190±14	0.02	0.04	0.95	1020±25	0.04	0.005	0.60
week 5	1688±33				1263±26			
week 9	1638±21				1381±29			
Study II (n=7-8)								
	GFR	p value: Ctrl vs GF	p value: GF vs CGF	p value: Ctrl vs CGF	GFR	p value: Ctrl vs GF	p value: GF vs CGF	p value: Ctrl vs CGF
Ctrl	1217±17	0.003	0.02	0.80	1087±18	0.02	0.03	0.98
GF	1853±32				1308±16			
CGF	1326±31				1101±10			
Study III (n=7-9)								
	week 0	week 4	week 6		week 0	week 2	week 4	week 6
chow	1267±9	1298±11	1227±14		1177±6	1116±11	1154±12	1157±9
chow+ABX	1235±11	1567±11	1733±16		1057±8	1203±9	1414±20	1575±17
adenine	1278±7	853±8	648±7		1112±12	914±11	732±14	513±11
adenine+ABX	1243±7	1040±9	829±9		1093±6	1150±17	877±19	631±16
p value: chow vs adenine	0.99	<0.0001	<0.0001		0.6	0.002	<0.0001	<0.0001
p value: adenine vs adenine+ABX	0.94	0.02	0.03		0.99	0.0003	0.37	0.56

SA-PO1194

Investigating the Kidney-Gut-Brain Axis in CKD: Effects of Choline Trimethylamine Lyase and SGLT2 Inhibitors

Su mi Lee,[1,2] Yitong Zhao,[1] Tiffany Tran,[1] Nikitha M. Vancheeswaran,[1] Lily Tran-Phung,[1] Joshua J. Jung,[1] Stanley L. Hazen,[3] Mark Fisher,[4,5] Wei Ling Lau.[1] *[1]Division of Nephrology, Department of Medicine, University of California-Irvine, Irvine, CA; [2]Department of Internal Medicine, College of Medicine, Dong-A University, Busan, Republic of Korea; [3]Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH; [4]Department of Neurology, University of California-Irvine, Irvine, CA; [5]Department of Pathology & Laboratory Medicine, University of California-Irvine, Irvine, CA.*

Background: Gut dysbiosis in CKD leads to increased uremic toxins including indoxyl sulfate (IS), p-cresyl sulfate (pCS) and trimethylamine N-oxide (TMAO). These toxins are associated with vascular injury and cognitive dysfunction. Choline trimethylamine lyase inhibitors such as iodomethylcholine (IMC) selectively block TMAO generation, while sodium-glucose cotransporter 2 (SGLT2) inhibitors such as canagliflozin have been shown to alter gut microbial composition. In this project, effects of IMC and canagliflozin therapy on the kidney-gut-brain axis were studied in CKD mice.

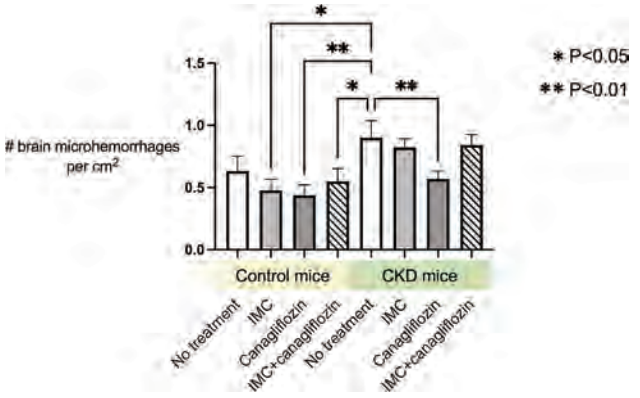
Methods: CKD was induced in male and female C57Bl/6J mice using dietary adenine. Controls (10-16 mice per group) and CKD animals (31-33 mice per group) were randomized to IMC, canagliflozin or IMC+canagliflozin treatment. Open field behavior test, serum levels of uremic toxins and brain microhemorrhage histology were analyzed.

Results: In CKD mice, serum creatinine was increased 4.5-fold while IS, pCS and TMAO levels were increased 6-fold compared to controls. On open field testing, CKD mice demonstrated decreased locomotor activity; higher serum creatinine, IS and pCS correlated with lower distance traveled. When stratified by sex, these findings remained significant in male mice only. Brain microhemorrhages were increased in CKD mice and correlated with decreased locomotor activity. IMC effectively reduced TMAO levels in CKD mice, but was noted to increase pCS in female CKD animals. Canagliflozin decreased serum TMAO and pCS, and decreased brain microhemorrhages (figure). The drug therapies did not improve locomotor scores.

Conclusions: Oral treatment with IMC or canagliflozin modified levels of gut-derived uremic toxins. The SGLT2 inhibitor decreased brain microhemorrhages but

did not improve behavior scores. Further studies are needed to elucidate the role of the kidney-gut-brain axis in CKD-associated cognitive dysfunction.

Funding: Other NIH Support - NINDS



SA-PO1195

Novel Single-Cell Sequencing Methods for Detection of Mosaic Chromosomal Alterations in the Kidneys

Gary Wang,[1] Xinyi E. Chen,[2] Amit Verma,[1] Nancy Zhang,[2] Parker C. Wilson.[1]
[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of Pennsylvania Wharton School, Philadelphia, PA.

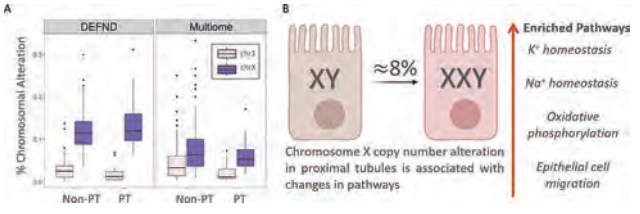
Background: Mosaic chromosomal alterations (mCA) are a type of somatic mosaicism characterized by large chromosomal gains or losses. We previously reported that mosaic loss of Y chromosome (LOY) increases with age and is enriched in an injured population of proximal tubule cells. However, the majority of these cells do not have LOY, which raises the possibility there are additional mCA we cannot detect. Here, we jointly profile genomic DNA and RNA by single-cell sequencing to unpack inaccessible chromatin regions and improve sensitivity for detection of mCA in the kidney.

Methods: We performed DEFND-seq (Olsen et al., bioRxiv 2023) and single cell multiome ATAC + gene expression (10X Genomics) on nuclei isolated from male rat kidney cortex aged 16 to 82 weeks. Split samples were subject to either standard nuclei processing (10X Multiome) or pretreatment with lithium diiodosalicylate to deplete nucleosomes. We generated 8 droplet-based single-cell libraries (DEFND = 4; Multiome = 4) and called mCA using a negative binomial model adjusting for cell-specific factors. We validated sex chromosome mCA using a 3-color digital PCR assay.

Results: A total of 40,031 cells passed filters and the number was similar between DEFND and Multiome libraries. DEFND had a 25-50% increase in genome-wide coverage compared to Multiomes, indicating we were able to "open" inaccessible regions for mCA analysis. We estimated mCA abundance for cell types and observed an increase in chromosome X (chrX) mCA compared to other chromosomes. The proportion of cells with a chrX mCA was higher in DEFND libraries, suggesting increased sensitivity in the DEFND assay. In contrast, chromosome 1 had a low probability of mCA and the proportion of cells was unchanged (Figure 1A). Approximately 8% of proximal tubule had a chrX mCA and enrichment analysis shows upregulation of oxidative phosphorylation and epithelial migration pathways (Figure 1B).

Conclusions: We hypothesize that sex chromosome mCA are enriched in the proximal tubule and are associated with increased oxidative stress. Our approach can be used to study the role of mCA as biomarkers of aging and kidney disease progression.

Funding: NIDDK Support



SA-PO1196

Inducible Deletion of MicroRNA Activity in Kidney Mesenchymal Cells Exacerbates Kidney Fibrosis

Hirofumi Sakuma, Naoki Nakagawa. *Asahikawa Medical University, Department of Internal Medicine, Division of Cardiology and Nephrology, Asahikawa, Japan.*

Background: Renal interstitial mesenchymal cell-specific deletion of Dicer results in hypoplastic kidneys with abnormal differentiation of nephron tubules and vasculature (Kidney International, 2015); however, the role of Dicer in these cells in adult kidney diseases remains unexplored. We developed a new mouse model and investigated the role of Dicer and Dicer-dependent miRNA activity in renal interstitial mesenchymal cells.

Methods: We generated Dicer conditional knockout (cKO) mice by crossing hemizygous *Pdgfr-β-CreER^{T2}* mice with homozygous Dicer floxed (*Dicer$^{FL/FL}$*) mice. *Dicer$^{FL/FL}$* mice without *CreER^{T2}* were used as controls. After administering oral tamoxifen, these mice underwent unilateral ureter obstruction (UUO) or intraperitoneal injection of folic acid (FA, 250 mg/kg). Fibrosis in the renal interstitium was assessed using immunofluorescent staining and real-time PCR (RT-PCR). RNA sequencing was performed using total RNA from Sham- or UUO-kidneys. Primary renal fibroblasts were transfected with miR-9-5p inhibitors (20 nM) and treated with 5 ng/mL TGF-β1 for 48 hours. RT-PCR was performed to evaluate *Pdgfrb* and *Acta2* expression in vitro assay.

Results: Compared with control mice, cKO mice significantly increased expression of PDGFR-β in injured kidneys by immunofluorescence staining and RT-PCR. The percentage of Sirius red staining in injured kidneys was also significantly elevated in cKO mice compared with that in control mice. Microarray analysis indicated decreased expression of *miR-9-5p*, *miR-344g-3p*, and *miR-7074-3p* in cKO mice. The major transcriptional changes in cKO mice were related to smooth muscle cell differentiation, actin cytoskeleton, and fibroblast proliferation. In vitro assays demonstrated significant upregulation of *Pdgfrb* and *Acta2* in primary renal fibroblasts transfected with miR-9-5p inhibitor following TGF-β1 treatment.

Conclusions: This study revealed that renal interstitial mesenchymal cell-specific deletion of Dicer increased activation of PDGFR-β and exacerbated renal fibrosis by decreasing levels of *miR-9-5p*, *miR-344g-3p*, and *miR-7074-3p*. Activation of PDGFR-β was sufficient to drive renal fibrosis, and these miRNAs are potential therapeutic targets for renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO1197

Unveiling the Role of Transgelin as a Prognostic and Therapeutic Target of Kidney Fibrosis via a Proteomic Approach

Kyu hong Kim,[1] Soie Kwon,[3] Eunjin Bae,[4] Kyung Don Yoo,[5] Seong Min Lee,[2] Seong Joon Park,[2] Jae Wook Lee,[6] Dong Ki Kim,[2] Yon Su Kim,[2] Seung Hee Yang.[2]
[1]Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [3]Chung Ang University Hospital, Seoul, Seoul, Republic of Korea; [4]Gyeongsang National University Changwon Hospital, Changwon, Gyeongsangnam-do, Republic of Korea; [5]Ulsan University Hospital, Ulsan, Republic of Korea; [6]National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea.

Background: This study investigated the effects of kidney fibrosis and identified potential biomarkers based on the proteomic profile of human derived primary cell and animal models.

Methods: Mass spectrometry-based proteomic analysis of transforming growth factor β-induced human-derived tubular epithelial cells and kidney tissue of a 5/6 nephrectomy rat model were performed.

Results: 351 differentially expressed proteins showing concurrent changes were identified. Among these, 69 proteins associated with the extracellular matrix, aging, and mitochondria were selected for gene set enrichment analysis. Network analysis of the selected proteins revealed five crucial proteins, of which transgelin showed the highest interactions with known fibrosis-related proteins. Consistent with the proteomics results, transgelin mRNA expression in the kidney tissue of the 5/6 nephrectomy model was elevated. Transgelin expression on kidney tissue gradually increased from intermediate to final fibrosis in the 5/6 Nx and unilateral ureteral obstruction mouse models. Subsequent validation in the kidney tissue and urine samples of patients with chronic kidney disease confirmed the upregulation of transgelin, particularly in the advanced stages of chronic kidney disease. Moreover, blocking transgelin in a cellular model of kidney fibrosis demonstrated its therapeutic potential.

Conclusions: In conclusion, transgelin is a promising biomarker and therapeutic target for kidney fibrosis in patients with chronic kidney disease. This study suggests transgelin as a potential noninvasive diagnostic biomarker and therapeutic intervention target for patients with chronic kidney disease. Further studies are warranted to elucidate the precise role of transgelin and its clinical utility in larger patient cohorts.

SA-PO1198

CD11b Deficiency Ameliorates AKI-to-CKD Progress via Promoting Alternative Activation of Macrophages

Yiqin Shi. *Department of Nephrology, Zhongshan Hospital, Fudan University, Shanghai, China.*

Background: Acute kidney injury (AKI), even if followed by renal recovery, is a risk factor for the future development of chronic kidney disease (CKD). Persistent chronic inflammation has been proposed to contribute to the progress of AKI-to-CKD. Macrophages are a heterogeneous cell group implicated in injury, repair, and fibrosis during AKI-to-CKD process. However, the underlying mechanism of how macrophages participate in the progress of disease is largely unclear. CD11b/CD18, a leukocyte adhesion molecule, expressed on neutrophils, eosinophils and macrophages, has been shown to mediate several adhesion-dependent processes. CD11b/CD18 also contributes to the polarization of macrophages.

Methods: To determine the underlying mechanism of how CD11b/CD18 participates in AKI-to-CKD, we use a long-term ischemia/reperfusion (I/R) model in $CD11b^{-/-}$ mice on C57BL/6 background. Wild-type (WT) and $CD11b^{-/-}$ mice with unilateral renal IRI were euthanized at day 3,7,14 after disease induction. Organ damage was histologically analyzed and flow cytometric analysis, real-time PCR were performed for the evaluation of leukocyte infiltration in kidney. *In vitro*, we used murine bone marrow-derived macrophage (BMDM) from WT and $CD11b^{-/-}$ mice to determine IL-4 induced alternatively activated (M2) macrophage associated gene expression.

Results: The extent of inflammation and fibrosis was alleviated in $CD11b^{-/-}$ mice, accompanied by an early increase of M2 macrophages in renal and higher activity of p-STAT6. We demonstrated both in vitro and in vivo that enhanced alternative activation in CD11b-knockout macrophages is regulated by the IL-4/STAT6 axis, which is mediated by the inactivation of the Src kinase family member Lyn. Importantly, the therapeutical administration of CD11b-neutralizing mAbs can effectively prevent AKI-to-CKD progression.

Conclusions: CD11b plays a critical role in limiting the alternative activation of macrophages and may be a potential therapeutic target during the AKI-to-CKD process.

SA-PO1199

APOE-Activating Noncoding RNA (AANCR) Regulates APOE in Kidney Cell Types

Lillian B. Elkin, Ma Wan, Ryan J. Snyder, Jason A. Watts. *National Institute of Environmental Health Sciences, Durham, NC.*

Background: Apolipoprotein E (*APOE*) is a lipid carrier protein and polymorphisms of the gene are predictive of the development of chronic kidney disease (CKD). In line with its role in kidney function, *APOE* knockout mice develop renal disease, indicating that *APOE* is necessary to maintain normal renal function. However, some studies have suggested it is *APOE* dysregulation in macrophages or changes in lipid profiles that lead to kidney disease. Hence, the question remains whether *APOE* function in renal epithelial cells contributes to CKD risk. Recently, we identified a non-coding RNA, *APOE*-Activating Noncoding RNA (AANCR), that regulates *APOE* in human cells through a novel mechanism involving R-loop mediated RNA polymerase pausing. In this project, we asked whether AANCR regulates *APOE* expression in renal cell types.

Methods: To quantify AANCR-mediated *APOE* expression and its effect on renal cell types, we measured gene expression in cultured human proximal tubule cells (HK-2) and murine inner medullary collecting duct cells (IMCD) and performed apoptosis assays in HK-2 cells.

Results: First, we measured AANCR and *APOE* expression in renal cells by RT-qPCR and found that both are expressed in proximal tubule and collecting duct cells. Next, to test if AANCR regulates *APOE*, we performed siRNA knockdown of AANCR and found a significant reduction in the expression of *APOE* in renal proximal tubule cells. RNA polymerase pausing is common at stress responsive genes, so we asked if AANCR-*APOE* are stress responsive in renal cells. We found AANCR is induced in response to both osmotic stress and heavy metal exposure. To explore whether AANCR induction has functional consequences for renal cell types, we asked if APOE has a cytoprotective role in the kidney. APOE is a secreted protein, so we treated cells with osmotic stress to induce APOE expression and then collected the conditioned media. We fractioned the media to have either high or low APOE protein. We found that cells treated with conditioned media with abundant APOE were more resistant to apoptosis induced by osmotic stress, whereas conditioned media without APOE was not protective.

Conclusions: We show that the non-coding RNA AANCR regulates *APOE* expression in renal cell types and plays a cytoprotective role in response to stress. Future work will address whether targeted modulation of *APOE* expression is protective in CKD.

Funding: Other NIH Support - Intramural Research Program of the NIH, National Institute of Environmental Health Sciences ES103361, Private Foundation Support

SA-PO1200

Serum Amyloid A1 Damages the Peritubular Capillary Network and Promotes Kidney Fibrosis

Yadie Xiang, Haiyan Fu. *State Key Laboratory of Organ Failure Research, National Clinical Research Center of Kidney Disease, Renal Division, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China, Guangzhou, China.*

Background: The deterioration of the peritubular capillary network causes renal tissue ischemia and hypoxia, accelerating chronic kidney disease (CKD). Finding ways to mitigate endothelial cell injury and restore capillary density has been a persistent challenge. This project examines the pathological role and molecular mechanisms of serum amyloid A1 (SAA1), identified by our team as a kidney injury-associated molecule. Using multi-omics analysis and traditional biological experiments, we study SAA1 in CKD patients, mouse models, and in vitro endothelial cell injury models. Our goal is to deepen understanding of CKD pathogenesis, identify therapeutic targets, and develop effective prevention and treatment strategies.

Methods: Proteomic analysis of renal tissue post-ischemia/reperfusion injury (IRI) in mice identified molecules driving renal fibrosis, validated in CKD mouse models and patient biopsy specimens. Gene knockout mice were used in CKD models induced by IRI or unilateral ureteral obstruction (UUO). We employed histology, pathology, immunology, biochemistry, and molecular biology to study expression characteristics and damage effects. In vitro, transcriptome sequencing and traditional experiments elucidated molecular mechanisms in an endothelial cell injury model.

Results: Proteomic analysis of renal tissue post-ischemia/reperfusion injury (IRI) in mice identified molecules driving renal fibrosis, validated in CKD mouse models and patient biopsy specimens. Gene knockout mice were used in CKD models induced by IRI or unilateral ureteral obstruction (UUO). We employed histology, pathology, immunology, biochemistry, and molecular biology to study expression characteristics and damage effects. In vitro, transcriptome sequencing and traditional experiments elucidated molecular mechanisms in an endothelial cell injury model.

Conclusions: SAA1 is critical in renal fibrosis development, causing endothelial cell damage, increasing vascular permeability, disrupting capillary integrity, exacerbating renal ischemia and hypoxia, and accelerating fibrosis via the CD36/JNK pathway. Targeting SAA1 significantly improves renal microcirculation and delays CKD progression. SAA1 vaccination shows promise as an innovative CKD therapy.

Funding: Government Support - Non-U.S.

SA-PO1201

Hematopoietic Mosaic Loss of Y Chromosome Promotes Renal Cell Senescence and Kidney Diseases

Yohei Arai,[1] Nicholas W. Chavkin,[1] Yuka Arai,[1] Jonatan Halvardson,[2] Josefin Bjurling,[2] Heather Doviak,[1] Lars A. Forsberg,[2] Kenneth Walsh.[1] *[1]University of Virginia School of Medicine, Charlottesville, VA; [2]Uppsala Universitet, Uppsala, Sweden.*

Background: Aging leads to the accumulation of senescent cells that, in turn, promote morbidity and mortality. Hematopoietic mosaic loss of Y chromosome (mLOY) with age is the most frequently acquired somatic mutation in males, and this condition has been associated with various age-associated diseases and reduced lifespan. The pathogenesis of kidney diseases is associated with the infiltration of immune cells in response to the kidney injury, and senescent cells accumulate in kidney in response to injury or advance age. However, the roles of hematopoietic mLOY in renal disease progression and senescent cell accumulation are unknown.

Methods: We investigated the association between the LOY percentage in leukocytes and the incidence of kidney diseases using male dataset derived from a prospective cohort study of a half million individuals with paired genetic and phenotype information. To assess the specific transcriptional signatures associated with hematopoietic mLOY, cross-sectional analyses were performed on a single-cell RNA sequencing dataset of renal biopsies from healthy control males and male patients with kidney diseases. A mouse model of hematopoietic mLOY was employed to examine whether hematopoietic mLOY is causally link to kidney diseases.

Results: A prospective cohort study (n=216,608) revealed an association between mLOY in blood and the incidence of kidney diseases during the follow-up period (median 14.8 years). The analysis of transcriptional signatures in human kidneys identified associations between disease progression, immune cell LOY and the accumulation of senescent cells. Hematopoietic mLOY causally led to renal dysfunction that was accompanied by senescent cell accumulation in murine models of advanced age and kidney injury. In aged mLOY mice, treatment with a senolytic agent suppressed the progression of renal dysfunction and prolonged lifespan.

Conclusions: Hematopoietic mLOY promotes renal cell senescence, contributing to the development of kidney disease. Senolysis could be a promising therapeutic strategy for hematopoietic mLOY.

Funding: Other NIH Support - NIA, NHLBI

SA-PO1202

Suppressing Exocytosis of Mast Cells and Its Therapeutic Efficacy for Peritoneal Fibrosis in Rats with Chronic Kidney Failure

Itsuro Kazama. *Miyagi Daigaku Kango Gakugun Daigakuin Kangogaku Kenkyuka, Kurokawa-gun, Japan.*

Background: In addition to their exocytotic release of chemical mediators, mast cells produce fibroblast-activating factors to facilitate the progression of organ fibrosis in chronic inflammatory diseases. The process of exocytosis in mast cells can be monitored electro-physiologically by the changes in the membrane capacitance (Cm).

Methods: Employing the standard patch-clamp whole-cell recording technique in rat peritoneal mast cells, we examined the effects of anti-allergic drugs on the changes in the Cm. Additionally, using rat models with chronic renal failure (CRF) induced by 5/6 nephrectomy, we actually examined the therapeutic efficacy of these drugs for peritoneal fibrosis complicated with CRF.

Results: Among anti-allergic drugs, second-generation antihistamines, such as olopatadine, loratadine and ketotifen, markedly suppressed the increase in the Cm and directly inhibited the exocytotic process, suggesting their potency as mast cell stabilizers. Of note, tranilast, a potent anti-allergic drug, most effectively and strongly suppressed the increase in the Cm. Therefore, using rat models with CRF, we examined the effects of tranilast (200 mg/kg) on the histop**a**thological features of CRF rat peritoneum. In the fibrotic areas of CRF rat peritoneum, mast cells proliferated *in situ* and increased their activity by producing fibroblast growth factors. Therapeutic intervention with tranilast actually slowed the progression of peritoneal fibrosis.

Conclusions: From these results, the activation of mast cells was considered to be responsible for the progression of peritoneal fibrosis in uremic condition. Additionally, the results suggested the therapeutic potency of mast cell stabilizers in the treatment of peritoneal fibrosis in CRF.

PUB001

Epidemiology of Patients with CKD from Eastern North Carolina (ENC) Hospitalized with COVID-19

Cameron T. Lawson. *East Carolina University, Greenville, NC.*

Background: Early meta-analysis by Jdiaa et al showed that patients with CKD were more likely to have worse outcomes from COVID–19 compared to patients with normal renal function. To our knowledge, a similar retrospective analysis of COVID-19 positive patients hospitalized in Eastern North Carolina has not been replicated. Our study aimed to describe demographics and compare outcomes of COVID-19 positive patients with and without baseline CKD hospitalized within the ECU Health System.

Methods: This retrospective, observational study involved a review of data from electronic health records of patients aged ≥ 18 years with laboratory-confirmed COVID-19 admitted to one of the ECU Health Systems from March to October 2020. We described patients' demographics, comorbidities, length of stay, disposition, and mortality. We further subcategorized patients into two groups: those with glomerular filtration rate (GFR) > 60 ml/min/1.73 m^2 and a second group with GFR < 60 ml/min/1.73 m^2. Categorical variables were compared by Chi-squared while continuous variables were compared by Mann-Whitney U Test and reported as medians with interquartile ranges (IQR). The Institutional Review Board of ECU Health approved the study protocol before the study began.

Results: Of the 446 hospitalized COVID-19 positive patients, the median age was 64.5 years, 49% were African American, followed by 30% Caucasians. 43% of the patients had underlying CKD at least stage IIIa and 6% had end-stage renal disease (ESRD) as per Kidney Disease Improving Global Outcomes (KDIGO) guidelines. The median BMI was 30 kg/m^2 and 40% had tobacco exposure. Patients with GFR < 60 ml/min/1.73 m^2 were mostly older > 70 years old, African-American (p-value <0.001), had underlying DM, HTN, and were more likely to be discharged to a skilled nursing facility (p-value <0.001). Patients who had GFR < 60 ml/min/1.73 m^2 had a higher risk of in-hospital death compared to those with GFR> 60 ml/min/1.73 m^2 (p-value <0.001).

Conclusions: Our data demonstrated higher mortality rates in COVID-19 positive African-American patients with GFR < 60 ml/min/1.73 m^2. It has been previously shown that ENC has a higher concentration of lower socioeconomic counties and an overall higher comorbidity index. Further data analysis is needed to determine if a GFR < 60 ml/min/1.73 m^2 conveys an additional mortality risk outside the lower socioeconomic status.

PUB002

Risk Factors and Clinical Outcomes of Hyponatremia in Patients with COVID-19 Admitted to St. Luke's Medical Center-Global City (SLMC-GC) from January 1, 2021, to December 31, 2021: A Case-Control Study

Jill Therese U. Au. *St Luke's Medical Center - Global City, Taguig, Philippines.*

Background: Studies have found that hyponatremia in COVID-19 can result from inflammation-induced non-osmotic release of antidiuretic hormone. This study was conducted to identify the risk factors associated with hyponatremia (Na < 135mmol/L) in COVID-19 patients. The clinical outcomes of COVID-19 patients with and without hyponatremia were also compared.

Methods: This case-control study included a total of 384 patients (192 patients each for the hyponatremic and normonatremic groups) aged 18 years old and above diagnosed with COVID-19 infection, who were admitted at SLMC-GC from January 1, 2021 to December 31, 2021. Data pertaining to the patients' demographic characteristics, comorbid conditions, drug exposure, and laboratory results upon admission were collected and analyzed. The clinical outcomes analyzed include in-hospital mortality, need for ICU admission, need for ventilator support, acute kidney injury, and length of hospital stay.

Results: Patients with hyponatremia were found to be significantly older with male predominance. The presence of acute kidney injury had a significant association with hyponatremia. As compared to the normonatremic group, patients with hyponatremia had higher creatinine levels upon admission as well as higher white blood cell count, neutrophil-to-lymphocyte ratio, absolute neutrophil count and inflammatory markers (ferritin, CRP, IL-6, procalcitonin) but lower absolute lymphocyte count. Hyponatremia in COVID-19 patients had also been found to carry about two to three times the risk for adverse outcomes, with a significantly higher proportion of prolonged hospitalization, acute kidney injury, in-hospital mortality, need for ICU admission and need for intubation. Binary logistic regression showed that the significant predictors of hyponatremia include age, presence of acute kidney injury, absolute lymphocyte count, and ferritin level.

Conclusions: Hyponatremia in COVID-19 patients is significantly associated with adverse clinical outcomes. Determination of serum sodium is rapid, inexpensive and widely available. It may be used in the local setting to identify COVID-19 patients at high risk for poor clinical outcomes who may benefit from more intensive monitoring and allow proper interventions to be put in place in a timely fashion.

PUB003

Dynamic Evolution of Renal Markers and Mortality Prediction in Hospitalized Hispanic Patients with COVID-19

Andrew Banuelos,[1] Rajdeep S. Gadh,[1] Wayne R. Kotzker,[1] Ivan Delgado-Enciso,[2] Martha A. Mendoza Hernandez,[3] Gustavo A. Hernandez-Fuentes,[2] Jose G. Esquivel,[2] Janet Diaz Martinez.[1] Hispanic Kidney Researchers. *[1]Florida Kidney Physicians, Coral Springs, FL; [2]Universidad de Colima, Colima, Mexico; [3]Mexican Institute of Social Security, Colima, Mexico.*

Background: Kidney dysfunction is common in hospitalized COVID-19 patients and is linked to higher in-hospital mortality. Mortality prediction studies often use renal function markers (BUN, eGFR, AKI) from admission or the first 48 hours. Few studies analyze the evolution of these parameters during hospitalization and their predictive capacity for survival or death. **Objective**: To assess the predictive power of BUN and eGFR for mortality at different time points during hospitalization in a cohort of hospitalized Hispanic COVID-19 patients.

Methods: Clinical data were collected at admission and at 2, 4, 6, and 8 days into hospitalization from a cohort of 515 COVID-19 patients at the General Hospital of the Mexican Social Security Institute, Mexico (February 2021 to December 2022). Using time-dependent ROC curve analysis, we calculated the area under the curve (AUC), sensitivity, specificity, and predictive values for BUN and eGFR(ml/min/1.73m2. Patients were stratified based on eGFR was ≥60 or<60 at admission. Values equal to or above the cutoff point were predictive of mortality for BUN and survival for eGFR. Predictive capacity was classified as 0.50-0.60 (failed), 0.61-0.70 (worthless), 0.71-0.80 (poor), 0.81-0.90 (good), and >0.90 (excellent).

Results: Mean age was 63.3±16.1 years, 61.9% being male. The median length of hospital stay was 7.0 days. BUN and eGFR predictive capacities were more relevant on days 6 [AUC, 0.775 and 0.672] and 8 [AUC, 0.790 and 0.659], respectively. BUN ≥ 25.5 on day 8 predicts death in patients with GFR ≥60 at admission, while patients with GFR< 60 require a BUN ≥ 57 for this parameter to predict mortality.

Conclusions: BUN had better predictive capacity for mortality than eGFR. A BUN value of 25.5 or higher on day 8 predicts death in patients with adequate renal function at admission, while patients with impaired renal function require a BUN level above 57 to predict mortality.

PUB004

Trend Analysis of Kidney Disease and COVID-19-Related Mortality, 1999-2020

Mohammad Gul Yousaf Khan,[2] Mohammad Ammar ur Rahman,[1] Luqman Munir,[1] Amna Khalid,[1] Ahsan Zil-E-Ali,[2] Umar Farooq.[2] NEURALKEy. *[1]King Edward Medical University, Lahore, Pakistan; [2]Penn State College of Medicine, Hershey, PA.*

Background: The interaction of kidney diseases and COVID-19 may present in various forms and may pose various challenges. Individuals with pre-existing kidney pathologies may face increased complications and risks if infected. On the other hand, some of the infected individuals with previously normal renal function have also been seen to develop AKI. The mortality due to COVID related kidney diseases is on the rise in the United States. In this study we explored these trends from 1999-2020, using age adjusted mortality rates (AAMR) to pinpoint incongruities between epidemiological groups.

Methods: Our study conducted an in-depth search of the CDC Wonder database, based on the incidence of sequalae of stroke-related Age-Adjusted Mortality Rate (AAMR) per 100,000 individuals. Employing Join point Regression Analysis, we assessed Parallelism and computed Annual Percent Changes (APC) with a 95% Confidence Interval. For a $p<0.05$, the test of parallelism was considered significant for unparallel.

Results: From 1999-2020, a total of 4778965 deaths were reported due to COVID related kidney diseases. The overall AAMR showed a rise from 1999-2011, with an APC of 0.38. Following this, the AAMR started to decline from 2011-2014, with an APC of -11.94. The AAMR then showed a rise again from 2014-2020, with an APC of 1.50. The highest mortality populations were males and African Americans. The geographical hotspots for mortality were rural and Midwest. Tests for parallelism revealed disparate trends across gender (p=0.0002), Black and White races (p=0.0089), urban versus rural demographics (p=0.001). However, the parallelism test in Midwest versus South (p=0.25) was not significant.

Conclusions: The recent rise in the mortality due to COVID related kidney diseases is concerning. Furthermore, the disparity among the demographic variables warrants more investigation, and the planning of targeted interventions.

PUB005

Dialysis Initiation Practices during the COVID-19 Pandemic among US Veterans in Veterans Affairs (VA) and Non-VA Settings

Virginia Wang,[1,2] Cynthia Coffman,[1,2] Cassie L. Meyer,[1] Lan Jiang,[3] Kaitlyn B. Goodwin,[1] Clarissa J. Diamantidis,[4] Ann M. O'Hare,[6,7] Vincent Mor,[3,5] Matthew L. Maciejewski,[1,2] Amal Trivedi.[3,5] *[1]Durham VA Health Care System, Durham, NC; [2]Duke University, Durham, NC; [3]Providence VA Medical Center, Providence, RI; [4]Wake Forest University School of Medicine, Winston-Salem, NC; [5]Brown University, Providence, RI; [6]VA Puget Sound Health Care System Seattle Division, Seattle, WA; [7]University of Washington, Seattle, WA.*

Background: Veterans undergoing dialysis are susceptible to fragmented care in both VA and non-VA settings and their initiation of dialysis may be particularly affected by disruptions in care during the COVID-19 pandemic.

Methods: In this retrospective cohort study, we compared dialysis initiation practices among Veterans initiating dialysis through the Veterans Affairs (VA) in VA or VA community care (VACC) (i.e., non-VA) settings in 2018-2022. Changes in dialysis initiation were assessed across COVID eras (January 2018-February 2020 [pre], March 2020-December 2020 [acute], January 2021-January 2022 [recovery]) and dialysis settings (VA and non-VA). Dialysis initiation outcomes included nephrology visit ≤12 months prior to dialysis onset, estimated glomerular filtration rate (eGFR) ≤90 days of dialysis onset, and receipt of arterio-ventricular (AV) access placement. Linear and logistic models were fit with inverse probability of treatment weights that adjusted for Veterans' demographic, clinical, and healthcare utilization characteristics, and area-level COVID infection and vaccination rates.

Results: In adjusted analyses, the 17,780 Veterans in the cohort initiated VA dialysis during the study period (58% pre, 19% acute, and 24% recovery COVID eras) and most (77%) received dialysis in VA community care settings. Overall, there was a diminishing mean rate of pre-dialysis nephrology visits across COVID eras (67% pre, 66% acute, 60% recovery; p-value <0.0001) that was present in both VA and non-VA settings. Across all COVID eras, mean eGFR was higher in VA (14.3 vs. 13.4 in VACC; $p<0.01$), indicating lower kidney function at dialysis initiation, and mean rate of AV placement was also slightly higher in VA (13% vs. 10% in VACC; $p<0.01$).

Conclusions: Among US Veterans, COVID-19 was associated with overall decrease in nephrology consultation prior to dialysis initiation. There were no observed changes in kidney function or AV placement at dialysis onset over time. However, differences in conditions of dialysis initiation among Veterans in VA and non-VA settings persisted throughout the pandemic. Future analysis should further examine pandemic-related outcomes in this vulnerable population.

Funding: Veterans Affairs Support

PUB006

Evaluating Tubulopathy and Podocytopathy in COVID-19 Patients with Proteinuria Using Urinary NGAL and Podocalyxin Levels

Zeynep Ural. *Kirikkale Yüksek Ihtisas Hospital, Kirikkale, Turkey.*

Background: Clinical observations have shown that renal dysfunction is frequently seen in hospitalized COVID-19 patients. The mechanisms and pathways of kidney involvement in COVID-19 patients are not yet fully understood. Podocalyxin is an anionic transmembrane protein localized on the apical surface of glomerular podocytes. Podocalyxinuria indicates glomerular level damage to podocytes and/or the presence of apoptotic and necrotic podocytes in the urine. NGAL protein is freely filtered by the glomeruli and mostly reabsorbed by the proximal tubules. NGAL expression is rapidly induced in response to renal tubular epithelial cell damage and inflammation, and it is thought to be a marker of both acute and chronic kidney damage.

Methods: Our study includes patients with proteinuria and hypoalbuminemia who were hospitalized and followed up with a diagnosis of COVID-19 at Gazi University Faculty of Medicine Hospital (n=72) and a control group (n=48). Urinary podocalyxin and NGAL levels were measured in these patients.

Results: Podocalyxin and NGAL levels were significantly higher in proteinuric patients. NGAL levels were significantly associated with COVID-19 severity and disease mortality.(both p value <0.05= Correlation analysis of podocalyxin showed significantly higher levels in patients with proteinuria greater than 1000 mg/day.

Conclusions: Current literature does not provide studies showing whether the kidney damage seen in COVID-19 patients with proteinuria, hematuria, and GFR loss is due to direct viral damage to the kidney glomeruli and podocytes or related to the septic and hemodynamic condition. Therefore, assessing the impact on glomeruli and predicting patient and renal prognosis non-invasively without kidney biopsy by measuring urinary podocalyxin and NGAL in COVID-19 patients with proteinuria, hematuria, and renal dysfunction will be possible. This study is the first to investigate the presence of podocyturia in COVID-19 patients.

Funding: Private Foundation Support

PUB007

Cefepime's Neurotic Nexus: Complexities of Antibiotic-Induced Neurotoxicity

Daniela Carralero Somoza, Graciela M. Luna, Umair S. Ahmed, Kaitlyn Cariaga. *Lakeland Regional Medical Center Inc, Lakeland, FL.*

Introduction: Cefepime is a widely used fourth generation cephalosporin. It is primarily renally excreted, requiring dose adjustment in patients with deranged renal function. Cefepime-induced neurotoxicity, though rare, presents with neurological symptoms such as confusion, hallucinations and seizures. This case delves into the development of status epilepticus in a patient with renal insuffiency treated with cefepime.

Case Description: 68-year-old female with pertinent right nephrectomy presented with generalized weakness, vomiting and diarrhea to the emergency department. Investigations revealed a urinary tract infection and acute kidney injury. Serum creatinine was 7.51 mg/dl (baseline 1.10 three months prior, and 3.68 one month before). Intravenous (IV) cefepime was started. Three days after starting IV cefepime, patient developed progressively worsening encephalopathy, leading to airway compromise and subsequent intubation. CT and MRI brain showed no acute abnormalities, while EEG revealed epileptiform discharges. Neurology was consulted and diagnosed status epilepticus and patient was started on anti-seizure medication. As dose of IV cefepime was not renally adjusted, there was concern about cefepime neurotoxicity. IV cefepime was stopped and patient was started on hemodialysis. Mental status improved and no further seizures were noted.

Discussion: Cefepime has an elimination half life of 2.5 hours in patients with normal kidney function. This is increased with deranged kidney function. Risk factors for cefepime neurotoxicity include high dose, decreased renal clearance and increased penetration into the central nervous sytem as a result of dysfunction of the blood-brain barrier. Discontinuation of cefepime is the most important intervention. Sometimes dialysis is needed for rapid drug removal if symptoms persist. The low molecular weight and low protein binding facilitate its removal with dialysis. This case reinforces the importance of renally adjusting medications. A high index of suspicion is needed especially in patients with risk factors as the prognosis of cefepime neurotoxicity depends on early recognition and management. The diagnosis was cefepime neurotoxicity rather than uremia as patient's mental status improved after initial management and remained good despite worse renal parameters on her dyalisis days later on the stay.

PUB008

Cryptogenic Liver Cirrhosis and Hepatorenal Syndrome (HRS) Management in Developing Countries

Marcelo R. Bacci,[1,2] Fernanda R. Ranieri,[1] João Victor D. Ferreira.[1] *[1]Faculdade de Medicina do ABC, Santo Andre, Brazil; [2]Praxis Clinical Research, Santo Andre, Brazil.*

Introduction: HRS is a renal dysfunction secondary to liver failure and portal hypertension. Increased vasodilator circulation causes reduced effective blood volume, activation of the renin angiotensin-aldosterone system. This hormone storm has engulfed the kidneys, necessitating the exclusion of other potential causes of their failure. In the past few decades, HRS definition has changed, which has contributed to the difficulty in understanding a correct diagnosis. In this case report, we describe a HRS female patient with a late referral to the nephrologist after hospital discharge.

Case Description: A 62-year-old female presented with jaundice, ascitis and confusion, requiring hospitalization. She had a history of liver disease with no proper investigation and 15 years of evolution. A nephrologist was called upon admission due to kidney failure. She had no history of drug abuse, alcohol consumption, sepsis or viral infection. There was no answer with volume expansion. The medical team performed a liver biopsy but kidney biopsy was not considered. The medical team did not classify the HRS properly as no data of previous creatinine was available. The patient evolved to permanent conventional dialysis. Following discharge, the patient visited an outpatient

nephrologist which classified as HRS non-acute kidney injury(NAKI) due to acute kidney disease(AKD). The liver biopsy revealed cryptogenic liver cirrhosis.

Discussion: There has been a recent change in the classification of HRS. What used to be HRS1 became HRS-AKI.HRS2 transitioned to HRS-NAKI, which further categorizes into AKD or CKD. We still have a thorough understanding of HRS new acronyms. It is common practice in developing countries to categorize HRS patients without considering their specific causes due to lack of resources. Brazil is a developing country with a universal health system, however there are few hospitals with proper liver-kidney support and integrated electronic medical records. Kidney and liver biopsies are not easy to get at the most of these hospitals. Liver dialysis is not available and usually these patients need to wait for an outpatient nephrologist for adequate treatment. In summary, knowledge about the new HRS classification still requires attention. A better educational training with a robust differential diagnosis and better access to the patient's medical history are keys to success.

PUB009

Incidence of AKI after Cardiac Surgery

Varisha Shahzad, Dabhóg Boyle, Orlaith Corcoran, Denise M. Sadlier.
Mater Misericordiae University Hospital, Dublin, Ireland.

Background: Cardiac surgery is a life-saving intervention, however, the development of cardiac surgery–associated acute kidney injury (CS-AKI) is associated with longer hospital stay, higher hospitalization costs and increased postoperative mortality. Here, the incidence of CS-AKI is described in patients undergoing cardiac surgery over a 1-year period examining the major risk factors in this patient population.

Methods: Local databases were used to collect data. 429 patients underwent cardiac surgery between the 1st January 2023 and 1st January 2024. For all patients, demographic data was collected including age, gender, past medical history and type of cardiac surgery. Serum creatinine was recorded on day 0, 1, 3, 5 and on discharge. Patients with end stage kidney disease requiring dialysis were excluded (n = 4). AKI was defined by AKIN criteria.

Results: Majority of patients had normal renal function pre-operatively (n = 380/425), of these 32% (n = 138) developed CS-AKI. Over 80% of these patients developed an acute kidney injury (AKI) on the first postoperative day. Out of these, 23 were female, 115 were male and 77 people were aged above 65 years. Around 81% (n=112) developed stage 1, 8% (n=11) stage 2 and 11% (n=15) stage 3 AKI. A total of 56 patients were active smokers of these only 25% (n = 14) developed CS-AKI. Breakdown of risk factors for the 138 patients with CS-AKI were as follows; hypertension (n=99), dyslipidaemia (n=75), heart disease (n=61), diabetes mellitus (n=41), obesity (n=14), smoking (n=14), structural abnormality (n=8), one patient had previously required RRT for a contrast-induced AKI. A large proportion of patients with stage 3 AKI (n=11) had undergone a cardiac bypass. The average duration of renal replacement therapy (RRT) for those requiring it (n=13) with stage 3 AKI was 17.4 days, of these 5 patients recovered renal function to be dialysis independent. While 6 other patients requiring RRT died from complications of surgery. The mean serum on discharge was 117.7 umol/L (range = 54 – 493 umol/L).

Conclusions: A post-operative AKI can have short- and long-term complications. Even if the renal function initially recovers patients are still at risk of developing premature chronic kidney disease. Studies are required to develop a system for AKI risk prediction in the setting cardiac surgery.

PUB010

Filtration Fiasco: A Case of Tenofovir-Alafenamide False Creatinine Elevation

Jeshanah Johnson, Jacob A. Nysather. *University of Cincinnati, Cincinnati, OH.*

Introduction: Human Immunodeficiency Virus (HIV) is a viral infection most transmitted by sexual contact and injection drug use. The development of anti-retroviral therapy has positively impacted life expectancy and reduced the progression of disease.[1] HIV treatment is composed of an integrase inhibitor and reverse transcriptase inhibitor.[2] Commonly used Biktarvy includes Tenofovir alafenamide (TAF), a reverse transcriptase inhibitor. This case explores the effect of TAF on the interpretation and monitoring of renal function.

Case Description: We report a case of a 50-year-old male with TAF false serum creatinine (SCr) elevation. He was diagnosed with HIV on a screening test (HIV-1 viral load 10,100 copies/mL) and started on Biktarvy. Pre-therapy SCr was 1.3 mg/dL and rose to a peak of 2.3 mg/dL six months later. Evaluation for acute kidney injury was unrevealing and other historical tenofovir nephrotoxicity including proximal tubulopathy and Fanconi Syndrome were ruled out. No signs of chronic kidney disease associated abnormalities were seen. A Cystatin-C (CysC) of 1.04 mg/L (SCr 1.77 mg/dL) showing a discordance. A 24-hr creatinine clearance of 46 and 24-hr urea nitrogen of 25 for a mean GFR of 35 (3 liters of volume), aligning with SCr estimation. A Tc-99m nuclear GFR scan showing a GFR 113 mL/min/1.73sq.m aligning with the CysC eGFR. The patient's SCr stabilized around 1.7 mg/dL. Of note, the patient remained TAF throughout evaluation and remains on treatment given disease control (HIV-1 viral load <20 copies/mL).

Discussion: TAF therapy has largely replaced previously used tenofovir disoproxil fumarate (TDF) which is associated with proximal tubular toxicity at the mitochondria. In this case, the presumed cause of SCr and CysC discordance is inhibition of creatinine secretion by unclear mechanism (e.g. trimethoprim). A small elevation in SCr of 0.1mg/dL was noted on initial clinical trials.[3] Our case demonstrates the need for individualized evaluation of SCr changes in those taking TAF due to the potential clinical impact on management of HIV.

PUB011

Incidence of Cardiac Surgery-Associated AKI in a Third-Level Hospital

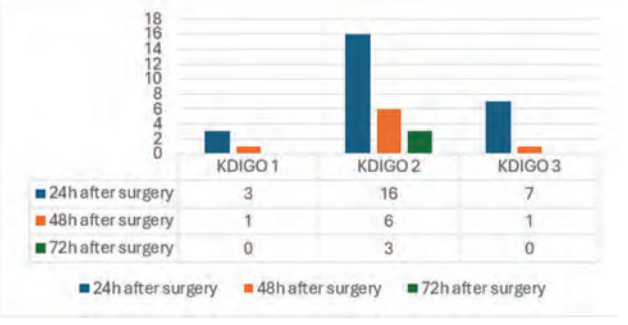
Ydris Z. Rosillo-Salgado, Mario Alamilla-Sanchez, Jose L. Torres Cuevas.
Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico.

Background: Acute kidney injury (AKI) is a common complication in cardiac surgery patients, the incidence of cardiac surgery-associated AKI is still around 40% increasing mortality, development of chronic kidney disease and has a significant impact on global health care costs. Identication risk factors that can prevent AKI

Methods: Prospective cohort included 51 patients who had cardiac surgery

Results: The mean preoperative eGFR was 75 ml/min/1.73 m2. The 37 of 51 participants (72%) developed AKI as defined by the KDIGO until 3 days after surgery. Stage 1 occurred in 26 (50.9%); stage 2 happened in 8 (15.6%) and stage 3 was in 3 (5.88%) patients of which 1 (1.9%) required hemodialysis. Day 1 after surgery AKI was present in 4 (10.8%), day 2 AKI occurs in 25 (67.5%) and day 3 AKI happened in 8 (21.6%) patients. All surgeries were elective and cardiopulmonary bypass (CPB) was utilized in 100%, and CPB mean time was 96.4min and aortic clamping mean time was 73.6min. The most frequent cardiac surgery was coronary artery bypass graft (CABG) 25 (49%), valvular surgery 24 (47.1%) and combined 2 (3.9%) in which AKI was present in 36%, 75% and 100% respectively according to the type of surgery. Patients with AKI had an average postoperative fluid balance of 3.7L vs 2.4L without AKI. Venous congestion with portal flow pulsatility >30% and abnormal morphology of renal intraparenchymal venous flow arises in 12 (32.4%) of 37 patients with AKI. On the 1st postoperative day, 9 (56%), on 2nd day 3 (50%) and on 3rd day 1 (33%) related to venous congestion. Overall mortality was 13.7% (n= 7), while for AKI mortality rate was 21% (n=7).

Conclusions: AKI was present in 70% of patients undergoing multifactorial cardiac surgery including type of surgery, drug use, cardiac dysfunction and venous congestion.



Día LRA	24h after surgery			48h after surgery			72h after surgery		
KDIGO 1	n=3			n=16			n= 7		
PFP %*	<30	30-49	>50	<30	30-49	>50	<30	30-49	>50
# patients	1	2	0	7	8	1	6	0	1
RVF**	Continuous	Anormal		Continuous	Anormal		Continuous	Anormal	
# patients	2	1		7	11		3	4	
KDIGO 2	n=1			**n=6**			n=1		
PFP %*	<30	30-49	>50	<30	30-49	>50	<30	30-49	>50
# patients	0	1	0	5	1	0	1	0	0
RVF**	Continuous	Anormal		Continuous	Anormal		Continuous	Anormal	
# patients	1	0		2	4		0	1	
KDIGO 3	n=0			n=3			n=0		
PFP %*	<30	30-49	>50	<30	30-49	>50	<30	30-49	>50
# patients	0	0	0	1	2	0	0	0	0
RVF**	Continuous	Anormal		Continuous	Anormal		Continuous	Anormal	
# patients	0	0		1	2		0	0	

* Porta flow pulsatility percentage %
** Renal venous flow. Continuous. Anormal: biphasic flow or monophasic flow

PUB012

Comparative Outcomes and Risk Analysis of Kidney Replacement Therapy in Adult Patients with AKI

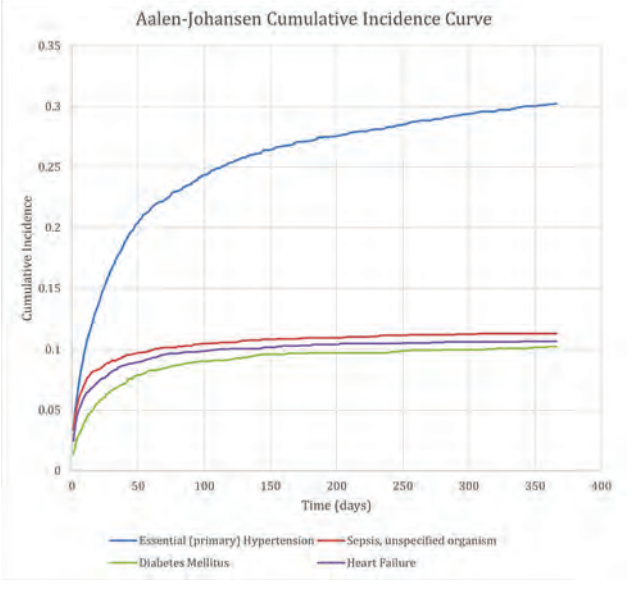
Sanat Subhash, Rupesh Raina, Prakash S. Gudsoorkar. *Akron Nephrology Associates/ Cleveland Clinic Akron General Medical Center, Akron, OH.*

Background: Acute kidney injury (AKI) is a condition present in nearly 7% of hospital admissions and 30% of ICU admissions with significant mortality and is linked to several major comorbidities including diabetes, sepsis, and heart failure. We utilized aggregated electronic healthcare patient data to analyze the incidence of AKI comorbidities, characterize epidemiological data, and compare patient outcomes between those on IHD (Intermittent Hemodialysis) and CKRT (Continuous Kidney Replacement Therapy).

Methods: A retrospective cohort assessment was performed using the TrinetX database. We studied the incidence rates of diabetes mellitus, primary hypertension, heart failure, and sepsis in ICU HD AKI patients at a 365-day period preceding AKI onset. Additionally, we evaluated clinical outcomes among ICU AKI HD patients compared to CKRT patients by measuring rehospitalization rates, intensive care unit (ICU) readmission, mechanical intubation/ventilation, and all-cause mortality risk at 30, 90, 180, and 365-days post-treatment.

Results: Hypertension (20.2%), sepsis (9.23%), and diabetes mellitus (7.28%) were the most common comorbidities in the AKI patient cohort. Comparative outcomes analysis showed increased mortality and ICU readmission in the CKRT AKI patient cohort and higher rehospitalizations in the HD AKI patient cohort. Both groups demonstrated similar ventilation/intubation rates.

Conclusions: Our ICU CKRT and HD cohort comparison indicates a significant increase in mortality and ICU readmission rates among CKRT patients. HD patients reported higher rehospitalization rates, while ventilation/intubation rates were similar between cohorts. The competing risks analysis for our HD AKI cohort demonstrated strong links between comorbidities and patients needing HD treatment.



PUB013

Valacyclovir-Induced Crystal Kidney Failure: An Underestimated Adverse Effect of a Well-Known Drug

Abraham Bell,[1] Stefan Milutinovic,[1] Gautam Maddineni,[1] Isaac Bell,[2] Meloney Oliveira.[1] *[1]Florida State University, Tallahassee, FL; [2]Nova Southeastern University, Fort Lauderdale, FL.*

Introduction: Valacyclovir is an oral antiviral drug used to treat herpetic infections. Valacyclovir related acute kidney injury (AKI) is described as a rare side effect. The mechanism of nephrotoxicity includes crystal deposition in the renal tubules resulting in intratubular obstruction and local interstitial inflammation. The risk of AKI increases with other risk factors for AKI are present such as chronic kidney disease, hypovolemic, overdose of the medication or concomitant use of known nephrotoxic medications. We used the FDA Adverse Events Reporting System (FAERS) to quantify the reported incidence of valacyclovir induced AKI.

Case Description: A 60 yo lady with a past medical history of hypothyroidism and hypertension presented to the ER with new visual hallucinations. Her symptoms were associated with new onset nausea, vomiting and generalized weakness. Five days prior to her acute presentation, she had been prescribed a 7-day course of valacyclovir to treat an acute herpes zoster lesion. Labs revealed a serum creatinine of 7 mg/dL (2 weeks prior serum creatinine was 0.8 mg/dL), UA with brown granular casts. Urine eosinophils were negative. She received IV fluids in the emergency department that were continued on admission and her renal function started to improve.

Discussion: Data published in FAERS suggests that the rate of AKI with concomitant valacyclovir is greater than 7.49% in over 1,434 cases since 1995. It is the second most common side effect associated with the drug reported in FAERS. The rate of AKI with concomitant acyclovir is 8.63% in reported cases since 1995, which is not significantly more in comparison to valacyclovir.

PUB014

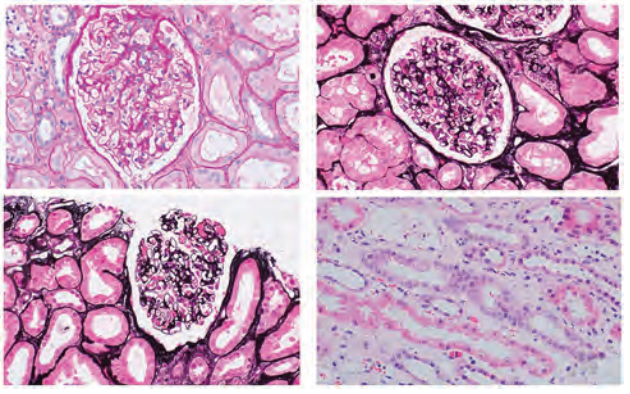
Vaping-Induced Acute Tubular Necrosis

Indira Tata, Victor A. Canela-Samaniego. Dallas Nephrology Associates. *Medical City Denton, Denton, TX.*

Introduction: E-cigarettes have gained popularity as a smoking cessation tool and perceived as a safer alternative to traditional cigarettes. These devices contain harmful compounds such as nicotine, heavy metals, and carcinogens. Recognizing their potential to cause direct lung injury and kidney damage is crucial for nephrologists and clinicians. This case report highlights AKI in a patient using e-cigarettes daily.

Case Description: A 60-year-old male with history of Hypertension presented with one-week of headache, and shortness of breath. His BP medications included amlodipine, Hydrochlorothiazide, and losartan. On exam, he was hypertensive with a BP of 240/130, appeared volume overloaded, and was progressively hypoxic. An echocardiogram revealed normal cardiac function. Initial lab tests showed a BUN of 39 mg/dl and creatinine of 2.29 mg/dl, normal electrolytes; LFTs; and CK. Complement levels, ANCA, anti-GBM titers, and infectious serologies were negative. Urinalysis showed no WBCs, eosinophils, granular casts, RBCs, protein, or crystals. Utox was negative, and a renal US showed normal kidneys with no hydronephrosis. Despite adequate diuresis, his oxygenation worsened. He reported increased daily use of e-cigarettes. Steroids were started, and his hypoxia quickly improved. A bronchoscopy with bronchoalveolar lavage (BAL) suggested Diffuse Alevolar Hemorrhage. Despite holding diuretics, his renal function continued to decline, leading to oliguria and necessitating urgent dialysis. A kidney biopsy revealed Acute Tubular Necrosis with 20% tubular atrophy, no immune component, and no microthrombi. While his uremic symptoms improved, he remains dialysis-dependent to this day.

Discussion: This case highlights severe acute kidney injury associated with vaping. Proposed mechanisms include oxidative stress and direct toxic cellular injury. Compounds in e-cigarettes, such as nicotine, propylene glycol, glycerol, and flavorings like diacetyl, have been implicated in cellular damage and inflammation. Healthcare providers should be aware of the risks associated with e-cigarettes, including potential kidney injury.



PUB015

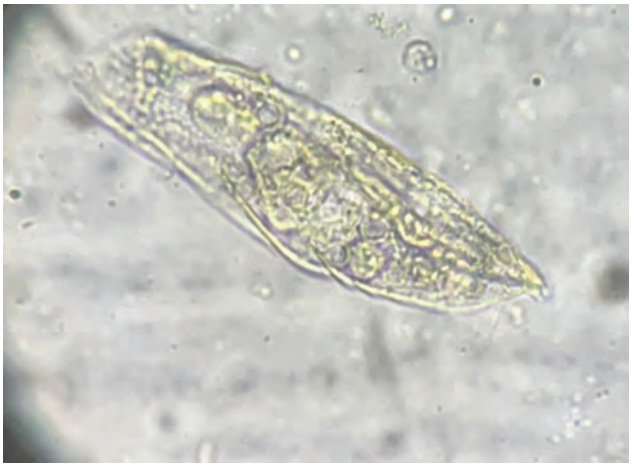
From Tubular Injury to Membranoproliferative Glomerulonephritis: A Complex Case of AKI

Adrian Llama,[1] Alejandro S. Garcia.[2] *[1]Yale University School of Medicine, New Haven, CT; [2]Yale New Haven Health System, New Haven, CT.*

Introduction: Acute kidney injury (AKI) is a common complication in hospitalized patients, with intrinsic causes like acute tubular injury (ATI), interstitial nephritis (IN), and glomerular injury accounting for 30% of cases. Rarely, aminoglycosides in antibiotic-loaded spacers for prosthetic joint infections can cause ATI and glomerular toxicity. IN is often drug-related, with penicillins strongly associated. Membranoproliferative glomerulonephritis (MPGN), a type of glomerular injury, can be triggered by infections.

Case Description: We present a 71-year-old woman with comorbidities including RA on prednisone and bilateral knee replacements who developed septic shock from a prosthetic joint infection. Despite surgery and tobramycin-vancomycin spacers, she had poor wound healing. Further debridement, spacer placement, and flap surgery were performed. Prednisone was reduced due to poor healing. Renal failure developed 14 days post-op without hemodynamic insults. Urine showed granular and RBC casts. Biopsy revealed severe ATI from tobramycin induced tubular injury, AIN, and MPGN. This case highlights the importance of multifactorial AKI. ATI was likely the main driver due to high-dose tobramycin spacers, but IN and MPGN suggest roles for drug exposure, and infection.

Discussion: Renal biopsy is crucial for rapidly progressive AKI with RBC casts, identifying pathological processes for targeted treatment. High suspicion for multifactorial AKI is needed. The patient's ATI was linked to prolonged exposure to tobramycin spacers, with higher doses and longer duration increasing AKI risk. IN treatment is usually corticosteroids, but evidence is limited and was deferred to avoid poor wound healing and recurrent infection. Prednisone reduction may have contributed by unmasking doormant AIN. MPGN was also present with immunoglobulin and complement deposits. Ampicillin was stopped, infection treated, steroids deferred, and spacer remained to avoid surgical risks. She made a full recovery.



PUB016

Sex-Based Differences in Cisplatin-Induced Nephrotoxicity

Dianet Sanchez Vega, Dana Hammouri, Barbara O'Steen, Leah J. Siskind, Levi J. Beverly. *University of Louisville School of Medicine, Louisville, KY.*

Background: Cisplatin is a potent chemotherapeutic agent, but its efficacy is limited by dose-dependent nephrotoxicity, with 30% of patients developing kidney injury, subsequently increasing the risk of chronic kidney disease. Sex-based differences are implicated as a biological variable of cisplatin-induced nephrotoxicity (CIN) and in immunological responses, but are greatly understudied. Given the crucial role of the immune system in mediating CIN, we hypothesize that sex-based immunological variations contribute to differential susceptibility to CIN.

Methods: Male and female B6:129 mice were administered weekly doses of vehicle or cisplatin (5 or 7 mg/kg) for four weeks. Kidney function (transdermal GFR measurements), and immunological differences in the kidney (flow cytometry) were assessed.

Results: Males treated with cisplatin exhibited a significant increase in kidney leukocytes, specifically resident macrophages. Transdermal GFR measurements showed a trending decrease in treated male mice. Conversely, treated female immune response was not statistically different than vehicle treated. Transdermal GFR measurements showed no significant difference between vehicle treated females and cisplatin treated females.

Conclusions: Data indicate sex differences in a repeated low dose cisplatin model. Data suggest that kidney function in females, but not males was preserved in this model and that this could be in part be due to differences in immunological responses to cisplatin. This study highlights the importance of considering sex as a biological variable in CIN and advocates for sex-specific strategies to mitigate its adverse effects. Further studies will aid in gaining mechanistic insight for these sex specific differences for the development of more effective treatments.

Funding: NIDDK Support

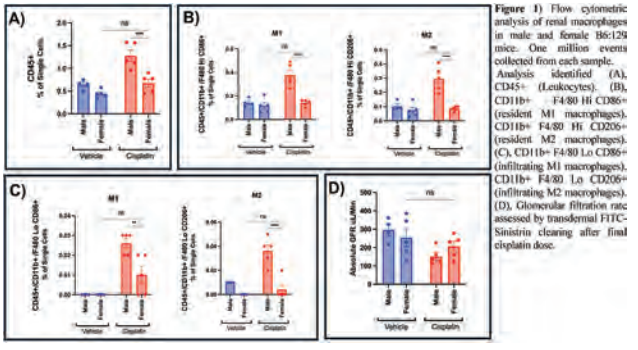


Figure 1) Flow cytometric analysis of renal macrophages in male and female B6:129 mice. One million events collected from each sample. Analysis identified (A), CD45+ (Leukocytes). (B), CD11b+ F4/80 Hi CD86+ (resident M1 macrophages), CD11b+ F4/80 Hi CD206+ (resident M2 macrophages). (C), CD11b+ F4/80 Lo CD86+ (infiltrating M1 macrophages), CD11b+ F4/80 Lo CD206+ (infiltrating M2 macrophages). (D), Glomerular filtration rate assessed by transdermal FITC-Sinistrin clearing after final cisplatin dose.

PUB017

Levothyroxine as an Unusual Cause of Acute Interstitial Nephritis

Hassan H. Allahrakha, Roberto L. Collazo-Maldonado. *Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Acute interstitial nephritis (AIN), a common cause of acute kidney injury (AKI), is accompanied by histologic findings of interstitial inflammation, edema, and tubulitis. We report a patient who presented with AIN after starting levothyroxine, a medication used to treat hypothyroidism.

Case Description: A 79-year-old male with a history of hypothyroidism and chronic kidney disease (CKD) presented with a two-week history of a painless, urticarial rash and intermittent diarrhea after starting levothyroxine. Laboratory findings were significant for a serum creatinine of 3.57 mg/dL, potassium of 5.6 mmol/L, CO_2 of 11 mmol/L, and peripheral eosinophilia (eosinophils 12%). Serologic work-up showed normal levels of C3, C4, antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, and anti-glomerular basement membrane antibodies. Serum and urine protein electrophoresis was normal; however, urinalysis showed trace proteinuria. Renal ultrasound revealed echogenic kidneys consistent with CKD. The patient was diagnosed with AIN, and started on treatment for the AIN with IV Solu-Medrol (500 mg) for three days. He was discharged on a prednisone taper. The patient's AKI, metabolic acidosis, and rash improved following IV steroids. He was switched from Mylan Levothyroxine to Armor Thyroid for thyroid supplementation at discharge.

Discussion: Levothyroxine is a rare cause of AIN. AIN should be considered in cases of unexplained AKI, especially after new medication administrations. This case emphasizes the importance of considering levothyroxine as a cause of AKI and AIN. In addition, the offending agent should be discontinued upon a diagnosis of drug-induced AIN.

PUB018

The Role of Terlipressin in AKI Secondary to Hepatorenal Syndrome (AKI-HRS)

Syeda S. Bukhari, Subodh J. Saggi, Susan Grossman. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Terlipressin is the most common vasoconstrictor used worldwide. It can be administered as a first-line agent for treatment of Acute Kidney injury secondary to Hepatorenal Syndrome. The pathophysiology includes increased intrahepatic resistance and vascular tone. Activation of the vasodilatory response leads to both splanchnic and systemic vasodilation. Progressive vasodilation leads to vasoconstrictive system activation, resulting in decreased blood flow to kidneys and the development of Acute kidney injury.

Case Description: We represent a case of a 74-year-old male with a past medical history of decompensated cirrhosis secondary to alcohol use disorder and HCV infection, HTN, OSA, Atrial flutter, and COPD presented to the Emergency Department with a three-day history of abdominal pain, distension and shortness of breath. On presentation vitals were B.P 108/61, HR>110. Physical examination showed a distended abdomen with ascites. Labs included serum creatinine>2.8 (baseline serum creat>0.9) and cystatin C 2.68. Abdominal sonogram normal. The patient was admitted to MICU for Decompensated Cirrhosis complicated with Hepatorenal syndrome and hepatic encephalopathy. The patient was given albumin challenge 25gm q6H, midodrine and octreotide for 2 days, and Terlipressin for 3 days. Lactulose and rifaximin was also started. Renal function markedly improved from serum creat 2.8 to serum creat 1.2. after the terlipressin was initiated. The patient got clinically better and was downgraded to floors.

Discussion: In one of the large randomized controlled trials, the efficacy of terlipressin was proven with some additional side effects of pulmonary edema. Therefore, caution should be taken before using terlipressin in patients with volume overload like anasarca, jugular venous distention, hypoxemia secondary to pulmonary congestion, and elevated right ventricular systolic pressures. Other possible options for treatment of AKI-HRS include placement of Trans jugular intrahepatic portosystemic shunt to decrease portal hypertension and Liver transplantation with kidney transplantation if there was prolonged damage to the kidneys. AKI-HRS prevention includes preventing volume depletion through careful use of diuretics, and lactulose, prevention of variceal bleeding, and discontinuation of nephrotoxic medications such as Ace/Arbs, Nsaids, contrast, and certain antibiotics.

PUB019

Prevalence of AKI in Patients Treated with Cisplatin

Jose L. Ortega, Enrique F. Morales Lopez, Mario Alamilla-Sanchez, Ydris Z. Rosillo-Salgado, Jose L. Torres Cuevas, Carolina Gonzalez-Fuentes, Victor M. Ulloa Galvan, Martin B. Yama Estrella, Jorge D. Salazar Hurtado, Jesús O. Rubio. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico.*

Background: Cisplatin is a potent chemotherapy used in a wide spectrum of malignant tumors, however it has been associated to nephrotoxicity manifested by acute kidney injury and electrolyte disorders. The main objective of this study is to describe the frequency and the outcomes in patients with nephrotoxicity induced by cisplatin.

Methods: Retrospective cohort of 30 patients treated with cisplatin in a single Mexican third level healthcare center, data were collected from electronic clinical records. Descriptive analysis was performed with central tendency characteristics. Univariate logistic regression (odds ratios [OR], 95% CI) was used to evaluate renal outcomes and mortality

Results: Of the 30 participants, 21 (70%) were men, the more frequent comorbidity was arterial hypertension, 7 patients (23.3%) and only one patient had the diagnosis of chronic kidney disease. The median of glomerular filtration rate was 67 (55-77), 15 (50%) had acute kidney injury and 8 (26.7%) progressed to acute kidney disease, the mortality in the follow up was 10%. The more frequent electrolyte disorder was hypomagnesemia recorded in 16 (53.3%) of the participants, 14 (46.7%) was moderate (0.9-1.6 mg/dl), no severe hypomagnesemia (<0.9 mg/dl) was identified. Acute kidney injury was not associated to mortality but patients who had progression to acute kidney disease had a significant risk of mortality with a OR= 1.42, 95% CI, (1.11-1.81).

Conclusions: Nephrotoxicity induced by cisplatin is mainly manifested by acute kidney injury and hypomagnesemia, identified in 50% and 53.3% respectively. Patients with no recovery and progression to acute kidney disease had a significant risk to mortality, the limitation to aggressors of kidney function after nephrotoxicity induced by cisplatin could influence in the patient's prognostic.

PUB020

A Case of Allopurinol-Induced Toxic Epidermal Necrolysis Complicated by Kidney Failure

Steven Pham,[1] Gabriel C. Graham,[1] Kayla Nguyen.[2] *[1]Unity Health, Searcy, AR; [2]Kaiser Permanente, Bakersfield, CA.*

Introduction: Toxic epidermal necrolysis (TEN) is a life-threatening condition marked by extensive blistering, rapidly developing exanthema, and mucosal involvement, with mortality exceeding 30%. Acute kidney injury (AKI) is defined by a sudden decline in kidney function, characterized by elevated creatinine level or reduced urine output. AKI is associated with a high incidence in TEN cases, but the full manifestation remains unclear. We report a case of allopurinol-induced TEN leading to severe oliguria and AKI.

Case Description: An 89-year-old female presented with a full-body rash. Two weeks prior, she was hospitalized, during which she received rocephin, and was discharged with a prednisone taper and diphenhydramine as needed. Skin biopsy at that time showed lichenoid dermatitis secondary to allopurinol that was started two weeks earlier. Upon rehospitalization, she had a diffuse, painful macular rash covering 65-75% of her body. Her dermatological symptoms worsened daily and there was positive Nikolsky's sign along with numerous bullae. Skin sloughing affected her torso and mucous membranes. Repeat skin biopsy confirmed TEN. Her creatinine rose from 2.3 mg/dL to 5.3 mg/dL, with inadequate urine output despite adequate fluid resuscitation and oral intake given through a nasogastric tube. Transfer to any nearby tertiary burn centers was not feasible due to the unavailability of a skin biopsy result at that time. After discussing with her family, a decision was made to move towards comfort-directed care due to a significantly poor prognosis. She expired shortly after care withdrawal.

Discussion: Managing TEN is challenging due to invasive skin exfoliation, with current protocols primarily providing supportive care. Extensive fluid loss from wounds can decrease renal blood flow if not promptly resuscitated. The loss of extracellular fluid and albumin, compounded by oliguria, disrupts protective barriers and facilitates bacterial translocation. Infections, due to the compromised skin barrier, can precipitate renal dysfunction. Additionally, stress-induced vasoconstriction from skin exfoliation exacerbates renal impairment. Consequently, AKI in TEN is associated with a high risk of sepsis and multi-organ failures, indicating a poor prognosis.

PUB021

Atypical Case of Hemolytic Uremic Syndrome Caused by Shiga Toxin-Producing Aeromonas Species

Soloman Kreik.[2,1] *[1]University of Michigan, Ann Arbor, MI; [2]San Ysidro Health, San Diego, CA.*

Introduction: Hemolytic uremic syndrome (HUS) is a leading cause of acute kidney injury in infants and young children, rarely effecting adults. It is defined as a triad of renal insufficiency, hemolytic anemia, and thrombocytopenia associated with shiga-like toxin (SLT). SLT is an antigen associated with diarrhea and plays a role in the pathogenesis of HUS. Commonly, the toxin is produced by E. Coli or Shigella species; however, recent studies show active SLT produced by Aeromonas spp. We present an atypical case of HUS caused by SLT producing A. hydrophila.

Case Description: A 77 year old female with past medical history of hypertension presented with one day of worsening lethargy. The patient complained of bloody diarrhea and diffuse abdominal pain. She endorsed eating raw oysters a day prior. On examination her abdomen was diffusely tender to palpation. Initial labs revealed a creatinine of 3.1 hemoglobin of 10.1 and a platelet count of 102. CBC and CMP were otherwise unremarkable. The patient was bolused with normal saline and started on maintenance fluids. Peripheral blood smear returned with schistocytes, LDH was elevated at 346 and haptoglobin was low at 28. The patient's stool antigens returned positive for Shiga toxin and blood culture showed Aeromonas Hydrophila bacteremia. At day 9 the patient's renal function subsequently returned to baseline.

Discussion: HUS is a microvascular occlusive disease that damages the glomeruli due to accumulation of platelets and sheared red blood cells. Isolation of A. hydrophila producing SLTs is concerning, as these toxins are associated with HUS. Aeromonas spp. producing SLTs could be an emergent pathogen in the pathophysiology fo HUS. This was a rare phenomenon, which is now proven by PCR amplification of the stx1 and stx2 gene in many similar cases. Our patient's HUS diagnosis demonstrated a prodromal illness of diarrhea, development of renal failure, thrombocytopenia and anemia. Early identification will allow prompt management and the prevention of long-standing renal failure.

Lab results on admission

Test	Patient	Reference range
Creatinine	3.1 mg/dL	0.6 – 1.1 mg/dL
Hemoglobin	10.1 g/dL	11.6 – 15 g/dL
Platelet count	102,000 µL	150,000 – 450,000 µL
LDH	346 U/L	140 – 280 U/L
Haptoglobin	28 mg/dL	41 – 165 mg/dL

PUB022

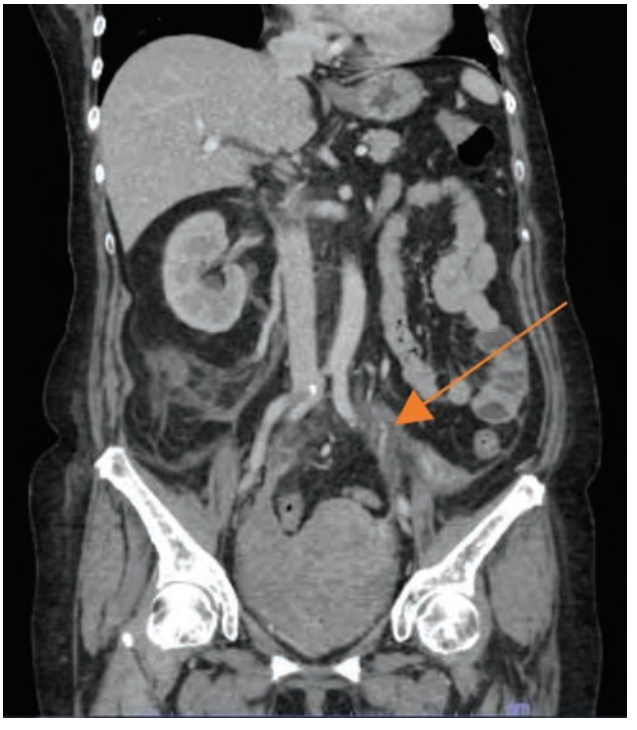
An Unusual Case of Retroperitoneal Fibrosis Masking Severe Hydronephrosis

Garo Kalfayan,[1] Arian Gower,[1,2] Jasprit Takher.[1] *[1]Los Robles Regional Medical Center, Thousand Oaks, CA; [2]Renal Consultants Medical Group, Thousand Oaks, CA.*

Introduction: Acute kidney injury (AKI) increases morbidity and mortality. Hydronephrosis is dilatation and distension of the renal collecting system of one or both kidneys due to obstruction of urine outflow distal to the renal pelvis. This a unique case as the degree of hydronephrosis is being undervalued due to the retroperitoneal fibrosis.

Case Description: A 75 year old female presented with progressively worsening abdominal pain. Initial laboratory evaluation demonstrated blood urea nitrogen (BUN) of 19 mg/dL and creatinine of 1.09 mg/dL. Lab values approximately 2 years prior were 10 mg/dl and 0.60 mg/dl. Computed Tomography showed extensive inflammatory changes in the lower pelvis, centered mostly around the cervix and extending into bilateral lower retroperitoneum. Ultrasound demonstrated very mild bilateral hydronephrosis. Nuclear medicine renal with Lasix showed significant renal impairment with an element of renal obstruction that cannot be excluded. Creatinine worsened to 6.46 mg/dl and BUN 48 mg/dL. It was hypothesized that imaging was incorrectly portraying the degree of hydronephrosis, and potentially it may be worse than a mild degree. Right sided percutaneous nephrostomy tube was placed with 2,175 mL output in 24 hour period. Creatinine improved to 3.76 mg/dL and BUN 46 mg/dL. Ultrasound six days later confirmed resolution of hydronephrosis, and return of creatinine to 0.48 mg/dL and BUN to 14 mg/dL.

Discussion: The resolution of hydronephrosis and AKI after percutaneous nephrostomy tube placement with significant output confirmed the hypothesis that imaging was potentially inaccurately portraying the degree of hydronephrosis. This can help guide future treatment when considering whether retroperitoneal fibrosis may be masking the degree of hydronephrosis.



Retroperitoneal fibrosis appreciated on Coronal CT Abdomen (red arrow)

PUB023

Interstitial Nephritis with Tenofovir-Containing Pre-exposure Prophylaxis (PrEP)

Matthias Bergmann,[1] Mark E. Williams,[2,1] Nathan H. Raines.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Joslin Diabetes Center, Boston, MA.*

Introduction: Use of pre-exposure prophylaxis (PrEP) for people at high risk of HIV infection has increased worldwide. Emtricitabine/tenofovir disoproxil (TDF) has been most used but is known to rarely cause tubular dysfunction and tubular necrosis (TN) through drug accumulation and mitochondrial damage. Emtricitabine/tenofovir alafenamide (TAF) has been approved for PrEP as an alternative agent with less nephrotoxicity, attributed to better plasma stability and lower plasma levels of the active agent. We present the case of a 51-year-old man using TDF-based PrEP who developed acute kidney injury (AKI) from interstitial nephritis (IN).

Case Description: A 51-year-old man with type 1 diabetes mellitus on insulin injections, hypertension on amlodipine, and HIV-PrEP with emtricitabine/tenofovir underwent urgent renal biopsy for AKI. Creatinine was elevated to 3.9 from 1.6 mg/dL at a 3-months follow-up visit and increased further to 4.6 mg/dL within one week. Urine albumin to creatinine ratio (UACR) had increased from 233 to 826 mg/g. A1c was stable at 6.7%, chemistry was without any significant abnormalities, and renal ultrasound was unremarkable. Complement levels were normal and serum protein electrophoresis showed no monoclonal abnormalities. HBsAg, HCV-Ab, and HIV screen were negative. Urine sediment showed only few fine granular casts. Renal biopsy showed IN. He was initiated on 60 mg prednisone daily for two weeks followed by a slow taper. Tenofovir-containing PrEP was discontinued. Within two months, creatinine decreased to 2.24 from 4.67 mg/dL and UACR decreased to 172 from 826 mg/g.

Discussion: We report the case of a 51-year-old man using tenofovir-containing HIV-PrEP who presented with AKI and underwent renal biopsy showing IN. TDF has been described to cause TN while TAF is thought to be less nephrotoxic. Our patient was initially considered for conversion to TAF due to suspected tenofovir toxicity. However, renal biopsy showed IN. Creatinine and UACR decreased within two months of initiation of high-dose prednisone and discontinuation of all tenofovir-containing agents. This case emphasizes the importance of a renal biopsy for AKI with PrEP to avoid missed treatment opportunities. Our patient would likely have been continued on an alternative tenofovir-containing agent and would not have been treated with glucocorticoids without the histopathologic diagnosis of IN.

PUB024

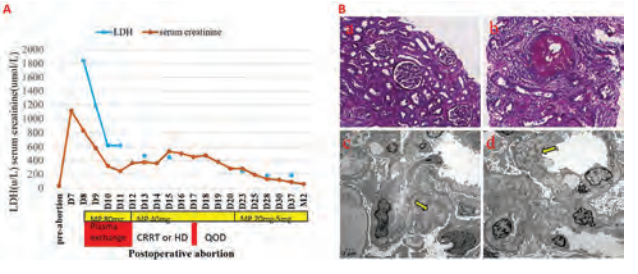
Complete Recovery from AKI: A Rare Case of Postpartum Atypical Hemolytic Uremic Syndrome

Ling Hong, Zhihua Zheng. *The Seventh Affiliated Hospital Sun Yat-sen University, Shenzhen, China.*

Introduction: As a critical disease in pregnancy, atypical hemolytic uremic syndrome (aHUS) features thrombocytopenia, acute kidney injury and the non-immune microangiopathy degeneration of hemolytic anemia. Its clinical course is disruptive and progressive. Pregnancy-related aHUS mostly progresses to end-stage renal disease (ESRD) with a high incidence. Here, a pregnant woman who developed hemolytic anemia and acute renal failure after induced abortion was reported.

Case Description: During her third month of pregnancy, a female aged 45 underwent an artificial abortion one month ago. One week after the abortion, she developed increased vaginal bleeding, abdominal pain and oliguria. Serum creatinine (Scr) increased from 36 to 1,114 umol/L. Laboratory examination showed hemolytic changes: increased proportions of helmet cells in peripheral blood (11%), significantly increased lactate dehydrogenase (LDH, 1,845 U/L), decreased haptoglobin (< 0.0706 g/L) and decreased platelets (38*10^9/L). The Coombs test was negative. She was diagnosed with thrombotic microangiopathy (TMA). Renal biopsy showed that renal tubule epithelial cells were granular denaturated and shed to form a bare basement membrane under a light microscope. In addition, electron microscopy showed endothelial cell swelling with loss of fenestrae and subendothelial electron-lucent widening. C5b-9 exhibited a significant increase by the quantitative detection of complement-related indicators, which was classified as aHUS. Corticosteroid impulse therapy combined with plasma exchange, the transfusion of fresh frozen plasma, hemodialysis and other treatments were given successively. Consequently, urine volume completely recovered, and Scr decreased from 1,184 to 78 umol/L. The patient was off dialysis, and hematological indicators were in complete remission.

Discussion: Postpartum acute kidney injury can be caused by a variety of reasons, of which the rare cause of aHUS can be life-threatening. The outcome of complete renal function recovery in this case confirmed that timely identification and early treatment can save patients' lives, preserve renal function, and avoid dialysis.



PUB025

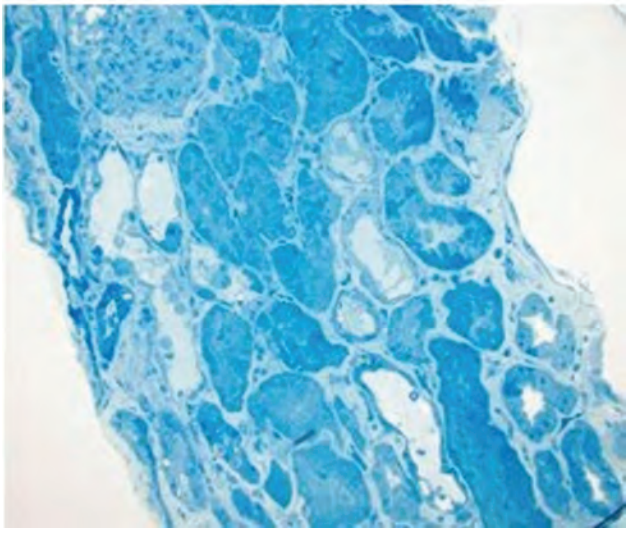
Toxic Attack: Organophosphate-Induced Acute Tubular Necrosis

Garo Kalfayan,[1] Arian Gower,[1,2] Jasprit Takher.[1] *[1]Los Robles Regional Medical Center, Thousand Oaks, CA; [2]Renal Consultants Medical Group, Thousand Oaks, CA.*

Introduction: Although organophosphate (OP) induced renal injury has been documented sporadically, there has not been an identified pathophysiology. The biopsy proven acute tubular necrosis due to organophosphate poisoning is unique as it may provide information into the pathophysiology of the disease process.

Case Description: A 73-year-old male presented to the emergency department after ingesting approximately 240 ml of a glyphosate-based herbicide as a suicide attempt. He was found to have elevated creatinine of 3.9 mg/dL and BUN of 40 mg/dL. Urine studies revealed urine sodium of 38 mmol/L and urine creatinine of 101 mg/dL, FENa of 1.1%, consistent with intrinsic etiology. Conservative management with lactated ringers 100 ml/hr was started initially. The patient's creatinine continued to trend upwards to 5.60 mg/dL, and a renal biopsy was performed. Due to worsening renal failure, the patient was placed on hemodialysis. The patient subsequently developed acute respiratory failure secondary to aspiration and required intubation. As his condition deteriorated the patient's family elected for hospice care, and patient later expired. Biopsy was found to report acute tubular necrosis due to toxic exposure to organophosphate.

Discussion: Organophosphate poisoning occurs in nearly three million people worldwide per year with symptoms involving the autonomic nervous system, neuromuscular junction, and central nervous system. Sporadically OP poisoning can cause AKI, with patients potentially developing ATN. This case illustrates organophosphates ability to perhaps cause direct damage to renal tubules. The biopsy results demonstrated acute injury and necrosis of the proximal tubules with focally prominent cytoplasmic swelling and near circumferential shedding of necrotic epithelial cells. This case illustrates OP ability to cause direct injury as the pathophysiology behind the disease process.



Acute Tubular Necrosis

PUB026

In a Bind

Zachary S. Grissom, Tyler Sims, Eun Y. Lee. *University of Kentucky College of Medicine, Lexington, KY.*

Introduction: A 55-year-old woman with suspected Sevelamer-induced colonic ulcer after admission for acute on chronic respiratory failure and an acute kidney injury (AKI).

Case Description: A 55-year-old female was admitted for acute respiratory failure and an oliguric AKI due to acute tubular necrosis (ATN) in setting of influenza A infection. She developed hyperphosphatemia (peak phosphorus level of 7.5 mg/dL) which was treated with 1,600mg oral Sevelamer carbonate 3x daily. She was placed on mechanical ventilation and subsequently transferred to an academic center. Within 24 hours of Sevelamer initiation and transfer, the patient experienced multiple episodes of hematochezia. Sigmoidoscopy demonstrated a 15 mm cratered linear ulcer in the cecum opposite the Ileocecal valve. Biopsy showed a single crystalloid structure with a tree-bark appearance and rusty color, consistent with a Sevelamer-induced ulcer. Sevelamer was promptly discontinued, and kidney function improved with supportive measures.

Discussion: This case demonstrates the rare finding of a Sevelamer-induced colonic ulcer in the setting of an AKI. Sevelamer is a non-metal hydrogel polymer that binds phosphorus in the GI tract and is widely used to treat hyperphosphatemia; it is generally preferred over calcium-based binders due to reduced risk of hypercalcemia (1). Injury to the gastrointestinal mucosa by direct deposition of Sevelamer crystals is a rare cause of hematochezia and should be considered in any patient taking Sevelamer who presents with intestinal hemorrhage (2). 1. Zeng Q, Zhong Y, Yu X. Meta-analysis of the efficacy and safety of sevelamer as hyperphosphatemia therapy for hemodialysis patients. Vol. 45, Renal Failure. Taylor and Francis Ltd.; 2023. 2. Nambiar S, Pillai UK, Devasahayam J, Oliver T, Karippot A. Colonic Mucosal Ulceration and Gastrointestinal Bleeding Associated with Sevelamer Crystal Deposition in a Patient with End Stage Renal Disease. Case Rep Nephrol. 2018;2018:1–3.

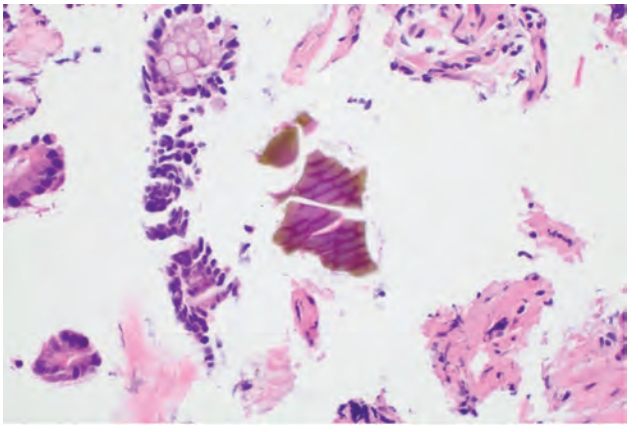


Figure 1. Sevelamer-associated colonic ulcer in the setting of an AKI demonstrating characteristic "tree bark" appearance.

PUB027

Use of Vasopressors in Patients with AKI on Continuous Kidney Replacement Therapy

Ambika Ramesh,[1] Akshith Doddi,[1] Aisha Abbasi,[1] Mohammad A. Al-Mamun,[3] Ankit Sakhuja,[1,2] Khaled Shawwa.[1] *[1]West Virginia University, Morgantown, WV; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]West Virginia University School of Pharmacy, Morgantown, WV.*

Background: To investigate whether use of any specific vasopressor is associated with increased mortality or adverse outcomes (kidney recovery and hypervolemia) in patients with acute kidney injury (AKI) receiving continuous kidney replacement therapy (CKRT).

Methods: Patients were included if they had AKI and underwent CKRT between 1/1/2012-1/1/2021 at a tertiary academic hospital. Cox proportional hazard model was used to assess the relationship between time-dependent vasopressors and in-hospital mortality. The relationship between vasopressors and daily fluid balance was assessed using Generalized Estimation Equation.

Results: There were 641 patients with AKI that required CKRT. In-hospital mortality occurred in 318 (49.6%) patients. Those who died were older (63 vs 57 years), required mechanical ventilation at time of CKRT (80% vs 63%), had higher SOFA score (10.6 vs 9) and lactate (6 vs 3.3 mmol/L). In multivariable model, increasing doses of norepinephrine (NE) [HR 4.4 (95% CI: 2.3-7, p<0.001)] per 0.02 mcg/min/kg and vasopressin [HR 2.6 (95% CI: 1.9-3.2, p=0.01)] per 0.02 unit/min during CKRT were associated with in-hospital mortality. Dobutamine, epinephrine and phenylephrine were not associated with in-hospital mortality. Baseline vasopressor values measured at CKRT initiation were not associated with in-hospital mortality. The model was adjusted for vasopressor doses and fluid balance prior to CKRT initiation, time-dependent daily fluid balance and vasopressor doses, SOFA score, septic shock, age, sex, Charlson comorbidity index, mechanical ventilation and baseline lactate. NE was the most commonly used vasopressor (18% of the time). All vasopressors, except dobutamine, were associated with positive daily fluid balance. Phenylephrine had the lowest coefficient 0.6 (0.45-0.73) liters per 1 mcg/kg/min increase, whereas the other vasopressors ranged between 2.4-4.3 L per 1-unit increase. Mean values of individual vasopressors were not associated with doubling of creatinine or persistent need of dialysis at day 30.

Conclusions: The associations between norepinephrine and vasopressin with in-hospital mortality could be related to their common use in this cohort.

PUB028

Renal Sarcoidosis Presenting as an Isolated Manifestation: A Rare Clinical Entity

Aseel Zghayer, Maria M. Picken, David J. Leehey. *Loyola University Chicago Stritch School of Medicine, Chicago, IL.*

Introduction: Sarcoidosis is a multisystem disorder with accumulation of non-necrotizing granulomas in the lungs and other organs. Renal involvement in sarcoidosis is rare, and its exact incidence remains uncertain. When present, it may manifest as interstitial nephritis, with or without granulomas, nephrocalcinosis, or hypercalciuria. Here, we describe a rare presentation of sarcoidosis with renal involvement as the only manifestation.

Case Description: A 65-year-old man with a history of chronic lymphocytic leukemia (CLL) in remission presented with lethargy, weight loss and anorexia. He was found to have acute kidney injury (AKI) on chronic kidney disease (CKD) of unclear etiology and hypercalcemia (total calcium 14.2 mg/dL). Urinalysis revealed +1 protein without hematuria or pyuria. 24-h urine protein was 1.2 g. Further workup showed low parathyroid hormone (PTH), normal PTH-related peptide (PTHrP), low 25-hydoxy vitamin D_3 (7 ng/mL) and normal 1,25-dihydroxy vitamin D_3 (43 pg/mL), and high angiotensin-converting enzyme (ACE) levels. Bone marrow biopsy showed no evidence of plasma cell neoplasm or a lymphoproliferative disorder and CT chest abdomen pelvis showed no acute abnormality. Kidney biopsy revealed interstitial nephritis with noncaseating granulomas consistent with sarcoidosis (Figure 1). He was treated with prednisone with improvement of hypercalcemia and renal function.

Discussion: The diagnosis of renal sarcoidosis is challenging in the absence of involvement of other organs with sarcoidosis. In our case, the normal level of 1,25-dihydroxy vitamin D_3 ($1,25(OH)_2D_3$) despite low 25-hydroxy vitamin D_3 ($25(OH)D_3$) levels with an elevated $1,25(OH)_2D_3/25(OH)D_3$ ratio suggested calcitriol production due to granulomatous processes (Rohmer et al., Ocul Immunol Inflamm 2020;28:341-7). In such instances, renal sarcoidosis should be considered in the differential diagnosis, particularly when encountering cases of acute or chronic renal failure with uncertain causes. Early identification and treatment can facilitate renal function recovery and reduce the risk of interstitial fibrosis.

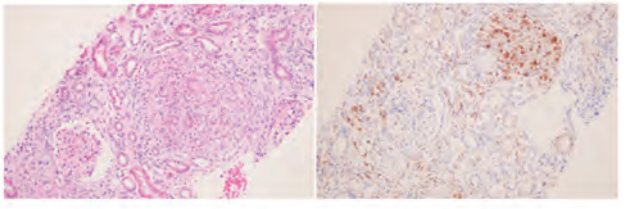


Figure 1. H&E and CD68 stains showing interstitial infiltrates with small epithelioid non-caseating granuloma.

Figure 1.

PUB029

Tobramycin Nephrotoxicity after Intra-articular Instillation

Kunal Bailoor,[1,2] Zeenat Y. Bhat.[1] [1]*University of Michigan, Ann Arbor, MI;* [2]*University of Michigan Center for Bioethics and Social Sciences in Medicine, Ann Arbor, MI.*

Introduction: Tobramycin powder is often instilled intra-articularly during operative management of septic arthritis with purportedly reduced risk of toxicity relative to systemic therapy. We present a case of tobramycin nephrotoxicity resulting in AKI requiring hemodialysis.

Case Description: A 70-year-old man who had a history of CKD3 with a baseline serum creatinine of 1.2 as well as osteoarthritis with history of right prosthetic knee replacement was hospitalized for lower extremity cellulitis. He had a complex medical history, most notable for prior bilateral lung transplant in 10/2011 for end stage COPD, atrial fibrillation, and type 2 diabetes mellitus. He initially presented with severe right lower leg pain and swelling; he was noted to have a new DVT. He was started on anticoagulation and IV cefepime. On evaluation, he was noted to have significant right knee effusion; joint aspiration reveled WBC count of 81,000 and synovial fluid culture growing Citrobacter koseri. He was taken to the OR and after joint washout, had 4 grams of vancomycin powder and 3 bottles of tobramycin powder (approximately 3.6 grams) instilled into the joint. There was no significant blood loss or intra-operative hypotension. His pre-operative serum creatinine was 1.2; approximately 12 hours after returning from the OR, his SCr had risen to 1.63 with hyperkalemia to 6.1. Despite attempts at medical management, the patient became rapidly oliguric with persistent hyperkalemia requiring initiation of hemodialysis. Serum tobramycin levels checked 48 hours after the patient returned from the OR were notable for a serum tobramycin level of 36.8 micrograms per milliliter, and a serum vancomycin level of 19.5 micrograms per milliliter. The patient received daily hemodialysis treatments until serum tobramycin levels dropped to below 1 microgram per milliliter. He had renal recovery and was able to stop hemodialysis approximately one month after his operation.

Discussion: Intra-articular antibiotic administration is often felt to be a safer alternative to systemic therapy with reduced risk of systemic toxicity; however, e present a case were there was significant systemic absorption of an intra-articular aminoglycoside resulting in nephrotoxicity. Aminoglycoside toxicity from intra-articular administration should be considered on the differential diagnosis of post-operative AKI for patients with septic arthritis who undergo this procedure.

PUB030

Association between Net Ultrafiltration Intensity and Mortality in Patients with AKI Undergoing Low-Dose Continuous Kidney Replacement Therapy

Keisuke Okamoto, Hidetada Fukushima, Masahiko Kawaguchi, Kazuhiko Tsuruya. *Nara Kenritsu Ika Daigaku, Kashihara, Japan.*

Background: Continuous kidney replacement therapy (CKRT) is a preferred dialysis modality for hemodynamically unstable acute kidney injury (AKI) patients in the intensive care unit (ICU). Several retrospective studies have reported that a higher net ultrafiltration (UF) intensity is associated with better patient survival, under the standard KDIGO-recommended delivered CKRT dose of 20 to 25 mL/kg/h. In Japan, however, the CKRT doses are usually below the KDIGO recommendation due to government health insurance system restrictions, and the association between the net UF and the mortality under lower than the KDIGO-recommended delivered CKRT dose has remained unknown.

Methods: We consecutively evaluated 603 patients who required CKRT in the ICU at Nara Medical University Hospital between January 1, 2012, and December 31, 2021. The following patients were excluded: those with end-stage kidney disease, deceased within 24 hours of ICU admission, CKRT for nonrenal indications, or CKRT duration exceeding 28 days. We categorized patients into four groups by median net UF intensity and delivered CKRT dose, and assessed ICU mortality using multivariable logistic regression.

Results: Of the 603 patients, 494 were included in this study. The median net UF intensity was 3.7 mL/kg/day, and the delivered CKRT dose was 13.2 mL/kg/h. We categorized 494 patients into four groups based on median net UF intensity and delivered CKRT dose: 129 in low net UF intensity-low delivered CKRT dose, 118 in low-high, 118 in high-low, and 129 in high-high groups. The adjusted odds ratios (95% confidence intervals) for ICU mortality via multivariable logistic regression were as follows: low-low 1.54 (0.76–3.12); low-high 0.52 (0.23–1.20); high-low, reference; high-high 0.41 (0.19–0.90).

Conclusions: In this cohort of AKI patients who underwent low-dose CKRT, higher net UF intensity with above-median delivered CKRT dose was independently associated with decreased ICU mortality, compared to higher net UF intensity with below-median delivered CKRT dose. These findings underscore the importance of optimizing CKRT dosing strategies in improving outcomes for AKI patients in the ICU.

PUB031

Recovery from Kidney Failure Associated with Pulmonary Hypertension following Use of Vasodilators

Batoul Dekmak, Emmanuel A. Aydin-Ghormoz, Swati Mehta, Geovani Faddoul. *Albany Med Health System, Albany, NY.*

Introduction: Pulmonary hypertension (PH) and kidney dysfunction are co-morbidities affecting patient outcomes. Chronic kidney disease (CKD) contributes to WHO group IV PH, while kidney injury frequently occurs in PH patients, indicating poor prognosis. The mechanisms involve cardiorenal syndrome and neurohormonal activation. Targeted therapies for PH may offer renal protective benefits, suggesting a beneficial approach for these conditions. We report a case of decompensated heart failure due to severe PH, resulting in acute kidney injury (AKI) from cardiorenal syndrome (CRS). The patient required continuous renal replacement therapy (CRRT) and experienced renal function normalization after vasodilator therapy.

Case Description: A female in her 60s with severe tricuspid regurgitation and right-sided heart failure due to pulmonary hypertension presented with a two-week history of bilateral lower extremity edema and increased abdominal girth, indicating an acute exacerbation of right-sided heart failure. Initial intravenous diuretics led to suboptimal response and kidney injury from CRS. The patient developed shock, necessitating the cessation of diuretics. CRRT was started, followed by hemodialysis (HD). Concurrently, intravenous epoprostenol, oral sildenafil, and ambrisentan were administered, leading to the resolution of kidney failure.

Discussion: The pathogenesis of CKD involves hemodynamic changes, inflammation, and oxidative stress, leading to glomerulosclerosis and kidney atrophy. PH-targeted therapies, including endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5Is), and prostacyclin analogues, influence kidney function due to their vasoactive properties. Sildenafil, a PDE5I, offers nephroprotective effects such as lowering blood pressure and reducing ischemia-reperfusion injury. The endothelin system, with its ET-A and ET-B receptors, plays a crucial role in vascular tone regulation. Selective ET-A blockade shows superior renal protection compared to dual ET-A/ET-B

antagonism, as evidenced by preclinical and clinical studies. Prostanoids like epoprostenol demonstrate renal protective effects, improving outcomes in various kidney dysfunction contexts. Overall, these targeted therapies offer promising renal benefits in patients with PH and CKD.

PUB032

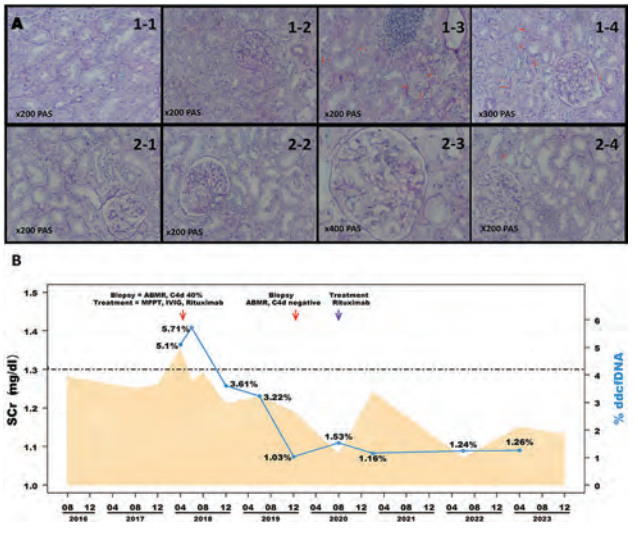
Continuous Routine Detection of Donor-Derived Cell-Free DNA Guides the Diagnosis and Treatment of Subclinical Rejection

Dongrui Cheng,[1] Haider Cuello Garcia,[2,3] Tingya Jiang.[3] *[1]Nanjing General Hospital of Nanjing Military Command Research Institute of Nephrology, Nanjing, China; [2]Jiangsu University, Zhenjiang, China; [3]AlloDx Biotech, Shanghai, China.*

Introduction: Donor-derived cell-free DNA (ddcfDNA) has been closely associated with antibody-mediated rejection (ABMR), however, there are few reports on using ddcfDNA to diagnose and treament evaluation for subclinical ABMR (subABMR). This study imployed a serial ddcfDNA testing in one KTx with subABMR.

Case Description: A 64-year-old man experience subclinical ABMR (subABMR) with devolpment DSA (A11, MFI=1530), and increase ddcfDNA (5.1%) after 4 years of transplantation. The result of biopsy shows 40% of peritubular capillaries with C4d positivity (Fig 1A, 1-4). The patient was treated with a combination of 200 mg of Rituximab and Intravenous Immunoglobulin. During follow-up, ddcfDNA levels were assessed in the first month post-treatment and subsequently every 6 months. DdcfDNA levels were decreased over time, at 24 months post-treatment, the ddcfDNA % value decreased to 1.03%. At this point, a repeat biopsy of the transplanted kidney revealed decrease pathological features of rejection with resolution of tubulitis. C4d staining changed from being positive in 40% ptc to negative; however, Glomerulonephritis (g=1) and ptc (>10%) remained positive (**Fig. 1A, 2-2, 2-3, 2-4**). Following a total surveillance duration of 28 months, it was found that the value increased by 48.5% during the fifth examination of the ddcfDNA. And considering the second biopsy showed ABMR, we promptly administered 200 mg of RIX, resulting in a subsequent decrease in ddcfDNA values. The patient has been followed up for nearly 5 years since then, with stable ddcfDNA levels and negative antibody status (**Fig. 1B**).

Discussion: This study highlights the utility of ddcfDNA as a biomarker for detecting subABMR. Monitoring ddcfDNA levels allowed for precise evaluation of treatment response and adjustment of therapy dosage. The study suggests that ddcfDNA may be is a reliable biomarker for subABMR.



PUB033

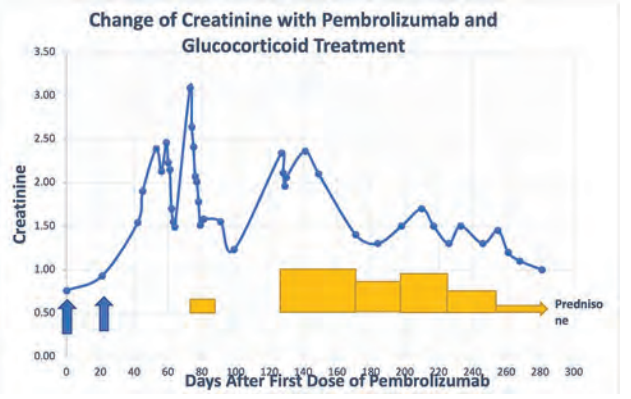
Pembrolizumab-Induced AKI

Abhi Lohana, Buse Eglenen Polat, Neeharika Muddana. *Camden Clark Medical Center, Parkersburg, WV.*

Introduction: Pembrolizumab, a monoclonal antibody targeting the programmed death 1 (PD-1) receptor, has revolutionized cancer therapy by enhancing T-cell-mediated anti-tumor immune responses. Despite its efficacy, Pembrolizumab is associated with immune-related adverse events (irAEs), including acute kidney injury (AKI), a rare but serious complication.

Case Description: An 86-year-old female with hypertension and type 2 diabetes mellitus was diagnosed with stage IV squamous cell lung cancer and initiated Pembrolizumab treatment. Within weeks, her renal function deteriorated, evidenced by declining glomerular filtration rate and rising creatinine levels. Pembrolizumab was discontinued after the second cycle due to significant creatinine elevation. Despite kidney protective measures, renal function did not improve. Urinalysis revealed an elevated urine protein/creatinine ratio, suggestive of AIN. Treatment with slow prednisone taper led to gradual improvement, with creatinine normalization and establishment of a new baseline glomerular filtration rate.

Discussion: The incidence of immune checkpoint-induced acute kidney injury (ICI-AKI) is estimated to range between 2-3%. Acute interstitial nephritis (ATIN) is the most common pathology in this context. Diagnosis is challenging due to multiple AKI risk factors in cancer patients. Clinical features such as sterile pyuria, white blood cell casts, and sub-nephrotic range proteinuria, commonly associated with ICPI-AKI, lack sensitivity and specificity and may manifest in other causes of ATIN. Increased vulnerability to ICPI-AKI is observed in patients experiencing other immune-related adverse effects (irAEs) linked to ICIs and PPIs. Current guidelines recommend initiating empirical treatment for ICPI-AKI without awaiting tissue diagnosis unless a three-fold increase in creatinine or suspicion of alternative causes for AKI arises. Prednisone, coupled with the discontinuation of the immune checkpoint inhibitor, constitutes the recommended therapeutic approach in the management of ICPI-AKI.



PUB034

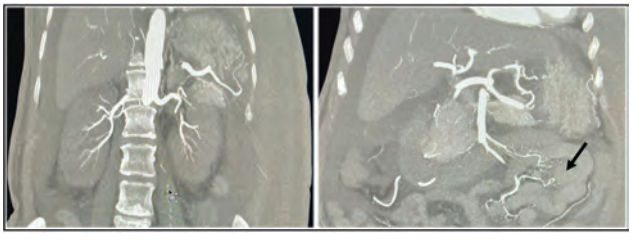
Polyarteritis Nodosa with Bilateral Renal Ischemia Masking as Nephrotic Syndrome in a Diabetic Patient: A Case Report

Stephanie Joyce R. Liao. *Chong Hua Hospital, Cebu City, Philippines.*

Introduction: Polyarteritis nodosa (PAN) is a necrotizing vasculitis primarily affecting medium-sized arteries. While PAN may present with mild proteinuria and microhematuria, signs of glomerulonephritis are rare. We report a complex case of PAN in which bilateral renal ischemia accelerated the underlying diabetic kidney disease, hence presenting with nephrotic syndrome and obscuring the diagnosis of PAN.

Case Description: A 72-year-old Filipino diabetic female with a four-month history of bilateral pitting edema and worsening hypertension presented to our institution with oliguria and increasing creatinine from 3.2 mg/dL to 4.3 mg/dL (eGFR of 10 mL/min/1.73m2). She was previously managed as rapidly progressive glomerulonephritis at another institution. Workup revealed negative results for ANA, ANCA, hepatitis, and anti-GBM. Abnormal findings include low C3, elevated LDH, nephrotic range proteinuria with UACR of 4744 ug/mg, and hypoalbuminemia. The initial impression was immune complex glomerulonephritis. However, kidney biopsy results were consistent only with those for diabetic kidney disease. She was readmitted for hematochezia, and endoscopy only revealed multiple gastric ulcers. The persistence of gastrointestinal (GI) bleeding prompted CT angiography, which showed irregular narrowing of the distal branches of both renal and superior mesenteric arteries with a beading appearance. Patient developed seizures, and a CT scan of the brain showed acute frontal lobe infarct. With the clinical presentation and angiographic findings, PAN was now highly considered. Repeat MPPT and intravenous cyclophosphamide infusion were given. However, massive GI bleeding persisted, and the patient eventually died.

Discussion: The differential diagnosis of PAN is broad, and diagnosis is often delayed due to the wide range of conditions that resemble and complicate the clinical signs. Risk factors for early mortality included older age, renal, CNS, and GI involvement. This case highlights the importance of considering PAN as a possible cause of progressive renal failure, even in patients with nephrotic features, and the potential implications of delayed diagnosis and treatment.



PUB035

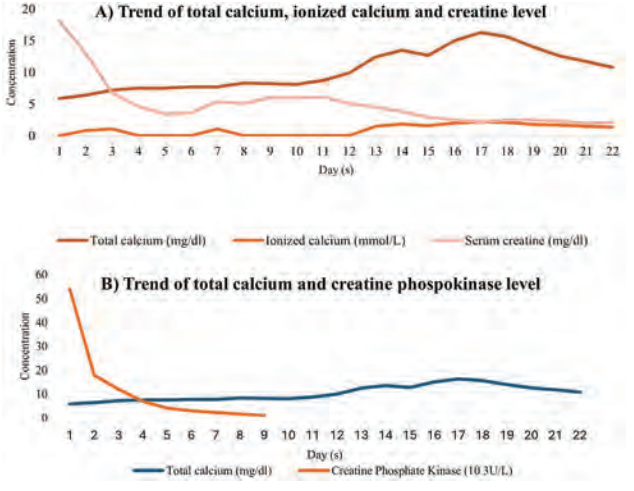
Hypercalcemia in the Recovery Phase of Pigment-Induced Acute Tubular Necrosis

Usha Kumari,[1] Sanjana K. Maheshwari,[2] Syed M. Raza.[1] [1]*The University of Tennessee Health Science Center, Memphis, TN;* [2]*Dow University of Health Sciences, Karachi, Pakistan.*

Introduction: Acute tubular necrosis (ATN) is a common intrinsic cause of renal failure. Common etiologies are severe hypovolemia, nephrotoxins, or sepsis. Rhabdomyolysis or skeletal muscle injury leads to pigment induced ATN. Hypercalcemia has been described in cases of rhabdomyolysis. However, in this case, hypercalcemia occurred well after a decline in creatine phosphokinase (CPK) levels, possibly related to post ATN diuresis and prolonged immobility.

Case Description: We describe a case of a 23-year-old Hispanic male with a history of travel through the desert who presented with abdominal discomfort, myalgias, and respiratory distress. He initially developed an oliguric acute kidney injury due to rhabdomyolysis, followed by recovery by the end of the second week, marked by polyuria. He then developed symptoms of nausea and headaches, besides polyuria. Laboratory values showed increasing total calcium, as shown in figure (A) The trend of serum calcium and CPK levels is shown in figure (B). The vitamin D 25-OH level was low, and the parathyroid gland was appropriately suppressed. The electrocardiogram was unremarkable. Hypercalcemia was initially unresponsive to increasing volume replacement and calcitonin. Patients eventually received pamidronate with a gradual decline in calcium to a normal level. The alkaline phosphate was normal initially and peaked at 145 U/L when calcium started to trend down. Hypercalcemia was presumed to be related to dehydration during the polyuric phase of ATN. On the 22nd day of stay, the polyuria and hypercalcemia had resolved, and the patient was discharged. Lab values were normal on the 2-week follow-up post-hospital discharge.

Discussion: ATN is a very common acute illness in hospitalized patients. This case highlights that life-threatening hypercalcemia can present late with a prolonged course in the setting of acute kidney injury. It is crucial to closely monitor patients with ATN following their discharge.



PUB036

Obstructive Nephropathy Unmasking a Suicide Attempt with Ethylene Glycol Poisoning

Katherine Andrade, Hira Tahir, Henry Yip, Farah Daccueil, Louisette Soussan. *Stony Brook University, Stony Brook, NY.*

Introduction: Ethylene glycol (EG) poisoning is a life-threatening condition that requires early diagnosis to prevent complications and death. This is a patient with obstructive nephropathy from EG poisoning who successfully recovered after fomepizole and renal replacement therapy.

Case Description: 67-year-old male presented with acute encephalopathy. Vitals showed blood pressure 180/74 mmHg, respirations 22, and temperature 35.5 °C. Laboratory included K 5.8 mg/dL, bicarbonate <6 mmol/L, serum creatinine 2.2 mg/dL, BUN 22 mg/dL, lactic acid 12.7 mmol/L, urine toxicology, and ethanol normal. CT head non-revealing and CT abdomen and pelvis bilateral obstructing calculus resulting in hydronephrosis. He was taken for urgent bilateral stent placement by urology and admitted to MICU for urosepsis. Nephrology was consulted for persistent acidosis, acute kidney injury, and electrolyte derangements. Nephrology investigation showed anion gap 35 mmol/L, osmolar gap 100, ethylene glycol level 293 mg/dL, pH 7.1. Formal ethylene glycol toxicity was made, and oxalate monohydrate stones found; He was treated with IV fluids, vasopressors, IV antibiotics, fomepizole, and continuous renal replacement therapy. He fully recovered and was discharged to inpatient psychiatry after confessing suicidal attempt.

Discussion: EG is a dangerous sweet-tasting, colorless, and odorless liquid used as an industrial compound. It causes significant morbidity and mortality if left untreated. More than 5,000 cases of intentional or unintentional toxicity are reported in the United States yearly, affecting mostly adult men. EG is broken down into glycolic acid, oxalic acid, glyoxylic acid, and glycolaldehyde causing kidney injury, central nervous system, and cardiopulmonary compromise. The glycolic acid is known to cause severe high anion gap metabolic acidosis, high osmolar gap, and oxalate precipitation causing kidney injury. In our case, he had acute encephalopathy, severe acidosis, high osmolar gap, and obstructive nephropathy with bilateral oxalate monohydrate stones unmasking an unknown suicide attempt. EG poisoning is challenging to diagnose and manage due to non-specific symptoms, limitations on direct EG quantification methods, and the shortened duration of an elevated osmolar gap in chronic alcohol abusers. High suspicion can prevent irreversible, and life-threatening complications.

PUB037

Postdischarge Follow-Up of Patients with Liver Disease and AKI

Varsha Swamy, Jay L. Koyner, Matthew T. Cerasale. *The University of Chicago Medicine, Chicago, IL.*

Background: Acute Kidney Injury (AKI) in the setting of liver disease is complicated and associated with adverse outcomes, but much of the data is from the Intensive Care Unit. We sought to better understand the outcomes for ward-based patients with cirrhosis and AKI.

Methods: We conducted quality initiative via a retrospective chart review of all patient encounters on the Liver Hospitalist Service from January 1st – June 31st, 2023 with at least 2 serum creatinines (SCr). Baseline SCr function was defined as the mean SCr within 6 months to 1 year prior to admission. Diagnosis and staging of AKI was based on KDIGO SCr-criteria. Diagnosis of liver cirrhosis and of source of AKI was determined via chart review. The outcomes of interest were around incidence and severity of AKI, inpatient nephrology consultation, and post-discharge follow up.

Results: Of 141 admissions, 23 patients had multiple encounters during the study period. The final cohort consisted of 103 patients, 59 (57%) who had cirrhosis, 34 (33%) who had history of liver transplant, 5 (5%) with acute liver injury, and 5 (5%) with other. Of those with cirrhosis, 24 (41%) had AKI on admission or developed AKI during their hospitalization (Table). The etiologies of AKI included: Volume-responsive (11), Hepatorenal Syndrome (6), Acute Tubular Necrosis (1), Sepsis (1), and Multifactorial (5). Nephrology was consulted on 7 patients with AKI, 6 with Stage 3 and 1 patient with Stage 1. Outpatient Nephrology follow up, readmission rates, and other long-term outcomes are in the table. All patients with Nephrology follow up were readmitted within 90-days, but there was more mortality in the No AKI group.

Conclusions: Among ward based (non-ICU) patients with liver dysfunction, patients scheduled for Nephrology follow up were more likely to be readmitted. Future interventions should look to prevent readmissions while ensuring more follow-up for patients with cirrhosis and AKI.

Patients with Cirrhosis with AKI status and post-discharge outcomes

	Length of Stay	90-day Readmission	Liver Transplant within 6 months	Mortality
No AKI (n=35)	7.1 (9.2)	15 (43%)	7 (9%)	2 (6%)
Stage I Follow up (n=1)	4	1 (100%)	0	0
Stage I No follow up (n=9)	6.6 (3.2)	5 (55%)	3 (33%)	0
Stage II Follow up (n=1)	4	1 (100%)	0	0
Stage II No follow up (n=6)	8.8 (5.6)	4 (67%)	1 (17%)	0
Stage III Follow up (n=3)	19 (11)	3 (100%)	0	0
No follow up (n=4)	13 (9)	0	0	0

PUB038

Syphilis-Associated Membranous Nephropathy

Patrick J. Jenkinson,[1] Hafsa K. Tareen,[2] Benjamin R. Wagner.[1] [1]*University of Michigan, Ann Arbor, MI;* [2]*Aga Khan University Hospital Clinical Laboratories, Karachi, Pakistan.*

Introduction: Syphilis, known as "The Great Masquerader," can present with a myriad of systemic manifestations. Renal sequelae have been documented, though rarely. Here, we report a case of biopsy-proven syphilis-associated membranous nephropathy.

Case Description: A 35-year-old man with a history of well-controlled HIV presented with six weeks of fatigue, arthralgias, headache, neck stiffness, lower extremity edema, and a diffuse maculopapular rash – including over the palms and soles. He was ultimately diagnosed with secondary syphilis, complicated by aseptic meningitis, for which IV penicillin G was initiated. Upon presentation, he was found to have new onset nephrotic-range proteinuria with urine protein/creatinine ratio 4.49. Creatinine was normal and at the patient's baseline. Kidney biopsy was performed to investigate his heavy proteinuria. Light microscopy of the glomerular basement membranes revealed pinhole defects on silver stain. Immunofluorescence demonstrated an IgG and C1q dominant

membranous glomerulopathy that was negative for PLA2R. Electron microscopy showed scattered, subendothelial electron dense deposits along with diffuse podocyte foot process effacement. There was no evidence of HIVAN. After a two-week course of penicillin G, the patient achieved complete remission, with urine protein/creatinine ratio 0.28.

Discussion: According to the CDC, the incidence of syphilis is at its highest rate since 1950, and continues to rise. Despite this, renal sequelae of syphilis may be under-recognized due to a lack of awareness among clinicians. Syphilis-associated membranous nephropathy is due to immune complex-mediated podocyte injury. Treponemal antigens – among others – have been identified as causative. Prompt initiation of penicillin G can lead to reversal of kidney injury, including complete resolution of nephrotic-range proteinuria.

PUB039

AKI in a Young Pregnant Woman with Hypertriglyceridemia-Induced Severe Acute Pancreatitis Treated with Urgent Plasma Exchange

Diana Yusim, Jyotsana Thakkar. *UPMC, Pittsburgh, PA.*

Introduction: Acute kidney injury (AKI) is a common complication of severe acute pancreatitis in critically ill patients. It is associated with substantial risk of mortality, especially when kidney replacement therapy (KRT) is needed. We present a case of a pregnant patient who developed AKI secondary to hypertriglyceridemia (HTG) induced severe acute pancreatitis requiring plasma exchange and KRT.

Case Description: A 34-year-old female G1P0 at 34 weeks gestation presented with diffuse abdominal pain. Lipase level was 7,686 U/L and triglyceride level was >10,000 mg/dl. CT abdomen showed severe edematous pancreatitis with extensive intra-abdominal fluid involving the omentum and retroperitoneum with diffuse gastric and bowel wall thickening. She required urgent C-section due to fetal distress. She received insulin drip and one session of plasma exchange with nadir of triglycerides to 514 mg/dl. Her baseline creatinine was 0.7mg/dl, peaked at 4.5 mg/dl, associated with oliguria necessitating CKRT initiation. She was subsequently transitioned to hemodialysis for two weeks followed by complete resolution of acute tubular necrosis and renal recovery.

Discussion: Pancreatitis is a risk factor for AKI. The release of activated pancreatic enzymes and free radicals into the bloodstream in acute pancreatitis triggers an inflammatory cascade that impairs renal perfusion leading to AKI. Patients frequently develop hypovolemia, sepsis, tubular necrosis, and abdominal compartment syndrome. Hypertriglyceridemia has been hypothesized as an independent risk factor for AKI in pancreatitis. One proposed mechanism is accumulation of free fatty acids (FFA) in renal parenchyma induced by breakdown of triglycerides by pancreatic lipase. The FFA accumulation damages renal parenchyma. Our case is unique as our patient had no prior history of hyperlipidemia and presented in the third trimester with severe HTG induced pancreatitis and AKI requiring CKRT and plasmapheresis with recovery of renal function. Management should focus on volume resuscitation, monitoring compartment pressures, and kidney replacement therapy when indicated.

PUB040

Implementing the AKI in Care Transitions Program: A Mixed-Methods Study

Heather P. May,[1] Caroline B. Ledet,[1] Joan M. Griffin,[1] Kianoush Kashani,[1] Andrea G. Kattah,[1] Rozalina G. Mccoy,[2] Andrew D. Rule,[1] Angeliki G. Tinaglia,[1] Erin F. Barreto.[1] ACT Study Group. *[1]Mayo Clinic Minnesota, Rochester, MN; [2]University of Maryland School of Medicine, Baltimore, MD.*

Background: The AKI in Care Transitions (ACT) Program was designed to address barriers to post-AKI care delivery by promoting follow-up with primary care. In a clinical trial comparing ACT to usual care, mixed methods were used to assess the feasibility and acceptability of ACT implementation among health care staff and trial participants.

Methods: The study included health care staff who delivered ACT and trial participants who were adults with stage 3 AKI during hospitalization and discharged home without dialysis needs. Patients randomized to the ACT group received kidney health education before discharge and coordination of post-discharge laboratory and clinician (primary care physician, pharmacist) follow-up within 14 days. ACT implementation was evaluated using surveys and interviews, which were coded to identify themes.

Results: Feasibility and acceptability of ACT were high among all participants (Figure 1). However, qualitative data revealed implementation considerations that could threaten future scale and spread. Scheduling was complex, requiring coordinated efforts from care team members from multiple departments. Clinicians perceived that engaging more frequently with ACT patients improved their comfort level with the workflow and opinions on sustainability and reduced the perceived burden of ACT. Many patients and clinicians felt ACT was more valuable in the presence of chronic kidney disease or incomplete AKI recovery at discharge, relative to other patients.

Conclusions: Primary care-based transitions of care for AKI survivors represents a feasible solution to the gaps identified in post-AKI care. Post-AKI care delivery models are likely to meet implementation challenges related to the diffusivity of AKI across practice settings and patients' and clinicians' knowledge and perceived value of post-AKI care.

Funding: Other NIH Support - Agency for Healthcare Research and Quality (HS028060-01)

Figure 1. Select survey results (n, %)

	Agree	Neutral	Disagree
Feasibility of Intervention Measure			
ACT seems implementable	10 (100)	0	0
ACT seems easy to use	8 (80)	1 (10)	1 (10)
Acceptability of Intervention Measure			
ACT meets my approval	9 (90)	1 (10)	0
I welcome ACT	10 (100)	0	0
Acceptability of ACT to trial participants			
Nurse education was worthwhile	17 (89)	2 (11)	0
PCP/Pharmacist visit was worthwhile	13 (68)	0	1 (10)
I would recommend ACT to others	18 (95)	1 (10)	0

PUB041

Usability Testing of Discharge Summary Template for AKI

Jia Hwei Ng,[1,2] Katherine L. Dauber-Decker,[1] Fatima Malik,[1] Richard L. Amdur,[1] Michael A. Diefenbach.[1] *[1]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.*

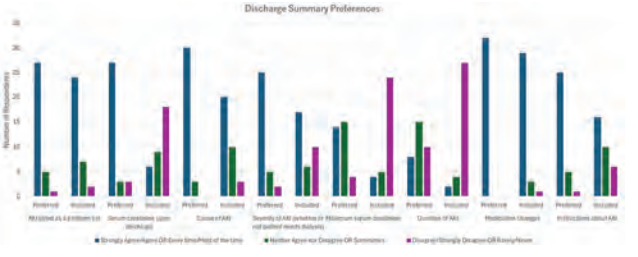
Background: Acute kidney injury (AKI) survivors experience suboptimal transitions post-hospitalization due to inadequate communication between inpatient and outpatient providers. We aimed to design a discharge summary template that improves AKI information sharing in the electronic health record (EHR).

Methods: First, we conducted a preliminary survey among clinicians to guide the AKI content. Second, we designed an EHR mockup of the AKI template and conducted think aloud usability testing, where participants verbalized their though process as they interacted with the mockup.

Results: We surveyed 47 clinicians: 45% worked inpatient, 15% outpatient, and 40% in both. Specialties included 78% internal medicine, 8% nephrology, and 13% others, with roles as 28% resident/fellow, 57% attendings, and 15% nurse practitioners. The median years practicing was 10 (range 3-18). A notable discrepancy existed between the AKI information clinicians wanted and what they typically included in discharge summaries (Figure 1). During usability testing, key themes identified were in categories of content, usefulness, visibility, workflow, and navigation (Figure 2).

Conclusions: Usability testing of the AKI template showed the need for improved content and functionality. Future iterations will incorporate clinician and patient feedback.

Funding: NIDDK Support



Clinician preferences versus actual inclusion of AKI-related information in discharge summaries.

Code Category	Theme	Illustrative Quotes	Planned Changes to the Discharge Summary
Content	The need for more detailed serum Creatinine levels	*I would want the serum creatinine on admission, peak, and discharge*	We will pull the serum creatinine levels from the time of admission, peak, and time of discharge.
	Fluid intake recommendation	*Fluid recs are so individualized. May want to say "as per your doctor's instructions".*	We will remove the standardized recommendation for fluid intake, and allow the recommendation to be individualized.
	The use of plain language makes the content clear to the patient.	*I like the wording. This is more plain English*	We will keep future iterations of the discharge instructions at a 4th grade reading level. We will also perform separate usability testing among patients to test the language of the content.
	The need to add details about dialysis-related information	*If patient is on dialysis... [want to know] if they have dialysis access and when they started it...Small percentage of patients but that kind of information is helpful*	Although the AKI template was originally designed for those with AKI Stage 2 and AKI 3 who do not require dialysis, the providers noted that they do not want multiple versions of an AKI template. Thus, we will include a section related to dialysis in the next iteration.
	The need for the AKI instruction template to be congruent with the overall message to prevent conflicting information	*It has to be congruent with overall message and instructions. Especially, if it's filled out by different providers- they should look at overall message and avoid conflicting messages.*	We will remove specific fluid and dietary recommendation from the standardized template.
Usefulness	The presence of an AKI template is deemed as useful for both the provider and the patient.	*It would make my life easier but also better equipped to take care of patients post discharge*	N/A
Visibility	Some information needs to be placed at certain locations for better visibility.	*Cause of AKI should be on top of screen*	We will place the "Cause of AKI" text box at the top of the screen.
Workflow	Pre-populated information makes the workflow smooth.	*I like the fact you can click through the buttons, and it can generate the text for you. It's standardized and pulls the numbers for you.*	N/A
	Redundancy of work	*It's potentially redundant- at least some sections in it and will probably make the provider of the discharge summary spend more time filling it out*	We will remove sections in the AKI template that are already in the general discharge instruction section.
Navigation	The purpose of the checkboxes was unclear.	*So, by clicking these checkboxes this is going to populate the education and care plan?*	We will add instructions to explain that the checkboxes should be used to provide patient-facing information and discharge instructions.

Usability feedback on the AKI discharge summary template, showing thematic categories, illustrative quotes, and subsequent planned changes to enhance the template.

PUB042

Dengue Virus-Induced Acute Interstitial Nephritis

Nolan Interial, Aanusha Ghouri, Eman Alshaikh, Ali I. Gardezi. *University of Wiscosnin School of Medicine and Public Health, Madison, WI.*

Introduction: Acute Interstitial Nephritis (AIN) is a common cause of acute kidney injury, manifests as inflammation within the kidney's interstitial tissue. While AIN is often attributed to medications, infections can also be causal factors. This case presents a rare instance of AIN induced by Dengue fever.

Case Description: A 57-year-old male with history of hypertension and hyperlipidemia presented with myalgias and dark urine after recent travel to Europe and Africa. Home medications were Amlodipine, Atorvastatin and Sildenafil. Vital signs were unremarkable. Blood work revealed creatinine (Cr) 2.93 mg/dL (baseline 1.2 since 2022), BUN 33 mg/dL, potassium 5.3 mmol/L, bicarbonate 18 mmol/L, phosphorus 6.9 mg/dL, creatine kinase (CK) 1,088,400 U/L, ALT 608 U/L and AST 3,494 U/L. Urinalysis showed brown urine, 3+ blood and 2+ protein but no RBCs. Imaging studies were unremarkable. Upon holding Atorvastatin and administering fluids, CK level gradually improved. Autoimmune and infectious work up revealed positive Dengue virus IgM and IgG. The rest of the work up was negative. Creatinine levels peaked at 4.0 mg/dl on hospital day 3, subsequently decreased to 3.5 mg/dl. However, over the following 9 days, there was no further improvement, which prompted a kidney biopsy revealing AIN with mild to moderate acute tubular necrosis (ATN). The patient was discharged on Prednisone taper for two weeks. Two weeks post-discharge, creatinine levels decreased to 2.4 mg/dl.

Discussion: AIN is an immune-mediated syndrome characterized by the presence of inflammatory cell infiltration in glomerular interstitial space. This histological finding can be elicited by several mechanisms, while commonly triggered by medication allergies, systemic infections, including viral ones like CMV, EBV, HBV, and HIV, can also induce AIN. Limited literature exists regarding the histological etiology of kidney injury in Dengue fever. There have been reports of ATN secondary to severe rhabdomyolysis in dengue fever but there has not been any reported case of AIN. Even though amlodipine has been reported to cause interstitial nephritis, the patient had been taking it for more than a year before the presentation, without any worsening of his renal functions.

PUB043

Postacute AKI Follow-Up Reduces 30-Day Readmission Rate

Desiree Mytych, Christina M. Cruz, Jeffrey S. Stoff, Kenneth M. Ralto. *UMass Memorial Medical Center, Worcester, MA.*

Background: Acute kidney injury (AKI) is a frequent hospital complication which is associated with high rates of rehospitalization, mortality, and increased healthcare cost (estimated at $9,230* per readmission after AKI). Furthermore, guideline-directed medical therapies and diuretics are often stopped or reduced during an episode of AKI which has been shown to worsen patient outcomes. We developed an AKI follow-up clinic to provide post-acute care to this vulnerable population which historically has received little nephrology care after discharge.

Methods: Education regarding the AKI follow-up clinic was provided to the hospital medicine providers, and referrals were made via the electronic medical record approximately 24-48 hours prior to discharge. Patients were scheduled within 7-21 days of discharge, depending on their clinical status and anticipated needs. The focus for this clinic was to assess the degree of renal recovery after AKI, coordinate ongoing nephrology care if indicated, and reinitiate nephroprotective medications and diuretics as appropriate.

Results: The 30-day readmission rate for patients with AKI was reduced from a historical average of 19.4% to 10.0% in those patients who attended the AKI follow-up clinic. Over 99% of AKI clinic patients underwent a clinic intervention, including diagnostic testing and/or medication changes. We identified a sub-group of AKI survivors who were particularly high-risk for readmission: patients who were over 65 years-old and had either congestive heart failure or cirrhosis.

Conclusions: Providing prompt subspecialty follow-up care for AKI survivors reduced the risk of 30-day readmission in this population. The AKI clinic provided an opportunity to resume diuretics and guideline-directed medical therapy in a timely manner.

PUB044

Semaglutide-Induced Severe AKI Requiring Hemodialysis

Boris Livitz, Jagraj Singh, Lia Sepanek, Elnaz Mahbub, Frances E. Mccarthy, Louis R. Spiegel. *Stony Brook Southampton Hospital, Southampton, NY.*

Introduction: Glucagon-like peptide-1 (GLP-1) receptor agonists, notable for their cardio and nephroprotective effects, are growing in popularity for the management of type 2 diabetes and obesity. We present a rare case of a patient with normal baseline renal function who developed severe acute kidney injury (AKI) with uremia requiring emergent dialysis shortly after starting semaglutide.

Case Description: A 61-year-old female with type 2 diabetes, hypertension, and hyperlipidemia presents with a four week history of nausea, vomiting, diarrhea, and poor oral intake. Patient began semaglutide three months prior; other medications were unchanged. She has no known kidney disease. On arrival, she was lethargic and tremulous, but hemodynamically stable. Initial labs notable for sodium 129 mmol/L, potassium 2.9 mmol/L, bicarbonate 13 mmol/L, chloride 82 mmol/L, BUN 135 mg dL, creatinine 14.2 mg/dL, eGFR 3 mL/min/1.73m^2, magnesium 0.6 mmol/L, uric acid 26.8 mg/dL, and positive serum ketones. Imaging showed no acute pathology. Nephrology was consulted, recommending emergent hemodialysis (HD) and ICU admission. She was started on IV fluids, electrolyte repletion, and rasburicase. Nephrotoxic medications were held and she received DDAVP for bleeding at an IV site. After HD, labs trended towards optimal levels. Once improved she was transferred to the general floor and later discharged with nephrology follow-up.

Discussion: GLP-1 receptor agonists enhance insulin secretion, reduce glucagon levels, and slow gastric emptying. Originally developed for diabetes, some have been recently approved for obesity. With the rise in use, closer examination of adverse effects is needed. While gastrointestinal effects are common, AKI remains rare, typically linked to dehydration. A post hoc analysis of the STEP 1, 2, and 3 trials revealed that semaglutide did not worsen renal outcomes regardless of patients' baseline renal function.[1] A meta-analysis of FDA data indicated liraglutide had the highest risk of AKI, followed by semaglutide.[2] Our patient developed AKI with uremia without existing renal disease. Extensive workup ruled out other causes such as immunologic, obstruction, etc., suggesting the presentation was due to semaglutide.

PUB045

Renal Oxalosis from Excess Dietary Intake: A Guide to Improve Kidney Function

Muhammed Khalfan, Hong Yang, Yinelka G. Silverio De Castro, Jerin Karingattil, James Drakakis. *NYU Langone Hospital - Long Island, Mineola, NY.*

Introduction: Hyperoxaluria may be due to hereditary defects of key enzymes of oxalate metabolism or from excess intake or increased enteric absorption. High dietary intake is related to ingestion of vitamin C, spinach, rhubarb, or beets. Acute kidney injury (AKI) is due to calcium oxalate crystals desposited within tubules causing acute tubular injury. Renal recovery is possible with correction of the underlying cause. However, the insult may also be severe enough to require dialysis and can even lead to end stage renal disease. We present a case of oxalate nephropathy (intake related) whereby kidney function improved significantly with strict dietary oxalate restriction.

Case Description: 69 year old female with no past history was found with serum creatinine 2.4 mg/dL. Baseline one year prior 0.9 mg/dL. UA without blood or RBC and urine protein quantification 144 mg/g. Renal ultrasound with increased echogenicity and non obstructing kidney stones. Kidney biopsy showed acute tubular injury with multifocal tubular oxalate crystal deposition (renal oxalosis); 30% tubular atrophy and interstitial fibrosis. This was not primary oxalosis related to inherited enzyme defect (genetic testing negative). Nor prior surgeries or predisposing conditions to suggest enteric form. History was elucidated that she was on a diet rich in oxalate. With very tight restriction of 50-100 mg oxalate per day (ingesting foods <5 mg oxalate per serving), creatinine improved to 1.26 mg/dL (10 months after initial diagnosis).

Discussion: The prognosis of acute oxalate nephropathy is variable, with insult severe enough to warrant renal replacement in at least one half of paitents. Treatment depends on underlying cause but generally includes hydration, oral calcium supplementation, correction of hyperoxalauria causing conditions and as in our case, low oxalate diet. Literature review reveals most patients do not make a complete recovery in terms of renal function. Our patient bolstered her urine output to upward of 3 liters per day, and lowered oxalate intake to <100 mg per day. Serum creatinine improved in less than 1 year from diagnnosis to 1.26 from 2.4 mg/dL. This cause illustrates the importance of dietary modification in renal oxalosis from excess intake and the potential for significant renal recovery, otherwise described as being unlikely.

PUB046

Lacosamide-Induced Thrombotic Microangiopathy

Khaled Al-Baqain, Said Sharawi, Zeid Khitan. *Marshall University, Huntington, WV.*

Introduction: Drug-induced thrombotic microangiopathy is a life-threatening condition that is characterized by anemia, thrombocytopenia, and acute kidney failure without ADAMTS13 deficiency. Many drugs have been identified to cause TMA including quinine, antimicrobials, and cancer therapies. In this case we will describe a rare case of lacosamide induced TMA

Case Description: An 84-year-old female who presented to the hospital with intracranial hemorrhage. She then underwent craniotomy and was intubated for seizure. The patient was then started on lacosamide and valproic acid for her seizures. On admission hemoglobin was 13 and platelets were 250. 6 days into her admission, schistocytes started appearing on automated differential. Also, her hemoglobin dropped to 7.5 and platelets count gradually dropped until they reached a nadir of 54. Peripheral smear showed schistocytes, D-Dimer was positive, RPI was low, LDH was mildly elevated, but she had normal pt/INR, fibrinogen. Creatinine increased from 0.7 to 1.4 and the patient remained non oliguric. Nephrology team was consulted for AKI and MAHA. ADAMTS13 level was collected, lacosamide was held and valproic acid was continued. The patient was started on 60 IV methyl prednisone every eight hours. She also received 2 units of fresh frozen plasma. Three sessions of plasma exchange were performed. ADAMTs 13 came back at 50% making the diagnosis of drug induced thrombotic microangiopathy (DITMA) more likely. Patient platelets improved back to baseline. She was then stable and was discharged home.

Discussion: The patient in this case started having signs of TMA 6 days after starting lacosamide, which improved after discontinuation of the medication. ADAMTS13 of 50% differentiated between drug induced TMA and TTP. DITMA can sometimes be challenging to diagnose, especially in the ICU setting. Although literature on lacosamide induced TMA is scarce, this case sheds the importance of keeping TMA as a differential in the setting of new onset thrombocytopenia and anemia after starting new medications.

PUB047

A Long Road to Diagnosis: A Case with Unexpected Twists

Klement Yeung, Tushar S. Malavade. *University of Toronto, Toronto, ON, Canada.*

Introduction: It is often thought that cases of obstructive acute kidney injury (AKI) are straightforward to diagnose and manage. The following case report explores how experienced physicians navigated an unusual case and the convoluted path taken to arrive at the eventual diagnosis.

Case Description: A 74 year-old previously healthy male presented to the hospital with syncope in the context of six weeks of nausea, vomiting, anorexia and one year of nocturia. Labwork showed potassium of 8.1mmol/L and creatinine (Cr) of 14.97mg/dL (baseline of 1.07mg/dL). EKG showed peaked T-waves. After management of hyperkalemia, significant arrhythmias persisted so dialysis was initiated. A renal ultrasound showed bilateral hydronephrosis and ascites. Presuming prostactomegaly as the case of the obstruction, a foley catheter was placed and drained 445mL of urine, but he became oligoanuric. Urine microscopy showed one heme-granular cast. Urine albumin to creatinine ratio was 101mg/g. A serologic work-up was negative and kidney biopsy was consistent with acute tubular necrosis (ATN). However, a repeat ultrasound showed no improvement in bilateral hydronephrosis and ascites. A paracentesis revealed malignant cells on cytology. Discussions were held regarding pursuing a contrast-enhanced CT for work-up of malignancy. However, in the context of severe AKI, a shared decision was made to delay the CT as it can impede renal recovery. Serum tumor markers revealed elevated Ca19-9, CA125, and CEA. A colonoscopy showed two colonic masses. We obtained a contrast-enhanced CT as we felt the potential information we would gain outweighed the risks, which showed metastatic malignancy with retroperitoneal masses causing bilateral ureteric obstruction and hydronephrosis. Nephrostomy tubes were inserted and the patient experienced significant renal recovery. He was discharged with a Cr of 1.4 mg/dL (eGFR of 53mL/min/1.73m2).

Discussion: From this case, we learned it is imperative to re-evaluate initial assumptions when an element of the case is unusual, such as why he became oligoanuric after a foley was placed if the obstruction was relieved and why he had new-onset ascites. Persistent anomalies prompted additional studies, which led to the uncovering of the previously unknown metastatic malignancy, the true cause of the patient's AKI. This case highlighted the dangers of early diagnostic closure and the importance of thorough investigation.

PUB048

HIV-Associated Immune Complex Kidney Disease in a Patient with Normal Complement Levels

Kaitlin Markoja, Karishma Iyer, Lukman Cheraghvandi, Donghyang Kwon, Negiin Pourafshar. *MedStar Georgetown University Hospital, Washington, DC.*

Introduction: HIV infection is frequently complicated by renal dysfunction. There is a variety of renal pathology associated with HIV.

Case Description: A 35-year-old male with a medical history including HIV (CD4 257 cells/mm^3, viral load 36 copies/mL) not on antiretroviral therapy (ART) and schizophrenia presented with shortness of breath. He was treated for community acquired pneumonia at another facility three months prior, where his serum creatinine (SCr) was 4.5-5 mg/dL. At our institution, he was afebrile, not hypoxic, and hypertensive with systolic blood pressure 160-180 mmHg. Laboratory results showed elevated blood urea nitrogen at 84 mg/dL and SCr at 10.76 mg/dL. Urinalysis had moderate proteinuria and 5 red blood cells per high-power field, with a urine protein to creatinine ratio of 2.0 g/g. CT of the chest, abdomen, and pelvis revealed dense left lower lobe pneumonia, and blood cultures later confirmed Streptococcus pneumoniae infection. He was treated with ceftriaxone, yet SCr remained elevated. Serologic investigation was unremarkable. Renal biopsy revealed interstitial edema with a lymphoplasmacytic infiltrate with occasional eosinophils in the interstitium. Tubules showed epithelial flattening and cellular debris, tubular loss, interstitial fibrosis, and vascular wall thickening. Immunofluorescence revealed 1+ IgG granular positivity, while electron microscopy detected occasional immune-complex deposits in the mesangium, accompanied by mesangial matrix expansion, concerning for HIV-associated immune complex kidney disease (HIVICK). With blood pressure reduction and treatment for infection, SCr decreased to 6 mg/dL. SCr remained stable two months later and after ART initiation.

Discussion: HIVICK involves immune complex deposition, which can occur in situ or via secondary deposition. Proposed viral antigens include p24 and gp120. Previous studies suggest that HIVICK is more prevalent in patients with higher viral loads, hepatitis co-infection, and low complement levels. However, our patient had low HIV viremia, no hepatitis, and normal complement levels. Renal biopsy is crucial to discern HIV-associated renal pathologies accurately. Treatment strategies for HIVICK warrant further exploration, particularly considering the overall higher risk for immunosuppression in this population and each patient's unique clinical profile.

PUB049

A PerPLEXing Case of Refractory Thrombotic Thrombocytopenic Purpura

Katharine Goebel, Barbara Garay Nontol, Ibrahim Mohsin, Srimathi Manickaratnam. *University of Connecticut, Farmington, CT.*

Introduction: Thrombotic thrombocytopenic purpura (TTP) typically presents with thrombocytopenia, microangiopathic hemolytic anemia, and renal dysfunction. Fever, fatigue and other neurological symptoms can be associated with it. Plasmapheresis (PLEX), often combined with corticosteroids, is the gold standard treatment for TTP. Recent trials have shown that caplacizumab improves platelet levels and reduces mortality, exacerbations, hospital stays and PLEX procedures. We present a unique case of refractory TTP complicated by FFP-induced anaphylaxis managed successfully with caplacizumab and PLEX.

Case Description: A 35-year-old female presented with petechiae, dark urine, and bruising for 3 days. Initial workup revealed platelets of 9000, Hgb 11.2 g/dL, creatinine 1.6 mg/dL (baseline 0.6 mg/dL), hematuria on urinalysis, and positive hemolysis labs, indicative of TTP. Treatment included steroids and daily PLEX with FFP. However, during the fifth PLEX session, she developed anaphylaxis, requiring intubation. PLEX was resumed the next day due to worsening thrombocytopenia and creatinine levels. She underwent 19 PLEX sessions, escalated to twice daily for five days. Caplacizumab was administered from day 9 for 17 days. Additionally, she received one dose of bortezomib while awaiting caplacizumab. Her clinical course was complicated by multiple thromboembolic events, necessitating anticoagulation therapy. Due to bleeding risks, caplacizumab was discontinued. She was discharged home with a low dose of steroid taper with normal platelet count and renal functions.

Discussion: TTP is a life-threatening hematologic disorder with high mortality if untreated. Standard treatment involves PLEX with FFP due to bleeding risk. Body weight influences the FFP volumes used in PLEX. High volume and multiple treatments increase FFP-related anaphylaxis risk, as seen in our case. Despite anaphylaxis, PLEX with FFP was resumed. Caplacizumab, later administered, significantly improved platelet count and reduced PLEX sessions, decreasing FFP usage. Despite challenges, favorable outcomes with caplacizumab mirror trial results, affirming its efficacy. Early caplacizumab initiation may expedite platelet count recovery and decrease PLEX sessions, mitigating FFP-related risks.

PUB050

Spontaneous Tumor Hemorrhage: A Case of AKI

Ramandeep Kaur,[1] Thomas S. Truglio,[2] Brian D. Remillard,[2] Clay A. Block.[2] *[1]Dartmouth Health, Lebanon, NH; [2]Dartmouth Hitchcock Medical Center, Lebanon, NH.*

Introduction: We present a case of spontaneous hemorrhage in a yolk sac tumor resulting in hemorrhagic ascites causing intra-abdominal hypertension, hydronephrosis and acute kidney injury (AKI).

Case Description: A 22-year-old man with previous medical history of asthma presented with abdominal distention and loss of appetite for 3 weeks. The serum creatinine (SCr) at presentation was 0.8 mg/dL (reference range 0.8-1.5 mg/dL) and hemoglobin (Hgb) 7.8 g/dL (reference range - 13.7 -16.5 g/dL). Computed tomographic (CT) imaging demonstrated multiple lesions in the liver, omental and paralumbar masses, a retroperitoneal (RP) hematoma and ascites. Alpha fetoprotein was 18,158 ng/mL (reference range - < 8.3 ng/mL). Biopsy of a liver lesion identified non-seminomatous yolk sac tumor. Chemotherapy with bleomycin, etoposide and cisplatin was initiated, but abdominal distention progressed. By day 5, Hgb had fallen to 5.7 g/dL. SCr rose to 2.4 mg/dL. The worsening ascites was refractory to diuretics. Tumor lysis syndrome was excluded on the basis of normal uric acid and potassium. Ultrasound-guided paracentesis demonstrated intraabdominal hypertension (IAH) with direct pressure measurement of 20 mmHg; mild right-sided hydronephrosis was also observed. The hematocrit of the ascitic fluid was 26.8% suggesting hemorrhagic ascites. CT angiography and the tagged red blood cell scintigraphy failed to identify an actively bleeding vessel. Tumor neovascularity in the large omental and paralumbar mass fed by the right and left gastroepiploic arteries and lumbar arteries without an active extravasation was noted. IAH was resolved with recurrent large volume paracentesis leading to normalization of kidney function. Multiple red blood cell transfusions stabilized the hemoglobin.

Discussion: Spontaneous hemorrhage in yolk sac tumor as a cause of hemorrhagic ascites resulting in IAH and AKI is not well studied, but incidence of 15% in hepatocellular carcinoma has been reported. The etiology likely involves rapid tumor growth and spontaneous and/or chemotherapy related necrosis. Our patient had bleeding prior to the presentation since he came with RP hematoma; suggesting spontaneous necrosis had occurred. IAH results in high renal vein and parenchymal pressure, thereby reducing renal perfusion pressure. Ascites, particularly with IAH, can cause hydronephrosis and AKI.

PUB051

AKI Compared between Critically Ill Patients with Cirrhosis, Neoplasm, and Heart Failure

Kelly Silva,[1] Maria E. Juliao,[2] Stephanie E. Leoni,[2] Ana C. Marchesini,[2] Carolina S. Garcia,[3] Cecília Amaral Peixoto Rabelo,[2] Victor Arthur Ohannesian,[2,1] Miguel Angelo Goes.[2,3] *[1]Sociedade Beneficente Israelita Brasileira Albert Einstein, Sao Paulo, Brazil; [2]Faculdade Israelita Ciências de Saúde Albert Einstein, São Paulo, Brazil; [3]Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil.*

Background: Acute kidney injury (AKI) might occur in critically ill patients in the ICU with cirrhosis (Cirrh), neoplasms (Neopl), and heart failure (HF). Thus, we studied and evaluated the frequency of AKI in these three conditions, and we also compared a subset of patients with AKI and without AKI in the HF group.

Methods: Our study, a retrospective analysis, meticulously examined 76 patients in the HF group, 27 in the Cirrh group, and 56 in the Neopl group admitted to the ICU. We compared demographic and clinical data, AKI development, and the need for kidney replacement therapy (KRT), mechanical ventilation, inotropes, and vasoactive drugs. Subsequently, we compared the subgroups with and without AKI from the HF group. Multivariate analysis was also performed, ensuring the robustness of our findings.

Results: The Cirrh group had higher total bilirubin levels and lower platelets. The HF group had higher serum urea and creatinine levels and a higher CKD frequency on admission. There also were higher inotrope requirements, development of AKI, and the need for KRT within 28 days of hospitalization. The subgroup of patients with HF and AKI had lower mean arterial pressure (MAP) and ejection fraction (34.6±2.1%, 51.8±2.2%; p<0.001) at hospital admission. While MAP, serum urea levels (OR 1.036; CI, 95% 1.006-1.067; p=0.02), and ejection fraction at hospital admission had an independent association with AKI in the HF group.

Conclusions: Our study's findings underscore the significant frequency of AKI in patients with HF. Moreover, we discovered that ejection fraction, MAP, and urea levels on admission were independently associated with AKI in critically ill patients with HF. These insights are crucial for understanding and managing AKI in this patient population.

PUB052

Light at the End of the Tunnel: A Case of Eculizumab in Gemcitabine-Induced Thrombotic Microangiopathy

Katherine Andrade, Hira Tahir, Henry Yip, Fatima D. Sheikh, Randolph A. Hennigar. *Stony Brook University, Stony Brook, NY.*

Introduction: Gemcitabine-induced thrombotic microangiopathy (G-TMA) is a rare life-threatening condition that is underrecognized, underdiagnosed, and underreported. We report a case of a patient with the classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and kidney failure due to G-TMA treated with Eculizumab.

Case Description: 50-year-old female with metastatic Mullerian adenocarcinoma on Gemcitabine presented with shortness of breath and leg edema. Vitals included a blood pressure 170/78 mmHg, temperature 37.2°C, respiration 18, and heart rate 96 bpm. Labs were significant for serum creatinine (Scr) 1.9 mg/dL on initial presentation which peaked at 4.3 mg/dL, BUN 53 mg/dL, K 5.9 mmol/L, hemoglobin 7.7 g/dL, platelets 82 K/uL, LDH 514 IU/L, haptoglobin 17 mg/dL, reticulocyte count 4% and urinalysis with small blood and protein 100+. Full paraproteinemia and glomerulonephritis workup was non-revealing, and ADAMTS13 was 89% ruling out thrombotic thrombocytopenic purpura. Although Gemcitabine was discontinued, the acute kidney injury, anemia, and thrombocytopenia continued to worsen. A kidney biopsy confirmed TMA likely due to Gemcitabine therapy which prompted initiation of weekly Eculizumab. She had renal recovery with improved Scr to 2.8mg/dL, hemoglobin to 9.4 g/dL, and platelets to 334 K/uL.

Discussion: TMA is classified as primary or secondary. Secondary causes can be due to infection, autoimmune disorder, cancer, or drugs like Gemcitabine. Adverse effects include edema, new onset/exacerbated hypertension, thrombocytopenia, and TMA. The first case of G-TMA was reported in 1994 and its incidence is estimated between 0.02% and 2.2%. It is associated with increased mortality up to 60% and renal injury resulting in end-stage kidney disease. The mechanism is unknown and limited data is available regarding optimal management. Treatment options can include plasma exchange and Eculizumab- a monoclonal anti-C5 antibody that inhibits complement indicated in treating atypical hemolytic uremic syndrome. In our case, she was treated with Eculizumab for G-TMA with partial renal recovery. G-TMA is a challenging diagnosis with unknown recurrence rates and high morbidity-mortality rates in need of therapy guidelines for better outcomes.

PUB053

Severe Rhabdomyolysis-Induced AKI Requiring Hemodialysis in an Adolescent with Influenza A

Sura Alsaffar, Anil K. Mongia. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Viral infections like Influenza A and Covid -19 related infection can cause rhabdomyolysis and subsequent AKI. Most of these AKI resolve with conservative management. We here in report an adoloscent with Influenza A with severe rhabdomyolysis induced AKI requiring hemodilaysis.

Case Description: A 15-year-old male presented with a history of fever, cough, running nose, headache, phonophobia, sore throat, dysphonia, and decreased appetite. He had no known history of liver, kidney, or muscle disorders. He denied any recent history of trauma, immobility (travel, surgery), seizures, new medications, or drug abuse. Physical examination revealed bilateral thigh tenderness and abnormal gait. Laboratory tests were positive for Influenza A, elevated AST/ ALT and elevated BUN/creatinine. Aggressive intravenous fluid resuscitation was initiated. His creatine kinase (CK) levels (>900,000 U/L) started to rise rapidly along with worsening urine output and renal funnction. He developed complete anuria on Day 5 requiring hemodialysis which was done daily initially and then switched to every other day. The patient's urine output and renal function started to improve around Day 8. His CK levels decreased, and urine output returned to normal. Renal function upon discharge showed a creatinine level of 1.6 mg/dL, which further improved to 0.8 mg/dL on subsequent follow up.

Discussion: Monitoring musculoskeletal and renal involvement is important when treating patients with severe acute influenza infection. This case highlights the critical nature of rhabdomyolysis induced acute kidney injury post influenza A infection which in some cases may need renal replacement therapy like hemodialysis.

lab results

Day of hospitalization	Serum creatinine	Blood urea nitrogen	creatine phosphokinase	Aspartate aminotransferase/Alanine transaminase
2	4.8	42	941531	3693/891
6	5.5	38	118380	2003/460
15	8.1	89	6636	147/141
21	4.5	69	1397	66/114

PUB054

Masquerading IgG4 Disease or a Disease Caught in Evolution

Sobia N. Khan,[1] Monica P. Revelo Penafiel.[2] *[1]Stony Brook University, Stony Brook, NY; [2]University of Utah Health, Salt Lake City, UT.*

Introduction: IgG4-related disease (IgG4-RD), a systemic disease characterized by IgG4-positive plasma cells, storiform fibrosis, and tissue eosinophilia. We present a unique case of IgG4 disease which initially has acute interstitial nephritis on kidney biopsy.

Case Description: 64-year-old male with hypertension presented for acute kidney injury. Vitals stable, takes bisoprolol-HCTZ daily. Na 129, K 3.2, BUN 41, SCr 3.2, +ANA, C3/C4 normal. Last known creatinine ~0.9. History revealed has completed Bactrim DS, 2 weeks ago, NSAIDs in past 2 months. Urinalysis: no hematuria, urine-protein to creatinine ratio ~500. SPEP/UPEP with M-spike. Immunofixation with IgG kappa monoclonal antibody. Bone marrow biopsy: 10-15% CD138 positive plasma cells, diagnosed with smoldering multiple myeloma. Native kidney biopsy revealed acute interstitial nephritis with mild interstitial fibrosis and tubular atrophy, diagnosis of acute interstitial nephritis was made with co-trimoxazole or NSAIDs being possible drug culprits. He was treated with Prednisone, acute kidney injury improved but developed residual chronic kidney disease with creatinine of 1.74. MM labs remained stable with no treatment planned. Eight months later, readmitted with AKI and weight loss, repeat kidney biopsy: acute tubular damage, mixed interstitial inflammatory infiltrate with IgG4 positive plasma cell and obliterative arteriopathy consistent with IgG 4 mediated interstitial nephritis. Immunohistochemical stains for IgG4: aggregates of >10 IgG4 positive plasma cells. Serum Immunoglobulin: IgA 148, IgM 35, IgE 110, IgG 2530, normal complement level. CT/MRI of spine, lumbar region, and pelvis negative for cancer. Treated with prednisone and Rituximab.

Discussion: IgG4-RD, a fibroid inflammatory disorder. Pathogenesis unclear, thought to involve a persistent antigenic stimulus possibly from chronic infection triggering polyclonal expansion of B cells. These signals promote IgG 4 class switching, plasma cell expansion and local fibrotic response. Our case is atypical as the general manifestations of IgG4-RD include lymphadenopathy and weight loss. Weight loss is a prominent symptom in patients with exocrine pancreatic insufficiency, but our patient only had kidney involvement. This case highlights the importance of including IgG4 disease in the differential diagnosis of acute kidney injury.

PUB055

Oliguria in Leptospirosis-Associated AKI Is Associated with Worse Outcomes: A Study Based on Novel Prognostic Score System

Renan G. Diniz,[1,2] Luiz P. Neto,[2] Raoni d. Domingues da Silva,[2] Leticia M. De Araujo,[2] Gdayllon C. Meneses,[2] Gabriela Galdino,[2] Geraldo B. Silva Junior,[3] Alice C. Martins,[2] Elizabeth D. Daher.[2] *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Universidade Federal do Ceara, Fortaleza, Brazil; [3]Universidade de Fortaleza, Fortaleza, Brazil.*

Background: Leptospirosis (LPT) is a neglected tropical zoonosis, with high incidence in some regions of the world. Its severe forms manifest with acute kidney injury (AKI) and lung hemorrhage, associated with systemic inflammatory response and high mortality rates. Prognostic scores and early identification of AKI and endothelial biomarkers have been the subject of recent studies. This study aimed to evaluate the association between oliguric and non-oliguric LPT with clinical scores and endothelial and AKI biomarkers.

Methods: This prospective study incçuded patients with LPT admitted in three hospitals in Brazil. Patients were divided into two groups: those with oliguria (O), and without oliguria (NO). Clinical data, blood, and urine samples were obtained and clinical scores applied. A specific prognostic score system for leptospirosis prognosis was used (QUICK-LEPTO - a new validated score that involves age, lethargy, tachypnea, blood pressure and hematocrit), as well as SOFA (sequential organ failure assessment) score.

Results: Among the total of 44 patients, 81.8% were male. Average age was 40.8 years. Creatinine level was 3.9mg/dL in O vs 2.1mg/dL in NO (p=0.2). Mortality rate was 18% in O and 6.1% in NO (p=0.3). Hemoptysis was more prevalent in O (27% vs. 3%; p-0.043). The QUICK-LEPTO score was worse in O patients (median score 3 vs. 2; p=0.03), while the QUICK-SOFA surprisingly showed no significant difference between the groups. Biomarkers V-CAM, I-CAM, FGF23, Ang1, MCP-1 did not differ significantly between the groups. Syndecan, was higher in O group (774 ± 424 ng/mL vs. 419 ± 380 ng/mL, p = 0.037). NGAL was higher in QLEPTO scores 2 to 6 in O group (472±21 vs. 370±93; p=0,03).

Conclusions: This study indicates that oliguric LPT patients had more hemoptysis and worse results in QLEPTO, despite no differences in QSOFA. QLEPTO is emerging as a new valuable score also for association with some organ injury biomarkers. Further studies with larger samples can help to elucidate more valuable parameters and biomarkers associated with oliguric AKI in LPT aiming to identify early cases with poor prognosis, aiding the early introduction of clinical management.

PUB056

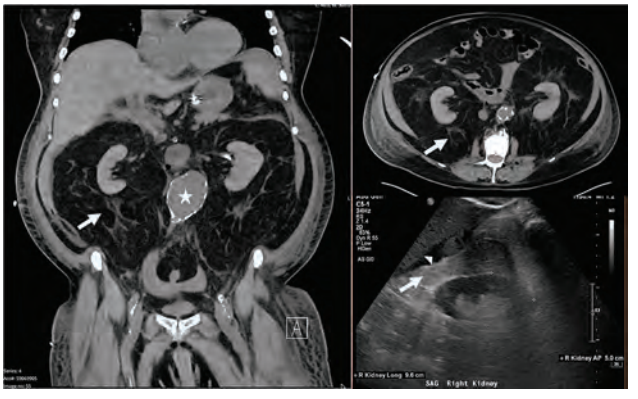
Incidental Finding of Retroperitoneal Lipomatosis

Kristen N. Tillquist,[1] Nadia Al Haddad,[1] Abhilash Koratala,[2] Nathaniel Reisinger.[1] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Knowledge of imaging findings is key to the appropriate diagnosis and treatment of AKI. Here we present a rare incidental finding.

Case Description: A 70-year-old man with hypertension and diabetes presented with complaints of abdominal pain found to be in septic shock due to ascending cholangitis with mixed bacteremia. He was treated with fluids, antibiotics, and percutaneous cholecystostomy with course complicated by acute dyspnea due to pulmonary edema and pulseless cardiac arrest further complicated by AKI for which we were consulted. Exam revealed increased work of breathing and abdominal distention. Urine sediment examination revealed pigmented granular casts. Serum creatinine was 3.33 mg/dL rising from a baseline of 1.03. Echocardiography revealed severe biventricular failure. Right heart catheterization showed right atrial pressure of 8 mmHg with pulmonary capillary wedge pressure of 8 mmHg. Imaging findings in caption.

Discussion: Retroperitoneal liposmatosis is a rare diagnosis consisting of symmetric lipomatous hyperplasia of perinephric adipose tissue. Presentation is usually asymptomatic and incidental, found on imaging obtained for other indications as in our case. Pathology has been described with symptomatic abdominal distention and rarely urinary obstruction. On CT, this appears as marbling of hypoattenuating and hyperattenuating tissue in the retroperitoneal space surrounding the kidneys. On ultrasound, this entity appears as hyperechoic tissue in the hepatorenal and splenorenal recess which can easily be mistaken for hemorrhage. We also considered retroperitoneal fibrosis leading to obstruction without hydronephrosis, but the CT showed fat characteristics that did not affect the collecting system area and urine sediment findings were consistent with ATN.



Left: coronal CT with retroperitoneal lipomatosis (arrow), aortic aneurysm (star)
Right top: transverese CT with retroperitoneal lipomatosis (arrow)
Right lower: sagittal ultrasound with retroperitoneal lipomatosis (arrow), liver subcapsular hematoma (arrowhead)

PUB057

Improving Outcomes for Kidney Patients by Increasing Patient Activation

Lee A. Fleisher,[1] Judith H. Hibbard.[2] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of Oregon, Eugene, OR.*

Background: Effective self-management is essential for patients who have chronic conditions, including kidney disease. Studies show that patient activation (PA), an individual's knowledge, skills and confidence to manage their health is a critical factor in influencing outcomes in kidney patients. Using the Patient Activation Measure (PAM), a 13-item survey, kidney patients who score higher are more likely to follow treatment regimens and achieve better clinical outcomes. This presentation addresses: 1) How much difference can clinical teams make in helping patients gain self-management capabilities? 2) Does incentivizing clinicians make a difference in achieving greater gains in PAM scores, 3) Is it possible for patients who are sicker, older, and economically disadvantaged to make gains in their PAM scores?

Methods: Two populations were compared, a population receiving kidney care and whose patient care plans were designed to support greater PA, and a general population of patients who received ambulatory care, with no special intervention to increase PA. We examine gains in PAM scores over time in both populations and look specifically at gains among patients disadvantaged in some way.

Results: In the general care population, without tailored-interventions and no clinician incentive, PAM scores increased, but score improvement rarely reaches a 3-point threshold considered clinically meaningful. Findings from a forthcoming Lewin report will be discussed, showing gains in activation when clinicians are incentivized to support activation in patients with kidney disease (including dialysis and transplant patients).

Average score change in the report [not publicly released yet] will be shared and compared to the average score change in general care population.

Conclusions: These findings highlight the important role that incentives play in directing the clinical team to help patients gain in PA, especially compared to those who are not incentivized. Findings indicate that patient characteristics were not key determinants of gains in activation: even those who are older, sicker, and economically-disadvantaged, made dramatic gains when clinicians are incentivized to support activation. Speakers will discuss the importance for insurers to provide financial incentives for clinicians to devote time and resources to activate chronic kidney disease patients, resulting in improved care and increasing equity in care

Funding: Commercial Support - Phreesia

PUB058

Seizures as an Uncommon Presentation of Cisplatin-Induced Nephrotoxicity

Taniya Thomas,[1] Omar Ali,[2] Aman Pal,[2] Swati Mehta,[2] Krishnakumar D. Hongalgi.[2] *[1]Albany Medical College, Albany, NY; [2]Albany Medical Center, Albany, NY.*

Introduction: Cisplatin is a platinum-based chemotherapeutic agent which is commonly used for the treatment of solid tumors. Nephrotoxicity is a well-known complication of this medication and thought to occur due to tubular cell injury and death. We report a case of seizures due to cisplatin induced electrolyte derangements in a patient with osteosarcoma.

Case Description: A 21-year-old female presented with a one week history of poor oral intake and muscle weakness followed by a witnessed tonic-clonic seizure, on a pertinent background of osteosarcoma currently being treated with cisplatin and doxorubicin. She was found to have new-onset electrolyte disturbances with serum potassium 2.3 mmol/L, magnesium 0.7 mg/dL, phosphate <1.0 mg/dL, and calcium 6.8 mg/dL. Urine electrolytes revealed elevated potassium and magnesium. There was no evidence of metabolic acidosis (bicarbonate 25mmol/L) or acute kidney injury (AKI) with a creatinine of 0.74mg/dL and urine output of 2L/day. Urine studies were consistent with magnesium and potassium wasting. CT head was unremarkable for gross changes. Cisplatin was discontinued, electrolytes were repleted daily to maintain certain goals, and amiloride was initiated to decrease magnesium and potassium wasting. Over the course of her hospitalization, her oral intake and electrolytes continued to improve, eventually only requiring magnesium supplementation upon discharge after a week.

Discussion: Nephrotoxicity is a well-established side effect of cisplatin chemotherapy, commonly manifesting with AKI and hypomagnesemia. Persistent hypomagnesemia has been shown to inhibit the sodium-potassium pump and inhibit the release of parathyroid hormone (PTH), resulting in hypokalemia, hypophosphatemia and hypocalcemia, respectively. Our case emphasizes routine electrolyte monitoring and prompt medical management of electrolyte disturbances in patients receiving platinum-based chemotherapy to prevent complications.

PUB059

From Health to Harm: Acute Oxalate Nephropathy in a Weightlifter

Sandeep Kaur, Ryann Sohaney. *Henry Ford Hospital, Detroit, MI.*

Introduction: Oxalate nephropathy is a rare condition characterized by deposition of calcium oxalate within the kidney tubules, typically associated with acute tubular injury. This phenomenon arises from an excess of urinary calcium oxalate, leading to the precipitation of insoluble calcium oxalate crystals within the kidney tubules.

Case Description: A healthy 33-year-old male presented with four days of nausea and vomiting. Laboratory work up showed his serum creatinine (SCr) was 5.4 mg/dL and BUN was 53 mg/dL, compared to a SCr of 1 mg/dL four years prior. Urinalysis revealed 27 RBC/hpf and no protein; with imaging showing no hydronephrosis. A kidney biopsy demonstrated diffuse acute tubular injury with associated calcium oxalate deposition in tubular lumens (see figure 1), consistent with acute oxalate nephropathy. SCr improved modestly to 4.8 mg/dL after 48 hours of aggressive hydration. The patient reported no prior abdominal surgeries, diarrhea, or vitamin C supplements. Upon further questioning, the patient disclosed a rigorous weight training regimen, along with the use of several supplements including a pre-workout and creatine. He was eating a high protein diet and juicing with an abundance of spinach. He was instructed to discontinue juicing and all supplements. Subsequent investigation post-discharge revealed normal vitamin B6 levels, SCr 3.8 mg/dL, 24-hour urine oxalate 76 mg/day (normal <45 mg/day), urine sodium 528 mmol/volume, urine calcium 216 mg/volume, uric acid 954 mg/volume, creatinine clearance 68 mL/min, and total urine volume 6L/day.

Discussion: Secondary hyperoxaluria from excessive ingestion of high oxalate foods is uncommon. Juicing of green leafy vegetables provides large oxalate loads (spinach: ~650mg oxalate/cup). Exercise supplementation, widely used by amateur and professional athletes, is believed to enhance athletic performance yet is largely unregulated. With the escalating popularity of juicing and exercise supplementation, consulting healthcare professionals can help individuals navigate risks and benefits.

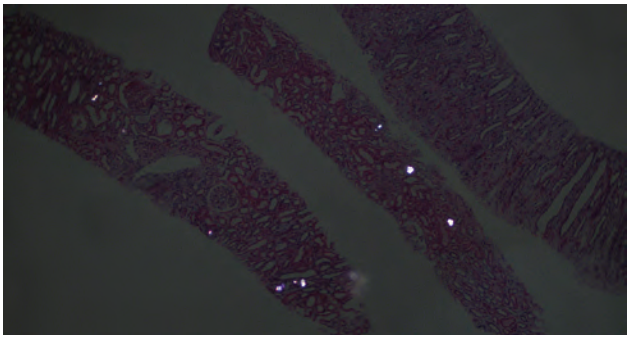


Figure 1: H&E stain with oxalate crystals under polarized light

PUB060

Non-ICU Administration of Norepinephrine for HRS

Akash Hazari, Alexandra Rosario Aulet, Roberto L. Collazo-Maldonado. *Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Addition of vasoconstrictor is the standard of care for treatment of patients with HRS-AKI. Terlipressin is the only FDA approved vasoconstrictor but it is not available in all hospitals. Norepinephrine is equally effective but it requires the patient to be transferred to the ICU for administration. However ICU beds are in high demand and here we present a case for norepinephrine use for HRS in a specialized liver floor outside of the ICU.

Case Description: 67 yo Caucasian female was admitted with decompensated alcoholic cirrhosis with MELD score of 37, and ascites. Nephrology was consulted for creatinine of 1.98mg/dL elevated from baseline of <1 mg/dL. After 48 hours, the diagnosis of HRS-AKI was done using the ICA 2024 criteria. The patient creatinine went up to 2.1 mg/dL and patient was started on non-ICU specialized liver unit protocol for norepinephrine administration for HRS via central line with a goal to increase the MAP up to 15 mmHg from the baseline of 61 without exceeding the dose of 10mg/min. Therapy was continued for 7 days with the highest dose administered of 6 mcg/min and creatinine improved back to baseline. The patient did not develop any complication throughout the course of norepinephrine administration and was started on midodrine after completion of therapy.

Discussion: Treatment of HRS-AKI with norepinephrine is a safe and cost effective choice for treatment of HRS-AKI without the need for the patient to be transferred to the intensive care unit using a protocol in a specialized non-ICU liver unit barring other indications for ICU transfer.

PUB061

Validation of the Spanish Translation for "Standardized Clinical Assessment and Management Plan" (SCAMP) for the Evaluation of Patients with AKI

Enrique J. Robiou Vivero, L. M. Perez-Navarro, Rafael Valdez-Ortiz. NefrologíaHGM. *Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico.*

Background: Acute Kidney Injury (AKI), a syndrome characterized by the sudden renal excretory function loss defined by changes in urine volume and serum creatinine, affects 10-15% of hospitalized patients, particularly those in ICU, conferring an elevated mortality rate. Currently, timing to start and stop renal replacement therapy (RRT) consider multiple biomarkers and resources, not available everywhere. We must count on different, simple, available tools to facilitate clinicians' decision-making.

Methods: With the authorization of SCAMPs original author, we developed the validation process of it's Spanish Translation following Ortíz-Gutierrez guidelines. We applied the translated format to 68 doctors and fellows of Internal Medicine, Nephrology, and Intensive Care for validation through a standardized clinical vignette that allowed evaluating all the items.

Results: We conducted the analyses on each item conforming "SCAMP", dividing them into 5 domains. First domain identifies risk factors and probable causes of AKI; second domain examines patient's actual state and mortality risk; third domain evaluates RRT classical indications; fourth domain recommends starting or not RRT, while the last domain recommends continuing or discontinuing RRT. We identified several aspects to improve about SCAMP with an overall Cronbach's alpha between 0.6-0.75 on 4 of 5 domains and 0 on the last one. The average time of fulfilling the process was 9.48 ± 1.86 minutes, perceived by the applicants as adequate, considering the translation to be simple, clear in most of the domains except for the ones in which SCAMP asks reasons to overlook the recommendations. SCAMP Spanish Translation was considered a useful and practical tool for the assessment of patients with AKI.

Conclusions: SCAMP is a useful, practical, simple, clear and accurate tool to decide whether to start or not RRT in patients with AKI, based on the clinical assessment. Complementing the findings of the original authors of SCAMP.

Validity analyses			
Domain	Objective	Number of Items	Chonbach's alpha
1	Risk factors and probable causes of AKI	19	0.61
2	Actual state of the patient and mortality risk	12	0.75
3	Classical indications for RRT	19	0.69
4	Recommendation of starting or not RRT	4	0.75
5	Recommendation of continuing or discontinuing RRT	3	0
Viability analyses			
Mean time		9.48 ± 1.86 minutes	
Simplicity		89%	
Clarity		78%	
Utility		83%	

PUB062

Two Cases of Interstitial Cystitis and Nephrology Consultation

Gwendolyn R. Derk, Rob Rope. *Oregon Health & Science University, Portland, OR.*

Introduction: Interstitial cystitis is a poorly understood disorder that is primarily managed by urology. There is not a standard of practice regarding the interdisciplinary management and the necessity of nephrology involvement. We present two cases of nephrological consultation for management of interstitial cystitis.

Case Description: Case #1: A 61-year-old Hispanic female with seropositive rheumatoid arthritis and fibromyalgia developed interstitial cystitis 2 years ago managed by urogynecology and rheumatology. She had a normal GFR, sterile urine with microscopic hematuria, no proteinuria nor leukocoria, negative ANA and normal inflammatory markers. She was started on amitriptyline, gabapentin, duloxetine and multimodal pain medications without any response. She was started on hydroxychloroquine with no response after 3 months then switched to methotrexate without any reduction in bladder pain. Cystoscopy revealed Hunner's lesions which did not respond to triamcinolone kenalog nor botulinum toxin injections. She underwent hydrodistention procedures, implantation of a sacral neuromodulator device, pelvic floor physical therapy, and behavioural therapy without improvement. At this point, nephrology was consulted for a trial of off-label cyclosporine therapy prior to offering cystectomy. Case #2: A 39-year-old Chinese male developed ulcerating eosinophilic interstitial cystitis with hematuria and pyuria from ketamine use vs primary cystitis. Final workup was consistent with interstitial cystitis. The patient was treated with trials of antibiotics, fesoterodine, oxybutynin, trospium chloride, and mirabegron over the course of 3 years. He underwent cystectomy and ileal conduit urostomy. He subsequently developed bilateral narrowing of his ureters and moderate to severe bilateral hydronephrosis, chronic kidney disease, and recurrent acute kidney injuries requiring bilateral nephrostomy tubes. He subsequently developed bilateral narrowing of his ureters and moderate to severe bilateral hydronephrosis, chronic kidney disease, and recurrent acute kidney injuries requiring bilateral nephrostomy tubes.

Discussion: Multidisciplinary management and early involvement of nephrology may result in improved outcomes in patients suffering from interstitial cystitis. Given the complex and potentially intransigent nature of the disease, nephrologists should be aware of potential standard and off-label treatments for these patients.

PUB063

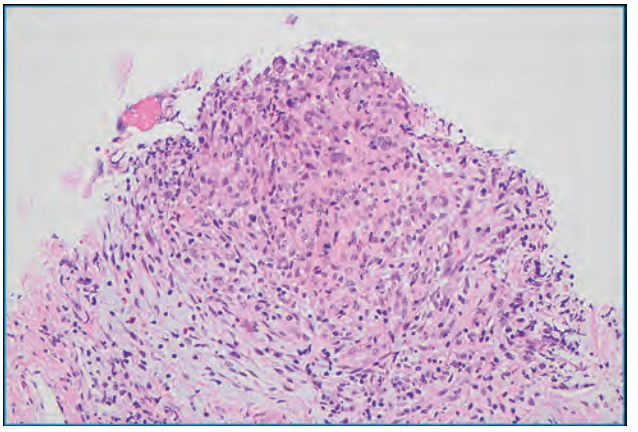
Granulomatous Interstitial Nephritis Secondary to Levetiracetam

Romela Petrosyan, Sujal I. Shah. *Brigham and Women's Hospital, Boston, MA.*

Introduction: Granulomatous interstitial nephritis is detected in approximately 0.5-0.9% of kidney biopsies. Retrospective studies and clinical experience suggest that removal of the offending agent and prompt treatment with corticosteroids result in improvement of renal function. Levetiracetam has not been typically implicated to cause renal toxicity. Here, we report a case of non-necrotizing granulomatous interstitial nephritis secondary to levetiracetam in a patient with APOL1 G1 homozygocity.

Case Description: 53-year-old male with epilepsy and chronic pain presented with severe acute interstitial nephritis after taking omeprazole prescribed by his primary care physician for gastritis with serum creatinine rising from a baseline of 1mg/dL to 4mg/dL. Proton pump inhibitors were added to patient's allergy list and the patient was treated with prednisone taper. Renal function initially improved and subsequently worsened, potentially implicating another culprit. Patient had 312mg of mostly tubular proteinuria which remained unchanged, but his serum creatinine worsened from 2mg/dL to 4mg/dL prompting a repeat kidney biopsy. Kidney biopsy demonstrated a drug-related, active severe granulomatous interstitial nephritis. At the time, patient also experienced a breakthrough seizure and his levetiracetam dose was increased.

Discussion: This case highlights association between levetiracetam, a common and essential anti-seizure therapy, in inducing granulomatous interstitial nephritis in a patient with a background of APOL1 nephropathy. This comes following repeat kidney biopsy after initial corticosteroid treatment for acute interstitial nephritis thought to be secondary to proton pump inhibitors. This case also enforces the significance of repeat kidney biopsy following insufficient response to corticosteroids and removal of a commonly implicated offending agent.



PUB064

Successful Treatment of Human Immunodeficiency Virus-Associated Thrombotic Microangiopathy with Eculizumab

Natasha Freeman, Pietro A. Canetta. *Columbia University Irving Medical Center, New York, NY.*

Introduction: In the era of highly active antiretroviral therapy (HAART), thrombotic microangiopathy (TMA) is a rare manifestation of advanced human immunodeficiency virus (HIV) infection. Management of infection-associated TMA has traditionally included supportive care and antimicrobial agents, rather than anti-complement therapy such as eculizumab.

Case Description: A 62-yo man with advanced HIV and chronic kidney disease stage 3B presented with 3 days of abdominal pain, vomiting, and diarrhea. Laboratory workup revealed severe thrombocytopenia, hemolytic anemia (with schistocytes on peripheral smear), acute kidney injury (AKI), ADAMTS13 activity of 72%, uncontrolled HIV (CD4 count 61 cells/ml, HIV viral load > 10 million copies/ml) (Table 1). A broad infectious workup revealed norovirus GI/GII and influenza A H3 infections and was otherwise negative including for Shiga-toxin producing *Escherichia coli*. Complement factor H autoantibody testing was negative, and he declined genetic testing for complement-mediated TMA risk genes. On day 3, he was started on eculizumab and hemodialysis. On day 8, HAART was resumed. All laboratory parameters improved dramatically by day 10, and hemodialysis was stopped on day 26. He received 5 doses of eculizumab while hospitalized and was discharged on day 31 with resolution of AKI and hemolysis. He was transitioned to maintenance ravulizumab post-discharge, and kidney function remained stable at least 2 weeks after original presentation.

Discussion: HIV-associated TMA is well-recognized but only rarely reported to be successfully treated with eculizumab, as our case illustrates. The underlying pathophysiology and optimal duration of anti-complement therapy for this indication is unknown and warrants further investigation.

Table 1. Laboratory values throughout clinical course

	Day 1 (admission)	Day 3 (prior to HD and eculizumab)	Day 10 (1 week after eculizumab, on HD)	Day 31 (hospital discharge, off HD)	Day 55 (two weeks post-discharge, off HD)
Hemoglobin (g/dl)	12.1	5.7	7.3	8.3	9.4
Platelets (x103/ul)	5	11	90	129	152
Creatinine (mg/dl)	6.99*	9.40	5.68	2.82	3.62
Blood urea nitrogen (mg/dl)	100	162	62	73	43
Haptoglobin (mg/dl)	< 20	< 20	63	94	161
Lactate dehydrogenase (U/L)	2769	1900	911	260	224
Bilirubin (mg/dl)	1.2	1.5	0.6	0.2	NA

HD, hemodialysis; NA, not available;
*Baseline creatinine from 1 week prior was 2.1 mg/dl

PUB065

Demystifying the Atypical Presentation of Complement-Mediated Thrombotic Microangiopathy

Allysha Yasuda,[1] Chelsea Takamatsu,[2] Meleesa Nocera.[3] *[1]Banner - University Medical Center Tucson, Tucson, AZ; [2]The University of Arizona, Tucson, AZ; [3]The University of Arizona College of Medicine Tucson, Tucson, AZ.*

Introduction: Complement-mediated thrombotic microangiopathy (CM-TMA), also known as atypical hemolytic uremic syndrome (aHUS), is a rare disease characterized by diffuse endothelial blood vessel damage secondary to overactivation of the complement immune system. The classic presentation includes the triad of hemolytic anemia, thrombocytopenia, and acute kidney injury. CM-TMA occurs more commonly in children, but when it occurs in adults, identifying both the diagnosis and underlying etiology requires extensive workup via multi-disciplinary collaboration.

Case Description: We present a male veteran with a complex medical history notable for Crohn's disease treated with increasing doses of his biologic agent, presenting with new-onset liver cirrhosis, splenomegaly, pulmonary hypertension, and the triad of CM-TMA. Our patient's presentation of CM-TMA posed a diagnostic dilemma with overlapping multiorgan dysfunction. However, while awaiting definitive diagnostic confirmation for CM-TMA with genetic complement screening results pending for weeks, ruling out other infectious, hematologic, rheumatologic, autoimmune, and iatrogenic explanations for our patient's condition led us to diagnose CM-TMA and begin urgent treatment. Our patient received infusions of a novel monoclonal complement C5 inhibitor, Ravulizumab, prior to esoteric tests resulting to prevent further, irreversible organ damage.

Discussion: In highlighting the diagnostic workup for and the evolving management of this rare disease, we intend to guide clinicians managing similar patients with confounding pathologies in a clear algorithmic approach to minimize the devastation of CM-TMA.

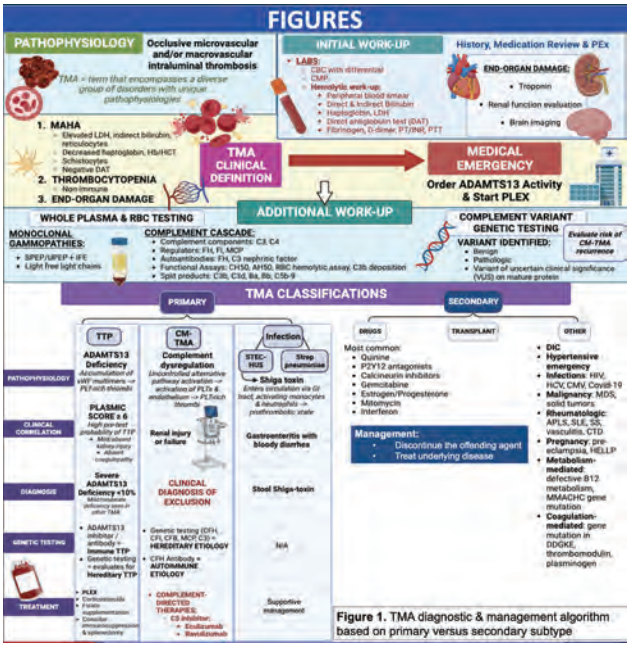


Figure 1. TMA diagnostic & management algorithm based on primary versus secondary subtype

PUB066

Squeeze the Kidneys Tight Enough: Acute Can Look like Chronic

Ashish Gummadi. *The University of Mississippi Medical Center, Jackson, MS.*

Introduction: Looking at the serum creatinine - physicians can guess on the timeframe of kidney insult. We report an extremely rare example of clinical diagnosis of acute tubular injury where the serum creatinine has increased from 0.8 mg/dL to 5 mg/dL in less than 24 hours while patient had the kidney insult during the hospital stay.

Case Description: 36-year-old female with multiple prior pregnancies complicated with abortions and fetal demise was admitted to OBGYN service for management of right Bartholin's abscess after she failed prior incision and drainage attempts in the ED. she was getting treated with Bactrim for the abscess and underwent Marsupialization of Bartholin's cyst abscess under general anesthesia with propofol along with intraop 30 mg IV Toradol. She spent nearly 15 minutes of her intraoperative time with mild hypotension and inappropriately normal heart rate in 70s. Post operatively she became oliguric during the 1st 24 hours post procedure and put out only 300 mL of urine. Her creatinine went up from 0.8 mg/dL to 5 mg/dL. Increased echogenicity of kidneys was noted on the kidney ultrasound. PTH levels became abnormal within 48 hours-168 pg/mL and then remained elevated even at 2 weeks-201 pg per mL. Clinical diagnosis of acute tubular injury based on her urine electrolytes and clinical course. Her serum creatinine went up by nearly 1 point every 24 hours and reached the peak value of 7.5 mg /dl. Her creatinine recovered to 1.9 mg/dL at 2 weeks mark and she was lost to follow up.

Discussion: When there is increased echogenicity of the kidneys along with elevated iPTH it is often thought to be secondary to chronic kidney disease. Cr of 5 mg/dl in a patient with baseline Cr of 0.8mg/dl would make one look for the kidney insult in the prior 3-5 days range. This is a very rare example of clinical diagnosis of dense acute tubular injury in native kidneys where ultrasound and iPTH values loose their specificity with respect to CKD diagnosis. We know the rate of rise of Serum Creatinine usually falls in the range of 0.8-1.2 mg/dl per day in cases of Acute tubular injury but can Kidneys leak Creatinine stored in the organ itself is a question that remains unanswered. The initial rise in Cr of 0.8 to 5 mg / dl was out of proportion to the expected changes. Eventually her Cr rate of rise from D3 to D4 of hospitalisation started to follow usual expected changes.

PUB067

Improved Kidney Function in Anticoagulant-Related Nephropathy Using N-acetylcysteine

Madeline S. Chung, Brad H. Rovin, Sergey V. Brodsky. *The Ohio State University Wexner Medical Center, Columbus, OH.*

Introduction: Anticoagulant-related nephropathy (ARN) is a recognized condition marked by unexplained acute kidney injury (AKI) accompanied by hematuria while under anticoagulant therapy. Initially associated with warfarin, ARN now encompasses direct oral anticoagulants and antiplatelet agents. Its pathogenesis involves several factors, including tubular obstruction by red blood cell (RBC) casts and cytotoxicity of tubular cells due to intracellular accumulation of hemoglobin degradation products, notably free iron. Clinical outcomes are generally poor, with most patients failing to regain kidney function, leading to progressive kidney failure. Studies show a one-year mortality rate of 39%. Research in mice indicates that treatment with N-acetylcysteine (NAC) improves interstitial fibrosis and tubular atrophy (IFTA) in ARN by reducing oxidative stress. Here, we present a case of a 54-year-old woman diagnosed with biopsy-proven ARN, whose kidney function stabilized after initiating oral NAC.

Case Description: Our patient was noted to have a significant increase in her serum creatinine (sCr) to 5.2 mg/dL from a baseline of 1.09 mg/dL a year earlier. Further evaluation revealed elevated anti-myeloperoxidase (MPO) antibody levels, active urine sediment with RBC casts, and subnephrotic-range proteinuria. Kidney biopsy confirmed ARN, ruling out the suspected ANCA-associated vasculitis but showing moderate mesangial IgA staining suggestive of a form of IgA nephropathy. Additionally, Prussian Blue staining revealed iron deposition in tubular epithelial cells. Her serum creatinine remained elevated, prompting a second biopsy five months later, which showed increased IFTA and more tubules with iron deposition. The patient received a six-month course of glucocorticoids and started oral NAC twice daily at this time, maintaining dialysis independence with improvements in sCr and proteinuria after 15 months.

Discussion: Early recognition and intervention in ARN are crucial due to its association with accelerated chronic kidney disease progression and increased mortality rates. While treatment options remain limited, antioxidant therapy with NAC shows promise in mitigating oxidative stress-induced damage, particularly in patients requiring ongoing anticoagulation. This is significant for individuals like ours with mechanical aortic valves, where discontinuing anticoagulants is not feasible.

PUB068

Apixaban-Related Acute Interstitial Nephritis: A Rare Adverse Effect

Vipin Varghese, Amro Abdelghani, Zeenat Y. Bhat. University of Michigan. *University of Michigan Division of Nephrology, Ann Arbor, MI.*

Introduction: Apixaban is widely prescribed for the prevention of stroke and systemic embolism in atrial fibrillation and the management of venous thromboembolism. Its favorable efficacy and safety profile has escalated its use. However, emerging evidence suggests that apixaban may be associated with adverse renal effects. Here we report a case of apixaban related acute interstitial nephritis.

Case Description: A 62-year-old female with atrial fibrillation, hypertension, hyperlipidemia initially presented to hospital after elevated creatinine on outpatient labs. Patient denied any symptoms apart from fatigue and continued to make urine. She reported the initiation of apixaban 1 month prior to admission. She reported no proton pump inhibitor or antibiotic use. Patient was afebrile and normotensive on admission. She appeared euvolemic and had no rashes or skin changes. Initial laboratory findings were notable for sCr 4.5 mg/dL, serum sodium 137 mmol/L, serum potassium 3.7 mmol/L, serum bicarbonate 20 mmol/L, blood urea nitrogen 50 mg/dL, white blood cell count 8.8 x109/L with 5.3% eosinophils on differential. Urinalysis was noted to have positive leukocyte esterase, 30 mg/dL protein, 50 red blood cells per high power field, and 26 white blood cells per high power field with few eosinophils. Urine protein creatinine ratio with 1.69 g/g protein. Urine culture was found to have no growth. Serologic work up was unremarkable. Serum creatinine peaked at 4.6 mg/dL. A renal biopsy was completed and notable for diffuse interstitial infiltrate enriched in eosinophils and mononuclear inflammatory cells. Immunofluorescence and electron microscopy were unremarkable.

A diagnosis of acute interstitial nephritis was made. Apixaban was discontinued and transitioned to warfarin. Patient was started on prednisone 1 mg/kg (80 mg daily). Serum creatinine improved to 3.5 mg/dL at the time of discharge. Patient was continued on steroid taper. Two weeks after discharge, sCr had improved to 1.54 mg/dL.

Discussion: This case report highlights the importance of vigilance regarding apixaban-induced AIN, particularly as the use of apixaban continues to rise. While AIN remains a relatively rare side effect of apixaban therapy, clinicians should maintain a high index of suspicion when evaluating patients with unexplained renal dysfunction and be prepared to promptly diagnose and manage this potentially reversible condition.

PUB069

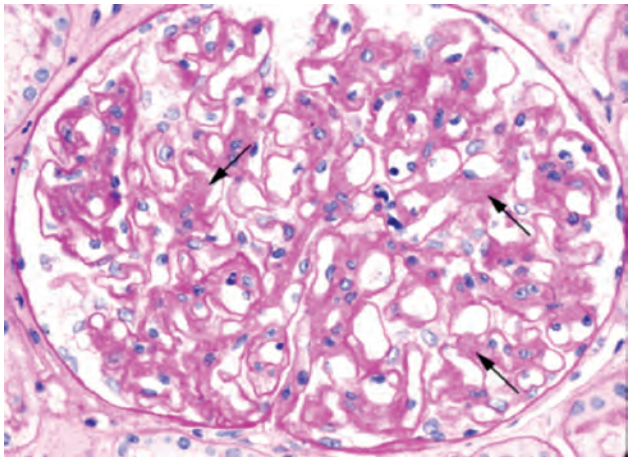
Fibrillary Glomerulonephritis

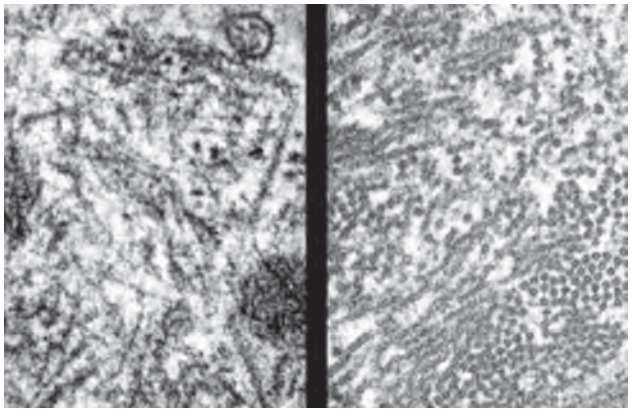
Abdulkader Farran. *Ascension Michigan, Warren, MI.*

Introduction: AGE: 68 GENDER: Female ALLERGIES: None BP at Home: SBP 140-150s. PMH: HTN,OSA,COPD,CHpEF. Review of labs shows evidence of volume depletion in the past, hyaline casts. SH: tobacco use Current Meds: Losartan, Diltiazam, Lasix, Metolazon Worsening renal disease. Physical exam: Bilateral Pitting edema, Irregular rhythm 5.6 bun31 Cr 2.87 glucose113 GFR 18ml/min, CL 101 uric acid 4.4 Ca 8.4 phos 3.3, includes holding ARB therapy, renal ultrasound, UACR

Case Description: Next follow up visit: The patient's lab results show a worsening anemia and a need for an urgent kidney biopsy. Kidney ultrasound showed no hydronephrosis with R 9.5 cm, L 9 cm kidney. The cause of the condition remains unknown. Hospital course: The patient was prescribed IV steroid pulse for three days and received two units of PRBC. Urgent biopsy was held, and GI consultation was conducted. EGD/ colonoscopy showed only polyp which was removed with no malignancy, serology work up was negative. EGD/ colonoscopy showed was negative, serology work up was negative.

Discussion: Fibrillary glomerulonephritis is a condition characterized by hematuria, proteinuria, kidney function impairment, hypertension, and monoclonal gammopathy. Diagnosis involves kidney biopsy, electrophoresis, immunofixation, serum free light chain levels, and other tests. Patients without known cancer should undergo age and risk appropriate cancer screening, while those with imamunotactoid glomerulopathy should be screened for monoclonal gammopathy. Management approach: Addressing underlying causes, immunosuppressive therapy, and supportive care.





PUB070

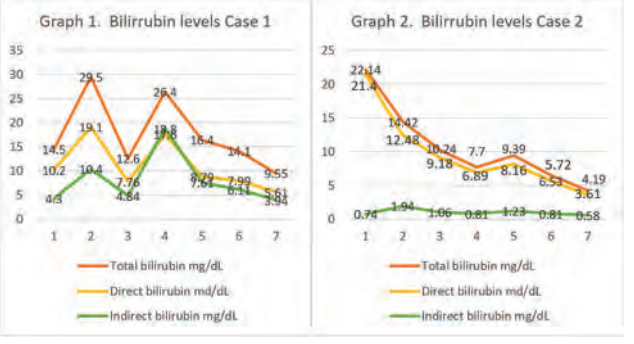
Double Plasma Molecular Adsorption System as Treatment of Liver Failure: A Case Series

Mariana N. Zavala, Rodrigo Lopez, Ricardo A. Garza Treviño, Diana Carolina Sanchez Guerrero, Daniel Alvarez Lara, Carlos Cortez Hernandez, Lilia M. Rizo Topete. *Christus Muguerza Sistemas Hospitalarios SA de CV, Monterrey, Mexico.*

Introduction: The use of extracorporeal liver support systems (ECLS) as a bridge to liver transplantation or recovery has improved in recent years. We present two cases in which double plasma molecular adsorption system (DPMAS) was applied, resulting in progressive improvements in clinical condition and laboratory values of bilirubin and inflammatory markers.

Case Description: Case 1 - A 55-year-old female with AIH for 4 years, in treatment with immunosuppressants. She began one week before with jaundice, Grade I hepatic encephalopathy, and ascites. Laboratory test: Hb 8.9 g/dL, platelets 54,000, INR 2.84, aPTT 55.9 s; Cr 0.73 mg/dL; urea 72.8 mg/dL; BT 14.5 mg/dL, BD 10.2 mg/dL, BI.3 mg/dL; AST 97 U/L; ALT 60 U/L; GGT 43 UI/dL. MELD score of 28 points and Child-Pugh C. On the fifth day laboratory values: Cr 1.71 mg/dL, BUN 61.7 mg/dL, BT 21.9 mg/dL, BD 15.7 mg/dL; we performed 3 sessions of DPMAS, on alternate days, with TPE2000 filter cartridge HA330 II and BS 330. Each session lasted 6 hrs with a plasma volume of 1.5 for DPMAS and 1 time for TPE. The Qb was 130-150 ml/min and Qr post 1300 -1400 ml. RRT technique was CVVHDF. IL-6 decreased from 2707 pg/mL to 993 pg/mL. **Case 2 -** A 51-year-old male with Chronic Hepatitis C, who began 12 hours before admission with Grade II hepatic encephalopathy and mucocutaneous jaundice. On admission, the laboratory tests were: Hb 12.4 g/dL, platelets 219,000, INR 1.94, aPTT 46.9 s; Cr 2.38 mg/dL; urea 38 mg/dL; BT 22.14 mg/dL, BD 0.74 mg/dL, BI 21.4 mg/dL; AST 297 U/L; ALT 402 U/L; GGT 169 UI/dL, ALP 135 U/L. On the third day with worsening of his clinical condition, it was decided to start MARS for two sessions and later two DPMAS sessions.

Discussion: The DPMAS is a blood purification method that is safe and effective for reducing bilirubin levels and inflammatory markers, making it an important option for bridging to transplant or recovery. This could be observed in our patients, in whom the bilirubin and IL-6 levels decreased significantly after treatment with DPMAS.



PUB071

AKI and Hyponatremia in a Patient with Crohn Disease: A Case Report

Ritu Chandra Prakash Tated. *New York Medical College, Valhalla, NY.*

Introduction: Crohn's disease (CD) and ulcerative colitis are examples of inflammatory bowel disease (IBD), which frequently has systemic symptoms that extend outside of the digestive tract. Although they are less frequent, renal and urologic problems can present serious treatment difficulties. Glomerulonephritis is an uncommon but serious extraintestinal manifestation. This case report demonstrates an uncommon correlation between immunoglobulin A nephropathy (IgAN), the most common glomerulonephritis worldwide and Crohn's disease.

Case Description: A week-long history of malaise, flu-like symptoms, and myalgias brought this 47-year-old White female patient to the emergency room. She had a history of Crohn's disease following ileostomy. Severe electrolyte abnormalities and acute kidney damage (AKI) with a creatinine level of 10.7 mg/dL were discovered during laboratory examinations. Renal ultrasonography revealed modest bilateral renal enlargement without hydronephrosis or calculi, despite stable vitals and an unremarkable physical examination. Urine culture came back negative, but urinalysis revealed severe hematuria, pigmented granular casts, and proteinuria. The patient's sodium and creatinine levels gradually improved subsequent to fluid restriction, desmopressin and hypertonic saline. Subsequently, a kidney biopsy demonstrated IgAN. Notably, at the time of the development of renal failure, the patient was not receiving immunosuppressive medicine and was not going through an aggressive flare-up of Crohn's disease.

Discussion: This case emphasizes the need of keeping an eye out for renal involvement in individuals with IBD. The patient's abrupt renal failure and biopsy-proven IgAN demonstrate the intricate interactions between systemic immune responses and renal pathology in inflammatory bowel disease. Although uncommon, IgAN requires regular renal function monitoring in individuals with inflammatory bowel disease (IBD) in order to facilitate the early identification and treatment of any renal consequences. This report supports the use of an integrated strategy to patient management that takes into account both extraintestinal and gastrointestinal IBD symptoms. It is critical to research the pathogenic processes that connect IgAN and IBD and to ascertain if the two conditions are coincidental or suggest that they share common etiopathogenic pathways.

PUB072

Acute Kidney Injury following Ingestion of Topical Minoxidil

Santoshi M. Kandalam, Sean P. Mahoney, Doree Morison. *Tulane University, New Orleans, LA.*

Introduction: Our case presents the dangers of ingesting a 5% topical minoxidil solution as well as the factors that may have contributed to the accidental ingestion.

Case Description: A 24-year-old, spanish-speaking male with no past medical history presented with altered mental status. The patient was not able to participate in the interview. The patient was reportedly agitated and confused, which prompted his family to call EMS. They denied drug use. He was distressed about hair loss and drank approximately one ounce of 5% topical minoxidil. The patient did not realize the minoxidil was meant to be applied topically, likely due to a language barrier. The exam was remarkable for tachycardia to 130, tachypnea, forceful movements of extremities against restraints, and difficulty to arouse. Patient was normotensive, afebrile, and denied abdominal pain. Labs were notable for sodium 119, chloride 73, bicarb 28 with an anion gap of 18, and creatinine of 3.81 with an unknown baseline. UDS was negative for ethanol. UA wnl. VBG with a pH of 7.38. EKG showed sinus tachycardia. Imaging, including a CXR and CT head, showed no abnormalities. Patient was given IV fluids with significant improvement in his Cr and was discharged without requiring any hemodialysis during hospitalization.

Discussion: The maximum recommended dose of oral Minoxidil is 100mg/day. Our patient consumed approximately 1500mg. Minoxidil has been known to cause transient increases in creatinine and blood urea nitrogen, generally resolved with supportive care. Long term studies have shown that minoxidil can cause irreversible kidney damage. There have been a select few case reports discussing severe poisoning after ingestion of topical minoxidil solution, with the most prevalent symptom being profound hypotension. Co-ingestion with alcohol or underlying hepatic disease are considerations in many other toxic alcohol poisonings and may have had a factor in our case. These medications and other cosmetics products are becoming increasingly available over the counter and often do not have black box warnings. This case highlights the importance of obtaining a thorough history and workup, especially in patients who may have a language barrier. Though minoxidil poisonings are rare, understanding the pathophysiology of Minoxidil and the impact on the renal system may lead to better understanding of toxic alcohols such as propylene glycol.

PUB073

A Case of Refractory Anemia from Symptomatic Aluminum Toxicity

Sahil Patel,[1] Alison Nguyen,[1] Renu Regunathan-Shenk.[1,2] *[1]Inova Fairfax Hospital, Falls Church, VA; [2]Virginia Nephrology Group, Falls Church, VA.*

Introduction: Aluminum toxicity is an uncommon disorder seen in patients on hemodialysis (HD) and chronic kidney disease (CKD) because of the availability of non-aluminum containing phosphate binders and removal of aluminum from dialysis fluid.

Case Description: 65-year-old-female Nepali immigrant with a history of end-stage-renal-disease (ESRD) due to unclear etiology on HD who was admitted for subacute confusion, weakness, diffuse pain and fatigue. She started HD in Nepal about 3 months prior to immigrating to the United States (US), and had missed dialysis for 3 weeks because she was unable to establish care here. Her laboratory workup was consistent with ESRD, hyperphosphatemia, hypocalcemia, and severe anemia. She was treated with HD and received supportive care with transfusions, iron, erythropoietin stimulating agents, activated vitamin D, and phosphate binders. Despite these measures, when she started outpatient dialysis she was found to have severe anemia, hypercalcemia, hypophosphatemia and hypoparathyroidism on the initial outpatient tests. An aluminum level was checked that revealed a value of 110 ug/L. This number was confirmed with the Deferoxamine stimulation testing. She started Deferoxamine 5 mg/kg weekly as chelation therapy. As the aluminum levels decreased, her symptoms and laboratory values improved (Table 1).

Discussion: Aluminum toxicity, now rarely reported in developed countries, occurs mainly from ingestion of aluminum containing phosphate binders, exposure to aluminum containing dialysis fluid, or environmental exposures. It is not routinely screened in all dialysis centers in the US given elimination of aluminum from the water supply and from phosphate binders. Our patient likely had aluminum exposure while in Nepal prior to her arrival in the US. Her treatment refractory anemia and poorly controlled hyperparathyroidism were emblematic of aluminum toxicity. This case report highlights the importance of screening for aluminum levels among immigrants with ESRD.

Laboratory values as the patient was treated with Deferoxamine.

Date	Aluminum (ug/L)	Hemoglobin (g/dL)	Parathyroid (pg/mL)	Calcium (mg/dL)	Phosphorus (mg/dL)
5/18/23	-	3.9	-	6.5	9.7
5/25/23	-	8.0	-	7.7	3.2
6/6/23	110	6.5	<7	11.6	2.2
7/1/23	92	6.9	60	10.8	2.1
7/6/23	90	7.5	88	10.0	2.8
10/13/23	25	12.9	180	8.5	3.2

PUB074

Increase in Hemoglobin Levels in Patients with Advanced CKD with Severe Anemia and Major Adverse Kidney Events

Jonathan Chavez,[1,2] Guillermo Garcia-Garcia,[1] Ramon Medina,[1,2] Karla Hernandez Morales,[1] Jahir R. Camacho,[1] Edgar J. Carmona,[1] Alexa N. Oseguera Gonzalez,[1] César Murguía Soto,[1] Maria de la Luz Alcantar Vallin,[1] Alejandro Martínez Gallardo González,[2] Guillermo Navarro Blackaller.[1] *[1]Universidad de Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico.*

Background: In advanced CKD the worse the hemoglobin (Hb) values, the higher the risk of major adverse kidney events (MAKE). The existing evidence regarding this relationship is scarce. We carried out a retrospective cohort in patients with advanced CKD and severe anemia, who had increases in Hb level during follow-up, we looked for the association with MAKE.

Methods: In a retrospective cohort study, we included patients with CKD G3b-G5 without dialysis and severe anemia at baseline (Hb <8.0 gr/dL). Our objectives were to analyze whether there was an association between reach Hb >10gr/dL or >12gr/dL and the risk of MAKE, defined as the start of KRT and death, also analyzed the individual components of MAKE

Results: Between 2018 and 2023, a total of 174 patients with CKD G3b-5 and severe anemia (median Hb 7.05 g/dL) were included; the age was 38.5 years, 64% were male. During follow, 32 and 11 patients elevated the Hb >10 g/dl and >12 g/dl, 88.5% used erythropoietin. Patients who achieved an Hb >10 g/dL had an associated reduction in the risk of MAKE (HR 0.46, p = 0.002), especially in reducing the risk of KRT (HR 0.463, p = 0.002), but not for mortality (HR 0.88, p = 0.834), interestingly, use of EPO were associated with increasing this risk (HR 7.78, p = 0.03). We found no benefit in MAKE or its components in patients who achieved Hb >12 g/dL, nor in granular changes in the Hb level.

Conclusions: In our cohort of patients with advanced CKD and severe anemia, we found that those who during their follow-up increased their Hb value >10 g/dL had an association with a reduced risk of MAKE, mainly due to the KRT component.

PUB075

Single-Center, 1-Year Experience of the Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI) Desidustat in Dialysis-Dependent Patients with CKD-Related Anemia

Rajeev Bhatia, Ajay Marwaha, Sonali Raheja. *Shriman Superspeciality Hospital, Jalandhar, India.*

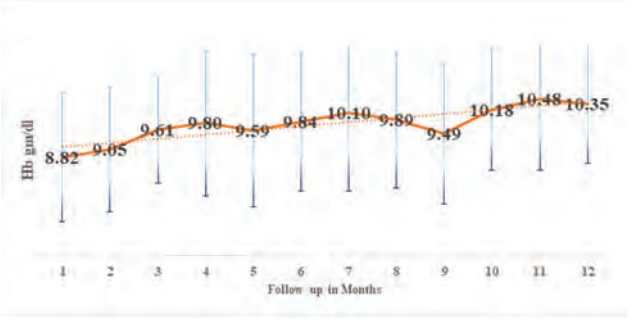
Background: Chronic kidney disease-induced anemia is due to relative deficiency of Erythropoietin from kidneys. In the dialysis-dependent category, patient become dependent on erythrocyte-stimulating agents. Newer HIF PHIs showed promise of correcting anemia in dialysis-dependent CKD anemia patients. Our study is a retrospective analysis of usage of HIF PHI in dialysis-dependent patients.

Methods: This is a single center retrospective analysis of one year experience at Shrimann hospital, Jalandhar. We enrolled patient who are diagnosed with CKD – Anemia and dialysis dependent at our center. These patients were started on Treatment of Desidustat 100 mg and 50 mg thrice in a week and every monthly their Hemoglobin monitored.

Results: In present study, we have enrolled total 58 patients. Out of this 36 (62%) were male and 22 (38%) were female. All patient received dialysis for 3 times in a

week. Patient received IV iron according to iron profile. Out of 57 patients, majority had diabetic Kidney Disease (n=42, 73.6%), Hypertension (45, 78.9%), CAD (4, 7%), ADPKD (2, 3.5%) and one case of post-transplant (1, 1.7%), Multiple Myeloma (1,1.7%), IgAN (1,1.7%), Majority of our patient received treatment of Desidustat 100 mg (n=32, 55.2%) and 50 mg (n= 26, 44.8%) for CKD anemia thrice a week. Mena Serum creatinine 7.56 ± 3 mg/ dl and eGFR 8.72 ± 5.7 mL/min/1.73m^2. Mean Serum Iron 29.74 ± 46.5 mcg/dl. Baseline Hb at the start of treatment was 8.82 ± 1.8 gm/dl at the end of study Hb was 10.35 ± 1.7 gm/dl (p= 0.002, One way ANOVA) test) showed in Figure 1. Mean difference from baseline observed was 1.53 gm/dl in dialysis dependent patients. In present study al patients maintained good compliance with the treatment of Desidustat. Out of 58 patients, we have not observed any thrombosis of AV fistula or Fistula failure, treatment failure, or hyperkalemia with HIF-PHI treatment.

Conclusions: Desidustat showed a promising outcome in terms of improvement of Hb in CKD-anemia. Long-term, one year data showed desidustat is a safe alternative to erythropoietin analogue.



PUB076

Hematuria Rescues Urothelium

Jonathan M. Barasch,[1] Katherine Xu,[1] Tian Shen,[1] Aryan S. Ghotra,[1] Kivanc Nesanir,[2] Rachel Sturley.[1] *[1]Columbia University, New York, NY; [2]University of Richmond, Richmond, VA.*

Background: Hematuria is a frightening complication of urinary diseases. Hematuria may be pathogenic because heme carries lipophilic Fe^{2+} which damages cells. In addition, iron is limiting for bacterial growth, but bacteria express heme transporters and siderophore receptors. Hence, hematuria may accelerate UTI and tissue damage.

Methods: We loaded the urinary system with ferric iron or with heme by phenylhydrazine (PHZ) hemolysis. UTI was titrated in male-females (20uL of 10^7 UTI89 CFU) and tissue damage monitored by $CK20^+$ superficial shedding versus preserved $CK5^+$ basal cells. RNA was captured by (1) physical isolation of urothelia from bladder mucosa (2) and by 4-thiouracil pulse labeling of nascent RNA in vivo in Upk2Cre;$Uprt^{f/f}$ urothelia. RNAscope probed anatomical expression of induced genes.

Results: UTI induced detachment and shedding of superficial cells (6-12hrs post infection). Ferric iron worsened and ferric iron deficiency suppressed bacterial growth and shedding. In contrast, hematuria did not affect bacterial growth but surprisingly prevented shedding (n=75 mice). Retention of superficial cells and suppression of erythema were grossly visibile even after bacterial invasion. Urothelial RNA demonstrated that pyroptosis genes mediate heme sensitive cell death. Indeed, GsdmD KO mice suppressed urothelial shedding and accordingly hematuria suppressed GsdmD RNA expression. Upstream regulators of GsdmD, such as Nlrp3 and cleaved casp1 and 11 proteins were depressed by hematuria in superficial and intermediate cells. Pyroptosis associated cytokines, chemokines, neutrophil chemoattractants, interleukins and inflammatory cell death regulators were quantitatively downregulated. In accordance, neutrophil invasion of the infected bladder was suppressed. Heme is captured in urothelia by HRG1, which in turn transports heme into the cytoplasm where upregulated BMAL, NPAS2, and HMOX1 metabolize heme to Carbon Monoxide (detectable with our Palladium-based fluorescence quenched probes) and iron (detectable by Perls and Turnbull's staining). However, HRG1 KO and HMOX KO still demonstrated rescue by hematuria. Rather, multiple TLR components mediate heme's activity since KO prevented urothelial rescue.

Conclusions: Hematuria, a frightening sign of urological disease, is surprisingly anti-inflammatory and cell protective in UTI-Cystitis.

Funding: NIDDK Support

PUB077

Dapsone-Induced Methemoglobinemia

Ariella Rubel, Alan Araiza, Raphael J. Rosen. *The Stamford Hospital, Stamford, CT.*

Introduction: Methemoglobinemia is a state in which hemoglobin-associated iron is oxidized to Fe3+, resulting in allosteric changes to hemoglobin that inhibit oxygen release to peripheral tissues. It is often secondary to oxidizing substances like benzocaine, nitrates, and dapsone, a sulfa derived antibiotic that can be used for pneumocystis jiroveci (PCP) prophylaxis. Methemoglobinemia presents with nonspecific headache, weakness, and fatigue along with unexplained hypoxemia and cyanosis that do not improve with supplemental oxygen. The saturation gap, or the difference between a depressed pulse oximetry reading (SpO2) and a normal oxygen saturation (SaO2) on arterial blood gas (ABG), is characteristic. This is an artifact of pulse oximetry technology, which measures SpO2 by calculating the difference between absorption of distinct light wavelengths for hemoglobin and oxy-hemoglobin. As oxyhemoglobin falls, SpO2 drops, plateauing around 85%. In contrast, ABG measures oxygen partial pressure directly to estimate SaO2, neither of which change in methemoglobinemia.

Case Description: An 84-year-old woman presented with rapidly progressive glomerulonephritis and, after kidney biopsy showed diffuse cellular crescents, was diagnosed with PR-3 ANCA vasculitis. She had no pulmonary manifestations. She was treated with pulse-dose steroids, cyclophosphamide, and plasma exchange. G6PD level was normal and she was given dapsone for PCP prophylaxis. Despite kidney recovery and decreasing PR-3 ANCA titer, she developed worsening hypoxia. Hemoptysis and cough were absent. Chest X-ray was clear and chest computed tomography (CT) showed no evidence of pneumonia or diffuse alveolar hemorrhage. VQ scan excluded pulmonary embolism. Echocardiogram with bubble study was normal. A trial of furosemide did not improve oxygenation. Pulse oximeter measured oxygen saturation of 88% with no improvement after administration of 6 liters oxygen by nasal cannula. ABG demonstrated oxygen partial pressure of 100 mmHg. Serum methemoglobin level was elevated to 7.6%. With withdrawal of dapsone therapy and addition of high dose oral ascorbic acid, hypoxia resolved.

Discussion: Glucocorticoids are the basis of ANCA vasculitis treatment, causing iatrogenic immunocompromise and necessitating PCP prophylaxis. While hypoxemia has many potential culprits in syndromes that include pulmonary manifestations, dapsone use should prompt consideration of methemoglobinemia.

PUB078

Safety and Efficacy of Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitors Compared with Erythropoiesis-Stimulating Agents in Patients with Nondialysis-Dependent CKD: Analysis of Real-World Data

Masayuki Yamanouchi,[1] Tatsuya Suwabe,[1] Kengo Furuichi,[3] Takashi Wada.[2] *[1]Toranomon Hospital, Minato-ku, Japan; [2]Kanazawa University, Kanazawa, Japan; [3]Kanazawa Medical University, Kahoku-gun, Japan.*

Background: Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs) are expected to be an alternative to erythropoietin stimulating agents (ESAs) due to their ease of administration. However, evidence for the safety and efficacy of HIF-PHIs compared to ESAs is limited in the real-world clinical settings.

Methods: We emulated a target trial, using a 1:1 propensity score matching, to compare the safety and efficacy of outcomes in patients with non-dialysis dependent chronic kidney disease and renal anemia who initiated HIF-PHIs with those initiated ESAs. The primary safety outcomes were the first occurrence of MACE; composite of cardiovascular death, myocardial infarction, or stroke, expanded MACE; MACE plus hospitalization for either heart failure or a thromboembolic event, MAKE; composite of initiating kidney replacement therapy, experiencing over a 40 % eGFR decline from baseline, and all-cause mortality. The primary efficacy outcome was the mean changes in Hb level from baseline to month 21 through 24 (non-inferiority margin, -0.75 g/dL).

Results: During a median follow-up of 14 (IQR, 10-24) months, compared with patients initiating ESAs (n = 269), those initiating HIF-PHIs (n = 263) had a similar risk of MACE (Hazard ratio (HR) 0.80; [95% confidence interval (CI), 0.31-2.10]), expanded MACE (HR 0.81 [0.40-1.63]), MAKE (HR 1.01 [0.72-1.42]), and all-cause mortality (HR 1.41 [0.50-3.99]). The mean (±SE) changes in Hb level from baseline to month 21 through 24 were 1.62±0.16 g/dL in the HIF-PHIs group and 1.38±0.08 g/dL in the ESAs group.

Conclusions: There were no statistically significant differences in safety and efficacy between HIF-PHIs and ESAs. The results may help guide the choice of treatment of renal anemia.

PUB079

Alignment of ChatGPT with Expert Opinion in Nephrology Polls

Justin Pham, Charat Thongprayoon, Jing Miao, Iasmina Craici, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Healthcare professionals often face complex clinical scenarios that do not have straightforward solutions, necessitating professional collaboration. This is common in nephrology, where soliciting peer insight is crucial for informed decision making. ChatGPT, a sophisticated language model, has demonstrated its problem-solving utility in several fields. However, its alignment with prevailing medical opinions in the context of intricate clinical scenarios remains unexplored. This study seeks to evaluate how closely ChatGPT's responses align with the nephrology community's prevailing opinions by comparing responses to real-world clinical questions.

Methods: Nephrology polls were collected from the social media site X using the hashtag #AskRenal, resulting in 271 questions. These were presented to ChatGPT-4, which generated answers without prior knowledge of the poll outcomes. This was

repeated one week later using the same questions presented in a randomized order to assess internal consistency. The responses given by ChatGPT-4 during the two rounds of inquiry were compared to the poll results (inter-rater) and between each other (intra-rater) using Cohen's kappa statistic (κ). The questions were also grouped into seven categories based on subject matter, and subgroup analysis was performed.

Results: 60.2% of responses from ChatGPT matched the poll results in the first round of inquiry (κ=0.42) and 63.1% matched in the second (κ=0.46). The two rounds had an internal agreement rate of 90.4% (κ=0.86). The included table presents subgroup data.

Conclusions: ChatGPT-4 demonstrates moderate capability in replicating prevailing professional opinion in nephrology polls, with varying performance levels between question categories and high internal consistency. While AI-based language models have potential to assist with decision making in complex clinical scenarios, their reliability has yet to be fully proven and they should be integrated cautiously.

Agreement by question category

	Round 1	Round 2	Intra-rater
CKD, ESRD, dialysis, & transplant	62% (κ=0.4)	64% (κ=0.5)	90% (κ=0.9)
Electrolyte & acid-base disorders	62% (κ=0.5)	54% (κ=0.4)	92% (κ=0.9)
Glomerular disease, AKI, & critical care	51% (κ=0.3)	58% (κ=0.4)	87% (κ=0.8)
Mineral, bone, & stone diseases	78% (κ=0.7)	89% (κ=0.8)	89% (κ=0.8)
Pharmacology	65% (κ=0.5)	65% (κ=0.5)	100% (κ=1.0)
Tubular, interstitial, & cystic disorders	50% (κ=0.1)	25% (κ=-0.1)	75% (κ=0.6)
Other	73% (κ=0.6)	80% (κ=0.7)	93% (κ=0.9)

PUB080

Examining Global and Regional Interest in Kidney Transplantation Awareness

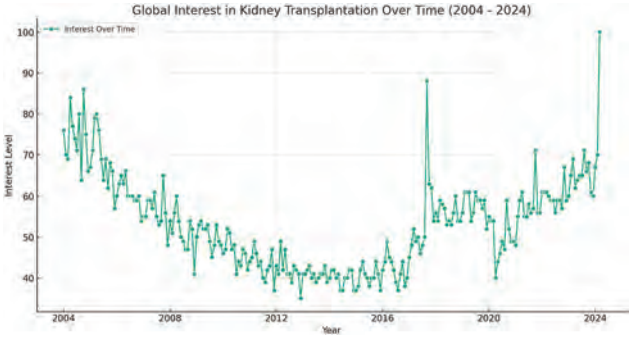
Oscar A. Garcia Valencia,[1] Charat Thongprayoon,[1] Jing Miao,[1] Napat Leeaphorn,[2] Pooja Budhiraja,[3] Supawadee Suppadungsuk,[1] Iasmina Craici,[1] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic in Florida, Jacksonville, FL; [3]Mayo Clinic Arizona, Scottsdale, AZ.*

Background: Kidney transplantation is a vital treatment for end-stage kidney disease, offering enhanced quality of life and survival rates. Given the increasing use of the internet for health-related information, analyzing online search trends can provide insights into public engagement and awareness. This study used Google Trends™ to examine global and regional interest in kidney transplantation.

Methods: A comprehensive investigation using the phrase "kidney transplantation" was conducted on Google Trends, covering the period from its creation in January 2004 until March 2024. The analysis was centered on global engagement, with a detailed examination of patterns across regions and nations. The interest was assessed using Google Trends indices, with each data point reflecting a monthly search volume score

Results: Across the two decades, a dynamic fluctuation in global interest was observed, marked by significant peaks and valleys. The highest interest occurred in March 2024, reaching an index score of 100, while the lowest was recorded in December 2012 with a score of 35. A pronounced increase in interest was seen in March 2024 when compared to the same period in 2023 (escalating from 69 to 100) suggesting an increase in global attention towards kidney transplantation. Regional analysis highlighted distinct variations with South Dakota, Missouri, and Maryland leading in the United States. Globally, Sudan, Nepal, and Pakistan emerged as the countries with the highest interest with the US ranking sixth.

Conclusions: The study reveals a significant global and regional interest in kidney transplantation, highlighted by recent peaks in search volume. The variations in interest levels may reflect differences in healthcare needs, awareness, and resource availability. This study provides valuable insights into the global and regional landscape of kidney transplantation interest, emphasizing the importance of harnessing online platforms to enhance public awareness, education, and engagement.



PUB081

Identification of Kidney Cell Types in Single-Cell RNA Sequencing and Single-Nucleus RNA Sequencing Data Using Machine-Learning Algorithms

Siddharth S. Madapoosi,[1] Adam Tisch,[1] Stephen A. Blough,[1] Jan S. Rosa,[1] Sean Eddy,[1] Abhijit S. Naik,[1] Christine P. Limonte,[2] Phillip J. McCown,[1] Rajasree Menon,[1] Sylvia E. Rosas,[3] Chirag R. Parikh,[4] Laura H. Mariani,[1] Matthias Kretzler,[1] Ahmed Mahfouz,[5] Fadhl Alakwaa.[1] Kidney Precision Medicine Project (KPMP). *[1]University of Michigan, Ann Arbor, MI; [2]University of Washington, Seattle, WA; [3]Joslin Diabetes and Endocrinology Research Center, Boston, MA; [4]Johns Hopkins University, Baltimore, MD; [5]Leids Universitair Medisch Centrum, Leiden, Netherlands.*

Background: Single-cell RNA (scRNA) and single-nucleus RNA (snRNA) sequencing offer researchers valuable insight into the biological states of kidney cells. Manual cell-type annotation requires extensive domain expertise, is time-consuming, and limits broad scalability.

Methods: We compared the ability of different machine learning (ML) algorithms including support vector machines, random forests (RF), multilayer perceptrons (MLP), k-nearest neighbors (KNN), and XGBoost to predict kidney cell types from scRNA/snRNA-seq data. We used publicly available human kidney datasets comprised of 62,120 cells from 40 donor biopsies included in 5 expert-annotated sc/snRNA-seq studies. We integrated all 5 studies using the Seurat rPCA integration protocol and used inter-dataset combinations of 4 training datasets and the fifth for performance testing. We compared the performance of the different ML algorithms using F1 scores and percentage of unknown cells.

Results: Upon integration of all 5 datasets, we identified a total of 16 harmonized cell types. All 5 algorithms predicted these cell types with high accuracy (median F1=0.94 and 1.8% unknown cells). No algorithm was superior to the others overall (p>0.05) and all algorithms successfully rejected cell types naive to training data, in particular RF, MLP, and KNN models. F1 scores were lower across ML algorithms when using snRNA-seq data for testing, particularly for proximal tubule and fibroblast cells.

Conclusions: ML algorithms were able to accurately annotate adult kidney cell types from scRNA-seq, and to a lesser extent, snRNA-seq data. Our study methodology may be applied across other validation cohorts with the expectation that prediction accuracy improves over time.

Funding: NIDDK Support, Other NIH Support - JDRF

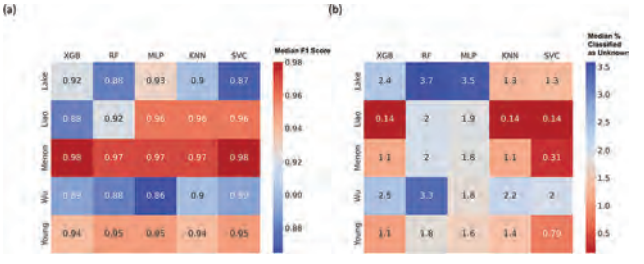


Figure 1. Heatmaps demonstrating the performances of each classification algorithm on each testing dataset by (a) median F1 score or (b) median % of cells classified as unknown.

PUB082

Evaluating the Acceptability and Feasibility of a Low-Sodium Educational Program Using Immersive Virtual Reality in Patients on Hemodialysis: A Study Protocol

Milad Hasankhani,[1] Geovana Martin-Alemañy,[1] Kaitlyn Pawelczyk,[2] Kenneth R. Wilund.[1] *[1]The University of Arizona, Tucson, AZ; [2]University of Illinois Urbana-Champaign, Urbana, IL.*

Background: About 80% of hemodialysis (HD) patients in the U.S. have uncontrolled hypertension, primarily due to chronic volume overload. HD patients are often prescribed low-sodium diets to prevent thirst and fluid accumulation. However, the poor compliance highlights the pressing need for innovative strategies to reduce sodium intake to minimize cardiovascular risks associated with HD.

Methods: This study employs an exploratory, non-randomized, open-label trial using a mixed-methods approach. Twenty patients who meet the inclusion criteria will be provided access to the VR program during their regular dialysis sessions. The program includes five educational modules, each approximately thirty minutes, and incorporating interactive games and other knowledge building activities in an engaging environment to help patients learn low-sodium meal planning and shopping. Oculus Quest 2 headsets will be used to deliver the VR experience, ensuring patient safety and comfort. Quantitative and qualitative data will be collected through surveys measuring engagement, satisfaction, VR content quality, and sodium-related knowledge.

Results: Results will focus on the acceptability and feasibility of the low-sodium educational program delivered through immersive virtual reality. The target rates for recruitment, retention, and adherence are set at or above 75%. The study anticipates a positive impact on participants' dietary sodium knowledge post-intervention.

Conclusions: This program has the potential to advance HD patient's knowledge on better management of their dietary sodium intake and related health conditions, with implications for broader applications of VR in health education and patient engagement.

PUB083

The Kidney Mobile Health Registry: A Digital Research Approach

Eloise Salmon,[1] Ashley E. Rahimi,[1] Rebecca Scherr,[1] Michael Arbit,[1] Tina Creguer,[1] Hailey Desmond,[1] Abigail R. Smith,[2] Susan F. Massengill,[3] Zubin J. Modi.[1,4] *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]Northwestern University Feinberg School of Medicine, Chicago, IL; [3]Levine Children's Hospital, Charlotte, NC; [4]University of Michigan Susan B Meister Child Health Evaluation and Research Center, Ann Arbor, MI.*

Background: Mobile health (mHealth) technologies offer a novel approach to research and data collection. Despite mHealth use in other chronic disease states, kidney focused initiatives are limited. The Kidney Mobile Health Registry is designed to assess the feasibility of mHealth use in targeted kidney disease study populations.

Methods: Three observational cohort studies were selected as pilots for the mobile registry (Figure 1). The registry was built in collaboration with CareEvolution (*Ann Arbor, MI*) and is offered via the MyDataHelps (MDH) application. Individuals are invited to participate or can enroll independently, consenting electronically within MDH. Enrollment is uncapped and includes both children and adults.

Results: The studies were moved to production following beta testing in a phased approach. All studies have launched as of March 2024, with recruitment to date detailed in Figure 2.

Conclusions: MHealth offers a novel research and disease management approach. Further exploration of recruitment, retention, and engagement strategies specific to kidney disease populations are needed.

Funding: NIDDK Support, Private Foundation Support

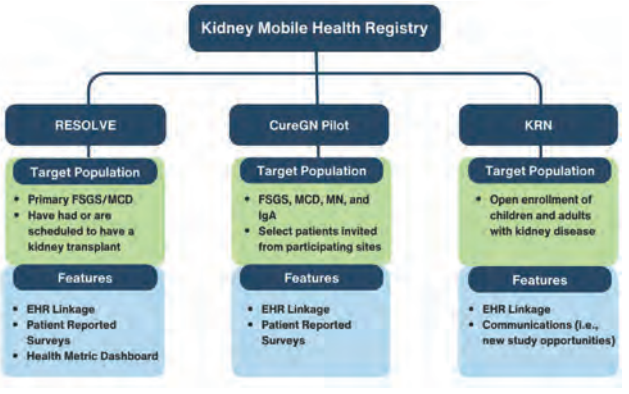


Figure 1. Registry Structure

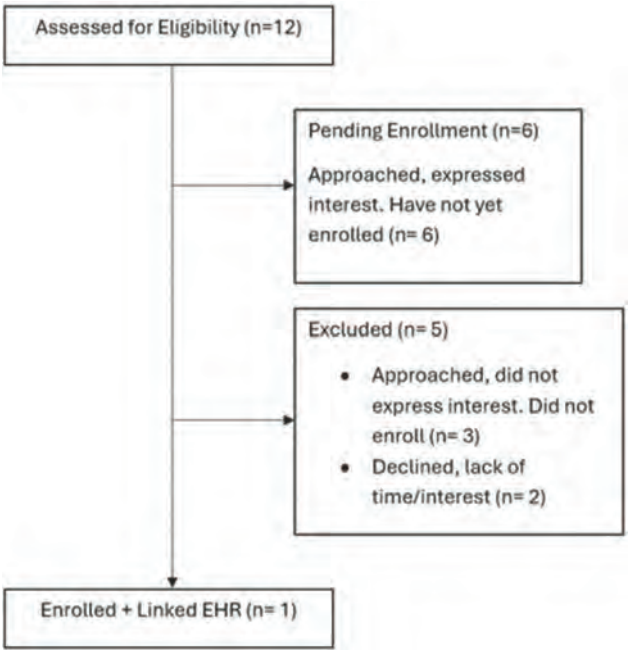


Figure 2. Registry Consort

PUB084

Cardiovascular Risk Stratification Using Predicted Coronary Artery Calcium Score from a Machine-Learning Model

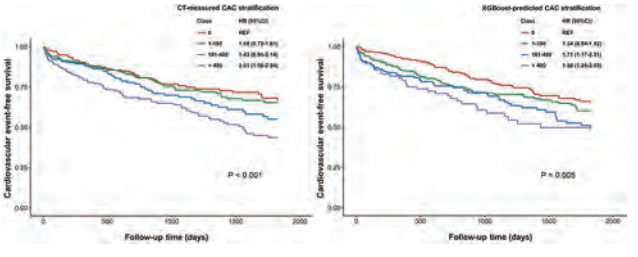
Kullaya Takkavatakarn,[1,2] Pooja Anand Gownivaripally,[1] Girish N. Nadkarni,[1] Lili Chan.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*

Background: Cardiovascular disease (CVD) is a common complication in patients with chronic kidney disease (CKD). Coronary artery calcium (CAC) score is a clinically validated marker of CVD risk but not readily accessible for many patients. We aimed to develop and validate machine learning (ML) models to predict CAC groups and assessed the use for risk stratification of CVD events.

Methods: We obtained electronic health record (EHR) data from patients with non-dialysis CKD stages 3-5, defined by an eGFR of less than 60 mL/min/1.73 m2 for at least 3 months, and without a history of CVD at the Mount Sinai Health System who underwent a CAC scan. CAC scores were categorized into 4 groups (0, 1-100, 101-400, and > 400). We divided the cohort into a training and test dataset (70/30) then developed and validated four models, decision tree (DT), random forest (RF), XGBoost, and deep neural network (DNN), to predict CAC score groups. Area under the receiver operating characteristic curve (AUROC) was used to evaluate model performances. We utilized Cox regression to assess the association between CAC group and the best-performing ML model-predicted CAC group with CVD events within 5 years. Risk discrimination was measured using C-statistics.

Results: We included 648 patients; the median age was 70 (IQR 63-77) and the median CAC score was 64 (IQR 0-306). XGBoost yielded the best AUROC (0.72; 95%CI 0.63 to 0.79), followed by RF (0.71; 95%CI 0.63 to 0.78), DNN (0.64; 95%CI 0.53 to 0.71), and DT (0.61; 95%CI 0.52 to 0.68). 210 (32%) had CVD events during the 5-year follow-up. CT scan-measured CAC and the XGBoost-predicted CAC risk stratification were significantly associated with CVD events (Figure1). The C-statistics were 0.67 and 0.66 respectively.

Conclusions: ML-derived CAC risk stratification is comparable to CT scan-measured CAC risk stratification in predicting CVD events. Implementing ML techniques on EHR data can serve as an alternative approach for assessing CAC and improving CVD risk prediction, particularly in settings with limited resources.



PUB085

Exploring the Connection between Serum Lead Levels and Kidney Function among the Obese Population: Analysis of NHANES, 2017-2020

Chutawat Kookanok,[1,2] Sansanee Thotsiri,[3] Methavee Poochanasri,[2] Kamonluk Rodsom,[1] Narathorn Kulthamrongsri,[4] Ariya Mongkolporn,[5] Varissara Sinkajarern,[6] Thutpharritchn Phoonakh,[6] Wanprapit Noree,[7] Urairat Chuenchaem,[8] Ekamol Tantisattamo.[1] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Phramongkutklao Hospital, Bangkok, Thailand; [3]Mahidol University Ramathibodi Hospital, Bangkok, Thailand; [4]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [5]Thammasart University Faculty of Science and Technology, Khlong Nueng, Thailand; [6]Vimut Hospital, Bangkok, Thailand; [7]University of Illinois Chicago, Chicago, IL; [8]Bumrungrad International Hospital, Bangkok, Thailand.*

Background: Lead, a common toxic substance found in air pollution and consumer products, is known for its association with renal damage, notably lead nephropathy. National-scale evidence on how obesity influences this link is limited and uncertain. This study investigates whether obesity exacerbates the risk of kidney damage from lead toxicity.

Methods: A national study of 6,789 adults, using NHANES 2017-2020 data, analyzed the correlation between serum lead levels (Pb-S) and eGFR. Participants were categorized into non-obesity and obesity groups based on BMI, with three linear regression models employed (Table 1). Receiver operating characteristic (ROC) curve analysis was also conducted for each BMI category to predict advanced kidney disease (eGFR < 60) based on Pb-S levels.

Results: The study population had an average BMI of 29.9±7.3 kg/m^2, with 41.5% classified as obese. The average Pb-S level was 1.04±0.68 μg/dL, and average eGFR was 96.1±19.8 mL/min/1.73 m^2. In the final adjusted model, eGFR declined significantly in the total group by 0.96 (95% CI: -1.81 to -0.11) and in the obese group by 1.97 (95% CI: -3.41 to -0.54) per unit increase in Pb-S (Table 1). Pb-S demonstrated a notable predictive ability for advanced kidney disease, with obesity achieving a sensitivity of 63%, specificity of 68%, and an ROC-AUC of 0.77.

Conclusions: A significant negative correlation between Pb-S and eGFR, amplified by obesity was founded among US adult, suggest the kidney function monitoring among those with history of lead exposure especially those with obesity in order to early detection of kidney injury.

	Model 1		Model 2		Model 3	
	β-Coefficients (95% CI)	P-value	β-Coefficients (95% CI)	P-value	β-Coefficients (95% CI)	P-value
Total	-8.35 (-9.02,-7.67)	**<0.001**	-1.08 (-1.92,-0.23)	**0.013**	-0.96 (-1.81,-0.11)	**0.027**
Non-obesity	-7.60 (-8.43,-6.76)	**<0.001**	-0.89 (-1.95,0.17)	0.099	-0.70 (-1.76,0.37)	0.200
Obesity	-10.46 (-11.63,-9.29)	**<0.001**	-2.13 (-3.56,-0.71)	**0.003**	-1.97 (-3.41,-0.54)	**0.007**

Table 1: Table of correlation analysis between serum lead levels (Pb-S) and estimated glomerular filtration rate (eGFR) using three different logistic regression models. The first model included only Pb-S, the second model added age, race, smoking, and drinking, and the third model further included dyslipidemia, hypertension, diabetes, coronary artery disease, congestive heart failure, and stroke.

PUB086

Role of Artificial Intelligence (AI) in Renal Diet

Harshil Fichadiya,[1] Vraj Patel,[2] Iasmina Craici.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Canton Medical Education Foundation, Canton, OH.*

Background: Patients with advanced CKD and ESRD experience hypertension, hyperkalemia and hyperphosphatemia and frequently struggle with maintaining a low sodium, potassium and phosphorous diet. Part of this struggle is from lack of understanding of foods containing higher amount of these electrolytes and lack of an organized diet plan. Consultation with a renal dietician may help them create a dietary plan, however the high CKD patients to renal dieticians ratio and subesequent difficulty with frequent monitoring of dietary plans make this option less feasible for many patients. An AI tool that can monitor daily dietary electrolyte intake and suggest dietary plans per patient preference may be more affordable and accessible to majority of patients.

Methods: We used ChatGBT- 4 to i) Assess electrolyte content of various foods and suggest a renal friendly alternate ii) Devise a daily renal dietary plan for vegan, vegeterian and meat based diet (K<60 Meq, Na <2g, Phos <1g/kg/day) for 70 kg patient iii) Assesed if Chat-GBT was able to modify the dietary plan based on patient preference for episodic food craving while maintaining compliance with renal diet.

Results: Chat GBT 4 devise a wonderful vegan, vegeterian and meat based dietary plan (including breakfast, lunch and dinner) with renal electrolyte restriction as mentioned above. It was able to accomodate a small serving of high potassium food high phosphorous food (orange & cookie), when asked to modify diet to include episodic cravings that our patients may feel. It was also able to suggest alternates to high potassium foods, eg apple juice, cranberry juice or grape as an alternate to orange juice.

Conclusions: Though simple, this intervention has the potential to be highly effective in helping advanced CKD and ESRD patients maintain compliance with a renal friendly diet. While daily access to a renal dietician may be difficult, this intervention will allow patients to devise daily renal friendly dietary plan based on their food preference while accomodationing for episodic non-renal friendly food craving in real time. Long term effective compliance with a renal friendly diet will translate into better bone health, slower CKD progression and reduction in episodes of dangerous hyperkalemia between dialysis sessions. In summary AI will complement the role of a renal dietician by facilitating effective implementation of dietary goals set by the dietician.

PUB087

Real-World Data Acquisition Methodology for Studying Cardiovascular Functional Capacity in CKD

Nolan Groninger,[1] Nikita F. Samanani,[1] Cody A. Altherr,[2] Gayatri Narayanan,[1] Sharon M. Moe,[1] Kenneth Lim.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Indiana Center for Musculoskeletal Health, Indianapolis, IN.*

Background: Cardiopulmonary exercise testing (CPET) is a diagnostic tool that generates hundreds of data points from ventilatory, cardiac and hemodynamic assessments during graded exercise. Unfortunately, there currently exists a paucity of epidemiologic datasets incorporating CPET data in patients with chronic kidney disease (CKD). Translational bottlenecks also exist to obtain and process the data for research purposes. Herein, we developed a methodology to create a novel centralized "CPET data hub" for capturing, automating data transfer and creating data linkages with important clinical information.

Methods: At Indiana University Health, CPET data is acquired by a specialized software (Breeze) that pushes a summary image report onto our electronic medical record system. To address this, we created a unique CPET data hub—a centralized data acquisition and processing hub enabling real-time capture of CPET output (linked to our hospital SQL server). The CPET data hub houses a digital platform (involving the development of algorithms via data mining methods and query modules) to process and calculate computed variables uniformly. CPET data on the hub is then linked to clinical information obtained through the Regenstrief Institute Informatics and the Indiana Network for Patient Care. CPET data is merged with clinical information including demographics, comorbidities, imaging, laboratory data and longitudinal outcome data.

Results: To date, our CPET data hub has captured comprehensive CPET data from n=1,953 adult ambulatory referral patients who underwent CPET testing. The cohort includes n=773 males and n=712 females. Approximately 37% have CKD stage 3; 4% have CKD stage 4; and 3% have end-stage renal disease or a history of kidney transplantation. The CPET data hub and linkage to important clinical outcomes (ongoing work) has led to the development of the "Cardiorespiratory Fitness in Patients with Chronic Kidney Disease in Indiana (FIT-INDY) cohort".

Conclusions: As automation processes becomes readily available through the integration of computer science into medical research, it is necessary that we incorporate data acquisition methodologies into nephrology to assess real-world health outcomes for patients with CKD. The feasibility of epidemiologic studies incorporating CPET data is enabled by the CPET data hub.

Funding: Other NIH Support - NCATS

PUB088

Pilot Study of a Remote Blood Self-Collection Device in Cure Glomerulonephropathy (CureGN)

Taylor A. Hill-Horowitz,[1] Suzanne Vento,[1] Lawrence B. Holzman,[3] Christine B. Sethna.[1,2] On behalf of CureGN Investigators. *[1]Cohen Children's Medical Center, Queens, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [3]Penn Medicine, Philadelphia, PA.*

Background: Long-term biospecimen collection is a challenge in longitudinal cohort studies, especially for participants not actively followed clinically. TAP Micro Select is an FDA 510(k) cleared device that uses microneedles and a vacuum mechanism for self-collection of blood, allowing participants to provide biosamples remotely. This study aimed to determine the feasibility, reliability, and tolerability of the TAP device for remote blood collection for routine labs in the longitudinal CureGN study of primary glomerular disease.

Methods: Active participants at select CureGN sites were eligible. Participants were mailed materials for using the TAP device for at-home blood collection. Participants returned biosamples in a pre-paid shipper. Blood was processed for serum creatinine, albumin, and cystatin-C. In addition, samples from healthy controls were drawn both by venipuncture and TAP device. Control TAP samples were held at ambient temperatures for 24-72 hours (h) to simulate participant shipping. Outcomes were percent enrolled of those approached, time to receive samples, lab completion rate, participant satisfaction, and concordance of TAP samples with venipuncture.

Results: Of 47 participants approached, 39 (ages 14-85 years, 69% male) consented to the study (83% recruitment). The primary reason for declining was "dislike of handling blood." Of the 22 who completed the blood draw, participants shipped their collected samples a median of 4.4 days [IQR 0.2-15.6] after receiving materials. Median time in transit was 27h [IQR 24-29]. Labs were successfully resulted for 91% (N=20/22) of samples (2 QNS). Satisfaction surveys show that 20/22 rated discomfort 1-2 of 10, 13/18

would choose TAP over venipuncture, and 12/16 said the option of TAP would increase their likelihood of research participation. Main participant concerns were the force needed to push the activation lever and difficulty obtaining enough blood. For 17 healthy controls, analyses comparing samples obtained by TAP vs venipuncture did not vary by assay or time (ICC ≥0.98).

Conclusions: Self-collection of blood with the TAP device was well-tolerated and strongly correlated with venipuncture under study conditions. Thus, remote blood collection with the TAP device is a feasible alternative to venipuncture and may improve collection of biosamples in longitudinal studies.

Funding: NIDDK Support

PUB089

In Vitro Evaluation of a Continuous Potassium Monitoring System in Simulated Dialysis Conditions

Jean-Baptiste Valsamis,[1] Rita Roshni,[1] Citsabehsan Devendran,[1] Fenge Lin,[1] Kaixuan Wang,[1] Cody J. Lensing,[2] Sahan Ranamukha,[1,2] Victor J Cadarso.[1]
[1]Proton Intelligence Australia, Pty Ltd., Melbourne, VIC, Australia; [2]Proton Intelligence, Inc., Vancouver, BC, Canada.

Background: Potassium (K+) dysregulation is a life-threatening condition. During a dialysis session, a patient's K+ levels often begin above the normal range and end below the normal range, before rebounding after the session. We have developed a continuous K+ monitor (CKM) capable of measuring dynamic K+ levels in real-time. In this report, we mimic dialysis conditions in vitro to characterize the sensors' ability to measure rapidly shifting K+ levels.

Methods: The potentiometric sensor probes consist of a working electrode (WE) that measures K+ directly, selectively, and sensitively and a reference electrode (RE). Eight sensors were immersed in fluid controlled by a pump system able to control K+ levels. We simulated dialysis conditions over 5 hours by changing K+ concentration from 7 mmol/L to 4.5 mmol/L and back to 6 mmol/L. The electrical potential was recorded every 30 seconds, and analyzed by retrofitting to the K+ concentration using a 3 parameters function to account for sensitivity, offset, and drift. Parameters were estimated for each sensor individually using least square fit method.

Results: All sensors responded rapidly during K+ changes (Figure). One sensor showed a faulty RE and one showed a time lag of 15 minutes, and were excluded. With the 6 remaining sensors, the average sensitivity was 48 ± 3.5 mV/dec, the drift was 0.84 ± 0.24 mV/h, and the offset was 2.87 ± 14.2 mV. Compared to the programed K+ profile, MARD was <1% and average accuracy was <0.1 mmol/L (defined as the standard deviation of the difference between estimated K+ and reference K+).

Conclusions: The CKM sensors responded accurately to changing K+ levels across the physiological range during a simulated dialysis session. In vivo testing is needed to further support these results.

Funding: Commercial Support - Proton Intelligence, Inc.

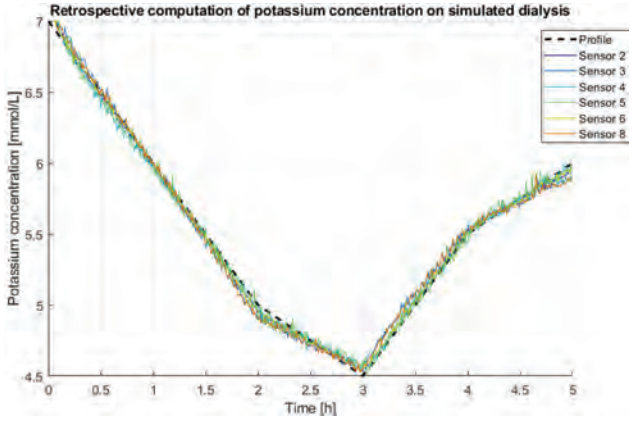


Figure: CKM sensor probes tested in a simulated in vitro dialysis session. Profile represents the programmed K+ concentrations.

PUB090

Optimizing Microfluidic Gradient Generating Surface Plasmon Resonance (SPR) Chips for High-Throughput Biochemical Reaction Kinetics in Renal Physiology

Daniela Molnar, Kiley Kuykendall, Jonathan M. Berman. *New York Institute of Technology College of Osteopathic Medicine at Arkansas State University, Jonesboro, AR.*

Background: Motivated by the desire to study the activity of proteases, and protease inhibitors and activators in urine, we are developing a novel surface plasmon resonance technique which enables monitoring of these reactions over a wide range of simultaneous substrate concentrations, facilitating high-throughput measurement of proteolysis against peptides from protease-regulated macromolecules such as Epithelial Sodium Channel (ENaC).

Methods: This study focuses on optimizing microfluidic chips for channel design, polydimethylsiloxane (PDMS) adhesion to glass, and gold-thin film sputter coating parameters while fabricating sensor chips. We developed a gradient generator chip design, which was cast from 3D-printed resin molds. BK7 glass slides were sputter coated with a gold thin-film. Both glass and PDMS were functionalized using oxygen plasma from a high voltage-high frequency generator to form covalent bonds.

Results: We systematically examined effects of gold coaching thickness, and deposition time on sensor chip functionality. Our results demonstrate successful gradient generation, and assembly of biomolecule monolayers on the gold surface.

Conclusions: Future work will integrate with the SPR design to measure real-world reaction kinetics, advancing our understanding of protease-substrate interaction and regulation in the kidney.

PUB091

Impact of Type 2 Diabetes Mellitus and CKD on Bone Mineral Density in Elderly Patients with Hip Fractures

Debajyoti M. Roy,[1] Chee Yong Ng,[1] Vyjayanti Vasudevan,[2] Sreekanth Koduri,[1] Wenxiang Yeon.[1] *[1]Changi General Hospital, Singapore, Singapore; [2]Singapore American School, Singapore, Singapore.*

Background: Diabetes mellitus (T2DM) and chronic kidney disease (CKD) are common medical conditions in the elderly and have been associated with increased risk of bone fractures due to their negative impact on bone quality. When DM and CKD occur in combination, the negative impact on BMD may be greater due to the complex interplay between the two conditions. This study investigates potential differences in the impact of T2DM and CKD on BMD in elderly patients with fragility hip fracture when these conditions occur alone versus when in combination. We also investigate the relationship of worsening HBA1c to BMD in the groups with and without CKD.

Methods: A cross-sectional study was conducted on 715 elderly patients (age ≥65 years) with fragility hip fracture admitted to a hospital between Jan 2018 and Dec 2020. The study population was divided into four groups: Group 1 - No CKD or Diabetes (n=201), group 2 - No CKD with diabetes present (n=188), group 3 - CKD present with no diabetes (n=166), group 4 - Both CKD and diabetes present (n=160). BMD was measured using dual-energy X-ray absorptiometry (DXA) at the femoral neck. The data were analyzed using analysis of variance (ANOVA) and post-hoc testing with Bonferroni correction.

Results: The mean age of the study population was 75.6±6.8 years, and 62.5% were female. The mean body mass index (BMI) was 25.1+/-3.7 kg/m2. Of the cohort 326 had CKD & 160 T2DM. Table 1 depicts patient groups and variables

Conclusions: 1.In elderly patients with hip fracture, Group 2(T2DM+/CKD-) T score was higher as compared to Group 1 (T2DM-/CKD-). 2.There is a positive linear association between higher HBA1C and T score in Group 2 (T2DM+/CKD-). This association is however lost in the presence of CKD. 3.The post operative LOS was longer in Group 4 (CKD+/T2DM+), 10.4 days compared to Group 1 (T2DM-/CKD-), 8.6 days (P-0.04).

Funding: Clinical Revenue Support

Table : Patient variables

Variables	Group 1 (CKD-/T2DM-) n=201	Group 2 (CKD-/T2DM+) n=188	Group 3 (CKD+/T2DM-) N=166	Group 4(CKD+/T2DM+) N=160	p value (ANOVA)
eGFR	60(0.17)	60(0.0)	47(20.0)	44(16.5)	<0.001
Albumin (g/L)	37(6)	37(6)	37(7.0)	36(5.0)	0.12
HBA1c	-	6.8(1.7)	-	6.4(1.6)	<0.0001
Calcium (mmol/L)	2.2(0.1)	2.3(0.1)	2.3(0.2)	2.2(0.1)	0.19
Phosphate (mmol/L)	1.1(0.3)	1.1(0.3)	1.1(0.3)	1.1(0.3)	0.06
25(OH)D	21.8(17.4)	22.3(16.6)	24.4(18.6)	21.1(17.2)	0.10
T score (hip)	-3.2(1.2)	-2.9(1.3)	-3.2(1.4)	-3(1.4)	0.03
LOS (days)	8.6(6)	8.9(6.5)	9.7(6.5)	10.4(6.9)	0.02

PUB092

A Difficult Case of Calciphylaxis: Continuous Warfarin Use in a Patient with Calciphylaxis

Rupinder Kaur, Sindhu Yarrabelli, Saikiran Mandyam, Bhoomi Shah, Nowoghomwenma C. Ibie. *Southeast Health, Dothan, AL.*

Introduction: Calciphylaxis, or calcific uremic arteriolopathy (CUA), is a poorly understood, challenging complication of end-stage renal disease (ESRD) whose incidence has been increasing in the United States. Several risk factors have been associated with CUA, including warfarin. This article presents a difficult case of calciphylaxis that requires continued warfarin use in a patient with a history of antiphospholipid antibody syndrome with 50-60 episodes of deep venous thrombosis (DVTs), given unsuccessful trials with other anticoagulants in this patient.

Case Description: A 46-year-old male with PMH of ESRD on peritoneal dialysis for 4 months, p-ANCA vasculitis, antiphospholipid syndrome with recurrent DVTs on warfarin, and hypertension presented with violaceous plaques and central eschar-like necrosis in bilateral distal upper inner thighs associated with significant tenderness. The clinical presentation raised suspicions of Calciphylaxis; treatment was initiated with sodium thiosulfate and sevelamer while continuing peritoneal dialysis. A skin biopsy revealed patchy, mild small-vessel vasculitis with calcification and epidermal ischemic necrosis, consistent with CUA. Initially, warfarin was temporarily halted. However, given the patient's unsuccessful trials with Eliquis in the past and his extensive history of venous thromboembolism, ongoing warfarin therapy was deemed necessary, particularly considering his history of heparin-induced thrombocytopenia and allergy to rivaroxaban. Following education on the risks and benefits associated with calciphylaxis and warfarin, the decision was made to continue warfarin. The patient was recommended to follow up with hematology at a tertiary facility for further recommendations on anticoagulation.

Discussion: Once thought to be an uncommon condition, calciphylaxis has increased in frequency as more people require hemodialysis or peritoneal dialysis for ESRD. Given the poorer prognosis of CUA, which includes over 80% mortality in cases of severe CUA, prompt identification and treatment initiation are crucial. As anticoagulants, especially warfarin, have been linked with calciphylaxis, more research is required to understand the pathophysiology and to develop substitute interventions in a complex scenario such as this one where the risk of stopping warfarin outweighs the benefit.

PUB093

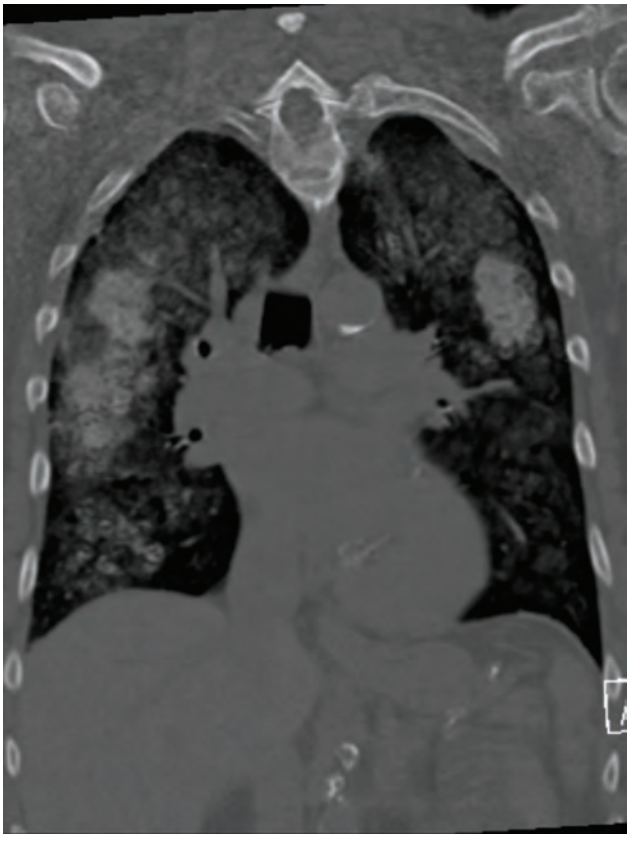
Metastatic Pulmonary Calcification in CKD

Ashley Golbus,[1] Natalie T. Freidin.[2] *[1]Medical University of South Carolina College of Medicine, Charleston, SC; [2]Medical University of South Carolina Department of Medicine, Charleston, SC.*

Introduction: Metastatic calcification, that outside of the cardiovascular system, is observed in 0.5-3% of living dialysis patients. In patients with CKD, the mechanism can involve elevated calcium phosphate product, secondary, or tertiary, hyperparathyroidism. Sites of calcification can include the lung tissue (metastatic pulmonary calcification or MPC).

Case Description: We present a case of a 75-year-old male with a history of ESRD on hemodialysis, hypertension, hyperlipidemia, two vessel coronary artery disease s/p recent PCI, severe aortic stenosis, and chronic heart failure, presenting with hypoxemic respiratory failure. Pertinent labs included: PTH 666.8 pg/mL, phosphorous 7.9 mg/dL, and calcium 9.1 mg/dL. Chest X-ray (CXR) demonstrated bilateral multifocal patchy and confluent airspace opacities, favored to represent pulmonary edema. Non-contrast chest CT showed diffuse bilateral ground glass opacities and centrilobular groundglass nodularity (note subpleural sparing) with upper lobe predominant patchy, hyperdense parenchymal consolidations and calcifications (Figure 1). These findings were determined to represent MPC. After a complicated hospital course, valve replacement was not a feasible option and he was transitioned to hospice care and died.

Discussion: MPC is apparent on CXR as confluent or patchy airspace opacities and on CT as diffuse calcified nodules, diffuse or patchy areas of ground glass opacities or consolidation, and confluent high attenuation parenchymal consolidation. In rare cases, this can cause acute respiratory failure with a rapidly progressive chest shadow that mimics pneumonia or pulmonary edema. These imaging findings in patients with chronic kidney disease or on dialysis should lead to consideration of MPC as a differential diagnosis.



PUB094

Efficacy of Peridialytic Cinacalcet in Controlling Hyperparathyroidism in Non-observant Patients on Chronic Hemodialysis in Western French Guiana

Arriel Makembi,[1,2] Florence Fermigier.[2] *[1]Universite de Kinshasa Faculte de Medecine, Kinshasa, Congo (the Democratic Republic of the); [2]Centre Hospitalier de l'Ouest Guyanais Franck Joly, Saint-Laurent-du-Maroni, French Guiana.*

Background: Secondary hyperparathyroidism (HPT) is one of the most common complications in chronic kidney disease and hemodialysis (HD). The side-effects of these drugs have been shown to affect compliance with therapy and the lack of control of HPT, hence the interest of this study, which aims to measure the effectiveness of daily administration of calcimimetic drugs on the control of HPT through compliance with therapy.

Methods: Prospective and interventional study over 6 months evaluating the efficacy of administering Cinacalcet in dialysis session to treat hyperparathyroidism. 60% of the patients were identified with 9N PTH. We compared three groups. G1: Patients on intravenous Etelcalcetide at the end of the dialysis session three times a week, G2: Patients on non-observing Cinacalcet that we put on Cinacalcet 3 times a week at the end of the dialysis session and 4 times at home and G3: Patients on Cinacalcet observing that we kept under a daily dose at home. For therapeutic adjustment, biological monitoring was performed once per month. The primary outcome was the reduction of plasma PTH at 6 months stratified as follows: 25%, 50%, and normalization. Secondary and tertiary outcomes were improvement in serum calcium and reduction in alkaline phosphatase. Significance threshold: $p<0.005$

Results: 32% of the patients were non-compliant with nausea and vomiting as the main reason and were treated with an anti-emetic drug. All patients were on calcium and vitamin D supplementation. The distribution of patients in the department was as follows: G1: 43%, G2: 32%, and G3: 6%. 19% were not treated as enrolled. In terms of general characteristics, the groups were comparable. In groups 2 and 3, the mean PTH rate was higher. The PTH rate decreased in the first 2 groups as follows 25% in 25% of the patients in the first group and 30% in the second group, 50% in 16% of the patients in the first group and 20% in the second group, it normalized in 4.2% of the patients in the first group and in 18% in the second group. The mean level of serum calcium was higher in the second group. Alkaline phosphatase levels also decreased significantly in the first two groups.

Conclusions: The perdialytic administration of Cinacalcet seems to be an interesting alternative in the control of hyperparathyroidism in non-compliant chronic hemodialysis patients.

PUB095

A Diagnostic (Non)Dilemma

Ann R. Finke, Cortney Lee, Juan-Carlos Aycinena, Madhumathi Rao, Muhammad Qasim. *University of Kentucky, Lexington, KY.*

Introduction: Primary Hyperparathyroidism (pHPT) is a very common disease and should be thought of anytime persistent hypercalcemia is found. Having a normal range PTH level does not rule out pPHT and one should always obtain a 24hr urine Ca and evaluate end organ effects. A high bone turnover state is expected in pHPT with an elevated ALP.

Case Description: 51 y/o M with PMHx of HIV on ART, CKD3, left knee avascular necrosis, and CHF presented for evaluation of hypercalcemia noted since 2017. Initially intermittent, serum calcium became persistently elevated to 11.2-11.8mg/dL (ionized Ca 5.8 mg/dL) over two years. He had no history of kidney stones or medications associated with hypercalcemia. Laboratory workup was notable for hypercalciuria (792mg/day), normal PTHrP, vitamin D 25 levels (35-68ng/mL), vitamin D 1,25 levels (48-69pg mL) and persistently normal PTH (26-34pg/mL) and alkaline phosphatase (54 u/L) levels. Other workup included a DEXA scan with osteopenia, and a bone scan without focal uptake. Sestamibi parathyroid scan was negative, but neck ultrasound revealed a potential target lesion. Given the atypical presentation further validation was sought with undecalcified bone biopsy after double tetracycline labelling. Histology showed elevated bone turnover consistent with increased parathyroid activity, supporting the diagnosis of Normohormonal Primary Hyperparathyroidism (NHpHPT).

Discussion: Classically, pHPT is recognized by the combination of hypercalcemia, with elevated or non-suppressed PTH levels. An absence of PTH elevation in our patient prompted a search for other causes of hypercalcemia including Familial Hypocalciuric Hypercalcemia (FHH), excessive dietary Ca intake, medications and Calcitriol mediated diseases, that were differentiated by elevated urinary calcium and normal vitamin D25 and vitamin D1, 25 levels. NHpHPT is defined by PTH level of 21-65pg/mL in patients with hypercalcemia. The most accepted hypotheses explaining the lower PTH levels is a lower physiological PTH setpoint. Accordingly, intraoperative PTH drop during parathyroidectomy (PTX) remains a 50% decrease to ensure sufficient resection of glandular tissue. Diagnosis can further be aided by assessing the end organ effects, specifically on the bones and kidneys. A lack of ALP elevation prompted a bone biopsy that showed high bone turnover consistent with pHPT. Ultimately, the patient underwent a parathyroidectomy.

PUB096

A Rare Case of Oncologic Osteomalacia

Sunayna Gurnani, Maham Ali. University of Michigan Fellowship. *University of Michigan, Ann Arbor, MI.*

Introduction: Oncogenic osteomalacia is a paraneoplastic syndrome characterized by hypophosphatemia due to FGF-23 secreting tumors. FGF 23 acts on the proximal tubules to reduce α hydroxylation of Vitamin D2 and reduce phosphate reabsorption. The secreting tumors must be identified swiftly as the treatment lies in complete excision of the tumor.

Case Description: A 52 year old male with Stage IV prostatic adenocarcinoma with known metastasis to ribs, humerus and pelvis who presented with severe fatigue and diffuse myalgias. Laboratory evaluation revealed serum Phosphate 0.5 mg/dl (2.7-4.6 mg/dL), Corrected serum calcium 7.2 (8.6-10.3 mg/dl), Alkaline phosphatase 765 (40-116 U/L), PTH 55 (10-65 pg/mL). Further evaluation revealed FePhos 62% with FGF 23 level of 3481 pg/ml (< 59 pg/ml). The patient was treated with IV Calcitriol along with judicious phosphate repletion however, the patient remained hypophosphatemic to < 2 mg/dL.

Discussion: Oncogenic osteomalacia is generally associated with mesenchymal tumors found in bone and soft tissue. It is rarely associated with malignant or metastatic disease. In the systematic review completed by Bosman et al of 895 cases of TIO, 10% of cases were reported malignant per histology. In this review, 98% of patients were noted to have hypophosphatemia and low Vitamin D levels, and FGF 23 levels were found to be related to tumor size ($r = 0.344$, $P < 0.001$). In 2020, the FDA approved the use of Burosumab for hypophosphatemic hyperphosphaturic TIO in patients whose lesions are not amenable to excision. Novel therapies such as FGF Receptor tyrosine kinase inhibitor Infigratinib are underway.

PUB097

PTH Variability Is Associated with Increased Risk of Mortality in Patients on Hemodialysis

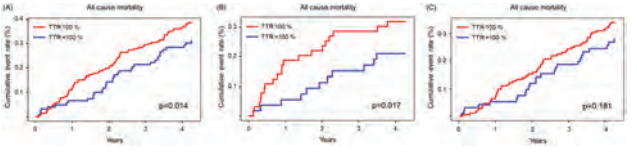
Tadashi Kato,[1] Kiryu Yoshida,[2] Tomohiro Saito,[1] Noriyuki Kato,[3] Masahide Mizobuchi,[1] Hiroaki Ogata,[2,5] Fumihiko Koiwa,[4] Hirokazu Honda.[1]
[1]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Shinagawa, Japan; [2]Division of Nephrology, Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan; [3]Saiyu Clinic, Koshigaya, Japan; [4]Division of Nephrology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [5]Department of Medical Education, Showa University School of Medicine, Shinagawa, Japan.

Background: Elevated parathyroid hormone (PTH) levels are associated with cardiovascular events, bone disease, and mortality in patients undergoing maintenance hemodialysis. PTH levels widely vary in hemodialysis patients, but it is unclear PTH variability would affect mortality.

Methods: A total of 331 maintenance hemodialysis patients at Saiyu Clinic who had measured PTH at least twice a year were included in the study. The association between all-cause mortality, cardiovascular events, and fractures was evaluated in patients with PTH concentrations always between 60 and 240 (Time in Terget range (TTR) 100%) and those without PTH concentrations (TTR < 100%).

Results: There were 122 patients with TTR 100% and 209 patients with TTR < 100%; over the 4-year observation period, patients with TTR 100% had significantly decreased all-cause mortality than those with TTR < 100% (HR 1.68, 95% CI 1.11-2.53) (Figure A). Subgroup analysis by the presence or absence of pharmacological intervention showed no difference in all-cause mortality in the ntreatment group (HR 2.73, 95% CI 1.20-6.24) (Figure B), but showed significant difference in no-tratment group (HR 1.39, 95% CI 0.86-2.24) (Figure C).

Conclusions: Even one deviation of PTH concentrations from the optimal range during a one-year period was associated with an increase in all-cause mortality. However, this effect was not seen when patients were receiving pharmacological intervention. The results suggest that early intervention is desirable when PTH levels vary from the optimal range in patients with secondary hyperparathyroidism.



PUB098

Penile Calciphylaxis: A Rare Complication in a Patient with ESKD

Jee H. Kim, Stela Teferici, Hyun Joon Cho, Nitzy N. Munoz Casablanca. *NYC Health and Hospitals Elmhurst, Elmhurst, NY.*

Introduction: Calciphylaxis, a rare but potentially devastating complication, predominantly affects patients with end-stage kidney disease (ESKD) undergoing dialysis, with a reported prevalence of 1-4%. Penile calciphylaxis is an even rarer manifestation, with limited data on its prevalence due to the scarcity of reported cases. This case further highlights the rarity of this presentation.

Case Description: A 61-year-old male with a history of ESKD on hemodialysis since 2020, HTN, DM, and PAD s/p bilateral below-knee amputation presented with week-long urinary retention. Despite initial drainage of 800cc of urine with catheter placement, he developed phimosis, balanitis, and purulent discharge. A 14-day course of antibiotics for a urinary tract infection was completed, but symptoms persisted. A penile incision was performed, yet he continued to have penile pain and developed new-onset black discoloration of the glans penis. Computed tomography of the abdomen/pelvis showed surrounding soft tissue calcifications and gas within the corpora cavernosa and scrotum. Penectomy and urethrostomy were performed. Histopathological examination revealed extensive tissue necrosis, acute inflammatory infiltrates with abscess formation, and multifocal calcification involving medium-sized arteries. Laboratory evaluation showed parathyroid hormone at 372 pg/mL, with calcium levels in the 7-8 mg/dL range and phosphorus levels in the 3-4 mg/dL range. Albumin was 2.9 g/dL. No medications linked to calciphylaxis (phosphate binders, calcium supplements, warfarin, iron) were in use. Based on the findings suggestive of penile calciphylaxis, two doses of sodium thiosulfate 25g were administered. However, the treatment was discontinued due to concerns about prolonged QTc interval. Fortunately, on six-month follow-up, no new lesions or associated pain suggestive of calciphylaxis have developed.

Discussion: This case highlights the diagnostic challenge of penile calciphylaxis in ESKD. Initial symptoms, such as those seen here, can mimic a UTI or represent superimposed infection, potentially delaying diagnosis of calciphylaxis. Maintaining high suspicion for calciphylaxis is crucial in ESKD patients with unexplained skin lesions and persistent pain despite treatment for other causes due to the high morbidity and mortality associated with the condition.

PUB099

Severe Hypercalcemia by PTH-independent Extrarenal Production of 1,25-Hydroxyvitamin D

Ravi S. Patel,[1] Roberto L. Collazo-Maldonado,[1] Avani R. Patel,[2] Alexandra Rosario Aulet.[1] *[1]Methodist Dallas Medical Center, Dallas, TX; [2]Meharry Medical College School of Medicine, Nashville, TN.*

Introduction: Humoral hypercalcemia of malignancy is a condition characterized by elevated serum calcium levels due to exogenous production of parathyroid hormone-related protein (PTHrP). However, in rare cases, PTHrP may be normal and elevated serum calcium can be secondary to increased 1,25 hydroxy vitamin D production. Hypercalcemia of malignancy due to increased 1,25 hydroxy Vitamin D production can be challenging to diagnose due to its infrequency, but it may help discern the underlying cause of hypercalcemia.

Case Description: An 82 yo Hispanic woman presented to the ED due to confusion and generalized weakness. A clinical diagnosis of severe hypercalcemia with acute metabolic encephalopathy was made as her serum calcium levels were >14 mg/dl and creatinine 1.29 mg/dl on admission. She was recently diagnosed with Non-Hodgkin lymphoma (NHL) with metastasis to her liver and lungs. Her parathyroid hormone level was 12.4 pg/ml and parathyroid hormone-related protein level was <2.0 pmol/L. The patient's 1,25 hydroxy vitamin D levels, which resulted later, were markedly elevated at 186. The patient was treated with aggressive volume expansion, calcitonin, zoledronic acid, and steroids resulting in a quick improvement in her calcium levels and mentation. The patient was discharged in stable condition with a calcium level of 10.8 mg/dl with an improvement in kidney function with follow up with oncology.

Discussion: In patients with NHL, the most common cause of hypercalcemia (accounting for up to 80%) is the secretion of PTHrP, known as humoral hypercalcemia of malignancy. However, in rare cases, elevated levels of 1,25 hydroxy vitamin D can also cause hypercalcemia of malignancy despite normal PTHrP levels due to increased a1 hydroxylase activity by macrophages and lymphocytes.

PUB100

Hungry Bone Syndrome (HBS) as an Outcome of Parathyroidectomy for Treatment of Hyperparathyroidism in a Third-Level Hospital in a Medium-Income Country

Nicte Alaide R. García, Carolina Gonzalez-Fuentes, Karen Hopf, Jorge D. Salazar Hurtado, Manuel Camacho Luna, Michelle Sánchez, Mario Alamilla-Sanchez, Martin O. Carbajal. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico.*

Background: Hyperparathyroidism is a common disorder of mineral metabolism that is due to excessive secretion of PTH from one or more of the four parathyroid glands. It can be classified as primary, secondary and tertiary. In ESRD the definitive treatment in severe disease is parathyroidectomy. HBS is one complication after the surgery.

Methods: Retrospective cohort study with information (Jan 2023 and Jan 2024) in a third level hospital "Centro Médico Nacional 20 de Noviembre". The goal was to describe and analyze the incidence of HBS on patients with hyperpharatidoidism primary, secondary and tertiary treated with parathyroidectomy. We made a Principal Component Analysis (PCA) to observe the factors that have more impact.

Results: 51 cases were included. There were 16 patients with primary, 29 patients with secondary and 5 with tertiary hyperparathyroidism. Patients with ERSRD with secondary and tertiary hyperparathyroidism were mainly in Hemodialysis (71%) as Kidney Replacement Therapy (n=25). The mean value of PTH before surgery was 728 pg/ml among all patients. 80% patients (n=41) have AP >100 mg/dl as a parameter of high bone replacement. 30% patients (n=15) develop hungry bone syndrome. 86% of patients (n=13) that developed HBS have 3 ½ surgery. We made a PCA we observed that the principal components that predict to developed HBS in our population were AP, PTH and the surgery 3 ½ and patients have more risk if they have the three of them together.

Conclusions: The principal components observed that predict the developed HBS in our population were AP, PTH and the surgery 3 ½ and patients have more risk to develop HBS if they have them together.

	Surgery	PTH	AP
CP1	-0.274	0.428	0.316
CP2	0.387	0.244	0.508

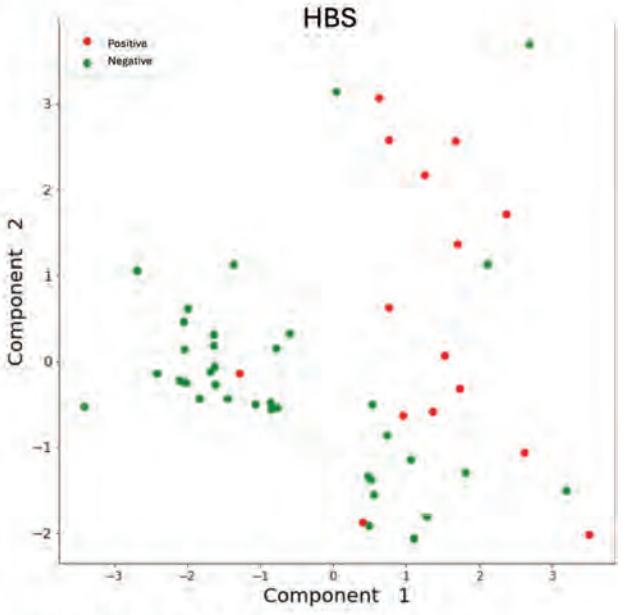


Figure 1. Distribution of principal components.

PUB101

Bibliometric Analysis of Renal Osteoporosis in Nondialysis-Dependent CKD

Liangmei Chen, Chaoying Kuang, Fanna Liu. *nephrology, Guangzhou, China.*

Background: Chronic kidney disease (CKD) can cause abnormalities in biochemical markers, particularly affecting bone mineral metabolism, leading to deterioration of bone health. To date, many CKD osteoporosis (OP) studies have focused primarily on dialysis patients. Skeletal health in non-dialysis CKD patients has not received sufficient attention, and only a limited number of studies have found a correlation between reduced BMD and poor renal prognosis in non-dialysis patients. Bibliometric analyses help us to take control of the history and current status of this research field, explore its hot trends, and provide some basis for future research on CKD OP.

Methods: All research-based articles and reviews in the field of CKD OP from 2000 to 2023 were searched in the Web of Science database through a developed search strategy. Information from different countries, institutions, journals and scholars was analysed and their contributions compared using CiteSpace and VOSviewer software. Analyse the frequency and prominence of keywords to fully present the current state of research and trajectory of the field.

Results: A bibliometric study of studies related to CKD OP in CKD between 2000 and 2023 reveals that the attention received by this field is increasing year by year. The leading countries, institutions and authors in this field are from Europe and the United States. Disorders of bone metabolism have been the focus of research into CKD OP since 2000. Future trends in CKD OP research may focus on the study of the effect of vitamin D dosage and treatment regimen on improving CKD OP Relationship between bone metabolism-related indicators such as intact Parathyroid hormone and FGF23 and CKD OP and fracture risk in CKD patients. A prospective study of new calcium mimetics in the field of CKD OP. Mechanistic studies on the mechanisms regulating indolyl sulfate-induced oxidative stress in osteoblasts and the exploration of Nrf2 as a target for the prevention of bone loss in CKD patients.

Conclusions: CKD OP has received increasing attention, and research hotspots in recent years have focused on the exploration of risk factors, drug development and clinical treatment. For the risk of developing CKD OP in non-dialysis patients, age, advanced stage of renal failure (G5), and NBAP are risk factors, and overweight or obesity, 25-(OH)-vitamin D, and iPTH are protective factors.

PUB102

Current and Future State of Hyperphosphatemia Management

Stephen Regan. *Spherix Global Insights, Exton, PA.*

Background: The hyperphosphatemia treatment landscape is evolving with the FDA's recent approval of tenapanor, the pending availability of generic iron-based phosphate binders, and the prospect of oral-only ESRD medications entering the Prospective Payment System (PPS), also known as the "dialysis bundle," starting January 1, 2025. As nephrologists continue to adjust their hyperphosphatemia treatment approach, they aim to expand the proportion of patients who maintain an optimal phosphorus level and to reduce their medication burden.

Methods: Data were collected via independent online surveys of 228 US nephrologists in February and May 2024.

Results: While nephrologists report that their use of calcium-based phosphate binders in their hemodialysis patients is declining, treatment rates with sevelamer (46%) and iron-based phosphate binders (16%) are holding steady. With the eventual availability of a generic ferric citrate product, nephrologists project that their use of calcium-based binders and sevelamer will decline, while their use of ferric citrate products and tenapanor will expand. However, the potential for oral-only medications to eventually enter the dialysis bundle is likely to alter their treatment approach further. As nephrologists have become more familiar with tenapanor, the proportion of those who view the agent as a substantial advance in hyperphosphatemia treatment (75%) has expanded over time. Tenapanor's user base among nephrologists (61%) has continued to increase month-over-month since its launch, as physicians have been prescribing the agent to a higher volume of their dialysis patients. Among the pipeline agents in development for hyperphosphatemia, oxylanthanum carbonate (OLC) has advanced to late-stage clinical development, with most nephrologists expressing interest in the product due to its bioequivalence to lanthanum carbonate, reduced pill burden, and smaller pill size. A substantial proportion of nephrologists (44%) project that OLC will have a definite role in the treatment of hyperphosphatemia.

Conclusions: Pending adequate medication access, nephrologists expect to have more treatment options available to them to help reduce the proportion of patients who do not reach their target phosphorus range, along with the potential added benefit of improving quality of life for their hyperphosphatemia patients.

PUB103

Clinical Manifestations of Pseudo-clubbing and Management in the Setting of Severe Secondary/Tertiary Hyperparathyroidism with ESKD

Adarsh S. Jones, Alyssa C. Weyer, Arda Akoluk. *The University of Texas at Tyler, Tyler, TX.*

Introduction: Secondary hyperparathyroidism frequently complicates chronic kidney disease (CKD) and can evolve into tertiary hyperparathyroidism due to prolonged parathyroid gland stimulation. This progression significantly impacts bone metabolism and overall health. We report a case of a 27-year-old male patient with severe long-standing secondary/tertiary hyperparathyroidism and end-stage renal disease (ESRD), presenting with pseudoclubbing of the fingers and thumbs.

Case Description: Patient is a 27 year old man with a history of bilateral congenital renal hypoplasia on peritoneal dialysis at six months of age, cadaveric kidney transplant recipient at 6 years old, which failed in October 2020, leading to a transition to hemodialysis. Currently, he undergoes hemodialysis four times per week, for 18 to 20 hours weekly, with excellent clearance. Recent lab findings have been significant for elevated blood urea nitrogen, creatinine, Phosphorous, PTH (1409-1846 pg/mL), and a normal calcium consistent with severe tertiary hyperparathyroidism. Patient noted to have pseudoclubbing on physical exam, which is indicative of significant systemic effects. The patient's current hemodialysis regimen has led to excellent clearance, although severe hyperparathyroidism and pseudo clubbing persist, necessitating ongoing comprehensive management. The patient is on calcimimetics and active vitamin D analogs to suppress PTH secretion and manage mineral metabolism. Given the severity of hyperparathyroidism and presence of pseudoclubbing, surgical intervention (parathyroidectomy) is currently being considered.

Discussion: This case underscores the complexity of managing severe secondary/tertiary hyperparathyroidism in ESRD patients. Pseudoclubbing, although rare, requires meticulous clinical attention and intervention. A multidisciplinary approach involving nephrologists, endocrinologists, and surgeons is crucial for optimizing outcomes. Continuous monitoring of labs, individualized treatment plans, and proactive management of complications are vital for improving quality of life and prognosis in patients with advanced renal disease and associated endocrine disorders. Further research is needed to explore optimal management practices for patients with similar presentations, including rare manifestations like pseudoclubbing.

PUB104

Investigating the Immunomodulatory Impact of Wharton's Jelly Mesenchymal Stem Cells (WJ-MSCs) on Cobalt Chloride (CoCl2)-Induced Damage to HK-2 Cells

Zih Han Liao, Ming Ling Kuo. *Chang Gung University Graduate Institute of Biomedical Sciences, Taoyuan, Taiwan.*

Background: End stage renal diseases (ESRD) are usually caused by chronic kidney diseases (CKD) and renal dysfunction. Hypoxia, induced by reduced oxygen delivery, plays a crucial role in kidney damage by triggering inflammation, oxidative stress, mitochondrial dysfunction, and DNA damage. Studies indicate that hypoxia-inducible factor 1α (HIF-1α) regulates metabolic remodeling in renal tubular epithelial cells (RTECs) and promotes interstitial fibrosis. Promising results have been shown with the use of mesenchymal stem cells (MSCs) in CKD models, such as reducing oxidative stress, improving mitochondrial function, and decreasing inflammation. Interferon-gamma (IFN-γ) has been found to enhance MSCs' therapeutic effects on renal fibrosis, which is closely related to renal hypoxia, though the mechanisms remain unclear. This study aims to investigate whether IFN-γ primed Wharton's Jelly-MSCs (IFNγ-MSCs) can protect HK-2 cells, human proximal tubule epithelial cells, from hypoxia-induced damage. We generated a hypoxic environment with $CoCl_2$ and treated HK-2 cells with IFNγ-MSCs to explore their potential protective effects against kidney injury.

Methods: The differentiation ability and cell surface marker profile of WJ-MSCs were confirmed. We mimicked hypoxia in HK-2 cells using $CoCl_2$ and pretreated them with conditioned media from IFNγ-MSCs to assess the efficacy of MSCs against cell injury. Cell viability was measured using Cell Counting Kit-8. Gene and protein expressions related to hypoxia, oxidative stress, and apoptosis were evaluated via RT-qPCR and western blot. Mitochondrial ROS production and membrane potential were detected using MitoSOX and MitoTracker, respectively.

Results: Our findings indicated that $CoCl_2$ effectively induced cytotoxicity in HK-2 cells and upregulated genes and proteins associated with hypoxia, oxidative stress, and apoptosis. IFNγ-MSCs alleviated $CoCl_2$-induced apoptosis in HK-2 cells by suppressing the Bax/Bcl-2 ratio. Additionally, IFNγ-MSCs downregulated the gene expressions of *BNIP3*, *NIX*, *NRF2*, *HO1*, and *iNOS*, as well as the protein expressions of HIF-1α, Nrf-2, and HO-1. These results suggest that IFNγ-MSCs might reverse hypoxia and reduce oxidative stress, thereby protecting HK-2 cells from apoptosis.

Conclusions: In summary, our findings suggest that IFNγ-MSCs can alleviate $CoCl_2$-induced HK-2 cells injury by reducing oxidative stress and reversing hypoxia.

PUB105

First-in-Class Phase 3 Clinical Trial Candidate Rilparencel Expresses Nephron Markers and Acquires Glomerular Epithelial and Tubular Features

Prakash Narayan,[1] Brooke Bauer,[1] Howard Trachtman,[2] Guido Filler,[3] Benjamin S. Freedman,[4] Joseph Stavas,[1] Emily L. Butler,[1] Andrew T. Bruce.[1] *[1]ProKidney, Winston-Salem, NC; [2]Renal Strategies LLC, New York, NY; [3]Western University, London, ON, Canada; [4]University of Washington, Seattle, WA.*

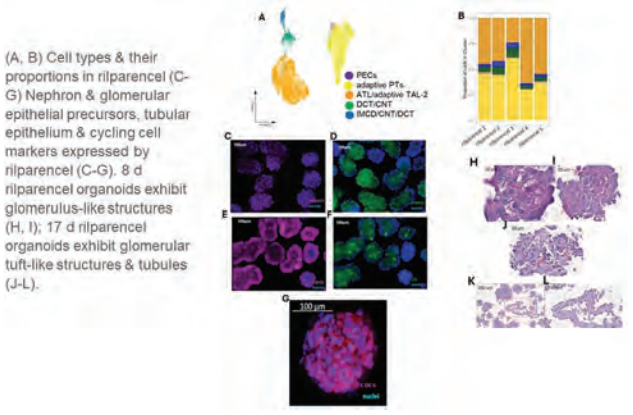
Background: Kidney cortical administration of rilparencel, a biopsy-derived autologous kidney epithelial cell platform, improves glomerular, tubular and urine concentrating profiles in chronic kidney disease (CKD) models & may support kidney function in type 2 diabetes (T2D)&CKD patients. We tested the hypothesis that rilparencel expresses markers spanning the nephron & acquires glomerular epithelial & tubular features.

Methods: Banked rilparencel samples from 5 T2D&CKD patients (NCT02836574) were analyzed with scRNAseq & kidney cell types & states identified with unsupervised clustering & projection on to the KPMP single cell CKD atlas. Organoids from rilparencel were grown for up to 17 d, sectioned & stained with periodic acid Schiff. Human rilparencel (discarded kidneys, NDRI) organoids in 3D culture were immunofluorescent antibody stained for nephron & glomerular epithelial precursors, HOXA11 & PTPRO (GUDMAP ATLAS-D2K), respectively, tubular epithelial markers, LTL & CD13 & the cycling cell marker, CDC6.

Results: KPMP-anchored molecularly profiled cell types constituting rilparencel include glomerular parietal epithelial cells (PECs), adaptive proximal tubules (PTs), ascending thin limb (ATL) & adaptive thick ascending limb-2 (TAL-2), distal convoluted tubule (DCT), connecting tubule (CNT) & intermediate collecting duct (IMCD). Proportions of each cell type were consistent amongst samples. Immunoflourescent antibody staining confirmed nephron & glomerular epithelial precursors, tubular epithelium & cycling cells. Sectioning of rilparencel organoids revealed morphologic features consistent with glomerular epithelium & tubules.

Conclusions: An integrated, cross-validating approach indicates that rilparencel expresses markers spanning the nephron & acquires glomerular epithelial & tubular features in culture. Increased nephron mass with both functional compartments may underlie beneficial effects of cortical delivery of rilparencel.

Funding: Commercial Support - ProKidney



PUB106

Effect of a High-Fat Diet on the Progression of Diabetic Nephropathy and End-Organ Damage

Melissa Lowe,[1] Ruslan Bohovyk,[1] Vladislav Levchenko,[1] Christine A. Klemens,[1,3] Alexander Staruschenko.[1,2] *[1]University of South Florida Morsani College of Medicine, Tampa, FL; [2]The James A. Haley Veterans Hospital, Tampa, FL; [3]University of South Florida Hypertension and Kidney Research Center, Tampa, FL.*

Background: The high-fat Western diet (HFD) is a key contributor to the growing rate of obesity, which is a global health concern. Obesity increases the risk of metabolic syndrome leading to chronic illnesses like diabetes. Diabetic Nephropathy (DN) is a complication prevalent in Type 2 Diabetes (T2D), which eventually leads to end-stage renal disease or kidney failure. This study aimed to assess how HFD impacts diabetic severity and the progression of kidney, heart, and liver injury in T2D.

Methods: Young (12 weeks old) and aged (>38 weeks old) male and female Type 2 Diabetic Nephropathy (T2DN) rats, a non-obese T2D model, were placed on either normal (NFD) or HFD calorically balanced diets for 12 weeks. Glucose tolerance testing was performed every three weeks and total body weight (TBW), and 24-hour urine sampling were measured weekly. Kidney, heart, and liver functions were analyzed at the end of the study. RNA-Seq, lipidomic, and microbiome analyses were also performed.

Results: HFD males' glucose intolerance and fasting blood glucose levels increased progressively and became significant by week 9 (aged rats) and week 6 (young rats). In contrast, glucose tolerance and fasting blood glucose were not affected in the females. The HFD did not affect 2-kidney/TBW ratios in all groups except young females. Heart weight/TBW ratios in females were significantly reduced on the HFD in both age groups. Studies are ongoing in young animals; however, old animals revealed a significant increase in albuminuria, KIM-1 staining, and medullary protein casts in the aged HFD female group, while there was no further progression of renal damage in the males. There was a significant increase in glucosuria in male HFD animals, and the HFD also increased lipid deposits in the liver for both sexes. No changes in cardiac fibrosis were observed. Microbiome analysis revealed a significant decrease in gut microbiota alpha diversity in males on HFD, while no significant changes were observed in females.

Conclusions: In conclusion, the HFD appears to have a more deleterious effect on glucose handling in both old and young T2DN males than in female rats. More profound renal effects in the aged female group are most likely due to already severe kidney injury in male T2DN rats, as we have previously reported.

Funding: NIDDK Support, Other NIH Support - NHLBI

PUB107

Mitochondrial AKT1 Signaling and Kidney Injury: Unraveling Mechanistic Insights into Metabolic Syndrome-Induced Kidney Dysfunction

Hugo Y. Lin,[1,2] Yu-Min Ko,[4] Ming-Yu Yang.[3] *[1]Kaohsiung Medical University Chung Ho Memorial Hospital, Kaohsiung, Taiwan; [2]Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan; [3]Chang Gung University, Taoyuan, Taiwan; [4]Kaohsiung Medical University, Kaohsiung, Taiwan.*

Background: Metabolic syndrome (MetS) is associated with kidney diseases, but the etiology is inconclusive. We hypothesized that renal tubular mitochondrial AKT1 (mito-AKT1) signaling plays a mechanistic role in the pathogenesis of kidney injuries in MetS.

Methods: We executed the study with 8-week C57BL/6 male mice fed a high-fat diet for four months, compared with mice fed a standard chow diet. To examine the role of mito-AKT1 translocation, the cell viability of HK-2 cells treated with heat shock protein 90 (Hsp90) was examined.

Results: In our murine MetS model, body weight significantly increased. The kidney size as a percentage of body weight remained similar between the groups. For the glucose tolerance test, fasting glucose levels were significantly higher in MetS mice than those on a regular diet ($p<0.05$). From 15 to 120 minutes, glucose levels were consistently elevated. The intraperitoneal glucose tolerance test curve differed between three and six months, with the area under the curve (AUC) value being higher at six months ($p=0.013$). Fasting hyperinsulinemia and insulin resistance, as measured by the Homeostatic Model Assessment for Insulin Resistance, were also elevated. Regarding renal function, serum BUN and creatinine levels in MetS mice did not change significantly. However, proteinuria and urine KIM-1 levels were elevated, which indicated renal tubular injuries. Histological examination revealed significant increases in glomerulosclerosis index, tubulointerstitial fibrosis, tubular dilatation, and tubular vacuolation score. To further investigate the role of mito-AKT1 signaling during MetS in renal tubules, we examined the mito-AKT1 protein. We observed an increased accumulation of phosphorylated AKT1 ($p=0.030$) in the mitochondria of proximal tubules after MetS. This AKT1 translocation was confirmed using immunohistochemistry staining and western blot analysis of mitochondrial proteins. Cell viability significantly decreased in the group treated with palmitic acid and the Hsp90 inhibitor, compared to the vehicle-treated group ($p<0.01$).

Conclusions: These findings shed new light on the mechanistic role of renal tubular mito-AKT1 in MetS-induced kidney injuries and may be used to develop new strategies for preventing and treating kidney diseases.

Funding: Government Support - Non-U.S.

PUB108

Spatial-omic Profiling of Human Kidney Tissues Using SeqStain Stratifies Disease Pathology

Anirudh Vattikota,[1] Mohamed Youssef,[1] Sowmya Gurusamy Kamaraj,[1] Ishwarya Venkatesh,[2] Ameera M. Shaw,[2] David J. Cimbaluk,[2] Vineet Gupta.[1] Internal Medicine. *[1]The University of Texas Medical Branch at Galveston, Galveston, TX; [2]Rush University Medical Center, Chicago, IL.*

Background: A deep understanding of the pathophysiology of the tissue microenvironment is crucial for scientific advancements. Newer multiplex imaging-based methods are providing important details about the histoarchitecture of tissue. We previously developed a novel user-friendly tissue imaging method, called SeqStain, allows rapid immunofluorescence based multiplexed tissue imaging and analyses. Here, we utilize this approach to understand the complex spatial organization of cells and their relationships with each other with both healthy subjects, and patients with diabetic nephropathy and lupus nephritis.

Methods: We generated antibodies conjugated with fluorescently-labelled-DNA oligonucleotides for analyzing multiple kidney-specific antigens using sequential cycles of staining and de-staining on each tissue section. We probed different areas of histologically relevant to the kidney and used conventional fluorescence microscopy for imaging the tissues and HALO software for image analyses.

Results: We analyzed both paraffin-fixed and frozen tissue sections using commercially available reagents and a confocal microscope. This allowed us to precisely image up to 20 antigens on single tissue specimens for healthy subjects, as well as from patients with lupus nephritis (LN) and diabetic nephropathy (DN). Analysis of various cellular biomarkers indicated enrichment of specific cellular clusters into distinct neighborhoods.

Conclusions: SeqStain is a versatile, gentle, and easy to use method for multiplex imaging making it highly effective in mapping the spatial relationship of cells within the kidney. The spatial relationship maps generated by this method will offer valuable new insights into disease pathophysiology and enhance future diagnostics and treatments for LN and DN.

Funding: Private Foundation Support

PUB109

Modulation of Kidney Disorders in Type 2 Diabetes: Evaluating the Role of Probiotics in a Rat Model of Diabetic Kidney Disease

Eloiza O. Silva,[1,2] Luciana Soares C. Santos,[1,2] Maria De Fatima Vattimo,[2] Giulia T. Cabreira,[1] Julia F. Santos,[1] Monique M. Pinheiro,[1] Vitória C. Costa.[1] *[1]Faculty of Medical Sciences of Santa Casa de São Paulo, Sao Paulo, Brazil; [2]Universidade de Sao Paulo, Sao Paulo, Brazil.*

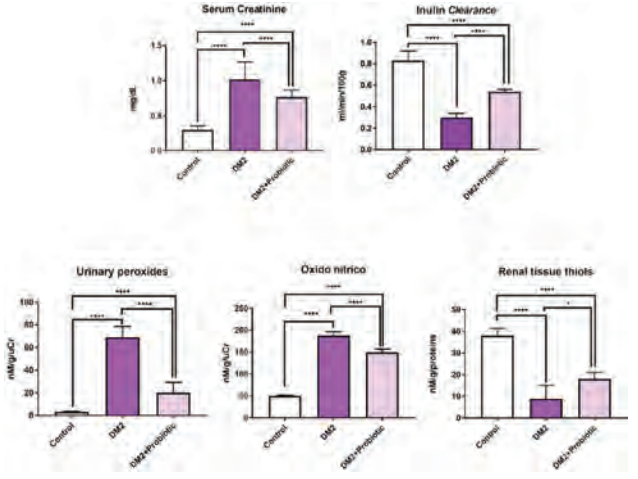
Background: To prevent the progression of Diabetic Kidney Disease (DRD), some strategies have been used. Currently there is Investigated the use of foods enriched with probiotics which, through their effects on microflora modulation, can contribute to glycemic control and mitigate complications of DM2 such as DRD. The objective of our study is to evaluate the effects of probiotics on the function, oxidative profile and renal histology of rats with DM2 and DRD.

Methods: Male Wistar rats were randomized into the following groups: Control (CT n=5) animals that received 0.9% saline solution (SF) (nicotinamide diluent (NA), 0.4 ml i.p. single dose) and after 15 min buffer citrate (streptozotocin diluent (STZ) at pH 4.2 and, i.p., single dose); Type 2 Diabetes Mellitus (DM2 n=5): animals received (NA; 100 mg/kg), i.p., single dose, in 0.9% SF after 15 minutes they received (STZ; 60 mg/kg), i.p., single dose ; Type 2 Diabetes Mellitus + Probiotic (DM2+P n=5): DM2

animals that received probiotic strains (bifidabacterium longum, bifidabacterium bifidum and lactobacillus rhamnosus, dose 10 10 CFU/mL); by gavage, 6 weeks. Renal function (serum creatine-CrS and inulin clearance-Clin) and redox profile were evaluated.

Results: The DM2 group demonstrated a reduction in inulin clearance, an increase in CrS and redox disorders. On the other hand, diabetic animals that received probiotics demonstrated attenuation in the deterioration of renal function perceived by an increase in Clin, a reduction in CrS and redox disorders.

Conclusions: The probiotic confirmed its renoprotective effect, providing a relevant positive effect on the morbidity of DKD in DM2 rats.



PUB110

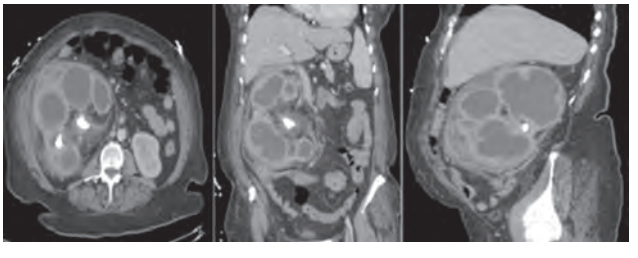
A Rare Case of Xanthogranulomatous Pyelonephritis

Cameron T. Lawson. *East Carolina University, Greenville, NC.*

Introduction: Xanthogranulomatous pyelonephritis (XPN) is a rare variant of chronic pyelonephritis occurring in the setting of obstructive uropathy and recurrent urinary tract infections (UTIs). It accounts for less than 1% of all cases of pyelonephritis. Diabetes is a known systemic risk factor. Localized symptoms such as flank pain and dysuria may be attributed to nephrolithiasis or UTI without prompting a need for further workup. We present a case of XPN which resulted in kidney loss and dialysis dependence.

Case Description: A 54-year-old Hispanic female with a history of HTN, type 2 DM, kidney stones and recurrent UTIs presented with two years duration of intermittent right flank pain that acutely worsened one week prior to hospital admission. Most recent antibiotic use was one month prior. On physical exam patient appeared clinically stable, blood work was notable for a creatinine of 1.26 mg/dL, WBC of 11k/uL, and a urine culture growing Proteus Mirabilis. Renal ultrasound showed a 4 cm stone chronically obstructing the right ureteropelvic junction. CT scan demonstrated right-sided staghorn calculus with perinephric inflammation and a pathognomonic bear paw sign. Patient subsequently underwent right-sided nephrectomy. Postoperative hospital course was complicated by hemorrhagic shock, IVC thrombus, and persistent kidney failure. Patient remained dialysis dependent.

Discussion: XPN is a difficult diagnosis given that there are no specific symptoms until late stage. Exact etiology remains largely unknown. Malek et al proposed a three-stage classification of XPN, with stage II or diffuse type being the most common type and characterized by destruction of renal parenchyma (higher attenuation on CT) and dilated calyces (lower attenuation), mimicking a bear's paw. Our case highlights the importance of high clinical suspicion of XPN in diabetic patients with recurrent UTIs and kidney stones. Perinephric inflammatory changes are known predictors of poor outcomes. Early clinical and radiologic suspicion along with awareness of risk factors play an important role in preventing disease progression and avoiding late-stage complications including ESRD.



Bear paw sign

PUB111

Characteristics, Clinical Outcomes, and Safety of New Users of Finerenone with CKD and Type 2 Diabetes in Routine Clinical Practice in Japan: A FOUNTAIN Platform Analysis

Keizo Kanasaki,[1] Daloha Rodriguez Molina,[4] Kanae Yoshikawa-Ryan,[2] Satoshi Yamashita,[2] Suguru Okami,[2] Fangfang Liu,[4] Alfredo E. Farjat,[4] Nikolaus G. Oberprieler,[4] Csaba P. Kovesdy,[3] Atsuhisa Sato,[5] David Vizcaya.[4]
[1]Department of Internal Medicine 1, Faculty of Medicine, Shimane University, Izumo, Japan; [2]Bayer Yakuhin Ltd., Medical Affairs & Pharmacovigilance, Osaka, Japan; [3]University of Tennessee, Memphis, TN; [4]Bayer AG, Leverkusen, Germany; [5]Department of Internal Medicine, Division of Nephrology and Hypertension, International University of Health and Welfare School of Medicine, Minatoku, Japan.

Background: In clinical trials, finerenone reduced risks of cardiovascular and renal complications among patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Evidence regarding finerenone use in real-world clinical settings is limited. This study aims to describe clinical characteristics, outcomes, and safety of new users of finerenone in Japan.

Methods: A retrospective observational cohort study using electronic health records and claims data from Japanese hospital-based databases provided by Real-World Data, Co. was conducted. Persons initiating finerenone from July 2021 to August 2023 with prior CKD and T2D were included. Prevalence of comorbidities and use of concomitant medication during the previous 365 and 180 days were calculated. Occurrence of kidney failure, a composite cardiovascular outcome, and hyperkalemia was assessed during follow-up.

Results: A total of 92 new users of finerenone were identified during the study period. Patient characteristics are described in Table 1. Median follow-up was 49 days. We observed no case of kidney failure and only one of a composite cardiovascular outcome. No patients showed serum potassium >5.5mmom/l or fatal hyperkalemia/hospitalization associated with hyperkalemia during follow-up. Results from ongoing analysis of several hundred finerenone users in one additional database will be presented at the conference presentation.

Conclusions: Early evidence from clinical practice in Japan suggests that finerenone is used for patients across risk stages and comedications. This study is the first database study conducted on evaluation of finerenone use in Japan.

Funding: Commercial Support - Bayer

	Finerenone initiators N = 92
Age years, median (IQR)	**74 (68-80)**
Male, n (%)	**64 (70%)**
Comorbidities, n (%)	
Hypertension	**86 (93%)**
Hyperlipidemia	**65 (71%)**
Congestive heart failure	**62 (67%)**
Peripheral vascular disease	**62 (67%)**
eGFR, mL/min/1.73m2, median (IQR)	
<25	**17 (18%)**
25-<45	**52 (57%)**
45-<60	**18 (20%)**
≥60	**5 (5%)**
missing	**0 (0%)**
Cardiovascular drug at baseline	
ACEI or ARB, n%	**68 (74%)**
Beta-blockers	**31 (34%)**
CCB	**43 (47%)**
Glucose-lowering therapies at baseline	
Insulins	**31 (34%)**
Metformin	**30 (33%)**
SGLT2i	**61 (66%)**
GLP-1 agonists	**31 (34%)**

PUB112

MRI-Based Kidney Volume and Resistive Index in Patients with Progressive vs. Stable Diabetic Kidney Disease (DKD)

Paul Hockings,[1,3] Kianoush Makvandi,[4] Robert J. Unwin,[2] Johannes Hulthe,[1] Seema Baid-Agrawal.[4] *[1]Antaros Medical, Molndal, Sweden; [2]University College London, London, United Kingdom; [3]Chalmers Tekniska Hogskola AB, Goteborg, Sweden; [4]Sahlgrenska universitetssjukhuset, Goteborg, Sweden.*

Background: Multiparametric Magnetic Resonance Imaging (MRI) can non-invasively assess kidney structure and function but there are few longitudinal studies.

Methods: In this prospective study: - 38 DKD subjects aged 18–79 years and 20 age- and gender-matched healthy volunteers (HV) were included at baseline - 31 DKD subjects (2 stage 2, 13 stage 3, 14 stage 4, and 2 stage 5) and 17 HV were re-examined at 2 years ± 6 months Measured glomerular filtration rate (mGFR) was obtained using iohexol clearance. Kidney volume and renal artery resistive index (RARI) were measured by MRI. Subjects were classed as stable (S) or as progressors (P) if they met at least one of the following criteria at 2 years: - decrease in mGFR slope of >5 mL/year/1.73m^2 - worsening UACR category - any major adverse kidney event defined as: >sustained decrease in eGFR of >40% >doubling of serum creatinine from baseline >development of kidney failure with mGFR <15 ml/min/1.73m^2 >death from renal cause

Results: 8/31 (26%) DKD subjects and 4/17 (24%) HVs progressed. Mean 2-year mGFR decline in DKD patients was 2.7±5.4 and in HV 1.9±10.7 (ml/min/1.73m^2). Figure 1 shows correlation between both baseline and 2-year kidney volumes and RARI (R^2 0.91 and 0.78, respectively). Figure 2 shows changes in kidney volume and RARI for HV and DKD subjects who were either stable (S) or progressors (P).

Conclusions: Baseline vs 2-year follow up for both kidney volumes and RARI are highly correlated. Progressors tend to have larger decreases in kidney volume than stable subjects. Subjects with DKD tend to have larger increases in RARI than HV subjects. Larger studies are needed to confirm these results.

Funding: Commercial Support - Antaros Medical; AstraZeneca

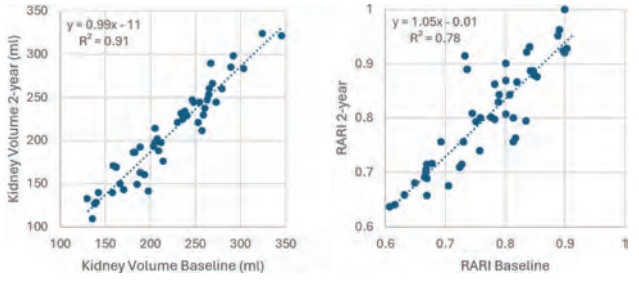


Figure 1: Correlation between baseline and 2-year kidney volumes and RARI.

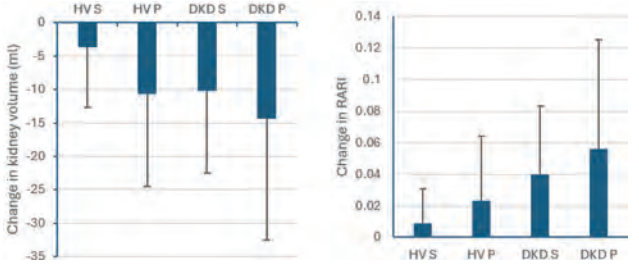


Figure 2: Changes in kidney volume and RARI for Healthy Volunteers (HV) and subjects with Diabetic Kidney Disease (DKD) who were either stable (S) or progressors (P).

PUB113

CKD Testing among Patients with Diabetes in the US Military Health System

Robert Nee,[2,1] James D. Oliver,[1] Hava Marneweck,[3] Amanda Banaag,[3] Fang Xu,[4] Alain K. Koyama,[4] Yoshihisa Miyamoto,[4] Meda E. Pavkov,[4] Tracey L. Koehlmoos.[1] *[1]Uniformed Services University of the Health Sciences, Bethesda, MD; [2]Walter Reed National Military Medical Center, Bethesda, MD; [3]Henry M Jackson Foundation for the Advancement of Military Medicine Inc, Bethesda, MD; [4]Centers for Disease Control and Prevention, Atlanta, GA.*

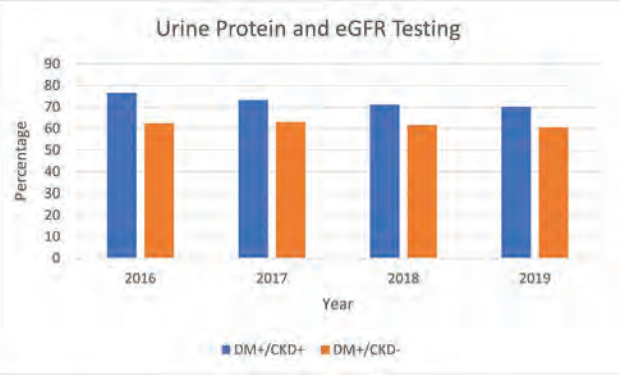
Background: Despite guideline recommendations, annual chronic kidney disease (CKD) testing that includes both urine albumin-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR) remains low (<50%) among U.S. adults with diabetes mellitus (DM). As an integrated health care system with universal coverage, we hypothesized that CKD testing rates among DM adults in the Military Health System (MHS) would be higher than the overall national trend.

Methods: Using the MHS Data Repository (2016–2019), we analyzed the annual prevalence of non-pregnant DM adults with and without CKD based on ICD-10 codes who were tested for urine protein only (urine albumin, uACR, urine protein, urine protein-creatinine ratio [uPCR]); eGFR only; or both urine protein and eGFR. We also assessed race stratification and specialties of ordering providers.

Results: For 2019, 186,616 (6.2%) of 2,989,368 adults had DM (median age 60 [IQR 53–64] years; male 52.4%; White 32.3%, Black 17.4%, Asian American/Pacific Islander 4.9%, Native American/Alaskan Native 0.5%, Missing 30.3%; median eGFR = 79 [IQR 58–97] ml/min/1.73m^2, median uACR = 16.9 [IQR 6.6–56.6] mg/g). Sixty-one percent (61%) of DM+/CKD- and 70% of DM+/CKD+ were tested for both urine protein/eGFR (Fig). Racial categories were significantly associated with both urine protein/eGFR testing in the two cohorts in 2019 (p<0.0001). Among DM+/CKD- patients, 66% of urine protein and 55% of eGFR labs were ordered by primary care providers.

Conclusions: CKD testing rates among DM adults in the MHS were higher than other national-level data. However, there is a substantial opportunity to improve early detection of CKD in this high-risk population. *The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy of the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense, the Department of Health and Human Services, or the U.S. government.*

Funding: Other U.S. Government Support



PUB114

Impact of Gasdermin Gene on CKD in Iraqi Persons with Diabetes

Riyadh M. Alsaegh,[1,2] Ameer F. Al-Tu'ma,[1] Ameer R. Al-Saegh.[2] Al-Nahrain Medical College, Clinical Biochemistry Team for DSDMD-PhD Research Project-2024. *[1]University of Kerbala, Kerbala, Iraq; [2]Saegh Center for Nephrology and Kidney Transplantation, Karbala, Iraq.*

Background: Pyroptosis links diabetes and DN via GSDMD. Study examines SNP rs59118283's impact on this process.

Methods: This case-control study included 160 participants. Biochemical parameters, GSDMD, and IL-18 levels were measured. GSDMD (rs59118283) was genotyped using PCR and Sanger sequencing.

Results: The rs59118283 SNP in the GSDMD gene was successfully amplified (476 bp product) and confirmed by sequencing. Genotype distribution showed no significant differences in odds ratios for diabetic nephropathy (DN) and type 2 diabetes mellitus (T2DM) patients compared to healthy controls (0.4 and 0.8, respectively). This aligns with studies suggesting genetic markers like GSDMD influence disease susceptibility, modulated by other factors. Significant differences in HbA1c levels, particularly in DN patients with the insertion genotype, indicate its impact on glycemic control. The genetic impact on CKD progression in T2DM is independent of demographic factors, highlighting the need for further research into genetic and environmental interactions.

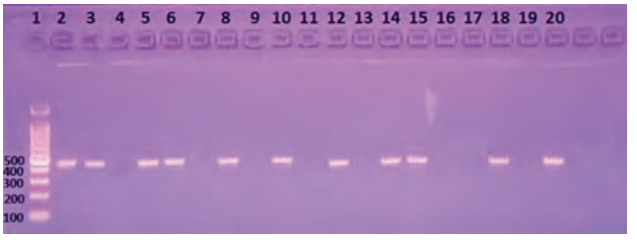
Conclusions: The GSDMD gene polymorphism (rs59118283) showed no significant association with CKD stages 2 and 3 in T2DM patients versus healthy controls. Significant biochemical variations suggest genetic factors in disease progression, warranting further research.

Funding: Government Support - Non-U.S.

SNP and SNP interaction of rs59118283 for GSDMD gene

Correlation between Parameters and rs59118283		Blood urea mg/dl	Serum creatinine mg/dl	GFR ml/mi	GSDMD ng/ml	Interleukin-18 pa/ml	RBS mg/dl	HbA1c%
Insertion	DN:n. (37)	59±13.2	1.4±0.3	56±15	48.9±21.8	125.6±35.9	1991.5±227	101.3±22.9
	Control:n. (77)	25.3±7.2	0.6±0.2	110.3±13.9	947.6±303.4	60.2±15.2	89.8±11.7	5.1±0.4
	P value	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
	DM:n. (38)	25.2±6.2	0.7±0.1	99.4±11.7	1816.3±261.7	80.8±23.6	267.7±100.3	9.5±1.8
	Control:n. (77)	25.3±7.2	0.6±0.2	110.3±13.9	947.6±303.4	60.2±15.2	89.8±11.7	5.1±0.4
	P value	≤ 0.95	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
Deletion	DN:n. (5)	61±4.4	1.5±0.2	49±7	1845.6±272.1	113.4±24.3	258±148.9	7.6±0.3
	Control:n. (3)	27.3±9.6	0.8±0.2	99.7±12.5	1743±116.1	82.7±5.3	88.7±21.01	4.8±0.1
	P value	≤ 0.05	≤ 0.05	≤ 0.05	0.6	0.1	≤ 0.05	≤ 0.05
	DM:n. (2)	29.5±5	0.99±0.1	84.5±3.5	1608.8±64.4	89.6±31.4	225.5±122.3	8.5±1.3
	Control:n. (3)	27.3±9.6	0.8±0.2	99.7±12.5	1743±116.1	82.7±5.3	88.7±21.01	4.8±0.1
	P value	0.8	0.3	0.2	0.24	0.7	0.13	≤ 0.05

Single nucleotide polymorphism,GFR: glomerular filtration rate,GSDMD: Gasdermin D,RBS: random blood sugar. HbA1c:Hemoglobin A1c.



1. Lane 1: Marker (100-1000 bp)
2. Lanes 2-9: DN (476 bp)
3. Lanes 10-15: Diabetic (476 bp)
4. Lanes 16-20: Control (476 bp)

PUB115

Effect of SGLT2 Inhibitor Therapy on Urinary Podocyte Markers in Diabetic Kidney Disease

Chuanlei Li,[1,2] Cheuk-Chun Szeto.[1,2] *[1]Departments of Medicine & Therapeutics, Prince of Wales Hospital, Hong Kong, Hong Kong; [2]Li Ka Shing Institute of Health Sciences (LiHS), Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong.*

Background: Sodium glucose cotransporter 2 inhibitor (SGLT2i) is a standard treatment for kidney and cardiovascular protection in diabetic kidney disease (DKD). Previous studies suggested that urinary level of podocyte-associated molecules may predict the progression of DKD. We determined the effect of SGLT2i on the urinary podocyte-associated molecules levels in patients with DKD.

Methods: We studied 24 DKD patients who were started on SGLT2i treatment and 25 patients who were not treated (control group). Urinary levels of podocyte-associated molecules, their corresponding mRNA levels in urinary sediment, estimated glomerular filtration rate (eGFR), and urine albumin-creatinine ratio (UACR) were measured at baseline and then again at 3 months.

Results: Urinary levels of podocin, podocalyxin, nephrin and synaptopodin did not change from baseline to 3 months in the SGLT2i treatment group. However, in the control group, urinary podocin, podocalyxin, and synaptopodin levels increased from (4.63 ± 4.84 to 18.49 ± 22.22 ng/μmol-Cr, 489.75 ± 480.62 to 1399.53 ± 1265.27 ng/mmol-Cr, and 38.61 ± 42.56 to 78.50 ± 85.61 ng/μmol-Cr, p = 0.0006, 0.0002, and 0.03, respetively) over 3 months, while unriary nephrin level did not change significantly. Urinary sediment podocin, podocalyxin, nephrin and synaptopodin mRNA levels did not change from baseline to 3 months in control and SGLT2i treatment groups. There were no significant correlations between urinary podocyte-associated marker levels and eGFR and UACR at baseline, and there was no significant correlation between urinary sediment mRNA levels of nephrin, podocin, podocalyxin, synaptopodin and eGFR or UACR at baseline. After 3-month treatment, podocalyxin mRNA level had a significant inverse correlation with eGFR (r = -0.392, p = 0.009) but not UACR. In the control group, the change in podocalyxin (r = -0.389, p = 0.017) and nephrin (r = -0.471, p = 0.010) mRNA level had significant inverse correlations with the change in eGFR and UACR, respectively.

Conclusions: SGLT2i has a small but significant effect on preventing the progressive rise in urinary podocyte-associated molecule levels but not sediment mRNA level. Our result suggests that SGLT2i therapy may affect podocyte function in DKD.

PUB116

Decrease of Hemoglobin A1c (HbA1c) in Patients with Type 2 Diabetes, Suboptimal Glycemic Control, in Advanced CKD, and Major Adverse Kidney Events

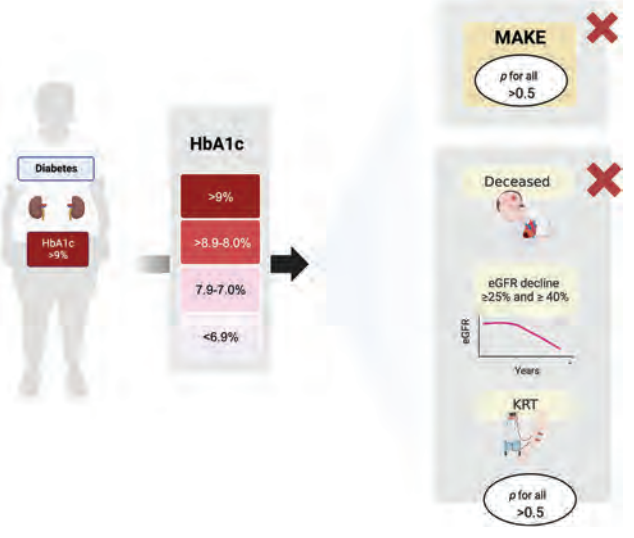
Jonathan Chavez,[1,2] Guillermo Garcia-Garcia,[1] Ramon Medina,[1,2] Zarahi Andrade,[1] Juárez Correa de León,[1] Eduardo M. Hernández,[1] Jorge L. Padilla Armas,[1] Rebeca L. Ornelas Ruvalcaba,[1] Jose S. Cabrera Aguilar,[1] Guillermo Navarro Blackaller,[1] Maria de la Luz Alcantar Vallin,[1] Alejandro Martínez Gallardo González.[2] *[1]Universidad de Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico.*

Background: In subjects with type 2 diabetes (DM), poor glycemic control, and advanced chronic kidney disease (CKD), the kidney benefit of the reduction of glycated hemoglobin (HbA1c) is not well established.

Methods: In a retrospective cohort, we included patients with DM, CKD grade 3b-5, and HbA1c >9%, to evaluate the risk of developing major adverse kidney events (MAKE) defined as the start of kidney replacement therapy (KRT), ≥ 25% or ≥ 40% decline in the glomerular filtration rate (eGFR) from baseline, and death; according to the HbA1c groups at the end of the follow-up, divided by >75 mmol/mol (≥9.0%), 74-64 mmol/mol (8.9-8.0%), 64-53 mmol/mol (7.9-7.0%) and <52 mmol/mol (<7.0%). We described their characteristics and analyzed their risks adjusting for confounding variables.

Results: During 2015 to 2023, 111 patients were included. In 46 (41.4%) the HbA1c at the end of follow-up (60 months) was still >75 mmol/mol (≥9%), each patient had a mean of 4.9 HbA1c measurements. The mean age was 59 years and 46% were male, baseline eGFR was 25 ml/min/1.73m^2. MAKE occurred in 67% of cases. In a multivariate analysis, the risk of MAKE was not associated with the HbA1c groups. Nor was it associated with any of the MAKE components individually, nor in certain subgroups. When evaluating the magnitude of percentage changes in HbA1 with the initiation of KRT, we did not find any association.

Conclusions: With advanced CKD and poor glycemic control, changes in HbA1c during long follow-up are not associated with MAKE or its individual components.



PUB117

Modifying Effect of Albuminuria on the Association between Joslin Kidney Panel Biomarkers and Kidney Failure among Patients with Diabetes: Findings from the ACCORD/ACCORDION Trial

Balamurugan Tangiisuran,[1,2] Hetal Shah,[1,2] Andrzej Galecki,[4,3] James P. Lash,[5] Andrzej S. Krolewski,[1,2] Alessandro Doria.[1,2] *[1]Joslin Diabetes Center, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]University of Michigan Medical School, Ann Arbor, MI; [4]University of Michigan, Department of Biostatistics, School of Public Health, Ann Arbour, MI; [5]University of Illinois Chicago College of Medicine, Chicago, IL.*

Background: The Joslin Kidney Panel (JKP) includes 21 serum proteins identified as predictors of risk of kidney failure (KF) in patients with diabetes. Our goal was to evaluate the association with KF and the predictive performance of JKP biomarkers in patients with type 2 diabetes with and without albuminuria at baseline.

Methods: A case-cohort analysis of the ACCORD/ ACCORDION cohort was carried out by selecting a 15% random sub-cohort plus all KF cases outside the sub-cohort. JKP biomarkers were measured in baseline serum samples using a custom multiplex Olink® assay. Weighted Cox models (adjusted by clinical KF predictors and trial treatment assignments) were used to assess the association between baseline JKP biomarkers and KF during follow-up by baseline albuminuria status.

Results: A total of 1,393 subjects were included in the study: 432 with albuminuria (urinary ACR >30 mg/g) and 961 with normoalbuminuria at baseline. There were 129 and 127 KF events in the albuminuric and normoalbuminuric strata, respectively, during a median follow-up of 6.1 years (IQR 4.0-9.4). Fifteen JKP markers showed a significant association with KF in the albuminuria stratum, with the axon-guidance protein EFNA4 showing the strongest effect (HR 3.96, 95% CI 2.05 – 7.67). By contrast, only six biomarkers were associated with KF in normoalbuminuric participants and with smaller HRs than in albuminuric participants. In an interaction analysis, 13 biomarkers showed significant differences in their effect on KF risk between albuminuria and normoalbuminuria strata. Addition of the JKP biomarkers to clinical predictors increased the C-index from 0.70 to 0.76 ($p<0.0001$) in the albuminuria stratum and from 0.58 to 0.67 ($p<0.0001$) in the normoalbuminuria stratum.

Conclusions: Currently available biomarkers of increased KF risk are more strongly associated with KF in albuminuric than in normoalbuminuric subjects with type 2 diabetes. While these proteins improve KF risk discrimination in both groups, the combined performance of clinical and biomarker predictors is lower among normoalbuminuric subjects. Studies are needed to identify novel biomarkers allowing better KF risk prediction in normoalbuminuria.

Funding: NIDDK Support

PUB118

Superimposed Focal Segmental Glomerulosclerosis Lesions Worsen Kidney Prognosis in Diabetic Nephropathy (DN)

Maria Jose Vargas-Brochero,[1] Miriam Machado,[1] Nancy Daniela Valencia-Morales,[1] Marta I. Casal Moura,[1] Sana Abouzahir,[1] Sanjeev Sethi,[1] Maria Jose Soler.[2] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Hospital Universitari Vall d'Hebron, Barcelona, Spain.*

Background: Patients with biopsy-proven DN may have superimposed focal and segmental glomerulosclerosis(FSGS), and its implications for kidney prognosis have been scarcely assessed. This study aims to assess how the presence of FSGS in patients with DN affects kidney prognosis

Methods: Historical cohort study of biopsy-proven DN from 2010 to 2022. Exclusion criteria included ESKD at diagnosis, primary glomerulopathies, metastatic cancer, pregnancy, transplant of any organ, or lack of follow-up. Primary outcome was comparing the progression to ESKD (defined as an estimated glomerular filtration rate(eGFR)<15 mL/min/1.73m2, kidney transplant, or renal replacement therapy need. Time-to-event analysis was conducted using the Kaplan-Meier (ESKD as the event of interest). Cox proportional hazard regression was used to determine predictive factors associated with ESKD

Results: 67 patients; mean age 61.6y, 38(56.7%) male, and 56(83.6%) white. 37 (55.2%) had FSGS lesions. FSGS cohort had a higher presence of non-white ethnicity n=10 (27%)(p=0.009), higher Albumin/creatinine ratio (ACR) (***p=0.014***), higher IFTA ***(p=0.009)***, and percentage of class IV (***p=0.037)***, there were no differences regarding the body mass index. 26 (38.8%) reached ESKD during follow-up; the median follow-up was 3.3 years, and the median survival was 4.13 years. Estimated kidney survival was 86.6 % (78.7-95.1%) at one year, with a significant difference in the FSGS group (long-rank p=0.04). In the multivariate Cox regression model, FSGS (HR, 2.9; 95% CI 1.04 to 8.10), stroke (HR, 5.6; 95% CI 1.8 to 17.7), and albumin (HR, 0.2; 95% CI 0.94 to 0.43), were independently associated with progression to ESKD

Conclusions: Our study characterizes a population with DN and demonstrates how superimposed FSGS is related to a higher risk of progression to ESKD

Table 1 Univariate and Multivariate Cox regression associations between baseline patient characteristics and risk of ESKD

Univariate Cox					
Baseline Patient Characteristic	Total (67)	NO ESKD (41)	ESKD (26)	HR (95% CI)	p
Clinical characteristics					
SBP (per 10mmHg) Mean(SD)	136(17.2)	132.5(17.3)	141.5(16)	1.25(1.06-1.5)	***0.045***
Retinopathy, n(%)	39(58.2%)	20(95.1%)	19(73%)	2.84(1.17-6.9)	***0.02***
Peripheral vascular disease, n(%)	21 (31.3%)	9 (21.9%)	12(46.1%)	2.56(1.17-5.5)	***0.01***
Stroke, n(%)	10 (14.9%)	4(9.7%)	6(23%)	2.59(1.0-6.6)	***0.04***
GLP1-RA, n(%)	12(17.9%)	3(7.3%)	9(34.6%)	3.55(1.54-8.2)	***0.003***
Hemoglobin (per 1 g/dL) mean(SD)	11.1(2.08)	11.5(2.1)	10.4(1.8)	0.60(0.67-0.95)	***0.015***
Serum creatinine (per 1 mg/dl) mean(SD)	2.24 (0.79)	2.02(0.77)	2.58 (0.71)	2.15(1.32-3.52)	***0.002***
eGFR (per 1 ml/min/1.73m²) median[IQR]	28 [21-38]	31 [26,42]	21 [20,30.7]	0.92(0.87-0.97)	***0.003***
Albumin (per 1 g/dL) median[IQR]	N=66(98.5%) 3.9 [3.25-4.1]	4 [3.6,4.1]	3.3[2.9,4]	0.36(0.2-0 65)	***<0.001***
Serum Glucose (1 md/dl) mean(SD)	168(56.1)	157(44)	185 ± 70	1.008(1.002-1.015)	***0.014***
HA1c (per 1%) median[IQR]	62 (92.5%) 7 [6.3-8.12]	6.7 [6.3 7.6]	7.4[6.6,8.5]	1.23(1.01-1.49)	***0.035***
Albumin/creatinuria Ratio (per 300 mg/g) median[IQR]	52(77.6%) 1622[500,3833]	1272[236,2698]	2776[1260,4166]	1.09 (1.03-1.15)	***0.003***
Biopsy characteristics					
Advance glomerulosclerosis, n(%)	15(22.4%)	6(14.6%)	9(34.6%)	2.3(1.03-5.2)	***0.042***
Moderate /severe arteriolar hyalinosis , n(%)	53(79.1%)	33(80.5%)	20(76.9%)	3.4(1.02-11.3)	***0.046***
FSGS, n(%)	37(55.2%)	19(46.3%)	18(69.2%)	2.3(1.01-5.6)	***0.046***
Multivariable cox regression					
Baseline Patient Characteristic				HR (95% CI)	p
FSGS, n(%)	37(55.2%)	19(46.3%)	18(69.2%)	2.9(1.04-8.1)	0.041
Stroke, n(%)	10 (14.9%)	4(9.7%)	6(23%)	5.66(1.81-17.7)	0.003
Albumin (per 1 g/dL)	3.9 [3.25-4.1]	4 [3.6,4.1]	3.3[2.9,4]	0.20(0.09-0.43)	<0.001

PUB119

Neurotuberculosis in a Patient with CKD: A Rare Case Report of the Lethal Duo

Abhijit S. Chavan, Prabhakar Yadav, Himanshu Shekhar. *Tata Main Hospital, Jamshedpur, India.*

Introduction: One of the leading causes of deaths worlwide has been infections with Mycobacterium tuberculosis (TB), which is endemic in certain nations where also prevalance of CKD has been on an rising trend. In patients with CKD, the incidence of TB has been 10–15 times greater than that in the general population, considering the immunocompromised state associated with CKD. The clinical presentation of TB in CKD patients is often insidious and atypical. Patients frequently present with symptoms like fever, anorexia, and weight loss which may mimic uremia and mask diagnosis of Nuero-tuberculosis.

Case Description: A 66 year old gentlemen, a known case of CKD stage V due to underlying diabetic Nephropathy, presented with complains of easy fatigabilty since a month. He was found to have a right sided plueral effusion and a serum creatinine of 5.6 mg/dl. Subsequently patient underwent a diagnostic tap which favoured diagnosis of extra-pulmonary TB (pleural fluid: cells- 550/cumm lymphocytes-90%, ADA- 54 IU/L, lights criteria ratio-1.2). Patient was started on Anti-tubercular drug therapy as per National TB guidelines including Isoniazid, Rifampicin, ethambutol and Pyrazinamide as per weight based dosing and dose adjusted for CKD staging. Two weeks later patient complained of uremic symptoms and drowsiness. On further investigations, he had urea of 157 mg/dl, creatinine of 8.4 mg/dl demanding initiation of hemodialysis. After initial 3 sessions of hemodialysis patient did not show any improvement and underwent an MRI Brain with diffusion imaging suggestive of a T2 heterointense lesion measuring 1.20 x 1.28 cm is seen in left posterior frontal lobe showing mild perilesional edema and heterogeneous diffusion restriction on DWI images. On the context of an established extra-pulmonary TB and the intra-parenchymal CNS lesion a diagnosis of Tuberculoma was made.

Discussion: Tuberculomas, occur secondary to a primary infection, the focus being lungs or lymph nodes, occuring in the background of CKD is a very rare extrapulmonary manifestation of TB. The performance of TB screening and diagnostic tests is suboptimal in the CKD population, making a timely diagnosis a challenging task. Considering the high prevalance of CKD in TB endemic areas, a missed diagnosis of TB in CKD population could have significant public health implications and poor patient outcomes.

PUB120

Unveiling the Continuum: Tracking Urinary Transforming Growth Factor (TGF)-β1 in Diabetic Nephropathy Follow-Up

Akshay R. Kulkarni, Atul Sajgure, Charan B. Bale, Pavan Wakhare, Nilesh Shinde, Abhijit S. Chavan, Debapriya Saha, Anuja P. Makan, Shreeharsh Godbole, Chetan U. Phadke, Abhishek S. Borle, Gaurav Singh, Tushar A. Dighe. *Dr. D. Y. Patil Medical College, Hospital & Research centre, Pimpri, Pune, Pune, India.*

Background: Diabetic nephropathy (DN) is a leading cause of end-stage kidney disease (ESKD). Accumulating evidence points to transforming growth factor beta-1(TGF-β1), a potent profibrotic mediator, as a significant mediator in the development of DN.

Methods: It was a prospective observational study including 10 cases of diabetic Nephropathy in group A and 10 healthy controls in group B, age ≥ 18 years. Patients with

urinary tract infection, pregnancy, CKD stage Vd patients on maintenance hemodialysis and post renal transplant cases were excluded. Patients clinical characteristics and examination findings were recorded at visit 1 and follow up after 3 months (visit 2). Patients received standard of care treatment during the follow up. Urinary TGF-β1 levels were determined in a 24 hours urine sample using Miltenyi-MACSQuant-10 flowcytometer, each sample run in triplicates and average of the three taken. The biochemical tests were performed using dimension ExL clinical chemistry system (SIEMENS). Quality of life was assessed using Karnofsky performance status scale.

Results: In group A, the mean value of urinary TGF-β1 on visit 1 was 88.33 ± 12.44 ng/24 hours and on visit 2 was 69.25 ± 13.56 ng/24 hours. The reduction in the TGF-β1 levels on follow up in group A was statistically significant (p< 0.001). The mean value in the group B was 29.03± 3.23 ng/24 hours, significantly low compared to group A (p<0.001). In group A there was no significant correlation between urinary TGF β1 levels and 24 hours urine protein, on visit 1 and 2(r = 0.341 and r=0.505) or UPCR on visit 1 and 2 (r = 0.154,p = 0.672 and r= 0.120,p= 0.742). Also, the change in urinary TGF-β1 levels(between visit 1 & 2) didn't correlate with change in 24 hours urine protein (r=0.258, p=0.472), UPCR(r=0.240, p=0.505) or eGFR(r=-0.268, p=0.455). The median Karnofsky performance status was 80 on visit 1 and 90 on visit 2 in group A, while it was 100 in group B.

Conclusions: Urinary TGF- β1 levels reduced significantly on follow up after 3 months amongst diabetic nephropathy patients but that change didn't correlate with the change in proteinuria and eGFR. There was no significant correlation between urinary TGF- β1 levels and proteinuria, serum creatinine level or eGFR.

PUB121

Tirzepatide Improves Glycemic Control Better than Dulagutide in Patients Undergoing Hemodialysis

Emiko Otsuka,[1] Mineaki Kitamura,[1] Shinichi Abe,[2] Satoshi Funakoshi,[2] Tomoya Nishino.[1] *[1]Nagasaki Daigaku Daigakuin Ishiyakugaku Sogo Kenkyuka, Nagasaki, Japan; [2]Nagasaki Kidney Center, Nagasaki, Japan.*

Background: Glycemic control is crucial to reduce cardiovascular events and mortality in patients with type 2 diabetes undergoing hemodialysis. On the other hand, some anti-diabetic drugs are of limited use or contraindicated in patients undergoing hemodialysis. Tirzepatide is a novel dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) agonist that can be used in patients undergoing hemodialysis. However, the safety and efficacy of tirzepatide in patients undergoing hemodialysis remain unclear. We aimed to compare the glycemic control between dulaglutide and tirzepatide in patients undergoing hemodialysis.

Methods: This study is a retrospective single-center study. We included patients with type 2 diabetes undergoing hemodialysis whose prescriptions for diabetes were transitioned from dulaglutide to tirzepatide at the Nagasaki Renal Center between June 2023 and August 2023. Blood glucose levels were evaluated using continuous glucose monitoring (CGM) for 7 days in both periods before and after switching from dulaglutide to tirzepatide. Time in range (TIR), time above range (TAR), time below range (TBR), and mean blood glucose levels, were analyzed using the Wilcoxon signed-rank test.

Results: We analyzed 14 patients (61.9 ± 9.9 years, male: female =11:3). After switching to tirzepatide, TIR increased to 50.8% from 42.7% (p=0.02), TAR decreased to 37.8% from 48.4% (p=0.02), and mean glucose levels decreased to 137.4 mg/dL from 156.6 mg/dL (p=0.006). However, TBR did not show significant change before and after switching to tirzepatide (11.3% and 8.9%) (p=0.75). Furthermore, there were obvious improvements in glycemic control on hemodialysis days; TIR increased from 44.8% to 52.2% (p=0.02), TAR decreased from 40.9% to 32.6% (p=0.07), and TBR did not increase (13.7% and 14.3%) (p=0.76). In contrast, there were no significant changes in TIR (47.9% and 51.7%) (p=0.25), and mean glucose levels (157.9 mg/dL and 141.3 mg/dL) (p=0.08), on non-hemodialysis days.

Conclusions: Tirzepatide improves glycemic control without increasing hypoglycemia compared to dulagutide in patients with type 2 diabetes undergoing hemodialysis.

PUB122

Impact of Once-Weekly Semaglutide on eGFR and Hemoglobin A1c (HbA1c) among Patients with Type 2 Diabetes and CKD: An Observational Study

James J. Amamoo,[1] Sunny T. Sheth,[1] Brenna L. Brady,[2] Anh Thu Tran,[2] Lin Xie,[1] Josh Noone,[1] Sherif Mehanna,[1] George L. Bakris.[3] *[1]Novo Nordisk Inc., Plainsboro, NJ; [2]Merative, Cambridge, MA; [3]University of Chicago Medical Center, Chicago, IL.*

Background: Of ~35 million patients living with type 2 diabetes (T2D) in the US, 30–40% also have CKD, which is associated with increased morbidity and mortality. Therefore, managing comorbidities is of utmost importance. This real-world study assessed the changes in eGFR and HbA_{1c} in adults with T2D and CKD following initiation of once-weekly (OW) semaglutide subcutaneous injection.

Methods: This exploratory non-interventional, longitudinal, retrospective cohort study included patients aged ≥18 years with evidence of T2D and CKD (eGFR <60 mL/min/1.73 m^2) pre-index, newly initiating OW semaglutide (index selection period: January 2018–September 2022) from the Merative™ MarketScan® Laboratory Database. Other key inclusion criteria included persistence to OW semaglutide of ≥6 months, and no evidence of dialysis or kidney transplant at baseline. The first prescription fill for OW semaglutide served as the index date. Patients were followed over a variable post-period, the end of which was the first of OW semaglutide discontinuation, end of continuous eligibility or end of study data. Change in eGFR and HbA_{1c} from the last value taken prior to index date were assessed over a variable period for all patients with ≥6 months' of follow-up and over a fixed 12-month follow-up.

Results: A total of 254 patients qualified for the analyses. Mean (SD) baseline eGFR and HbA_{1c} were 45.1 (10.5) mL/min/1.73 m^2 and 7.8 (1.6)%, respectively. The mean (SD) changes in eGFR and HbA_{1c} values from baseline to post-index were 2.0 (10.9) mL/min/1.73 m^2 and –1.1 (1.6)%, respectively. In a subgroup of patients with 12 months' follow-up (n=99), mean (SD) eGFR and HbA_{1c} at baseline were 45.2 (10.8) mL/min/1.73 m^2 and 7.5 (1.7)%, respectively. The mean (SD) changes in eGFR and HbA_{1c} values from baseline to 12 months post-index were 4.5 (12.8) mL/min/1.73 m^2 and –1.2 (1.5)%, respectively.

Conclusions: In this exploratory real-world study, initiation of OW semaglutide was associated with improvements in both eGFR and HbA_{1c} in adults with T2D and CKD over 12 months, demonstrating its potential utility in this patient population.

Funding: Commercial Support - Novo Nordisk Inc.

PUB123

A Randomized Controlled Clinical Trial to Evaluate the Efficacy and Safety of FX CorAL Dialyzers during Hemodialysis Treatment in Chinese Patients on Maintenance Hemodialysis: Study Protocol

Liangying Gan,[1] Bingbin Zhao,[2] Lily Zhang,[2] Yuanying Guo,[3] Qing Lin,[2] Bettina Griesshaber,[4] Kakiu Ho,[5] Manuela Stauss-Grabo,[4] Li Zuo.[1] *[1]Peking University People's Hospital, Beijing, China; [2]Fresenius Medical Care, Beijing, China; [3]Fresenius Medical Care, Shanghai, China; [4]Fresenius Medical Care, Bad Homburg, Germany; [5]Fresenius Medical Care, Hong Kong, China.*

Background: Dialyzers are designed to eliminate uremic toxins during dialysis treatment, this is especially important as the accumulation of small and middle molecular weight uremic solutes is associated with increased morbidity and mortality. The FX CorAL dialyzers are a series of high flux hemodialyzers with a modified membrane surface, resulting in improved clearance performance and hemocompatibility. This study tests the hypothesis of non-inferiority of efficacy and safety comparing FX CorAL to WEGO dialyzer.

Methods: In the two-stage, prospective, multicenter, randomized, parallel controlled, open, non-inferior study, a total of 238 adult Chinese maintenance hemodialysis patients will be enrolled and randomized in a 1:1 fashion to the investigational group (FX CorAL, Fresenius Medical Care AG) and the control group (WEGO HF, Shandong Weigao Blood Purification Products, China). Each patient will undergo regular thrice weekly HD treatment. The study consists of two mid-week HD treatments in sequence for study dialyzer evaluations (Stage I with surface area 1.4 m^2: FX CorAL 60 vs. WEGO HF14; Stage II with surface area 1.8 m^2: FX CorAL 80 vs. WEGO HF18), and a washout period including two HD treatments between Stage I and II (figure 1). The primary endpoints are clearance of creatinine and urea nitrogen at 60 min after start of dialysis, and reduction ratio of β2-microglobulin during HD treatment. The secondary endpoints include removing performance of other uremic solutes, inflammatory markers, and safety.

Results: The study is ongoing and will be completed in 2027.

Conclusions: This study will add insights to the efficacy and safety profiles for FX CorAL dialyzer. It is hypothesized that the uremic toxin clearance performance of FX CorAL is non-inferior (and potentially superior) to the comparator dialyzer.

Funding: Commercial Support - Fresenius Medical Care

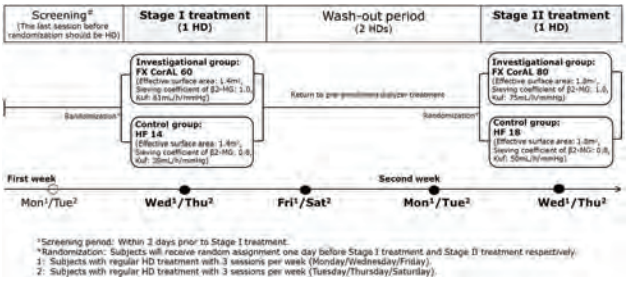


Figure1. Study flowchart.

PUB124

A Case of Multidrug Intoxication Including Calcium Channel Blocker Treated with Plasmapheresis

Alissa A. Ice, Edward Gould. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Amlodipine, a dihydropyridine calcium channel blocker (CCB), has a large volume of distribution and is primarily hepatically metabolized with an extended half-life. Despite amlodipine being highly protein bound, there is a paucity of evidence for the potential role of plasmapheresis (PLEX) in toxicity management. We present an overdose case with refractory shock necessitating both ECMO and PLEX treatment.

Case Description: A 47 year old male with HTN, DMII, prostate cancer, gout, and PTSD presented following an intentional overdose of 900mg of amlodipine and a large quantity of an unknown medication, reportedly either triamterene-hydrochlorothiazide or amitriptyline. He presented with profound distributive shock and acute hypoxemic respiratory requiring several vasopressors and eventually intubation. Labs were notable for potassium 1.7, phosphorous <0.7, bicarb 9, Cr 2.32, glucose 597, anion gap 18, lactic acid 6.6 (peaked at 15.3), AST 57, ALT 71, WBC 29.4, VBG 7.26/30/40/13, CPK 6718, troponin 0.33 (peaked at 1.59). EKG demonstrated anterolateral ST depressions but no evidence of QT prolongation and TTE without wall motion abnormalities and EF >70%. He was seen by toxicology and started on insulin, glucagon, calcium chloride, sodium bicarb, lipid, and methylene blue infusions. In addition to electrolyte supplementation, he was started on VA-ECMO and underwent one session of PLEX followed by CRRT given persistent oliguric AKI and severe metabolic derangements. His course was further complicated by lower limb ischemia and ARDS, and the family elected for comfort measures.

Discussion: Although dihydropiridine CCBs have affinity for the L-type calcium channels within the vascular smooth muscle, this pharmacological selectivity can be altered in the setting of toxicity. In addition to the profound cardiovascular repercussions, CCB also inhibit beta islet cells, leading to hyperglycemia. This finding has been described to associate with the severity of the intoxication. Conventional treatment includes hemodynamic support and calcium administration. Given CCBs are highly protein bound, hemodialysis is not recommended, but there may be some utility in PLEX in select cases. Previous case studies have demonstrated a reduction in amlodipine plasma concentrations of approximately 36%. In the setting of profound CCB overdose and associated vasoplegia, PLEX should be considered.

PUB125

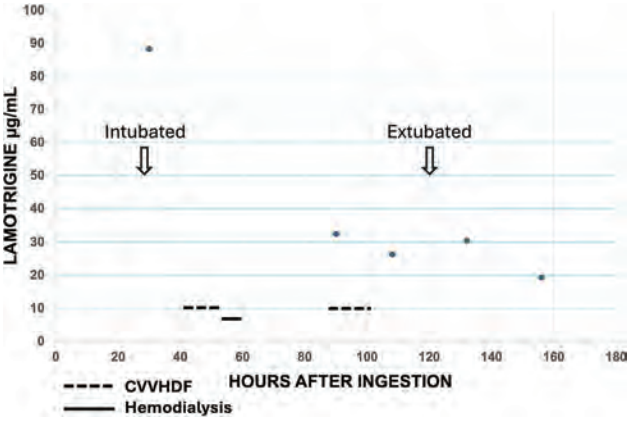
Dialysis for Lamotrigine Intoxication in a Teenager

Elliott Huang, Hilda E. Fernandez. *Columbia University, New York, NY.*

Introduction: Lamotrigine (LTG) is a rare cause of acute intoxication. A 1993 pharmocokinetic study of a dose of LTG was conducted in healthy volunteers, patients w CKD and ESRD on iHD. The elimination half-life of LTG was approximately 25 h in subjects w normal renal function and 50 h in uremic patients. iHD shortened the elimination half-life from 59.6 +/- 28.1 h during the interdialysis period to 12.2 +/- 6.4 h during the dialysis period; 17% of the dose was extracted by HD. Clinical reports of 2 to 5 iHD treatments have been associated w neurologic improvement. LTG levels > 25 µg/mL have been associated w severe toxicity in adults. Ingestions > 4.5gm of LTG have been associated w severe morbidity and mortality.

Case Description: 16 yo F w h/o depression intentionally ingested a total of 6 g of LTG and unknown small amounts of lurasidone and fluoxetine. She was taken to ER for headache and dizziness 3 h post ingestion. At 27 h after ingestion, she developed hypotension requiring pressor support and had a GTC seizure requiring intubation for airway protection. There was no AKI. Poison Control recommended hemodialysis to clear LTG. CVVHDF was initiated 41 h after ingestion and continued until 55 h after ingestion. She was switched to 4 h iHD when she was stable off pressors. CVVHDF was resumed at 89 h after ingestion for 12 h, then discontinued w Poison Control advice. She had improvements to her mental status and was extubated at 120 h. LTG levels were sent daily but results were not available until dialysis was discontinued (Figure). She was transferred to inpatient psychiatry on day 8.

Discussion: Sixty-three percent of LTG was cleared after a combination of CVVHDF and iHD within 48 hours. Subsequent CVVHDF for 12 hours cleared an additional 19% of LTG. A rebound in LTG level was seen the next day off dialysis; however, patient already had recovery from AMS. Due to the severity of clinical presentation and delay in LTG levels resulting, we performed dialysis for 3 consecutive days in this patient w clinical improvement.



Lamotrigine intoxication

PUB126

Relative Change in Itch Intensity Determines Treatment Satisfaction of Patients with CKD-Associated Pruritus

Joerg Latus,[1] Thilo Schaufler,[2] Isabelle Morin,[2] Warren Wen,[3] Joel M. Topf.[4] *[1]Robert-Bosch-Krankenhaus GmbH, Stuttgart, Germany; [2]CSL Vifor, Glattbrugg, Switzerland; [3]Cara Therapeutics Inc, Stamford, CT; [4]Oakland University William Beaumont School of Medicine, Rochester, MI.*

Background: Four in ten patients on hemodialysis (HD) report suffering from moderate or severe CKD-associated pruritus (CKD-aP) and associated conditions such as: sleep problems, fatigue, depressive symptoms, and reduced quality of life. Burden of itch and itch relief are highly subjective.

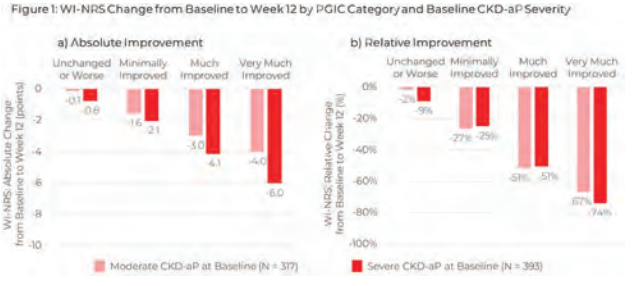
Methods: HD patients in KALM-1 and -2 (NCT03422653 and NCT03636269) trials received either difelikefalin or placebo 3 times per week for 12 weeks. Itch intensity was assessed with the weekly mean of the Worst Itching Intensity Numerical Rating Scale (WI-NRS; range 0 [no itch] to 10 [worst itch imaginable]) as moderate (KALM-1: >4 to <7; KALM-2 ≥5 to <7) or severe (≥7) at baseline. Patient Global Impression of Change (PGIC) asked patients after 12 weeks how their itch changed (1 [very much improved] to 7 [very much worse]). This exploratory analysis reports absolute and relative change in WI-NRS relative to PGIC-assessed treatment satisfaction stratified by baseline itch severity independent of treatment exposure.

Results: Patients with moderate or severe CKD-aP at baseline reporting their itch to be "much improved" had a mean reduction of ≥3 WI-NRS points. Those "very much improved" had a mean reduction of ≥4 WI-NRS points (see Figure 1a). Relative improvement by PGIC category was highly consistent across baseline severity groups, independent of treatment received, with patients reporting their itch having "much improved" seeing a 50% reduction from their baseline WI-NRS value. Those "very much improved" saw a reduction of ~ 70% from baseline (see Figure 1b). Spearman correlation (95% confidence interval) between the PGIC and relative change in WI-NRS in patients with moderate CKD-aP was 0.63 (0.55 – 0.69) and 0.71 (0.66 – 0.76) in patients with severe CKD-aP at baseline, respectively.

Conclusions: While patient-reported treatment satisfaction should be the main goal in subjective conditions such as CKD-aP, this analysis demonstrates that the relative change on the validated WI-NRS scale can offer valuable decision support for nephrology professionals assessing treatment benefit.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma, Cara Therapeutics

Figure 1: WI-NRS Change from Baseline to Week 12 by PGIC Category and Baseline CKD-aP Severity



PUB127

Improving Dialysis Initiation in Stage 5 CKD: A Quality Improvement Project at a Safety Net Hospital

Elaine J. Oldford,[1,2] Annika K. Khine.[1] *[1]Los Angeles General Medical Center, Los Angeles, CA; [2]Keck Medicine of USC, Los Angeles, CA.*

Background: At Los Angeles General Medical Center (LAGMC), a large safety net training institution, residents and fellows rotate through specialty clinics, serving a primarily Hispanic and underserved population. In LAGMC renal clinic, we implemented a quality improvement project in patients with eGFR <20 ml/min/1.73m2, by scheduling them in an attending-directed CKD clinic rather than with resident trainees for follow-up visits. This study evaluates the impact of this intervention on inpatient and outpatient dialysis initiation and the use of permanent dialysis access.

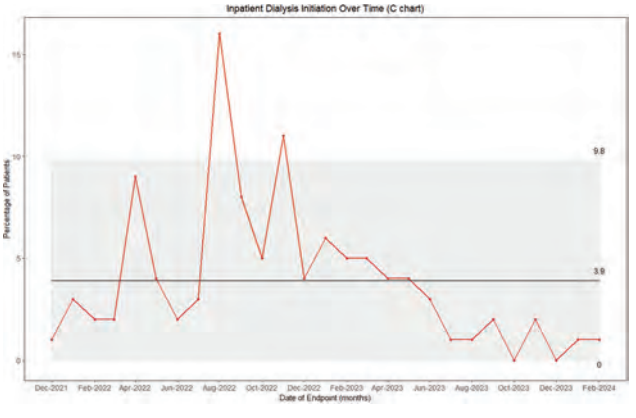
Methods: In this retrospective observational study, medical records of 244 CKD Stage V patients at LAGMC renal clinic from January to July 2022 were reviewed. We determined the endpoint for each patient as dialysis initiation (inpatient or outpatient) or the end point date of February 2024 if not yet on dialysis. The intervention began in October 2022, transferring patients from resident panels to attending panels for follow-up visits, with a 3-month run-in period.

Results: 167 of patients initiated dialysis, with 105 (63%) as inpatient and 62 (37%) as outpatient. There was a decreasing trend in inpatient initiations and an increasing trend in outpatient initiations over time. Inpatient dialysis initiations resulted in an average hospital stay of 7 days, with 22% of patients requiring temporary dialysis catheters. There was also an increase in permanent vascular access (AVF/AVG) over time of CKD Stage V patients at the endpoint.

Conclusions: Quality improvement that have CKD Stage V patients seen directly by attending nephrologists can decrease the rates of inpatient "crash" start dialysis and increase vascular access.

Access Type Present at End Point

	Dec 2021-Sep 2022	Oct-Dec 2022	Jan 2023-Feb 2024
AVF/AVG	5	4	34
PD	10	1	11
TDC	49	24	38



PUB128

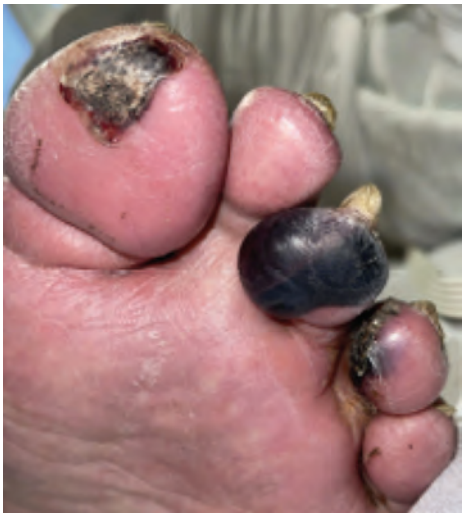
Midodrine-Induced Ischemic Vascular Injury: A Case Report in Patients on Hemodialysis

Hillary Vo,[1,3] Shehpar Khan,[1] Samir Nangia.[1,2] *[1]Dallas Renal Group, Dallas, TX; [2]Burnett School of Medicine, Fort Worth, TX; [3]Arkansas College of Osteopathic Medicine, Fort Smith, AR.*

Introduction: Midodrine is an alpha-agonist that increases blood pressure by inducing vasoconstriction. It is widely prescribed due to its efficacy in managing hemodialysis-associated hypotension in ESRD patients. Midodrine is generally well-tolerated by most patients. However, despite its rarity, we present a case highlighting an adverse effect of midodrine.

Case Description: We present the case of a 68-year-old male with ESRD on hemodialysis, with a history of type 2 diabetes-associated nephropathy, CAD, and CHF with EF 20-25%. The patient was initiated on Midodrine 10mg three times a day for hypotension. He presented after 3 weeks with numbness, discoloration of digits, and gangrenous lesions. He denied any specific injury or use of calcium-based phosphorus binders. ABI of the left lower extremity was as low as 0.5. ANCA and ANA tests were negative, and cryoglobulin was absent, ruling out autoimmune systemic vasculitis. Initial lab results indicated well-controlled levels of calcium, iPTH, and phosphorus. A punch biopsy was performed to rule out calciphylaxis, which showed no calcium deposits, thrombi, or evidence of vasculitis.

Discussion: While current literature generally indicates the safety of midodrine, this case appears to be one of the few documented instances of midodrine-induced ischemic vascular injury observed in hemodialysis patients. Further research should prioritize discontinuing the medication to evaluate the persistence of symptoms. The primary aim of this report is to increase awareness of ischemic vascular injury as a potential side effect of midodrine and to encourage heightened vigilance among physicians.



PUB129

Determination of Fracture Risk in a Hemodialysis Unit in Ecuador Using the FRAX Tool without Bone Mineral Density (BMD)

Ana Y. Navarro,[1] Ailiyomar Perez,[2] Ricardo J. Lino.[3] *[1]Fresenius Medical Care, Quito, Ecuador; [2]Menydial, Ambato, Ecuador; [3]Baxter Ecuador SA, Quito, Ecuador.*

Background: Patients with chronic kidney disease (CKD) present mineral bone disease which is developing from earlier stages, producing osteoporotic fractures that aggravate their morbidity and mortality during the treatment, so prevention plays a fundamental role in preserving the quality of life of patients.

Methods: cross-sectional, correlational and descriptive study. It included 209 patients. As inclusion criterion: patients between 40 and 90 years old, on hemodialysis. Excluded were: patients with malignant disease, bedridden patients and patients receiving antiresorptive treatments. Demographic variables and serum levels of biochemical markers that guide the diagnosis of bone mineral disease were evaluated. cross-sectional, correlational and descriptive study. It included 209 patients. As inclusion criterion: patients between 40 and 90 years old, on hemodialysis. Excluded were: patients with malignant disease, bedridden patients and patients receiving antiresorptive treatments. Demographic variables and serum levels of biochemical markers that guide the diagnosis of bone mineral disease were evaluated.

Results: 60.28% men and 39.71% women, with an average age of 61.85±10.75. 77.55% were at risk of major osteoporotic fracture, of which 43.75% were women and 56.24% men, with an average age of 64.78±9.88. Differentiating the higher risk group vs. the lowest risk was recorded: BMI 24.53vs 25.98; calcium 8.26 vs 8.4; Pth 385.91 vs 359.2; in albumin and phosphorus there were no significant differences. The variables resulted with sensitivity and specificity of 95% confidence. In hip fracture, 27.27% of patients were at risk, of which 49.12% were women and 58.87% were men, with an average age of 71.73±8.89; BMI, calcium and albumin were lower than in those patients without significant risk of hip fracture, respectively, 23.64 vs 25.30; 8 vs 8.25; 3.72 vs 3.88; the opposite occurred with Pth 434 vs 358.92; which is expected, again the phosphorus without relevant meanings and the confidence index for the significant variables was 95% for sensitivity and specificity

Conclusions: The risk of major osteoporotic fracture and hip fracture in the hemodialysis unit was high. The frax tool proved to be assertive for patients on hemodialysis, even without the use of BMD, the results show the association of variables that allow diagnosing mineral disease.

PUB130

Prevalence of the Chronic Inflammatory State and Relationship with Prealbumin and Morbimortality in Patients with CKD

Ana Y. Navarro,[1] Ailiyomar Perez,[2] Ricardo J. Lino.[3] *[1]Fresenius Medical Care Ecuador, Quito, Ecuador; [2]Menydial, Riobamba, Ecuador; [3]Baxter Ecuador SA, Quito, Ecuador.*

Background: The chronic inflammatory state is common in patients on hemodialysis (HD), the evaluation of the clinical and nutritional status of patients on HD is essential. High mortality in HD may be associated with protein wasting síndrome energy (PEW), decreased levels of prealbumins, the objective of this work is to determine the prevalence of c-reactive protein (CRP) ≥ 9mg/L and its relationship with prealbumins <30 mg/dl, morbidity and mortality in a dialysis unit, Ecuador

Methods: cross-sectional, prospective study, 334 patients on HD, over 18 years old, with more than 3 months on dialysis, without active infectious processes at the time of sample collection, which included determination of serum levels of prealbumin and c-reactive protein, morbidities and mortalities were recorded during a period of 6 months (November 2022-April 2023), averages, percentages were determined, the Statistical analysis was performed analysis of variance and chi square

Results: 55.9% men, Women 44.01%, most common etiologies DM2 43.71%, HTN 38.92%, others 17.37%. Patients with CRP ≥ 9 mg/L 40.11%, CRP <9 mg/L 59.88%. In the distribution of CRP <9 with prealbumin < 30, 87 patients were found, of these, 32% presented comorbidities, died 1%. CRP < 9 with prealbumin ≥ 30 occurred in 113 patients, 19% with comorbidities, 3 % deaths. CRP ≥ 9 and prealbumin < 30 evidence in 73 patients, 63% with comorbidities, 18 % deceased. CRP ≥ 9 and prealbumin ≥ 30 were evident in 61 patients, 30% with comorbidities, 2% deceased. A greater number of cases with comorbidities is evident in the group with CRP ≥ 9 mg/L and prealbumin <30 mg/dl with chi square 35.535 and statistical significance p= 0.0000, CI 95.0%; with a greater number of deaths in this group of patients chi square 28.258 and statistical significance p= 0.0000, CI 95.0%

Conclusions: CRP is present in the patients of our center in more than a 1/4 of the cases, are closely related to nutritional status, using prealbumin as indicator, the high incidence of morbidity and mortality in these patients is demonstrated, which imposes the need to establish early detection measures for these factors in order to carry out preventive and therapeutic management to improve the quality of life of patients and their clinical conditions.

PUB131

Serum Transferrin Levels Predict Hemodialysis (HD) Adequacy and Mortality in Patients on Maintenance Hemodialysis

Sonoo Mizuiri,[1] Yoshiko Nishizawa,[1] Toshiki Doi,[1,2] Aiko Okubo,[1,2] Kenichi Morii,[1,2] Kazuomi Yamashita,[1] Kenichiro Shigemoto,[1] Kazuyoshi Karasuda,[1] Takao Masaki.[2] *[1]Iryo Hojin Ichiyokai Harada Byoin, Hiroshima, Japan; [2]Hiroshima Daigaku Byoin, Hiroshima, Japan.*

Background: Tarantino et al. reported that transferrin levels can be used to evaluate 3 important factors (Kt/Vurea, geriatric nutritional index [GNRI], and C-reactive protein [CRP]) in 78 hemodialysis (HD) patients. We investigated if transferrin levels can predict HD adequacy and mortality.

Methods: Subjects were 454 HD patients. Clinical data including serum transferrin, transferrin saturation (TSAT), ferritin, Kt/Vurea, predialysis β2-microglobulin (β2MG), serum albumin, GNRI, CRP, Agatston coronary artery calcium score (CACS), and postdialysis body composition using bioelectrical impedance were assessed at baseline. The patients were followed up for 400 days.

Results: Age, the dialysis duration, and the prevalence of diabetes in all patients were 72±13 years, 66 (35–134) months, and 44.7%, respectively. Patients with transferrin levels ≥200 mg/dL (n=152) had a significantly lower age (69±13 vs. 73±13 years), TSAT (19 [13–27] vs. 24 [18–31] %), ferritin (73±78 vs. 170±145 ng/mL), CRP (0.11 [0.04–0.34] vs. 0.19 [0.06–0.63] mg/dL), β2MG (26.7 [22.9–31.3] vs. 28.1 [24.8–31.8] mg/L), and extracellular water/total body water, but higher serum albumin levels (3.7 [3.4–3.9] vs. 3.4 [3.1–3.7] g/dL), GNRI (93±7 vs. 88±9), and lean tissue index (12.2 [10.7–14.2] vs. 11.1 [9.7–13.0] kg/m^2) than patients with transferrin levels <200 mg/dL (n=302) (P <0.05). Sex, dialysis duration, prevalence of diabetes, Kt/Vurea, and CACS were not significantly different between the 2 groups. Multiple linear regression showed that serum albumin levels, CRP levels, and Kt/Vurea were significant determinants for transferrin levels (P <0.001). Kaplan–Meier analysis showed a better 1-year survival rate in patients with transferrin levels ≥200 mg/dL than patients with transferrin levels <200 mg/dL (P <0.01). After adjusting for age, sex, dialysis duration, diabetes, serum albumin and CRP, transferrin levels were a significant predictor for 1-year all-cause mortality in HD patients (hazard ratio: 0.99, P <0.05).

Conclusions: In patients on maintenance HD, measurement of serum transferrin levels can be used to evaluate Kt/Vurea, albumin, and CRP. Patients with transferrin levels ≥200 mg/dL had higher 1-year survival rate than patients with transferrin levels <200 mg/dL, despite the presence of iron deficiency.

Funding: Private Foundation Support

PUB132

Clinical Performance of the New Plasma Filter PX2 in Therapeutic Plasma Exchange

Jana Schmitt,[1] Christine Gillen,[2] Ansgar Erlenkoetter,[1] Lena Rauber,[1] Anja Derlet-Savoia,[1] Manuela Stauss-Grabo.[1] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care Adsorber Tec GmbH, Krems, Austria.*

Background: Therapeutic plasma exchange (TPE) belongs to field of therapeutic apheresis and therefore the recommendations of the American Society for Apheresis (ASFA) are applied. TPE is a method for extracorporeal blood treatment designed to remove high molecular weight substances, such as immunoglobulins and pro-inflammatory factors. TPE is indicated for diseases which are associated with increased concentrations of plasma components and where a rapid depletion of these molecules mitigates or stops a pathogenic process. The usual dose of TPE is equivalent to 1.0-1.5 times the plasma volume (PV), which corresponds to removal of 63–72% of the plasma constituents. Treatment dose, defined as the plasma volume to be exchanged to achieve the desired clinical outcome for various diseases, are determined by the ASFA Guidelines.

Methods: The study (NCT06382675) is an interventional, single arm study assessing the clinical performance and safety of the new plasma filter PX2 (Fresenius Medical Care, Bad Homburg, Germany), applied for extracorporeal blood purification during plasmapheresis therapy. In preclinical studies, the filter showed excellent hemocompatibility. 272 TPE treatments, performed according to the clinical practice, will be evaluated, by assessing e.g., the delivered treatment dose, sieving coefficients of plasma constituents, and the incidence of hemolysis, clotting or clogging of the filter. Blood and filtrate samples are drawn before, after every 0.5 PV treated and at the end of the treatment. The performance benchmark – defined as achieved absolute plasma separation volume in comparison to planned plasma separation volume – will be used to analyze if the new filter will be able to deliver the treatment dose and thus the expected clinical outcome.

Results: The study is designed to clinically evaluate the PX2 plasma filter regarding sieving coefficients and safety. In addition, the influence of patients factors on TPE treatment success (delivery of treatment dose) will be assessed through subgroups analysis. The results of the subgroup analysis will be presented as descriptive analysis.

Conclusions: The study aims to evaluate the clinical performance and safety of a newly developed plasma filter. Moreover, the study aims to broaden the knowledge about patient factors influencing the treatment success.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH

PUB133

Optimizing Intracranial Pressure Management in AKI: A Novel Approach Using Enhanced Sodium Concentration in Continuous Kidney Replacement Therapy

Zeinab A. Abdulrahman,[1] Harry J. Dounis,[1] Avais Masud,[1] Sion Kim,[2] Supreet Kaur,[1] Sushil Mehandru.[1] *[1]Jersey Shore University Medical Center, Neptune TWP, NJ; [2]St. Mary Medical Center, Langhorne, PA.*

Introduction: Hypertonic saline treats elevated intracranial pressure (ICP) and cerebral edema by causing osmotic dehydration, avoiding complications like acute kidney injury and pulmonary edema. Maintaining therapeutic hypernatremia in patients needing renal replacement therapy is challenging as dialysis dilutes serum sodium, reducing hypertonic saline efficacy.

Case Description: A 25-year-old male with a history of polysubstance abuse presented in cardiac arrest and was resuscitated after 25 minutes. The patient was comatose with no response to stimuli, non-reactive pupils, and absent corneal and oculocephalic reflexes. A CT scan showed diffuse cerebral edema with potential herniations. Laboratory results revealed acute kidney injury with serum sodium of 142 mmol/L, necessitating continuous venovenous hemodiafiltration (CVVHDF). For cerebral edema, 3% hypertonic saline was administered. To maintain a serum sodium of 150-155 mEq/L, dialysis bath solution adjustments were made. This involved infusing 10 ml of a 23.4% hypertonic saline solution into a 2.5-liter bag of dialysis solution. Each ml of the 23.4% solution contained 4 mEq of sodium, adding a total of 40 mEq to the bag. This resulted in 40 mEq sodium/2.5 liters = 16 mEq/L added to the 140 mEq/L in the dialysis solution, reaching 156 mEq/L. Adjustments maintained serum sodium between 146-153 mEq/L during hospitalization. Despite efforts, the patient's neurological status did not improve, leading to hospice care.

Discussion: This case highlights the complexity of managing patients with anoxic brain injury and cerebral edema undergoing dialysis. Conventional intermittent hemodialysis can exacerbate ICP; thus, CVVHDF is preferable due to its continuous nature and lesser impact on systemic and cerebral hemodynamics. Increasing dialysis bath sodium concentration can effectively maintain a desired hyperosmolar state. For patients with increased ICP undergoing renal replacement therapy, a dialysis bath sodium concentration of 150-160 mEq/L, achieved by augmenting standard solutions with hypertonic saline, is crucial for managing cerebral edema. This strategy stabilizes patients in critical care settings.

PUB134

Using Ecological Momentary Assessment to Redefine Postdialysis Fatigue

Cramer J. Kallem,[1] Maria-Eleni Roumelioti,[2] Jennifer L. Steel,[1] Sarah J. Erickson,[2] Alaa A. Alghwiri,[1] Jonathan G. Yabes,[1] Mark L. Unruh,[2] Manisha Jhamb.[1]
[1]University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]University of New Mexico School of Medicine, Albuquerque, NM.

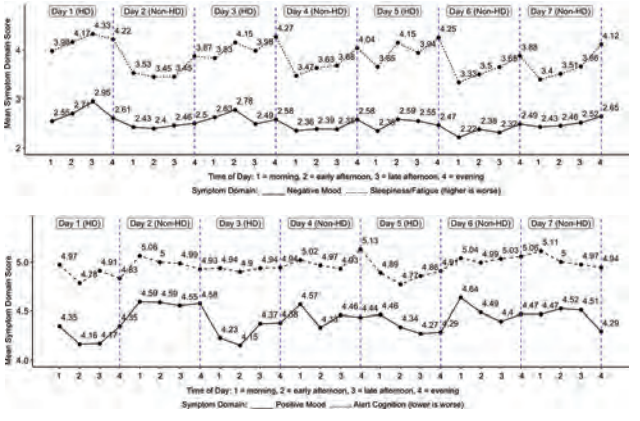
Background: Patients with ESKD have a high symptom burden and many report an acute exacerbation of symptoms immediately following hemodialysis (HD). While post-dialysis fatigue has been studied, very few studies have used ecological momentary assessment (EMA) to examine post-HD symptom experiences.

Methods: Participants in the Technology Assisted Collaborative Care (TACcare) trial completed an automated telephone-administered version of the Daytime Insomnia Symptom Scale (DISS) at 4 timepoints daily for 7 consecutive days. The DISS yields 4 symptom domain scores: Positive mood (PM), negative mood (NM), alert cognition (AC), and sleepiness/fatigue (SF). Post-HD symptom scores were compared to the corresponding timepoints on non-HD days via mixed models adjusting for age, race, sex, and Charlson Comorbidity Index. Demographic, psychosocial, and disease-specific characteristics were compared between patients who did versus did not show a post-HD increase of ≥1 point in the sum of SF and NM.

Results: 160 HD patients were enrolled [mean age=58±14 years, 55% men, 52% White]. In the post-HD period, patients reported significantly lower PM [mean difference (MD)= -0.22, 95% CI (-0.29, -0.14), p<0.001] and AC [MD= -0.13, 95% CI (-0.18, -0.08), p<0.001] and significantly higher NM [MD=0.12, 95% CI (0.05, 0.19), p<0.001] and SF [MD=0.51, 95% CI (0.42, 0.61), p<0.001] symptoms, compared to non-HD days. Patients who endorsed an increase in symptoms (NM or SF ≥1 point) in the post-HD period reported lower baseline fatigue (on FACIT-F) than those who did not (p=0.02); no other between-group differences were observed.

Conclusions: Patients with ESKD tend to experience worsening of both fatigue and mood symptoms after HD treatments. Our findings align with recent critiques that the post-dialysis fatigue label does not fully describe the post-HD symptom burden patients experience. Future studies should utilize EMA to assess a broader range of potential post-HD symptoms.

Funding: NIDDK Support



PUB135

Effect of Dialysis Dose on Nutritional Status of Patients on Hemodialysis

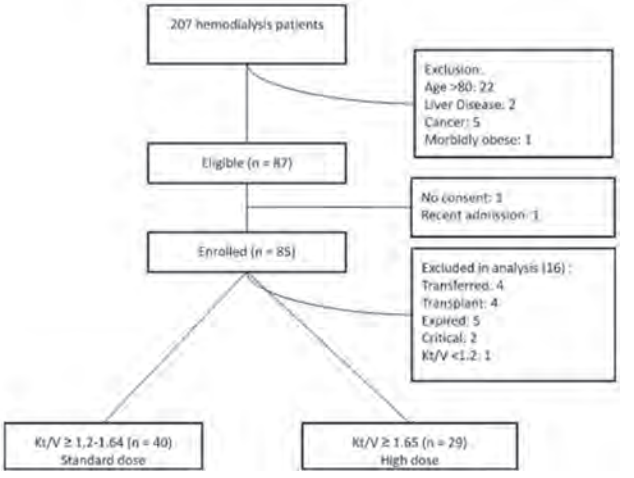
Kiara Marie H. Padua, Antonio V. Cayco, Mary Rose Bisquera. *Makati Medical Center, Makati City, Philippines.*

Background: Malnutrition is common among dialysis patients and impacts morbidity and mortality. Underdialysis causes malnutrition, but it is not known if high dialysis doses (Kt/V ≥1.65) lead to greater intradialytic nutrient loss, inflammation and protein catabolism. This study challenged the hypothesis that a higher dialysis dose increases the risk of malnutrition.

Methods: This is a pilot, single-center, prospective cohort. Aidamea online Kt/V was averaged for 6 months and compared with the change in dry weight, body mass index (BMI), mid-upper arm circumference (MUAC) for anthropometrics, modified SGA score, albumin, blood urea nitrogen (BUN), creatinine, and total lymphocyte count (TLC) as laboratory parameters.

Results: There is an inverse correlation between high Kt/V and anthropometric parameters and BUN. As Kt/V increases, it is more likely to have a BMI <18.5 (OR 2.6), SGA B (OR 1.19) and TLC <1500 (OR 1.07), and less likely to have albumin <3.4 (OR 0.25), though associations were not statistically significant.

Conclusions: The discordant results may be due to the high sieving coefficient for albumin, adequate protein repletion, and use of a single-use dialyzer in the center. A longer observation period may be needed. Thus, it is essential to individualize the approach when interpreting each parameter.



Patient Flow Diagram

Parameters	Correlation coefficient	P-value
Dry weight	-0.5615	**<0.001**
BMI	-0.3598	**0.002**
MUAC	-0.3339	**0.005**
End SGA score	0.1046	0.393
Albumin	0.0663	0.588
Crea	-0.0945	0.440
BUN	-0.2695	**0.025**
TLC	-0.0821	0.502

Correlation of HD doses to Nutritional Parameters

PUB136

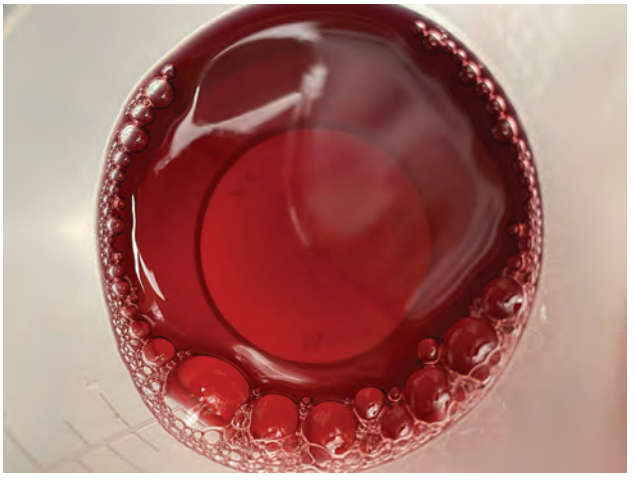
Vitamin B12 as an Obstacle to Hemodialysis in the Intensive Care Unit (ICU)

Varsha Suresh, Sungsoo Kim, Phoenix Xu, Noor Shahin, Michael Chang, Martin Sedlacek. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Normally total body stores of vitamin B12 are between 1 and 5mg. Log scales higher 5-10g amounts of hydroxocobalamin are used as antidote for cyanide, forming cyanocobalamine in equimolar proportion. Because of a catecholamine independent hypertensive effect such high doses are also used in vasoplegic shock, similar to methylene blue. Dialysis clearance of vitamin B12 has been used to estimate middle molecule clearance. Here we present a case where a 5g dose of hydroxocobalamine impeded hemodialysis by triggering blood leak alarms.

Case Description: A 91 year old woman with metastatic breast cancer underwent surgery for a pathologic facture of her left femor. Her postoperative course was complicated by vasoplegic shock with AKI which was treated with three vasopressors and hydroxocobalamine. A drop in Hb and red colored urine (picture) raised concern for hemolysis but haptoglobin was normal and the urine sediment showed only rare RBC and calcium oxalate crystals. The patient developed oligoanuria and a family decision was made for a trial of dialysis support. However, the patient could not be dialyzed because of intractable blood leak alarms, despite several dialyzer sets used and the dialysate consistently testing negative for heme. The patient then was started on CVVH which was well tolerated. Red effluent was noted. The patient did not recover and passed away.

Discussion: Very high doses of hydroxocobalamine cause urine to be colored red for weeks. Hydroxocobalamine is cleared by dialysis but interferes with the blood leak alarm on hemodialysis machines, effectively rendering hemodialysis impossible. As in our patient, CVVH is not impeded but red effluent is usually noted. This side effect is important to consider if hemodialysis is needed for the treatment of toxic alcohol ingestion or drug toxicity. As there was no autopsy we do not know if the patient had oxalate nephropathy, a reported side effect of hydroxocobalamine with unclear pathophysiology.



PUB137

Intradialytic Heartbeat Irregularities (IR) Predict Increased Mortality in Patients on Chronic Hemodialysis (HD)

Dan Sapoznikov, Michal Dranitzki Elhalel, Rebecca Backenroth, Dvora Rubinger. *Hadassah University Medical Center, Jerusalem, Israel.*

Background: The pressent study was undertaken to define the significance of asymptomatic IR during HD.

Methods: Beat to beat systolic blood pressure (SBP) and interbeat interval (IBI) were monitored duriing HD in 96 age-matched HD patients (Pt). IR were defined as ≥5 irregular beats over 10 min during HD. Hemodynamic variability indices were assessed using Finometer device and beatscope software.

Results: IR were detected im 29 Pt (IR(+)). The representative clinical data in IR (+) and in Pt with regular beats (IR (-) n=67) are listed in Table 1. There were no marked differences between groups regarding the proportion of diabetes (DM), hypertension, ischemic heart disease, history of previous arrhrythmia. biochemical measurements or anthypertensive medication. Kaplan Meier showed a significant decreased survival at 2 to 5, but not at 7 years (y) or later in IR (+) (Figure 1).

Conclusions: Intradialytic IR were more frequent in Pt with a background of smoking and LV systolic dysfunction. In these Pt, decreased SBP at the end of HD and increased variabilities of CO and TPR might have contributed to hemodynamic instability. IR were associated with significntly enhanced mortality in HD.

Table 1.

	IR (-) (n=67, age 66±9 y)	IR (+) (n=29, age 65±12 y)	p
Males/Females	41/26	25/4	0.015
DM (n/%)	34/51	9/31	NS
Hypertension (n/%)	65/97	27/93	NS
Ischemic heart disease (n/%)	53/79	19/66	NS
Smokers (n/%)	26/39	19/66	0.025
LV systolic dysfunction (n/%)	18/28	13/52	0.031
Δ SBP (mmHg)* #	1±27	-13±20	0.012
IBI (msec) **	887 (249)	834 (102)*	0.033
sdCO (l/min)*^	0.46 (0.21)	0.60 (0.16)^	0.001
sdTPR (mmHG.s/ ml)**	0.08 (0.06)	0.11 (0.11)*	0.040

*mean ± SD ; # post dialysis SBP change; **Median (interquartile range); sd: standard deviation; CO: cardiac output; TPR:: total peripheral resistance; ^ determined in 16 IR (+).

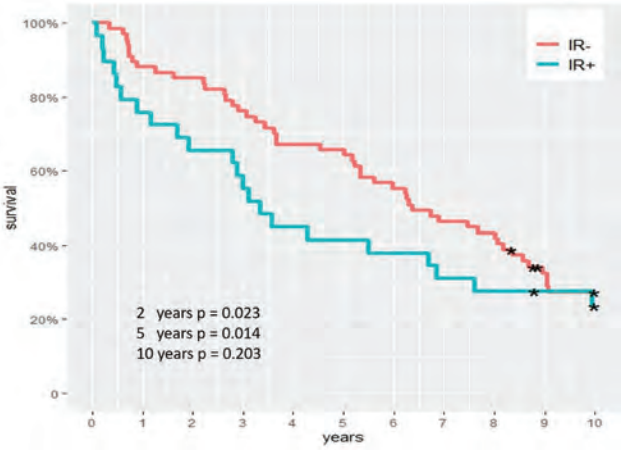


Figure 1.

PUB138

Predictors of Intradialytic Hypotension in Critically Ill Patients Undergoing Kidney Replacement Therapy: A Systematic Review

Rafaella Maria da Cunha Lyrio,[1] Tess M. Calcagno,[5] Estevão F. Sampaio,[3] Rafael Hennemann Sassi,[2] Rogerio Passos.[4] *[1]Universidade Salvador, Salvador, Brazil; [2]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [3]Hospital Geral Ernesto Simões Filho, Salvador, Brazil; [4]Sociedade Beneficente Israelita Brasileira Albert Einstein, São Paulo, Brazil; [5]Cleveland Clinic, Cleveland, OH.*

Background: This systematic review aims to identify predictors of intradialytic hypotension (IDH) in critically ill patients undergoing renal replacement therapy (RRT) for acute kidney injury (AKI).

Methods: A comprehensive search of PubMed was conducted from 2002 to April 2024. Inclusion criteria comprised studies involving critically ill adults undergoing RRT for AKI. Exclusion criteria included pediatric patients, non-critically ill individuals, those with chronic kidney disease, and those not undergoing RRT. The primary outcome was identifying predictive tools for hypotensive episodes during RRT sessions.

Results: The review analyzed data from 8 studies involving 2,873 patients. Various machine learning models were assessed for their predictive accuracy. The Extreme Gradient Boosting Machine (XGB) model emerged as the top performer, achieving an area under the receiver operating characteristic curve (AUROC) value of 0.828 (95% CI: 0.796–0.861). It was closely followed by the deep neural network (DNN) with an AUROC of 0.822 (95% CI: 0.789–0.856). Notably, all AUROC values from machine learning models surpassed those of other predictors. The SOCRATE score, incorporating cardiovascular SOFA score, index capillary refill, and lactate level, showed increasing IDH incidence rates with the number of parameters, yielding an AUROC of 0.79 (95% CI: 0.69–0.89, $P < 0.0001$), indicating robust predictive accuracy. Peripheral perfusion index (PPI) and heart rate variability (HRV) exhibited AUROCs of 0.721 (95% CI: 0.547–0.857) and 0.761 (95% CI: 0.59–0.887), respectively. Additionally, pulmonary vascular permeability index (PVPI) and mechanical ventilation displayed significant diagnostic performance, with an area under the curve (AUC) of 0.68 (95% CI: 0.53–0.83) and 0.69 (95% CI: 0.54–0.85), respectively. A PVPI ≥ 1.6 at the onset of intermittent hemodialysis (IHD) sessions predicted IDH associated with preload dependence with a sensitivity of 91% (95% CI: 59–100%) and specificity of 53% (95% CI: 42–63%).

Conclusions: Machine learning models and clinical parameters offer promise in predicting IDH in critically ill AKI patients undergoing RRT. Further research is needed to manage hypotensive episodes effectively and improve patient outcomes.

PUB139

Association of Monocyte-Lymphocyte Ratio with Cardiovascular Events and All-Cause Mortality in Patients with ESKD

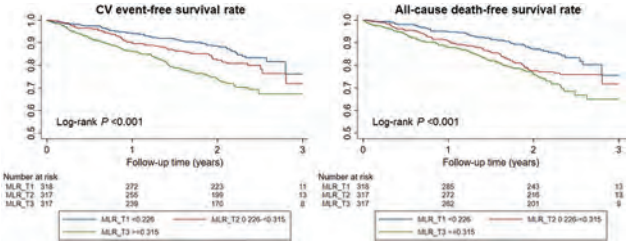
Ahmed Kabeil,[1] Cameron J. Bergeron,[1] Yamini Mallisetty,[1] Zhongji Han,[1] Chi-Yang Chiu,[1] Csaba P. Kovesdy,[1,2] Keiichi Sumida.[1] *[1]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [2]VA Memphis Medical Center, Memphis, TN.*

Background: Monocyte to lymphocyte ratio (MLR) represents a pro-inflammatory immune microenvironment and has been associated with adverse clinical outcomes, including cardiovascular disease (CVD). However, little is known about its association with clinical outcomes in patients with end-stage kidney disease (ESKD).

Methods: In a nationwide prospective cohort of 952 patients receiving maintenance hemodialysis from 2011-2013, we examined the association of baseline MLR with subsequent risk of CV events (CV-related hospitalization and CV death) and all-cause mortality, using the Kaplan-Meier method and Cox proportional hazards models with adjustment for age, sex, dialysis vintage, vascular access type, BMI, systolic blood pressure, Charlson Comorbidity Index, ischemic heart disease, diabetes mellitus, serum albumin, hemoglobin, infectious hospitalization, culture-positive bacteremia, and antibiotic or antifungal use. MLR was categorized into tertiles (<0.226, 0.226-<0.315, and ≥0.315).

Results: Overall, patients were 60±13 years old; 53% were male; 40% were African American; and 57% were diabetic. The mean dialysis vintage was 4.3±3.8 years. During a median follow-up of 2.2 years, 184 and 207 cases experienced CV events and death, respectively. The rates of CV events and all-cause death were higher in those with higher MLR (log-rank *P* <0.001, Figure). The adjusted hazard ratios (HRs) [95% CI] of CV events and all-cause mortality for the highest (vs. lowest) tertile was 1.88 [1.29-2.74] and 1.47 [1.02-2.11], respectively. Similar associations were seen when MLR was treated as a continuous variable (1.18 [1.06-1.31] and 1.19 [1.07-1.31], per 0.1 higher MLR, respectively).

Conclusions: A higher MLR was independently associated with higher risk of CV events and all-cause mortality in patients with ESKD, suggesting the potential of MLR as a simple, cost-effective prognostic biomarker in ESKD.



PUB140

Accuracy of Inferior Vena Cava (IVC) and Lung Point-of-Care Ultrasonography (POCUS) as an Adjunct in the Evaluation of Hypervolemia among Patients on Maintenance Hemodialysis

Denise C. De Los Reyes, Annabelle S. Lim, Vonn Velasco. *Saint Luke's Medical Center, Quezon City, Philippines.*

Background: Fluid overload is a burdensome problem among maintenance hemodialysis patients that is associated with morbidity and mortality.[1] There is no gold standard to predict or estimate dry weight.[2] It is traditionally determined clinically but can be complex, varied, and confounded by several factors. Incorporating a simple, quick, and more objective method using point-of-care ultrasound (POCUS) gives a more accurate evaluation of fluid volume status.[3]

Methods: This is an observational, cross-sectional study involving 45 examinations among 29 adults on maintenance hemodialysis. A primary investigator performed IVC and lung POCUS before and after dialysis using a handheld ultrasound device. Results were recorded and validated by a nephrologist trained in POCUS. Another fellow who is blinded to the POCUS findings performed the clinical volume status assessment.

Results: Using the cut-off scores for lung B-lines, IVC diameter, and IVC-CI examinations, there were 37.78%, 33.33%, and 68.89%, respectively, which had hypervolemia at pre-dialysis, and 24.44%, 15.56%, and 71.11%, respectively which had hypervolemia at post-dialysis. The sensitivity of lung B-lines, IVC diameter, and IVC-CI were 61.5%, 53.8%, and 61.5%, respectively, and specificity of 65.6%, 75%, and 28.1%, respectively. The AUC-ROC of all three parameters, 0.636, 0.644, and 0.448, did not reach AUC > 0.7. Post-hemodialysis, there were 27.27% by lung B-lines, 15.91% by IVC diameter, and 70.45% by IVC collapsibility index who already had negative hypervolemia by clinical assessment. This finding is consistent with the fact that physical examination (crackles and peripheral edema) is helpful when signs of congestion are present, but their absence does not exclude congestion. The interrater reliability and agreement of lung and IVC POCUS were also similar to that of the nephrology fellow and the nephrologist trained in POCUS.

Conclusions: This study cannot strongly conclude IVC and lung POCUS as a single method to accurately identify hypervolemia among adult hemodialysis patients but the real-time changes can help assess a patient's physiologic response to fluid volume changes. Integrating insonation into clinical assessment can be used as an adjunct in objectively estimating fluid status and guiding clinicians in their day-to-day practice.

PUB141

Can Post-Dilution Online Hemodiafiltration Provide a Valid Means of Preserving the Global Environment?

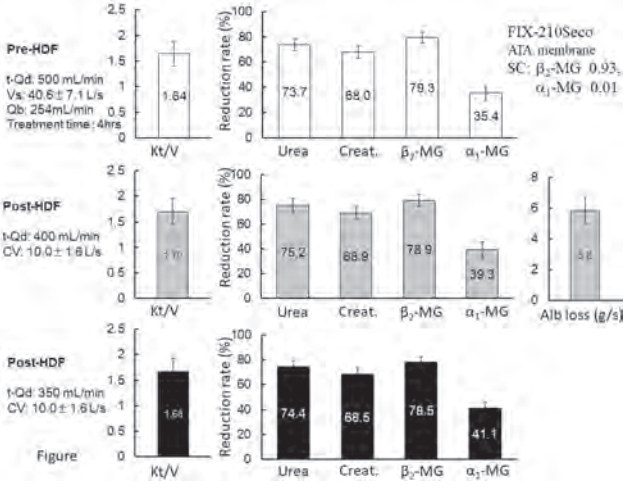
Kenji Sakurai,[1] Yoshitaka Kurihara,[1] Hiromi Hosoya,[1] Fumi Yamauchi,[1] Takeshi Saito,[1] Daisuke Ishii,[3] Toru Hyodo,[2] Kenichi Kokubo.[4] *[1]Hashimoto Clinic, Sagamihara, Japan; [2]Fureai Clinic IZUMI, Yokohama, Kanagawa, Japan; [3]Dept. of Urology Kitasato Univ. Hospital, Sagamihara, Japan; [4]Kitasato Univ. School of Allied Health Sciences, Sagamihara, Japan.*

Background: There are numerous open issues with dialysis therapy related to reducing climate change and preserving the global environment that need to be urgently addressed. Hemodiafiltration (HDF) has become common due to its excellent removal performance. In Japan, in-end 2022, 55.1% of dialysis patients underwent HDF, and 69% were receiving pre-dilution on-line HDF (pre-HDF). Reducing dialysate usage is a readily applicable method of preserving water resources and reducing the burden of waste fluid disposal. We switched from pre-HDF to post-HDF with high-flux hemodiafilter, which allowed the total dialysate flow rate (t-Qd) to be reduced by 20% and 30%, and evaluated the removal efficiency of each mode.

Methods: A study involved 14 patients who received pre-HDF (t-Qd 500 mL/min) using FIX-210Seco (Nipro) at our institution. While keeping the Qb and dialysis time unchanged, we performed post-HDF with t-Qd of 400 mL/min and evaluated the removal efficiency. The substitution fluid volume (Vs) was then adjusted to avoid excessive albumin loss so that an optimal convection volume (CV) (the sum of Vs and the net ultrafiltration volume) could be set for each patient. Next, the effect of this method in reducing the volume of dialysate and raw water required was evaluated using the volume data after the settings had been modified. Finally, the removal efficiency at this CV was evaluated again with t-Qd of 350 mL/min.

Results: The removal efficiency results obtained for each mode are shown in Figure. Even during the first month after modification of the settings, the dialysiate amount and the raw water volume required could be reduced by 4368L and 6720L, respectively.

Conclusions: Post-HDF using high-flux hemodiafilter at lower t-Qd exhibited favorable solute-removal efficiency. This type of post-HDF should be more widely used as a means of reducing climate change and preserving the global environment.



Figure

PUB142

Mortality Trends of Patients with Systemic Lupus Erythematosus on Dialysis in the Japanese Society for Dialysis Therapy (JSDT) Registry: Web-Based Analysis of Dialysis Data Archives (WADDA) System

Nanako Oshiro,[1] Kentaro Kohagura,[1] Kenya Kusunose,[2] Kunitoshi Iseki.[3] *[1]Dialysis Unit, University of the Ryukyus Hospital, Nishihara-cho, Japan; [2]Department of Cardiovascular Medicine, Nephrology and Neurology, Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Japan; [3]Nakamura Clinic, Urasoe-city, Japan.*

Background: There are few reports about the gender-specific prognosis of the dialysis patients with systemic lupus erythematosus (SLE), particularly in recent years since 2015 when treatment with multitarget regimen for lupus nephritis became widely practiced in Japan. We examined the prognosis of SLE on dialysis by gender.

Methods: We used the JSDT annual data of dialysis patients from 2017 to 2022 obtained from the WADDA system. Relative risks (RRs) with 95% confidence intervals (CIs) were obtained from 2017 to 2022 in reference to non-SLE dialysis patients. We examined those with age less than 60 years.

Results: The average of annual number of patients was total 20,087/SLE 437 (female) and total 50,927/SLE 152 (male). The crude mortality rate of all dialysis patients was around 2.5%, and for females, it was around 2.3%, both remaining relatively stable. On the other hand, among patients with SLE, the crude mortality rate of both the overall patient population and females has increased year by year. In female patients with SLE, there was no significant increase in all-cause mortality from 2017 to 2019; 2017 (RR: 1.14, 95% CI: 0.66-1.97, p=0.6188), 2018 (RR: 1.26, 95% CI: 0.73-2.18, p=0.3923), and 2019 (RR:1.51, 95% CI: 0.92-2.47, p=0.0950), respectively. However, continuously since 2020 to 2022: 2020 (RR: 1.76, 95% CI: 1.11-2.80, p=0.0151), 2021(RR 1.91, 95% CI:1.22-3.00, p=0.0042), and 2022 (RR 2.50, 95% CI: 1.69-3.70, p<0.001). In male patients, there was no consistent changes observed: 2017 (RR 0.69, 95% CI: 0.22-2.12, p=0.5183), 2018 (RR 2.21, 95% CI:1.21-4.04, p=0.0091), 2019 (RR 0.73, 95%CI: 0.23-2.24, p=0.5801), 2020 (RR 2.59, 95% CI :1.46-4.60, p=0.0009), 2021 (RR 0.67, 95% CI: 0.21-2.05, p=0.4794). and 2022 (RR 2.15, 95% CI: 1.18-3.93, P=0.0118).

Conclusions: This study revealed an increased risk of all-cause mortality among female dialysis patients with SLE under 60 years old since 2020.

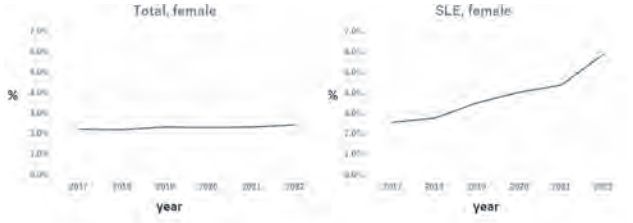


Figure1. The crude mortality among all female dialysis patients under 60, and among dialysis patients under 60 with SLE. SLE=systemic lupus erythematosus.

PUB143

Impact of Hemodialysis Center Accreditation on Patient Mortality: Korean Nationwide Cohort Study

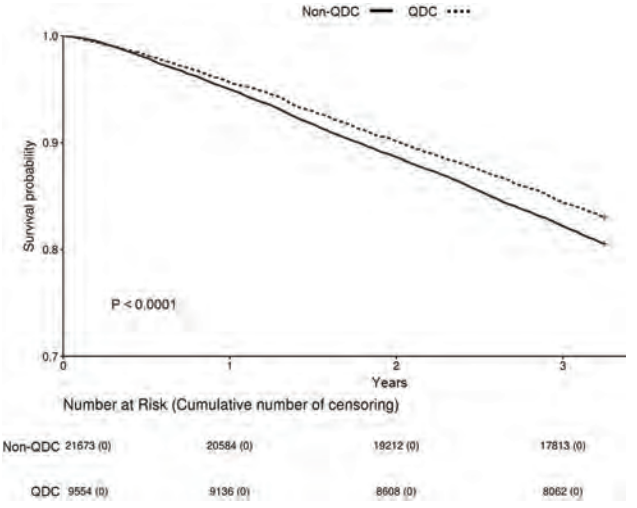
Hayne C. Park, Do Hyoung Kim, Ajin Cho, Young-Ki Lee. *Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea.*

Background: Since hemodialysis (HD) patients are prone to various complications and high mortality, they need to be treated in HD units with professional personnel, proper equipment, and facilities. The Korean Society of Nephrology has been conducting HD unit accreditation program since 2016. This study was performed to evaluate whether qualified dialysis center (QDC) reduced mortality of HD patients.

Methods: This longitudinal, observational cohort study included 31,227 HD from 832 facilities. HD units were classified into two groups: the hospitals that have been certified as QDC between 2016 and 2018 (n = 219) and hospitals that have never been certified as QDC (non-QDC, n = 613). Baseline characteristics and patient mortality were compared between QDC vs. non-QDC groups using Korean HD quality assessment data from 2018. Multivariate logistic regression and Cox proportional hazards model was used to compare patient mortality between two groups.

Results: Among study subjects, 30.6% of patients were treated at QDC and 69.4% were treated at non-QDC. The patients in the QDC were younger, had a longer dialysis duration, lower serum phosphorus and calcium levels, and higher hemoglobin and single-pool Kt/V levels compared to the patients from non-QDC group. After adjusting for demographic and clinical parameters, QCD independently reduced mortality risk (hazard ratio, 0.897; 95% confidence interval, 0.847–0.950; $P < 0.001$).

Conclusions: HD unit accreditation program may reduce the risk of death among patients undergoing HD.



A total of 5848 deaths occurred during 35.6 ± 8.5 months. After censoring 3515 (10.1%) cases who received kidney transplantation during follow-up, QDC group showed better survival compared to non-QDC group ($P < 0.001$). Abbreviations: QDC, qualified dialysis center.

PUB144

Fatigue Has the Highest Diurnal Symptom Variability in Patients on Dialysis

Elife Ozturk,[1] Aidan W. Smith,[1] Jessica Noelmans,[1] Martijn A. Spruit,[2] Jeroen Kooman,[1] Marc H. Hemmelder.[1] *[1]Maastricht Universitair Medisch Centrum+, Maastricht, Netherlands; [2]Ciro-Horn, Horn, Netherlands.*

Background: Patients treated with dialysis (hemodialysis (HD) and peritoneal dialysis (PD) have a high burden of disease. The amount of and the burden of symptoms experienced by dialysis patients is often underestimated. Limited data are available regarding the diurnal variability of symptoms. We therefore analyzed the diurnal variability of symptoms in HD and PD patients.

Methods: This prospective study was performed as a single center study. Patients completed baseline questionnaires on quality of life (SF-12), symptom burden (DSI), anxiety and depression (HADS), general level of daytime sleepiness and patient activation measurement(self-efficacy). After installing of a mobile application (Your Research®) on the patients' smartphone, patients received 8 times a day during 7 consecutive days a questionnaire on symptom burden. Symptoms were scored on a scale from 1 (no symptoms) to 7 (most severe intensity). The diurnal variability of 4 frequently occurring symptoms (fatigue, anxiety, muscle soreness and headache) was assessed with the with-in subject standard deviation (WS-SD). In case of HD, WS-SDw was also calculated on HD days and non-HD days.

Results: 25 dialysis patients were included (15 HD and 10 PD). Ten patients answered <50% of the questionnaires by mobile app and were excluded from the analyses. The remaining 15 patients (53% male, age 59 years) had an overall median symptom score of 4 for fatigue and 1 for anxiety, muscle soreness and headache. Median fatigue scores were not different between HD days versus non-HD days or between both dialysis modalities. Median WS-SD for fatigue was 1,01 (IQR 0,34). Median WS-SD was 0 for anxiety (IQR 0,44), 0,44 for muscle soreness (IQR:0,83) and 0,32 for headache (IQR: 0,50).

Conclusions: Fatigue is clearly the most intense symptom for HD and PD patients compared to anxiety, muscle soreness and headache. Fatigue does not exacerbate on HD versus non-HD days in HD patients. The expected symptom variability within and between days seems lower than expected. This may suggest that a simple spot check of symptom burden may sufficient to understand the symptoms throughout the day.

PUB145

Early Monitoring of Arrhythmias in Patients on Hemodialysis with Wearable Devices: A Multicenter, Cross-Sectional Observational Study

Yu Shaobin, Zeng Xiaoxi. *West China Hospital of Sichuan University, Chengdu, China.*

Background: To further test the applicability of wearable devices for arrhythmia monitoring and early warning in HD patients

Methods: This study was a multicenter cross-sectional investigation involving five tertiary general hospitals from March 2022 to December 2023. This portion of the study mainly involved validating the reliability and feasibility of the use of wearable devices with long-term ECG monitoring capabilities (Lepu ER1 single-lead ambulatory ECG recorders and ECG chest belts) for the real-time dynamic detection of arrhythmia and heart rate variability, with ambulatory ECG recorders (CT-086S) that are used in clinical practice taken as the gold standard.

Results: A total of 538 maintenance HD patients from 5 tertiary general hospitals, were included in the study. 1. Reliability assessment: In the feasibility analysis of monitoring arrhythmia, a total of 185 patients with HD were included in the study. This study revealed that the heart rate variability metric measured by the Lpepu ER1 was positively correlated with others measured by ct-086S. 1.3 The sensitivity, specificity, and accuracy of diagnosing atrial fibrillation in HD patients were 88.9%, 93.8%, and 93.5%, respectively. The positive predictive value was 42.1%, and the negative predictive value was 99.4%. 2. Feasibility Assessment: A total of 353 HD patients from 4 medical centers wore Lepu ER1 single-lead dynamic electrocardiogram recorders. 72.5% of HD patients were monitored by Lepu ER1 single-lead dynamic electrocardiographic recorder with arrhythmia during dialysis. It is worth noting that among the 47 patients with clinical symptoms, 91.5% of them were also monitored by wearable devices for the occurrence of arrhythmia, and only 8.5% of patients were not monitored for arrhythmia when clinical symptoms appeared. However, among patients without clinical symptoms, 69.6% were still monitored with arrhythmia. There was a statistically significant difference in the correlation between the occurrence of clinical symptoms and arrhythmia monitored by wearable devices in the two groups.

Conclusions: Wearable devices equipped have the ability to continuously and dynamically monitor arrhythmias in patients with heart disease, particularly for the detection of atrial fibrillation. Heart rate variability parameters show a positive correlation with dynamic electrocardiogram assessments.

Funding: Government Support - Non-U.S.

PUB146

Post-dilution High-Volume Online-Hemodiafiltration Versus High-Flux Hemodialysis Mortality Outcome in Patients with End-Stage Kidney Disease

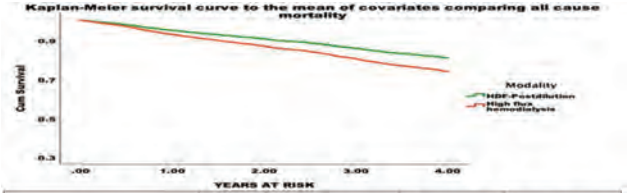
Alkhateeb K. Alkemary,[1,2] Ayman S. Fadlallah,[1] Imed Helal,[1] Mohammed A. Alhomrany,[1] Saeed Al-Ghamdi,[1] Dujanah H. Mousa,[1] Ali Alharbi.[1]
[1]Diaverum Holding AB branch, Riyadh, Saudi Arabia; [2]Cairo University Kasr Alainy Faculty of Medicine, Cairo, Egypt.

Background: Several studies showed improved survival with high volume online hemodiafiltration (OL-HDF) over high-flux hemodialysis (HF-HD), but still with some limitations.

Methods: A retrospective multicentre cohort study with the main predictor high-volume post-dilution OL-HDF with convective volume ≥ 22 Litres/ session versus HF-HD. The primary endpoint was all-cause mortality during the 48-month follow-up period. 8006 patients were screened; 480 (6%) were excluded due to a change of dialysis modality, 790 (9.8%) were excluded for not being capable of achieving convective volume ≥ 22 Litres/ session, 6736 patients were analysed; 2324 (34.5%) were on high-volume OL-HDF & 4412 (65.5%) were on HF-HD.

Results: Online HDF group included significantly younger patients than HF-HD group with the age (mean±SD) (57.7±16.9) & (51.9±15.1) years, respectively, (p-value <0.001). And a significantly lower proportion of diabetic patients in the OL-HDF group (41.3%) than in the HF-HD group (52.4%), (p-value <0.001), with a significantly lower proportion of patients with a high Charlson comorbidity index > 6, (29.5%) versus (47.1%). And a significantly higher proportion of patients with arteriovenous fistula (95.7%) versus (71.1%). Patients on OL-HDF showed significantly lower overall mortality in comparison to HF-HD n(%) 304(13%) & 842(19.1%) respectively, (p-value <0.001), with a lower cardiovascular and cerebrovascular mortality rate of 171 (7.4%) & 484(11%) (p-value <0.001), and lower infection-related mortality 92(4%) & 268(6.1%) (p-value <0.001). Multivariate Cox-regression analysis showed survival advantage of OL-HDF versus HF-HD (HR, 0.72: 95% CI [0.63-0.83]) (p-value <0.001).

Conclusions: Patients with kidney failure who received high-volume OL-HDF had a lower risk of all cause mortality, cardiovascular mortality, and infection-related mortality than those who received HF-HD.



	patient at risk	All cause mortality events n(%)	Cardiovascular mortality events n(%)	Infection related mortality events n(%)
on-line High Volume postdilution HDF	2324	304(13%)	171(7.4%)	92(4%)
High Flux HD	4412	842(19.1%)	484(11%)	268(6.1%)
Adjusted HR HDF versus HD HR(95CI) P-VALUE		0.72(0.63-0.83)	0.69(0.57-.083)	0.71(0.55-0.92)
		P-VALUE < 0.001	P-VALUE < 0.001	P-VALUE < 0.001

HR adjusted to mean of significant covariates in the model (age-gender-comorbidity index-body mass index -diabetes-dialysis vintage - vascular access

Caplan-Meier Survival Curve

PUB147

Detrimental Effects of Diet Selection in Hospitalized Patients with ESKD

Hanna Larson,[1] Drishti Jain,[2] Karen A. Griffin,[1] Kavitha Vellanki.[1] *[1]Loyola University Medical Center, Maywood, IL; [2]Loyola University Chicago Stritch School of Medicine, Maywood, IL.*

Background: End-Stage Renal Disease (ESRD) patients are at increased risk of emergent dialysis and mortality with hyperkalemia (K ≥5.5 mmol/l). There is limited data on outcomes from prescribed diets for hospitalized ESRD patients. Our study aims to evaluate outcomes of medically prescribed diets in hospitalized ESRD patients on maintenance hemodialysis.

Methods: Our study is a single-institution retrospective cohort study (1/2020-12/2023). Exclusion criteria comprised patients with critical illness requiring ICU care, rhabdomyolysis, hyperkalemia or NPO on admission, and receiving bone marrow/ stem cell transplant or chemotherapy (associated with cell lysis/K release). Cohort patients were defined by diet prescribed on admission: renal or non-renal diets. Primary outcomes included arrhythmias and additional dialysis for hyperkalemia. Secondary outcomes included additional medications or labs to manage hyperkalemia, and 30-day readmissions.

Results: The 195 study patients had 842 admissions. After applying exclusion criteria, 489 admissions were analyzed. Primary and secondary outcomes are outlined in Table 1. On admission, non-renal diets were prescribed more frequently (Table 1). Hyperkalemia occurred less on renal diets, as did episodes of additional dialysis, and the need for extra medications and labs to manage hyperkalemia. Readmissions within 30 days were less if on a renal diet (Table 1).

Conclusions: Preliminary analysis reveals more interventions occur to manage hyperkalemia in hospitalized ESRD patients prescribed a non-renal diet and readmissions are more frequent. Further studies are needed to understand the risks and outcomes of diet prescription practices in hospitalized ESRD patients to determine steps to improve outcomes.

Table 1: Demographics, Incidences and Outcomes of Hyperkalemia (K+ ≥ 5.5 mmol/L)

Cohort: Hospitalizations meeting inclusion criteria	N=195 N=489		
Age (yrs)	63.24 (± 15.0)		
Race			
White	27.7% (N=54)		
Black	41.5% (N=81)		
American Indian	0.5% (N=1)		
Asian	2.6% (N=5)		
Pacific Islander	0.5% (N=1)		
Other	26.7% (N=52)		
Preference not indicated	0.5% (N=1)		
Sex			
Male	56.9% (N=111)		
Female	43.1% (N=84)		
	Renal Diet Cohort (N=201)	**Non-Renal Diet Cohort (N=288)**	**P-value (<0.05)**
Avg. Length of Hospitalization (days)	6.2 (±6.8)	6.2 (±6.3)	0.80
Potassium min (mmol/L)	3.8 (± 0.6)	3.8 (±0.5)	0.47
Potassium max (mmol/L)	4.8 (± 0.7)	4.8 (±0.7)	0.52
Hospitalizations with ≥1 incidence of hyperkalemia	29 (14.4%)	45 (15.6%)	0.71
Number of hyperkalemia incidences per hospitalization (avg.)	1.8 (± 1.3)	1.5 (±0.9)	0.25
Diet order changed to renal diet after hyperkalemic event	0 (0.0%)	18 (40.0%)	<0.05*
Primary Outcomes of Hyperkalemia			
Cardiac Arrythmias	0% (N=0)	2.2% (N=1)	0.42
Additional Dialysis Session	24% (N=7)	38% (N=17)	0.22
Secondary Outcomes of Hyperkalemia			
Additional Medications	37.9% (N=11)	44.4% (N=20)	0.58
1. Insulin	63.5% (N=7)	65.0% (N=13)	0.94
2. Bicarbonate	9.1% (N=1)	0.0% (N=0)	0.17
3. Diuretic	12.2% (N=2)	15.0% (N=3)	0.82
4. Calcium	72.7% (N=8)	30.0% (N=6)	<0.05*
5. Cation-exchange resin	45.5% (N=5)	60.0% (N=12)	0.44
Additional Laboratory Work	41.4% (N=12)	35.5% (N=16)	0.61
1. BMP	83.3% (N=10)	100% (N=16)	0.09
2. Other	18.2% (N=2)	6.3% (N=1)	0.38
Readmission within 30 days	6.9% (N=2)	20% (N=9)	0.12

PUB148

Quality of Life in Patients on Hemodialysis vs. Peritoneal Dialysis

Amgad E. El Agroudy. *Arabian Gulf University, Manama, Bahrain.*

Background: Chronic diseases, including chronic kidney disease, affect patients' quality of life. Hemodialysis and peritoneal dialysis are renal replacement methods in these patients. This work aimed to study the relationship between Quality of Life (QOL) scores in patients with end-stage renal disease (ESRD) on hemodialysis and peritoneal dialysis.

Methods: This study was done at one center in Bahrain from May to July 2023. A standard QOL Index score instrument in Arabic form was used on 76 hemodialysis (HD) and 38 peritoneal dialysis (PD) patients. The inclusion criteria included dialysis for at least 3 months and an age of more than 18 years with no severe morbidities or psychological diseases.

Results: The mean age of HD and PD patients was 58.7 ± 11.2 and 55.9 ± 12.1 years, respectively. Thirty-five (46.1%) of HD patients and seventeen (44.7%) of PD patients were females. In most dimensions, the QOL score of patients treated with PD was better than that of the HD group. The number of hospital admissions was statistically significantly higher in the HD group (p = 0.007); however, there was no significant difference in the causes of admissions (p = 0.131). In this study, we observed the highest QOL score in the family subscale (93.2 ± 9.2 and 98.6 ± 4.7), followed by the psychological/spiritual subscale (81.1 ± 16.7 and 97.6 ± 3.9) in HD and PD groups, respectively), but it was statistically significantly higher in the PD group (p <0.001).

Conclusions: Our findings show that patients starting PD had better QOL scores in all domains than patients starting HD. Moreover, patients on PD maintained more active social support and ultimately felt better emotional well-being and physical health than those undergoing HD.

PUB149

Effects of Repetitive Transcranial Magnetic Stimulation on Cognitive Function and Intestinal Flora in Patients on Maintenance Hemodialysis

Hua Liu. *The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: To investigate the effects of repetitive transcranial magnetic stimulation (rTMS) on cognitive function and intestinal microflora in maintenance hemodialysis (MHD) patients with subjective cognitive decline (SCD).

Methods: One-way blind design was used, thirty-three MHD patients with MMSE score ≥24, SCD-Q9 score ≥5 and SCD were enrolled in this study, the intervention group (rTMS Group) and the Sham group (Sham group) were randomly assigned 1:1 according to the random number method. The cognitive function was measured at baseline and at the end of the experiment, before and after intervention, the changes of each index were compared between the two groups.

Results: MMSE score in rTMS group was significantly higher than that in Sham group after intervention (27.94 ± 1.25 VS 26.94 ± 1.39, P = 0.037). In the 5 parts of MMSE score, there was only a significant difference in the memory ability (P = 0.039). After intervention, the SCD-Q9 score in rTMS group were significantly lower than those in Sham group (6.09 ± 1.06 vs 7.09 ± 1.25, P = 0.018), only the ability of daily activity memory was significantly different between the two groups (P = 0.037). After intervention, there was no significant difference in α-diversity (Fig.1) and β-diversity (Fig.2) between the two groups. The results showed that the composition of intestinal flora was similar between the two groups at family level and genus level after intervention (Fig.3). Lefse analysis was used to screen the flora with statistical difference between the two groups after intervention (Fig.4, Table.1), there were 5 distinct microbial communities at the family level, Marinifilaceae, Flavobacteriaceae, RF39, Carnobacteriacea were the most abundant in rTMS group, while Wohlfahrtiimonadaceae was the most abundant in Sham group. At the level of 17 genera, the abundance of Faecalibacterium, Alistipes and Odoribacter in rTMS group was higher than that of Erysipelatoclostridium in Sham group (Fig.5).

Conclusions: rTMS therapy may alter the cognitive function of MHD patients with SCD, improve their memory, and affect the abundance of some intestinal flora, which may modulate the differential flora associated with SCD, it is suggested that the therapy may affect cognitive function during SCD by regulating the flora.

PUB150

Removal of Middle Molecules with Hemodiafiltration plus Hemoadsorption in Patients with Kidney Failure

Thiago A. Reis,[1,2] Bruno P. Biluca,[1] Maria G. Guimaraes,[4] Jessica L. Andrade,[1,3] Miguel Angelo Goes,[3] Andreia Watanabe,[6] Gonzalo Ramirez Guerrero,[5] Claudio Ronco,[5] Francisco R. Neves,[2] Antônio Luiz J. Almeida.[1] *[1]Fenix Nephrology, São Paulo, Brazil; [2]Laboratory of Molecular Pharmacology, University of Brasília, Brasília, Brazil; [3]Discipline of Nephrology, Federal University of São Paulo, São Paulo, Brazil; [4]Nephrology Department, Hospital Ana Nery, Salvador, Brazil; [5]International Renal Research Institute of Vicenza, Vicenza, Italy; [6]Department of Pediatrics, Pediatric Nephrology Unit, Instituto da Criança e do Adolescente, University of São Paulo School of Medicine, São Paulo, Brazil.*

Background: Hemodiafiltration (HDF) promotes a higher clearance of middle molecules compared to hemodialysis for patients with kidney failure. Whether the association of HDF plus hemoadsorption (Fig. 1a) using cartridges with styrene-divinylbenzene resin further enhances the removal of middle molecules is yet to be defined. We prospectively analyzed the removal of middle molecules in four patients undergoing simultaneous hemoadsorption in series with HDF.

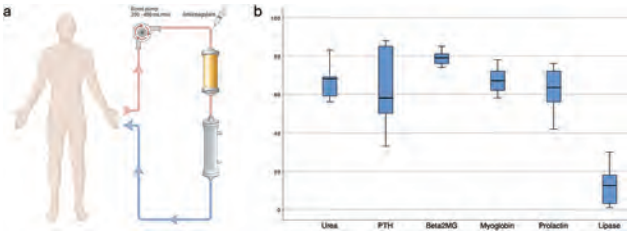
Methods: Patients underwent 3-hour sessions of online HDF with post-filter replacement plus hemoadsorption. We measured the pre- and post-session concentrations of five middle molecules and albumin.

Results: Four patients performed a total of 23 sessions. Dialysis characteristics are presented in Table 1. In the sum of the 23 session, blood flow was 400 mL/min (IQR 350-400 mL/min), convective post-filter flow was 115 mL/min (IQR 105-115 mL/min), and dialysate flow was 500 mL/min (IQR 500-800 mL/min). The reduction ratio [i.e.,1 - (pre-session/post-session)] of parathormone (9.4 kDa), ß2-microglobulin (12 kDa), myoglobin (17 kDa), Prolactin (25 kDa), and lipase (33 kDa) are depicted in (Fig. 1b). There was a statistically significant increase in albumin (66 kDa) concentration between pre- and post-session (38.3 vs 40.0 g/L, p = 0.002).

Conclusions: Compared to previous results in HDF trials, where patients carried out 4-hour HDF stand-alone sessions, 3-hour HDF plus hemoadsorption sessions provide an equivalent or superior reduction ratio of five middle molecules.

Hemodiafiltration prescription

Patients	Number of sessions	Blood flow (mL/min)	Dialysate flow (mL/min)	Post-filter replacement flow (mL/min)	Vascular Access	Filter type/area
Patient 1	8	350	500	115	AVF - 15 G	Fx CorDiax 1000/2.3 m2
Patient 2	5	400	600	115	AVF - 15 G	Fx CorDiax 1000/2.3 m2
Patient 3	6	400	800	105	AVF - 15 G	Fx CorDiax 1000/2.3 m2
Patient 4	5	420	500	115	Tunnelled 14 Fr	Fx CorDiax 1000/2.3 m2



PUB151

Is a Bioimpedance Assay an Effective Tool for Evaluating Cardiac Parameters in Patients with ESKD Undergoing Hemodialysis? A Cross-Sectional Study from North India

Dinesh Khullar, Vandana Prasad, Rahul Grover, Sahil Bagai, Kulwant Singh, Prof Narinder P. Singh, Deepak Kumar, Abhishek Singh, Anish K. Gupta. *Max Super Speciality Hospital, Saket, Delhi, India.*

Background: Hemodynamic stress caused by either fluid overload or depletion is a major contributor to cardiac complications in dialysis. Study aimed to investigate the role of BIA in assessing fluid status and its correlation with cardiac parameters in hemodialysis patients.

Methods: In cross-sectional study, 39 patients with ESKD undergoing hemodialysis at least three times a week for three months and had a preserved ejection fraction (EF>40%) were enrolled. Exclusion criteria included patients undergoing diuretics those with sepsis, limb amputations, pacemakers, metallic intravascular devices, malignancies, or pregnancy. The study investigated the levels of N-terminal pro-b-type natriuretic peptide (NT-pro BNP) and performed echocardiography (ECHO-2D) before and after hemodialysis. Hydration status of patients was assessed using 4-electrode BIA device (Fresenius Medical Care, Germany). This was done before dialysis, 30 minutes after dialysis, and before subsequent dialysis. Patients categorized into two groups based on hydration status: Group-A had overhydration (OH/ECW ratio ≥15%), while Group-B had normal hydration (OH/ECW ratio<15%).

Results: Among 39 patients, 69.2% were in Group A, while remaining 30.8% were in Group B. Mean age was 57.3±11.4 years for Group A and 54.0±16.3 years for Group B. Both groups matched for age, sex, BMI, biochemical, hemodynamic, and echocardiographic parameters. Before and after dialysis, no significant differences observed in various cardiac parameters between two groups, except for changes in aortic root diameter, left atrial diameter, and A wave velocity in Group A. NT-proBNP levels showed a significant decline after dialysis in groups A and B (p0.001). Hydration status (OH/ECW) before dialysis exhibited a negative correlation with left ventricular ejection fraction (LVEF)(r-0.434,p0.006) and NT-proBNP levels (r-0.708,p0.001). Post-dialysis OH/ECW displayed a negative correlation with LVEF(r-0.744,p0.001), and peak late transmitral filling wave velocity (A)(r-0.342,p0.033).

Conclusions: BIA-evaluated hydration levels were correlated with LVEF. By controlling OH/ECW during BIA-guided dialysis, we can potentially reduce the risk of cardiac morbidity.

PUB152

High Ultrafiltration Rate and Mortality among Patients Undergoing Hemodiafiltration at St. Luke's Medical Center-Global City: A Retrospective Cohort Study

Andrew Solomon R. Echavez. *St. Luke's Medical Center Global City, Taguig, Philippines.*

Background: Effective hemodiafiltration (HDF) and volume clearance over shorter treatment times were made possible by the development of hydrostatic ultrafiltration and other technical advancements. Ultrafiltration is commonly used to treat fluid overload; however, it is uncertain if its rate influences outcomes. The study therefore aims to determine the association between high UFR and mortality; and the predictors of mortality in end-stage renal failure patients receiving hemodiafiltration.

Methods: This was a retrospective analytical cohort study of the medical data of all patients >18 years old undergoing maintenance hemodiafiltration at the St. Luke's Medical Center-Global City from January 2018 to December 2022. Records review was done to gather data on clinical and demographic variables, laboratory findings, UFR values, and mortality.

Results: A total of 296 patients were included in the study and 93 (31.4%) were observed to have high UFR. The mean age was significantly higher among those without high UFR (67.3 years) than those with high UFR (61.4 years) (p-value = 0.002). Among those with high UFR, the mortality rate was 34.4% with median follow-up time of 4 years. Among those without high UFR, the mortality rate was 27.6% with median follow-up time of 4 years. High UFR was not seen to be significantly associated with mortality (HR=1.3, 95%CI=0.7 to 2.4, p-value = 0.443). Increasing age was significantly associated with higher risk for mortality (HR=1.03, 95% CI=1.02 to 1.05, p-value <0.0001).

Conclusions: High UFR was not associated with increased risk of mortality in end-stage renal failure patients receiving hemodiafiltration. Only increasing age significantly predicts risk for mortality in this group of patients. Future prospective studies conducted in multiple centers are needed to validate the findings of the current study.

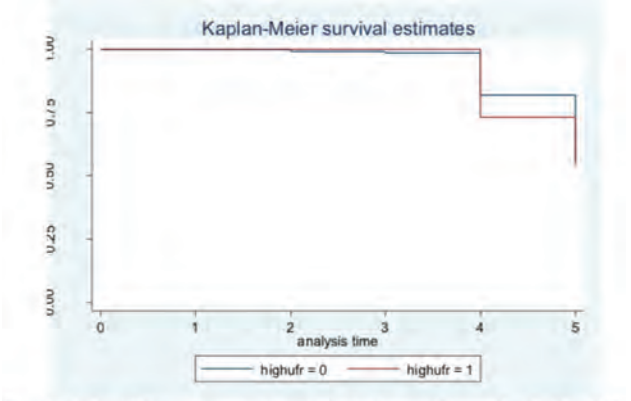


Figure 1. Kaplan Meier curve comparing survival rates between those with and without high UFR.

PUB153

Self-Efficacy Predicts Patient-Reported Outcomes Measurement Information System (PROMIS) Health-Related Quality of Life Outcomes in Turkish Patients on Dialysis Better than the 36-Item Short Form Health Survey (SF-36)

Krister Cromm,[1,2] Ngoc Pham,[1] Özlem K. Tunçel,[3] Mirja Humpert,[1] Tatiana De los Ríos,[1] Manuela Stauss-Grabo,[1] Gulay Asci,[3] Ercan Ok,[3] Hayriye Elbi.[3] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Charite Universitatsmedizin Berlin, Berlin, Germany; [3]Ege Universitesi, Izmir, Turkey.*

Background: Recent research has emphasized the importance of psychosocial factors on health-related quality of life (HRQL). Self-efficacy (SE) and social support (SS) emerged as particularly relevant. The purpose of this study was to understand the degree to which these two variables are also useful in predicting HRQL in Turkish patients using standard SF-36 and new PROMIS-29 measures.

Methods: 177 patients (mean age: 55.5±13.4) on in-center or home hemodialysis in Izmir, Turkey filled out electronic surveys. A series of ANCOVA models was employed to examine the relationship between HRQL scores and domains as dependent variables, and SE and SS as predictor variables. HRQL was measured by SF-36 mental (MCS) and physical composite scores (PCS), PROMIS mental (MHS) and physical health (PHS) composite scores as well as 7 PROMIS-29 domain scores. SE and SS were measured with the MOS-SSS and GSE scales. Covariates included demographic characteristics and disease impact (KDQOL-36 burden, symptoms, and effects of kidney disease scales).

Results: SE was a significant predictor for MHS ($F(1,138)=19.57$, $p<.0001$; $R^2=.60$ for whole MHS model) as well as MCS ($F(1,138)=5.84$, $p=0.02$; $R^2=.47$ for whole MCS model) over and above the covariates. SE was related to PHS ($F(1,138)=5.52$, $p=0.02$; $R^2=.43$ for whole PHS model) but not to PCS. SS was not significantly related to any composite scores. SE was a significant predictor for all PROMIS-29 domains except for Physical Function and Pain Intensity. The Tangible Support domain of SS was a significant predictor for Sleep Disturbance only ($F(1,138)=4.27$, $p=0.04$; $R^2=.42$ for whole Sleep Disturbance model).

Conclusions: In line with previous research, our results show that SE is a significant predictor for mental health. PROMIS includes a broader range of HRQL subdomains than SF-36, leading to more explained variance of SE on physical health. This suggests that PROMIS may provide a more sensitive assessment of HRQL. The Social Support domains appear to be less useful for predicting HRQL, though the Tangible Support domain does show a relationship with the PROMIS-29 Sleep Disturbance domain.

Funding: Commercial Support - Fresenius Medical Care

PUB154

Salicylate Intoxication: When Bicarbonate Is Not Enough

Alexis F. Mena,[1] Jose D. Mena.[2] *[1]Universidad UTE Facultad de Ciencias de la Salud Eugenio Espejo, Quito, Ecuador; [2]Nephrology Associates of the Carolinas, PA, Shelby, NC.*

Introduction: Accidental or intentional overdose of salicylates is a medical emergency that can precipitate severe metabolic derangements and in some cases death. In 2014 more than 24,700 salicylate intoxication cases were documented in the US. We present a case of acute aspirin overdose with emphasis in the indications of renal replacement therapy.

Case Description: A 47-year-old male with a past medical history of polysubstance abuse, depression and CKD presented to the emergency department after being found unresponsive. On arrival, vital signs showed a heart rate of 120 bpm, respiratory rate of 35, SpO2 97% on room air and blood pressure of 130/80. On physical exam he was tachypneic, lethargic and non responsive to voice commands. Breath sounds were clear bilaterally. Labs showed a creatinine 1.46 mg/dl (baseline), sodium 138 mmol/L, potassium 4.1 mmol/L, CO2 13 mmol/L. Blood gas: pH 7.42, pO2 63 mmHg, pCO2 20.1 mmHg. Urine toxicology was positive for cocaine. Salicylate level was 96.8 mg/dL. He was started on sodium bicarbonate infusion and poison control was contacted. Despite initial management, salicylate levels didn't improve. He was started on intermittent hemodialysis (iHD) and was continued for 6 hours with improvement in salicylate levels from 89.6 mg/dL pre iHD to 14.7 mg/dL post iHD.

Discussion: The history of substance abuse in a patient with encephalopathy and anion gap metabolic acidosis should raise the concern for salicylate toxicity. Initial treatment includes discussion with poison control, fluid resuscitation and bicarbonate administration. The goal of bicarbonate is to generate alkalemia to minimize the passage of salicylate to the central nervous system and to increase the excretion of salicylate alkalinizing the urine. The low volume of distribution, absence of tissue binding and the small size of salicylate, make iHD the best way to remove this drug. Dialysis is recommended when salicylate levels are above >100 mg/dl or >90 mg/dl with impaired kidney function. It is also recommended in the presence of encephalopathy or new hypoxemia and if standard therapy fails. In this case, iHD was continued for 6 hours with improvement in salicylate levels and improvement in his symptoms. Guidelines recommend to stop dialysis when clinical improvement is apparent and when salicylate levels are below 19 mg/dL. If salicylate levels are not available, iHD should be performed for at least 4 to 6 hours.

PUB155

Effectiveness of Dialysis Transition Unit to Improve Patients' Decision-Making and Self-Management Skills

Warda Munawar, Veronica Hammer, Chel Lee, Danielle E. Fox, Meghan J. Elliott, Jennifer M. MacRae. *University of Calgary Cumming School of Medicine, Calgary, AB, Canada.*

Background: Dialysis initiation is a stressful time for people living with kidney failure. As a quality improvement initiative, we created a dialysis transition unit (DTU) in Calgary, Alberta with the goal of providing person-focused dialysis care for patients starting hemodialysis. Objectives:To compare patient's perception of participation in self-management and receipt of dialysis transition/chronic care counseling using PACIC-20, (Patient Assessment of Chronic Illness Care) between patients starting hemodialysis in the DTU and in a traditional facility-based HD unit (HDU).

Methods: PACIC-20, anxiety (GAD-7) and depression (PHQ-9) scores were captured prospectively (June 1, 2021-June 30, 2022) on patients starting hemodialysis on the DTU and the HDU at dialysis initiation and two weeks later. Our primary outcome of interest was between-group differences in PACIC-20 scores at 2 weeks after dialysis initiation.

Secondary outcomes included between-group differences in PACIC-20 subcategories and between-group differences for the change in patient-reported outcome measures of GAD-7 and PHQ-9 at 2 weeks.

Results: A total of 26 DTU and 26 HDU participants completed data collection (mean age 62.6 ± 17.7 years; 42.3% females). The PACIC-20 scores at two weeks were similar (DTU 3.60 ± 0.6 and HDU 3.26 ± 0.95, P = 0.21). All PACIC-20 subcategories were similar between groups except for problem solving, which trended higher in DTU (4.09 ± 0.9 vs 3.39± 1.36, p=0.06). The subcategory, patient activation was associated with improved anxiety in DTU (p= 0.02) but not HDU (p= 0.35). The between-group difference was significant for PHQ-9 for DTU (p= 0.007) but non-significant for GAD-7 (p=0.05).

Conclusions: While we did not find a significant difference in the overall patient perception of self management (PACIC-20) when transitioning to a specialized DTU (vs HDU), we did find improved problem-solving scores and lower depression scores for DTU. Further research on the role of a DTU to optimize patient care is needed.

PUB156

COVID-19 Pandemic in Dialysis: Urban and Suburban Outcomes in a Small Dialysis Organization

Shruti Kore,[1,2] George N. Coritsidis,[2] Steven Weiss.[3] *[1]New York Medical College, Valhalla, NY; [2]Westchester Medical Center, Valhalla, NY; [3]Atlantic Dialysis Management Services, New York, NY.*

Background: The COVID-19 pandemic was devastating to the ESRD population, contributing to a decrease in prevalence of dialysis patients. Atlantic Dialysis Management Services (ADMS), a small dialysis organization, provides dialysis to the NYC and Long Island areas. We reported early findings, in 2020, describing increased mortality, and reviewed the progression of these findings into 2021.

Methods: A retrospective EMR review of 13 ADMS facilities comprising 4 boroughs of NYC and Long Island from February 1, 2020 to August 31, 2020 Wave (W1) and September 1, 2020 to February 28, 2021 Wave (W2). Aggregate data was used to calculate values for combined wave categories. We reviewed the demographic characteristics, COVID-19 status, years on dialysis (vintage), mortality (overall and COVID-19 related), presence/absence of a social security number, insurance, and comorbidities. Adjusted odds ratio analysis was performed.

Results: There were 2147 patients in Wv1 and 1658 in Wv2. The total ADMS population decreased by 22.8% by Wv2 with a total of 911 deaths, despite admissions. *215* or 31% were covid related deaths in W1, decreasing to 11% in W2. Living in NYC and being Hispanic had significantly higher odds ratio for infectivity and COVID related mortality in W1 but not in W2. COVID-19 related mortality was significantly associated with age, vintage, ethnicity, and dialyzing in a NYC borough. Patient infection, overall deaths, and COVID-19 related deaths on Long Island more than doubled from W1 to W2. Overall mortality was significantly associated with age, vintage, diabetes, but not ethnicity, and only with NYC boroughs with nursing home patients.

Conclusions: Ethnicity and urban dwelling was associated with increased COVID-19 mortality in W1, but not overall mortality, likely due to housing differences. These factors likely lost significance in W2 due to COVID-19's spread into other communities. As the pandemic expanded into suburbia, mortality increased, likely due to rapid spread/novelty of the infection, and unique safety challenges. Overall COVID-19 mortality decreased by W2, possibly due to an increased knowledge of infection control and treatment. Mortality's association with age, diabetes, vintage and entities with nursing home patients represents strain on the healthcare system that may be repeated in future pandemics.

PUB157

Incidence and Predictive Factors of Intradialytic Hypertension in Patients Undergoing Hemodialysis? An Observational Study from North India

Dinesh Khullar, Harleen Singh, Rahul Grover, Sahil Bagai, Kulwant Singh, Prof Narinder P. Singh, Deepak Kumar, Abhishek Singh, Anish K. Gupta. *Max Super Speciality Hospital Saket, New Delhi, India.*

Background: Cardiovascular issue associated with hemodialysis is intradialytic hypertension (IDH), affecting approximately 15% of patients. To enhance our comprehension of IDH, study sought to ascertain its incidence and identify factors that predict its development in hemodialysis patients.

Methods: An observational study was carried out in 174 patients over the age of 18 years, undergoing hemodialysis at least twice a week for at least three months. IDH was defined as systolic BP increase of ≥10 mm Hg occurring during dialysis, starting after the first hour and continuing for at least 30 minutes after the session's completion, observed in at least 4 out of 6 successive dialysis sessions. Blood tests including CBC, and KFT were performed before dialysis. ECHO-2D was conducted at baseline. BP, pulse rate, and Mean Arterial Pressure were monitored hourly and 30 minutes post-dialysis. Four-electrode BIA device (Fresenius, Germany) utilized for assessment of hydration status. Patients were categorized into two groups - IDH-group A and non-IDH group B.

Results: The incidence of IDH was 34.5%, with half of patients being male and average age was 55.4±15 years. The non-IDH group B (65.5%) consisted of 58.7% males, with mean age of 57.3±12.8 years. The most common cause of ESKD in both groups was chronic glomerulonephritis, accounting for 55% of group A and 44.7% of group B. Hypertension (86.7%) and diabetes (48.8%) were prevalent in both groups. A negative correlation was found between IDH and BMI (r-0.16,p0.037), and hemoglobin levels (r-0.21,p0.006). IDH was positively correlated with Hydration status(r0.19,p0.011), left ventricular hypertrophy (LVH) (r0.16,p0.034), and number of antihypertensive medications (r0.3,p0.01), particularly ACE/ARB use (r0.39,p0.01). The multivariate analysis revealed that hydration status (p0.037), LVH (p0.04), and ACE/ARB use (p0.02) were independent predictors of IDH.

Conclusions: Almost one-third of patients with hemodialysis experience IDH, which is a clinically relevant phenomenon. The risk factors associated with IDH include hydration status, LVH, and the use of ACEi/ARB.

PUB158

ESKD Is Often Not Identified as a Cause of Death in Death Certificates

Nicholas S. Kowalczyk, Anthony Chang. *The University of Chicago Medicine, Chicago, IL.*

Background: Many studies have found high error rates in death certificates, as most healthcare professionals have minimal to no training regarding how to complete this important task. A recent multicenter study demonstrated that most pathologists did not recognize end-stage kidney disease (ESKD) as either an underlying or contributing cause of death (COD) in autopsy reports of ESKD patients. Therefore, we conducted this study to determine whether a similar omission could be observed in the death certificates of ESKD patients.

Methods: We identified 60 deceased patients with ESKD in our electronic medical record (EMR) between August 1, 2022 and January 30, 2024. Inclusion criteria were a diagnosis of ESKD, being on dialysis for at least 1 year, and a viewable death certificate in the EMR. Patients that were 18 years or younger or had any history of kidney transplant or malignancy were excluded.

Results: The average age of patients was 62 years with sex equally split. Time on dialysis ranged from 1 to 20 years with a mean of at least 5.6 years. The common co-morbidities were hypertension (28/60, 47%), diabetes (28/60, 47%), heart disease including coronary artery disease, heart failure, and arrhythmias (35/60, 58%), and other cardiovascular disease including cerebrovascular disease and peripheral vascular disease (16/60, 27%). Cardiovascular causes were the most common immediate COD (27/60, 45%) followed by infection (13/60, 22%), ESKD (10/60, 17%), and hemorrhage (6/60, 10%). ESKD was listed as an immediate or proximate COD in 22 (37%) of 60 death certificates. The majority (41/60, 68%) of death certificates were completed by trainees, and the remaining 27% (16/60) were hospitalists, physician assistants, advanced practice nurses, or primary care physicians. Of the trainees, 29% (12/41) identified ESKD as a COD. Non-trainees identified ESKD as a COD in 8/19 (42%) of cases.

Conclusions: The majority (63%) of providers failed to recognize ESKD as a cause of death in death certificates. The failure to identify ESKD as an underlying or contributing COD emphasizes the decreasing sense of urgency that is commonplace among healthcare providers ever since the advent of dialysis. This study identifies an important practice gap regarding the inaccurate completion of death certificates in the setting of ESKD, which shortchanges the nephrology community and their ESKD patients.

PUB159

Rare Case of Enteropathogenic Escherichia coli Causing Hemolytic Uremic Syndrome

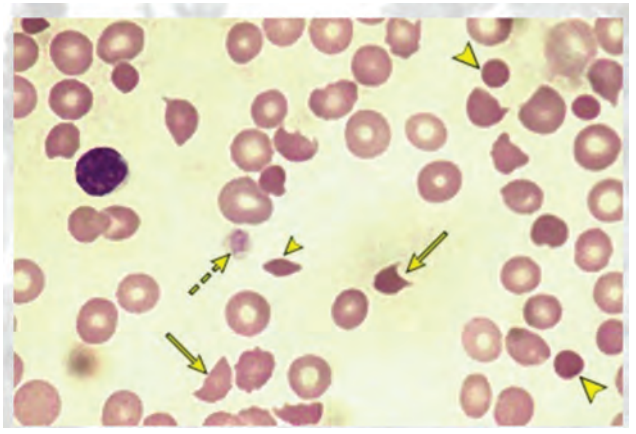
Bhoomi Shah, Nabeel Siddiqui, Rupinder Kaur, Greeshma A. Thomas, Karen Terry, Sagar Kulkarni. *Southeast Health, Dothan, AL.*

Introduction: Association of Shigella and EnteroHemorrhagic E.Coli strain O157:H71 causing HUS has long been established and is known as typical HUS. Atypical HUS is caused by mutation causing abnormal complement activation. EPEC is a rare cause of diarrhea in adults and people who live in developed countries.

Case Description: A 40-year-old female with no significant medical history presented with complaints of nausea, vomiting, and diarrhea for 3 days. She also had blood in her urine and decreased urine output. Her diarrhea was watery in nature with few streaks of blood. She also reported a fever spike of 100.5 F. She had associated decreased appetite and abdominal pain. She denied any blood in vomitus, recent travel, or eating outside food. Her vital signs were revealing of tachycardia and fever. Her abdomen was diffusely tender to palpation. Her labs showed decreased hemoglobin, elevated creatinine 6.27, platelets 14000, troponin 9888, bilirubin 3.29, and CK 1122. Her ADAMTS-13 levels were low. Peripheral smear showed schistocytes. She also had elevated LDH, ferritin, and low haptoglobin. She was transfused with 8 units of PRBCs. She underwent plasma exchange due to concerns of TTP-HUS from STEC, but the stool studies were positive for EPEC. Therefore, she was started on steroids and later transitioned to supportive treatment. She also required dialysis and aggressive management of her hypertension.

Discussion: Though most cases of HUS are associated with Shigella and EHEC O157:H71, thorough work up is required to rule out causes including genetic causes, atypical HUS to provide appropraite treatment to the patient. EPEC causes watery diarrhea

and EHEC causes bloody diarrhea. Appropriate management depends on the underlying cause of the microangiopathy whcich is not always established and includes a wide range of treatment options from supportive care to RBC transfusion, plasma exchange, dialysis and anti-complement therapy.



PUB160

Hemodiafiltration: Impact of Private Health Insurance on Mortality

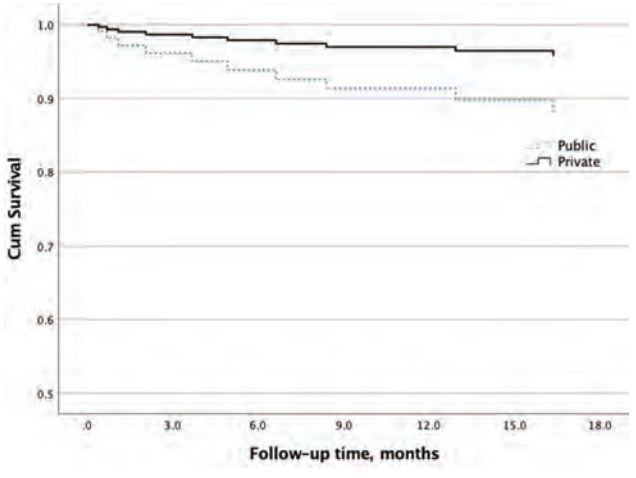
Eduardo D. Luciano,[1] Érica P. Rocha,[4] Cynthia M. Borges,[3] Christiane Kojima,[4] Sandra Reis,[6] Maria G. Rosa,[3] Aline Cordeiro,[5] Whelington F. Rocha,[1] Adolfo M. Silva,[1] Andréa O. Magalhães,[1] Rosilene M. Elias.[2] Nefrostar. *[1]Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil; [2]Universidade de Sao Paulo, Sao Paulo, Brazil; [3]Universidade Estadual de Campinas, Campinas, Brazil; [4]Universidade Estadual Paulista Julio de Mesquita Filho, Sao Paulo, Brazil; [5]Universidade de Taubate, Taubate, Brazil; [6]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.*

Background: High-volume hemodialfiltration (HDF) is associated with an improved survival. However, in Brazil, HDF is allowed only for patients with private insurance (approximately 20% of population). It is not known whether the better survival rate observed in patients with private health insurance is related to the dialysis therapy or to the global care associated with a better economic situation. We had the opportunity to evaluate the impact of HDF on mortality rate in patients with private and public health insurance.

Methods: all patients who received HDF in both clinics were included (private, N=83, 35.3% with diabetes, age 53± 17 years) and public (N=40, 51.2% with diabetes, age 61± 2 years). Patients were followed until death, withdraw from dialysis or end of the study (May-9-2024). The nephrology team was the same in both facilities.

Results: during a median follow-up of 16.9 months there were 11 deaths (5 from the public and 6 from the private facility). In a Cox survival analysis revealed a not significant difference between public and private facilities (p=0.099, HR=0.336) after adjustments for age (p=0.047, HR=1.065) and diabetes (p=0.775, HR=1.202)

Conclusions: Despite the differences in global care and economic status, HDF confers similar survival rate for patients with private and public insurance. Whether this benefit will be confirmed in a larger population deserves further evaluation.



PUB161

ESKD with Renal Artery Stenosis

Christian J. Wiscombe, Lark Steafo, Sami S. Zarouk. *Corewell Health Beaumont Hospital, Royal Oak, MI.*

Introduction: Atherosclerosis is the leading cause of renal artery stenosis accounting for 90% of all renovascular lesions. Complications that arise secondary to renal artery stenosis can include hypertension, ischemic nephropathy, and destabilizing cardiac syndrome. In patients with a single functioning kidney, these complications can lead to rapidly declining kidney function. Patients can present from a spectrum of hypertension, acute kidney injury, or worsening chronic kidney disease.

Case Description: A 71-year-old Caucasian woman with history of hypertension, atrophic right kidney, and chronic kidney disease stage IIIb A1 was evaluated for uncontrolled hypertension. She presented for second opinion regarding hypertension and kidney disease. Her blood pressure was 190/90 and eGFR at 36 cc/min which appeared to be her baseline for several years. Workup for primary hyperaldosteronism was negative and doppler of the renal arteries was negative. Five months later the patient was admitted through the emergency room with a creatinine of 13 mg/dL on routine screening. She was hypotensive and had melena. Renal angiography revealed total occlusion of the renal arteries bilaterally and she was initiated on hemodialysis. Over time she became nonoliguric, requiring less dialysis time and ultrafiltration. She was referred to a vascular surgeon to re-evaluate her left renal artery. Repeat aortogram revealed >90% left ostial stenosis with a greater than 70% proximal renal artery stenosis. She underwent renal artery angioplasty and stenting. She was able to discontinue dialysis 11 months after her start date. She has remained dialysis free for the last 7 months with eGFR at 33 cc/min and tolerating the use of Valsartan.

Discussion: Multiple studies have been designed to evaluate the role of renal artery stent placement in chronic kidney disease patients with renal artery stenosis. Limited small retrospective studies have been performed to evaluate the role of renal stenting in dialysis patients. We believe the patient had acute tubular necrosis with a single partially functioning left kidney with renal artery stenosis that recovered over time. The initial angiogram failed to demonstrate the patency of the left renal artery. We would like to bring attention to the importance of evaluating the urine output as a marker for renal flow in spite of a false reporting of occlusion of the renal artery on angiogram.

PUB162

Topical Oxygen Therapy Use in Patients with ESKD in Qatar: A Case Series

Ali Mahgoub, Robert A. Menzies, Talal K. Al Enizi, Abdullah I. Hamad, Hassan A. Al-Malki. *Hamad Medical Corporation, Doha, Qatar.*

Background: End-stage kidney disease (ESKD) is an increasing healthcare concern. The major etiology is attributed to diabetes worldwide. Diabetic foot disease (DFD) is a serious complication as its the major cause of non-traumatic lower extremity amputations. ESKD is a known independent risk factor for foot ulcers in patients with diabetes, furthermore they are predisposed to other ulcerating conditions such as calcific uremic arteriolopathy (CUA). Topical oxygen therapy (TOT) has emerged as one of the modalities to improve wound healing in patients with DFD. It can be provided as an in-center treatment during hemodialysis (HD) thus bypassing some of the difficulties encountered with hyperbaric oxygen therapy. In this case series we aimed to evaluate the use of TOT in patients with ESKD.

Methods: 6 patients receiving HD were identified, 5 patients diagnosed with DFD and 1 with CUA. All patients received standard of care which included thrice weekly wound examination, debridement as needed, dressing, wound swab and antibiotics if signs of infection were found. TOT was started thrice weekly during HD for 1.5 hours at 40–50 millibars of pressure and was continued till wound closure or for a total of 20 sessions. Wound dimensions were obtained before initiation of TOT and when an outcome is met.

Results: All patients included received standard of care alone for at least 2 months prior to TOT without significant improvement. All patients had hypertension and diabetes. One patient was excluded as he travelled abroad. All patients tolerated the treatment without reported side effects. 3/5 patients improved with topical oxygen therapy on completion of 20 sessions. Patient 1 had complete wound closure. Patient 2 and 3 achieved significant improvement; their wounds dimensions has improved to 0.6x.0.4 cm from 1.1x0.8 cm and 0.7x0.5 cm from 4x2.2 cm respectively. Patient 4 and 5 did not complete treatment as they developed infections requiring hospitalization.

Conclusions: Topical oxygen therapy is a well-tolerated adjuvant therapy that was associated with higher rates of wound healing amongst patients with end-stage kidney disease. it can be provided as an in-center treatment therefore improving patient's adherence and convenience. Prospective trials are needed to further evaluate safety and efficacy of TOT in patients with end-stage kidney disease.

PUB163

Changes of Arterial Oxygen Saturation during Hemodialysis

Lin-Chun Wang,[1] Andrea Nandorine Ban,[1] Vincent Filardi,[1] Xiaoling Ye,[1] Peter Kotanko,[1,2] Hanjie Zhang.[1] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

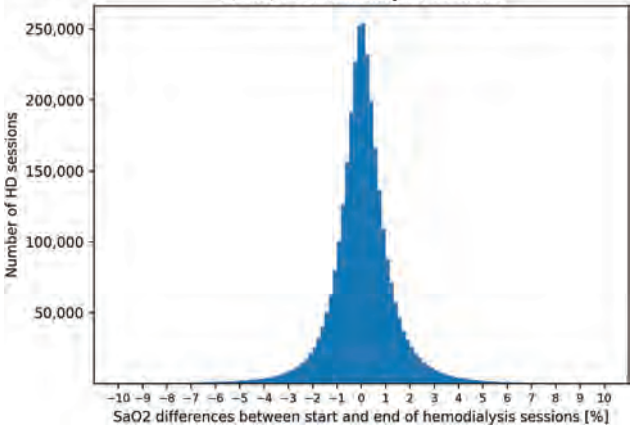
Background: The study of intradialytic arterial oxygen saturation (SaO_2) in hemodialysis (HD) patients is an under-explored area. We aim to describe the dynamics of SaO_2 in HD patients with arteriovenous (AV) access during HD.

Methods: SaO_2 levels during HD were measured using the Crit-Line monitor (CLM; Fresenius Medical Care, Waltham, MA). CLM measurements were recorded at 10-second intervals and transmitted into Amazon Web Services (AWS) via Apache KAFKA, a real time streaming software. We extracted CLM data between January 2021 and July 2023. CLM values with the following characteristics were deemed implausible and excluded: $SaO_2 \leq$ 0 or ≥99.9; hematocrit <15% or >60%. We then excluded the sessions with the standard deviation of SO_2<0.1%, an SaO_2 interquartile range of zero, and sessions less than 60 total minutes of recordings. SaO_2 at HD start was calculated as the mean SaO2 between minutes 5 and 20. SaO_2 at the HD end was calculated as the mean SaO_2 in the last 5-20 minutes. The sessions with less than 5 minutes of measurements either at the start or at the end of the session were filtered.

Results: SaO_2 from over 3 million HD sessions from 49,580 patients with AV access are analyzed. The mean SO_2 at the start was 96.42±3.6% and 96.45±3.75% at the end, indicating an average intradialytic SO_2 increase of 0.03% [95% CI: 0.0289 - 0.0325] (**Figure 1**).

Conclusions: Our results showed that SaO_2 during HD remain similar at the start and end of HD. These data provide a rich source for future research into SaO_2 and its clinical outcome associations. Exploring intradialytic SaO_2 in depth will offer valuable insights to improve patient care and optimize treatment procedures.

Figure 1



SaO_2, arterial oxygen saturation.

PUB164

Predictive Factors of Catheter-Related Bloodstream Infection among Patients on Hemodialysis

Sandra L. Diaz, Mary Anne C. Lu. *Cotabato Regional and Medical Center, Cotabato City, Philippines.*

Background: Catheter-related bloodstream infection (CRBSI) is a one of the major cause of morbidity and mortality among end stage renal disease patients undergoing hemodialysis using central venous catheter (CVC). The study aimed to investigate the predictors of catheter-related bloodstream infections (CRBSI) with end-stage renal disease (ESRD) patients on hemodialysis through a central venous catheter.

Methods: We conducted a retrospective analytical study to investigate the predictive factors and associated outcome of CRBSI among ESRD patients undergoing hemodialysis at Cotabato Regional and Medical Center. A total of 42 patients who have central venous access(CVC) were included in this study from January 1, 2020 to December 31, 2022. We obtained the patient's demographic data, laboratory results at admission, information regarding catheter infections, culture results, and other information from electronic medical records.

Results: The study involved patients with a mean age of 48±15 years, with more females (59.5%, 25 patients) than males (40.5%, 17 patients). The primary causes of hemodialysis were diabetes mellitus (38.1%) and hypertension (35.7%), which were also the most common co-morbidities. Non-tunneled catheters were the majority of the central venous access used in the study. Sepsis is a significantly associated outcome of CRBSI among hemodialysis using central venous catheter with p value of 0.05. According to logistic regression analysis, the development of CRBSI was predicted by ages greater than 71 with a p-value of 0.023.

Conclusions: We conclude that ESRD patients undergoing hemodialysis with venous catheters, who are 71 years of age or older, are at an increased risk of developing CRBSI and sepsis is a significantly associated outcome.

PUB165

Surveillance of Patients on Dialysis in a Large Polysomnography Database in Okinawa, Japan

Kunitoshi Iseki.[1,2] *[1]Nakamura Clinic, Urasoe, Japan; [2]Okinawa Heart and Reanal Assocation, Naha, Japan.*

Background: Sleep disturbance is a major cause of lowering quality of life (QOL) and may contribute to high mortality rate of chronic dialysis patients. Overnight polysomnography (PSG) is the precise method to diagnose sleep disturbance such as obstructive sleep apnea (OSA). However, there is a few reports on characteristics of OSA among dialysis patients based on PSG database.

Methods: Since September 1990, we have a large PSG database: the Okinawa Nakamura Clinic Sleep (ONSLEEP) registry (Nakamura K, et al. J Clin Sleep Med 2021). By reviewing medical records, we surveyed hemodialysis (HD) patients by the end of March, 2024. Baseline data at the first PSG such as age, body mass index (BMI), and apnea hypopnea index (AHI) were obtained. Also, we collected dialysis-related date such as the start date of chronic dialysis therapy and primary cause of end-stage renal disease. To compare those not-on dialysis, we used data of the previous report (N=6,483).

Results: There were 374 dialysis patients (men 302, women 72). The median (interquartile range, IQR) age, BMI and AHI at PSG were 57.0 (49.0-67.0) years, 27.2 (23.6-30.8) kg/m^{2}and 32.3 (13.9-66.4) per hour. PSG was performed before starting dialysis in 204 patients (54.5%). Demographics at the PSG were compared between after and before starting dialysis therapy (Table 1). Those who tested PSG before starting dialysis were significantly higher BMI and AHI.

Conclusions: Results support the notion that continuous positive airway pressure (CPAP) therapy may lowered the death risk, and they survived until start dialysis therapy. Whether the use of CPAP is effective to retard the progression of CKD remained to be studied.

Baseline characteristics at the time of PSG. Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

PSG Timing	Total	After start of HD	Before start of HD	P-value
N of patients	374	170 (45.5%)	204 (54.5%)	
Age, years	57.0 (49.0-67.0)	58.5 (50.0-69.0)	56.5 (47.0-65.0)	0.008
Men, %	302 (80.7%)	142 (83.5%)	160 (78.4%)	0.21
Height, cm	163 (156-168)	163 (157-168)	163 (155-168)	0.48
Weight, kg	71.5 (62.0-83.0)	66.0 (55.9-76.0)	77.1 (67.0-87.6)	<0.001
BMI, kg/m^2	27.2 (23.6-30.8)	24.5 (22.1-27.6)	29.4 (25.8-32.0)	<0.001
AHI, /hour	32.3 (13.9-66.4)	29.9 (11.0-60.8)	34.7 (15.4-77.9)	0.027

PUB166

Prevalence of Protein-Energy Wasting in Patients with CKD on Hemodialysis in Mexico

Gabriela Luna,[1] Edgar Solis,[1] Geovana Martin-Alemañy,[2] Karla Davalos,[1] Alondra Muñoz,[1] María Escobar,[1] Laura Lagunes,[1] Tania Sepúlveda,[1] Diana Flores,[1] Luz Piña,[1] Ingrid Diez,[1] Ludwig Romero,[1] Jorge Navarro,[1] Juan M. Ardavin Ituarte,[1] Sergio Hernández-Estrada.[1] *[1]Médica Santa Carmen, Querétaro, Mexico; [2]University of Arizona, Nutritional Sciences and Wellness, Tucson, AZ.*

Background: The protein energy wasting (PEW) contributes to increasing the high rates of morbidity and mortality known in patients with chronic kidney disease. The objective of the study was to know the prevalence of PEW using the Malnutrition Inflammation Score (MIS).

Methods: In this multicenter cross-sectional study in adults hemodialysis (HD) patients the prevalence of PEW was calculated using the MIS tool for its diagnosis, its clinical and nutritional characteristics were described. Generalized linear model analysis was applied to evaluate the associations with different risk factors.

Results: 3347 adult HD patients were evaluated from September 2020 to December 2023 from 11 kidney health facilities in Mexico. Prevalence of PEW was 35.5% (95% CI: 33.9% to 37.2%). It was observed that an increase in the triceps skinfold (OR: 0.95 95% CI 0.93-0.96), in the mid-arm muscle circumference (OR: 0.98 CI 95% 0.98-0.99) and serum creatinine (OR: 0.90 95% CI 0.87-0.93) were associated with a decrease in the probability of being diagnosed with PEW (p= 0.000).

Conclusions: We found a prevalence of PEW of 35.5% in patients on HD, these results are in line with what is reported in the literature where a worldwide prevalence has been calculated 28-54%.

Figure 1. Prevalence of PEW in hemodialysis patients by state of Mexico

Table 3. Generalized linear model analysis for factors associated with protein-energy wasting

		Odds ratio (IC 95%)	*p*
Clinic History			
Age	<60 y	**REFERENCE**	
	>60 y	1.17 (0.94 - 1.46)	0.15
Comorbidities	Type 2 diabetes mellitus	1.00 (0.81 - 1.23)	0.96
	HTN	1.03 (0.73 - 1.45)	0.84
	Heart disease	1.19 (0.90 - 1.58)	0.21
Residual uresis	None	**REFERENCE**	
	Yes	0.89 (0.73 - 1.10)	0.30
Replacement therapy			
Previous replacement therapy	None	**REFERENCE**	
	Yes	1.09 (0.89 - 1.34)	0.37
HD frequency	<3 sessions per week	**REFERENCE**	
	3 sessions per week	1.14 (0.85 - 1.52)	0.37
Nutritional assessment			
Gastrointestinal symptoms	None	**REFERENCE**	
	Constipation	1.17 (0.93 - 1.46)	0.16
	Dyspepsia	1.22 (0.92 - 1.62)	0.15
	Abdominal pain	1.22 (0.93 - 1.62)	0.14
	Abdominal distension	1.31 (0.92 - 1.87)	0.12
Body composition			
Tricipital skinfold (mm)		0.95 (0.93-0.96)	0.000
Mid-arm muscle circumference (mm)		0.98 (0.98-0.99)	0.000
Biochemical parameters			
Hemoglobin (g/dL)		0.96 (0.92-1.01)	0.13
Creatinine (mg/dL)		0.90 (0.87-0.93)	0.000
Cholesterol	≥100 mg/dl	**REFERENCE**	
	<100 mg/dl	1.14 (0.88 - 1.47)	0.29

HTN: hypertension, HD: hemodialysis, TLC: Total lymphocyte count. *p* <0.05.

PUB167

Abstract Withdrawn

PUB168

Temperature Regulation to Counter Inflammation Associated with Hemodialysis (TRIAD) Study

Srikanth Bathini.[1,2] [1]*Asian Institute of Nephrology and Urology, Hyderabad, India;* [2]*Krishna Institute of Medical Sciences Hospital Group, Secunderabad, India.*

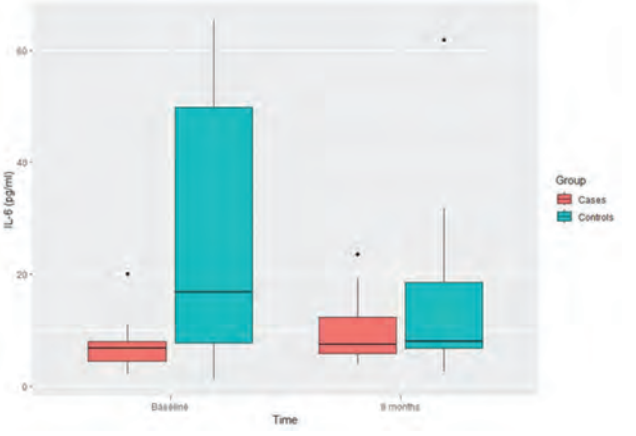
Background: CKD is a chronic inflammatory state. Inflammatory markers (IL-6, TNF- α) have been associated with adverse outcomes in CKD. The role of cool dialysate over standard temperature dialysate in preventing intra-dialytic hypotension is well known. The effect of a cool dialysate over inflammation is not known. We studied the effect of a cooled dialysate on inflammatory markers.

Methods: This is a prospective, randomised, open label study, with 13 patients in each group. Two groups with standard dialysate (36.5^{0}C) and cooler dialysate (one degree lesser than the core body temperature, never going below 35^{0}C) were studied. The inflammatory markers IL-6 and TNF-α were noted at baseline and at 8 months post randomization.

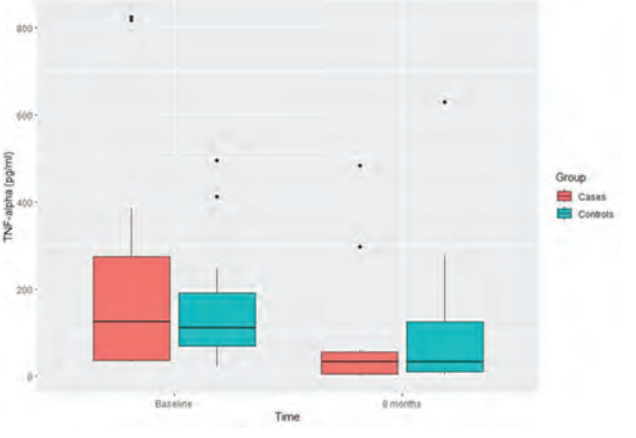
Results: The mean change in dialysate temperature from core body temperature was 0.90 ^{0}C in the cooled dialysate group. Cooled dialysate group had significantly lower intra-dialytic hypotension($p = 0.041$). There was a statistically higher level of IL-6 ($p < 0.05$) at baseline in the control group. However, at 8 months, the difference was insignificant($p>0.05$). There was no difference in TNF-α levels between both the groups at baseline and at 8 months post intervention($p>0.05$).

Conclusions: The use of a cooled dialysate did not significantly lower inflammatory marker level in ESKD patients, but was was significantly associated with lower intradialytic hypotension. We recommend a larger trial to confirm the effect of cooled dialysate on the inflammatory milieu.

Funding: Private Foundation Support



IL - 6 levels at baseline and after 8 months (pg/ml)



TNF-alpha levels at baseline and at 8 months (pg/ml)

PUB169

Distractions as Anxiolytics during Hemodialysis: A Pilot Study

Yash A. Patel, Sundus Sardar, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Background: In-center hemodialysis is an emotional burden for patients. While its correlation with fatigue and depression is well-documented, little research exists on its correlation with anxiety and on anxiolytic interventions. This study aims to determine how to better analyze the anxiolytic effects of distractions during hemodialysis.

Methods: Subjects were recruited at the Penn State Hershey Medical Center's Outpatient Dialysis Unit. After an hour of a self-selected activity during treatment, subjects completed the State-Trait Anxiety Inventory (STAI) to determine their state (situational) and trait (personal) anxiety levels. The STAI-provided norm table was used to assign percentiles to each subject. Subjects were then grouped by activity and a two-tailed analysis was performed to compare mean state and trait anxiety percentiles for each group.

Results: 14 out of 30 eligible individuals consented to the study. The average age was 57, and 2 subjects were older than the oldest age group (50-69) on the STAI norm table. 79% of subjects participated in a hobby. Average enjoyment was above 7/10 across all groups. No significant difference was found between mean state (s) and trait (t) anxiety percentiles in any of the 5 groups: TV/Radio (n=8, s=27.4%, t=36.6%, p=0.40), Social Media/Communication (n=2, s=48.5%, t=65.5%, p=0.70), Sleeping (n=2, 67.5%, t=53%, p=0.82), Games (n=1, s=33%, t=59%, N/A), or Reading (n=1, s=55%, t=59%, N/A).

Conclusions: This pilot study did not find significant changes to subjects' anxiety during hemodialysis with any of the above distractions but does elucidate considerations for future studies through its limitations. A multi-center interventional design would be more powerful and allow for analysis of less common distractions like reading. However, assigning interventions may blunt their anxiolytic effect, as subjects may perform activities they do not enjoy. Additionally, the STAI norm table excludes individuals older than 69, preventing accurate analysis for those patients. High school graduates struggled with the STAI vocabulary, and completion of a lengthy survey may alter anxiety levels and mask anxiolytic effects. Use of a custom inventory may therefore be preferable to the STAI. Through this study, it is evident a carefully tailored method is necessary to better understand anxiety and the anxiolytic effects of distractions during hemodialysis.

PUB170

Investigation of Core Symptoms during Hemodialysis Period in Chinese Middle-Aged and Young Patients on Maintenance Hemodialysis: A Network Analysis

Nina Zhang. *Department of Nursing, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Recent epidemiological studies have found that the population of young and middle-aged maintenance hemodialysis (MHD) survivors has gradually increased. MHD is one of the most important treatments for patients withend-stage renal disease. Due to renal dysfunction and long-term dialysis treatment, MHD patients are prone to various physiological and emotional symptoms, which seriously affect their quality of life. Network analysis is a new method for estimating and visualizing the structure and interaction of various symptoms of diseases. By identifying core and bridging symptoms, it helps to determine the key mechanisms of symptom occurrence and implement precise interventions for some key symptoms.

Methods: A convenience sampling method was used to collect information from 197 young and middle-aged patients at Shanghai Sixth People's Hospital between November 2023 and February 2024. Dialysis symptom index was used to investigate the prevalence and severity of 30 symptoms in MHD patients,and a symptom network model based on Fruchterman—Reingold algorithm was constructed to analyze the central indicators and deternfine the core symptoms and bridge symptoms.

Results: The top five commonly occurring symptoms were dry skin (73.92%), fatigue (70.6%), dry mouth (68.37%), waking up easily (67.82%) and difficulty in falling asleep (66.16%). The most severe symptoms were dry skin,followed by pruritus, fatigue, dry mouth and waking up easily. The symptom network analysis showed that dry skin was most strongly associated with pruritus (weight=0.67) among physiological symptoms,irritability was most strongly associated with anxiety (weight=0.32) among mood symptoms. The centrality index showed that the intensity of sadness was the most centrality (r_s=1.65) and was identified as the core symptom; fatigue had the highest mediation centrality (r_b=2.76) and irritability had the highest close centrality (r_c=1.45). Irritability,sadness,and inattention were identified as bridge symptoms,and their bridge centrality was 0.34,0.21,and 0.20.

Conclusions: Dry skin and sadness are respectively the most severe symptom and core symptom in Chinese middle-aged and young MHD patients,while irritability, sadness and in attention are the bridge symptoms. Medical staff can formulate precise interventions based on core symptoms and bridge symptoms to improve the level of symptom management.

PUB171

Association between Blood Pressure Variability and Prognosis in Diabetic Patients on Maintenance Haemodialysis

Siqi Peng, Shuangxin Liu. *Guangdong Provincial People's Hospital, Guangzhou, China.*

Background: Patients receiving dialysis who also have diabetes mellitus have high mortality. This study aimed to explore blood pressure variability (BPV) in diabetic patients treated with hemodialysis and analysis of prognosis.

Methods: This study retrospectively colected pre-dialysis and intra-dialysis blood pressure (BP) of maintenance hemodialysis (MHD) patients in the haemodialysis centre of Guangdong Provincial People's Hospital in March 2020. The patients were divided into diabetic and non-diabetic groups, and the differences in mean pre-dialysis and dialysis BP and BPV were compared between the two groups. They were also grouped according to whether they had diabetic kidney disease (DKD), whether they were taking antihypertensive drugs, and the absolute value of BP for subgroup analysis.BPV was expressed as the standard deviation (SD) and coeffi cient of variatioil (CV) of multiple BP readings and the average real variability (ARV). Survival analysis was performed using the multivariate Cox proportional hazard model, and Kaplan-Meyer survival analyses with log-rank tests were performed to show differences between groups.

Results: A total of 208 patients were included, of whom 81 had diabetes mellitus. Compared with the non-diabetic group, the diabetic group showed a non-significant difference in absolute BP levels, and greater SBP variability in both pre-dialysis and intra-dialysis. According to the Kaplan-Meier estimator, high SBP SD and CV in dialysis were associated with high all-cause mortality (log-rank 7.12, p = 0.008). Cox multivariate analysis also showed a significant association between diabetes combined with high SBP variability and all-cause mortality (HR 2.259; 95% CI 1.017 -5.018).

Conclusions: Compared with nondiabetic patients, SBP variability is higher in diabetic patients with MHD, both pre-dialysis and intra-dialysis. Diabetes mellitus combined with high dialysis BPV is independently associated with increased all-cause mortality.

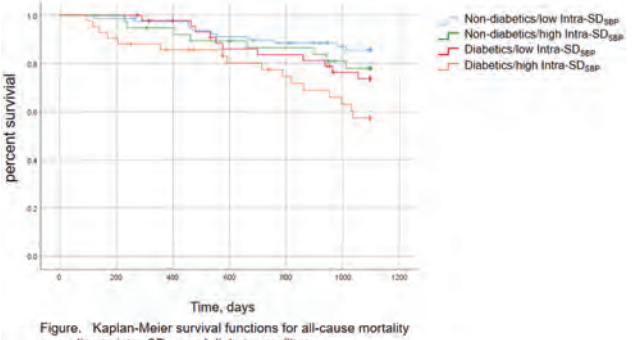


Figure. Kaplan-Meier survival functions for all-cause mortality according to intra-SD$_{SBP}$ and diabetes mellitus

PUB172

Prevalence of Hepatitis B Virus Antibody Levels Seroconversion in Patients on Hemodialysis: Mexican Cohort at Medica Santa Carmen

Sergio Hernández-Estrada, Alicia Pineirua, Edgar Solis, Juan M. Ardavin Ituarte. Medica Santa Carmen. *Médica Santa Carmen, Mexico City, Mexico.*

Background: Chronic Hemodialysis (HD) patients (px) are immunocompromised and hepatitis B virus (HBV) infection is a major concern due to increased susceptibility and poor vaccine response. Current recommendation related to HBV is to give vaccines during stage 5 in order to reach immunization and generate protective antibody levels of HBV (HbsAb). In Mexico, international HBV vaccination schedules for HD px are not necessarily accomplished (three double doses of 20 mcg/1ml for 6 months) and HbsAb are below what is desirable.

Methods: We reviewed 1,967 HD px in Medica Santa Carmen kidney network and the main objective was to analyze seroconversion status with HbsAb over 10 mUI/ml. Vaccination status was uncertain for most px. Median, interquartile range and proportions were estimated. We compared groups with Man-Whitney U-test and chi square test. A regression model adjusted for significant variables was performed.

Results: Seroconversion with HbsAb over 10 mUI/ml and 100 mUI/ml were 39% (760px) and 25% (487px) respectively. Comparative results by dividing HbsAb ≥10 vs HbsAb <10 mUI/ml groups are shown in the table. Significant differences were found in the HbsAb ≥10 mUI/ml group related to lower percentage of diabetes, hypertension, smoking and ischemic cardiopathy. In a multivariate analysis, age (OR 0.977, IC 0.970-0.984) and HD vintage (OR 1.004, IC 1.004-1.009) were statistically significant for seroconvertion status.

Conclusions: In Mexico, individuals with protective levels of HbsAb is scarce. Immunized against the HBV group had lower weight, BMI and higher Kt/v. Younger patients and vintage in HD are related to better chances of being immunized.

Funding: Clinical Revenue Support

N (%)	HbsAb <10 mUI/ml 1207 (61%)	HbsAb ≥10 mUI/ml 760 (39%)	*p value
Age	53 (39 - 64)	35 (30 - 50)	0.00
Male	693 (57.4)	430 (56.6)	0.72
HD vintage (months)	29.5 (17 - 59)	58 (24 - 86)	0.00
Diabetes	593 (50)	151 (20.1)	0.00
Smoking	202 (17)	92 (12.4)	0.00
Hypertension	1090 (91)	625 (83.4)	0.00
Ischemic cardiopathy	73 (6)	26 (3.5)	0.01
Social security	1010 (83.7)	716 (94.2)	0.00
Weight (kg)	66.8 (58.8-76.9)	62.4 (53.3-72.8)	0.00
BMI	26.15 (23.2-29.7)	24.3 (21.8-27.8)	0.00
KT/V	1.30 (1.15-1.49)	1.35 (1.17-1.53)	0.01
Hemoglobin (g/dl)	10.3 (9.2-11.6)	10.4 (9.2-11.6)	0.34
Albumin (g/dl)	4.16 (3.92-4.38)	4.27 (4.02-4.48)	0.00
Phosphorus (mg/dl)	4.84 (3.76-6.05)	4.85 (3.61-6.28)	0.89
Leukocytes (10^9/L)	5.86 (4.78-7.06)	5.45 (4.51-6.62)	0.00
Potassium (mEq/l)	5.32 (4.83-5.87)	5.35 (4.91-5.80)	0.47

* Non parametric U Mann Whitney and Chi2 test, respectively

Variable	OR (IC 95%)	p value
Age	0.977 (0.970 - 0.984)	0.0001
HD vintage (months)	1.007 (1.004 - 1.009)	0.0001
Generalized linear model adjusted for smoking, hypertension, DM, ischemic cardiopathy, social security, BMI, Weight, Kt/v, albumin, leukocytes		

PUB173

Joint Modeling of Longitudinal Ferritin Trajectories and COVID-19 Infections in Native American, Hispanic, and White Patients on Hemodialysis

Mingzhao Hu,[1] Talia Quandelacy,[3] Yuedong Wang,[2] Peter Kotanko,[5] Baqiyyah Conway.[3,4] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]University of California Santa Barbara, Santa Barbara, CA; [3]University of Colorado Anschutz Medical Campus, Aurora, CO; [4]The American Academy of Epidemiology, Inc., Tyler, TX; [5]Renal Research Institute, New York, NY.*

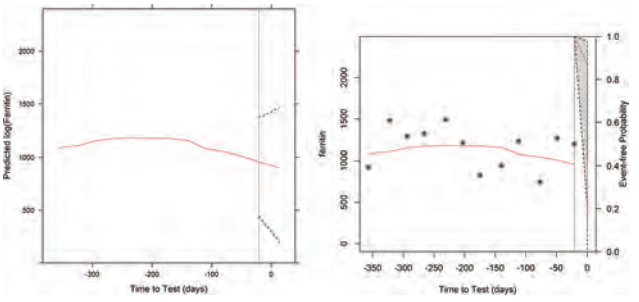
Background: American Indians/Alaska Natives (AIAN) and Hispanic individuals in the U.S. are overrepresented in the hemodialysis (HD) population and were hardest hit by COVID-19. Early in the pandemic, hyperferritinemia was linked to COVID-19 infections. Joint modeling learns from both longitudinal and time-to-event data for predictive accuracy and dynamic estimation. We investigated the predictive utility of ferritin w/ COVID-19 infection in a cohort of AIAN, Hispanic and White HD patients.

Methods: We followed 2,242 HD patients from 1/2020 to 3/2022. Baseline ferritin was the average between days 365 and 14 till COVID-19 diagnosis (day 0). In non-infected control, a random date matching the distribution of diagnosis dates was chosen as the "test date". Longitudinal ferritin trajectories were modeled with a linear mixed effects model and COVID-19 infection with a Cox model. A joint model linked these to measure the association between COVID-19 infection and ferritin.

Results: Cumulative COVID-19 incidence was 36%. In exploring ferritin's link with potential confounders, the longitudinal submodel coefficients highlighted age had a strong positive link while albumin, creatinine, hemoglobin and WBCs were not linked. The joint model revealed a marginal association between ferritin and infection risk (HR = 1.001, $p < 0.001$). Males had lower COVID-19 risks while diabetes was not linked. AIAN patients had almost twice the risk of White patients (HR = 1.948, $p < 0.001$) while Hispanics also had higher risk than White (HR = 1.328, $p < 0.001$). Vaccination greatly reduced the risk (HR < 0.001, $p < 0.001$).

Conclusions: Joint modeling indicated a weak link of ferritin with COVID-19 infection, however, dynamic predictions via joint models did not strongly support early detection via ferritin alone. AIAN and Hispanic patients had higher infection risk than White patients, while vaccination nearly eliminated the risk.

Funding: Other NIH Support - Funding Disclosure: This research, "Hyperferritinemia, COVID-19 Prediction, and Prognosis in Native American and Hispanic Dialysis Patients" [1OT2OD032581-02-300], was funded by the National Institutes of Health (NIH) Agreement No. 1OT2OD032581-02. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the NIH.



Dynamic prediction for a typical patient. Left: Longitudinal. Right: Survival.

PUB174

User-Friendly Features of Moda-flx Show High Usability Success Rates

Stephanie Wall, Nicholas Hyun, Vitas B, Emiline Victoria Hernandez, Clayton Poppe, Osman Khawar. *Diality, Inc., Irvine, CA.*

Background: The Moda-flx Hemodialysis System™ prioritizes user-friendliness, safety, and connectivity, aiming to enhance the dialysis experience for users. By incorporating features such as automatic priming, Bluetooth connectivity for blood pressure monitoring, and automatic saline bolus delivery during treatment and rinseback, Diality aims to enhance usability and patient outcomes, thereby affirming the company's dedication to patient-centric innovation in renal care.

Methods: Three simulated-use formative usability studies and a summative usability study involving Certified Clinical Hemodialysis Technicians and Nephrology Nurses as representative users were used for data collection. Tasks were tailored to match the operational requirements of the Moda-flx Hemodialysis System™, prioritizing scenario-driven interactions to provide users with genuine, real-world experiences.

Results: Nine Nephrology nurses and six Certified Clinical Hemodialysis Technicians from diverse backgrounds participated in a simulated-use summative usability study. They received three hours of training in small groups, including presentations and hands-on sessions, with a minimum 1-hour decay period before evaluation. The study showed a remarkable 98.33% success rate across 285 tasks related to the discussed user-friendly features, affirming their ease of use.

Conclusions: The Moda-flx Hemodialysis System, designed with a focus on user-friendliness, represents a significant advancement in renal care. By incorporating features such as automatic priming, Bluetooth-enabled blood pressure connectivity and monitoring, automatic saline bolus delivery during treatment and at rinseback features, Diality aims to enhance patient comfort and treatment adherence. The study's impressive 98.33% success rate across 285 tasks validates the effectiveness of these user-friendly enhancementsand reinforces Diality's commitment to patient-centric innovation in dialysis device design.

Funding: Commercial Support - Diality

Outcome Distribution of Moda-Flx User-Friendly Features

User-Friendly Feature	Tasks Completed Successfully	Tasks Completed Successfully with Difficulty	Close Call	Use Error	Overall Success Rate
Heparin Pump	111	3	4	2	98.33%
Saline Administration	59	0	0	1	98.33%
Priming/Self-Test	43	2	0	0	100%
Blood Pressure	58	0	0	2	96.67%
Totals	271	5	4	5	98.33%

PUB175

Prolonged Intermittent Kidney Replacement Therapy in the Intensive Care Unit: A Single-Center Experience

Deepak Chandramohan,[1] Calvin C. Baker,[1] Katrina Eggleston,[2] Javier A. Neyra,[1] Ashita J. Tolwani,[1] Yan Lu.[1] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]DaVita Inc, Denver, CO.*

Background: Prolonged intermittent renal replacement therapy (PIRRT) is a viable RRT option for critically ill hemodynamically unstable patients. Herein, we report a single-center experience of PIRRT delivery to critically ill adults in the ICU.

Methods: This retrospective observational case-series study included non-surgical critically ill adults admitted to the ICU at an acute care hospital affiliated with the University of Alabama at Birmingham. This hospital offers only PIRRT (not CRRT) through the Tablo® Hemodialysis System to ICU patients. We analyzed 38 PIRRT treatments from 15 patients between August 2022 and January 2024. Treatments were administered with a blood flow rate of 150-300 ml/min and a dialysate flow rate of 100 ml/min. No protocol anticoagulation was utilized, but systemic anticoagulation was used if medically indicated. The primary process endpoint was premature filter clotting, defined as clotting of the filter before completion of treatment, and the secondary endpoint was the full treatment completion rate without interruptions.

Results: The median age was 55 years(IQ1-IQ3: 43-79); 46.7% were men, 66.6% Black and 73.3% had AKI. 93.3% were on vasopressors, 66.6% on mechanical ventilation, and 53.3% had septic shock. The median Sequential Organ Failure Assessment (SOFA) score was 12 (10-13), and the median Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 25 (22-29). The dialysis catheter was placed in the internal jugular vein in 66.6% of instances and the femoral vein in 33.3%. The median blood flow rate was 250 ml/min (233.2-250), and the dialysate flow rate was 100ml/min for all treatments. Patients received a median of 2 (1-3) treatments. The median individual treatment duration was 8 hours(6-10). Premature filter clotting occurred in 9 out of 38 treatments (23.6%), and the time to filter clotting was 5.4 hours (3.5-7.6). The treatment completion rate was 94.5% (77-100). The mortality rate was 33.3%; and 40% of patients were transferred to an academic quaternary center for medical and surgical procedures, while 13.3% were transferred to be started on CRRT.

Conclusions: While the provision of PIRRT without protocol anticoagulation to critically ill adults requiring RRT is safe and feasible, about one of four treatments had premature clotting.

PUB176

Outcome of Peripheral Arterial Disease in Patients with ESKD on Hemodialysis

Ashraf O. Oweis,[1] Sameeha A. Alshelleh.[2] *[1]Jordan University of Science and Technology Faculty of Medicine, Irbid, Jordan; [2]The University of Jordan, Amman, Jordan.*

Background: Patients on hemodialysis are at higher risk for cardiovascular complications due to increased risk of atherosclerosis. This has been associated with higher morbidity and mortality rates. Peripheral arterial disease (PAD) is an important complication of atherosclerosis that is manifested significantly in these patients. However, it has not been extensively studied in our region.

Methods: A retrospective analysis was performed from the years 2010- 2021. ESRD patients that were diagnosed with PAD during this period were studied, diagnosis was done through CT- Angiography. Predefined end points were death and amputation

Results: The mean age for the patients was 65.9 (SD± 12.96). Most patients were either with DM (84.6%) or HTN (91%). The prevalence of amputation was 44.7%, using univariate analysis DM was a strong predictor for amputation (P=0.001) as long as coronary artery disease (P=0.001). On multivariate analysis only DM (P=0.003) was associated with higher prevalence of amputation Time to death was 16.9 months (SD±25.6), 11.3 months (SD±9.1) for patients with amputation vs. 21.1 (SD±32.7) for those without amputation

Conclusions: End stage renal disease patients with PVD especially with PVD have higher mortality and majority are diabetic which necessitate earlier recognition of PVD and modified risk factors like better control of DM and its complications in addition to other risk factors like HTN, dyslipidemia and metabolic disorders of CKD.

Table 2: Univariate and multivariate analysis for mortality or need for amputation

	Univariate analysis				Multivariate analysis			
	Amputation		Death		Amputation		Death	
Variable		P value		P value		P value		P value
Age, mean (±SD)	65.8 (12.1)	0.7	69.2(11.2)	**0.04**	65.8 (12.1)	0.83	69.2(11.2	0.28
DM	44.7%	**0.001**	41%	**0.002**	44.7%	**0.003**	41%	0.12
HTN	40.8%	0.66	44.2%	**0.007**	40.8%	0.97	44.2%	0.19
CAD	23.7%	**0.001**	28.6%	0.58	23.7%	0.49	28.6%	0.22
CHF	17.8%	0.86	28%	0,90	17.8%	0.32	28%	0.05
Atrial fibrillation	5.4%	0.81	6.8%	0.86	5.4%	0.90	6.8%	0.93
Stroke	6.8%	0.16	14.7%	**0.002**	6.8%	0.25	14.7%	0.11
Dyslipidemia	28.8%	0.95	30.1%	0.85	28.8%	0.50	30.1%	0.92

PUB177

Factors Associated with Adherence to Antihypertensive Treatment and Complications Due to Inadequate Adherence in Patients Undergoing Hemodialysis at the Hospital Regional Puebla ISSSTE

Sergio V. Pérez Reyes, Alexis Perez Reyes, Maria J. Gonzalez Farris, Kriscia M. Hernandez, José L. Gálvez-Romero, Brenda Lima. *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico.*

Background: Poor medication adherence hampers hypertension control and increases the risk of adverse health outcomes. Medication adherence can be measured with direct and indirect methods. In México not exist any study to evaluate the medication adherence in patiens under hemodialysis. For this is important to assess Mexican hypertensive patients' adherence rate to hypertension therapeutic regimen and to identify the strongest predictors of adherence rate among such patients.

Methods: A descriptive comparison design and convenience sampling were used. The sample comprised 113 participants who came to their regular sessions at hemodialysis in a ISSSTE hospital. The Hill-Bone Compliance to High Blood Pressure Therapy Scale indirectly assesses adherence to hypertension therapy in three behavioral domains: appointment keeping, diet and medication adherence. Secondary objectives to evaluate if there is a relationship between adherence to treatment and years on hemodialysis, levels of urea, potassium, creatinine, albumin and ferritin.

Results: 113 patients were evaluated, of which 54 were women and 59 men. The length of stay on hemodialysis was from 1 to 12 years. 89.4% have been on hemodialysis for less than 6 years.85.8% of patients obtained a good adherence result.14.2% of patients have moderate-poor adherence to antihypertensive treatment. We found that albumin levels above 3.5 g/dl were correlated with better adherence to pharmacological treatment ($p \leq .0405$). During the time of patient evaluation, 5 deaths were reported, all belonging to the group with poor adherence to pharmacological treatment.

Conclusions: This is the first study to be include hemodialysis patients in Mexico. Adherence to taking antihypertensive medications was good overall among the study participants; these participants, however, they agreed to have a high consumption of table salt and forget to take their medication at least once a week. The HBCHBPT Scale has high versatility globally and has been used in various settings by various healthcare worker cadres and researchers. The scale has several strengths, including high adherence phenotyping capabilities, contributing to the paradigm shift toward personalized health care.

Funding: Government Support - Non-U.S.

PUB178

Electrocardiographic (ECG) Changes and Asymptomatic Cardiac Arrhythmias in Patients with Chronic Kidney Failure on Hemodialysis

Alondra J. Quesnel Samperio,[1] Paola Gomez-Aviles,[1] Armando Castillo García,[1] Aranza García,[2] Marianela Rodney,[3] Ivana A. Rosales Stevenson,[1] Marco E. Bello,[2] Mario Jimenez Hernandez.[2,1] *[1]Universidad de las Americas Puebla, Cholula, Mexico; [2]Unidad de Nefrologia, Hospital Universitario, BUAP, Puebla, Mexico; [3]Instituto Cardiorenal de Puebla, Puebla, Mexico.*

Background: Chronic kidney disease (CKD) is a current public health problem that has increased over the years. In Mexico, the incidence and prevalence of types of arrhythmias in CKD patients undergoing hemodialysis have not been studied, nor have risk factors associated with their development been identified. The objective of this study was to determine the frequency of arrhythmias in patients with CKD undergoing hemodialysis and to evaluate their overall health status to identify risk factors associated with the development of these electrocardiographic changes both before and after hemodialysis.

Methods: A descriptive, observational, prospective study was conducted at Hospital Universitario Puebla from May 2023 to April 2024. A systematic search identified 58 CKD patients undergoing hemodialysis. Clinical, laboratory, and pre- and post-hemodialysis electrocardiogram data were collected.

Results: The analysis included 58 patients with a mean age of 63.75 years; 51.72% were male. The most common arrhythmias were atrioventricular block (10.3%), bundle branch block (9.5%), prolonged QT interval (9.5%), and sinus bradycardia (8.6%). Older age groups were more predisposed to prolonged QT interval, while younger age groups had a higher prevalence of atrioventricular block. A history of heart disease and kidney disease secondary to diabetic nephropathy were associated as risk factors (p=0.03). The presence of arterial hypertension was not identified as a risk factor (p=0.65).

Conclusions: Atrioventricular block was the most common arrhythmia in hemodialysis patients. The types of arrhythmias observed in our CKD population were not as prevalent as reported in other populations.

AGE	First degree atriovent ricular Block	Prolonged QT interval	Sinus Bradycardia	Right Bundle Branch Block	Extrasystoles	Atrial Fibrillation	Sinus Tachycardia
(26 - 49)	1	0	0	1	0	0	0
(50 - 59)	1	1	0	1	1	0	0
(59 - 62)	2	1	0	0	1	0	1
(63 - 66)	0	1	1	0	1	1	0
(66 - 67)	0	0	1	0	0	0	0
(68 - 71)	2	1	2	0	0	0	0
(72 - 77)	1	1	1	1	0	0	0
(77 - 89)	0	2	0	1	0	0	0

Table 1. Arrhythmia relationship with patient age.

PUB179

An Underrecognized Cause of Unexplained High Anion Gap Metabolic Acidosis on Continuous Kidney Replacement Therapy: A Case Series of Euglycemic Ketoacidosis

Htun M. Aung,[1] Aye M. Thida,[2] Anjali Acharya.[1,3] *[1]New York City Health and Hospitals Jacobi, Bronx, NY; [2]SUNY Downstate Health Sciences University, Brooklyn, NY; [3]Albert Einstein College of Medicine, Bronx, NY.*

Introduction: Euglycemic ketoacidosis (EKA) on continuous renal replacement therapy (CRRT) first appeared in the literature in 2018 after Coutrot et al. described 18 patients (15%) who developed EKA on CRRT using a glucose-free solution. Subsequently, in 2020, Sriperumbuduri et al. proposed pathophysiologic mechanisms of EKA on CRRT as 1) glucose losses from CRRT with glucose-free solutions; 2) compromised caloric intake; and 3) stress of critical illness. These conditions create a state of low-insulin, high-glucagon levels, leading to increased lipolysis and ketogenesis causing ketoacidosis, while on the other hand, causing increased glycogenolysis and gluconeogenesis to maintain euglycemia. However, the EKA on CRRT is still under-recognized at the provider level.

Case Description: We present the clinical characteristics of 3 patients who developed euglycemic ketoacidosis on continuous renal replacement therapy (Table 1). Case 1: A 79-year-old female had a history of chronic kidney disease (CKD) stage 3A, hypertension (HTN), diabetes mellitus type 2 (DM-2), and heart failure with reduced ejection fraction (HFrEF). Case 2: An 82-year-old male had a history of CKD stage 2, HTN, DM-2, adenocarcinoma of colon, and HFrEF. Case 3: A 73-year-old male had a history of CKD stage 5, HTN, DM-2, and HFrEF.

Discussion: Providers should consider EKA as one of the differential diagnoses of high anion-gap metabolic acidosis when evaluating a patient on CRRT, especially using a glucose-free solution. The beta-hydroxybutyrate test is easily available in most laboratories, and once the diagnosis of EKA is made, management is feasible and could potentially avoid catastrophic complications.

Table 1: Clinical Characteristics of Patients

	Case 1	Case 2	Case 3
Age (years) and sex	79. Female	82. Male	73. Male
Diabetes mellitus type and HbA1c	Type 2. 5.4 %	Type 2. 7.1%	Type 2. 8.5%
Diabetes medications	Metformin	Metformin	Glipizide
Baseline serum creatinine (mg/dL)	1.2	0.8	7
Admission diagnosis	Heart failure exacerbation	Septic shock	Heart failure exacerbation
At the time of diagnosis of euglycemic ketoacidosis			
BUN (mg/dL)	14	38	26
Creatinine (mg/dL)	0.7	1	2.2
CO2 (mEq/L)	16.8	11.2	14.8
Albumin-corrected anion gap (mEq/L)	21.4	28.6	26.4
Lactate (mmol/L)	1.1	1.6	1.4
Glucose (mg/dL)	160	166	178
Beta-hydroxybutyrate (mmol/L)	4.09	>8	5.25
Vasopressor(s)	Yes	Yes	Yes
Use of glucose-free solution	Yes	Yes	Yes
Time from continuous renal replacement therapy start to the diagnosis of euglycemic ketoacidosis (hours)	91	99	100
Intervention to euglycemic ketoacidosis	Insulin + D5W	Oral feed	D10W
Time from diagnosis to resolution of euglycemic ketoacidosis after intervention (hours)	60	72	48
ICU length of stay (days)	8	17	17
Outcomes	Expired	Survived	Survived

PUB180

Recanalization of Filter-Bearing Inferior Vena Cava Occlusion: Management Conundrum

Ivana Boktor,[1] Ahmed E. Ali,[2] Rakesh K. Varma,[3] Ammar Almehmi.[4] *[1]George Walton Comprehensive High School, Marietta, GA; [2]Mayo Foundation for Medical Education and Research, Rochester, MN; [3]The University of Texas Southwestern Medical Center, Dallas, TX; [4]The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: Central venous occlusion is a common complication of long-term hemodialysis catheters that is detrimental to vascular access survival. Occlusion of filter-bearing inferior vena cava (IVC) in dialysis population is life-threatening and often challenging to treat. We report unusual case of a patient with complicated dialysis access history who became catheter-dependent via right femoral vein and presented with total occlusion of IVC below the filter level.

Case Description: A 47-year-old female on chronic hemodialysis presented with poor functioning of her right femoral dialysis permanent catheter. Past medical history was remarkable for end-stage kidney disease 1996 due to pre-eclampsia, systemic lupus erythematosus, multiple deep venous thromboses that required IVC filter placement and chronic oral anticoagulation. After failing peritoneal dialysis and multiple dialysis accesses, she became catheter-dependent via right femoral vein. Notably, she was off dialysis 2009-2015 after receiving kidney transplant. During this admission, a venogram through the existing catheter demonstrated complete occlusion of IVC accompanied by extensive collateralization (Fig 1-a). After removing the catheter over the wire, supra-renal IVC was recanalized using stiff guidewire and Kumpe catheter under fluoroscopy guidance. This was followed by sequential balloon angioplasty of the occluded IVC and stent deployment extending from the inferior cavoatrial junction to the superior margin of the IVC filter. Final angiogram demonstrated a wide patent IVC with brisk blood flow into the right atrium (Fig1-b). Dialysis therapy was resumed immediately after intervention and the catheter remains functioning up till now.

Discussion: Treatment of filter-bearing IVC occlusions in dialysis population poses specific technical challenges. Recanalization of these occlusions, such as in our case, is vital, especially among those who exhausted dialysis access options and are not candidates for other treatment modalities such as transplant and peritoneal dialysis.

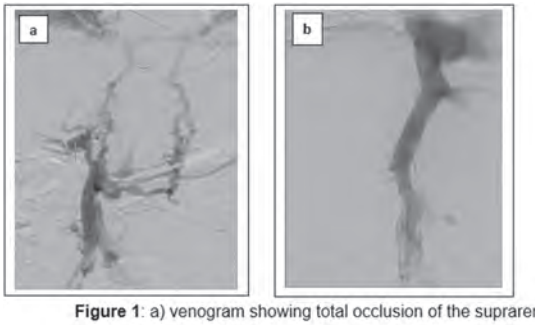


Figure 1: a) venogram showing total occlusion of the suprarenal IVC vein. b) venogram showing patent IVC after stenting and angioplasty.

PUB181

Successful Use of Droxidopa to Treat Intractable Hypotension Attributed to Vasodilatory Shock Due to Autonomic Failure in a Patient with ESKD Who Is Dependent on Continuous Kidney Replacement Therapy

Ramanath B. Dukkipati, Yasemin B. Balin, Anuja P. Shah, Tiane Dai. *Harbor-UCLA Medical Center, Torrance, CA.*

Introduction: Droxidopa is a synthetic amino acid precursor, which acts as a prodrug to the neurotransmitter norepinephrine. It is used to treat neurogenic orthostatic hypotension caused by primary autonomic failure. The goal of our use of Droxidopa is to remove dependence on vasopressors in a patient who was receiving CRRT, as he was deemed unstable to transition to intermittent hemodialysis (iHD).

Case Description: 61-year-old male patient, who has End Stage Kidney Disease, was admitted with hypotension(blood pressure 84/64 mmHg) and no cause of hypotension could be detected after extensive work-up. Primary autonomic failure (vasodilatory shock) was diagnosed based on exclusion of other causes of shock and therefore as receiving vasopressors and CRRT (continuous renal replacement therapy) as a renal replacement therapy. Many attempts and interventions (including midodrine 20 mg three times a day use) to wean off vasopressors and transition to intermittent hemodialysis were not successful over two months. We initiated Droxidopa at 100 mg three times a day in this patient and titrated the dose. We saw that once Droxidopa was initiated in our patient, vasopressors could be weaned off in 48 hours and we could transition to intermittent hemodialysis (as blood pressure improved to 109/75 mmHg) with no requirement of any vasopressors. During the period of initiation and use of Droxidopa no other interventions were made which led us to firmly believe that Droxidopa was the intervention that

treated our patient. No adverse reactions were observed. Droxidopa use (vs. non-use) was associated with successful weaning of vasopressors and transition to Hemodialysis from CRRT.

Discussion: In a patient with intractable hypotension who therefore required being in the ICU to receive CRRT for many months, initiation and titration of Droxidopa successfully made the transition from CRRT to iHD with no further dependence on vasopressors. Droxidopa can be used to treat severe vasoppressors requiring neurogenic orthostatic hypotension caused by primary autonomic failure in Dialysis patients.

PUB182

High Prevalence of Obstructive Sleep Apnoea among Patients with ESKD on Haemodialysis in India

Arghya Majumdar. *Manipal Hospital, Dhakuria, Kolkata, India.*

Background: Patients with end- stage kidney disease (ESKD) may be affected with sleep disorders like insomnia, obstructive sleep apnoea (OSA), hypoventilation, central sleep apnoea, central disorders of hypersomnolence, circadian rhythm sleep–wake disorders, parasomnias and restless legs syndrome. OSA needs special mention as CKD is a comorbidity of OSA and contributes to the course of OSA. The objective of this study was to delineate the prevalence of OSA in ESKD patients on hemodialysis (HD) in India and to document the comorbidities in these patients, which might have an association with OSA.

Methods: The study was a descriptive study with cross- sectional design conducted on 75 patients more than 18 years of age, with CKD stage 5 on MHD attending the Haemodialysis center of a tertiary care hospital in Kolkata, India. Stratified sampling was used and a pre-designed and pre-tested semi-structured schedule was used to collect data. The statistical software SPSS 20 was used for the analysis

Results: The mean age of the 75 patients studied, was 62 years, of whom 57% were male. The prevalence of OSA was 65.3%, of whom 42.7% had moderate and 22.6 % had mild disease. The median Apnoea Hypopnoea Index (AHI) was 15. A statistically significant association was observed between AHI score and Body Mass Index (BMI), alcoholism, hypertension, chronic liver disease, frequency of dialysis per week**,** magnesium levels and ejection fraction. Binary logistic regression of factors showed a statistically significant association with BMI (p=0.000, 95% CI=1.304-2.067) and reduced ejection fraction (p=0.017, 95% CI=0.019-0.682).

Conclusions: A high prevalence of OSA was noted in ESKD patients on maintenance hemodialysis in India. The patients tended to be obese. A high level of awareness and regular screening is mandated in this patient population to diagnose these cases early so that the quality of life, morbidity and mortality can be improved with CPAP therapy.

PUB183

A Curious Case of Dialysis-Associated Reaction

Omar Dodin, Sreelakshmi Ravula, Nadia M. Alqurini. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Hemodialysis is a renal replacement therapy where the patient's blood comes in contact with different membranes. This may trigger a cascade of inflammatory responses leading to dialyzer reactions, broadly classified into types A (IgE mediated) and B (complement mediated). Symptoms range from mild itching to dyspnea, hypotension and cardiac arrest.

Case Description: Our case is a 53 years old female with Hx of ESRD from DM. She was switched from peritoneal dialysis due to delayed abdominal wound healing. She was tolerating her treatments well without complications. She presented with low back pain and fever and was found to have Tunneled dialysis catheter associated Staph epidermidis bacteremia and was admitted to ICU for septic shock. CRRT was provided (NXstage machine/gamma sterilized polyether sulfone membrane). As she became hemodynamically stable, dialysis was attempted using Optiflux F160NR single use dialyzer (an ebeam sterilized polysulfone membrane). Within the first few minutes, she developed dyspnea and hypotension requiring prompt cessation of hemodialysis. Dialyzer reaction was suspected. For her second session the filter was prerinsed using sterile normal saline. She tolerated well for the first hour but then developed the same symptoms again. Ultrafiltration was attempted at a rate of 2.5ml/kg/hr which was lower than 10ml/kg/hr ultrafiltration while on CRRT. Her workup showed normal cardiac function, no pericardial effusion and no pulmonary embolism. For her third session, we premedicated her with methyl prednisone, diphenhydramine, and famotidine one hour prior to dialysis. She did not develop symptoms. She received 9 hemodialysis sessions during her hospital course which she tolerated well without complaints. No similar events were recorded in other patients in the unit. We couldn't reuse filters or obtain a different type per institution policy.

Discussion: Our patient's recurring symptoms of dyspnea and hemodynamic instability while receiving intermittent hemodialysis were suggestive of allergic reaction. Cardiac, volume, sepsis, Medication side effects and related etiologies were ruled out. Resolution of her symptoms only after premedicating her with steroids, H1 and H2 antagonists confirmed our suspicions. Dialysis reactions are rare but can cause life-threatening complications and nephrologists need to have a high index of clinical suspicion for timely diagnosis and treatment.

PUB184

Triglyceride and Glucose Index as a Predictor of Adverse Cardiovascular Events in Patients on Hemodialysis

Dae Kyu Kim,[1] Seok hui Kang,[3] Hyun Kyu Kim,[1] Jeong-Yeun Lee,[1] Soo-Young Yoon,[1] Jin Sug Kim,[1] Yang Gyun Kim,[2] Ju young Moon,[2] Kyunghwan Jeong,[1] Sangho Lee,[2] Hyeon Seok Hwang.[1] K-cohort Study Group. *[1]Kyung Hee University Medical Center, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [3]Yeungnam University Medical Center, Daegu, Republic of Korea.*

Background: The triglyceride and glucose (TyG) index have recently been established as an indicator of insulin resistance, which has the predictive values for cardiovascular (CV) disease. However, the clinical significance of the TyG index in hemodialysis (HD) patients remains unknown.

Methods: A total of 759 patients were enrolled in a prospective multicenter K-cohort from June 2016 to December 2023. The TyG index and echocardiographic parameters were examined at baseline. Circulating endostatin and VAP-1 were measured as vascular injury markers. The primary endpoint was defined as atherosclerotic CV events, cardiac events, and all-cause death.

Results: TyG index were positively correlated with circulating endostatin ($\rho = 0.134$, $P = 0.025$) and vascular adhesion protein-1 level ($\rho = 0.130$, $P = 0.012$). However, TyG index was not significantly correlated with left ventricular systolic and diastolic function, and left ventricular mass index. Patients in tertile 3 of the TyG index showed the highest cumulative event rate of CV events ($P < 0.001$) and cardiac events ($P = 0.001$). In multivariate Cox regression analysis, patients in tertile 3 of the TyG index were significantly associated with a 2.43-fold increased risk of CV events [95% confidence interval (CI) 1.32 – 4.47] and a 2.14-fold increased risk of cardiac events (95% CI 1.27 – 3.61) compared to patients in tertile 1 of the TyG index. However, patient mortality rate did not differ between the TyG index tertiles.

Conclusions: The TyG index was positively correlate with vascular injury markers, and significantly associated with increased risk of atherosclerotic CV events in HD patients. Our study suggests that the TyG index is useful to identify HD patients at high risk of atherosclerotic CV events.

PUB185

Falls in Hemodialysis Centers

Elhadi A. Eltayeb.[1,2] *[1]North Riyadh Hemodialysis Center, Riyadh, Saudi Arabia; [2]King Abdelaziz Medical City, Riyadh, Saudi Arabia.*

Background: 25% of dialysis population fall every year; the outpatient HD center is a particularly high risk- location for falls this is attributed to high prevalence of old age and comorbidities, HD treatment related complications, and frailty. Falls remain a significant cause of morbidity and mortality and contribute to a substantial burden to annual health care costs. A serious fall injury can precipitate functional decline, loss of independence, nursing home placement, and death.

Methods: North Riyadh hemodialysis center is outpatient dialysis facility which looks after 300 hemodialysis patient. We noted on our hemodialysis patients increasing number of falls occurred at the community level. We extended our routine falls screening tool to assess the frequency and outcomes of out of center falls over twelve months' period. Our falls screening tools document type of injuries sustained, hospital admission and also include measures to reduce impact and risk of falls.

Results: The majority of reported falls occurred at out of center (**Fig 1**). Out of center falls are common in males (**64%**), elderly patients (**47%**), patients with multiple comorbidities, frailty, hemodialysis vintage >5 yrs. (**50%**), previous falls, and polypharmacy. Majority of patients sustained soft tissue injuries (**45%**), fractures (**14%),** and head injuries (**14%**). 21 of patients required hospital admission. On further follow up **12%** of patients died of other medical causes.

Conclusions: Falls among prevalent hemodialysis population are under reported, On our HD population the majority of falls taking place at the community level. Identifying patient with high risk of falls may result in measures to reduce the impact on this vulnerable hemodialysis population. We recommend outpatient falls screen tools to record falls at the community level and have protocols on falls prevention including mulitargeted multidisciplinary approach, staffand patient education are important in prevention and reducing impact of falls

PUB186

Five-Year Mortality Outcomes of High-Volume Hemodiafiltration in Mexico: Insights from Real-World Data

Salvador L. Gil, Alfredo Fuentes Mercado, Erika E. Jaime Borja, Victor H. Gomez Johnson, Magdalena Madero. *Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico*.

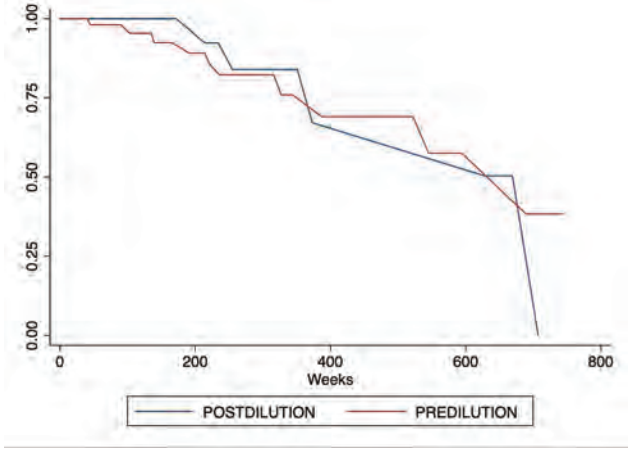
Background: High volume hemodiafiltration (HDF) offers significant benefits for patients undergoing renal replacement therapy. The objective of this study is to evaluate real world data and assess mortality between pre and post dilutional HDF modalities.

Methods: In this observational, cross-sectional, retrospective study we analyzed all prescribed sessions over a 5-year period in our HDF clinic to evaluate overall mortality rates and assess mortality differences between pre- and post-dilutional HDF modalities. The statistical analysis was made using mortality rates and Mantel-Cox test.

Results: 89 patients of whom 66.3% were female were included with a total of 26,047 HDF sessions over the past five years. During the study period, outcomes included 16 deaths, 23 kidney transplants, 5 peritoneal dialysis transition, 1 loss to follow-up, and 2 cases of kidney function recovery. The distribution of vascular access types revealed 59 tunneled catheters, 10 non-tunneled catheters, and 20 arteriovenous fistulas. Patients were further categorized based on HDF modality (table 1.) Mortality rates demonstrated no significant differences between the two HDF modalities, yielding an overall mortality rate of 0.8 per 1,000 population—0.7 for pre-dilution HDF and 0.8 for post-dilution HDF (*logrank*: 0.9785).

Conclusions: No mortality differences were found between pre and post dilutional OL- HDF. Larger studies are warranted to confirm our findings.

	HDF postdilutional n=60	HDF predilutional n=29	p-value
Age (y)	39.5 (31-54.5)	35 (28-46)	0.11
Length of session (min)	187 (184-194)	187 (183-197)	0.84
Etiology Diabetic Kidney Disease n(%)	10 (16.6)	1 (3.4)	0.20
Unknown etiology n (%)	21 (35)	11 (37.9)	0.20
Other n (%)	29 (48.3)	17 (58.6)	0.20
Convective volume (L)	24.8 (23.7-26)	39.9 (33-46.3)	≤0.001
Ultrafiltration rate (ml/kg/hr)	11.5 ± 3.3	11.3 ± 3.5	0.65
Blood flow (ml/min)	389 (373-404)	394 (382-404)	0.59



PUB187

Misleading Dialysate Discoloration after Vitamin B12 Infusion: A Case Report

Niloufar Ebrahimi, Sayna Norouzi, Amir Abdi Pour. *Loma Linda University Medical Center, Loma Linda, CA.*

Introduction: Hemodialysis (HD) blood leaks through the dialyzer, may lead to hemolysis, and blood loss and potentially cause hemorrhagic shock in patients undergoing HD. A semipermeable membrane separates blood from the dialysate in the HD machine circuit. An alarm is triggered when blood leaks through the dialyzer membrane and blood flow ceases. Vitamin B12 is easily removed by HD and may appear in the dialysate, causing a red discoloration. Consequently, the dialysate color change can falsely trigger the dialysis machine's blood leak alarm.

Case Description: A 75-year-old Hispanic male with a history of type 2 diabetes mellitus, hypertension, chronic kidney disease stage 3, and chronic systolic heart failure was admitted with acute respiratory failure due to fluid overload. His hospitalization course was complicated by cardiac tamponade, cardiogenic shock, upper gastrointestinal bleeding, and oliguric acute kidney injury requiring dialysis. The patient was initially started on continuous renal replacement therapy (CRRT) and, upon hemodynamic status improvement, was transitioned to intermittent HD. The patient had received a vitamin B12 infusion while in shock, which triggered a false blood leak alarm on the HD machine in two separate sessions. HD was terminated, and a dialysate test confirmed no evidence of blood. The serum vitamin B12 was measured > 2000 pg/mL. The patient remained in kidney failure, necessitating dialysis; therefore, CRRT was resumed with red-color effluent (Figure 1).

Discussion: The dialysate outflow line sensors on HD machines are designed to detect blood, reducing the risk of potential complications from a blood leak. False blood alarms may occur due to non-blood contaminants. Administering high doses of vitamin B12 can trigger blood leak alarms, leading to dialysis treatment termination.

CRRT red-colored effluent

PUB188

Exploring Adequacy Parameters and Survival Patterns in a Brazilian Cohort Undergoing Hemodiafiltration

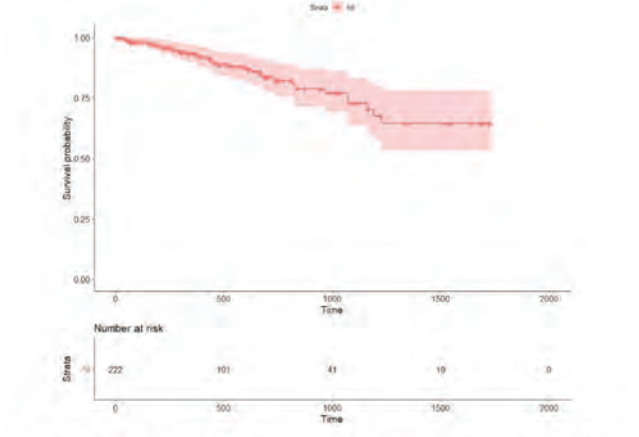
Érica P. Rocha, Christiane Kojima, Daniel M. Costa, Andréa O. Magalhães, Tales D. Vieira, Luis Gustavo Modelli de Andrade, Carolina S. Martins. Nefrostar Kidney Care. *Universidade Estadual Paulista Julio de Mesquita Filho, Botucatu, Brazil.*

Background: Recent evidence suggests a survival benefit of hemodiafiltration compared to conventional hemodialysis. We aimed to analyze the baseline characteristics and survival patterns among patients undergoing hemodiafiltration in a real-world scenario.

Methods: We included a cohort of patients undergoing hemodiafiltration therapy at the NefroStar clinics, ranging from October 2018 to May 2023. We retrieved baseline patient characteristics, the dialysis access method, monthly biochemical exams classified in Kidney Disease Outcomes Quality Initiative (KDOQI) bundles, hospitalization rate, and the follow-up data.

Results: We analyzed a cohort of 223 patients who exclusively underwent hemodiafiltration. The mean convective volume was 67±30 liters per week. The majority of patients achieved the KDOQI-recommended bundles, ranging from 70% for phosphorus to 87% for potassium. The majority of hospitalizations were attributed to vascular access complications, ranging from 2.4% to 15.9%, followed by cardiovascular issues (5.3% to 9.9%) and clinical hospitalization (1.4% to 8.4%). The incidence of catheter-related bloodstream infectious density ranged from 0.02 to 0.1 per 1000 catheters per day. Univariate Kaplan-Meier analysis revealed survival rates for hemodiafiltration at 180 days, with a rate of 93% (90 – 97%), at 730 days, a rate of 83% (77-90%), and at 1095 days, a rate of 73% (63-83%).

Conclusions: We showed significantly lower rates of hospitalization, fewer catheter-related bloodstream infections, and reduced mortality in a real-world cohort of hemodiafiltration patients. These factors warrant further in-depth investigation, particularly with the aim of mitigating mortality rates in the Brazilian dialysis population.



Kaplan-Meier Survival Analysis in a Cohort of Patients exclusively Treated with Hemodiafiltration in Brazil.

264x222mm (96 x 96 DPI)

PUB189

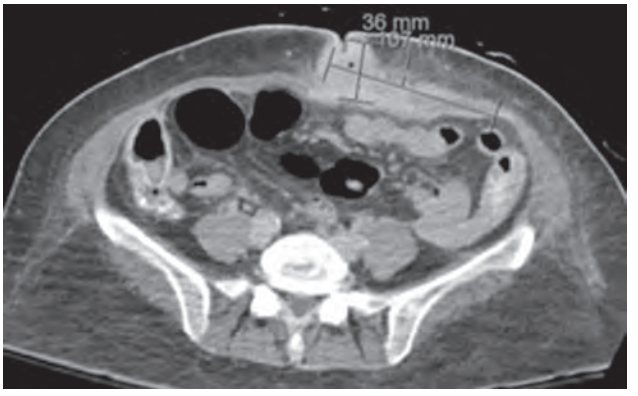
Cat-Induced Pasteurella Peritonitis in a Patient on Peritoneal Dialysis

Matthew Knapp, Shivangi Patel. *Morristown Medical Center, Morristown, NJ.*

Introduction: *Pasteurella multocida* remains a rare, but established cause of peritonitis in peritoneal dialysis (PD) patients.

Case Description: Here we present a 79-year-old female with a medical history of coronary artery disease and end stage renal disease secondary to diabetes mellitus and hypertension, on chronic PD. She presented to her nephrology clinic with fevers and chills and reported that her kitten had chewed through her PD catheter during her overnight PD session. Intraperitoneal ceftazidime was initiated and peritoneal fluid cultures were drawn, which would later reveal *Pasteurella multocida*. Initial CT imaging was unremarkable. Oral levofloxacin was added to her antibiotic regimen. Her symptoms developed into pain and induration around the catheter site. She was hospitalized for IV ceftriaxone and PD catheter removal, and then transitioned to oral cefdinir. Despite this therapy, interval CT findings [Figure] suggested abscess formation along the catheter tract. IV ceftriaxone was restarted and a percutaneous drainage catheter was placed with successful evacuation of the collection. Blood and peritoneal cultures remained negative. She was discharged on 10 days of oral cefixime, recovered well and has since had a new PD catheter placed.

Discussion: *Pasteurella* is a gram-negative coccobacilli that is a common inhabitant of the upper airways of healthy pets, such as cats and dogs. Transmission occurs through biting, scratching, or other contact with nasopharyngeal secretions. Pasteurellosis generally features soft tissue or lower respiratory tract infections, both of which may progress to abscess formation. Given that Pasteurella is isolated from approximately 75% of cat-inflicted wounds, and the bacterium's prevalence in household pets, this case underscores the duty of the clinician to inform the patient of risk factors and adequate preventative measures, such as catheter site protection. Additionally, our case suggests that prolonged IV antibiotics may be necessary when intraabdominal pathology is identified to prevent abscess formation.



PUB190

Influence of Variable Inflow Volume, Dwell Duration, and Dialysate Glucose Concentration on Ultrafiltration Volume in Patients on Automated Peritoneal Dialysis: pPD Study

Tatiana De los Ríos,[1] Isabel Garcia,[2] Jana Schmitt,[1] Manuela Stauss-Grabo,[1] Saynab Atiye.[1] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Hospital Universitario Son Espases, Palma, Spain.*

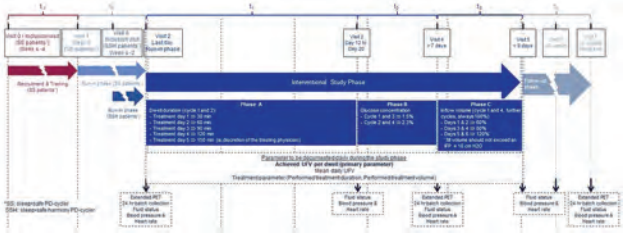
Background: In current practice, optimization of peritoneal dialysis (PD) prescription relies heavily on clinical techniques and a trial-and-error process, as prescription must be tailored to achieve a number of outcome goals, given the peritoneal membrane transport characteristics of the patient. So far, developments in practice have made important contributions to the notion of precision PD (pPD). Given the many demands of a PD prescription, ultimately, pPD refers to the process of finding the optimal profile of PD treatment that fits the patient's lifestyle while maintaining homeostasis. The pPD study is designed to investigate the influence of 'dialysis dose variables' (dwell duration, glucose concentration, inflow volume) on ultrafiltration volume per defined dwells in automated peritoneal dialysis (APD) patients.

Methods: This is a prospective, multicenter, interventional pilot study. Ten patients with total weekly Kt/V ≥ 1.7 and treated with the sleep safe or sleep safe harmony PD-cycler (Fresenius Medical Care, Bad Homburg, Germany) will be included. After a training phase and a run-in period of up to 6 weeks, depending on the PD cycler used prior to the study, the interventional phase will be initiated. The interventional phase has 3 subphases; in each of them, one of three 'dialysis dose variables' will be varied: dwell duration (phase A), glucose concentration (phase B), and inflow volume (phase C). This will be followed by a follow-up period of 4 weeks (see figure).

Results: Due to the small sample size, statistical analyses will comprise descriptive statistics and hypothesis testing using non-parametric tests where appropriate.

Conclusions: In this study, dose variables will be evaluated over a wide range, to become part of the clinical toolbox not only for delivering optimal treatment but as a method for peritoneal membrane function assessment. This study aims to collect additional diagnostic information while making repeated observations in the same patient during which the PD prescription undergoes systematic adaptations.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH



PUB191

Systolic Blood Pressure (SBP) and Risk of Mortality in Patients on Maintenance Peritoneal Dialysis (PD): A Systematic Review and Meta-Analysis

Viangkaeo Lee,[1] Haleh Siami,[1,2] Vanessa-Giselle Peschard,[1] Mohsen Malekinejad,[1] Emily X. Huang,[1,3] Peggy Tahir,[1] Chi-yuan Hsu.[1] *[1]University of California San Francisco, San Francisco, CA; [2]Islamic Azad University, Tehran, Islamic Republic of Iran; [3]Bates College, Lewiston, ME.*

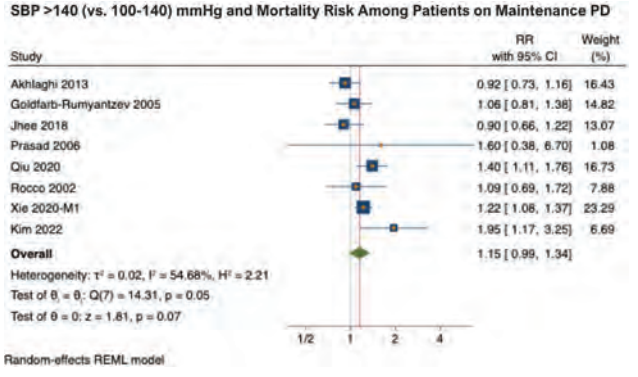
Background: A great deal of uncertainty exists regarding management of hypertension among maintenance PD patients. The International Society for Peritoneal Dialysis (ISPD) recommends targeting SBP <140 mmHg based on "very low" quality evidence. Recognizing the lack of randomized controlled trials, we conducted a systematic review of observational studies to examine the association between SBP and all-cause mortality.

Methods: We searched PubMed, Web of Science, Embase, CINAHL and Cochrane Library databases up to April 2023 and abstracts from the 2019-2023 ASN, ISN, and NKF meetings followed by dual study screening and data extraction. We included patients on any non-acute PD types regardless of kidney failure cause. We defined SBP 100-140 mmHg as reference, pre-specified decision rules to group data for pooling, and combined data to estimate pooled risk ratios (RR) using random-effects models.

Results: Of 3,546 peer-reviewed records, 28 full-text studies and 1 abstract were eligible (and 1 conference abstract). Out of eight assessed bias domains, most studies had issues with comparability of the BP groups and the incomplete capture of prognostic factors. Based on one-time baseline measurement (i.e. not time-updated), SBP >140 (vs. 100-140) mmHg was associated with a 15% increase in risk of all-cause mortality (RR=1.15; 95%CI: 0.99-1.34) (Figure). SBP <100 (vs. 100-140) mmHg was associated with even higher risk (RR=1.79; 1.38-2.32). Similar results were seen in sensitivity analyses. There was high degree of heterogeneity across all meta-analyses (I^2 range: 54-88%).

Conclusions: The existing epidemiologic literature provides limited guidance due to a high degree of heterogeneity and concerns regarding bias. But it does lend some support to the current ISPD guideline targeting SBP <140 mmHg. SBP <100 mmHg is associated with highest risk of death, but that is not a plausible consideration as a treatment target.

Funding: NIDDK Support, Private Foundation Support



PUB192

The "Silent" Threat: Group G Streptococcus Peritonitis in Peritoneal Dialysis

Lucinda Lau,[1] Stefano Benincasa,[1] Rachel S. Nash.[1,2] *[1]Rowan University Cooper Medical School, Camden, NJ; [2]Cooper University Health Care, Camden, NJ.*

Introduction: Peritoneal dialysis (PD) is a therapy for patients with end-stage renal disease (ESRD). PD carries an increased risk of peritonitis, often secondary to poor technique. A small subset of patients may present with "silent" peritonitis, or peritonitis in the absence of fever and abdominal pain, making diagnosis and treatment challenging. Identification of a causative organism can be an added barrier further delaying care.

Case Description: A 95-year-old female with a history of ESRD on PD presented with two days of progressive fatigue, confusion, and lower leg pain and swelling. On exam, a shallow, ulcerated wound with purulent drainage was found on the left lateral leg. Laboratory testing was significant for leukocytosis and group G streptococcus (GGS) grown on blood cultures. Treatment with vancomycin and ceftriaxone did not yield significant improvement, prompting investigation of PD dialysate as a potential source. The patient was afebrile with persistent leukocytosis and no clinical signs of peritonitis. Peritoneal fluid analysis revealed increased cellularity with neutrophilic predominance suggesting peritonitis despite negative cultures. Intraperitoneal ceftriaxone and prophylactic fluconazole were added to the patient's nightly PD dwell. Repeat blood and PD fluid cultures were negative. However, the patient was ultimately transitioned to comfort measures before passing shortly thereafter.

Discussion: Commonly, PD peritonitis is caused by gram positive organisms, such as Staphylococcus and Streptococcus species, with the ability to create biofilms on nonbiologic surfaces. GGS is a rare cause of peritonitis, more commonly present on the skin and in the urogenital and gastrointestinal tracts. Still, research investigating its effect on the presentation of peritonitis is sparse. It is important to remain cognizant of PD peritonitis in patients receiving PD therapy even in the absence of classic symptomatology. Risk factors such as advanced age, dementia, altered mentation from sepsis, or uncommon organisms may create an atypical presentation, delaying diagnosis and treatment. High rates of morbidity in peritonitis with concomitant bacteremia make early treatment even more crucial.

PUB193

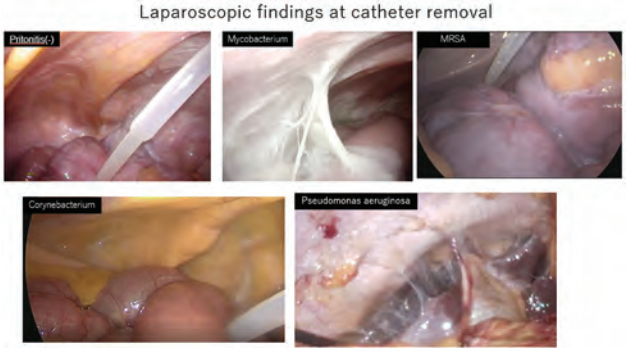
Report of Laparoscopic Findings of PD Catheter Replacement after Catheter Removal Due to Refractory Peritonitis in Patients on PD

Hiroaki Io,[1] Hiroyuki Iwasaki,[1] Toshiki Kano,[1] Kunimi Maeda,[1] Yusuke Suzuki.[2] *[1]Juntendo University Nerima Hospital, Nephrology & Blood Purification Center, Tokyo, Japan; [2]Juntendo University Faculty of Medicine, Tokyo, Japan.*

Introduction: There are no reports of laparoscopic findings in peritoneal dialysis (PD)-related peritonitis. We have previously reported laparoscopic imaging findings at the end of PD (KI Reports 2016, Nephrology 2023), and repeated peritonitis is a risk factor for peritoneal degeneration (Semin Dial 2020).

Case Description: We investigated laparoscopic findings observed during catheter removal and re-placement for intractable peritonitis at our hospital. Intraperitoneal findings were variable. In cases of Mycobacterium/MRSA, strong pseudo membrane formation and adhesions were observed, and differences in localization and severity were observed. In all cases several years had passed without complications of encysted peritoneal sclerosis. In the case of Corynebacterium, there was almost no evidence of inflammatory changes in the abdominal cavity, and PD was reintroduced 2 months later. In the case of Pseudomonas aeruginosa, there were strong signs of intraperitoneal adhesions and fibrin occlusion, which led to the removal of the PD catheter. Three years later, due to the patient's strong desire to restart PD, laparoscopic observation showed that the adhesions were improving over time and were easy to remove with forceps, so PD was reintroduced. However, due to insufficient water removal, the patient was used in PD+HD combination therapy.

Discussion: Although it is difficult to infer the intraperitoneal cavity from clinical findings, we believe that the decision to re-place a PD catheter should be made carefully in cases of peritonitis that exhibit strong inflammatory changes, especially Pseudomonas aeruginosa. Laparoscopic findings at the time of PD catheter removal in patients with refractory peritonitis may be helpful in evaluating the possibility of restarting PD.



PUB194

Peritoneal Dialysis in Developmental Disability

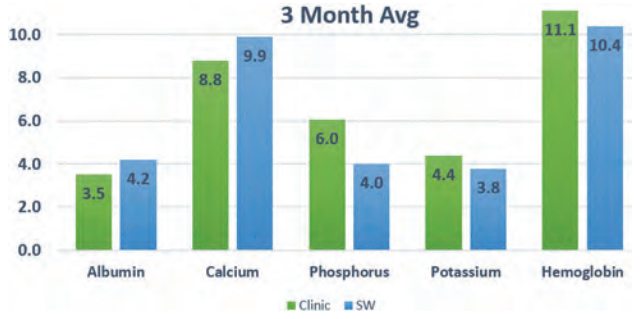
Stacey Rall, Amy Peregord, Catherine M. Poslaiko, Tracey A. Doss-Simmons, Rachel L. Perlman. Canton PD Unit. *University of Michigan Michigan Medicine, Ann Arbor, MI.*

Introduction: Although not well described, peritoneal dialysis (PD) should be considered for adults patients who cannot participate in their own care. SW is a 30 yo with renal dysplasia and significant developmental disabilities (dd) due to cerebral palsy. We present our experiences as an interdisciplinary team managing SW's care with the goal of increasing provider confidence in providing PD to patients with significant dd.

Case Description: Social Work: SW is minimally verbal, requires a wheelchair and is totally dependent on her parents. Her cognitive disability impacts her ability to express what she is feeling or experiencing, even to her parents. MD: We were concerned about how SW would tolerate PD and how we would assess her well-being. Catheter was placed in the OR with careful attention to exit site location based on her kyphoscoliosis, incontinence, and need to avoid her pulling on it. SW typically sleeps well and we use a cycler program for safety and simplicity. She has had no peritonitis over 3 years. RN: Visits require parent involvement and 2-3 staff for blood draws. Care has become routine and works smoothly at home and clinic. We had initial concerns but have seen her thrive and travel with family. Dietitian: Nutrition challenges have included selective eating and

meeting calorie needs. Interventions include a focused, liberalized diet and powdered phosphate binders. SW has stable weight and routine labs are favorable compared to our clinic and KDOQI guidelines (see table). Parents: We were responsible for making decisions for our daughter, we could not engage her in the process, and we could not agree on a course of action. We were paralyzed with fear because it seemed like PD required specialized training. We found a clinic that was warm, welcoming and had a very "can do" attitude. Our daughter has now been on PD for 3 years. At every turn, we have felt supported by the clinic staff.

Discussion: Take aways: Interdisciplinary collaboration, including with parents, has enabled successful PD. We modified some practices to meet SW's needs, but caring for her is not disruptive to our clinic.



PUB195

Clinical Performance of the Therapy Option FlexPoint (Flexible Volume and Dwell Time Management) of the PD Cycler Sleep Safe Harmony

Jana Schmitt,[1] Maite Rivera Gorrin,[2] Tatiana De los Ríos,[1] Manuela Stauss-Grabo.[1]
[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Hospital Universitario Ramon y Cajal, Madrid, Spain.

Background: While adequate removal of fluid, uremic toxins and sodium may be regarded as cornerstones of clinical homeostasis, modern peritoneal dialysis (PD) therapy should ideally deliver also on a number of other fronts that relate to lifestyle and quality of life. FlexPoint therapy option – flexible volume and dwell time management – of the Fresenius PD cycler sleep safe harmony allows to shorten cycle phases where no effective dialysis takes place without compromising patient's comfort and dialysis targets. The prescribed therapy is automatically adjusted within defined, medically acceptable limits for residual volume, inflow volume, dwell duration, as part of flexible management, without triggering alarms. In addition to medically reasonable default values, physicians can adapt the limit values for the individual options to the patient.

Methods: The study (NCT06390592) is an interventional, randomized, crossover trial designed to evaluate whether usage of the therapy option FlexPoint influences the efficacy of APD treatments, by assessing total Kt/V, mean daily ultrafiltration, as well as the hydration status of PD patients. During the six-week clinical phase 24 patients are continuously treated with the sleep safe harmony PD-cycler according to their prescription. The clinical phase is divided into 3 study phases of 2 weeks each which only differ in the FlexPoint settings. The patient's treatment during the clinical phase will follow a randomized scheme of treatment sequences using a Williams 6*3 cross-over design. To evaluate patient perspectives, questionnaires on quality of life and sleep are completed. Patient-reported outcomes and clinical data are recorded at baseline and the end of the second treatment week during the clinical phase.

Results: For primary analysis, three pairwise comparisons between the treatment settings will be performed to assess equivalence with respect to total Kt/V. All secondary efficacy and safety variables are summarized descriptively by treatment setting and where appropriate also for pairwise treatment differences.

Conclusions: The study aims to demonstrate that individualized volume and dwell time management during the treatment does not influence the PD treatment efficacy but improves the patient's well-being.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH

PUB196

Gastrointestinal Manifestations of Long-Term Effects after COVID-19 Infection in Patients on Peritoneal Dialysis: A Single-Center Observational Study

Zhen Zhuang, Yuehong Li, Mingxia Cao, Wen Wen. *Beijing Tsinghua Changgung Hospital, Beijing, China.*

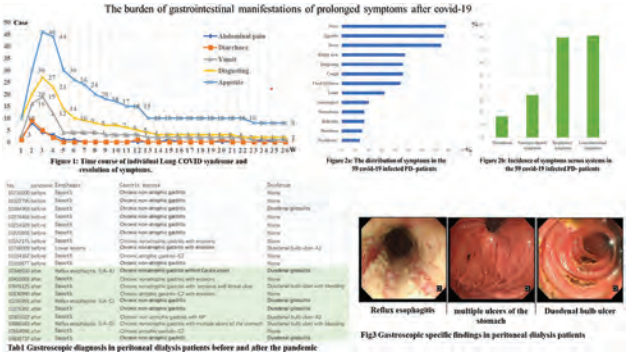
Background: Long-term symptoms of peritoneal dialysis patients after COVID-19 infection, especially gastrointestinal (GI) symptoms, may be a potential risk factor for long-term prognosis of peritoneal dialysis patients.

Methods: A retrospective analysis was conducted on peritoneal dialysis patients who were regularly followed up at the peritoneal dialysis center from January 2020 to July 2023. Clinical and laboratory examination data were collected for analysis. The occurrence and severity of gastrointestinal symptoms after COVID-19 infection were evaluated by questionnaires using the gastrointestinal symptom rating scale (GSRS). A total of 20 patients underwent gastroscopy.

Results: 1. A total of 67 patients were included. 59 patients (88.1%) were found to be positive for the COVID-19 virus. Gastrointestinal symptoms were observed in 81.4% of cases (Fig 2). Gastrointestinal symptoms were noted to appear later but had a longer duration (Fig 1). 2. It was summarized that 10 patients in each of group (before and after the epidemic, time node 2022/12/01) completed gastroscopy. None of them had serious complications such as bleeding and peritonitis. Pations in the post-epidemic group had more gastrointestinal symptoms and more positive findings under gastroscopy (Chart 1 and 2). There were more complex and higher-grade lesions under gastroscopy in this group (Tab 1) (Fig 3). 3. It was found that Pations in the post-epidemic group had a higher history of taking hormones or NSAIDs drugs, lower plasma albumin and serum sodium levels, and higher CRP (Tab 2).

Conclusions: The gastrointestinal symptoms are more common in patients with peritoneal dialysis after COVID-19 infection, including reflux esophagitis and peptic ulcer. The symptoms of long COVID after the epidemic are related to the nutritional and inflammatory status of patients. Gastroscopy is of great significance in diagnosing gastrointestinal diseases in PD patients.

Funding: Government Support - Non-U.S.



PUB197

Concordance between Dialysate-to-Plasma (D/P) Ratios for Urea and Creatinine in Peritoneal Equilibration Testing: A Retrospective Observational Cohort Study

Lohith S. Chatragadda,[1] Susie L. Hu,[2] Ankur Shah.[2] *[1]University of Rhode Island, Kingston, RI; [2]Brown University Warren Alpert Medical School, Providence, RI.*

Background: Peritoneal equilibration testing (PET) is a crucial tool for assessing peritoneal membrane function in patients undergoing peritoneal dialysis (PD). The dialysate-to-plasma (D/P) ratios of urea and creatinine are commonly used to evaluate peritoneal transport characteristics. This study aimed to assess the concordance between D/P Glucose and D/P creatinine in PET and identify factors associated with discordance.

Methods: A retrospective observational cohort study was conducted using data from PD patients who underwent PET between 1/1/2015 and 12/31/2021 at a single PD center. Demographic, clinical, and PET data were collected from electronic medical records. Concordance between D/P urea and D/P creatinine was assessed using the spearman rank correlation coefficient.

Results: A total of 67 PD patients (mean age: 54.5±2.1 years; 40.3% male) were included in the study. The mean 4 hour D/P glucose and D/P creatinine were 0.78±0.02 and 0.37±0.05, respectively. Spearmans rho between 2h and 4h Glucose was .9058 and Spearmans rho between 2h and 4h Creatinine was .8713. Discordance between 4h glucose and 4h creatinine was observed in 20 (29.8%) patients. Spearmans rho between D/P glucose and D/P creatinine was 0.79. In discordant pairs, 4h creatinine was better correlated than 4h glucose with 4h UF (rho .23 vs .19).

Conclusions: In this retrospective observational cohort study, we found a strong correlation between D/P glucose and D/P creatinine in peritoneal equilibration testing (PET) among peritoneal dialysis (PD) patients. The high Spearman's rho values between the 2-hour and 4-hour measurements for both glucose and creatinine suggest that these markers provide consistent information about peritoneal transport characteristics over time. However, discordance between 4-hour D/P glucose and 4-hour D/P creatinine was observed in nearly 30% of patients. This finding highlights the potential limitations of relying on a single marker to assess peritoneal membrane function. In cases of discordance, 4-hour D/P creatinine showed a slightly stronger correlation with 4-hour ultrafiltration compared to 4-hour D/P glucose, suggesting that creatinine may be a more reliable indicator of peritoneal transport when the two markers are discordant.

PUB198

Refined Management of Serum Potassium Is Necessary in Patients on Peritoneal Dialysis

Mingxia Cao, Yuehong Li, Zhen Zhuang. *Beijing Tsinghua Changgung Hospital, Beijing, China.*

Background: Chronic renal failure is a high risk factor for hyperkalemia but is generally considered to be rare in peritoneal dialysis patients.

Methods: 86 patients with peritoneal dialysis who were followed up regularly every month in the outpatient clinic from January 2022 to February 2023 were selected as the research subjects and followed up for one year. Collect general data such as gender, age, dialysis age, primary disease, weight, blood pressure, urine output, etc. Dialysis data: peritoneal dialysis method, whether the abdomen is persistent, treatment volume, ultrafiltration volume, Kt/v, Ccr, etc; biochemical indicators : Hemoglobin, parathyroid hormone, NT-proBNP, albumin, blood sugar, calcium, phosphorus, potassium, sodium, chlorine, carbon dioxide, etc.

Results: 1. There were 48 patients with CAPD and 38 patients with APD. There were no statistics on weight, age, kt/v, diastolic blood pressure, hemoglobin, parathyroid hormone, BNP, albumin, blood sugar, calcium, potassium, chloride, and carbon dioxide between the two groups (Tab1). 2. The incidence of hyperkalemia was 12.98%, if the threshold for diagnosing hyperkalemia defined as K>5.0 mmol/l (2.33% K≥5.5mmol/L) (Fig1). 62.5% of patients with hyperkalemia relapse within one year (Fig2). 3. There were 50 patients dwell abdomen. The occurrence of hyperkalemia was related to dry abdomen (P=0.031). (Tab2)

Conclusions: The study found that peritoneal dialysis patients are also a high-risk group for hyperkalemia, especially those with poor residual renal function or dry abdomen. The threshold for diagnosing hyperkalemia defined as K>5.0 mmol/l, which significantly improves the diagnostic efficiency of hyperkalemia. We can detect the risk of hyperkalemia early, avoid recurrence of hyperkalemia, and reduce the risk of cardiovascular mortality in patients with peritoneal dialysis.

	dry(n=36)	dwell(n=50)	P
weight	71.33±13.96	67.31±11.46	0.147
age	66.22±8.55	57.46±16.41	0.004
dialysisage	12.53±9.17	21.9±17.35	0.004
ktv	1.77±0.42	1.64±0.49	0.177
Ccr	73.33±21.26	62.43±24.73	0.036
urine	0.89±0.51	0.48±0.45	<0.01
filling	7.2±1.87	8.63±1.47	<0.01
UF	0.53±0.52	0.64±0.5	0.306
systolic	141.64±13.19	136.28±15.77	0.1
diastolic	79.31±9.2	79.4±9.6	0.964
HGB	118.11±15.49	115.78±16.66	0.512
IPTH	189.91±140.59	221.31±138.6	0.306
BNP	7544.78±9380.78	11974.64±19689.44	0.215
ALB	35.14±3.76	37.08±4.34	0.033
Glu	8.51±4.4	7.42±3.2	0.19
Ca	2.19±0.15	2.29±0.16	0.004
P	1.79±0.35	1.83±0.61	0.704
K	4.62±0.66	4.2±0.59	0.002
Na	140.47±3.25	140.09±2.64	0.555
Cl	101.41±4.09	98.75±3.6	0.002
C02	24.66±3.17	26.36±3.01	0.014

PUB199

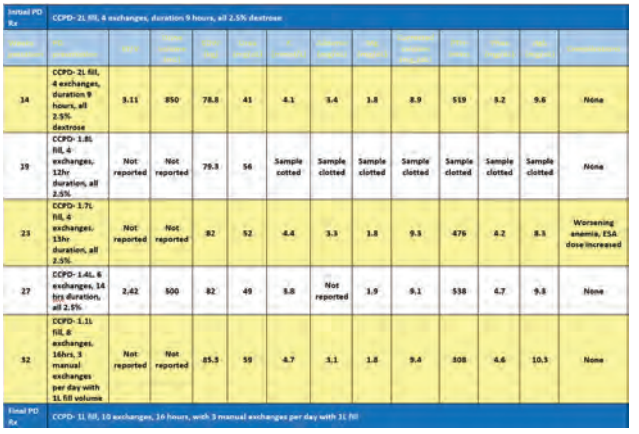
A Case of Persevering on Peritoneal Dialysis through Pregnancy

Farah Abifaraj,[1] Elias C. Ghandour,[2,3] Bernard G. Jaar.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]MedStar Good Samaritan Hospital, Baltimore, MD; [3]MedStar Union Memorial Hospital, Baltimore, MD.*

Introduction: Hemodialysis (HD) is often the preferred modality in pregnancy as patients undergoing PD have been found to be less likely to deliver successfully, historically. There have also been concerns over difficulty achieving necessary clearance with peritoneal dialysis as a pregnancy progresses, resulting in various possible maternal and/or fetal complications.

Case Description: We present a case of a patient with end stage renal disease due to biopsy proven class IV lupus nephritis on continuous cyclic peritoneal dialysis (CCPD) who was maintained on PD throughout her pregnancy. She required careful lab monitoring and frequent prescription adjustment to maintain adequate clearance throughout her pregnancy. She went into labor spontaneously at 33 weeks and had an uncomplicated vaginal delivery.

Discussion: With close monitoring, and careful adjustment of the dialysis prescription and a patient's willingness to adjust to the changing and intensifying prescription, PD can be safely maintained throughout a pregnancy.



PUB200

Frequency of Routine Blood Work among Patients on Chronic Dialysis: A Narrative Review

Alessandro Cau,[1] Rajinder SIngh,[1,2] Adeera Levin.[1,3] British Columbia Renal Agency. *[1]The University of British Columbia, Vancouver, BC, Canada; [2]Vancouver General Hospital, Vancouver, BC, Canada; [3]Saint Paul's Hospital, Vancouver, BC, Canada.*

Background: Home dialysis patients, including both those on hemodialysis and peritoneal dialysis, undergo monthly blood testing to identify and correct harmful laboratory abnormalities such as hyperkalemia and assess for dialysis adequacy. The frequency and utility of testing, however, is not supported by available evidence and is largely based on historical practice and expert consensus. While early identification and correction of critical laboratory values may theoretically lead to improved clinical outcomes, unnecessary testing has implications on patient quality of life, practitioner workload, use of healthcare resources and the environment. Frequent monitoring of a highly variable laboratory value (i.e., phosphate) will lead to over- or under-treatment where no outcome data exists.

Methods: PubMed search identified literature on blood work frequency amongst dialysis patients of any modality. Search strategy included keywords related to blood work, lab work, frequency, and dialysis modalities. Separate searches were also performed to identify studies addressing a similar question in patients with other chronic diseases such as kidney transplant recipients and diabetes. Reference lists of relevant studies were also screened. Studies were included if they were relevant to our population of interest and addressed either the evidence behind or consequences of routine monthly blood work.

Results: Overall, there are no randomized controlled studies on this topic to date. There were four observational studies comparing outcomes between in-centre hemodialysis patients undergoing monthly blood work and those receiving less frequent blood work. Of those four studies, two were conducted in Canada, one in Lebanon and one in Korea. There were no studies of patients on home dialysis including peritoneal dialysis or hemodialysis.

Conclusions: There is a paucity of evidence underpinning monthly routine lab testing among home dialysis patients. Furthermore, there is little available evidence to suggest that it is unsafe to undergo less frequent testing. More high-level evidence is needed to inform an appropriate testing frequency in these patients which in turn, has the potential to transform care at the patient, provider, system, and planetary levels.

PUB201

Analysis of Anemia Management Protocol in Home Dialysis

Paul W. Davis, David Ramirez, Elsa Olson, Andrea G. Kattah. *Mayo Clinic Minnesota, Rochester, MN*.

Background: Anemia is a common complication of chronic kidney disease with multiple possible etiologies and management options. Given the prevalence of anemia within patients on dialysis, diagnosis and management can be burdensome with a significant impact to quality of care. To provide safe and effective care for patients on dialysis, many in-center dialysis units utilize nursing protocols for managing anemia with success. The objective was to assess the effectiveness of a similar protocol for home dialysis patients.

Methods: An anemia management protocol outlining decisions for identifying home dialysis patients with anemia and assessing for need of intravenous iron repletion and/or erythrocyte stimulating agents (ESA) was implemented on 5/1/2022. Patient data were assessed for effects on hemoglobin, ferritin, and transferrin saturation (TSAT) before and after the date of implementation. ESA drugs were mailed from a central pharmacy and iron was repletion was given either at home or at an infusion center for peritoneal dialysis (PD).

Results: A cohort of 133 home dialysis patients, encompassing both PD and home hemodialysis (HHD), was analyzed from 5/1/2022 to 5/31/2023. The median hemoglobin levels were 10.5 g/dL (IQR: 9.7-11.3) prior to protocol implementation and 10.5 g/dL (IQR: 9.7-11.5) post-implementation; p-value 0.56. Median ferritin levels increased from 405 ng/mL (IQR: 237-610) pre-implementation to 424 ng/mL (IQR: 263-737) post-implementation; p-value 0.19. Median transferrin saturation (TSAT) rose from 28% (IQR: 20.5-36) to 30% (IQR: 24-38); p-value 0.11. Among patients receiving erythropoiesis-stimulating agents (ESAs), the incidence of hemoglobin values exceeding 12 g/dL decreased from 28 cases pre-implementation to 12 cases post-implementation.

Conclusions: Overall, it appears that implementation of anemia management protocol was at least as effective as solely provider directed management. There was a trend toward fewer episodes of Hb > 12 mg/dL which could represent lower exposure to ESAs. Other potential benefits of such a protocol include reduced provider burden and reduced unit cost and improved patient safety with lower ESA exposure and fewer blood transfusions; however, further analysis and studies are needed to elucidate statistically significant results and other impacts, including implementation of newer agents such as hypoxia-inducible factor prolyl hydroxylase Inhibitors.

PUB202

The Impact of Urgent-Start Peritoneal Dialysis on Related Peritonitis, Mechanical Complications, and Hospitalization Rate in Qatar

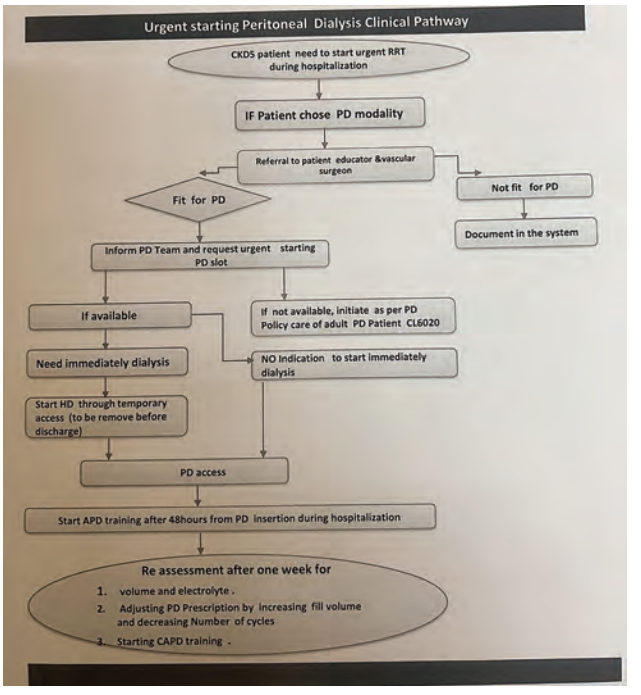
Mohammed E. Hussain, Mohamad M. Alkadi, Hanaa Ahmed, Sahar Aly, Reyrita Katrina P. Tariga, Michelle cruz Futotana, Thoraya A. Alabdulla, Abdullah I. Hamad, Hassan A. Al-Malki. *Hamad Medical Corporation, Doha, Qatar*.

Background: Urgent start Peritoneal dialysis by starting PD 48 hrs. after catheter insertions is a safe, efficient with a significant reduction in bacteremia comparing to HD in acute unplanned dialysis settings.

Methods: We identified CKD-5 patients during ED visits as either having an earlier plan for PD as a dialysis modality or having no plan. Emergency and urgency need to start dailysis was evaluated. We created an Urgent Start PD pathway for those patients without the emergency need to start or who had an emergency need and became stable after starting HD through a temporary dialysis catheter (review attached Clinical pathway). We enrolled twenty-four patients (14 % of all PD patients) from October 2022 till April 2024, all of them were started on APD as the PD model, the final PD model was decided after completing both APD and CAPD training. Body surface area was the main factor that affected APD Prescription (duration, number of cycles, fill volume). PD-related peritonitis, mechanical complications and hospitalization rates were estimated till April 2024.

Results: PD-related peritonitis rate is significantly reduced (Zero episodes) compared with Conventional starting PD (0.26 episodes/patient/year) with no ED visit related to PD complications. One patient developed a small inguinal hernia that was conservatively managed without surgical intervention.

Conclusions: In this limited observation, Urgent start PD seems to be associated with decreased PD-related peritonitis rate and hospitalization rate with minor resolved incidence of mechanical complications. A larger number of patients and a longer duration are needed to generalize the findings of these observations.



PUB203

Serum Potassium Behavior in Patients on Peritoneal Dialysis: A National Cohort Study from the Dominican Republic Health System

Sergio O. Hernandez-Ordonez,[1,2] Erwin I. Campos,[1,3] Elianny Polanco,[1] Zulma Lara,[1] Miguel A. Cuevas Budhart,[4] Alfonso Ramos.[1] *[1]Macrotech, Santo Domingo, Dominican Republic; [2]Universidad Nacional Autonoma de Mexico Departamento de Educacion Medica, Tlalnepantla, Mexico; [3]Hospital Salvador B. Gautier, Santo Domingo, Dominican Republic; [4]Instituto Mexicano del Seguro Social Coordinacion de Investigacion en Salud, Ciudad de Mexico, Mexico*.

Background: Dyskalemia in peritoneal dialysis (PD) patients is clinically important due to its association with increased morbidity and mortality. The aim of this study is to describe the alterations in serum potassium (K^+) values in a national cohort of PD patients within the National Health System (SNS) of the Dominican Republic.

Methods: This is a cross-sectional cohort study of 1,080 prevalent PD patients. Biochemical, demographic, and clinical variables were recorded. Simple frequencies were evaluated, with measures of central tendency and dispersion. For differences between groups and due to their heterogeneity, the non-parametric Kruskal-Wallis test was used. To identify differences in means, the X^2 test was used for categorical variables. The population was stratified into three groups based on the following K^+ cut-off points: hypokalemia <3.5 mmol/L, hyperkalemia >5.1 mmol/L, and normokalemia for values between these margins.

Results: The cohort mean age was 56yo, 59% where male, 91% hypertensive, 48% DM, 67 use diuretics and 82% CAPD. The mean K^+ level was 4.7±0.83 mmol/L. The variables with significant differences according to K+ levels were weight (p=0.017), phosphorus (P) (p<0.001), and albumin (p=0.004). The correlation betwen K^+ with albumin and time on dialysis (r=-0.026, p=0.391) was not significant. However, a positive correlation was found between P and K^+ levels (r=0.253, p<0.001). The variables that best explain hypokalemia (regression model) are P (β=0.603, p<0.001, 95% CI:0.492-0.740), albumin (β=0.595, p=0.016, 95% CI:0.389-0.909), diuretics (β=0.512, p=0.009, 95% CI:0.309-0.847), and PD modality (β=1.866, p=0.029, 95% CI:1.067-3.264). The variables that best explain hyperkalemia were age (β=1.024, p<0.001, 95% CI:1.024-1.035), P (β=1.361, p<0.001, 95% CI:1.242-1.492), and type of therapy (β=2.367, p<0.001, 95% CI:1.446-3.875)

Conclusions: In our cohort, hyperkalemia is the most common disorder and is associated with higher albumin levels and hyperphosphatemia, indicating a link to greater food intake and better nutritional status. Hypokalemia was observed with hypophosphatemia and hypoalbuminemia. Since diuretic use is associated with hypokalemia, we recommend closer monitoring of potassium levels in patients with residual renal function who use diuretics.

Funding: Commercial Support - Macrotech

PUB204

Effusion Confusion: The Tale of a Pleuro-Peritoneal Fistula

Fiona Murphy,[1,2] Luke Harris,[2] Bradley R. Salonen.[1] [1]*Mayo Clinic Minnesota, Rochester, MN;* [2]*University of Galway, Galway, Ireland.*

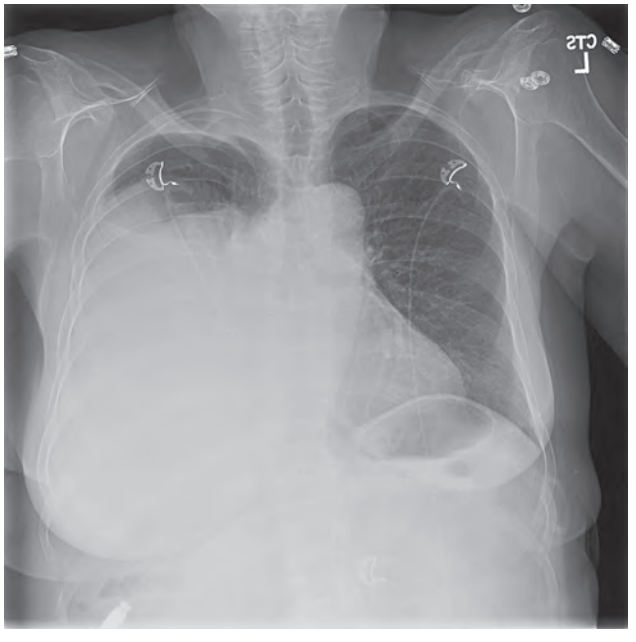
Introduction: Pleural effusions are common in patients on peritoneal dialysis (PD). A pleuroperitoneal fistula (PPF) is an important cause. Delays in diagnosis can lead to worsening of pleural effusions, particularly if a mistaken suspicion of fluid overload leads to the escalating use of high osmolar peritoneal dialysate fluids and volumes with the aim to achieve better ultrafiltration.

Case Description: A 78-year-old female presented with 10 days of dyspnoea. She had autosomal dominant polycystic kidney disease (PCKD) on PD. She was commenced on PD 12 weeks prior. She has right sided stage IIIA lung cancer in remission. On examination she was tachypneic, with absent breath sounds on the right and volume overloaded. Blood workup was unremarkable. Chest X-ray (CXR) showed a right pleural effusion. Pleural tap was performed. She was diagnosed with a PPF, given that pleural glucose was significantly higher than serum, in addition to her unilateral effusion. (Table 1) A dialysis catheter was placed and she transitioned to hemodialysis.

Discussion: In a patient undergoing peritoneal dialysis with a unilateral pleural effusion, special consideration must be given to a possible PPF. The estimated incidence is less than 2%. A risk factor for PPF is PCKD. PCKD leads to high intra-abdominal pressure could lead to an increased pleuroperitoneal pressure gradient. For diagnostics a pleural glucose concentration higher than serum is highly suggestive of a PPF. The long-term management of a PPF depends on its severity and patient preference.

Pleural Fluid Analysis

	Serum	Pleural
pH	7.4	7.52
Glucose mg/dL	82	231
LDH U/L	160	31
Protein g/dL	67	0.3



Admission CXR

PUB205

A Retrospective Analysis of Peritoneal Dialysis Catheter Reinsertion over 11 Years

Emma C. Morganti, Bhrigu Raj Sood. *Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.*

Background: Increasing peritoneal dialysis uptake is limited by the shortened treatment time on PD compared with in-centre HD. A transition from PD to HD is costly, and associated with morbidity and impaired quality of life. There are numerous reasons why a PD catheter may need to be removed, and there is significant variability in patients having opportunity to return to PD. We retrospectively analysed a sample of PD catheter insertions to assess impact of our practice to reduce permanent transfer to HD over 11 years in our renal unit.

Methods: A sample of 583 of 1061 PD catheter insertions from 01/01/2013 to 31/12/2023 in a renal unit were reviewed. Electronic databases were reviewed for catheter duration, removal reason, whether reinserted, interim management and duration of management where available.

Results: The 583 catheters reviewed related to 448 distinct patients. 21.4% remained in situ at the completion of follow up (31/12/2023). Of the removed, 45% were removed for reasons which would not warrant consideration of reinsertion (transplantation 14.4%, death 11.5%, failure of PD 9.4%, patient preference 9.4%, regain of native renal function 0.7%). Of the 55% which were removed for reasons which could allow for potential reinsertion (infection, malposition, accidental removal, hernias or leak), 53.8% were reinserted. The percentage of patients having reinsertion of catheters varied across years from 43.5 to 72.7%. Interim management for 83 of the reinserted catheters showed 8.4% had a catheter reinserted on the same day, 49% had no interim renal replacement therapy, and 42.2% had interim haemodialysis.

Conclusions: PD is often the preferred form of renal replacement therapy for many patients, but a significant proportion transfer to HD within 2 years of starting PD. Supporting appropriate patients to return to PD varies amongst units. In this sample 54% of catheters removed for an indication which did not preclude reinsertion were reinserted, allowing ongoing access for PD. There is little information available to compare this with practices from other units. This study is limited as it is only sample of the data, and it was difficult to delineate decisions processes around whether reinsertion was appropriate from the available records. Going forward, we would aim to review all PD catheter insertions and removals for the time period and analyse what variables impacted outcomes.

PUB206

A Rare Case of Stenotrophomonas maltophilia-Refractory Peritonitis in a Patient on Automated Peritoneal Dialysis

Laurene M. Asare, Aisha Abbasi, Jade M. Teakell. *The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.*

Introduction: *Stenotrophomonas maltophilia* is a multidrug-resistant gram-negative bacillus common among the severely immunocompromised population and is associated with a high morbidity and mortality. Additionally, *S. maltophilia* in peritoneal dialysis (PD) population is also associated with loss of PD catheter and poor prognosis. We present a case of *S. maltophilia* refractory peritonitis in a PD patient.

Case Description: An 85 year-old woman with end stage kidney disease on peritoneal dialysis was admitted for refractory peritonitis and PD catheter dysfunction. Four weeks prior, the patient was diagnosed with *S. maltophilia* peritonitis. Initial effluent cell count was 800/uL (51% neutrophils, 38% monocytes). Treated with empiric intra-peritoneal vancomycin and cefepime followed by cefpodoxime for 4-weeks. Despite symptomatic improvement, repeat peritoneal effluent analysis showed greater than 600 WBC/uL (74% neutrophils, 25% monocytes) suggestive of refractory peritonitis. Antibiotics were changed to trimethoprim/sulfamethoxazole and levofloxacin, and PD catheter was removed. She transitioned to temporary thrice weekly hemodialysis with plan to return to PD.

Discussion: *S. maltophilia* is an emerging multidrug-resistant opportunistic pathogen; it can be found in water, soils, and on rhizomatous plants. *S. maltophilia* peritonitis is a rare finding in patients on peritoneal dialysis. Its presence poses a therapeutic challenge and is often associated with poor prognosis. We present here a case of an elderly patient found to have refractory *S. maltophilia* peritonitis. *S. maltophila* infections commonly present in patients who are immunocompromised although our patient was immunocompetent. Interestingly, this patient is an avid vegetable gardener, and thus touch-contamination may have been the source. International guidelines recommend dual antibiotic coverage for environmental gram-negative bacteria such as *Pseudomonas* and *Stenotrophomonas*; special attention was paid to treatment of Stenotrophomonas in most recent guideline update. This case highlights the importance of considering this organism in patients with PD peritonitis regardless of their immunocompetence, the importance of hand hygiene, and also spotlights the resistant nature of the organism prompting us to be more vigilant when presented with such case.

PUB207

Urgent Bedside PD Catheter

Tushar S. Malavade,[1,2] Naeim G. Salah.[1,2] [1]*University Health Network, Toronto, ON, Canada;* [2]*University of Toronto, Toronto, ON, Canada.*

Introduction: PD catheter for ESRD is an elective procedure is done by surgeons, interventional radiologists (IR), or nephrologists. We describe a successful bedside PD catheter insertion and immediate initiation of PD in a uremic patient, with hypoxia, and hyperkalemia with no bowel preparation.

Case Description: A 38-year-old patient with diabetic nephropathy was on 5/week HD for 5 years. He had failed multiple accesses for HD including temporary and tunneled catheters, AV grafts, trans-lumbar dialysis catheter. The accesses were complicated with CRBSIs, and central venous stenosis needing multiple interventions including angioplasties, and thrombolytics. He had inefficient HD and persistent pruritus, leading

to the pulling of the HD catheter on multiple occasions. He was recently admitted with infective endocarditis, mitral regurgitation, and heart failure. His tunnelled internal jugular catheter was again dislodged. While waiting 2 days for a new HD catheter placement by IR, he developed uremia in the form of myoclonus, orthopnea, hypoxia needing Oxygen and refractory hyperkalemia. IR staff evaluated all the vascular accesses and concluded that no further HD CVC could be placed. A decision was taken to place a bedside PD catheter on an urgent basis. The bowel prep was given 3 hours before the procedure. The patient was hypoxic needing 6 lits of O2 and with 30° head elevation. Under mild sedation, using ultrasound, a midline supraumbilical coiled double-cuffed Tenchkoff PD catheter was inserted at the bedside by the nephrology team. After confirming good inflow and outflow, we were able to start the PD on the table itself with 4.25% dextrose PD solution and continued with low volume, supine, cycler PD with 4.25% solution. His UF was 1.3 lits in 24 hours. There were no complications like leak, bleeding or perforation. After a week, the patient was on room air, with no uremic features and electrolyte imbalances. His PD was continued with low volume cycler, supine PD.

Discussion: Bedside PD catheter placement for the immediate start of PD is not commonly done. Our patient did not have any vascular access for HD and we had to do urgent PD catheter insertion and start PD immediately as life life-saving measure as he was getting uremic, hypoxic and hyperkalemic and with no bowel preparation. Fortunately, there was no PD leak in short-term follow-up.

PUB208

Optimizing Renin Angiotensin-Aldosterone System Inhibition (RAASi) for Kidney Function Preservation in Peritoneal Dialysis (PD): A Quality Improvement (QI) Project

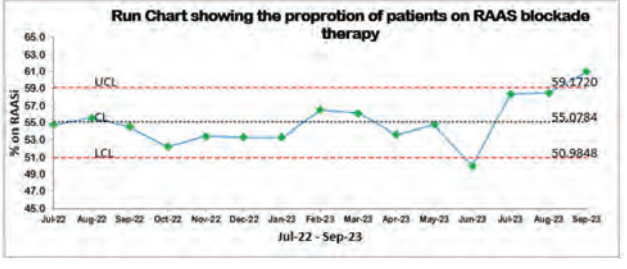
Mona Aflaki, Wen Qing Wendy Ye, Fatema Zaidi, Arifuddin Saad Mohammed, Joshua Shapiro, May Alabdulaaly, Bourne L. Auguste. *University of Toronto, Toronto, ON, Canada.*

Background: Preserving residual kidney function is crucial for improving outcomes in PD. RAASi helps preserve kidney function, protect cardiovascular health, and regulate blood pressure (BP). However, it is often discontinued due to concerns about hyperkalemia, and hypotension. Using QI methodology, we explored reasons for discontinuation and developed solutions to improve RAASi in PD patients. We aimed to develop and implement solutions using QI methods to increase the proportion of patients on RAASi.

Methods: We reviewed charts of 54 PD patients at Sunnybrook Health Sciences Centre between July 2022-Sept 2023. Data on RAASi usage, baseline potassium (K), and residual urine output were collected. Root-cause analyses, using surveys and Pareto charts, identified gaps in RAASi usage.

Results: Our analysis revealed only 55% of patients were prescribed a RAASi (Figure 1). The median residual urine volume was 861.8 ± 72.3 mL, and the average serum K was 4.4 ± 0.1 mmol/L. The root-cause analysis identified two reasons for the low prescription: cessation of RAASi before PD initiation and failure to restart therapy. We implemented the PD Passport in electronic medical records to identify patients not on RAASi to ensure monitoring of urine output, serum K, and BP every six months, with initiation of RAASi if appropriate. There was a slight increase in patients on RAASi after the project was announced between July-Sept 2023, suggestive of a possible Hawthorne effect prior to initiation of formal interventions.

Conclusions: The PD Passport, launched in May, aims to increase RAASi use by 20%. We will evaluate its impact on prescription rates, residual urine volume, hyperkalemia, and BP. We demonstrate the feasibility of using QI principles in PD to enhance care. With the PD Passport, we aim to preserve residual kidney function with RAASi, while monitoring patients to maximize benefits and minimize side effects. This initiative promises improved patient outcomes and PD management.



PUB209

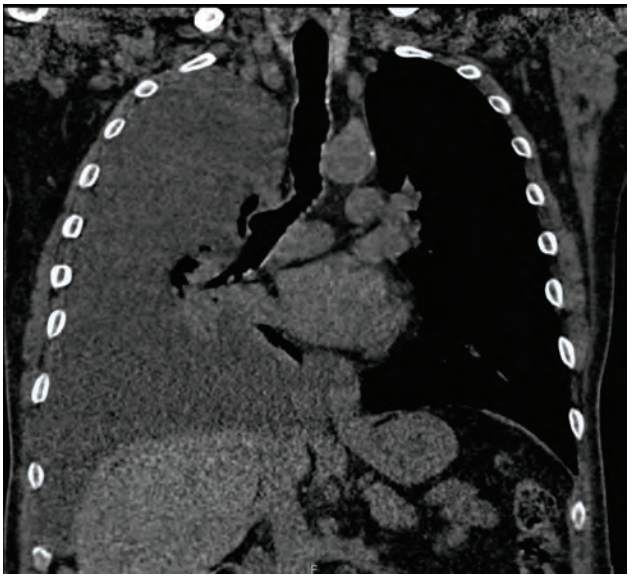
Pleuroperitoneal Communication: A Rare Complication of Peritoneal Dialysis Observed in an Ecuadorian Hospital

Jorge A. Valdivieso,[1] Wilson S. Penafiel,[1] Andrés R. Monge,[1] Michella Dirani,[3] Michael I. Anstead,[4] Carina V. Coronel,[2] Monica G. Fernandez.[2] *[1]Universidad de Las Americas Facultad de Ciencias de la Salud, Quito, Ecuador; [2]Universidad Central del Ecuador, Quito, Ecuador; [3]Universidad San Francisco de Quito, Quito, Ecuador; [4]University of Kentucky, Lexington, KY.*

Introduction: Pleuroperitoneal communication (PPC) is a rare complication seen in approximately 1.6% of patients with end-stage renal disease who undergo peritoneal dialysis. Although there have been several reports where its diagnosis and management have followed a straightforward path, we encounter a case in which the accessibility to some of the diagnostic tools has become a limitation for its final treatment. The gold standard for diagnosis is Tc-99m scintigraphy, which is noninvasive, low in radiation, simple, safe, and cost-effective. The treatment of choice is video-assisted thoracic surgery (VATS).

Case Description: A 65-year-old male with a history of end-stage renal disease treated with peritoneal dialysis presented to the emergency department with a productive cough, fever, inferior limb edema, and dyspnea. A Computed Tomography (CT) Scan revealed a right unilateral pleural effusion. A cytology analysis of the pleural fluid showed an elevated glucose concentration. TC-99m scintigraphy was not available to confirm the diagnosis. The ultimate decision was to discontinue peritoneal dialysis and initiate hemodialysis instead. One month after follow-up the patient did not reveal any signs of hydrothorax.

Discussion: PPC represents a rare complication in patients undergoing peritoneal dialysis. While TC-99m scintigraphy and VATS are the gold standards for diagnosing and treating this condition, their advanced and complex nature renders them unavailable at every healthcare center. Consequently, alternative treatment strategies, such as discontinuing peritoneal dialysis and transitioning to hemodialysis, may need to be considered, despite potential compromises to patient well-being.



Chest CT. Coronal view shows right hydrothorax.

PUB210

Early Fusariosis after Peritoneal Dialysis Drain Placement

Bibi Maryam, Adolfo Diaz-Barba. *The University of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Introduction: Fusarium peritonitis has been reported in people with long-standing peritoneal dialysis (PD) catheters and usually occurs on average of 48 months after peritoneal drain placement. We present a case of invasive fusariosis manifested by *Fusarium* peritonitis within one week of peritoneal drain placement.

Case Description: A 40-year-old man with chronic alcohol use was admitted to our intensive care unit with one-month history of vague abdominal pain. CT abdomen and pelvis revealed free intraperitoneal air in pelvis near the proximal rectosigmoid colon suggestive of ruptured diverticulitis with a potential loculated fluid collection as well as large volume ascites with a markedly enlarged cirrhotic liver. Paracentesis was performed and peritoneal fluid was sent for culture which was sterile. IR placed a peritoneal drain on day 11 and peritoneal fluid cultures were collected which showed growth of ampicillin susceptible E. faecium and *Candida lusitaniae*. On day 20, peritoneal cultures collected from day 15 showed growth of mold, and he was started on empiric liposomal amphotericin B. The mold was later identified as *Fusarium* and antifungal was switched to voriconazole. The family opted for comfort care and patient passed away on day 25 of the hospitalization.

Discussion: One of the risk factors for developing *Fusarium* peritonitis is indwelling PD catheter as well as long-retained peritoneal drains for chronic dialysis. The optimal treatment of *Fusarium* remains unclear, but voriconazole, itraconazole or polyenes have been reported with some treatment success. Usually, it takes several months for the *Fusarium* infections to develop after a catheter placement, but in our patient, he developed *fusarium* peritonitis within 5 days of peritoneal drain placement. This early growth during hospitalization and lack of growth first sampling of peritoneal fluid suggests that the patient might have acquired it from the inpatient hospital setting. *Fusarium* should be on the differential for early peritonitis especially in patients with risk factors such as ESLD, chronic ascites and presence of a peritoneal catheter and empiric antifungals with activity against molds should be considered. Aggressive management of *Fusarium* peritonitis is essential to prevent disseminated disease.

PUB211

Prevalence of Metabolically Associated Fatty Liver Disease in Patients Undergoing Peritoneal Dialysis

Jose A. Solis Rojas, Gloria G. García Villalobos, L. M. Perez-Navarro. *Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico*.

Background: Metabolically Associated Fatty Liver Disease (MAFLD) in Chronic Kidney Disease (CKD) patients undergoing renal replacement therapy (RRT) has been reported to have a prevalence of up to 58%. Patients on peritoneal dialysis (PD) have an increased risk for MAFLD due to prolonged exposure to high concentrations of glucosa. The aim of this study is to determine the prevalence of MAFLD in PD patients evaluated using elastography.

Methods: Cross-sectional study conducted in adults with CKD on PD, from April to May 2024. Data were collected from medical records and elastography was performed. Data are presented as absolute and relative frequencies, means±SD. Student's t-test and Spearman correlation were performed, with a 95%CI and p-value ≤0.05.

Results: 22 patients were included. 82% of the patients exhibited MAFLD, of which 23% showed suggestive data of chronic hepatopathy. No association was found between MAFLD, the use of dialysis solutions, and RRT duration. An association was identified between GGT levels and MAFLD (r=0.51 p= 0.008), with a negative correlation observed with albumin concentrations (r=-0.448 p= 0.01). Daily glucose load was associated with total bilirubin levels (r=0.486 p=0.01), TP (r=0.418 p=0.03), and INR (r=0.408 p=0.03).

Conclusions: A high prevalence of MAFLD was identified, higher than reported in other studies, with the presence of advanced fibrosis in a significant percentage of patients, along with the absence of elevation in most serum biomarkers. Therefore, it is necessary to promote screening for MAFLD, supported by imaging studies such as elastography.

Demographic characteristics	Total Patients (n=22)
Age (years)	48.95±15.13
Gender (male)	14 (63.6%)
Coexisting Condition, n (%)	
- Diabetes	11 (50%)
- Systemic Arterial Hypertension	17 (77%)
- Overweight and Obesity	8 (36%)
- Dyslipidemia	12 (54%)
DPCA/ DPA	15/7
Biochemical Parameters	
Albumin (g/dL)	3.40 ± 0.55
Bilirubin (mg/dL)	0.43 ± 0.18
Alkaline Phosphatase (U/L)	161.8 ± 251.3
LDH U/L	217.05 ± 65.2
TGO (U/L)	19.5 ± 11.1
TGP (U/L)	17.8 ±11.2
GGT (U/L)	36.5 ±36.5
HDL (mg/dL)	46.2 ± 16.3
LDL (mg/dL)	87.1 ± 19.6
Cholesterol (mg/dL)	171.9 ± 34.2
Triglycerides (mg/dL)	156.61 ± 59.1
PT (seconds)	10.9 ± 0.80
INR (seconds)	0.98 ± 0.09
Elastography (Kpasc)	9.07 ± 3.12
Daily Glucose Exposure (grams/day)	135 ± 42.51

Demographic characteristics of the population

PUB212

Comprehensive Evaluation of Clinical Consequences in Diverse Fistula Elevation Procedures

Masayoshi Nanami, Yasuyuki Mimura, Akihiro Kuma, Yukiko Hasuike, Takahiro Kuragano. *Department of Cardiovascular and Renal Medicine, Hyogo Medical University, Nishinomiya, Japan*.

Background: Arteriovenous fistula (AVF) superficialization is a recommended alternative autologous vascular access (VA) in patients for whom conventional AVF creation is not possible because of insufficient superficial veins. This procedure utilizes a deeply located vein as an outflow conduit in AVF creation and makes the vein accessible for cannulation. Tunnel transposition (TT) is employed in a standard manner as a superficialization technique. However, TT tends to be exclusively applied to the basilic vein in the upper arm because of anatomical considerations and inherent procedural limitations. We recently reported that elevation transposition can serve as a simplified minimally invasive substitute for TT (Contrib Nephrol. 2019;198:1-11). In AVF superficialization employing elevation transposition (i.e., fistula elevation procedure [FEP]), three potential outflow veins are available in the upper arm: the cephalic, basilic, and brachial veins. This study was performed to comprehensively evaluate the clinical consequences of three valid FEP techniques, ascertain whether they are reasonable alternatives to autologous VA, and determine which, if any, have superior performance.

Methods: The demographic and outcome data of 111 patients who underwent the FEP were retrospectively collected and analyzed. The outcomes of the three fistula techniques were assessed and compared in terms of patency rates, requirements for VA intervention therapy (VAIVT), and complication rates.

Results: The basilic, cephalic, and brachial vein-based FEP was performed in 63.1%, 23.4%, and 13.5% of cases, respectively. The overall cumulative primary and secondary patency rates were 76.2% and 98.2% at 1 year and 70.7% and 97.0% at 2 years, respectively. VAIVT was required in 32.4% of cases, and the patency rates at 1 and 2 years after VAIVT were 65.3% and 62.0%, respectively. There were no significant differences in these patency rates among the three FEP types. Minor complications occurred in only 4.5% of cases.

Conclusions: Our results suggest that the FEP provides three equivalently reliable options to accommodate the deeply located venous anatomy of the upper arm on individual-patient basis. The diversity of the FEP may help to expand the applicability of autologous VA.

PUB213

Effect of Transdermal Nitroglycerin (NTG) Cream on Postdialysis Parameters on Brescia-Cimino Arteriovenous Fistula (AVF)

Tanmay P. Vagh. *Mahatma Gandhi University of Medical Sciences & Technology, Jaipur, India.*

Background: Important factor in AVF failure is inadequate blood flow through access.NTG cream[made up of 25mg Injection NTG+5gm NIVEA cream(as the base is same in NTG ointment & nivea cream & this decision of making this combination has been made because of unavailability of NTG ointment in the market)] at the point of vascular access at wrist on AVF to increase blood flow by vasodilation & prevent thrombosis by inhibiting platelet aggregation. Aim is to evaluate the changes in post dialysis parameters after application of NTG cream on AVF.

Methods: 86 patients came to the Nephrology Department at Mahtma Gandhi University of Medical Sciences & Technology, Jaipur, India between October 2023 to March 2024, whom had fistula as the initial vascular access for hemodialysis were placed into 2 groups;study group(n=43) & control group(n=43). Study group received NTG cream application 24 hour prior to dialysis at 8 hourly(such 3 application) & also 1 hour prior coming for dialysis, & advised to continue the same for 4 weeks. The control group received no application. In both groups the blood flow rate(Qb), ultrafiltrate rate(UFR), blood output at the drainage vein, urea reduction ratio(URR) measured after 4 weeks.

Results: The distribution were according to age, gender, duration of dialysis & native disease was almost similar in both groups(Table 1). All fistulas were functioning well immediately after operation. During the study no patient had any reaction to the NTG including nausea, hypotension, or headache. In the study group, Qb[from 150ml/min to 250ml/min maximum 300ml/min], UFR, and blood output at the drainage vein, URR(increased from 0.55 to maximum 0.67) were significantly increased after 4 weeks of NTG cream application. In control group, all parametes were unchanged.

Conclusions: The most important factors in performing AVF are good surgical technique & patent central veins. However adequate blood flow cannot be established even in the presence of these factors so, in this study of NTG cream application showen significant improvement in study group, whereas there was no change in control group.

Patients age, gender, duration of hemodialysis, native diseases, post dialysis parameters.

	Age(Years)	Gender(F/M)	Duration of hemodialysis(Months)	Diabetes mellitus	Hypertension	Obstructive Nephropathy	Post dialysis parameters
Control group	46+/-7	8/35	7+/-2.5	29	11	3	Qb(ml/min)-140+/-25 UF(ml)-2.5+/-1.0 URR-0.36+/-0.04
Study group	49+/-9	10/33	8+/-3.5	31	10	2	Qb(ml/min)-260+/-20 UF(ml)-3.5+/-0.4 URR-0.55+/-0.12

Qb-blood flow, UF-Ultrafiltrate, URR-urea reduction ratio

PUB214

Thoughts on the Integrated Management of Vascular Access in Elderly Patients with Maintenance Hemodialysis (MHD)

Hua Liu. *The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: Although the use of arteriovenous fistulas (AVFs) has better clinical outcomes in the general hemodialysis population, the use of AVFs is uniquely challenging due to the high rate of immature vascular access and limited life expectancy in older hemodialysis patients.

Methods: This article reviews the vascular access development plan and clinical data of 6 elderly patients, and summarizes the integrated vascular access management strategies of elderly patients with MHD based on literature review and guideline recommendations.

Results: Case 1: Male patient with renal transplantation failure 10 years after kidney transplantation, who had previously had right AVF occlusion and the left side could not meet the establishment conditions, established the ulnar AVF of the right forearm after comprehensive evaluation, and started using it one month after surgery, and had good function. Case 2: Male patient with stage 5 CKD, diabetes, hepertension, coronary heart disease and gastric cancer, his left forearm catheter over 1 month, the right internal jugular vein TCC + left forearm ulnar AVF was established, and the AVF was started 3 months after surgery and the TCC was removed. Case 3: Male patient with CKD stage 5 stage and diabetes mellitus, in order to establish AVF in advance, and the left forearm blood vessel did not meet the surgical conditions, and the right cephalic vein branch was multiple and relatively tortuous, and the right radial artery-cephalic vein AVF was established in the first stage, and the fistula began to be used normally within 1 month after the re-examination was reconstructed and repaired after the tortuous cephalic vein was reconstructed and repaired. Case 4: Female patient with CKD stage 5 who underwent regular hemodialysis with TCC for 2 months were required to be admitted to the hospital with AVG, evaluated that the left radial artery, especially the cephalic vein, did not meet the surgical conditions, and the right vascular condition was acceptable.

Conclusions: We believe that it is necessary to comprehensively consider the basic conditions of elderly patients. Individualized planning and implementation of designated vascular access and standardized postoperative follow-up. Regardless of whether the catheter is started for hemodialysis, the possibility of AVF or AVG should be comprehensively evaluated. Standardize the clinical pathway for the use of arteriovenous fistula.

PUB215

Vascular Access Outcomes among Patients on Maintenance Hemodialysis in Perpetual Succour Hospital: A 3-Year Cross-Sectional Analysis

Joel John C. Mejos, Grecia Darunday, Eratosthenes S. Polito, Ruben A. Maguad. *Perpetual Succour Hospital, Cebu City, Philippines.*

Background: Vascular access is the key in successful management of chronic hemodialysis (HD) patients. Though native arteriovenous fistula (AVF) is considered the access of choice, many patients in our country initiate HD through central venous catheter (CVC). The ideal vascular access should have specific characteristics among which the most important are the following: ease of placement; delivery of adequate blood flow for effective HD; good primary patency rates; low rates of complications; long-lasting life; and low economic costs. Hence, successful HD depends on creation and maintenance of adequate vascular access.

Methods: This is a single center, cross-sectional study of ESRD patients on maintenance hemodialysis enrolled in Perpetual Succour Hospital Hemodialysis Unit from April 1, 2021, to November 30, 2023.

Results: There were 260 hemodialysis patients included, with successful vascular access outcome (73.13%) and were younger (57.2 ± 14.1). Those with failed vascular access were females (54.2%), unemployed (61.4%) and had diabetes mellitus (DM) (50.6%) as the primary etiology of their ESRD. Those with failed vascular access were hypertensive (86.7%), with concomitant CAD, MI (57.8%) and DM (56.6%). Proportion of those with failed and successful vascular access significantly differ among hypertensives (p=0.012), diabetics (p=0.039), with chronic glomerulonephritis (p=0.011), and among those with malignancy (p=0.003). And the association of clinical outcomes (death or not) and failure or success of vascular access is statistically significant, p= <0.001.

Conclusions: Our study showed that failed vascular access were more associated with female gender, DM as the primary etiology of ESRD and with other co-morbid conditions such as hypertension and CAD or MI. Successful vascular outcome were among those of younger age group compared to those whose vascular access failed, probably due to better vascular condition and fewer co-morbidities. Lastly, 87% of patients on AVF were alive however, most of those who died also had AVF (59.1%) and CVC (36.4%), and proportion of those who were alive and dead with different vascular access significantly differ, p<0.001.

Clinical Outcomes of Different Vascular Access

Access	All HD Patients n = 260	Clinical Outcomes		p-value
		Alive n = 194	Dead n = 66	
AV Graft	3 (1.2)	2 (1.0)	1 (1.5)	<.001
AVF	209 (80.4)	170 (87.6)	39 (59.1)	
CVC	42 (16.2)	18 (9.3)	24 (36.4)	
LI	6 (2.3)	4 (2.1)	2 (3.0)	

PUB216

A Single-Center Descriptive Study on the Catheter Salvage Rate of Catheter-Related Bloodstream Infection Treated with Antibiotic Lock Therapy among Patients on Hemodialysis

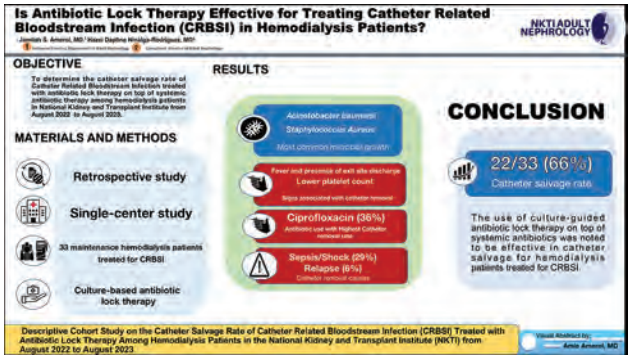
Jamilah S. Amerol. *National Kidney and Transplant Institute, Quezon City, Philippines.*

Background: Catheter Related Bloodstream Infection is a common complication of hemodialysis patients with tunneled catheter as route of access for renal replacement therapy. Antibiotic lock therapy along with systemic antibiotics has been one of the treatments offered for CRBSI with aim of catheter salvage especially for patients with multiple access failure however no local studies has been published yet to determine the catheter salvage rate against catheter removal rate using antibiotic lock therapy.

Methods: A retrospective and descriptive design to identify ESRD patients treated with antibiotic lock treatment in a single-center for bloodstream infections due to catheter use for 1 year study period. The demographic and clinical characteristics of the subjects were then compiled using Univariate Descriptive statistics.

Results: Out of the 33 patients included in the study, 23 patients (66%) had catheter salvage while the remaining 11 (33%) had catheter removal. Findings revealed that there were no significant differences between the two groups in terms of age, sex distribution, comorbidities, or etiology of ESRD. Most prevalent microbial growths were Staph aureus and A. Baumanii. The presence of fever and discharge were significantly higher among catheter removal group. A trend towards lower mean platelet count was likewise seen. Catheter removal was significantly higher among patients given with Ciprofloxacin lock therapy.

Conclusions: The collective understanding of the significant factors influencing catheter removal and salvage may help tailor more targeted interventions and better patient care. This study assessed the catheter salvage rate of patients receiving hemodialysis who have a catheter-related bloodstream infection treated with antibiotic lock treatment. This study sought to serve as a foundation for future research projects, policy proposals as well as plans to improve services to ESRD patients on hemodialysis with central line bloodstream infection.



PUB217

Reimaging Patient Safety for Dialysis

Sobia N. Khan, Mansoor Ahmed, Navdeep Kaur, Sandeep K. Mallipattu.
Stony Brook University, Stony Brook, NY.

Introduction: Arteriovenous fistula/graft (AVF/AVG) are commonly used for dialysis. Vascular access related morbidity accounts for 20% of hospitalization. Blood vessel rupture, a serious complications of AVF.

Case Description: 79-year-old male with End Stage Kidney disease on hemodialysis through Left AVF was admitted. Nephrology was consulted for hemodialysis. Patient was initially evaluated by a nephrology fellow and the case was discussed with the attending physician. Hemodialysis was initiated through the AVF. Physical examination of the fistula was described as a thrill and a bruit without any signs or concerns for erythema, even though the attending physician noted the presence of scabs on the patient's access, prompting consideration for vascular evaluation. Despite this observation, the patient underwent dialysis again during which bleeding from AVF was observed at the conclusion of treatment. The vascular team was immediately notified, he was taken to the operating room where AVF was ligated.

Discussion: We have implemented follow-up strategy to prevent similar catastrophes in the future. Nephrology team received dedicated lectures with strong emphasis on physical examination skills. They were instructed to include images of AVF/AVG after obtaining patient consent, which heightened their awareness of the importance of thorough physical examination. They were encouraged to promptly consult the vascular surgery team if any concerns arose. In the hemodialysis unit nurses received more frequent dialysis education sessions to accommodate the increased turnover rate among them. Significant improvements were observed. Almost all charts now include images of dialysis access. Additionally, fellows are more aware of the patient access conditions. We have also noticed an increase in phone calls from dialysis unit nurses ensuring better communication and patient care.

PUB218

Effect of Glycemic Control in Outcomes of Dialysis Vascular Access Surgery

Jin Huang,[1] Jimmy Pak,[2] Bradley R. Cohn,[2] Aida Shirazi,[1] Sijie Zheng.[2]
[1]Kaiser Permanente San Francisco Medical Center, San Francisco, CA; [2]The Permanente Medical Group Inc, Oakland, CA.

Background: Arteriovenous fistula (AVF) and arteriovenous graft (AVG) are the preferred dialysis accesses and one of the quality measurements. Hyperglycemia is recognized to be an independent risk factor of adverse surgical outcomes. However, it is unclear the optimal pre-surgery diabetic control and the underlying patient characteristic that are associated with adverse outcomes of AVF/AVG surgery. Currently there are no specific guidelines regarding acceptable preoperative glucose thresholds for AVF/AVG surgery nationally or regionally at Kaiser Permanente Northern California (KP NCAL).

Methods: We are conducting a retrospective cohort study of adult KP NCAL members with advanced chronic kidney disease, who underwent AVF/AVG surgery between January 1, 2013 and December 31, 2023. Pre-surgery diabetic control was measured by HgA1c, glucose or fructosamine. Patient characteristics including demographics, eGFR, comorbidity, and medications were obtained. The adverse clinical outcomes considered are operative complications (infection, hematoma, occlusion, maturation issue, open wound, steal), re-operation, all-cause ER visits, readmissions, MI and death within 30 days postop. We have designed logistic regression models to assess association between pre-surgery diabetic control and adverse clinical outcome of AVF/AVG surgery.

Results: A total of 9,981 patients with advanced CKD underwent AVF/AVG surgery. The mean age (±SD) was 65.6 (±13.4) years old, 40.4% were females, 31.9% were White, 16.1% were Asian, 11.0% Black, and 22.6% were Hispanic. Majority of patients (83.0%) had AVF surgery. The average preoperative HgA1c was 6.8 (SD 1.49, range 3.6-16.2). Our model estimates the odds ratio of adverse outcomes of AVF/AVG surgery with worsening glycemic control adjusting for patient's demographics, eGFR, comorbidity, and medications.

Conclusions: Our study examines the surgical risks associated with hyperglycemia and aims to provide guidance regarding preoperative glucose management to improve surgical outcomes and avoid unnecessary delay of lifeline creation for patients with kidney failure requiring maintenance hemodialysis.

PUB219

Mortality within 12 Months following Bacteraemia in Patients Dialysing through Tunnelled Lines: Effect of the Organism Isolated

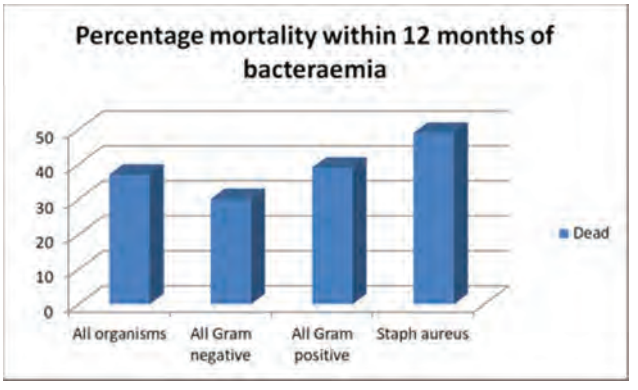
Takudzwa J. Dhlandhlara, David Makanjuola. *St Helier Hospital, Carshalton, United Kingdom.*

Background: Haemodialysis (HD) patients are at risk of dialysis access-associated infections. The risk is more in patients dialysing with lines. The most commonly implicated organism is Staph aureus (SA), accounting for 27-39% of bacteraemias. SA has a tendency to cause metastatic infections e.g. endocarditis, septic emboli, and discitis. We looked at bacteraemias in patients dialysing with lines to see if there was a difference in the mortality related to the kind of organism isolated.

Methods: This retrospective cohort study was on HD patients who had positive blood cultures between 2019 –2022. Data on blood cultures and survival were collected from an electronic database and statistical analysis was done with Microsoft Excel.

Results: There were 506 bacteraemias in 275 patients. 168 were male. Median age at time of bacteraemia was 67 years (range 19-91). Organisms responsible for the bacteraemias were: Gram negatives 93 (23.8%), Gram positives 296 (75.7%), of which staphylococcus aureus SA species were 85 (85.7%). The percentage of patients who died within 12 months of a bacteraemia was 37% in the whole population. For those with Gram negative bacteraemia, it was 30% and for those with Gram positive bacteraemia, it was 39%. In those with SA bacteraemia, the mortality rate was 49%.

Conclusions: While the causes of death within 1 year of the infection are varied it is intriguing that the lowest survival of patients was in the group of those who had had SA bacteremia. Our data suggest that the type of organism causing the bacteraemia is important, as the mortality in those with SA appears worse compared with other Gram positive and with Gram negative organisms. This might be due to the difficulty eradicating SA as it causes a biofilm on the line, and can cause metastatic infections.



PUB220

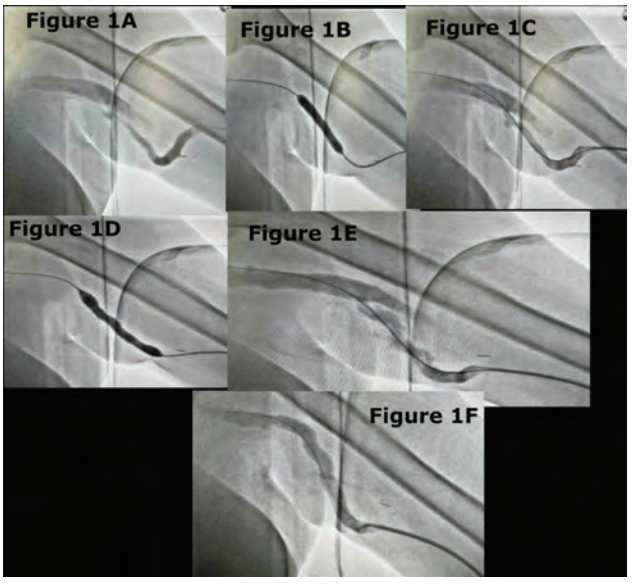
Treatment of Severe Outflow Stenosis Leading to Steal Syndrome

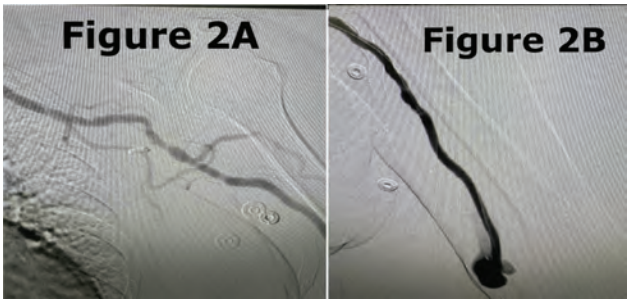
Sylvester Barnes IV, Ahmet E. Yassa. *Loyola University Medical Center Department of Nephrology, Maywood, IL.*

Introduction: 67-year-old F with ESRD on dialysis via a left brachiobasilic AV fistula created several years ago with multiple previous interventions was referred to interventional nephrology for venous pressures of 300 mmHg on 400 ml/min pump flow.

Case Description: Access was obtained and angiogram showed an extremely hypoplastic basilic vein draining to the brachial system via a perforator vein. Balloon angioplasty was performed incrementally with 4x40, 6x40, and 8x40 compliant Powerflex balloons. Due to the high recurrence likelihood and the severe stenosis, an 8x60 drug-eluting Lutonix balloon was deployed. Patient had significant discomfort and arm swelling upon balloon deflation, with angiogram showing extravasation. Immediate balloon occlusion was done, but due to continued swelling and extravasation, an 8x100 Viabahn stent was deployed. Post-procedure, fistula had excellent flow(Fig. 1). Later, patient developed left-hand numbness and pain during dialysis concerning for steal syndrome. Vascular surgery performed angiogram showing significant stenosis in the axillary/brachial artery junction with subsequent angioplasty and symptom improvement(Fig. 2).

Discussion: Extravasation can occur in dialysis access interventions with covered stents used as bailout procedures. In this case, despite successful angioplasty of the significantly diseased segment of the basilic vein, there was enough flow resistance to prevent steal syndrome. The stent deployment increased flow, reducing resistance and unmasked arterial stenosis in the upper brachial artery leading to successful treatment and resolution of steal syndrome.





PUB221

Safety of the Placement of Tunneled Catheters for Hemodialysis Inserted under Ultrasound Guidance without Fluoroscopy

Javier Rivera Flores,[1] Mauricio Arvizu Hernández.[2] *[1]Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: The installation of a tunneled access for hemodialysis traditionally requires fluoroscopy; however, in Mexico, the availability of this instrument is limited. The objective of the study is to determine if the placement of tunneled catheters for hemodialysis without fluoroscopy is safe using ultrasound guidance and calculating the intravascular portion based on the patient's height.

Methods: This is a retrospective, observational, and descriptive study conducted at the National Institute of Medical Sciences and Nutrition Salvador Zubirán. Patients who received a tunneled vascular access without the use of fluoroscopy, only using real-time ultrasound guidance. The intravascular portion of the catheter was calculated by considering the patient's height in centimeters and dividing it by 10. A chest X-ray was performed to corroborate the appropriate path and position of the catheter tip, distinguishing four locations: cavo-atrial junction, right atrium, deep portion of the right atrium, right ventricle, and any other location.

Results: A total of 317 tunneled access placements without fluoroscopy were performed between january 2018 to december 2023 ;in 99% the indication was chronic hemodialysis. 167 were women (52.6%) and 150 were men (47.4%). In 291 patients (91.8%), the right jugular vein was used, in 25 patients (7.9%) the left jugular vein was used, and only 1 femoral access (0.3%). No vascular or pleuropulmonary injuries were reported. The catheter tip was located at the cavo-atrial junction in 59 patients (18.6%), in the right atrium in 231 patients (72.9%); in 20 patients (6.3%) the tip was observed in the deep portion of the right atrium or right ventricle and was retracted to locate it in the right atrium. The tip was located in another anatomical region in 7 patients (2.2%), in which cases replacement by the Interventional Radiology team was necessary. All accesses showed immediate adequate functionality.

Conclusions: The placement of tunneled catheters for hemodialysis with ultrasound guidance without fluoroscopy is safe and cost-effective. The calculation of the intravascular portion considering height allowed the tip to be located in the right atrium in 72.9% of the catheters. The placement was considered successful based on the tip location and AV functionality in more than 98% of cases.

PUB222

Impact of Prepared Vascular Access on Mortality and Medical Expenses in Elderly and Nonelderly Japanese Patients with CKD Stage G5: A Retrospective Cohort Study

Yuji Kamijo, Takayuki Nimura, Yuki Nakayama, Daiki Aomura, Kosuke Yamaka, Koji Hashimoto, Makoto Harada. *Shinshu University School of Medicine, Matsumoto, Japan.*

Background: Patients with chronic kidney disease (CKD) stage 5 (CKDG5) have greater dialysis requirements that increase the risk of cardiovascular disease and mortality. The elevated costs associated with CKDG5 are a serious concern. The impact of prepared vascular access (VA) through planned VA creation on mortality and medical expenses remains unclear in Japanese patients with CKDG5.

Methods: We conducted a retrospective cohort study of 157 patients with CKD who started hemodialysis (HD) at Shinshu University Hospital from April 2016 to March 2021 and analyzed the relationship between the presence of a prepared VA and mortality and hospitalization expenses in elderly and non-elderly patients with CKDG5.

Results: The presence of a prepared VA was associated with lower mortality in non-elderly patients but not in elderly patients. Medical expenses, emergency HD, and hospitalization duration were significantly lower in patients with a prepared VA in both age groups. The contribution of a prepared VA to mortality and medical expenses remained consistent after adjusting for sex, performance status, comorbidities, and nutritional status.

Conclusions: A prepared VA has several benefits; however, the prognostic benefit was not observed in elderly patients with CKDG5. From a prognostic perspective, we should consider patient's general condition and predicted prognosis in proactive decision-making regarding the selection of renal replacement therapy and VA preparation in elderly patients.

PUB223

Bacteraemia in Patients on Kidney Replacement Therapy: A 4-Year Single-Centre Experience

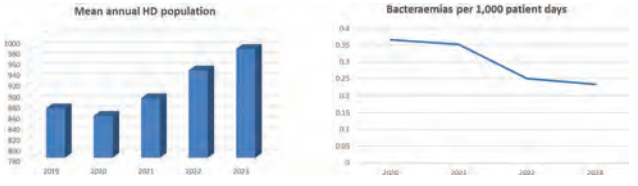
David Makanjuola, Christy R. Ratnakumar, Jahanzaib Chatha, Takudzwa J. Dhlandhlara, Olusegun O. Olalowo. *Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.*

Background: Infection is a common cause of morbidity and mortality in patients on renal replacement therapy (RRT). The majority of bacteraemias in haemodialysis (HD) patients are related to the vascular access. We decided to look at our dialysis cohort to see whether there was a difference in the incidence and types of bacteraemias based on the type of HD access and what the annual trends were over the last 4 years.

Methods: Retrospective review of patients on RRT who had bacteraemias between May 2019 to March 2024. Data collected included RRT type, blood culture results and dialysis access. Statistical analysis was done with Microsoft Excel.

Results: There were 501 bacteraemias, 435 (87%) were from patients undergoing HD. Median age was 67 years (range 19-91). The HD population rose from 872 to 982 between 2019 and 2023. The bacteraemias fell over this period from 0.36 to 0.23 bacteraemias per 1,000 patient days (figure 1). Micro-organisms isolated from HD patients were gram positive 336 (77%), and Gram negative 88(20%). Of the Gram positive organisms, 28(6.4%) were Enterococci; 275 (63%), were staphylococci [MSSA - 105 (24%) MRSA - 8 (1.8%) coagulase negative - 161 (37%)]. Dialysis access related bacteraemias were as follows: AV fistula/graft 58(13%), Tunnelled dialysis lines 332 (76 %), non-tunnelled dialysis lines 35 (8%).

Conclusions: In this cohort of patients, bacteremias were more common in HD patients. The predominant organisms isolated were Gram positive and the majority of these were coagulase negative staphylococci. The incidence of MRSA was one tenth that of MSSA. Bacteraemias were much more likely to occur in patients dialysing through lines as compared with AV fistulae or grafts. This lends weight to the drive to increase the proportion of patients dialysing through AVFs or AVGs.



PUB224

In a Heartbeat: Rapid Assessment of Cardiac Output after Arteriovenous Fistula Creation Using Point-of-Care Ultrasonography

Nasir A. Shah,[1,2] Blake Cochran,[3] Zoltan Endre,[1,2] Tracie Barber,[4] Jonathan H. Erlich.[1,2] *[1]University of New South Wales School of Clinical Medicine, Sydney, NSW, Australia; [2]Prince of Wales Hospital and Community Health Services, Randwick, NSW, Australia; [3]University of New South Wales School of Biomedical Sciences, Sydney, NSW, Australia; [4]University of New South Wales School of Mechanical and Manufacturing Engineering, Sydney, NSW, Australia.*

Background: Up to 44% of patients treated with haemodialysis develop heart failure. Though numerous observational studies have found associations between arteriovenous fistula (AVF) flow and cardiac function, the exact contribution of AVF flow on the incidence of heart failure remains unclear. The aim of this pilot study was to use point-of-care ultrasound (POCUS) to assess cardiac output (CO) after arteriovenous fistula creation.

Methods: POCUS was used to assess left ventricular outflow tract (LVOT) diameter and LVOT velocity time integral before and after AVF creation. These values were used to calculate CO. Measurements were taken preoperatively, within 1 hour of AVF creation, and after AVF maturation.

Results: Nine patients were included in the study. In all patients, there was no significant difference in CO between measurements performed prior to AVF creation and those taken immediately post-operatively. Six patients had repeat CO measurements after AVF maturation. Four patients had an increase in CO and 2 had a decrease. Overall, there was no significant between-group difference when comparing pre-operative CO to measurements taken after AVF maturation ($p = 0.77$).

Conclusions: This small study using POCUS to assess CO showed some patients increase and others decrease their CO after AVF creation. Individual patient data suggests the possibility of a functional difference where some patients are unable to increase their CO after AVF creation. Whether this inability to mount a compensatory change in CO is associated with additional changes to cardiac imaging, biochemical markers of heart failure, or clinical outcomes such as incident heart failure and all-cause morbidity/mortality needs to be examined further.

PUB225

Hyperkalaemia: Problem or Epi-phenomenon following Thrombectomy for Arteriovenous Fistulae and AV Grafts

Amy J. Forrester, Florence Coath, Stephen Henihan, Mikel Suarez, Benjamin R. Hawthorn, Karanam Munige Randika C. Wijerathne, Subash Somalanka, David Makanjuola. *Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.*

Background: Arteriovenous fistulae/grafts (AVF/G) are felt to be superior to haemodialysis catheters (HDC). Their Achilles' heel is thrombosis. This often requires intervention to 'rescue' the AVF/G, including percutaneous mechanical thrombectomy with thrombolysis [PMT] or venoplasty and stent insertion. Clot disruption by PMT carries a risk of hyperkalaemia. Some centres have protocols which do not allow PMT to be carried out if potassium (K) is > 5.0 mmol/l prior. Hyperkalaemia is less of a concern when performing thrombectomy by suction/Fogarty balloon. In our centre we perform PMT using Angiojet, a rheolytic thrombectomy device. Hence we decided to find out the magnitude of potassium rise following PMT.

Methods: Data were prospectively collected from electronic records for patients who underwent PMT for thrombosed AVF/G between November 2021 – January 2024. Demographic characteristics, K pre and post-PMT, need for dialysis prior to procedure and complications associated with HDC insertion were recorded.

Results: 15 procedures were performed in 32 patients. AVF:AVG = 19:13. M:F=20:12. Median age was 61 years (range 40-83). Mean time interval between thrombosis and thrombectomy was 3.02 days (range 1-7). Mean K at time of thrombosis was 5.34mmol/l (range 4 - 7.1). 28 patients had a HDC inserted pre-procedure, of which 21 patients had K > 5.0mmol/l. One non-functioning HDC needed re-insertion. Mean pre-PMT K was 4.54mmol/l (range 4.2 - 5.3). Mean post-PMT K was 4.72mmol/l (range 3.7-5.7); samples were obtained between 1 - 26 hours (mean 7.44) after the procedure. Mean change in K pre and post procedure ('delta K') was +0.19mmol/L (range -0.9 to +1.3).

Conclusions: We report the outcomes of PMT in AVF/G with focus on change in K pre and post-procedure. The average potassium change was +0.19 mmol/L. None of the patients had severe or life-threatening hyperkalaemia following PMT. Some protocols mandate measures to reduce the K prior to PMT, in some cases this means performing dialysis through a new HDC. The rise in potassium following the procedure in our patients is quite small and suggests that the threshold for instituting potassium lowering measures prior to PMT could be raised without necessarily causing severe or life-threatening hyperkalaemia following the procedure.

PUB226

Bloodstream Infections in the Context of Hemodialysis Care: Experience in a Wide Mexican Renal Health Network

Alicia Pineirua, Edgar Solis, Sergio Hernández-Estrada, Juan M. Ardavin Ituarte. Medica Santa Carmen. *Medica Santa Carmen, Mexico City, Mexico.*

Background: Infections are the 2nd cause of morbidity and mortality among hemodyalisis (HD) patients with chronic kidney disease (CKD). Preventing blood stream infections (BSIs) is challenging due to several factors. In our cohort, about 60% of patients use catheters, which is below the national average. Here we detail the experience and trends in BSI rates at our centers from 2019 to 2023, considering the interventions implemented.

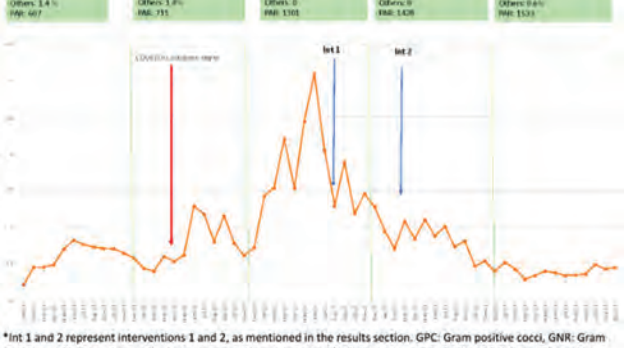
Methods: Data on BSI rates and isolated microorganisms were extracted from our electronic records. Catheter-days BSI rates were calculated. Through a chronological timeline, we described the interventions implemented in accordance with our protocols.

Results: By the end of 2023, around 2,300 individuals were receiving HD at our centers. The annual infection rates from 2019 to 2023 were 0.73, 0.81, 1.24, 0.42, and 0.50, respectively. COVID-19 lockdown in Mexico started on Apr 2020. By 2021, we started taking care of over 1,000 individuals from a new HD clinic, lacking established BSI prevention protocols, which led to a spike in BSI rates. We implemented these measures: Formed small teams within large centers (over 500 patients) to better assess BSI risk (Int 1). Developed an emergency alert and used gentamycin preventive locks when an outbreak was detected (Int 2). The strategies resulted in a 66% reduction in BSIs, sustained during follow-up. The most frequently isolated gram-positive cocci (GPC) and gram-negative rods (GNR) were S. aureus and Enterobacter sp., respectively. We did not observe increased antibiotic resistance with the use of gentamycin locks.

Conclusions: The enhancement of surveillance for individuals at higher risk of BSIs through the establishment of specialized teams within large HD centers, and the use of gentamicin preventive locks has proven effective in reducing BSI rates.

Funding: Clinical Revenue Support

Figure 1.- BSI rates per month, from 2019 to 2023.



*Int 1 and 2 represent interventions 1 and 2, as mentioned in the results section. GPC: Gram positive cocci, GNR: Gram negative rods. Proportion in the box represents the percentage of infections caused by GPC or GNR during the entire year. PAR: Patients at risk during the year (mean).

PUB227

Identifying Global Awareness of SGLT2 Inhibitors through Google Search Trend Analysis

Harshil Fichadiya,[1] Vraj Patel,[2] Wisit Cheungpasitporn,[1] Iasmina Craici.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Canton Medical Education Foundation, Canton, OH.*

Background: SGLT-2i has been identified as therapy with profound benefit in disease involving multiple organs. Initially introduced as anti-hyperglycemic drugs, they are now used for heart failure, proteinuric and early stages of non-proteinuric CKD, hyponatremia, hypomagnesemia. We performed a google trend analysis of SGLT2i related google search since 2004 and assessed the trend of this search overtime in different areas of the World. This may be an indirect measure of public awareness, availability, and utility of these medicines in different regions globally

Methods: A retrospective analysis of Google Trends was conducted for the term "SGLT-2 inhibitors" from 2004 until April 30, 2024. Search trends were assessed over time as well as per nation.

Results: A sustained rise is seen in the search trends for SGLT2i since Jan 2017 with this trend continuing to rise exponentially due to recent trials determining its benefit. The number of google searches per region have been distributed in different shades of blue with the darkest shade representing region with the highest number of searches and the lightest shade representing region with the lowest number in Fig 1. Grey represents areas with lack of enough data for the term. Highest search rates were seen in Japan, Taiwan, Hong Kong and lowest search rates were seen in Russia, China, some eastern European and South American countries. Certain areas in Central Asia, Africa, Middle east and South America did not have enough data to compute a search number.

Conclusions: Google trends are an indirect indicator of public awareness and use of SGLT-2i, given the recently identified multisystem benefit of SGLT-2i, it is important to assess the discrepancy in awareness and distribution of these drugs. Areas with lower awareness can be identified with the distribution map in Fig 1 and targeted efforts to increase awareness about kidney disease and benefit of SGLT-2i should be focused on these areas from a global health perspective. Major contributing factors to low awarness are socioeconomic disparities, unequal market distribution & lack of internet and medical literature access & efforts to mitigate these should be made to ensure equity in global health.

PUB228

Incident CKD among Canadian Immigrants: A Population-Based Cohort Study

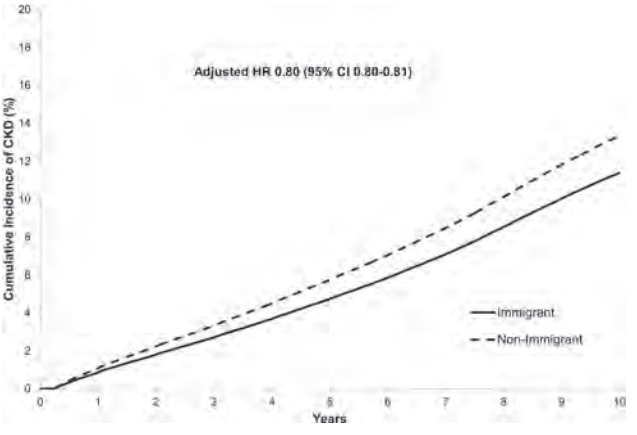
Gregory L. Hundemer,[1] Ida-Ehosa I. Olaye,[2] Ayub Akbari,[1] Manish M. Sood.[1] *[1]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [2]University of Ottawa, Ottawa, ON, Canada.*

Background: A "healthy immigrant effect" has been demonstrated for a number of chronic health conditions including cardiovascular disease, diabetes, and dementia; however, the link between immigrant status and chronic kidney disease (CKD) remains uncertain. We sought to compare the risk for incident CKD among Canadian immigrants and non-immigrants.

Methods: We conducted a population level, observational cohort study of adult Ontario residents, including foreign-born immigrant Canadian citizens and non-immigrant Canadian citizens by birth, with normal baseline kidney function (outpatient estimated glomerular filtration rate [eGFR] ≥70 mL/min/1.73m^2) between 2007-2020 utilizing provincial health administrative data. We used multivariable Cox proportional hazard regression modeling to evaluate the relationship between immigrant status and incident CKD (outpatient eGFR <60 mL/min/1.73m^2).

Results: The study cohort included 10,440,210 Ontario residents, consisting of 22% immigrants and 78% non-immigrants. The mean (SD) age and eGFR were 45 (17) years and 102 (16) mL/min/1.73m^2, respectively, and 54% of individuals were female. A total of 117,028 immigrants (5%, 7 events per 1000 person years) and 984,277 non-immigrants (12%, 16 events per 1000 person years) developed incident CKD during follow-up. Immigrants experienced a 20% lower adjusted risk for incident CKD compared to non-immigrants (adjusted hazard ratio [HR] 0.80 [95% confidence interval [CI] 0.80-0.81]) - see **Figure**. Both refugee immigrants (adjusted HR 0.87 [95% CI 0.86-0.89]) and non-refugee immigrants (adjusted HR 0.79 [95% CI 0.79-0.80]) experienced a lower risk for incident CKD compared to non-immigrants.

Conclusions: Immigrants experience a lower risk for incident CKD compared to non-immigrants. These findings provide evidence of a "healthy immigrant effect" in relation to kidney health.



Adjusted Cumulative Incidence Curves for Chronic Kidney Disease among Immigrants Versus Non-Immigrants.

PUB229

Call to Address Diabetes and CKD Disparities Leveraging the Project ECHO Model

Nicolas Cuttriss. EDAN Diabetes and CKD Disparities Learning Collaborative. *ECHO Diabetes Action Network, Chevy Chase, MD.*

Background: Racial, ethnic and socioeconomic disparities in diabetes and CKD outcomes are disheartening. Due to the shortage of specialists, the majority of adults with complex diabetes and CKD will be treated by primary care professionals (PCPs). From a health equity and population health level perspective, approaches to improving the care of diabetes and CKD must target this care setting and population. The Project ECHO® (Extension for Community Healthcare Outcomes) model is a proven tele-education and mentoring model that is designed to explicitly target frontline PCPs to address health disparities and improve patient outcomes.

Methods: To address the urgent need to offer diabetes-related ECHO programs with CKD program content, the ECHO Diabetes Action Network (EDAN) facilitated a learning collaborative to implement ECHO programing to address Diabetes Disparities & CKD in primary care. Selected "hubs" were ECHO Colorado, Rutgers, and University of Washington. Shared guiding principles drove programing. Topics, case presentation materials and evaluation tools were share. Hubs included multidisciplinary and interprofessional faculty (nephrologist, endocrinologist, behavioral health specialist, primary care clinician, pharmacist, diabetes educator, community health worker and patient advocate). Participant recruitment prioritized PCPs in safety-net/community-focused settings such as FQHCs.

Results: ECHO programs were completed within 5 months (Sep2022–Jan2023). 582 total learners participated from 70 community clinics across the country. 33% (+/- 19%) of learners participated in ≥50% of the teleECHO sessions across programs. Average weekly participation (31 +/-11) varied across hub sites. Learner evaluations demonstrated low baseline confidence in managing diabetes-related CKD. Post-program evaluation, including learner confidence and knowledge surveys. The collaborative created a replication toolkit to support additional organizations launch diabetes and CKD-related programming.

Conclusions: The care of people with diabetes and CKD falls on PCPs and community health centers due to limited access to specialists. This is compounded for minorities, the underserved and those with disparities. Implementation of the ECHO model is a strategy to explicitly address disparities in CKD through education, mentoring and collaboration among all stakeholders in the healthcare system while improving clinician satisfaction.

Funding: Commercial Support - Bayer Healthcare

PUB230

A Decade of Diversity: Exploring Ethnic Disparities in Kidney Donation in the Northeast United States

Oscar Y. Pena Zapata.[1,2] *[1]St Vincent's Medical Center, Bridgeport, CT; [2]Quinnipiac University Frank H Netter MD School of Medicine, North Haven, CT.*

Background: Over the past decade, substantial changes have affected the landscape of kidney transplantation in the Northeastern United States (Region I), comprising Connecticut, Maine, Massachusetts, New Hampshire, and Rhode Island. This region has seen a steady increase in kidney transplants, reflecting the growing trend nationwide. Still, disparities remain in kidney donation across ethnic groups. We aim to explore these disparities, utilizing data from the United Network for Organ Sharing (UNOS).

Methods: We included the UNOS database from 2013 to 2023 within Region I. Total kidney transplants, waiting lists, deceased kidney donors, and living kidney donors, categorized by ethnicity were obtained.

Results: Kidney transplants increased from 678 in 2013 to 1,004 in 2023. In 2023, 5,085 patients were on the kidney waiting list, with distribution: White 57.8%, Black 19.45%, Hispanic 15.05%, and Asian 6.6%. White patients received in 2023, 58.0% of kidney transplants, followed by Black 21.4%, Hispanic 13.0%, and Asian 6.6%. Compare to 2012, where white patients: 69.6%, Black 18.1%, Hispanic 9.1%, and Asian 2.8% In 2023, White donors constituted most deceased organ donors at 73.9%, down from 81.6% in 2013. Black deceased donors were in 2023 6.1%, up from 2013 5.1%. Both Hispanic and Asian deceased donors increased. In 2023, 81.9% of living donors were White, 8.1% Hispanic, 4.7% Black, and 4.1% Asian. Black living donors decreased from 6.1% in 2013 to 4.7% in 2023. Blacks received a lower proportion of kidney transplants compared to their waiting list representation, with similar disparities in both deceased and living kidney donations.

Conclusions: The ethnic disparity persists within Region I. To ensure everyone has access to life-saving treatments, it is imperative to promote equity, diversity, and inclusion in organ donation and transplantation. Collaborative initiatives involving healthcare providers, policymakers, and community organizations are essential to address these disparities and foster a supportive transplantation system.

Table 1. Comparison of UNOS Kidney transplant data from 2013 to 2023

Category	2023 (%)	2013 (%)
Kidney Deceased Donor by Ethnicity		
White	73.9	81.6
Black	6.1	5.1
Hispanic	16.3	9.0
Asian	1.3	0.4
Living Donor by Ethnicity		
White	81.9	82.7
Black	4.7	6.1
Hispanic	8.1	7.3
Asian	4.1	1.0

PUB231

Identifying Global Awareness of Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) through Google Search Trend Analysis

Harshil Fichadiya,[1] Vraj Patel,[2] Wisit Cheungpasitporn,[1] Iasmina Craici.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Canton Medical Education Foundation, Canton, OH.*

Background: GLP-1 RA initially introduced as anti-glycemic agents are now found beneficial in HF, ASCVD & CKD and most popularly in treatment of Obesity. This has made GLP1RA a popular choice among patients with a higher BMI and diabetes requiring a kidney transplant. We performed a google trend analysis of GLP1RA related google search since 2004 and assessed the trend of this search overtime and in different areas of the World. This may be an indirect measure of public awareness, availability, and utility of these drugs in different regions globally.

Methods: A retrospective analysis of Google Trends was conducted for the term "GLP-1 Receptor Agonist" from its inception in 2004 until May 21, 2024. Search trends were assessed over time as well as per nation.

Results: Search started trending up from 2020 & increased exponentially from September 2023. The number of google searches per region have been distributed in different shades of blue in Fig 1 with the darkest shade representing region with the highest number of searches and the lightest shade representing region with the lowest number. Grey represents areas with lack of enough data for the term. Highest search rates were seen in Denmark, USA, South Korea and lowest search rates were seen in Russia, Vietnam and Turkey. Many African, some Eastern European and some central Asian countries did not have enough data to compute a search number. Search trends more or less corelated with search trends of obesity and to a lesser extent to diabetes and CKD.

Conclusions: GLP1RA are found to be beneficial in treatment of multiple disorders like HF, obesity, diabetes and CKD which are major contributors to morbidity and mortality in the current time. Equal awarness, distribution and access to these drugs is essential from a global health perspective. Map in Fig 1 helps us identify area with low awarness (as indicated indirectly by low google search trend) such that targeted efforts can be channeled to these areas to improve access and awareness. Some common causes of low awarness maybe socioeconomic disparities, high cost & lack of medical literature access and efforts should be made to mitigate these

PUB232

STARx Health Care Transition Readiness Scores among Arabic-Speaking Youth with Chronic Conditions

Yara Abumohsen, Peter Said, Maria E. Ferris. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: We assessed Healthcare transition (HCT) readiness among Arabic-speaking youth with chronic conditions—an often-underrepresented group in HCT literature. Using the STARx Questionnaire our study examined 107 youths (mean age 13.3 years) with diverse chronic conditions, such as kidney issues, thalassemia, and diabetes mellitus.

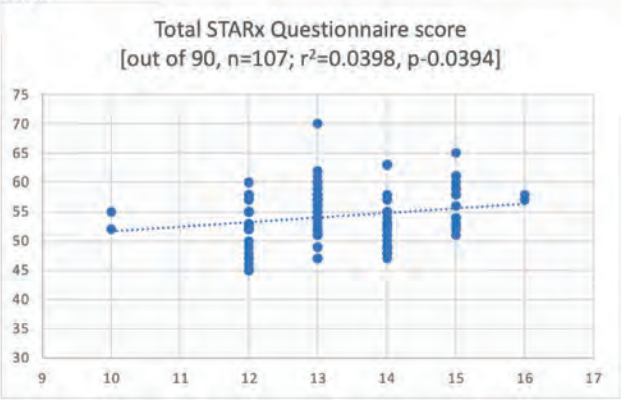
Methods: The 18-item self-administered STARx Questionnaire has been utilized in 15 countries to determine HCT. After Arabic translation/back translation from and to English, the questionnaire was administered at Zagazig Hospital in Egypt.

Results: The HCT readiness assessment revealed an overall score of 54.30 out of 90, with a weak positive correlation between age and the STARx Questionnaire score (Linear regression line: r^2=0.0398, p-0.0394, Figure 1). Further analysis using the STARx Questionnaire showed that the scores for the disease knowledge, self-management,

and provider communication subdomains were 15±1/20, 15±2/25, and 12±2/20, respectively with a significant positive correlation with age. The percentages of possible maximum score in each domain were 75±6, 61±7, and 62±10, respectively. Significant sex differences emerged, with males having significantly lower scores in the following questions: "How easy or hard is it to take care of yourself?" (p=0.0364), "How often do you forget to take your medication?" (p=0.0025), "how often did you need someone to remind you to take your medicines?" (p=0.0032), and "how often did you take your medicines on your own?" (p=0.0316).

Conclusions: In this Arabic-speaking cohort of youth with chronic conditions, the average HCT readiness score was 54/90 with the best domain in disease knowledge. As in other countries, we observed significant sex differences in self-management and medication adherence which require attention to improve long-term outcomes. Providers need to develop strategies to augment HCT readiness.

Figure 1: Relationship between youth age and total STARx Questionnaire score



PUB233

Planning for Locally Provided Haemodialysis Care in Badu Island in the Torres Strait: Kikirrui dan Walmai Project

Jaquelyne T. Hughes, Candice M. Liddy-Stokes, Katie Cundale, Karla J. Canuto. *Flinders University College of Medicine and Public Health, Adelaide, SA, Australia.*

Background: Diabetes is a very common cause of morbidity in the Torres Strait, the remote island region of Australia that has been inhabited for many thousands of years by Torres Strait Islander people. Morbidity and mortality related to diabetes and kidney disease emerged post-colonisation, and in the 1990s, Tribal leaders across all Island clusters endorsed the Torres Strait Health Strategy. This strategy identified that investment in health infrastructure – including buildings, staffing needs, and care models – are critical to ensure locally provided, culturally safe care was available for adults living with diabetes-related kidney failure. Tribal Elders from the main island of the Western Cluster of the Torres Strait, Badu Island, prioritised locally available haemodialysis as key health infrastructure. Here, we describe the community-defined infrastructure needs for safe and quality haemodialysis care on Badu Island.

Methods: Badu Island Tribal elders sought to establish a culturally knowledgeable, Torres Strait Islander-led team to engage community members on Badu, Mabuiag, and Moa Islands, as well as community members living in Cairns. The research and its conduct was approval by Maluilgal Tribal Governance, and supported by an Australian National Health and Medical Research Council Fellowship.

Results: The team met with communities in the Torres Strait in October 2023 and in Cairns in December. At each meeting, the attendees supported the pursuit of a dialysis unit on Badu Island. The need to also pursue funding to support community-led restorative health initiatives was also discussed. A report consolidating those engagement visits was relied upon to make a Commonwealth Government Grant, approximating $3.5million to support a new build of 4-chair haemodialysis unit.

Conclusions: Tribal governance was the persisting attribute in bringing together a report that summarised a health plan for locally delivered haemodialysis. The zageth will continue with the award of funds to commence building, and parallel zageth to identify a clinical training pathway for Torres Strait Islander clinicians to provide dialysis care and related health care.

Funding: Government Support - Non-U.S.

PUB234

Conducting a Patient Panel Discussion to Highlight the Intersection of Humanism and Health Equity

Asheen Zariat, Andrea Bilger, Mlka Mengesha, Lawrence B. Holzman, Yuvaram N. Reddy. *University of Pennsylvania, Philadelphia, PA.*

Background: Medical humanism is defined as "attitudes and actions that demonstrate interest in and respect for the patient that addresses the patient's concerns and values." While research shows physicians' implicit biases about minority patients affects their care, there is less research on the possibility of an "empathy gap" for these patients. Encouraging humanism in medicine could be one way of countering bias which may exacerbate disparities in outcomes for Black patients experiencing Chronic Kidney Disease (CKD). Patients as teachers is a pedagogical technique that has been noted to be impactful in changing attitudes of clinicians. In honor of Dr. Sidney Kobrin, a highly esteemed nephrologist and humanist who unexpectedly died in 2023, we conducted a panel discussion which aims to honor his legacy of humanism while furthering our understanding of how to practice humanism in a way that incorporates an understanding of health disparities and social determinants that drive these disparities

Methods: We conducted a panel discussion of 2 patients and 1 staff member who worked extensively with Dr. Kobrin, including self-identified Black individuals with CKD and women. This 60-minute panel discussion ocurred during a larger Humanism symposium with an audience of 200+ people. Questions explored panelist perspectives on aspects of humanism embodied by Dr. Kobrin, how these aspects of humanism address power differentials, medical mistrust, and barriers to care, and how can clinicians incorporate these principles into their daily practice. Afterwards, a 20 minute reflection session was conducted with 3 audience members.

Results: Recordings of the panel discussion and reflection session will by analyzed and coded by two independent coders who will generate a summary of broad themes regarding humanism's role in medicine and in addressing health disparities. We will assess whether this panel discussion might lead to new ideas on how to provide more humanistic, equitable care.

Conclusions: This project will bring together people from different racial and socioeconomic groups and different power structures to identify broad themes of humanism that have the potential to address health inequities. This experience could be especially empowering for patients of marginalized backgrounds who may not see themselves represented in their providers.

PUB235

Ethics of Dialysis in People with Advanced Kidney Disease Who Inject Drugs

Rachel E. Brobst, Jean Lee, Alexandra Green, Suzanne Boyle. *Temple University Hospital, Philadelphia, PA.*

Background: Barriers such as unstable housing, lack of insurance, and social stigma make it challenging to secure outpatient dialysis for people who inject drugs (PWID) with advanced kidney disease. We describe four cases from our center and propose a bioethical framework for guiding clinicians in dialysis planning.

Methods: Cases were obtained through review of medical records from 2022-2024. Inclusion criteria were: PWID, chronic xylazine wounds, CKD stage 5 or end-stage kidney disease, and life-prolonging goals of care. We described their baseline characteristics, time of initial presentation (each presented for nonhealing leg wounds), management decisions regarding dialysis, and long-term outcomes.

Results: See Image 1

Conclusions: These are challenging cases as there are no established guidelines for determining outpatient dialysis candidacy. Decisions are often driven by unfounded stereotypes which typically default to declaring the patient unfit. We propose evaluating patients through the lens of four bioethical principles: autonomy, beneficence, nonmaleficence, and justice. This strategy permits evaluation of the risks and benefits to the individual, system, and society. In each of the outlined cases, the patients' goal is life prolongation (autonomy), and 3 have begun dialysis (beneficence). Nonmaleficence is often cited when discussing long-term dialysis candidacy, due to concern patients may inject into catheters, increase risk of infection, and hasten death. Two patients have tunneled catheters and have not used their catheters to inject drugs. Justice is the most nuanced of the principles, given the systemic barriers to placing high-risk patients in dialysis units and the psychosocial barriers to accessing appropriate dialysis care, as evidenced by the 120 hospital visits for these patients since time of identification. In summary, PWID with concomitant advanced kidney disease present a unique challenge. Patients and clinicians can implement a systematic framework with these four bioethics principles to evaluate outpatient dialysis candidacy.

Patient	Age	Sex	Housing Status	Initial Presentation	Decision	Long-term Outcomes	# hospitalizations since presentation
#1	37	Male	Housed	11/2023	HD started 01/2024 for hyperkalemia; HD unit assigned, left AMA, lost unit	Presents every ~2 weeks to ED needing emergent HD. No unit assigned	24
#2	41	Male	Unhoused	01/2024	Managed conservatively	Remains off HD. Attended 1 follow up appointment	9
#3	56	Male	Unhoused	05/2022	Attended follow up appointments, managed conservatively	Started HD 11/2023 for hyperkalemia. Assigned HD unit 04/2024	53
#4	42	Male	Housed	10/2022	HD started 01/2024 for hyperkalemia/acidemia.	Presents every ~2 weeks to ED needing emergent HD. No unit assigned	34

Results

PUB236

Using Social Media/Mainstream Media Surrounding Transplantation Education: Perspective on CKD

Shahid N. Muhammad. *Coventry University, Coventry, United Kingdom.*

Background: The use of social media (SM) today provides unparalleled opportunities to provide and receive education, access to communication and engagement. SM/ mainstream media (MM) such as television, newspapers, magazines, and radio stations are also being used to prompt education surrounding specific Long-Term Conditions (LTCs). Certainly, use of SM is not limited by constraints of time and geography. Three questions being proposed here: 1) Is there a Faith stance on using SM/ MM to prompt organ donation/ transplantation education? 2) Can those who follow Faith donate organs? and 3) Does the Healthcare Scientist have a role providing the public education surrounding organ donation/ transplantation? Chronic Kidney Disease (CKD) will be used to provide a LTC example.

Methods: There is a need for multi-channel approaches so that the issue is a more widely known social norm in primary care, where healthcare scientists will know underlying pathologies. If those with Faith decide to donate an organ, they must do so out of free will without being morally or socially forced and without economic pressures. If the deceased indicated during life (in a will) that they do not want to donate organs, then no one is authorized to do this on the deceased person's behalf.

Results: More educational campaigns via SM/ MM involving healthcare scientists and Faith communities are required. Bridging gaps in health literacy (HL) is also important. This is where healthcare scientists have an important role, to provide health science transparency where other health professionals are challenged. Clarity of terminology to help increase HL on topics relating to organ donation/ transplantation is now especially required owing to more time being spent online.

Conclusions: 1) The Faith stance on use of social media to prompt organ donation/ education has not been investigated. 2) Those who follow Faith can donate organs, and 3) More research is required to shed light on what is the most effective approach for healthcare scientists in above context.

PUB237

Exploring the Educational Implications of Declining Nephrology Fellowship Interest: A Comparative Analysis of Internal Medicine Specialties Using GPT-4

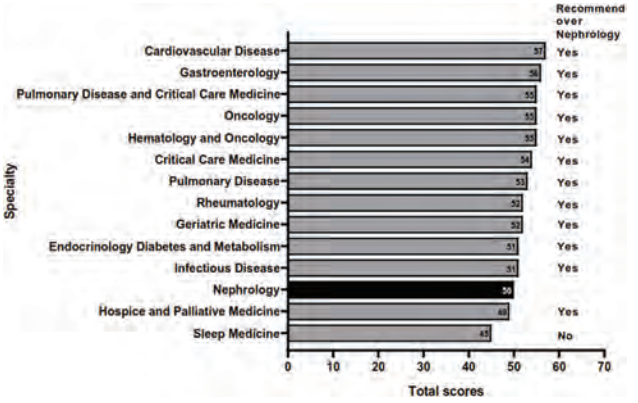
Oscar A. Garcia Valencia, Charat Thongprayoon, Iasmina Craici, Wisit Cheungpasitporn, Jing Miao. *Mayo Clinic Minnesota, Rochester, MN.*

Background: The 2024 US fellowship match shows a concerning decline in interest in Nephrology with an 11% drop in candidates and only 66% of positions filled. We used Chat GPT to discern the factors affecting this trend and devise educational strategies to attract more trainees.

Methods: Using GPT-4, we compared Nephrology to 13 Internal Medicine specialties based on factors such as intellectual complexity, work-life balance, procedures, research, patient interactions, career demand, and remuneration. The model assigned scores (1-10) based on how well each specialty performed. The cumulative score determined ranking. To mitigate bias, we instructed GPT-4 to prioritize other specialties over Nephrology in hypothetical reverse scenarios.

Results: In GPT-4's evaluations Nephrology ranked only above Sleep Medicine. It lagged in crucial aspects such as a healthy work-life balance, strong patient relationships, and meeting career demands. While the match fill rate was 66%, slightly higher than Geriatric Medicine's 45%, there was a decline ranging from 4% to 14% across five critical criteria, encompassing intellectual challenge, procedural engagement, career prospects, research and academic opportunities, and financial compensation.

Conclusions: Nephrology's attractiveness is declining compared to other Internal Medicine specialties. This trend is concerning and calls for a reassessment of the factors influencing specialty choices among medical residents. The insights provided by AI can be used to redesign nephrology training programs, curriculum, and mentorship initiatives and apply them to improve medical education and career guidance. Further educational research and interventions are needed to comprehensively reassess nephrology education and training, and specific areas for future research and educational initiatives should be proposed to address the declining interest in the specialty.



PUB238

Awareness of Nephrology Fellows regarding Hepatitis B Vaccination in Patients with CKD Approaching Dialysis

Sobia N. Khan. *Stony Brook University, Stony Brook, NY.*

Background: Dialysis patients face a heightened risk of hepatitis B infection due to their immunocompromised state and frequent exposure to body fluids. Vaccinating these patients is cost effective than monthly monitoring of antigen/ antibody titers. Due to immunosuppression, they are prone to becoming chronic carriers. Our goal is to raise awareness, enhance knowledge and improve the hepatitis B vaccination rate among chronic kidney disease (CKD) patients.

Methods: We developed a tool including questionnaire to evaluate Nephrology fellows' perception of the importance of Hepatitis B vaccination in CKD patients, followed by one-on-one discussion with a nephrology attending. This study was conducted over a year.

Results: In the year prior to the educational intervention, 34 new patients were admitted to our outpatient dialysis unit, of these 10 patients (29%) were vaccinated meaning 24 patients (71%) were unvaccinated before starting dialysis. After implementing the educational program, a follow-up questionnaire revealed that the fellows' proficiency in hepatitis B vaccination knowledge increased from 70% to 90% following the lecture. This indicated a significant improvement in awareness and understanding which we hope will translate into higher vaccination rate among CKD patients. We reviewed new ESRD admissions a year later to assess the impact of improved awareness among fellow physicians. Charts of newly admitted patients revealed that 46 patients started chronic dialysis. Among them 15 (32%) needed vaccination at the initiation of dialysis while 31 (67%) were vaccinated beforehand. Table 1

Conclusions: The data indicated that although fellows' clinical knowledge improved after the educational intervention, their effectiveness in ensuring patients received the vaccination did not show significant improvement. To enhance the fellows' efficiency in vaccination, the next step could be to ensure standardizing the process of Hepatitis B vaccination in CKD patients, which can be implemented by order bundle set for chronic kidney disease in the electronic medical records (EMR).

Table 1: Analysis pre and post intervention

	Pre	Post
New patients	34	46
Vaccinated before dialysis	24	31
Received vaccination after Dialysis	10	15

PUB239

Importance of the Nephrologist in Teaching AKI

Juan P. Gomez Villarreal, Paola Borbolla-Flores, Ricardo A. Garza Treviño, Mara C. Olivo Gutierrez, Lilia M. Rizo Topete. *Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico.*

Background: Acute Kidney Injury (AKI) is associated with high mortality and morbidity, and the cost of treating patients with AKI is substantial. However, there are currently several challenges in early recognition. One of them is the concepts that should

be taught from basic science to postgraduate medical students. The use of new tools to teach AKI definition and early recognition is important for improving healthcare and medical practice.

Methods: We conducted a survey in 321 participants, that included medical students, general practitioners, and those with different specialties. This survey was able through google forms we evaluated the knowledge of AKI with the next questions. Which of the following classifications is correct for defining acute kidney injury? How is acute kidney injury defined? What is considered the first cause of acute kidney injury? Which of the following parameters tells us about acute deterioration of renal function? What is considered to be the first cause of acute kidney injury? Which of the following parameters tells us about acute deterioration of renal function? Do you consider urinary sediment to be a diagnostic tool for acute kidney injury? Do you consider this a risk factor for the development of acute kidney injury?

Results: The most relevant findings were in risk factors, in which the poll had more opportunities to grow because they did not associate premature birth and preeclampsia with 64% and 46.7%, respectively, 30.8% did not think that urine sediment is a diagnostic tool, about the classification the poll uses KDIGO in the 69.1%, AKIN in 18.6%, and RIFLE in 5.9%.

Conclusions: There has been a growth in the knowledge of AKI, but there is still work to be done in teaching the risk factors and diagnostic tools. We must also reinforce correct classification using technology and educational meetings or conferences.

PUB240

Decoding the Renal Puzzle: Idiopathic Distal Renal Tubular Acidosis in a 23-Year-Old Woman with Nephrocalcinosis and Metabolic Acidosis

Graciela M. Luna, Daniela Carralero Somoza, Umair S. Ahmed, Kaitlyn Cariaga. *Lakeland Regional Medical Center Inc, Lakeland, FL.*

Introduction: Distal Renal Tubular Acidosis (dRTA) is a cause of normal anion gap metabolic acidosis. Its etiology encompasses various factors, including autoimmune diseases, genetic mutations affecting chloride-bicarbonate exchanger genes, and drug-induced occurrences, such as with lithium, amphotericin B and Toluene inhalation due to glue sniffing. dRTA can also manifest as an idiopathic disorder.

Case Description: A 23-year-old female with an unremarkable medical history presented to the emergency department with nausea, vomiting, bilateral flank pain and fever. Prior to seeking emergency care, the patient had visited an urgent care facility where she was provisionally diagnosed with a urinary tract infection and treated with Bactrim. Upon admission, her creatinine level was 1.14 mg/dL, serum potassium was 2.9 mmol/L), serum bicarbonate 10 mmol/L, and an anion gap of 12. Urine pH was 6.0. CT abdomen/pelvis disclosed severe bilateral nephrocalcinosis in the renal pyramids and the presence of calculi. Urine anion gap was positive. Subsequent investigations ruled out rheumatoid arthritis, Sjogren's disease, lupus and multiple myeloma. Patient was discharged on PO sodium bicarbonate and potassium chloride which was switched as an outpatient to potassium citrate. 24 hour urine collection recommended as an outpatient prior to starting potassium citrate to evaluate for hypocitraturia could not be done due to financial constraints.

Discussion: Distal RTA is an uncommon disorder. Pathophysiology of distal RTA involves damage to alpha-intercalated cells in the distal tubule, impairing the secretion on hydrogen ions, consequently raising the urine pH and causing metabolic acidosis. Hypokalemia occurs due to the failure of H/K ATPase. This case highlights the importance of checking a urine anion gap in patients with normal anion gap metabolic acidosis and the need to consider distal RTA in patients who have nephrocalcinosis. Timely diagnosis of distal RTA is crucial to preventing long-term complications such as nephrocalcinosis and nephrolithiasis, allowing early initiation of alkali and potassium supplementation. Furthermore, distal RTA can sometimes be the first manifestation of an underlying autoimmune condition and once it is diagnosed, attempts should be made to identify the cause of the distal RTA.

PUB241

A Case of Multifactorial Severe Hypophosphatemia

Andrew Murphy, Matthew Sangoi, Toni Sabbouh. *Pennsylvania Hospital, Philadelphia, PA.*

Introduction: Hypophosphatemia is defined as serum phosphate < 2.5 mg/dL. It is induced by internal redistribution, decreased intestinal absorption, or urinary wasting. We present a case of multifactorial severe hypophosphatemia in the setting of chronic alcoholism and presumed refeeding syndrome.

Case Description: A 69 year old male with a history of alcohol use disorder presented to the ED with generalized muscle weakness, recurrent falls and confusion. He reported consuming 2 bottles of wine daily for several years, with his last drink 24 hours prior to presentation. He reported a history of caloric restriction with intentional weight loss followed by a recent increase in caloric intake in the preceding week. His initial presentation was consistent with sepsis from contained sigmoid perforation due to foreign body ingestion, likely a chicken bone. Labs revealed phosphorus < 1, potassium 2.0, magnesium 1.4, lactate 8.5, WBC 6.1 with 34% band neutrophils, mild alkalosis (venous pH 7.43), pCO_2 42, HCO_3 24. He was admitted to the ICU and received volume resuscitation, IV antibiotics, management of alcohol withdrawal, intravenous phosphate, potassium and magnesium. Repeat labs showed improved phosphorus to 1.9, however serum corrected calcium decreased from 9.5 to 7.5 mg/dL. He continued to receive further repletion of electrolytes with eventual normalization.

Discussion: The etiology of this patient's severe hypophosphatemia was multifactorial from chronic alcoholism and refeeding syndrome. Refeeding syndrome was likely present in this case given the patient's malnutrition and weight loss with recent significantly increased caloric intake resulting in severe hypophosphatemia, hypokalemia and hypomagnesemia. His generalized muscle weakness can be explained by alcoholism and severe electrolyte derangements. Fortunately, he did not develop respiratory failure which is a complication of severe hypophosphatemia as a result of decreased intracellular ATP. For patients with severe hypophosphatemia (< 1 mg/dL), IV phosphate repletion is recommended with level monitoring every six hours. This patient developed hypocalcemia in the setting of phosphate repletion, which is a known complication and should be monitored closely.

PUB242

A Case of Hyponatremia Due to Unilateral Renal Hypoperfusion from a Type B Aortic Dissection

Andrew A. Lin,[1] Nadia Al Haddad,[2] Kristen N. Tillquist,[2] Jordana B. Cohen,[1] Nathaniel Reisinger.[1] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]Penn Medicine, Philadelphia, PA.*

Introduction: Hypoosmolar hyponatremia in euvolemic patients has a broad differential diagnosis and significant potential morbidity. Much of the underlying pathophysiology in hypoosmolar, euvolemic hyponatremia stems from ADH secretion, whether from ectopic overproduction or the body attempting to regulate perceived osmolar and volume status. Here, we present a case of severe symptomatic hyponatremia due to unilateral renal hypoperfusion.

Case Description: A 64-year-old male with a past medical history of hypertension and type A aortic dissection presented with a new type B aortic dissection. Blood pressure was elevated to the 170s/90s and was quickly controlled with carvedilol, hydralazine, and clonidine. On admission, the patient's sodium was 137. Late on hospital day 2, the patient became confused and unable to follow commands. The sodium was now 120 with urine sodium 30, urine osmolality 786, and serum osmolality 259. On physical exam, he was euvolemic with a blood pressure of 121/89. Jugular venous distention, pulmonary rales, and edema were absent. Repeat urine sodium was 10 and urine osmolality was 521. The patient received multiple 3% hypertonic saline boluses which stabilized his sodium at 128 on day 4. Review of the patient's imaging demonstrated the right renal artery arising from the false lumen of his dissection with decreased contrast uptake, versus the left renal artery which arose from the true aortic lumen. We hypothesized that the patient's hyponatremia was due to unilateral renal hypoperfusion causing increased renin secretion by the right kidney, leading to stimulation of sodium resorption by angiotensin II, and ultimately increased ADH secretion leading to hyponatremia. The patient was placed on fluid restriction and his sodium stabilized at 133; he was discharged with instructions for close nephrology follow-up.

Discussion: While renal hypoperfusion such as in unilateral renal artery stenosis can cause hyponatremia, this is usually accompanied by hypertension (hyponatremic hypertensive syndrome). Here, the patient's euvolemia and initial urine studies suggested SIADH until revisiting his abdominal imaging. A high degree of clinical suspicion is thus required for alternative anatomic causes of hyponatremia and ADH secretion in response to perceived hypovolemia.

PUB243

A Unique Case of Hypokalemic Periodic Paralysis with Resolution after Successful Surgery for Cervical Stenosis

Ahmed A. Zaher, Matthew D. Nguyen, Ramy M. Hanna. *University of California Irvine Nephrology Hypertension & Kidney Transplantation, Orange, CA.*

Introduction: Hypokalemic periodic paralysis is a rare neuromuscular condition that presents with episodic severe muscle weakness, often triggered by strenuous exercise or high carbohydrate diets, that can be further divided into two major types, primary and secondary. The primary type could be genetically inherited or sporadic. The most common mutation causing this condition is CACNA1S gene mutation and the SCN4A gene mutation. The secondary type could be caused by any renal or gastrointestinal pathology causing loss of potassium, along with certain drugs like loop diuretics, thiazide diuretics, laxatives, corticosteroids, beta adrenergic agonists, insulin, and glucose. Here we present a unique case of a 29-year-old white male patient who presented with periodic paralysis attributed to his hypokalemic status.

Case Description: This previously healthy patient did not have any of the secondary causes or any other known condition to cause his periodic paralysis. His serum potassium was between 3.6 to 3.8 mmol/L, and genetic analysis proved that he has a mutation in his CACNA1S gene. Moreover, he has a mutation in 11B-HSD gene causing him to have aberrant mineralocorticoid excess. He reported several episodes of loss of consciousness which is atypical of primary hypokalemic periodic paralysis. Later, after he was treated for cervical stenosis as he was investigated for symptoms of cervical radiculopathy, he reported complete resolution of his symptoms and declines any further episodes of loss of consciousness. At this time, potassium supplements were stopped, given no indication to continue them. However, he was advised to continue to take amiloride if his serum potassium levels dropped below 4 mmol/L.

Discussion: The patient's clinical presentation is believed to be attributed to his cervical spine lesion instead of his hypokalemic periodic paralysis. More research is required to determine the level of genetic penetrance in each case to customize the treatment accordingly with precision medicine, improving outcomes and minimizing potential adverse effects.

PUB244

Chronic Hypokalemia Secondary to Distal Renal Tubular Acidosis Induced by Sodium Valproate

Abhi Lohana, Usman Akbar, Neeharika Muddana. *Camden Clark Medical Center, Parkersburg, WV.*

Introduction: Sodium Valproate is a commonly prescribed medication for the treatment of various conditions, including mood disorders and epilepsy. However, it can lead to rare adverse effects, such as valproate-induced distal renal tubular acidosis (dRTA), which results in a non-anion-gap metabolic acidosis with associated hypokalemia. We report a case of dRTA in a patient with a history of chronic hypokalemia attributed to long-term sodium valproic acid therapy.

Case Description: A 61 y.o. female with a past medical history of hypertension, anxiety, depression, and tobacco dependence with half a pack per day, was admitted to the hospital for concern of bilateral lower extremity muscle pain and weakness for the last 5 days which worsened to numbness and led to difficulty ambulating. She mentioned that she has been told on multiple outpatient visits that she had low potassium for the last 1-2 years and no workup was done in the past. She does not recall any family history of hypokalemia. Her home medications include sodium valproate, lisinopril, olanzapine, and ondansetron. On arrival at ED the patient was found to have a Potassium level of 1.8 was a significant drop from her previous labs. On further evaluations, the patient had non-anion gap metabolic acidosis in the blood. Urine studies showed an alkalotic pH of 7.0, potassium of 44, sodium of 93 and chloride of 116 concerning of urine anion gap of 21 suggesting renal tubular acidosis. Other labs like thyroid function tests and renin aldosterone studies were within normal limits.

Discussion: Valproate-induced dRTA is a rare and idiosyncratic side effect of long-term valproic acid therapy. DRTA is characterized by impaired acid secretion in the distal renal tubules, leading to metabolic acidosis and hypokalemia. In this case, the patient's chronic hypokalemia was likely exacerbated by valproate use, which prompted the development of dRTA. This case emphasizes the importance of recognizing valproate-induced distal renal tubular acidosis as a rare but potentially serious complication of long-term valproic acid therapy. Prompt diagnosis and appropriate management are vital for the patient's well-being.

PUB245

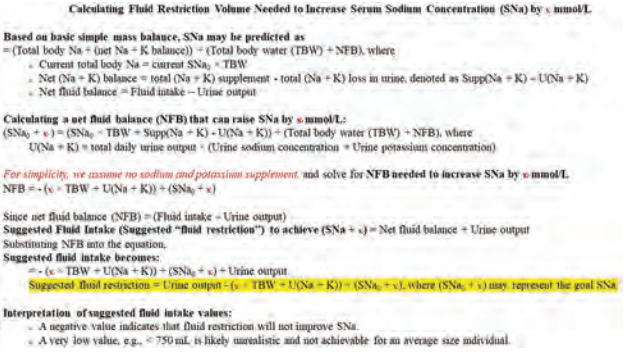
Fluid Restriction in Hyponatremia

Phuong-Chi T. Pham,[1] P.M. T. Pham,[3] Phuong-Thu T. Pham.[2] *[1]UCLA Medical Center Olive View, Sylmar, CA; [2]Ronald Reagan UCLA Medical Center, Los Angeles, CA; [3]VA Greater Los Angeles Healthcare System, Los Angeles, CA.*

Introduction: Fluid restriction (advised as fluid intake of 500 mL below average daily urine output, Hyponatremia Expert Panel 2007) to correct hyponatremia for euvolemic/hypervolemic hyponatremia is often minimally effective or ineffective. We present a case illustrating how failure of fluid restriction can be mathematically predicted.

Case Description: A 48-year-old male with non-ischemic heart failure with ejection fraction of 30%, presents for volume overload. Nephrology is consulted for persistent hyponatremia ranging from 122-126 mmol/L despite fluid restriction in the setting of loop diuretic use. On the day of consult, serum sodium (SNa) is 126 mmol/L. Chart review reveals daily fluid restriction of 1.8L/d with urine output averages 4L/d. Urine studies: sodium 66-95 (average 80.5) mmol/L, potassium 35-39 (average 37) mmol/L. Urine electrolyte free water clearance (EFWC) = Urine volume*(1-[urine Na + urine K]/serum Na) = 4*(1-(80.5+37)/126)=0.3L/d. Fluid "restriction" of 1.8L/d, albeit much less than urine output of 4L/d, exceeds daily EFWC of 0.3L/d. Fluid intake greater than EFWC cannot correct hyponatremia.

Discussion: As illustrated, fluid restriction to a volume below urine output in this case (i.e., 1.8L << 4L/d) exceeds the daily EFWC (i.e., 1.8L/d fluid intake > 0.3L/d electrolyte-free water lost in urine) and can never correct SNa. The suggestion to reduce fluid intake to 500 mL less than average daily urine output should be revised to be lower than daily EFWC. Alternatively, fluid restriction may be suggested to be [Urine output - $(x \times TBW + U(Na + K)) \div (SNa_0 + x)$], where x is the change in SNa desired. A negative value predicts that fluid restriction is ineffective. See figure for equation derivation and definitions of terms. Alternatively, for stable patients with euvolemic hyponatremia who are at goal SNa, advice to not exceed a predicted fluid intake volume may be given. In this case, x is set at zero. The fluid intake volume that would not worsen hyponatremia is [Urine output - $(U(Na + K)) \div (SNa_0)$].



PUB246

A Clinical Roadmap to Managing a Patient with Gitelman Syndrome

Jerin Karingattil, Yinelka G. Silverio De Castro, Eliot Sachsenmeier, James Drakakis. *NYU Langone Hospital - Long Island, Mineola, NY.*

Introduction: Gitelman syndrome is a salt wasting tubulopathy whereby the classic findings are hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria. The cause is an inactivating mutation in the SLC12A3 gene which encodes the thiazide sensitive sodium-chloride cotransporter on the apical membrane of the distal convulted tubule. There is significant variability in the phenotypic manifestatons of the disease. In any case, management includes liberal salt intake and supplementation of potassium and magnesium as the hallmarks. However, literature providing specific guidance and dosing in this arena is lacking.

Case Description: 44 year old male initially presented to the ER with palpitations and near syncope. He was found to have a serum potassium of 2.3 mmol/L and serum magnesium of 1.2 mg/dL. Both were supplemented intravenously and he was discharged with outpatient follow up. Renal magnesium loss was confirmed with 24 hour urine magnesium of 220 mg and fractional excretion of magnesium of 11%. Urine calcium was low at 60 mg per day. Genetic testing was pursued given the high suspicion for Gitelman syndrome, revealing compound heterozygous mutations in SLC12A3. As his electrolytes were in disarray and blood pressure low (~90/50 mm Hg) a treatment regimen was sought. The goal being a strategy that would be both effective, well tolerated and safe.

Discussion: Specific management of Gitelman syndrome with a prevalence of only 1-10 per 40,000 is not precisely outlined or defined. Much additional information is needed to understand the appropriate options, as supportive evidence is lacking. In this particular case, we settled upon the following: potassium chloride 40 mEq per day, magnesium chloride to provide 640 mg elemental magnesium per day, and sodium chloride tablets 2 grams three times per day. Adjustements were made along the way to

arrive at an overall stable electrolyte panel. On a recent visit, BP measured 116/80 mm Hg with serum magnesium 1.4 mg/dL and potassium 3.7 mmol/L. He has not had any additional hospitalizations for related metabolic disturbances. Future practice may be guided by this framework with the realization that goal electrolyte values may be lower than the expected range. Long term outcomes in such patients are also potential areas for further investigation.

PUB247

Unmasking the Enigma: A Case Report on Hyponatremia and Chimeric Antigen Receptor T Cell (CAR-T) Therapy in Mantle-Cell Lymphoma

Ahmad Matarneh, Sundus Sardar, Rafael Portela, Muhammad Abdulbasit, Navin Verma, Naman Trivedi, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Introduction: Chimeric Antigen Receptor T-cell (CAR-T) therapy is a new treatment for relapsed and refractory hematologic cancers. CAR-T cells are modified T-cells that express receptors targeting specific antigens on cancer cells, leading to their apoptosis and destruction. CAR-T therapy is associated with a unique adverse effects, such as cytokine release syndrome (CRS) and neurotoxicity. It can also cause electrolyte abnormalities, such as hyponatremia, hypophosphatemia, and hypokalemia. Here, we present a challenging case of hyponatremia following CAR-T therapy.

Case Description: A 66-year-old male, known to have a history of Mantle cell lymphoma, diagnosed 8 months prior to presentation. Initially treated with R-CHOP, then underwent CAR-T therapy. Two months ago, he underwent Tecartus CAR-T therapy, which was complicated by grade 2 CRS. This was managed with tocilizumab, anakinra, and dexamethasone. He was noted with hyponatremia on outpatient labs, sodium levels at 119 meq/l. Upon presentation, he was completely asymptomatic. Exam showed orthostatic hypotension; treated with normal saline 0.9%, but sodium levels remained low. His serum osmolality was low(258mosm/kg), urine sodium was high(53meq/l), and urine osmolality was high(463mosm/l), suggesting syndrome of inappropriate antidiuretic hormone secretion. He was initiated on urea powder. Despite that, his sodium levels remained around 128meq/l. Considering the orthostatic vitals, bedside ultrasound findings revealed features consistent with a hypovolemic state, including an inferior vena cava diameter of 2.1cm and respiratory collapse exceeding 50%. Given these findings, he was given intravenous fluids which resulted in improvement in his levels, discharged with instructions to maintain a liberal intake of oral fluids. Follow-up labs showed sodium increase.

Discussion: Hyponatremia, can complicate CAR-T treatment, and is frequently associated with CRS. The prompt identification and management of hyponatremia are crucial to ensure optimal outcomes for patients undergoing CAR-T therapy. CRS can be treated with immunosuppression. Treating hyponatremia in CAR-T-related cases poses challenges as one of the pathophysologies is volume depletion. Supportive measures with hydration, coupled with addressing potential underlying CRS, can aid in management.

PUB248

Inhalation Burn from a Fire Extinguisher: A Rare Cause of Acute Phosphate Toxicity

Madhab Ray, Brian Y. Young, Hiba Hamdan, Lindsey R. Goetz. *University of California Davis, Davis, CA.*

Introduction: Dry chemical fire extinguishers often contain monoammonium phosphate (MAP). Inhalation of MAP can cause upper and lower airway damage leading to acute respiratory distress syndrome. It is also a rare cause of acute phosphate toxicity, leading to a potentially fatal constellation of metabolic derangements including hyperphosphatemia, hypocalcemia, and high anion gap metabolic acidosis in addition to acute kidney injury.

Case Description: A 44-year-old male with psychiatric illness and no known kidney disease presented in cardiac arrest after intentionally expelling a fire extinguisher containing MAP into his mouth. He had a prolonged resuscitation and was admitted with acute respiratory failure, non-oliguric AKI, severe, mixed metabolic and respiratory acidosis, hyperkalemia, and marked hyperphosphatemia. Initial chemistry showed: Na 146, K 6.8, Cl 104, C02 9, Ca 11.7, Phos 40, BUN 24, Cr 1.29, anion gap 41, lactic acid 4.8. Arterial blood gas showed: pH 6.77, pCO2 100, pO2 12. The patient was treated initially with inotropes and mechanical ventilation along with bicarbonate infusion. As there was no clinical improvement despite robust urine output, sustained low-efficiency dialysis was started. His metabolic derangements resolved within 24 hours and his creatinine stabilized near 1.3 off dialysis. Unfortunately, the patient died of severe hypoxic brain injury. His family donated his kidneys for transplantation. One of the allografts (for which data are available) functioned well without evidence of acute phosphate nephropathy on subsequent biopsy.

Discussion: Organophosphorus poisoning often results from use of pesticides. However, poisoning from inorganic phosphate like MAP is rare. MAP is used as a fertilizer, stabilizing agent to reduce cadmium mobility in soil, and fire retardant or extinguisher. It is recognized to cause respiratory compromise, yet its metabolic consequences are infrequently reported. MAP inhalation and ingestion lead to very high phosphorus levels and a high anion gap metabolic acidosis, due in part to the contribution from the inorganic phosphate anion. It is important to remain aware of this rare poisoning. There is no antidote available. Treatment is supportive and the outcome is often fatal. In this case rapid initiation of dialysis resolved the metabolic abnormalities and prevented long term damage to the kidneys.

PUB249

Unusual Presentation of Sjogren Disease with Proximal Renal Tubular Acidosis

Jee Hoon Kim, Eric Siddall. *Columbia University, New York, NY.*

Introduction: Sjogren's disease (SD) has many renal manifestations. We present a case of type 2 (proximal) renal tubular acidosis (pRTA) with Fanconi syndrome and tubulointerstitial nephritis (TN) treated with maintenance mycophenolate mofetil (MMF), tacrolimus (TAC) and low dose steroids in a SD patient.

Case Description: 69-year-old female with history of SD presented for evaluation of elevated creatinine (Cr). The patient's SD symptoms were bone pain, stiffness in her lower extremities eventually leading to a wheelchair bound state and dry mucous membranes. She denied any family history of kidney disease. Labs showed a Cr 1.36 mg/dl, bicarbonate 18 mmol/L, potassium 3.2 mmol/L, glucose 96 mg/dl, phosphate 1.7 mg/dl, uric acid 1.6 mg/dl, vitamin D 25 OH 19 ng/ml, vitamin D 1, 25 OH 15 pg/ml. Urinalysis was significant for pH 6, sterile pyuria and glucosuria. Her fractional excretion of phosphate was 34.6%. Lab work was consistent for pRTA. Due to the sterile pyuria, a renal biopsy was done which showed acute on chronic TIN with severe activity. The patient started 50 mg of prednisone daily. Metabolic derangements were treated orally. Unfortunately, her TIN quickly relapsed when steroids were tapered prompting initiation of MMF with another steroid taper. She again relapsed when steroids were weaned. At this point, a multitargeted immunosuppression regimen was initiated with prednisone 10 mg/day, MMF 1000 mg twice daily, and TAC with a trough goal 4-7. On this regimen, the patient's Cr has remained stable at 1.2 mg/dl with no additional flares for the last 9 years. Her prednisone was also tapered down to 5 mg. Clinically, the patient's bone pain and wheelchair bound state improved after treatment with active vitamin D and oral phosphate.

Discussion: TIN is the most common kidney manifestation in SD. Most patients are treated with 1 mg/kg of prednisone with a taper. Maintenance therapy usually involves MMF or azathioprine. TAC is rarely used for TIN in SD. In this patient's biopsy, the TIN appeared similar to acute cellular rejection and thus was treated with transplant immunosuppressive medications. PRTA occurs in around 3% of patients with SD. PRTA can lead to Fanconi's syndrome resulting in a normal anion gap metabolic acidosis, phosphaturia, glycosuria and aminoaciduria. Treatment usually involves supplementation of bicarbonate and electrolytes such as potassium and phosphate.

PUB250

Exploring Therapeutic Effects of Continuous Kidney Replacement Therapy in Patients with Severe Acidosis Using Deep Learning-Based Causal Inference

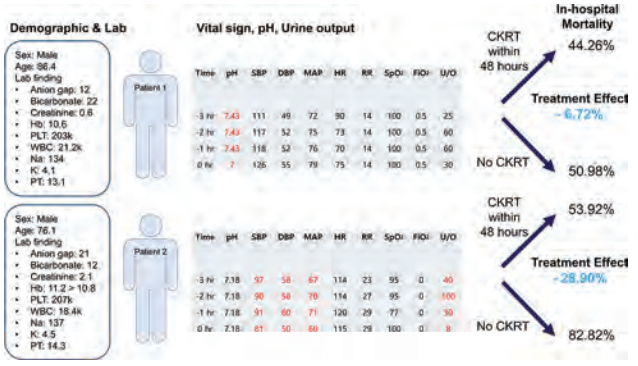
Min Woo Kang, Sehoon Park, Yong Chul Kim, Kook-Hwan Oh, Dong Ki Kim. *Seoul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea.*

Background: Continuous kidney replacement therapy (CKRT) is an essential treatment for uncontrolled severe metabolic acidosis. However, CKRT can increase workload and lead to complications, thus necessitating its selective application to patients who stand to benefit significantly. This study aims to investigate the therapeutic effect of CKRT in patients with severe acidosis by utilizing a deep learning-based causal inference model to assess its potential impact on in-hospital mortality.

Methods: The Medical Information Mart for Intensive Care III (MIMIC-III) dataset was utilized, and patients with data available within the first 48 hours after intensive care unit (ICU) admission were selected. Patients experiencing severe acidosis with a pH <7.2 within the initial 48 hours were selected. Treatment was defined as the application of CKRT within 48 hours of ICU admission, and the outcome was defined as in-hospital mortality. The dataset was randomly divided into an 85:15 ratio for train and test data. The Generative Adversarial Nets for Inference of Individualized Treatment Effects (GANITE) model was applied on training the model, and its performance was evaluated in the test data.

Results: In the train data, the model demonstrated an accuracy and Area Under Receiver Operating Characteristic Curve (AUROC) of 0.883 and 0.887 (0.880–0.893), respectively, while in the test data, it showed 0.841 and 0.824 (0.804–0.843). The model was well calibrated. The probability change of average in-hospital mortality with CKRT treatment for all severe acidosis patients was +15% and +14% in the train and test data, respectively. However, in the patient who underwent CKRT, the application of CKRT resulted in an average reduction of in-hospital mortality probability by 13% in both the train and test data.

Conclusions: Developing a model that strategically represents the therapeutic effects of CKRT for individual patients could be expected to aid decision-making in the future application of CKRT treatment.



Examples

PUB251

Primary Aldosteronism with Hypercortisolism in a 47-Year-Old Man

Tamar Mosulishvili,[1] Dylan M. Ofri,[2] Charles W. Hopley.[2] *[1]Dartmouth College Geisel School of Medicine, Hanover, NH; [2]Dartmouth Hitchcock Medical Center, Lebanon, NH.*

Introduction: Despite its high prevalence, PA remains underdiagnosed and undertreated. There is a need for clinicians to be well-versed in additional features that PA can present with, to initiate appropriate and timely diagnostic workup.

Case Description: A 47-year-old man with extensive CV history, including persistent HTN (on several medications) and hypokalemia, presented with diaphoresis, lethargy, nausea, abdominal cramps, and muscle aches. Chart review revealed multiple admissions with HTN and hypokalemia. On admission, he was mildly ill-appearing, VSS and WNL, Weight 121.9kg, BMI 37. PE: unremarbakle with negative Cushingoid signs. Labs notable for K 2.5, Cl 83, HCO3- 36, AG 16. BUN 37 with creatinine 1.57. Glucose was 326, with Hgb A1c at 14.3%. A CT abdomen showed a 12mm left adrenal nodule. Empirical treatment for PA was initiated with potassium, IV fluids and insulin. Aldosterone was 16ng/dl and renin activity was 1.3ng/ml/hr. Adrenal venous sampling revealed unilateral left aldosterone hypersecretion with cortisol-corrected aldosterone ratio > 4 at 17, further supported by non-dominant adrenal vein cortisol corrected aldosterone (0.4) to IVC (2.3) (R/IVC) ratio of less than one at 0.17. Notably, left adrenal gland cortisol was significantly higher at 1117 (right at 172), suggestive of adrenal adenoma producing concomitant high levels of cortisol and aldosterone. The shared decision for left laparoscopic adrenalectomy was made.

Discussion: This case demonstrates an interesting and rare presentation of primary aldosteronism with additional features. Since laparoscopic adrenalectomy can be curative for unilateral adenomas, adrenal venous sampling to determine lateralization is recommended. In the case of this patient, secondary hyperaldosteronism and hypertension likely due to primary hyperaldosteronism with elevated cortisol levels are potentially suggestive of aldosterone and cortisol co-producing adenoma (A/CPA). About 10% of patients with PA also have A/CPA, and in patients with PA and single adenoma, the prevalence of A/CPA is 9.7 – 20%. Patients with A/CPA are more prone to metabolic abnormalities and have higher risk of cardiovascular events. Characterization of A/CPAs prior to surgery is critical since the removal of A/CPAs can result in post-op adrenal crisis and required management with hydrocortisone replacement therapy.

PUB252

Hyponatremia, mg vs. mEq Gone Terribly Wrong: A Cautionary Tale

Shubha Ananthakrishnan, Andrea Broka, Niti Madan. *UC Davis Health, Sacramento, CA.*

Introduction: We present a case of a rapid hyponatremia correction due to an improper medication dose conversion calculation. Hyponatremia, a common electrolyte disorder, remains a nephrologist nightmare as it can lead to osmotic demyelination syndrome (ODS). Management of hyponatremia remains challenging and involves an understanding of the relationship between, weight, osmolality, tonicity, and different unit measures.

Case Description: 59-year-old female > 50% total body surface area burns complicated by tracheoesophageal fistula s/p complex repair, recurrent aspiration pneumonia, severe malnourishment, chronic hyponatremia, thought due to SIADH managed with salt tabs, presented due to malfunction NG tube, and was found to be hyponatremic at 119 mmol/L. After endoscopic NG tube placement, she was restarted on diet and Salt tabs, 3 tabs q 8 hours (EMR order Thermotabs/chloride 287 mg Sodium 180 mg, Potassium 15mg (540 mg of sodium equal to 72 mEq in 24 hour) with slow improvement on her serum sodium. However, given NG tube clogging issues, the night team changed her tablets into a liquid formulation 540 mEq q8 hr (EMR order liquid sodium chloride 4 mEq/ml). The[SA1] conversion unfortunately was done assuming milligrams and mEq were the same with the patient mistakenly getting **23 times** the intended amount of sodium through the NG tube in liquid form, that caused a sodium correction[SA2] from 123 to 145 mmol/L in the next few hours. CT brain showing subarachnoid hemorrhage. MRI brain the next day also showed T2/FLAIR hyperintensity in the pons concerning for myelinolysis.

Discussion: Electrolytes dosing errors are well-known and associated with high morbidity and mortality. In general, when a system fails to prevent an adverse outcome, poor communication is almost always a contributing factor. We also identified that a non-standardized sodium formulation's units in EMR orders (tablets registered in milligrams, while liquid formulations with their concentration mEq/ml) contributed to the adverse event. Our systems heavily rely on the provider's knowledge, increasing the risk of human error. We hope that standardizing EMR listing of electrolytes replacements to include the mEq content for each formulation and automatically calculate the total prescribed dose will aid in avoiding future errors.

PUB253

Analysis of the Impact of the Rate of Severe Hyponatremia Correction on Clinical Outcomes

Ana Gabriela J. T. Melo, Marcia Fernanda Arantes de Oliveira, Lucia Andrade, Jose M. Vieira Jr. *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Hyponatremia correction is well known associated with a extremely rare, albeit severe event, osmotic demyelination. Guidelines therefore strongly recommend a rate of correction no faster than 6 mEq/L/24h. Here, we sought to investigate whether faster correction of severe hyponatremia is associated with longer length of hospital stay (LOS) and mortality.

Methods: We reviewed medical records for hospitalized patient who had severe hiponatremia (Na< 125 mEq/L) during a year. Variables related to hyponatremia diagnosis and other clinical characteristics were assessed. Then we analyzed through regression analysis whether the rate of Na correction within 24h above 6 mEq/L was independently associated with either prolonged LOS (defined as above the median duration time) or mortality.

Results: We evaluated N=304 hyponatremic (Na<125 mEq/L) patients. Overall, age was 60 IQR 47-69; 86% had chronic (>48h) hyponatremia, 37% were admitted in the ICU, and 18% were under dialysis. Out of 304, 129 patients (42.5%) had Na correction rate higher than 6 mEq/L/d (rapid correction, RC). RC group had lower baseline Na levels (122 IQR 116-124 vs 123 IQR 120-125 mEq/L, P=0.001), but compared to controls had similar age, baseline sCr, heart failure, cirrhosis, cancer, AKI and CKD diagnosis, but less hypertension and diabetes cases. The hospital LOS was significantly higher for RC group (23 IQR 11-52 vs 19 IQR 10-33 days, p=0.012), but after regression analysis the model found other variables associated with prolonged LOS (> 20d): admission in the ward, type of hyponatremia and ICU admission. Overall mortality was 20% and did not differ between groups. Besides the Na correction rate cutoff of 6 mEq/L/d, sensitivity analysis showed that neither 10 mEq/L/d nor the rate of Na correction (as a continuous variable) remained as predictor of hospital LOS or mortality. Lactate, vasopressor use and heart failure were independent variables associated with mortality in this cohort.

Conclusions: Our study strongly suggest that the rate of correction of a severe hyponatremia above the limits defined by current guidelines does not impact on LOS and mortality, and appears to be safe regarding these outcomes.

PUB254

Peripartum Hyponatremia: A Case Report of Complications in Preeclampsia

Khushleen Jaggi. *San Mateo Medical Center, San Mateo, CA.*

Introduction: Preeclampsia, characterized by new-onset hypertension and end-organ dysfunction after 20 weeks of gestation, carries the potential for severe complications such as eclampsia and HELLP syndrome. Peripartum hyponatremia, associated with adverse outcomes, presents a serious concern when coupled with preeclampsia.

Case Description: 39 year old with hypothyroidism, obesity (BMI 38.1), IVF pregnancy and gestational hypertension was admitted at 36 weeks for labor induction due to severe preeclampsia. At 35 weeks, she developed headaches, proteinuria (urine protein to creatinine ratio 1.1), and elevated AST levels (66 U/L). Estimated GFR and platelets were normal. Upon admission, she received misoprostol, oxytocin, and artificial rupture of membranes for labor induction. Her serum sodium decreased from 131-134 mmol/L three weeks before admission to 129 mmol/L on admission, reaching a nadir of 122 mmol/L the next day. Patient was euvolemic, with low serum osmolality (262 mOsm/kg), high urine osmolality (290 mOsm/kg), urine sodium of 29 mmol/L, normal TSH (1.44), and low morning cortisol (1.3, likely due to antenatal betamethasone). Fetal intolerance prompted a C-section. Postpartum hemorrhage from uterine atony prompted ICU transfer for hemorrhagic shock. Fluid restriction and sodium chloride tablets improved serum sodium. Treatment was continued until delivery, after which serum sodium promptly normalized. Follow-up labs at 6 weeks and 5 months postpartum showed normal electrolytes.

Discussion: While rare, severe hyponatremia in preeclampsia patients can lead to maternal symptoms like nausea, headache, confusion, and seizures, with fetal

manifestations including jaundice, seizures, and tachypnea. It is associated with adverse outcomes, including stillbirth and postpartum ICU admissions. Treatment in this population is challenging due to limited medication options, with fluid restriction and sodium chloride tablets typically used. Delivery of the fetus is often necessary for definitive treatment, especially in cases of moderate to severe hyponatremia. While pregnant women may have physiological alterations in sodium homeostasis causing mild hyponatremia, the exact etiology of severe hyponatremia in preeclampsia patients remains unclear. Close monitoring and timely intervention are needed to avoid adverse outcomes. Further research is needed to understand the underlying physiology contributing to hyponatremia.

PUB255

Unveiling the Effects: The Influence of Trimethoprim Sulfamethoxazole (TMP-SMX) on Electrolyte and Acid-Base Disturbances

Emily Vazquez Morales, Juan J. Adams Chahin, Adriel Gonzalez Rivera, Ileana E. Ocasio Melendez. *Universidad de Puerto Rico Recinto de Ciencias Medicas, San Juan, Puerto Rico.*

Introduction: Trimethoprim sulfamethoxazole (TMP-SMX) is an antibiotic commonly used as treatment and prophylaxis for infectious processes including Pneumocystis jirovecii pneumonia (PCP) in HIV patients, but it has been associated with various metabolic disturbances including renal tubular acidosis. This case will describe the chronology of a patient's metabolic derangements after medication was started.

Case Description: A 53-year-old woman with alcohol and drug abuse was brought to the ED due to loss of consciousness requiring intubation upon arrival due to alcohol withdrawal symptoms. On initial laboratory tests, patient tested positive to HIV and days later she developed respiratory distress. Chest CT scan was performed and demonstrated right lower lobe necrotizing pneumonia. HIV viral load was elevated at 5,920 with an associated low CD4 count of 31. Opportunistic infections were high on the differential which included PCP and prophylactic treatment with TMP-SMX was began. Nephrology service was consulted approximately 5 days after initiation of therapy due to increasing trend in serum creatinine levels, hyperkalemia, normal anion gap metabolic acidosis and hyponatremia. Urine spots yielded a urine anion gap of 44.6. Alkali therapy was initiated, and hyperkalemia management was provided, and type 4 renal tubular acidosis was highly suspected due to temporal association with TMP-SMX administration. The offending agent was discontinued after discussion with ID and Pulmonology services. Patient's serum creatinine, hyponatremia, hyperkalemia, and non-anion gap metabolic acidosis resolved afterwards.

Discussion: Our case represents a patient who developed several metabolic disturbances TMP-SMX may cause. There are no accepted treatments for TMP-SMX induced RTA and literature has demonstrated that patients improve after withdrawal of medication. Although patients often show improvement after discontinuing treatment, it may sometimes be delayed and can increase the patient's morbidity. Therefore, it is crucial to consistently evaluate for hyperkalemia, hyponatremia, metabolic acidosis and increases in serum creatinine levels after initiating medication.

PUB256

Hyperkalemia: Room for Improvement?

Juan Rodríguez Mansilla, Claudia Diez, Alba Santos, Sandra L. Castro Molano, Natalia R. Romero, Mario Colomer, Elisabeth M. Martí, Javier Perez-Contreras. *Hospital General Universitario Dr Balmis Servicio de Nefrologia, Alicante, Spain.*

Background: Patiromer and sodium zirconium ciclosilicate mitigate the risk of RASi-associated hyperkalemia, avoiding decreasing or stopping its dose. Our aim was to evaluate how physicians from different specialties treat hyperkalemia.

Methods: A survey with different items related to the prevalence of hyperkalemia, severity assessment, and acute and chronic treatment was coducted among physicians in one hospital.

Results: 68 surveys were included: 51.5% women, age 37.1±10.6 years. Medical specialties enrolled were 38.2% Nephrologists, 14.3% internal medicine, 14.3% GPs, and 33.2% other. Among all the surveys, 43.2% assess 5 or more patients per month with hyperkalemia, of which 17.6±8.3% are moderate and 8.1±6.1% are severe. Although 92.6% of the surveyed identify peaked T waves as a sign of severity, 26.5% acknowledge not requesting an ECG in all patients. In acute hyperkalemia:100% adjust treatment according to the patient's blood glucose and 96.6% to the acid-base status; 86.2% prescribe diuretics and 69% use new binders, although 51% are unaware of their financing conditions in Spain. The use of new binders has reduced the use of diuretics in 31% of respondents. After correcting a mild hyperkalemia, only 50% of physicians recommend analytical review, within a time frame of 30(15-90) days. After correcting a moderate hyperkalemia, 88.2% recommend review and within a time: 30(15-30) days, p=0.006. After severe hyperkalemia is corrected, 98.5% recommend analytical review, significantly earlier, within 10(4-30) days (p<0.001). In chronic hyperkalemia, 16.2% of physicians discontinue treatment with RASi and 52.9% reduce their dose. Although 42.6% always recommend a low-potassium diet and 47.1% do so sometimes, 26.5% of surveyed are unaware of culinary techniques to reduce potassium and 33.8% are unaware of hidden potassium sources (such as sodium-free salt) When starting a RASi/MRA in a patient with normal renal function, 67.6% recommend analytical review to assess potassium and it is recommended within 30(15-90) days. If initiated in a patient with renal disease, 88.2% recommend review, significantly earlier within 30(15-30) days, (p=0.004).

Conclusions: The management of hyperkalemia is adequate in our area although there is room for improvement. Strategies to improve the maintenance of cardio-nephro-protective treatment are essential.

PUB257

Recurrent Cerebral Salt Wasting in Subarachnoid Hemorrhage

Jamie R. Greathouse, Sukhman Dhaliwal, Evelyn C. Aldana Barrientos, Salma Yasin. *Temecula Valley Hospital, Temecula, CA.*

Introduction: Hyponatremia occurs in over 50% of patients with subarachnoid hemorrhage (SAH) due to various etiologies such as diuretic therapy, SIADH, and cerebral salt wasting (CSWS) (Nakajami, 2017). Differentiating between SIADH and CSWS is challenging due to similar diagnostic results. SIADH and CSWS present with increased urinary sodium and volume but differ in management. This case highlights the diagnostic difficulties and management of CSWS.

Case Description: 49-year-old male presented with a severe headache. Imaging showed a SAH. A ventricular drain was placed, and the patient was put on a sodium goal, nimodipine, and intra-arterial verapamil for vasospasm. During admission, the patient developed high urinary output and hyponatremia. Initial treatment with fluids and desmopressin failed. Hypertonic fluids and fludrocortisone were started. Despite this, sodium levels dropped, necessitating increased hypertonic fluid rates and NaCl tablets. Recurrence of high urinary output with hyponatremia called for monitoring of hypertonic fluids and overall fluid balance until complete resolution.

Discussion: Hyponatremia in CNS disease is often due to SIADH; however, CSWS can be on the differentials, especially in SAH. Proposed CSWS mechanisms include impaired sympathetic input to the kidneys and elevated levels of brain natriuretic peptide (BNP). Disruption of neural input and BNP release decreases sodium reabsorption and inhibits renin release, leading to hyponatremia without potassium wasting (Sherlock, 2006). CSWS is uncommon but significant in acute brain injuries like SAH. Characterized by renal sodium excretion leading to hyponatremia, CSWS poses diagnostic challenges due to its overlap with SIADH. Prompt differentiation is critical as CSWS requires salt replacement and volume repletion, whereas SIADH is managed with fluid restriction (Luo & Wang, 2022).

Figure 1. Daily Serum Sodium with Select Urine Sodium

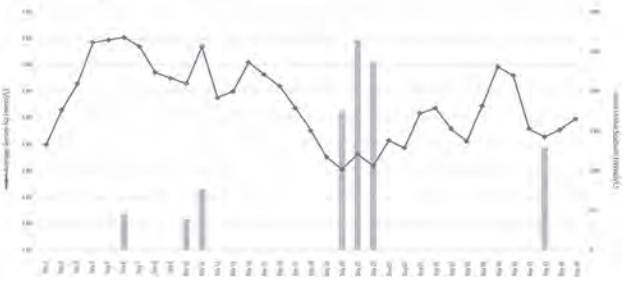
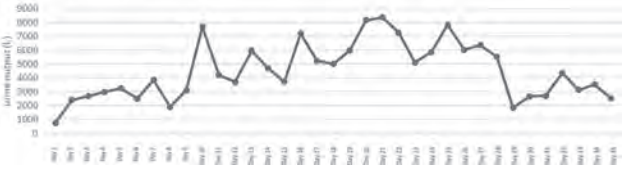


Figure 2. Daily Urine Output



PUB258

Respiratory Acidosis in Salicylate Toxicity: An Unusual Initial Presentation

Hoon Chang,[1] Jonas Kwok,[1] Christina H. Brotman.[1,2] *[1]Renal, Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA; [2]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA.*

Introduction: Salicylate toxicity is classically associated with mixed respiratory alkalosis and increased anion-gap metabolic acidosis. We present a case of primary respiratory acidosis in a patient with severe salicylate toxicity.

Case Description: A 59-year-old female with major depressive disorder on sertraline and quetiapine presented to the emergency room after being found unconscious next to an empty bottle of aspirin. Upon arrival, she was hypotensive with blood pressure of 83/71 mmHg and tachycardic with a heart rate of 115 bpm, and had a Glasgow Coma

Score of 7. Initial laboratory data were notable for creatinine of 0.76 mg/dL, serum bicarbonate of 14 mmol/L, and phosphorus of 6.7 mg/dL. Venous blood gas showed a pH of 7.26 and pCO2 of 49 mmHg. Salicylate level was 115 mg/dL, with the urine toxicology screen otherwise negative. Due to a witnessed seizure, she was intubated for airway protection. Subsequent arterial blood gas revealed a pH of 7.15, pCO2 of 85 mmHg, bicarbonate of 21.4 mmol/L, and a lactic acid level of 1.7 mmol/L. She was initiated on a continuous bicarbonate infusion, underwent placement of a non-tunneled dialysis catheter, and started on intermittent hemodialysis. The repeat salicylate level was 38.1 mg/dL, and she was transitioned to continuous kidney replacement therapy due to worsening vasodilatory shock and concerns for early cerebral edema based on head imaging.

Discussion: The traditional acid-base disturbance associated with salicylate toxicity is the co-occurrence of metabolic acidosis from increased anaerobic metabolism and respiratory alkalosis from hyperventilation due to direct stimulation of the respiratory centers within the cerebral medulla. Respiratory acidosis is typically considered in cases of co-ingestion and is a rare presentation of isolated salicylate ingestion. However, it is important to recognize that hypoventilation is a late or severe manifestation of salicylate toxicity and is a harbinger of respiratory failure. In this case, the patient developed severe cardio-pulmonary collapse, acute kidney failure, and cerebral edema within the first 12 hours of presentation. This highlights the importance of early recognition and prompt management of primary respiratory acidosis in severe salicylate toxicity.

PUB259

A Case of Graves Disease Presenting as Hypokalemic Periodic Paralysis

Krishna Mohita Kuruvada, Milagros Yunes. *Montefiore Medical Center, New York, NY.*

Introduction: Thyrotoxic periodic paralysis(TPP) is a rare complication of hyperthyroidism and is a treatable form of hypokalemic periodic paralysis(HPP). While hereditary channelopathies primarily underlie HPP, acquired cases are seen with hyperthyroidism and tend to affect males more frequently. We describe a case of thyrotoxicosis that presented with severe hypokalemia and sudden onset paralysis.

Case Description: 37-year-old male with no medical history presented with acute paralysis of upper and lower extremities. He had experienced severe muscle weakness and painful cramps intermittently over the past few months, worsened by exercise. He also noted weight loss, heat intolerance, and dry skin. Examination revealed thyromegaly, mild proptosis, power of 0/5 in upper and lower limbs, and hyporeflexia. Laboratory tests showed severe hypokalemia (< 2 mEq/L) and mild metabolic acidosis (pH 7.25, bicarbonate 16 mEq/L). The possibility of distal RTA was considered with the combination of hypokalemia and metabolic acidosis, however, thyroid studies were pursued as his exam findings were concerning for hyperthyroidism. Thyroid studies revealed low TSH (<0.05 μIU/mL), elevated free T4 (3 ng/dL), free T3 (>20 pg/mL), thyroid-stimulating immunoglobulin (326%), thyroid-binding inhibitor (34 IU/L), and thyroid peroxidase antibody (>1000 IU/mL). Ultrasound showed an enlarged, hypervascular and heterogeneous thyroid gland. These findings were consistent with Graves' thyrotoxicosis. The patient was started on potassium supplementation, methimazole 20 mg daily, and atenolol 50 mg twice daily with which his weakness improved. The resolution of symptoms with potassium replacement and treatment for Graves' disease suggests that severe hypokalemia in this patient represents a case of hypokalemic periodic paralysis caused by thyrotoxicosis.

Discussion: Thyroid hormone increases Na+/K+-ATPase activity on muscle membranes leading to intracellular potassium influx. Patients experience sudden, painless episodes of muscle weakness during periods of stress. Bulbar and respiratory muscles are minimally involved. Acute episodes are managed with potassium supplementation and treatment of hyperthyroidism. Beta blockers inhibit the Na+/K+-ATPase and can be used for symptom control. This case illustrates the importance of checking thyroid studies in patients with HPP as restoration of euthyroidism eliminates episodes.

PUB260

Licorice: Treat or Poison?

Anita Kamarzarian, Tuan Nguyen, Sharona Hariri, Hoang Anh Nguyen, Sapna Gopal, Phuong-Chi T. Pham, Golriz Jafari. *UCLA Medical Center Olive View, Sylmar, CA.*

Introduction: Patients take many supplements considering them to be safe. Licorice has been used as a sweetener in candies and treats. Furthermore it is used in complimentary medicine for treatment of variety of conditions.

Case Description: 64 year old woman with diagnosis of stage 1**B** HR+ Her2- Left breast IDC, DCIS s/p lumpectomy, completed adjuvant radiation 6 months ago who was recommended by onclology to take anastrozole for 5 years as adjuvant therapy which she refused and instead saw a Chinese traditional practitioner and was started on supplements that included licorice 6 grams/day. She presented to the ED with complaints of L flank pain for one day. Workup of the L flank pain including CT Abd/pelvis, urinalysis, and urine culture did not reveal any abnormalities. However, incidentally found to have severe hypokalemia, K of 1.9 mmol/L,ABG: PH of 7.49 PCO2 of 38mmHg, Bicarbonate of 29 mmol/L, severe HTN and prolonged QTC 509 mS. Serum aldostrone and renin were depressed, her 24 hour urine potassium was 185 mmol/24 HR. She requried admission and recieved total of 700 meq of KCL over 48 hours.

Discussion: Pseudo-hyperaldosteronism is a condition that clinically mimics hyperaldosteronism with suppression of plasma renin activity and aldosterone levels. Hypokalemia, metabolic alkalosis, and HTN can be seen in this condition. Dietary causes include prolonged overconsumption of licorice. 11Bhdryoxysteroid dehydrogenase type 2 enzyme is responsible for conversion of cortisol to inactive cortisone. Licorice, specifically glycyrrhizic acid and its hydrolytic product Glycyrrhetinic acid are potent competitive inhibitors of 11-BHSD2 and lead to excess cortisol which avidly binds to the mineralocorticoid receptor resulting in cortisol-induced mineralocorticoid effect of sodium retention and urinary potassium waisting. Glycyrrhizic acid onsumption in excess of 100 to 200 mg daily has been noted to cause clinically significant complications. In addition to electrolyte abnormalities, licorice induced HTN and hypertensive encephalopathy, hypokalemic myopathy manifesting as flaccid paralysis, and QT prolongation and possible torsade de pointes with fatal arrhythmias can be seen. Our patient was asymptomatic, which in fact put her at higher risk of cardiac complications and sudden death given her prolonged QT findings. Presenting to the ED with non related flank pain potentially saved her life.

PUB261

A Matter of Fluid: Managing a Rare Case of Diabetes Insipidus and Multiple Sclerosis-Driven Hypernatremia

Henry Yip,[1] Claire Kim,[1,2] Katherine Andrade,[1] Rula A. Abdulrahman.[1]
[1]Stony Brook University Hospital, Stony Brook, NY; [2]Stony Brook University Renaissance School of Medicine, Stony Brook, NY.

Introduction: Transient central diabetes insipidus (CDI) is a rare condition which may result in hypernatremia and is rarely associated with multiple sclerosis (MS). Here we report a case of new onset hypernatremia, likely secondary to CDI in a patient with MS after exhibiting mental status changes.

Case Description: A 55-year-old female with MS and neurogenic bladder with suprapubic catheter was admitted for urosepsis. On initial labs, she had an acute kidney injury (AKI), bland urinalysis with concentrated urine and she produced normal range urine output (UOP). Following AKI resolution, she developed stroke like symptoms followed by polyuria up to 6L/24h resulting in hypernatremia of 167mmol/L and urine osmolarity 140mmol/L. Non-contrast stroke imaging showed no acute cerebral vascular accidents. She was started on intravenous fluid (IVF) repletion, which was unable to keep up with UOP, and was treated with intranasal desmopressin. Following desmopressin administration her urine output decreased to 1.2-1.8L/24h, which she reports to be closer to her baseline and her hypernatremia was ultimately resolved with continued IVF.

Discussion: CDI is a polyuric, hypotonic state typically due to injury to the hypothalamic track and inability to release vasopressin. MS produces demyelinated plaques which have a broad range of symptoms, and rarely has been seen to cause CDI. Although multiple cases describe transient CDI following cerebral vascular accidents, trauma and acute MS flairs there is limited data regarding overall incidence or mechanism of this injury. This makes management of hypernatremia difficult as in addition to supportive management with fluid repletion, the underlying cause must also be addressed. In our case we believed her hypernatremia was driven by transient CDI and her MS as noted with her mental status change and negative stroke work up. Given the relative lack of data, she was started on IVF, and empirically treated with desmopressin. Managing both hypernatremia, and new onset CDI in MS, this unique patient presented a unique challenge and highlights a relatively under explored topic. To date, there are only a few prior cases reporting CDI presenting in a patient with MS, and our report aims to highlight the association and areas of future research.

PUB262

Beyond the Bottle: Lactic Acidosis as a Consequence of Alcoholic Ketoacidosis

Graciela M. Luna, Daniela Carralero Somoza, Kaitlyn Cariaga, Umair S. Ahmed. *Lakeland Regional Medical Center Inc, Lakeland, FL.*

Introduction: Alcoholic ketoacidosis (AKA), a consequence of chronic alcohol use disorder in malnourished individuals. Ketoacidosis is caused by accumulation of ketone bodies when glucose availability is limited for metabolic energy. Lactic acidosis (LA) is classically type A acidosis due localized or systemic hypoperfusion. LA in the absence of evidence of hypoperfusion is type B acidosis.

Case Description: A 60-year-old male with a past medical history significant for alcohol abuse presented to the emergency department after a fall. No abdominal pain, fever, dizziness, lightheadedness, or loss of consciousness reported. On admission, vital signs were stable. Physical exam was unremarkable. Investigations revealed leukocytosis and metabolic acidosis. Serum lactic acid was elevated at 21.8 mmol/L on admission. Urinalysis showed presence of 3+ ketones. Liver function tests were unremarkable except for marginally elevated AST peaking at 109 u/l. Blood alcohol level was 179 on presentation. Beta-hydroxybutyrate was checked due to concerns for AKA and was 45.70

on presentation. HIV screen was negative. Patient was started on D5 water to help with ketoacidosis. Urine ketones and serum beta-hydroxybutyrate normalized 48 hours after admission with subsequent resolution of lactic acidosis.

Discussion: Type B LA causes include medications such as Metformin, malignancy, HIV infection, thiamine deficiency and mitochondrial dysfunction. Patients with chronic alcohol use disorder and malnutrition are at risk for developing AKA. Ketoacidosis usually presents after alcohol ingestion has ceased and after a binge episode. When ethanol levels start to decrease, catecholamines and cortisol rise, increasing lipolysis, accelerating the production of ketones. During the metabolism of ethanol, high amounts of NADH are generated. The reduction of NAD+ and consequential accumulation and imbalance of NADH in the metabolism of ethanol has several important consequences including an inhibition of the citric acid cycle and hepatic gluconeogenesis. The LA seen in AKA is due to an abnormal redox state. This case highlights the need to assess for unusual causes of LA when there is no evidence of either systemic or local hypoperfusion. This can help identify any underlying problem such as AKA, thiamine deficiency or HIV when there may sometimes be no other clues about these diagnoses.

PUB263

A Case of Unresolving Hypokalemia

Omar Dodin, Sreelakshmi Ravula, Nadia M. Alqurini. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Renal Tubular acidosis are a group of disorders that occur in the tubules of nephrons. They have multiple causes and all result in acidosis and electrolyte defects. Type 1 RTA is caused by a defect of H+ secretion in distal tubules, due to multiple drugs, autoimmune or genetic disorders causing: acidosis, Urine pH>5.5 and hypokalemia.

Case Description: Our case is a 35 years old female with Hx of SCD s/p splenectomy and allo SCT complicated by steroid refractory GVHD, for which she is currently on belumosudil. She also has acyclovir resistant HSV rectal lesions for which she was on cidofovir-stopped 08/13, restarted on 1/2024 then stopped again on 2/17/2024. Pt has long Hx of hypokalemia since 2014. On her last admission for sickle cell crisis, she was found to have a serum potassium of **2.1**. She was placed on maximum oral and IV potassium of total around **160 Meq** with amiloride which only raised potassium to **3.4.** On follow up after discharge, she was found to have serum potassium of around 3. She states that her chronic hypokalemia has become more severe and persistent over the last year, since her BMT. She has been getting regular IV potassium infusions in addition to taking PO supplementation. Although Pt had always denied any emesis/diarrhea or Poor PO intake some of her labs are suggestive of malnutrition including her urine potassium which was **18.6** and **25.4** on 2 consecutive days, with **urine pH of 6-7 during inpatient stay**. She was discharged with following admissions for IV potassium needed to maintain serum potassium above 3.

Discussion: We conclude that Pt has a mixed etiology of potassium malabsorption, cidofovir use and RTA 1, as she has low urine potassium which goes against RTA 1 but at the same time still doesn't achieve full compensation even with IV replacement and observed oral compliance and high potassium diet. A final solution would be bilateral Nephrectomy with at least 3 times/week HD with IV potassium supplementation if needed to improve potassium control and decrease risk of sudden death. Literature previously reported hypokalemia post BMT, SCT but by themselves they are amenable to oral and may need temporary IV management. Antiretroviral induced Fanconi has been rarely noted previously. This case shows that: 1-Hypokalemia can be refractory when multifactorial and certain pathologies have additive effects. 2-Full treatment is sometimes difficult as therapy ends up being too radical for Pt.

PUB264

Hypermagnesemia Caused by Laxatives in a Patient with Colitis and AKI

Nazia Habib, Omar Ali, Muhammad R. Khan, Swati Mehta, Krishnakumar D. Hongalgi. *Albany Medical College, Albany, NY.*

Introduction: Hypermagnesemia is uncommon but can be a potentially serious clinical condition with high morbidity and mortality. Magnesium (Mg) containing products are widely used by the general population. Although generally well tolerated in patients with normal renal function, their use in the elderly can result in severe hypermagnesemia particularly with concomitant renal failure and bowel disorders. We report a case of symptomatic hypermagnesemia with laxative use in the setting of acute kidney injury (AKI) and colitis

Case Description: 62 y/o male with history of COPD, hypertension, and chronic back pain, on chronic opioid was transferred from community hospital with severe colitis leading to shock. Patient is chronically constipated due to his opioid use. He initially presented with acute abdominal pain and nausea. CT abdomen showed severe colitis with significant stool burden but no obstruction and was given magnesium citrate. Labs revealed Cr of 2.3 mg/dl, WBC 16, Hemoglobin of 15 Mg 8.7 and lactic acid (LA) of 3.1. Patient respiratory status declined and was intubated. At our facility, Mg was 7.9, creatinine 2.9, and BUN of 62. Repeat CT Abd /pelvis shows interval worsening of bowel thickening. He was started on loop diuretics and isotonic fluids for hypermagnesemia, and his Mg level improved gradually. However, the patient's condition declined over the next few days with worsening shock, AKI and respiratory failure. As per family wishes, the patient was placed on comfort care and no other interventions pursued.

Discussion: Magnesium is an important intracellular cation in several enzymatic pathways. Serum magnesium level is affected by magnesium intake, absorption and excretion. In this case, impaired excretion and increased absorption of Mg due to colitis lead to hypermagnesemia and related complications. It is important to monitor for hypermagnesemia with laxative use in a patient with AKI, and colitis. Initial treatment consists of cessation of magnesium-containing medications and therapy with intravenous isotonic fluids plus a loop diuretic. Renal replacement treatment is often required in patients with severe or symptomatic hypermagnesemia in patients with moderate to severe AKI. Early recognition and treatment of hypermagnesemia can be highly effective to prevent significant morbidity and mortality.

PUB265

Mineralocorticoid-Responsive Hyponatremia in Elderly Patients

Matthew Ray,[1,2] Rakin Solaiman.[3] *[1]MultiCare Health System, Spokane, WA; [2]University of Washington, Seattle, WA; [3]Providence Sacred Heart Medical Center, Spokane, WA.*

Introduction: Hyponatremia is a common electrolyte disturbance. We present the case of a 69-year old female after recent surgery who presented with profound, symptomatic hypotonic hyponatremia. She was unresponsive to initial treatments of hypertonic saline and DDAVP, but received fludrocortisone with improvement in her symptoms and hyponatremia. This case highlights the importance of considering mineralocorticoid deficiency in the differential diagnosis of hyponatremia.

Case Description: This is the case of a 69-year old female who underwent right hip arthroplasty and subsequently presented to the hospital with acute encephalopathy, with initial serum sodium 104. Despite large volume of 3% saline with DDAVP and fluid restriction, she demonstrated minimal improvement in her serum sodium. Subsequently based on her lab findings with high volume urine output and elevated urine sodium levels, mineralocorticoid deficiency was suspected. Sshe was started on fludrocortisone with appropriate initial improvement, and she was discharged with follow-up with outpatient nephrology.

Discussion: Euvolemic hyponatremia has a broad differential diagnosis, and is a more misunderstood of the dysnatremias. Potential etiologies include various medications, inappropriate antidiuresis, severe hypothyroidism, and glucocorticoid deficiency, as well as low solute intake. However this patient did not have other secondary findings. The syndrome of mineralocorticoid responsive hyponatremia of the elderly has been reported in several cases and a case series, mainly from Japan. These share several key features: lack of volume depletion, no overt hormonal cause of hyponatremia, response to mineralocorticoids, or no improvement with fluid restriction alone. Our case bears concern given her marked urine output with urine sodium wasting with normal hemodynamic parameters. Few cases share this magnitude of hyponatremia and do not demonstrate the lack of response to hypertonic saline. This patient's profound hyponatremia was suspected to be multifactorial however did not begin to improve until administrtion of mineralocorticoid Mineralocorticoid deficiency is a rare but treatable cause of hyponatremia. Clinicians should consider this on the differential, especially in cases of refractory hyponatremia. Early recognition and treatment of mineralocorticoid deficiency can lead to a favorable outcome and prevent serious complications associated with hyponatremia

PUB266

A Rare Case of Sjogren Syndrome Associated with Acquired Gitelman Syndrome

Leonardo R. Ramirez Botana. *LSU Health Shreveport, Shreveport, LA.*

Introduction: Acquired renal tubular disorder has been detected in various disease processes, specifically autoimmune diseases. Gitelman syndrome is an autosomal recessive disease characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. This case reported an acquired Gitelman syndrome associated with Sjögren's syndrome.

Case Description: A 61-year-old female with past medical history of Sjögren's syndrome, bronchiectasis, hypothyroidism was admitted due to right hip pain after a fall. She has been presenting with muscle weakness and cramping of lower extremities for several weeks. On phhysical examination was found low blood pressure, right lower hip pain, decreased range of motion and externally rotate right lower extremity. Initial laboratory results was found elevated white blood cell count, severe hypokalemia and metabolic alkalosis, hypocalcemia and hypomagnesemia. Urine spot chloride was reported 26 mEq/L, greater than 20 mEq/L, having with this value a differential diagnostic with intermittent diuretic use, and urine calcium excretion and maganesium are low as well. Renal magnesium wasting and hypomagnesemia are found in Gitelman syndrome, as well as, spot urine calcium/creatinine ratio of less than 44 mg/g, as our patient. This urine labs are explained due to the sodium chloride cotransporter (NCC) in Gitelman syndrome are shed into the urine in nanovesicles called urine exosomes and reducing the NCC activity in urine exosomes has been described in patients with Gitelman syndrome

Discussion: Our patients who was found with an unexplained hypokalemia, metabolic alkalosis and persistently elevated urine chloride for a Gitelman syndrome. It was reviewed other more common etiologies to excluded, and her home medications side effects was revised. In other cases, that has been reported a phenotype resembling Gitelman syndrome that can result from autoimmune diseases, most commonly in patients with Sjögren's disease–associated interstitial nephritis, for that reason, renal biopsy and genetic studies were ordered and will be follow up the results. The diagnosis of acquired Gitelman syndrome in our cases was based upon the clinical and laboratory findings. The hip was surgical repair and treated her electrolyte abnormalities and hypovolemia. Oral supplementation with substantial doses of sodium, potassium chloride and magnesium salts was ordered as fisrt line of therapy

PUB267

Amphotericin-Induced Apparent Mineralocorticoid Excess (AME)

Aldo E. Torres Ortiz. Tulane Nephrology and Hypertension. *Tulane University, New Orleans, LA.*

Introduction: AME is a syndrome characterized by a genetic or acquired deficiency in 11 beta-Hydroxysteroid dehydrogenase type 2 (11 beta-HSD2), which results in overactivation of the mineralocorticoid receptor. Licorice and certain medications such as azoles are known to induce AME. Amphotericin has a different mechanism of action, and to our knowledge, there are no prior case reports of AME induced by amphotericin.

Case Description: 64 year-old female with newly diagnosed acute myeloid leukemia, was admitted to the hospital for induction chemotherapy. Hospital course was complicated by neutropenic fever, secondary to mucormycosis of the abdomen, for which she was started on amphotericin B. Three days after the initiation of this medication, patient developed persistent hypokalemia, metabolic alkalosis and difficult to control hypertension for which Nephrology was consulted. Upon chart review, patient's blood pressure in office visits and on the first 25 days of admission had been <120/80 mm/Hg. Work-up for secondary hypertension revealed increased Cortisol/cortisone ratio on 24 hour urine collection of 0.6. Rest of work-up, including renal artery dopplers and metanephrines was unremarkable. Aldosterone and renin were low at 1.9 ng/dL and 1.1 ng/mL/hr respectively. Creatinine remained unchanged at her baseline of 0.5-0.7 mg/dL. Patient's blood pressure was controlled with maximum doses of Nifedipine and Lisinopril, showing a dramatic improvement after addition of spironolactone. Blood pressure, potassium and bicarbonate levels normalized after completion of amphotericin therapy.

Discussion: After review of all medications given in the Hospital, the only one with a clear temporal relation with the onset of hypertension was amphotericin B. This medication has a different mechanism of action than azoles, and to our knowledge, this is the first case report of amphotericin-induced apparent mineralocorticoid excess syndrome. Hypokalemia is a known side effect of hypokalemia secondary to amphotericin B, which is known to be secondary to tubular toxicity causing concentration gradients between the cytoplasm of distal tubule cells and the tubular lumen. This case can potentially explain a different mechanism of hypokalemia.

PUB268

Ominous Hyponatremia

Golriz Jafari, Hoang Anh Nguyen, Phuong-Chi T. Pham, Sapna Gopal, Anita Kamarzarian. *UCLA Medical Center Olive View, Sylmar, CA.*

Introduction: Hyponatremia is the most common electrolyte disorder in hospitalized patients and a signal for an underlying disorder. The differential diagnosis is broad and often times multifactorial in etiology. It is important to note that some less common causes may be overlooked in the initial evaluation.

Case Description: A 52-year-old man presents to the emergency room for right upper abdominal pain and found to have severe asymptomatic hyponatremia of 112 mmol/L. He had poor po intake, 30 lb. weight loss over the last months and drinks about 1.5L water daily. He has no known significant medical problems except vitreous hemorrhage, 30 pack year tobacco use and is originally from El Salvador. Initially he was thought to have hyponatremia due to hypovolemia vs. low solute state and initially treated with NS. His initial Uosm 495 and urine Na 89 mmol/L were consistent with hypovolemia. Na corrected to124 mmol/L, but then plateaued and relowered to 119 mmol/L. He was thought to have underlying SIADH from pain, lung lesion found on CXR and new diagnosis of TB. Despite fluid restricted and salt tabs, Na did not improve and renal was consulted. Repeat Uosm was 588 and urine Na 98 remained elevated and patient was noted to have hyperkalemia of K 6.1 mmol/L on admit without evidence of AKI. Patient was not hypotensive or orthostatic; AM Cortisol was low normal 5.4 mcg/dL however cosyntropin stimulation test was abnormal suggesting adrenal insufficiency. Further work up of lung lesion with CT revealed that patient had primary lung cancer with diffuse metastasis to brain, peritoneum, pericardium, liver, kidneys and adrenal glands. Patient was treated with hydrocortisone and fludrocortisone with improvement in Na to 129 mmol/L on discharge.

Discussion: Hyponatremia can be the first sign of an underlying malignancy. Often in malignancy patients, the etiology can be multifactorial including hypovolemia, low solute intake, SIADH, renal salt wasting or adrenal insufficiency. A thorough and detailed evaluation should be done to consider all possible etiologies and provide the optimal treatment.

PUB269

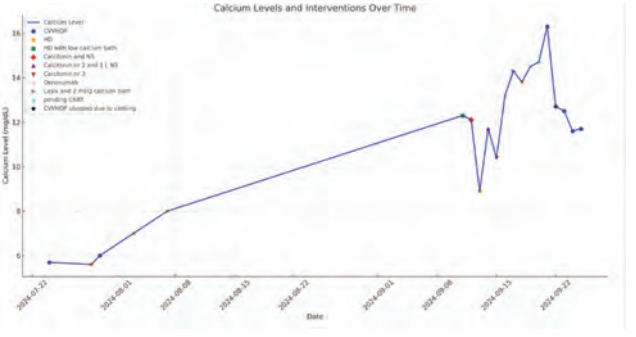
Hypercalcemia: Immobility's Insidious Impact and Navigating Rhabdomyolysis

Stela Teferici,[1] Nitzy N. Munoz Casablanca,[1] Hameeda T. Khan.[1,2] *[1]NYC Health and Hospitals Elmhurst Department of Emergency Medicine and Urgent Care, Queens, NY; [2]Mount Sinai Health System, New York, NY.*

Introduction: Hypercalcemia is a well-recognized complication. This case report explores less frequent etiologies: hypercalcemia occurring during the recovery phase of rhabdomyolysis and hypercalcemia due to immobilization.

Case Description: A 33-year-old man was found intoxicated on the street. On presentation, he displayed dilated pupils, tachypnea, and altered mental status, necessitating endotracheal intubation. Drug screen showed cocaine, benzodiazepines, and opioids. Additionally, he reported ingesting a banned weight-loss substance, raising concern for serotonin syndrome. He developed renal failure from rhabdomyolysis (creatine kinase level of 69,020 U/L), requiring renal replacement. Hospital course was further complicated by bacterial pneumonia with superimposed fungal infection, requiring eventual tracheostomy and percutaneous endoscopic gastrostomy tube placement. Despite kidney recovery and normal urine output, hypercalcemia recurred (12 mg/dl) and was unresponsive to several interventions (see Diagram 1). Work up showed low Vitamin D levels, low Parathyroid hormone level (PTH 7 pg/ml, phosphorus relatively normal, and mildly elevated Alkaline phosphatase (160 IU/L). Elevated collagen telopeptide 2369 pg/ml indicated PTH-independent hypercalcemia. Imaging revealed no abdominal or pelvic mass making malignancy unlikely. Normocalcemia was eventually achieved with calcium-free hemodialysis. Diagram 1.

Discussion: Rhabdomyolysis, though initially often causing hypocalcemia from muscle uptake, can lead to rebound hypercalcemia in up to a third of patients during recovery, due to the release of deposited calcium. However, our patient developed severe hypercalcemia despite resolution of rhabdomyolysis with workup indicating hypercalcemia of immobilization. Prolonged immobilization can cause bone resorption and hypercalcemia, especially in critically ill patients with high bone turnover. Fluid administration, pamidronate, and calcium-free dialysis are some methods used to correct severe hypercalcemia. Our case highlights one of the less common causes of hypercalcemia



PUB270

Electrolytes and Maintenance Intravenous (IV) Fluids

Jaicy Pottokaran, Mark S. Segal, Larry T. Patterson. *University of Florida, Gainesville, FL.*

Background: Isotonic saline is the recommended standard treatment of choice for maintenance intravenous (IV) infusion in pediatric population (NEJM, Oct 2015) since the recognition of hyponatremia as a complication following hypotonic IV fluids. We studied the change in incidence of electrolyte abnormalities before and after the 2015 publication. We also determined the risk factors for the development of abnormal electrolytes and their associated morbidity and mortality.

Methods: Data from the Integrated Data Repository (IDR) over a 10-yr period. Inclusion criteria: Children 2 months to 19 yrs who received IV fluids 24 hrs after admission from January 2012 to January 2022. Those with abnormal sodium levels on admission, patients with head trauma or stroke for whom hypernatremia was indicated, were excluded. SAS 9.4 version was used for statistical analysis.

Results: We examined data from 104,911 patient hospital days in 5916 patients from two time periods 2012 to 2016 and 2017 to 2021. See Table on Demographics for more details. Sodium levels were done in 5,915 patients and the incidence of hypernatremia fell from 9% in 2012 to 16 to 7% in 2017 to 2021 (Chi Squared 115, P value <0.0001). The incidence of hyponatremia was the same in both year time periods (10%). The incidence of hyperkalemia was the same in both time periods (1%), but the incidence of significant hyperchloremia increased from 7% from 2012 to 2016 to 16% from 2017 to 2021 (p value <0.0001). The incidence of hypochloremia events fell from 5% from 2012 to 2016 to 3% from 2017 to 2021 (p value <0.0001). The incidence of both alkalosis and acidosis increased from the period of 2012-16 to 2017-21 from 8% to 11% (p value <0.0001) and 5% to 7% (p value <0.0001), respectively.

Conclusions: Isotonic fluid use has not significantly changed the incidence of hyponatremia, but the incidence of hypernatremia has significantly decreased. We will discuss the incidence of a number of complications of maintenance IVF along with associated morbidity and mortality.

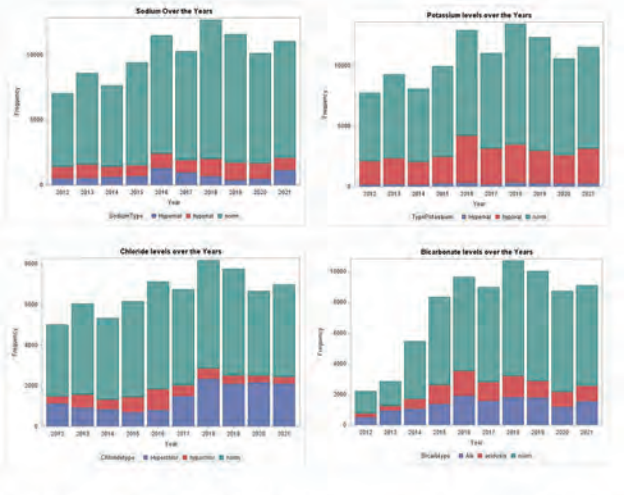


Fig 1: Sodium, Potassium, Chloride and Bicarbonate level changes over the years 2012 to 2021, North Florida

PUB271

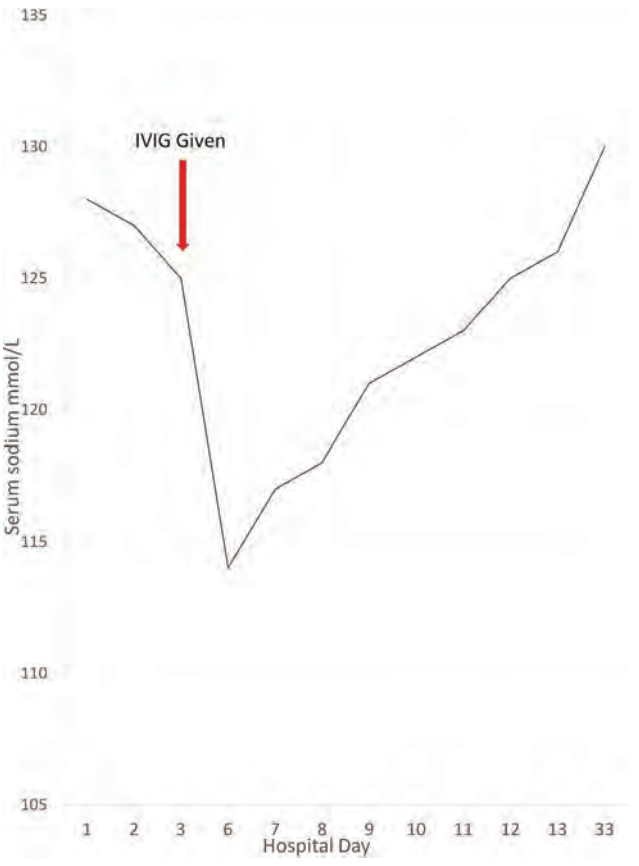
True Hyponatremia Secondary to Intravenous Immunoglobulin Infusion

Neepa Shah, Claudia Waters, Siddhartha Kattamanchi, Rebecca Blonsky.
Marshfield Clinic Health System, Marshfield, WI.

Introduction: Intravenous immunoglobulin infusion (IVIG) is used to treat a number of autoimmune disorders. However, IVIG can cause sodium disorders. Here we present a case of hyponatremia due to IVIG.

Case Description: The patient is a 96 year old female with history significant for chronic hyponatremia and ITP presented following a fall complicated by a displaced femoral neck fracture requiring surgical intervention. Serum sodium at baseline is approximately 130 to 132 mmol/L and at the time of admission sodium was 128 mmol/L. The patient was thrombocytopenic due to underlying ITP, thus was given platelets and IVIG due to need for surgical intervention. Following IVIG her serum sodium fell to a nadir of 113 mmoL/L. Nephrology was consulted for hyponatremia. Based on workup, the patient was diagnosed with true hyponatremia due to increased extracellular water concentrations as a result of the IVIG. The patient was treated with high protein diet, oral sodium chloride 2 grams PO TID, fluid restriction and diuretics. With treatment the patient's sodium improved and was 126 mmoL/L by discharge.

Discussion: Plasma comprises approximately 93% plasma water and 7% proteins and lipids. Any medical condition causing increased proteins and lipids in the blood will cause automated chemistry to interpret this as a low serum sodium. IVIG can cause post-infusion hyperprotenemia leading to pseudohyponatremia. However, the sucrose used as a carrier in commercial IVIG is osmotically active and can lead to the movement of water from the intracellular compartment to the extracellular compartment causing a true hyponatremia. Patients with impaired free water excretion, such as those with kidney disease can lead to further worsening of this hyponatremia.



PUB272

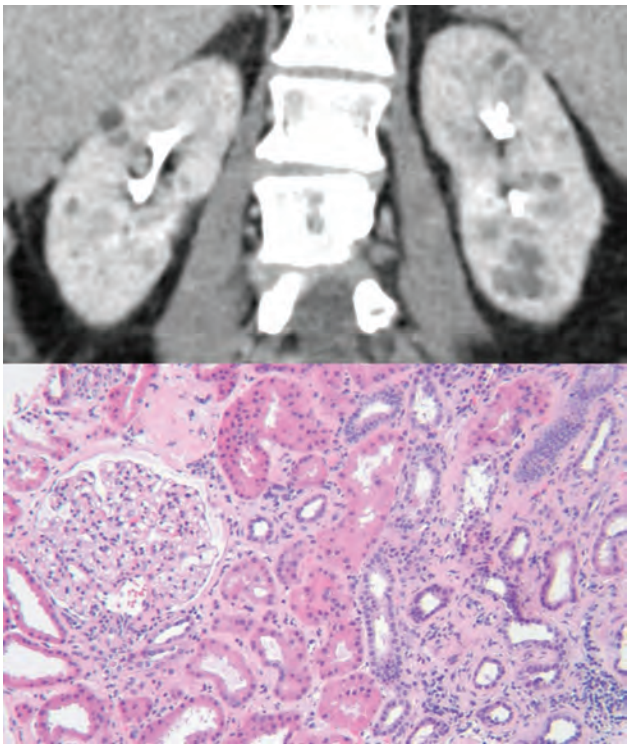
An Unusual Case of CKD and Kidney Cysts: It's All in the Family

Daniel A. Moreno, Meloney Oliveira, Roger A. Rodby, Stephen M. Korbet.
Rush University Medical Center, Chicago, IL.

Introduction: Autosomal dominant kidney disease with renal cysts and family history of progressive kidney disease suggests diagnoses such as polycystic kidney disease, tuberous sclerosis or von Hipple-Lindau syndrome. We present a rare and unusual case in which genetic testing was essential in establishing the diagnosis.

Case Description: A 55 yo woman with HTN was referred for evaluation of chronic kidney disease (CKD). The kidney function had been normal (SCr of 0.7 mg/dl) but over the next few yrs the SCr increased to 1.9 mg/dl. There was no history of NSAID abuse. The urinalysis was normal and the UAC and UPC ratios were normal at 30 and 140 mg/g, respectively. Uric acid and magnesium levels were normal. Serologic evaluation (ANA, Scl 70 Ab, SSA/SSB, RF, SIEP and UIEP) was negative. CT imaging revealed bilateral renal cysts (Image). The pt's father and paternal grandfather had HTN and ESRD of unknown etiology requiring dialysis at ages 50 and 70, respectively. The pt underwent a renal biopsy which demonstrated non-diagnostic moderate tubule-interstitial fibrosis and global sclerosis and severe arterial sclerosis (Image). Genetic testing revealed a heterozygous whole gene deletion of hepatocyte nuclear factor1 β (HNF1β).

Discussion: HNF1β is expressed in the kidney and regulates tubular transport and architecture. It is autosomal dominant and mutations exhibit incomplete penetrance with variable expressivity and result in progressive tubule-interstitial kidney disease and renal cysts. Mutations in HNF1β are an addition to the differential of autosomal dominant tubule-interstitial kidney disease (ADTKD) which previously included mutations in ADTKD-UMOD, -MUC1 and -REN. This case demonstrates the vital role genetic testing can play in making a diagnosis in a patient with CKD of unknown origin.



CT kidneys and H&E light microscopy

PUB273

Assessing Global and National Trends in Public Awareness and Interest in Polycystic Kidney Disease, 2004-2024

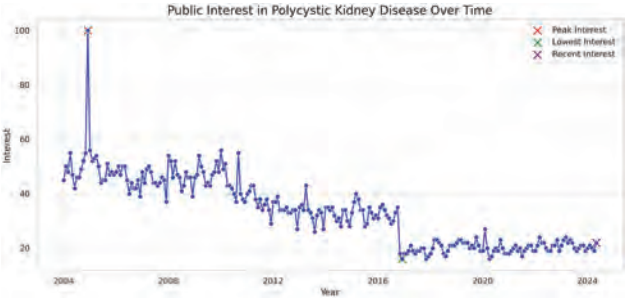
Justin Pham,[1,2] Charat Thongprayoon,[2] Jing Miao,[2] Iasmina Craici,[2] Wisit Cheungpasitporn.[2] *[1]Mayo Clinic College of Medicine and Science, Rochester, MN; [2]Mayo Clinic Minnesota, Rochester, MN.*

Background: Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous renal cysts that can lead to worsening kidney function and varios sequelae. Recent advancements in treatment options have made it possible to slow disease progression. In this context, public interest and awareness of PKD play a crucial role in early diagnosis, timely management, and support for affected individuals and their families. This study aims to analyze the trends in global and national public interest and awareness of PKD.

Methods: We conducted a comprehensive analysis of Google Trends data for the search term “polycystic kidney disease” over a period of 245 months, from January 2004 to May 2024. The worldwide trend was examined, along with specific data from the United States. The relative search volume was used as a measure of public interest, with the peak interest assigned a score of 100.

Results: The global highest public interest in PKD was observed in December 2004 (score: 100), while the lowest interest occurred in December 2016 (score: 16). As of May 2024, the interest score was 22, slightly lower than the previous year. Among the top 10 regions with the highest relative search volume, Poland ranked first, followed by the United States and Pakistan. In the United States, the peak interest in PKD was recorded in September 2010 (score: 100), and the lowest interest was observed in May 2020 (score: 28). The most recent data from May 2024 showed an interest score of 44. Missouri, Vermont, and Kansas were the top three states with the highest relative search volume for PKD.

Conclusions: There has been a decrease in online interest and awareness of PKD over the past two decades. The findings underscore the need for targeted interventions and campaigns to raise awareness about PKD, its symptoms, and the importance of early diagnosis and management. Nephrologists, patient advocacy groups, and policymakers should collaborate to develop strategies that effectively reach and educate the public about this disorder.



PUB274

A Family with Variants in Multiple ADPKD Genes

Hisae Tanaka,[1] Takehiko Wada,[2] Michio Nakamura,[3] Yuko Ohnuki,[4] Akinari Sekine,[2] Takuya Fujimaru,[5] Takayasu Mori,[5] Eisei Sohara,[5] Shinichi Uchida,[5] Masafumi Fukagawa,[1] Hirotaka Komaba.[1] *[1]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; [2]Nephrology Center, Toranomon Hospital, Tokyo, Japan; [3]Department of Transplant Surgery, Tokai University School of Medicine, Isehara, Japan; [4]Department of Medical Ethics, Tokai University School of Medicine, Isehara, Japan; [5]Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.*

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease characterized by progressive cyst formation and enlargement of the kidneys, often leading to end-stage kidney disease (ESKD). ADPKD is thought to be caused by mutations in one of two genes (*PKD1* or *PKD2*). Recent advances in genetic technologies have enabled the identification of new variants of the ADPKD genes and revealed the complexity of the genetic inheritance of this disease.

Case Description: A 30-year-old female was referred to our hospital for evaluation of progressively worsening kidney function and potential living donor kidney transplantation. She was diagnosed with multicystic dysplastic kidney of the right kidney in her fetal period. At the age of 4, a renal cyst developed in the left kidney and the number of cysts increased with age. Later, her kidney function gradually declined and she developed ESKD in her late 20s. Laboratory tests showed a serum creatinine of 3.75 mg/dL, an eGFR of 13 mL/min/1.73m^2, and a urine protein/creatinine ratio of 2.6. Abdominal CT showed multiple kidney cysts in both kidneys with only one small hepatic cyst. It was later recognized that her biological father had been clinically diagnosed with ADPKD and had been on hemodialysis since the age of 50. Next-generation sequencing revealed a heterozygous *PKD2* pathogenic variant, accompanied by *PKD1* and *IFT140* variants of uncertain clinical significance, in both the patient and her father, but not in her mother. The patient eventually received a kidney transplant from her mother.

Discussion: Genetic testing could help identify the cause of ESKD in this patient and exclude genetic risk in her mother, a kidney donor candidate. The lack of genetic difference between this patient and her father does not support the possibility that digenic effects of *PKD1* and/or *IFT140* variants led to the atypical ADPKD manifestations in this patient. Further studies are required to investigate the putative impact of these variants on the development of ADPKD.

PUB275

Innovative Approaches for Increasing Community Engagement in ADPKD

Priya Deshpande. *Mount Sinai Health System, New York, NY.*

Background: The purpose of this project is to increase community engagement and awareness by creating podcasts that address important topics for patients with ADPKD using a culturally sensitive approach in both English and Spanish. This study is sponsored by the PKD Cure Foundation.

Methods: Podcasts in both English and Spanish were created with a patient stakeholder (a native Spanish speaker), two nutritionists, one of whom is a native Spanish speaker and a physician (fluent in both English and Spanish). To date 6 episodes (3 in English and 3 in Spanish) of the podcast series were created. Topics include: Nutrition in ADPKD, “I was diagnosed with ADPKD, what do I do next?,” and Transplantation in ADPKD (to be published). The podcasts were recorded on Zoom, edited, and then published on Spotify platform. Analytics were collected using Spotify analytics. The podcasts were promoted on Facebook (Meta), X and Instagram. An optional “yes” or “no” one question survey in both English and Spanish was administered (“Did this podcast increase your knowledge about this topic?”). The podcast series was also promoted by word of mouth to our patients in our PKD Clinic.

Results: A total of 14 individuals, primarily male with a median age of 43, followed this podcast series. Followers were primarily from the US (76%) and 10% of the followers were from Spanish speaking regions/countries. The most listened to podcasts in both English (52%) and Spanish (23%) were about nutrition and lifestyle. Three audience

members who listened to the English version of the nutrition episode and three voters who listened to the Spanish version of the nutrition episode felt that the episode improved their overall understanding of nutrition in ADPKD.

Conclusions: This study supports the feasbility of using to help disseminate information and promote patient engagement about ADPKD. The results show that the podcasts are reaching the Spanish speaking population. The most popular episode was about nutrition and lifestyle in ADPKD. These results support the further development of patient facing podcasts in both ADPKD and other conditions.

Funding: Private Foundation Support

PUB276

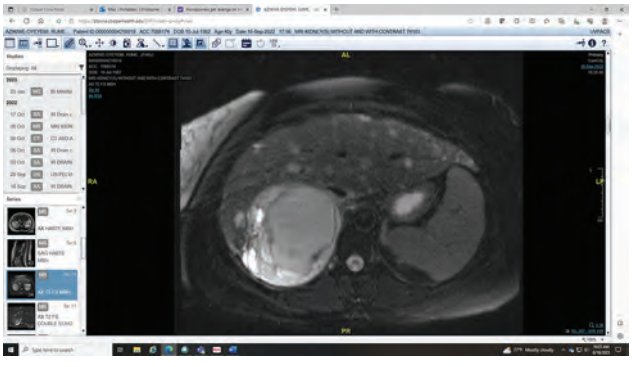
Use of Gadolinium-Enhanced MRI in a Patient with ADPKD and a Cyst Infection

Karen Cohen, Elizabeth Ives, Christopher B. McFadden. *Rowan University Cooper Medical School, Camden, NJ.*

Introduction: Autosomal dominant polycystic kidney disease presents significant complications to patients. One such complication is infection of a cyst. Identification of the infected cyst has proven challenging with imaging techniques including ultrasound and computer tomography (CT). Localization of the infected cyst is required with cysts larger than 5 cm for source control.

Case Description: A 40-year-old woman with PMH of ADPKD and CKD 3a presented with flank pain and fever. Creatinine was 2.17 mg/dl and white blood cell count 13.8 x109/l. A urinalysis revealed 2+ blood; blood and urine cultures remained negative. Computer tomography (CT) of the abdomen and pelvis without contrast revealed innumerable cysts with no signs of infection. On hospital day three, antibiotics were broadened from ceftriaxone to ertapenem. Renal bladder ultrasound revealed enlarged bilateral kidneys (R 9.0 x 7.7 x 2.7 cm and L 8.1 x 7.4 x 17.1 cm) with innumerable simple and hemorrhagic cysts. No cyst wall thickening or hyperemia was detected. She continued to have fevers with a maximum temperature of 103.1 °F. On hospital day seven, a pre and post gadolinium MRI was completed and revealed a right upper pole cyst with inflammatory changes consistent with a large (8 cm) infected cyst. Following drainage of the cyst, her pain improved and fever resolved.

Discussion: The accuracy of MRI in detecting infected renal cysts in ADPKD patients with abnormal kidney function is largely unknown due to previous contraindication of gadolinium-based contrast media (GBCM) in patients with an eGFR <30 mL/min per 1.73 m^2. Recent guidelines no longer advise against use of type 2 GBCM contrast in patients with eGFR <30. This case adds to the body of research that gadolinium enhanced MRI is an effective and safe method of localizing renal cyst infections. Importantly, it may be the best method to localize infected cysts in patients at risk for radiocontrast nephropathy.



Axial T2 fat saturated showing decreased T2 hyperintensity of the large inflamed cyst (large arrow) relative to the surrounding cysts (small arrow).

PUB277

Evaluating Physician Confidence and Barriers in Prescribing Tolvaptan for ADPKD Management

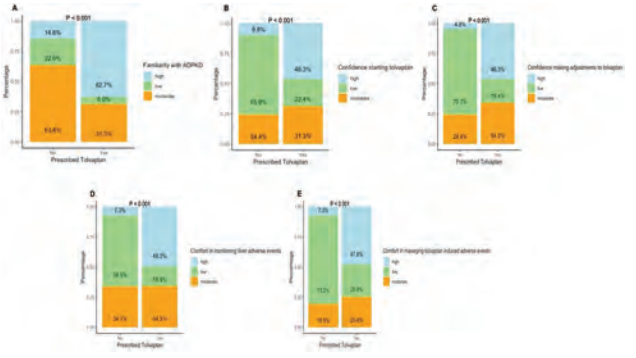
Niloufar Ebrahimi, Mehrbod Vakhshoori, Amir Abdi Pour, Sayna Norouzi. *Loma Linda University Medical Center, Loma Linda, CA.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the leading genetic cause of end-stage kidney disease in adults. The FDA approved tolvaptan in 2018 as the first treatment for ADPKD patients at risk of rapid disease progression. This study evaluates physicians' confidence and identifies barriers to prescribing tolvaptan for ADPKD management.

Methods: A survey assessed physicians' backgrounds, ADPKD management experience, familiarity with and use of tolvaptan, confidence in prescribing, barriers to prescribing, and needs for support and education. Distributed online via LinkedIn and X, the survey received 110 responses; 108 respondents who had managed at least one ADPKD patient in the past five years met the study's criteria. Data normality was tested with the Shapiro-Wilk test. Categorical and continuous variables were described using frequency (percentage) and median (IQR). Group differences were analyzed using chi-square, t-tests, or Mann-Whitney tests as appropriate. Statistical analyses were conducted in RStudio, with P-values < 0.05 considered significant.

Results: Participants were predominantly male (80.6%) with a median of 12 (7-20) years in practice. The median number of ADPKD patients seen in the past five years was 10 (7.5-22.5). Of the respondents, 62.0% had prescribed tolvaptan. Prescribers were mainly nephrologists, handling significantly more ADPKD patients than non-prescribers (98.5% vs. 80.45%, P<0.001 and 15 [10-30] vs. 9 [5-18.75], P=0.001, respectively). Tolvaptan prescribers exhibited higher level of familiarity with ADPKD (62.7% vs. 14.6%), confidence in starting (46.3% vs. 9.8%), adjusting tolvaptan (46.3% vs. 4.9%), comfort in monitoring liver adverse events (49.3% vs. 7.3%), and managing side effects (47.8% vs. 7.3%) compared to non-prescribers (Figure 1).

Conclusions: Addressing barriers to tolvaptan prescription is an essential step toward optimizing patient care.



Comparison of tolvaptan prescribers vs. non-prescribers

PUB278

Cystic Autosomal Dominant Alport Syndrome Masquerading as Polycystic Kidney Disease: Implications for Family Screening and Transplantation

Janewit Wongboonsin,[1,2] Anna Verwillow,[1,4] Judith A. Savige,[3] Ana C. Onuchic-Whitford.[1,5] *[1]Brigham and Women's Hospital, Boston, MA; [2]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [3]The University of Melbourne, Melbourne, VIC, Australia; [4]Massachusetts General Hospital, Boston, MA; [5]Boston Children's Hospital, Boston, MA.*

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) and Alport syndrome (AS) are two common monogenic kidney diseases. While their phenotypes are typically distinct, renal cysts may occur in autosomal dominant AS (ADAS), potentially leading to diagnostic confusion. Herein, we describe a family where a prior diagnosis of ADPKD was corrected to ADAS, resulting in implications for family screening and transplantation.

Case Description: A 61-year-old woman presented to our clinic for evaluation as a kidney donor for her brother with ADPKD. She had persistent microscopic hematuria since age 38, negative cystoscopy, normal kidney function and one kidney cyst. Review of her brother's case revealed that 4 months prior, at age 72 and after years without medical follow-up, he presented to another hospital in renal failure and was started on hemodialysis. He was reportedly diagnosed with ADPKD after an ultrasound demonstrated bilateral kidney cysts and genetic testing found a variant in *PKD1*. We further evaluated him in our clinic with an MRI that showed small, atrophic kidneys (~8cm) with scattered small (<1.5cm) bilateral cysts. Review of his genetic panel revealed a heterozygous variant of uncertain significance in *PKD1* (p.Asn2353Ser) and a heterozygous likely pathogenic variant in *COL4A4* (p.Gly481Val – a glycine substitution in Gly-X-Y motif). His sister's genetic test identified the same 2 variants, and the *PKD1* variant was deemed Benign. His diagnosis was thus reverted and both siblings were diagnosed with ADAS. Audiologic screening revealed mild (sister) and moderate (brother) bilateral sensorineural hearing loss. Another sibling tested negative for the *COL4A4* variant and became a kidney donor for the brother, who was transplanted successfully.

Discussion: The phenotypic heterogeneity of AS may pose a challenge for its clinical diagnosis. The identification of kidney cysts in AS further complicates this, adding AS as a differential diagnosis for cystic diseases. Thorough family history, review of clinical course, and careful visual inspection of renal imaging become important steps to avoid misdiagnosis. This case also highlights the key role of genetic testing, especially in the setting of atypical imaging, advanced chronic kidney disease, and assessment of family members as kidney donors.

PUB279

Coexistence of Alport Syndrome and Autosomal Dominant Polycystic Kidney Disease: A Case Report

Abdelrahman Ibrahim, Zena Altawallbeh, Laith Al-Rabadi. *University of Utah Health, Salt Lake City, UT.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Alport Syndrome (AS) are genetic kidney disorders, which affect individuals in different ways. ADPKD, which usually appears in adulthood, is marked by multiple fluid-filled cysts in the kidneys. However, ADPKD can also be diagnosed early in life, when based on family history, with advanced imaging such as MRI. Meanwhile, AS affects renal glomeruli, the inner ears and eyes. Histologically, AS shows segmental thinning and thickening of the glomerular basement membrane (GBM), which can occur just with the thinning of the GBM in an early stage of the disease. Both of these conditions lead to end-stage renal disease (ESRD). While ADPKD arises from gene mutations influencing kidney development and function, AS is linked to mutations in collagen genes essential for kidney structure and function. We present a case of a 34-year-old woman with early-onset ADPKD, exhibiting proteinuria of 1.5 grams, which is atypical for ADPKD, that has subsequently resolved. Additionally, she reported hearing loss. Along with a subsequent biopsy, genetic testing identified an autosomal recessive AS gene mutation. Patient's functions are stable, with normal creatinine and glomerular filtration rates. Maternal ADPKD history with renal failure requiring transplantation is noted, but two siblings also are asymptomatic.

Methods: Genetic analysis was conducted with next-generation sequencing (NGS), in conjunction with copy number variation (CNV) analysis. Mutations were confirmed through polymerase chain reaction (PCR) and Sanger sequencing. Renal ultrasound and biopsy were carried out, and audiological and ophthalmological examinations were ordered.

Results: Genetic analysis revealed a pathogenic deletion in COL4A3 c.4265-4273 del (p.Ser1422_Gly1424del), as well as a pathogenic mutation in PKD1 gene, consistent with ADPKD. Renal ultrasound showed enlarged kidneys, consistent with polycystic kidney disease while renal biopsy indicated borderline-thin GBM.

Conclusions: This case emphasizes an extremely rare concurrence of AS and ADPKD, underscoring the importance of considering the factor of overlapping inherited kidney diseases. Therefore, comprehensive genetic and familial evaluations in such cases should be requested for accurate diagnosis and management, particularly in cases with atypical overlapping disease symptoms.

PUB280

Progressive CKD Is Associated with Multiple Kidney Cyst Formation in Adult and Elderly Patients with Genetic Variations of Kidney Disease

Joseph C. Mihindu.[1,2] *[1]Saratoga Hospital, Saratoga Springs, NY; [2]Glens Falls Hospital, Glens Falls, NY.*

Introduction: CKD affects about 10 % of the global population. Common etiologies including Diabetes, Hypertension(HTN), Glomerulonephritis etc. are well known; a large number of patients however have CKD of unknown etiology. Genome wide association studies have revealed multiple genetic variations associated with CKD renal phenotype. This abstract documents 2 patients with autosomal recessive (AR) and 2 patients with Autosomal dominant(AD) genetic variations associated with progressive CKD and multiple cyst formation (MRC) in adult and elderly population. Some of the AR variations in homozygous state would have caused severe CKD in early infancy associated with cystic renal changes. None of these patients had evidence of Autosomal Dominant or Resessive Polycystic Kidney Disease Gene variation.

Case Description: Initials Age Race Sex [Presenting Phenotype] [Genetic variation] [Phenotype in Homozygous disease]: JBL 89 W F [CKDG4,HTN,MRC] [AR INPP5E] [Joubert's Syndrome, Nephronophthisis,CKD, Hepatic fibrosis] GW 74 W F [CKDG2,HTN,MRC] [AR CC2D2A] [COACH syndrome, Nephronophthisis, CKD, Hepatic fibrosis] AEP 80 WM [CKDG5,HTN,MRC] [AR or AD NMNA] [Lipodystrophy, Insulin resitance, Proteinuria, Premature CVD] BJF 65 W F [CKDG5, MRC] [ADTKD-UMO] [Chronic Tunbulointerstitial Nephritis, Progressive CKD]

Discussion: These case studies are in agreement with recent studies showing the association of genetic variations with progressive CKD. Two patients (JBL and GW) have specific AR variations. The AD state of these variations is associated with severe CKD and Nephronophthisis in early infancy. In conclusion, the following hypothesis is set forth: the Autosomal Dominant gene which protected these 2 patients from the development of severe disease in early life may lose its dominant function with advancing years. This may result in the resurgence of the Ressessive varient leading to the development of Cystic disease and CKD in later years. These case studies show the importance of genetic variants in the development of CKD.

PUB281

Suspected Hepatocyte Nuclear Factor 1-beta (HNF1B) Glomerulocystic Kidney Disease: A Case Report of Recurrent Hypomagnesemia and Kidney Cysts in a 30-Year-Old Woman

Syed Salman Hamid Hashmi,[1,2] George C. Bonifant.[1,2] *[1]Staten Island University Hospital, Staten Island, NY; [2]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY.*

Introduction: Hepatocyte Nuclear Factor 1-beta (HNF1B) glomerulocystic kidney disease (GCKD) is a rare genetic disorder characterized by renal cysts, renal dysfunction, and extrarenal manifestations like hypomagnesemia, diabetes, and liver abnormalities. This case report presents a 30-year-old female with polycystic kidney disease (PCKD) and chronic hypomagnesemia, whose clinical presentation raises the suspicion of HNF1B GCKD.

Case Description: A 30-year-old female with a history of polycystic kidney disease (PCKD), transaminitis, chronic hypomagnesemia, and recurrent urinary tract infections presented with abdominal pain, nausea, and vomiting. These symptoms typically coincided with low magnesium levels. Her vital signs were stable. Laboratory tests revealed a magnesium level of 0.8 mg/dL. A CT scan showed multiple cortical and parapelvic cysts in both kidneys and multiple kidney stones over 6 mm. Urinalysis indicated small leukocyte esterase. Despite taking 2 grams of magnesium daily, her levels remained low, suggesting a genetic cause. Urinary fractional excretion of magnesium was elevated. The presence of renal cysts, hypomagnesemia, bicornuate uterus, kidney stones, and transaminitis suggested a potential diagnosis of HNF1B-related genetic kidney cystic disease (GCKD). She was discharged with high-dose oral magnesium lactate, amiloride, and is receiving weekly magnesium infusions. She was referred for genetic testing for HNF1B mutations and the results are pending.

Discussion: HNF1B GCKD is often underdiagnosed due to its phenotypic variability. The diagnosis is considered in patients with renal cysts and systemic features like hypomagnesemia and hyperglycemia. This patient's recurrent hypomagnesemia despite supplementation, transaminitis, renal cysts, and bicornuate uterus align with HNF1B GCKD. Management focuses on symptom relief, electrolyte balance, and renal function monitoring. Magnesium supplementation is crucial, and genetic testing is recommended. Amiloride blocks ENaC channels in the distal nephron, creating an electrical gradient favoring magnesium absorption via transient receptor potential melastatin channels. This case underscores the importance of considering HNF1B GCKD in patients with PCKD and chronic hypomagnesemia.

PUB282

Lessons Learned from Patient Engagement in the Polycystic Kidney Disease Research Resource Consortium (PKD RRC)

Vinamratha Rao,[1] Susan Gleason,[3] Jullie Hoggan,[3] Sarit Neter,[3] Taslima Rahman,[3] Terry J. Watnick,[4] Lisa M. Guay-Woodford,[2] Reem Mustafa.[1] *[1]The University of Kansas Medical Center, Kansas City, KS; [2]The Children's Hospital of Philadelphia, Philadelphia, PA; [3]Polycystic Kidney Disease Research Resource Consortium, Bethesda, MD; [4]University of Maryland School of Medicine, Baltimore, MD.*

Background: Polycystic Kidney Disease (PKD) is a prevalent inherited kidney disease that often leads to renal failure and profoundly impacts patient quality of life. The Polycystic Kidney Disease Research Resource Consortium (PKD RRC) aims to advance PKD research through resource development and sharing. The Patient Engagement Group (PEG) was established to integrate patient and stakeholder voices into PKD research resource development, aiming for a patient-driven agenda in PKD research.

Methods: Expert and participant input from various research initiatives, patient organizations, and literature reviews established the PEG framework. Structured recruitment, introductory webinars, and nominations yielded a diverse group of 10 participants, including individuals with PKD, caregivers, and patient advocates. Monthly virtual meetings with educational sessions familiarized members with objectives and projects undertaken by PKD RRC subcommittees. PEG members served as subcommittee liaisons, integrating patient perspectives into research resource development processes.

Results: Patient engagement in the PKD RRC included sharing experiences, learning opportunities, and continuous feedback to refine engagement strategies. While participant input did not routinely alter resource development plans, inclusion of patient perspectives added a patient voice dimension to subcommittee decision-making. For PEG members, involvement fostered personal growth and empowerment, enhancing their understanding of the disease and the research landscape. In particular, PEG members highlighted the importance of balancing data security with research efficiency to maintain trust and participation in clinical trials. Proposed future steps include ongoing innovation in engagement methods and inclusive recruitment. Achieving diversity in the PEG remains challenging but essential for representing the spectrum of patient experiences and needs.

Conclusions: This novel patient engagement initiative in a research resource consortium demonstrates the potential of involving patients in research resource development and establishing patient perspectives as a valuable research resource. The lessons learned highlight the need for effective communication, continuous education, and inclusive practices for effective patient engagement.

Funding: NIDDK Support

PUB283

Genetic Testing in Nephrology and Kidney Transplant Clinics in an Academic Center with a Predominant Minority Population

Luis N. Madera Marin, Pablo Garcia, Christos Argyropoulos, Namita Singh. *University of New Mexico School of Medicine, Albuquerque, NM.*

Background: Chronic kidney disease (CKD) affects about 14% of the adults in the US. Accurate diagnosis of any clinical condition is key to appropriate and successful management. A recent multi-center study showed that genetic testing with a CKD-focused 385 gene panel called Renasight® substantially refined clinical diagnoses and had widespread implications for treatment strategies. We aimed to review the diagnostic yield of Renasight® in our patient population as well as the impact of test results on management decisions.

Methods: We conducted a retrospective chart review on all adult patients who underwent Renasight® testing through nephrology and/or kidney transplant clinics. Hospital EMR and Natera® organ health portal (clinical genetic testing company providing Renasight® testing) were utilized as sources.

Results: A total of 28 individuals underwent Renasight® testing between 7/1/2020 and 4/15/2024. Of the entire cohort: mean age was 43 years, 57% males, and 57% identified their ethnicity as Hispanic or Latino. The majority of the patients (75%) were referred from transplant clinics. Mean serum creatinine at initial visit for non-ESKD patients (n=17) was 2.34 mg/dL (S.D. 2.07). Family history of kidney disease was found to be positive in about 36 percent. FSGS was noted to be the most common reason for test order. Renasight® test reported positive significant gene abnormality in 4 (14%), with an additional 17 people (60%) with a variable of undetermined significance (VUS) or carrier mutation. Negative result aided in decision making for all 3 potential living donors to proceed. Out of the 4 positive results, 2 positive APOL1 mutations confirmed the suspected FSGS diagnosis. Both these patients self-identified as African Americans. One patient previously diagnosed as CKD, unspecified was found to have likely pathogenic CFI gene, associated with aHUS and C3G, which is postulated to significantly impact treatment strategies in future.

Conclusions: In our primarily Hispanic/ Latino population, we noted a diagnostic yield of 14% for significant gene abnormalities. Positive results impacted management in 3 out of 4 cases, and negative report supported decision to proceed with living donor evaluation in all tested for this indication.

PUB284

A Young Woman with Autosomal Dominant Polycystic Kidney Disease and Recurrent Kidney Stones Coexisting with Gitelman Syndrome

Ang Lu, Chien-Chou Chen, Shih-Hua P. Lin. *Tri-Service General Hospital, Taipei, Taiwan.*

Introduction: Autosomal dominant polycystic kidney disease (ADPKD), the leading genetic cause of end-stage kidney disease, is characterized by bilateral renal cysts, chronic kidney disease, and recurrent urinary tract infections (UTIs). Gitelman syndrome (GS), the most common inherited tubulopathy, involves a salt-losing nephropathy featured by hypokalemia, metabolic alkalosis, magnesium wasting, and hypocalciuria. The coexistence of ADPKD and GS is rarely reported. We present a case of a young female with recurrent UTIs, renal stones, cystic kidney disease, and hypokalemia, diagnosed through genetic analysis.

Case Description: A 26-year-old female with history of cystic kidney disease, recurrent UTIs and chronic hypokalemia (3.1 mmol/L) presented with fever, and dysuria for days. Her family history included a mother with ADPKD and an aunt on hemodialysis after bilateral nephrectomy. On admission, she had UTI with bilateral renal stones, hypokalemia, and hypomagnesemia (2.8 and 0.8 mmol/L) and received ureteroscopy with laser lithotripsy. Urine biochemistry showed renal potassium and magnesium wasting and hypocalciuria. Her recurrent renal stones, electrolyte imbalances, and cystic kidney disease, along with family history, raised suspicion of genetic disorder. The molecular sequencing revealed possible PKD1 and NHF1B mutations. Following treatment with oral magnesium and potassium supplements, no recurrent episodes occurred.

Discussion: This is the first case demonstrating the coexistence of ADPKD and GS diagnosed via whole exome sequencing. The PKD1 gene is releated with ADPKD, causing to renal cysts and stone formation. Hepatocyte nuclear factor-1β is a DNA-binding transcription factor essential for kidney development, and its mutations cause tubulointerstitial abnormalities and GS. This case highlights the importance of genetic analysis for early diagnosis and management to prevent complications and improve outcomes.

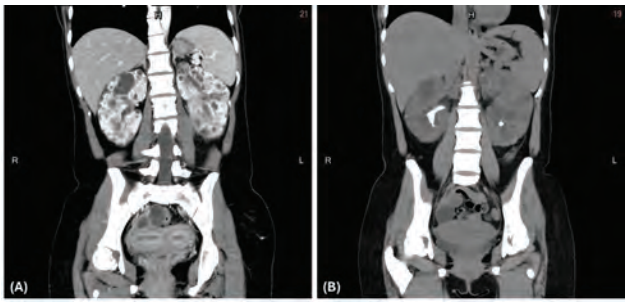


Figure 1-A: Polycystic kidneys and bicornuate uterus 4 years prior. Figure 1-B: Multiple renal stones with partial right staghorn stone on admission.

PUB285

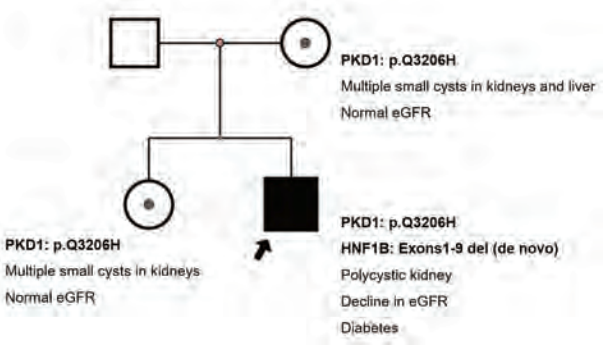
Atypical ADPKD Due to Complex Genotypes of Both PKD1 and HNF1B Pathogenic Variants: An Educational Case Report

Mengshi Li, Ruilian You, Zhiying Liu, Jiayi Zhang, Yang Li, Xu-jie Zhou, Hong Zhang. *Peking University First Hospital, Beijing, China.*

Introduction: ADPKD is the most common genetic cause of renal failure in adults. Advances in next-generation sequencing have revealed complex genotypes, including mosaicism, digenic inheritance, diallelic variants, and genetic modifiers. Understanding the phenotypes associated with variants is crucial for clinicians, as genetic variability significantly influences the severity of ADPKD.

Case Description: A 33-year-old Han Chinese male presented with enlarged kidneys, numerous small cysts, deteriorating renal function, early-onset diabetes mellitus, proteinuria, and a family history of CKD and renal cysts. His mother and sister had multiple renal cysts consistent with ADPKD but only moderately enlarged kidneys and normal renal function. This suggested an atypical ADPKD form, with rapid cyst development, renal decline, and early-onset diabetes, lacking common ADPKD-associated extra-renal manifestations. Whole-exome sequencing identified a heterozygous PKD1 variant (c.9618G>T, p.Q3206H), inherited from his mother and confirmed in his sister, classified as likely pathogenic. Additionally, a heterozygous deletion of exons 1-9 in the HNF1B gene, absent in his pedigree, was confirmed by real-time quantitative PCR. A comprehensive treatment strategy was implemented, including insulin therapy, blood pressure control, and symptom management. At latest follow-up, proteinuria had decreased, but renal function continued to decline slowly.

Discussion: Distinguishing HNF1B-related cystic kidney disease from PKD1/PKD2 variants is crucial. HNF1B-related disease typically features small cysts, normal kidney size, progressive CKD, and early-onset diabetes, overlapping with ADTKD. However, its presentation, prognosis, and pathogenesis differ significantly from PKD1/PKD2-related ADPKD. Genetic testing is recommended for patients with atypical ADPKD features, which is important for diagnosis, genetic counseling, and prognosis. Further research on ADTKD variants in unexplained ADPKD cases is valuable.



PUB286

Clinical Overlap and Diagnostic Challenges: Differentiating HNF1B Mutation Disease from Gitelman Syndrome

Mariem Borcheni, Hanna Ghanayem, Nilofar Behbahani-Nejad, Joel M. Topf. Ascension St. John Team. *Ascension St John Hospital, Detroit, MI.*

Introduction: Hepatocyte nuclear factor 1 beta (HNF1B) mutation disease, is a rare genetic disorder characterized by a range of clinical manifestations, such as development of renal cysts, chronic kidney disease, electrolyte imbalances, and early-onset diabetes mellitus. HNF1B mutations are relatively rare, with an estimated prevalence of less than 1 in 100,000 individuals. One of the significant challenges in diagnosing this disease is its

clinical overlap with other disorders, such as Gitelman's syndrome. Both conditions can exhibit similar symptoms, including chronic hypomagnesemia and hypokalemia, making differentiation between them difficult.

Case Description: A middle-aged female with no significant past medical history, has been evaluated for chronic hypomagnesemia and hypokalemia, initially assumed to be due to Gitelman's syndrome. She was hospitalized for labor induction. Physical exam and vitals were normal. Laboratory findings showed a magnesium level of 1.2mEq/L and a potassium level of 3.5mmol/L, despite daily supplements. Other electrolytes and creatinine were normal. Of note, prior abdominal imaging showed bilateral renal cysts. The patient was given Intravenous magnesium sulfate which failed to improve magnesium level. She had a successful delivery with no complications and was then discharged home. On follow-up visit at the nephrology clinic, a full workup showed a potassium level of 4.1 mmol/L, magnesium level of 1.3mEq/L, fractional excretion of magnesium of 12%, normal kidney function and calcium level. Therefore, a genetic testing was ordered and came back positive for a single heterozygous mutation of HNF1B consistent with a deletion in a whole gene. Given the association between HNF1B mutation and Maturity Onset Diabetes of the Young (MODY), diabetes screening was performed and results were normal. The patient and her daughter, who also had bilateral renal cysts, were then referred for genetic counseling.

Discussion: This case highlights the importance of the diagnostic complexities of HNF1B mutation disease, particularly due to its symptomatic overlap with conditions like Gitelman's syndrome. Genetic testing plays a crucial role in differentiating these disorders, enabling more precise treatment and better patient outcomes.

PUB287

HNF1B Mutation Misdiagnosed as Polycystic Kidney Disease

Trang D. Tran, Alyssa C. Weyer, Arda Akoluk. *The University of Texas at Tyler, Tyler, TX.*

Introduction: HNF1b-related kidney disease, also known as autosomal dominant tubulointerstitial kidney disease (ADTKD) with renal cysts, is a rare genetic disorder caused by mutations in the HNF1b gene. It is characterized by the development of kidney cysts, tubulointerstitial fibrosis, and progressive renal dysfunction, and extrarenal manifestations that can be found in these patients are pancreatic failure, transaminitis, and genital tract abnormalities. Patients often present with features similar to Polycystic Kidney Disease (PKD), including hypertension, proteinuria, and renal insufficiency.

Case Description: A 40 year old woman was evaluated by a Nephrologist after being informed that she had PKD based on magnetic resonance imaging. These images were captured during her pregnancy, for which she was noted to have fetal loss due to unknown causes. Pertinent laboratory results were random blood glucose level of 734 mg/dL, glycated hemoglobin 13%, erythrocyte sedimentation rate level was elevated at 26 mm/hr, urinalysis showed ketone bodies and sugar >1000 mg/dL. The results showed that her fasting glucose level was 398 mg/dL and serum C-peptide was 0.78 ngl/mL. Serum creatinine and eGFR were 0.6 mg/dL and 110, respectively. She was informed during a pregnancy that the fetus was presumed to have autosomal dominant PKD as evidenced by several small cysts in the maternal kidneys on magnetic resonance imaging. There was also a previous ultrasound that indicated a large cyst. Patient denied any family history of PKD. Patient reported that she was diagnosed with type 1 diabetes mellitus, which was misdiagnosed. It was deemed that the patient has Maturity-onset diabetes of the young, type 5 (MODY-5) due to testing negative for Anti-GAD, anti-IAA and anti-ICA antibodies, which is unique to type 1 diabetes.

Discussion: Considering the patient had a cyst in the left kidney, negative for diabetes related antibodies, bicornuate uterus, pancreatic insufficiency, the patient was presumed to have MODY5 with the HNF1B score of 20. Upon further investigation to establish a working diagnosis, DNA sequencing revealed whole gene deletion of 17q12 deletion consistent with HNF1B mutation. Genetic testing plays a role in identifying specific mutations that can guide clinical management and counseling, particularly in cases where invasive procedures such as kidney biopsies are contraindicated, such as in pregnant individuals.

PUB288

Patient-Centered Insights on Treatment Adherence and Social Determinants of Health in Autosomal Dominant Polycystic Kidney Disease

Vanessa Holliday, Savanna Moore, Elise Hoover. *PKD Foundation, Kansas City, MO.*

Background: The Polycystic Kidney Disease Foundation (PKDF) advocates, educates, and funds research for PKD, the most common genetic kidney disease in the United States (U.S.), estimated to affect around 600,000 individuals. This study explores patient treatment adherence among patients within the Autosomal Dominant Polycystic Kidney Disease (ADPKD) population, examining the influence of social determinants of health (SDOH). Understanding these factors is essential for effective treatment strategies, aligning with Healthy People 2030's recognition of social determinants' impact on health outcomes. PKDF is uniquely positioned to address this issue, thereby empowering clinicians, researchers, and patients towards improved healthcare approaches and overall health outcomes.

Methods: The study, conducted via an online survey and the ADPKD Registry, adopted a SDOH framework to investigate factors affecting treatment adherence among individuals diagnosed with ADPKD. Approved by an Institutional Review Board, this study includes U.S. individuals who reported partaking in various treatment or management strategies for ADPKD such as diet and lifestyle interventions, non-kidney related medications, kidney related medications, dialysis, and others.

Results: Among 489 participants, 95% are non-Hispanic, 92% white, 69% female, and 71% pre-transplant. Of 487 participants identified as partaking in a treatment(s), 62% reported diet and lifestyle interventions, 54% kidney-related medications, and 40% non-kidney related medications. Of those who encountered treatment barriers, unclear clinician guidance, nephrologist transitions, and financial constraints were cited.

Conclusions: The study, encompassing primarily non-Hispanic, white, female, and pre-transplant participants, identified key treatments such as diet and lifestyle interventions, and medications for kidney and non-kidney related conditions. Although a non-significant number of participants reported barriers to treatment, such as unclear guidance, nephrologist transitions, and financial constraints, these underline areas for improved patient care. The findings emphasize the importance of specialized intervention and improved affordable access to enhance care for individuals diagnosed with ADPKD.

PUB289

Symptom Burden and Health Care Resource Utilization in Patients with Polycystic Kidney Disease

Maham Ali,[1] Michael Heung,[1] Gauri Bhutani,[2] Elise Hoover,[3] Savanna Moore,[3] Areeba Jawed.[1] *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]University of Wisconsin-Madison, Madison, WI; [3]PKD Foundation, Madison, WI.*

Background: Patients with PKD experience a variety of renal and extrarenal symptoms; however, there is limited data on prevalence of symptom burden in this population. We assessed the frequency of patient reported symptoms in PKD and impact on healthcare resource utilization.

Methods: Single center retrospective study of all patients with a diagnosis of PKD (N:355) seen between 7/1/20 and 6/30/23. Patients with ESKD and those lost to follow up were excluded (n:130). Of 225 patients who met inclusion criteria, 112 (49.8%) symptom related encounters were further analyzed.

Results: Study population mean age was 48±15 yrs, and 60% were female. Mean eGFR closest to encounter was 50±29 ml/min with mean duration of clinic follow up 4±3.3 yrs to the time of encounter. Most reported symptoms were cardiovascular (30%), flank pain (16%), and urinary symptoms other than hematuria (8%) whereas 17.8% of encounters were related to non-PKD symptoms. Most common PKD related diagnosis were medication side effects (25%, of which 6% were related to Tolvaptan), hypertension (22%), urinary tract infections (9.8%), and suspected cyst rupture (7.1%). In 20.5% of encounters, the final diagnosis attributed to presenting symptoms were non-PKD related. Providers managed most symptoms with either medication change (30%) or further testing (21.4%) and referred only 6.2% of patients to the emergency department (ED).

Conclusions: Patients with PKD experience diverse symptoms affecting different organ systems. A sizable percentage of encounters were related to non-PKD associated concerns and nephrologists managed most of these without additional referrals to specialty physicians or the ED, suggesting limited additional resource utilization. The substantial proportion of non-PKD related queries may reflect the close relationship PKD patients share with their providers and the comprehensive medical care provided by nephrologists.

Chief Complaint	N:112
Urinary Symptoms - Hematuria	1 (0.8%)
Urinary symptoms - other than hematuria	9 (8%)
Flank Pain	18 (16%)
CVS/Pulmonary	34 (30%)
- Blood Pressure - high	22 (19.6%)
- Blood Pressure - low	4 (3.5%)
- Increased Edema or weight gain	4 (3.5%)
- Chest pain or chest discomfort	1 (0.8%)
- Dizziness/lightheadedness	0 (0%)
- Palpitations	1 (0.8%)
- Shortness of breath	1 (0.8%)
- Other – e.g. wheezing	1 (0.8%)
Constitutional symptoms	2 (1.78%)
Neurologic	4 (3.5%)
Other - Group by organ system	
- Eye	1 (0.89%)
- Ear Nose Throat	3 (2.6%)
- GI	10 (8.9%)
- Reproductive Health	3 (2.6%)
- MSK	7 (6.2%)
- Mental health	0 (0%)
- Other	20 (17.8%)

PUB290

Variable Clinical Presentation of DNAJB11-Related Kidney Disease in a Large Family Cluster

Federico Yandian,[1,2] Lucia Facal,[1,2] Lucia Spangenberg,[3] Víctor E. Raggio,[4] Paula Parnizari,[2] Jose Boggia,[2] Oscar A. Noboa.[2] *[1]Médica Uruguaya, Montevideo, Uruguay; [2]Hospital de Clinicas Doctor Manuel Quintela, Montevideo, Uruguay; [3]Institut Pasteur, Montevideo, Montevideo, Uruguay; [4]Departamento de Genetica, Facultad de Medicina UDELAR, Montevideo, Uruguay.*

Introduction: We report a case of DNAJB11-kidney diseaseand its phenotype variability within the family.

Case Description: A 28-year-old woman with histopathologic diagnosis of chronic tubular interstitial nephritis presented to our clinic with a history of kidney insufficiency that progressed to ESRD in the following 3 years. She did not show microhematuria or proteinuria. CT scan without evidence of kidney or hepatic cysts at the time of kidney biopsy. She had a family history of renal disease. Her mother developed kidney failure requiring initiation of RRT at 45 years. Several of her mother's cousins developed kidney failure. The patient's cousin, a 35-year-old female with renal cysts but with preserved kidney function and normal urinalysis has a diagnosis of Autosomal Dominant Polycystic Kidney Disease (ADPKD) and has a 4 year-old daughter with renal cysts. Another cousin, a 40-year-old male has a diagnosis of ADPKD that developed kidney failure at 40 years. His deceased father, paternal grandma and paternal uncle developed kidney failure and also had a diagnosis of ADPKD with hepatic involvement. A presumptive diagnosis of Autosomal Dominant Tubulointerstitial Kidney Disease was made in the index case. Exome sequencing (100x, 100 paired/end) revealed a non-coding novel DNAJB11 mutation (chr3:186295418, -/T, hg19) in the index case and her two cousins.

Discussion: Renal disease associated with DNAJB11 mutations is an emerging field in nephrology that requires attention due to its clinical impact. This genetic entity has a variety of presentations, including renal cystic disease and tubulointerstitial nephropathy. Renal cystic disease related to DNAJB11 manifests with the formation of multiple kidney cysts, which can result in progressive renal dysfunction and eventual kidney failure. These cysts can be simple or complex and are often associated with arterial hypertension and hematuria. On the other hand, tubulointerstitial nephropathy associated with DNAJB11 is characterized by inflammation and fibrosis of the renal tissue, leading to tubular dysfunction and loss of renal function. In summary, DNAJB11-kidney diseaseencompasses a wide range of clinical presentations, from renal cyst formation to tubulointerstitial nephropathy, underscoring the importance of its early recognition and proper management in clinical practice.

PUB291

Mosaicism in a Patient with ADPKD: A Case Report

Nenzi Marzano,[1] Carlotta Caprara,[1,2] Thiago A. Reis,[3] Diego Pomare' Montin,[1,4] Sofia M. Pretto,[1] Matteo Rigato,[1,2] Fiorella Gastaldon,[2] Claudio Ronco,[1] Monica Zanella,[1,2] Valentina Corradi.[1,2] *[1]International Renal Research Institute (IRRIV) Foundation, Vicenza, Italy; [2]UOC Nefrology, ULSS 8 Berica, San Bortolo Hospital, Vicenza, Italy; [3]Laboratory of Molecular Pharmacology, University of Brasilia, Brasilia, Brazil; [4]Universita degli Studi di Firenze, Firenze, Italy.*

Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD), considered the most frequent genetic renal disease, is characterized by renal involvement with progressive bilateral development of renal cysts and volumetric increase of kidneys, causing loss of renal function leading to chronic kidney disease (CKD). ADPKD has a complex inheritance and a wide phenotypic variability. In some cases, it is necessary to perform genetic testing to achieve a definitive diagnosis. The occurrence of mosaicism, described by a few cell populations with different genomes, may modify the presentation of the disease, modulate its clinical course, and better define an ADPKD population.

Case Description: The case describes a 47-year-old woman presenting typical ultrasound and computed tomography features of ADPKD. She had CKD stage 3b and hypertension. There was no family history of ADPKD, prompting an investigation with a genetic test. Next Generation Sequencing (NGS, nephropathies solution gene panel) did not detect the presence of any genomic variants. The CGH array negative result confirmed the NGS analysis. Multiple Ligation-dependent Probe Amplification (MLPA) for the investigation of large rearrangement of PKD1 and PKD2 genes showed a large deletion (PKD1 gene, exons 3-33) present in heterozygosis with a percentage of cells close to the resolution limits of the used technique (<25-30%). The MLPA analysis was repeated after a revision of the used kit, making it possible to better define the border of the deletion. The new result showed a deletion in heterozygosis of exons 2-34 in PKD1: NC_000016.10: g. (2136179_2119520) (2097184_2094247) del, chr16:2094247: 2136179: del.

Discussion: We concluded that the mutation is present as mosaic, a genetic condition of difficult detection since there are no election methods for its molecular identification. The deletion present in mosaic may have contributed to the attenuated reduction in kidney function compared to PKD1 protein-truncating mutations. The variant is not reported, but due to the type of mutation and the patient's clinical picture, it is to be considered as likely pathogenic. This case highlights how a stepwise genetic approach might be useful when standard methods do not allow to reach a definitive diagnosis.

PUB292

A Possible Correlation between Nephronophthisis and Glaucoma

Harini K. Venkatesh, Mina El-Kateb, Ali Hussain. *Henry Ford Macomb Hospital, Clinton Township, MI.*

Introduction: Cilia perceive extracellular signals like growth factors, chemicals and light for normal kidney development and maintenance. 'Ciliopathies' are autosomal recessive genetic diseases caused by their dysfunction. Most commonly affected are the kidneys causing Nephronophthisis (NPH), but the brain, eye, face, liver, heart and skeleton are also involved. Several associations between NPH and other conditions have been discovered. This case report describes an unusual combination of glaucoma and NPH leading to profound visual and renal function loss.

Case Description: A 20-year-old African American male presented with progressive vision loss after undergoing retinal cryotherapy and laser at the age of 4 for an unknown retinopathy. He had end-stage renal disease (ESRD) secondary to infantile NPH confirmed by genetic testing, having already failed transplantation twice. Eye examination noted decreased visual acuity bilaterally with only preserved light perception; he also had horizontal nystagmus, elevated intraocular pressure, retinal dystrophy and optic atrophy. Despite the discontinuation of steroids after the failure of his second allograft, tonometry continued to suggest open-angle glaucoma, concerning for a different disease process.

Discussion: Over 90 gene mutations are involved in ciliopathies, of which more than 20 give rise to NPH. NPH has 3 forms – infantile, juvenile and adult; while the latter two produce tubulointerstitial fibrosis, infantile NPH causes a more severe medullary cystic kidney disease that quickly progresses to ESRD. Retinopathy in conjunction with NPH, is a rare autosomal recessive disease affecting 1 in a million, called Senior-Loken syndrome that presents with childhood-onset hyperopia, photophobia and nystagmus. Glaucoma has been recognized in other ciliopathies. In this case, despite the estimated 3% risk of permanent glaucoma following steroid cessation, dysfunctional cilia impairing aqueous humor outflow in the anterior segment of the eye may be responsible. Life expectancy with NPH may vary depending on the onset of ESRD. Although renal transplantation is the only solution currently, specific signaling pathways like cAMP/PKA, mTOR and Hedgehog are potential sites for therapy. Identification of patients with NPH and new associations adds to the literature and maximizes pathological discoveries, thus paving the way for better treatment.

PUB293

Inferior Vena Cava (IVC) Compression Secondary to ADPKD: A Diagnostic Dilemma

Abdel-Rauof M. Akkari, Ahmad Matarneh, Sundus Sardar, Fnu Varnika, Umar Farooq, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Introduction: Adult polycystic kidney disease (ADPKD) is one of the most common life-threatening genetic diseases. It is an inherited condition where fluid-filled cysts develop and enlarge in both kidneys and multiple other organs. It is the fourth leading cause of kidney failure, with over 50% of ADPKD patients developing kidney failure by age 50. Interestingly, cysts can enlarge and become symptomatic, with variable symptoms ranging from non-specifiC to mass effect. We present an interesting case of a patient who had symptoms of inferior vena cava (IVC) compression that improved with bilateral nephrectomies.

Case Description: A 51-year-old female with a history of ESRD secondary to ADPKD had been receiving hemodialysis (HD) for several years. She was relatively stable on hemodialysis; however, she was usually noted to have bilateral lower limb edema despite having clear chest sounds. The usual thought process was that her target EDW needed to be changed, and more ultrafiltrate needed to be removed. However, every time we tried, her edema persisted. On abdominal examination, we found a distended abdomen. There was suspicion that this might be related to IVC compression. A bedside ultrasound showed large kidneys, leading to the decision to proceed with a CT scan of the abdomen. The CT scan revealed bilateral enlarged kidneys (left: 22x22x12 cm, right:29x19x12 cm) with evidence of IVC compression secondary to mass effect. She was referred to the urology team, who performed bilateral nephrectomies. Her symptoms improved tremendously postoperatively, and she is currently undergoing HD with no active complaints.

Discussion: ADPKD remains one of the leading causes of kidney failure. If the kidneys are large enough, they can cause symptoms related to the mass effect. Symptoms related to mass effect compression against surrounding organs are not uncommon. It can compress vascular structures, leading to symptoms of ischemia if compressing the aorta, or symptoms of IVC distention. IVC compression symptoms are mainly related to lower circulatory venous congestion, which can cause edema, congestion, and discomfort. A point of interest is when it causes these symptoms in patients who are in ESRD, making it difficult to judge their volume status. The incidence of IVC compression in ADPKD is not well established, but removal of kidneys appears to result in symptomatic relief.

PUB294

Cystinosis Presenting with Complications in an Adult: A Difficult Case

Abdullah Masood, Andrew Polyak, Aryeh Moskovits, Geronimo E. Banayat. *Trinitas Regional Medical Center, Elizabeth, NJ.*

Introduction: Cystinosis is a rare autosomal recessive disease caused by a defect in lysosomal transport protein causing accumulation of cysteine in lysosomes which causes multiple deleterious effects in body organs, especially the kidneys and eyes. It is the most common cause of Fanconi syndrome in children. It is caused by mutations in the *CTNS* gene, which encodes the lysosomal cystine carrier protein *cystinosin*. Incidence is generally 1:200000 but up to 1:3000 in certain consanguineous populations. Herein we present a case of a 21 y/o M with cystinosis presenting with status epilepticus and AKI on CKD requiring haemodialysis.

Case Description: A 21 y/o M with PMH of cystinosis with CKD, HTN and seizures came to the ED with bradypnea and status epilepticus. Vitals were: Temp 98.3, Pulse 106, RR 10, BP 132/67. Labs were Na 137, K 3.4, Cl 97, HCO3 19, AGAP 21, Cr 4.42, BUN 20 Urine pH 5.5, Urine Cl 31.8, Urine K 39, Urine Na 33 UAG 27.6. US kidney was normal, MRI brain showed no acute changes. Patient was on levocarnitine and cysteamine at home and had not required haemodialysis yet. At this admission, he had COVID-19 and aspiration pneumonia secondary to the seizures leading to VDRF. He was started on Keppra and Meropenem. Patient developed severe hyperchloremic, hypokalaemic metabolic acidosis with polyuria and was started on dialysis. Amiloride was started as well. Patient improved, electrolytes became stable and was extubated to trach, PEG tube placed for feeding and discharged to LTAC.

Discussion: Cystinosis was first described in 1903 in Switzerland but evidence of the mutation is nearly 2000 years old. It can be divided into infant, juvenile, and ophthalmopathy type. Our patient had the infant type which kidney disease is the most common. This patient had a preexisting diagnosis but generally spectrometric detection of cysteine in WBC, slit lamp and gene studies can be used to diagnose. Cysteine depleting therapy like cysteamine bitartrate delays the progression to ESRD as seen in this patient. Carnitine supplementation has not really shown much improvement in outcomes. Kidney transplant however shows an excellent prognosis in this disease. Cysteinosis remains an enigmatic disease with few case reports and epidemiological studies in adults. Much more study is needed to truly tackle the new adult population living with this disease with monitoring and treatment.

PUB295

Kidney Failure in Familial Mediterranean Fever: Heller Revisited

Jan V. Meulen. *Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands.*

Introduction: In 1955 Heller introduced the term Familial Mediterranean Fever (FMF) for a hereditary syndrome, manifesting itself in infancy or adolescence. The syndrome was already known as periodic disease and found in Jews, Arabs, and Armenians. Heller chose the adjective Mediterranean because 45 of his 74 patients (pts) were Sephardic Jews i.e. coming from Egypt, Libya, Tunis, Algeria and Morocco (SJ). Twenty pts had marked proteinuria and 3 pts died of chronic renal failure (CRF) due to amyloidosis. None of his 74 pts were Ashkenazi Jews i.e. from Central and Eastern Europe (AJ). Heller's explanation was that AJ have another ethnicity than SJ. A study of 100 Armenians with FMF in California (AC) found no marked proteinuria or amyloidosis. The explanation: AC had different mutations as compared to SJ. Colchicine, introduced as a prophylactic in 1972, prevents CRF. The pathogenetic gene, the MEFV, was found in 1997. Almost 75% of all FMF pts have the mutants M694V, M694I, V726A and M680I. Homozygosity for M694V is significantly associated with a severe form of FMF and CRF.

Case Description: After the earthquake in 1988, "Doctors without Borders" from the Netherlands set up a hemodialysis (HD) unit in Armenia. Nine pts started HD because of acute renal failure and 47 pts because of CRF. Eleven CRF pts had periodic disease (table). The term FMF and colchicine as prophylactic were unknown in Armenia at that time.

Discussion: The finding that Armenians with FMF in Armenia (AA) develop CRF, suggests that they have similar mutants as SJ. Most likely, the presence of these mutants is due to the fact that SJ and AA have not been exposed to genocide. Whereas at present the highest prevalence of FMF is in the non-Mediterranean part of Turkey and neighbouring Armenia, one may question the adjective "Mediterranean". However, from a historical point of view, the adjective should remain. It reflects that the Jewish community in these Arabic countries lived in harmony with the Muslims.

Table. Diagnoses of 47 CRF patients starting HD.

Chronic glomerulonephritis	13
Periodic disease (Familial Mediterranean Fever)	11
Chronic pyelonephritis	6
Analgesics nephropathy	1
Diabetes mellitus	1
Amyloidosis due to Ankylosing Spondylitis	1
Adult polycystic kidney disease	1
Unknown	13

PUB296

Uncovering the Hidden Genetic Causes of Kidney Diseases: A Whole-Genome Sequencing (WGS) Study

Silvia Giovanella,[1] Alessandra Terracciano,[3] Francesco Emma,[3] Angela Ferrulli,[2] Francesca Testa,[4] Maria Ferri,[1,4] Gabriele Donati,[1,4] Michele Rossini,[5] Giovanna Valenti,[2] Antonio Pisani,[6] Laura Massella,[3] Riccardo Magistroni.[1,4]
[1]Universita degli Studi di Modena e Reggio Emilia, Modena, Italy; [2]University of Bari, Department of Biosciences, Biotechnologies and Environment, Bari, Italy; [3]Bambin Gesù Children Hospital, Rome, Italy; [4]Azienda Ospedaliero-Universitaria di Modena, Modena, Italy; [5]University Hospital Bari, Bari, Italy; [6]Azienda Ospedaliera Universitaria Federico II, Napoli, Italy.

Background: Employing a genomic approach holds promise in elucidating the etiology of CKD. Our prior study ('DECIDE') demonstrated a yield of 36% in a select population (n=692) undergoing gene panel, with an additional 12% diagnostic rate upon further investigation. This study showed that a large proportion of our patients lacked a final diagnosis despite a high suspicion of genetic disease. This spurred the creation of an Italian consortium comprising 4 clinical centers specialized in genetic kidney diseases. We propose to assess the diagnostic yield of Whole Genome Sequencing (WGS) in unresolved cases.

Methods: The consortium will conduct WGS analysis on 300 patients (100 index cases in trios) with suspected genetic kidney disease who tested negative in initial genetic analyses. Collaboration with AIRP (Italian Patients' Association for Kidney Diseases) will ensure that our protocols align with patient expectations. During recruitment, clinical data will be centralized in RedCAP, with emphasis on family history, age of onset, and lacking diagnosis despite thorough diagnostic evaluation, to prioritize patients with a high suspicion of a genetic condition. The genomic analysis will utilize Illumina's NovaSeq 6000 sequencing platforms. Variants will be classified following ACMG guidelines. The clinical impact of new genomic diagnoses will be assessed by determining whether they will guide tailored therapies, prevent futile treatments, and facilitate cascade testing. In a subset of patients with cystic manifestations, identified variants will undergo evaluation through functional studies focusing on renal concentrating ability alterations.

Results: Our goal is to identify new pathogenic variants that may have been missed by previous analyses. Integration of genetic results with functional assessment could allow evaluation of the potential of personalized medicine in rare cystic conditions other than ADPKD.

Conclusions: A genetic diagnosis may hold direct clinical implications. By leveraging WGS and advanced bioinformatics, we aim to unearth novel insights contributing to our comprehension of the mechanisms underlying renal diseases. Funded by the European Union - Next Generation EU - PNRR M6C2 - Investment 2.1 Valorization and Enhancement of NHS Biomedical Research.

Funding: Government Support - Non-U.S.

PUB297

A Rare Find of Glucocorticoid-Remediable Aldosteronism

Elizabeth Cho, Jie Tang. *Brown University Warren Alpert Medical School, Providence, RI.*

Introduction: Glucocorticoid remediable aldosteronism (GRA), is a rare genetic form of hyperaldosteronism caused by an unequal cross-over of steroid 11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) genes, leading to an increased aldosterone synthesis driven by ACTH. Here, we present a case of GRA diagnosed by ACTH stimulated adrenal vein sampling (AVS) and confirmed by genetic testing.

Case Description: A 24-year-old female was referred for hypertension. She was found to have elevated blood pressure (BP) at age 16 after falling from a horse ride. At age 20, she was again hypertensive and developed mild hypokalemia. Since then, her BP has not been controlled on maximum doses of amlodipine, chlorthalidone, and lisinopril. She has no other medical history, is a nonsmoker, rarely drinks alcohol, never used illicit drugs. She was adopted. Her only compliant was involuntary 80 lbs weight gain over the past three years. Vitals: BP 150/98, heart rate 88 bpm; physical exam was unremarkable. Laboratory tests showed normal renal and liver functions, normal thyroid function, normal electrolytes except potassium 3.1 mEq/L, plasma renin activity was <0.1 ng/mL/hr, serum aldosterone was19.4 ng/dL; CT showed normal adrenal glands. Shortly after, ACTH-stimulated adrenal vein sampling (AVS) was performed which showed dramatic aldosterone responses to ACTH without lateralization (see Table). Genetic test confirmed pathogenic CYP11B1 and CYP11B2 fusion. She responded to low dose prednisone and spironolactone 50 mg twice a day.

Discussion: GRA diagnosis is often overlooked due to fluid clinical presentations. Work up starts by confirming hyperaldosteronism. In this case, AVS was very helpful in securing the diagnosis with dramatic aldosterone response to ACTH. A prompt diagnosis of GRA is crucial to establish an effective treatment regimen.

ACTH-stimulated adrenal vein sampling result

	Pre-ACTH			Post-ACTH		
	IVC	R Adrenal Vein	L Adrenal Vein	IVC	R Adrenal Vein	L Adrenal Vein
Aldosterone (ng/dL)	1	14	14	41	5505	5279
Cortisol (mcg/dL)	1.7	5	4.3	10.5	321.6	320.7

PUB298

Fumarate Hydratase-Deficient Renal Cell Carcinoma

Emad S. Khater. *SehaKidney Care, Abu Dhabi, United Arab Emirates.*

Introduction: Fumarate hydratase FH deficiency is very rare disorder. characterized by educed FH enzyme activity. Fumarate hydratase-deficient renal cell carcinoma RCC is a rare pathological subtype.

Case Description: We reported a 33 years old male know to have diabetes and hypertension well controlled presented with complains of right side loin pain. and visible haematuria. no family history or renal disease.renal function normal. Urine showed RBC. Clinical examination unremarkable. CT showed large infiltrating tumour in the right kidney. biopsy of renal mass showed renal RCC. However, as the patient is young. translocation related tumours considered hence immunohistochemistry performed it showed diagnosis of a fumarate hydratase-deficient RCC. plan was to start the patient on immunotherapy in the form bevacizumab and erlotinib and to repeat the CT if CT improved then to do nephrectomy.

Discussion: Fumarate catalysed to malet by fumarate FH enzyme in Krebs cycles. deficiency of FH enzyme due to Genetic disorder lead to accumulation fumarate intracellularly and extracellularly. Its rare disorder. mode of transmission is autosomal recessive. accumulation of fumarate may function as an oncometabolite in homozygous FH deficiency causes sever neonatal neurological defect, dysmorphic feature and brain abnormalities. prognosis is poor most of severely affected child do not survive. The heterozygotes form majority of cases are healthy. however, they may develop tumours like cutaneous leiomyomata uterine fibroids and uterine myomas also may develop RCC known as Hereditary Leiomyomatosis with Renal Cell carcinoma HLRCC. In regards to RCC associated with FH deficiency defined as a rare pathological subtype (WHO 5th edition 2022) due to mutations in the FH gene. Diagnosed based on a molecular and immunohistochemical biomarkers. The incidence is very rare and only a few hundreds of cases reported. average age onset between 20 -25. Unfortunately its highly metastasize and very invasive. main treatment is nephrectomy. immunotherapy considered new hope in these patients treatment. Family member of high risk needs early genetic counselling and testing also renal surveillance. Conclusion, FH deficiency is an autosomal recessive disease due to accumulation of fumarate. It may associated with RCC FH deficient. Its rare disease very invasive in young age with RCC advised to investigate for FH deficiency as possible cause.

PUB299

Gordon, You're Bananas! A Case of Resistant Hyperkalemia

Ashley Tang, Huy Truong, Shonit Nandakumar, Rajesh Gulati. *Riverside Community Hospital, Riverside, CA.*

Introduction: Gordon syndrome, also known as familial hyperkalemic hypertension or pseudohypoaldosteronism type II, is a type IV renal tubular acidosis (RTA) and presents during adolescence or young adulthood. Its pathology is due to gene mutations that affect electrolyte transporters in the renal distal tubules and can be difficult to clinically identify from other common diagnoses. In this case, we highlight Gordon syndrome as an alternative diagnosis for a patient with suspected acute heart failure exacerbation nonresponsive to standard treatments.

Case Description: A 30-year-old male with a history of hypertension presents for worsening dyspnea and leg edema. His family history was significant for early onset hypertension. On exam, he was tachycardic, hypertensive, and had diffuse lung crackles and severe edema. Labs indicated hyperkalemia, NAGMA, and elevated BNP. A transthoracic echocardiogram and renal ultrasound were unremarkable. Repeated furosemide and potassium binder doses had inadequate responses, triggering other renal workup. Loop diuretics were discontinued in favor of thiazide diuretics, and he improved, discharging home with instructions to obtain outpatient genetic testing for Gordon syndrome. Labs were significant for an elevated renin, low aldosterone, and normal metanephrine and normetanephrine. Two months later, he was re-evaluated for intermittent edema after being compliant with a thiazide, and his symptoms and laboratory abnormalities were primarily resolved.

Discussion: Gordon syndrome, although rare, can resemble more prevalent disorders like heart failure, but can be differentiated by distinct lab results and early onset hypertension. This patient's volume status and hyperkalemia were also unresponsive to standard heart failure treatments, and in the setting of unremarkable renal and adrenal workup, his ongoing NAGMA, hyperkalemia promoted investigation into a type 4 RTA. His renin was elevated, likely from furosemide administration and its activation of the renin-angiotensin-aldosterone system. His aldosterone however remained suppressed, and he responded well once transitioned to thiazides, which coincides with Gordon syndrome's pseudohypoaldosterone nature and its sensitivity to that drug class. Recognizing these diagnostic hallmarks in the early stages can expedite accurate diagnosis and the initiation of appropriate treatment, thereby improving patient care outcomes.

PUB300

Answering the Call for Genetic Testing: Recurrent Hypomagnesemia Secondary to the Gitelman-Like ADTKD-HNF1

Andrew Yanik, Taylor R. Moody, Anne Cioletti, Sarah Gilligan. *University of Utah Health, Salt Lake City, UT.*

Introduction: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of inherited kidney disorders characterized by early onset chronic kidney disease. Mutations to the transcription factor hepatocyte nuclear factor 1B (HNF1B) are associated with renal cysts, diabetes, and tubular dysfunction. We report the case of a patient with recurrent hypomagnesemia and hypokalemia secondary to *HNF1B* mutation.

Case Description: A 22-year-old female with history of non-diabetic gastroparesis requiring tube feeds and total parenteral nutrition was seen by nephrology for refractory hypomagnesemia and hypokalemia. Since early adolescence she had recurrent hypomagnesemia and hypokalemia as low as 0.9 and 2.4, respectively. She was managed with thrice daily oral magnesium and potassium and daily IV magnesium through indwelling catheters. Due to frequent hospital admissions for central line-associated bloodstream infections, her long-term IV access was discontinued. A formal workup for hypomagnesemia showed an elevated 24-hour urinary magnesium of 578 mg/d and an elevated fractional excretion of magnesium of 17% with serum magnesium of 1.1 mg/dL. Interestingly, her genetic testing years prior revealed no pathogenic mutations causing Gitelman syndrome but instead showed a heterozygous whole gene deletion of HNF1B. She is currently managed with magnesium oxide thrice daily, IV mag thrice weekly, and amiloride. She was recently started on SGLT2 inhibition with improvement in her magnesium levels.

Discussion: HNF1B is a transcription factor encoded by the *HNF1B* gene on chromosome 17q12, mutations in which can present as tubular dysfunction similar to Gitelman syndrome. HNF1B has downstream targets that regulate the Na-K-ATPase pump in the basolateral membrane of the distal convoluted tubule (DCT). Loss of HNF1B limits active transcellular magnesium reabsorption and disrupts potassium handling, resulting in hypomagnesemia and hypokalemia. Several case reports demonstrated improvement in hypomagnesemia in patients with HNFB1 mutation when SGLT2 inhibitors are used as treatment for associated diabetes, but to our knowledge they have not been used for this indication in a non-diabetic patient. This case demonstrates the value of genetic testing, gives insight into the presentation of ADTKD-HNF1B, and suggests yet another indication for SGLT2 inhibitors.

PUB301

Mitochondrial Nephropathy with m.5538G>A Mutation within the tRNA-Trp Region Treated with Imeglimin: A Case Report

Mari Ikeda,[1] Toshiyuki Imasawa,[2] Tomohiko Inoue,[3] Mamiko Ohara,[1] Tomo Suzuki.[1] *[1]Kameda Medical Center, Kamogawa, Japan; [2]Chiba-East National Hospital, Chiba, Japan; [3]St. Marianna University School of Medicine Hospital, Kawasaki, Japan.*

Introduction: Mitochondrial nephropathy (MN) is a genetic disease characterized by a defect in oxidative phosphorylation, with a diverse clinical presentation, urinary protein in more than 90% of cases, and decreased kidney function reported in about 70% of cases. Although CoQ10 and taurine have been reported to be effective in improving kidney function in some cases, most cases are difficult to treat. We report the first case of mitochondrial nephropathy treated with imeglimin after genetic and mitochondrial function analysis.

Case Description: This case is a 25-year-old male with mild proteinuria who was diagnosed with minor glomerular abnormalities in his first kidney biopsy at age 15. Due to increased urinary protein (urine protein creatinine ratio 2.2 g/gCr) and decreased kidney function (serum creatine 1.24 mg/dL), we performed second kidney biopsy at age 22. Light microscopy showed segmental glomerulosclerosis lesions. Electron microscopy revealed many abnormal mitochondria in the podocytes. Serum lactate was 27.8 mg/dL and cerebrospinal fluid lactate was 35.5 mg/dL after admission. Therefore, we considered mitochondrial disease (MD). We further suspected MD when cultured dermal fibroblasts showed decreased oxygen consumption and decreased respiratory chain enzyme activity complex III and complex IV, leading us to perform genetic testing. Genetic analysis of frozen sections of kidney tissue confirmed with m.5538G>A mutation in the tRNA-Trp region. Similarly, we detected the same genetic mutations in blood, urine, and skin fibroblasts. The rate of urine, blood, and skin fibroblast of heteroplasmy were 64.0%, 32.4%, and 73.3%, respectively. We treated him on olmesartan and dapagliflozin for chronic kidney disease with severe persistent urinary protein. In addition, we added imeglimin in the hope of improving new-onset diabetes and reducing complex III activity. Approximately one year after the start of imeglimin treatment, renal function declined at a faster rate, but proteinuria and lactate/pyruvate ratio decreased, suggesting that mitochondrial function may have improved.

Discussion: Imeglimin may be effective in MN with reduced complex III activity, but the long-term effects need to be verified.

PUB302

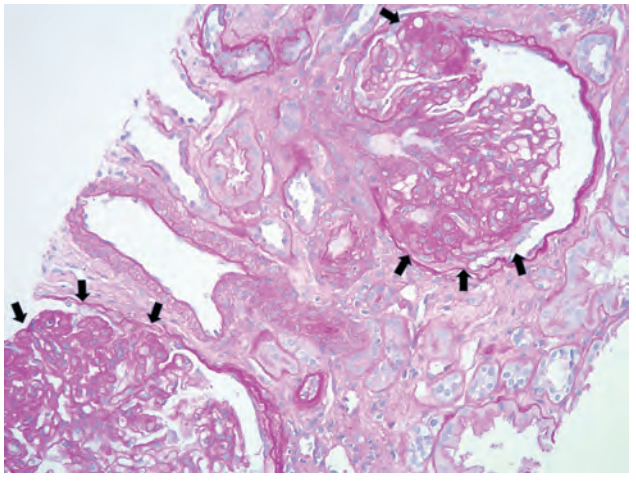
PAX2 Mutation Associated with Focal Segmental Glomerulosclerosis

Manuel A. Santos Carrasquillo,[1] Leal C. Herlitz,[2] Surafel K. Gebreselassie,[1] Scott D. Cohen.[1] *[1]Cleveland Clinic Florida, Weston, FL; [2]Cleveland Clinic, Cleveland, OH.*

Introduction: FSGS is a heterogenous disorder with a variety of causes including immunologic factors, genetics, medications, and infections. Recognizing the potential pathogenic etiology is essential in the appropriate management of patients. Knowledge of genetic etiologies will avoid unnecessary patient exposure to the toxic effects of immunosuppression.

Case Description: A 19-year-old male presented with abnormal kidney function, eGFR 42 ml/min/1.73m2, serum creatinine of 2.2 mg/dl along with a nephrotic range proteinuria of 4.1 g/g on a random urine sample. Serum albumin was 4.5 g/dl. On physical examination, the patient had a blood pressure of 125/78, examination was remarkable for 1+ peripheral edema. A kidney biopsy was performed which showed FSGS with mild to moderate tubular atrophy and interstitial fibrosis. 6 out of 28 glomeruli were globally sclerotic with 7 FSGS lesions, some of which were perihilar in location, there was also moderate foot process effacement. Genetic testing was ordered and returned with a PAX2 gene mutation. The patient was referred for genetic counseling as well as ophthalmology and audiology evaluations. He was started on Losartan 25 mg once daily; on 3 month follow up the proteinuria decreased to 1.4 g/g with a serum creatinine of 2.4 mg/dl, eGFR 40 ml/min/1.73m2.

Discussion: Mutations in PAX2 are associated with autosomal dominant adult-onset FSGS. PAX2 is a transcription factor that plays an essential role in kidney development and was previously found to be associated with congenital abnormalities of the kidney and urinary tract (CAKUT) including reduced nephron mass. The reduction in nephron mass can lead to glomerular hyperfiltration and adaptive FSGS. PAX2 may also have a direct effect on the podocyte as it suppresses the expression of WT1, a nuclear protein expressed in these cells. Genetic testing can play an integral role in the diagnostic evaluation and treatment of patients with FSGS.



PUB303

ABCC6/MRP6 Gene Mutation with Associated Membranous Nephropathy

Samir D. Patel, Ryan E. Fekrat, Gayathri Dileep, Matthew D. Nguyen, Ramy M. Hanna. *University of California Irvine Nephrology Hypertension & Kidney Transplantation, Orange, CA.*

Introduction: Multidrug resistant associated protein 6 (ABCC6/MRP6) is found in the liver and kidneys and functions in ATP-dependent export for systemic delivery related to modulators of calcification. Mutation of ABCC6 results in ectopic mineralization characterized in cases of pseudoxanthoma elasticum (PXE) and dystrophic cardiac malfunction (DCC). Neural epidermal growth factor-like 1 protein (NELL-1) has been associated with a rare form of membranous nephropathy (MN) with little proposed mechanistic link. Here we present a 54-year-old female with known ABCC6/MRP6 and NELL1 positive MN with no evidence of serological factor, rheumatoid factor, cryoglobulin, or M-protein abnormality, implying a possible link between ABCC6 mutation and NELL1 positive MN.

Case Description: Our patient is a 54-year-old female with a known ABCC6/MRP6 gene mutation on outside testing presented with initially normal renal function (BUN 6 mg/dl, sCr 0.5 md/dl). However, 24-hour urine collection shows 1.1 grams of protein with findings of an increase in urine protein to 4.4 grams (within nephrotic level range) with a peak UPCR of 7 grams at an outside hospital. Serological testing was negative with exception of isolated low C4. There was no evidence of rheumatoid factor, cryoglobulin, or M-protein abnormalities. Renal biopsy reflects membranous nephropathy, NELL1 positive. glomerulomegaly, mesangial IgM deposits, and mild to moderate arteriosclerosis. She was advised cancer screening for secondary MGN/NELL membranous nephropathy. She currently is on a RAAS inhibitor for blood pressure control. Her proteinuria decreases when on steroids to less than 350 mg.

Discussion: Our case presents as NELL1 positive MN in an adult female with negative findings of most common associations of secondary MN such as sarcoidosis, hematopoietic stem cell therapy (HSCT), autoimmune disease, infection, or malignancy with the additional presentation of ABCC6 mutation and low complement activation and no cancer as of report timing. Negative lipoid acid supplementation and target antigens in cases of secondary MN additionally are not always associated with identifiable causes. In our case, we propose the association of NELL1 positive finding with mutant or aberrant ABCC6-MN in conjunction with negative cancer findings. Supplemental ABCC6/MRP6 therapy may improve prognosis in patients with NELL1-MN.

PUB304

Fabry Disease Baseline Phenotype in Migalastat-Treated Patients: A Single-Centre Experience

Elena-Emanuela Rusu,[1,2] Gener Ismail.[1,2] *[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [2]Nephrology Department, Fundeni Clinical Institute, Bucharest, Romania.*

Background: Fabry disease (FD) is a rare lysosomal storage disease causing progressive kidney, heart and nervous system disorders. Migalastat is an oral FD specific treatment that provides a suitable alternative in patients with amenable genetic variants. The aim of our retrospective study is to present the clinical phenotype of FD amenable patients evaluated and initiated on migalastat in the Expert Center for Rare Diseases of the Reno-Urinary System between 2020 – 2024.

Methods: All patients had comprehensive assessment for target organ manifestations of FD. Renal function was assessed using eGFR, albumin creatinine ratio and proteinuria. Also, 7 patients underwent kidney biopsy (KB).

Results: Our study included 12 adult (6M/6F) patients with confirmed diagnosis of FD by the genetic test and amenable GLA variants. Seven patients presented classic FD phenotype, while five patients presented late-onset FD phenotype. Seven patients started "de novo" migalastat and 5 were switched from enzyme replacement therapy (ERT). In naïve patients, the main indications were: heart disease (5 cases), kidney damage (1 case), neurological involvement (2 cases). In patients switched from ERT, the most frequent indication was the patient decision. At baseline, average age of the patients was 47.5 +/- 16.1 years old (range 24-75). Alfa-GLA activity was reduced in 10 patients, mean 1.6 +/- 1.8 mol/L/h. Overall baseline mean eGFR was 79.6 26.7 mL/min/1.73 m2. Five patients presented CKD stage 3, three patients presented kidney transplantation, 2 patients were in CKD stage 2, one patient with CKD stage 1, and 1 patient without clinical kidney involvement. Six patients presented normal UACR, four patients showed microalbuminuria, and 2 patients presented macroalbuminuria. KB was performed before ERT in 3 cases, before switch in 1 case, and in 3 naïve patients before migalastat treatment. Eight patients presented left ventricular hypertrophy. There was a statistically significant difference in eGFR in the males versus females (p=0.048), but no difference between classic versus late-onset phenotype. Left ventricular mass index were significantly high in late onset phenotypes.

Conclusions: Migalastat has been successfully initiated in this cohort of disease-specific naïve and previously treated patients with amenable mutations, after a complete patient evaluation by a multidisciplinary FD team.

PUB305

Genetics in Thrombotic Microangiopathy

Yaman Kouatli, Krista L. Lentine, Thanh-Mai N. Vo, Aliza Anwar Memon. *Saint Louis University, St Louis, MO.*

Introduction: The underlying molecular mechanisms in complement mediated Thrombotic Microangiopathy (C-TMA) tend to overlap but unify at the common end-point of endothelial injury. Literature has shown that complement activation is triggered at the endothelial surface. Some triggers like infection is the first presentation of TMA even in the genetically susceptible individuals. In this case, we discuss the unmasking of C-TMA after an infection.

Case Description: A 30-year-old African American male presented with acute pancreatitis and acute kidney injury (AKI). Workup was significant for creatinine 5.4 mg/dl, hemoglobin 10.3g/dl, platelets 21x10*3/uL, 2+ Schistocytes, reticulocyte 1.7%, bilirubin 1, Fibrinogen 365mg/dL, D-dimer >20, PT 1.5, APTT 28, C3 102, C4 23, and direct Coombs test negative. The ADAMTS13 activity at 67%. A genetic panel for C-TMA was sent and decision was made to start the patient on complement inhibitor therapy until genetic study was pending. Unfortunately, the patient left hospital against medical advice and two days later presented at an outside hospital. There he was started on hemodialysis for worsening renal failure and underwent a kidney biopsy which showed chronic TMA. Genetic results were positive for C-TMA due to the presence of a splice variant in CFHR1 in combination with large CFHR1-3 deletion which makes the patient in effect CFHR1-null.

Discussion: C-TMA is caused by the dysregulation of alternate pathway (AP), perpetuating the downstream effects of the complement pathway. Only 50-60% of cases of C-TMA are caused by genetic variants and the absence of the gene does not exclude the diagnosis. C-TMA is not a monogenic disease and familial forms are only reported in 20% of patients. More genetic variants are emerging as genetic testing is becoming frequent and patient registries continue to expand. Due to the variable penetrance in familial cases of C-TMA, most patients present at an advanced age and often require a second hit such as an infection, pregnancy, and vaccination to unmask the TMA. The studies done so far to compare the enrichment of the variant frequency have been geographically limited and the issue of race has not been addressed in the field of TMA genetics. The data on the incidence of C-TMA and complement genetics is lacking in black individuals. Further studies are needed to explore the frequency of genetic variants in the African American population.

PUB306

Hereditary Angiopathy with Nephropathy, Aneurysms, and Muscle Cramp (HANAC) Syndrome: There Is More to Explore!

Nahida Baigam, Rajesh Mohandas, Siddhartha D. Bajracharya. *LSU Health New Orleans, New Orleans, LA.*

Introduction: Structural integrity of the glomerular basement membrane (GBM) is essential to maintain the selectivity of the slit diaphragm and filtration barrier. One of the key components of the GBM is Collagen Type 4. Mutations in Collagen Type 4 underlie the well-known hereditary disorder, Alport's syndrome. We report a more uncommon hereditary disorder affecting the kidneys due to mutations in Collagen Type 4

Case Description: A 30-year-old man with bilateral congenital cataracts and cerebral palsy (CP) was referred for asymptomatic microscopic hematuria. He did not report muscle pain or cramps, neurological symptoms, gross hematuria, hearing issues, polydipsia, or polyuria. He had hypertension but was not on medications. His estimated Glomerular filtration has declined from 66 to 57 mL/min/1.73m^2. Otherwise, his lab work was within normal limits. He did not have a family history of CKD, but his mother and sister had CP. We performed a renal biopsy, which showed Thin Glomerular Basement Membrane Disease (TBMN) and genetic test was performed, which revealed a pathogenic mutation in COL4α1.

Discussion: The glomerular basement membrane in humans contains two separate networks of type 4 collagen. The sub-endothelial GBM comprised of α1/α2 networks, while the thicker sub-epithelial layer comprised of α3/α4/α5 networks. Defects in α3/α4/α5 cause Alport's syndrome, while mutations in COL4α1 mutations can cause diverse clinical presentations hereditary angiopathy with nephropathy, aneurysms, and muscle cramps, the HANAC syndrome, and non-syndromic congenital cataracts. Renal involvement can cause thin basement membrane with microscopic hematuria and renal cysts and less often CKD. Earlier genetic testing could have avoided the need for a biopsy in this patient. Worldwide, 13.4% of the population has CKD; among the causes, Primary glomerular disease is more than 8% and familial 10%. COL4 A disorders have significant similarities. All patients with suspected Alport syndrome or TBMN disease should receive genetic testing for the COL4 variants because up to 27% of cases are caused by a de novo pathogenic variant. The penetrance of COL4A1-related disorders is close to 100%, with the clinical presentation differing widely. Genetic testing allows for the early detection of exceptionally rare kidney diseases like HANAC syndrome.

PUB307

Apparent Steroid Sensitivity in Congenital Nephrotic Syndrome Type 1 (NPHS1)

Mohammad S. Al-Awad, Essa Abuhelaiqa, Awais Nauman. *Hamad Medical Corporation, Doha, Qatar.*

Introduction: Congenital Nephrotic Syndrome (CNS) Type1 is an autosomal recessive disease caused by mutation in NPHS1 gene. NPHS1 encodes for Nephrin which is essential for maintaining slit diaphragm integrity. Herein we report a case of CNS Type1 that was treated with multiple Immunosuppressants with numerous relapses and remission giving an apparent impression of steroid sensitivity

Case Description: A 21 y.o male, diagnosed with Nephrotic Syndrome at age of 20 months, Received Steroids initially with partial response. Later, The patient continued to exhibit low grade proteinuria less than 1 g/24hr with sharp interval increases reminiscent of relapses. Despite treatment with Cyclophosphamide, Mycophenolate Mofetil and Cyclosporin, his relapses persisted Kidney Biopsy at age of 10 years when he was in partial remission revealed no Glomerular Proliferative changes or Segmental Sclerosing lesions with minimal IFTA, Negative IF. EM Showed moderate and non-global foot process effacement and was decided to have Minimal Change Disease in partial remission. He was maintained on Cyclosporine and Prednisone and continued to have frequent relapses. Therefore, he was given Rituximab, other therapies were tapered off as there was partial improvement of proteinuria. The patient had preserved GFR through all clinical course. and noted that the patient had fluctuation of proteinuria with no particular relationship with Immunosuppression therapy which led to the suspicion of CNS type1. He was referred to Genetic Testing which revealed NPHS1-related disorder with Homozygous mutation of (TTC>GTC): c.2617 T>G in exon 19 of the NPHS1 gene

Discussion: CNS type1 (NPHS1) Classically is characterized by prenatal onset of massive proteinuria followed by severe steroid-resistant nephrotic syndrome apparent at birth with rapid progression to end-stage renal failure. When NPHS1 patients are on therapy partial improvement in proteinuria can give an apparent impression of steroid sensitivity resulting in continued use of various immunosuppressive which are potentially toxic. Genetic testing can confirm the diagnosis thereby avoiding pernicious side effects of immunosuppression. Our patient had relapsing-remitting Nephrotic syndrome with no relation to therapy. It is therefore imperative to maintain high index of suspicion and low threshold for considering genetic testing in childhood Nephrotic Syndrome

PUB308

Duplication Syndrome and Its Association with Kidney Disease

Mercedes Malone. *University of Florida, Jacksonville, FL.*

Introduction: Williams-Beuren Syndrome (WS) refers to a segment on chromosome 7 that, when absent, is associated with WS. Conversely, duplicating this segment can lead to Duplication 7 Syndrome (Dup 7). Duplication syndrome is a rare genetic disorder characterized by developmental delay, impairment of the kidneys, and behavioral abnormalities. Here, we describe a case of 7q11.23 duplication exhibiting such features. Duplication syndrome follows an autosomal dominant inheritance pattern and is characterized by an extra copy of a region on the long (q) arm of chromosome 7. Due to its rarity, duplication syndrome may be misinterpreted as a psychological disorder due to the limited information available about the condition and also remains a critical etiology for kidney disease. In the current case, the 7q11.23 duplication was identified many years after the initial presentation.

Case Description: A 19-year-old male with a solitary kidney presented to our nephrology clinic for persistent chronic kidney disease of unknown etiology. His medical history included autism absence seizures, chronic kidney disease stage 3a, and developmental disorder. During infancy, he faced unexplained growth issues and episodes of pneumonia, prompting negative tests for cystic fibrosis. His family history revealed a father with epilepsy. On examination, he was afebrile with no notable physical abnormalities except for agitation. Initial laboratory tests returned unremarkable results with a creatinine of 1.45 mg/dl. Neurological evaluations showed no abnormalities to explain his persistent behavioral symptoms. A psychiatric assessment highlighted speech and behavariol issues. Despite multiple medication trials yielding no improvement, consultation with a geneticist was pursued, considering a potential genetic association due to his solitary kidney. A breakthrough occurred when the geneticist identified a 7q11.23 duplication, shedding light on the underlying cause of his complex medical presentation.

Discussion: Diagnosing rare genetic conditions like 7q11.23 duplication syndrome requires teamwork and thorough exploration of family medical history. Early identification and intervention are vital for managing kidney disease and seizures, offering clarity and psychological relief. While treatment options may be limited, understanding the illness's cause brings psychological benefits and encourages further learning.

PUB309

A Rare Case of HNF1B and NR3C1 Genetic Mutations Leading to Severe Electrolyte Derangements and Impaired Glucose Control

Saeed Razaq, Khudija Nayab, Eric L. Wallace, Arun Rajasekaran. *The University of Alabama at Birmingham, Birmingham, AL.*

Introduction: HNF1B plays a crucial role in the development the kidney/liver/pancreas by regulating gene expression. HNF1B gene mutations cause structural kidney defects and electrolyte abnormalities. Non-renal consequences, notably MODY type 5, are also noted. Our case describes a patient incorrectly diagnosed with type 1 diabetes but was found to have a pathogenic HNF1B mutation and a likely pathogenic NR3C1 mutation, both contributing to her hyperglycemia, as well as hallmark features of ADTKD.

Case Description: 37-year-old female with insulin-dependent diabetes, autonomic neuropathy, hypomagnesemia, hypokalemia, hypophosphatemia, and cachexia presented with worsening fatigue and CKD. She was wheelchair bound, hypotensive, and cachectic. She denied PPI/laxative/diuretic use; denied family history of kidney disease. K 2.6 mmol/L, Cl 93 mmol/L, CO2 37 mmol/L, BUN 12 mg/dL, Cr 0.7 mg/dL, eGFR 114 mL/min/1.73m^2 [CKD Epi 2021; likely an overestimate of actual GFR given cachexia], Mg 1.1 mg/dL, Phos 1.9 mg/dL, Albumin 3.1 g/dL, HbA1c 15.9. Urinalysis - pH 6.3 and absent dipstick proteinuria. UACR 321 mg/g and UPCR 1987 mg/g [tubular proteinuria]. Kidney USG: B/L kidneys 10.5 cm, normal echogenicity, and no kidney cysts. Targeted gene panel of blood revealed a pathogenic HNF1B whole gene deletion [heterozygous, AD inheritence] at chromosome 17q12 and likely pathogenic NR3C1 mutation at chromosome 5 [heterozygous, AD inheritence]. She requires frequent IV crystalloids, magnesium, and potassium replacement therapy. Genetic counselling was provided and she is being followed at the Rare Genetic Kidney Disease Clinic at UAB.

Discussion: The case report explores the intricate relationship between HNF1 Beta mutation, potential tubulointerstitial nephritis, and MODY5 phenotype. HNF1B gene shows significant variability in mutation carriers, often without family history due to spontaneous mutations. Kidney involvement is common, with early manifestation and diverse phenotypes including electrolyte abnormalities. Pancreatic involvement is also notable. Our patient has a HNF1B 17q12 genetic variant that has been observed at a frequency of < 0.014% of the general population. Not much is known regarding NR3C1 mutations. We highlight the importance of genetic testing and counselling in tailoring individualized treatment.

PUB310

Alport Syndrome in a Woman with Proteinuria and Familial Hematuria

Jordan Hartman. *The University of Texas at Tyler, Tyler, TX.*

Introduction: Approximately 80% of Alport cases are due to X-linked gene mutations in COL4A5, although homozygous variants exist in people with autosomal recessive disease. The best screening tool for Alport syndrome is urinalysis with evidence of hematuria[1]. The diagnosis should be considered in patients with persistent microscopic hematuria or gross hematuria, although definitive diagnosis is by genetic testing[3].

Case Description: A 27-year-old female with a history of major depressive disorder presented to the clinic as a referral due to profound proteinuria on screening urinalysis by OBGYN for first trimester screening. Family history revealed persistent hematuria in the patient, her mother and brother. Autoimmune workup including Lupus was unremarkable with negative ANA. No signs of systemic inflammation were present, and inflammatory markers were within normal limits. We decided to perform genetic testing with NATERA Renasight Kidney Gene panels to determine if there is any hereditary explanation for her hematuria, ultimately avoiding a very high-risk kidney biopsy procedure during pregnancy. Her genetic testing came back positive c.2452G>A (p.Gly818Arg) mutation for COL43A gene. We have decided that Alport syndrome is the most likely explanation for her benign hematuria. We plan to obtain kidney biopsy following the delivery of her baby for confirmation of the diagnosis. However, with family history of multiple family members, genetic testing showing mutation the mutation above, and negative extensive work up, her most likely diagnosis is currently Alport Syndrome.

Discussion: algorithm for diagnosing CKD. Genetic testing is emerging as a valuable component for the evaluation of CKD cause. The prevalence of genetic causes of CKD is expected to increase in future years as our screening methods and diagnostic tools become more available and cost effective[3]. In our case, it helped prevent possible complications that can arise with kidney biopsy during pregnancy, and gave us more information for reproductive counseling. We believe that genetic testing should be considered as an initial diagnostic tool in CKD diagnosis.

PUB311

Adult Kwashiorkor Presenting with Extreme Hypernatremia and Edematous State: A Therapeutic Challenge

Jose F. Bernardo,[1] Marco A. Dominguez,[2] Carlos R. Valenzuela.[2] [1]*Clinica Medica Cayetano Heredia, Lima, Peru;* [2]*Hospital Nacional Cayetano Heredia, Lima, Peru.*

Introduction: Children with severe chronic malnutrition often present with either Marasmus or Kwashiorkor (an edematus state) and dysnatremia. There is a paucity of data on the effects that chronic malnutrition can have on sodium metabolism in the adult population. We present the case of an elderly female whose initial chief complaint was progressive weakness, decreased oral intake and weight loss. At time of her hospital admission, she had an edematous state and extreme hypernatremia.

Case Description: 72 years old female with history of depression on treatment with mirtazapaine. She had history of decreased apetite and weight loss for the past 6 months. In the past month she presented to the ER for up to three occasions complaining of progressive weakness and confusion and agitation and was found to be hypoglycemic. In this admission he was brought with a hstory of an episode of tonic-clonic seizure followed by loss of consciousness. On admission his BP was 100-60, HR 56, afebrile, looked older than stated age, her skin was dry and had areas of desquamation, severely decreased muscle mass, bilateral, peripheral edema up to thigh area, lungs were clear, heart no gallop, neurologic: slow response to painful stimuli and no focal motor deficit. All other systems were negative. Her Hb/Hct 15, Glucosa 46 mg/dl, Urea/Cr 102/2.2 mg/dl. Electrolytes showed: Na 193 mEq/L, K 5.24 mEq/L, Cl 117 mEq/L, Alb 3.9 g/dl, Total protein 7.2 3.9 g/dl. Total Cholesterol 102 mg/dl, Triglycerides 75 mg/dl. ABGs pH 7.32, HCO3 16, pCO2 32. PO2 86, lactate 1.6

Discussion: This case illustrates the concomitnt presence of an edematous state along with severe dehydration and hypernatremia. The combination of anemia, hypogycemia and hypocolesterolemia corroborated the presence of severe malnutrition, Kwashiorkor type. She has underlying severe chronic kidney disease, on admission she was not hypotensive but she had bradycardia. Her serum K levels wele slightly elevated potassium level and had a compensated metabolic acidosis both premonitory signs of a bad outcome. Her volumen status was deemed expanded because of the presence of moderate edema. She was then prescribed IV albumin and IV furosemide and subsequently evolved with a fatal cardiac arrest. The combination of severe edema and severe hypernatremia in adult patients with Kwashiorkor constitutes a therapeutic challenge.

PUB312

Kidney Biopsy in Elderly Patients: Is It Really the Case to Desist?

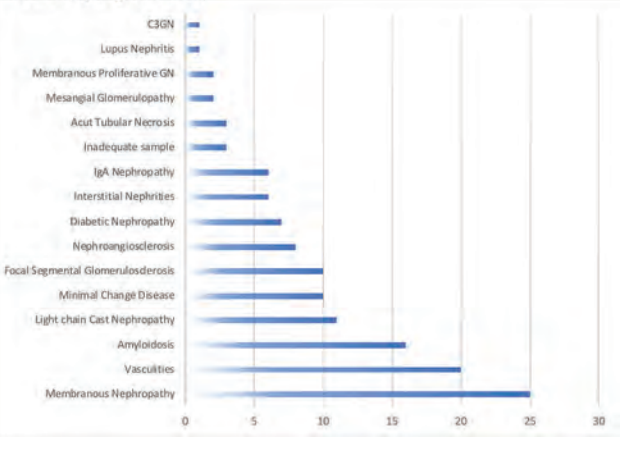
Adele Mitrotti, Francesca Digennaro, Eleni Ioannou, Donatella Cappiello, Marica Giliberti, Vincenzo Di leo, E. D. Stea, Adriano Montinaro, Paola Pontrelli, Michele Rossini, Loreto Gesualdo. *Universita degli Studi di Bari Aldo Moro, Bari, Italy.*

Introduction: Italy is the second country in the world for elderly population, after Japan, with an estimated population over 75 years of 11,7% while 7,18% are those over 80s. Of those, 42,3% have three or more chronic diseases (ISTAT data 2019). We investigated our kidney biopsy (KB) database from 2002 to 2024, looking at all the KB performed in patients over 80s, in our nephrology unit.

Case Description: We performed a KB in a 84 female with acute kidney injury and nephrotic syndrome, approaching dialysis. We diagnosed a “Light Chain Cast Nephropathy” in the setting of Multiple Myeloma with multiple osteolytic lesions. She rapidly started steroids and Bortezomib showing rapid and stable improvement of clinical symptoms and laboratory tests. We wondered if age still represent a limit to perform KB. From 2002 to 2024 we performed 7150 KB; 1,8% were performed in patients with an age over 80. Of the 131 patients, 54 were females and 77 were males, with a median age of 82 (range 80 to 96). Figure 1 shows renal biopsy diagnoses. The most frequent diagnoses were Membranous Nephropathy (19%), Vasculitis (15,2%), Amyloidosis (12,2%), followed by Light chain Cast Nephropathy (8,3 %), Minimal Change Disease and Focal Segmental Glomerulosclerosis (7,6% respectively).

Discussion: These diagnoses may represent a challenge, particularly in elderly patients with comorbidities. Personalized therapy can help in slow the progression of renal damage, improving their outcome even in vulnerable patients, as occurred in our case report. We will investigate the outcomes of each patient related to clinical presentation, diagnose, comorbidities and treatment. Our preliminary data show the importance of histological diagnosis, confirming the power of renal biopsy even in advanced ages, in order to identify the underlying pathology and evaluate which is the most appropriate personalized treatment option.

Table 2: Biopsy Diagnoses in 80s.



PUB313

Project on Geriatric Assessment in Nephrology Unit: Evaluation of Frailty and Vulnerability, Physical Capacity, and Kidney Function

Francisco Javier Lavilla. *Clinica Universidad de Navarra, Pamplona, Spain.*

Background: Improve geriatric assessment in Nephrology Unit.

Methods: Phase 1: Evaluation of subjective well-being (SWB) (1 to 10) and experience on diet, exercise, sleep, self-care, medication adherence, daily activity, socio-familial environment, and emotional state (1 to 3). **P 2:** Evaluation anthropometric (AM) (BMI, circumference upper extremity relaxed-contracted), grip strength (GS). **P 3:** Study orthostatic hypotension (OH) (diastolic DBP, systolic SBP) in supine (SUP), orthostatic (ORT), and late orthostatic (ORT LATE). **P 4:** Evaluation frailty index (FI) (FRAIL, Clinical Frailty Scale, VIG FRAIL), SPPB, Get Up and Go Test (GUGT). **P 5:** Study analytical variables (SAV). **P 6:** Follow-up vulnerable elderly (VE)

Results: 506 consultations : ages 65-74y (A) 166, 75-84 (MA) 268, over 85 (L) 70, and under 65 (C) 332. 67% male In elderly **SWB:** SWB by groups: C 7.47, A 7.46, MA 7.13, L 7.71. Influencing factors >65 y: emotional state (t 4.351 p<0.001) and exercise (t 2.312 p 0.021). In elderly with CKD, socio-familial environment (t 2.723 p 0.007). Social vulnerability: 27.7% without CKD, 29.9% with CKD (p=0.737). **AM - GS:** Age associated with strength (r -0.297 p<0.001), better with CKD (r -0.405 p<0.001). Lower strength in CKD (24.8 vs 28.3 p=0.071). **OH:** In CKD where DBP decreases (DBP SUP to DBP ORT 5.7 vs -2.32 p<0.001) and DBP SUP to DBP ORT LATE 6.1 to -1.36 p=0.003). **FI:** Age associated with SPPB (r -0.471 p=0.001), FRAIL (r=0.419 p<0.001), Clinical Frailty Scale (r=0.476 p<0.001), VIG FRAIL (r=0.490 p=0.003), GUGT (r=0.406 p=0.013). In CKD, age associated with SPPB (r -0.470 p=0.008), FRAIL (r=0.363 p=0.005), Clinical Frailty Scale (r=0.375 p=0.004), VIG FRAIL (r=0.524 p=0.009), GUGT (r=0.512 p=0.006). **SAV:** Age associated with eGFR CREAT (r -0.165 p=0.026), eGFR CYS (r=-0.363 p=0.006), eGFR CREATCYS (r=-0.347 p<0.001), and Hb (r=-0.250 p<0.001). **VE:** Social vulnerability: 27.7% without CKD, 29.9% with CKD (p=0.737). SWB worse in negative environments (6.31 vs 7.51 p=0.002), especially in CKD (5.63 vs 7.69 p=0.025).

Conclusions: In elderly age correlates with grip strength and frailty, especially in CKD. Elderly with CKD exhibit greater diastolic OH. eGFR by cystatin better associated with age and Hb. Significant vulnerability, slightly higher in CKD, affects SWB. CKD impacts elderly patients' emotional, physical, hemodynamic status, and vulnerability.

PUB314

Implementation of the "Life-Sustaining Treatment Decision-Making Act" in Decisions Regarding Dialysis: A 5-Year Single-Center Experience

Seokjin Hwang, Soyoung Lee, Sua Lee, Bo Sun Park. *Daejeon Eulji University Hospital, Daejeon, Daejeon, Republic of Korea.*

Background: The legislation on life-sustaining treatment decisions was enacted in 2016 and has been in effect since February 2018 in South Korea due to social resistance to the implementation of life-sustaining treatment (LST) in patients with end-of-life care. Since then, patients at the end-of-life have been able to decide to receive or discontinue LST. These include cardiopulmonary resuscitation (CPR), mechanical ventilation (MV), hemodialysis (HD), and chemotherapy (CTX).

Methods: This was a retrospective chart review of patients who discontinued LST from August 2018 to May 2023 under the law on life-sustaining treatment decisions at single-center. We classified each patient based on underlying diseases, whether to implement existing LST, and whether to self-determine life-sustaining treatment.

Results: A total of 105 patients included in the study. Group 1 include patients previously had no dialysis treatment. Group 2 include patient with previous hemodialysis. This table shows the baseline characteristics of those patients (Table 1). The implementation of withdrawing LST was investigated for each group (Figure 1).

Conclusions: Our data shows the composition of patients' implementation of LST termination decisions in a single center in Korea over 5 years. Comparing the dialysis and non-dialysis groups, there is a significant statistical difference in decision not to undergo MV (p=0.024). Patients' decisions not to undergo CPR, HD, or CTX do not show a statistical difference between those two groups.

	Total (n=105)	Goup 1 (Non HD) (n=94)	Group 2 (HD) (n=11)	P value
Sex. Male	66	58	8	0.743
Age (year)	68.9 ± 15.1	69.2 ± 14.9	66.4 ± 16.3	0.557
Documented death	81	72	9	1.0
Days between documentation and death (day)	11.5 ± 31.1	12.3 ± 32.9	4.6 ± 3.8	0.481
Comobidities				
Malignancy	69	66	3	0.007*
Infection	57	52	5	0.534
Cardiovascular disease	20	15	5	0.033*
Respiratory disease	54	49	5	0.675
Liver failure	29	27	2	0.723
Renal failure	50	39	11	<0.001
Mechanical ventilation	37	29	8	0.015*
CPR survivor	25	19	6	0.021*
ICU care	50	40	10	0.003*
Patient decision- making	11	10	1	1.0

Table 1. **Baseline characteristics of patients who decide to withdraw life-sustaining treatment. Values are mean ± SD unless otherwise specified. HD, hemodialysis; CPR, cardiopulmonary resuscitation; ICU, intensive care unit.**

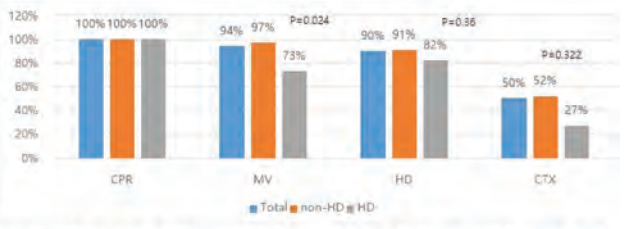


Figure 1. **Proportions of life-sustaining treatment (LST) which were withdrawn in total patients, previous Non-HD patients and previous HD patients.**

PUB315

Glomerular Injury and Differences in Colocalization of Glomerular IgA, IgG, and Complement C3 in Patients with IgA Vasculitis with Nephritis

Lea Novak,[1] Stacy D. Hall,[1] Dana V. Rizk,[1] Bruce A. Julian,[1] Mark Haas,[2] Jan Novak.[1] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Cedars-Sinai Medical Center, Los Angeles, CA.*

Background: IgA vasculitis is usually a self-limited disease but some children and adults with nephritis (IgAVN) progress to kidney failure. Routine immunofluorescence of kidney-biopsy specimens from IgAVN patients show glomerular immunodeposits with IgA as dominant or co-dominant immunoglobulin with variable staining for IgG and complement C3 (C3). The goal of this study was to assess pairwise colocalization of IgA, IgG, and C3 and correlate the data with kidney histologic findings.

Methods: Remnant frozen kidney biopsies from 23 IgAVN patients (age range 5-67 yr, mean 20.2 yr) were stained for IgA, IgG, C3, and nuclei. Using confocal microscopy, four-fluorochrome images of glomeruli in multiple optical planes were acquired for each slide. Sixty regions of interest were selected and Pearson correlation coefficient (PCC) colocalization data were generated for each IgA-C3, IgA-IgG, and IgG-C3 pairwise comparison. Mean value of PCC for each pairwise comparison for each slide was calculated and the colocalization of the pairs was evaluated. To correlate results with Oxford MEST-C scores, biopsies were divided into paired groups: M0/M1, E0/E1, S0/S1, T0/(T1+T2), and C0/(C1+C2). Differences in PCC in IgA-C3, IgA-IgG, and IgG-C3 colocalization for these paired groups were evaluated.

Results: Glomerular staining for IgA, IgG, and C3 was identified in all 23 biopsies including those without IgG on routine immunofluorescence (n=16). Immune complexes exhibited higher PCC for IgA-C3 or IgA-IgG than for IgG-C3 (P=0.002 and P=0.023,

respectively). Comparison of colocalization data with MEST-C scores showed higher IgA-C3 colocalization in biopsies with endocapillary hypercellularity (E1) compared to biopsies without (E0; P=0.034). In contrast, biopsies with segmental glomerulosclerosis (S1) showed lower IgA-IgG colocalization compared to biopsies without (S0; P=0.044).

Conclusions: IgG was detected in all biopsies, including those without IgG on routine immunofluorescence. IgA, IgG, and C3 components of glomerular immunodeposits showed pairwise colocalization. Colocalization studies suggested that complement likely contributes to the kidney injury in IgAVN biopsies with endocapillary hypercellularity. In contrast, segmental glomerulosclerosis showed differences only in IgA-IgG colocalization.

Funding: NIDDK Support, Private Foundation Support

PUB316

Clinical Implications of Appropriate Molecular and Glomerular Models

Robert L. Luke. *Maine Medical Center, Portland, ME.*

Background: Proteinuria is associated with deposition of immunoglobulin and complement because these proteins initiate damage to the glomerular capillary wall, particularly basement membrane, long considered the definitive layer because dextran accumulated before, but not after the lamina densa. Only a small percent of animals developed proteinuria after antigen/adjuvant challenge, however, and dextran had been unrealistically represented as impervious rigid spheres. In this study partial draining malleable dextran defines inherent glomerular dysfunction in two diseases that are devoid of immunoglobulin or complement, minimal change disease and diabetic nephropathy.

Methods: A flow dependent fiber formulation separates podocyte from basement membrane and a cylindrical glomerular tuft separates filtering basement membrane bordered by capillaries from non-filtering basement membrane bordered by mesangium. These models are introduced with the permeability of $a_1$acidglycoprotein, albumin, transferrin, IgG, and $a_2$macroglobulin in newly reported patients with primary glomerular disease and completed using hydrostatic pressures, vascular dimensions, and permeability of dextran, albumin, and IgG in similar patients obtained from the literature. Linear regression yields fiber density from slope and trans-epithelial shunt from intercept; glomerular volume is concomitantly apportioned between vascular and mesangial regions.

Results: Fiber density was similar in controls and patients; urinary protein was proportional to trans-epithelial shunts and mesangial volume. Dextran does not accumulate beneath slit pore because flow reduces its effective size. Most albumin is blocked by lamina densa, but significant amounts leak, is blocked by slit diaphragm, and must return locally to circulation to explain low proximal tubular albumin. Lower fiber densities revealed by proteins and large dextran are compatible with retrieval route that begins in lamina rara externa and continues back across lamina densa into mesangial channels that are indistinct in minimal change disease, but prominent in diabetic nephropathy, a flow path driven by periodic reversed hydraulic pressure.

Conclusions: Realistic macromolecular models trace a loop through glomerulus that is critical to protein homeostasis. Tubular reabsorption is overwhelmed if podocyte seal is compromised in minimal change disease or if mesangial recovery is compromised in diabetic nephropathy.

PUB317

Double Trouble: A Rare Case of Cephalosporin-Induced Myeloperoxidase Glomerulonephritis with Acute Interstitial Nephritis

Mario Mekhail, Sabrina Bulancea, Jonathan London, Shemrine Mark, Jorgio Auguste, Papiya Begum, Neeru Kumar. *Long Island Community Hospital, Patchogue, NY.*

Introduction: Myeloperoxidase (MPO) glomerulonephritis and acute interstitial nephritis (AIN) are distinct pathological entities that have rarely been reported to occur concurrently.

Case Description: A 76-year-old female with PMH HTN and HLD presented to the ED with worsening bilateral lower extremity edema and a non-pruritic rash which started on her arms and spread to the trunk, back and groin. Of note, she was hospitalized 12 days prior for a UTI and received ceftriaxone and later cefpodoxime. On exam, vitals were stable and she was afebrile; she had bilateral lower extremity pitting edema and a maculopapular rash on the upper extremities, torso, and groin. Labs revealed WBC 31.7, Hb 9.9, absolute eosinophil count 1.4, BUN 49, and Cr 3.5. She was admitted for acute kidney injury due to possible AIN given diffuse rash, elevated eosinophils, and recent cephalosporin use. Further studies revealed positive MPO-ANCA antibodies, negative PR3-ANCA antibodies, low C4, positive ANA, positive RF, and negative GBM. A subsequent renal biopsy demonstrated MPO-positive, pauci-immune type, subacute crescentic glomerulonephritis, active necrotizing vasculitis involving two small arteries and global glomerulosclerosis, and active interstitial inflammation. Her clinical condition improved with hemodialysis, steroids, and rituximab.

Discussion: MPO glomerulonephritis is a form of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis, characterized by immune complex deposition and inflammation within the glomeruli [1]. AIN is an immune-mediated renal injury primarily affecting the renal interstitium, often induced by medications such as antibiotics [2]. To date, there have been four cases in medical literature reporting concurrent MPO glomerulonephritis and drug-induced AIN [3-6]. The pathophysiological mechanisms underlying this dual renal insult from cephalosporin use remain unclear but may involve a combination of immune-mediated processes and drug-induced hypersensitivity reactions. The simultaneous manifestation of both conditions poses diagnostic and therapeutic challenges that require further research regarding the optimal management strategy.

PUB318

Urine Proteomics of Primary vs. Secondary Focal Segmental Glomerulosclerosis: Is There a Potential Noninvasive Urine Biomarker?

Ilario Russo,[1,2] Shane A. Bobart,[4] Poemlarp Mekraksakit,[1] Maria Jose Vargas-Brochero,[1] Pajaree Krisanapan,[1,3] Coraima C. Nava Chavez,[1,6] Cristine Charlesworth,[7] Benjamin J. Madden,[7] Sanjeev Sethi,[5] Fernando C. Fervenza.[1]
[1]Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN; [2]Universita degli Studi di Bari Aldo Moro Dipartimento di Medicina di Precisione e Rigenerativa e Area Jonica, Bari, Italy; [3]Thammasat University Hospital, Khlong Nueng, Thailand; [4]Houston Methodist, Houston, TX; [5]Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester, MN; [6]Hospital General Universitario Gregorio Maranon, Madrid, Spain; [7]Mayo Clinic Minnesota, Rochester, MN.

Background: Focal Segmental Glomerulosclerosis (FSGS) is a histological pattern of glomerular injury. It is classified into primary, secondary and genetic, each requiring distinct management. No reliable biomarkers can distinguish among them. We evaluated urine protein profile among a cohort of patients phenotyped as presumed primary, genetic or secondary FSGS to see if this could further differentiate these patients.

Methods: 21 patients with an FSGS lesion were classified as primary, secondary, or genetic FSGS using a clinico-pathological approach (De Vriese 2017). Primary was defined as serum albumin (SA) <3.5 g/dL, proteinuria >3.5g/24h, and diffuse foot process effacement (FPE; >80%). Secondary FSGS was defined as SA >3.5 g/dL, and segmental FPE, regardless of proteinuria. Genetic was defined by the presence of a disease-causing mutation (NPHS2, n= 3, COL4A, n=3, both MYO1E and ITGB4 mutation, n=1). Each group included 7 patients. Total protein concentration for each sample was determined by bicinchoninic acid assay, and 9 ug of protein from each sample was separated by SDS-PAGE. Baseline characteristics are shown in Table 1.

Results: SDS page gel urinary proteomics showed proteins with MW from 250 to 10 (kDa) with the majority of protein running as a 66.5 kDa band compatible with albumin. However, there were no observable differences in any molecular fraction that could help to differentiate patients with primary, secondary or genetic forms of FSGS.

Conclusions: Our analysis indicates that the urine proteomic profile does not provide additional information regarding the underlying cause of the FSGS lesion nor has the ability to differentiate different forms of FSGS.

Patient #	Age at Labs	Sex	Analysis Group	Proteinuria g/day	Serum Albumin mg/dL	Serum Creatinine mg/dL	Biopsy Diagnosis	EM FPE
1	43	F	PRIMARY	7.1	2.4	1.9	FSGS, Tip variant	Diffuse
2	35	F	PRIMARY	7.2	2.7	0.9	FSGS	Diffuse
3	52	M	PRIMARY	8.7	2.4	2.1	FSGS, collapsing	Diffuse
4	32	M	PRIMARY	10.6	2.2	3.3	FSGS	Diffuse
5	66	M	PRIMARY	12.1	2.7	1.2	FSGS, tip variant	Diffuse
6	36	F	PRIMARY	8.6	2.8	0.8	FSGS	Diffuse
7	72	F	PRIMARY	6.1	3.0	2.3	FSGS	Diffuse
8	52	M	SECONDARY	10.5	3.7	4.4	FSGS	Segmental
9	53	M	SECONDARY	4.3	4.2	3.4	FSGS	Diffuse
10	19	M	SECONDARY	7.0	4.0	1.4	FSGS	Segmental
11	51	M	SECONDARY	8.5	4.2	3.3	FSGS	Extensive
12	55	M	SECONDARY	1.2	4.3	1.1	Unsampled FSGS	Segmental
13	77	M	SECONDARY	5.2	3.6	2.4	FSGS	Extensive
14	51	F	GENETIC	6.0	3.1	2.8	FSGS	Diffuse
15	56	F	GENETIC	3.9	3.7	0.8	Unsampled FSGS	Segmental
16	66	M	GENETIC	1.4	4.0	1.7	FSGS	Diffuse
17	42	M	GENETIC	8.6	3.6	3.6	FSGS	Extensive
18	48	M	GENETIC	3.0	4.8	1.0	FSGS, DN	Segmental
19	56	M	GENETIC	4.6	4.0	2.8	FSGS	Segmental
20	34	M	SECONDARY	8.0	4.2	1.8	FSGS	Segmental
21	57	M	GENETIC	0.5	4.0	1.0	FSGS	Diffuse

Table 1.

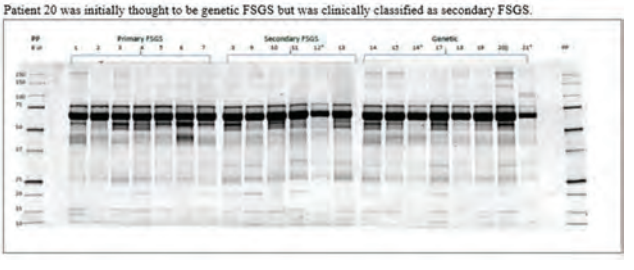


Figure 1.

PUB319

Analysis of Clinicopathological Characteristics of Patients with Malignancy and Membranous Nephropathy: A Literature Review

Hong Cheng,[1] Guo-qin Wang,[1] Xiaoying Hu,[1] Nan Ye,[1] Xiao-yi Xu,[1] Weiyi Guo,[1] Li-jun Sun,[1] Hong-rui Dong,[1] Xiaoyi Zhao.[2] [1]*Beijing Anzhen Hospital Affiliated to Capital Medical University, Chaoyang-qu, China;* [2]*Affiliated Hospital of Chifeng University, Neimenggu, China*.

Background: The incidence of malignancy patients with membranous nephropathy (MN) has gradually increased, but the clinical and pathological characteristics of these patients are still unclear.

Methods: Patients diagnosed with renal biopsy-proven MN and comorbid malignancy detected within 5 years before and after MN diagnosis were included. The control group were diagnosed with renal biopsy-proven IMN with 5 years of follow-up data. We present a comprehensive analysis of MN with concomitant malignancy in our cohort and literature review.

Results: A total of 19 MN patients with concomitant malignancy were evaluated at our center; among them, 68.4% were male, and the median age was 57.0 (45.0, 69.0) years, with digestive system malignancy (36.8%) ranking as the predominant type. IHC showed that the highest percentage for PLA2R-only positivity (68.4%) followed by THSD7A-only positivity (15.8%). Only 2 of 5 patients expressed the same specific MN antigen on kidney and tumor. Screening 17 articles encompassing 21 patients in whom MN-specific antigen staining was performed on both renal and tumor tissues simultaneously. Among these patients, 71.4% were male, and the median age was 61.0 years (56.3, 72.8), with 33.3% digestive system malignancy. Notably, THSD7A accounted for the highest proportion of MN antigens (66.7%); among these patients, 78.6% also exhibited positive tumor THSD7A staining. The clinicopathological data of the above two cohorts were pooled and compared with IMN patients at our center. MN patients with malignancy were older at the time of renal biopsy (P=0.017), had a lower eGFR (P=0.035) and demonstrated a lower rate of CR/PR after treatment (P<0.001). The rate of PLA2R positivity in the glomeruli was significantly lower (P<0.001), while the rate of THSD7A positivity was significantly higher (P<0.001). Renal tissue IgG subclass staining showed that the rate of IgG4 positivity was significantly decreased (P<0.001), with the increased rate of IgG2 (P=0.033).

Conclusions: Malignancy screening should be more actively performed for MN patients with the above characteristics.

PUB320

Nogo-B May Mediate the Glomerular Endothelial Cell Injury of Hypertensive Nephropathy by Enhancing the Inflammatory Phenotype

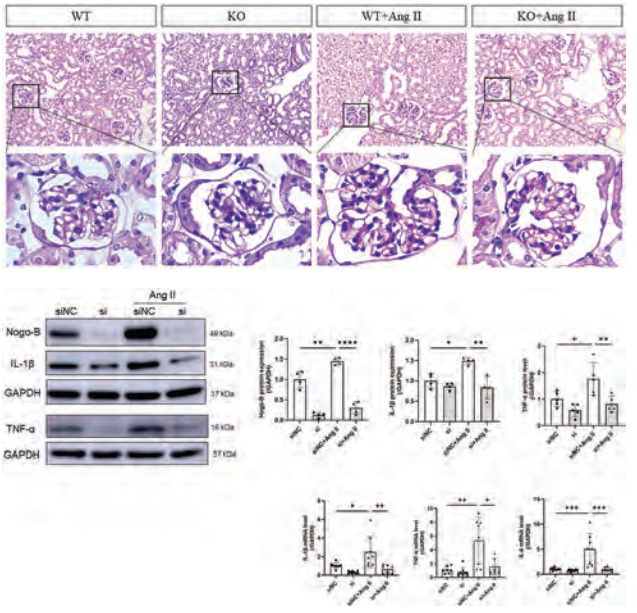
Haosen Xu, Ting Zhang, Huan Jiang, Peimin Liu, Xiaoyan Bai. *Guangdong Provincial People's Hospital, Guangzhou, China*.

Background: Nogo-B is an endoplasmic reticulum resident protein, which is mostly expressed in vascularendothelial cells and smooth muscle cells. Previous studies have elucidated the relationship betweenhypertension and Nogo-B in endothelial cells, but whether Nogo-B is involved in glomerularendothelial cell injury in hypertensive nephropathy and its mechanism is not clear.

Methods: The localization of Noao-B was proved by immunohistochemistry lHC) and immunofluorescence lFstaining in renal tissue of hypertensive patients, and the relationship between it and systolic bloodpressure (SBP) and UACR was analyzed. In animal experiments, lHC, IF, PAS, gRT-PCR andWestern blot were employed to prove the localization of Nogo-B and analyze the relationship betweenits expression level and the degree of renal injury in Ang ll-induced Nogo-B KO and control mice. inthe vitro, the level of Nogo-B in endothelial cells (Ea.hy926) was knocked down by small interferingRNA (siRNA), and the correlation between Nogo-B expression and cell phenotypes were explored.

Results: Nogo-B is expressed in glomerular endothelial cells and increased in hypertensive nephropathy. lt ispositively correlated with the patients' SBP and UACR, n animal experiments, the renal pathologicadamage of Noao-B KO mice treated with hypertension was mild. The level of Nogo-B in endothelialcells is up-regulated in hypertensive environment and inflammatory markers including TNF-a, lL-1Band lL-6 were up-regulated. Knockdown of Nogo-B by siRNA reduces the inflammatory phenotype ofendothelial cells in hypertensive environment.

Conclusions: Nogo-B may mediate the glomerular endothelial cell injury of hypertensive nephropathy by enhancingthe inflammatory phenotype.



PUB321

Contribution of the p38MAPK Signaling Pathway and the Egr-1 Transcription Factor in Glomerulosclerosis

Heitor M. Braz, Maria Oliveira-Souza, Guilherme G. Lopes, Juliana M. Pessoa. *Universidade de Sao Paulo Instituto de Ciencias Biomedicas, Sao Paulo, Brazil*.

Background: Chronic kidney disease (CKD), characterized by the progressive loss of kidney function, is one of the most serious public health problems. Its progression is followed by focal and segmental glomerulosclerosis (FSGS). This study aims to look at how ERK/p38MAPK and Egr-1 pathways interact in the signaling of Adriamycin (ADR)-induced FSGS.

Methods: 8-week-old BALB/c mice received a single dose of ADR via the tail vein (10 mg/kg) and the control (CTL) group received 0.9% NaCl solution. Both groups were monitored for 28 days and then euthanized. Kidney function, morphology and protein expression were evaluated. Immortalized mouse podocytes were treated by ADR [10^{-6} M] for 15 min and 24 h followed by protein expression Statistical analyses were done using *t* test with Welch correction.

Results: The ADR treatment did not change the creatinine and urea plasmatic levels when compared with the CTL group. [Creatinine,mg/dL: (CTL: 0.23±0.05 vs. ADR:0.25±0.12, p= 0.7427), Urea, mg/dL: (CTL: 59.60±4.97 vs. ADR: 70.76±60.39, p=0.6181). ADR showed a higher urinary flow rate than the CTL animals [µL/min (CTL: 0.11±0.06 vs. ADR: 0.91±0.38, p=0.0005). The ADR treatment induced a body weight loss when compared to the CTL group. [g (CTL: 2.00±1.05 vs. -2.75±2.71, p=0.0013). Food and water intake were not different between the groups. [Food intake, g/24h (CTL: 5.60±1.50 vs. ADR: 6.25±1.66, p=0.4054), (Water intake, ml/24h (CTL: 2.40±0.84 vs. ADR: 3.62±1.50, p=0.0655). About podocyte protein expression, the p38MAPK was increased after ADR treatment for 15 min or 24h [arbitrary units, 15 min: (CTL: 0.5130±0.13 vs. ADR: 3.16±1.35, p= 0.0289), (arbitrary units, 24h: (CTL: 0.30±0.12 vs. ADR: 1.61±0.54, p=0.0142). However, the Egr-1 was significantly increased after 24 h of treatment with ADR [10^{-6}M] [AU, 24h: (CTL: 0.13±0.06 vs. ADR: 0.93±0.16, p= 0,0009, n=4). About the glomeruloesclerosis index (GSI), there were significant differences between the groups. [GSI: (CTL: 0,04±0,05 vs. 2,39±0,81, p=0,0101)].

Conclusions: Our results indicate that the activation of p38MAPK by an insult corroborates the activation of the nuclear transcription factor Egr-1 and thus the development of FSGS as shown in the treated animals with ADR.

Funding: Government Support - Non-U.S.

PUB322

Comparison of Histopathologic Findings with Patterns of Immunofluorescence Staining in Native Kidney Biopsies Diagnostic for IgA Nephropathy

Selin Kurt, Lanny T. DiFranza. *Montefiore Medical Center, New York, NY.*

Background: Although IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis worldwide, there is still much to be understood about the relationship of glomerular complement deposition to disease activity and prognosis. Prior studies suggest the degree of C3 deposition may represent an important pathogenetic and clinical prognostic factor. Our study aims to investigate the relationship between morphologic pathologic features observed by light microscopy (and documented using the Oxford scoring system) with results of immunofluorescent staining techniques for examining IgA and C3 deposition.

Methods: A total of 57 cases (n = 57) of IgAN, each representing a unique patient, and diagnosed by 3 different renal pathologists, are included in this study. Case data are collected retrospectively, and correlation matrix analysis is used to examine the relationship between intensity of C3 and IgA staining and the rendered Oxford scores for each biopsy.

Results: Cases with C3 staining show higher total scores by the Oxford scoring system [r= 0.22, CI: 90%; p = 0.05]. Significant positive correlations between the intensity of C3 and IgA staining [r= 0.59, CI: 90%; p = <0.001], and between C3 staining intensity and mesangial cellularity score (M) [r= 0.19, CI: 90%; p = 0.06] are found. Although not reaching the level of statistical significance, a positive correlation is demonstrated between C3 staining intensity and endocapillary hypercellularity (E), interstitial fibrosis/tubular atrophy (T), and crescent (C) scores, but C3 staining intensity, and segmental sclerosis (S) score show a negative correlation. Interestingly, correlation analyses resulted in quite disparate findings when comparing series of cases diagnosed by separate pathologists, suggesting there may be a high degree of interobserver variability in assessment of these pathologic findings.

Conclusions: C3 deposition may play an important role in IgAN pathogenesis, and with the advent of complement inhibiting drugs, updates to the diagnostic approach and clinical management of IgAN are necessary. Further higher-powered studies examining the molecular, clinical, and histopathologic relationships of complement activity in IgAN should help elucidate the utility of these novel complement-inhibiting therapies in the management of IgAN.

PUB323

Post-COVID-19 Vaccine Activation of IgA Vasculitis

Yasameen Fardi, Niraj Desai, Meghan Kapp. *University Hospitals, Cleveland, OH.*

Background: A 69 year old female with hypertension and longstanding microscopic hematuria received Pfizer BioTech SARS-COV-2 vaccine. Three weeks post vaccination, the patient developed diffuse abdominal pain and a palpable, right lower extremity purpuric rash.

Methods: Skin biopsy was consistent with leukocytoclastic vasculitis. Serologic workup was negative. Kidney function was normal, but there was newly identified proteinuria on urinalysis and redemonstrated microscopic hematuria. Urine protein/creatinine ratio was 1.6 g/g. Histopathologic examination revealed mild mesangial hypercellularity and immunofluorescense showed IgA dominant mesangial staining (Fig 1). Electron microscopy showed mesangial deposits. The constellation of symptoms and biopsy findings were consistent with an IgA Vasculitis, suspected to be associated with recent SARS-CoV-2 vaccination. The patient was treated with ace inhibition and sglt2 inhibition, resulting in reduction in proteinuria to less than 200 mg/g and preservation of renal function. The rash resolved with no additional intervention.

Results: Development of abdominal pain, purpuric rash and sub-nephrotic proteinuria after vaccination raises possibility that SARS-CoV-2 vaccination may have triggered a de-novo IgA vasculitis or, given the longstanding, unexplained microscopic hematuria, may have exacerbated a pre-existing, otherwise quiescent IgA nephropathy.

Conclusions: In susceptible individuals, an aberrant immune response triggered by vaccination may result in production and deposition of galactose deficient-IgA1 in glomeruli, activating an inflammatory cascade leading to glomerular injury and possibly a systemic vasculitis. However, despite the temporal association, both a causative link between, and pathogenic mechanisms underlying SARS-CoV-2 vaccination and IgA vasculitis remain incompletely elucidated.

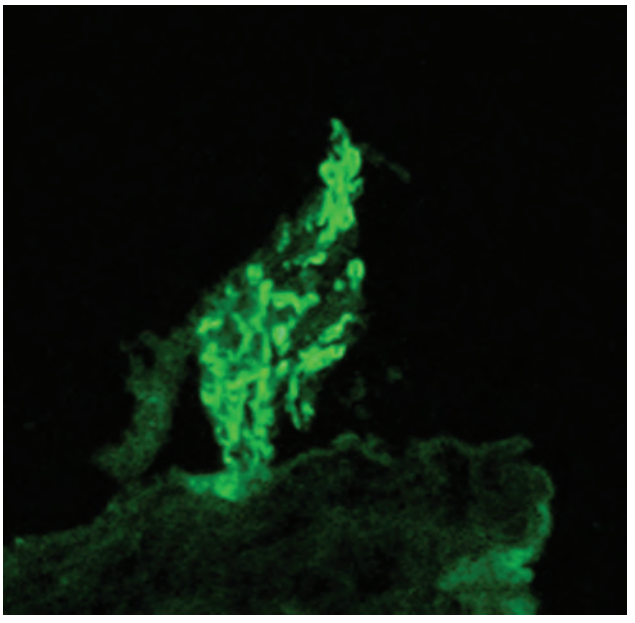


Figure 1

PUB324

Chronic Limited Renal Thrombotic Microangiopathy and Podocytopathy Secondary to Cabozantinib

Sanjana Bukkapatnam, Alyssa C. Weyer, Arda Akoluk. *The University of Texas at Tyler, Tyler, TX.*

Introduction: Thrombotic microangiopathy (TMA) is a condition characterized by thrombi in the microcirculation, often leading to kidney dysfunction. Podocytopathy is caused by damage to podocytes which are essential cells in the kidney's filtration barrier. Cabozantinib, a tyrosine kinase inhibitor, is linked to such renal complications. This case report presents such a case of chronic limited renal TMA and podocytopathy secondary to cabozantinib.

Case Description: Patient is a 79 year old male with a history of hepatocellular carcinoma (HCC), type 2 diabetes mellitus, and a history of hepatitis C, cirrhosis who presented to the Nephrology clinic for nephrotic syndrome. Briefly, he was diagnosed with HCC based on MRI imaging and elevated alpha-fetoprotein. He underwent treatment with Y-90 with some benefit, and was subsequently started on atezolizumab and bevacizumab. His course was complicated upon interval development of lung adenocarcinoma, and he had disease progression of his HCC. Both malignancies were thought to be covered on this regimen, though the patient developed proteinuria and hypoalbuminemia so bevacizumab was held and cabozantinib was added to atezolizumab. However, his proteinuria was noted to worsen. Workup included normal complement levels, kappa/lambda light chains, serum protein electrophoresis, negative double stranded DNA, but positive ANA. This prompted a kidney biopsy, which revealed changes consistent with chronic phase of TMA, and ultrastructural features of podocytopathy (Figure 1). It was determined that cabozantinib was causing his worsening proteinuria and TMA with podocytopathy, and thus his treatment regimen has changed to lenvatinib and pembrolizumab.

Discussion: Cabozantinib is a TKI used in a variety of malignancies, and chronic limited renal TMA and podocytopathy are significant but rarely documented complications of this chemotherapeutic agent [1]. Cabozantinib inhibits angiogenesis, and in this manner, may disrupt vascular integrity in the kidneys, thus inducing TMA and podocyte injury [2]. Podocytopathy compromises the glomerular filtration barrier, causing a nephrotic syndrome type presentation in [3]. This case thus illustrates the importance of vigilant monitoring for renal side effects in patients initiated on cabozantinib so this medication can be dose-adjusted or discontinued so as to prevent irreversible renal impairment.

PUB325

High Serum Vascular Endothelial Growth Factor (VEGF) Level Is Associated with Vascular Lesions in Glomerular Diseases

Gessica Sabrine Braga Barbosa, Renata D. Zen, Wagner Dominguez, Viktoria Woronik, Cristiane B. Dias. *Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Vascular endothelial growth factor (VEGF) is a pro-angiogenic factor essential for vascular homeostasis. However, it has been pathogenically involved in tumor growth and diabetic retinopathy, which can be treated with VEGF inhibitors (VEGFi). The implication of VEGFi and kidney damage is well described, but the association between serum VEGF level (sVEGF) and histological vascular lesions in glomerular diseases is limited.

Methods: We evaluated sVEGF in patients with primary glomerular disease, including IgA nephropathy, focal segmental glomerulosclerosis, minimal change disease and membranous nephropathy at the time of kidney biopsy. We then analyzed the sVEGF in two comparative groups regarding the presence or absence of vascular lesions (VL) on renal histology. Patients under 50 years of age were included and those with diabetes, systemic autoimmune diseases and chronic infections were excluded.

Results: Of all patients with glomerular diseases (N=20), the median age was 31.5 years [27.2;43.5], with a predominance of females (55%) and white ethnicity (75%). Most patients had vascular lesions at the time of kidney biopsy (85%). The arterial intimal fibrosis/thickening was the most common lesion (88.2%), followed by arteriolar hyalinosis (29.4%) and thrombotic microangiopathy (5.8%). A higher sVEGF was detected in the group with VL (568.8 ± 97.0 vs 77.4 ± 13.8, p = 0.0001). Other laboratory findings at the time of kidney biopsy were as follows: proteinuria level 4.8g/g or g/24h [1.9;6.0], albumin level 2.4g/dL [1.7;3.2], serum creatinine level 1.24 mg/dL [0.88;2.6], hemoglobin level 11.8 g/dL [10.7;13.7], C3 level 125.5mg/dL [100.3;136.3], and C4 level 29.1mg/dL [22.3;40.2], no difference between the groups, except for the platelet level, which was higher in the VL group (337,000/mm^3 vs 190,000/mm^3, p = 0.019). There was no difference in the sVEGF or in the presence of VL between patients with a history of hypertension and those without.

Conclusions: Serum VEGF level is higher in glomerular diseases with histologic vascular lesions. More studies are needed to define the mechanisms of this increase and the relationship with glomerulopathies, whether it is a reparative effect, secondary or involved in the development of vascular lesion.

Funding: Government Support - Non-U.S.

PUB326

Effects of Anti-GBM Serum on Kidney Function and Glomerulosclerosis in Mice

Alex Frias Hernandez, Frederikke E. Sembach, Maria K. Ougaard, Ditte M. Jensen, Michael Christensen. *Gubra AS, Horsholm, Denmark.*

Background: Antibody-induced glomerulonephritis (GN) is a condition characterized by an inappropriate autoimmune response to renal antigens, such as glomerular basement membrane (GBM), leading to progressive glomerulosclerosis and rapidly declining renal failure, for which few treatment options exist. Understanding the underlying mechanisms of GN is crucial for developing effective therapeutic strategies. In this study, our objective was to investigate the induction of antibody-induced GN using anti-GBM serum on kidney biomarkers, histology and transcriptome signatures.

Methods: Male C57BL/6J mice (n=12) were randomly assigned to three groups (n=4 per group) and received an injection of vehicle, 100, or 200 µl of anti-GBM serum. We measured urinary albumin-creatinine ratio (ACR) as an indicator of kidney function. Renal endpoints included urinary albumin-creatinine ratio (ACR), AI-assisted glomerulosclerosis score, histology analysis of fibrosis (Collagen type 3, Col3), and RNA sequencing (RNA-seq) analysis.

Results: Compared with vehicle controls, both doses of anti-GBM serum significantly increased urinary ACR, suggesting renal insufficiency and glomerular damage. AI-based histopathological scoring confirmed significant glomerulosclerosis increase in the anti-GBM serum-treated groups. Furthermore, IHC image analysis indicated renal fibrotic damage as shown by the increase of Col3. Consistent with this, RNA-seq analysis revealed upregulated gene expression programs indicative of kidney extracellular matrix remodelling (eg, Col1a1, Col3a1, Col4a1) and inflammation (eg, CD68, Ccl2, Il1b).

Conclusions: Anti-GBM serum induces the rapid onset of renal failure, glomerulosclerosis, and fibrosis in the murine model of antibody-induced GN. The antibody-induced GN model in mice is very useful for testing test compounds with potential nephroprotective effects in autoimmune GN.

Funding: Commercial Support - Gubra

PUB327

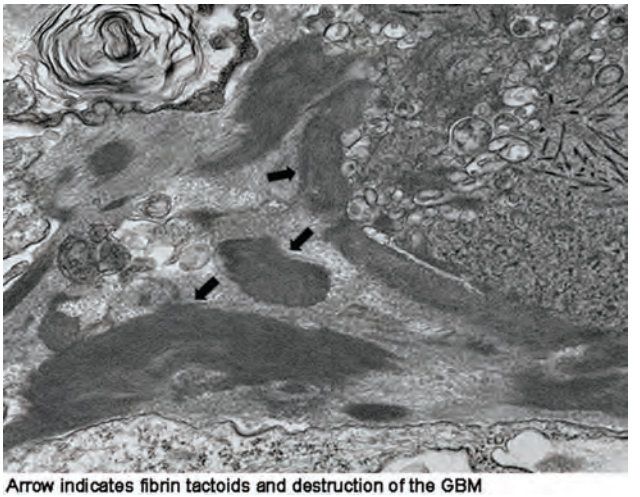
A Case of ANCA-Associated Vasculitis with Glomerulonephritis Unmasked by Electron Microscopy

Priscilla Koirala, Alessia Buglioni, Charat Thongprayoon, Wisit Cheungpasitporn, Jing Miao. *Mayo Clinic Minnesota, Rochester, MN.*

Introduction: Risk of progression to ESKD remains high in ANCA vasculitis with glomerulonephritis (AAV GN). Early diagnosis is critical for enhancing renal outcomes, yet it proves to be a challenge because active AAV GN lesions may not always be visible under light microscopy (LM), attributed to the focal nature of these lesions. We present a case where electron microscopy (EM) played a key role in identifying active necrotizing AAV GN.

Case Description: A 63-year-old healthy female presented with hypertensive emergency. Creatinine was elevated to 2.1 mg/dL from 0.8 mg/dL 1.5 years prior and 1.15 mg/dL 8 months earlier. UA showed microscopic hematuria and mild proteinuria. Serologic testing showed high levels of MPO (>8 U), positive p-ANCA, equivocal PR3 and negative c-ANCA. ANA, dsDNA, GBM ab, cryoglobulin, SPEP and immunofixation, were unremarkable. After addressing hypertension, persistent hematuria and AKI indicated potential glomerular disease. A subsequent kidney biopsy revealed FSGS (10%), global glomerulosclerosis (50%) and moderate interstitial fibrosis with tubular atrophy (40-50%) under LM, suggesting a prior occurrence of AAV GN. Although LM did not identify current AAV GN lesions, the presence of high MPO antibodies and ongoing AKI led to the administration of pulse dose steroids and rituximab, which resulted in reduced creatinine levels. EM further confirmed the AAV GN diagnosis by revealing crescent formation and fibrinoid necrosis.

Discussion: The case highlights the difficulties in diagnosing AAV GN accurately, emphasizing the risk of misdiagnosis resulting from the localized nature of the lesions. Recent study suggests that kidneys may continue to function adequately, even when only a small fraction of glomeruli remained unaffected in AAV GN. Precise diagnosis and prompt treatment is needed to maintain normal glomerular function and enhance renal prognosis.



Arrow indicates fibrin tactoids and destruction of the GBM

AAV GN on EM

PUB328

A Rare Case of "No Change Disease" Presenting as an Unexplained Nephrotic Syndrome

Jusong Choi,[1] Sherif Badra,[2] Jeongheun Kim.[1] [1]*Georgia Nephrology, Lawrenceville, GA;* [2]*Florida Kidney Physicians, Riverview, FL.*

Introduction: "Nephrotic syndrome" delineates a unique set of clinical and laboratory manifestations of kidney disease. It is precisely characterized by pronounced proteinuria (> 3.5 g/24 hours), hypoalbuminemia (< 3.5 g/dL), and peripheral edema. Here, we present a case illustrating nephrotic syndrome in the absence of distinct histologic evidence substantiating the pathological process.

Case Description: 60 year-old female with history of hypertension and a previous tuberculosis infection treated. Referred by PCP due to albuminuria on urinalysis after contracting COVID-19 in September 2023. Her sole symptom post-COVID-19 was foamy urine, prompting to obtain an ACR which showed 1.8 g/g, and a subsequent test in following month revealed 2.6 g/g. She maintains a preserved eGFR with a baseline creatinine level of 0.6 mg/dL. No prior history of albuminuria from the previous lab. The initial workup results were as follows: Creatinine: 0.59 mg/dl Albumin: 3.6 g/dl UA: Positive for occult blood and 3+ protein, but negative for red and white cells C3 and C4 within normal limits Negative results for Anti-GBM, ANA, PR3, MPO, parvovirus B19,

RPR, hepatitis, HIV, PLA2R antibodies Without further delay, a biopsy was performed, and the results showed it to be unremarkable except for arteriosclerosis. Post-biopsy, a 24-hour urine protein of 5.2g was collected, and both UPEP and SPEP with IFE, urine cytology were unremarkable. Subsequently, her proteinuria worsened up to 7.7 g/g along with worsening hypoalbuminemia to 2.2 g/dL, resulting in nephrotic syndrome. The decision was made to start Prednisone 50 mg daily. With the initiation of prednisone, both proteinuria and hypoalbuminemia improved within 4 weeks and continue to be in remission with 24-hour urine protein at 120 mg at week 7 of treatment.

Discussion: Likely diagnosis for this case is post-COVID Minimal Change Nephrotic Syndrome. This case underscores the importance for clinicians to recognize that podocyte foot process effacement does not always correlate with proteinuria. Variances in podocyte effacement observed between MCNS and other types of nephrotic range proteinuria disorders may suggest diverse mechanisms of podocyte injury in these conditions. Extensive foot process effacement is typically associated with the presence of a full nephrotic syndrome, characterized by concurrent nephrotic range proteinuria and hypoalbuminemia.

PUB329

A Patient with Minimal Change Disease with AKI

Ashok A. Varughese,[1] Abdallah Sassine Geara,[2] Tammy Yu.[2] [1]*Lower Bucks Hospital, Bristol, PA;* [2]*University of Pennsylvania, Philadelphia, PA.*

Introduction: Minimal change disease (MCD) accounts for about 10% of nephrotic syndrome in adults. While MCD typically presents with a rapid onset of nephrotic syndrome, it can also be associated with acute kidney injury in about 18% of cases. Most cases of MCD are considered idiopathic; it has been associated with a variety of secondary causes though no clear association with an underlying disease or event has been established.

Case Description: A 68-year-old male presents to the emergency department for progressive leg swelling, abdominal distension, dark urine, and shortness of breath for two weeks. Medical history was notable for hypertension treated with lisinopril, hyperlipidemia, type II diabetes mellitus, osteoarthritis managed with Ibuprofen daily for the past 1 year. Laboratory tests revealed serum creatinine of 5.32 mg/dL, blood urea nitrogen of 52 mg/dL. The patient become anuric within 24 hours of admission and required one session of hemodialysis. The differential diagnosis was broad and was favoring acute tubular necrosis possibly due to NSAIDs use. Since the etiology was not clear, without a clear hypovolemic or hypoperfusion event, the patient underwent a kidney biopsy which demonstrated on light microscopy focal acute tubular necrosis acute, the immunofluorescence stainings were found to be negative, electron microscopy revealed global podocyte foot process effacement, consistent with minimal change disease associated with acute tubular necrosis.

Discussion: Identifying the etiology of MCD can be challenging. In this case, multiple causes were plausible, but the exact cause remains unclear. Rapid progression into nephrotic syndrome and anuric AKI are uncommon in MCD. The patient had a history of using Ibuprofen daily for arthritis, which has been associated with MCD in rare cases, though there was no concurrent interstitial nephritis seen on kidney biopsy a common accompanying finding in NSAIDs-induced MCD.

PUB330

Atypical Even for Atypical Hemolytic Uremic Syndrome (aHUS)

Sunny R. Parmar, Melissa Baker, Jagmeet S. Dhingra, Leal C. Herlitz, Ali Mehdi. *Cleveland Clinic, Cleveland, OH.*

Introduction: Atypical hemolytic uremic syndrome (aHUS) involves overactivation of the alternative complement pathway leading to complement-mediated acute kidney injury (AKI). This dysregulation occurs in the presence of a genetic predisposition or an acquired loss of regulation, usually resulting in an elevated serum membrane attack complex (sMAC) level. Here we present a case of aHUS where fluid phase levels were normal with indirect evidence of complement activation on the kidney biopsy.

Case Description: A 28 year old male with hematuria and flu-like symptoms presented with an AKI (Cr peak 4.4; baseline 1.1), anemia and thrombocytopenia. Thrombotic microangiopathy (TMA) was suspected given low haptoglobin, high lactate dehydrogenase, and schistocytes on peripheral smear. Interestingly, the patient had a similar presentation a year prior following a COVID-19 infection. Empiric plasmapheresis was initiated until ADAMTS13 resulted back normal. Stool Shiga toxin was negative. Empiric terminal complement blockade with eculizumab was started for presumed aHUS. Serologic complement assays including factors I, B, H, factor H antibody, and sMAC were all normal. Only factor Bb level was elevated. After the platelet count improved, a kidney biopsy was obtained demonstrating acute TMA of glomeruli and arterioles. IgG kappa deposition was noted in the vessels, consistent with tissue deposition of eculizumab. Six weeks following hospitalization, Cr was down to 1.4 with normal complete blood count. Genetic testing is pending.

Discussion: This patient's case highlights a severe AKI from TMA due to aHUS and emphasizes that evidence of complement pathway overactivation in aHUS may not always be present in the fluid phase. Despite normal fluid phase assays, the IgG kappa kidney deposition (indicating eculizumab deposition) indirectly reflected tissue level alternative complement activation which was being modulated by the drug. Tissue deposition of eculizumab in this context has been well described previously in the renal pathology literature *(Herlitz et al, JASN, 2012, PMID: 22677550)*. Continued improvement of the patient's renal and hematologic parameters with eculizumab therapy supports this interpretation. Learning Points: AHUS should remain in the differential even with normal serologic complement assays. Empiric eculizumab therapy is key and its deposition in kidney tissue can provide further diagnostic certainty.

PUB331

Diabetic Kidney Disease in a Patient without Diabetes? A Case of Myeloproliferative Neoplasm (MPN)-Associated Glomerulopathy

Kavita Mistry, Leigh-Anne Dale, Seymour Rosen, Stewart H. Lecker. *Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: Myeloproliferative neoplasms (MPNs) are now recognized to cause a wide spectrum of renal disease, including thrombotic complications, extramedullary hematopoiesis, vascular nephrosclerosis, and glomerulopathy. The biological basis for vascular nephrosclerosis and glomerulopathy in MPNs remains to be elucidated, although has been presumed to result from increased cytokine levels.

Case Description: A 66-year-old man recently diagnosed with primary myelofibrosis (PMF) was referred to onconephrology clinic for acute kidney injury. He had initially presented 4 months prior with several weeks of night sweats and weight loss. Bone marrow biopsy was performed for evaluation of severe anemia and revealed JAK2 V617F and exon 12 mutated PMF. At the time of ruxolitinib initiation, his creatinine was noted to have risen to 2.06 mg/dL from 1.5 mg/dL, prompting nephrology referral. In onconephrology clinic, vital signs were remarkable for hypertension to 185/96 with no abnormalities on physical exam. Creatinine was 1.9 mg/dL with albumin of 3.9 g dL and 9.5 g/g proteinuria with spot urine albumin to creatinine ratio 7123 mg/g. SPEP and UPEP revealed no M spike. Renal biopsy was performed and revealed glomerular, tubulointerstitial and vascular changes compatible with diabetic nephropathy, including mesangial matrical increase and mild thickening of the glomerular basement membrane, as well as fibrotic and hyaline changes of the arterioles. The patient denied any history of diabetes. Fructosamine test was sent to evaluate for diabetes mellitus in the setting of frequent blood transfusions and was normal at 257 umol/L. In the absence of the appropriate clinical context for diabetes, his biopsy findings were ultimately attributed to MPN-associated glomerulopathy, which closely resembles the glomerular changes of diabetes.

Discussion: This report adds to a growing literature describing cases of MPN-associated glomerulopathy, an entity whose pathologic description resembles that of diabetic glomerulosclerosis. Given the lack of clinical association between diabetes and MPN, the close pathologic parallels between diabetic nephropathy and MPN-associated glomerulopathy could suggest common causal mechanisms for both diseases and a possible role for cytokine-mediated glomerular damage in diabetic kidney disease.

PUB332

Renal Riddles: Decoding a Case of Lupus Nephritis

Karteek Chennupati, Russell Vo, Leonel Abarca Jr, Morgan G. Fairweather. *Texas Health Harris Methodist Hospital Fort Worth, Fort Worth, TX.*

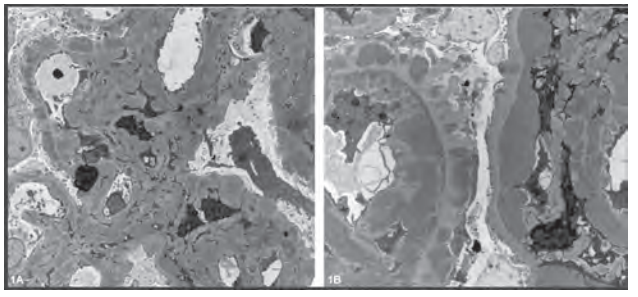
Introduction: Systemic lupus erythematosus (SLE) is characterized by the production of autoantibodies resulting in immune-mediated injury often involving multiple organs. Current literature suggests that anti-dsDNA antibodies facilitate the pathogenesis of the disease process. However, the absence of anti-dsDNA antibodies cannot exclude the diagnosis of lupus as up to 15 to 35% of individuals with lupus test negative.

Case Description: 24-year-old male presented with diffuse swelling and hypertensive urgency refractory to recent initiation of anti-hypertensives. Physical exam revealed a discoid, hypopigmented rash on both shoulders, non-scarring alopecia areata, and anasarca. Work-up revealed nephrotic range proteinuria, elevated Scr, and hypoalbuminemia. ANA 1:160, low C3 and C4, negative anti-dsDNA antibodies, and positive anti-Smith antibodies. Renal biopsy showed an abundance of immune complex deposits on electron microscopy consistent with class V lupus nephritis. The patient was initiated on high-dose steroids, mycophenolate mofetil, hydroxychloroquine, and atovaquone and discharged with outpatient follow-up.

Discussion: Lupus nephritis is a secondary membranous nephropathy caused by the deposition of immune complexes derived from anti-dsDNA antibodies throughout the glomeruli. Depending on the test used, the specificity for anti-dsDNA antibodies ranges from 80 to 97%. Studies suggest that the presence of anti-Smith antibodies correlates with younger age of onset, higher rates of alopecia, and transaminitis. Male gender is associated with higher mortality rates as compared with female patients with similar baseline features and treatment. Renal involvement in SLE patients poses a higher mortality rate in cases presenting with acute kidney injury and those that fail to achieve remission at 1 year.

Physical Exam Findings in Lupus Nephritis Patients (N=300)

Lupus Specific Findings:	
Malar rash	80%
Photosensitive dermatitis	50%
Generalized maculopapular rash	26.67%
Discoid rash	20%
Lupus non-specific findings	
Non-scarring alopecia	86.67%
Oral ulcers	56.67%
Vasculitic lesions	33.34%
Raynauds phenomenon	6.67%



Renal Biopsy
1A: EM, 1800X with multiple immune complex deposits
1B: EM, 4400X uranyl acetate staining multiple immune complex deposits and effacement of podocytes.

PUB333

Clinical and Pathological Characteristics of Lupus Nephritis in Elderly Patients

Tatsuaki Kosaka, Shinya Yamamoto, Hideki Yokoi, Motoko Yanagita.
Kyoto Daigaku Igakubu Fuzoku Byoin, Kyoto, Japan.

Background: Systemic lupus erythematosus (SLE) predominantly affects young women and is frequently complicated by lupus nephritis. Less than 10% of SLE cases manifest after the age of 65 years and lupus nephritis is less prevalent in elderly SLE patients. The prognosis of lupus nephritis in the elderly could be poor owing to numerous complications. Despite its clinical significance, the clinical and pathological characteristics of lupus nephritis in the elderly population remain unclear, and we investigated the data from our institution.

Methods: We retrospectively collected data from 40 patients diagnosed with lupus nephritis by renal biopsy between 2017 and 2023 at our hospital. We obtained data at the time of renal biopsy and after treatment, and the patients were divided into two age groups: younger (< 65 years) and older (≥ 65 years) patients. Statistical analyses were conducted using *t*-tests and chi-squared tests. Additionally, the outcomes were assessed in these patients.

Results: There were 8 patients (5 women and 3 men) in the elderly group and 32 patients (29 women and 3 men) in the younger group. Compared to the younger group, the elderly group exhibited significantly lower levels of eGFR, anti-DNA antibody, and anti-Sm antibodies. There were no significant differences in BMI, blood pressure, serum albumin, C3, C4, CH50, urinary RBC score, urinary protein or the frequency of rapid progressive glomerulonephritis. The most common renal histologic type in the elderly patients was ISN/RPS Class IV (± V) (3 patients). 75 percent of the elderly patients underwent treatment with steroids, and 83.3% of them additionally received immunosuppressive drugs. The complete or partial remission rate of lupus nephritis among the treated elderly patients was 83.3%. Two patients died from infection (within 2 months of starting treatment) and CO_2 narcosis, respectively.

Conclusions: We revealed the clinical and pathological characteristics of lupus nephritis in elderly patients. Lower eGFR and titers of specific antibodies were observed in the elderly patients than in the younger patients. Although the remission rate with treatment was favorable, mortality due to infection, which was likely associated with immunosuppression, was noted. Management strategies for lupus nephritis in elderly patients should carefully consider the risk of infection.

PUB334

A Unique Disease of C1q Nephropathy and Lymphadenopathy: Coincidence or Not?

Ipek Burkut Sarioguz, Justin D. Merszei. *Greater Houston Kidney Specialists, Houston, TX.*

Introduction: C1q nephropathy, characterized by mesangial immunoglobulin and complement deposition with a predominance of C1q, represents a rare renal disease with a very low prevalence world wide varying from 0.2 to 2.5%. We present a case of a patient with a seven-year history of widespread lymphadenopathy who was referred for evaluation of Chronic Kidney Disease Stage 3. Renal biopsy unexpectedly revealed C1q nephropathy coexisting with diabetic nephropathy.

Case Description: A 59-year-old African American female, with a medical history of widespread lymphadenopathy, congestive heart failure, hypertension and type 2 diabetes mellitus, presented with CKD Stage 3.Despite, more than 10 years of follow-up by oncology for a possible B cell disorder, diagnostic workup, including bone marrow showed polyclonal B cell proliferation without definitive evidence of malignancy. Previous biopsy of lymph nodes demonstrated atypical lymphoid infiltrate. On first presentation, PR3 was positive without vasculitis symptoms. She had proteinuria 2694mg/gr with GFR 37ml/min and elevated sedimentation rate 86mm/h.ANA and RF were negative and C3,C4 were normal. A kidney biopsy showed immune complex mediated glomerulonephritis with strong C1q immunofluorescence with background of diabetic nephropathy.

Discussion: C1q complement deposition in the glomeruli suggests an immune complex mechanism underlying the disease process.However, the exact mechanism by which immune complexes selectively target renal mesangial cells remains uncertain. Given the common occurrence of false positive results for PR3 and the lack of clinical evidence supporting its significance in isolation, we chose not to rely solely on PR3 testing for diagnosis.B-cell activation may have resulted in glomerular immunoglobulin deposition and lympadenopathy, which allows binding of C1q to the Fc portion of the IgG antibodies;therefore rituximab, a monoclonal antibody targeting CD20 on B cells, was administered as a first-line treatment. Recent studies reported complete remission for patients with C1q nephropathy by using a single dose or two doses of rituximab. While rituximab is a well-established treatment for various autoimmune conditions, C1q nephropathy still presents a significant clinical challenge. Further research is needed to elucidate the mechanisms driving immune complex formation in such cases and to optimize therapeutic strategies for improved patient outcomes.

PUB335

Hydralazine-Induced Vasculitis: A Case Report with Negative Kidney Biopsy

Nabeel Siddiqui, Abdelrahman N. Shehata, Mohamad N. Jajeh, Courtney Syfrett, Maria F. Kewish, Omer Farooq, Nowoghomwenma C. Ibie. *Southeast Health, Dothan, AL.*

Introduction: Hydralazine, a commonly used vasodilator for hypertension, can rarely induce vasculitis, a serious adverse effect. This condition is characterized by the formation of autoantibodies that attack blood vessels, leading to inflammation and tissue damage. In severe cases, such as pulmonary-renal syndrome, it can be rapidly progressive and life-threatening. Here, we present a case of hydralazine-induced p-ANCA vasculitis with a negative renal biopsy.

Case Description: 62yoM with CHF, HTN, CVA, T2DM, and PVD presents w/ hemoptysis, SOB, 30lb unintentional weight loss in 6 wks. Also: decr. appetite, nocturnal dyspnea, weakness, joint pain, and night sweats. He initially went to his PCP, who diagnosed him with pneumonia and prescribed Levaquin and Bactrim. He reported stopping his Plavix 3 days before presentation due to worsening hemoptysis. He was admitted for non-life-threatening hemoptysis, AKI, and acute blood loss anemia. Temp: 97.9F, HR: 69, RR: 20, BP: 182/75, O2 sat: 95% on 2L O2. Labs: BUN: 45, Cr: 4.43 (baseline 1.06), UA: 3+ blood, >100 RBC's, Hg: 6.8. CXR: bilateral diffuse pulmonary opacities, upper lobe predom. CT: scattered ground-glass, consolidative opacities. Rx: Vancomycin, Zosyn, pulse dose steroids, and 1 unit PRBC's. Bronchoscopy showed diffuse alveolar hemorrhage. Elevated: Myeloperoxidase, p-ANCA, ANA, dsDNA, MPO antigen, anti-histone antibodies. Hydralazine, which he was taking for greater than 10 years was held. Renal biopsy: no obvious vasculitis. His hemoptysis and kidney function improved and he was discharged on a steriod taper.

Discussion: Hydralazine-induced vasculitis, potentially dose-dependent, occurs in a minority of patients, with increased risk associated with higher doses and longer duration of use. While commonly affecting the kidneys and skin, our patient lacked skin manifestations. Management involves discontinuation of the drug, with severe cases requiring immunosuppressive therapy. Our patient responded well to steroids alone, underscoring the need for further research to guide treatment strategies for similar cases.

PUB336

A Challenging Clinical Scenario of ANCA-Associated Vasculitis Featuring Rapidly Progressive Crescentic Glomerulonephritis, Neutropenic Colitis, and Pancytopenia

David Pagan Maldonado, Andres Aranda, Linda G. Ruiz Fabian, Erick I. Marrero Santiago, Fatima D. Flores Arevalo, Cristian X. Rivera Benitez, Faviola M. Negrón, Valeria E. López Martínez, Zulmarie Rodriguez Cruz, Jorge C. Collazo Meléndez, Sarah Diaz Gonzalez, Valeria Mora, David A. Maldonado-Ruiz, Juan A. Morciego, Javier A. Morciego. *Universidad Autonoma de Guadalajara, Zapopan, Mexico.*

Introduction: With a peak incidence between 65 and 75 years, though it can occur at any age, ANCA-associated vasculitis (AAV) exhibits a slight male predominance. AAV shows geographical and race/ethnic differences in prevalence and encompasses various clinicopathologic phenotypes, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA (EGPA), and renal-limited necrotizing and crescentic glomerulonephritis (NCGN). It primarily affects small vessels (arteries, arterioles, venules, and veins) in any organ. The activity in the bone marrow is typically diagnosed through a biopsy with the presence of granulomas, accompanied by serum antibodies and systemic symptoms.

Case Description: We present a 58-year-old with ANCA GPA vasculitis diagnosed 3 years ago. Initial symptoms included episcleritis, blurred vision, rhinitis, sinusitis, headaches, and migraines. Treatment included methotrexate, prednisone, and folic acid. In late August 2023, polyarthralgia, polyarthritis, and macroscopic hematuria emerged. Creatinine rose to 6.0, urea to 250, with neutropenic colitis due to Clostridium difficile. Suspected acute kidney injury or vasculitis activity required renal replacement therapy. A bone marrow biopsy showed no vasculitis response. Tests for ANA, SSA/Ro, HIV, HCV, HBV were negative. Kidney biopsy revealed small vessel pauciimmune vasculitis. Improvement followed rituximab induction. Glomerular filtration rate is 30 ml/min, and the patient is hemodialysis free

Discussion: This case underscores the significance of performing biopsies to diagnose AAV in patients with systemic activity. Even though the patient's bone marrow biopsy showed no evidence of granulomas and they were exposed to methotrexate despite prophylactic treatment, it is possible that systemic vasculitis activity affected the bone marrow, which went undiagnosed in the sample obtained. These cases emphasize the need for a comprehensive clinical evaluation and interdisciplinary management.

PUB337

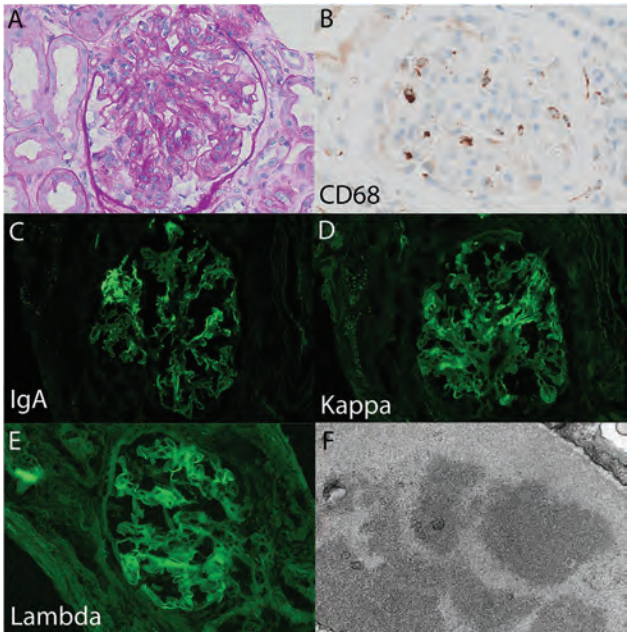
Untargeted Therapy: A Case of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin A Kappa Deposits

Victor D. Hoang,[1,2] Javier F. Sevilla Rodriguez,[2] Sarwat Gilani,[2] John L. Musa.[3] *[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [3]Audie L Murphy Memorial Veterans' Hospital, San Antonio, TX.*

Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare disorder, and the majority of affected patients do not have a detectable plasma/B-cell clone. This complicates management, and current therapy is based on data from small cohorts.

Case Description: A 77-year-old male presented with 2 weeks of melena and new bilateral lower extremity pitting edema. His labs were notable for serum creatinine of 1.5 mg/dL from a baseline of 1.2 mg/dL, and hemoglobin of 8.7 g/dL. Urinalysis was notable for 3+ protein and moderate blood with no cellular casts. Urine protein-creatinine ratio was 8.3. Extensive serologic workup was unremarkable. SPEP noted possible monoclonal spike in gamma region, which may be free kappa light chain measuring 0.1 g/dL. Renal biopsy demonstrated focal endocapillary proliferative and crescentic glomerulonephritis with IgA kappa restricted deposits (Figure 1). Hematology was consulted. Bone marrow biopsy noted no abnormal lymphocyte population and 0.6% polyclonal plasma cells. After inter-disciplinary discussion and risk/benefit discussion with the patient, therapy was initiated with bortezomib, cyclophosphamide, and dexamethasone.

Discussion: This case demonstrates the multi-disciplinary approach required to effectively treat cases of PGNMID. Specifically in cases where no plasma cell clone is found, there is still debate on ideal therapy.



Focal endocapillary proliferative glomerulonephritis (A) with infiltrating mononuclear cells of histiocytic lineage highlighted by CD68 stain (B). Frozen immunofluorescence studies show IgA (C) and kappa light chain (D) restricted deposits that are negative for lambda light chain (E). Electron micrograph shows mesangial deposits with no substructures (F).

PUB338

Kidney Involvement in Systemic Lupus Erythematosus (SLE): Beyond Lupus Nephritis

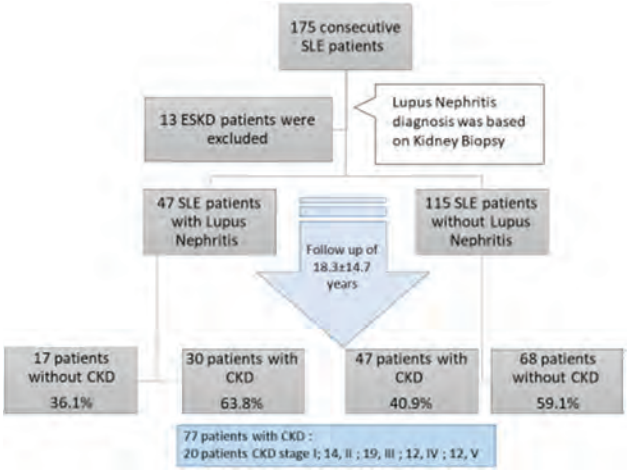
Keren Cohen-Hagai,[1,2] Sydney Benchetrit,[1,2] Dorin Bar-Ziv,[1,2] Mohamad Kabaha,[1,2] Moshe Shashar,[3] Oshrat Tayer Shifman.[1,2] *[1]Meir Medical Center, Kfar Saba, Israel; [2]Tel Aviv University Faculty of Medicine, Tel Aviv, Israel; [3]Laniado Hospital, Netanya, Israel.*

Background: Systemic lupus erythematosus (SLE) frequently involves the kidneys, contributing to morbidity among this population and may result in chronic kidney disease (CKD). While CKD diagnosis has significant clinical and therapeutic implications, it is still underdiagnosed even in high-risk population for CKD such as SLE. We aimed to detect prevalence and long-term clinical outcomes of non-dialysis dependent CKD among SLE patients

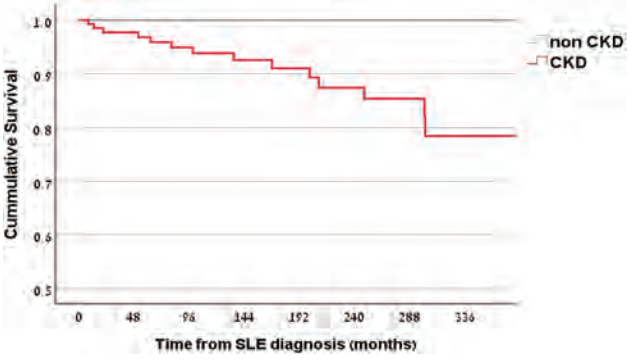
Methods: A retrospective study, conducted between 2014–2023 and included adults with a diagnosis of SLE for at least 1 year. CKD was defined as either eGFR<60 ml/min/1.73m^2 or albuminuria persisting in ≥2 consecutive tests spaced at least 3 months apart

Results: A total of 162 SLE patients were included, of them 57 had albuminuria, 43 had eGFR<60, and 23 patients had both. Out of the CKD patients, 61.1% never had a diagnosis of LN. Odds ratio for having CKD was 2.6 (95%CI 1.3-5.2, p=0.01) in patients with LN as cpmpared to patients without LN. CKD was associated with higher rates of diabetes, hypertension and heart disease (p=0.03, <0.01, <0.01 respectively). Rates of severe SLE exacerbations and severe infections were higher among CKD patients (p<0.01;<0.01). Despite comparable follow-up time, CKD patients had significantly higher mortality rates vs. non-CKD (23.4% vs 0, p<0.001 on univariate and multivariate analysis (Figure 2, p<0.01)

Conclusions: CKD is prevalent among SLE patients, including those without diagnosed LN, and is associated with elevated rates of morbidities, disease exacerbations, and mortality. These findings underscore the importance of proactive monitoring and intervention to alleviate the substantial morbidity and mortality burden associated with CKD in SLE.



study flowchart



age- and sex-adjusted cox model

PUB339

Complete Response in a Patient with New-Onset Lupus Nephritis following COVID-19 Vaccination

Won-Hee Cho. *SahmYook Medical Center, Dongdaemun-gu, Seoul, Republic of Korea.*

Introduction: Recent studies have suggested a potential association between the coronavirus disease 2019 (COVID-19) vaccination and the development or exacerbation of LN. Here, we present a case of a patient who was diagnosed with LN class IV after receiving the COVID-19 vaccine and achieved a complete response through immunosuppressive therapy.

Case Description: A woman in her 50s presented with nephrotic syndrome, deteriorating kidney function 1 month after receiving a Pfizer-BioNTech COVID-19 vaccine. Her creatinine level was normal prior to vaccination, but she developed edema 1 week after receiving the vaccine. All serologic tests were negative, but the patient showed positive results for both anti-nuclear antibodies (ANA) and anti-double stranded (ds) DNA, as well as low complement C3 levels. An emergency kidney biopsy confirmed diffuse proliferative crescentic LN class IV. Induction therapy involved intravenous methylprednisolone and cyclophosphamide, followed by maintenance therapy with prednisolone and mycophenolate mofetil. At the 18-month follow-up, the patient achieved a complete response, experiencing full recovery of kidney function, improvement in proteinuria, and even seroconversion to negative for both ANA and anti-dsDNA. In the repeat biopsy conducted two years later, the activity index significantly decreased compared to the initial biopsy. However, persistent disease activity was evident, accompanied by a slight increase in the chronicity index.

Discussion: Timely diagnosis and prompt immunosuppressive therapy are crucial for achieving favorable outcomes, even in severe cases of LN that occur after COVID-19 vaccination. Additionally, a repeat biopsy may contribute to assessing disease activity at the tissue level and predicting prognosis.

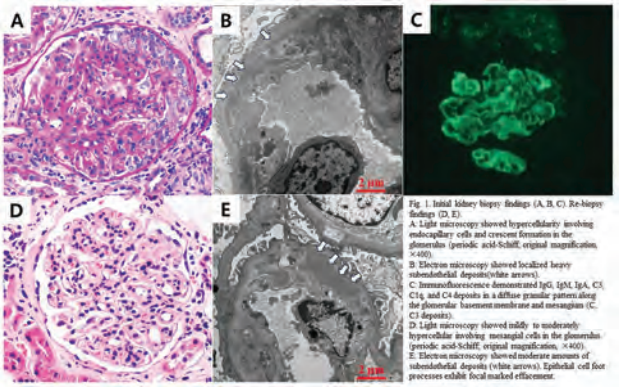


Fig. 1. Initial kidney biopsy findings (A, B, C). Re-biopsy findings (D, E).
A. Light microscopy showed hypercellularity involving endocapillary cells and crescent formation in the glomerulus (periodic acid-Schiff, original magnification, ×400).
B. Electron microscopy showed localized heavy subendothelial deposits(white arrows).
C. Immunofluorescence demonstrated IgG, IgM, IgA, C3, C1q, and C4 deposits in a diffuse granular pattern along the glomerular basement membrane and mesangium (C, C3 deposits).
D. Light microscopy showed mildly to moderately hypercellular involving mesangial cells in the glomerulus (periodic acid-Schiff, original magnification, ×400).
E. Electron microscopy showed moderate amounts of subendothelial deposits (white arrows). Epithelial cell foot processes exhibit focal marked effacement.

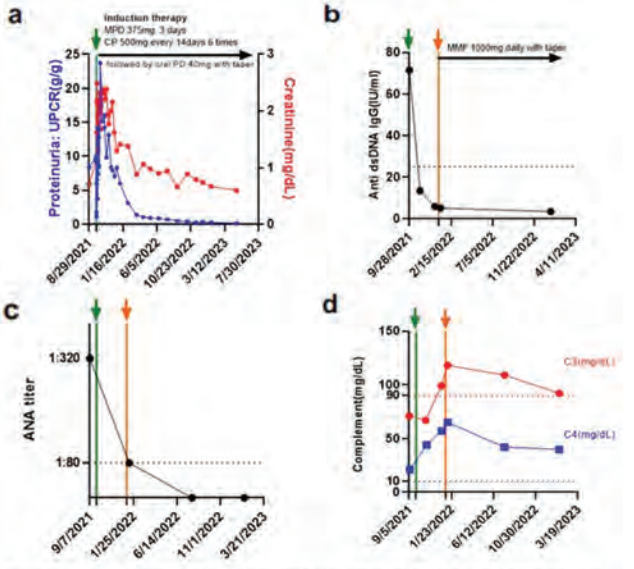


Figure2: (a) Time course of urine protein creatinine ratio(UPCR) and serum creatinine with end of induction therapy(green arrow), followed by maintenance therapy of prednisolone and mycophenolate mofetil(orange arrow). Serological parameters (b) anti-ds DNA-IgG, (c) antinuclear antibody(ANA), and (d) complement C3 and C4 are plotted in relation to induction therapy. Dotted lines represent normal limits. MPD, methylprednisolone; CP, cyclophosphamide; PD, prednisolone; MMF, mycophenolate mofetil.

PUB340

Lithium-Induced Nephrotic Syndrome: A Rare Complication of a Known Kidney Offender

Megha E. Pendyala,[1] Reshub R. Pendyala,[2] Prashant Pendyala.[3]
[1]Williamsville Central School District, East Amherst, NY; [2]Nichols School, Buffalo, NY; [3]Buffalo General Medical Center, Buffalo, NY.

Introduction: Lithium is commonly used effective medication for treatment of bipolar and unipolar disorders. A variety of renal complications have been well described with Lithium usage. Nephrogenic diabetes insipidus, chronic interstitial nephropathy and renal tubular acidosis being the common ones. Nephrotic syndrome is a rare but known complication.

Case Description: A 34 yr old lady presented to the emergency room with complaints of generalized edema and weight gain of 25 lbs in a 3-day period. She has known history of severe depression and suicidal ideation. She has been taking Lurasidone, Clonazepam, Desvenlafaxine and Mydayis. She was started on Lithium Carbonate 4 months prior. No NSAID intake. She was found to have anasarca. The Lithium level was normal (1.14 mmol/l). She had 17gm of urine protien. The total cholesterol was 405 mg/dl, serum albumin of 1.5gm/dl. Creatinine was mildly elevated at 1.32gm/dl. Serology for Hepatitis and HIV were negative. Rheumatoid Factor, Antinuclear and anti DNA antibodies were also negative. Lithium was discontinued. Two weeks later the urine protein had decreased to 12.5 gm and serum albumin was 1.7gm/dl. Four weeks later her edema had resolved. Her proteinuria had completely resolved and serum albumin 2.9gm/dl with a normal creatinine. In a six month follow up she did not have any proteinuria; her serum albumin and cholesterol were normal. She did not get a kidney biopsy and was not started on steroids

Discussion: Lithium induced nephrotic syndrome is a rare occurrence. Only around 30 cases have been reported. Our patient was on Lithium for 4 months prior to the onset of symptoms. Usual duration described was 1 to 12 months. These patients respond well to discontinuation of lithium with most of them recovering within few weeks. The Lithium

levels in our patient were therapeutic showing that it is likely an idiosyncratic reaction and not a result of toxicity. Review of literature shows that usually these patients do not need treatment with steroids and there is no need for kidney biopsy. However, if the symptoms persist beyond 6 weeks, a kidney biopsy to exclude other causes and treatment with prednisone have been done in the case reports. Kidney biopsy usually shows minimal change disease. This case provides an example of a rare renal side effect of Lithium that occurs after relative short duration of treatment.

PUB341

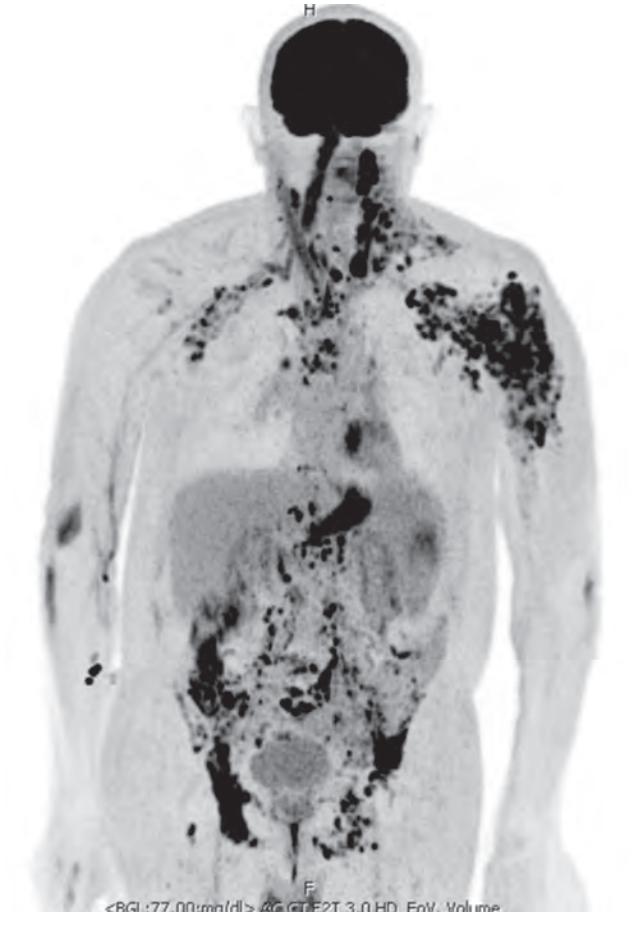
Nephrotic Syndrome Secondary to Renal AA Amyloidosis Predating Hodgkin Lymphoma Diagnosis: A Case Report

Sherida Edding, Jennifer A. Tuazon. *Northwestern Memorial Hospital, Chicago, IL.*

Introduction: AA amyloidosis is the most prevalent form of systemic amyloidosis. Common causes are chronic bacterial infections, inflammatory and autoimmune conditions. Association with solid and hematologic malignancies are uncommon. The kidneys are the most affected organ with nephrotic syndrome phenotype, though incidence is less than 1%. We present a rare case of a patient with nephrotic syndrome from AA amyloidosis with initially unknown etiology and later on proven to be from Hodgkin's Lymphoma.

Case Description: Patient is a 72M of Bosnian origin with no known medical history presenting 1 year prior with lower extremity and scrotal edema with creatinine 1.7, low albumin and proteinuria of 7g. Renal biopsy showed amorphous material and immunoperoxidase stain positive for AA amyloidosis. Infectious and autoimmune workup were unrevealing. Imaging showed retroperitoneal lymph nodes though biopsy negative for malignancy. Multiple myeloma workup negative. Patient seen by Oncology and advised treatment but was lost to follow. He presents again one year later with hemiplegia and aphasia, severe AKI on CKD (Creatinine ~10), proteinuria (~15g with 7g albumin), and a new neck mass. Workup revealed acute stroke concerning for hypercoagulable state. Patient initially resistant to invasive measures but eventually agreed on dialysis initiation. Biopsy of neck mass was pursued and was consistent with classical Hodgkin's lymphoma. PET-CT showed metastatic disease. Treatment options discussed though decision made to defer for now. Patient maintained on chronic dialysis.

Discussion: Though rare, undiagnosed malignancy should always be considered in patients with nephrotic syndrome from biopsy-proved AA amyloidosis. This case highlights the importance of thorough investigation including a complete malignancy workup in such patients.



PUB342

Characterization of Screening Patterns and Identification of Patients with Lupus Nephritis in a Community Rheumatology Setting

Nehad Soloman,[1] Jawad Bilal,[1] Romy Cabacungan,[1] Scott Milligan,[2] Andrew Sharobeem,[1] John Tesser,[1] Henry Leher.[3] *[1]Arizona Arthritis & Rheumatology Associates, P.C., Phoenix, AZ; [2]Trio Health Analytics, Louisville, CO; [3]Aurinia Pharmaceuticals Inc, Victoria, BC, Canada.*

Background: Lupus nephritis (LN) is a serious but common complication of systemic lupus erythematosus (SLE) characterized by proteinuria and decreased renal function. As delays in LN diagnosis may lead to nephron loss and delayed administration of disease-modifying therapies, current treatment recommendations suggest regular screening of patients with SLE for kidney involvement. Given the importance of early identification and treatment of LN, we assessed screening patterns for kidney involvement in patients with SLE in care of community rheumatologists in the United States.

Methods: Patient selection criteria: ≥2 diagnosis codes for SLE separated by >30 days, in care of the American Rheumatology Network (ARN) between July 2018 and June 2023, and >365 days observation. Individual patient observation windows were calculated from the first date of observation by ARN (index date) to the last encounter date, up to June 30, 2023. Patients were suspected of having probable LN if they had any of the following qualifying events during their observation window: an ICD-10 code for LN, an ICD-10 code suggestive of LN (e.g., kidney issues or related testing), or laboratory results indicative of proteinuria or reduction in estimated glomerular filtration rate (eGFR >20% less than observed at earliest observation and where lower eGFR measure is <72 mL/min/1.73 m^2 and not already categorized by ICD-10 code).

Results: 8631 of >540,000 patients with data in the ARN database met all study criteria. Of these, 5314 (62%) had at least one qualifying event during their observation window; 24% of patients had a diagnosis of LN by ICD-10 code, whereas an additional 38% had laboratory values or other ICD-10 coding suggestive of LN. Of the 62% of patients with probable LN, 97% had record of an eGFR assessment compared to 66% and 62% of patients, respectively, who had record of protein assessment by urine test strip or urine protein.

Conclusions: This study suggests that most patients with SLE will develop renal involvement over the course of their disease. These data support increased routine screening of SLE patients for LN via regular utilization of urine protein testing, consistent with the LN treatment guidelines.

Funding: Commercial Support - Aurinia Pharmaceuticals, Inc.

PUB343

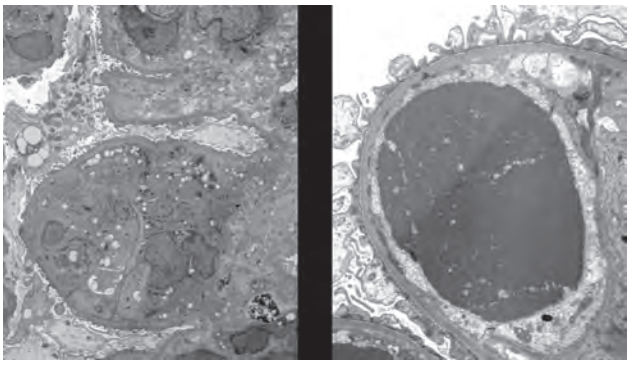
A Muddy Brown Presentation: A Case of Monoclonal Gammopathy of Renal Significance Associated with IgM Kappa Proliferative Glomerulonephritis with Monoclonal Immune Deposits and Leukocytoclastic Rash

Cindy Le, Alex Y. Ge, Hima B. Doppalapudi, Vijay K. Vanguri, Konstantin Abramov. *University of Massachusetts Chan Medical School, Worcester, MA.*

Introduction: Monoclonal gammopathy of renal significance (MGRS) is a diagnostic term, first introduced in 2012, used to describe patients who have renal disorders secondary to monoclonal gammopathies but who do not otherwise meet criteria for a hematologic malignancy. This case illustrates a unique presentation of proliferative glomerulonephritis (PGNMID) with IgM kappa immune deposits that presented with a leukocytoclastic rash.

Case Description: A 75-year-old man presented with hematuria, vomiting, and hematochezia. His serum creatinine was 3.78 mg/dL. Urine sediment showed muddy brown and granular casts initially attributed to acute tubular necrosis secondary to hypovolemia. He developed a leukocytoclastic rash. His renal function continued to decline requiring dialysis. Renal biopsy showed proliferative glomerulonephritis with monoclonal immune deposits. Hematologic workup identified an IgM kappa-producing B-cell clone, confirming a diagnosis of MGRS. He was treated with cyclophosphamide, bortezomib, dexamethasone, and rituximab, with resolution of his monoclonal paraprotein and recovery of his kidney function.

Discussion: Although not well studied, about 40-45% of patients with MGUS who underwent kidney biopsy also had MGRS-related disease. Furthermore, IgM kappa is a rare immunoglobulin class in PGNMID. The leukocytoclastic rash this patient presented with appears to be uncommon. It is unclear if there is a direct relation between this patient's rash and MGRS. When association is suspected between monoclonal gammopathies and cutaneous manifestations, it would be expected that the immune complex deposits in the skin would be the same as the monoclonal gammopathy. However, the skin biopsy was positive for IgG but his kidney biopsy was positive for IgM. It is possible that clonal antigens from the patient's B-cell clone triggered formation of immune deposits, which then deposited in the skin.



PUB344

Sparsentan (SPAR) in Combination with a SGLT2 Inhibitor (SGLT2i) and Steroid as First-Line Treatment for IgA Nephropathy (IgAN): A Case Report

Ray R. Goshtaseb,[1] Agness Pelts Block,[2] Christopher Gisler.[2] *[1]UCLA, Department of Medicine, Nephrology Division, Los Angeles, CA; [2]Travere Therapeutics, Inc., San Diego, CA.*

Introduction: SPAR is a nonimmunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA) approved in the US and EU for the treatment of adults with IgAN at risk of rapid disease progression. Early clinical experience from a limited number of patients suggests that an SGLT2i added to SPAR is generally well tolerated and may have additive benefit on proteinuria reduction in IgAN. However, the use of SPAR in combination with an SGLT2i in the first-line setting has not been evaluated in a clinical trial. We present a case of SPAR + SGLT2i + steroid combination therapy as a first-line treatment for IgAN.

Case Description: A 51-year-old Asian woman with biopsy-proven IgAN presented with substantial proteinuria (24-h urine protein excretion [UPE] of 10.9 g/d), gross hematuria, an estimated glomerular filtration rate (eGFR) of 61 mL/min/1.73 m^2, and slightly elevated blood pressure (BP) at diagnosis. She is receiving SPAR (400 mg/d; dose increased after 2 weeks at 200 mg/d) in combination with the SGLT2i dapagliflozin (10 mg/d) and a tapering dose of prednisone (60 to 5 mg). All medications were initiated simultaneously following diagnosis. After 6 mo, proteinuria was markedly reduced (UPE of <0.5 g/d), eGFR and BP improved, and hematuria resolved (**Table**). The combination treatment was well tolerated, with no safety concerns; liver function tests were stable and within normal limits.

Discussion: This case supports the efficacy and safety of SPAR in combination with an SGLT2i and steroid in the first-line setting, highlighting a rapid reduction in proteinuria despite high levels at treatment initiation, together with improvement in kidney function and resolution of hematuria with the combination treatment.

Clinical Assessments at Baseline and Follow-up

	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

BP, blood pressure; eGFR, estimated glomerular filtration rate; UPE, urine protein excretion.

PUB345

An Unanticipated Case of C1Q Nephropathy Diagnosed after Re-biopsy

Shan Pandya, Tamara R. Batarseh, Ashwin R. Shetty. *Swedish Hospital, Chicago, IL.*

Introduction: C1q nephropathy is a rare, poorly understood glomerulonephropathy that typically occurs in older children or younger adults. It is characterized by C1q protein deposition in the mesangium without features of Systemic Lupus Erythematosus (SLE). Treatment generally consists of immunosuppressants however specific regimens are not well established. We present a case of a patient with new onset edema and proteinuria with initial renal biopsy suggesting Minimal Change Disease (MCD) vs Focal Sclerosing Glomerulonephritis (FSGS) and repeat biopsy confirming C1Q nephropathy.

Case Description: A 39 y/o Hispanic female presented to the hospital for 5 days of bilateral edema from her ankles to her abdomen. Creatinine was 0.5 mg/dL. Urinalysis showed 4+ protein and trace blood without RBCs. A spot urine Protein:Cr was 8.9 g/g and albumin was 2.2 g/dL. Secondary workup for autoimmune and infectious glomerular etiologies revealed high SS-A and SS-B. Renal biopsy showed one glomerulus with segmental sclerosis, diffuse podocyte effacement, and prominent mesangial/paramesangial deposits with no glomeruli on immunofluorescence. Her proteinuria improved to 1.3 g/g after a 4 week prednisone taper for presumed MCD vs FSGS, but increased to 5.3 g/g off steroids. Rheumatology follow-up determined she did not have SLE. An 8 week steroid taper improved her proteinuria to 0.35 g/g, but worsened to 7.6 g/g after several months off steroids. A repeat renal biopsy revealed FSGS with likely C1q nephropathy variant with 2+ granular staining with C1q. Steroids were resumed. Rituximab and mycophenolate were considered, however lack of insurance delayed treatment. Despite continued steroids, her proteinuria increased to 6.7 g/g and she eventually started mycophenolate. She is currently improving with 5mg prednisone, mycophenolate, and tacrolimus. Her most recent proteinuria was 0.89 g/g and Cr was 0.55 mg/dL.

Discussion: This case highlights the importance of considering C1Q nephropathy as part of the differential with presentations similar to MCD and FSGS as well as the value of considering a second biopsy with recurrent relapses. Moreover, the events of this case span over four years due to difficulties in obtaining specialty appointments, affordable medications, and consistent care. This case also highlights the detriments of inaccessibility to healthcare when attempting to treat nephropathies in a timely manner.

PUB346

Granulomatosis with Polyangiitis: Role of Nephrologist in Management of a Rare Systemic Disease

Usha Kumari, Dhirisha Bhatt, Omer M. Asif Siddiqui, Margaret C. Hastings. *The University of Tennessee Health Science Center, Memphis, TN.*

Introduction: Granulomatosis with polyangiitis (GPA) is a rare form of systemic vasculitis primarily affecting the upper respiratory tract, lungs, and kidneys and associated with antineutrophil cytoplasmic antibodies (ANCA). This case highlights the importance of the nephrologist in the interdisciplinary management of GPA with a multisystemic presentation.

Case Description: A 39-year-old African American female presented with a saddle nose deformity and chest pain. A computed tomography (CT) scan revealed mediastinal lymphadenopathy, numerous lung masses, and total obstruction of the nares. A nasal biopsy showed pyogenic granuloma. Serum creatinine (SCr) was 0.59 mg/dl. Anti-proteinase 3 titers were positive (1:160). Urine studies showed microhematuria and low-grade proteinuria with a urine protein:creatinine ratio (UPC) of 0.85. A kidney biopsy showed pauci-immune focal necrotizing glomerulonephritis, consistent with ANCA-associated vasculitis. Corticosteroids and rituximab were initiated by nephrology. A month later, SCr increased to 2.86 mg/dl. She developed severe headaches, periorbital edema, and vision changes, leading to the diagnosis of dacryocystitis. A lacrimal gland biopsy showed marked acute inflammation due to histiocytosis, plasma cells, and lymphocytes. Pulse steroids and rituximab were re-administered, followed by steroid tapering per the PEXIVAS protocol and the addition of avacopan. Though renal function improved, she had worsening orbital symptoms. She received another cycle of pulse-dose steroids and two doses of cyclophosphamide, with improvement in eye and nasal symptoms. At her most recent visit, SCr was 0.86 mg/dl and UPC was 0.45. Continued immunosuppression with rituximab for 18–24 months, along with avacopan, was planned.

Discussion: A multidisciplinary team including nephrology, rheumatology, pulmonology, and ophthalmology managed the patient. The nephrologist played a crucial role in diagnosing the disease with a renal biopsy (performed when normal renal function and only mild abnormalities in urine were present) and initiating immunosuppression. Successful management of this complex case exemplifies the invaluable contribution of the nephrologist as part of the interdisciplinary team navigating the challenges posed by systemic GPA.

PUB347

Thrombotic Microangiopathy in Scleroderma: Is It Always a Crisis?

Loai Dweik,[1] Leal C. Herlitz,[2] Kristen Tomaszewski,[2] Corey J. Cavanaugh.[2] *[1]Cleveland Clinic Akron General, Akron, OH; [2]Cleveland Clinic, Cleveland, OH.*

Introduction: Thrombotic microangiopathy (TMA) is a pathological lesion seen across many diseases, initiated by endothelial injury and/or dysfunction. In systemic sclerosis (SS), the presentation has classically been described as a rapid onset of hypertension with declining kidney function and RNA polymerase III (RNApolIII) positivity. Prompt initiation of Angiotensin Converting Enzyme inhibitor (ACEi) is crucial for treatment. Here we describe an atypical case of TMA in SS and the use of complement targeted therapy.

Case Description: This case describes a 66-year-old female with a medical history of hypothyroidism, SS and myositis overlap who presented with muscle weakness and acute renal failure. Physical examination revealed blood pressure (BP) of 143/75, wheezing, decreased breath sounds on auscultation, purple discoloration of fingertips with ulceration and calcinosis of second and third right fingertips. Creatinine was 1.4mg/dl from a baseline of 0.8-0.9 mg/dl and platelets 145 k/uL, electrolytes and blood counts were otherwise normal. The patient had positive ANA and Anti-SSA titers. RNApolIII, C3, C4 were normal. Despite her BP, she was started on captopril. Kidney biopsy was pursued and revealed acute thrombotic angiopathy and microangiopathy, as evidenced by widespread fibrin thromboses, and intimal edema within arteries and arterioles with accumulation of schistocytes. There was no adventitial fibrosis or onion skinning, reflective of a relatively acute onset.

Discussion: The findings of an unexpected amount of thromboses, normal BP readings on ACEi, and lack of RNAPolIII, cued pathology and nephrology to consider a complement mediated injury. Thus, as the patient exhibited deterioration in renal function, with creatinine rising to 1.95 mg/dl and worsening thrombocytopenia to 99 k/uL, the decision was made to start eculizumab. ADAMTS13, Factor B, H, and I testing were normal. Genetic testing is currently pending. After 1 month follow-up, creatinine remains stable at a level of 1.8mg/dl. It is important to consider TMA in patients with SS and acute renal failure, even in the absence of elevated BP. The report highlights the diverse nature of TMA even within a single disease entity like SS. TMA in SS should be classified as ACEi responsive or non-responsive. The use of complement targeting therapy should be considered in atypical cases, and those not responding to ACEi.

PUB348

A Unique Presentation of Fabry Disease with Progressive Bilateral Hearing Loss

Iskandar Berbari, Fayaz A. Khan, Amit K. Rajput. *TriHealth Inc, Cincinnati, OH.*

Introduction: Fabry disease is the second most prevalent lysosomal storage disease and can affect multiple organs, including the kidneys and the vertebrobasilar system. Fabry Nephropathy presents with proteinuria and progressive renal failure. We present a case of a patient who presented with nephrotic range proteinuria and progressive hearing loss, who was found to have Fabry disease.

Case Description: A 32-year-old male with a past medical history of progressive bilateral hearing loss, initially presented for evaluation of nephrotic range proteinuria. He attributed his hearing loss to a traumatic ear injury and reports "compensating with his other ear". He also reports a history of acroparasthesias in his hands triggered by cold weather, generalized fatigue, and a single episode of self-limiting hematuria which occurred a year prior. The patient was referred for a UACR of 3.2g with Creatinine within normal range and GFR>60. Given the concern for Alport disease, a renal biopsy was performed. The biopsy demonstrated numerous podocyte inclusions concerning for Fabry disease. There was also evidence of glomerulomegaly, thickened GBM, and segmental sclerosis likely due to hyperfiltration/proteinuria. Genetic testing done was positive for GLA mutation and enzyme testing showed deficiency in alpha galactosidase, confirming the diagnosis of Fabry disease. The patient was started on Fabrazyme infusions. Proteinuria (UPCR of 0.5g), paresthesia, and fatigue all improved significantly after starting enzyme replacement therapy. The patient reported improvement in hearing loss, but still required the use of hearing aids.

Discussion: This is a case of Fabry disease with an atypical presenting symptom. Fabry disease is an X-linked disorder and results in accumulation of globotriaosylceramide (Gb3) within lysosomes in a wide variety of cells. Multiple organs, including the kidneys, can be affected. Proteinuria and progressive renal decline occur secondary to accumulation of Gb3 in the glomeruli, distal tubule, and vascular smooth muscle cells. It is essential to keep a high index of suspicion of unexplained nephrotic range proteinuria accompanied by paresthesia in patients. Our case demonstrated the importance of early diagnosis with kidney biopsy leading to resolution of proteinuria and symptoms after initiation of enzyme replacement.

PUB349

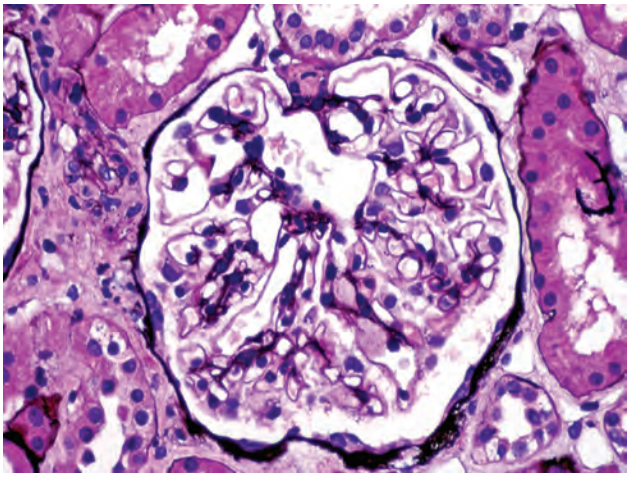
NELL-1-Positive Membranous Nephropathy

Alejandro Valdesuso,[1] Sobia Mansoor,[1] Satoru Kudose,[2] Larissa Kruger Gomes.[1,3] *[1]Landmark Medical Center, Woonsocket, RI; [2]Columbia University, New York, NY; [3]Kent Hospital, Warwick, RI.*

Introduction: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults with over 20 novel target antigens discovered. NELL-1 is the second most common after PLA2R.

Case Description: 57-year-old male with PMHx of HTN and obesity was referred to the nephrology clinic for proteinuria. Patient was well until 3 months prior when he presented to the ED with lower extremity edema and shortness of breath and was diagnosed with a right lower extremity DVT and PE. BMP showed normal serum creatine. He was started on Eliquis. Persistent lower extremity edema led to a 24-hour urine protein test which showed 12 g of protein. A previous UA 7 months earlier showed no proteinuria. Nephrological work up was negative for glomerular basement membrane, c-ANCA, p-ANCA and PLA2R antibodies, with normal C3 and C4 levels. Kidney biopsy revealed segmental membranous nephropathy, mild tubular atrophy and interstitial fibrosis, severe arteriosclerosis and mild arteriolosclerosis. Immunohistochemical staining for NELL-1 was positive. Patient's lisinopril was increased to highest tolerated dose, and vitamin supplements he was taking were stopped. However, high-grade proteinuria persisted prompting the initiation of rituximab.

Discussion: NELL-1 MN, while mostly seen in adults like PLA2R MN, typically has a higher age of onset. Mercury-containing indigenous remedies and lipoic acid supplements have been associated with NELL-1 MN, with discontinuation resulting in remission. Unfortunately, the patient's supplements did not contain these agents. Compared to PLA2R MN, NELL-1 MN has a more robust association with malignancy with as many as 10-33% of cases. In the case, age-appropriate cancer screening as well as PAN CT scan was done; however, no malignancy was found. Still, close follow up is recommended. Finally, NELL-1 MN is more resistant to treatment and more likely to recur. Patient's proteinuria has decreased to 2.7 mg/mg after two sessions of rituximab, but he has not achieved remission yet.



PUB350

A Case of AL Amyloidosis: A Common Cause of Nephrotic Syndrome without the Damage

Ashley Tang, Hira H. Al-adroos, Arthur Galoustian. *Riverside Community Hospital, Riverside, CA.*

Introduction: AL amyloidosis, the most common subtype of systemic amyloidosis, is characterized by the overproliferation of immunoglobulin-associated proteins by plasma cells. These unstable proteins misfold into amyloid fibrils and deposit into various tissues. Approximately two-thirds of patients will develop nephrotic syndrome from amyloid deposition in the glomeruli, leading to progressive renal dysfunction and failure. We present a unique case of AL amyloidosis with nephrotic syndrome in the absence of renal impairment.

Case Description: A 79-year old male, with a history of dyslipidemia and paroxysmal atrial fibrillation, presents for worsening edema and dyspnea on exertion non-responsive to loop diuretics. On outpatient echocardiogram, he had new aortic regurgitation, pleural effusion, and spot urinalysis with albuminuria 3000mg. Metabolic panel showed BUN 20, creatinine 1.0, and eGFR 77. Urine studies revealed a protein/creatinine ratio 13.6. An echocardiogram revealed left ventricular hypertrophy with speckling suspicious for amyloidosis infiltration. A renal ultrasound showed a simple cyst but otherwise unremarkable. His renal biopsy was Congo red positive AL amyloidosis associated with lambda-light changes and acute tubular injury. A bone marrow biopsy confirmed increased abnormal plasma cells and amyloid deposition within vessels. He was discharged home with diuretics and angiotensin-converting enzyme inhibitors for his nephrotic syndrome and plans to enroll in a clinical trial for his AL amyloidosis.

Discussion: The kidney glomeruli are the most frequent site of AL amyloid accumulation, leading to proteinuria. Notably, >5g/day and reduced eGFR <50 are closely associated with the development of end-stage renal disease. Existing criteria measure the severity of the nephrotic syndrome with progression to ESRD as an inverse correlation of proteinuria to eGFR. In this patient, his protein/creatinine ratio can be approximated as proteinuria around 13.6g/day but with a normal eGFR. There is no evidence of that relationship, nor did his acute tubular injury seen on the renal biopsy manifest on labs. While an unusual case without renal damage, it solidifies the use of proteinuria not only for the detection of AL amyloidosis and its organ involvement but also reaffirms the ongoing significance as a biomarker of damage or response to therapy further down the line.

PUB351

Idiopathic Nodular Glomerulosclerosis in a New Uncontrolled Hypertensive and Passive Smoker: A Case Report

Mehrbod Vakhshoori, Amir Abdi Pour, Yan Chen Wongworawat, Sayna Norouzi. Post-doctoral Scholar Research Program. *Loma Linda University Medical Center, Loma Linda, CA.*

Introduction: Idiopathic nodular glomerulosclerosis (ING) is a rare disease characterized by mesangial expansion with increased nodularity in absence of diabetes or other specific diseases. Despite its unknown pathogenesis, the presence of longstanding hypertension (HTN) and active smoking are associated with this disease leading to a new term "smoking-modified HTN-associated nodular glomerulosclerosis (SHaNGS)". Herein we report a case of ING in a passive smoker with uncontrolled HTN.

Case Description: A 60-year-old female with history of polyneuropathy, monoclonal gammopathy of undetermined significance (MGUS), hypothyroidism, onychomycosis (POEMS syndrome), and HTN was referred due to increased creatinine level (1.4 mg/dl). She denied active smoking but reported long-standing exposure to cigarette smoking being surrounded by heavy smoker family members and then working as a bartender. Further workups showed hematuria (50 RBC/high power field), proteinuria (urine-protein-creatinine ratio: 2.4 g/g, increased to 2.9 g/g) with normal renal ultrasound (Table 1). Kidney biopsy results showed evidence of diffuse and focal nodular mesangial expansion without hypercellularity, negative staining for amyloid, fibrillary glomerulonephritis and immunoglobulins (both direct and pronase digested immunofluorescence), finally diagnosed as ING (Figure 1 A&B).

Discussion: This case highlights a rare case of ING secondary to heavy passive smoking and uncontrolled HTN.

Table 1. Laboratory data of the patient on first and most recent visit

Laboratory data	First visit	Most recent visit	Reference range (unit)
White blood cell	4.60	4.27	4.80-11.80 (*10³/l)
Red blood cell	2.97	2.63	3.80-5.30 (*10^12/l)
Hemoglobin	8.9	8.1	11-16 (g/dl)
Platelets	192	136	140-340 (*10³/l)
Sodium	138	139	134-147 (mMol/l)
Potassium	4.6	5.4	3.5-5 (mMol/l)
Blood urea nitrogen	53	35	7-20 (mg/dl)
Creatinine	1.8	1.7	0.7-1.3 (mg/dl)
HbA1C	5.4	-	%
Total protein	7.5	6.7	6.3-8.2 (g/dl)
Albumin	3.6	3.4	3.2-4.6 (g/dl)
Aspartate aminotransferase	17	18	0-35 (U/l)
Alanine aminotransferase	11	12	7-45 (U/l)
Alkaline phosphatase	72	64	37-132 (U/l)

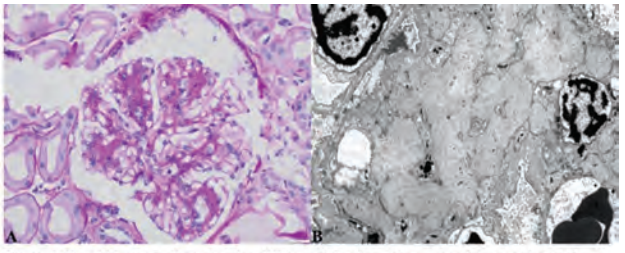


Figure 1. Renal biopsy findings showing diffuse and focal nodular mesangial expansion without hypercellularity (A: light microscopy, B: electron microscopy).

PUB352

An Unexpected Case of C3 Glomerulopathy in the Setting of Monoclonal Gammopathy and Cryoglobulinemic Vasculitis

Kelly V. Liang, Kimberly P. Liang, Al-Ola Abdallah, Timothy A. Fields. *The University of Kansas Medical Center, Kansas City, KS.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) can be associated with cryoglobulinemia, monoclonal gammopathy of renal significance (MGRS), C3 glomerulonephritis (C3GN), and vasculitis. MGRS has rarely been associated with C3GN via monoclonal immunoglobulin impairment of regulation of the complement alternative pathway (CAP). We present a case of C3GN due to MGRS in a patient with Type I cryoglobulinemia, monoclonal gammopathy of undetermined significance (MGUS), and granulomatosis with polyangiitis (GPA).

Case Description: A 57-year-old female with history of Type 1 cryoglobulinemic vasculitis (livedo on bilateral legs, ulcers, fatigue in 2022), IgG lambda MGUS, recurrent ulcerative chronic sinusitis and nasal septal perforation suggestive of GPA, was referred to Nephrology in April 2023 for proteinuria and microscopic hematuria. She was on methotrexate and intermittent prednisone for vasculitis. Hepatitis B and C were negative. Bone marrow biopsy (BMBx) in 2019 showed normocellular bone marrow (30-40%), 2% blasts and <5% monoclonal lambda plasma cells (PC). In July 2022, Kappa/Lambda ratio: 0.36, M protein: 1.2, urine M-protein: detectable but not measurable. In April 2023, urine protein/Cr ratio (UPCR) was 1.6. Kidney biopsy showed MPGN with C3-dominant deposits consistent with C3GN (Congo red negative). In May 2023, CAP functional assay confirmed overactivity, and genetic test for CAP mutations was negative, confirming acquired dysregulation of CAP from monoclonal gammopathy. Repeat BMBx in June 2023 showed 12% monoclonal PC. She was started on bortezomib (Velcade) and dexamethasone (Vd), then switched to daratumumab in Oct 2023 due to neuropathy from Velcade. Creatinine is preserved and UPCR <0.5 since July 2023.

Discussion: This case illustrates a rare and distinct subtype of C3GN associated with monoclonal IgG lambda, which can cause dysregulation of the CAP via enhancement of C3 convertase by acting as anti-complement factor H (CFH) autoantibody, thus interfering with normal CFH regulation of C3 convertase. Although MPGN is commonly associated with cryoglobulinemia and vasculitis, this case highlights the role of monoclonal gammopathy as a potential etiology of C3GN and MGRS. Recognition of this entity is important as clone-directed treatment may improve outcomes and differs greatly from treatment for vasculitis.

PUB353

Urine IgG4 May Be a Specific Biomarker to Monitor the Progression of Phospholipase A2 Receptor (PLA2R)-Positive Primary Membranous Glomerulopathy (pMGN)

Ping L. Zhang,[1] Gabriel N. Maine,[1] Devin Young,[2] Atul Singh,[1] Dilip Samarapungavan.[1] *[1]Corewell Health, Royal Oak, MI; [2]Oakland University, Rochester, MI.*

Introduction: PLA2R is known to be closely related to IgG4 in the serum of patients with pMGN. Our recent study indicated that PLA2R staining in the glomeruli of renal biopsies remained positive in different stages of pMGN (usually graded as stage 1 to 4, subepithelial to resolving deposits by electron microscopy [EM]). IgG4 staining was positive in stage 1-2 p-MGN. In contrast, its staining faded away in glomerular basement membranes (GBM) due to its low affinity to GBM in stage 3-4 pMGN. This pilot study was to determine if urine IgG4 was reduced in stage 3- 4 pMGN when compared to stage 1-2 pMGN.

Case Description: Patient #1 had nephrotic range proteinuria. His transplant renal biopsy showed De Novo pMGN with positive stains for both PLA2R and IgG4, and stage 1 subepithelial deposits by EM. Patient #2 also had nephrotic range proteinuria and his transplant renal biopsy showed recurrent pMGN with positive PLA2R but focal/weak IgG4 staining. The EM for patient #2 showed stage 3-4 intramembranous vacuoles. Urine IgG4 levels were measured in both transplant patients with pMGN. Relative urine IgG4 concentrations were comapred against measurements from normal urine (< 0.03 mg/dl, negative control) and a positive control (peak IgG4 of 6.64 mg/dl). Patient #1 had a urine IgG4 level at 3.13 mg/dl and urine protein/creatinine ratio (UPCR) at 7.55 mg/mg, thus producing 0.415 mg/dl IgG4 per unit urine protein by dividing two indices (see Table below). Similarly, patient #2 had urine IgG4 level at 2.10 mg/dl and UPCR at 4.96 mg/mg, thus generating 0.423 mg/dl IgG4 per unit urine protein by dividing two indices. There was no significant difference in urine IgG4 levels between them.

Discussion: Our pilot study suggests that IgG4 immuno-staining may only reflect stages of immune complex deposits seen by EM but cannot correlate with the urine level of IgG4. However the urine IgG4 measurement may serve as a non-invasive biomarker to monitor progression of pMGN. Additional studies are required to further validate this claim.

Table 1. Two patients with primary membranous glomerulopathy

Patients	Serum Creatinine (mg/dl)	Urine Pro/Cr Ratio (mg/mg)	Urine IgG4 (mg/dl)	Urine IgG per unit protein
Pt #1 44 male with de novo pMGN	1.50	7.55	3.13	0.415
Pt #2 46 male with recurrent pMGN	1.35	4.96	2.10	0.423

PUB354

Beyond the Virus: A Case Report on Tip Lesion Variant of FSGS after COVID-19 Infection

Manpreet Chahil,[1] Larissa Kruger Gomes,[1] Michael B. Stokes.[2] [1]*Kent Hospital, Warwick, RI;* [2]*Columbia University, New York, NY.*

Introduction: Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of nephrotic syndrome and has been seen associated with COVID-19 infection and vaccination. FSGS is a pattern of glomerular injury seen at the glomerular visceral epithelial cell (the podocyte) level and defined as the presence of sclerosis in parts of some glomeruli. Appropriate therapy is based on the classification of the FSGS lesion into either primary, secondary, genetic, or undeterminate forms.

Case Description: A 72-year-old male with history of DVT and PE (on Xarelto) presented to the hospital with progressively worsening diffuse body swelling, dyspnea, and fatigue developing over the course of one month in the setting of prior COVID-19 infection 4 weeks ago. Initial vital signs on arrival revealed elevated BP 172/103 but otherwise the patient was hemodynamically stable. Initial chest x-ray revealed trace right and left small pleural effusions. Initial BMP was notable for creatinine elevated at 1.84, BUN 66, and K 5.9. Urinalysis revealed >500 protein, 2+ blood. Initial urine studies were suspicious for nephrotic syndrome given total urine protein >4000 g/dL and urine creatinine 376.6 mg/dL. Further work-up during admission revealed negative SPEP and UPEP, normal C2 and C3, negative p-ANCA and c-ANCA, and nonreactive hepatitis A, B, and C antibodies. Renal ultrasound was negative. Kidney biopsy revealed FSGS tip variant; patchy acute tubular injury; minimal tubular atrophy and interstitial fibrosis; mild arterio- and arteriosclerosis. Following results of kidney biopsy, the patient was started on high dose steroids.

Discussion: It is important to recognize post-COVID Renal Syndrome to raise awareness for conditions such as FSGS which are steroid responsive to further assist in diagnosing renal complications earlier in patients who present with nephrotic range proteinuria post COVID infection. Literature review has revealed cases on tip-variant FSGS being one of the most frequent FSGS variants associated with COVID vaccination and post-COVID infection. By understanding the pathophysiological mechanisms underlying renal involvement post-COVID, including direct viral invasion, immune-mediated injury, and endothelial dysfunction, this report highlights the complexity of renal manifestations in the context of viral infections.

PUB355

A Multicenter Study on the Related Factors of Pathological Classification in Patients with Primary IgA Nephropathy

Sijie Yang, Zhu Zhou. *First Affiliated Hospital of Kunming Medical University, Kunming, China.*

Background: The aim of this study is to analyze the correlation between pathological staging and clinical data of patients with primary IgA nephropathy. To find the influencing factors of pathologic staging in patients with IgA nephropathy. It is expected to intervene these factors at an early stage to provide clinical ideas for controlling renal pathological damage.

Methods: Pathological typing and clinical data of a total of 204 patients diagnosed with IgA nephropathy by renal puncture biopsy and meeting the inclusion and exclusion criteria were collected from eight centers, including the First Affiliated Hospital of Kunming Medical University, Dali Prefecture People's Hospital, Baoshan City People's Hospital, Wulumu People's Hospital, Pu'er People's Hospital, the First People's Hospital of Anning City, Yuxi City People's Hospital, and the Armed Police Force General Hospital of Yunnan Province. The correlation between the pathologic typing and clinical data of these patients was analyzed.

Results: 1.High urinary PH (P=0.040), high 24-hour urinary protein (P=0.013), and history of alcohol consumption (P=0.016) are independent risk factors for endocapillary hypercellularity (E) lesions. 2.High blood total bilirubin (P=0.013) and high blood C4 (P=0.004) are protective factors for segmental glomerulosclerosis (S) lesions. High blood urea nitrogen (P=0.006) is an independent risk factor for them. 3.High blood urea nitrogen (P=0.044) and high blood creatinine (P<0.001) are independent risk factors for tubular atrophy/interstitial fibrosis (T) lesions. 4.High blood total bilirubin (P=0.046) is a protective factor for cellular or fibrocellular crescents (C) lesions.

Conclusions: 1.High urinary PH, high 24-hour urinary protein, and history of alcohol consumption are independent risk factors in the typing of intracapillary hyperplasia (E). 2.High blood total bilirubin and high blood C4 are protective factors in the typing of segmental glomerulosclerosis(S). High blood urea nitrogen is an independent risk factor for it. 4.High blood urea nitrogen and high blood creatinine are independent risk factors in the typing of tubular atrophy/interstitial fibrosis (T). 5.High blood total bilirubin is a protective factor in the typing of cellular or fibrocellular crescents (C) lesions.

Funding: Government Support - Non-U.S.

PUB356

A Case of Secondary Membranous Nephropathy Caused by Rheumatoid Arthritis Accompanied by Double Positive for Anti-GBM Antibodies and Proteinase 3 (PR3)-ANCA

Saki Kawamori,[1] Hitoshi Suzuki,[1,2] Mingfeng Lee,[1] Yukako Umezawa,[1] Yuya Sasatsuki,[1] Masahiro Muto,[1] Hisatsugu Takahara,[1] Shigeki Tomita,[1] Yusuke Suzuki.[2] [1]*Juntendo Daigaku Igakubu Fuzoku Urayasu Byoin, Urayasu, Japan;* [2]*Juntendo Daigaku Igakubu Daigakuin Igaku Kenkyuka, Bunkyo-ku, Japan.*

Introduction: The underlying mechanism of double positive for ANCA and anti-GBM antibody is unclear. Up to a third of patients with anti-GBM disease are positive for ANCA, mainly with specificity to myeloperoxidase. It is postulated that GBM damage from ANCA-associated vasculitis exposes the antigens which leads to the production of GBM autoantibodies. However, there are no literature that describe the association between membranous nephropathy and dual positive for ANCA and anti-GBM antibody.

Case Description: 71-year-old man was diagnosed with rheumatoid arthritis (RA) due to the appearance of polyarthral pain, synovitis, and a positive anti-CCP antibody at two months ago. Disease modifying anti-rheumatic drugs (DMARDs) and low dose steroid were initiated. Recently, he was referred to our hospital by pointing out of proteinuria. Laboratory data was as follows: eGFR, 29 mL/min/1.73 m^2, anti-GBM antibodies, 143 U/mL, PR3-ANCA, 4.2 U/mL and C-reactive protein, 2.4 mg/dL. Examination of anti-nuclear antibody and anti-double stranded DNA IgG antibody were negative. Urinalysis showed mild proteinuria (0.7 g/gCr) and no microscopic hematuria. No pulmonary lesions were observed. Antiglomerular basement membrane nephritis or ANCA-associated nephritis were suspected, however, pathological analysis of kidney biopsy specimens indicated no crescentic formation and peritubular capillaritis. Meanwhile, spike formation was observed in the glomerular basement membrane by PAM staining, and the fluorescent analysis showed the deposition of granular IgG (IgG1 dominant) and complement 3 on the basement membrane. Electron microscopy showed a wide range of subepithelial electron dense deposits. Glomerular PLA2R1 and THSD7A were negative. Thus, he was diagnosed as secondary membranous nephropathy caused by RA. Intensified treatment of RA resulted in remission of proteinuria.

Discussion: This is the first case of membranous nephropathy with double positive for anti-GBM antibody and PR3-ANCA in patients with RA. Several reports indicated that membranous nephropathy complicated by anti-GBM antibody or PR3-ANCA often progresses renal dysfunction rapidly. Careful observation is necessary for the appearance of vasculitis and pulmonary lesions.

PUB357

Retrospective Analysis of a Large Brazilian Center on Systemic Vasculitis and Evaluation of C3 Levels Behavior

Liliana M. Kassar, Felipe Carvalho Barros Sousa, Karoline W. Silva, José Guilherme R. Gonçalves, Vinícius S. Silveira, Viktoria Woronik, Luis Yu, Cristiane B. Dias, Lectícia Jorge. *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: Systemic small vessel vasculitis are characterized by necrotizing inflammation with little or no deposition of immune complexes. Activation of the alternative complement pathway is part of the disease's pathophysiological mechanism. This study aims to identify the profile of these vasculitis in a large Brazilian center and the behavior of complement levels over time.

Methods: Patients diagnosed with vasculitis between February 2012 and September 2023 were included. The evaluated data included age, sex, creatinine, estimated glomerular filtration rate by CKD-EPI, proteinuria, hematuria, ANCA positivity, serum C3 levels at diagnosis, and the average C3 levels after 6-12 months of follow-up.

Results: 48 patients were diagnosed with vasculitis through biopsies during this period, with 60% being women. The median age was 60 years (14-83), serum creatinine 3.7 mg/dL (SD ± 1.7), eGFR 17 mL/min (7-79), proteinuria 1.43g (0.05-8.4), 96% had hematuria, admissional C3 was 107 (41-174), 38% c-ANCA positive and 43% p-ANCA positive. Chi-square test was conducted to assess the association between serum C3 and the intensity of C3 in renal biopsy (p 0.56). Tukey and Bonferroni tests were performed to evaluate C3 variation during treatment, no statistically significant difference was found (p 0.29).

Conclusions: We couldn't identify changes in the behavior of C3 levels in the present study. The local activation of the alternative complement pathway is well established in ANCA-associated vasculitis, however this could be difficult to identify in the usual laboratory assays. Therefore, identifying patterns of mild changes on systemic C3 levels in patients with vasculitis might be feasible utilizing larger samples.

PUB358

Exostosin-Associated Membranous Nephropathy Secondary to Lupus with Castleman-Like Features

Abdullah Jalal, Atinuke O. Aluko, Dilan A. Patel, Ying M. Chen.
Washington University in St Louis, St Louis, MO.

Introduction: Membranous Nephropathy (MN), an immune-mediated kidney disease characterized by subepithelial immune complex deposition, is caused by circulating autoantibodies targeting podocyte surface antigens. The landmark identification of the M-type phospholipase A2 receptor (PLA2R) as the major podocyte autoantigen has led to a paradigm shift in the diagnosis and management of MN in the past two decades. By utilizing laser microdissection of glomeruli followed by mass spectrometry, more putative podocyte autoantigens have been identified recently. Herein we present a case of MN secondary to systemic lupus erythematosus (SLE) with Castleman Disease (CD)-like features diagnosed on the basis of positive exostosin (EXT) staining on kidney biopsy.

Case Description: 42 year old female with history of PLA2R-negative MN noticed increased foamy urine without other systemic manifestations, including skin rash. Prior secondary MN evaluation was unremarkable except for positive ANA (1:1280). Over 6 months her urine protein to creatinine ratio rose from 1.42 g/g to 4.6 g/g with new hypocomplementemia prompting repeat renal biopsy. Pathology unchanged from previous with exception of scattered mesangial deposits and positive EXT2 staining. Amidst her proteinuria evaluation she developed new right subpectoral lymphadenopathy. PET/CT revealed multiple hypermetabolic lymph nodes (LNs) above and below the diaphragm. Excisional LN biopsy showed reactive follicular hyperplasia with partial vascular proliferation of nodes and onion skinning of follicles concerning for CD, a rare lymphoproliferative disorder. Although high levels of interleukin 2 receptor and vascular endothelial grow factor support the diagnosis of CD, she does not have any clinical manifestations of CD.

Discussion: Our patient received a preliminary diagnosis of CD; however, autoimmune conditions like SLE can resemble CD and must be excluded for precise diagnosis. Adding complexity to the case, the patient's renal pathology was atypical for lupus MN given the lack of full-house immunofluorescence staining, numerous subepithelial electron dense deposits with scattered mesangial deposits. The advent of novel autoantigens like EXT1/2 will aid in accurate and specific MN diagnosis, with significant implications for patient management and targeted treatment.

PUB359

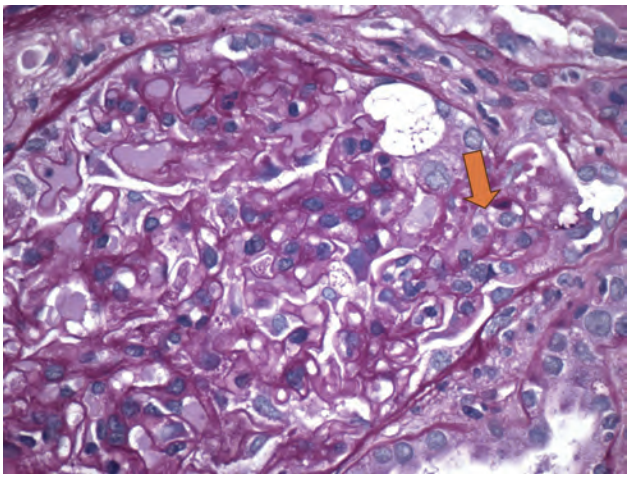
Tip Variant of Focal Segmental Glomerulosclerosis in a Patient with COVID-19

Haya H. Al Suradi,[1,2] Larissa Kruger Gomes,[2] Michael B. Stokes.[3]
[1]Kent Hospital, Warwick, RI; [2]Brown University, Providence, RI; [3]Columbia University, New York, NY.

Introduction: Focal segmental glomerulosclerosis (FSGS) is a clinicopathological syndrome with nephrotic range proteinuria, histology with focal and segmental glomerular sclerosis, and diffuse podocytopathy. FSGS can be classified based on histologic variants into 5 categories, important to recognize for prognostication and treatment options. We present a case of tip variant FSGS with preceding COVID infection.

Case Description: A 72-year-old male with history of provoked DVT and recent COVID infection, he presented with gradually worsening lower limb swelling over the past month. Patient also had bilateral upper limb and abdominal swelling, and exertional dyspnea. On presentation, patient is hypertensive at 172/103, and otherwise hemodynamically stable. Physical examination is notable for bilateral lower and upper limb pitting edema with normal cardiopulmonary exam. CBC is unremarkable. Notable labs showed elevated creatinine at 1.83 mg/dL up from normal baseline 0.98, BUN 66 mg/dL, K 5.9 mmol/L, albumin of 2.1. Due to concern of nephrotic syndrome, urine studies were completed with UPCR 11.07. Additional work-up requested by nephrology included Hba1c, ANCA, HIV, viral hepatitis, SPEP/UPEP & immunofixation, and PLA2R Ab with unremarkable results. Ultimately, the patient underwent renal biopsy showing tip variant FSGS. The patient was started on prednisone 1 mg/kg with improvement in UPCR to 2.71. He has ongoing improvement of proteinuria and symptoms.

Discussion: Tip variant portends the most favorable prognosis with complete remission of FSGS. Our case shows nephrotic range proteinuria after COVID infection that has been described in the literature, although no clear etiology has been found, genetic predisposition has been postulated with viral infections being a second hit. Fortunately, our patient had a favorable response to steroids.



Tip lesion. Endocapillary foam cells (arrow) prolapsing into proximal tubule (*)

PUB360

A Rare Case of Atypical IgA-Mediated Anti-GBM Disease with ANCA-Associated Glomerulonephritis

Kristina K. Nasr, Sean Pickthorn, Nattawat Klomjit. *University of Minnesota Twin Cities, Minneapolis, MN.*

Introduction: Atypical anti-GBM has been used to describe seronegative cases of anti-GBM disease and constitutes up to 10% of anti-GBM cases. Patients can have milder symptoms and atypical pathological findings, such as linear deposition of IgA or IgM. Current conventional assays are unable to detect these classes of immunoglobulin. Approximately 30% of anti-GBM glomerulonephritis (GN) cases have concomitant ANCA GN. However, coexisting atypical anti-GBM and ANCA GN is very rare. We present the first case of seronegative atypical IgA-mediated anti-GM with MPO-ANCA GN.

Case Description: The patient is a 64-year-old male with a history of well-controlled type 2 diabetes. Two months prior, he developed myalgias and unintentional weight loss after a COVID-19 infection. He was diagnosed with polymyalgia rheumatica and treated with prednisone 20 mg/day. Initially, myalgias improved but symptoms recurred when the dose was reduced to 5 mg/day. At a subsequent visit, he endorsed a new cough, and his BP was elevated at 164/94 mmHg. Laboratories showed creatinine (Cr) 2.01 mg/dl, CRP 64.0 mg/l, normal C3 and C4 complement, P-ANCA 1:320, MPO >134.0 U/ml and negative anti-GBM. Monoclonal protein was negative with normal kappa/lambda ratio. Urinalysis showed RBC 17/hpf without RBC casts, UACR 142 mg/g and UPCR 0.39 g/g. Kidney biopsy showed focal necrotizing and crescentic glomerulonephritis in 23% of glomeruli with a vasculitis lesion in one artery and no significant fibrosis. Immunofluorescence showed linear GBM staining for IgA (3+), kappa (1+) and lambda (2+). Overall results were consistent with atypical anti-GBM and ANCA-GN. He was started on methylprednisolone 500 mg x 3 days and plasmapheresis (PLEX) for 5 days until Cr improved (as serologic levels of IgA anti-GBM were unavailable to guide the duration of PLEX). He then started oral cyclophosphamide. At 3-month follow-up, he felt better with improved energy. Cr improved to 1.45 mg/dl. MPO titer decreased to 2.0 U/ml with normal ESR and CRP. UA showed resolution of hematuria.

Discussion: Atypical anti-GBM may present with ANCA-GN. Treatment with cyclophosphamide and PLEX can improve kidney outcomes in these patients.

PUB361

A Curious Case of C3 Glomerulonephritis

Zoheb Backer, Omar H. Maarouf. *Thomas Jefferson University, Philadelphia, PA.*

Introduction: C3 Glomerulopathy(C3G) is a group of rare kidney diseases that is caused by genetic or acquired dysregulation of the alternate complement pathway resulting in predominant C3 deposition in the glomeruli. C3G encompasses two disorders, C3 glomerulonephritis(C3GN) and dense deposit disease. It is a histopathological diagnosis supplemented by low C3 levels. A kidney biopsy is necessary to confirm diagnosis. Currently, there is no high-quality evidence to guide therapy. Here, we present a case of C3GN with normal complements and high ANA titers.

Case Description: A previously healthy 32-year-old presented with dyspnea. Initial physical exam revealed hypertension, hypoxia and peripheral edema. Initial labs showed serum creatinine (SCr) of 1.96 mg/dL, albumin 2.1 g/dL, UA with 3+ protein, 32 RBC/HPF, 66 WBC/HPF. His spot urine protein creatinine ratio (UPCR) was elevated at 5.86 g/g with 24-hour collection yielding 5.4g of protein. Paraproteins were negative. Urine toxicology was negative. Imaging was significant for CXR showing diffuse bilateral

opacities, ECHO with EF of 40%. A renal US showed abnormal echogenicity. Infectious workup was negative for Hepatitis B, Hepatitis C, HIV, COVID-19 and flu. Autoimmune workup was remarkable for positive ANA at a titer of 1:1280 with negative ds-DNA antibody. His C3, C4 levels were normal and ANCA antibodies were negative. A kidney biopsy was obtained that showed C3GN without any crescents. He was placed on a steroid taper following a pulse dose, in addition to mycophenolate mofetil at 500 mg twice daily and uptitrated to 2g daily after one week. SCr trended down to 1 mg/dL, repeat UPCR showed a rapid improvement in proteinuria to 2.3 g/g. He was discharged for outpatient C3 dysregulation workup and follow up.

Discussion: C3G is a rare disease with an incidence of about one in a million. It affects children or young adults. C3 level is typically low, although it can be normal as in our case. ANA was strongly positive signifying possible underlying autoimmune condition triggering his C3GN. C3G is likely more than a single disease entity. With multiple trials ongoing for proximal complement activation blockade, a better understanding of its various presentations and associations along with newer drugs available may help us personalize care to patients and improve outcomes.

PUB362

A Rare Case of Anti-GBM Disease Complicated by Thrombotic Microangiopathy

Samantha J. Itchon, Mehdi Yavari, Yasser Ellaicy, Mirjana Dimitrijevic, Raghavendra Kamath. *Ascension Michigan, Detroit, MI.*

Introduction: Anti-glomerular basement membrane (GBM) disease is a small vessel vasculitis marked by antibodies targeting type IV collagen in the glomerular and alveolar basement membranes. This leads to rapidly progressive glomerulonephritis and/or alveolar hemorrhage. Pulmonary involvement often occurs in patients with factors like smoking, infection, or hydrocarbon exposure. Kidney manifestations typically present as acute injury with proteinuria, nephritic sediment, and hematuria. Thrombotic microangiopathy (TMA) involves thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ damage. We present a case of anti-GBM disease complicated by TMA in a patient with hydrocarbon exposure.

Case Description: A 59-year-old female with chronic obstructive pulmonary disease, hypertension, and cystic kidney disease presented with a two-week history of hematuria, diarrhea, and fatigue. Labs revealed a creatinine level of 10.36, nephrotic range proteinuria, and elevated anti-GBM IgG antibodies. Kidney biopsy showed crescentic glomerulonephritis. The patient developed TMA, requiring multiple blood and platelet transfusions, managed with steroids and plasma exchange. Respiratory distress and hemoptysis necessitated intubation, and bronchoscopy confirmed alveolar hemorrhage. She began immunotherapy with rituximab. Post-extubation, outpatient treatment included plasma exchange, hemodialysis, and steroid tapering.

Discussion: This case highlights the rare occurrence of anti-GBM disease complicated by TMA in a patient with hydrocarbon exposure. Literature indicates TMA often arises during anti-GBM treatment, with poor renal outcomes despite ADAMTS-13 activity above 10% in most cases [1]. Initially presenting with diarrhea, Shiga toxin-induced hemolytic uremic syndrome was unlikely. Clinical improvement with rituximab, steroids, and plasma exchange suggests TMA was a complication of anti-GBM disease, emphasizing the disease's complex immune dysregulation. Works Cited: 1. Nakamura, Yoshihiro, et al. "Clinical Characteristics of Anti-GBM Disease with Thrombotic Microangiopathy: A Case Report and Literature Review." CEN Case Reports, vol. 13, no. 1, 22 May 2023, pp. 37–44, www.ncbi.nlm.nih.gov/pmc/articles/PMC10201029/, https://doi.org/10.1007/s13730-023-00797-4. Accessed 8 May 2024.

PUB363

A Case of Spontaneous Remission of Idiopathic Minimal Change Disease in an Adult

Seshma Ramsawak,[1] Andrea R. Linares,[2] Jagmeet S. Dhingra.[1]
[1]Cleveland Clinic, Cleveland, OH; [2]Cleveland Clinic Florida, Weston, FL.

Introduction: Spontaneous early remission of primary minimal change disease (MCD) in adults is rare (5-10%). To mitigate risks of nephrotic syndrome such as thromboembolic events and infections, early initiation of treatment in adults is recommended. We present a case of complete spontaneous remission of MCD in an elderly adult with conservative management.

Case Description: A 73-year-old female with recently diagnosed hypertension, presented with dyspnea, lower extremity edema and an 8-pound weight gain. Evaluation revealed a serum creatinine of 1.5mg/dL (baseline 0.8 mg/dL) and hypoalbuminemia. Spot urine protein creatinine ratio (UPCR) was 7.28 mg/mg. Initial serological work up including ANA, ANCA, HIV, hepatitis, monoclonal screen and primary membranous testing were negative. No inciting factors including medications or recent illness were identified. A kidney biopsy was performed and showed findings of MCD. Due to the age at diagnosis, an evaluation to exclude underlying malignancy was performed. CT chest abdomen pelvis was unremarkable. Mammogram and gynecologic evaluation were normal and colonoscopy 9 months prior was also normal. The patient was managed with a combination of olmesartan, spironolactone and dapagliflozin, with plan to initiate steroid therapy if she remained nephrotic as patient expressed concerns over side effects associated with steroid use. She was monitored clinically and over the ensuing three months, UPCR improved with conservative therapy and she had complete remission 4 months post- biopsy. Her most recent UPCR was 0.1 mg/mg and creatinine stable at 1.2 mg/dl.

Discussion: The majority of MCD cases achieving spontaneous remission are due to secondary causes. The mainstay of therapy for patients diagnosed with MCD, in addition to supportive measures, is immunosuppressive therapy. The goal is to induce remission thereby minimizing adverse outcomes associated with nephrotic syndrome. Glucocorticoid monotherapy is first line but alternative glucocorticoid sparing options are also available. Treatment with these agents have inherent risk. This case highlights a rare occurrence of spontaneous complete remission of idiopathic MCD in an adult patient. Physicians should be cognizant of the risk versus benefit ratio of immunosuppressive agents, especially in an elderly population.

PUB364

Focal Segmental Glomerulosclerosis after COVID-19 Vaccine: A Case Report and Literature Review

Mehrbod Vakhshoori, Sayna Norouzi, Yan Chen Wongworawat, Amir Abdi Pour. Post-doctoral Scholar Research Program. *Loma Linda University Medical Center, Loma Linda, CA.*

Introduction: We present a case of de novo focal segmental glomerulosclerosis (FSGS) occurring approximately two months after receiving the Moderna COVID-19 vaccine.

Case Description: A 77-year-old man with no personal or family history of kidney disease was admitted with dizziness, anasarca and acute kidney injury. On Admission, blood pressure was high (150/86 mmHg) and lab tests showed elevated serum creatinine (Cr) (1.8 mg/dl with normal baseline Cr), low albumin (2.3 g/dl), and significant proteinuria (urine-protein-to-creatinine ratio of 13.37 g/g). Kidney biopsy revealed complete effacement of podocytes and early-stage FSGS (Figure 1 A&B). Detailed history and workups were negative except for report of receiving Moderna COVID-19 vaccine approximately two months prior. Treatment with prednisone (60 mg/day) was started, leading to complete resolution of proteinuria, normalization of Cr levels and overall symptoms (Figure 1 C&D).

Discussion: This case highlights the significance of maintaining a high level of clinical suspicion for FSGS as a potential complication of COVID-19 vaccines (Table 1). Further studies are still needed to establish causality.

Table 1. Summary of case report studies reported *de novo* FSGS post COVID-19 vaccination

First author, publication year	Age (year)	Sex	Symptoms onset time (days)	Vaccine type, dose	Laboratory data					Treatment
					Time Cr (mg/dl)	Last Cr (mg/dl)	Urine proteinuria	Last proteinuria	Urine albumin (g/gCr)	Last Albumin (g/dl)	
Dormann et al., 2021	20	Female	5	BioNTech/Pfizer, 1st	0.47	Normal (exact value not reported)	UPCR: 1.0-3 g/g	UPCR: 3-5 g/g	2.1 g/dl	2.3 g/dl	Glucocorticoids
Frongillo et al., 2022	24	Female	60	BioNTech/Pfizer, 2nd	NR	NR	NR	NR	NR	NR	Glucocorticoids
Hörtenhuber et al. 2021	42	Female	2	BioNTech/Pfizer, 1st	0.89	0.51	UPCR: 12.8 g/g	UPCR: ~0.91	1.4	4.2	Glucocorticoids, plasma exchange
Jha et al., 2022	21	Male	120	AstraZeneca, 1st	1.04	1.06	UPCR: 21 g/g	UPCR:19.43 g/g	0.9	1.21	Glucocorticoids, plus tacrolimus + plus rituximab
Khan et al. 2022	24	Male	60	Moderna, NR	1.4	NR	9 g	NR	NR	NR	Glucocorticoids, plus Mycophenolate
Liu et al. 2022	29	Male	7	BioNTech/Pfizer, 1st	1.23	1.03	UPCR: 4.83 g/g	UPCR: 8.16 g/g	2.7	4.4	Glucocorticoids
Rajasekhiran et al. 2022	NR	NR	NR	Not specified, 1st	NR	NR	NR	NR	NR	NR	Glucocorticoids
Ray et al. 2022	35	Female	9	AstraZeneca, 2nd	1.9	NR	Urine protein: 2+	NR	1.2	NR	NR
Sirpal et al., 2021	24	Male	21	Moderna, 2nd	NR	NR	24-hour proteinuria: 5.2g	NR	2	2.7	Glucocorticoids
Timmermans et al., 2022	47	Male	>14	BioNTech/Pfizer, 2nd	0.8	NR	Urine protein: 4.5 g/l	NR	2.04	NR	NR
Patient 1	77	Male	60	Moderna, 4th	1.03	0.70	UPCR: 13.39 g/g	UPCR: 4.16 g/g	2.5	2.9	Glucocorticoids

Cr: creatinine, NR: not reported, UPCR: urine protein-to-creatinine ratio

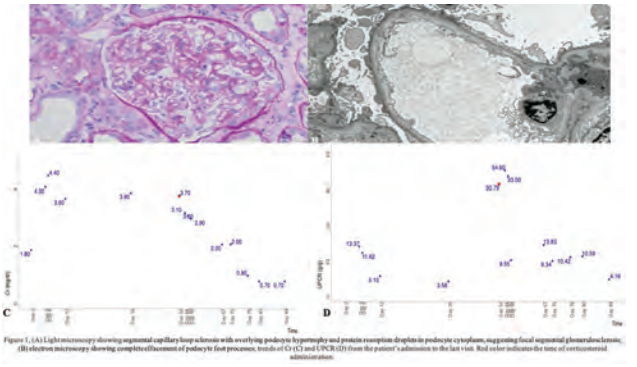


Figure 1. (A) Light microscopy showing segmental capillary loop sclerosis with overlying podocyte hypertrophy and protein reabsorption droplets in podocyte cytoplasm, suggesting focal segmental glomerulosclerosis. (B) electron microscopy showing complete effacement of podocyte foot processes, trends of Cr (C) and UPCR (D) from the patient's admission to the last visit. Red color indicates the time of corticosteroid administration.

PUB365

A Case of Hydralazine-Induced ANCA-Associated Vasculitis

Iskandar Berbari, Mohammad Amin Eshghabadi, Amit K. Rajput. *TriHealth Inc, Cincinnati, OH.*

Introduction: ANCA vasculitis is a systemic autoimmune disease that results in small-vessel inflammation caused by pathogenic autoantibodies directed against proteinase-3 or myeloperoxidase. Hydralazine is a commonly used antihypertensive which is known to precipitate drug-induced lupus. However, it can also cause a drug induced ANCA vasculitis, which presents with a necrotizing and crescentic glomerulonephritis. We present a case of hydralazine induced ANCA vasculitis.

Case Description: A 69-year old female with chronic sinusitis and CKD 3B attributed to HTN, presented for a 3-week history of nausea, vomiting, and poor PO intake. Work up revealed an AKI (Cr 7.8mg/dL from a baseline of 1.6mg/dL), with new onset hematuria, non-nephrotic range proteinuria (UPCR 0.5g), and an elevated ESR. Her antihypertensive regimen included hydralazine, hydrochlorothiazide, and nifedipine. Given concerns for an underlying glomerulonephritis, she underwent a renal biopsy, which showed pauci-immune (ANCA) focal necrotizing and crescentic GN. Anti-histone Ab levels were elevated at 6.1 units and there was dual ANCA positivity (pANCA >1:1280; MPO 254;SP3 49). The patient was started on solumedrol IV for 3 days and transitioned to PO prednisone with a four-month taper. She was also given rituximab 1000mg weekly for two doses, followed by 500mg every four months for maintenance therapy. She initially had improvement in her renal function (Cr 5mg/dL), but unfortunately was re-admitted due to worsening renal function and required initiation of hemodialysis.

Discussion: As clinicians, we should always be cognizant of the potential harms of the medications we prescribe. Hydralazine can cause a drug-induced ANCA vasculitis associated with elevated ANA, anti-histone antibodies, and dual ANCA positivity (MPO-ANCA and anti-PR3 antibodies) in one third of patients. Patients who develop these complications should immediately stop the offending agent and receive immunosuppressive therapy. Unfortunately, a literature review shows that 27% of patients progress to ESRD despite treatment, demonstrating the importance of early diagnosis. Nephrologists should keep a high level of suspicion when patients on these medications present with worsening renal function and a nephritic syndrome.

PUB366

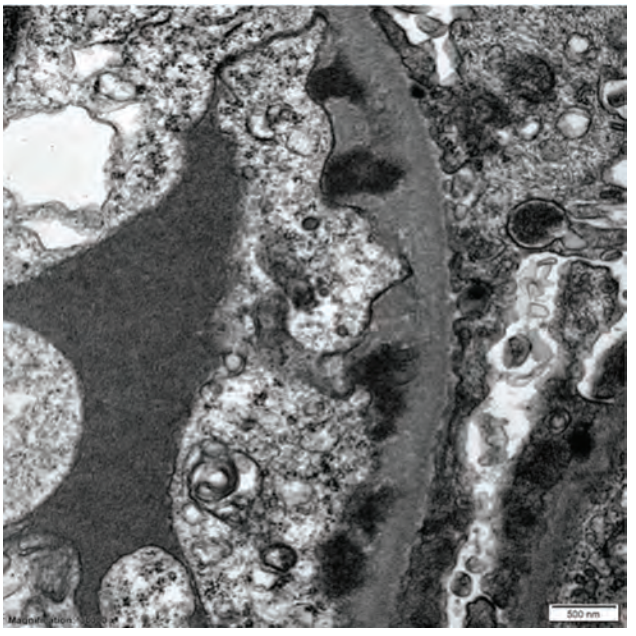
C3 Glomerulonephritis in Intravenous (IV) Drug Use

Divya Ravi. *Unity Hospital, Rochester, NY.*

Introduction: C3 glomerulopathy includes a group of disorders where there is dysregulation and overactive stimulation of the alternative pathway of the complement system. The common triggers are monoclonal antibodies, autoimmune diseases and infections. We present a case of C3 glomerulonephritis in a patient with IV drug use.

Case Description: A 30 year old male patient with past medical history of asthma, GERD, anxiety and IV fentanyl and cocaine use presented with complaints of intermittent fever, chills and dark urine since 3 months. He was found to be febrile with mild left sided CVA tenderness. He had AKI with creatinine elevated to 2.4 from baseline of 1.0-1.2. Urinalysis showed RBC casts along with moderate proteinuria. Patient was started on vancomycin and cefepime while awaiting cultures. Glomerulonephritis workup was sent and revealed elevated C3 and CRP but negative auto-immune panel. Protein-creatinine ratio was 9310 mg/day. Blood cultures were negative and TEE was negative for vegetations. He was started on suboxone for opiate use disorder. Patient underwent a kidney biopsy which showed diffuse active intracapillary proliferation glomerulonephritis with C3 containing immune complex deposits. The patient was started on lisinopril and offered immunosuppressive therapy but wanted to complete COVID19 vaccination first. On follow up, he was found to have improvement of proteinuria (97 mg/day) and creatinine returned back to his baseline (1.0-1.2)

Discussion: Previous cases of C3 glomerunephritis have been associated in other pro-inflammatory states like auto-immune flares and infections. In our patient, while infection and autoimmune disease was ruled out, we found presence of C3 deposits and glomerular disease which improved with cessation of IV drug use. This raises an important question of whether transient bacteremia or an inflammatory state brought on by IV drug use can induce C3 glomerulopathy.



PUB367

Clinical Utility of the International Risk-Prediction Tool in Japanese Patients with IgA Nephropathy

Sayumi Kawamura, Yukihiro Wada, Keiichi Matsuzaki, Tetsuya Abe, Akizumi Tsutsumi, Yasuo Takeuchi. *Kitasato Daigaku Igakubu, Sagamihara, Japan.*

Background: Recently, International Risk-Prediction Tool (IRPT) in IgA nephropathy (IgAN) has been reported. However, the utility of IRPT remains completely unelucidated. We attempted to validate the value of IRPT in Japanese patients with IgAN.

Methods: We retrospectively reviewed 145 patients (male 51.0%) with IgAN in our hospital since 2014. We collected clinical indicators, pathology, and treatment options during the observation period (mean 37 months). According to IRPT score, patients were divided into quartiles from prognostic score (PS) I to IV group. The study outcomes were end-stage kidney disease (ESKD) and estimated glomerular filtration rate (eGFR) 30% reduction.

Results: At baseline, mean proteinuria and eGFR were 1.5 g/gCr and 60.0 ml/min/1.73 m^2, respectively. 40.0% of patients received corticosteroid, and 36.6% underwent tonsillectomy plus corticosteroid pulse therapy (TSP). Baseline proteinuria and eGFR reduction were remarkable as IRPT-score increased (Proteinuria: PS I/II/III/IV, 0.5/1.1/1.6/3.0 g/gCr, $p<0.001$; eGFR: PS I/II/III/IV, 81.7/63.9/55.1/38.6 ml/min/1.73 m^2, $p<0.001$). Degree of M1, E1, S1, and C1-2 lesions in the Oxford classification were comparable among the study groups, whereas tubulointerstitial (T1-2) lesions were significant in PS-III or PS-IV compared to PS-I or PS-II groups. Rate of patients receiving steroid therapy or TSP were comparable between the study groups. The proportion of patients who were treated with RAS inhibitor is significantly higher in PS-III or IV than in PS-I or II group. During a follow-up period, 5.6% and 15.9% of patients progressed to the ESKD and eGFR 30% reduction. Incidence of high and super high risk for dialysis proposed from Japanese Society of Nephrology (JSN) was significantly higher in PS-III or IV group compared to PS-I or II group (PS-I/II/III/IV, 2.7/33.3/61.0/83.2%, $p<0.001$). On Kaplan-Meier analysis, the cumulative renal survival rate to developing the ESKD or eGFR 30% reduction was significantly higher in group PS-IV than in group PS-I to II ($p<0.001$). However, there was no significant difference in the renal outcomes between PS I to III groups.

Conclusions: IRPT is useful to assess disease severity and predict renal prognosis as well as JSN-classification. Especially, IRPT might be helpful to evaluate mid stage or advanced Japanese patients with IgAN.

PUB368

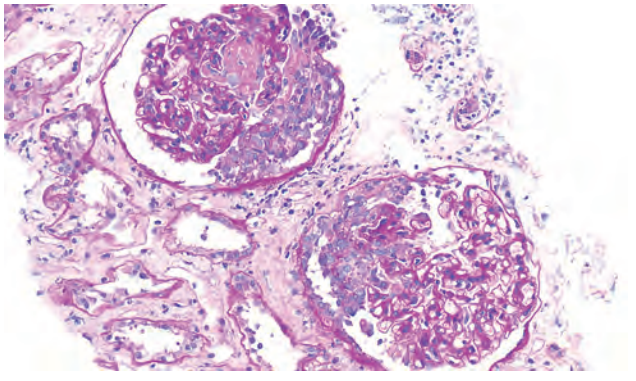
A Novel Therapeutic Approach to ANCA-Negative Crescentic IgA Nephropathy

Maximillian Bzdula, Jordan L. Barry, Marco Khiella, Mohammed Sadique Hussain, Mohammed S. Hammad, Tauseef A. Sarguroh. *Franciscan Health Inc, Mishawaka, IN.*

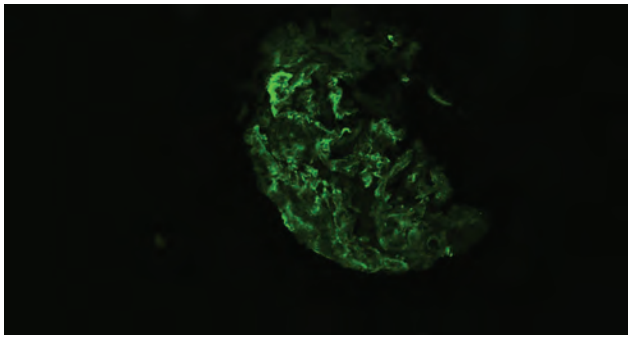
Introduction: IgA nephropathy is an autoimmune disorder caused by dysregulation of mucosal IgA immunoglobulins that results in deposition within the renal mesangium with variable presentations. Rarely, IgA nephropathy may lead to rapidly progressive glomerulonephritis(RPGN), characterized by gross hematuria, edema, hypertension, and acute kidney injury.

Case Description: A 48 year old male with a past medical history of hypertension and type 2 diabetes mellitus presented with two days of painless, gross hematuria. Initial labs showed creatinine(Cr) 2.5mg/dl, eGFR 31ml/min, INR 1.3, platelets 253, and a urinalysis significant for moderate blood, >100 urine RBCs, and urine protein to creatinine ratio(UPCR) of 6.7. During hospitalization, the patient's Cr peaked at 3.0, ASO >2,100, negative ANCA, and Kappa/Lambda ratio of 2.01. Kidney biopsy revealed IgA nephropathy with focal crescents. The Oxford classification score was M0 E1 S0 T1 C2. In the hospital, the patient was treated with 1g IV methylprednisolone for 3 days, followed by oral prednisone for 1 week and losartan upon discharge. On follow-up, the patient was transitioned to empagliflozin, budesonide, and sparsentan with improvement of Cr to 1.9mg/dl and UPCR of 0.5.

Discussion: IgA nephropathy may lead to RPGN with poor prognosis and a 5-year progression to renal failure of 70%. The case presented as an IgA nephropathy with RPGN and negative ANCA titers. While standard treatment includes steroids and cyclophosphamide or mycophenolate mofetil, the prognosis remains poor. There is sparse research on alternative modalities. We desribe a positive outcome with the triad of novel therapies of sparsentan, budesonide and empagliflozin.



Cellular crescents and necrosis



IgA

PUB369

Pauci-Immune Glomerulonephritis (GN) in a Patient with Scleroderma: Importance of Urine Sediment and Kidney Biopsy

Stephanie S. Pavlovich, Nina Mehta, Vanessa Moreno, Shannon L. Murphy. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Introduction: Up to 10% of patients with systemic sclerosis can develop scleroderma renal crisis (SRC), a syndrome of malignant hypertension, microangiopathic hemolytic anemia, and progressive AKI. Kidney biopsy is not typically done in patients who have classic symptoms, especially with anti-RNA Polymerase III antibodies; however, biopsy can be critical in establishing a diagnosis in patients who have unusual disease features. We present a case of pauci-immune ANCA-associated GN in a patient with systemic sclerosis and a high pre-test probability for SRC.

Case Description: A 49-year-old man with untreated scleroderma presented with hemoptysis, fatigue, one week of right upper quadrant abdominal pain, and mild unintentional weight loss over three months. On physical exam, he was afebrile, with a blood pressure of 147/84 mmHg, and had bilateral sclerodactyly, skin tightness, and clear lung fields. Laboratory data showed creatinine of 2.9 mg/dL (from 0.62 mg/dL three months prior), urine protein creatinine ratio of 3.5 g/g, and hemoglobin of 5.1 g/dL with iron deficiency. A CT chest showed extensive bilateral lower lobe airspace opacities with air bronchograms. Bronchoscopy was not consistent with diffuse alveolar hemorrhage. Given worsening renal function (peak creatinine of 4.24 mg/dL) and a positive RNA Polymerase III antibody, a presumptive diagnosis of SRC with superimposed pneumonia was made and he was treated with enalapril and antibiotics. However, his clinic course worsened with recurrent, severe hemoptysis. Urine sediment showed dysmorphic red blood cells, red blood cell casts, and granular casts, prompting kidney biopsy, which showed diffuse pauci-immune crescentic GN. MPO-ANCA titer was positive. Enalapril was stopped and he was treated with IV solumedrol, cyclophosphamide, and plasma exchange with resolution of hemoptysis and improvement of creatinine to 2.33 mg/dL on discharge.

Discussion: This case illustrates the importance of examining urine sediment to guide biopsy in patients with suspected SRC, particularly if atypical features are present, and if an alternate diagnosis may require steroid therapy. We add to a body of cases reporting MPO-ANCA vasculitis in patients with systemic sclerosis, potentially identifying an association between scleroderma and small vessel vasculitis.

PUB370

A Case of Spontaneous Resolution of Secondary Membranous Nephropathy

Nimrah H. Imam, Joseph Tasch. *Fairfield Medical Center, Lancaster, OH.*

Introduction: Membranous nephropathy (MN) is the most common cause of adult-onset nephropathy. Primary MN is characterized by the presence of antibodies to the M-type phospholipase A2 receptor (PLA 2R). The most common causes of secondary MN are infectious, autoimmune disorders, or neoplasms. Here we present a unique case of secondary MN that spontaneously resolved despite progressive primary colon malignancy.

Case Description: An 82-year-old gentleman with no known history of kidney diseases presented to clinic with proteinuria. The patient's only complaints included leg swelling and unintentional weight loss of 15-20 pounds over the previous 3 years. He was noted to have a microalbumin to creatinine ratio of 5000 mg/g. One year prior, his urine microalbumin to creatinine ratio was 57 mg/g. His serum creatinine had been 0.9 mg/dL. Work up for his proteinuria included an SPEP with immunofixation, serum free light chains, hepatitis B/C serologies, anti-PLA 2R antibody, and rheumatoid factor which were all unremarkable. Kidney biopsy revealed membranous glomerulonephritis with several globally sclerosed glomeruli. IgG subclass staining showed IgG1 predominance and absent IgG4 and PLA 2R, suggestive of secondary membranous glomerulonephritis. On electron microscopy, the immune type deposits showed a mixture of electron dance and loosened deposits suggestive of prolonged disease course. Approximately 40 to 50% of the glomeruli in the biopsy were already sclerosed globally. The patient was later evaluated for several malignancies with a CT chest/abdomen/pelvis with IV contrast and a PSA screen. Patient had been recommended to undergo a screening colonoscopy but refused. He was found to have a large right sided pulmonary nodule. Patient had undergone a bronchoscopy in 2022 with pathology showing no evidence of malignant cells. A follow up PET scan showed low level activity. Patient remained on therapy with losartan, HCTZ, and spironolactone. Several months later, the patient's microalbumin to creatinine ratio trended to 361 mg/g, which persisted for months. He was later diagnosed via repeat colonoscopy to have primary colon cancer but proteinuria had already resolved at that time.

Discussion: Resolution of secondary membranous nephropathy is not known to resolve without treatment of the suspected cause.

PUB371

Crescentic Glomerulonephritis with Dual Autoantibody Positivity in the Setting of Polycystic Kidney Disease

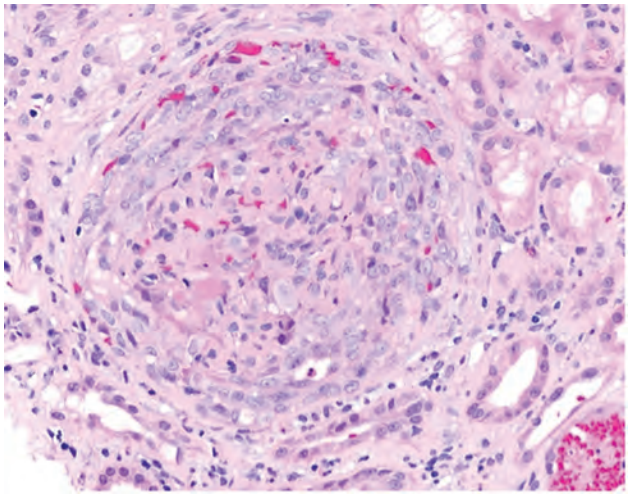
Lonnie Luu, Laura C. Luu, Yogesh Sanghvi, Guruswamy Ramamurthy. *HCA Healthcare Inc, Nashville, TN.*

Introduction: This is the sole documented case of a patient with PCKD diagnosed with dual seropositive glomerulonephritis for anti-GBM and ANCA.

Case Description: 71 yo M with PMH of PCKD, CKD3A, BPH, DM2, HTN, HLD, and PAD presented to the ED with bilateral leg edema, SOB, lightheadedness, fatigue, decreased urine production, flank pain and cough with hemoptysis. UA revealed elevated urine protein and a large amount of urine blood. Renal US showed multiple bilateral renal cysts. Chest CT showed bilateral infiltrates and pleural effusions. Pt developed anuria and metabolic acidosis and was started on HD. Pt was also dyspneic and hypoxic necessitating Bipap. Immunology was positivite for p-ANCA. Pt was started on IV methylprednisone

1g/day x 3 days then prednisone 40mg PO/day, rituximab 1g/day with plasmapheresis and MWF HD. Additional serology results were also positive for anti-GBM ab. Following a confirmatory renal biopsy, the patient was switched to cyclophosphamide 100mg/day. Anti-GBM ab levels began to downtrend from 8.0 to 5.1 with Rituximab treatment. Anti-GBM levels further decreased to 2.7 on Cyclophosphamide. During admission, he developed hemoptysis and hypoxia 2/2 to alveolar hemorrhage which required intubation. Pt suffered from multiple episodes of pulmonary effusions and hemothorax secondary to recurrent alveolar hemorrhage. Finally, he contracted COVID pneumonia during his admission. Ultimately, his POA decided to withdraw care due to poor prognosis, and unfortunately, pt expired shortly after extubation.

Discussion: This case presents a unique diagnositic challenge as pt's baseline CKD3A 2/2 PCKD along with his initial clinical presentation was consistent with AKI leading to volume overload and pulmonary edema. Furthermore, GN rarely presents with PCKD with only 3 cases seen based on a literature review which may lead to cases such as this being easily overlooked.



PUB372

Type B Insulin Resistance Syndrome Associated with Lupus Nephritis

Muhammad Qasim,[1] Kanza Mustafa,[2] Ann R. Finke,[1] Tyler Sims,[1] Sayee Sundar Alagusundaramoorthy,[1] Taha Ayach,[1] Virgilius Cornea.[1] *[1]University of Kentucky College of Medicine, Lexington, KY; [2]Yusra Medical and Dental College, Islamabad, Pakistan.*

Introduction: Type B insulin resistance(TBIR) syndrome is a rare disease entity caused by IgG polyclonal Ab that antagonize the insulin receptor. Systematic review in 2020, 119 cases described in literature. 50% have coexisting autoimmune disorder. 35% associated with systematic lupus erythematosus (SLE).

Case Description: 33 yo M with no past medical history presented with 1 week of hematuria, fatigue, polyuria, polydipsia admitted for new onset diabetes. Progressed to DKA with uncontrolled hyperglycemia. Labs C3 34, C4 7, CRP 15.5 mg/L, ANA Speckled 1:1280. RF <10. Anti DNA Screen 1:80, Smith Ab IgG 61, SmRNP Ab IgG 143. Glutamate Decarboxylase Ab <5. Insulin Ab 0.4 [0-0.4 U/mL]. HgbA1c 8.6%. Developed AKI Stage III; Cr 0.74 mg/dL on admit, peaked at 2.49 mg/dL. Renal biopsy (Fig 1):mesangial proliferative lupus nephritis(LN). Revised lupus classification, Class II. NIH protocol initiated, 40mg dexamethasone. Required up to 215,000 U Insulin/day, then dexamethasone held for hyperglycemia. Initiated cyclophosphamide(CYC)15 mg/kg. Plasmapheresis(PLEX) initiated as per NIH recommendations. Rituximab administered with PLEX session 3 and 6. 11 days of PO CYC + 2nd pulse dose dexamethasone. Relapsed 1 month after PLEX with persistent hyperglycemia and required 5 more PLEX sessions. He had 2 more courses of dexamethasone. 5 months post diagnosis remains stable on outpatient management: U500 Insulin 1400 U 3x daily.

Discussion: We present the complexity of managing a rare case of TBIR syndrome coalesced with overlapping SLE/LN and the challenges related to pulse dose steroids, plasmapheresis and immunosuppressants. Renal biopsy of LN strengthened our suspicion for TBIRS. Inability to tolerate glucocorticoids due to hyperglycemia. Treatment also consisted of CYC, PLEX, Rituximab. AKI resolved with CYC, PLEX x 6, 1 dose of Rituximab and dexamethasone pulse.

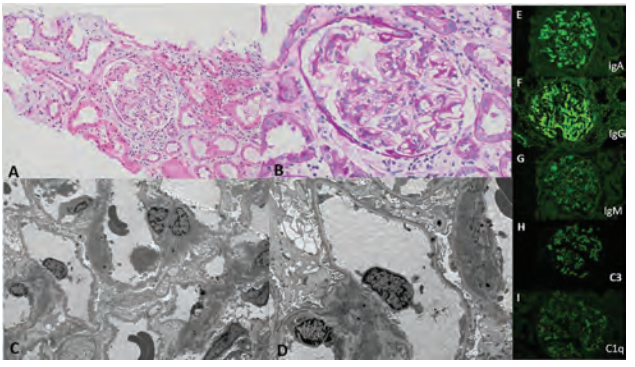


Fig 1 A-H&E ATN, B-PAS Hypercellular mesangium, C-D: EM Mesangial + Subendothelial dense deposit. E-I: IF Full House

PUB373

Glucocorticoid Monotherapy as Induction Therapy for Class 1/2 Lupus Nephritis Is Associated with Higher Renal Relapse and Poorer Kidney Outcomes

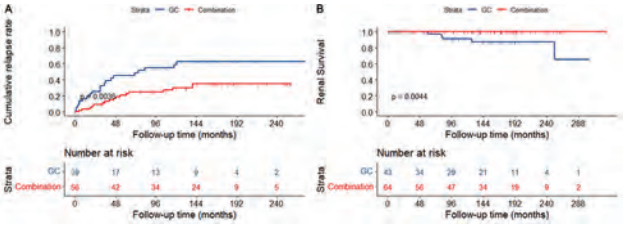
Xiuzhi Jia, Huajing Peng, Rui H. Tang, Xi Xia, Wei Chen. *The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: For class I/II lupus nephritis (LN), the efficacy of immunosuppressive therapy is less clear.

Methods: A total of 128 patients with first biopsy-proven class I/II LN were included and divided into glucocorticoid alone induction therapy (GC monotherapy) group and GC in combination with other immunosuppressant induction therapy (combination therapy) group according to treatment regimens for induction therapy. The rates of remission, relapse, end-stage renal disease (ESRD), and risk factors related to the outcomes were analyzed.

Results: During the median follow-up of 94 (IQR 30–169) months, all the 96 patients achieved remission. Renal relapse occurred in 37 cases (38.9%), of which 20 (51.3%) were in GC monotherapy group and 17 (30.4%) were in combination therapy group. Kaplan-Meier curve showed that the cumulative renal relapse rate in the GC monotherapy group was much higher than that in the combination group (p = 0.0036). GC monotherapy was significantly associated with higher renal relapse (hazard ratio (HR) = 2.526, 95% confidence interval (CI) 1.211–5.267, p = 0.013). Multivariate cox regression analyses showed that partial remission (HR = 4.073, 95% CI 1.760–9.425, p = 0.001) and GC monotherapy (HR = 2.502, 95% CI 1.145–5.466, p = 0.021) were independent risk factors for class I/II LN renal relapse. The median follow-up time with ESRD as the endpoint was 151 (IQR 76–193) months. At the end of follow-up, 5 (4.7%) patients developed ESRD, all of whom were in GC monotherapy group. The 10-year, 15-year, 20-year and 25-year renal survival rates for class I/II lupus nephritis were 99%, 95%, 95%, and 90%, respectively, with GC monotherapy group had significantly poorer long-term renal outcomes (91.7% vs 100%, 87% vs 100%, 87% vs 100%, 65% vs 100%, P=0.010).

Conclusions: Patients with class I/II LN treated with glucocorticoid induction therapy alone have higher renal relapse rate and poor long-term renal prognosis. Prospective randomized controlled trial studies with large samples are necessary to further explore the clinical benefits of combination therapy in the treatment of class I/II LN.



PUB374

Complement 3 Glomerulopathy and Subsequent Atypical Hemolytic Uremic Syndrome

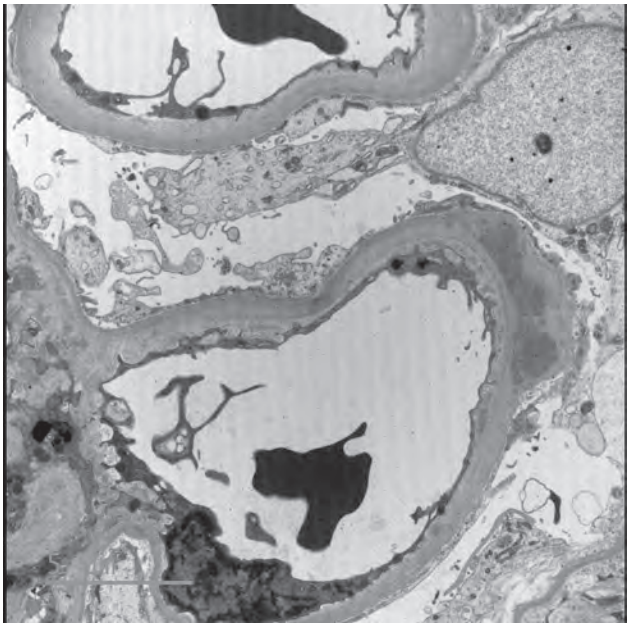
Christian Nguyen,[1] Brendan Schmidt,[1] Ramyashree R. Nyalakonda,[2] Morgan G. Fairweather,[1] Ihsan Housini,[1] Obiajulu Kanu.[3] *[1]Texas Health Harris Methodist Hospital Fort Worth, Fort Worth, TX; [2]University of North Texas Health Science Center, Fort Worth, TX; [3]UNC Health, Chapel Hill, NC.*

Introduction: Complement 3 glomerulopathy (C3G) is a collection of rare renal diseases that can be driven by genetic anomalies or, more commonly, acquired protein dysfunction that results in C3 deposition into the renal tissues. We present the case of an

80-year-old female with prior concerns of renal cell carcinoma that developed rapidly progressive renal dysfunction, progressing to dialysis and subsequently diagnosed with C3 glomerulonephritis (C3GN). Treatment was initiated with pulse-dose methylprednisolone, mycophenolate mofetil (MMF), and eculizumab – a novel treatment regimen relying on the augmentation of steroid and MMF treatment with eculizumab rather than transitioning therapy to eculizumab alone as previously described in severe cases of C3G. Interestingly, our patient later developed atypical hemolytic uremic syndrome (aHUS).

Case Description: An 80-year-old female with a medical history of diastolic heart failure and chronic kidney disease stage 3a returned to the emergency room after a previous admission for a complicated UTI. Her new complaints were shortness of breath, 20lbs of weight gain and productive cough.

Discussion: C3G is characterized by the deposition of C3 complement within the renal tissues due to a dysregulation of the C3 complement activation pathway. Another recently described phenomenon, aHUS, is also posited to be due to dysfunction of the alternate pathway of complement activation. While individually each syndrome is considered rare, the lack of literature may be due to limited reporting as opposed to non-occurrence coinciding with the novelty and relatively recent characterization of each disease process. This report adds to the growing literature describing the clinical course, diagnosis and treatment of C3G as well as C3G in relation to aHUS.



Ultrastructural study shows subepithelial and rare subendothelial deposits.

PUB375

Impact of SARS-CoV-2 Vaccination and/or COVID-19 in the Clinical Course of Patients with IgA Nephropathy

Sophia Lionaki,[1,2] Angeliki Sardeli,[1] Smaragdi Marinaki,[2,5] Dimitra Gkalitsiou,[3] Kriki Pelagia,[4] Minas Karagiannis,[1] Konstantia Kantartzi,[4] Georgios Moustakas,[3] Marios Papasotiriou,[6] Eirini Grapsa,[2] Stylianos A. Panagoutsos.[4]
[1]Panepistemiako Geniko Nosokomeio Attikon, Athens, Greece; [2]Ethniko kai Kapodistriako Panepistemio Athenon, Athens, Greece; [3]Geniko Nosokomeio Athenon Giorgos Gennematas, Athens, Greece; [4]Demokriteio Panepistemio Thrakes, Komotini, Greece; [5]Laiko General Hospital, Athens, Greece; [6]Panepistemio Patron, Patra, Greece.

Background: To explore the impact, if any, of SARS-CoV-2 vaccination and/or COVID-19 in the disease course of patients with IgA nephropathy (IgAN).

Methods: This is a multicenter, retrospective study of patients with biopsy-proven IgAN, who were vaccinated against SARS-CoV-2 or were infected or both. Patients with ESKD prior to vaccination or infection were excluded. Adverse effects of vaccination, doses administered, immunosuppressive therapy and outcome of glomerular disease, clinical picture of infection, need for hospitalization and outcome of infection were recorded.

Results: Included patients (N=51) with IgAN were 46.5(±16.58) years old and 30 (58.8%) were males. The time interval from IgAN diagnosis was 80.27 (±71.5) and 41(80.4%) were vaccinated within 65.9 (±77.7) months from the diagnostic kidney biopsy with 3 (±0.75) doses while 19.8% of patients were on immunosuppressive therapy at the time of vaccination. 14.6% of patients reported systemic and 26.8% local side effects from vaccination. In total, 37(72.5%) patients were infected of whom 72.9% had been vaccinated. 85.3% of patients had symptoms at the time of testing for SARS-CoV-2. One patient was hospitalized and all had complete recovery. One patient (2.7%) experienced recurrence of IgAN within 3.5 months after infection.

Conclusions: In this study, SARS-CoV-2 vaccination was shown safe for patients with IgAN while it was associated with an uncomplicated outcome of the related infection.

PUB376

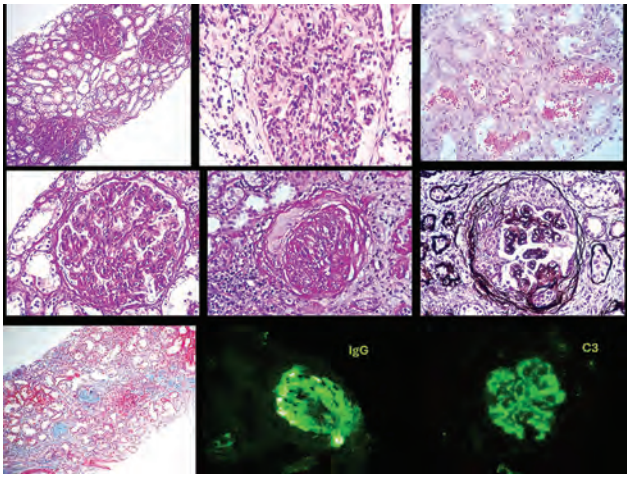
Postinfectious Glomerulonephritis Secondary to Pathological Puerperium

Guillermo Navarro Blackaller,[1,2] Rebeca L. Ornelas Ruvalcaba,[1,2] Jonathan Chavez,[1,2] Guillermo Garcia-Garcia,[1,2] Jose S. Cabrera Aguilar,[1,2] Jenifer M. Langarica López,[1,2] Ramon Medina,[1,2] Maria de la Luz Alcantar Vallin,[1,2] Jorge L. Padilla Armas,[1,2] Alexa N. Oseguera Gonzalez,[1,2] César Murguía Soto.[1,2]
[1]Universidad de Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico.

Introduction: Post-infectious glomerulonephritis (PIGN) is a disease with nephritic syndrome with decreased complement usually secondary to an infection of the skin or throat by beta-hemolytic streptococcus, histopathologically with endocapillary proliferation, C3 deposits at the level of the capillary and mesangial wall, IgG-positive IF and subepithelial immune complex deposits.

Case Description: A 22-year-old woman, with type 1 diabetes mellitus for 12 years, with a pregnancy of 38 weeks gestation, presented an infection of the site of cesarean section infection at 3 weeks, with previous treatment with clindamycin and cephalotin. Blood cultures with S. epidermidis and acute kidney injury KDIGO 3 (Cr 5.1mg/dl), hematuria (80% acanthocytes), proteinuria (580mg/day) and hypertension. Complement 15 mg/dL (normal 79 – 152) and normal C4, ANAs, ANCAs, HIV-HCV-HBV negative, albumin 2.78 g/dl., Procalcitonin 5 ng/ml (<0.5 ng/ml), requiring vasopressor amines, hemodialysis, and antibiotic therapy was escalated to meropenem. Renal biopsy: Postinfectious glomerulonephritis (23 glomeruli with cell crescents, pattern with extracapillary proliferation, mesangial proliferation, endocapillary hypercellularity, double contours. IF: IgG (+++), C3 (++), diffuse granular pattern). At one month with a 50% decrease in proteinuria, normal complement, no hematuria, Cr.s 1.9mg/dl, no hemodialysis required.

Discussion: Treatment is based on treating the infection with antibiotics and the current evidence in RCTs shows no benefit from steroid use, however no persistently low C3 rule out C3 glomerulopathy



PUB377

Syphilis as a Cause of Secondary Membranous Nephropathy

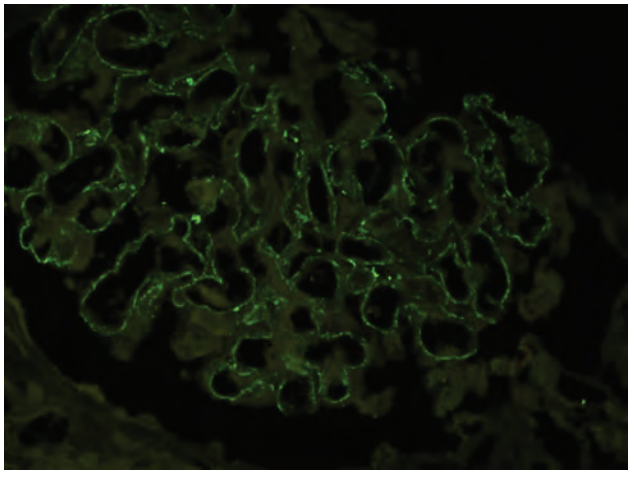
Rogelio Maya-Quinta,[1] Adolfo Del Bosque-Aguirre,[1] Fanny Y. Henriquez,[1] Mariana G. Garcia Zubizar,[1] Kamil Sardarli.[2] *[1]Tecnologico de Monterrey Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico; [2]University of California San Diego, La Jolla, CA.*

Introduction: Membranous nephropathy (MN) can arise from secondary and congenital syphilis. In these cases, immunofluorescence microscopy demonstrates the presence of treponemal antigens within the glomeruli, indicating direct antigen involvement and a immunological response against these within the kidney. Effective treatment of syphilis can lead to the resolution of MN without commonly used immunosuppressive medications.

Case Description: 50-year-old male with no medical history presents with progressive lower extremity and genital edema for 4 weeks. Labs reported creatinine 0.8 mg/dl, albumin 1.1 mg/dl, cholesterol 282 mg/dl, UA with 3+ protein, and a 24-hour urine protein of 43.92 g. He was given single 500 mg dose of methylprednisolone IV due to suspicion of a primary MN. Subsequently, the patient presented a rash characterized by erythematous macules on the palms and soles, as well as non-painful ulcers with

erythematous base and irregular borders in the genitalia. Additional labs showed normal complement levels, negative ANCA panel, negative ANAs, negative anti-PLA2R, negative HBsAg and anti-HCv, negative HIV, negative QuantiFERON and a positive VDRL (1:16) with reactive FTA-ABS. A renal biopsy was performed and reported histopathologic characteristics of MN with sclerosing scarring segmental lesions and treponemal antigen deposits. Benzathine penicillin G was given once a week for three consecutive weeks. The patient had a favorable response with partial reduction of the edema and proteinuria; therefore, he was discharged. However, due to persisting residual edema an additional course with dicloxacillin was given, resulting in complete resolution of symptoms and illness remission.

Discussion: In patients with unexplained glomerulonephritis or proteinuria, syphilis should be considered as a possible cause. Accurate diagnosis and prompt treatment can resolve kidney issues without immunosuppressants.



Glomerulus with treponemal antigen deposits

PUB378

A Rare Coexistence: Minimal Change Disease and Guillain-Barre Syndrome in a Patient with Polysubstance Abuse

Adam W. Tsen. *The University of Texas Medical Branch at Galveston, Galveston, TX.*

Introduction: Minimal Change Disease (MCD) and Guillain-Barre Syndrome (GBS) are distinct clinical entities with unique pathophysiological mechanisms. MCD, characterized by nephrotic syndrome and podocyte effacement on renal biopsy, is commonly associated with autoimmune disorders and certain medications. GBS, on the other hand, is an acute autoimmune neuropathy leading to ascending motor weakness and areflexia. Here, we present a rare case of concurrent MCD and GBS in a patient with a history of polysubstance abuse.

Case Description: A 50-year-old female with a past medical history of heart failure with reduced ejection fraction (HFrEF), polysubstance abuse, and untreated hypothyroidism presented with worsening shortness of breath, vomiting, and hyperbilirubinemia. Evaluation revealed acute kidney injury, likely exacerbated by congestive heart failure, and bilateral tibial axonal motor neuropathy consistent with GBS. Further investigations confirmed a diagnosis of MCD based on renal biopsy findings.

Discussion: The coexistence of MCD and GBS in this patient highlights the importance of considering multiple etiologies in individuals with complex medical histories, particularly those with a history of polysubstance abuse. The underlying mechanisms linking these two conditions remain unclear but warrant further investigation. Management requires a multidisciplinary approach, addressing both renal and neurological manifestations to optimize patient outcomes.

PUB379

A Decade of Biopsy-Proven Kidney Diseases: Temporal Trends and Clinical Correlates from a Single Tertiary Center in Saudi Arabia, 2013-2022

Sultan Al Dalbhi,[1] Manal E. Alotaibi.[2] *[1]Prince Sultan Military Medical City, Riyadh, Saudi Arabia; [2]Umm Al-Qura University, Makkah, Saudi Arabia.*

Background: Kidney biopsy is the gold standard for diagnosing glomerular diseases. Large-scale epidemiologic studies describing the prevalence of kidney diseases are limited. This study aims to determine the spectrum of biopsy-proven kidney disease at a tertiary center; Prince Sultan Military Center in Saudi Arabia over ten years

Methods: This cross-sectional observational study analyzed data from 1027 patients who underwent kidney biopsies from 2013 to 2022. We included all patients with native kidney biopsies, excluding transplant and donor biopsies. The data included demographic and clinical characteristics stratified by year, age, sex, and diagnosis to determine epidemiologic trends. Temporal trends in biopsy diagnoses were analyzed using time-series methods to determine changes in diagnosis frequencies over the past decade. Associations between biopsy diagnoses and clinical characteristics (age, gender, BMI, co-morbidities, transplant status) were evaluated using multivariate logistic regression models. Outcomes and treatment responses for the most common biopsy diagnoses were assessed, focusing on diseases with significant prevalence changes over time.

Results: The study included 1027 patients. The median age was 55 years with a nearly equal distribution of male and female patients. The most common biopsy diagnoses were focal segmental glomerulonephritis (FSGS) 14.6% and diabetic nephropathy 13.6%, followed by IgA nephropathy 9.7% and lupus nephritis 8.8%. The COVID-19 pandemic led to a reduction in the number of biopsies performed, but the distribution of diagnoses remained relatively stable.

Conclusions: This study catalogs the spectrum of biopsy-proven kidney diseases over ten years. These findings highlight the need for a standardized national kidney biopsy registry to enhance glomerular disease research.

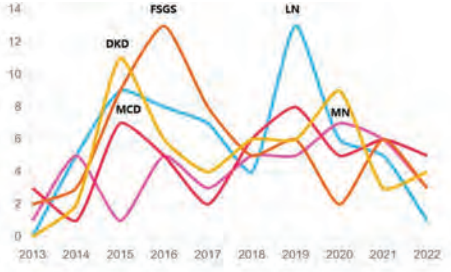


Figure: Temporal Trends in Biopsy Diagnoses (2013-2022)

DKD Diabetic Kidney Disease DKD/Diabetic Nephropathy **FSGS** Focal Segmental Glomerulosclerosis **MCD** Minimal Change Disease **MN** Membranous Nephrology **LN** Lupus Nephritis

PUB380

C3 Glomerulonephritis, Rare Association with Multiple Myeloma: A Case Report

Leonel P. Román López,[1] Virgilia Soto,[2] Octavio R. Garcia-Flores.[1] *[1]Hospital Juarez de Mexico, Mexico City, Mexico; [2]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico.*

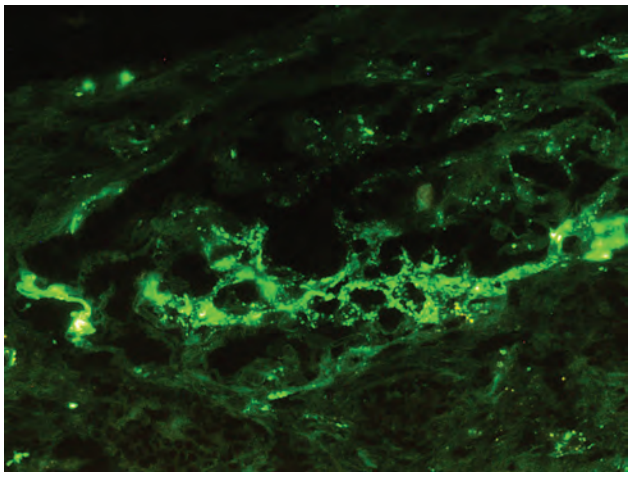
Introduction: In C3 glomerulonephritis, a monoclonal protein can cause kidney damage indirectly. Acting as an autoantibody, the protein cannot be detected in kidney biopsy, which promotes deregulation of the alternative pathway of the complement system.

Case Description: 43-year-old male with a history of abused substances. Beginning current condition of bromuria for 8 years, with remission and exacerbation. The presence of bromuria increases, during realitation of laboratory evidence of deteriorating function kidney and proteinuria in subnephrotic rank, electrophoresis urine presence of predominant kapa chains and igg, as well as a bone marrow aspiration is carried out with a predominance of >20% plasma cells, diagnostic multiple myeloma, renal biopsy diagnosis of C3 nephropathy.

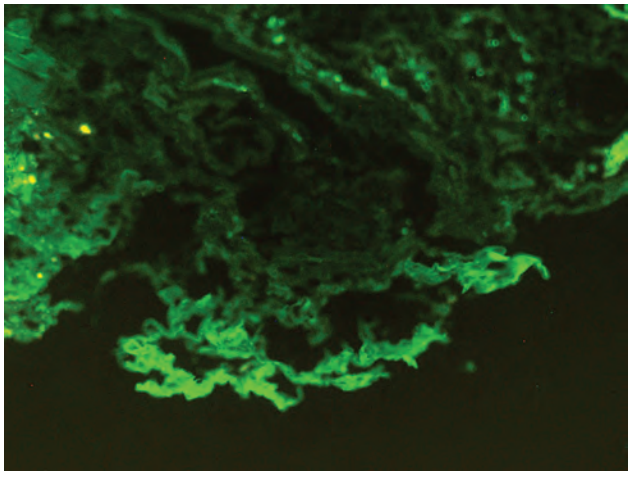
Discussion: There are few cases of C3 nephropathy associated with multiple myeloma. The pathophysiology remains unknown, however, in the presence of C3 nephropathy it is required to search intentionally for multiple myeloma. More studies are required to denote whether treatment directed at the neoplasia reduces kidney injury. In this case it was not a satisfactory answer.

Labs

DATE	URINARY PROTEIN	ALBUMINURIA	CREATININE	URINARY SEDIMENT	GLOBULINS	TOTAL SERUM PROTEINS	RELATION ALB/GLOB	IGG
24.04.23			2.86 MG/DL	NOT ACTIVY	6.3	10.6	0.68	
15.07.23			4.67 MG/DL	NOT ACTIVY	6.14	10.5	0.72	
31.07.23	1.305 GR/24HRS	34.9		NOT ACTIVY	6.3	10.8	0.71	
21.08.23	0.9 GR/24HRS		2.65 MG/DL	NOT ACTIVY	4.1	8.1	0.5	3340



Immunofluorescense, with presense deposit inmunocomplex with intersticion.



Immunofluorescence, not present a reaction for chain kappa.

PUB381

A Case of Rapidly Progressive Nephrotic-Range Proteinuria in a Patient with Purpuric Rash

Dean Mellas, Xueguang (Gary) Chen. *Southern Illinois University School of Medicine, Springfield, IL.*

Introduction: IgA Vasculitis (IgAV) [formerly known as Henoch-Schonlein Purpura] is a systemic vasculitis involving IgA deposition in small vessels within various tissue types including the skin, joints, GI tract, and kidneys. It is often accompanied by a tetrad of signs/symptoms including palpable purpura, arthralgia, abdominal pain, and kidney disease.

Case Description: A 77-year-old male with purpuric skin rash and skin biopsy-proven IgA vasculitis was referred by his dermatologist to the nephrology clinic after having found an acute kidney injury (serum creatinine: 1.5) along with hematuria and rapidly progressing proteinuria. Random total protein/creatinine ratio was 3.11 g/g, and 24-hour urine collection showed total protein 4.4 g. Renal biopsy was obtained showing Crescentic IgA Nephropathy. The patient was urgently admitted to the hospital and treated with pulse dose Methylprednisolone along with Cyclophosphamide. His kidney disease and proteinuria during his hospital stay stabilized on the immunosuppressive treatment, and he was discharged home one week later. Follow up in the nephrology clinic after 3 months of oral steroids showed stabilization of kidney function and proteinuria with creatinine level 1.4 mg/dL and urine protein/creatinine ratio 0.66 g/g.

Discussion: IgA Vasculitis is not common among the adult population. The kidney involvement in IgA Vasculitis (termed IgAV nephritis) is more prevalent among adults than children, and long-term kidney prognosis tends to be worse in adults. Many patients present with only mild hematuria and proteinuria that is self-limited, but some patients may present with nephrotic range proteinuria. This case demonstrated the importance of close nephrology follow up in adults with new diagnosis of IgA Vasculitic rash as the initiation of immunosuppression can prevent the progression of nephrotic range proteinuria.

PUB382

Crescentic IgA Nephropathy: Levamisole-Induced?

Zeyad J. Rifai, Heather Rowe, Nirali B. Ramani. *Southern Illinois University School of Medicine, Springfield, IL.*

Introduction: Immunoglobulin A (IgA) nephropathy is the most common primary glomerulonephritis (GN) worldwide and results from galactose- deficient IgA1 deposition within mesangial cells triggering an autoimmune response. Less than 10% of cases present as rapidly progressive GN. Levamisole is a cocaine adulterant, classically associated with ANCA vasculitis, that has a variable pattern of immunologic disturbance of renal significance.

Case Description: A 58-year- old female with a history of IV drug-use induced hepatitis C, with a negative viral load for two years following glecaprevir-pibrentasvir therapy, presented to the hospital with one month of intermittent hematuria, vague abdominal discomfort, malaise, and bilateral lower extremity worsening large violaceous plaques with early signs of ulceration. She admitted to frequent cocaine use and heavy NSAID usage for her abdominal discomfort and malaise but was unable to quantify either substance. Serum creatinine was at her baseline of 1.0 mg/dL, however, her urine protein creatinine ratio was 25 mg/mg with 219 RBC/HPF. Serologic, antiphospholipid, celiac and hepatitis workup were completely unremarkable. There was significant concern for ANCA negative levamisole induced vasculitis in the setting of cocaine usage versus NSAID induced glomerulonephritis. A renal biopsy was obtained revealing mesangial staining for IgA, IgM, C3 with diffuse mesangial hypercellularity, with 77% of glomeruli with fibrocellular crescents. This represented an Oxford classification of M1, E0, S0, T0, C2. The patient was discharged on losartan, moderate dose prednisone and cyclophosphamide. Outpatient follow-up with notable improvement in proteinuria and hematuria, she currently has preserved renal function with a creatinine of 1.0 mg/dL.

Discussion: This unusual presentation of possible levamisole induced crescentic IgA nephropathy (cIgAN) is confounded by the possibility of superimposed ANCA negative levamisole induced vasculitis as the underlying mechanism for the crescentic glomerular injury. There is no literature on levamisole induced cIgAN, we aim to share the first potential association between levamisole and development of cIgAN based on histologic findings. Alternatively, the cIgAN may be the outcome of hepatotoxicity resu from the resolved hepatitis C infection, however the patient's presentation and the timeline is more suggestive of a levamisole induced process.

PUB383

ANCA-Associated Vasculitis with Atypical Findings of Renal Medullary Angiitis

Heather Rowe, Zeyad J. Rifai, Nirali B. Ramani. *Southern Illinois University School of Medicine, Springfield, IL.*

Introduction: Renal medullary angiitis is a poorly understood marker of systemic vasculitis that is frequently mistaken for acute interstitial nephritis due to the presence of neutrophils on microscopy. Medullary angiitis and the associated systemic vasculitis are rarely documented in the literature.

Case Description: A 71-year-old male presented with constitutional symptoms of malaise, unintentional weight loss, decreased appetite, and worsening renal function. Urinalysis revealed 310 RBCs/high-powered field and a serum creatinine of 3.7 mg/dL. Comprehensive serologic workup revealed an antineutrophil complement antibody titer of 1:640 and proteinase-3 antibody positivity. Given the severity of his constitutional symptoms and the overt suspicion for ANCA vasculitis, the patient was started on prednisone 60mg daily and underwent renal biopsy. Light microscopy showed pauci-immune focal necrotizing crescentic glomerulonephritis with severe medullary angiitis characterized by lymphocytic inflammation and scattered eosinophils surrounding the vasa recta and mild interstitial fibrosis and tubular atrophy. Immunofluorescence confirmed the pauci immune ANCA associated type, while electron microscopy revealed nonspecific mild podocyte effacement. The patient underwent induction with rituximab and was discharged with scheduled maintenance doses of rituximab. The patient continues to follow up with nephrology for his chronic kidney disease (new baseline serum creatinine 1.96 mg/dL).

Discussion: The impressive serologic findings despite vague constitutional symptoms without a rash are an exceedingly rare presentation of this poorly understood diagnosis. We emphasize the necessity of achieving complete immunologic resolution, evidenced by negative serologic markers, via rituximab, to prevent further neutrophil-induced endothelial cell activation and vascular damage. Establishing a standardized guideline for this subset of ANCA vasculitis cases concentrated on serial titer monitoring is an area of interest.

PUB384

Crystalline Nephropathy: A Hidden Complication of Bariatric Surgery

Aakash Padodara, Katelyn Kaufman, Carlos A. Fernandez Bojanini, Gabriel A. Valle. *University of Miami Health System, Miami, FL.*

Introduction: Oxalate nephropathy (ON) is an uncommon etiology of kidney disease characterized by the accumulation of calcium oxalate crystals in the renal parenchyma. It is a pleomorphic disorder which can present as Acute or Chronic Kidney injury and frequently progresses to end stage renal disease. Although the exact prevalence of this condition is unknown, ON was identified in 1% of 2265 consecutive kidney biopsies and it is often associated with specific conditions such as primary and enteric hyperoxalurias or ethylene glycol toxicity.

Case Description: A 74-year-old male with type 2 diabetes, heart failure with preserved exection fraction, atrial fibrillation, CVA, and chronic kidney disease 3b and morbid obesity s/p remote Roux-en-Y gastric bypass (RNYGB) was noted to develop rapidly progressive deterioration of his kidney function following an episode of Herpes Zoster infection treated with Valacyclovir. After 6 weeks of conservative management his eGFR declined to 8 mL/min/1.73m^2 and was associated with insidious uremic symptoms necessitating hospitalization for initiation of dialysis. A kidney biopsy showed diffuse severe epithelial cell injury with features consistent with ON, diabetic glomerulosclerosis, Class IIa, moderate interstitial fibrosis, 18% global glomerular sclerosis and arteriosclerosis.

Discussion: The mechanism of ON in gastric bypass surgery, specifically jejunoileal bypass and RYGB surgery, encompasses increased dietary oxalate availability as undigested fatty acids bind to intraluminal calcium in the small intestine leaving a large load of unbound oxalate to be absorbed in the colon. Subsequent hyperoxaluria and the formation of calcium oxalate crystals within the tubules and renal parenchyma cause tubular obstruction, interstitial inflammation and scarring. ON remains largely an unsuspected diagnosis, is progressive in nature and has a poor prognosis. Clinicians should recognize the potential risks of this hyper absorptive complication of RYGB in patients who develop renal dysfunction and institute measures to forestall the progression of this disorder.

PUB385

Unveiling the Hidden Culprit: Glomerulonephritis and Hand Lesions Leading to Infective Endocarditis

Mohammed Alshehri,[1,2] Ali A. Abdi,[3] Hussain M. Al mosa.[2] *[1]King Khalid University College of Medicine, Abha, Saudi Arabia; [2]Aseer Central Hospital, Abha, Saudi Arabia; [3]Fakeeh Care, Jeddah, Saudi Arabia.*

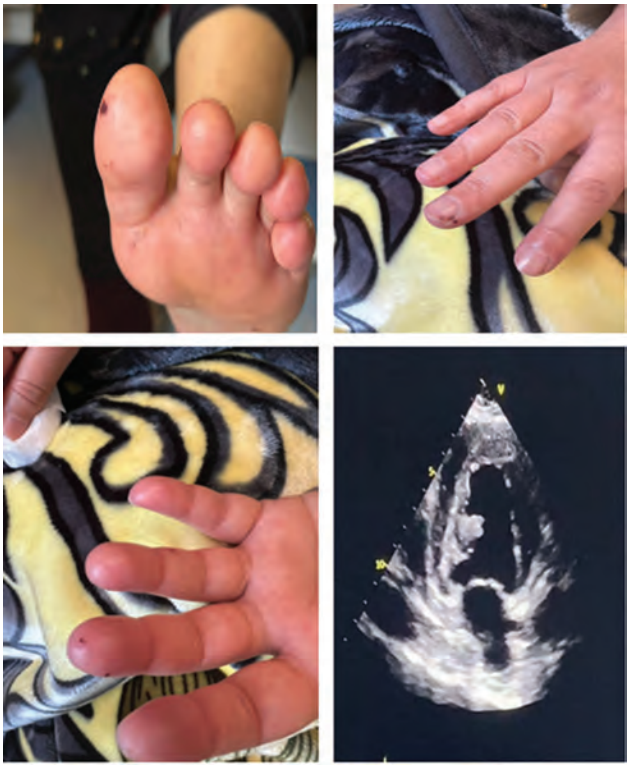
Introduction: We present a case of Rapidly Progressive Glomerulonephritis associated with Staphylococcus aureus mitral valve infective endocarditis (IE). The patient developed lesions on the palms and soles, which led to the discovery of a large vegetation.

Case Description: A 31-year-old woman with hypertension was advised to go to the ER for high serum creatinine (2.3 mg/dl). Blood pressure was 199/153 mmHg, heart rate 94 bpm, oxygen saturation 99%, and temperature 36.8°C. Urine dipstick showed +3 blood and +2 protein. CBC was unremarkable, but creatinine rose to 4 mg/dl with sub-nephrotic range proteinuria and 10-20 RBCs in urine. Steroid was started, and kidney biopsy was arranged. Immunological workup revealed low C3, with negative ANA, ANCA, hepatitis, and HIV. The biopsy showed significant atrophy, leading to tapering of steroid and dialysis/transplant discussion. Two weeks later, she presented with sepsis, anuria, lethargy, and serum creatinine of 6.2 mg/dl. Exam of her palms and soles revealed Osler's nodes, Janeway lesions, and splinter hemorrhages. She had thrombocytopenia without hemolysis. Blood cultures were positive for MSSA. Echocardiograms showed a sub-mitral vegetation (2.6x1.2 cm). A CT angiogram ruled out renal artery stenosis but detected splenic infarction. The patient remained on dialysis and underwent surgical removal of the vegetation and mitral valve replacement.

Discussion: Subacute IE can present with an indolent course, causing delayed diagnosis. We present a case initially showing nephritis and low C3. Classical signs of microemboli and positive blood cultures led to the diagnosis. Consistently low C3 level suggests clinicians should consider an echocardiogram in cases of unexplained glomerulonephritis.

Summary of kidney biopsy findings

LM	IF	EM
The specimen contains 15 glomeruli; 2 (~13%) are globally sclerosed. +Glomerular ischemia, marked corrigation, focal fibrous obliteration, and thickened Bowman	Staining shows granular nonspecific mesangial C3 (1+), focal segmental IgM (1+), and trace Kappa and Lambda light chains in a sclerotic tuft.	Mesangium shows segmental expansion with increased matrix and segmental capillary obliteration. The GBM is corrugated and thickened, without attenuation, double contouring, or lamellation. The foot processes are effaced over a long segment, and focal microvillous transformation of podocyte cytoplasm is noted. No definite immune/complement dense deposits are identified.



2A&B

PUB386

Beyond the Bowel: A Case of Ulcerative Colitis-Associated Membranous Nephropathy

Nathan Aleger. *Tulane University School of Medicine, New Orleans, LA.*

Introduction: Glomerulonephritis is a rare extraintestinal manifestation of Ulcerative Colitis (UC) and presents clinical challenges in management. We present a case of glomerulonephritis in a 68-year-old male with a history of UC, highlighting the importance of vigilance for extraintestinal manifestations in inflammatory bowel diseases.

Case Description: A 68-year-old male with UC on adalimumab presented with worsening lower extremity edema, dyspnea on exertion, and hematochezia. Laboratory investigations revealed anemia, elevated serum creatinine, and nephrotic range proteinuria. Immunological workup demonstrated positive Anti-Phospholipase A2 receptor IgG. Renal biopsy confirmed Membranous Nephropathy. Treatment initially involved corticosteroids, adalimumab, and lisinopril, with subsequent adjustments including infliximab, losartan, azathioprine, and empagliflozin due to UC flares and renal deterioration. Transition to Ustekinumab led to improved UC symptoms and reduced proteinuria.

Discussion: The association between UC and glomerulonephritis underscores the need for comprehensive screening and monitoring of renal function in UC patients. The positive response to corticosteroid therapy suggests an autoimmune component, necessitating further research into underlying immunological pathways. This case emphasizes the challenges in managing UC-related glomerulonephritis and highlights the importance of multidisciplinary care. Early recognition of extraintestinal manifestations is crucial for optimizing patient outcomes, warranting further studies for better therapeutic strategies.

PUB387

C3 Glomerulopathies: Navigating Diagnostic and Therapeutic Challenges in Anticoagulated Patients

Atousa Jahanshahi, Mauricio A. Pedroza. *Jefferson Einstein Philadelphia Hospital, Philadelphia, PA.*

Introduction: C3 glomerulopathies are rare kidney disorders marked by dysregulated complement pathways, leading to C3 deposition in the glomeruli. They're classified into Dense Deposit Disease (DDD) and C3 glomerulonephritis (C3GN).

Case Description: A 56-year-old male with history of hypertension, mechanical aortic valve replacement on anticoagulation and autoimmune hemolytic anemia, seen initially for elevated creatinine at 2.4, in January 2023, attributed to pigment nephropathy or Coumadin-associated nephropathy given presence of microscopic hematuria; despite

considering glomerular issues, a biopsy was not pursued given overall stable kidney function and anticoagulation. A year later he experienced worsening kidney function, with serum creatinine of 4.1 mg/dL, leading to hospitalization. Laboratory tests revealed persistent proteinuria, hematuria, and low C3 and C4 level. Kidney biopsy showed mesangial and capillary loop C3 deposition, ultrastructural examination showed very rare electro-dense deposits within the mesangium, no deposits within the glomerular basement membrane. Biopsy was complicated by perinephric hematoma requiring transfusion. Treatment with Prednisone and mycophenolate mofetil (MMF) was initiated, and the patient was referred to a glomerular disease center.

Discussion: This case underscores the challenges in treating glomerular diseases, particularly in anticoagulated patients, requiring a thorough, individualized approach. Symptoms include varying degrees of proteinuria, hematuria, low C3 levels, and kidney dysfunction with hypertension. Diagnosis relies on kidney biopsy, with immunofluorescence and electron microscopy aiding differentiation. Further tests may be needed for causative factors and tailor treatment. Treatment, often comprising MMF and glucocorticoids, alongside supportive care.

PUB388

A Case of Membranous-Like Glomerulopathy with Masked IgG-kappa Deposits (MGMID) in an Otherwise Healthy Young Man without Autoimmune Disease

Stephen R. Sammons, Laith Al-Rabadi, Monica P. Revelo Penafiel, Siddhartha Kakani. *University of Utah Health, Salt Lake City, UT.*

Introduction: MGMID is characterized histologically by immunoglobulin deposits that are absent on routine frozen immunofluorescence (IF) but show strong staining for IgG and Kappa when IF is performed on formalin-fixed, paraffin embedded tissue. MGMID is largely seen in young patients with a female predominance and is associated with nonspecific autoimmune serologies and monotypic immunoglobulin deposition without underlying hematologic malignancy.

Case Description: A 27 y/o man with no known past medical history was evaluated for subnephrotic proteinuria found on routine labs. He takes no medications and denies any symptoms. Labs were notable for normal serum creatinine, absence of hematuria, and unrevealing serological workup. Renal biopsy revealed a membranous glomerulopathy pattern with IF showing weak IgM & C3 staining in glomeruli, however IF was performed on a paraffin embedded sample which revealed IgG, Kappa, C3, and C1q staining in glomerular capillary walls, consistent with MGMID pattern.

Discussion: This case of MGMID is unique as the patient is male and lacks features commonly seen in other MGMID patients including hematuria and positive autoimmune serologies. It is vital to consider MGMID when examining cases of glomerular disease with membranous pattern and particularly when only weak C3 staining is detected on IF.

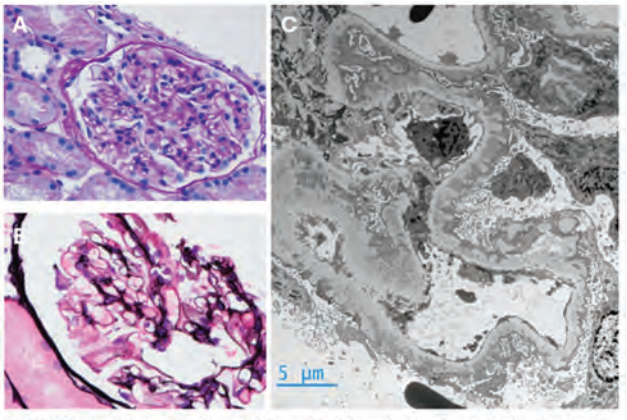


Figure 1. Representative images from renal biopsy showing membranous glomerulopathy changes with A) H&E staining on light microscopy, B) Jones silver stain on light microscopy, and C) electron microscopy

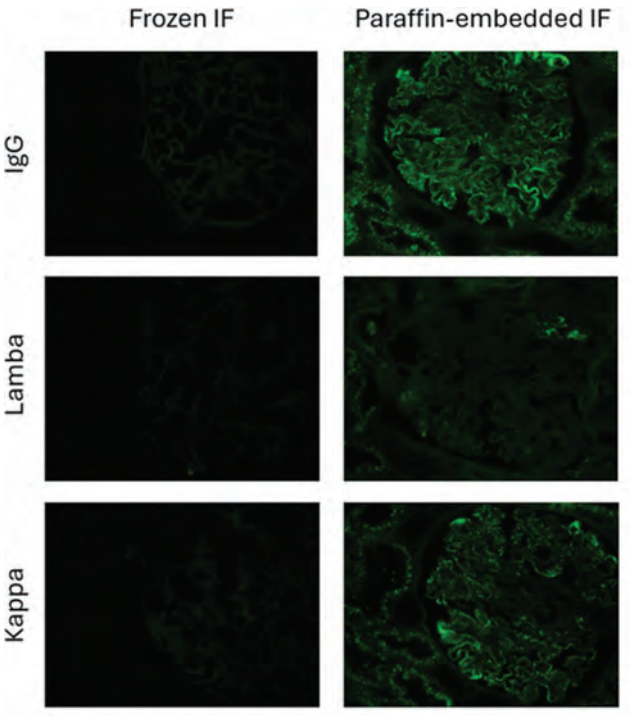


Figure 2. IF images from renal biopsy showing staining of IgG, Lamba, and Kappa on routine frozen IF and on paraffin-embedded IF following Pronase digestion.

PUB389

A Young Woman with Sick Kidney in Biopsy

Giuliani T. Oliveras Maldonado, Fabiola Feliciano Bonilla, Carlos Cortes. *VA Caribbean Healthcare System, San Juan, Puerto Rico.*

Introduction: Rapidly progressive glomerulonephritis is characterized by a rapid decline in renal function over days to weeks with U/A with proteinuria, hematuria, dysmorphic RBC's, and RBC casts. Incidence in the United States is 7 cases per 1 million persons, while in the United Kingdom it is 2 cases per 1 million. Common etiologies include immune complex-mediated RPGN, such as lupus, IgA vasculitis, or C3 glomerulonephritis. Here we present a difficult to treat case of a young woman with rapidly progressive glomerulonephritis.

Case Description: This is a case of a 27-y/o female without medical history, who presented to the emergency room with nausea, vomiting, and diarrhea over two days. Vital signs revealed high blood pressure, tachycardia, hgb 6 g/dL. Labs revealed serum creatinine: 17, BUN: 116, Na:126, K: 5.5, CO2: 13. U/A with protein >500 mg/dL, large blood, microhematuria and urine protein/creatinine 6.6 g/day. After, patient developed pleuritic chest pain, with pericardial effusion and pericardial friction rub. Emergent hemodialysis was started with improvement after 4 days of HD and pulse steroids. Other labs revealed (+) Coombs test, high ferritin and LDH levels, (+) ANA/Ro pattern, low C3, (-) C4, (-) scleroderma AB, (-) anti-RNP AB, (-) anti-Sm AB, (+) anti-Ro AB, (-) anti-dsDNA AB, and (+) lupus anticoagulant. Kidney biopsy confirmed Diffuse Proliferative Lupus Nephritis Class IV. Treatment begun with Hydroxychloroquine, Mycophenolate and high dose steroids. After treatment patient remained dependent on HD.

Discussion: Kidney biopsy is required for LN diagnosis, prognosis, and adequate management. Prognosis of disease worsens with advancing WHO histopathology classes, particularly in LN Class 4, where early initiation of therapy significantly improves disease outcomes. Treatment involves pulse steroids with methylprednisolone for 1-3 days followed by oral prednisone along with either cyclophosphamide (500 mg IV every two weeks for 3 months) or mycophenolate mofetil (2-3 g/day for 6 months). Monitoring disease includes assessments of blood pressure, renal function, proteinuria, urinary sediment, C3/C4 levels, and anti-dsDNA AB measured at least biannually. Earlier disease detection is vital as achieving complete kidney response during treatment provides a 5-year patient and kidney survival of more than 90% vs 69% (patient) and 45% (kidney) for those not achieving complete remission.

PUB390

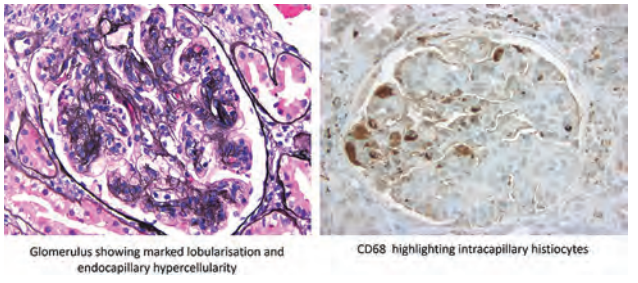
A Rare Case of Histiocytic Glomerulopathy

Ujjwala Murari,[1] Prathap Simhadri,[2] Md. Shahrier Amin,[1] Anthony J. Parravani.[1]
[1]West Virginia University Health Sciences Center, Morgantown, WV; [2]AdventHealth Centra Care, Altamonte Springs, FL.

Introduction: Histiocytic glomerulopathy is a rare kidney disorder characterized by presence of histiocytes within glomeruli leading to damage and dysfunction.

Case Description: 38 year old white female with history of Hypertension and hypothyroidism referred to the CKD Clinic for worsening generalised swelling. Labs showed creatinine of 1.24mg/dl (baseline creatinine a month ago <1) with GFR 56, Electrolytes within normal limit, Hemoglobin 11.6g/dl, platelets 301 K. Urine studies showed nephrotic range proteinuria (10 grams), albumin 4g/dl which prompted to check serological work up include C3-68 and C4-21, rheumatoid factor is <15, ANA, dsDNA and hepatitis B/C were negative. Kappa and lambda chain ratio 1.5 with no M protein. In view of nephrotic proteinuria shared decision was taken to proceed with kidney biopsy. Light microscopy: The glomeruli enlarged, marked endocapillary, mesangial hypercellularity. Many foamy histiocytes are noted within the capillary loops, confirmed by a CD68 immunostaining. Immunofluorescence: There is granular capillary wall staining in the glomeruli for C3 (2+). Electron Microscopy :The loops are distended by lipid laden cells and swollen endothelial cells. No crystals are seen Since the biopsy showed histiocytic glomerulopathy further work up ordered like EBV, Parvovirus, Cytomegalovirus and EBV Ig M and Ig G antibody positive and PCR negative. Ferritin levels were 155, Fibrin 564. Plan is to start on steroids.

Discussion: Histiocytic glomerulopathy is multifactorial disorder with complex interplay of genetics, immunological and environmental factors contributing to its pathogenesis. Further research is needed to elucidate the precise mechanisms underlying the development and progression of this condition. In the above case the possible factor could be EBV (Epstein bar virus) stimulating an immune response leading to accumulation of histiocytes in the kidney



Glomerulus showing marked lobularisation and endocapillary hypercellularity

CD68 highlighting intracapillary histiocytes

PUB391

Decoding the Kidney Conundrum: Dive into the Glomerulonephritis Mystery!

Sonakshi Mirchandani,[1,2] Ana Chavez Velasquez,[1,2] Rahul Paryani.[2] *[1]Texas Health Resources, HEB/Denton, TX; [2]Texas Christian University, Fort Worth, TX.*

Introduction: ANCA-associated glomerulonephritis (GN) comprises over half of RPGN cases, Typically, patients present with acute kidney injury (AKI) and active urinary sediment. Kidney biopsies often reveal necrotizing and crescentic glomerulonephritis with minimal (pauci immune) complex deposits and normal serum complements. Here, we describe a rare case of myeloperoxidase (MPO)-ANCA glomerulonephritis with concurrent immune complex deposition and low complement levels.

Case Description: A 77-year-old female with a medical history of OA, gout, hypertension, and type 2 diabetes presented in 2019 with AKI Cr 2.34 Baseline(0.9-1.1), hematuria (65 RBC), and significant proteinuria (Urine Protein Creatinine UP/C 3g). Biopsy indicated IgA nephropathy with acute crescentic changes. Serology showed MPO pANCA positivity and low C4. Treatment involved IV Solumedrol and cyclophosphamide which were later transitioned to oral immunosuppressants once creatinine stabilised. In 2021, she experienced an intestinal angioedema due to ACE inhibitor(c1 esterase), leading to treatment discontinuation. A relapse occurred in 2022, necessitating oral immunosuppressants. In August 2023, she had another AKI episode(Cr 3.1 UP/C 6g) and underwent a second biopsy, revealing MPO-ANCA mediated focal necrotizing and focal sclerosing glomerulonephritis with concurrent immune complex and crescent formation, IF with granular capillary wall staining for IgG, IgA, IgM, C3, C1Q, kappa and lambda chains and electron Microscopy (EM) with immune complex dense deposits with 90% epithelial foot process effacement. Serology -MPO ANCA positive 1:40. low C4 <2.9, normal complement C3 at 95, Anti ds DNA negative, ANA negative, HIV negative. Treatment involved IV Rituximab and steroids with significant improvement for Cr to 1.7 She developed facial angioedema and AKI, prompting a third biopsy(April 2024) pending results showing improvement with Rituximab and planned avacopan therapy.

Discussion: Immune complex deposition in ANCA-associated vasculitis (AAV) GN is atypical, as AAV is typically "pauci-immune." Recent studies classify AAV/GN into "pauci-immune" (PI) and "immune complex" (IC) groups, with IC deposits potentially exacerbating ANCA effects and role of complement activation causing worsened proteinuria. Early recognition is crucial for preserving renal function, with rituximab and avacopan showing promise in treatment.

PUB392

Hesitating on Receiving Treatment for Rapidly Proliferative Glomerulonephritis

Fabiola Feliciano Bonilla, Gabriel J. Torres-Rivera, Carlos Cortes.
VA Caribbean Healthcare System, San Juan, PR.

Introduction: ANCA vasculitis, is an inflammatory condition affecting small arteries and causing tissue damage in various organs. Renal involvement can lead to ESRD with a high mortality rate. Prevalence ranges from 4.6 to 21.8 cases per 1 million person-years globally. RPGN is a severe renal manifestation, such as nephrotic proteinuria, hypertension, and azotemia. Diagnosis involves serological testing for ANCAs and kidney biopsy. This is a case of RPGN with ANCA(+) in a patient hesitant to receive therapy.

Case Description: A 73 y/o female with PMHx of active smoking, breast cancer, and HTN who was referred to nephrology clinic due to elevated serum creatinine, hematuria, and foamy urine for 4 months. Vital signs with 152/94 mmHg, 78 bpm, and 96% oxygen. Laboratory revealed UPCR of 4.6 grams/day and a creatinine of 2.12 mg/dL from 0.88. Biomarkers showed an ANA titer 1:2560, RF 22, p-ANCA (+), ESR 95; CRP 31.7. Started Solumedrol 500 mg IV every 12 hours for 3 days and a kidney biopsy was done. Differential diagnoses of ANCA vasculitis, lupus nephritis, and C3GN considered. Workup showed MPO (+), C3 138, C4 12, anti-dsDNA(-), anti-Smith (-), and anti-GBM (-). Despite steroid induction, renal function and HTN worsened. Rituximab initiated and she developed sudden headache and blurry vision. MRI revealed an acute ischemic left occipital stroke and an old lacunar infarct. Final biopsy showed immune complex-mediated necrotizing glomerulonephritis with epithelial crescents and interstitial fibrosis. Despite advice to continue therapy, she refused due to perceived association with her acute stroke. Also, denied cyclophosphamide and agreed to receive azathioprine and prednisone. On follow-up, she continued to have severe proteinuria and de novo CHF due to poor compliance with regimen.

Discussion: ANCA glomerulonephritis requires induction and maintenance therapy. Severe cases may require treatment such as methylprednisolone, cyclophosphamide, and plasmapheresis with prednisone. Maintenance therapy, rituximab or azathioprine with prednisone, this is crucial for preventing relapse. Patient involvement in treatment and education is essential for achieving goals and ensuring compliance. Despite advancements, relapse rates remain significant. Close monitoring for treatment resistance and lack of remission enables healthcare providers to optimize outcomes for ANCA GN patients.

PUB393

"A" Is for Adult: Nonclassic Presentation of IgA Vasculitis

Hannah Freibert,[1] Tyler Sims.[2] *[1]University of Kentucky College of Medicine, Lexington, KY; [2]University of Kentucky, Lexington, KY.*

Introduction: IgA vasculitis (IgAV), formerly Henoch-Schönlein purpura, is an immune-mediated disease which most commonly affects children but also occurs in adults. Here we discuss the diagnosis and treatment of an IgAV patient with a history of multiple chronic immune-mediated disorders.

Case Description: A 46-year-old woman was evaluated by nephrology due to proteinuria in the setting of newly diagnosed leukocytoclastic vasculitis (LCV) on skin biopsy. Patient with history of T2DM, autoimmune hemolytic anemia, eosinophilic asthma on mepolizumab, and chronic sinusitis. The patient presented with one month of pruritic rash with blistering on all extremities and polyarthralgia. Skin punch biopsy revealed small-vessel LCV. Steroid taper initially helped, but symptom regression occurred on decreased steroid dose. She was readmitted and noted to have leukocytosis, eosinopenia, 24-hour urine protein 1528 mg/day. Workup including complement levels, ANA, Anti Beta 2 Glycoprotein, cryoglobulins, ANCA and kappa lambda light chain ratio were all negative. A kidney biopsy showed significant 2-3+ IgA granular staining, minimal IgG staining, minimal c3, normal cellularity, minimal tubular atrophy consistent with IgA vasculitis. A 2nd skin biopsy with immunofluorescence also confirmed the diagnosis. She was started on high dose steroid taper and mycophenolate, alongside lisinopril and empagliflozin in the setting of her proteinuria.

Discussion: IgA vasculitis (IgAV) is an immune-mediated disease which most commonly affects children. It is characterized by IgA and complement deposition along with subsequent leukocyte inflammation, forming immune complexes within affected organs. IgAV may result from an immune reaction to infectious triggers. Patients often have a tetrad of findings: palpable purpura without underlying thrombocytopenia or coagulopathy, arthralgias, abdominal pain, and kidney disease. Biopsy of the dermis or kidney is indicated in unusual presentations or with concern for renal involvement. Pursuing a tissue biopsy to make the diagnosis of IgAV in adults is of notable consequence as adults are at increased risk of recurrent disease and IgAV-associated end stage kidney disease.

PUB394

A 30-Year-Old Caucasian Man with Phospholipase A2 Receptor-Associated Primary Membranous Nephropathy

Htun M. Aung,[1] Nidhi Varma.[1,2] *[1]New York City Health and Hospitals Jacobi, Bronx, NY; [2]Albert Einstein College of Medicine, Bronx, NY.*

Introduction: Primary membranous nephropathy (MN) is more commonly seen in Caucasian males over the age of 40 years. We present a unique case of anti-phospholipase A2 receptor (PLA2R)-associated primary MN in a 30-year-old Caucasian male who presented with end-stage kidney disease (ESKD).

Case Description: A 30-year-old Caucasian male patient with a history of chronic kidney disease stage 3B and obesity presented to the emergency department with fatigue, dizziness, and shortness of breath. History was notable for NSAID use a year ago that he had stopped. He denied illicit drug use or contrast exposure. He was not taking any medications at the time of presentation. A chart review revealed that he was evaluated for serum creatinine (sCr) of 2.5 mg/dl and 1.5-gram proteinuria at a different hospital a year ago. Serologies with antinuclear antibody (Ab) and anti-double-stranded DNA Ab were negative. His CKD was thought to be secondary to NSAID use. But, he was lost to follow-up and presented to our hospital a year later with renal failure. He was anuric with a blood pressure of 193/99 mmHg, sCr of 17.4 g/dL, bicarbonate 9.6 mEq/L, venous pH of 7.1, serum albumin of 4.2 g/dL, and creatine phosphokinase of 205 U/L. There was no urinary retention. He was emergently started on hemodialysis for uremic symptoms. Urinalysis showed 4+ protein and RBCs of 13.6 per high-power field. The urine protein-creatinine ratio was 3,960 mg/gm. The right kidney was 12.8 cm, and the left was 13.9 cm on ultrasound. Renal artery stenosis was ruled out. Serological workup was negative except for the PLA2R Ab of 37. He underwent a kidney biopsy which revealed advanced membranous glomerulopathy stage 3 (PLA2R-positive), with extensive global and focal segmental sclerosing features, severe tubular atrophy and interstitial fibrosis with focal acute tubular injury, and severe arteriosclerosis and hyalinosis with focal intimal fibrin. He was not a candidate for immunosuppressive therapy due to his poor renal prognosis. He was continued intermittent hemodialysis on discharge.

Discussion: Anti-PLA2R Ab is highly specific for the diagnosis of primary MN. In a young person with decreased GFR and proteinuria, PLA2R Ab should be considered to help with the diagnosis. Adding PLA2R Ab at the time of his first evaluation could have elucidated the cause of his chronic kidney disease and possibly prevented ESKD.

PUB395

A Rare Late Presentation of Galloway Mowat Syndrome (GAMOS) with Membranous Nephropathy

Sandeep R. Sasidharan, Tahir A. Jatoi, Eugene K. Yeboah, Subodh J. Saggi. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: GAMOS is a rare autosomal recessive disorder initially described in 1968. It is characterized by various neurological and renal abnormalities, with heterogeneous clinical and histopathological phenotypes reported. Renal presentations range from asymptomatic proteinuria to SRNS. Here, we present a unique case of GAMOS diagnosed in an elderly black male with a WDR73 gene deletion.

Case Description: A 64-year-old male with recurrent DVT on AC, UC, HTN, and CKD. He presented with worsening proteinuria due to membranous nephropathy despite being on Tacrolimus and low-dose steroids along with enalapril. He complained of increased urinary frequency with frothing. He was vitally stable and exam unremarkable. Labs were creat of 1.0, alb 3.5, UPCR 2.8, C3 127, C4 41, urinalysis showed protein >500 and rest were negative. The genetic test was negative for APOL1 and positive for WDR73 gene deletion. Biopsy showed 5/25 globally sclerosed glomeruli, with 20% mild to moderate interstitial fibrosis. IF had a granular pattern along capillary walls for 3+ IgG, 1+C3, 2+ kappa, and 2+ lambda light chains, rest negative, including M-type PLA2R. EM showed a markedly irregular contour of BM with subepithelial and intramembranous electron-dense deposits. Diagnosed as membranous glomerulonephritis stage 2-3, PLA2R negative. THSD7A and NELL-1 antigens are pending. Patient was advised Rituximab infusion and will follow up with his nephrologist in Barbados.

Discussion: Homozygous mutations in WDR73 were first implicated in patients with GAMOS in 2014. Recently, via whole exon sequencing and high-throughput exon sequencing, mutations were identified in the Kinase, Endopeptidase, and Other Proteins of Small Size (KEOPS) complex genes responsible for GAMOS. The complex comprises four subunits: LAGE3, OSGEP, TP53RK, and TPRKB. A fifth member of the complex, C14ORF142, has been identified recently. Our patient has a deletion of the WDR73 gene and presents late in life with only proteinuria. The reported life expectancy was between 0.3 to 28 years of age, with most individuals not surviving beyond their teenage years, with the commonest causes of death being nephrotic syndrome or seizures. We aim to contribute to the existing knowledge base by presenting the first known case of GAMOS in an elderly male.

PUB396

Focal Segmental Glomerulosclerosis Associated with Mitochondrial Disease

Jessica M. Segarra, Federico Yandian, Lucia Facal, Jose Boggia, Víctor E. Raggio, Lucia Spangenberg. *Universidad de la Republica Uruguay, Montevideo, Uruguay.*

Introduction: Mitochondrial diseases include myopathy, neurological diseases, and multisystem diseases. The most frequent mutation is DNAt.3243 >G and is associated in 80% with mitochondrial encephalomyopathy syndrome, lactic acidosis and MELAS-like stroke episodes.

Case Description: SF 32 years old, with short stature, HT, DM, hearing loss, dyslipidemia, hypertrophic cardiomyopathy and ESRD-HD, a renal biopsy was performed that describes a FSGS pattern and in the ME 100% pedicellar fusion. With the suggestion of mitochondrial disease, a genetic study is requested that reports the m.3243A>G mutation in the mitochondrial gene MT-TL1 related to MELAS. Exome sequencing detected 2 variants of uncertain significance in the Gene: MYH9. Later he had a similar stroke and maintains prophylaxis with arginine. Family history mother with DM and hearing loss

Discussion: For MELAS there are clinical criteria available at https://www.ncbi.nlm.nih.gov/sites/books/NBK1233/ The case described presents seizures, acute focal lesions on neuroimaging, elevated plasma lactate and a pathogenic variant. The MYH9 gene mutation is related to macrothrombocytopenia and sensorineural deafness, no definitive functional mutation has been identified in this gene. A better clinicopathological approach is needed for an accurate differential diagnosis, allowing clinicians to perform a comprehensive evaluation of the pattern of FSGS injury for the development of appropriate treatments

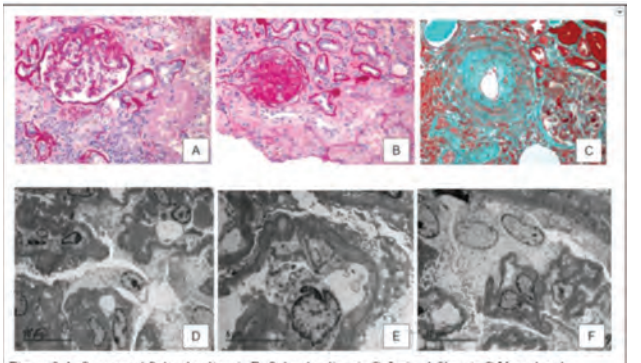


Figura 2 A. Segmental Sclerohyalinosis B. Sclerohyalinosis C. Intimal fibrosis C.Vacuolated podocytes E. Pedicellar fusion 100% F. Lipid inclusions

PUB397

Management of Cardiovascular Risk Factors in Lupus Nephritis

Zohreh Gholizadeh Ghozloujeh, Roy O. Mathew, Amir Abdi Pour, Sayna Norouzi. *Loma Linda University, Loma Linda, CA.*

Background: Patients with Lupus Nephritis (LN) show a higher prevalence of subclinical atherosclerosis and an elevated risk of cardiovascular disease (CVD) compared with healthy individuals. This study aims to examine the differences in the management of hypertension and hyperlipidemia to assess how these variations in treatment impact the prevalence of CVD in patients with LN.

Methods: A retrospective data review of 128 patients over 14 years was performed. Cardiovascular risk factors were defined as the presence of at least one of the following: hyperlipidemia, diabetes, and hypertension. Treatment management was characterized by administering antihypertensive, antidiabetic, and lipid-lowering therapies. The rates of myocardial infarction, stroke, and new diagnoses of peripheral vascular disease were compared between patients with and without cardiovascular risk factors.

Results: Patients with a cardiovascular risk factor (Group A) were older (Median age = 41 vs. 35 years, $p = 0.038$) and had a significantly longer duration of disease (Median = 65 vs. 50 months, $p = 0.025$) than patients without a risk factor (Group B). However, the gender distribution was similar in both groups (Male: 14% vs. 20%, $p = 0.420$). A higher number of patients in Group A received treatment (54.8% vs. 11.4%, $p<0.001$). The comparison between mean systolic blood pressure and laboratory data is shown in Table 1. Myocardial infarction and stroke were observed in 1.1% and 9.7% of patients in Group A, respectively, while no incidents were observed in Group B. Additionally, during management, 6.5% of patients in Group A were newly diagnosed with peripheral vascular disease, whereas no cases were diagnosed in Group B. However, none of these differences in the rate of CVD incidences were statistically significant.

Conclusions: Our results suggest that despite effective management of cardiovascular risk factors in patients with LN, there was a higher rate of cardiovascular events. These findings might be due to the higher age and longer disease duration in our population, although more studies with larger sample sizes are needed to confirm these results.

Median/IQR (25%-75%)	Group A (n=93)	Group B (n=35)	P value
HbA1c (%)	5.65 (5.2-5.9)	5.3 (4.9-5.8)	0.087
LDL (mg/dL)	103 (82-128.6)	103 (82-128.6)	0.503
Systolic BP (mmHg)	117 (107.5-132.6)	115.17 (107.4-126)	0.168

PUB398

Burden of Acute Glomerulonephritis in 204 Countries and Territories, 1990-2021: A Global Benchmarking Analysis

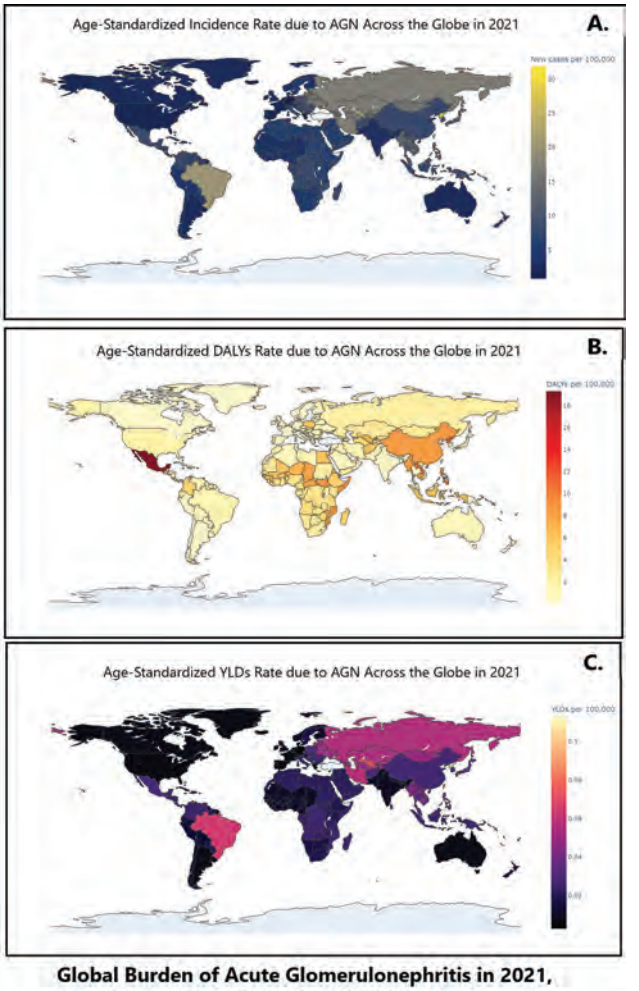
Muhammad Waqas,[1] Adan Irfan,[8] Kushagrita Singh,[2] Shruthi Katam,[3] Ashwinikumar Shandilya,[5] Mohit Lakkimsetti,[4] Vishrant Amin,[6] Juhi Patel,[6] Hardik Desai.[7] *[1]Jinnah Sindh Medical University, Karachi, Pakistan; [2]Government Medical College and Hospital, Chandigarh, Chandigarh, India; [3]Sri Venkateswara Medical College, Tirupati, India; [4]Mamata Medical College, Khammam, India; [5]Rural Medical College, Pravara Institute of Medical Sciences, Ahmednagar, India; [6]Gujarat Medical Education and Research Society Medical College & Hospital Valsad, Valsad, India; [7]Gujarat Adani Institute of Medical Science, Bhuj, India; [8]Shalimar Medical and Dental College, Lahore, Pakistan.*

Background: Acute Glomerulonephritis (AGN) poses an escalating threat to global health, significantly influencing morbidity and mortality rates. This study is the first of its kind to estimate the worldwide burden of AGN over three decades, inclusive of the initial two years of the COVID-19 pandemic, which significantly complicated the management of non-COVID cases.

Methods: Utilizing the GBD 2021 framework, we assessed the incidence, prevalence, mortality, disability-adjusted life years (DALYs), and years lived with disability (YLDs) of AGN globally, stratified by age, sex, year, and location.

Results: The total percentage change (TPC) in prevalence of AGN increased by 2% (95% UI: 2-3%) from 2019-2021. The highest unadjusted incidence rate (IR) was observed in Eastern Europe at 18.21 per 100,000 (95% UI: 15.39-21.43) in 2021, followed by the highest mortality rate (MR) in Central Latin America at 0.44 per 100,000 (95% UI: 0.38-0.51). Nationally, the highest IR was observed in North Korea at 33.51 per 100,000, while the highest MR was recorded in Mexico at 0.74 cases per 100,000 in 2021. The highest incidence count occurred in individuals aged 10-14 years with 52,933 cases, while the highest number of deaths was in those aged 75-79 years at 1,201 in 2021. Males continued to experience a higher burden of AGN over the last three decades.

Conclusions: In 2021, AGN led to 10,760 global deaths, underscoring the need for targeted strategies. Collaboration among public stakeholders, policymakers, and clinicians is essential to enhance detection, management, and reduce its global impact.



Global Burden of Acute Glomerulonephritis in 2021, Age-Standardized Rate (Per 100,000 person years). A: Incidence Rate, B: DALYs Rate, C: YLDs Rate

PUB399

A Rare Presentation of Primary Systemic Lupus Erythematosus (SLE) Tubulointerstitial Nephritis (TIN)

Sandeep R. Sasidharan,[1] Tahir A. Jatoi,[1] Fnu Pariya,[1] Susan Grossman,[2] Marie-Alex Michel.[2] *[1]SUNY Downstate Health Sciences University, New York City, NY; [2]VA New York Harbor Healthcare System, New York, NY.*

Introduction: SLE is an inflammatory disease with systemic effects, and 50% of them present with signs of nephropathy, which involve the parenchyma's glomerular, vascular, and tubular aspects.TIN is a well-recognized feature of lupus nephritis (LN) in 66% of SLE kidney biopsies (KB). SLE TIN is recognized in two forms, i.e., secondary, coexisting with lupus glomerulonephritis, and primary: develops with no or mild glomerular or vascular involvement. We present a rare case of primary SLE TIN in an elderly male.

Case Description: A 76-year-old male with a history of MI with PCI, HTN, COPD, h/o CVA, resolved DM2, h/o AKI d/t prerenal/over diuresis, and BPH. He presented with 3 days of intense red rash on his face and bilateral hands associated with pruritis and facial puffiness. No h/o NSAID use, beta lactams. Hydrochlorothiazide was stopped as a source. However, he continued to have persistent proteinuria > 2 g/d. The lab was positive for ANA 1:320, EBV IgG>600, EBV nuclear antigen 544, ESR 74, Beta2microglobulin 2.7, and IgG 544, but IgG subclasses normal, SPEP showed the faint band in the gamma region, kappa 27.2, lambda 20.4, ratio 1.33, rest of nephritic panel was normal. UPCR started at 1.2g/d and trended up to 4.5g/d. KB showed mild mesangial hypercellularity, moderate foot process effacement, and chronic interstitial nephritis with associated tubular atrophy. Before a skin biopsy, he had another rash episode in sun-exposed areas of bilateral shin with persistent proteinuria. He was started on prednisone with a diagnosis of SLE TIN, with improvement in his renal function and proteinuria.

Discussion: Primary SLE TIN is rare, with only 16 reported cases in the literature. In our patient, the diagnosis was challenging, with differential including AIN, Schnitzler syndrome, dermourticariopathy with renal dysfunction, and IgG4 nephropathy. Finally diagnosed with SLE after fulfilling 4 out of 11 criteria per ACR. To our knowledge, our

patient is the first to have nephrotic range proteinuria, with KB showing both foot process effacement and mesangial hypertrophy. As seen with our patient, primary SLE TIN is known to have a good response to steroids with a good prognosis as seen with our patient. We report this case to increase awareness of this unique diagnosis.

PUB400

Avacopan as Adjuvant Therapy for ANCA-Associated Vasculitis: A Case Report

Sanjeev Gupta,[1,2] Anastasios Papanagnou,[3] Amol Mittal,[1,2] Savneek S. Chugh.[1,2] *[1]Westchester Medical Center Health Network, Valhalla, NY; [2]New York Medical College, Valhalla, NY; [3]NewYork-Presbyterian Hudson Valley Hospital, Cortlandt Manor, NY.*

Introduction: The anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis are severe systemic disorders marked by small-vessel vasculitis. This involve autoantibodies against neutrophil proteins, particularly leukocyte proteinase 3 (PR3) or myeloperoxidase (MPO). Standard treatment for ANCA vasculitis often includes high-dose steroids, rituximab, or cyclophosphamide. Rituximab is the preferred option, but patients who do not respond sufficiently might be switched to cyclophosphamide. However, cyclophosphamide's significant side effects necessitate its limited use. We present a case of partial response to rituximab, who, instead of increasing steroids or using cyclophosphamide, was treated with avacopan, resulting in a favorable outcome.

Case Description: A 48-year-old male with hyperlipidemia presented with rash on palms and soles, and shortness of breath. Initial workup showed hemoglobin of 11.8 g/dl, platelet count of 437k/mm, BUN of 16mg/dl, and creatinine of 1.34mg/dl. Urinalysis indicated 3+ protein and 136 RBCs. Further tests revealed a urine protein-to-creatinine ratio of 1.3, negative hepatitis panel, negative ANA, and normal C3 and C4. Anti-MPO antibodies were 109 units, anti-PR3 antibodies were 2.35 units, and anti-GBM ab was negative. Kidney biopsy confirmed ANCA-associated renal disease with focal glomerular fibrinoid necrosis and crescents. The patient received 60 mg prednisone and 1 g Rituximab. He returned with worsening creatinine and shortness of breath within a week, was diagnosed with cardiac tamponade, and underwent a pericardial window. Despite moderate increased prednisone, his creatinine continued to rise with active sediments in urine. Avacopan was initiated. Within a week, his creatinine improved to baseline, and urine analysis normalized. He completed 4 rituximab doses and 52 weeks of avacopan. Eighteen months later, his creatinine remains stable at 1.3mg/dl.

Discussion: Avacopan, used as an induction therapy alongside rituximab and steroids, provides an alternative to high-dose steroids, typically tapered within a month to reduce toxicity. Despite the lack of case reports on avacopan as adjuvant therapy for partial responders to standard ANCA vasculitis treatment, our patient's positive outcome highlights its potential benefit. To date, the patient's kidney function remains stable, emphasizing avacopan's role in vasculitis management

PUB401

Light Deposited All Over (Lighted All Over)

Fnu Pariya,[1] Sandeep R. Sasidharan,[1] Tahir A. Jatoi,[1] Susan Grossman,[2] Marie-Alex Michel.[2] *[1]SUNY Downstate Health Sciences University, New York City, NY; [2]VA New York Harbor Healthcare System, New York, NY.*

Introduction: Light-chain deposition disease (LCDD) is the deposition of monoclonal light chains in multiple organs. It is a rare disease characterized by deposition of nonamyloid immunoglobulin light chains, which do not stain with Congo red and do not exhibit a fibrillar structure when examined ultra structurally. The incidence of LCDD is unknown.

Case Description: 76-year-old man with history of HTN, HLD, CVA, CKD prostate cancer s/p radical prostatectomy, and severe IPF with light smoking history. He came to ED for raised creatinine thought due to chlorthalidone use. Systemic review revealed nocturia, four times a night, more than usual. Vitals were normal. Labs showed BUN/Cr of 41/2.7, no electrolyte abnormality, ALP 499, AST 151, ALT 232, GGT 770, CBC normal except eosinophils at 9%, ANA positive 1: 80, negative for Hepatitis A, B, C, AMA, AntiSm, Urine protein initially 30. He was discharged with outpatient follow ups. GI considered DILI but with worsening LFT requested liver biopsy. Biopsy showed mild hepatitis with biliary ductal inflammation, sclerosing cholangitis with portal and peri portal fibrosis. Other labs showed Bence Jones proteins on UPEP, k/l ratio of 19, no monoclonal spike. UPCR 197g/day. Renal ultrasound was normal. MRCP showed no liver or biliary pathology but slight prominence of pancreatic duct in the head of pancreas. Fat pad biopsy was negative for amyloid. Renal labs and LFT continued to be elevated hence tried on ursodiol. Rheumatology followed for eosinophilia without asthma or allergy. Autoimmune work up including ACE, Vitamin D ratio, lysozyme, SSA, SSB, centromere, Scl70, C3, C4, dsDNA was negative. Extensive infectious work up was negative. A bone marrow biopsy showed 15% plasma cell with kappa restriction. Heme started him on high dose steroids and Bortezomib with prophylaxis. LFT Down trended with chemotherapy however, the kidney function continued to worsen, and patient had to be initiated on hemodialysis.

Discussion: Symptomatic extrarenal LCDD is rare. We present a case with involvement of multiple organ systems. Liver with biliary ductal involvement with fibrosis. Pulmonary with interstitial fibrosis. Cardiac with diastolic dysfunction. Other systems likely involved include pancreas with a ductal prominence, and possible peripheral neuropathy. To our knowledge, this is the first ever case involving so many organ systems.

PUB402

Diagnostic Challenges and Multidisciplinary Management in Atypical Lupus Nephritis

Israr Baloch, Sharon E. Maynard. *Lehigh Valley Health Network, Allentown, PA.*

Introduction: SLE is a complex autoimmune disorder affecting multiple organs, with LN being one of its most severe complications, potentially leading to significant morbidity due to renal impairment and progression to ESRD. Diagnosing LN is challenging, especially in patients not fully meeting SLE criteria. This case report discusses a 40-year-old male with LN, highlighting diagnostic challenges and the importance of multidisciplinary management.

Case Description: 40M with PMH significant for migraines, tobacco, and NSAID use presented with bilateral hand swelling, pain, and poor dentition. Denies dry mouth, fever, diarrhea, rash, and weight loss. Found to have positive ANA and AKI. Initial labs showed serum creatinine of 1.58, 200 mg proteinuria, no hematuria or pyuria. Diagnosis of LN was initially considered, but pt did not meet full criteria for SLE, and AKI was attributed to NSAID use. AKI resolved after discontinuing NSAIDs, and pt was sent home for a 5-month follow-up. However, at the follow-up visit, serum creatinine increased, along with worsening proteinuria. Repeat labs showed serum creatinine of 1.38 and UPCR of 2 g. Repeat serological workup now remarkable for +ANA, low C3 and C4, and elevated ESR, platelets, and CRP. New cardiac murmur noted on PE. Given rapidly worsening renal function and proteinuria, pt started on prednisone 60 mg daily and MMF 500 mg BID, with renal biopsy planned due to concerns for RPGN. A new murmur raised concerns for SBE, prompting an Echo and BCx. TEE revealed MV vegetations, but BCx remained -ve. Further serologic workup revealed positive APLA. Hem recommended warfarin, with Lovenox bridging for NBTE. Renal Bx revealed findings consistent with LN; however, limited sampling prevented precise classification within LN, and activity/chronicity indices could not be calculated. Pt was also started on atovaquone for PJP ppx with plans for close outpatient follow-up.

Discussion: This case underscores the importance of considering LN in patients with suggestive clinical and laboratory findings, even if they do not meet full SLE criteria. Careful medication management and a multidisciplinary approach are essential in managing complex cases like this one. The patient's outcome highlights the potential for successful treatment with a coordinated, patient-centered approach.

PUB403

Treatment of ANCA-Associated Glomerulonephritis in a Patient with Bacteremia and Vertebral Osteomyelitis: A Challenging Clinical Dilemma

Bahjat Azrieh, Melissa L. Swee, Abdullah Thayyil. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Introduction: ANCA-associated vasculitis (AAV) involves an autoimmune response that produces antibodies targeting neutrophil antigens, leading to necrotizing and crescentic glomerulonephritis. While modern immunosuppressive therapies have improved outcomes, infections remain a significant risk. Older age and high disease activity at diagnosis are critical prognostic factors. This case highlights the challenge of balancing immunosuppression with infection management.

Case Description: A 77-year-old man with a history of anti-glomerular basement membrane disease leading to chronic kidney disease (CKD) stage 3a was admitted for a burn injury, which worsened his kidney function. He was readmitted with acute kidney injury (AKI) and diagnosed with microscopic polyangiitis and crescentic glomerulonephritis with IgA deposits. Despite treatment with Rituximab and high-dose corticosteroids, he developed Enterobacter Cloacae bacteremia and vertebral osteomyelitis. His condition further complicated with disseminated Herpes Zoster infection and progression to end-stage kidney disease (ESKD), requiring dialysis. He ultimately succumbed to refractory septic shock three months after diagnosis.

Discussion: The treatment of ANCA-associated small vessel vasculitis and glomerulonephritis primarily involves high-dose corticosteroids and cyclophosphamide. However, balancing immunosuppression with infection risk is challenging, especially in elderly patients. Despite remission in the majority of patients, relapse is common, particularly in those with anti-PR3 positivity. This case underscores the need for accurate prognostic tools and strategies to mitigate infection risks while managing AAV. Lower dose steroid regimens and new agents like Avacopan may offer safer alternatives without compromising efficacy.

Labs

	7/30/2023	7/29/2023	6/12/2023
Na	134	135	138
K	4.2	4.4	4.3
Cl	100	99	105
CO2	21	22	24
Anion Gap	12	14	9
BUN	54	56	36
Creatinine	6.15	5.91	1.62
eGFR	9	9	44
Calcium	8.4	8.1	8.5
Phosphorus		4.9	4.5

PUB404

Rituximab to the Rescue in Refractory Anti-GBM Disease

Pratap Kumar Upadrista,[1,2] Purva D. Sharma,[1,2] Prashant N. Bhenswala.[1,2]
[1]Northwell Health, New Hyde Park, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.

Introduction: Anti GBM antibody disease is an aggressive disease that presents with rapidly progressive glomerulonephritis and pulmonary involvement with diffuse alveolar hemorrhage. The standard treatment includes steroids, PLEX and Cytoxan until anti-GBM Ab titers become negative. However, some cases are refractory to this conventional therapy. We present here such a case of anti GBM disease with severe lung and kidney involvement that did not respond to PLEX, cyclophosphamide and steroids with persistently high anti GBM Ab titers treated successfully with Rituximab.

Case Description: A 65 y/o M with Hx of DM, HLD, MVR and CABG presented with dyspnea, fatigue, hemoptysis and oliguria for a week. He had a baseline serum creatinine of 0.84 mg/dL. He was a non-smoker and did not use any illicit drugs. At presentation, he was anemic (7.1 g%) from his baseline of 10 g% and had anuric AKI with a Scr of 3.6 mg/dL which peaked at 6.3 mg/dL and was started on HD. He had 2.9g proteinuria and hematuria. CT chest GGOs suggestive of hemorrhage vs pulmonary edema. Work up showed anti GBM antibodies >8.0. The pt was initiated on daily PLEX (1 Plasma volume with 5% albumin + Plasma) pulse followed by oral steroids and oral cyclophosphamide. Renal biopsy showed anti-GBM glomerulonephritis with segmental glomerular necrosis and cellular crescents (88%). As his Anti-GBM antibodies titers were still >8, even after 14 sessions of PLEX, Cytoxan and Steroids. Rituxan was started for refractory anti GBM abs with pulmonary symptoms. The patient continued to be on hemodialysis. Within 2 months, his anti GBM ab titers slowly improved to negative, with improved pulmonary symptoms. Kidney transplant eval is underway.

Discussion: Management of refractory anti GBM disease with dialysis dependent AKI and lung hemorrhage with persistently high Ab titers even after PLEX, Cytoxan and steroids is challenging. There is limited literature on use of Rituximab to achieve remission. Rituxan removes CD 20 positive B cells by inducing apoptosis, antibody and complement mediated cytotoxicity resulting in lowered anti GBM ab production. Our patient was successfully managed with Rituximab with improvement in lung hemorrhage and enabling him to get kidney transplant evaluation.

PUB405

A Case Report of C3 Glomerulonephritis: A Rare and Poorly Understood Disease

Alexandra Conforti. *St. Luke's University Health Network, Bethlehem, PA.*

Introduction: Cases of C3 Glomerulopathies are rare, with an incidence of one to three cases per million. The pathogenesis is caused by excessive activation of the alternative complement pathway that leads to dense deposit formation leading GN. The disease is often caused by autoantibodies that target C3 or C5 convertase, although the pathophysiology remains poorly understood. Currently, there are no disease-specific treatments available. Immunosuppressive agents can be helpful but are not universally curative or effective. The progression to end-stage-renal disease occurs in 50% of adults in 10 years. This is a case of a middle-aged female without significant medical history who presented after a mechanical fall with uremic symptoms and was diagnosed with rapidly progressive C3GN.

Case Description: 64-year-old female presented to the hospital after have a mechanical fall one week prior, complaining of visual hallucinations, nausea, and decreased appetite. She had a prior history notable for schizoaffective disorder, bipolar, and prior DVT. Lab work on presentation was significant for severe AKI (Cr of 7.1 from a baseline of 1.0), normochromic normocytic anemia, severe metabolic acidosis, and hypoalbuminemia. Initial UA with 3+ proteinuria, innumerable RBCs, 20-30 WBCs with multiple hyaline case. Serologies for glomerulonephritis work up were significant for low C3 (56) and reactive hepatitis B core total antibody Patient underwent a renal biopsy that showed diffuse crescenteric GN with severe activity and moderate chronicity concerning C3 glomerulopathy. She subsequently underwent bone marrow biopsy that ruled out monoclonal gammopathy of renal significance. She underwent an unremarkable genetic renal panel that tested 13 genes implicated in C3GN. The patient was initiated on solumedrol and mycophenolate but unfortunately did not have renal recovery and became dialysis dependent.

Discussion: C3GN are extremely rare conditions from underlying complement dysregulation. The diagnosis merely relies on renal biopsy immunofluorescence, light microscopy, and complement biomarker findings. Autoantibodies and monoclonal gammopathy are most associated with complement dysregulation, however genetic variants are a potential cause. An imperative need remains for studying the history of C3GN to better understand pathophysiology and genetic biomarkers to establish an optimal treatment through clinical trails.

PUB406

Clinical Characteristics and Laboratory Findings in Primary vs. Secondary Membranous Nephropathy in Western Mexico

Milagros M. Flores Fonseca,[1] Alejandro Garcia-Rivera,[1] Omar H. Sanchez-Vazquez,[1] Sandra F. Velasco,[2] Samantha I. Verdugo.[1] *[1]Instituto Mexicano del Seguro Social Delegacion Jalisco, Guadalajara, Mexico; [2]Universidad de Guadalajara Centro Universitario de Ciencias Exactas e Ingenieria, Guadalajara, Mexico.*

Background: Membranous nephropathy (MN), a major cause of nephrotic syndrome in adults, occurs in primary and secondary forms. Accurate differentiation between these forms is essential for effective treatment and prognosis.

Methods: Retrospective observational, single-center study, in a third-level hospital in Western Mexico. We collected demographic, laboratory and kidney pathology data from patients biopsied and diagnosed with MN from January 2022-January 2023, and registered in the center's Glomerular Disease Registry.

Results: Overall, 81 participants were included in the study. The mean age was 35.4 y (SD ±16.3), 41 were female (50.6%), 61 patients (75.3%) presented with nephrotic syndrome and 30 patients (37%) had AKI at presentation. Table 1 shows primary and secondary MN's clinical, laboratory, and pathology characteristics. The most common cause of secondary MN was lupus nephritis.

Conclusions: Primary MN is associated with higher degree of proteinuria and a higher prevalence of nephrotic syndrome at presentation compared to secondary MN. AKI at presentation was more common in primary MN, and serum albumin levels were lower. Only 30.3% of those classified as primary MN had positivity for PLA2r antigen on biopsy, a lower prevalence compared to other cohorts.

Characteristic	Primary MN n=33	Secondary MN n=48	p value
Age	49.36 (± 11.2)	25.8 (11.8%)	0.550
Sex (female, %)	8 (24.2%)	33 (68.7%)	0.001
NS at presentation (n, %)	30 (90.9%)	31 (64.5%)	0.014
AKI at presentation (n, %)	16 (48.4%)	14 (29.1%)	0.077
Serum creatinine (mg/dL) *	1.74 (± 1.31)	1.13 (± 1.04)	0.122
eGFR at presentation (ml/min) *	66.37 (± 39.9)	103.6 (± 48.6)	0.083
Proteinuria (g/day) *	13.1 (± 7.9)	6.4 (± 4.9)	0.001
Serum albumin (g/dL) *	2.35 (± 0.8)	2.76 (± 0.76)	0.593
PLA2r antigen on biopsy (n, %)	10 (30.3%)	0 (0%)	0.001
Extracapillary proliferation (n, %)	1 (3.03%)	11 (22.9%)	0.013
Endocapillary proliferation (n, %)	1 (3.03%)	28 (58.3%)	0.001
Mesangial expansion (n, %)	4 (12.1%)	23 (47.9%)	0.044

PUB407

Podocytopathy Associated with IgA Nephropathy: Is It Really a Prognostic Factor?

Belén Gallegos, Angela M. Cordoba Hurtado, L. M. Perez-Navarro, Rafael Valdez-Ortiz, Virgilia Soto. *Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico.*

Background: In IgA nephropathy(IgAN) podocyte hypertrophy and tip- lesions are markers of podocyte damage, which tend to be treated with immunosuppression, so they have a better kidney prognosis. In Latin America there are no cohorts that evaluate the clinical course of these lesions.

Methods: Cases and controls.

Results: 37 patients with IgAN were evaluated, 27% presented podocytopathy(IgAN-P) and 73% IgAN without histological data in the optical microscopy of podocytopathy(IgAN-NP), with a mean follow-up of 41±32months. Clinically, IgA-P, independent of treatment prior to biopsy, is associated with higher baseline proteinuria, (ß of .044, p=0.01) mean of 3.9±3.0gr/gr vs 1.6±1.5gr/gr in the group with IgAN-NP). Kidney function in IgAP was slightly lower with a mean eGFR of 65.9±45ml/min/1.73m2 vs 80.2±36.4 ml/min/1.73m2 p=0.23, associated granular casts in podocytopathy (92% vs 80% p=0.02) describing probable associated acute tubular injury. Histologically, patients with podocytopathy presented 80% of podocyte hypertrophy and 20% of tip-type FSGS. MEST-C score had no differences between the groups, except for mesangial proliferation that was present in 96.3% of subjects with podocytopathy compared to 70% of subjects without podocytopathy, p=0.02. The prognosis based on the international SCORE was not statistically significant between the groups p=0.59. Association was found between immunosuppressive treatment prior to biopsy and the presence of podocytopathy (OR=8, 95% CI 1.4-44.9, p=0.018), in 50% vs 37% in the group without podocytopathy p=0.01, however once the histological diagnosis was obtained it was more common to decide to continue with

immunosuppressants in subjects with podocytopathy with 90% vs 63% (p=0.11). Finally, when evaluating MAKE outcomes, there were no differences between groups.

Conclusions: In previous reports the presence of podocytopathy reported as podocyte hypertrophy and tip-lesions was 16%. In our population this finding was more frequent (27%), with podocyte hypertrophy being more prevalent. Greater proteinuria and worse kidney function were observed compared to IgAN-NP, justifying a greater frequency of immunosuppressive therapy, impacting the kidney outcome being the same as that reported in patients without podocytopathy. Similar result to that observed in previous cohorts.

PUB408

Atypical Anti-glomerular Basement Membrane Disease: An Emerging Clinical Dilemma

George Vasquez-Rios,[1] Karla G. Carias Martinez,[2] Ravi K. Thimmisetty,[2] Pablo Garcia.[3] *[1]Glomerular Disease Center, Renal Medicine Associates, Albuquerque, NM; [2]Renal Medicine Associates, Albuquerque, NM; [3]University of New Mexico Health Sciences Center, Albuquerque, NM.*

Introduction: Atypical anti-glomerular basement membrane (anti-GBM) disease is a rare subtype of vasculitis that has been described as indolent and relatively benign at times. However, aggressive presentations might pose significant challenge specially in young individuals.

Case Description: We present a 35-year-old female with no relevant past medical history who presented to the hospital with anasarca, fatigue, and nausea. She was recently seen by her primary care provider, who recommended evaluation in the ED due to progressive functional deterioration. On examination, she was hypertensive (BP 150/90s), with HR of 80s, RR: 16, and T: 37°C. Additionally, she had evident anasarca and mild paleness. Laboratory markers revealed a serum Cr: 7 mg/dL (baseline: 0.7 mg/dL 3 months prior), BUN of 85 mg/dL, bicarbonate of 17 mmol/L, and hypoalbuminemia at 2 mg/dL. Urinalysis showed hematuria, RBC casts, and proteinuria, which was later quantified to be 8 gr in a 24-hour collection. An extensive GN and MGRS workup was pursued, which showed positive ANCA levels (MPO: 5.1 IU/mL, UNL>0.9 IU/mL) and negative serum anti-GBM antibodies. Imaging studies and comprehensive evaluation did not reveal significant pulmonary, bronchial, or extra-renal compromise.

Discussion: She received a pulse of steroids and started on hemodialysis due to oliguria, anasarca, and high BUN prior to kidney biopsy. Kidney biopsy demonstrated diffuse fibrotic crescents with extensive interstitial fibrosis and tubular atrophy (IFTA >70%). IF studies revealed moderate IgG dominance with no evidence of MPO or PR3 signals. Our team was concerned about kidney-limited atypical anti-GBM. After a careful multidisciplinary discussion considering marked IFTA, medication side-effect profile, and prognosis, the patient was treated with Rituximab. Three weeks later, we continue to monitor for potential kidney response, though we explained that the chances of significant improvement are low. Atypical anti-GBM disease is an emerging and obscure vasculitis presentation that is yet to be understood. Linear deposition with IgG on IF should also warrant careful evaluation for MGRS in the appropriate age group. Our case calls for caution within the nephrology community given the miriad of questions regarding prognosis, treatment, and recurrence risk after tranplant.

PUB409

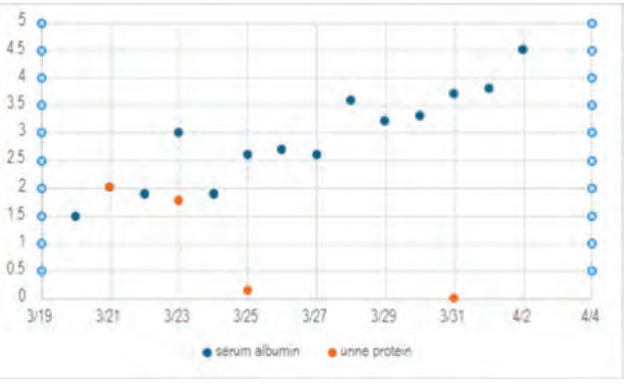
Relapsing Steroid-Resistant Primary FSGS Treated with Plasmapheresis

Dinah Goodman, Cristian A. Milla, Fnu Pariya, Arfa Amjad, Thin Thin Soe, Subodh J. Saggi, Sandeep Sasidharan, Mohammad W. Abushawer, Tahir A. Jatoi, Ao Wang, Fausto R. Cabezas, Moro O. Salifu, Okwudili Nnaji. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Focal Segmental Glomerulosclerosis (FSGS) constitutes 35% of Nephrotic Syndrome (NS) cases in the US, being the primary glomerular disease in End-Stage Kidney Disease (ESKD). Primary FSGS (pFSGS) presents with acute onset of NS, hematuria (50%), and hypertension (20%). Treatment focuses on reducing proteinuria, typically with Immunosuppression. This case report explores the use of plasmapheresis, a less common treatment, in a young man with relapsing steroid resistant (RSR) FSGS and severe NS.

Case Description: A 22 year old male with history of RSR pFSGS, and atrial fibrillation, presented with worsening edema. He had been treated with multiple immunosuppressive agents including cyclosporine, cyclophosphamide, rituximab, IvIG and was currently on MMF, Tacrolimus and prednisone. Vital signs were stable. On examination he had 3+ bilateral lower extremity edema. Labs showed proteinuria of >50g/d and creatinine at baseline of 0.6. He was initiated on high dose steroids and 5 sessions of plasmapheresis were given on Days 1,2,3,5,&7. After plasmapheresis, serum albumin decreased from <1.5 to 4.5, urine protein went from >2000 mg/dl to <4 mg/dl. The patient was discharged on a steroid taper with continued MMF/tacrolimus.

Discussion: pFSGS is thought to be secondary to a putative circulating permeability factor that causes podocyte dysfunction manifested by widespread foot process effacement. Proposed factors include suPar, CLCF1, microRNA, PAI-1, AT1R, DG, MMPs, POXp3, PARP1, anti-nephrin antibodies, and CD40. In this patient, the circulating factor is hypothesized to be an antibody released by plasma cells. This hypothesis is supported by the patient's dramatic response to plasmapheresis. This case provides an example of the benefit of plasmapheresis in patients with steroid resistant recurrent nephrotic syndrome due to pFSGS.



PUB410

A Rare Coexistence: Minimal Change Disease and Guillain-Barre Syndrome in a Patient with Polysubstance Abuse

Adam W. Tsen, Divya Monga. *The University of Texas Medical Branch at Galveston, Galveston, TX.*

Introduction: Minimal Change Disease (MCD) and Guillain-Barre Syndrome (GBS) are distinct clinical entities with unique pathophysiological mechanisms. MCD, characterized by nephrotic syndrome and podocyte effacement on renal biopsy, is commonly associated with autoimmune disorders and certain medications. GBS, on the other hand, is an acute autoimmune neuropathy leading to ascending motor weakness and areflexia. Here, we present a rare case of concurrent MCD and GBS in a patient with a history of polysubstance abuse.

Case Description: A 50-year-old female with a past medical history of heart failure with reduced ejection fraction (HFrEF), polysubstance abuse, and untreated hypothyroidism presented with worsening shortness of breath, vomiting, and hyperbilirubinemia. Evaluation revealed acute kidney injury, likely exacerbated by congestive heart failure, and bilateral tibial axonal motor neuropathy consistent with GBS. Further investigations confirmed a diagnosis of MCD based on renal biopsy findings.

Discussion: The coexistence of MCD and GBS in this patient highlights the importance of considering multiple etiologies in individuals with complex medical histories, particularly those with a history of polysubstance abuse. The underlying mechanisms linking these two conditions remain unclear but warrant further investigation. Management requires a multidisciplinary approach, addressing both renal and neurological manifestations to optimize patient outcomes.

PUB411

Patient Perspectives on Social Support-Related Facilitators and Barriers to Kidney Diet Adherence: A Photovoice Study

Bengucan Gunen,[1] Dahlia Stott,[2] Brandy-Joe Milliron,[2] Meghan Butryn,[4] Meera N. Harhay,[3] Ann C. Klassen.[1] *[1]Drexel University Dornsife School of Public Health, Philadelphia, PA; [2]Drexel University College of Nursing and Health Professions, Philadelphia, PA; [3]Drexel University College of Medicine, Philadelphia, PA; [4]Drexel University College of Arts and Sciences, Philadelphia, PA.*

Background: In the United States, 40% of adults with end stage kidney disease (ESKD) have obesity (body mass index, BMI, ≥30 kg/m^2). Most ESKD patients with obesity report a desire to lose weight, whether to improve transplant eligibility or quality of life. Weight loss attempts may be complicated by requirements to limit intakes of fluid, sodium, potassium, and phosphorus, while ensuring adequate protein and fiber intake. Poor renal diet adherence (RDA) increases the risk of hospitalization and mortality. Understanding family and community support for weight loss strategies and RDA among ESKD patients with obesity can help healthcare providers better assist patients and empower individuals to meet health goals.

Methods: Using a participatory Photovoice activity (Figure), we will qualitatively examine the relationship between received and provided social support, and RDA within an ongoing prospective cohort of adults with ESKD and obesity. Photovoice is a unique qualitative methodology in which participants photograph their home and community environment and, in collaboration with the research team, interpret the images. In June-September 2024, Photovoice participants will capture prompt-based photos of meals, snacks, food preparation methods, and food consumption settings; then discuss images in individual and group interviews. Images and interview content will be coded and analyzed using MAXQDA software and interpreted with 12-month clinical data.

Results: The study will enroll 10 ESKD patients with obesity. Among participants in the parent study who are eligible for the Photovoice substudy, median age is 58, median BMI is 35.2 kg/m², 45% are female, 94% are Black/African American. We will describe patients' attitudes towards renal dietary guidelines and how social support influences strategies used to maintain or improve RDA. Images will be interpreted and curated with input from the participants.

Conclusions: This study will produce participant-generated visuals and qualitative findings on diet-related sociobehavioral challenges experienced by ESKD patients with co-existing obesity in an urban setting, to inform obesity management and clinical nutrition care.

Funding: NIDDK Support

Figure. Steps for Photovoice activity

PUB412

Recurrent Priapism after Initiation of Oral Minoxidil

James Mcgee, Jordan L. Rosenstock, Maria V. DeVita. *Lenox Hill Hospital, New York, NY.*

Introduction: We present the case of a patient with end stage renal disease on dialysis and sickle cell trait presenting with multiple recurrent priapism episodes over four weeks which were associated with the initiation of minoxidil for hypertension. Priapism is considered a urological emergency which requires prompt medical attention to prevent adverse sequelae such as erectile dysfunction. While priapism has been associated with sickle cell trait and hemodialysis likely in the setting of occlusive events, minoxidil is not readily identified as a potential trigger in patients predisposed to this condition.

Case Description: This is a 46 year old male with a past medical history of end stage renal disease on thrice weekly hemodialysis for four years, hypertension, type 2 diabetes mellitus, and sickle cell trait. The patient presented to the emergency department with a painful erection which had lasted for 5-6 hours after hemodialysis. He had one prior episode approximately 3 years ago. He underwent cavernosal aspiration and injection of phenylephrine with resolution of the episode and the patient was discharged. Over the next four weeks, the patient presented twice more with similar episodes despite having started finasteride to prevent recurrence, and was treated similarly. Upon further questioning, the patient had been started on oral minoxidil 5mg daily for uncontrolled hypertension, two weeks prior to the first event. Once minoxidil was stopped, no further episodes of priapism have occurred in the following two months.

Discussion: Priapism is a urological emergency and requires prompt diagnosis and treatment. Here we present a case in which recurrent episodes of priapism appeared to be temporally associated with the initiation of minoxidil and resolved following its discontinuation. While topical minoxidil has been proposed as a treatment for erectile dysfunction, we are unaware of any previous reports of an association with priapism. Minoxidil and potentially other vasodilatory agents should be considered as a potential cause of priapism, particularly in patients with other predisposing factors.

PUB413

Intraperitoneal Nutrition Associated with Improved Albumin Levels in Malnourished Patients on Peritoneal Dialysis

Maiya Slusser. *Patient Care America, Pompano Beach, FL.*

Background: Malnutrition and hypoalbuminemia occur in 30%-50% of people receiving peritoneal dialysis (PD) which is associated with poor quality of life and poor health outcomes including increased risk of peritonitis and increased hospitalizations. Evidence suggests improving albumin levels by 0.1g/dL to 0.2g/dL can reduce the frequency of malnutrition-related challenges. Intraperitoneal nutrition (IPN) is a unique form of PD solution designed to help correct malnutrition. IPN is a combination of amino acids and dextrose that provides ultrafiltration while allowing amino acids to infuse during the dwell time to improve protein synthesis and replace protein lost during PD. IPN is commonly provided as a once daily, one-for-one replacement of a standard dialysis solution in the patients PD regimen.

Methods: Thirteen patients on automated PD who started on IPN therapy in 2021 were randomly selected and albumin was compared from baseline to measurements at month 3 and month 6 of IPN therapy.

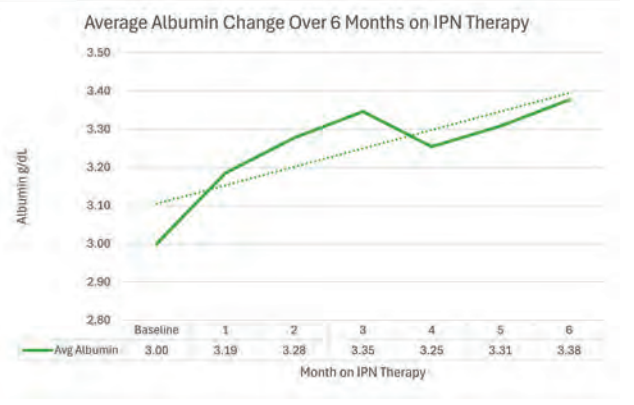
Results: A t-test was run and found the results to be statistically significant at both 3 and 6 months, 0.002 and 0.0004 respectively.

Conclusions: PD results in varying protein losses and has common side effects resulting in diminished appetite and poor oral protein intake leading to malnutrition. Malnutrition contributes to poor quality of life and costly adverse health outcomes for patients. IPN provides a non-invasive, low burden option to help correct malnutrition.

Funding: Commercial Support - Patient Care America

Baseline Characteristics	N (%)
Mean age	62.3 years ± 50 years
Mean dialysis vintage*	10.5 months ± 16 months
Sex, female	8 (61.5%)
Reason for IPN Referral	
Albumin trending <3.5g/dL	8 (61.5%)
Albumin trending <3.5g/dL and weight loss ≥5% over 3 months	4 (30.7%)
Albumin trending <3.5g/dL and BMI <20	1 (7.7%)
Medical history	
Diabetes	11 (84.6%)
Hypertension	11 (84.6%)
Anemia	10 (77%)
Gastroparesis	2 (15.4%)
Liver cirrhosis	1 (7.6%)
Chronic wound	2 (15.4%)
IPN Formulation	
5L, 50g AA, DE 2.5%	2 (15.4%)
6L, 60g AA, DE 1.5%	5 (38.5%)
6L, 60g AA, DE 2.5%	6 (46.2%)
Results	Albumin (g/dL)
Pre-IPN Mean	3.00 ± 0.53
3 Month Mean	3.35 ± 1.1
6 Month Mean	3.38 ± 0.90
Mean Change at 6 Months	0.38 ± 0.95

*based on 9 records, 4 patients dialysis vintage could not be determined



PUB414

Recurrent Exertional Rhabdomyolysis

Jinhua Zhao.[1,2] [1]*Case Western Reserve University School of Medicine, Cleveland, OH;* [2]*Louis Stokes Cleveland VA Medical Center, Cleveland, OH.*

Introduction: Rhabdomyolysis (Rhabdo) was first described by Larrey in 1812. The original "crush injury syndrome" was described by Bywater et al in 1941. Myoglobin was identified as the offending agent for AKI by Bywater et al in 1943. The prevalence of exertional rhabdo is ~12,000 cases annually in US. It is well described among athletes and military personnel, but may occur in anybody after unaccustomed exercise.

Case Description: 32 year-old male, a runner has "dark red urine" after each marathon or training. His urine (Fig. 1) appears to be heme loaded, it clears up in one day. It's a problem of 2 years. He also has sports related mild proteinuria. No myalgia. No family history. Meds: lisinopril 2.5mg, loratadine 10mg, omeprozole 20mg daily AM labs after the morning run: UA: dark brown color, protein 100mg/dL, Heme >1.0 mg/dL, RBC <1/hpf. Renal panel: Na 135, K 4.2, Cr 1.0. Myoglobin-Urine 3574 H Ng/Ml (ref 0 - 13) Myoglobin-Serum 72 Ng/Ml (ref 28 - 72) CK 484 H U/L (ref 46 – 171)

Discussion: Fig.2 showed the common cause of rhabdomyolysis (Ref 1): Diagnosis of rhabdo does not dependent on the presence of myoglobinemia and myoglobinuria as they are quickly cleared. CK >1,000 U/L is concerning for rhabdo without exercise, but has been frequently observed without apparent health consequences (Ref 2) with exercise. Exertional rhabdo may be the first manifestation of a genetic muscle disease that lowers the exercise threshold for developing muscle breakdown. The genetic testings for this patient are ordered and will be shared when available.

Table 1. Major Categories and Commonly Reported Causes of Rhabdomyolysis.

Category	Commonly Reported Cause
Trauma	Crush syndrome
Exertion	Strenuous exercise, seizures, alcohol withdrawal syndrome
Muscle hypoxia	Limb compression by head or torso during prolonged immobilization or loss of consciousness,* major artery occlusion
Genetic defects	Disorders of glycolysis or glycogenolysis, including myophosphorylase (glycogenosis type V), phosphofructokinase (glycogenosis type VII), phosphorylase kinase (glycogenosis type VIII), phosphoglycerate kinase (glycogenosis type IX), phosphoglycerate mutase (glycogenosis type X), lactate dehydrogenase (glycogenosis type XI) Disorders of lipid metabolism, including carnitine palmitoyl transferase II, long-chain acyl-CoA dehydrogenase, short-chain L-3-hydroxyacyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase, very-long-chain acyl-CoA dehydrogenase, medium-chain 3-ketoacyl-CoA, thiolase† Mitochondrial disorders, including succinate dehydrogenase, cytochrome *c* oxidase, coenzyme Q10 Pentose phosphate pathway; glucose-6-phosphate dehydrogenase Purine nucleotide cycle; myoadenylate deaminase
Infections‡	Influenza A and B, coxsackievirus, Epstein–Barr virus, primary human immunodeficiency virus, legionella species *Streptococcus pyogenes, Staphylococcus aureus* (pyomyositis); clostridium
Body-temperature changes	Heat stroke, malignant hyperthermia, malignant neuroleptic syndrome, hypothermia
Metabolic and electrolyte disorders	Hypokalemia, hypophosphatemia, hypocalcemia, nonketotic hyperosmotic conditions, diabetic ketoacidosis
Drugs and toxins	Lipid-lowering drugs (fibrates, statins), alcohol, heroin, cocaine
Idiopathic (sometimes recurrent)	

NEJM 2009, 361:6272

PUB415

Protein-Energy Wasting: Correlation between Geriatric Nutritional Risk Index and Malnutrition-Inflammation Index

L. M. Perez-Navarro, Juan J. Molina Garcia, Rafael Valdez-Ortiz, Gloria G. García Villalobos. *Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico*.

Background: Protein-energy wasting (PEW) in patients with chronic kidney disease (CKD) is common and can be detected using the Malnutrition-Inflammation Score (MIS) and the Geriatric Nutritional Risk Index (GNRI). The latter is easy to estimate; however, its performance in patients with stage 3-4 CKD has not been evaluated. Our aim was to determine the correlation between the GNRI and MIS scales in patients with CKD 3-4.

Methods: Cross-sectional study evaluated 44 patients with CKD stages 3-4. The GNRI and MIS scales were applied to classify nutritional risk (MIS: Normal 0-2 points, Mild Malnutrition 3-5, Moderate Malnutrition 6-8, Severe Malnutrition ≥9); GNRI: absent, mild, moderate, severe. Averages ±SD were estimated, and absolute and relative frequencies. The correlation between GNRI and MIS scores was estimated, and the nutritional status was compared using both instruments. A 95% CI was used, with a value of p <0.05.

Results: 44 patients were evaluated, with 27% in KDIGO 3a, 27% in KDIGO 3b, and 46% in KDIGO 4. 59% women. The mean BMI was 27.06±5.57. Through electrical bioimpedance, the phase angle was of 5.76±1.42. According to the GNRI scale, 23% of the patients had PEW vs 52% with MIS. The latter classified the patients as: 47% normal, 34% mild PEW, 7% moderate PEW, and 21% severe PEW vs 77% patients as normal, 14% with mild wasting, 7% moderate, and one with severe malnutrition according to GNRI. 57% of the patients had a BMI >25, of which 40% had PEW by MIS vs 20% by GNRI. The correlation between the MIS and GNRI scales was r2= 0.643 (p <0.001), and between BMI <25 and MIS-GNRI was 0.91 (p<0.001).

Conclusions: The correlation between MIS and GNRI in this population was moderate due to the high prevalence of obesity; GNRI, by using albumin and weight as main variables, has limited applicability and proper interpretation in obese patients. The correlation between MIS and GNRI increases when these tools are used in patients with a BMI <25.

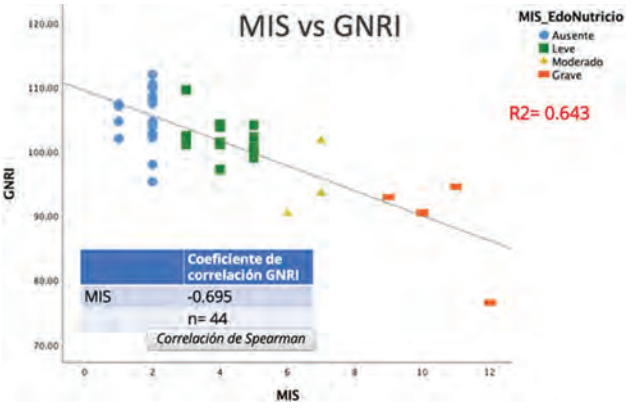


Fig. 1 Correlation between MIS and GNRI

PUB416

Public Awareness and Interest in Hypertension: An Analysis from 2004-2024

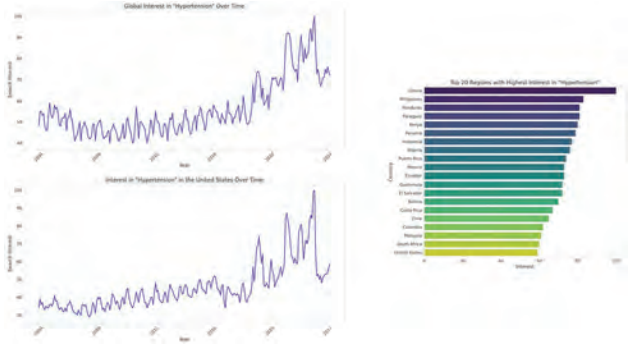
Sreyoshi F. Alam, Charat Thongprayoon, Jing Miao, Supawadee Suppadungsuk, Maria Lourdes Gonzalez Suarez, Iasmina Craici, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN*.

Background: Hypertension is a leading global health challenge, associated with an increased risk of cardiovascular diseases. The Internet serves as a vital resource for individuals seeking health-related information. This study aimed to analyze global and regional Internet search interest in hypertension using Google Trends™, providing insights into public awareness and interest over time.

Methods: We conducted a comprehensive Google Trends™ analysis for the search term “Hypertension” and “blood pressure” from January 2004 to March 2024. The investigation included worldwide trends and detailed analyses by country and region within the US. Google Trends™ indices were examined to identify patterns of interest and awareness, with a focus on peak and the lowest points of interest.

Results: The analysis demonstrated a statistically significant uptrend in public engagement and awareness concerning “Hypertension” and “Blood Pressure” globally and within the US, as evidenced by the slope analysis (p trends <0.05). February 2023 marked the zenith of global interest, registering a search interest score of 100. The trough of interest was in December 2008, with a score of 40. As of March 2024, the latest interest level was noted at 72. On a regional scale, Ghana, Trinidad & Tobago, Jamaica, Barbados, and Nigeria emerged as the top five countries with most pronounced interest. In the US, Arkansas, Mississippi, Alabama, West Virginia, and Louisiana were the regions with the highest interest.

Conclusions: The findings of our study underscore a significant increase in global and regional public interest regarding hypertension. The findings reveal pivotal insights into public health engagement dynamics, demonstrating an overarching trend towards heightened digital information-seeking behavior. The analysis illuminates significant regional disparities in search interest. These regional variations may reflect differing levels of awareness, prevalence, access to information, and the impact of health initiatives.



PUB417

Impact of Renal Macrophages on Blood Pressure Regulation via the Neuroimmune System

Norito Washimine,[1,2] Ryusuke Umene,[1,2] Chia-Hsien Wu,[1] Yasuna Nakamura,[1] Sayumi Matsuo,[1,2] Tomoya Nishino,[1,2] Tsuyoshi Inoue.[1] *[1]Nagasaki Daigaku Daigakuin Ishiyakugaku Sogo Kenkyuka, Nagasaki, Japan; [2]Department of Nephrology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan.*

Background: Hypertension affects over a billion people globally and is a risk factor for many diseases. Research shows that macrophages infiltrate various organs and regulate blood pressure. Previous studies noted increased macrophages and phenotype changes in hypertension, but the specific role of kidney macrophage infiltration remains unclear. Additionally, the nervous system influences immune cell dynamics through their neurotransmitter receptors, suggesting a neuro-immune interaction in blood pressure regulation. The precise mechanisms and their connection to the kidney remain unclear. This study aims to explore renal macrophage dynamics in hypertension development and the effects of different neural stimuli on macrophage function.

Methods: Hypertension was induced in mice using subcutaneous angiotensin II administration and oral saline intake. Immune cell subsets in the spleen and kidney were analyzed via flow cytometry. Hypertensive mice lacking macrophages or specific macrophage receptors were also created to assess blood pressure and immune cell changes. The effects of salt loading and pharmacological autonomic stimulation under angiotensin II administration on hypertension development were evaluated. A comprehensive genetic analysis of renal macrophages from hypertensive mice was conducted to identify factors related to hypertension suppression.

Results: The hypertensive group showed an increased number of renal macrophages compared to the control group. Hypertension was suppressed in mice without macrophages or macrophage-specific autonomic receptors. In angiotensin II-induced hypertensive mice, salt loading and pharmacological autonomic stimulation appeared to contribute to hypertension development. Renal macrophages were successfully isolated from hypertensive mice, and genetic analysis is underway to identify related factors.

Conclusions: Macrophages significantly contribute to hypertension pathogenesis through their kidney accumulation. Autonomic stimulation may regulate blood pressure via macrophages. Identifying factors linked to hypertension development from renal macrophages in hypertensive mice could offer new therapeutic targets for hypertension treatment. Stimulating the autonomic nervous system might help uncover underlying mechanisms.

PUB418

Renal ACE 2, Inflammation, and Oxidative Stress Cross-Talk in Diet-Induced, Salt-Sensitive Hypertension in Mice with Obesity

Jiahui Cai,[1] Feifei Sun,[1] Shasha Zhao,[1] Yunbo Sun,[1] Qiaoyun Pan,[1] Feng Yang,[1] Runyan Tan,[1] Danshu Wang,[1] Sandrine V. Pierre,[2] Yanling Yan.[1] *[1]Yanshan University, Qinhuangdao, China; [2]Marshall Institute for Interdisciplinary Research, Marshall University, Huntington, WV.*

Background: Obesity-induced salt-sensitive hypertension (ssHTN) is associated with inflammation and oxidative stress. Angiotensin Converting Enzyme type 2 (ACE2) is crucial in regulating blood pressure. This study aims to identify how renal ACE2, inflammation, and oxidative stress orchestrate to modulate blood pressure.

Methods: High-fat (HF)- induced obese C57BL/6J (B6) male mice were established as a model of ssHTN. Western blot was performed to monitor the effects of oxidative stress, inflammation, and Na/K-ATPase signaling pathway activation on ACE2 expression in the kidney. The related mechanisms affecting ACE2 expression were further verified *in vitro*.

Results: In the kidney of B6 mice, high salt (HS) stimulated signal transducer and activator of transcription 3 (Stat3), Extracellular Signal-Regulated Kinase 1/2 (Erk1/2) phosphorylation levels, and ACE2 expression. In our model of ssHTN caused by obesity, HF up-regulated phosphorylation of Stat3 and Erk1/2, as well as Heme Oxygenase-1 (HO-1) expression, but downregulated ACE2 expression compared with normal diet mice. These findings suggested that obese-mediated ssHTN was accompanied by inflammation and oxidative stress. The short-term activation of p-Stat3 and p-Erk1/2 by HS triggered a "defense response," contributing to significant upregulation of ACE2, which has the endogenous function of negative regulation of the renin-angiotensin system (RAS). However, persistent signaling activation caused by HF would disrupt the "defense response," leading to a dysfunctional ACE2 expression, which might ultimately contribute to the development of ssHTN. *In vitro* studies evidenced that Co(III) Protoporphyrin IX chloride (CoPP)-induced HO-1 attenuated IL-6-mediated p-Stat3 and p-Erk1/2 in porcine proximal tubular LLC-PK1 cells, suggesting the role of HO-1 in modulating the balance of "defense response."

Conclusions: Our studies reveal a novel association between ACE2 expression in the kidney and the activation of p-Erk1/2 and p-Stat3, which not only provides a theoretical basis for the role of ACE2 targets in ssHTN but also offers promising avenues for its clinical treatment.

Funding: NIDDK Support, Government Support - Non-U.S.

PUB419

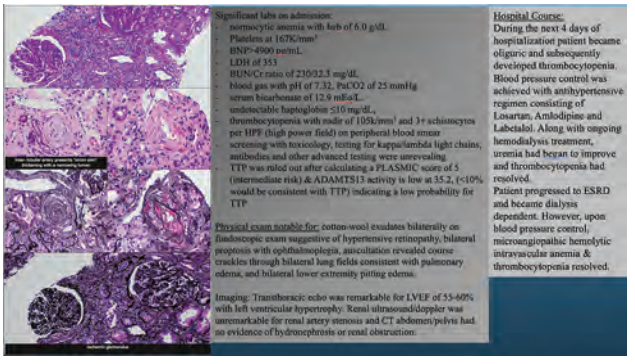
A Shearing Sensation: An Uncommon Cause of Thrombotic Microangiopathy

Angeli Patel, Craig Herrforth, Abhinav K. Rao, Matthew B. Madden. *Trident Medical Center, Charleston, SC.*

Introduction: Malignant Hypertension (MH) defined as a type of hypertensive emergency with severe increase in blood pressure often >200/120 mm Hg, hypertensive retinopathy (flame hemorrhages, cotton wool spots, papilledema) and renal damage (6). Thrombotic microangiopathy (TMA) is a coagulation system disorder resulting in extensive clot formation within small blood vessels. MH has a low prevalence and incident rate of 5/100,000 within the Caucasian population (7) & a prevalence of about 3.2% in the African American (AA) population (8). There is a paucity of reported cases of biopsy proven MH-TMA. Publications have reported a prevalence of up 25%, but variations exist due to results based on lab tests without confirmatory renal biopsy (7).

Case Description: A 43 y/o AA male with medical history of Tobacco Abuse, EtoH abuse & HTN presented with 1 week of abdominal discomfort & BP of 232/118mmhg. Notable initial findings & management found in figure 1. Extensive workup confirmed presence of TMA with renal biopsy findings showed inter- lobular artery "onion skin" thickening with a narrowing lumen, intimal fibrosis, ischemic glomerulus and thrombi within glomerular arteriole with features of chronic tubulointerstitial nephropathy.

Discussion: Microangiopathic hemolytic anemia (MAHA) defined as an intrinsic mechanical destruction of erythrocytes; underlying etiologies are grouped into primary TMA (TTP,HUS,aHUS) & secondary TMA (MH,DIC,Drug induced). The exact mechanism MH-TMA is unclear but the proposed theory consists of hypertension induced shearing & endothelial damage of arterioles and glomerular capillaries which advances to TMA (3). The challenge to swiftly identify MAHA is due to overlapping symptomatic presentations of TTP, HUS, atypical HUS/CM-TMA & MH-TMA. Ultimately, when presenting symptoms consist of severe hypertension, anemia, thrombocytopenia and progressive renal dysfunction should raise suspicion for MH induced TMA. Renal biopsy is the gold standard to assist in diagnostic confirmation of MH induced TMA & management entails aggressive blood pressure control.



PUB420

Prevalence of CKD and Its Relationship with Cardiovascular Risk: An Experience from Calcutta School Teachers' Cardiovascular Health Study Using Atherosclerotic Cardiovascular Disease (ASCVD) Model

Madhab Ray.[1,2] Healthy Heart Initiative Study Group. *[1]UC Davis Health, Sacramento, CA; [2]Tufts Medical Center, Boston, MA.*

Background: Cardiovascular disease (CVD) is the number one cause of death in high-income nations. Chronic kidney disease (CKD) shares most of the traditional risk factors with CVD. CVD event rates are much higher when CKD is a comorbidity. This study aimed to assess the relationship of CKD with CVD risk estimated by ASCVD model.

Methods: Cardiovascular risk factors and kidney function were evaluated in 4,140 schoolteachers in Calcutta, India in the summer of 2019 with joint approval of Tufts University IRB, Boston, and the local Ethics Committee, Calcutta. CVD risk was evaluated using the American College of Cardiology ASCVD risk calculator and stratified as mild (<5), moderate (>5 and <10) and high (>10). Kidney function was evaluated using serum creatinine level and eGFR calculated with CKD-Epi equation. Two-way Anova was used to evaluate the relationship between estimated GFR and ASCVD risk categories.

Results: The mean age of the participants was 44 years and 41% were male. Most participants (86%) were categorized as low risk for CVD, while 12% and 2% of the participants had moderate and high risk, respectively. Most participants had CKD G2 (n = 125, 52%) followed by G1 and G3 (n = 53, 22% each). Six participants had CKD G3B while number of participants in G4 and G5 were one in each category. There were no significant differences in the GFR among the different ASCVD risk categories (p-value > 0.05).

Conclusions: Our study failed to demonstrate any significant difference in GFR among the different CVD risk categories. In a randomized sample stratified by the CVD risk a high proportion of participants were found to be diabetic, previously not diagnosed. This discrepancy possibly led to under estimation of the CVD risk of the participants while their GFR was overestimated because of their underlying hyperglycemia. Further studies are necessary to ascertain the community burden of CKD and to explore the complex relationship between CKD and different traditional and nontraditional cardiovascular risk factors.

Cardiovascular risk categories and their relationship with estimated GFR

ASCVD Risk Category	Male	Female	Combined	GFR (mean) +/-SD
Low	78	114	192 (86%)	74.92 +/- 20.76
Moderate	21	7	28 (12%)	72.32 +/- 17.43
High	17	3	20 (2%)	76.95 +/27.29

Two-way Anova p value not statistically significant

PUB421

Hydralazine-Induced ANCA-Associated Vasculitis with Pulmonary Involvement

Shemrine Mark,[1] Jonathan London,[1] Mario Mekhail,[1] Olena Bolotova,[2,1] Ayse S. Durgun,[3,1] Mohammed S. Rahman.[2,1] *[1]Long Island Community Hospital, Patchogue, NY; [2]Brookhaven Nephrology Associates, Patchogue, NY; [3]NYU Langone Pulmonary Associates, East Patchogue, Patchogue, NY.*

Introduction: Hydralazine is a frequently used antihypertensive associated with ANCA vasculitis. Clinical symptoms range from benign to multiorgan involvement like alveolar hemorrhage and glomerulonephritis which can be fatal if not treated in a timely manner. It is important to be aware of this association for timely treatment and management.

Case Description: A 64-year-old male with a pmh of ESRD on hemodialysis for 5 years due to hypertensive nephropathy, Coronary artery disease presented to the emergency department for low hemoglobin. The patient complained of chronic fatigue, cough and denied any other complaints. Vitals were stable with conjunctival pallor on exam. The patient has had frequent hospital visits for weekly blood transfusions. Laboratory results showed hemoglobin of 6.2(13.7-17.5 g/dL). CT chest showed bilateral ground glass opacities. Evaluation of anemia included endoscopy, colonoscopy and bone marrow biopsy which were negative. Treatment included iron, darbepoetin alfa, weekly blood transfusion and pantoprazole. Due to recurrent transfusions and inflammatory changes on imaging autoimmune workup was done. Results showed ESR 51(0-15mm/hr), CRP 28.8(0-3mg/L), positive ANA, MPO ANCA >8(<1AI), anti-histone antibodies 2.1(0-0.9 units), low complement level and normal thyroid function. Hydralazine was discontinued and the patient was treated with pulse steroids. Patient had a lung biopsy which showed bronchiolar fibrosis with hemosiderin laden macrophages, perivascular chronic inflammation with necrosis consistent with treated granulomatosis with polyangiitis. Patient was reported to be on hydralazine for at least 2.5 years maximum dose 100 mg three times daily. Patient reported improvement in symptoms with stabilization of hemoglobin on follow up appointment.

Discussion: ANCA vasculitis is a rare disease with an incidence of 10-20 cases per million people. Of the patients with hydralazine induced vasculitis only 18% had pulmonary involvement. Mechanism is unclear. However, risk factors include thyroid disease, increased dose and duration of drug use, female sex and slow acetylators. Diagnosis is made through history, serology for anti-histone antibodies, ANCA, low complement and biopsy of affected organs. Treatment includes discontinuation of hydralazine and immunosuppressive therapy with pulse steroids, rituximab and or cyclophosphamide.

PUB422

Prehypertension and Hypertension among University Students in Bahrain: Study of Prevalence and Associated Risk Factors

Amgad E. El Agroudy. *Arabian Gulf University, Manama, Bahrain.*

Background: In the last twenty years, hypertension has become more common among younger age groups. Based on a global meta-analysis, the combined prevalence of hypertension and prehypertension were 4.0% and 9.7%, respectively. This study aimed to evaluate the prevalence of prehypertension and hypertension among university students and their associated risk factors.

Methods: Four hundred and eleven students aged between 18 and 25 (196 males and 215 females) were randomly selected to participate from College of Medicine and Medical Sciences (CMMS) and the College of Business Administration. The data was collected through a structured questionnaire, which gathered information about lifestyle habits. Trained students measured the participant's blood pressure and body mass index (BMI) according to standardized settings. All risk factors were studied according to the studying field and their gender.

Results: The mean age of the participants was 16.4±0.9 years. Of the total participants, 61.3% (n= 252) were normotensive, 30.7% (n= 126) were pre-hypertensive, and 8% (n= 33) were hypertensive. The prevalence of hypertension and prehypertension was higher in male students, 13.8% (n=27) and 44.9% (n= 88), compared to female students, 2.8% (n=6) and 17.7% (n=38), respectively. The results of the univariate analysis showed an association of hypertension with the field of study, gender, age, BMI, exercise frequency, frequency of eating junk food, and family history of hypertension ($p < 0.05$). Multivariate logistic regression analysis found a significant association between hypertension and pre-hypertension with gender, the field of study, and BMI.

Conclusions: The findings of the study revealed that hypertension and prehypertension are common among university students in Bahrain. The risk factors for these conditions include studying medicine, being male and being obese.

PUB423

Therapeutic Inertia of Hypertension and Physician Logic

Benjamin Strickland, Talar Markossian, Grant T. Hiura, Holly J. Kramer. *Loyola University Chicago, Chicago, IL.*

Background: Therapeutic Inertia (TI), the lack of escalation or initiation of blood pressure (BP) lowering medications during clinic visits with BP ≥ 140/90 mmHg occurs in majority of clinic visits among older adults. It remains a major barrier for achieving BP control. We reviewed a random selection of university affiliated outpatient primary care clinics with documented TI to elucidate reasons for not escalating treatment.

Methods: The source population included 7215 patients aged ≥65 with ICD-10 diagnosis of hypertension and ≥1 visit with uncontrolled BP at a university-affiliated clinic from January 2019 to December 2020. Uncontrolled BP was defined as a clinic systolic BP ≥140 mmHg and/or diastolic BP ≥ 90 mmHg confirmed with blood pressure measured 3 times in 1-minute intervals and averaged. Two investigators reviewed 101 unique patient outpatient clinic visits with documented TI in source population. A priori, reasons for TI were categorized as acute symptoms/illness, stress/pain, noncompliance, patient refusal, side effects and documentation of home BP < 140/90 mmHg. If more than one reason was present in a note, all reasons were included.

Results: The mean age of the 101 patients was 76.2 years (Standard Deviation [SD] 8.7) during the clinic visist. Comorbidities included diabetes mellitus in 35%, chronic kidney disease in 13% and cardiovascular diseases in 35%; 90% were covered by Medicare insurance. The mean total number of BP lowering medications was 1.8 (SD 0.92). Overall, 38% of charts lacked documentation justifying the TI; 51% overall had uncontrolled blood pressure at the subsequent clinic visit. Figure 1 shows the documented reasons for TI. Acute medical illness was the most common justification found(17%). No encounter had documentation of orthostatic hypotension. Overall 38% of encounters lacked documentation justifying the TI.

Conclusions: TI is common among older adults and may be due to clinician attention to acute illnesses, pain and stress. However, a substantial proportion of TI may not be justified.

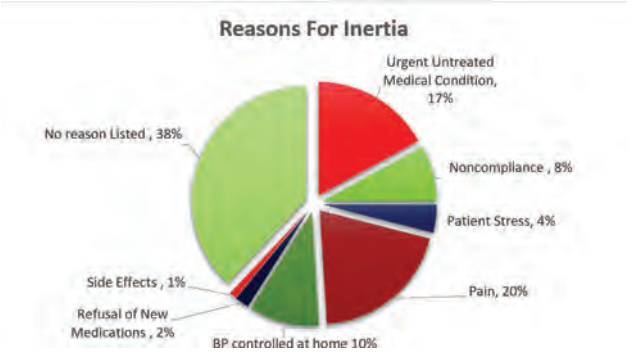


Figure 1

PUB424

Prospective Study on the Analysis of High-Sensitivity Troponin T in Patients with Hemodialysis: Cutoff Points and Cardiovascular Outcomes

Renato E. Eick,[1] Priscila Werner,[1] Gabriel Sartori Pacini,[2,1] Milton Kalil,[1] Mauricio L. André,[1] Renata A. Schuchmann,[2] Luiz Nasi,[1] Carlos A. Ferreira,[1] Anna C. Stein,[1] Camila M. Melere,[1] David Saitovich.[1] *[1]Hospital Moinhos de Vento, Porto Alegre, Brazil; [2]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil.*

Background: Patients with chronic kidney disease on dialysis may present troponin levels above the normal value even outside the context of suspected acute myocardial infarction. Even so, there is no clear established cutoff value in this population. Our aim was to evaluate and determine the basal troponin levels of each patient with CKD dialysis in a reference dialysis center in addition to assess cardiovascular outcomes.

Methods: We prospectively included consecutive patients with CKD on dialysis at a tertiary center in Southern Brazil. Mean, median and standard deviations of high-sensitive troponin T were assessed. Also, we correlated these values with other variables such as age, sex, hemoglobin levels, and iron measures to predicte an increased risk of cardiovascular mortality and mortality for other causes. The Receiver Operating Characteristic (ROC) curve was used to estimate the best cutoff point for pre-dialysis troponin levels to predict death within 24 months.

Results: During two-year follow-up, 88 dialytic patients were included. Mean age was 67 years, and most participants were male (62%). The troponin value using the pre-hemodialysis median was 64.7ng/L. In patients with previous ischemic heart disease and/or diabetes, this value is statistically higher. When we relate troponin to chest pain during dialysis or need to emergency room visits due to chest pain and death, the probability of death within 24 months is significantly higher in patients with troponin levels equal to or above 83.3 (p<0.001). The cut off value of 83.3 ng/L has a sensitivity of 75%, specificity of 80.9%, positive predictive value of 53.9% and negative predictive value of 91%, with accuracy of 79.5% to predict long-term mortality.

Conclusions: In our sample a cut off level of hS-TnT greater than 83.3 ng/L was associated with cardiovascular mortality and for other causes. Determining the median troponin value of a hemodialysis service and the basal troponin value of patients can improve the management of care by reducing the time to diagnose AMI and to avoid unnecessary measures, if the value remains constant at the patient's baseline.

PUB425

Feasibility of Near-Infrared Spectroscopy and Peripheral Arterial Disease Risk in CKD

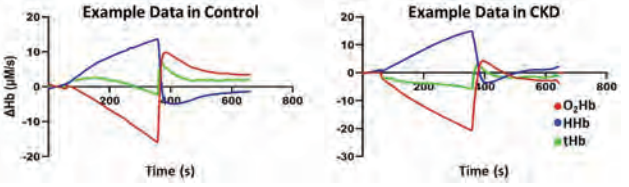
Stephanie E. Thompson, Ilhae Bok, Natasha Wiebe, Aminu K. Bello, Michael K. Stickland. *University of Alberta, Edmonton, AB, Canada.*

Background: Peripheral arterial disease (PAD) is common in chronic kidney disease (CKD). The role of microvasculature (MV) in the development and progression of PAD is recognized. Near-infrared spectroscopy (NIRS) tests muscle oxygen utilization (mVO2) and reactive hyperemia (MV function) non-invasively but its role in CKD and PAD is unknown. We evaluated NIRS feasibility and compared parameters in severe CKD with healthy controls. We explored its reliability and correlation with a MV referent test, velocity time integral (VTI).

Methods: A priori, feasibility was ≤10% of tests with i. discomfort and test termination ii. incomplete ischemic occlusion or iii. uninterpretable data. Participants completed baseline tests, Doppler US with reactive hyperemia from brachial and popliteal arteries for VTI and NIRS from the tibialis anterior muscle. An ischemic occlusion 50 mmHg above systolic BP for 5 minutes was used. The CKD group had repeat testing <14 days. Diagnostic accuracy testing was planned for NIRS and VTI correlations >0.7 and intraclass correlation coefficients (ICC) > 0.7.

Results: 39 CKD 5/5D and 20 controls participated. CKD participants were older with higher median systolic BP 135 mmHg [125,150] vs 109 [102,118], ABI 1.12 [1.03,1.20] vs 1.02 [0.89,1.06] and TBI 0.82 [0.77,0.92] vs 0.98 [0.93,1.03]. In CKD, 9 tests (23%) were terminated due to discomfort from the ischemic provocation vs none in controls. In CKD, 20% of tests had incomplete occlusions vs 10% in controls and 13% were uninterpretable vs 0% in controls. In CKD, brachial artery peak VTI was 55.8 cm [42.7, 71.3] vs 82.8 cm [76.2,97.3] in controls (P<0.001). Popliteal peak VTI results were similar. Median mVO2 was higher in CKD: 0.25 %/second [0.23,0.28] vs 0.20 [0.18,0.24] (P=0.007) and reactive hyperemic response was lower in CKD oxyhemoglobin recovery slope 0.61 μM/sec [0.50,0.93] vs 0.93 [0.69,1.21] (P=0.007) (Figure). No NIRS tests had correlations >0.7 and ICCs >0.7.

Conclusions: Ischemic provocation limited feasibility. mVO2 and reactive hyperemia from NIRS in CKD was consistent with muscle adaptations in PAD. Applications of NIRS in PAD should be evaluated in larger studies using alternative provocation tests.



PUB426

Examining Circadian Blood Pressure Patterns: Investigating the Interplay between Dipper Status and Arterial Stiffness Metrics

Chanwoo Nam, Negiin Pourafshar. *MedStar Georgetown University Hospital Nephrology Services, Washington, DC.*

Background: Compared with dippers, hypertensive individuals with a nondipping nocturnal blood pressure (BP) pattern, often present with heightened target organ damage and a bleaker cardiovascular prognosis, influenced by arterial stiffness. Tonometric pulse wave velocity (PWV) and Augmentation index (AI) have been confirmed as a non-invasive method for arterial stiffness evaluation. The purpose of this study was to assess the relationship between nocturnal blood pressure dipping and arterial stiffness in the hypertensive subjects.

Methods: This was a retrospective study of patients underwent ambulatory blood pressure monitoring (ABPM) between April 2021 and April 2022 at our institution. 41 subjects with essential hypertension were included, mean age 55.6 (42% female, 58% male). BP measured by ambulatory monitoring every 20 min between 07:00 am and 23:00 pm and every 30 min at night, throughout 48 hours with a Mobil-o-graph device. Carotid-femoral PWV and AI also measured as an index of aortic stiffness, by using the Mobil-o-graph which uses a validated transfer function. Dipping was defined as a 10-20% fall in nocturnal BP; extreme dipping as greater than 20%, nondipping as less than 10%, and reverse-dipping as 0% at most fall in nocturnal BP.

Results: The relationship between PWV and percent of fall in nocturnal SBP (percent of dipping) had negatively related with univariate generalized linear model (coefficient = -0.148, p-value = 0.007). Following multivariate adjustment for age, gender, mean arterial pressure and AI, percent of dipping becomes a variable without significant effect to model (coefficient = -0.408, p-value = 0.110). Age and percent of dipping has significant negative relationship (coefficient = -0.145, p-value = 0.0247) and age is strongly positively related with PWV (coefficient = 0.134, p-value = 0.000001). When multivariate adjustment is made for gender, mean arterial pressure and AI, percent of dipping remains significant variable to model (coefficient = -0.126, p-value = 0.009)

Conclusions: Percent of fall in nocturnal SBP has significant negative correlation with PWV. When adjusted with age, percent of fall in nocturnal SBP becomes insignificant variable. This is because age is a confounding variable to multivariate model. Elderly patients have less percent of fall in nocturnal SBP which leads to higher PWV.

PUB427

A System-Based Initiative to Improve Screening for Primary Aldosteronism (PA) in Patients with Resistant Hypertension

Medha Airy,[1] Michael Fordis,[1] Tresa Mcneal,[2] Derek Meeks,[1] Jacob S. Minor,[2] Daniel R. Murphy,[1] Michael J. Mcneal,[2] Jason E. King,[1] Michael O'Connor,[1] Abraham Mendoza,[1] Mohanram Narayanan,[2] Sara Bedrose,[1] Arindam Sarkar,[1] Jason D. Ramm,[1] Rory R. Laubscher,[1] Penny M. Coots,[2] Hania Janek,[2] Ashok Balasubramanyam,[1] F David D. Winter.[2] *[1]Baylor College of Medicine, Houston, TX; [2]Baylor Scott & White Medical Center Temple, Temple, TX.*

Background: PA is increasingly recognized as an under-screened etiology of resistant hypertension for all patients including those with chronic kidney disease. The specific aim was to increase the screening rates for PA by 25% over baseline.

Methods: The study aimed to change PA screening and referral practices of primary care clinicians operating in two diverse health systems: a health science university [HSU]

and a large health system [HS]. Customized interventions, adapted to each system's workflow, included live meetings; online modules in an indexed library to support just-in-time education, and point-of care education delivered via the EHR using a best practice advisory (BPA) to identify patients at risk for PA. Each health system collected data on three targeted metrics measured pre- and post-intervention: overall screening rates for PA [primary metric], referrals of patients with positive screening results to appropriate subspecialty department (i.e., nephrology, endocrinology, cardiology), and total diagnoses of PA after controlling for patient populations [secondary metrics].

Results: For the primary metric, baseline screening rates of 1.4% (HSU) and 0.015% (HS) of patients improved at post intervention to 7.1% (~5-fold increase) and 0.117% (~8-fold increase), respectively. A *z* test for independent proportions applied to each dataset indicated statistical significance ($p < 0.001$ for each analysis). Use of statistical control charts with special cause analysis allowed us to track for each of the three metrics whether intervention effects emerged, and if so, whether higher levels of performance continued and stabilized over time or degraded. Enhanced screening rates following the intervention were evident in the control charts, which continued during the 16-month post period. Regarding secondary metrics, rates of referral and diagnosis evidenced similar trends in meeting the conditions for detecting special cause, with elevated gains sustained longitudinally.

Conclusions: PA is an important cause of resistant hypertension. Increasing awareness of this diagnosis amongst clinicians can improve diagnosis and outcomes in patients.

PUB428

Study of Pulmonary Hypertension in Patients with CKD in a Teaching Hospital

Geetika Gorrepati. *Tulane University, New Orleans, LA.*

Background: Pulmonary hypertension is defined as a mean artery pressure >25 mm Hg and is a serious and progressive complication of chronic kidney disease and end-stage renal disease. Identifying pulmonary arterial hypertension (PAH) can be challenging but is important in this population since management strategizes differ from those for patients with ESKD who donot have PH.

Methods: This was an observational cross section study conducted on 85 patients of CKD stage 4 and 5 (based on KDIGO 2012 criteria) admitted to the medicine wards in Mamata academy of medical sciences, bachupally Hyderabad from the year 2022-2023

Results: In our study 35.2 % cases showed no PAH. Mild PAH noted in 23.5% cases, Moderate PAH noted in 36.4% cases and 4.7% showed severe PAH. systolic and diastolic blood pressure with PH showed significant association. Presence of haemodialysis significantly associated with PH. Significant association was seen with age and BMI. Low haemoglobin was also significantly associated with PH.

Conclusions: CKD patients have a higher prevalence of pulmonary hypertension. The prevalence of pulmonary hypertension is high in stage 5 CKD patients, and it is also higher in dialysis patients.

Funding: Private Foundation Support

PUB429

Racial and Ethnic Disparities in the Association of Sleep-Disordered Breathing Diagnosis with Hypertension Severity at Baseline in Youth Referred for Hypertension Disorders

Elizabeth A. Onugha,[1,2] Andrew M. South,[3] Sahar Siddiqui,[2,1] Ashna Pudupakkam,[2,1] Carol Vincent,[3] Fallon Campbell,[1,2] Giya Harry.[3] *[1]Texas Children's Hospital, Houston, TX; [2]Baylor College of Medicine, Houston, TX; [3]Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC.*

Background: Sleep-disordered breathing (SDB) is associated with a higher risk of hypertension (HTN). Black/African Americans with SDB have more severe disease and are more susceptible to uncontrolled HTN compared with White adults. While Black/African American youth have a higher prevalence of SDB compared to White youth, racial and ethnic disparities in the association of SDB with HTN severity remain unknown. We set out to describe racial/ethnic differences in the association of SDB with baseline HTN severity in youth.

Methods: Retrospective cross-sectional analysis of baseline data from the Study of the Epidemiology of Pediatric HTN (SUPERHERO), a multisite Registry of youth referred to subspecialty care for HTN disorders using electronic health record data. Inclusion criteria were an initial subspecialty clinic visit for HTN disorders identified by ICD-10 codes from 1/1/2016–12/31/2023 and age <19 years. Exclusion criteria were youth on dialysis, kidney transplantation, or pregnancy by ICD-10 codes, as well as missing race or ethnicity data and blood pressure not in the HTN range. The exposure was SDB identified by ICD-10 codes. The outcome was stage 2 vs. stage 1 HTN based on age, sex, and height-based U.S. guidelines. We conceptualized race/ethnicity as a social construct and defined it as an effect modifier. We estimated the associations with unadjusted generalized linear models with an interaction term and stratified models.

Results: Of our cohort of 5,562 participants, mean age was 13.3 years (SD 4.1), 38% were male, 58% were White, 22% were African Americans and 19% were Hispanic/Latino. 39% had stage 2 HTN and 6% (n=549) had a diagnosis of SDB. Overall stage 2 HTN risk by SDB was 0.9 (95% CL 0.9–1.0). There was no significant effect modification, and stratified analyses showed no significant association in any group.

Conclusions: In our large cohort of youth referred for hypertension disorders, we did not observe racial or ethnic differences in the association of SDB with HTN severity at baseline. Equitable screening for and management of SDB in all populations is imperative.

PUB430

Effect of Early Spironolactone Treatment on Albuminuria in Patients with CKD and Hypertension: A Randomized Controlled Trial

Nattakarn Anantasamit, Kamolwan Pakchotanon. *Bhumibol Adulyadej Hospital, Bangkok, Thailand.*

Background: Recent research emphasizes non-steroidal mineralocorticoid receptor antagonists (MRAs) for slowing chronic kidney disease (CKD) progression and reducing albuminuria. However, there is limited research on the efficacy of spironolactone, a more accessible and low-cost steroidal MRA.

Methods: This randomized controlled trial was conducted at Bhumibol Adulyadej Hospital, Bangkok, Thailand, from October 2023 to February 2024. Participants had hypertension and CKD stage 2-3 (eGFR 30-89 ml/min/1.73 m2) and were already receiving ACEI or ARB medication. Eleven patients were enrolled: five received spironolactone, and six did not. Both groups received standard hypertension care. Follow-up evaluations were conducted at 3 months.

Results: Patients receiving spironolactone showed a mean decrease in urinary albumin-to-creatinine ratio (UACR) of 655.00 ± 621.82 mg/g, compared to 320.50 ± 504.87 mg/g in the control group, resulting in a difference of 295.92 mg/g (95% CI: -942.33 to 350.49; p = 0.370). The change in eGFR was -8.64 ± 9.12 ml/min/1.73 m2 in the spironolactone group and -3.38 ± 14.62 ml/min/1.73 m2 in the control group, with a difference of -5.26 ml/min/1.73 m2 (95% CI: -16.77 to 6.69; p = 0.400). The change in systolic blood pressure (SBP) was -21.80 ± 20.64 mmHg vs. -22.00 ± 24.79 mmHg (difference: 0.20 mmHg, 95% CI: -39.74 to 10.49; p = 0.254). The mean serum creatinine levels were 1.61 ± 0.90 mg/dL in the spironolactone group and 1.10 ± 0.14 mg/dL in the control group, differing by 0.51 mg/dL (95% CI: 0.07 to 0.95; p = 0.009). The mean potassium levels were 4.90 ± 0.43 mmol/L and 4.23 ± 0.41 mmol/L, respectively, differing by 0.67 mmol/L (95% CI: 0.22 to 1.08; p = 0.003).

Conclusions: Spironolactone did not significantly decrease albuminuria in hypertensive CKD patients already on ACEI or ARB therapy but was associated with increased potassium and creatinine levels. The study's findings are limited by the small sample size and short duration.

PUB431

The Persistent Challenge of Resistant Hypertension in CKD

Jennifer Lafave, Meghan Weiss. *Spherix Global Insights, Exton, PA.*

Background: Many nephrology and cardiology patients suffer from both hypertension and chronic kidney disease (CKD). These patients are burdened with complicated treatment regimens that are difficult to follow, which makes it challenging to achieve target blood pressure goals.

Methods: Data from 156 US physicians (76 nephrologists and 80 cardiologists) was collected via an online survey conducted in March 2024.

Results: Physicians report that half (54%) of their CKD Stage 1 and 2 patients have hypertension as a comorbidity and as these patients advance in their CKD, the prevalence of hypertension increases substantially. Approximately one-third (36%) of CKD patients with hypertension are estimated to be poorly controlled on their current treatment regimen and 14% are classified as having "resistant" hypertension, which occurs when blood pressure levels remain elevated despite treatment with maximum tolerated doses of at least three antihypertensive drugs. Both nephrologists and cardiologists rank resistant hypertension as one of the most challenging cardiorenal conditions to manage and consider it to have a high unmet need for new treatment options. Physicians report that they struggle with optimizing and simplifying medication regimens that make it feasible for patients to adhere to treatment regimens. Nephrologists and cardiologists express strong interest in newly approved and pipeline agents for hypertension. They are eager to begin prescribing aprocintentan once it is available and report that more than one-quarter of their hypertensive CKD patients are candidates for treatment. Baxdrostat (an aldosterone synthase inhibitor) also garners high interest from specialists to treat uncontrolled hypertension. As new agents become available, physicians will primarily seek information related to their respective clinical trial data, degree of advancement over other available therapies, the ability to address multiple indications, and cost implications to help them determine appropriate candidates for treatment.

Conclusions: New pipeline products for hypertension, especially those tested in the CKD patient population, will offer nephrologists and cardiologists alternative treatment options to more effectively address one of the most challenging conditions that they face.

PUB432

Body Mass Index and Hypertension Risk among a Coptic Adolescent Population

Ivana Boktor,[1] Ahmed E. Ali,[2] Ammar Almehmi.[3] *[1]George Walton Comprehensive High School, Marietta, GA; [2]Mayo Foundation for Medical Education and Research, Rochester, MN; [3]The University of Alabama at Birmingham, Birmingham, AL.*

Background: Elevated Body Mass Index (BMI) is a significant risk factor for developing hypertension (HTN). Other factors, including family history, smoking, and energy drink consumption, can potentially increase risk for HTN. Limited data are available on the risk factors for HTN in Coptic adolescent population. This study sought to investigate association between these risk factors and HTN in Coptic adolescents.

Methods: A screening survey was conducted on 140 high school students who attended church services. After signing a consent form, each participant was interviewed and asked to answer the survey questions. The blood pressure was measured twice after 15 minutes of rest using Omron device. Both weight and height were measured, and BMI was calculated using CDC BMI calculator. Descriptive statistics, univariate, and multivariable logistic regression analyses were used to explore the relationship between the HTN and other potential variables.

Results: The cohort included 70 females (50%) and 70 males (50%) aged 16-21 years old. The overall prevalence of HTN was 45.7% (73% in males and 18.6% in females). Participants were categorized by BMI into normal (n=78), overweight (n=44), and obese (n=18) groups. Compared to normal weight group, the odds ratio (OR) for HTN in overweight and obesity groups was 7.2 (95% C.I. 3.1 – 16.6, p<0.001) and 1.9 (95% C.I. 0.67 – 5.5, p=0.27), respectively. After adjustment for potential confounders such as age, sex, family history of HTN, and consumption of energy drinks, the adjusted ORs were 4.9 (p=0.001) and 1.1 (p=0.9) in overweight and obesity groups, respectively. Among total cohort, hypertensive individuals exhibited significantly higher BMI compared to normotensive individuals (26.3 [23.5, 28.3] vs. 22.5 [20.6, 25.7], p=0.001). However, there was no association between HTN and other covariates (p>0.05). In multivariable logistic regression, the association between HTN and elevated BMI remains significant (adjusted OR 3.7, 95% C.I. 1.5 – 8.7; p=0.003).

Conclusions: Our findings are consistent with accumulative evidence about positive relationship between BMI and HTN, which is a part of the metabolic syndrome. Moreover, this is the first study to investigate risk factor profile for HTN in Coptic adolescents. Larger scale epidemiologic studies are needed to assess prevalence of HTN in this population and the best approach to manage these modifiable risk factors.

PUB433

Impact of Systemic Lupus Erythematosus on Cardiovascular Morphologic and Functional Phenotypes

Zishan Lin,[1] Wenfeng Wang,[1] Bingjing Jiang,[1] Jian He,[2] Yanfang Xu.[1] *[1]The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; [2]Southern Medical University Nanfang Hospital, Guangzhou, China.*

Background: Previous studies have established a correlation between systemic lupus erythematosus (SLE) and the cardiovascular system, but the potential causal implications of SLE on the cardiac and aortic morphology remain unclear. Cardiovascular magnetic resonance (CMR) imaging, a novel and non-invasive modality, uniquely assesses cardiovascular structure and function, serving as risk biomarkers. In this study, we conducted a Mendelian randomization (MR) analysis to ascertain the causal connection between SLE and CMR traits.

Methods: Genetic variants independently linked to SLE were selected from a genome-wide association study (GWAS) containing 5,201 cases and 9,066 controls as instrumental variables. A set of 82 CMR traits was obtained from a recent GWAS, serving as preclinical indicators to provide preliminary insights into the morphology and function of the four cardiac chambers and two aortic segments. Primary analysis employed a two-sample MR study using the inverse-variance weighted method. Heterogeneity testing, sensitivity analyses, and instrumental variable strength assessments confirmed the robustness of the findings.

Results: SLE exhibited a correlation with increased stroke volume (β=0.007, P=0.045), regional peak circumferential strain (β=0.013, 0.009, 0.013; P=0.002, 0.043, 0.006), and global peak circumferential strain of the left ventricle (β=0.010, P=0.022), as well as decreased left ventricular regional radial strain (β=-0.010, P=0.017) (Figure.).

Conclusions: This research presents evidence of a potentially causal association between traits of SLE and alterations in the structure and function of the cardiac and aortic systems, offering guidance for cardiac examinations and disease prevention in lupus patients.

Funding: Government Support - Non-U.S.

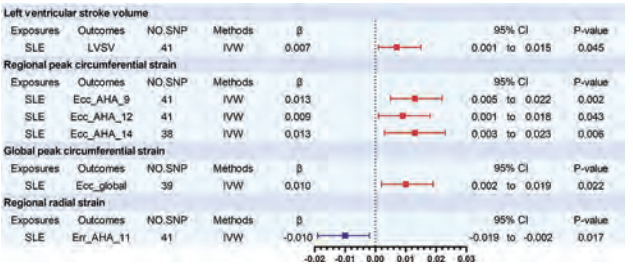


Figure. Significant associations of genetically predicted SLE traits with cardiovascular magnetic resonance traits

PUB434

Multiple Office Blood Pressure Measurement for Hypertension Diagnosis in Children

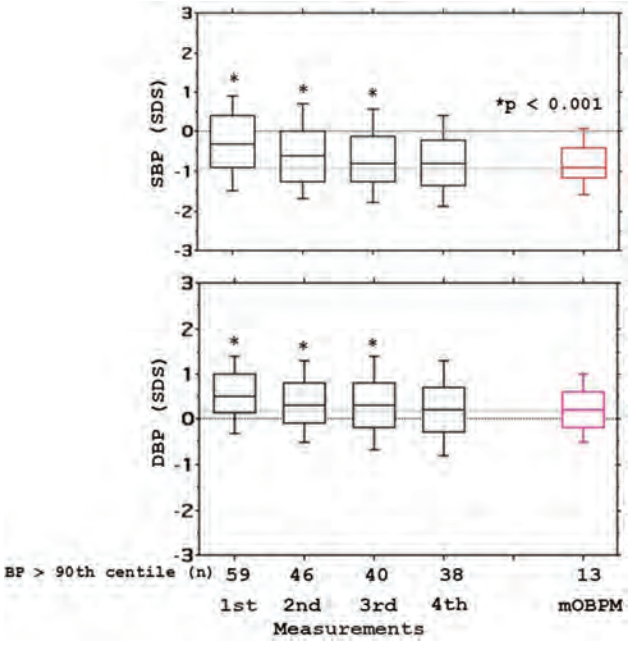
Letizia Dato,[1] Maria Cristina Mancuso,[2] Laura Viola,[3] Giacomo Tamburini,[2] Daniele Rossetti,[2] Andrea Gualtieri,[4] Gianluigi Ardissino.[2] *[1]Università del Piemonte Orientale, Division of Pediatrics, Department of Health Sciences, Novara, Italy; [2]Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Pediatric Nephrology, Dialysis and Transplantation Unit, Milan, Italy; [3]Ospedale di Stato, ISS San Marino, Pediatric Unit, San Marino, San Marino; [4]ISS San Marino, Health Authority, San Marino, San Marino.*

Background: Blood pressure (BP) measurement (M) in children may be challenging. International guidelines suggest measuring BP 3 times. In a previous study, we reported that the first 3 readings are unreliable. At our Centre, multiple Office BPM (mOBPM) is the standard practice for hypertension diagnosis in children since 2010. It consists of 10 serial readings taken at 3-minute intervals using a validated automated oscillometric device. After discarding outlier readings (<5th and >95th centile), the coefficient of variation (CV) and the remaining systolic (S) and diastolic (D) BP means are calculated by a software. This contribution is aimed at testing mOBPM in a children cohort to bolster its use as a practical tool to assess BP in children.

Methods: School children underwent mOBPM at baseline and after 12 months. After excluding series with a CV>15%, the mean SBP and DBP values obtained by mOBPM were compared with each of the first 4 M (t test for paired data). The number of children with BP>90th centile within those M was also determined.

Results: One hundred and seventy-five children (93 females, 53%) with a mean age of 8.6±0.3 and a mean BMI of 17.5±2.9 (BMI>20 n=34; 19%) were enrolled. Thirteen mOBPM were excluded for a CV>15% in SBP or DBP. As represented in **Figure 1**, the remaining 328 mOBPM showed that the mean of the first 3 SBP and DBP values were higher (p<0.001) than those obtained with mOBPM. The same held true for the mean of the 2nd and 3rd M, whereas the 4th was the first one not significantly different from mOBPM. The number of children with BP>90th centile by each reading and by mOBPM is also provided.

Conclusions: Relying on the first 3 M overestimates the number of hypertensive subjects, prompting unnecessary diagnostic and therapeutic pathways. The 4th is more reliable but mOBPM provides a better evaluation of BP particularly when initial readings show higher than normal values.



PUB435

Onconephrology's Public Awareness and Interest Landscape, 2020-2024: Trends Underscore Need for Enhanced Engagement

Priscilla Koirala, Charat Thongprayoon, Oscar A. Garcia Valencia, M. Salman Sheikh, Jing Miao, Iasmina Craici, Maria Lourdes Gonzalez Suarez, Swetha Rani Kanduri, Sandra Herrmann, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Onconephrology, a specialized field at the intersection of oncology and nephrology, addresses the complex kidney-related issues in cancer patients and survivors. With the Internet increasingly becoming a vital resource for healthcare information, this study aims to explore the global and United States-specific Internet search interest in onconephrology from 2020 to March 30, 2024, utilizing Google TrendsTM as an analytical tool.

Methods: This investigation utilized Google TrendsTM to analyze search queries for "Onconephrology" globally and within the United States. The period of study extended from January 2020 to March 2024. We examined the search interest over time, identifying peak interest points, the lowest interest, and trends in recent interest compared to the previous year. These indices were contextualized against the backdrop of onconephrology's evolving role in healthcare.

Results: Throughout the five-year study period, the peak global search interest for onconephrology was observed on October 6, 2019, with a value of 100, denoting its highest popularity. Conversely, the lowest interest was recurrently observed at several points, starting from March 31, 2019, each reflecting minimal search activity. In the USA, the peak interest was on January 9, 2022, with the lowest and most recent interests mirroring the global pattern. Both global and USA-specific analyses revealed minimal seasonal effects on search interest, suggesting that fluctuations were likely influenced by non-seasonal factors, possibly including significant academic or clinical developments within the field.

Conclusions: This analysis underscores a generally ascending yet fluctuating interest in onconephrology, manifest both globally and within the United States. Despite periods characterized by intermittent peaks of interest, this trend highlights the necessity of amplifying public and professional interaction with onconephrology through tailored information campaigns and enhanced digital platform education. Future endeavors should focus on improving the accessibility and comprehension of online onconephrology resources, addressing the evolving informational needs of both the general public and healthcare professionals.

PUB436

From Remedy to Etiology: Pauci-Immune Necrotizing and Crescentic Glomerulonephritis following Immune Checkpoint Inhibitor Therapy

Gagan Aulakh, William P. Ott, Arshdeep Singh. *Jersey City Medical Center, Jersey City, NJ.*

Introduction: Immune checkpoint inhibitors (ICI) block inspections before attacking foreign cells widely used in various cancers. Renal IRAEs (Immune-Related Adverse Events), observed in 2-5% of patients, encompass pathologies like acute interstitial nephritis (AIN) and different glomerulonephritides. Prompt steroid commencement should be done before kidney biopsy following suspected renal IRAEs

Case Description: 82-year-old Filipino male was evaluated for experiencing fatigue, lethargy, and nausea persisting for one week. The patient has medical history of non-small cell lung carcinoma, undergoing ICI therapy (nivolumab and ipilimumab). The patient had desquamating generalized painful black skin lesions two months before and showed perivascular dermatitis with eosinophils, raising concerns about a potential drug reaction. Vital signs were within normal limits and examination was unremarkable except for lethargy and skin lesions. The initial laboratory results indicated non-anion gap metabolic acidosis with BUN 149 mg/dL (7-30) and creatinine 8.94 mg/dL (0.7-1.2). His renal functions were within the normal range during baseline assessments conducted three weeks ago. As a result, a diagnosis of acute renal failure was established. Tests were negative for relevant antibodies and infections. Our differential diagnosis included considerations for AIN, immune complex glomerulonephritis, or thrombotic microangiopathy, likely associated with immunotherapy. Patient was initiated on high-dose steroids i.e. methylprednisolone 125 mg daily. The patient exhibited an improvement in next 3 days in urine output and creatinine level to 4.38 mg/dL. Ultimately, a renal biopsy was performed for definative diagnosis, revealing pauci-immune necrotizing and crescentic glomerulonephritis with granulomatous interstitial nephritis and eosinophils. Then he was discharged on oral prednisone 50 mg daily. Hemodialysis was not required throughout the entire hospitalization period.

Discussion: Renal IRAE could manifest following the co-administration of drugs such as Proton Pump Inhibitors, NSAIDs, or other nephrotoxic medications. Managing renal IRAEs involves halting ICI therapy and steroids. If no improvement then Mycophenolate Mofetil or monoclonal antibodies like Infliximab may be given.

PUB437

Fatal Case of Crystalglobulin-Induced Nephropathy with Cardiac Nonamyloid Immunoglobulin Deposition Disease

Yusuke Ushio, Shun Manabe, Anna Nakai, Momoko Seki, Hiroshi Kataoka, Junichi Hoshino. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Introduction: Crystalglobulin-induced nephropathy (CIN) is a rare renal disorder associated with multiple myeloma(MM). Crystal-induced organ damage occurs in various organs, and the diagnosis is based on the presence of crystals in the affected tissues. In the context of cardiac deposition of monoclonal immunoglobulin, AL amyloidosis and monoclonal immunoglobulin deposition disease (MIDD) can be differentiated. When amyloidosis is excluded and light and/or heavy chain immunostaining is positive, the cardiac variant of MIDD, cardiac non-amyloid immunoglobulin deposition disease (CIDD), is diagnosed. There has never been a report of CIN combined with CIDD. Here, we report a case of severe acute kidney injury with gradually reduced cardiac function diagnosed as CIN combined with CIDD.

Case Description: A 55-year-old Asian woman presented with leg edema two weeks after COVID-19 infection. She exhibited renal dysfunction with Cr of 1.89 mg/dL, urinary protein 3+, and urinary occult blood 2+, and presented to our hospital. At the time of admission, her Cr was 2.4 mg/dL, IgG-λ M-protein was positive, and cryoglobulin was negative. Despite the initiation of hemodialysis due to anuria shortly after admission, her condition progressively deteriorated. Renal biopsy revealed a MPGN-like pattern of injury with proteinaceous thrombi in the glomeruli, arterioles, and interlobular arteries. Immunofluorescence staining was positive for IgG1 and λ light chains, consistent with monoclonal proteinaceous thrombi. Electron microscopy showed crystal-like structures in the glomeruli and arteries. Myocardial biopsy revealed λ light chain deposition, confirmed by immunoelectron microscopy. Bone marrow biopsy showed 10% plasma cells. The patient was treated with dexamethasone, daratumumab, and bortezomib as for MM. However, her renal function didn't recover. With a gradual decline in cardiac function, lactic acidosis and hypotension persisted, and she passed away.

Discussion: Both CIN and CIDD are rare diseases associated with monoclonal protein. CIN might involve the cardiac system as infarction. However, in this case, the same monoclonal protein affected the kidneys as crystals but directly damaged cardiomyocytes as intact light chains. Evaluation of each affected organ might benefit the patient for accurate diagnosis and appropriate treatment.

PUB438

The Final Hit: A Case of IgA Nephropathy with Pembrolizumab

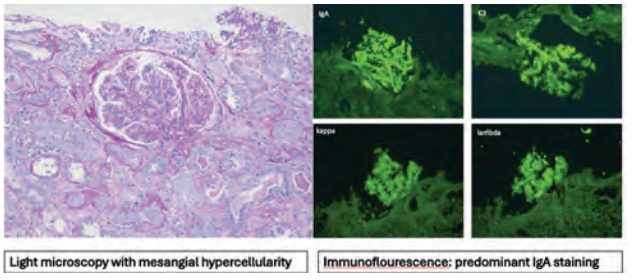
Sandipan Shringi,[1,2] Reginald Y. Gohh.[1,2] [1]*Rhode Island Hospital, Providence, RI;* [2]*Brown University Warren Alpert Medical School, Providence, RI.*

Introduction: Immune checkpoint inhibitors (ICI) have been implicated in the development of IgA Nephropathy (IgAN) and may not always respond to steroids leading to poor outcomes. We present a case of IgAN in a patient with lung cancer treated with pembrolizumab.

Case Description: A 73-year-old male presented with dark urine and dyspnea for a feew days and developed progressive AKI. He had a history of CAD, hypertension, DVT, tonsillectomy, soft palate invasive squamous cell carcinoma in 2012 treated with radiation, chronic dysphagia, and recently diagnosed bilateral lung squamous cell carcinoma in

2022 for which he was on carboplatin, paclitaxel and pembrolizumab for 3 months with latest dose 1 month ago. Physical exam was remarkable for tachypnea, bibasilar crackles without edema. Presentation labs were BUN 45 mg/dl, creatinine 2.77 mg/dl, Urinalysis with 3+ blood, >180 RBC, 51 WBC, 300 protein, urine culture had Enterococcus faecalis. UA 12 years ago had 6 RBC and one month ago had 3 RBCs. A chest radiograph showed multifocal interstitial and airspace opacities. Urine sediment had muddy brown casts, many isomorphic RBCs. C3 150 mg/dl, C4 28 mg/dl, ANCA, MPO, PR3, anti GBM were all negative, kappa chains 519 mg/L, lambda chains 216 mg/L, K/L ratio 2.4, serum IFE with 2 equivocal IgG kappa bands, urine IFE with equivocal IgG band. Renal biopsy had mesangial hypercellularity, focal endocapillary neutrophilic hypercellularity without crescents, several RBC casts, mild IFTA with predominant IgA staining on IF without C1q, fibrinogen or albumin and mesangial immune type electron dense deposits with partial foot process effacement on EM. He was treated with ceftriaxone but sCr did not improve and peaked at 9.4 mg/dl. He did not respond to pulse steroids which were then tapered. Due to poor overall health, he was not a candidate for chemotherapy or immunosuppression and transitioned to hospice. He died shortly after.

Discussion: IgAN occurs after four hits and our case was likely dormant for >10 years. It possibly got activated upon exposure to ICI but did not respond to steroids.



Light microscopy and Immunoflourescence

PUB439

Renal Thrombotic Microangiopathy Caused by Bevacizumab Treated with Eculizumab

Yasameen Fardi, Arash Rashidi, Daniel Grosser. *University Hospitals, Cleveland, OH.*

Background: 76 year old female diagnosed with hepatocellular carcinoma started Atezolizumab and Bevacizumab in March, 2023 and completed eight cycles in October, 2023. Prior to treatment her serum creatinine was 0.7mg/dL, urine albumin/creatinine 15mg/g. In November, she presented with creatinine 3.56 mg/dL, 3+ proteinuria on urine analysis.

Methods: Renal biopsy obtained revealed thrombotic microangiopathy with glomeruli showing double contours (Fig 1A), arterioles with mild to moderate subendothelial swelling (Fig 1B). Given these findings, she was started on Eculizumab, 900mg weekly for total of 4 doses. Eculizumab is a monoclonal antibody that targets complement protein C5, preventing cleavage of C5a and C5b and the formation of the terminal complement.

Results: When starting Eculizumab she required hemodialysis however after receiving three doses, she did not require further dialysis with signs of renal recovery.

Conclusions: Bevacizumab is a VEGF-A targeting monoclonal antibody that is associated with hypertension, proteinuria and renal TMA. VEGF-A increases endothelial cell survival and maintains vascular permeability. Inhibition of VEGF-A can cause damage of the glomerular filtration barrier and change in vascular tone. Initial treatment is drug discontinuation however our patient had no recovery after Bevacizumab was stopped. For this reason, Eculizumab was started with improvement of urine output and stabilization of serum creatinine off of dialysis. This case suggests further therapeutic role of Eculizumab for Bevacizumab associated TMA.

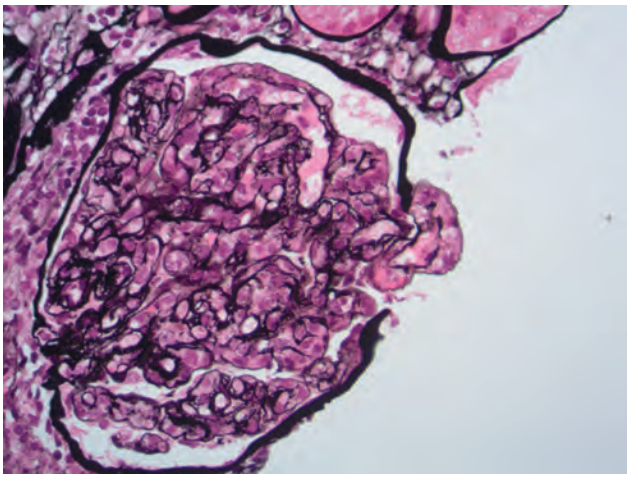


Figure 1A

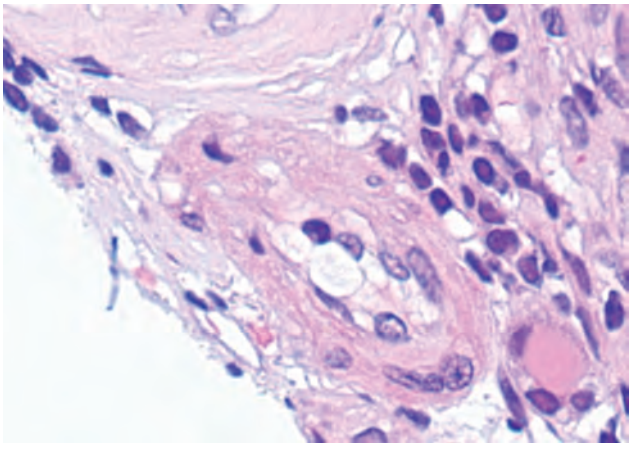


Figure 1B

PUB440

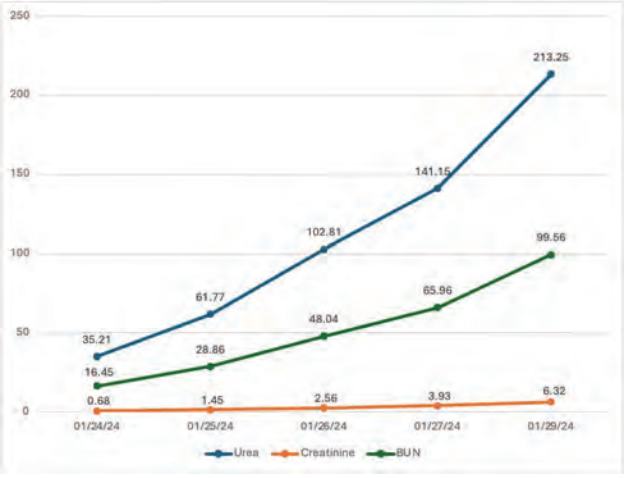
An Unusual Outcome after Hyperthermic Intraperitoneal Chemotherapy (HIPEC): AKI in a Patient Treated with HIPEC with Cisplatin

Jorge J. Font, Jorge E. Arch, Jose P. Castro, Fabiola Cassani, Javier Torres Figueroa. *Tecnologico de Monterrey - Campus Guadalajara, Zapopan, Mexico.*

Introduction: HIPEC stands at the forefront of innovative therapeutic approaches for managing select abdominal malignancies, revolutionizing the landscape of cancer treatment by combining an aggressive cytoreductive surgery with localized delivery of heated chemotherapy agents directly into the peritoneal cavity. Concerns regarding nephrotoxicity, particularly associated with the use of cisplatin, warrant attention. HIPEC has gained challenges such as excessive cost and the need for highly qualified personnel. In presenting this case, we exemplify the complexities of HIPEC-induced nephrotoxicity, highlighting the need for its timely recognition and management and the importance to consider and investigate post HIPEC CKD

Case Description: A 57-year-old Mexican female was hospitalized at the ICU after undergoing cytoreductive surgery and cisplatin-based HIPEC for peritoneal recurrence of ovarian cancer. Follow-up labs performed the next day revealed increased CR, urea, and BUN, suggesting impaired kidney function. Pre-op lab results did not indicate any type of risk factors or kidney injury before surgery. Renal function and diuresis continued to deteriorate over the following days. On the 4th day after surgery, presenting with anuria and unable to reverse her condition, the patient underwent an initial session of hemodialysis and has been dependent ever since with more than 5 months after surgery

Discussion: To our knowledge post HIPEC CKD information is scarce. AKI Post HIPEC has been noted as an important challenge due to the nephrotoxic properties of cisplatin but progression to CKD remains unclear. Nevertheless, the development of HIPEC-induced AKI with the possibility of CKD should not deter its use but rather emphasize the importance of raising awareness of searching for preventive strategies in aims of enhancing its effectiveness in improving patient clinical outcomes



PUB441

Prevalence of CKD Based on Estimated Glomerular Filtration Rate Using Creatinine and Cystatin C in Patients with Cancer Exposed to Conventional Chemotherapy: A Prospective Study

Renato A. Caires,[1] Lesley A. Inker,[2] Emmanuel A. Burdmann,[3] Veronica T. Costa e Silva.[1] *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Tufts Medical Center, Boston, MA; [3]Universidade de Sao Paulo Laboratorios de Investigacao Medica, Sao Paulo, Brazil.*

Background: Data on the impact of conventional chemotherapy (chemo) on development of chronic kidney disease (CKD) are largely based on retrospective surveys and rely on serum creatinine (SCr) to estimate the glomerular filtration rate (eGFR). We assessed the prevalence of CKD during chemo using eGFR equations based on SCr and cystatin C (SCysC)

Methods: This is a prospective cohort of patients with solid tumors exposed to chemo at São Paulo State Cancer Institute. eGFR was calculated through race-free CKD-EPI equations based on SCr (eGFRcr); SCysC (eGFRcys); or the combined version (eGFRcrcys) in three moments: before initiation of chemo (T0), during treatment (TM) and after end of chemo (TF). SCr and SCysC were measured through certified reference materials at the University of Minnesota. CKD was defined as eGFR<60mL/min/1.73m^2

Results: 485 adults with solid tumors were recruited between Oct2017 and Jan2019. Patients were 53±15y, 62.3% female. Most prescribed drugs were platinum-compounds (cisplatin, carboplatin, oxaliplatin) (53.7%), paclitaxel (39.8%), and doxorubicin (27.4%). Patients received a median of 4(3-6) cycles during 105(63-148) days of chemo. Median follow-up was 28(21-32) months. TM was collected 98(84-119) days after T0, and TF was collected 124(44-204) days after end of chemo. At this point, increased prevalence of CKD was observed in elderly, worse performance status, metastasis, or treated with cisplatin (Table)

Conclusions: In this cohort of adults with solid tumors, CKD developed more frequently in patients at higher risk. eGFRcr appeared to underestimate CKD prevalence compared to eGFRcys and eGFRcrcys in overall population and in most important subgroups

Funding: Government Support - Non-U.S.

	CKDcr eGFR<60mL/ min/1.73m^2	CKDcys eGFR<60mL/ min/1.73m^2	CKDcrcys eGFR<60mL/ min/1.73m^2
Overall			
T0 (N=485)	17 (3.5%)	52 (10.8%)	32 (6.6%)
TM (N=485)	24 (4.9%)	66 (13.6%)	38 (7.8%)
TF (N=328)	25 (7.6%)	43 (13.1%)	29 (8.8%)
Elderly			
T0 (N=96)	8 (8.3%)	25 (26.0%)	17 (17.7%)
TM (N=96)	12 (12.5%)	36 (37.5%)	23 (24.0%)
TF (N=62)	17 (27.4%)	27 (43.5%)	21 (33.9%)
Metastasis			
T0 (N=202)	7 (3.5%)	29 (14.4%)	19 (9.4%)
TM (N=202)	10 (5.0%)	31 (15.3%)	17 (8.4%)
TF (N=132)	10 (8.2%)	21 (17.2%)	15 (12.3%)
ECOG 2 or 3			
T0 (N=32)	2 (6.3%)	11 (34.4%)	6 (18.8%)
TM (N=32)	3 (9.4%)	8 (25.0%)	5 (15.6%)
TF (N=13)	4 (30.8%)	5 (38.5%)	4 (30.8%)
Platin			
T0 (N=244)	8 (3.3%)	32 (13.2%)	16 (6.6%)
TM (N=244)	14 (5.7%)	39 (16.0%)	22 (9.0%)
TF (N=168)	13 (7.7%)	22 (13.1%)	13 (7.7%)
Cisplatin			
T0 (N=94)	1 (1.1%)	5 (5.4%)	3 (3.2%)
TM (N=94)	5 (5.3%)	17 (18.1%)	11 (11.7%)
TF (N=67)	7 (10.4%)	11 (16.4%)	6 (9.0%)

CKDcr: CKD defined based on eGFRcr; CKDcys: CKD based on eGFRcys; CKDcrcys: CKD defined based on eGFRcrcys; GFR: estimated glomerular filtration rate; cr: creatinine; cys: cystatin C; crcys: creatinine and cystatin C; T0: sample collected before the start of antitumoral therapy; TM: sample collected in middle of treatment; TF: sample collected after the end of antitumoral treatment; CKD: chronic kidney disease; ECOG: Eastern Cooperative Oncology Group performance score.

PUB442

Antineoplastic Agents Associated with Hyponatremia and Modifiable Factors for the Associations

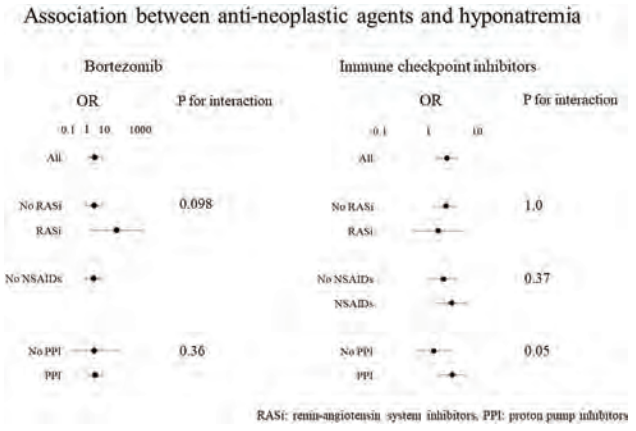
Yuki Miyaguchi,[1,2] Miho Murashima,[1] Kodai Suzuki,[1] Takahisa Kasugai,[1] Tatsuya Tomonari,[1] Masashi Mizuno,[1] Takayuki Hamano.[1] *[1]Nagoya Shiritsu Daigaku, Nagoya, Japan; [2]Nagoya Shiritsu Daigaku Igakubu Fuzoku Seibu Iryo Center, Nagoya, Japan.*

Background: Hyponatremia is associated with worse outcomes among patients with malignancy. In our previous study, we found that bortezomib (BOR), and immune checkpoint inhibitors (ICI) were significantly associated with hyponatremia. We aimed to identify modifiable factors for the associations.

Methods: This is a retrospective cohort study on patients with malignancy on anti-neoplastic agents at Nagoya City University Hospital from 2018 to 2020. We utilized logistic regression analyses using data at the time of each patient's lowest serum sodium concentration to examine the association of BOR and ICI with hyponatremia (Na ≤130 mmol/L) and effect modifications by rening-angiotensin system inhibitors (RASi), non-steroidal anti-inflammatory agents (NSAIDs) and proton pump inhibitors (PPI), as these factors are potentially modifiable.

Results: We included 2644 patients. Median age was 69 (58-75) years and median eGFR was 72.9 (58.1-88.1) mL/min/1.73m^2. Of these, 657(24.9%) developed hyponatremia and the lowest serum sodium concentration was 104 mmol/L. The use of BOR and ICI was associated with hyponatremia (OR 2.95 [1.25-6.97] and 2.40 [1.53-3.76], respectively) The incidence of hyponatremia was particularly high with simultaneous use of RASi and BOR (OR 48.6 [1.79-1330.70]), and with the use of PPI and ICI (OR 3.05 [1.69-5.49]) (p for interaction 0.098 and 0.05, respectively). No effect modifications were observed by NSAIDs. A sensitivity analysis using a mixed effects logistic regression showed similar associations and effect modifications.

Conclusions: Hyponatremia was common among those with malignancy. The concomitant use of BOR with RASi and ICI with PPI was especially associated with higher incidence of hyponatremia. Avoiding the contamitant use of RASi with BOR and use of PPI with ICI might reduce the incidence of hyponatremia.



PUB443

Acute Kidney Disease in Patients with COVID-19 and Cancer in Intensive Care: A Clinical and Retrospective Study

Germana A. Brito,[1] Joubert A. Alves,[1] Alexandre R. Fernandes,[1] Aline L. Baptista,[1] Marina H. Imanishe,[1] Benedito J. Pereira.[1,2] *[1]A C Camargo Cancer Center Centro Internacional de Pesquisa, Sao Paulo, Brazil; [2]Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: As cancer patients are a high-risk group for COVID-19, it is important to understand the potential complications they may experience, such as acute kidney disease (AKD). This study aimed to investigate the clinical characteristics and risk factors associated with AKD in cancer patients with COVID-19

Methods: The study was conducted retrospectively, using data from patients who were hospitalized with SARS-CoV2 infection. Demographic, clinical, and laboratory data were collected, and statistical analysis was performed using SPSS 29.0.

Results: In total, 143 patients were evaluated, of which 59.4% were male and aged 65.5±12.8 years. The majority (81.1%) had a solid tumor. During their hospital stay, 43.3% of patients developed AKD, with 25.8% requiring renal replacement therapy (RRT). Patients with AKD were more likely to have hypertension (64.5%) and cardiovascular diseases (32.3%). They also required more mechanical ventilation (MV) (71.7%), prone position (18.0%), and vasoactive drugs (VAD) (75.8%) (Table). The mortality rate was significantly higher in patients with AKD (72.6%) compared to those without AKD (39.5%). After 12 months, 44 patients were followed up, of which 84% did not have AKD and 16% developed AKD due to COVID-19 while in the ICU.

Conclusions: AKD in cancer patients with COVID-19 admitted to the ICU was more common in older patients with underlying hypertension or cardiovascular diseases. These patients required more invasive procedures such as MV, prone position, and VAD. The mortality rate was high even after discharge from the ICU.

Logistic regression of risk factors for AKD in patients with cancer and COVID-19 in the ICU

Variables	OR	95%CI	P-value
Hypertension	2.39	1.20-4.72	0.012
Age>60 y	2.46	1.15-5.25	0.020
Metastasis	0.55	0.27-1.14	0.111
Cadiovascular disease	2.69	1.19-6.08	0.017
Invasive mechanical ventilation	4.76	2.28-9.95	<0.001
Prone position	3.25	1.06-9.94	0.038
Vasoative drug	6.76	3.19-14.32	<0.001
Angiotensin Receptor Blocker	2.98	1.41-6.35	0.005
Angiotensin Converting Enzyme	2.26	1.00-5.09	0.049

PUB444

A Rare Case of Proliferative Glomerular Nephritis with Monoclonal Immunoglobulin Deposits

Justin D. Tse, Kiran Suryadevara, Jackson Wang. *Sutter Health, Roseville, CA.*

Introduction: Monoclonal gammopathies are an important cause of renal deposition diseases, known as monoclonal gammopathy of renal significance (MGRS). MGRS involves non-malignant or premalignant B-cells or plasma cells secreting monoclonal immunoglobulins that damage the kidneys. PGNMID, a new MGRS pathology, affects 1/4 of patients with detectable monoclonal gammopathy and presents with nephrotic syndrome, impaired kidney function, and hematuria. Here, we present a patient with PGNMID and diabetic glomerular sclerosis.

Case Description: We present a 78-year-old male with a history of depression, type 2 diabetes, peripheral vascular disease, HTN, HLD, and peripheral neuropathy who presented with abnormal labs: creatinine: 5.27mg/dL (baseline 1.10mg/dL), albumin: 1.1g/dL, and potassium: 5.6mmol/L. He had lower extremity bilateral edema. Urinalysis showed trace ketones, 3+ blood, and 500 protein. A comprehensive workup revealed UPC: 16g, kappa/lambda ratio of 2.04, beta 2 microglobulin level of 16.88 with SPEP beta 2 globulins increased relative to the beta 1 globulins. Renal biopsy indicated PGNMID (IgG3 kappa deposits) with diabetic changes. Hematological workup and bone marrow biopsy confirmed kappa-restricted plasma cell neoplasm. Due to progressive renal failure, he was started on hemodialysis with chemotherapy for continued management of his novel diagnosis.

Discussion: PGNMID and MGRS represent significant diagnostic challenges due to their specificity and complexity. Treatment depends on the type of kidney injury, guided by bone marrow biopsy to determine the clonal cell type. Clone-directed therapy could include rituximab, cyclophosphamide, bortezomib, and glucocorticoids. Daratumumab, a monoclonal anti-CD-38 antibody, can also be used if associated with multiple myeloma. If no clone or monoclonal protein is found, conservative therapy with anti-proteinuric agents and blood pressure control is recommended. When common causes like multiple myeloma or lymphoproliferative disorders are excluded, examining the secreted proteins helps distinguish between MGUS and MGRS pathology. Prompt diagnosis with a renal biopsy is essential, followed by a bone marrow biopsy to guide treatment. PGNMID is a rare and complex kidney disease requiring an interdisciplinary treatment approach. Its unique overlap with hematological disorders makes it a compelling subject for ongoing research.

PUB445

Long-Term Kidney Prognosis in Patients with Urologic Cancer after Nephrectomy

Sewon Oh, Yookyung Jang, Young Eun Choi, Tai yeon Koo, Myung-Gyu Kim, Sang-Kyung Jo. *Korea University, Seongbuk-gu, Republic of Korea.*

Background: Recent advances in medical technology have contributed to improved survival rates among cancer patients. Long-term outcomes are important for cancer survivors, and renal function plays a significant role in determining these outcome. We investigate the long-term renal functions in patients with urology cancers following surgery.

Methods: We analyzed the medical records of 1,661 patients with kidney, ureter and bladder cancer who underwent surgery without receiving chemotherapy at Korea university Anam Hospital and Guro Hospital from November 1999 to February 2019.

Results: Out of the total patients, 356 (21.4%) and 396 (23.8%) patients underwent partial nephrectomy(PN) and radical nephrectomy(RN), respectively. The average eGFR was 82.5±18.6 mL/min/1.73m^2 in the non-nephrectomy(NN) group, in the PN group it was 88.7±19.4 mL/min/1.73m^2, and in the RN group, it was 80.1±21.9 mL/min/1.73m^2. There was an average annual decrease of 4.4±17.3 mL/min/1.73m^2 in eGFR in patients who did not undergo nephrectomy adjusted by multiple factors. PN group exhibited a greater decline in eGFR compared to the NN (5.5±11.2 mL/min/1.73m^2,*P*=0.010). Furthermore, there was a greater decrease in eGFR in the RN group compared to the PN group (8.3±31.9 mL/min/1.73m^2,*P*=0.024). The risk of a 20% and 30% decline in eGFR showed no significant difference between NN and PN group (RR, 0.69, 95% CI, 0.45-1.07; RR, 0.72, 95% CI, 0.40-1.29). However, there was a significant increase in the risk of a 20% and 30% decline in eGFR observed in the RN group compared to NN group (RR, 1.58, 95% CI, 1.09-2.29, *P*=0.015 and RR, 2.00, 95% CI, 1.24-3.25,*P*=0.005).

Conclusions: The annual decline in eGFR was significantly different among patients who underwent PN, RN, and those who did not undergo nephrectomy. Preserving renal tissue is crucial for determining renal prognosis when undergoing nephrectomy.

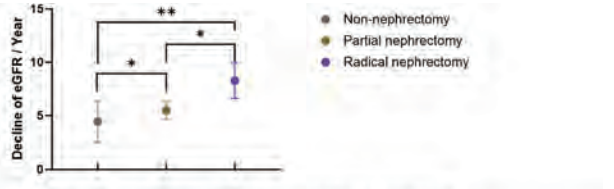


Figure 1. The average annual decrease in eGFR (mL/min/1.73m^2) by surgery type.
Adjusted by age, sex, baseline estimated glomerular filtration rate, body mass index, hemoglobin, white blood cell count, platelet count, serum potassium, serum chloride, serum albumin, total cholesterol, *C*-reactive protein, hypertension, diabetes mellitus, coronary artery disease and proteinuria.
*p < 0.05 **p < 0.01

PUB446

Relevance of Measured GFR in the Onconephrological Panorama: An Essential Tool to Apply Precision Medicine

Francesco Trevisani,[1] Fabiana Laurenti,[2] Mariadelina Simeoni,[3] Alessandra Cinque,[1] Arianna Bettiga,[1] Umberto Capitanio,[1] Andrea Salonia,[1] Massimo Locatelli,[1] Giorgio Pizzagalli,[1] Francesco Montorsi.[1] *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Universita degli Studi di Verona Dipartimento di Neuroscienze Biomedicina e Movimento, Verona, Italy; [3]Universita degli Studi della Campania Luigi Vanvitelli Dipartimento di Scienze Mediche Traslazionali, Napoli, Italy.*

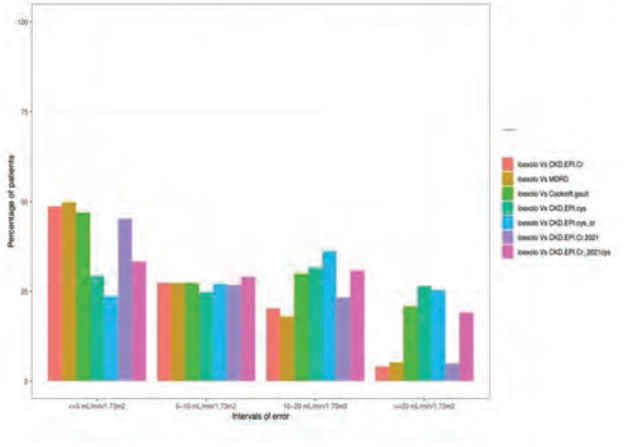
Background: An accurate assessment of renal function is fundamental in several categories of patients where the adequate medical or surgical treatment depends on the values of glomerular filtration rate (GFR). In particular, in the onco-nephrological scenario the determination of the "real" GFR can dramatically change the clinical algorithm and therefore the lifespan of patients. Unfortunately, the most used method to define the GFR is represented by eGFR which harbours a significant error in comparison to gold standards methods (mGFR). Aim of this study was to determine the extent of the error of eGFR compared to the mGFR in a consecutive cohort of patients affected by urological malignancies.

Methods: A consecutive cohort of 500 oncological patients affected by urological cancers enrolled in a single tertiary institution between 2018-2024 was collected in order to compare the most common eGFR formulas (Cockroft-Gault, MDRD, CKD-EPI 2012 and 2021, CKD-EPI cystatin, CKD-EPI creatinine and cystatin 2012 and 2021) with mGFR using Iohexol Plasma Clearance. True positives and False positives were classified in CKD stages based on eGFR and mGFR. Comparisons between groups were performed using Wilcoxon ranks sum test for numerical variables and Pearson's Chi square test for categorical ones.

Results: Clinical data: overall median age was 66 years, median BMI 25, Male:536, F:165, Diabetes: 10.9%, Hypertension: 53.8%, CKD stage I: 3.7%, II: 25.5%, IIIA: 28%, IIIB: 27.5%, IV: 13.4%, V: 1.74%, mean Creatinine: 1,44 mg/dl, cystatin: 1,24. We reported a huge discrepancy between the eGFR formulas and mGFR values, suggesting the essential role of mGFR in the clinical decision making algorithm (Figure 1 and 2).

Conclusions: In onco-nephrological scenario the use of eGFR remain debatable and misleading. mGFR is a crucial tool for a correct clinical decision based on precision medicine.

Figure 1: Overall population (oncological and non-oncological patients) percentages of patients with four different intervals of error in term of ml/min/1.73 m2



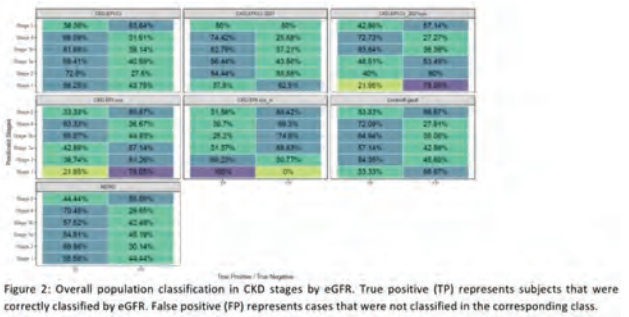


Figure 2: Overall population classification in CKD stages by eGFR. True positive (TP) represents subjects that were correctly classified by eGFR. False positive (FP) represents cases that were not classified in the corresponding class.

PUB447

Ectopic Cushing Syndrome: A Diagnostic Anomaly of Malignancy

Elizabeth F. Oguntuwase,[1] Carlos D. Flombaum,[2] Ilya Glezerman,[2] Victoria Gutgarts.[2] *[1]Weill Cornell Medicine, New York, NY; [2]Memorial Sloan Kettering Cancer Center, New York, NY.*

Introduction: Ectopic Cushing syndrome (ECS) occurs when Adrenocorticotropic hormone (ACTH) is produced outside the pituitary gland. This rare phenomenon increases mortality risk and may be a presenting sign of new or recurrent malignancy. We describe a patient with a history of breast cancer who presents with new metastatic cancer with hypertension, edema, hypokalemia and hypernatremia.

Case Description: 58-year-old female with history of breast cancer treated 9 years ago (on tamoxifen), Crohn's disease and nephrolithiasis was referred to the hospital for hypokalemia and concern for cord compression. She had a fall prior to admission with now pathological cervical and T12 fracture managed with dexamethasone and kyphoplasty. Her blood pressure was 161/87, Pulse 100bpm and oxygen saturation 90% on room air. Physical examination was notable for edema up to the thighs. Laboratory values; included potassium 2.7 (3.3-4.9)mEq/L, sodium 148 (133-143)mEq/L, carbon dioxide 24 (18-29)mEq/L, creatinine 0.7 (0.6-1.1) mg/dL. Fractional Excretion of potassium was 30.8% consistent with renal potassium wasting. PET scan showed metastasis involving the liver, lungs, adrenal, and osseous structures initially concerning for recurrent breast cancer based on prior history. Further work up showed cortisol level of 80.1 (5-25) mcg/dL, 24 hr cortisol 1428 (3.5-45) mcg/24h and ACTH of 610 (7.4-64.3) pg/mL consistent with ECS. Serum aldosterone of <4 (< 21) ng/dl, renin activity of 1.1 (0.6-3.0) ng/ml/hr. She was started on spironolactone 25mg twice daily and metyrapone 250mg every 8 hours. Ketoconazole was avoided due to transaminitis. Her potassium requirements declined, and she was no longer hypertensive. The biopsy from bone lesion was consistent with new small cell lung carcinoma with elevated Chromogranin A levels 2036 (<93) ng/ml.

Discussion: This case highlights the importance of recognizing ECS as a rare paraneoplastic phenomenon. Cortisol and ACTH levels should always be checked in a patient with malignancy, hypertension, and hypokalemia, despite exogenous steroids. Once the diagnosis of ECS is made, treatment is aimed at the cancer as well as steroidogenesis inhibitors (ketoconazole or metyrapone) and mineralocorticoid antagonists (spironolactone). Biopsy in new metastatic disease is key for appropriate diagnosis to avoid anchoring bias and assume that metastases are from prior malignancy.

PUB448

Atypical Acute Myeloid Leukemia Presentation: Spinal Metastasis and Neurogenic Bladder

Katie Gallagher, Prakash S. Gudsoorkar. *University of Cincinnati College of Medicine, Cincinnati, OH.*

Introduction: Central nervous system (CNS) involvement in acute myeloid leukemia (AML) is rare, with symptomatic involvement is much less common, only about 1-5% of cases. We present a case of AML, with a neurogenic bladder resulting from spinal metastasis.

Case Description: A 60-year-old male with AML complicated by renal dysfunction with baseline serum creatinine (SCr) 1.9-2.1 mg/dL presented with urinary retention. Diagnosed to have AML In (16) (FLT3-TKD mutation) 10 months before current presentation, treated with azacitidine & venetoclax. Admission labs were: Scr: 2.9 mg/dL, hemoglobin 9.4 g/dL, WBC count 9,300, and normal platelet count. Ultrasound: no urinary obstruction. Contrast MRI (Fig.1) showed multiple areas of white matter enhancement in the brain & diffuse T1 signal abnormalities with intramedullary lesions throughout the cervical and thoracic spine. Findings were suggestive of metastatic disease, with concern for an acute demyelinating process. Lumbar puncture results are in Tab.1 & Fig.2. A Foley catheter was placed & IV dexamethasone was started with intrathecal cytarabine, methotrexate and hydrocortisone. His urine output was 4-6 L/day, likely due to post-obstructive diuresis. Multiple voiding trials failed. Despite chemotherapy, he developed neurogenic bowel, causing diarrhea. SCr peaked at 5.6 mg/dL with acidosis. As symptoms progressed, he chose hospice care.

Discussion: CNS involvement in adults with AML is rare but more common in pediatric cases, affecting 1.1% of patients. Symptoms include encephalopathy, seizures, & cranial nerve palsies. Only 1-4% present with paraspinal or intracranial granulocytic sarcoma. Risk factors include hyperleukocytosis (>10^5/mcL), age <2 years, elevated LDH, prominent monocytic/myelomonocytic/monoblastic characteristics, APL/PML::RARA in relapse, and molecular/cytogenetic abnormalities like FLT3-ITD, inv(16) & chromosome 11 abnormalities. Acute urinary retention in our patient is rare and not reported in adults due to intraspinal involvement by AML.

Fig. 1

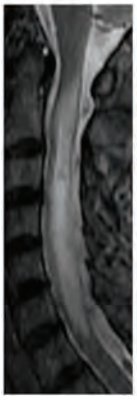


Fig. 2

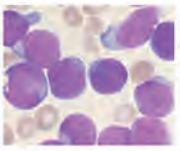


Table. 1

Component	Result
Color, CSF	Colorless
Clarity	Clear
Total Nucleated Cells, CSF	33 ↑
RBC, CSF	450 ↑
Neutrophil %, CSF	1
Lymphocytes %, CSF	4 ↓
Eosinophils %, CSF	0
Macrophage %, CSF	7
Other Cells %, CSF	88 (distinct population of CD34+ cells compatible with blasts)
Glucose, CSF	162 ↑
Immunological serologies for paraneoplastic spinal demyelination	Negative

Fig.1: Contrast MRI, multiple areas of diffuse T1 signal abnormalities with intramedullary lesions throughout the cervical and thoracic spine.

Fig.2: Lumbar puncture showing blast cells.

Table. 1: CSF (lumbar puncture results).

PUB449

Unveiling the Dual Threat: Glofitamab-Induced AKI via Tumor Lysis and Cytokine Release Syndromes

Akaljot Singh, Mragank Gaur, Prakash S. Gudsoorkar. *University of Cincinnati College of Medicine, Cincinnati, OH.*

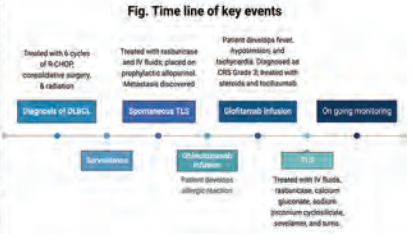
Introduction: Glofitamab, a monoclonal CD20-directed CD3 T-cell engager, treats refractory diffuse large B-cell lymphoma (DLBCL) but can induce acute kidney injury (AKI) via tumor lysis syndrome (TLS) and cytokine release syndrome (CRS). We report a case of a patient who developed AKI secondary to glofitamab infusion through both mechanisms simultaneously.

Case Description: A 78-year-old male with DLBCL presented with AKI. His baseline serum creatinine (SCr) was 1.6-1.8 mg/dL. Treated with 6 rounds of R-CHOP regimen, with some improvement 6 months ago. 6 weeks before admission, he developed spontaneous TLS, treated with rasburicase and IV fluids & was found to have metastatic recurrence of DLBCL. His tumor was treated with gemcitabine and oxaliplatin to no avail. Glofitamab was then started for DLBCL treatment. Due to CRS risk, the patient received obinutuzumab pretreatment. 30 minutes into the test dose, he experienced nausea, lethargy, and hypotension, leading to hospitalization. After stabilization, he tolerated the therapeutic dose of obintutuzumab 5 days later. Later, he received his first glofitamab infusion. Within 12 hours, he developed symptoms of CRS (fever, tachycardia, and hypotension) and was sent to ICU, received IV fluids, dexamethasone, and tocilizumab, which assisted with stabilizing his vitals. Key lab tests of CRS and TLS are in Table 1. For TLS, he was treated with IV fluids, sodium zirconium cyclosilicate, and sevelamer. His CRS resolved first, allowing him to be transferred back to the floor from the ICU. He continues to be treated for TLS, is recovering well, and is currently preparing for a 2nd dose of glofitamab.

Discussion: Glofitamab is a novel immunotherapy for DLBCL that can induce both CRS and TLS. While reports exist of these syndromes occurring simultaneously in response to other therapies, to our knowledge, glofitamab has not been previously reported to do so. As both CRS and TLS can cause AKI, albeit through different mechanisms, nephrologists should closely monitor patients receiving glofitamab for both syndromes.

Table: Key lab values pre-and post-glofitamab transfusion

Labs	Pre Glofitamab	Post Glofitamab	Reference interval
Sodium	151	145	133-146 mmol/L
Potassium	3.7	5.6	3.5-5.3 mmol/L
Chloride	110	117	98-110 mmol/L
Bicarbonate	24	15	21-33 mmol/L
BUN	29	107	7-25 mg/dL
Creatinine	1.8	3.52	0.60-1.30 mg/dL
Calcium	8.2	6.1	8.6-10.3 mg/dL
Free Calcium	-	1.55	4.40-5.40 mg/dL
Phosphorus	3.6	9.8	2.1-4.5 mg/dL
Magnesium	1.4	2.7	1.5-2.5 mg/dL
CRP	-	150	1.0-10.0 mg/L
Uric Acid	7.1	8.5	3.6-8.7 mg/dL
Ferritin	3,095.0	>7500	23.9-336.2 ng/mL
IL-6 levels	-	Awaited at the time of abstract submission	0-43.5 pg/mL



PUB450

AKI after Chimeric Antigen Receptor T Cell Therapy in Patients with Relapsed Hematological Malignancies: Experience of a Brazilian Cancer Center

Germana A. Brito, Benedito J. Pereira, Vanessa D. Bovolenta, Marjorie V. Batista, Jayr Schmidt Filho. *A C Camargo Cancer Center, Sao Paulo, Brazil.*

Background: Cytokine release syndrome (CRS) is the most frequent adverse event after chimeric antigen receptor T cell (CAR-T) therapy and can lead to multiple organ dysfunction. Acute kidney injury (AKI) is common, but usually mild. We aimed to assess the incidence of AKI, electrolyte disturbances, CRS, and mortality in a Brazilian cancer center.

Methods: We retrospectively evaluated patients with relapsed hematological malignancies treated with CAR-T therapy targeting CD-19 at the A.C. Camargo Cancer Center between November 2022 and April 2024.AKI was defined using KDIGO (Kidney Disease: Improving Global Outcomes) criteria. Laboratory test parameters, including serum creatinine and electrolytes collected daily in the pre and post-infusion period were retrospectively registered during hospital stay.

Results: Sixteen patients were included for analysis, age was 60,2 (36,4-67,1) years, 62,5% male. Fourteen (87,5%) had relapsed lymphoma and 12,5% acute lymphoid leukemia. CRS occurred in 87,5% of patients in a median of 3 (2-4,7) days after infusion; 81,2% of them were treated with tocilizumab and 62,5% with corticosteroids. CRS was similar in patients with and without AKI (Table). AKI occurred in 37,5% of patients 5 (3.2-15.2) days after infusion, stage 1,2, and 3 in 50%,33,3% and 16,7%% of cases, respectively. Only one patient required kidney replacement therapy.AKI recovery occurred in 83% of cases, 6 (4,5-11) days after AKI diagnosis. Most common electrolyte abnormalities were:hypokalemia(25%), hyponatremia(18,7%), and hypomagnesemia(18,7%). Mortality at 90 days post-infusion was 18,7%, occurring in 16,7% AKI patients and 20% without AKI (p=0,87).

Conclusions: This is the first study assessing AKI in patients treated with CAR-T therapy in Brazil, which included patients with relapsed hematological malignancies. CRS and AKI were frequently observed, AKI was usually mild and transitory.

Table. Baseline Characteristics of Patients with and without AKI

	All (n=16)	No AKI (n=10)	AKI (n=6)	p
Male, n (%)	10 (62,5%)	8 (80%)	2 (33,3%)	0,06
Age, median	60,2 (36,4-67,1)	60,2 (53,5-66,9)	52(29,1-66,6)	1,00
CAR T therapy, n(%)				0,69
Axicabtagene	2 (12,5%)	2 (20%)	0	
Tisagenlecleucel	14 (87,5%)	8 (80%)	6 (100%)	
Baseline Scr, mg/dL	0,85 (0,7-1,0)	0,8 (0,72-0,9)	0,95 (0,75-1,2)	0,41
Time until CRS	3 (2 – 4,75)	3 (2-3)	4 (2-5)	0,78
CRS, n (%)	14 (87,5%)	9 (90%)	5 (83,3%)	0,69
Grade 1	3 (21,4%)	3 (30%)	0	
Grade 2	9 (64,3%)	5 (50%)	4 (66,3%)	
Grade 3	2 (14,3%)	1 (10%)	1 (16,7%)	
Tocilizumab,n (%)	13 (81,2%)	8 (80%)	5 (83,3%)	0,62
Corticosteroids, n (%)	10 (62,5%)	6 (60%)	4 (66,6%)	1,0
ICU admission, n (%)	7 (43,7%)	4 (40%)	3 (50%)	0,7
Death, n (%)	3 (18,7%)	2 (20%)	1 (16,7%)	0,87

*CAR T=chimeric antigen receptor T cell;CRS= Cytokine release syndrome;Death in first 90 days after CAR T infusion;ICU= intensive care unit

PUB451

Outcomes following Treatment with Bortezomib in Patients with Multiple Myeloma Who Required Haemodialysis: A Single-Centre Experience

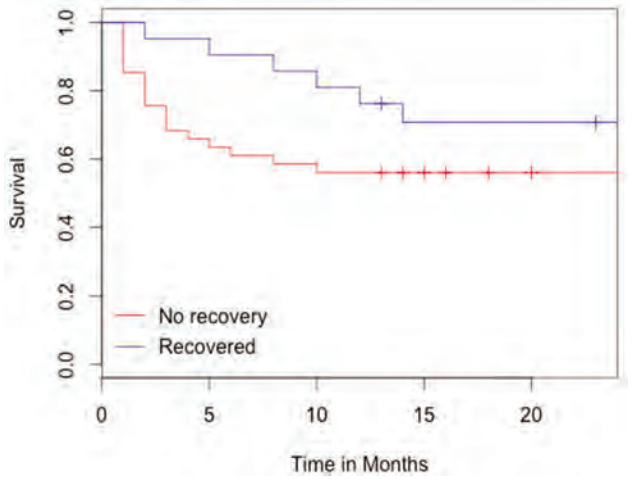
Mohammad Rabiul Islam Rony, Omaisa Mushtaq, Aoife Dervin, Simon C. Stern, James Croft, David Makanjuola. *St Helier Hospital, Carshalton, United Kingdom.*

Background: Renal impairment is a common complication of multiple myeloma (MM). About 10% present with acute kidney injury (AKI) needing haemodialysis (HD). Renal impairment is associated with increased morbidity and mortality. Bortezomib has resulted in a significant improvement in survival in comparison to other treatments. We looked at the survival and outcome of myeloma patients treated with Bortezomib, who also required HD during their treatment.

Methods: We analysed data from our electronic database on patients diagnosed with MM with associated renal impairment between 2010 to 2024. Patients who had HD at presentation, or after diagnosis of myeloma were included. Analyses were performed using Microsoft Excel and R.

Results: There were 116 patients. 68 (58.62 %) had HD. 62 (92%) received Bortezomib. Median age at diagnosis was 70 years (range 49-89 years), male to female ratio was 2.4:1. Median creatinine at initiation of HD was 645.5μmol/l. 20 (33%) recovered renal function. Median creatinine at stopping HD was 418μmol/L. Median duration on HD among patients who recovered function was 22.5 days. Survival at 3, 6 and 12 months was 90.4%, 90.4% and 70% respectively in patients who recovered renal function. In those who did not recover function, the 3, 6 and 12 month survival was 68%, 60.9% and 53.6% respectively. Survival in both groups is shown in the Kaplan Meier curve below.

Conclusions: In our patients, a significant proportion of those who had Bortezomib regained kidney function. Recovery occurred in most patients within 4 weeks, and was associated with improved survival at 3, 6 and 12 months. Newer agents available to patients with myeloma and severe kidney disease are likely to improve outcomes.



Survival of patients with recovered or non-recovered Renal function

PUB452

Incidence of AKI in Patients Admitted to Intensive Care Unit after Outpatient Chimeric Antigen Receptor T Cell Therapy: A Retrospective Single-Center Analysis

Adolfo Diaz-Barba, Noha Soror, Bibi Maryam, Taha Al-Juhaishi. *The University of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: Chimeric antigen receptor T-cell (CAR-T) therapy represents a new therapeutic option for patients with refractory hematological malignancies. New paradigms are being implemented to perform them in the outpatient setting. However, the multiple side effects often require hospital admission in different levels of care, including intensive care unit (ICU). We performed a retrospective analysis of ICU utilization, development of acute kidney injury (AKI) and need for renal replacement therapy (RRT), in patients who underwent outpatient CAR-T therapy in a National Cancer Institutes (NCI)-designated cancer center.

Methods: After obtaining IRB approval, we performed a retrospective chart review of 79 adult patients who underwent outpatient infusion of CAR-T therapy at Stephenson Cancer Center, Oklahoma City, between September 2019 and November 2023. We included patient whose indication for CAR-T was a hematological malignancy. We determined rates of ICU admission within 45 days after infusion, ICU admission diagnosis, development of AKI, need for RRT, length of stay and in-ICU mortality.

Results: We identified 79 patients who underwent ambulatory, FDA-approved CAR-T therapy infusion during the study period. Within 45 days of CAR-T infusion, 12.6% (10/79) of patients required ICU admission (one patient was excluded due to inability to obtain medical records during ICU stay). ICU admission diagnosis included (with some patients with more than one): distributive shock secondary to CRS grade 3-4 (4/9), sepsis (2/9), encephalopathy secondary to ICANS (2/9), acute hypoxic respiratory failure (2/10), hypovolemic shock (1/9). Among patients admitted to ICU, 11% (1/9) developed AKI. Of note, this patient who developed AKI required RRT for a total of 12 days (until date of death). Mean ICU length of stay was 4.8 days (1-16), and in-ICU mortality rate was 11% (1/9).

Conclusions: In this study, we found a lower rate of ICU admission compared to rates reported in similar studies. In majority of cases, ICU admission was due to CAR-T toxicities. Among patients admitted to ICU, one case developed AKI, and, notably, this case derived in fatal outcome. Kidney-specific toxicities are common with the advent of newer cancer therapies, which represents novel research pathways in nephrology.

PUB453

Percutaneous Kidney Biopsy in Patients with Metastatic Solid Malignancy and AKI on Systemic Anticancer Therapy

Tomaz Milanez,[1] Vinay Srinivasan,[2] Janja Ocvirk,[1] Edgar A. Jaimes.[3] *[1]Onkoloski Institut Ljubljana, Ljubljana, Slovenia; [2]Cooper University Health Care, Camden, NJ; [3]Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: Percutaneous renal biopsy (PRB) is the gold standard for assessing renal parenchymal disease and renal toxicity of systemic anticancer therapy (SAT). In pateints with solitary kidney (SK), PRBs are often deferred due to the perceived risk for major bleeding complications that may result in permanent loss of renal function. In this study we assessed the safety of PB and findings in patients receiving SAT including those with SK.

Methods: We retrospectively analyzed pathological findings of PRBs and the incidence of major complications of PRBs performed on native kidneys for the evaluation of AKI in patients with metastatic solid malignancy who received SAT and who underwent PRB between 2018 and 2023 at the Institute of Oncology Ljubljana, the University Medical Centre Ljubljana, and at Cooper University Hospital in Camden, NJ. All PRBs were performed under ultrasound guidance by a nephrologist.

Results: A total of 19 PRBs were performed in 18 patients and of these 11 PRBs where performed in patients with a SK. At the time of acute kdiney injury (AKI) 15 patients were being treated with immune check point inhibitors (ICIs) and 4 with a tyrosine kinase inhibitor (TKI). Five patients who developed AKI stage 3 during ICI therapy experienced at least one Grade 3 concomitant immune-related adverse event. Pathologic analysis revealed TMA in 5 patients exposed to TKIs, and acute interstitial nephritis in two, Acute tubular injury (ATI) in 5, and severe necrotizing granulomatous vasculitis in one patient exposed to ICIs. In a patient with severe ATI, the pathologic analysis also revealed IgA nephropathy. Based on pathological findings, SAT was changed in twelve patients after PRBs. One patient with TMA had progressive loss of renal function after discontinuation of TKI, while the other 3 had stable or improved renal function. After PRB, one patient experienced a large perinephric hematoma. In another patient, who had a SK, a follow-up ultrasound revealed an A-V fistula and 7 days after PRB. Both patients fully recovered.

Conclusions: Our results indicate that PRB in patients with AKI and receiving SAT are safe and informative even in patients with SK. Importantly, the observed pathological findings can have a significant impact in the cancer treatment plan for these patients. Major PRB complications were manageable even in patients with a SK.

Funding: NIDDK Support

PUB454

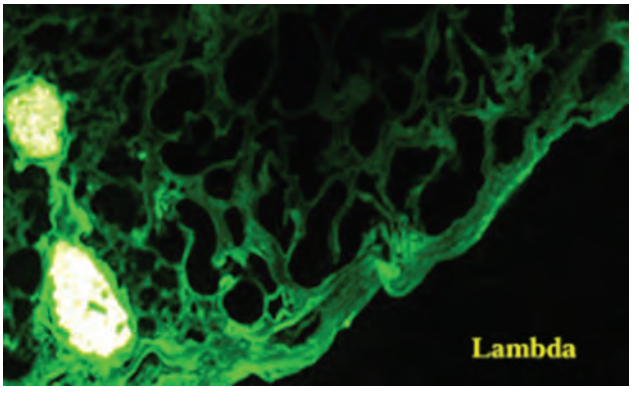
Complex Renal Involvement in Multiple Myeloma and Extramedullary Plasmacytoma: A Clinical Perspective

Carlos B. Gonzalez,[1] Mara C. Olivo Gutierrez,[1] Virgilia Soto,[2] Monica Sanchez Cardenas.[1] *[1]Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico; [2]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico.*

Introduction: This case involves a 43-year-old male patient with no prior comorbidities who was admitted to our unit with rapid deterioration of renal function and uremic syndrome. During evaluation, a left lung mass was detected. The objective of this report is to present a clinical case featuring a large plasmacytoma and severe renal function impairment as the initial manifestation of Multiple Myeloma (MM) in a young and healthy man.

Case Description: A 43-year-old previously healthy man experienced symptoms of asthenia, adynamia, emesis, and wasting syndrome during the two weeks prior to hospital admission. Initial laboratory tests revealed severe renal impairment, with creatinine at 20.1 mg/dL and BUN at 107 mg/dL, with no significant abnormalities in blood cell count. During evaluation, a 24-hour urine protein test showed 630 mg/dL. Incidentally, a large pulmonary mass (8.4 x 13.1 x 10 cm) was detected in the left apex. A renal biopsy (image 1) revealed active tubulointerstitial nephritis with intratubular lambda (+) casts, as well as minimal glomerular and vascular amyloidosis. A biopsy of the pulmonary mass confirmed the histological diagnosis of plasmacytoma associated with multiple myeloma.

Discussion: Amyloidosis is a heterogeneous disease characterized by the deposition of insoluble and toxic fibrillar protein aggregates in various tissues. Renal involvement is a common complication of hematologic malignancies, with monoclonal gammopathy of undetermined significance (MGUS) being the most common form. The incidence of solitary plasmacytomas affecting only soft tissues ranges from 1.4-4.5%, with 34% located as paraeskeletal tumors. The evaluation of new renal injury events in the context of newly appearing malignancies requires consideration of monoclonal disorders within the differential diagnosis; this is particularly true even in the context of solid tumors as the initial manifestation of the condition without significant abnormalities in blood cell counts.



PUB455

Characterization of Myoglobin Endocytic Function in Primary Human Proximal Tubular Epithelial Cells

Yoshio Funahashi,[1,2] Michael Hutchens.[1,3] *[1]Oregon Health & Science University, Portland, OR; [2]Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Portland VA Medical Center, Portland, OR.*

Background: The endocytic function of proximal tubular epithelial cells (PTEC) has important role in health and disease. Megalin is a multi-ligand endocytic receptor which mediates myoglobin uptake. We generated primary culture of PTEC from human kidneys (hPTEC), and characterized response to injury and myoglobin endocytic function.

Methods: Research-designated human donor kidneys were used to generate hPTEC. After dissection and digestion, hPTEC was isolated using cell strainers and fluorescence-activated cell sorting (FACS). After serum starvation or gentamicin treatment, cells were subjected to survival assay (MTT assay and FACS/DAPI), and injury assay (FACS/KIM-1). Megalin expression in hPTEC and HK2 were evaluated by western blotting (WB), quantitative polymerase chain reaction (qPCR), and immunofluorescence (IF). Cells were incubated with FITC conjugated myoglobin (FITC-Mgb) up to 120min, then FITC-Mgb uptake was evaluated by IF or intracellular FITC intensity using a plate reader. Megalin knockdown or inhibition was performed using siRNA or cilastatin (Cil). Dynamin inhibition was performed using dynasore (Dyn) and prochlorperazine (PCP).

Results: After FACS, hPTEC culture was 95% CD10/CD13 positive. hPTEC from 4 different kidneys with various cold ischemia time (16-26h) did not express KIM-1. hPTEC strongly expressed megalin by WB, qPCR and IF while HK2 did not. Serum starved cells demonstrated reduced viability and increased KIM-1 expression compared with control (MTT, DAPI, KIM-1, $p<0.05$ by One-way ANOVA). Compared with HK2, hPTEC demonstrated higher flux of FITC-Mgb uptake in first 20 min ($p=0.004$ by non-linear regression), which resulted in more FITC-Mgb uptake in hPTEC up to 120min. Megalin knockdown by siRNA caused reduced FITC-Mgb uptake in hPTEC ($p<0.0001$ by non-linear regression). Mgb uptake along a wide range of concentrations was reduced by Cil dose-dependently (Mgb:0 to 160ug/mL, Cil: 0 to 200mg/mL, $p<0.0001$ by non-linear regression). Dynamin inhibition by Dyn or PCP also reduced FITC-Mgb uptake.

Conclusions: hPTEC demonstrated healthy epithelial phenotype, high megalin expression, and megalin-mediated, dynamin-dependent endocytosis. They expressed KIM-1 in response to injury. hPTEC are a feasible platform for studies of endocytosis.

PUB456

Cellular Indices in Relation to D-dimer and Thrombin Levels in Patients with ESKD

Hamzah Hussain,[1,2] Fakiha Siddiqui,[1,3] Debra Hoppensteadt,[1] Emma Abulencia,[1] Elyse Fairand,[1] Jawed Fareed,[1] Vinod K. Bansal.[1] *[1]Loyola University Medical Center, Chicago, IL; [2]Hurley Medical Center, Flint, MI; [3]Universidad Catolica San Antonio de Murcia, Murcia, Spain.*

Background: End-stage renal disease (ESRD) is often associated with thromboinflamatory complications. Besides the biomarkers of thrombin generation such as D-Dimer (DD) and peak thrombin (PT) levels, cellular indicies (CI's) have been reported to change with the severity of ESRD. Such CI's as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic immune-inflammation index (SII), lymphocyte to monocyte ratio (LMR), neutrophil to monocyte ratio (NMR) and their relevance with biomarkers such as DD and PT were profiled in ESRD patients.

Methods: Citrated plasma samples from patients with confirmed ESRD were collected in the Hemodialysis Clinic at Loyola University Medical Center. 50 healthy plasma samples served as control. Commercially available sandwich ELISA methods were used for DD levels, and PT was quantified by using a fluorogenic method. Blood CI's were extracted from complete blood counts. Applicable statistical methods were performed and $p<0.05$ were considered significant.

Results: The ESRD group comprised 56.9% males and 43.1% females, with a median age of 66 years. Comparing controls to ESRD cohort, DD increased significantly from 7.1 to 905.8ng/mL ($p<0.05$) while PT levels decreased from 138.4 to 109.9nM ($p<0.05$). NLR increased from 1.6 to 3.4, SII increased from 444.5 to 583.2, and LMR decreased from 4.1 to 2.4 ($p<0.05$). PLR and NMR showed no significant difference. Table 1 represents the composite results. There was no correlation between DD and PT. There were varying degrees of correlation between cellular indicies.

Conclusions: These studies suggest that beside thromboinflmatory biomarkers, CI's may provide additional prognostic parameters in the risk stratification of ESRD. All of the CI's included in this study are increased except for LMR. CI's represent an emerging tool to risk stratify ESRD patients.

Table 1

Biomarker or CI	Controls Median (Range)	ESRD Median (Range)	p-value
DD (ng/ml)	7.1 (7.1-696.5)	905.8 (79.3-6385.1)	<0.05
PT (nM)	138.4 (81.3-224.3)	109.9 (0.0-245.4)	<0.05
NLR	1.6 (0.8-13.3)	3.4 (1.3-9.0)	<0.05
PLR	131.6 (58.8-1966.7)	138.3 (2.2-344.0)	0.51
SII	444.5 (186.7-1573.3)	583.2 (10.5-2424.0)	<0.05
LMR	4.1 (1.0-14.5)	2.4 (0.4-19.0)	<0.05
NMR	7.0 (2.3-39.0)	7.1 (2.8-48.0)	1.00

PUB457

Comparison of Spot Creatinine Estimation by StatSensor Creatinine Meter and Serum Creatinine Estimation by Conventional Enzymatic Method

Manoj Chandrasekar,[1] Manjunath S. Shetty,[1] Basavanagowdappa Hathur,[1] Prashant Vishwanath,[1] Akila Prashant,[1] Praveen Kulkarni,[1] Kiran K K,[1] Naman Chandra,[1] Abhijith Devaraju,[1] Dennis Begos,[2] John O. Oyelakin-Ogunbileje,[4] Vishakantha Murthy.[3] *[1]JSS Medical College, Mysore, India; [2]Nova Biomedical, Waltham, MA; [3]JSS Reasearch Foundation, Gaithersburg, MD; [4]Indiana University School of Medicine, Indianapolis, IN.*

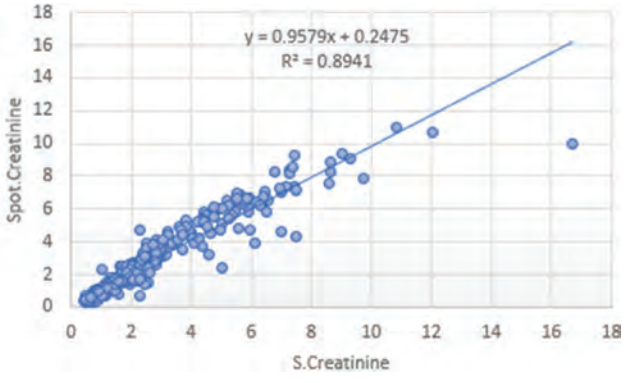
Background: The objective was to compare and validate creatinine measured by Nova StatSensor Creatinine meter against S.Creatinine measured by conventional enzymatic assay

Methods: Patients with renal dysfunction and age/sex matched healthy volunteers underwent Spot.creatinine measurement by Nova StatSensor Creatinine meter using capillary blood (finger prick) and Serum creatinine measurement by conventional enzymatic assay

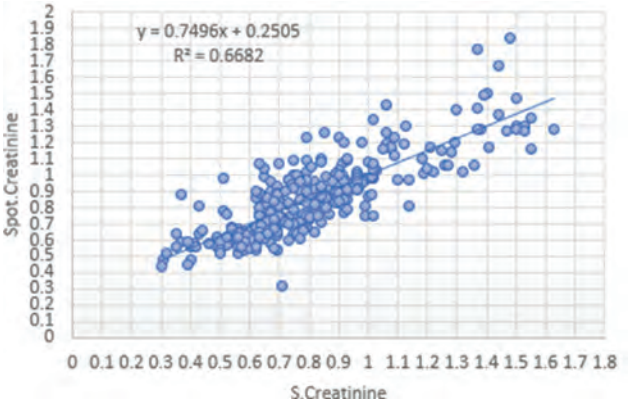
Results: A total of 618 (320 patients and 298 healthy volunteers) were included in the study. The baseline characteristics were similar Mean (±SD) Spot. Creatinine & S.Creatinine in the overall population was 1.9 (±1.9) & 1.8 (±1.8); 2.9 (± 2.2) & 2.8 (± 2.2) in patients; 0.86 (± 0.2) & 0.81 (± 0.2) in healthy volunteers A Pearson coefficient depicted a positive linear correlation between Spot. Creatinine and S.Creatinine, r (df)= 1, $p < 0.001$. The sensitivity and specificity of Spot. Creatinine was 91.2% and 96% respectively; PPV and NPV of 94.5% and 93.6% and an accuracy of 94.1%

Conclusions: Spot. Creatinine measurement using StatSensor Creatinine meter with capillary blood is simple, rapid, reliable and provides a good estimate of creatinine

Funding: Commercial Support - Nova Biomedical Corporation, Waltham, MA, USA



A positive, linear and strong relationship between Spot. Creatinine and S. Creatinine in patient population (r=0.89)



A positive, linear relationship of moderate strength between Spot. Creatinine and S.Creatinine in healthy population (r=0.66)

PUB458

Comprehensive Analysis of Glomerular Antigens in Membranous Nephropathy

Isohata Rina,[1] Hitoshi Suzuki,[1,2] Kenichiro Abe,[1] Mingfeng Lee,[1] Yukako Umezawa,[1] Yuya Sasatsuki,[1] Masahiro Muto,[1] Hiroaki Io,[2] Hisatsugu Takahara,[1] Shigeki Tomita,[1] Yusuke Suzuki.[2] *[1]Juntendo Daigaku Igakubu Fuzoku Urayasu Byoin, Urayasu, Japan; [2]Juntendo Daigaku Igakubu Daigakuin Igaku Kenkyuka, Bunkyo-ku, Japan.*

Background: For the diagnosis and treatment of membranous nephropathy (MN), it is essential to determine idiopathic or secondary onset. The phospholipase A2 receptor (PLA2R), thrombospondin type-1 domain-containing 7A (THSD7A), and neural epidermal growth factor-like 1 (NELL-1) have been reported as antigens for MN. Recently, EXT1/EXT2 reported as responsible antigens for secondary membranous nephropathy, however, their significance in diagnosis of each disease type is not clarified.

Methods: We recruited twenty four patients with MN diagnosed at our hospital from 2021 to 2023. We comprehensively analyzed the IgG subclasses on the glomeruli, PLA2R, THSD7A, NELL1, and EXT/EXT2, and verified their significance in the differential diagnosis of idiopathic or secondary MN.

Results: Of the idiopathic MN, 63% were positive for glomerular PLA2R and 16% for THSD7A, and all were negative for NELL-1. Glomerular IgG4 was dominant in 74% of idiopathic MN. On the other hand, in secondary MN, THSD7A was positive in 60% of patients, NELL-1 was positive in all cases, and PLA2R was negative in all cases. Half of the secondary MN caused by autoimmune diseases were positive for EXT1.

Conclusions: Regarding the differential diagnosis between idiopathic and secondary MN, staining with IgG subclass and PLA2R is useful for the diagnosis of idiopathic MN. NELL-1 and EXT1/EXT2 may be useful as markers of secondary MN, however, the further validation of caused antigens of positive for NELL-1 and EXT1/EXT2 is desired.

PUB459

Association between Thromboinflammatory Biomarkers and Cellular Indices in Patients with ESKD

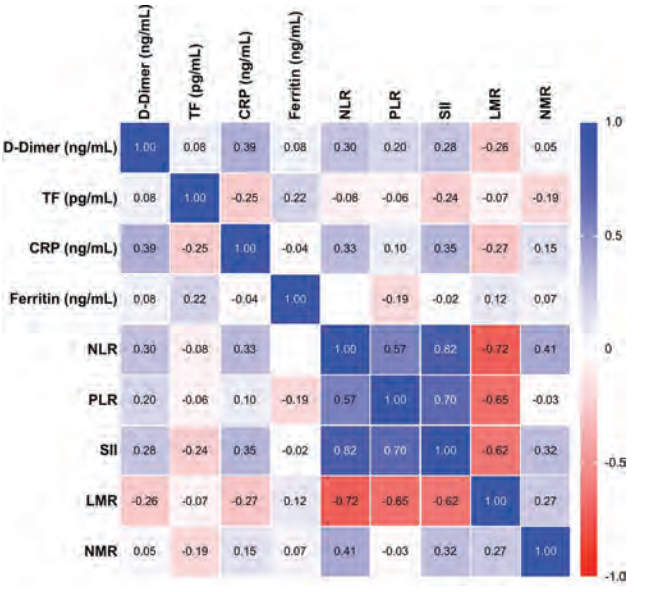
Hamzah Hussain,[1,2] Fakiha Siddiqui,[1,3] Debra Hoppensteadt,[1] Emma Abulencia,[1] Elyse Fairand,[1] Jawed Fareed,[1] Vinod K. Bansal.[1] *[1]Loyola University Medical Center, Chicago, IL; [2]Hurley Medical Center, Flint, MI; [3]Universidad Catolica San Antonio de Murcia, Murcia, Spain.*

Background: End-stage renal disease (ESRD) is often associated with chronic inflammation and hypercoaguable state. This results in the alteration of cellular indicies (CI's) like neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic immune-inflammation index (SII), lymphocyte to monocyte ratio (LMR), and neutrophil to monocyte ratio (NMR). Thromboinflammatory biomarkers (TIB's), like D-Dimer (DD), Tissue Factor (TF), Ferritin, and C-Reactive Protein (CRP), have also been observed to be abnormal in ESRD patients. This study was designed to find a possible relevance between these CI's and TIB's.

Methods: 79 citrated plasma samples from patients with confirmed ESRD were collected in the Hemodialysis Clinic. Patient complete blood counts and ferritin levels were collected from chart review and blood CI's were calculated. Sandwich ELISA methods were used to determine DD, TF, and CRP concentrations. A correlation analysis was performed and a correlation matrix was generated.

Results: The following figure depicts the composite data. DD showed correlation with CRP along with NLR, PLR, SII and is inversely related to LMR. Interestingly, TF showed inverse relationship with CRP, SII, and NMR. CRP showed a relationship with DD, NLR, and SII where-as it showed inverse relationships between TF and LMR. Ferritin showed positive relationship with TF and inverse relationship with PLR. Among the CI's, varying degrees of strong correlation were observed.

Conclusions: This data demonstrates that there is a complex interdependence between the CI's and TIB's in the pathogenesis of ESRD. Furthermore, this study shows that an integrated profiling of CI's and TIB's may have a prognostic role which will be helpful in the management and risk stratification of this complex syndrome.



PUB460

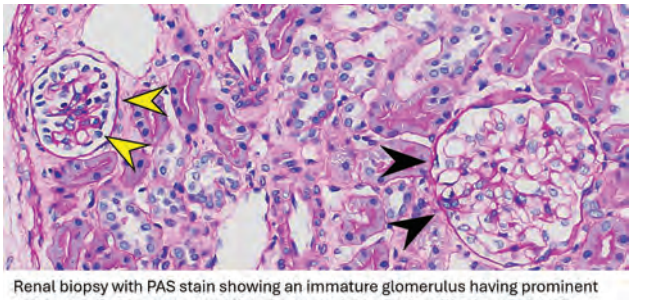
Intriguing Presentation of Proteinuria Associated with Immature Glomeruli in a Child with Horseshoe Kidney

Ganesh Prasanna,[1] Wesley Hiser,[2] Abhijeet Pal.[1] *[1]The University of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]Pathologists Bio-Medical Laboratories, Coppell, TX.*

Introduction: Horseshoe kidney, a congenital anomaly resulting from the fusion of the lower poles of both kidneys, affects about 1 in 500 children. While horseshoe kidney has been associated with various glomerulopathies, we report the first instance where evaluation for persistent proteinuria revealed immature glomeruli with segmental sclerosis on renal biopsy.

Case Description: A four-year-old boy presented in 2021 with incidental proteinuria with no other symptoms. He was born at term with no familial history of kidney disease. His blood pressure was normal, and his physical examination was unremarkable. Urinalysis showed proteinuria with urine protein creatinine ratio (UPCR) of 1.1 mg/mg (normal range <0.2 mg/mg), albumin creatinine ratio (ACR) of 0.6 mg/mg, and no hematuria. Serum creatinine was 0.3 mg/dL. Blood counts were within normal limits. Renal ultrasound revealed a horseshoe kidney. Renal biopsy showed forty-six glomeruli, of which six (13%) were immature, which is unusually high for his age. Four immature glomeruli also had segmental sclerosis. Six glomeruli (13%) were globally sclerosed. Remaining were normal with insiginificant foot process effacement. Initially, he was monitored with no therapy. However, due to persisting proteinuria (UPCR 1.11 mg/mg) over a two-year follow-up, losartan was started in January 2024. By April 2024, UPCR had reduced (0.8 mg/mg). The patient remains on follow-up.

Discussion: This is the first report of horseshoe kidney concomitant with proteinuria and immature glomeruli. At first, we opted to survey without treatment, hypothesizing that the proteinuria was due to developmentally abnormal nephrons, whose further scarring may resolve the proteinuria. Moreover, we were reassured by the non-severe degree of proteinuria and the absence of symptoms. But the persisting proteinuria prompted us to start therapy with losartan, which reduced the proteinuria. This case suggests that immature glomeruli might be a benign cause of proteinuria, while also indicating a developmental correlation with the horseshoe kidney.



Renal biopsy with PAS stain showing an immature glomerulus having prominent podocytes (Yellow arrowheads) and a normal glomerulus (Black arrowheads)

PUB461

Severe Hypertension in a Female Adolescent with Severe Chronic Obstructive Unilateral Hydronephrosis

Asma B. Shaoba, Oluwatoyin F. Bamgbola. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Hypertension is rare in patients with a unilateral ureteral obstruction (UUO) due to a functional compensation from the contralateral kidney. We describe an adolescent who had severe hypertension and an incidental finding of a congenital UUO. We postulated the mechanisms of hypertension and highlighted the decision-making dilemma on therapeutic intervention.

Case Description: A 15-year-old African American female was admitted for shortness of breath, pharyngitis, and fever. BMI was 29.3 kg/m2, T 102.7 F, HR 118/min, RR 26/min, and BP 158/101 mmHg. CT angiogram did not reveal pulmonary embolism. Instead, she had severe right-sided hydroureteronephrosis with extreme cortical thinning (Fig 1A). On renal US, right kidney measured 22.1 x 9.6 x 10.7 cm while left kidney was 11.4 x 6.0 x 6.0 cm. The washout times of the LK and RK on diuretic renogram were 7 (30%) and 46 (70%) minutes respectively (Fig 1B). Plasma renin activity, serum creatinine and aldosterone were normal. Her BP was controlled with labetalol and thereafter angiotensin-receptor blocker. A pediatric urologist contemplated a right-sided nephrectomy.

Discussion: Studies showed elevation of plasma renin in hypertensive acute UUO but it is often normal in chronic UUO. Plausible mechanisms for intrarenal generation of renin in the latter may include renal ischemia, ureterorenal reflex [prostaglandins], and distension of renal capsule with its sympathetic innervation. Given the rapid control of the BP, and absence of a prior acute pyelonephritis, we recommend supportive care rather than nephrectomy.

Figure 1: A contrast-enhanced CT scan imaging showing a severe obstructive right-sided hydronephrosis (blue arrow).

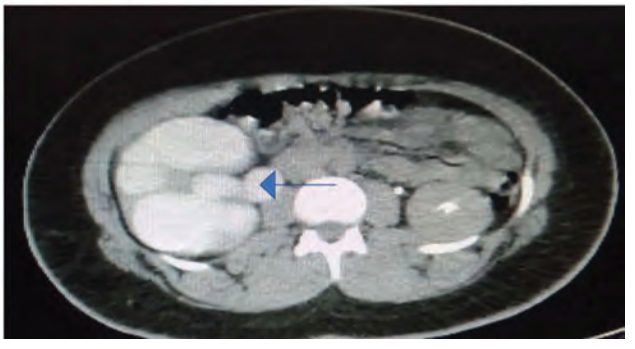
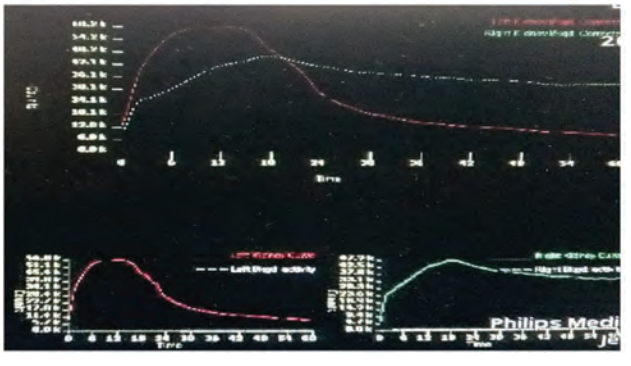


Figure 1 B: A diuretic MAG 3 renal scan showed a reduced renal uptake, and delayed excretion of radioisotope from the obstructed right kidney (broken green line).



PUB462

General Pediatrician Confidence in Managing First-Time Microscopic Hematuria or Proteinuria

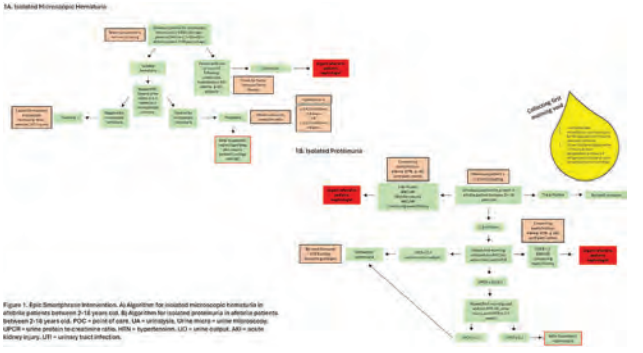
Kayla J. Erspamer, Kelsey L. Richardson, Abbie R. Bauer. *Oregon Health & Science University, Portland, OR.*

Background: Microscopic hematuria and proteinuria are frequently detected in the pediatric population and are often referred to pediatric nephrology. While both can signify renal disease, if either is detected in isolation without other symptoms it is more likely benign. Many articles include algorithms to help pediatricians in the initial workup of hematuria and proteinuria, but there have not been any studies analyzing if providing algorithms or electronic health care record tools improve management confidence. The purpose of this study is to determine pediatrician confidence in management of first-time microscopic hematuria and proteinuria with and without an algorithm.

Methods: Pre-intervention surveys (11 questions) were distributed to general pediatric and adolescent medicine clinicians via email with a link to the Qualtrics survey. Epic Smartphrases with the algorithm for isolated microscopic hematuria and isolated proteinuria in afebrile patients between 2-18 years old were made available in Epic to those surveyed with an email announcement in March 2024 (Figure 1). Post-intervention surveys (12 questions) will be distributed after at least six months of intervention.

Results: Forty-seven clinicians completed the pre-intervention survey (55%). Clinicians are more confident in interpreting rather than managing microscopic hematuria and proteinuria. For microscopic hematuria, 28%, 49%, and 23% marked confident, some confidence, and little confidence respectively for interpretation compared to 17%, 30%, and 47% for management. For proteinuria, 17%, 60%, and 23% marked confident, some confidence, and little confidence respectively for interpretation compared to 17%, 38%, and 40% for management. Ninety percent of respondents said yes when asked if they would use an Epic Smartphrase algorithm.

Conclusions: General pediatricians are more confident in interpreting rather than managing first-time microscopic hematuria and proteinuria. The majority of those surveyed would use an Epic Smartphrase algorithm and this type of intervention warrants further study.



PUB463

A Case of Proximal Renal Tubular Acidosis without Fanconi Syndrome

Isaac Esplin, Morgan E. Beebe, O. N. Ray Bignall. *Nationwide Children's Hospital, Columbus, OH.*

Introduction: Proximal renal tubular acidosis (pRTA) is characterized by impaired resorption of bicarbonate in the proximal tubule. This occurs most commonly with Fanconi syndrome, as isolated pRTA is rare. The most common inherited form is an autosomal recessive mutation in the Na/HCO3 transporter; infants with a sporadic form tend to spontaneously improve over time. We present a case of isolated pRTA confounded by a history of diarrhea in a neonate.

Case Description: A 4-week-old term baby girl presented with poor weight gain (+160 g from birth) and fussiness, found to have metabolic acidosis. Initial labs showed hypokalemia, hyperchloremia and anion gap metabolic acidosis (AGMA) with a gap of 15. After fluid resuscitation, subsequent labs showed a non-AGMA. Urine pH was 5.0 with no protein or glucose; urine chloride level was <15mmol/L. Mom reported persistent diarrhea, which was favored to be the cause of her acidosis. She began supplementation with potassium citrate during admission with improvement in labs. Two weeks later, she returned with recurrence of diarrhea, non-AGMA, and hypernatremia in the setting of adenovirus infection and overconcentrated formula due to improper preparation. Her acidosis improved with fluids and increase of potassium citrate. After two more weeks she was readmitted from Nephrology Clinic with persistent non-AGMA. The urine pH was 6.0 with a gap of -24.9. Mom reported persistent diarrhea, but inpatient stools were observed to be normal. A clinical diagnosis of isolated pRTA was then made; the family refused genetic testing. Magnesium citrate was added to regimen, with improvement in hypokalemia and bicarbonate levels prior to discharge. She continues to grow well in follow up.

Discussion: This case highlights pRTA without Fanconi syndrome as the cause of poor growth and non-AGMA in a neonate. It also demonstrates the difficulty in recognizing an isolated pRTA if more common etiologies are reported, especially when patients have confounding historical factors or lab results. An accurate history is paramount in making the diagnosis when genetic testing is unavailable to help distinguish between stool or renal bicarbonate losses, and a pRTA diagnosis should not be discounted in the absence of Fanconi syndrome.

PUB464

Factors Associated with Successful Transition from Pediatric to Adult Nephrology

Laura Nishi,[1,2] Jay H. Kang,[2] Cybele Ghossein.[1] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Northwestern Memorial HealthCare, Chicago, IL.*

Background: Young adults (YA) aged 18-26 with chronic kidney disease face challenges when transitioning from pediatric to adult care. To improve successful transition (ST) rates, Northwestern Medicine (NM) partnered with Lurie Children's Hospital to implement a transition of care program. To better understand risk factors for failure to transition, we retrospectively reviewed our 8-year clinic data.

Methods: YA seen in the transition clinic between 2014-2022 were included in the analysis. ST was defined as one visit to NM. We compared baseline kidney function, insurance, distance from clinic, average household income, and pediatric no-show rate for those YA who ST to those who did not.

Results: 166 total patients were seen, with 154 patients being eligible to transition. 92% of patients ST and 8% were lost to follow up (Table 1). YA who ST had lower baseline kidney function and were more likely to have private insurance. Those who did not ST were more likely to have no insurance. The other factors were not significantly correlated with ST.

Conclusions: Based on our retrospective study, baseline kidney function and insurance status are associated with ST in YA with kidney disease. Further prospective studies are needed to confirm our findings in this high-risk population.

Table 1. Characteristics of Study Patients

	Lost to follow up (N=13)	Successfully Transitioned (N=141)	P-value
Age (years)			
Mean (SD)	19.8 (1.17)	20.0 (1.97)	0.484
Sex			
Female	3 (23.1%)	70 (49.6%)	0.122
Male	10 (76.9%)	71 (50.4%)	
Distance to Clinic (Miles)			
Mean (SD)	21.1 (20.6)	39.1 (62.9)	0.306
Average Household Income ($)			
Mean (SD)	61400 (21400)	71200 (25700)	0.141
No Show Pediatric Center (%)			
Mean (SD)	10.5 (11.0)	7.0 (6.32)	0.284
INSURANCE			
Private	5 (38.5%)	82 (58.2%)	0.0148
Government	6 (46.2%)	58 (41.1%)	
None	2 (15.4%)	1 (0.7%)	
CKD EPI-CYSTATIN C			
Mean (SD)	110 (30.8)	85.6 (36.8)	0.0453

PUB465

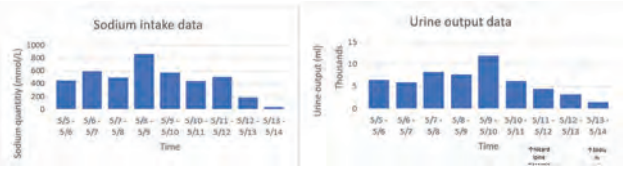
An Unusual Case of Renovascular Hypertension in a Pediatric Patient Associated with Hyponatremia and Polyuria Responding to Angioplasty and Losartan

Ayodele Obigbesan, Matthew Oelstrom, Omar N. Al Masri. *Marshfield Clinic Health System, Marshfield, WI.*

Introduction: Renovascular abnormalities are an important cause of secondary hypertension in pediatric population. Hyponatremia and polyuria are uncommon complications.

Case Description: This is a report of a 13-year-old female who developed hypertensive emergency secondary to unilateral renal artery stenosis. She presented with a two-week history of severe headaches, nausea, vomiting, polyuria and enuresis. Initial Blood Pressure (BP) was 196/132mmHg. It was safely lowered over 48 hours to 115-130mmHg range using Nicardipine infusion. Laboratory tests on admission showed Sodium 128 mmol/L, Potassium 2.1 mmol/L, Plasma Renin Activity (220ng/ml/hr, normal limit<2.4), and Aldosterone levels (45ng/dL, normal<21). Echocardiography revealed mild concentric left ventricular hypertrophy, with normal aorta. Computerized Tomography Angiography (CTA) showed delayed enhancement of the relatively small size right kidney with stenosis of the ostium of its main artery. Digital Subtraction Angiography done on hospital day #5, confirmed CTA findings and demonstrated presence of collateral flow through a hypertrophied right adrenal artery which explains kidney viability despite severe stenosis. Balloon angioplasty was successful in restoring blood flow with 15-20% residual stenosis. Post-procedure, she required less Nicardipine infusion and subsequently transitioned to oral Amlodipine. Polyuria and hyponatremia were observed upon admission and persisted despite achieving BP target early during hospitalization, after angioplasty it started to improve. Losartan 12.5mg was commenced on day 7 with further improvement in polyuria and no further need for salt supplementation (figure 1 and 2).

Discussion: Renovascular disease can lead to life threatening hypertensive emergencies. Excessive diuresis and hyponatremia have complicated the management of our case. It required efforts to replace losses using large volumes of fluids and sodium chloride to maintain homeostasis. Hyperfiltration due to Angiotensin II excess is the plausible underlying mechanism; this explains why It started to improve gradually following angioplasty and the addition of Losartan.



PUB466

Association of Maternal Hypertensive Disorders in Pregnancy and Offspring Kidney Function from Adolescence into Young Adulthood

Jo A. Kelly, Andrew M. South. *Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Maternal hypertension (HTN) during pregnancy is associated with significant health complications for the mother and offspring. Little research exists on its effect on offspring kidney function into young adulthood. Our aim is to estimate the association of maternal HTN during pregnancy with offspring kidney function in adolescence and young adulthood.

Methods: This is a secondary longitudinal analysis of data collected in a prospective cohort study of individuals born with very low or extremely low birth weight (birth weight <1500 g). Participants were assessed at 14–15 and 19–23 years old. Blood and first-morning urine samples were collected. We estimated the glomerular filtration rate (eGFR) using the original creatinine-based Schwartz equation in adolescents and the CKD-EPI 2021 creatinine-cystatin C equation in young adults. We calculated the albumin-to-creatinine ratio at both time points. We estimated the relationships with multivariable generalized linear models informed by directed acyclic graphs.

Results: Of the 213 included participants, 113 (53%) were female, 89 (42%) were Black, and 79 (37%) were exposed to maternal HTN. The mean eGFR was 130.2 mL/min/1.73 m2 in adolescence (n=124) and 168.7 mL/min/1.73 m2 in young adulthood (n=159). The median ACR was 5.3 mg/g in adolescence and 3.1 mg/g in young adulthood. Kidney function in adolescence was associated with kidney function in young adulthood (eGFR adjusted β 0.48 mL/min/1.73 m2, 95% CL 0.21–0.75; ACR adjusted β 0.19 mg/g, 95% CL 0.15–0.24). There was no significant association between maternal HTN and kidney function in both adolescence and young adulthood.

Conclusions: We found no significant association between maternal HTN in pregnancy and offspring kidney function in adolescence and young adulthood. The next step for this project is to perform a causal mediation analysis to estimate the direct effect of maternal HTN in pregnancy on young adult kidney function and the indirect effect mediated by adolescent kidney function.

Funding: NIDDK Support, Other NIH Support - NIDDK T35DK007400, NICHD P01HD047584, and P01HD084227

PUB467

A Rare Presentation: Male Neonate with Severe Bilateral Hydronephrosis and Normokalemic Acute Renal Tubular Acidosis

Victoria Gutierrez-Lorea,[1] Carol E. Perez Mena,[1,2] Jose A. Rodriguez.[2] *[1]Ponce Health Sciences University, Ponce, PR; [2]Hospital Episcopal San Lucas, Ponce, PR.*

Introduction: Among the most common causes of hydronephrosis in neonates are birth defects that lead to Ureteropelvic Junction obstruction (UPJ) and Vesicoureteral Reflux (VUR). If the obstructive uropathy is chronic, renal tubules lose their function leading to Renal Tubular Acidosis (RTA). Here we present a male neonate who presented with severe bilateral hydronephrosis which caused acute RTA.

Case Description: A male newborn patient born at 37 weeks gestational age with perinatal diagnosis of bilateral hydronephrosis and unremarkable physical exam was admitted for evaluation. Protocole laboratories, showed abnormal BUN (16 mg/dl), creatinine level (1.71 mg/dl) and normal values of potassium. The patient started exhibiting progressive decline in Carbon dioxide (CO2) levels despite adequate feeding and intravenous fluids. Acute RTA was suspected. ABG showing mild metabolic acidosis (PH 7.29, HCO3 21, CO2 44), ammonia levels at 40 mg/dl and unremarkable urine analysis. Patient was started on Sodium Citrate at 2mEq/kgdose every 8 hours. Result of Voiding Cysto-Urethrogram (VCUG) is seen on Figure 1. Patient was transferred to another facility for further evaluation.

Discussion: Severe bilateral hydronephrosis caused by UPJ and VUR which consequently leads to acute RTA is extremely rare in a neonate. We believe chronic obstructive nephropathy led to RTA with severe renal impairment. Although one hallmark of RTA is hypokalemia, the hypokalemic levels were likely masked by the administration of Sodium Citrate. Healthcare providers should be aware of unreliable potassium values in RTA patients taking sodium citrate.

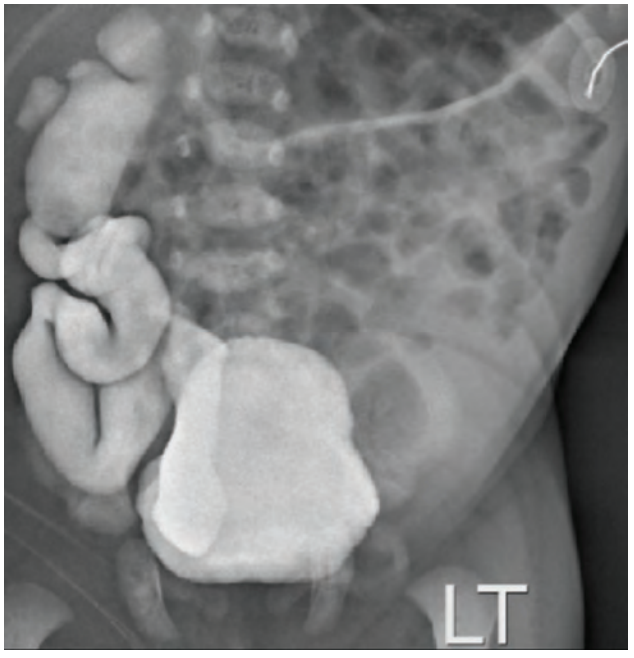


Figure 1: VCUG shows severe reflux from the right-sided ureter and significant dilation of the renal pelvic, calyces and infundibulum. No reflux is evident on the left.

PUB468

Establishment of Reference Values for Estimated Kidney Volume Using Ultrasonography in Japanese Pediatric Patients

Hideki Matsumura, Yuko Fujii, Tomoko Tanaka, Akihiko Shirasu, Akira Ashida. *Osaka Ika Yakka Daigaku, Takatsuki, Japan.*

Background: Ultrasonography serves as a noninvasive and effective screening modality for renal evaluation. Assessing renal dimensions is crucial, given the established correlation between renal function and kidney size. In pediatric populations, renal size varies with growth, necessitating the establishment of growth-specific reference values. Renal length reference values derived from ultrasonography are widely utilized in clinical practice due to their ease of measurement. However, we believe that renal length alone is inadequate for a comprehensive assessment of kidney size due to the variability in renal morphology. Consequently, we hypothesize that renal volume provides a more precise metric for evaluating kidney size and have investigated the reference values for renal volume in Japanese children with normal renal function.

Methods: We measured serum creatinine levels, body height and weight, and renal long and short diameters and depths via ultrasonography in pediatric patients under 18 years of age without renal disease. We included patients with eGFR within the reference range and excluded those with body height and weight significantly deviating from the reference values. We calculated kidney volume using the average of two ultrasound measurements of kidney size, approximated as an ellipsoid: long diameter × short diameter × thickness × π / 6.

Results: Out of 42 candidates, 29 patients meeting the criteria for body height, weight, and eGFR were included in the study. The median age of participants was 12 years. The strongest correlation was found between renal volume and body surface area ($r^2 = 0.852$), followed by age, body height, weight, or body mass index. Total kidney volume, defined as the sum of bilateral kidney volumes divided by body surface area, increased with growth, with multivariate analysis identifying age as the primary influencing factor. Thus, the reference value for total kidney volume can be expressed as total kidney volume/body surface area (mL/m^2) = 140 + age × 2. This reference value for renal volume showed a stronger correlation with the previously reported reference value for renal length diameter in Japanese children. Furthermore, renal volume correlates more strongly with eGFR than renal length diameter.

Conclusions: Renal volume is the more precise method for evaluating renal size.

PUB469

Posterior Urethral Valve Masquerading as Failure to Thrive

Staney A. John, Nikhila Aimalla, Omar N. Al Masri. *Marshfield Clinic Health System, Marshfield, WI.*

Introduction: Only half the cases of posterior urethral valves (PUV) are diagnosed antenatally with dilated kidneys and ureters. The rest, present later in life with failure to thrive (FTT), recurrent urinary tract infections (UTI) and nocturnal enuresis in older boys. Undiagnosed PUVs can have sequelae such as progression to chronic kidney disease, vesicoureteral reflux (VUR) and overactive bladder which can be prevented if picked up early.

Case Description: Patient is a 6 month old male, ex-35 weeker born small-for-gestational age with an otherwise normal prenatal course who presented with FTT. Since birth, his weight has been tracking below the 3rd centile. He had been tried from breast milk to various formulae over a period of time with minimal weight gain. He was having frequent spit-ups and took frequent small volume feeds; so was started on a proton pump inhibitor for possible gastroesophaegal reflux. There was also concerns of crying during voiding and stooling. He was admitted to the hospital and was started on scheduled feeds. His labs were unremarkable except for mild hyponatremia (132 mEq/L), 3+ red blood cells and 3+ leukocyte esterase in the urine. His C-reactive protein was moderately elevated. So a catheterized urine sample was obtained which also revealed the same findings and was sent for culture. The next day, his serum sodium dropped further (128 mEq/L) with a 4x rise in serum creatinine (0.8 mg/dL). Physical exam disclosed a new mass in the right iliac fossa. Ultrasonography revealed a massively distended urinary bladder with bilateral moderate-to-severe hydroureteronephrosis. A voiding cystourethrogram revealed dilatation and elongation of the posterior urethra, grade 5 VUR on the left and severe bladder trabeculation concerning for a PUV. An indweling Foley's catheter was placed and his serum sodium and creatinine normalized within the next few hours. Urine culture was sterile, but he was started on prophylactic antbiotics given his severe VUR and was referred to a higher facility for surgical correction.

Discussion: PUV is a rare yet serious cause of FTT in male children. This case was a reminder of how PUVs can be present even in babies who did not have oligohydramnios in-utero and have been voiding well. Chronic struggling to void against a tight urethra, fighting recurrent UTIs and a distended bladder which limits food intake can all contribute to poor weight gain in babies.

PUB470

Vacation in Egypt as Major Risk for Shiga Toxin Escherichia coli Infection in Children during 2023: Data from the ItalKid-HUS Network

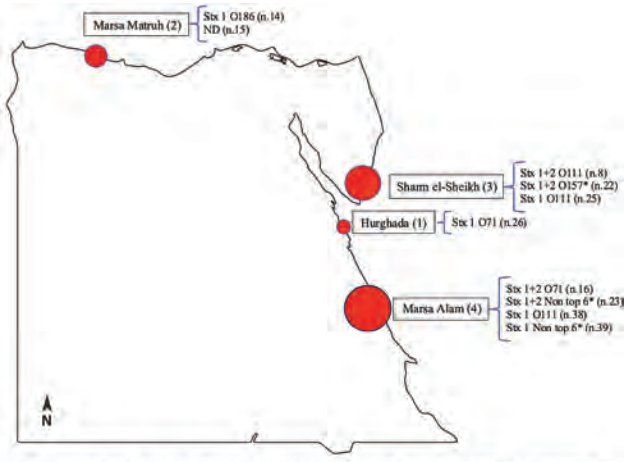
Thomas Ria,[1] Gianluigi Ardissino,[1] Maria Cristina Mancuso,[1] Laura Daprai,[5] Alessandra Gazzola,[2] Sara Arnaboldi,[6] Mario V. Luini,[3] Dario Consonni.[4] *[1]Centro per la Cura e lo Studio della Sindrome Emolitica Uremica, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna, Lodi, Italy; [3]Institute of Agricultural Biology and Biotechnology, National Research Council, Lodi, Italy; [4]Epidemiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]SC Patologia Clinica, Laboratorio di Microbiologia, Fondazione IRCCS CA' Granda, Ospedale Maggiore Policlinico, Milan, Italy; [6]Department of Food Safety, Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna "Bruno Ubertini" (IZSLER), Brescia, Italy.*

Background: Hemolytic uremic syndrome (HUS) is a severe thrombotic microangiopathy that may develop as a complication of Shiga toxin-producing *Escherichia coli* (STEC) infection. Although environmental sources of STEC are known, in individual cases the source of infection usually remains unknown. During 2023 we observed several cases of infection in children returning from vacations, thus we evaluated the association between the infection and travel patterns.

Methods: We analyzed all Shiga toxin genes-positive children with bloody diarrhea identified during 2023 by the ItalKid-HUS Network surveillance system in Northern Italy. Families of infected children were contacted and a short questionnaire regarding recent travels abroad was administered. The exposure time was considered since the 3rd day after the arrival abroad until the 5th day after the return home. A self-controlled case series (SCCS) design was used to calculate relative risk.

Results: Of 43 cases with STEC infection, 32 had uncomplicated infection while 11 developed HUS. Twenty-three subjects did not travel abroad, while 20 had travelled to several destinations. For 12 subjects (10 travelled to Egypt, 1 to Kosovo and 1 to Albania), we identified an association between infection and travelling. The relative risk associated to travelling to Egypt was 88-fold. Serotype analysis excluded the possibility of an epidemic given the variability of the strains found. Exposures analysis didn't provide evidence of a single potential source of the infection.

Conclusions: There is an elevated risk of acquiring STEC infection (thus of HUS) associated with travelling to Egypt. Specific investigations to identify the source are needed to develop effective preventive measures.



ND: not determined; Non Top 6: STEC whose serotype is not O157, O26, O103, O111, O104 or O145; *: Determined in stools by Real Time PCR only.

PUB471

Ophthalmologic Symptoms and Practice Patterns in Children and Young Adults in the NAPRTCS Cystinosis Registry

Sara A. Boynton,[1] Bradley A. Warady,[2] Larry A. Greenbaum,[3] Paul C. Grimm,[4] Alicia Neu,[1] Jodi M. Smith.[5] *[1]Johns Hopkins University, Baltimore, MD; [2]Children's Mercy Kansas City, Kansas City, MO; [3]Emory University, Atlanta, GA; [4]Stanford University, Stanford, CA; [5]Seattle Children's Hospital, Seattle, WA.*

Background: Launched in 2018, the NAPRTCS Cystinosis Registry is a prospective cohort study of children & young adults with cystinosis whose objective is to describe the clinical features of cystinosis and practice patterns of providers. The NAPRTCS Cystinosis Registry includes detailed information on ophthalmologic clinical outcomes and related care practices.

Methods: Children and young adults <25 years of age at a participating NAPRTCS center are eligible for inclusion in the NAPRTCS Cystinosis Registry. Data are collected from time of diagnosis, at time of registry entry, and every 6 months thereafter.

Results: The NAPRTCS Cystinosis Registry has collected clinical information on children & young adults with cystinosis since 2018 and includes information on 104 patients from 30 centers who were diagnosed from 12/1999 to 8/2023. Participants are primarily male (52.9%), majority White (77.9%), and over a quarter (28.8%) live ≥ 50 miles from the treating center. Median age is 16.5 months at diagnosis and 9 years at registry entry. At time of diagnosis corneal deposits were reported in 32.3% of participants and cysteamine eye drops were prescribed to 34.4%. At time of registry entry, a visit with an ophthalmologist was reported for 28.4% of participants and an ophthalmologic exam for 26.3%, 26.6% reported photophobia and 24.3% wore glasses. Of those participants with an exam, 72% had corneal crystals and 12% retinal changes. Throughout the follow up period, the majority of participants of were on cysteamine eye drops (73.7% at registry entry; 82.4% at 12 months; 84.2% at 24 months).

Conclusions: The NAPRTCS Cystinosis Registry provides a unique opportunity to gain insight into the pediatric cystinosis population and to further our understanding of the complex care needs of pediatric cystinosis patients. Children and young adults with cystinosis have significant ophthalmological clinical features necessitating treatment with cysteamine eye drops and close follow up.

	Scheduled 6-Month Visit								
	Registry Entry (N=95)	6 Months (N=87)	12 Months (N=85)	18 Months (N=73)	24 Months (N=57)	30 Months (N=45)	36 Months (N=38)	42 Months (N=28)	48 Months (N=23)
Clinical Feature	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)
Wear glasses	18/74 (24.3)	14/63 (22.2)	18/67 (26.9)	16/61 (26.2)	9/49 (18.4)	4/36 (11.1)	2/32 (6.3)	3/23 (13.0)	2/17 (11.8)
Wear sunglasses indoors	0/86 (0.0)	1/80 (1.3)	2/81 (2.5)	2/72 (2.8)	0/57 (0.0)	0/43 (0.0)	1/36 (2.8)	1/25 (4.0)	0/22 (0.0)
Photophobia	22/84 (26.2)	14/72 (19.4)	18/75 (24.0)	16/64 (25.0)	7/53 (13.2)	6/41 (14.6)	3/33 (9.1)	4/23 (17.4)	3/18 (16.7)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ophthalmologic Exam	25 (26.3)	17 (19.5)	19 (22.4)	9 (12.3)	6 (10.5)	5 (11.1)	3 (7.9)	2 (7.1)	1 (4.3)
Corneal crystals	18 (72.0)	12 (70.6)	12 (63.2)	6 (66.7)	6 (100)	4 (80.0)	3 (100)	2 (100)	1 (100)
Retinal changes	3 (12.0)	2 (11.8)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Corneal transplantation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Visual acuity = 20	14 (56.0)	10 (58.8)	11 (57.9)	6 (66.7)	3 (50.0)	3 (60.0)	2 (66.7)	2 (100)	1 (100)
Subspecialty visits in the last 6 months									
Ophthalmology	27 (28.4)	22 (25.3)	21 (24.7)	17 (23.3)	12 (21.1)	7 (15.6)	5 (13.2)	3 (10.7)	4 (17.4)

PUB472

Blue in the Face: Dapsone-Induced Methemoglobinemia in a Woman with Minimal Change Disease

Nicholas W. Salupo, James F. Simon. *Cleveland Clinic, Cleveland, OH.*

Introduction: Dapsone is a sulfone antibiotic effective for Pneumocystis jiroveci pneumonia (PJP) prophylaxis. It can induce methemoglobinemia, a potentially life-threatening condition marked by impaired oxygen delivery. While glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is a risk factor for developing methemoglobinemia, this complication can develop in its absence.

Case Description: A 23-year-old female with minimal change disease flare and a previous allergic reaction to trimethoprim-sulfamethoxazole was placed on prednisone 30 mg daily with concurrent dapsone for PJP prophylaxis. G-6-PD level measured prior to starting therapy was elevated at 15.8U/g Hb (9.8-15.5 U/g Hb). She immediately developed progressively worsening perioral cyanosis, burning sensation of her lips and face and difficulty concentrating. On evaluation 4 days later, pulse oximetry revealed 92% on room air. PaO2 was 93 mm Hg. There was no "saturation gap," however arterial methemoglobin was 7.3%. Dapsone was discontinued, and intravenous methylene blue administered, leading to rapid clinical improvement and resolution of methemoglobinemia.

Discussion: This case emphasizes the potential for dapsone-induced methemoglobinemia even in young individuals without classic risk factors, like G-6-PD deficiency or underlying respiratory disease. Early recognition of clinical features is crucial for prompt diagnosis and treatment. Methylene blue remains the first-line therapy for symptomatic methemoglobinemia. This case underscores the need to vigilantly monitor patients taking dapsone, regardless of age or traditional risk factors. A high index of suspicion for methemoglobinemia in the setting of unexplained cyanosis or hypoxia can potentially prevent more serious complications.

PUB473

Transthyretin (ATTR) Cardiac Amyloidosis with Kidney Involvement

Nihal Bashir. *Seha Kidney Care, AlAin, United Arab Emirates.*

Introduction: Amyloidosis refers to the extracellular deposition of fibrils arising from a variety of serum proteins. These fibrils adopt a beta-pleated sheet configuration that leads to characteristic histologic changes. Amyloid deposits can occur in a variety of organs, but morbidity and mortality from amyloid deposition most commonly occur when the heart, kidney, liver, or autonomic nervous system are affected. ATTR-CA (transthyretin) leads to a progressive restrictive physiology with reduced stroke volume, decreased compliance, and compromised cardiac output. Studies directly addressing the benefit of traditional heart failure (HF) medical therapy for ATTR-CA remain limited.

Case Description: 77 years old male known to have history of hypertension, dyslipidaemia, chronic kidney disease stage 3, he was following with cardiology in 2022 for symptoms of shortness of breath and chest pain and his ECHO showed sever aortic regurgitation and mild left ventricle global systolic dysfunction with restrictive filling pattern but no aortic stenosis. Two years later he was admitted with worsening renal function, anasarca and right arm cellulitis with Methicillin sensitive staphylococcus aureus (MSSA) bacteraemia. His ECHO showed sever aortic stenosis this time. His urine protein was negative during the 2 years follow up period. He was started on haemodialysis and underwent Cardiac scintigraphy which was strongly suggestive of Transthyretin amyloidosis. The patient was started on Tafamidis which prevents cleavage of transthyretin tetramers and may reduce deposition of amyloid. The patient currently on twice per week haemodialysis and his creatinine 150-200 micromole/L and on watchful followup for his renal function recovery.

Discussion: ATTR AMYLOIDOSIS In patients with ATTR cardiac amyloidosis and New York Heart Association (NYHA) functional class I to III HF symptoms, treatment with tafamidis is recommended rather than no disease-specific therapy. Tafamidis is given as tafamidis meglumine 80 mg daily or as tafamidis 61 mg daily. Tafamidis (either formulation) does not require specific monitoring and is continued indefinitely. The high cost of tafamidis is a major barrier to therapy. Tafamidis reduced the rate of mortality compared with placebo and reduced the rate of cardiovascular-related hospitalizations, it also reduced the rate of decline in six-minute walk distance and Kansas City Cardiomyopathy Questionnaire-Overall Summary.

PUB474

Unexplained Severe and Recurrent Hypoglycemia in a Patient with History of Miliary Tuberculosis, Systemic Lupus Erythematosus (SLE), and ESKD on Chronic Hemodialysis

Jose F. Bernardo,[1] Marco A. Dominguez,[2] Carlos R. Valenzuela.[2] *[1]Clinica Medica Cayetano Heredia, Lima, Peru; [2]Hospital Nacional Cayetano Heredia, Lima, Peru.*

Introduction: Hypoglycemia is defined by a plasma glucose below 70 mg/dl, with symptoms usually manifest whenever the levels are less than 55 mg/L. The brain needs continuous supply of glucose as a fuel. During fasting state, the serum glucose level is maintained as a result of the gluconeogenesis and glycogenolysis by theliver. Coma is usually the most common presentation of severe hypoglycemia. We describe a patient

on chronic hemodialysis with adequate oral intake presenting with recurrent episodes of agitation and seizures related to hypoglycemic attacks

Case Description: 34 years old male with history of ESRD on HD, hypertension, had a recent diagnosis of miliary tuberculosis (on standard dose reatment with isoniazid, rifampim, ethambutol and pirazinamide. He also a diagnosis of Systemic Erythematous Lupus, on maintenance with hydroxycloroquine. He was admitted on April 2024 for an episode of severe hypoglycemia. A month later he was admitted with 1 week of progressive weakness, dyspnea on exertion, agitation and confusion. On admission blood glucose was reported at 55 mg/dl atributed to poor oral intake. The patient presented to the ER with an episode of clonic-tonic seizures with loss of consciousnes for one hour. There was no history of decreased oral intake, nausea or vomiting and he was compliant with HD sessions. On admission: had a BP 122/68 mmHg, HR 110 bpm, afebrile, POx 94% on room air. Oral mucosa hydrated, no significant edema. Neurological exam: stupurous, no focal motor deficits. Imaging studies were non revealing. Blood glucose level was 65 mg-dl. He was managed with Dx10% for several hours with a persistent blood glucose of less than 100 mg/dl. An ACTH level was 26.87 pg/ml (7.20-63.30 pg/ml.

Discussion: Our patient was compliant with his chronic HD and medication, There was no history of depression. His food intake was closely observed while in the hospital. During his hospital stay, had repeated episodes of severe hypoglycemia. Diagnostic studies did not suggest the presence of an adrenal infarction and(or the presence of an insulinoma. His prescription of hydroxycloroquine was discontinued with marked and rapid improvement of his glucose levels. Hypoglycemia as a side effect of hydroxycloroquine has been previously described, the incidence however has not been well established.

PUB475

Rifampin as Rescue Therapy for Paxlovid-Associated Calcineurin Inhibitor Toxicity

Shejuti Paul, Sandeep Aggarwal. *University of Pennsylvania, Philadelphia, PA.*

Introduction: Ritonavir-nirmatrelvir (Paxlovid) is effective in treating COVID-19 but is a strong CYP inhibitor that can provoke life threatening calcineurin inhibitor toxicity (CNI). We present a novel case of treating severe CNI intoxication 2/2 to Paxlovid using rifampin as rescue therapy in a heart transplant recipient.

Case Description: The patient was a 40YO male with history of heart transplant in 2003 on tacrolimus and rapamycin, hypertension, and type II diabetes. He contracted covid-19 and was prescribed Paxlovid. Patient presented 3 days later with severe headache, tremors, tachycardia, and hypertension. Found to have acute kidney injury (AKI) with creatinine (Cr) 3.15 from baseline Cr 1.0. Tacrolimus level 53 and rapamycin 23. Tacrolimus and rapamycin held with no improvement. Treated with CYP inducer rifampin 300mg BID for 1 day and IV hydration for 3 days. Patient's symptom resolved. AKI improved with Cr near baseline. Subsequent troughs improved until no longer supratherapeutic. Restarted on rapamycin and tacrolimus day 4 of hospitalization.

Discussion: Paxlovid is a strong inhibitor of cytochrome P450 activity which when used with CNIs can provoke supra-therapeutic levels. Toxicity is associated with AKI, neurotoxicity, and HTN. The use of rifampin for CYP induction therapy resulted in resolution of symptoms, rapid reduction of CNI trough concentrations, and full renal recovery. As Paxlovid becomes more widely used for covid-19 treatment, we can expect more incidence of CNI toxicity. Rifampin is a potent CYP inducer and can be an effective rescue therapy for severe CNI toxicity. More studies are needed to understand drug-drug interactions and treatment of CNI toxicity.

Figure 1: Effect of Rifampin on CNI Concentration

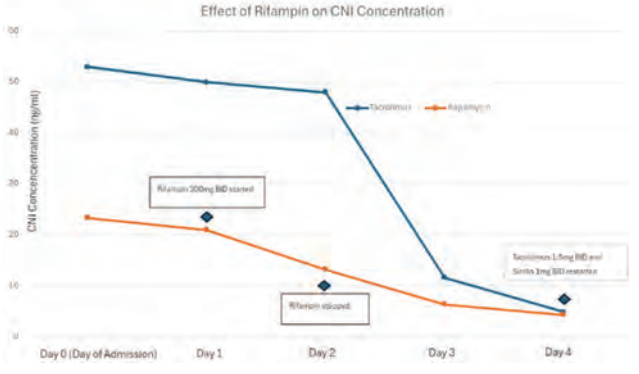
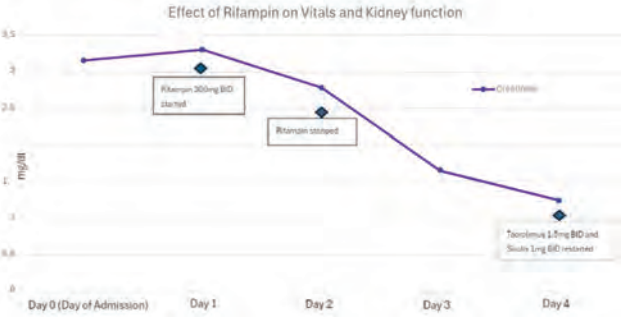


Figure 2: Effect of Rifampin on Kidney Function



PUB476

Valacyclovir Toxicity in Patients with ESKD: A Case Series

Nahom Eyasu,[1] Sonali Poobalasingham,[3] Danielle Feldman,[3] Ajai S. Rajabalan,[2,4] Jason Cobb.[1] *[1]Emory University, Atlanta, GA; [2]Wellstar Health System Inc, Marietta, GA; [3]Emory University Emory College of Arts and Sciences, Atlanta, GA; [4]Augusta University, Augusta, GA.*

Background: Valacyclovir (VCV), a cornerstone in managing herpes virus infections, poses unique challenges in ESRD patients. There is sparse literature on VCV toxicity in this population. More data is available regarding acyclovir toxicity, however, VCV has a longer duration of action and is becoming more commonly used.

Methods: We present two cases and a review of literature of VCV toxicity in ESRD patients.

Results: Case 1: A 33-year-old female with ESRD on peritoneal dialysis (PD) with a right-sided rash suspicious for zoster was prescribed oral VCV 1 g TID at an urgent care. Within 24 hours, she exhibited new-onset confusion and involuntary movements. Suspecting VCV toxicity, the medication was discontinued, and continuous PD provided symptom relief. Case 2: A 54-year-old man with ESRD on hemodialysis (HD) was started on oral VCV 1 g TID for zoster at an urgent care and presented to us with visual and auditory hallucinations. Suspecting VCV neurotoxicity, emergent HD was performed, resulting in symptom resolution after one treatment. Review: 19 total patients on different dialysis modalities: PD (9) and HD (10). Average age 61.6 years. 50% female (7), some case reports did not report gender. All HD patients appeared to respond to a single HD treatment. We were unable to determine specific treatment regimens for PD patients.

Conclusions: The literature on VCV toxicity in ESRD patients has been confined to only case reports and we are the first to present a literature review. VCV's longer duration makes it the treatment of choice for herpes zoster, however, the occurrence of VCV toxicity in ESRD patients is likely to rise if not dosed correctly. PD patients comprise 11-12% of ESRD patients but are involved in 47% of VCV toxicity cases. We suspect that PD patients are more susceptible to VCV toxicity, which raises questions about the differential impact of dialysis modalities on its clearance. In addition, the older age of patients may play a role as well. The critical clinical presentation of our patients underscores the importance of both vigilant monitoring and the need to inform primary and urgent care physicians about the dosing of VCV in the setting of renal dysfunction – 1 g oral daily for ESRD patients.

PUB477

Mind Matters: Muscle Relaxants and Kidney Health, a Case of Baclofen Neurotoxicity

Daniela Carralero Somoza, Graciela M. Luna, Umair S. Ahmed, Kaitlyn Cariaga. *Lakeland Regional Medical Center Inc, Lakeland, FL.*

Introduction: Drug adjustment in the setting of chronic kidney disease is something as physicians we stay vigilant. When prescribing muscle relaxants, the rule does not change. Although baclofen neurotoxicity in presence of CKD is rare, a few reported cases have been evaluated and we present one below.

Case Description: 75-year-old female with hypertension, Type 2 diabetes, hyperlipidemia, and CKD stage IV presented with altered mental status from an assisted living facility. Two days prior, the patient had been prescribed baclofen 10mg tid and was taking it as directed. CT scan of the head revealed no acute intracranial issues. Nephrology was consulted due to elevated creatinine (3.0) and BUN (49), with positive protein in urine analysis. Metabolic encephalopathy was deemed less likely due to uremia given renal parameters, while baclofen neurotoxicity was considered more probable given underlying kidney disease and recent baclofen use in the setting of low GFR. Hemodialysis was initiated due to progressing encephalopathy, leading to improved alertness following the first session.

Discussion: Approximately 10 to 15% of baclofen undergoes hepatic metabolism, while the remaining 85 to 90% is excreted by the kidneys. Baclofen penetrates CNS by directly crossing the blood brain barrier. Baclofen elimination is heavily dependent on renal clearance and patients with reduced kidney function are at higher risk for intoxication. While studies have examined the relationship between dosage and encephalopathy development with the use of baclofen, further data are required to comprehensively assess the safety profile and prescribing guidelines for this medication in CKD patients. This case emphasizes the ongoing quest to refine dose adjustments based on GFR and will serve as a gateway to explore the broader effects of baclofen in CKD. Nevertheless, it's imperative for clinicians to exercise caution, recognizing that even muscle relaxants such as baclofen can pose risks in individuals with compromised renal function.

PUB478

An Unusual Case of Recurrence of Crescentic IgA Nephropathy in Kidney Allograft

Syed S. Hasni, Carla L. Ellis, Sujay D. Paudel, Mohammed Javeed Ansari, Sookhyeon Park. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Introduction: IgA nephropathy (IgAN) is the most common cause of primary glomerular disease worldwide. Recurrence rates have been reported at around 20-30%. Long term graft survival was significantly lower in patients with recurrent IgAN. We describe a case of recurrent IgAN after kidney transplant with crescents.

Case Description: A 35-year-old female with past medical history of ESKD due to biopsy proven IgAN underwent deceased donor kidney transplant with six antigen mismatches. Immunosuppression consisted of Alemtuzumab with Methylprednisolone, followed by long-acting tacrolimus and Mycophenolate mofetil. The patient experienced multiple urinary tract infections (UTI) and was maintained at low immunosuppression. The patients' creatinine (cr) began to rise from 1.0 to 1.58 with hematuria and elevated urine UPCR of 0.39 g/g at 2.5 year follow up. Her DSA, non-invasive gene expression profile, and donor-derived cell-free DNA were all negative. A biopsy showed recurrent IgAN with focal crescents and glomerular fibrin (Image-1). The patient was started on Prednisone 20mg daily for 2 weeks and then 10mg daily along with Losartan 12.5 mg daily for proteinuria. Her cr became stable at 1.23 and UPCR decreased to 0.2 g/g without hematuria.

Discussion: Recurrent IgAN is common but recurrent crescentic IgAN is rare. Many factors can contribute to the recurrence of IgAN, such as lowering immunosuppression due to recurrent UTIs and steroid withdrawal. Nephrologists must be aware that IgAN can recur after renal transplantation with aggressive features. Close monitoring should be performed on urine sediment abnormalities, serum creatine, and proteinuria followed by prompt kidney allograft biopsy. Maintaining low dose of prednisone and ACEi or ARB may help to prevent recurrence of IgAN in a renal allograft.

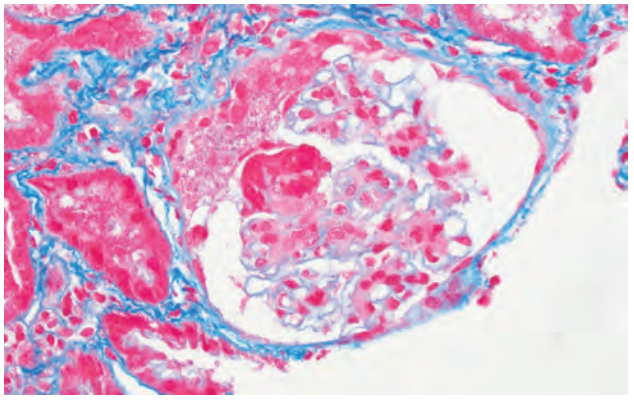


Image 1: Masson 's Trichrome (60x) showing a glomerulus with a cellular crescent and fibrin within capillary loops.

PUB479

Acceptance of Opt-Out Organ Donation in Saudi Arabia: Insights from a Cross-Sectional Study

Sami A. Alobaidi. *University of Jeddah, Jeddah, Saudi Arabia.*

Background: Existing research reveals varied attitudes towards organ donation in the Middle East. This study specifically investigates public opinion on opt-out organ donation registration in Saudi Arabia, addressing a research gap identified through comparative studies in Qatar and Saudi Arabia.

Methods: This study analyzed data from a cross-sectional survey conducted among 1,397 residents of Saudi Arabia. The questionnaire, adapted from a previous study in Qatar, included three sections to gather socio-demographic information, assess general awareness about organ donation, and explore participants' agreement with opt-out consent along with their beliefs related to organ donation using the Theory of Planned Behaviour (TPB) model. Statistical methods were employed to determine significant associations and trends.

Results: Among the participants, nearly half (44.4%) supported opt-out consent, with women and Saudi citizens showing considerable support at 25.7% and 39.1% respectively. Women and individuals with diploma/graduation-level education were significantly more likely to support opt-out ($p<0.001$ and $p=0.012$, respectively). Of the opt-out supporters, a vast majority were familiar with organ donation (98.06%), willing to promote it (93.05%), and believed that registration saves lives (98.38%). Furthermore, 86.75% expressed readiness to support with more information, and 85.78% if informed about their religion's perspective on donation. A large proportion believed that both living and posthumous donations positively impact life after death (92.25%). However, concerns were raised about inadequate care (33.44%) and bodily disfigurement (28.43%) post-mortem. Most felt healthy enough to donate (45.56%) and appropriate in age (57.67%).

Conclusions: The study reveals considerable openness among Saudis toward an opt-out organ donation system, suggesting a potential avenue for significantly increasing organ donation rates. While acknowledging cultural and familial influences, targeted interventions are vital to address specific barriers such as concerns about post-mortem care and bodily integrity. Implementing informed policies based on these insights could facilitate the successful adoption of an opt-out policy, enhancing organ donation rates in the region.

PUB480

Cystinuria following Successful Kidney Transplantation in a Small Child: A Rare but Serious Complication

Rainer Büscher, Anja K. Büscher. *University of Duisburg-Essen, Pediatrics II, Essen, Germany.*

Introduction: Cystinuria, an autosomal recessive hereditary renal-tubular disorder is the most common genetic cause of nephrolithiasis in children and characterized by the impaired reabsorption of the amnio acids cystine, ornithine, lysine and arginine. Mutations in the genes *SLC3A1* and *SLC7A9*, encoding defective cystine transporter subunits have been identified as being responsible for most cases.

Case Description: We describe the case of a seven year old girl with autosomal recessive polycysic kidney disease and *PKHD1*-mutaion who received peritoneal dialysis for 16 months. Kidney transplantation from a deceased donor was successfully performed at the age of 4 years and 10 months. The kidney donor died from brain damage at the age of 14 months (10 kg, 80 cm). Pre-existing medical conditions of the donor were excluded, blood chemistry was normal and both kidneys showed no abnormalities in ultrasound and CT scan. Creatinine normalized within 3 days following renal transplantation (RTx) and the girl showed an uncomplicated clinical course. Nine months after RTx she was admitted with acute post-renal kidney failure with renal pelvic dilatation caused by obstruction with kidney stones in the transplanted kidney. Kidney function normalized quickly after insertion of an ureteral double-J cathether. Cystine stones were diagnosed and two compound heterozygous, pathological mutations in the donor *SLC3A1*-gene (c.647C>T, o.T216M and c.1400T>C, p.M467T) were deteced later on. The second donor kidney could not be transplanted and did not show concrements. The clinical course of our patient was complicated by 5 ureterorenoscopic stone displacements, repeated insertions of ureteral double-J catheters and three episodes of pyelonephritis. The girl presents now a stable renal function for the past 20 months (GFR 65 ml/min/1.73m^2) after repeated surgery, urine alkalization and reduction of the tubular cystine-reabsorption.

Discussion: Teaching point: Deceased young donor clinical factors may have a major impact on patient and/or kidney allograft survival. Cystinuria of the donor in this case was not diagnosed in advance because of the young donor age and missing early clinical symptoms. In the context of time-pressured decision-making and despite the good clinical outcomes of RTx with young donors, one has to consider that rare inherited diseases can be transferred accidentally.

PUB481

Main Obstacles of Pre-kidney Transplant Work-Up: A Quality Assessment/ Process Improvement Program

Abdelrahman Elsebaie,[1,2] Natalie Witton,[2] Wilma M. Hopman,[1,2] David C. Holland,[1,2] M. Khaled Shamseddin.[1,2] Kingston Kidney Transplant Program (KKTP). *[1]Queen's University, Kingston, ON, Canada; [2]Kingston Health Sciences Centre, Kingston, ON, Canada.*

Background: Failure to complete a comprehensive pre-kidney transplant workup results in increased dialysis exposure and poorer post-transplant survivals. Failure also puts stress on transplant centers' resources, as referrals continue to come, patients who are in 'pending activation limbo' are either neglected or detract from new patients' evaluation. Candidates are worked-up by our transplant program after referral rather than by the

dialysis programs where candidates are universally referred to transplant centres after finalizing workup. We are aiming to assess metrics of quality at our program focusing on variability in the time taken for completion of pre-transplant workup among different coordinators, processes, and populations.

Methods: This is a single center retrospective study evaluating the duration and obstacles of pre-kidney transplant workup of all in limbo candidates who were evaluated at our program prior to January 1, 2021. Data will be compared with candidates' workup during a later period, when a more regular chart review was adopted by our newer coordinator to expedite workup.

Results: 112 candidate's files were reviewed by January 1, 2021. 54 (48.2%) candidates were in limbo [Age 54.5±10.7 years, female (44.4%), Caucasian (74.1%)], 38 files were closed due to patients' wishes or nonadherence and 20 others had expired. By March 1, 2024, 47 (87%) in limbo candidates received a transplant decision while 7 patients stayed in workup. Median time from assessment to transplant decision was 23.3 (14.3-37.1) months, while time from chart review to transplant decision was 7.7 (3-16) months. Patients who are still in workup live further away from our center, were assessed once (*P* 0.035), and have a longer median workup to date 44.6 (42.4-55.7) months. The median time to transplant decision of candidates with more frequent pre-transplant assessments compared with those with less frequent assessments was shorter (20.2 vs 27.1 months, *P* 0.037). Finally, at the time of transplant decision, 38 (81%) patients were on dialysis (24 on dialysis > 24 months, 9 (24%) on dialysis < 1 year).

Conclusions: Regular chart review and frequent assessments of pre-transplant candidates result in shorter workup and dialysis vintage.

PUB482

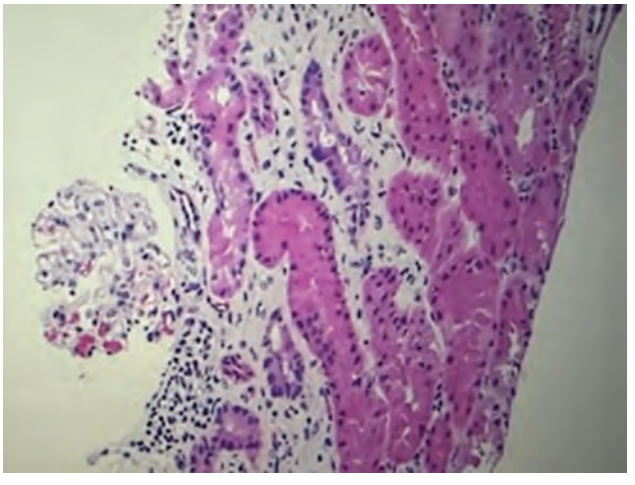
Does Size Matter?

Mansoor Khalid, Payaswini Vasanth. *Emory University, Atlanta, GA.*

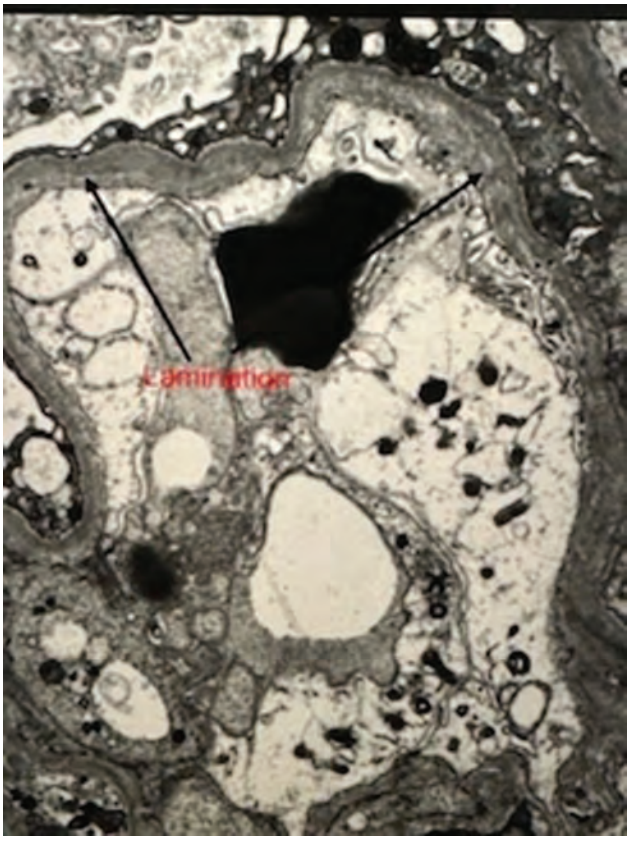
Introduction: Acute cellular rejection secondary to de novo Focal segmental glomerulosclorsis after pediatric en bloc renal transplant to a 48 year old female receptient with absence of focal segmental glomerulosclerosis in donor on renal biopsy prior to transplant.

Case Description: 48 year old female status post pediatric en bloc renal transplant. She had history of Hypertension, end stage renal disease on hemodialysis. Renal biopsy showed global sclerosis, moderate interstitial fibrosis and thrombotic microangiopathy. Donor : DBD, CPRA 70%, KDPI74%, CIT 12 hours, Terminal Cr 0.25, positive B cell cross match. Induction with thymoglobulin and immunosuppression with Belatacept, tacrolimus, prednsione and mycophenolate motefil. Weaned off tacrolimus 9 months per protocol. 12 months post transplant she had new Class 2 DSA at 5000 MFI and 12 grams proteinuria. Renal biopsy showed moderate tubulitis, extensive effacement and blunting of foot process, C4D negative. Treated with pulse dose steroids, plasma exchange, tacrolimus and prolonged steroid taper. Proteinuria decreased to 3 grams and serum creatinine stable at 0.85.

Discussion: Incidence of post transplant proteinuria is higher in adults who received pediatric kidneys compared to those who received adult kidney. Body surface area disparity of > 1.3 $m^{2,}$ recepient weight > 30 kg compared to donor, kidney/ recepient weight ratio <2g/kg is associated with higher risk of graft loss.(Transplantation 2020;104;1695-1702)



LM



EM

PUB483

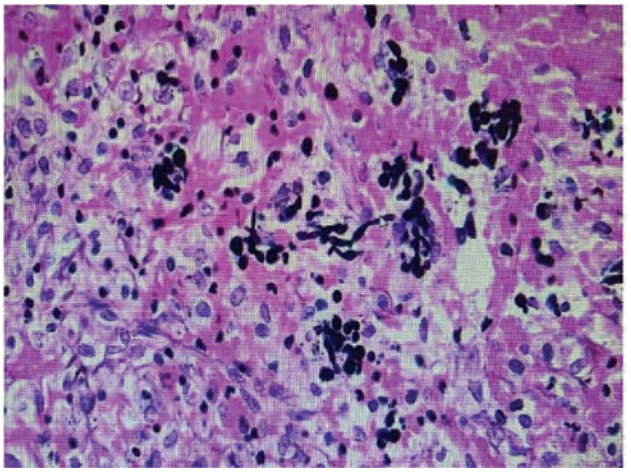
Mycotic Aneurysm of Transplant Renal Artery

Trey H. Richardson, Anthony J. Langone, Saed Shawar. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Kidney transplant recipients are at risk for infectious complications of surgery during the first three months after transplantation. Fungal infections, though rare, affect 0.1% to 5% of kidney transplant recipients. Herein, we present a case of a transplant recipient who developed a ruptured mycotic aneurysm that led to a transplant nephrectomy.

Case Description: A 72-year-old man with end-stage kidney disease from hypertension and type two diabetes underwent a deceased donor kidney transplant. He presented to the emergency department 22 days after transplantation with a fall. His hemoglobin was 6.1 mg/dl from a baseline of 8.0 mg/dl. A CT of his abdomen revealed a hematoma surrounding the allograft. The hematoma was evacuated and attributed anastomotic dehiscence. The allograft was resected in order to obtain hemostasis, and a patch angioplasty from a saphenous vein was performed. The vessel had a mycotic appearance, prompting the collection of cultures from perinephric fluid and the allograft. The allograft cultures grew Staphylococcus epidermidis, Staphylococcus capitis, Candida tropicalis, and Candida albicans [Figure 1]. Perinephric fluid cultures grew Candida tropicalis and Candida albicans. He was treated with vancomycin and micafungin. Micafungin was switched to fluconazole, which he continued for 4 months due to positive perinephric fluid cultures. His immunosuppressive medications were stopped. Prophylactic trimethoprim-sulfamethoxazole and valacyclovir were continued.

Discussion: Mycotic arteritis is a rare complication that leads to graft loss and should prompt an investigation for the source of infection. This patient likely developed the infection de novo, as there were no reports in UNOS of infections in the other organs procured from the donor. Donor organs can be contaminated during procurement, preservation, and intra-operative organ handling. Treatment involves antifungals and allograft nephrectomy.



Renal path with candida species

PUB484

Understanding What Patients and Families Living with Kidney Failure Want and Need to Know about Xenotransplantation: A Kidney Transplant Research Possibility

Tandrea Hilliard-Boone, Holly DePatie. *American Institutes for Research, Chicago, IL.*

Background: Advances in xenotransplantation offer great promise for an alternative supply of organs to meet the needs of people with life-threatening illnesses like kidney failure. However, this kidney transplant possibility has not yet been tested in clinical trials with humans, only early testing. The American Society of Nephrology (ASN) Kidney Health Initiative (KHI) formed a project team to assess perspectives about xenotransplantation and identify information needed to help ensure that future first-in-human (FIH) clinical studies are patient-centered and reflect the perspectives of those most affected by the research.

Methods: To understand what is most important for patients and families living with kidney failure to know about xenotransplantation and future clinical trials, the American Institutes of Research (AIR) conducted 39 virtual individual interviews with patients, care partners, and nephrologists between April 1, 2022 and May 14, 2022. We used qualitative thematic analysis to synthesize and cross-validate the data.

Results: Patients, care partners, and nephrologists shared perceived benefits of xenotransplantation, including expanding the supply of organs available, reducing long waiting times, and improving quality of life. Perceived risks included organ rejection, infection, or other complications. Nephrologists identified potential risks associated with a lack of available data related to short-and long-term health outcomes and safety. All participants expressed a need for information about xenotransplantation that is transparent, accessible, and understandable for diverse audiences and recommended strategies to help prepare clinicians to have conversations with patients and families about future clinical trials.

Conclusions: Breakthroughs in xenotransplantation offer great promise for addressing the critical organ donor shortage, particularly for those living with kidney failure. Our discussions with patients, care partners, and nephrologists underscore the need to prepare both clinicians and families for discussions about potential participation in a clinical trial for xenotransplantation.

PUB485

Catch It or Lose It: Timely Recognition and Conservative Management of Thrombotic Microangiopathy in a Kidney Transplant Recipient

Ahmad Matarneh, Sundus Sardar, Rafael Portela, Nasrollah Ghahramani, Gurwant Kaur. *Penn State Health Milton S Hershey Medical Center, Hershey, PA.*

Introduction: Thrombotic microangiopathy (TMA) is rare and potentially lethal complication in kidney transplant recipients, characterized by hemolytic anemia, thrombocytopenia, and kidney failure. TMA can be triggered by multiple factors including medications. Calcineurin inhibitors (CNIs) are associated with TMA. Prompt recognition and management are crucial to prevent severe outcomes, such as graft loss. This case highlights early TMA occurring two weeks after a kidney biopsy-proven chronic acute antibody-mediated rejection, where timely intervention led to a favorable prognosis and graft salvage.

Case Description: A 41-year-old man with end-stage kidney disease from adult polycystic kidney disease who received deceased donor kidney transplant six years ago. His immunosuppression included mycophenolate mofetil (1000mg twice daily) and extended-release tacrolimus (5mg daily). His kidney function declined over time, with creatinine rising from 2.2mg/dl to 3.5mg/dl, prompting a kidney biopsy. The biopsy showed acute T-cell-mediated rejection (grade 1A) and chronic active antibody-mediated rejection, treated with pulse steroids, IV immunoglobulin, and a tapering course of oral steroids. He presented to the hospital with bruising, abdominal pain, nausea, and diarrhea for 3 days. Labs revealed thrombocytopenia (35K/μL from 130K/μL), anemia (7.1g/dL from 8.9g/dL), and elevated creatinine (5.25 mg/dL, baseline 2.2mg/dL). Suspecting TMA, especially with recent supratherapeutic tacrolimus level. Workup showed high LDH (572 U/L), low haptoglobin (<10mg/dL), normal bilirubin (0.5mg/dL), and rare schistocytes on a peripheral smear. ADAMTS13 and Coombs tests were negative. Tacrolimus was replaced with belatacept. Platelet count, Hb, and kidney function improved with stopping tacrolimus. Early inclusion of TMA in the differential diagnosis enabled prompt treatment and favorable outcomes.

Discussion: The timely diagnosis of TMA in a kidney transplant recipient is critical and delay in diagnosis can lead to severe complications including graft loss. TMA in transplant recipients can be triggered by medications such as CNIs and mTOR inhibitors, antibody mediated rejection, viral infections (Hepatits C, HIV, BK Virus), genetic abnormalities in complement cascade. Prompt recognition and management of TMA can reduce graft loss and improve outcomes.

PUB486

Noninvasive Bladder Cancer Treated with Bacillus Calmette-Guérin in Kidney Transplant Recipients

Jessenia A. Contreras, Rana Sandhu. *Kaiser Permanente Northern California Region, San Francisco, CA.*

Introduction: Bacillus Calmette-Guérin (BCG) is best known as one of the discoveries for the protection against tuberculosis, which also was noted to have other benefits, such as a therapy for non-muscle invasive bladder cancer (NMIBC). In immunosuppressed patients, the use of BCG developed concerns because the creation was derived from being a re-culture of Mycobacterium bovis. The few cases found during literature review discussed the complications of intravesical BCG therapy in kidney transplant patients, such as subacute interstitial pneumonitis and disseminated Mycobacterium bovis infection. We have four cases of kidney transplant recipients who were treated with intravesical BCG therapy for NMIBC with no post-treatment complications.

Case Description: A 67-year-old man with history of pre-emptive kidney transplant due to autosomal dominant polycystic kidney disease (ADPKD) in 2022 and high-grade noninvasive papillary urothelial carcinoma (PUC) in 1988 status post (s/p) transurethral resection of bladder tumor (TURBT) in 1998 treated with intravesical BCG in 2019 due to recurrence. A 49-year-old man with history of renal transplant due to end-stage kidney disease (ESKD) caused by autosomal 17q12 microdeletion syndrome in 2005 and high-grade noninvasive PUC s/p TURBT in 2019 treated with intravesical BCG in late 2019. A 67-year-old man with history of kidney transplant due to ESKD from type one diabetes mellitus and hypertension early 2017 (previously on dialysis) and low-grade noninvasive PUC s/p TURBT in late 2017 treated with intravesical BCG therapy in 2019 due to recurrence. A 66-year-old man with history of renal transplant due to ESKD from focal segmental glomerulosclerosis (FSGS) in 1995 and high-grade noninvasive PUC s/p TURBT in 2017 treated with intravesical BCG in late 2017.

Discussion: All four cases did not exhibit post-treatment complications and are currently doing well. These cases depict that use of intravesical BCG may be safe for patients taking immunosuppression.

PUB487

Vanishing Kidney Allograft

Laura A. Imarhiagbe, Aimen Liaqat, Vasanthi Balaraman, Barry M. Wall. *The University of Tennessee Health Science Center College of Medicine, Memphis, TN.*

Introduction: Emphysematous pyelonephritis is a severe infection of the kidney characterized by necrosis and gas accumulation in kidney parenchyma, adjacent tissues and urinary collecting system. We present a case of severe emphysematous pyelonephritis with a very rapid evolution to complete destruction and a sonographically vanishing kidney allograft.

Case Description: 60-year-old female with a history of end stage renal disease from diabetic nephropathy received a deceased donor kidney transplant. Her immediate post operative course was complicated by early ureteral stricture and revision of ureteral anastomosis resulting in good allograft function with average creatinine of 2-2.5mg/dl on quadruple immunosuppression. She had two admissions for uncontrolled hyperglycemia and Escherichia coli (E. coli) urinary tract infection (UTI) at 3 months and Klebsiella UTI at 5 months post-transplant. At month 8, she presented with sepsis secondary to E. Coli UTI with bacteremia, diabetic ketoacidosis, and AKI requiring dialysis initiation. CT of the abdomen and pelvis at admission had normal findings of transplanted kidney. Ultrasound on day 3, performed due to worsening clinical condition and graft function was reported as no visible kidney allograft. Repeat CT showed complete liquefaction of

her transplant kidney replaced by pockets of air and abscess formation. She underwent transplant nephrectomy following unsuccessful abscess drainage. Surgical cultures were positive for E. Coli and Vancomycin resistant enterococcus faecium. Eventually, targeted antibiotic therapy resulted in complete resolution of her infection.

Discussion: Vanishing kidney is an advanced presentation of emphysematous pyelonephritis where a kidney previously visible sonographically disappears as layers of encasing gas pockets block penetration of ultrasonographic waves. While uncommon, it is a life-threatening disease with major risk factors including poorly controlled diabetes, immunosuppression, and urinary obstruction. E. Coli is the causative pathogen in 70% of cases. Emphysematous pyelonephritis frequently requires nephrectomy. High index of suspicion upon non visualization of kidney allograft on ultrasound warrants immediate confirmation with CT imaging, as early diagnosis and timely intervention are essential in this life-threatening condition.

PUB488

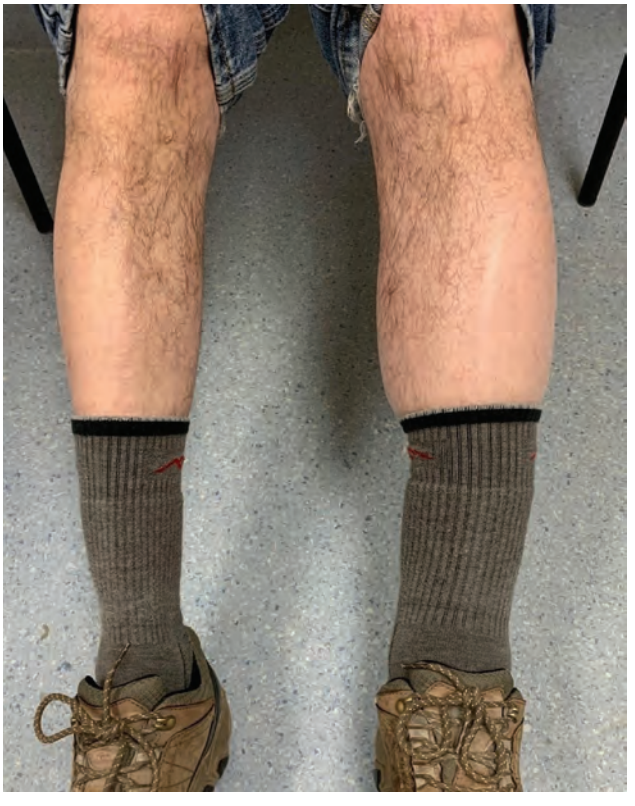
Postkidney Transplant May-Thurner Syndrome Causing Ipsilateral Left Lower-Extremity Edema and Left Lower-Quadrant Kidney Allograft Dysfunction

Macaulay A. Onuigbo, Marios Prikis, Erin Berg, Rachel Preston, Andrew Myhre, Selena Patterson, Ema Allen, Jaime Pineda. *The University of Vermont Medical Center, Burlington, VT.*

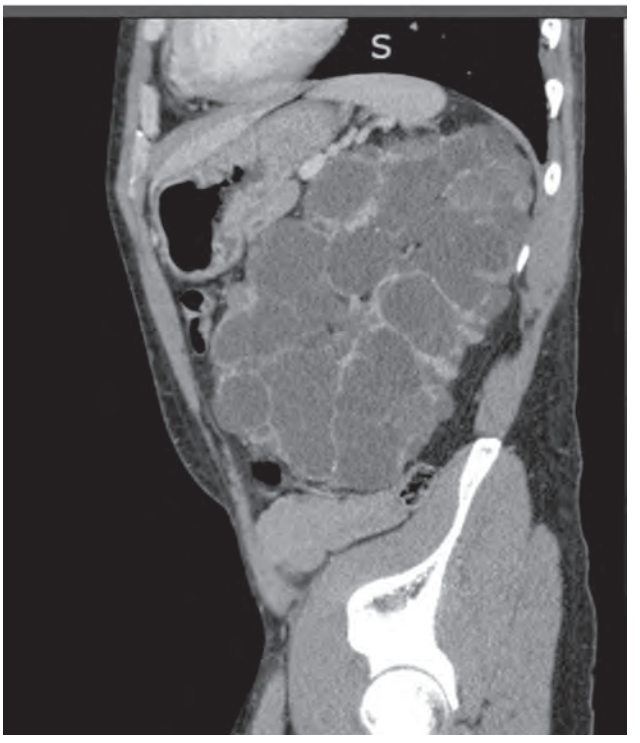
Introduction: May-Thurner syndrome (MTS) results from extrinsic venous compression of the iliocaval veins. We report progressive MTS post-DDK with ipsilateral left LE edema and DDK dysfunction.

Case Description: A 43-yo male with ESRD from ADPKD, on hemodialysis for 7 years received a DDK in 2024. 9 weeks later, he developed unilateral painless left LE swelling (Figure 1). Dopplers ruled out LE DVT but showed extrinsic 75%-90% narrowing of the left external iliac vein from compression by the large left ADPKD kidney and the left LQ DDK, consistent with MTS (Figure 2). DDK ultrasound and Duplex showed no hydronephrosis, and no renal artery stenosis. Serum creatinine that had promptly progressively declined to 1.60 mg/dL has since partially reversed this trend. An open left nephrectomy is planned.

Discussion: Our patient has May-Thurner syndrome with symptomatic ipsilateral LE edema and further complicated by new evidence of renal allograft dysfunction. To avoid further renal allograft compromise and to mitigate the lower extremity swelling, the patient will undergo an urgent open native left nephrectomy.



New left LE swelling 9 weeks post-DDK



Large ADPKD kidneys on prior CT

PUB489

Pretransplant Hypoalbuminemia Is Not Associated with Worse Outcomes among Simultaneous Pancreas and Kidney Transplant Recipients

Ekaterina Fedorova, Sofia Nehring Firmino, Brad C. Astor, Didier A. Mandelbrot, Dixon Kaufman, Jon S. Odorico, Sandesh Parajuli. *University of Wisconsin-Madison, Madison, WI.*

Background: Hypoalbuminemia is a well-known independent risk factor predictive of worse outcomes in surgical patients. Nonetheless, the role of pre-transplant hypoalbuminemia and its impact on post-transplant outcomes in patients undergoing simultaneous kidney-pancreas (SPK) transplantation remains unclear.

Methods: We retrospectively analyzed all SPK recipients at our center from 2001-2022, who had at least 2 weeks of pancreatic graft survival. Serum albumin levels measured within 6 weeks or closer to transplant were included. Recipients were categorized based on pretransplant albumin level normal (≥ 4.0 g/dl, N = 222), mild (≥3.5 - < 4.0 g/dl, N = 190), moderate (< 3.5 g/dl, N = 120). Multivariable logistic regression and Cox proportional hazard models were used to analyze associations with the length of stay (LOS), kidney delayed graft function (DGF), re-hospitalization within 30 days after discharge, and need for return to the operating room (OR) related to transplant surgical complications, along with acute rejection and uncensored and death-censored graft failure, within the first-year post-transplant.

Results: A total of 532 SPK recipients were included, 42% had normal serum albumin; 36% had mild and 23% had moderate hypoalbuminemia. The mean pre-transplant albumin level was 4.3 g/dl in normal, 3.7 g/dl in the mild, and 3.0 in the moderate group. After adjustment for multiple variables, with reference to normal pre-transplant albumin level, mild or moderate hypoalbuminemia was not associated with either increased or decreased risk for LOS, DGF, re-hospitalization or return to the OR. Also, mild, or moderate hypoalbuminemia was not associated with risk for either graft rejection or graft failure.

Conclusions: Among SPK recipients, pre-transplant hypoalbuminemia is not associated with worse outcomes. Pre-transplant albumin level should not be the determining factor in offering or rejecting these life-saving organs.

PUB490

BK Viremia in Kidney Transplantation

Rakhi Khanna, Andrea Pabon. Rush Nephrology. *Rush University Medical Center, Chicago, IL.*

Background: BK polyomavirus can cause BK nephropathy resulting in allograft dysfunction or premature allograft loss. Reducing immunosuppression has been the cornerstone of management, effectively treating BK viremia and BK virus associated nephropathy (BKVAN), which poses a challenge for clinicians, as it involves balancing and risking rejection. The optimal post-transplant screening approach for BK has not been determined and varies among transplant centers.

Methods: We examined the association of allograft function in kidney transplant recipients who had reduced immunosuppressive regimens from 3 to 2 agents due to BK viremia. We defined BK viremia as any patient with a positive result rather than a specific number of copies in the serum. This retrospective single-center analysis of 16 patients who received a kidney transplant and developed BK viremia post-transplant looked at changes in serum creatinine one month post-transplant and up to 10 years post-transplant.

Results: BK viremia onset ranged from 1-35 months post-transplant with an average onset of 10 months. All 16 had dose reduction or discontinuation of the antimetabolite agent. 7 of the 16 (44%) were with sustained BK viremia at last check within 3 months. 9 (56%) tested negative for BK viremia at last check within 3 months. Serum creatinine increased by 9 - 49%. Mean sCr increase was 22%. 0 of the 16 were challenged with reintroduction of the previously discontinued antimetabolite. Post-transplant complications included Crohn's exacerbation, bacteremia, pyelonephritis, antibody-mediated rejection, and urothelial tract carcinoma.

Conclusions: Our retrospective review of 16 patients followed for 10+ years aligns with the current KDIGO BK viremia screening recommendation. Of the total 16 patients this study included, >80 % had elimination of the antimetabolite agent; however, despite this regimen 44% of patients continue to have BK viremia. Over 22% had some rise and worsening of kidney function from one month baseline. We recommend that further attention be given to the patient population with BK viremia and further reduction of immunosuppression be considered, especially of the calcineurin inhibitor (CNI) along with bimonthly evaluation of BK viremia until its resolution, and evaluation by a kidney biopsy if the viremia persists.

PUB491

Use of the Monocyte-to-Lymphocyte Ratio to Predict Delayed Graft Function in Patients after Kidney Transplantation

Irin Jariyayothin. *Police General Hospital, Bangkok, Thailand.*

Background: Delayed graft function (DGF) is a significant complication following kidney transplantation, affecting graft survival. The monocyte-to-lymphocyte ratio (MLR) is being explored as a potential predictor of DGF, reflecting inflammatory and immune responses. Evaluating MLR's utility in predicting DGF could improve patient management post-transplantation.

Methods: Medical records of patients undergoing kidney transplantation at Police General Hospital from January 1989 to December 2023 were reviewed. DGF was defined as a temporary impairment of kidney function immediately after transplantation, requiring dialysis within the first week post-transplant. Clinical data and laboratory were collected. The optimal cut-off value for MLR was determined using receiver operating characteristic (ROC) curve analysis. Univariate and multivariate logistic regression models were performed to investigate the risk factors associated with DGF.

Results: A retrospective cohort study was conducted on 162 kidney transplant patients, of which 58 had DGF, while 104 did not. Clinical outcomes focused on DGF, with MLR investigated as a potential biomarker. In the receiver-operating characteristic (ROC) curve analysis, MLR, with an optimal cut-off value of 0.255 (AUC of 0.686; 95% CI 0.603, 0.769; P < 0.001), predicted the DGF with a sensitivity of 81.0% and specificity of 55.8%. The multivariate logistic regression analysis confirmed that MLR was an independent factor of DGF (MLR) >0.255 (Adj. OR 3.74 [95% CI 1.55, 9.02], P=0.003).

Conclusions: This study suggested that high MLR may associated with DGF. The MLR is an inexpensive and straightforward indicator to reflect systemic inflammation status to help clinicians improve kidney transplant care.

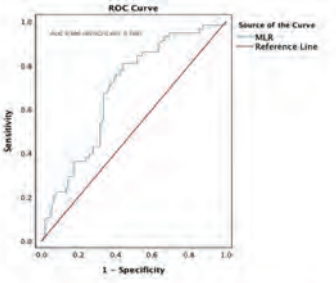


Figure 1 The ROC curve of the monocyte-to-lymphocyte ratio (MLR) for predicting delayed graft function showed statistically significant difference from the reference line (P<0.05)

Table 4 Area under the receiver operating characteristic curve of the monocyte-to-lymphocyte ratio (MLR) in predicted delayed graft function

	AUC	95%CI	P-value	Optimal cutoff point	Maximum of Youden index
MLR	0.686	0.603, 0.769	<0.001*	0.255	0.368

*Statistically significant at the 0.05 level (α=0.05)

PUB492

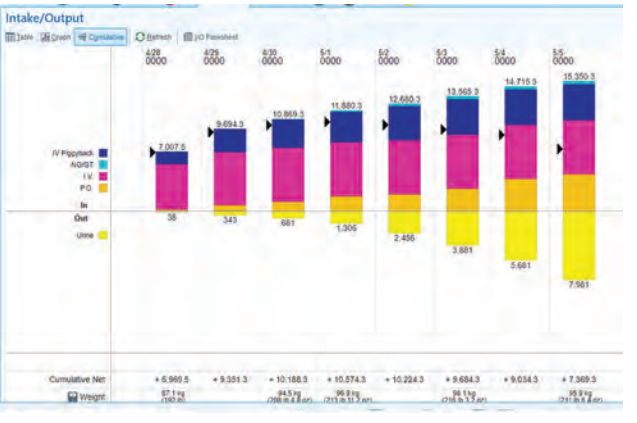
Can Post-transplant Congestive Nephropathy from Hypervolemia Cause Slow Graft Function?

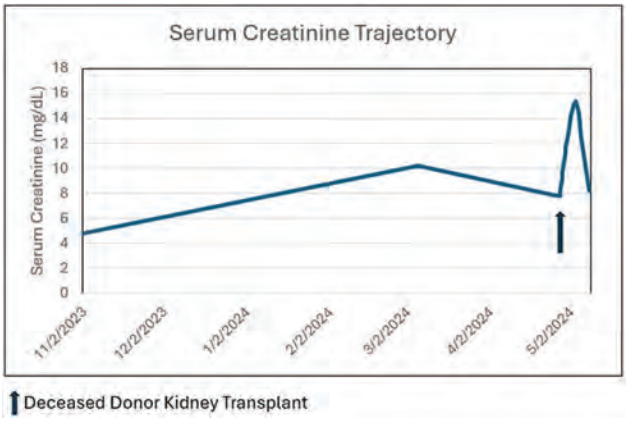
Macaulay A. Onuigbo, Marios Prikis, Rachel Preston, Erin Berg, Joshua Hsu, Jamie Vanvught, Jaime Pineda. *The University of Vermont Medical Center, Burlington, VT.*

Introduction: Low cardiac output alone does not define renal dysfunction in cardiorenal syndrome (CRS). Congestive nephropathy (CN) depicts the role of renal venous hypertension in CRS. Our understanding of CN is evolving. Furthermore, we do not have any known reports of CN in renal allografts.

Case Description: A 48-yo female with ESRD from Fabry's disease, who started hemodialysis in February 2020 was on Midodrine to sustain hemodialysis due to hypotension. She made about a cup of urine. She received a deceased donor kidney transplant in late April 2024. Due to peri-operative hypotension with systolic blood pressure in the 70s, she received multiple liters of IVF therapy perioperatively and post-operatively (Figure). She received IV albumin boluses and was restarted on oral Midodrine post-operatively. There was evidence of hypervolemia and fluid retention. She had slow graft function and subsequently responded well to combination IV Furosemide + IV Chlorothiazide infusions and subsequent switch to oral Torsemide 100 mg daily + oral Metolazone 5 mg daily with later fall in serum creatinine. She was discharged on post-op day #8 for outpatient management and monitoring of improving renal allograft function (Figure).

Discussion: To our knowledge, this is the first report of CN in a new renal allograft. The serum creatinine trajectory supports the speculation that both native kidneys and the newly transplanted renal allograft were simultaneously impacted by CN. The subsequent falling creatinine with decongestive diuresis supports this hypothesis. Further investigation is warranted.





PUB493

Validation of Donor-Derived Cell-Free DNA as a Biomarker for Antibody-Mediated Rejection in Kidney Transplant Recipients Late Post Transplantation

Grace K. Lee,[1] Anantharaman Vathsala,[2,3] Hersharan Sran,[2,3] Matthew D'Costa,[2] Zi Yun Chang,[2] Emmett Tsz Yeung Wong.[2,3] *[1]Department of Medicine National University Hospital, Singapore, Singapore; [2]National University Centre for Organ Transplantation, National University Hospital, Singapore, Singapore; [3]Department of Medicine National University of Singapore, Singapore, Singapore.*

Background: Antibody-mediated rejection (ABMR) is a leading cause of late allograft failure in kidney transplant recipients (KTRs). Plasma donor-derived cell-free DNA (dd-cfDNA) is a non-invasive diagnostic biomarker for ABMR early post-transplant. As most studies evaluated KTRs at <3 years post-transplant, it is unclear if dd-cfDNA is useful in distinguishing ABMR from other findings in allografts >3 years post-transplant when superimposed on chronic inflammation and fibrosis. We hypothesise that dd-cfDNA is sensitive and specific for diagnosing late ABMR.

Methods: We conducted a single-centre, prospective, observational, pilot study. We recruited 27 KTRs with allograft dysfunction at >3 years post-transplant in whom a biopsy was planned. Plasma dd-cfDNA (AlloSeq®, CareDx, Brisbane, CA) was sent at the time of biopsy. Diagnostic characteristics were performed for dd-cfDNA and DSA, and dd-cfDNA correlated with Banff lesion scores.

Results: The median age of KTRs was 53 years (IQR 40, 55); 14 (52%) were living donor KTRs. Eighteen (67%) were Chinese and 7 (26%) were Malays. The median time post-transplant was 7.8 years (4.9, 11.7). Four (15%) KTRs had ABMR. Median dd-cfDNA was higher in KTRs with ABMR (1.95% vs 0.24%, p=0.004). Using a cut off of 1%, the AUROC for dd-cfDNA was 0.97. Its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) to diagnose ABMR were 100%, 96%, 80%, 100%, vs. 100%, 91%, 67%, 100% for DSA. Combining dd-cfDNA with DSA achieved 100% sensitivity, specificity, PPV and NPV. Dd-cfDNA correlated positively with peritubular capillaritis (ptc, p=0.002) but not glomerulitis (g, p=0.070) scores when evaluated as continuous variables. Other than interstitial fibrosis (ci) scores (negative correlation, p=0.038), there was no significant correlation between dd-cfDNA and Banff chronicity scores.

Conclusions: In this pilot study, dd-cfDNA showed good diagnostic characteristics for ABMR late post-transplant and correlated positively with ptc scores. A lack of correlation between dd-cfDNA and chronicity scores suggests its utility as a predictor of late ABMR. This provides preliminary data for larger studies.

PUB494

Eco-friendly Innovation in Kidney Transplants: Outcomes from a Collaborative Artificial Intelligence (AI) Feedback Loop

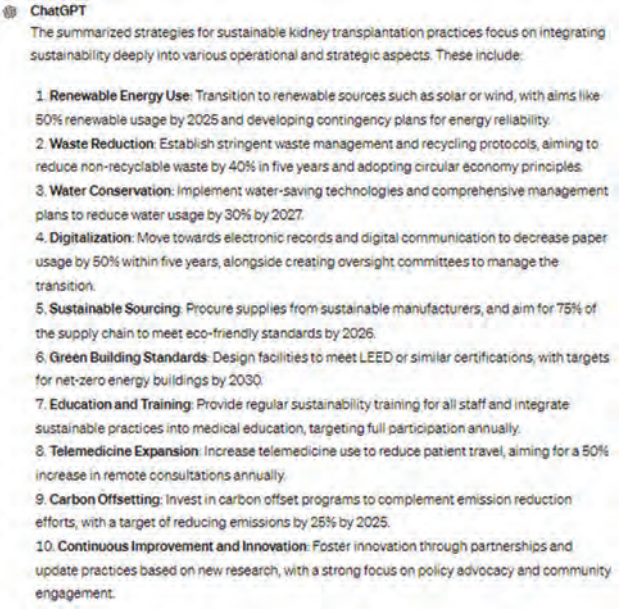
Suryanarayanan Balakrishnan,[1] Oscar A. Garcia Valencia,[1] Yasir Abdelgadir,[1] Charat Thongprayoon,[2] Jing Miao,[2] Napat Leeaphorn,[3] Iasmina Craici,[1] Wisit Cheungpasitporn.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Mayo Clinic Health System, Mankato, MN; [3]Mayo Clinic in Florida, Jacksonville, FL.*

Background: Negative environmental impact of kidney transplant is significant. Sustainable practices are crucial for reducing the environmental burden while ensuring optimal patient outcomes. ChatGPT-4.0 developed ten key strategies, which were further enhanced through a collaborative feedback process involving three other cutting-edge AI agents: Claude 3.0 Opus, Gemini Advanced, and Meta AI with Llama-3.

Methods: In April 2024, a multi-stage feedback loop approach was conducted, involving GPT-4.0 and three other AI agents (Claude 3.0 Opus, Gemini Advanced, and Meta AI with Llama 3), utilized a series of feedback loops to refine and improve ten critical strategies for establishing sustainable transplants. The feedback loops continued until all agents were satisfied with the final set of strategies, at which point the strategies were executed.

Results: The refinement process included six rounds and 29 communications encompassing initial feedback, subsequent revisions and final approvals. This iterative review led to a robust set of strategies, significantly enhancing the initial proposals. The strategies achieved specific targets (see Fig. 1), such as 50% renewable energy use by 2025, and a comprehensive sustainability plan included transitioning to renewable energy, water conservation, digital transformation and carbon offsets.

Conclusions: Our study demonstrated the potential of AI collaboration in creating sustainable medical practices for 'green' kidney transplants which can guide healthcare organizations. This model highlights the effectiveness of collaborative AI in developing sophisticated solutions to complex problems, potentially serving as a blueprint for future sustainability initiatives.



ChatGPT

The summarized strategies for sustainable kidney transplantation practices focus on integrating sustainability deeply into various operational and strategic aspects. These include:

1. **Renewable Energy Use**: Transition to renewable sources such as solar or wind, with aims like 50% renewable usage by 2025 and developing contingency plans for energy reliability.
2. **Waste Reduction**: Establish stringent waste management and recycling protocols, aiming to reduce non-recyclable waste by 40% in five years and adopting circular economy principles.
3. **Water Conservation**: Implement water-saving technologies and comprehensive management plans to reduce water usage by 30% by 2027.
4. **Digitalization**: Move towards electronic records and digital communication to decrease paper usage by 50% within five years, alongside creating oversight committees to manage the transition.
5. **Sustainable Sourcing**: Procure supplies from sustainable manufacturers, and aim for 75% of the supply chain to meet eco-friendly standards by 2026.
6. **Green Building Standards**: Design facilities to meet LEED or similar certifications, with targets for net-zero energy buildings by 2030.
7. **Education and Training**: Provide regular sustainability training for all staff and integrate sustainable practices into medical education, targeting full participation annually.
8. **Telemedicine Expansion**: Increase telemedicine use to reduce patient travel, aiming for a 50% increase in remote consultations annually.
9. **Carbon Offsetting**: Invest in carbon offset programs to complement emission reduction efforts, with a target of reducing emissions by 25% by 2025.
10. **Continuous Improvement and Innovation**: Foster innovation through partnerships and update practices based on new research, with a strong focus on policy advocacy and community engagement.

PUB495

Nonsteroidal Anti-inflammatory Drug (NSAID) Prescriptions in Living Kidney Donors

Mikayla Laube,[1] Robert R. Quinn,[1] Pietro Ravani,[1] Krista L. Lentine,[2] Rachel Jeong,[1] Ngan Lam.[1] *[1]University of Calgary, Calgary, AB, Canada; [2]Saint Louis University, St Louis, MO.*

Background: Current guidelines recommend that living kidney donors should avoid non-steroidal anti-inflammatory drugs (NSAIDs) due to their potential nephrotoxic effects. It is unclear if physicians are adhering to this guideline recommendation.

Methods: We conducted a population-based, retrospective cohort study of adult living kidney donors in Alberta, Canada, who donated between 2002 and 2019. We identified the proportion of living kidney donors who filled an NSAID prescription at least 1-year beyond date of donation. Of those donors who were prescribed an NSAID, we assessed how many underwent post-prescription laboratory testing for kidney function and potassium within 14 days.

Results: Of 759 living kidney donors in the study cohort, 273 (36%) had at least one NSAID prescription over a median follow up of 7.2 years (IQR 3.5-11.5). Donors with at least one NSAID prescription were more likely to be from lower socio-economic status, have an earlier donation date, have higher pre-donation eGFR, and have co-morbid gout and osteoarthritis at the index date. The proportion of donors with at least one prescription in follow-up remained stable over time (~10% per year). Family physicians accounted for 66% of all NSAID prescriptions. Of the donors with an NSAID prescription, 30% also filled at least one prescription for an opioid. Approximately, 10% of donors had measurements of serum creatinine or potassium within 14 days of the first NSAID prescription. The risk of acute kidney injury or hyperkalemia was uncommon in those that underwent laboratory testing (6% and 3% respectively).

Conclusions: Over one-third of living kidney donors are prescribed NSAIDs despite current guideline recommendations. Few donors had evidence of post-prescription laboratory testing, but adverse outcomes were uncommon in those who were tested. Further research assessing outcomes following NSAID use is recommended to better inform guidelines for living kidney donors.

PUB496

A Home Hospital Program Offers Versatility in Treating Cytomegalovirus (CMV) Viremia in a Kidney Transplant Recipient

Yinelka G. Silverio De Castro, Jerin Karingattil, Eliot Sachsenmeier, James Drakakis. *NYU Langone Hospital - Long Island, Mineola, NY.*

Introduction: Hospital at home (HaH) health care was initially driven by the COVID-19 pandemic as a way to administer comprehensive care to patients in the comfort of their own homes. NYU Langone's Home Hospital Program screens patients either in the emergency department or after they have already been admitted for inpatient stay. After transport home, they receive care through in-person and virtual visits with their team. Literature pertaining to involvement of kidney transplant (KT) patients in HaH initiative is limited. Publications describe it as a potential first line strategy for KT recipients with COVID-19. But what about application to those transplant recipients with other complications (provided they stable enough to be monitored at home)?

Case Description: 73 year old female with past history of Hodgkin's lymphoma (status post chemotherapy + radiation + autologous stem cell transplant) in 1996, end-stage-renal-disease with preemptive deceased donor KT in 2022. She presented to the ER at NYU Hospital Long Island after outpatient testing revealed whole blood CMV DNA PCR of 77426 IU/mL. Infectious disease consultation called for renally dosed standard induction Ganciclovir (2.5 mg every 24 hours for creatinine clearance 40 mL/min). After three days in the hospital, she was transferred to the HaH program. In her home, she received IV Ganciclovir via midline catheter for an additional 8 days. Ultimately, viral load (plasma) improved to 1570 IU/mL from plasma peak of 11900 IU/mL. At that point she was discharged on oral Valgancyclovir.

Discussion: The choice of CMV therapy is determined by several factors, one of which is inital viral load. While there is no established cut off for high viral load, usually >10,000 copies/mL is considered high. The duration of therapy may vary but is typically 21 days. Our otherwise asymptomatic patient received IV Ganciclovir while at home for the desired duration, administered by a registered nurse. In addition, immunosuppressants were administered, blood work (including daily Tacrolimus levels and weekly CMV viral loads) completed. Per day, she received at least two nurse visits, a hospitalist and nephrologist visit and vital sign monitoring. This case is one example whereby a HaH program offers a unique opportunity to manage a stable KT patient who requires a potentially long hospitalization.

PUB497

Characterization of Cytomegalovirus (CMV) Viremia and Disease in CMV High-Risk Kidney Transplant Recipients: A Single-Center Experience

Shanmugha Vigneshwar Padmanabhan, Martha Pavlakis, Barbra M. Blair, Bhavna Chopra. *Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Cytomegalovirus (CMV) infection in Kidney Transplant Recipients (KTRs) is associated with significant morbidity particularly in the high risk (HR) [donor positive (D+) and recipient negative (R-)] KTRs. We compared severity of CMV infection in CMV HR KTRs at our center after 6 months (mo) of valganciclovir prophylaxis (ppx) where post ppx, CMV PCR monitoring is NOT performed vs. published data where post ppx CMV PCR surveillance was done.

Methods: We reviewed records of CMV HR KTRs at our center from 2019-2022, to identify the frequency and severity of CMV viremia, disease burden, hospitalizations, and mortality. We then compared our outcomes to published literature in a similar setting (IS and ppx) where CMV PCR monitoring is performed post ppx for 3 mo (PMID: 27423138).

Results: Of the 71 CMV HR KTRs, induction was with Anti Thymocyte Globulin in 81%, Basiliximab in 15%, no induction in 4%. Maintenance IS consisted of Tacrolimus (T) / Mycophenolate (M) /Prednisone (P) in 52%, T/M in 38% and Belatacept (B) in 4%. 87% completed 6 months of valganciclovir. CMV viremia/infection was seen in 42%. Mean time to viremia was 224±181 days. Mean viral load was 4.43 ±1.3 log. Of those with CMV, 30% had a prior rejection episode, 90% were symptomatic, 70% required hospitalization, 17% required multiple hospitalizations and 13% had resistant CMV. All 3 KTRs on belatacept had CMV. Average length of stay per hospitalization was 12.8±10 days (total 361 hospital days). Eventually 2(6.7%) died. Treated with reduction in IS, ganciclovir or valganciclovir. Alternate therapies as Maribavir or Foscarnet was needed in 27%. Comparison with published data as shown in Table 1.

Conclusions: CMV infection is associated with increased morbidity among CMV HR KTRs. Post ppx CMV PCR monitoring may help with early detection of CMV viremia which may reduce disease burden and hospitalizations. More studies are needed to establish benefit and cost effectiveness.

	Study	Comparison group
Incidence of CMV (%)	42	40
CMV resistance rate (%)	13	15.8
Hospitalization rate in CMV (%)	70	47
Alternate therapies other than Valganciclovir/ Ganciclovir	27	5

PUB498

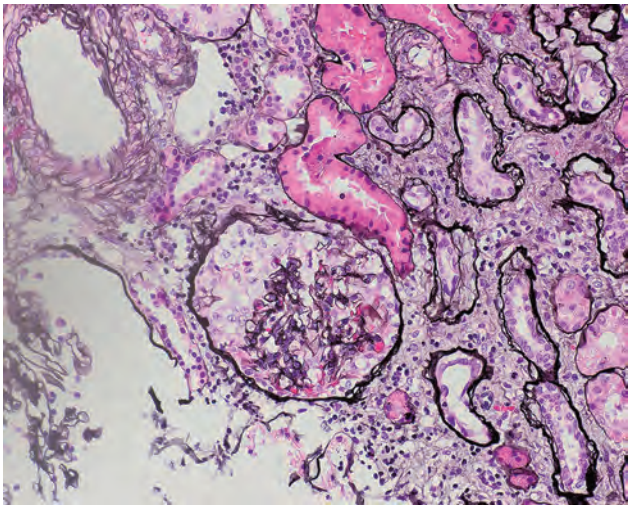
Collapsing Focal Segmental Glomerulosclerosis 5 Years after Transplant: Diagnosis, Treatment, and Outcome

Ulises Rodriguez Medina,[1] Claudia N. Aragon,[1] Kingsley I. Onuoha,[1] Paul B. Avila,[1] Namita Singh,[1] Pooja P. Singh,[1] Danniele G. Holanda,[2] Pablo Garcia.[1] *[1]University of New Mexico School of Medicine, Albuquerque, NM; [2]Arkana Laboratories, Little Rock, AR.*

Introduction: Collapsing FSGS involves segmental and global collapse of glomerular capillaries. Its etiology is often unclear; risk factors include genetic predisposition, immune abnormalities, and environmental exposure. Predominantly affects AA and rapidly progresses to ESKD. Recurrence rate after KT is about 20-50%, often leading to allograft loss. We present a case of recurrent FSGS after KT.

Case Description: A 39-yo Hispanic KT recipient with ESKD secondary to FSGS developed nephrotic syndrome five years post-transplant. Urine protein-creatinine was 8.8 g/g with eGFR of 105 ml/min. KT biopsy revealed collapsing FSGS with rare tubular cells showing weak nuclear staining for SV40. Tests for CMV, parvovirus, and HIV were negative. Genetic testing for APOL1 was negative in both patient and donor. Given the presence of SV40, JC virus PCR was checked and was positive. Patient was treated with 9 PLEX sessions and a prednisone taper, reducing proteinuria to 3.7 g/g. One month later, proteinuria increased to 5 g/g. Given the persistent positive JC virus, we discussed potential risks/benefits and treated him with rituximab 1g. Proteinuria declined significantly to 0.6 g/g after two months, and eGFR has remained stable at 110 ml/min.

Discussion: This case highlights the recurrence of FSGS five years after KT, relatively late for post-KT recurrent FSGS. Efficacy of treatment modalities in post-transplant FSGS, especially collapsing FSGS, remains challenging. However, our case suggests that combining PLEX, steroids, and rituximab is effective. JC virus infection can potentially lead to PML. Further studies are warranted to understand this population's risk-benefit profile with rituximab.



Bright Field Image, 400x (Jones Methenamine Silver Stain): Glomerular lesion with collapsing features, showing compressive podocyte hyperplasia and hypertrophy.

PUB499

Prevalence and Trends of Quantitative Bone Anomalies in Kidney Transplant Patients: A Single-Center Experience

Carlo Alfieri,[1,2] Margherita Di Naro,[1] Anna Regalia,[1] Simona Verdesca,[1] Mariarosaria Campise,[1] Paolo Molinari,[1] Chiara De liso,[1] Giuseppe Castellano.[1,2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Universita degli Studi di Milano, Milano, Italy.*

Background: Quantitative bone disorders are relevant in kidney transplanted patients (KTxps) especially during the first year of transplantation (KTx). We aim to report the preliminary data about our single center experience concerning the prevalence and the trend of quantitative bone anomalies in a cohort of KTxps.

Methods: We studied 469 kidney transplant patients (M=271, age 49±11 yrs) from 2004-2023. Post-KTx data at baseline (T0) and 12 months post-transplant (T12) were analyzed. Each patient had a DEXA at T0 and T12. BMD was given as g/cm2. BMD reduction of >5% in the first year of KTx was significant. T and Z-scores were calculated. Patients with T-score -1>T>-2.5 were osteopenic (OPN), and those with T-score<-2.5 were osteoporotic (OPS).

Results: Most patients had glomerulonephritis or autosomal dominant polycystic kidney disease (21% each). 82% received deceased donor transplants, and 68% underwent hemodialysis pre-transplant. 21% received anti-human thymocyte immunoglobulin

induction, and most were maintained on tacrolimus (91%) and mycophenolate (85%). 90% received steroids (mean cumulative dosage at T12: 2887±926 mg). 33% had Vitamin D supplementation, with mean levels of 17±4 ng/dL in the first year post-transplant. Femoral and vertebral BMD remained stable. F-OPN and V-OPN were present at T0 and T12 in 57% and 38% of patients, whereas F-OPS and V-OPS in 17% and 26% of patients. 14% showed significant femoral BMD worsening, associated with older age, higher BMI, and urinary protein excretion. 16% showed significant vertebral BMD worsening, also associated with higher urinary protein excretion. Multivariate analysis identified baseline BMD, age at transplant, and Prot U at T0 as significant factors for BMD worsening.

Conclusions: Our data shows prevalent bone anomalies in kidney transplant patients from the beginning. Despite vitamin D supplementation, levels remained low in the first year post-transplant, indicating a need for intervention to improve bone health. While BMD was generally stable, many patients showed osteopenia or osteoporosis, with some worsening. Older age at transplant and higher urinary protein excretion were linked to BMD worsening. Ongoing BMD monitoring can help track bone health and personalize interventions.

PUB500

International Survey of Nephrologists about Referral of Patients with Advanced CKD for Kidney Transplantation

Somaya Zahran,[1] Shaifali Sandal,[1] Jolanta Malyszko,[4] Gopal Basu,[2,3] Mohd Ghnaimat,[5] Maria cristina R. Castro,[6] Vivekanand Jha,[7] Marcelo Cantarovich.[1] ISN-TTS Working Group on Referral for Kidney Transplantation. *[1]McGill University, Montreal, QC, Canada; [2]The Alfred, Melbourne, VIC, Australia; [3]Monash University, Melbourne, VIC, Australia; [4]Uniwersytet w Bialymstoku, Bialystok, Poland; [5]The Specialty Hospital, Amman, Jordan; [6]Universidade de Sao Paulo, Sao Paulo, Brazil; [7]The George Institute for Global Health, Delhi, India.*

Background: Kidney transplantation (KTx) is the treatment of choice for patients with kidney failure and could be lifesaving in countries with limited access to dialysis. However, studies have shown low rates of referrals from high-income countries (HIC); 17-33% within the first year of chronic dialysis initiation, while data is lacking in low-income countries (LIC).

Methods: An ISN-TTS working group created a Knowledge, Attitude and Practice (KAP) survey, sent to nephrologists globally via the ISN mailing list. Responses are collected anonymously and sorted per respondents' countries income level. HIC and middle-high were combined into HIC and LIC and middle-low were combined into LIC. The survey is currently being administered. We report preliminary analysis of the first 100 responses to 9 compiled questions across KAP pillars.

Results: Respondents from 55 countries are 62% males, 60% 30-50 years, and 85% work at academic centers. Living and/or deceased donor KTx is available in 92.5% and HIC comprise 52%. Knowledge questions were answered similarly in both cohorts, except for referral of elderly patients (P=0.01), patients with nonadherence (P=0.014), or financial hurdles (P=0.027). Responses to attitude questions are shown in Fig 1. Based on participants' practice, patients in LIC vs. HIC were referred as follows: elderly <15% vs. 45% (P<0.0001), preemptively 70% vs. 90% (P<0.004), combined Tx 8% vs. 30% (P=0.0002); patients with cancer in remission 25% vs. 55% (P=0.007); financial difficulties 22% vs. 65% (P<0.0001).

Conclusions: Our results highlight KTx referral pattern differences between LIC and HIC. Educational activities should address practitioners' needs and optimize KTx referral for patients worldwide.

Case scenario questions, responses are based on comfort level (Likert scale:1 uncomfortable–5 very comfortable)

PUB501

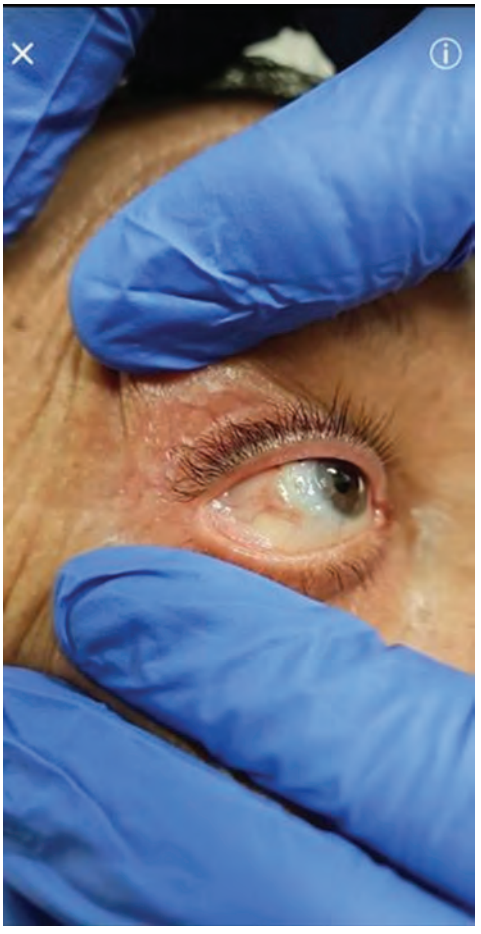
Conjunctival Squamous-Cell Carcinoma after Kidney Transplant

Muna Alnimri. *University of California Davis, Sacramento, CA.*

Introduction: Conjunctival squamous cell cancer (SCC) is rare affecting HIV patients and elderly exposed to extra UV light, the incidence increases post kidney transplant due to immunosuppression, treatemnt with wide excision, cryotherapy, local chemotherapy and radiation had been successful Prognosis depends on local invasion of the tumor to the orbit and the presence of distal metastasis. Our patient developed SCC 13 years post transplant

Case Description: 64 year old Hispanic male farm worker diagnosed with Hypertensive Nephrosclerosis on Hemodialysis received a kidney transplant in 2011 baseline creatinine 1mg/dl was maintained on Tacrolimus 2 mg bid imuran 50 mg as he did not tolerate Mycophenolate Mofetil and prednisone 5 mg. Presented in 2/24 with a right eye mass, tearing and eye discharge, followed by headach (figure 1) Orbital and head MRI showed fungating mass involving the temporal conjunctiva without invasion to the cornea. Biopsy of the lesion showed SCC. He underwent excision/debulking of the mass and pathology confirmed SCC with positive margins, Oncology consult suggested cryotherapy, local chemotherapy or radiation therapy The patient agreed to local chemptherapy with eye drops. Immunosuppression had been reduced with discontinuing imuran and lowering tacrolimus to a level of 3-5 with 5 mg prednisone.

Discussion: The risk of SCC increases with the duration of immunosuppression, 7% of transplant patients develop SCC after 10 years and 35% after 25 years, conjuctival SCC is rare with incidence of 0.02-2.8/100000, It usually grows slowly on the epithelial surface of the eye and rarely invades the orbit and spreads distally, treatment is wide excision of the conjunctive with reconstructive flaps, cryotherapy, topical chemotherapeutic eye drops like mytomycin, 5FU and interferon, prognosis is not bad if dicovered early, 5 years survival 85%.



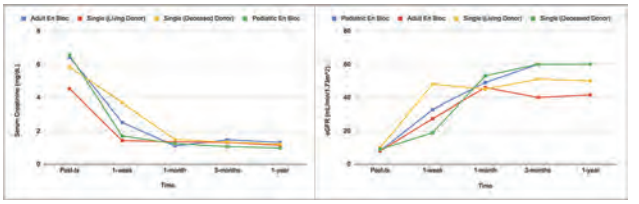


Figure 1. (left) Serum creatinine levels of en bloc vs. single kidney transplantation adult recipients post-transplant, 1-week, 1-month, 3-months, and 1-year post-op. (right) eGFR levels of en bloc vs. single kidney transplantation adult recipients post-transplant, 1-week, 1-month, 3-months, and 1-year post-op.

PUB502

Single-Center Experience of En Bloc vs. Single Kidney Transplantation: A Case Series

Yoon-Jung Chang.[1,2] *[1]The University of Toledo College of Medicine and Life Sciences, Toledo, OH; [2]The University of Toledo Medical Center, Toledo, OH.*

Introduction: Pediatric en bloc kidney recipients have been shown to demonstrate comparable outcomes with reduced potential risk for complications despite the reduced size and mass. This case series is focused on comparing the post-operative outcomes between recipients of en bloc kidneys from deceased donors and recipients of single kidneys from living or deceased donors.

Case Description: This case series includes a total of 61 patients - 12 pediatric en bloc recipients, 5 adult en bloc (horseshoe) recipients, and 11 per single kidney recipient groups. Living and deceased donor single kidneys had EPTS values ranging from 67 to 83 and a KDPI value of less than 50, whereas the EPTS and KDPI values of en bloc kidneys varied to a greater degree. The most prevalent primary renal disease among en bloc and single kidney recipients were hypertensive nephrosclerosis and diabetes mellitus type II, respectively. Not only did we see an increase in eGFR values and a decrease in serum creatinine values in the pediatric donors' recipients, but the rate of delayed graft function was also lower in pediatric en bloc kidney recipients (16.67%) compared to that of single kidney recipients from living (18.18%) or deceased donors (54.55%).

Discussion: The results from this institution, along with the literature published, support the notion that en bloc renal transplantations from pediatric donors result in superior outcomes. Though receiving organs from pediatric donors has been previously neglected due to technical complications, the continuous advancement in surgical techniques and increased demand for transplantations have allowed for further exploration in en bloc renal transplantations. As evidenced by the data, it may be crucial to take into account the positive outlook on long-term renal functions of the pediatric en bloc kidneys to decrease the wait time and increase the quality of life of the patients.

PUB503

A Case of Disseminated Histoplasmosis in Transplant Patient

Tahir A. Jatoi, Sandeep R. Sasidharan, Andrea Roche-Recinos, Mariana S. Markell. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Histoplasma(HP) capsulatum is a dimorphic fungus with a worldwide distribution. In a study from a hyperendemic area, 24% of the solid organ transplant(SOT) candidates had evidence of prior exposure to HP. In immunocompetent patients, HC is usually mild, but in immunocompromised patients like SOT recipients it develops into severe infection with dissemination to extrapulmonary organs. We present a case of disseminated histoplasmosis in a kidney transplant recipient

Case Description: 35 y.o. M with HTN, recurrent UTI, failed LDKT from 2006 and DDKT in 2022, presented for fever, melena, and diarrhea for a day with exposure to farm animals in a recent trip to Trinidad. Vital signs, system review and PE were otherwise unremarkable. Labs showed BUN/Creat of 78/3.2, from baseline of 2.6, HGB 6.2, K 6.6. He was transfused with 4u of PRBCs, and hyperkalemia was treated medically. Endo-Colonoscopy was delayed due to history of fever. He was on Tac 3mg BID and MMF 1gm BID. The patient was empirically started on treatment for C-Diff and UTI, blood and urine cultures were negative. Respiratory panel detected Rhinovirus/Enterovirus. CT abdomen and pelvis showed bilateral pulmonary nodules and multiple enlarged retroperitoneal and mesenteric lymph nodes. BAL was positive for fungal infection (FI). HP Urine Ag was positive (6.4 ng/mL). He improved Voriconazole and was switched to Itraconazole to cover broadly for 1 year. He became afebrile after 48 hours of antifungal treatment. Tacrolimus was reduced to 1mg bid, level on the day of discharge 9.3

Discussion: HP accounts for <5% of all invasive FI in SOT recipients, the infections can be devastating. Transplant-associated HP can occur as a de-novo infection from an environmental exposure which was most likely in our patient, or as the reactivation of a latent infection or donor-derived (DD) transmission. DD HP is seen in 1:10,000 transplants and occurs in the early post-transplant period. The agent of choice and duration of therapy depends on the severity of disease but all SOT with HP require therapy. Our patient initially came with a GI complaint and the disseminated infection was discovered incidentally. With rising incidence of FI due to climate change, clinicians must have a high index of suspicion in all diagnose infections among SOT recipients especially in those who visited endemic area's

PUB504

Investigation of Proteinuria in a Simultaneous Heart-Kidney Transplant Recipient with AL Amyloidosis

Brittany Samberg, Sunny R. Parmar, Yuan Huang, Itunu O. Owoyemi. *Cleveland Clinic, Cleveland, OH.*

Introduction: Although they are two of the most affected organs by AL amyloidosis, simultaneous heart and kidney transplants (SHK) are rarely performed regardless of the underlying disease process. Diagnostic work up for proteinuria requires a comprehensive work up and multidisciplinary shared decision making with management.

Case Description: A 57-year old male presents with worsening proteinuria. Notable history includes SHK 4 years prior for severe cardiac AL amyloidosis with chronic kidney disease stage 4. Initially he suffered delayed graft function requiring dialysis for 3 weeks post-transplant. Surveillance biopsy after 3 months showed cortical necrosis and renal MAG3 scan showed about 23% of the split differential function. Bortezomib and daratumumab were discontinued for recurrent CMV viremia. He was switched to sirolimus for tacrolimus toxicity sparing. Creatinine (Cr) improved to baseline of 1.8-2 mg/dL with urine protein-creatinine ratio (UPCR) average of 0.2 mg/mg. Relevant labs on presentation included Cr of 2 mg/dL, UPCR 2.98 mg/mg, HbA1c of 9.2%, and normal kappa/lambda free light chain ratio albeit elevation of the lambda light chain to 32.5. A repeat MAG3 scan showed 82% of native kidney function and 17% allograft kidney function. With these findings, he had biopsies of both native and transplant kidneys. The former revealed AL amyloidosis and the latter revealed subclinical Banff 2A acute cellular rejection in allograft without amyloid deposition.

Sirolimus was switched to tacrolimus, and he was treated with pulse steroids for subclinical rejection. Kidney function remains at baseline and UPCR has improved to 1mg/mg at most recent follow up.

Discussion: The patient's progressive proteinuria presented a diagnostic dilemma. The repeat MAG3 scan findings guided the decision to biopsy both native and allograft kidneys. Presumably native kidney amyloidosis was present pre-transplant, and this was less likely the culprit in the absence of allograft deposition or serologic evidence of recurrence. However, subclinical rejection in the allograft was notable and treated in addition to switching sirolimus to tacrolimus causing reduced proteinuria. The value of MAG3 studies and kidney biopsies in this case remain evident and may guide future diagnostic decisions.

PUB505

Increasing Transplant Awareness and Addressing Barriers to Transplantation among Patients on Dialysis

Sobia N. Khan, Sandeep K. Mallipattu. *Stony Brook University, Stony Brook, NY.*

Background: End Stage Kidney Disease patients require dialysis or kidney transplant to maintain life. Kidney transplant has been recognized as their best option. Our aim was to identify barriers for transplant among dialysis patients.

Methods: Patients were recruited from chronic dialysis unit requiring hemodialysis and age over 18. Patient with acute kidney injury on dialysis, dementia or hospice were excluded.

Results: 126 were screened, 40 recruited. Mean age 60 ± 16 years, male (57.5%). Comorbidities: HTN (85%), DM (32.5%), CAD (25%). Table 1 14 patients were identified, who have either refused or lost to follow up. They were interviewed to explore the reason for refusal. It was concerning to realize that the patients had several pschosocial barriers and lacked proper transplant education. Table 2

Conclusions: Our study data has indicated a crucial need for enhanced awareness and kidney transplant education. Building upon these findings, we have launched an educational initiative aimed at providing nephrology trainees with the necessary skills to recognize and address the psycho- social barriers for referral. The multifaceted project entails 2 components: Enhancing the communication abilities of nephrology fellows to navigate challenging interactions with patients and integrating transplant education into patient encounters. We expect to contribute to nephrology field by having defined a feasible means to identify and create more enrollment.

Table 1: Patient Characteristics

Age	60 ± 16
Gender, n	
Male	23
Female	17
Race/ Ethnicity	
Black	7
White	27
Asian	3
Hispanic	3
Other	
Comorbidities	
HTN	34
DM	13
CAD	10

Table 2: Reasons for Transplant refusal

Patient 1	Has failed transplant, so no desire to pursue it again
Patient 2	Content with hemodialysis
Patient 3	Was delisted due to medical comorbidities due to EF~14%, underwent vascularization, EF improved t0 30%, he was supposed to consider re-activation, but patient never followed up
Patient 4	BMI ~64, never saw the transplant team
Patient 5	Failed transplant, told us the transplant work up is too cumbersome
Patient 6	Last saw transplant team in 2015
Patient 7 & 8	Never saw the transplant team

PUB506

Terminal Effector Memory (TEMRA) CD8+ T Cell: The Key Lymphocyte Subset in BK Virus Infection Early after Kidney Transplantation

Lilin Liu, Jing Luo, Min Gu, Chunsun Dai, Hongdi Cao. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: BK virus associated nephropathy (BKVAN) is an important cause of early allograft failure after renal transplantation. Low immune status of renal recipients leads to the reactivation of BKV in renal tubular epithelial cells, and BK viruria is the early phase of BKV infection. Timely intervention of BK viruria could prevent the development of BKVN. Meanwhile, measurements of lymphocyte subsets can display the recipient's real-time lymphocyte subpopulations and functional status. Therefore, this study aimed to analyze the lymphocyte subsets of patients with BK viruria early after kidney transplantation to explore the key lymphocyte subsets of BKV infection and provide potential monitoring and targeting methods for clinical intervention.

Methods: Patients who received renal transplantation at the Kidney Disease Center of the Second Hospital of Nanjing Medical University from April 2022 to October 2022 were included in the study. The patients' lymphocyte subsets were analyzed using the BD FACS CantoII cytometer. The clinical characteristics and distribution differences of lymphocyte subsets were compared between BK viruria and BKV negative patients. Binary logistic regression method was used to analyze the lymphocyte subsets of BK viruria.

Results: A total of 67 renal recipients were included in the study, including 23 cases (34.2%) of BK viruria. There were statistical differences in terminal effector CD8+T cell ($CD8^+$ Temra) subsets and central memory $CD8^+$ T cell ($CD8^+$ TCM) subsets between the two groups ($p<0.05$), while no differences were found in other lymphocyte subsets. Binary logistic regression analysis suggested that high ratio of $CD8^+$ Temra and $CD8^+$ TCM is an independent risk factor for BK viruria ($p=0.039$, *95%CI:* 0.02-0.907).

Conclusions: High ratio of $CD8^+$ Temra and $CD8^+$ TCM is an independent risk factor for BK viruria early after renal transplantation. Abnormal differentiation of memory $CD8^+$ T cells might be a promising target for monitoring and treatment of BKV infection early after kidney transplantation.

Funding: Government Support - Non-U.S.

PUB507

Postkidney Transplant Thrombotic Microangiopathy Effectively Treated with Eculizumab in a Tertiary Care Center

Joyita Bharati, Jean M. Francis, Justine E. Dickson. *Boston Medical Center, Boston, MA.*

Background: Post-transplant thrombotic microangiopathy (PT-TMA) after kidney transplant is associated with a high risk of graft loss. Terminal complement pathway inhibition by anti-complement C5 antibody (eculizumab) effectively treats post-transplant TMA after kidney transplant related to complement disorders. Initial evaluation of PT-TMA is limited by the lack of availability of complement pathway analysis, including genetic tests.

Methods: We reviewed the charts of patients with PT-TMA treated with eculizumab at our center. Ten patients were identified. PT-TMA was defined as hemolytic anemia, schistocytes on peripheral smear, thrombocytopenia, and acute allograft dysfunction. Renal response was defined as eGFR>15 ml/min/1.73m^2 and dialysis independence. Complete renal response was defined as eGFR>45 ml/min/1.73 m^2.

Results: PT-TMA was diagnosed within a week (median 2.75 days) of kidney transplant in 7 out of 10 patients. Kidney biopsy was performed on 9 patients; 8 patients showed signs of acute TMA without evidence of active rejection. Genetic analysis was done in 5 patients. One patient had a pathogenetic variant in the CFHR1 gene. Eculizumab was started within 1-3 days after diagnosis in all patients. After a median of 9 days from diagnosis, platelets persistently improved to >150 X 10^9/L in all patients. Haptoglobin and lactate dehydrogenase levels improved after a median of 2 weeks. After a median last follow up of 35.2 months, renal response was noted in 8 out of 10 patients. Four patients had complete renal response. Six patients were started on belatacept after discontinuing tacrolimus, considering it as a potential trigger of PT-TMA.

Conclusions: Patients with early de-novo PT-TMA treated with eculizumab within 1-3 days of diagnosis had prompt hematological remission. All but two patients with late PT-TMA had improved kidney allograft function. PT-TMA after kidney transplant develops from different triggers in predisposed individuals, which are often indiscernible on immediate evaluation. Prompt eculizumab therapy may benefit PT-TMA irrespective of etiology, especially those developing early post-transplant, suggesting the role of complement activation. A prospective study on the effectiveness of eculizumab in treating PT-TMA from different etiologies is important to inform further practice.

PUB508

Transplant Renal Artery Stenosis

Brian Min, Sara Hashemi, Muhammad Haseeb Aslam, Sabita Budhathoki. Upstate Nephrology Dept. *SUNY Upstate Medical University Hospital, Syracuse, NY.*

Introduction: Transplant renal artery stenosis is a rare vascular complication that arises in approximately 1 to 26% of patients after receiving kidney transplant. It should raise awareness for prompt diagnosis as it can lead to volume overload, hypertension, worsening graft function, and allograft loss. We describe a case of transplant renal artery stenosis that was successfully revascularized and was able to maintain a stable allograft function thereafter.

Case Description: A 60 year old male with history of hypertension, diabetes, CKD stage 4 underwent deceased donor transplant with immediate graft function. During surgery, doppler ultrasound of artery and veins, including upper, middle, lower pole, and external iliac artery below and above anastomosis were within normal ranges. Post-operative course was uneventful other than a complication with bleeding from a small perihilar arterial branch, which was controlled by surgical reopening of the incision and by using hemostatic clips. Due to worsening hypertension during a follow-up visit 3 months post-transplantation, doppler ultrasound of transplant kidney was performed, which revealed increasing velocities of renal artery. This was remeasured 1 month after with worsening parameters. The renal artery waveform showed a sharp upstroke, without evidence for a parvus tardus waveform. Patient underwent a arteriography of the renal artery and was found to have stenosis at the anastomoses of the superior and inferior transplant renal arteries with the external iliac artery. Stenosis improved after balloon angioplasty with improvement of pressures of the superior and inferior transplant renal arteries, and thereby improving his worsening hypertension. Patient's kidney function has been stable without any evidence of loss of graft function.

Discussion: Transplant renal artery stenosis (TRAS) is a complication that should be sought out with doppler ultrasound. Symptoms that can arise are worsening hypertension, worsening graft function, volume overload, pulmonary edema. Our patient was promptly investigated for TRAS due to his worsening hypertension despite having stable allograft function, and was found to have stenosis of renal arteries at anastomosis sites. The pathophysiology for TRAS varies, and mainly is due to turbulent blood flow at anastomosis. Treatment is either angioplasty alone or angioplasty with stents, and generally have success rates of 90%.

PUB509

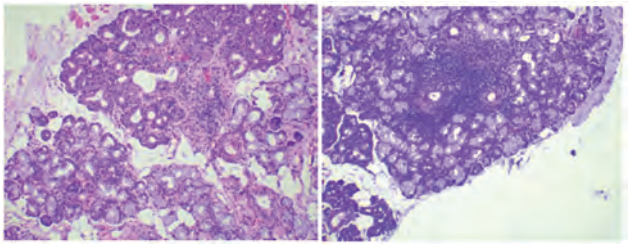
Cryoglobulinemia Secondary to Sjögren Syndrome after Kidney Transplant

Ada Noemi Chavez. *Hospital General San Juan de Dios, Ciudad de Guatemala, Guatemala.*

Introduction: The most frequent autoimmune disease that underlies non HCV-induced cryoglobulinaemia is Sjögren syndrome. Among the most common findings of Sjögren's syndrome from a hematological point of view are cytopenias: anemia, leukopenia, thrombocytopenia and also cryoglobulinemia and lymphoma. In post-kidney transplant patients, it is less common to find Sjögren's syndrome. Monoclonal gammopathy of undetermined significance (MGUS) has been observed in 20% of Sjogren's patients when serum immunoelectrophoresis is routinely performed. About 5% of patients with this abnormality may progress to develop lymphoma or another hematologic malignancy

Case Description: A 23-year-old female patient received a kidney transplant from a related living donor in July 2023. In September 2023, patient presented with difficult pancytopenia management, so autoimmune tests are performed and AntiRo >200 is evident, Sjögren's syndrome is diagnosed and a biopsy of minor salivary glands is performed where periductal lymphocytic sialadenitis is observed (Figure 1), patient persists with leukocyte count as follows: WBC 3060 Neutrophils 84 %, Hemoglobin in 9.16 g/dL, platelets in 126,000, peripheral blood smear was performed within normal limits, patient with refractory cytopenias for which cryoglobulins were performed which in 18%, rheumatoid factor 12.5 (normal), IgG 848.05, electrophoresis and negative protein immunofixation, creatinine at 1.87mg/dl, 24-hour urine protein at 186, refractory cytopenia is considered a manifestation of cryoglobulinemia type I secondary to Sjögren's syndrome, so it was decided to admit the patient to start treatment with plasmapheresis (5 sessions) and rituximab (1gr) for refractory presentation of cytopenias.

Discussion: Our patient presented refractory cytopenias secondary to cryoglobulinemia due to Sjögren's syndrome, which is a common cause not associated with HCV but a common cause of autoimmune disease. However, it is not common in post-transplant patients and currently our patient has no renal manifestations of the disease, there is no evidence of glomerulonephritis and the graft is functioning properly.



PUB510

Association of Postdonation Kidney Function and Risk of CKD in Living Kidney Donors at the Civil Hospital of Guadalajara, Mexico

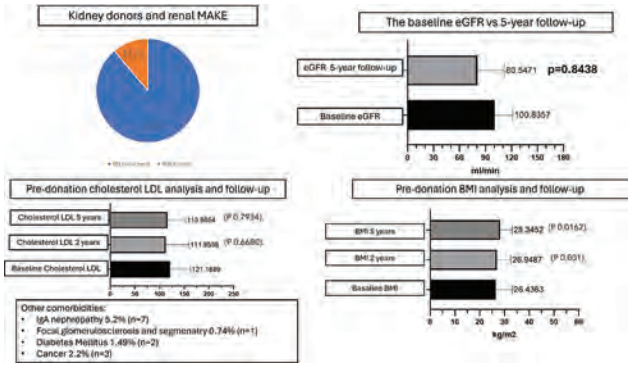
Jahir R. Camacho,[1,2] Guillermo Navarro Blackaller,[1,2] Edgar J. Carmona,[1,2] Ixchel De la Torre De la Vega,[1,2] Jonathan Chavez,[1,2] Ramon Medina,[1,2] Juárez Correa de León,[1,2] Fernando Cruz Aragon,[1,2] Maria de la Luz Alcantar Vallin.[1,2] *[1]Universidad de Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico.*

Background: In Mexico, according to figures from the National Transplant Center Registry, more than 90% of transplants are from living donors. This makes it difficult to estimate the risk attributable to donation. The outcome of donors in our country is unknown, in terms of risk of progression to CKD and comorbidities. In previous studies, some of which do not confer a higher risk, mainly in the first-world population.

Methods: Cross-sectional cohort study without retrospective intervention, Unicentro, of kidney donor patients from the program of the Civil Hospital of Guadalajara. In the period from January 2019 to December 2022, at the 5-year follow-up. Objective: Association of post-donation renal function from the year of donation and risk of chronic kidney disease with a 30% loss of GFR, renal replacement therapy.

Results: found with an average age of 39 years in total. The 93.2% (124) of donors do not have social or private security. The eGFR before donation was 102.21 ml/min/1.73 m2. (DE +/ 7.65ml/min/1.73m2). Only 11.1% achieved renal MAKE. + The estimated glomerular filtration rate was compared with the CKD-EPI formula with serum creatinine, baseline eGFR with a mean of 102.21 ml/min/1.73m2 SD +/- 7.65 ml/min/1.73m2 and at follow-up at the fifth year with a mean 80.5ml/min/1.73m2 SD +/- 9.78 ml/min/1.73m2 with a decrease in eGFR with a non-significant value of p=0.8438. + Kidney donors were analyzed, comparing their baseline pre-kidney donation BMI (26.4 kg/m2 SD +/- 1.78 kg/m2), at follow-up BMI 27.3 kg/m2 SD +/- 9.3 kg/m2 with a significant difference of p=0.0162Conclusion

Conclusions: In this study, we observed that although there was a significant difference in renal function at 5 years post-transplant, but 11.2% of our population had it MAKE RENAL..



PUB511

Impact of Genetic Testing on the Outcome of Kidney Transplant Recipient Evaluation

Yasar Caliskan, Fadee Abu Al Rub, Vidya Fleetwood, Bahar Bastani, Mustafa Nazzal, Chintalapati Varma, Henry B. Randall, Kate Rabideau, Dzuy Truong, Ava DeLonais-Dick, Rengin Elsurer Afsar, Baris Afsar, Krista L. Lentine. *Saint Louis University, St Louis, MO.*

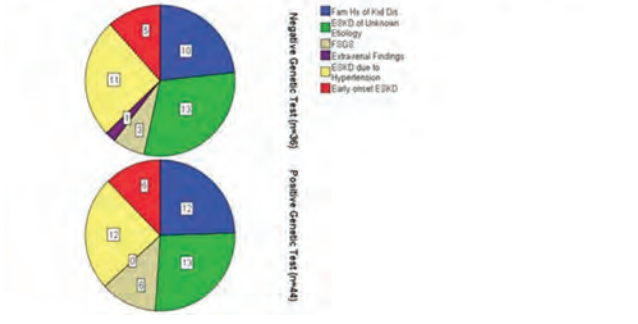
Background: Identifying a genetic etiology during evaluation of kidney transplant (KT) candidates can inform the risk of disease recurrence, guide KT management, and enable the assessment of living related donors. Despite these benefits, there is limited literature on the impact of genetic testing on recipient candidate outcomes.

Methods: Eighty patients who underwent KT evaluation in January 2021 to November 2022 were assessed. Patients with positive genetic test results were compared with patients without any identified kidney disease related genetic variants. The primary outcomes were waitlisting, KT and delayed graft function (DGF).

Results: Positive genetic test results were found in 44 (55%) patients, with *APOL1* high risk genotypes (20, 45%), *PKD1/2* (6, 14%) and *COL4A3-4* variants (4, 9%) being the most common. There were no significant differences between patients with positive and negative test results in terms of age, sex, self-identified race and cause of kidney disease. The criteria for testing are shown in Figure 1. During a median follow up of 2 yrs (IQR,1.75-2.58), 63% of the patients were waitlisted and 45% underwent KT. Waitlisting, deceased (DDKT) and living donor KT (LDKT) rates did not differ significantly between patients with positive and negative genetic results (Waitlisting: 28 (64%) vs 22 (61%), p=0.82; DDKT: 16 (36%) vs 14 (39%) and LDKT: 2 (5%) vs 3 (8%), p=0.58). DGF rates were similar between patients with positive and negative results (3 (7%) vs 3 (8%), p=0.59). Four patients with positive genetic test results developed biopsy confirmed rejection while no rejection episodes were recorded in patients with negative genetic results (p=0.039).

Conclusions: In this pilot study, genetic testing with positive findings in KT evaluations did not significantly impact waitlisting, transplant and DGF risk of recipient candidates. Higher rate of rejection in patients with positive genetic test results needs further studies.

Figure 1. Number of patients met each criteria for genetic testing according to positive (n=36) and negative genetic test results (n=44)



PUB512

Urinary Tract Infections in Kidney Transplant Recipients: A Single-Centre Experience

Nicholas Evans,[1] Rosa M. Montero.[2,1] *[1]St George's University of London, London, United Kingdom; [2]St George's University Hospitals NHS Foundation Trust, London, United Kingdom.*

Background: Urinary tract infections(UTIs) occur in 25% of kidney transplant recipients (KTR) within one year post-transplant(PTx) accounting for 45% of infective complications. Few reports are on the timeframe of recurrent UTIs >1yrs PTx. Recurrent UTIs are associated with bacteraemias, impaired allograft function, allograft loss, acute T-cell mediated rejection causing increased morbidity and mortality. We looked to determine the frequency, organisms and influencing factors for UTIs in our cohort.

Methods: A cross-sectional retrospective observational study of all KTR at our centre with a UTI from April 2022- April 2023. Clinical data was extracted from electronic patient records and microbiology electronic system. Recurrent UTIs was defined: 2 episodes of symptomatic acute bacterial cystitis in 6 months or 3 episodes within a year. Data on organism and sensitivities, immunosuppression(IS) regimens, deprivation scores 1 most deprived, 10 least deprived) were collected. Paired t-tests and ANOVA were used to perform statistical analysis with a $p<0.05$ significant level.

Results: 167 of 516 KTR had a UTI between 2022-2023 with a total of 294 UTIs in 167 KTR. 58 Male, 109 Female. Median age 59yrs(range 18-92yrs). 24% White, 20% Black, 16% Asian, 1% Chinese, 8% Other, 31% unknown. Number of UTIs in KTR: x1 65% (109), x2 20.4%(34), x3 6.6%(11), x4 3%(5), x5 0.6%(1), x6 1.2%(2), x7 0.6%(1), x8 0.6%(1), x10 1.8%(3). UTIs median 31 weeks (range 9 days to 16.4 years) PTx. Deprivation scores were insignificant (p=0.08). 20 different organisms were grown 54% Escherichia coli, 15.5% Enterococcus, 8.8% Klebsiella pneumonia, 7.7% staphylococcus organisms, 4.7% proteus, 3% pseudomonas, 6.3% combination of different organisms. Tacrolimus based IS regimens had more UTIs ($p<0.05$) compared to non-tacrolimus regimens. 24% UTIs were fully sensitive with 60% of all UTIs resistant to Amoxicillin, 16% other antibiotic resistant micro-organisms.

Conclusions: UTIs continue to be problematic up to 16yrs PTx. 32% of KTR had UTI between 2022-2023 with 35% of KTR having >2. Consistent with previous results females had more UTI and were predominantly gram-negative. Tacrolimus based regimens increased risk of UTIs. Up to 10 recurrent UTIs occurred PTx. Deprivation scores did not influence UTI occurence. We recommend reviewing IS regimens in KTR with recurrent UTIs to avoid allograft dysfunction, morbidity and mortality.

PUB513

Comprehensive Approach to Kidney Education and Support: Transplant Outcomes

Danielle Wentworth, Brendan T. Bowman, Theresa "Thessa" Churillo, Jessica Jenkins, Rebecca P. Peters, Sana F. Khan. *UVA Health, Charlottesville, VA.*

Background: The 2019 Advancing American Kidney Health Executive Order set a goal to increase the number of End-Stage Renal Disease (ESRD) patients receiving a kidney transplant. Per the USRDS 2023 Annual Data Report, only 7.9% of incident dialysis patients were preemptively transplanted or waitlisted prior to starting dialysis and 12.3% of prevalent dialysis patients were waitlisted. To help achieve high rates of preemptive transplant and waitlisting prior to dialysis, we designed a quality improvement (QI) project that provided comprehensive patient-centered nephrology care for patients at high risk of progression to ESRD.

Methods: Our prospective QI project began January 2021 with analysis performed through May 2024. Patients at high risk of developing ESRD were identified via EMR registry. Inclusion criteria were GFR < 30 mL/min and 2-year KFRE score >20%. Patients were offered enhanced education and support regarding all possible ESRD modality treatment choices. Patients were seen sequentially by an experienced nephrology nurse practitioner (NP), social worker, dietician, and home dialysis nurse. Patients received an additional NP visit for ESRD decision planning and to address outstanding educational needs. Patient modality choices were documented in the EMR and communicated to the primary nephrologist. Patient progress and coordination gaps were discussed during quarterly list management meetings.

Results: Our cohort included 42 patients (average age 65 years, GFR 16 ml/min, KFRE 53%), and 30 progressed to ESRD (71%). 11 ESRD patients were waitlisted (37%) with an average GFR of 16.3 mL/min at time of transplant referral. 4 waitlisted ESRD patients were transplanted (36%). Of our incident ESRD patients, 10 received a preemptive transplant or were waitlisted prior to starting dialysis (33%). Average time to transplant was 1.13 years after starting dialysis.

Conclusions: Development of a multidisciplinary high-risk nephrology care clinic at our institution helped us surpass national rates of kidney transplant waitlisting, both preemptively and for patients on dialysis. By maintaining a high percentage of our high-risk patients on the waitlist, we hope to improve access to transplantation and decrease the duration of dialysis dependence.

PUB514

A Case of Recovery of Native Kidney Function Years after Simultaneous Liver-Kidney Transplant

Stephen R. Sammons, Miklos Z. Molnar, Duha A. Jweehan, Isaac E. Hall, Suayp Oygen, Divya Raghavan. *University of Utah Health, Salt Lake City, UT.*

Introduction: Simultaneous Liver-Kidney (SLK) transplantation is often considered in End Stage Liver Disease (ESLD) patients with significant renal dysfunction. Prior to the implementation of the Organ Procurement and Transplantation Network's (OPTN) 2017 policy on SLK allocation, criteria were variable and of particular concern was the potential recovery of native renal function following SLK. Here we describe a case of a patient who underwent an SLK transplant and was found to have native renal recovery eight years later.

Case Description: A 45-year-old female with ESLD due to autoimmune hepatitis who underwent liver transplant in 2009 with subsequent failure and resulting hepatorenal syndrome (HRS) followed by SLK in 2015 presented to the hospital after unintentional acetaminophen overdose complicated by acute kidney injury (AKI). Ultrasound of her kidney graft showed severe atrophy with a lack of renal cortex blood flow despite patent vessels. She briefly required dialysis for uremia followed by rapid renal recovery. A nuclear medicine (NM) study using Tc99m MAG3 was later performed which found functioning native kidneys with minimal activity in the kidney graft. Immunosuppression decisions were deferred to the liver transplant service in the setting of kidney graft loss.

Discussion: Native renal recovery following SLK is a known phenomenon particularly in patients with HRS. NM studies are more commonly done in the post-SLK period and are not usually considered years after SLK. This case features a patient who received an SLK prior to the 2017 SLK policy updates and who was found eight years later to have renal graft loss with recovery of native renal function. Reviewing this patient's pre-transplant data shows she would not have been an SLK candidate under current criteria. This case illustrates the importance of careful policy decisions regarding SLK allocation.

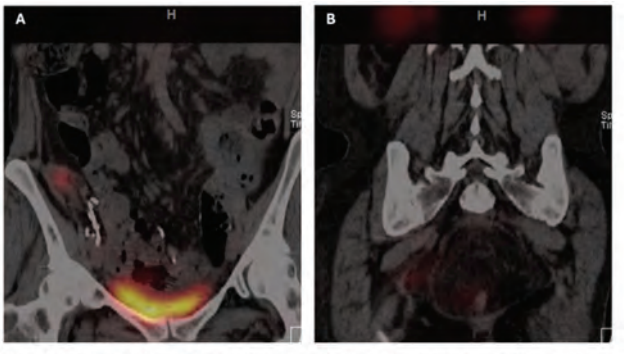


Figure 1. NM renal study with coronal images showing A) minimal radiotracer uptake in the kidney graft parenchyma with no apparent activity in the collecting system and B) partially visualized native kidneys with activity throughout all phases of exam

PUB515

A Comparison of Close Family Members and Other Relationships in Live Kidney Donor Evaluation

Ritah R. Chumdermpadetsuk, Adriana Montalvan, Stalin Canizares, Maria B. Rivera, Amy Evenson, Devin Eckhoff, Martha Pavlakis, Bhavna Chopra. *Beth Israel Deaconess Medical Center, Boston, MA.*

Background: While initially live kidney donations (LKD) were largely restricted to biological relatives, there is currently more variety in the types of donor-recipient relationships. We examined the LKD evaluation process to compare behaviors and characteristics of close family members (CFM) versus other relationships.

Methods: Single institution retrospective chart review of referrals for LKD between 1/2009-12/2022. Referrals were identified using the Organ Transplant Tracking Record database and cross referenced with billing data. Elimination at each stage of evaluation was compared between CFM (spouses, parents, siblings, and children) and non-CFM using Chi square test.

Results: In sum, 1861 referrals were reviewed, including 477 (25.6%) CFM and 1384 (74.4%) non-CFM, resulting in 146 approvals and 125 donations. CFM were more likely to complete medical (med) and psychosocial (psych) workup (WU). Among those who completed WU, CFM were less likely to have med and psych contraindications (CI). Overall, CFM were more likely to be approved and to donate. However, once approved, there was no difference in donation between the 2 groups ($p = 0.61$). The top med CI for both was obesity, eliminating 60/124 (48.3%) CFM and 203/399 (50.9%) non-CFM, followed by hypertension (HTN) and malignancy concerns for CFM; nephrolithiasis and HTN for non-CFM. The top psych CI was substance use disorder (SUD) for CFM; young donor age for non-CFM.

Conclusions: We saw a high proportion of non-CFM referrals, suggesting increased awareness and acceptance to be considered as donors. Non-CFM were more often eliminated due to med or psych CI. CFM showed greater commitment to complete LKD evaluation, but once approved, both groups were equally likely to follow through with donation.

	Close family member (n = 477)	Other (n = 1384)	p value
Positive crossmatch (%)	3 (1.4)	7 (1.8)	0.75
Begin medical workup (%)	248 (52.0)	503 (36.3)	< 0.01
Complete medical workup (%)	211 (44.2)	468 (33.8)	< 0.01
Medical contraindication (% complete workup)	124 (57.8)	399 (85.3)	< 0.01
Complete psychosocial workup (%)	170 (35.6)	169 (12.2)	< 0.01
Psychosocial contraindication (% complete workup)	28 (16.5)	60 (35.5)	< 0.01
Recipient too ill or dead (%)	14 (2.9)	33 (2.4)	0.51
Approved (%)	83 (17.4)	63 (4.6)	< 0.01
Donate (%)	70 (14.7)	55 (4.0)	< 0.01
Donate (% approved)	70 (84.3)	55 (87.3)	0.61

PUB516

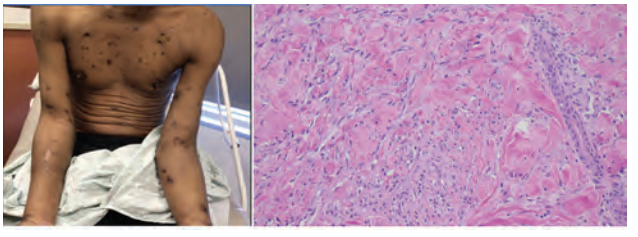
Kaposi Sarcoma in a Nonadherent Transplant Patient

Dominik Thomas, Sarah Gilligan, Suayp Oygen, Duha A. Jweehan, Isaac E. Hall, Miklos Z. Molnar, Divya Raghavan. *University of Utah Health, Salt Lake City, UT.*

Introduction: Kaposi Sarcoma (KS) is an angioproliferative cancer caused by human herpesvirus 8 (HHV-8). Most cases of post-transplant KS arise after HHV-8 reactivation triggered by immunosuppression with 60-times higher risk of KS in solid organ transplant recipients than the general population. We present a kidney transplant patient who develops KS shortly after transplant.

Case Description: 53-year-old Somali man with end-stage renal disease due to diabetic nephropathy underwent kidney transplant with induction with thymoglobulin, and maintained on belatacept, mycophenolate sodium (MPS), and prednisone. Acute antibody-mediated rejection and Banff IIA acute cellular rejection is found four months after transplant due to non-adherence with belatacept infusions and treated with thymoglobulin, steroids, intravenous immunoglobulin, and therapeutic plasma exchange. Belatacept was subsequently switched to tacrolimus. He develops lymphadenopathy and a core biopsy of his axillary lymph nodes shows reactive lymphoid tissue. He has worsening disseminated rash two months later with initial rash noticed one month post-transplant. Biopsy of skin lesions shows KS. HHV-8 was checked and found to be 162,000 copies/ml. HIV was negative. Prior lymph node biopsy was found without features of KS and negative staining for HHV-8. MPS was switched to everolimus, a mammalian target of rapamycin inhibitor (mTORi), with regression of KS skin lesions. His graft function remained stable with serum creatinine around 1.5 mg/dL.

Discussion: This patient developed progression KS despite nonadherence to immunosuppression which then worsened after treatment for rejection. Management of post-transplant KS focuses on reducing immunosuppression, switching to mTORi, and/or chemotherapy. In one study, conversion to mTORi and reducing immunosuppression induced response in over 80% of patients. Chemotherapy is usually reserved for cases of extensive KS and best understood in AIDS-related KS. We were able to control KS by switching to an mTORi.



PUB517

Rare Vascular Complications in a Kidney Allograft

Arpita Joshi, Raul F. Garcia Maya, Raviprasenna K. Parasuraman. *University of Michigan, Ann Arbor, MI.*

Introduction: The occurrence of vascular complications in kidney transplant ranges 6-30% and has a significant impact on allograft and patient outcomes.

Case Description: Case 1: A 54-year-old male with ESKD from hypertension received a DDKT. He developed an AKI 5 weeks later. Ultrasound showed a 3 cm large extrarenal pseudoaneurysm (EPSA) at the site of anastomosis of the renal artery to the right external iliac artery. Endovascular intervention with occlusion of the pseudoaneurysm and intentional exclusion of transplant renal arteries was performed to prevent rupture and leak with eventual allograft failure. Case 2: A 25-year-old with ESKD from Alport's syndrome and LUKT had an AKI, proteinuria, microscopic hematuria with ipsilateral leg edema 3 weeks later. Biopsy negative. External compression of the right common iliac vein by a 6 cm hilar lymphocele causing renal vein congestion was seen on imaging. Aspiration of the lymphocele resolved the findings.

Discussion: EPSAs occur in 1% of transplants. Infections commonly cause EPSAs and can cause irreversible arterial damage. EPSA in our case was due to complex vasculature with 3 renal arteries on 2 aortic patches. Infected ESPAs or larger than 2.5 cm are at high risk for rupture and need intervention, usually allograft nephrectomy. Iliac vein stenosis is a rare, reversible cause of allograft AKI, ipsilateral leg edema, proteinuria and microscopic hematuria. This can be due to perihilar fluid collections or hematomas, surgical clamp injury and faulty suturing. In our case, a lymphocele led to a nutcracker-like phenomenon and renal vein congestion. Evolution and standardization of surgical techniques may have contributed to a decrease in vascular complications but the incidence remains substantial.

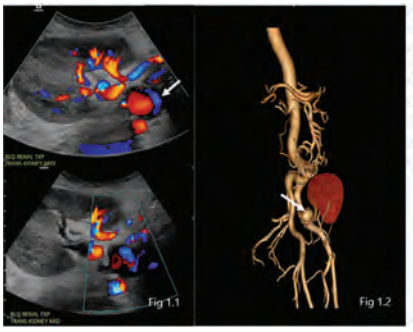


Fig 1.1 Arrow points to a pseudoaneurysm at the site of the renal artery anastomosis. The Yin-Yang sign indicates turbulent mixing of blood flow diagnostic for a pseudoaneurysm.

Fig 1.2 Arrow points to extra renal pseudoaneurysm at the site of anastomosis

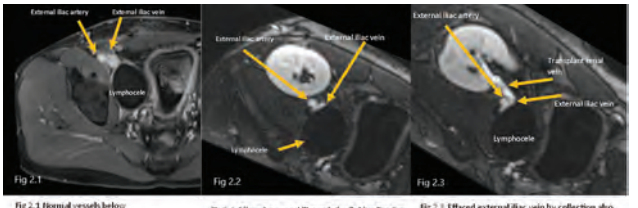


Fig 2.1 Normal vessels below anastomosis and adjacent to collection

Fig 2.2 Effaced external iliac vein by fluid collection

Fig 2.3 Effaced external iliac vein by collection also at level of renal transplant vein anastomosis

PUB518

An Atypical Case of Post-transplant Lymphoproliferative Disorder of the Bladder in a Kidney Transplant Recipient

Gurbir S. Sehmbey, Dominik Thomas, Sarah Gilligan, Suayp Oygen, Duha A. Jweehan, Isaac E. Hall, Miklos Z. Molnar, Divya Raghavan. *University of Utah Health, Salt Lake City, UT.*

Introduction: Post-transplant lymphoproliferative disorder (PTLDs) represents a spectrum of abnormal lymphoid or plasma cell proliferations that arise in individuals receiving chronic immunosuppression for solid organ transplantation. PTLD encompasses a spectrum of manifestations from benign polyclonal lymphoproliferation to fully developed lymphomas.

Case Description: We present a case of a 50-year-old female with ESRD and history of two kidney transplants. The first transplant was from a living unrelated donor in 2003; graft loss occurred five years later due to pulmonary renal syndrome caused by p-ANCA microscopic polyangiitis. The second transplant in 2012 was from a deceased donor. Both transplants were complicated by recurrent ESBL E. coli UTIs requiring IV ertapenem and bilateral native nephrectomies in 2014. Her kidney function remained stable while on Azathioprine 100 mg, prednisone 5mg and tacrolimus 3mg twice daily for immunosuppression after the second transplant for 8 years. In April 2020, she presents with gross hematuria. Renal ultrasound reveals an irregular hypoechoic mass with vascularity within the bladder. She subsequently underwent a cystoscopy showing 3 masses: 8cm, 5cm and 6cm – the 5cm mass was resected. Pathology revealed PTLD (monomorphic subtype, EBV-, DLBCL GCB). The MIB1=70%. cMYC was expressed on 30-40% of cells and BCL2 and BCL6 were expressed in most tumor cells. The sample also stained strongly for CD10 and CD20. Therefore, she did not have a double expressor or double hit lymphoma. She was treated with weekly rituximab for 4 weeks and 4 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Immunosuppression was decreased. A repeat cystoscopy and CT abdomen showed resolution of lesions in the bladder.

Discussion: PTLD is a serious complication after solid organ transplantation. Risk factors for developing PTLD include Epstein-Barr virus (EBV) infection, recipient age, transplanted organ, type of immunosuppression, and genetics. PTLD has a reported incidence of 1-5% in kidney transplant recipients. Outcomes following a diagnosis of PTLD can vary, with 5- and 10-year survival rates of 53% and 45% respectively. Although PTLD can happen in almost every organ system in the body, occurrence in urinary bladder is very rare.

PUB519

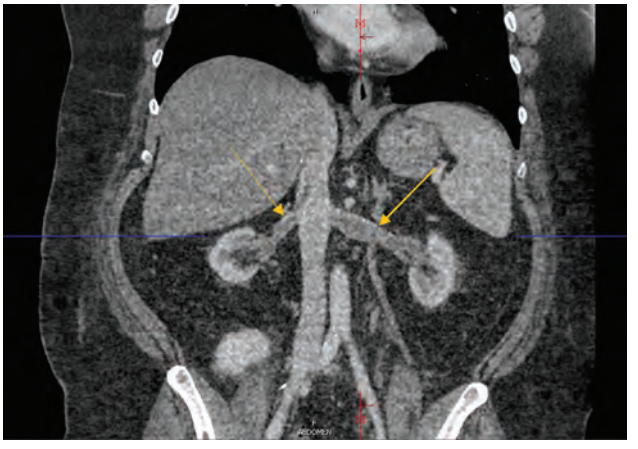
Bilateral Native Renal Vein Thrombosis in a Liver and Kidney Transplant Recipient

Andrew Slater, Alfonso Santos, Rohan V. Mehta, Amer A. Belal, Kawther Alquadan. *University of Florida, Gainesville, FL.*

Introduction: Renal vein thrombosis (RVT) is a rare condition predominantly linked to nephrotic syndrome, hereditary hypercoagulable disorders, malignancies, and sepsis in adults. The incidence of native RVT after simultaneous liver and kidney transplantation (SLKT) is unknown. In this case, we present an incidental finding of bilateral native kidney vein thrombosis in a liver and kidney transplant recipient.

Case Description: A 44-year-old male received SLKT. Thirteen months post-transplant, bilateral native renal vein thrombosis extending into the inferior vena cava (IVC) below the diaphragm appeared on a CT scan during a preop workup for incisional hernia repair. The renal allograft was free of venous thrombosis based on the CT scan and a Doppler study. A focused investigation for the underlying cause of thrombosis ensued. The family history of thromboembolism was negative. Tests including Lupus anti-coagulant; anti-cardiolipin IgG and IgM; anti-beta-2 Glycoprotein IgG and IgM; factor V Leiden and prothrombin (20210G>A) mutations yielded negative results. Genetic mutations implicated in myeloproliferative neoplasm including JAK2 (V617F), Calreticulin (CALR Exon 9), and MPL mutations were not detected. Similarly, paroxysmal nocturnal hemoglobinuria was ruled out by flow cytometry. The function of the renal and liver allografts remained stable, and proteinuria was not detected. With apixaban treatment, a CT scan showed complete resolution of the bilateral native renal vein thrombosis after 3 months.

Discussion: This case highlights the incidental finding of native RVT after SLKT, a pathology with an unknown clinical incidence. When found, it warrants a complete comprehensive workup for an underlying etiology. The most efficacious type and duration of anticoagualation is unknown, and this decision should be multi-disciplinary and collaborative with the patient.



Bilateral RVT extending into the IVC with renal vein dilation (yellow arrows).

PUB520

Safety of SGLT2 Inhibitors in Kidney Transplant Recipients with Type 2 Diabetes Mellitus (T2DM) or New-Onset Diabetes after Transplant (NODAT): A Single-Centre Experience

Wigdan Hamza, Komal Moqeem, Aisha Riaz, Natasha A. Moore, Elham Asgari, Caroline Dudreuilh. *Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom.*

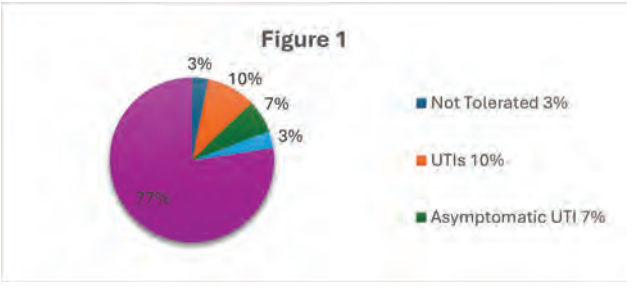
Background: Sodium/Glucose Transporter 2 inhibitors (SGLT2i) have demonstrated significant renoprotective effects in native kidney disease. However, evidence of their safety in kidney transplant recipients (KTRs) is lacking. Attention was drawn to the potential increased risk of urinary tract infections (UTIs) in the setting of immunosuppression. We aim to present our local experience on the safety of SGLT2i in KTRs with pre-existing type 2 diabetes mellitus (T2DM) or new-onset diabetes after transplant (NODAT).

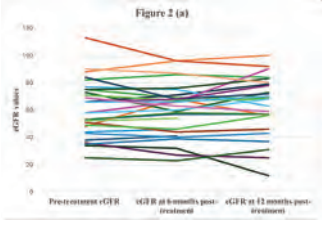
Methods: A retrospective analysis of 31 KTRs with either pre-existing T2DM or NODAT, who were commenced on SGLT2i, was conducted. Pre-treatment eGFR (estimated glomerular filtration rate) was recorded (using CKD-EPI equation) and further assessed at 6 and 12 months following initiation of SGLT2i. Treatment complications and adverse events were reviewed during the follow-up period.

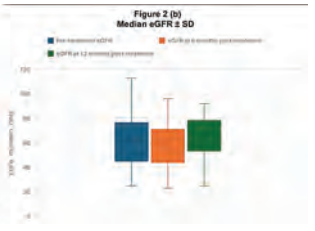
Results: SGLT2i were started for 21/31 (67.7%) KTRs diagnosed with NODAT and 9/31 (29%) with pre-existing T2DM. The median duration of SGLT2i treatment was 23 months (± 12.9). Among 31 KTRs, 5 patients developed uncomplicated UTIs (16%) (Figure 1). eGFR remained stable following SGLT2i initiation with a median value of

62ml/min/1.73m² (±22.8) pre-treatment and 68 ml/min/1.73m² (±18.6) 12 months post treatment (Figure 2). One patient developed acute rejection due to non-compliance with immunosuppression. No patient developed euglyceamic diabetic ketoacidosis or genital fungal infections.

Conclusions: Our data suggests that SGLT2i are not associated with significant adverse effects. UTIs were the most frequent complications. The incidence, however, is similar to KTRs who were not on SGLT2i as reported in the literature. One of the limitations of our study is the small sample size, however, we conclude that SGLT2i can be safely prescribed in diabetic KTRs.







PUB521

Clinical and Histopathological Features of Anti-AT1 Receptor Antibody-Mediated Acute Rejection in Kidney Transplant Recipients: A Case Series

Claudia G. Olano,[1] Andrea L. Urrutia,[1] Sami M. Akram.[2] *[1]Harbor UCLA Medical Center, Torrance, CA; [2]Loma Linda University, Loma Linda, CA.*

Introduction: According to US renal Data System (USRDS), one in five patients will lose their kidney allograft within 5 years of transplantation, and over half will experience allograft loss by 10 years (**1**). Allograft loss is associated with a high burden of psychologic and medical morbidity, with patients faring poorly across many traditional measures of quality of care, including anemia management and phosphate control (**2**, 3). The most common cause of graft loss during life is alloimmunity (5).

Case Description: Patients: There were four kidney transplant recipients between the ages 34 – 60 (table 1). There were two males and two females. Blood groups are shown in Table 1. The causes of primary renal disease and the comorbidities recorded in Table 1. One patient had biopsy proven TMA as the cause of renal failure. There was one case of second renal transplant. One patient had Living unrelated donor kidney transplant (case 1) and the three others had deceased donor kidney transplant. The case number 2 received donation after cardiac death (DCD). No patient had zero mismatch organ (table 1). In all cases, complement-dependent T-cell and B-cell cross match were negative prior to the operation. T cell antibody and B cell antibody cross match was done with pronase tested donor cells. In case #1 of living unrelated donor, cross match was performed using multiple techniques, automated flow, and serology. Case one and four had zero panel reactive antibodies (PRA), while cases two and three were severe and moderately sensitized respectively (case 2 PRA 85/75, case 3 PRA 45/62). In case number two there were both Class I DSA and Anti AT1R. Relapse of her underlying TMA was reason. This patient was prescribed Ultimiris resulting in stabilizing of serum creatinine.

Discussion: In conclusion, testing for anti AT1R antibody should be done early if not prior to kidney transplantation. Injury in Acute Rejection mediated by anti AT1R antibodies may be due to mitochondrial dysfunction. Repertoire to treat Acute rejection by inhibiting ERK ½ signaling pathway is about to grow explosively. There is an opportunity to influence the therapy of acute rejection and improve graft as well as patient survival

PUB522

Sepsis-Induced Thrombotic Microangiopathy (TMA) in Simultaneous Pancreas-Kidney (SPK) Transplantation: Diagnosis and Treatment Dilemmas

Atousa Jahanshahi, Ananthalaxmi Vangapalli, Sudhindra Pydimarri, Richard Gargiulo. *Jefferson Einstein Philadelphia Hospital, Philadelphia, PA.*

Introduction: TMA is an acute life-threatening condition characterized by the formation of microscopic blood clots in capillaries and small arteries, causing microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ damage.

Case Description: 50-year-old female, with end-stage-renal-disease from diabetes, SPK transplantation in 2018, with baseline creatinine of 1.3mg/dl presented with a week-long history of diarrhea, dysuria, weakness, oliguria, and bilateral flank pain. Found to have acute kidney injury, neutropenia, elevated tacrolimus level (see Table 1). Due to severe neutropenia, mycophenolate was held, and G-CSF initiated. Tacrolimus dose was adjusted for goal level 4 – 6ng/ml. As she was afebrile and initial cultures were negative, patient was monitored off antibiotics. On day four, hemoglobin dropped to 5.8gm/dL with negative hemolytic workup. By day eight, platelet count decreased to 18 x10^3/mcL, with signs of MAHA (see Table 1). Despite daily plasma exchanges and reduced tacrolimus levels, her condition worsened, developing hypotension, and altered mental status. After extensive negative workup, repeat blood cultures revealed ESBL Klebsiella pneumonia bacteremia. She was started on vancomycin and meropenem with clinical improvement. At discharge, creatinine improved to baseline and blood counts and hemolysis stabilized.

Discussion: This case highlights the challenge of diagnosing sepsis-induced TMA in the transplant population, with many potential etiologies to consider including Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS), thrombotic thrombocytopenic purpura, complement-mediated TMA (CM-TMA), and drug-induced TMA (DITMA). Antibiotics were vital in her clinical improvement. When managing TMA syndromes in transplant and other immunosuppressed patients, consideration of sepsis in the differential diagnosis is crucial, particularly if standard treatments fail.

Table 1.

	Admission	Day 4	Day 8
Creatinine mg/dl, BUN mg/dl	9.44, 103	6.58, 72	3.25, 46
Tacrolimus level ng/mL	20.1	14.3	9.3
Hgb gm/dL, Platelet x10^3/mcL	8.2, 182	5.8, 92	9, 18
WBC x10^3/mcL, Neuro absolute 10^3/mcL	0.4, 0.3	0.6, 0.4	0.4, 0.1
Reticulocyte, LDH IU/L, Haptoglobin mg/dL, Fibrinogen mg/dLc		1.04%, 130, 169	8.2%, 307, <8
influenza/RSV/COVID/ HIV/Parvo B19/ CMV DNA PCR/ stool: O&P/E.coliO:157/salmonella/shigella/ campylobacter/C.diff/Cryptosporidium/Giardia			negative
HIT antibody/ANA/ Direct Coombs test/ Antiphospholipid antibodies/ ADAMTS13IU/mL			negative

PUB523

Donor Sex Disparities in CKD Progression: A UNOS Analysis

Fausto R. Cabezas, Andrea Roche-Recinos, Subodh J. Saggi, Angelika C. Gruessner. *SUNY Downstate Health Sciences University, New York City, NY.*

Background: Living donor kidney transplantation (LDKT) remains the gold standard for the treatment of ESRD. However, there is scarce prospective data on long term outcomes for kidney donors. Retrospective studies with follow-up time of 10 years or more have shown a modest risk increase in all-cause mortality, hypertension and ESRD. As a higher proportion of living donors are female, we aim to assess sex disparities amongst kidney donors requiting listing for kidney transplantation (KT).

Methods: We queried the UNOS/OPTN database for all adults listed for a primary KT between 1/1/2014 and 12/31/23. Probabilistic linkage was used to link the donor record to the waitlist information. Comprehensive statistical methods were applied to assess the development over time and to describe possible sex differences.

Results: 51,700 primary LDKTs performed during the study period, 64% of donors were female (p=0.007). In contrast, of 519 donors (1%) who were listed for KT, 64% were male (p<0.0001) (fig 1). Baseline characteristics were similar in between the groups (table 1). Only males were more likely to have hypertension and diabetes at the time of listing. There was no significant difference in time from donation to listing between the groups.

Conclusions: Male kidney donors are more likely to progress to require kidney transplant listing. Higher rates of diabetes and hypertension are likely associated with faster decline in kidney function amongst males. Prospective research assessing long term outcomes in donors is warranted.

	Female	Male	p
Listed patients (%)	185 (36)	334 (64)	<0.0001
Age at listing	59 (28-81)	60 (28-81)	0.11
Race (%)			
Office on the web Frame			
Black	84 (35)	156 (65)	0.89
Hispanic	73 (37)	123 (63)	
Other	20 (32)	42 (68)	
	8 (38)	13 (62)	
Time between donation and Listing	13 (0 – 28)	16 (0-29)	0.47
Diagnosis at listing (%)			
Diabetes	40 (34)	76 (66)	0.04
Hypertension	55 (31)	120 (69)	
Glomerular Disease	24 (33)	49 (67)	
Congenital, familial	7 (78)	2 (22)	
Days on Waitlist	93 (3-2975)	56 (1-2608)	
EPTS score at listing	43 (2-96)	46 (2-96)	0.92
On dialysis at listing (%)	92 (50%)	181 (54%)	0.33

Table 1. Baseline Characteristics

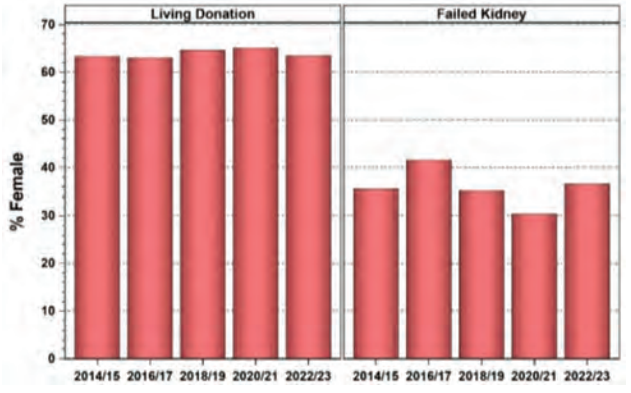


Figure 1. Rate of female LDKT donors and waitlisting

PUB524

Safety and Diagnostic Yield of Kidney Transplant Biopsies in an Interventional Nephrology Program: A Retrospective Single-Center Study

Kingsley I. Onuoha, J. Pedro Teixeira, Pablo Garcia, Jonathan G. Owen. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Kidney transplant (KT) biopsy remains the gold standard in diagnosing rejection. However, biopsy carries risk of complications which must be weighed against the diagnostic yield, and variability exists between providers and centers in aggressiveness of pursuing transplant biopsy. We created a renal biopsy registry at our center for both research and quality improvement purposes. We reviewed all transplant biopsies performed to determine the rate of complications and diagnostic yield.

Methods: We performed a retrospective chart review of all KT biopsies performed by our Interventional Nephrology program between 11/27/2017 and 4/9/2024. Data collected included pathological diagnosis and complications. Major bleeding was defined as the need for secondary interventional procedure, need for blood transfusion, need for surgery, hospitalization, hematoma >5 cm, or death. Minor bleeding was defined as hemoglobin drop of >1.5 g/dL, hematoma <5 cm, or uncomplicated gross hematuria. Diagnoses of rejection included all forms of rejection, including borderline cases.

Results: A total of 282 biopsies were performed, of which 154 (54.6%) were KT biopsies. Major bleeding events occurred in 3 KT patients (1.95%). All 3 patients presented with gross hematuria. The first patient was found to have an arteriovenous fistula and died of an unrelated cardiac event before planned IR embolization. The second patient developed urinary obstruction secondary to bleeding and required a nephrostomy tube for 51 days. The third patient required 1 unit of blood and was observed in the hospital until the hematuria resolved. Minor bleeding occurred in 2 additional patients (1.3%), manifest in both as hemoglobin drop >1.5 g/dL. Of the KT biopsies, 65/154 (42%) revealed evidence of rejection.

Conclusions: In our center, major bleeding after KT biopsy was uncommon relative to the frequency of transplant rejection diagnoses. Our findings support the consideration of an aggressive approach to KT biopsy for detection of rejection. Further analyses of our registry are planned to determine factors most likely associated with rejection (e.g., donor-specific antibodies, time since transplant, cell-free DNA levels) to improve the screening process for biopsy referral and help personalize the decision-making process for individual patients.

PUB525

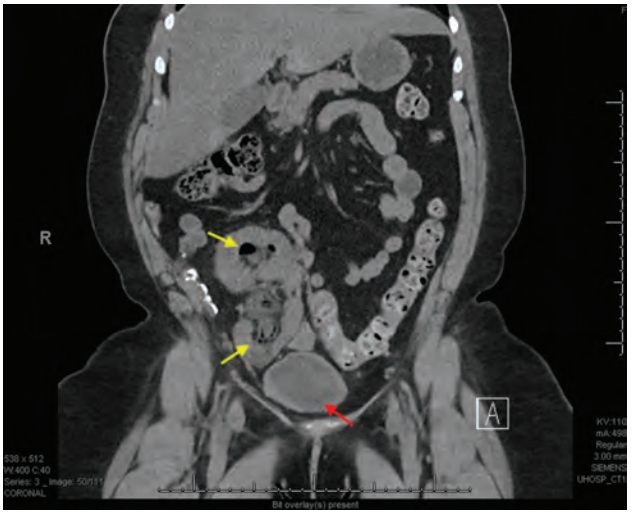
An Unusual Case of Transplant Kidney Emphysematous Pyelitis and Cystitis

Taylor R. Moody, Sarah Gilligan, Isaac E. Hall, Duha A. Jweehan, Miklos Z. Molnar, Suayp Oygen, Divya Raghavan. *University of Utah Health, Salt Lake City, UT.*

Introduction: Emphysematous cystitis, pyelitis, and pyelonephritis are rare but serious complications of urinary tract infections (UTIs) with gas-producing bacteria. We present a case of emphysematous UTI in a kidney transplant recipient concomitant with rejection.

Case Description: A 36-year-old woman with history of end-stage kidney disease of unclear etiology who underwent a living related kidney transplant in 2001 complicated by cellular and antibody-mediated rejection in 2017 and recurrent UTIs presented with worsening kidney function and allograft pain. She initially presented a month prior with allograft pain and dysuria and was treated for *Escherichia coli* (*E. coli*) UTI. Computed tomography (CT) and urinalysis 10 days prior to admission were unremarkable. Testing revealed a persistently positive class II donor specific antibody. Kidney biopsy showed chronic active antibody mediated rejection and she was started on high-dose intravenous steroids with plan for therapeutic plasma exchange (TPE). She continued to report significant allograft pain and repeat CT scan demonstrated emphysematous transplant pyelitis and emphysematous cystitis. Antibiotics were started and surgical intervention was not recommended. Repeat urine culture grew *E. coli*. Further rejection treatment was deferred and she was discharged home with clinical improvement. Her serum creatinine was down to 1.73 mg/dl on discharge from a peak of 2.35 mg/dl during hospitalization.

Discussion: This case demonstrates the importance of thorough evaluation prior to initiating treatment for allograft rejection. If this patient had received potent immunosuppression as planned, her emphysematous pyelitis may have progressed to emphysematous pyelonephritis which is associated with increased risk of allograft loss and mortality.



Emphysematous pyelitis (yellow arrows) and cystitis (red arrow) on CT.

PUB526

Influence of Anemia Prior to Kidney Transplant in Early Graft Function

Jose L. Torres Cuevas, Manuel Camacho Luna, Victor M. Ulloa Galvan, Martin B. Yama Estrella, Ydris Z. Rosillo-Salgado, Francisco Velasco Garcia Lascurain, Christian P. Flores, Citlali Fernandez Vivar, Mayra M. Matias Carmona, Jose H. Cano Cervantes. *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico.*

Background: Modifiable factors associated to better allograft function are relevant to de success of the kidney transplant. Anemia, complication associated to chronic kidney disease could influence in allograft function.

Methods: Retrospective, cross-sectional study, included transplant kidney receptors of a single Mexican third level healthcare center performed in 2017-2019. Univariate logistic regression (odds ratios [OR], 95% CI) were used to evaluate allograft function associations, spearman correlation coefficient (SCC) was also performed to continuous variables.

Results: A total of 97 participants were included (52% from living kidney donors), the median age was 33 (25-48), 61 (62.9%) were women and 51 (52.6%) were living kidney donors, mean hemoglobin (Hb) pre-transplant was 11.53 ± 2.18, median transferrin saturation (TS) was 28.2 (17-35). Anemia (Hb < 11 g/dl) prevalence was 77.3% and iron deficiency (TS <20 %) in 34%. Inmediate graft function (IGF) defined as serum

creatinine decrease of at least 70% of preoperative value in the first week was recorded in 75 participants (77.3%), delayed graft function (DGF), defined by requirement of dialytic therapy in the first week after kidney transplantation, was identified in 11 participants (11.3%). The OR for IGF by anemia and iron deficiency were OR= 0.74, 95% CI, (0.28- 1.93) and OR=0.87, 95% IC, (0.32- 2.36) respectively. SCC between hemoglobin previous transplant and the glomerular filtration rate after 3 months was 0.13, *p:* 0.19.

Conclusions: Anemia previous a kidney transplant doesn't influence in the early kidney function. Kidney transplantation in living kidney donors shouldn't be delayed by a specific hemoglobin target. Therapeutic interventions to increase hemoglobin previous kidney transplant in receptors of a cadaveric donor could be avoided.

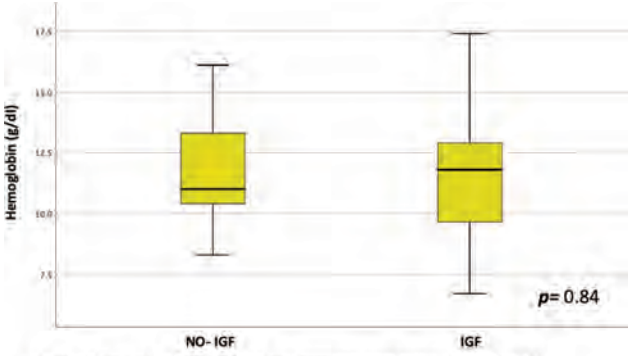


Figure 1. Comparation of hemoglobin pre-transplant in patients with IGF vs No-IGF.

PUB527

Graft Kidney Artery Stenosis in a Deceased Donor Kidney Transplant Recipient with Autosomal Dominant Polycystic Kidney Disease: A Case Report

Byung Min Ye, Seo Rin Kim, Il Young Kim, Soo Bong Lee, Dong Won Lee.
Pusan National University School of Medicine, Yangsan, Republic of Korea.

Introduction: This paper presents a case study of a rare instance of transplant renal artery stenosis caused by mechanical compression from the native polycystic kidney in a recipient with ADPKD who received a kidney from a deceased donor.

Case Description: A 53-year-old man received a kidney transplant from a deceased donor. On the fourth day post-surgery, underwent color Doppler ultrasound (Fig 1-A) and CT angiography (Fig 1-B) to assess vascular issues, revealing renal artery stenosis in the transplanted kidney. The patient underwent reoperation to correct TRAS, we confirmed that the right native polycystic kidney compressed the transplanted kidney, causing it to rotate medially, resulting in the stenosis of the renal artery. (Fig 2-A) Right nephrectomy of the native polycystic kidney, and straightening of the renal artery of the transplanted kidney to relieve compression. (Fig 2-B) After the surgical resection, renal function and urine output were well-maintained, and the blood pressure remained stable.

Discussion: Our focus on TRAS is due to its classification as one of the reversible complications linked to hypertension, as well as its association with the dysfunction of transplanted kidneys. This perspective underscores the importance of early detection and management of TRAS to ensure successful outcomes for the transplant recipients. We hope that by introducing this case, we can gain some insights for dealing with similar patients who develop renal artery stenosis.

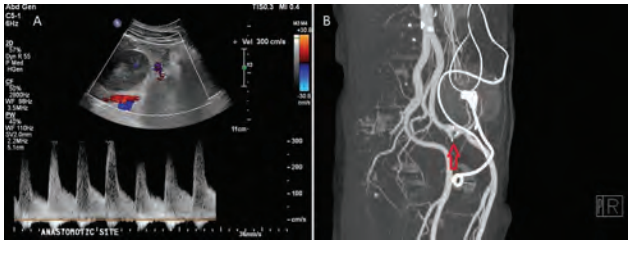


Figure 1. A: US color Doppler kidney. Peak velocity in the anastomotic site of renal artery is increased, more than 250 cm/s., B: CT angiography. Revealing renal artery stenosis in the transplanted kidney. (arrow)

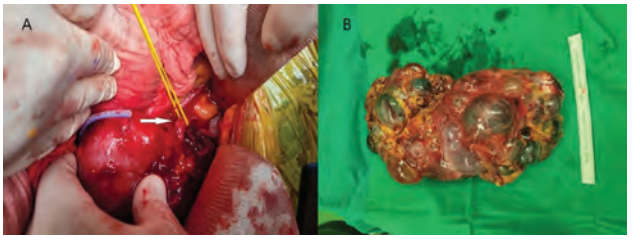


Figure 2. A: The transplant renal artery stenosis was confirmed through surgical intervention., B: Surgical resection of the right native polycystic kidney.

PUB528

Comparison of Anti-human T-lymphocyte Immunoglobulin (r-ATLG) vs. Anti-thymocyte Globulin (r-ATG) as Induction Agents in Kidney Transplantation: A 5-Year Retrospective, Single-Center, Observational Study

Vijay Kumar Sinha, Amit Devra, Ravi K. Singh, Prashant Pandey.
Jaypee Hospital, Noida, India.

Background: T cell depletion agents, Anti-Thymocyte Globulin (r-ATG) and Anti-Human T-Lymphocyte Immunoglobulin (r-ATLG), are routinely employed as induction therapies in kidney transplantation. This study systematically evaluates the short-term and long-term outcomes of kidney transplants at our center, focusing on the comparative efficacy and safety profiles of these agents.

Methods: This retrospective cohort study analyzed data from kidney transplant recipients treated at a tertiary care hospital in India between 2017 and 2024. A total of 603 patients were included, with 381 receiving ATG and 222 receiving ATLG as induction therapy. All patients were maintained on a standard regimen of triple immunosuppressive therapy. Follow-up assessments included evaluations for graft rejection, infections, development of de novo diseases, and overall graft survival

Results: The mean follow-up duration was 60 months. The mean doses administered were 5.4 ± 1.4 mg/kg for ATLG and 2.37 ± 1.2 mg/kg for ATG. Baseline demographic and clinical characteristics were well-matched between the two groups. HLA matching showed <3/6 in 95 patients (42.7%) with ATLG and in 318 patients (83.4%) with ATG, while >3/6 HLA matching was found in 127 patients (57.2%) with ATLG and 63 patients (16.5%) with ATG. Serum creatinine levels at discharge and during follow-up intervals were comparable between groups. The incidence of de novo diseases was higher in the ATG group (12 cases, 3.1%) compared to the ATLG group (3 cases, 1.3%). However, the incidence of infections was similar between the two groups.

Conclusions: Both ATG and ATLG demonstrated similar efficacy in terms of short-term and long-term graft rejection rates in kidney transplant recipients.

	ATG(n=381) (n=38, Rejection 10%)	ATLG (n=222) (n=24, Rejection 10.7%)
Rejection within 1 month		
Acute Cellular Rejection	7(1.8%)	6(2.7%)
Acute ABMR	NR	NR
Rejection in 1 month to 6 month		
Acute Cellular Rejection	11(2.8%)	8(3.6%)
Acute ABMR	1(0.2%)	1(0.2%)
Rejection after 6 months		
Acute Cellular Rejection	9(2.3%)	7(3.1%)
Acute ABMR	10(2.6%)	2(0.9%)

Rejection Analysis between (ATLG and ATG)

PUB529

Malakoplakia in the Transplanted Kidney

Edward Mwarangu,[1] Ramya Krishna Velagapudi,[1] Prathap Simhadri,[2] Mohammad Atari,[1] Pradeep Vaitla.[1] *[1]The University of Mississippi Medical Center, Jackson, MS; [2]AdventHealth, Ormond Beach, FL.*

Introduction: Malakoplakia is a rare chronic granulomatous disease associated with gram-negative infection especially Escherichia coli. This disease is induced by defective phagolysosomal activity of the macrophages and mainly affects the urinary bladder but has been shown to affect any solid organ, however isolated malakoplakia of the renal allograft is rare.

Case Description: **Case 1** - A 66-year-old male with a deceased donor kidney transplant (DDKT), course complicated with transplant pyelonephritis. He acknowledged adherence to his medication. Six months post-transplant he developed urinary tract infection (UTI) secondary to E.Coli. A routine allograft ultrasound showed a mass which

was biopsied and negative for rejection. A follow up MRI showed masses within the renal transplant and a repeat biopsy showed malakoplakia. He was started on Bactrim and a repeat MRI four months later showed unchanged malakoplakia and his antibiotics switched to cefuroxime **Case 2** - A 39-year-old female patient with a simultaneous pancreas and kidney transplant course complicated by disseminated nocardia. Developed acute pyelonephritis 1.5 years post-transplant. An allograft US showed a mass which was biopsied showing acute rejection and malakoplakia. The patient was treated for rejection and antibiotics for urinary tract infection, malakoplakia and discharged with plans to stop upon resolution. A repeat MRI six months later showed resolution of Malakoplakia. **Case 3** - A 62-year-old male with DDKT, course complicated by transplant pyelonephritis at eight weeks post-transplant. He presented few weeks later with an acute kidney injury (Creatinine 3.01, baseline 1.5-.18), CT imaging showed a nodular mass on the allograft, which was biopsied revealing malakoplakia. Malakoplakia resolved within 6 months after treatment of UTI.

Discussion: Malakoplakia can present as granulomatous renal mass and should be considered as a differential diagnosis while evaluating renal masses in transplant recipients.

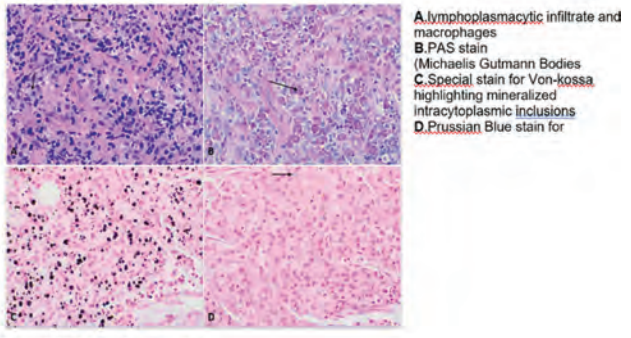


Figure 1: Histological examination

PUB530

Paradoxical Association of Predonation Urine Protein with Kidney Function in Living Kidney Donors without Obesity

Ekamol Tantisattamo,[1,2] Chutawat Kookanok,[1,3] Kamonluk Rodsom,[1,4] Voramol Rochanaroon,[1] Tatchaya Kanthajan,[1] Vitchapong Prasitsumrit,[1] Tulaton Sodsri,[1] Adivitch Sripusanapan,[1] Smuch Siramongkholkarn,[1,5] Phuuwadith Wattanachayakul.[1,6] *[1]University of California Irvine School of Medicine, Orange, CA; [2]VA Long Beach Healthcare System, Long Beach, CA; [3]Phramongkutklao College of Medicine, Bangkok, Thailand; [4]Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; [5]Mahidol University Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand; [6]Jefferson Einstein Philadelphia Hospital, Philadelphia, PA.*

Background: Clinical significance of pre-donation proteinuria in living kidney donors (LKD) is unknown. We aim to examine the association between pre-donation urinary protein:creatinine ratio (UPCR) and the risk of kidney function decline in LKD.

Methods: A retrospective cohort study using OPTN/SRTR included adult LKD undergoing donation between 6/1972 and 9/2022. The association between pre-donation UPCR and time-to-event of ≥35% decline in post-donation eGFR from pre-donation eGFR was examined by multiple Cox regression.

Results: Of 174,311 adult LKD, the mean±SD age was 41±12 years and 60% were female. Mean pre-donation UPCR was 2.12 ±9.23 mg/g of Cr and UPCR at immediate post-donation, 6-, 12-, and 24-months post-donation were 1.23±6.54, 1.44±8.26, 1.72±9.26, and 1.37±7.96 mg/g of Cr, respectively. The median (IQR) pre-donation eGFR was 91 (75, 111) mL/min/1.73 m^2. Median eGFR at immediate post-donation, 6-, 12-, and 24-months post-donation were 50 (40, 62), 54 (44, 67), 55 (45, 68), and 57 (47, 70) mL/min/1.73 m^2, respectively. Out of 38,780 LKD with post-donation eGFR data at 6, 12, or 24 months, 31,054 LKD had the event of ≥35% decline in post-donation eGFR from pre-donation eGFR with a median time to follow-up of 6.77 months (IQR 5.93, 12.67). The incidence rate of the event was 0.08 person-months. After adjusting for age, race/ethnicity, U.S. citizenship, education level, history of pre-donation BMI, hypertension, diabetes, and pre-donation SBP and DBP, every 1 mg/g of Cr increase in pre-donation UPCR was associated with a 0.8% lower risk for the event (HR 0.992, 95%CI 0.985, 0.998). Obesity status was an effect measured modifier with a decreased risk of a decline in eGFR ≥35% observed in LKD with pre-donation normal weight and overweight, but not obesity ($HR_{normal\ weight}$ 0.988, 95%CI 0.977, 0.999; $HR_{overweight}$ 0.989, 95%CI 0.978, 0.999; and $HR_{obesity}$ 1.003, 95%CI 0.991, 1.014).

Conclusions: Pre-donation UPCR is inversely associated with the risk for a significant decline in post-donation eGFR in LKD with normal weight and overweight. Relatively less glomerular hyperfiltration in non-obese LKD may contribute to a reno-protective effect regardless of the degree of pre-donation proteinuria.

PUB531

Don't Get Burned Twice by the Same Post-transplant Lymphoproliferative Disorder (PTLD): A Case Highlighting the Progression and Advancement in PTLD Management in One Transplant Patient

Rania Salam, Farah Daccueil, Heesuck Suh, Henry Yip, Katherine Andrade. *Stony Brook University Hospital, Stony Brook, NY.*

Introduction: PTLD, incidence is reported at 2-20% in solid organ transplant and throughout the decades carried a high risk of allograft lost as well as other hematologic and systemic complication. Management of immunosuppressant of transplanted patient with PTLD and management of PTLD itself has evolved over the years. Our case illustrated how far we have come in management of transplant patients with PLTD and the importance of surveillance.

Case Description: 29 year old female with ESRD secondary to C1q nephropathy diagnosed in 1999 who received DDRT 2002 complicated by acute rejection in 2005 from immunosuppression reduction and eventual hold of immunosuppression for PTLD diagnosis in 2003 (mesenteric LN and appendix). She subsequently received another DDRT in 2006. She had a stable graft function and was followed closely by nephrology and oncology with regular PET scans. Eventually in 2023, had rising EBV titers, fatigue and high fever. She was referred to inpatient by nephrologist for further workup. Exam revealed fever 39.5 C, tachycardia, and normotensive. Labs marked for WBC 3.43, Hb 8.1, Ht 27.0 ESR 56, EBV plasma 44,900. CT scan showed large right-sided mediastinal mass measuring 7.8 cm. Bronchoscopy and mediastinal node biopsy, possible lymphoma. Cytology diagnosed PTLD Hodgkin type. Hematology recommended 6 cycles of A+AVD (Brentuximab vedotin, Doxorubicin, Vinblastine, Dacarbazine). Tacrolimus dose slight reduced with trough in range and MMF also reduced. Tumor burden significantly reduced and patient is reported to be doing well.

Discussion: PTLD often managed by reducing immunosuppression risking graft loss. However with advancement in treatment, patients are allowed to receive targeted treatment, maintain adequate transplant immunosuppression; with higher chances of graft preservation and improved quality of life. Our patient's presentation showcases this progression, where her first transplant complicated by rejection after immunosuppression was reduced/held. Second transplant was preserved by timely diagnosis and targeted treatment of PTLD with chemotherapy.

PUB532

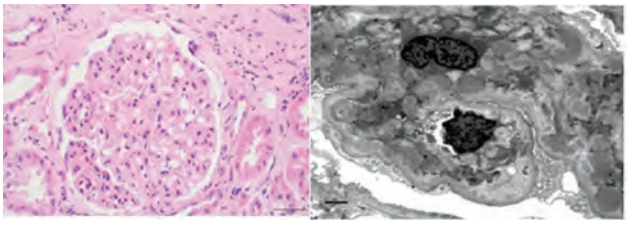
Recurrent Lupus Nephritis in a Kidney Transplant Patient

Ahsan Sajjad,[1] Rida Amer,[1] Amanda Tchakarov,[2] Sreedhar A. Mandayam,[3,1] Muhammad Daoud Butt.[4] *[1]Prolato Clinical Research Center, Houston, TX; [2]The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX; [3]The University of Texas MD Anderson Cancer Center Anne C Brooks Brain and Spine Center, Houston, TX; [4]Universiti Malaya Faculty of Medicine, Kuala Lumpur, Malaysia.*

Introduction: Lupus nephritis (LN) is a severe manifestation of SLE. The recurrence of LN post-renal transplantation is an uncommon event, particularly in patients without a prior diagnosis of SLE.

Case Description: A 60-year-old female with a history of CKD due to IgA nephritis underwent renal transplantation in 1999. In 2023, she presented with worsening proteinuria, lacrimal gland enlargement, Jaccoud's arthropathy, and b/l lower extremities pitting edema. Renal allograft biopsy revealed diffuse lupus nephritis ISN/RPS Class IV, 19% global sclerosis of glomeruli, and 20% interstitial fibrosis with tubular atrophy. CKD onset followed a miscarriage in 1997, progressing to end-stage renal failure during a subsequent pregnancy in 1998, necessitating transplantation. Absence of prior SLE diagnosis and prolonged immunosuppression (Cellcept and Cyclosporine) suggest undiagnosed chronic SLE, possibly reactivated or newly manifested as LN in the allograft. Biopsy shows immune complex-mediated glomerulonephritis with endocapillary hypercellularity, neutrophils and a few wire-loops/hyaline thrombi. By immunofluorescence, there is positivity for IgA, IgG, IgM C3, C1q, kappa and lambd. Corresponding mesangial and subendothelial electron-dense deposit are present ultrastructurally. **Diagnosis:** Immune complex-mediated glomerulonephritis, Findings consistent with borderline changes of T-Cell mediated rejection per Banff criteria. Severe Interstitial inflammation(i3) and Mild tubulitis(t1). Peritubular capillaries were focally positive for C4d by immunohistochemistry. Moderate arterial and hyaline arteriolar sclerosis. Global sclerosis of 19%(3/16) of glomeruli and approximately 20% interstitial fibrosis with tubular atrophy

Discussion: Lupus nephritis is found in approximately 30-50% of SLE patients, with recurrence post-transplantation being rare, occurring in about 1-2% of cases. This case underscores the diagnostic challenge and the necessity of considering SLE in patients with renal allografts presenting with proteinuria. The long-term immunosuppressive therapy may have masked the underlying SLE, delaying the diagnosis until the renal allograft biopsy revealed lupus nephritis.



PUB533

10-Year Kidney Allograft Survival in Patients from a Safety Net Transplant Program Introduction

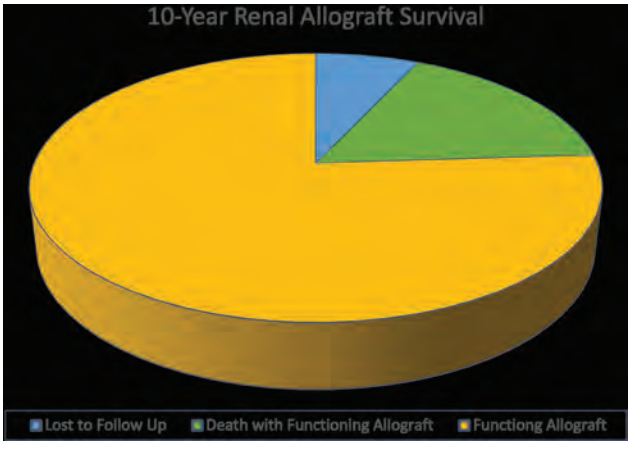
Anuja P. Shah,[1,2] Ibrahim Elali,[1,2] Ramanath B. Dukkipati,[1,2] Kamyar Kalantar-Zadeh,[1,2] Lilly M. Barba.[1,2] *[1]Harbor-UCLA Medical Center, Torrance, CA; [2]The Lundquist Institute, Torrance, CA.*

Background: Data regarding 1-year and 5-year renal allograft survival is readily available from transplant databases. The 10-year allograft function rates data particularly in a safety net hospital in an underserved metropolitan area is scarce. Lower socioeconomic status (SES) is a barrier to transplantation. Patients on Medicaid have lower rates of transplantation than those with commercial insurance. Long term allograft survival rates of lower SES renal transplant recipients are not known.

Methods: In order to shed light on the long-term allograft survival, we reviewed the outcomes of transplants performed in 2014, the most recent 10 year allograft survival available, from a single center safety net hospital transplant program.

Results: 29 renal transplants were performed in the year 2014. 14 % of recipients were African American, 21% were Asian, 3% Caucasian, and 62% were Hispanic. All patients were participants in the Medicaid program. 2 patients were lost to follow up. Of the 27 other patients, 22 (81%) continue to have functioning allografts; 5 patients died with functioning allografts. No patients lost allograft function and returned to chronic renal replacement therapy

Conclusions: Patients from an underserved population can achieve long term excellent renal allograft function. Socioeconomic barriers to transplantation do not necessarily carry forward as barriers to long term allograft survival. The care structure of these patients being followed long term in renal transplant clinic may have had a positive impact on the long-term allograft function observed in this population. Safety net transplant programs are important to maintain access to positive renal outcomes in low SES patients with ESRD.



PUB534

Anuria in Transplant Renal Artery Stenosis (TRAS) with Pseudoaneurysm: A Rare Presentation of an Uncommon Co-occurrence

Joy Kumar,[1,2] Tanisha Mishra,[1,2] Shankar Prasad Nagaraju,[1,2] Attur R. Prabhu,[1,2] Dharshan Rangaswamy.[1,2] *[1]Kasturba Medical College Manipal, Manipal, India; [2]Manipal Academy of Higher Education, Manipal, India.*

Introduction: TRAS and pseudoaneurysm are notorious post-transplant vascular complications with reported incidence of 1-23% and 1% respectively. Decline in graft function, worsening or resistant hypertension with volume overload and flash pulmonary edema in severe cases due to RAAS activation is commonly seen. However, anuria is a rare but alarming manifestation.

Case Description: A 54-year-old male was evaluated for acute onset dyspnea and anuria. Hypoxia with bilateral coarse crepitations due to pulmonary edema was evident on CXR. BP was elevated to 210/110 mmHg. Acute increase in Cr to 4.26 mg/dl as compared to his post-transplant baseline Cr range of 0.7-0.9 mg/dl signaled graft dysfunction. Post cadaveric renal transplantation, he had achieved good graft function and urine output with nadir Cr of 0.67 mg/dl and received induction anti-thymocyte globulin along with triple immunosuppression maintenance. No improvement in urine output was seen after initial stabilization in the ED with O2, intravenous diuretics and nitroglycerin infusion support. Hemodialysis was started while transplant renal artery doppler was suggestive of TRAS with low velocity (30cm/sec) parvus tardus waveform at the hilum. A graft renal artery angiography diagnosed TRAS with pseudoaneurysm. Therapeutic angioplasty with stenting led to improvement in renal function, urine output and blood pressure recordings. Dialysis was stopped. The patient was discharged with serum Cr of 0.97 mg/dl.

Discussion: Acute onset anuria is an uncommon yet emergent sign in post transplant patients requiring urgent investigation and management to prevent graft loss and mortality. While post-renal obstruction is the usual etiology, evaluation for renal and prerenal vascular compromise causing anuria is important. A high index of suspicion is crucial to evaluate for TRAS in the background of graft dysfunction and worsening hypertension post transplantation while ruling out graft rejection, post transplant infections, calcineurin nephrotoxicity and post renal obstruction. Stenting has shown improved outcomes in management of TRAS and pseudoaneurysm.

PUB535

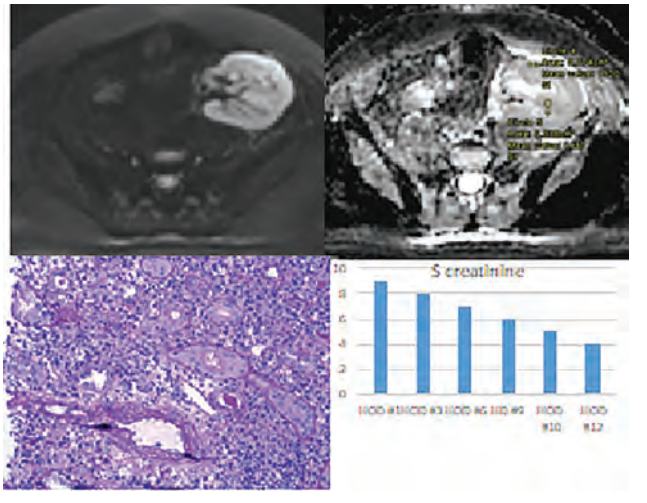
Evaluation of Allograft Rejection with MRI, Attenuation Diffusion Coefficient (ADC) Mapping: A Case Report

Sami M. Akram,[1] Michael A. Staton,[1] Lilly M. Barba,[2] Rafael Villicana.[1] Transplant Nephrology and Radiology. *[1]Loma Linda University, Loma Linda, CA; [2]Harbor-UCLA Medical Center, Torrance, CA.*

Introduction: The movement of water is the essence of life, and is central to kidney function. The kidney moves water by filtration, reabsorption, excretion, and secretion via aquaporin channels. Therefore, Diffusion-Weighted MRI Imaging with attenuation diffusion coefficient (ADC) maps can assess renal pathology but seldom utilized. Therefore, we report a case of allograft rejection evaluated by ADC map.

Case Description: A 26-year-old male with end stage kidney disease (ESKD) due to congenital kidney disease, had 0-mismatch diseased donor kidney transplant (DDKT), two years ago with thymoglobulin induction. He presented with oliguria of one week duration. He was non-complaint with therapy. Vital signs were within normal limits. Physical exam was remarkable for pitting leg edema. Laboratory exam showed serum creatinine of 9mg/dL; WBC 6.7 k/mcL; Hemoglobin, 8.3mg/dL; potassium 5.3mMol/L. Donor specific antibodies (DSA) were present. Allograft ultrasound showed mildly increased cortical echogenicity with mild pelviectasis. Renal indices were normal. MRI with ADC mapping showed uniformly low values in upper, mid and low consistent with restricted diffusion. Histology revealed acute Antibody mediated Rejection (AMR). Had good clinical respoonse to therapy.

Discussion: Diffusion-weighted imaging measures the Brownian motion of water molecules within a voxel by acquiring phase information of moving water molecules between the first and the second gradient MRI pulse sequence. Computer software generates ADC map. ADC is affected by the number of cells, the integrity of the cell membranes, and the amount of fibrosis, all of which restrict diffusion of water molecules. Ghar and Djasty et al described heterogeneity of ADC map in kidneys with acute tubular necrosis (ATN) when compared to kidneys with acute rejection (AR). T-cell and antibody mediated rejctions are high cellularity states, therefore ADC maps can be a useful tool in the initial evaluation and longitudinal follow-up transplant recipients. Further study of this modality is needed.



PUB536

Financial Toxicity in Kidney Failure

Lindsey Maclay,[1] Anne M. Huml,[2] Kyle J. Woodward,[1] Miko Yu,[1] Sumit Mohan,[1] Syed A. Husain.[1] *[1]Columbia University Irving Medical Center, New York, NY; [2]Cleveland Clinic, Cleveland, OH.*

Background: Financial toxicity (FT), defined as the combined objective (oFT) and subjective (sFT) economic burden of medical care, has not been explored in end-stage kidney disease (ESKD). We sought to describe the prevalence of FT experienced by patients with ESKD.

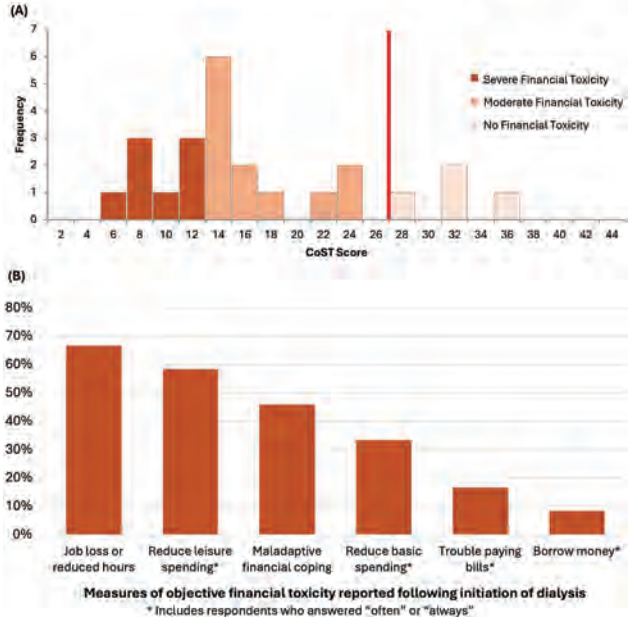
Methods: Cross-sectional survey of patients with ESKD undergoing inpatient dialysis, kidney transplant evaluation, or transplant follow-up at our center. The survey, derived from prior studies, measured sFT via the validated Comprehensive Score for Financial Toxicity (CoST) tool, and oFT via patient-reported changes in employment, spending, or maladaptive financial coping mechanisms. Based on prior literature, sFT was defined as CoST <26 (44-26 none, 14-25 moderate, 0-13 severe).

Results: Among 24 respondents, 19 (79%) were on dialysis and 5 (19%) had a functioning kidney transplant after prior dialysis. Median time since incident kidney failure was 2.5 years (IQR 1.6-6.4). Median age was 55 years (IQR 40-69), 38% were female, 39% self-reported Hispanic/Latino ethnicity, 46% had Black/African American race, and 21% had White race. 14 (58%) had Medicaid primary or dual coverage, while 6 (25%) had private insurance. Median CoST was 14 (IQR 12-22), with 20 respondents (83%) reporting any sFT (COST<26) and 8 (33%) reporting severe sFT (Fig. 1A). 14 reported (58%) household income decrease after dialysis start, with 8 (33%) experiencing >50% reduction. Measures of oFT were common, including 16 (67%) respondents with job loss/reduction and 11 (46%) with maladaptive financial coping mechanisms including withdrawal of emergency savings or utilization of credit card debt (Fig. 1B).

Conclusions: Most patients with ESKD experience FT. Further research is needed to understand risk factors for and consequences of financial toxicity in this population.

Funding: NIDDK Support

Figure 1. Prevalence of financial toxicity among patients with ESKD. (A) CoST scores as a measure of subjective financial toxicity. (B) Measures of objective financial toxicity.



PUB537

BK Nephropathy Treatments in Kidney Transplant Recipients

Vanessa M. Ogungbesan,[1] Nisha Gurung,[1] Dewanshi Maniar,[1] Rosa M. Montero.[2,1] *[1]St George's University of London, London, United Kingdom; [2]St George's University Hospitals NHS Foundation Trust, London, United Kingdom.*

Background: BK virus is a polyoma virus(BKPyV) and an important cause of allograft loss in kidney transplant recipients(KTR). Currently there are no effective treatments for BKPyV with centres using combination therapies strategies. It is unclear whether the increase in BK viraemia is due to immunosuppression(IS), assays or screening. We looked to determine the treatments used for management of BK in our centre.

Methods: An observational retrospective single centre experience looking at BKPyV. All KTR 2001-2023 with detectable BK(plasma/urine) were identified from the electronic renal database(cv5). Maintenance IS regimens were recorded: Tacrolimus(Tac), Mycophenolate Mofetil(MMF), Prednisolone(P), Sirolimus(Sir) and Azathioprine(Aza). BKpyV erradication treatments included; reduction of MMF(1), cessation of MMF(2) reduction in Tac(3), introduction of Ciprofloxacin(Cip)(4), Leflunomide(5), P(6) and cessation of Aza(7).

Results: 7%(37/525) KTR were found to have BKPyV(34 viraemia, 3 viuria) between 2001-2023. 10 female, 27 male. Median age 59yrs(26-84yrs). 9 White, 10 Asian, 7 Black, 4 Chinese, 4 Other, 3 Unknown. Primary kidney disease: IgA 8, CKD 7, FSGS 4, Renovascular 2, T2DM 2, Congenital kidney disease 1, Glomerulonephritis 3, Malignant hypertension 1, APKD 3, SLE 2, Unknown 4. BK occurred following treatment for rejectionx2, 1xdrain removal and 1xureteric stent removal. 3 KTR had biopsy proven BK nephropathy. Peak BKPyV viraemia 2.9 million copies/ml, peak viruria 1.28E+10 copies/ml. BKPyV viraemia median 3mths post-transplant(1mth-8yrs), viuria median 4 months(1mth-12yrs). Treatments included; 2 KTR (1,3), 1 KTR (1,3,4), 7 KTR (1,3,6), 3 KTR (1,3,4,6), 1 KTR (1,3,5,6), 1 KTR (2,3,4), 2 KTR (2,3,6), 8 KTR with (2,3,4,6), 7 KTR (2,3,4,5,6), 1 KTR (2,3,5,6), 1 KTR (2,3,6,7),1 KTR (3), 1 KTR (3,4,6), 1 KTR (3,6) and 1 KTR no changes. Commonest treatment was cessation of MMF, reduction in Tac, Cip ranging from 2-12wks and P with maintenance therapy of Tac+P. 5 KTR had 1 recurrence of BKPyV viraemia, 4 KTR had 2 episodes of recurrence with prolonged treatment with Cip. Remission of BKPyV was between 1mth-12yrs (median 2yrs).

Conclusions: Over 22 yrs our centre has used a variety of treatments for BKPyV. Remission was seen in 28 KTR. The commonest intervention was to stop MMF however, despite these interventions 4 KTR lost their allografts highlighting the ineffective treatments for BK.

PUB538

A Formidable Foe: BK Virus, an Association with Early Cancer Development: A Case Report

Zeeshan Azeem, Prince M. Anand, Adrian Carlson. *Medical University of South Carolina, Lancaster, SC.*

Introduction: Urothelial cancer of the bladder is the most common malignant neoplasm of the urinary system. Kidney transplant recipients have a significantly higher risk of urothelial malignancy compared to the general population; it typically presents about 8.5 years after transplantation. BK-polyoma virus (BKPyV) is a well-established cause of urothelial malignancy in kidney transplant recipients. We present a rare case of urothelial carcinoma of the urinary bladder diagnosed three months after kidney transplantation.

Case Description: A 71-year-old woman underwent a deceased donor kidney transplant (DDKT) due to end-stage renal disease secondary to diabetes mellitus. The intraoperative cystoscopy for ureteral anastomosis showed no evidence of growth in the urinary bladder. However, one month later, at the time of the ureteral stent removal, a papillomatous growth was noted near the site of ureteral anastomosis. Subsequently, a repeat cystoscopy and excisional biopsy revealed urothelial cancer. Concurrently, elevated levels of plasma BKPyV were noted, which continued to rise despite the reduction in immunosuppression. The tumor tissue was positive for SV40 stain, suggesting a possible causal correlation with BKPyV identified in the cancer tissue.

Discussion: Despite the widely known presentation of BKPyV viremia in kidney transplant patients, the presentation of malignancy is typically delayed. This case highlights the need for a high index of suspicion for any bladder lesion in post-transplant patients with elevated levels of BKPyV. Early diagnosis with biopsy and SV 40 immunostaining is crucial for improved patient outcomes.

PUB539

Post-transplant Hospitalization Rates in a Safety Net Hospital

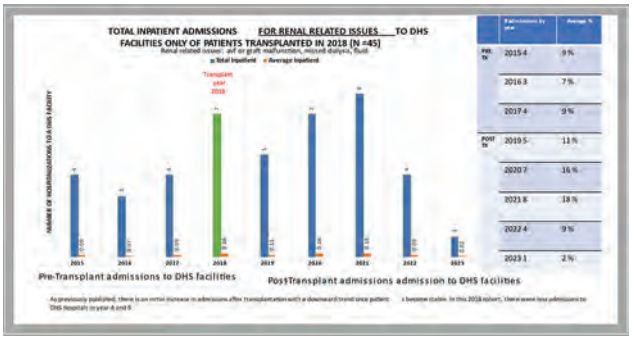
Anuja P. Shah, Ibrahim Elali, Kamyar Kalantar-Zadeh, Lilly M. Barba. *Harbor-UCLA Medical Center, Torrance, CA.*

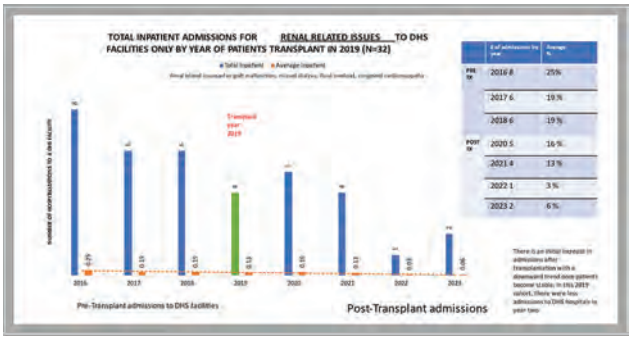
Background: USRDS reports hospitalization rates in ESRD patients in the Medicare population. Post transplantation, admission rates increase and then decrease to below pretransplant levels. It is not known if these trends are consistent in the Medicaid population. Less is known about hospitalization related to dialysis and renal disease.

Methods: Analysis: We retrospectively reviewed the medical records of patients that received a kidney transplant during 2018 and 2019. For 2018 transplants, data collected 3 yrs pre and 5 years post-transplant on 45 patients. For patients transplanted in 2019, data collected 3 yrs pre and 4 years post-transplant on 32 patients. Data was collected on ER visits and hospital admissions for related to their kidney disease only. Non-kidney related admissions were censored as this time overlapped with the COVID pandemic. Censoring COVID related admissions would make this data more comparable to historical data. Only admissions to the County of Los Angeles Hospitals were captured

Results: Both Groups showed an increase in hospitalization rates post-transplant years 1 and 2. For patients transplanted in 2018, hospitalizations decreased by year 4 post-transplantation. For patients transplanted in 2019, hospitalizations decreased by year 3 post-transplant.

Conclusions: Rates of hospitalization post-transplant in patients with lower socioeconomic status mirror hospitalization trends in the Medicare population. This cohort uniquely confirms the trend toward lower hospitalization after the initial years post-transplant in the same group of patients. Only hospitalizations at the safety-net system were captured; these patients were followed closely by the transplant center, and outside hospitalizations were not reported.





PUB540

Anti-human Leukocyte Antigen (HLA) Antibodies in Patients with ESKD on Kidney Transplantation Protocol

Victor M. Xulú Díaz, Elio Perez, Karla Escobar Castro, Ada Noemi Chavez.
Hospital General San Juan de Dios, Guatemala, Guatemala.

Background: Renal transplant is the chosen treatment for the ESRD (End-Stage Renal Disease), so identifying factors possibly associated with complications such as rejection helps to improve renal graft survival.

Methods: Retrospective cross-sectional observational study, 150 files were selected; sex, age, medical records, type of renal transplant protocol, record of infectious processes, as well as records of exposure to sensitization factors were reviewed.

Results: The average age of the parties was 30 years old, the youngest was 13 years old and the oldest was 75 years old; 46.7% were female and 53.3% were male. 71.3% of patients had transfusion exposure, 30% of patients had previous pregnancy exposure and 8% of the parties had a previous transplant record; 5.3% had diabetes mellitus, and 31.3% of the patients had infections. The 64% of patients were on cadaveric transplant protocols, 36% were on living-donor transplant protocols.

Conclusions: The prevalence of anti-HLA antibodies in patients with chronic renal disease undergoing renal transplant protocol at the Hospital General San Juand de Dios was found to be 33.3%. Previous transplant record was associates with anti-HLA antibodies generation in renal transplant protocol patients.

Table 1. Antibody reagent panel

Characteristics	PRA Positive n = 50 (33.3)	PRA Negative n=100(66.7)	p
Age in years, mean (SD)	31.2 (10.87)	30.5(12.63)	0.748
Sex, n (%)			
Female	29 (41.4)	41 (56.6)	0.057
Male	21 (26.3)	59 (73.8)	
Number of transfusions, mean (SD)	1.54 (1.50)	1.47 (1.84)	0.816
Number of pregnancies, mean (SD)	0.828(1.26)	0.878(1.91)	0.901
Protocol type, n (%)			
Cadaveric	27 (26.1)	69 (71.9)	0.104
Living	23 (42.6)	31 (57.4)	
Background			
DM, n (%)			
Yes	5 (62.5)	3 (37.5)	0.118
No	45 (31.7)	97 (68.3)	
Infections, n (%)			
Yes	16 (34.0)	31 (66.0)	0.999
No	34 (33.0)	69 (67.0)	
Risk factors			
Previous transplant, n (%)			
Yes	10 (83.3)	2 (16.7)	<0.001
No	40 (29.0)	98 (71.0)	
Pregnancies, n (%)			
Yes	11 (52.4)	10 (47.6)	0.292
No	18 (36.7)	31 (63.3)	
Transfusions, n (%)			
Yes	39 (36.4)	68 (63.6)	0.252
No	11 (25.6)	32 (74.4)	

SD: Standard Deviation; PRA: Panel- reactive antibody; DM: Diabetes mellitus.

PUB541

Accuracy of Donor-Derived Cell-Free DNA (Dd-cfDNA) Compared with Kidney Allograft Biopsy in the Diagnosis of Allograft Rejection among Adult Filipino Patients in a Tertiary Medical Center

Mae Madeleine N. Ang, Brian Michael I. Cabral, Angel Joaquin M. Amante.
St. Luke's Medical Center - Global City, Taguig, Philippines.

Background: In the Philippines, transplant surveillance primarily involves monitoring common laboratory parameters (creatinine, proteinuria). Allograft biopsy, the gold standard for diagnosing allograft rejection, is not part of surveillance protocols. Donor-derived cell-free DNA (dd-cfDNA) quantifies fragmented DNA that rises in allograft injury. It is non-invasive, has short turnaround time and has been shown to rise prior to laboratory indicators. No study has been done yet among Filipinos involving dd-cfDNA in the diagnosis of allograft rejection since the test became available locally in April 2023.

Methods: This is a cross-sectional descriptive study in a tertiary medical center in the Philippines. All data were obtained from electronic medical records. Rejection discrimination was analyzed through area under the curve (AUC), sensitivity (SN), specificity (SP), predictive values, and likelihood ratios. Histologic changes associated with dd-cfDNA levels of >1% were analyzed similarly. Box and Whisker Plots were used to determine differences in dd-cfDNA mean levels in those with and without rejection and between classes of rejection (ABMR and TCMR).

Results: Dd-cfDNA significantly discriminates allograft rejection vs no rejection (AUC 0.86, SN 72.73%, SP 100%) and ABMR from non-rejection (AUC 0.94, SN 88.89% SP 100%). It did not discriminate TCMR from non-rejection (AUC 0.55, SN 50, SP 40%). dd-cfDNA level of >1% occurred significantly in: Acute, active ABMR rejection; moderate microvascular inflammation; donor specific antibodies; any microvascular inflammation; chronic active ABMR; and severe peritubular capillary multilayering. Mean dd-cfDNA scores for ABMR is significantly higher (p=0.0394***)*** than those without ABMR. There was no difference in mean levels between rejection and non-rejection (p=0.1790) and TCMR versus non-rejection.

Conclusions: Accuracy of dd-cfDNA in diagnosing allograft rejection cannot definitively be concluded based on this study alone. However, findings trend similarly to the DART Cohort and ADMIRAL Study. Dd-cfDNA accuracy values in identifying allograft rejection trend comparably. Mean dd-cfDNA levels in ABMR is significantly higher than in TCMR and in no rejection. Histologic findings associated with dd-cfDNA level of >1% are similar.

PUB542

Kidney Transplant Candidacy in a Patient with Recurrent Infection: Balancing Improved Quality of Life vs. Potential Infection Risk

Marrey Ruby L. Quizon, Ekamol Tantisattamo. *UCI Health, Orange, CA.*

Introduction: In the field of kidney replacement therapy, the definitive management is kidney transplant (KT). While recurrent infection is generally a contraindication for KT, a balance between improved quality of life from KT and increased risk of post-transplant infection can be justified. We report a case of man with recurrent soft tissue infections above the arteriovenous fistula (AVF) site who underwent KT and subsequent AVF removal for infection source control.

Case Description: A 57-year-old man with ESKD who underwent a deceased donor kidney transplant (DDKT) 2 months prior was admitted for management of purulent cellulitis on his left arm AVF. For the past few years, he had chronic issues with this fistula including thrombosis requiring stent placement. He also had episodes of nonpurulent cellulitis over an area of the AVF, managed by vancomycin courses during his dialysis sessions. These episodes had occurred every 3-4 months for the past year. He was originally planned for AVF revision to eliminate infection source, but he received a kidney offer and underwent DDKT. The AVF revision was postponed with a plan to be addressed six months post-transplant. However, around two months post-transplant, he again developed cellulitis over the AVF, but now with purulence. Given the severity of infection in the setting of immunosuppressed state, AVF ligation and removal of the underlying infected stent was performed. He had no systemic symptoms and blood cultures were negative. He recovered well and was discharged with intravenous antibiotics.

Discussion: Our patient had recurrent soft tissue infections over his AVF, suggesting bacterial seeding of the stent or refractory skin infection and failed antimicrobial treatment. While KT improved his survival and quality of life, post-transplant immunosuppressed state contributed to a more severe purulent form of his usual cellulitis overlying a high-flow vascular access, which, while fortunately did not occur for him, may increase the risk of bacteremia and associated systemic sequelae. Patients with a history of prior infection should receive close monitoring and definitive treatment to get rid of the source of recurrent infections ideally prior to KT. However, KT while the infection is controlled and then followed by infection source elimination can be considered in selected patients.

PUB543

Emphysematous Pyelonephritis as a Presentation of Delayed Venous Allograft Thrombosis

Marrey Ruby L. Quizon, Nyein Nyein Htun, Ekamol Tantisattamo.
University of California Irvine, Irvine, CA.

Introduction: While transplant allograft thrombosis commonly manifests during the immediate post-transplant period, a delayed onset may occur and lead to allograft loss. We present a case of a kidney transplant (KT) recipient who presented with anuric acute kidney injury and emphysematous pyelonephritis.

Case Description: A 45-year-old woman with ESKD who underwent a deceased donor kidney transplant 1 month prior presented with nausea and vomiting for two days. She had been doing well post-KT with a serum creatinine of 1.3 mg/dL 1 week prior. She had anuric AKI over 24 hours prior to admission with a creatinine of 5 mg/dL. An abdomen and pelvic CT scan showed severe emphysematous pyelonephritis of the transplant kidney and a 7 cm air-fluid collection in the abdomen, contiguous with the transplant kidney. Within hours after admission, she progressed to septic shock. Allograft function remained unimproved despite initial management of antibiotics and fluids. Therefore, transplant allograft nephrectomy was performed to eliminate the infection source. Pathology showed liquefactive necrosis and emphysematous changes of the transplant kidney, and thrombosis of the transplant renal vein. Hypercoagulable work-up is pending and she reinitiated hemodialysis and is referred for pretransplant evaluation for the second KT.

Discussion: Vascular complication is a major concern during the acute post-transplant period. But a late onset of the venous allograft thrombosis may occur and lead to allograft loss complicated by severe life-threatening infections like emphysematous pyelonephritis. Early diagnosis by imaging and transplant allograft nephrectomy are warranted to reverse immunosuppressed status and avoid mortality.

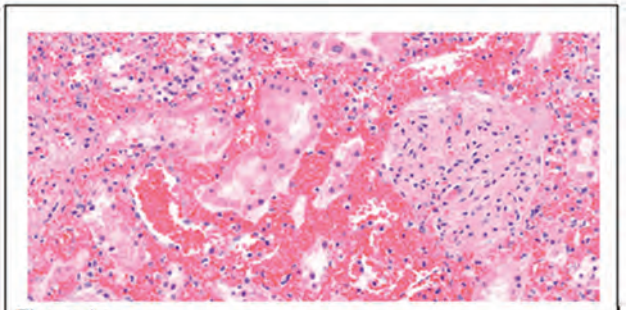


Figure 1a

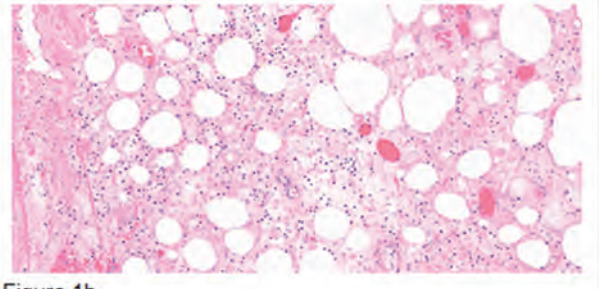


Figure 1b

Figure 1: Transplant kidney biopsy shows a) glomeruli, necrotic tubule and hemorrhage and b) perinephric fat necrosis.

PUB544

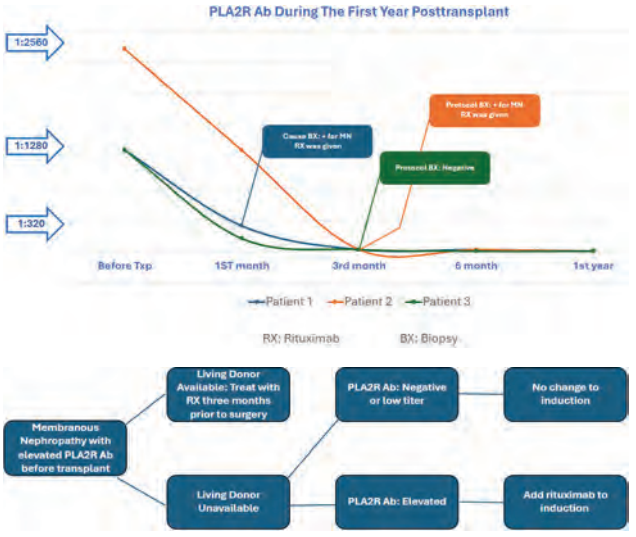
Management of Primary Membranous Nephropathy (PMN) after Transplant

Fadee Abu Al Rub,[1] Sana J. Shaikh,[2] Krista L. Lentine.[1] [1]*Saint Louis University, St Louis, MO;* [2]*University of California Davis, Davis, CA.*

Introduction: PLA2R Ab were identified as the underlying cause in about 70% of PMN cases. After transplant (TXP), PMN recurrence rate is about 31%. A more aggressive disease and a higher level of PLA2R Ab in native kidneys can predict recurrence.

Case Description: We reviewed records of 6 kidney TXP patients with biopsy (Bx) proven MN, 3 of them had negative PLA2R Ab at the time of surgery, and had no complications. We followed the other three for one-year and here we report their course: All patients received Thymo for induction, and their maintenance regimen consisted of: Tacrolimus, MMF +/- and prednisone. One patient had a 3-month protocol biopsy which showed PLA2R-positive MN despite intact renal function and negative serum PLA2R titers. He received Rituximab (RX) 1 gm x 2 doses 14 days apart. Another patient had a cause biopsy for elevated cell free DNA at the end of the first month, and it showed MN recurrence. He had high PLA2R titers and mild proteinuria. He was treated with RX as above. The third patient had a protocol biopsy which was negative, and no alteration in immunosuppression needed to be made.

Discussion: Since It was observed that patients with positive anti-PLA2R Ab testing before TXP, who continued to have high titers despite induction and maintenance immunosuppression, were likely to develop an early recurrence of MN. It is reasonable to consider pre-emptive Rituximab: First, at the time of TXP in those with high titers of anti-PLA2R Ab, and in the first month post-transplant if the titers of anti-PLA2R ab remain elevated. We also suggest treating a living donor recipient candidate before surgery, if his PLA2R level is elevated, to avoid recurrence. It is noted here too that cell-free DNA technology was helpful in detecting MN recurrence, as it triggered the biopsy decision. More studies are needed to evaluate its sensitivity in screening for glomerulonephritis recurrence in an allograft.



PUB545

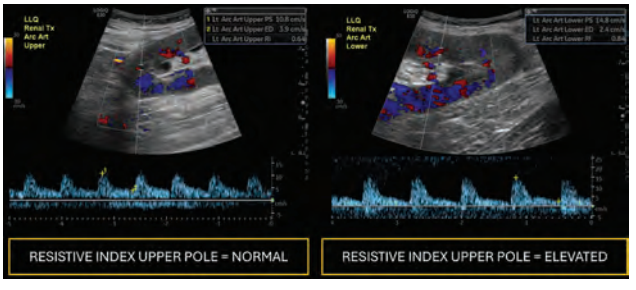
Value of Mercaptoacetyltriglycine (MAG3) Scintigraphy in Functional Assessment of Kidney Transplant: A Case Study

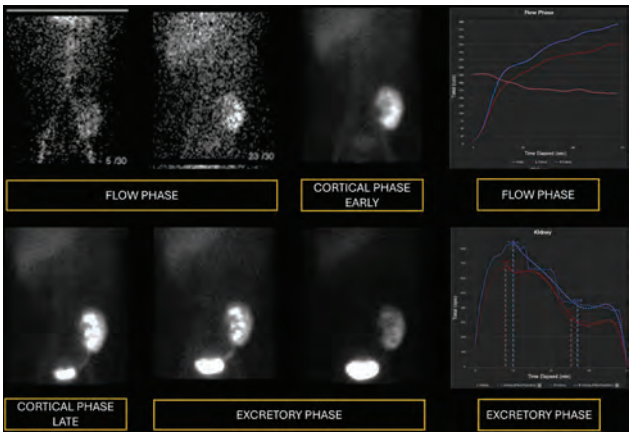
Gaelle Haddad, Akash Sharma. *Mayo Clinic in Florida, Jacksonville, FL.*

Introduction: Post-renal transplant malfunctions, such as acute tubular necrosis (ATN), graft rejection, infection, and ischemic damage can be challenging to differentiate due to overlapping symptoms. Accurate diagnosis and management typically require multiple imaging modalities and biopsies. MAG-3 renal scintigraphy may offer complementary renal parenchymal function assessment. We present a case of a 33-year-old woman with a transplanted kidney with complications. MAG-3 scintigraphy provided meaningful functional corroboration of inferred ultrasound findings, with limited CT assessment.

Case Description: A 33-year-old woman with a donor kidney transplant experienced recurrent urinary tract infections after transplant. During routine follow-ups, a renal biopsy showed borderline cellular rejection, treated with steroids. Progressive creatinine level increase warranted a full work up; imaging revealed mild hydronephrosis, and cystoscopy was suggestive of vesicoureteral reflux. A renal biopsy showed mesangial expansion without recurrent rejection. Functional assessment with MAG-3 scintigraphy revealed regional abnormality in the lower half of the kidney, suggesting regional dysfunction. A contemporaneous ultrasound demonstrated elevated regional resistive index in the lower pole, corroborating the regional dysfunction.

Discussion: This case shows value of MAG-3 scintigraphy in functional assessment of kidney transplants. A regional abnormality such as in this case is atypical, and can point to uncommon underlying pathology, such as infection or traumatic/iatrogenic vascular insult and not ATN. Scintigraphy can yield a more expansive differential diagnosis and is complementary to other modalities such as US.





PUB546

The Silent Invader, Cytomegalovirus Nephritis: A Rare Presentation in Early Post-transplant Period

Abinaya Srikanthan, Arjun L. Kalaria, Rajil B. Mehta. *UPMC, Pittsburgh, PA.*

Introduction: Cytomegalovirus (CMV) is a formidable pathogen and an important cause of morbidity and mortality among transplant recipients. Among its deleterious manifestations, CMV nephritis emerges as a significant complication, with profound implications on allograft function and outcomes. This is particularly true in those who are CMV seronegative and receive an allograft kidney from a CMV seropositive donor are particularly high risk (HR). We present a case of a 33-year-old kidney transplant recipient with an unusual early presentation of CMV nephritis.

Case Description: A 33-year-old M with end stage kidney disease (ESKD) secondary to presumed hypertension, status post deceased donor kidney transplant (37 yo donor, CMV HR, EBV R+) in 09/2023, presented with an allograft acute kidney injury (AKI) 3 months post-transplant. His immediate post-transplant course was uncomplicated. He was maintained on valgancyclovir prophylaxis dosed per eGFR for CMV HR. In January 2024 he presented with an allograft AKI, labs were relevant for a serum creatinine (Cr) of 7.1 (baseline Cr 2 mg/dl) and a CMV PCR level of 414 IU/mL. A kidney biopsy performed revealed glomerulitis and interstitial nephritis with positive CMV immunostaining, and borderline acute T cell mediated rejection. As per infectious disease recommendations, he was treated with Maribavir 400mg BID x 8 weeks for refractory CMV nephritis and immunosuppression was lowered. Response to treatment was monitored by weekly CMV PCR levels. CMV viremia resolved on treatment, but he represented with nephrotic range proteinuria (persistent protein excretion >3.5 gm/day). A repeat biopsy performed in April 2024 revealed acute antibody mediated rejection (ABMR) with no evidence of CMV nephritis. He was found to have new donor specific antibodies and is currently undergoing treatment with plasmapheresis and remains on Maribavir with no indication for dialysis.

Discussion: CMV nephritis is a serious complication in renal transplant recipients. This is a rare presentation of CMV nephritis as he presented with low copies of CMV. Nephrotic range proteinuria in the setting of CMV nephritis is also a rare presentation. His ABMR was likely an unintended consequence of decreasing immunosuppression during treatment of CMV nephritis. Appropriate prophylaxis and early detection of CMV infection is particularly important in CMV HR transplant patients.

PUB547

Comparison of Estimated Glomerular Filtration Rate in Mexican Kidney Transplant Recipients

Samantha I. Verdugo,[1] Milagros M. Flores Fonseca,[1] Alejandro Garcia-Rivera,[1] Omar H. Sanchez-Vazquez,[1] Luis A. Camacho-Murillo,[1] Sandra F. Velasco.[2] *[1]Instituto Mexicano del Seguro Social Delegacion Jalisco, Guadalajara, Mexico; [2]Universidad de Guadalajara Centro Universitario de Ciencias Exactas e Ingenieria, Guadalajara, Mexico.*

Background: Assessment of glomerular filtration rate (GFR) is important in the follow-up of patients after receiving a kidney transplant (KT). Several studies have evaluated the performance of based creatinine eGFR-equations in KT. The purpose of our study was to compare the two current main eGFR-equations, MDRD and the CKD-EPI 2021, in Mexican KT recipients (KTR).

Methods: For each kidney transplant recipient, we collected data on age, gender, serum creatinine, eGFR (mL/min/1.73m2), maintenance immunosuppression who were under follow up between June 2023 and May 2024 from the HGRl 110 Oblatos, IMSS. For all patients, race was chosen “not African-American” and eGFR was calculated using the MDRD and CKD–EPI formulas.

Results: Overall, 98 participants were included in the study, in whom 294 eGFR values were measured and estimated. Mean age 37.33 SD ± 10.59, 68% male and a mean time from transplantation to GFR evaluation was 10.43 years ± 6.43 years. The mean MDRD eGFR was 61.78 ± 22.57 mL/min/1.73 m^2 and mean CKD EPI eGFR was 71.47 ± 24.52 mL/min/1.73 m^2. When analyzed according to gender or age groups none significant were observed in terms of age, creatinine or eGFR. When correlation analysis was performed, there was a negative low correlation between the MDRD and gender (R=-0.21, p = 0.038) and a strong positive correlation between eGFR equations (R= 0.975, p<0.01). The combined CKD-EPI and MDRD equation are in a Bland Altman plot (Figure 1A), with the bias and its 95% CI.

Conclusions: Although there is a strong association between these creatinine-based equations in estimating GFR in Mexican kidney transplant patients. We need to confirm in our population, if the rise of creatinine provides outcome prediction in KT or if our attention should move forward to other markers in the reinforcement of eGFR power.

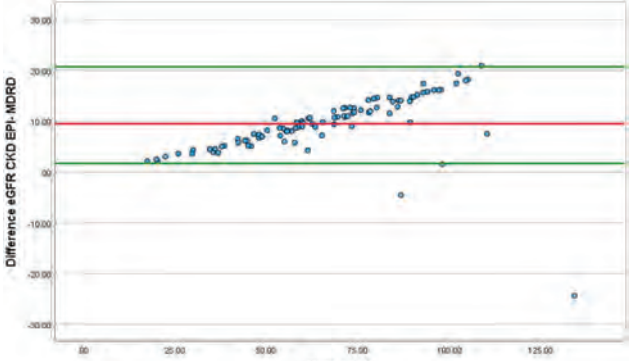


Figure 1. Bland- Altman plot with absolute bias (CI) between eGFR for CKD-EPI and MDRD equations

PUB548

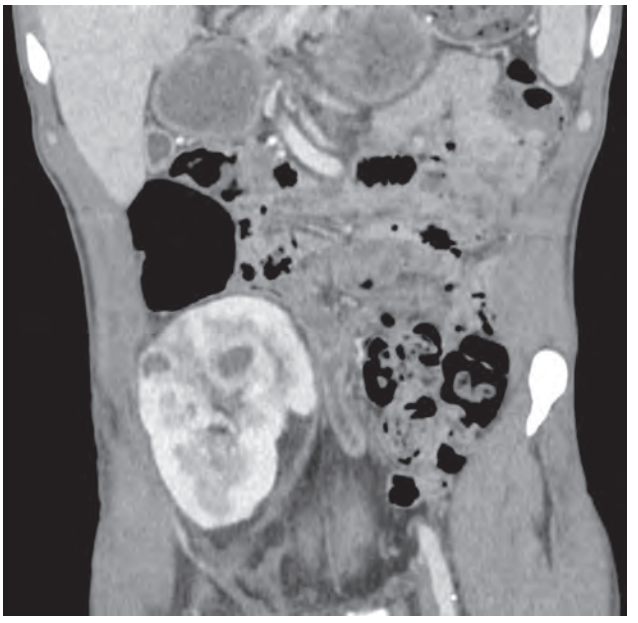
Multiple Embolic Strokes in Kidney Transplant Recipient Due to Kidney Allograft Abscesses after Urinary Tract Infection (UTI)

Dinah Goodman, Ao Wang, Mary C. Mallappallil, Muhammad Azhar, Isha Puri. *New York City Health and Hospitals Corporation, New York, NY.*

Introduction: Intrarenal and perinephric abscess formations are infrequent infectious complications in kidney allograft recipients. There have been reported cases of abscesses within the allograft but no reported cases of ischemic embolic strokes from such abscesses

Case Description: 63 year old male post deceased donor kidney transplant presented with altered mental status, fever and leukocytosis. He tested positive for COVID-19 at an outside hospital 2 days prior. Because of febrile illness blood cultures and urine cultures were drawn which both resulted positive for Enterococcus faecalis. He was initially emperically treated for bacterial/viral meningitis but therapy was de-escalated after results from a lumbar puncture were negative and urine and blood cultures were positive for E. Faecalis. After 5 days of appropriate antibiotic therapy he was afebrile with improving leukocytosis however continued to have altered mentation, hence, a brain MRI was done which showed multiple bilateral ischemic strokes in anterior left pons, medial right occipital lobe and medial temporal lobes bilaterally likely embolic in nature. A transesophageal echocardiogram did not show any vegetations. A kidney allograft ultrasound was done which showed a 3.0x1.3x3.1 cm complex fluid collection within the right lower quadrant of kidney midpole, the findings were suspicious for abscess. He then underwent a CT Abdomen and pelvis which showed multiple rim-emhancing fluid collections measuring up to 3.6 cm concerning for pyelonephritis with renal abscess. Due to lack of a tranplant surgeon at our facility he was then transferred out to his transplant center for drainage of the abscess

Discussion: A renal allograft abscess is a relatively rare condition. Embolic CVA from bacterial emboli of renal abscess source has not been reported so far to the best of our kowledge. Appropriate antimicrobial therapy and drainage are recommended for treating renal abscesses



PUB549

The First Case in Uzbekistan of Successful Pregnancy and Natural Birth in a Patient on Dialysis

Olimkhon N. Sharapov,[1,2] Botir Daminov,[2,1] Sabit Azizov.[1] *[1]Republican Specialized Scientific Practical Medical Center of Nephrology and Kidney transplantation, Tashkent, Uzbekistan; [2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.*

Introduction: Improvement of hemodialysis services in Uzbekistan, in particular the transition to single use of disposable dialyzers from reusable ones in 2019, has significantly improved the quality of life of dialysis patients. The reproductive system in these patients also improved as a result of this; one such patient experienced pregnancy and subsequent natural childbirth for the first time in the history of Uzbekistan.

Case Description: Patient A. 39 years old, with ESRD and a detected pregnancy of 18 weeks. History: 17 years ago, she fell ill with glomerulonephritis, has been receiving HD for 9 years. Obstetric history-has 1 normal birth and 1 abortion at 11 weeks. After experiencing nausea, vomiting, malaise and abdominal discomfort, she was sent for screening to determine if she was pregnant. Based on the results of two consecutive screenings, pregnancy was detected, 18 weeks, without pathologies and with progression. At 29-30 weeks of pregnancy, she was hospitalized. During the examination: BP-100/60 mmHg, HR-80 beats per minute, daily diuresis 2.0-2.5 liters. CBC: Hb-81, erythrocytes-2.7, leukocytes-8.5, platelets-192, ESR-63. Proteinuria-0.3. Blood: urea-6.9, creatinine-284, total protein-63, ferritin-2826.2, calcium-2.01, phosphorus 0.75, cholesterol-6.3, glucose-4.2, PTH-445.8 pg/ml, Vitamin D - 10.2 ng/ml. Hormones: Chorionic gonadotropin - 263240 mlU/ml, free estriol - 2.82. Tests for HIV, hepatitis B, C, and TORCH infections showed negative results. Ultrasound revealed moderate hepatomegaly, chronic cholecystitis, bile stagnation and bilateral shrinkage of both kidneys. On 09/07/2022, after hemodialysis session at 14:45 the patient was transferred to the maternity ward, at 16:50, a live premature boy was born, weighing 1554 g, length 42 cm, with an Apgar score of 5/7 points. A premature newborn corresponds to a gestational age of 29 weeks. After 5 days, she was discharged home. The child stayed in the neonatal pathology department. Incubator nursing, respiratory therapy NCPAP, treatment - Curasurf, antibacterial therapy (ampisul, merkacin) were carried out. After his condition improved, he was safely discharged home. Now, the health of mother and child is satisfactory. The child grows and develops.

Discussion: This case indicates that improving the quality of dialysis services improves the reproductive system of dialysis patients.

PUB550

Global Trends in Endothelin A Receptor Antagonist Research for Kidney Disease Management

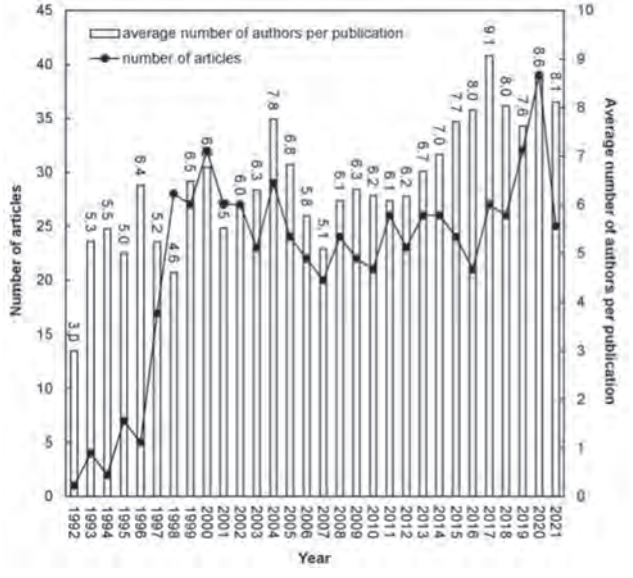
Pajaree Krisanapan,[1,2] Supawadee Suppadungsuk,[2] Charat Thongprayoon,[2] Tibor Fulop,[4,3] Karim Soliman,[3] Jing Miao,[2] Wisit Cheungpasitporn.[2]
[1]Thammasat University Hospital, Khlong Nueng, Thailand; [2]Mayo Clinic Minnesota, Rochester, MN; [3]Medical University of South Carolina, Charleston, SC; [4]Ralph H Johnson VA Health Care System, Charleston, SC.

Background: Chronic kidney disease (CKD) is a growing global health concern, with millions of people affected worldwide. Endothelin A (ETA) receptor antagonists have shown promise in slowing CKD progression by reducing proteinuria. This study examines the evolution of ETA receptor antagonist research in CKD over the past 30 years, including collaboration patterns, author contributions, and publication trends.

Methods: We conducted a bibliometric analysis of research papers published from 1992 to 2023, focusing on kidney diseases and ETA receptor antagonists. We used specific keywords to identify relevant articles and assessed author contributions using the Y-index, which combines publication numbers and impact.

Results: The findings show a significant increase in collaborative research efforts for ETA Receptor antagonist research in kidney diseases, as evidenced by a rise in the average number of authors per article. The United States emerged as a leading contributor to this research area, with the University of Groningen standing out as a major hub for collaborative projects. Among researchers, H.J.L. Heerspink was recognized for his extensive contributions. Of note, there has been a steady increase in the annual publication rate, culminating in a significant peak in the most recent period.

Conclusions: ETA receptor antagonist research in CKD is characterized by growing global collaboration and a strong focus on understanding and treating this disease. With leading authors and institutions driving research, the future of ETA receptor antagonist therapy for CKD looks promising. Further studies are needed to fully explore the potential of ETA receptor antagonists in slowing CKD progression and improving patient outcomes.



PUB551

Vascular Aging (VA) Analyzed by Dermal Autofluorescence (DA) on the Risk of Initiating Renal Replacement Therapy (RRT) and Mortality in Patients with Nondialysis-Dependent CKD Stages 1 to 5

Secundino Cigarran,[1] Ana Maria Sanjurjo Amado,[2] Amaia Santidrián Novo,[1] Raquel Vázquez Rodríguez,[1] Jose Rios,[3] Miguel Perez Fontan,[4] Guillermina Barril.[5] *[1]Hospital Ribera Polusa, Lugo, Spain; [2]Hospital Publico da Mariña, Burela, Spain; [3]Hospital Clinic de Barcelona, Barcelona, Spain; [4]Complexo Hospitalario Universitario A Coruna, A Coruna, Spain; [5]Fundacion Investigaciones Biomedicas, Madrid, Spain.*

Background: CKD is age-related disease that displays multiple features of accelerated ageing and considered as an early aging process measured through VA. Aim is to examine VA as risk for RRT and mortality in CKD stage 1-5ND.

Methods: Oservational, prospective, longitudinal study, 1064 pts followed 14 years, 59.8% male, 40.2% female.X age 72.07±14.13 yr. Markers of nutrition, inflammation, and cardiovascular risk evaluated. Kidney Failure Risk Equation (KFRE) for CKD progression. Mortality was considered for all causes. Frailty by Clinical Frailty Scale. VA from advanced glycation end products (AGEs) by AGEs Reader (Diagnoptics Technologies BV, Groningen, the Netherlands). Koetsier formula. (Vascular Age = AFD - 0.83/0.024). Tertil low (<73 yrs, 594 pts), medium (73-107 yrs, 509 pts), and high (>107 yrs, 501 pts). Lowest tertile was reference.

Results: VA 20.05±31.85 years over chronological. Significance with Charlson comorbidity, Frailty, higher 5-year mortality, KFRE, FRAX for osteoporotic fracture, and risk of hip fracture. VA > 15.6 yrs was independent risk for RRT or death as competitive event (Log Rank; p < 0.001), mean time to RRT 15.08 yrs (50% 15.33 years). Conversely, VA<15.6 yrs mean time to RRT 21.30 years (50% 28 years) Figure 1. Mortality low tertile 9.6% i16.3% medium and 30.6% high (Log Rank; p < 0.001, HR 2.70; 95% CI 1.669-4.399; p < 0.001) Figure 2.

Conclusions: VA>15.6 years start RRT 13 years earlier and 50% higher mortality than <15.6 yrs.VA is a predictor of RRT and mortality. DA is a useful tool for risk RRT & mortality in CKD.

Funding: Private Foundation Support

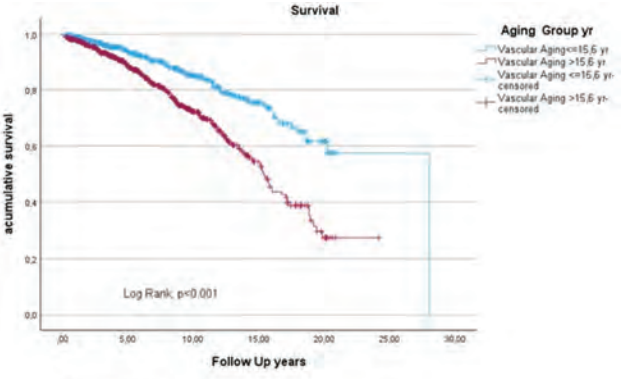
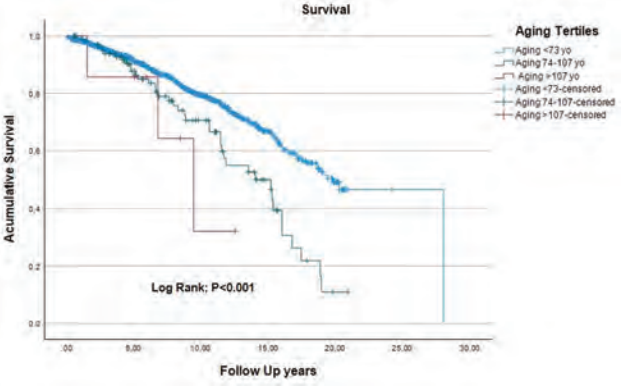


Fig 1 RRT risk in Vascular Age groups



PUB552

Frequency of CKD Patient Referrals to Nephrology Clinics Using the Kidney Failure Risk Equation at Kaiser Permanente Northern California

Jessenia A. Contreras, Jessica B. Lapasia. *Kaiser Permanente Northern California Region, San Francisco, CA.*

Background: Early detection of chronic kidney disease (CKD) is a fundamental goal in caring for patients with kidney disease. Timely implementation of a CKD care plan for patients, and regular follow up with a nephrology care team, can help delay the onset of end-stage kidney disease (ESKD). Referrals to a nephrologist for CKD care are often placed by primary care providers (PCPs), prompted by certain lab abnormalities. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that patients with CKD stage 3B through 5 be referred to a nephrologist. Although early education about healthy lifestyle habits and ESKD treatment options has been shown to improve patient outcomes, a subset of patients continues to have delayed detection of CKD. The kidney failure risk equation (KFRE), which is a four-variable risk equation, is an added tool to help identify patients at risk for CKD progression. In 2021, the KFRE was incorporated into PCP referral guidelines at Kaiser Permanente Northern California (KPNC). This study aims to evaluate the frequency of CKD referrals in the three years before and after the incorporation of KFRE.

Methods: A KPNC statistical analyst will help collect data using the following inclusion criteria: patients ≥18 years old, with at least one estimated Glomerular Filtration Rate (eGFR) < 45 ml/min/1.73m2 prior to the initial referral to KPNC Nephrologist, and at least two eGFR < 60 ml/min/1.73m2 three months apart in the 3 years prior to referral. Data will be collected over a 6-year period, 3 years before and after KFRE incorporation. Statistical analysis will be performed by the analyst.

Results: This is an ongoing study, currently in the data collection phase. Projected completion of data collection and evaluation will be by August/September 2024.

Conclusions: There is wide variability in the referral of patients with CKD to a nephrologist. The KFRE is an important tool that can help identify patients at higher risk for progression of CKD. By incorporating the KFRE into PCP referral guidelines at KPNC, the number of appropriate CKD referrals to nephrology was enhanced. These patients can then have access to available treatments to help slow their progression to ESKD.

PUB553

Association between Multimorbidity and the Risk of Major Adverse Cardiovascular Events and Mortality in Patients with Nondialysis-Dependent CKD

Kazuhiro Okamura,[1] Shigeru Tanaka,[1] Hiromasa Kitamura,[2] Kazuhiko Tsuruya,[3] Takanari Kitazono,[1] Toshiaki Nakano.[1] *[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Department of Nephrology, Nara Medical University, Kashihara, Japan.*

Background: Multimorbidity, defined as the coexistence of two or more comorbidities, is associated with poor life prognosis and the onset of cardiovascular disease among the general population. It remains unclear whether the accumulation of comorbidities, including non-cardiovascular comorbidities, is associated with poor prognosis in patients with chronic kidney disease (CKD), a high-risk group for cardiovascular risk.

Methods: We investigated 4,420 patients with non-dialysis CKD who participated in the Fukuoka Kidney disease Registry (FKR) study and had confirmed comorbidities at the time of research registration. We defined 23 comorbidities, including hypertension, diabetes, and dyslipidemia. Patients were divided into three groups based on the number of comorbidities: one or fewer (1265 patients), two (1205 patients), and three or more (1,950 patients). We assessed the association between the number of comorbidities and the incidence of major adverse cardiovascular events (MACE) (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) and all-cause mortality using the Cox proportional hazards model.

Results: During the five-year observation period, 229 patients developed MACE, and 456 died. The multivariable-adjusted hazard ratios for MACE and all-cause mortality were significantly higher (2.90 and 2.20, respectively) in the group with three or more comorbidities compared to the group with one or fewer comorbidities.

Conclusions: In non-dailysis CKD patients, the multimorbidity is associated with an increased risk of MACE and all-cause mortality. The accumulation of all types of comorbidities, not just cardiovascular comorbidities, was found to be associated with poor outcomes in CKD patients as their number increased.

PUB554

SGLT2 Inhibitor Prescribing Practices in a Large Health System

Robert Kosalka, Fitsum T. Hailemariam. *Thomas Jefferson University Sidney Kimmel Medical College, Philadelphia, PA.*

Background: Sodium-glucose transport protein 2 (SGLT2) inhibitors are a class of medication that act on the renal proximal convoluted tubules to reduce the reabsorption of glucose. They were primarily used in diabetics to assist with glucose control and are now approved for the treatment of heart failure and chronic kidney disease (CKD). Once started on SGLT2 inhibitors, patients must be monitored for a decline in renal function especially if they are also put on angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and/or diuretics, as they can lead to decreases in kidney function and dehydration/hypotension.

Methods: This is a retrospective cohort study of patients who were prescribed SGLT2 inhibitors in the Jefferson Health System. Data was sourced from the electronic medical record (EMR) using a customized query that returned the most recent 3 glomerular filtration rate (GFR) measurements, diagnostic codes, prescribed ACEi or ARB therapy, and prescribed diuretics.

Results: Eleven thousand and eighteen adults with SGLT2 inhibitors in their medication lists were analyzed. Of these, 5956 (54.1%) patients had no GFR on record, 8744 (79.4%) were diagnosed with diabetes, 7152 (64.9%) were on concurrent ACEi/ARB therapy and 3579 (32.5%) were on diuretics.

Conclusions: SGLT2 inhibitors have become the standard of care in patients with diabetes, CKD, cardiovascular disease, and heart failure. However, the proportion of patients in our study with CKD and heart failure was lower than expected, 6.9% and 1.9%, respectively. The concurrent use of ACEi/ARB medications and diuretics can be safe provided there is adequate monitoring of the fluid status and renal function. A substantial proportion (54.1%) of these patients do not have kidney function recorded in the EMR. This analysis highlights the need for improved clinical practices to ensure all patients are being safely monitored.

GFR > 60mL/min	GFR <. 60mL/min	No GFR on record	Diagnosed with heart failure	Diagnosed with diabetes mellitus	Prescribed ACEi/ARB	Prescribed diuretic
4300 (39.0%)	762 (6.9%)	5956 (54.1%)	213 (1.9%)	8744 (79.4%)	7152 (64.9%)	3579 (32.5%)

PUB555

Impact of Smoking Intensity and Initiation Age on Cardio-Cerebrovascular Disease and Mortality Risk in Patients with CKD: A Nationwide Population-Based Cohort Study

Sehyun Jung,[1] Seong Geun Kim,[6] Semin Cho,[4] Hyuk Huh,[8] Jung Hun Koh,[3] Jeongmin Cho,[4] Minsang Kim,[3] Min Woo Kang,[3] Eunjeong Kang,[3] Sehoon Park,[3] Yaerim Kim,[5] Dong Ki Kim,[3] Kyungdo Han,[7] Soojin Lee.[2] *[1]Gyeongsang National University Hospital, Jinju, Republic of Korea; [2]Eulji University Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-do, Republic of Korea; [3]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [4]Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Gyeonggi-do, Republic of Korea; [5]Keimyung University Daegu Dongsan Hospital, Daegu, Republic of Korea; [6]Inje University Sanggye Paik Hospital, Nowon-gu, Seoul, Republic of Korea; [7]Soongsil University Department of Statistics and Actuarial Science, Dongjak-gu, Seoul, Republic of Korea; [8]Inje University Busan Paik Hospital, Busan, Busan, Republic of Korea.*

Background: Tobacco use is a significant modifiable risk factor for numerous diseases. While previous research had shown the adverse health outcomes related to smoking, the impact of smoking initiation age and intensity on chronic kidney disease (CKD) patients remains further investigation.

Methods: We conducted a retrospective cohort study with National Health Insurance Database of South Korea, encompassing 652,223 adults aged 20 and above, who underwent national health screening in 2009. Participants with CKD were identified, and their smoking status, smoking initiation age, pack-years, and clinical outcomes were assessed. Cox regression analysis was employed to investigate the association between smoking parameters and the risk of cardio-cerebrovascular diseases (CCVDs) and all-cause mortality, adjusting for potential confounders.

Results: The risks of CCVDs and all-cause deaths according to the smoking initiation age and pack years were assessed. Among CKD patients, higher pack-years and younger smoking initiation ages were associated with elevated risks of CCVDs and all-cause mortality. Participants with pack years < 20 and smoking initiation age below 20 exhibited an increased risk of all-cause death (HR 1.83; 95% CI 1.67-2.00). Among high-risk groups (with 30, 40, and 50 pack years), those with smoking initiation age below 20 showed elevated risk of CCVDs and all-cause death (Figure 1).

Conclusions: Our findings highlight the importance of smoking cessation in CKD patients, as early initiation and higher intensity of smoking are associated with heightened risks of CCVDs and all-cause mortality. Encouraging smoking cessation, particularly in younger individuals, may mitigate the burden of cardiovascular diseases and mortality among CKD population.

Figure 1. Risk of CCVDs and all-cause deaths according to pack-year and smoking age

	N	MI or Stroke	Duration	Incidence rate (/1000PY)	Univariable model	Multivariable model	Death	Duration	Incidence rate (/1000PY)	Univariable model	Multivariable Model*
Non-smoker	402039	20093	3070831.47	3.627	1 (ref.)	1 (ref.)	58202	3639667.07	10.496	1 (ref.)	1 (ref.)
Pack-year < 20 & smoking age < 20	30586	270	282669.41	0.9552	0.27 (0.13, 0.55)	1.14 (1.008, 1.291)	498	285590.34	1.7561	0.167 (0.153, 0.182)	1.832 (1.674, 2.006)
Pack-year < 20 & smoking age ≥ 20	126213	4758	1132742.43	4.2004	0.746 (0.725, 0.77)	1.15 (1.109, 1.193)	8747	1148445.27	7.6097	0.726 (0.709, 0.743)	1.142 (1.102, 1.195)
Pack-year ≥ 20 & smoking age < 20	19833	1273	167284.3	7.6098	1.354 (1.279, 1.433)	1.744 (1.641, 1.853)	2515	171496.78	13.4831	1.292 (1.239, 1.347)	1.781 (1.704, 1.863)
Pack-year ≥ 20 & smoking age ≥ 20	75650	5226	619036.21	10.0376	1.791 (1.741, 1.843)	1.367 (1.321, 1.413)	12478	640392.59	18.4849	1.87 (1.833, 1.908)	1.352 (1.32, 1.385)
Pack-year < 30 & smoking age < 20	33243	332	311567.87	1.0647	0.247 (0.245, 0.251)	1.282 (1.171, 1.403)	946	315350.17	2.6621	0.233 (0.227, 0.27)	1.735 (1.621, 1.855)
Pack-year < 30 & smoking age ≥ 20	161805	7196	1440126.61	4.9949	0.877 (0.854, 0.901)	1.205 (1.167, 1.245)	15215	1464968.99	9.0207	0.861 (0.844, 0.878)	1.21 (1.182, 1.258)
Pack-year ≥ 30 & smoking age < 20	11479	1011	94885.83	10.6561	1.886 (1.734, 1.99)	1.827 (1.709, 1.954)	1367	99956.55	18.6781	1.794 (1.712, 1.879)	1.815 (1.728, 1.906)
Pack-year ≥ 30 & smoking age ≥ 20	38038	3878	321852.05	12.6484	1.518 (1.348, 2.259)	1.379 (1.326, 1.435)	5030	324879.87	24.6553	2.372 (2.316, 2.43)	1.648 (1.591, 1.706)
Pack-year < 40 & smoking age < 20	43096	404	395900.44	2.0369	0.341 (0.336, 0.347)	1.38 (1.28, 1.487)	1479	398619.34	3.7103	0.353 (0.335, 0.372)	1.789 (1.675, 1.868)
Pack-year < 40 & smoking age ≥ 20	182480	8832	1634763.41	5.5005	0.978 (0.954, 1.003)	1.254 (1.196, 1.275)	16487	1643834.51	10.0274	0.957 (0.939, 0.974)	1.228 (1.202, 1.255)
Pack-year ≥ 40 & smoking age < 20	6625	759	54033.26	18.8717	2.436 (2.264, 2.622)	1.915 (1.774, 2.068)	1334	54667.78	29.5407	2.265 (2.144, 2.392)	1.802 (1.702, 1.907)
Pack-year ≥ 40 & smoking age ≥ 20	17583	2102	137013.24	16.5416	2.756 (2.638, 2.884)	1.581 (1.518, 1.653)	4738	144014.35	32.8986	3.38 (3.285, 3.477)	1.629 (1.565, 1.456)
Pack-year < 50 & smoking age < 20	45836	3024	419345.14	2.4439	0.436 (0.407, 0.462)	1.484 (1.359, 1.556)	1839	422382.75	4.3487	0.414 (0.395, 0.434)	1.776 (1.69, 1.867)
Pack-year < 50 & smoking age ≥ 20	192329	10009	1694228.8	5.9077	1.05 (1.026, 1.076)	1.251 (1.214, 1.29)	18763	1728291.16	10.8501	1.037 (1.019, 1.055)	1.241 (1.215, 1.268)
Pack-year ≥ 50 & smoking age < 20	3885	519	30608.56	16.956	3.026 (2.775, 3.301)	1.961 (1.797, 2.13)	974	32404.37	30.0577	2.901 (2.725, 3.092)	1.794 (1.681, 1.912)
Pack-year ≥ 50 & smoking age ≥ 20	7534	975	57949.85	16.8318	3.027 (2.839, 3.228)	1.359 (1.265, 1.447)	2462	60857.7	40.4654	3.948 (3.79, 4.112)	1.648 (1.402, 1.528)

*Multivariable model was adjusted for age, sex, alcohol consumption, regular physical activity, BMI, eGFR and metabolic syndrome.

PUB556

An Application Study of the Simple Insulin Sensitivity Index for the Assessment of the Level of Insulin Resistance in People with Different Kidney Function

Guang Yang,[1,2] Xin Shen,[1,2] Bokai Cheng,[1,2] Qingli Cheng.[1,2] *[1]Department of Geriatric Nephrology, The Second Medical Centre, Chinese PLA General Hospital, Beijing, China; [2]National Clinical Research Centre for Geriatric Diseases, Beijing, China.*

Background: Chronic Kidney Disease (CKD) has become an important global public health issue, and with the increasing prevalence of metabolic risk factors, the risk of developing CKD also increases. Insulin resistance (IR) is a core pathogenic mechanism of many related risk factors of CKD, making it crucial in the prevention and control of CKD. Therefore, we need to better assess the level of IR in the CKD population.

Methods: The M-value of HECT test was applied to accurately assess the IR level of the subjects and analyse the differences of IR level in people with different blood creatinine levels. Simple insulin sensitivity index (ISI) was calculated based on fasting glucose, insulin, and OGTT results to analyse the test efficacy of ISI for IR level assessment in people with different renal functions.

Results: The subjects exhibited a progressive decline in IR levels (M-values) as their blood creatinine levels increased, and this difference was found to be statistically significant (P=0.016). A correlation regression analysis was conducted to assess the relationship between ISI and M-value. The results indicated that 1/FIN, HOMA-IR, FINS/FBG, QUICKI, McAuley, Matsuda, Gutt, Disposition, Stumvoll, and Avignon were significantly correlated with M-value, with correlation coefficients (r) ranging from 0.325 to 0.577 ($p<0.01$). However, Insulinogenic and Belfiore showed no significant correlation with M-values (p=0.948, 0.831 respectively). The effectiveness of each ISI was evaluated based on renal function grouping, and ANOVA analysis revealed that Matsuda ($p<0.01$), INS/GLU, McAuley, Gutt, and Stumvoll ($p<0.05$) indices could effectively differentiate between groups in terms of IR levels. Among these, McAuley, Matsuda, and Stumvoll indices were particularly responsive to changes in IR levels across different groups.

Conclusions: As kidney function decreases, the level of insulin resistance in subjects increases. The simple ISI-McAuley, Matsuda, and Stumvoll indices show better testing efficiency in identifying trends of insulin resistance compared to the gold standard M value in populations with varying levels of kidney function.

Funding: Government Support - Non-U.S.

PUB557

Prevalence of CKD in Sahuayo, Michoacán, Mexico and Its Associated Risk Factors

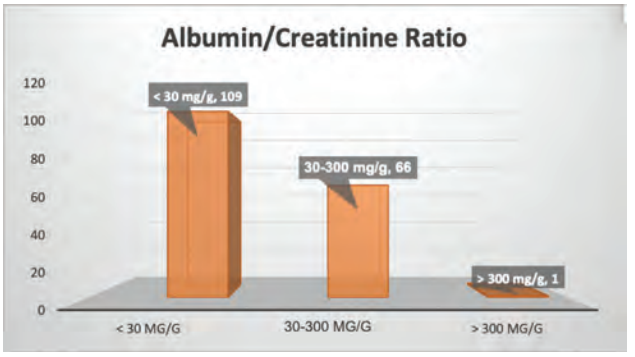
Alberto Corona.[1,2] *[1]Hospital Santa Maria de Sahuayo, Sahuayo, Mexico; [2]Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Sahuayo, Mexico.*

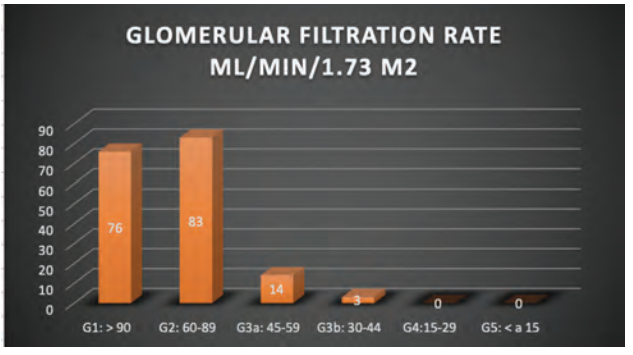
Background: Chronic Kidney Disease (CKD) has been described as the most neglected chronic disease; However, it represents a serious public health problem in Mexico and the world. Between 8 and 10% of the adult population have some form of kidney damage, and every year millions die prematurely of complications related to CKD.

Methods: A Kidney Disease detection campaign was carried out at the ISSSTE Sahuayo facilities on World Kidney Day 2024. Attendees were given information about kidney health; They were questioned for background and glucose, blood pressure, anthropometry as well as serum creatinine and microalbuminuria (Mission Urinalysis Reagent Strips (Urine)) were taken. 176 subjects were evaluated, including a population of all ages. The GFR was estimated with the CKD-EPI formula and CKD was defined according to the KDIGO guidelines. The data were analyzed using descriptive and inferential statistics with logistic regression analysis.

Results: The CKD classification, by glomerular filtration rate, was: G1: 76, G2: 83, G3A: 14, G3B: 3, G4: 0 and G5: 0; with established prevalence (GFR <60 ml/min 1.73 m2) of 9.6%. Regarding the albumin/creatinine ratio in urine, it was: A1: 109, A2: 66, A3: 1; with prevalence of ratio greater than 30 mg/gr: 38%

Conclusions: In the population of Sahuayo, there is a significant percentage of patients with CKD, similar to that observed worldwide, there is a direct relationship with chronic-degenerative diseases such as diabetes, hypertension, dyslipidemia, hyperuricemia, as well as habits such as smoking and alcoholism; Most of the patients captured were not found in advanced stages of kidney damage, which is why it is important to provide preventive measures to reduce its progression.





PUB558

Copper Accumulations as a Uremic Toxin in CKD

Tomofumi Moriyama, Kensei Taguchi, Yuya Yamashita, Kei Fukami. *Division of Nephrology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan.*

Background: 95% of copper (Cu) in the body is excreted into the bile; meanwhile, the rest is excreted by the kidney. Excess Cu accumulation is known to produce reactive oxygen species in Wilson's disease, and the higher level of serum Cu, the more likely to develop kidney injury. However, it remains unknown whether the relationship between Cu accumulation and kidney injury. We demonstrated that serum Cu level was negatively correlated with serum creatinine level in diabetic rats; thus, we hypothesize that Cu might be accumulated as a uremic toxin with progression of kidney injury. In the present study, we investigated serum Cu levels in patients with CKD and explored how Cu accumulation occurs in CKD and induces kidney injury.

Methods: 115 patients with CKD who admitted to our hospital were enrolled to conduct a retrospective clinical study to investigate the relationship between serum Cu and CKD. Low-dose cisplatin (5 mg/kg per week x 4 weeks) was injected into wild-type mice to induce CKD. Serum and urinary levels of Cu, gene expressions of Cu transporters in liver and kidney, and expression pattern of Cu transporters in the liver and kidney were analyzed. LLC-PK1 cells, cultured proximal tubular cells (PTC) were co-incubated with Cu to investigate if Cu accumulation causes PTC damages.

Results: Serum Cu level was increased in CKD stage 4 and 5 when compared to earlier stages. Under 65-year-old and female showed higher level of serum Cu. ATP7B and CTR1 gene expressions in the livers were reduced and serum Cu levels were increased in CKD rodents. The increased level of serum Cu was associated with the increase in its urinary excretion. CTR1, a transporter responsible for Cu intake into PTC, was expressed on basolateral plasma membrane of PTC under basal condition, but CTR1 was translocated into nucleus in the CKD rodents. Co-incubation with Cu increased α-SMA, TGF-β, and cleaved caspase3, suggesting that high level of cooper causes PTC injury and fibrosis.

Conclusions: We identified that Cu was accumulated with progression of kidney impairment in patients with CKD and high amount of Cu induced PTC apoptosis and profibrotic reaction, indicating that Cu can be considered a uremic toxin. Liver metabolism and excretion of Cu is suppressed with the decrease in liver ATP7B and CTR1 in the context of CKD, which leads to increase urinary Cu levels that induces PTC damages and renal fibrosis.

PUB559

Effects of Irisin Secretion on the Development of Kidney Injury in a Mouse Model of Uremic Sarcopenia

Teruyuki Okuma,[1,2] Seiji Ueda,[1] Hajime Nagasawa,[1] Yusuke Suzuki.[2] *[1]Shimane Daigaku Igakubu Fuzoku Byoin, Izumo, Japan; [2]Juntendo Daigaku, Bunkyo-ku, Japan.*

Background: The prevalence of sarcopenia is high in patients with chronic kidney disease (CKD). Sarcopenia is known to be closely associated with reduced physical activity and mortality. Recently, it has been reported that skeletal muscles after exercise secrete bioactive substances called myokines, which are associated with metabolic improvement and muscle mass increase. Irisin, one of myokines has been found to play an important role in maintaining endothelial function and is believed to be a factor for the development of atherosclerotic vascular diseases in patients with sarcopenia. In CKD condition, Irisin is reported to be decreased and its levels are associated with the severity of atherosclerosis. We investigated the impacts of exercise on Irisin kinetics and the role of Irisin in the development of renal injury in a mouse model of uremic sarcopenia.

Methods: We performed 5/6 nephrectomy on C57BL/6J mice as a model of uremic sarcopenia and treated them with or without exercise intervention for 8 weeks. And kaempferia parviflora (KP) which is an activator of SIRT1 was also tested to investigate the involvements of SIRT1-PCG1α-Irisin axis in uremic sarcopenic condition. We measured serum Irisin, the expression levels of FNDC5 (a precursor of Irisin), SIRT1-PCG1α expressions in skeletal muscle, muscle mass, grip strength, renal function, pathological changes, and especially endothelial damage.

Results: The expression levels of SIRT1, PGC1α and FNDC5 in the skeletal muscles of CKD model mice were significantly decreased. In addition, glomerular endothelial damage assessed by glycocalyx staining were observed in the CKD model mice along with a decrease in serum Irisin levels. Exercise intervention not only improved FNDC5 expression and serum Irisin levels but also halted progressive renal function loss by promoting eNOS activation and improving glomerular endothelial injury. Further, KP administration ameliorated the decreased levels of SIRT1-PGC1α in CKD model mice and subsequently enhanced FNDC5 expression and Irisin release, thus contributing to the prevention of endothelial injury and renal damage.

Conclusions: Exercise intervention and KP administration may activate the SIRT1-PGC1α axis and promote Irisin secretion, and thereby contributing to the prevention of endothelial dysfunction and halting the progression of renal damage in CKD.

PUB560

Bioelectrical Impedance Markers as Predictors of CKD Progression

Timothy E. Yen,[1] Xiaoqian Zhu,[1] Maria Clarissa Tio,[1] Yoshitsugu Obi,[1] Michael E. Hall,[1] Neville R. Dossabhoy,[1] Tariq Shafi.[2] *[1]The University of Mississippi Medical Center, Jackson, MS; [2]Houston Methodist Hospital, Houston, TX.*

Background: Bioelectric Impedance Analysis (BIA) objectively quantifies body composition metrics which change during CKD progression. The predictive utility of BIA metrics for outcomes in CKD, especially in advanced disease, is unknown.

Methods: We analyzed 3,632 participants from the Chronic Renal Insufficiency Cohort (total-CRIC) (data provided by NIDDK CR) and a sub-group of 1771 participants with advanced CKD (<30 eGFR, mL/min/1.73 m^2) which was comprised of individuals who started with or progressed to advanced CKD during the study. We analyzed BIA metrics—total body water (TBW, kg), vector length (VL, Ω), phase angle (PA, °), and fat free mass (FFM, kg) as continuous variables. We used multivariable Cox proportional hazard models to examine the associations of each BIA metric with incident CKD progression (≥50% eGFR decline or ESKD) in total-CRIC, and with incident ESKD in the advanced CKD group. We calculated three risks scores--the 2-year and 5-year Kidney Failure Risk Equation (KFRE), and CKD Prognosis Consortium (CKD-PC) 3-year risk score for 40% eGFR decline or ESKD--and evaluated if BIA metrics improved prediction of CKD progression or ESRD compared to using these risk scores alone (Harrel's C).

Results: In the total population, mean age was 58 years, 46% were women, 42% were Black persons, and mean eGFR was 42. In unadjusted models, TBW, VL and FFM were associated with CKD progression in total-CRIC, while VL and FFM were associated with ESKD in advanced CKD. Associations were statistically insignificant after multivariable adjustment (Table). Addition of the BIA parameters did not significantly improve prediction of CKD progression or ESRD (Harrel's C) compared to models using KFRE or CKD-PC risk alone in either group.

Conclusions: BIA, although widely available and easily implementable, did not improve prediction of CKD progression beyond existing risk factors. Our study highlights the limitations of existing technologies and the need for innovation to advance precision medicine for individuals with CKD.

Table. BIA Metrics associations with ESKD / CKD Progression

Study Population	Survival Event	BIA metrics	Unadjusted	Fully Adjusted
			HR (95% CI)	HR (95% CI)
Total-CRIC	CKD Progression	Total Body Water	**1.004 (1.001, 1.007)**	1.002 (0.998, 1.006)
		Vector Length	**0.692 (0.566, 0.845)**	1.054 (0.945, 1.175)
		Fat Free Mass	**1.011 (1.004, 1.019)**	0.996 (0.991, 1.001)
		Phase Angle	0.995 (0.980, 1.011)	0.993 (0.975, 1.011)
Advanced CKD	ESKD	Total Body Water	1.006 (1.000, 1.011)	1.002 (0.997, 1.007)
		Vector Length	**0.658 (0.575, 0.753)**	1.033 (0.901, 1.184)
		Fat Free Mass	**1.013 (1.007, 1.018)**	0.996 (0.988, 1.005)
		Phase Angle	1.002 (0.996, 1.008)	0.998 (0.987, 1.010)

*Fully adjusted models included age, sex, race, systolic blood pressure, diabetes, cardiovascular disease, smoking, statins, ACE/ARB, diuretics, beta blockers, eGFR (CKD-EPI 2021), and urine protein/creatinine as adjusters

** sex variable was excluded in TBW analysis as it is used in TBW calculation

PUB561

Prevalence of Albuminuria and Risk Factors for CKD in a Screening Program in Mexico

Juan M. Ardavin Ituarte,[1,2] Alicia Pineirua,[1] Edgar Solis,[1] Sergio Hernández-Estrada.[1] Medica Santa Carmen. *[1]Medica Santa Carmen, Mexico City, Mexico; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

Background: "Check Your Kidney" (CYK) is a screening program to assess for risk factors of CKD in a Renal Health Network in Mexico. The present study reports the prevalence of albuminuria and CKD risk factors in CYK participants.

Methods: In 2023, 8 CYK campaigns took place in 5 HD clinics across Puebla, Mexico City, Jalisco, and Guanajuato. Evaluation included a risk factor questionnaire, anthropometric measurements, BPM, glucometer, and urine albumin/creatinine ratio tests. Chi-square, Student's t-test, and Mann-Whitney U test were used for analysis where applicable, along with multiple logistic regression, to assess the risk of albuminuria.

Results: A total of 1089 participants were evaluated, with a mean age of 47 years ± 15); 61% were women. The most common CKD risk factor was obesity, with 76% of participants having a BMI ≥ 25 and 35% > 30. This was followed by chronic use of potentially nephrotoxic medications in 26%, known hypertension (HTN) in 23%, and known diabetes mellitus (DM2) in 15%. Capillary glucometry identified 20 additional participants with probable undiagnosed DM2 (random capillary glucose > 200 mg/dL) for a total prevalence of 17%, and blood pressure measurement (SBP ≥ 160 or DBP ≥ 100) identified 44 more with probable HTN for a total prevalence of 27%. Albuminuria > 30 mg/g was detected in 25% and ≥ 300 mg/g in 2% of all participants; in 39% ($p < 0.001$) and 7% ($p < 0.001$) respectively of participants with DM2; and in 36% ($p > 0.001$) and 3% ($p=0.16$) of participants with HTN. The risk association remained significant only for DM2 in the logistic regression analysis after adjusting for age, sex, and other reported risk factors, with an OR = 1.72 (CI 1.19 - 2.49, $p = 0.004$) for albuminuria > 30 mg/g and OR = 6.17 (CI 2.36 - 16.1, $p < 0.001$) for albuminuria ≥ 300 mg/g. Four percent of the patients had all three risk factors (DM2, HTN, and obesity); however, no interaction effect was found between these covariates for the risk of albuminuria.

Conclusions: The prevalence of albuminuria was higher than reported in other populations, but there may be measurement and selection bias. The prevalence of obesity, DM2, and HTN is consistent with that reported in the Mexican population. The most relevant risk factor for albuminuria, as expected, was DM2.

Funding: Clinical Revenue Support

PUB562

Predictors of CKD Progression in Dogs: Results from a Real-World Animal Health Study

James Jackson, Dean A. Taylor, Sophie Barlow, Mollie Lowe. *Adelphi Real World, Bollington, United Kingdom.*

Background: Real world evidence is used to substantiate the benefit of medical intervention in human healthcare, but is less commonly employed in animal healthcare research. We aimed to understand the predictors of canine chronic kidney disease (CKD) progression using a real-world dataset.

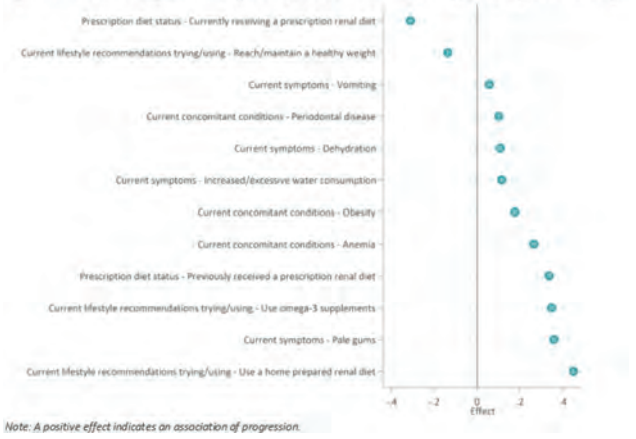
Methods: Data were drawn from the Adelphi Real World Canine CKD Disease Specific Programme™, a cross-sectional survey of veterinarians in the United States from Dec 22 – Jan 24. Vets reported demographics, international renal interest society (IRIS) stage, time since diagnosis, symptoms, comorbidities, lifestyle and treatment goals, for dogs with CKD. A ten-fold elastic net regression (ENR) analysis was conducted.

Results: Overall, 100 vets provided data on 308 dogs. Mean [SD] dog age was 11.4 [3.4] years, 53% were at ideal weight and mean [SD] time since CKD diagnosis was 11.8 [15.6] months. In total, 21% of dogs were at IRIS stage 1, 49% stage 2, 21% stage 3, and 8% stage 4. Overall, 21% had progressed to a higher IRIS stage, from stage at diagnosis to current classification. ENR analysis showed that using a home prepared renal diet was most strongly associated with disease progression. Presence of pale gums, obesity and

anemia were also associated with disease progression. Receiving a prescription renal diet and maintaining a healthy weight were associated with no disease progression (Figure 1).

Conclusions: This real-world data demonstrated the importance of using a prescription renal diet over a home prepared diet, and the need for owner vigilance with their dog's weight and gum colour. Vets should prioritise owners' understanding of the importance of optimal CKD management to help slow disease progression.

Figure 1: Elastic net regression coefficient plot to show predictors of CKD progression in dogs.



PUB563

Hyperkalemia and CKD

L. M. Perez-Navarro, Enrique J. Robiou Vivero, Rafael Valdez-Ortiz.
Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico.

Background: Hyperkalemia (HK) is a frequent complication of chronic kidney disease (CKD), with a prevalence of between 14-20%, which is associated with different factors, such as the use of some antihypertensives (ARA's, IECAS), age, gender, Diabetes Mellitus (DM), cancer. Our aim was to determine the prevalence and factors associated with HK in patients with CKD.

Methods: Transversal study. Patients with CKD who attended the nephrology service of the Hospital General de México during the period Feb 2019 to August 2022 were included. The prevalence and factors associated with HK (K>5) by CKD stage were estimated using regression logistics (95% CI).

Results: 1249 patients were included, with an average age of 55±16 years; 52% of the population female. The prevalence of HK was 26% (321). The standardized B coefficient for the relationship between serum levels and GFR was -0.334, (p<0.0001). Figure 1 shows the prevalence of HK by severity grade across CKD stages. The factors associated with HK are presented in Figure 2.

Conclusions: An association between HK and the use of commonly prescribed medications, such as oral hypoglycemics and loop diuretics, was identified from the early stages of CKD, along with the presence of diabetes mellitus. It is necessary to intentionally screen for HK from the early stages of CKD and to implement pharmacological treatment with the aim of reducing the risk of CKD progression, death, and cardiovascular events.

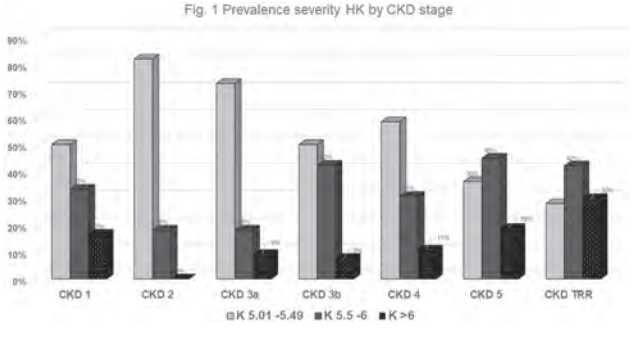


Figure 1. Prevalence of HK by severity grade across CKD stages

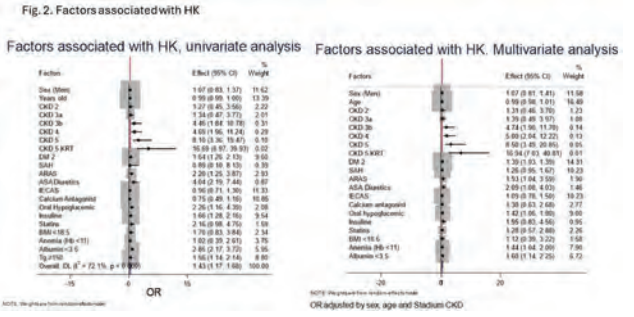


Figure 2. Factors associated with HK

PUB564

Evaluation of Serum Beta-2 Microglobulin (B2M) in Patients with CKD and People Living with HIV (PLHIV) and CKD

Andrea Torres Rojas,[1,2] Monserrat Álvarez Zavala,[2,4] Karina Sánchez Reyes,[2,4] Jonathan Chavez,[5] Pedro Martínez Ayala,[3] Adriana Valle Rodriguez,[3] Jaime Federico Andrade Villanueva,[3,2] Vida V. Ruiz Herrera,[3] Luz A. González Hernández.[3,2] Estudio Inmunológico de la Infección por VIH e Inmunodeficiencias Humanas. *[1]Doctorado en Biología Molecular en Medicina, Dpto Biología Molecular y Genómica, CUCS-UDG, Guadalajara, Mexico; [2]Instituto de Investigación en Inmunodeficiencias y VIH (InIVIH), CUCS-UDG., Guadalajara, Mexico; [3]Hospital Civil de Guadalajara Unidad Hospitalaria Fray Antonio Alcalde, Unidad de VIH., Guadalajara, Mexico; [4]Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Guadalajara, Mexico; [5]Hospital Civil de Guadalajara Unidad Hospitalaria Fray Antonio Alcalde, Servicio de Nefrología., Guadalajara, Mexico.*

Background: Chronic kidney disease (CKD) is one of the main co-morbidities in people living with HIV (PLHIV). In CKD, Cystatin C (CC) and creatinine are the most sensitive markers of renal function. However in HIV, these decrease after the use of antirretroviral therapy (ART), so renal function is underestimated. Beta-2 Microglobulin (B2M) has gained importance as a marker of glomerular and/or tubular damage in CKD. So, we determined and compared serum B2M levels in both groups of patients and correlated with estimated glomerular filtration rate (eGFR) with CKD-EPI equation with creatinine and B2M in order to find a reliable renal function marker for PLHIV.

Methods: Analytical cross-sectional study, in which we included 163 patients with CKD and 102 PLHIV with CKD under ART with undetectable viral loads from the Hospital Civil de Guadalajara. Clinical assessment, laboratory studies and measurement of serum B2M by ELISA were performed.

Results: Comparisons between the groups were significant for B2M, with an increase by stage. There is also a negative correlation between eGFR and B2M in both groups. A ROC curve was performed to define a cut-off point for early renal damage in PLHIV (>2.37 µg/mL (AUC 0.9622, SE 91%, SP 95%)). In PLHIV, using CKD-EPI B2M equation (133 x $B2M^{-0.852}$) eGFR was estimated and compared to CKD-EPI creatinine equation (median: 27.4 vs 52.24 mL/min *p* 0.0001) and there is a redestribution by stage. Bland & Altman analysis revealed a bias of -15.69±17.99 with a 95% CI (-50.95,+19.58).

Conclusions: CKD stratification in PLHIV has been a challange due to the impact of ART, inflammation and immune reconstitution over CC and creatinine. Since B2M is less variable, it is a promising marker for correct classification and follow-up of CKD in PLHIV.

Funding: Government Support - Non-U.S.

Clinical-demographic characteristics and determination of serum B2M

	PLHIV with CKD (n=102)		CKD (n=163)		p-value
Age (years) median (IQR)	51 (40,59)		55 (35,66)		0.4316[a]
Males, n (%)	93 (91.1%)		111 (68%)		<0.0001[a]
Females, n (%)	9 (8.9%)		52 (31.9%)		
T CD4+ (cels/ pL) median (IQR)	496 (323,707)		-		-
Viral loads (copies/mL) median (IQR)	39 (39,39)		-		-
Creatinine (mg/dL) mean (IQR)	1.47 (1.29,1.98)		5.22 (1.83, 11.14)		<0.0001[b]
Serum B2M (µg/mL) median (IQR)	6.27 (3.42, 8.36)		12.57 (4.92, 13.87)		<0.0001[b]
eGFR with CKD-EPI creatinine equation					
CKD stage II	4.37 (2.59, 6.43)		3.31 (2.50, 3.81)		0.3633[b]
CKD stage III	5.52 (3.66, 8.03)		4.77 (3.63, 5.39)		0.0050[b]
CKD stage IV	8.64 (8.06, 10.78)		13.80 (13.32,14.17)		0.3369[b]
CKD stage V	12.71 (9.89, 14.06)		3.31 (2.50, 3.81)		0.6859[b]
eGFR with CKD-EPI B2M equation					
CKD stage II	2.22 (1.77, 2.38)		2.13 (0.27, 2.44)		0.7273[b]
CKD stage III	3.67 (3.01, 4.85)		4.21 (3.74, 5.19)		0.0244[b]
CKD stage IV	8.02 (7.03, 9.27)		9.90 (6.46, 12.56)		0.1473[b]
CKD stage V	13.50 (13.30,14.25)		13.90 (13.47, 14.19)		0.5829[b]
eGFR with CKD-EPI	Creatinine	B2M	Creatinine	B2M	
CKD stage II (eGFR < 60 mL/min) (%)	28.1%	8.9%	3.1%	1.85%	<0.0001[a]
CKD stage III (eGFR 30-59 mL/min) (%)	58.3%	38.6%	29.1%	33.9%	
CKD stage IV (eGFR 15-29 mL/min) (%)	9.3%	49.5%	14.2%	17.9%	
CKD stage V (eGFR <15 mL/min) (%)	4.1%	2.9%	53.4%	46.2%	

Qualitative variables expressed as frequencies and percentages, and nonparametric variables as medians and interquartiles. IQR: Interquartiles. [a]: Chi-square. [b]: Mann-Whitney test

PUB565

Mortality Outcomes of Patients with CKD Underdoing Transcatheter Aortic Valve Replacement at Cooper University Hospital

Michael Chau,[1,2] Krystal Hunter,[2] Christopher B. McFadden.[1,2] *[1]Rowan University Cooper Medical School, Camden, NJ; [2]Cooper University Health Care, Camden, NJ.*

Background: Chronic kidney disease (CKD) is a major risk factor for valvular heart disease, specifically aortic valve calcification. The prevalence and progression of aortic stenosis is higher and faster in patients with CKD thus many of these patients undergo transcatheter aortic valve replacement (TAVR) in their respective lifetimes. Many studies have reported that in-hospital morbidity and mortality are significantly higher in CKD patients when compared to non-CKD patients. However, there are few studies that further distinguish CKD into its different stages and categorize patients on their risk relative to their CKD category. The purpose of this study is to elucidate the mortality outcomes in patients with different stages of CKD following TAVR surgery.

Methods: An IRB approved retrospective study was conducted on patients who underwent TAVR at Cooper University Hospital between 02/2020 and 12/2022. The primary outcome was the 1-year mortality rate after TAVR surgery. Patients with CKD were stratified by their estimated glomerular filtration rate (eGFR) calculated with the CKD-EPI Creatinine Equation (2021). Statistical analyses were performed on this dataset to compare outcomes at different stages of CKD on patients who underwent TAVR.

Results: When compared to patients with CKD3a, patients with CKD3b or worse have greater odds of mortality at the 1-year and 3-year mark after undergoing TAVR. When compared to patients with CKD3b, patients with CKD4 did not have a significant difference in mortality at the 1-year and 3-year mark but patients with CKD1, 2, and CKD3a had lower odds of mortality.

Conclusions: Despite advances in technology and increased in operative experience, patients with CKD who undergo TAVR experience a higher risk of morbidity and mortality. Studies have noted that patients who have advanced CKD such as in dialysis patients are at an even higher risk compared with CKD patients not on dialysis. Our retrospective study shows that the increased risk of mortality after TAVR in CKD patients begins at CKD3b or at an eGFR of 45 mL/min. These results emphasize the importance of risk stratifying these patients prior to obtaining a TAVR surgery, paying particularly special attention to those who have CKD3b.

PUB566

Level of Proteinuria before and after Spironolactone in Combination with ACE Inhibitor or ARB in Filipino Patients with CKD: A Retrospective Cohort Study

Ellani Louise A. Huilar, Brian Michael I. Cabral, Monica Therese Cating-Cabral. *St. Luke's Medical Center - Global City, Taguig City, Philippines.*

Background: In the Philippines, prevalence of chronic kidney disease has been increasing due to comorbidities such as diabetes mellitus and hypertension. Proteinuria has been associated with progression of chronic kidney disease and its reduction shows renoprotective effects to CKD patients. Standard treatments to block the renin angiotensin aldosterone system such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are not enough to halt or slow the progression due to *aldosterone breakthrough*. Hence, blocking the aldosterone by mineralocorticoid receptor antagonist could benefit patients with CKD. Spironolactone, a steroidal MRA, specifically works by competitively blocking aldosterone, decreases inflammation, and improves proteinuria.

Methods: The study was a non-interventional, retrospective or historical cohort investigation using clinical data from chart review of patients from July 2020 to July 2023 in outpatient clinics. Laboratory results were obtained through electronic medical records and were compared in patients who used spironolactone (n=49).

Results: In a population of 49 chronic kidney disease patients on spironolactone dosed at 12.5mg to 50mg per day, random urine protein creatinine ratio decreased from 2.53±2.3 at baseline to 1.78±1.6 with a p-value of 0.005 (p=0.005). The serum creatinine, sodium and estimated glomerular filtration rate showed no statistical significance. Potassium showed statistical significance but has clinically insignificant results.

Conclusions: Reduction of proteinuria by blocking aldosterone breakthrough using mineralocorticoid receptor antagonists such as spironolactone, plays an important part in slowing the progression of CKD. In the Philippines, the use of spironolactone as well as monitoring of proteinuria by RUPCR has not been a common practice. Therefore, further studies are needed to transform the standard of care in treating blood pressure and cardiovascular disease in ESRD.

Clinical Variables	Median, Range (minimum, maximum)		Z	P
	Baseline	Spironolactone		
RUPCr (mg/mg)	1.89 (0.33-12.70)	1.29 (0.13-7.10)	-5.148	<0.001
Creatinine (µmol/L)	1.79 (1.14-4.23)	1.76 (1.05-4.84)	-0.344	0.731
eGFR (mL/min/1.73m^2)	36 (15-65)	37 (15-77)	-0.728	0.467
Serum sodium (mmol/L)	140 (132-149)	142 (134-148)	-1.452	0.146
Serum potassium (mmol/L)	4.2 (2.50-5.00)	4.4 (3.60-6.10)	-3.290	0.001

Table 1. RUPCr, Creatinine, eGFR, serum sodium, and serum potassium at baseline and after treatment with spironolactone with results of the Wilcoxon signed rank test (Z and P-values)

PUB567

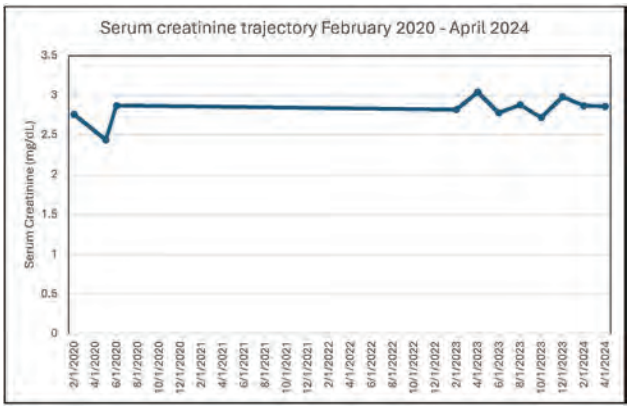
CKD Nonprogressors: A Commonly Underrecognized Syndrome?

Lynn Do, Macaulay A. Onuigbo. *The University of Vermont Medical Center, Burlington, VT.*

Introduction: NKF-KDOQI 2002/KDIGO 2005 guidelines established CKD stages 1-5 to optimize CKD care. Is CKD progression inevitable, unless of course managed properly? A population-based cohort study of 129,486 CKD patients found that with advancing age, CKD regression and death were more likely than CKD progression or kidney failure. We describe nonprogression over several years in CKD III and CKD IV, respectively.

Case Description: Case 1 - A male liver transplant recipient (July 2018, then aged 49 years), developed post-transplant AKI needing hemodialysis for a week. Pre-transplant creatinine was 0.81 mg/dL, peaked at 7.41 mg/dL, and subsequently stabilized (Figure). It was 1.79 mg/dL (eGFR=44) in May 2024. He was hypertensive in October 2018, and was on Losartan 25 mg daily for 17 months, which was discontinued during a hospitalization with sepsis in March 2020. He has since then not received any CKD-modifying agent. **Case 2 -** A now 75-yo male patient has a history of AKI on CKD in February 2020 from pyelonephritis, with peak serum creatinine of 5.39 mg/dL, that subsequently improved to 2.76 mg/dL (eGFR=23), 12 days later, hypertension, BPH, morbid obesity (BMI 33.13 kg/m^2), and known bilateral renal cysts completed his recent annual Nephrology review in April 2024. Latest creatinine was 2.86 mg/dL (eGFR=22) from April 2024 (Figure). Current medications include Carvedilol, Amlodipine, Torsemide, Baby ASA, Ezetimibe, Finasteride, Tamsulosin and Rosuvastatin. He was never on any other CKD-modifying agent.

Discussion: Clearly, there are patients with later stage CKD who remain stable over several years, the so-called CKD non-progressors. Determinants of such CKD stability call for further investigation; the role of pharmacologic agents in such stabilization, in our opinion, remains to be fully truly elucidated.



PUB568

Male Sex and Anemia Are the Most Pivotal Risk Factors for Progression of Kidney Dysfunction and All-Cause Mortality, Especially in Elderly Patients with CKD

Yuta Kimura, Takahito Moriyama, Yoshitaka Miyaoka, Yoshihiko Kanno, Rie Suzuki. Dept of Nephrology, Tokyo Medical University. *Department of Nephrology, Tokyo medical University, Tokyo, Japan.*

Background: Two decades have been passed since the definition of chronic kidney disease(CKD) was advocated in 2003. Hypertension and the diabetes have been recognized as the most important risk factors for progression of CKD, cardio-vascular events, and mortality. However, the recent therapeutic strategies and managements might change those risks. This study analyzed about the renal survival and all-cause mortality and risk factors for them in elderly patients and non-elderly patients in recent data.

Methods: The 311 out-patients with CKD on January 2017 were divided into two groups according to their age over and under 65 [elderly patient group (EPG: ≥ 65 years old, n=193), non-elderly patient group (NEPG: < 65 years old, n=118)]. The clinical and laboratory findings, treatments, and the survival rate until progression to end stage kidney disease (ESKD) and all-cause mortality were compared between both groups. The risk factors were analyzed by Cox regression analysis in each group.

Results: The mean arterial pressure (MAP) was significantly lower and the diabetes patients were significantly higher in EPG (EPG vs. NEPG; MAP:92.0 vs. 96.4 mmHg, p=0.006, diabetes: 42.0 vs. 26.3 %, p=0.005). The hemoglobin (Hb) (12.1 vs. 13.2 g/dL, p<0.001), and eGFR(31.2 VS.38.0mL/min/1.73m', p<0.001) were significantly lower, and the blood urea nitrogen (27.7 vs. 22.4 mg/dL, p<0.001) and uric acid (6.66 vs. 6.27 mg/dL, p=0.01) were significantly higher in EPG. The survival rates were similar between both groups (EPG vs. NEPG:58.1 vs. 66.7 %, p=0.093). The univariate and multivariate analysis indicated that CKD stage and amount of proteinuria were significant risk factors in both groups. Moreover, the male and lower Hb were significant risk factors in EPG [male: hazard ratio (HR) 2.56, 95% confidence interest (CI) 1.27-5.17, p=0.009, Hb: HR 1.46, 95% CI 1.27-5.17, p=0.009], but not in NEPG.

Conclusions: CKD stage and proteinuria were the significant risk factors for progression of CKD and all-cause mortality in both elderly and non-elderly CKD patients rather than hypertension and diabetes. Moreover, the male and anemia were also the significant risk factors in especially elderly CKD patients. These results indicated that the risk factors of CKD and all-cause mortality have changed in these two decades.

PUB569

Impact of Dapagliflozin on Anemia Status of Patients with CKD

Ioannis Griveas.[1,2] *[1]Noseleutiko Idryma Metochikou Tameiou Stratou, Athens, Greece; [2]Athens-Nephrology Private Clinic, Athens, Greece.*

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated cardiovascular and renal benefits in patients with type 2 Diabetes Mellitus, Heart Failure, or Chronic Kidney Disease (CKD). At the same time, there are scattered data which support the hypothesis that SGLT2i may increase hematocrit (Hct) and hemoglobin (Hb). The increase in hemoglobin was strongly associated with the cardiorenal benefits of these drugs. Aim of our study was to investigate the impact of a SGLT2i representative such as Dapagliflozin on anemia status of patients with CKD.

Methods: 22 stable CKD patients, that were receiving Dapagliflozin, were enrolled in our study for a period of one year. 72 years was the mean age of our patients. 16 patients were diabetic, one had FSGS, one had ischemic nephropathy, one had IgA nephropathy, 2 patients had membranous nephropathy and one patient with unknown primary cause of CKD. None of our patients was receiving erythropoietin or Fe supplementations. For a period of one year we measured Hct, Hb, GFR, proteinuria in our study group.

Results: After one year period, Hct was significantly increased from 42.06±4.85 to 44.34±4.74 (p<0.05). Hb was also increased from 13.8±1.63 to 14.36.34±1.50, p=0.63. The above notice was combined with decrease of GFR after one year of giving Dapagliflozin (from 38.66±13.92 mils/min to 34.38±11.59 mils/min, p<0.05). At the same time, proteinuria remained stable over the study period (936.28±1371.10 to 864.47±1256.83, p=NS).

Conclusions: Dapagliflozin use was associated with higher Hct levels in patients with CKD. Our study group is small, but represents the whole spectrum of CKD aetiology. More studies with larger populations are needed to confirm our first impression that SGLT2 inhibitors may be considered as an adjunct therapy to reduce anemia incidence in patients with CKD.

PUB570

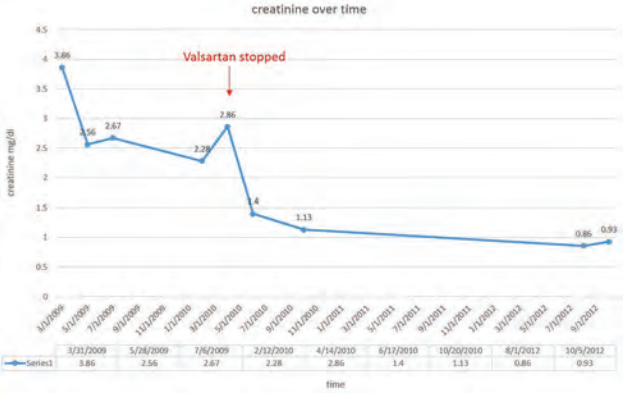
A Case of CKD Mimicry

Martin Sedlacek,[1] Martha L. Graber.[2] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Dartmouth College, Hanover, NH.*

Introduction: CKD is treated with medications to delay disease progression, resulting in an increase in serum creatinine that is expected and beneficiel. Here we present the case of a patient who complained of lightheadedness and palpitations while he was treated for CKD. After stopping valsartan and fenofibrate his kidney function returned to normal with no sign of kidney disease for several years.

Case Description: A 56 y/o man was referred for stage 4 CKD since about 9 months in the context of type 2 diabetes mellitus, HTN, dyslipidemia and a history of colonic polyps and hand surgery. His diabetes was diet controlled with his last HbA1c 6.1%. He was treated with valsartan 320mg daily for years. His other medications were fenofibrate 145mg daily, rosuvastatin 10mg daily and ASA 325mg daily. There was no history of severe illness, radiocontrast studies or NSAID use. BP was 131/81 and he was overweight. Urinalysis and urine sediment were normal and there was no microalbuminuria. Laboratory tests were negative for complications of CKD. Renal ultrasound and Duplex were normal. The patient complained of dizziness and palpitations and underwent a cardiology evaluation which was negative. The patient stopped Valsartan himself and his symptoms resolved. HTN was treated with Atenolol. His serum creatinine improved and for the next years he had no more evidence of kidney disease with normal blood and urine testing (figure 1).

Discussion: The clinical diagnosis of CKD depends on blood and urine tests which can be affected by medications. The patient had a lasting but reversible creatinine increase by valsartan (hemodynamic effect) and fenofibrate (increased creatinine generation). Rosuvastatin has been associated with hematuria and albuminuria (not in this patient). Patient complaints of medication side effects are statistically non significant in most CKD studies, often implying that they might not be relevant for treatment decisions. This case shows that in the individual patient, ignoring symptoms of medication side effects can lead to morbidity and even iatrogenic disease.



PUB571

Effects of Prebiotic on Metagenome and Lipid Metabolism in Patients with CKD: Findings from the TarGut CKD Study

Anvesha Srivastava, Dominic S. Raj. TarGut-CKD Study Group. *The George Washington University, Washington, DC.*

Background: Patients with chronic kidney disease (CKD) have dysbiosis and dysmetabolism. Dysbiosis in CKD could promote progression of CKD through alterations in immune response, blood pressure regulation and metabolic changes. The aim of the study is to define the impact of p-inulin supplementation on gut microbiota-related metabolites, as well as the plasma lipid metabolism.

Methods: In a non-randomized, open-label, 3-phase pilot trial, we examined the effect of oligofructose-enriched inulin (p-inulin) on functional metagenome and alterations in plasma, urine and stool metabolites in 15 patients with CKD (TarGut CKD). The study consisted of a pre-treatment phase (8 weeks), a p-inulin treatment phase (12 weeks), and a post-treatment phase (8 weeks).

Results: Abundance of *Bifidobacterium adolescentis*, *Bifidobacterium longum* and *Lachnospiraceae* species were increased during the treatment phase. Microbial pathways related to carbohydrate, lipid, amino acid and purine metabolism were altered during the treatment phase. Differential enrichment in microbiota generated metabolites and lipids metabolites was evident between study phases. Specifically, levels of secondary bile acids were reduced significantly in plasma, urine and stool during the treatment phase. Despite an increase in abundance of short chain fatty acid (SCFA)-producing bacteria during p-inulin consumption, there was no parallel increase in SCFA. Several polar and non-polar lipids were altered during the study phases, which was associated with specific microbiota.

Conclusions: This study indicates that prebiotics alters functional metagenome, metabolic pathways and metabolites that transcends carbohydrate metabolism in patients with CKD. The clinical significance of our findings needs to be confirmed in an adequately powered clinical trial.

Funding: NIDDK Support

PUB572

Perspectives of Patients and Care Partners on Prognostic Discussions in CKD: A Qualitative Study

Shivani S. Tauh,[1] Pietro Ravani,[1] Shannan Love,[1] Kathryn M. King-Shier,[3] Robert R. Quinn,[1] Ngan Lam,[1] Ping Liu,[2] Maoliosa Donald,[2] Meghan J. Elliott.[1] *[1]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [2]University of Calgary, Calgary, AB, Canada; [3]University of Calgary Faculty of Nursing, Calgary, AB, Canada.*

Background: The incidence and prevalence of chronic kidney disease (CKD) is expected to rise over the next decade. Adults with severe CKD must navigate difficult decisions related to kidney replacement therapy and the competing risk of death without kidney failure. In this qualitative study, we sought to explore the experiences of patients with CKD and their care partners related to discussions about kidney failure risks and mortality, and to elicit their preferences for discussing and using prognostic information.

Methods: We purposively sampled patients with non-dialysis-dependent CKD (eGFR <30 mL/min/1.73m^2) followed in multi-disciplinary CKD clinics and their care partners in Alberta, Canada. We conducted online or telephone-based, semi-structured interviews that centered around eliciting personal experiences and responses to clinical vignettes that included risk estimates for kidney failure and mortality. Interviews were audio recorded and transcribed verbatim. Data were coded iteratively and in duplicate and analyzed through reflexive thematic analysis.

Results: We conducted interviews with 22 patients and 7 care partners. Participants emphasized the quality of communication and interactions with their healthcare team as the greatest influences on their prognostic understanding. Participants' experiences and preferences related to prognostic discussions are elaborated across the following themes: 1) Alignment of discussion context with informational readiness (*appropriate timing, setting, roles*), 2) Level of directness in conveying individual risk (*sensitivity, frankness, professional obligation*), 3) Quality of personal and therapeutic relationships impacting preferences (*reliance on trust and support structures*), and 4) Perceived value and applicability of prognostic information (*personalized information, utility in care planning*).

Conclusions: The perceived quality of prognostic discussions among patients with CKD and their care partners was influenced by contextual factors, individual preferences, and communication styles. Strategies tailored to individuals' readiness and the collaborative CKD care setting may improve understanding of clinical outcomes of severe CKD and use of prognostic information in treatment planning.

PUB573

A Phase 2b Dose-Finding Study to Evaluate Effects of Balcinrenone/Dapagliflozin vs. Dapagliflozin in Patients with CKD and Albuminuria

Patrick B. Mark,[1] Anna Eriksson,[6] Nicolas J. Guzman,[3] Erika De Sousa Amorin,[6] Maria Leonsson Zachrisson,[6] Samvel B. Gasparyan,[5] Yunyun Jiang,[4] Hiddo J. Heerspink.[2] *[1]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, United Kingdom; [2]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands; [3]Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD; [4]Biometrics, Late Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD; [5]Biometrics, Late Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [6]Late-stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden.*

Background: Despite current standard of care with SGLT2i being recommended for the treatment of chronic kidney disease (CKD), there is still an unmet need for managing residual risk of disease progression. Balcinrenone is a novel selective mineralocorticoid receptor (MR) modulator, expected to maintain the cardio-renal treatment benefits of MR antagonists with a reduced risk of hyperkalaemia. The combined usage of balcinrenone and dapagliflozin is therefore expected to provide complementary and additive kidney and cardiovascular protection. MIRACLE Phase II study (NCT04595370) in heart failure (HF) and CKD suggested potential for reduced albuminuria and low risk of hyperkalaemia with balcinrenone/dapagliflozin.

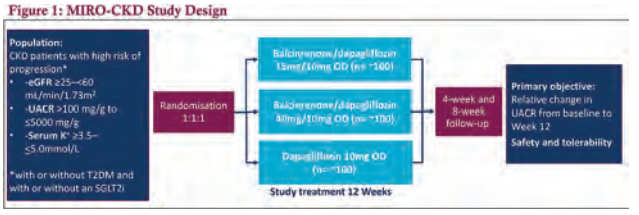
Methods: This Phase IIb, international, randomized, double-blind, parallel-group trial is enrolling adult patients with CKD, albuminuria and potassium 3.5 to ≤5mmol/L (NCT06350123; Figure). Participants will be randomised 1:1:1 to three treatment arms: balcinrenone/dapagliflozin 15/10mg, balcinrenone/dapagliflozin 40/10mg and dapagliflozin 10mg for 12 weeks followed by an 8-week wash-out period to assess off-drug effects. This study will evaluate the effect of balcinrenone/dapagliflozin on urinary albumin-to-creatinine ratio (UACR), compared with dapagliflozin, as well as safety and tolerability. eGFR will be monitored throughout the study, to assess any acute changes and its reversibility.

Results: The primary endpoint is the relative change in UACR from baseline to week 12. Safety and tolerability will be assessed from adverse events (including AEs of special interest; hyperkalaemia, adverse renal events and hypotension), vital signs and safety laboratory parameters throughout the study.

Conclusions: The MIRO-CKD study will assess efficacy, safety and tolerability of the combination of balcinrenone and dapagliflozin with the aim to identify an optimal dose for a future Phase III study in patients with CKD.

Funding: Commercial Support - AstraZeneca

Figure 1: MIRO-CKD Study Design



PUB574

Effects of Coronary Artery Bypass Grafting on Kidney Function and Associated Risk Factors in Patients with CKD: A 12-Month Prospective Study

Mohammad Rahmanian,[1] Shiva Samavat,[3] Reza Ghotbein,[5] Nasrin Borumandnia,[4] Behrang Nooralishahi.[2] *[1]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran; [2]Tehran Heart Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran; [3]Chronic Kidney Disease Research Center (CKDRC), Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Islamic Republic of Iran; [4]Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran; [5]Shahid Beheshti University of Medical Sciences School of Medicine, Tehran, Islamic Republic of Iran.*

Background: This study aims to investigate the impact of coronary artery bypass grafting (CABG) on the 12-month glomerular filtration rate (GFR) in Iranian patients with chronic kidney disease (CKD) and to identify the factors associated with changes in GFR.

Methods: One hundred patients undergoing CABG were enrolled in the study. GFRs were assessed at 3-, 6-, and 12-months post-surgery. Analyses were conducted to obtain the trend of GFR. Additionally, a linear regression analysis using the Generalized Estimating Equations (GEE) approach was conducted to explore the effect of various predictors on the trend of GFR. The B coefficient was reported for each parameter to measure the estimated change in GFR for each unit increase in the parameter, holding all other parameters constant.

Results: Prior to surgery, the mean GFR was 62.5. At 3-, 6-, and 12-months post-surgery, the mean GFRs were 58.1, 58.4, and 56.8, respectively, showing a decreasing trend (P value<0.05). Among various possible predictors, gender, age, pre-op hemoglobin, AKI during admission, intra-aortic balloon pump (IABP), and renal replacement therapy (RRT) showed a statistically significant effect on the trend of GFR (P < 0.05). However, no significant correlations were found between the GFR trend and factors such as body surface area (BSA), smoking, ejection fraction (EF), type of surgery, hypertension, diabetes, cerebrovascular accident (CVA), and anemia (P > 0.05).

Conclusions: The declining trend of GFR and its predictive factors, including gender, age, pre-operation hemoglobin, AKI during admission, IABP, and RRT, should be considered when CKD patients undergo CABG. .

Parameter		B coefficient	95% Wald Confidence Interval for B		p-value
			Lower	Upper	
Gender	Male	13.634	6.307	20.961	.000
	Female	reference			
HTN	Yes	-2.529	-9.489	4.431	.476
	No	reference			
DM	Yes	1.232	-5.869	8.372	.730
	No	reference			
CVA	Yes	4.787	-3.640	13.214	.368
	No	reference			
IABP	Yes	-7.831	-14.683	-.978	.025
	No	reference			
Type Of Surgery	Non-Elective	-6.351	-12.934	.231	.059
	Elective	reference			
Smoking	Yes	-10.438	-21.084	.209	.055
	No	reference			
AKI During Admission	Yes	9.170	3.884	14.457	.001
	No	reference			
RRT During Admission	Yes	-22.581	-29.710	-15.451	.000
	No	reference			
Anemia	Yes	1.827	-5.865	9.519	.642
	No	reference			
Time	12month	-5.925	-10.375	-1.475	.009
	6month	-5.702	-9.531	-1.872	.004
	3month	-5.283	-9.150	-1.417	.007
	1month	-9.797	-17.184	-2.410	.009
	before op	reference			
AGE		-.866	-1.233	-.500	.000
BSA		-2.029	-15.873	11.815	.774
EF		-.057	-.363	.250	.718
pre-op Hb		2.888	.788	4.989	.007

Abbreviations: HTN: hypertension, DM: diabetes, CVA: cerebrovascular accident, IABP: intra-aortic balloon pump, AKI: acute kidney injury, RRT: renal replacement therapy, op: operation, BSA: body surface area, EF: ejection fraction, Hb: hemoglobin

The results of the linear regression analysis.

PUB575

GFR Recovery in a Patient with Stage 4 CKD and Chronic Uncontrolled Gout after Treatment with Intravenous (IV) Pegloticase

Eddie M. Rodriguez,[1,2] Sergio F. Santiago Calderon,[2] Hector Quintero Alvarez.[2]
[1]Bayamon Medical Center, Bayamon, Puerto Rico; [2]Universidad Central de Bayamon, Bayamon, Puerto Rico.

Introduction: Gout has been associated as an important comorbidity for cardiovascular disease, Diabetes Mellitus type 2, increase risk of death, and chronic kidney disease. Kidney biopsies have shown urate deposition in kidney tissue and there is a chronic inflammatory component that may be contributing to GFR loss in CKD patients with uncontrolled gout. But a correlating between chronic gout stabilization and renal protection outcomes has not been established, in part due to lack of effective therapies to significantly impact urate tissue in chronic uncontrolled gout.

Case Description: A 59 y/o male with past medical history of coronary artery disease, Diabetes Mellitus Type 2, chronic kidney disease stage 4 and uncontrolled Gout with Tophi and recurrent flares. Patient usually treated flares with prednisone and avoided colchicine and NSAIDS due to CKD status. Due to failure of conventional therapies of uric acid lowering therapy he was started on Pegloticase infusion IV every 2 weeks. After 6 months of treatment in addition of controlling flares and tophi dissolution he has shown a consistent improvement in eGFR which has increased after each visit. Initial eGFR prior initiation of treatment was 28 ml/min. After 6 months of treatment latest eGFR is 70 ml/min which shows dramatic improvement after stabilizing uncontrolled gout and the removal of the urate burden from tissues.

Discussion: Improvement of GFR with by controlling inflamation and reducing urate burden in CKD patient with chronic gout is a promising treatment alternative. At the moment Pegloticase is indicated for treatment of patients with uncontrolled gout regardless of GFR since it does not require dose adjustments related to GFR, but the indication is to reduce flares and tophi disolution. So far there is only anecdotal data that patients may present benefits in term of GFR recovery after treatment with Pegloticase. The findings of his case proposes that treatment with pegloticase IV could be beneficial for patients with uncontrolled gout in terms of eGFR recovery and also reduction in CKD progression by stabilizing chronic uncontrolled gout. Potentially this may leed to future controlled trials which may further evaluate pegloticase as a treatment for GFR recovery and GFR protection in patients with CKD and chronic gout.

PUB576

Modulating Branched-Chain Amino Acid Catabolism: A New Approach to Ameliorate Cisplatin- and Unilateral Ureteral Obstruction (UUO)-Induced Kidney Injury

Hisakatsu Sone, Byung Rho Lee, Samuel V. Vitale, Dan Heo, Sang-Ho Kwon.
Augusta University Medical College of Georgia, Augusta, GA.

Background: Cisplatin chemotherapy can lead to chronic kidney disease in cancer patients. We have identified that endogenous renal microRNA-messenger RNA (miRNA-mRNA) interactions mediate attenuation of branched-chain amino acid catabolism in cisplatin-induced kidney injury. This study examines the roles of branched-chain amino acid catabolism in maladaptive cellular processes associated with cisplatin nephrotoxicity and unilateral ureter obstruction (UUO) injury.

Methods: To understand the role of BCAA catabolism in the murine models of kidney injury, we conducted marker analyses for renal fibrosis and ferroptosis.

Results: Enhancing branched-chain amino acid catabolism reduces renal ferroptosis and fibrosis in cisplatin- and UUO-induced kidney injury.

Conclusions: Our study reveals a novel regulatory interaction between BCAA catabolism and ferroptosis in proximal tubule cells, as well as fibrosis in chronically injured kidneys. Modulating the BCAA pathway could offer therapeutic potential for alleviating kidney injury caused by cisplatin and UUO.

Funding: NIDDK Support

PUB577

Cyclo-glycylproline (cGP) Ameliorates Kidney Failure in Mice with Adenine-Induced Kidney Failure and db/db Mice

Koichi Kikuchi, Shun Watanabe, Takafumi Toyohara, Takehiro Suzuki, Tetsuhiro Tanaka, Takaaki Abe. *Tohoku Daigaku, Sendai, Japan.*

Background: Chronic kidney disease (CKD) is a worldwide public health problem with increasing prevalence, poor outcomes and high cost. Progression of CKD leads to accumulation of uremic toxins such as indoxyl sulfate (IS), trimethlyamine-N-oxide (TMAO), and phenyl sulfate (PS), which further accelerates the progression of CKD and is involved in a variety of CKD-related complications. Therefore, the reduction of the accumulated uremic toxins is important for the protection against CKD.

Methods: Cyclo-glycylproline (cGP) is a cyclic dipeptide containing a condensation bond between glycine and proline. C57BL6 mice were fed a diet containing 0.2% adenine for 6 weeks to create a renal failure model. After the mice were created, they were switched to a normal diet and a diet containing 0.001% cGP for 2 weeks. Blood, urine, and organ samples were collected after administration. Similarly, db/db mice, a diabetic model mouse, were administered a diet containing 0.0031% cGP for 6 weeks, and blood, urine, and organ samples were collected. Plasma creatinine levels and urinary toxins were measured using LCMS/MS. Fibrosis of the renal cortex was also analyzed using Image J.

Results: In mice with adenine-induced renal failure, serum creatinine levels were significantly ($p<0.05$) lower in the renal failure (RF) + cGP-treated group than in the RF group, suggesting improved renal function. In addition, a comparison of the residual tubular area of the kidneys showed that the residual tubular area was significantly increased in the cGP-treated group (RF group: 43%, RF + cGP group: 62%). No reduction in urinary toxins was observed. Next, db/db mice treated with cGP for 6 weeks also had significantly lower plasma creatinine levels compared to the control group. In addition, a comparison between before and after cGP treatment showed that plasma PS levels were significantly reduced in addition to plasma creatinine levels after cGP treatment, suggesting that cGP may be a novel therapeutic agent for DKD, as we have reported PS as an aggravating factor in the onset and progression of diabetic kidney disease (DKD) in a previous study.

Conclusions: It is suggested that oral administration of cGP may improve renal function in renal failure model mice and diabetes model mice.

PUB578

Nephroprotective Effects of Dapagliflozin in the Adenine-Diet Induced Mouse Model of CKD

Maria K. Ougaard, Alex Frias Hernandez, Michael Christensen.
Gubra, Hørsholm, Denmark.

Background: Translational models are essential to identify improved treatment options for chronic kidney disease (CKD). However, most preclinical CKD models do not demonstrate reduced glomerular filtration rate (GFR) or improvement by standard of care, including sodium-glucose cotransporter type 2 inhibitor (SGLT2i) therapy. Here, we evaluated the SGLT2i dapagliflozin in the adenine diet-induced (ADI) mouse model of CKD.

Methods: Male C57BL/6J mice (11 weeks old) were randomised into study groups based on body weight. From day 1, mice received control diet (CTRL mice) or 0.2% adenine-supplemented diet (ADI mice). ADI mice were administered with vehicle or dapagliflozin (10 mg/kg, PO, BID) for 3 weeks. Transdermal GFR (tGFR), urine albumin-to-creatinine ratio (uACR), and urine cystatin C (uCYC) was measured at termination.

Plasma was collected for evaluation of urea, creatinine, and cystatin C levels. The left kidney was weighed and processed for histomorphometric assessment of fibrosis (Col1a1 and Col3a1), tubular injury (KIM-1) and macrophage infiltration (F4/80).

Results: Compared to vehicle-dosed ADI mice, dapagliflozin significantly improved tGFR (520 vs 278 μL/min/100 g body weight ± SEM, p<0.01), uACR (146 vs 279 μg/mg± SEM, p<0.001) and uCYC (122.9 vs 518.2 ng/mL ± SEM, p<0.001). Furthermore, dapagliflozin significantly improved plasma levels of CYC (885.1 vs 1884.2 ng/mL ± SEM, p<0.001), creatinine (10.4 ± SEM vs 29.1 mmol/l ± SEM, p<0.001) and urea (11.6 ± SEM vs 22.7 mmol/l ± SEM, p<0.001). Renal benefits of dapagliflozin therapy were supported by reductions in %-area of Col1a1, Col3a1, KIM-1 and F4/80 IHC.

Conclusions: Dapagliflozin improves functional, biochemical, and histological hallmarks of CKD. These findings support nephroprotective effects of dapagliflozin in CKD and clinical translatability of the ADI mouse model of CKD.

Funding: Commercial Support - Gubra

PUB579

Dose-Dependent Nephroprotective Effects of an ALK5 Inhibitor in the Unilateral Ureteral Obstruction (UUO) Mouse Model of Kidney Fibrosis

Ditte M. Jensen, Alex Frias Hernandez, Maria K. Ougaard, Michael Christensen, Frederikke E. Sembach. *Gubra, Hørsholm, Denmark.*

Background: Development of renal fibrosis is a hallmark of chronic kidney disease (CKD) and an essential factor for progressive loss of kidney function and development of end-stage kidney disease. The unilateral ureteral obstruction (UUO) mouse is a widely used surgery-induced model of CKD with rapid induction of renal inflammation and fibrosis. Here, we characterized the effect of an anti-fibrotic TGF-β type 1 receptor kinase inhibitor (ALK5 inhibitor, ALK5i) on renal outcomes in the UUO mouse.

Methods: Male C57BL/6J mice (9 weeks old) were randomised into study groups based on body weight and were either sham-operated or underwent UUO surgery. UUO mice received vehicle or ALK5i (3, 10 or 30 mg/kg, PO, BID) for 8 days. Vehicle-dosed sham-operated mice served as controls. At termination, both kidneys were weighed, and the obstructed left kidney was processed kidney hydroxy proline (HP) and for quantitative histological assessment of macrophage infiltration (F4/80), fibrosis (Col1a1, Col3a1), myofibroblast activation (α-SMA) and tubular injury (KIM-1). Plasma was sampled for measurement of KIM-1 levels.

Results: UUO mice displayed marked kidney tubular injury, macrophage infiltration, myofibroblast activation, and fibrosis as compared to sham-operated animals. ALK5i dose-dependently improved kidney histology, plasma KIM-1 levels, and kidney HP (0.148 vs 0.214 μg/mg).

Conclusions: ALK5i exerted dose-dependent nephroprotective effects in the UUO mouse. Given the rapid induction of fibrosis and inflammation, the UUO mouse is optimal for screening of compounds with potential anti-inflammatory and anti-fibrotic effects.

Funding: Commercial Support - Gubra

PUB580

Effect of Lisinopril on Glomerular and Tubular Injury in a Surgical Rat Model of Progressive CKD and Kidney Failure

Ditte M. Jensen, Alex Frias Hernandez, Maria K. Ougaard, Michael Christensen. *Gubra, Hørsholm, Denmark.*

Background: Development of renal fibrosis is a hallmark of chronic kidney disease (CKD), underlying the progressive loss of kidney function and progression to end-stage kidney disease. The 5/6 nephrectomy (Nx) rat model of CKD displays progressive albuminuria, glomerulosclerosis, tubulointerstitial fibrosis, and loss of kidney function. Here, we characterised the effect of lisinopril, a standard ACE inhibitor, on kidney histopathology, renal biochemical markers, and kidney function in 5/6 Nx rats.

Methods: Male Wistar rats (9 weeks old) underwent either sham operation or 2/3 nephrectomy of the right kidney at week -4 and full nephrectomy of left kidney at week -2. Rats were randomised into study groups at week -1 based on plasma urea, creatinine, and body weight. Sham rats received vehicle and 5/6 Nx rats received either vehicle or Lisinopril (20 mg/kg, PO, QD), for a total of 8 weeks, starting on day 1. Urine was sampled for analysis of albumin-to-creatinine ratio (ACR) (week 7) and the glomerular filtration rate (GFR) (week 8). Terminal plasma was sampled for analysis of urea albumin and creatinine. The remaining right kidney was harvested for quantitative histological assessment of glomerulosclerosis (PAS staining), macrophage infiltration (CD68), tubular injury (KIM-1), and fibrosis (Col1a1).

Results: The 5/6 Nx rat model displayed significant increase of renal biomarkers, GFR decline, glomerulosclerosis, tubular injury, renal macrophage infiltration and fibrosis as compared to sham-operated rats. Treatment with lisinopril significantly reduced albumin-to-creatinine ratio and significantly reduced tubular injury. The 5/6 Nx rat model is applicable for probing preclinical drug candidate for CKD.

Conclusions: 5/6 Nx rats displayed loss of kidney function including declined GFR and increased albuminuria as well as key histopathological features of chronic kidney disease. Treatment with Lisinopril significantly reduced ACR and tubular injury.

Funding: Commercial Support - Gubra

AUTHOR INDEX

The number refers to the location of the body of the abstract in the publication section

KEYWORD INDEX

The number refers to the location of the body of the abstract in the publication section

FR-OR100

Finerenone and Kidney Outcomes in Patients with Heart Failure: The FINEARTS-HF Trial

Finnian R. McCausland,[1] Muthiah Vaduganathan,[1] Brian Claggett,[1] Ian J. Kulac,[1] Akshay Desai,[1] Pardeep Jhund,[6] Alasdair D. Henderson,[6] Meike Daniela Brinker,[2] Robert M. Perkins,[2] Markus Scheerer,[2] Patrick Schloemer,[2] Carolyn S.P. Lam,[8] Michele Senni,[9] Sanjiv Shah,[3] Adriaan A. Voors,[7] Faiez Zannad,[4] Bertram Pitt,[5] John McMurray,[6] Scott D. Solomon.[1] *[1]Brigham and Women's Hospital, Boston, MA; [2]Bayer AG, Leverkusen, Germany; [3]Northwestern University Feinberg School of Medicine, Chicago, IL; [4]INSERM, Paris, France; [5]University of Michigan, Ann Arbor, MI; [6]University of Glasgow, Glasgow, United Kingdom; [7]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [8]National Heart Centre Singapore, Singapore, Singapore; [9]Aziende Socio Sanitarie Territoriale Papa Giovanni XXIII, Bergamo, Italy.*

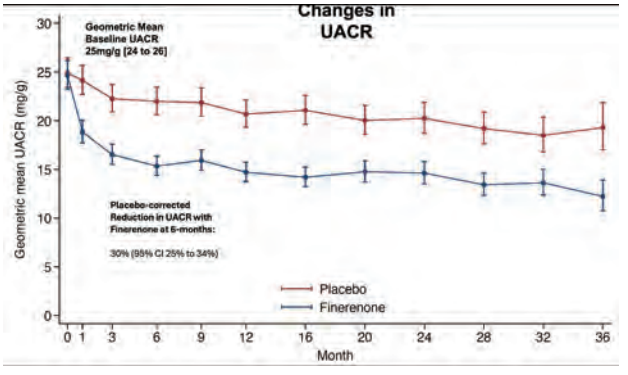
Background: Finerenone has kidney protective effects in patients with chronic kidney disease (CKD) with type 2 diabetes, but effects on kidney outcomes in patients with heart failure (HF) with and without diabetes and/or CKD are not known.

Methods: FINEARTS-HF was a global, randomized clinical trial of finerenone vs. placebo among patients with HF with mildly reduced or preserved ejection fraction. A secondary outcome was a sustained ≥50% eGFR decline or kidney failure (sustained eGFR decline <15 mL/min/1.73m^2; initiation of chronic dialysis; renal transplant). In this prespecified analysis, we also report effects of finerenone on: 1) sustained ≥57% eGFR decline or kidney failure; 2) changes in UACR.

Results: Among 6,001 participants, mean eGFR was 62±20mL/min/1.73m^2; 48% had eGFR<60mL/min/1.73m^2. Overall, 5,797 had baseline UACR data (median 18 [7, 67]mg/g; UACR<30mg/g: 61%; 30-<300mg/g: 30%; ≥300mg/g: 10%). Over 2.6 years median follow-up, the incidence of the composite kidney outcome (≥50% eGFR decline or kidney failure) was low and not affected by finerenone (75 vs. 55 events; HR 1.33; 95%CI 0.94,1.89). Similar results were observed for ≥57% eGFR decline or kidney failure (41 vs. 31 events; HR 1.28; 95%CI 0.80, 2.05). Finerenone reduced UACR by 30% (95%CI 25%, 34%) by 6 months vs. placebo, an effect that persisted throughout follow-up (**Fig.**), irrespective of diabetes ($P_{interaction}$=0.48). Among those with baseline UACR<300mg/g, finerenone reduced the risk of new-onset of macroalbuminuria by 38% (HR 0.62; 95%CI 0.53, 0.73), irrespective of diabetes ($P_{interaction}$=0.96).

Conclusions: Finerenone did not modify eGFR-based kidney outcomes but led to early and sustained reductions in albuminuria and reduced the risk of new-onset of macroalbuminuria, among patients in FINEARTS-HF at low risk of adverse kidney outcomes.

Funding: Commercial Support - Bayer



FR-OR101

Personalized Recommendations for AKI Using a Kidney Action Team: A Multicenter Randomized Controlled Trial

Abinet M. Aklilu,[1] Steven Menez,[2] Yu Yamamoto,[1] Jack Bitzel,[2] Celia P. Corona Villalobos,[2] Kyle D. O'Connor,[1] Kyra A. Shelton,[1] Sophia Faulkner,[1] Amrita Makhijani,[1] Bashar A. Kadhim,[1] Chirag R. Parikh,[2] Francis P. Wilson.[1] *[1]Internal Medicine, Yale University School of Medicine, New Haven, CT; [2]Internal Medicine, Johns Hopkins University, Baltimore, MD.*

Background: AKI alerts have not improved patient outcomes but AKI care bundles have. We investigated if timely personalized recommendations for AKI are more effective at improving patient outcomes.

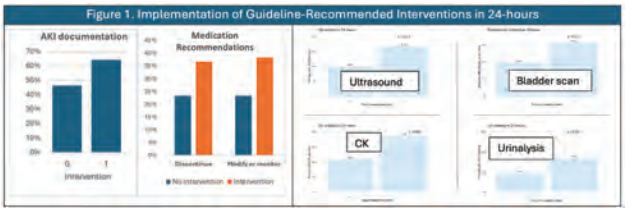
Methods: KAT-AKI was a 1:1 randomized investigator-blinded trial conducted at 2 large US hospital systems, Yale and Johns Hopkins, evaluating the effectiveness of rapid, expert-led diagnosis and management recommendations at creatinine-based AKI diagnosis. A physician and pharmacist "Kidney Action Team" (KAT) screened patients with new AKI at the time of an automated AKI alert that was not visible to clinicians. For patients who passed screening, the KAT remotely reviewed their chart and provided structured recommendations in 5 major categories (general diagnostics, volume, potassium, acidosis, medications). Patients were then randomized to either receive a KAT Recommendation Note in their chart or no KAT Note. The primary clinical outcome was a composite of AKI progression, dialysis or mortality within 14 days. The primary process outcome was proportion of recommendations implemented within 24h of randomization.

Results: The trial included 4003 patients 786(20%) of whom were in an ICU. The median(IQR) age was 72(61-81)yrs, 47% were female and 41% had CKD. The median(IQR) time from automated AKI detection to randomization was 56(33-83)min. Nearly all (96%) had at least one general recommendation and 55% had at least one medication-specific recommendation. The process outcome was significantly higher in the intervention arm (0.25[0-0.50] vs 0[0-0.33], p<0.001). The intervention particularly improved ordering of urinalysis, orthostatic vitals, creatine kinase, obstruction evaluation, AKI documentation and medication changes.(Figure) However, there was no difference in the primary clinical outcome, individual components or post-AKI hospital LOS.(Table)

Conclusions: Personalized early recommendations improved AKI documentation and process outcomes but did not change clinical outcomes.(NCT04040296)

Funding: Other U.S. Government Support

14-day Outcomes	Control	Intervention	p-value
Primary composite outcome, n (%)	329 (16.5%)	344 (17.3%)	0.554
AKI progression, n (%)	261 (13.1%)	270 (13.6%)	0.722
Dialysis, n (%)	30 (1.5%)	31 (1.6%)	0.987
Mortality, n (%)	185 (9.2%)	191 (9.6%)	0.762
Length of stay, days, median (IQR)	5.2 (2.2, 9.4)	5.1 (2.1, 10.0)	0.760



FR-OR102

Effects of Semaglutide on Kidney Parameters in Patients with Obesity and Nondiabetic CKD

Hiddo J. Heerspink,[1] Ellen M. Apperloo,[1] Niels Jongs,[1] Secundino Cigarran,[2] Maria Jose Soler,[3] Josep M. Cruzado,[4] Annemarie B. van der Aart,[11] Gozewijn D. Laverman,[5] Jacobien Verhave,[12] Sofia B. Ahmed,[6] Roland E. Schmieder,[7] Christoph Wanner,[8] David Cherney,[9] Jose L. Gorriz.[10] *[1]Clinical Pharmacy and Pharmacology, Universiteit Groningen Faculteit Medische Wetenschappen, Groningen, Netherlands; [2]Nephrology Service, Hospital Ruber Internacional, Madrid, Spain; [3]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [4]Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; [5]Ziekenhuisgroep Twente, Almelo, Netherlands; [6]University of Alberta, Edmonton, AB, Canada; [7]Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany; [8]Universitatsklinikum Wurzburg Deutsches Zentrum fur Herzinsuffizienz, Wurzburg, Germany; [9]University of Toronto, Toronto, ON, Canada; [10]Universitat de Valencia, Valencia, Spain; [11]Martini Ziekenhuis, Groningen, Netherlands; [12]Rijnstate, Arnhem, Netherlands.*

Background: Semaglutide is a glucagon like peptide 1 receptor agonist which reduces albuminuria and the risk of kidney failure in patients with type 2 diabetes and chronic kidney disease (CKD). We assessed the effects of semaglutide in patients with overweight/obesity and albuminuric CKD without diabetes.

Methods: We conducted a multicenter randomized placebo-controlled clinical trial in adults with CKD (eGFR ≥25 mL/min/1.73m^2, urine albumin-to-creatinine ratio [UACR] ≥30 and <3500 mg/g), body mass index ≥27 kg/m^2 and HbA1c <6.5% without use of hypoglycemic agents. Participants were randomized to 24 weeks treatment with subcutaneous semaglutide 2.4 mg/week or placebo adjunctive to renin-angiotensin-system inhibition when indicated. The primary endpoint was percentage change from baseline in UACR at week 24. Secondary endpoints included change in iohexol measured GFR, estimated GFR, body weight, and systolic blood pressure (BP). Safety was monitored throughout.

Results: Of 125 screened participants, 101 were randomized to semaglutide or placebo. Mean age was 55.8 (SD 12) years, 40 (39.6%) were female, median UACR was 251 mg/g (IQR 100, 584), eGFR 65.0 (SD 25) mL/min/1.73m^2. Chronic glomerulonephritis (N=25) and hypertensive CKD (N=27) were the most common CKD etiologies. At week 24, the placebo-corrected geometric mean change from baseline in UACR with semaglutide was -52.1% (95%CI -65.2, -34.1; p<0.0001). Compared to placebo, mGFR was changed at week 24 with semaglutide by -1.9 mL/min/1.73m^2 (95%CI -8.0, 4.3). Corresponding changes in eGFR-creatinine and eGFR-cystatin C were -1.1 (95%CI -4.8, 2.6) and +2.1 mL/min/1.73m^2 (95%CI -1.7, 5.9), respectively. Semaglutide compared to placebo changed body weight by -9.1 kg (95%CI -11.1, -7.1) and systolic BP by -6.3 mmHg (95%CI -11.1, -1.5). Gastrointestinal adverse events were more often reported in the semaglutide (N=30) versus placebo group (N=15).

Conclusions: Treatment with semaglutide for 24 weeks in patients with overweight/obesity and CKD without diabetes resulted in a robust and clinically meaningful reduction in UACR. These results support further trials to assess long-term efficacy and safety of semaglutide in these patients.

Funding: Commercial Support - Novo Nordisk provided a grant to the University Medical Center Groningen to conduct this investigator initiated clinical trial

FR-OR103

Long-Term Effects of Empagliflozin in CKD

William G. Herrington, Natalie Staplin, Nikita Agrawal, Richard Haynes. EMPA-KIDNEY Collaborative Group. *Renal Studies Group, CTSU, NDPH, University of Oxford, Oxford, United Kingdom*.

Background: We observed the cardiorenal effects of ~2 years of empagliflozin within EMPA-KIDNEY for an additional ~2 years of post-trial follow-up (PTFU).

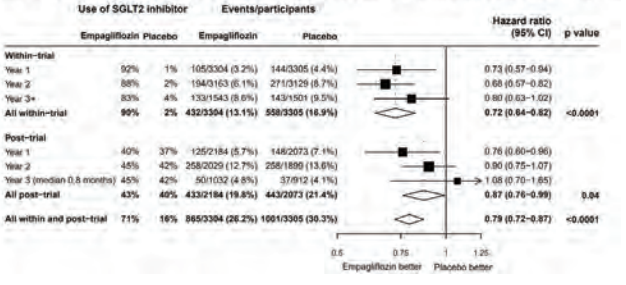
Methods: Patients with an eGFR 20-<45; or 45-<90 and urine ACR of ≥200 mg/g were randomized to empagliflozin versus placebo and provided with allocated treatment for a median of 2 years. Post-trial, participants were then prospectively observed off study treatment. Local doctors were free to commence an open-label SGLT2 inhbitor (blinding to original allocation was maintained). The primary composite outcome was kidney disease progression or CV death for the entire follow-up period (i.e. within-trial + PTFU periods combined).

Results: Of 6609 randomized participants, 4895 entered PTFU and were followed for a median of 2 years. During the post-trial period, any SGLT2 inhibitor use was similar between groups (average use empagliflozin 43% vs placebo 40%). Over the entirety of follow-up a primary outcome occurred in 865/3304 participants (26.2%) in the empagliflozin group and in 1001/3305 (30.3%) in the placebo group (HR=0.79, 95%CI 0.72-0.87). Relative effects on the primary outcome were similar across the key subgroups (by diabetes, eGFR & uACR). There was a 13% (0.87, 0.76-0.99) reduction in risk of the primary outcome post-trial (Figure). This meant the absolute differences in the primary outcome were 57 (SE14) per 1000 at the end of the within-trial period and still 45 (14) at the end of PTFU. Allocation to empagliflozin reduced risk of kidney disease progression (23.5% vs 27.1%), the composite of death or end-stage kidney disease (16.9% vs 19.6%), and CV death (3.8% vs 4.9%).

Conclusions: EMPA-KIDNEY PTFU quantifies more completely the total effects of the short period of 2 years of empagliflozin. Study empagliflozin continued to exert benefit on cardiorenal outcomes for a period after its discontinuation. The post-trial benefit was smaller than the benefit when taking study treatment and appeared to be temporary. To maximize the cardiorenal clinical benefits of SGLT2 inhibitors therefore requires long-term treatment of patients with CKD.

Funding: Commercial Support - Boehringer Ingelheim

Effect of allocation to empagliflozin on progression of kidney disease or CV death



FR-OR104

Efficacy and Safety of HSK21542 for Moderate-to-Severe CKD-Associated Pruritus: A Phase 3 Trial in Hemodialysis Patients

Bi-Cheng Liu,[1] Jianghua Chen,[2] Aimin Zhong,[3] Yaling Bai,[8] Yan Xu,[4] Bi hu Gao,[5] Yanlin Li,[6] Yu Wang.[7] *[1]Zhongda Hospital Southeast University, Nanjing, China; [2]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [3]Jiangxi Provincial People's Hospital, Nanchang, China; [4]The Affiliated Hospital of Qingdao University, Qingdao, China; [5]The Affiliated Zhong-Shan Hospital of DaLian University, Dalian, China; [6]Zhongshan hospital of Traditional Chinese Medicine, Zhongshan, China; [7]The First Affiliated Hospital of Nanchang University, Nanchang, China; [8]The Fourth Hospital of Hebei Medical University and Hebei Tumor Hospital, Shijiangzhuang, China*.

Background: Chronic kidney disease-associated pruritus (CKD-aP) is a common and distressing condition that often presents in patients on hemodialysis(HD), which reduced quality of life and an increased risk of death.HSK21542 is a peripherally restricted and selective agonist of kappa opioid receptors that are considered to be important in treating CKD-aP. Here we reported the results from the phase 3 trial of HSK21542 in HD pts with CKD-aP (21542-302; NCT05135390).

Methods: In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned patients undergoing hemodialysis who had moderate-to-severe pruritus to receive either intravenous HSK21542 (at a dose of 0.3 μg per kilogram of body weight) or placebo three times per week for 12 weeks. The primary outcome was the percentage of patients with an improvement (decrease) of at least 4 points from baseline at week 12 in the weekly mean score on the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS). The secondary outcomes included the percentage of patients with an improvement of at least 3 points in the WI-NRS score at week 12, the change from baseline in itch-related quality-of-life measures, and safety.

Results: A total of 545 patients underwent randomization. The percentage of patients with a decrease of at least 4 points in the WI-NRS score at week 12 was significantly greater in the HSK21542 group than in the placebo group (37.2% vs. 15.0%, P<0.001). The imputed percentage of patients with a decrease of at least 3 points in the WI-NRS score was 51.0% in the HSK21542 group, as compared with 24.2% in the placebo group (P<0.001). HSK21542 also resulted in a significant improvement from baseline to week 12 in itch-related quality of life as measured by the 5-D itch scale and the Skindex-10 scale. HSK21542 was generally safe and well tolerated throughout. Dizziness and hypotension were more common in the HSK21542 group than in the placebo group.

Conclusions: Patients treated with HSK21542 had a significant reduction in itch intensity and improved itch-related quality of life as compared with those who received placebo.

Funding: Commercial Support - This study was funded by Haisco Pharmaceutical Group Co., Ltd.

FR-OR105

Efficacy and Safety of Tac or MMF for Children with Steroid-Sensitive but Frequent Relapse or Steroid-Dependent Nephrotic Syndrome: A Nationwide, Multicentre Randomized Study

Fei Liu,[1] Jingjing Wang,[1] Weili Yan,[3] Jianhua Zhou,[4] Xiaoyun Jiang,[5] Fei Zhao,[6] Xiaochuan Wu,[15] Shuzhen Sun,[7] Mo Wang,[8] Hong Xu,[9] Jing Chen,[9] Cuihua Liu,[10] Shipin Feng,[11] Xuhui Zhong,[2] Haidong Fu,[1] Lingfei Huang,[1] Daqing Ma,[12,13] Jie Ding,[2] Qing Ye,[14] Jianhua Mao.[1] *[1]Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hang Zhou, China; [2]Department of Pediatric Nephrology, Peking University First Hospital, Beijing, China; [3]Department of Clinical Epidemiology and Clinical Trial Unit, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China; [4]Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China; [5]Department of Pediatric Nephrology and Rheumatology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [6]Department of Pediatric Nephrology, Children Hospital of Nanjing Medical University, Nanjing, China; [7]Department of Pediatric Nephrology and Rheumatism and Immunology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China; [8]Department of Nephrology, Children Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory, Chongqing, China; [9]Department of Nephrology, Children's Hospital of Fudan University, Shanghai, China; [10]Department of Nephrology and Rheumatology, Zhengzhou Key Laboratory of Pediatric Kidney Disease Research, Children Hospital Affiliated to Zhengzhou University, Zhengzhou, China; [11]The Affiliated Women's and Children's Hospital, School of Medicine, UESTC; Chengdu Women's and Children's Central Hospital, Chengdu, China; [12]Perioperative and Systems Medicine Laboratory, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China; [13]Division of Anaesthetics, Pain Medicine & Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital, London, United Kingdom; [14]Department of Laboratory Medicine, Children Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China; [15]Department of Pediatrics, The Second Xiangya Hospital of Central South University, Hunan, China*.

Background: Both tacrolimus (TAC) and mycophenolate mofetil (MMF) are recommended for children with frequently relapsing nephrotic syndrome (FRNS) and steroid-dependent nephrotic syndrome (SDNS). However, their comparative effectiveness and safety have not been evaluated through randomized controlled studies.

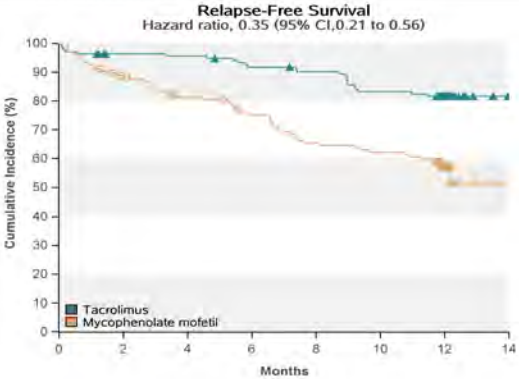
Methods: In this multicenter, randomized, open-label, controlled trial, 270 children aged 2-18 years with FRNS/SDNS were allocated at a 1:1 ratio to receive either TAC (0.025-0.05 mg/kg, orally twice daily) or MMF (10-15 mg/kg, orally twice daily) for one year, along with a tapering regimen of steroids. The primary endpoint was 1-year relapse-free survival. Relapse frequency, cumulative steroid dosage and safety profiles were also evaluated. The trial was prospectively registered at ClinicalTrials.gov (NCT04048161).

Results: A total of 243 out of 270 patients completed the trial, and their data were analyzed and reported. Compared with MMF, TAC significantly reduced the risk of relapse by 65% (HR = 0.35, 95% CI: 0.21–0.56, P <0.0001) in the intention-to-treat analysis. This difference was also significant after adjusting for the per-protocol analysis

(HR = 0.36, 95% CI: 0.22–0.58, P <0.0001). Among the relapsed patients, the median time to first relapse was 225.5 days in the TAC group and 165.5 days in the MMF group. The TAC group had fewer annual relapses (mean [SD], 0.319 [0.936] vs. 0.778 [1.274]) and a reduced cumulative dose of steroid (0.221 [0.103] vs. 0.337 [0.222] mg/kg/d) than did the MMF group. The safety profile was similar in both groups, with infections being the most common adverse event.

Conclusions: In children with FRNS/SDNS, a 1-year course of TAC therapy significantly extended the period of relapse-free survival in comparison to MMF treatment.

Funding: Commercial Support - The STAMP trial was sponsored by Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd., Hangzhou, Zhejiang, China, Government Support - Non-U.S.



FR-OR106

Deferoxamine for the Prevention of Cardiac Surgery-Associated AKI: The DEFEAT-AKI Randomized Clinical Trial

David E. Leaf,[1,2] Megan L. Krajewski,[3,2] Edy Y. Kim,[4,2] Jochen D. Muehlschlegel,[5] Aranya Bagchi,[6,2] Shahzad Shaefi.[3,2] *[1]Division of Renal Medicine, Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA; [4]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA; [5]Johns Hopkins University, Baltimore, MD; [6]Massachusetts General Hospital, Boston, MA.*

Background: Multiple lines of evidence support a central role of free iron in the pathogenesis of acute kidney injury (AKI). Patients undergoing cardiac surgery may be particularly susceptible to iron-mediated AKI due to the profound hemolysis that occurs from cardiopulmonary bypass and intraoperative transfusion of red blood cells.

Methods: In an NIH-funded, phase II, multicenter, double-blind trial, we randomly assigned adult patients undergoing coronary artery bypass graft and/or valve surgery with cardiopulmonary bypass considered to be at high-risk of AKI to receive a 12-hour IV infusion of deferoxamine (30 mg/kg) or an equal volume of saline placebo beginning immediately after induction of anesthesia. The primary outcome was the occurrence of AKI within 7 days, defined according to the KDIGO consensus criteria, incorporating changes in serum creatinine, urine output, and kidney replacement therapy. Secondary outcomes included AKI stage, receipt of kidney replacement therapy, atrial fibrillation, prolonged receipt of invasive mechanical ventilation, sepsis, and time to liberation from IV vasoactive medications.

Results: We enrolled 301 patients from 3 large academic medical centers in Boston, MA and assigned 151 to deferoxamine and 150 to placebo. AKI occurred in 99 patients (65.6%) in the deferoxamine group and in 108 (72.0%) in the placebo group (relative risk, 0.91; 95% CI, 0.78–1.06). Rates of secondary outcomes were similar between groups (**Table**), as were rates of adverse events.

Conclusions: Among adult patients undergoing cardiac surgery, prophylactic administration of IV deferoxamine did not reduce the occurrence of AKI.

Funding: NIDDK Support

Outcome*	Deferoxamine (n=151)	Placebo (n=150)	Relative Risk (95% CI)
Primary outcome			
AKI	99 (65.6)	108 (72.0)	0.91 (0.78–1.06)
Stage 1	60 (39.7)	59 (39.3)	1.01 (0.76–1.34)
Stage 2	31 (20.5)	39 (26.0)	0.79 (0.52–1.20)
Stage 3	8 (5.3)	10 (6.7)	0.79 (0.32–1.95)
Secondary outcomes			
Kidney replacement therapy	5 (3.3)	4 (2.7)	1.24 (0.34–4.53)
Atrial fibrillation**	33 (32.4)	32 (35.6)	0.91 (0.61–1.35)
Prolonged (>24h) IMV	31 (20.5)	27 (18.0)	1.14 (0.72–1.81)
Sepsis	7 (4.6)	2 (1.3)	3.48 (0.73–16.48)
Time (h) to liberation from IV vasoactive medications – median (IQR)	29 (20–59)	30 (15–50)	N/A

Data are shown as no. (%) unless otherwise specified.
Abbreviations: h, hours; IMV, invasive mechanical ventilation.
*All outcomes were assessed within the first 7 days postoperatively unless otherwise specified
**For atrial fibrillation, only patients without atrial fibrillation at baseline were included (102 deferoxamine-treated patients at 90 placebo-treated patients)

FR-OR107

Effect of a Perioperative Hypotension Avoidance Strategy vs. a Hypertension Avoidance Strategy on the Risk of AKI

Amit X. Garg.[1,2] Maura Marcucci,[3,4] Meaghan S. Cuerden,[5] Jessica M. Sontrop,[5] PJ Devereaux.[3] Perioperative Ischemic Evaluation-3 (POISE-3) Investigators. *[1]Medicine, Western University, London, ON, Canada; [2]Population Health Research Institute, Hamilton, ON, Canada; [3]McMaster University, Hamilton, ON, Canada; [4]Humanitas University, Milan, Italy; [5]London Health Sciences Centre, London, ON, Canada.*

Background: Acute kidney injury (AKI) is a common complication of the over 200 million noncardiac surgeries performed worldwide each year. We conducted a pre-specified substudy of the POISE-3 trial to determine whether a peri-operative hypotension-avoidance strategy versus a hypertension-avoidance strategy alters the risk of postoperative AKI (substudy protocol publication: PMID 35024154).

Methods: This was a two-group, open-label, randomized trial of 7307 high-risk patients from 110 hospitals in 22 countries undergoing noncardiac surgery. Patients were ≥ 45 years old and took at least one antihypertensive medication. hypotension-avoidance strategy ... target intraopertive mean arterial pressure (MAP) ≥80 mmHg ... on day of surgery and for 2 days after, aim to hold renin-angiotensin-aldosterone system inhibitors ... stepwise use other long-term antihypertensive medications if SBP ≥130 mmHg hypertension-avoidance strategy ... target intraoperative MAP ≥60 mmHg ... continue all antihypertensive medications before and after surgery. The primary outcome was postoperative AKI, defined as an increase in serum creatinine concentration of either ≥26.5 μmol/L (≥0.3 mg/dL) within 48 hours of randomization or ≥50% within 7 days of randomization.

Results: The hypotension-avoidance group (n=3654) vs. the hypertension-avoidance group (n=3653), ... used fewer antihypertensive medications .....specifically, 6% vs. 38% of patients used an ACEi or ARB on the day of surgery, ...6% vs. 47% one day after surgery, ... 7% vs. 50% two days after surgery. ... spent less intraoperative time with a MAP < 80 mmHg (average 28% vs. 45% of the time) ... had no difference in mean SBP/DBP/MAP outside the operation (day of surgery and two days after surgery) ... had no difference in the risk of AKI ..... (15.1% vs. 14.4%; relative risk 1.05 [95% CI, 0.93 to 1.19]). Results were consistent with multiple alternate continuous and categorical definitions of AKI and in the subgroup with baseline chronic kidney disease.

Conclusions: In this trial of patients undergoing noncardiac surgery, the risk of postoperative AKI did not differ between patients randomized to receive a hypotension-avoidance strategy versus a hypertension-avoidance strategy. Trial registration: NCT03505723.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR108

Impact of Semaglutide on Infections and COVID-19: Data from the FLOW Trial

Brian Rayner,[1] Kenneth W. Mahaffey,[2] Johannes F. Mann,[3,4] Richard E. Pratley,[5] Katherine R. Tuttle,[6,7] Nicolas Belmar,[8] Heidrun Bosch-Traberg,[8] Ole K. Jeppesen,[8] Minh Chau Tran,[8] Gil Chernin,[9] Peter Rossing.[10,11] *[1]Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; [2]Stanford Center for Clinical Research, Department of Medicine, Stanford School of Medicine, Palo Alto, CA; [3]KfH Kidney Centre, München, Germany; [4]University Hospital, Friedrich-Alexander University, Erlangen, Germany; [5]Translational Research Institute, AdventHealth Research Institute, Orlando, FL; [6]Division of Nephrology, University of Washington School of Medicine, Seattle, WA; [7]Providence Medical Research Center, Providence Inland Northwest Health, Spokane, WA; [8]Novo Nordisk A/S, Søborg, Denmark; [9]Hebrew University of Jerusalem, Kaplan Medical Center, Rehovot, Israel; [10]Steno Diabetes Center Copenhagen, Herlev, Denmark; [11]Department of Clinical Medicine, Kobenhavns Universitet, Copenhagen, Denmark.*

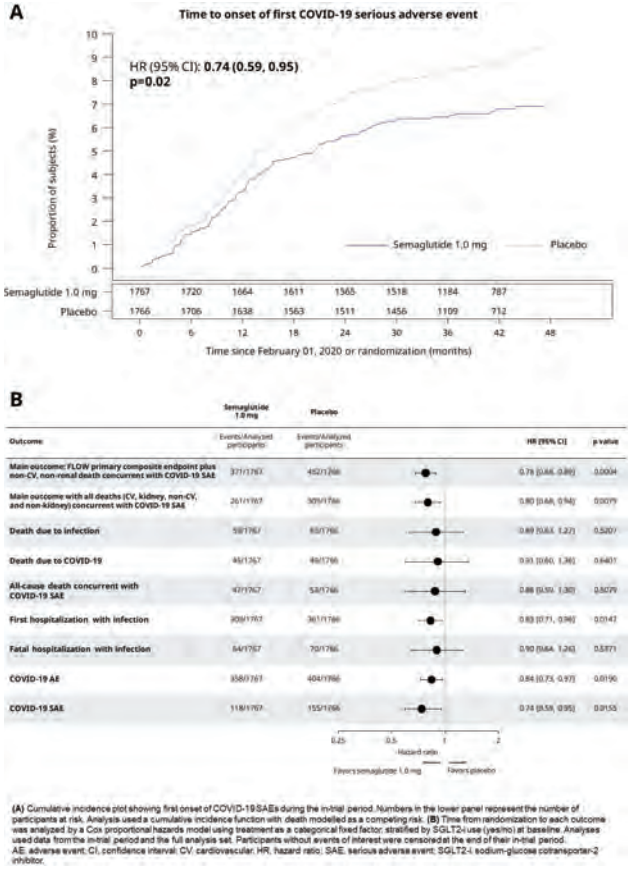
Background: In the FLOW trial, once-weekly subcutaneous semaglutide 1.0 mg reduced the risk of major kidney and cardiovascular (CV) events in people with type 2 diabetes (T2D) and chronic kidney disease (CKD). This analysis assessed the impact of semaglutide on the incidence of infection adverse events (AEs) and COVID-19 AEs in people with T2D and CKD.

Methods: The main outcome of this analysis was time from randomization to the primary FLOW study outcome (composite of onset of kidney failure, sustained reduction in eGFR, kidney death, or CV death, regardless of COVID-19) including non-CV, non-kidney death concurrent with a COVID-19 serious AE (SAE). A pre-defined MedDRA search was applied for COVID-19 events. Other infection SAEs were collected by standard AE reporting.

Results: Participants (N=3533) had a mean (SD) age of 66.6 (9.0) years, and HbA_{1c} of 7.8% (1.3) at baseline. 73.6% received a COVID-19 vaccine during the trial. Semaglutide reduced the risk of the main outcome compared to placebo (hazard ratio [HR] [95% CI] 0.78 [0.68, 0.89]; p=0.0004). The semaglutide group also had a lower incidence of infection SAEs (17.9% vs 21.3%; p=0.01), and COVID-19 SAEs (6.7% vs 8.8%; p=0.02). Semaglutide also reduced the risk of an additional endpoint comprising the primary composite outcome including all-cause death concurrent with a COVID-19 SAE (HR [95%CI] 0.80 [0.68, 0.94]; p=0.0079). Semaglutide reduced the risk of a COVID-19 AE or SAE, and risk of hospitalization with an infection (**Figure**).

Conclusions: In the FLOW trial, semaglutide was associated with lower rates of infection SAEs, COVID-19 AEs and COVID-19 SAEs, in people with T2D and CKD.

Funding: Commercial Support - Novo Nordisk A/S



(A) Cumulative incidence plot showing first onset of COVID-19 SAEs during the in-trial period. Numbers in the lower panel represent the number of participants at risk. Analysis used a cumulative incidence function with death modelled as a competing risk. (B) Time from randomization to each outcome was analyzed by a Cox proportional hazards model using treatment as a categorical fixed factor, stratified by SGLT2-i use (yes/no) at baseline. Analyses used data from the in-trial period and the full analysis set. Participants without events of interest were censored at the end of their in-trial period.
AE, adverse event; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; SAE, serious adverse event; SGLT2-i, sodium-glucose cotransporter-2 inhibitor.

FR-OR109

Effect of Semaglutide on Mortality Outcomes in the FLOW Trial

Richard E. Pratley,[1] Kenneth W. Mahaffey,[2] Johannes F. Mann,[7,8] Katherine R. Tuttle,[3,4] Peter Rossing,[5,6] Thomas Idorn,[9] Jens-Peter David,[9] Heidrun Bosch-Traberg,[9] Ole K. Jeppesen,[9] Willem A. Bax,[10] Pieter Gillard,[11] Mustafa Arici,[12] Minara Shamkhalova,[13] Vlado Perkovic.[14] FLOW Trial Committees and Investigators. *[1]AdventHealth Translational Research Institute, Orlando, FL; [2]Department of Medicine, Stanford Center for Clinical Research, Stanford University School of Medicine, Palo Alto, CA; [3]Division of Nephrology, University of Washington School of Medicine, Seattle, WA; [4]Providence Medical Research Center, Providence Inland Northwest Health, Spokane, WA; [5]Steno Diabetes Center Copenhagen, Herlev, Denmark; [6]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [7]KfH Kidney Centre, Munich, Germany; [8]University Hospital, Friedrich-Alexander University, Erlangen, Germany; [9]Novo Nordisk A/S, Søborg, Denmark; [10]Medical Centre Alkmaar, Alkmaar, Netherlands; [11]Department of Endocrinology, University Hospitals Leuven - KU Leuven, Leuven, Belgium; [12]Faculty of Medicine, Hacettepe University, Ankara, Turkey; [13]Department of Diabetic Kidney Disease, Endocrinology Research Centre, Moscow, Russian Federation; [14]University of New South Wales, Sydney, NSW, Australia.*

Background: In FLOW, semaglutide 1.0 mg (sema) reduced the risk of major kidney and cardiovascular (CV) events. Here, we assess the effect of sema on mortality outcomes.

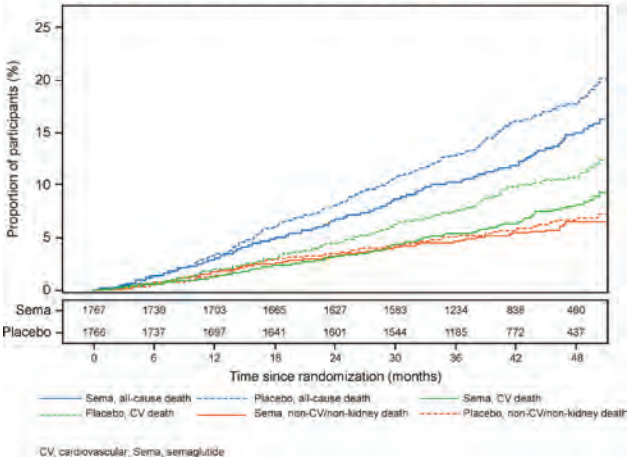
Methods: Participants (≥18 years with T2D and CKD) were randomized 1:1 to receive once-weekly subcutaneous sema or placebo. Cause of death was confirmed by an event adjudication committee.

Results: Compared with placebo, sema reduced the risk of all-cause death (HR [95% CI] 0.80 [0.67, 0.95]), CV death (0.71 [0.56, 0.89]), and death of undetermined cause (0.62 [0.42, 0.91]; **Figures 1, 2**). The most common causes of CV death were sudden cardiac death (2.8% sema vs 3.8%) placebo and heart failure (0.3% vs 0.7%). Sema had no effect on non-CV/non-kidney or kidney death. The most common causes of non-CV/non-kidney death were infection (3.3% vs 3.7%) and malignancy (1.4% vs 1.2%; **Figure 2**).

Conclusions: In FLOW, sema reduced the risk of all-cause and CV death by 20% and 29%, and death of undetermined cause by 38%, relative to placebo.

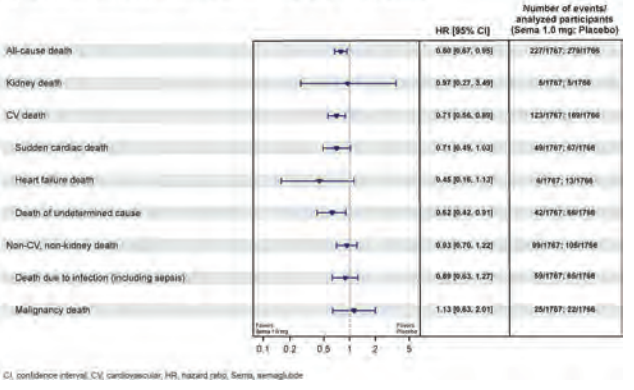
Funding: Commercial Support - Novo Nordisk

Figure 1. Time from randomization to different causes of death



CV, cardiovascular; Sema, semaglutide

Figure 2. Time from randomization to death from CV and non-CV causes



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; Sema, semaglutide

FR-OR110

Effects of 3.0 mEq/L [K+] Dialysate with Sodium Zirconium Cyclosilicate (SZC) vs. 2.0 mEq/L [K+] Dialysate without SZC on Cardiac Arrhythmia Rates

Wolfgang C. Winkelmayer,[1] David M. Charytan,[2] Christopher B. Granger,[3] John P. Middleton,[4] Charles A. Herzog,[5,6] Glenn M. Chertow,[7] James M. Eudicone,[8] James A. Tumlin.[9] ADAPT Investigators. *[1]Baylor College of Medicine, Houston, TX; [2]New York University Grossman School of Medicine, New York, NY; [3]Duke University Duke Clinical Research Institute, Durham, NC; [4]Duke University Medical Center, Durham, NC; [5]Hennepin Healthcare System Inc, Minneapolis, MN; [6]University of Minnesota Medical School, Minneapolis, MN; [7]Stanford University School of Medicine, Stanford, CA; [8]AstraZeneca Pharmaceuticals LP, Wilmington, DE; [9]NephroNet, Inc., Atlanta, GA.*

Background: K^+ homeostasis may be a modifiable risk factor for atrial fibrillation (AF) and clinically significant cardiac arrhythmias (CSCA) in patients receiving hemodialysis (HD). The optimal approach to managing serum K^+ (sK^+) and dialysate K^+ (dK^+) is uncertain.

Methods: ADAPT was a prospective, randomized, open-label 2×2 crossover trial. Adults receiving HD 3 d/wk for ≥3 mo with hyperkalemia (two predialysis sK^+ measurements 5.1–6.5 mEq/L) underwent placement of an implantable cardiac loop recorder and were randomized 1:1 to one of two crossover sequences: A) $2.0K^+/2.5Ca^{2+}$ mEq/L dialysate bath without SZC ($2.0K^+$/noSZC) for 8 wks followed by $3.0K^+/2.5Ca^{2+}$ mEq/L dialysate bath with SZC on non-HD days ($3.0K^+$/SZC) for 8 wks, or B) vice versa. SZC starting dose (on non-HD days) was 5 g, up titrated weekly to 15 g to maintain predialysis sK^+ 4.0–5.5 mEq/L. sK+ was measured pre-HD and <30 min prior to rinse back once weekly. The primary outcome was the rate of AF episodes >2 min duration. Key secondary outcomes included rate of CSCA and proportion of sK^+ values within an 'ideal' window of 4.0-5.5 mEq/L.

Results: Overall, 88 pts (mean age 57.1 yrs, 51.1% male, mean sK^+ 5.5 mmol/L) were randomized. Over 25.5 person yrs (PY), 296 AF episodes were recorded among 9 (10.2%) patients. The crude AF rate was lower with $3.0K^+$/SZC (9.7/PY) vs $2.0K^+$/noSZC (13.4/PY); modelled rate ratio (RR): 0.52; 95% CI 0.41; 0.65; *P*<0 001. The rate of CSCA was lower with $3.0K^+$/SZC (6.8/PY) than $2.0K^+$/noSZC (10.2/PY); RR: 0.47; 95% CI 0.38; 0.58; *P*<0.001. The mean proportion of monitoring time spent in AF (0.22% vs 0.53%; RD: -0.30%; 95% CI -1.11%; 0.45%) did not differ significantly between exposure groups. Pts with $3.0K^+$/SZC had lower odds of sK+ being outside the ideal window; OR: 0.27; 95% CI 0.12; 0.35. Hypokalemia occurred in 33 pts with $3.0K^+$/SZC vs 58 patients with $2.0K^+$/noSZC. Hyperkalemia occurred in 3 pts with $3.0K^+$/SZC vs 1 pt with $2.0K^+$/noSZC. Adverse events occurred in 37 vs 28 pts with $3.0K^+$/SZC vs $2.0K^+$/noSZC.

Conclusions: Among patients receiving maintenance HD with a history of hyperkalemia, a combination of dK^+ 3.0 mEq/L and SZC on non-HD days reduced the rates of AF, CSCA, and post-HD hypokalemia compared with dK^+ 2.0 mEq/L and no SZC.

Funding: Commercial Support - AstraZeneca

FR-OR111

Haemodiafiltration or Haemodialysis for Kidney Failure: Totality of Evidence Based on Individual Patient Data Meta-Analysis from Randomised Controlled Trials

Peter J. Blankestijn,[1] Robin W. Vernooij,[1,2] Michiel L. Bots.[2] The CONVINCE Scientific Committee and the HDF Pooling Project Investigators. *[1]Department of Nephrology and Hypertension, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands.*

Background: Recently a 23% lower mortality risk was reported in patients with kidney failure treated with high-dose haemodiafiltration compared to conventional high-flux haemodialysis (NEJM 2023). Nevertheless, it remains unclear whether treatment effects differ across subgroups, whether there is a dose-response relationship with convection volume, and the effects on cause-specific mortality. The goal of this individual patient data meta-analysis was to analyse the effect of haemodiafiltration on death from any cause compared with standard haemodialysis.

Methods: We searched MEDLINE, Embase, and CENTRAL from inception to until July 2024 for all randomised controlled trials, comparing online haemodiafiltration with haemodialysis, that were designed to measure mortality outcomes. The primary outcome was all-cause mortality. Hazard ratios were generated using Cox proportional hazards regression models reporting hazard ratios (HR) and 95% confidence intervals (95% CI). Subgroup analyses on predefined patient characteristics and dose-response analyses, using natural splines, on convection volume were performed (PROSPERO registration: CRD42024511514).

Results: Five trials (CONTRAST, ESHOL, Turkish HDF study, French HDF study, CONVINCE, n=4153 patients; 2070 receiving haemodialysis, 2083 receiving haemodiafiltration) proved eligible. After a median follow-up of 30 months (Q1-Q3: 24-36), all-cause mortality occurred in 477 patients (23.3%) treated with haemodiafiltration compared with in 558 patients (27.2%) treated with haemodialysis (HR: 0.84; 95%CI: 0.74 to 0.95). There was no evidence for a differential effect across subgroups. A graded relationship between convection volume and mortality risk was apparent: as the convection volume increases, the mortality risk decreases.

Conclusions: Online haemodiafiltration reduces all-cause mortality and cardiovascular mortality compared with haemodialysis in patients with kidney failure. Results do not differ across patient and treatment characteristics and the risk reduction appears dose-dependent.

Funding: Government Support - Non-U.S.

FR-OR112

Exploratory Post Hoc Analysis of the CONVINCE Randomized Controlled Trial: Differential Treatment Effects of Hemodiafiltration (HDF) and Hemodialysis (HD) on Quality of Life

Krister Cromm,[1] Felix Fischer,[2] Claudia M. Barth,[3] Bernard J. Canaud,[4] Jorgen B. Hegbrant,[5] Giovanni Strippoli,[6] Mark Woodward,[7] Michiel L. Bots,[8] Peter J. Blankestijn,[8] Matthias Rose.[2] The CONVINCE Scientific Committee and CONVINCE Investigators. *[1]Fresenius Medical Care AG, Bad Homburg, Germany; [2]Center for Patient-Centered Outcomes Research, Charite - Universitatsmedizin Berlin, Berlin, Germany; [3]B. Braun Avitum AG, Melsungen, Germany; [4]Universite de Montpellier, Montpellier, France; [5]Lunds Universitet, Lund, Sweden; [6]Universita degli Studi di Bari Aldo Moro, Bari, Italy; [7]The George Institute for Global Health, Sydney, NSW, Australia; [8]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands.*

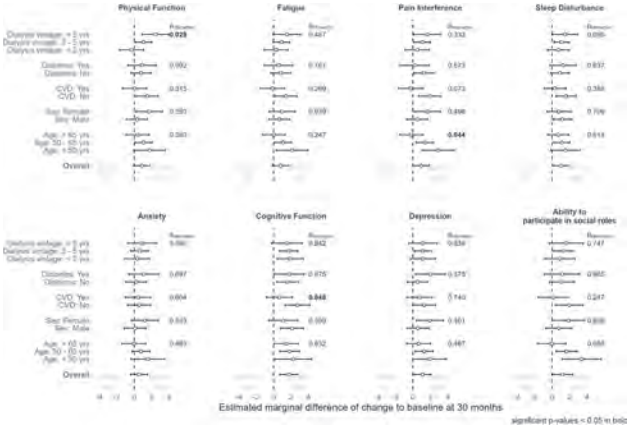
Background: The CONVINCE trial provided compelling evidence that high-dose HDF is associated with a reduction in all-cause mortality when compared to standard high-flux HD. On average, participants receiving HDF also reported a slower decline in their self-reported health status. So far, it is unclear whether there are specific patient groups for whom HDF is particularly effective in maintaining quality of life.

Methods: Out of 1360 participants of the multicenter, randomized controlled CONVINCE trial comparing HDF with HD, 1211 (89%) provided data on eight domains of self-reported health status (Physical Function, Fatigue, Pain Interference, Sleep Disturbance, Anxiety, Cognitive Function, Depression, Ability to Participate in Social Roles and Activities). These were assessed every 3 months over the course of the trial. We investigated differential treatment effects of HDF compared to HD by age group (<50 yrs (n = 240), 50-65 yrs (514), >65 yrs (606)), biological sex (male (856), female (504)), history of cardiovascular disease (yes (612), no (748)), diabetes at baseline (yes (481), no (879)) and dialysis vintage (<2 yrs (548), 2-5 yrs (414), >5 yrs (395)) by testing the significance of interaction terms between treatment and respective subgroup in a longitudinal linear mixed model.

Results: We observed significant differential treatment effects for dialysis vintage on physical function (p = 0.028), for age on pain interference (p = 0.044) and for history of cardiovascular disease on cognitive function (p = 0.048).

Conclusions: High-dose HDF has overall benefits on quality of life. These benefits may vary slightly between patient subgroups, but these differences appear to be small. Findings should be weighed carefully due to multiple statistical comparisons.

Funding: Government Support - Non-U.S.



FR-OR113

Varoglutamstat Increases Glomerular Filtration in Elderly Patients without Signs of Proteinuria and Potentially Offers a New Approach to Treat Diabetic Kidney Disease (DKD)

Frank T. Weber,[1] Christine Wenzkowski,[1] Michael Karl Schaeffer,[1] Sylvia Schell-Mader,[1] Antje Meyer,[1] Stefan Tasler,[1] Katharina Fuchs,[1] Asger R. Bihlet,[2] Kevin Carroll,[5] Tobias B. Huber.[3,4] *[1]Vivoryon Therapeutics N.V., Halle (Saale), Germany; [2]NBCD A/S, Herlev, Denmark; [3]Department of Medicine, Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [4]Hamburg Center for Kidney Health, Hamburg, Germany; [5]KJC Statistics Ltd, Dublin, Ireland.*

Background: Varoglutamstat is an oral, small molecule inhibitor of glutaminyl cyclases (QPCT/L) designed to target Alzheimers disease pathology. In the phase 2b VIVIAD study, effects on kidney function as judged by a significant and clinical meaningful improvement of the estimated glomerular filtration rate (eGFR) were observed over time by slope analysis.

Methods: VIVIAD (NCT04498650) is a multicenter, randomized, placebo-controlled, double-blind, parallel group dose-finding Phase 2b study in 259 patients with Mild Cognitive Impairment (MCI) and early Alzheimers disease (AD) with a treatment duration between 48 and 96 weeks. Participants received 300 mg or 600 mg varoglutamstat, or placebo, twice-daily.

Results: A significant increase of 3.4 mL/min/1.73m2/year ($p<0.001$) the annualized rate of change of eGFR vs placebo was found in the overall study population. Further investigations in patients with diabetes (N=32) showed an increase of > 8 mL/min/1.73m2/year (p=0.02). Additional effects in the diabetes subgroup included a reduction in liver transaminases (AST/ALT) of 6 units average, a mild weight loss (- 4 kg), and a reduction in mean arterial pressure (- 5 mmHg) at week 48. Semi quantitative urine dip-stick evaluation did not reveal signs of sustained proteinuria. The safety assessment showed that varoglutamstat was safe and well-tolerated. There were no meaningful differences in adverse events observed in renal and metabolic system organ classes versus placebo or the total population. Earlier preclinical data suggest beneficial effects for varoglutamstat on inflammation and fibrosis. However, the specific functional improvement of the kidney was unexpected and additional mechanistic studies are ongoing.

Conclusions: The significant increase in eGFR and several findings of the VIVIAD study support a further development in a new indication like diabetic kidney disease. The precise molecular mechanism of action of varoglutamstat is under investigation. Importantly, a clinical study in a relevant population and with additional endpoints like measures of albuminuria/proteinuria (UACR/UPCR), inflammation and fibrosis-related biomarkers, in addition to eGFR slope analysis, is in planning.

FR-OR114

Replacing Mycophenolate Mofetil by Everolimus in Kidney Transplant Recipients to Increase Vaccine Immunogenicity: The PREPARE-iVAC Trial

A. Lianne Messchendorp, Jan-Stephan Sanders. The RECOVAC Consortium. *Nephrology, Universitair Medisch Centrum Groningen, Groningen, Netherlands.*

Background: Vaccine immunogenicity is diminished in kidney transplant recipients (KTR) due to the use of immunosuppressive agents. Patients on long-term everolimus (EVR) elicit a higher immune response after vaccination compared to patients on mycophenolate mofetil (MMF). Whether short-term replacement of MMF by EVR improves vaccine immunogenicity needs yet to be established.

Methods: In this multicenter, open-label randomized controlled trial, KTR were randomized 1:1 to continue MMF or replace MMF by EVR (ClinicalTrials.gov:NCT05924685). After randomization, patients received a COVID-19 vaccination (mRNA Omicron XBB.1.5) at 6 weeks and two herpes zoster (HZ) vaccinations (Recombinant Zoster Vaccine) at 10 and 14 weeks. Primary objective was to investigate whether vaccine immunogenicity was superior in the EVR group by comparing neutralizing antibody titers 28 days after COVID-19 vaccination, for which a minimum sample size of 88 patients was calculated. Secondary objectives were to evaluate antibody responses 28 days after COVID-19 and HZ vaccination and safety of replacing MMF by EVR.

Results: A total of 110 KTR from 7 UMCs across the Netherlands were randomized, 55 to MMF and 55 to EVR. Neutralizing Omicron XBB.1.5 titers (PRNT50) after COVID-19 vaccination were comparable between the MMF and EVR group (log10 difference -0.07 [-0.37-0.22], p=0.62). Results were supported by SARS-CoV-2 S1-specific IgG levels (4280 (1425-14250) vs. 3870 (1018-9535) BAU/mL, p=0.38). After second HZ vaccination however, the VZV gE-specific IgG titer was higher in the EVR group (1101 (440-2078) vs. 2192 (888-4523) 50% endpoint titer, p=0.004). Next to usual side effects of EVR (edema, oral ulcers, thrombocytopenia), more bacterial infections were observed with EVR (11.1 vs. 27.3%, p=0.03), which were in general easily manageable. There were no cases of acute rejection.

Conclusions: Short-term replacement of MMF by EVR does not improve COVID-19 vaccine immunogenicity but may enhance HZ vaccine immunogenicity in KTR. This discrepancy may be explained as patient have received multiple prior COVID-19 vaccinations, whereas this was a primary HZ vaccination. These data indicate that replacing MMF by EVR may be a valuable strategy to improve vaccine immunogenicity in case of novel viral threats and contribute to pandemic preparedness.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-OR91

Impact of Targeted Hyponatremia Correction on 30-Day Mortality and Rehospitalization Rate

Julie Refardt,[1,2] Laura Potasso,[2] Anissa Pelouto,[3] Claudia Gregoriano,[8] Markus Koster,[6] Ivana Dora Vodanovic,[10] Dario Norello,[4] Svenja Ravioli,[5] Sadrija Cukoski,[5] Lana Sambula,[10] Nikola Rapsch,[5] Sophie Monnerat,[2] Julia Beck,[2] Deborah R. Vogt,[2] Martina L. Bontognali,[6] Philipp Schuetz,[8] Adrienne A. Zandbergen,[3] Alessandro Peri,[4] Darko Kastelan,[10] Gregor Lindner,[7] Jörg D. Leuppi,[9] Beat Mueller,[8] Volker R. Burst,[5] Ewout J. Hoorn,[3] Mirjam Christ-Crain.[2] The HIT Study Group. *[1]Endocrinology, Erasmus MC, Rotterdam, Netherlands; [2]Endocrinology, Universitatsspital Basel, Basel, Switzerland; [3]Nephrology, Erasmus MC, Rotterdam, Netherlands; [4]Endocrinology, Careggi University Hospital, Florence, Italy; [5]Nephrology, Universitatsklinikum Koln, Cologne, Germany; [6]Endocrinology, Kantonsspital St Gallen, Sankt Gallen, Switzerland; [7]Endocrinology, Kantonsspital Solothurn, Solothurn, Switzerland; [8]Endocrinology, University Hospital Aarau, Aarau, Switzerland; [9]Endocrinology, Kantonsspital Baselland, Liestal, Switzerland; [10]Klinicki Bolnicki Centar Zagreb, Zagreb, Croatia.*

Background: Chronic hyponatremia is associated with increased mortality and rehospitalization rates, but it is unclear whether this relationship is causal. This leads to uncertainties in correction, which is therefore often slow or non-existent. The aim of this study was therefore to evaluate the direct effects of targeted hyponatremia correction versus routine care on mortality and rehospitalization rates.

Methods: Randomized controlled, superiority, parallel-group, international multi-center trial with blinded outcome assessment. Hospitalized participants with hyponatremia <130 mmol/L from nine tertiary centers across Europe were assigned to undergo either targeted correction of plasma sodium levels according to guidelines (intervention) or routine care for hyponatremia (control). The primary outcome was the combined risk of death or rehospitalization within 30 days of study inclusion.

Results: 2174 patients were included in the primary analysis of which 1079 (49.6%) were randomized to the intervention and 1095 (50.4%) to the control group. Through the intervention, 641 (60.4%) patients reached normonatremia, compared to 493 (46.2%) patients in the control group. Within 30 days, death or rehospitalization occurred in 93 (8.6%) and 138 (13.0%) patients in the intervention group, compared to 93 (8.5%) and 151 (14.0%) patients in the control group, leading to a combined event rate of 21.0% (224/1079 patients) in the intervention group and 22.2% (239/1095 patients) in the control group, estimated absolute difference in proportions [95% CI] -1.2% [-4.7, 2.3], p=0.50. This result was robust in the per protocol analysis and in subgroup analyses considering hyponatremia etiology, severity or correction rate.

Conclusions: In this large hyponatremia intervention trial, targeted plasma sodium correction did not reduce 30-day mortality and rehospitalization rates. This suggests that in hospitalized patients, chronic hyponatremia is a marker of disease severity rather than a cause of worse outcome.

Funding: Government Support - Non-U.S.

SA-OR92

VALIANT: A Randomized, Multicenter, Double-Blind, Placebo (PBO)-Controlled, Phase 3 Trial of Pegcetacoplan for Patients with Native or Post-transplant Recurrent Glomerulopathy (C3G) or Primary Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

Carla M. Nester,[1] Andrew S. Bomback,[2] María Gema Ariceta Iraola,[3] Yahsou Delmas,[4] Bradley P. Dixon,[5] Daniel P. Gale,[6] Larry A. Greenbaum,[7] Seung Hyeok Han,[8] Nicole Isbel,[9,10] Christoph Licht,[11] Antonio Mastrangelo,[12] Masashi Mizuno,[13] Maria Izabel N. de Holanda,[14] Matthew C. Pickering,[15] Giuseppe Remuzzi,[16] Nicole Van De Kar,[17] Marina Vivarelli,[18] Patrick D. Walker,[19] Dean Wallace,[20] Daniel Zecher,[21] Li Li,[22] Zhongshen Wang,[22] Luis López Lázaro,[23] Johan Szamosi,[23] Fadi Fakhouri.[24] *[1]University of Iowa, Stead Family Children's Hospital, Iowa City, IA; [2]New York-Presbyterian/Columbia University Irving Medical Center, New York, NY; [3]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [4]Service de Néphrologie, Centre Hospitalier Universitaire de Bordeaux Groupe hospitalier Pellegrin, Bordeaux, France; [5]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [6]University College London, London, United Kingdom; [7]Emory University School of Medicine, Atlanta, GA; [8]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [9]Princess Alexandra Hospital, Brisbane, QLD, Australia; [10]The University of Queensland, Brisbane, QLD, Australia; [11]The Hospital for Sick Children, Toronto, ON, Canada; [12]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [13]Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Nagoya, Japan; [14]Hospital Federal de Bonsucesso, Ruschel Medicina, Rio de Janeiro, Brazil; [15]Imperial College London, London, United Kingdom; [16]Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; [17]Radboudumc Amalia Children's Hospital, Nijmegen, Netherlands; [18]Ospedale Pediatrico Bambino Gesu IRCCS, Rome, Italy; [19]Arkana Laboratories, Little Rock, AR; [20]Royal Manchester Children's Hospital, Manchester, United Kingdom; [21]Krankenhaus Barmherzige Bruder Regensburg, Regensburg, Germany; [22]Apellis Pharmaceuticals Inc, Waltham, MA; [23]Swedish Orphan Biovitrum AB, Stockholm, Sweden; [24]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.*

Background: VALIANT (NCT05067127) is a double-blind, PBO-controlled trial investigating the efficacy/safety of pegcetacoplan (PEG), a C3/C3b inhibitor, in adolescents (≥12 yrs) and adults with native or post-transplant recurrent C3G or primary IC-MPGN.

Methods: Patients (pts) received PEG (SC infusion 2x/wk) or PBO (randomized 1:1) for 26 wks. The primary endpoint was log-transformed ratio of uPCR at wk 26 vs. baseline to measure proteinuria reduction vs. PBO.

Results: 124 pts were randomized to PEG (n=63) or PBO (n=61). The primary endpoint was met:68.3% (95% CI –76.3, –57.7) uPCR reduction in PEG vs. PBO arms at wk 26 (p<0.0001; **Table**). Results were consistent across all subgroups (disease type, age, and transplant status). Robust reductions in C3c staining and clinically meaningful eGFR stabilization were observed with PEG vs. PBO (**Table**). Treatment-emergent AE frequency and severity were similar between arms. None of the 4 serious infections (3 PEG; 1 PBO) were attributed to encapsulated bacteria. 1 death occurred in the PEG arm due to COVID-19 pneumonia (unrelated to PEG).

Conclusions: PEG, a C3/C3b inhibitor, is the first therapy to achieve significant and clinically meaningful reductions in proteinuria (68.3% vs. PBO) and C3c staining and eGFR stabilization, compared with PBO in pts ≥12 yrs with C3G or primary IC-MPGN and was well tolerated.

Table. VALIANT disposition and primary and key secondary efficacy outcomes (wk 26 vs. BL, unless otherwise specified)

	PEG (N=63) --- C3G (n=51) Primary IC-MPGN (n=12) --- Adolescents (n=28) Adults (n=35) --- Native (n=58) Posttransplant (n=5)	PBO (N=61) --- C3G (n=45) Primary IC-MPGN (n=16) --- Adolescents (n=27) Adults (n=34) --- Native (n=57) Posttransplant (n=4)	Difference in PEG vs. PBO arms	P-value for PEG vs. PBO arms
Primary Endpoint (Overall Population)				
uPCR change, LS mean log-transformed ratio (95% CI)	–67.3% (–74.9, –57.5%)	3.2% (–8.3, 16.2%)	Relative reduction (95% CI): 68.3% (–76.3, –57.7)	p<0.0001[a]
Key Secondary Endpoints (Overall Population)				
Composite renal endpoint (≥50% uPCR and ≤15% eGFR reductions) at wk 26, n (%)	32 (50.8)	2 (3.3)	OR (95% CI): 29.4 (6.5, 132.2)	p<0.0001[a]
≥50% uPCR reduction, n (%)	39 (61.9)	3 (4.9)	OR (95% CI): 32.1 (8.8, 116.9)	p<0.0001[a]
C3G histologic index activity score change, adjusted LS mean change (95% CI)[b]	n=35 –3.5 (–4.7, –2.2)	n=34 –2.5 (–3.8, –1.2)	Adjusted LS mean difference (95% CI): –1.0 (–2.8, 0.8)	p=0.2753[a]
Reduced C3c renal biopsy staining of ≥2 OOM, n (%)[b]	n=35 26 (74.3)	n=34 4 (11.8)	OR (95% CI): 27.4 (6.5, 115.9)	Nominal p<0.0001
eGFR change, LS mean change (95% CI), mL/min/1.73m²	–1.6 (–6.0, 2.8)	–7.9 (–11.7, –4.2)	Adjusted LS mean difference (95% CI): 6.3 (0.5, 12.1)	Nominal p=0.0322

BL, baseline; C3G, C3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; LS, least squares; OOM, orders of magnitude; OR, odds ratio; PBO, placebo; PEG, pegcetacoplan; pts, patients; SE, standard error; uPCR, urine protein to creatinine ratio; wk, week.
Data cut-off date: June 20, 2024. Includes all randomized pts. Endpoints listed in order of hierarchical testing. [a]2-sided p value. [b]In adults with evaluable BL and wk 26 renal biopsies.

SA-OR93

Semaglutide Reduced Risks of Major Kidney Outcomes Irrespective of CKD Severity in the FLOW Trial

Katherine R. Tuttle,[1,2] Johannes F. Mann,[3,4] Ekaterina Sokareva,[11] Brian Rayner,[5] Giuseppe Pugliese,[6] Richard E. Pratley,[7] Vlado Perkovic,[8] Kenneth W. Mahaffey,[9] Naoki Kashihara,[10] Ole K. Jeppesen,[11] Janusz Gumprecht,[18] Ricardo Correa-Rotter,[12] David Cherney,[13,14] Heidrun Bosch-Traberg,[11] Mustafa Arici,[15] Peter Rossing.[16,17] *[1]Providence Medical Research Center, Providence Health and Services, Spokane, WA; [2]Nephrology, University of Washington School of Medicine, Seattle, WA; [3]KfH Nierenzentrum fur Kinder und Jugendliche Munster, Munster, Germany; [4]Nephrology, Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany; [5]Groote Schuur Hospital, Observatory, South Africa; [6]Universita degli Studi di Roma La Sapienza, Rome, Italy; [7]AdventHealth Central Florida, Orlando, FL; [8]University of New South Wales, Sydney, NSW, Australia; [9]Stanford University School of Medicine, Stanford, CA; [10]Kawasaki Ika Daigaku, Kurashiki, Japan; [11]Novo Nordisk A/S, Bagsvaerd, Denmark; [12]Instituto Nacional de Ciencias y Nutrition Salvador Zubiran, Ciudad de Mexico, Mexico; [13]Toronto General Hospital, Toronto, ON, Canada; [14]University of Toronto, Toronto, ON, Canada; [15]Hacettepe Universitesi, Ankara, Turkey; [16]Steno Diabetes Center Copenhagen, Herlev, Denmark; [17]Kobenhavns Universitet, Kobenhavn, Denmark; [18]Slaski Uniwersytet Medyczny w Katowicach Wydzial Nauk Medycznych w Zabrzu, Zabrze, Poland.*

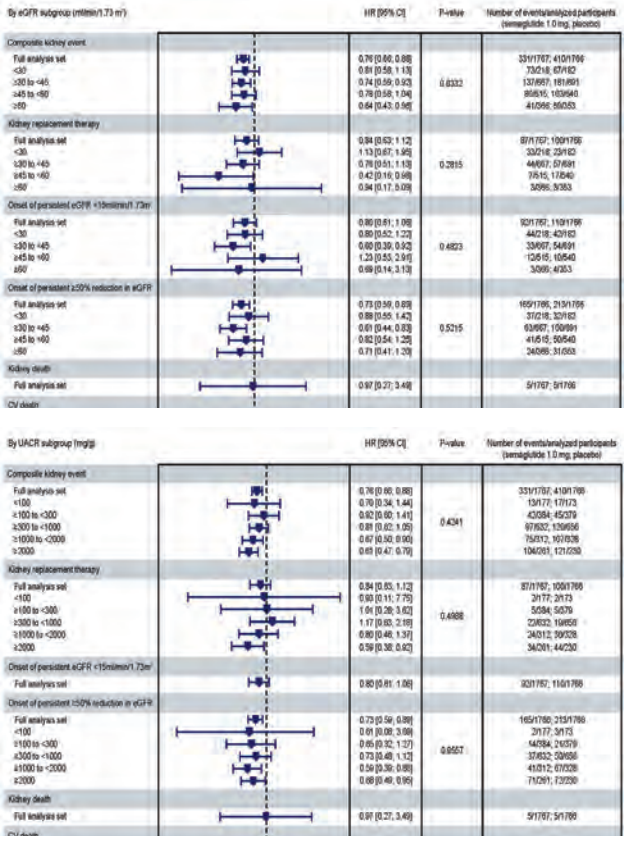
Background: Semaglutide reduced risks of major kidney outcomes, cardiovascular (CV) events, and death from any cause in participants with type 2 diabetes (T2D) and chronic kidney disease (CKD) in the FLOW trial. The aim of this analysis was to assess kidney outcomes by baseline CKD severity.

Methods: Participants had T2D with eGFR 50–75 mL/min/1.73m² and urine albumin–creatinine ratio (UACR) >300–<5000 mg/g, or eGFR 25–<50 mL/min/1.73m² and UACR >100–<5000 mg/g. They were randomized to subcutaneous semaglutide 1 mg once weekly or placebo. The FLOW primary outcome was a composite of kidney failure (initiation of chronic kidney replacement therapy, eGFR <15 ml/min/1.73m²), ≥50% eGFR decline, or death due to kidney or CV causes. Participants were categorized by baseline eGFR and UACR.

Results: Among 3533 participants, 30% (n=1069) were women. At baseline, their mean age was 67 years, mean eGFR was 47 mL/min/1.73 m^2, and median UACR was 568 mg/g. The hazard ratio for the primary outcome was 0.76 (95% CI 0.66–0.88) for semaglutide versus placebo over a median of 3.4 years. Consistent results were observed across eGFR and UACR categories (**Figure**).

Conclusions: Semaglutide safely reduced risks of major kidney outcomes irrespective of CKD severity defined by baseline eGFR or UACR in participants with T2D and CKD in the FLOW trial.

Funding: Commercial Support - Novo Nordisk



SA-OR94

Pain Coping Skills Training for Patients Receiving Hemodialysis: The HOPE Consortium Randomized Clinical Trial

Laura M. Dember,[1] Jesse Y. Hsu,[1] Rajnish Mehrotra,[2] Kerri L. Cavanaugh,[3] Sahir Kalim,[4] David M. Charytan,[5] Michael J. Fischer,[6] Manisha Jhamb,[7] Kirsten L. Johansen,[8] William Becker,[9] Francis J. Keefe,[10] David M. White,[11] Paul L. Kimmel,[12] Daniel Cukor.[5] HOPE Consortium. *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]University of Washington, Seattle, WA; [3]Vanderbilt University Medical Center, Nashville, TN; [4]Massachusetts General Hospital, Boston, MA; [5]New York University Grossman School of Medicine, New York, NY; [6]University of Illinois Hospital & Health Sciences System, Chicago, IL; [7]University of Pittsburgh School of Medicine, Pittsburgh, PA; [8]Hennepin Healthcare System Inc, Minneapolis, MN; [9]Yale University School of Medicine, New Haven, CT; [10]Duke University School of Medicine, Durham, NC; [11]American Association of Kidney Patients, Tampa, FL; [12]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.*

Background: Chronic pain is common among individuals undergoing maintenance hemodialysis and contributes to poor quality of life, depression, and anxiety. Pharmacologic management of pain is challenging in this patient population.

Methods: In this multicenter randomized controlled trial, patients undergoing hemodialysis and experiencing chronic moderate or severe pain were randomly assigned 1:1 to a cognitive behavioral intervention called pain coping skills training or to usual care. The intervention consisted of 12 weeks of remotely delivered coach-led sessions followed by 12 weeks of daily telephone-based interactive voice response sessions. The primary outcome was pain interference measured by the Brief Pain Inventory (BPI) Interference subscale at 12, 24, and 36 weeks, with change from baseline to 12 weeks serving as the primary endpoint. Secondary outcomes included pain intensity, pain catastrophizing, quality of life, depression, and anxiety.

Results: 643 patients enrolled at 16 centers and 103 affiliated dialysis facilities were randomized to pain coping skills training (319 participants) or usual care (324 participants), yielding a cohort with 44.8% female, 45.9% Black, and 18.5% Hispanic participants. At Week 12 (primary endpoint), the pain coping skills training group had a larger reduction in the BPI Interference score compared with usual care [between-group difference (95% CI) -0.49 (-0.85, -0.12); p=0.009]. The effect persisted at Week 24 [difference -0.48 (-0.86, -0.11)] but was diminished at Week 36 [difference -0.34 (-0.72, 0.04)]. A decrease in BPI Interference ≥1 point (minimal clinically important difference) occurred in 50.9% of those in pain coping skills training vs 36.6% in usual care at 12 weeks [OR (95% CI) 1.79 (1.28, 2.49)], and 55.0% vs 42.8% at 24 weeks [OR 1.59 (1.13, 2.24)]. Favorable changes with the intervention were also apparent for secondary outcomes of pain intensity, quality of life, depression, and anxiety at Weeks 12 and/or 24, and for pain catastrophizing at Weeks 24 and 36.

Conclusions: Among patients undergoing maintenance hemodialysis, pain coping skills training had benefits on pain interference and other pain-associated outcomes. Clinicaltrials.gov NCT04571619

Funding: NIDDK Support

SA-OR95

Prospective Randomized Trial of Humacyte's Acellular Tissue Engineered Vessel vs. Autologous Arteriovenous Fistula for Hemodialysis Access

Mohamad A. Hussain,[1] Charles K. Ozaki,[1] Ernest E. Moore,[3] Zakaria Khondker,[2] Shamik J. Parikh,[2] Laura E. Niklason.[2] *[1]Vascular and Endovascular Surgery, Brigham and Women's Hospital, Boston, MA; [2]Humacyte Global Inc, Durham, NC; [3]Ernest E Moore Shock Trauma Center, Denver Health Main Campus, Denver, CO.*

Background: Arteriovenous fistulas (AVFs) are a preferred method for initial vascular access in patients requiring hemodialysis (HD). Failure of AVF maturation can drive increased catheter use and associated increased morbidity/mortality. An alternative vascular access option that offers the benefits of AVFs, including a low infection rate, without the associated maturation failure, is needed.

Methods: We conducted a phase 3, prospective, multicenter, two-arm, randomized controlled trial in 242 subjects with HD undergoing surgical vascular access creation. Receipt of the Acellular Tissue Engineered Vessel (ATEV) or autologous AVF was randomized. Co-primary outcomes were 6-month functional patency and 12-month secondary patency after access creation. Secondary outcomes included comparisons of access usability and infection rates.

Results: Mean participant age was 58.6 years; 29% were female. ATEV recipients had higher rates of 6-month functional patency (81% vs 68% for AVF) and 12-month secondary patency (68% vs 62% for AVF) (p=0.0071; joint test for co-primary endpoints). Mean duration of ATEV use was also significantly higher than AVF (7.5 vs 6.1 months, p=0.0162). Female ATEV subjects experienced higher rates of 6-month functional patency (89% vs. 55% for AVF) and 12-month secondary patency (81% vs. 49% for AVF) (p<0.0001; joint test). Access-related infection rates were comparable (ATEV 5.8% vs AVF 4.1%). No unexpected safety events were observed.

Conclusions: Humacyte ATEV had better access functional patency and usability versus AVFs at one year. Female subjects experienced improved outcomes, supporting ATEV consideration as a novel access option for subjects at high risk for AVF non-maturation. (CLN-PRO-V007; ClinicalTrials.gov, NCT03183245).

Funding: Commercial Support - Humacyte Global, Inc.

Co-primary Endpoints.

	Overall Subjects		
	ATEV (n=123)	AVF (n=119)	p-value
Functional Patency 6 months	81.3% (100)	66.4% (79)	0.0071
Secondary Patency 12 months	68.3% (84)	62.2% (74)	
Duration of Usability 12 months	7.5 months (SD=4.2)	6.1 months (SD=4.5)	0.0162
	Female Subjects		
	ATEV (n=37)	AVF (n=33)	p-value
Functional Patency 6 months	89.2% (33)	54.5% (18)	<0.0001
Secondary Patency 12 months	81.1% (30)	48.5% (16)	

SD: standard deviation

SA-OR96

Efficacy and Safety of Dapagliflozin in Patients with CKD Stages 4-5

Chi-Chih Hung, Yi-Wen Chiu, Shang-Jyh Hwang. DAPA advKD Trial Investigators. *Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.*

Background: Importance: Dapagliflozin improves renal outcome in patients with chronic kidney disease (CKD), but the effect of late initiating dapagliflozin when estimated glomerular filtration rate (eGFR) <25 mL/min/1.73m^2 remains uncertain. Objective: To evaluate the efficacy and safety of dapagliflozin in patients with CKD stage 4 and 5.

Methods: Design: Dapagliflozin and Renal Surrogate Outcomes in Advanced Chronic Kidney Disease (DAPA advKD) trial (NCT05196347) was an investigator-led, randomized, open-label, trial designed to recruit 180 patients with eGFR 10-30 mL/min/1.73m^2 and eGFR decline ≥2.5 mL/min/1.73m^2/yr. Interventions: Patients were randomized 2:1 to dapagliflozin (5-10 mg/d) + integrated CKD care or integrated CKD care alone. Main outcomes: The primary outcome was a preservation of eGFR decline ≥0.75 ml/min/1.73m^2/yr. The 1st secondary outcome (renal endpoint) was a composite of renal replacement therapy, eGFR <5 mL/min/1.73m^2, renal or cardiovascular (CV) death, or a >50% decline in eGFR. The 2nd secondary outcome (renal and CV endpoint) was a composite of renal outcome as above, acute kidney injury (AKI) and heart failure. Predefined safety outcomes were measured.

Results: Over a median of 1.62 years, total eGFR slope (mL/min/1.73m^2/yr) were -2.24 (-4.70 to -0.62) and -3.67 (-7.16 to -1.25) in the dapagliflozin and control groups, respectively; the primary outcome of eGFR slope difference was 1.06 (0.10 to 2.32) (p=0.019, linear mixed model). The secondary (renal) outcome occurred in 24/120 (20%) and 21/60 (35%) participants in the dapagliflozin and control groups, respectively (hazard ratio, 0.50 (0.28 to 0.89), p=0.019). The secondary (renal and CV) outcome occurred in 25/120 (21%) and 21/60 (35.0%) participants in the dapagliflozin and control groups, respectively (hazard ratio, 0.52 (0.29 to 0.93), p=0.028). There were higher incidence of AKI and heart failure in the control group, but higher incidence of eGFR dip in the dapagliflozin group. There was no difference of 5p- major adverse CV event and electrolyte imbalance.

Conclusions: Among patients with eGFR 10-30 mL/min/1.73m^2, the risks of eGFR decline and composite renal outcomes were lower with dapagliflozin than with control group.

Funding: Other NIH Support - KMUH Hospital Grant, Commercial Support - AstraZeneca

SA-OR97

Safety and Efficacy of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Shuchi Anand,[1] Suneeta Chimalapati,[6] Maria E. Montez-Rath,[1] Angie Goldsberry,[5] Melanie Chin,[5] Colin J. Meyer,[5] Samina Khan,[5] Rafael José Esteban de la Rosa,[4] Arlene B. Chapman,[2] Bradley A. Warady,[3] Glenn M. Chertow.[1] *[1]Stanford University, Stanford, CA; [2]University of Chicago Pritzker School of Medicine, Chicago, IL; [3]Children's Mercy Kansas City, Kansas City, MO; [4]Universidad de Granada, Granada, Spain; [5]Reata, Boston, MA; [6]Biogen Inc, Cambridge, MA.*

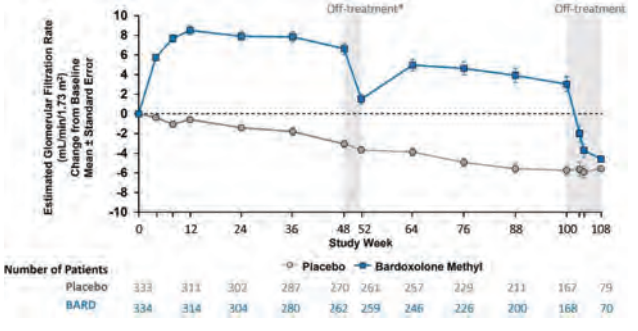
Background: Interstitial fibrosis is a universal finding in nephrectomy samples from patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). Bardoxolone methyl (BARD) activates the nuclear-factor-related factor 2 pathway, hypothesized to attenuate inflammation and fibrosis.

Methods: A phase 3, randomized 1:1, placebo-controlled clinical trial (NCT03918447) was designed to test the efficacy of BARD among patients with ADPKD and reduced eGFR (30-90ml/min/1.73 m^2 for patients 12-55 years, 30-44ml/min/1.73 m^2 for patients 56-70 years) and evidence of rapid eGFR decline (≥ 2.0ml/min/year for 2 years). The primary endpoint was off-treatment change from baseline eGFR at week 108 and the secondary endpoint was change from baseline at end of treatment (week 100). The trial was stopped prematurely by the sponsor, prior to meeting target enrollment.

Results: A total of 667 patients were enrolled, and eGFR (mean [SD]) at baseline were similar between randomized groups (BARD 51.6 [15.5] vs placebo 51.2 [16.8] mL/min/1.73m^2, respectively). 79 and 70 patients randomized to the placebo and Bard group had week 108 eGFR. There was no difference in the off-treatment (week 108) change from baseline (0.97 [95% CI –1.25, 3.19] mL/min/1.73m^2), although end of treatment (week 100) eGFR was higher among patients randomized to the BARD group (7.9 [95% CI 6.41, 9.47] mL/min/1.73m^2; **Fig 1**)). A majority of patients (89% placebo, 94% BARD) had treatment-emergent adverse events (TEAEs). The most common AEs in the group randomized to BARD were muscle spasms, aminotransferase elevations, and nausea. No one experienced serious cardiac events; one death occurred in the study (avalanche accident).

Conclusions: Among the subset of patients with available data on the primary endpoint in the FALCON trial, there was no evidence for preservation of eGFR among patients randomized to BARD at the end of 100 weeks of treatment and an 8-week washout period.

Funding: Commercial Support - Reata



SA-OR98

Small Molecule Premature Termination Codon Readthrough Therapy: A Phase 2 Pediatric and Adult Trial in Nonsense Mutation Alport Syndrome

Daniel P. Gale,[1,2] Detlef Bockenhauer,[1,8] Melanie M. Chan,[1,6] Katie Wong,[2,1] Johannes Pospiech,[3] Tobias Bohnenpoll,[3] Philipp Skroblin,[3] Olivier Radresa,[3] Uwe Andag,[3] Nicole Endlich,[4] Behzad Najafian,[5] Sumit Aggarwal.[7] *[1]Renal Medicine, University College London, London, United Kingdom; [2]UK National Registry of Rare Kidney Diseases (RaDaR), Bristol, United Kingdom; [3]Evotec International GmbH, Gottingen, Germany; [4]Nipoka GmbH, Greifswald, Germany; [5]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA; [6]Imperial College London, London, United Kingdom; [7]Eloxx Pharmaceuticals Inc, Watertown, MA; [8]Department of Paediatrics, Katholieke Universiteit Leuven, Leuven, Belgium.*

Background: Alport syndrome is the second commonest Mendelian kidney disease and shows strong correlation between severity and mutation type, with Nonsense Mutation Alport Syndrome usually associated with kidney failure by late adolescence. ELX-02 is a small molecule that induces readthrough of premature (but not native) stop codons and is efficiently taken up by cells expressing megalin, allowing full length protein to be made by podocytes or tubular cells in the presence of a nonsense mutation.

Methods: An open label study was performed in 3 patients with autosomal recessive Alport syndrome, aged 13, 13 and 19, who each had the stop codon *COL4A4*:p.(Ser969Ter) *in trans* with another pathogenic *COL4A4* variant. Participants required eGFR >60ml/min/1.73m^2 and >0.5g per day proteinuria. Each received 0.75mg/kg subcutaneous ELX-02 daily for 8 weeks with follow-up for a further 12 weeks. Proteinuria was assessed before, during and after treatment. Filtration Slit Density (FSD), with automated 3D-SIM (structured illumination microscopy), and Foot Process Width (FPW), with stereology in a masked fashion, were assessed in pre- and post-treatment kidney biopsies.

Results: No significant safety signals were observed. Immunostaining for Collagen IV alpha 5 chain was globally (2 patients) or partially (1 patient) absent before treatment and detectable segmentally following treatment in all 3 patients. FSD improved in all patients after 2 months' treatment: pre-treatment 1.0 (48.5% of the mean (±standard deviation) of 2.06 (±0.12) in healthy individuals), 1.54 (74.8%) and 0.8 (38.8%); post-treatment: 1.5 (72.8%), 1.75 (85.0%) and 1.73 (80.6%), p=0.06, paired t-test. FPW was significantly reduced in 2 patients, changing by -19%, +6% and -45% respectively. Proteinuria was variable but reduced in 2 of the 3 patients during or following treatment.

Conclusions: This first evidence of efficacy of a gene-targeted therapy in a podocyte-based Mendelian disease justifies a follow-on randomised-controlled study to quantify the potential for clinical benefit. Therapeutic readthrough of premature termination codons in Alport Syndrome suggests other genes expressed by megalin-expressing kidney cells may be targetable with this approach.

Funding: Commercial Support - Eloxx Pharmaceuticals Inc

SA-OR99

Associations of APOL1 Biallelic and Monoallelic Kidney Disease Variants with CKDs in West Africans: H3Africa KDRN Study

Rasheed A. Gbadegesin,[1] Ifeoma I. Ulasi,[5] Yemi R. Raji,[2] Manmak Mamven,[3] Adebowale A. Adeyemo,[4] Titilayo O. Ilori,[7] Adaobi Solarin,[6] Paul L. Kimmel,[8] Frank C. Brosius,[9] Matthias Kretzler,[10] Jeffrey B. Hodgin,[10] Martin Pollak,[11] Barry I. Freedman,[12] Winfred W. Williams,[13] Rulan S. Parekh,[14] Dwomoa Adu,[15] Akinlolu Ojo.[16] *[1]Pediatrics, Duke University School of Medicine, Durham, NC; [2]University of Ibadan, Ibadan, Oyo, Nigeria; [3]University of Abuja, Abuja, Federal Capital Territory, Nigeria; [4]National Human Genome Research Institute, Bethesda, MD; [5]Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [6]Lagos State University, Ojo, Lagos, Nigeria; [7]Boston University, Boston, MA; [8]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [9]University of Arizona, Tucson, AZ; [10]University of Michigan, Ann Arbor, MI; [11]Beth Israel Deaconess Medical Center, Boston, MA; [12]Wake Forest University School of Medicine, Winston-Salem, NC; [13]Massachusetts General Hospital, Boston, MA; [14]Women's College Hospital, Toronto, ON, Canada; [15]University of Ghana Medical School, Accra, Greater Accra, Ghana; [16]The University of Kansas Medical Center, Kansas City, KS.*

Background: Background: Apolipoprotein L1 gene (*APOL1*) variants are risk factors for chronic kidney disease (CKD) among African Americans (AA). Data are sparse on the genetic epidemiology and clinical association of *APOL1* variants with CKD in West Africans, a major group among the AA population.

Methods: The Human Health and Heredity in Africa (H3Africa) Kidney Disease Research Network studied 8,355 participants from Ghana and Nigeria: 4,712 participants with CKD stages 2-5, 866 participants with biopsy proven glomerular diseases, and 2777 controls (eGFR ≥90 ml/min/1.73m2 and no proteinuria). The association of CKD with high-risk carriers (two *APOL1* alleles) and low-risk carriers (<2 *APOL1* alleles) was determined by fitting logistic regression models controlling for covariates, including clinical site, age, and sex.

Results: Monoallelic and biallelic *APOL1* variant prevalence were 43.0% and 29.7%, respectively. Compared with low-risk carriers, the adjusted odds of CKD and focal segmental glomerulosclerosis (FSGS) among high-risk carriers were 1.25 (95%CI: 1.11-1.40) and 1.84 (95%CI 1.30-2.61), respectively. Compared with those with no *APOL1* variant (G0/G0), persons with one APOL1 variant (G0/G1, G0/G2) had higher odds of CKD (OR 1.18, 95% CI 1.04-1.33) and FSGS (adjusted OR 1.61; 95% CI 1.04-2.48). Covariates did not modify the association of 1-2 *APOL1* variants with CKD or FSGS.

Conclusions: Both monoallelic (G1/G0, G2/G0) and biallelic (G1/G1, G2/G2, G1/G2) risk variants have 18% and 25% higher odds of CKD, and 61% and 84% higher odds of FSGS, respectively. Individuals with monoallelic *APOL1* variant should be classified as being at high risk for CKD and FSGS.

Funding: NIDDK Support, Other NIH Support - NHGRI

SA-OR100

Safety and Efficacy of Low-Dose CD19-Targeted CAR T Cells in Refractory Pediatric Systemic Lupus Erythematosus (SLE)

Xue He,[1] Yingzi Zhang,[2] Fei Liu,[1] Qiu-yu Li,[1] Jingjing Wang,[1] Jianhua Mao.[1]
[1]Nephrology, Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China; [2]Chongqing Precision Biotech Co., Ltd., Chongqing, China.

Background: Recent advancements indicate that CAR T cell therapy shows promise for treating SLE, there remains a significant lack of data in pediatrics. This study evaluates the safety and efficacy of CAR T-cell therapy in pediatric SLE by utilizing autologous CD19-targeted CAR T cells (MC-1-50) to treat refractory pediatric SLE.

Methods: In this Phase I/II study (NCT06222853), MC-1-50 CAR T cells were manufactured by the PRIMCAR manufacturing platform. Most patients(pts) were preconditioned with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) daily for 3 days, while some received dosage reduction due to infections or intolerance. Toxicity was graded by CTCAE V5.0, CRS and ICANS were graded by ASTCT criteria.

Results: AS of August 2024, 11 pts were infused with MC-1-50 (Table). 9 pts (81.8%) experienced CRS, all at grade 1. 2 pts (18.2%) experienced grade 1 ICANS. There were no unexpected adverse events (AE) or seriou AE reported. 5 pts were followed for over 3 months (3M), with 4 achieving SRI-4 response. Notably, for Pt 5, though there was persistent proteinuria at 3M, all other active indicators had normalized, and her scr levels had declined from a peak of 786 to 169μmol/L, accompanied by a urine output from 50-100ml/day to 1000mL/day. The other pts exhibited varying degrees of improvement. CAR T cells expansion was observed in all dose levels, and B cells were rapidly eliminated within 7 days after infusion while its reconstitution was observed in most pts by 2M. It was noted that the majority of these B cells were predominantly naive B cells.

Conclusions: The treatment of refractory pediatric SLE with a low dose of CD19-targeted CAR-T Cells (MC-1-50) demonstrated an excellent safety profile while exhibiting high efficacy.

Funding: Other NIH Support - National Key Research and Development Program of China (2021YFC2702002,2022YFC2705103), Commercial Support - Chongqing Precision Biotech Co., Ltd.

Disease characteristics and safety outcomes.

ID	Age	Gender	Duration of disease(Years)	Kidney biopsy	Dose	CRS	ICANS	Follow-up period	SLEDAI-2K Baseline	SLEDAI-2K at present
PBC053-001	12	F	3	/	1×10^5/kg	1	1	5M	12	0
PBCP53-002	12	F	5	LN-IV	1×10^5/kg	1	/	4M	12	8
PBC053-003	12	M	5	/	1×10^5/kg	1	/	3M	16	0
PBC053-004	17	F	11	/	0.3×10^5/kg	1	/	3M	12	2
PBC053-005	15	F	2	LN-IV	1×10^5/kg	/	/	2M	12	4
PBC053-006	15	F	7	LN-IV+V	1×10^5/kg	1	/	2M	18	6
PBC053-007	15	F	6	LN-IV	1×10^5/kg	/	/	1M	12	8
PBC053-008	19	F	9	/	3×10^5/kg	1	1	1M	23	6
PBC053-010	6	F	2	LN-V	3×10^5/kg	1	/	14D	10	6
PBC053-011	11	F	0.4	LN-II	0.3×10^5/kg	1	/	14D	12	8
PBC053-012	13	F	5	LN-IV	0.3×10^5/kg	1	/	14D	8	8

SA-OR101

Felzartamab for IgA Nephropathy: Final Results of the IGNAZ Study

Jonathan Barratt,[1] Jürgen Floege,[2] Richard A. Lafayette,[3] Brian M. Schwartz,[4] Uptal D. Patel,[4] Paul Manser,[4] Lisa Kivman,[4] Stefan Haertle,[5] Nicola Faulhaber,[5] Anjali G. Thakur,[5] Sean Barbour.[6] *[1]University of Leicester, Leicester, United Kingdom; [2]Div. Nephrology and Cardiology, RWTH Aachen University, Aachen, Germany; [3]Glomerular Disease Center, Stanford Medicine, Palo Alto, CA; [4]Human Immunology Biosciences, Inc., a Biogen Company, South San Francisco, CA; [5]MorphoSys AG, Planegg, Germany; [6]Division of Nephrology, The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada.*

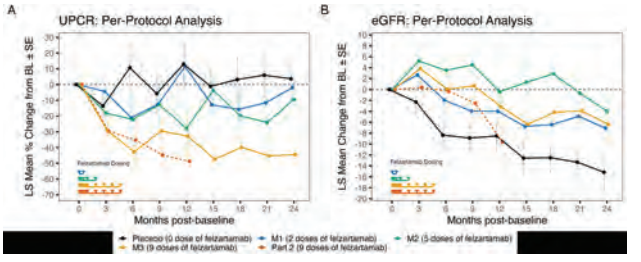
Background: Felzartamab is a monoclonal antibody that binds to CD38 on plasma cells–the likely source of pathogenic Gd-IgA1 and autoantibodies in IgA nephropathy (IgAN). The randomized, double-blind, placebo-controlled phase 2a IGNAZ study assessed the efficacy and safety of felzartamab vs placebo (PBO) in patients with IgAN. Final 24-month data are reported.

Methods: Patients aged 18–80 years with biopsy-confirmed IgAN, proteinuria ≥1.0 g/d (≥0.5 g/d for Japanese patients), and eGFR ≥30 mL/min per 1.73m2 using renin-angiotensin inhibitors ≥3 months were randomized 1:1:1:1 in Part 1 to PBO (n=12) or felzartamab in 1 of 3 arms: 2 doses in 15 days (M1; n=12), 5 doses in 2 months (M2; n=11), and 9 doses in 5 months (M3; n=13). In Part 2, 6 Japanese patients received open-label M3.

Results: Patients were 67% men, with a mean age of 41.6 years, UPCR of 1.7 g/g, and eGFR of 74.6 mL/min per 1.73m2. In Part 1, 40/48 patients completed treatment. Treatment with felzartamab led to rapid, clinically meaningful reductions in UPCR vs PBO, with the greatest effect in the M3 arm (Fig A). Mean eGFR declined less in the felzartamab arms vs PBO (Fig B). Among felzartamab arms, IgA reductions were rapid and durable (lasting 19 months after the last dose); IgG recovered by 6–9 months. Efficacy in Part 2 was similar to that of the Part 1 M3 arm. Treatment-emergent AEs were typically grade 1 or 2 and were not dose-dependent. The most common treatment-related AE was infusion-related reaction (IRR), usually on dose one. There was one treatment-related serious AE of IRR. Five patients discontinued felzartamab for IRR/hypersensitivity. The infection incidence was similar across felzartamab arms; all were grade 1 or 2 and non-serious.

Conclusions: Felzartamab was generally well tolerated and led to sustained proteinuria reduction and reduced eGFR decline vs PBO, indicating potential disease modification in patients with IgAN. Investigation of felzartamab in patients at high risk for loss of kidney function is warranted.

Funding: Commercial Support - Human Immunology Biosciences, Inc., a Biogen Company



SA-OR102

Long-Term Results from the ORIGIN Phase 2b Study of Atacicept for the Treatment of IgA Nephropathy (IgAN)

Jonathan Barratt,[1] Sean Barbour,[2] Robert M. Brenner,[3] Kerry Cooper,[3] Xuelian Wei,[3] Necmi Eren,[4] Jürgen Floege,[5] Vivekanand Jha,[6] Sung Gyun Kim,[7] Bart D. Maes,[8] Richard K. Phoon,[9] Harmeet Singh,[10] Vladimir Tesar,[11] Richard A. Lafayette.[12] ORIGIN Phase 2b Study Team. *[1]University of Leicester, Leicester, United Kingdom; [2]The University of British Columbia, Vancouver, BC, Canada; [3]Vera Therapeutics, Inc., Brisbane, CA; [4]Kocaeli Universitesi, Kocaeli, Turkey; [5]Rheinisch-Westfalische Technische Hochschule Aachen, Aachen, Germany; [6]The George Institute for Global Health India, New Delhi, India; [7]Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea; [8]AZ Delta vzw, Roeselare, Belgium; [9]The University of Sydney, Sydney, NSW, Australia; [10]Western Nephrology, Arvada, CO; [11]Univerzita Karlova, Praha, Czechia; [12]Stanford University, Stanford, CA.*

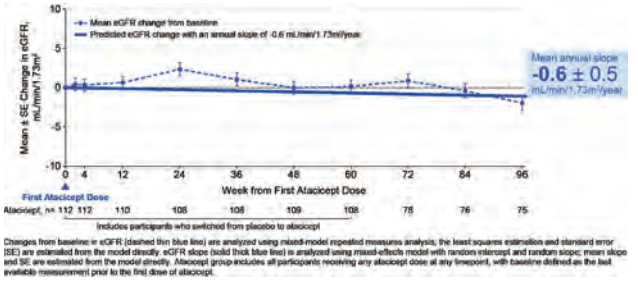
Background: B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL) play key roles in IgAN pathogenesis. Atacicept is a humanized TACI-Fc fusion protein that inhibits both BAFF and APRIL and is self-administered at home by subcutaneous injection. The ORIGIN Phase 2b study met the primary endpoint with a statistically significant and clinically meaningful UPCR reduction compared to placebo at 24 weeks, with a further reduction and eGFR stabilization through 36 weeks. This analysis reports 96-week results from the open-label extension (OLE).

Methods: Participants with IgAN who received atacicept or placebo in the 36-week Phase 2b, randomized, blinded study period were enrolled in an OLE and received atacicept 150 mg for an additional 60 weeks. Key efficacy outcomes were changes in galactose-deficient IgA1 (Gd-IgA1), percentage of participants with hematuria, UPCR, and eGFR over 96 weeks. Long-term safety data were also evaluated.

Results: There were 113 participants who received ≥1 atacicept dose. Over 96 weeks, there were sustained reductions (mean ±SE) in Gd-IgA1 (-65.9% ±1.7%), the percentage of participants with hematuria (-75.0%, 95% CI -87.3, -58.8; in participants with baseline hematuria), and UPCR (-52.2% ±4.7%). Importantly, long-term eGFR was maintained near baseline levels with a mean annualized slope of -0.6 ±0.5 mL/min/1.73m^2/year at 96 weeks (Figure). Safety data showed atacicept was generally well tolerated.

Conclusions: Gd-IgA1, hematuria, and UPCR reductions with eGFR stabilization through 96 weeks demonstrate that atacicept offers a potentially safe, long-term, disease-modifying treatment for IgAN. Specifically, the conversion of an eGFR profile in patients with IgAN from one of steady decline to one representative of the general population without kidney disease[1] supports the potential of atacicept to decrease the high lifetime risk of kidney failure in patients with IgAN. 1. Baba M. PLoS One 2015.

Funding: Commercial Support - Vera Therapeutics, Inc.



Changes from baseline in eGFR (dashed thin blue line) are analyzed using mixed-model repeated measures analysis, the least squares estimates and standard error (SE) are estimated from the model directly. eGFR slope (solid thick blue line) is analyzed using mixed-effects model with random intercept and random slope; mean slope and SE are estimated from the model directly. Atacicept group includes all participants receiving any atacicept dose at any timepoint, with baseline defined as the last available measurement prior to the first dose of atacicept.

SA-OR103

SC0062, a New Selective Endothelin Receptor Type A Antagonist in IgA Nephropathy

Hiddo J. Heerspink,[1,2] Xiaoying Du,[3,4] Yan Xu,[5] Yanning Zhang,[6] Bin Liu,[7] Guangyu Bi,[8] Chengyun Xu,[9] Qun Luo,[10] Henglan Wu,[11] Jianxin Wan,[12] Liou Cao,[13] Rong Wang,[14] Qiuling Fan,[15] Hong Cheng,[16] Lixia Xu,[17] Jiyi Huang,[18] Aimin Zhong,[19] Qingfeng Peng,[20] Yongjiang Hei,[21] Yiwei Wang,[21] Bo Zhou,[21] Liqin Zhang,[21] Jianghua Chen.[3,4] 2-SUCCEED Study Group & BioCity Team.
[1]Universitair Medisch Centrum Groningen Afdeling Klinische Farmacie en Farmacologie, Groningen, Netherlands; [2]The George Institute for Global Health, Sydney, NSW, Australia; [3]Kidney Disease Center, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [4]National key Clinical Department of Kidney Diseases, Hangzhou, China; [5]Department of Nephrology, The Affiliated Hospital of Qingdao University, Qingdao, China; [6]Department of Nephrology, General Hospital of Northern Theatre command, Shenyang, China; [7]Department of Nephrology, Wuxi People's Hospital, Wuxi, China; [8]Department of Nephrology, Northern Jiangsu People's Hospital, Yangzhou, China; [9]Department of Nephrology, Nanchang University Second Affiliated Hospital, Nanchang, China; [10]Department of Nephrology, Ningbo No 2 Hospital, Ningbo, China; [11]Department of Nephrology, First Hospital of Jiaxing, Jiaxing, China; [12]Department of Nephrology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; [13]Department of Nephrology, Jiading District Central Hospital Affiliated Shanghai University of Medicine & Health Sciences, Shanghai, China; [14]Department of Nephrology, Shandong Provincial Hospital, Jinan, China; [15]Department of Nephrology, Shanghai General Hospital, Shanghai, China; [16]Department of Nephrology, Beijing Anzhen Hospital Affiliated to Capital Medical University, Beijing, China; [17]Department of Nephrology, Guangdong Provincial People's Hospital, Guangzhou, China; [18]Department of Nephrology, The First Affiliated Hospital of Xiamen University, Xiamen, China; [19]Department of Nephrology, Jiangxi Provincial People's Hospital, Nanchang, China; [20]Department of Nephrology, Zhuzhou Central Hospital, Zhuzhou, China; [21]Research and Development Division, Biocity Biopharmaceutics Co., Ltd., Wuxi, China.

Background: Endothelin-1 upregulation and endothelin receptor type A (ETA) activation causes proteinuria, kidney inflammation and fibrosis in patients with IgA nephropathy (IgAN). A phase 2 trial was designed to characterize the efficacy, safety and optimal doses of SC0062 in patients with IgAN (2-SUCCEED, NCT05687890).

Methods: We conducted a randomized placebo-controlled double-blind trial in adults with biopsy proven IgAN and eGFR ≥30 mL/min/1.73m^2 with urinary protein: creatinine ratio (UPCR) ≥0.75 g/g or proteinuria ≥1 g/24h despite using maximum tolerated doses of ACEIs or ARBs. Patients were randomized 1:1:1:1 to SC0062 5, 10, 20 mg or matching placebo once daily. The primary efficacy outcome was percent change from baseline in UPCR in 24h urine samples after 12 weeks of treatment. Secondary endpoints included changes in eGFR over time. Safety outcomes including treatment emerging adverse events (TEAE) and serious adverse events (SAE) were recorded throughout the trial.

Results: A total of 131 patients (mean age 42 years [standard deviation (SD) 11]; mean eGFR 72 mL/min/1.73 m^2 [SD 24] and median 24h UPCR 1.2 g/g [Q1-Q3 0.90-1.53]) were randomized to placebo (n=34) or SC0062 5 mg (n=33), 10 mg (n=32), or 20 mg (n=32). SC0062 reduced UPCR versus placebo throughout the treatment period. At Week 12, placebo-corrected geometric mean changes (95% confidence interval) from baseline in UPCR with SC0062 5, 10, and 20 mg were −27.8% (−42.9, −8.6), −20.4% (−37.2, 0.8), and −38.1% (−51.3, −21.3), respectively. The proportion of participants with a reduction in UPCR ≥ 30% from baseline in the placebo, SC0062 5, 10 and 20 mg dose groups were 33.3%, 48.5%, 62.5%, and 71.0%, respectively. No differences in eGFR were observed among treatment groups. The proportion of participants with TEAEs or SAEs was balanced among treatment groups. The rates of peripheral edema were lower in the SC0062 5, 10 and 20 mg groups, at 3%, 0% and 0%, respectively, compared to 14.7% in the placebo group.

Conclusions: In patients with IgA nephropathy and significant proteinuria, the novel ETA selective antagonist SC0062 showed a clinically meaningful reduction in proteinuria and a favorable safety profile with no risk of peripheral edema.

Funding: Commercial Support - Biocity Biopharmaceutics Co., Ltd., Research and Development Plan of "Ling Yan" of the Science Department of Zhejiang Province Technology (2023C03074), National Natural Science Foundation of China Project (U21A20350)

SA-OR104

Out-of-Sequence Placement of Deceased Donor Kidneys Is Exacerbating Inequities

Miko Yu,[1] Syed A. Husain,[1] Joel T. Adler,[2] Lindsey Maclay,[1] Jesse D. Schold,[3] Sumit Mohan.[1] *[1]New York-Presbyterian/Columbia University Irving Medical Center, New York, NY; [2]Dell Seton Medical Center at The University of Texas, Austin, TX; [3]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Deceased donor kidney allocation in the US follows an objective algorithm that is designed to balance equity & utility. Organ procurement organizations (OPOs) have the ability to circumvent this system & are increasingly turning to out-of-sequence (OOS) allocation of organs, allowing them to allocate at their own discretion.

Methods: Using SRTR transplant registry & offer data from 2020-23, we identified all organ offers for deceased donor kidneys, including those placed OOS. We examined the prevalence of OOS allocation, using Gini coefficients as a measure of inequality at the center level.

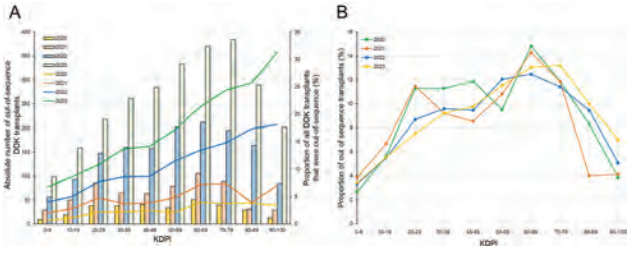
Results: From 2020 to 2023, OOS allocation increased nearly 9-fold, from 342 to 2,882 kidneys, representing 1 in 7 deceased donor kidney transplants – including kidneys across the quality spectrum (**Figure 1**). By 2023, 91% of OPOs were using OOS allocation. Only 14 transplant centers accounted for a third of all OOS transplants, creating a system-wide inequity that is reflected in the persistently high Gini coefficient despite the rapid OOS increase (**Table 1**). OOS recipients include a greater proportion of older, white & male recipients as well as those with private insurance & preemptive patients.

Conclusions: There has been a sharp increase in OOS allocation of deceased donor kidneys across the spectrum of organ quality. Most of these kidneys are being placed at a small number of transplant centers, creating preferential access to transplantation for a subset of patients & exacerbating patient & system-level inequities in access to transplantation.

Funding: NIDDK Support, Other NIH Support - NIH grants DK114893, DK116066, DK126739 and DK130058, Private Foundation Support

Gini coefficients for all OPOs and transplant centers, ranging from 0 (perfect equality) to 1 (perfect inequality)

Center Type	Year	In-sequence Gini	Out-of-sequence Gini
OPO	2020	0.31	0.89
	2021	0.31	0.65
	2022	0.32	0.53
	2023	0.32	0.47
Transplant center	2020	0.49	0.93
	2021	0.50	0.82
	2022	0.48	0.78
	2023	0.48	0.72



SA-OR105

Xenotransplantation and Physiologic Homeostasis: Case Report of a First Living Human Recipient

Sul A Lee,[1] Marie-Camille Lafargue,[1] Winfred W. Williams,[1] Hannah M. Gilligan,[1] Kassem Safa,[1] Abraham Cohen Bucay,[1] Pitchaphon Nissaisorakarn,[1] Ayman Al Jurdi,[1] Harald Jüppner,[1] Susan Low,[2] Michael Curtis,[2] Leonardo V. Riella.[1] Mass General Kidney Transplant Team and eGenesis Team.
[1]Massachusetts General Hospital, Boston, MA; [2]eGenesis Inc, Cambridge, MA.

Background: Although kidney transplantation is the preferred treatment for ESKD, organ shortages severely limit timely access to transplants. Pig-to-human xenotransplantation has been proposed to address this issue, but concerns remain about meeting the physiologic needs of a living human and the potential incompatibility between humans and pigs. Here, we present several physiologic aspects of a gene-edited porcine xenograft in the first living human recipient during 51 days of follow-up.

Methods: A 62-year-old male with ESKD due to diabetes on hemodialysis, who was facing ongoing vascular access challenges, had no living donor options and an expected wait time for a deceased donor kidney exceeding 5 years, was selected for xenotransplantation with a 69-gene-edited porcine kidney donor.

Results: Kidney excretory function was assessed by BSA-adjusted 24-hour urine creatinine clearance (CrCl), Cr-based estimated GFR (eGFR), and cystatin C-based eGFR. The xenograft eGFR was 45-55 ml/min/1.73m^2 with a strong correlation among Cr- and Cystatin C-based eGFR (r=0.9). The 24-hour urine CrCl was generally higher than Cr-based eGFR by 7-14 ml/min/1.73m^2. Despite concerns about inefficient human angiotensinogen activation by pig renin, the recipient maintained hemodynamic stability post-transplantation. To gauge human anti-diuretic hormone compatibility on porcine kidneys, the osmoregulatory function of the xenograft was evaluated. The electrolyte-free water excretion was 0.5-1.5 L/day with fluctuating serum sodium levels within the normal range. The urine osmolality ranged between 220-670 mOsm/kg H_2O. No albuminuria or hematuria was observed post-transplantation. The recipient developed hypocalcemia (8.0±0.5 mg/dL) and hyperphosphatemia (6.7±0.7 mg/dL) post-transplantation, possibly in part related to iatrogenic hypoparathyroidism from prior parathyroidectomy (PTH undetectable). Fractional excretion of phosphorus stayed low (<10%) despite elevated intact fibroblast growth factor 23 (FGF-23).

Conclusions: This case report suggests that the xenograft maintained excretory function, hemodynamic stability, and urinary concentrating capacity during follow-up. While lack of PTH may have contributed to hypocalcemia and reduced phosphate excretion, further investigation into the potential incompatibility of human FGF23 on porcine kidneys is needed.

TH-PO1165

Remote Ischemic Preconditioning Can Prevent Contrast-Induced AKI (CIAKI) by Reducing Neutrophil Extracellular Traps (NETs)

Mengqing Ma,[1] Xin Wan,[1] Changchun Cao.[2,1] *[1]Nanjing First Hospital, Nanjing, China; [2]Sir Run Run Hospital Nanjing Medical University, Nanjing, China.*

Background: To explore the protective effect of remote ischemic preconditioning (RIPC) in CIAKI by reducing NETs.

Methods: A prospective randomized controlled trial was conducted. Patients who underwent coronary angiography (CAG) in Sir Run Run Hospital, Nanjing Medical University from October 2021 to December 2022 were enrolled in the RIPC group and the control group at a 1:1 ratio. Patients in the RIPC group were inflated/deflated with a sphygmomanometer cuff to cause unilateral upper limb ischemia and reperfusion. During inflation, the pressure was 50 mmHg higher than the patient's systolic blood pressure. The Doppler probe showed that the brachial artery blood flow was completely blocked. At the same time, the fingertip oxygen saturation of the upper limb on the test side could not be measured and the radial artery pulsation disappeared; the inflation/deflation time was 5 min/5 min, 4 cycles. Serum samples were collected from each group of patients before, 2 hours after and 12 hours after CAG, and the levels of MPO, NE and IL-33 were detected.

Results: A total of 100 eligible CAG patients were included in this study, and the incidence of CIAKI was 11%. The incidence of CIAKI in the RIPC group and the control group was (6% vs 16%, P<0.001). There were significant differences in MPO, NE and IL-33 before and after angiography, and their expression gradually increased 2h and 12h after CAG. The levels of MPO, NE and IL-33 in the RIPC group after surgery were significantly lower than those in the control group. The levels of MPO, NE and IL-33 in CIAKI patients at 2h and 12h after surgery were significantly higher than those in non-CIAKI patients. The results of AUC showed that the performance of the clinical model in predicting CIAKI was 0.767. NE (0.873, 95% CI 0.803-0.943, P<0.001), MPO (0.882, 95% CI 0.813-0.951, P<0.001) and IL-33 (0.844, 0.766-0.921, P<0.001) at 12 hours after surgery had better prediction of CIAKI. After combining with clinical indicators, the AUC was 0.909 (0.829-0.989, P<0.001), which significantly improved the prediction performance of CIAKI.

Conclusions: RIPC before angiography can reduce the level of NETs, reducing the incidence of CIAKI. Serum MPO, NE and IL-33 12 hours after CAG can better predict the occurrence of CIAKI and improve the predictive effect of the CIAKI clinical model.

Funding: Other NIH Support - National Natural Science Foundation of China(82170698)

TH-PO1166

Advancing Community Care and Access to Follow-Up after AKI Hospitalization: The AFTER AKI Randomized Controlled Trial

Neesh I. Pannu,[1] Kerry Mcbrien,[2] Coralea Bignell,[2] Eleanor C. Benterud,[2] Taylor Palechuk,[1] Tyrone Harrison,[2] Braden J. Manns,[2] Matthew T. James.[2] *[1]Medicine, University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; [2]University of Calgary, Calgary, AB, Canada.*

Background: Acute kidney injury (AKI) is associated with development and progression of chronic kidney disease (CKD). Gaps in guideline recommended care for CKD are common after AKI.

Methods: In this randomized controlled trial conducted in Alberta, Canada, hospitalized adults with Kidney Disease Improving Global Outcomes (KDIGO) stage 2 or greater AKI were randomized to a risk-guided, transition of care intervention versus usual discharge practices at hospital discharge. For people in the intervention group, we used a validated risk index to predict risk of severe CKD after AKI to risk stratify patients. People at low risk (<1%) received patient education alone. People at medium risk received additional clinical guidance, provided to their primary care physician. People at high risk (>10%) were referred to Nephrology. The primary outcome was the proportion of patients with CKD who were receiving guideline-concordant care at 90 days after discharge based on use of ACE inhibitors or ARBs, statins, and nephrology specialist follow-up. Processes of care and safety were also evaulated.

Results: We recruited 155 patients into the trial; mean (SD) age 60 (15) years, 91 (60%) were male. 90 days after discharge, 99 (64%) participants had CKD defined by estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 or albumin to creatinine ratio (ACR) >30 mg/g. The proportion of participants with CKD after hospitalization with AKI who received guideline-concordant care was 59% in the intervention group versus 24% in the usual-care group (absolute risk difference [RD] 35 %, 95% CI, 17 to 53%; P < 0.001; risk ratio 2.47, 95% CI, 1.43 to 4.25). ACE inhibitor or ARB use was higher with the intervention (67 versus 46%, RD 21%, 95% CI, 2-40] %), as was statin use (78 versus 58%, RD 20%, 95% CI, 2 to 38 %). Among 18 (12%) participants with eGFR <30 mL/min/1.73m^2 at 90 days, the proportion who received nephrology follow-up was also greater with the intervention (73 versus 29%, RD 44, 95% CI, 2 to 87%). The risk of adverse events was similar in the groups, except for hyperkalemia, which was more frequent in the intervention group (15% versus 5%).

Conclusions: A risk-guided intervention for patients with AKI increased CKD-guideline concordant care early after hospital discharge.

Funding: Government Support - Non-U.S.

TH-PO1167

Acute Kidney Disease Detection in an Outpatient Setting: A Pragmatic Randomized Controlled Trial

David R. Chang,[1,2] Hsiu-Yin Chiang,[4,3] Yu-Ting Lin,[4,3] Zi-Han Lin,[4] Hung chieh Yeh,[1] Chin-Chi Kuo.[4,1] *[1]Division of Nephrology, China Medical University Hospital Department of Internal Medicine, Taichung, Taiwan; [2]Department of Biomedical Informatics, Harvard Medical School, Boston, MA; [3]Department of BioMedical Informatics, China Medical University, Taichung, Taiwan; [4]Big Data Center, China Medical University Hospital, Taichung, Taiwan.*

Background: Outpatient acute kidney injury or disease (AKD_{OPT}) is underrecognized due to fragmented data. No randomized controlled trials (RCTs) of AKD_{OPT} alert system have been reported.

Methods: Taiwan's National Health Insurance MediCloud enables integration of serum creatinine (S-Cre) data across institutions within 180 days before a visit. We developed an AKI Detection System (AKIDS) to screen for AKD_{OPT} and suggest nephrology referrals (**Fig 1**). This pragmatic RCT assessed AKIDS's effectiveness in reducing the 1-year risk of composite kidney outcome (CKO) — including ESKD, S-Cre doubling, and a 40% eGFR decline — in cancer-free adult outpatients. CKO risks were estimated using Cox proportional hazard models.

Results: Among 9,907 AKD_{OPT} patients, the adjusted hazard ratio (aHR) for 1-year CKO with AKIDS was 0.91 (95% CI: 0.81, 1.03), with an adjusted absolute risk reduction (aARR) of 11 per 1,000 patients (95% CI: 10, 13). Among 213 high-risk patients who adhered to nephrology follow-up in 3 months, AKIDS was associated with a 39% reduced risk of 1-year CKO (0.61; 95% CI: 0.42, 0.89) and an aARR of 160 per 1,000 patients (95% CI: 122, 198), with a number needed to treat of 6 (95% CI: 5, 8). The AKIDS's time-to-event curve for 1-year CKO was consistently lower (**Fig 2**).

Conclusions: This RCT demonstrates the effectiveness and resource efficiency of AKIDS in AKD_{OPT} care by targeting high-risk outpatients for nephrology referral. Studies are needed to evaluate its generalizability in healthcare systems with varying levels of data interoperability.

Funding: Government Support - Non-U.S.

Figure 1. The design of Acute Kidney Injury Detection System (AKIDS) developed by Big Data Center at CMUH. Targeting on the appointed outpatient visits, the AKIDS automatically integrate the S-Cre and eGFR measurements from the Taiwan's NHI and local EMRs and screen for AKD_{OPT} based on a prespecified S-Cre and eGFR fluctuation criteria within a 180-day period prior to the index outpatient clinic. Patients with AKD_{OPT} are further classified into stable (>0.3 mg/dL increase) and deteriorating (otherwise) subgroups based on the last two S-Cre. Cases A, B, and C illustrate the S-Cre dynamics of AKD_{OPT}, with A and B being stable subtypes and C representing the deteriorating subtype. AKIDS provide suggestions of nephrology referral based on the latest eGFR and AKD_{OPT} deteriorating status. ***Abbreviations***: AKD_{OPT}, acute kidney disease in outpatient setting; CMUH, China Medical University Hospital; eGFR, estimated glomerular filtration rate; EMRs, electronic medical records; NHI, National Health Insurance; OPT, outpatient; S-Cre, serum creatinine.

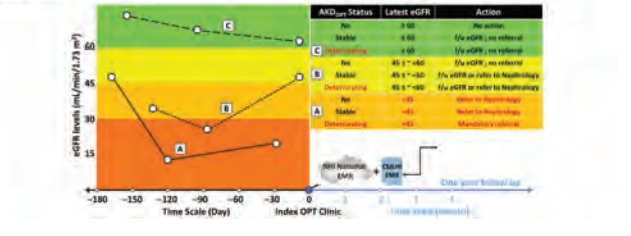
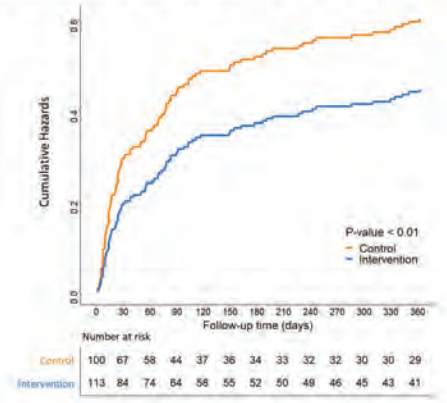


Figure 2. Adjusted time to event curves for 1-year CKOs of patients requiring referral who adhered to the nephrology follow-up care within 3 months.



TH-PO1168

Validation of a Combined Biomarker Including FGF-23, Erythropoietin, and Klotho for Development AKI and Clinical Outcomes in Patients in the Intensive Care Unit (ICU)

Luis Michea,[1] Luis Toro,[1] Veronica Rojas,[1] Daniela Ponce,[1] Carlos Irarrazabal,[2] Danilo Fischer,[2] Carlos Romero,[1] Julia Guerrero.[3] *[1]Hospital Clinico Universidad de Chile, Santiago, Chile; [2]Universidad de los Andes, Santiago, Chile; [3]Clinica Alemana de Santiago, Santiago, Chile.*

Background: Acute kidney injury (AKI) is a common complication in patients in critical care units (CCUs) associated with increased morbidity and mortality. The development of AKI is associated with increased plasma levels of Fibroblast Growth Factor 23 and Erythropoietin, with a reduction in Klotho. Previously, our group evaluated a combined biomarker using these molecules (named FEK) in a single-center clinical study, observing that critically ill patients with high levels of the FEK biomarker had a higher rate of AKI and worse clinical outcomes. Our objective was to evaluate in a multicenter study whether this combined biomarker predicts the development of AKI and clinical outcomes in critically ill patients.

Methods: Prospective multicenter cohort of 3 critical care units in Chile. Adult patients admitted to the Critical Care Unit with serum creatinine levels in normal ranges were recruited between 2019 and 2022. The diagnostic accuracy of the FEK biomarker in predicting AKI during the first 48 hours after admission was determined by ROC analysis. Secondary outcomes were life support therapy requirements and mortality in the first 28 days of hospitalization. The combined biomarker was compared against serum creatinine, NGAL, and TIMP-2*IGFBP7.

Results: 280 patients were recruited, age: 61.3 ± 15.7 years, female: 47%, serum creatinine at admission: 0.71 ± 0.16 mg/dL. During follow-up, 50% developed AKI, 27% required vasoactive drugs, 11% required emergency dialysis, and 10% died. When evaluating the diagnostic capacity of AKI, it was observed that plasma levels of the combined FEK biomarker were significantly higher in patients who developed AKI compared to those who did not. The area under the curve to predict AKI was 0.83 [0.78-0.88]. Finally, patients with high levels of the FEK biomarker had a higher rate of life support therapy requirements and mortality at 28 days of hospitalization (OR: 4.3 [1.6-13.5]).

Conclusions: Our results show that the combined biomarker FEK has a high diagnostic capacity for the development of AKI in critically ill patients and is associated with worse short-term clinical outcomes. Our results suggest that this combined biomarker could be helpful for decision-making in patients admitted to critical care units.

Funding: Government Support - Non-U.S.

TH-PO1169

Evaluation of the Anticoagulant Effect of Effluent Ionized Calcium iCa to Measure Regional Citrate Anticoagulation (RCA) Performance vs. Post-filter Ionized Calcium iCa: A Single-Center Non-inferiority Randomized Controlled Trial (RCT)

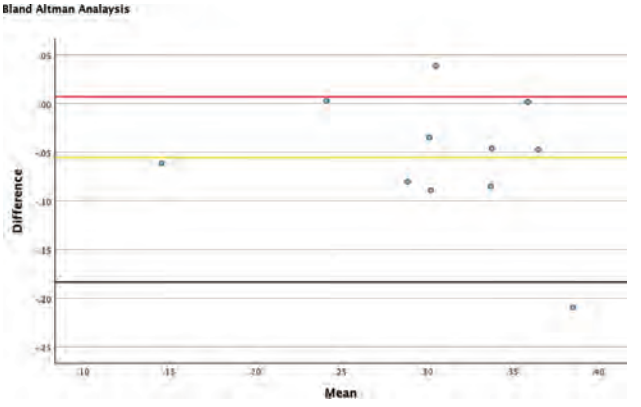
Niroj Mali, Ping Fu. *Nephrology, West China Hospital of Sichuan University, Chengdu, China.*

Background: This study aimed to evaluate the feasibility of using effluent fluid instead of postfilter ionized calcium (iCa) measurements for assessing anticoagulation in continuous renal replacement therapy (CRRT) with regional citrate anticoagulation in critically ill patients. Using citrate in CRRT is to prevent clotting within the circuit by chelating calcium, which is essential for the coagulation cascade.

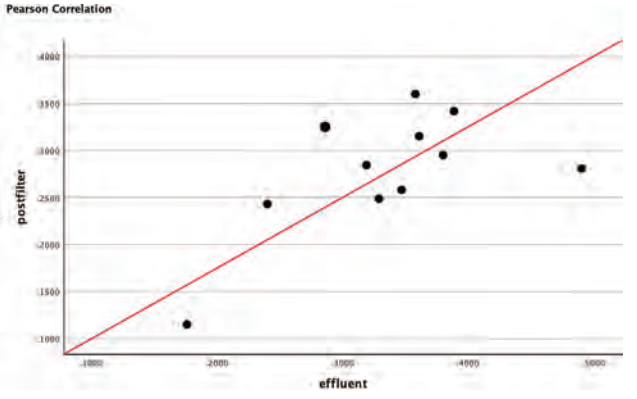
Methods: A two-arm, parallel, placebo-controlled, single-center RCT was conducted to assess and compare the efficacy and safety of different target ranges of effluent fluid ionized calcium and post-filter ionized calcium in continuous renal replacement therapy (CRRT) with regional citrate anticoagulation

Results: In total, 11 critically ill patients with 91 paired samples of CVVHDF with a mean age of 57.7 and a male-to-female ratio of 7:4. The mean post-filter ionized calcium was 0.28 ± 0.12 mmol/L, and the mean ionized calcium level of effluent fluid was 0.33 ± 0.11 mmol/L. r = 0.631, P value = 0.03, which is statistically significant, i.e., P<0.05. Bland-Altman analysis showed that the mean difference of ionized calcium between two sampling sites in continuous renal replacement therapy patients was -0.06 mmol/L with a 95% confidence interval ranging from -0.18 to 0.007 mmol/L.

Conclusions: Our results suggested there was a significant correlation between the two sampling points, and we explored the possibility of using effluent fluid for iCa measurements instead of postfilter iCa.



Bland-Altman analysis



Pearson correlation analysis

TH-PO1170

Sodium Zirconium Cyclosilicate (SZC) to Enable Renin Angiotensin-Aldosterone System Inhibitor (RAASi) Use for Diabetic Kidney Disease: The CRYSTAL Study

Weiming Wang,[1] Leyi Gu,[2] Xiujuan Zang,[3] Na Liu,[4] Yangbin Pan,[11] Chunming Jiang,[5] Ying Li,[6] Gengru Jiang,[7] Zhiguo Mao,[8] Jun Xue,[9] Rong Zhou,[10] Hao Xu,[1] Jian Liu.[1] *[1]Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China; [2]Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, China; [3]Songjiang Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [4]Tongji University Dongfang Hospital, Shanghai, China; [5]Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital, Nanjing, China; [6]Jiading District Central Hospital Affiliated Shanghai University of Medicine & Health Sciences, Shanghai, China; [7]Shanghai Jiaotong University School of Medicine Xinhua Hospital, Shanghai, China; [8]Shanghai Changzheng Hospital, Shanghai, China; [9]Huashan Hospital Fudan University, Shanghai, China; [10]Yangpu Hospital Affiliated to Tongji University School of Medicine, Shanghai, China; [11]Shanghai Pudong Hospital, Shanghai, China.*

Background: RAASi, the preferred treatment for Diabetic Kidney Disease (DKD), can induce hyperkalemia, and reduction/discontinuation of RAASi will affect its cardio-renal benefits. This study evaluated the efficacy of SZC in maintaining RAASi use in stage 3–4 DKD patients.

Methods: This multicenter, open-label, randomized controlled, phase IV trial enrolled stage 3–4 DKD patients with hyperkalemia (sK >5.0 mmol/L) within 90 days prior to enrollment and randomized them 1:1 to SZC (SZC + RAASi) or control (RAASi-only) groups, with a 24-week follow-up (12-week RAASi titration + 12-week maintenance). The primary endpoint was the proportion of patients with increased RAASi dose by week 12.

Results: By June 28, 2024, this study included 86 patients in the intention-to-treat (ITT) set, and 56 adhered to study protocol (per-protocol, PP). The mean age of the ITT set was 58.7 years old, and 59.3% were male. Both ITT and PP analyses showed a significantly higher proportion of patients in the SZC group achieved increased dose of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB) than control at week 12 (ITT: 55.8% vs. 27.9%, p<0.05; PP: 71.4% vs. 28.6%, p<0.05; **Figure 1**). In the PP set, a higher proportion of the SZC group received ≥50% of the labeled maximum dose than control at weeks 12 (60.7% vs. 42.9%) and 24 (53.6% vs. 35.7%). From baseline to week 24, the SZC group had decreased mean UACR (-63.5 mg/g), whereas that in the control group increased (+316.9 mg/g). Adverse events occurred in 62.8% of the SZC group and 72.1% of the control group.

Conclusions: This study showed that using SZC to manage hyperkalemia can help optimize RAASi treatment for Chinese stage 3–4 CKD patients with diabetes and hyperkalemia. This can facilitate the use of RAASi at higher, guideline-recommended doses to achieve its cardio-renal benefits for DKD pts experiencing hyperkalemia.

Funding: Commercial Support - AstraZeneca China

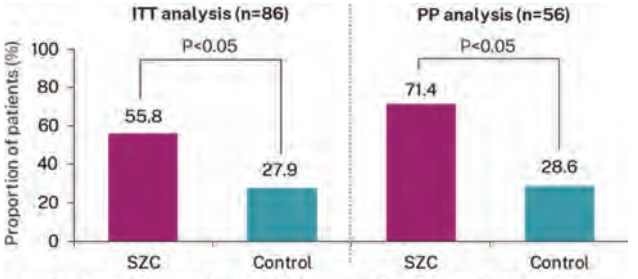


Figure 1. Proportion of patients with increased ACEi/ARB dose at week 12

TH-PO1171

Can Exogenous Ketones Prevent the Effects of High Salt on Renal Vascular Resistance during Sympathoexcitation?

Soolim Jeong,[1,2] Nina L. Stute,[2] Sofia O. Sanchez,[1] Orlando M. Gutierrez,[3] Zachary Schlader,[1] Austin Robinson.[1] *[1]Indiana University Bloomington, Bloomington, IN; [2]Auburn University, Auburn, AL; [3]The University of Alabama at Birmingham, Birmingham, AL.*

Background: Renal vascular resistance (RVR) is the opposition to blood flow by renal arteries. At the population level, dietary salt increases RVR and subsequently blood pressure (BP), which is associated with cardiovascular disease risk. However, recent data indicate exogenous ketones may offset adverse cardiorenal effects of salt. Therefore, we investigated whether dietary ketone and salt supplementation influences RVR and BP during sympathoexcitation (cold pressor test).

Methods: Thirteen participants were included in this analysis (10 M/3 F, age 30 ± 9 years. BMI: 26 ± 3 kg/m^2; mean ± SD). In this registered clinical trial (NCT05545501) participants were randomized to three 10-day conditions: A) control; B) high salt; C) high salt and ketone supplementation. Renal blood velocity (RBV) in the renal artery was measured in the decubitus position using Doppler ultrasound during a 3-minute baseline, 3-minute cold pressor test, and 2-minute recovery. We measured brachial BP with a validated oscillometric BP monitor. We calculated RVR as mean BP divided by RBV. We also calculated renal vascular conductance (RVC), the ease of blood flow through the renal arteries, as RBV divided by mean BP. Statistical analyses included ANOVA with α set at ≤ 0.05.

Results: Baseline BP did not differ between conditions for systolic (control: 107 ± 10, salt: 109 ± 14, ketone and salt: 107 ± 8 mmHg, p=0.91) or diastolic BP (control: 64 ± 6, salt: 63 ± 7, ketone and salt: 64 ± 5, p=0.90). Further, there were no differences for baseline RVR (control: 1.9 ± 0.6, salt: 2.1 ± 1.0, ketone and salt: 2.0 ± 0.8 mmHg/cm/s, p=0.86) or RVC (control: 0.6 ± 0.2, salt: 0.6 ± 0.2, ketone and salt: 0.6 ± 0.2 cm/s/mmHg, p=0.99). There were no effects of diet during CPT and REC for delta MAP (p=0.99), RVR (p=0.89), or RVC (p=0.58).

Conclusions: We observed no changes in blood pressure, renal vascular resistance, or renal vascular conductance between the three diets in our preliminary dataset; however, additional data is needed.

Funding: Other NIH Support - NIH grants (K01, TL-1 and American Heart Association fellowships)

TH-PO1172

Immunosuppression Minimization In Kidney Transplant Recipients with Transplant Excellence Based on the TruGraf Test

Venkat Ram Peddi, Parul S. Patel, Allison Gourley, Jalyn R. Vickroy. *California Pacific Medical Center, San Francisco, CA.*

Background: We prospectively evaluated the utility of serial TruGraf testing to guide immunosuppression (IS) management following Kidney Transplant (KT).

Methods: Pts undergoing KT and meeting inclusion (primary txp; cPRA <50; no DSA; non-African American recipients) and exclusion (multi-organ and HLA-identical living related recipients) criteria are consented at the time of KT. Pts who consent enter Part I of the study, receive Thymo induction (≥3 mg/kg), have steroids withdrawn at 30 d post-txp, and maintained on MMF and Tacro IS. Pts are followed with weekly labs. Pts qualifying for Part II of the study (eGFR >45 mL/min; BK viremia <10,000 copies/mL; no acute rejection episodes) are randomized 2:1 to study group : standard of care at 3mos post-txp. All pts also receive serial TruGraf testing monthly for mos 3-9, and at 12 mos post-txp. Study group receive TruGraf results in real time and used to guide IS reduction. If result is Transplant eXcellence (TX), first step in IS minimization is to decrease MMF dose followed by decrease in Tac target trough to between 3 & 6 ng/mL. Control group are managed per center standard of care & TruGraf samples will be analyzed at end of the study.

Results: Enrollment is completed and IS minimization is ongoing. 82 pts were enrolled. 73 pts completed 3 mos posttxp follow-up & qualified to be randomized into Part II of the study (52 to study arm and 21 to control arm); 57 pts completed the study; 40 pts in the study arm and 17 in the control arm. Renal function and IS results are shown in the Table below. To date, DSA was checked in 30 pts who completed the study. 25/30 (83.3%) had no DSA; 3/30 (10%) had de novo Class I DSA; and 2/30 (6.7%) had de novo Class II DSA. One study arm pt with elevated serum creat level and TruGraf TX had borderline acute rejection on biopsy (1/52 or 2%).

Conclusions: Results of this study are anticipated to provide helpful information necessary for IS minimization and have the potential to individualize pt care and improve outcomes by reducing infections and malignancies while maintaining good graft function.

Funding: Commercial Support - Transplant Genomics

Results 12 m

	Study (N=40)	Control (N=17)
eGFR	73.70	75.64
S. Creatinine (mg/dL)	1.20	1.23
Tacro level (ng/mL)	6.88	7.26
MMF dose (mg/day)	1054	1719

TH-PO1173

Social Network Interventions to Reduce Racial/Ethnic Living Donor Kidney Transplants (LDKT) Disparities: Preliminary Results from the Friends and Family of Kidney Transplant Patients Study

Jonathan Daw,[1] Jennifer M. Kirk,[1] Ashton Verdery,[1] Selena E. Ortiz,[4] Rhiannon D. Reed,[5] Jayme E. Locke,[5] David Kloda,[5] Brian A. Mccauley,[3] Deirdre L. Sawinski,[2] Peter P. Reese.[3] *[1]Department of Sociology & Criminology, The Pennsylvania State University, University Park, PA; [2]Department of Medicine, Weill Cornell Medicine, New York, NY; [3]Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [4]Department of Health Policy & Administration, The Pennsylvania State University, University Park, PA; [5]Department of Surgery, University of Alabama at Birmingham, Birmingham, AL.*

Background: Kidney transplants are often the optimal therapy for those w/ end-stage kidney disease; LDKT are particularly beneficial. Yet, LDKT rates are low & substantial racial/ethnic disparities in LDKT are a key driver of disparities in outcomes. Hence, more research is needed to boost LDKT & reduce racial/ethnic disparities.

Methods: This 2x2 factorial clinical trial in 2 transplant centers randomized 158 transplant candidates to the following groups: 1) the Script intervention: sets of advice & an example script on how to initiate LDKT discussions w/ potential living donors; 2) the Search intervention: advice on which friends/family members were least likely to have LDKT contraindications; 3) the Combined Intervention; or 4) No Intervention controls.

Results: Gender, age, & race/ethnicity did not differ by intervention group at baseline. At a median of 11 months post-enrollment, 17% of participants remained active on the waitlist, 3.8% died, 52% became/remained waitlist inactive. Only 11% of participants received LDKT, including 15% of controls, while 27% of the Search group received a deceased donor kidney transplant. Results indicate that neither intervention significantly increased the likelihood of LDKT (*See Table*). Notably, Non-Hispanic (NH) Black participants remained significantly (p=.01) less likely to receive LDKT.

Conclusions: We aimed to increase LDKT & ameliorate racial/ethnic disparities through the implementation of Script & Search interventions. Findings indicate neither intervention alone nor in combination significantly influenced LDKT. These results underscore the need for further investigation into alternative strategies to increase LDKT, particularly among racial/ethnic minorities.

Funding: NIDDK Support

Multivariable Logistic Regression Analysis of Interventions & Race/Ethnicity on LDKT

	Model 1			Model 2			Model 3			Final Model		
Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Script Intervention	0.64	0.35, 1.07	.11	0.59	0.32, 1.00	.06	0.59	0.32, 1.01	.07	0.59	0.32, 1.00	.06
Search Intervention	1.01	0.61, 1.67	>.9	0.92	0.54, 1.56	.8	0.94	0.52, 1.65	.8	0.92	0.54, 1.56	.8
Race/Ethnicity												
NH White				—	—		—	—		—	—	
NH Black				0.14	0.02, 0.53	.01	0.13	0.02, 0.53	.01	0.14	0.02, 0.53	.01
Other				0.43	0.06, 1.73	.3	0.42	0.06, 1.72	.3	0.43	0.06, 1.73	.3
Combined Intervention							1.06	0.58, 1.86	.9			

TH-PO1174

VIRENO Study: A Novel Approach for Early Outcome Prediction after Kidney Transplantation

Patrick Affeldt,[1] Katharina Burkert,[1] Rabi R. Datta,[1] Franziska Grundmann,[1] Martin Kann,[1] Florian Klein,[1] Christine E. Kurschat,[1] Dirk L. Stippel,[1] Michael N. Thomas,[1] Katharina Tuschen,[2] Alexander Weidemann,[2] Benjamin Wilde,[3] Veronica Di Cristanziano,[1] Roman-Ulrich Mueller.[1] The VIRENO Study Group. *[1]Universitatsklinikum Koln, Koln, Germany; [2]Krankenhaus Koln-Merheim, Koln, Germany; [3]Universitat Duisburg-Essen, Duisburg, Germany*.

Background: Achieving balanced immunosuppression remains a significant challenge following kidney transplantation (KTx). VIRENO is a prospective multicenter study designed to examine the combination of clinical and viro-immunological parameters as predictors of major complications after KTx.

Methods: Viro-immunological monitoring was conducted before KTx, 3 weeks and 6 months after KTx. This monitoring included measurements such as the humoral response to BK polyomavirus (BKPyV) and cytomegalovirus (CMV), T-cell reactivity against CMV, and the viral load of torque teno virus (TTV). Clinical outcomes were tracked for 12 months post-transplantation, with clinically relevant infection- and rejection-related events as outcomeparamter. Clinical and viro-immunological parameters were used to develop predictive models for infectious and immunological events through logistic regression. The best models were then integrated for predicting infections and immunological events to create the VIRENO-score, to stratify patients by adverse event risk after KTx.

Results: A total of 196 patients were followed for the first year post-KTx. Relevant infectious events occurred in 95 patients, while 36 patients experienced at least one immunological event (biopsy-proven rejection / de novo donor-specific antibodies). The best predictive model for significant infections included variables such as baseline plasma TTV-DNA load, CMV serostatus of the donor and recipient, recipient's blood type, type of donation (deceased vs. living), recipient's ethnicity, and differences in HLA alleles between donor and recipient (Area under the curve (AUC) 0.781). For immunological events, the predictive model included nine variables, including baseline CMV-IgG levels, presence of underlying genetic renal diseases, recipient's body mass index, and the number of HLA mismatches and different HLA constellations (AUC 0.799).

Conclusions: The combination of viro-immunological and clinical parameters is a promising tool for predicting major adverse events after KTx. Validation in further cohorts and a prospective trial using the models to guide immunosuppression will now be the crucial steps towards implementation in clinical practice.

Funding: Other NIH Support - The present study was supported by the Koeln Fortune Program of the Faculty of Medicine of the University of Cologne (Germany) and by the Clinical Leave Program of DZIF (Deutsches Zentrum für Infektionsforschung)

TH-PO1175

Phase I/IIa Trial of Autologous Regulatory T Cell Therapy Together with Donor Bone Marrow Infusion in Kidney Transplantation

Rainer Oberbauer,[1] Moritz Muckenhuber,[2] Jasmin Mucha,[2] Roman Reindl-Schwaighofer,[1] Andreas Heinzel,[1] Anna M. Weijler,[2] Gabriela Berlakovich,[2] Nina Worel,[5] Michael Wolzt,[3] Thomas Lion,[5] Matthias Edinger,[4] Thomas Wekerle.[2] *[1]Nephrology, Medizinische Universitat Wien, Vienna, Austria; [2]Surgery, Medizinische Universitat Wien, Wien, Austria; [3]Clinical Pharmacology, Medizinische Universitat Wien, Wien, Austria; [4]Hematology, Krankenhaus Barmherzige Bruder Regensburg, Regensburg, Germany; [5]CCRI, Medizinische Universitat Wien, Wien, Austria*.

Background: In preclinical models combining Treg therapy with donor bone marrow transplantation leads to mixed hematopoietic chimerism and tolerance without myelosuppressive recipient conditioning.

Methods: A single center, controlled, first-in-human phase I/IIa trial is conducted in HLA-mismatched living donor kidney transplant recipients. In vitro expanded polyclonal recipient Tregs and MNC-separated donor bone marrow cells are administered within 3 days after transplant. No irradiation or cytotoxic drugs are given. IS consists of thymoglobulin, belatacept, sirolimus and steroids. Starting at 6 months, sirolimus and steroids are gradually withdrawn in study group patients. A parallel control group receives the same IS, but no Tregs & bone marrow. Total leukocyte donor chimerism and safety are co-primary endpoints. Immune monitoring accompanying the trial includes NGS of the TCR repertoire, flow cytometric leukocyte subset analysis, scRNAseq and protocol biopsies (at 6, 12, 24, 36 and 60 months) including transcriptomic analysis. ClinTrials.gov NCT03867617.

Results: Thirteen patients have been enrolled and twelve treated according to the predetermined sample size of six per group. One patient was enrolled but not treated as the Treg cell product was out-of-specification (77% viable cells at 80% cut-off). Treg (1.0-1.5x10^7 cells/kg) and bone marrow cell (0.7-1.9x10^8 nucleated cells/kg) infusions were well tolerated. The study group developed low levels of total leukocyte donor chimerism whereas no chimerism was detectable in the control group. Leukocyte subset analysis and transcriptomics analysis of biopsies (MMDx) are ongoing. TCR repertoire sequencing revealed clonal deletion of donor-specific T cells. The study group shows a favorable clinical course, with GFRs of 33-99 ml/min/1.72m^2 at median follow-up 32 months and no infusion-related safety signals were observed. IS reduction has been completed in three patients currently maintained on belatacept monotherapy and is in progress in all other patients.

Conclusions: Combined Treg therapy and bone marrow transplantation is safe and feasible and induces low-level chimerism which is sufficient to cause clonal deletion of donor specific T cells.

Funding: Government Support - Non-U.S.

TH-PO1176

A Hypertension Management App for Salt Restriction in Patients with CKD: The CureApp-CKD Trial

Takayuki Kawaoka, Yusuke Sakaguchi, Yuki Kawano, Tatsufumi Oka, Yohei Doi, Isao Matsui, Jun-Ya Kaimori, Yoshitaka Isaka. *Osaka Daigaku, Suita, Japan*.

Background: Excessive salt intake is harmful to the kidney. In real-world clinical settings of patients with chronic kidney disease (CKD), however, salt restriction is often challenging. Mobile app-based interventions might be useful to reduce salt intake.

Methods: This open-label, single-center, randomized controlled trial involved patients with CKD stages G1-G5 who had a history of hypertension and an estimated 24-hour urinary sodium excretion of ≥100 mmol. Patients randomized to an intervention group used CureApp HT, a hypertension-management app that enables individualized lifestyle modification, in addition to lifestyle counseling by nephrologists for 12 weeks. Patients in the control group received lifestyle counseling only. The primary outcome was a change in the estimated 24-hour urinary sodium excretion from baseline to 12 weeks. Key secondary outcomes were office blood pressure, brachial-ankle pulse wave velocity (baPWV), urinary protein-to-creatinine ratio (UPCR), brain natriuretic peptide (BNP), and body weight. This study was registered at the Japan Registry of Clinical Trials (jRCTs052220164).

Results: A total of 101 patients were randomized, with 51 assigned to the intervention group and 50 to the control group. The mean (standard deviation) estimated 24-hour urinary sodium excretion at baseline was 145 (33) mmol. More patients in the intervention group reported that their salt intake behaviors had "significantly improved" or "somewhat improved" than those in the control group (76% vs. 40%; P<0.001). Despite the subjective improvement, there was no significant between-group difference in changes in the estimated 24-hour urinary sodium excretion (between-group difference, 0.9 mmol; 95% confidence interval [CI], -17.8 to 19.7; P=0.9). Secondary outcomes, including blood pressure levels, baPWV, UPCR, BNP, and body weight, were also not significantly different between groups.

Conclusions: Further advancements in mobile app-based interventions might be needed to effectively suppress salt intake behaviors in patients with CKD.

TH-PO1177

Rilparencel Autologous Cell Therapy in Patients with Diabetes and Advanced CKD: Phase 2 Interim Results

Joseph Stavas,[1] Arnold L. Silva,[2] Theodore F. Saad,[3] Emily L. Butler,[1] Navdeep Tangri,[4] Bruce F. Culleton.[1] *[1]ProKidney, Raleigh, NC; [2]Boise Kidney & Hypertension Institute, Boise, ID; [3]Nephrology Associates, Newark, DE; [4]Department of Internal Medicine, University of Manitoba, Winnipeg, MB, Canada*.

Background: Cell-based therapies in patients with chronic kidney disease (CKD) may repair diseased nephrons and stabilize kidney function. We describe an interim analysis of an open label phase 2 trial (NCT05018416) with *rilparencel*, an autologous cell product made from kidney biopsy tissue.

Methods: The study objectives are to evaluate efficacy and safety measured by change in eGFR slope from baseline to after last injection and procedure- and product-related serious adverse events. Patients with type 1 or 2 diabetes, eGFR 20-50 ml/min/1.73/m^2 and UACR 30-5000 mg/g are randomized into one of two cohorts. Cohort 1 subjects receive two percutaneous *rilparencel* injections: one into the cortex of each kidney 3 to 5 months apart; Cohort 2 subjects receive at least one injection, and a 2nd injection only after a pre-defined biochemical trigger. eGFR slope is presented for only Cohort 1 given its alignment with an ongoing phase 3 trial. Safety data is aggregated across both cohorts.

A post-hoc analysis compares eGFR slope in Cohort 1 with a 10:1 matched synthetic control group. The control group was identified from a subject-level clinical trial database and matched with Cohort 1 based on risk of kidney failure (Klinrisk model).

Results: 49 subjects received the 1st injection (n=24 Cohort 1; n=25 Cohort 2) and 34 subjects received a 2nd injection (n=22 Cohort 1; n=12 Cohort 2); 28 subjects have not completed the study and remain in follow up (n=11 Cohort 1; n=17 Cohort 2). 13 Cohort 1 subjects have greater than 12 months follow up post 2nd injection. Mean age is 63 yrs; 54% are female. At baseline, mean (SD) eGFR is 27.9 (9.5) ml/min/1.73/m^2; median [IQR] UACR is 239 [4, 2392] mg/g. Annualized eGFR slope in Cohort 1 is -1.1 ml/min/1.73/m^2/year (95% CI -3.5, 1.3). Average change in eGFR in the matched control group is -4.0 ml/min/1.73/m^2 over 12-months. Two hematomas and 2 episodes of acute kidney injury occurred after kidney biopsy; 1 hematoma occurred after 83 injections. There were no product-related SAEs.

Conclusions: Interim findings suggest *rilparencel* can stabilize kidney function in patients with diabetes and advanced CKD. Procedure-related AEs are infrequent and typical given the interventions. A global phase 3 study is ongoing to determine efficacy and safety of *rilparencel.*

Funding: Commercial Support - ProKidney

TH-PO1178

Radiofrequency Renal Denervation in Patients with Severe CKD, Including Patients on Dialysis: Analysis from the Global SYMPLICITY Registry DEFINE

Markus P. Schlaich,[1] Felix Mahfoud,[2] Krzysztof Narkiewicz,[7] Luis M. Ruilope,[3] Faisal Sharif,[6] Flavio L. Ribichini,[4] Michael Böhm.[5] *[1]Dobrey Hypertension Center, University of Western Australia, Perth, WA, Australia; [2]Medicine, Universitatsspital Basel, Basel, Switzerland; [3]Medicine, Hospital 12 de Octobre, Madrid, Spain; [4]Universita degli Studi di Verona Scuola di Medicina e Chirurgia, Verona, Italy; [5]Universitatsklinikum des Saarlandes, Homburg, Germany; [6]University of Galway, Galway, Ireland; [7]Gdanski Uniwersytet Medyczny, Gdansk, Poland.*

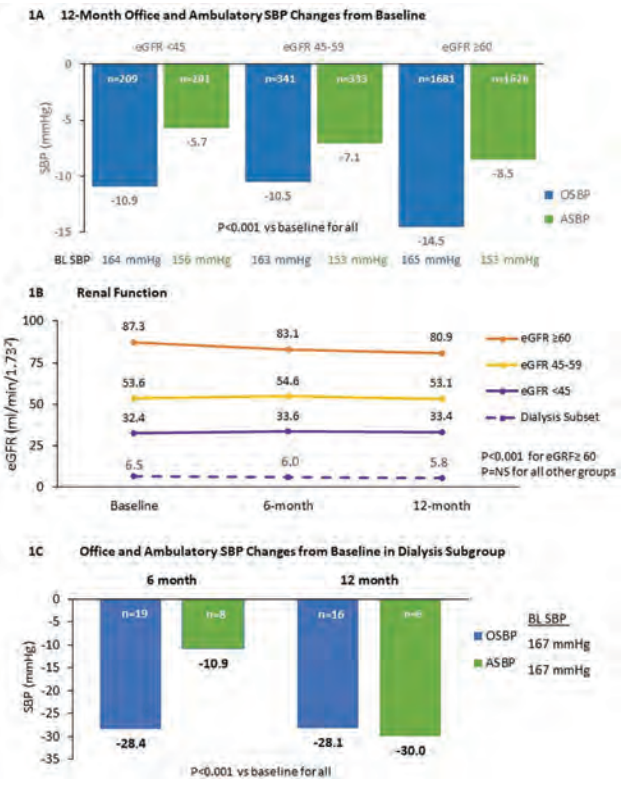
Background: There is a paucity of data regarding the effect of renal denervation in patients with severe chronic kidney disease (CKD).

Methods: This analysis from the Global SYMPLICITY Registry DEFINE assessed blood pressure (BP) and renal function in patients with uncontrolled hypertension treated with radiofrequency (RF) RDN. BP and eGFR changes from baseline through 12 months were compared across three groups according to baseline eGFR (mL/min/1.73m^2): eGFR <45, eGFR 45-59, and eGFR ≥60, adjusted for baseline BP. Furthermore, we assessed these changes among a subset of 36 patients on dialysis.

Results: Baseline office SBP (OSBP) was similar between eGFR subgroups (p=0.28), although ambulatory SBP (ASBP) was higher in those with eGFR<45, p=0.037; **Fig 1A**). Patients in the <45 eGFR subgroup were significantly older, were more likely to have ischemic heart disease, heart failure, or diabetes. At 12 months, each eGFR subgroup had clinically meaningful SBP drops from baseline **(Fig1A)**. At 12 months, eGFR remained stable in the two lower eGFR subgroups (**Fig1B)**. Estimated GFR declined by 5.7±15.8 ml/min/1.73 m^2 in the eGFR ≥60 subgroup. Patients on dialysis (72% on hemodialysis, 33% on peritoneal dialysis) had substantial drops in both OSBP and ASBP after RF RDN **(Fig1C).** Among the dialysis subgroup there were 2 deaths and 2 vascular complications.

Conclusions: Patients with moderate to severe CKD including those requiring dialysis experienced significant OSBP and ASBP reductions from baseline through 12 months after RF RDN. The eGFR of patients with moderate to severe CKD remained stable through 12 months. The data showed that RDN is efficacious and safe for BP reduction in CKD, which needs to be further evaluated.

Funding: Commercial Support - Medtronic



TH-PO1179

Impact of Adjunctive Active Vitamin D on Kidney Function during Treatment of Secondary Hyperparathyroidism (SHPT) with Extended-Release Calcifediol (ERC) in Nondialysis-Dependent CKD (ND-CKD)

Akhtar Ashfaq,[1] John Choe,[1] Stephen A. Strugnell,[1] Nilay Patel,[1] Stuart M. Sprague,[2] Keith C. Norris,[3] Edgar V. Lerma,[4] Charles W. Bishop.[1] OPKO Health. *[1]Renal Division, OPKO Health Inc, Miami, FL; [2]NorthShore University HealthSystem, Evanston, IL; [3]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [4]Nephrology, University of Illinois Chicago College of Medicine, Chicago, IL.*

Background: Sustained reductions of intact parathyroid hormone (iPTH) with ERC are associated with slower estimated glomerular filtration rate (eGFR) decline without safety concerns in ND-CKD patients with SHPT. Marked iPTH reductions require serum 25-hydroxyvitamin D (25D) of ≥50 ng/mL, and adequate exposure is limited by increased volume of distribution in obesity and the current ERC dose ceiling (60 mcg/day).

Methods: This prospective study examined whether adjunctive active vitamin D could safely improve iPTH control and the related eGFR stabilizing effect of ERC in 78 ND-CKD adults unable to achieve iPTH normalization after 38 weeks of treatment, defined as baseline (BL). Participants had mean age of 66 years, BMI of 35 kg/m^2, 41% were female, 63% White, 36% Black and 19% Hispanic. At ERC initiation, participants had eGFR 15-<60 mL/min/1.73 m^2, plasma iPTH 85-<500 pg/mL, serum 25D 10-<30 ng/mL, corrected serum calcium (Ca) 8.4-<9.8, serum phosphorus (P) 2.0-<5.0, and absence of nephrotic range proteinuria (≤3 mg/mg creatinine). They were randomized to continuing daily ERC (60 mcg) with (n=40) or without (n=38) immediate-release adjunctive daily oral calcitriol (0.25 mcg; n=12), doxercalciferol (0.5 mcg; n=14) or paricalcitol (1.0 mcg; n=14) for 14 weeks. Measurements of eGFR, iPTH, 25D, Ca, P and fibroblast growth factor 23 (FGF23) were obtained at BL and study end.

Results: There were no significant BL inter-group differences. Mean BL 25D was 67 ng/mL and rose 11-13 ng/mL in both groups (p<0.001). Mean BL iPTH was 143 pg/mL and fell by 35% (p<0.001) with adjunctive therapy versus 4% without. Mean Ca and FGF23 increased with adjunctive therapy (p<0.001) by 0.5 mg/dL and 47 pg/mL, respectively, versus 0.0 and 2.0 without. Mean P remained unchanged. Mean BL eGFR was 25.4 mL/min/1.73m^2 and fell by 10% (p<0.05) with adjunctive therapy versus 4% without.

Conclusions: Although adjunctive active vitamin D enabled more iPTH reduction (35%) in CKD patients taking ERC for 52 weeks, it increased serum Ca by 0.5 mg/dL, FGF23 by 136% and hastened eGFR decline by 10%. Higher doses of ERC alone may be more suitable for improving iPTH control and eGFR stabilization in obese patients.

Funding: Commercial Support - OPKO Health

TH-PO1180

Evaluation of an At-Home Creatinine Assay for CKD Management: Pilot Method Comparison Study and Clinical Implications

Vissaagan Gopalakrishnan,[1] Amrutha Anilkumar,[1] Supriya Chavan,[1] Bharath B. Rangaswamy,[1] Richard E. Williams,[1] Anh N. Hoang,[1] James Januzzi.[1,2] *[1]Jana Care, Boston, MA; [2]Division of Cardiology, Massachusetts General Hospital Department of Medicine, Boston, MA.*

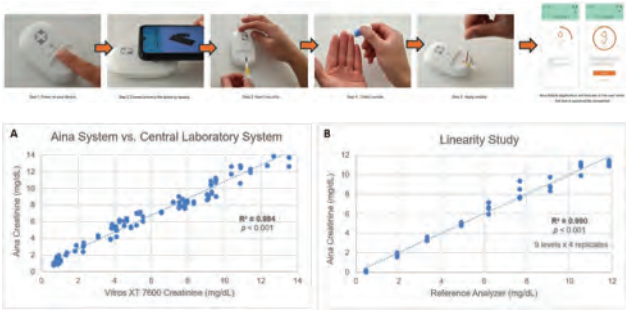
Background: Chronic kidney disease (CKD) management relies on regular serum creatinine monitoring, traditionally requiring phlebotomy and central laboratory analysis. There is a large unmet need for reliable at-home tools to measure creatinine, empowering patients, increasing testing compliance, and enabling timely interventions. A smartphone-enabled, low-cost reader system for analyte-specific strips is being developed for patient use in chronic disease management. The initial application is a fingerstick creatinine assay for self-administered at-home use (Fig 1).

Methods: The candidate creatinine assay was evaluated in a pilot study involving study participants across a range of CKD stages. The primary endpoint was a comparison of the fingerstick assay's performance to a central laboratory reference method (Vitros XT 7600 Integrated System, QuidelOrtho). Additional studies included a linearity study across a range of creatinine concentrations, and an interference study involving creatine and ascorbic acid.

Results: Among 50 study participants (mean age 49.7 ± 15.5 years) with a range of CKD severity (mean creatinine 5.74 mg/dL), the assay demonstrated strong agreement with the Vitros XT 7600, achieving correlation coefficients (R) of 0.98 (Fig 2A). Additionally, the linearity study confirmed a direct relationship (R= 0.99) across the tested creatinine concentrations, validating accuracy across the spectrum of CKD severity (Fig 2B). The interference study showed no interference of creatine and ascorbic acid at 6 times physiological concentrations (300μM).

Conclusions: The development of a reliable at-home creatinine assay represents a significant advancement towards the scalable monitoring of CKD progression and early detection of kidney function decline, addressing a critical gap in management practices. By enabling regular monitoring, this assay has the potential to promote equitable health access and improve disease management.

Funding: Commercial Support - Jana Care, Inc.



A: Creatinine Result ComparisonB: Linearity Study

TH-PO1181

Efficacy and Safety of AND017 for Treatment of Anemia in Dialysis-Dependent CKD

Yusha Zhu,[1] Xiaoqiang Ding,[2] Suzanne Wilson,[1] Xiaolu Li,[1] Ping Du,[1] Qi Zhu,[1] Geoffrey A. Block,[3] Pablo E. Pergola.[4] *[1]Kind Pharmaceuticals LLC, Redwood City, CA; [2]Zhongshan Hospital Fudan University, Shanghai, China; [3]US Renal Care Inc, Decatur, GA; [4]Renal Associates PA, San Antonio, TX.*

Background: AND017 is an oral hypoxia-inducible factor prolyl-hydroxylase inhibitor developed for the treatment of renal anemia. It was evaluated in a Phase II clinical trial of patients with end-stage kidney disease (ESKD) in the US and China (NCT05265325).

Methods: This open-label, active-controlled study involved patients with ESKD receiving stable hemodialysis, home hemodialysis, or peritoneal dialysis, on stable erythropoiesis-stimulating agent (ESA) treatment for at least 6 weeks. The trial evaluated two starting dosing regimens of AND017: 10 mg three times per week (TIW) and 16 mg once per week (QW), compared to the active control ESA treatment. Patients were randomized 1:1:1 to one of the treatment groups and were treated for 20 weeks. Dose adjustment was allowed for both AND017 and ESA in the study to maintain hemoglobin (Hb) levels within the target range of 10.0-11.0 g/dL in the US or 10.0-12.0 g/dL in China.

Results: A total of 175 patients were enrolled: 59 in the AND017 10 mg TIW group, 57 in the AND017 16 mg QW group, and 59 in the ESA group. Baseline Hb levels were balanced across treatment groups. The primary efficacy outcome was the mean change in Hb levels from baseline, averaged over Weeks 17-21. AND017 TIW and QW groups demonstrated similar capability in maintaining Hb level with ESA treatment (within the non-inferiority margin). Treatment-emergent adverse events (TEAEs) occurred in 81.4% of patients in the AND017 10 mg TIW group, 75.4% in the AND017 16 mg QW group, and 66.1% in the ESA group. Treatment-related adverse events (TRAEs) were reported in 6.8%, 10.5%, and 3.4% of patients, respectively. A total of 48 patients experienced serious adverse events (SAEs), with 32.2% patients in the AND017 10 mg TIW group, 28.2% in the AND017 16 mg QW group, and 22.0% in the ESA group; none were assessed as related to the study drug or active control.

Conclusions: AND017 was safe and well tolerated in patients with ESKD on stable dialysis. At both TIW and QW dosing frequencies, AND017 effectively maintained Hb levels within the target range after 20 weeks of treatment and demonstrated non-inferiority to ESA treatment.

TH-PO1182

Effect of Hemodialysis with Citrate on Vascular Calcification

W. Charles O'Neill, Jose E. Navarrete. *Renal Division, Emory University, Atlanta, GA.*

Background: Medial arterial calcification (MAC) is a serious problem in hemodialysis (HD) patients that leads to poor outcomes. Citrate, which can inhibit calcium crystallization, is used in some HD solutions but its effect on vascular calcification is unknown. We have shown that MAC can be conveniently measured on standard mammograms (MGs) and correlates with MAC in other locations and with cardiovascular outcomes. Therefore, we used mammography to measure changes in MAC in female HD patients during HD with and without citrate.

Methods: In this cross-over study in 4 outpatient units, patients with pre-existing MAC on MGs were recruited to 1 year periods of HD with and without citrate (Citrasate and Naturalyte, Fresenius) with MGs and measurements of serum Mg and ionized Ca (iCa), and plasma citrate every 6-months (NCT04956120). Lengths of calcified arteries were summed manually and the rate of change determined from the slope of values from the 3 MGs at the start, middle, and end of each arm. Data are means ± SE with analysis by paired t-test, or medians (interquartile range) for MAC with analysis by Wilcoxon test.

Results: 28 of 30 subjects have completed the study, 12 starting on the citrate arm. Durations of the arms did not differ (citrate: 383 ± 8 days; no citrate 407 ± 15). Dialysis adequacy, dialysate Ca, and pre-HD serum total Ca, iCa, and phosphorus did not differ between arms; pre-HD Mg was lower in the citrate arm (2.28 ± 0.05 vs. 2.42 ± 0.07 mg/dl, p=0.003. The change in serum Mg or iCa with HD did not differ significantly between arms. Pre-HD plasma citrate was similar (133 ± 8 vs. 127 ± 6 uM) but was substantially greater after HD with citrate (364 ± 17 vs. 144 ± 9 uM, p<0.001). The change in MAC was greater during citrate HD: 44 (21-121) mm/yr vs. 10 (-5-35), p=0.0002, or 35 (14-104) %/yr vs.12 (-3-23), p=0.002. 22 subjects had a greater change during citrate HD (median: 51 %/yr), while only 6 had a greater change without citrate (median: 14 %/yr). The change in MAC did not correlate with pre-HD serum iCa, P, or Mg.

Conclusions: Citrate HD unexpectedly promoted vascular calcification, which was not explained by changes in mineral metabolism or dialysis adequacy. This result may be related to known effects of citrate to promote or stabilize bone mineralization. Further studies are needed to determine the underlying mechanism and whether this is associated with adverse clinical outcomes.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

TH-PO1183

Abstract Withdrawn

TH-PO1184

Double vs. Single Icodextrin Dose in Older Incident Patients on Incremental Continuous Ambulatory Peritoneal Dialysis (CAPD): Results from the DIDo (Double Icodextrin Dose) Study

Eric Goffin,[1] Clémence Béchade,[3] Cécile Courivaud,[5] Karlien Francois,[7] Bert Bammens,[2] Michel Y. Jadoul,[1] Olivier Devuyst,[1] Martin E. Wilkie,[8] Aurélie Bertrand,[4] Thierry Lobbedez.[6] DIDo Study Group. *[1]Nephrology, Cliniques universitaires Saint-Luc, Bruxelles, Belgium; [2]Nephrology, Katholieke Universiteit Leuven, Leuven, Belgium; [3]CHU Clemenceau, Caen, France; [4]Support en Méthodologie et Calcul Statistique, Universite catholique de Louvain, Louvain-la-Neuve, Belgium; [5]Nephrology, Centre Hospitalier Universitaire de Besancon, Besancon, France; [6]Nephrology, CHU Clemenceau, Caen, France; [7]Nephrology, Vrije Universiteit Brussel, Brussel, Belgium; [8]Nephrology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom.*

Background: Icodextrin, a high MW glucose polymer, provides sustained ultrafiltration (UF) in PD patients through colloid osmosis, leading to improved clinical outcomes. Icodextrin is limited to one bag/day. Improved UF and technical survival have been observed with an off-label use of two bags/day.

Methods: DIDo is a prospective, international, 1:1 randomized controlled trial. It investigates superiority and safety of using two vs one icodextrin bag/day to extend the duration of incremental (3 bags/day) CAPD in older (> 60 yrs) incident patients. After a 2-months *run-in period*, patients were randomized to two icodextrin + one glucose (group A) or one icodextrin + two glucose - the reference treatment - (group B) daily. Hypothesis was that group A would remain longer on 3 exchanges/day. Primary outcome was a composite of excessive predefined hypertonic dialysates use, transfer to another dialysis modality or death at M9. Secondary outcomes included mortality, daily UF, technique survival, and rates of peritonitis and hospitalizations at M18. SAEs and side-effects potentially related to icodextrin (low serum sodium, hypotension, skin rash and sterile peritonitis) were assessed.

Results: 41 patients were randomized to group A and 42 to group B. Baseline characteristics (demographics, comorbidities, lab and CAPD parameters, and medications), were well balanced between groups. Median FU was 31 months. At M9, the proportion of patients who discontinued 3 exchanges/day was similar between group A and B [16 (39%) *vs*. 21 (50%)]. There were no differences between both arms in any primary outcome component, nor significant interaction with clinical characteristics. The results were similar at M18 [(24 (59%) *vs*. 24 (57%)]. Patients in group A had significantly higher (>400 mL) daily net UF at all time points. Rates of peritonitis, hospitalizations, residual urine output and all AEs were similar between groups.

Conclusions: In older patients on incremental CAPD, a double icodextrin dose initiated at PD onset did not reduce the cumulative incidence of the composite primary outcome compared to a single icodextrin dose. Significantly enhanced UF was observed in patients receiving the double icodextrin dose while no safety issues were observed.

Funding: Commercial Support - Baxter Healthcare, Private Foundation Support

TH-PO1185

Community Health Worker Intervention for Latinos Receiving Hemodialysis: A Randomized Controlled Trial

Lilia Cervantes,[1] Neil R. Powe,[2] Daniel Cukor,[3] Brenda Beaty,[1] Lauren Mcbeth,[1] Romana Hasnain,[4] Michel Chonchol.[1] *[1]Medicine, University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [2]University of California San Francisco Department of Medicine, San Francisco, CA; [3]NYU Langone Health, New York, NY; [4]Denver Health Main Campus, Denver, CO.*

Background: Latino groups face a disproportionate burden of ESKD, social and structural issues, and subsequent kidney health disparities. While community health worker (CHW) interventions serve to reduce health disparities, effectiveness for Latinos with ESKD remains unknown.

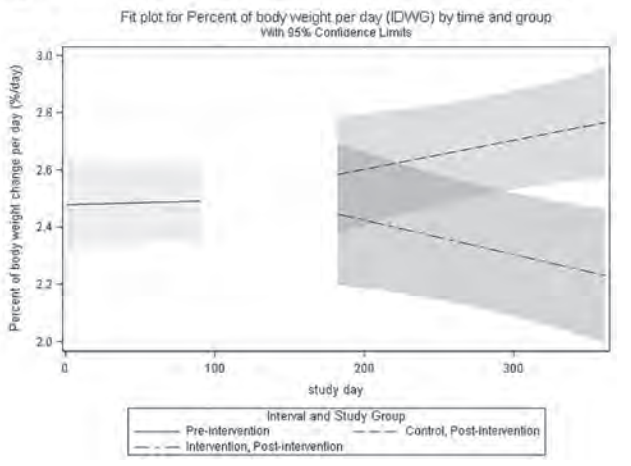
Methods: In a randomized controlled trial, we tested a multi-level CHW intervention among Latino adults with ESKD receiving hemodialysis. Participants were randomized to receive resources for social needs, culturally responsive dietary education, and support from a CHW, or to usual care (i.e., standard treatment). A longitudinal segmented linear model with generalized estimating equations evaluated the effect of the intervention on the primary outcome of interdialytic weight gain (IDWG%) and the secondary outcome of a Patient Activation Measure (PAM).

Results: 139 individuals at 5 urban Denver dialysis facilities from 10/7/2020 to 4/29/2022 were recruited and 68 randomized to the CHW arm and 71 to the control arm **(Table 1)**. Baseline characteristics and demographic factors were similar between the groups. The post-intervention slopes differed between the intervention and control, corresponding to a decrease of 0.04% in IDWG per 30 days for intervention participants and an increase of 0.03% per 30 days for usual care (p=0.01) (**Figure 1)**. The median change in PAM for the intervention group was 1.8 points (IQR -2.2, 5.5) compared to -2.2 (IQR -7.4, 2.5) for the usual care group; Wilcoxon text p=0.005.

Conclusions: Among Latino individuals with ESKD receiving standard in-center hemodialysis, a multicomponent CHW intervention reduced IDWG and improved patient activation as compared to usual care.

Funding: NIDDK Support

Figure 1. IDWG (% body weight per day) by time and group



Characteristic	Control N=71	Intervention n=68	Standardized Mean Difference (SMD)
Age, mean (SD), years	55.6 (13.4)	58.0 (12)	0.19
Female, n (%)	30 (42)	38 (56)	0.28
Spanish Language, n (%)	59 (83)	55 (81)	0.06
Education, Less than High School, n (%)	53 (75)	50 (74)	0.03
Family Income, <$25,000, n (%)	48 (68)	49 (71)	0.07
Social Challenges			
Low or Marginal Health Literacy, n (%)	62 (87)	61 (90)	0.08
Brief Health Literacy Score	10.0 (5)	9.3 (5)	0.15
Worried about Losing Home, n (%)	20 (28)	19 (28)	0.01
Unable to afford balanced meals in past 1 year, sometimes / often true, n(%)	35 (49)	33 (49)	0.02

TH-PO1186

Cost Utility of High-Dose Online Hemodiafiltration Compared with High-Flux Hemodialysis: Economic Evaluation of the Multinational, Randomized Controlled CONVINCE Trial

Aniek E. Schouten,[1] Felix Fischer,[2] Peter J. Blankestijn,[3] Robin W. Vernooij,[1,3] Carinna Hockham,[4] Giovanni Strippoli,[5,6] Bernard J. Canaud,[7,8] Jorgen B. Hegbrant,[9] Claudia M. Barth,[10] Krister Cromm,[2,8] Andrew Davenport,[11,12] Matthias Rose,[2,13] Mark Woodward,[4,14] Michiel L. Bots,[1] G. A. de Wit,[1,15] Geert Frederix,[1] Miriam P. van der Meulen.[1] The CONVINCE Scientific Committee. *[1]Department of Epidemiology and Health Economics, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [2]Center for Patient-Centered Outcomes Research, Department for Psychosomatic Medicine, Charite - Universitatsmedizin Berlin, Berlin, Germany; [3]Department of Nephrology and Hypertension, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [4]George Institute for Global Health, School of Public Health, Imperial College London, London, United Kingdom; [5]The Department of Precision and Regenerative Medicine and Ionian Area, Universita degli Studi di Bari Aldo Moro, Bari, Italy; [6]The School of Public Health, University of Sydney, Sydney, NSW, Australia; [7]School of Medicine, Montpellier Universite d'Excellence, Montpellier, France; [8]Global Medical Office, Fresenius Medical Care AG, Bad Homburg, Germany; [9]Division of Nephrology, Department of Clinical Sciences, Lunds Universitet, Lund, Sweden; [10]Medical Scientific Affairs, B Braun Avitum AG, Melsungen, Germany; [11]Department of Renal Medicine, Royal Free Hospital, London, United Kingdom; [12]Department of Renal Medicine, Division of Medicine, University College London, London, United Kingdom; [13]Centre of Internal Medicine and Dermatology, Department of Psychosomatic Medicine, Charite - Universitatsmedizin Berlin, Berlin, Germany; [14]George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia; [15]Centre for Public Health, Healthcare and Society, National Institute of Public Health and the Environment, Bilthoven, Netherlands.*

Background: High-flux hemodialysis (HD) and high-dose hemodiafiltration (HDF) are established treatments for patients with kidney failure. HDF has been associated with improved survival rates compared to HD. This study evaluated the cost-effectiveness of HDF compared to HD.

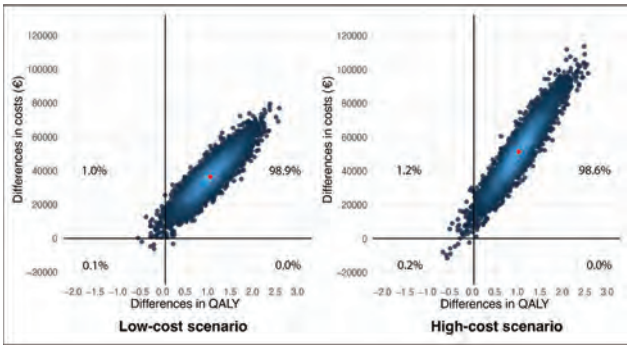
Methods: Cost–utility analyses were performed from a societal perspective alongside the multinational randomized controlled CONVINCE trial, with a two-year and a lifetime time-horizon using a Markov model. Costs of dialysis sessions were based on published data. Other healthcare resource use, productivity losses and quality of life were collected in the eCRF or by country-adapted, self-reported questionnaires. Scenario and probabilistic sensitivity analyses were performed.

Results: HDF was associated with higher utility values compared to HD (0.80 vs 0.78 per year alive), and higher costs (€775 difference per year alive), mainly due to increased dialysis costs (€4/session). Combining these findings with observed mortality in

the model resulted in a quality-adjusted life year (QALY) gain of 1.00, with incremental costs per QALY (ICER) ranging from €36,590 to €51,386. The ICER was €15,768 when excluding all costs in additional life years. Sensitivity analyses showed the probability of cost-effectiveness was >75% at willingness-to-pay threshold of €60,000/QALY, and <30% at €20,000/QALY.

Conclusions: Compared to HD, HDF resulted in an additional year in perfect health at increased costs. The probability of cost-effectiveness is mainly driven by dialysis costs in life years gained. At a €60,000/QALY threshold, probability of HDF being cost-effective exceeded 75%. As costs may differ between countries and centers, we recommend translating our results to local settings.

Funding: Government Support - Non-U.S.



TH-PO1187

Ferric Citrate for the Prevention of Renal Failure in Adults with Advanced CKD: The FRONTIER Trial

Geoffrey A. Block,[1] Steven K. Burke,[2] Martha Block,[1] Stephanie Brillhart,[1] Amanda Leppink,[1] Gerard J. Smits,[6] Mohammad R. Mizani,[5] Pablo E. Pergola,[3] F. David Newby,[4] Varshasb Broumand,[5] Bryce S. Foote,[2] Mary O. Dittrich.[1]
[1]US Renal Care, Plano, TX; [2]Akebia Therapeutics Inc, Cambridge, MA; [3]Renal Associates PA, San Antonio, TX; [4]Nephrology and Hypertension Specialists, PC, Dalton, GA; [5]South Texas Renal Care Group, San Antonio, TX; [6]CSC, Inc., Santa Barbara, CA.

Background: In a prior study of patients (pts) with advanced CKD, Ferric Citrate (FC) significantly reduced time to a composite endpoint of death, dialysis or kidney transplant. Important study design limitations constrain the interpretation of these findings.

Methods: In this 9-month, randomized, double-blind, placebo-controlled clinical trial, pts with eGFR ≤20 ml/min/1.73m^2 were randomized 1:1 to receive fixed dose (2 tablets/meal) FC or matching placebo. The primary endpoint was time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality. Secondary endpoints were time to first hospitalization and individual components of the primary endpoint. Analysis used ITT with ANCOVA adjusting for age, baseline eGFR, and history of diabetes, ASCVD and CHF.

Results: 289 pts were randomized to FC (n=144) or placebo (n=145). The treatment arms were well balanced with no statistical differences in pt characteristics. We observed a statistically non-significant 27% reduction in risk of the primary composite endpoint, (Fig. 1, p=0.12). Individual components of the primary endpoint are shown in Fig. 1. 24% of pts randomized to FC experienced ≥1 serious adverse events vs 32% of pts given placebo. FC was associated with a statistically non-significant reduction in mean hospitalizations (p=0.46), mean hospital days (p=0.41) and time to first hospitalization (p=0.22) (Fig. 2). Similarly, there was a statistically non-significant reduction in time to first ESA use (p=0.79) and time to first IV iron use (p=0.07).

Conclusions: In pts with advanced CKD, fixed dose FC resulted in clinically meaningful, though statistically non-significant, reductions in time to the composite endpoint of death or dialysis, hospitalization, ESA use and IV iron use. The sample size of the trial likely reduced the ability to demonstrate statistically significant results. These findings strongly suggest that re-purposing FC for prevention of kidney failure in pts with advanced CKD may meaningfully improve outcomes.

Funding: Commercial Support - Akebia Therapeutics Inc

Figure 1

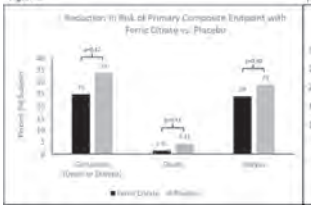
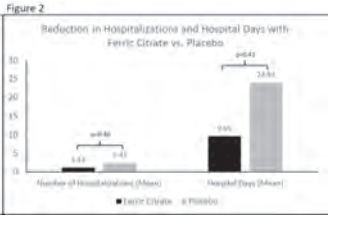


Figure 2



TH-PO1188

Effects of Oxylanthanum Carbonate in Patients Receiving Maintenance Hemodialysis with Hyperphosphatemia

Geoffrey A. Block,[1] Glenn M. Chertow,[2] Guru Reddy,[3] Sanjay S. Mourya,[3] Martha Block,[1] Steve Hasal,[3] Shalabh Gupta,[3] Pablo E. Pergola.[4] *[1]US Renal Care Inc, San Antonio, TX; [2]Stanford University School of Medicine, Stanford, CA; [3]Unicycive Therapeutics, Inc., Los Altos, CA; [4]Renal Associates PA, San Antonio, TX.*

Background: In patients with chronic kidney disease (CKD) on dialysis, hyperphosphatemia is managed by reducing dietary intake of phosphate (P) and phosphate lowering therapies. Oxylanthanum carbonate (OLC) is a phosphate binder in development with high potency and low pill burden. This study assessed the general tolerability of OLC in hyperphosphatemic CKD patients on hemodialysis.

Methods: We conducted a Phase 2, open-label, single-arm, multicenter, multidose study in adult patients with hyperphosphatemia receiving maintenance hemodialysis. The primary objective was to evaluate the tolerability of OLC at clinically effective doses (goal serum P ≤5.5 mg/dL). The study included Washout, Titration, and Maintenance Periods. Eligible patients had serum P ≥4.0 mg/dL and ≤7.5 mg/dL for at least 8 weeks prior to screening while on stable hemodialysis and P-lowering regimens. Patients started titration when their serum P was >5.5 mg/dL and entered maintenance once their serum P was ≤5.5 mg/dL, or after 6 weeks, whichever was sooner. The starting dose of OLC during titration was 1500 mg/day (500 mg TID). We assessed tolerability based on the incidence of discontinuations due to adverse drug reactions (ADRs).

Results: A total of 86 patients were treated with OLC during the study. At screening, serum P was ≤5.5 mg/dL in 51 (59%) patients on a stable P-binder regimen. A total of 78 patients entered maintenance, and 71 (91%) patients had serum P <5.5 mg/dL on a median dose of 1500 mg/day. The most common ADRs were gastrointestinal and included diarrhea (9%) and vomiting (6%); all other ADRs were reported in <5% of patients. Two patients discontinued due to ADRs during titration and 1 patient during maintenance.

Conclusions: In this open-label study, use of OLC enabled adequate control of serum P in >90% of patients who entered maintenance. OLC was safe and generally well-tolerated with ADRs commonly seen in this patient population and with other P binders.

Funding: Commercial Support - Unicycive Therapeutics, Inc.

Patients with Treatment-Emergent Adverse Events (TEAEs)

	TEAEs (N=86) n (%)	ADRs (N=86) n (%)
Serious AEs	5 (6)	0
AEs Leading to Discontinuation	5 (6)	3 (4)
Common AEs		
Diarrhea	10 (12)	8 (9)
Vomiting	5 (6)	5 (6)

TH-PO1189

Which Patients Benefit the Most from Hemodiafiltration Compared with Hemodialysis? Prediction of Individualized Treatment Effects

Peter J. Blankestijn,[1] Robin W. Vernooij,[1,2] Michiel L. Bots.[2] The CONVINCE Study Group. *[1]Department of Nephrology and Hypertension, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands.*

Background: High-dose haemodiafiltration (HDF) reduces all-cause death. No differences in treatment effects are found for specific patient populations when defined on a single characteristic in subgroup analyses. Yet, it is unclear to what extent individual patients, characterized by a combination of clinical characteristics, may benefit from HDF. This study aimed to develop and internally validate a treatment effect prediction model to determine which individual patients would benefit most from well dosed HDF, compared with haemodialysis (HD), in terms of survival.

Methods: Individual participant data from five randomized controlled trials (CONTRAST, ESHOL, Turkish HDF study, French HDF study, CONVINCE) comparing HDF with HD on all-cause mortality were used to derive a Royston-Parmar model for exploring the prediction of absolute treatment effect of HDF based on pre-specified patient and disease characteristics, notably age, sex, body mass index, diabetes mellitus, history of cardiovascular disease, creatinine levels, and c-reactive protein levels. Internal validation of the model was performed using internal-external cross validation.

Results: Among 4153 participants, with a median follow-up of 30 months (Q1-Q3: 24-36), death from any cause occurred in 558 patients (27.2%). The median predicted survival benefit of HDF compared with HD was 6.9 (Q1–Q3: 5.6–9.0) months, with a range of 2 to 42 months. Patients who were predicted to benefit most from HDF were younger, less likely to have diabetes or a cardiovascular history and had higher serum creatinine levels. Internal-external cross validation showed adequate discrimination and calibration.

Conclusions: All-cause mortality is reduced by HDF compared with HD in ESKD patients. Yet, the absolute survival benefit seems to considerably differ between individual patients. Our results suggest that the effects of HDF on absolute survival can be predicted using a combination of readily available patient and disease characteristics. This prediction model approach exemplifies the potential of prediction algorithms in supporting clinical decision-making for the choice of treatment options.

Funding: Government Support - Non-U.S.

TH-PO1190

Amino Acids Supplementation and Exercise Intervention in Hemodialysis Patients: Effects on Muscle and Fatigue, A Randomized Controlled Trial

Emad Samaan,[1] Ammar Y. Ali,[2] Ahmed R. Moustafa,[2] Mirna Shahin,[2] Hala I. Gamaleldin,[2] Sara M. Abdelgawad,[3] Alaa A. Awad,[2] Mohamed Elgamal,[2] Hanan M. Elberashi,[1] Alaa A. Sabry.[1] *[1]Mansoura Nephrology and Dialysis Unit, Mansoura University Faculty of Medicine, Mansoura, Egypt; [2]Mansoura University Faculty of Medicine, Mansoura, Egypt; [3]Mansoura Nephrology and Dialysis Unit, Mansoura University, Mansoura, Egypt.*

Background: Limited data exists on the effects of intradialytic exercise and ketoanalogue(KA) supplementation on muscle mass, function and fatigue in Hemodialysis (HD) patients

Methods: In a randomized controlled trial, 80 HD patients were assigned to one of four groups: (1) KA supplementation only, (2) intradialytic exercise only, (3) both interventions combined, and (4) a control group with standard care. Over 3 months, KA was given as one tablet per 10 KG of patient weight daily, and exercises included knee extensions, hip abductions with ankle weights. Outcomes measured were muscle mass by bioimpedance, quadriceps rectus femoris and vastus intermedius thickness by ultrasonography (US), functional assessments (sit-to-stand test, hand grip strength), and fatigue (Modified Fatigue Impact Scale (MFIS)).

Results: There were no statistically significant differences in baseline parameters between groups. The KA supplementation only- group showed a statistically significant improvement in MFIS, with median values changing from 26(IQR 37) pre-trial to 16.5(15) post-trial (p=0.01), and in the sit-to-stand test showed significant improvements in the number of unaided trials, with median values increasing from 8.5(7) to 10(7) (p=0.02). Hand grip strength also improved from 22.2(14.7) to 25.6(3.6)(p=0.008). The combined interventions group showed significant MFIS improvement, with median values from 29(32) pre-trial to 24(20) post-trial (p=0.03), and hand grip strength improved from 13.1(10) to 21(14.2)(p=0.006). No significant differences in improvement of fatigue scores or hand grip strength were found between the KA supplementation and combined interventions groups. The intradialytic exercise only- group had a significant increase in hand grip strength from 16.1(13.5) to 21.8(7.8)(p=0.006). The control group showed no significant changes. There were no significant differences among groups in anthropometric measures, quadriceps muscle US measurements, or Skeletal Muscle Index assessed by bioimpedance.

Conclusions: KA supplementation could enhance physical performance in HD patients, as evidenced by improvements in fatigue and functional strength. However, the effects on muscle mass were not significant.

TH-PO1191

Long-Term Experience of Treating CKD-Associated Pruritus (CKD-aP) with Difelikefalin at a Large Dialysis Organization in the United States

Rachel A. Lasky,[1] Despina Ruessmann,[2] Linda Ficociello,[1] Maria Gil Mir,[3] Hans-Juergen Arens,[3] Michael S. Anger.[1] *[1]Global Medical Office, Fresenius Medical Care, Waltham, MA; [2]Medical Affairs, CSL Vifor Pharma Group, Glattbrugg, Switzerland; [3]Frenova, Fresenius Medical Care, Bad Homburg, Germany.*

Background: Difelikefalin (DFK), a selective κ-opioid receptor agonist, is the first medication approved for treatment of moderate-to-severe CKD-aP among patients (pts) on chronic hemodialysis. The ability of DFK to lower itch has been shown in clinical and real-world studies. However, long-term, real-world experience of DFK treatment has not been described. The current analysis aims to describe the routine clinical use of DFK in pts for up to 6 months.

Methods: The analysis included in-center hemodialysis pts aged 18-89 years having 1) DFK initiated between 12/1/2022 and 12/31/2023, 2) completed at least one Worst Itch Numeric Rating Scale (WI-NRS) assessment during the 90 days before DFK treatment start and one during DFK treatment, and 3) received ≥ 30 doses of DFK during the first 12 weeks. Pts were then categorized into groups based on their treatment experience after 12 weeks, including those who 1) continued DFK without a gap, 2) paused treatment for 14-44 days then restarted DFK (short gap), 3) paused treatment for > 44 days then restarted DFK (long gap), and 4) discontinued DFK. Each WI-NRS available was determined to be during treatment with DFK (within 14 days of last DFK treatment) or after DFK treatment.

Results: Of 619 pts included in the analysis (56% male, 44% female), 70 had baseline moderate itch and 549 had baseline severe itch. On average, pts were 66.2 years old with a dialysis vintage of 4.1 years. The mean itch score for all groups before DFK treatment ranged between 8.3 and 8.5. A mean itch reduction of at least 3 points on the WI-NRS assessment while being treated with DFK was observed for each group (Table 1). The mean itch score increased for all groups during a gap in DFK treatment or after discontinuation.

Conclusions: Despite differences in treatment patterns after initial 12 weeks of DFK treatment, all pt groups experienced a reduction in itch while receiving DFK. Mean itch scores also increased in all groups after pausing or discontinuing DFK treatment.

Funding: Commercial Support - CSL Vifor

Table 1. Mean (sd) itch scores before, during, and after DFK treatment by treatment group

	Continued DFK (n=367)	Short gap‡ + restart (n=110)	Long gap‡ + restart (n=38)	Discontinued DFK (n=104)
Before DFK start				
# assessments	367	110	38	104
Mean score	8.3 (1.5)	8.5 (1.5)	8.5 (1.4)	8.4 (1.6)
During DFK treatment*				
# assessments	420	77	21	77
Mean score	5.1 (2.9)	5.2 (3.1)	2.9 (2.9)	4.8 (3.1)
During gap / after DFK discontinuation				
# assessments	1	85	50	65
Mean score	**	7.3 (2.8)	8.0 (1.9)	6.4 (3.8)

* between day 7 and gap (+ 7 days) of treatment
** Cells with n < 5 are not reported.
‡ 14-44 days.
‡ > 44 days days

TH-PO1192

DIalysis Symptom COntrol-Pruritus Outcome Trial (DISCO-POT): A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Crossover Trial

David T. Collister,[1,2] Kathy Cherepak,[3] Navdeep Tangri,[1,3] Michael Walsh.[4,5] DISCO-POT Investigators. *[1]Medicine, University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; [2]Medicine, University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [3]Chronic Disease Innovation Center, Winnipeg, MB, Canada; [4]Medicine, McMaster University Faculty of Health Sciences, Hamilton, ON, Canada; [5]Population Health Research Institute, Hamilton, ON, Canada.*

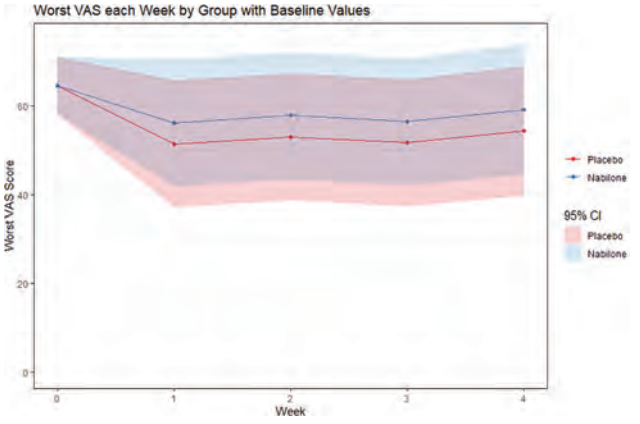
Background: Uremic pruritus affects 50% of patients with kidney failure and negatively impacts quality of life. Itch often persists despite effective pharmacologic treatments. Cannabinoids may reduce pruritus. We evaluated nabilone, a synthetic cannabinoid, to treat uremic pruritus.

Methods: Eligible participants were adults age≥25 years receiving in-center or home hemodialysis at least 2x weekly or peritoneal dialysis daily for at least 90 days and at least moderate itch defined by a mean worst visual analogue scale (VAS) >40mm during a 1-week screening period. Participants were randomly allocated to oral nabilone 0.5mg daily x 1 week then nabilone 0.5mg twice a day x 3 weeks or an identical placebo regimen. Then, after a 2-week washout, participants received an identical regimen of nabilone or placebo, whichever they did not receive in the first treatment period. The primary outcome was the difference in worst VAS over the last 24 hours over each 4 week crossover period.

Results: Of 14 participants randomized, the mean (SD) age was 60.5 (12.7) years, 4 (28.6%) were female sex, 8 (57.1%) had diabetes, and all were on hemodialysis for a mean (SD) of 3.29 (0.73) sessions per week for a mean (SD) 4.04 (0.50) hours/treatment. The mean (SD) worst VAS was 69mm (25). Baseline co-interventions included topical emollients in 12 (85.7%) and alpha 2 delta ligands in 7 (50%). Self-reported and pill count adherence was >90%. Nabilone did not reduce the worst VAS to a greater extent than placebo (Figure 1). The worst VAS was 4.79 (95% CI -3.95 to 13.5, p=0.28) higher with nabilone compared to placebo, indicating worse itch. Nabilone also had no effect on other measures of itch, sleep, quality of life or adverse events.

Conclusions: This small trial detected no effect of nabilone on uremic pruritus compared to placebo. (ClinicalTrials.gov NCT05180968)

Funding: Government Support - Non-U.S.



TH-PO1193

Abstract Withdrawn

TH-PO1194

Real-World Effectiveness of Patiromer among Hemodialysis (HD) Patients: 1-Year Follow-Up on a Retrospective Cohort

Meijiao Zhou,[1] Despina Ruessmann,[2] Linda Ficociello,[1] Maria Gil Mir,[3] Hans-Juergen Arens,[3] Michael S. Anger.[1] *[1]Global Medical Office, Fresenius Medical Care, Waltham, MA; [2]Medical Affairs, CSL Vifor Pharma Group, Glattbrugg, Switzerland; [3]Frenova, Fresenius Medical Care, Bad Homburg, Germany*.

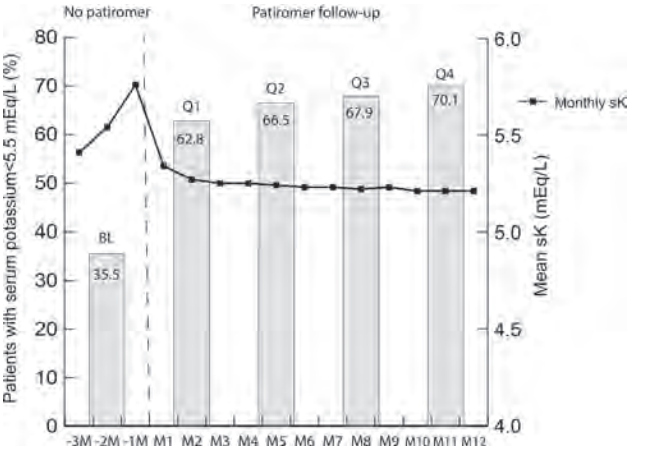
Background: Patiromer (PAT) is a sodium-free, non-absorbed, calcium-based potassium (K^+) binding polymer indicated for treating hyperkalemia. This study aimed to describe PAT utilization and evaluate the changes in serum K^+ (sK) before and after PAT prescription in hemodialysis (HD) patients (pts) over a one-year follow-up period.

Methods: Adult Fresenius Kidney Care HD pts first prescribed PAT monotherapy between 1/2016- 12/2022 were included in the analysis. Eligible pts were on thrice-weekly HD for at least 90 days at the start of PAT and had available sK lab values in the 91 days prior to PAT initiation (baseline; bl; -3M to -1M) and during one year of PAT treatment (follow up; fup; Q1 to Q4; M1 to M12). Changes in lab measurements and prescribed dialysate were compared between bl and fup.

Results: At bl, pts (n=10854) had mean age of 60 years, HD vintage 58 months, 42% were female, 67% had diabetes, 20% had congestive heart failure, and 92% were not on K^+ binders. As shown in the figure, sK increased from 5.41 to 5.76 mEq/L before PAT initiation and decreased to 5.34- 5.21 mEq/L after PAT initiation. % of pts with sK<5.5 mEq/L nearly doubled from bl to Q4. Most pts initiated PAT at 8.4 g (91%) once daily (56%). Over fup, the average PAT dosage was one 8.4 g packet per day. Serum calcium was 8.93 mg/dL at bl and 8.96 mg/dL at Q4; serum sodium was 136.8 and 137.0 mEq/L at bl and Q4, respectively. % pts with calcium-phosphate product <4.4 $mmol^2/L^2$ increased from 58.7% at bl to 63% at Q4. Dialysate calcium and sodium remained stable during the study period. % of pts prescribed one or more treatments with 1 mEq/L K^+ bath decreased from 17.1% at bl to 11.0% at Q4.

Conclusions: Maintenance HD pts prescribed PAT experienced reductions in sK that were maintained over a year-long fup. % pts achieving sK<5.5 mEq/L nearly doubled from 35.5% at bl to 70.1% at Q4.

Funding: Commercial Support - CSL Vifor



TH-PO1195

SPARKLE: A Multicenter, Open-Label Study to Evaluate the Safety and Diagnostic Efficacy of ACE-MBCA in Patients with Known or Suspected Focal Liver Lesions and Severe Renal Impairment

Anna Laura Croci Chiocchini,[1] Andreas L. Norlin,[2] Nadilka Hettiarachchige,[2] David I. Ortiz Melo.[3] *[1]Nephrology, IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Bologna, Italy; [2]Ascelia Pharma AB, Malmo, Sweden; [3]Duke University, Durham, NC.*

Background: ACE-MBCA (Ascelia Pharma Manganese Based Contrast Agent, proposed trade name Orviglance) is an oral manganese-based liver-specific MRI contrast agent. Over 35 million Americans have renal disease, those severely affected at higher risk of safety concerns associated with Gadolinium Based Contrast Agents (GBCAs). This phase 3 study evaluates the safety and efficacy of ACE-MBCA in patients with focal liver lesions and severe renal impairment, a group for which the FDA has issued a black-box warning for all GBCAs due to the kidneys' reduced ability to remove the GBCAs from the bloodstream. The study uniquely includes patients with severe kidney disease, often excluded due to high safety risks, addressing a critical gap in imaging research and providing insights into the safety and efficacy of ACE-MBCA for liver MR contrast agent alternatives.

Methods: In this global phase III study, patients (N=85) with known or suspected focal liver lesions and severe renal impairment received a liver MRI before and 4±1 h after the administration of ACE-MBCA (800 mg). The primary analysis, improvement in visualization of focal lesions, was evaluated by 3 independent readers by qualitative scoring of the change in two co-primary variables, lesion contrast (LC) and border delineation (BD) (scores from 1= poor to 4= excellent). Safety follow-ups, at 24 (± 4) h, 48 (± 4) h, and 5 (± 2) days post-dose.

Results: In 85 patients, the primary analysis showed highly significant ($p<0.001$) improvement of the mean LC and BD scores in combined MRI (CMRI: combined contrast-enhanced + unenhanced MRI) compared to unenhanced MRI: Across the 3 readers, the mean (SD) LC increased by between 0.65 (0.622) and 0.95 (0.824) score points and mean (SD) BD was increased by between 0.81 (0.678) and 1.02 (0.909) score points. No patients were withdrawn from the study. The most reported post-dose AEs were mild to moderate nausea (16.1%), diarrhea (13.8%), vomiting (9.2%), and blood urea increased (3.4%). No drug-related serious AE or deaths were reported.

Conclusions: ACE-MBCA 800 mg significantly improves diagnostic efficacy over unenhanced MR, offering a promising future diagnostic tool for kidney-impaired patients who currently lack safer options for contrast-enhanced liver MRI.

Funding: Commercial Support - Ascelia Pharma AB

TH-PO1196

Azithromycin for the Prevention of Hemolytic Uremic Syndrome in Shiga Toxin-Positive Diarrhea: A Proof of Concept

Gianluigi Ardissino,[1] Letizia Dato,[2] Maria Cristina Mancuso,[1] Thomas Ria,[1] Laura Daprai,[3] Alessandra Gazzola,[4] Alessandra Bazzucchi,[3] Michela Piccoli,[3] Ilaria Possenti,[5] Alice Monzani,[2] Laura Martelli,[6] Angela Amoroso,[6] Giovanni Raimondo Pieri,[5] Antonio Vergori,[7] Sonia Monticone,[2] Marta Cerutti,[2] Cristina Partenope,[2] Anna Elisabetta Bussolini,[8] Alessandra C. Ferrari,[9] Elisa La Barba,[10] Giulia M. Smylie,[11] Simone V. Benatti,[12] Mario V. Luini.[13] ItalKid-HUS Network. *[1]Center for HUS Prevention, Control and Management, Pediatric Nephrology, Dialysis and Transplantation Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; [2]Division of Pediatrics, Department of Health Sciences, Università del Piemonte Orientale, Novara, Italy; [3]Laboratory of Microbiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]Experimental Zooprophylactic Institute of Lombardy and Emilia-Romagna, Lodi, Italy; [5]Pediatric Unit, Pediatric Hospital C. Arrigo, Alessandria, Italy; [6]Pediatric Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [7]Pediatric Unit, Ospedale F. Del Ponte, Varese, Italy; [8]Pediatric Unit, ASST Settelaghi, Tradate, Italy; [9]Pediatric Unit, ASST Cremona, Cremona, Italy; [10]Pediatric Unit, ASST Lariana, Cantù, Italy; [11]Pediatric Unit, Ospedale di Busto Arsizio, ASST Valle Olona, Busto Arsizio, Italy; [12]Clinic of Infectious Diseases, Dept of Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy; [13]Institute of Agricultural Biology and Biotechnology – IBBA-CNR, National Research Council, Lodi, Italy.*

Background: During the last decade, it has become increasingly common to diagnose Shiga Toxin *Escherichia Coli*-related (STEC) infection before Hemolytic Uremic Syndrome (HUS) has developed, providing a potential window of treatment opportunity that, besides generous rehydration, goes underexploited. Antibiotic treatment is historically contraindicated in Shiga Toxin-positive diarrhea on the assumption that it may trigger STEC-HUS. However, this concept is based on weak evidence mostly concerning bactericidal agents and may not apply to bacteriostatic antibiotics. Several *in vitro* and *in vivo* studies both on animal models and on humans indicate that azithromycin may be safe and effective in preventing HUS or mitigating disease severity.

Methods: All STEC infections were treated with azithromycin 10 mg/kg/die orally until diarrhea remission (maximum of 5 days).

Results: Twenty-seven patients (median age 4.4 years) with STEC-positive diarrhea were treated with azithromycin. The treatment was started after a median time of 4 days since the onset of symptoms (2 days since the onset of bloody diarrhea) and it was continued for a median time of 5 days. Of the treated patients, 19% were positive for Stx1, 44% for Stx2, 37% for both Stx1 and Stx2. One out of 27 patients developed HUS after the first dose of azithromycin. No treatment-related side effect was observed.

Conclusions: Azithromycin seems safe and may represent a useful therapeutic option in patients with STEC-positive diarrhea to prevent HUS. A controlled study is necessary but, in the meantime, STEC-infected patients should be treated based on the currently available evidence.

TH-PO1197

GFR Changes Following Urinary Tract Infection (UTI) in Children with Vesicoureteral Reflux (VUR)

David S. Hains, Michelle C. Starr, Andrew L. Schwaderer. *Pediatrics, Indiana University School of Medicine, Indianapolis, IN.*

Background: The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial examined whether continuous antibiotic prophylaxis (CAP) prevented recurrent UTIs in children with VUR. Kidney scarring by dimercaptosuccinic acid (DMSA) scan was a secondary outcome. CAP did not prevent kidney scarring at 2-year study conclusion. Intra-patient changes in kidney function were not assessed. We determined eGFR changes in RIVUR participants with vs without UTI.

Methods: We calculated eGFR via Schwartz formula in RIVUR participants aged ≥6 months with entry and exit serum creatinine measurements available. Exposure: study and lifetime UTIs. Outcome: ΔeGFR, calculated as 2-year exit eGFR minus entry eGFR. We also performed multivariable linear regression.

Results: Children with >1 study UTI had a mean ΔeGFR 12.3 lower than those with ≤1 UTI (*P*=.03). Children with >1 symptomatic UTI receiving placebo had a mean ΔeGFR 19.9 lower than those with ≤1 UTI (*P*=.01). Children with >1 febrile UTI receiving placebo had a lower net ΔeGFR by 27.1.vs. those with ≤1 UTI (*P*=.02). In multivariable analysis, the association between >1 study febrile UTI and ΔeGFR remained after adjustments in the overall cohort and placebo group. No difference was seen between among those treated with CAP. While no differences existed in any groups with a single study UTI, this does not account for individuals that had multiple UTIs at entry. Thus, we examined lifetime UTIs and found those that had >1 lifetime UTI had lower net ΔeGFR (Table). Finally, ΔeGFR was not associated with new DMSA scar formation during the study.

Conclusions: Multiple UTIs may have a detrimental effect on kidney function. CAP may preserve eGFR. Our findings indicate that recurrent febrile UTIs are associated with a decrease in eGFR of up to 27 mL/min/1.73². DMSA scans do not reflect clinically relevant changes in kidney function.

Table. Change in Kidney Function in Children Aged 6 Months or Older[a]

	Unadjusted Mean (Standard Deviation) ΔeGFR[2 b]			Adjusted Difference in ΔeGFR (95% CI), mL/min/1.73[2c]
	Overall	>1 UTI	≤1 UTI	
Overall	9.5 (24.1)			
Prophylaxis (N=89)	6.8 (21.4)			
Placebo (N=99)	11.9 (26.2)			
UTI During Study (N=188)		-1.9 (20.5)	10.4 (24.2)	-8.6 (-21.8 to 4.6)
Prophylaxis (N=89; 4 with >1 UTI)		8.3 (28.4)	6.7 (21.3)	-8.0 (-30.6 to 14.5)
Placebo (N=99; 10 with > 1 UTI)		-5.9 (16.5)	14.0 (26.4)	-11.3 (-30.4 to 7.8)
Febrile UTI During Study (N=188)		-4.0 (23.5)	10.2 (24.0)	-16.7 (-32.1 to -1.3)
Prophylaxis (N=89; 4 with > 1UTI)		8.3 (28.4)	6.7 (21.3)	-8.0 (-30.6 to 14.5)
Placebo (N=99; 5 with > 1 UTI)		-13.9 (15.0)	13.3 (26.0)	-22.3 (-43.5 to -1.0)
Lifetime UTI (N=188)[d]		3.7 (3.2)	11.8 (2.1)	-2.7 (-6.8 to 1.5)
Prophylaxis (N=89; 22 with > 1UTI)		2.7 (4.3)	8.1 (2.7)	2.1 (-5.5 to 9.6)
Placebo (N=99; 32 with > 1 UTI)		4.3 (4.6)	15.6 (3.1)	-5.1 (-10.1 to -0.1)
Number of Lifetime UTIs[d]	Unadjusted Median (IQR) ΔeGFR[2 e]			
	Overall	Prophylaxis (N=89)	Placebo (N=99)	
1	10.1 (-5.4, 25.4)	6.6 (-8.7, 24.4)	16.2 (-1.3, 32.5)	
2	4.0 (-8.6, 21.3)	3.4 (-14.7, 10.7)	9.3 (-8.6, 29.3)	
3	6.1 (-15.2, 26.3)	18.0 (-4.0, 37.5)	0.59 (-15.8, 25.8)	
4	1.1 (-6.5, 6.5)	1.1 (-0.07, 2.2)	-1.2 (-13.0, 10.7)	
5	-7.3 (-19.3, 5.2)	NA	-7.3 (-19.3, 5.2)	
Adjusted Difference in ΔeGFR (95% CI) for each additional lifetime UTI	-2.6 (-11.4, 6.3)	2.3 (-10.0, 14.6)	-5.5 (-17.7, 6.7)	

Abbreviations: ΔeGFR, change in estimated glomerular filtration rate; UTI, urinary tract infection

[a] All ΔeGFR values represent the eGFR in ml/min/1.73 m² at 2-year exit minus the eGFR at enrollment

[b] Given normality, statistical comparisons are reported with mean with standard deviation and comparisons were performed using 2-tailed t test

[c] Adjusted difference in ΔeGFR between groups after adjustment for eGFR at enrollment, bowel and bladder dysfunction at baseline (absent or present, not toilet trained), and age in months (6-11, 12-23, 24-36 and ≥36) using ordinary least squares.

[d] Includes index UTI and UTI prior to index if applicable

[e] Given non-normality, statistical comparisons were reported as medians with IQR and comparisons between were performed using ANOVA.

TH-PO1198

Effect of Pravastatin on Kidney Disease Outcomes in Adult Patients with Early-Stage Autosomal Dominant Polycystic Kidney Disease

Berenice Y. Gitomer,[1] Wei Wang,[1] Anna Ostrow,[1] Kristen L. Nowak,[1] Diana George,[1] Erin R. Coleman,[1] Nayana Patel,[2] Anna Jovanovich,[1] Jelena Klawitter,[1] Zhiying You,[1] Michel Chonchol.[1] *[1]Medicine, University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [2]Radiology, University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: We previously showed that pravastatin slowed the rate of increase in height adjusted total kidney volume (HtTKV) over 3-years in children and young adults with autosomal dominant polycystic kidney disease (ADPKD). To assess whether pravastatin has similar kidney benefits in adults we performed a randomized, placebo-controlled, clinical trial in patients with ADPKD and preserved kidney function.

Methods: 150 patients, aged 25-60 years with an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73m² were randomized to receive either 40 mg/day pravastatin or a placebo over 2-years. Total kidney volume was assessed by magnetic resonance imaging and renal blood flow by magnetic resonance angiography. Kidney function was measured by iothalamate (mGFR) and estimated using a cystatin-based equation. Patients with baseline and 2-year data were included in the analyses. The primary outcome was the annual % change in HtTKV. Secondary outcomes were the annual rate of decline in mGFR and the change in renal blood flow.

Results: The mean age of patients was 40±10 years and 65% were female. Eleven subjects withdrew and 1 subject was excluded from the analyses. Among the 138 patients who completed the study, there were no significant differences in changes in HtTKV, measures of kidney function or renal blood flow between placebo and pravastatin treated patients (Table 1).

Conclusions: Pravastatin did not affect the rate of cyst growth. The minimal effects on renal blood flow observed in the study are consistent with the known effect of statins on the vasculature.

Funding: Other U.S. Government Support

Table 1 Effect of Pravastatin on kidney volume and function

Parameter	Overall, N	Placebo	Pravastatin	p-value[1]
HtTKV (height corrected total kidney volume)				
Change/year (%)	-3.9 (-7.7, 6.7) n = 130	-3.1 (-7.4, 6.8) n = 64	-4.3 (-8.0, 6.6) n = 66	0.2
mGFR				
Change/year (ml/min/1.73m²)	-1.7 (-5.7, 1.8) n = 98	-2.3 (-5.1, 1.6) n = 49	-1.4 (-6.4, 2.0) n = 49	>0.9
eGFR Cystatin C/Creatinine				
Change/year (ml/min/1.73m²)	-3.0 (-6.0, 0.5) n = 135	-3.5 (-6.7, -0.5) n = 68	-2.5 (-5.5, 0.0) N = 67	0.3
Renal Blood Flow				
Change/year (ml/min/1.73m²)	-24.2 (-61.2, 12.3) n = 115	-32.7 (-62.1, -0.8) n = 58	-15.1 (-50.7, 14.4) n = 57	0.2

All data is presented as median (IQR).

[1] Wilcoxon rank sum test comparing annual change in placebo vs. pravastatin treatment.

TH-PO1199

Outcomes of the DUPLEX Trial in Patients with Genetic Focal Segmental Glomerulosclerosis (gFSGS)

Jennifer Lai Yee,[1] Wu Gong,[2] Jula K. Inrig,[2] Michelle N. Rheault,[3] Radko Komers,[2] Howard Trachtman.[1] *[1]Department of Pediatrics, Division of Nephrology, University of Michigan, Ann Arbor, MI; [2]Travere Therapeutics, Inc., San Diego, CA; [3]Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN.*

Background: gFSGS, caused by mutations in podocyte genes, is generally refractory to most available treatments. The DUPLEX trial evaluated the efficacy and safety of sparsentan (SPAR) vs irbesartan (IRB) in patients with FSGS. Overall, the trial showed a greater reduction of proteinuria with SPAR treatment; however, it is uncertain if SPAR's efficacy varies by underlying pathogenesis. Therefore, this post hoc analysis aims to assess the efficacy of SPAR in the subset of DUPLEX patients with gFSGS.

Methods: A total of 355 study patients were genotyped by the FSGS panel of Prevention Genetics. Patients with pathogenic or likely pathogenic variants in podocyte genes were classified to have gFSGS with Mendelian inheritance. The outcome analysis examined changes in proteinuria (percentage reduction; achieving complete remission [CR; urine protein-to-creatinine ratio <0.3 g/g at any time]) and proportion of patients reaching end-stage kidney disease (ESKD; estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2, dialysis, or transplant) with SPAR vs IRB.

Results: Overall, 8.7% (n=31) were identified to have gFSGS. At baseline, patients with gFSGS were younger and had higher eGFR vs the overall DUPLEX population, and most had nephrotic-range proteinuria. SPAR showed a more rapid and more pronounced reduction in proteinuria vs IRB, and this effect was sustained (**Table**). The same pattern was observed in the subset of patients with *NPHS2* mutations. CR was achieved only in SPAR-treated patients with gFSGS (n=1 [8%] vs n=0), whereas reaching ESKD was more frequent with IRB (n=3 [17%] vs n=1 [8%]).

Conclusions: There was more pronounced early antiproteinuric response to SPAR vs IRB in patients with gFSGS that was sustained over the treatment period. The findings support a recommendation for SPAR administration to reduce proteinuria and achieve long-term kidney health benefits in this high-risk group of patients with gFSGS.

Funding: Commercial Support - Travere Therapeutics, Inc.

Outcomes

All gFSGS		SPAR (n=13)	IRB (n=18)
Reduction in proteinuria, %*	Week 12	−53 (−67 to −33)	−25 (−44 to 2)
	Week 36	−63 (−74 to −48)	−35 (−52 to −12)
	Week 108	−49 (−66 to −23)	−27 (−49 to 3)
Complete remission, n (%)	At any time	1 (8)	0 (0)
ESKD, n (%)	At any time	1 (8)	3 (17)

ESKD, end-stage kidney disease; gFSGS, genetic focal segmental glomerulosclerosis; IRB, irbesartan; LS, least square; SPAR, sparsentan.
*Geometric LS Mean Percent Change from Baseline (95% CI).

TH-PO1200

RGLS8429 Increases Urinary PC1 and PC2 and May Reduce Height-Adjusted Total Kidney Volume (htTKV) in Patients with ADPKD

Alan S. Yu,[1] Rekha Garg,[2] Keith A. Bellovich,[3] Arnold L. Silva,[5] Claire S. Padgett,[2] Edmund C. Lee,[2] Tania M. Valencia,[2] Timothy L. Kline,[4] Adriana Gregory,[4] Kevin Carroll,[6] Vishal Patel.[7] *[1]The University of Kansas Medical Center, Kansas City, KS; [2]Regulus Therapeutics Inc, San Diego, CA; [3]St. Clair Nephrology Research, Detroit, MI; [4]Mayo Clinic Minnesota, Rochester, MN; [5]Boise Kidney and Hypertension Institute, Boise, ID; [6]KJC Statistics Limited, Cheadle, United Kingdom; [7]The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: ADPKD is caused by mutations in either PKD1 or PKD2, leading to reduced expression or function of PKD-encoded proteins PC1 and PC2. This results in widespread dysregulated gene expression, hyperproliferation of renal tubular epithelia, formation of multiple cysts, progressive enlargement of the kidneys, and declining renal function. The microRNA miR-17 inhibits PKD1 and PKD2 and is implicated in the dysregulated gene expression observed in ADPKD. RGLS8429 is an anti-miR-17 oligonucleotide that derepresses miR-17 mRNA targets, including PKD1 and PKD2, leading to increased PC1 and PC2 and amelioration of PKD in multiple mouse models.

Methods: We conducted a randomized, double-blind, placebo-controlled, Phase 2a MAD study in patients with ADPKD evaluating RGLS8429 in 3 weight-based cohorts (1, 2, 3 mg/kg). The key inclusion criteria were Mayo Class 1C, 1D, or 1E, and an eGFR between 30-90 mL/min/1.73 m2. The treatment duration was 12 weeks with RGLS8429 or placebo subcutaneous injection Q2W x 7 doses, with an end of study visit 4 weeks after the last dose. We measured urinary PC1 and PC2 levels before and at multiple points after randomization. An exploratory analysis of the change in htTKV from the baseline compared to the end of study was conducted.

Results: We enrolled 42 subjects (32 RGLS8429, 10 placebo) with balanced baseline characteristics between RGLS8429 group and placebo. RGLS8429 was well tolerated. RGLS8429 treatment raised urinary PC1 and PC2 levels in a dose-dependent manner. The change from baseline to end of study in PC1 and PC2 levels was statistically significant in the 3 mg/kg cohort (n=11) compared to the placebo cohort (n=9). Geometric least squares mean percent change in htTKV over 16 weeks was 2.5, 1.4, -0.6, and -0.6 for placebo, 1, 2, and 3 mg/kg groups, respectively. 70% of subjects receiving 3 mg/kg had a reduction in htTKV.

Conclusions: Results provide clinical proof of dose-responsive RGLS8429 mechanistic activity on PC1 and PC2. Exploratory analysis suggests a reduction of htTKV at 2 and 3 mg/kg doses over a relatively short treatment period. Findings validate miR-17 as a potential therapeutic target for ADPKD. A Phase 2/3 registrational trial is being planned.

Funding: Commercial Support - Regulus Therapeutics

TH-PO1201

Stopping Eculizumab Treatment Safely in Atypical Haemolytic Uraemic Syndrome (SETS aHUS): A Multicentre, Open-Label, Prospective, Single-Arm Trial of the Safety and Impact of Eculizumab Withdrawal

Neil S. Sheerin,[1,2] Sally A. Johnson,[2] Edwin K. Wong,[2] Luke Vale,[4] Michal Malina,[2] Giovany Orozco Leal,[5] Ciara A. Kennedy,[3] Sarah Dunn,[3] David Kavanagh.[1,2] *[1]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom; [2]National Renal Complement Therapeutics Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; [3]Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, United Kingdom; [4]London School of Hygiene & Tropical Medicine, London, United Kingdom; [5]Population and Health Sciences Institute, Newcastle University, Newcastle upon Tyne, United Kingdom.*

Background: Atypical Haemolytic Uraemic Syndrome (aHUS) is a rare disease which without treatment is associated with high morbidity and mortality. Eculizumab, a monoclonal complement inhibitor, is an effective treatment but the optimal way to use this high-cost medication has not been determined. The SETS aHUS trial aimed to establish the safety of eculizumab withdrawal and the effectiveness of a monitoring protocol to detect disease relapse and safe reintroduction of treatment if disease relapse occurs.

Methods: The SETS aHUS multicentre, open label, prospective, single arm trial enrolled participants from 15 UK hospitals with embedded qualitative and health economic analyses. Patients over two years of age with aHUS who were receiving eculizumab therapy for at least six months were eligible to withdraw from treatment, replacing it with monitoring to assess disease activity with re-introduction of treatment if relapse occurred. The primary outcome measure was harm to a participant as a consequence of eculizumab withdrawal during the 2-year trial period. Participants met a primary outcome if there was a permanent reduction in estimated glomerular filtration rate (GFR), requirement for kidney replacement therapy or significant extra-renal manifestation of disease. The Bayes factor single arm binary model was used to monitor and analyse the trial data, applying pre-trial stopping rules. The trial is registered with the European Union Drug Regulating Authority (EudraCT 2017-003916-37).

Results: One of 28 participants (3.6%) who withdrew from treatment met a primary outcome. Four participants relapsed, all with pathogenic genetic variants in complement proteins. Only participants with an identified cause of complement dysregulation relapsed. It was possible, by monitoring and rapid participant access, to successfully reintroduce eculizumab treatment. Based on the pre-trial analysis plan, withdrawal from treatment is not associated with a greater risk to patients compared to remaining on treatment.

Conclusions: Withdrawal of eculizumab treatment with monitoring of disease activity was not associated with an increased risk of harm compared to continuation of eculizumab.

Funding: Government Support - Non-U.S.

TH-PO1202

Rituximab for Adult-Onset Frequently Relapsing or Steroid-Dependent Nephrotic Syndrome: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

Yoshitaka Isaka,[1] Shoichi Maruyama,[2] Mika Sakaguchi,[14] Hiroki Hayashi,[13] Yusuke Kaida,[11] Shin Goto,[10] Tatsuo Tsukamoto,[12] Akito Maeshima,[15] Yoichiro Ikeda,[3] Norihiko Sakai,[4] Naoki Sawa,[5] Kengo Furuichi,[6] Kunihiro Yamagata,[7] Yusuke Sakaguchi,[1] Maki Shinzawa,[1] Takehiko Wada,[5] Yugo Shibagaki,[8] Keiju Hiromura.[9] A-TEAM. *[1]Osaka Daigaku, Suita, Japan; [2]Nagoya Daigaku, Nagoya, Japan; [3]Tokyo Daigaku, Bunkyo-ku, Japan; [4]Kanazawa Daigaku, Kanazawa, Japan; [5]Toranomon Byoin, Minato-ku, Japan; [6]Kanazawa Ika Daigaku, Kahoku-gun, Japan; [7]Tsukuba Daigaku, Tsukuba, Japan; [8]Sei Marianna Ika Daigaku, Kawasaki, Japan; [9]Gunma Daigaku, Maebashi, Japan; [10]Niigata Daigaku, Niigata, Japan; [11]Kurume Daigaku, Kurume, Japan; [12]Igaku Kenkyujo Kitano Byoin, Osaka, Japan; [13]Fujita Ika Daigaku, Toyoake, Japan; [14]Kinki Daigaku, Higashiosaka, Japan; [15]Saitama Ika Daigaku Sogo Iryo Center, Kawagoe, Japan*.

Background: Among adult-onset nephrotic syndromes, side effects of long-term steroid use are problematic in patients with frequently relapsing nephrotic syndrome (FRNS) and patients with steroid-dependent nephrotic syndrome (SDNS). We investigated the efficacy and safety of rituximab on FRNS or SDNS patients.

Methods: We performed a multicenter, double-blind, randomized, placebo-controlled trial at 13 centers in Japan. Adult-onset FRNS or SDNS patients with urinary protein <0.3 g/gCr on at least two urine protein determinations after initiation of steroid therapy for the most recent relapse were enrolled. Patients received rituximab (375 mg/m^2) or placebo twice a week apart, and at 25 weeks. The dose of steroids was reduced and discontinued every 4 weeks in principle. Subjects who relapsed (urinary protein 1 g/g Cr or higher) within 49 weeks from the start date of the investigational drug could receive rituximab treatment once they were in remission after treatment with steroids. The primary endpoint was the relapse-free period. Safety endpoints were frequency and severity of adverse events. Patients who received their assigned intervention were included in analyses. This trial is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN000041475.

Results: 66 patients received the assigned intervention (32 were given rituximab and 34 placebo). The median relapse-free period was significantly longer in the rituximab group (not reached, 95% CI -/-) than in the placebo group(29.8 week, 20.1/-; hazard ratio: 0.16, 0.05-0.46; p=0.0008). The recurrence-free rate at 49 weeks was 86.5% in the rituximab group and 37.2% in the placebo group (p<0.0001). The recurrence-free rate at 49 weeks for patients who entered the treatment phase after relapse was 66.7% (2 of 3 patients) in the rituximab group and 100% (20 of 20 patients) in the placebo group. Four patients (12.5%) in the rituximab group and 2 (5.9%) in the placebo group had at least one serious adverse event.

Conclusions: Rituximab is an effective and safe treatment for the prevention of adult-onset FRNS and SDNS relapse.

Funding: Commercial Support - Zenyaku Kogyo Co., Ltd.

TH-PO1203

AMPLITUDE: A Phase 2/3 Adaptive Trial of Inaxaplin in APOL1-Mediated Kidney Disease

Glenn M. Chertow,[1] George Manos,[2] Ogo I. Egbuna.[2] *[1]Stanford University School of Medicine, Palo Alto, CA; [2]Vertex Pharmaceuticals Incorporated, Boston, MA.*

Background: Two variants in *APOL1* drive progressive, proteinuric nephropathies called APOL1-mediated kidney disease (AMKD). Inaxaplin (IXP), an oral inhibitor of APOL1, reduced proteinuria by 47.6% in persons with 2 *APOL1* variants and FSGS in a Ph2 study. We report interim data from an *APOL1* genotyping study, describe the Ph2/3 IXP trial (AMPLITUDE) design in a broader AMKD population, and provide interim baseline data from the Ph2 portion of AMPLITUDE.

Methods: Our genotyping study is enrolling up to 4000 participants of recent African ancestry with FSGS or nondiabetic kidney disease and UPCR≥0.5g/g. One blood sample is collected to verify *APOL1* genotype by PCR to optimize care and inform eligibility for clinical trials. Our Ph2/3, randomized, double-blind, placebo-controlled, adaptive trial is enrolling persons (Ph2:18-65yrs; Ph3:10-65yrs) with 2 *APOL1* variants, UPCR≥0.7 to <10g/g, and eGFR≥25 to <75mL/min/1.73m^2. In the Ph2 portion, participants received IXP (different doses) or placebo for 12wks to select a dose for evaluation of IXP efficacy/safety in ~400 participants in the Ph3 portion. For the final analysis, the primary endpoint is reduction in rate of decline of kidney function (eGFR slope) by IXP vs placebo; secondary endpoint is time to composite clinical outcome (sustained decline of ≥30% from baseline in eGFR, onset of ESKD, or death). Final analysis will occur when ≥2yrs of eGFR data and ~187 composite clinical outcomes are obtained.

Results: The genotyping study interim analysis included 2866 participants of whom 674(23.5%) have 2 *APOL1* variants; 36 of these participants enrolled in the completed Ph2 portion of AMPLITUDE. A 45mg IXP once daily dose was selected for Ph3 after review of Ph2 efficacy/safety data by an independent data monitoring committee. Among 64 participants dosed, 34(53.1%), 24(37.5%), and 6(9.4%) have *G1/G1, G1/G2,* or *G2/G2* genotypes. The mean (SD) age was 42.7 (11.0) yrs and mean (SD) baseline eGFR was 42.8 (14.0) mL/min/1.73m^2. Ph3 is ongoing in 9 countries.

Conclusions: The high prevalence of 2 *APOL1* variants in participants with recent African ancestry and proteinuric CKD reinforces the importance of *APOL1* genotyping to optimize kidney disease management and enable referral to clinical trials of APOL1-targeted therapies. Our Ph2/3 trial will evaluate the effects of IXP on preserving kidney function and reducing proteinuria in a broad AMKD population.

Funding: Commercial Support - Vertex Pharmaceuticals

TH-PO1204

Zanubrutinib for the Treatment of Primary Membranous Nephropathy (PMN): Results of a Single-Arm Feasibility Study

Richard A. Lafayette,[1] Sean Barbour,[2] Yanyan Chen,[4] Zhen Yao,[4] Shengnan Chen,[4] Guisen Li,[5] Ming-Hui Zhao.[3] *[1]Stanford University Medical Center, Stanford, CA; [2]University of British Columbia, Vancouver, BC, Canada; [3]Renal Division, Peking University First Hospital, Beijing, China; [4]BeiGene Co., Ltd, Shanghai, China; [5]Sichuan Provincial People's Hospital, Chengdu, China*.

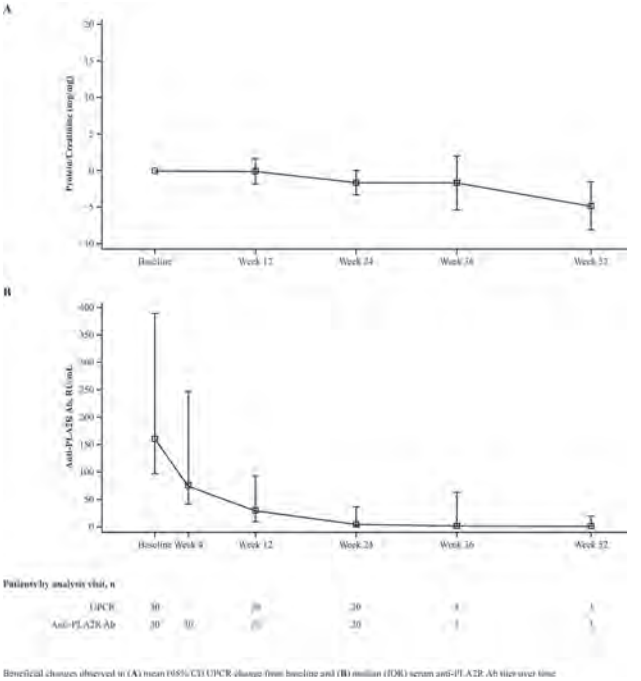
Background: Bruton tyrosine kinase (BTK) plays a key role in B cell modulation and is a potential therapeutic target in PMN, an antibody-driven glomerular disease. The efficacy and safety of zanubrutinib, a highly selective inhibitor of BTK, is being evaluated in a 2-part, phase 2/3 open-label study in patients (pts) with PMN. Here, part 1 is presented.

Methods: After a 12-wk run-in with optimal supportive care, pts with anti-phospholipase A2 receptor (PLA2R) antibody (Ab) >50 RU/mL and urinary protein-creatinine ratio (UPCR) >3.5 g/g receive zanubrutinib 160 mg BID for 64 wks, followed by a 40-wk observation period. Primary endpoint: change from baseline in UPCR at wk 24; secondary endpoints: anti-PLA2R Ab titer, serum albumin, overall remission rate, safety.

Results: Of 30 pts, most were men (66.7%) and Asian (93.3%). At baseline, median (range) UPCR was 7.5 g/g (3.6, 14.8), serum anti-PLA2R Ab was 161.0 (51.4, 1219.8) RU/mL, serum albumin was 23.5 (15.4, 42.3) g/L, and eGFR was 85.2 (39.8, 123.0) mL/min/ 1.73m^2. As of July 15, 2024, the median duration of exposure was 26.5 wks, and 20 pts had completed the wk 24 visit (5 pts discontinued early). At 24 wks, median change from baseline in UPCR was -1.5 g/g (-8.8, 5.7); 6 pts (30%) had partial remission (UPCR 0.3–3.5 g/g and ≥50% decrease from baseline, stable eGFR), and the immunological response rate (anti-PLA2R titer reduction to <14 RU/mL) was 60% (**Figure**). Overall, 26 pts (87%) had treatment-emergent adverse events (TEAEs), mostly (≥15% pts) upper respiratory tract infections (27%), rash (20%), and hypokalemia (17%). 4 pts (13%) had severe TEAEs (treatment-related in 1 pt).

Conclusions: Zanubrutinib appears to be generally well tolerated and shows activity in pts with PMN.

Funding: Commercial Support - BeiGene Co., Ltd.



Beneficial changes observed in (A) mean (95% CI) UPCR change from baseline and (B) median (IQR) serum anti-PLA2R Ab titer over time

TH-PO1205

Phase II Results of an Investigational RNA Therapeutic to Complement Factor B, IONIS-FB-LRx, for Treatment of IgA Nephropathy

Sean Barbour,[1] Michelle A. Hladunewich,[3] Angela Makris,[7] Sven-Jean Tan,[8] Richard A. Robson,[9] Muh Geot Wong,[4] Jason Choo Chon Jun,[5] Ashley Frazer-Abel,[6] Lixuan Yin,[2] Terry Barrett,[2] Richard Geary,[2] Eugene Schneider,[2] Jon L. Ruckle,[2] Michael Mccaleb,[2] Gary T. Brice.[2] *[1]The University of British Columbia, Vancouver, BC, Canada; [2]Ionis Pharmaceuticals Inc, Carlsbad, CA; [3]Sunnybrook Research Institute, Toronto, ON, Canada; [4]Royal North Shore Hospital, St Leonards, NSW, Australia; [5]Singapore General Hospital, Singapore, Singapore; [6]University of Colorado Anschutz Medical Campus, Aurora, CO; [7]Liverpool Hospital Renal Clinic, Liverpool, NSW, Australia; [8]The Royal Melbourne Hospital, Melbourne, VIC, Australia; [9]NZCR, Auckland, New Zealand.*

Background: Overactivity of the complement Alternative Pathway (AP) has been implicated in pathogenesis of primary IgA nephropathy (IgAN). An antisense oligonucleotide to complement factor B (FB), IONIS-FB-L_{Rx} (ISIS 696844, RO7434656) targets FB mRNA in the liver leading to reduction of AP activation in IgAN patients.

Methods: An exploratory, single-arm, global open-label Ph2 trial (NCT04014335) recruited patients with biopsy-confirmed IgAN with renal C3 deposits, hematuria, and 24-hr protein excretion >1.5g/d, eGFR>40mL/min/1.73m^2 despite maximum tolerated RAAS blockade including 6 patients on stable doses of SGLT2i. Patients received monthly subcutaneous (SC) administration of IONIS-FB-L_{Rx} for 24 weeks followed by voluntary treatment extension. Primary endpoint was change in 24-hr proteinuria at week 29 (or 4 weeks after last dose) compared to baseline (BL).

Results: 23 patients were enrolled (25-62 yr of age, 40% Female, 13 Asian, 9 White, 1 other). One subject discontinued study drug at week 17 to initiate SGLT2i. Median 24-hr proteinuria at BL was 2.0 g/d (IQR 1.64, 4.78 g/d). At week 29, a 43% (95% CI: 23%, 58%) geometric mean reduction of 24-hr proteinuria was observed. Reductions in UPCR and UACR were also observed. There was no change in mean eGFR at week 29 compared to BL (mean±SD; BL 70.4 ±21.6; week 29 73.2±19.9 mL/min/1.73m2). There was sustained reduction of 24-hr proteinuria in all 7 patients who opted for treatment extension, including 4 patients treated for >12 mo. There were selective reductions of plasma complement FB and Factor Bb, serum AP activity, urinary Factor Ba and urinary sC5b-9 without changes in serum CH50. There was one treatment emergent SAE assessed as not related to study drug and transient and reversible ALT elevations (3-5X fold ULN) without a change in serum bilirubin were observed in 3 subjects, all of whom remained on study and completed treatment.

Conclusions: IONIS-FB-L_{Rx} met primary endpoints in patients with biopsy-confirmed IgAN. This Ph2 open-label study provides consistent clinical evidence supporting ongoing Ph3 study of IONIS-FB-L_{Rx} /RO7434656 to reduce the progression of IgAN (NCT05797610).

Funding: Commercial Support - Ionis Pharmaceuticals

TH-PO1206

Single-Center, Phase 2, Open-Label Trial Evaluating the Efficacy and Safety of Obinutuzumab in Treatment of Immunosuppression-Resistant Primary FSGS, or Contraindication to High-Dose Corticosteroids

Ladan Zand,[1] Eddie L. Greene,[1] Wisit Cheungpasitporn,[1] Maria Jose Vargas-Brochero,[1] Miriam Machado,[1] Sanjeev Sethi,[2] Pierre M. Ronco,[3] Fernando C. Fervenza.[1] *[1]Division of Nephrology and Hypertension, Mayo Clinic Department of Internal Medicine, Rochester, MN; [2]Laboratory Medicine and Pathology, Mayo Clinic Minnesota, Rochester, MN; [3]Hopital Tenon, Paris, France.*

Background: We investigated the efficacy and safety of obinutuzumab, a type II anti-CD20 antibody, in patients with primary FSGS who were resistant/dependent on immunosuppressive therapy.

Methods: Patients were treated with 2 doses of obinutuzumab (1 gram), 2 weeks apart at baseline and 6 months. Primary outcome was change in proteinuria from baseline to 6 and 12 months. Secondary endpoints were complete (proteinuria <0.3g/d) or partial (50% reduction in proteinuria & proteinuria < 3.5 g/d) remission, & rates of serious adverse events.

Results: Twenty patients were enrolled. Average age 45.3±17.5 years, 55% male. Systolic BP: 132±17.5 mmHg, diastolic BP: 77.1±9.5 mmHg. Patients had failed 2-3 prior therapies. There was significant improvement in proteinuria: baseline [10.7 (7.5 – 13.7)] g/d to 12 months [3.8 (1.5 – 8.6)] g/d (p=0.001), significant improvement in serum albumin, cholesterol, & eGFR (**Table 1**). By 12 months, 8 patients (40%) reached CR/PR, none relapsed. 3 serious adverse events (SAE): 2 in one patient hospitalized for suicidal ideation and pseudo-seizures, 1 SAE was development of follicular lymphoma. SAEs were unrelated to obinutuzumab. Most common AE was infusion-related reaction occuring in 7 patients (none resulted in therapy discontinuation). There were 7 infections, none required hospitalization.

Conclusions: Obinutuzumab significantly reduced proteinuria in patients with primary FSGS who had failed 2-3 prior therapies. Reduction in proteinuria was associated with an improvement in eGFR and serum albumin with an acceptable side effect profile.

Funding: Commercial Support - Genentech

Patients laboratory and urine study data

	Baseline N=20	6 months (N=20)	12 months N=20	P-value*
Serum creatinine (mg/dL)	1.67 ± 0.83	1.65 ± 0.81	1.44 ± 0.81	0.15
eGFR (ml/min/1.73m2)	48 (28, 89)	48 (34, 93)	62 (37, 95)	0.04
Serum albumin (g/dL)	2.5 ± 0.6	3.1 ± 0.8	3.5 ± 0.8	<0.001
Total cholesterol (mg/dL)	285 ± 120	277 ± 132	213 ± 49	0.002
LDL cholesterol (mg/dL)	194 ± 122	175 ± 148	122 ± 40	0.008
Proteinuria (g/d)	10.7 (7.5, 13.7)	7.3 (4.0, 10.3)	3.8 (1.5, 8.6)	0.001
B-cell counts (cells/µl)	160 (75, 251)	0 (0, 1)	0 (0, 0)	<0.001

*p-value is the comparison between baseline and 12 months (paired t-test or Wilcoxon test).

Results are reported as averages ± SD or median and interquartile range.